EPFL

Thèse n° 8727

New Vinylation and Alkynylation Strategies with Hypervalent Iodine Reagents and Diazo Compounds

Présentée le 24 septembre 2021

Faculté des sciences de base
Laboratoire de catalyse et synthese organique
Programme doctoral en chimie et génie chimique

pour l'obtention du grade de Docteur ès Sciences

par

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2021

À mes parents,

Acknowledgements

First and foremost, I would like to express my gratitude to Jérôme for giving me the opportunity to realize my PhD at the LCSO. Thank you for your everyday dedication and constant support in my work. During these four years, I really appreciated the freedom and trust you could give me. I believe I have been able to fully unveil my potential as a researcher under your guidance. Your calm and respectful attitude are other qualities that make you an excellent mentor and I could not have wished better to go through this PhD adventure.

I would like to thank Professor Jieping Zhu for having accepted to serve as the president of the thesis defense committee and Professor Uttam Tambar, Professor Marcos Suero and Professor Nicolai Cramer for serving as jury members at my thesis defense and taking the time to examine my research work.

The most important part of this four years has certainly been the human encounters. I would like to thank all past and present members of the LCSO I had the chance to meet. Thank you for the stimulating environment you have created and for the countless moments of fun we have shared. In no particular order, I would like to express my gratitude to the following people:

Paola, thank you for welcoming me in your lab and giving me some tricks for a good start in the PhD. What a performance to play every day la commedia dell'arte from the most insignificant chit-chats and gossips of the BCH, brava!

Dr. Durga, of course, lot of the work presented in this manuscript could not have been possible without your help and I am thankful for that. Beyond an amazing chemist, you are an extremely humble person with who I could share some inspiring philosophical reflections.

Dani, "ma muse", at least for what concerns chemistry, everybody knows that. Merci pour tout ces bons moments ensemble en dehors du labo.

Mingming, it has been a real pleasure to have shared almost four years having you around. You are always easy-going and happy.

Mon gros Rwann-R ! Je n'aurai pas pu espérer mieux pour commencer ce doctorat que tomber avec un type comme toi dans le labo. La rigolade ! J'essaie de me rappeler un jour sans mais y'en pas eu je crois. Tes prises de position assumées, ton style légendaire et ta sympathie, le mélange explosif pour la synthèse quotidienne du bonheur. Merci poto !

Alec, le jeuno! Je crois que tu m'as plus appris qu'à l'inverse finalement. Merci pour ton aide précieuse au labo et j'espère te voir dans le monde de la recherche dans quelques années (si j'y suis toujours ?).

Phil and Johannes, as you were always together, I do not want to separate this beautiful couple here. Thanks both of you for the good moments and situations you have created.

Vince, la bonne tranche belge du lab ! Une belle rencontre pour cette deuxième moitié de doctorat, toujours avec un big smile. Merci d'avoir réussi à motiver mes gibolles engourdies le long du lac.

Stian-Ba, mon frère d'armes dans la bataille quotidienne au front du PhD. Merci pour tout ton soutient et bien évidemment les nombreux moments à reconstruire le monde lors de nos séances troquet. On a toujours débriefé de la façon la plus sobre possible, ce qui fût très important pour mon équilibre ! Et bien sûr que tout le monde viendra rabiner "À la bonne fiole" !

Marion, j'ai toujours su apprécier ton énergie débordante dans la routine d'une journée au labo. Merci pour la complicité dont tu as fait preuve au cours de ces quatre belles années.

Ju-Ju, merci pour ta sympathie ! Merci de ta collaboration sur le projet thiirane, qui sent bon une excellente aventure PhD pour toi. On se sera bien marré ensemble.

Merci Stefano! Le LCSO n'irait pas très loin sans toi au quotidien. Merci pour tes précieux conseils en chimie, mais aussi en matière de sécurité auxquels j'ai ~~pas~~ toujours prêté la plus grande attention.

Francky, le champion toutes catégories confondues. Merci pour tes talents de chimiste, avec lesquels j'ai toujours apprécié confronter les miens (si tant est que j'en ai). Merci pour les innombrables bon moments à l'extérieur du labo. Ta capacité à organiser des activités et soirées aura galvaniser la première partie de mon PhD.

Énorme merci à Éliott évidemment ! Deux ans et demi ensemble avec un chiant comme moi en labmate… On a eu le temps de discuter passion chimie, de critiquer tout ce qui est bon à critiquer, et d'avoir de franche rigolades. Tu es un atout sur pour le LCSO et je suis certain de ta réussite pour la fin de ton doctorat. En tant que biérologue assumé du LCSO, merci de m'avoir fait découvrir des potions parfois bonnes, parfois moins bonnes, mais jamais inintéressantes.

Il grande Luca, thanks for the good vibes and knowledge you bring to the group. I have really appreciated to share a peaceful office with you for the last months.

Nina, merci pour ta bienveillance au quotidien… mais aussi pour toutes tes insultes injustifiées à mon égard, tout cela m'a beaucoup aidé.

Stephanie, my BFF (best freaky friend), merci d'avoir su apporter une touche d'irrationnel dans ce monde trop borné qu'est la chimie. Please, don't change anything!

There is many more members of the LCSO with whom I could not spend enough time with, nevertheless, they all contributed to keep a good atmosphere and I thank you all for that.

Additional acknowledgments will go to the other organic chemists of our neighbor groups, the LCSA and LSPN laboratories. Thank you all for having created an intellectually stimulating environment. I owe a special thanks to Raphy, Benoit and Jack (special special thanks for having proofread the English of this thesis) who always helped me progress through this PhD in the friendliest manner.

I wish to thank the experts whom I have collaborated with:

Thank you Dr. Matt Wodrich for all the computational work you have done. I got a clearer idea about what does DFT really means.

Aurélien, mon NMR-geek préféré, merci pour ton aide précieuse sur ces machines qui font peur.

Double mercis à Rosario et Farzaneh pour les nombreuses structures X-ray résolues. J'en profite également pour vous adresser ici mes excuses quant aux molécules un peu moins ordonnées que j'ai pu vous envoyer.

Je tiens également à remercier toutes les personnes impliquées dans les services que sont la RMN, la spectrométrie de masse ou le magasin, essentiels au bon fonctionnement de l'ISIC. Merci Véronique et Anne-Lene pour votre aide indispensable sur le plan administratif.

Une grande embrassade commune ira à tout mes amis, de Lausanne et d'ailleurs. Que ce soit pour quelques heures, une journée, un week-end ou des vacances, et sans pour autant en être

conscient, vous avez su alléger mon esprit du poids qu'a pu représenter ce doctorat. Vous avez donc largement contribué à sa réussite. Merci à tous !

À toute ma famille, merci pour votre amour, votre soutient et votre confiance. Romain, fraté, si j'essaie d'avoir un œil critique sur ma situation c'est bien grâce à toi. Baignant dans un environnement homogène de personnes captivées par leur domaine, comme je l'ai été ces quatres années, tu m'as largement aidé à relativiser. Merci. Mes ultimes remerciements seront adressés à mes parents, mes véritables héros, toujours à mes côtés, toujours là pour me porter.

Abstract

Unsaturated carbon-carbon bonds are essential in organic chemistry. A myriad of natural products and bioactive compounds incorporate alkenes or alkynes in their structures. In addition, these motifs are exceptionally versatile. They can be converted in various other functionalities, and have important applications in applied domains such as chemical biology and material science. The development of new vinylation and alkynylation strategies is therefore highly desirable.

The rapid access to complex molecules from readily available starting materials is an important goal of research in modern organic synthesis. In this context, the difunctionalization of diazo compounds is particularly interesting with the possibility to introduce two new functional groups on the same carbon atom. The utilization of hypervalent iodine reagents to realize non-classical electrophilic vinylation and alkynylation of diazo compounds can be an efficient strategy to synthesize elaborated building blocks incorporating unsaturated C-C bonds. In this thesis, the use of copper catalysis has been investigated to realize new coupling reactions between diazo compounds and hypervalent iodine reagents.

The development of a sequential copper-catalyzed oxy-alkynylation/intramolecular [4+2] cycloaddition of allenes and arenes was investigated at first. This one-pot protocol allowed the construction of complex polycylic architectures with high efficiency from aryldiazo esters and ethynylbenziodoxolone reagents (EBX). The mild reaction conditions (23 to 90 °C) for the dearomatization step was unusual compared to previous literature reports and DFT computations showed that substituents on the aryl ring resulted in favorable dispersive interactions, decreasing the activation energy barrier of the cycloaddition. The bicyclo[2.2.2]octadiene products were successfully applied as ligands for rhodium. The prepared diene-rhodium complexes were extensively characterized by NMR spectroscopy and X-ray crystallography. Finally, an enantiopure ligand having a pseudo C_2-symmetry was used in the conjugate addition of phenylboronic acid to cyclohexenone and furnished the β-functionalized ketone in good yield and with high enantioselectivity.

The vinylation reactions of diazo compounds are scarce. A successful copper-catalyzed vinylation of diazo compounds with vinylbenziodoxolone reagents (VBX) as partners was reported. The transformation allowed an unprecedented *gem*-oxy-vinylation at the carbene center, providing functionalized α-vinyl-hydroxyacid derivatives in high atom and step economy. The products were obtained in excellent yields and contained synthetically versatile functional groups for post-modifications. The development of an enantioselective version of this reaction was limited and further investigations will be required to obtain high enantioselectivities. In addition, a practical synthesis of alkyl-substituted VBX reagents has been established; VBX reagents being limited to aryl substituents until then.

Multicomponent reactions provide efficient means to rapidly access molecular diversity. A copper(I)-catalyzed three-component reaction utilizing diazo compounds, alcohols as nucleophiles and vinyl- or ethynylbenziodoxole reagents, was successfully developed. The transformation allowed the synthesis of highly functionalized allyl and propargyl ethers. The scope is broad, and extensive variations of the three partners of the reaction is possible, leading to maximal structural diversity. Extension of this work to *N*-nucleophiles was not as straightforward as anticipated, but good results could be obtained with anilines, trifluorodiazoethane and EBX reagents as components.

Questions about the reaction mechanisms of the copper-catalyzed difunctionalizations of diazo compounds with VBX and EBX reagents have been frequent all-along this research work. Preliminary results of in-depth mechanistic investigations have been obtained. The initial assumption

of an internal alkyne transfer step was first invalidated by DFT computations and was latter refuted experimentally. A complexation between the carboxylate of ethynylbenziodoxolone reagents and the copper catalyst was characterized by NMR spectroscopy and contrasted to a alkyne-copper interaction observed with ethynylbenziodoxole reagents. These two possible complexes were supported by DFT calculations. Finally, non-classical sigmoidal kinetic profiles of the oxy-alkynylation reaction were obtained by *in situ* ^{19}F NMR monitoring and the Cu-EBX complex is presumably involved in the observed induction periods.

Keywords: vinylation, alkynylation, diazo compounds, hypervalent iodine reagents, VBX, EBX, copper catalysis, carbenes, molecular complexity, multi-component reactions, chiral ligands.

Résumé

Les composés insaturés sont essentiels en chimie organique. De nombreuses molécules naturelles et de nombreux principes actifs incorporent des alcènes ou des alcynes dans leurs structures. De nature polyvalente, ces groupes fonctionnels peuvent être facilement interconvertis en d'autres fonctions chimiques d'intérêt. De plus, les alcènes et les alcynes font l'objet d'applications dans divers domaines tels que la biologie chimique et la science des matériaux. Le développement de nouvelles stratégies de vinylation et d'alcynylation est donc un important enjeu de recherche.

L'obtention de molécules complexes à partir de matières premières simples et disponibles est un des objectifs principaux en synthèse organique moderne. La difonctionnalisation des dérivés diazo est intéressante car elle offre la possibilité d'introduire simultanément deux nouveaux groupes fonctionnels sur un même atome de carbone. L'utilisation de réactifs d'iode hypervalent pour réaliser la vinylation et l'alcynylation de composés diazo de manière électrophile peut être une stratégie efficace pour la synthèse de molécules avancées comportant des liaisons doubles et triples dans leurs structures. L'étude de cette thèse porte sur l'utilisation de catalyseurs au cuivre pour réaliser de nouvelles réactions de couplage entre des composés diazo et des réactifs d'iode hypervalent.

Dans un premier temps, le développement d'une séquence d'oxy-alcynylation/cycloaddition [4+2] a été réalisé. Ce protocole one-pot permet la construction d'architectures polycyliques complexes à partir aryldiazo esters et de réactifs EBX. La température inhabituellement basse (23 à 90 °C) pour l'étape de déaromatisation a pu être élucidée grâce à des calculs DFT, dont les résultats indiquent l'effet des substituants du cycle aromatique pour diminuer l'énergie de l'état de transition. Les bicyclo[2.2.2]octadiènes obtenus ont pu être utilisés en tant que ligands chiraux dans l'addition conjuguée de l'acide phenylboronique sur la cyclohexénone catalysée au rhodium.

Les réactions de vinylation de composés diazo sont rares. L'insertion de composés diazo dans les réactifs VBX a pu être réalisée grâce à la catalyse au cuivre, fournissant des dérivés d'acide α-vinyl-hydroxylé de manière atome-économique. Les produits ont été obtenus avec d'excellents rendements et contiennent divers groupes fonctionnels pour de futures manipulations synthétiques. La version énantiosélective de cette réaction reste néanmoins limitée et des recherches supplémentaires seront nécessaires pour obtenir des excès énantiomériques plus élevés. Par ailleurs, un nouveau protocole pour la synthèse des réactifs VBX ayant des substituants alkyles a été développé.

Les réactions multicomposants permettent de synthétiser en une étape des molécules souvent complexes. Une réaction à trois composants entre des dérivés diazo, des alcools et des réactifs vinyl- ou alcynylbenziodoxoles catalysée par du cuivre(I) a pu être développée avec succès. Ainsi, cette transformation permet la synthèse convergente d'éthers allyliques et propargyliques hautement fonctionnalisés. L'étendue de la réaction est large et de nombreuses variations des trois partenaires sont possibles, offrant une grande diversité structurelle. Des premiers résultats pour l'extension de cette réaction à des nucléophiles azotés tel que des anilines ont pu être obtenus.

Les mécanismes réactionnels des différentes réactions de difonctionnalisation des composés diazo avec les réactifs VBX et EBX, catalysées par le cuivre ont suscités de fréquentes questions tout au long de ce travail de recherche. Des résultats préliminaires ont été obtenus grâce à des calculs DFT, des études par spectroscopie RMN et des études cinétiques.

Mots clés: vinylation, alcynylation, composés diazo, réactifs d'iode hypervalent, VBX, EBX, catalyse au cuivre, carbenes, complexité moléculaire, réaction multicomposants, ligands chiraux.

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Abbreviations, Acronyms and Symbols

$[\alpha]_D^{20}$	specific rotation at 25 °C at the sodium D line
Ac	acetyl
aq.	aqueous
Å	Ångström
Ar	aryl
atm	atmosphere
BDA	2,6-di-*tert*-butyl-4-methylphenyl diazoacetate
BHT	butylhydroxytoluene
Bn	benzyl
boc	*tert*-butyloxycarbonyl
BOX	bisoxazoline
br	broad
Bu	butyl
BX	benziodoxol(on)e
°C	degrees centigrade
c	concentration
calcd	calculated
cat.	catalytic
CBX	CyanoBenziodoXolone
Cbz	carboxybenzyl
CPA	chiral phosphoric acid
Cy	cyclohexyl
δ	NMR chemical shift in ppm
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DCE	dichloroethane
DCM	dichloromethane
dec.	decomposed
DFT	density functional theory
DIBALH	di*iso*butylaluminium hydride
DIPEA	di*iso*propylethylamine
DMAP	4-dimethylamino pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
EBX	ethynyl benziodoxolone
EBX'	ethynyl benziodoxole
EDA	ethyl diazoacetate
EDG	electron donating group
ee	enantiomeric excess
e.g.	exempli gratia
El	electrophile
eq.	equation
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate

EWG	electron withdrawing group
g	gram
gem	geminal
h	hour(s)
HFIP	hexafluoro *iso*propanol
HPLC	high pressure liquid chromatography
Hz	hertz
i	iso
int	intermediate
J	coupling constant
kcal	kilocalories
L	liter
LiHMDS	lithium hexamethyldisilazane
LUMO	Lowest Unoccupied Molecular Orbital
m	multiplet
m/z	mass per electronic charge
M	mol/L
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl
mg	milligram
min	minute(s)
mL	milliliter
µL	microliter
mmol	millimol
HOMO	Highest Occupied Molecular Orbital
M.p.	melting point
MS	mass spectrometry
ν	frequency (cm^{-1})
*n*BuLi	*n*-butyllithium
n.d.	not detected
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
n.r.	no reaction
Nu	nucleophile
p	para
PIDA	phenyliodide diacetate
PIFA	phenyliodide ditrifluoroacetate
Ph	phenyl
PMP	paramethoxyphenyl
ppm	parts per million
Pr	propyl
Py	pyridine
q	quartet
quint.	quintet
quant.	quantitative
RCY	radiochemical yield
R_f	retention factor
RT	room temperature
s	singlet
sat.	saturated
S_N	nucleophilic substitution

sol.	solution
t	triplet
T	temperature
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
*t*Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tos	tosyl
TS	transition state
VBX	vinyl benziodoxolone
VBX'	vinyl benziodoxole

1

Introduction

1. Introduction

Organic chemistry occupies an important place in our lives. The study of organic molecules and interactions between them has offer to humanity a better understanding of the nature and the underlying mechanisms of life. But organic chemistry is something more than observation. The creation of new organic molecules has given us durable materials, perfumes to wear, or dyes to color our world. Associated to biology, organic chemistry plays a key role for the development of new medicines or agricultural products to sustain our vital needs of health and nutrition. However, environmental concerns and rarefaction of raw materials are crucial challenges that mankind is currently facing and synthetic chemists must rethink their strategies toward the construction of complex organic molecules. Therefore, the development of innovative synthetic methods utilizing readily available feedstocks, environmentally benign reagents and catalysts for the elaboration of high value chemicals are foremost objectives. In addition, the increasing demand for sophisticated molecular architectures needs cost-effective and time-saving solutions. New reactions with simultaneous formation of multiple bonds are especially attractive, providing molecular complexity in a step-economy manner.[1] High atom-economy is another important feature in the quest for synthetic efficiency, with the benefit to decrease emissions of waste.[2]

In a conventional manner, strategic bond disconnections to build molecules led to logical synthons based on the inherent polarity of the neighboring atoms and functional groups.[3] The identified synthons can be then easily traced back to corresponding stable reagents. Non-classical retro-synthetic analysis can be however an interesting approach for the development of new reagents and methodologies, often not considered by organic chemists.[4] These disconnections can provide new ways to access chemical functions or give a straightforward approach to functionality patterns that would require multiple steps with conventional methodologies. Carbon-carbon unsaturated bonds possess exceptional versatility and are present in organic molecules from all areas of chemistry. In this context vinylation and alkynylation are important reactions classically realized through a normal polarity-driven reactivity by taking advantage of nucleophilic synthons. The non-traditional utilization of electrophilic synthons of alkenes and alkynes is underexplored and can lead to the development of transformations allowing the introduction of these privileged functions in convenient ways. Our group has investigated the utilization of environmentally sustainable hypervalent iodine reagents, to help the transfer of various electrophilic functional groups able to accelerate the access to elaborated molecular structures. The use of hypervalent iodine reagents for the development of new vinylation and alkynylation reactions can meet the challenge of alkene and alkyne Umpolung.

In this thesis, our research on new vinylation and alkynylation strategies for the difunctionalization of diazo compounds will be presented. Our goal was to exploit the full potential of diazo compounds by combining the nucleophilic attack of a heteroatom with the simultaneous introduction of an alkenyl or an alkynyl group through the use of hypervalent iodine molecules. Overall, these transformations allow a fast gain in molecular complexity by focusing on the functionalization of a single carbon atom. The importance of unsaturated bonds will be first discussed, with a particular attention on the achievements in the field of electrophilic olefination and alkynylation (Chapter 2.1). Then, the properties and use of hypervalent iodine compounds in organic chemistry with a special focus on alkenyl and alkynyl transfer reagents will be presented (Chapter 2.2). Next, an overview of

[1] P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197.

[2] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695.

[3] a) E. J. Corey, X. M. Cheng, *The Logic of Chemical Synthesis*. New York: Wiley **1995**; b) E.J. Corey, *Angew. Chem. Int. Ed.* **1991**, *30*, 455; c) E. J. Corey, *Chem. Soc. Rev.* **1988**, *17*, 111.

[4] D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.

the transformation of diazo compounds and details about the different existing strategies for the difunctionalization of metal carbenes will be described (Chapter 2.3). In the final part of the introduction, the singular chemistry merging diazo compounds with hypervalent iodine reagents will be reviewed (Chapter 2.4). Then, the objectives of our research work will be described (Chapter 3). The results of the different projects investigated during these four years of PhD will be then detailed. First, the utilization of products from the oxy-alkynylation of diazo compounds in a low-temperature intramolecular [4+2] cycloaddition reaction will be disclosed (Chapter 4). The resulting diene products led to efficient ligands for rhodium-catalysis. Next, our attempts towards the enantioselective oxy-alkynylation of vinyldiazo compounds will be discussed (Chapter 5). In a following section, the difunctionalization of diazo compounds with new vinyl hypervalent iodine reagents to access allylic esters will be described (Chapter 6). In this chapter, the development of the transformation, as well as the preparation of the hypervalent iodine starting materials will be presented. The obtained products were well suited for various post-modifications. An important extension of our previous works allowed us to achieve the vinylation and alkynylation of diazo compounds in association with an additional external nucleophile. These three-component reactions provided a new strategy for the synthesis of highly diversified ether products in a convergent way (Chapter 7). Finally, preliminary studies on the reaction mechanism common to the key transformations presented in the thesis will be exposed (Chapter 8). A general conclusion will summarize the important achievements of this work, and provide an outlook for future research directions (Chapter 9). The last chapter will compile the experimental and characterization data (Chapter 10).

2

Background

2. Background

2.1. Alkenes and Alkynes

Alkenes and alkynes are ubiquitous chemical functions that occupy a central place in organic chemistry. As unsaturated carbon-carbon bonds they are of great utility in applied fields such as materials science and biological chemistry.

2.1.1. Structure, Occurrence and Transformation

Many important synthetic agrochemicals and pharmaceutical drugs possess unsaturated carbon-carbon bonds in their structure (Figure 1). Chemists have used the planar character, high lipophilicity and the relative inertness of the C=C bond to shape molecules. A typical example of such application is found in the nonsteroidal estrogen *trans*-diethylstilbestrol (**2.2**). The molecule mimics the structure of estradiol (**2.1**) by opening of rings A and B. Only the *E*-isomer showed significant estrogen activity.[5] Cyproheptadine (**2.3**) is an antihistamine used to treat allergic reactions.[6] Conformational analyses showed a butterfly-like structure with a bent tricyclic dibenzosuberene moiety and a piperidine separated by a certain distance to be recognized by the targeted receptor.[7] The iron-containing nucleoside **2.4** is a potential organometallic drug.[8] The easy complexation between the diene and the iron metal is a key interaction for the cytostatic effect of the compound.

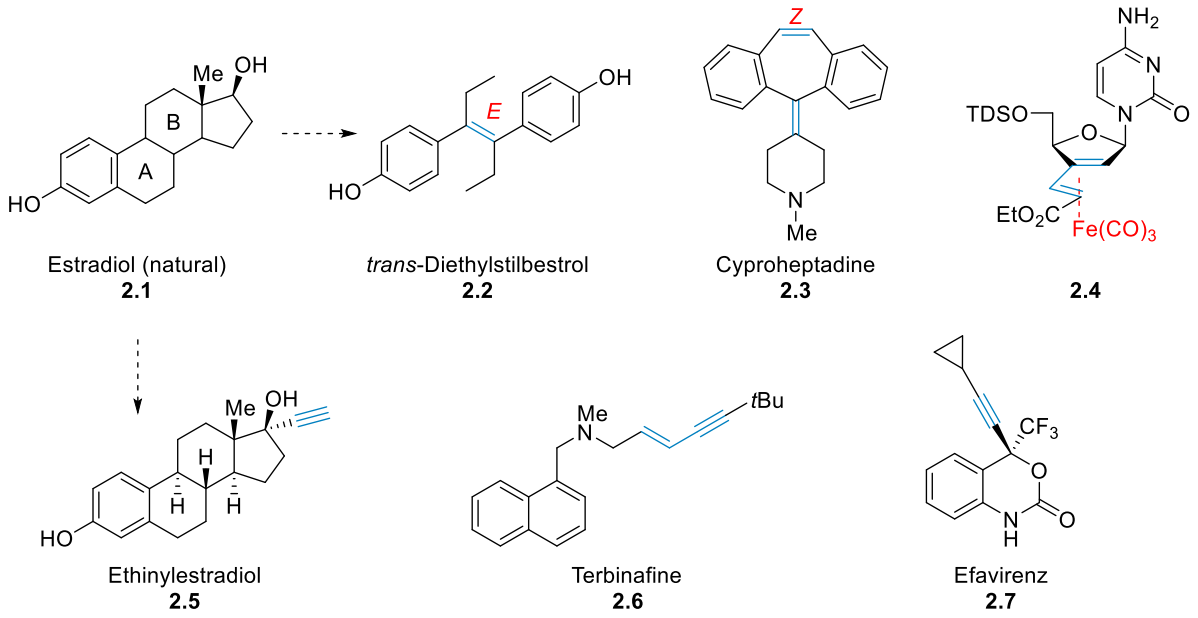


Figure 1. Representative examples of synthetic molecules incorporating alkenes and alkynes.

[5] E. C. Dodds, L. Goldberg, W. Lawson, R. Robinson, *Nature* **1938**, *141*, 247.

[6] M. I. Loza, F. Sanz, M. I. Cadavid, M. Honrubia, F. Orallo, J. A. Fontenla, J. M. Calleja, T. Dot, F. Manaut, M. M. Cid, R. Dominguez, J. A. Seijas, M. C. Villaverde, *J. Pharm. Sci.* **1993**, *82*, 1090.

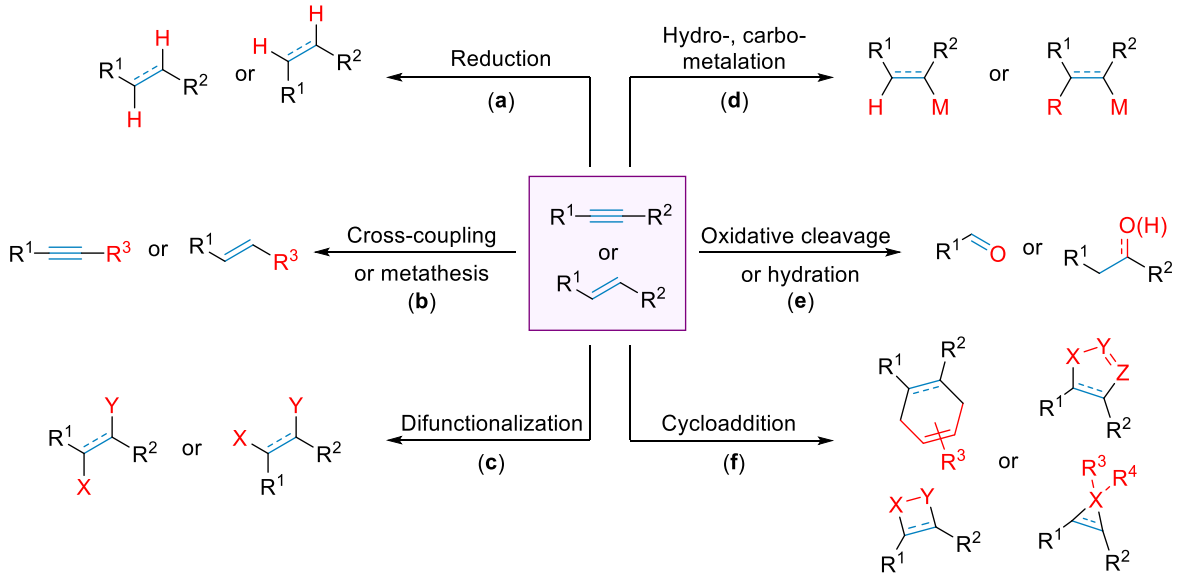
[7] T. Fujiwara, K. Ohira, K. Urushibara, A. Ito, M. Yoshida, M. Kanai, A. Tanatani, H. Kagechika, T. Hirano, *Bioorg. Med. Chem.* **2016**, *24*, 4318.

[8] D. Schlawe, A. Majdalani, J. Velcicky, E. Heßler, T. Wieder, A. Prokop, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **2004**, *43*, 1731.

The acetylene function can be used to tune important biophysical properties such as metabolism or lipophilicity. Ethinylestradiol (**2.5**) is a widely used contraceptive in birth control medication that showed an enhanced metabolic resistance compare to natural Estradiol (**2.1**), lacking the terminal alkyne.[9] The enyne motif present in Terbinafine (**2.6**) accounts for the activity and the high lipophilicity of the molecule that tends to accumulate in skin and nails.[10] Terbinafine is an effective pharmaceutical fungicide used to treat common skin infections. Finally, Efavirenz (**2.7**) is an important antiretroviral medication for the treatment of HIV incorporating a trifluoromethyl propargyl chiral center, essential for its high potency.[11]

The alkene function is of fundamental importance in organic synthesis. Synthetic manipulations taking advantage of the C=C bond have been thoroughly studied since the emergence of the field. With one extra π bond, the C≡C bond exhibits a similar reactivity pattern compared to the alkene. The most important approaches for the derivatization of alkenes and alkynes include (Scheme 1):

- Selective hydrogenation (**a**)
- Cross-coupling reaction (**b**)
- Difunctionalization (**c**)
- Hydro- and carbometalation (**d**)
- Oxidation and hydration (**e**)
- Cycloaddition (**f**)



Scheme 1. Important transformations of unsaturated C-C bonds used in organic chemistry.

The selective hydrogenation of alkene is often realized using molecular hydrogen as the reductant in the presence of a metal catalyst. The process has stimulated the development of well-known catalysts (heterogeneous and homogeneous).[12] The partial reduction of alkynes is an efficient way to access alkenes with controlled geometric purity (*E* or *Z*).[13] Cross-coupling and

[9] Norethynodrel, *IARC Monogr. Eval. Carcinog. Risk Chem. Hum.* **1979**, *21*, 461.
[10] S. Abdel-Rahman, Newland, *Clin. Cosmet. Investig. Dermatol.* **2009**, 49.
[11] S. D. Young, S. F. Britcher, L. O. Tran, L. S. Payne, W. C. Lumma, T. A. Lyle, J. R. Huff, P. S. Anderson, D. B. Olsen, S. S. Carroll, D. J. Pettibone, J. A. O'Brien, R. G. Ball, S. K. Balani, J. H. Lin, I.-W. Chen, W. A. Scheif, V. V. Sardana, W. J. Long, V. W. Byrnes, E. A. Emini, *Antimicrob. Agents Chemother.* **1995**, *39,* 2602.
[12] 2002 Nobel lecture of W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998.
[13] H. Lindlar, R. Dubuis, *Org. Synth.* **1966**, *46*, 89.

metathesis are important strategies to access functionalized olefins and alkynes.[14] The vicinal difunctionalization of alkenes and alkynes is still an intensive topic of research and can involve polar or radical intermediates, frequently associated to metal catalysis for controlled selectivity.[15] In this context, the Sharpless dihydroxylation reaction is a conclusive example.[16] Hydro- and carbometalations are important reactions for accessing organometallic species that are versatile intermediates for further transformations. The hydroboration of alkenes is an important example of this reaction class.[17] Acetylenic compounds easily undergo metalation in a similar fashion as olefins and represent a straightforward method to access versatile vinyl organometallic species.[18] Olefins and alkynes are good precursors of carbonyl compounds. For example, oxidative cleavage of alkenes can lead to aldehydes or carboxylic acids,[19] while the Wacker process is a standard reaction for the preparation of methyl ketones.[20] Hydration of alkynes produces enols that tautomerize into the corresponding ketones.[21] Cycloadditions involving alkenes or alkynes is another reaction category of paramount importance.[22] Cycloadditions allow the simultaneous formation of multiple bonds, often proceeding in a perfect atom economical manner and high selectivity can be achieved using various methods. Therefore, it is a powerful tool for the rapid introduction of chemical complexity into molecules. The Diels-Alder reaction is perhaps the most important cycloaddition reaction and involves a diene and an olefin (dienophile) as partners.[23] The 1,3-dipolar cycloaddition of alkynes with organic azides is an extensively used reaction. Initially discovered by Huisgen, and later revisited by Sharpless with the advent of "Click Chemistry" using copper(I) catalysis, the formation of aromatic 1,2,3-triazoles is fast, selective and compatible with various reaction media.[24] This particular cycloaddition reaction is receiving widespread uses in surface sciences and in bioconjugation strategies and has stimulated the upsurge in interest in alkyne chemistry.[25] Other important reactions, not described here, take advantage of the C=C or C≡C bond properties to functionalize the proximal positions, e.g. allylic and propargylic positions.

The electron-rich nature of unsaturated C-C bonds makes them particularly good ligands for various transition metals. The bonding involves donation of the π electrons to an empty d_σ orbital of the metal, accompanied by back donation from a metal d_π orbital into the π* orbital of the alkene or alkyne (LUMO). This fundamental interaction is involved in most of the metal-catalyzed transformation

[14] For cross-coupling reaction, see: a) A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722; For metathesis of unsaturated bonds, see: b) R. H. Grubbs, *Angew. Chem. Int. Ed.* **2006**, *45*, 3760; c) R. R. Schrock, *Angew. Chem. Int. Ed.* **2006**, *45*, 3748.

[15] Selected recent reviews: a) X.-W. Lan, N.-X. Wang, Y. Xing, *Eur. J. Org. Chem.* **2017**, *2017*, 5821; b) H. Jiang, A. Studer, *Chem. Soc. Rev.* **2020**, *49*, 1790;

[16] H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.

[17] G. Zweifel, H. C. Brown, in *Organic Reactions*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2011**, 1–54.

[18] A. B. Flynn, W. W. Ogilvie, *Chem. Rev.* **2007**, *107*, 4698.

[19] T. J. Fisher, P. H. Dussault, *Tetrahedron* **2017**, *73*, 4233

[20] R. A. Fernandes, A. K. Jha, P. Kumar, *Catal. Sci. Technol.* **2020**, *10*, 7448.

[21] L. Hintermann, A. Labonne, *Synthesis* **2007**, *2007*, 1121.

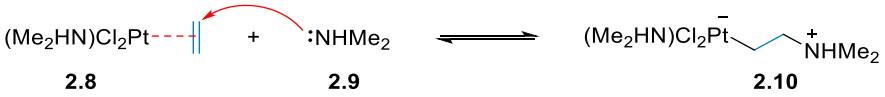
[22] M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49.

[23] K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668 and references therein.

[24] a) R. Huisgen, G. Szeimies, L. Möbius, *Chem. Ber.* **1967**, *100*, 2494, b) V. V. Rostovtsev, L. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596; c) H. Kolb, K. B. Sharpless, *Drug Discov Today.* **2003**, 8, 1128; d) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

[25] M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952.

of olefinic and acetylenic compounds. As illustrated with the Zeise's salt (**2.8**), depletion of the electron density from the π bond of ethylene makes the nucleophilic attack of secondary amine **2.9** possible (Scheme 2). In addition, olefins or dienes can act as spectator ligands and be fine-tuned to improve the electronics, the steric hindrance or the chiral environment around a metal.



2.8 **2.9** **2.10**

Scheme 2. Metal-activation of olefin and nucleophilic attack.

In summary, unsaturated C-C bonds are present in diverse molecules with applications ranging from medicine to material science. Synthetic chemists have exploited the high versatility of such functions to access other functionalities and molecular scaffolds of importance. Alongside their utilization, numerous synthetic routes to access alkenes and alkynes have been developed.

2.1.2. Synthetic Methods to Access Alkenes and Alkynes

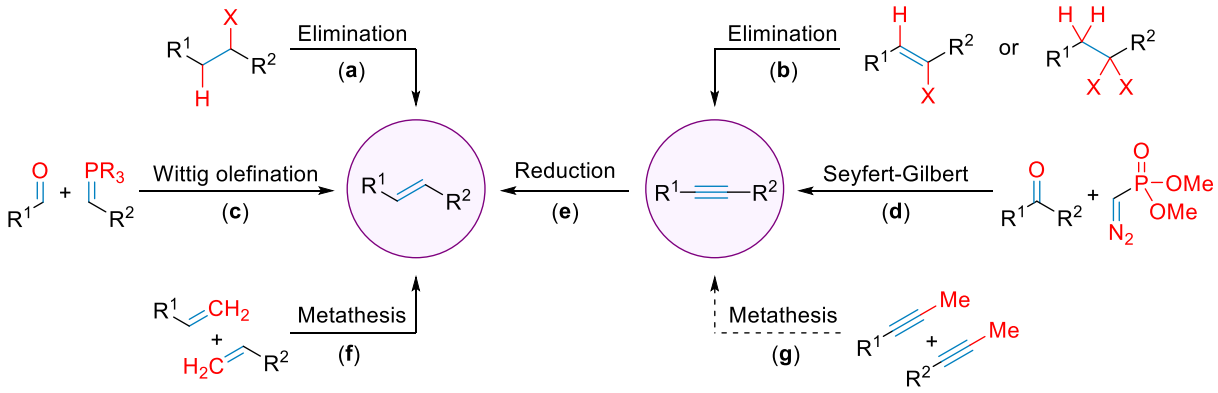
The access to alkenes or alkynes can be classified into two general strategies: *Interconversion of an existing functional group* into an alkene or an alkyne and *direct vinylation and alkynylation* of a substrate. In this section, we will first give an overview of the most frequent synthetic methods used to install new C=C and C≡C bonds and then we will detail the important approaches using electrophilic vinyl and alkynyl synthons.

2.1.2.1. Common Functional Group Interconversions to Alkenes and Alkynes

Regarding functional group interconversions, β-elimination reactions of alcohols, amines, alkyl halides and similar compounds is one of the principal method to generate alkenes (**a**) (Scheme 3).[26] A similar elimination strategy can be applied to vinyl halide or alkyl dihalide precursors to furnish the corresponding alkynes (**b**).[27] An important method to construct a new unsaturated bond consists of coupling abundant carbonyl compounds to a carbanion equivalent, followed by intramolecular elimination. The Wittig olefination is widely used in organic synthesis and involves phosphonium ylides with the generation of phosphine oxide as driving force (**c**).[28] The Seyfert-Gilbert homologation gives a ready access to alkynes using a diazo phosphonate reagent under basic conditions (**d**). A conceptually close strategy, reported by Corey and Fuchs, employs carbon tetrabromide and triphenylphosphine as reactants to access terminal alkynes. As previously mentioned, the reduction of internal alkynes is a useful approach for the stereoselective (*cis* or *trans*) synthesis of disubstituted alkenes (**e**).[29] Finally, olefin metathesis is an appealing strategy that allows the exchange of substituents between different alkenes (**f**).[30] The related alkyne metathesis follows a similar mechanism and has been successfully

[26] P. Hjerrild, T. Tørring, T. B. Poulsen, *Nat. Prod. Rep.* **2020**, *37*, 1043.
[27] R. Shaw, A. Elagamy, I. Althagafi, R. Pratap, *Org. Biomol. Chem.* **2020**, *18*, 3797.
[28] a) D. H. A. Rocha, D. C. G. A. Pinto, A. M. S. Silva, *Eur. J. Org. Chem.* **2018**, *2018*, 2443; b) D. Rocha, D. Pinto, A. Silva, *Synlett* **2013**, *24*, 2683; c) K. Molnár, L. Takács, M. Kádár, F. Faigl, Z. Kardos, *Synth. Commun.* **2017**, *47*, 1214.
[29] a) S. Fu, N.-Y. Chen, X. Liu, Z. Shao, S.-P. Luo, Q. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 8588; b) A. Fürstner, *J. Am. Chem. Soc.* **2019**, *141*, 11.
[30] O. M. Ogba, N. C. Warner, D. J. O'Leary, R. H. Grubbs, *Chem. Soc. Rev.* **2018**, *47*, 4510.

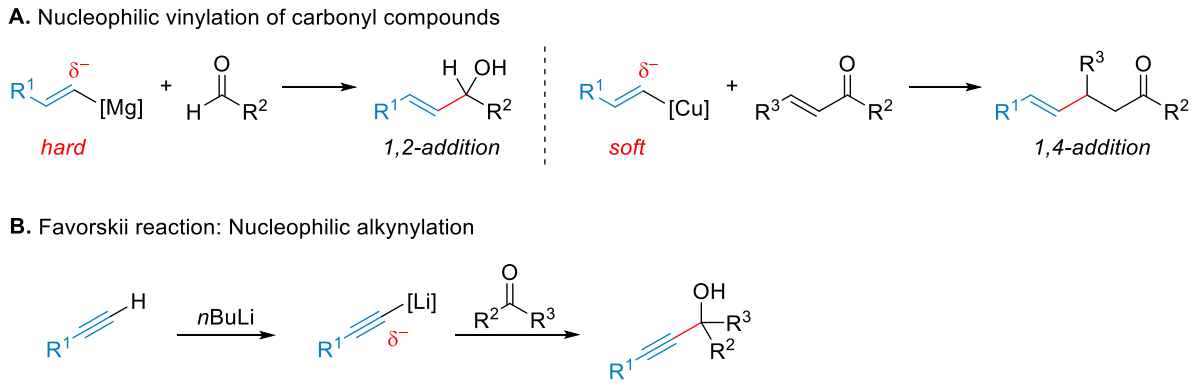
applied for the redistribution of alkyne bonds, albeit to a lesser extent for intermolecular reactions (**g**).[31]



Scheme 3. Overview of the principal synthetic methods to acess alkenes and alkynes

2.1.2.2. Classical Vinylation and Alkynylation Reactions

The second strategy to install unsaturated hydrocarbons consists of transferring an already-existing C=C or C≡C bond into a substrate molecule. In this case, the polarity of the transfer reagent needs to be taken into account. Olefins are not easily deprotonated (pKa = 40 to 50) but several vinylmetallic reagents are accessible and can be added to various electrophilic functions. For example, vinyl Grignard reagents readily add to aldehydes to form allyl alcohol derivatives while the softer vinylcuprate undergoes 1,4-addition with α,β-unsaturated carbonyl compounds (Scheme 4. A).[32] In contrast to nucleophilic vinyl synthons, metal acetylides are generated by mild deprotonation of terminal alkynes (pKa ≈ 25). Alkynyl anions efficiently add to various electrophiles such as alkyl halides, carbonyls or imines. For example, the so-called Favorskii reaction has been the subject of vigorous research and is nowadays a powerful methodology to access enantioenriched propargylic alcohols (Scheme 4. B).[33]



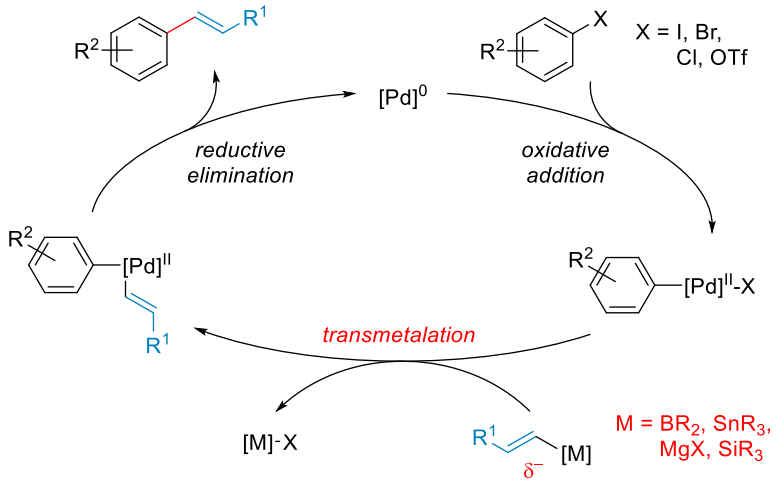
Scheme 4. Nucleophilic vinylation and alkynylation of carbonyl compounds.

[31] A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 2794.

[32] a) R. M. Peltzer, J. Gauss, O. Eisenstein, M. Cascella, *J. Am. Chem. Soc.* **2020**, *142*, 2984; For a review on conjugate addition, see: b) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824.

[33] Y. Sempere, E. M. Carreira in *The Catalytic, Enantioselective Favorskii Reaction: In Situ Formation of Metal Alkynylides and Their Additions to Aldehydes* **2020**, *100*, 207–254.

The formation of Csp^2-Csp^2 and Csp-Csp^2 bonds is dominated by cross-coupling reactions. Vinylmetallic species are particularly interesting in organometallic chemistry due to their ability to transmetalate. It is not surprising that a range of nucleophilic vinyl reagents have been used in classical cross-coupling reactions with transition metal catalysts like palladium (Scheme 5).[34]



Scheme 5. Simplified mechanism for the Pd-catalyzed vinylation of aromatic halides.

The Sonogashira cross-coupling reaction is a useful method for the synthesis of aryl alkynes.[35] This reaction between terminal alkynes and aryl halides is performed under palladium catalysis, and a copper co-catalyst in association with a base is often used to generate *in situ* the active Cu-acetylide species.

2.1.2.3. Electrophilic Transfer Reagents

Through a logical retrosynthetic analysis, breaking the covalent linkage between an unsaturated carbon-carbon bond to any molecular residue often leads to a nucleophilic alkene or alkyne synthon. These rational disconnections are based on the ready access to the corresponding nucleophilic reagents. The manipulation of electrophilic olefin or acetylene synthons is often less considered by synthetic chemists due to the lack of the adequate corresponding reagents. Nevertheless, this reverse approach holds potential to ease the installation of C-C unsaturated bonds into substrates and offers a way to directly functionalize standard nucleophiles with an alkene or an alkyne.

A C=C or a C≡C bond bearing a common leaving group (X) such as a halide (or a pseudohalide) would be a logical hypothesis for electrophilic olefins and alkynes. Nevertheless, nucleophiles never substitute directly the leaving group since the LUMO is the C-C π* and not the required C-X σ*.[36] As a consequence, very few reports for the regio- and stereoselective vinylation or alkynylation of nucleophiles without the help of transition metals have been reported. For example, the functionalization of enolate nucleophiles seems trivial but is often plagued by low selectivity

[34] S. E. Denmark, C. R. Butler, *Chem. Commun.* **2009**, 20.
[35] R. Chinchilla, C. Nájera, *Chem. Soc. Rev.* **2011**, *40*, 5084.
[36] C. F. Bernasconi, Z. Rappoport, *Acc. Chem. Res.* **2009**, *42*, 993.

(isomerization and poly-substitutions) and is limited to highly reactive alkenyl and alkynyl halides.[37] It is only very recently that more practical and general methods have appeared, still with important limitations.[38] Similarly, the direct functionalization of heteroatoms by vinyl or alkynyl halides is not well-developed, with very few methods described.[39] Overall, the utilization of vinyl and alkynyl halides for the functionalization of classical nucleophiles has been hampered by the low reactivity of these reagents. However, in association with transition metal catalysts, the full potential of vinyl and alkynyl halides is uncovered. Thanks to their easy oxidative addition, vinyl and alkynyl halides have been extensively involved in metal-catalyzed cross-coupling or C-H activation reactions for the creation of new C-C and heteroatom-C bonds (Scheme 6). Functionalization of nucleophilic (hetero)aryl derivatives is accessible through cross-coupling or directed C-H functionalization, typically using palladium catalysts (**a**).[40] Csp^2-Csp and Csp-Csp bond formation is realized by Sonogashira-type reactions (Cu, Pd or Fe cat.)[41] and via the Cadiot-Chodkiewicz reaction (Cu cat.),[42] respectively (**b**). The alkenylation and alkynylation of unactivated aliphatic C-H bonds can be accomplished using palladium or nickel catalysis by directing group strategy (**c**).[43] Cross-electrophile coupling of vinyl halides with alkyl halides has recently emerged has a powerful complementary tool for the creation of Csp^2-Csp^3 bond, with the recent renewal of interest in nickel catalysis.[44] Heteroatoms are also potential nucleophilic partners in cross-coupling reactions (**d**).[45] For instance, amination of vinylhalides and alkynyl halides has been reported with several catalyst systems, giving access to valuable enamine, emamide or ynamide products.[46] The formation of vinyl ethers from alcohols and (*E*)-vinyl iodides was

[37] a) A. S. Kende, P. Fludzinski, *Tetrahedron Lett.* **1982**, *23*, 2369; b) A. S. Kende, P. Fludzinski, *Tetrahedron Lett.* **1982**, *23*, 2373.

[38] For more recent and improved procedures, see: a) Y. Zaid, C. D. Mboyi, M. P. Drapeau, L. Radal, F. O. Chahdi, Y. K. Rodi, T. Ollevier, M. Taillefer, *Org. Lett.* **2019**, *21*, 1564; b) T. B. Poulsen, L. Bernardi, J. Alemán, J. Overgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 441.

[39] For vinylation, see: a) D. E. Jones, R. O. Morris, C. A. Vernon, R. F. M. White, *J. Chem. Soc.* **1960**, 2349; b) M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli, M. Montanucci, *J. Org. Chem.* **1983**, *48*, 4795; For alkynylation, see: c) S. I. Miller, C. E. Orzech, C. A. Welch, G. R. Ziegler, J. I. Dickstein, *J. Am. Chem. Soc.* **1962**, *84*, 2020; d) G. R. Ziegler, C. A. Welch, C. E. Orzech, S. Kikkawa, S. I. Miller, *J. Am. Chem. Soc.* **1963**, *85*, 1648; For mechanistic considerations, see: e) G. Modena, *Acc. Chem. Res.* **1971**, *4*, 73.

[40] For cross-coupling examples, see: a) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020; b) C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719; c) C. Vila, V. Hornillos, M. Giannerini, M. Fañanás-Mastral, B. L. Feringa, *Chem. Eur. J.* **2014**, *20*, 13078; d) N. Liu, Z.-X. Wang, *J. Org. Chem.* **2011**, *76*, 10031; e) A. S. Dudnik, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2010**, *49*, 2096; For C-H functionalization, see: f) Z. Ruan, S. Lackner, L. Ackermann, *ACS Catal.* **2016**, *6*, 4690; g) N. Sauermann, M. J. González, L. Ackermann, *Org. Lett.* **2015**, *17*, 5316.

[41] a) Y. Zhou, Y. Zhang, J. Wang, *Org. Biomol. Chem.* **2016**, *14*, 6638; b) X. Fu, S. Zhang, J. Yin, D. P. Schumacher, *Tetrahedron Lett.* **2002**, *43*, 6673.

[42] K.S. Sindhu, A.P. Thankachan, P.S. Sajitha, G. Anilkumar, *Org. Biomol. Chem.* **2015**, *13*, 6891.

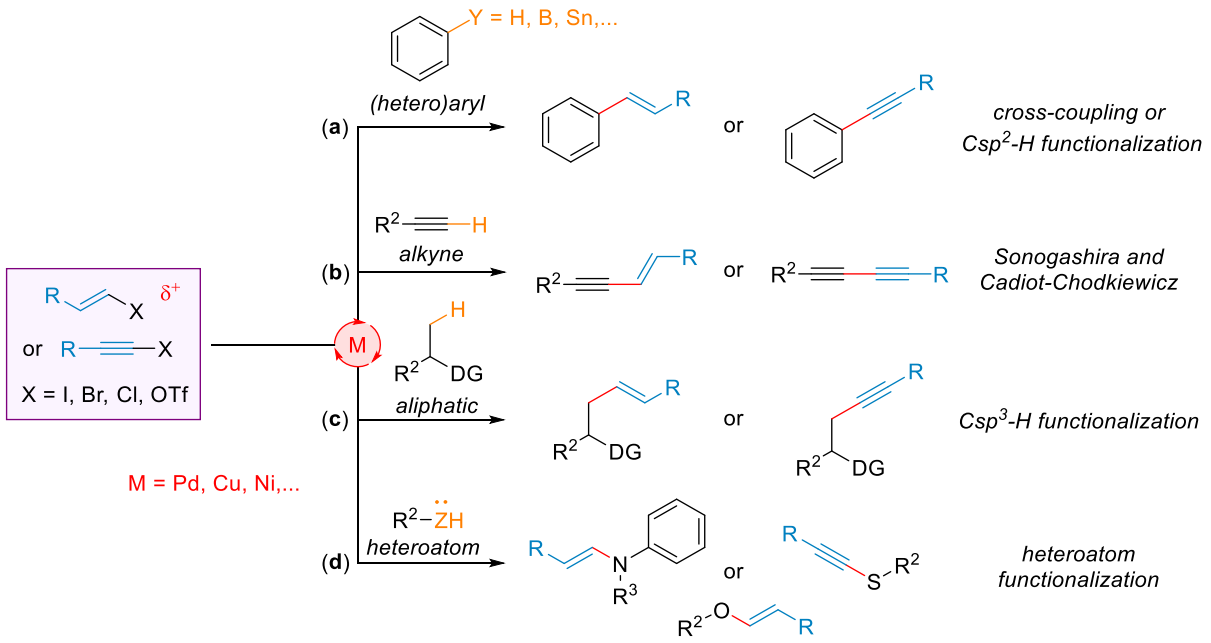
[43] For vinylation, see: a) Q.-F. Wu, P.-X. Shen, J. He, X.-B. Wang, F. Zhang, Q. Shao, R.-Y. Zhu, C. Mapelli, J. X. Qiao, M. A. Poss, J.-Q. Yu, *Science* **2017**, *355*, 499; b) Y.-J. Liu, Z.-Z. Zhang, S.-Y. Yan, Y.-H. Liu, B.-F. Shi, *Chem. Commun.* **2015**, *51*, 7899; c) N. Thrimurtulu, S. Khan, S. Maity, C. M. R. Volla, D. Maiti, *Chem. Commun.* **2017**, *53*, 12457; For alkynylation, see: d) J. He, M. Wasa, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 3387; e) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984.

[44] a) A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2014**, *136*, 14365; b) K. A. Johnson, S. Biswas, D. J. Weix, *Chem. Eur. J.* **2016**, *22*, 7399.

[45] For an overview of Cu-catalyzed vinylation and alkynylation of heteroatom nucleophiles, see: K. Jouvin, G. Evano, in *Copper-Mediated Cross-Coupling Reactions*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2013**, 187–238.

[46] For the synthesis of enamines, see: a) V. G. Landge, J. Rana, M. Subaramanian, E. Balaraman, *Org. Biomol. Chem.* **2017**, *15*, 6896; b) J. Barluenga, C. Valdés, *Chem. Commun.* **2005**, 4891; c) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Commun.* **2004**, 1400; For the synthesis of enamides, see: d) J. R. Dehli, J. Legros, C.

reported by Buchwald.[47] A general procedure for the copper-catalyzed Csp-S coupling of thiols and bromoalkynes has been recently proposed.[48]



Scheme 6. Examples of modern metal-catalyzed transformations with vinyl and alkynyl halides.

Palladium and copper have been the most successful metals for such processes, but other transition metals (Ni, Fe, Co, Au, Rh, etc.) have received increasing attention recently.[49] The geometry of the transferred olefin is usually retained during the transformation. Vinyl and alkynyl halides have been also successfully employed in radical chemistry.[50]

Other electrophilic reagents to transfer olefin and acetylene moieties have been investigated, albeit with less interest. The electrophilic vinylation and alkynylation of soft carbon nucleophiles using stoichiometric lead(IV) reagents has been reported.[51] However, the high toxicity of such compounds has led to very few synthetic uses. Vinyl and alkynyl sulfones are important electrophilic transfer reagents, notably used for the functionalization of transient nucleophilic radicals generated *via*

Bolm, *Chem. Commun.* **2005**, 973; For the synthesis of ynamides, see: e) A. Coste, G. Karthikeyan, F. Couty, G. Evano, *Angew Chem. Int. Ed.* **2009**, *48*, 4381; f) J. R. Dunetz, R. L. Danheiser, *Org. Lett.* **2003**, *5*, 4011; g) P.-Y. Yao, Y. Zhang, R. P. Hsung, K. Zhao, *Org. Lett.* **2008**, *10*, 4275.

[47] G. Nordmann, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 4978.

[48] É. Godin, J. Santandrea, A. Caron, S. K. Collins, *Org. Lett.* **2020**, *22*, 5905.

[49] Selected examples, a) Y. Cai, A. D. Benischke, P. Knochel, C. Gosmini, *Chem. Eur. J.* **2017**, *23*, 250; b) Z. Xia, V. Corcé, F. Zhao, C. Przybylski, A. Espagne, L. Jullien, T. Le Saux, Y. Gimbert, H. Dossmann, V. Mouriès-Mansuy, C. Ollivier, L. Fensterbank, *Nat. Chem.* **2019**, *11*, 797; c) J. Mao, G. Xie, J. Zhan, Q. Hua, D. Shi, *Adv. Synth. Catal.* **2009**, *351*, 1268.

[50] Selected examples, a) N. R. Patel, C. B. Kelly, M. Jouffroy, G. A. Molander, *Org. Lett.* **2016**, *18*, 764; b) L. Huang, A. M. Olivares and D. J. Weix, *Angew. Chem. Int. Ed.* **2017**, *56*, 11901; c) J. Xie, S. Shi, T. Zhang, N. Mehrkens, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2015**, *54*, 6046; d) X.-L. Lyu, S.-S. Huang, H.-J. Song, Y.-X. Liu, Q.-M. Wang, *RSC Adv.* **2019**, *9*, 36213.

[51] a) M. G. Moloney, J. T. Pinhey, *J. Chem. Soc., Perkin Trans. I* **1988**, 2847; b) C. J. Parkinson, J. T. Pinhey, M. J. Stoermer, *J. Chem. Soc., Perkin Trans. I* **1992**, 1911; c) M. G. Moloney, J. T. Pinhey, E. G. Roche, *Tetrahedron Lett.* **1986**, *27*, 5025.

photoredox catalysis.[52] Sulfonylacetylenes have also been successfully employed for the functionalization of organolithium compounds and Grignard reagents under transition metal-free conditions.[53]

The alkene and alkyne functionalities play a crucial role in synthetic chemistry and other frontier sciences. Chemists have developed robust tools in order to install the C=C and C≡C bonds into molecular scaffolds. Among them, the direct transfer of pre-functionalized alkenes or alkynes to a substrate is an efficient strategy that exploits the inherent nucleophilicity of the corresponding anions. The complementary electrophilic approach has been mostly developed utilizing alkenyl and alkynyl halides in association with transition metal catalysts. New reagents able to generate cationic equivalents are still highly desirable. The introduction of "super" leaving groups, such as hypervalent iodine moieties, can broaden the scope of substrates susceptible to undergo electrophilic vinylation and alkynylation in convenient manner. This particular class of reagent has been largely used in this thesis work and will be presented in details in the following section.

[52] For selected recent examples, see: a) Schaffner, A.-P.; Darmency, V.; Renaud, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 5847; b) Noble, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 11602; c) Heitz, D. R.; Rizwan, K.; G. A. Molander, *J. Org. Chem.* **2016**, *81*, 7308; d) J. Yang, J. Zhang, L. Qi and Y. Chen, *Chem. Commun.* **2015**, *51*, 5275; e) M. Ociepa, J. Turkowska and D. Gryko, *ACS Catal.* **2018**, *8*, 11362; f) J. Jia, Y. A. Ho, R. F. Bulow, M. Rueping, *Chem. Eur. J.* **2018**, *24*, 14054.

[53] a) L. Marzo, I. Pérez, F. Yuste, J. Alemán, J. L. García Ruano, *Chem. Commun.* **2015**, *51*, 346; b) F. Esteban, L. Boughani, J. L. García Ruano, A. Fraile, J. Alemán, *Org. Biomol. Chem.* **2017**, *15*, 3901.

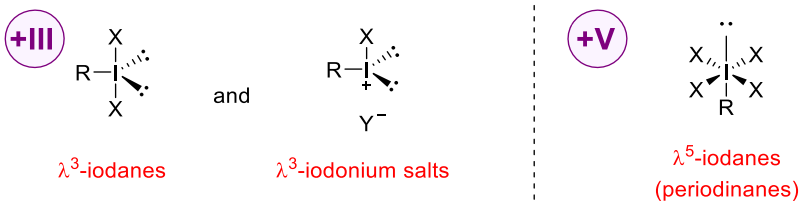
2.2. Hypervalent Iodine Compounds

Like other halogen atoms, iodine normally forms one single σ-bond in organic molecules, fulfilling its valence shell. However, due to the large size and polarizability of the iodine atom, extension of its valence is easily attainable generating a *hypervalent bond*. The presence of this particular bond explains the special structural features and reactivity pattern of hypervalent iodine compounds. Indeed, hypervalent iodine compounds generally possess structures and reactivity similar to that of transition metal derivatives, but have the advantage of environmental sustainability, efficient utilization of natural resources and cost.[54] Hypervalent iodine chemistry has become a useful tool in organic synthesis with the design of numerous shelf-stable reagents for selective oxidations or functional group transfer reactions.

In this chapter, key structural elements of hypervalent iodine compounds will be covered, with a special attention given to benziodoxol(on)es. The applications of these compounds in organic synthesis will be addressed with a focus on hypervalent iodine reagents designed for the transfer of vinyl and alkynyl functions.

2.2.1 Structure and Bonding of Organic Hypervalent Iodine Compounds

Organic compounds of polyvalent iodine are classified in two main classes according to the resulting oxidation state of the iodine (Figure 2):



R = carbon ligand (Ar); X = halogen, C-, N- or O-ligand; Y = counterion

Figure 2. Structural features of λ^3-iodanes and λ^5-iodanes.

- *λ^3-Iodanes*: λ^3-Iodanes are trivalent iodine derivatives, with 10 electrons and a +3 oxidation state at the iodine center. The compounds adopt a trigonal bipyramidal geometry. The two most electronegative ligands (X) are weakly bonded and occupy the *trans* apical positions approaching an ideal angle X-I-X of 180°. The equatorial positions are occupied by a third, least electronegative ligand and the two remaining electron pairs. The X-I-R angle is approximately 90°. The three groups attached to the iodine are forming a characteristic T-shape structure, nicely observable by X-ray crystallography with elongated distances between I and the X ligands. λ^3-Iodonium salts are structurally comparable to λ^3-iodanes. The main difference resides in the appreciation of the coordination strength of the ligand Y. When the counterion Y is weakly coordinating, a cationic iodine complex is obtained. In this case, a longer I-Y distance is expected and a pseudo-trigonal bipyramidal geometry is often observed.

- *λ^5-Iodanes* also called *periodinanes*: λ^5-Iodanes are pentavalent iodine derivatives, with 12 electrons and a +5 oxidation state at the iodine center. An octahedral geometry is observed in this

[54] A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328.

case. The apical positions are occupied by one carbon ligand (R) and the remaining electron pair, while four orthogonal ligands (X) are in the equatorial plane.

The electrons of a nonhybridized 5p orbital of the iodine atom and one electron of each ligand X are forming a linear 3-center-4-electron (3c-4e) bond. The so-called *hypervalent bond* (Figure 3). The four electrons involved in the bond are distributed in a bonding molecular orbital delocalized over the three centers and in a non-bonding molecular orbital localized on the peripheral centers.

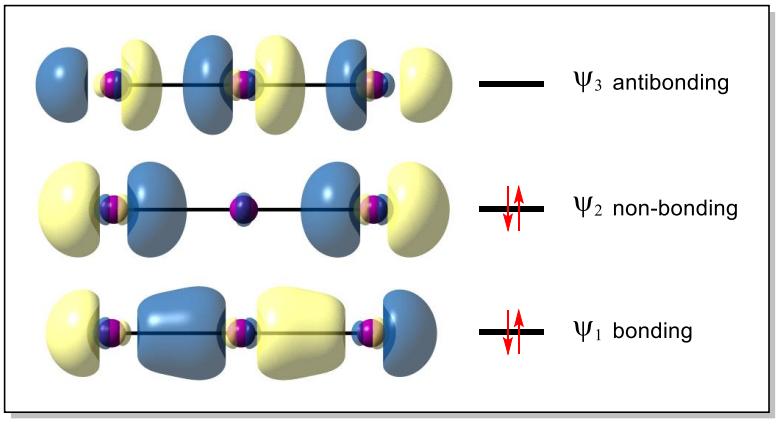


Figure 3. Molecular orbitals of the hypervalent X-I-X bond.

The hypervalent bond is longer, weaker and more polarizable compared to a classical covalent bond and is responsible for the high electrophilic reactivity of λ^3-iodanes. Moreover, the involvement of two 3c-4e bonds in periodinane derivatives results in an important electron deficiency and justify their use as oxidants.

Of particular interest are the hypervalent iodine compounds bearing an aryl ligand at the equatorial position (R = Ar). Conjugation between the lone pairs of the iodine and the π-orbitals of the aromatic ring tends to stabilize the overall structure.[55] In fact, only aryl hypervalent iodines are stable enough to be practically isolated. Further stabilization can be obtained when the iodine atom is locked in a heterocycle, resulting in a rigid bicyclic structure (Figure 4). In general, a tethered carboxylic acid is utilized to stabilize the hypervalent iodine center by an oxygen-iodine bond. In this case, a very good overlapping between the iodide lone pairs and the π-system of the phenyl ring is present. Such enhanced effect does not exist in acyclic iodanes resulting in a lower stability. In addition, the five-membered ring confines the orientation of the lone pairs on oxygen and increases the energy barrier for reductive elimination between the *trans* axial ligands.[56] The so-called benziodoxolones **2.11** are well-known hypervalent iodine reagents originating from cheap 2-iodobenzoic acid. They are exceptionally stable to air and moisture and are very convenient to handle. Importantly, the properties of the reagents can be easily modulated by introduction of substituents (R^1) in α position of the oxygen atom (benziodoxole, **2.12**). The inductive effect of the oxygen ligand will influence the length, and therefore the reactivity of the *trans* I-X bond.[57] Methyl (R^1 = CH_3) and trifluoromethyl (R^1 = CF_3) substituents are the most encountered and the presence of further substituents (R^2) on the aryl core is also known to influence the reactivity of cyclic hypervalent iodine reagents.[58] Other ligands different

[55] V. V. Zhdankin, *Rev. Heteroat. Chem.* **1997**, *17*, 133.
[56] T.-Y. Sun, X. Wang, H. Geng, Y. Xie, Y.-D. Wu, X. Zhang, H. F. Schaefer III, *Chem. Commun.* **2016**, *52*, 5371.
[57] M. Ochiai, T. Sueda, K. Miyamoto, P. Kiprof, V. V. Zhdankin, *Angew. Chem. Int. Ed.* **2006**, *45*, 8203.
[58] P. K. Sajith, C. H. Suresh, *Inorg. Chem.* **2013**, *52*, 6046.

from carboxylate or alkoxide have been investigated, notably, the replacement of oxygen by nitrogen (benziodazolone, **2.13**) enables the presence of an additional substituent (R^3) and opens access to other properties.[59]

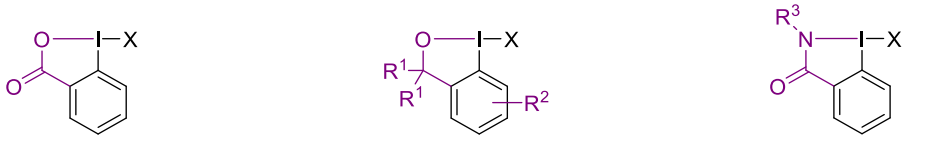


Figure 4. Commonly used benziodoxol(on)e scaffolds.

2.2.2. Atom and Functional Group Transfer Reagents

The inherent reactivity of iodane and periodinane reagents resides in the high-energy hypervalent bond. λ^5-Iodanes have been mostly used as selective oxidants and rarely as functional group transfer reagents, and no further attention will be drawn on these popular oxidants, which are not relevant to the topic of this thesis.

The enhanced reactivity of iodine(III) compounds, compared to classical organohalides, have been exploited by synthetic chemists to facilitate the transfer of various atoms or functional groups. In this context, benziodoxol(on)es are frequently encountered (Figure 5). While the cyclic ligand is often used to stabilize the electrophilic hypervalent iodine atom or influence its reactivity (*vide supra*), the other ligand is meant to be transferred onto a nucleophilic substrate. Benziodoxol(on)es represent one of the most important classes of iodine(III) reagents and are widely used as electrophilic or radical reagents for halogenation (**2.14**),[60] acetoxylation (**2.15**),[61] azidation (Zhdankin reagent, **2.17**),[62] amination (**2.18**),[63] cyanation (**2.19**),[64] or, trifluoromethylation with the famous Togni's reagents (**2.20**).[65] It is important to notify that all the ligands transferred are ordinarily nucleophilic in nature.[66] Ethynylbenziodoxolones (EBX, **2.21**) are recognized for direct, mild, and efficient electrophilic alkynylation. EBX reagents have been of prime importance and remain a cornerstone for the research in our group. Their synthesis and applications will be presented in the next section.

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[59] a) W. Wolf, L. Steinberg, *Chem. Commun*. **1965**, 449; b) D. G. Naae, J. Z. Gougoutas, *J. Org. Chem*. **1975**, *40*, 2129; c) T. M. Balthazor, D. E. Godar, B. R Stults, *J. Org. Chem*. **1979**, *44*, 1447; d) V. V. Zhdankin, R. M. Arbit, M. McSherry, B. Mismash, V. G. Young, *J. Am. Chem. Soc.* **1997**, *119*, 7408; e) V. V. Zhdankin, A. Y. Koposov, L. Su, V. V. Boyarskikh, B. C. Netzel, V. G. Young, *Org. Lett.* **2003**, *5*, 1583; f) S. Alazet, J. Preindl, R. Simonet-Davin, S. Nicolai, A. Nanchen, T. Meyer, J. Waser, *J. Org. Chem.* **2018**, *83*, 12334.

[60] a) M. Wang, Y. Zhang, T. Wang, C. Wang, D. Xue, J. Xiao, *Org. Lett.* **2016**, *18*, 1976; b) H. Egami, T. Yoneda, M. Uku, T. Ide, Y. Kawato, Y. Hamashima, *J. Org. Chem.* **2016**, *81*, 4020.

[61] G. Shan, X. Yang, Y. Zong, Y. Rao, *Angew. Chem. Int. Ed.* **2013**, *52*, 13606.

[62] a) A. Sharma, J. F. Hartwig, *Nature* **2015**, *517*, 600; b) S. Alazet, F. Le Vaillant, S. Nicolai, T. Courant, J. Waser, *Chem. Eur. J.* **2017**, *23*, 9501.

[63] X.-H. Hu, X.-F. Yang, T.-P. Loh, *ACS Catal.* **2016**, *6*, 5930.

[64] a) F. Le Vaillant, M. D. Wodrich, J. Waser, *Chem. Sci.* **2017**, *8*, 1790; b) R. Frei, T. Courant, M. D. Wodrich, J. Waser, *Chem. Eur. J.* **2015**, *21*, 2662.

[65] For a review, see: J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650.

[66] a) For a recent review, see: D. P. Hari, P. Caramenti, J. Waser, *Acc. Chem. Res.* **2018**, *51*, 3212; b) Y. Li, D. P. Hari, M. V. Vita, J. Waser, *Angew. Chem. Int. Ed.* **2016**, *55*, 4436.

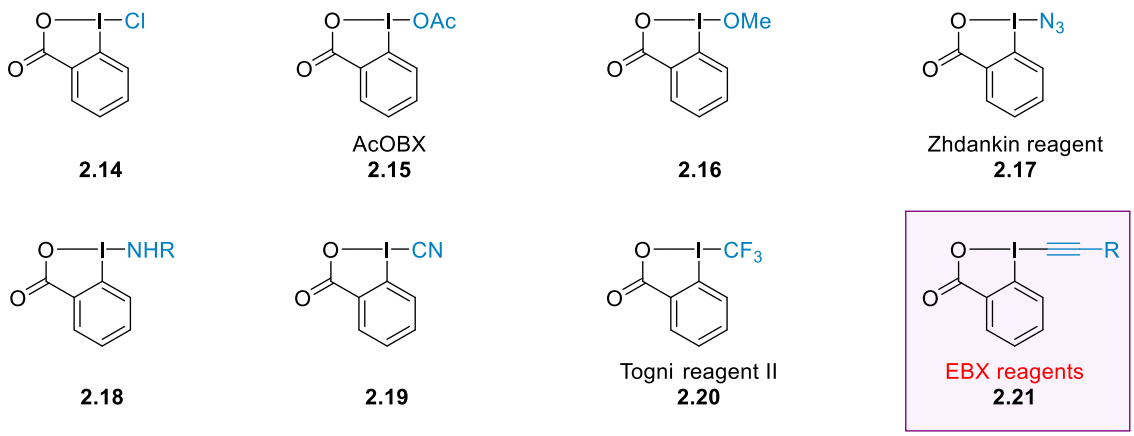

Figure 5. Commonly encountered benziodoxolone-based transfer reagents.

The user-friendly handling and exceptional reactivity of benziodoxolones are convincing advantages that encourage chemists to develop and apply new reagents of this type (Figure 6). In 2016, the group of Olofsson disclosed a straightforward synthesis of Vinylbenziodoxolones reagents (VBX, **2.22**).[67] In theory, this new class of reagent would allow a facile transfer of pre-functionalized olefins. VBX reagents were of major importance in our work and a complete review about these particular hypervalent iodine compounds will be addressed in the next chapter. Recently, a serie of new fluorinating reagents based on the widely used Togni's reagents has been reported (**2.23**).[68] Our group reported the synthesis and use of electrophilic indole and pyrrole benziodoxolone reagents (**2.24** and **2.25**).[69] The Yoshikai research group reported the access to other heteroaryl iodine(III) through the cyclization of alkynes tethered to a variety of nucleophilic moieties (**2.26**).[70] The interrupted addition of *N*-, *O*- or *S*-nucleophiles into readily available EBX reagents led to the formation of new (hetero)vinylbenziodoxolone reagents (*X*-VBX, **2.27**). Our group and others have recently exploited these enamide, enol and thioenol hypervalent iodine reagents.[71] Suero and co-workers developed a new class of diazo linked benziodoxolone reagents (**2.28**), for the selective transfer of diazo compounds and used them as hidden carbyne synthetic equivalents.[72] Recently, the Katayev group described the synthesis and reactivity of a hypervalent iodine-based nitrooxylating reagent (**2.29**).[73]

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[67] E. Stridfeldt, A. Seemann, M. J. Bouma, C. Dey, A. Ertan, B. Olofsson, *Chem. Eur. J.* **2016**, *22*, 16066.

[68] V. Matoušek, J. Václavík, P. Hájek, J. Charpentier, Z. E. Blastik, E. Pietrasiak, A. Budinská, A. Togni, P. Beier, *Chem. Eur. J.* **2016**, *22*, 417.

[69] a) P. Caramenti, S. Nicolai, J. Waser, *Chem. Eur. J.* **2017**, *23*, 14702; b) P. Caramenti, J. Waser, *Helv. Chim. Acta* **2017**, *100*, e1700221; c) P. Caramenti, R. K. Nandi, J. Waser, *Chem. Eur. J.* **2018**, *24*, 10049; d) E. Grenet, J. Waser, *Org. Lett.* **2018**, *20*, 1473; e) E. Grenet, A. Das, P. Caramenti, J. Waser, *Beilstein J. Org. Chem.* **2018**, *14*, 1208.

[70] B. Wu, J. Wu, N. Yoshikai, *Chem. Asian J.* **2017**, *12*, 3123.

[71] a) J. Wu, X. Deng, H. Hirao, N. Yoshikai, *J. Am. Chem. Soc.* **2016**, *138*, 9105; b) J. Wu, K. Xu, H. Hirao, N. Yoshikai, *Chem. Eur. J.* **2017**, *23*, 1521; c) B. Liu, C.-H. Lim, G. M. Miyake, *J. Am. Chem. Soc.* **2018**, *140*, 12829; d) P. Caramenti, N. Declas, R. Tessier, M. D. Wodrich, J. Waser, *Chem. Sci.* **2019**, *10*, 3223; e) J. Wu, X. Deng, N. Yoshikai, *Chem. Eur. J.* **2019**, *25*, 7839.

[72] a) Z. Wang, A. G. Herraiz, A. M. del Hoyo, M. G. Suero, *Nature* **2018**, *554*, 86; b) Z. Wang, L. Jiang, P. Sarró, M. G. Suero, *J. Am. Chem. Soc.* **2019**, *141*, 15509.

[73] R. Calvo, A. Le Tellier, T. Nauser, D. Rombach, D. Nater, D. Katayev, *Angew. Chem. Int. Ed.* **2020**, 59, 17162.

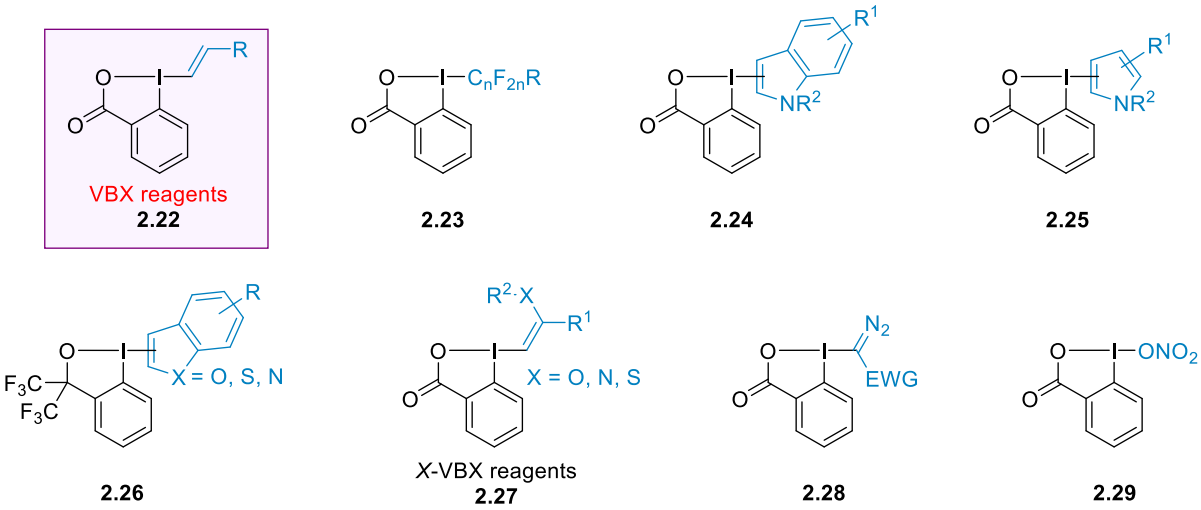


Figure 6. Recently developed cyclic hypervalent iodine reagents.

It is important to mention that the majority of the cyclic reagents presented here, have also their corresponding acyclic iodonium salts known and applied in various transformations. Thanks to the presence of the internal carboxylate ligand, the benziodoxolone reagents have the advantage to be more stable, and therefore isolable. The reactivity/stability window often dictates the use of hypervalent iodonium salts or benziodoxol(on)e reagents.

2.2.3. Hypervalent Iodine Alkene and Alkyne Transfer Reagents

We have emphasized in section 2.1.2., that the electrophilic transfer of alkenes and alkynes is not conventional but can be a complementary approach to introduce these valuable functionalities. Despite the remarkable applications of vinyl and alkynyl halides in transition metal catalyzed transformations, their limited reactivity have encouraged chemists to investigate the more reactive trivalent iodine analogues.

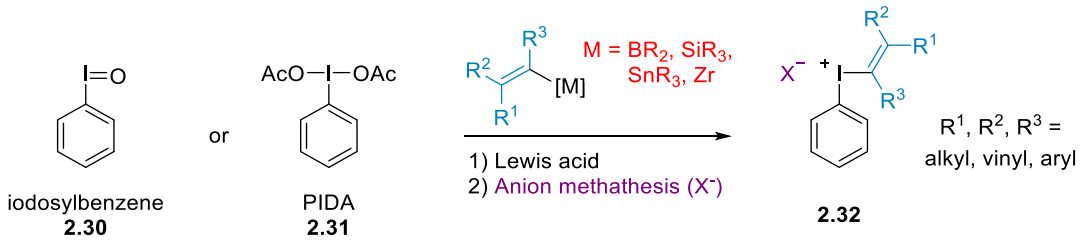
2.2.3.1. Vinylation

The preparation of hypervalent iodine compounds incorporating an alkene ligand has been first achieved as early as 1914 and several other methods have been described in the following years.[74] However, these approaches were rather ineffective and it is more recently that convenient syntheses for alkenyl-(aryl)iodonium salts **2.32** have emerged (Scheme 7).[75] Readily available and stable λ^3-iodanes precursors, such as iodosylbenzene (**2.30**) or PIDA (**2.31**), are reacted with silyl- or boron-alkenes in presence of Lewis acids. These reactions generally proceed well through metal exchange with the iodane. Retention of the olefin geometry is usually observed. However, the fast decomposition of (*Z*)-vinyliodonium salts at room temperature through reductive *anti* β-elimination

[74] G. F. Koser, in *Halides, Pseudo-Halides and Azides: Part 2,* John Wiley & Sons, Ltd., Chichester, UK, **1983**, 1265–1351.

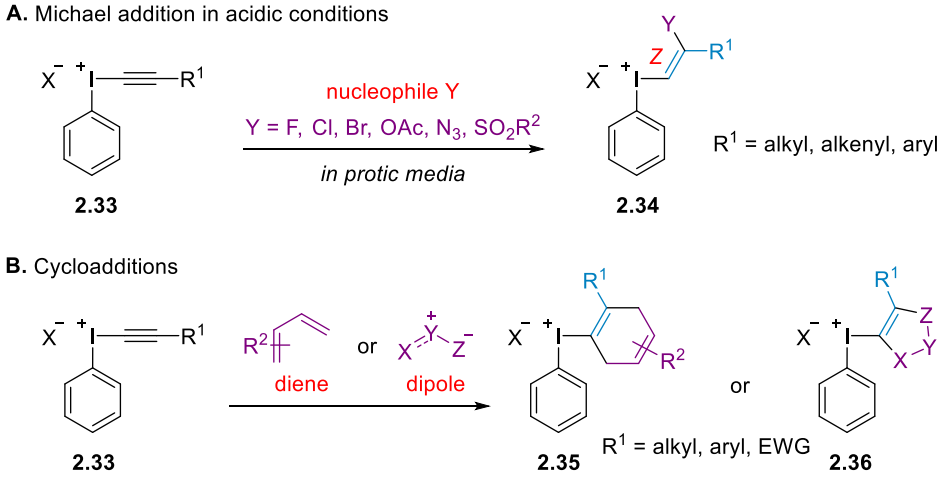
[75] a) M. Ochiai, K. Sumi, Y. Nagao, E. Fujita, *Tetrahedron Lett.* **1985**, *26*, 2351; b) M. Ochiai, K. Sumi, Y. Takaoka, M. Kunishima, Y. Nagao, M. Shiro, E. Fujita, *Tetrahedron* **1988**, *44*, 4095; c) M. Ochiai, M. Toyonari, T. Nagaoka, D.-W. Chen, M. Kida, *Tetrahedron Lett.* **1997**, *38*, 6709.

(R^1 = H) makes their utilization unpractical.[76] Related strategies employing vinylstannanes or vinylzirconium have also been reported to broaden the functional group compatibility.[77]



Scheme 7. Common preparation of vinyliodonium salts from λ³-iodanes precurs.

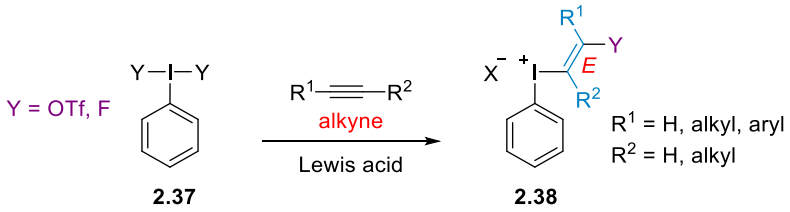
Simple Michael addition on electron-poor alkynyl-(aryl)iodonium salts **2.33** constitutes an alternative method for the synthesis of β-functionalized vinyliodonium salts **2.34** (Scheme 8. A). Such interrupted substitution proceeds in a stereoselective manner in protic solvents to afford *Z*-isomers, and has been reported with various halogens,[78] oxygen,[79] azide[80] and sulfur[81] nucleophiles. The highly polarized triple bond in alkynyliodonium salts **2.33** can also act as good partner in cycloaddition reactions with various dienes and dipoles (Scheme 8. B).[82] The resulting vinyl hypervalent compounds **2.35** or **2.36** can be isolated and submitted to further transformations.



Scheme 8. Alkynyliodonium salts as precursors to functionalized vinyliodonium salts.

[76] M. Ochiai, K. Oshima, Y. Masaki, *J. Chem. Soc. Chem. Commun.* **1991**, 869.
[77] a) P. Stang, J. Ullmann, *Angew. Chem. Int. Ed.* **1991**, *30*, 1469; b) X. Huang, X.-H. Xu, *J. Chem. Soc., Perkin Trans. I*, **1998**, 3321.
[78] M. Ochiai, Y. Kitagawa, M. Toyonari, K. Uemura, K. Oshima, M. Shiro *J. Org. Chem.* **1997**, *62*, 8001.
[79] a) M. Ochiai, Y. Kitagawa, S. Yamamoto, *J. Am. Chem. Soc.* **1997**, *119*, 11598; b) M. Ochiai, Y. Nishi, M. Hirobe, *Tetrahedron Lett.* **2005**, *46*, 1863.
[80] T. Kitamura, P. J. Stang, *Tetrahedron Lett.* **1988**, *29*, 1887.
[81] a) M. Ochiai, K. Oshima, Y. Masaki, *Tetrahedron Lett.* **1991**, *32*, 7711; b) E. Zawia, D. J. Hamnett, W. J. Moran, *J. Org. Chem.* **2017**, *82*, 3960; c) E. Zawia, W. J. Moran, *Molecules* **2016**, *21*, 1073.
[82] a) E. Kotali, A. Varvoglis, A. Bozopoulos, *J. Chem. Soc., Perkin Trans. I* **1989**, 827; b) G. Maas, M. Regitz, U. Moll, R. Rahm, F. Krebs, R. Hector, P. J. Stang, C. M. Crittell, B. L. Williamson, *Tetrahedron* **1992**, *48*, 3527; c) B. L. Williamson, P. J. Stang, A. M. Arif, *J. Am. Chem. Soc.* **1993**, *115*, 2590; d) P. Murch, A. M. Arif, P. J. Stang, *J. Org. Chem.* **1997**, *62*, 5959; e) P. J. Stang, V. V. Zhdankin, *J. Am. Chem. Soc.* **1991**, *113*, 4571.

The addition of electron-poor λ^3-iodane precursors across unactivated C≡C bonds is one last strategy to access alkenyliodonium salts (Scheme 9).[83] This method is highly stereoselective and gives access to the thermodynamically favored (*E*)-vinyliodonium salts **2.38**, through vinyl cation intermediates.[84] The initial scope of compatible substrates was limited to terminal alkynes (R^2 = H), until a recent procedure developed by the Novák group, allowing the extension of the methodology to alkynes having various functionalities and structural motifs.[85]



Scheme 9. Access to alkenyliodonium salts from unactivated alkynes.

Recently, new synthetic routes based on the oxidation of vinyl iodide precursors were exploited but remain restricted to very few specific compounds having functional groups compatible with such oxidative conditions.[86]

Simultaneously to their development, alkenyl-(aryl)iodonium salts have been applied as electrophilic vinyl reagents. The exceptional lability of the phenyliodonium group (ca. 10^{12} times greater than the iodine itself)[87] enabled the smooth functionalization of many heteroatom nucleophiles such as boron (**a**),[88] nitrogen (**b** and **c**),[75b,89] oxygen (**d**),[80,89a-b,] halides (**e**),[81a,88a,89a-b,90] sulfur (**f**),[75b,89a,91] silicon (**g**),[80] and phosphorus (**h**)[89b,92] (Scheme 10). Different mechanistic pathways for the alkenylation of heteroatoms have been proposed according to the nucleophile, the nature of the substituents on the vinyliodonium reagent and the reaction conditions employed.

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[83] a) T. Kitamura, R. Furuki, H. Taniguchi, P. J. Stang, *Tetrahedron Lett.* **1990**, *31*, 703; b) T. Kitamura, R. Furuki, H. Taniguchi, P. J. Stang, *Tetrahedron* **1992**, *48*, 7149; c) T. M. Kasumov, N. Sh. Pirguliyev, V. K. Brel, Y. K. Grishin, N. S. Zefirov, P. J. Stang, *Tetrahedron* **1997**, *53*, 13139; d) S. Hara, M. Yoshida, T. Fukuhara, N. Yoneda, *Chem. Commun.* **1998**, 965; e) S. Hara, K. Yamamoto, M. Yoshida, T. Fukuhara, N. Yoneda, *Tetrahedron Lett.* **1999**, *40*, 7815.

[84] M. Ochiai, M. Hirobe, A. Yoshimura, Y. Nishi, K. Miyamoto, M. Shiro, *Org. Lett.* **2007**, *9*, 3335.

[85] B. L. Tóth, F. Béke, O. Egyed, A. Bényei, A. Stirling, Z. Novák, *ACS Omega* **2019**, *4*, 9188.

[86] a) Á. Mészáros, A. Székely, A. Stirling, Z. Novák, *Angew. Chem. Int. Ed.* **2018**, *57*, 6643; b) K. Kepski, C. R. Rice, W. J. Moran, *Org. Lett.* **2019**, *21*, 6936.

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[88] a) T. Guan, M. Yoshida, S. Hara, *J. Org. Chem.* **2007**, *72*, 9617; b) S. Hara, T. Guan, M. Yoshida, *Org. Lett.* **2006**, *8*, 2639.

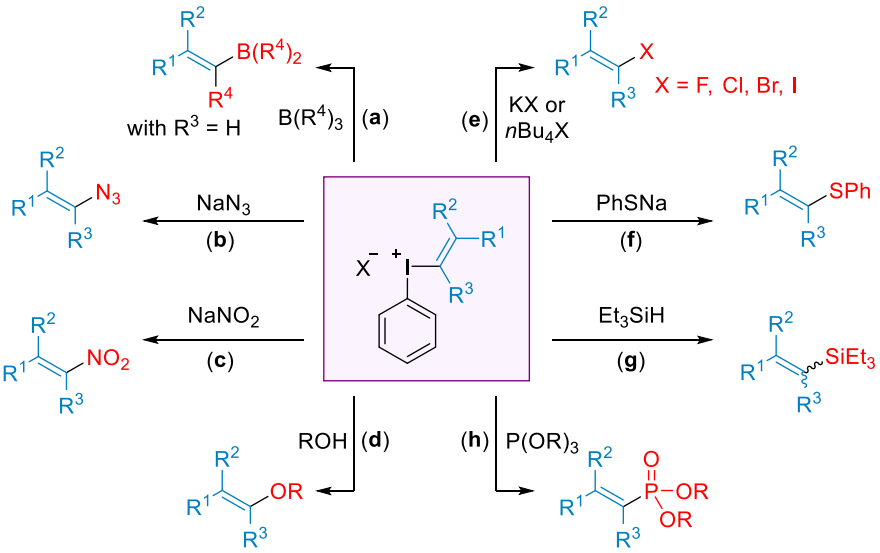
[89] a) I. Papoutsis, S. Spyroudis, A. Varvoglis, *Tetrahedron* **1998**, *54*, 1005; b) N. S. Zefirov, A. S. Koz'min, T. Kasumov, K. A. Potekhin, V. D. Sorokin, V. K. Brel, E. V. Abramkin, Yu. T. Struchkov, V. V. Zhdankin, P. J. Stang, *J. Org. Chem.* **1992**, *57*, 2433; c) M. Ochiai, K. Sumi, Y. Nagao, E. Fujita, *Tetrahedron Lett.* **1985**, *26*, 2351.

[90] M. Ochiai, K. Oshima, Y. Masaki, *J. Am. Chem. Soc.* **1991**, *113*, 7059.

[91] a) M. Ochiai, S. Yamamoto, T. Suefuji, D.-W. Chen, *Org. Lett.* **2001**, *3*, 2753; b) J. Yan, H. Jin, Z. Chen, *J. Chem. Res.* **2007**, *2007*, 233.

[92] S. Thielges, P. Bisseret, J. Eustache, *Org. Lett.* **2005**, *7*, 681.

It includes: the generation of vinyl cations (S_N1-type reaction), in-plane vinylic substitution (S_N2-type reactions), ligand coupling reactions at the iodine(III) center, and β-addition-elimination reactions.[93]



Scheme 10. Electrophilic vinylation of heteroatom nucleophiles with iodonium salts.

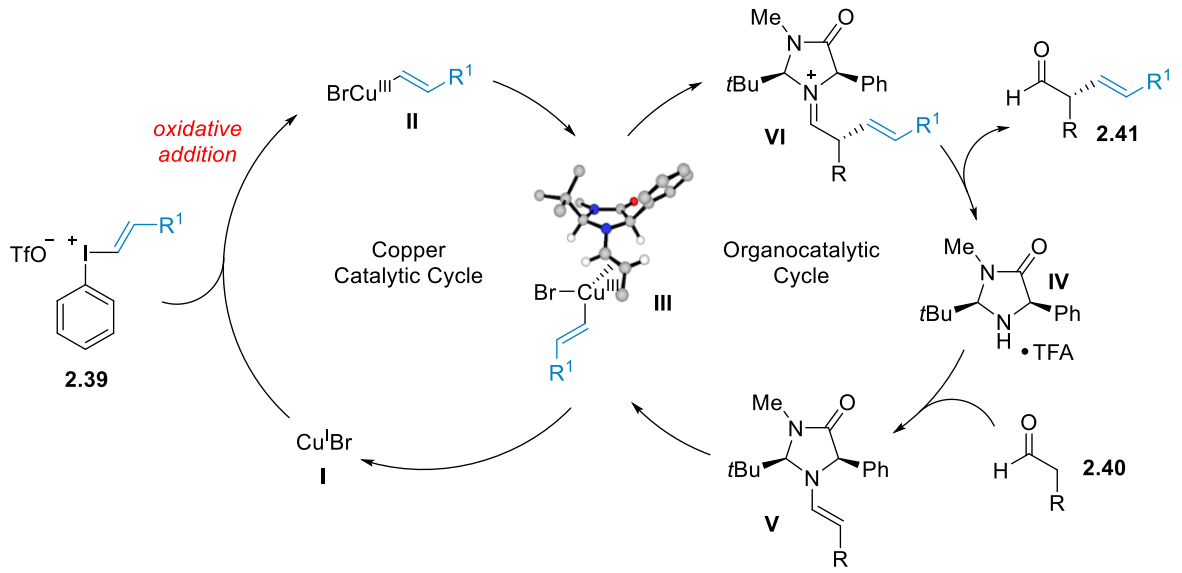
The first exploitation of alkenyl-(aryl)iodonium salts for the direct functionalization of a carbon atom was realized using 1,3-indandione as nucleophile in presence of a strong base.[94,75b] The reaction was later generalized to other β-dicarbonyl compounds and a nickel-catalyzed enantioselective version has since been proposed.[95] Nevertheless, a major drawback of the reaction was the uncontrolled divinylation of substrates with active methylene groups. It is only recently that an enantioselective α-vinylation of aldehydes was achieved *via* the synergistic combination of copper and chiral amine catalysis by the group of MacMillan (Scheme 11).[96] The authors postulated the generation of a highly electrophilic Cu(III)-vinyl complex **II** resulting from the oxidative addition of the Cu(I) catalyst **I** into the weak hypervalent alkenyl-iodane bond of **2.39**. Addition of the enamine **V**, generated by the condensation of the chiral amine catalyst **IV** with aldehyde **2.40**, to the Cu(III)-vinyl complex **III** would deliver the enantioenriched α-alkenylated aldehyde product **2.41**.

[93] M. Ochiai, *J. Organomet. Chem.* **2000**, *611*, 494.

[94] F. M. Beringer, S. A. Galton, *J. Org. Chem.* **1965**, *30*, 1930.

[95] a) M. Ochiai, T. Shu, T. Nagaoka, Y. Kitagawa, *J. Org. Chem.* **1997**, *62*, 2130; For Ni-catalyzed asymmetric transformation, see: b) J. Guo, L. Lin, Y. Liu, X. Li, X. Liu, X. Feng, *Org. Lett.* **2016**, *18*, 5540.

[96] E. Skucas, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2012**, *134*, 9090.

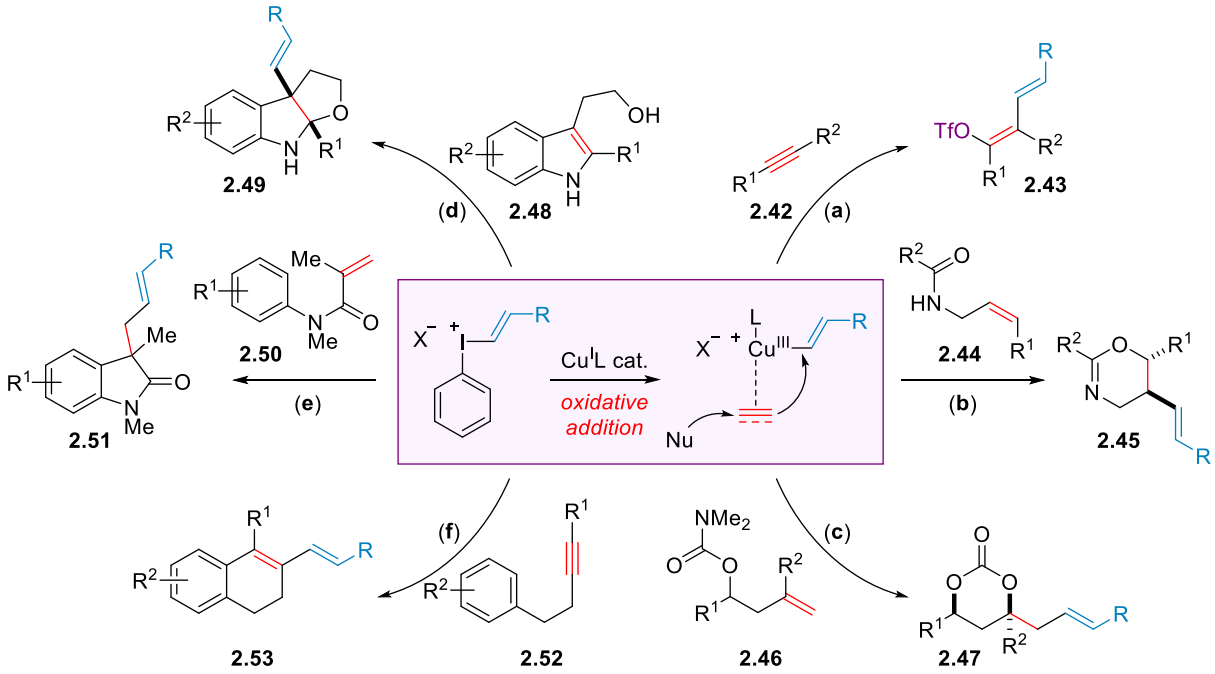


Scheme 11. Mechanism for the enantioselective α-vinylation of aldehyde.

While metal-free alkenylation of *C*-nucleophiles has been limited,[75,97] numerous strategies employing soft transition metal, such as copper, have been reported to enable the formation of the new carbon-carbon bond. The direct coupling of vinyliodonium salts with Gilman reagents is an early example of a copper-involve transformation.[75,98] An efficient α-vinylation method for phosphonates, sulfonates, sulfoxides, and carbonyl derivatives through telescopic C-H zincation/copper-catalyzed cross-coupling reaction has been described recently by Wang and Liu.[99] However, most of the recent methodologies have relied on the excellent capability of hypervalent iodine salts to generate π-acidic Cu(III) intermediates (Scheme 12). The Gaunt research group has been interested in the difunctionalization of various π-bonds systems by exploiting this phenomenon. The vinyl-triflation of internal alkynes **2.42** was achieved with high (*Z*)-stereoselectivity, however moderate regioselectivity was obtained in case of unsymmetrical alkynes (**a**).[100] This transformation represents a rare example in which the counterion (TfO^-) of the iodonium salt reagent is incorporated in the final product **2.43**. Intramolecular oxy-alkenylation of olefin tethered to amide **2.44** and carbamate **2.46** was also realized to access oxazines **2.45** and 1,3-carbonates **2.47** respectively (**b** and **c**).[101] Both reactions proceed with good diastereoselectivities, under mild conditions and are tolerant to a wide range of functional groups. A vinylation/cyclization cascade of tryptophols **2.48** was reported by the You group (**d**).[102] Moreover, C-H functionalizations of aromatic compounds were accomplished using the combination of alkenyliodonium salt with a copper(I) catalyst. Li and co-workers reported an efficient access to a variety of highly functionalized oxindoles **2.51** *via* a carbocyclization strategy (**e**),[103] and the Gaunt group reported examples of intramolecular carbovinylation of internal alkynes **2.52** (**f**).[104] In addition,

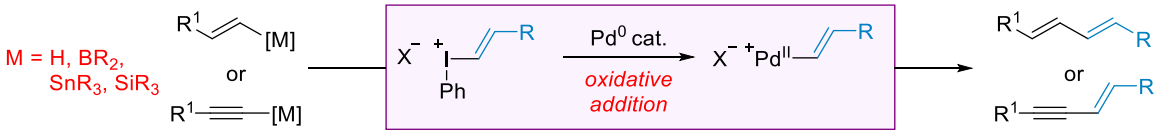
[97] M. Ochiai, Y. Takaoka, K. Sumi, Y. Nagao, *J. Chem. Soc., Chem. Commun.* **1986**, 1382.
[98] P. J. Stang, T. Blume, V. V. Zhdankin, *Synthesis* **1993**, *1993*, 35.
[99] C. Liu, Q. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 4727.
[100] M. G. Suero, E. D. Bayle, B. S. L. Collins, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 5332.
[101] a) E. Cahard, N. Bremeyer, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2013**, *52*, 9284; b) D. Holt, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2015**, *54*, 7857.
[102] C. Liu, W. Zhang, L.-X. Dai, S.-L. You, *Org. Lett.* **2012**, *14*, 4525.
[103] B. Zhou, W. Hou, Y. Yang, H. Feng, Y. Li, *Org. Lett.* **2014**, *16*, 1322.
[104] A. J. Walkinshaw, W. Xu, M. G. Suero, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 12532.

various electron-deficient (hetero)arenes such as nicotinonitrile, benzimidazole, oxazole, and pentafluorobenzene were efficiently alkenylated using copper catalysis.[105]



Scheme 12. Cu(I)-catalyzed vinylation of unsaturated C-C bonds with alkenyl-(aryl)iodonium salts.

Alkenyl-(aryl)iodonium salts have also found applications in palladium-catalyzed cross coupling reactions for the formation of Csp^2-Csp^2 and Csp-Csp^2 bonds (Scheme 13). Due to the high reactivity of the hypervalent bond, mild reaction conditions for the oxidation of the palladium catalyst can be expected. Therefore, vinyliodonium salts constitute a serious alternative to vinyl halides for the functionalization of sensitive substrates. Using this strategy, the vinylation of several nucleophilic coupling partners (M = H,[106] B,[107] Sn,[108] Si[109]) to access conjugated diene and enyne products was realized. Carbonylative versions of these transformations were reported as well.[109,110]



Scheme 13. Pd-catalyzed cross-coupling reaction using vinyliodonium salts.

[105] C. Liu, Q. Wang, *Org. Lett.* **2016**, *18*, 5118.

[106] For terminal alkene, see: a) R. M. Moriarty, W. R. Epa, A. K. Awasthi, *J. Am. Chem. Soc.* **1991**, *113*, 6315; b) S.-K. Kang, K.-Y. Jung, C.-H. Park, S.-B. Jang, *Tetrahedron Lett.* **1995**, *36*, 8047; c) S.-K. Kang, H.-W. Lee, S.-B. Jang, T.-H. Kim, S.-J. Pyun, *J. Org. Chem.* **1996**, *61*, 2604; For terminal alkyne, see: d) N. Sh. Pirguliyev, V. K. Brel, N. S. Zefirov, P. J. Stang, *Tetrahedron* **1999**, *55*, 12377.

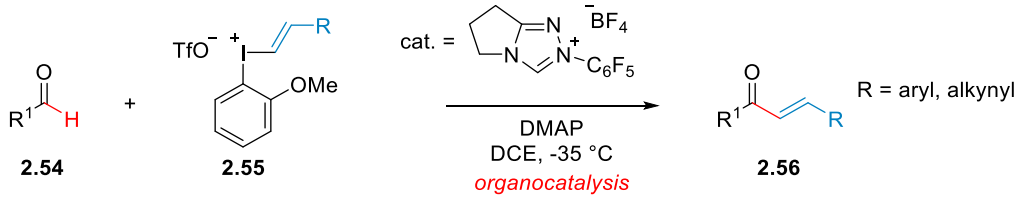
[107] S.-K. Kang, H.-W. Lee, S.-B. Jang, P.-S. Ho, *J. Org. Chem.* **1996**, *61*, 4720.

[108] R. J. Hinkle, G. T. Poulter, P. J. Stang, *J. Am. Chem. Soc.* **1993**, *115*, 11626.

[109] S.-K. Kang, T. Yamaguchi, R.-K. Hong, T.-H. Kim, S.-J. Pyun, *Tetrahedron* **1997**, *53*, 3027.

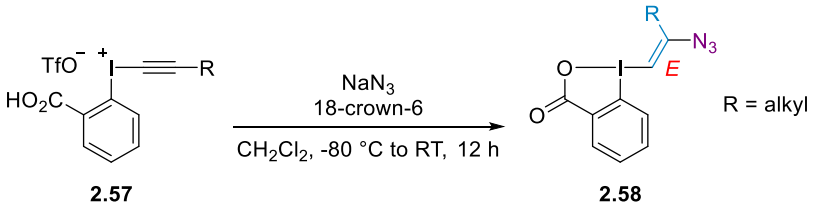
[110] Selected examples, a) S.-K. Kang, K.-H. Lim, P.-S. Ho, W.-Y. Kim, *Synthesis* **1997**, *1997*, 874; b) M. Yoshida, A. Komata, S. Hara, *J. Fluor. Chem.* **2004**, *125*, 527; c) S.-K. Kang, T. Yamaguchi, P.-S. Ho, W.-Y. Kim, H.-C. Ryu, *J. Chem. Soc., Perkin Trans. I* **1998**, 841.

A direct C-H olefination of aldehydes **2.54** with vinyliodonium salts **2.55**, catalyzed by *N*-heterocyclic carbenes, was reported by Kalek and Rajkiewicz (Scheme 14).[111] This recent organocatalyzed transformation establishes a metal-free alternative for a selective transfer of vinyl groups using hypervalent iodine reagents.



Scheme 14. NHC-catalyzed formation of α,β-unsaturated ketones

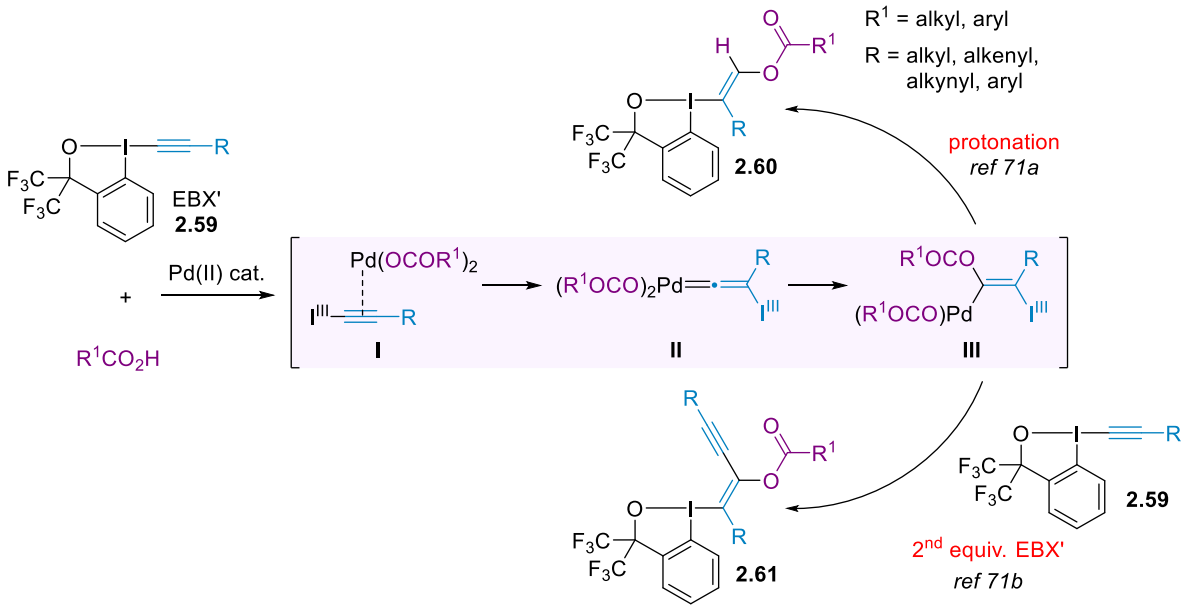
Neutral vinylbenziodoxolones reagents (VBX) are far less common than vinyliodonium salts and their application has been hampered by their scarcity. In fact, this reagent class was first reported as unexpected products from a Michael addition reaction of sodium azide on alkynyl-benzoic-iodonium salts **2.57** (Scheme 15).[112] It is interesting to notice that the *trans* olefin was formed in VBX **2.58**. The opposite olefin geometry is usually observed in such addition reactions with alkynyliodonium salts.



Scheme 15. First reported vinylbenziodoxolones.

Reports on VBX reagents have remained latent for almost two decades until the work of Yoshikai and co-workers on the stereoselective conversion of ethynylbenziodoxole (EBX', **2.59**) to *O*-VBX' reagents **2.60** by nucleophilic addition of carboxylic acids under Pd(II) catalysis (Scheme 16).[71a] Mechanistic experiments and DFT calculations supported an unprecedented alkyne-to-vinylidene conversion *via* a 1,2-iodine(III) shift (intermediate **I** to intermediate **II**), followed by a migratory insertion of the vinylidene-Pd(carboxylate)$_2$ species to furnish **III**. Subsequent protonation would deliver the new *O*-VBX' compounds **2.60**. Later, the same group reported the 1,1-carboxy-alkynylation of EBX' reagents **2.59** by trapping of the intermediate **III** with a second equivalent of alkynyl hypervalent iodine.[71b] The resulting *O*-VBX' reagents of these methodologies were successfully engaged in Pd(0)-catalyzed cross coupling reactions and make possible the synthesis of highly functionalized olefins.

[111] A. A. Rajkiewicz, M. Kalek, *Org. Lett.* **2018**, *20*, 1906.
[112] T. Kitamura, T. Fukuoka, Y. Fujiwara, *Synlett* **1996**, *1996*, 659.

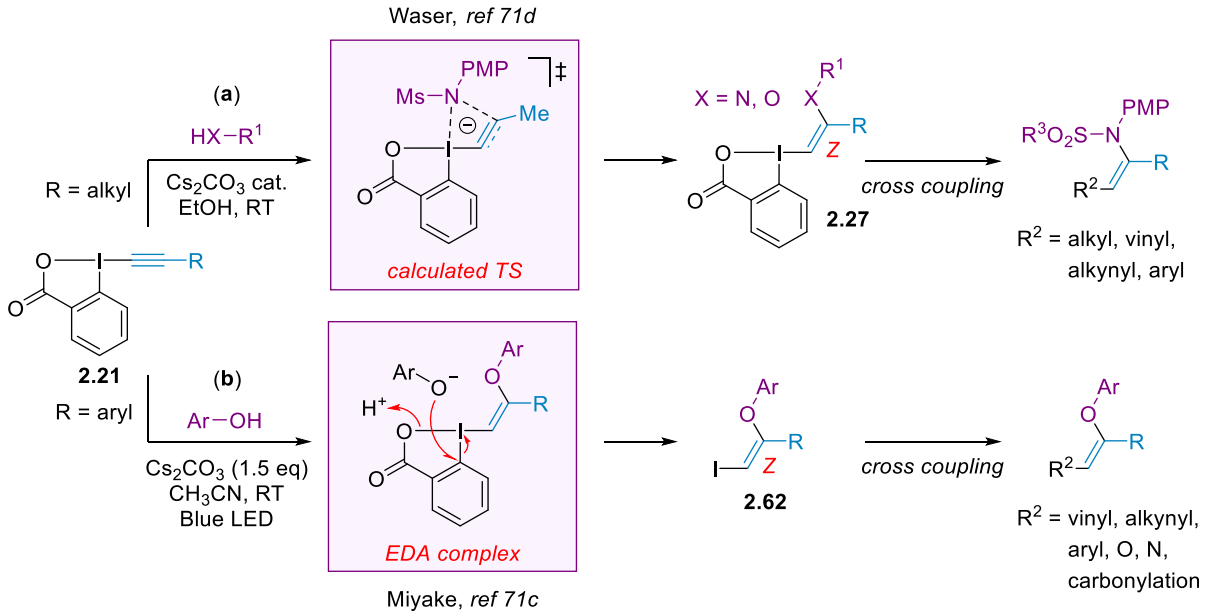


Scheme 16. Pd-catalyzed conversion of EBX' to functionalized *O*-VBX' reagents.

The strategy of nucleophilic addition to EBX reagents **2.21** was further extended by our group and the Miyake group (Scheme 17). We reported the synthesis of new *N*- and *O*-VBX reagents **2.27** from sulfonamides and phenols, in presence of a catalytic amount of cesium carbonate in protic solvent (**a**).[71d,113] The reaction is highly stereoselective furnishing the *Z*-products in a clean manner. The mild reaction conditions were adapted to the late-stage functionalization of several natural and bioactive molecules. DFT calculations supported a β-addition transition state in which the nucleophile is directed by proximal interactions with the iodine(III) center. Finally, *X*-VBX reagents **2.27** were employed as practical *Z*-enamides and *Z*-enol ethers coupling partners, otherwise challenging to access in high geometric purity. Miyake and co-workers reported similar conditions for the addition of phenol to EBX reagents **2.21** (**b**).[71c] However, the *in situ* formed *O*-VBX reagents were rapidly reduced to the corresponding vinyl iodide products **2.62** under the influence of visible light (Blue LED). The synthesis of halovinylbenziodoxole reagents following a similar strategy has been reported recently.[71e] In 2020, we continued to explore the reactivity of *O*-VBX reagents, employing them as masked oxy-allyl cation surrogates for the functionalization of phenols under mild basic conditions.[114]

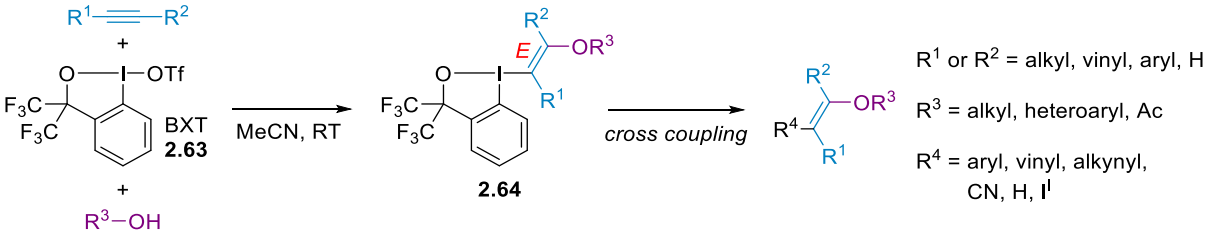
[113] For an extension of this work with unsubstituted EBX, see: D. Shimbo, A. Shibata, M. Yudasaka, T. Maruyama, N. Tada, B. Uno, A. Itoh, *Org. Lett.* **2019**, *21*, 9769.

[114] N. Declas, J. Waser, *Angew. Chem. Int. Ed.* **2020**, *59*, 18256.



Scheme 17. Stereoselective formation of *N*- and *O*-VBX and subsequent transformations

The group of Yoshikai extended their work on hetero-vinylbenziodoxole reagents reporting a iodo(III)-etherification of alkynes to access *O*-VBX **2.64** using benziodoxole triflate (BXT, **2.63**) and alcohols as partners (Scheme 18).[115] The 1,2-difunctionalization is regio- and stereoselective, accommodates a large array of functionalities and operates under very simple conditions. The strategy is somehow similar to the addition of iodane across alkynes we detailed previously, with the major advantage to utilize alcohol as third component instead of being restricted to the iodane counterion. Again, the authors harnessed the hypervalent iodine bound reactivity in several mild Pd-catalyzed cross coupling reactions to access highly functionalized olefin products.

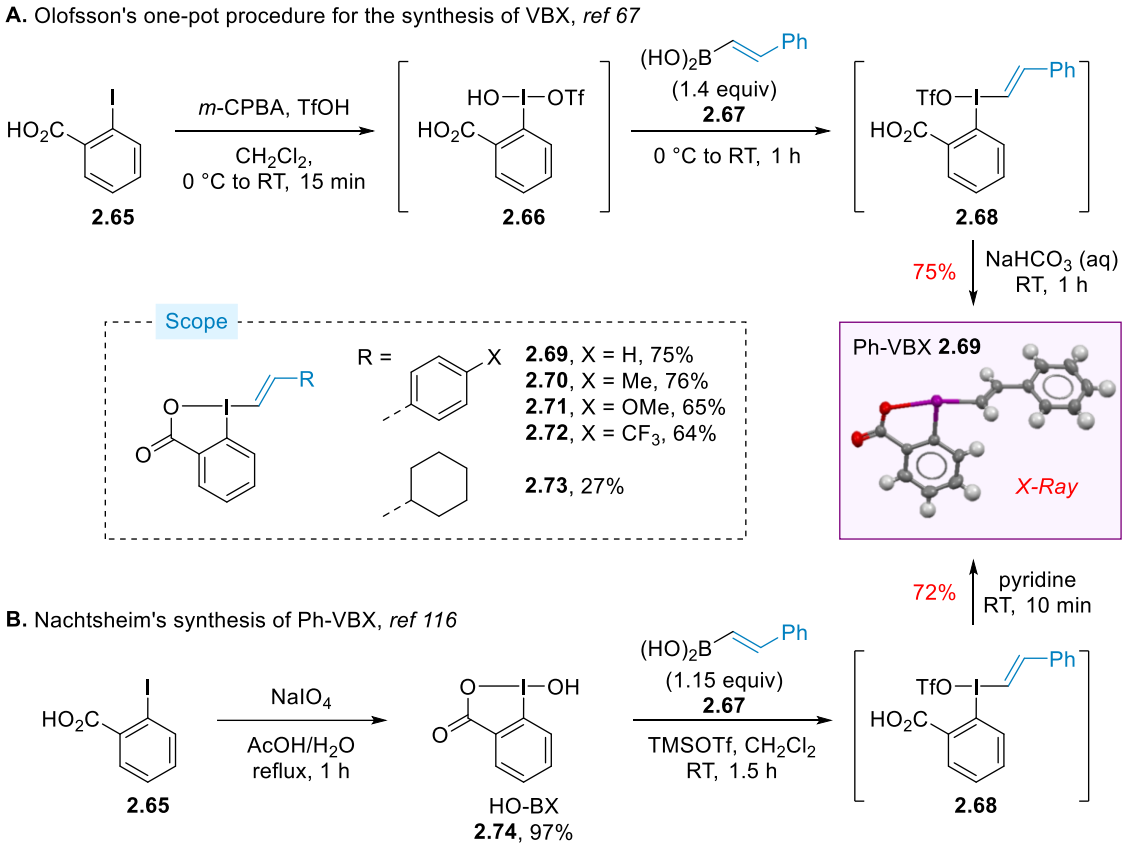


Scheme 18. Iodo(III)-etherification of alkynes with BXT and alcohols.

The utilization of EBX reagents to access *X*-VBX reagents with ancillary functionalities has gained increasing importance these recent years. In parallel, the synthesis of VBX reagents by a conventional approach from iodane precursors has also been investigated by several research groups. In 2016, Olofsson and co-workers had a major contribution to the field by proposing a practical one-pot procedure for the synthesis of VBX reagents starting form 2-iodobenzoic acid (Scheme 19. A).[67] The acronym *VBX* was coined for the first time. Oxidation of 2-iodobenzoic acid (**2.65**) with *m*-CPBA in presence of triflic acid forms the iodane intermediate **2.66**. Sequential addition of phenylvinylboronic acid (**2.67**) gave the iodonium salt **2.68**, which is then cyclized by addition of aqueous sodium bicarbonate. The overall sequence furnishes crystalline Ph-VBX (**2.69**) in 75% yield. The scope was

[115] a) W. Ding, J. Chai, C. Wang, J. Wu, N. Yoshikai, *J. Am. Chem. Soc.* **2020**, *142*, 8619; For a similar strategy employing FXT instead of BXT, see: b) J. Chai, W. Ding, J. Wu, N. Yoshikai, *Chem. Asian J.* **2020**, *15*, 2166.

essentially limited to aryl-substituted derivatives, as a low yield was obtained with cyclohexyl substituent (**2.73**). Importantly, the procedure required the handling of dry *m*-CPBA and strong triflic acid. The yield was diminished with phenylvinylboronate pinacol ester instead of boronic acid **2.67**, and vinylsilane precursors were ineffective.



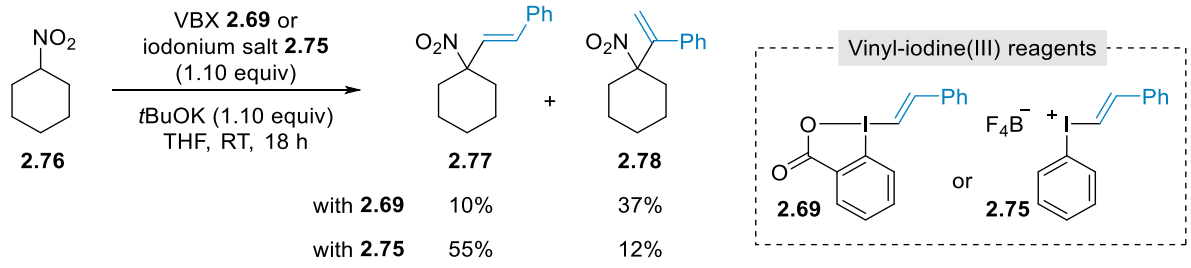
Scheme 19. First reports for the synthesis of VBX reagents from 2-iodobenzoic acid (**2.65**).

In 2017, another synthetic route to access Ph-VBX was proposed by Nachtsheim (Scheme 19, B).[116] The methodology required the pre-synthesis of hydroxylbenziodoxolone (HO-BX, **2.74**). This compound is readily prepared by oxidation of 2-iodobenzoic acid **2.65** by sodium periodate in aqueous media.[117] Activation of HO-BX (**2.74**) with TMSOTf, followed by iodane-boron ligand exchange produces the intermediate **2.68**, which is cyclized to the final Ph-VBX (**2.69**) in good yield. In this case, the utilization of a vinylboronate pinacol ester precursor resulted in a significant loss of yield.

In addition to their synthetic protocol, Olofsson and co-workers made a comparative study between the reactivity of Ph-VBX (**2.69**) and acyclic vinyl-(phenyl)iodonium salt **2.75** for the *C*-alkenylation of nitrocyclohexane (**2.76**) under basic conditions (Scheme 20).[67] They observed the terminal alkene **2.78** as major product in the case Ph-VBX, while the isomer **2.77** was obtained preferentially with the iodonium salt. The change in product distribution indicates a mechanistic difference between the two reactions, which was not clarified by the authors. However, ligand exchange with the nitroalkane anion followed by reductive elimination at the iodine(III) center is likely

[116] A. Boelke, L. D. Caspers, B. J. Nachtsheim, *Org. Lett.* **2017**, *19*, 5344.
[117] J. Brand, J. Waser, *Synthesis* **2012**, *44*, 1155.

to happen in the case of iodonium salt **2.75** with the highly labile tetrafluoroborate counterion, while another pathway can be expected for the vinylbenziodoxolone.



Scheme 20. Reactivity comparison between VBX **2.69** and vinyliodonium salt **2.75**.

With robust and convenient syntheses established, aryl-substituted VBX reagents have quickly found applications in various methodologies (Figure 7). The group of Nachtsheim reported a directed iridium-catalyzed C-H vinylation of 2-vinylanilines derivatives.[116] VBX reagents proved to be successful radical acceptor partners in photoredox-catalyzed transformations. Several 1,2-imino alkenylations of olefins were reported using a cascade photoredox decarboxylation-cyclization sequence of oxime precursors by the group of Leonori.[118] Our group has been particularly interested in merging hypervalent iodine chemistry and photoredox-catalyzed transformations. We reported interesting preliminary results employing Ph-VBX as radical acceptor in a photocatalyzed decarboxylation-fragmentation of cyclic oximes.[119] Recently, we disclosed one example of decarboxylative vinylation of the *C*-terminus of a dipeptide through photoredox catalysis.[120] An organo-photoredox catalyzed three-component radical difunctionalization of unactivated alkenes has been reported by Studer and Jiang.[121] In their methodology, they reported one example using Ph-VBX to achieve amido-alkenylation, albeit in low yield. Functionalization of more classical nucleophiles have been also investigated. Olofsson and co-workers disclosed the first electrophilic vinylation of thiols using VBX reagents under basic conditions.[122] The scope of the transformation was broad with respect to thiols, however, vinylation with alkyl-substituted VBX gave only modest yields. The same group continued their investigations on transition metal free transformations with a methodology for the alkenylation of *P*-nucleophiles.[123] The reaction proceeded with complete regioselectivity in favor of the terminal alkenes. Lastly, we reported the alkenylation of *in situ* generated sulfenate anions generated *via* retro-Michael reaction of sulfanyl esters.[124]

[118] J. Davies, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed,* **2017**, *56*, 13361.
[119] F. Le Vaillant, M. Garreau, S. Nicolai, G. Gryn'ova, C. Corminboeuf, J. Waser, *Chem. Sci.* **2018**, *9*, 5883.
[120] M. Garreau, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2019**, *58*, 8182.
[121] H. Jiang, A. Studer, *Chem. Eur. J.* **2019**, 25, 516.
[122] L. Castoldi, E. M. Di Tommaso, M. Reitti, B. Gräfen, B. Olofsson, *Angew. Chem. Int. Ed.* **2020**, *59*, 15512.
[123] L. Castoldi, A. A. Rajkiewicz, B. Olofsson, *Chem. Commun.* **2020**, *56*, 14389.
[124] S. G. E. Amos, S. Nicolai, A. Gagnebin, F. Le Vaillant, J. Waser, *J. Org. Chem.* **2019**, *84*, 3687.

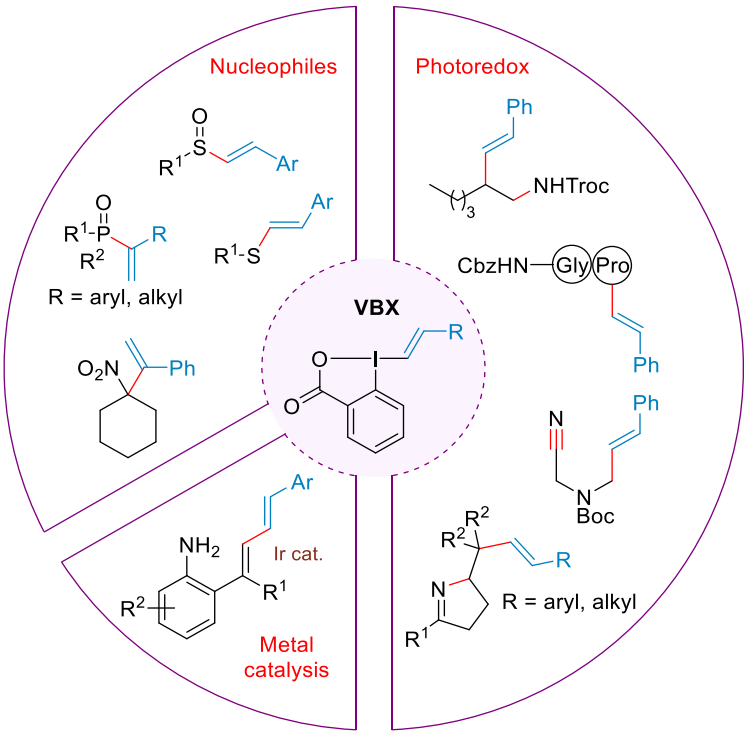


Figure 7. Overview of the recent applications of VBX reagents.

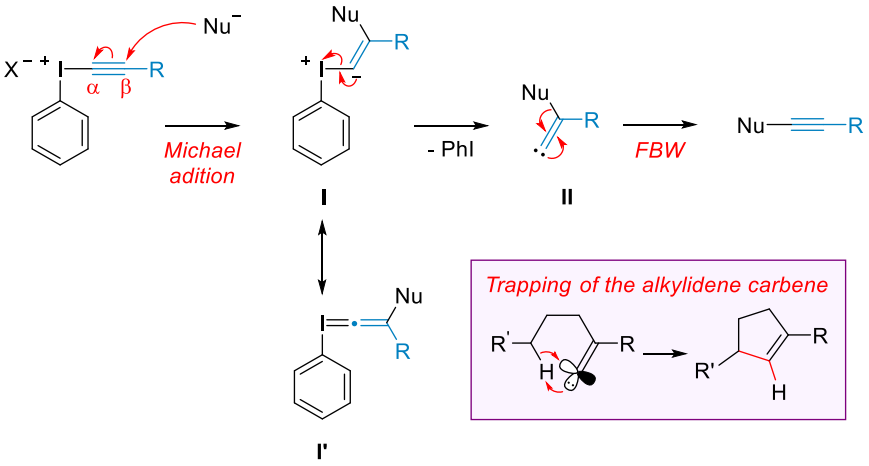
Vinylation reactions using VBX reagent are scarce. It is important to recall that the first practical synthesis was reported in 2016. Since then, different domains such as metal-catalysis, radical or classical polar chemistry have successfully applied VBX, which suggest a prosperous future for this new reagent class. Last year, our group reviewed the recent synthetic methods and applications of VBX and hetero-VBX reagents.[125]

2.2.3.2. Alkynylation

The first alkynylation using alkynyl-(aryl)iodonium salts was reported by Beringer.[94] The mechanism of this α-alkynylation of 1,3-diketone was elucidated later by Ochiai (Scheme 21).[126a] As we have seen in the previous section, soft nucleophiles add in β-position relative to the iodine(III) of the reagent to generate iodonium ylide **I**, with the relative resonance structure "iodo-allene" **I'**. In absence of anion re-capture (e.g. protonation), the irreversible loss of the aryliodide moiety results in alkylidene carbene **II**. Such highly reactive species undergo Fritsch-Buttenberg-Wiechell rearrangements (1,2-shift) to produce alkynes. The involvement of a carbene intermediate was supported by intramolecular trapping of the intermediate by 1,5-C-H insertion. Carbon-labeling experiments have been used to identify the migratory aptitude of the alkylidene substituents.[126a,b]

[125] N. Declas, G. Pisella, J. Waser, *Helv. Chim. Acta* **2020**, *103*, e20000191.

[126] a) M. Ochiai, M. Kunishima, Y. Nagao, K. Fuji, M. Shiro, E. Fujita, *J. Am. Chem. Soc.* **1986**, *108*, 8281; b) L. I. Dixon, M. A. Carroll, T. J. Gregson, G. J. Ellames, R. W. Harrington, W. Clegg, *Org. Biomol. Chem.* **2013**, *11*, 5877.



Scheme 21. Mechanism for the alkynylation of nucleophile with alkynyl hypervalent iodine.

Concerning their synthesis, alkynyl-(aryl)iodonium salts are generally prepared by reaction of a λ^3-iodane precursor with terminal alkynes,[127] or silylated,[128] borylated[129] and stannylated[130,82c] alkynes, in analogy to the relative vinyl-(aryl)iodonium salts (Scheme 22). One-pot procedures to access alkynyliodonium salts from iodoarenes and *m*-CPBA have been developed.[131] In addition to dicarbonyls (**a**), various inherent nucleophilic heteroatoms, such as nitrogen (**b**), oxygen (**c**), phosphorus (**d**) or sulfur (**e**) can be efficiently alkynylated with alkynyliodonium salts.[132]

[127] a) L. Rebrovic, G. F. Koser, *J. Org. Chem.* **1984**, *49*, 4700; b) P. J. Stang, B. W. Surber, Z. C. Chen, K. A. Roberts, A. G. Anderson, *J. Am. Chem. Soc.* **1987**, *109*, 228; c) M. Yoshida, N. Nishimura, S. Hara, *Chem. Commun.* **2002**, 1014.

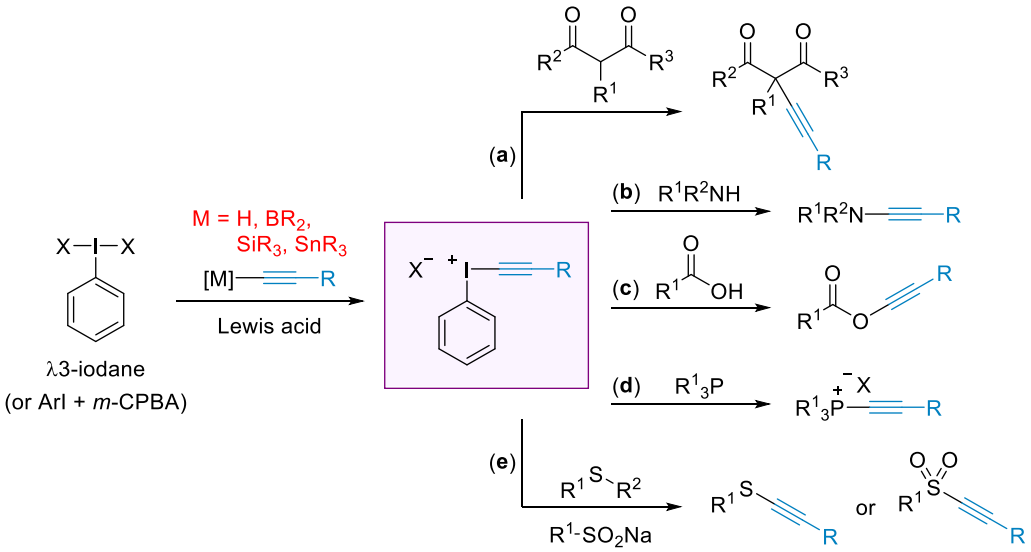
[128] a) M. Ochiai, M. Kunishima, K. Sumi, Y. Nagao, E. Fujita, M. Arimoto, H. Yamaguchi, *Tetrahedron Lett.* **1985**, *26*, 4501; b) T. Kitamura, P. J. Stang, *J. Org. Chem.* **1988**, *53*, 4105; c) T. Kitamura, *Synthesis* **1998**, *1998*, 1416.

[129] M. Yoshida, K. Osafune, S. Hara, *Synthesis* **2007**, *2007*, 1542.

[130] a) P. J. Stang, B. L. Williamson, V. V. Zhdankin, *J. Am. Chem. Soc.* **1991**, *113*, 5870; b) K. S. Feldman, J. C. Saunders, M. L. Wrobleski, *J. Org. Chem.* **2002**, *67*, 7096; c) D. J. Wardrop, J. Fritz, *Org. Lett.* **2006**, *8*, 3659.

[131] a) E. A. Merritt, B. Olofsson, *Eur. J. Org. Chem.* **2011**, *2011*, 3690; b) M. J. Bouma, B. Olofsson, *Chem. Eur. J.* **2012**, *18*, 14242; c) D. J. Hamnett, W. J. Moran, *Org. Biomol. Chem.* **2014**, *12*, 4156.

[132] Selected examples with *N*-nucleophiles, a) P. Murch, B. L. Williamson, P. J. Stang, *Synthesis* **1994**, *1994*, 1255; b) B. Witulski, C. Alayrac, L. Tevzadze-Saeftel, *Angew. Chem. Int. Ed.* **2003**, *42*, 4257; c) I. F. D. Hyatt, M. P. Croatt, *Angew. Chem. Int. Ed.* **2012**, *51*, 7511; d) T. Kitamura, M. H. Morshed, S. Tsukada, Y. Miyazaki, N. Iguchi, D. Inoue, *J. Org. Chem.* **2011**, *76*, 8117; with *O*-nucleophiles, e) P. J. Stang, M. Boehshar, H. Wingert, T. Kitamura, *J. Am. Chem. Soc.* **1988**, *110*, 3272; f) P. J. Stang, T. Kitamura, M. Boehshar, H. Wingert, *J. Am. Chem. Soc.* **1989**, *111*, 2225; with *P*-nucleophiles, g) M. Ochiai, M. Kunishima, Y. Nagao, K. Fuji, E. Fujita, *J. Chem. Soc., Chem. Commun.* **1987**, 1708; h) P. J. Stang, C. M. Crittell, *J. Org. Chem.* **1992**, *57*, 4305; with *S*-nucleophiles, i) K. Miyamoto, Y. Nishi, M. Ochiai, *Angew. Chem. Int. Ed.* **2005**, *44*, 6896; j) M. Ochiai, T. Nagaoka, T. Sueda, J. Yan, D.-W. Chen, K. Miyamoto, *Org. Biomol. Chem.* **2003**, *1*, 1517.



Scheme 22. Synthesis and utilization of alkynyl-(aryl)iodonium salts with nucleophiles.

Alkynyliodonium salts have also been privileged partners in copper-mediated transformations.[133] Stang and Kitamura reported an efficient coupling reaction between vinylcopper(I) and alkynyliodonium salts.[134] The overall reaction sequence gives access to conjugated enynes in a stereoselective manner starting from terminal alkynes. The authors proposed the involvement of a Cu(III) active intermediate. Alkynyliodonium salts undergo easy oxidative addition of several transition metals which can help to the transfer of C≡C bonds into coordinated substrates.[135]

Ethynylbenziodoxolones (EBX) were first synthesized and studied structurally by Ochiai.[136] A few years later, several EBX reagents with aryl, alkyl or silyl substituents, as well as the corresponding benziodoxoles were reported in an improved two-step procedure (Scheme 23. A).[137] However, their applications in organic chemistry were neglected until recently. Our group reawakened interest for EBX reagents by proposing efficient alkynylation strategies employing these compounds.[138] Since then, more practical syntheses of EBX have emerged, making this particular class of reagents available for the synthetic chemist community. Olofsson and co-workers developed an advantageous one-pot procedure from 2-iodobenzoic acid (**2.65**), however, it requires the use of non-commercial ethynylboronate ester precursors (Scheme 23. B).[131b] Our group disclosed a scalable synthesis of the well-established TIPS-EBX (**2.79**) from the simple terminal alkyne starting material (Scheme 23. C).[139]

[133] a) A.-M. Sun, X. Huang, *Tetrahedron* **1999**, *55*, 13201; b) D.-Y. Yang, J. He, S. Miao, *Synth. Commun.* **2003**, *33*, 2695; c) T. Kitamura, C. H. Lee, Y. Taniguchi, Y. Fujiwara, M. Matsumoto, Y. Sano, *J. Am. Chem. Soc.* **1997**, *119*, 619.

[134] P. J. Stang, T. Kitamura, *J. Am. Chem. Soc.* **1987**, *109*, 7561.

[135] a) P. J. Stang, C. M. Crittell, *Organometallics* **1990**, *9*, 3191; b) P. J. Stang, R. Tykwinski, *J. Am. Chem. Soc.* **1992**, *114*, 4411; c) A. J. Canty, T. Rodemann, B. W. Skelton, A. H. White, *Organometallics* **2006**, *25*, 3996; d) A. J. Canty, M. G. Gardiner, R. C. Jones, T. Rodemann, M. Sharma, *J. Am. Chem. Soc.* **2009**, *131*, 7236.

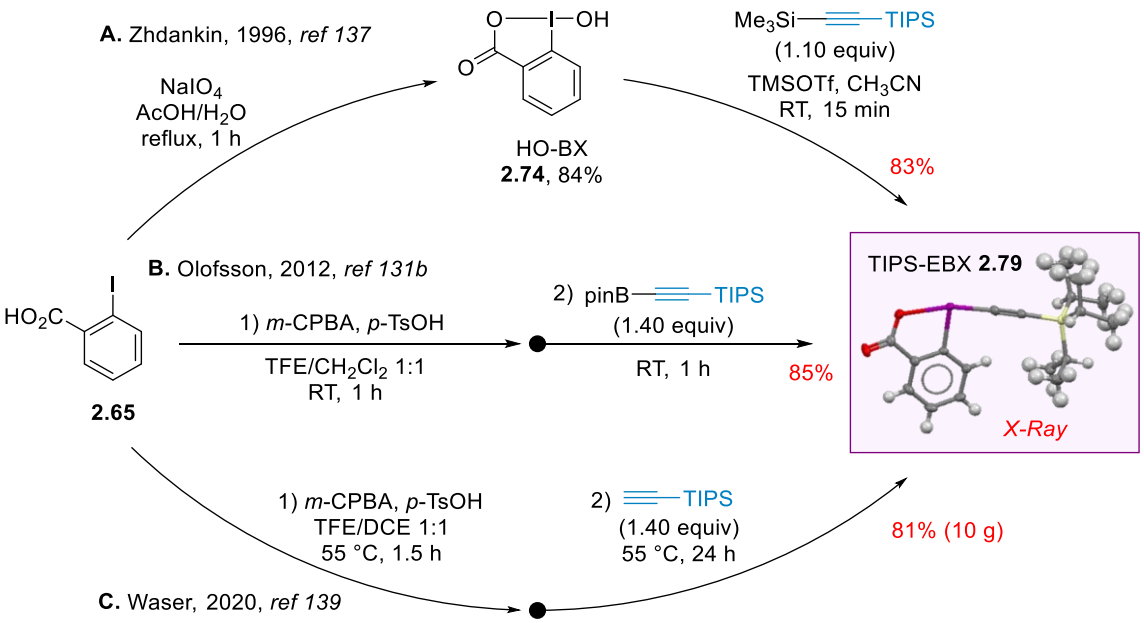
[136] M. Ochiai, Y. Masaki, M. Shiro, *J. Org. Chem.* **1991**, *56*, 5511.

[137] V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 6547.

[138] J. P. Brand, D. F. González, S. Nicolai, J. Waser, *Chem. Commun.* **2011**, *47*, 102.

[139] D. P. Hari, P. Caramenti, L. Schouwey, M. Chang, S. Nicolai, D. Bachert, T. Wright, C. Orella, J. Waser, *Org. Process Res. Dev.* **2020**, *24*, 106.

Diminished yields are obtained for substituents other than TIPS and borylated or silylated alkynes are usually employed in these cases.



Scheme 23. Improvements of the synthesis of TIPS-EBX.

In the last decade, alkynylation using EBX reagents has emerged as a complementary and mild alternative to other classical methods. EBX reagents have rapidly shown their superiority as effective electrophilic reagents over the less stable alkynyliodonium salts. For comparison, VBX reagents did not receive such attention. This may be due to the more developed chemistry of vinyliodonium salts. Several reviews have been devoted to the utilization of EBX reagents and selected representative applications are given below (Figure 8).[66] Our group and others have successfully applied EBX reagents in various transformations. Notably, the regioselective C-H-alkynylation of (hetero)arenes using π-acidic metal catalysis (gold and platinum) has been successful for indoles,[140] pyrroles,[140] thiophenes,[140] anilines,[141] furans[142] and benzofurans.[143] Several directed Ru-, Rh- and Ir-catalyzed C-H-alkynylations of arenes have been documented as well.[144] Hashmi and co-workers recently reported a Au-catalyzed C-H functionalization of cyclopropenes using benziodoxole derivatives (EBX', X = $(CF_3)_2$).[145] Metal-catalyzed domino cyclization-alkynylation strategies to access heterocycles functionalized at remote positions were disclosed by our group.[146] The Patil research group reported

[140] a) J. Brand, J. Charpentier, J. Waser, *Angew. Chem. Int. Ed.* **2009**, *48*, 9346; b) J. P. Brand, C. Chevalley, R. Scopelliti, J. Waser, *Chem. Eur. J.* **2012**, *18*, 5655; c) G. L. Tolnai, S. Ganss, J. P. Brand, J. Waser, *Org. Lett.* **2013**, *15*, 112.

[141] J. P. Brand, J. Waser, *Org. Lett.* **2012**, *14*, 744.

[142] Y. Li, J. P. Brand, J. Waser, *Angew. Chem. Int. Ed.* **2013**, *52*, 6743.

[143] Y. Li, J. Waser, *Beilstein J. Org. Chem.* **2013**, *9*, 1763.

[144] Selected examples, a) C. Feng, T.-P. Loh, *Angew. Chem. Int. Ed.* **2014**, *53*, 2722; b) F. Xie, Z. Qi, S. Yu, X. Li, *J. Am. Chem. Soc.* **2014**, *136*, 4780: c) D. Kang, S. Hong, *Org. Lett.* **2015**, *17*, 1938.

[145] Y. Yang, P. Antoni, M. Zimmer, K. Sekine, F. F. Mulks, L. Hu, L. Zhang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2019**, *58*, 5129.

[146] a) Y. Li, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 5438; b) J. P. Brand, C. Chevalley, J. Waser, *Beilstein J. Org. Chem.* **2011**, *7*, 565.

an elegant atom-economical Au-catalyzed 1,2-oxy-alkynylation of *N*-allenamides with EBXs,[147] while a Pd-catalyzed oxy- and amino-alkynylation of unactivated olefins through a tethered approach has been reported earlier by our group.[148]

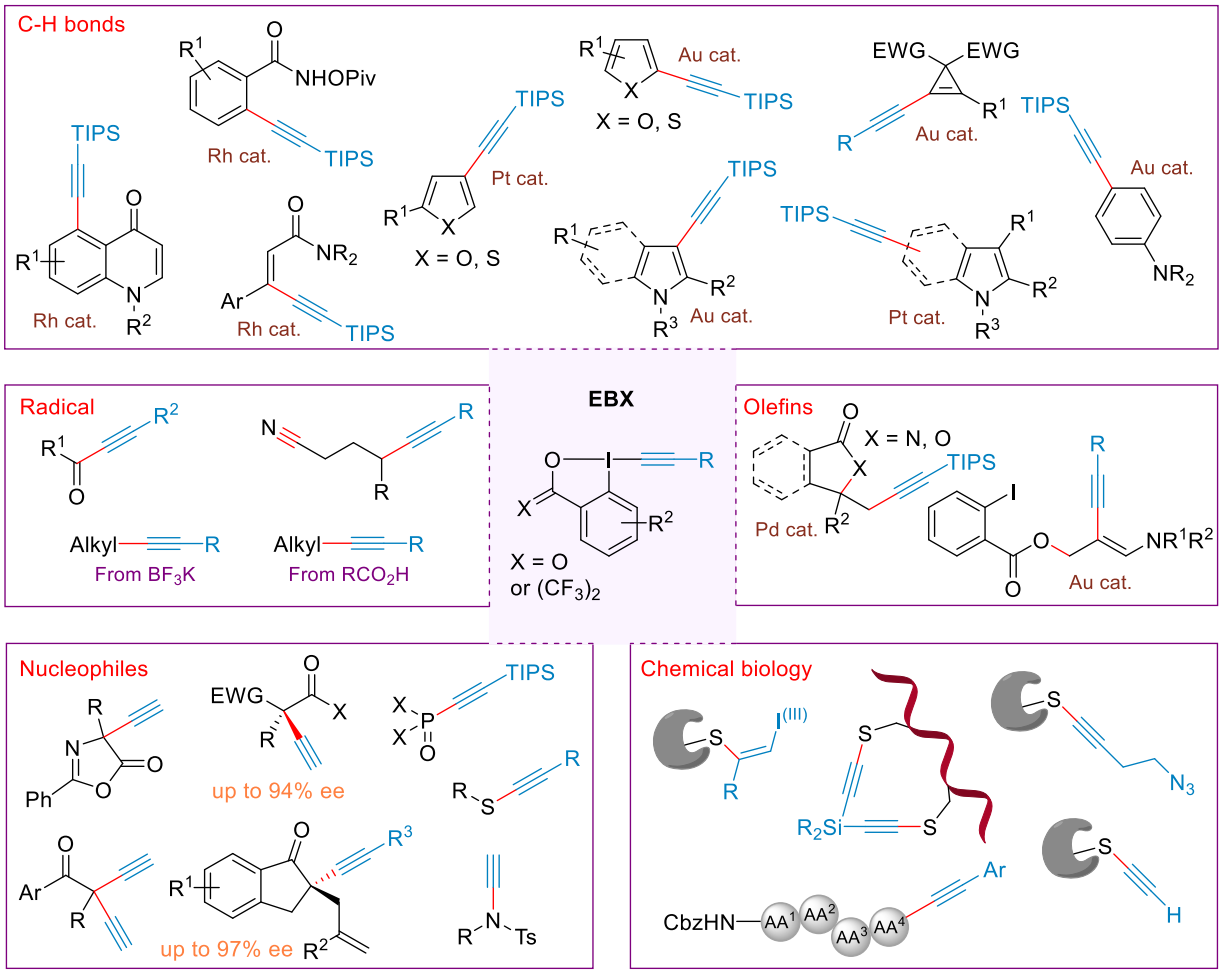


Figure 8. Selected examples of EBX applications.

The enantioselective alkynylation of stabilized enolates using phase-transfer catalysis has been studied by our group and the Maruoka group.[149] Other interesting alkynylations of *C*-nucleophiles have been reported.[150] The functionalization of radicals with EBXs has extended the possibility of somophilic alkynylation strategies for the creation of new Cp^3-Csp bonds.[151] The advent of photoredox catalysis has encouraged our group and many others to apply EBX reagents under such conditions.[152] Recently,

[147] S. Banerjee, B. Senthilkumar, N. T. Patil, *Org. Lett.* **2019**, *21*, 180.

[148] a) S. Nicolai, S. Erard, D. F. González, J. Waser, *Org. Lett.* **2010**, *12*, 384; b) S. Nicolai, C. Piemontesi, J. Waser, *Angew. Chem. Int. Ed.* **2011**, *50*, 4680.

[149] a) D. Fernández González, J. P. Brand, J. Waser, *Chem. Eur. J.* **2010**, *16*, 9457; b) D. Fernández González, J. P. Brand, R. Mondière, J. Waser, *Adv. Synth. Catal.* **2013**, *355*, 1631; c) X. Wu, S. Shirakawa, K. Maruoka, *Org. Biomol. Chem.* **2014**, *12*, 5388.

[150] a) A. Utaka, L. N. Cavalcanti, L. F. Silva, *Chem. Commun.* **2014**, *50*, 3810; b) P. Finkbeiner, N. M. Weckenmann, B. J. Nachtsheim, *Org. Lett.* **2014**, *16*, 1326.

[151] For a recent review on the alkynylation of radicals, see: F. Le Vaillant, J. Waser, *Chem. Sci.* **2019**, *10*, 8909.

[152] Selected examples, a) Q.-Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 11196; b) F. Le Vaillant, T. Courant, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 11200; c) H. Huang, G.

we developed a mild photoredox-catalyzed decarboxylative-alkynylation reaction for the functionalization of small peptides.[120] EBX reagents were also utilized for the convenient alkynylation of heteroatoms such as nitrogen[153] or phosphorus.[154] Most importantly, the extraordinarily fast and simple alkynylation of thiols under basic conditions with EBX reagents has enabled the modification of sulfur-containing molecules.[155] Our group is currently investigating the selective alkynylation of cysteine as a powerful chemical biology tool for the labeling and stapling of peptides and small proteins.[156] In collaboration with the Fierz group, we recently developed a "doubly orthogonal" labeling protocol exploiting the Michael addition of thiols onto EBX reagents to generate *S*-VBX-biomolecule conjugates under physiological conditions.[157] The group of Miyake recently reported the addition of two equivalents of thiol to EBX reagents for the regioselective synthesis of 1,2-dithioalkenes. The *in situ* formation of *S*-VBX intermediates was proved experimentally.[158]

Surprisingly, only few reports have associated EBX reagents to copper catalysts (Scheme 24). A Cu(I)-catalyzed C-H alkynylation-cyclization sequence for the construction of quinazolines **2.81** from amidines **2.80** was investigated by Ohno and co-workers in 2010 (**a**).[159] The same group utilized EBX reagents for a convenient preparation of ynamide **2.83** in presence of copper iodide as catalyst (**b**).[153b] Copper catalysis has been effectively used to control radical reactions. Shen and Wang reported a $Cu(OTf)_2$-catalyzed amino-alkynylation of tethered alkenes **2.84** with EBX reagents (**c**).[160] The reaction is similar to the Pd(II)-catalyzed strategy previously reported by our group,[148b] with the additional advantage to functionalize internal olefins and employing only 1 mol% of catalyst loading. The authors could confirm the presence of alkyl radical intermediates in the reaction and proposed two possible mechanisms involving either Cu^{I}/Cu^{II} or Cu^{II}/Cu^{III} redox couples. Han and co-workers reported a similar Cu(II)-catalyzed radical reaction for the oxy- or amino-alkynylation of olefin tethered ketoxime **2.86** (**d**).[161] Recently, a Cu(I)-catalyzed [2+2+1] heteroannulation of EBX reagents with silver nitrite (**2.89**) and olefin **2.90** has been disclosed by Li and co-workers (**e**).[162] The transformation grants a facile access to functionalized isoxazolines **2.91**. The copper(I) catalyst is believed to activate the C≡C bond of the EBX through coordination to help the nucleophilic attack of the nitrite anion.

Zhang, Y. Chen, *Angew. Chem. Int. Ed.* **2015**, *54*, 7872; d) H. Huang, G. Zhang, L. Gong, S. Zhang, Y. Chen, *J. Am. Chem. Soc.* **2014**, *136*, 2280; e) S. P. Morcillo, E. M. Dauncey, J. H. Kim, J. J. Douglas, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2018**, *57*, 12945.

[153] a) T. Aubineau, J. Cossy, *Chem. Commun.* **2013**, *49*, 3303; b) Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2014**, *16*, 3138.

[154] C. C. Chen, J. Waser, *Chem. Commun.* **2014**, *50*, 12923.

[155] a) R. Frei, J. Waser, *J. Am. Chem. Soc.* **2013**, *135*, 9620; b) R. Frei, M. D. Wodrich, D. P. Hari, P.-A. Borin, C. Chauvier, J. Waser, *J. Am. Chem. Soc.* **2014**, *136*, 16563; c) M. D. Wodrich, P. Caramenti, J. Waser, *Org. Lett.* **2016**, *18*, 60; d) C. C. Chen, J. Waser, *Org. Lett.* **2015**, *17*, 736.

[156] a) D. Abegg, R. Frei, L. Cerato, D. Prasad Hari, C. Wang, J. Waser, A. Adibekian, *Angew. Chem. Int. Ed.* **2015**, *54*, 10852; b) J. Ceballos, E. Grinhagena, G. Sangouard, C. Heinis, J. Waser, *Angew. Chem. Int. Ed.* **2021**, 60, 9022; c) R. Tessier, R. K. Nandi, B. G. Dwyer, D. Abegg, C. Sornay, J. Ceballos, S. Erb, S. Cianférani, A. Wagner, G. Chaubet, A. Adibekian, J. Waser, *Angew. Chem. Int. Ed.* **2020**, *59*, 10961.

[157] R. Tessier, J. Ceballos, N. Guidotti, R. Simonet-Davin, B. Fierz, J. Waser, *Chem* **2019**, *5*, 2243.

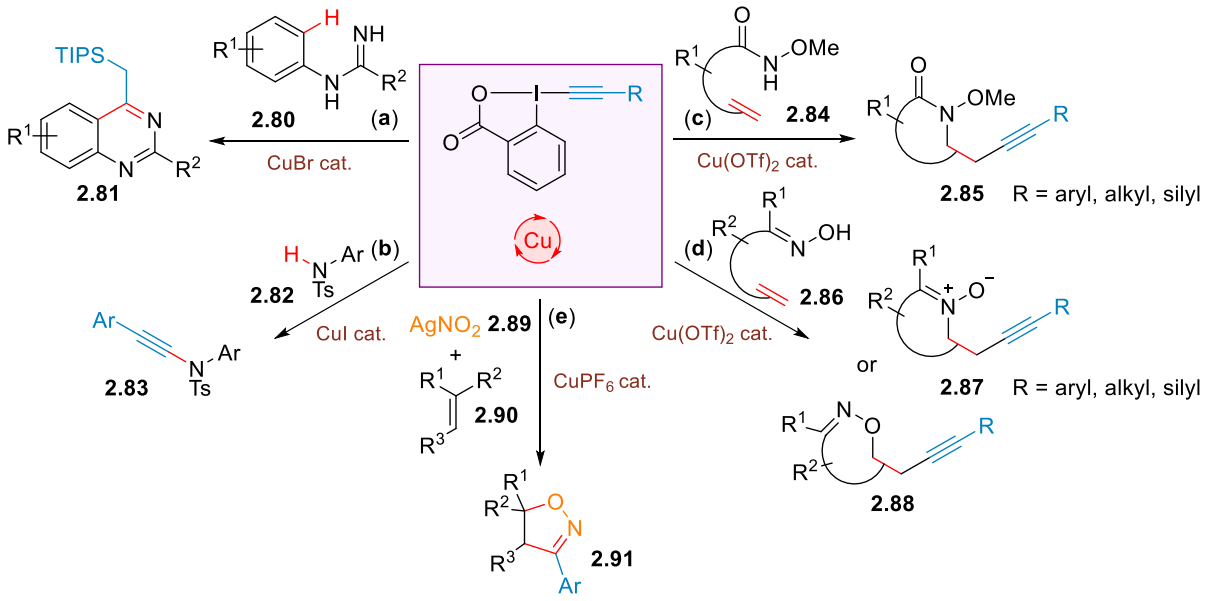
[158] B. Liu, J. V. Alegre-Requena, R. S. Paton, G. M. Miyake, *Chem. Eur. J.* **2020**, *26*, 2386.

[159] a) Y. Ohta, Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2010**, *12*, 3963; For a recent scope extension, see: b) R. Takai, D. Shimbo, N. Tada, A. Itoh, *J. Org. Chem.* **2021**, *86*, 4699.

[160] K. Shen, Q. Wang, *Chem. Sci.* **2017**, *8*, 8265.

[161] W.-J. Han, Y.-R. Wang, J.-W. Zhang, F. Chen, B. Zhou, B. Han, *Org. Lett.* **2018**, *20*, 2960.

[162] C.-Y. Wang, F. Teng, Y. Li, J.-H. Li, *Org. Lett.* **2020**, *22*, 4250.



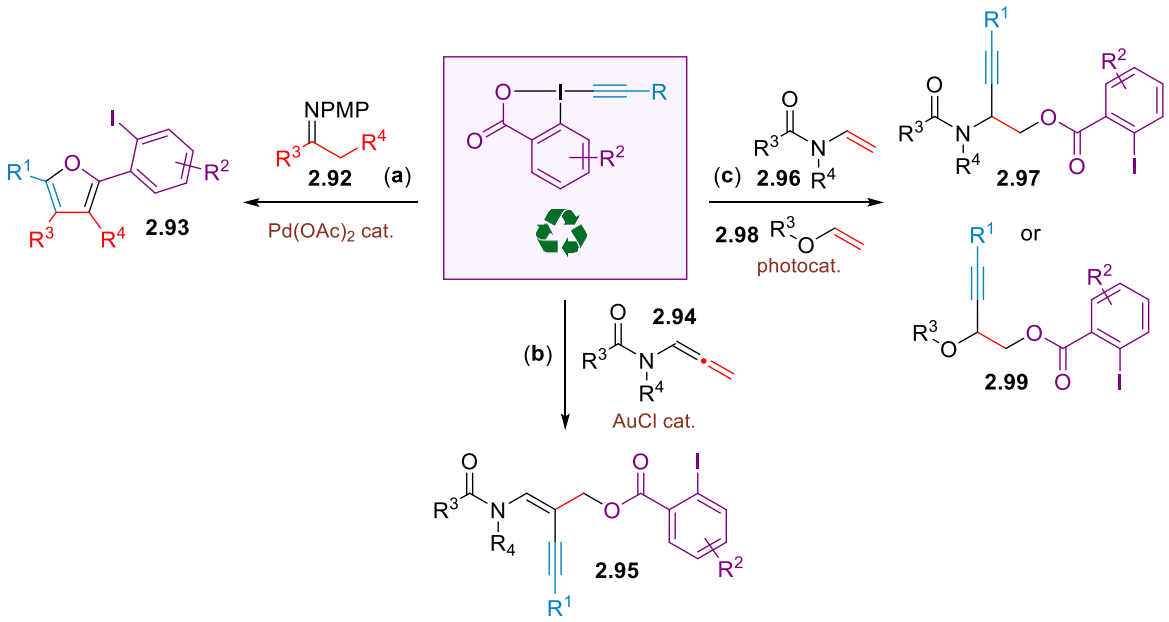
Scheme 24. Copper-catalyzed transformations with EBX reagents.

In summary, EBX reagents have been extensively used during the last decade and had a strong impact in organic synthesis as advantageous electrophilic alkyne synthons. They have demonstrated their usefulness for the alkynylation of radicals, and will probably continue to be used in photoredox-catalyzed transformations considering the current expansion of the field. EBXs were also employed as superior reagents for the mild alkynylation of heteroatoms such as thiols, allowing modification of biomolecules. Hetero-VBXs can be obtained *via* addition of nucleophiles across the C≡C bond of EBX reagents. Nevertheless, it is probably in association with various transition metal catalysts that EBX reagents have found the most applications, and notably for the alkynylation of C-H aromatic bonds under mild reaction conditions. To date, only few examples of copper-catalyzed transformations with EBX reagents have been reported. Both Cu(I) and Cu(II) catalysts were successfully employed and involved in different roles such as the functionalization of heteroatoms, the generation of radical intermediates, or as activators of the EBX reagent itself.

2.2.3.3. Conclusion and Perspective

A wide range of new methodologies have become possible through the electrophilic installation of unsaturated C-C bonds. The goal for selective and mild reactions conditions are important factors that justify the utilization of vinyl- and alkynyl-hypervalent iodines as superior reagents, when the organo halide counterparts can lack reactivity. However, vinyl and alkynyl halides are not always directly comparable to iodine(III) reagents and different reactivities are often encountered. Nowadays, iodonium salts tend to be avoided to the advantage of the more stable benziodoxolone reagents. Convenient syntheses of EBX reagents have been well described. Efforts toward the synthesis of aryl-substituted VBX reagents have been accomplished but the development of more general synthetic methods is desirable, especially concerning the limited access to alkyl-substituted VBXs. The utilization of 2-iodobenzoic acid as a precursor is another advantage of the cyclic reagents, avoiding the need of fluorinated counterions of iodonium salts. Alternatively, benziodoxole reagents can be obtained from 2-iodobenzyl alcohol precursors to modulate the reactivity of the hypervalent bond. As detailed in the precedent sections, both VBX and EBX reagents are applicable in a broad spectrum of transformations and new utilizations of these compounds are

currently being researched. However, the quest for high efficiency in organic synthesis brings up the question about the release of stoichiometric aryl iodide as substantial waste in most of the transformations we have covered. In the context of our work, we will tackle the utilization of EBX and VBX as alkynyl- and vinyl-group transfer reagents, but a particular interest will be dedicated toward the valorization of the 2-iodobenzoate by-product. To date, only a small number of methodologies employing EBX reagents takes advantage of the core of the reagent (Scheme 25).[163] No examples with VBX reagents are known. Yoshikai and co-workers reported an unexpected palladium-catalyzed condensation of imine **2.92** and EBX reagents to afford multisubstituted furan products **2.93** (**a**).[164] Unusual aspects such as cleavage of the C–C triple bond and partial incorporation of the 2-iodobenzoate moiety into the final products were observed in this transformation. The addition of the two ligands of the benziodoxolone reagent on a C=C bond is particularly well suited for a perfect atom-economical reaction. Such a process has been used by the Patil group in a gold-catalyzed 1,2-oxy-alkynylation of allenenamides **2.94** (**b**).[147] Finally, our group recently disclosed a photocatalyzed oxy-alkynylation of ene-carbamates **2.96** and enol ethers **2.98** using EBX reagents (**c**).[165]



Scheme 25. Atom-economical reactions with EBX reagents: Valorization of 2-iodobenzoate part.

[163] For recent reviews on atom-economical reactions with hypervalent iodine reagents, see: a) A. Boelke, P. Finkbeiner, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2018**, *14*, 1263; b) G. Grelier, B. Darses, P. Dauban, *Beilstein J. Org. Chem.* **2018**, *14*, 1508.

[164] B. Lu, J. Wu, N. Yoshikai, *J. Am. Chem. Soc.* **2014**, *136*, 11598.

[165] S. G. E. Amos, S. Nicolai, J. Waser, *Chem. Sci.* **2020**, *11*, 11274.

2.3. Difunctionalization of Metal Carbenes

A carbene is a molecule possessing a neutral divalent carbon atom having only six electrons in its valence shell. The recent growth of carbene chemistry started in the 1950s when Doering, Winstein and Woodward dimensioned the term *carbene* in a nocturnal Chicago taxi.[166] Since then, these fascinating species have played a crucial role in many important synthetic organic reactions. [167] The odd electronic configuration of carbene enables the simultaneous creation of two new bonds on the divalent carbon: a fast entry to molecular complexity.

In this chapter, the structure and interaction of carbenes with transition metals will be presented to better appreciate their reactivity pattern. A summary about the important aspect and synthetic transformations of diazo compounds, which are ubiquitous precursors of carbenes will then be covered. The different strategies for the difunctionalization of diazo compounds will be detailed in the last part, with a special attention to alkenylation and alkynylation reactions.

2.3.1. Structure, Bonding and Reactivity of Metal Carbenes

Free carbenes are rarely stable.[168] Methylene, $:CH_2$, is the simplest carbene and reacts rapidly with a wide variety of species, even alkanes. Carbenes form very strong binding with metal atoms (unfavorable free carbene release). Taming the high reactivity of carbenes through transition metal carbene complexes have accelerated the study and applications of these particular molecules.

Metal carbene complexes contain a metal-carbon double bond, M=C. Therefore, the carbon atom adopts a sp^2 hybrid structure with a trigonal planar geometry and approximately 120° between each substituents. The shape of the molecular orbitals of carbenes enables binding interactions with the metal and dictates the overall geometry of the complex (Figure 9. A).[169] Two different representations of metal carbene are encountered, based on the free carbene state:

- *Singlet carbene*: Singlet carbenes are spin-paired, possessing a filled sp^2 orbital and an empty orthogonal p_z orbital. In this case, a strong carbon to metal donation (σ) predominates over a metal to carbon back-donation (π). As a consequence, the carbon atom tends to be positively charged. The CR_2 carbene ligand is considered as a $2e^-$ lone-pair donor (L ligand).

- *Triplet carbene:* On the other hand, triplet carbenes have two unpaired electrons distributed over the sp^2 and the p_z orbital. In this situation, a stronger π interaction between the metal and the carbene fragment occurs. Electrons will be transferred to a greater extent on the carbon atom, which will accommodate a partial negative charge. CR_2 is acting like a X_2-type ligand.

[166] See footnote 9 in W. von E. Doering, L. H. Knox, *J. Am. Chem. Soc.* **1956**, *78*, 4947.
[167] R. A. Moss, M. P. Doyle, in *Contemporary Carbene Chemistry*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2013**.
[168] With a major exception to NHC, see: S. P. Nolan, in *N-Heterocyclic Carbenes in Synthesis*; John Wiley, Weinheim, Chichester, **2006**.
[169] R. H. Crabtree, in *The Organometallic Chemistry of the Transition Metals*; Wiley, Hoboken, NJ, USA, **2014**, *11*, 290–316.

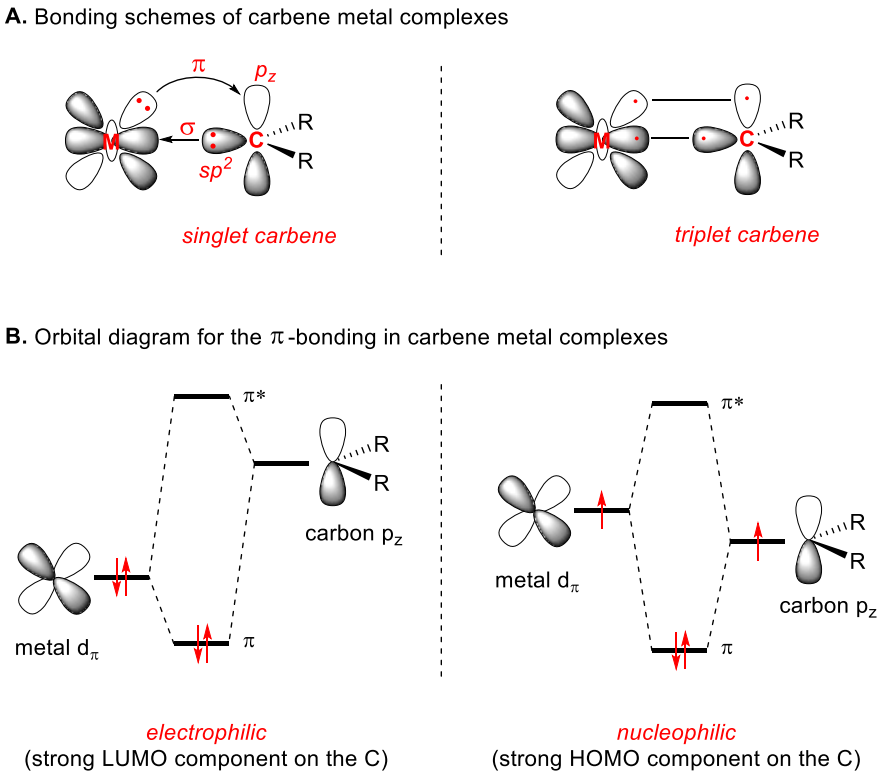


Figure 9. Bonding scheme of carbene metal complexes and detail of the M=CR_2 π-bond.

It is most important to remember that the reactivity of a metal carbene will mainly depend on the frontier molecular orbitals component of the M=CR_2 π-bond (Figure 9. B). The ability of the metal to "release" electrons into the empty p orbital of the carbon atom is therefore the main criteria and is modulated by the nature of the metal, as well as the spectator ligands associated to it. Originally, two classes of isolable carbene complexes were distinguished according to their reactivity patterns: *Fischer carbenes* with an electrophilic reactivity and related to the parent singlet carbenes, and *Schrock carbenes* being nucleophilic and related to triplet carbenes. Today, with the development of many classes of carbene complexes, especially associated to late transition metal catalysts and their use as transient intermediates, the Fischer/Schrock denomination has lost its justification. A rough reactivity trend is given bellow (Figure 10).

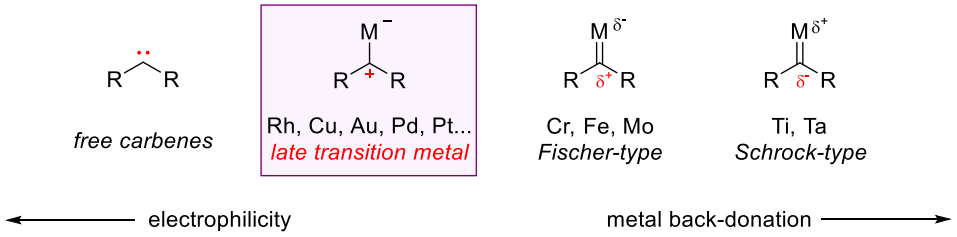


Figure 10. Reactivity trend of carbenes.

In the context of our work, we will now focus our attention on the highly electrophilic carbene complexes of late transition metals and not take into consideration the other classes. Late transition metal carbenes complexes have been studied by spectroscopy. Kodadek and co-workers investigated the formation and structure of carbene **2.102**, generated from [Rh^{III}(tpp)I] and ethyl diazoacetate at

-40 °C in CD_2Cl_2 (Figure 11. A).[170] First, the structure of **2.100** was supported by IR ($\nu_{N=N}$ = 2338 cm^{-1}) and NMR (J_{Rh-H} = 2.4 Hz). Above -20 °C, the carbenoid **2.100** evolved to the carbene complex **2.101**, which appears less stable than the iodo-adduct **2.102**. The first observation of a copper(I) carbene was accomplished by Straub and Hofmann, who studied the resonance signal at δ = 230 ppm of the carbene carbon atom of complex **2.104** by ^{13}C NMR spectroscopy (Figure 11. B).[171] The resonance signals arising from the diastereotopic *tert*-butyl groups indicates that the carbene plan is orthogonal to that of the iminophosphanamide ligand plan. Several others carbene complexes have been characterized by X-ray crystallography.[172] For example, Nishiyama and co-workers reported the preparation of dicarbonylcarbene complexes of ruthenium(III).[173] Single X-ray analysis of **2.105**, clearly indicated a metal-carbon double bond (1.88 Å) and a sp^2 configuration of the carbene carbon atom (Figure 11. C).

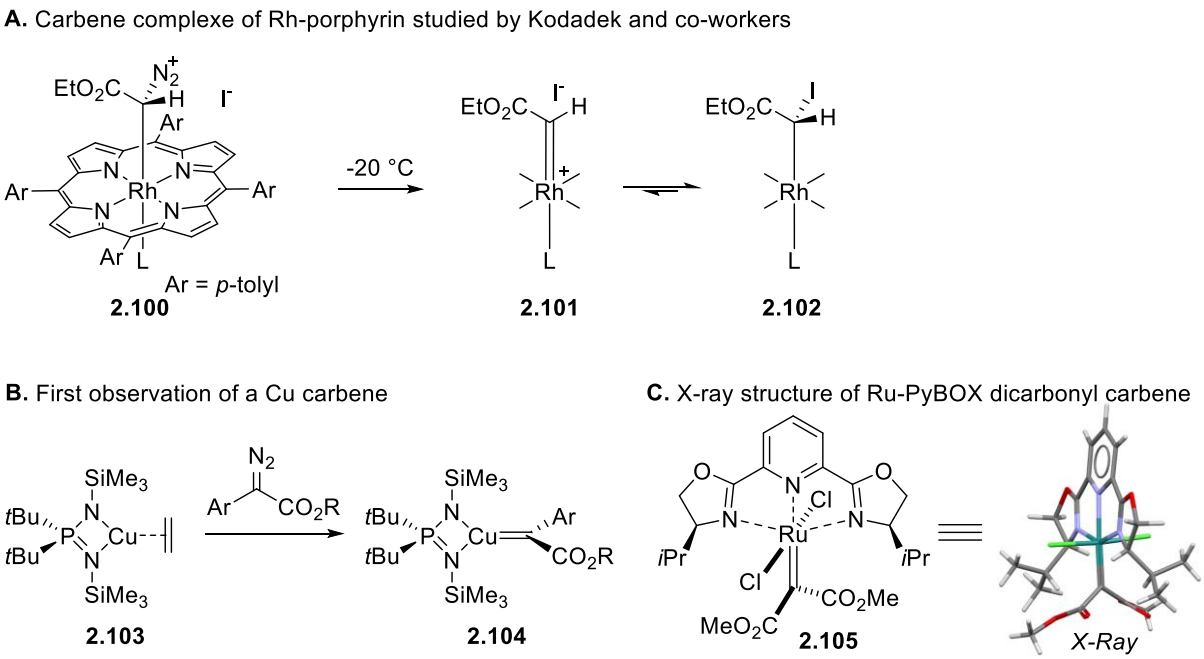


Figure 11. Carbene complexes of transition metals studied by NMR and X-Ray.

2.3.2. Metal-Catalyzed Transformations of Diazo Compounds

Diverse methods are available in the literature for the generation of metal carbenes, but the most common way employs diazo compounds as precursor (Scheme 26). Coordinately unsaturated transition metal complex **I** undergoes nucleophilic attack of the diazo compound. The required free coordination site might be available or generated by ligand dissociation. For this reason, Lewis bases often inhibit the reaction of metals with diazo compounds. The irreversible loss of nitrogen from the metal-associated diazo compound intermediate **II** results in the formation of the electrophilic metal

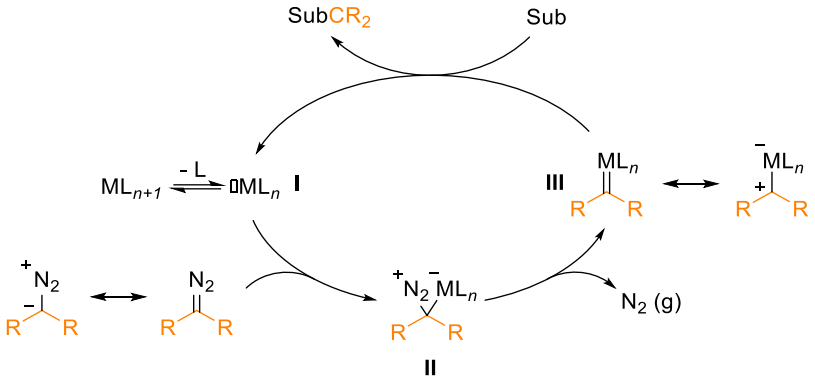
[170] a) J. L. Maxwell, K. C. Brown, D. W. Bartley, T. Kodadek, *Science* **1992**, *256*, 1544; b) D. W. Bartley, T. Kodadek, *J. Am. Chem. Soc.* **1993**, *115*, 1656.

[171] B. F. Straub, P. Hofmann, *Angew. Chem. Int. Ed.* **2001**, *40*, 1288.

[172] E. Galardon, P. L. Maux, L. Toupet, G. Simonneaux, *Organometallics* **1998**, *17*, 565; b) C.-M. Che, J.-S. Huang, F.-W. Lee, Y. Li, T.-S. Lai, H.-L. Kwong, P.-F. Teng, W.-S. Lee, W.-C. Lo, S.-M. Peng, Z.-Y. Zhou, *J. Am. Chem. Soc.* **2001**, *123*, 4119.

[173] H. Nishiyama, K. Aoki, H. Itoh, T. Iwamura, N. Sakata, O. Kurihara, Y. Motoyama, *Chem. Lett.* **1996**, *25*, 1071.

carbene **III**. Transfer of the carbene moiety to the incoming substrate releases the original metal catalyst **I**.

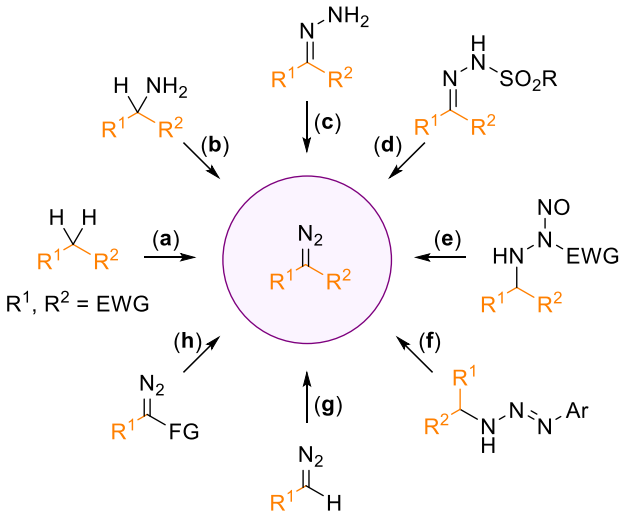


Scheme 26. Metal carbene formation from diazo compounds

An important feature of the process concerns the change in polarity of the carbenic carbon when the diazo is converted into the metal carbene. The nucleophilic attack of the metal carbene by another diazo molecule is a severe side reaction that lead to the formation of homo-dimer olefinic side products.

Diazo compounds are not directly obtained from natural sources, but are easily accessible *via* numerous synthetic routes.[174] The long-standing interest in the chemistry of diazo compounds have supplied a considerable number of effective and versatile synthetic methods for their preparation. Major synthetic routes are listed below (Scheme 27):

- Diazo-group transfer onto activated methylene (**a**)
- Diazotization of aliphatic amine (**b**)
- Oxidation of hydrazone (**c**)
- Basic treatment of sulfonylhydrazones (**d**)
- Cleavage of *N*-alkyl-*N*-nitroso compounds (**e**)
- Triazene fragmentation (rare) (**f**)
- Functionalization of diazomethyl (**g**)
- Modification of a diazo compound (**h**)



Scheme 27. Classical methods to access diazo compounds.

[174] G. Maas, *Angew. Chem. Int. Ed.* **2009**, *48*, 8186.

Diazo compounds may suffer from their lack of stability depending on their substitution pattern.[175] Diazomethane, the simplest diazo compound, is a highly sensitive and explosive gas and frequently replaced by safer trimethylsilyldiazomethane.[176] Electron-rich diazo compounds, such as diazoalkanes, are powerful reagents in organic syntheses but are often unstable and difficult to handle. Intensive investigations on their generation and utilization in continuous flow processes have received increasing attention these last years.[177] The so-called *stabilized* diazo compounds incorporate an electron-withdrawing group at the vicinal position. Ethyl diazoacetate (EDA) is the most commonly used diazo compound and is commercially available as a concentrated solution. It is not surprising that α-diazocarbonyl compounds have been the most studied class in transition metal catalyzed transformations.[178] More recently, stable aryldiazoacetates and vinyldiazoacetates, with a particular donor/acceptor substitution pattern have been recognized to have an enhanced selectivity and reactivity in several metal catalyzed transformations.[179] Finally, diazo ketoesters and diesters precursors are the most stable and have been widely used, even if harsher reaction conditions for dinitrogen extrusion are required. The corresponding metal carbenes have been subsequently classified by the terms *donor* and *acceptor* to specify the electron-donating or -withdrawing effects of the groups attached to the carbenic carbon (Figure 12).[180]

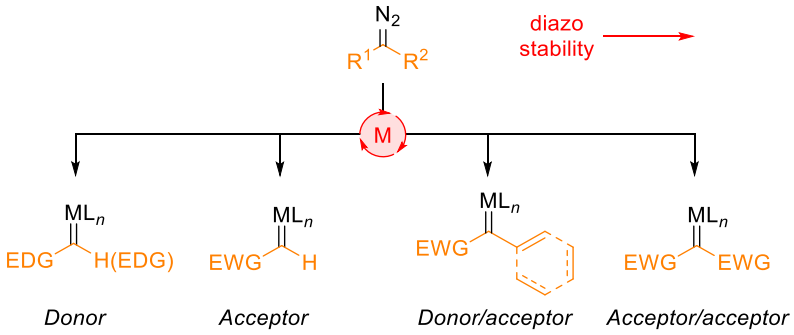


Figure 12. Range of metal carbenes and stability of the diazo precursors

Identifying sustainable and safer surrogates of diazo compounds is an interesting approach for the generation of metal carbenes.[181] Sulfonium[182] and iodonium ylides (**a**),[183] cyclopropenes (**b**),[184]

[175] S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller, J. A. Bull, *Org. Process Res. Dev.* **2020**, *24*, 67.

[176] For a recent *in situ* generation of CH_2N_2, see: B. Morandi, E. M. Carreira, *Science* **2012**, *335*, 1471.

[177] a) K. J. Hock, R. M. Koenigs, *Chem. Eur. J.* **2018**, *24*, 10571; b) E. M. D. Allouche, A. B. Charette, *Synthesis* **2019**, *51*, 3947; c) Y. Gao, J. Wang, *Chin. J. Org. Chem.* **2018**, *38*, 1275.

[178] A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981.

[179] a) K. Liao, S. Negretti, D. G. Musaev, J. Bacsa, H. M. L. Davies, *Nature* **2016**, *533*, 230; b) C. Werlé, R. Goddard, P. Philipps, C. Farès, A. Fürstner, *J. Am. Chem. Soc.* **2016**, *138*, 3797.

[180] H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417.

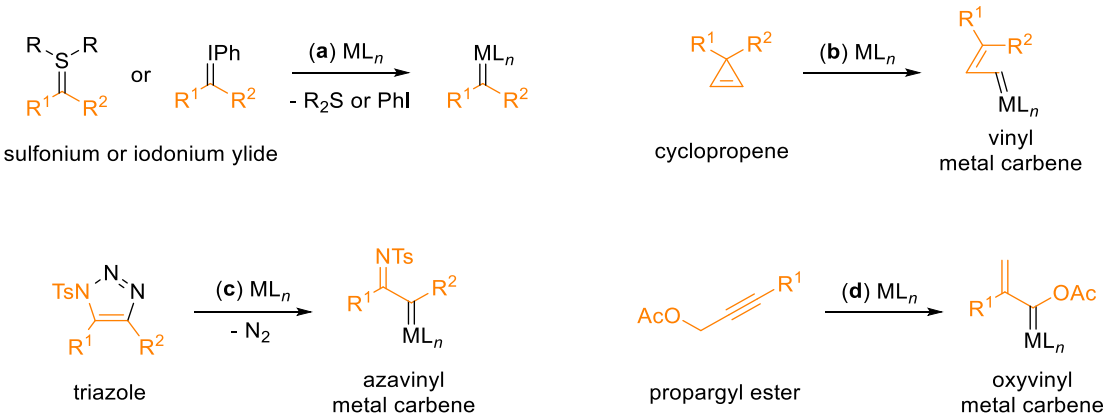
[181] M. Jia, S. Ma, *Angew. Chem. Int. Ed.* **2016**, *55*, 9134.

[182] J. D. Neuhaus, R. Oost, J. Merad, N. Maulide, *Top. Curr. Chem.* **2018**, *376*, 15, 1.

[183] P. Müller, *Acc. Chem. Res.* **2004**, *37*, 243.

[184] P. Li, X. Zhang, M. Shi, *Chem. Commun.* **2020**, *56*, 5457.

triazoles (**c**)[185] or propargylic esters (**d**)[186] are examples of convenient precursors to access functionalized metal carbenes (Scheme 28).



Scheme 28. Examples of non-diazo precursors of metal carbenes.

The close proximity of the transition metal to the carbene center allows the tuning of electronic and steric factors that can grant extraordinary levels of chemo-, regio- and enantioselectivity and can open new reactivity pathways. For this reason, metal carbene chemistry has been rapidly exploited in diverse transformations. The cyclopropanation of styrene with ethyl diazoacetate catalyzed by a chiral salicylaldiminato copper(II) complex was one of the very first catalytic asymmetric reaction reported.[187] Today, metal carbene intermediates are at the forefront of powerful chemical reactions catalyzed by engineered metalloenzymes.[188] Important transformations of metal carbenes generated from decomposition of diazo compounds include cyclopropanation (**a**),[189] C-H activation (**b**),[190] X-H (X = N, O, S, Si, etc.) bond insertions (**c**),[191] ylide formations with subsequent transformations (**d**),[192] and other reactions such as the Buchner ring expansion (**e**), the Wolff rearrangement (**f**), selective β-H elimination (**g**) or cross-diazo dimerization (**h**) (Scheme 29).[178]

[185] a) A. V. Gulevich, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2013**, *52*, 1371; b) B. Chattopadhyay, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2012**, *51*, 862; c) Y. Wang, Z. Wang, Y. Tang, *Chem. Rec.* **2020**, *20*, 1.

[186] a) R. Kazem Shiroodi, V. Gevorgyan, *Chem. Soc. Rev.* **2013**, *42*, 4991; b) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326.

[187] H. Nozaki, H. Takaya, S. Moriuti, R. Noyori, *Tetrahedron* **1968**, *24*, 3655.

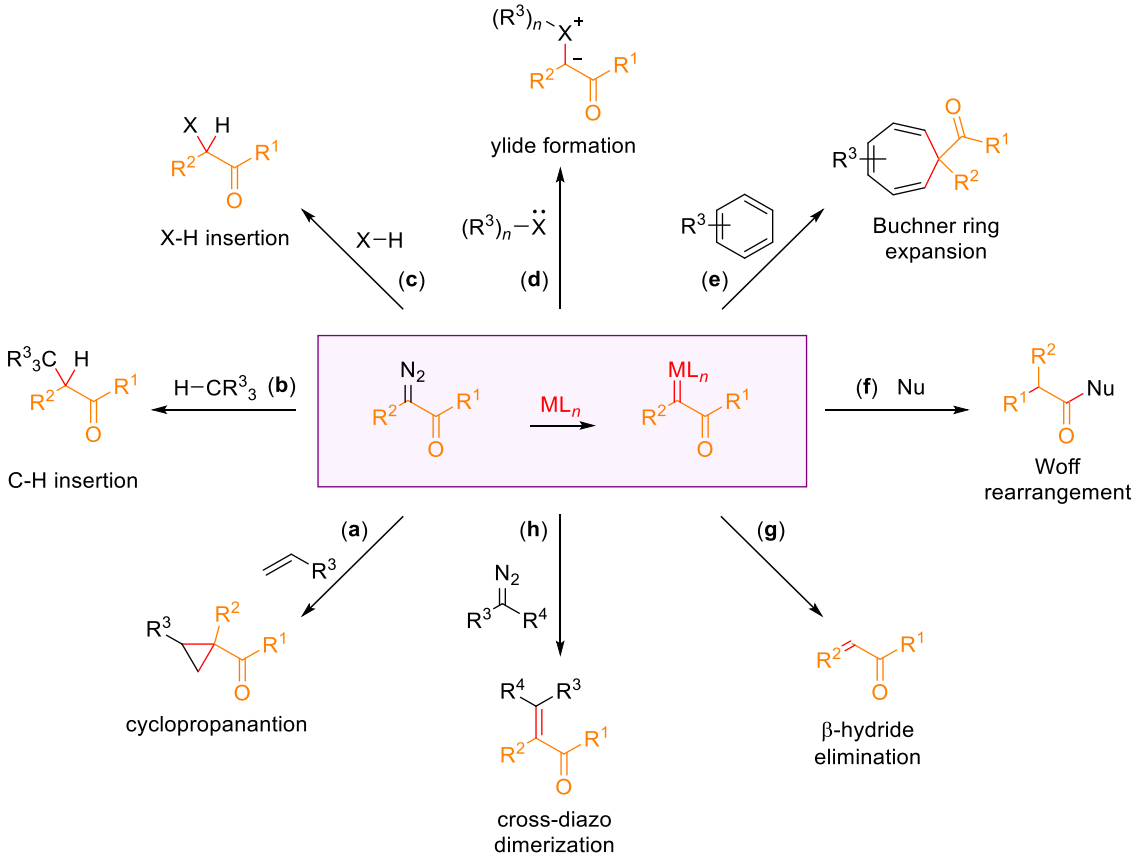
[188] a) K. Chen, F. H. Arnold, *Nat. Cat.* **2020**, *3*, 203; For 2018 Nobel lecture of F. H. Arnold, see: b) F. H. Arnold, *Angew. Chem. Int. Ed.* **2019**, *58*, 14420.

[189] A. Roy, S. P. Goswami, A. Sarkar, *Synth. Commun.* **2018**, *48*, 2003.

[190] M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704; b) B. Wang, D. Qiu, Y. Zhang, J. Wang, *Beilstein J. Org. Chem.* **2016**, *12*, 796.

[191] a) D. Gillingham, N. Fei, *Chem. Soc. Rev.* **2013**, *42*, 4918; b) S.-F. Zhu, Q.-L. Zhou, *Acc. Chem. Res.* **2012**, *45*, 1365.

[192] D. M. Hodgson, F. Y. T. M. Pierard, P. A. Stupple, *Chem. Soc. Rev.* **2001**, *30*, 50; b) A. Padwa, *Helv. Chim. Acta* **2005**, *88*, 1357.



Scheme 29. Overview of the metal-carbene transformation of α-diazocarbonyl compounds.

2.3.3. Metal-Catalyzed Difunctionalization of Diazo Compounds

The direct introduction of two different functional groups to the carbon center of the diazo compound, namely *gem*-difunctionalization, is a powerful process for accessing elaborated chemical structures from simple starting materials (Scheme 30). Indeed, carbenes (and carbenoids) are one of the rare species offering the possibility of unsymmetrical double functionalization at one carbon center in a single operation. The main strategies to realize such a multicomponent reaction involve metal carbene/onium ylide formation or metal carbene/migratory insertion. Non-carbene pathways (radical-involved process[193] or *via* procarbonium ions intermediates[194]) have been exploited to a lesser extent.

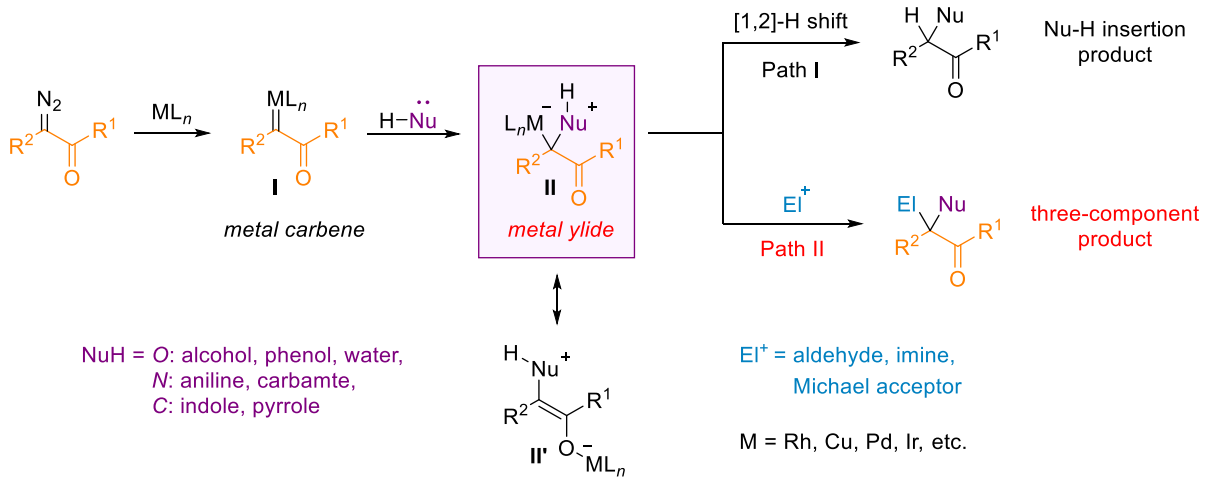
Scheme 30. General equation for metal-catalyzed difunctionalization of diazo compounds.

[193] Y. Zheng, R. Bian, X. Zhang, R. Yao, L. Qiu, X. Bao, X. Xu, *Eur. J. Org. Chem.* **2016**, *2016*, 3872.

[194] a) G. Chen, J. Song, Y. Yu, X. Luo, C. Li, X. Huang, *Chem. Sci.* **2016**, *7*, 1786; b) H. Li, X. Shangguan, Z. Zhang, S. Huang, Y. Zhang, J. Wang, *Org. Lett.* **2014**, *16*, 448; c) H. Mao, Z. Tang, H. Hu, Y. Cheng, W.-H. Zheng, C. Zhu, *Chem. Commun*. **2014**, *50*, 9773.

2.3.3.1. Multicomponent Reactions through Onium Ylide Intermediates

Carbene insertion reactions into X-H bonds (X = N, O,…) are well established transformations, although the development of new catalytic methods is continuing.[195] In such reactions, a protic nucleophile (Nu-H) adds to metal carbene **I** to generate a metal-onium ylide **II**, which undergoes intramolecular [1,2]-H shift to furnish the corresponding insertion product (Scheme 31. Path I).



Scheme 31. Three-component reactions based on trapping of ylide intermediates.

In other circumstances, the nucleophilic metal-onium ylide intermediate **II** can be trapped in the presence of a matched electrophile (El^+) to create a new bond, resulting in a three-component reaction (Scheme 31. Path II). In this case, stabilization of the active ylide intermediate by mesomeric effect is essential to delay the proton transfer and favor the electrophilic trapping. The Hu group has pioneered this new type of difunctionalization reactions that maximizes molecular complexity.[196] Such a process has been applied to trap metal-oxonium and -ammonium ylides with several electrophiles partners such as imines,[196,197] carbonyl compounds,[198] Michael acceptors[199] or azodicarboxylates,[200] and after that, asymmetric three-component reactions using various chiral catalytic systems were

[195] Selected examples for N-H insertion, a) M.-L. Li, J.-H. Yu, Y.-H. Li, S.-F. Zhu, Q.-L. Zhou, *Science* **2019**, *366*, 990; b) S.-F. Zhu, B. Xu, G.-P. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2012**, *134*, 436; c) Y. Zhu, X. Liu, S. Dong, Y. Zhou, W. Li, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2014**, *53*, 1636; d) V. Arredondo, S. C. Hiew, E. S. Gutman, I. D. U. A. Premachandra, D. L. Van Vranken, *Angew. Chem. Int. Ed.* **2017**, *56*, 4156; For O-H insertion,: e) X.-L. Xie, S.-F. Zhu, J.-X. Guo, Y. Cai, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 1636; f) F. Tan, X. Liu, X. Hao, Y. Tang, L. Lin, X. Feng, *ACS Catal.* **2016**, *6*, 6930; For S-H insertion, g) Y.-Z. Zhang, S.-F. Zhu, Y. Cai, H.-X. Mao, Q.-L. Zhou, *Chem. Commun.* **2009**, 5362.

[196] a) Y. Wang, Y. Zhu, Z. Chen, A. Mi, W. Hu, M. P. Doyle, *Org. Lett.* **2003**, *5*, 3923; For a review, see: b) X. Guo, W. Hu, *Acc. Chem. Res.* **2013**, *46*, 2427.

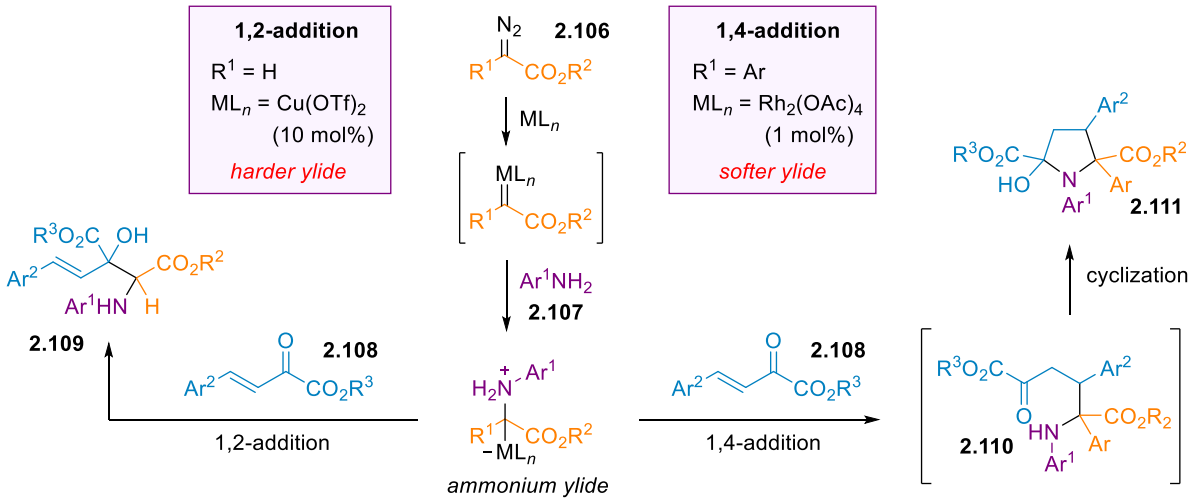
[197] Selected examples, a) Z. Kang, Y. Wang, D. Zhang, R. Wu, X. Xu, W. Hu, *J. Am. Chem. Soc.* **2019**, *141*, 1473; b) H. Huang, X. Guo, W. Hu, *Angew. Chem. Int. Ed.* **2007**, *46*, 1337.

[198] Selected examples, a) Y. Wang, Z. Chen, A. Mi, W. Hu, *Chem. Commun.* **2004**, *0*, 2486; b) C.-D. Lu, H. Liu, Z.-Y. Chen, W.-H. Hu, A.-Q. Mi, *Org. Lett.* **2005**, *7*, 83; c) X. Guo, H. Huang, L. Yang, W. Hu, *Org. Lett.* **2007**, *9*, 4721.

[199] Selected examples, a) Y. Zhu, C. Zhai, L. Yang, W. Hu, *Eur. J. Org. Chem.* **2011**, *2011*, 1113; b) Y. Zhu, C. Zhai, Y. Yue, L. Yang, W. Hu, *Chem. Commun.* **2009**, 1362; c) X. Han, M. Gan, H. Qiu, J. Ji, X. Zhang, L. Jiang, W. Hu, *Synlett* **2011**, *2011*, 1717.

[200] H. Huang, Y. Wang, Z. Chen, W. Hu, *Adv. Synth. Catal.* **2005**, *347*, 531.

developed.[201] Several transition metal catalysts have been successful, but rhodium(II) largely predominated. Copper(I) catalysts have been frequently used as well. The realization of this trapping process also supported the existence of protic metal ylide intermediates and the stepwise pathways of O-H, N-H and C-H insertions that were under debate until then.[202] In contrast, the insertions of apolar nucleophiles (e.g. C-H alkane or Si-H silane) are concerted, without such defined ylide intermediates, and are not applicable in this strategy.[203] As a representative example, Hu and co-workers developed a three-component reaction of diazoacetates **2.106** with anilines **2.107** and α,β-unsaturated carbonyl compounds **2.108** (Scheme 32).[199a] The regioselectivity (1,2-addition vs 1,4-addition) of the trapping step is controlled on the basis of the HSAB properties of the metal ylide intermediate. The harder ammonium ylide generated from an acceptor copper carbene selectively undergoes 1,2-addition on the α-keto ester to give the corresponding product **2.109**, whereas a softer ylide intermediate obtained from a donor/acceptor rhodium carbene adds in a 1,4-fashion to the Michael acceptor to furnish pyrrolidine derivatives **2.111** after cyclization of **2.110**.



Scheme 32. Regioselective three-component reaction governed by HSAB properties of the metal ylide.

2.3.3.2. Multicomponent Reactions through Migratory Insertions

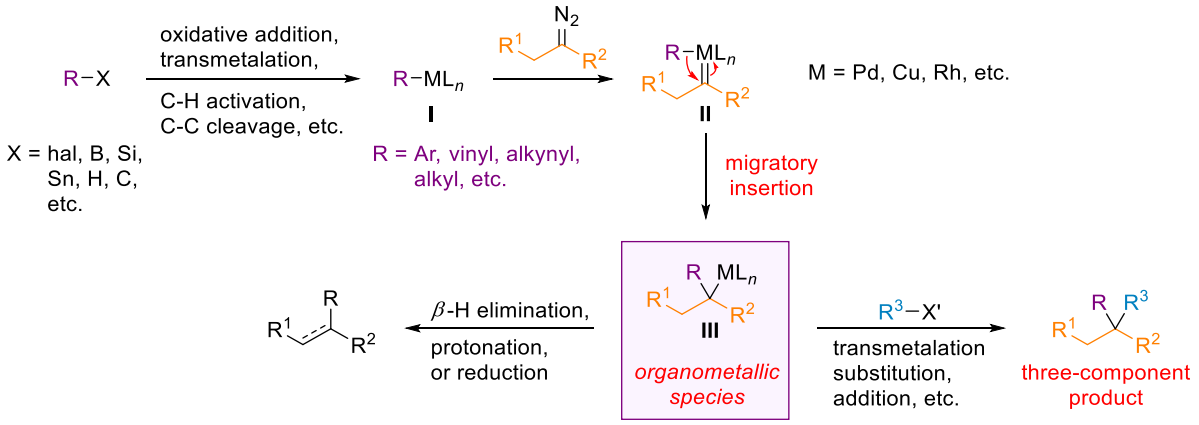
Another important tool to realize a carbene difunctionalization takes advantage of the migratory insertion aptitude of metal carbenes (Scheme 33).[204] When a suitable ligand (R) is coordinated to the metal carbene **II**, migratory insertion of the ligand to the unsaturated carbenic carbon produces new metal complex **III**. This process is often an energetically favorable event by creation of a new carbon-carbon bond. Trapping of the organometallic species **III** with a third component in a cascade reaction results in the difunctionalization.

[201] Selected examples, a) H. Qiu, M. Li, L.-Q. Jiang, F.-P. Lv, L. Zan, C.-W. Zhai, M. P. Doyle, W.-H. Hu, *Nat. Chem.* **2012**, *4*, 733; b) D. Zhang, H. Qiu, L. Jiang, F. Lv, C. Ma, W. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 13356; c) X. Zhang, H. Huang, X. Guo, X. Guan, L. Yang, W. Hu, *Angew. Chem. Int. Ed.* **2008**, *47*, 6647; d) X.-Y. Guan, L.-P. Yang, W. Hu, *Angew. Chem. Int. Ed.* **2010**, *49*, 2190; e) X. Ma, J. Jiang, S. Lv, W. Yao, Y. Yang, S. Liu, F. Xia, W. Hu, *Angew. Chem. Int. Ed.* **2014**, *53*, 13136; f) J. Che, L. Niu, S. Jia, D. Xing, W. Hu, *Nat. Commun.* **2020**, *11*, 1511; For a recent personal account, see: g) D. Zhang, W. Hu, *Chem. Rec.* **2017**, *17*, 739.

[202] J. Xue, H. L. Luk, M. S. Platz, *J. Am. Chem. Soc.* **2011**, *133*, 1763 and references therein.

[203] E. Nakamura, N. Yoshikai, M. Yamanaka, *J. Am. Chem. Soc.* **2002**, *124*, 7181.

[204] For a recent review, see: Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* **2017**, *117*, 13810.



Scheme 33. Three-component reactions based on carbene migratory insertion.

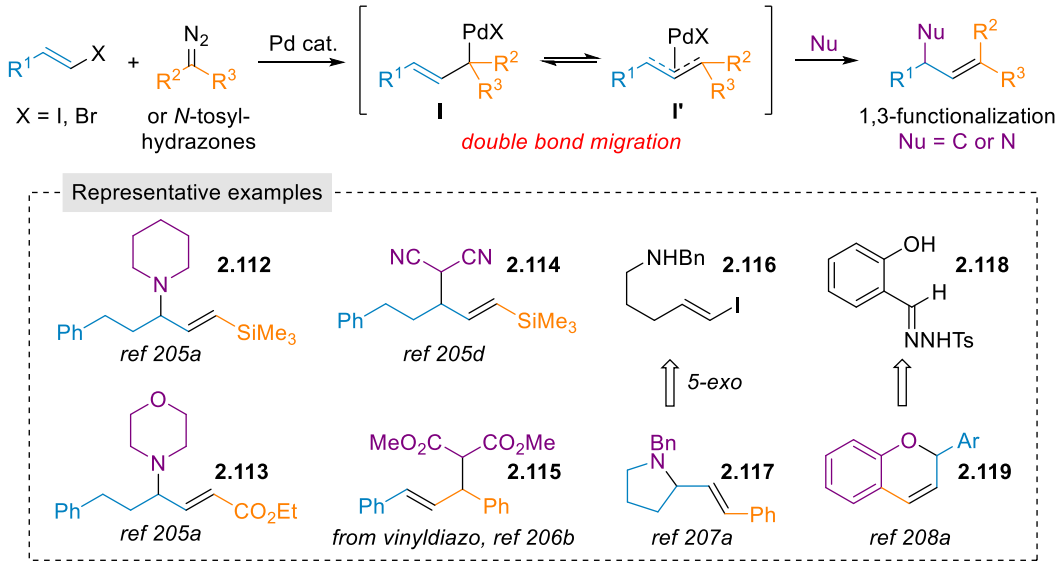
The early work of Van Vranken is particularly relevant within the context of this thesis work. Migratory insertion of a vinyl ligand into a palladium carbene generates a π-allyl palladium species **I** that can be easily trapped by an external nucleophile to afford three-component products (Scheme 34). This cascade process was successful with various diazo compounds (or generated *in situ* from *N*-tosylhydrazones), *N*- and *C*-nucleophiles and functionalized vinyl halides as electrophilic partners, for the formation of allylamines like **2.112** or **2.113** and dicyano vinylsilane **2.114**.[205] The inevitable migration of the double bond through a η^3-allyl palladium intermediate **I'**, resulted in a 1,3-relationship between the nucleophile and the vinyl group. Liang and co-workers alternatively produced π-allyl palladium intermediates from vinyl carbene precursors and utilized arylhalides as coupling partners for the formation of **2.115**.[206] The reaction was extended to cyclisation sequences with substrates containing both electrophilic and nucleophilic ends such as amine-tethered vinyl iodide **2.116**.[207] However, oxy-vinylation of diazo compounds are scarce. The reports of the groups of Wang and Liu for the coupling between phenol-substituted-*N*-tosylhydrazones **2.118** and bromostyrenes for the construction of 2*H*-chromenes **2.119** are the only existing examples.[208]

[205] With *N*-nucleophiles, a) S. K. J. Devine, D. L. Van Vranken, *Org. Lett.* **2007**, *9*, 2047; b) R. Kudirka, S. K. J. Devine, C. S. Adams, D. L. Van Vranken, *Angew. Chem. Int. Ed.* **2009**, *48*, 3677; c) I. D. U. A. Premachandra, T. A. Nguyen, C. Shen, E. S. Gutman, D. L. Van Vranken, *Org. Lett.* **2015**, *17*, 5464; with *C*-nucleophiles, d) S. K. J. Devine, D. L. Van Vranken, *Org. Lett.* **2008**, *10*, 1909; P.-X. Zhou, Y.-Y. Ye, Y.-M. Liang, *Org. Lett.* **2013**, *15*, 5080.

[206] a) P.-X. Zhou, Y.-Y. Ye, L.-B. Zhao, J.-Y. Hou, X. Kang, D.-Q. Chen, Q. Tang, J.-Y. Zhang, Q.-X. Huang, L. Zheng, J.-W. Ma, P.-F. Xu, Y.-M. Liang, *Chem. Eur. J.* **2014**, *20*, 16093; b) Y.-Y. Ye, P.-X. Zhou, J.-Y. Luo, M.-J. Zhong, Y.-M. Liang, *Chem. Commun.* **2013**, *49*, 10190.

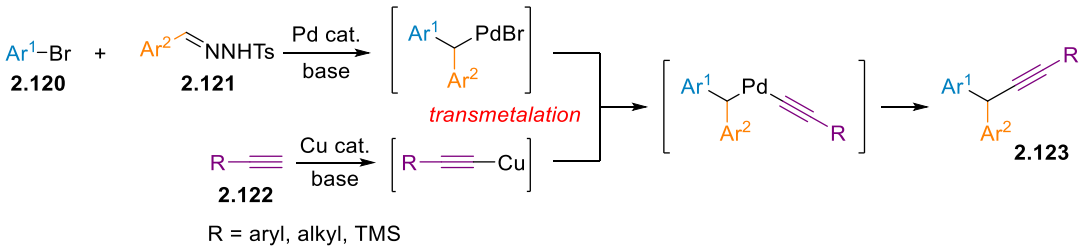
[207] Selected examples, a) A. Khanna, C. Maung, K. R. Johnson, T. T. Luong, D. L. Van Vranken, *Org. Lett.* **2012**, *14*, 3233; b) P.-X. Zhou, Z.-Z. Zhou, Z.-S. Chen, Y.-Y. Ye, L.-B. Zhao, Y.-F. Yang, X.-F. Xia, J.-Y. Luo, Y.-M. Liang, *Chem. Commun.* **2013**, *49*, 561; c) E. S. Gutman, V. Arredondo, D. L. Van Vranken, *Org. Lett.* **2014**, *16*, 5498.

[208] Only two cyclization strategies with phenols have been reported, a) Y. Xia, Y. Xia, Y. Zhang, J. Wang, *Org. Biomol. Chem.* **2014**, *12*, 9333; b) X. S. Shang, N. T. Li, H. X. Siyang, P. N. Liu, *J. Org. Chem.* **2015**, *80*, 4808.



Scheme 34. Vinylation of diazo compounds by nucleophilic trapping of π-allyl palladium intermediates.

Benzyl palladium species generated *via* carbene migratory insertion may also participate in three-component reactions, when β-hydride elimination is restricted. Several intramolecular carbopalladations of olefins exploiting Pd-catalyzed carbene migratory insertion have been described.[209] However, true three-component reactions involving intermolecular transmetalation of the benzyl palladium intermediate are limited. This elegant approach is more challenging due to the competing direct coupling of the electrophile and the organometallic reagent. The group of Van Vranken found that the combination of aryl iodides, $TMSCHN_2$, and tributylphenyltin under palladium catalysis could afford the desired three-component product but in very low yields.[210] In 2010, the Wang group reported a successful difunctionalization of aryl *N*-tosylhydrazones **2.121** with aryl bromides **2.120** and terminal alkynes **2.122**, providing a convergent synthetic method to access benzhydryl acetylene derivatives **2.123** (Scheme 35).[211] In this case, the catalytic concentration of the active organometallic copper acetylide might be important to favor the formation of the palladium carbene intermediate over the Sonogashira side reaction.



Scheme 35. Aryl-alkynylation of carbenes *via* Pd-benzyl intermediates reported by Wang.

[209] a) R. Kudirka, D. L. Van Vranken, *J. Org. Chem.* **2008**, *73*, 3585; b) D. Arunprasath, P. Muthupandi, G. Sekar, *Org. Lett.* **2015**, *17*, 5448; c) M. Paraja, C. Valdés, *Chem. Commun.* **2016**, *52*, 6312; d) M. Paraja, M. Carmen Pérez-Aguilar, C. Valdés, *Chem. Commun.* **2015**, *51*, 16241.

[210] K. L. Greenman, D. S. Carter, D. L. Van Vranken, *Tetrahedron* **2001**, *57*, 5219.

[211] L. Zhou, F. Ye, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 13590.

Similar to palladium, copper(I) carbene migratory insertion occurs to generate a new organocopper intermediate that can further react. On the other hand, Cu(I) catalysts generally perform under redox neutral conditions, at the difference of the Pd(0)/Pd(II) manifold, and have the advantage to circumvent β-H elimination. The transfer of terminal alkynes into diazo compounds has been particularly successful taking advantage of the easy formation of copper acetylide species. Numerous syntheses of functionalized internal alkynes (or allenes *via* alkyne isomerization) have been reported, with protodemetalation often being the terminal step of the catalytic cycle.[212] Heterocycles and arenes bearing acidic proton could be functionalized in a similar way.[213] Apart from direct reprotonation, trapping strategies with several compatible electrophiles were developed, notably by Wang and co-workers. A Cu-catalyzed three-component reaction between α-diazocarbonyl compounds **2.106**, ethynyltriisopropylsilane (**2.124**) and alkyl halides **2.125** was efficient to rapidly access complex propargyl esters **2.126** containing all-carbon quaternary centers (Scheme 36. A).[214] Concerning the mechanism of the reaction, the authors proposed the formation of propargyl copper intermediate **IV**, obtained after carbene migratory insertion of intermediate **III**, which is then isomerized to the corresponding Cu-enolate **V**. Cation exchange with the base afforded a more nucleophilic enolate **VI** which is then trapped by electrophile **2.125** to give final product **2.126**. The utilization of aldehydes as electrophiles resulted in the formation of versatile enyne products **2.128** with complete *Z*-selectivity, after a dehydration reaction (Scheme 36. B).[215] Trapping of copper allene intermediates has also been reported.[216]

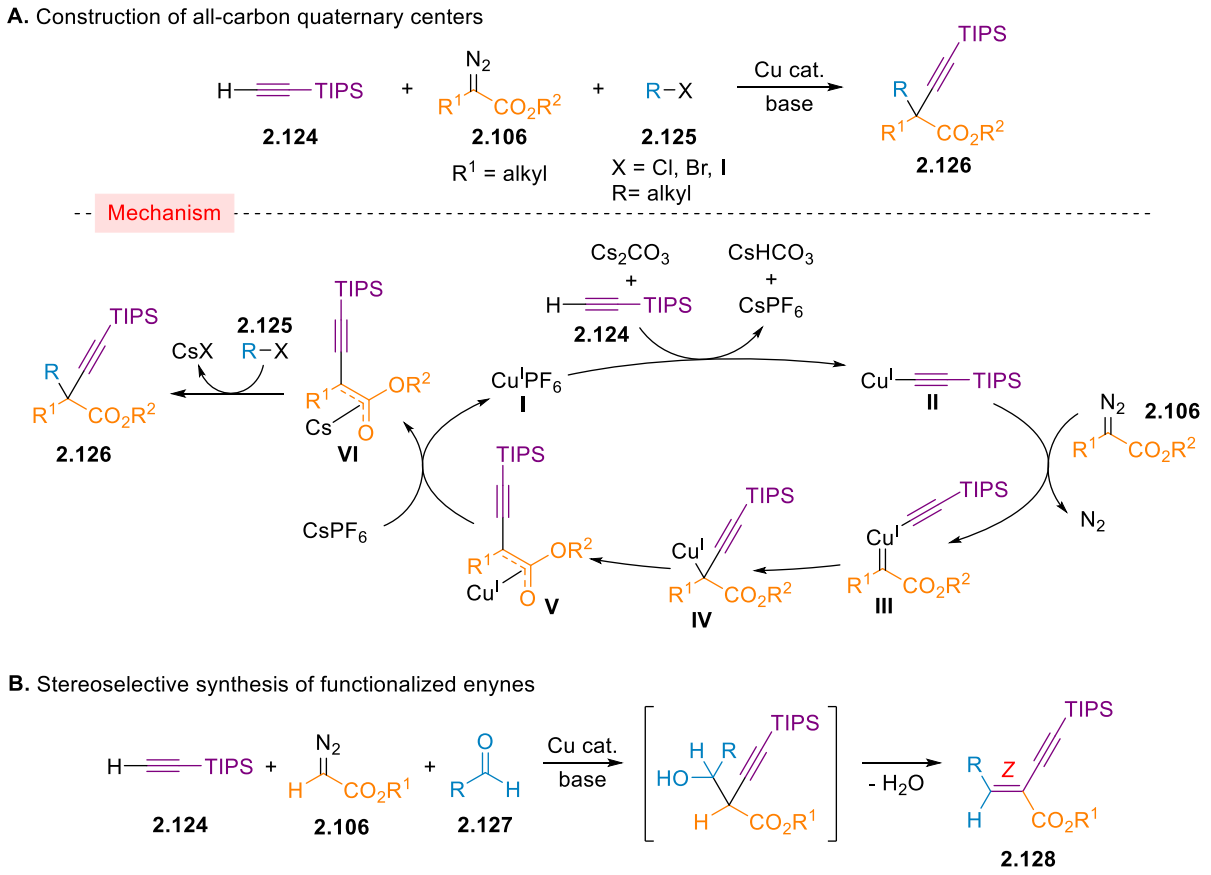
[212] Selected examples, a) A. Suárez, G. C. Fu, *Angew. Chem. Int. Ed.* **2004**, *43*, 3580; b) F. Ye, X. Ma, Q. Xiao, H. Li, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 5742; c) C.-B. Liu, W. Meng, F. Li, S. Wang, J. Nie, J.-A. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 6227; d) M. Hassink, X. Liu, J. M. Fox, *Org. Lett.* **2011**, *13*, 2388; e) F. Ye, C. Wang, X. Ma, M. L. Hossain, Y. Xia, Y. Zhang, J. Wang, *J. Org. Chem.* **2015**, *80*, 647; f) W.-D. Chu, L. Zhang, Z. Zhang, Q. Zhou, F. Mo, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2016**, *138*, 14558.

[213] Selected examples, a) X. Zhao, G. Wu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 3296; b) S. Xu, G. Wu, F. Ye, X. Wang, H. Li, X. Zhao, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 4669; c) A. Biswas, U. Karmakar, A. Pal, R. Samanta, *Chem. Eur. J.* **2016**, *22*, 13826.

[214] C. Wang, F. Ye, C. Wu, Y. Zhang, J. Wang, *J. Org. Chem.* **2015**, *80*, 8748.

[215] a) C. Wu, Z. Liu, Z. Zhang, F. Ye, G. Deng, Y. Zhang, J. Wang, *Adv. Synth. Catal.* **2016**, *358*, 2480; b) Y. Zhou, F. Ye, Q. Zhou, Y. Zhang, J. Wang, *Org. Lett.* **2016**, *18*, 2024.

[216] F. Ye, M. L. Hossain, Y. Xu, X. Ma, Q. Xiao, Y. Zhang, J. Wang, *Chem. Asian J.* **2013**, *8*, 1404.



Scheme 36. Three-component reactions employing Cu-acetylides/carbene migratory insertions.

Rhodium complexes have been used as catalysts in carbene migratory insertion/difunctionalization cascades owning to their exceptional ability of transmetalation with organoboron compounds. In 2011, the Yu group reported the first example of Rh(I)-catalyzed carbene coupling reaction by using α-diazoesters, arylboronates, and alkyl halides as substrates.[217] Later, the same group developed a Rh(III)-catalyzed three-component reaction of diazo diesters, arylboronic acids, and *N*-chlorosuccinimide, providing a facile route for the synthesis of α-aryl-α-chloro 1,3-dicarbonyl compounds.[218] Other sporadic examples of difunctionalization of diazo compounds with different transition metal catalysts have been achieved.[219]

[217] Y.-T. Tsoi, Z. Zhou, W.-Y. Yu, *Org. Lett.* **2011**, *13*, 5370.

[218] F.-N. Ng, Y.-F. Lau, Z. Zhou, W.-Y. Yu, *Org. Lett.* **2015**, *17*, 1676.

[219] a) J. Huang, L. Li, H. Chen, T. Xiao, Y. He, L. Zhou, *Org. Chem. Front.* **2017**, *4*, 529; b) A. J. Wommack, J. S. Kingsbury, *Tetrahedron Lett.* **2014**, *55*, 3163.

2.4. Functionalization of Diazo Compounds with Hypervalent Iodine Reagents

Hypervalent iodine(III) reagents and diazo compounds have played a critical role in many organic transformations. On the one hand, electrophilic hypervalent iodine reagents enable a practical transfer of various valuable functional groups into target molecules, often associated with late transition metal catalysis. On the other hand, metal carbenes obtained from diazo decomposition have been recognized as advantageous C1 synthons with the possibility to introduce two new functionalities on the same carbon atom in one event. The intermolecular combination of diazo compounds and hypervalent iodine reagents is a research concept attracting significant attention in recent years.[220]

2.4.1. Metal-Free Reactions

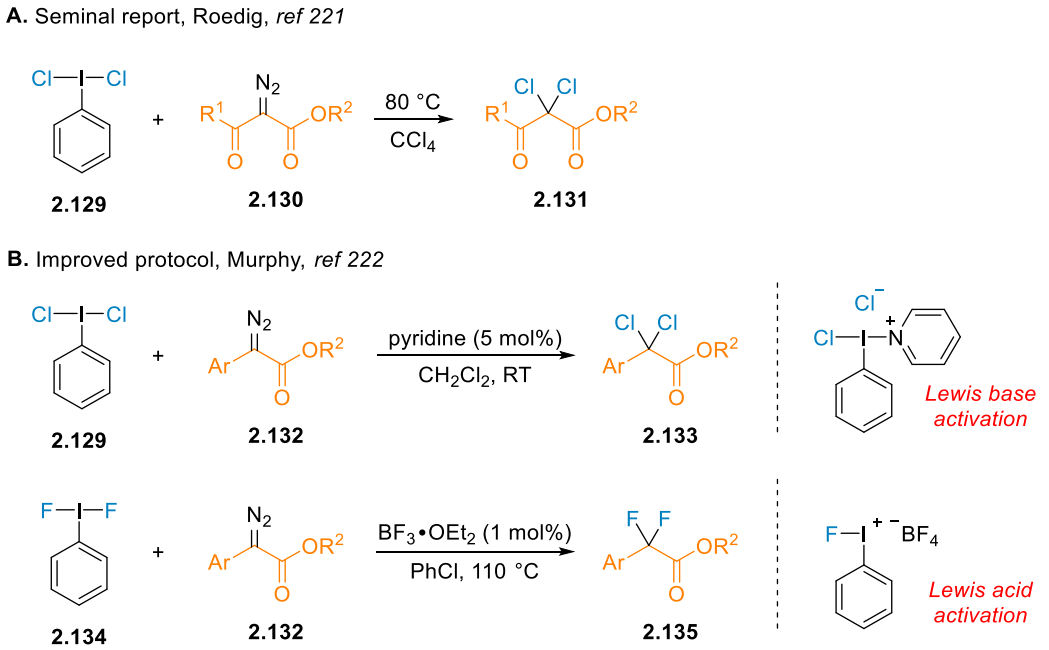
The very first functionalization of diazo compounds with hypervalent iodine reagents was reported as early as 1964 by Roedig and co-workers.[221] In this case, the combination of iodobenzene dichloride ($PhICl_2$, **2.129**) with diazo ketoesters **2.130** at 80 °C resulted in a geminal dichloration reaction in moderate yield (Scheme 37. A). This reaction represents the first example where both ligands of the iodine(III) reagent are delivered into the final product **2.131**. The Murphy research group recently revisited this transformation (Scheme 37. B). The catalytic activation of the aryl-λ^3-iodane species with a Lewis base promoted the formation of a non-symmetrical iodonium salt. This species was more reactive towards the nucleophilic attack of the diazo compound. With milder reaction conditions established, the reaction scope was extended to aryldiazoesters **2.132**, and a *gem*-difluorination protocol was developed using Lewis acid catalysis.[222] The groups of Gouverneur and Wang reported similar outcomes by using $BF_3{\bullet}OEt_2$ to achieve the *gem*-difluorination of trifluoromethyl- and phosphonate-substituted diazo compounds respectively.[223]

[220] For a recent review, see: R. Zhao, L. Shi, *Angew. Chem. Int. Ed.* **2020**, *59*, 12282.

[221] A. Roedig, H. Aman, E. Fahr, *Liebigs Ann.* **1964**, *675*, 47.

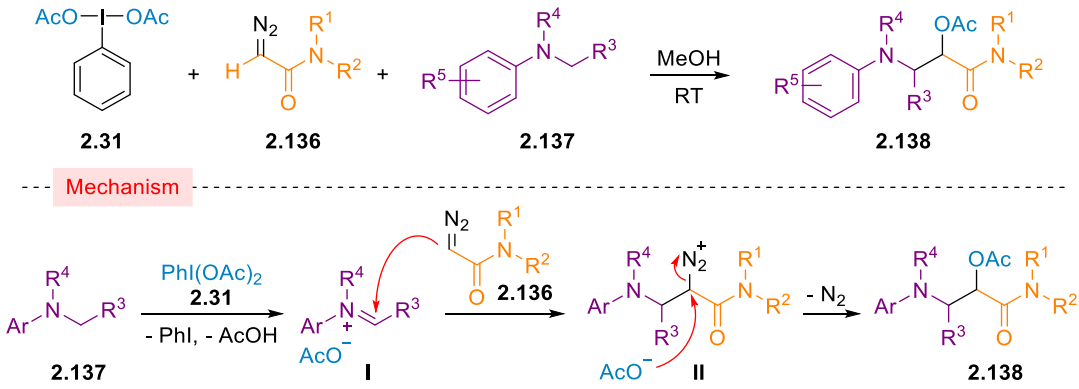
[222] a) J. Tao, R. Tran, G. K. Murphy, *J. Am. Chem. Soc.* **2013**, *135*, 16312; b) G. K. Murphy, F. Z. Abbas, A. V. Poulton, *Adv. Synth. Catal.* **2014**, *356*, 2919; c) G. S. Sinclair, R. Tran, J. Tao, W. S. Hopkins, G. K. Murphy, *Eur. J. Org. Chem.* **2016**, *2016*, 4603; d) Z. Zhao, K. G. Kulkarni, G. K. Murphy, *Adv. Synth. Catal.* **2017**, *359*, 2222.

[223] a) E. Emer, J. Twilton, M. Tredwell, S. Calderwood, T. L. Collier, B. Liégault, M. Taillefer, V. Gouverneur, *Org. Lett.* **2014**, *16*, 6004; b) Y. Zhou, Y. Zhang, J. Wang, *Org. Biomol. Chem.* **2016**, *14*, 10444.



Scheme 37. Geminal dihalogenation of carbonyl compounds.

In 2018, Studer and co-workers disclosed a simple method for the difunctionalization of diazoamides **2.136** with dialkyl anilines **2.137** and PIDA (**2.31**) to provide α-acetoxy-β-amino amides **2.138** (Scheme 38).[224] In this metal-free three-component reaction, PIDA (**2.31**) plays the dual role of oxidant and acetoxy transfer reagent. The proposed mechanism involves iminium ion **I**, formed after amine single-electron transfer (SET) oxidation and subsequent deprotonation by PIDA. Combination of iminium **I** with diazo compound **2.136** and displacement of nitrogen in diazonium **II** by nucleophilic attack of the acetate anion results in the final product.

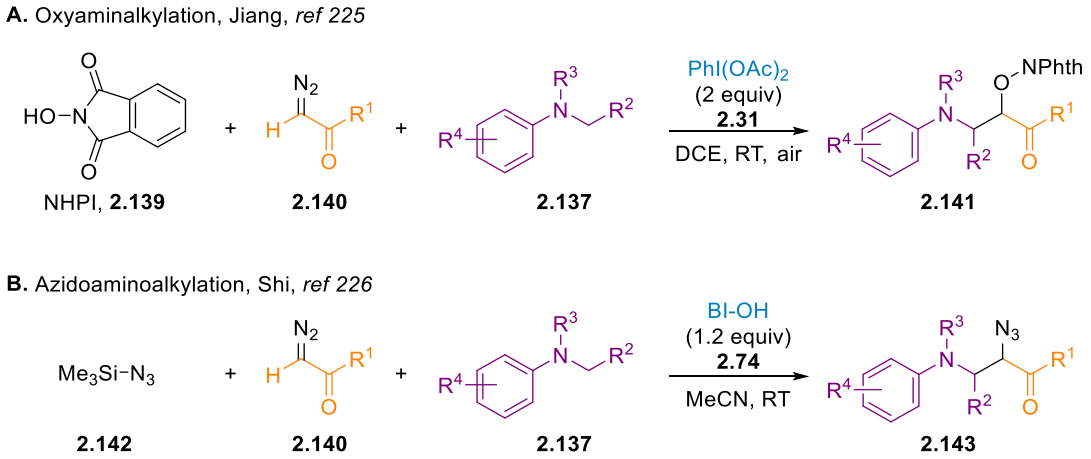


Scheme 38. Three-component reaction for the acetoxyaminoalkylation of diazo amides.

A comparable carbo-oxygenation of diazoketone substrates **2.140** with amine **2.137**, *N*-hydroxyphthalimide (NHPI, **2.139**) and PIDA (**2.31**) to generate α-oxy-β-amino ketones **2.141** was developed by Jiang and co-workers (Scheme 39. A).[225] However, the authors proposed a different reaction mechanism involving radical intermediates. Another similar methodology has been developed by Shi for the *gem*-difunctionalization of diazoketone compounds **2.140** with trimethylsilyl azide

[224] N. Döben, H. Yan, M. Kischkewitz, J. Mao, A. Studer, *Org. Lett.* **2018**, *20*, 7933.
[225] N.-N. Wang, W.-J. Hao, T.-S. Zhang, G. Li, Y.-N. Wu, S.-J. Tu, B. Jiang, *Chem. Commun.* **2016**, *52*, 5144.

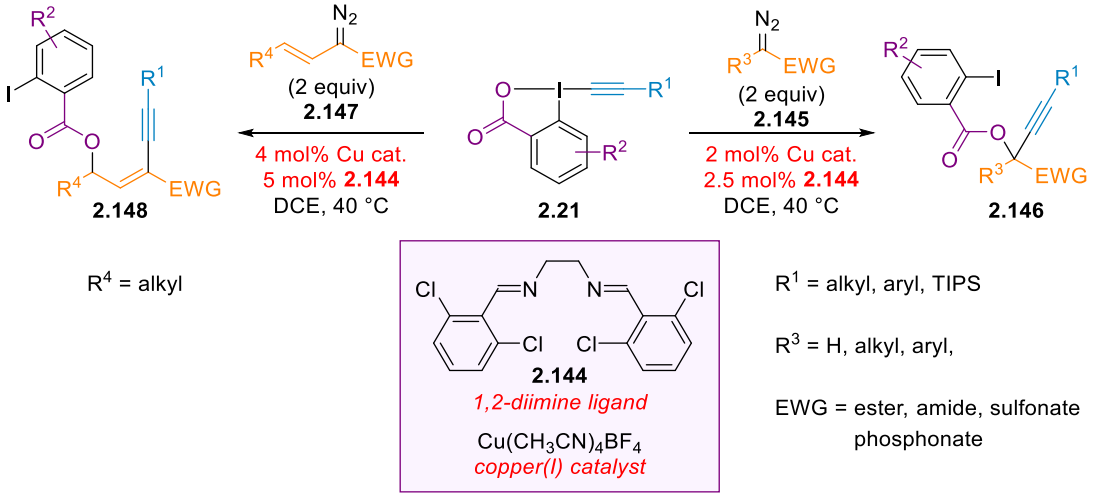
(**2.142**) and amine **2.137**, and utilizing hydroxybenziodoxolone (HO-BX, **2.74**) to initiate the radical process (Scheme 39. B).[226] It should be noted that no part of the hypervalent iodine reagent is incorporated in the final product in these two examples.



Scheme 39. Radical difunctionalization of diazoketone compounds triggered by iodine(III) oxidants.

2.4.2. Metal-Catalyzed Reactions

The first metal catalyzed transformation of diazo compounds with hypervalent iodine reagents was reported in 2016 by our group. We developed an oxy-alkynylation of diazo compounds using EBX reagents (Scheme 40).[227]



Scheme 40. Copper(I)-catalyzed oxy-alkynylation of diazo compounds with EBX reagents.

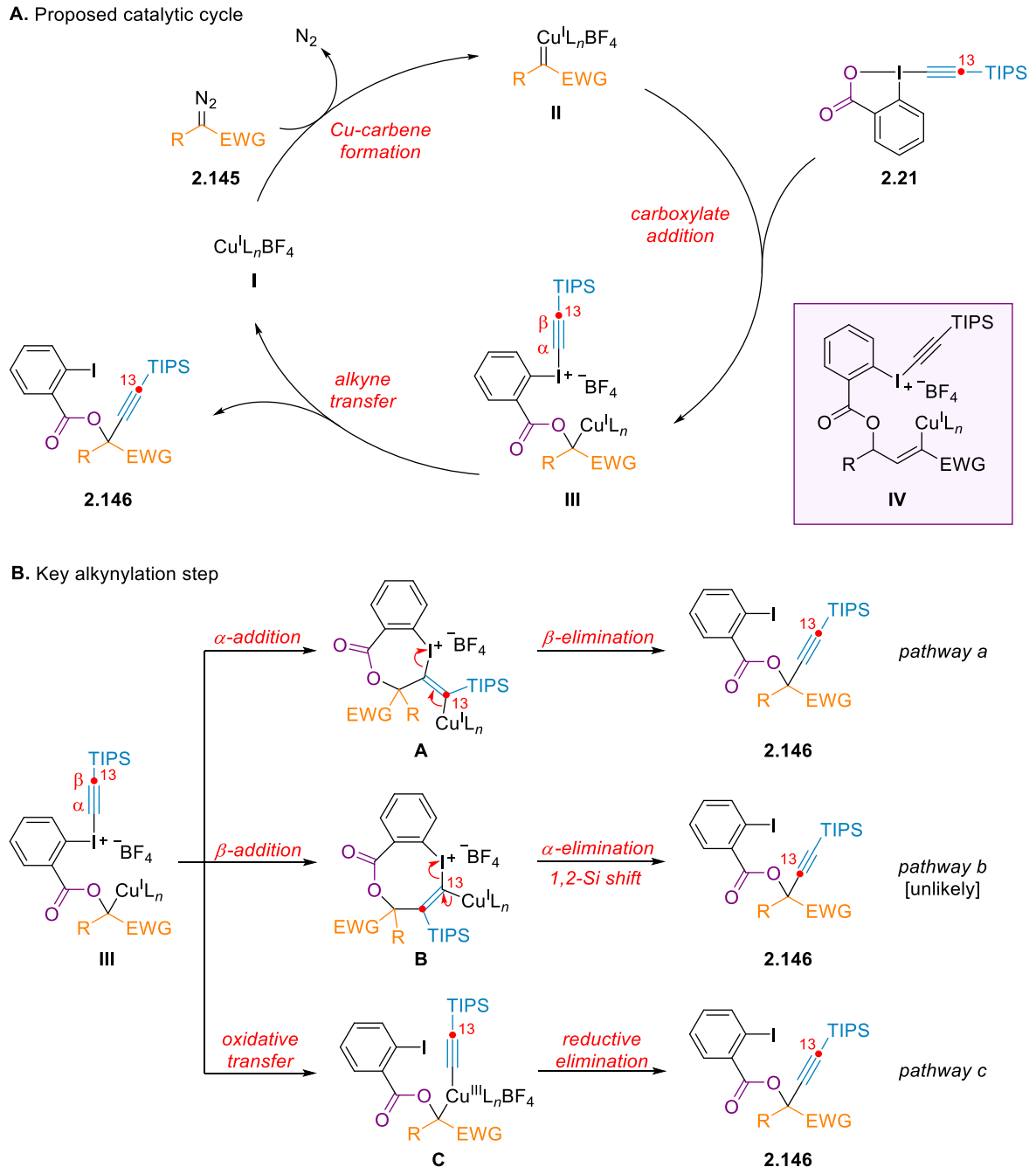
Compared with the above mentioned difunctionalizations, the complete incorporation of the hypervalent iodine reagent results in a highly atom-economical transformation. The reaction is catalyzed by $Cu(CH_3CN)_4BF_4$. In absence of the catalyst, no product was obtained. Other late transition metal catalysts such as Rh(II), Pd(II), Au(III), Au(I) or Pt(II), known to easily generate metal carbenes from diazo precursors, were ineffective. A major yield improvement was observed when 1,2-diimine **2.144** was used as the ligand. With the optimized reaction conditions, two equivalents of

[226] D. Zhu, Y. Yao, R. Zhao, Y. Liu, L. Shi, *Chem. Eur. J.* **2018**, *24*, 4805.
[227] D. P. Hari, J. Waser, *J. Am. Chem. Soc.* **2016**, *138*, 2190.

diazo substrate **2.145** were used. The mild reaction conditions allowed extensive variations on the alkyne substituent (R^1) and on the benziodoxolone core (R^2), as well as various functionalities on the diazo (EWG and R^3). In addition, vinyl diazo compounds **2.147** were compatible and selectively gave enyne products **2.148**. Controlling the regioselectivity with vinyl carbenes is challenging, as they display electrophilic reactivity at both the carbenoid and the vinylogous center.[228]

A reaction mechanism was postulated, based on previous literature reports and experimental evidence (Scheme 41. A). The Cu(I) catalyst **I** reacts first with the diazo compound **2.145** to generate the copper carbene intermediate **II**. The carboxylate part of the EBX reagent **2.21** would add to the highly electrophilic carbene and give the organocopper species **III**. Finally, intramolecular alkyne transfer delivers the product and releases the Cu(I) catalyst **I**. The key alkynylation event was unprecedented and three putative pathways from the alkynyliodonium salt intermediate **III** have been proposed (Scheme 41. B): nucleophilic attack on either the α or β position of the alkyne (pathways a and b), or oxidative alkyne transfer to the copper center (pathway c). In the case of the pathway a, α-addition of the nucleophilic C-Cu bond to the alkyne would result in cyclic vinyliodonium salt **A**, that would ultimately collapse to the product **2.146** after β-elimination of the catalyst and rupture of the hypervalent bond. Alternatively, a concerted reaction at the α-position could also be envisaged considering the soft nature of organocopper nucleophiles.[155b,c] The β-addition (pathway b) would first provide the eight-membered ring intermediate **B**. At this stage, α-elimination produces a vinylidene carbene that undergoes rapid 1,2-silicon shift to furnish the final product **2.146**. This mechanism would be in agreement with previous reports on the β-addition of nucleophiles onto alkynyl hypervalent iodine reagents, followed by vinylidene rearrangement. However, ^{13}C labeling of the alkyne β-carbon atom meant this hypothesis was discarded with NMR analysis. Finally, oxidative alkyne transfer to generate Cu(III) species **C**, and subsequent reductive elimination would lead to the observed product **2.146** (pathway c).[135] For vinyl diazo substrate, the corresponding key intermediate **IV** was assumed.

[228] J. H. Hansen, H. M. L. Davies, *Chem. Sci.* **2011**, *2*, 457.

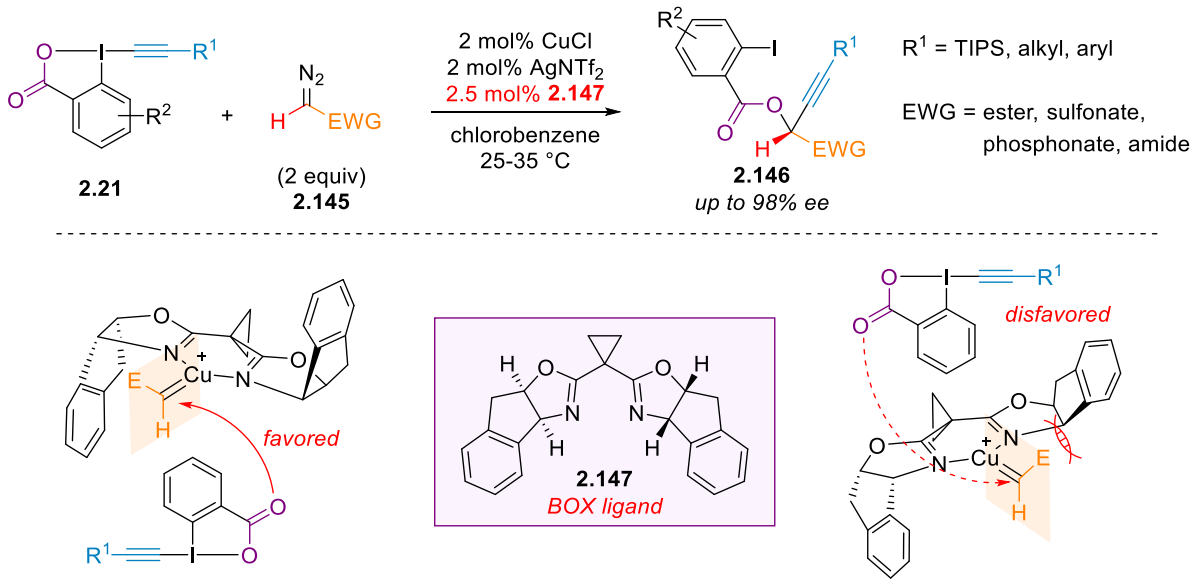


Scheme 41. Proposed mechanism for the Cu-catalyzed oxy-alkynylation of diazo compounds.

Our group then succeeded to implement an enantioselective version of the transformation (Scheme 42).[229] Despite numerous advancements in multicomponent reactions with diazo compounds, no reports of copper-catalyzed enantioselective difunctionalization were known until then. Replacement of the achiral diimine ligand **2.144** by the C_2-chiral bisoxazoline (BOX) ligand **2.149** was the key parameter to achieve high enantioselectivity. Other classes of chiral ligands (diimine, salen, trisoxazoline, biphosphine and phosphinooxazolines) gave either low selectivity or low conversion. The copper counterion also had an impact on the reaction outcome, and non-coordinating NTf_2^- was found to be the best. Acceptor-only diazo esters (R = H) were essential for good reactivity, as well as

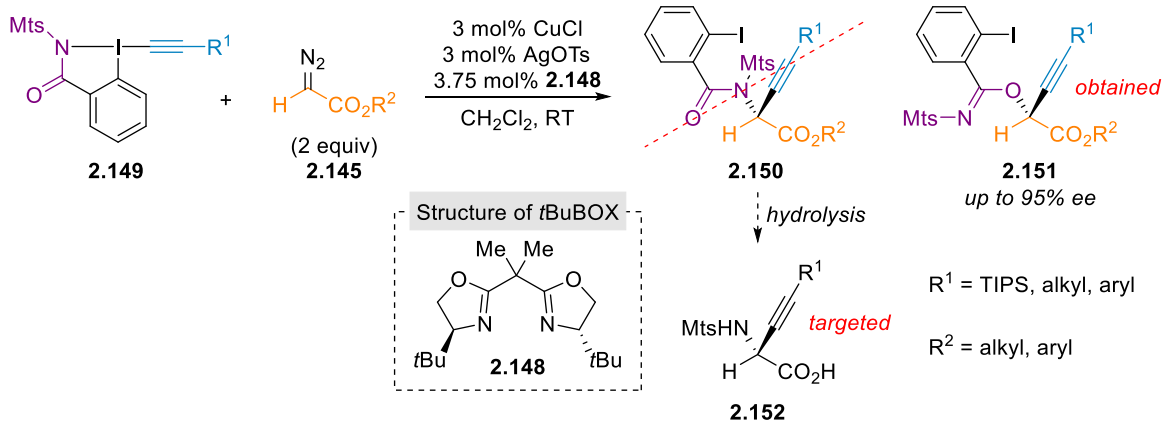
[229] D. P. Hari, J. Waser, *J. Am. Chem. Soc.* **2017**, *139*, 8420.

increasing the steric difference between the two carbene substituents and thus provided the desired propargylic ester products in high yield and with high levels of enantioselectivity. The stereochemical outcome of the products could be predicted with a stereoinduction model considering the geometry of bis-imino copper carbene[171] and the C_2-symmetry of BOX ligand **2.147**. The carboxylate of the EBX reagent **2.21** attacks the carbene center in the free quadrant opposite to the ester group (E), followed by stereospecific alkynylation with retention of configuration.



Scheme 42. Enantioselective copper-catalyzed oxy-alkynylation.

With the advantage of incorporating the two iodine(III) ligands and a well-understood enantioselective transformation in hand, we envisaged to use unexplored ethynylbenziodazolone (EBZ) reagents **2.149** to access enantioenriched alkynylated α-amino acids derivatives **2.150** *via* amino-alkynylation (Scheme 43). Despite the successful implementation of the reaction (high yield and high enantioselectivity), a chemoselective *O*- vs *N*-addition of the amide to the carbene was obtained.[230] Cleavage of the resulting imidate function would generate propargyl hydroxy acids instead of the targeted propargyl amino acids **2.152**.

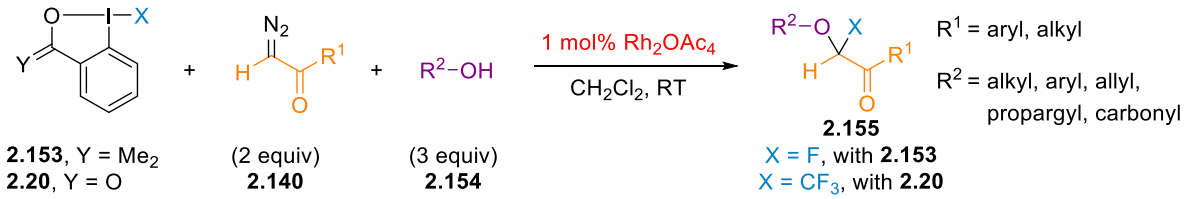


Scheme 43. Oxy-alkynylation of diazo compounds using EBZ reagents.

[230] D. P. Hari, L. Schouwey, V. Barber, R. Scopelliti, F. Fadaei-Tirani, J. Waser, *Chem. Eur. J.* **2019**, *25*, 9522.

Further attempts to constrain C-N bond formation at the carbene center were directed towards the design and use of new cyclic ethynyl hypervalent iodine reagents possessing an amidine ligand.[231] Unfortunately, no reactivity was obtained in this case.

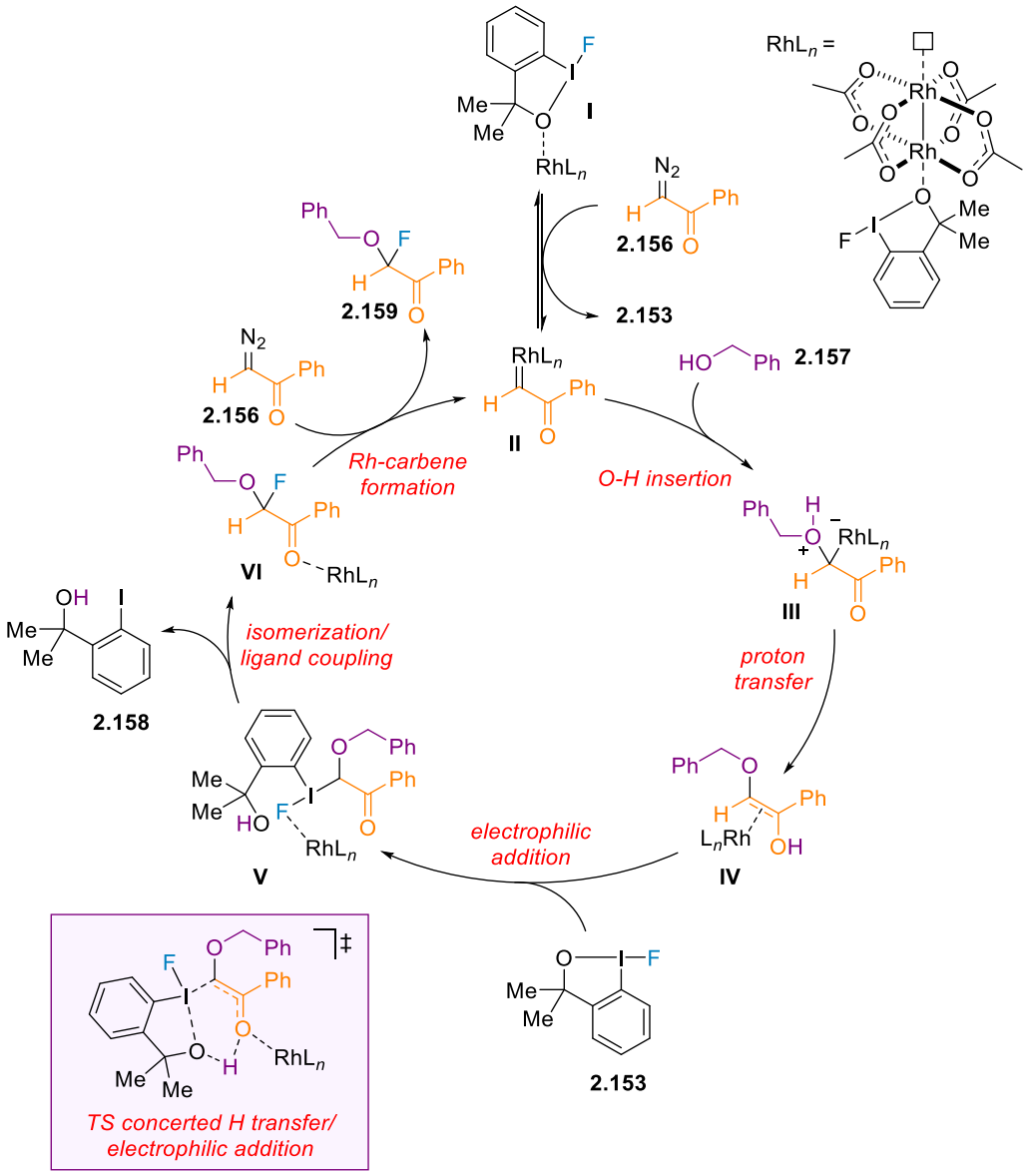
In 2016, Szabó and co-workers also succeeded at merging hypervalent iodine and diazo chemistries with the help of metal catalysis.[232] The group described an efficient rhodium-catalyzed three-component reaction for the oxy-fluorination and oxy-trifluoromethylation of diazo compounds **2.140** with fluoro-benziodoxole **2.153** and trifluorobenziodoxolone (Togni reagent, **2.19**) (Scheme 44). In comparison to our work, the iodobenzoate ligand was not incorporated in the final products **2.155** and various alcohols (primary, secondary, tertiary), phenols and carboxylic acids could be employed to introduce the second functionality. The moderate atom-efficiency of the transformation has to be contrasted with the high structural diversity attainable using such a three-component reaction. Rhodium(II) acetate dimer (Rh_2OAc_4) proved to be the optimal catalyst and various diazo ketones (R^1) were compatible. Remarkably, the mild reaction conditions allowed the handling of a wide range of functionalities such as halide, allyl, propargyl, boronic ester or the direct functionalization of cholesterol. In one example, the authors reported the incorporation of 2-iodobenzylalcohol from the hypervalent iodine reagent in the absence of external nucleophile.



Scheme 44. Rh-catalyzed three-component reaction with fluorinating hypervalent iodine reagents, diazo compounds and *O*-nucleophiles.

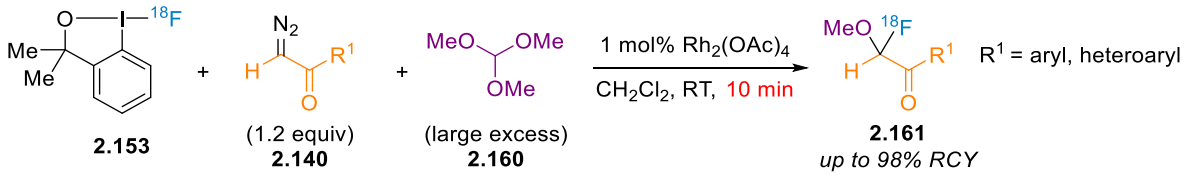
The mechanisms of both reactions were investigated by means of density functional theory, in collaboration with the Himo group.[233] The calculations show that the two reactions follow almost identical mechanisms (Scheme 45). Preliminary interactions between Rh_2OAc_4 and all the different compounds present in the reaction media (fluoro-benziodoxole **2.153**, 2-diazo-1-phenylethan-1-one (**2.156**) and benzyl alcohol (**2.157**)) were calculated and resulted in a stabilized Rh-complex **I** in which two benziodoxole molecules are bound to the electrophilic axial sites of the paddlewheel-shaped complex. The catalytic cycle starts with the diazo substrate **2.156** replacing **2.153** as ligand followed by nitrogen extrusion to generate Rh-carbene **II**. Insertion of alcohol **2.157** and proton transfer (formally O-H insertion) would result in Rh-bound enol intermediate **IV**. Then, a concerted proton transfer-electrophilic addition with fluoro-benziodoxole **2.153** would form **V** with a new C-I(III) bond. Subsequent isomerization of the hypervalent bond with the Rh catalyst acting as a Lewis acid and ligand coupling (reductive elimination) leads to **VI** and the release of **2.158** as by-product. Decoordination of the final three-component product **2.159** from the catalyst by a new incoming diazo molecule closes the catalytic cycle.

[231] Unpublished results of E. Le Du and J. Waser.
[232] W. Yuan, L. Eriksson, K. J. Szabó, *Angew. Chem. Int. Ed.* **2016**, *55*, 8410.
[233] B. K. Mai, K. J. Szabó, F. Himo, *ACS Catal.* **2018**, *8*, 4483.



Scheme 45. Simplified mechanism for the Rh-catalyzed oxy-fluorination of diazo compounds.

The Szabó group further exploited the oxy-fluorination reaction by developing a fast fluorine-18 labelling method for the synthesis of biologically relevant α-fluoro ether motifs **2.161** (Scheme 46).[234] In this case, trimethyl orthoformate (**2.160**) was used instead of regular alcohols due to undesired electrophilic fluorination when downscaling the reaction.



Scheme 46. ^{18}F-labelling of α-diazoketones.

[234] M. A. Cortés González, X. Jiang, P. Nordeman, G. Antoni, K. J. Szabó, *Chem. Commun.* **2019**, *55*, 13358.

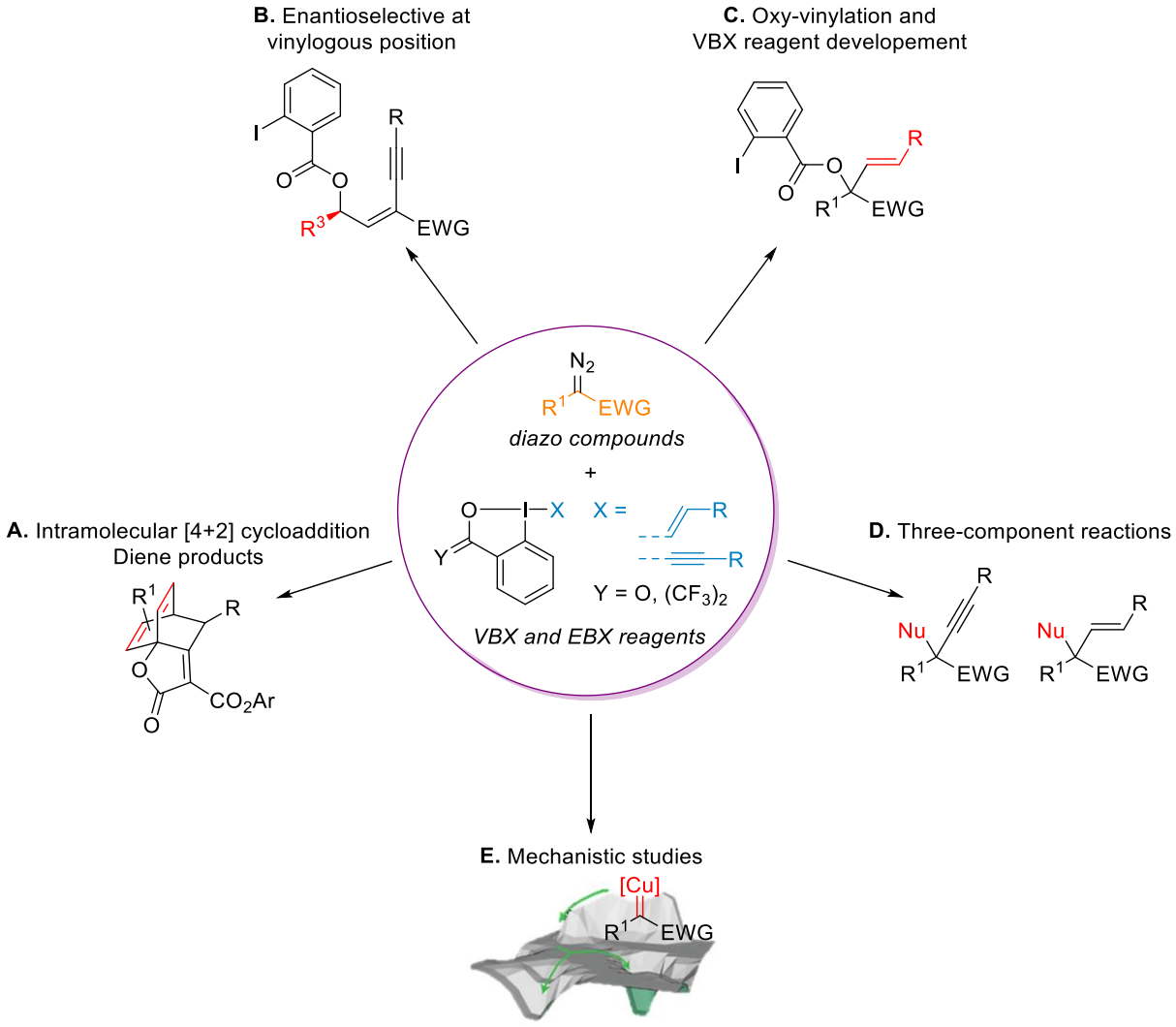
Hypervalent iodine and diazo are high-energy molecules. The rupture of the hypervalent bond and the irreversible loss of molecular nitrogen are strong driving forces that can be controlled with the help of transition metal catalysts. The difunctionalization of metal carbenes with hypervalent iodine reagents is a strategy that can allow the rapid construction of complex molecular structures through non-classical disconnections. Investigations of combining the reactivity of carbene intermediates and iodine(III) reagents has just started, and a lot of potential can be expected for the future.

3

Goal of the Thesis

3. Goal of the Thesis

The exceptional versatility of olefins and alkynes and their omnipresence in natural products or applied sciences justify the intensive research efforts directed toward these privileged functions. Metal-carbenes are known to be involved in various type of transformations. Recently, these reactive intermediates have been employed in multi-component reactions for a rapid increase in molecular complexity. In particular, transient ylide intermediates generated from the insertion of nucleophiles into metal-carbenes generated from diazo compounds have been intercepted with various electrophiles to simultaneously introduce two new functionalities on the carbene carbon atom. To the best of our knowledge, very few methodologies reported electrophilic vinylation and alkynylation of diazo compounds. Our group started to investigate the difunctionalization of diazo compounds with EBX reagents, resulting in oxy-alkynylation reactions. The goal of this PhD work was to broaden this concept to other classes of substrates (Scheme 47).



Scheme 47. Development of new vinylations and alkynylations of diazo compounds with hypervalent iodine reagents.

Our first objective would be to exploit an unusual low temperature intramolecular [4+2] cycloaddition reaction of tethered aryl propargyl-ester products obtained by insertion reaction

of diazo compounds into EBX reagents (Scheme 47. A). The resulting complex diene products would be useful as ligands in metal catalysis.

Extension of the enantioselective oxy-alkynylation of diazo compounds with hypervalent iodine reagents, is an important goal of this thesis. We believe that the implementation of a related transformation with vinyl diazo substrates, would be an interesting way to access enantioenriched conjugated enyne products (Scheme 47. B). From our previous work, we already identified that chiral bisoxazoline copper(I) complexes were providing only low reactivity with disubstituted diazo partners. Therefore, the investigation and design of new chiral ligands would be required to achieve an efficient transformation.

At the start of this PhD work, very few reports made use of VBX as electrophilic alkene reagents. We considered to apply VBX reagents in the difunctionalization of diazo compounds (Scheme 47. C). This transformation would offer a new approach to forge Csp^3-Csp^2 bonds and give access to elaborated building blocks bearing several functional groups (alkene, ester, iodide). In addition, the development of such oxy-vinylation reaction would be complementary to the work of Van Vranken restricted to the functionalization of allylic positions with external *C*- and *N*-nucleophiles. Based on our group expertise in the synthesis of hypervalent iodine reagents, we envisaged to improve the synthetic methods to access VBX reagents, which are so far limited to a few specific substrates.

The insertion of benziodoxolone reagents into carbenes constitutes a powerful reaction with minimal generation of waste, not often considered with iodine(III) transfer reagents. Nevertheless, the exclusive incorporation of the iodobenzoate ligand as nucleophile seriously hampered the diversity of structures accessible. The implementation of vinylations and alkynylations of metal carbenes occuring with an additional functionalization by an external nucleophilic partner would allow a convergent method to access highly functionalized and structurally diverse products (Scheme 47. D).

Copper catalysts have been used in numerous transformations with vinyl- and alkynyl-iodonium salts, however, little is known about their interaction with VBX or EBX reagents. Mechanistic studies of the copper-catalyzed functionalization of diazo compounds with benziodoxol(on)e reagents would deepen our knowledge on this particular chemistry, and could open opportunities to identify the key reactivity of cyclic hypervalent iodine reagents associated to copper catalysis (Scheme 47. E).

4

Unusual Low-Temperature Intramolecular [4+2] Cycloaddition of Allenes with Arenes for the Synthesis of Diene Ligands

4. Unusual Low-Temperature Intramolecular [4+2] Cycloaddition of Allenes with Arenes for the Synthesis of Diene Ligands[235]

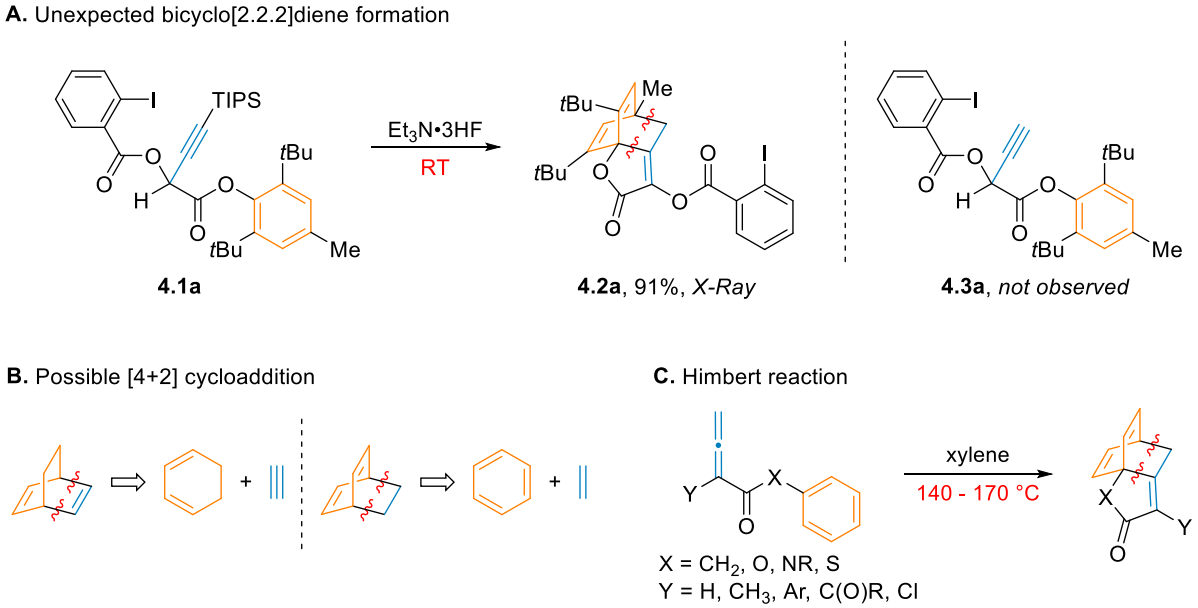
This chapter presents our efforts towards the development of an intramolecular [4+2] cycloaddition of allenes with arenes that lead to the formation of bicyclo[2.2.2]octadienes. The project was initiated in our group by Dr. Durga Hari and the key transformation allows a rapid synthesis of polycylic architectures with high efficiency, atom and step economy. As an important application, the diene products were envisaged as ligands for metal catalysis.

4.1. Serendipitous Reaction Discovery

During the investigations of the product modifications of enantioenriched allylic esters obtained from our previous project, *Enantioselective Copper-Catalyzed Oxy-Alkynylation of Diazo Compounds* (see section 2.4.2.),[229] a bicyclo[2.2.2]octadiene product **4.2a** was isolated in high yield after attempting the desilylation of the alkyne **4.1a** with hydrofluoric acid (Scheme 48. A). This unexpected molecular structure was undoubtedly assigned by X-ray crystallography.[236] Bicyclo[2.2.2]octadienes are well-established products, usually obtained by a Diels-Alder reaction between cyclohexadienes and alkynes.[237] The other convergent [4+2] approach, consisting of the cycloaddition between an arene and a carbon-carbon double bond has been less investigated due to the high stability of the aromatic ring (Scheme 48. B). We quickly postulated a [4+2] cycloaddition between a *in situ* formed allene intermediate and the tethered aryl ester. Such a transformation has been first described by Himbert and Henn for allenecarboxanilides,[238] and next extended to various allenecarboxylic acid derivatives like ester (X = O),[239] amides (X = NR)[240] or thioesters (X = S) (Scheme 48. C).[241] More recently, Vanderwal and Houk unveiled the concerted mechanism of this unusual intramolecular cycloaddition by DFT studies and extended the scope to all-carbon tethered allenes (X = CH_2).[242] High reaction temperatures are normally needed for the dearomatization to occur, while the whole reaction sequence was performed at room temperature in our case. Examples at

[235] "" The texts in between are direct quotations from our manuscript, D. P. Hari, G. Pisella, M. D. Wodrich, A. V. Tsymbal, F. F. Tirani, R. Scopelliti, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 5475.
[236] The X-ray structure of **4.2a** is available at the Cambridge Crystallographic Centre, CCDC number 1848760.
[237] Selected examples, a) N. Kumar, M. Kiuchi, J. A. Tallarico, S. L. Schreiber, *Org. Lett.* **2005**, *7*, 2535; b) M. Dai, D. Sarlah, M. Yu, S. J. Danishefsky, G. O. Jones, K. N. Houk, *J. Am. Chem. Soc.* **2007**, *129*, 645; c) K. Ishihara, M. Fushimi, J. Am. Chem. Soc. **2008**, 130, 7532; d) J.-P. Krieger, G. Ricci, D. Lesuisse, C. Meyer, J. Cossy, *Angew. Chem. Int. Ed.* **2014**, *53*, 8705; e) K. B. Hamal, R. Bam, W. A. Chalifoux, *Synlett* **2016**, *27*, 2161; f) M. Hatano, T. Sakamoto, T. Mizuno, Y. Goto, K. Ishihara, *J. Am. Chem. Soc.* **2018**, *140*, 16253.
[238] For seminal report with allenecarboxanilides, see: G. Himbert, L. Henn, *Angew. Chem. Int. Ed.* **1982**, *21*, 620.
[239] a) G. Himbert, D. Fink, *Tetrahedron Lett.* **1985**, *26*, 4363; b) G. Himbert, D. Fink, M. Stürm, *Z. Naturforsch. B* **1994**, *49*, 63.
[240] a) L. Henn, G. Himbert, K. Diehl, M. Kaftory, *Chem. Ber.* **1986**, *119*, 1953; b) G. Himbert, K. Diehl, H.-J. Schlindwein, *Chem. Ber.* **1986**, *119*, 3227; c) K. Diehl, G. Himbert, *Chem. Ber.* **1986**, *119*, 3812; d) H.-J. Schlindwein, K. Diehl, G. Himbert, *Chem. Ber.* **1989**, *122*, 577; e) G. Himbert, H.-J. Schlindwein, *Z. Naturforsch. B* **1992**, *47*, 1785; f) G. Himbert, D. Fink, *J. Org. Chem.* **1996**, *338*, 355.
[241] G. Himbert, D. Fink, *J. Prakt. Chem.* **1994**, *336*, 654.
[242] Y. Schmidt, J. K. Lam, H. V. Pham, K. N. Houk, C. D. Vanderwal, *J. Am. Chem. Soc.* **2013**, *135*, 7339.

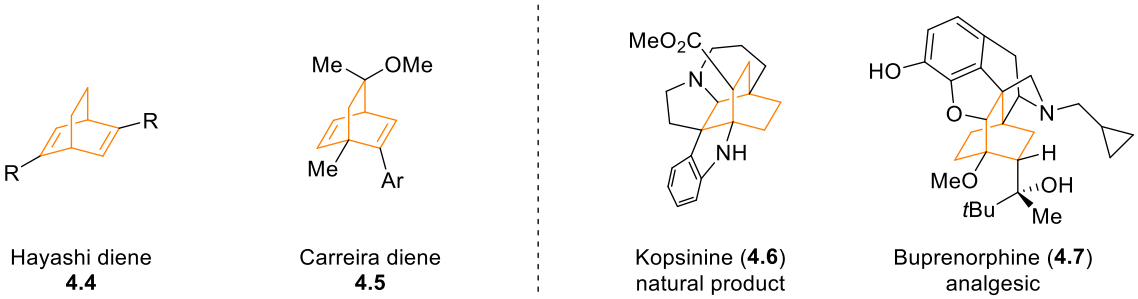
ambient temperatures required conformationally constrained amides[243] or were performed under light irradiation.[244]



Scheme 48. Unexpected observation: Himbert reaction at room temperature.

A useful feature of bicyclo[2.2.2]octadienes is their ability to form kinetically stable complexes with various late transition metals. The groups of Hayashi and Carreira pioneered the use of chiral bicyclo[2.2.2]octadienes ligands such as **4.4** or **4.5** in various enantioselective transformations (Figure 13).[245] Reduction of the cyclic diene gives access to a bicyclo[2.2.2]octane skeleton, an important motif found in numerous bioactive natural products, such as the alkaloid kopsinine (**4.6**),[246] or synthetic compounds, such as the broadly prescribed opioid analgesic buprenorphine (**4.7**).[247] The bicyclo[2.2.2]octane core has been also investigated as a saturated bioisostere of benzene.[248]

[243] a) L. S. Trifonov, A. S. Orahovats, Helv. Chim. Acta **1986**, *69*, 1585; b) L. S. Trifonov, A. S. Orahovats, *Helv. Chim. Acta* **1987**, *70*, 1732; c) L. S. Trifonov, A. S. Orahovats, *Helv. Chim. Acta* **1987**, *70*, 262; d) L. S. Trifonov, A. S. Orahovats, *Helv. Chim. Acta* **1989**, *72*, 59; e) X. Mo, B. Chen, G. Zhang, *Angew. Chem. Int. Ed.* **2020**, *59*, 13998.
[244] U. Streit, F. Birbaum, A. Quattropani, C. G. Bochet, *J. Org. Chem.* **2013**, *78*, 6890.
[245] For comprehensive reviews, see: a) R. Shintani, T. Hayashi, *Aldrichimica Acta* **2009**, *42*, 31; b) C. Defieber, H. Grützmacher, E. M. Carreira, *Angew. Chem. Int. Ed.* **2008**, *47*, 4482.
[246] D. W. Thomas, H. Achenbach, K. Biemann, *J. Am. Chem. Soc.* **1966**, *88*, 3423.
[247] M. Connock, A. Juarez-Garcia, S. Jowett, E. Frew, Z. Liu, R. Taylor, A. Fry-Smith, E. Day, N. Lintzeris, T. Roberts, A. Burls, R. S. Taylor, *Health Technol. Assess.* **2007**, *11*, 1.
[248] For a review, see: P. K. Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 2839.



Hayashi diene **4.4** | Carreira diene **4.5** | Kopsinine (**4.6**) natural product | Buprenorphine (**4.7**) analgesic

Figure 13. Popular chiral diene ligands and relevance of the bicyclo[2.2.2]octane structure.

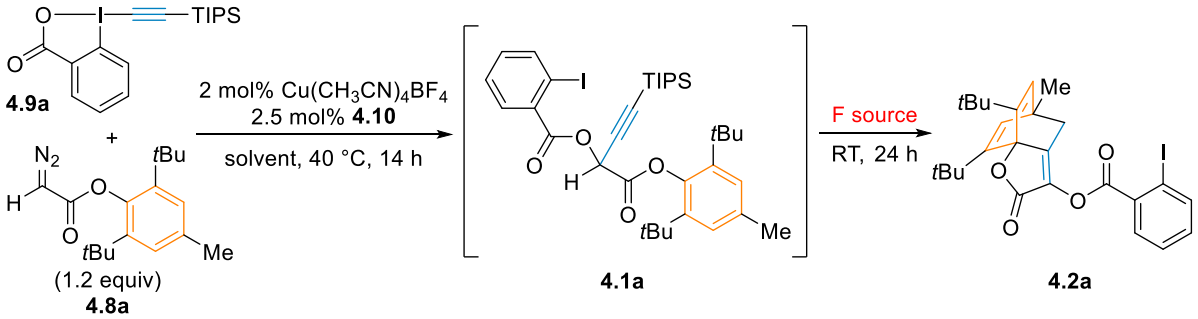
Considering the exceptionally mild conditions we obtained for this transformation, we sought to develop a convenient one-pot oxy-alkynylation/cycloaddition procedure to easily access valuable bicyclo[2.2.2]octadiene products.

4.2. Previous Work of the Group: Optimization and Scope[249]

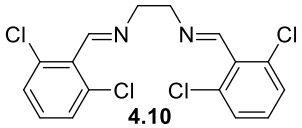
"We started our investigations on developing a one-pot oxy-alkynylation/Himbert reaction by screening various fluoride sources, using 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (BDA, **4.8a**) with TIPS-EBX (**4.9a**), diimine ligand **4.10** and $Cu(CH_3CN)_4BF_4$ as the copper source in DCE (Table 1).[227] Compound **4.2a** was obtained in 88% yield when $Et_3N•3HF$ was used, whereas trissulfonium difluorotrimethylsilicate (TASF) gave the desired product in 26% yield only (entries 1 and 2). The use of tetrabutylammonium fluoride (TBAF) and pyridine hydrofluoride (Py•HF) resulted in decomposition of the oxy-alkynylated product **4.1a** (entries 3 and 4). One equivalent of $Et_3N•3HF$ was sufficient, whereas a sub-stoichiometric amount led to a lower yield (entries 5 and 6). Addition of $Et_3N•3HF$ at the start of the reaction did not lead to the formation of the desired product **4.2a** (entry 7). We were able to reduce the amount of diazo **4.8a** to 1.2 equivalents without a change in yield (entry 8). Finally, the yield could be improved to 94% by lowering the concentration of the reaction (entry 9). Furthermore, the reaction proved to be easily scalable, as the yield did not change on gram scale."

[249] This work was performed by Dr. D. P. Hari.

Table 1. Optimization of the reaction under acidic conditions.[a]



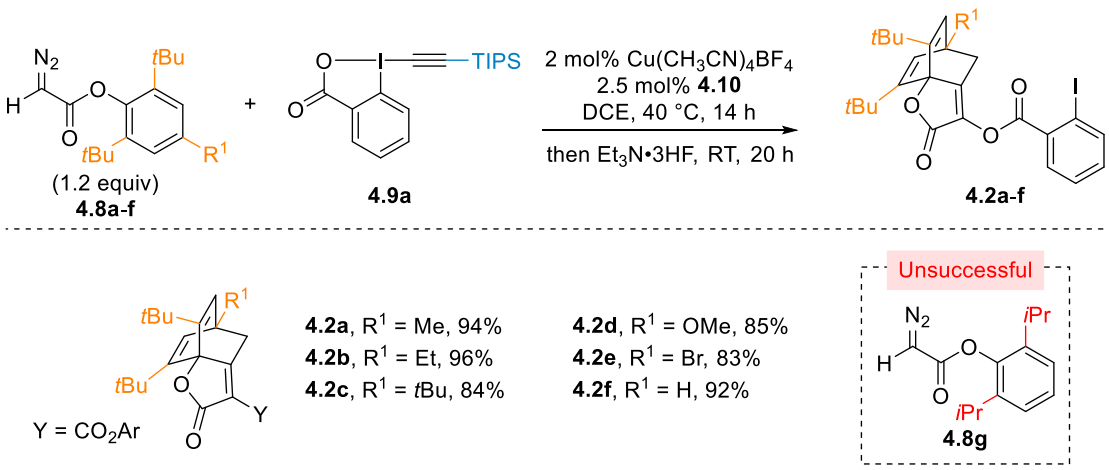
Entry	Fluoride source (x equiv)	Solvent	Yield[b] (%)
1	$Et_3N•3HF$ (2.0)	DCE	88
2	TASF (2.0)	DCE	26
3	TBAF (2.0)	DCE	< 5
4	Py•HF (2.0)	DCE	< 5
5	$Et_3N•3HF$ (1.0)	DCE	88
6	$Et_3N•3HF$ (0.5)	DCE	65
7[c]	$Et_3N•3HF$ (1.0)	DCE	< 5
8[d]	$Et_3N•3HF$ (1.0)	DCE	87
9[e]	$Et_3N•3HF$ (1.0)	DCE	94



4.10

[a]Reaction conditions: 0.30 mmol of BDA (**4.8a**), 0.15 mmol of TIPS-EBX (**4.9a**), Cu cat. (2.0 mol%), **4.10** (2.5 mol%), DCE (0.05 M). [b]Yield after purification by column chromatography. [c]$Et_3N•3HF$ was added at the start of the sequence. [d]1.2 equiv of BDA instead of 2.0 equiv [e]0.025 M instead of 0.05 M.

With the optimized conditions in hand we began to explore the generality of the method. The scope of the reaction was first examined using TIPS-EBX (**4.9a**) and diazo esters bearing *tert*-butyl substituents in *ortho* positions of the benzene ring (Scheme 49). *Para*-substituted products **4.2a**-**f** with various alkyls (Me, Et, *t*Bu), ether, bromine or hydrogen were obtained in very good yield regardless of the stereoelectronic effects of the substituents. In contrast, the *ortho* substituents had a major effect on the reaction outcome. When 2,6-di-*iso*-propyl-phenyl 2-diazoacetate (**4.8g**) was subjected to the standard reaction conditions, we could not observe the formation of the desired product **4.2g**. Heating to higher temperatures led to decomposition.

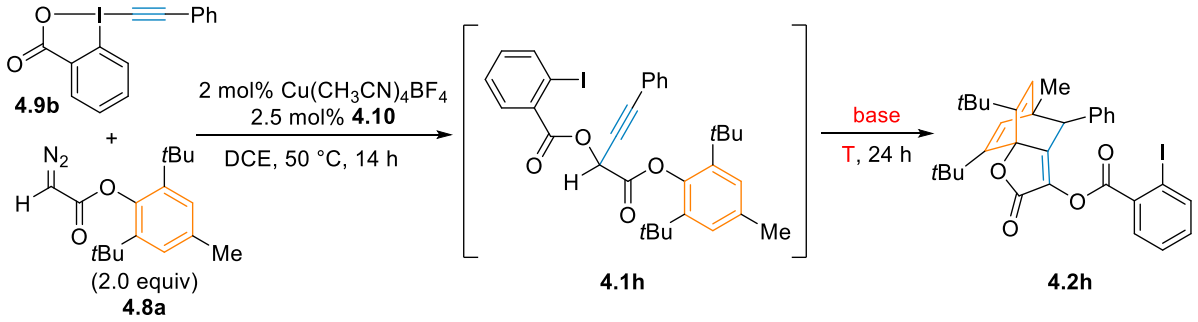


Scheme 49. Initial scope limited to diazo esters with *ortho tert*-butyl substituents.

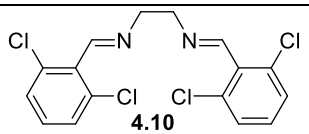
Therefore, we envisaged the reaction of functionalized EBX reagents with BDA (**4.8a**) to develop the scope and access products of higher molecular complexity. We turned our attention to basic conditions for the alkyne to allene isomerization to occur, as no removable protecting group was present in this case. (Table 2). Employing Ph-EBX (**4.9b**), the oxy-alkynylation step was efficient at 50 °C. The subsequent addition to the reaction mixture of inorganic base such as K_2CO_3, Cs_2CO_3 or K_3PO_4, furnished the desired product **4.2h** in high yields (entries 1 to 3).[250] In contrast, the use of DBU (entry 4) led to rapid decomposition of the intermediate (**4.1h**). The carbonate base is not compatible with the oxy-alkynylation step and needs to be added afterwards. Cs_2CO_3 was selected and the cycloaddition step could be performed at room temperature without any loss of yield (entry 5). Reduction to 1.1 equivalents of base did not impact the yield, and diminution of the reaction concentration to *c* = 0.025 M improved the final yield up to 91% (entries 6 and 7). The synthesis of compound **4.2h** was also performed on gram-scale.

[250] The structure of **4.2h** was confirmed by X-ray analysis (available at the Cambridge Crystallographic Centre, CCDC number 1848773).

Table 2. Optimization of the reaction in basic conditions with Ph-EBX.[a]



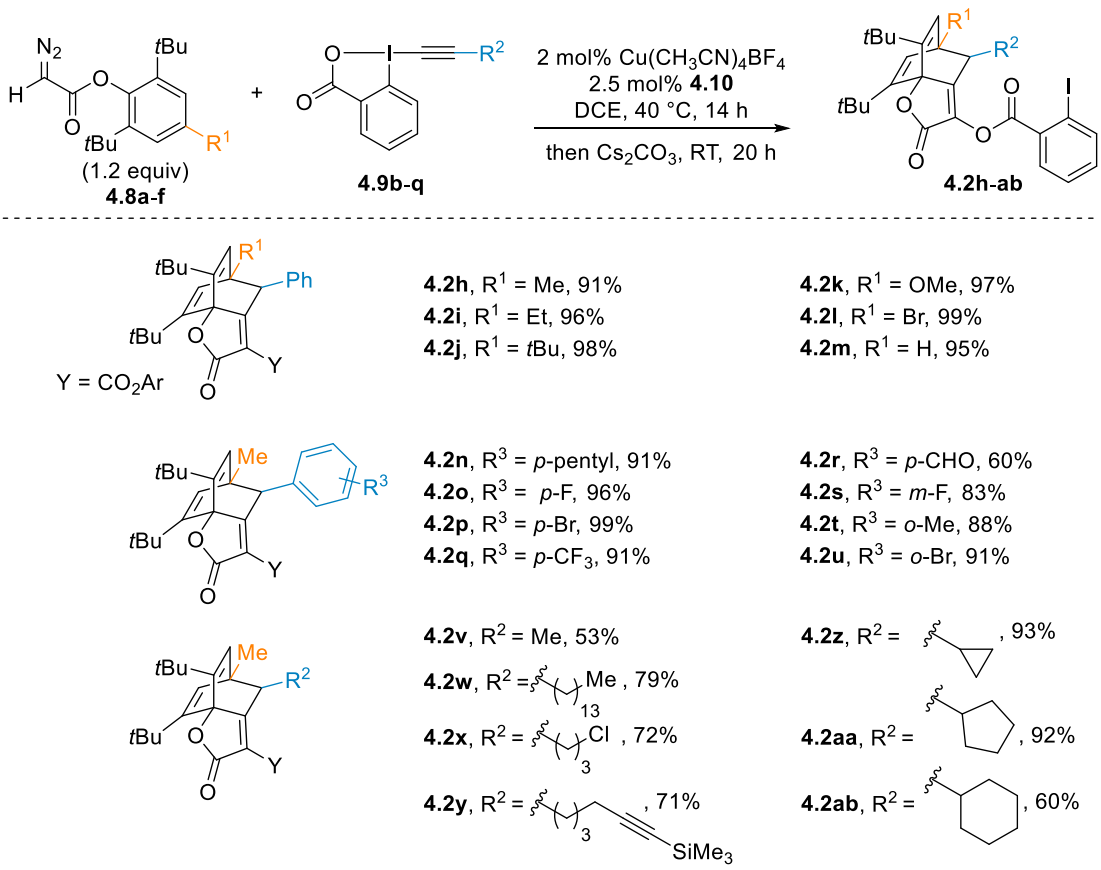
Entry	Base (x equiv)	Temperature (°C)	Yield[b] (%)
1	K_2CO_3 (2.5)	50	85
2	Cs_2CO_3 (2.5)	50	88
3	K_3PO_4 (2.5)	50	87
4	DBU (2.5)	50	dec.
5	Cs_2CO_3 (2.5)	RT	88
6	Cs_2CO_3 (1.1)	RT	87
7[c]	Cs_2CO_3 (1.1)	RT	91


4.10

[a]Reaction conditions: 0.30 mmol of BDA (**4.8a**), 0.15 mmol of Ph-EBX (**4.9b**), Cu cat. (2.0 mol%), **4.10** (2.5 mol%), DCE (0.05 M). [b]Yield after purification by column chromatography. [c]0.025 M instead of 0.05 M.

Under these conditions, "various benzene diazo esters bearing an alkyl chain, an ether, a halogen or a hydrogen substituent in *para* position gave excellent yields (Scheme 50, products **4.2i**-**m**). We then turned our attention to the scope of aryl-EBX reagents using **4.8a**. The desired products **4.2n**-**u** bearing alkyl, fluorine, bromine, trifluoromethyl or aldehyde in *para*, *meta* or *ortho* position were obtained in 60-99% yield, demonstrating the tolerance of the reaction towards functional groups and substitution patterns. Next, the scope of alkyl-EBX reagents was examined.[251] Methyl- and long alkyl chain- derived EBX reagents worked well in the reaction, giving products **4.2v** and **4.2w** in 53% and 79% yield, respectively. The reaction was also successful in the case of chlorine and alkynyl groups bearing alkyl EBX reagents (products **4.2x** and **4.2y**). The reaction was not limited to linear alkyl-EBX reagents: Cyclo-propyl, -pentyl, and -hexyl substituted products **4.2z**-**ab** were obtained in 60-93% yield. The formation of product **4.2z** exclusively indicated that radical intermediates were probably not involved in the reaction."

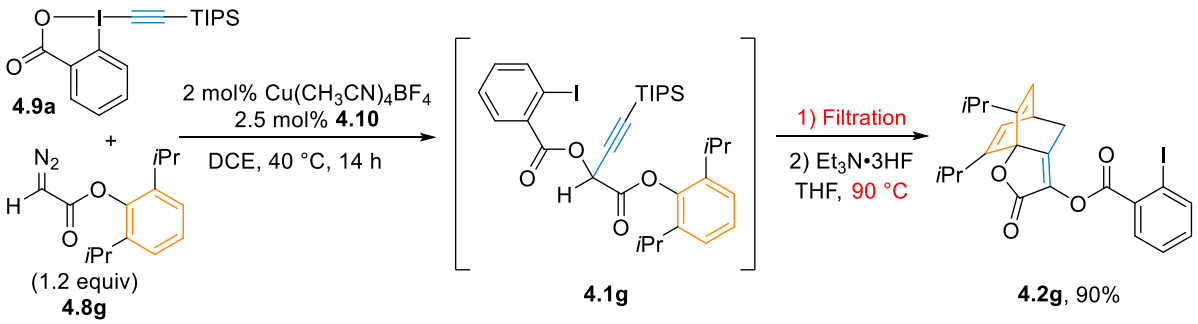
[251] The reaction with alkyl-EBXs required 50 °C to form allenes, which undergo spontaneous cyclization to give the corresponding Himbert products.



Scheme 50. Scope of the reaction with different EBX reagents.

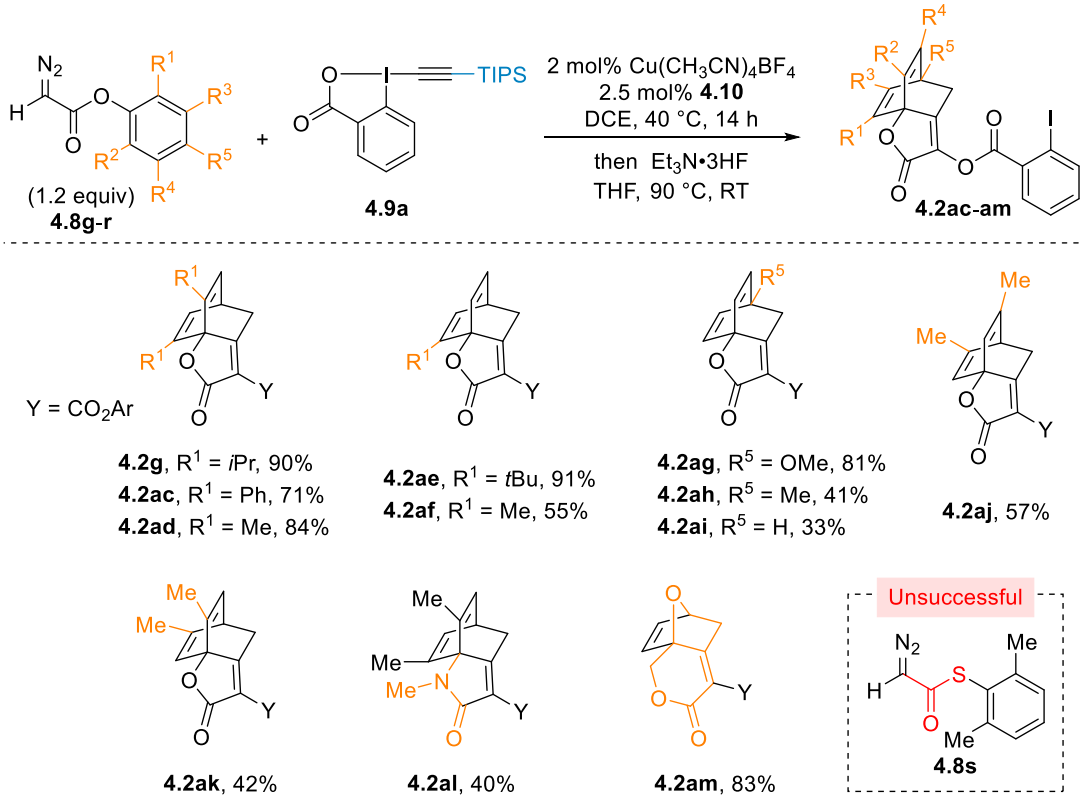
4.3. Scope Extension

In the course of the project, we realized the importance of the *tert*-butyl groups in the *ortho* positions of the aryl diazo ester substrate to realize the Himbert reaction at room temperature. Indeed, 2,6-di-*iso*-propyl-phenyl 2-diazoacetate (**4.8g**) successfully gave the desired intermediate product of oxy-alkynylation **4.1g** but failed to deliver the final cycloadduct **4.2g** and was degraded when heating (see section 4.2.). We wondered if the copper salt could induce the decomposition of the intermediate **4.1g** under prolonged heating time. To our delight, removal of the catalyst by simple filtration over celite and exposure of the intermediate to $Et_3N{\bullet}3HF$ at 90 °C in THF gave the product **4.2g** in excellent yield (Scheme 51). This temperature is still significantly lower than reported for similar substrates lacking the oxygen (ester) substituent on the allene (140 °C).[239a]



Scheme 51. Successful synthesis of **4.2g** after removal of the Cu salt and heating.

We envisaged a similar approach under basic conditions to access products with various substituents on the bicyclo[2.2.2]octadiene core. Unfortunately, the intermediate products bearing alkyl, aryl or silyl groups on the alkyne rapidly decomposed at 90 °C in the presence of Cs_2CO_3. In consequence the scope extension was directed toward different diazo ester substrates and only TIPS-EBX (**4.9a**) as partner under acidic conditions (Scheme 52). Other benzene disubstituted diazo esters such as *ortho* diphenyl- and dimethyl-benzene were well tolerated furnishing the desired products **4.2ac** and **4.2ad** in good yields. We then investigated *ortho* mono-substituted benzene diazo esters, substrates **4.8j** and **4.8k** underwent the desired transformation successfully to give the products **4.2ae** and **4.2af** as single diastereoisomers in 91% and 55% yield, respectively.[252] "Substitutions at different positions than *ortho* were envisaged: *p*-Substituted and unsubstituted benzene diazo esters gave the corresponding products **4.2ag**-**ai** in moderate to good yield. Dimethyl-substituted benzene diazo esters also gave the desired products **4.2aj** and **4.2ak** in moderate yields." Different heteroatoms than oxygen were considered for the fused five-membered ring. The amide tethered product **4.2al** was obtained in 40% yield however the corresponding thioester diazo compound **4.8s** was not compatible in the oxy-alkynylation reaction. Finally, the furan-derived diazoester **4.8r** underwent the dearomatization reaction in satisfying manner providing the new [5,5,6] ring system **4.2am** in 83% yield.



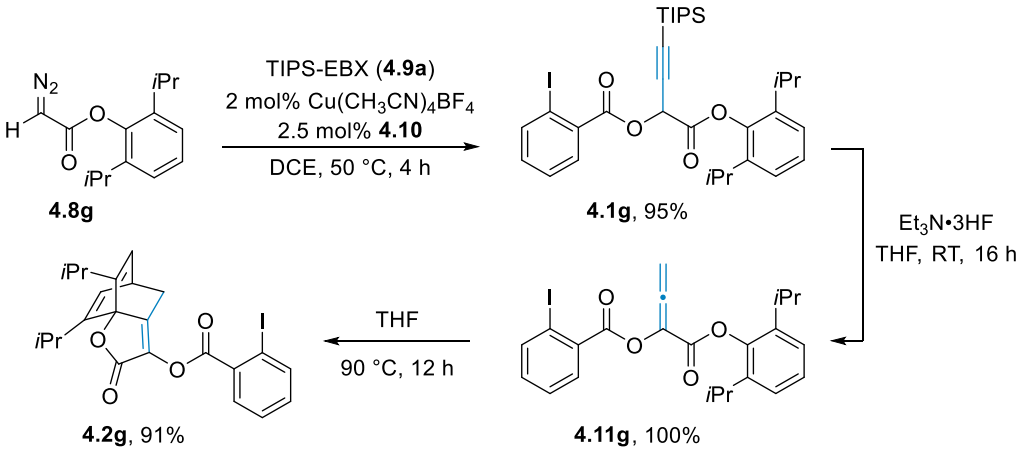
Scheme 52. Extension of the scope of the reaction with various diazo esters at 90 °C.

4.4. Mechanism Investigations

In order to confirm our hypothesis of an allene intermediate we made the deconvolution of our putative oxy-alkynylation/allene formation/[4+2] cycloaddition sequence (Scheme 53). The investigation was realized with diazo substrate **4.8g** as no spontaneous Himbert reaction should occur

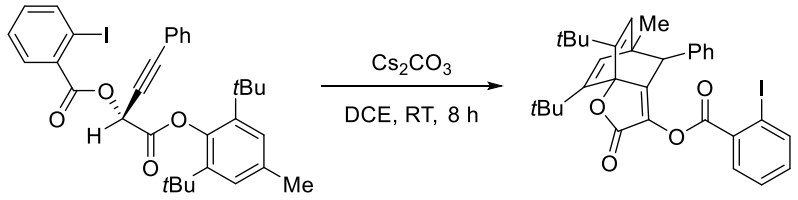
[252] The structure of the diastereoisomers was assigned in analogy to the work in ref 242.

at ambient temperature. First, the product of oxy-alkynylation **4.1g** was obtained in good yield and the copper catalyst removed by purification on silica. In the presence of $Et_3N•3HF$, **4.1g** was cleanly converted to allene **4.11g** at room temperature. The allene intermediate was successfully isolated and submitted to the next reaction step. Upon heating to 90 °C, [4+2] cycloaddition then occurred to furnish **4.2g** in 91% yield. It confirms the role of the copper catalyst for the oxy-alkynylation of the diazo compound, the role of Et3N•3HF for the desilylation/allene formation step and the need of thermal activation for the cycloaddition to occur.



Scheme 53. Isolation of the reaction intermediates.

We wondered if, when starting with an enantioenriched alkyne, a transfer of chirality to the final product could be possible (Scheme 54). The intermediate allene would need a chiral axis, which is not the case with **4.11g**. To this end, an extra substituent is required. However, racemic **4.2h** was isolated from enantioenriched phenyl-substituted alkyne **4.1h**.[253] It supports the formation of a racemic allene intermediate.

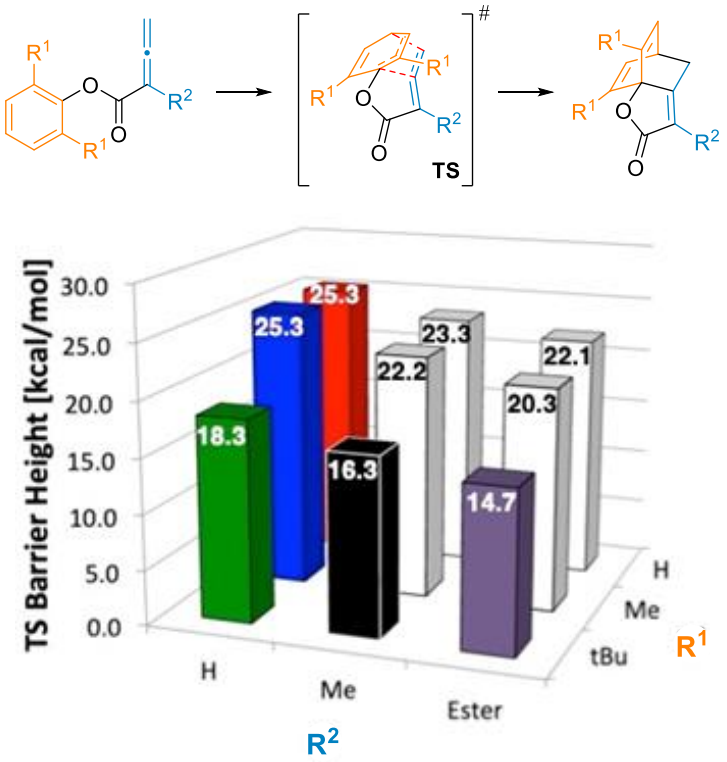


Scheme 54. Loss of chiral information in the formation of the allene intermediate under basic conditions.

"Having established that the reaction most probably proceeds *via* a [4+2] cycloaddition of the allene with the arene ring, we turned to density functional theory computations (at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP level, see section 10.2.7. for full computational details) to better understand the observed amazing reactivity.[254] When comparing the transition state energies of nine different cycloadditions in dependence of the substituents on the benzene ring and allene, computations clearly show the favorable nature that bulky *tert*-butyl groups have on the transition state barrier heights (Figure 14). The free energies with *tert*-butyl groups (14.7-18.3 kcal/mol) were significantly lower than with methyl (20.3-25.3 kcal/mol) or hydrogen (22.1-25.3 kcal/mol),

[253] **4.1h** was obtained in 81% ee using our own methodology, see: ref 229.
[254] The DFT calculations were performed by Dr. M. D. Wodrich form the LCMD group at EPFL. The figures 14 and 15 were directly taken from ref 235.

independently from the substituent on the allene. In addition, the reactivity was further enhanced by the carboxy substituent on the allene, although the effect was weaker. These results are in good accordance with the reaction rates observed experimentally.



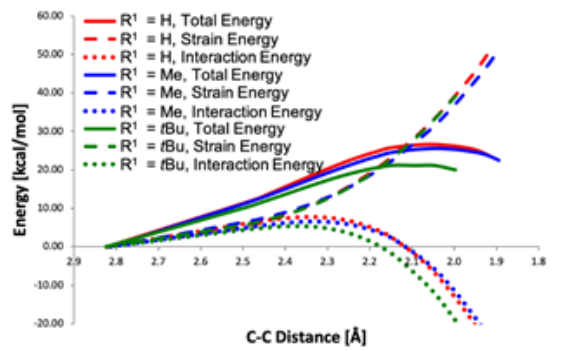
Ester = 2-iodobenzoate. Free energies computed at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP level.
Note that column colors correspond to those of the activation strain model computations in Figures 15. A and B.

Figure 14. Free energies of transition states in dependence of substituents on the benzene and the allene.

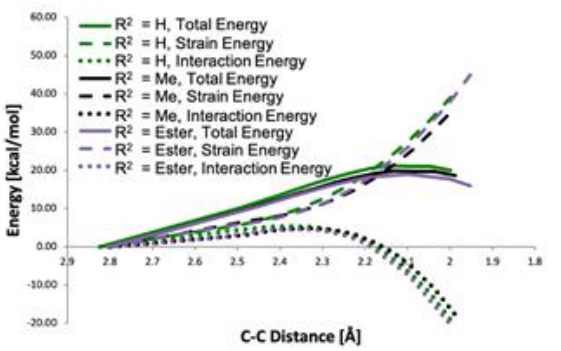
To gain additional insight, we analyzed the energetic profiles of these nine reactions using the activation strain model.[255] Initially, we speculated that the bulky *tert*-butyl groups in R^1 could diminish the planarity of the benzene ring, lowering the distortion energy and making it easier to break aromaticity. However, the calculation results showed that the presence of the bulky substituents in R^1 causes energetically favorable dispersive interactions at longer C-C distances, whereas no major difference in strain energy was observed (Figure 15. A). This resulted in an earlier, lower energy transition state for the *tert*-butyl containing variant relative to methyl or hydrogen. Substitution on the allene is characterized by a more complicated picture in which both the unfavorable strain energy and stabilizing interaction energy are influenced by the substituent (Figure 15. B). Replacing the hydrogen atom with either a methyl or a carboxy group slightly reduces the strain energy. However, this substitution also results in a less favorable interaction energy for the methyl variant while the ester variant provides a more favorable interaction. Overall, this results in the ester having a lower energy transition state barrier relative to either a hydrogen or methyl group."

[255] F. M. Bickelhaupt, K. N. Houk, *Angew. Chem. Int. Ed.* **2017**, *56*, 10070 and references cited therein.

A. Dependence of R^1 group on the benzene for R^2 = H on the allene



B. Dependence of R^2 group on the allene for R^1 = *t*Bu on the benzene



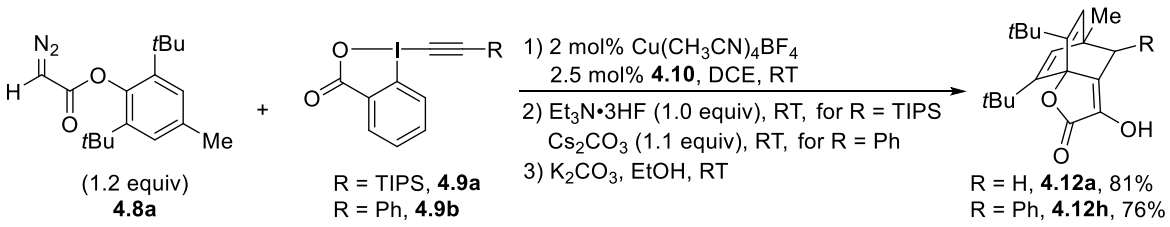
Ester = 2-iodobenzoate. Activation strain model computed at the M06-2X/def2-SVP level.
Note that the plots depict electronic energies, as opposed to free energies.

Figure 15. Activation strain model results.

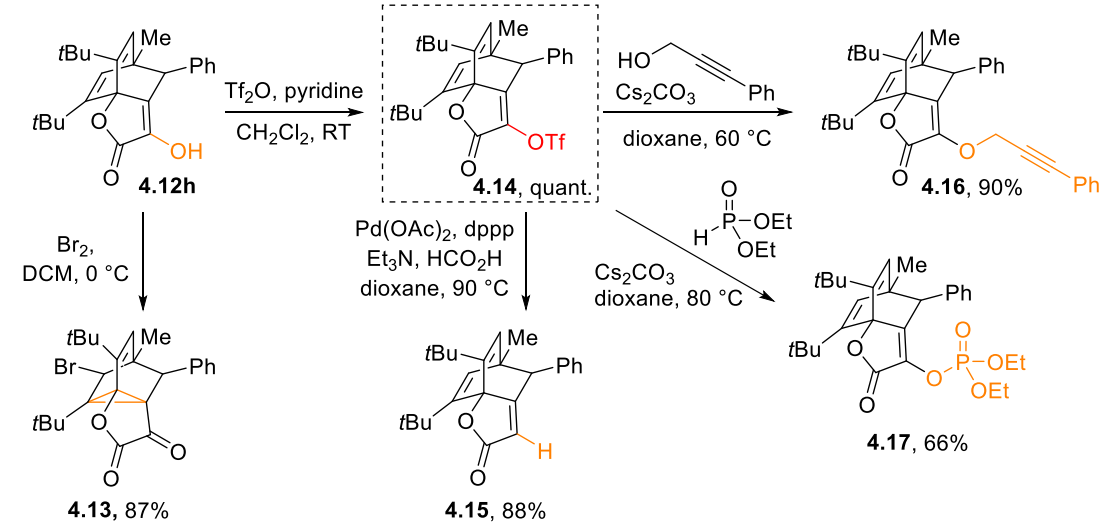
4.5. Product Derivatization[256]

In order to perform follow-up modifications, we prepared ketoesters **4.12a** and **4.12h**, obtained in their enol form (Scheme 55. A). Pleasingly, the reactions were performed on gram-scale in a one-pot fashion after final cleavage of the iodobenzoyl ester in presence of K_2CO_3 in ethanol.

A. Scale-up synthesis of **4.12a** and **4.12h**



B. Functionalization of the products



Scheme 55. Product modifications.

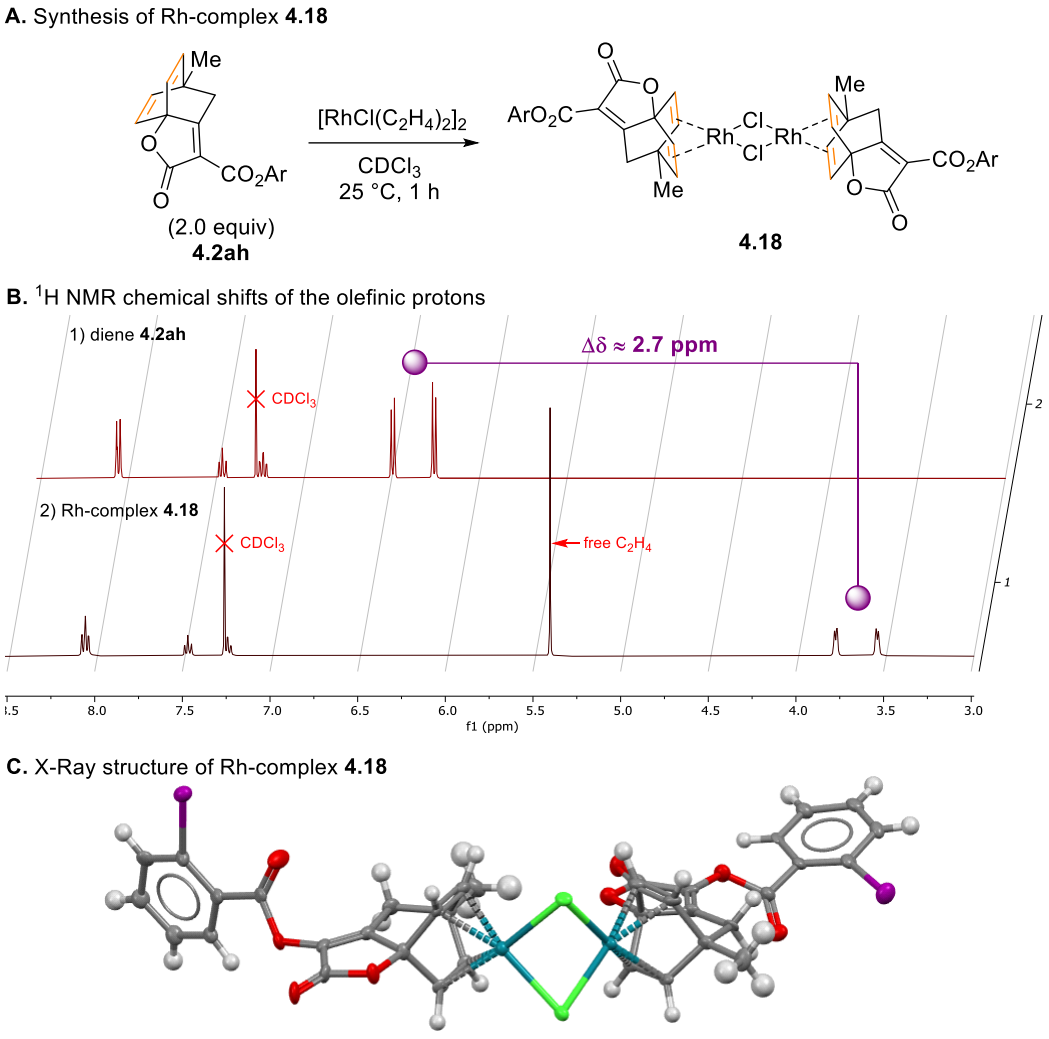
[256] This work was performed by Dr. D. P. Hari.

With sufficient quantities of material, product modifications were carried out (Scheme 55. B). Bromination of **4.12h** yielded highly strained cyclopropane **4.13** in 87% yield, through formation of a bromonium species.[257] The enol **4.12h** was quantitatively transformed into the corresponding triflate **4.14** by reaction with triflic anhydride. Compound **4.14** could serve as a convenient platform for further modifications through reaction with the vinyltriflate: Palladium-catalyzed reduction of **4.14** with formic acid gave unsaturated lactone **4.15** in good yield. Vinylic substitution of the triflate **4.14** with 3-phenylprop-2-yn-1-ol or diethyl phosphonate under basic conditions gave access to products **4.16** and **4.17** respectively. Several attempts to reduce or open the butenolide **4.12a** using classical conditions such as $LiAlH_4$ or potassium hydroxide failed.

4.6. Utilization of the Diene Products as Ligands for Rhodium(I)-Catalyzed Reactions

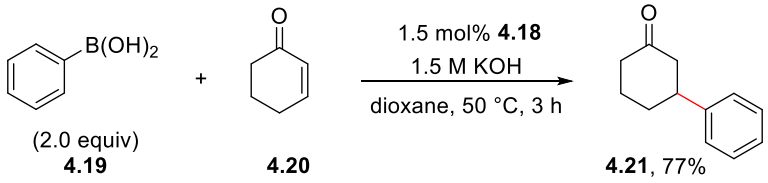
As mentioned previously, bicyclo[2.2.2]octadienes bind to low-valent metals *via* both alkene groups. Metal-bicyclo[2.2.2]octadiene complexes are particularly attractive because they are sufficiently stable to be isolated. We considered to use our products for the formation of rhodium complexes. Given the easy access to diene **4.2a** under mild conditions, we first attempted a complexation with $[RhCl(C_2H_4)_2]_2$ by entropically driven displacement of ethylene. No complexation could be observed by *in situ* monitoring of the reaction in $CDCl_3$ up to 50 °C, probably due to excessive steric hindrance of the two *ortho tert*-butyl substituents. In contrast, dimer complex **4.18** was cleanly formed in one hour at room temperature, by just mixing non-substituted diene **4.2ah** with $[RhCl(C_2H_4)_2]_2$ (Scheme 56, A and B). In addition, **4.18** was conveniently precipitated by addition of diethyl ether to the reaction mixture and collected as a bright yellow solid by filtration. X-ray quality crystals of **4.18** could be obtained, allowing us to confirm its structure (Scheme 56. C).[258]

[257] The structure of **4.13** was confirmed by X-ray analysis (available at the Cambridge Crystallographic Centre, CCDC number 1850113).
[258] Available at the Cambridge Crystallographic Centre, CCDC number 1945514.



Scheme 56. Complexation of **4.2ah** with $[RhCl(C_2H_4)_2]_2$ in $CDCl_3$ and X-ray structure.

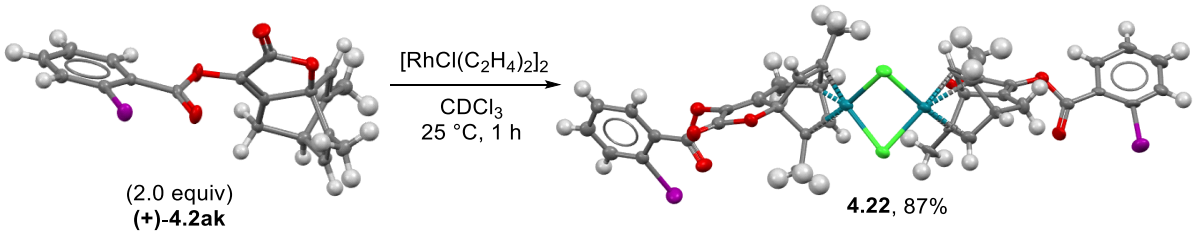
Complex **4.18** was then utilized as a catalyst for the conjugate addition of phenylboronic acid (**4.19**) to cyclohexenone (**4.20**) (Scheme 57). The transformation proceeded well under standard conditions (3 mol% of Rh),[259] furnishing the β-arylated ketone **4.21** with 77% yield. It is important to mention that the basic aqueous media might lead to the cleavage of the iodobenzoyl part and it is difficult to firmly draw the actual active catalyst.



Scheme 57. Conjugate addition of phenylboronic acid (**4.19**) on cyclohexenone (**4.20**) with Rh-diene **4.28** as catalyst.

[259] Y. Otomaru, K. Okamoto, R. Shintani, T. Hayashi, *J. Org. Chem* **2005**, *70*, 2503.

When considering the high performance of pure C_2-symmetric chiral bicyclo[2.2.2]octadiene ligands developed by the group of Hayashi in rhodium-catalyzed asymmetric addition, we turned our attention to compound **4.2ak** having a pseudo-C_2-symmetry (Scheme 58).



Scheme 58. Synthesis of Rh-complex **4.22** from **(+)-4.2ak**.

Enantiopure **(+)-4.2ak** was isolated by preparative chiral HPLC and we assigned its absolute configuration by X-Ray crystal analysis.[260] Complexation of **(+)-4.2ak** with $[RhCl(C_2H_4)_2]_2$ formed the corresponding complex **4.22** in a pure dimeric form which was isolated in good yield after purification on silica. X-ray quality crystals of complex **4.22** were grown and compared with the diene reported by Hayashi and co-workers (Figure 16).[261] The immediate coordination sphere around the rhodium was not distorted by the lower symmetry of ligand **4.22**: all bonds between the metal and the olefins were of same length, and within error margin also identical to those in complex **4.23**. In contrast, the ^{13}C and even more the ^{1}H NMR signals on the olefins were clearly separated for complex **4.22**, indicating that this ligand will induce a non-symmetrical electronic environment. From this point of view, it is clearly different from the classical Hayashi dienes with a pure C_2-symmetry.

[260] Available at the Cambridge Crystallographic Centre, CCDC number 2027173.
[261] T. Nishimura, Y. Ichikawa, T. Hayashi, N. Onishi, M. Shiotsuki, T. Masuda, *Organometallics* **2009**, *28*, 4890.

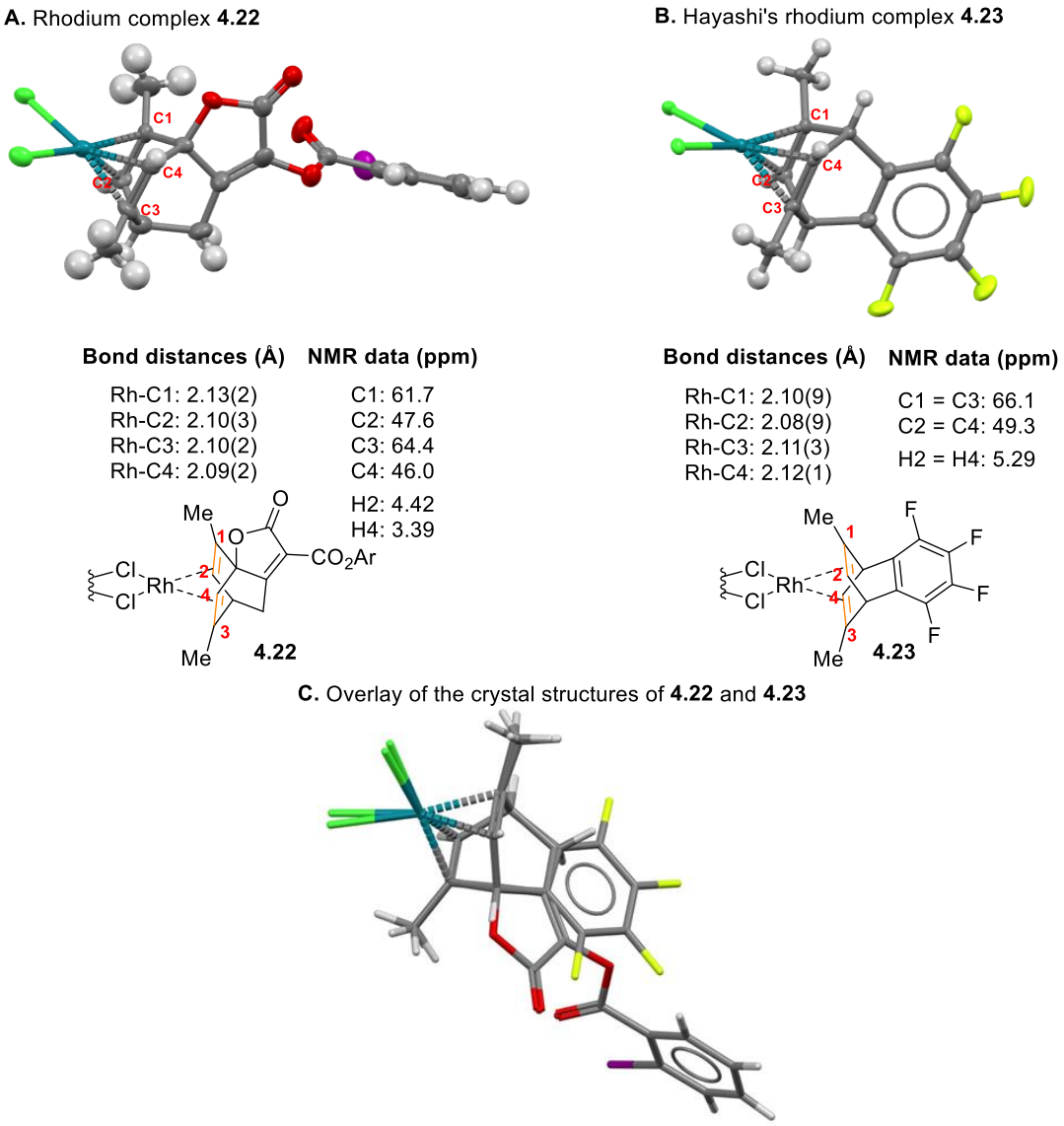
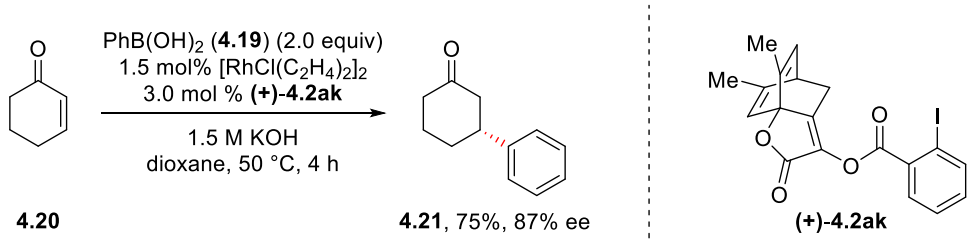


Figure 16. Rh-C bond lengths and ^{1}H and ^{13}C NMR comparisons of rhodium(I) complex **4.22** and Hayashi's complex **4.23**. Overlay of the two X-Ray structures.[262]

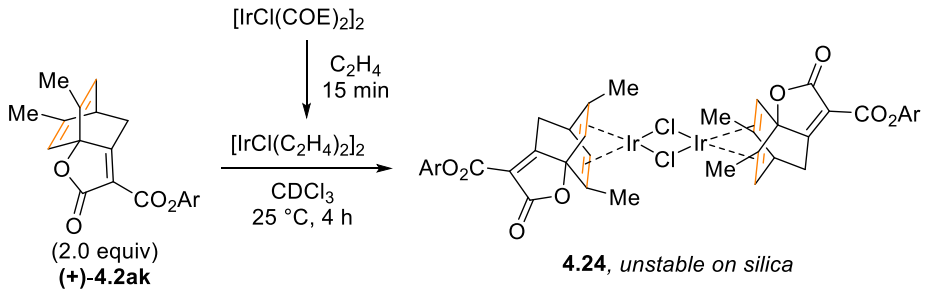
To prove the application potential of **(+)-4.2ak** in asymmetric catalysis, the chiral ligand was used for the rhodium-catalyzed conjugate addition of boronic acids to enone (Scheme 59). In this respect, the active catalyst **4.22** was pre-formed *in situ* by treatment of **(+)-4.2ak** with $[Rh(C_2H_4)_2]_2$, and subsequent addition of phenyl boronic acid (**4.19**) and cyclohexenone (**4.20**) provided the expected β-functionalized ketone **4.21** in 75% yield with 87% ee. This result is promising when considering that the methyl substituent is smaller than the phenyl or benzyl groups used in previous works[259] and no attempt was made to optimize the reaction conditions.

[262] The mirror image of the reported structure for **4.23** was used in order to have the same absolute configurations.



Scheme 59. Enantioselective conjugate addition with ligand **(+)-4.2ak**.

Over the past decade, chiral bicyclo[2.2.2]octadiene ligands have also been successful in various iridium-catalyzed asymmetric transformation.[263] In order to increase the versatility of diene **(+)-4.2ak**, we considered the preparation and application of an iridium(I) complex (Scheme 60). In this case, initial bubbling of ethylene gas to a solution of the precursor $[IrCl(COE)_2]_2$ was required to displace the competitive cyclooctene molecules.[264] Addition of ligand **(+)-4.2ak** led to partial complexation and the moderate stability of the iridium-complex **4.24** on silica, compared to the rhodium analogue, rendered the purification difficult. The utilization of **(+)-4.2ak** with iridium catalysis was not further investigated.



Scheme 60. Attempt for the synthesis of Ir(I)-complex from **(+)-4.2ak**.

4.7. Conclusion and Outlook

In summary, a highly efficient strategy for the rapid assembly of bicyclo[2.2.2]octadienes starting from simple diazo esters and EBX reagents has been developed. This one-pot sequential oxy-alkynylation/[4+2] cycloaddition reaction proceeds between 25 and 90 °C, an unusual low temperature range for such dearomatization reaction. The reaction tolerated a broad range of functional groups on both diazo esters and EBX reagents. Removal of the copper catalyst for the reactions proceeding at higher temperature was however required.

Isolation of the reaction intermediates supports a key [4+2] cycloaddition of an *in situ* formed allene with the tethered arene ring. DFT calculations shed light on the exceptionally low activation energy for the dearomatization step: counter-intuitive favorable dispersive interactions in the transition state combined with a weaker donor-effect of carboxyl substituents on the allene significantly decreased the energy transition state barrier.

The obtained products were transformed into useful building blocks and preliminary results indicated that other polycyclic ring systems could also be accessed using this strategy. Notably, this

[263] M. Nagamoto, T. Nishimura, *ACS Catal.* **2017**, *7*, 833.

[264] The complexation procedure was adapted from, M. Dieckmann, Y.-S. Jang, N. Cramer, *Angew. Chem. Int. Ed.* **2015**, *54*, 12149.

methodology allows straightforward access to versatile diene ligands for rhodium catalysis with easy variation of the nature and position of the substituents. A large steric environment on the olefins can, however, prevents the complexation. The prepared rhodium(I)-complexes could be extensively characterized and enantiopure pseudo C_2-symmetric ligand **(+)-4.2ak** was successfully used in the enantioselective 1,4-addition of phenylboronic acid (**4.19**) to cyclohexenone (**4.20**) with 87% enantioselectivity.

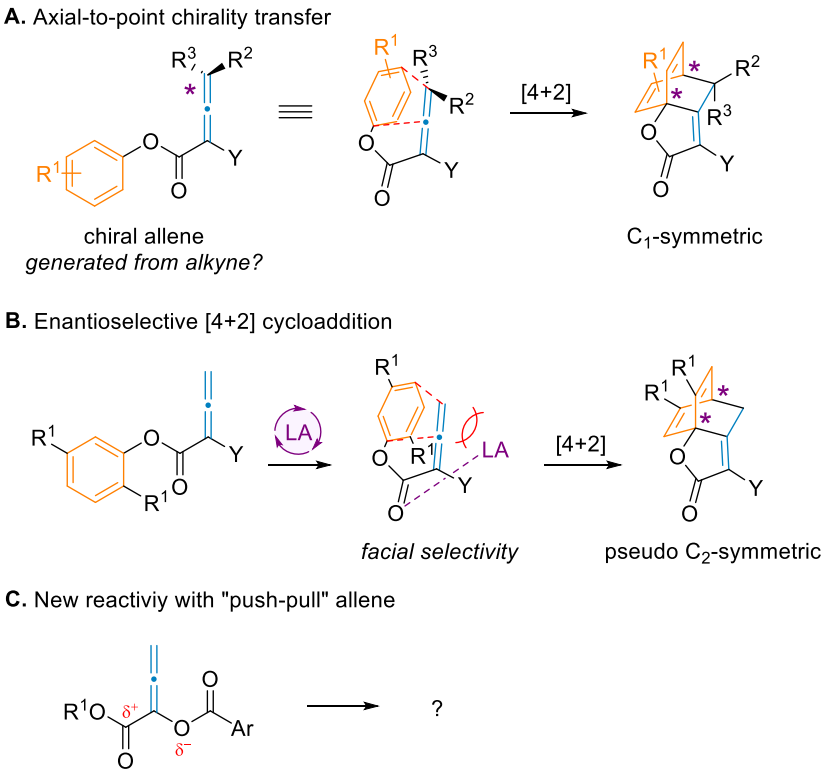
We consider our work on this intramolecular [4+2] cycloaddition of allenes with arenes complete, but several follow-up investigations remain possible. To our knowledge, synthetic methods to access enantioenriched bicylo[2.2.2]octadienes mostly rely on the chiral pool or require resolution *via* preparative HPLC and therefore, the development of an enantioselective cycloaddition step would be highly valuable. For instance, C_1-symmetric diene ligands could be accessed by axial-to-point chirality transfer during the [4+2] cycloaddition (Scheme 61. A). Various enantioselective syntheses of allenes have been described,[265] including enantioselective isomerizations and rearrangements of alkynes.[266] A more challenging approach to access enantioenriched pseudo C_2-symmetric ligand like **4.2ak**, would require the desymmetrization of the enantiotopic faces of the arene (Scheme 61. B). The activation of the allenoate through the carbonyl lone pair with a chiral Lewis acid would be a possible strategy.[267] Further fundamental study and reactivity investigation of this new type of "push-pull" allene substrates could be envisaged (Scheme 61. C). Only few examples of such allenes are reported in the literature, likely because of their tedious synthesis.[268]

[265] For recent reviews, see: a) W.-D. Chu, Y. Zhang, J. Wang, *Catal. Sci. Technol.* **2017**, *7*, 4570; b) R. K. Neff, D. E. Frantz, *ACS Catal.* **2014**, *4*, 519; c) J. Ye, S. Ma, *Org. Chem. Front.* **2014**, *1*, 1210.

[266] For representative examples, see: a) H. Liu, D. Leow, K.-W. Huang, C.-H. Tan, *J. Am. Chem. Soc.* **2009**, *131*, 7212; b) T. Inokuma, M. Furukawa, T. Uno, Y. Suzuki, K. Yoshida, Y. Yano, K. Matsuzaki, Y. Takemoto, *Chem. Eur. J.* **2011**, *17*, 10470; c) Y. Wang, W. Zhang, S. Ma, *J. Am. Chem. Soc.* **2013**, *135*, 11517.

[267] a) J. M. Wiest, M. L. Conner, M. K. Brown, *J. Am. Chem. Soc.* **2018**, *140*, 15943; b) Y. Xu, Y. J. Hong, D. J. Tantillo, M. K. Brown, *Org. Lett.* **2017**, *19*, 3703; c) R. Guo, B. P. Witherspoon, M. K. Brown, *J. Am. Chem. Soc.* **2020**, *142*, 5002.

[268] For few occurrences in methodology, see: a) G. R. Boyce, S. Liu, J. S. Johnson, *Org. Lett.* **2012**, *14*, 652; b) A. Kondoh, S. Ishikawa, T. Aoki, M. Terada, *Chem. Commun.* **2016**, *52*, 12513; c) N. A. Nedolya, L. Brandsma, N. I. Shlyakhtina, A. I. Albanov, *Chem. Heterocycl. Compds.* **2001**, *37*, 1173; d) M. J. Sleeman, G. V. Meehan, *Tetrahedron Lett.* **1989**, *30*, 3345.



Scheme 61. Potential future work on allene/arene [4+2] cycloaddition.

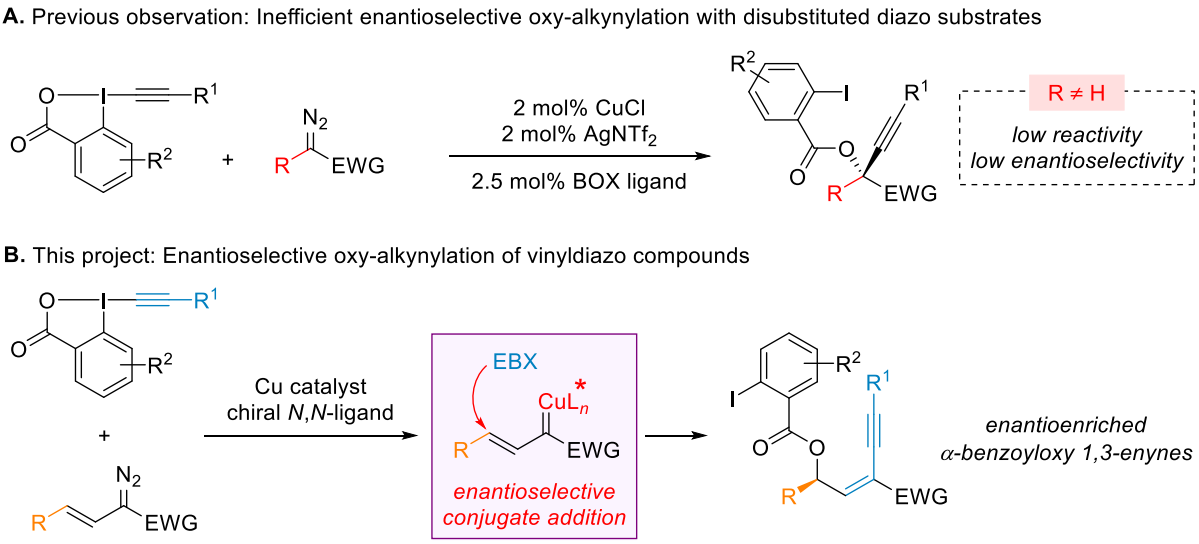
5

Progress toward the Development of the Enantioselective Conjugate Oxy-Alkynylation of Diazo Compounds

5. Progress toward the Development of the Enantioselective Conjugate Oxy-Alkynylation of Diazo Compounds

5.1. Objectives of the Project

The work achieved in our group on the atom-economical copper-catalyzed insertion of EBX reagents onto diazo compounds and its following enantioselective variant extension were efficient methods to access highly functional α-hydroxyl α-alkynyl ester motifs.[227,229] However, the low reactivity and enantioselectivity achieved with disubstituted diazo ester substrates was a major limitation of the methodology (Scheme 62. A). Our intention was to develop related enantioselective transformations in the continuity of these pioneer projects. We reasoned that vinyldiazo compounds account for a different situation with creation of the chiral center at a remote position to the carbene center (Scheme 62. B).

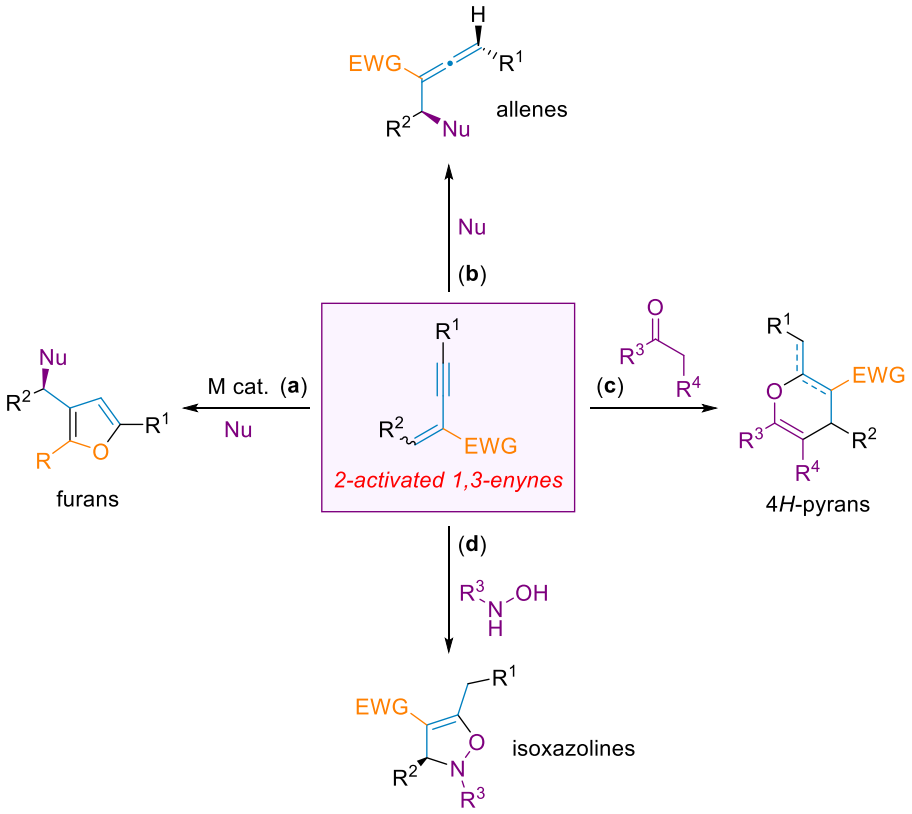


Scheme 62. Envisaged enantioselective conjugate oxy-alkynylation of diazo compounds.

The successful development of an enantioselective conjugate oxy-alkynylation of vinyldiazo substrates with EBX reagents would allow a rapid access to enantioenriched conjugated enynes, which are molecular motifs that can be found in bioactive molecules.[269] More importantly, activated 1,3-enynes with an electron-withdrawing group (EWG) at the 2-position, such as ester or amide are powerful synthons for the rapid construction of elaborated building blocks and pharmaceutically

[269] a) P. Nussbaumer, I. Leitner, K. Mraz, A. Stuetz, *J. Med. Chem.* **1995**, *38*, 1831; b) A. G. Myers, A. M. Hammond, Y. Wu, J. -N. Xiang, P. M. Harrington, E. Y. Kuo, *J. Am. Chem. Soc.* **1996**, *118*, 10006.

relevant compounds (Scheme 63),[270] such as furans (**a**),[271] allenes (**b**),[272] 4*H*-pyrans (**c**),[273] and 4-isoxazolines (**d**).[274]



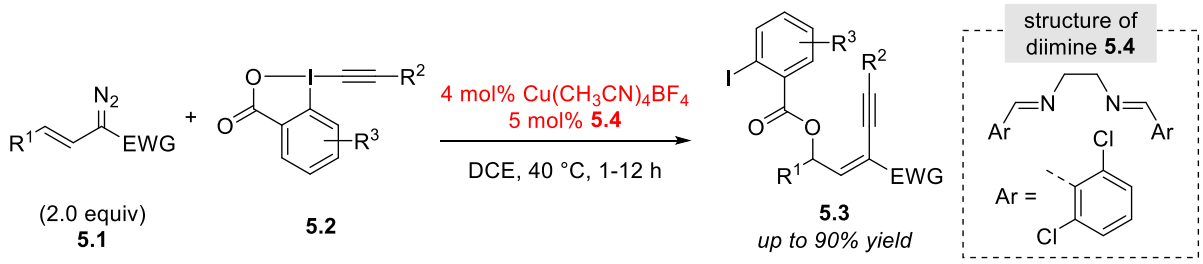
Scheme 63. Applications of 2-activated 1,3-enynes in enantioselective transformations.

This chapter will present our efforts for the implementation of an enantioselective conjugate oxy-alkynylation of vinyldiazo compounds

5.2. Optimization of the Reaction

The reaction conditions for the functionalization of vinyldiazo compounds **5.1** with EBX reagents **5.2** in a racemic manner are reiterated below (Scheme 64).[229] Key for the successful transformation was the formation of the active catalyst by pre-mixing $Cu(CH_3CN)_4BF_4$ and the *N*,*N*-diimine ligand **5.4**.

[270] For a recent review, see: X. Bao, J. Ren, Y. Yang, X. Ye, B. Wang, H. Wang, *Org. Biomol. Chem.* **2020**, *18*, 7977.
[271] Selected examples of furans synthesis, a) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164; b) T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 7679; c) Y. Xiao, J. Zhang, *Angew. Chem. Int. Ed.* **2008**, *47*, 1903; d) L. Zhou, M. Zhang, W. Li, J. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 6542; e) Z. Li, J. Peng, C. He, J. Xu, H. Ren, *Org. Lett.* **2020**, *22*, 5768.
[272] Selected examples of allene synthesis, a) H. Qian, X. Yu, J. Zhang, J. Sun, *J. Am. Chem. Soc.* **2013**, *135*, 18020; b) Q. Yao, Y. Liao, L. Lin, X. Lin, J. Ji, X. Liu, X. Feng, *Angew. Chem. Int. Ed.* **2016**, *55*, 1859; c) P. H. Poulsen, Y. Li, V. H. Lauridsen, D. K. B. Jørgensen, T. A. Palazzo, M. Meazza, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2018**, *57*, 10661.
[273] a) Z. Yue, W. Li, L. Liu, C. Wang, J. Zhang, *Adv. Synth. Catal.* **2016**, *358*, 3015; b) Z. Wang, Y. Zhu, J. Zhang, J. Li, M. Wu, X. Yan, Y. Li, L. Chen, *Tetrahedron Asymmetry* **2017**, *28*, 1708; c) Y. Zhu, Z. Wang, J. Zhang, J. Yu, L. Yan, Y. Li, L. Chen, X. Yan, *Eur. J. Org. Chem.* **2018**, 347.
[274] a) W. Li, X. Yu, Z. Yue, J. Zhang, *Org. Lett.* **2016**, *18*, 3972; b) X. Yu, B. Du, K. Wang, J. Zhang, *Org. Lett*. **2010**, *12*, 1876.



Scheme 64. Racemic Cu-catalyzed conjugate oxy-alkynylation reaction.

Since the transformation was optimal under such copper catalysis, we focused our screening on suitable chiral *N*,*N*-ligands. Several classes have found applications in enantioselective copper carbene-based transformations and were therefore envisaged.[275] The most encountered structures are: bis(oxazoline) (BOX),[276] 1,2-diimine,[277] bis(azaferrocene),[278] semicorrin[279] and *N*-Heterocyclic Carbene (NHC)[280] (Figure 17).

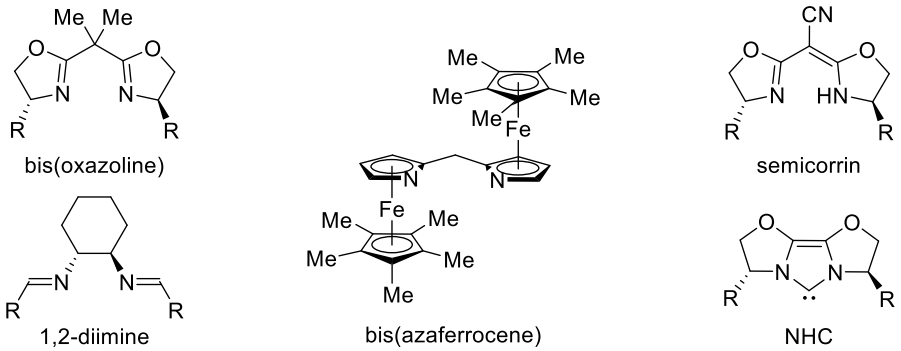


Figure 17. Common chiral ligands used in copper carbene chemistry.

5.2.1. Screening of BOX Ligands

Despite the poor results (low reactivity and enantioselectivity) we have observed using BOX ligands with disubstituted diazo ester substrates, we decided to first examine this class of ligand as they have been already synthesized within our group or were directly commercially available (Table 3).

[275] For a review on Cu-catalyzed reactions of diazo compounds, see: X. Zhao, Y. Zhang, J. Wang, *Chem. Commun.* **2012**, *48*, 10162.

[276] Selected examples using BOX ligands, a) R. E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005; b) C. J. Flynn, C. J. Elcoate, S.E. Lawrence, A. R. Maguire, *J. Am. Chem. Soc.* **2010**, *132*, 1184; c) Q. Xiao, Y. Xia, Y. H. Li, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2011**, *50*, 1114; For a review, see: d) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2011**, *111*, PR284.

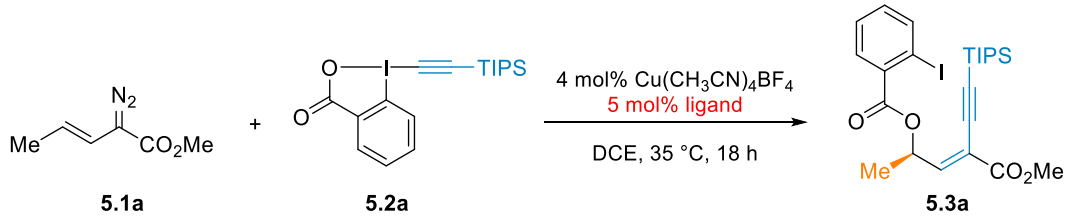
[277] Selected examples using chiral diimine ligands, a) L. A. Dakin, S. E. Schaus, E. N. Jacobsen, J. S. Panek, *Tetrahedron Lett.* **1998**, *39*, 8947; b) Y.-Z. Zhang, S.-F. Zhu, L.-X. Wang, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2008**, *47*, 8496.

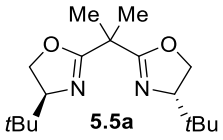
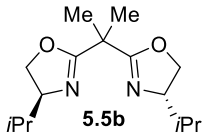
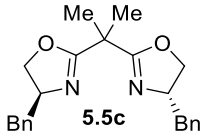
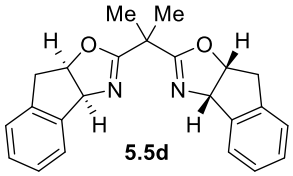
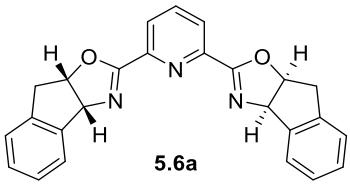
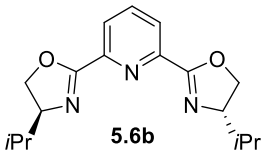
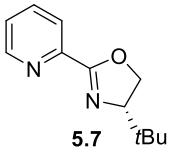
[278] Selected examples using bis(azaferrocene), a) T. C. Maier, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 4594; b) S. Son, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 1046.

[279] A. Pfaltz, *Synlett* **1999**, *1999*, 835.

[280] D. Janssen-Müller, C. Schlepphorst, F. Glorius, *Chem. Soc. Rev.* **2017**, *46*, 4845.

Table 3. Yields and enantiomeric excess obtained using BOX, PyBOX and PyOX ligands.[a]



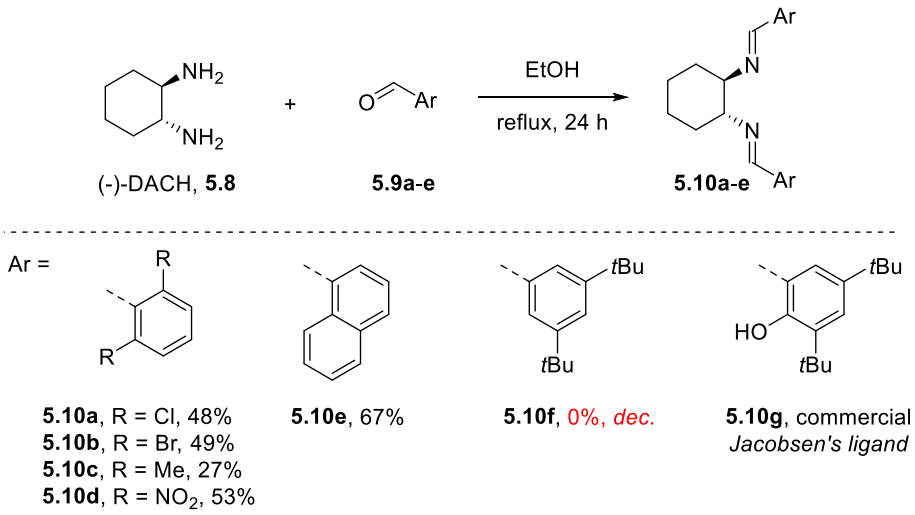
Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	 5.5a	27	0
2	 5.5b	11	0
3	 5.5c	8	0
4[d]	 5.5d	11	0
5	 5.6a	4	0
6	 5.6b	15	11
7	 5.7	9	9

[a]Reaction conditions: 0.30 mmol of vinyldiazo **5.1a**, 0.15 mmol of TIPS-EBX (**5.2a**), $Cu(CH_3CN)_4BF_4$ (4 mol%), ligand (5 mol%), DCE (0.05 M). [b]Yield after purification by column chromatography. [c]Obtained by chiral HPLC. [d]Obtained after 18 h at 35 °C, then 2 h at 60 °C.

With vinyldiazo **5.1a**, TIPS-EBX (**5.2a**) and using $Cu(CH_3CN)_4BF_4$ as copper source, only low yields and no enantioinduction were observed (entries 1 to 4). A significant decrease of reactivity was noticed: the reactions had to be performed overnight instead of two hours for the racemic reaction. This set of results confirmed the inefficacity of BOX ligands when two substituents are present on the diazo, and clearly indicated the need of another *N*,*N*-type of chiral ligand for our transformation to proceed in a satisfactory manner. In addition, PyBOx ligands **5.6a** and **5.6b** were tested (entries 5 and 6). A small ee could be measured with ligand **5.6b** having *iso*-propyl substituents. Finally, PyOX-type ligand **5.7** was investigated and furnished the product **5.3a** with low yield and low enantioselectivity (entry 7).

5.2.2. Screening of Chiral Diimine Ligands

Considering the diimine structure of ligand **5.4** employed in the racemic transformation, we turned our attention to the easily accessible C_2-symmetric diimines derived from chiral 1,2-diaminocyclohexane (DACH).[281] The ligands **5.10a**-**e**, with different stereoelectronic properties, were easily prepared by condensation of commercially available (*R*,*R*)-(-)-DACH (**5.8**) with the corresponding aromatic aldehydes **5.9a**-**e** (Scheme 65). Only **5.10f** could not be isolated conveniently due to its instability. Salen ligand **5.10g** (Jacobsen's ligand) was available in our laboratory.[282]



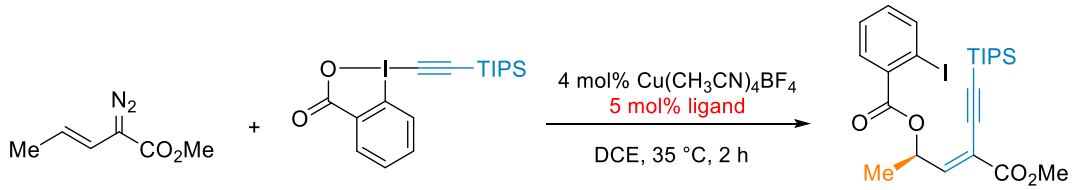
Scheme 65. Preparation of DACH-derived diimine ligands **5.10**.

This series of ligand was then screened in the reaction between vinyldiazo **5.1a** and TIPS-EBX (**5.2a**), and with $Cu(CH_3CN)_4BF_4$ as copper source (Table 4). The expected product **5.3a** was formed in good yields with ligands **5.10a**, **5.10b** and **5.10c** having *ortho* substitutents (entries 1 to 3). Low conversion was however obtained with ligand **5.10d** having the nitro groups (entry 4), and with **5.10e** incorporating naphthyl substituents (entry 5). In addition, absolutely no conversion was observed with the salen ligand **5.10g** (entry 6). Regarding the enantioselectivity, the best result obtained was low (10% ee, entry 1), but confirmed the possibility to develop the desired enantioselective copper-catalyzed reaction. The other ligands **5.10b**-**e** gave ee values as low as the margin of error of the HPLC (entries 2 to 5).

[281] Z. Li, R. W. Quan, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5889.

[282] a) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, *J. Am. Chem. Soc.* **1991**, *113*, 7063; b) L. Deng, E. N. Jacobsen, *J. Org. Chem.* **1992**, *57*, 4320; c) S. Chang, N. H. Lee, E. N. Jacobsen, *J. Org. Chem.* **1993**, *58*, 6939.

Table 4. Yields and enantiomeric excess obtained with DACH-based ligands **5.10a-g**.[a]



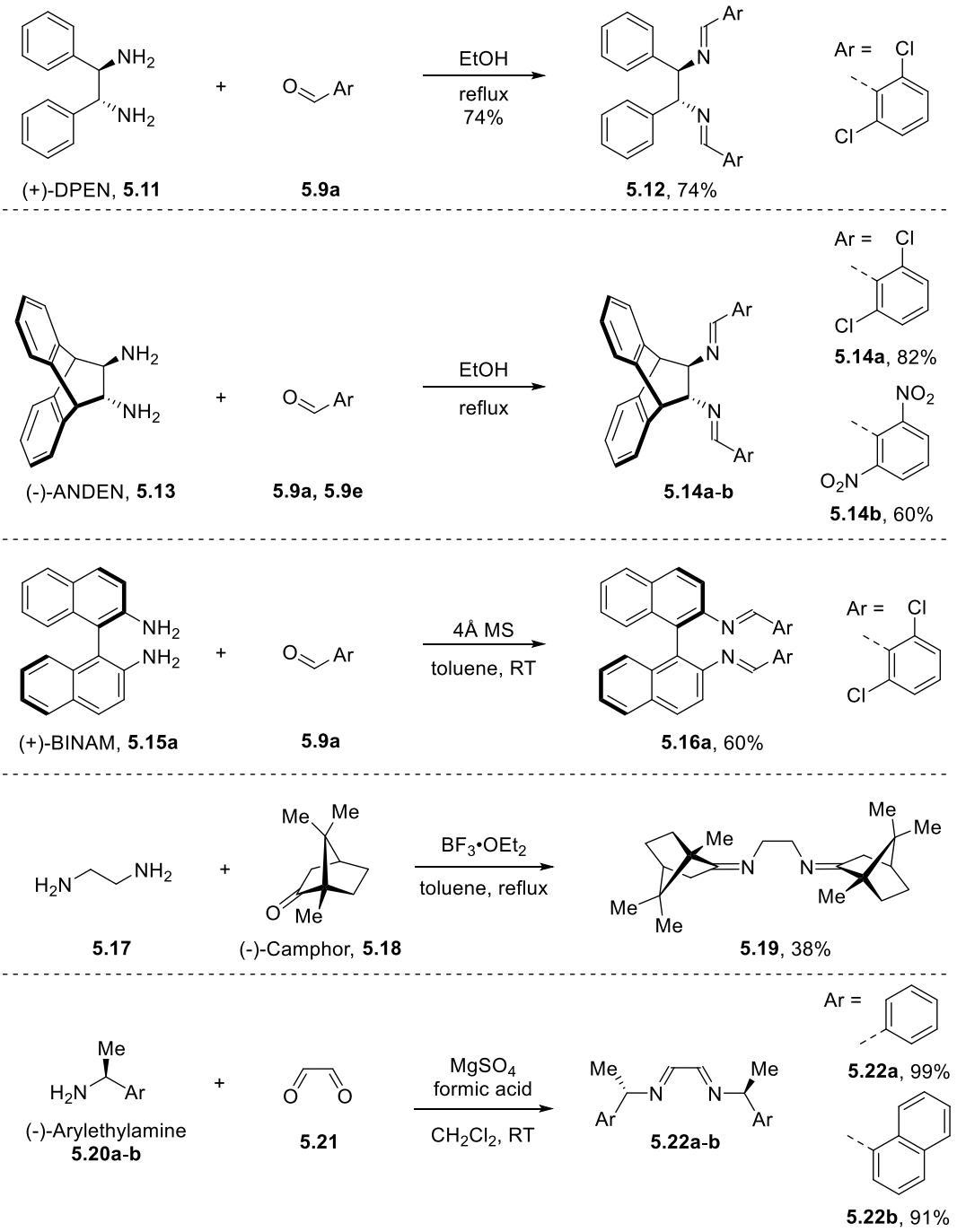
5.1a **5.2a** **5.3a**

Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	**5.10a**	72	10
2	**5.10b**	65	3
3	**5.10c**	71	5
4[d]	**5.10d**	10	0
5	**5.10e**	6	3
6	**5.10g**	no conv.	-

[a]Reaction conditions: 0.30 mmol of vinyldiazo **5.1a**, 0.15 mmol of TIPS-EBX (**5.2a**), $Cu(CH_3CN)_4BF_4$ (4 mol%), ligand (5 mol%), DCE (0.05 M). [b]Yield after purification by column chromatography. [c]Obtained by chiral HPLC. [d]Obtained after 18 h at 35 °C, then 2 h at 60 °C.

Having a proof-of-concept established, we decided to investigate other chiral diimine ligands. A variety of diimines having various structures were synthesized by condensation reactions between readily available diamines and aryl aldehydes (Scheme 66). The molecule **5.12** was built with the (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethylenediamine ((+)-DPEN, **5.11**) framework,[283] while ligands **5.14a** and **5.14b** were derived from (*R*,*R*)-(-)-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene ((-)-ANDEN, **5.13**) structure.[284] The chiral axial ligand **5.16a** was obtained from (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine ((+)-BINAM, **5.15a**).[285] (*S*)-(-)-Camphor (**5.18**) was condensed with ethylenediamine (**5.17**) to form the ketimine **5.19**.[286] In this latter case, the reaction was catalyzed by $BF_3 \bullet OEt_2$. In addition, the alternative 1,2-diimines **5.22a** and **5.22b** were prepared by condensation between glyoxal (**5.21**) and (*S*)-(-)-1-phenylethylamine (**5.20a**) and (*S*)-(-)-1-(1-naphthyl)ethylamine(**5.20b**) respectively.[287]

[283] Y. Nguyen, A. J. Lough, J. Chin, *Angew. Chem. Int. Ed*. **2008**, *47*, 8678.
[284] H. Mihara, Y. Xu, N. E. Shepherd, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 8384.
[285] M. Shi, C.-J Wang, A. S. C. Chan, *Tetrahedron Asymmetry* **2001**, *12*, 3105.
[286] A. Caselli, G. B. Giovenzana, G. Palmisano, M. Sisti, T. Pilati, T. *Tetrahedron Asymmetry* **2003**, *14*, 1451.
[287] R. Hilgraf, A. Pfaltz, *Adv. Synth. Catal.* **2005**, *347*, 61.

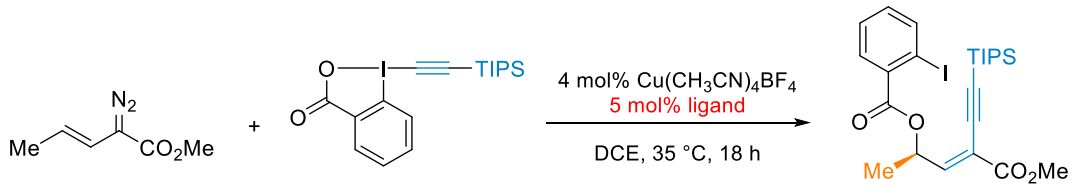


Scheme 66. Preparation of diimine ligands.

The prepared ligands were then tested in the enantioselective oxy-alkynylation of our model substrate **5.1a**, using TIPS-EBX (**5.2a**) as partner (Table 5). A very low yield and enantioselectivity was obtained using the DPEN-derived ligand **5.12** (entry 1). Similar unsatisfactory results were observed with ANDEN-based ligands **5.14a** and **5.14b**, giving low yield and no measurable enantioselectivity (entries 2 and 3). The BINAM-derived ligand **5.16a** gave the most interesting outcome, furnishing **5.3a** in a low yield but with encouraging enantioselectivity (30% yield with 30% ee, entry 4). In this case, the reaction proceeded more cleanly, in a similar fashion to the DACH-based ligands previously screened (see Table 4). Unfortunately, only a small conversion was observed with ligand **5.19** containing the

camphor skeleton (entry 5). Finally, ligands **5.22a** and **5.22b** derived from glyoxal were not adapted as well (entries 6 and 7).

Table 5. Yields and enantiomeric excess obtained with diimine ligands.[a]



5.1a **5.2a** **5.3a**

Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	**5.12**	10	4
2	**5.14a**	7	5
3	**5.14b**	7	0
4[d]	**5.16a**	31	30
5	**5.19**	5	0
6	**5.22a**	10	0
7	**5.22b**	9	5

[a]Reaction conditions: 0.30 mmol of vinyldiazo **5.1a**, 0.15 mmol of TIPS-EBX (**5.2a**), $Cu(CH_3CN)_4BF_4$ (4 mol%), ligand (5 mol%), DCE (0.05 M). [b]Yield after purification by column chromatography. [c]Obtained by chiral HPLC. [d]Obtained after 2 h at 35 °C.

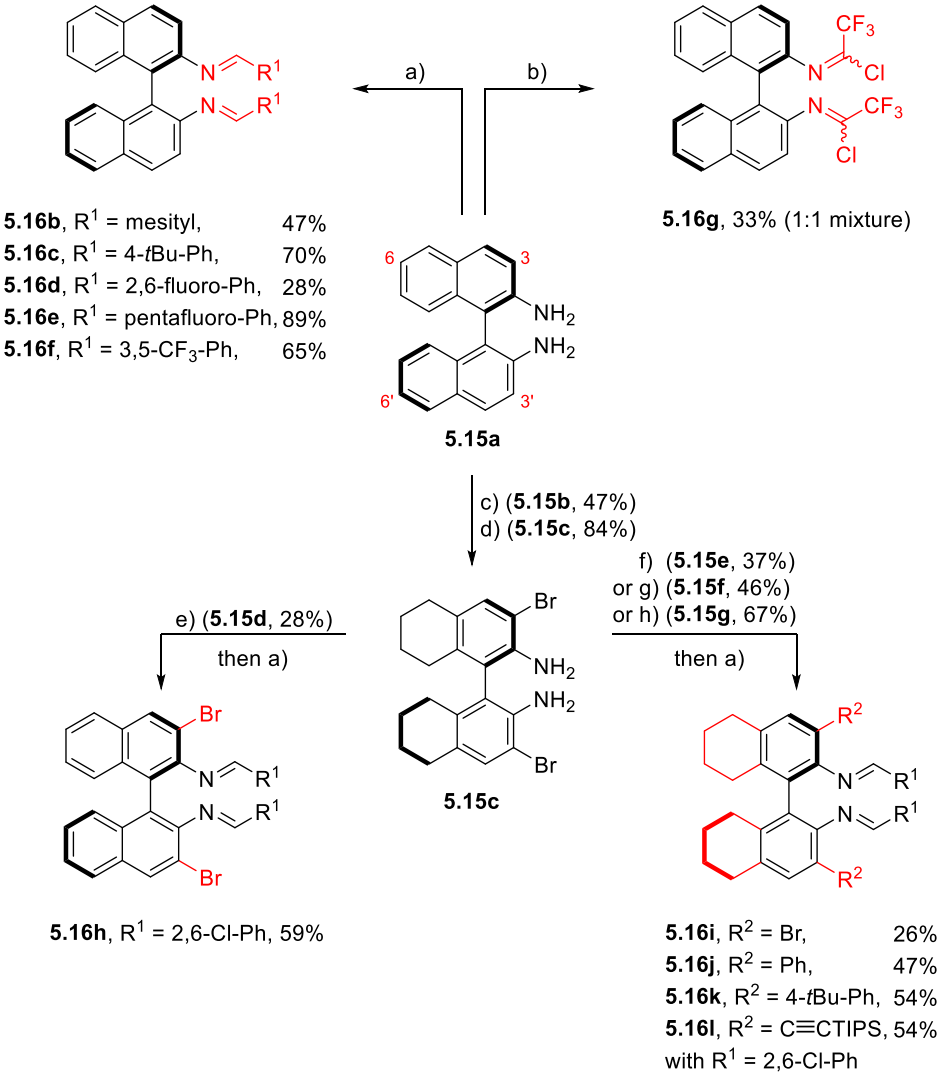
At this stage of the project we were encouraged by the 30% of enantiomeric excess obtained with the axial chiral BINAM-derived diimine ligand **5.16a** (Table 5, entry 4). Several structural variations are possible on such molecular scaffold and we were interested to study their different effects on the conjugate oxy-alkynylation reaction. We identified three main possible sites to modify the BINAM framework (Scheme 67):

- The imine moieties (R^1): Several new ligands were accessed by condensation reaction of different aldehydes with (+)-BINAM (**5.15a**). Ligands **5.16b** and **5.16c** having sterically hindered substituents, and ligands **5.16d-f**, having electron-poor fluorinated aryl groups were successfully synthesized. Other electron-rich aromatic and aliphatic aldehydes have been successfully used in the condensation reaction but the resulting diimine products rapidly decomposed (not shown). Condensation of TFA on **5.15a** followed by a chlorination step furnished the stable ketimine **5.16g** as an inseparable 1:1 mixture of diastereomers, which were not used for the next investigations.[288]

- The α-positions (R^2): Introduction of substituents at the 3,3'-positions is known to exert a considerable effect on the reactivity and stereoselectivity of binaphthyl-controlled asymmetric

[288] J. Pedroni, N. Cramer, *Org. Lett.* **2016**, *18*, 1932.

transformations.[289] The synthesis of 3,3'-substituted BINAM compounds can be fastidious.[290] We selected the route developed by Maruoka and co-workers,[291] using partially hydrogenated H_8-BINAM **5.15b** to then selectively halogenate the 3,3'-positions over the competitive highly reactive 6,6'-positions with NBS and furnish the common intermediate **5.15c**.[292] The ligand **5.16h**, having bromide substituents in the 3,3'-positions was obtained after a rearomatization with DDQ of **5.15c**, followed by the double condensation with the aldehyde **5.9a**.



[a]Reagents and conditions: a) R^1CHO, 4Å MS, toluene, reflux; b) TFA, PPh_3, Et_3N, CCl_4, 0 to 80 °C; c) Ni/Al alloy 50%, 1% NaOH aq., H_2O/*i*PrOH 1:1, reflux; d) NBS, THF, 0 °C; e) DDQ, benzene, reflux; f) $PhB(OH)_2$, $Pd(OAc)_2$, PPh_3, $Ba(OH)_2•8H_2O$, DME/H_2O 1:1, reflux; g) 4-*t*Bu-$PhB(OH)_2$, $Pd(OAc)_2$, PPh_3, $Ba(OH)_2•8H_2O$, DME/H_2O 1:1, reflux; h) (triisopropylsilyl)acetylene, $Pd(PPh_3)_2Cl_2$, CuI, ethanolamine, THF/H_2O 1:1, 60 °C. Yields are given above.

Scheme 67. Preparation of various BINAM-type ligands.[a]

[289] a) N. D. Shapiro, V. Rauniyar, G. L. Hamilton, J. Wu, F. D. Toste, *Nature* **2011**, *470*, 245; b) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.

[290] a) M. Yoshimura, M. Muraoka, T. Nakatsuka, H. Huang, M. Kitamura, *J. Org. Chem.* **2010**, *75*, 4315; b) C. C. Scarborough, R. I. McDonald, C. Hartmann, G. T. Sazama, A. Bergant, S. S. Stahl, *J. Org. Chem.* **2009**, *74*, 2613.

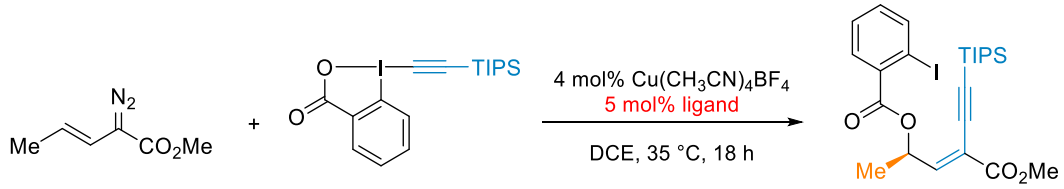
[291] T. Kano, Y. Tanaka, K. Osawa, T. Yurino, K. Maruoka, *J. Org. Chem.* **2008**, *73*, 7387.

[292] P. Yan, A. C. Millard, M. Wei, L. M. Loew, *J. Am. Chem. Soc.* **2006**, *128*, 11030.

- The binaphthyl backbone: Having a saturated binaphthyl skeleton modify the bite angle of the diimine ligands. Only the condensation step and no rearomatization reaction was required to access **5.16i** from the intermediate **5.15c**. The more functionalized compounds **5.16j** and **5.16k** bearing aromatics at the 3,3'-positions were synthesized after a Suzuki coupling and the condensation sequence. To access **5.16l**, the TIPS-alkyne groups were introduced by Sonogashira coupling followed by condensation reaction with **5.9a**. A more bulky R^2 substituent (3,5-bis(trifluoromethyl)phenyl) was successfully introduced but the last condensation step could not be realized because of excessive steric hindrance (not shown).

The obtained BINAM diimine ligands **5.16b**-**l** were tested in the enantioselective oxy-alkynylation of vinyldiazo compound **5.1a** (Table 6). In comparison with the initial ligand **5.16a** (entry 1), diminished yields and enantiomeric excess were obtained with the mesityl-substituted ligand **5.16b** and the more bulky ligand **5.16c**, bearing a *tert*-butyl (entries 2 and 3). Similarly, the fluorinated ligands **5.16d**, **5.16e** and **5.16f** gave no, or extremely low yield and ee (entries 4 to 6). The electron-withdrawing effect induced by the fluorine atoms could decrease the imine coordinating strength and negatively affect the catalyst activity. Unfortunately, 3,3'-brominated ligand **5.16h** did not improved the outcome of the reaction furnishing the product in a low yield and no enantioselectivity (entry 7). In contrast, the saturated analogue **5.16i** gave an excellent yield and a similar enantioselectivity (30% ee) compared to the parent ligand **5.16a** (entry 8). To our dismay, the more sophisticated α-functionalized ligands **5.16j**, **5.16k** and **5.16l** did not give the expected improvements. The enantioselectivities obtained remained very low and the yield below 50% (entries 9 to 11).

Table 6. Yields and enantiomeric excess obtained with the ligands **5.16b-l**.



5.1a **5.2a** **5.3a**

Entry[a]	Ligand	Yield (%)[b]	ee (%)[c]
1[f]	**5.16a**	31	30
2	**5.16b**	20	12
3	**5.16c**	6	6
4[d]	**5.16d**	7	0
5[d]	**5.16e**	6	4
6	**5.16f**	7	0
7[g]	**5.16h**	13	2
8[g]	**5.16i**	98	30
9[g]	**5.16j**	36	12
10	**5.16k**	40	10
11	**5.16l**	11	5

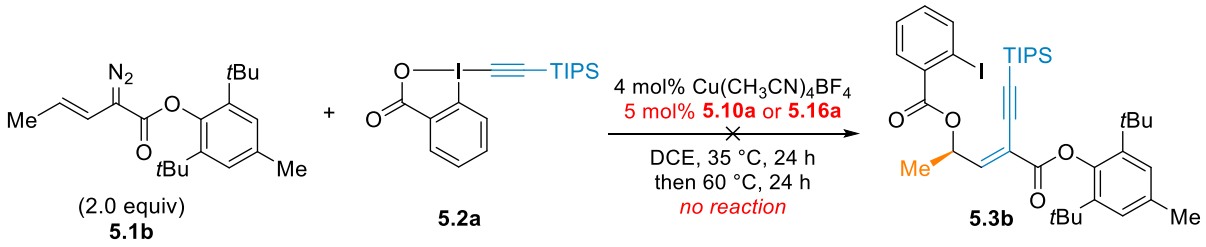
[a]Reaction conditions: 0.30 mmol of vinyldiazo **5.1a**, 0.15 mmol of TIPS-EBX (**5.2a**), $Cu(CH_3CN)_4BF_4$ (4 mol%), ligand (5 mol%), DCE (0.05 M). [b]Yield after purification by column chromatography. [c]Obtained by chiral HPLC. [d]CuCl (4 mol%) + AgOTs (4 mol%) instead of $Cu(CH_3CN)_4BF_4$ (4 mol%). [f]Obtained after 2 h. [g]Obtained after 24 h at 35 °C.

Despite all the efforts made to increase the enantioselectivity of the copper-catalyzed conjugate oxy-alkynylation reaction, the results were disappointing (maximum of 30% ee). In addition, disparate conversions and yields were obtained and we wondered how efficient the ligand-metal interaction can be in certain cases. Indeed, copper species not coordinated to *N*,*N*-ligands could also catalyse the reaction in a racemic way. Several late transition metals other than copper have been reported to catalyse efficiently the carbene formation from vinyl diazo precursors.[293] Among them, we screened few commercial catalysts of rhodium(II), ruthenium(I), gold(I) and silver(I) and no formation of the targeted product could be detected in all cases, confirming the importance of copper as catalyst.

[293] For Rh-catalyzed examples, see: a) H. M. L. Davies, A. M. Walji, *Angew. Chem. Int. Ed.* **2005**, *44*, 1733; b) X. Wang, X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2011**, *133*, 16402; c) A. G. Smith, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 18241; For Ag-catalyzed example, see: d) ref 228; For Ru-catalyzed example, see: e) F. Cambeiro, S. López, J. A. Varela, C. Saá, *Angew. Chem. Int. Ed.* **2012**, *51*, 723; For Au-catalyzed examples, see: f) F. Wei, C. Song, Y. Ma, L. Zhou, C.-H.Tung, Z. Xu, *Sci. Bull.* **2015**, *60*, 1479.

5.2.3. Attempts on Others Vinyldiazo Compounds

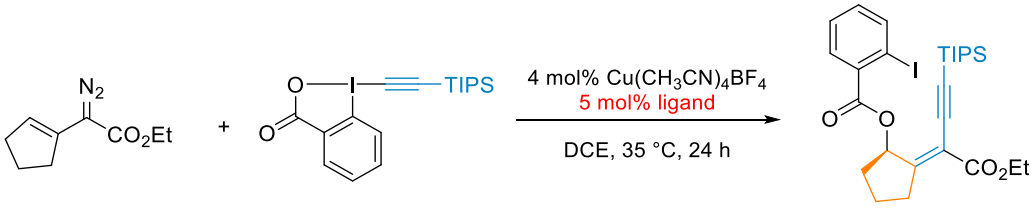
We decided to investigate different vinyldiazo compounds, other than our first model substrate **5.1a**, as only low enantioselectivity could be achieved. Highly hindered aryl substituents on the diazo substrates provided excellent levels of enantioselectivity in our previous project.[229] Vinyldiazo compound **5.1b** having a BHT-ester motif, was engaged in the oxy-alkynylation reaction with TIPS-EBX (**5.2a**), using $Cu(CH_3CN)_4BF_4$ and chiral ligands **5.10a** (DACH-based) or **5.16a** (BINAM-based) as catalysts (Scheme 68). Under these conditions, no formation of the expected product **5.3b** was detected and further heating of the reaction to 60 °C led to the minor formation of unidentified by-products (TLC). The important steric hindrance of the BHT motif could prevent the copper carbene formation from diazo **5.1b**.



Scheme 68. Attempt of oxy-alkynylation with bulky vinyldiazo ester **5.1b**.

The substituent effect at the vinylic position, where the chiral centre is created was also examined. The more rigid cyclic vinyldiazo **5.1c**, was studied with the most promising *N*,*N*-ligands identified so far (Table 7). Only 10% ee was obtained using the ligand **5.16a** (entry 1). Similar yields with lower ee were obtained with ligands **5.10a** (DACH-based) and **5.12** (DPEN-based) (entries 2 and 3). Lastly, employing the BOX ligand **5.5b** resulted in a slightly better enantioselectivity but a consequent loss of yield (entry 4). This result indicated again that BOX ligands are inadequate for the oxy-alkynylation of substituted diazo compounds despite their potential to induce higher level of enantioselectivity.

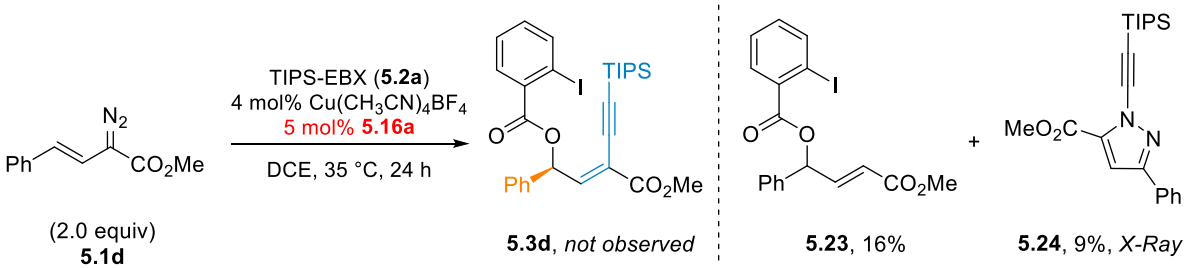
Table 7. Yields and enantiomeric excess for the oxy-alkynylation of cyclic vinyldiazo ester **5.1c**.[a]



Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	**5.16a**	47	10
2	**5.10a**	57	7
3	**5.12**	41	0
4	**5.5b**	12	19

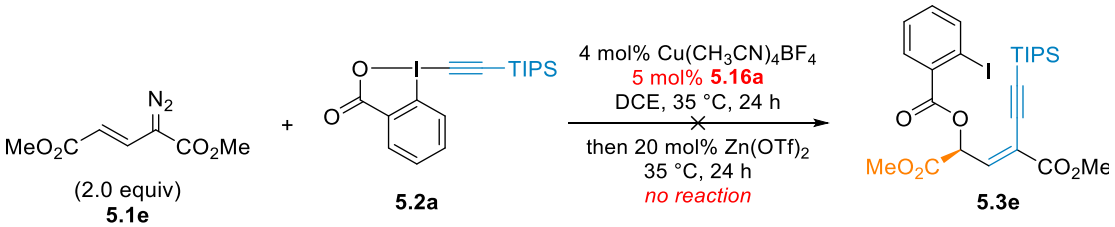
[a]Reaction conditions: 0.30 mmol of vinyldiazo **5.1c**, 0.15 mmol of TIPS-EBX (**5.2a**), $Cu(CH_3CN)_4BF_4$ (4 mol%), ligand (5 mol%), DCE (0.05 M). [b]Yield after purification by column chromatography. [c]Obtained by chiral HPLC.

The phenyl-substituted vinyldiazo ester **5.1d** was prepared and used in the oxy-alkynylation reaction with **5.16a** as ligand (Scheme 69). To our surprise, the expected product **5.3d** was not detected. The major product isolated was **5.23**, probably resulting from the proto-demetalation of the vinyl-copper intermediate. The other product *N*-alkynylated pyrazole **5.24** is believe to be formed by electrocyclization of the diazo **5.1d** followed by electrophilic alkynylation with TIPS-EBX (**5.2a**).[294] Therefore, the liberation of iodobenzoate in the media could also participate to the formation of product **5.17**. In view of this results, the substrate **5.1d** was not further examined.



Scheme 69. Failed oxy-alkynylation of phenyl-substituted vinyl diazo ester **5.1d**.

In order to modulate the reactivity of the vinyl carbene, an electron-withdrawing ester group was installed at conjugated position. Unfortunately, no reaction was observed when **5.1e** was submitted to the oxy-alkynylation reaction with TIPS-EBX (**5.2a**), in presence of $Cu(CH_3CN)_4BF_4$ and **5.16a** as ligand (Scheme 70). After 24 hours, 20 mol% of $Zn(OTf)_2$ was added to the reaction mixture to further activate the EBX reagent **5.2a**, but no evolution occurred after an extra 24 hours.



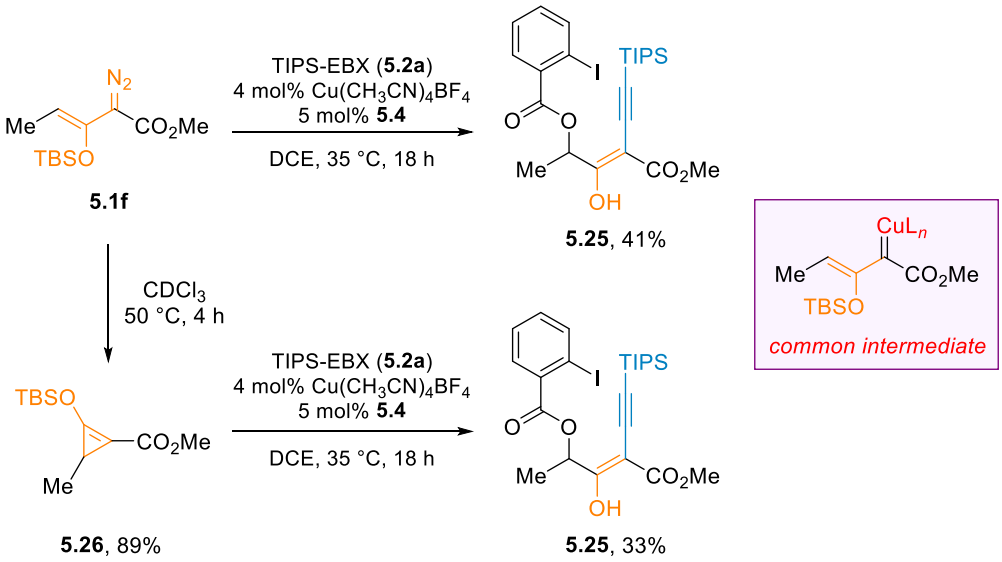
Scheme 70. Absence of reactivity with electron-poor vinyldiazo substrate **5.1e**.

Enoldiazo compounds have been recently introduce by Doyle and co-workers,[295] and we wondered if this particular class of vinyldiazo ester could be successful in the conjugate oxy-alkynylation reaction (Scheme 71). The reaction between TBS-protected enoldiazo compound **5.1f** and TIPS-EBX (**5.2a**) was performed in a racemic manner, and furnished the enol **5.25** in a moderate yield. Upon heating, thermal extrusion of nitrogen from the enoldiazo compound **5.1f** cleanly formed the donor-acceptor cyclopropenes **5.26**.[296] Ring-opening of the latter by the copper catalyst generates a vinyl copper carbene intermediate, which undergoes the oxy-alkynylation reaction with EBX reagent **5.2a**, to give **5.19** in a comparable yield than diazo **5.1f**.

[294] Compound **103** is reported to slowly undergo an electrocyclization reaction to form a pyrazole: J. R. Manning, H. M. L. Davies, *Org. Synth.* **2007**, *84*, 334.

[295] a) Q.-Q. Cheng, Y. Deng, M. Lankelma, M. P. Doyle, *Chem. Soc. Rev.* **2017**, *46*, 5425; b) X. Xu, P. Y. Zavalij, W. Hu, M. P. Doyle, *J. Org. Chem.* **2013**, *78*, 1583.

[296] Y. Deng, C. Jing, M. P. Doyle, *Chem. Commun.* **2015**, *51*, 12924.



Scheme 71. Conjugate oxy-alkynylation of enoldiazo or donor-acceptor cyclopropene.

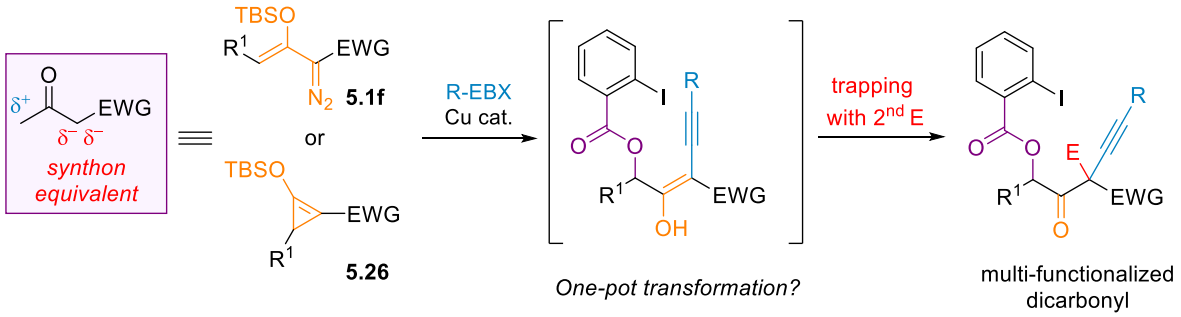
Finally, no enantioselective reactions with the molecules **5.1f** and **5.26** have been attempted and no further investigations on the enantioselective conjugate functionalization of vinyldiazo compounds with EBX reagents were conducted.

5.3. Conclusion

Several investigations have been realized to optimize the enantioselective oxy-alkynylation of vinyldiazo compounds with EBX reagents. The proof of concept to develop an enantioselective transformation has been established, however, the maximum of enantioselectivity attained was low. The best results (30% ee) were obtained using BINAM-based diimine ligands. Various structurally different ligands were screened but did not improve the enantioselectivity of the reaction. The utilization of metal catalysts other than copper was inefficient. Next, sterically and electronically different vinyldiazo substrates were tested. Several substrates were not reacting under the standard conditions and no improvement of the ee could be achieved.

Additional parameters can still be examined: other well-established *N*,*N*-ligands and catalysts have not been screened. Importantly, we focused only on TIPS-EBX (**5.2a**) as partner, while different substituents on the alkyne or on the aromatic core of the hypervalent iodine reagent could drastically impact the reaction outcome. At this stage, we decided to stop our investigations toward the enantioselective conjugate oxy-alkynylation of vinyldiazo compounds.

The transformation obtained with the enoldiazo compound and the corresponding cyclopropene led to the formation of a highly functionalized enol compound. This new transformation could be investigated more deeply. One-pot alkynylation and trapping of the stabilized enolate with a second electrophile would introduce a supplementary functionality on the molecule (Scheme 72). The functionalized dicarbonyl products could serve as complex structural skeletons for the synthesis of elaborated heterocycles.



Scheme 72. Exploiting the reactivity of enol diazo compounds with EBX reagents.

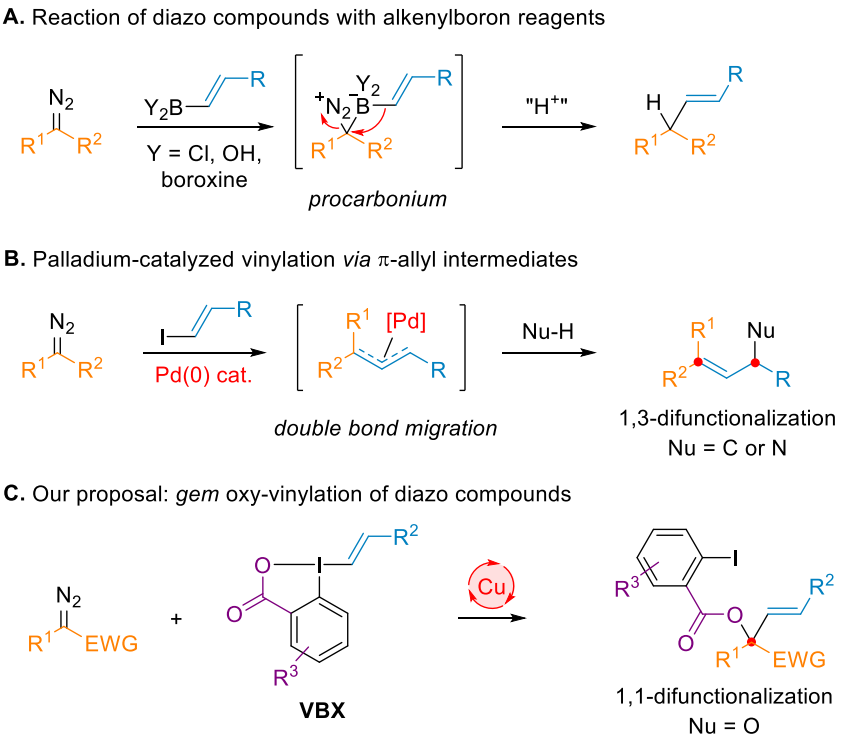
Other types of cyclopropenes are known to generate vinyl metal carbene intermediates.[184] Potential transformations involving EBX reagents, and cyclopropene as carbene precursors could be investigated considering the expertise of our group with small-ring molecules.

6

Copper-Catalyzed Oxy-Vinylation of Diazo Compounds

6. Copper-Catalyzed Oxy-Vinylation of Diazo Compounds

In this chapter, our work on the oxy-vinylation of diazo compounds will be presented. This transformation is in continuity with the previous work developed in our group and constitutes a complementary approach to the existing methods for the vinylation of diazo compounds. Only few strategies for the direct introduction of an olefin onto a carbene center have been described. Reports on transition metal-free reaction of alkenylboron reagents with diazo compounds or *N*-tosylhydrazones often proceed at elevated temperatures and are limited to the insertion of only one functionality (Scheme 73. A).[297] Another interesting approach, first reported by Van Vranken and co-workers, employing vinyliodides as coupling partners allows to introduce an allylic stereocenter and a nucleophile at the same time (Scheme 73. B).[205] Nevertheless, the reaction proceeds *via* a π-allyl palladium species, resulting into a 1,3 relationship between the nucleophile and the vinyl group (see section 2.3.3.2. for details). In addition, such transformations have been successfully reported with *C*- and *N*-nucleophiles, but no report of external oxy-vinylation exists to the best of our knowledge. Our strategy for the implementation of a *gem* oxy-vinylation of diazo compounds with VBX reagents will be presented in this chapter (Scheme 73. C).



Scheme 73. Strategies for the vinylation of diazo compounds.

In addition, the α-vinyl-hydroxycarbonyl motif can be found and used for the synthesis of bioactive compounds (Figure 18). For instance, symbioramide (**6.1**) exhibited antileukemic activity.[298] The α-hydroxy-ß,γ-dehydro fatty acid contained in **6.1** is seldom found from natural sources and was accessed by a sequential nucleophilic alkynylation of aldehyde follow by partial reduction of the C≡C

[297] a) C. Peng, W. Zhang, G. Yan, J. Wang, *Org. Lett.* **2009**, *11*, 1667; b) M. C. Pérez-Aguilar, C. Valdés, *Angew. Chem. Int. Ed.* **2012**, *51*, 5953; c) H.C. Brown, A. M. Salunkhe, *Synlett* **1991**, *1991*, 684; For a review on reaction of diazo compounds with organoborons, see: d) H. Li, Y. Zhang, J. Wang, *Synthesis* **2013**, *45*, 3090.
[298] J. Kobayashi, *J. Nat. Prod.* **1989**, *52*, 225.

bond.[299] Compound **6.2**, containing a versatile Weinreb amide motif, was described by Crews and co-workers as an advanced synthetic intermediate en route for the synthesis of amphidinolides G and H.[300] Vinclozolin (**6.3**) is a common fungicide for plant treatment, possessing a tetra-substituted vinyl-hydroxyamide fragment. The vinyl-diol fragment encountered in travoprost (**6.4**) can be easily accessed from α-vinyl-hydroxyester precursors. Travoprost (**6.4**) is an effective medication for the treatment of high pressure inside the eye.[301]

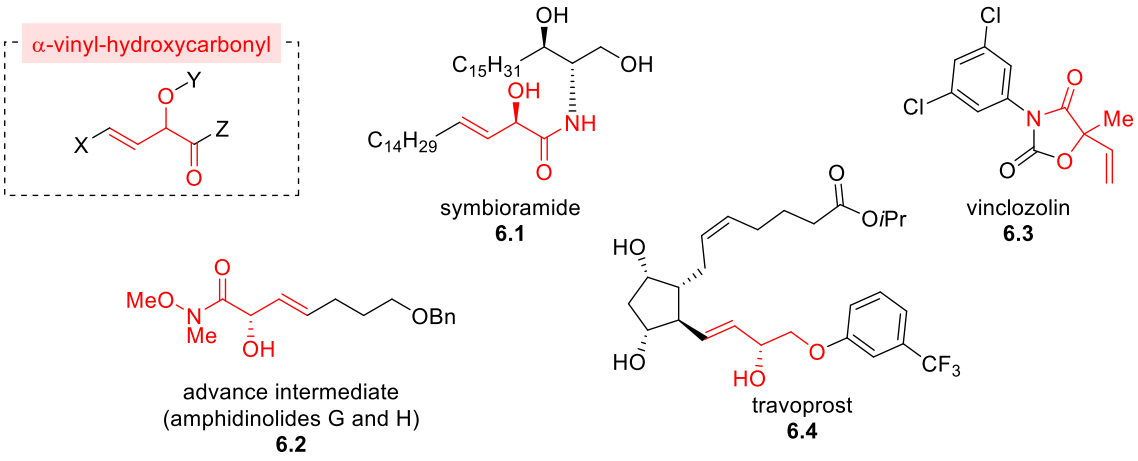


Figure 18. Selected synthetic applications and occurrence of the α-vinyl-hydroxyacid derivatives.

6.1. Reaction Discovery and Optimization

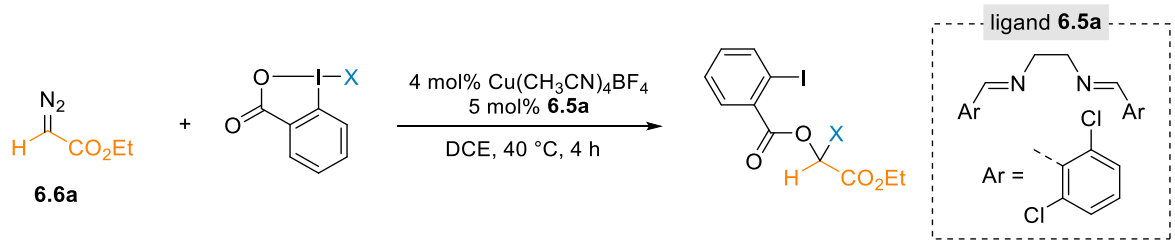
After the successful Cu(I)-catalyzed insertion of diazo compounds into the hypervalent bond of EBX reagents developed by our group,[227] we considered other related difunctionalization reactions. At LCSO, we are familiar with hypervalent iodine reagents such as azido-benziodoxolone (ABX) and cyano-benziodoxolone (CBX). Our interests were also directed toward other recently developed functional group transfer reagents. Indeed, our group just reported the synthesis and applications of electrophilic indole- and pyrrole-BX reagents and the group of Olofsson published their first study on VBX reagents. We engaged the aforementioned hypervalent iodine reagents in the optimal reactions conditions previously established for the oxy-alkynylation reaction with ethyl diazoacetate (**6.6a**), using catalytic $Cu(CH_3CN)_4BF_4$ and ligand **6.5a** (Table 8).

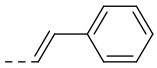
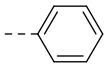
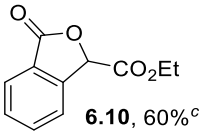
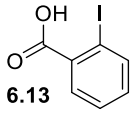
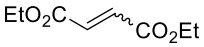
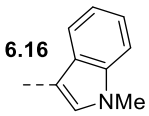
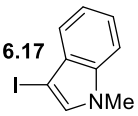
[299] For the first total synthesis, see: a) M. Nakagawa, J. Yoshida, T. Hino, *Chem. Lett.* **1990**, *19*, 1407; b) J. Yoshida, M. Nakagawa, H. Seki, T. Hino, *J. Chem. Soc., Perkin Trans. I* **1992**, 343.

[300] A. F. Petri, J. S. Schneekloth, A. K. Mandal, C. M. Crews, *Org. Lett.* **2007**, *9*, 3001.

[301] L. T. Boulton, D. Brick, M. E. Fox, M. Jackson, I. C. Lennon, R. McCague, N. Parkin, D. Rhodes, G. Ruecroft, *Org. Proc. Res. Dev.* **2002**, *6*, 138.

Table 8. Difunctionalization of diazo ester **6.6a** with various iodine(III) reagents.[a]



Entry	Reagent (X =)	Conv[b]	Product[c] (%)	Other product(s)
1	 **6.7a**	full	**6.8a**, 90	-
2	 **6.9**	full	-	 **6.10**, 60%[c]
3	 **6.11**	full	**6.12**, 10	 **6.13**
4	 **6.14**	no conv.	-	 **6.15**
5[d]	 **6.16**	dec.	-	 **6.17**

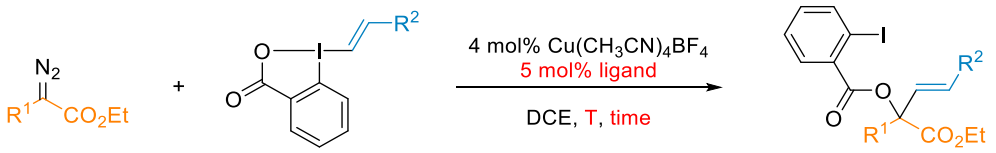
[a]Reaction conditions: 0.20 mmol of diazo (**6.5a**), 0.10 mmol of hypervalent iodine reagent, $Cu(CH_3CN)_4BF_4$ (4 mol%), ligand **6.5** (5 mol%), DCE (0.04 M). [b]Conversion estimated by TLC analysis. [c]Yield after purification by column chromatography. [d]The reaction was performed by Dr. P. Caramenti.

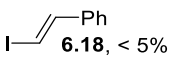
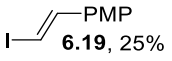
We were pleased to see that the oxy-vinylation of EDA (**6.6a**) with Ph-VBX (**6.7a**) proceeded very cleanly, furnishing the product **6.8a** in 90% yield (entry 1). Having this first result in hand, we attempted the difunctionalization reaction with phenyl-benziodoxolone (Ph-BX, **6.9**), expecting similar reactivity for the vinyl and the aryl groups. In this case, the desired oxy-arylation product was not observed and the lactone **6.10** was isolated (entry 2). The more electron-poor benzoate iodine(III) ligand was selectively transferred resulting in the formation of lactone **6.10** and release of iodobenzene.[302] The product of oxy-azidation **6.12** was formed in 10% yield with ABX (**6.11**), however, 2-iodobenzoic acid (**6.13**) was the main product identified, probably as a result of radical decomposition pathways (entry 3). CBX reagent (**6.14**) was unreactive under these reaction conditions, leading to the dimerization of the diazo compound into diethyl maleate and fumarate side-products (entry 4). In presence of the copper catalyst, a fast decomposition of indole-BX **6.16** to 3-iodoindole (**6.17**) was observed and no other products could be isolated out of the resulting complex mixture (entry 5).

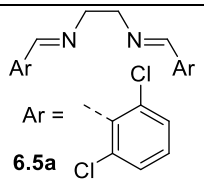
[302] J. Malmgren, S. Santoro, N. Jalalian, F. Himo, B. Olofsson, *Chem. Eur. J.* **2013**, *19*, 10334.

After the very good preliminary result obtained with Ph-VBX (**6.7a**) and EDA (**6.6a**) we decided to explore the generality of the oxy-vinylation reaction by screening different key diazo substrates and VBX reagents in a pre-scope study (Table 9). Using phenyl-substituted diazo ester **6.6k** and Ph-VBX (**6.7a**) as substrates, with $Cu(CH_3CN)_4BF_4$ and diimine ligand **6.5** as catalyst, the corresponding product **6.8af** was isolated in 80% yield (entry 2). Unfortunately, an important reduction of the reaction efficiency was observed with the more electron-rich VBX **6.7b** (entry 3). A higher temperature, as well as a longer reaction time, was required for complete conversion of the hypervalent iodine reagent. In addition, a substantial formation of iodoalkene side-product **6.19** was obtained. We believe that the higher reaction temperature could result in a competitive oxidative addition of the Ar-I(III) bond to copper(I). Furthermore, no reaction occurred using the cyclohexyl-substituted substrate **6.7j** even after prolonged reaction time at higher temperature (entry 4). We therefore turned our attention to bisoxazoline (BOX) ligands, which had also been successful in our previous work. In fact, when using *t*Bu-BOX ligand **6.5b**, the reaction was accelerated and could be performed in four hours at room temperature to give **6.8a** in 95% yield, albeit in nearly racemic form (entry 5). We then investigated non chiral ligands which could be equally efficient than **6.5b**. When BOX ligand **6.5c** lacking the *tert*-butyl groups was used, no product could be obtained (entry 6). Speculating that steric hindrance around the nitrogen atoms could be important, we synthesized tetramethyl-substituted ligand **6.5d**. Indeed, with **6.5d** the reactivity was fully restored (entry 7). Using ligand **6.5d**, a much better yield could be obtained with reagent **6.7b** (entry 8), and the reaction was quantitative with alkyl-substituted VBX **6.7j** (entry 9), whereas no product was obtained with diimine ligand **6.5a** (entry 4). In contrast, the reaction was not successful for disubstituted diazo compounds with ligand **6.5d** (entry 10). From the results obtained, we decided to use either ligand **6.5a** or **6.5d** depending on the presence or not of a second substituent (R^1) on the diazo compound. Finally, control experiments were performed and no product could be obtained for the reaction of EDA (**6.6a**) and Ph-VBX (**6.7a**) in the absence of $Cu(CH_3CN)_4BF_4$ (4 mol%) or without a *N*,*N*-ligand (entries 11 and 12). Importantly, only the *E*-olefin was obtained in all the reactions, indicating no isomerization during the transfer of the double bond.

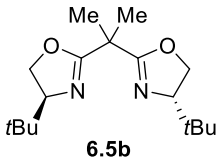
Table 9. Optimization of the insertion of diazo compounds into VBX reagents.[a]



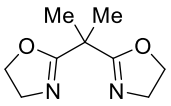
Entry	Ligand	Diazo (R^1 =)	VBX (R^2 =)	Product	T (°C)	Time (h)	Yield[b] (%)	Side-product
1	**6.5a**	H	Ph	**6.8a**	40	4	90	-
2	**6.5a**	Ph	Ph	**6.8af**	40	4	80	 **6.18**, < 5%
3	**6.5a**	H	PMP	**6.8b**	60	24	50	 **6.19**, 25%
4	**6.5a**	H	Cy	**6.8j**	60	24	< 5	-
5[c]	**6.5b**	H	Ph	**6.8a**	25	4	95	-
6	**6.5c**	H	Ph	**6.8a**	60	24	< 5	-
7[d]	**6.5d**	H	Ph	**6.8a**	25	4	95	-
8[d]	**6.5d**	H	PMP	**6.8b**	25	4	81	-
9[d]	**6.5d**	H	Cy	**6.8j**	25	4	99	-
10	**6.5d**	Ph	Ph	**6.8af**	40	4	< 5	-
11	-	H	Ph	**6.8a**	40	24	< 5	-
12	**6.5a**	H	Ph	**6.8a**	40	24	-	-



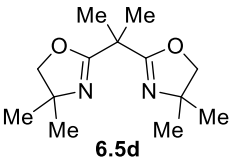
6.5a



6.5b



6.5c

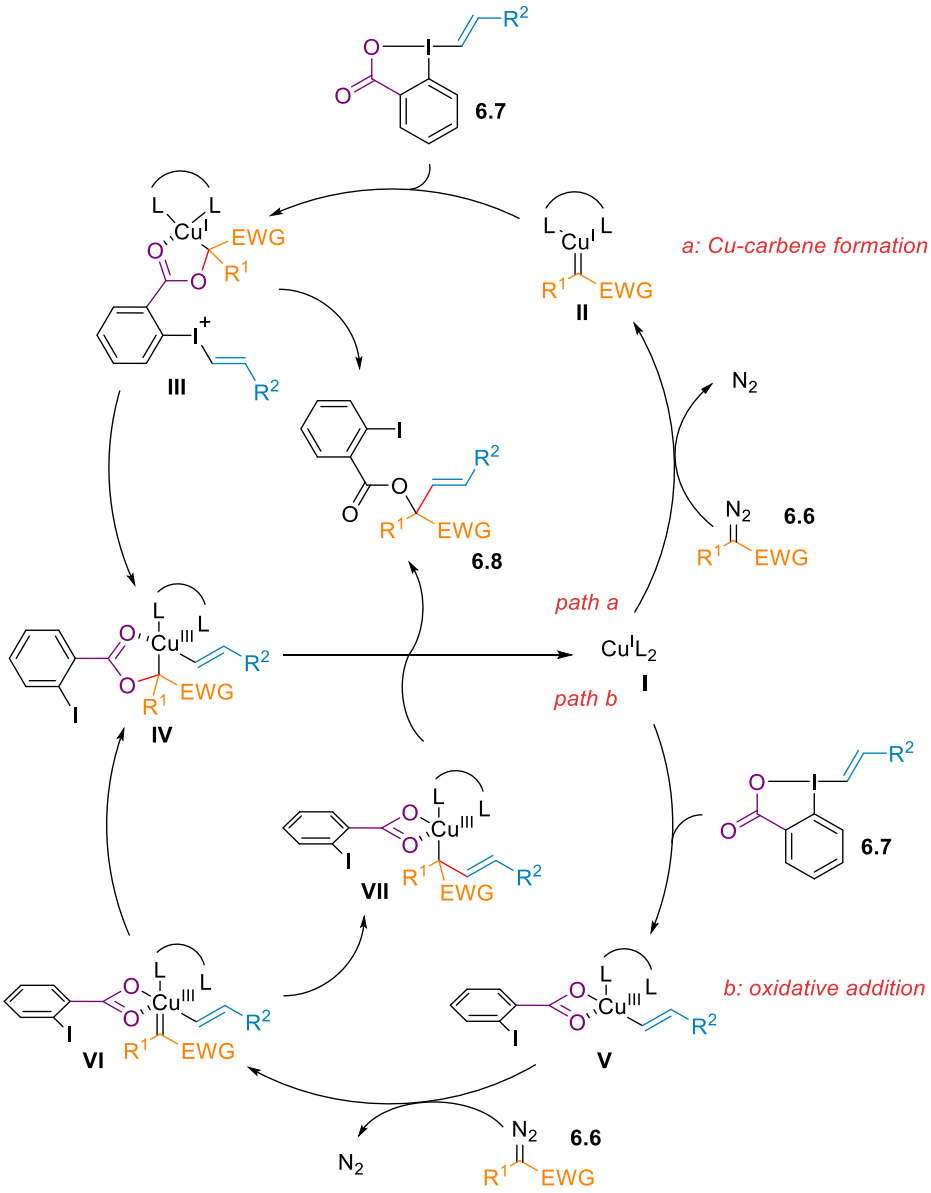


6.5d

[a]Reaction conditions: 0.20 mmol of diazo, 0.10 mmol of VBX, $Cu(CH_3CN)_4BF_4$ (4 mol%), ligand (5 mol%), DCE (0.04 M). [b]Yield after purification by column chromatography, when > 5%. [c]13% of enantiomeric excess was obtained. [d]Reaction was carried out on 0.20 mmol scale.

6.2. Proposed Mechanisms

Only speculative reaction mechanisms can be proposed following two pathways according to literature (Scheme 74). The first possibility is similar to the mechanism proposed for the oxy-alkynylation reaction we described previously (path a).[227] The initial step is the decomposition of diazo compound **6.6** by Cu(I) catalyst **I** to give carbene complex **II**. Nucleophilic attack of the carboxylate group of VBX **6.7** would then give ylide **III**, in analogy to the methodologies based on oxonium ylide intermediates.[196] At this stage, several possibilities can be considered. Oxidative transfer of the vinyl group to Cu(I) would lead to intermediate **IV**, and final reductive elimination would deliver the desired product **6.8** and re-form the Cu(I) catalyst **I**. Alternatively, direct nucleophilic attack on the alkenyliodonium **III** to give **6.8** without oxidation to Cu(III) could be also considered (see section 2.4.2.)



Scheme 74. Putative mechanisms for the Cu(I)-catalyzed oxy-vinylation of diazo compounds.

A second approach would take into account the strong oxidizing properties of vinyl-iodine(III) reagents (see section 2.2.3.1.). Path b would start with a fast oxidative addition of the VBX reagent **6.7** to the Cu(I) catalyst **I** to form a highly electrophilic vinyl-Cu(III) intermediate **V**. Then complex **V** would react with diazo compound **6.6** to form the copper carbene intermediate **VI** after exclusion of nitrogen. The nucleophilic carboxylate group would then add to the carbene center to form organocopper species **IV**, which undergoes the final reductive elimination step. From complex **VI**, 1,2-shift of the vinyl group followed by C-O reductive elimination via intermediate **VII** could be also considered as a second possibility.[204] It is interesting to note that this mechanistic pathway would involve a Cu(III)-carbene intermediate, whereas all reports on diazo transformations involving a copper carbene have been proposed to proceed *via* Cu(I) so far.

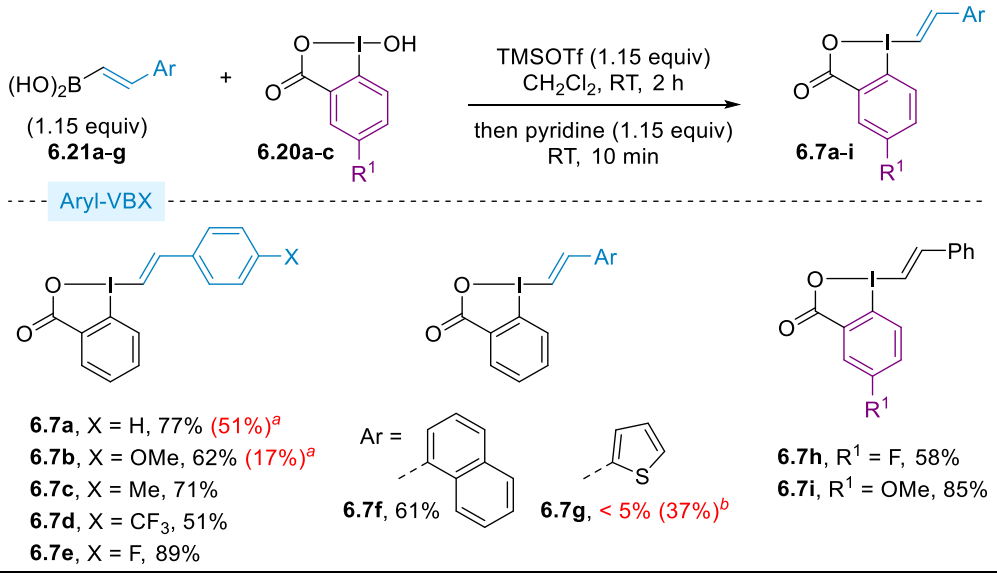
6.3. Development of New Methods for the Synthesis of VBX Reagents

At the beginning of this work (2018), two synthetic methods to access VBX reagents were reported (see section 2.2.3.1.): The advantageous one-pot synthesis from 2-iodobenzoic acid (**6.13**)

described by the Olofsson group,[67] and the stepwise approach from hydroxyl-benziodoxolone (**6.20a**) proposed by the Nachtsheim group.[116] Both strategies used vinylboronic acid precursors and were limited to aryl-substituted olefins, with the exception of Cy-VBX (**6.7j**) reported in low yield. In the context of our work, we rapidly faced difficulties to access VBX reagents in a convenient manner, especially alkyl-substituted VBX reagents which were not well documented.

6.3.1. Aryl-VBX

The procedure described by Olofsson and co-workers was successfully reproduced for the preparation of Ph-VBX (**6.7a**), however, the preparation of PMP-VBX (**6.7b**) was more challenging and only low yield was obtained (Scheme 75). We therefore preferred the protocol reported by Nachtsheim and co-workers starting from the readily available HO-BX (**6.20a**), and furnishing the desired PMP-VBX (**6.7b**) in 62% yield. In addition, the preparation of Ph-VBX (**6.7a**) on a multigram scale could be achieved utilizing this second approach. These conditions were easily extended to obtain other aryl-substituted reagents **6.7c-e** bearing alkyl, methoxy, trifluoromethyl or fluoro groups. The methodology was also applicable for accessing naphthyl VBX **6.7f**, but could not be used to access thiophene VBX **6.7f**. However, this heteroaryl-substituted VBX **6.7f** was synthesized later in 37% yield, using the procedure developed for alkyl-VBX (see section 6.3.2.). Modification of the aromatic core of the VBX reagents was also possible to give compounds **6.7h** and **6.7i** bearing a fluoro and a methoxy group in 58% and 85% yield respectively.



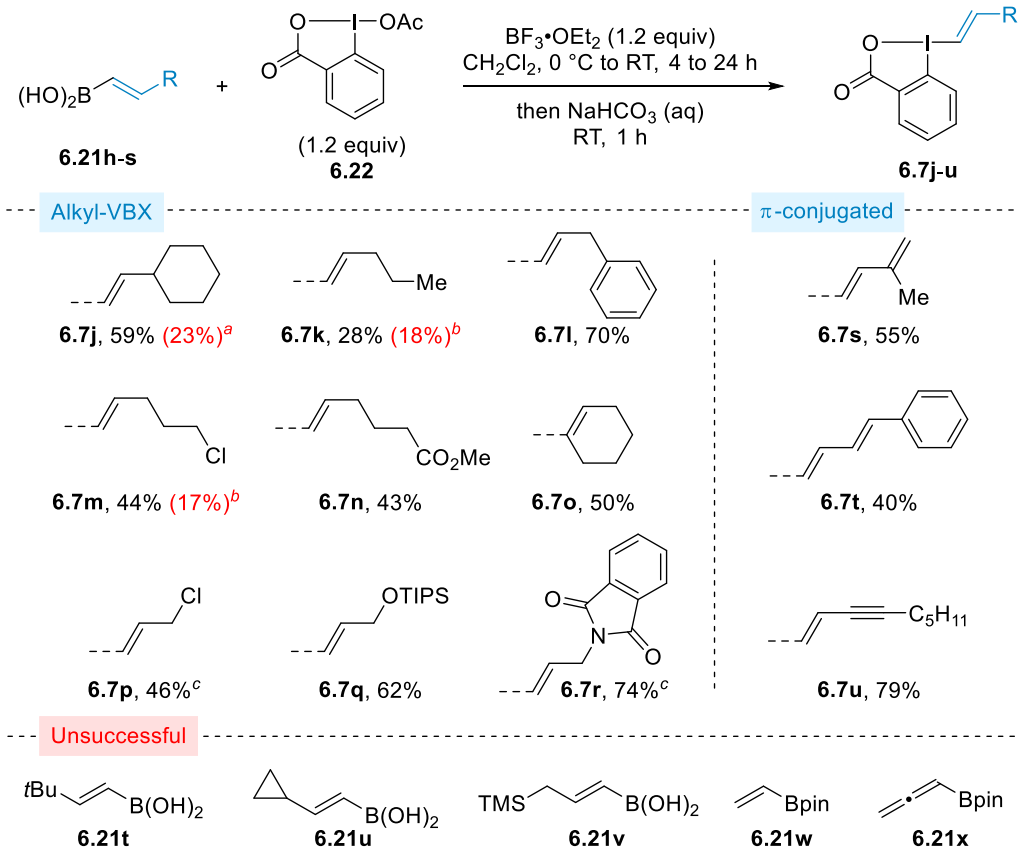
[a]Using Olofsson's procedure: 1) 2-iodobenzoic acid, *m*-CPBA (1.10 equiv), TfOH (1.50 equiv), CH_2Cl_2, 0 °C to RT, 15 min; 2) vinylboronic acid (1.40 equiv), RT, 1 h; 3) $NaHCO_3$ (aq), RT, 1 h. [b]Using AcO-BX and BF_3•OEt_2 instead of HO-BX and TMSOTf, see section 6.3.2.

Scheme 75. Preparation of aryl-substituted VBX reagents.

6.3.2. New Method for the Synthesis of Alkyl-Substituted VBX

We were interested to extend the scope of VBX reagents beyond aryl substituents. However, only the synthesis of cyclohexyl-substituted VBX reagent **6.7j** in low yield has been reported by Olofsson and coworkers. The alternative protocol using HO-BX (**6.20a**) and TMSOTf, did not improve the low yield obtained for alkyl-VBX reagents. For instance, **6.7k** and **6.7m** with a primary alkyl chains were synthesized in only 18% and 17% yield, respectively. Pleasingly, changing the iodane(III) precursor to acetoxy-benziodoxolone (AcO-BX, **6.22**), and employing BF_3•OEt_2 as an activator provided the

alkyl-VBX reagents in greatly improved yield after final cyclisation under mild basic aqueous conditions (Scheme 76). This BF_3-promoted procedure was first reported by Ochiai and co-workers for the synthesis of alkenyl-(aryl)iodonium tetrafluoroborates.[75c] Cy-VBX (**6.7j**) was obtained in good yield and a range of other alkyl-substituted VBX reagents were successfully synthesized applying this new protocol. Reagents **6.7k**-**n** bearing primary alkyl groups could be obtained in 28 – 74% yield. Notably, this mild protocol allowed the synthesis of reagents with functionalized alkyl chains, including phenyl, chloro and ester substituents (reagents **6.7l**-**n**). The tri-substituted olefin/cyclohexene substrate **6.7o** could be obtained in 50% yield. Substitution in the allylic position is especially interesting to get useful building blocks for synthetic and medicinal chemistry, yet it makes the reagent synthesis more challenging. Gratifyingly, VBX reagents **6.7p**, **6.7q** and **6.7r** incorporating allylic chloro, oxygen and nitrogen substituents could be all accessed efficiently. In the case of **6.7p** and **6.7r**, we found that the addition of trifluoroethanol as co-solvent ensured good homogeneity of the reaction mixture and drastically improved the yield.



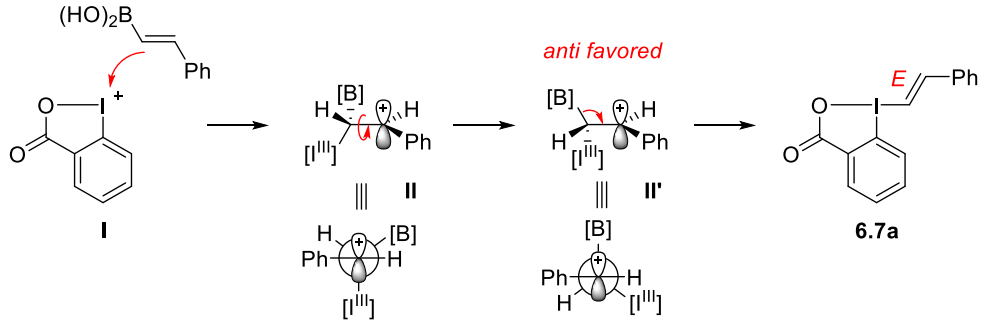
[a]Using Olofsson's procedure. [b]Using Nachtsheim's procedure. [c]CH_2Cl_2/TFE 9:1 instead of CH_2Cl_2.

Scheme 76. Preparation of aryl-substituted VBX reagents.

Conjugated dienes and enynes are other classes of sensitive compounds that can be found in natural products and serves as unique platforms for further synthetic transformations. However, they have never been introduced onto VBX reagents. We succeeded to prepare the diene-VBX reagents **6.7s** and **6.7t** in 55% and 40% yield respectively. The reagent **6.7u** bearing a conjugated enyne motif was obtained in 79% yield. In general, this method gave inferior results for the synthesis of aryl-substituted VBX reagents, with the notable exception of thiophene-substituted reagent **6.7g**, which could be accessed in 37% yield using this protocol (see Scheme 75). Several vinylboron precursors were not efficient under these reaction conditions. Vinylboronic acid having *tert*-butyl (**6.21t**) and cyclopropyl (**6.21u**) substituents furnished the corresponding VBX reagents in extremely low yield (ca. 10%). Not

too surprisingly, allyltrimethylsilane derivative **6.21v** decomposed under the acidic reaction conditions used. When the commercially available vinyl- and allenylboron-pinacol ester (**6.21w** and **6.21x**) were employed, no VBX product was detected. Olofsson and Nachtsheim already showed the superiority of boronic acid compared to the ester derivatives and we suspected a low stability for these eventual VBX reagents.[303]

All the obtained reagents were shelf-stable and could be conveniently isolated in pure form *via* simple precipitation from the crude products. Currently, the synthesis of VBX reagents is limited to *trans*-olefin containing compounds. Indeed, (*trans*)-Ph-VBX (**6.7a**) was obtained independently of the geometry of the alkenyl boronic acid precursor (Scheme 77). We believe that the vinylation step occurs through cationic intermediate **II** after initial electrophilic attack of iodonium **I** on the C=C bond. The low energy rotational barrier around the C1-C2 bond results in favorable *anti*-relationship between the large iodine(III) and the phenyl substituent (intermediate **II'**). Elimination of the boron aligned to the vacant orbital, produces the *E* product exclusively.

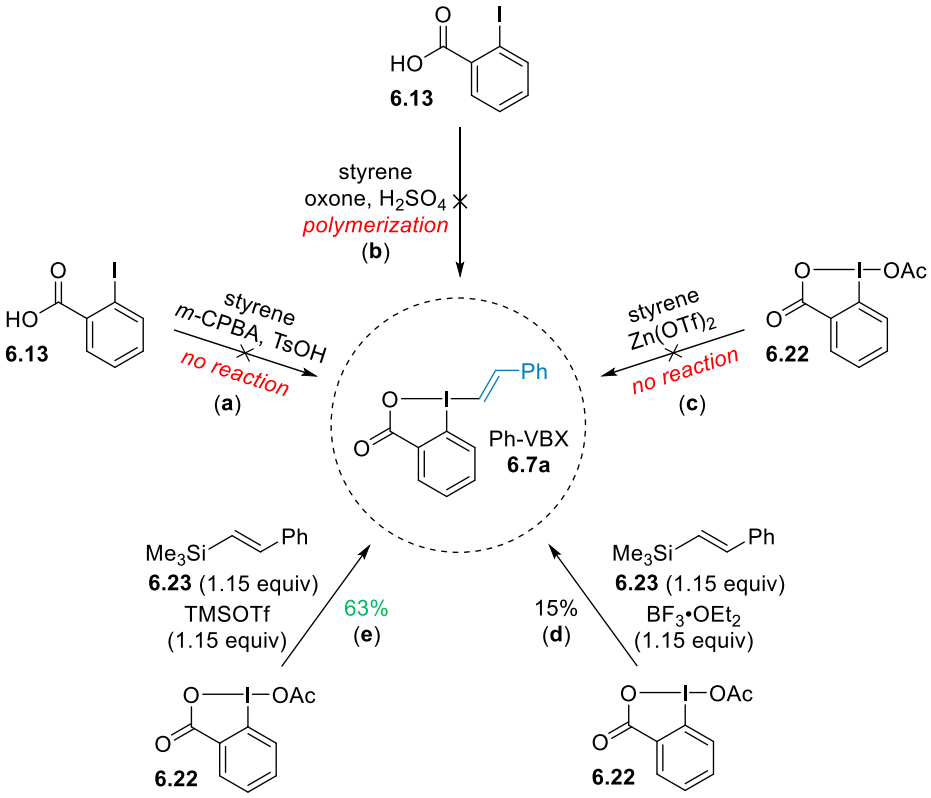


Scheme 77. Thermodynamically favored formation of *trans*-Ph-VBX reagent **6.7a**.

6.3.3. Investigation of Alternative Synthetic Routes

A large array of VBX reagents incorporating various functionalities and motifs on the olefin, and on the core structure of the reagent were successfully synthesized. However, an important difficulty during the preparation of VBX reagents concerned the synthesis and handling of the vinylboronic acid precursors. Alkenylboronic acids are available from alkynes in geometrically pure form but the practicality of their synthesis and their isolation in high purity can be challenging. We explored other synthetic routes to access VBX reagents without the compulsory need for boronic acids (Scheme 78). A protocol using readily available terminal olefins as starting materials would be highly desirable. In this context, a one-pot synthesis of Ph-VBX (**6.7a**) starting from 2-iodobenzoic acid (**6.13**) and styrene as precursors and with *m*-CPBA as the oxidant and *para*-toluene sulfonic acid as the activator was attempted based on the practical TIPS-EBX synthesis reported by our group, however no reaction on the olefin was observed in this case (**a**).[139] A similar approach developed by Zhdankin and co-workers for the preparation of aryl-benziodoxolones utilized oxone as oxidant in strong acidic media (H_2SO_4).[304] Applying such reaction conditions led only to traces of Ph-VBX (**6.7a**), and polymerization of styrene (**b**). In the work of our goroup on indole- and pyrrole-BX reagents, activation of Ac-OBX (**6.22**) with cheap $Zn(OTf)_2$ was sufficient for the nucleophilic attack of the heterocycle to occur.[69] Unfortunately, the same methodology was not applicable with styrene as no reaction was observed in this case (**c**).

[303] M. Ochiai, T. Ito, Y. Takaoka, Y. Masaki, *J. Am. Chem. Soc.* **1991**, *113*, 1319.
[304] M. S. Yusubov, R. Y. Yusubova, V. N. Nemykin, V. V. Zhdankin, *J. Org. Chem.* **2013**, *78*, 3767.

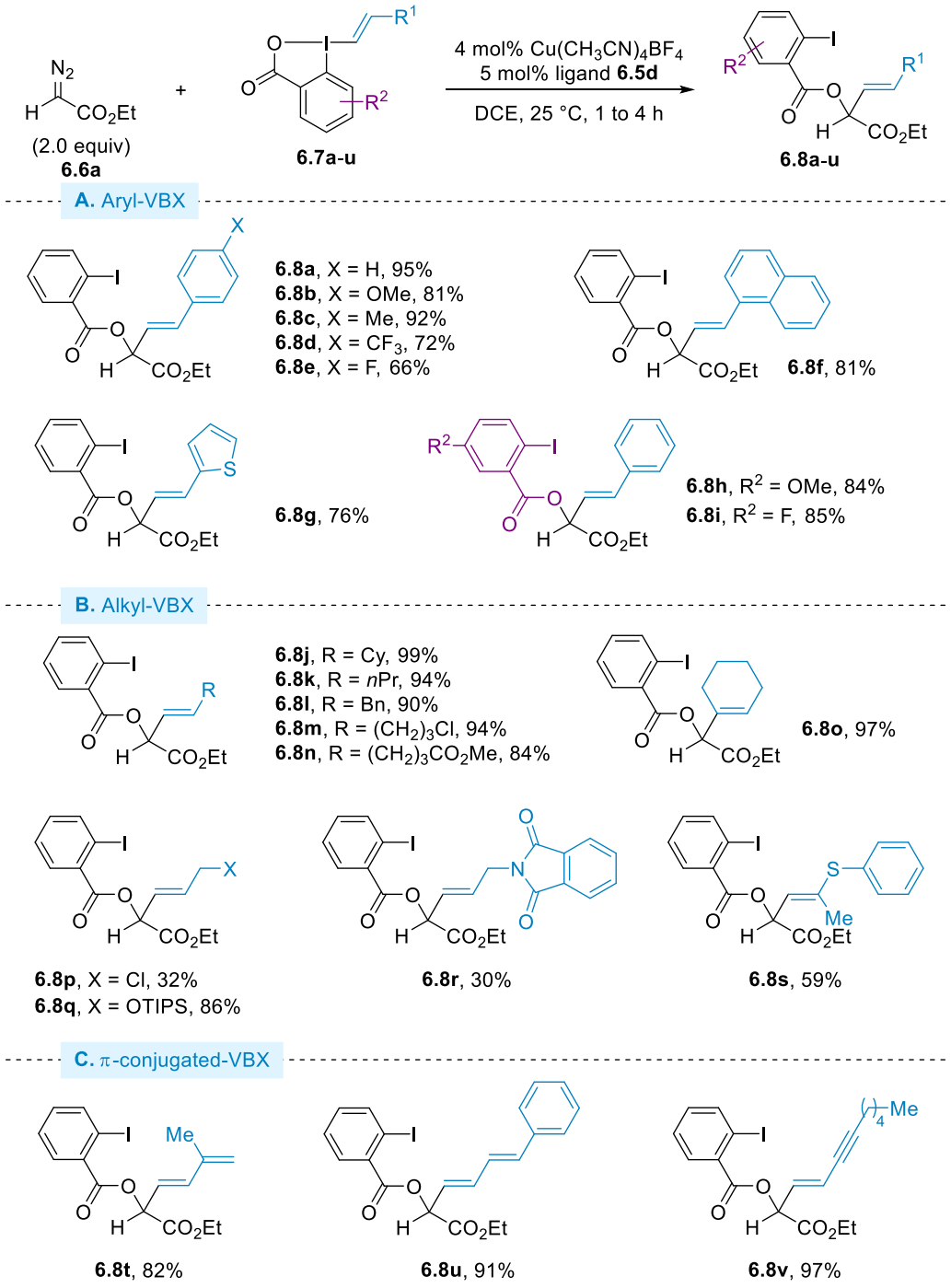


Scheme 78. Investigations for the synthesis of Ph-VBX without boronic acid precursor.

Alkenylsilanes have been successfully applied for the synthesis of vinyl(aryl)iodonium salts,[75b] but were reported to be unreactive in the VBX synthesis described by Olofsson. The desired Ph-VBX reagent (**6.7a**) could be obtained in low yield (15%) using the reaction conditions established for the synthesis of alkyl-substituted reagents using vinyltrimethylsilane precursor **6.23** (**d**). Further screenings allowed us to identify TMSOTf as superior Lewis acid activator furnishing Ph-VBX (**6.7a**) in good yield (**e**). For time reasons, no further investigation was spent on the development of this reaction, however, this additional synthetic method opens opportunities to extend the scope of VBX reagents. It is important to mention that vinyltrimethylsilane derivatives need nevertheless to be synthesized before utilization in the synthesis of VBX reagents.

6.4. Scope and Limitation of the Oxy-Vinylation Reaction

With the optimized conditions in hand and several VBX reagents prepared, we first investigated the scope of aryl-substituted VBX reagents using EDA (**6.6a**) as carbene precursor (Scheme 79. A). Electron-rich arenes were well tolerated, with PMP-VBX (**6.7b**) affording product **6.8b** in 81% yield. *Para*-methyl substitution did not impact the yield and gave **6.8c** in 92% yield. VBX reagents with electron-withdrawing trifluoromethyl and fluoride substituents furnished **6.8d** and **6.8e** in slightly diminished yields. A naphthyl-substituted VBX led to the formation of **6.8f** in 81% yield. A good yield was also obtained for thiophene-substituted **6.8g** (76% yield). Both electron-rich and -poor substituents on the benziodoxolone backbone were tolerated, affording **6.8h** and **6.8i** in very good yield.



Scheme 79. Scope of VBX reagents.

Next, we examined alkyl-substituted VBX reagents (Scheme 79. B). We were delighted to find that the vinylation reaction proceed well in most cases. VBXs bearing simple aliphatic chains (Cy, *n*Pr and Bn) provided the desired allylic esters **6.8j-l** in 90 – 99% yield. The incorporation of terminal handle functions such as a chloride (**6.8m**) or an ester (**6.8n**) group could also be achieved in similar high yields. Pleasingly, the cyclohexene-VBX **6.7o** delivered the trisubstituted alkene **6.8o** in excellent yield, underlining the little impact of the olefin congestion on the reaction outcome. VBXs with chlorides, silyl ethers and protected-amines in the allylic position delivered the corresponding products **6.8p-r**. These results demonstrate the potential of the methodology to incorporate sensitive functional groups, which could be further exploited in synthetic transformations. Nevertheless, a lower yield was

obtained for **6.8p** and **6.8r**, maybe due to the low solubility of the corresponding VBX reagents in DCE. The reaction was also successful with *S*-VBX reagent furnishing the functionalized thio-vinyl ether **6.8s** in 59% yield.[305] π-Conjugated systems were readily incorporated (Scheme 79. C). An isoprene skeleton was introduced to give **6.8t** in 82% yield. Conjugated diene **6.8u** and enyne **6.8v** were also successfully synthesized.

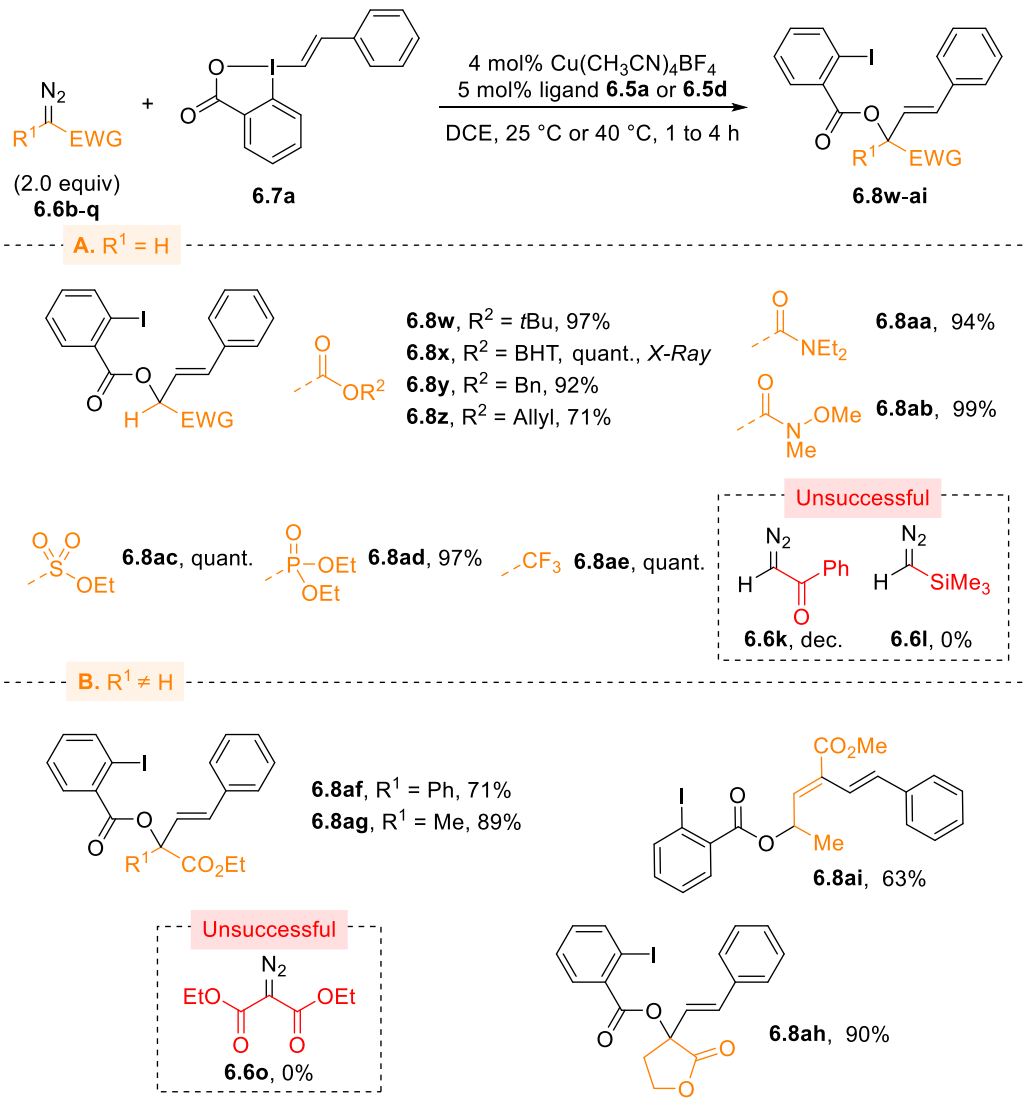
We next applied the reaction to a variety of electronically and sterically different diazo compounds (Scheme 80. A). Variation of the ester substituent was examined first. Excellent yields were obtained in all cases. Bulky esters such as *t*Bu or BHT were tolerated giving oxy-vinylation products **6.8w** and **6.8x** in quantitative yield. The structure of **6.8x** was further confirmed by X-ray analysis.[306] The benzyl ester product **6.8y** was obtained in 92% yield and product **6.8z** with an allyl group in 91% yield. Other electron-withdrawing groups than esters were then examined: 2-Diazo-*N,N*-diethylacetamide underwent the oxy-vinylation to provide **6.8aa** in 94% yield. The versatile Weinreb amide derivative **6.8ab** was isolated in 99% yield, opening access to aldehyde or ketone products. Sulfonate- and phosphonate-diazoesters were efficient coupling partners, generating synthetically useful allyl-sulfonate and allyl-phosphonate products **6.8ac** and **6.8ad** in quantitative yields.[307] Notably, the molecule **6.8ae** incorporating a trifluoromethyl group was isolated in quantitative yield as well. Organofluorine compounds are of significant importance in the pharmaceutical, agrochemical and materials industry.[308] Diazoketone **6.6k** was incompatible with this protocol and resulted in degradations products from a Wolff rearrangement pathway. No conversion was obtained using trimethylsilyldiazomethane (**6.6l**). Other diazo compounds lacking an electron-withdrawing group were not investigated due to their lower stability, but could be suitable substrates in this transformation. Finally, disubstituted diazo compounds were investigated using diimine ligand **6.5a** and 40 °C as reaction temperature (Scheme 80. B). Products **6.8af** and **6.8ag** with tertiary allylic centers were formed in 71% and 89% yield, showing the impact of a substituent at this position (for **6.8a**, R^2 = H, 95% yield). The presence of a second electron-withdrawing group completely suppressed the reactivity, as exemplified with diacceptor diazo **6.6o**, which never decomposed under these reaction conditions. A cyclic diazo compound afforded the desired product **6.8ah** in 90% yield. Diene product **6.8ai** was formed when starting from a vinyl diazo precursor, although with slightly diminished yield. In our previous projects we already observed the preferential attack of the nucleophile at the vinylogous position of the carbene (see section 5. and ref 227).

[305] Dr. R. Tessier is acknowledged for the generous gift of *S*-VBX reagent.

[306] Available at the Cambridge Crystallographic Centre, CCDC number 1897009.

[307] a) D. Enders, N. Vignola, O. W. Berner, *Tetrahedron* **2005**, *61,* 3231; b) A. Le Flohic, C. Meyer, J. Cossy, *Tetrahedron* **2006**, *62*, 9017; c) B. J. Rowe, C. D. Spilling, *J. Org. Chem.* **2003**, *68*, 9502; d) B. Yan, C. D. Spilling, *J. Org. Chem.* **2008**, *73*, 5385.

[308] a) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, John Wiley & Sons, Ltd, Chichester, UK, **2009**; b) For a review on recent fluorine-containing drugs, see: b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432.



Scheme 80. Scope of diazo compounds.

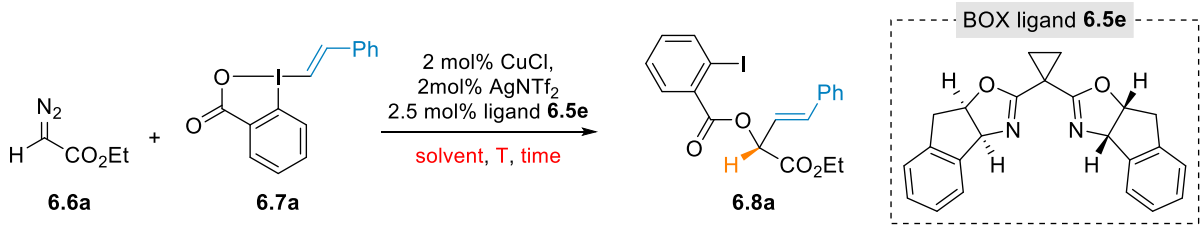
6.5. Preliminary Results for an Enantioselective Transformation

To give more impact to the oxy-vinylation reaction, we turned our attention to the development of an enantioselective version of this transformation, which would give access to enantioenriched substituted allylic esters. We decided to focus our efforts on unsubstituted diazo esters (R^1 = H) as they showed high reactivity in association with BOX ligands, unlike disubstituted diazo substrates ($R^1 \neq$ H) requiring diimine ligands and higher temperature to react. In addition, we had a good precedent for the oxy-alkynylation reaction proceeding well with BOX ligands in high enantioselective manner and we assumed similar reaction mechanisms for the two transformations (see section 2.4.2.).

First, we applied our optimal indane-BOX ligand **6.5e** to the oxy-vinylation of EDA (**6.6a**) with Ph-VBX (**6.7a**) (Table 10). No conversion was observed with the best reaction conditions established in our previous work, i.e. pre-formation of a cationic Cu(I) catalyst by stirring CuCl, $AgNTf_2$ and the BOX ligand **6.5e** at room temperature in chlorobenzene as solvent (entry 1). Further increase of the temperature up to 60 °C did not induce any conversion. The low solubility of Ph-VBX (**6.7a**) in chlorobenzene could account for the absence of conversion. When DCE was used as the solvent,

product **6.8a** was isolated in 64% yield with encouraging 39% ee, however only after 18 h of reaction at 70 °C and with substantial VBX degradation.

Table 10. Reactivity and enantiomeric excess obtained with previously optimized conditions.[a]

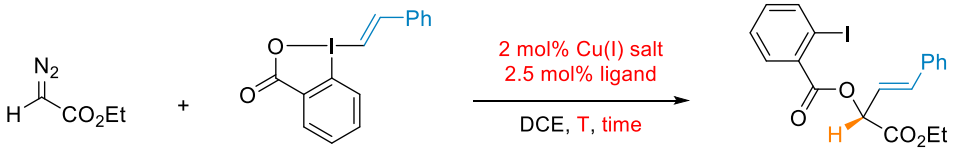


Entry	Solvent	T (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	PhCl	25 to 60	24	-	-
2	DCE	25 to 70	18	64	39

[a]Reaction conditions: 0.20 mmol of EDA (**6.6a**), 0.10 mmol of Ph-VBX (**6.7a**), CuCl (2 mol%), $AgNTf_2$ (2 mol%), ligand (2.5 mol%), solvent (0.02 M). [b]Yield after purification by column chromatography. [c]Obtained by chiral HPLC.

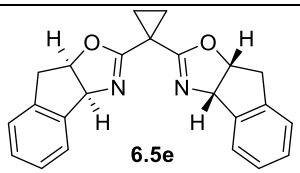
The high temperature needed for the reaction to proceed significantly differed from the low ambient temperature found using $Cu(CH_3CN)_4BF_4$ and *t*Bu-BOX ligand **6.5b** as catalytic system during the optimization of the racemic reaction. Therefore, we investigated the effect of the copper salt, in association with the chiral BOX ligands **6.5e** and **6.5b** in order to restore a good reactivity (Table 11). At 60 °C, a very long time was required to detect the formation of **6.8a** when CuCl/$AgNTf_2$ in association with BOX ligand **6.5e** was utilized to catalyze the reaction (entry 1). In contrast, when $Cu(CH_3CN)_4BF_4$ was used as the catalyst precursor, full conversion of Ph-VBX (**6.7a**) was observed after only 6 h (entry 2). The product **6.8a** was obtained with 23% of enantiomeric excess. Interestingly, $Cu(OTf)_2$ with ligand **6.5e** efficiently catalyzed the reaction at only 35 °C, which was not the case with the previous copper salts (entry 3). Low ee was also obtained with this catalytic system. We noted that a temperature bellow 60 °C was important to avoid the formation of side-products. For comparison, *t*Bu-BOX ligand **6.5b** was tested with the same set of copper salts. The reaction could be carried out at 35 °C using CuCl/$AgNTf_2$, however conversion of the VBX reagent was still uncompleted after 48 h and furnished **6.8a** with a low 15% ee (entry 4). As previously established, $Cu(CH_3CN)_4BF_4$ with ligand **6.5b** was efficient to catalyze the reaction: Full conversion of Ph-VBX (**6.7a**) was observed in few minutes at 35 °C and in less than 1 h at 25 °C (entries 5 and 6). A similar result was obtained using $Cu(OTf)_2$ (entry 7). In summary, $Cu(CH_3CN)_4BF_4$ and $Cu(OTf)_2$ were more efficient copper sources than the *in situ* generated $CuNTf_2$. An important increase of reactivity was noticed when changing indane-BOX **6.5e** to *t*Bu-BOX **6.5b**. The enantioselectivity was moderately better with **6.5e**, although low ee levels were achieved with both ligands.

Table 11. Investigation of the copper salt effect with ligand **6.5e** and **6.5b**.[a]

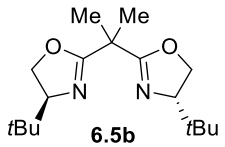


6.6a **6.7a** **6.8a**

Entry	Cu(I) salt	Ligand	T (°C)	Time	Conv[b]	ee[c] (%)
1	$CuCl/AgNTf_2$	**6.5e**	60	48 h	low	n.d.
2	$Cu(CH_3CN)_4BF_4$	**6.5e**	60	6 h	full	23
3	$Cu(OTf)_2$	**6.5e**	35	18 h	full	15
4	$CuCl/AgNTf_2$	**6.5b**	35	48 h	half	15
5	$Cu(CH_3CN)_4BF_4$	**6.5b**	35	5 min	full	17
6	$Cu(CH_3CN)_4BF_4$	**6.5b**	25	< 1 h	full	13
7	$Cu(OTf)_2$	**6.5b**	35	15 min	full	13



6.5e



6.5b

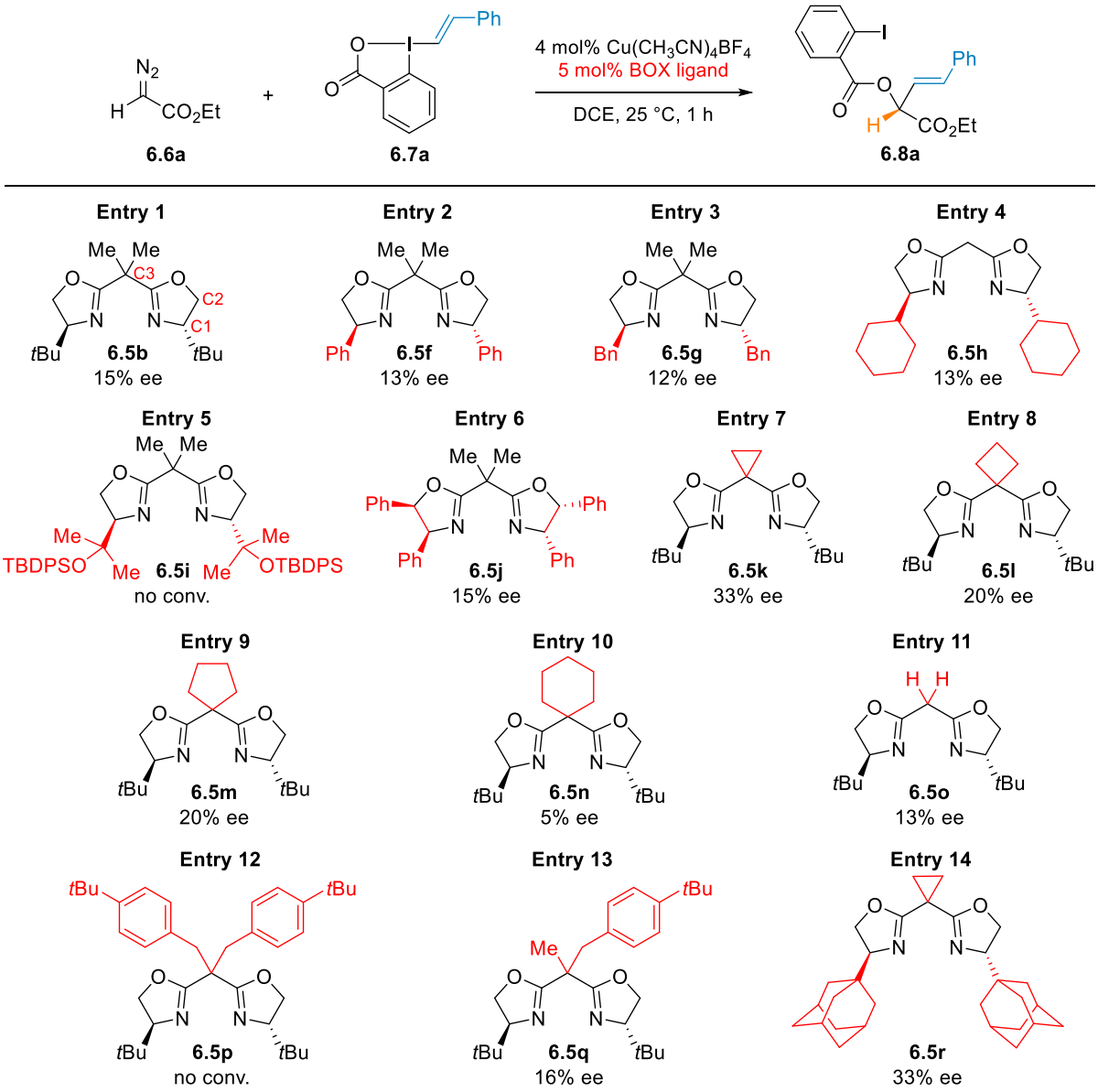
[a]Reaction conditions: 0.20 mmol of EDA (**6.6a**), 0.10 mmol of Ph-VBX (**6.7a**), Cu cat (2 mol%), ligand (2.5 mol%), solvent (0.02 M). [b]Conversion of **6.7a** estimated by TLC analysis. [c]Obtained by chiral HPLC.

We continued our investigations by screening various BOX ligands, using EDA (**6.6a**) with Ph-VBX (**6.7a**) and $Cu(CH_3CN)_4BF_4$ (4 mol%) as copper source to insure good reactivity at ambient temperature (Table 12). First, we examined the effect of the groups on the oxazoline chiral atoms (C1).[309] Substituents with aryl rings such as Ph (**6.5f**) or Bn (**6.5g**) did not improve the enantioselectivity despite potential attractive π-interactions with the VBX reagent (entries 2 and 3). Modulation of the steric hindrance at this key position is often a straightforward strategy to impact the selectivity. In our case, introduction of cyclohexyl substituents (**6.5h**) did not change the outcome, furnishing **6.8a** in low ee (entry 4). Utilization of BOX ligand **6.5i** having large silyl-protected tertiary alcohols resulted in a racemic reaction (entry 5).[310] Addition of extra substituents in the α-positions to the oxygen atoms (C2) did not improve the low ee obtained so far, as exemplified with the tetraphenyl-substituted ligand **6.5j** (entry 6). Then, we evaluated the effect of substituents on the spacer carbon atom (C3). It has been reported that variation of the ring size in spirocyclic bisoxazoline directly affect the bite angle of the ligand. [311] We synthesized and studied a range of spirocyclic ligands **6.5k**-**n** in the reaction. Pleasingly, an increase to 33% of enantioselectivity was obtained with the cyclopropyl motif (**6.5k**) (entry 7). Four- and five-membered rings (**6.5l** and **6.5m**) gave lower ee values (entries 8 and 9) and the cyclohexyl derivative (**6.5n**) furnished **6.8a** with only 5% ee (entry 10). The common synthetic intermediate **6.5o** was also utilized as a ligand to deliver the product with a similar ee to the initial *t*Bu-BOX **6.5b** with the dimethyl substituents on the spacer (entry 11). Having identified a critical position influencing the enantioselectivity, we further screened ligand **6.5p** with a double benzyl

[309] For a practical review on BOX ligands, see: G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2011**, *111*, PR284.
[310] Dr. D. Perrotta is acknowledged for the synthesis of the ligand **6.5i**.
[311] S. E. Denmark, C. M. Stiff, *J. Org. Chem*. **2000**, *65*, 5875 and references cited therein.

substituent at the C3 position. Unfortunately, no reaction was observed in this case (entry 12). The replacement of one benzyl group by a methyl (**6.5q**) restored the catalytic activity, however with low ee (entry 13).[312] With ligand **6.5k**, incorporating the cyclopropyl-spirocyclic module giving the best result so far, we prepared **6.5r** combining bulky adamantyl groups at C1 and the cyclopropyl at C3. Unfortunately, with **6.5r** the ee obtained was similar to **6.5k** (entry 14).

Table 12. Screening of BOX ligands.[a]



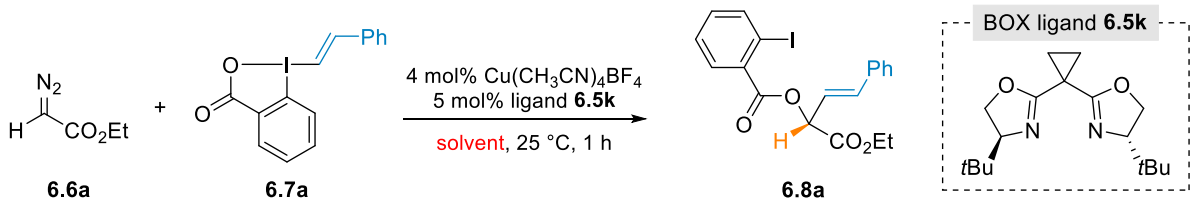
[a]Reaction conditions: 0.20 mmol of EDA (**6.6a**), 0.10 mmol of Ph-VBX (**6.7a**), $Cu(CH_3CN)_4BF_4$ (4 mol%), BOX ligand (5 mol%), solvent (0.02 M). The ee was measured by chiral HPLC.

Other tested chiral *N*,*N*-ligands including, PyBOX, PyOx and diimine gave correct conversions but no enantioselectivity, whereas mixed *P*,*N*-ligands such as PHOX and phosphoramidite were ineffective in the reaction. Therefore, selecting **6.5k** as ligand, we investigated the influence of the solvent (Table 13). Similar ee were obtained in dichloromethane and dichloroethane (entries 1 and 2). Less polar aromatic solvents, such as toluene and chlorobenzene afforded the product **6.8a** in ca. 10% ee (entries 3 and 4). THF gave another poor outcome (entry 5). Acetonitrile and chloroform were

[312] Dr. D. P. Hari is acknowledged for the synthesis of the ligand **6.5q**.

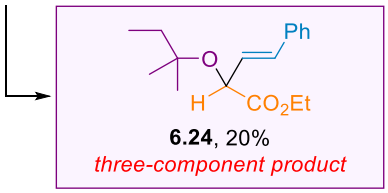
inappropriate, and probably deactivated the copper(I) catalyst as no diazo decomposition was observed (entries 6 and 7). Binary solvent systems constiting of DCE and another solvent having an available lone pair were envisaged. The underlying strategy was to influence the enantioselectivity by adding molecules able to coordinate the catalyst. When DCE/dioxane 1:1 was used as solvent, diminution of the ee was observed (entry 8). A small increase of enantioselectivity up to 40% ee was obtained with DCE/acetone 1:1 (entry 9). Finally, working with a mixture of DCE/*tert*-amyl alcohol 1:1 resulted in the unexpected formation of **6.24** in 20% yield (entry 10). Interestingly the compound **6.24** constituted a three-component reaction product, with incorporation of the alcohol nucleophile instead of the classical 2-iodobenzoate part of the VBX reagent. Despite numerous attempts to develop a three-component reaction between a diazo compound, a hypervalent iodine reagent and an external nucleophile, it was the first time we could detect such product. This result was further exploited (see section 7.1.).

Table 13. Screening of solvents.[a]



6.6a **6.7a** **6.8a**

Entry	Solvent	Conv.[b]	ee[c] (%)
1	DCE	full	33
2	DCM	full	33
3	toluene	full	13
4	PhCl	full	10
5	THF	half	< 5
6	MeCN	-	-
7	$CHCl_3$	-	-
8	DCE/dioxane 1:1	full	17
9	DCE/acetone 1:1	full	40
10	DCE/*tert*-amyl alcohol 1:1	full	30



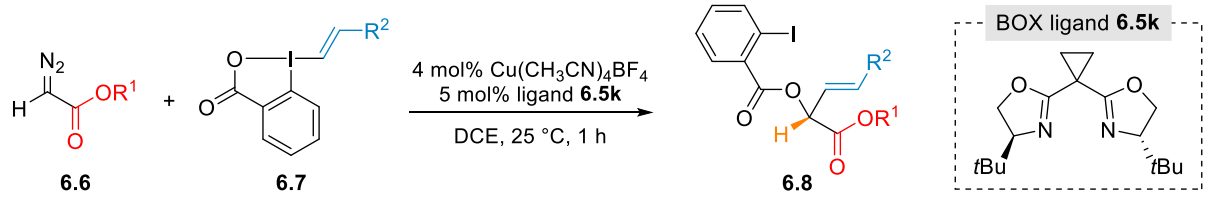
6.24, 20%
three-component product

[a]Reaction conditions: 0.20 mmol of EDA (**6.6a**), 0.10 mmol of Ph-VBX (**6.7a**), $Cu(CH_3CN)_4BF_4$ (4 mol%), ligand **6.5k** (5 mol%), solvent (0.02 M). [b]Conversion of **6.7a** estimated by TLC analysis. [c]Obtained by chiral HPLC.

A screening of the copper counterions influence was attempted using CuCl with AgX, with X = SbF_4, PF_6, OTf, ClO_4, NTf_2 and BF_4. However, in all cases no conversion was obtained. It is difficult to rationalize such results and we speculated either a non-innocent silver effect or a human error.

Other reaction parameters such as decreasing the temperature, slow-addition of the diazo compound or addition of molecular sieves did not improve the reaction outcome. Lastly, the influence of sterically demanding ester substituents on the diazo compound was verified (Table 14). Improved enantioselectivity was achieved with bulkier esters (R^1): diazo **6.6d** having a BHT substituent gave 50% ee for **6.8x** (entry 2), and cumyl-ester furnished the product **6.8aj** in 40% ee (entry 3). Finally, replacing the phenyl by a larger cyclohexyl substituent on the VBX reagent (R^2) did not impact the enantioselectivity of the reaction (entry 4).

Table 14. Influence of the reagents substituents on the enantioselectivity.[a]



6.6 + 6.7 → 6.8

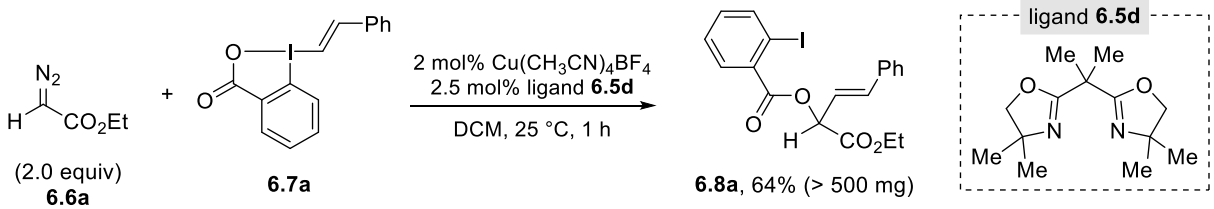
Entry	Diazo (R^1 =)	VBX (R^2 =)	Product	Conv.[b]	ee[c] (%)
1	Et	Ph	**6.8a**	full	33
2	BHT	Ph	**6.8x**	full	50
3	$C(CH_3)_2Ph$	Ph	**6.8aj**	full	40
4	Et	Cy	**6.8j**	full	30

[a]Reaction conditions: 0.20 mmol of diazo **6.6**, 0.10 mmol of VBX **6.7**, $Cu(CH_3CN)_4BF_4$ (4 mol%), ligand **6.5k** (5 mol%), solvent (0.02 M). [b]Conversion of VBX **6.7** estimated by TLC analysis. [c]Obtained by chiral HPLC.

At this stage, the enantioselective transformation was not further developed. In summary, catalytic systems composed of a cationic copper(I) salt and a chiral BOX ligand were found to be very efficient in terms of conversion but moderate ee could be achieved. Further investigation of ligand structures would be required to improve the enantioselectivity.

6.6. Product Modifications

After having explored the scope and limitations and obtained good preliminary results for the implementation of an enantioselective variation of the methodology, we concentrated our efforts on synthetic modifications of the allylic ester products. To start, compound **6.8** was synthesized on 2.0 mmol scale, using 2.0 mol% of catalyst loading (Scheme 81). The reaction was somehow sensitive to the scale-up, furnishing **6.8a** in moderate yield. The conversion of the VBX reagent **6.7a** was not completed and important dimerization of EDA (**6.6a**) was observed. The slow-addition of the diazo compound could help to increase the yield.



(2.0 equiv) **6.6a** + **6.7a** → **6.8a**, 64% (> 500 mg)

Scheme 81. Scale-up synthesis of **6.8a** utilizing a low catalyst loading.

With this material in hand, we identified the different reactive sites of the molecule **6.8a**. Our first strategy was to take advantage of the allylic ester in metal-catalyzed reactions to introduce

nucleophiles at the γ-position and to valorize the benzoate group acting as a leaving group (Table 15). Classical conditions for Tsuji-Trost reaction with diethyl malonate (**6.25**) as nucleophile under palladium(0) catalysis were unsuccessful, with no conversion of the starting material **6.8a** (entries 1 and 2). Iridium(I) with phosphinooxazolines (PHOX, **6.26**) as the ligand has been utilized by Helmchen and co-workers for the asymmetric allylic alkylation of various phenyl-substituted allylic substrates.[313] Applying these conditions led to a fast decomposition of our substrate **6.8a**, and resulted in a complex reaction mixture (entry 3). The recent work published by Zhang and co-workers, having a similar allylic system as **6.8a**, and utilizing primary amines as nucleophiles to access chiral α,β-unsaturated γ-amino esters motivated us to investigate such strategy.[314] Unfortunately, using benzylamine (**6.27**), $[Pd(Allyl)Cl]_2$ as catalyst and the chiral diphosphine **6.28** no reaction was observed (entry 4). Allylic ester **6.8** remained unreacted as well when utilizing the simpler catalyst system $Pd_2(dba)_3$/dppe (**6.29**) (entry 5). Phosphoramidite ligand **6.30** with $[Ir(COD)Cl]_2$ catalyst was also inappropriate to realize the desired allylic substitution (entry 6).[315] We found that palladium(0)-catalyzed substitution with azide ion **6.31** was also unsuccessful with derivative **6.8a** despite several reports on related molecules (entry 7).[316]

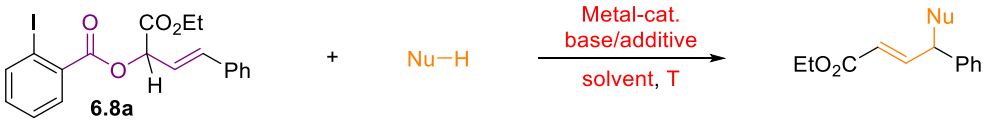
[313] C. García-Yebra, J. P. Janssen, F. Rominger, G. Helmchen, *Organometallics* **2004**, *23*, 5459.

[314] C. Xia, J. Shen, D. Liu, W. Zhang, *Org. Lett.* **2017**, *19*, 4251.

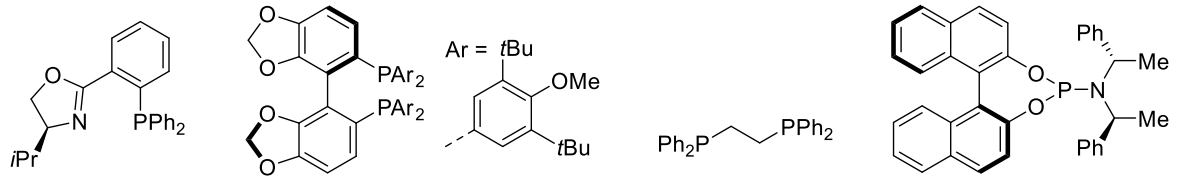
[315] K. Tissot-Croset, D. Polet, A. Alexakis, *Angew. Chem. Int. Ed.* **2004**, *43*, 2426.

[316] a) D. R. Deardorff, C. M. Taniguchi, S. A. Tafti, H. Y. Kim, So Y. Choi, K. J. Downey and T. V. Nguyen, *J. Org. Chem*. **2001**, *66*, 7191; b) S.-I. Murahashi, Y. Tanigawa, Y. Imada, Y. Taniguchi, *Tetrahedron Lett.* **1986**, *27*, 227; c) S.-I. Murahashi, Y. Taniguchi, Y. Imada, Y. Tanigawa, *J. Org. Chem.* **1989**, *54*, 3292.

Table 15. Metal-catalyzed allylic functionalization.[a]



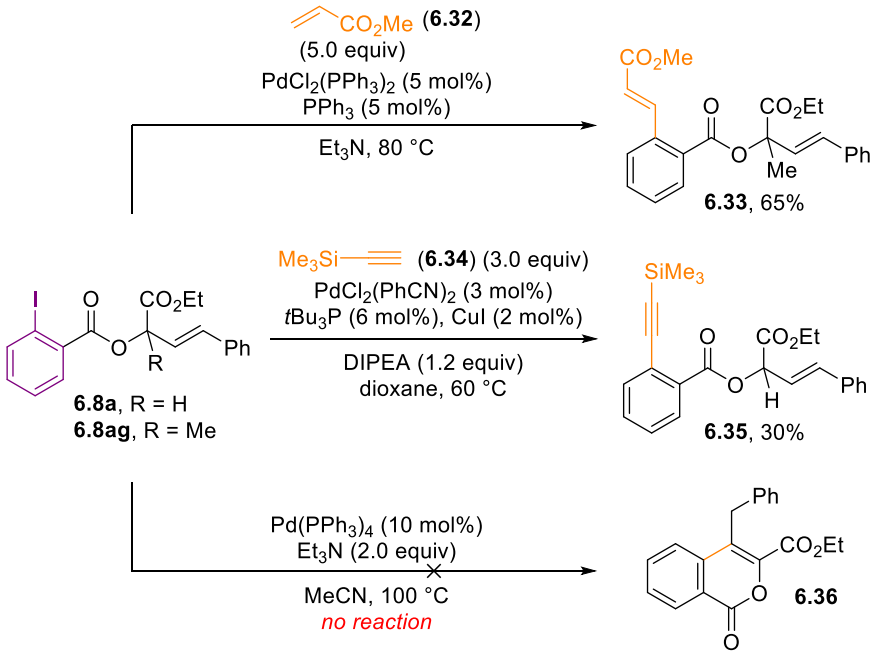
Entry	Nu-H	Metal-cat + Ligand	Base, Additive	Solvent	T (°C)	Outcome
1		$Pd(PPh_3)_4$ (5 mol%)	NaH	THF	25 to 50	no conv.
2	EtO_2C, EtO_2C **6.25**	$Pd(PPh_3)_4$ (5 mol%)	Cs_2CO_3	toluene	25 to 50	no conv.
3		$[Ir(COD)Cl]_2$ (2 mol%) PHOX (**6.26**) (4 mol%)	NaH	THF	67	dec.
4		$[Pd(Allyl)Cl]_2$ (5 mol%) SegPHOS (**6.28**) (10 mol%)	Et_3N, CsF	THF	25	no conv.
5	NH_2 **6.27**	$Pd_2(dba)_3$ (10 mol%) dppe (**6.29**) (20 mol%)	-	THF	25	no conv.
6		$[Ir(COD)Cl]_2$ (1 mol%) Phosphoramidite (**6.30**) (2 mol%)	-	THF	25 to 65	no conv.
7	NaN_3 **6.31**	$Pd(PPh_3)_4$ (5 mol%)	-	THF/H_2O	25 to 50	no conv.



(*S*)-*i*Pr-PHOX (**6.26**) (*R*)-DTBM-SegPHOS (**6.28**) dppe (**6.29**) (*S,S,S*)-Phosphoramidite **6.30**

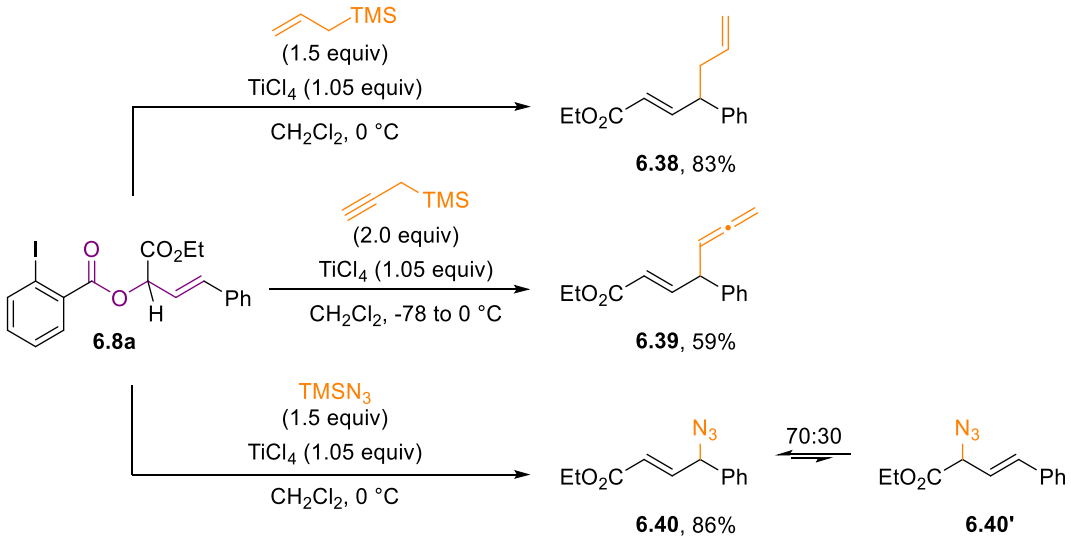
Considering the failures obtained with the metal-catalyzed allylic substitution attempts, we wondered if the aryl-iodide present in **6.8a** could interfere by oxidative addition to Pd(0) or Ir(I). Indeed, Heck reaction of compound **6.8ag** (R = Me) with methyl acrylate (**6.32**) furnished the expected product **6.33** in 65% yield (Scheme 82). In comparison, the Sonogashira cross-coupling with trimethylsilylacetylene (**6.34**) gave the alkynylated product **6.35** in only 30% yield. Finally, we targeted the functionalized isocoumarin **6.36** through an intramolecular Heck cyclization but no reaction was observed at high temperature. Woodcock and Branchaud have published an interesting study to rationalize the unfavorable conformational effect of similar ester-tethered compounds in Heck cyclization.[317]

[317] S. R. Woodcock, B. P. Branchaud, *Tetrahedron Lett.* **2005**, *46*, 7213.



Scheme 82. Pd-catalyzed cross-coupling reaction for product modifications.

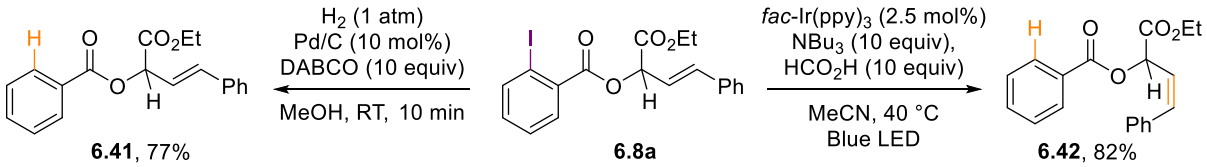
Competitive scenarios between oxidative addition of Ar-I bonds vs π-allyl complex to Pd(0) has not been widely studied to the best of our knowledge. In our case, palladium was not adapted for the activation of the allylic system and we turned our attention to Lewis acids. $TiCl_4$ proved to be the best promoter among other Lewis acids tested (BF_3•OEt_2, TMSOTf, $SnCl_4$ and $ZnCl_2$) to facilitate the displacement of the 2-iodobenzoate moiety with silane nucleophiles in a S_N2' fashion. Using this strategy, the γ-position of compound **6.8a** was functionalized with an allyl (**6.38**), an allenyl (**6.39**) and an azide (**6.40**) in overall good yields (Scheme 83). Noteworthy, allyl azide **6.40** underwent spontaneous Winstein rearrangement at room temperature to furnish **6.40**/**6.40'** as a 70:30 mixture of regioisomers.[318]



Scheme 83. Allylic functionalization of **6.8a** through Lewis acid activation.

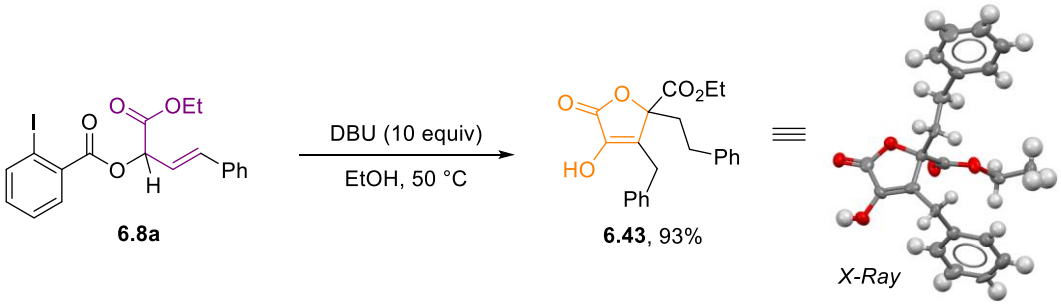
[318] a) A. S. Carlsona, J. J. Topczewski, *Org. Biomol. Chem.* **2019**, *17*, 4406; b) A. A. Ott, C. S. Goshey, J. J. Topczewski, *J. Am. Chem. Soc.* **2017**, *139*, 7737.

As seen previously, the presence of the iodine can be troublesome for further modifications. Hydrogenolysis of the iodoarene **6.8a** was achieved with hydrogen and poisoned Pd/C to give product **6.41** in 77% yield (Scheme 84). The reaction was completed in methanol and at ambient temperature in 10 minutes to avoid possible reduction of the olefin.[319] A complementary approach using visible light photoredox-catalysis was develop using *fac*-Ir(ppy)$_3$ as catalyst, and formic acid as the hydrogen atom donor.[320] In addition to the deiodination, a clean *E* to *Z* isomerization of the olefin was observed, providing **6.42** in good yield.[321]



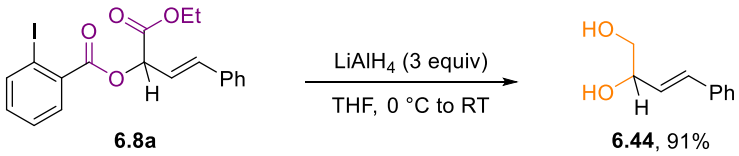
Scheme 84. Deiodination of **6.8a** *via* hydrogenolysis or photochemistry.

When **6.8a** was treated with DBU in ethanol polyfunctionalized butenolide **6.43** was formed in excellent yield (Scheme 85). Migration of the double bond to form an α,β-unsaturated ester was initially targeted. This unexpected product resulted from the formation of a α-keto ester followed by dimerization and cleavage of the iodobenzoate parts. The structure of **6.43** was unambiguously attributed by X-ray analysis.



Scheme 85. Formation of butenolide **6.43**.

Finally, the two ester groups in **6.8a** were readily reduced with $LiAlH_4$ to produce vinyl diol **6.44** (Scheme 86).



Scheme 86. Reduction of **6.8a** to access diol **6.44**.

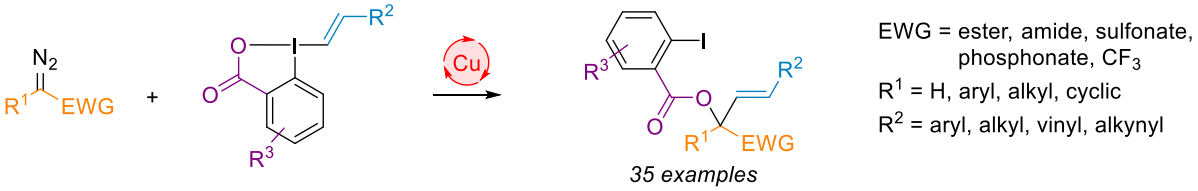
[319] N. Faucher, Y. Ambroise, J.-C. Cintrat, E. Doris, F. Pillon, B. Rousseau, *J. Org. Chem.* **2002**, *67*, 932.

[320] J. D. Nguyen, E. M. D'Amato, J. M. R. Narayanam, C. R. J. Stephenson, *Nat. Chem.* **2012**, *4*, 854.

[321] For photocatalyzed isomerization of alkenes, see: K. Singh, S. J. Staig, J. D. Weaver, *J. Am. Chem. Soc.* **2014**, *136*, 5275.

6.7. Conclusion and Perspectives

To conclude, we have developed a copper-catalyzed insertion of diazo compounds into vinylbenziodoxolone (VBX) reagents (Scheme 87). The transformation provides access to useful α-alkenyl-α-hydroxyacid derivatives in very high yields and extends the restricted chemistry for the vinylation of diazo compounds.



Scheme 87. Summary of the developed oxy-vinylation reaction.

Throughout the optimization studies we identified two sets of reaction conditions depending on the nature of the diazo substrate: copper(I) catalyst with a BOX ligand was selected for acceptor-only diazo compounds (R^1 = H), enabling the transformation at ambient temperature, while a diimine ligand was used with disubstituted diazo substrates ($R^1 \neq$ H), as BOX ligand was ineffective in this case. The reaction is tolerant to a broad scope of functional groups on the diazo, including ester, amide, sulfonate, phosphonate and trifluoromethyl and accommodate various secondary substitution patterns (alkyl, aryl and cyclic). Investigations of non-stabilized diazo compounds have not been undertaken yet. On the VBX partner, extensive variations of the olefin are possible with various (hetero)aromatic substituents and aliphatic residues bearing important functional groups and structural motifs useful in organic synthesis.

The obtained products were successfully valorized in a range of follow-up functionalizations exploiting the key features of the molecules, namely the allyl, the aryl iodide, and the ester(s). The principal limitation of the methodology concerns the insufficient enantioselectivity attained with chiral BOX ligands, especially considering the potential of the products as chiral building blocks. In this direction, further screening of chiral ligand seems the most adequate approach, although time-consuming.

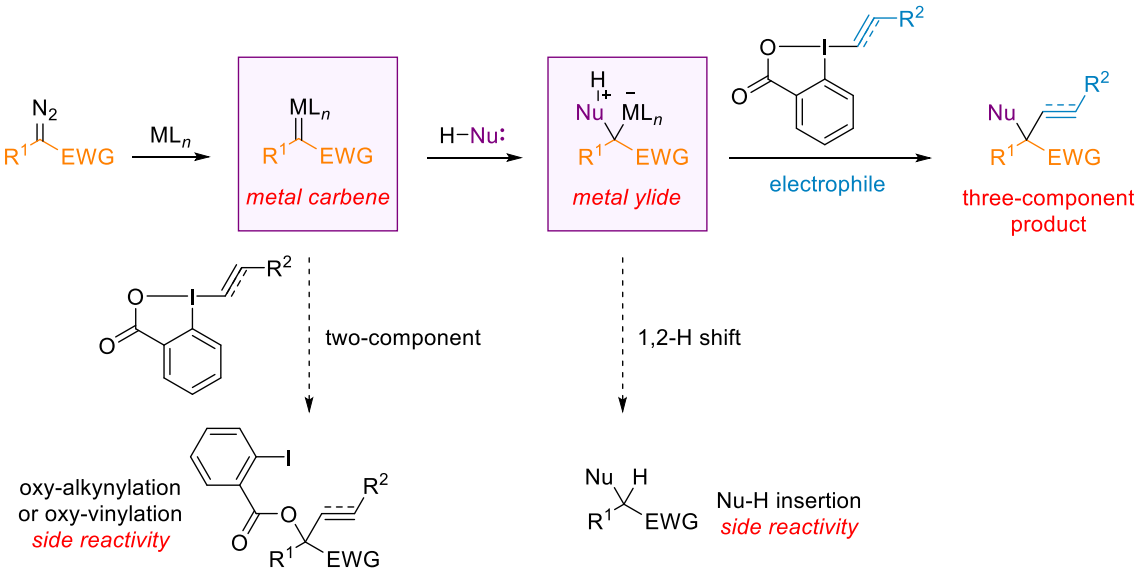
Within this project, significant advancements have been made concerning the preparation of vinylbenziodoxolones. We reported a practical protocol for the synthesis of new alkyl-substituted VBX reagents from AcO-BX and vinylboronic acids as precursors. The reagents were obtained in moderate to good yields and accommodated functionalized arenes, alkanes, dienes and enynes. Gratifyingly, the majority of the prepared VBX reagent were successfully employed in the oxy-vinylation reaction. However, the utilization of non-commercial boronic acids as vinyl source might be restricting for a user-friendly preparation of the reagents. Very few alternative synthetic routes have been explored but we could already identified vinylsilanes as suitable precursors, which could open opportunities for the introduction of novel functionalities. The ultimate goal to utilize unactivated alkenes remains.

7

Three-Component Reaction for the Synthesis of Highly Functionalized Propargyl- and Allyl-Ethers

7. Three-Component Reaction for the Synthesis of Highly Functionalized Propargyl- and Allyl-Ethers[322]

The exploitation of the nucleophilic carboxylate group of EBX and VBX reagents for the *gem*-difunctionalization of diazo compounds is interesting in the point of view of atom economy. In addition to act as a valuable oxygen source, the iodobenzoate can be further functionalized or used in down-stream transformations. However, a major limitation concerns the product diversity attainable with such transformations. Incorporation of an external nucleophile different from 2-iodobenzoate in order to develop a multicomponent reactions would be highly desirable. Based on the strategy developed by the Hu group to intercept transient metal-ylide, generated from the insertion of metal carbenes into X-H bonds (X = N, O,…), with various electrophiles, we wondered if hypervalent iodine reagents could be suitable partners in such process (Scheme 88). In fact, our first proposal to exploit the reactivity of diazo compounds was directed toward this concept, however in presence of copper catalysts, the two-component oxy-alkynylation reaction was observed.



Scheme 88. Strategy for the development of three-component reactions.

In this chapter, we will report our approach for the implementation of three-component reactions with EBX and VBX as terminal electrophiles. To realize such transformations, two major side reactivities have to be controlled: 1) Carboxylate attack of the benziodoxolone on the metal carbene will lead to the formation of two-component products that we know well; 2) Final trapping of the key metal ylide intermediate by the hypervalent iodine reagent has to be efficient enough to compete with the intramolecular 1,2-H shift leading to Nu-H insertion products.

7.1. Initial Attempts

Donor-acceptor diazo compounds form stabilized metal-ylide intermediates, that are able to delay the competitive [1,2]-H shift proton transfer and favor the electrophilic trapping. This class of diazo compounds has been the most frequently employed in multicomponent reactions involving metal-ylide intermediates. Rhodium acetate dimer (Rh_2OAc_4) has been extensively used as catalyst by

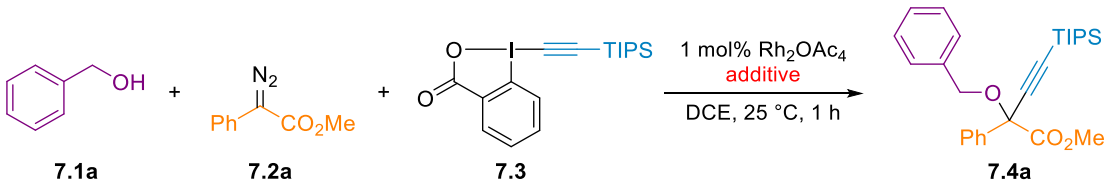
[322] "" The texts in between are direct quotations from our manuscript, G. Pisella, A. Gagnebin, J. Waser, *Chem. Eur. J.* **2020**, *26*, 10199.

the Hu group to realize three-component reactions involving *O*-, *N*- or *C*-nucleophiles (see section 2.3.3.1.). From our own experience, no competitive bimolecular reaction between the diazo compound and the EBX reagent was expected with rhodium(II) catalysts. In addition, the methodology developed by Szabó and co-workers was successful with electrophilic fluorinating benziodoxol(on)e reagents, diazocarbonyl compounds and a variety of *O*-nucleophiles and was catalyzed by Rh_2OAc_4.[232]

Considering this knowledge, we started our investigations using benzyl alcohol (**7.1a**), donor-acceptor diazo **7.2a** and TIPS-EBX (**7.3**) as partners for the formation of the three-component product **7.4a**, with Rh_2OAc_4 as catalyst (Table 16). Unfortunately, only the product of O-H insertion **7.5** was observed by ^{1}H NMR (entry 1). The diazo **7.2a** was rapidly consumed, while TIPS-EBX (**7.3**) remained unreacted. We assumed that EBX reagent **7.3** was not reactive enough to trap the Rh-ylide intermediate. $Zn(NTf_2)_2$ was used as additive in order to activate the EBX reagent through carboxylate coordination (entry 2).[323] In this case, the O-H insertion product **7.5** was isolated in 58% yield, along with product **7.6** in 32% yield resulting from the insertion of 2-iodobenzoate without incorporation of the alkyne. Phosphoric acid diesters derived from chiral BINOL have been used in synergy with Rh_2OAc_4 by Hu and co-workers as bifunctional Brønsted acid to simultaneously stabilize the Rh-ylide and activate the electrophile (imine) by protonation.[324] In our case, when 5 mol% of (-)-CPA **7.7** was added to the rhodium catalyst, only O-H insertion product **7.5** was observed (entry 3). We reasoned that the oxonium-ylide intermediate could be deprotonated to suppress the [1,2]-H shift. However, the addition of triethylamine or K_2CO_3, did not prevent the formation of **7.5** (entries 4 and 5). When sodium methoxide was used as the nucleophile, no reaction was observed (entry 6). The alcoholate anion possibly deactivated the rhodium catalyst. Finally, a reverse approach was attempted by means of sulfur ylide intermediates. In contrast to electrophilic metal carbenes, sulfur ylides are nucleophilic species.[325] Therefore, we expected the electrophilic attack of EBX **7.3** in a first time and nucleophilic displacement of the sulfide auxiliary by the alcohol **7.1a** in a second time. Unfortunately, the rhodium-catalyzed addition of tetrahydrothiophene (THT, **7.8**) on diazo compound **7.2a** did not formed the expected sulfur ylide intermediate (no diazo decomposition by TLC) (entry 7).

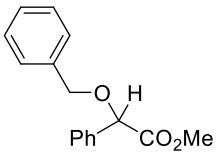
[323] R. Koller, K. Stanek, D. Stolz, R. Aardoom, K. Niedermann, A. Togni, *Angew. Chem. Int. Ed.* **2009**, *48*, 4332.
[324] W. Hu, X. Xu, J. Zhou, W.-J. Liu, H. Huang, J. Hu, L. Yang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 7782.
[325] V. K. Aggarwal, J. G. Ford, A. Thompson, R. V. H. Jones, M. C. H. Standen, *J. Am. Chem. Soc.* **1996**, *118*, 7004.

Table 16. Attempt of Rh-catalyzed three-component reaction with alcohol **7.1a**, diazo **7.2a** and EBX **7.3**.[a]

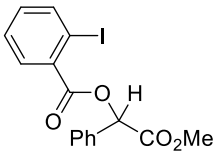


7.1a **7.2a** **7.3** **7.4a**

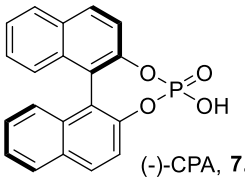
Entry	Additive	Product[b]
1	-	**7.5**
2	$Zn(NTf_2)_2$ (0.5 equiv)	**7.5**, 58%[c] + **7.6**, 32%[c]
3	(-)-CPA **7.7** (5 mol%)	**7.5**
4	Et_3N (1.2 equiv)	**7.5**
5	K_2CO_3 (1.2 equiv)	**7.5**
6[d]	-	-
7	THT (**7.8**) (1.0 equiv)	-



7.5



7.6



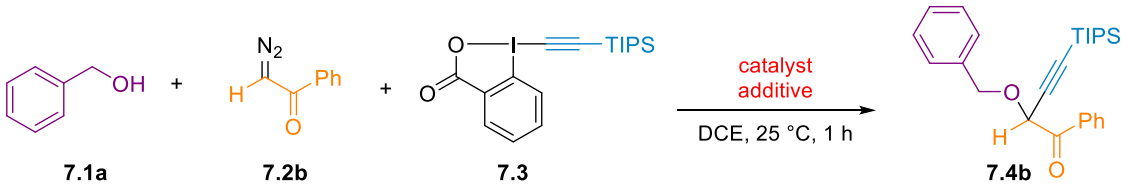
(-)-CPA, **7.7**

THT (**7.8**)

[a]Reaction conditions: 0.10 mmol of BnOH (**7.1a**), 0.12 mmol of diazo **7.2a**, 0.10 mmol of TIPS-EBX (**7.3**), Rh_2OAc_4 (1 mol%), DCE (0.05 M). [b]Crude ^1H NMR analysis. [c]Yield after purification by column chromatography. [d]MeONa was used instead of BnOH.

Diazoketones were more reactive substrates than diazoesters in the oxy-trifluoromethylation reaction developed by Szabó and co-workers.[232] Therefore, compound **7.2b** was prepared and engaged in the three-component reaction with TIPS-EBX (**7.3**) and BnOH (**7.1a**) (Table 17). When Rh_2OAc_4 was used as catalyst, only the O-H insertion product **7.9** could be detected (entry 1). Addition of sodium acetate as base did not prevent the formation of **7.9** (entry 2). We then turned our attention to other metal catalysts. Unfortunately, no reaction was observed with $Cu(acac)_2$ (entries 3 and 4), and full decomposition of the α-diazoketone **7.2b** was obtained with $Zn(OTf)_2$ (entry 5).

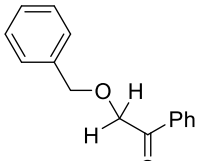
Table 17. Attempt of three-component reaction with diazoketone **7.2b**.[a]



7.1a 7.2b 7.3 7.4b

Entry	Catalyst	Additive	Product[b]
1	Rh_2OAc_4 (1 mol%)	-	**7.9**
2	Rh_2OAc_4 (1 mol%)	NaOAc (2.0 equiv)	**7.9**
3	$Cu(acac)_2$ (5 mol%)	-	-
4	$Cu(acac)_2$ (5 mol%)	THT (**7.8**) (1.0 equiv)	-
5	$Zn(OTf)_2$ (20 mol%)	-	dec.

THT (**7.8**)

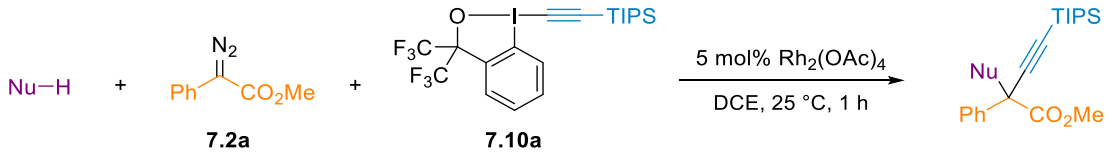


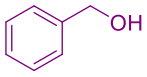
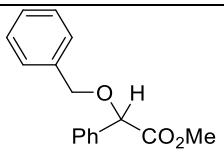
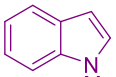
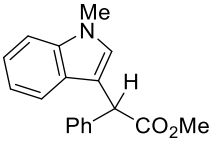
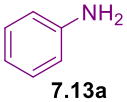
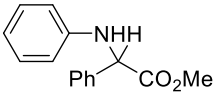
7.9

[a]Reaction conditions: 0.10 mmol of BnOH (**7.1a**), 0.12 mmol of diazo **7.2b**, 0.10 mmol of TIPS-EBX (**7.3**), DCE (0.05 M). [b]Crude ^{1}H NMR analysis.

Lastly, we tested benziodoxole-based reagent (TIPS-EBX', **7.10a**), having a hexafluroroisopropyl ligand.[137] A range of reactions with various nucleophiles was performed using the initial donor-acceptor diazo **7.2a** and 5 mol% of rhodium acetate dimer (Table 18). In all cases, fast Nu-H insertion was observed. The slow addition of the diazo compound in the case of aniline did not change the outcome.

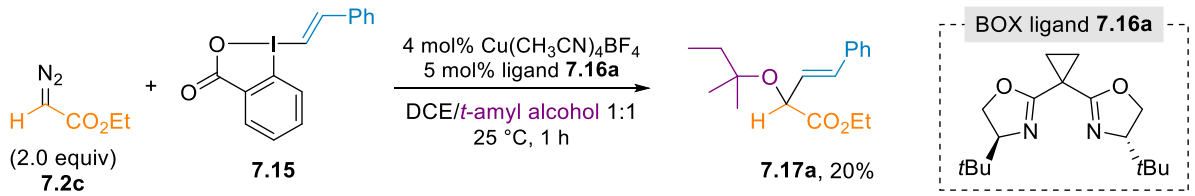
Table 18. Attempt of three-component reaction with *O*-, *N*- and *C*- nucleophiles, using TIPS-EBX' **7.10a**.[a]



Entry	Nucleophile	Product[b]
1	 **7.1a**	 **7.5**
2[c]	 **7.11**	 **7.12**
3	 **7.13a**	 **7.14**

[a]Reaction conditions: 0.10 mmol of nucleophile, 0.12 mmol of diazo **7.2a**, 0.10 mmol of TIPS-EBX' (**7.10a**), Rh_2OAc_4 (5 mol%), DCE (0.05 M). [b]Crude ^1H NMR analysis. [c]Addition of the diazo compound over 1 h.

In view of these results, we concluded that electrophilic EBX reagents were not suited to intercept metal-ylides before the proton transfer event. The project to develop multi-component reactions with hypervalent iodine reagents, diazo compounds and external nucleophiles was not further investigated until we obtained an unexpected result during our optimization of the enantioselective oxy-vinylation of diazo compounds (see section 6.5.). When ethyl diazoacetate (**7.2c**) was reacted with Ph-VBX (**7.15**) in presence of $Cu(CH_3CN)_4BF_4$ as catalyst and BOX ligand **7.16a** in a mixture of DCE/*tert*-amyl alcohol 1:1 as solvent, the product **7.17a** incorporating the *tert*-amyl alcohol instead of the 2-iodobenzoate nucleophile was isolated in 20% yield (Scheme 89). Despite that the nucleophile was used as the solvent, it was the first time we could detect and isolate a three-component product.

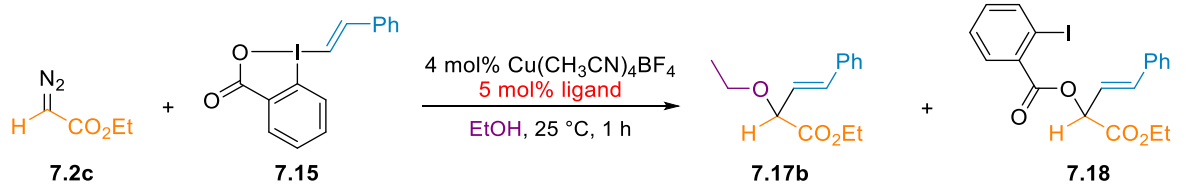


Scheme 89. First observation of a three-component product.

7.2. Optimization of the Three-Component Reaction with Alcohol Nucleophiles

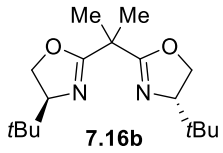
At first, reactions using ethanol only as solvent were performed (Table 19). *t*Bu-BOX ligand **7.16b** and diimine ligand **7.16c** were compared and furnished the desired product **7.17b** in ca. 50% yield. The competitive two-component product **7.18** was formed in both cases.

Table 19. Three-component reaction with ethanol (solvent), EDA (**7.2c**) and Ph-VBX (**7.15**).[a]

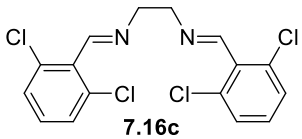


7.2c **7.15** **7.17b** **7.18**

Entry	Ligand	Yield[b] (%) 7.17b/7.18
1	**7.16b**	50/28
2	**7.16c**	53/21



7.16b

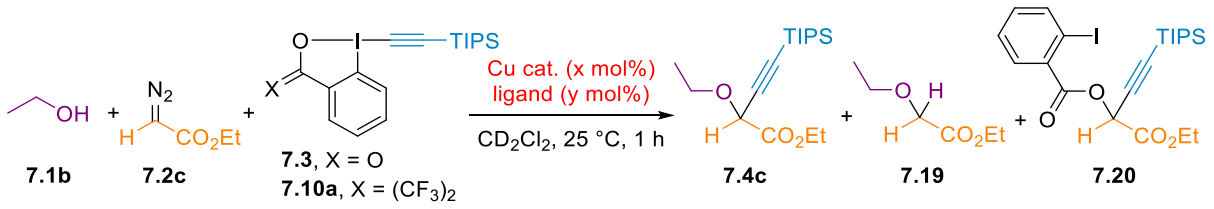


7.16c

[a]Reaction conditions: 0.60 mmol of EDA (**7.2c**), 0.30 mmol of Ph-VBX (**7.15**), $Cu(CH_3CN)_4BF_4$ (4 mol%), ligand (5 mol%), EtOH (0.04 M). [b]Yield after purification by column chromatography.

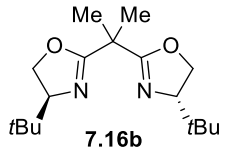
TIPS-EBX (**7.3**) delivered the expected three-component product **7.4c** under similar reaction conditions. Therefore, the optimization of the reaction was continued using this hypervalent iodine reagent (Table 20). "Using $Cu(CH_3CN)_4BF_4$ as copper source, diimine **7.16c** or bisoxazoline **7.16b** as ligands and ethanol as solvent, the desired product **7.4c** could be obtained in 50% and 63% yield, respectively (entries 1 and 2). However, despite using ethanol as solvent, a significant amount (32% and 30%) of the two-component product **7.20** was still obtained. Furthermore, when only 10 equivalents of ethanol were used, the yield of **7.4c** dropped to 22% (entry 3), showing that these conditions would not be useful to develop a general three-component reaction. We therefore decided to modify the hypervalent iodine reagent. We turned to hexafluoroisopropanol-benziodoxole derivative (TIPS-EBX', **7.10a**), expecting a lower nucleophilicity of the oxygen atom. Indeed, in this case only the three-component product **7.4c** was obtained in 62% yield (entry 4)." In comparison, alkynyl-iodonium salt **7.21** decomposed under these reaction conditions (entry 5). "An enhanced reactivity was observed in absence of the BOX ligand, resulting in quantitative formation of product **7.4c** together with O-H insertion product **7.19** (entry 6). Gratifyingly, the same result was obtained when only 10 equivalents of ethanol (**7.1b**) were used (entry 7). The yield of **7.4c** decreased to 80% and 53% respectively with 4 and 2 equivalent of ethanol (**7.1b**) (entries 8 and 9). Using a higher catalyst loading, **7.4c** could be still obtained in 62% yield with only 2 equivalents of ethanol (**7.1b**) (entry 10)." Diminution to only 1 equivalent of the diazo compounds **7.2c** resulted in reduction of the yield by half (entry 11).

Table 20. Screening of the electrophilic alkyne source, catalyst loading and ligands for the optimization of the three-component reaction.[a]

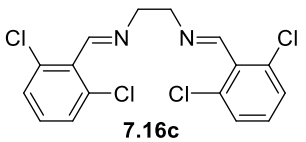


7.1b **7.2c** **7.3**, X = O **7.10a**, X = $(CF_3)_2$ **7.4c** **7.19** **7.20**

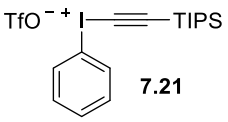
Entry	EBX (1.0 equiv)	EDA (7.2c) (v equiv)	EtOH (7.1b) (w equiv)	Cu cat. (x mol%)	Ligand (y mol%)	Yield[b] (%) 7.4c/7.19/7.20
1	**7.3**	2.0	solvent	$Cu(CH_3CN)_4BF_4$ (4 mol%)	**7.16c** (5 mol%)	50/n.d./32
2	**7.3**	2.0	solvent	$Cu(CH_3CN)_4BF_4$ (4 mol%)	**7.16b** (5 mol%)	63/n.d/30
3	**7.3**	2.0	10.0	$Cu(CH_3CN)_4BF_4$ (4 mol%)	**7.16b** (5 mol%)	22/n.d./52
4	**7.10a**	2.0	solvent	$Cu(CH_3CN)_4BF_4$ (4 mol%)	**7.16b** (5 mol%)	62/n.d./-
5	**7.21**	2.0	solvent	$Cu(CH_3CN)_4BF_4$ (4 mol%)	**7.16b** (5 mol%)	-/n.d./-
6	**7.10a**	2.0	solvent	$Cu(CH_3CN)_4BF_4$ (4 mol%)		100/48/-
7	**7.10a**	2.0	10.0	$Cu(CH_3CN)_4BF_4$ (4 mol%)		100/47/-
8	**7.10a**	2.0	4.0	$Cu(CH_3CN)_4BF_4$ (4 mol%)		80/49/-
9	**7.10a**	2.0	2.0	$Cu(CH_3CN)_4BF_4$ (4 mol%)		53/51/-
10	**7.10a**	2.0	2.0	$Cu(CH_3CN)_4BF_4$ (10 mol%)		62/38/-
11	**7.10a**	1.0	2.0	$Cu(CH_3CN)_4BF_4$ (10 mol%)		34/42/-



7.16b



7.16c



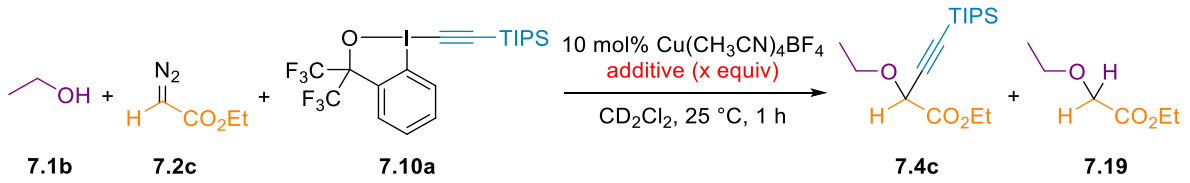
7.21

[a]Reaction conditions: 0.08 mmol of hypervalent iodine, CD_2Cl_2 (0.10 M). [b]Determined by ^1H NMR analysis of the reaction mixture. The hypervalent iodine reagent **7.3**/**7.10a** and the diazo compound **7.2c** are used as limiting reagents to calculate the yield of **7.4c**/**7.19** and **7.20**, respectively.

Having established that using benziodoxole-type EBX' **7.10** suppressed the formation of the two-component product and that removal of the ligand was beneficial for the formation of the three-component product **7.4c**, we screened several additives in order to reduce the O-H insertion side reaction (Table 21). The effect of base was investigated at first. No reaction was observed when proton sponge (**7.22**) was added (entry 1). Inorganic bases such as LiOH, Cs_2CO_3 and NaOAc also led to the deactivation of the copper catalyst and stopped the reaction (entries 2 to 4). Only $NaHCO_3$ was tolerated but was not effective to prevent the formation of **7.19** and furnished the three-component

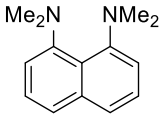
product **7.4c** with a diminished yield (entry 5). We hypothesized that stabilization of the oxonium-ylide intermediate trough hydrogen bonding could be beneficial to delay the proton transfer. However, the addition of 40 equivalents of HFIP lead to the only formation of the O-H insertion product **7.19** (entry 6). Finally, we tried again the combination of (-)-CPA catalyst **7.7** with the metal catalyst to stabilize the ylide intermediate, however **7.4c** was obtained in only 13% of yield vs 85% for **7.19** (entry 7).

Table 21. Screening of additives for the optimization of the three-component reaction.[a]

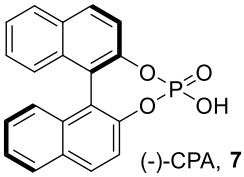


7.1b **7.2c** **7.10a** **7.4c** **7.19**

Entry	Additive	Yield[b] (%) 7.4c/7.19
1	proton sponge (**7.22**) (2.0 equiv)	-
2	LiOH (2.0 equiv)	-
3	Cs_2CO_3 (2.0 equiv)	-
4	NaOAc (2.0 equiv)	-
5	$NaHCO_3$ (2.0 equiv)	50/36
6	HFIP (40 equiv)	0/100
7	(-)-CPA (2.0 equiv)	13/85



7.22

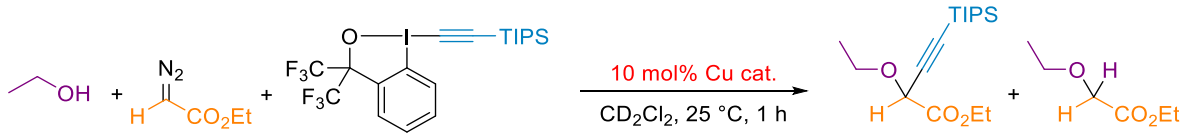


(-)-CPA, **7.7**

[a]Reaction conditions: 0.16 mmol of ethanol (**7.1b**), 0.16 mmol of EDA (**7.2c**), 0.08 mmol of TIPS-EBX' (**7.10a**), $Cu(CH_3CN)_4BF_4$ (10 mol%), CD_2Cl_2 (0.1 M). [b]Determined by ^1H NMR analysis of the reaction mixture. The hypervalent iodine reagent **7.10a** and the diazo compound **7.2c** are used as limiting reagents to calculate the yield of **7.4c** and **7.19**, respectively.

None of the additives screened were found to improve the formation of the three-component product **7.4c**. "At this point, different copper salts were examined (Table 22). Complexes with non-coordinating counterions performed better (entries 1 to 3) than copper halogenides (entries 4 and 5) or thiophenecarboxylate (TC, entry 6). No product **7.4c** was obtained when using CuI, CuCN, Cu(II) trifluoroacetylycetonate or $Cu(OAc)_2$ as catalyst (entries 7 to 10). The best result was obtained with PF_6^- as counterion, giving **7.4c** in 74% yield, with only 18% of O-H insertion product **7.19** formed (entry 1)."

Table 22. Screening of copper catalysts for the optimization of the three-component reaction.[a]



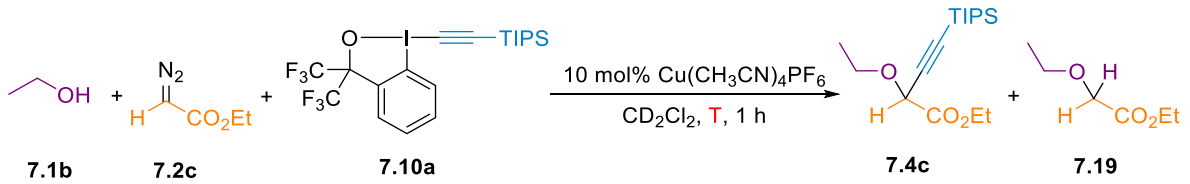
7.1b **7.2c** **7.10a** **7.4c** **7.19**

Entry	Cu cat.	Yield[b] (%) 7.4c/7.19
1	$Cu(CH_3CN)_4PF_6$	74/18
2	CuOTf•toluene	60/33
3	$Cu(OTf)_2$	47/11
4	CuBr	16/24
5	$CuCl_2$	30/17
6	CuTC	10/40
7	CuI	-
8	CuCN	-
9	$Cu(C_5H_4F_3O_2)_2$	-
10	$Cu(OAc)_2$	-

[a]Reaction conditions: 0.16 mmol of ethanol (**7.1b**), 0.16 mmol of EDA (**7.2c**), 0.08 mmol of TIPS-EBX' (**7.10a**), $Cu(CH_3CN)_4BF_4$ (10 mol%), CD_2Cl_2 (0.1 M). [b]Determined by ^1H NMR analysis of the reaction mixture. The hypervalent iodine reagent **7.10a** and the diazo compound **7.2c** are used as limiting reagents to calculate the yield of **7.4c** and **7.19**, respectively.

With $Cu(CH_3CN)_4PF_6$ identified as the best catalyst, fine-tuning of the last parameters were investigated (Table 23). For cheap alcohols a larger excess is reasonable, and **7.4c** could be obtained in 94% yield with 4 equivalents of ethanol (**7.1b**) (entry 1). No improvement of yield was observed when the reaction was performed at 0 °C (entry 2). Importantly, the slow addition of diazo **7.2c** as a diluted solution in DCM (0.6 M, addition rate 1 mL/h) gave better results when the reaction was performed on scope scale (entry 3). To have a reference, an equimolar reaction between EBX' **7.10a**, diazo compound **7.2c** and ethanol (**7.1b**) was carried out and furnished the three-component product **7.4c** in 37% yield alongside with the O-H insertion product **7.19** in 17% yield.

Table 24. Fine-tuning of the last parameters for the optimization of the three-component reaction.[a]

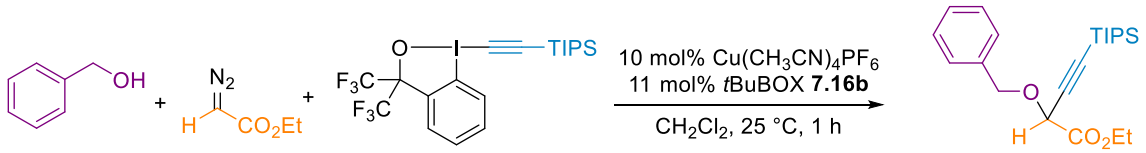


7.1b 7.2c 7.10a 7.4c 7.19

Entry	EDA 7.2c (v equiv)	EtOH 7.1b (w equiv)	Temperature (°C)	Yield[b] (%) 7.4c/7.19
1	2.0	4.0	25	94 (84)[c]/11
2	2.0	4.0	0	95/11
3[d]	2.0	4.0	25	94[c]/n.d.
4	1.0	1.0	25	37/17

[a]Reaction conditions: 0.08 mmol of TIPS-EBX' (**7.10a**), $Cu(CH_3CN)_4BF_4$ (10 mol%), CD_2Cl_2 (0.1 M). [b]Determined by ^1H NMR analysis of the reaction mixture. The hypervalent iodine reagent **7.10a** and the diazo compound **7.2c** are used as limiting reagents to calculate the yield of **7.4c** and **7.19**, respectively. [c]Yield after purification by column chromatography. [d]The diazo compound **7.2c** was added as a 0.6 M solution in CH_2Cl_2 in 1 h via syringe pump. Reaction performed on scope scale (**7.10a**, 0.30 mmol) in CH_2Cl_2.

Finally, we re-examined the reaction of diazo **7.2c**, EBX' **7.10a** and benzyl alcohol (**7.1a**) in presence of chiral BOX ligand **7.16b** under the optimized reaction conditions (Scheme 90). The product **7.4d** was obtained in poor yield owing to the presence of the donor ligand, and in racemic form. Therefore, the development of an enantioselective method was not considered.



(4.0 equiv) **7.1a** (2.0 equiv) **7.2c** **7.10a** **7.4d**, 30%, < 1% ee

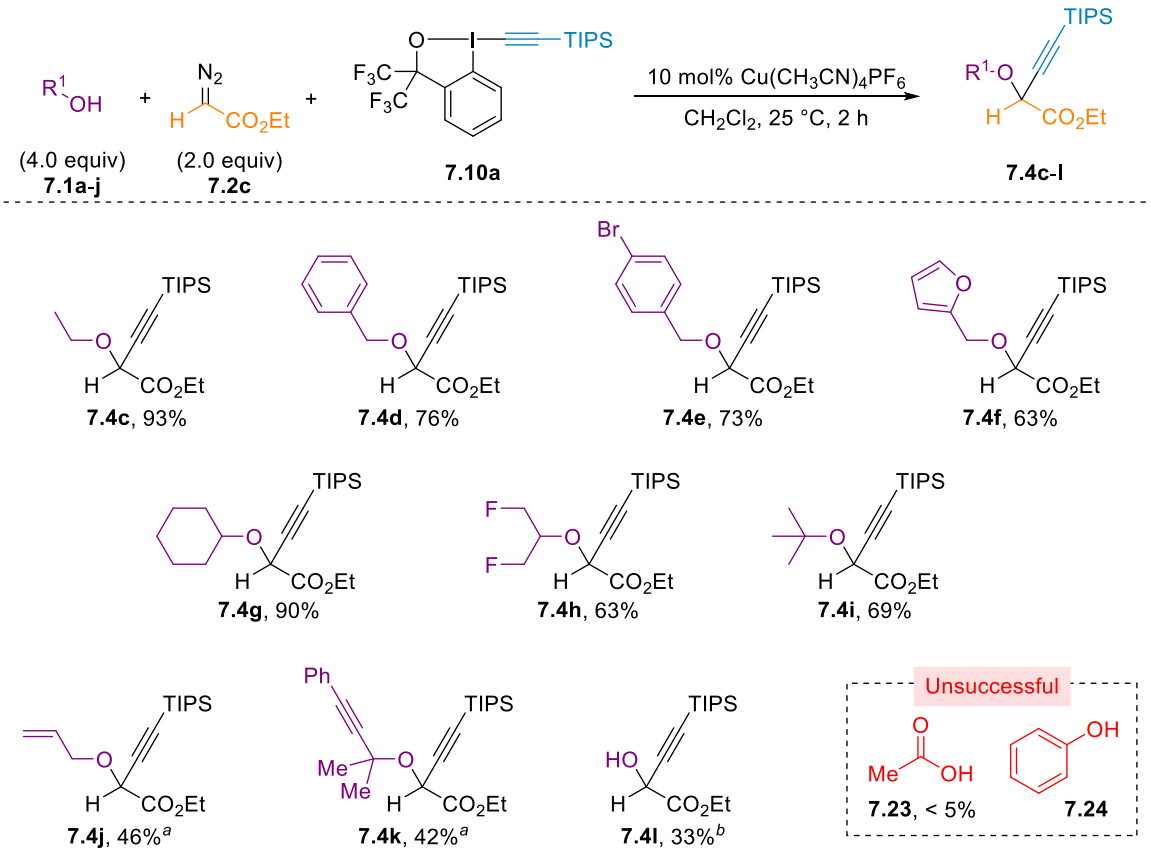
Scheme 90. Application of chiral BOX ligand **7.16b** to the optimized reaction conditions.

7.3. Scope and Limitations

7.3.1. Variation of the Alcohol Partner

"With optimized conditions in hand, we started to investigate the scope of the three-component reaction. First, we employed a variety of alcohols with TIPS-EBX' (**7.10a**) and ethyl diazoacetate **7.2c** as the two other partners (Scheme 91). On 0.3 mmol scale, propargylic ether **7.4c** was isolated in 93% yield. Benzyl alcohol provided the corresponding product **7.4d** in a slightly diminished yield. Introducing a bromo substituent in the para position gave **7.4e** in 73% yield. A heteroaromatic ring was also tolerated providing product **7.4f** from furfuryl alcohol in 63% yield. We also examined secondary alcohols. Cyclohexanol was well tolerated and furnished the corresponding product **7.4g** in 90% yield. We were pleased to see that the more electron-poor 1,3-difluoro-2-propanol gave the desired product **7.4h** in good yield. Sterically hindered *tert*-butanol still reacted remarkably well to give the corresponding three-component product **7.4i** in 69% yield. Such *tert*-butyl ethers represent a synthetic challenge and are classically accessed by strong acid

catalyzed addition of isobutene to alcohols.[326] In the case of an allyl substituent, no reaction was observed at room temperature, but at 40 °C **7.4j** was obtained in moderate yield. A similar temperature was needed to access the bis-propargyl ether derivative **7.4k** in 42% yield. These results may indicate a coordination of π-bonds to the cationic copper catalyst.[327] Dissociation would be needed to allow the diazo compound to coordinate and form the metal carbene, requiring a higher reaction temperature. We then examined other *O*-nucleophiles than alcohols. Water was a suitable partner and gave the functionalized propargylic alcohol **7.4l** in 33% yield." Other *O*-nucleophiles were unsuccessful under the reaction conditions. Only trace amounts of the desired product was observed with acetic acid (**7.23**), while a complex reaction mixture was obtained with phenol (**7.24**). No further investigations with other carboxylic acids or phenol derivatives have been realized. For example, *ortho*- and *para*-substituents on the aromatic ring could prevent side reactivity of phenol derivatives.



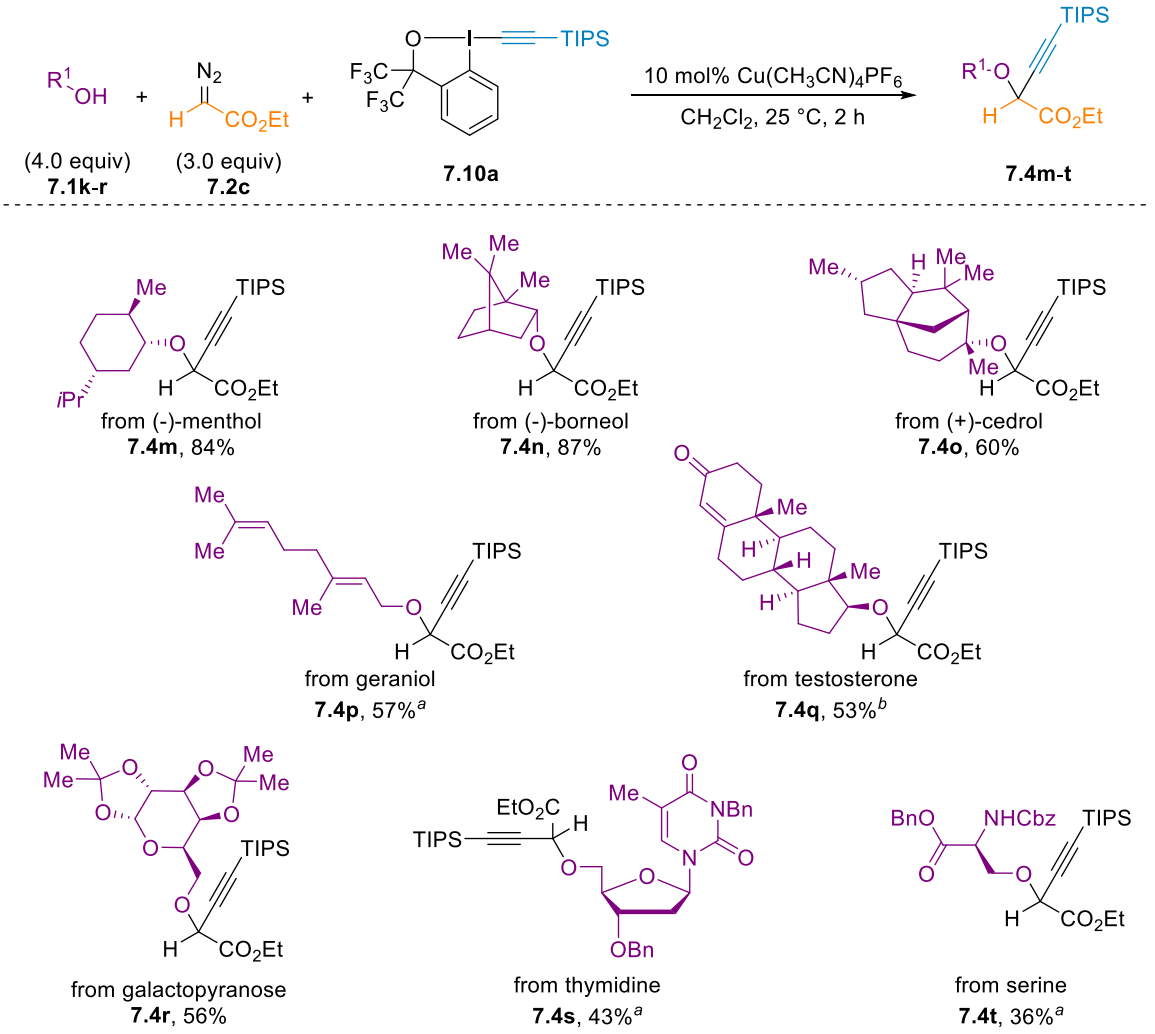
[a]Reaction conducted at 40 °C. [b]10.0 equivalent of water was used.

Scheme 91. Scope of the three-component reaction with alcohols.

"Next, we turned our attention to more complex alcohol-containing natural products (Scheme 92). We were pleased to see that several terpenes such as (-)-menthol and (-)-borneol were easily functionalized and gave the corresponding three-component products **7.4m** and **7.4n** in very good yields. (+)-Cedrol, possessing a tertiary alcohol, was converted to **7.4o** in 60% yield. Geraniol was a successful nucleophile partner, providing **7.4p** in 57% yield, despite the presence of two potentially coordinating double bonds. Other types of natural products and biomolecules were then engaged in the three-component reaction. Notably, testosterone, protected galactose, protected thymidine and

[326] H. C. Beyerman, G. J. Heiszwolf, *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 203.
[327] R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* **1973**, *95*, 3300.

protected serine all furnished the desired propargylic ether (**7.4q**, **7.4r**, **7.4s** and **7.4t**) in moderate yields showing the breadth of the scope for alcohols."



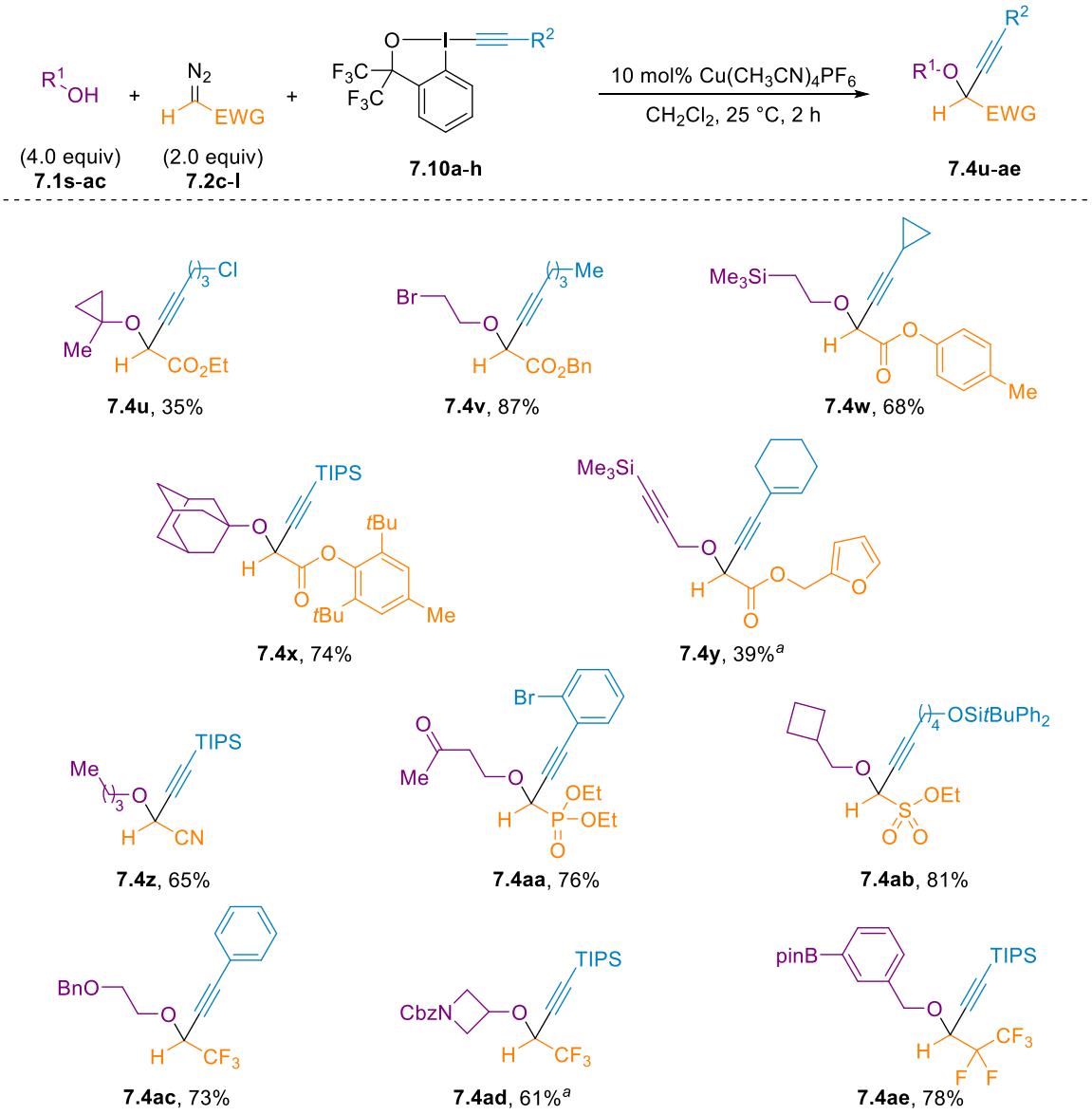
[a]Reaction conducted at 40 °C. [b]3.0 equivalent of alcohol was used. When applicable, ca. 1:1 d.r. was obtained.

Scheme 92. Three-component reaction for the functionalization of natural products and biomolecules.

7.3.2. Simultaneous Variation of the Three Partners

"The main strength of multi-component reactions resides in the structural diversity of accessible compounds. Therefore, we decided to simultaneously vary each of the three components of the reaction to further investigate the flexibility of our methodology (Scheme 93). We were pleased to see that diazo esters bearing various substituents, such as alkyl (**7.4u** and **7.4v**), aryl (**7.4w**), bulky aryl (**7.4x**) or heteroaromatic (**7.4y**) were tolerated. Other diazo compounds bearing diverse versatile functionalities (nitrile (**7.4z**), phosphonate (**7.4aa**), sulfonate (**7.4ab**), and perfluorinated alkyls (**7.4ac**, **7.4ad** and **7.4ae**)) were successfully applied. The scope of EBX' partners was also broad, including alkyl chains (**7.4u**, **7.4v**, **7.4w** and **7.4ab**), alkenyl (**7.4y**) and aromatic substituents (**7.4aa** and **7.4ac**) that contained several functional groups like halide (**7.4u** and **7.4aa**) or a silyl ether (**7.4ab**) and carbocycles, such as a cyclopropane (**7.4w**). In addition, further versatile functional groups were tolerated on the alcohols, including a bromide (**7.4v**), a ketone (**7.4aa**), protected hydroxy (**7.4w** and **7.4ac**) or a boronic ester (**7.4ae**) groups. Several carbocyclic or heterocyclic motifs important for medicinal chemistry such

as cyclopropyl (**7.4u**), cyclobutyl (**7.4ab**), azetidinyl (**7.4ad**), or adamantyl (**7.4x**) were also tolerated on the alcohol. In general, the reactions occurred smoothly, to afford products in good yields. By-products and a diminished yield were obtained for the synthesis of **7.4u**, cyclopropyl alcohols being prone to ring-opening in presence of Cu(I) catalyst.[328] The multiple unsaturations of substrate **7.4y** could explain that only partial conversion of the EBX' reagent was observed, resulting in a moderate yield."



[a]Reaction conducted at 40 °C.

Scheme 93. Substrate scope with simultaneous variation of the three components.

In the vast amount of possible three-component reactions several limitations were identified (Figure 19). Diazo amides **7.2m** and **7.2n** were not suitable reagents, furnishing only traces of the desired three-component products, despite a number of attempts with different alcohols and EBX' partners. Diazo compound **7.2o** having the redox-active leaving group NHPI,[329] recently introduce by Mendoza and co-workers, was unreactive under our reaction conditions. As observed in our previous

[328] H. Zhang, G. Wu, H. Yi, T. Sun, B. Wang, Y. Zhang, G. Dong, J. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 3945.
[329] M. Montesinos-Magraner, M. Costantini, R. Ramírez-Contreras, M. E. Muratore, M. J. Johansson, A. Mendoza, *Angew. Chem. Int. Ed.* **2019**, *58*, 5930.

methodologies, diazoketone **7.2b** was not compatible with EBX' reagents and copper salts. Primary alcohol **7.1ad**, incorporating an azide function decomposed in presence of the copper catalyst. The terminal alkyne **7.1ae** led to a complex reaction mixture. Coordination of the C-C triple bond to the catalyst or formation of a copper acetylide could induce undesired reaction pathways. Alcohols with diminished nucleophilicity, such as trifluoroethanol **7.1af** were unreactive. With EBX' **7.10i** bearing an aldehyde, only small conversions to the desired products were observed with various alcohols and diazo partners. Azide derivative **7.10j** led to complex reactions mixture. Finally, the diyne hypervalent iodine reagent **7.10k** rapidly decomposed in presence of the copper catalyst.

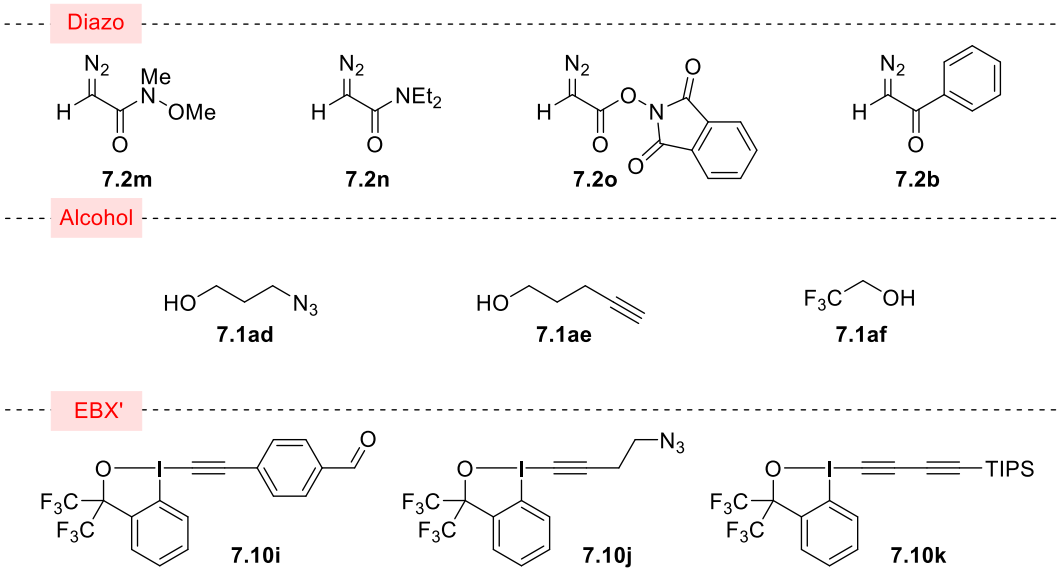
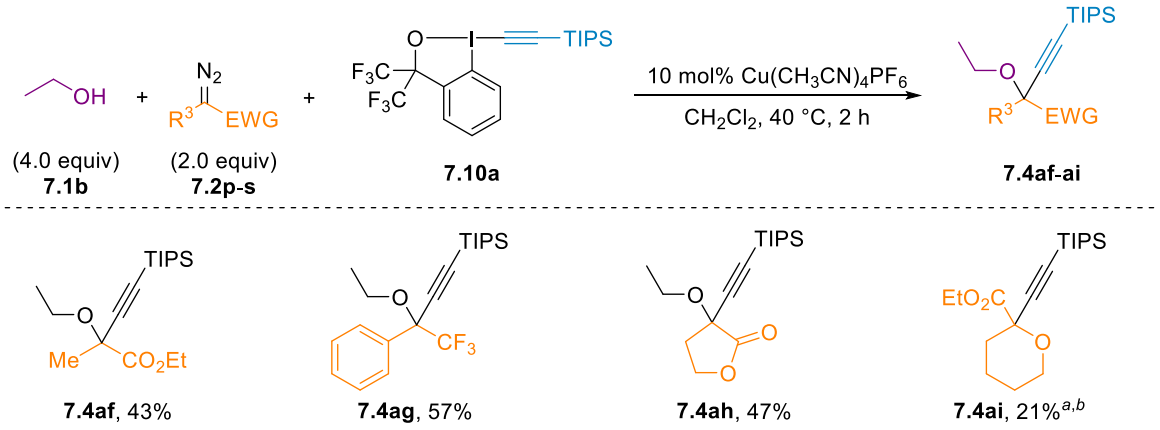


Figure 19. Unsuccessful substrates identified.

7.3.3. Disubstituted Diazo Compounds and Application to the Synthesis of Efavirenz and Structural Analogues

We continued to investigate the scope with disubstituted diazo compounds (Scheme 94). With the extra substitution, the reaction temperature was increased to 40 °C. "Diazo compounds bearing a methyl or a phenyl substituent furnished **7.4af** and **7.4ag** in 43% and 57% yield respectively, without the need to reoptimize the reaction conditions. A cyclic diazo compound provided **7.4ah** in moderate yield. Finally, we investigated a substrate having a pendant hydroxy group for intramolecular nucleophile attack. The desired tetrahydropyran **7.4ai** was formed, albeit in low yield."

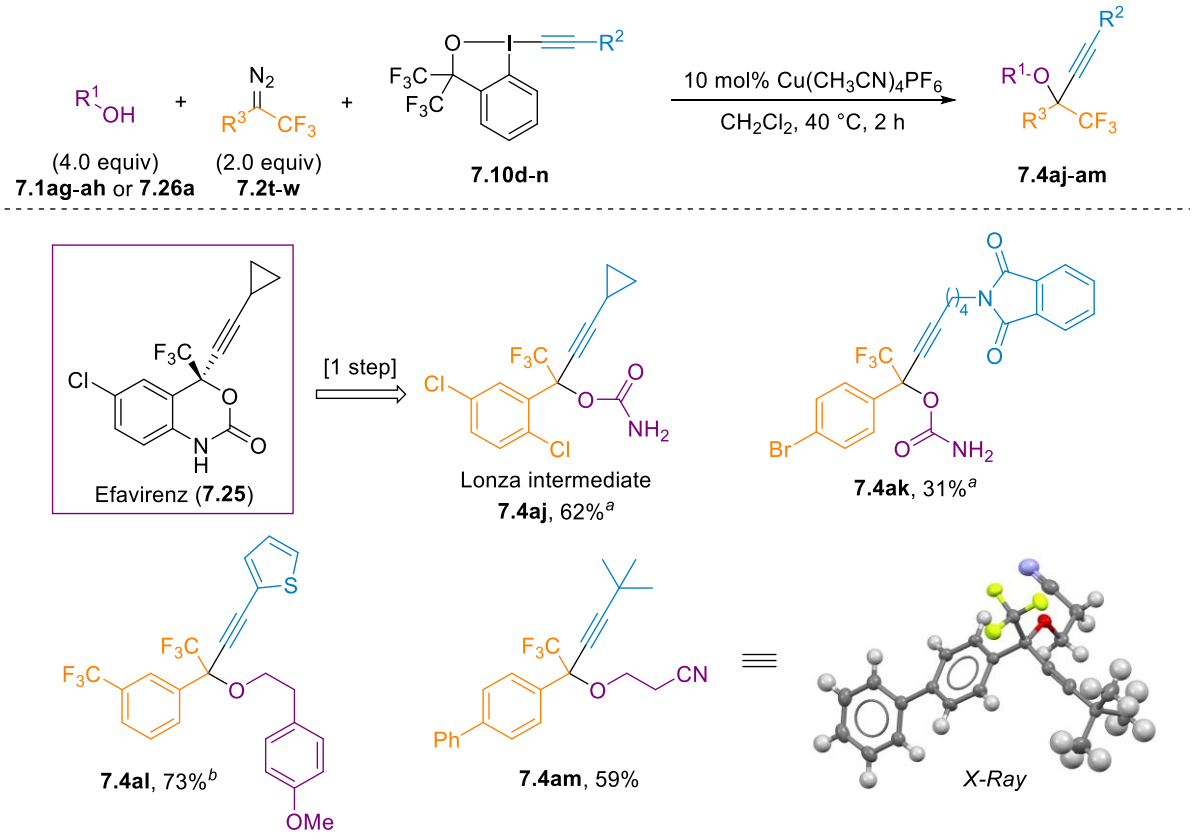


[a]Reaction conducted at 25 °C. [b]No alcohol was used.

Scheme 94. Scope of the three-component reaction: disubstituted diazo compounds.

The good efficiency of the three-component reaction with trifluoromethyl-substituted diazo compounds is especially interesting. We recognized a common structural patern between **7.4ag** and Efavirenz (**7.25**), an approved antiretroviral drug used in HIV treatment and decided to apply our methodology to access the advanced intermediate **7.4aj** (Scheme 95).[330] We envisaged the use of *tert*-butyl carbamate (Boc-NH_2, **7.26a**) as nucleophile after having discovered that *O*-attack followed by loss of the *tert*-butyl was occuring with this carbamate when attempting *N*-transfer reactions (see section 7.4.1.2.). "In this case, the number of equivalents of reagents, as well as the catalyst loading, could be reduced as there was no competitive O-H insertion pathway. The desired molecule **7.4aj** was obtained in good yield without the formation of products from N-H insertion.[331] "Our methodology also gave access to structurally diverse analogues. The carbamate derivative **7.4ak** particularly suited for further modifications with the presence of a protected amine and an aryl bromide, was obtained in 31% yield. The poly-trifluoromethylated compound **7.4al**, bearing a thiophene on the alkyne, was synthesized in good yield. Finally, the propargyl ether **7.4m** bearing a nitrile group was accessed in moderate yield. The structure of **7.4m** was further characterized by X-ray analysis.[332]"

[330] D. Dai, X. Long, A. Kulesza, J. Reichwagen, B. Luo and Y. Guo (Lonza Ltd), PCT Int. Appl. WO2012097510, **2012**.
[331] E. C. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 12066.
[332] Available at the Cambridge Crystallographic Centre, CCDC number 1985456.



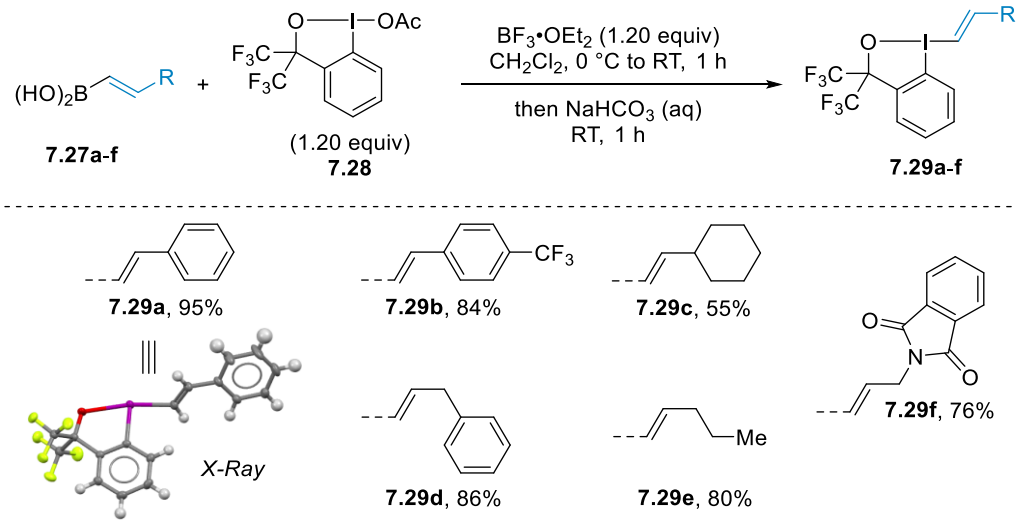
[a]$BocNH_2$ **7.26a** (1.3 equiv), **7.2t-u** (1.3 equiv) and $Cu(CH_3CN)_4PF_6$ (5 mol%) were used. Reaction conducted at 25 °C. [b]Yield determined by ^{19}F NMR spectroscopy.

Scheme 95. Application of CF_3-derived diazo compounds to the formal synthesis of Efavirenz (**7.25**) and structural analogues.

7.3.4. Three-Component Reaction with VBX' Reagents

The three-component reaction was then envisaged to access vinyl ether products using VBX' reagents. Less nucleophilic bis-trifluoromethyl vinylbenziodoxoles have however never been reported. Gratifyingly, applying the reaction conditions we developed to access alkyl-substituted benziodoxolones (see section 6.3.2.), i.e. activation of AcO-BX (**7.28**) with BF_3•OEt_2, provided a range of new bis-trifluoromethyl VBX' reagents in overall very good yields (Scheme 96). The hypervalent structure of Ph-VBX' (**7.29a**) was confirmed by X-ray analysis.[333] We believe the superior solubility of the reagents owing to the trifluoromethyl groups, facilitated a cleaner formation of this reagent as compared to classical benziodoxolone analogues.

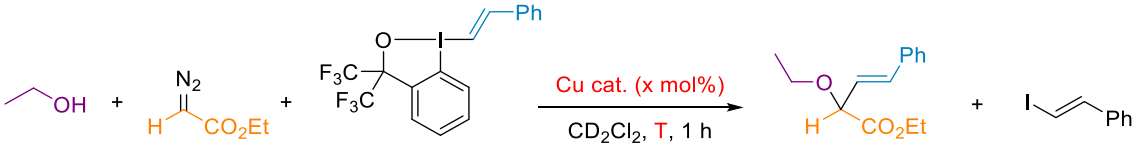
[333] Available at the Cambridge Crystallographic Centre, CCDC number 1993681.



Scheme 96. Synthesis of bis-trifluoromethyl VBX' reagents.

With several VBX' reagents synthesized, we started to investigate the three-component reaction (Table 25). Using $Cu(CH_3CN)_4PF_6$ as catalyst, Ph-VBX' (**7.29a**), EDA (**7.2c**) and ethanol (**7.1b**) as reagents, the expected product was obtained, albeit in only 22% yield (entry 1). This result reflected the partial conversion of the limiting VBX' reagent. Moreover, an important formation of iodoalkene **7.30** was detected. Reducing the catalyst loading to 5 mol% slightly improved the yield and diminished the degradation, however the conversion of **7.29a** was still not completed (entry 2). We suspected the formation of **7.30** as a result of a possible attack of ethanol (**7.1b**) on the Ar-I bond. Indeed, reducing the stoichiometry of the alcohol partner to 3 equivalents furnished **7.17b** in 35% yield (entry 3). Diminution of the reaction temperature to prevent the degradation of VBX' **7.29a** resulted in almost no conversion (entry 4). Finally, replacing $Cu(CH_3CN_4)PF_6$ by $Cu(CH_3CN_4)BF_4$ and using more diluted conditions gave **7.17b** in 40% yield (entry 5). The reaction was not further optimized with ethanol as substrate. We expected improved VBX' stability and therefore better yields with less nucleophilic alcohols.

Table 25. Re-optimization of the reaction conditions with Ph-VBX' (**7.29a**).[a]

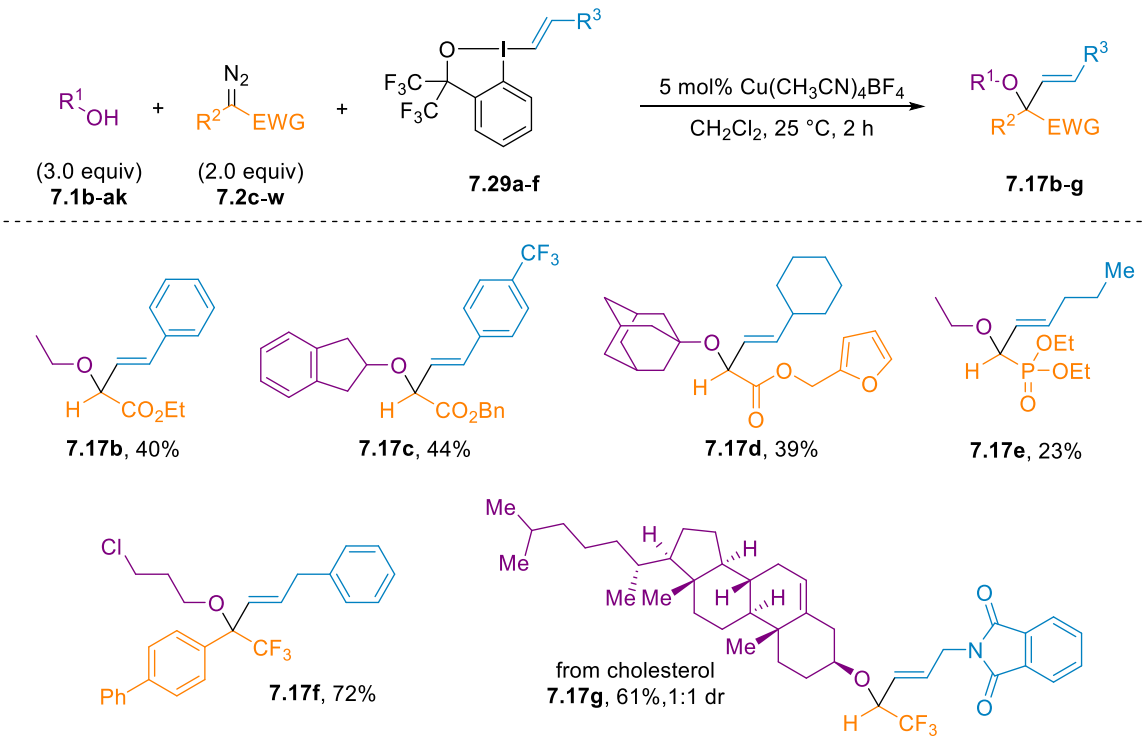


7.1b **7.2c** **7.29a** **7.17b** **7.30**

Entry	EtOH (7.1b) (w equiv)	Cu cat. (x mol%)	T (°C)	Conversion[b] 7.29a (%)	Yield[b] (%) 7.17b/7.30
1	4.0	$Cu(CH_3CN)_4PF_6$ (10 mol%)	25	62	22/40
2	4.0	$Cu(CH_3CN)_4PF_6$ (5 mol%)	25	53	24/29
3	3.0	$Cu(CH_3CN)_4$ PF_6 (5 mol%)	25	50	35/12
4	3.0	$Cu(CH_3CN)_4PF_6$ (5 mol%)	0	< 5	< 5/< 5
5[c]	3.0	$Cu(CH_3CN)_4BF_4$ (5 mol%)	25	n.d.	40/n.d.

[a]Reaction conditions: 0.16 mmol of EDA (**7.2c**), 0.08 mmol of Ph-VBX' (**7.29a**), CD_2Cl_2 (0.1 M). [b]Determined by ^1H NMR analysis of the reaction mixture. [c]Reaction performed on scope scale (**7.29a**, 0.30 mmol) in DCM (0.075 M).

Primary, secondary, and tertiary alcohols were combined with different VBX' reagents and diazo compounds to give the corresponding three-component products (Scheme 97). Functionalized allylic ethers bearing esters (**7.17b**, **7.17c** and **7.17d**) were obtained in 39 – 44% yield. Various structural motifs, such as furan (**7.17d**), indanyl (**7.17c**) and adamantyl (**7.17d**) could be incorporated in the molecules. Allylic phosphonate (**7.17e**) was formed in 23% yield. Interestingly, improved yields were obtained with the diazo compounds incorporating a trifluoromethyl motif. Starting from disubstituted diazo **7.2w**, three-component product **7.17f**, having an alkyl chloride chain was obtained in good yield. Finally, the vinylation of cholesterol was achieved in 61% yield to afford **7.17g** with a trifluoromethyl and a phthalimide group.



Scheme 97. Three-component reaction with VBX' reagents.

7.4. Mechanistic Investigations

To gain insights into the mechanism, several experiments were carried out. First, when ethyl diazoacetate (**7.2c**) was reacted with ethanol (**7.1b**) in presence of 10 mol% of $Cu(CH_3CN)_4PF_6$, we observed the formation of **7.19** by ^1H NMR spectroscopy analysis of the reaction mixture (Figure 20, Spectrum C). In addition, minor formation of maleate/fumarate side products **7.30** was observed. However, no three-component product **7.4c** was detected after the subsequent addition of TIPS-EBX' (**7.10a**) to this solution (Spectrum D). This indicates that **7.19** is not an intermediate in the catalytic cycle and the O-H insertion is likely only a background reaction. The reference ^1H NMR spectrum of TIPS-EBX' (**7.10a**) and $Cu(CH_3CN)_4PF_6$ are given for comparison (Figure 20, Spectrum B and A).

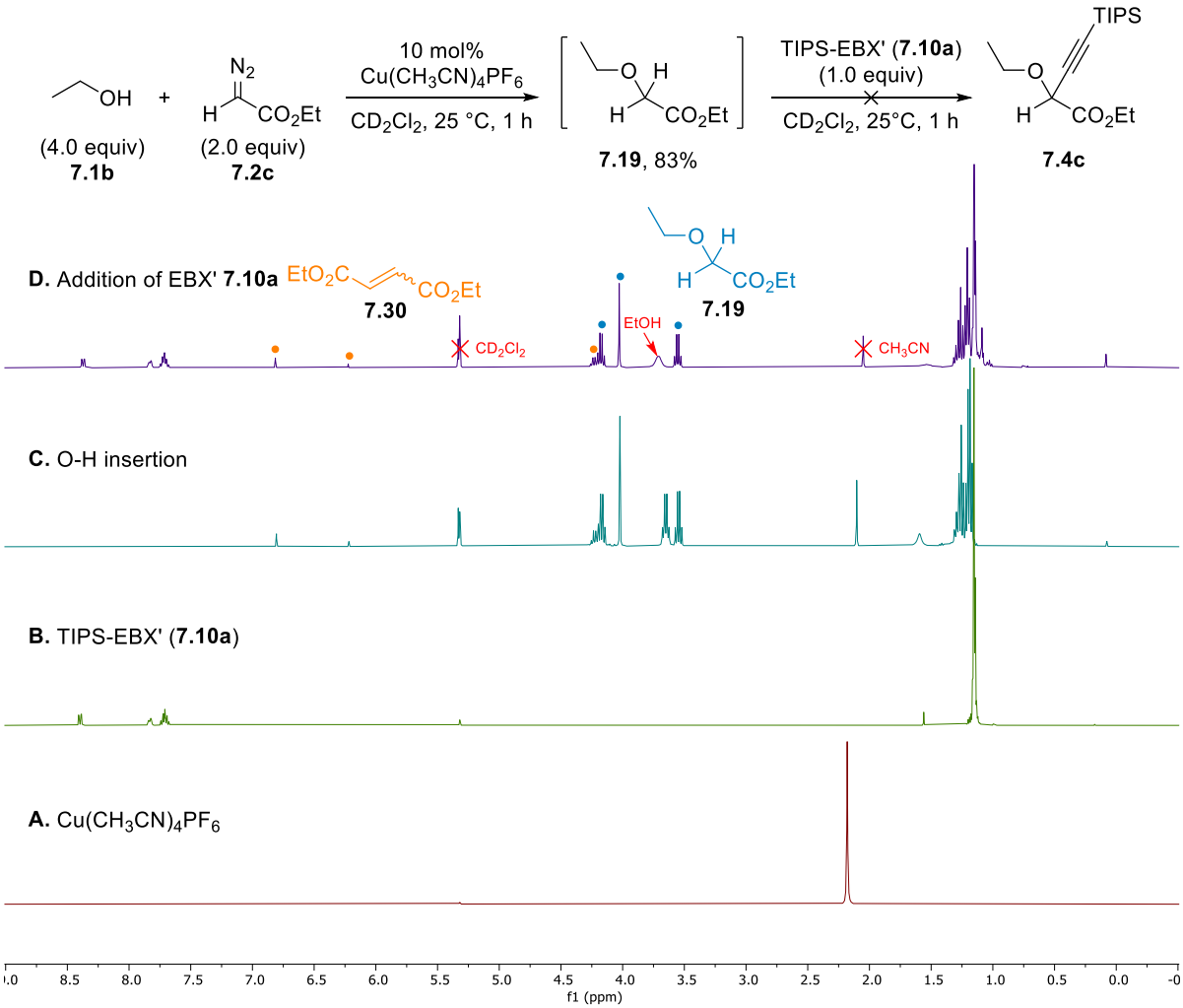


Figure 20. Sequential addition of the alcohol **7.1b** and of the EBX' reagent **7.10a**.

In absence of ethanol (**7.1b**), rapid evolution of nitrogen occurred and we mainly observed the formation of diethyl fumarate/maleate (**7.30**) (Figure 21, Spectrum C). Other products resulting from a minor decomposition (ca. 10%) of the hypervalent iodine reagent **7.10a** could not be identified. The reference ^1H NMR spectrum of TIPS-EBX' (**7.10a**) and ethyldiazo acetate (**7.2c**) are given for comparison (Figure 21, Spectrum B and A).

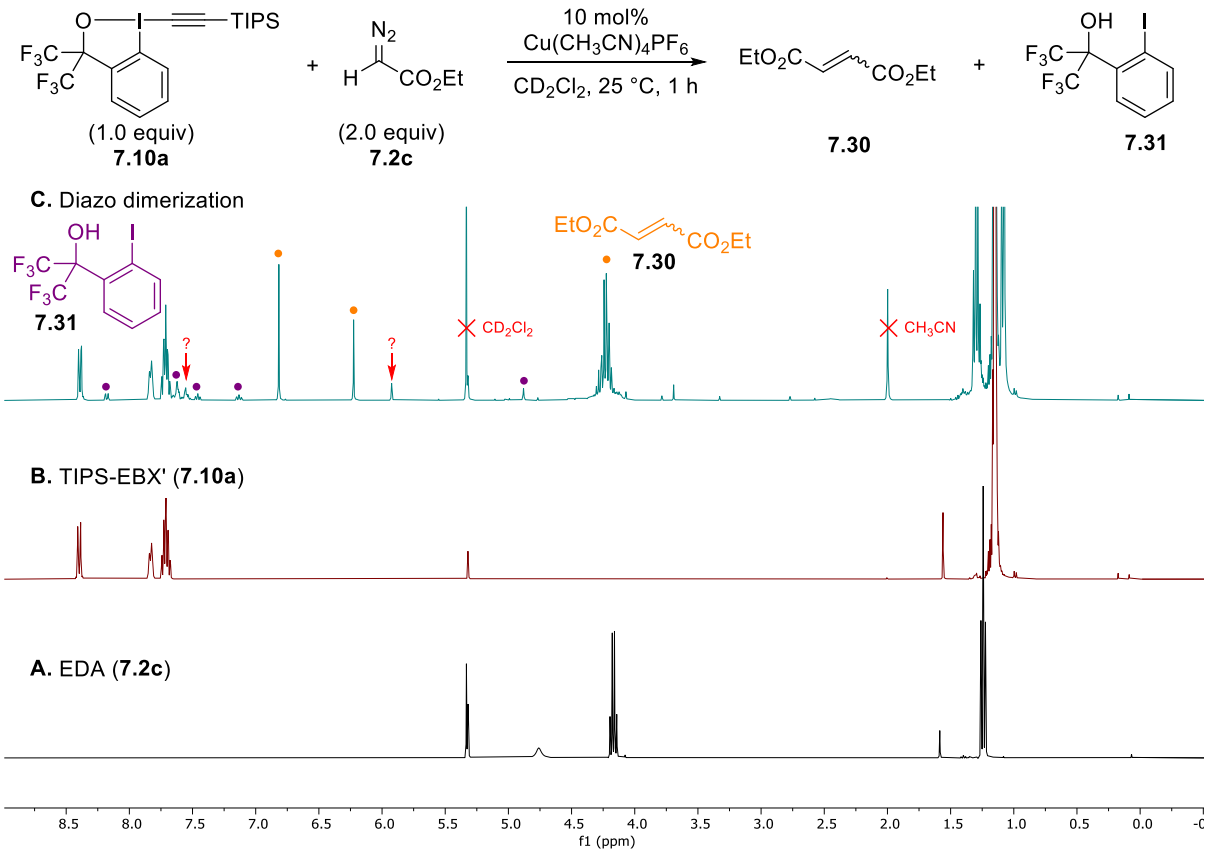
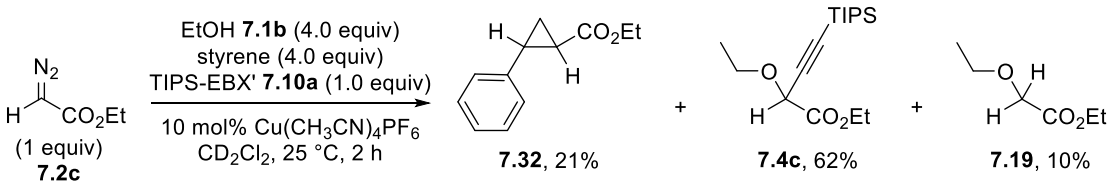


Figure 21. Self-dimerization of ethyl diazoacetate (**7.2c**) in absence of ethanol.

"We attempted the trapping of a potential Cu carbene intermediate through a cyclopropanation reaction using one equivalent of ethyl diazoacetate (**7.2c**) and 4 equivalents of ethanol (**7.1b**) and styrene (Scheme 98, see Figure S5 in section 10.5.4.). Cyclopropane **7.32** was obtained in 21% NMR yield, and the three-component product **7.4c** was formed in 62% yield. Aside from supporting the existence of a metal carbene, this competitive experiment, also shows that attack of ethanol to form a putative oxonium ylide is faster than cyclopropanation."



Scheme 98. Competitive experiment between three-component reaction and cyclopropanation.

Then, NMR titration experiments were carried out using $Cu(CH_3CN)_4PF_6$ in combination with EBX' **7.10a**. Progressive shifts of the aromatic protons were observed upon addition of the copper salt (see Figure S2 in section 10.5.4.). The proton H^a, *ortho* to the iodine atom, was the most affected and variation of its chemical shift was plotted against the $Cu(CH_3CN)_4PF_6$ equivalents (Figure 22). A significant diminution of the variation of the chemical shift was observed above one equivalent of copper salt. A similar titration profile was obtained with ^{19}F NMR, however, the chemical shift of the trifluoromethyl groups were affected by very small changes (see Figure S3 in section 10.5.4.).

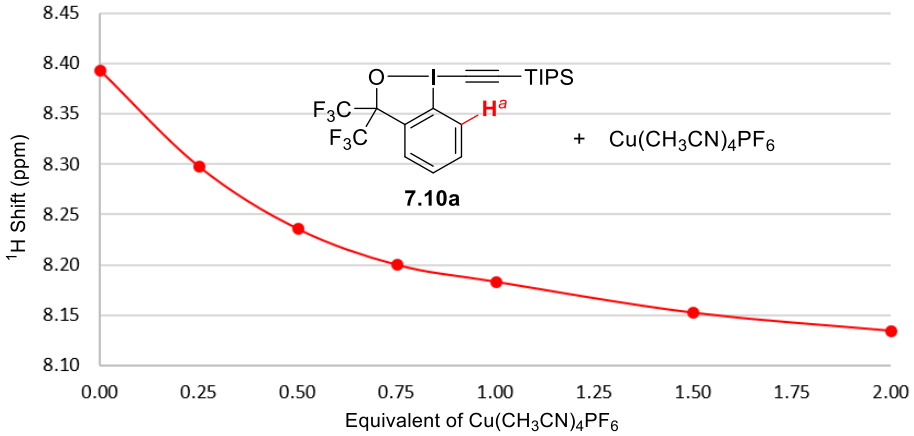


Figure 22. Chemical shift value of H^a function of the equivalent of $Cu(CH_3CN)_4PF_6$.

Finally, a ^{13}C NMR spectrum of an equimolar mixture of $Cu(CH_3CN)_4PF_6$ and **7.10a** in CD_2Cl_2 showed major changes in the ^{13}C-alkyne signals (Figure 23). Major changes of C1 ($\Delta\delta$ = 0.7 ppm, 71.1 Hz) and C2 ($\Delta\delta$ = 3.4 ppm, 339.5 Hz) were observed. Noteworthy, the signal of C2 was broaden, possibly due to the quadropolar effect of ^{63}Cu and ^{65}Cu nuclei.[334] Other ^{13}C signals remained almost unchanged in presence of the copper salt. In comparison, when ethanol (**7.1b**, 4.0 equiv) and $Cu(CH_3CN)_4PF_6$ (1.0 equiv) were mixed together in CD_2Cl_2, no chemical shift (^1H and ^{13}C NMR) or ligand exchange with the acetonitrile was observed and the initial copper complex was recovered after evaporation (see Figure S4 in section 10.5.4.).

[334] A. Marker, M. J. Gunter, *J. Magn. Reson.* **1982**, *47*, 118.

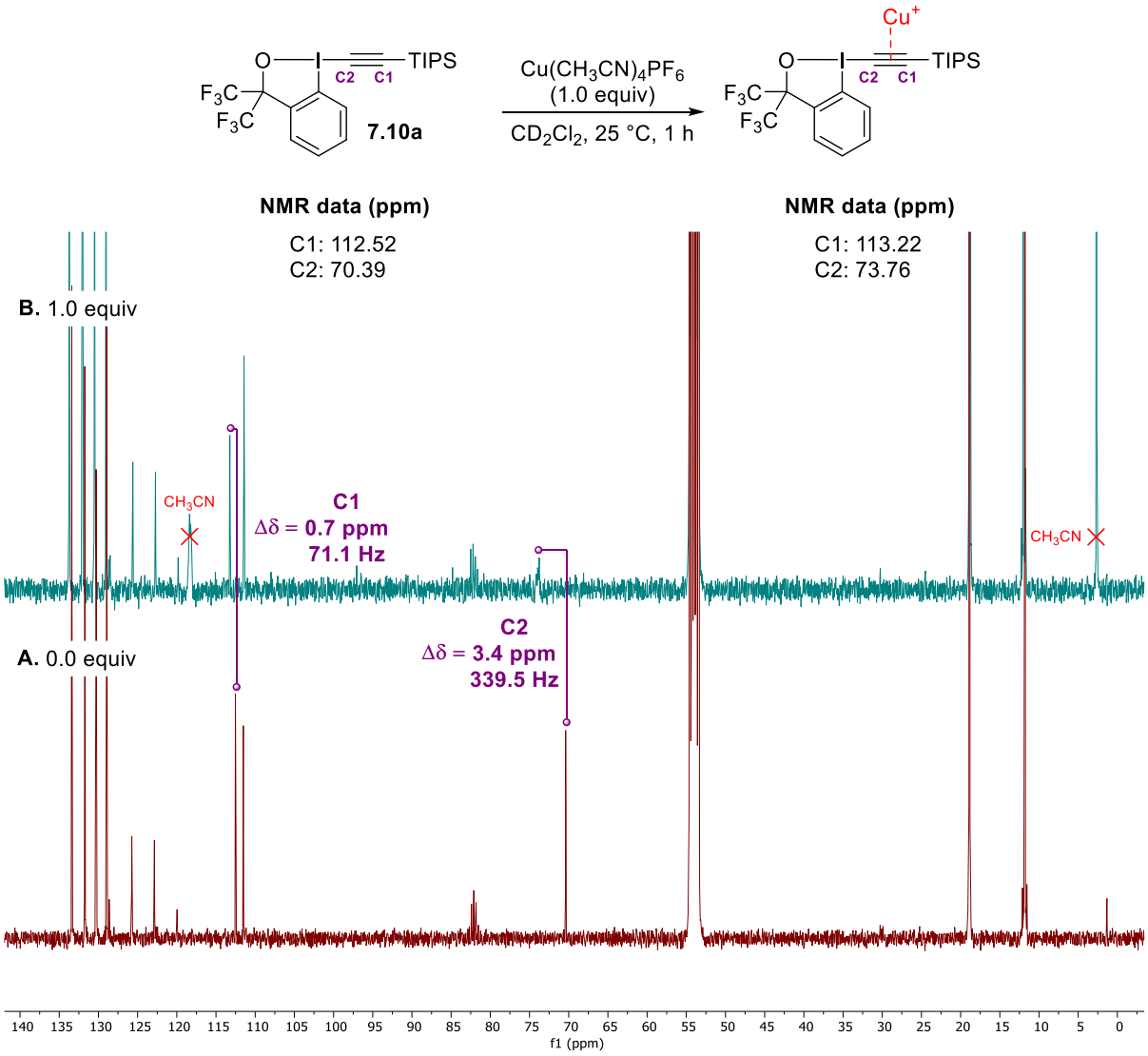


Figure 23. ^{13}C NMR spectrum comparison of TIPS-EBX' (**7.10a**) with 0.0 equiv and 1.0 equiv of $Cu(CH_3CN)_4PF_6$.

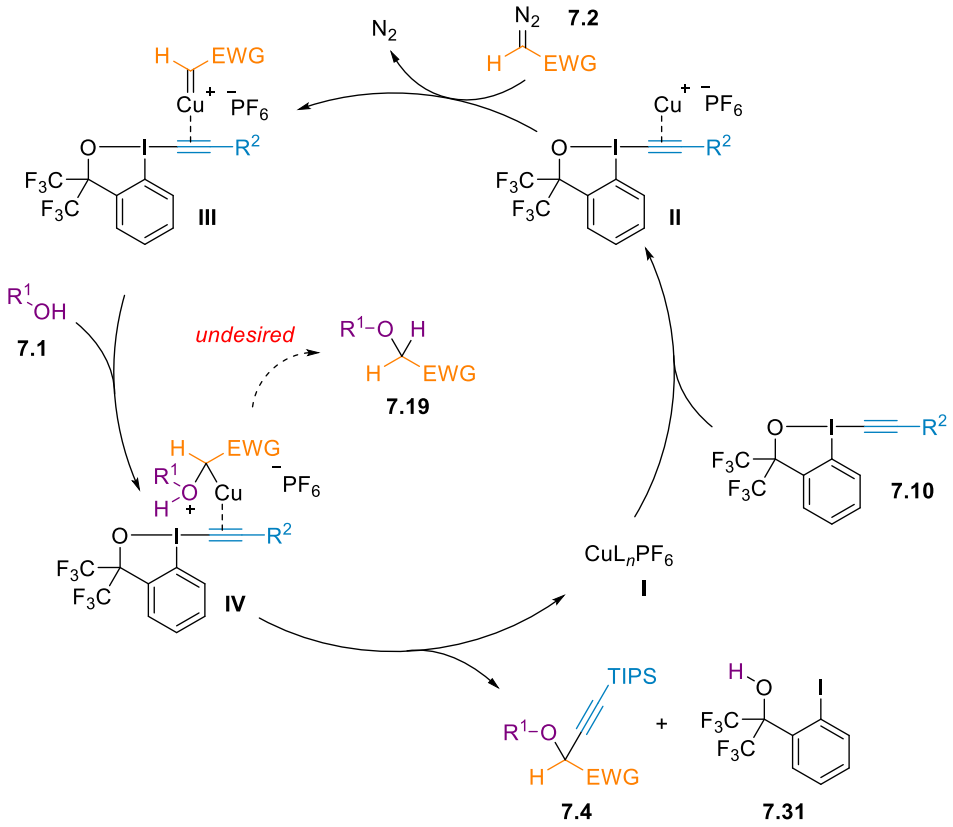
These NMR studies indicated an interaction between the Cu catalyst and the EBX' reagent **2a**. The strong effect of Cu(I) on the proton *ortho* to the iodine, as well as the smaller variation observed in ^{19}F NMR supports binding to the alkyne rather than to the oxygen atom. Considering the π-electrophilic character of cationic copper(I) salts,[335] it is reasonable to assume such interaction, however, the larger ^{13}C chemical shift observed at C2 vs C1 cannot exclude a partial interaction with the iodine(III) atom. Complete oxidative addition of the reagent onto copper to form a Cu(III) intermediate is less probable.[336] Unfortunately, our efforts to grow a suitable crystal for X-Ray analysis of this Cu-EBX' complex has not been successful yet.

Based on the results of our own experiments and the relevant literature on metal-ylide based multicomponent reactions, we can propose a tentative catalytic cycle (Scheme 99). Copper(I) catalyst **I**, with non-nucleophilic anion PF_6^- would first coordinate the hypervalent iodine reagent **7.10** to form

[335] Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817.

[336] The formation of Cu^{III} intermediates by oxidative addition with hypervalent iodine reagents has been proposed: a) D. Holt, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2015**, *54*, 7857; b) M. G. Suero, E. D. Bayle, B. S. L. Collins, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 5332; c) A. J. Hickman, M. S. Sanford, *Nature* **2012**, *484*, 177.

the π-complex **II**. Then, diazo **7.2** decomposition would generate the electrophilic copper carbene **III**, with alkyne-bound EBX'. At this stage, it is difficult to establish if decoordination of the EBX' reagent is required for the copper carbene formation, however, the constant low concentration (slow addition) of the diazo compound suggests at least an accumulation of complex **II**. Furthermore, in presence of *N*,*N*-ligands the three-component pathway was significantly slowed-down in favor of the O-H insertion reaction. This observation is in agreement with the need for several available coordination sites on the catalyst and would sugest a copper bound EBX' complex for the three-component reaction to occur. The diminished reactivity obtained with alcohols incorporating alkenes and alkynes indicates other potential competitive interaction with Cu. From carbene **III**, attack of the external alcohol **7.1** forms oxonium-ylide intermediate **IV**, which is rapidly trapped by inner sphere alkynylation. Final deprotonation by the released alcoholate by-product generates the three-component product **7.4** and iodide **7.31**, releasing the copper catalyst. Undesired 1,2-H shift on the transient ylide **IV** produces the O-H insertion product **7.19**.



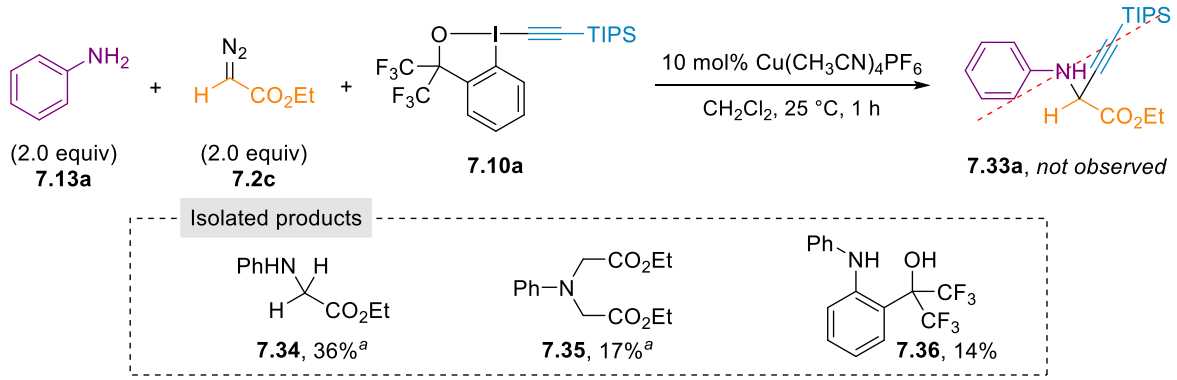
Scheme 99. Proposed catalytic cycle.

7.5. Extension to *N*-Nucleophiles

Having succeeded with the development of the three-component reaction with alcohols, we envisaged to react other potential protic nucleophiles in a similar fashion. Considering that our work on the two-component reactions combining the reactivity of diazo compounds and hypervalent iodine reagents was limited to oxygen insertion despite the utilization of EBZ reagent,[230] interception of *N*-ylide intermediates would constitute an important extension of our prior methodologies.

7.5.1. Aryl amines

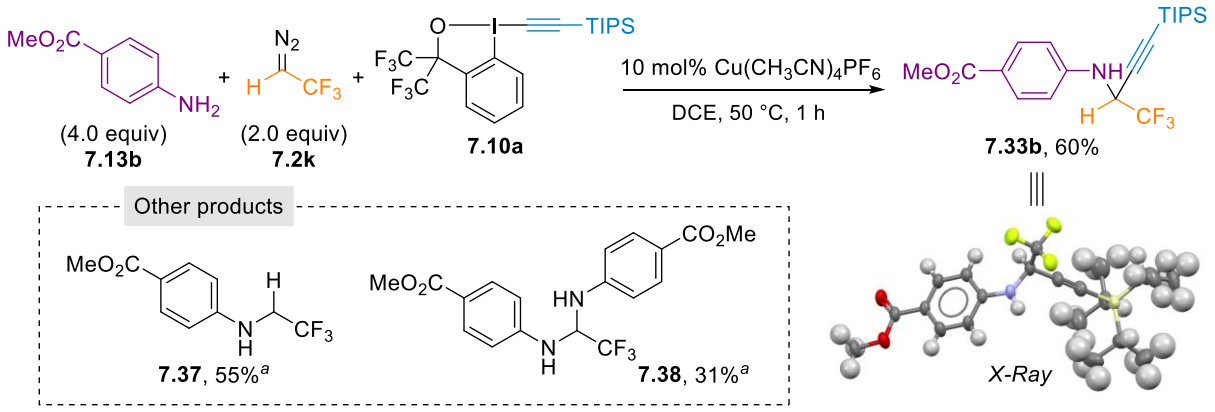
Anilines have been particularly employed in three-component reactions with metal carbenes. The resulting ammonium ylides were notably trapped with electrophiles such as imines, aldehydes, or Michael acceptors. We started our investigations using aniline (**7.13a**), EDA (**7.2c**) and TIPS-EBX' (**7.10a**) as partners and in the presence of $Cu(CH_3CN_4)PF_6$ as catalyst, which corresponded to our optimized conditions with alcohols (Scheme 100). Unfortunately, under such reaction conditions the expected three-component product was not detected. The EBX' reagent **7.10a** was partially consumed, and a mixture of products was identified: The product of N-H insertion **7.34** was isolated in 36% yield, the product **7.35** corresponding to a double N-H insertion was obtained in 17% yield and the cross-coupling reaction between the aniline and iodine(III) reagent provided diaryl amine **7.36** in 14% yield.



[a]Yield calculated using the EBX' **7.10a** as limiting reagent.

Scheme 100. Attempt of Cu-catalyzed three-component reaction with aniline (**7.13a**).

Repeating the reaction with ligands (diimine **7.16c** or *t*Bu-BOX **7.16b**) gave a similar outcome. The reaction was tried with $Cu(OTf)_2$ as catalyst, which has been successfully employed with alcohols. Unfortunately, only the products of N-H insertion **7.34** and **7.35** were observed as well with this copper(II) catalyst. The addition of a base ($NaHCO_3$) did not produce any three-component product. Finally, increasing the temperature up to 60 °C (DCE as solvent) only favored the formation of **7.36** and other degradations of the EBX' reagent. In the majority of these reactions, we noticed an extremely fast N-H insertion reaction. Therefore, we decided to investigate other diazo substrates and aniline derivatives. To our delight, using trifluorodiazoethane **7.2k** and the electron-poor aniline **7.13b**, provided crystalline product **7.33b** in 60% yield on small scale at 50 °C in DCE (Scheme 101).



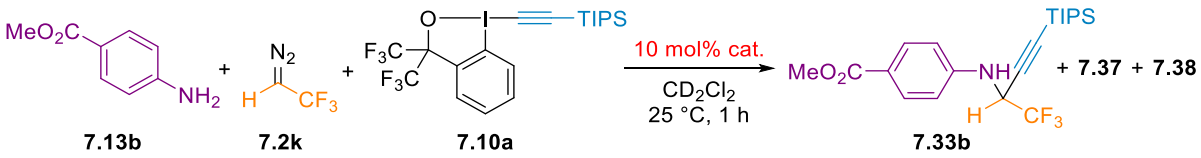
[a]Yield calculated using the EBX' **7.10a** as limiting reagent.

Scheme 101. Formation of trifluoromethyl propargyl aniline derivatives *via* three-component reaction.

Alongside the expected desired compound, the product of N-H insertion **7.37** was formed in 55% yield. Reducing the number of equivalents of the diazo compound could eventually prevent this side reaction. In addition, the symmetrical aminal **7.38** was isolated in 31% yield. This compound could be formed after addition of aniline **7.13b** onto an imine intermediate resulting of the oxidation of product **7.37**. Interestingly, a similar reaction profile was obtained using silver hexafluoroantimonate (10 mol% $AgSbF_6$) as catalyst.

The reaction was repeated at ambient temperature to compare the copper(I) and silver(I) catalysts (Table 26). In both cases complete conversion of TIPS-EBX' (**7.10a**) was observed. A cleaner reaction was obtained with $AgSbF_6$, furnishing **7.33b** in 74% NMR yield, while the N-H insertion product **7.37** and the aminal **7.38** were formed in 26% and 62% yield, respectively (entry 1). A diminished yield for the formation of **7.33b** was obtained with the copper catalyst. The side-product **7.37** was also formed to a lesser extent, however, the major compound was **7.38** with 80% yield (entry 2). Several minor side-products (< 5% yield) in the crude ^{19}F NMR were not identified.

Table 26. Comparison of $AgSbF_6$ and $Cu(CH_3CN)_4PF_6$ as catalyst.[a]

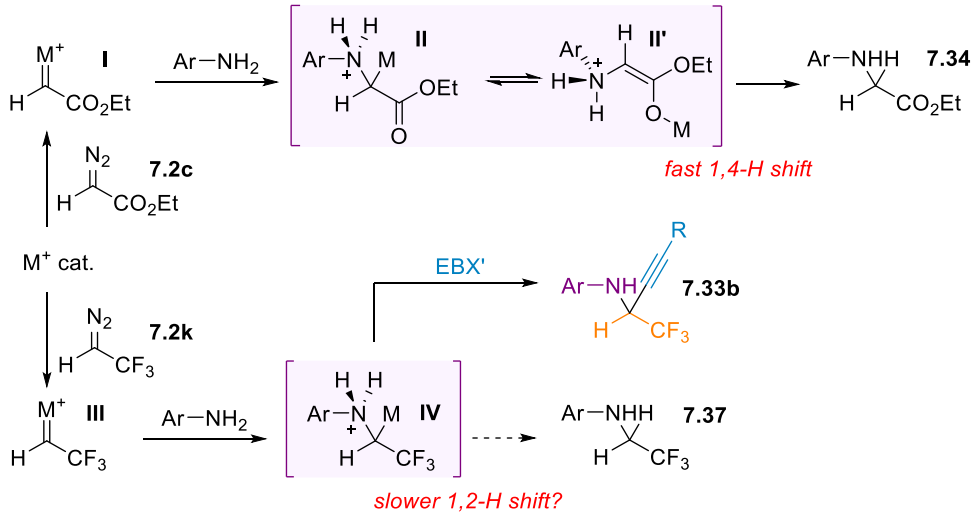


Entry	Catalyst	Conv. EBX' (%)	Yield[b] (%) 7.33b/7.37/7.38
1	$AgSbF_6$	100	74/26/62
2	$Cu(CH_3CN)_4PF_6$	100	50/18/80

[a]Reaction conditions: 0.40 mmol aniline (**7.13b**), 0.20 mmol diazo (**7.2k**), 0.10 mmol of TIPS-EBX' (**7.10a**), catalyst (10 mol%), CD_2Cl_2 (0.05 M). [b]Determined by ^{19}F NMR analysis of the reaction mixture. The hypervalent iodine reagent **7.10a** is used as limiting reagent to calculate the yields of **7.33b**, **7.37** and **7.38**.

The transformation seems, however limited to CF_3-diazo compounds. When benzocaine (**7.13b**), TIPS-EBX' (**7.10a**) and EDA (**7.2c**) were used as substrates, under silver or copper catalysis, the desired three-component product was not formed. A highly speculative possibility to rationalize this outcome would consider the reactivity of the corresponding secondary ammonium-ylide intermediates (Scheme 102). Intermediate **II**, generated from the nucleophilic attack of the

metal-carbene intermediate **I**, can equilibrate to its enol form **II'**. At this stage, a fast 1,4-H shift, through a five-membered ring transition state could deliver the N-H insertion product **7.34**. In contrast, protic ammonium-ylide **IV**, from trifluorodiazoethane **7.2k** cannot tautomerize. In this case, a slower 1,2-H shift can be expected and trapping of **IV** by the EBX' reagent would be possible. However, this explanation is in contradiction with the wide utilization of donor-acceptor diazo esters in multicomponent strategy, known to generate stable enol-ylide intermediates.

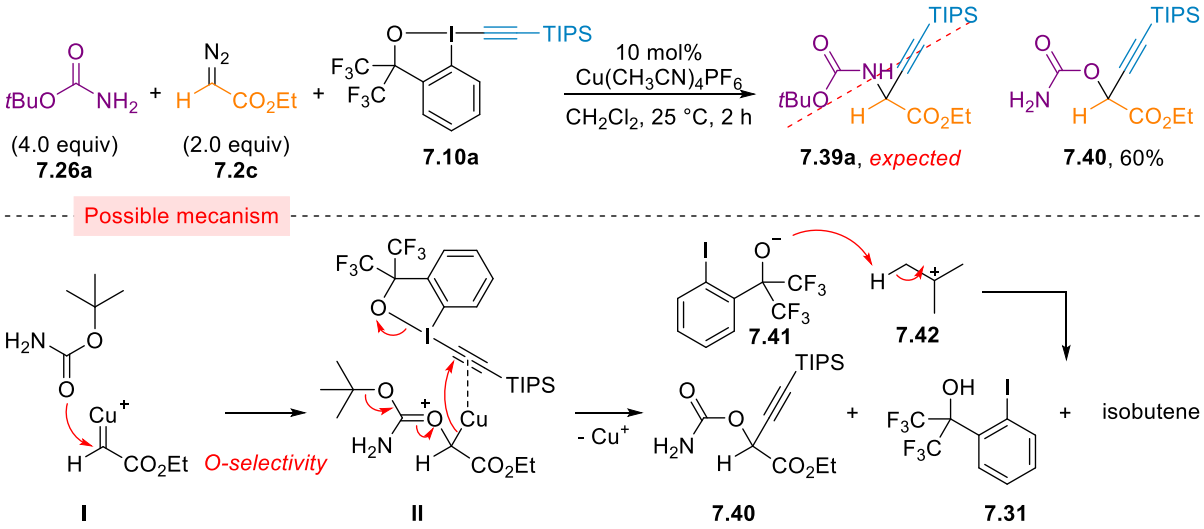


Scheme 102. Comparison of the ammonium-ylide intermediates from EDA (**7.2c**) and trifluorodiazoethane (**7.2k**).

7.5.2. Attempts with Carbamates

Carbamates are interesting as nucleophile components for several reasons. Their easy deprotection to access free amino compounds can increase the potential synthetic value of the products. Carbamates are less-coordinating than anilines and should not poison the transition metal catalyst. Less side-reactivity with the electrophile can also be expected. However, the decreased electron density of the nitrogen atom can also significantly hamper the attack on the metal-carbene intermediate. Hu and co-workers reported the utilization of carbamates in Mannich-type multicomponent process. The transformation used a dual/cooperative catalysis strategy with Rh_2OAc_4 and phosphoric acid.[337] An important methodology developed by Fu and Lee utilized a cationic copper(I) catalyst for the insertion of donor acceptor diazo compounds into carbamates N-H bond.[331] Based on these reports, we attempted to use *tert*-butyl carbamate (Boc-NH_2, **7.26a**) in association with ethyl diazoacetate (**7.2c**) and TIPS-EBX' (**7.10a**) in presence of 10 mol% of $Cu(CH_3CN)_4PF_6$ for the generation of α-alkynylated amino acid derivatives (Scheme 103). Surprisingly, a selective oxygen attack followed by the cleavage of the *tert*-butyl group was obtained, furnishing **7.40** in 60% yield. Initial oxygen vs nitrogen attack of the copper carbene **I** by Boc-NH_2 (**7.26a**) would form oxonium-ylide intermediate **II**. Release of *tert*-butyl cation **7.42** and generation of the non-nucleophilic hexafluorobenzyl alcoholate by-product **7.41**, after trapping of **II** by TIPS-EBX' (**7.10a**), would lead to the product **7.40**. However, it is difficult to rationalize the oxophilicity of the Cu carbene, especially considering the work of Fu, utilizing a Cu(I)/bis(azaferrocene) catalyst.

[337] J. Jiang, H.-D. Xu, J.-B. Xi, B.-Y. Ren, F.-P. Lv, X. Guo, L.-Q. Jiang, Z.-Y. Zhang, W.-H. Hu, *J. Am. Chem. Soc.* **2011**, *133*, 8428.

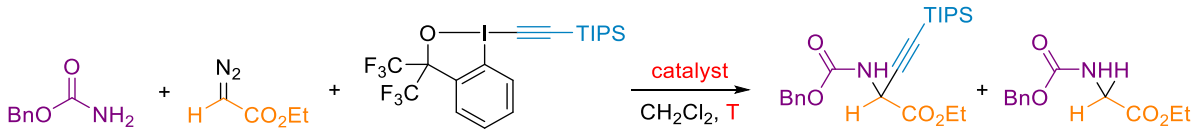


Scheme 103. Oxy-alkynylation instead of the expected amino-alkynylation with Boc-NH_2 (**7.26a**).

We further exploited this unexpected result for the convergent synthesis of the Lonza intermediate (**7.4aj**) of Efavirenz (**7.25**) presented earlier (see section 7.3.3.). Compared to alcohol nucleophiles, no competitive O-H insertion pathway was existing in this case. In consequence, the quantities of the diazo and carbamate partners could be diminished to 1.3 equivalent and only 5 mol% of copper catalyst was employed.

Then, we turned our attention to other carbamate substrates not subjected to the cleavage of the protecting group. When benzyl carbamate (Cbz-NH_2, **7.26b**) was engaged under similar reaction conditions using copper catalysis, the amino ester product **7.39b** was formed only in traces (Table 27, entry 1). Importantly, no product of N-H insertion **7.43** or oxygenation was detected. The reaction was investigated using Rh_2OAc_4 as catalyst, and in this case a fast and clean insertion of EDA (**7.2c**) into the N-H bond of the carbamate **7.26b** was obtained, but no three-component product was detected (entry 2). At this point, comparative experiments to probe the N-H insertion reaction were realized: In the absence of EBX' reagent **7.10a**, mainly self-dimerization products of the diazo compound were obtained with $Cu(CH_3CN)_4PF_6$ as catalyst (entry 3). The N-H insertion reaction was inefficient. In contrast, Rh_2OAc_4 catalyzed well the formation of **7.43**, which was formed in 80% yield (entry 4). Therefore, we attempted the association of copper and rhodium catalysts: Rh(II) would form the ammonium-ylide and Cu(I) would activate the EBX' reagent. Using this strategy, the expected three-component product was formed in slightly better yield, however, the major product was still **7.43** (entry 5).

Table 27. Three-component reaction with Cbz-NH_2 (**7.26b**). Comparison of Cu(I) and Rh(II) catalysts.[a]



7.26b **7.2c** **7.10a** **7.39b** **7.43**

Entry	Catalyst	T (°C)	Yield[b] (%) 7.39b/7.43
1	10 mol% $Cu(CH_3CN)_4PF_6$	25	ca. 5/n.d.
2	5 mol% Rh_2OAc_4	25	n.d./82
3[c]	10 mol% $Cu(CH_3CN)_4PF_6$	40	-/< 10
4[c]	5 mol% Rh_2OAc_4	40	-/80
5	10 mol% $Cu(CH_3CN)_4PF_6$ + 5 mol% Rh_2OAc_4	25	15/60

[a]Reaction conditions: 0.20 mmol Cbz-NH_2 (**7.26b**), 0.10 mmol EDA (**7.c**), 0.05 mmol TIPS-EBX' (**7.10a**), CH_2Cl_2 (0.1 M). [b]Determined by ^1H NMR yield with addition of 0.05 mmol of CH_2Br_2 as an internal standard after the reaction. [c]No EBX' reagent was used.

In view of these results, the reaction was not further optimized.

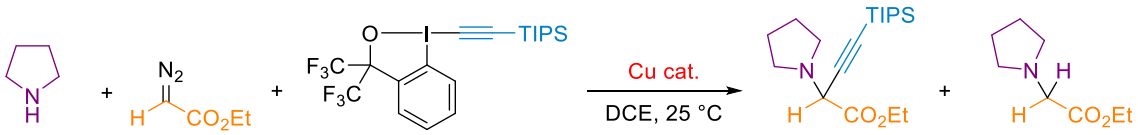
7.5.3. Attempts with Alkyl amines

In our previous attempts to use *N*-nucleophiles in three-component reactions with diazo compounds and hypervalent iodine reagents, we have demonstrated the superiority of copper as catalyst over other transition metals, notably rhodium. Aliphatic amines strongly coordinate, and therefore easily inhibit, the activity of metal catalysts. We considered to use the few copper catalysts that have been successful for the insertion of diazo compounds into the N-H bond of alkyl amines. Pérez and co-workers have reported copper(I) complexes containing homoscorpionate ligand (Tp*Cu, **7.47**) as efficient catalysts for the insertion of acceptor-only diazo compounds into N-H bonds of aliphatic amines.[338] The same group has shown later that [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I) chloride (IPrCuCl, **7.48**) was also a powerful catalyst for similar reactions.[339] We tried these two copper(I) catalysts in a three-component reaction utilizing pyrrolidine (**7.44**), ethyl diazoacetate (**7.3c**) and TIPS-EBX' (**7.10a**) as partners (Table 28). Unfortunately, both catalysts were unsuccessful and the starting materials were not reacted (entries 1 and 2). Heating of the reactions resulted in decomposition of EBX' reagent **7.10a**. In parallel, the reported N-H insertion reactions catalyzed by complexes **7.47** and **7.48** were repeated. Indeed, a fast and clean reaction between pyrrolidine (**7.44**) and EDA (**7.3c**) was obtained using Tp*Cu (**7.47**) at ambient temperature (entry 3). However, we could not reproduce the reaction catalyzed by IPrCuCl (**7.48**) (entry 4). Finally, no reaction occurred with $Cu(CH_3CN)_4PF_6$ as catalyst (entry 5).

[338] M. E. Morilla, M. M. Díaz-Requejo, T. R. Belderrain, M. C. Nicasio, S. Trofimenko, P. J. Pérez, *Chem. Commun.* **2002**, 2998.

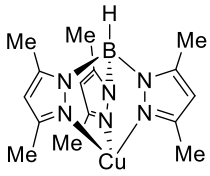
[339] M. R. Fructos, T. R. Belderrain, M. C. Nicasio, S. P. Nolan, H. Kaur, M. M. Díaz-Requejo, P. J. Pérez, *J. Am. Chem. Soc.* **2004**, *126*, 10846.

Table 28. Three-component reaction with pyrrolidine (**7.44**) as nucleophile partner.[a]

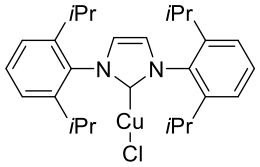


7.44 **7.3c** **7.10a** **7.45** **7.46**

Entry	Cu cat.	Yield[b] (%) 7.45/7.46
1	5 mol% Tp*Cu (**7.47**)	n.d./n.d.
2	10 mol% IPrCuCl (**7.48**)	n.d./n.d.
3[c]	5 mol% Tp*Cu (**7.47**)	-/> 90
4[c]	10 mol% IPrCuCl (**7.48**)	-/ n.d.
5[d]	10 mol% $Cu(CH_3CN)_4PF_6$	n.d./n.d.



Tp*Cu (**7.47**)



IPrCuCl (**7.48**)

[a]Reaction conditions: 0.20 mmol pyrrolidine (**7.44**), 0.10 mmol EDA (**7.3c**), 0.05 mmol TIPS-EBX' (**7.10a**), DCE (0.1 M). [b]Determined by ^{1}H NMR yield with addition of 0.05 mmol of CH_2Br_2 as an internal standard after the reaction. [c]No EBX' was used, 0.10 mmol pyrrolidine (**7.44**), 0.10 mmol EDA (**7.47**). [d]Reaction in CH_2Cl_2 (0.1 M).

In summary, no three-component product was detected with pyrrolidine (**7.44**) and the use of aliphatic amines as nucleophiles seems more challenging than aryl amines or carbamates due to their stronger basicity. Nevertheless, the successful N-H insertion reaction catalyzed by Tp*Cu (**7.47**) and the absence of reaction in the presence of TIPS-EBX' (**7.10a**), supports an initial copper-hypervalent iodine reagent interaction.

7.6. Conclusion and Future Work

Excellent results on the three-component reaction between alcohols, diazo compounds and ethynylbenziodoxole reagents were obtained (Figure 24). This new methodology allows a straightforward access to a large variety of propargyl ethers. The three partners can be extensively varied, leading to maximal structural diversity and complexity of the products. Key to avoid the competitive two-component reaction between hypervalent iodine reagents and diazo compounds was the use of bis-trifluoromethyl derived benziodoxoles instead of classical benziodoxolones. Under mild copper(I) catalysis and without *N*,*N*-donor ligand, the competitive insertion reaction of diazo into the O-H bond of alcohol was limited, but was not totally suppressed. The three-component strategy was successfully applied to access allyl ether products using VBX' reagents as electrophiles, without the need of extensive re-optimization of the reaction conditions. Various alcohol partners could be employed, however, unsatisfactory results were obtained with other *O*-nucleophiles. Further investigations will be required to include phenols and carboxylic acids into the transformation.

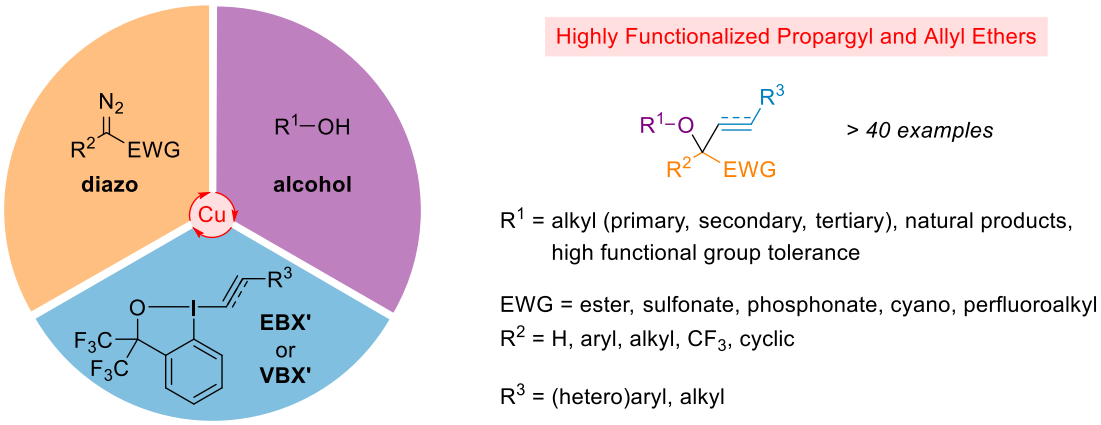


Figure 24. Overview of the three-component reaction to access propargyl- and allyl-ethers.

The drastic diminution of yield observed in the presence of a donor ligand, would require us to consider another approach for the implementation of an enantioselective transformation. A possible strategy would be to use asymmetric counteranion-directed catalysis.[340]

The existence of copper carbene and ylide intermediates were deduced from the cyclopropanation of styrene and the formation of O-H insertion products and sounds reasonable based on the literature precedent. A catalytic cycle following the classical step order of three-component reactions involving oxonium-ylides can be postulated. Furthermore, a complexation between the copper salt and the C≡C bond of the hypervalent iodine reagent was identified and we believe such interaction is playing an important role in the efficient utilization of EBX' reagent as electrophile and accounts for the superiority of copper catalysts over other transition metals in this transformation.

Important efforts have been directed toward the utilization of *N*-nucleophiles. Anilines were suitable partners in the special case of trifluorodiazoethane as the carbene precursor. Fluoroalkyl diazo compounds are gaining increasing attention these recent years for the introduction of fluorinated groups into organic compounds.[341] Three-component reactions using anilines, fluorinated diazo compounds and hypervalent iodine reagents are currently under development in our laboratory by Dr. Nieves Ramirez. The transformation allows a convergent access to useful trifluoroethylamine, bioisosteres of amides.[342] Beyond fluoroalkyl diazo compounds, this reaction could be well suited for the difunctionalization of *in situ* generated non-stabilized diazo compounds, which have remained unexplored in our group.[177] Investigations with carbamates have allowed us to identify *tert*-butyl carbamate as NH_2-carbamate surrogate for the synthesis of an advanced intermediate of Efavirenz. Nevertheless, the application of *N*-nucleophiles is limited at the moment.

[340] a) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518; b) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nature Chem.* **2012**, *4*, 603.

[341] For recent reviews on fluoroalkyl diazo compounds, see: a) P. K. Mykhailiuk, *Chem. Rev.* **2020**, *120*, 12718; b) P. K. Mykhailiuk, R. M. Koenigs, *Chem. Eur. J.* **2019**, *25*, 6053.

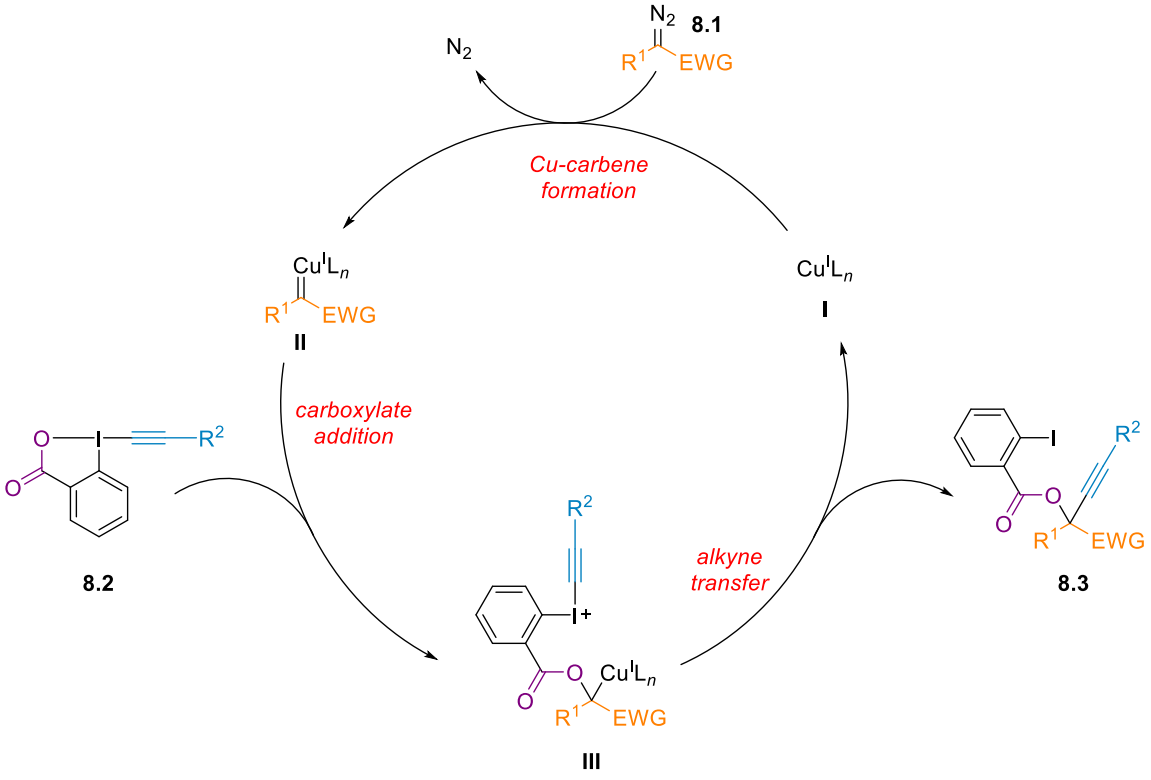
[342] S. Kumari, A. V. Carmona, A. K. Tiwari, P. C. Trippier, *J. Med. Chem.* **2020**, *63*, 12290.

8

Mechanistic Studies on the Two-Component Oxy-Alkynylation Reaction

8. Mechanistic Studies on the Two-Component Oxy-Alkynylation Reaction

Throughout this thesis work, important vinylation and alkynylation strategies of diazo compounds have been successfully developed utilizing hypervalent iodine reagents. In-depth mechanistic investigations of our seminal reaction on the oxy-alkynylation of diazo compounds with EBX reagents was considered opportune at this stage of our work. Indeed, a good comprehension of each elementary step will help to rationalize the difference in reactivity and enantioselectivity observed with disubstituted diazo compounds or VBX reagents compared to the efficient enantioselective transformation developed with EBX reagents and acceptor-only diazo compounds. [229] With an established model for the mechanism, our objective would be to identify catalytic systems able to improve the low enantioselectivity reached for the oxy-vinylation reaction. Implementation of machine learning techniques could be a future research direction within our group. In addition to the data already collected on the influence of ligands on enantioselectivity, a mechanistic hypothesis is required to determine key parameters for rate and selectivity of the reaction. In this chapter, our first results on the mechanistic studies of the oxy-alkynylation of diazo compounds will be presented. The generalized mechanism proposed so far is presented bellow (Scheme 104). For a detailed description see section 2.4.2.



Scheme 104. Simplified mechanism for the copper-catalyzed oxy-alkynylation of diazo compounds.

8.1. Density functional theory computations[343]

To start, we turned to density functional theory computations (M06 geometries at the PBE0-dDsC/TZ2P level, see section 10.6.1. for computational details), on a prospective mechanism

[343] The DFT calculations were performed by Dr. M. D. Wodrich form the LCMD group at EPFL.

using a set of simplified substrates (methyldiazo acetate **8.1a**, H_3Si-substituted EBX **8.2a** and catalyst **8.4a**, consisting of copper and a truncated diimine ligand) was investigated at first (Figure 25).

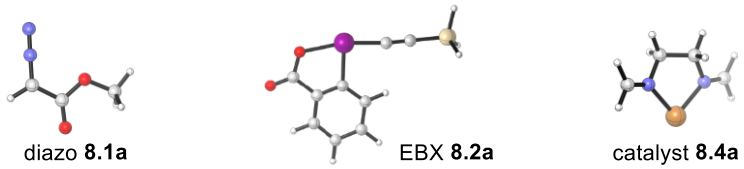


Figure 25. Optimized structures of the substrates used for preliminary DFT investigations.

Three possible pathways were envisaged: Pathway (A), with a direct copper carbene formation from **8.1a**, as postulated in our first mechanism. Pathway (B) with initial coordination of the copper **8.4a** to the carboxylate ligand of the iodine(III) reagent **8.2a** prior to the carbene formation. And Pathway (C) with initial coordination of the copper **8.4a** to the alkyne of the EBX reagent **8.2a**, as we have characterized such interaction with benziodoxole reagents (see section 7.4.).

- The pathway (A) (Figure 26) starts with coordination of diazo **8.1a** to the copper ion **8.4a**, thus giving **int-A1**, which is calculated to be 9.9 kcal/mol lower in energy than **int-A0**. From **int-A1**, N_2 can dissociate via **TS-A1** to give the copper carbene **int-A2** and molecular nitrogen. The calculated barrier for this step is 12.8 kcal/mol relative to **int-A1**. Nucleophilic attack of the carboxylate of the EBX reagent **8.2a** to **int-A2**, proceeds without transition state to give iodonium salt **int-A3**, which is 12.0 kcal/mol lower in energy in comparison to **int-A2**. To allow the C-C bond formation step, a Berry pseudorotation of the *trans* alkyne ligand via **TS-A3** higher of 10.0 kcal/mol compare to **int-A3**, is possible after loss of the confined benziodoxolone structure. The angle between the alkyne ligand and the axial oxygen atom is determined to be 92°. **Int-A4**, is calculated to be nearly isoenergetic to **TS-A3**, at only 0.04 kcal/mol lower in energy and with a C-I-O angle of 69°. The key alkynylation takes places through **TS-A4** with simultaneous decupration and creation of the new carbon-alkyne bond by transfer of the electron density of the Cu-C bond to the new C-C bond and breaking of the C-I bond. Such direct alkyne transfer was highly speculative in our first assumptions, however, it is the only transition state that could be localized. The other envisaged pathways consisting of the carbocupration of the alkyne bond to form a seven-membered ring intermediate followed by β-elimination or the oxidative transfer to form a copper(III) acetylide before reductive elimination were not found by the DFT calculations (see section 2.4.2. for details). At **TS-A4**, the Cu-C-C atom triad shows a nearly flat angle of 168°. The calculated barrier of this step (**TS-A4**) is 14.2 kcal/mol relative to **int-A4**. At **TS-A4**, the critical C-C bond distance is 2.44 Å. **Int-A5**, consisting of the catalyst coordinated to the carbonyl of the ester product, is 87.6 kcal/mol lower in energy than **TS-A4**. Finally, releasing of the product **8.3a** and regeneration of copper catalyst **8.4a** is calculated to be endergonic by 6.8 kcal/mol.

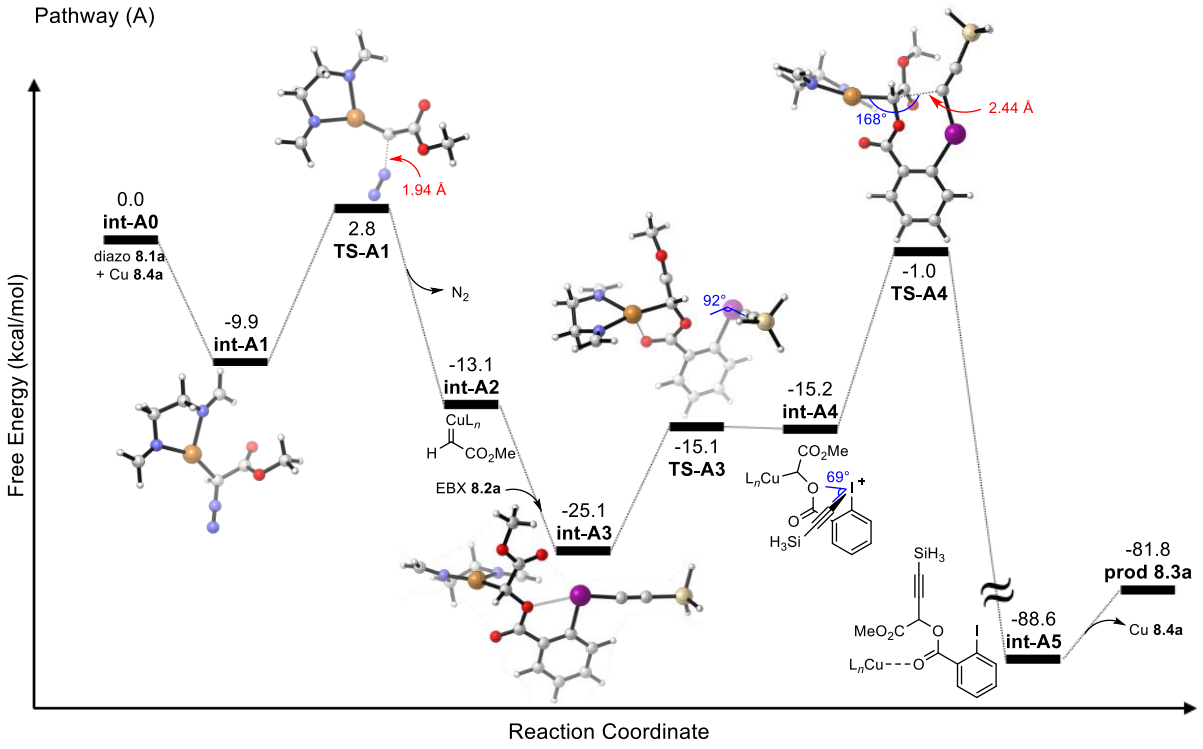


Figure 26. Pathway A.

- In pathway (B) (Figure 27), initial coordination of copper complex **8.4a** by EBX reagent **8.2a** gives **int-B1**, calculated to be -17.6 kcal/mol lower in energy than the starting **int-B0**. Association of diazo **8.1a** to the Cu-carboxylate **int-B1**, produces **int-B2**, calculated to be 8.1 kcal/mol lower in energy than **int-B0**. Formation of the copper carbene proceeds through **TS-B2** with a barrier of 18.1 kcal/mol relative to **int-B2** for the loss of N_2, generating pseudo **int-B3** endergonic of 3.2 kcal/mol relative to **int-B2**. **Int-B3** is intercepted by the carboxylate ligand to form iodonium **int-B4** with an energetic loss of -25.1 kcal/mol. Therefore, **int-B4** is as much as 17.0 kcal/mol lower than **int-B2**. **Int-B4** being a common intermediate with **int-A3**, A and B are convergent pathways at this point. Pseudo rotation of the alkyne ligand, followed by the C-C bond formation is similar to pathway (A).

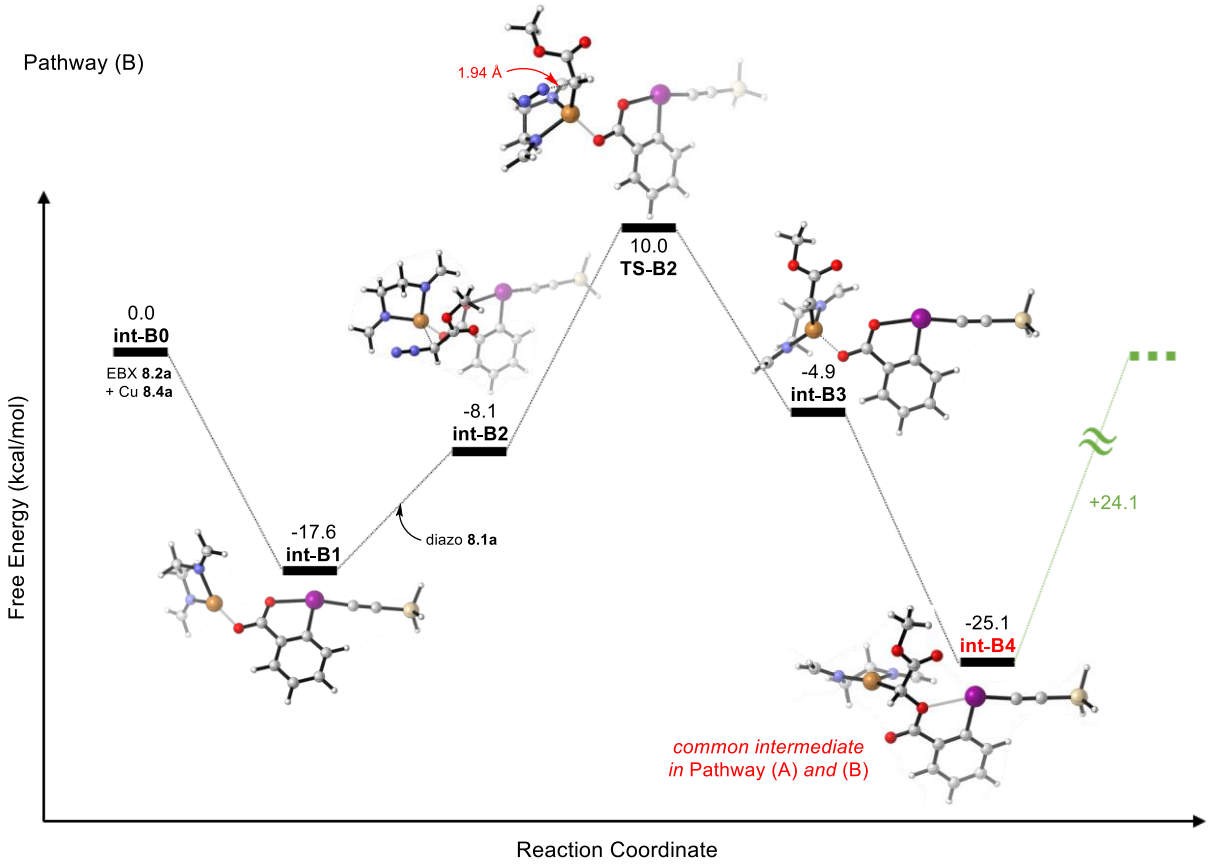


Figure 27. Pathway B.

- For pathway (C) (Figure 28), initial strong coordination of copper catalyst **8.4a** with EBX reagent **8.2a** through the alkyne generates **int-C1**, calculated at -22.8 kcal/mol lower in energy than **int-C0**. However, interaction between the diazo compound and the activated triple bond led to a 1,3-dipolar cycloaddition with a high energy barrier of 30.6 kcal/mol at **TS-C2**. The resulting pyrazole is calculated to be low in energy at -33.0 kcal/mol. At **int-C3**, continuing the computation resulted in several unrealistic rearrangements with transition states at excessive energy.

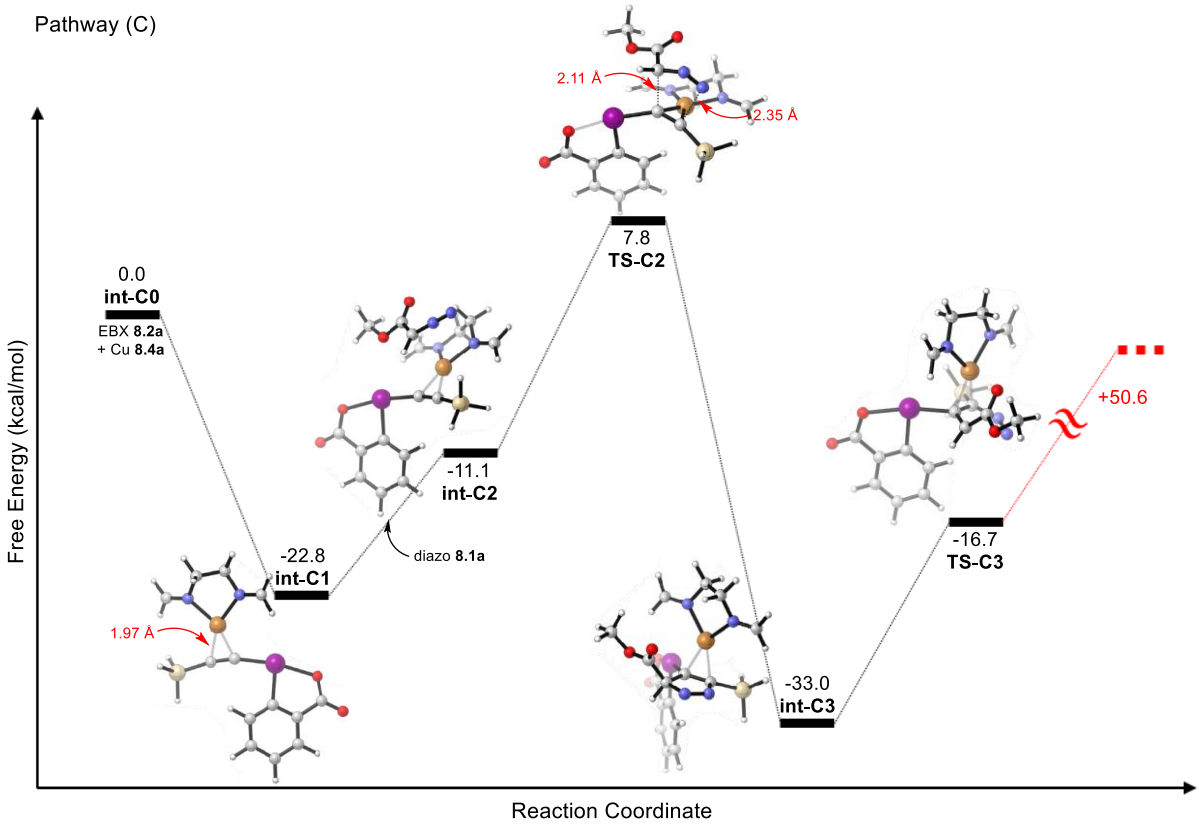


Figure 28. Pathway C.

From the results of the initial DFT computations, pathway (C) was discarded as the expected product was not formed, still a favorable alkyne-copper interaction was supported. For the initial steps: only 12.7 kcal/mol is required for the carbene formation in pathway (A) (**int-A1** to **TS-A1**) vs 27.6 kcal/mol for pathway (B) (**int-B1** to **TS-B2**), and 30.6 kcal/mol for pathway (C) (**int-C1** to **TS-C2**). The reversible binding of the copper catalyst from the substrates are: 9.9 kcal/mol in pathway (A), 17.6 kcal/mol in pathway (B), and 22.8 kcal/mol in pathway (C). These calculations would support a favorable Cu-EBX interaction at **int-C1**, reversible at 25 °C, which could therefore enter the productive pathway (A). Then, a total energy of 24.1 kcal/mol is needed for the alkyne transfer step (**int-A3** to **TS-A4**) which is possible at 25 °C, but would require prolonged reaction time.

Therefore, we decided to focus on pathway (A) for the comparison of different EBX reagents bearing TIPS (**8.2b**), phenyl (**8.2c**) and methyl (**8.2d**) substituents, in addition to the initial H_3Si-EBX (**8.2a**), and with tetramethyl-substituted BOX-Cu catalyst **8.4b** and diimine-Cu catalyst **8.4c**. With catalyst **8.4b** (Figure 29), the first part of the reaction, i.e. formation of the copper carbene, followed a similar trend than with the truncated catalyst **8.4a** used previously. The energy barrier of **TS-A1** for the nitrogen dissociation were close (12.7 kcal/mol for **8.4a** vs 12.5 kcal/mol for **8.4b**). After formation of the electrophilic copper carbene at **int-A2**, nucleophilic attack of the different EBX reagents were calculated for the formation of **int-A3**, and were all relatively close in energy. For TIPS-EBX (**8.2b**) at -18.6 kcal/mol and for Me-EBX (**8.2d**) at -20.1 kcal/mol. For Ph-EBX (**8.2c**), **int-A3** was located slightly lower in energy at -23.7kcal/mol (9.7 kcal/mol lower relative to **int-A2**). Stabilization of the charged iodine by the conjugated aromatic substituent could possibly diminish the energy of the corresponding **int-A3**. At this stage, pseudorotation of the alkyne ligand around the I(III) center was found feasible with energies from 8.4 to 11.4 kcal/mol required to attain **TS-A3**. However, the C-C bond formations were found to be at higher energy barriers than in the preliminary computations. The size of the alkyne substituent impacted significantly the energy required to reach

TS-A4. The calculated barrier from the lowest **int-A3** were as follow: For H_3Si-susbtituent, 24.9 kcal/mol, for Me-substituent, 26.2 kcal/mol, for Ph-substituent, 27.4 kcal/mol and for the larger TIPS-substituent an energy as high as 33.5 kcal/mol was required. The high-energy transition states **TS-A4** calculated did not reflect the experimental observations (fast reactions at ambient temperature) and suggested an incorrect proposition for the alkyne transfer in pathway (A).

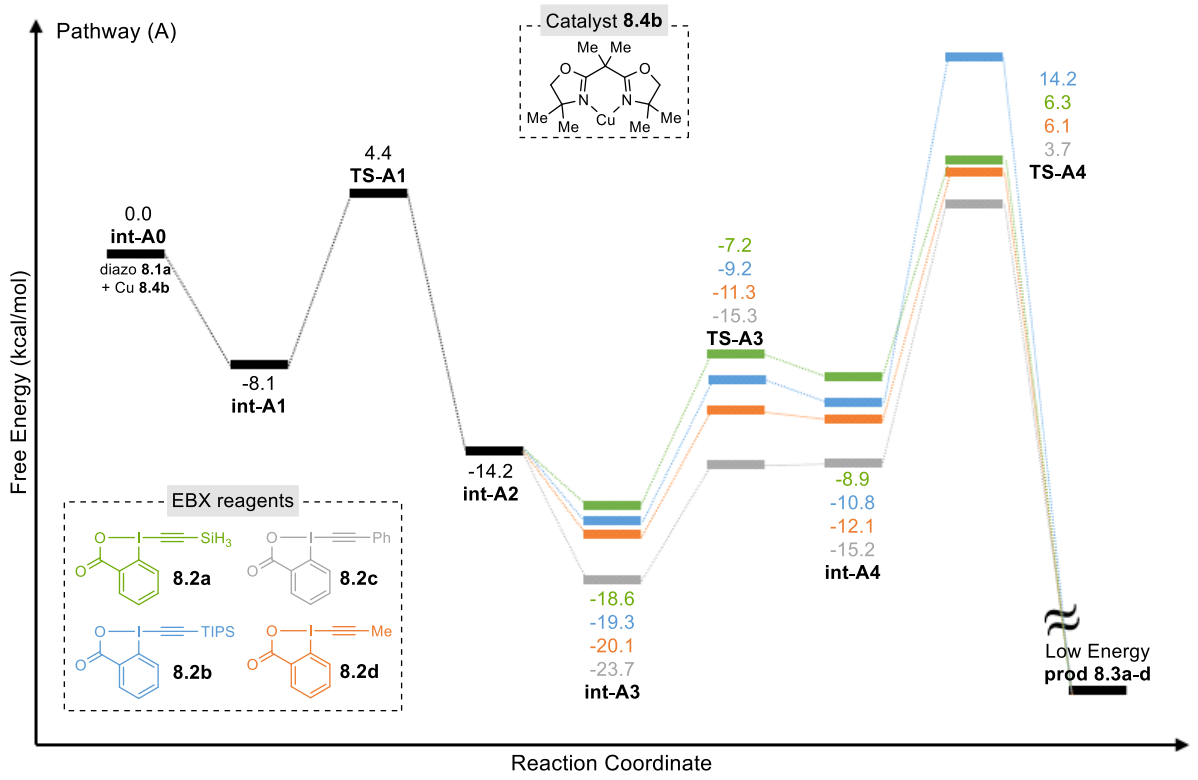


Figure 29. Investigation of the Pathway (A) with catalyst **8.4b**.

Pathway (A) was also examined with catalyst **8.4c**, lacking the *ortho* chlorine substituents when compared to the diimine ligand used experimentally (Figure 30). Overall, less energy divergence between the EBX reagents was observed, with **int-A3** calculated between -21.3 and -23.7 kcal/mol. The key alkynylation step was calculated to require an energy of 27.3, 27.4 and 26.7 kcal/mol for H_3Si (**8.2a**), Me (**8.2d**) and Ph (**8.2c**) substituents, respectively, which is still too high considering the experimental reaction temperature (40 °C) with such diimine ligand. A slightly lower overall energy barrier of 25.9 kcal/mol was calculated with TIPS-substituent (**8.2b**), meaning ca. 80 °C to expected the formation of the oxy-alkynylation product.

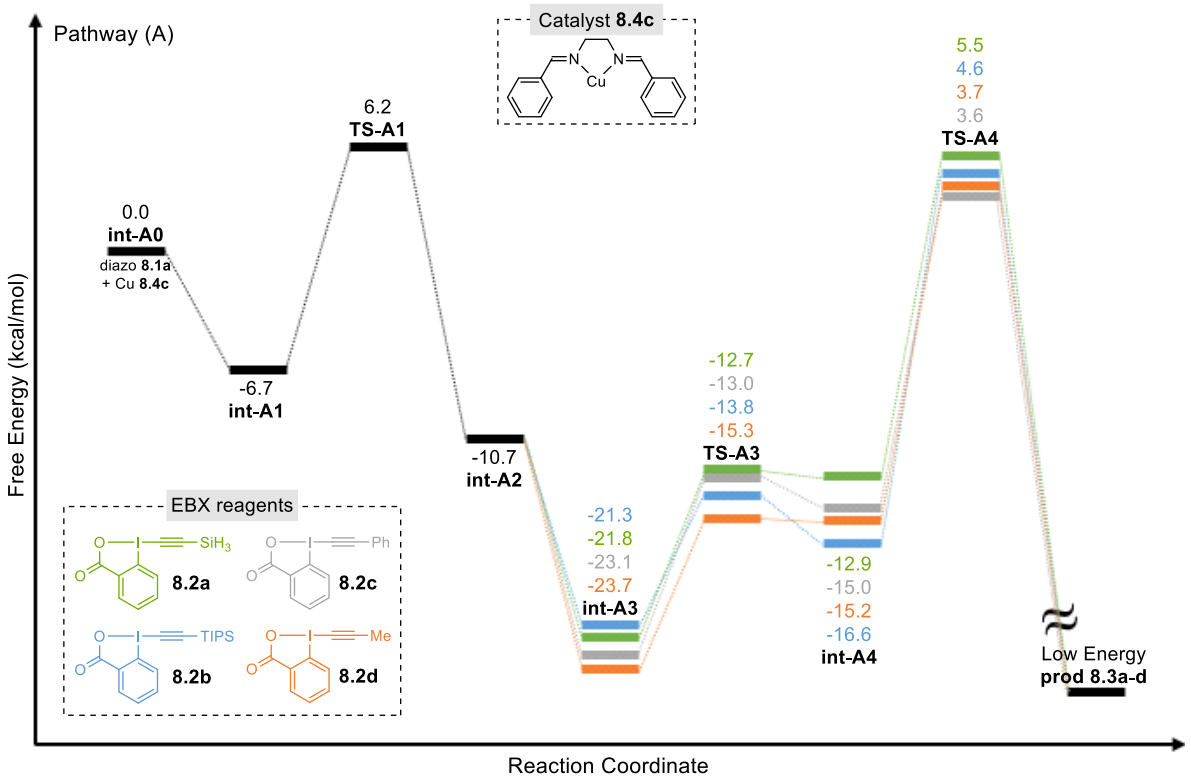


Figure 30. Investigation of the Pathway (A) with catalyst **8.4c**.

Catalysts **8.4b** and **8.4c**, with TIPS-EBX (**8.2b**) and diazo **8.1a** as substrates are compared below (Figure 31). The major issue concerns the alkynylation step (**TS-A4**), which is not fitting our experimental observations. Excessive energetic barriers are required (33.5 kcal/mol with **8.4b** and 25.9 kcal/mol with **8.4c**) for the carbon-carbon formation to happen. Moreover, with acceptor-only diazo compound such as **8.1a**, the oxy-alkynylation was efficient at ambient temperature with catalyst **8.4b**, while 40 °C was required with catalyst **8.4c**, which is in contradiction with the predicting model evaluating a favorable energetic barrier with catalyst **8.4c**.

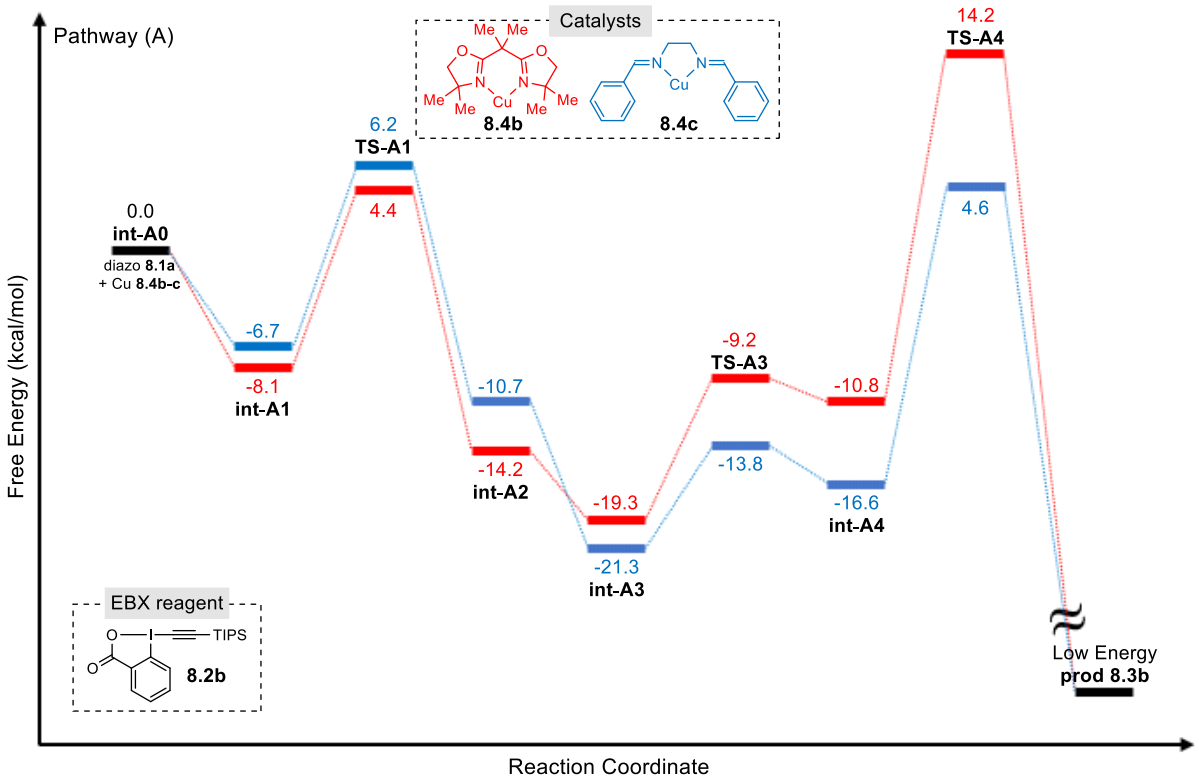


Figure 31. Comparison of catalysts **8.4b** and **8.4c** with TIPS-EBX (**8.2b**) in pathway A.

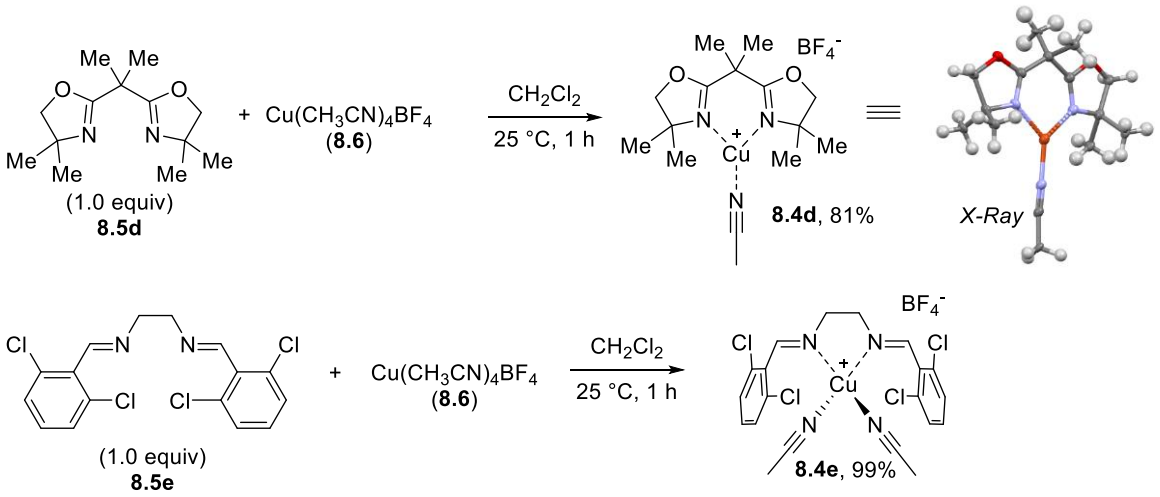
In summary, with the help of DFT computations we could investigate three possible pathways using simplified substrates. The pathway with direct formation of the copper carbene or on the pre-formed EBX-Cu complex led to a common mixed iodonium-organocopper intermediate. However, the copper carbene formation on the free catalyst was found favorable. For the intramolecular transfer of the alkyne to happen, first Berry pseudo-rotation of the alkyne ligand around the I(III) center was required and found possible with an energy barrier at 10.0 kcal/mol. However, formation of the C-C bond necessitated a quite high energy transition state, having an aligned Cu-C-C atom arrangement, at 24.0 kcal/mol. The key step was further investigated with catalysts and reagents used experimentally. In this case, the energy barriers were calculated between 26 to 33 kcal/mol, and are not reflecting the usual mild temperatures of our reaction conditions.

8.2. Efforts toward the identification of reaction intermediates and resting-state intermediates

In parallel to the DFT computations, comparison of the copper catalysts incorporating BOX and diimine ligands was envisaged. The copper complexes of BOX **8.4d** and diimine **8.4e** were prepared in good yields by simple coordination with $Cu(CH_3CN_4)BF_4$ (**8.6**) in dichloromethane at 25 °C and evaporation of the solvent under air-free conditions (Scheme 105). The two complexes were characterized by NMR spectroscopy, giving access to the number of acetonitrile molecules coordinated to the copper atom. [BOX•$Cu(CH_3CN)$]BF_4 **8.4d** was further analyzed by X-Ray spectroscopy and adopted a trigonal planar structure, as reported by Fürstner and co-workers for a related Cu(I)-BOX complex.[344] In contrast, the Cu(I) complex of diimine **8.4e**, is expected to adopt a tetrahedral geometry,

[344] M. Buchsteiner, L. Martinez-Rodriguez, P. Jerabek, I. Pozo, M. Patzer, N. Nöthling, C. W. Lehmann, A. Fürstner, *Chem. Eur. J.* **2020**, *26*, 2509.

with two available coordination sites occupied by acetonitrile molecules. This fundamental coordinating difference could be involved in the different reactivity outcomes observed between the two complexes.



Scheme 105. Preparation of the copper catalysts of BOX (**8.4d**) and diimine (**8.4e**) ligands.

The prepared catalysts were successfully used in control oxy-alkynylation reactions between EDA (**8.1b**) and TIPS-EBX (**8.2b**) (Table 29). The product **8.3e** was formed in high yields in both cases, and we could confirm the slightly higher temperature (40 °C) required with catalyst **8.4d** for the reaction to start (entries 1 and 2). In contrast, when a catalytic amount of $Cu(CH_3CN)_4BF_4$ (**8.6**), without ligand, was added to a mixture of reactants no product could be detected and the diazo substrate **8.1b** remained unreacted (entry 3). Further addition of ligand **8.5d** did not initiated the reaction. A rapid formation of maleate/fumarate products was however observed when the copper catalysts were mixed with the diazo partner only (not shown).

Table 29. Comparison of the copper complexes catalytic activity.[a]

8.1b **8.2b** **8.3e**

Entry	Cu cat.	Temperature (°C)	Yield[b] (%) 8.3e
1	[BOX•Cu(CH₃CN)]BF₄ **8.4d**	25	>95
2	[diimine•Cu(CH₃CN)₂]BF₄ **8.4e**	40	>90
3[c]	$Cu(CH_3CN)_4BF_4$ (**8.6**)	40	n.r.

[a]Reaction conditions: 0.20 mmol EDA (**8.1b**), 0.10 mmol TIPS-EBX (**8.2b**), Cu cat. (4 mol%), CH_2Cl_2 (0.05 M). [b]Determined by ^1H NMR yield with addition of 0.10 mmol of CH_2Br_2 as an internal standard after the reaction. [c]Addition of BOX **8.5d** (5 mol%) after 1 h of reaction. n.r. = no reaction.

Therefore, we hypothesized an interaction between the EBX reagent and the copper catalysts. Indeed, the stoichiometric reaction of $Cu(CH_3CN)_4BF_4$ (**8.6**) with TIPS-EBX (**8.2b**), instantaneously resulted in a blue colored solution, incomprehensible by NMR spectroscopy and suggested the presence of paramagnetic Cu(II) species. In contrast, upon addition of 1 equivalent of [BOX•Cu(CH₃CN)]BF₄ **8.4d** to EBX **8.2b**, the solution stayed uncolored and the presence of the BOX

ligand, likely prevented the oxidation of the Cu(I) by the hypervalent iodine reagent. ^{13}C NMR spectrum of the CD_2Cl_2 solution was recorded and did not show important changes in the alkyne signals (carbons C1 and C2) (Figure 32). However, important modifications of the signals in the area near the carboxylate occurred. The peaks of C4 and C5 were excessively broadened and could not be detected. Displacement of Δδ = 0.8 ppm, 81.2 Hz for C3, *ipso* to iodine(III), was measured. The C3 peak was also largely broadened but detectable.

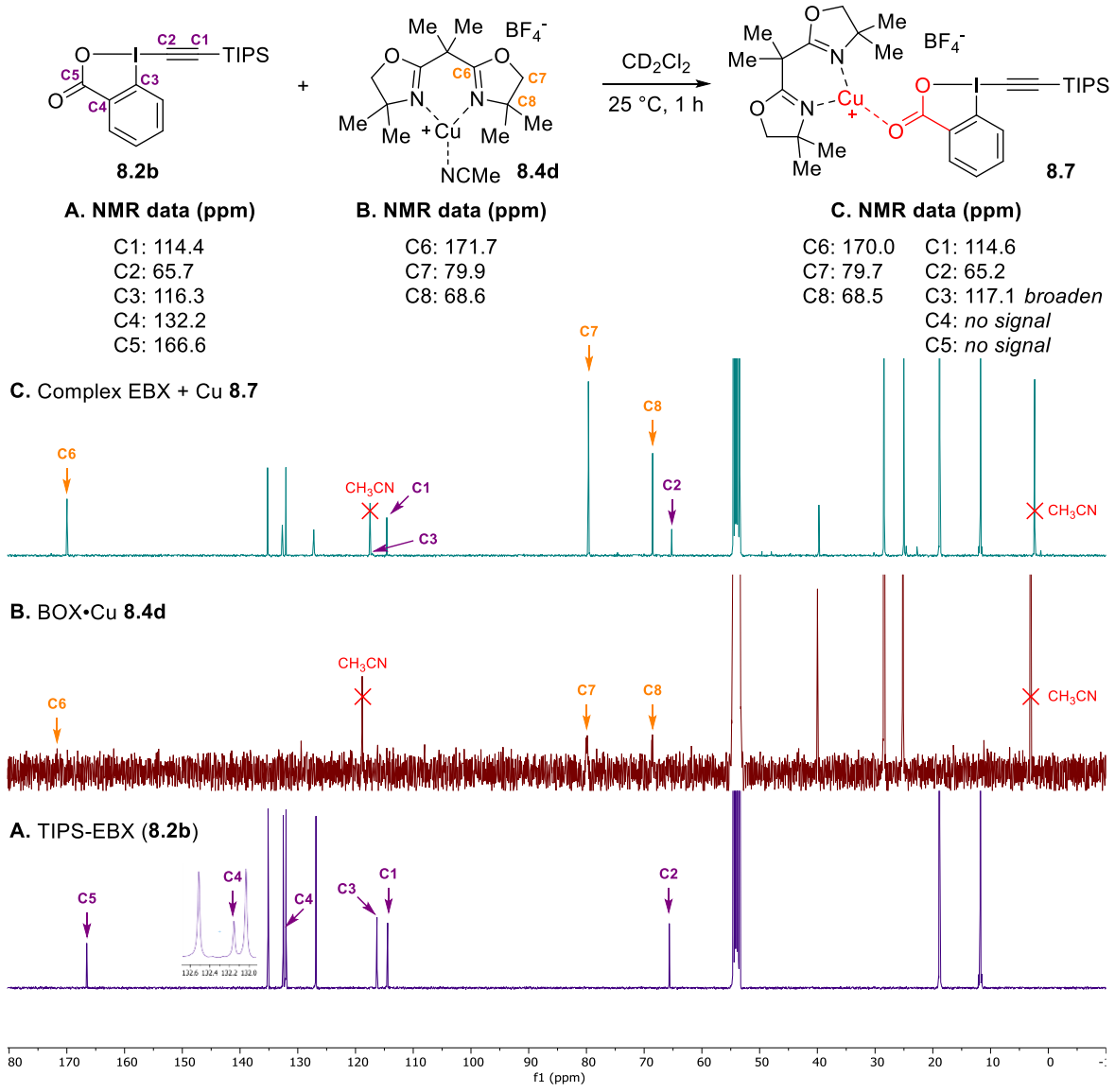
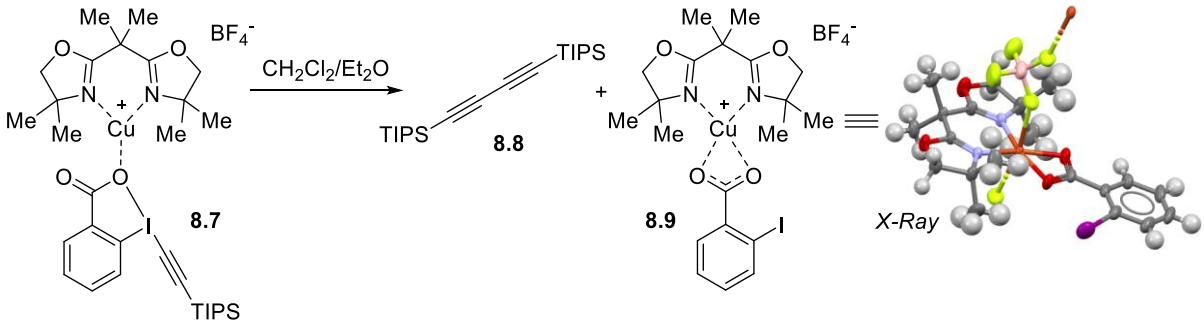


Figure 32. ^{13}C NMR of the TIPS-EBX (**8.2b**) complexed with BOX•Cu **8.4d**.

The coordination between Cu complex **8.4d** and EBX reagent **8.2b** is believed to occur though the carboxylate ligand, such as that drawn in **8.7**. Broadening of the signals makes the NMR interpretation challenging, however, it is clear that atoms near to the copper center are more affected by the broadening effect of Cu.[345] Interestingly, our attempt to crystalize the postulated complex **8.7** resulted in the formation of blue crystals of copper(II) **8.9**, with formation of diyne product **8.8** in the liquid phase (Scheme 106). Possibly, the BOX ligand significantly slows down the oxidation rate of the copper but may not be able to prevent it for an extended period of time.

[345] V. Vinković, Z. Raza, V. Šunjić, *Spectrosc. Lett.* **1994**, *27*, 269.

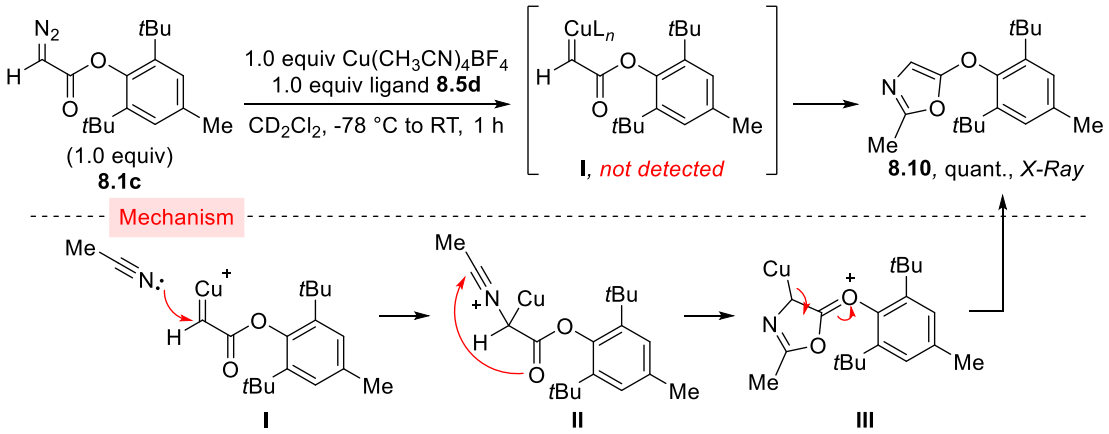


Scheme 106. Oxidation of the Cu(I) complex **8.7** over time.

Through these first studies, we could determine the structures of the initial copper catalysts that have been extensively used all along our work. The presence of the ligand seems important to prevent the fast oxidation of the copper(I) salt by the iodine(III) reagent and preserve its activity towards diazo compounds. A tentative structure for the interaction between TIPS-EBX (**8.2b**) and [BOX•Cu(CH_3CN)]BF_4 **8.4d** has been proposed, however, it is difficult to establish if such a complex is active in the catalytic cycle or is off-loop. Displacement of the coordinated EBX in complex **8.7** by a diazo molecule to initiate the reaction is possible. The DFT calculations suggested a favorable coordination of copper through the alkyne of the hypervalent iodine reagent. However, the simulation was realized with a biased Cu complex having a truncated ligand and H_3Si as substituent on the alkyne. The utilization of the sterically demanding tetramethyl-substituted BOX ligand and the larger TIPS substituent could explain a preferential coordination to the more accessible carboxylate in this case. A copper-alkyne interaction was characterized by ^{13}C NMR when Cu(CH_3CN)$_4PF_6$ without *N*,*N*-ligand was use in a similar complexation experiment with ethynylbenziodoxole derivatives (see Figure 23 in section 7.4.).

To continue our mechanistic investigations, we attempted to generate a copper carbene. Our aim was to characterize this intermediate, before reacting it with EBX reagent and support the implication of a copper carbene in the oxy-alkynylation reaction (Scheme 107). We used variable-temperature NMR to follow the eventual formation of the copper carbene intermediate **I** resulting from the decomposition of sterically hindered diazo **8.1c**, known to undergo slow self-dimerization. Being a highly electron-deficient species, the signal for the copper(I)-carbene carbon atom was expected to be downfield. Straub and Hofmann observed such a signal at δ = 230 ppm by ^{13}C NMR spectroscopy at -33 °C.[171] Unfortunately, no characteristic signal of a carbene was detected in the scan window of 0 to 400 ppm, with a temperature gradient from -78 °C to 25 °C over 1 h. Instead, clean conversion of BDA (**8.1c**) to oxazole **8.10** was observed. The formation of **8.10** likely resulted from the immediate attack of residual acetonitrile on the transient copper carbene **I**, followed by cyclisation of the carbonyl to the nitrile-ylide intermediate **II** and further aromatization/demetalation of **III**.[346] Despite supporting the formation of a Cu carbene, no characterization of such species has been realized and the utilization of *in situ* generated carbene intermediate in the oxy-alkynylation seemed not as straightforward as envisaged.

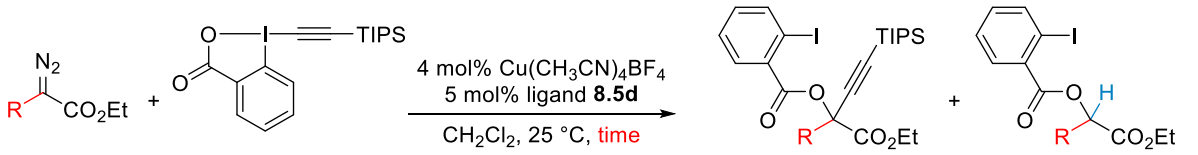
[346] a) K. J. Doyle, C. J. Moody, *Tetrahedron* **1994**, *50*, 3761; b) T. Ibata, K. Fukushima, *Chem. Lett.* **1992**, *21*, 2197; c) J. A. Flores, K. Pal, M. E. Carroll, M. Pink, J. A. Karty, D. J. Mindiola, K. G. Caulton, *Organometallics* **2014**, *33*, 1544.



Scheme 107. Formation of oxazole **8.10** by reaction of Cu carbene **I** with acetonitrile.

Finally, we explored the alkyne-transfer step. A comparative study of reactivity between EDA (**8.1b**) and the methyl-substituted diazo **8.1d** with TIPS-EBX (**8.2b**), in the presence of catalytic $Cu(CH_3CN)_4BF_4$ and BOX ligand **8.5d**, indicated an important difference of reactivity between the two diazo substrates (Table 30). With substrate **8.1b**, full conversion of TIPS-EBX (**8.2b**) was observed in less than 5 minutes at ambient temperature, furnishing the desired product in 89% isolated yield (entry 1). In contrast, the conversion of TIPS-EBX (**8.2b**) was only 50% after 2 hours of reaction with substrate **8.1d**. In several of our previous projects, we had already identified a lower reactivity when disubstituted diazo compounds were used in combination with BOX ligands. Here, the expected product was isolated in a low 22% yield, along with product **8.11f** in 10% yield. The formation of **8.11f** likely resulted from a protodematalation and supported a mechanistic scenario with alkynylation as last step.

Table 30. Reactivity comparison between substrates **8.1b** and **8.1d**.[a]

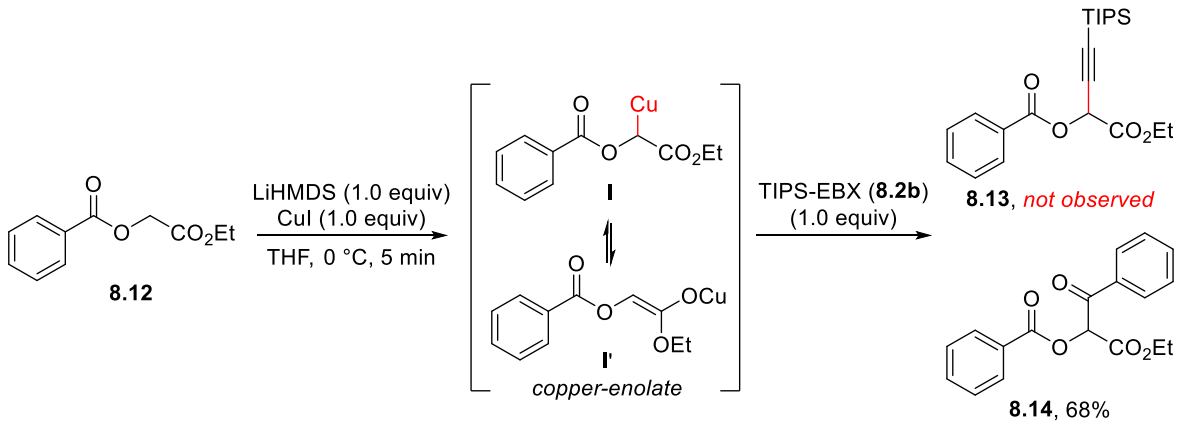


Entry	Diazo (R =)	Time	Conversion[b] (%)	Yield[c] (%)	Side product[c] (%)
1	H (**8.1b**)	5 min	100	89	n.d. (**8.11e**)
2	Me (**8.1d**)	2 h	53	22	10 (**8.11f**)

[a]Reaction conditions: 0.40 mmol diazo, 0.20 mmol TIPS-EBX (**8.2b**), $Cu(CH_3CN)_4BF_4$ (4 mol%), ligand **8.5d** (5 mol%), CH_2Cl_2 (0.05 M). [b]Determined by ^1H NMR yield with addition of 0.20 mmol of CH_2Br_2 as an internal standard after the reaction. [c]Yield after purification by column chromatography.

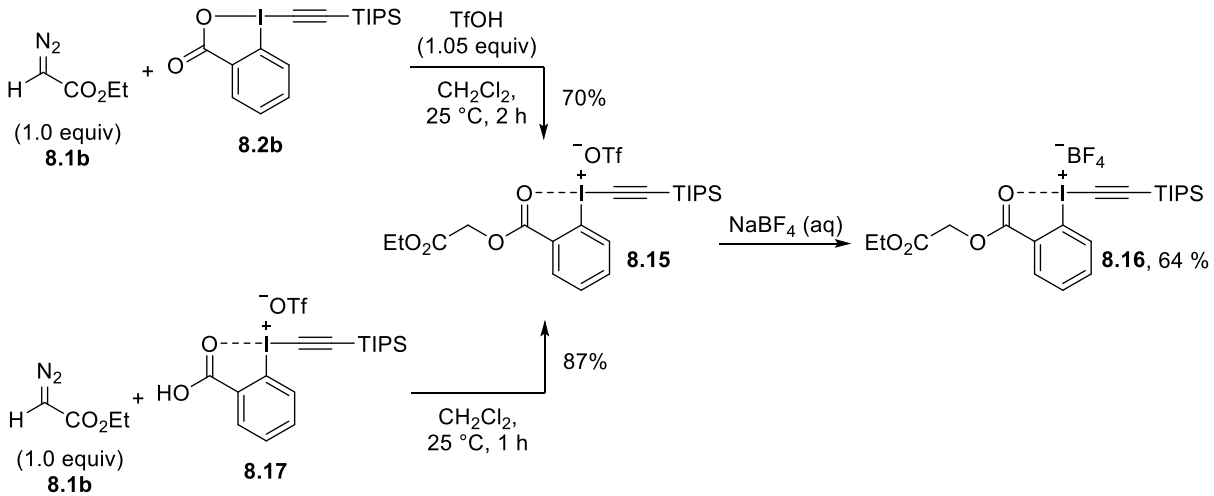
We wondered if a corresponding oxo-ester **8.12** could be metalated and alkynylated with EBX reagents (Scheme 108).[347] Unfortunately, preparation of the copper-enolate intermediate **I/I'** resulted in the intermolecular nucleophilic attack of the benzoic ester and product **8.14** was probably formed before addition of the EBX reagent. The expected alkynylated product **8.13** could not be detected.

[347] P. A. Evans, M. J. Lawler, *J. Am. Chem. Soc.* **2004**, *126*, 8642.



Scheme 108. Attempt for the alkynylation of oxo-ester **8.12** through copper-enolate **I**.

Based on this result, another strategy was envisioned by employing pseudo-cyclic alkynyliodonium salt **8.16** to study the internal alkyne transfer (Scheme 109). The alkylation of the EBX carboxylate was achieved using a procedure reported by Suero and co-workers using EDA (**8.1b**) and triflic acid to activate TIPS-EBX (**8.2b**).[72a] Simple anion metathesis from **8.15** furnished the desired tetrafluoroborate iodonium salt **8.16** in good yield.[348] Alternatively, the triflate intermediate **8.15** can be obtained by alkylation of the already-activated iodonium salt **8.17**. It is interesting to notice that the carboxylic acid function reacted well with the diazo compound to accomplish the O-H insertion reaction. The increased acidity due to the electron-withdrawing effect of the cationic I(III) atom, makes the deprotonation by EDA (**8.1b**) possible. No reaction between 2-iodobenzoic acid and ethyldiazo acetate can be expected under such conditions.



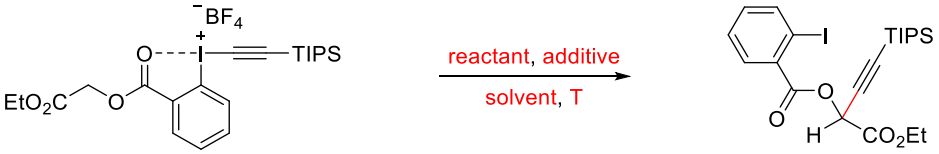
Scheme 109. Preparation of pseudo-cyclic alkynyliodonium **8.16**.

The prepared iodonium salt **8.16** was then used under various reaction conditions possible to achieve the alkyne transfer (Table 31). In presence of [BOX•Cu(CH_3CN)]BF_4 **8.4d**, no reaction was observed at 25 °C (entry 1). In order to deprotonate the α-position to the carbonyl, the addition of a base was envisaged. Unfortunately, no reaction was observed as well with 1 equivalent of potassium carbonate (entry 2). With addition of triethylamine, rapid degradation of the hypervalent iodine salt was observed, resulting in the formation of product **8.18** (entry 3). A similar issue was encountered in abscence of copper catalyst (entry 4). Therefore, mesitylcopper (**8.19**) was considered for the

[348] M. Reitti, P. Villo, B. Olofsson, *Angew. Chem. Int. Ed.* **2016**, *55*, 8928.

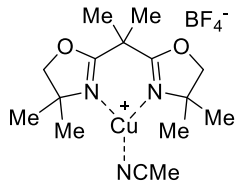
irreversible cupration of the carbonyl α-position (entry 5). The expected product **8.3e** was not detected under these conditions, and a complex reaction profile was obtained. Finally, addition of LiHMDS at -78 °C, resulted in partial decomposition of the iodonium salt **8.16** to the product **8.18** (entry 6).

Table 31. Attempts of alkyne transfer with **8.16** for the formation of the product **8.3e**.[a]

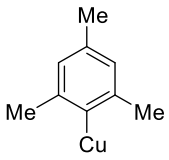


8.16 **8.3e**

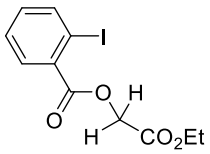
Entry	Reactant	Additive	Solvent	T (°C)	Observation	Product isolated[b]
1	5 mol% **8.4d**	-	CH_2Cl_2	25	n.r	-
2	5 mol% **8.4d**	K_2CO_3 (1.0 equiv)	CH_2Cl_2	25	n.r	-
3	5 mol% **8.4d**	Et_3N (1.0 equiv)	CH_2Cl_2	25	dec.	**8.18**
4	-	Et_3N (1.0 equiv)	CH_2Cl_2	25	dec.	**8.18**
5	MesCu (**8.19**) (1.0 equiv)	-	THF	0	dec.	-
6	LiHMDS (1.0 equiv)	-	THF	-78 to -20	dec.	**8.18**



[BOX•Cu(CH_3CN)]BF_4, **8.4d**



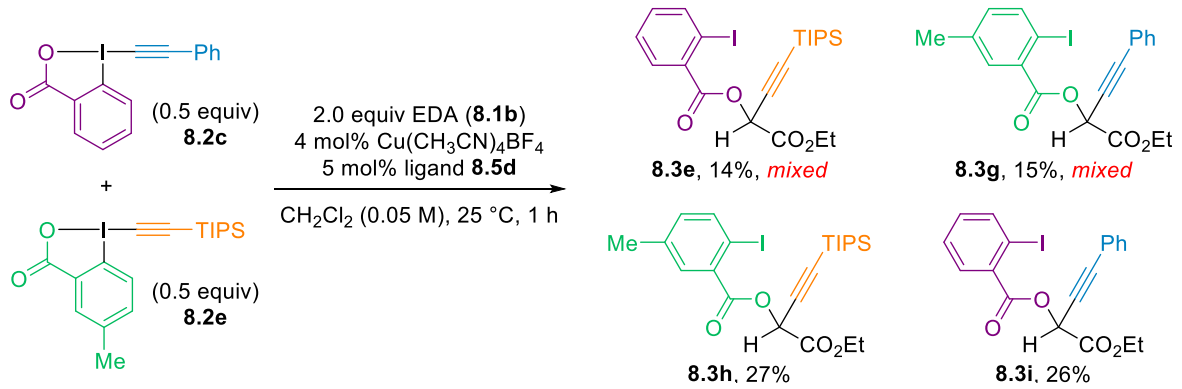
MesCu (**8.19**)



8.18

[a]Reaction conditions: 0.10 mmol alkynyliodonium salt (**8.16**), solvent (0.05 M). [c]Isolated product by PTLC. The yield was not determined. n.r. = no reaction.

Considering the successful development of the three-component oxy-alkynylation reaction based on the trapping of ylide intermediates and the high energy transition state calculated by DFT for the internal alkyne transfer step in the case of the two-component reaction, we wondered if a bimolecular alkynylation could be a possible pathway. To examine this possibility, a competitive experiment with two EBX reagents having different alkyne and benzoate ligands on the iodine(III) was performed using EDA (**8.1b**) as diazo partner and the catalytic system of Cu(CH_3CN_4)BF_4 with BOX ligand **8.5d** (Scheme 110). A significant proportion of cross-over products was obtained: **8.3e** (14% yield), and **8.3g** (15% yield). The two-component products **8.3h** and **8.3i** were determined at 27% and 26% yield, respectively.



Scheme 110. Competitive experiment between two EBX reagents.

This important result is consistent with a pathway in which the carboxylate and the alkyne component are added to the carbene in a stepwise fashion, however, it invalidated our mechanism with intramolecular alkyne delivery as final step. The higher proportion of regular products over the cross-over products at *c* = 0.05 M, indicated a possible competition between intramolecular and intermolecular alkynylation, making the proposition of a reaction mechanism challenging. Deeper investigations on the influence of the reaction concentration and substituent effect on the aryl ring would be required to better understand the intra- and intermolecular pathway.

8.3. Kinetic Studies

Understanding the kinetic of the copper-catalyzed oxy-alkynylation reaction can shed light on the mechanism. Investigation of influencing parameters such as the concentration of catalyst and reactants, temperature, or the effect of additives on the reaction rate provides information on the rate-determining step or activation energy. For our studies, we envisaged the use of reaction progress kinetic analysis by ^{19}F NMR monitoring. The high reaction rate (complete conversion in 5 min at *c* = 0.05 M at 25 °C) observed at ambient temperature utilizing EDA (**8.1b**) and TIPS-EBX (**8.2b**) as reactants with [BOX•Cu(CH$_3$CN)]BF$_4$ **8.4d** as catalyst was inappropriate to determine the rate law by using the method of initial rates without significant changes in concentration. Instead, EBX **8.2f**, having a fluorine tag, was chosen to follow the rate disappearance of the reagent and the formation of product **8.3j**. The utilization of sterically-demanding BDA (**8.1c**) was advantageous as it significantly increased the reaction time and could be used in a nearly stoichiometric amount, thus avoiding the formation of diazo dimerization side-products. Gratifyingly, we could develop an experimental protocol with addition of the catalyst **8.4d** at -78 °C, resulting in an unreacted solution stable for several hours in the NMR tube at this temperature. Under standard conditions, monitoring of the reaction progress was achieved at 0 °C, giving a complete reaction profile over 40 minutes (Figure 33).[349]

[349] The reaction mixture could be transferred in the NMR probe at -20 °C without evolution of the reaction. The warming phase to 0 °C take approximately 5 min and was not included in the curves.

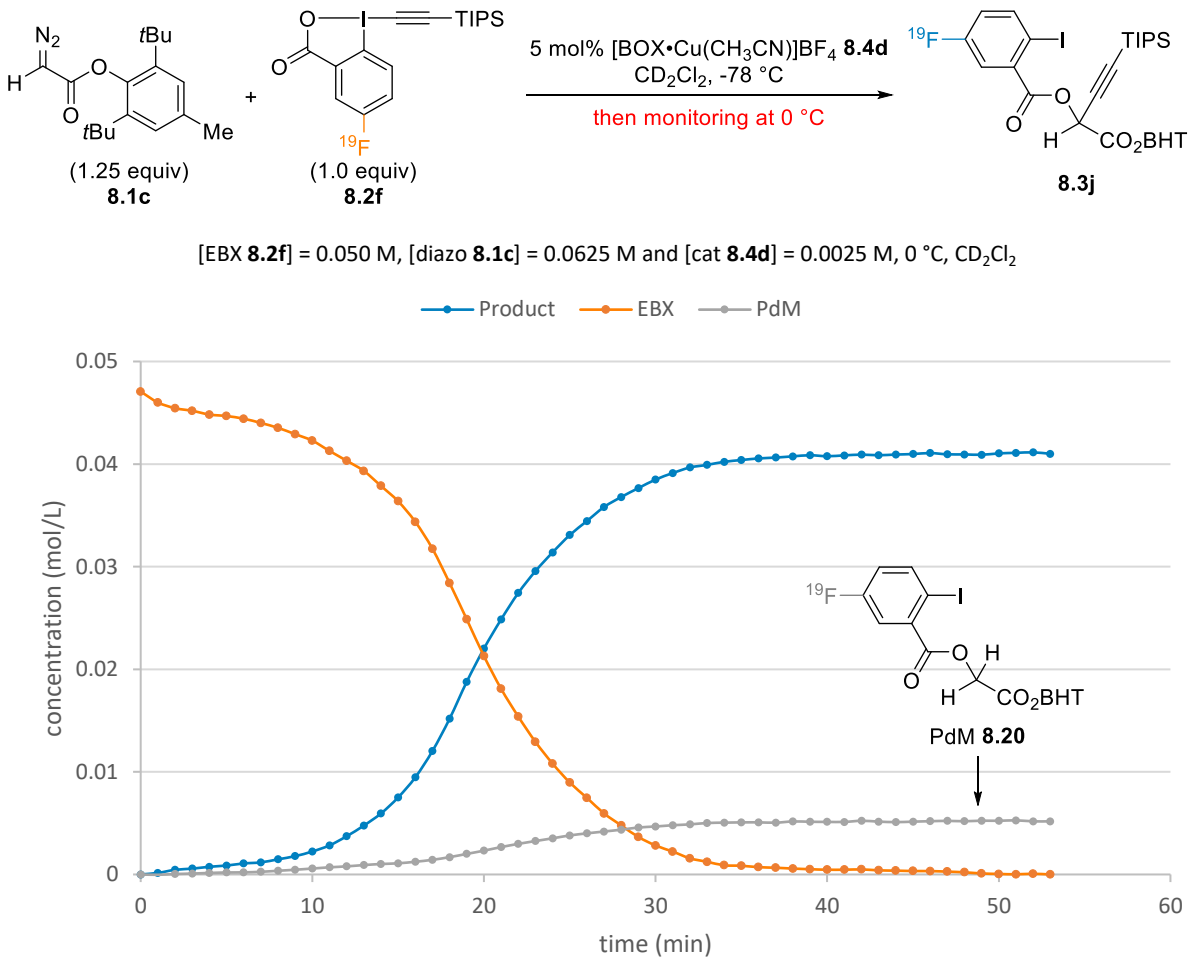


Figure 33. Equation for reaction progress kinetic analysis by ^{19}F NMR monitoring and temporal profile at 0 °C.

Interestingly, the obtained profile did not correspond to a conventional first-order kinetic behavior. The reaction exhibited a sigmoidal kinetic profile,[350] complicating attempts to obtain rate equation *via* regular initial rate measurements. Examples of sigmoidal kinetics have been encountered in autocatalytic reaction,[351] progressive catalyst activation,[352] or autoinduction, where a product accelerates the reaction rate but cannot be formed in the absence of another catalyst.[353] In addition, the proto-demetalated product (PdM, **8.20**) followed a similar formation profile to product **8.3j**, likely through a common rate-determining step.

A simple way to probe the influence of the reaction products on the reaction rate is to add a portion of these compounds to the initial conditions (Figure 34). The length of the induction period was significantly shortened when 0.10 equivalent of product **8.3j** (blue) and PdM **8.20** (grey) was added at the start of the reaction compared to the absence of additive (yellow). The common di-ester motif of

[350] M. P. Mower, D. G. Blackmond, *J. Am. Chem. Soc.* **2015**, *137*, 2386.

[351] a) D. G. Blackmond, C. R. McMillan, S. Ramdeehul, A. Schorm, J. M. Brown, *J. Am. Chem. Soc.* **2001**, *123*, 10103; b) F.G. Buono, D. G. Blackmond, *J. Am. Chem. Soc.* **2003**, *125*, 8978; c) M. Quaranta, T. Gehring, B. Odell, J. M. Brown, D. G. Blackmond, *J. Am. Chem. Soc.* **2010**, *132*, 15104.

[352] a) T. Rosner, A. Pfaltz, D. G. Blackmond, *J. Am. Chem. Soc.* **2001**, *123*, 4621; b) S. Shekhar, P. Ryberg, J. F. Hartwig, J. S. Mathew, D. G. Blackmond, E. R. Strieter, S. L. J. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 3584.

[353] a) S. P. Mathew, M. Klussmann, H. Iwamura, D. H., Jr. Wells, A. Armstrong, D. G. Blackmond, *Chem. Commun.* **2006**, 4291; b) P. H. Phua, S. P. Mathew, A. J. P. White, J. G. de Vries, D. G. Blackmond, K. K. Hii, *Chem. Eur. J.* **2007**, *13*, 4602.

compounds **8.3j** and **8.20** could account for an interaction with the copper catalyst. One possibility would be a competitive binding between the EBX **8.2f** and product **8.3j** (or **8.20**) to the copper catalyst, then, fast exchange of the product **8.3j** (or **8.20**) by diazo **8.1c** would allow its decomposition and explain the acceleration phase after ca. 10% of conversion. Nevertheless, the curves still presented inflexion points and have to be interpreted with care. To verify if a catalyst activation could account for the induction period, pre-mixing of EBX **8.2f** with the catalyst **8.4d** for 1 h at 0 °C was realized before addition of the diazo compound. In this case, a similar profile to the control reaction was obtained, discarding this possibility (green).

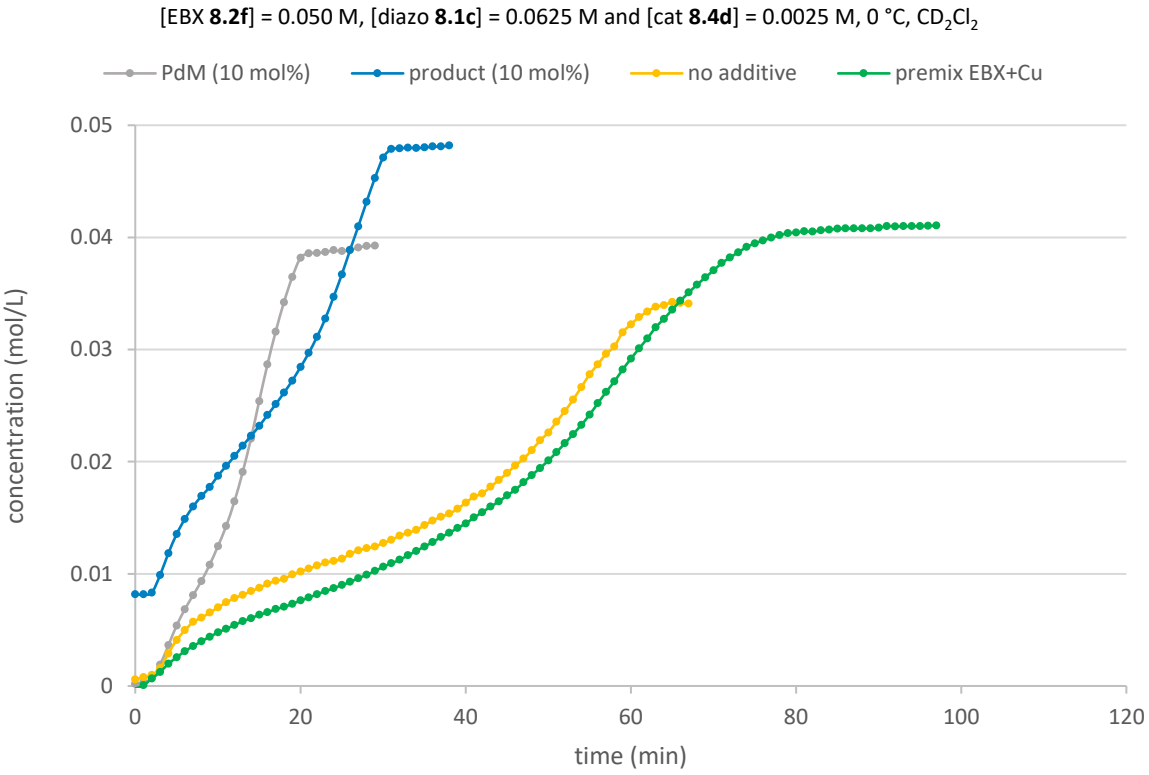


Figure 34. Product formation profiles when the reaction was carried out in the presence and absence of additives and with pre-mixing of EBX **8.2j** with Cu catalyst **8.4d**.

Despite the impossibility to derive the theoretical kinetic equation from the obtained curves, we continued our investigations for qualitative interpretations. The influence of the diazo concentration on the reaction profile was monitored (Figure 35). As expected, the reaction finished faster at higher concentrations of diazo compounds. It is however interesting to notice that at low diazo concentration ([diazo] = 0.050 M, orange), corresponding to an equimolar quantity of diazo **8.1c** and EBX reagent **8.2f**, the reaction never entered the "acceleration" phase and could not reach completion after an extended reaction time.

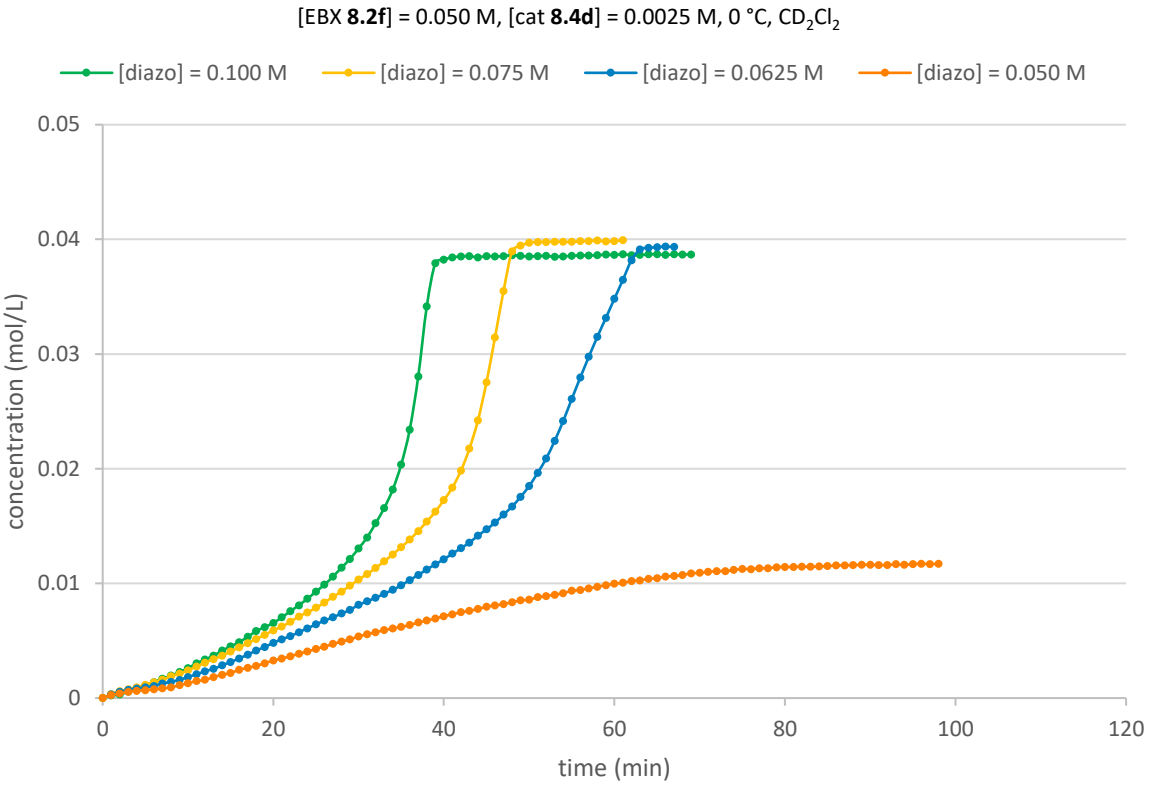


Figure 35. Product formation profiles at different concentrations of the diazo compound.

A similar effect was observed with the EBX reagent, however, in the opposite direction (Figure 36). At higher concentrations of hypervalent iodine reagent, the reaction was progressing extremely slowly (orange and yellow). This observation also supports an initial interaction between EBX reagent **8.2f** and copper catalyst **8.4d** that would need to be overcome by diazo compound **8.2c.** Therefore, the rate-determining step would be the dissociation of the Cu-EBX pre-complex or the carbene formation, indicating again that the energies obtained from DFT calculations for the internal alkyne transfer are too high.

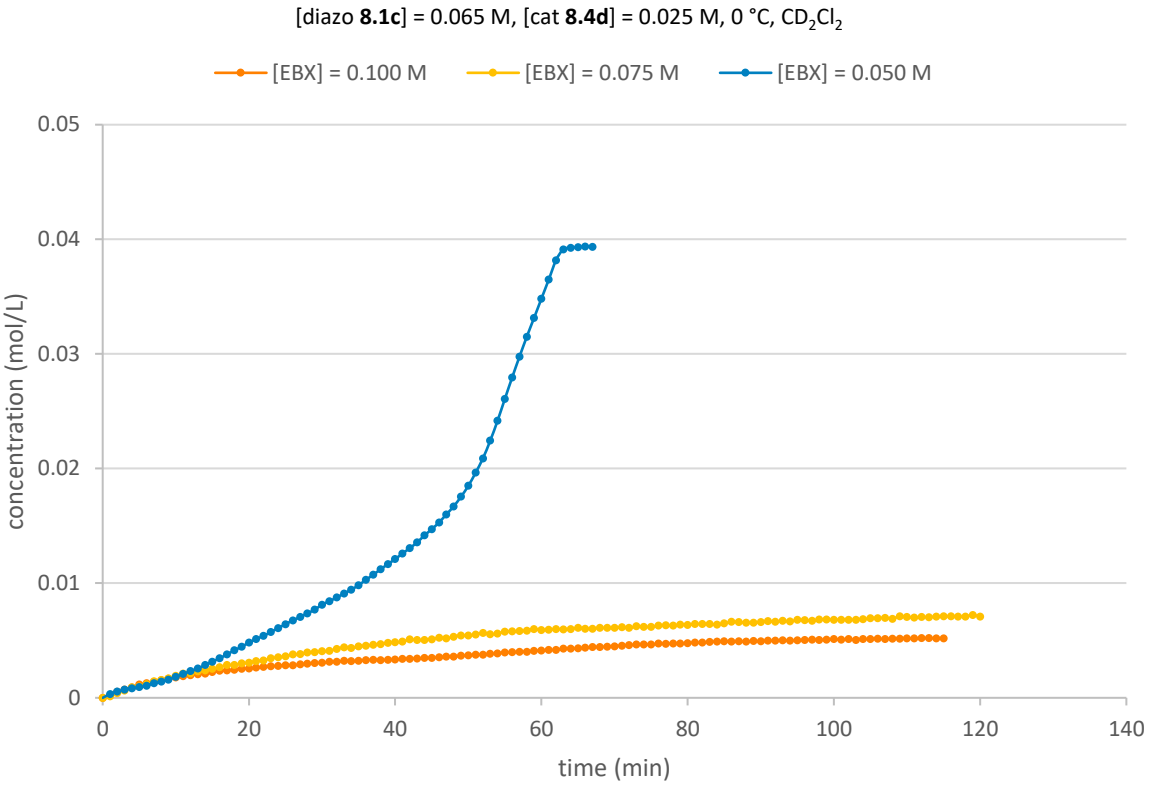


Figure 36. Product formation profiles at different concentrations of EBX reagent **8.2f**.

Finally, the formation of the product was monitored at different concentrations of copper catalyst **8.4d** (Figure 37). A counter-intuitive effect was observed. At higher concentrations of catalyst, the induction period was longer, therefore longer overall reaction time were needed to reach completion. For instance, the reaction was completed in 34 minutes at [**8.4d**] = 0.025 M (5 mol%) (blue), while 39 minutes was required at [**8.4d**] = 0.050 M (10 mol%) (yellow). However, once the acceleration phase is attained fast reaction rate is observed: At [**8.4d**] = 0.050 M (yellow), formation of 50% yield was observed in the last 6 minutes. A larger proportion of PdM **8.20** was observed at higher catalyst concentration, which accounted for the missing oxy-alkynylation product **8.3j**. Importantly, at very low concentrations of catalyst [**8.4d**] = 0.013 M (2.5 mol%) (orange), the reaction stopped at ca. 50% of conversion.

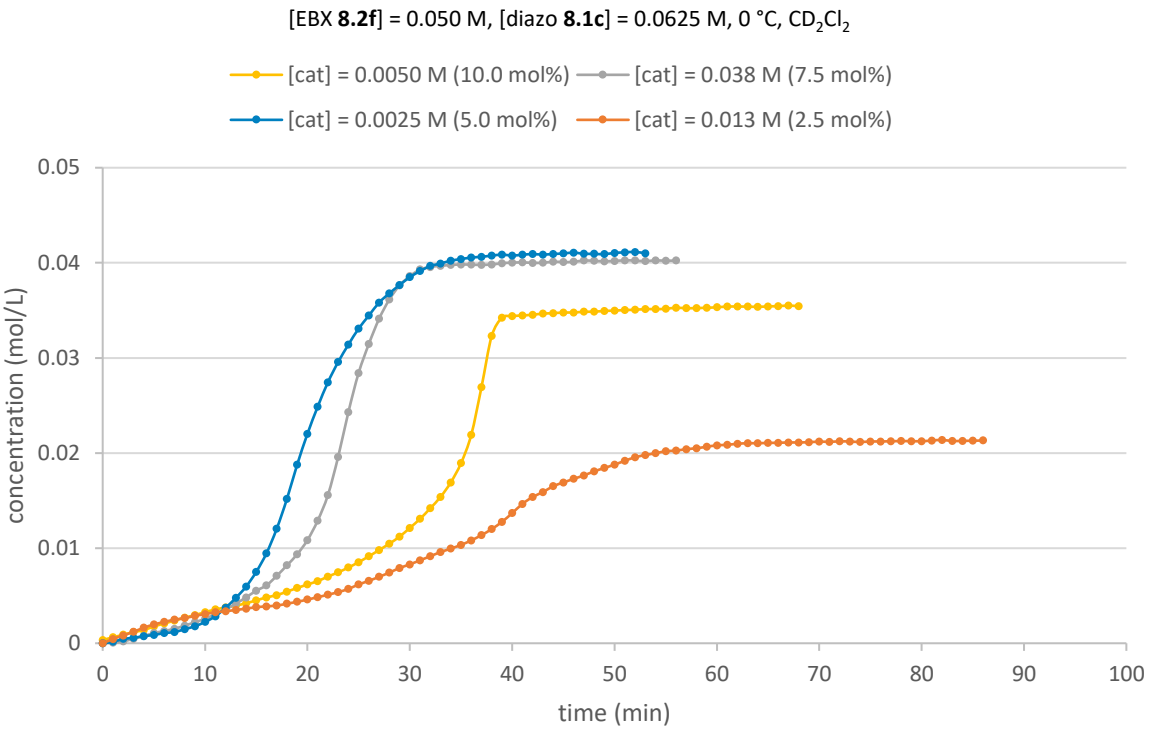


Figure 37. Product formation profiles at different concentrations of copper catalyst.

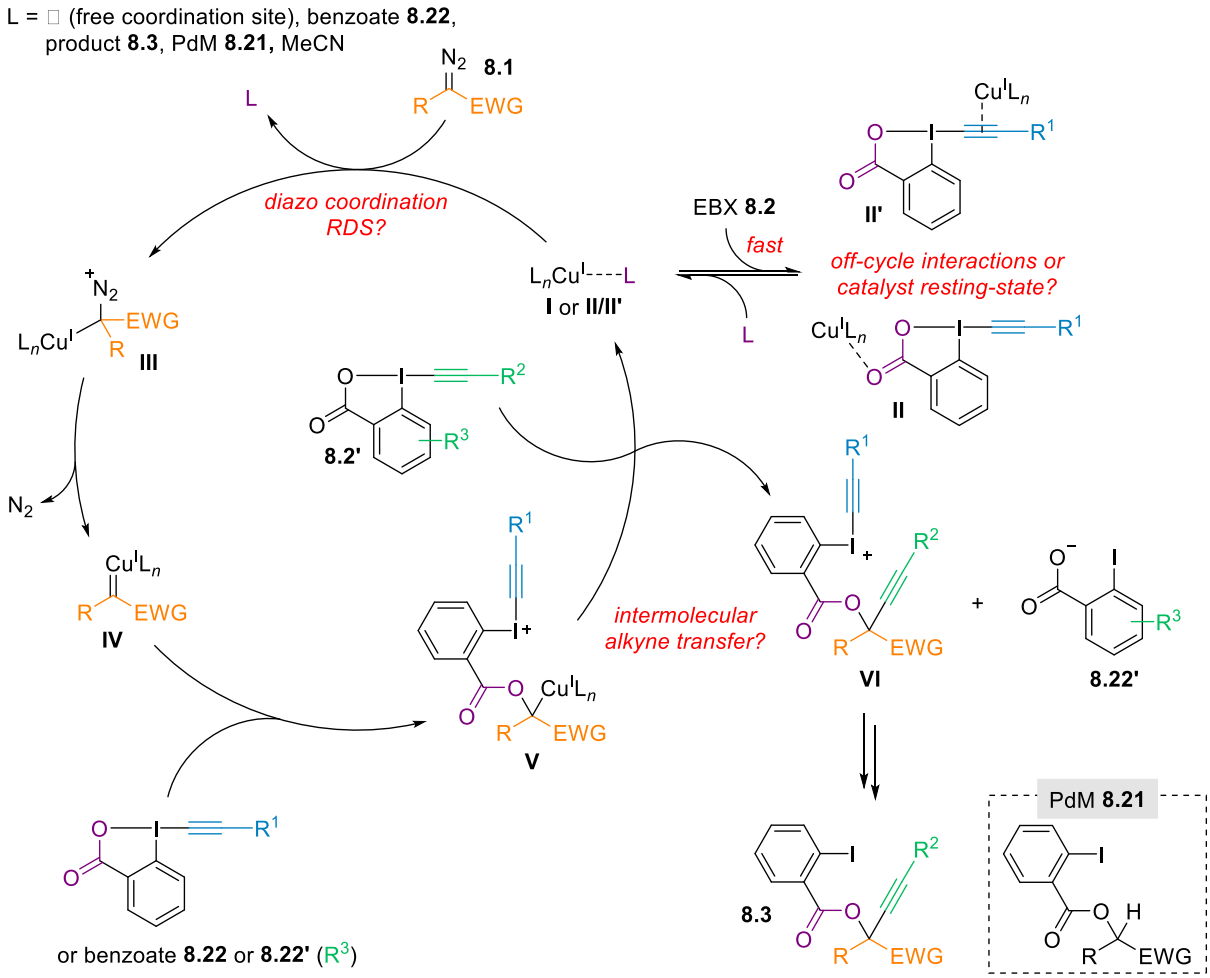
8.4. Conclusion and Perspectives

Several investigations have been conducted in order to probe the mechanism of the oxy-alkynylation reaction. At first, DFT calculations were efficient to locate the key iodonium ylide intermediate resulting of two convergent postulated pathways. Despite an interesting pseudo-rotation/isomerization of the alkyne around the iodine atom, our first assumption of an intra-molecular alkyne delivery was calculated to require a high-energy transition state. The difficulty of such a step was later confirmed experimentally in a competitive experiment in which an important proportion of mixed product was measured, supporting an intermolecular alkynylation step (or at least a mixed inter- and intramolecular reaction).[354]

A complex between the BOX-Cu catalyst and the carboxylate of the EBX reagent was detected by NMR spectroscopy and a tentative structure has been proposed. This interaction has been calculated to be favorable by DFT calculation, but a Cu-alkyne interaction lower in energy has also been identified and is in agreement with our previous observations when ethynylbenziodoxole reagents (EBX') were mixed with $Cu(CH_3CN)_4PF_6$. Concerning kinetic studies, a convenient experimental protocol has been set-up, allowing reaction progress kinetic analysis by ^{19}F NMR monitoring. However, non-classical reaction profiles have been obtained and it is difficult to firmly rationalize the observed induction period. Addition of 0.10 equivalent of oxy-alkynylation product (or proto-demetalated product) at the beginning of the reaction drastically diminished the induction period. Variation of the amount of additive would be required to better estimate such effect. In line with these first results, we also established that high EBX/diazo ratios led to the deactivation of the copper catalyst, with the reaction never overcoming the induction period. Similarly, at high catalyst concentrations, longer induction periods have been recorded. At this stage, we can postulate a catalyst deactivation by the

[354] Further DFT computations are ongoing to locate an intermolecular transition state for the alkynylation step, but have not yet been successful.

EBX reagent, progressively released through the advancement of the reaction. With these new considerations, a more detailed picture of the mechanism is proposed below (Scheme 111).



Scheme 111. Revised mechanism with new considerations.

The first interaction would be a rapid and reversible formation of EBX bound copper complex **II** or **II'**. Displacement of the equilibrium towards **I** could be influenced by the presence of product **8.3** or PdM **8.21**. Slow substitution by diazo substrate **8.1** generates the carbenoid **III**, followed by nitrogen released to form the copper carbene **IV**. Importantly, the active catalyst for the diazo decomposition could be **II** as well. Disappearance of EBX **8.2** in the course of the reaction would lead to increased concentration of active catalyst **I**, hence the acceleration profiles observed. After formation of electrophilic copper carbene **IV**, fast addition of carboxylate (EBX or benzoate) can be expected resulting in the iodonium-ylide intermediate **V**. Here, intermolecular alkynylation by an external EBX molecule **8.2'** has been observed. However, possible intramolecular alkyne transfer cannot be ruled out at this stage of the investigation. Final product **8.3** would be formed after utilization of the iodonium salt intermediate **VI** as alkynylating reagent instead of EBX in the last step of another turnover (not drawn).

While trying to support our former mechanism a more complex one has emerged. An interaction between the copper catalyst and the EBX reagent is likely to occur, but it is difficult to rationalize the role and the effect of such species. The key alkynylation step remains ambiguous at the moment. Important investigations are still needed to propose a reliable mechanism hypothesis useful for future methodology developments.

9

General Conclusion

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Outlook

9. General Conclusion – Outlook

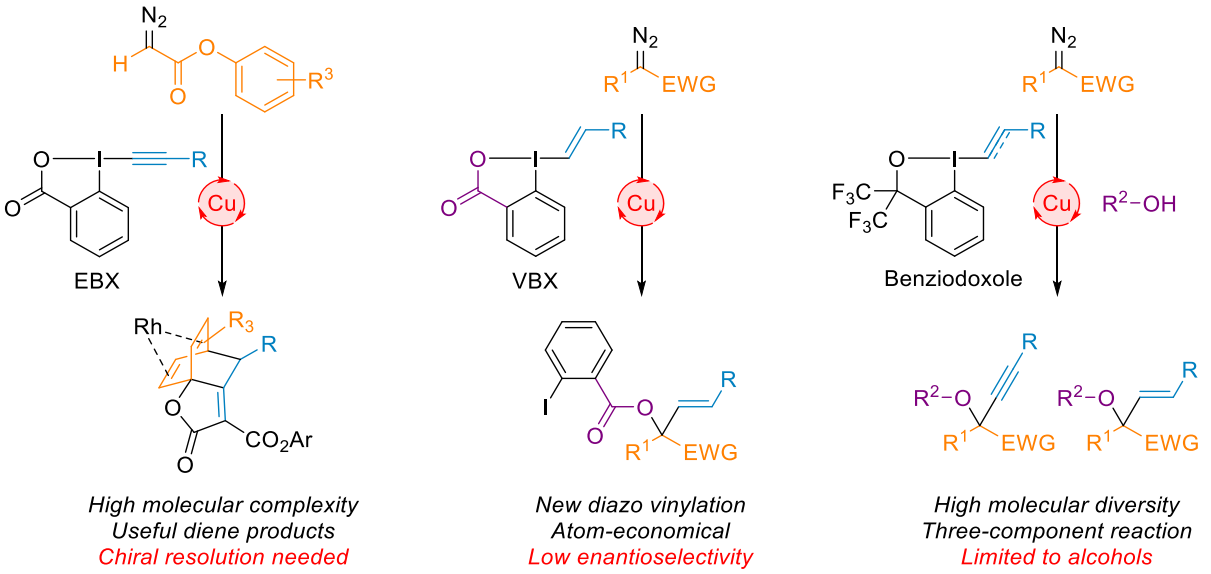
The research work presented in this dissertation was aimed to the development of new vinylation and alkynylation strategies of diazo compounds with hypervalent iodine reagents. Our goal was to maximize molecular complexity in a convergent manner through the difunctionalization of transient metal carbenes using non-conventional electrophilic vinyl and alkynyl transfer reagents (Scheme 112).

A strategy for the rapid construction of bicyclo[2.2.2]octadienes was presented in the first part of the thesis. This one-pot oxy-alkynylation/[4+2] cycloaddition sequence was developed in collaboration with Dr. Durga Hari and allowed the fast formation of four new bonds (three C-C and one C-O) to access polyfunctionalized diene products. This unusual low temperature dearomatization reaction could be rationalized through favorable intramolecular dispersive interactions and a donor effect of the carboxyl substituent on the allene intermediate. The bicyclooctadiene products could be further exploited as ligand for rhodium catalysis. Application of a pseudo-C_2 symmetric ligand induced high enantioselectivity in the benchmark conjugate addition of phenylboronic acid to cyclohexenone. Development of an enantioselective [4+2] cycloaddition step would be highly desirable to avoid the resolution of the racemic ligand.

Next, the extension of an enantioselective oxy-alkynylation reaction was envisaged with vinyl diazo compounds. Despite the investigation of several catalyst systems and substrates, the maximum enantioselectivity achieved with a chiral diimine copper(I) complex was disappointing. No further research effort to access enantioenriched α-benzoyloxy-1,3-enynes are envisaged at the present moment.

In addition to propose a new strategy for the vinylation of diazo compounds, the objective to broaden the difunctionalization reaction with other class of hypervalent iodine reagents could be realized by employing vinylbenziodoxolones. With these substrates, the simultaneous introduction of new C-O and C-Csp^2 bonds on the same carbon atom was successfully achieved allowing a convenient synthesis of α-vinyl-hydroxyacid derivatives. The good outcome of the process depended on the catalyst system used. BOX copper(I) as catalyst was particularly efficient with diazo compounds having only one substituent, while diimine copper(I) was used with disubstituted diazo compounds. The utilization of chiral BOX ligands induced enantioselectivity in the transformation, however, further optimization would be required to develop an efficient asymmetric variant. Importantly, the obtained products were engaged in several post-modifications harnessing the various functionalities available on the molecules.

In spite of the excellent results achieved for the difunctionalization of diazo compounds with EBX and VBX reagents, the introduction of external nucleophiles instead of 2-iodobenzoate from the hypervalent iodine reagent was a long-term objective in our group as it could add one extra dimension of diversity in the chemical structures attainable. To realize such a three-component process, the utilization of benziodoxole reagents having a non-nucleophilic ligand was the main factor to suppress any competitive two-component pathway. Secondly, an undesired O-H insertion pathway could be drastically limited by employing copper(I) salts having non-coordinating anions as catalysts and without additional donor *N*,*N*-ligands. The transformation displayed a broad scope, especially with respect to the alcohol partners which was an important goal of this project. The extension to *N*-nucleophiles has been challenging but could be achieved with anilines and trifluorodiazoethane. Dr. Nieves Ramirez is currently investigating this new three-component reaction.



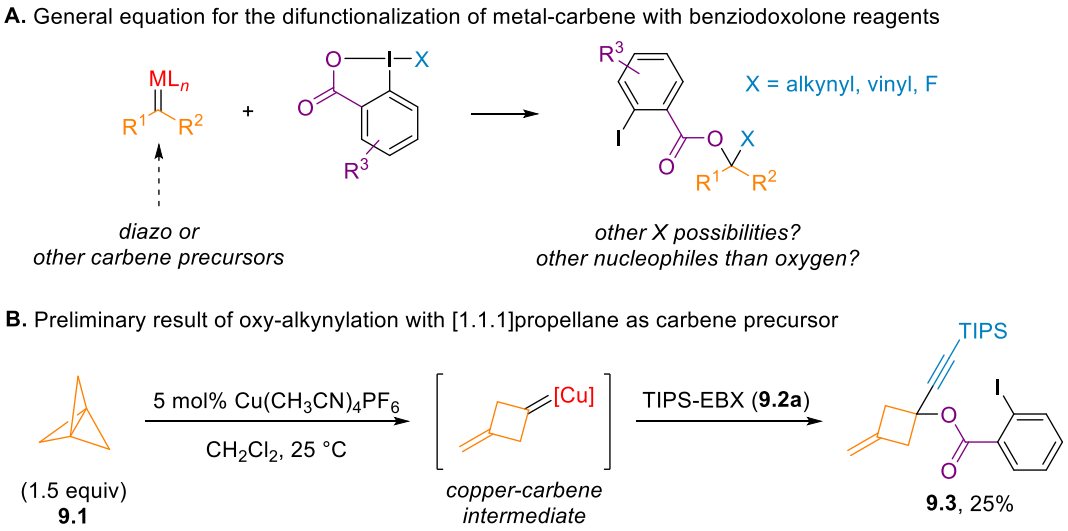
Scheme 112. Copper-catalyzed vinylation and alkynylation of diazo compounds with hypervalent iodine reagents developed during this PhD work.

Similarities in the mechanisms of the two- and three-component reactions, as well as vinylation and alkynylation of diazo compounds with hypervalent iodine reagents can be expected. Therefore, the last part of the thesis was dedicated to mechanistic studies on our seminal two-component oxy-alkynylation reaction. An internal alkyne delivery alkynylation step was proposed at first, but was considered inaccurate by DFT calculations and later disproved by a control experiment. A copper-EBX interaction was detected by NMR spectroscopy and would correspond to a favorable Cu-carboxylate complex supported by the DFT calculations. In contrast, a similar experiment with benziodoxole derivatives indicated an interaction through the alkyne group. This different modes of binding could explain the preferential benzoate insertion with benziodoxolone reagents. Finally, an induction period was observed when the reaction progress was monitored by *in situ* NMR, complicating the attempts to obtain suitable kinetic data. At the present moment, it is difficult to rationalize such phenomena. Additional in-depth investigations are required to have a stronger mechanism hypothesis.

Several further interesting developments can be envisaged starting from the results presented in this thesis:

The atom-economical addition of benziodoxol(on)e-based reagents on carbenes intermediates is certainly not limited to the alkyne and alkene functions (Scheme 113. A). During our exploratory phase, the product of oxy-azidation resulting of the insertion of diazo compounds into azidobenziodoxolone was detected in low yield. Important optimizations would be required for a selective formation of the desired product. Szabó and co-workers have reported one example of oxy-fluorination with a benziodoxole reagent.[232] The reaction was catalyzed with rhodium and utilized a diazo ketone substrate, which was not tolerated in our methodologies. So far, the insertion of secondary ligands other than oxygen has not been possible, as illustrated by our attempt to use ethynylbenziodazolone (EBZ) reagents to access alkynylated α-amino acids derivatives.[230] It is clear that the good combination of hypervalent iodine reagents, diazo compounds and catalyst could provide various transformations of this kind. The identification of carbene precursors other than diazo compound could be also rewarding for the development of new methodologies. For example, an interesting preliminary result has been obtained utilizing [1.1.1]propellane (**9.1**) as carbene precursor (Scheme 113. B). In this case, a cyclobutane copper carbene intermediate is probably involved, and

oxy-alkynylation reaction with TIPS-EBX (**9.2**) resulted in a functionalized molecule that could be easily employed in further transformations.[355]



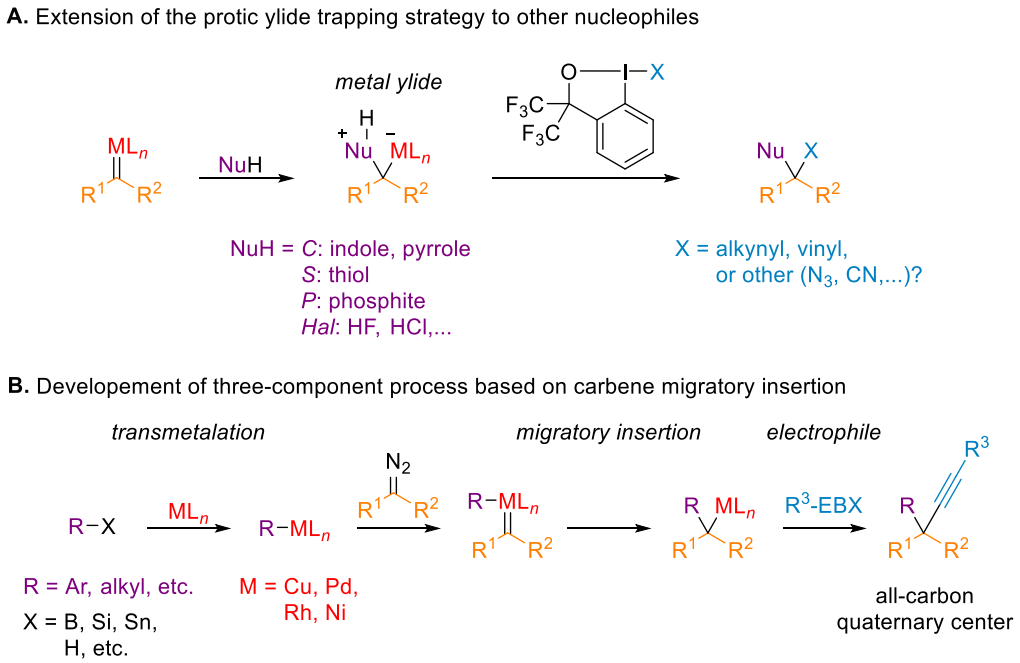
Scheme 113. Proposed future directions for atom-economical reactions of benziodoxol(on)e reagents with metal-carbene intermediate.

Several other classes of protic nucleophiles, appropriate to generate ylide intermediates, such as indoles,[356] pyrroles,[201b] or thiols[357] could be employed in three-component reactions for the creation of new C-C or C-S bonds (Scheme 114. A). The investigation of other hypervalent iodine electrophiles could be also envisaged. Another potential interesting approach based on metal-carbene migratory insertion could unlock new difunctionalization reactions with simultaneous creation of two C-C bonds, that could result in the formation of complex all-carbon quaternary center (Scheme 114. B).[204] Various transition metals such as palladium, copper or rhodium have been successfully employed as catalysts for the initial transmetalation step. A main challenge of this concept would be to avoid the potential cross-coupling products between the nucleophiles and the hypervalent iodine reagents.

[355] a) D. Lasányi, G. L. Tolnai, *Org. Lett.* **2019**, *21*, 10057; b) S. Yu, A. Noble, R. B. Bedford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2019**, *141*, 20325.

[356] a) M. Li, X. Guo, W. Jin, Q. Zheng, S. Liu, W. Hu, *Chem. Commun.* **2016**, *52*, 2736; b) See: ref 201a.

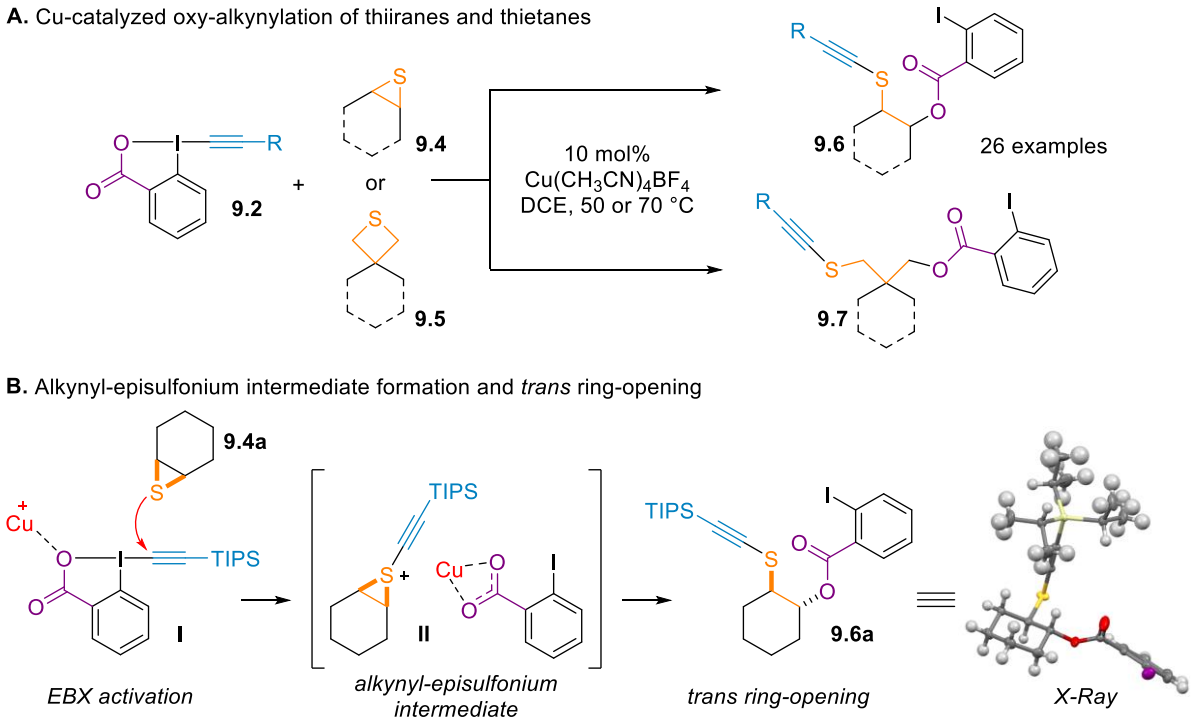
[357] a) G. Xiao, C. Ma, D. Xing, W. Hu, *Org. Lett.* **2016**, *18*, 6086; b) G. Xiao, C. Ma, X. Wu, D. Xing, W. Hu, *J. Org. Chem.* **2018**, *83*, 4786.



Scheme 114. Possibilities of new difunctionalization of metal carbene via three-component reaction.

Finally, other important points not directly linked to the core subject of this thesis, deserve comments. In the course of this research work, new methods for the preparation of VBX reagents have been disclosed. Notably, the synthesis of alkyl-substituted VBX reagents is now established, as well as the synthesis of benziodoxole derivatives. While the synthetic routes still require improvements, especially concerning the precursor materials, the application of VBX reagents in new methodologies can be expected in various area of chemistry. Little is known about the association of copper catalysts with EBX and VBX reagents (see section 2.2.3.2.). The activation of these iodine(III) reagents by cationic copper(I) salts has been advantageous in the reactions presented in this work, but is not limited to the functionalization of diazo compounds. An interesting atom-economical oxy-alkynylation of thiiranes **9.4** and thietanes **9.5** has been developed in collaboration with Julien Borrel, using such paradigm (Scheme 115. A). Two examples of oxy-vinylation with VBX reagents have been reported as well. The key alkynylsulfonium intermediate **II** is believe to be formed by nucleophilic attack of the episulfide **9.4a** on the activated Cu-EBX complex **I**. Exclusive *trans* ring-opening of sulfonium **II** by the benzoate nucleophile was supported by the X-ray structure analysis of the cyclic derivative **9.6a** (Scheme 115. B).[358]

[358] J. Borrel, G. Pisella, J. Waser, *Org. Lett.* **2020**, *22*, 422.



Scheme 115. Copper-catalyzed oxy-alkynylation of C-S bonds in thiiranes and thietanes with hypervalent iodine reagents.

Beyond the difunctionalization of diazo compounds, the association of inexpensive and earth-abundant copper with hypervalent iodine reagents can open new directions for vinylation and alkynylation strategies.

10

Experimental Part

10. Experimental Part

10.1. General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. Heating was realized using heating blocks/mantles with external temperature control, unless indicated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et_2O, CH_3CN, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 10 ppm, *Karl-Fischer* titration). The solvents were degassed by Freeze-Pump-Thaw method when mentioned. All chemicals were purchased from Acros, Aldrich, TCI, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC aluminium plates and visualized with UV light, permanganate stain, CAN stain or Anisaldehyde stain. Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. ^{1}H NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in $CDCl_3$, CD_2Cl_2, DMSO-d_6, C_6D_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal dichloromethane signal at 5.32 ppm, the internal DMSO signal at 2.50 ppm, the internal C_6D_6 signal at 7.16 ppm or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation).^{13}C NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz spectrometer in $CDCl_3$, CD_2Cl_2, DMSO-d_6, C_6D_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal dichloromethane signal at 54.0 ppm, the internal DMSO signal at 39.5 ppm, the internal C_6D_6 signal at 128.4 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, br = broad). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API (Waters) or (APPI) LTQ Orbitrap ELITE ETD (Thermo Fisher). HPLC measurements were done on a Agilent 1260 Infinity autosampler using a CHIRALPAK IA, IB, IC or ID column from DAICEL Chemical. The diffraction data for crystal structures were collected at low temperature using Cu (323) or Mo (520) K_α radiation on a Rigaku SuperNova dual system in combination with Atlas type CCD detector. The data reduction and correction were carried out by *CrysAlis^{Pro}*.[359] The solutions and refinements were performed by *SHELXT*[360] and *SHELXL*[361], respectively. The crystal structures were refined using full-matrix least-squares based on F^2 with all non-H atoms defined in anisotropic manner. Hydrogen atoms were placed in calculated positions by means of the "riding" model.

CAUTION: Diazo compounds are toxic and potentially explosive and should be handled with care in a well-ventilated hood.[175]
CAUTION: Benziodoxol(on)es are high energy compounds and should be manipulated with care.

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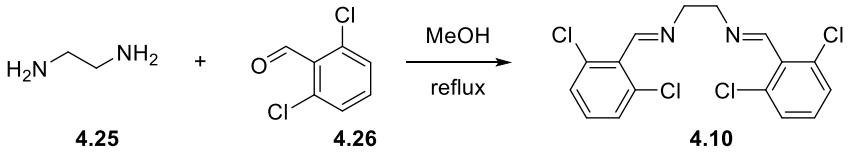
[359] *CrysAlis^{Pro}*, Rigaku Oxford Diffraction, release 1.171.40.68a, **2019**.
[360] *SHELXT* - Integrated space-group and crystal-structure determination¸ G. M. Sheldrick**,** *Acta Crystallogr.*, *Sect. A* **2015**, *71*, 3.
[361] *SHELXL* - Crystal structure refinement, G. M. Sheldrick**,** *Acta Crystallogr.*, *Sect. C* **2015**, *71*, 3.

10.2. Unusual Low-Temperature Intramolecular [4+2] Cycloaddition of Allenes with Arenes for the Synthesis of Diene Ligands

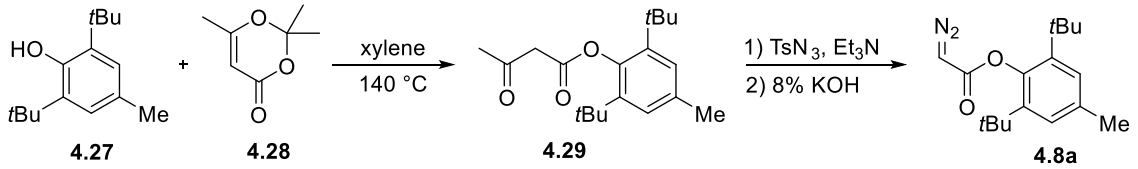
(1*E*,1'*E*)-*N*,*N*'-(Ethane-1,2-diyl)bis(1-(2,6-dichlorophenyl)methanimine) (4.10)



Ethane-1,2-diamine (**4.25**) (0.670 mL, 10.0 mmol, 1.00 equiv) and 2,6-dichlorobenzaldehyde (**4.26**) (3.50 g, 20.0 mmol, 2.00 equiv) were dissolved in MeOH (100 mL). The reaction mixture was stirred under reflux for 5 h. It was allowed to cool to room temperature and the resulting precipitate was collected by vacuum filtration. Recrystallization in EtOH (30 mL) afforded (1*E*,1'*E*)-*N,N'*-(ethane-1,2-diyl)bis(1-(2,6-dichlorophenyl)methanimine) **4.10** as white crystals (2.39 g, 6.39 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 2H, N=C*H*), 7.40 – 7.29 (m, 4H, *Ar*), 7.20 (dd, *J* = 8.8, 7.3 Hz, 2H, *Ar*), 4.14 (s, 4H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 134.7, 132.8, 130.2, 128.7, 62.2. The values of the NMR spectra are in accordance with reported literature data.[362]

10.2.1. Preparation of Diazo Compounds

2,6-Di-*tert*-butyl-4-methylphenyl 2-diazoacetate (4.8a)



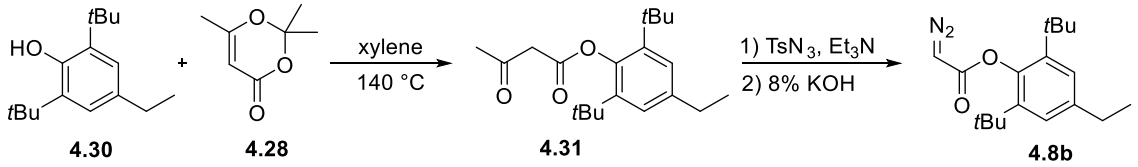
Following a reported procedure,[229] a mixture of 2,6-di-*tert*-butyl-4-methylphenol (**4.27**) (5.51 g, 25.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4.28**) (3.32 mL, 25.0 mmol, 1.00 equiv), and xylene (5 mL) was stirred at 140 °C for 1.5 h. After cooling to room temperature, the reaction mixture was directly loaded on silica and was purified by column chromatography using EtOAc/pentane 2:98 as eluent to afford 2,6-di-*tert*-butyl-4-methylphenyl 3-oxobutanoate (**4.29**) as a pale yellow solid (5.77 g, 19.0 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.08 (s, 0.22H, O*H* of enol form), 7.31 – 7.24 (m, 1H, Ar*H* of enol and keto form), 7.24 – 7.18 (m, 2H, Ar*H* of enol and keto form), 5.38 (s, 0.2H, vinyl *H* of enol form), 3.81 (s, 1.56H, CH_3COCH_2 of keto form), 3.03 (m, 2H, 2 x C*H*$(CH_3)_2$ of enol and keto form), 2.41 (s, 2.32H, CH_3COCH_2 of keto form), 2.08 (s, 0.6H, CH_3 of enol form), 1.28 – 1.21 (m, 12H, 2 x CH(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$), Enol form: δ 177.7, 171.5, 144.5, 140.5, 126.5, 123.9, 88.7, 23.7, 22.7, 21.4; ^{13}C NMR (101 MHz, $CDCl_3$), Keto form: δ 199.9, 165.7, 145.1, 140.2, 126.8, 124.0, 49.6, 30.4, 27.4, 27.3. The values of the NMR spectra are in accordance with reported literature data.[229]

Following a reported procedure,[229] to a solution of 2,6-di-*tert*-butyl-4-methylphenyl 3-oxobutanoate (**4.29**) (5.48 g, 18.00 mmol, 1.00 equiv) in MeCN (22 mL) was added triethylamine (3.26 mL, 23.40 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (3.9 g, 19.8 mmol, 1.1 equiv) in MeCN (22 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (90 mL) was added and stirred vigorously for 4 h. The reaction mixture was diluted with water (50 mL), extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced

[362] J. C. Andrez, *Tetrahedron Lett.* **2009**, *50*, 4225.

pressure. The crude product was purified by column chromatography using Et_2O/pentane 2:98 as eluent to afford 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) as a yellow solid (4.80 g, 16.64 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 2H, Ar*H*), 5.00 (s, 1H, C*H*N_2), 2.32 (s, 3H, ArC*H*$_3$), 1.36 (s, 18H, 2 x *t*Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 145.1, 142.4, 134.8, 127.0, 47.3, 35.3, 31.5, 21.5. The values of the NMR spectra are in accordance with reported literature data.[363]

2,6-Di-*tert*-butyl-4-ethylphenyl 2-diazoacetate (4.8b)

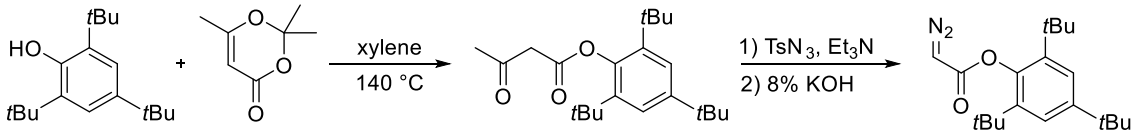


Following a slightly modified procedure,[229] a mixture of 2,6-di-*tert*-butyl-4-ethylphenol (**4.30**) (2.34 g, 10.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4.28**) (1.90 g, 12.0 mmol, 1.20 equiv), and xylene (2 mL) was stirred at 140 °C for 2 h. After cooling to room temperature, the xylene was evaporated and the residue was purified by flash column chromatography using EtOAc/pentane 2:98 as eluent to afford 2,6-di-*tert*-butyl-4-ethylphenyl 3-oxobutanoate (**4.31**) as a white solid (2.75 g, 8.64 mmol, 86%). M.p. 84.5 – 86.6 °C; R_f = 0.34 (EtOAc/pentane 2:98), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.15 (s, 0.54H, O*H* of enol form), 7.15 (s, 2H, Ar*H* of enol and keto form), 5.33 – 5.32 (m, 0.54H, vinyl *H* of enol form), 3.73 (s, 0.9H, CH_3COCH_2 of keto form), 2.66 – 2.60 (m, 2H, ArCH_2CH_3 of enol and keto form), 2.40 (s, 1.3H, CH_3COCH_2 of keto form), 2.07 (s, 1.7H, CH_3 of enol form), 1.34 (s, 8.3H, *t*Bu of keto form), 1.33 (s, 9.7H, *t*Bu of enol form), 1.27 – 1.23 (m, 3H, $ArCH_2CH_3$ of enol and keto form); ^{13}C NMR (100 MHz, $CDCl_3$), Enol form: δ 177.4, 173.3, 145.1, 142.2, 140.7, 125.7, 90.5, 35.3, 31.4, 28.8, 21.5, 15.4; ^{13}C NMR (100 MHz, $CDCl_3$), Keto form: δ 200.1, 167.7, 145.4, 141.8, 141.1, 125.9, 50.7, 35.3, 31.5, 30.8, 28.8, 15.4; IR (ν_{max}, cm^{-1}) 3000 (w), 2965 (m), 2875 (w), 1758 (w), 1724 (w), 1668 (m), 1633 (m), 1425 (m), 1403 (m), 1366 (w), 1318 (w), 1266 (w), 1230 (s), 1227 (s), 1206 (s), 1187 (s), 1146 (s), 982 (w), 933 (w); HRMS (ESI) Calcd for $C_{20}H_{30}NaO_3^+$ $[M+Na]^+$ 341.2087; found 341.2087.

Following a slightly modified procedure,[229] to a solution of 2,6-di-*tert*-butyl-4-ethylphenyl 3-oxobutanoate (**4.31**) (1.59 g, 5.00 mmol, 1.00 equiv) in acetonitrile (6 mL) was added triethylamine (660 mg, 6.50 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (1.1 g, 5.5 mmol, 1.1 equiv) in acetonitrile (6 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (25 mL) was added and the reaction mixture was stirred vigorously for 4 h. The reaction mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography using Et_2O/pentane 3:97 as eluent to afford 2,6-di-*tert*-butyl-4-ethylphenyl 2-diazoacetate (**4.8b**) as a yellow solid (1.10 g, 3.64 mmol, 73%). M.p. 126.5 – 128.0 °C; R_f = 0.35 (Et_2O/pentane 3:97), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 2H, Ar*H*), 5.01 (s, 1H, C*H*N_2), 2.63 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 1.37 (s, 18H, 2 x *t*Bu), 1.26 (t, *J* = 7.6 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 145.3, 142.4, 140.8, 125.8, 47.4, 35.4, 31.5, 28.8, 15.4; IR (ν_{max}, cm^{-1}) 3105 (m), 2964 (m), 2872 (w), 2475 (w), 2114 (s), 1718 (s), 1697 (s), 1597 (w), 1426 (m), 1364 (m), 1332 (s), 1263 (w), 1224 (m), 1191 (m), 1181 (s), 1108 (s), 928 (m); HRMS (ESI) Calcd for $C_{18}H_{26}N_2NaO_2^+$ $[M+Na]^+$ 325.1886; found 325.1887.

[363] M. P. Doyle, V. Bagheri, T. J. Wandless, N. K. Harn, D. A. Brinker, C. T. Eagle, K. L. Loh, *J. Am. Chem. Soc.* **1990**, *112*, 1906.

2,4,6-Tri-*tert*-butylphenyl 2-diazoacetate (4.8c)

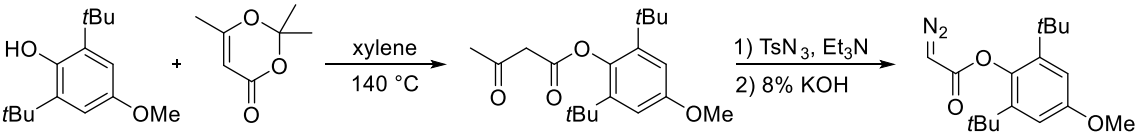


4.32 **4.28** **4.33** **4.8c**

Following a slightly modified procedure,[229] a mixture of 2,4,6-tri-*tert*-butylphenol (**4.32**) (2.62 g, 10.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4.28**) (1.90 g, 12.0 mmol, 1.20 equiv), and xylene (2 mL) was stirred at 140 °C for 2 h. After cooling to room temperature, the xylene was evaporated and the residue was purified by flash column chromatography using EtOAc/pentane 2:98 as eluent to afford 2,4,6-tri-*tert*-butylphenyl 3-oxobutanoate (**4.33**) as a white solid (2.65 g, 7.65 mmol, 76%). M.p. 88.9 – 89.6 °C; R_f = 0.40 (EtOAc/pentane 2:98), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 0.54H, O*H* of enol form), 7.35 – 7.32 (m, 2H, Ar*H* of enol and keto form), 5.33 (s, 0.54H, vinyl *H* of enol form), 3.73 (s, 0.92H, CH_3COCH_2 of keto form), 2.40 (s, 1.4H, CH_3 of keto form), 2.07 (s, 1.6H, CH_3 of enol form), 1.37 – 1.28 (m, 27H, 3 x *t*Bu of keto and enol form); ^{13}C NMR (100 MHz, $CDCl_3$), Enol form: δ 177.4, 173.2, 147.2, 144.7, 141.4, 123.3, 90.5, 35.6, 34.8, 31.6, 31.5, 21.5; ^{13}C NMR (100 MHz, $CDCl_3$), Keto form: δ 200.2, 167.7, 147.6, 145.1, 141.1, 123.5, 50.8, 35.5, 31.5, 30.7; IR (ν_{max}, cm^{-1}) 3001 (w), 2963 (s), 2912 (w), 2869 (w), 2113 (w), 1761 (m), 1725 (m), 1668 (m), 1633 (m), 1479 (w), 1431 (m), 1405 (m), 1365 (m), 1226 (s), 1210 (s), 1136 (m), 1108 (s), 978 (w); HRMS (ESI) Calcd for $C_{22}H_{34}NaO_3^+$ $[M+Na]^+$ 369.2400; found 369.2407. Two carbons of keto form were not resolved at 100 MHz.

Following a slightly modified procedure,[229] to a solution of 2,4,6-tri-*tert*-butylphenyl 3-oxobutanoate (**4.28**) (1.52 g, 5.00 mmol, 1.00 equiv) in acetonitrile (6 mL) was added triethylamine (660 mg, 6.50 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (1.1 g, 5.5 mmol, 1.1 equiv) in acetonitrile (6 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (25 mL) was added and the reaction mixture was stirred vigorously for 4 h. The reaction mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using Et_2O/pentane 3:97 as eluent to afford 2,4,6-tri-*tert*-butylphenyl 2-diazoacetate (**4.8c**) as a yellow solid (1.40 g, 4.24 mmol, 85%). M.p. 130.5 – 131.5 °C; R_f = 0.4 (Et_2O/pentane 2:98):, $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 2H, Ar*H*), 5.01 (br s, 1H, C*H*N_2), 1.38 (s, 18H, 2 x *t*Bu), 1.32 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 147.3, 145.0, 141.7, 123.4, 47.4, 35.6, 34.8, 31.6, 31.5; IR (ν_{max}, cm^{-1}) 3101 (w), 2962 (m), 2910 (m), 2872 (w), 2252 (w), 2113 (s), 1702 (s), 1596 (w), 1478 (w), 1432 (w), 1365 (s), 1338 (m), 1278 (w), 1192 (s), 1161 (s), 1135 (s), 1107 (s), 975 (w); HRMS (ESI) Calcd for $C_{20}H_{30}N_2NaO_2^+$ $[M+Na]^+$ 353.2199; found 353.2198.

2,6-Di-*tert*-butyl-4-methoxyphenyl 2-diazoacetate (4.8d)



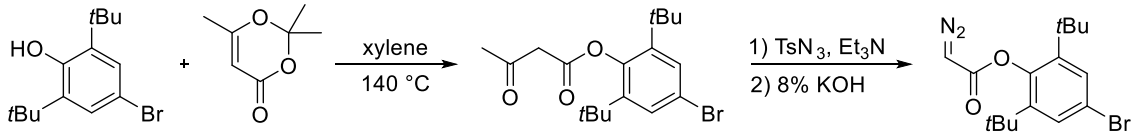
4.34 **4.28** **4.35** **4.8d**

Following a slightly modified procedure,[229] a mixture of 2,6-di-*tert*-butyl-4-methoxyphenol (**4.34**) (5.91 g, 25.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4.28**) (4.43 g, 30.0 mmol, 1.20 equiv), and xylene (5 mL) was stirred at 140 °C for 2 h. After cooling to room temperature, the xylene was evaporated and the residue was purified by flash column chromatography using EtOAc/pentane 3:97 as eluent to afford 2,6-di-*tert*-butyl-4-methoxyphenyl 3-oxobutanoate (**4.35**) as a white solid (6.64 g,

20.0 mmol, 80%). M.p. 67.0 – 70.5 °C; R_f = 0.46 (EtOAc/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.15 (s, 0.55H, O*H* of enol form), 6.87 (s, 2H, Ar*H* of enol and keto form), 5.32 (s, 0.55H, vinyl *H* of enol form), 3.80 (s, 3H, ArOC*H*$_3$ of enol and keto form), 3.73 (s, 0.9H, CH_3COCH_2 of keto form), 2.40 (s, 1.35H, CH_3COCH_2 of keto form), 2.07 (s, 1.65H, C*H*$_3$ of enol form), 1.33 (s, 8.1H, *t*Bu of keto form), 1.32 (s, 9.9H, *t*Bu of enol form); ^{13}C NMR (100 MHz, $CDCl_3$), Enol form: δ 177.4, 173.5, 156.2, 143.6, 140.7, 111.5, 90.4, 55.2, 35.6, 31.2, 21.5; ^{13}C NMR (100 MHz, $CDCl_3$), Keto form: δ 200.1, 167.9, 156.5, 143.3, 141.1, 111.7, 55.2, 50.6, 35.5, 31.3, 30.8; IR (ν_{max}, cm^{-1}) 2966 (s), 2913 (s), 2118 (w), 1758 (m), 1724 (m), 1634 (s), 1596 (m), 1408 (s), 1310 (m), 1223 (s), 1181 (s), 1143 (s), 1064 (s), 979 (w), 922 (w), 861 (w); HRMS (ESI) Calcd for $C_{19}H_{28}NaO_4^+$ $[M+Na]^+$ 343.1880; found 343.1884.

Following a slightly modified procedure,[229] to a solution of 2,6-di-*tert*-butyl-4-methoxyphenyl 3-oxobutanoate (**4.35**) (1.6 g, 5.0 mmol, 1.0 equiv) in acetonitrile (6 mL) was added triethylamine (660 mg, 6.50 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (1.1 g, 5.5 mmol, 1.1 equiv) in acetonitrile (6 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (25 mL) was added and stirred vigorously for 4 h. The reaction mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 5:95 as eluent to afford 2,6-di-*tert*-butyl-4-methoxyphenyl 2-diazoacetate (**4.8d**) as a yellow solid (600 mg, 1.97 mmol, 40%). M.p. (Dec.) 125.3 – 130.0 °C; R_f = 0.31 (EtOAc/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H, Ar*H*), 5.01 (s, 1H, C*H*N_2), 3.80 (s, 3H, ArOC*H*$_3$), 1.36 (s, 18H, 2 x *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 156.4, 143.9, 141.0, 111.6, 55.2, 47.4, 35.6, 31.4; IR (ν_{max}, cm^{-1}) 3105 (w), 2961 (m), 2114 (s), 1712 (s), 1593 (m), 1427 (w), 1365 (s), 1180 (s), 1149 (s), 1103 (w), 1064 (m), 919 (w), 862 (w); HRMS (ESI) Calcd for $C_{17}H_{24}N_2NaO_3^+$ $[M+Na]^+$ 327.1679; found 327.1679.

4-Bromo-2,6-di-*tert*-butylphenyl 2-diazoacetate (4.8e)



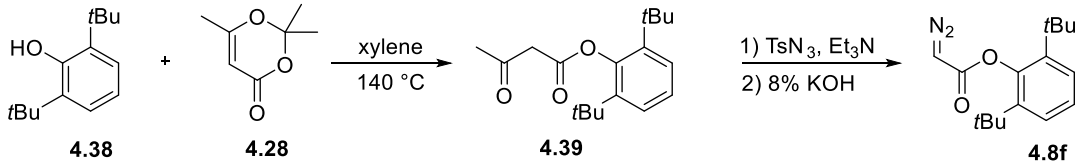
4.36 **4.28** **4.37** **4.8e**

Following a slightly modified procedure,[229] a mixture of 4-bromo-2,6-di-*tert*-butylphenol (**4.36**) (2.85 g, 10.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4.28**) (1.90 g, 12.0 mmol, 1.20 equiv), and xylene (2 mL) was stirred at 140 °C for 2 h. After cooling to room temperature, the xylene was evaporated and the residue was purified by flash column chromatography using EtOAc/pentane 2:98 as eluent to afford 4-bromo-2,6-di-tert-butylphenyl 3-oxobutanoate (**4.37**) as a pale yellow solid (3.00 g, 8.12 mmol, 81%). M.p. 86.3 – 91.6 °C; R_f = 0.4 (EtOAc/pentane 2:98), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 0.8H, O*H* of enol form), 7.44 – 7.41 (m, 2H, Ar*H* of enol and keto form), 5.32 (s, 0.8H, vinyl *H* of enol form), 3.73 (s, 0.4H, CH_3COCH_2 of keto form), 2.39 (s, 0.6H, CH_3COCH_2 of keto form), 2.08 (s, 2.4H, CH_3 of enol form), 1.32 (s, 3.6H, *t*Bu of keto form), 1.31 (s, 14.4H, *t*Bu of enol form); ^{13}C NMR (100 MHz, $CDCl_3$), Enol form: δ 178.0, 172.7, 146.5, 145.1, 129.3, 119.5, 90.2, 35.7, 31.2, 21.6; ^{13}C NMR (100 MHz, $CDCl_3$), Keto form: δ 199.6, 167.2, 146.8, 144.7, 129.6, 119.9, 50.5, 35.6, 31.3, 30.8; IR (ν_{max}, cm^{-1}) 3001 (w), 2965 (m), 2875 (w), 1762 (w), 1725 (w), 1672 (m), 1629 (m), 1565 (w), 1480 (w), 1407 (m), 1367 (m), 1313 (w), 1261 (m), 1218 (s), 1187 (s), 1148 (s), 1110 (s), 1026 (w), 976 (w), 933 (w); HRMS (ESI) Calcd for $C_{18}H_{25}BrNaO_3^+$ $[M+Na]^+$ 391.0879; found 391.0884.

Following a slightly modified procedure,[229] to a solution of 4-bromo-2,6-di-*tert*-butylphenyl 3-oxobutanoate (**4.37**) (1.85 g, 5.00 mmol, 1.00 equiv) in acetonitrile (6 mL) was added triethylamine (660 mg, 6.50 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl

azide (1.1 g, 5.5 mmol, 1.1 equiv) in acetonitrile (6 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (25 mL) was added and the reaction mixture was stirred vigorously for 4 h. The reaction mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using Et_2O/pentane 3:97 as eluent to afford 4-bromo-2,6-di-*tert*-butylphenyl 2-diazoacetate (**4.8e**) as a yellow solid (0.85 g, 2.4 mmol, 48%). M.p. 152.5 – 154.2 °C; R_f = 0.36 (Et_2O/pentane 3:97), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 2H, Ar*H*), 5.03 (brs, 1H, C*H*N_2), 1.35 (s, 18H, 2 x *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 146.7, 145.3, 129.4, 119.7, 47.5, 35.7, 31.3; IR (ν_{max}, cm^{-1}) 3119 (m), 2999 (w), 2967 (m), 2875 (w), 2479 (w), 2291 (w), 2121 (s), 1723 (s), 1700 (s), 1563 (m), 1366 (m), 1338 (s), 1261 (m), 1218 (m), 1184 (s), 1110 (s), 1031 (w), 920 (m); HRMS (ESI) Calcd for $C_{16}H_{22}BrN_2O_2^+$ $[M+H]^+$ 353.0859; found 353.0860.

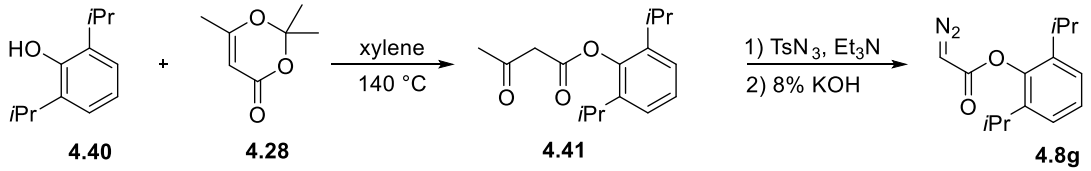
2,6-Di-*tert*-butylphenyl 2-diazoacetate (4.8f)



Following a slightly modified procedure,[229] a mixture of 2,6-di-*tert*-butylphenol (**4.38**) (2.06 g, 10.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4.28**) (1.90 g, 12.0 mmol, 1.20 equiv), and xylene (2 mL) was stirred at 140 °C for 2 h. After cooling to room temperature, the xylene was evaporated and the residue was purified by flash column chromatography using EtOAc/pentane 2:98 as eluent to afford 2,6-di-*tert*-butylphenyl 3-oxobutanoate (**4.39**) as a pale yellow solid (2.40 g, 8.26 mmol, 83%). M.p. 61.4 – 62.0 °C; R_f = 0.30 (EtOAc/pentane 2:98)3, $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.11 (s, 0.95H, O*H* of enol form), 7.33 (d, *J* = 7.9 Hz, 2H, Ar*H* of enol and keto form), 7.15 (dd, *J* = 8.3, 7.5 Hz, 1H, Ar*H* of enol and keto form), 5.34 (d, *J* = 0.8 Hz, 0.95H, vinyl *H* of enol form), 3.73 (s, 0.1H, CH_3COCH_2 of keto form), 2.40 (s, 0.15H, CH_3 of keto form), 2.08 (s, 2.85H, CH_3 of enol form), 1.35 (s, 0.9H, *t*Bu of keto form), 1.34 (s, 17.1H, *t*Bu of enol form); ^{13}C NMR (100 MHz, $CDCl_3$), Enol form: δ 177.5, 173.1, 147.3, 142.7, 126.2, 125.7, 90.4, 35.4, 31.4, 21.53; IR (ν_{max}, cm^{-1}) 3079 (w), 2962 (w), 2871 (w), 1758 (w), 1724 (w), 1630 (m), 1481 (w), 1403 (m), 1364 (m), 1317 (m), 1270 (m), 1221 (s), 1183 (s), 1147 (s), 1110 (s), 1024 (w), 977 (m), 933 (m); HRMS (ESI) Calcd for $C_{18}H_{26}NaO_3^+$ $[M+Na]^+$ 313.1774; found 313.1776. Keto form carbons were not resolved at 100 MHz.

Following a slightly modified procedure,[229] to a solution of 2,6-di-*tert*-butylphenyl 3-oxobutanoate (**4.39**) (1.45 g, 5.00 mmol, 1.00 equiv) in acetonitrile (6 mL) was added triethylamine (660 mg, 6.50 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (1.1 g, 5.5 mmol, 1.1 equiv) in acetonitrile (6 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (25 mL) was added and the reaction mixture was stirred vigorously for 4 h. The reaction mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using Et_2O/pentane 3:97 as eluent to afford 2,6-di-*tert*-butylphenyl 2-diazoacetate (**4.8f**) as a yellow solid (0.96 g, 3.5 mmol, 70%). M.p. 88.6 – 90.7 °C; R_f = 0.32 (Et_2O/pentane 3:97), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.9 Hz, 2H, Ar*H*), 7.15 (dd, *J* = 8.3, 7.5 Hz, 1H, Ar*H*), 5.02 (br s, 1H, C*H*N_2), 1.38 (s, 18H, 2 x *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 147.5, 143.0, 126.3, 125.8, 47.5, 35.4, 31.5; IR (ν_{max}, cm^{-1}) 3108 (w), 3002 (w), 2962 (w), 2915 (w), 2873 (w), 2111 (s), 1714 (s), 1579 (w), 1483 (w), 1417 (w), 1369 (s), 1358 (s), 1338 (m), 1272 (w), 1224 (m), 1185 (s), 1152 (s), 1112 (s); HRMS (ESI) Calcd for $C_{16}H_{22}N_2NaO_2^+$ $[M+Na]^+$ 297.1573; found 297.1578.

2,6-Di*iso*propylphenyl 2-diazoacetate (4.8g)

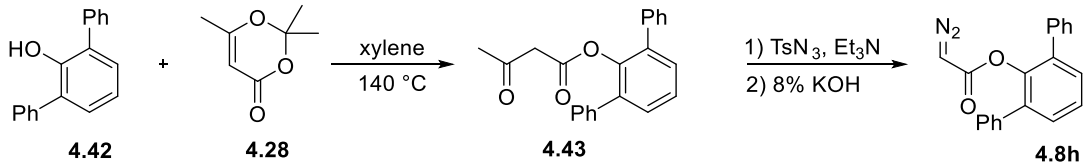


4.40 **4.28** **4.41** **4.8g**

Following a slightly modified procedure,[229] a mixture of 2,6-di*iso*propylphenol (**4.40**) (4.46 g, 25.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4.28**) (4.43 g, 30.0 mmol, 1.20 equiv), and xylene (5 mL) was stirred at 140 °C for 2 h. After cooling to room temperature, the xylene was evaporated and the residue was purified by flash column chromatography using EtOAc/pentane 2:98 as eluent to afford 2,6-di*iso*propylphenyl 3-oxobutanoate (**4.41**) as a colorless thick oil (5.00 g, 19.1 mmol, 76%). R_f = 0.35 (EtOAc/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.08 (s, 0.22H, O*H* of enol form), 7.31 – 7.24 (m, 1H, Ar*H* of enol and keto form), 7.24 – 7.18 (m, 2H, Ar*H* of enol and keto form), 5.38 (s, 0.2H, vinyl *H* of enol form), 3.81 (s, 1.56H, CH_3COCH_2 of keto form), 3.03 (m, 2H, 2 x $CH(CH_3)_2$ of enol and keto form), 2.41 (s, 2.32H, CH_3COCH_2 of keto form), 2.08 (s, 0.6H, CH_3 of enol form), 1.28 – 1.21 (m, 12H, 2 x $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$), Enol form: δ 177.7, 171.5, 144.5, 140.5, 126.5, 123.9, 88.7, 23.7, 22.7, 21.4; ^{13}C NMR (100 MHz, $CDCl_3$), Keto form: δ 199.9, 165.7, 145.1, 140.2, 126.8, 124.0, 49.6, 30.4, 27.4, 27.3; IR (ν_{max}, cm^{-1}) 2966 (m), 2876 (w), 1760 (m), 1723 (m), 1634 (w), 1447 (m), 1410 (w), 1360 (m), 1315 (m), 1222 (s), 1140 (s), 1102 (m), 1053 (w), 976 (w); HRMS (ESI) Calcd for $C_{16}H_{22}NaO_3^+$ $[M+Na]^+$ 285.1461; found 285.1467.

Following a slightly modified procedure,[229] to a solution of 2,6-di*iso*propylphenyl 3-oxobutanoate (**4.41**) (1.31 g, 5.00 mmol, 1.00 equiv) in acetonitrile (6 mL) was added triethylamine (660 mg, 6.50 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (1.1 g, 5.5 mmol, 1.1 equiv) in acetonitrile (6 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (25 mL) was added and stirred vigorously for 4 h. The reaction mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using Et_2O/pentane 3:97 as eluent to afford 2,6-di*iso*propylphenyl 2-diazoacetate (**4.8g**) as a yellow thick oil (620 mg, 2.52 mmol, 50%). R_f = 0.36 (Et_2O/pentane 3:97), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 1H, Ar*H*), 7.23 – 7.20 (m, 2H, Ar*H*), 5.09 (br s, 1H, CHN_2), 3.05 (sept, *J* = 6.9 Hz, 2H, 2 x $CH(CH_3)_2$), 1.27 (d, *J* = 6.9 Hz, 12H, 2 x $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 145.1, 140.8, 126.7, 123.9, 46.3, 27.5, 23.4. The characterization data slightly differ from the reported values.[364]

[1,1':3',1''-Terphenyl]-2'-yl 2-diazoacetate (4.8h)



4.42 **4.28** **4.43** **4.8h**

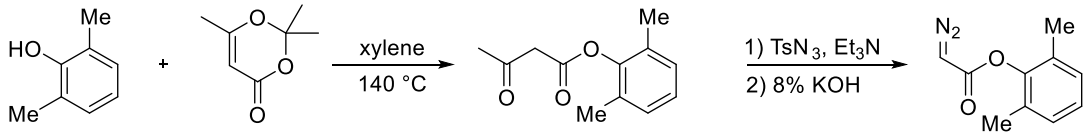
Following a slightly modified procedure, a mixture of [1,1':3',1''-terphenyl]-2'-ol (**4.42**) (2.46 g, 10.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4.28**) (1.90 g, 12.0 mmol, 1.20 equiv), and xylene (2 mL) was stirred at 140 °C for 2 h. After cooling to room temperature, the xylene was evaporated and the residue was purified by flash column chromatography using EtOAc/pentane 10:90 as eluent to afford [1,1':3',1''-terphenyl]-2'-yl 3-oxobutanoate (**4.43**) as a white solid (2.91 g, 8.81 mmol, 88%). M.p. 80.2 – 81.3 °C; R_f = 0.38 (EtOAc/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$)

[364] D. A. Nicewicz, J. S. Johnson, *J. Am. Chem. Soc.* **2005**, *127*, 6170.

δ 11.47 (s, 0.08H, O*H* of enol form), 7.51 – 7.31 (m, 13H, Ar*H* of enol and keto form), 4.89 (s, 0.08H, vinyl *H* of enol form), 3.12 (s, 1.8H, CH_3COCH_2 of keto form), 1.83 (s, 0.25H, CH_3 of enol form), 1.69 (s, 2.75H, CH_3 of keto form); ^{13}C NMR (100 MHz, $CDCl_3$), Enol form: δ 176.9, 170.5, 144.4, 137.7, 136.0, 128.9, 128.2, 127.4, 126.5, 88.9, 21.2; ^{13}C NMR (100 MHz, $CDCl_3$), Keto form: δ 199.3, 165.1, 144.7, 137.5, 135.8, 130.1, 129.0, 128.4, 127.7, 126.8, 49.6, 29.0; IR (ν_{max}, cm^{-1}) 3058 (w), 3032 (w), 1957 (w), 1888 (w), 1760 (s), 1721 (s), 1632 (w), 1601 (w), 1500 (w), 1463 (m), 1422 (m), 1361 (m), 1319 (m), 1223 (m), 1175 (s), 1128 (s), 1077 (w), 1022 (w), 975 (w), 921 (m); HRMS (ESI) Calcd for $C_{22}H_{18}NaO_3^+$ $[M+Na]^+$ 353.1148; found 353.1149. One carbon of enol form was not resolved at 100 MHz.

Following a slightly modified procedure, to a solution of [1,1':3',1''-terphenyl]-2'-yl 3-oxobutanoate (**4.43**) (1.65 g, 5.00 mmol, 1.00 equiv) in acetonitrile (6 mL) was added triethylamine (660 mg, 6.50 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (1.1 g, 5.5 mmol, 1.1 equiv) in acetonitrile (6 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (25 mL) was added and stirred vigorously for 4 h. The reaction mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using Et_2O/pentane 10:90 as eluent to afford [1,1':3',1''-terphenyl]-2'-yl 2-diazoacetate (**4.8h**) as a yellow solid (0.71 g, 2.3 mmol, 45%). M.p. 130.3 – 135.6 °C; R_f = 0.22 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.32 (m, 13H, Ar*H*), 4.54 (s, 1H, C*H*N_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 144.6, 137.7, 136.2, 130.1, 129.0, 128.3, 127.5, 126.6, 46.4; IR (ν_{max}, cm^{-1}) 3115 (w), 3059 (w), 3032 (w), 2253 (w), 2115 (s), 1707 (s), 1599 (w), 1500 (w), 1462 (w), 1421 (w), 1367 (s), 1341 (m), 1229 (m), 1181 (s), 1143 (s), 1077 (w), 973 (w), 913 (m); HRMS (ESI) Calcd for $C_{20}H_{14}N_2NaO_2^+$ $[M+Na]^+$ 337.0947; found 337.0947.

2,6-Dimethylphenyl 2-diazoacetate (4.8i)

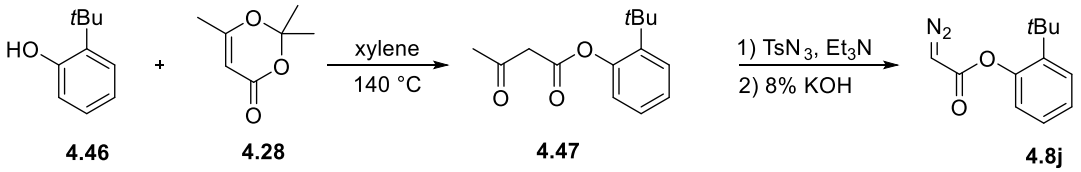


Following a slightly modified procedure,[229] a mixture of 2,6-dimethylphenol (**4.44**) (1.22 g, 10.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4.28**) (1.90 g, 12.0 mmol, 1.20 equiv), and xylene (2 mL) was stirred at 140 °C for 2 h. After cooling to room temperature, the xylene was evaporated and the residue was purified by flash column chromatography using EtOAc/pentane 3:97 as eluent to afford 2,6-dimethylphenyl 3-oxobutanoate (**4.45**) as a white solid (1.60 g, 7.76 mmol, 78%). M.p. 46.8 – 47.9 °C; R_f = 0.28 (EtOAc/pentane 3:97), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 0.12H, O*H* of enol form), 7.07 (s, 3H, Ar*H* of enol and keto form), 5.31 (m, 0.12H, vinyl *H* of enol form), 3.75 (s, 1.76H, CH_3COCH_2 of keto form), 2.38 (s, 2.64H, CH_3 of keto form), 2.19 (s, 5.28H, 2 x ArCH_3 of keto form), 2.16 (s, 0.72H, 2 x ArCH_3 of enol form), 2.06 (s, 0.36H, CH_3 of enol form); ^{13}C NMR (100 MHz, $CDCl_3$), Enol form: δ 177.7, 170.7, 147.6, 130.4, 128.5, 125.9, 88.7, 21.4, 16.2; ^{13}C NMR (100 MHz, $CDCl_3$), Keto form: δ 199.8, 164.8, 147.8, 130.1, 128.6, 126.2, 49.5, 30.4, 16.4; IR (ν_{max}, cm^{-1}) 2983 (w), 2926 (w), 1761 (s), 1722 (s), 1663 (w), 1631 (w), 1477 (m), 1444 (w), 1410 (w), 1363 (w), 1320 (m), 1262 (m), 1226 (m), 1167 (s), 1142 (s), 1093 (w), 1028 (w), 983 (w), 926 (w); HRMS (ESI) Calcd for $C_{12}H_{14}NaO_3^+$ $[M+Na]^+$ 229.0835; found 229.0843.

Following a slightly modified procedure,[229] to a solution of 2,6-dimethylphenyl 3-oxobutanoate (**4.45**) (1.03 g, 5.00 mmol, 1.00 equiv) in acetonitrile (6 mL) was added triethylamine (660 mg, 6.50 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (1.1 g, 5.5 mmol, 1.1 equiv) in acetonitrile (6 mL) was added slowly. The reaction mixture was allowed to warm

to room temperature and stirred for 20 h. 8% aqueous KOH solution (25 mL) was added and the reaction mixture stirred vigorously for 4 h. The reaction mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using Et_2O/pentane 5:95 as eluent to afford 2,6-dimethylphenyl 2-diazoacetate (**4.8i**) as a yellow solid (0.50 g, 2.6 mmol, 53%). M.p. 80.5 – 81.6 °C; R_f = 0.25 (Et_2O/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 3H, Ar*H*), 5.02 (brs, 1H, C*H*N_2), 2.21 (s, 6H, 2 x C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 147.8, 130.6, 128.5, 126.0, 46.2, 16.3. One carbon was not resolved in the literature reported values.[365]

2-(*Tert*-butyl)phenyl 2-diazoacetate (4.8j)



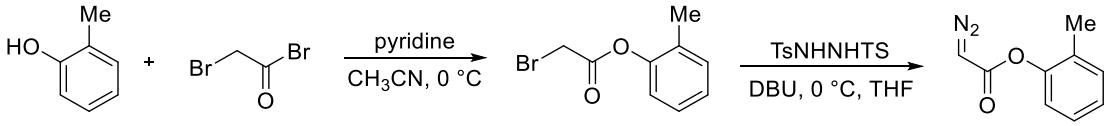
4.46 **4.28** **4.47** **4.8j**

Following a slightly modified procedure,[229] a mixture of 2-(*tert*-butyl)phenol (**4.46**) (1.50 g, 10.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4.28**) (1.90 g, 12.0 mmol, 1.20 equiv), and xylene (2 mL) was stirred at 140 °C for 2 h. After cooling to room temperature, the xylene was evaporated and the residue was purified by flash column chromatography using EtOAc/pentane 3:97 as eluent to afford 2-(*tert*-butyl)phenyl 3-oxobutanoate (**4.47**) as a colorless oil (1.70 g, 7.26 mmol, 73%). R_f = 0.29 (EtOAc/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 0.25H, O*H* of enol form), 7.42 – 7.39 (m, 1H, Ar*H* of enol and keto form), 7.32 – 7.14 (m, 2H, Ar*H* of enol and keto form), 7.09 – 7.01 (m, 1H, Ar*H* of enol and keto form), 5.29 (d, *J* = 0.8 Hz, 0.25H, vinyl *H* of enol form), 3.73 (s, 1.5H, CH_3COCH_2 of keto form), 2.38 (s, 2.25H, C*H*$_3$ of keto form), 2.06 (s, 0.75H, C*H*$_3$ of enol form), 1.35 (s, 9H, *t*Bu of enol and keto form); ^{13}C NMR (100 MHz, $CDCl_3$), Enol form: δ 177.7, 171.3, 148.5, 141.3, 127.2, 126.9, 125.8, 123.9, 89.6, 34.5, 30.1, 21.4; Keto form: δ 199.8, 165.9, 149.0, 140.9, 127.3, 127.0, 126.1, 123.7, 50.3, 34.4, 30.4, 30.2; IR (ν_{max}, cm^{-1}) 3066 (w), 2998 (w), 2962 (w), 2916 (w), 2873 (w), 1763 (s), 1723 (s), 1665 (w), 1629 (w), 1578 (w), 1487 (m), 1443 (m), 1408 (m), 1364 (m), 1316 (m), 1251 (m), 1221 (s), 1188 (s), 1143 (s), 1088 (m), 1051 (w), 1024 (w), 979 (w), 929 (w); HRMS (ESI) Calcd for $C_{14}H_{18}NaO_3^+$ $[M+Na]^+$ 257.1148; found 257.1161.

Following a slightly modified procedure,[229] to a solution of 2-(*tert*-butyl)phenyl 3-oxobutanoate (**4.47**) (1.17 g, 5.00 mmol, 1.00 equiv) in acetonitrile (6 mL) was added triethylamine (660 mg, 6.50 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (1.1 g, 5.5 mmol, 1.1 equiv) in acetonitrile (6 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (25 mL) was added and the reaction mixture was stirred vigorously for 4 h. The reaction mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using Et_2O/pentane 5:95 as eluent to afford 2-(*tert*-butyl)phenyl 2-diazoacetate (**4.8j**) as a yellow oil (0.21 g, 0.96 mmol, 20%). R_f = 0.22 (Et_2O/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.31 – 7.14 (m, 2H, Ar*H*), 7.09 (dd, *J* = 7.8, 1.5 Hz, 1H, Ar*H*), 5.03 (brs, 1H, C*H*N_2), 1.39 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 148.8, 141.2, 127.2, 126.8, 125.8, 124.1, 47.0, 34.5, 30.2; IR (ν_{max}, cm^{-1}) 3111 (w), 2995 (w), 2962 (w), 2913 (w), 2869 (w), 2483 (w), 2291 (w), 2112 (s), 1707 (s), 1486 (m), 1444 (w), 1365 (s), 1340 (m), 1286 (w), 1188 (s), 1147 (s), 1084 (s), 1051 (w), 975 (w), 929 (m); HRMS (ESI) Calcd for $C_{12}H_{14}N_2NaO_2^+$ $[M+Na]^+$ 241.0947; found 241.0951.

[365] B. Xu, J. A. Gartman, U. K. Tambar, *Tetrahedron* **2017**, *73*, 4150.

2-Methylphenyl 2-diazoacetate (4.8k)

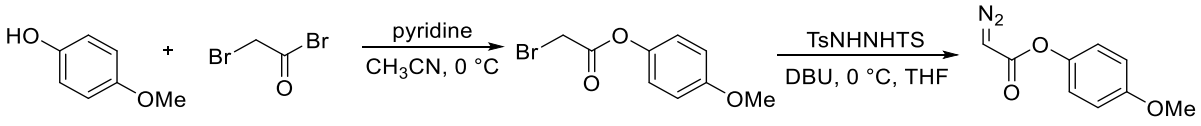


4.48 **4.49** **4.50** **4.8k**

Following a reported procedure,[366] bromoacetyl bromide (**4.49**) (1.31 mL, 15.0 mmol, 1.50 equiv) was added to a stirred solution of *o*-cresol (**4.48**) (1.08 g, 10.0 mmol, 1.00 equiv) and pyridine (1.61 mL, 20.0 mmol, 2.00 equiv) in acetonitrile (50 mL) at 0 °C over 10 min. The mixture was stirred for further 5 min at 0 °C and then quenched with water (30 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 2:98 as eluent to afford *o*-tolyl 2-bromoacetate (**4.50**) as a colorless oil (1.9 g, 8.3 mmol, 83%). R_f = 0.42 (EtOAc/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.16 (m, 3H, Ar*H*), 7.07 (dd, *J* = 7.7, 1.5 Hz, 1H, Ar*H*), 4.09 (s, 2H, C*H*$_2$), 2.26 (s, 3H, ArC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 148.9, 131.3, 130.0, 127.0, 126.5, 121.4, 25.2, 16.0; IR (ν_{max}, cm^{-1}) 3064 (w), 3032 (w), 2961 (w), 2116 (w), 1758 (s), 1586 (w), 1492 (m), 1461 (w), 1423 (w), 1261 (s), 1221 (m), 1174 (s), 1129 (s), 1112 (s), 1039 (w), 952 (w); HRMS (ESI) Calcd for $C_9H_{10}BrO_2^+$ $[M+H]^+$ 228.9859; found 228.9861.

Following a reported procedure, *N,N*′-Ditosylhydrazine (2.72 g, 8.00 mmol, 2.00 equiv) was added to a solution of *o*-tolyl 2-bromoacetate (**4.50**) (0.92 g, 4.0 mmol, 1.0 equiv) in tetrahydrofuran (20 mL) and the mixture was cooled to 0 °C. 1,8-Diazabicycloundec-7-ene (3.0 mL 20 mmol, 5.0 equiv) was added dropwise over 20 min at 0 °C. Upon completion of addition of 1,8-diazabicycloundec-7-ene the reaction was quenched by a saturated aqueous Na_2CO_3 solution (30 mL). The reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 1:20 Et_2O/pentane as eluent to afford *o*-tolyl 2-diazoacetate (**4.8k**) as a yellow oil (0.400 g, 2.27 mmol, 57%). R_f = 0.22 (Et_2O/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.13 (m, 3H, Ar*H*), 7.08 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar*H*), 4.99 (brs, 1H, C*H*N_2), 2.23 (s, 3H, ArC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 149.0, 131.1, 130.4, 126.9, 126.1, 122.0, 46.5, 16.1; IR (ν_{max}, cm^{-1}) 3115 (w), 2113 (s), 1702 (s), 1590 (w), 1492 (w), 1462 (w), 1366 (s), 1341 (m), 1219 (s), 1172 (s), 1144 (s), 1108 (s), 1041 (w), 975 (w), 928 (w); HRMS (ESI) Calcd for $C_9H_8N_2NaO_2^+$ $[M+Na]^+$ 199.0478; found 199.0479.

4-Methoxyphenyl 2-diazoacetate (4.8l)



4.51 **4.49** **4.52** **4.8l**

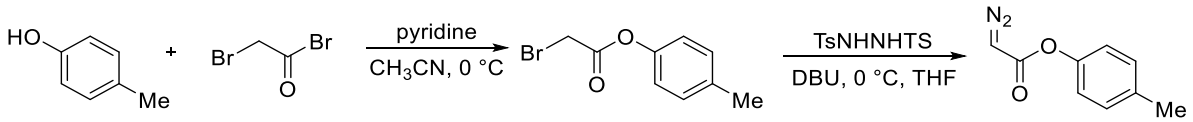
Following a reported procedure,[366] bromoacetyl bromide (**4.49**) (1.31 ml, 15.0 mmol, 1.50 equiv) was added to a stirred solution of 4-methoxyphenol (**4.51**) (1.24 g, 10.0 mmol, 1.00 equiv) and pyridine (1.61 mL, 20.0 mmol, 2.00 equiv) in acetonitrile (50 mL) at 0 °C over 10 min. The mixture was stirred for further 5 min at 0 °C and then quenched with water (30 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 5:95 as eluent to afford 4-methoxyphenyl 2-

[366] L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2013**, *135*, 58.

bromoacetate (**4.52**) as a colorless oil (2.2 g, 9.0 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 9.1 Hz, 2H, Ar*H*), 6.90 (d, *J* = 9.0 Hz, 2H, Ar*H*), 4.03 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 157.6, 143.9, 121.8, 114.5, 55.6, 25.5. The values of the NMR spectra are in accordance with reported literature data.[367]

Following a reported procedure,[366] *N,N'*-Ditosylhydrazine (2.72 g, 8.00 mmol, 2.00 equiv) was added to a solution of 4-methoxyphenyl 2-bromoacetate (**4.52**) (0.98 g, 4.0 mmol, 1.0 equiv) in tetrahydrofuran (20 mL) and the mixture was cooled to 0 °C. 1,8-Diazabicycloundec-7-ene (3.0 mL, 20 mmol, 5.0 equiv) was added dropwise over 20 min at 0 °C. Upon completion of the addition of 1,8-diazabicycloundec-7-ene, the reaction was quenched by a saturated aqueous Na_2CO_3 solution (30 mL). The reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using EtOAc/pentane 10:90 as eluent to afford 4-methoxyphenyl 2-diazoacetate (**4.8l**) as a yellow solid (0.600 g, 3.12 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 9.1 Hz, 2H, Ar*H*), 6.89 (d, *J* = 9.0 Hz, 2H, Ar*H*), 4.95 (brs, 1H, C*H*N_2), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 157.2, 143.9, 122.4, 114.4, 55.5, 46.6. The values of the NMR spectra are in accordance with reported literature data.[366]

***p*-Tolyl 2-diazoacetate (4.8m)**



4.53 **4.49** **4.54** **4.8m**

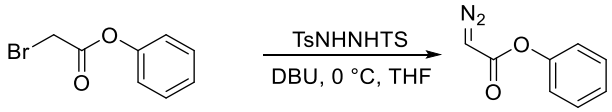
Following a reported procedure,[366] bromoacetyl bromide (**4.49**) (1.31 mL, 15.0 mmol, 1.50 equiv) was added to a stirred solution of *p*-cresol (**4.53**) (1.08 g, 10.0 mmol, 1.00 equiv) and pyridine (1.61 mL, 20.0 mmol, 2.00 equiv) in acetonitrile (50 mL) at 0 °C over 10 minutes. The mixture was stirred for further 5 minutes at 0 °C and then quenched with water (30 mL). The reaction mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford *p*-tolyl 2-bromoacetate (**4.54**) as a colorless oil (2.1 g, 9.2 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 2H, Ar*H*), 7.05 – 6.95 (m, 2H, Ar*H*), 4.04 (s, 2H, CH_2), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 148.4, 136.2, 130.2, 120.9, 25.7, 21.0. The values of the NMR spectra are in accordance with reported literature data.[368]

Following a reported procedure,[366] *N,N'*-Ditosylhydrazine (3.40 g, 10.0 mmol, 2.00 equiv) was added to a solution of *p*-tolyl 2-bromoacetate (**4.54**) (1.15 g, 5.00 mmol, 1.00 equiv) in tetrahydrofuran (20 mL) and the mixture was cooled to 0 °C. 1,8-Diazabicycloundec-7-ene (3.8 mL, 25 mmol, 5.0 equiv) was added dropwise over 20 minutes at 0 °C. The reaction was stirred 2 h at 0 °C before being quenched by a saturated aqueous Na_2CO_3 solution (30 mL). The reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford *p*-tolyl 2-diazoacetate (**4.8m**) as a yellow oil (0.450 g, 2.55 mmol, 51%). R_f = 0.33 (EtOAc/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.14 (m, 2H, Ar*H*), 7.03 – 6.98 (m, 2H, Ar*H*), 4.95 (br s, 1H, C*H*N_2), 2.34 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 135.7, 130.1, 121.5, 46.9, 21.0; IR (ν_{max}, cm^{-1}) 3115 (w), 2112 (s), 1699 (s), 1508 (m), 1364 (s),

[367] M.-A. Tehfe, S. Schweizer, A.-C. Chany, C. Ysacco, J.-L. Clément, D. Gigmes, F. Morlet-Savary, J.-P. Fouassier, M. Neuburger, T. Tschamber, N. Blanchard, J. Lalevée, *Chem. Eur. J.* **2014**, *20*, 5054.
[368] G. Himbert, D. Fink, K. Diehl, *Chem. Ber.* **1988**, *121*, 431.

1342 (s), 1193 (s), 1167 (s), 1143 (s), 923 (m), 831 (m), 728 (m); HRMS (ESI) Calcd for $C_9H_9N_2O_2^+$ [M+H]$^+$ 177.0659; found 177.0656. One carbon was not resolved at 100 MHz.

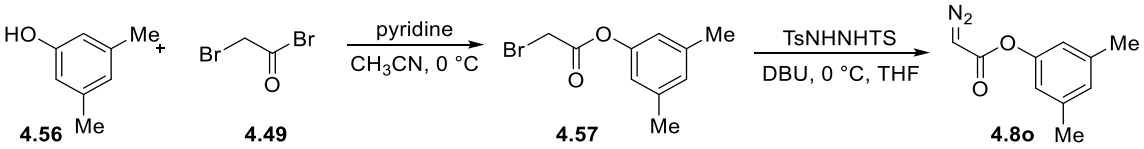
Phenyl 2-diazoacetate (4.8n)



4.55 **4.8n**

Following a reported procedure,[366] *N,N'*-Ditosylhydrazine (3.40 g, 10.0 mmol, 2.00 equiv) was added to a solution of phenyl 2-bromoacetate (**4.55**) (1.07 g, 5.00 mmol, 1.00 equiv) in tetrahydrofuran (20 mL) and the mixture was cooled to 0 °C. 1,8-Diazabicycloundec-7-ene (3.8 mL, 25 mmol, 5.0 equiv) was added dropwise over 20 minutes at 0 °C. The reaction was stirred 2 h at 0 °C before being quenched by a saturated aqueous Na_2CO_3 solution (30 mL). The reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 7:93 as eluent to afford phenyl 2-diazoacetate (**4.8n**) as a yellow oil (0.460 g, 2.84 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H, Ar*H*), 7.24 – 7.18 (m, 1H, Ar*H*), 7.08 (m, 2H, Ar*H*), 4.87 (br s, 1H, C*H*N_2). The values of the NMR spectra are in accordance with reported literature data.[369]

3,5-Dimethylphenyl 2-diazoacetate (4.8o)



4.56 **4.49** **4.57** **4.8o**

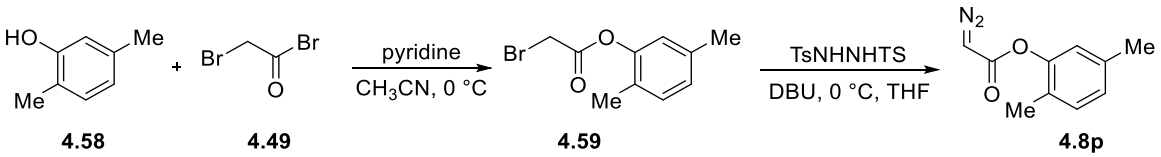
Following a reported procedure,[366] bromoacetyl bromide (**4.49**) (1.31 mL, 15.0 mmol, 1.50 equiv) was added to a stirred solution of 3,5-dimethylphenol (**4.56**) (1.22 g, 10.0 mmol, 1.00 equiv) and pyridine (1.61 mL, 20.0 mmol, 2.00 equiv) in acetonitrile (50 mL) at 0 °C over 10 minutes. The mixture was stirred for further 5 minutes at 0 °C and then quenched with water (30 mL). The reaction mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford 3,5-dimethylphenyl 2-bromoacetate (**4.57**) as a colorless oil (2.0 g, 8.3 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (tt, *J* = 1.6, 0.8 Hz, 1H, Ar*H*), 6.74 (dt, *J* = 1.5, 0.7 Hz, 2H, Ar*H*), 4.03 (s, 2H, CH_2), 2.32 (m, 6H, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 150.4, 139.6, 128.2, 118.7, 25.7, 21.4. The values of the NMR spectra are in accordance with reported literature data.[368]

Following a reported procedure,[366] *N,N'*-Ditosylhydrazine (3.40 g, 10.0 mmol, 2.00 equiv) was added to a solution of 3,5-dimethylphenyl 2-bromoacetate (**4.57**) (1.21 g, 5.00 mmol, 1.00 equiv) in tetrahydrofuran (20 mL) and the mixture was cooled to 0 °C. 1,8-Diazabicycloundec-7-ene (3.8 mL, 25 mmol, 5.0 equiv) was added dropwise over 20 minutes at 0 °C. The reaction was stirred 2 h at 0 °C before being quenched by a saturated aqueous Na_2CO_3 solution (30 mL). The reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford 3,5-dimethylphenyl 2-diazoacetate (**4.8o**) as a yellow oil (0.480 g, 2.52 mmol, 51%). R_f = 0.38 (EtOAc/pentane 5:95), $KMnO_4$;

[369] T. Torna, J. Shimokawa, T. Fukuyama, *Org. Lett.* **2007**, *9*, 3195.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (tt, *J* = 1.6, 0.8 Hz, 1H, Ar*H*), 6.75 (dt, *J* = 1.5, 0.8 Hz, 2H, Ar*H*), 4.94 (br s, 1H, C*H*N_2), 2.32 (d, *J* = 0.8 Hz, 6H, 2 x C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 150.5, 139.4, 127.8, 119.4, 46.9, 21.4; IR (ν_{max}, cm^{-1}) 3109 (w), 2922 (w), 2112 (s), 1701 (s), 1618 (m), 1364 (s), 1342 (m), 1292 (m), 1219 (s), 1161 (s), 1143 (s), 849 (m), 726 (m); HRMS (ESI) Calcd for $C_{10}H_{11}N_2O_2^+$ $[M+H]^+$ 191.0815; found 191.0812.

2,5-dimethylphenyl 2-diazoacetate (4.8p)

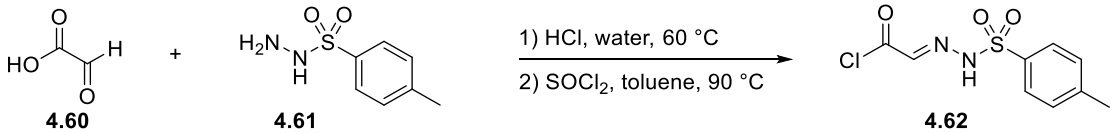


4.58 **4.49** **4.59** **4.8p**

Following a reported procedure,[366] bromoacetyl bromide (**4.49**) (1.31 mL, 15.0 mmol, 1.50 equiv) was added to a stirred solution of 2,5-dimethylphenol (**4.58**) (1.22 g, 10.0 mmol, 1.00 equiv) and pyridine (1.61 mL, 20.0 mmol, 2.00 equiv) in acetonitrile (50 mL) at 0 °C over 10 minutes. The mixture was stirred for further 5 minutes at 0 °C and then quenched with water (30 mL). The reaction mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford 2,5-dimethylphenyl 2-bromoacetate (**4.59**) as a colorless oil (1.9 g, 8.3 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.01 – 6.95 (m, 1H, Ar*H*), 6.88 – 6.81 (m, 1H, Ar*H*), 4.05 (s, 2H, C*H*$_2$), 2.32 (s, 3H, C*H*$_3$), 2.17 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 148.9, 137.2, 131.2, 127.5, 126.8, 122.0, 25.4, 21.0, 15.8. The values of the NMR spectra are in accordance with reported literature data.[368]

Following a reported procedure,[366] *N,N'*-Ditosylhydrazine (4.77 g, 14.0 mmol, 2.00 equiv) was added to a solution of 2,5-dimethylphenyl 2-bromoacetate (**4.59**) (1.70 g, 7.00 mmol, 1.00 equiv) in tetrahydrofuran (28 mL) and the mixture was cooled to 0 °C. 1,8-Diazabicycloundec-7-ene (5.3 mL, 35 mmol, 5.0 equiv) was added dropwise over 20 minutes at 0 °C. The reaction was stirred 2 h at 0 °C before being quenched by a saturated aqueous Na_2CO_3 solution (40 mL). The reaction mixture was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford 2,5-dimethylphenyl 2-diazoacetate (**4.8p**) as a yellow oil (0.802 g, 4.22 mmol, 60%). R_f = 0.43 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.7 Hz, 1H, Ar*H*), 6.96 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar*H*), 6.88 (d, *J* = 1.7 Hz, 1H, Ar*H*), 4.98 (br s, 1H, C*H*N_2), 2.32 (s, 3H, C*H*$_3$), 2.17 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 137.1, 131.0, 127.3, 127.1, 122.7, 46.7, 21.0, 15.9; IR (ν_{max}, cm^{-1}) 3110 (w), 2112 (s), 1701 (s), 1498 (m), 1365 (s), 1340 (s), 1183 (s), 1167 (s), 1143 (s), 920 (w), 831 (m), 730 (w); HRMS (ESI) Calcd for $C_{10}H_{10}N_2NaO_2^+$ $[M+Na]^+$ 213.0634; found 213.0632. One carbon was not resolved at 100 MHz.

***p*-Toluenesulfonylhydrazone of glyoxylic acid chloride (4.62)**



4.60 **4.61** **4.62**

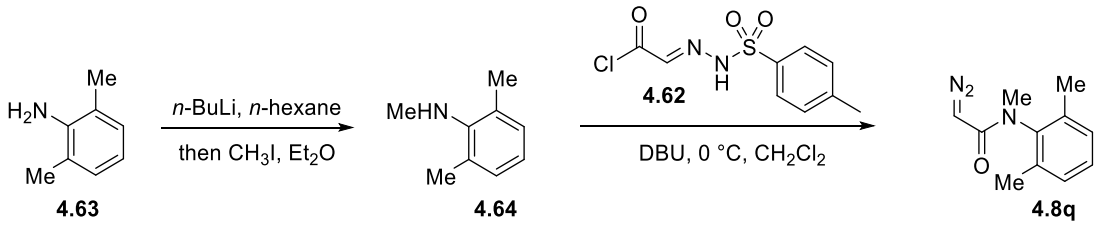
Following a modified procedure,[370] a solution of glyoxylic acid (**4.60**) (37.0 g, 50% in water, 0.25 mole, 1.00 equiv) in water (250 mL) was placed in a 500 mL Erlenmeyer flask and warmed to 60 °C. This solution was then treated with a warm (60 °C) solution of *p*-toluenesulfonylhydrazide (**4.61**) (47.0 g,

[370] C. J. Blankley, F. J. Sauter, H. O. House, J. H. Ham, R. E. Ireland, *Org. Synth.* **1969**, *49*, 22.

0.250 mole, 1.00 equiv) in aqueous hydrochloric acid (125 mL, 2.5 M, 0.310 mole, 1.25 equiv). The resulting mixture was stirred at 60 °C until all the hydrazine was solidified (about 5 minutes is required). The reaction mixture was cooled to room temperature and then allowed to stand in a refrigerator overnight, the solid was collected by filtration, washed with cold water (2 times), and allowed to dry for 2 days. Glyoxylic acid *p*-toluenesulfonylhydrazone was collected as a white solid (55.5 g, 0.23 mole, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (br s, 1H, CO_2H), 12.27 (br s, 1H, N*H*Ts), 7.73 – 7.67 (m, 2H, Ar*H*), 7.47 – 7.41 (m, 2H, Ar*H*), 7.18 (s, 1H, COC*H*N), 2.39 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6, 144.0, 137.5, 135.7, 129.9, 127.1, 21.1. The values of the NMR spectra are in accordance with reported literature data.[371]

Following a modified procedure,[370] thionyl chloride (6.03 mL, 83.0 mmol, 2.00 equiv) was added to a suspension of glyoxylic acid *p*-poluenesulfonylhydrazone (10.0 g, 41.3 mmol, 1.00 equiv) in dry toluene (50 mL). The reaction mixture was stirred at 85 °C for 30 min, until the gaz evolution has ceased. The resulting orange reaction mixture was then cooled to room temperature and filtered through Celite. The filtrate was recovered, concentrated under reduced pressure and the residual solid was treated with hot toluene (10 mL, 65 °C). The reaction mixture was cooled to room temperature and the solid was filtered, washed with cold toluene (2 x 10 mL) and then washed with pentane to afford *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (**4.62**) as pale yellow prisms (7.46 g, 28.6 mmol, 69 % yield). ^{1}H NMR (400 MHz, CD_3CN) δ 10.36 (br s, 1H, N*H*Ts), 7.86 – 7.75 (m, 2H, Ar*H*), 7.43 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.29 (d, *J* = 0.8 Hz, 1H, COC*H*N), 2.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3CN) δ 165.8, 146.5, 137.7, 135.8, 131.0, 128.7, 21.6. The values of the NMR spectra are in accordance with reported literature data.[372]

2-Diazo-*N*-(2,6-dimethylphenyl)-*N*-methylacetamide (4.8q)



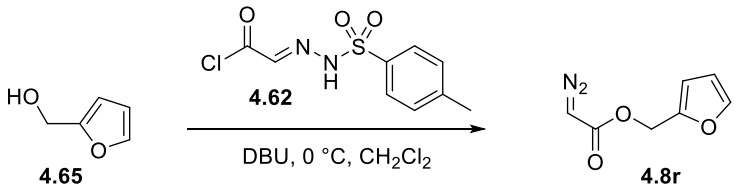
Following a slightly modified procedure,[373] a solution of *n*-BuLi (4.35 mL, 2.50 M in *n*-hexane, 11.0 mmol, 1.10 equiv) was added to a solution of 2,6-dimethylaniline (**4.63**) (1.23 mL, 10.0 mmol, 1.00 equiv) in *n*-hexane (15 mL) at -20 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The solvent of the reaction mixture was evaporated and the light-yellow solid was dissolved in diethyl ether (30 mL). The obtained solution was slowly added to a solution of iodomethane (0.65 mL, 10.50 mmol, 1.05 equiv) in diethyl ether (10.0 mL) at -20 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was then quenched with H_2O (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product *N*,2,6-trimethylaniline (**4.64**) was obtained as a yellow oil (1.28 g, 9.44 mmol, 94%) and used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.5 Hz, 2H, Ar*H*), 6.82 (t, *J* = 7.4 Hz, 1H, Ar*H*), 2.79 (s, 3H, NHCH_3),

[371] H. Lei, J. Atkinson, *J. Org. Chem.* **2000**, *65*, 2560.
[372] H. O. House, C. J. Blankley, *J. Org. Chem.* **1968**, *33*, 53.
[373] K. Liu, Q. Wu, W. Gao, Y. Mu, L. Ye, *Eur. J. Inorg. Chem.* **2011**, *2011*, 1901.

2.30 (s, 6H, 2 x C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 129.3, 129.1, 121.9, 35.5, 18.5. The values of the NMR spectra are in accordance with reported literature data.[374]

Following a slightly modified procedure,[375] to a solution of *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (**4.62**) (1.30 g, 5.00 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) were added *N*,2,6-trimethylaniline (**4.64**) (744 mg, 5.50 mmol, 1.10 equiv) and then DBU (1.89 mL, 12.5 mmol, 2.50 equiv) dropwise at 0 °C. After stirring for 2 h at the same temperature, the reaction was stirred 30 min at room temperature and then poured into saturated NH_4Cl solution (10 mL). The organic layer was then extracted with CH_2Cl_2 (3 x 10 mL), washed with saturated brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced. The crude product was purified by column chromatography using EtOAc/pentane 25:75 as eluent to afford 2-diazo-*N*-(2,6-dimethylphenyl)-*N*-methylacetamide (**4.8q**) as a yellow solid (609 mg, 3.00 mmol, 60%). R_f = 0.48 (EtOAc/pentane 25:75), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.07 (m, 3H, Ar*H*), 4.30 (s, 1H, CN_2H), 3.18 (s, 3H, NHC*H*$_3$), 2.21 (s, 6H, 2 x C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 140.0, 136.6, 129.1, 128.6, 46.2, 34.3, 17.7; IR (ν_{max}, cm^{-1}) 2989 (m), 2116 (s), 1706 (s), 1509 (m), 1369 (s), 1343 (m), 1216 (s), 1204 (s); HRMS (ESI) Calcd for $C_{11}H_{14}N_3O^+$ $[M+H]^+$ 204.1131; found 204.1128.

Furan-2-ylmethyl 2-diazoacetate (4.8r)

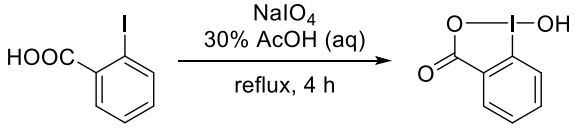


Following a slightly modified procedure,[375] to a solution of *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (**4.62**) (1.30 g, 5.00 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) were added furfuryl alcohol (**4.65**) (475 µL, 5.50 mmol, 1.10 equiv) and then DBU (1.89 mL, 12.5 mmol, 2.50 equiv) dropwise at 0 °C. After stirring for 2 h at the same temperature, the reaction was stirred 30 min at room temperature and then poured into saturated NH_4Cl solution (10 mL). The organic layer was then extracted with CH_2Cl_2 (3 x 10 mL), washed with saturated brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced. The crude product was purified by column chromatography using 1:30 EtOAc/pentane as eluent to afford furan-2-ylmethyl 2-diazoacetate (**4.8r**) as a yellow oil (534 mg, 3.21 mmol, 64%). M.p. 76 – 78 °C; R_f = 0.33 (EtOAc/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 1.9, 0.9 Hz, 1H, Ar*H*), 6.42 (dd, *J* = 3.3, 0.8 Hz, 1H, Ar*H*), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1H, Ar*H*), 5.14 (s, 2H, C*H*$_2$O), 4.78 (br s, 1H, CN_2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 149.5, 143.5, 111.0, 110.7, 58.3, 46.5; IR (ν_{max}, cm^{-1}) 3117 (m), 2112 (s), 1691 (s), 1383 (s), 1348 (s), 1238 (s), 1173 (s), 1153 (s), 1004 (s), 921 (m), 740 (s); HRMS (ESI) Calcd for $C_7H_6N_2NaO_3^+$ $[M+Na]^+$ 189.0271; found 189.0269.

[374] S. L. Cockroft, J. Perkins, C. Zonta, H. Adams, S. E. Spey, C. M. R. Low, J. G. Vinter, K. R. Lawson, C. J. Urch, C. A. Hunter, *Org. Biomol. Chem.* **2007**, *5*, 1062.
[375] T. Hashimoto, N. Uchiyama, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 14380.

10.2.2. Preparation of EBX Reagents

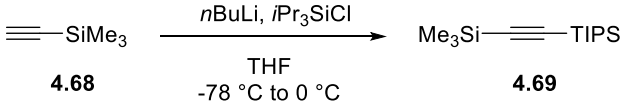
1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (4.67)



4.66 **4.67**

Following a reported procedure,[376] $NaIO_4$ (7.24 g, 33.8 mmol, 1.05 equiv) and 2-iodobenzoic acid (**4.66**) (8.00 g, 32.2 mmol, 1.00 equiv) were suspended in 30% (v/v) aq. AcOH (48 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (180 mL) and allowed to cool to room temperature, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 20 mL) and acetone (3 x 20 mL), and air-dried in the dark to give the pure product **4.67** as a white solid (8.3 g, 31 mmol, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (dd, *J* = 7.7, 1.4 Hz, 1H, Ar*H*), 7.97 (m, 1H, Ar*H*), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1H, Ar*H*), 7.71 (td, *J* = 7.6, 1.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4. The values of the NMR spectra are in accordance with reported literature data.[376]

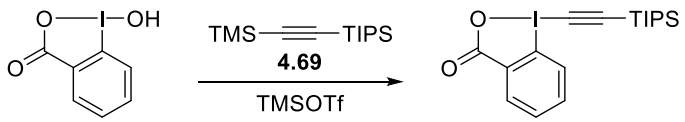
Tri*iso*propylsilyl trimethylsilylacetylene (4.69)



4.68 **4.69**

Following a reported procedure,[377] *n*BuLi (2.50 M in hexanes, 12.0 mL, 29.9 mmol, 0.98 equiv) was added dropwise to a stirred solution of ethynyltrimethylsilane (**4.68**) (3.0 g, 30 mmol, 1.0 equiv) in THF (48 mL) at -78 °C. The mixture was then warmed to 0 °C and stirred for 5 min. The mixture was then cooled back to -78 °C and chlorotri*iso*propylsilane (6.4 mL, 30 mmol, 1.0 equiv) was added dropwise. The mixture was then allowed to warm to room temperature and stirred overnight. A saturated solution of ammonium chloride (40 mL) was added, and the reaction mixture was extracted with diethyl ether (2 x 60 mL). The organic layer was washed with water and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain a colorless liquid which was further purified by Kugelrohr distillation (56 – 57 °C/0.25 mm of Hg) to yield **4.69** as a colorless liquid (7.16 g, 28.0 mmol, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (m, 21H, TIPS), 0.18 (s, 9H, TMS). The values of the NMR spectra are in accordance with reported literature data.[377]

1-[(Tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (4.9a)



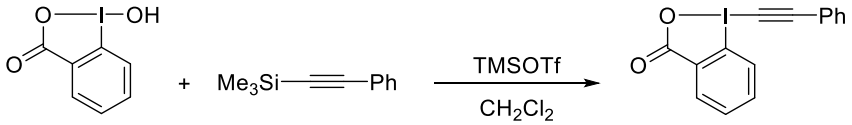
4.67 **4.9a**

Following a reported procedure,[378] 2-iodosylbenzoic acid (**4.67**) (21.7 g, 82.0 mmol, 1.00 equiv) was charged in oven-dried three-neck 1 L flask equipped with a magnetic stirrer. After 3 vacuum/nitrogen cycles, anhydrous acetonitrile (500 mL) was added *via* canula and cooled to 0 °C. Trimethylsilyltriflate (16.4 mL, 90.0 mmol, 1.10 equiv) was added dropwise *via* a dropping funnel over 30 min (no

[376] L. Kraszkiewicz, L. Skulski, *Arkivoc* **2003**, *2003*, 120.
[377] C. J. Helal, P. A. Magriotis, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 10938.
[378] J. P. Brand, J. Waser, *Angew. Chem. Int. Ed.* **2010**, *49*, 7304.

temperature increase was observed). After 15 min, (trimethylsilyl)(tri*iso*propylsilyl)acetylene (**4.69**) (23.0 g, 90.0 mmol, 1.10 equiv) was added *via* canula over 15 min (no temperature increase was observed). After 30 min, the suspension became an orange solution. After 10 min, pyridine (7.0 mL, 90 mmol, 1.1 equiv) was added *via* syringe. After 15 min, the reaction mixture was transferred in a one-neck 1L flask and reduced under vacuum until a solid was obtained. The solid was dissolved in CH_2Cl_2 (200 mL) and transferred in a 1 L separatory funnel. The organic layer was added and washed with 1 M HCl (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (2 x 200 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (ca. 120 mL) afforded **4.9a** as colorless crystals (30.1 g, 70.2 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (m, 1H, Ar*H*), 8.29 (m, 1H, Ar*H*), 7.77 (m, 2H, Ar*H*), 1.16 (m, 21H, TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 134.6, 132.3, 131.4, 131.4, 126.1, 115.6, 114.1, 64.6, 18.4, 11.1. The values of the NMR spectra are in accordance with reported literature data.[378]

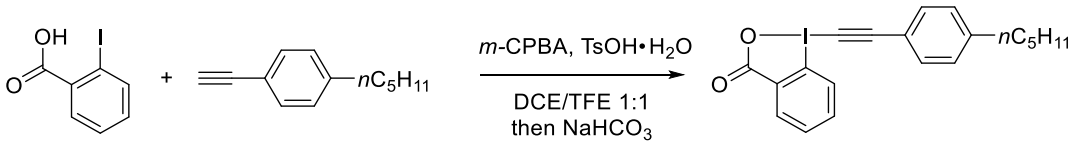
1-[Phenylethynyl]-1,2-benziodoxol-3(1*H*)-one (4.9b)



4.67 **4.70** **4.9b**

Following a reported procedure,[140b] trimethylsilyl triflate (7.50 mL, 41.5 mmol, 1.10 equiv) was added to a suspension of 2-iodosylbenzoic acid (**4.67**) (10.0 g, 37.7 mmol, 1.00 equiv) in CH_2Cl_2 (100 mL) at room temperature. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of trimethyl(phenylethynyl)silane (**4.70**) (8.10 mL, 41.5 mmol, 1.10 equiv) (slightly exothermic). The resulting suspension was stirred for 6 h at room temperature, during this time a white solid was formed. A saturated solution of $NaHCO_3$ (100 mL) was then added and the mixture was stirred vigorously. The resulting suspension was filtered on a glass filter of porosity 4. The two layers of the mother liquors were separated and the organic layer was washed with saturated solution of $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting mixture was combined with the solid obtained by filtration and boiled in CH_3CN (*ca* 300 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **4.9b** as a white solid (6.08 g, 17.4 mmol, 46 %). ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.46 (m, 1H, Ar*H*), 8.28 (m, 1H, Ar*H*), 7.80 (m, 2H, Ar*H*), 7.63 (m, 2H, Ar*H*), 7.48 (m, 3H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 134.9, 132.9, 132.5, 131.6, 131.3. 130.8, 128.8, 126.2, 120.5, 116.2, 106.6, 50.2. The values of the NMR spectra are in accordance with reported literature data.[140b]

1-((4-Pentylphenyl)ethynyl)-1,2-benziodoxol-3(1*H*)-one (4.9c)

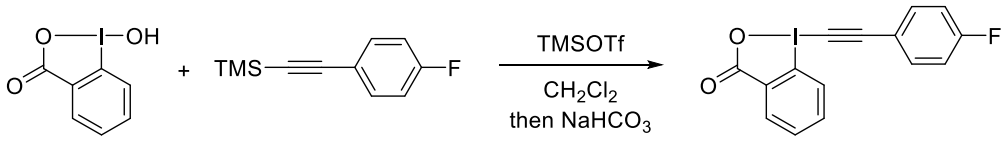


4.66 **4.71** **4.9c**

In a sealed tube, 2-iodobenzoic acid (**4.66**) (1.00 g, 4.03 mmol, 1.00 equiv), *para*-toluenesulfonic acid monohydrate (775 mg, 4.03 mmol, 1.00 equiv) and *m*-CPBA (70%, 994 mg, 4.44 mmol, 1.10 equiv) were suspended in DCE/TFE 1:1 (12 mL) and stirred for 1 h at 55 °C. After 1 h, 1-ethynyl-4-pentylbenzene (**4.71**) (1.1 mL, 5.6 mmol, 1.4 equiv) was added and the reaction was stirred at 55 °C for 24 h. After 24 h, the solvent was evaporated and the residue was redissolved in CH_2Cl_2 (20 mL) and stirred vigorously with saturated $NaHCO_3$ solution (30 mL). After 1 h, the reaction mixture was transferred into a separating funnel and the layers were separated. The aqueous layer was extracted

with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting solid was boiled in MeCN (20 mL), then filtered and the collected solid was further purified by flash column chromatography using EtOAc as eluent. Trituration in pentane afforded **4.9c** as a pale yellow solid (191 mg, 0.457 mmol, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.40 (m, 1H, Ar*H*), 8.28 – 8.21 (m, 1H, Ar*H*), 7.79 – 7.74 (m, 2H, Ar*H*), 7.56 – 7.48 (m, 2H, Ar*H*), 7.26 – 7.23 (m, 2H, Ar*H*), 2.71 – 2.60 (m, 2H, ArCH_2), 1.69 – 1.54 (m, 2H, ArCH$_2$CH_2), 1.40 – 1.27 (m, 4H, CH_2CH_2CH$_3$), 0.90 (t, *J* = 6.8 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 146.7, 135.0, 133.0, 132.6, 131.7, 131.5, 129.0, 126.3, 117.7, 116.4, 107.4, 49.4, 36.2, 31.5, 31.0, 22.6, 14.1. The values of the NMR spectra are in accordance with reported literature data.[119]

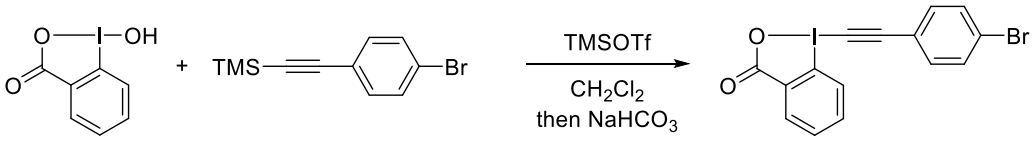
1-[4-Fluorophenylethynyl]-1,2-benziodoxol-3(1*H*)-one (4.9d)



4.67 **4.72** **4.9d**

Following a reported procedure,[379] trimethylsilyl triflate (1.0 mL, 5.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**4.67**) (1.32 g, 5.00 mmol, 1.00 equiv) in CH_2Cl_2 (15 mL) at room temperature. The resulting suspension was stirred for 1 h, followed by the drop wise addition of ((4-fluorophenyl)ethynyl)trimethylsilane (**4.72**) (1.1 mL, 5.5 mmol, 1.1 equiv), which was dissolved in CH_2Cl_2 (1 mL). The resulting suspension was stirred for 6 h. A saturated solution of $NaHCO_3$ (20 mL) was then added and the mixture was stirred vigorously for 30 min, the two layers were separated and the organic layer was washed with saturated solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH_3CN (20 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **4.9d** as a white solid (750 mg, 2.05 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 – 8.34 (m, 1H, Ar*H*), 8.29 – 8.16 (m, 1H, Ar*H*), 7.85 – 7.69 (m, 2H, Ar*H*), 7.68 – 7.53 (m, 2H, Ar*H*), 7.17 – 7.05 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 164.0 (d, *J* = 253.9 Hz), 135.2 (d, *J* = 8.8 Hz), 135.0, 132.6, 131.7, 131.50, 126.4, 116.9 (d, *J* = 3.6 Hz), 116.4 (d, *J* = 22.4 Hz), 116.3, 105.5, 50.5. The values of the NMR spectra are in accordance with reported literature data.[379]

1-[4-Bromophenylethynyl]-1,2-benziodoxol-3(1*H*)-one (4.9e)



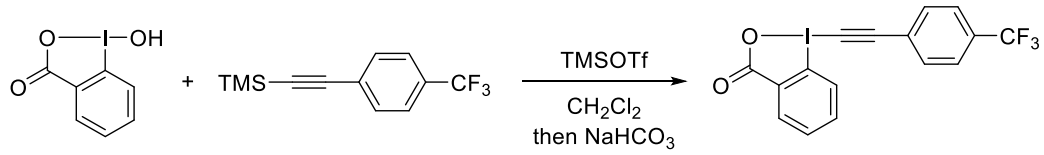
4.67 **4.73** **4.9e**

Following a reported procedure,[152b] trimethylsilyl triflate (1.0 mL, 5.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**4.67**) (1.32 g, 5.00 mmol, 1.00 equiv) in CH_2Cl_2 (15 mL) at room temperature. The resulting suspension was stirred for 1 h, followed by the drop wise addition of ((4-bromophenyl)ethynyl)trimethylsilane (**4.73**) (1.17 g, 5.50 mmol, 1.10 equiv), which was dissolved in CH_2Cl_2 (1 mL). The resulting suspension was stirred for 6 h. A saturated solution of $NaHCO_3$ (20 mL) was then added and the mixture was stirred vigorously for 30 min, the two layers were separated and the organic layer was washed with saturated solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH_3CN (20 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **4.9e** as a pale yellow solid (1.00 g, 2.34

[379] K. Jia, F. Zhang, H. Huang, Y. Chen, *J. Am. Chem. Soc.* **2016**, *138*, 1514.

mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 – 8.30 (m, 1H, Ar*H*), 8.30 – 8.13 (m, 1H, Ar*H*), 7.84 – 7.72 (m, 2H, Ar*H*), 7.58 (d, 2H, *J* = 8.5 Hz, Ar*H*), 7.46 (d, 2H, *J* = 8.5 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 135.1, 134.3, 132.7, 132.3, 131.9, 131.4, 126.3, 125.7, 119.6, 116.3, 105.4, 52.1. The values of the NMR spectra are in accordance with reported literature data.[152b]

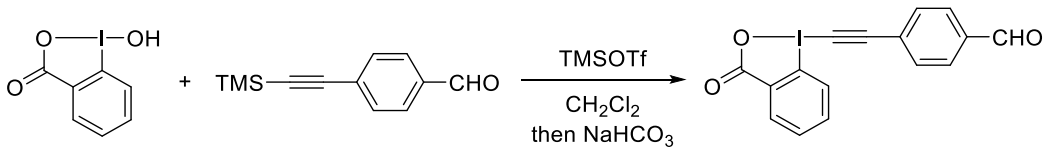
1-[4-Trifluoromethylphenylethynyl]-1,2-benziodoxol-3(1*H*)-one (4.9f)



4.67 **4.74** **4.9f**

Following a reported procedure,[164] trimethylsilyl triflate (0.80 mL, 4.4 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**4.67**) (1.06 g, 4.00 mmol, 1.00 equiv) in CH_2Cl_2 (15 mL) at room temperature. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of trimethyl((4-(trifluoromethyl)phenyl)ethynyl)silane (**4.74**) (1.07 g, 4.40 mmol, 1.10 equiv). The resulting suspension was stirred for 6 h. A saturated solution of $NaHCO_3$ (20 mL) was then added and the mixture was stirred vigorously for 30 min, the two layers were separated and the organic layer was washed with saturated solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was recrystallized in CH_3CN (ca 20 mL) to afford **4.9f** as a pale yellow solid (850 mg, 2.04 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.38 (m, 1H, Ar*H*), 8.28 – 8.19 (m, 1H, Ar*H*), 7.84 – 7.74 (m, 2H, Ar*H*), 7.74 – 7.65 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 135.0, 133.0, 132.6, 132.2 (q, *J* = 33.0 Hz), 131.7, 131.2, 126.3, 125.7 (q, *J* = 3.6 Hz), 124.4, 123.4 (q, *J* = 272.6 Hz), 116.1, 104.2, 53.7. The values of the NMR spectra are in accordance with reported literature data.[164]

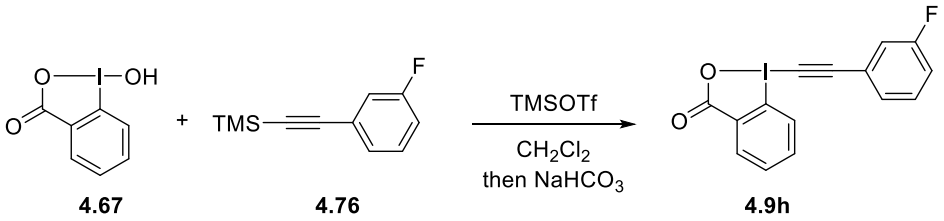
1-((4-Formylphenyl)ethynyl)-1,2-benziodoxol-3(1*H*)-one (4.9g)



4.67 **4.75** **4.9g**

Following a reported procedure,[152d] trimethylsilyl triflate (0.89 mL, 4.9 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**4.67**) (1.19 g, 4.49 mmol, 1.00 equiv) in CH_2Cl_2 (15 mL) at room temperature. The resulting suspension was stirred for 1 h, followed by the drop wise addition of ((4-formylphenyl)ethynyl)trimethylsilane (**4.75**) (1.00 g, 4.94 mmol, 1.10 equiv), which was dissolved in CH_2Cl_2 (1 mL). The resulting suspension was stirred for 6 h. A saturated solution of $NaHCO_3$ (20 mL) was then added and the mixture was stirred vigorously for 30 min, the two layers were separated and the organic layer was washed with saturated solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH_3CN (20 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **4.9g** as a yellow solid (0.80 g, 2.1 mmol, 41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H, C*H*O), 8.35 (d, *J* = 9.1 Hz, 1H, Ar*H*), 8.14 (dd, *J* = 7.4, 1.7 Hz, 1H, Ar*H*), 8.02 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.96 – 7.88 (m, 3H, Ar*H*), 7.82 (t, *J* = 7.3 Hz, 1H, Ar*H*); ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.6, 166.3, 136.7, 135.3, 133.2, 131.9, 131.4, 129.8, 127.7, 126.1, 116.4, 102.9, 56.6. The values of the NMR spectra are in accordance with reported literature data.[152d]

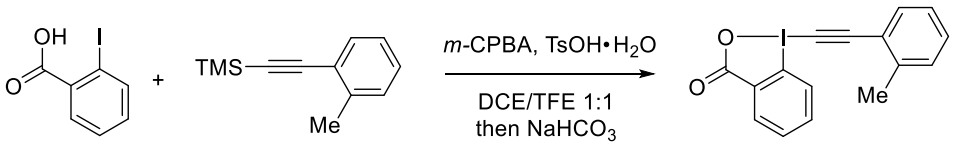
1-[3-Fluorophenylethynyl]-1,2-benziodoxol-3(1*H*)-one (4.9h)



4.67 **4.76** **4.9h**

Following a reported procedure,[379] trimethylsilyl triflate (1.0 mL, 5.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**4.67**) (1.32 g, 5.00 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) at room temperature. The resulting suspension was stirred for 1 h, followed by the drop wise addition of ((3-fluorophenyl)ethynyl)trimethylsilane (**4.76**) (1.1 mL, 5.5 mmol, 1.1 equiv). The resulting suspension was stirred for 6 h. A saturated solution of $NaHCO_3$ (20 mL) was then added and the mixture was stirred vigorously for 30 min, the two layers were separated and the organic layer was washed with saturated solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH_3CN (20 mL). The mixture was cooled down, filtered and the collected solid was dried under high vacuum to afford **4.9h** as a colorless solid (787 mg, 2.15 mmol, 43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (dd, *J* = 8.2, 0.8 Hz, 1H, Ar*H*), 8.13 (dd, *J* = 7.4, 1.7 Hz, 1H, Ar*H*), 7.91 (ddd, *J* = 8.2, 7.2, 1.7 Hz, 1H, Ar*H*), 7.81 (td, *J* = 7.3, 0.9 Hz, 1H, Ar*H*), 7.64 – 7.59 (m, 1H, Ar*H*), 7.58 – 7.53 (m, 2H, Ar*H*), 7.47 – 7.37 (m, 1H, Ar*H*); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 161.8 (d, *J* = 245.6 Hz), 135.3, 131.9, 131.3, 131.2 (d, *J* = 8.7 Hz), 129.0 (d, *J* = 2.9 Hz), 127.7, 122.4 (d, *J* = 9.6 Hz), 119.2 (d, *J* = 23.4 Hz), 118.1 (d, *J* = 21.1 Hz), 116.4, 102.5 (d, *J* = 3.3 Hz), 53.8; ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.7. One carbon was not resolved at 100 MHz. The values of the NMR spectra are in accordance with reported literature data.[379]

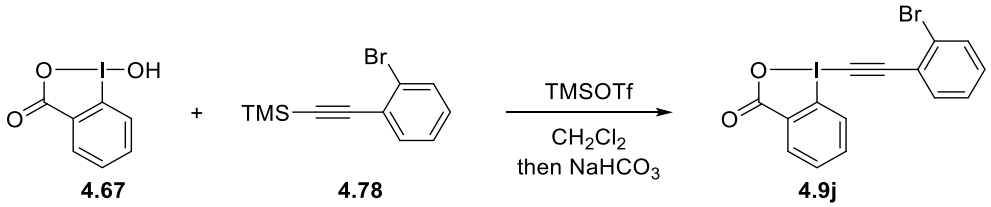
1-[2-Methylphenylethynyl]-1,2-benziodoxol-3(1*H*)-one (4.9i)



4.66 **4.77** **4.9i**

In a sealed tube, 2-iodobenzoic acid (**4.66**) (1.00 g, 4.03 mmol, 1.00 equiv), *para*-toluenesulfonic acid monohydrate (775 mg, 4.03 mmol, 1.00 equiv) and *m*-CPBA (70%, 994 mg, 4.44 mmol, 1.10 equiv) were suspended in DCE/TFE 1:1 (12 mL) and stirred for 1 h at 55 °C. After 1 h, trimethyl(*o*-tolylethynyl)silane (**4.77**) (1.2 mL, 5.6 mmol, 1.4 equiv) was added and the reaction was stirred at 55 °C for 24 h. After 24 h, the solvent was evaporated and the residue was redissolved in CH_2Cl_2 (20 mL) and stirred vigorously with saturated $NaHCO_3$ solution (30 mL). After 1 h, the reaction mixture was transferred into a separating funnel and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography using EtOAc as eluent to afford **4.9i** as a pale yellow solid (0.4 g, 1.1 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.36 (m, 1H, Ar*H*), 8.32 – 8.22 (m, 1H, Ar*H*), 7.82 – 7.68 (m, 2H, Ar*H*), 7.56 (dd, *J* = 7.7, 1.4 Hz, 1H, Ar*H*), 7.37 (td, *J* = 7.6, 1.4 Hz, 1H, Ar*H*), 7.30 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.27 – 7.21 (m, 1H, Ar*H*), 2.53 (s, 3H, ArC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 141.9, 134.8, 133.4, 132.5, 131.5, 131.4, 130.7, 129.9, 126.2, 126.0, 120.4, 116.3, 105.7, 53.2, 20.8. The values of the NMR spectra are in accordance with reported literature data.[379]

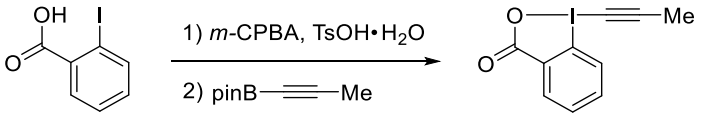
1-[2-Bromophenylethynyl]-1,2-benziodoxol-3(1*H*)-one (4.9j)



4.67 **4.78** **4.9j**

Following a reported procedure,[152b] trimethylsilyl triflate (1.0 mL, 5.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**4.67**) (1.32 g, 5.00 mmol, 1.00 equiv) in CH_2Cl_2 (15 mL) at room temperature. The resulting suspension was stirred for 1 h, followed by the drop wise addition of ((2-bromophenyl)ethynyl)trimethylsilane (**4.78**) (1.17 g, 5.50 mmol, 1.10 equiv). The resulting suspension was stirred for 6 h at room temperature. A saturated solution of $NaHCO_3$ (20 mL) was then added and the mixture was stirred vigorously for 30 min, the two layers were separated and the organic layer was washed with saturated solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH_3CN (ca. 20 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **4.9j** as a white solid (1.50 g, 3.51 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (td, *J* = 7.3, 2.1 Hz, 2H, Ar*H*), 7.84 – 7.74 (m, 2H, Ar*H*), 7.68 (d, *J* = 1.1 Hz, 1H, Ar*H*), 7.61 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar*H*), 7.36 (dtd, *J* = 22.4, 7.5, 1.5 Hz, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 135.2, 134.7, 133.0, 132.7 , 131.8, 131.3, 127.6, 126.8, 126.4, 123.2, 116.5, 104.3, 55.4. The values of the NMR spectra are in accordance with reported literature data.[152b]

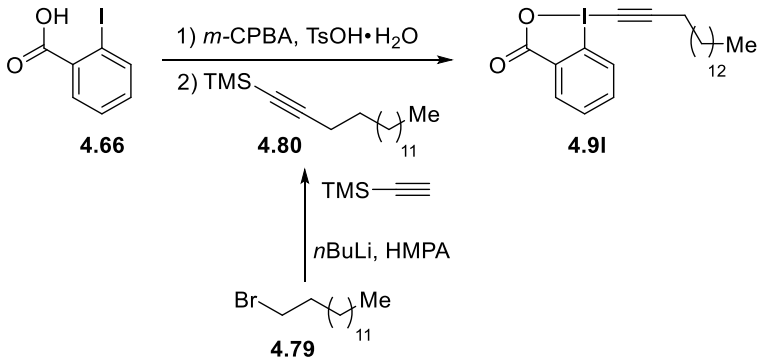
Propynyl-1,2-benziodoxol-3(1*H*)-one (4.9k)



4.66 **4.9k**

Following a reported procedure,[155b] 2-iodobenzoic acid (**4.66**) (1.07 g, 4.30 mmol, 1.00 equiv), *para*-toluenesulfonic acid monohydrate (818 mg, 4.30 mmol, 1.00 equiv) and *m*-CPBA (70%, 1.17 g, 4.73 mmol, 1.10 equiv) were dissolved in CH_2Cl_2 (7 mL) and 2,2,2-trifluoroethanol (7 mL). The mixture was stirred at room temperature under nitrogen for 1 h, after which propynyl-1-boronic acid pinacol ester (4.85 g, 21.2 mmol, 1.40 equiv) was added in one portion. The reaction mixture was stirred for 2.5 h at room temperature, filtered and concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (30 mL) and under vigorous stirring, saturated aq. $NaHCO_3$ (30 mL) was added. The mixture was stirred for 15 min, the two layers were separated and the aqueous phase was extracted with additional portions of CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate as eluent to afford **4.9k** as a white solid (1.03 g, 3.60 mmol, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 – 8.35 (m, 1 H, Ar*H*), 8.22 – 8.14 (m, 1 H, Ar*H*), 7.79 – 7.68 (m, 2 H, Ar*H*), 2.27 (s, 3 H, CCC*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 134.8, 132.5, 131.6, 126.4, 115.6, 105.1, 39.0, 5.7. The values of the NMR spectra are in accordance with reported literature data.[155b]

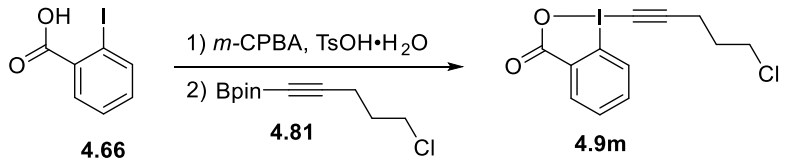
Hexadecynyl-1,2-benziodoxol-3(1*H*)-one (4.9l)



Following a reported procedure,[155b] to a mixture of trimethylsilylacetylene (8.33 g, 85.0 mmol, 1.20 equiv) and dry THF (46 mL) was added at -78 °C under nitrogen 2.5 M *n*BuLi in hexanes (33.9 mL, 85.0 mmol, 1.20 equiv) over 10 min. The resulting light yellow solution was stirred at -78 °C for 1 h, after which a mixture consisting of 1-bromotetradecane (**4.79**) (19.6 g, 70.7 mmol, 1.00 equiv), hexamethylphosphoramide (HMPA, 14.2 mL, 78.0 mmol, 1.10 equiv) and dry THF (23 mL) was slowly added *via* cannula over 20 min. The reaction mixture was stirred for 1 h at -78 °C, followed by 24 h of stirring at room temperature. The reaction was quenched at 0 °C with saturated aq. NH_4Cl (50 mL) and diluted with water (10 mL) and EtOAc (50 mL). The two layers were separated and the aq. layer was extracted with additional portions of EtOAc (3 x 50 mL). The combined organic layers were washed with water (2 x 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The light brown crude liquid was finally pushed through a small plug of silica gel with pentane as eluent to afford pure hexadec-1-yn-1-yltrimethylsilane (**4.80**) as a colorless liquid (19.3 g, 65.5 mmol, 92.7% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19 (t, *J* = 7.1 Hz, 2H, CCC*H*$_2$), 1.54 – 1.44 (m, 2H, C*H*$_2$), 1.42 – 1.18 (m, 22H, C*H*$_2$), 0.87 (t, *J* = 6.7 Hz, 3H, CH_2CH_3), 0.13 (s, 9H, TMS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 107.7, 84.3, 32.2, 29.9, 29.8, 29.7, 29.6, 29.3, 29.0, 28.9, 22.9, 20.0, 14.3, 0.3. The values of the NMR spectra are in accordance with reported literature data.[155b]

Following a reported procedure,[155b] 2-iodobenzoic acid (**4.66**) (8.00 g, 32.2 mmol, 1.00 equiv), *para*-toluenesulfonic acid monohydrate (6.13 g, 32.2 mmol, 1.00 equiv) and *m*-CPBA (70%, 8.74 g, 35.5 mmol, 1.10 equiv) were dissolved in CH_2Cl_2 (60 mL) and 2,2,2-trifluoroethanol (60 mL). The mixture was stirred at room temperature under nitrogen for 1 h, after which hexadec-1-yn-1-yltrimethylsilane (**4.80**) (13.3 g, 45.1 mmol, 1.40 equiv) was added in one portion. The reaction mixture was stirred for 14 h at room temperature, filtered and concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (400 mL) and under vigorous stirring, saturated solution of $NaHCO_3$ (400 mL) was added. The mixture was stirred for 1 h, the two layers were separated and the aqueous layer was extracted with additional portions of CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using EtOAc as eluent to afford **4.9l** as a white solid (6.02 g, 12.9 mmol, 40%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 – 8.37 (m, 1H, Ar*H*), 8.21 – 8.14 (m, 1H, Ar*H*), 7.80 – 7.70 (m, 2H, Ar*H*), 2.59 (t, *J* = 7.1 Hz, 2H, CCC*H*$_2$), 1.65 (p, *J* = 7.1 Hz, 2H, $CCCH_2CH_2$), 1.52 – 1.40 (m, 2H), 1.39 – 1.19 (m, 20H, C*H*$_2$), 0.86 (t, *J* = 6.7 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 134.7, 132.5, 131.7, 131.6, 126.2, 115.7, 109.9, 39.5, 32.1, 29.8, 29.7, 29.6, 29.5, 29.2, 29.1, 28.3, 22.8, 20.6, 14.3. The values of the NMR spectra are in accordance with reported literature data.[155b]

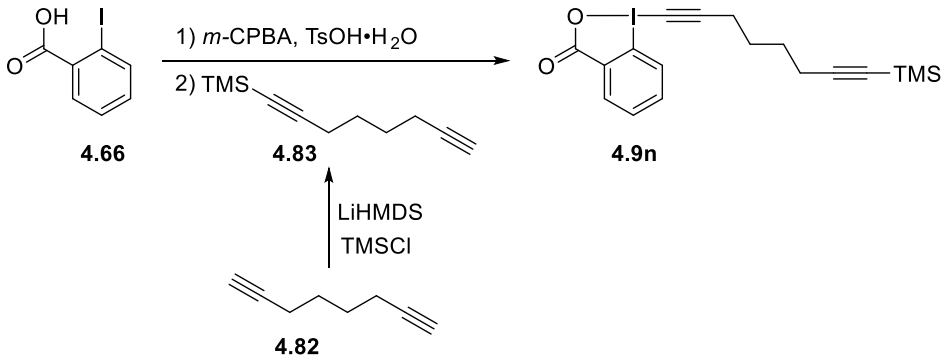
(5-Chloropent-1-ynyl)-1,2-benziodoxol-3(1*H*)-one (4.9m)



4.66 **4.81** **4.9m**

Following a reported procedure,[155b] 2-iodobenzoic acid (**4.66**) (3.76 g, 15.2 mmol, 1.00 equiv), *para*-toluenesulfonic acid monohydrate (2.88 g, 15.2 mmol, 1.00 equiv) and *m*-CPBA (70%, 4.11 g, 16.7 mmol, 1.10 equiv) were dissolved in CH_2Cl_2 (30 mL) and 2,2,2-trifluoroethanol (30 mL). The mixture was stirred at room temperature under nitrogen for 1 h, after which 5-chloro-1-pentynyl-1-boronic acid pinacol ester **4.81** (4.85 g, 21.2 mmol, 1.40 equiv) was added in one portion. The reaction mixture was stirred for 90 min at room temperature, filtered and concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (15 mL) and under vigorous stirring, saturated solution of $NaHCO_3$ (15 mL) was added. The mixture was stirred for 10 min, the two layers were separated and the aqueous layer was extracted with additional portions of CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate as eluent to afford **4.9m** as a white solid (3.76 g, 10.8 mmol, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 – 8.34 (m, 1H, Ar*H*), 8.22 – 8.13 (m, 1H, Ar*H*), 7.82 – 7.68 (m, 2H, Ar*H*), 3.71 (t, *J* = 6.1 Hz, 2H, ClC*H*$_2$CH$_2$), 2.82 (t, *J* = 6.9 Hz, 2H, CCC*H*$_2$CH$_2$), 2.18 – 2.05 (m, 2H, ClCH$_2$C*H*$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 134.9, 132.5, 131.6, 131.6, 126.4, 115.8, 107.1, 43.4, 41.2, 30.7, 18.0. The values of the NMR spectra are in accordance with reported literature data.[155b]

8-(Trimethylsilyl)octa-1,7-diyn-1-yl-1,2-benziodoxol-3(1*H*)-one (4.9n)



4.66 **4.83** **4.9n**

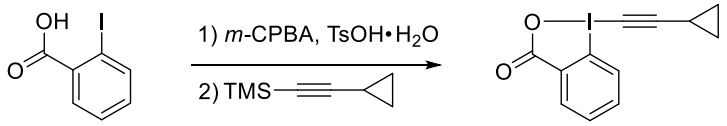
4.82

Following a reported procedure,[227] to a solution of 1,7-octadiyne **4.82** (10.6 g, 100 mmol, 1.00 equiv) in dry THF (150 mL) was added at -78 °C under nitrogen 1 M lithium bis(trimethylsilyl)amide in THF (100 mL, 100 mmol, 1.00 equiv). The solution was stirred at -78 °C for 30 min, after which trimethylsilyl chloride (TMSCl, 13.0 mL, 100 mmol, 1.00 equiv) was added dropwise. The reaction was warmed to room temperature and stirred for 2 h. The reaction was cooled to 0 °C and quenched by adding water (10 mL). The mixture was diluted with 1 M HCl (200 mL) and extracted with diethyl ether (100 mL and 2 x 75 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by vacuum distillation using a 20 cm Vigreux column (oil bath set to 98 °C at 0.3 mbar) furnishing pure trimethyl(octa-1,7-diyn-1-yl)silane (**4.83**) as a colorless liquid (8.37 g, 46.9 mmol, 47%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 – 2.17 (m, 4H), 1.93 (t, *J* = 2.7 Hz, 1H, CC*H*), 1.68 – 1.57 (m, 4H), 0.13 (s, 9H, TMS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 107.0, 84.9, 84.2, 68.6, 27.7, 27.6, 19.5, 18.1, 0.3. The values of the NMR spectra are in accordance with reported literature data.[227]

Following a reported procedure,[227] 2-iodobenzoic acid (**4.66**) (8.43 g, 33.3 mmol, 1.00 equiv), *para*-toluenesulfonic acid monohydrate (6.40 g, 33.3 mmol, 1.00 equiv) and *m*-CPBA (70%, 9.04 g, 36.7

mmol, 1.10 equiv) were dissolved in CH_2Cl_2 (60 mL) and 2,2,2-trifluoroethanol (60 mL). The mixture was stirred at room temperature under nitrogen for 1 h, after which trimethyl(octa-1,7-diyn-1-yl)silane (**4.83**) (8.32 g, 46.7 mmol, 1.40 equiv) was added. The reaction mixture was stirred for 15 h at room temperature and then filtered and concentrated under reduced pressure. The resulting light being solid was dissolved in CH_2Cl_2 (500 mL) and under vigorous stirring, saturated solution of $NaHCO_3$ (500 mL) was added. The mixture was stirred for 1 h, the two layers were separated and the aqueous layer was extracted with additional portions of CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate as eluent to afford **4.9n** as a white solid (4.2 g, 9.9 mmol, 30%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (dd, *J* = 6.7, 2.3 Hz, 1H, Ar*H*), 8.17 (dd, *J* = 7.8, 1.5 Hz, 1H, Ar*H*), 7.82 – 7.66 (m, 2H, Ar*H*), 2.63 (t, *J* = 6.8 Hz, 2H, CH_2), 2.29 (t, *J* = 6.7 Hz, 2H, CH_2), 1.83 – 1.62 (m, 4H, 2 x CH_2), 0.13 (s, 9H, TMS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 134.8, 132.4, 131.7, 131.5, 126.3, 115.7, 109.1, 106.4, 85.4, 40.0, 27.7, 27.3, 20.2, 19.4, 0.3. The values of the NMR spectra are in accordance with reported literature data.[227]

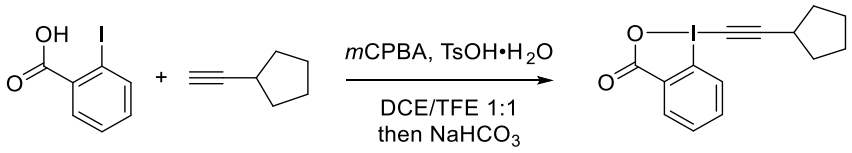
2-Cyclopropylethynyl-1,2-benziodoxol-3(1*H*)-one (4.9o)



4.66 **4.9o**

Following a reported procedure,[227] 2-iodobenzoic acid (**4.66**) (6.41 g, 25.8 mmol, 1.00 equiv), *para*-toluenesulfonic acid monohydrate (4.91 g, 25.8 mmol, 1.00 equiv) and *m*-CPBA (70%, 7.00 g, 28.4 mmol, 1.10 equiv) were dissolved in CH_2Cl_2 (48 mL) and 2,2,2-trifluoroethanol (48 mL). The mixture was stirred at room temperature under nitrogen for 1 h, after which (cyclopropylethynyl)trimethylsilane (5.00 g, 36.2 mmol, 1.40 equiv) was added in one portion. The reaction mixture was stirred for 12 h at room temperature, filtered and concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (400 mL) and under vigorous stirring, a saturated solution of $NaHCO_3$ (400 mL) was added. The mixture was stirred for 1 h, the two layers were separated and the aqueous layer was extracted with additional portions of CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate as eluent to afford **4.9o** as a white solid (2.11 g, 6.76 mmol, 26 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (dd, *J* = 7.0, 2.1 Hz, 1H, Ar*H*), 8.18 – 8.09 (m, 1H, Ar*H*), 7.81 – 7.63 (m, 2H, Ar*H*), 1.59 (tt, *J* = 8.2, 5.0 Hz, 1H, C*H*), 1.07 – 0.85 (m, 4H, CH_2CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 134.7, 132.3, 131.7, 131.4, 126.2, 115.9, 113.3, 35.0, 9.8, 1.1. The values of the NMR spectra are in accordance with reported literature data.[227]

2-Cyclopentylethynyl-1,2-benziodoxol-3(1*H*)-one (4.9p)

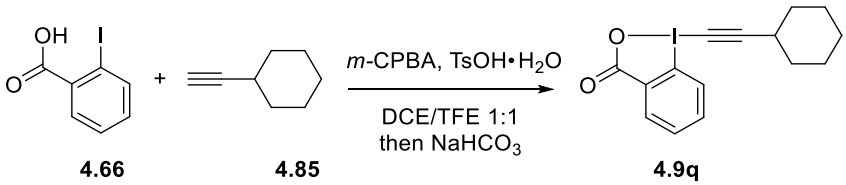


4.66 **4.84** **4.9p**

In a sealed tube, 2-iodobenzoic acid (**4.66**) (1.00 g, 4.03 mmol, 1.00 equiv), *para*-toluenesulfonic acid monohydrate (775 mg, 4.03 mmol, 1.00 equiv) and *m*-CPBA (77%, 994 mg, 4.44 mmol, 1.10 equiv) were suspended in DCE/TFE 1:1 (12 mL) and stirred for 1 h at 55 °C. After 1 h, ethynylcyclopentane (**4.84**) (0.65 mL, 5.6 mmol, 1.4 equiv) was added and the reaction was stirred at 55 °C for 24 h. After 24 h, the solvent was evaporated and the residue was redissolved in CH_2Cl_2 (20 mL) and stirred

vigorously with saturated solution of $NaHCO_3$ (30 mL). After 1 h, the reaction mixture was transferred into a separating funnel and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with saturated solution of $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography using ethyl acetate as eluent to afford **4.9p** as a white solid (0.95 g, 2.8 mmol, 70%). Mp (Dec.): 151.5 – 156.6 °C; R_f = 0.21 (EtOAc), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 – 8.34 (m, 1H, Ar*H*), 8.14 (dd, *J* = 7.4, 1.8 Hz, 1H, Ar*H*), 7.79 – 7.67 (m, 2H, Ar*H*), 3.05 – 2.92 (m, 1H, CCC*H*), 2.10 – 2.00 (m, 2H, 1 x C*H*$_2$), 1.85 – 1.70 (m, 4H, 2 x C*H*$_2$), 1.69 – 1.62 (m, 2H, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 134.6, 132.3, 131.5, 131.6, 126.0, 115.6, 114.0, 38.6, 33.7, 31.5, 25.1; IR 3070 (w), 2960 (m), 2869 (w), 2239 (w), 2169 (w), 1610 (s), 1560 (m), 1440 (w), 1344 (m), 1301 (w), 1110 (w), 1010 (w), 910 (m); HRMS (ESI) Calcd for $C_{14}H_{14}IO_2^+$ $[M+H]^+$ 341.0033; found 341.0037.

2-Cyclohexylethynyl-1,2-benziodoxol-3(1*H*)-one (4.9q)

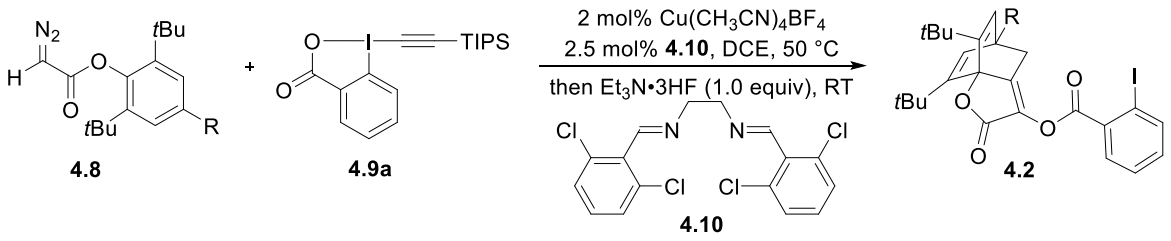


4.66 **4.85** **4.9q**

In a sealed tube, 2-iodobenzoic acid (**4.66**) (1.00 g, 4.03 mmol, 1.00 equiv), *para*-toluenesulfonic acid monohydrate (775 mg, 4.03 mmol, 1.00 equiv) and *m*-CPBA (77%, 994 mg, 4.44 mmol, 1.1 equiv) were suspended in DCE/TFE 1:1 (12 mL) and stirred for 1 h at 55 °C. After 1 h, ethynylcyclohexane (**4.85**) (0.74 mL, 5.6 mmol, 1.4 equiv) was added and the reaction was stirred at 55 °C for 24 h. After 24 h, the solvent was evaporated and the residue was redissolved in CH_2Cl_2 (20 mL) and stirred vigorously with a saturated solution of $NaHCO_3$ (30 mL). After 1 h, the reaction mixture was transferred into a separating funnel and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with saturated solution of $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography using ethyl acetate as eluent to afford **4.9q** as a white solid (0.85 g, 2.4 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.33 (m, 1H, Ar*H*), 8.21 – 8.10 (m, 1H, Ar*H*), 7.83 – 7.67 (m, 2H, Ar*H*), 2.80 – 2.73 (m, 1H, CCC*H*), 1.95 – 1.89 (m, 2H, 1 x C*H*$_2$), 1.81 – 1.69 (m, 2H, 1 x C*H*$_2$), 1.62 – 1.53 (m, 3H), 1.45 – 1.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 134.6, 132.3, 131.5, 131.4, 126.0, 115.5, 113.6, 39.1, 32.2, 30.7, 25.5, 24.7. The values of the NMR spectra are in accordance with reported literature data.[136]

10.2.3. One-Pot Oxy-Alkynylation/Himbert Reaction

General procedure A

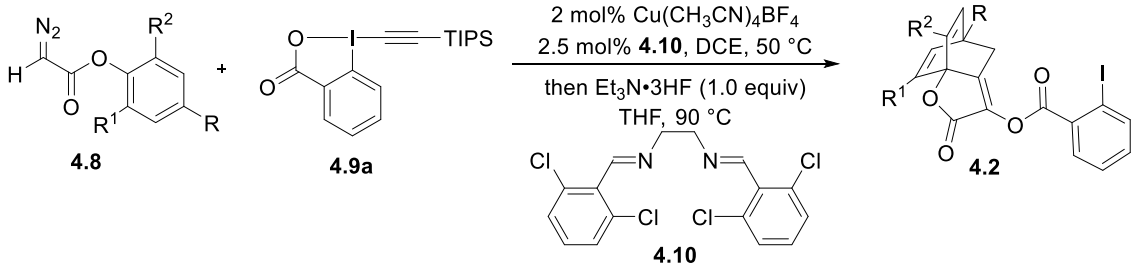


4.8 **4.9a** **4.10** **4.2**

A flame dried 5 mL microwave vial was charged under nitrogen with $Cu(CH_3CN)_4BF_4$ (1.0 mg, 3.0 µmol, 0.02 equiv), ligand **4.10** (1.4 mg, 3.8 µmol, 0.025 equiv) and dry DCE (1 mL). The resulting solution was stirred at 30 °C for 1 h and then added to a mixture of 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (0.15 mmol, 1.0 equiv), diazo compound **4.8** (0.18 mmol, 1.2 equiv) and dry DCE (5

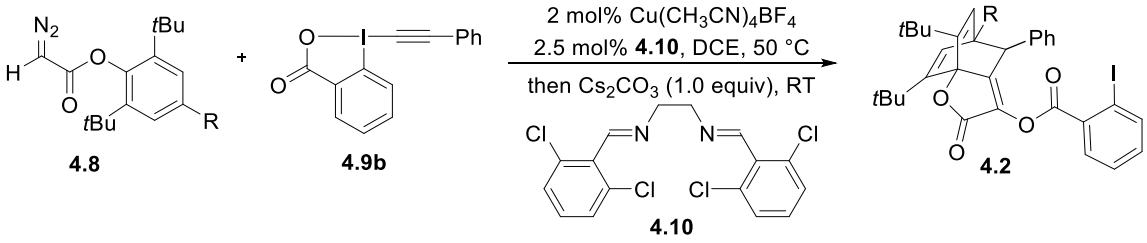
mL) in 20 mL microwave vial over 2 min and the resulting reaction mixture was stirred at 50 °C. Next, the reaction mixture was cooled down to room temperature and triethylamine trihydrofluoride (24 µL, 0.15 mmol, 1.0 equiv) was added and the reaction mixture was stirred. After the reaction was completed (monitored by TLC, EtOAc/pentane or Et_2O/pentane), the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (EtOAc/pentane or Et_2O/pentane) directly without any further work-up.

General procedure B



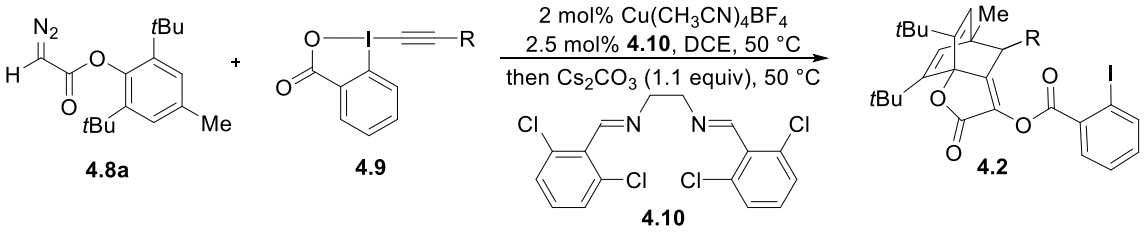
A flame dried 5 mL microwave vial was charged under nitrogen with $Cu(CH_3CN)_4BF_4$ (1.0 mg, 3.0 µmol, 0.02 equiv), ligand **4.10** (1.4 mg, 3.8 µmol, 0.025 equiv) and dry DCE (1 mL). The resulting solution was stirred at 30 °C for 1 h and then added to a mixture of 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (0.15 mmol, 1.0 equiv), diazo compound **4.8** (0.18 mmol, 1.2 equiv) and dry DCE (5 mL) in 20 mL microwave vial over 2 min and the resulting reaction mixture was stirred at 50 °C. The solvent was evaporated and the residue was filtered through a small plug of silica gel using Et_2O (*ca* 15 mL). The Et_2O was evaporated and the crude redissolved in THF (6 mL) in a 20 mL microwave vial. Next, triethylamine trihydrofluoride (24 µL, 0.15 mmol, 1.0 equiv) was added and the reaction mixture stirred at 90 °C. After the reaction was completed (monitored by TLC, EtOAc/pentane or Et_2O/pentane), the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (EtOAc/pentane or Et_2O/pentane) directly without any further work-up.

General procedure C



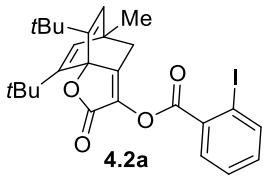
A flame dried 5 mL microwave vial was charged under nitrogen with $Cu(CH_3CN)_4BF_4$ (1.0 mg, 3.0 µmol, 0.02 equiv), ligand **4.10** (1.4 mg, 3.8 µmol, 0.025 equiv) and dry DCE (1 mL). The resulting solution was stirred at 30 °C for 1 h and then added to a mixture of Ph-EBX (**4.9b**) (0.15 mmol, 1.0 equiv), diazo compound **4.8** (0.18 mmol, 1.2 equiv) and dry DCE (5 mL) in 20 mL microwave vial over 2 min and the resulting reaction mixture was stirred at 50 °C. Next, the reaction mixture was cooled down to room temperature and Cs_2CO_3 (54.0 mg, 0.165 mmol, 1.10 equiv) was added and the reaction mixture was stirred. After the reaction was completed (monitored by TLC, EtOAc/pentane or Et_2O/pentane), the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (EtOAc/pentane or Et_2O/pentane) directly without any further work-up.

General procedure D



A flame dried 5 mL microwave vial was charged under nitrogen with $Cu(CH_3CN)_4BF_4$ (1.0 mg, 3.0 µmol, 0.02 equiv), ligand **4.10** (1.4 mg, 3.8 µmol, 0.025 equiv) and dry DCE (1 mL). The resulting solution was stirred at 30 °C for 1 h and then added to a mixture of R-EBX (**4.9**) (0.15 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (0.18 mmol, 1.2 equiv) and dry DCE (5 mL) in 20 mL microwave vial over 2 min and the resulting reaction mixture was stirred at 50 °C. Next, Cs_2CO_3 (54.0 mg, 0.165 mmol, 1.10 equiv) was added and the reaction mixture was stirred at 50 °C. After the reaction was completed (monitored by TLC, EtOAc/pentane or Et_2O/pentane), the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (EtOAc/pentane or Et_2O/pentane) directly without any further work-up.

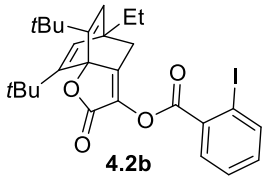
7,8-Di-*tert*-butyl-5-methyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2a)



Following general procedure **A**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (52 mg, 0.18 mmol, 1.2 equiv), afforded **4.2a** as a white solid (75.0 mg, 0.141 mmol, 94%). M.p. 162.3 – 162.7 °C; R_f = 0.37 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.02 (m, 2H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 (td, *J* = 7.6, 1.7 Hz, 1H, Ar*H*), 5.81 (s, 2H, 2 x *t*BuCC*H*), 2.36 (s, 2H, $CH_3CC\mathit{H}_2$), 1.62 (s, 3H, CHCCH_3), 1.16 (s, 18H, 2 x *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 162.1, 157.8, 151.3, 141.7, 133.7, 132.5, 132.2, 132.2, 129.4, 128.1, 95.0, 92.9, 41.6, 38.6, 35.2, 29.1, 22.2; IR (ν_{max}, cm^{-1}) 3058 (w), 2961 (w), 2871 (w), 1783 (s), 1758 (m), 1718 (w), 1692 (w), 1583 (w), 1472 (w), 1365 (w), 1333 (w), 1292 (w), 1233 (s), 1155 (m), 1086 (s), 1057 (m), 1004 (s), 923 (w); HRMS (ESI) Calcd for $C_{26}H_{30}IO_4^+$ $[M+H]^+$ 533.1183; found 533.1191.

Large scale procedure: Following general procedure **A**, 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (860 mg, 2.00 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (692 mg, 2.40 mmol, 1.20 equiv) were stirred for 12 h. Next, triethylamine trihydrofluoride (0.33 mL, 2.0 mmol, 1.0 equiv) was added and the reaction mixture further stirred for 24 h. The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography using Et_2O/pentane 1:20 as eluent to afford **4.2a** as a white solid (1.00 g, 1.88 mmol, 94%).

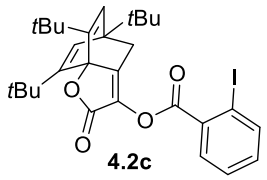
7,8-Di-*tert*-butyl-5-ethyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2b)



4.2b

Following general procedure **A**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-ethylphenyl 2-diazoacetate (**4.8b**) (54.4 mg, 0.180 mmol, 1.20 equiv), afforded **4.2b** as a white solid (79.0 mg, 0.145 mmol, 96%). M.p. 164.0 – 166.5 °C; R_f = 0.39 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.02 (m, 2H, Ar*H*), 7.44 (td, *J* = 7.7, 1.2 Hz, 1H, Ar*H*), 7.20 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.88 (s, 2H, 2 x *t*BuCC*H*), 2.34 (s, 2H, EtCCH_2), 1.97 (q, *J* = 7.5 Hz, 2H, CH_2CH$_3$), 1.20 – 1.12(m, 21H, 2 x *t*Bu and CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 162.1, 157.8, 151.5, 141.7, 133.6, 132.6, 132.2, 130.2, 129.7, 128.1, 94.9, 92.7, 46.1, 36.1, 35.4, 29.2, 28.1, 9.6; IR (ν_{max}, cm^{-1}) 3063 (w), 2962 (m), 2871 (w), 2255 (w), 1778 (s), 1710 (w), 1583 (w), 1464 (m), 1429 (w), 1363 (w), 1273 (m), 1236 (s), 1191 (m), 1088 (s), 1008 (s), 913 (m); HRMS (ESI) Calcd for $C_{27}H_{31}INaO_4^+$ $[M+Na]^+$ 569.1159; found 569.1173.

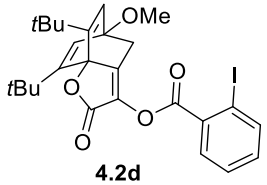
5,7,8-Tri-*tert*-butyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2c)



4.2c

Following general procedure **A**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2,4,6-tri-*tert*-butylphenyl 2-diazoacetate (**4.8c**) (59.5 mg, 0.180 mmol, 1.20 equiv) were stirred for 12 h. Next, triethylamine trihydrofluoride (24 μL, 0.15 mmol, 1.0 equiv), afforded **4.2c** as a white solid (72.0 mg, 0.125 mmol, 84%). M.p. 183.0 – 187.5 °C; R_f = 0.4 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 7.9, 3.7, 1.4 Hz, 2H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.20 (td, *J* = 7.6, 1.7 Hz, 1H, Ar*H*), 6.04 (s, 2H, 2 x *t*BuCC*H*), 2.39 (s, 2H, EtCCH_2), 1.17 (s, 18H, 2 x *t*Bu), 1.14 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 162.2, 158.6, 151.3, 141.7, 133.6, 132.6, 132.2, 129.7, 128.3, 128.1, 94.9, 92.2, 52.6, 35.5, 32.5, 31.9, 29.2, 26.4; IR (ν_{max}, cm^{-1}) 3081 (w), 2961 (m), 2871 (w), 2255 (w), 1782 (s), 1711 (w), 1584 (w), 1467 (w), 1430 (w), 1359 (w), 1274 (w), 1234 (s), 1190 (m), 1141 (m), 1084 (s), 1035 (w), 1008 (m), 911 (s), 832 (w); HRMS (ESI) Calcd for $C_{29}H_{36}IO_4^+$ $[M+H]^+$ 575.1653; found 575.1660.

7,8-Di-*tert*-butyl-5-methoxy-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2d)

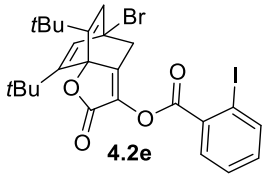


4.2d

Following general procedure **A**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methoxyphenyl 2-diazoacetate (**4.8d**) (59 mg, 0.18 mmol, 1.2 equiv), afforded **4.2d** as a white solid (70.0 mg, 0.128 mmol, 85%). M.p. 159.5 – 160.8 °C; R_f = 0.23 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.01 (m, 2H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.18 (s, 2H, 2 x *t*BuCC*H*), 3.61

(s, 3H, OC*H*$_3$), 2.67 (s, 2H, OCH$_3$CC*H*$_2$), 1.18 (s, 18H, 2 x *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 162.1, 154.2, 149.7, 141.7, 133.7, 132.5, 132.8, 129.6, 128.2, 128.1, 94.9, 91.3, 82.6, 53.4, 35.7, 35.4, 29.0; IR (ν_{max}, cm^{-1}) 3060 (w), 2996 (w), 2960 (m), 2870 (w), 2835 (w), 1767 (s), 1706 (m), 1635 (w), 1584 (w), 1563 (w), 1469 (w), 1427 (w), 1392 (w), 1363 (w), 1310 (m), 1273 (m), 1240 (s), 1191 (m), 1137 (m), 1089 (s), 1029 (m), 1008 (m), 966 (w), 932 (w); HRMS (ESI) Calcd for $C_{26}H_{30}IO_5^+$ $[M+H]^+$ 549.1132; found 549.1139.

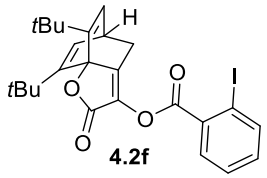
5-Bromo-7,8-di-*tert*-butyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2e)



4.2e

Following general procedure **A**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 4-bromo-2,6-di-*tert*-butylphenyl 2-diazoacetate (**4.8e**) (64 mg, 0.18 mmol, 1.2 equiv), afforded **4.2e** as a white solid (74.0 mg, 0.124 mmol, 83%). M.p. 146.5 – 147.5 °C; R_f = 0.28 (Et_2O/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 7.8, 3.0, 1.4 Hz, 2H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.21 (s, 2H, 2 x *t*BuCC*H*), 3.04 (s, 2H, BrCC*H*$_2$), 1.18 (s, 18H, 2 x *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 161.9, 153.7, 151.1, 141.8, 133.9, 132.2, 132.2, 132.1, 128.8, 128.1, 95.1, 90.8, 53.9, 43.1, 35.4, 28.9; IR (ν_{max}, cm^{-1}) 2997 (w), 2963 (w), 2869 (w), 2259 (w), 1789 (s), 1766 (m), 1705 (w), 1583 (w), 1466 (w), 1365 (w), 1275 (w), 1236 (s), 1189 (w), 1124 (m), 1081 (s), 1035 (w), 1007 (m), 911 (m); HRMS (ESI) Calcd for $C_{25}H_{26}BrINaO_4^+$ $[M+Na]^+$ 618.9951; found 618.9958.

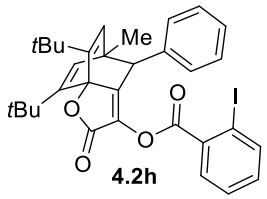
7,8-Di-*tert*-butyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2f)



4.2f

Following general procedure **A**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butylphenyl 2-diazoacetate (**4.8f**) (50 mg, 0.18 mmol, 1.2 equiv), afforded **4.2f** as a white solid (72.0 mg, 0.138 mmol, 92%). M.p. 146.5 – 147.8 °C; R_f = 0.31 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 2H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.10 (d, *J* = 6.5 Hz, 2H, 2 x *t*BuCC*H*), 3.88 – 3.83 (m, 1H, CHC*H*CH$_2$), 2.48 (d, *J* = 2.6 Hz, 2H, CHC*H*$_2$), 1.17 (s, 18H, 2 x *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 162.1, 156.2, 151.4, 141.7, 133.6, 132.7, 132.2, 130.4, 128.1, 126.6, 94.9, 92.7, 36.4, 35.4, 31.6, 29.2; IR (ν_{max}, cm^{-1}) 3070 (w), 2961 (w), 2870 (w), 1779 (s), 1710 (w), 1584 (w), 1465 (w), 1428 (w), 1363 (w), 1269 (m), 1233 (s), 1174 (m), 1128 (s), 1075 (s), 1030 (m), 1008 (s), 966 (w); HRMS (ESI) Calcd for $C_{25}H_{28}IO_4^+$ $[M+H]^+$ 519.1027; found 519.1044.

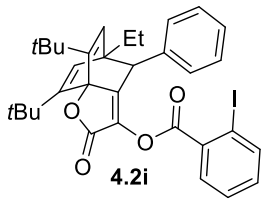
7,8-Di-*tert*-butyl-5-methyl-2-oxo-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2h)



Following general procedure **C**, starting from 1-[phenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9b**) (52.5 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2h** as a white solid (83.0 mg, 0.137 mmol, 91%). M.p. 190.0 – 191.5 °C; R_f = 0.37 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar*H*), 7.25 – 7.13 (m, 5H, Ar*H*), 7.06 (td, *J* = 7.6, 1.9 Hz, 1H, Ar*H*), 7.00 (dd, *J* = 7.2, 2.3 Hz, 2H, Ar*H*), 5.93 (s, 1H, *t*BuCC*H*), 5.63 (s, 1H, *t*BuCC*H*), 3.63 (s, 1H, ArC*H*), 1.31 (s, 3H, CHCC*H*$_3$), 1.29 (s, 9H, *t*Bu), 1.22 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 162.0, 159.1, 152.3, 150.1, 141.3, 136.8, 133.5, 133.2, 132.4, 131.7, 130.7, 130.4, 129.4, 128.2, 127.6, 127.4, 94.4, 92.7, 53.6, 46.6, 35.4, 35.3, 29.2, 29.1, 20.2; IR (ν_{max}, cm^{-1}) 3063 (w), 2962 (m), 2871 (w), 2256 (w), 1777 (s), 1703 (w), 1582 (w), 1463 (w), 1363 (w), 1236 (s), 1091 (s), 1007 (m), 910 (m); HRMS (ESI) Calcd for $C_{32}H_{33}INaO_4^+$ $[M+Na]^+$ 631.1316; found 631.1325.

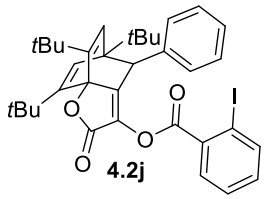
Large scale procedure: Following general procedure **C**, 1-[phenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9b**) (670 mg, 2.00 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (865 mg, 3.00 mmol, 1.50 equiv) were stirred for 12 h. Next, Cs_2CO_3 (720 mg, 2.20 mmol, 1.10 equiv) was added and further stirred for 20 h. The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography using Et_2O/pentane 1:20 as eluent to afford **4.2h** as a white solid (1.10 g, 1.80 mmol, 90%).

7,8-Di-*tert*-butyl-5-ethyl-2-oxo-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2i)



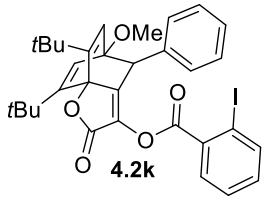
Following general procedure **C**, starting from 1-[phenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9b**) (52.5 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-ethylphenyl 2-diazoacetate (**4.8b**) (68.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2i** as a white solid (90.0 mg, 0.145 mmol, 96%). M.p. 68.0 – 74.5 °C; R_f = 0.32 (Et_2O/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.22 – 7.13 (m, 5H, Ar*H*), 7.10 – 6.94 (m, 3H, Ar*H*), 6.04 (s, 1H, *t*BuCC*H*), 5.74 (s, 1H, *t*BuCC*H*), 3.66 (s, 1H, ArC*H*), 1.68 – 1.50 (m, 2H, C*H*$_2$CH$_3$), 1.29 (s, 9H, *t*Bu), 1.23 (s, 9H, *t*Bu), 1.04 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 161.9, 160.0, 152.5, 150.2, 141.3, 136.9, 133.2, 132.3, 131.7, 130.7, 130.6, 129.3, 128.8, 128.2, 127.6, 127.4, 94.5, 92.5, 52.5, 51.1, 35.6, 35.5, 29.2, 29.1, 25.8, 9.6; IR (ν_{max}, cm^{-1}) 3063 (w), 2962 (m), 2871 (w), 2255 (w), 1777 (s), 1700 (w), 1583 (w), 1463 (w), 1364 (w), 1272 (w), 1236 (s), 1184 (m), 1130 (w), 1091 (s), 1036 (m), 1007 (s), 911 (m); HRMS (ESI) Calcd for $C_{33}H_{36}IO_4^+$ $[M+H]^+$ 623.1653; found 623.1655.

5,7,8-Tri-*tert*-butyl-2-oxo-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2j)



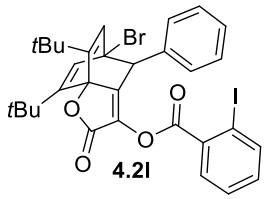
Following general procedure **C**, starting from 1-[phenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9b**) (52.5 mg, 0.150 mmol, 1.00 equiv) and 2,4,6-tri-*tert*-butylphenyl 2-diazoacetate (**4.8c**) (74.5 mg, 0.225 mmol, 1.50 equiv), afforded **4.2j** as a white solid (96.0 mg, 0.148 mmol, 98%). M.p. 84.5 – 89.5 °C; R_f = 0.35 (Et_2O/pentane 4:96), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.9, 1.3 Hz, 1H, Ar*H*), 7.21 – 7.04 (m, 5H, Ar*H*), 7.03 – 6.95 (m, 3H, Ar*H*), 6.18 (s, 2H, 2 x *t*BuCC*H*), 3.82 (s, 1H, ArC*H*), 1.32 (s, 9H, *t*Bu), 1.23 (s, 9H, *t*Bu), 0.88 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 161.7, 161.5, 151.6, 150.0, 141.5, 139.0, 133.3, 132.0, 131.7, 131.6, 130.7, 131.0, 129.0, 128.4, 127.5, 127.3, 127.2, 126.9, 95.0, 91.7, 57.5, 50.8, 35.7, 35.6, 33.9, 29.2, 29.1, 27.0; IR (ν_{max}, cm^{-1}) 3085 (w), 2961 (m), 2872 (w), 2255 (w), 1778 (s), 1694 (w), 1583 (w), 1467 (m), 1431 (w), 1397 (w), 1367 (w), 1271 (w), 1236 (s), 1184 (m), 1136 (m), 1082 (s), 1040 (m), 1009 (m), 912 (m); HRMS (ESI) Calcd for $C_{35}H_{39}INaO_4^+$ $[M+Na]^+$ 673.1785; found 673.1788. All six carbons of phenyl group are different due to adjacent *t*Bu group.

7,8-Di-*tert*-butyl-5-methoxy-2-oxo-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2k)



Following general procedure **C**, starting from 1-[phenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9b**) (52.5 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methoxyphenyl 2-diazoacetate (**4.8d**) (68.5 mg, 0.225 mmol, 1.50 equiv), afforded **4.2k** as a white solid (91.0 mg, 0.146 mmol, 97%). M.p. 153.9 – 157.8 °C; R_f = 0.13 (Et_2O/pentane 4:96), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.31 – 7.26 (m, 1H, Ar*H*), 7.24 – 7.14 (m, 4H, Ar*H*), 7.10 – 7.04 (m, 3H, Ar*H*), 6.33 (d, *J* = 1.3 Hz, 1H, *t*BuCC*H*), 5.98 (d, *J* = 1.2 Hz, 1H, *t*BuCC*H*), 4.05 (s, 1H, ArC*H*), 3.51 (s, 3H, OCH_3), 1.29 (s, 9H, *t*Bu), 1.24 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 161.9, 156.4, 150.9, 148.1, 141.6, 135.8, 133.3, 132.4, 131.7, 130.7, 129.7, 128.5, 128.1, 127.7, 127.6, 126.9, 94.4, 91.3, 85.6, 53.8, 52.1, 35.7, 35.5, 29.1, 29.0; IR (ν_{max}, cm^{-1}) 3063 (w), 2961 (m), 2253 (w), 1783 (s), 1706 (w), 1583 (w), 1465 (w), 1430 (w), 1364 (w), 1307 (m), 1270 (m), 1236 (m), 1187 (m), 1130 (m), 1090 (s), 1036 (w), 1007 (m); HRMS (ESI) Calcd for $C_{32}H_{33}INaO_5^+$ $[M+Na]^+$ 647.1265; found 647.1265.

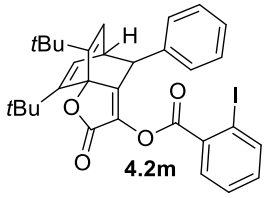
5-Bromo-7,8-di-*tert*-butyl-2-oxo-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2l)



4.2l

Following general procedure **C**, starting from 1-[phenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9b**) (52.5 mg, 0.150 mmol, 1.00 equiv) and 4-bromo-2,6-di-*tert*-butylphenyl 2-diazoacetate (**4.8e**) (79.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2l** as a white solid (100 mg, 0.149 mmol, 99%). M.p. 178.6 – 180.1 °C; R_f = 0.28 (Et_2O/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.27 – 7.17 (m, 5H, Ar*H*), 7.13 – 7.05 (m, 3H, Ar*H*), 6.37 (s, 1H, *t*BuCC*H*), 6.01 (s, 1H, *t*BuCC*H*), 4.10 (s, 1H, ArC*H*), 1.30 (s, 9H, *t*Bu), 1.24 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 162.0, 155.1, 152.1, 149.9, 141.5, 135.5, 133.8, 133.5, 131.9, 131.7, 130.3, 130.2, 130.1, 128.2, 128.1, 127.7, 94.6, 90.9, 61.3, 56.0, 35.6, 35.5, 29.0, 28.9; IR (ν_{max}, cm^{-1}) 3064 (w), 2962 (m), 2871 (w), 2255 (w), 1785 (s), 1702 (w), 1650 (w), 1606 (w), 1584 (w), 1464 (w), 1430 (w), 1365 (w), 1235 (s), 1184 (m), 1123 (m), 1080 (s), 1033 (m), 1005 (s), 911 (s); HRMS (ESI) Calcd for $C_{31}H_{31}BrIO_4^+$ $[M+H]^+$ 673.0445; found 673.0451.

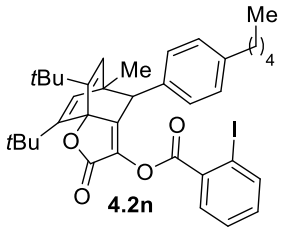
7,8-Di-*tert*-butyl-2-oxo-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl-2-iodobenzoate (4.2m)



4.2m

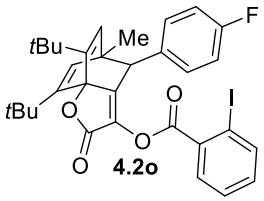
Following general procedure **C**, starting from 1-[phenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9b**) (52.5 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butylphenyl 2-diazoacetate (**4.8f**) (62.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2m** as a white solid (85.0 mg, 0.143 mmol, 95%). M.p. 159.5 – 162.3 °C; R_f = 0.25 (Et_2O/pentane 4:96), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.47 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar*H*), 7.25 – 7.14 (m, 4H, Ar*H*), 7.11 – 7.03 (m, 3H, Ar*H*), 6.24 (d, *J* = 6.5 Hz, 1H, *t*BuCC*H*), 5.86 (d, *J* = 6.3 Hz, 1H, *t*BuCC*H*), 4.00 (d, *J* = 2.4 Hz, 1H, ArC*H*), 3.80 (td, *J* = 6.4, 2.5 Hz, 1H, ArCHC*H*), 1.26 (s, 9H, *t*Bu), 1.23 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 162.1, 156.4, 152.3, 150.4, 141.3, 139.0, 133.3, 132.6, 131.8, 131.7, 128.5, 128.1, 127.7, 127.3, 127.2, 125.0, 94.4, 92.9, 48.8, 45.4, 35.5, 35.4, 29.2, 29.1; IR (ν_{max}, cm^{-1}) 3068 (w), 2960 (m), 2870 (w), 2255 (w), 1777 (s), 1706 (w), 1583 (w), 1466 (w), 1430 (w), 1363 (w), 1272 (m), 1241 (m), 1170 (m), 1127 (s), 1083 (s), 1032 (m), 1008 (s), 912 (m); HRMS (ESI) Calcd for $C_{31}H_{31}INaO_4^+$ $[M+Na]^+$ 617.1159; found 617.1172.

7,8-Di-*tert*-butyl-5-methyl-2-oxo-4-(4-pentylphenyl)-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2n)



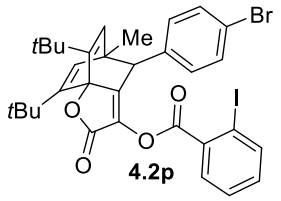
Following general procedure **C**, starting from 1-[4-pentylphenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9c**) (63.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2n** as a white solid (93.0 mg, 0.137 mmol, 91%). M.p. 189.6 – 192.5 °C; R_f = 0.38 (Et_2O/pentane 4:96), $KMnO_4$;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.23 – 7.12 (m, 2H, Ar*H*), 7.05 (td, *J* = 7.6, 2.0 Hz, 1H, Ar*H*), 6.98 (d, *J* = 8.0 Hz, 2H, Ar*H*), 6.89 (d, *J* = 8.1 Hz, 2H, Ar*H*), 5.91 (s, 1H, *t*BuCC*H*), 5.64 (s, 1H, *t*BuCC*H*), 3.58 (s, 1H, ArC*H*), 2.51 – 2.44 (m, 2H, ArCH_2), 1.47 (p, *J* = 7.6 Hz, 2H, $ArCH_2CH_2$), 1.40 – 1.08 (m, 25H, $CHCCH_3$, 2 x *t*Bu, and $CH_2CH_2CH_3$), 0.85 (t, *J* = 7.1 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 161.9, 159.4, 152.2, 150.0, 142.2, 141.3, 133.8, 133.5, 133.1, 132.5, 131.6, 130.6, 130.5, 129.2, 128.2, 127.5, 94.4, 92.7, 53.3, 46.7, 35.4, 35.3, 31.5, 31.1, 29.2, 29.1, 22.5, 20.2, 14.0; IR (ν_{max}, cm^{-1}) 2959 (w), 2930 (w), 2867 (w), 1782 (s), 1703 (w), 1584 (w), 1464 (w), 1363 (w), 1237 (m), 1188 (w), 1146 (w), 1092 (s), 1007 (m), 911 (w), 848 (w); HRMS (ESI) Calcd for $C_{37}H_{44}IO_4^+$ $[M+H]^+$ 679.2279; found 679.2282. One carbon was not resolved at 100 MHz.

7,8-Di-*tert*-butyl-5-methyl-2-oxo-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2o)



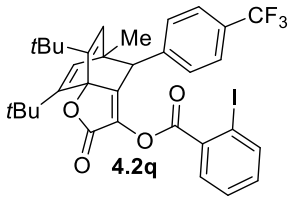
Following general procedure **C**, starting from 1-[4-fluorophenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9d**) (55.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2o** as a white solid (90.0 mg, 0.144 mmol, 96%). M.p. 197.3 – 198.7 °C; R_f = 0.36 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.39 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar*H*), 7.26 – 7.21 (m, 1H, Ar*H*), 7.10 (td, *J* = 7.6, 1.7 Hz, 1H, Ar*H*), 7.01 – 6.95 (m, 2H, Ar*H*), 6.88 (t, *J* = 8.7 Hz, 2H, Ar*H*), 5.92 (s, 1H, *t*BuCC*H*), 5.61 (s, 1H, *t*BuCC*H*), 3.63 (s, 1H, ArC*H*), 1.30 (s, 3H, $CHCCH_3$), 1.28 (s, 9H, *t*Bu), 1.22 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 162.2 (d, *J* = 246.6 Hz), 161.8, 158.8, 152.3, 150.4, 141.5, 133.5, 133.4, 132.6 (d, *J* = 3.3 Hz), 132.1, 131.7, 130.8 (d, *J* = 6.1 Hz), 130.2, 127.8, 115.1 (d, *J* = 21.3 Hz), 94.6, 92.6, 52.8, 46.5, 35.5, 35.4, 29.2, 29.1, 20.2; IR (ν_{max}, cm^{-1}) 3063 (w), 2961 (w), 2931 (w), 2871 (w), 2256 (w), 1779 (s), 1702 (w), 1604 (w), 1584 (w), 1509 (m), 1471 (w), 1431 (w), 1364 (w), 1273 (w), 1234 (s), 1187 (w), 1146 (w), 1093 (s), 1033 (w), 1006 (m), 912 (m), 900 (w); HRMS (ESI) Calcd for $C_{32}H_{32}FINaO_4^+$ $[M+Na]^+$ 649.1222; found 649.1229. One carbon was not resolved at 100 MHz.

4-(4-Bromophenyl)-7,8-di-*tert*-butyl-5-methyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2p)



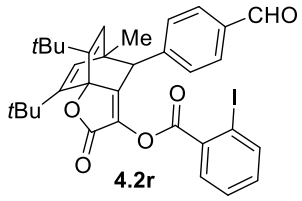
Following general procedure **C**, starting from 1-[4-bromophenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9e**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2p** as a white solid (102 mg, 0.149 mmol, 99%). M.p. 196.5 – 199.3 °C; R_f = 0.37 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.39 – 7.30 (m, 3H, Ar*H*), 7.29 – 7.23 (m, 1H, Ar*H*), 7.11 (td, *J* = 7.6, 1.8 Hz, 1H, Ar*H*), 6.88 (d, *J* = 8.4 Hz, 2H, Ar*H*), 5.91 (s, 1H, *t*BuCC*H*), 5.60 (s, 1H, *t*BuCC*H*), 3.60 (s, 1H, ArC*H*), 1.30 (s, 3H, CHCC*H*$_3$), 1.27 (s, 9H, *t*Bu), 1.21 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 162.0, 158.4, 152.5, 151.0, 141.5, 135.9, 133.5, 133.3, 132.2, 131.7, 131.4, 130.9, 130.9, 130.1, 127.8, 121.6, 94.5, 92.6, 53.0, 46.5, 35.5, 35.4, 29.2, 29.1, 20.2; IR (ν_{max}, cm^{-1}) 3062 (w), 2961 (m), 2930 (w), 2871 (w), 2255 (w), 1779 (s), 1704 (w), 1585 (w), 1484 (w), 1464 (w), 1431 (w), 1363 (w), 1272 (w), 1236 (s), 1183 (w), 1146 (w), 1091 (s), 1034 (w), 1008 (m), 911 (m), 850 (w), 737 (s); HRMS (ESI) Calcd for $C_{32}H_{32}BrINaO_4^+$ $[M+Na]^+$ 709.0421; found 709.0433.

7,8-Di-*tert*-butyl-5-methyl-2-oxo-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2q)



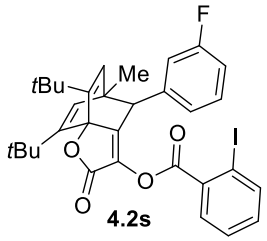
Following general procedure **C**, starting from 1-[4-trifluoromethylphenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9f**) (62.5 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2q** as a white solid (92.0 mg, 0.136 mmol, 91%). M.p. 190.0 – 191.5 °C; R_f = 0.35 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.47 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.30 – 7.24 (m, 1H, Ar*H*), 7.20 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.14 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.08 (td, *J* = 7.6, 1.8 Hz, 1H, Ar*H*), 5.93 (s, 1H, *t*BuCC*H*), 5.61 (s, 1H, *t*BuCC*H*), 3.70 (s, 1H, ArC*H*), 1.32 (s, 3H, CHCC*H*$_3$), 1.29 (s, 9H, *t*Bu), 1.22 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 161.9, 158.0, 152.7, 150.9, 141.5, 141.0, 133.5, 133.2, 132.1, 131.6, 131.0, 130.0, 129.8 (q, *J* = 32.3 Hz), 129.6 (q, *J* = 2.0 Hz), 127.7, 125.2 (q, *J* = 3.0 Hz), 123.9 (q, *J* = 272.7 Hz), 94.4, 92.5, 53.3, 46.5, 35.5, 35.4, 29.2, 29.1, 20.2; IR (ν_{max}, cm^{-1}) 3061 (w), 2963 (m), 2872 (w), 2257 (w), 1781 (s), 1703 (w), 1619 (w), 1584 (w), 1465 (w), 1425 (w), 1364 (w), 1326 (s), 1272 (w), 1236 (m), 1168 (m), 1129 (s), 1092 (s), 1006 (m), 912 (m); HRMS (ESI) Calcd for $C_{33}H_{32}F_3INaO_4^+$ $[M+Na]^+$ 699.1190; found 699.1195.

7,8-Di-*tert*-butyl-4-(4-formylphenyl)-5-methyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2r)



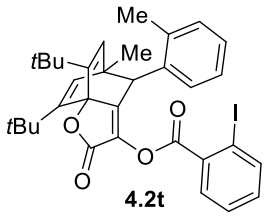
Following general procedure **C**, starting from 1-((4-formylphenyl)ethynyl)-1,2-benziodoxol-3(1*H*)-one (**4.9g**) (56.5 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2r** as a white solid (57 mg, 0.09 mmol, 60%). M.p. 99.0 – 103.4 °C; R_f = 0.19 (Et_2O/pentane 20:80), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H, C*H*O), 7.92 – 7.85 (m, 1H, Ar*H*), 7.75 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.47 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.25 – 7.22 (m, 3H, Ar*H*), 7.10 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.97 (s, 1H, *t*BuCC*H*), 5.63 (s, 1H, *t*BuCC*H*), 3.78 (s, 1H, ArC*H*), 1.35 (s, 3H, CHCC*H*$_3$), 1.32 (s, 9H, *t*Bu), 1.25 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 168.4, 161.7, 157.9, 152.8, 150.9, 143.9, 141.6, 135.6, 133.6, 133.3, 133.1, 131.8, 131.8, 131.0, 130.0, 129.6, 127.8, 94.7, 92.6, 53.6, 46.7, 35.5, 35.4, 29.2, 29.1, 20.3; IR (ν_{max}, cm^{-1}) 3060 (w), 2962 (m), 2871 (w), 2256 (w), 1777 (s), 1702 (m), 1607 (w), 1582 (w), 1465 (w), 1428 (w), 1364 (w), 1269 (m), 1235 (s), 1186 (m), 1090 (s), 1032 (w), 1006 (m); HRMS (ESI) Calcd for $C_{33}H_{33}INaO_5^+$ $[M+Na]^+$ 659.1265; found 659.1268.

7,8-Di-*tert*-butyl-4-(3-fluorophenyl)-5-methyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2s)



Following general procedure **C**, starting from 1-[3-fluorophenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9h**) (55.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2s** as a white solid (78.0 mg, 0.125 mmol, 83%). M.p. 175.5 – 177.8 °C; R_f = 0.36 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.44 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.26 – 7.21 (m, 1H, Ar*H*), 7.19 – 7.06 (m, 2H, Ar*H*), 6.87 (tdd, *J* = 8.4, 2.6, 1.0 Hz, 1H, Ar*H*), 6.81 (d, *J* = 7.7, 1.6 Hz, 1H, Ar*H*), 6.72 (dt, *J* = 10.1, 2.1 Hz, 1H, Ar*H*), 5.92 (s, 1H, *t*BuCC*H*), 5.63 (s, 1H, *t*BuCC*H*), 3.65 (s, 1H, ArC*H*), 1.32 (s, 3H, CHCC*H*$_3$), 1.29 (s, 9H, *t*Bu), 1.22 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 162.4 (d, *J* = 246.2 Hz), 161.8, 158.3, 152.6, 150.5, 141.5, 139.4 (d, *J* = 7.1 Hz), 133.5, 133.3, 132.1, 131.8, 130.8, 130.3, 129.6 (d, *J* = 8.3 Hz), 127.8, 125.2 (d, *J* = 2.1 Hz), 116.1 (d, *J* = 22.1 Hz), 114.5 (d, *J* = 21.0 Hz), 94.6, 92.6, 53.3, 46.5, 35.5, 35.4, 29.2, 29.1, 20.2; IR (ν_{max}, cm^{-1}) 3062 (w), 2961 (m), 2871 (w), 2255 (w), 1777 (s), 1702 (w), 1614 (w), 1587 (m), 1485 (m), 1440 (w), 1390 (w), 1364 (w), 1266 (m), 1235 (s), 1191 (w), 1152 (m), 1091 (s), 1034 (w), 1006 (m), 959 (w), 912 (m); HRMS (ESI) Calcd for $C_{32}H_{32}FINaO_4^+$ $[M+Na]^+$ 649.1222; found 649.1229.

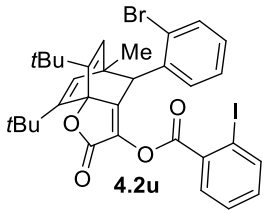
7,8-Di-*tert*-butyl-5-methyl-2-oxo-4-(o-tolyl)-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2t)



4.2t

Following general procedure **C**, starting from 1-[*o*-tolylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9i**) (54.5 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2t** as a white solid (82.0 mg, 0.132 mmol, 88%). M.p. 200.0 – 202.5 °C; R_f = 0.38 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.20 – 6.96 (m, 6H, Ar*H*), 6.80 – 6.70 (m, 1H, Ar*H*), 5.95 (s, 1H, *t*BuCC*H*), 5.67 (s, 1H, *t*BuCC*H*), 3.95 (s, 1H, ArC*H*), 2.36 (s, 3H, ArC*H*$_3$), 1.32 (s, 3H, CHCC*H*$_3$), 1.30 (s, 9H, *t*Bu), 1.24 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 161.9, 160.2, 152.4, 149.8, 141.3, 138.0, 135.3, 133.8, 133.2, 132.3, 131.7, 131.0, 130.4, 130.3, 127.6, 127.6, 127.3, 125.9, 94.4, 92.8, 48.5, 47.5, 35.5, 35.3, 29.1, 29.1, 20.8, 19.4; IR (ν_{max}, cm^{-1}) 3060 (w), 2961 (m), 2931 (w), 2872 (w), 2254 (w), 1776 (s), 1697 (w), 1584 (w), 1465 (m), 1364 (w), 1232 (s), 1188 (m), 1147 (m), 1091 (s), 1006 (m), 912 (m); HRMS (ESI) Calcd for $C_{33}H_{35}INaO_4^+$ $[M+Na]^+$ 645.1472; found 645.1481.

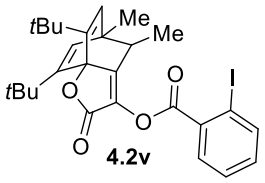
4-(2-Bromophenyl)-7,8-di-*tert*-butyl-5-methyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2u)



4.2u

Following general procedure **C**, starting from 1-[2-bromophenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9j**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2u** as a white solid (94.0 mg, 0.137 mmol, 91%). M.p. 212.5 – 214.0 °C; R_f = 0.37 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.46 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar*H*), 7.35 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.16 (td, *J* = 7.6, 1.3 Hz, 1H, Ar*H*), 7.08 (td, *J* = 7.6, 1.7 Hz, 1H, Ar*H*), 7.02 (td, *J* = 7.6, 1.7 Hz, 1H, Ar*H*), 6.85 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 5.96 (s, 1H, *t*BuCC*H*), 5.63 (s, 1H, *t*BuCC*H*), 4.36 (s, 1H, ArC*H*), 1.42 (s, 3H, CHCC*H*$_3$), 1.30 (s, 9H, *t*Bu), 1.23 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 161.9, 159.2, 152.6, 150.5, 141.4, 136.6, 133.5, 133.3, 132.9, 132.5, 131.7, 130.9, 130.6, 129.3, 129.0, 127.6, 127.5, 127.1, 94.4, 92.7, 50.9, 47.6, 35.5, 35.4, 29.2, 29.1, 19.4; IR (ν_{max}, cm^{-1}) 3062 (w), 2961 (m), 2871 (w), 2255 (w), 1779 (s), 1707 (w), 1584 (w), 1565 (w), 1467 (m), 1435 (w), 1390 (w), 1364 (w), 1313 (w), 1272 (w), 1234 (s), 1187 (m), 1146 (m), 1089 (s), 1029 (m), 1005 (s), 911 (s); HRMS (ESI) Calcd for $C_{32}H_{32}BrINaO_4^+$ $[M+Na]^+$ 709.0421; found 709.0423.

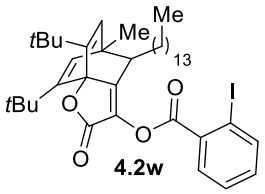
7,8-Di-*tert*-butyl-4,5-dimethyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2v)



4.2v

Following general procedure **D**, starting from propynyl-1,2-benziodoxol-3(1*H*)-one (**4.9k**) (43.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2v** as a white solid (43.0 mg, 0.079 mmol, 53%). M.p. 170.5 – 174.8 °C; R_f = 0.27 (Et_2O/pentane 7:93), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 8.0, 3.2, 1.4 Hz, 2H, Ar*H*), 7.45 (td, *J* = 7.7, 1.2 Hz, 1H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.80 (s, 1H, *t*BuCC*H*), 5.70 (s, 1H, *t*BuCC*H*), 2.56 (q, *J* = 7.0 Hz, 1H, C*H*CH_3), 1.51 (s, 3H, CHCC*H*$_3$), 1.18 (s, 9H, *t*Bu), 1.17 (s, 9H, *t*Bu), 1.04 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 162.4, 161.5, 151.5, 150.4, 141.7, 133.6, 132.9, 132.6, 132.2, 130.0, 129.9, 128.1, 94.9, 92.5, 44.9, 42.5, 35.2, 35.2, 29.2, 29.1, 19.5, 15.3; IR (ν_{max}, cm^{-1}) 3059 (w), 2962 (m), 2872 (w), 2255 (w), 1778 (s), 1704 (w), 1583 (w), 1469 (w), 1430 (w), 1390 (w), 1365 (w), 1271 (m), 1235 (s), 1154 (m), 1091 (s), 1043 (m), 1008 (m), 958 (w), 912 (m); HRMS (ESI) Calcd for $C_{27}H_{31}INaO_4^+$ $[M+Na]^+$ 569.1159; found 569.1161.

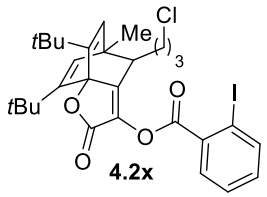
7,8-Di-*tert*-butyl-5-methyl-2-oxo-4-tetradecyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2w)



4.2w

Following general procedure **D**, starting from hexadecynyl-1,2-benziodoxol-3(1*H*)-one (**4.9l**) (70.5 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2w** (86.0 mg, 0.118 mmol, 79%) as a colourless oil. R_f = 0.34 (Et_2O/pentane 7:93), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar*H*), 8.05 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.79 (s, 1H, *t*BuCC*H*), 5.70 (s, 1H, *t*BuCC*H*), 2.50 (dd, *J* = 6.2, 4.3 Hz, 1H, C*H*CH_2), 1.62 – 1.54 (m, 4H, CHC*H*$^a{}_2$ and CHCC*H*$_3$), 1.31 – 1.09 (m, 43H, CHC*H*$^b{}_2$, 12 x C*H*$_2$, and 2 x *t*Bu), 0.88 (t, *J* = 6.8 Hz, 3H, CH_2C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 162.0, 161.4, 152.0, 149.6, 142.0, 133.7, 133.5, 132.5, 132.0, 130.8, 130.0, 128.0, 95.3, 92.8, 48.0, 45.2, 35.2, 35.2, 31.9, 31.2, 30.1, 29.7, 29.7, 29.6, 29.5, 29.4, 29.4, 29.2, 29.1, 28.7, 22.7, 20.2, 14.1; IR (ν_{max}, cm^{-1}) 3057 (w), 2957 (m), 2924 (s), 2854 (m), 1781 (s), 1698 (w), 1583 (w), 1464 (m), 1433 (w), 1389 (w), 1363 (w), 1270 (w), 1234 (s), 1154 (w), 1089 (s), 1035 (w), 1006 (m); HRMS (ESI) Calcd for $C_{40}H_{57}INaO_4^+$ $[M+Na]^+$ 751.3194; found 751.3200. Two carbons were not resolved at 100 MHz.

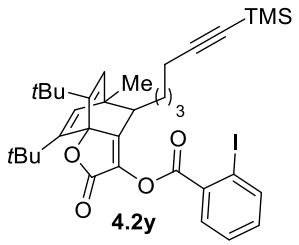
7,8-Di-*tert*-butyl-4-(3-chloropropyl)-5-methyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2x)



4.2x

Following general procedure **D**, starting from (5-chloropent-1-ynyl)-1,2-benziodoxol-3(1*H*)-one (**4.9m**) (52.5 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2x** as a white solid (66.0 mg, 0.108 mmol, 72%). M.p. 124.0 – 128.2 °C; R_f = 0.29 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 8.05 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.80 (s, 1H, *t*BuCC*H*), 5.72 (s, 1H, *t*BuCC*H*), 3.46 – 3.37 (m, 2H, ClCH_2CH$_2$), 2.62 – 2.49 (m, 1H, C*H*CH$_2$), 1.85 – 1.66 (m, 3H, ClCH$_2$CH_2 and ClCH$_2$CH$_2$C$H^a{}_2$), 1.61 – 1.49 (m, 4H, ClCH$_2$CH$_2$C$H^b{}_2$ and CHCCH_3), 1.18 (s, 9H, *t*Bu), 1.16 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 162.3, 160.2, 152.2, 150.1, 141.9, 133.9, 133.4, 132.5, 131.9, 130.6, 130.3, 128.2, 95.2, 92.7, 47.2, 45.1, 45.0, 35.3, 35.2, 31.1, 29.1, 29.1, 28.1, 20.2; IR (ν_{max}, cm^{-1}) 3060 (w), 2960 (m), 2870 (w), 2254 (w), 1778 (s), 1698 (w), 1583 (w), 1464 (w), 1390 (w), 1364 (w), 1274 (w), 1235 (s), 1192 (w), 1154 (w), 1128 (w), 1093 (s), 1034 (w), 1007 (m), 913 (m); HRMS (ESI) Calcd for $C_{29}H_{34}ClINaO_4^+$ [M+Na]$^+$ 631.1083; found 631.1090.

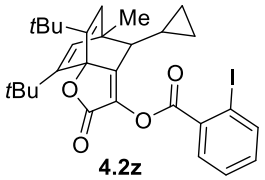
7,8-Di-*tert*-butyl-5-methyl-2-oxo-4-(6-(trimethylsilyl)hex-5-yn-1-yl)-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2y)



4.2y

Following general procedure **D**, starting from 8-(trimethylsilyl)octa-1,7-diyn-1-yl-1,2-benziodoxol-3(1*H*)-one (**4.9n**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2y** as a yellow thick oil (73.0 mg, 0.107 mmol, 71%). R_f = 0.27 (Et_2O/pentane 7:93), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 8.05 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.45 (td, *J* = 7.7, 1.2 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.79 (s, 1H, *t*BuCC*H*), 5.71 (s, 1H, *t*BuCC*H*), 2.54 (t, *J* = 5.0 Hz, 1H, C*H*CH$_2$), 2.08 (t, *J* = 6.4 Hz, 2H, CCCH_2), 1.61 – 1.55 (m, 4H, CHC$H^a{}_2$ and CHCCH_3), 1.44 – 1.31 (m, 5H, CHC$H^b{}_2$, CHCH$_2$CH_2CH_2CH$_2$CC), 1.18 (s, 9H, *t*Bu), 1.16 (s, 9H, *t*Bu), 0.11 (s, 9H, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.2, 160.8, 152.1, 149.6, 141.9, 133.8, 133.4, 132.4, 132.1, 130.8, 130.1, 128.1, 107.0, 95.2, 92.8, 84.7, 47.8, 45.1, 35.2, 35.2, 30.3, 29.1, 29.1, 28.9, 27.4, 20.2, 19.6, 0.2; IR (ν_{max}, cm^{-1}) 3058 (w), 2960 (m), 2870 (w), 2173 (w), 1781 (s), 1700 (w), 1578 (w), 1465 (w), 1430 (w), 1392 (w), 1364 (w), 1270 (w), 1235 (s), 1190 (w), 1154 (w), 1092 (s), 1034 (w), 1007 (m); HRMS (ESI) Calcd for $C_{35}H_{45}INaO_4Si^+$ [M+Na]$^+$ 707.2024; found 707.2043.

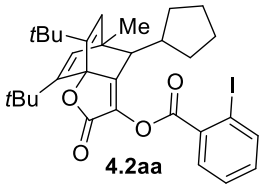
7,8-Di-*tert*-butyl-4-cyclopropyl-5-methyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2z)



4.2z

Following general procedure **D**, starting from 2-cyclopropylethynyl-1,2-benziodoxol-3(1*H*)-one (**4.9o**) (47.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2z** as a white solid (80.0 mg, 0.140 mmol, 93%). M.p. 185.4 – 188.5 °C; R_f = 0.37 (Et_2O/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar*H*), 8.07 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.82 (s, 1H, *t*BuCC*H*), 5.76 (s, 1H, *t*BuCC*H*), 1.71 (d, *J* = 9.5 Hz, 1H, C*H*CCH$_3$), 1.64 (s, 3H, CHCC*H$_3$*), 1.21 (s, 9H, *t*Bu), 1.16 (s, 9H, *t*Bu), 0.66 – 0.52 (m, 1H, cyclopropyl-C*H*), 0.47 – 0.28 (m, 3H, cyclopropyl-C*H$_2$* and C*H^a*$_2$), 0.22 – 0.10 (m, 1H, cyclopropyl-C*H^b*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 162.2, 160.3, 151.5, 150.3, 142.1, 133.8, 132.9, 132.6, 131.8, 130.7, 130.6, 128.1, 95.4, 92.4, 52.9, 46.4, 35.2, 35.2, 29.3, 29.1, 20.9, 12.9, 5.6, 3.0; IR (ν_{max}, cm^{-1}) 3061 (w), 2997 (w), 2960 (m), 2931 (w), 2871 (w), 2254 (w), 1773 (s), 1701 (w), 1583 (w), 1467 (w), 1429 (w), 1389 (w), 1364 (w), 1318 (w), 1272 (w), 1235 (s), 1192 (w), 1156 (w), 1091 (s), 1033 (m), 1007 (m), 962 (w), 912 (m); HRMS (ESI) Calcd for $C_{29}H_{33}INaO_4^+$ $[M+Na]^+$ 595.1316; found 595.1325.

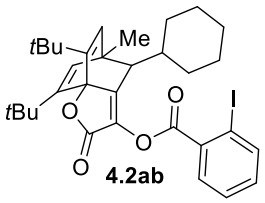
7,8-Di-*tert*-butyl-4-cyclopentyl-5-methyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2aa)



4.2aa

Following general procedure **D**, starting from 2-cyclopentylethynyl-1,2-benziodoxol-3(1*H*)-one (**4.9p**) (51.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2aa** as a white solid (83.0 mg, 0.138 mmol, 92%). M.p. 169.0 – 171.2 °C; R_f = 0.27 (Et_2O/pentane 7:97), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (td, *J* = 7.4, 6.8, 1.4 Hz, 2H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.80 (s, 1H, *t*BuCC*H*), 5.69 (s, 1H, *t*BuCC*H*), 2.75 (d, *J* = 2.9 Hz, 1H, C*H*CCH$_3$), 2.15 – 2.02 (m, 1H, cyclopentyl-*H*), 1.77 (dt, *J* = 11.0, 7.3 Hz, 1H, cyclopentyl-*H*), 1.62 – 1.56 (m, 4H, cyclopentyl-*H* and CHCC*H$_3$*), 1.49 – 1.31 (m, 6H, cyclopentyl-*H*), 1.18 (s, 9H, *t*Bu), 1.16 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 162.2, 159.1, 152.2, 148.8, 142.0, 134.1, 133.7, 132.4, 132.1, 131.1, 130.9, 128.1, 95.3, 93.2, 51.3, 45.5, 41.1, 35.2, 35.1, 33.0, 30.1, 29.2, 29.1, 25.1, 23.9, 21.1; IR (ν_{max}, cm^{-1}) 3059 (w), 2956 (m), 2866 (w), 2254 (w), 1775 (s), 1690 (w), 1583 (w), 1464 (w), 1431 (w), 1390 (w), 1363 (w), 1272 (w), 1234 (s), 1186 (m), 1153 (w), 1094 (s), 1034 (w), 1005 (m), 912 (m); HRMS (ESI) Calcd for $C_{31}H_{38}IO_4^+$ $[M+H]^+$ 601.1809; found 601.1818.

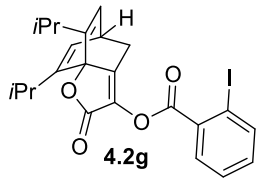
7,8-Di-*tert*-butyl-4-cyclohexyl-5-methyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2ab)



4.2ab

Following general procedure **D**, starting from 2-cyclohexylethynyl-1,2-benziodoxol-3(1*H*)-one (**4.9q**) (53.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (65.0 mg, 0.225 mmol, 1.50 equiv), afforded **4.2ab** as a white solid (55.0 mg, 0.089 mmol, 60%). M.p. 185.0 – 190.5 °C; R_f = 0.27 (Et_2O/pentane 7:93), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar*H*), 8.06 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.78 (s, 1H, *t*BuCC*H*), 5.72 (s, 1H, *t*BuCC*H*), 2.45 (d, *J* = 2.0 Hz, 1H, C*H*CCH$_3$), 1.75 – 1.54 (m, 8H, cyclohexyl-*H* and CHCC*H*$_3$), 1.47 – 1.43 (m, 1H, cyclohexyl-*H*), 1.34 – 1.22 (m, 2H, cyclohexyl-*H*), 1.17 (s, 9H, *t*Bu), 1.16 (s, 9H, *t*Bu), 1.11 – 0.93 (m, 3H, cyclohexyl-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 162.1, 159.4, 152.6, 148.8, 142.0, 134.4, 133.7, 132.4, 132.2, 131.0, 130.6, 128.1, 95.2, 93.1, 54.4, 45.5, 39.1, 35.2, 35.1, 34.3, 31.2, 29.2, 29.1, 27.2, 26.9, 26.1, 21.2; IR (ν_{max}, cm^{-1}) 3060 (w), 2967 (w), 2958 (m), 2929 (m), 2855 (w), 2255 (w), 1774 (s), 1689 (w), 1583 (w), 1464 (w), 1390 (w), 1364 (w), 1271 (w), 1234 (s), 1187 (m), 1093 (s), 1034 (w), 1006 (m), 912 (m); HRMS (ESI) Calcd for $C_{32}H_{39}INaO_4^+$ $[M+Na]^+$ 637.1785; found 637.1789.

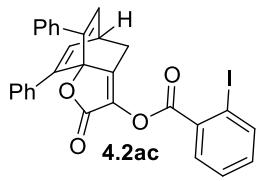
7,8-Di*iso*propyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2g)



4.2g

Following general procedure **B**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-di*iso*propylphenyl 2-diazoacetate (**4.8g**) (44 mg, 0.18 mmol, 1.2 equiv), afforded **4.2g** as a white solid (66.0 mg, 0.135 mmol, 90%). M.p. 99.1 – 100.3 °C; R_f = 0.3 (Et_2O/pentane 7:93), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.02 (m, 2H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.05 (dd, *J* = 6.3, 1.4 Hz, 2H, 2 x *i*PrCC*H*), 3.92 (tt, *J* = 6.3, 2.6 Hz, 1H, CHC*H*CH$_2$), 2.62 – 2.55 (m, 2H, CH$_3$C*H*CH$_3$), 2.46 (d, *J* = 2.6 Hz, 2H, CHC*H*$_2$), 1.10 (d, *J* = 6.9 Hz, 6H, *i*Pr), 1.03 (d, *J* = 6.7 Hz, 6H, *i*Pr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 162.0, 154.0, 149.9, 141.7, 133.7, 132.4, 132.2, 129.5, 128.1, 125.7, 95.0, 90.5, 36.8, 32.2, 27.9, 21.9, 21.4; IR (ν_{max}, cm^{-1}) 3063 (w), 2964 (m), 2931 (w), 2872 (w), 1779 (s), 1709 (w), 1583 (w), 1465 (w), 1430 (w), 1270 (m), 1235 (s), 1174 (m), 1098 (s), 1071 (s), 1009 (m), 957 (w), 916 (w); HRMS (ESI) Calcd for $C_{23}H_{24}IO_4^+$ $[M+H]^+$ 491.0714; found 491.0718. Three carbons were resolved from two *i*Pr groups at 100 MHz.

2-Oxo-7,8-diphenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2ac)

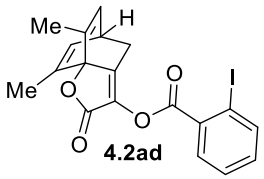


4.2ac

Following general procedure **B**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and [1,1':3',1''-terphenyl]-2'-yl 2-diazoacetate (**4.8h**) (57 mg,

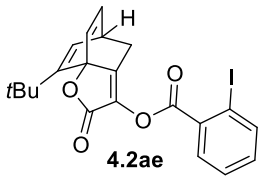
0.18 mmol, 1.2 equiv), afforded **4.2ac** as a white solid (60.0 mg, 0.107 mmol, 71%). M.p. 172.5 – 175.6 °C; R_f = 0.4 (Et_2O/pentane 33:66), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 4.2, 1.4 Hz, 1H, Ar*H*), 7.93 (dd, *J* = 4.1, 1.4 Hz, 1H, Ar*H*), 7.38 – 7.19 (m, 11H, Ar*H*), 7.12 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.54 (d, *J* = 6.3 Hz, 2H, 2 x PhCC*H*), 4.12 (tt, *J* = 6.4, 2.6 Hz, 1H, CHC*H*CH_2), 2.72 (d, *J* = 2.6 Hz, 2H, CHC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 161.8, 152.3, 144.2, 141.8, 133.8, 133.6, 132.2, 132.1, 131.5, 130.3, 128.4, 128.2, 128.1, 95.1, 88.6, 37.9, 31.9; IR (ν_{max}, cm^{-1}) 3056 (w), 2954 (w), 2919 (m), 2854 (w), 2249 (w), 1946 (w), 1780 (s), 1760 (s), 1713 (w), 1582 (w), 1492 (w), 1465 (w), 1427 (w), 1264 (m), 1234 (s), 1183 (m), 1097 (s), 1031 (w), 1008 (m), 960 (w), 911 (m); HRMS (ESI) Calcd for $C_{29}H_{19}INaO_4^+$ $[M+Na]^+$ 581.0220; found 581.0224.

7,8-Dimethyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2ad)



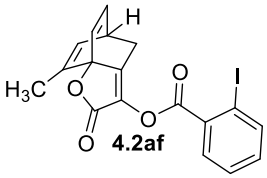
Following general procedure **B**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2,6-dimethylphenyl 2-diazoacetate (**4.8i**) (34.5 mg, 0.180 mmol, 1.20 equiv), afforded **4.2ad** as a white solid (55.0 mg, 0.127 mmol, 84%). M.p. 127.6 – 128.9 °C; R_f = 0.37 (Et_2O/pentane 5:25), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 5.2, 1.6 Hz, 1H, Ar*H*), 8.04 (dd, *J* = 5.3, 1.7 Hz, 1H, Ar*H*), 7.45 (td, *J* = 7.7, 1.2 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.09 (dq, *J* = 6.2, 1.7 Hz, 2H, 2 x CH_3CC*H*), 3.85 (tt, *J* = 6.2, 2.6 Hz, 1H, CHC*H*CH_2), 2.47 (d, *J* = 2.6 Hz, 2H, CHC*H*$_2$), 1.85 (d, *J* = 1.7 Hz, 6H, 2 x C*H*$_3$CCH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 162.0, 152.2, 141.8, 139.5, 133.8, 132.2, 129.4, 128.6, 128.1, 95.1, 89.9, 37.5, 32.5, 14.4; IR (ν_{max}, cm^{-1}) 3051 (w), 2977 (w), 2944 (w), 2916 (w), 2257 (w), 1779 (s), 1757 (s), 1708 (m), 1582 (w), 1562 (w), 1467 (w), 1437 (w), 1283 (m), 1234 (s), 1205 (m), 1172 (s), 1128 (m), 1086 (s), 1029 (m), 1012 (s), 912 (m); HRMS (ESI) Calcd for $C_{19}H_{16}IO_4^+$ $[M+H]^+$ 435.0088; found 435.0081. One carbon was not resolved at 100 MHz.

7-(*Tert*-butyl)-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2ae)



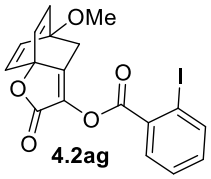
Following general procedure **B**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2-(*tert*-butyl)phenyl 2-diazoacetate (**4.8j**) (39.5 mg, 0.180 mmol, 1.20 equiv), afforded **4.2ae** as a white solid (63.0 mg, 0.136 mmol, 91%). M.p. 145.3 – 147.3 °C; R_f = 0.38 (Et_2O/pentane 15:85), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.02 (m, 2H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.51 – 6.44 (m, 2H, *t*BuCC*H* and OCCHC*H*), 6.09 (d, *J* = 6.5 Hz, 1H, OCC*H*CH), 4.02 – 3.97 (m, 1H, CHC*H*CH_2), 2.58 – 2.44 (m, 2H, CHC*H*$_2$), 1.15 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 162.0, 153.5, 151.4, 141.7, 135.1, 133.7, 132.4, 132.2, 130.2, 128.1, 125.5, 95.0, 89.8, 38.1, 34.9, 31.6, 28.4; IR (ν_{max}, cm^{-1}) 3068 (w), 2961 (w), 2870 (w), 1781 (s), 1710 (w), 1583 (w), 1465 (w), 1429 (w), 1363 (w), 1333 (w), 1271 (m), 1236 (s), 1183 (m), 1136 (m), 1099 (s), 1059 (m), 1029 (w), 1008 (m), 951 (w); HRMS (ESI) Calcd for $C_{21}H_{20}IO_4^+$ $[M+H]^+$ 463.0401; found 463.0401. One carbon was not resolved at 100 MHz.

7-Methyl-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2af)



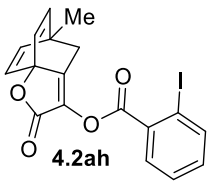
Following general procedure **B**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and *o*-tolyl 2-diazoacetate (**4.8k**) (32 mg, 0.18 mmol, 1.2 equiv), afforded **4.2af** as a colorless thick gel (35.0 mg, 0.083 mmol, 55%). R_f = 0.25 (Et_2O/pentane 15:85), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.10 – 8.01 (m, 2H, Ar*H*), 7.45 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.57 – 6.42 (m, 2H, OCCHC*H* and CH_3CC*H*), 6.09 (d, *J* = 5.7 Hz, 1H, OCC*H*CH), 3.99 (tt, *J* = 5.9, 2.6 Hz, 1H, C*H*CH_2), 2.62 – 2.40 (m, 2H, CHC*H*$_2$), 1.86 (d, *J* = 1.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.0, 151.7, 141.8, 140.0, 135.2, 133.8, 132.2, 132.2, 131.0, 129.7, 128.1, 127.8, 95.1, 88.5, 38.5, 32.1, 14.3; IR (ν_{max}, cm^{-1}) 3063 (w), 2917 (w), 1782 (s), 1759 (s), 1710 (w), 1584 (w), 1563 (w), 1466 (w), 1435 (w), 1336 (w), 1286 (m), 1236 (s), 1203 (m), 1175 (m), 1150 (m), 1096 (s), 1064 (m), 1029 (m), 1009 (m); HRMS (ESI) Calcd for $C_{18}H_{14}IO_4^+$ $[M+H]^+$ 420.9931; found 420.9937.

5-Methoxy-2-oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2ag)



Following general procedure **B**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 4-methoxyphenyl 2-diazoacetate (**4.8l**) (35 mg, 0.18 mmol, 1.2 equiv), afforded **4.2ag** as a colorless thick gel (53.0 mg, 0.122 mmol, 81%). R_f = 0.25 (Et_2O/pentane 25:75), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 3.3, 1.4 Hz, 1H, Ar*H*), 8.03 (dd, *J* = 3.2, 1.5 Hz, 1H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.62 (d, *J* = 7.8 Hz, 2H, 2 x CH_3OCC*H*), 6.46 (d, *J* = 7.8 Hz, 2H, 2 x CH_3OCCHC*H*), 3.64 (s, 3H, OC*H*$_3$), 2.71 (s, 2H, OCH_3CC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 161.9, 149.4, 141.9, 136.1, 133.9, 132.2, 132.0, 129.5, 129.4, 128.2, 95.2, 85.7, 85.2, 54.0, 36.2; IR (ν_{max}, cm^{-1}) 3071 (w), 2942 (w), 2836 (w), 1788 (s), 1760 (m), 1581 (w), 1564 (w), 1504 (w), 1465 (w), 1429 (w), 1352 (m), 1314 (w), 1276 (m), 1237 (s), 1198 (m), 1168 (m), 1095 (s), 1010 (m), 913 (w); HRMS (ESI) Calcd for $C_{18}H_{14}IO_5^+$ $[M+H]^+$ 436.9880; found 436.9881.

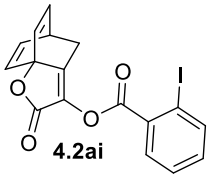
5-Methyl-2-oxo-4,5-dihydro-2H-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2ah)



Following general procedure **B**, starting from 1-[(triiso-propylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and *p*-tolyl 2-diazoacetate (**4.8m**) (32 mg, 0.18 mmol, 1.2 equiv), afforded **4.2ah** as a white solid (26.0 mg, 62.0 µmol, 41%). M.p. 128 – 130 °C; Rf = 0.35 (EtOAc/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dt, *J* = 7.8, 1.3 Hz, 2H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.48 (d, *J* = 7.4 Hz, 2H, 2 x OCC*H*), 6.24 (d, *J* = 7.4 Hz, 2H, 2 x H_3CCC*H*), 2.41 (s, 2H, CH_3CC*H*$_2$), 1.72 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 162.3, 152.9, 144.6, 142.0, 133.9, 132.4, 132.4, 129.1, 128.3, 124.3, 95.2, 87.3, 50.3, 31.1, 19.7; IR (ν_{max},

cm^{-1}) 2988 (s), 2904 (m), 2114 (s), 1707 (m), 1370 (s), 1216 (m), 1077 (m), 1049 (s); HRMS (ESI) Calcd for $C_{18}H_{14}IO_4^+$ [M+H]$^+$ 420.9931; found 420.9927.

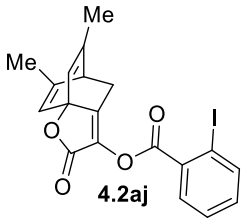
2-Oxo-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2ai)



4.2ai

Following general procedure **B**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and phenyl 2-diazoacetate (**4.8n**) (30 mg, 0.18 mmol, 1.2 equiv), afforded **4.2ai** as a colorless thick gel (20.0 mg, 0.049 mmol, 33%). R_f = 0.50 (Et_2O/pentane 33:67), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.02 (m, 2H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.7, 1.8 Hz, 1H, Ar*H*), 6.54 – 6.49 (m, 4H, 4 x vinyl C*H*), 4.13 (p, *J* = 3.5 Hz, 1H, CHC*H*CH_2), 2.52 (d, *J* = 2.6 Hz, 2H, CHCHC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 162.0, 151.2, 141.8, 134.5, 133.8, 132.2, 132.2, 131.5, 130.0, 128.2, 95.1, 87.1, 39.3, 31.8; IR (ν_{max}, cm^{-1}) 3060 (w), 2953 (w), 2924 (w), 2856 (w), 1783 (s), 1760 (s), 1583 (w), 1492 (w), 1465 (w), 1428 (w), 1344 (w), 1286 (m), 1270 (m), 1238 (s), 1192 (m), 1128 (m), 1109 (s), 1079 (m), 1071 (w), 1054 (w), 1010 (m), 938 (w); HRMS (ESI) Calcd for $C_{17}H_{12}IO_4^+$ [M+H]$^+$ 406.9775; found 406.9779.

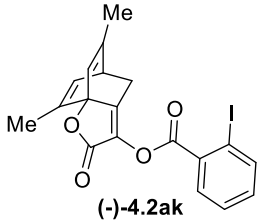
6,9-Dimethyl-2-oxo-4,5-dihydro-2H-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (4.2aj)



4.2aj

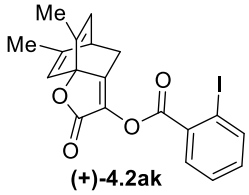
Following general procedure **B**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 3,5-dimethylphenyl 2-diazoacetate (**4.8o**) (34 mg, 0.18 mmol, 1.2 equiv), afforded **4.2aj** as a white solid (37.0 mg, 85.0 µmol, 57%). M.p. 169 – 171 °C; R_f = 0.33 (EtOAc/pentane 10:90), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (ddd, *J* = 7.9, 2.2, 1.4 Hz, 2H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.02 (p, *J* = 1.8 Hz, 2H, 2 x OCC*H*), 3.48 (h, *J* = 2.4 Hz, 1H, C*H*CH_2), 2.51 (d, *J* = 2.6 Hz, 2H, C*H*$_2$), 1.91 (d, *J* = 1.6 Hz, 6H, 2 x C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 162.3, 152.9, 144.6, 142.0, 133.9, 132.4, 132.4, 129.1, 128.3, 124.3, 95.2, 87.3, 50.3, 31.1, 19.7; IR (ν_{max}, cm^{-1}) 2988 (s), 2924 (s), 2114 (s), 1378 (s), 1215 (m), 1074 (s), 1048 (s); HRMS (ESI) Calcd for $C_{19}H_{16}IO_4^+$ [M+H]$^+$ 435.0088; found 435.0080.

(-)-(5S,7aR)-6,8-Dimethyl-2-oxo-4,5-dihydro-2H-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (-)-(4.2ak) and (+)-(5R,7aS)-6,8-Dimethyl-2-oxo-4,5-dihydro-2H-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (+)-(4.2ak).



(-)-4.2ak

and

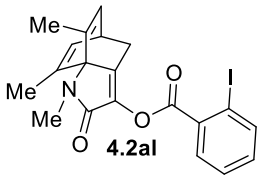


(+)-4.2ak

Following general procedure **B**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2,5-dimethylphenyl 2-diazoacetate (**4.8p**) (34 mg, 0.18

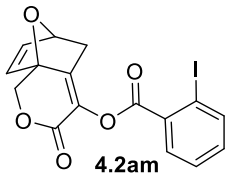
mmol, 1.2 equiv), afforded **4.2ak** as a white solid (28.0 mg, 64.0 µmol, 42%). The obtained racemic mixture was resolved by preparative chiral HPLC, Chiralpak IB, *i*PrOH/hexanes 3.5:96.5, 18 mL/min, tr (+) = 14.9 min. and tr (-) = 16.4 min. λ = 254 cm^{-1}. M.p. 125 – 126 °C; R_f = 0.27 (Et_2O/pentane 10:90), $KMnO_4$; $[\alpha]_D^{20}$ = +7.78 (c = 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 7.9, 3.6, 1.4 Hz, 2H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.08 (dt, *J* = 6.1, 1.7 Hz, 1H, CH_3C=C*H*), 5.99 (p, *J* = 1.8 Hz, 1H, OCC*H*), 3.65 (dq, *J* = 6.1, 2.4 Hz, 1H, C*H*CH_2), 2.49 (d, *J* = 2.6 Hz, 2H, CH_2), 1.89 (d, *J* = 1.7 Hz, 3H, CH_3), 1.84 (d, *J* = 1.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 162.2, 152.6, 145.7, 142.0, 140.5, 133.9, 132.4, 132.4, 129.3, 128.3, 127.6, 123.3, 95.2, 88.7, 44.0, 31.8, 19.5, 14.4.; IR (ν_{max}, cm^{-1}) 2987 (w), 2965 (w), 2359 (w), 2341 (w), 1757 (s), 1705 (m), 1428 (m), 1228 (s), 1128 (s), 1114 (m), 1102 (s), 1052 (s), 1006 (s), 818 (m), 767 (m), 727 (s); HRMS (ESI) Calcd for $C_{19}H_{16}IO_4^+$ $[M+H]^+$ 435.0088; found 435.0083. The crystal structure of **(+)-4.2ak** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 2027173. $[\alpha]_D^{20}$ of **(-)-4.2ak** was not determined.

1,7,8-trimethyl-2-oxo-1,2,4,5-tetrahydro-5,7a-ethenoindol-3-yl 2-iodobenzoate (4.2al)



Following general procedure **B**, starting from 1-[(triiso-propylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and 2-diazo-*N*-(2,6-dimethylphenyl)-*N*-methylacetamide (**4.8q**) (37 mg, 0.18 mmol, 1.2 equiv), afforded **4.2al** as a white solid (27.0 mg, 60.0 µmol, 40%). M.p. 149 – 151 °C; Rf = 0.23 (EtOAc/pentane 25:75), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, 2H, Ar*H*), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.19 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.13 (dq, *J* = 6.2, 1.6 Hz, 2H, 2 x CH_3C=C*H*), 3.79 (tt, *J* = 6.3, 2.6 Hz, 1H, CHCH_2), 3.36 (s, 3H, NCH_3), 2.31 (d, *J* = 2.6 Hz, 2H, CH_2), 1.84 (d, *J* = 1.6 Hz, 6H, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 162.7, 143.2, 141.7, 139.4, 134.3, 133.5, 133.2, 132.4, 130.2, 128.2, 95.1, 75.3, 37.8, 31.8, 31.2, 16.4; IR (ν_{max}, cm^{-1}) 2990 (s), 2922 (s), 2114 (s), 1702 (m), 1372 (s), 1215 (s), 1075 (s), 1050 (s); HRMS (ESI) Calcd for $C_{20}H_{19}INO_3$+ $[M+H]^+$ 448.0404; found 448.0416.

3-Oxo-5,6-dihydro-1*H*,3*H*-6,8a-epoxyisochromen-4-yl 2-iodobenzoate (4.2am)

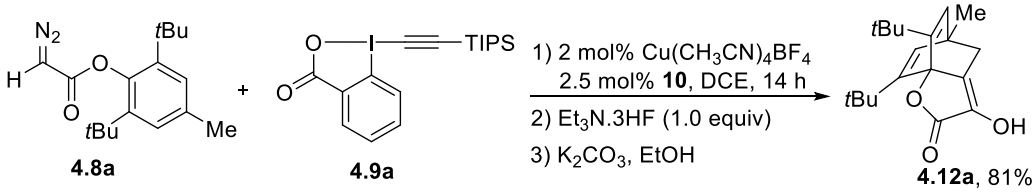


Following general procedure **B**, starting from 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (64.0 mg, 0.150 mmol, 1.00 equiv) and furan-2-ylmethyl 2-diazoacetate (**4.8r**) (30 mg, 0.18 mmol, 1.2 equiv), afforded **4.2am** as a white solid (51.0 mg, 0.124 mmol, 83%). M.p. 203.5 – 205.5 °C; R_f = 0.3 (EtOAc/pentane 20:80), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.7, 1.7 Hz, 2H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.67 (dt, *J* = 5.9, 1.4 Hz, 1H, OCHC*H*), 6.63 (d, *J* = 5.7 Hz, 1H, OCC*H*), 5.28 (dd, *J* = 4.3, 1.7 Hz, 1H, OC*H*), 4.90 (d, *J* = 11.3 Hz, 1H, OCCH^a_2), 4.80 (d, *J* = 11.2 Hz, 1H, OCCH^b_2), 2.88 (dd, *J* = 16.1, 4.2 Hz, 1H, OCHCH^a_2), 2.35 (d, *J* = 16.2 Hz, 1H, OCHCH^b_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 158.8, 144.5, 141.6, 140.2, 133.6, 132.8, 132.1, 132.0, 130.6, 128.1, 94.8, 83.0, 79.4, 67.7, 33.1; IR (ν_{max}, cm^{-1}) 2952 (w), 2366 (w), 1738 (s), 1623 (w), 1583 (w), 1563 (w), 1467 (w), 1429 (w), 1401 (w), 1331 (w), 1275 (m), 1239 (s), 1209 (m), 1149 (s), 1130 (m), 1104 (s), 1074

(m), 1039 (m), 1014 (m), 988 (w), 952 (w), 912 (w); HRMS (ESI) Calcd for $C_{16}H_{11}INaO_5^+$ [M+Na]$^+$ 432.9543; found 432.9547.

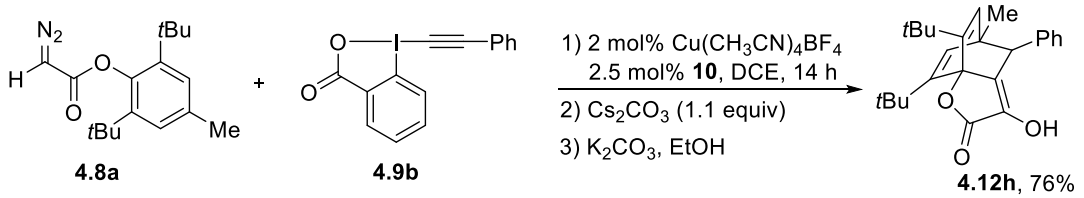
10.2.4. Product Derivatization and Applications

7,8-Di-*tert*-butyl-3-hydroxy-5-methyl-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-2-one (4.12a)



A flame dried 20 mL microwave vial was charged under nitrogen with $Cu(CH_3CN)_4BF_4$ (25 mg, 0.08 mmol, 0.02 equiv), ligand **4.10** (37 mg, 0.10 mmol, 0.025 equiv) and dry DCE (10 mL). The resulting solution was stirred at 30 °C for 1 h and then added to a mixture of TIPS-EBX (**4.9a**) (1.72 g, 4.00 mmol, 1.00 equiv), 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (1.4 g, 4.8 mmol, 1.2 equiv) and dry DCE (150 mL) in 250 mL round-bottom flask over 2 min and the resulting reaction mixture was stirred at 50 °C for 14 h. Next, the reaction mixture was cooled down to room temperature and triethylamine trihydrofluoride (0.67 mL, 4.0 mmol, 1.0 equiv) was added and the reaction mixture stirred. After 24 h, the solvent was evaporated under reduced pressure. The crude residue was dissolved in EtOH (80 mL) and K_2CO_3 (0.83 g, 6.0 mmol, 1.5 equiv) was added and the reaction mixture stirred at room temperature. After 20 h, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography using EtOAc/pentane 1:10 as eluent to afford **4.12a** as a white solid (0.980 g, 3.24 mmol, 81%). M.p. 189.0 – 190.3 °C; R_f = 0.43 (EtOAc/pentane 15:85), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 2H, 2 x *t*BuCC*H*), 5.04 (brs, 1H, O*H*), 2.18 (s, 2H, CH_3CCH_2), 1.60 (s, 3H, CHCCH_3), 1.10 (s, 18H, 2 x *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 151.8, 140.8, 132.4, 131.6, 92.7, 41.5, 36.0, 35.0, 29.2, 22.5; IR (ν_{max}, cm^{-1}) 3348 (m), 3298 (w), 3054 (w), 2958 (w), 2929 (w), 2866 (w), 1747 (s), 1711 (s), 1461 (w), 1384 (m), 1376 (m), 1328 (w), 1241 (m), 1221 (m), 1202 (m), 1160 (m), 1104 (s), 1046 (w), 900 (w); HRMS (ESI) Calcd for $C_{19}H_{26}NaO_3^+$ [M+Na]$^+$ 325.1774; found 325.1786.

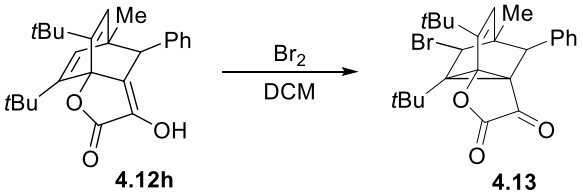
7,8-Di-*tert*-butyl-3-hydroxy-5-methyl-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-2-one (4.12h)



A flame dried 20 mL microwave vial was charged under nitrogen with $Cu(CH_3CN)_4BF_4$ (25 mg, 0.08 mmol, 0.02 equiv), ligand **4.10** (37 mg, 0.10 mmol, 0.025 equiv) and dry DCE (10 mL). The resulting solution was stirred at 30 °C for 1 h and then added to a mixture of Ph-EBX (**4.9b**) (1.4 g, 4.0 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**4.8a**) (1.73 g, 6.00 mmol, 1.50 equiv) and dry DCE (150 mL) in 250 mL round-bottom flask over 2 min and the resulting reaction mixture was stirred at 50 °C for 14 h. Next, the reaction mixture was cooled down to room temperature and Cs_2CO_3 (1.44 g, 4.40 mmol, 1.10 equiv) was added and the reaction mixture stirred. After 20 h, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The crude residue was dissolved in EtOH (80 mL) and K_2CO_3 (0.83 g, 6.0 mmol, 1.5 equiv) was added and the reaction mixture stirred at

room temperature for 20 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography using EtOAc/pentane 1:10 as eluent to afford **4.12h** as a white solid (1.15 g, 3.04 mmol, 76%). M.p. 178.5 – 182.3 °C; R_f = 0.44 (EtOAc/pentane 15:85), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 5.0, 1.9 Hz, 3H, Ar*H*), 7.05 – 6.98 (m, 2H, Ar*H*), 5.84 (d, *J* = 0.8 Hz, 1H, *t*BuCC*H*), 5.50 (d, *J* = 0.8 Hz, 1H, *t*BuCC*H*), 4.80 (s, 1H, O*H*), 3.46 (s, 1H, ArC*H*), 1.30 (s, 3H, CHCC*H*$_3$), 1.22 (s, 9H, *t*Bu), 1.15 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 152.8, 150.8, 142.3, 137.3, 133.4, 133.0, 129.6, 129.1, 128.1, 127.4, 92.5, 51.5, 46.5, 35.2, 35.2, 29.2, 29.1, 20.5; IR (ν_{max}, cm^{-1}) 3350 (w), 3060 (w), 2962 (m), 2872 (w), 2255 (w), 1747 (s), 1735 (m), 1603 (w), 1458 (w), 1387 (w), 1365 (m), 1313 (w), 1242 (w), 1200 (m), 1150 (w), 1101 (s), 1046 (w), 912 (m); HRMS (ESI) Calcd for $C_{25}H_{31}O_3^+$ $[M+H]^+$ 379.2268; found 379.2273.

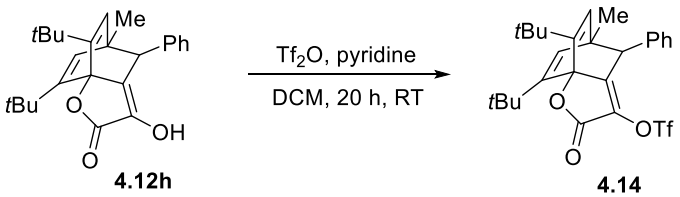
3-Bromo-7,8-di-*tert*-butyl-5-methyl-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-2,3(3a*H*)-dione (4.13)



4.12h **4.13**

A solution of bromine (16 mg, 0.10 mmol, 2.0 equiv) in dry CH_2Cl_2 (1 mL) was slowly added to a vigorously stirred solution of **4.12h** (19 mg, 0.05 mmol, 1.0 equiv) in dry CH_2Cl_2 (1 mL) at 0 °C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for 14 h. Next, an aqueous solution of Na_2SO_3 (5 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 1:15 EtOAc/pentane as eluent to afford **4.13** as a pale yellow solid (20.0 mg, 0.044 mmol, 87%). M.p. 201.5–205.3 °C; R_f = 0.35 (EtOAc/pentane 7:93), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 3H, Ar*H*), 6.74 – 6.68 (m, 2H, Ar*H*), 4.92 (d, *J* = 1.1 Hz, 1H, *t*BuCC*H*), 4.17 (d, *J* = 1.2 Hz, 1H, *t*BuCC*H*Br), 3.39 (s, 1H, ArC*H*), 1.35 (s, 9H, *t*Bu), 1.34 (s, 9H, *t*Bu), 1.25 (s, 3H, CHCC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 161.8, 141.4, 133.6, 128.9, 128.0, 127.7, 123.4, 63.9, 62.9, 49.6, 46.6, 46.1, 35.5, 33.9, 32.1, 29.1, 19.9; IR (ν_{max}, cm^{-1}) 2967 (m), 2932 (m), 2875 (m), 1806 (s), 1751 (s), 1601 (w), 1492 (w), 1457 (w), 1370 (m), 1325 (m), 1265 (m), 1235 (m), 1173 (w), 1147 (m), 1090 (m), 1062 (m), 1032 (w), 946 (w); HRMS (ESI) Calcd for $C_{25}H_{30}BrO_3^+$ $[M+H]^+$ 457.1373; found 457.1373. One carbon was not resolved at 100 MHz.

7,8-Di-*tert*-butyl-5-methyl-2-oxo-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl trifluoromethanesulfonate (4.14)

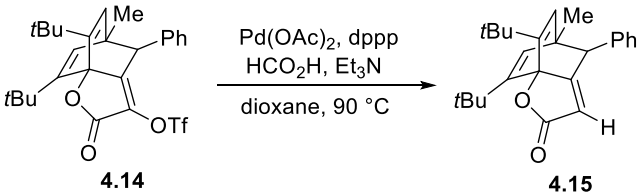


4.12h **4.14**

To a solution of **4.12h** (303 mg, 0.800 mmol, 1.00 equiv) and pyridine (0.129 mL, 1.60 mmol, 2.00 equiv) in CH_2Cl_2 (40 mL) was added triflic anhydride (2.4 mL, 1.0 M, 2.4 mmol, 3.0 equiv) at 0 °C in 10 min. The mixture was allowed to warm to room temperature and stirred for 20 h. Next, the reaction mixture was quenched with water (30 mL) and the layers were separated. The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 1:40 EtOAc/pentane as eluent to afford **4.14** as a white solid (408 mg, 0.800

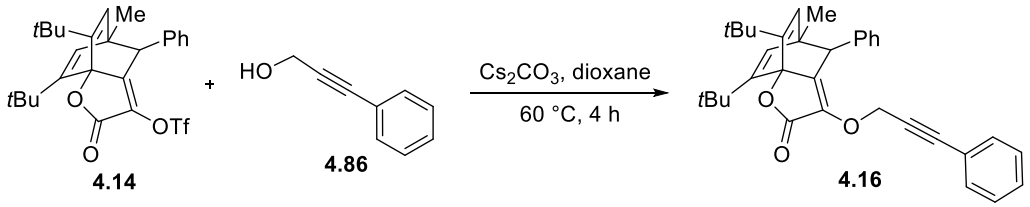
mmol, quant.). M.p. 187.5 – 191.5 °C; R_f = 0.5 (EtOAc/pentane 98:2), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 3H, Ar*H*), 7.01 – 6.98 (m, 2H, Ar*H*), 5.95 (s, 1H, *t*BuCC*H*), 5.67 (m, 1H, *t*BuCC*H*), 3.65 (s, 1H, ArC*H*), 1.32 (s, 3H, CHCC*H*$_3$), 1.24 (s, 9H, *t*Bu), 1.17 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 162.8, 151.6, 149.1, 135.3, 134.2, 131.1, 130.5, 129.1, 128.4, 128.1, 118.0 (q, *J* = 321.2 Hz), 92.6, 53.7, 46.7, 35.4, 35.3, 29.0, 28.9, 20.0; IR (ν_{max}, cm^{-1}) 3064 (w), 2964 (m), 2874 (w), 1788 (s), 1697 (w), 1603 (w), 1432 (s), 1392 (w), 1365 (w), 1316 (w), 1214 (s), 1182 (m), 1138 (s), 1072 (s), 1035 (w); HRMS (ESI) Calcd for $C_{26}H_{30}F_3O_5S^+$ $[M+H]^+$ 511.1761; found 511.1765.

7,8-Di-*tert*-butyl-5-methyl-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-2-one (4.15)



A mixture of **4.14** (51 mg, 0.10 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 25 µmol, 0.25 equiv), dppp (25 mg, 0.06 mmol, 0.60 equiv), and dioxane (1.0 mL) was placed in a 2 mL microwave vial under nitrogen. Formic acid (15 µL, 0.40 mmol, 4.0 equiv) and triethylamine (55 µL, 0.40 mmol, 4.0 equiv) were added to the reaction mixture. The resulting mixture was stirred at 90 °C for 18 h and then quenched with water (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 1:30 Et_2O/pentane as eluent to afford **4.15** as a colorless semi solid (32.0 mg, 0.088 mmol, 88%). R_f = 0.28 (Et_2O/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 3H, Ar*H*), 7.03 – 6.99 (m, 2H, Ar*H*), 5.84 (s, 1H, *t*BuCC*H*), 5.54 – 5.51 (m, 2H, *t*BuCC*H* and C(O)C*H*), 3.47 (d, *J* = 1.9 Hz, 1H, ArC*H*), 1.29 (s, 3H, CHCC*H*$_3$), 1.24 (s, 9H, *t*Bu), 1.17 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 175.4, 152.4, 150.0, 139.1, 132.6, 129.3, 129.2, 128.2, 127.4, 109.7, 96.6, 52.9, 46.4, 35.4, 35.4, 29.1, 29.1, 20.5; IR (ν_{max}, cm^{-1}) 2961 (m), 2872 (w), 1797 (w), 1762 (s), 1652 (w), 1457 (w), 1390 (w), 1363 (w), 1314 (w), 1247 (w), 1218 (w), 1128 (w), 1097 (w), 1047 (w); HRMS (ESI) Calcd for $C_{25}H_{31}O_2^+$ $[M+H]^+$ 363.2319; found 363.2316.

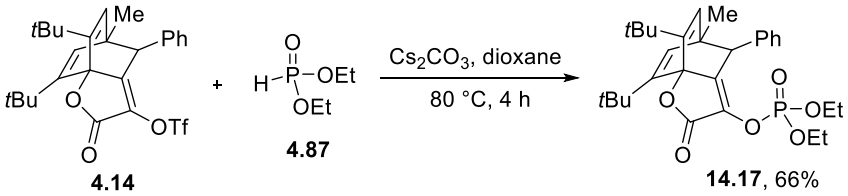
7,8-Di-*tert*-butyl-5-methyl-4-phenyl-3-((3-phenylprop-2-yn-1-yl)oxy)-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-2-one (4.16)



A mixture of **4.14** (51 mg, 0.10 mmol, 1.0 equiv), Cs_2CO_3 (65.5 mg, 0.200 mmol, 2.00 equiv), and dioxane (1.0 mL) was placed in a 2 mL microwave vial under nitrogen. 3-Phenylprop-2-yn-1-ol (**4.86**) (66 mg, 0.50 mmol, 5.0 equiv) was added slowly to the reaction mixture over 5 min and it was stirred at 60 °C for 4 h. The reaction mixture was quenched with water (10 mL) and transferred to a separating funnel. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 1:15 Et_2O/pentane as eluent to afford **4.16** as a pale yellow thick gel (44.5 mg, 0.090 mmol, 90%). R_f = 0.33 (Et_2O/pentane 7:93), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 8H, Ar*H*), 7.38 – 7.26 (m, 2H, Ar*H*), 5.82 (s, 1H, *t*BuCC*H*), 5.48 (s, 1H, *t*BuCC*H*), 4.53 (d, *J* = 15.9 Hz, 1H, OCH^a_2), 4.37 (d, *J* = 15.9 Hz, 1H, OCH^b_2), 3.74

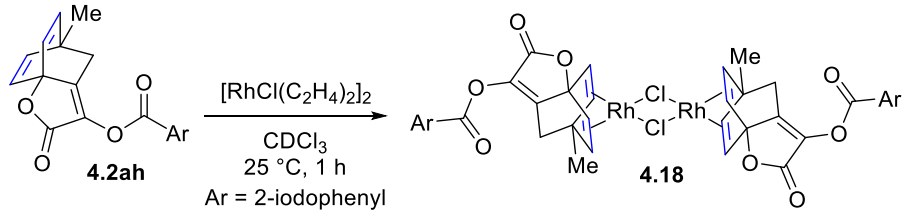
(s, 1H, ArC*H*), 1.30 (s, 3H, CHCC*H*$_3$), 1.23 (s, 9H, *t*Bu), 1.11 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 153.3, 150.7, 148.3, 139.1, 135.9, 132.8, 131.7, 129.5, 129.1, 128.8, 128.3, 128.2, 127.5, 122.1, 92.2, 87.6, 84.1, 58.6, 52.7, 46.4, 35.3, 35.2, 29.2, 29.1, 20.8; IR (ν_{max}, cm^{-1}) 3061 (w), 2961 (m), 2871 (w), 2252 (w), 1769 (s), 1684 (w), 1601 (w), 1491 (w), 1453 (w), 1389 (w), 1366 (w), 1316 (w), 1244 (w), 1191 (w), 1148 (w), 1099 (s), 1034 (w), 988 (w), 954 (w), 913 (m); HRMS (ESI) Calcd for $C_{34}H_{37}O_3^+$ $[M+H]^+$ 493.2737; found 493.2741.

7,8-Di-*tert*-butyl-5-methyl-2-oxo-4-phenyl-4,5-dihydro-2*H*-5,7a-ethenobenzofuran-3-yl diethyl phosphate (4.17)



A mixture of **4.14** (51 mg, 0.10 mmol, 1.0 equiv), Cs_2CO_3 (65.5 mg, 0.200 mmol, 2.00 equiv), and dioxane (1.0 mL) was placed in a 2 mL microwave vial under nitrogen. Diethyl phosphonate (**4.87**) (69 mg, 0.50 mmol, 5.0 equiv) was added slowly to the reaction mixture over 5 min and the reaction mixture stirred at 80 °C for 4 h. The reaction mixture was quenched with water (10 mL) and transferred to a separating funnel. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 1:10 EtOAc/pentane as eluent to afford **4.17** as a colorless thick gel (34.0 mg, 0.066 mmol, 66%). R_f = 0.25 (EtOAc/pentane 15:85), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 3H, Ar*H*), 7.02 – 6.91 (m, 2H, Ar*H*), 5.80 (s, 1H, *t*BuCC*H*), 5.47 (s, 1H, *t*BuCC*H*), 4.09 – 3.80 (m, 2H, OC*H*$_2$CH$_3$), 3.73 (d, *J* = 3.4 Hz, 1H, ArC*H*), 3.49 – 3.26 (m, 2H, OC*H*$_2$CH$_3$), 1.23 (s, 3H, CHCC*H*$_3$), 1.19 – 1.04 (m, 12H, *t*Bu and OCH$_2$C*H*$_3$), 1.10 (s, 9H, *t*Bu), 0.90 (td, *J* = 7.1, 1.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (d, *J* = 3.1 Hz), 157.0 (d, *J* = 4.8 Hz), 152.0, 149.9, 137.4, 133.5, 130.6 (d, *J* = 7.5 Hz), 130.2, 129.6, 127.9, 127.2, 92.2, 64.9 (d, *J* = 6.6 Hz), 64.3 (d, *J* = 6.2 Hz), 52.6, 46.4, 35.3, 35.2, 29.1, 29.0, 20.3, 15.9 (d, *J* = 7.3 Hz), 15.7 (d, *J* = 7.1 Hz); IR (ν_{max}, cm^{-1}) 2962 (m), 2872 (w), 2246 (w), 1779 (s), 1703 (w), 1601 (w), 1481 (w), 1456 (w), 1393 (w), 1365 (w), 1295 (m), 1265 (w), 1189 (w), 1149 (w), 1099 (m), 1056 (s), 1033 (s), 967 (w), 918 (m); HRMS (ESI) Calcd for $C_{29}H_{39}NaO_6P^+$ $[M+Na]^+$ 537.2376; found 537.2390.

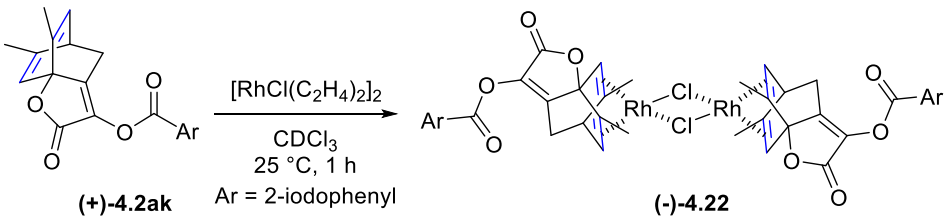
Preparation of [RhCl(4.2ah)]$_2$ (4.18)



Under inert atmosphere, [RhCl(C_2H_4)$_2$]$_2$ (6.5 mg, 17 µmol, 1.0 equiv) and 5-methyl-2-oxo-4,5-dihydro-2H-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate **4.2ah** (14.1 mg, 33.0 µmol, 2.0 equiv) were stirred in $CDCl_3$ (1.7 mL) at 25 °C. Within 1 h, [RhCl(C_2H_4)$_2$]$_2$ was fully converted into [RhCl(**4.2ah**)]$_2$ (**4.18**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (td, *J* = 7.5, 1.4 Hz, 4H, Ar*H*), 7.47 (td, *J* = 7.6, 1.2 Hz, 2H, Ar*H*), 7.28 – 7.20 (m, 2H, Ar*H*), 3.77 (dd, *J* = 5.5, 1.9 Hz, 4H, 2 x OCC*H*), 3.54 (dd, *J* = 5.9, 1.9 Hz, 4H, 2 x H$_3$CCC*H*), 2.30 (s, 4H, CHC*H*$_2$), 2.25 (s, 6H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 161.6, 149.2, 142.1, 134.2, 132.5, 131.8, 128.9, 128.4, 95.5, 88.8 (d, *J* = 3.9 Hz), 56.3 (d, *J* = 10.8 Hz), 49.2 (d, *J* = 11.0 Hz), 47.5 (d, *J* = 2.5 Hz), 39.2, 21.4. The complex can be isolated by precipitation in Et_2O to furnish **4.18** as a yellow solid (18.6

mg, 17.0 µmol, 100%). The crystal structure of **4.18** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 1945514.

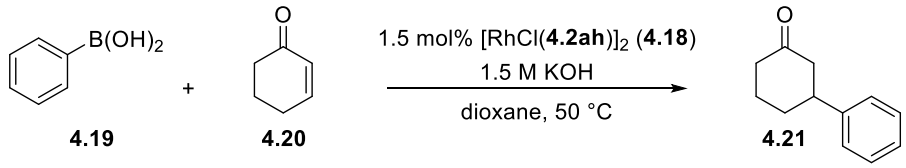
Preparation of [RhCl((+)-4.2ak)]$_2$ (-)-(4.22)



(+)-4.2ak **(-)-4.22**

Under inert atmosphere, [RhCl(C_2H_4)$_2$]$_2$ (15.9 mg, 41.0 µmol, 1.0 equiv) and (+)-(5R,7aS)-6,8-dimethyl-2-oxo-4,5-dihydro-2H-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate **(+)-(4.2ak)** (35.6 mg, 82.0 µmol, 2.00 equiv) were stirred in $CDCl_3$ (4.1 mL) at 25 °C for 1 h. After complete complexation (monitored by ^{1}H NMR), the reaction mixture was directly loaded and purified by flash column chromatography using EtOAc/pentane 1:2 as eluent to furnish **(-)-4.22** as a yellow solid (41.0 mg, 36.0 µmol, 87%). R_f = 0.45 (EtOAc/pentane 50:50); $[\alpha]_D^{20}$ = -26.11 (c = 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.8, 1.4 Hz, 4H, Ar*H*), 7.47 (td, *J* = 7.6, 1.2 Hz, 2H, Ar*H*), 7.28 – 7.21 (m, 2H, Ar*H*), 4.42 (s, 2H, OCC*H*=C), 3.50 (d, *J* = 5.3 Hz, 2H, C*H*CH$_2$), 3.39 (s, 2H, CH$_3$C=C*H*CH), 2.45 – 2.26 (m, 4H, C*H*$_2$), 1.62 (s, 6H, C*H*$_3$), 1.51 (s, 6H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 161.7, 147.9 (br s), 142.1, 134.2, 132.5, 131.9, 129.2, 128.4, 95.4, 91.4 (d, *J* = 4.2 Hz), 64.4 (d, *J* = 9.3 Hz), 61.7 (d, *J* = 12.3 Hz), 47.6 (d, *J* = 10.8 Hz), 47.4 (d, *J* = 3.6 Hz), 46.0 (d, *J* = 11.1 Hz), 31.7 (d, *J* = 1.7 Hz), 21.4, 15.7. The crystal structure of **(-)-4.22** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 2027174. The complex **(-)-4.22** decomposed in the mass spectrometer and therefore the accurate mass was not obtained.

1,4-Addition of boronic acid 4.19 to enone 4.20 catalyzed by [RhCl(4.2ah)]$_2$ (4.18).

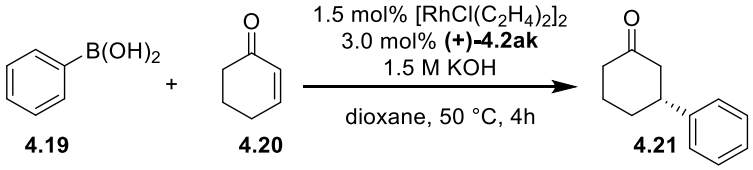


4.19 **4.20** **4.21**

An oven-dried 10 mL microwave vial was successively charged with [RhCl(**4.2ah**)]$_2$ **4.18** (8.4 mg, 7.5 µmol, 0.015 equiv), degassed dioxane (2.0 mL) and a 1.5 M degassed solution of KOH in water (167 µL, 0.250 mmol, 0.50 equiv) and the resulting mixture was stirred for a further 10 minutes at room temperature. Subsequently, phenylboronic acid (**4.19**) (122 mg, 1.00 mmol, 2.00 equiv) and 2-cyclohexenone (**4.20**) (48.5 µL, 0.50 mmol, 1.00 equiv) was added to this solution. After stirring at 50 °C for 3 h, the reaction mixture was quenched with saturated NH_4Cl in water (5 mL) and extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using Et_2O/pentane 1:20 as eluent to afford 3-phenylcyclohexanone (**4.21**) as a colorless oil (67.0 mg, 0.385 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.27 – 7.20 (m, 3H), 3.02 (tt, *J* = 11.6, 4.0 Hz, 1H), 2.65 – 2.33 (m, 4H), 2.21 – 2.04 (m, 2H), 1.94 – 1.69 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 144.5, 128.8, 126.8, 126.7, 49.1, 44.9, 41.3, 32.9, 25.7. The value of the NMR spectra are in accordance with reported literature data.[380]

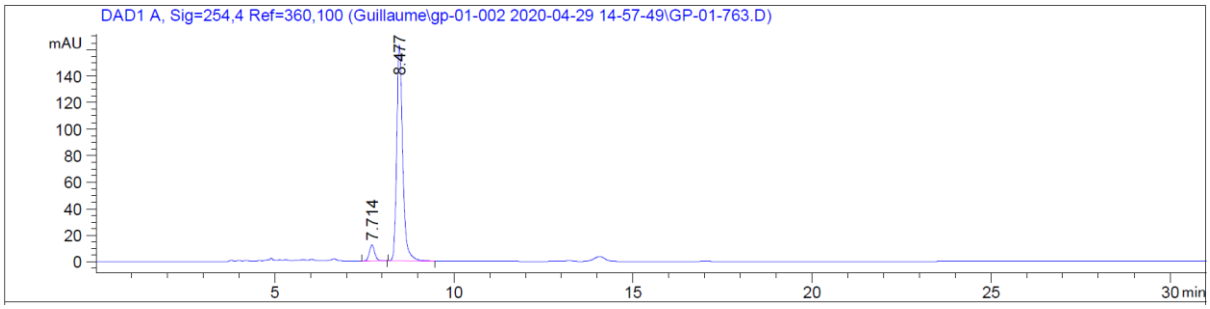
[380] Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579.

Enantioselective Rh-catalyzed 1,4-addition of boronic acid 4.19 to enone 4.20.



4.19 **4.20** **4.21**

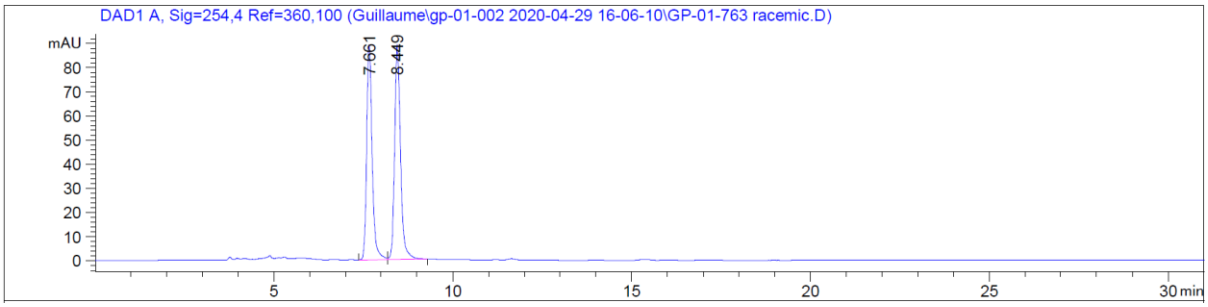
An oven-dried 10 mL microwave vial was charged with $[RhCl(C_2H_4)_2]_2$ (1.6 mg, 4.1 µmol, 0.015 equiv) and (+)-(5S,7aR)-6,8-dimethyl-2-oxo-4,5-dihydro-2H-5,7a-ethenobenzofuran-3-yl 2-iodobenzoate (**4.2ak**) (3.6 mg, 8.2 µmol, 0.030 equiv) and degassed dioxane (1.1 mL) under inert atmosphere. After stirring 1 h at room temperature, a 1.5 M degassed solution of KOH in water (91 µL, 0.14 mmol, 0.50 equiv) was added and the reaction mixture was stirred for further 10 minutes at room temperature. Subsequently, phenylboronic acid (**4.19**) (67 mg, 0.55 mmol, 2.00 equiv) and 2-cyclohexenone (**4.20**) (26 µL, 0.27 mmol, 1.00 equiv) were added to this solution. After stirring at 50 °C for 4 h, the reaction mixture was quenched with saturated NH_4Cl in water (5 mL) and extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using Et_2O/pentane 1:20 as eluent to afford 3-phenylcyclohexanone (**4.21**) as a colorless oil (36.0 mg, 0.207 mmol, 75%). $[\alpha]_D^{20}$ = +17.00 (c = 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H, Ar*H*), 7.27 – 7.20 (m, 3H, Ar*H*), 3.02 (tt, *J* = 11.6, 4.0 Hz, 1H, C*H*Ph), 2.65 – 2.33 (m, 4H, 2 x COC*H*$_2$), 2.21 – 2.04 (m, 2H, C*H*$_2$), 1.94 – 1.69 (m, 2H, C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 144.5, 128.8, 126.8, 126.7, 49.1, 44.9, 41.3, 32.9, 25.7; Chiral HPLC conditions: ee = 87%, Chiralpak IA 95:5, Hexane/iPrOH, 0.8 mL/min, 30 min. tr (minor) = 7.7 min. and tr (major) = 8.5 min, λ = 254 nm. The value of the NMR spectra are in accordance with reported literature data.380 Absolute configuration of the major enantiomer (drawn) was determined by comparison with $[\alpha]_D$ given in the literature.[381]



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.714	BB	0.1599	128.21254	12.26813	6.3354
2	8.477	BB	0.1759	1895.54675	162.76753	93.6646
Totals :				2023.75929	175.03567	

[381] M. Pucheault, S. Darses, J.-P. Genet, *Tetrahedron Lett.* **2002**, *43*, 6155.

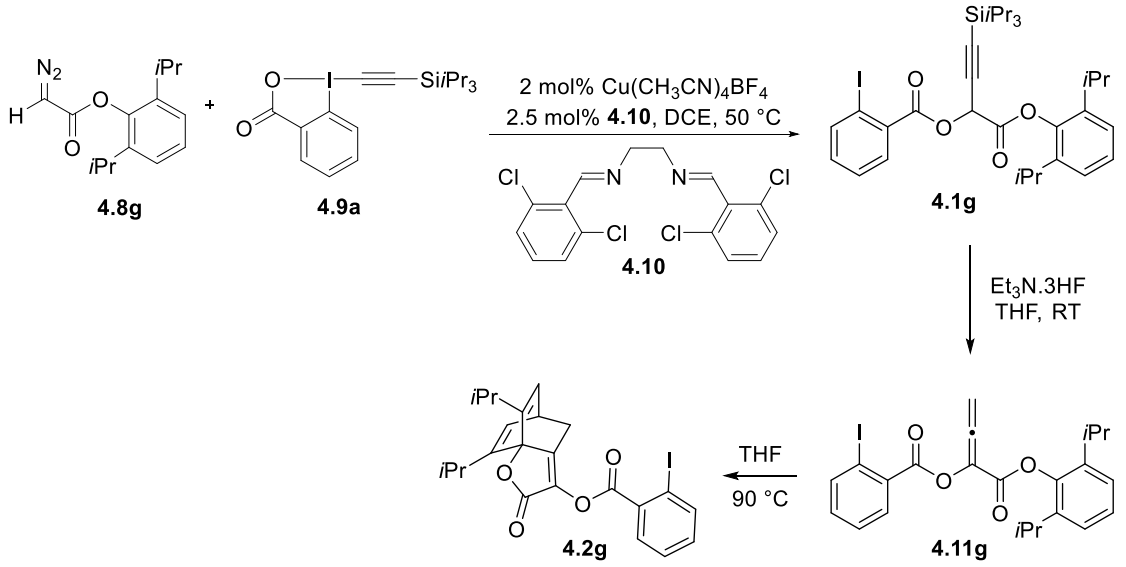


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.661	BV	0.1597	943.93439	89.04942	47.9240
2	8.449	VB	0.1745	1025.71448	89.00008	52.0760
Totals :				1969.64886	178.04950	

10.2.5. Control Experiments

Isolation of the reaction intermediates



A flame dried 5 mL microwave vial was charged under nitrogen with $Cu(CH_3CN)_4BF_4$ (1.9 mg, 6.0 µmol, 0.02 equiv), ligand **4.10** (2.8 mg, 7.5 µmol, 0.025 equiv) and dry DCE (2 mL). The resulting solution was stirred at 30 °C for 1 h and then added to a mixture of 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**4.9a**) (129 mg, 0.300 mmol, 1.00 equiv), 2,6-di*iso*propylphenyl 2-diazoacetate (**4.8g**) (89,0 mg, 0.180 mmol, 1.20 equiv) and dry DCE (10 mL) in 20 mL microwave vial over 2 min and the resulting reaction mixture was stirred at 50 °C for 4 h. After this time, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography using EtOAc/pentane 1:50 as eluent to afford **4.1g** as a colorless oil (185 mg, 0.286 mmol, 95%). R_f = 0.53 (EtOAc/pentane 3:97), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.96 (m, 2H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.25 – 7.13 (m, 4H, Ar*H*), 6.31 (s, 1H, OC*H*), 3.11 (hept, J = 6.8 Hz, 2H, 2 x C*H*$(CH_3)_2$), 1.30 – 1.15 (m, 12H, 2 x CH(C*H*$_3)_2$), 1.16 – 1.08 (m, 21H, TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.4, 145.1, 141.7, 140.7, 133.5, 133.4, 132.0, 128.2, 127.2, 124.2, 96.9, 94.6, 91.7, 64.0, 27.2, 23.7 (br), 18.7, 11.3; IR (ν_{max}, cm^{-1}) 3685 (m), 3662 (m), 2970 (s), 2901 (s), 1781 (m), 1740 (m), 1464 (m), 1407 (m), 1393 (m),

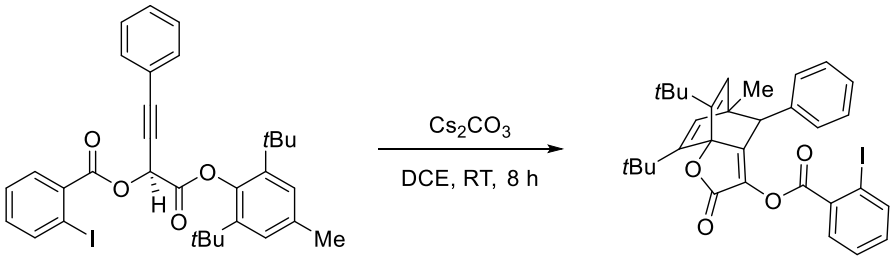
1384 (m), 1241 (s), 1066 (s), 1016 (s), 882 (m), 791 (m), 740 (m), 679 (m); HRMS (ESI) Calcd for $C_{32}H_{43}INaO_4Si^+$ $[M+Na]^+$ 669.1868; Found 669.1875.

In a flame dried 20 mL microwave vial, 1-(2,6-diisopropylphenoxy)-1-oxo-4-(triisopropylsilyl)but-3-yn-2-yl 2-iodobenzoate (**4.1g**) (129 mg, 0.200 mmol, 1.00 equiv) was dissolved in THF (8 mL) under nitrogen. Then, triethylamine trihydrofluoride (33 µL, 0.200 mmol, 1.00 equiv) was added and the reaction mixture was stirred at room temperature for 16 h. After this time, the solvent was evaporated and the crude product was purified by flash column chromatography using EtOAc/pentane 1:30 as eluent to afford **4.11g** as a colorless oil (100 mg, 0.204 mmol, 100%). R_f = 0.29 (EtOAc/pentane 3:97), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 7.9, 3.6, 1.4 Hz, 2H, Ar*H*), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.25 – 7.14 (m, 4H, Ar*H*), 5.94 (s, 2H, C*C*H_2), 3.02 (hept, *J* = 6.9 Hz, 2H, 2 x C*H*$(CH_3)_2$), 1.21 (d, *J* = 6.9 Hz, 12H, 2 x CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 163.9, 161.1, 145.5, 141.8, 140.6, 133.6, 133.3, 132.1, 128.2, 126.9, 124.2, 116.2, 95.0, 90.7, 27.7, 24.0 (br), 22.9 (br); IR (ν_{max}, cm^{-1}) 3661 (m), 2970 (s), 2901 (s), 1739 (s), 1465 (m), 1384 (m), 1276 (m), 1246 (m), 1225 (s), 1085 (s), 1065 (s), 1011 (s), 880 (m), 794 (m), 738 (s); HRMS (ESI) Calcd for $C_{23}H_{23}INaO_4^+$ $[M+Na]^+$ 513.0533; Found 513.0538.

In a flame dried 20 mL microwave vial, THF (6 mL) was added to 1-(2,6-diisopropylphenoxy)-1-oxobuta-2,3-dien-2-yl 2-iodobenzoate (**4.11g**) (73 mg, 0.15 mmol, 1.00 equiv) under nitrogen. The resulting reaction mixture was stirred at 90 °C for 12 h. After this time, the solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography using Et_2O/pentane 10:90 as eluent to furnish **4.2g** as a white solid (67 mg, 0.137 mmol, 91%).

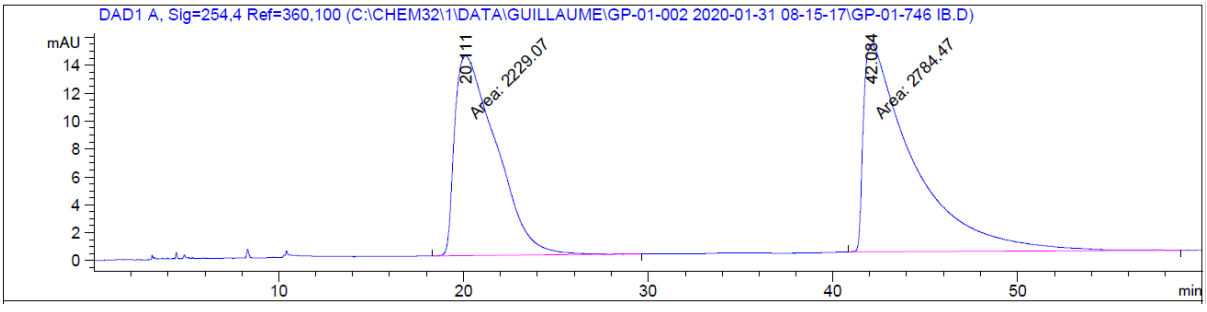
Racemization of the intermediate product

Enantioenriched (81% ee) (**4.1h**) was prepared according to a procedure of our previously reported work.[229]



4.1h, 81% ee **4.2h**, 91%, 0% ee

In a flame dried 20 mL microwave vial, Cs_2CO_3 (54.0 mg, 0.165 mmol, 1.10 equiv) was added to a solution of (*S*)-1-(2,6-di-tert-butyl-4-methylphenoxy)-1-oxo-4-phenylbut-3-yn-2-yl 2-iodobenzoate (81% ee, **4.1h**) (91 mg, 0.15 mmol, 1.00 equiv) in DCE (5 mL) and the reaction mixture was stirred at room temperature for 8 h. After this time, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography using Et_2O/pentane 5:95 as eluent to afford **4.2h** as a white solid (83.0 mg, 0.137 mmol, 91%). Chiral HPLC conditions: ee = 0%; Chiralpak IB 99.75:0.25 Hexane/*i*PrOH, 1 mL/min, 60 min. tr (1) = 20.1 min. and tr (2) = 42.0 min. λ = 254 cm^{-1}.

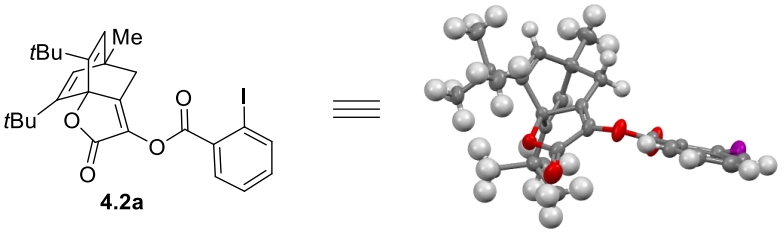


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.111	MM	2.5997	2229.07227	14.29075	44.4611
2	42.084	MM	3.1237	2784.46704	14.85644	55.5389
Totals :				5013.53931	29.14719	

10.2.6. Crystal Structures

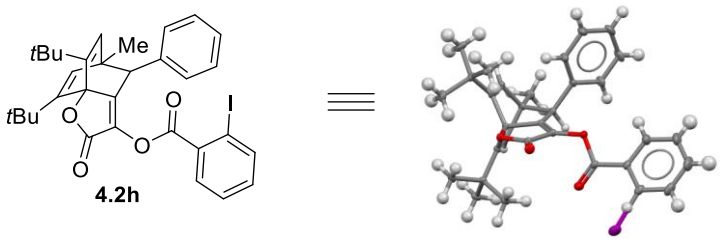
CCDC 1848760



4.2a

Empirical formula	$C_{26}H_{29}IO_4$	
Formula weight	532.39	
Temperature	292(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 8.7662(4) Å	α = 94.559(3)°.
	b = 11.9386(6) Å	β = 98.326(3)°.
	c = 12.1637(4) Å	γ = 106.805(4)°.
Volume	1195.86(9) $Å^3$	
Z	2	
Density (calculated)	1.479 Mg/m^3	
Absorption coefficient	1.368 mm^{-1}	
F(000)	540	
Crystal size	0.412 x 0.276 x 0.145 mm^3	
Θ range for data collection	2.570 to 29.772°.	
Index ranges	-11 ≤ h ≤ 12, -12 ≤ k ≤ 16, -16 ≤ l ≤ 16	
Reflections collected	9791	
Independent reflections	5617 [R_{int} = 0.0224]	
Completeness to *Θ* = 25.242°	99.9 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.855 and 0.730	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5617 / 0 / 287	
Goodness-of-fit on F^2	1.030	
Final *R* indices [I>2σ(I)]	R_1 = 0.0366, wR_2 = 0.0751	
R indices (all data)	R_1 = 0.0515, wR_2 = 0.0825	
Largest diff. peak and hole	0.501 and -0.675 $e.Å^{-3}$	

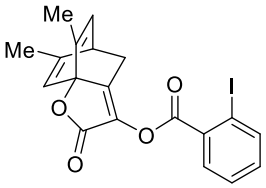
CCDC 1848773



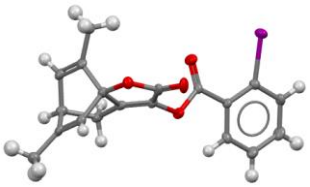
4.2h

Empirical formula	$C_{32}H_{33}IO_4$	
Formula weight	608.48	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 9.3288(15) Å	α = 65.569(4)°.
	b = 12.5347(10) Å	β = 87.392(9)°.
	c = 13.9206(11) Å	γ = 69.207(9)°.
Volume	1375.7(3) $Å^3$	
Z	2	
Density (calculated)	1.469 Mg/m^3	
Absorption coefficient	1.199 mm^{-1}	
F(000)	620	
Crystal size	0.520 x 0.441 x 0.206 mm^3	
Theta range for data collection	2.980 to 34.999°.	
Index ranges	-15 ≤ h ≤ 15, -20 ≤ k ≤ 20, -21 ≤ l ≤ 22	
Reflections collected	32700	
Independent reflections	11876 [R_{int} = 0.0225]	
Completeness to Θ = 25.242°	98.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7469 and 0.5376	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11876 / 0 / 351	
Goodness-of-fit on F^2	1.093	
Final R indices [I > 2σ(I)]	R_1 = 0.0361, wR_2 = 0.0799	
R indices (all data)	R_1 = 0.0485, wR_2 = 0.0885	
Largest diff. peak and hole	2.927 and -2.092 $e.Å^{-3}$	

CCDC 2027173

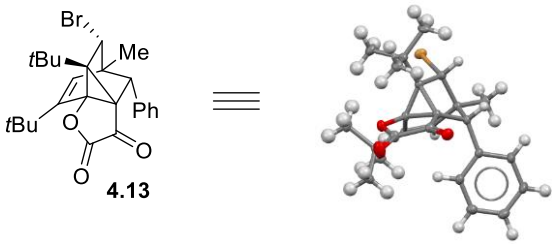


(+)-4.2ak



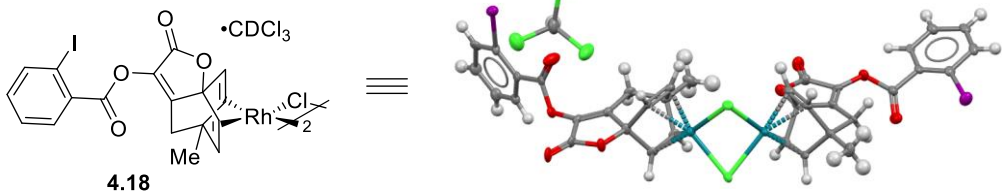
Empirical formula	$C_{19}H_{15}IO_4$	
Formula weight	434.21	
Colour	Colourless	
Shape	Needle	
Temperature	140.00(10) K	
Wavelength	0.71073 Å	
Radiation type	Mo*Kα*	
Crystal system	Orthorhombic	
Flack Parameter	-0.015(15)	
Hooft Parameter	-0.006(14)	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.4295(3) Å	α = 90°.
	b = 14.3717(5) Å	β = 90°.
	c = 31.6622(12) Å	γ = 90°.
Volume	3380.7(2) Å^3	
Z	8	
Z'	2	
Density (calculated)	1.706 g/cm^3	
Absorption coefficient	1.914 mm^{-1}	
Crystal size	0.53 x 0.06 x 0.03 mm^3	
Θ range for data collection	3.029 to 29.429°.	
Mesured reflections	36614	
Independent reflections	8423	
Refl's I≥2σ(I)	6816	
R_{int}	0.0357	
Parameters / restraints	437 / 0	
Goodness-of-fit on F^2	1.064	
Final *R* indices [I > 2σ(I)]	R_1 = 0.0333, wR_2 = 0.0670	
R indices (all data)	R_1 = 0.0493, wR_2 = 0.0742	
Largest diff. peak and hole	0.616 and -0.674 e.Å^{-3}	

CCDC 1850113



Empirical formula	$C_{25}H_{29}BrO_3$	
Formula weight	457.39	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 15.6484(15) Å	α = 90°.
	b = 9.8378(7) Å	β = 112.228(8)°.
	c = 15.4117(12) Å	γ = 90°.
Volume	2196.3(3) $Å^3$	
Z	4	
Density (calculated)	1.383 Mg/m^3	
Absorption coefficient	1.895 mm^{-1}	
F(000)	952	
Crystal size	0.365 x 0.363 x 0.360 mm^3	
Theta range for data collection	1.406 to 34.998°.	
Index ranges	-25 ≤ h ≤ 25, -15 ≤ k ≤ 11, -24 ≤ l ≤ 24	
Reflections collected	45712	
Independent reflections	9569 [R_{int} = 0.0416]	
Completeness to Θ = 25.242°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7469 and 0.6329	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9569 / 0 / 269	
Goodness-of-fit on F^2	1.148	
Final R indices [I > 2σ(I)]	R_1 = 0.0406, wR_2 = 0.0686	
R indices (all data)	R_1 = 0.0870, wR_2 = 0.0856	
Largest diff. peak and hole	0.573 and -0.542 e.$Å^{-3}$	

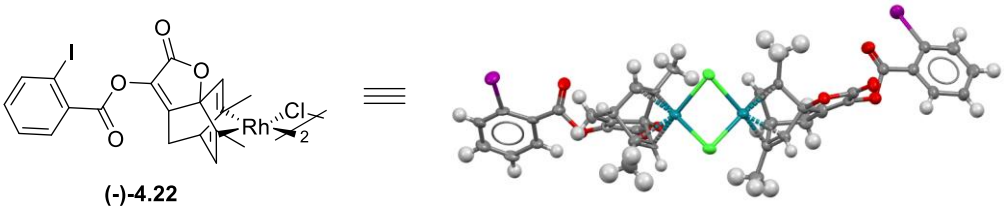
CCDC 1945514



4.18

Empirical formula	$C_{37}H_{27}Cl_5I_2O_8Rh_2$	
Formula weight	1236.45	
Temperature	100.00(10) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 7.9093(11) Å	α = 108.577(12)°.
	b = 13.7923(19) Å	β = 92.892(11)°.
	c = 19.266(3) Å	γ = 91.997(12)°.
Volume	1986.8(5) Å^3	
Z	2	
Density (calculated)	2.067 Mg/m^3	
Absorption coefficient	2.772 mm^{-1}	
F(000)	1188	
Crystal size	0.220 x 0.097 x 0.068 mm^3	
Θ range for data collection	2.582 to 26.372°.	
Index ranges	-9 ≤ h ≤ 9, -17 ≤ k ≤ 13, -24 ≤ l ≤ 23	
Reflections collected	8493	
Independent reflections	8493	
Completeness to *Θ* = 25.242°	98.6 %	
Absorption correction	Gaussian	
Max. and min. transmission	1.000 and 0.588	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8493 / 737 / 491	
Goodness-of-fit on F^2	0.933	
Final *R* indices [I > 2σ(I)]	R_1 = 0.0697, wR_2 = 0.1388	
R indices (all data)	R_1 = 0.1395, wR_2 = 0.1508	
Largest diff. peak and hole	1.499 and -1.374 e.Å^{-3}	

CCDC 2027174



(-)-4.22

The structure was determined as a twin with three molecules of CH_2Cl_2. One unit of **(-)-20b**, as well as the three molecules of CH_2Cl_2 were removed from the above representation for clarity reason.

Empirical formula	$C_{39.5}H_{33}Cl_5I_2O_8Rh_2$	
Formula weight	1272.53	
Colour	Clear intense yellow	
Shape	Needle	
Temperature	140.00(10) K	
Wavelength	1.54184 Å	
Radiation type	Cu*Kα*	
Crystal system	Triclinic	
Flack Parameter	-0.016(7)	
Space group	*P*1	
Unit cell dimensions	a = 8.0196(2) Å	α = 93.373(5)°.
	b = 15.8266(11) Å	β = 97.318(3)°.
	c = 17.0926(9) Å	γ = 96.178(4)°.
Volume	2133.47(19) $Å^3$	
Z	2	
Z'	2	
Density (calculated)	1.981 g/cm^3	
Absorption coefficient	20.924 mm^{-1}	
Crystal size	0.37×0.02×0.02 mm^3	
Θ range for data collection	2.816 to 72.429°.	
Mesured reflections	10540	
Independent reflections	10540	
Refl's I≥2σ(I)	8334	
R_{int}	n/a	
Parameters / restraints	992 / 1052	
Goodness-of-fit on F^2	1.151	
Final *R* indices [I > 2σ(I)]	R_1 = 0.0635, wR_2 = 0.1680	
R indices (all data)	R_1 = 0.0842, wR_2 = 0.1890	
Largest diff. peak and hole	2.128 and -2.547 e.$Å^{-3}$	

10.2.7. Computational Details

The geometries of all structures were optimized using the M06-2X[382,383] density functional in tandem with the def2-SVP basis set[384] using the "ultrafine" integration grid and the SMD implicit solvent model[385] (in tetrahydrofuran) as implemented in Gaussian09.[386] Refined energy estimates were obtained on the M06-2X/def2-SVP geometries through single point energy computations using the PBE0[387,388] density functional appended with a density dependent dispersion correction[389] (-dDSC) and the TZ2P basis set as implemented in ADF.[390] Reported free energies include PBE0-dDsC/TZ2P electronic energies, M06/def2-SVP uncorrected free energy corrections, and solvation correction (at the PBE0-dDsC/TZ2P level) using COSMO-RS.[391]

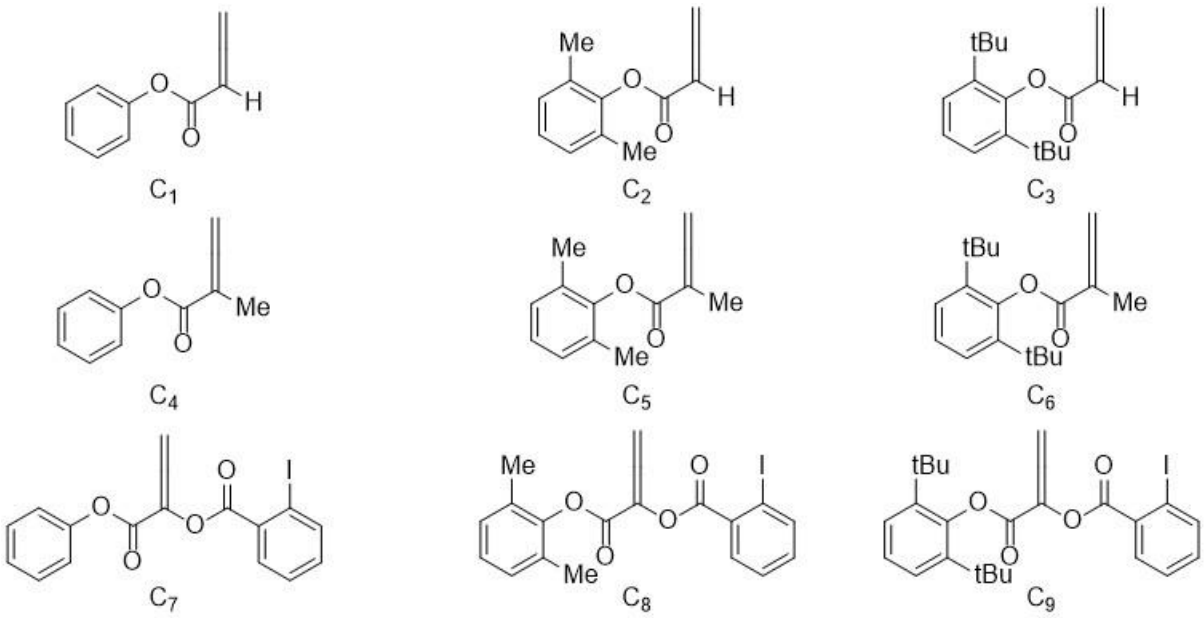


Figure S1. Schematic depiction of relevant compounds.

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Table S1. Computed free energies for reactant, transition state, and product of C1 – C9 relevant to the reactant. Values in kcal/mol.

Compound	Reactant	Transition State	Product
C1	0.00	25.29	-36.07
C2	0.00	25.28	-37.15
C3	0.00	18.30	-41.38
C4	0.00	23.25	-36.32
C5	0.00	22.15	-38.71
C6	0.00	16.25	-41.31
C7	0.00	22.07	-33.96
C8	0.00	20.29	-36.51
C9	0.00	14.68	-40.71

Table S2. Computed energies, free energies and solvation corrections (in hartree) of relevant compounds.

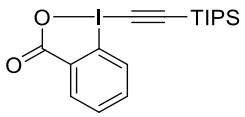
Compound	M06-2X/def2-SVP Electronic Energy	M06-2X/def2-SVP Free Energy Correction	PBE0-dDsC/TZ2P//M06-2X/def2-SVP Electronic Energy	Solvation Correction
C1 – Reactant	-535.660485	0.115453	-5.882364	-0.014746
C1 – TS	-535.617528	0.119650	-5.846487	-0.014519
C1 – Product	-535.680127	0.124302	-5.907232	-0.015909
C2 – Reactant	-614.199300	0.165579	-7.351969	-0.015602
C2 – TS	-614.157995	0.171586	-7.317906	-0.015381
C2 – Product	-614.223114	0.176433	-7.382658	-0.014683
C3 – Reactant	-849.772979	0.331232	-11.711835	-0.018823
C3 – TS	-849.738859	0.333412	-11.684717	-0.018951
C3 – Product	-849.808169	0.337372	-11.761901	-0.011665
C4 – Reactant	-574.928934	0.141236	-6.615322	-0.014856
C4 – TS	-574.887718	0.144938	-6.581929	-0.014908
C4 – Product	-574.951522	0.150158	-6.644298	-0.015631
C5 – Reactant	-653.467394	0.193920	-8.084606	-0.015760
C5 – TS	-653.428103	0.197060	-8.052369	-0.015832
C5 – Product	-653.494318	0.201848	-8.118429	-0.016245
C6 – Reactant	-889.040804	0.356440	-12.444611	-0.019038
C6 – TS	-889.008836	0.358190	-12.428794	-0.010703
C6 – Product	-889.079516	0.363561	-12.490830	-0.019871
C7 – Reactant	-1251.829112	0.187822	-9.901926	-0.026683
C7 – TS	-1251.788131	0.190415	-9.867835	-0.028202
C7 – Product	-1251.849800	0.197190	-9.928381	-0.028557
C8 – Reactant	-1330.367868	0.239743	-11.370473	-0.028151
C8 – TS	-1330.329533	0.241703	-11.339615	-0.028642

C8 – Product	-1330.393078	0.246804	-11.402967	-0.028571
C9 – Reactant	-1565.940676	0.402229	-15.729831	-0.031708
C9 – TS	-1565.910105	0.403203	-15.707217	-0.031909
C9 – Product	-1565.978305	0.407324	-15.776023	-0.032103

The Cartesian coordinates of the structures are given in separate files available on the online publication, see: D. P. Hari, G. Pisella, M. D. Wodrich, A. V. Tsymbal, F. F. Tirani, R. Scopelliti, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 5475.

10.3. Progress toward the Development of the Enantioselective Conjugate Oxy-Alkynylation of Diazo Compounds

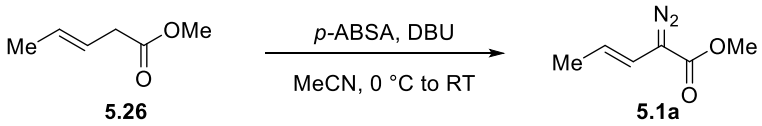
The synthesis of TIPS-EBX (**5.2a**) has been reported in section 10.2.2.



5.2a

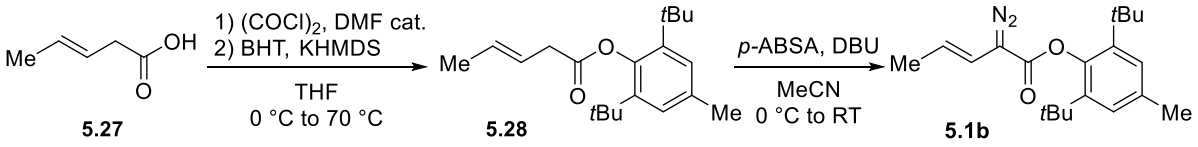
10.3.1. Preparation of Vinyldiazo Compounds

Methyl (*E*)-2-diazopent-3-enoate (5.1a)



Following a reported procedure,[227] to a stirring solution of methyl trans-pent-3- enoate (**5.26**) (1.00 g, 8.76 mmol, 1.00 equiv) and *p*-acetamidobenzenesulfonyl azide (3.16 g, 13.1 mmol, 1.50 equiv) in dry CH_3CN (20 mL) at 0 °C, was added DBU (2.65 mL, 17.5 mmol, 2.00 equiv) slowly in 5 min. The reaction mixture was stirred at 0 °C for 1 h and then 12 h at room temperature. The reaction mixture was quenched with NH_4Cl (saturated solution, 20 mL). The aqueous layer was extracted with Et_2O (3 x 40 mL) and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using pentane as eluent to afford **5.1a** as an orange oil (950 mg, 6.78 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (dd, *J* = 15.8, 1.7 Hz, 1H, CH_3CHCH), 5.38 – 5.29 (m, 1H, CH_3CHCH), 3.79 (s, 3H, OCH_3), 1.84 (dd, *J* = 6.7, 1.7 Hz, 3H, CH_3CHCH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 120.4, 112.6, 52.0, 18.2. One carbon was not resolved at 100 MHz. The values of the NMR spectra are in accordance with reported literature data.[227]

2,6-Di-tert-butyl-4-methylphenyl (*E*)-2-diazopent-3-enoate (5.1b)

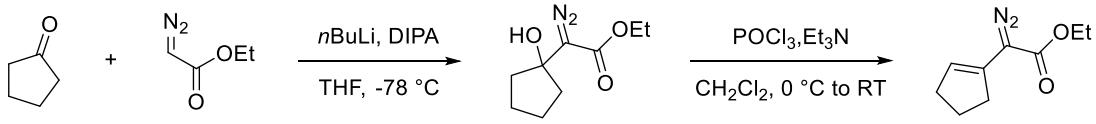


Two drops of DMF were added to a stirring solution of (*E*)-pent-3-enoic acid (**5.27**) (1.0 mL, 9.9 mmol, 1.1 equiv) and oxalyl chloride (0.86 mL, 9.9 mmol, 1.1 equiv) in THF (10 mL). The solution was stirred at RT for 1 h. In the meantime, KHMDS (13 mL, 9.4 mmol, 0.7 M in toluene, 1.1 equiv) was added to a stirred solution of butylated hydroxytoluene (2.0 g, 8.9 mmol, 1.0 equiv) in THF (10 mL) at 0 °C. The first solution was cooled to 0 °C and was slowly added in 15 min into the second. The reaction mixture was allowed to warm up to room temperature and then refluxed for 12 h. It was allowed to cool to room temperature and the reaction was quenched with NH_4Cl (saturated solution, 30 mL). The aqueous layer was extracted with DCM (3 x 25 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 1:99 as eluent to afford **5.28** as a white solid (993 mg, 3.18 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 2H, Ar*H*), 5.68 (m, 1H, Me*H*C=C), 3.34 – 3.30 (m, 1H, C=C*H*CH_2), 2.31 (s, 3H, CH_3 in BHT), 1.77 – 1.73 (m, 3H, CH_3), 1.58 (s, 2H, CH_2), 1.31 (s, 18H, *tBu* in BHT); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 146.3, 142.4, 134.9, 130.7, 127.5,

122.6, 40.1, 35.7, 31.9, 22.0, 18.4; IR (ν_{max}, cm^{-1}) 3668 (w), 2970 (s), 2906 (m), 1757 (m), 1393 (m), 1366 (m), 1276 (s), 1260 (s), 1133 (m), 1107 (s), 1074 (s), 1066 (s), 1058 (s), 770 (s), 752 (s); HRMS (ESI) Calcd for $C_{20}H_{30}NaO_2^+$ $[M+Na]^+$ 325.2138; found 325.2136.

To a stirring solution of 2,6-di-tert-butyl-4-methylphenyl (*E*)-pent-3-enoate (**5.28**) (500 mg, 1.65 mmol, 1.00 equiv) and *p*-acetamidobenzenesulfonyl azide (596 mg, 2.48 mmol, 1.50 equiv) in dry CH_3CN (3.3 mL) at 0 °C, was added DBU (0.50 mL, 3.3 mmol, 2.0 equiv) slowly in 5 min. The reaction mixture was stirred at 0 °C for 1 h and then 5 h at room temperature. The reaction mixture was quenched with NH_4Cl (saturated solution, 20 mL). The aqueous layer was extracted with Et_2O (3 x 25 mL) and the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 0.5:99.5 as eluent to afford **5.1b** as a red solid (431 mg, 1.31 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2H, Ar*H*), 5.89 – 5.72 (m, 1H, Me*H*C=C), 5.58 – 5.32 (m, 1H, C=C*H*CH_2), 2.32 (s, 3H, C*H*$_3$ in BHT), 1.88 (m, 3H, C*H*$_3$), 1.33 (s, 18H, *tBu* in BHT); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165. 4, 145.2, 142.4, 134.8, 127.1, 121.2, 112.3, 35.3, 31.6, 21.6, 18.3. One carbon was not resolved at 100 MHz; IR (ν_{max}, cm^{-1}) 3666 (w), 3333 (w), 2970 (s), 2910 (m), 2902 (m), 2080 (m), 1703 (s), 1342 (m), 1306 (m), 1250 (s), 1215 (m), 1187 (s), 1105 (s), 1054 (s), 963 (m), 937 (m), 881 (m), 724 (s); M.p. 69.2 – 70.4 °C; HRMS (ESI) Calcd for $C_{20}H_{28}N_2NaO_2^+$ $[M+Na]^+$ 351.2043; found 351.2036.

Ethyl 2-(cyclopent-1-en-1-yl)-2-diazoacetate (5.1c)

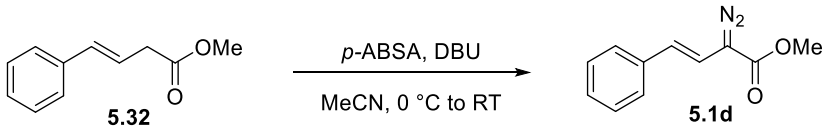


5.29 **5.30** **5.31** **5.1c**

Following a slightly modified reported procedure,[227] LDA in THF (4 mL), freshly made from *n*BuLi (4.40 mL, 11.0 mmol, 2.5 M in hexanes, 1.10 equiv) and diisopropylamine (1.70 ml, 12.0 mmol, 1.20 equiv) was added slowly in 15 min to a solution of ethyl diazoacetate (**5.30**) (1.20 mL, 10.0 mmol, 1.00 equiv) and cyclopentanone (**5.30**) (0.890 mL, 10.0 mmol, 1.00 equiv) in dry THF (6 mL) at -78 °C. The resulting solution was stirred at -78 °C for 1 h and quenched with NH_4Cl (saturated solution, 30 mL). The reaction mixture was extracted with Et_2O (2 x 30 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 10:90 as eluent to afford **5.31** as a yellow oil (1.77 mg, 8.94 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (q, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 3.26 (s, 1H, O*H*), 2.10 – 1.99 (m, 2H, cy-C*H*$_2$), 1.97 – 1.63 (m, 6H, cy-C*H*$_2$), 1.28 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 78.6, 60.8, 39.3, 22.9, 14.4. One carbon was not resolved at 100 MHz.The values of the NMR spectra are in accordance with reported literature data.[227]

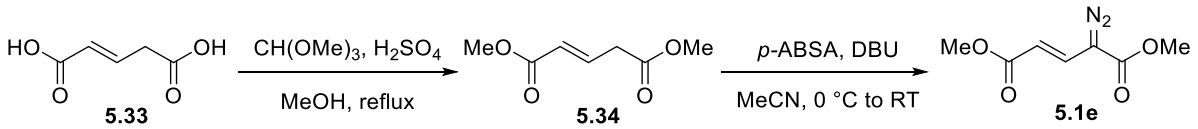
A solution of $POCl_3$ (1.10 mL, 11.4 mmol, 1.5 equiv) in dry DCM (7 mL) was slowly added to a solution of ethyl 2-diazo-2-(1-hydroxycyclopentyl)acetate (**5.31**) (1.50 g, 7.57 mmol, 1.00 equiv) and NEt_3 (4.22 mL, 30.3 mmol, 4.00 equiv) in dry DCM (35 mL) at 0 °C, over 30 minutes using syringe pump. The resulting solution was warmed to room temperature and further stirred for 12 h. The solution was washed with water (2 x 30 mL) and dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using pentane as eluent to afford **5.1c** as an orange oil (455 mg, 2.52 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 – 5.84 (m, 1H, olefinic *H*), 4.26 (q, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 2.55 – 2.39 (m, 4H, Cy-C*H*$_2$), 2.04 – 1.81 (m, 2H, Cy-C*H*$_2$), 1.29 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 124.4, 124.2, 60.8, 33.9, 33.7, 22.6, 14.4. One carbon was not resolved at 100 MHz.The values of the NMR spectra are in accordance with reported literature data.[227]

Methyl (*E*)-2-diazo-4-phenylbut-3-enoate (5.1c)



Following a reported procedure,[293a] DBU (0.60 mL, 4.0 mmol, 2.00 equiv) was added slowly in 5 min to a stirring solution of methyl (*E*)-4-phenylbut-3-enoate (**5.32**) (352 mg, 2.00 mmol, 1.00 equiv) and *p*-acetamidobenzenesulfonyl azide (721 mg, 3.00 mmol, 1.50 equiv) in dry CH_3CN (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then 12 h at room temperature. The reaction mixture was quenched with NH_4Cl (saturated solution, 10 mL). The aqueous layer was extracted with Et_2O (3 X 15 mL) and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using pentane as eluent to afford **5.1d** as an orange oil (161 mg, 0.800 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 5H, Ar*H*), 6.49 (d, *J* = 16.0 Hz, 1H, PhCH=C*H*), 6.20 (d, *J* = 16.0 Hz, 1H, PhC*H*=CH), 3.86 (s, 3H, OC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 136.8, 128.7, 127.1, 125.9, 123.1, 111.3, 77.3, 52.3. The values of the NMR spectra are in accordance with reported literature data.[294]

Dimethyl (*E*)-4-diazopent-2-enedioate (5.1e)



Following a reported procedure,[392] sulfuric acid (25 µL, 0.50 mmol, 0.10 equiv) was added to a stirring solution of (*E*)-pent-2-enedioic acid (**5.33**) (650 mg, 5.00 mmol, 1.00 equiv) and trimethyl orthoformate (1,70 mL, 15.0 mmol, 3.00 equiv) in MeOH (1.3 mL). The resulting solution was stirred under reflux for 16 h. It was allowed to cool to RT and EtOAc (15 mL) and water (15 mL) were added. The two layers were separated and the organic layer was successively washed with HCl (1.0 N, 10 mL), $NaHCO_3$ (10 mL) and brine (10 mL). The organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to obtain an oil which was further purified by Kugelrohr distillation to afford **5.34** as a colorless oil (618 mg, 3.91 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (dt, *J* = 15.7, 7.2 Hz, 1H, C=C*H*CH$_2$), 5.93 (dt, *J* = 15.7, 1.6 Hz, 1H, C(O)C*H*=C), 3.73 (s, 3H, OC*H*$_3$), 3.70 (s, 3H, OC*H*$_3$), 3.23 (dd, *J* = 7.2, 1.6 Hz, 2H, C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 166.3, 140.7, 121.7, 52.3, 51.8, 37.3.The values of the NMR spectra are in accordance with reported literature data.[393]

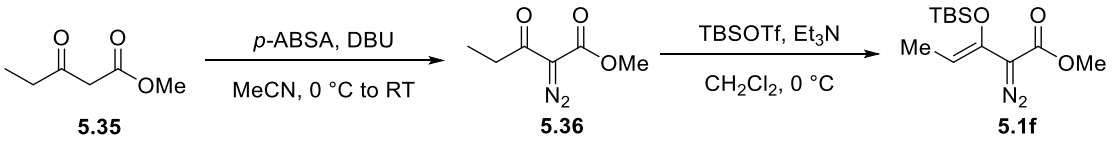
DBU (0.55 mL, 3.8 mmol, 1.5 equiv) was slowly added in 5 min to a stirring solution of dimethyl (*E*)-pent-2-enedioate (**5.34**) (400 mg, 2.50 mmol, 1.0 equiv) and *p*-acetamidobenzenesulfonyl azide (668 mg, 2.78 mmol, 1.10 equiv) in dry CH_3CN (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then 12 h at room temperature. The reaction mixture was quenched with NH_4Cl (saturated solution, 20 mL). The aqueous layer was extracted with Et_2O (3 x 25 mL) and the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 1:99 as eluent to afford **5.1e** as an orange solid (114 mg, 0.620 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 15.8 Hz, 1H, C=C*H*CN$_2$), 5.71 (d, *J* = 15.7 Hz, 1H, C(O)C*H*=C), 3.84 (s, 3H, OC*H*$_3$), 3.74 (s, 3H, OC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 164.0, 131.5, 111.7, 53.1, 52.1. One

[392] M. Loegers, L. E. Overman, G. S. Welmaker, *J. Am. Chem. Soc.* **1995**, *117*, 9139.

[393] I. J. S. Fairlamb, A. F. Lee, F. E. M. Loe-Mie, E. H. Niemelä, C. T. O'Brien, A. C. Whitwood, *Tetrahedron* **2005**, *61*, 9827.

carbon was not resolved at 100 MHz.The values of the NMR spectra are in accordance with reported literature data.[394]

Methyl ((tert-butyldimethylsilyl)oxy)-2-diazopent-3-enoate (5.1f)

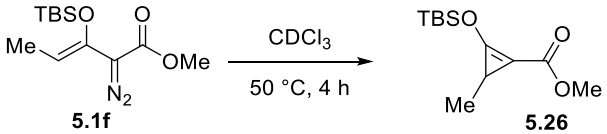


5.35 5.36 5.1f

Following a slightly modified reported procedure,[395] DBU (0.521 mL, 3.46 mmol, 1.50 equiv) was added slowly in 5 min to a stirring solution of methyl 3-oxopentanoate (**5.35**) (0.29 mL, 2.3 mmol, 1.00 equiv) and *p*-acetamidobenzenesulfonyl azide (609 mg, 2.54 mmol, 1.10 equiv) in dry CH_3CN (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then 12 h at room temperature. The reaction mixture was quenched with NH_4Cl (saturated solution, 20 mL). The aqueous layer was extracted with Et_2O (3 x 25 mL) and the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 1:99 as eluent to afford **5.36** as an orange oil (220 mg, 1.41 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H, C*H*$_3$), 2.86 (q, *J* = 7.3 Hz, 2H, C*H*$_2$CH$_3$), 1.13 (t, *J* = 7.3 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 162.3, 76.0, 52.6, 34.2, 8.7. The values of the NMR spectra are in accordance with reported literature data.[396]

Tert-butyldimethylsilyl trifluoromethanesulfonate (0.290 mL, 1.27 mmol, 1.10 equiv) was added slowly in 2 min to a stirring solution of methyl 2-diazo-3-oxopentanoate (**5.36**) (180 mg, 1.15 mmol, 1.00 equiv) and triethylamine (0.250 mL, 1.73 mmol, 1.50 equiv) in DCM (12 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then quenched with $NaHCO_3$ (saturated solution, 15 mL). The aqueous layer was extracted with DCM (2 x 15 mL) and the combined organic layers were washed with $NaHCO_3$ (saturated solution, 20 mL), brine (20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 2:98 as eluent to afford **5.1f** as a mixture of diastereomers (*Z*/*E* 85:15) as an orange oil (228 mg, 0.840 mmol, 73%). *Z*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (q, *J* = 7.0 Hz, 1H, olefinic *H*), 3.78 (s, 3H, OC*H*$_3$), 1.67 (d, *J* = 7.0 Hz, 3H, *H*$_3$C=C), 0.95 (s, 9H, ^{t}*Bu* in TBS), 0.15 (s, 6H, C*H*$_3$ in TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 132.7, 107.8, 51.6, 25.4, 18.0, 11.6, -4.9. One carbon was not resolved at 100 MHz. The values of the NMR spectra are in accordance with reported literature data.[397]

Methyl 2-((tert-butyldimethylsilyl)oxy)-3-methylcycloprop-1-ene-1-carboxylate (5.26)



5.1f 5.26

A solution of methyl 3-((tert-butyldimethylsilyl)oxy)-2-diazopent-3-enoate (**5.1f**) (100 mg, 0.370 mmol, 1,00 equiv) in $CDCl_3$ (4 mL) was stirred at 50 °C for 4 h until the yellow color fades. The solvent was removed under educed pressure to afford methyl 2-((tert-butyldimethylsilyl)oxy)-3-methylcycloprop-1-enecarboxylate **5.26** as a clear yellow oil (80 mg, 0.33 mmol, 89 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H, O*Me*), 2.33 (q, *J* = 4.8 Hz, 1H, C*H*), 1.24 (d, *J* = 4.9 Hz, 3H, C*H*$_3$), 0.97 (s, 9H, *tBu* in TBS),

[394] M. P. Doyle, M. Yan, W. Hu, L. S. Gronenberg, *J. Am. Chem. Soc.* **2003**, *125*, 4692.

[395] C. Zhu, G. Xu, J. Sun, *Angew. Chem. Int. Ed.* **2016**, *55*, 11867.

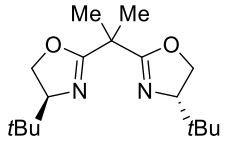
[396] L. Zhou, M. P. Doyle, *Org. Lett.* **2010**, *12*, 796.

[397] E. Nadeau, D. L. Ventura, J. A. Brekan, H. M. L. Davies, *J. Org. Chem.* **2010**, *75*, 1927.

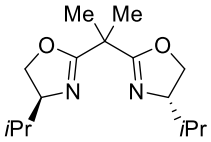
0.32 (s, 6H, *Me* in TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 149.1, 77.7, 51.8, 25.8, 24.9, 19.9, 18.4, -4.6, -4.7. The values of the NMR spectra are in accordance with reported literature data.[296]

10.3.2. Preparation of Ligands

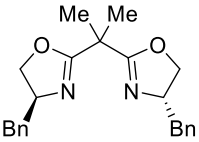
Ligands **5.5a**, **5.5b**, **5.5c**, **5.5d**, **5.6a**, **5.6b**, **5.7** and **5.10g** were directly obtained from chemical suppliers.



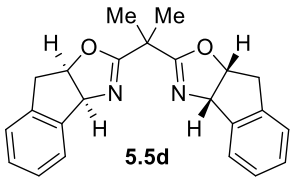
5.5a



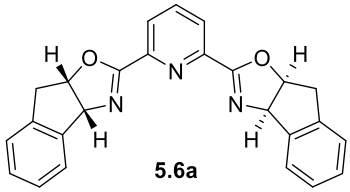
5.5b



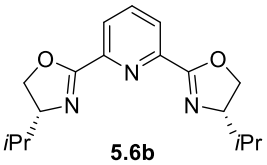
5.5c



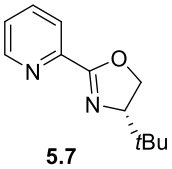
5.5d



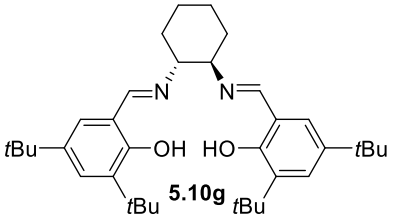
5.6a



5.6b

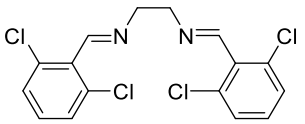


5.7



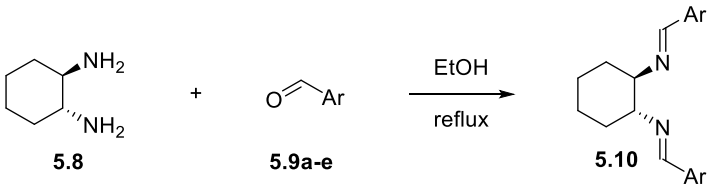
5.10g

Ligand **5.4** has been reported in section 10.2.



5.4

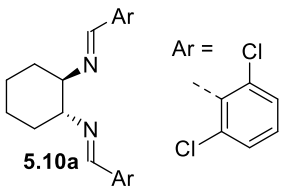
General procedure A: Synthesis of ligands 5.10a-e[398]



5.8 **5.9a-e** **5.10**

(1*R*,2*R*)-cyclohexane-1,2-diamine (**5.8**) (53.0 mg, 0.460 mmol, 1.00 equiv) and the corresponding arylaldehyde **5.9ae** (0.92 mmol, 2.00 equiv) were dissolved in EtOH (2.0 mL). The reaction mixture was stirred under reflux for 1 h to 12 h. After cooling at room temperature, the resulting precipitate was collected by vacuum filtration and washed with cold EtOH. Recrystallization from EtOH afforded the corresponding 1,2-diimines **5.10a**-**e**.

(1*E*,1'*E*)-*N*,*N*'-((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(1-(2,6-dichlorophenyl)methanimine) (5.10a)

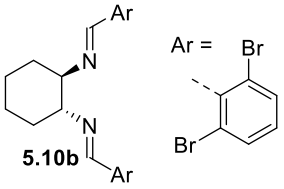


5.10a

Following the general procedure **A**, **5.10a** was obtained as white crystals (95 mg, 0.22 mmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 2H, N=C*H*), 7.27 (m, 4H, Ar*H*), 7.16 (dd, *J* = 8.7, 7.3 Hz, 2H, Ar*H*), 3.96 – 3.39 (m, 2H, NC*H*), 1.89 (m, 4H, CH_2), 1.62 – 1.36 (m, 4H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 135.3, 133.4, 130.4, 129.1, 75.4, 33.4, 24.7. The values of the NMR spectra are in accordance with reported literature data.[398]

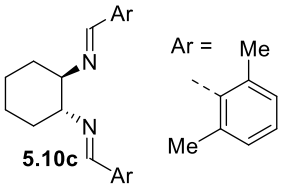
[398] J. Wu, Y. Chen, J. S. Panek, *Org. Lett.* **2010**, *12*, 2112.

(1*E*,1'*E*)-*N*,*N*'-((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(1-(2,6-dibromophenyl)methanimine) (5.10b)



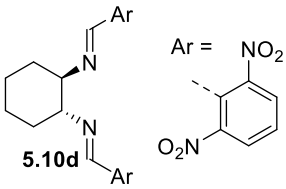
Following the general procedure **A**, **5.10b** was obtained as white crystals (138 mg, 0.23 mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 2H, N=C*H*), 7.52 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.01 (t, *J* = 8.0 Hz, 2H, Ar*H*), 3.95 – 3.47 (m, 2H, NC*H*), 2.00 – 1.79 (m, 4H, CH_2), 1.63 – 1.43 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 156.1, 132.3, 130.5, 124.7, 74.7, 33.1, 24.3. The values of the NMR spectra are in accordance with reported literature data.[398]

(1*E*,1'*E*)-*N*,*N*'-((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(1-(2,6-dimethylphenyl)methanimine) (5.10c)



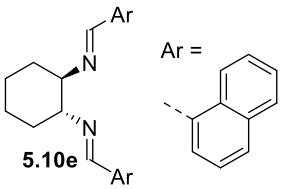
Following the general procedure **A**, **5.10c** was obtained as white crystals (43 mg, 0.12 mmol, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 2H, N=C*H*), 7.08 (t, *J* = 7.5 Hz, 2H, Ar*H*), 6.96 (d, *J* = 7.5 Hz, 4H, Ar*H*), 3.54 – 3.37 (m, 2H, NC*H*), 2.28 (s, 12H, CH_3), 1.97 – 1.78 (m, 4H, CH_2), 1.66 – 1.45 (m, 4H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 137.3, 134.1, 128.5, 128.3, 75.6, 33.6, 24.5, 20.6. The values of the NMR spectra are in accordance with reported literature data.[398]

(1*E*,1'*E*)-*N*,*N*'-((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(1-(2,6-dinitrophenyl)methanimine) (5.10d)



Following the general procedure **A**, **5.10d** was obtained as a brown clear solid (115 mg, 0.244 mmol, 53%). M.p. (Dec.) 174.2 – 174.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 2H, N=C*H*), 8.18 (d, *J* = 8.2 Hz, 4H, Ar*H*), 7.68 (t, *J* = 8.2 Hz, 2H, Ar*H*), 3.71 – 3.35 (m, 2H, NC*H*), 1.93 – 1.72 (m, 4H, CH_2), 1.68 – 1.32 (m, 4H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 150.2, 130.4, 128.7, 128.5, 74.4, 31.4, 24.3; IR (ν_{max}, cm^{-1}) 3666 (m), 2987 (s), 2974 (s), 2902 (s), 1538 (s), 1405 (m), 1393 (m), 1350 (s), 1274 (m), 1258 (m), 1078 (s), 1066 (s), 1052 (s), 1030 (s), 907 (m), 822 (m), 766 (s), 748 (s), 710 (m); HRMS (ESI) Calcd for $C_{20}H_{19}N_6O_8^+$ $[M+H]^+$ 471.1259; found 471.1265.

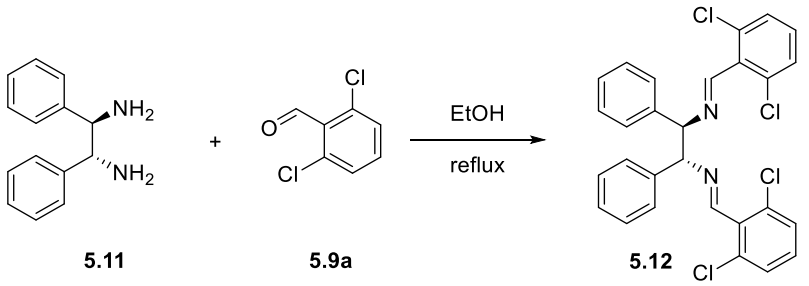
(1*E*,1'*E*)-*N*,*N*'-((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(1-(naphthalen-1-yl)methanimine) (5.10e)



Following the general procedure **A**, **5.10e** was obtained as a white-off solid (122 mg, 0.310 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 2H, N=C*H*), 8.57 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.78 (t, *J* = 7.9 Hz, 4H, Ar*H*), 7.73 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.38 (ddt, *J* = 7.2, 5.0, 3.6 Hz, 4H, Ar*H*), 7.22 (ddd, *J* = (8.4, 6.8, 1.4 Hz, 2H, Ar*H*), 3.71 – 3.56 (m, 2H, NC*H*), 2.09 – 1.88 (m, 6H, CH_2), 1.59 (tt, *J* = 9.0, 3.2 Hz, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 133.4, 132.1, 130.9, 130.2, 128.3, 127.8, 126.5, 125.8, 125.1, 124.3, 74.7, 33.0, 24.5. The values of the NMR spectra are in accordance with reported literature data.[399]

[399] N. Duguet, A. Donaldson, S. M. Leckie, J. Douglas, P. Shapland, T. B. Brown, G. Churchill, A. M. Z. Slawin, A. D. Smith, *Tetrahedron: Asymmetry* **2010**, *21*, 582.

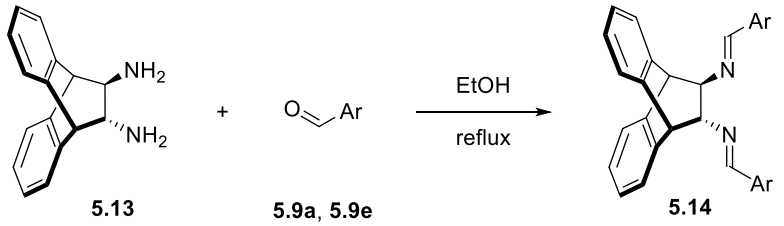
(1*E*,1'*E*)-*N*,*N*'-((1*R*,*2R)*-1,2-Diphenylethane-1,2-diyl)bis(1-(2,6-dichlorophenyl)methanimine) (5.12)



5.11 **5.9a** **5.12**

(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (**5.11**) (85 mg, 0.40 mmol, 1.00 equiv) and 2,6-dichlorobenzaldehyde (**5.9a**) (140 mg, 0.801 mmol, 2.00 equiv) were dissolved in EtOH (1 mL). The reaction mixture was stirred under reflux for 12 h. After cooling at room temperature, the resulting precipitate was collected by vacuum filtration and washed with cold EtOH to afford **5.12** as a white solid (155 mg, 0.300 mmol, 74%). M.p. 148.3 – 149.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 2H, N=C*H*), 7.43 – 7.34 (m, 2H, Ar*H*), 7.31 – 7.23 (m, 6H, Ar*H*), 7.21 – 7.10 (m, 8H, Ar*H*), 4.90 (s, 2H, NC*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 140.4, 135.5, 132.4, 130.2, 128.9, 128.6, 128.1, 127.2, 82.6; IR (ν_{max}, cm^{-1}) 2854 (w), 1653 (m), 1578 (m), 1558 (m), 1429 (m), 1371 (w), 1187 (w), 1094 (w), 1050 (m), 1016 (m), 833 (m), 780 (s), 764 (s), 748 (m); HRMS (ESI) Calcd for $C_{28}H_{21}Cl_4N_2^+$ $[M+H]^+$ 525.0453; found 525.0466.

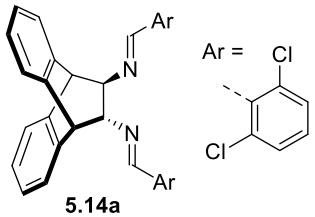
Ligands **5.14a** and **5.14b** were synthetized following a reported procedure:[283]



5.13 **5.9a**, **5.9e** **5.14**

A mixture of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-diamine (**5.13**) (20.0 mg, 0.08 mmol, 1.00 equiv) and the corresponding arylaldehyde (**5.9**) (2.00 equiv) in EtOH (1.4 mL) was stirred under reflux for 14 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in EtOH/hexane 1:1 (1.4 mL) and stirred for 2 h at room temperature. Then, the solid was filtered and washed with EtOH/hexane 1:1 (3 x 0.5 mL) and dried under reduced pressure to afford the corresponding 1,2-diimines **5.14a** or **5.14b**.

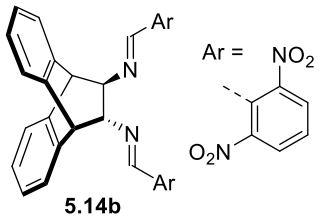
(1*E*,1'*E*)-*N,N'*-((11*R*,12*R*)-9,10-Dihydro-9,10-ethanoanthracene-11,12-diyl)bis(1-(2,6-dichlorophenyl) methanimine) (5.14a)



5.14a

5.14a was obtained as a white solid (38 mg, 70 µmol, 82%). M.p. 174.3 – 176.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 2H, N=C*H*), 7.11 – 6.72 (m, 14H, Ar*H*), 4.00 (s, 2H, NC*H*), 3.40 (s, 2H, C*H* on bridged); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 142.0, 141.0, 135.0, 133.7, 130.7, 128.9, 126.8, 126.7, 126.3, 124.3, 78.6, 52.5; IR (ν_{max}, cm^{-1}) 3660 (w), 2989 (s), 2974 (s), 2900 (s), 1455 (w), 1433 (m), 1409 (m), 1395 (m), 1383 (m), 1276 (m), 1260 (m), 1074 (s), 1064 (s), 1054 (s), 762 (s), 748 (s); HRMS (ESI) Calcd for $C_{30}H_{21}Cl_4N_2^+$ $[M+H]^+$ 549.0453; found 549.0454.

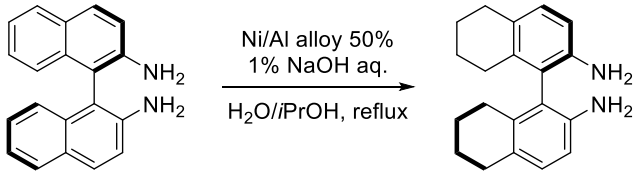
(1*E*,1'*E*)-*N*,*N*'-((11*R*,12*R*)-9,10-Dihydro-9,10-ethanoanthracene-11,12-diyl)bis(1-(2,6-dinitrophenyl) methanimine) (5.14b)



5.14b

5.14b was obtained as a beige solid (30 mg, 50 µmol, 60%). M.p. (Dec.) 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 2H, N=C*H*), 8.21 (d, *J* = 8.2 Hz, 4H, Ar*H*), 7.68 (t, *J* = 8.2 Hz, 2H, Ar*H*), 7.41 – 7.29 (m, 4H, Ar*H*), 7.20 – 7.08 (m, 4H, Ar*H*), 4.29 (s, 2H, NC*H*), 3.67 (s, 2H, C*H* on bridged); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 150.1, 141.2, 140.9, 130.6, 129.0, 128.8, 126.8, 126.7, 126.4, 124.4, 76.7, 50.9; IR (ν_{max}, cm^{-1}) 3662 (w), 2987 (s), 2972 (s), 2902 (m), 1532 (m), 1405 (m), 1395 (m), 1379 (m), 1348 (m), 1276 (m), 1260 (m), 1068 (s), 1058 (s), 1028 (m), 764 (s), 748 (s); HRMS (ESI) Calcd for $C_{30}H_{21}N_6O_8^+$ $[M+H]^+$ 593.1415; found 593.1413.

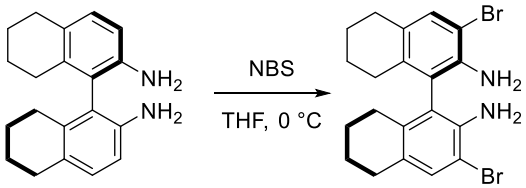
(*R*)-5,5',6,6',7,7',8,8'-Octahydro-[1,1'-binaphthalene]-2,2'-diamine, H_8-BINAM (5.15b)



5.15a 5.15b

Following a slightly modified procedure,[291] KOH (200 mL, 50.0 mmol, 1% in water, 50.0 equiv) was gradually added to a stirring mixture of (*R*)-1,1'-binaphthyl-2,2'-diamine (**5.15a**) (284 mg, 1.00 mmol, 1.00 equiv) and Ni-Al alloy 50% (2.0 g) in *i*PrOH (100 mL) and water (100 mL) over 1 h at 90 °C. After 24 h of stirring, the reaction mixture was cooled to room temperature. The mixture was filtered through Celite, and the filter cake was washed with EtOAc. The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 33:67 as eluent to afford H_8-BINAM **5.15b** as a white solid (136 mg, 0.465 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J* = 8.1 Hz, 2H, Ar*H*), 6.62 (d, *J* = 8.1 Hz, 2H, Ar*H*), 3.27 (br s, 4H, NH_2), 2.72 (t, *J* = 6.2 Hz, 4H, H_2CC_{Ar}), 2.36 – 2.12 (m, 4H, H_2CC_{Ar}), 1.81 – 1.61 (m, 8H, H_2CCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 136.7, 129.7, 128.1, 122.4, 113.6, 29.8, 27.4, 23.9, 23.7. The values of the NMR spectra are in accordance with reported literature data.[291]

(*R*)-3,3'-Dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (5.15c)

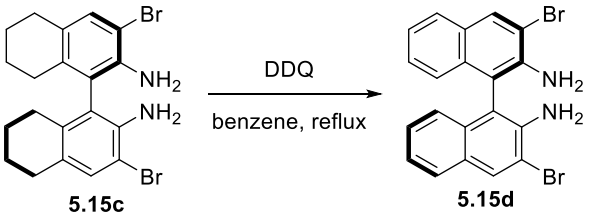


5.15b 5.15c

Following a reported procedure,[291] NBS (161 mg, 0.900 mmol, 2.00 equiv) was added to a stirring solution of (*R*)-H_8-BINAM (**5.15b**) (132 mg, 0.450 mmol, 1.00 equiv) in anhydrous THF (2.2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 min. The mixture was then quenched with $NaHCO_3$ (saturated solution, 3 mL) and saturated Na_2SO_3 (saturated solution, 3 mL). The reaction mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 3:97 as eluent to afford **5.15c** as a white solid (170 mg, 0.378 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 1.1 Hz, 2H, Ar*H*), 3.60 (br s, 4H, NH_2), 2.70 (t, *J* = 6.3 Hz, 4H, H_2CC_{Ar}), 2.21 (dt, *J* = 17.2, 6.2 Hz, 2H, H_2CC_{Ar}), 2.08 (dt, *J* = 17.5, 6.4 Hz, 2H, H_2CC_{Ar}), 1.77 – 1.59 (m, 8H, H_2CCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 136.1, 132.8, 129.5,

122.8, 107.5, 29.5, 27.2, 23.6, 23.4. The values of the NMR spectra are in accordance with reported literature data.[291]

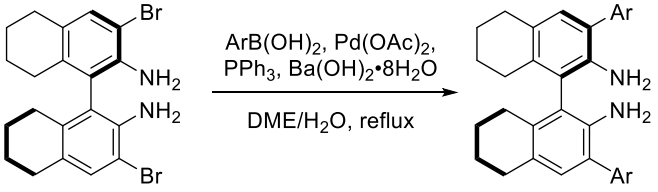
(*R*)-3,3'-Dibromo-[1,1'-binaphthalene]-2,2'-diamine (5.15d)



5.15c **5.15d**

Following a reported procedure,[291] DDQ (139 mg, 0.850 mmol, 5.00 equiv) was added to a stirring solution of (*R*)-3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (**5.15c**) (55 mg, 0.12 mmol, 1.00 equiv) in benzene (2.5 mL) at room temperature. The reaction mixture was stirred at reflux for 5 min. It was allowed to cool to room temperature. The crude product was purified by flash column chromatography using EtOAc/pentane 4:96 as eluent to afford **5.15d** as a white solid (15 mg, 30 µmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 2H, Ar*H*), 7.80 – 7.69 (m, 2H, Ar*H*), 7.30 – 7.18 (m, 4H, Ar*H*), 7.03 – 6.94 (m, 2H, Ar*H*), 4.13 (s, 4H, N*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 132.9, 132.7, 129.1, 127.9, 127.8, 124.3, 123.9, 113.8, 113.1. The values of the NMR spectra are in accordance with reported literature data.[291]

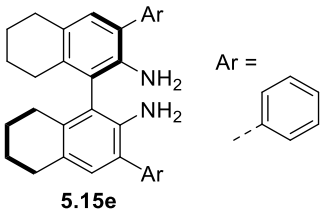
The compounds **5.15e** and **5.15f** were prepared following a reported procedure:[291]



5.15c **5.15e** or **5.15f**

A mixture of (*R*)-3,3'-dibromo-[1,1'-binaphthalene]-2,2'-diamine (**5.15c**) (1.00 equiv), $Pd(OAc)_2$ (0.10 equiv), PPh_3 (0.40 equiv), $Ba(OH)_2{\cdot}8H_2O$ (4.00 equiv), and arylboronic acid (3.00 equiv) in degassed DME/H_2O (10:1, *c* = 0.09 M) was refluxed for 20 h under an argon atmosphere. After cooling to RT, the resulting mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude products were purified by flash column chromatography using EtOAc/pentane 1:99 as eluent to afford the corresponding binaphtylamines **5.15e** and **5.15f**.

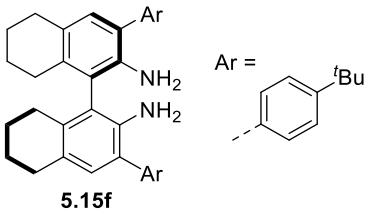
(*R*)-3,3'-Diphenyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (5.15e)



5.15e

5.15e was obtained as a white solid (40 mg, 70 µmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 4H, Ar*H*), 7.46 – 7.38 (m, 4H, Ar*H*), 7.35 – 7.28 (m, 2H, Ar*H*), 6.93 (s, 2H, Ar*H*), 3.35 (s, 4H, N*H*$_2$), 2.76 (td, *J* = 6.2, 2.5 Hz, 4H, *H*$_2$CC$_{Ar}$), 2.47 – 2.15 (m, 4H, *H*$_2$CC$_{Ar}$), 1.74 (tdd, *J* = 15.4, 7.8, 4.0 Hz, 8H, *H*$_2$CC*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5, 139.1, 136.1, 130.8, 129.6, 129.1, 127.9, 127.3, 126.2, 122.8, 29.8, 27.5, 24.0, 23.8. The values of the NMR spectra are in accordance with reported literature data.[291]

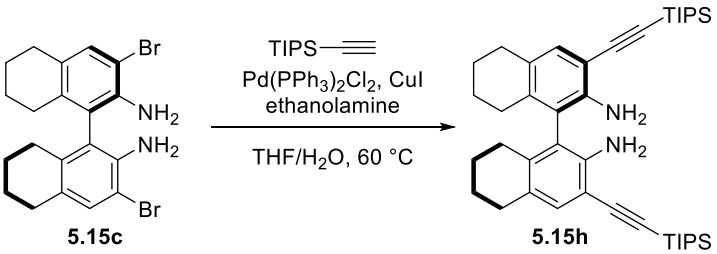
(*R*)-3,3'-Bis(4-(*tert*-butyl)phenyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (5.15f)



5.15f

5.15f was obtained as a white solid (20 mg, 50 mmol, 37%). M.p. 156.2 – 157.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 8H, Ar*H*), 6.93 (s, 2H, Ar*H*), 3.56 (br s, 4H, NH_2), 2.76 (td, *J* = 6.1, 2.5 Hz, 4H, H_2CC_{Ar}), 2.45 – 2.17 (m, 4H, H_2CC_{Ar}), 1.84 – 1.60 (m, 8H, H_2CCH_2), 1.36 (s, 18H, *tBu*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 139.4, 137.6, 135.8, 130.7, 129.2, 127.7, 126.0 (2 x C), 122.8, 35.0, 31.9, 29.8, 27.5, 24.0, 23.8. IR (ν_{max}, cm^{-1}) 3467 (w), 3367 (w), 2961 (s), 2928 (s), 2860 (m), 2835 (m), 1605 (m), 1588 (m), 1513 (m), 1457 (s), 1396 (m), 1361 (m), 1265 (m), 1109 (m), 910 (s), 837 (s); HRMS (ESI) Calcd for $C_{40}H_{49}N_2^+$ $[M+H]^+$ 557.3890; found 557.3892.

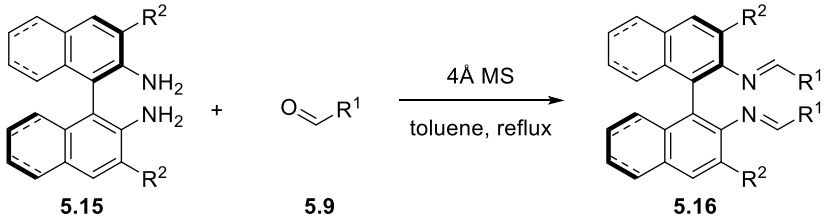
(*R*)-3,3'-Bis((triisopropylsilyl)ethynyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (5.15h)



5.15c **5.15h**

To a solution of (*R*)-3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (**5.15c**) (45.0 mg, 0.100 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (4.2 mg, 6.0 µmol, 0.06 equiv) and CuI (0.8 mg, 4 µmol, 0.04 equiv) in THF (0.65 mL) was added ethynyltriisopropylsilane (65 µL, 0.30 mmol, 3.00 eqiuv) and dropwise a solution ethanolamine (25 µL, 0.40 mmol, 4.00 equiv) in water (650 µL). The mixture was stirred at 60 °C for 18h. The reaction mixture was allowed to cool to room temperature and filtered through Celite with toluene and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 2:98 as eluent to afford **5.15h** as a white solid (44 mg, 7.0 µmol, 67%). M.p. 165.6 – 166.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2H, Ar*H*), 3.94 (br s, 4H, NH_2), 2.68 (t, *J* = 6.1 Hz, 4H, H_2CC_{Ar}), 2.28 (dt, *J* = 17.5, 6.0 Hz, 2H, H_2CC_{Ar}), 2.14 (dt, *J* = 17.8, 6.2 Hz, 2H, H_2CC_{Ar}), 1.68 (tdd, *J* = 12.8, 6.4, 3.3 Hz, 8H, H_2CCH_2), 1.12 (s, 42H, *TIPS*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 137.6, 132.1, 126.8, 120.2, 105.9, 104.1, 94.8, 28.9, 26.9, 23.1, 22.9, 18.6, 11.2; IR (ν_{max}, cm^{-1}) 3476 (m), 3382 (m), 2939 (s), 2891 (m), 2864 (s), 2139 (s), 1603 (s), 1590 (m), 1455 (s), 1228 (m), 997 (m), 907 (s), 882 (s); HRMS (ESI) Calcd for $C_{42}H_{65}N_2Si_2^+$ $[M+H]^+$ 653.4681; found 653.4673.

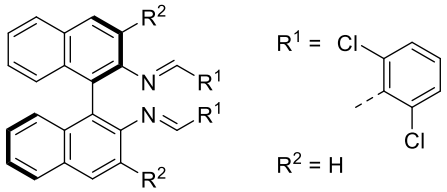
General procedure B: Synthesis of ligands 5.16a-k[285]



5.15 **5.9** **5.16**

(*R*)-(+)-1,1'-Binaphthyl-2,2'-diamine (**5.15**) (1.00 equiv), the corresponding aldehyde (**5.9)** (4.00 equiv) and 4 Å MS were stirred in dry toluene (*c* = 0.18 M) at reflux for 2 to 18 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane/Et_3N 250:10:1 as eluent to afford the corresponding 1,2-diimines **5.16a-k**.

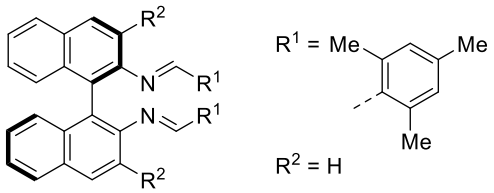
(*R*)-(1*E*,1'*E*)-*N*,*N*'-([1,1'-Binaphthalene]-2,2'-diyl)bis(1-(2,6-dichlorophenyl)methanimine) (5.16a)



5.16a

Following the general procedure **B**, **5.16a** was obtained as a yellow solid (127 mg, 0.210 mmol, 60%). ^{1}H NMR (400 MHz, C_6D_6) δ 8.69 (s, 2H, *H*C=N), 7.82 (dd, *J* = 8.8, 0.8 Hz, 2H, Ar*H*), 7.73 (dt, *J* = 8.2, 0.9 Hz, 2H, Ar*H*), 7.56 (dq, *J* = 8.4, 0.9 Hz, 2H, Ar*H*), 7.42 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.19 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 2H, Ar*H*), 7.06 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H, Ar*H*), 6.60 (d, *J* = 8.1 Hz, 4H, Ar*H*), 6.18 (t, *J* = 8.1 Hz, 2H, Ar*H*); ^{13}C NMR (101 MHz, C_6D_6) δ 156.2, 148.7, 135.0, 134.1, 132.6, 132.4, 129.8, 129.2, 128.2, 127.8, 127.6, 126.8, 126.7, 125.1, 119.0. The values of the NMR spectra are in accordance with reported literature data.[400]

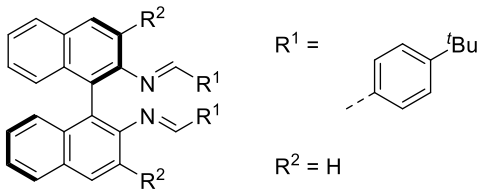
(*R*)-(1*E*,1'*E*)-*N*,*N*'-([1,1'-binaphthalene]-2,2'-diyl)bis(1-mesitylmethanimine) (5.16b)



5.16b

Following the general procedure **B, 5.16b** was obtained as a yellow solid (110 mg, 0.200 mmol, 57%). M.p. 186.2 – 188.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 2H, *H*C=N), 8.06 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.98 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.47 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.40 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 2H, Ar*H*), 7.28 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 2H, Ar*H*), 7.13 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.72 (s, 4H, Ar*H*), 2.14 (s, 6H, CH_3), 1.86 (s, 12H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.9, 149.5, 139.7, 138.7, 133.4, 131.8, 130.2, 129.9, 129.4, 128.5, 126.9, 126.7, 126.1, 125.2, 119.8, 21.2, 20.6; IR (ν_{max}, cm^{-1}) 3684 (m), 3674 (m), 3327 (w), 2987 (s), 2972 (s), 2900 (s), 1610 (m), 1451 (m), 1407 (s), 1395 (s), 1381 (s), 1252 (m), 1231 (m), 1076 (s), 1050 (s), 879 (m), 808 (m), 748 (m); HRMS (ESI) Calcd for $C_{40}H_{37}N_2^+$ $[M+H]^+$ 545.2951; found 545.2964.

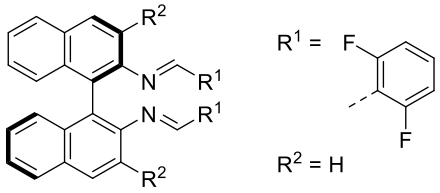
(*R*)-(1*E*,1'*E*)-*N*,*N*'-([1,1'-Binaphthalene]-2,2'-diyl)bis(1-(4-(*tert*-butyl)phenyl)methanimine) (5.16c)



5.16c

Following the general procedure **B**, **5.16c** was obtained as a yellow solid (141 mg, 0.250 mmol, 70%). M.p. 142.8 – 143.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 2H, *H*C=N), 8.05 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.98 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.45 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.41 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 2H, Ar*H*), 7.34 (s, 8H, *Ar*), 7.28 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H, *Ar*), 7.07 (d, *J* = 8.5 Hz, 2H, Ar*H*), 1.23 (s, 18H, *tBu*); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.6, 154.5, 148.5, 133.6, 133.0, 131.4, 129.3, 128.3, 126.6, 126.3, 126.0, 125.7, 124.0, 119.6, 34.8, 31.0; IR (ν_{max}, cm^{-1}) 3676 (m), 3660 (m), 2987 (s), 2970 (s), 2902 (s), 1453 (m), 1405 (s), 1393 (s), 1381 (m), 1248 (m), 1231 (m), 1066 (s), 1048 (s), 891 (m), 879 (m); HRMS (ESI) Calcd for $C_{42}H_{41}N_2^+$ $[M+H]^+$ 573.3264; found 573.3278.

(*R*)-(1*E*,1'*E*)-*N*,*N*'-([1,1'-Binaphthalene]-2,2'-diyl)bis(1-(2,6-difluorophenyl)methanimine) (5.16d)



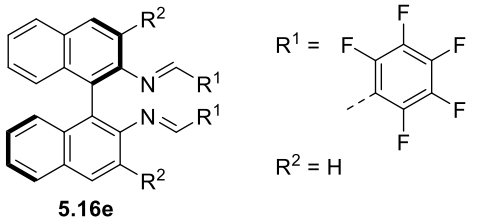
5.16d

Following the general procedure **B**, **5.16d** was obtained as a yellow solid (53 mg, 0.10 mmol, 28%). M.p. 106.7 – 108.1 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 8.80 (s, 2H, *H*C=N), 7.73 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.67 (dd, *J* = 8.1, 1.2 Hz, 2H, Ar*H*), 7.52 (dd, *J* = 8.5, 1.1 Hz, 2H, Ar*H*), 7.28 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.15 – 7.11 (m, 2H, Ar*H*), 7.02 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 2H, Ar*H*), 6.35 – 6.26 (m, 2H, Ar*H*), 6.22 – 6.12 (m, 4H, Ar*H*); ^{13}C NMR (101 MHz, C_6D_6) δ 161.8 (dd, *J* = 258.8, 6.4 Hz), 151.1, 149.4, 133.9, 132.1, 131.3 (t, *J* = 10.9 Hz), 129.2, 126.8, 126.6, 124.9, 118.8, 114.3 (t, *J* = 12.0 Hz), 111.3 (m),

[400] H. Suga, A. Kakehi, S. Ito, H. Sugimoto, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 327.

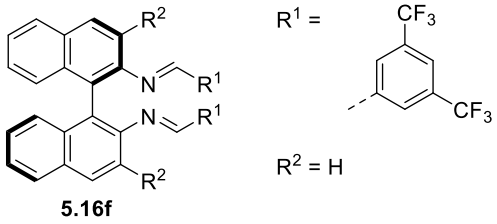
111.2; IR (ν_{max}, cm^{-1}) 3672 (m), 2989 (s), 2970 (s), 2900 (s), 1409 (m), 1393 (m), 1381 (m), 1276 (m), 1260 (m), 1238 (m), 1078 (s), 1070 (s), 1056 (s), 1016 (s), 784 (m), 760 (s), 748 (s); HRMS (ESI) Calcd for $C_{34}H_{21}F_4N_2^+$ $[M+H]^+$ 533.1635; found 533.1642.

(*R*)-(1*E*,1'*E*)-*N,N'*-([1,1'-Binaphthalene]-2,2'-diyl)bis(1-(perfluorophenyl)methanimine) (5.16e)



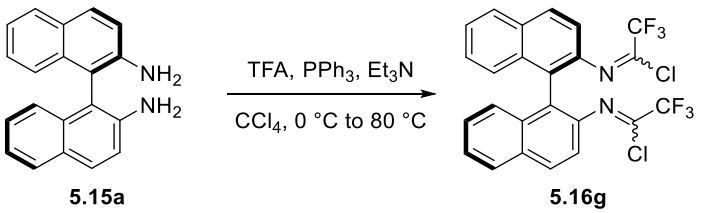
Following the general procedure **B**, **5.16e** was obtained as a yellow solid (200 mg, 0.310 mmol, 89%). M.p. 74.8 – 75.7 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 8.46 (s, 2H, *H*C=N), 7.78 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.68 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.40 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.27 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.15 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 2H, Ar*H*), 7.04 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4 (q, *J* = 2.8 Hz), 148.4, 146.3 (dd, *J* = 254.2, 6.3 Hz), 142.7 (m, *J* = 258.9 Hz), 137.9 (m, *J* = 248.96 Hz), 133.8, 132.6, 130.0, 128.5, 128.1 (dd, J = 35.8, 24.2 Hz) 127.3, 127.0 (d, *J* = 5.5 Hz), 125.9, 118.5, 111.8 (dt, *J* = 11.2, 6.5 Hz); IR (ν_{max}, cm^{-1}) 3676 (m), 2987 (s), 2974 (s), 2902 (s), 1522 (m), 1495 (m), 1409 (s), 1393 (s), 1379 (m), 1250 (m), 1227 (m), 1074 (s), 1068 (s), 1050 (s), 1014 (s), 978 (m), 895 (m), 869 (m), 810 (m), 750 (m); HRMS (ESI) Calcd for $C_{34}H_{15}F_{10}N_2^+$ $[M+H]^+$ 641.1070; found 641.1082.

***(R)*-(1*E*,1'*E*)-*N,N'*-([1,1'-Binaphthalene]-2,2'-diyl)bis(1-(3,5-bis(trifluoromethyl)phenyl)methanimine) (5.16f)**



Following the general procedure **B, 5.16f** was obtained as a yellow solid (167 mg, 0.230 mmol, 65%). M.p. 62.2 – 62.8 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 7.85 (d, *J* = 8.7 Hz, 2H, *H*C=N), 7.83 (s, 2H, Ar*H*), 7.80 – 7.76 (m, 2H, Ar*H*), 7.53 (dd, *J* = 8.4, 1.1 Hz, 2H, Ar*H*), 7.47 (s, 6H, Ar*H*), 7.24 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.21 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H, Ar*H*), 7.06 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H, Ar*H*); ^{13}C NMR (101 MHz, C_6D_6) δ 155.4, 146.1, 138.6, 134.3, 133.0, 131.9 (q, *J* = 33.5 Hz), 129.9, 129.7, 128.5, 127.4, 127.2, 126.1, 124.0 – 123.6 (m), 123.5 (q, *J* = 273.17 Hz), 117.7; ^{19}F NMR (376 MHz, C_6D_6) δ -63.00; IR (ν_{max}, cm^{-1}) 2925 (s), 2852 (s), 1645 (s), 1579 (s), 1558 (s), 1433 (s), 1208 (s), 1183 (s), 1000 (s), 882 (s), 783 (s); HRMS (ESI) Calcd for $C_{38}H_{21}F_{12}N_2^+$ $[M+H]^+$ 733.1508; found 733.1503.

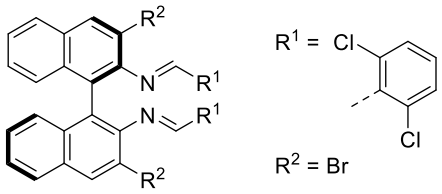
(*R*)-*N*',*N*''-([1,1'-Binaphthalene]-2,2'-diyl)bis(2,2,2-trifluoroacetimidoyl chloride) (5.16g)



The ligand **5.16g** was synthetized following a reported procedure,[288] a two-necked round bottomed flask equipped with a reflux condenser and a magnetic stirring bar was charged with tripenylphosphine (461 mg, 1.76 mmol, 5.00 equiv), evacuated and backfilled with nitrogen. CCl_4 (0.3 mL) and freshly distilled Et_3N (0.10 mL, 0.70 mmol, 2.00 equiv) were added. The mixture was cooled to 0 °C, then TFA (0.05 mL, 7.0 µmol, 2.00 equiv) was added dropwise and the mixture was stirred a 0 °C for 10 min. (+)-(*R*)-2,2'-diamino-1,1'-binaphtalene (**5.15a**) (100 mg, 0.350 mmol, 1.00 equiv) was added portionswise followed by addition of CCl_4 (0.3 mL) and the mixture was stirred at 0 °C for 10 min. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced

pressure. The resulting solid was triturated with pentane and the suspension stirred vigorously for 10 min, then filtered over a pad of celite and the solid washed thoroughly with pentane. The filtrate was recovered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 99:11 as eluent to afford **5.16g** as a mixture of diastereomers (*Z*,*E*/*E*,*Z* 1:1) as a yellow solid (60 mg, 0.12 mmol, 33%). M.p. 126.5 – 128.3 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 8.14 (d, *J* = 8.8 Hz, 1H, Ar*H*), 8.08 (dd, *J* = 8.8, 0.8 Hz, 1H, Ar*H*), 8.03 – 7.95 (m, 2H, Ar*H*), 7.72 (d, *J* = 8.7 Hz, 1H, Ar*H*), 7.66 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.55 (dddd, *J* = 9.3, 8.1, 6.7, 1.2 Hz, 2H, Ar*H*, 7.51 – 7.45 (m, 2H, Ar*H*), 7.38 (d, *J* = 8.6 Hz, 1H, Ar*H*), 7.35 – 7.28 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3 (q, *J* = 38.2 Hz), 142.6 (q, *J* = 40.4 Hz), 141.0, 137.3, 133.8, 132.2, 131.9, 130.6, 129.5, 128.7, 128.5, 128.4, 128.3, 127.8, 127.5, 127.2, 127.1, 125.8, 124.2, 123.5, 115.7 (q, *J* = 288.8 Hz), 117.9 (q, *J* = 277.6 Hz); IR (ν_{max}, cm^{-1}) 2359 (s), 3065 (s), 2925 (s), 2854 (s), 2341 (s), 1728 (s), 1388 (s), 1322 (s), 1221 (s), 1204 (s), 1153 (s), 1100 (s), 909 (s), 873 (s), 820 (s), 749 (s), 739 (s).

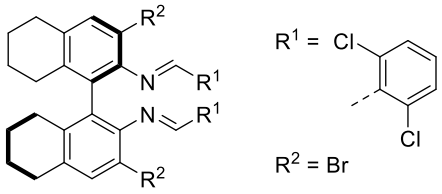
(*R*)-(1*E*,1'*E*)-*N*,*N*'-(3,3'-Dibromo-[1,1'-binaphthalene]-2,2'-diyl)bis(1-(2,6-dichlorophenyl) methanimine) (5.16h)



5.16h

Following the general procedure **B**, **5.16h** was obtained as a yellow solid (12 mg, 2.0 µmol, 59%). M.p. 203.9 – 204.8 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 8.91 (s, 2H, *H*C=N), 8.13 (s, 2H, Ar*H*), 7.40 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.24 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.05 (t, *J* = 7.5 Hz, 2H, Ar*H*), 6.99 – 6.90 (t, *J* = 7.5 Hz, 2H, Ar*H*), 6.58 (d, *J* = 8.1 Hz, 4H, Ar*H*), 6.13 (t, *J* = 8.1 Hz, 2H, Ar*H*); ^{13}C NMR (101 MHz, C_6D_6) δ 160.9, 148.3, 135.7, 133.3, 132.9, 132.5, 131.6, 130.8, 128.8, 127.6, 127.4, 126.5, 126.0, 123.6, 115.0; IR (ν_{max}, cm^{-1}) 2956 (s), 2921 (s), 2852 (s), 2278 (s), 1643 (s), 1578 (s), 1431 (s), 1207 (s), 1185 (s), 1001 (s), 879 (s), 779 (s), 747 (s); HRMS (ESI) Calcd for $C_{34}H_{19}Br_2Cl_4N_2^+$ $[M+H]^+$ 752.8664; found 752.8661.

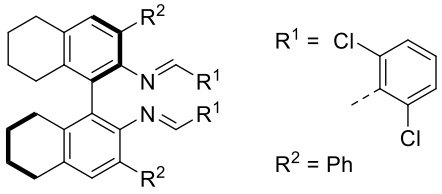
(*R*)-(1*E*,1'*E*)-*N*,*N*'-(3,3'-Dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(1-(2,6-dichlorophenyl)methanimine) (5.16i)



5.16i

Following the general procedure **B**, **5.16i** was obtained as a yellow solid (13 mg, 2.0 µmmol, 26%). M.p. 190.2 – 192.3 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 8.98 (s, 2H, *H*C=N), 7.32 (s, 2H, Ar*H*), 6.73 (d, *J* = 8.0 Hz, 4H, Ar*H*), 6.25 (t, *J* = 8.1 Hz, 2H, Ar*H*), 2.57 – 2.41 (m, 6H, H_2C-C$_{Ar}$), 2.20 – 2.10 (m, 2H, H_2C-C$_{Ar}$), 1.60 – 1.41 (m, 8H, H_2C-CH_2); ^{13}C NMR (101 MHz, C_6D_6) δ 160.7, 147.2, 135.9, 135.4, 133.5, 131.9, 130.8, 130.8, 129.1, 110.5, 29.6, 27.8, 23.4, 23.1; IR (ν_{max}, cm^{-1}) 3461 (w), 3363 (w), 2959 (s), 2930 (s), 2858 (m), 2362 (w), 2341 (w), 1607 (m), 1588 (m), 1459 (s), 1440 (m), 910 (s), 837 (s); HRMS (ESI) Calcd for $C_{34}H_{27}Br_2Cl_4N_2^+$ $[M+H]^+$ 760.9290; found 760.9288.

(*R*)-(1*E*,1'*E*)-*N*,*N*'-(3,3'-Diphenyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(1-(2,6-dichlorophenyl)methanimine) (5.16j)

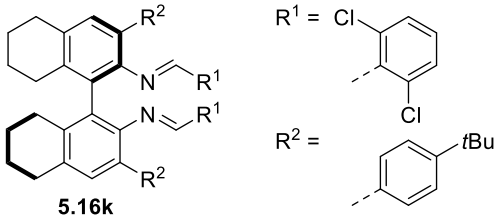


5.16j

Following the general procedure **B**, **5.16j** (12 mg, 2.0 µmol, 47%) was obtained as a yellow solid. M.p. 91.2 – 93.5 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 8.69 (s, 2H, *H*C=N), 7.57 – 7.49 (m, 4H, Ar*H*), 7.18 – 7.16 (m, 2H, Ar*H*), 7.14 – 7.07 (m, 4H, Ar*H*), 7.04 – 6.96 (m, 2H, Ar*H*, 6.67 (d, *J* = 8.1 Hz, 4H, Ar*H*, 6.19 (t, *J* = 8.0 Hz, 2H, Ar*H*), 2.97 – 2.71 (m, 6H, H_2C-C$_{Ar}$), 2.55 (ddd, *J* = 17.1, 7.8, 4.1 Hz, 2H, H_2C-C$_{Ar}$), 1.82 – 1.67 (m, 8H, H_2C-CH_2); ^{13}C NMR (101 MHz, C_6D_6) δ 158.8, 147.1, 140.8, 135.2, 134.8, 134.2, 132.0, 131.2, 131.1, 130.4, 130.2, 129.8, 128.5, 128.1, 126.1, 29.9, 27.8, 23.7, 23.2; IR

(ν_{max}, cm^{-1}) 2929 (s), 2855 (s), 2279 (s), 1635 (s), 1579 (s), 1558 (s), 1452 (s), 1432 (s), 1203 (s), 781 (s), 697 (s), 617 (s); HRMS (ESI) Calcd for $C_{46}H_{37}Cl_4N_2^+$ $[M+H]^+$ 757.1705; found 757.1704.

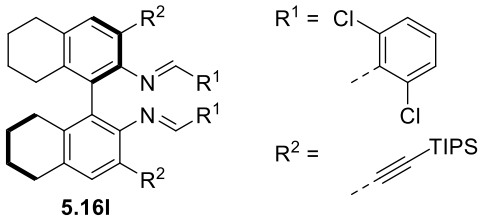
(*R*)-(1*E*,1'*E*)-*N*,*N*'-(3,3'-Bis(4-(*tert*-butyl)phenyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(1-(2,6-dichlorophenyl)methanimine) (5.16k)



5.16k

Following the general procedure **B**, **5.16k** was obtained as a yellow solid (34 mg, 4.0 µmol, 54%). M.p. 118.2 – 119.7 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 8.84 (s, 2H, *H*C=N), 7.67 – 7.58 (m, 4H, Ar*H*), 7.40 – 7.29 (m, 6H, Ar*H*), 6.80 (d, *J* = 8.1 Hz, 4H, Ar*H*), 6.30 (t, *J* = 8.0 Hz, 2H, Ar*H*), 3.05 – 2.84 (m, 6H, H_2C-C_{Ar}), 2.74 – 2.60 (m, 2H, H_2C-C_{Ar}), 1.88 – 1.73 (m, 8H, H_2C-CH_2), 1.33 (s, 18H, *tBu*); ^{13}C NMR (101 MHz, C_6D_6) δ 159.1, 149.0, 147.6, 138.3, 135.6, 135.0, 134.5, 132.6, 131.6, 131.3, 130.5, 130.2, 128.8, 128.6, 125.5, 34.5, 31.5, 30.3, 28.2, 24.0, 23.6; IR (ν_{max}, cm^{-1}) 2928 (s), 2858 (m), 2281 (m), 2959 (s), 2830 (m), 1715 (m), 1634 (m), 1578 (m), 1559 (m), , 1449 (s), 1432 (s), 1363 (m), 1268 (m), 1203 (m), 1095 (m) 837 (s); HRMS (ESI) Calcd for $C_{54}H_{53}Cl_4N_2^+$ $[M+H]^+$ 869.2957; found 869.2972.

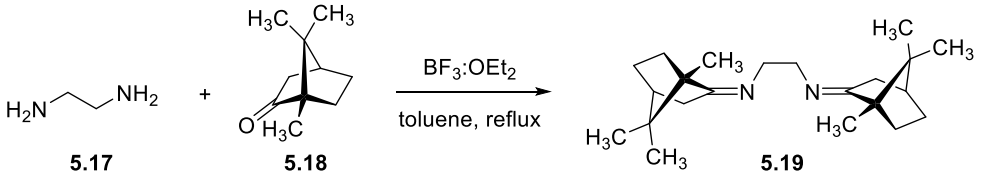
(*R*)-(1*E*,1'*E*)-*N*,*N*'-(3-(((2*S*,4*S*)-1-isopropyl-2,4-dimethylsiletan-1-yl)ethynyl)-3'-((triisopropylsilyl)ethynyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(1-(2,6-dichlorophenyl)methanimine) (5.16l)



5.16l

Following the general procedure **B**, **5.16l** was obtained as a yellow solid (32 mg, 3.0 µmol, 54%). M.p. 126.4 – 128.0 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 9.27 (s, 2H, *H*C=N), 7.35 (s, 2H, Ar*H*), 6.79 (d, *J* = 8.1 Hz, 4H, Ar*H*), 6.29 (t, *J* = 8.1 Hz, 2H, Ar*H*), 2.70 (dt, *J* = 17.5, 6.1 Hz, 2H, H_2C-C_{Ar}), 2.49 (t, *J* = 6.2 Hz, 4H, H_2C-C_{Ar}), 2.22 (dt, *J* = 17.5, 5.7 Hz, 2H, H_2C-C_{Ar}), 1.72 – 1.44 (m, 8H, H_2C-CH_2), 1.11 – 1.00 (m, 42H, TIPS); ^{13}C NMR (101 MHz, C_6D_6) δ 158.7, 150.3, 137.1, 136.1, 134.2, 134.0, 131.5, 130.4, 129.9, 128.8, 110.8, 106.2, 92.5, 29.5, 28.0, 23.4, 23.0, 18.7, 11.5; IR (ν_{max}, cm^{-1}) 2932 (s), 2862 (s), 1630 (m), 1578 (m), 1555 (m), 1447 (s), 1434 (s), 1205 (m), 1066 (s), 880 (s), 1055 (s), 1091 (m), 839 (m); HRMS (ESI) Calcd for $C_{56}H_{69}Cl_4N_2Si_2^+$ $[M+H]^+$ 965.3748; found 965.3751.

(1*R*,1'*R*,2*E*,2'*E*,4*S*,4'*S*)-*N*,*N*'-(Ethane-1,2-diyl)bis(1,7,7-trimethylbicyclo[2.2.1]heptan-2-imine) (5.19)

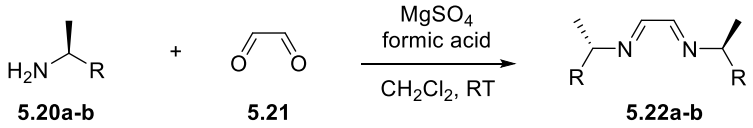


5.17 5.18 5.19

Synthetized following a reported procedure,[286] in a round-bottom flask surmounted with a Dean-Stark apparatus, (*S*)-(-)-camphor (**5.17**) (609 mg, 4.00 mmol, 2.00 equiv) and ethane-1,2-diamine (**5.18**) (0.135 mL, 2.00 mmol, 1.00 equiv) were dissolved in toluene (14 mL). Boron trifluoride ethyl etherate (0.025 mL, 0.10 mmol, 0.10 equiv) was added to the solution. The reaction mixture was stirred under reflux for 18 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using Et_3N/pentane 4:96 as eluent to afford **5.19** as a white powder (22 mg, 0.77 mmol, 38%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.40 – 3.22 (m, 4H, H_2CN), 2.33 (dt, *J* = 16.7, 4.0 Hz, 2H, CH_2), 1.91 – 1.83 (m, 4H, CH_2), 1.77 (ddq, *J* = 11.1, 7.5, 3.8 Hz, 2H, CH_2), 1.63 – 1.52 (m, 2H, CH_2), 1.25 – 1.11 (m, 4H, C*H* bridged-head & CH_2), 0.87 (s, 6H, Me), 0.82 (s, 6H, Me), 0.68 (s, 6H, Me); ^{13}C NMR (101 MHz, DMSO-

d_6) δ 181.1, 53.6, 53.0, 46.9, 43.8, 35.6, 32.4, 27.5, 20.0, 19.3, 12.0. The values of the NMR spectra are in accordance with reported literature data.[401]

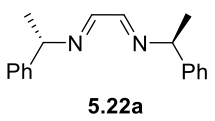
Ligands **5.20a** and **5.20b** were synthetized following a reported procedure:[287]



5.20a-b **5.21** **5.22a-b**

A mixture of glyoxal (**5.21**) (1.00 equiv), the corresponding amine **5.20a** or **5.20b** (2.05 equiv), formic acid (0.17 equiv) and $MgSO_4$ (4.0 equiv) in CH_2Cl_2 (0.5 M) was stirred at 20 °C for 30 mins. The reaction mixture was filtered over Celite and evaporated. The residue was dissolved in DCM, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to yield the corresponding imines **5.22a** and **5.22b**.

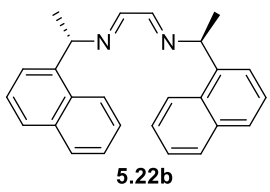
(1*E*,2*E*)-N1,N2-Bis((S)-1-phenylethyl)ethane-1,2-diimine (5.22a)



5.22a

5.22a was obtained as a white-off solid (1.08 g, 4.10 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 2H, N=C*H*), 7.32 – 7.14 (m, 10H, Ar*H*), 4.43 (q, *J* = 6.7 Hz, 2H, C*H*), 1.50 (d, *J* = 6.7 Hz, 6H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 144.1, 129.1, 127.7, 127.1, 70.2, 24.5. The values of the NMR spectra are in accordance with reported literature data.[402]

(1E,2E)-N1,N2-Bis((S)-1-(naphthalen-1-yl)ethyl)ethane-1,2-diimine (5.22b)



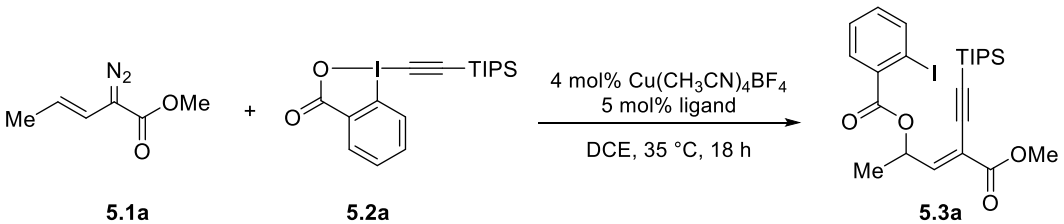
5.22b

5.22b was obtained as a grey solid (470 mg, 1.29 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 2H, N=C*H*), 8.14 (dd, *J* = 8.6, 1.5 Hz, 2H, Ar*H*), 7.88 (dd, *J* = 7.9, 1.7 Hz, 2H, Ar*H*), 7.78 (dt, *J* = 8.3, 1.1 Hz, 2H, Ar*H*), 7.69 (dd, *J* = 7.3, 1.2 Hz, 2H, Ar*H*, 7.60 – 7.44 (m, 6H, Ar*H*), 5.42 (q, *J* = 6.7 Hz, 2H, C*H*), 1.75 (d, *J* = 6.7 Hz, 6H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 139.9, 134.4, 131.1, 129.4, 128.2, 126.5, 126.0, 125.9, 124.4, 123.7, 65.3, 24.1. The values of the NMR spectra are in accordance with reported literature data.[402]

10.3.3. Enantioselective Conjugate Oxy-Alkynylation of Diazo Compounds

*10.3.3.1. Screening of ligand with TIPS-EBX (**5.2a**) and vinyldiazo **5.1a** as substrates*

(*E*)-4-(Methoxycarbonyl)-6-(triisopropylsilyl)hex-3-en-5-yn-2-yl 2-iodobenzoate (71)



5.1a **5.2a** **5.3a**

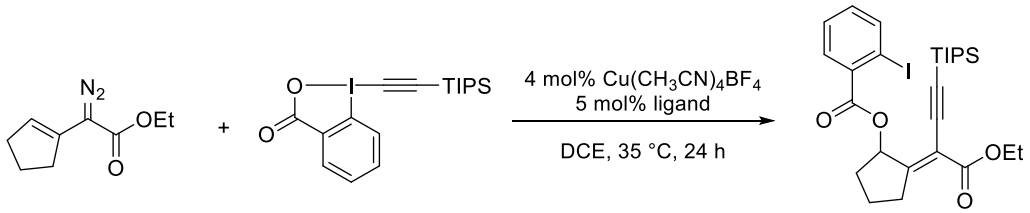
A flame dried 10 mL microwave vial was charged under nitrogen with $Cu(CH_3CN)_4BF_4$ (1.9 mg, 6.0 µmol, 0.04 equiv), ligand (7.5 µmol, 0.05 equiv) and dry DCE (1 mL). The resulting solution was stirred at room temperature for 1 h and then was added a mixture of TIPS-EBX (**5.2a**) (64 mg, 0.15 mmol, 1.00 equiv) and methyl (*E*)-2-diazopent-3-enoate (**5.1a**) (300 µL, 1 M in pentane, 0.300 mmol, 2.00 equiv) in dry DCE (2 mL) in 5 min. The resulting reaction mixture was stirred at 35 °C for 2 h to 24 h. After the reaction

[401] Z. Raza, S. Dakovic, V. Vinkovic, V. Sunjic, *Croat. Chem. Acta* **1996**, *69*, 1545.
[402] C. L. Winn, F. Guillen, J. Pytkowicz, S. Roland, P. Mangeney, A. Alexakis, *J. Organomet. Chem.* **2005**, *690*, 5672.

was completed (monitored by TLC), the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using EtOAc/pentane 2:98 as eluent to furnish **5.3a** as a colorless oil. Chiral HPLC conditions: Chiralpak IC 99.50:0.50 Hexane/*i*PrOH, 1 mL/min, 30 min. tr (1) = 10.7 min. and tr (2) = 12.6 min. λ = 254 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.92 (m, 1H, Ar*H*), 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.40 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.27 (d, *J* = 7.7 Hz, 1H, *H*C=C), 7.15 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.05 (dq, *J* = 7.8, 6.7 Hz, 1H, OC*H*), 3.80 (s, 3H, O*Me*), 1.58 (d, *J* = 6.7 Hz, 3H, *Me*), 1.13 (m, 21H, *TIPS*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 164.9, 151.0, 141.8, 135.1, 133.1, 131.1, 128.4, 118.2, 102.8, 98.9, 94.5, 71.7, 53.1, 19.1, 19.1, 11.7. The values of the NMR spectra are in accordance with reported literature data.[227]

10.3.3.2. Attempts on Others Vinyldiazo Compounds

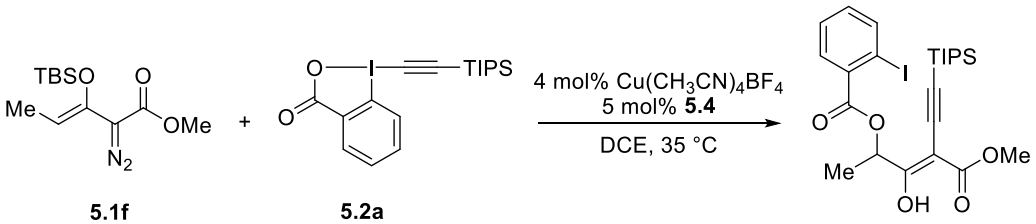
(*E*)-2-(1-Ethoxy-1-oxo-4-(triisopropylsilyl)but-3-yn-2-ylidene)cyclopentyl 2-iodobenzoate (5.3c)



5.1c **5.2a** **5.3c**

A flame dried 10 mL microwave vial was charged under nitrogen with $Cu(CH_3CN)_4BF_4$ (1.9 mg, 6.0 µmol, 0.04 equiv), ligand (7.5 µmol, 0.05 equiv) and dry DCE (1 mL). The resulting solution was stirred at room temperature for 1 h and then was added a mixture of TIPS-EBX (**5.2a**) (64 mg, 0.15 mmol, 1.00 equiv) and ethyl 2-(cyclopent-1-en-1-yl)-2-diazoacetate (**5.1c**) (54 mg, 0.30 mmol, 2.00 equiv) in dry DCE (2 mL) in 5 min. The resulting reaction mixture was stirred at 35 °C for 24 h. After the reaction was completed (monitored by TLC), the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using EtOAc/pentane 2:98 as eluent to furnish **95** as a colorless oil. Chiral HPLC conditions: Chiralpak ID 99.75:0.25 Hexane/iPrOH, 1.5 mL/min, 20 min. tr (1) = 8.1 min. and tr (2) = 8.6 min. λ = 250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.90 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.15 – 7.06 (m, 1H, *Ar*), 6.05 (ddd, *J* = 4.8, 3.2, 1.7 Hz, 1H, OC*H*), 4.23 (qd, *J* = 7.1, 2.3 Hz, 2H, OCH_2CH_3), 3.20 – 3.07 (m, 1H, $C{=}CCH_2$), 2.91 – 2.79 (m, 1H, $C{=}CCH_2$), 2.14 – 1.79 (m, 4H, H_2CCH_2), 1.31 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.02 – 0.93 (m, 21H, *TIPS*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 165.4, 165.3, 142.0, 134.4, 133.2, 132.2, 128.2, 115.1, 101.1, 98.4, 95.0, 79.4, 61.6, 33.5, 33.4, 24.4, 19.0, 14.6, 11.7. The values of the NMR spectra are in accordance with reported literature data.[227]

(*Z*)-3-Hydroxy-4-(methoxycarbonyl)-6-(triisopropylsilyl)hex-3-en-5-yn-2-yl 2-iodobenzoate (5.25)

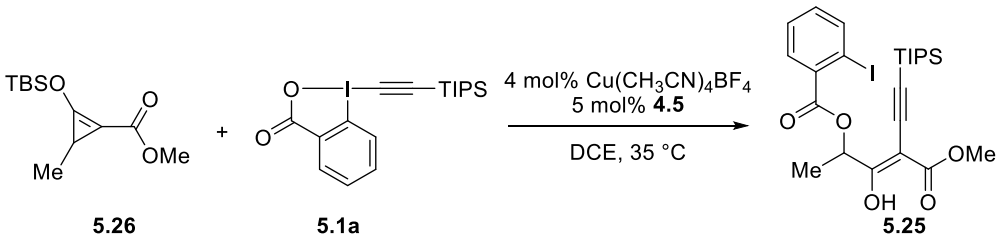


5.1f **5.2a** **5.25**

A flame dried 10 mL microwave vial was charged under nitrogen with $Cu(CH_3CN)_4BF_4$ (1.9 mg, 6.0 µmol, 0.04 equiv), ligand (**5.4**) (2.8 mg, 7.5 µmol, 0.05 equiv) and dry DCE (1 mL). The resulting solution was stirred at room temperature for 1 h and then was added a mixture of TIPS-EBX (**5.2a**) (64 mg, 0.15 mmol, 1.00 equiv) and methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-diazopent-3-enoate (**5.1f**) (40 mg, 0.15 mmol, 1.00 equiv) in dry DCE (2 mL) in 5 min. The resulting reaction mixture was stirred at 35 °C for 18

h. After the reaction was completed (monitored by TLC), the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using EtOAc/pentane 2:98 as eluent to furnish **5.25** as a colorless oil (34 mg, 0.06 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.12 (s, 1H, *enol*), 7.99 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.90 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.41 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.15 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.01 (q, *J* = 6.8 Hz, 1H, C*H*), 3.83 (s, 3H, O*Me*), 1.67 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.11 (s, 21H, *TIPS*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.6, 173.1, 165.7, 141.9, 134.8, 133.3, 131.9, 128.4, 98.9, 97.6, 94.7, 89.1, 70.4, 53.0, 19.1, 17.7, 11.8; HRMS (ESI) Calcd for $C_{24}H_{33}INaO_5Si^+$ $[M+Na]^+$ 579.1034; found 579.1028.

Using methyl 2-((tert-butyldimethylsilyl)oxy)-3-methylcycloprop-1-enecarboxylate (**5.26**) (36.2 mg, 0.15 mmol, 1.00 equiv) instead of methyl 3-((tert-butyldimethylsilyl)oxy)-2-diazopent-3-enoate (**5.1f**) as starting material, afforded **5.25** as a colorless oil (27 mg, 5.0 µmol, 33%).

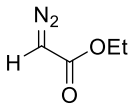


5.26 **5.1a** **5.25**

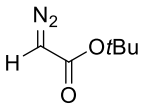
10.4. Copper-Catalyzed Oxy-Vinylation of Diazo Compounds

10.4.1. Preparation of Diazo Compounds

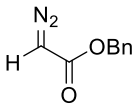
Ethyl 2-diazoacetate (**6.6a**), *tert*-butyl 2-diazoacetate (**6.6b**) and benzyl 2-diazoacetate (**6.6d**) were directly purchased from chemical suppliers



6.6a

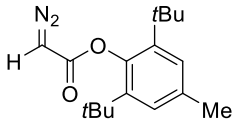


6.6b

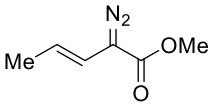


6.6d

The synthesis of 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**6.6c**) has been reported in section 10.2.1. The synthesis of methyl (*E*)-2-diazopent-3-enoate (**6.6q**) has been reported in section 10.3.1.

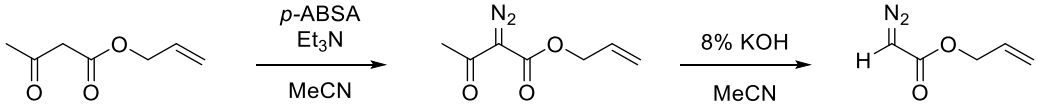


6.6c



6.6q

Allyl 2-diazoacetate (6.6e)



6.46 **6.47** **6.6e**

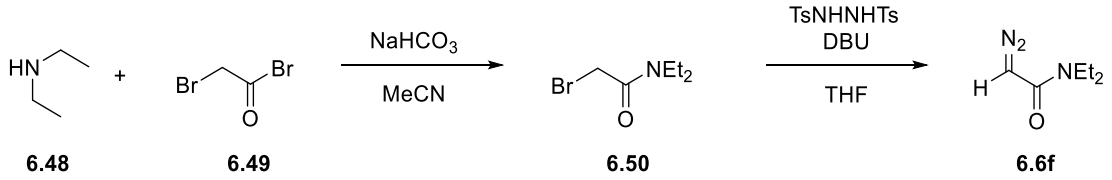
Following a reported procedure,[403] to a solution of allyl acetoacetate (**6.46**) (1.10 mL, 8.00 mmol, 1.00 equiv) and 4-acetamidobenzenesulfonyl azide (2.11 g, 8.80 mmol, 1.10 equiv) in MeCN (40 mL) at 0 °C was added dropwise Et_3N (2.23 mL, 16.0 mmol, 2.00 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The solvent was removed under reduced pressure. The residue was suspended in diethyl ether (50 mL) and the solid removed by filtration. The solvent was removed under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 15:85 as eluent to afford) allyl 2-diazo-3-oxobutanoate (**6.47**) as a yellow oil (1.23 g, 7.34 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H, C*H*CH_2), 5.40 – 5.26 (m, 2H, CHC*H*$_2$), 4.73 (dt, *J* = 5.8, 1.3 Hz, 2H, C*H*$_2$O), 2.48 (s, 3H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 161.2, 131.6, 119.3, 66.0, 28.4. One carbon was not resolved at 101 MHz. The values of the NMR spectra are in accordance with reported literature data.[403]

To a solution of allyl 2-diazo-3-oxobutanoate (**6.47**) (0.840 g, 5.00 mmol, 1.00 equiv) in MeCN (15 mL) was added 8% aqueous KOH solution (25 mL) and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with water (15 mL), extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 10:90 as eluent to afford allyl 2-diazoacetate (**6.6e**) as a yellow oil (154 mg, 1.22 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H, C*H*CH_2), 5.38 – 5.20 (m, 2H, CHC*H*$_2$), 4.77 (s, 1H, C*H*N_2),

[403] P. Müller, Y. F. Allenbach, S. Grass, *Tetrahedron: Asymmetry*, 2005, **16**, 2007.

4.65 (dt, *J* = 5.7, 1.5 Hz, 2H, C*H*$_2$O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 132.4, 118.5, 65.2, 46.4. The values of the NMR spectra are in accordance with reported literature data.[404]

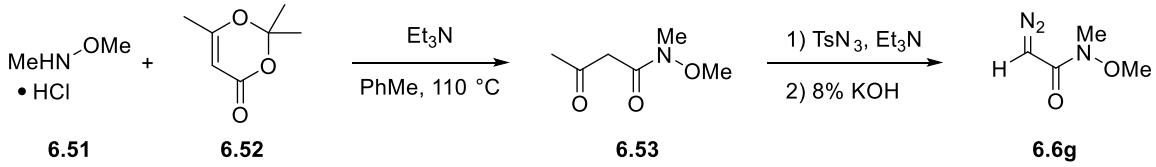
2-Diazo-*N*,*N*-diethylacetamide (6.6f)



6.48 **6.49** **6.50** **6.6f**

Following a reported procedure,[405] diethyl amine (**6.48**) (0.73 g, 10 mmol, 1.0 equiv) and $NaHCO_3$ (2.52 g, 30.0 mmol, 3.00 equiv) were dissolved in dry CH_2Cl_2 (20 mL) and bromoacetyl bromide (**6.49**) (1.75 mL, 20.0 mmol, 2.00 equiv) was added slowly at 0 °C and the reaction was stirred for 6 h at room temperature, quenched with 100 mL of H_2O and the solution was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with water (100 mL) and dried over $MgSO_4$, the solvent was evaporated and the residue was used in the next step without purification. The resulting 2-bromo-*N,N*-diethylacetamide (**6.50**) and *N,N'*-ditosylhydrazine (2.10 g, 6.08 mmol, 0.60 equiv) were dissolved in dry THF (20 mL) and cooled down to 0 ˚C, then DBU (2.30 mL, 15.2 mmol, 1.52 equiv) was added dropwise and stirred at room temperature for 1 h and then quenched with saturated solution of $NaHCO_3$ (50 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and purified by column chromatography using EtOAc/pentane 30:70 as eluent to afford the corresponding 2-diazo-*N,N'*-diethylacetamide (**6.6f**) as a yellow oil (0.725 g, 5.14 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (s, 1H, C*H*N_2), 3.26 (br s, 4H, 2 x C*H*$_2$CH$_3$), 1.14 (t, *J* = 7.2 Hz, 6H, 2 x CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 46.4, 41.4, 13.9. The values of the NMR spectra are in accordance with reported literature data.[406]

2-Diazo-*N*-methoxy-*N*-methylacetamide (6.6g)



6.51 **6.52** **6.53** **6.6g**

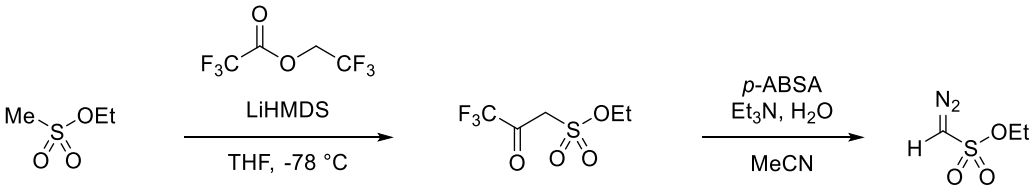
Following a reported procedure,[407] a mixture of *N,O*-dimethylhydroxylamine hydrochloride (**6.51**) (2.44 g, 25.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**6.52**) (5.00 mL, 37.5 mmol, 1.50 equiv) and triethylamine (3.85 mL, 27.5 mmol, 1.10 equiv) was dissolved in toluene (75 mL) and refluxed for 2 h. The reaction mixture was cooled to room temperature and washed with aqueous hydrochloric acid (90 mL, 1.0 M) and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 50:50 as eluent to afford *N*-methoxy-*N*-methyl-3-oxobutanamide (**6.53**) as a yellow oil (2.40 g, 16.5 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.65 (s, 0.13H, O*H* of enol form), 5.32 (s, 0.13H, vinyl *H* of enol form) 3.60

[404] M. Bolsønes, H. T. Bonge-Hansen, T. Bonge-Hansen, *Synlett*, **2014**, *25*, 221.
[405] S. Chanthamath, S. Thongjareun, K. Shibatomi, S. Iwasa, *Tetrahedron Lett.* **2012**, *53*, 4862.
[406] D. Gauthier, R. H. Dodd, P. Dauban, *Tetrahedron* **2009**, *65*, 8542.
[407] S. Müller, F. Sasse, M. E. Maier, *Eur. J. Org. Chem.* **2014**, 1025.

(s, 3H, OC*H*$_3$), 3.50 (s, 1.74H, CH_3COCH_2 of keto form), 3.13 (s, 2.6H, *N*-C*H*$_3$ of keto form), 3.11 (s, 0.4H, enol form of *N*-C*H*$_3$), 2.17 (s, 2.6H, C*H*$_3$COCH$_2$ of keto form), 1.89 (s, 0.4H, enol form of C*H*$_3$); Keto form, ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 167.8, 61.1, 48.3, 31.8, 30.0; Enol form, ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 172.2, 86.5, 21.6. Two carbons were not resolved at 101 MHz. The values of the NMR spectra are in accordance with reported literature data.[407]

Following a reported procedure,[408] to a solution of *N*-methoxy-*N*-methyl-3-oxobutanamide (**6.53**) (0.73 g, 5.0 mmol, 1.0 equiv) in MeCN (6 mL) was added triethylamine (660 mg, 6.50 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (1.1 g, 5.5 mmol, 1.1 equiv) in MeCN (6 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (25 mL) was added and stirred vigorously for 4 h. The reaction mixture was diluted with water (15 mL), extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 50:50 as eluent to afford 2-diazo-*N*-methoxy-*N*-methylacetamide (**6.6g**) as a yellow oil (350 mg, 2.71 mmol, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 1H, C*H*N_2), 3.60 (s, 3H, OC*H*$_3$), 3.12 (s, 3H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 61.3, 46.1, 33.0. The values of the NMR spectra are in accordance with reported literature data.[409]

Ethyl diazomethanesulfonate (6.6h)

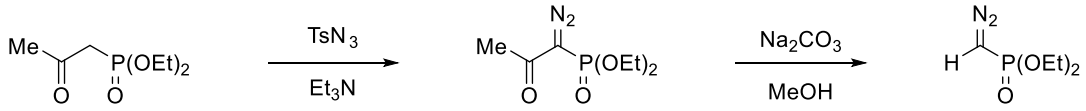


6.54 **6.55** **6.6h**

Following a reported procedure,[410] to a solution of ethyl methanesulfonate (**6.54**) (1.86 g, 15.0 mmol, 1.00 equiv) in dry THF (50 mL) was added a 1 M LiHMDS solution in hexane (18 mL, 18 mmol, 1.2 equiv) at -78 °C. After stirring the reaction mixture for 30 min at this temperature, 2,2,2-trifluoroethyl trifluoroacetate (2.4 mL, 18 mmol, 1.2 equiv) was added rapidly in one portion *via* syringe. After 10 min, the reaction mixture was poured into a solution of diethyl ether (20 mL) and 5% HCl (50 mL). The mixture was extracted with diethyl ether (3 x 50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. The resulting ethyl 3,3,3-trifluoro-2-oxopropane-1-sulfonate (**6.55**) was immediately dissolved in dry MeCN (30 mL). To this solution was added *p*-ABSA (4.32 g, 18.0 mmol, 1.20 equiv), Et_3N (2.5 mL, 18 mmol, 1.2 equiv), and water (0.27 mL, 15 mmol, 1.0 equiv). After stirring the reaction mixture overnight at room temperature, the solvent was removed under reduced pressure and the residue was filtered on short plug of silica gel and washed with a mixture of ethyl acetate (100 mL) and hexane (100 mL). The filtrate was concentrated under vacuum and the residue was purified by column chromatography using EtOAc/pentane 10:90 as eluent to afford the corresponding ethyl diazomethanesulfonate (**6.6h**) as a yellow oil (0.9 g, 6 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (s, 1H, C*H*N_2), 4.26 (q, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 1.41 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.4, 52.4, 14.6. The values of the NMR spectra are in accordance with reported literature data.[410]

[408] P. Müller, P. Polleux, *Helv. Chim. Acta* **1994**, *77*, 645.
[409] H. Mao, A. Lin, Y. Shi, Z. Mao, X. Zhu, W. Li, H. Hu, Y. Cheng, C. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 6288.
[410] T. Ye, C. Zhou, *New J. Chem.* **2005**, *29*, 1159.

Diethyl (diazomethyl)phosphonate (6.6i)

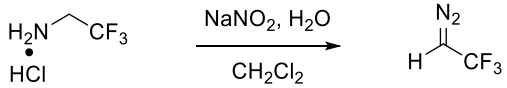


6.56 **6.57** **6.6i**

Following a reported procedure,[411] a mixture of diethyl (2-oxopropyl)phosphonate (**6.56**) (1.15 mL, 6.00 mmol, 1.00 equiv), tosyl azide (1.3 g, 6.6 mmol, 1.10 equiv) and triethylamine (6 mL) was stirred at room temperature for 18 h. After evaporation of the triethylamine under reduced pressure, the residue was dissolved in diethyl ether (50 mL). The precipitate was filtered off, the filtrate was evaporated and the residue was purified by column chromatography using EtOAc/pentane 50:50 as eluent to afford the corresponding diethyl (1-diazo-2- oxopropyl)phosphonate (**6.57**) as a yellow oil (0.810 g, 3.68 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 – 4.19 (m, 4H, 2 x C*H*$_2$CH$_3$) 2.19 (s, 3H, C*H*$_3$), 1.30 (t, *J* = 7.0 Hz, 6H, 2 x CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1 (d, *J* = 13.2 Hz), 63.4 (d, *J* = 5.6 Hz), 27.1, 16.0 (d, *J* = 6.8 Hz). The values of the NMR spectra are in accordance with reported literature data.[407]

Following a reported procedure,[229] to a solution of diethyl (1-diazo-2-oxopropyl)phosphonate (**6.57**) (694 mg, 3.15 mmol, 1.00 equiv) in MeOH (9.0 mL) was added Na_2CO_3 (401 mg, 3.78 mmol, 1.20 equiv). The mixture was stirred at room temperature for 15 min. The precipitate was filtered off, the filtrate was evaporated and the residue was purified by column chromatography using EtOAc/pentane 50:50 as eluent to afford the corresponding diethyl (diazomethyl)phosphonate (**6.6i**) as a yellow oil (533 mg, 2.99 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 – 4.08 (m, 4H, 2 x C*H*$_2$CH$_3$), 3.75 (d, *J* = 11.1 Hz, 1H, C*H*N$_2$), 1.34 (td, *J* = 7.1, 0.7 Hz, 6H, 2 x CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.6 (d, *J* = 5.3 Hz), 16.1 (d, *J* = 6.9 Hz). One carbon was not resolved at 101 MHz. The values of the NMR spectra are in accordance with reported literature data.[407]

2,2,2-Trifluorodiazoethane (6.6j)

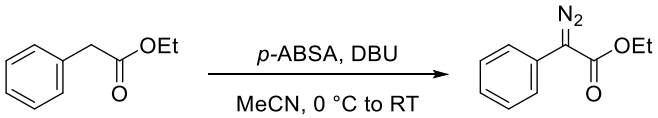


6.58 **6.6j**

Following a reported procedure,[412] under argon, 2,2,2-trifluoroethanamine hydrochloride (**6.58**) (0.678 g, 5.00 mmol, 1.00 equiv) and sodium nitrite (0.379 g, 5.50 mmol, 1.10 equiv) were dissolved in degassed CH_2Cl_2 (10 mL). Degassed water (1.00 mL, 55.5 mmol, 11.1 equiv) was added slowly at 0 °C. The solution was stirred for 2 h at 0 °C and 1 h at room temperature. The aqueous layer was frozen in the freezer overnight (-18 °C) and the organic layer was dried over a plug of potassium carbonate, transferred into a vial, sealed and stored at -18 °C. The concentration of the obtained solution was determined to be 0.37 M by ^{19}F NMR analysis (according to an internal reference, $PhCF_3$). ^{19}F NMR (377 MHz, CH_2Cl_2) δ -55.56. The values of the NMR spectra are in accordance with reported literature data.[412]

[411] S. Chanthamath, S. Ozaki, K. Shibatomi, S. Iwasa, *Org. Lett.* **2014**, *16*, 3012.
[412] S. Hyde, J. Veliks, B. Liégault, D. Grassi, M. Taillefer, V. Gouverneur, *Angew. Chem. Int. Ed.* 2016, **55**, 3785.

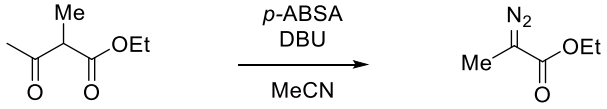
Ethyl 2-diazo-2-phenylacetate (6.6m)



6.59 **6.6m**

Following a reported procedure,[413] DBU (1.50 mL, 10.0 mmol, 2.00 equiv) was added slowly to a stirred solution of ethyl 2-phenylacetate (**6.59**) (0.80 mL, 5.0 mmol, 1.00 equiv) and *p*-ABSA (1.80 g, 7.50 mmol, 1.50 equiv) in dry MeCN (20 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature. After stirring for 14 h, the reaction mixture was quenched with water (15 mL), and extracted with diethyl ether (3 x 15 mL). The organic layers were combined and washed with 10% NH_4Cl (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 3:97 as eluent to afford the corresponding ethyl 2-diazo-2-phenylacetate (**6.6m**) as a red oil (0.80 g, 4.2 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H, Ar*H*), 7.43 – 7.35 (m, 2H, Ar*H*), 7.22 – 7.14 (m, 1H, Ar*H*), 4.34 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 1.35 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 128.8, 125.6, 125.6, 124.0, 61.1, 14.6. One carbon was not resolved at 101 MHz. The values of the NMR spectra are in accordance with reported literature data.[414]

Ethyl 2-diazopropanoate (6.6n)



6.60 **6.6n**

Following a reported procedure,[415] DBU (1.8 mL, 12 mmol, 3.0 equiv) was added slowly to a stirred solution of ethyl 2-methylacetoacetate (**6.60**) (0.60 mL, 4.0 mmol, 1.0 equiv) and *p*-ABSA (1.4 g, 6.0 mmol, 1.5 equiv) in MeCN (80 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature. After stirring for 12 h, the reaction mixture was quenched with 1 M HCl (8 mL), and extracted with hexane (3 x 40 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using Et_2O/pentane 2:98 as eluent to afford the corresponding ethyl 2-diazopropanoate (**6.6n**) as a yellow oil (241 mg, 1.88 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 1.94 (s, 3H, N_2CCH_3), 1.25 (t, *J* = 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 60.7, 14.5, 8.4. One carbon was not resolved at 101 MHz. The values of the NMR spectra are in accordance with reported literature data.[416]

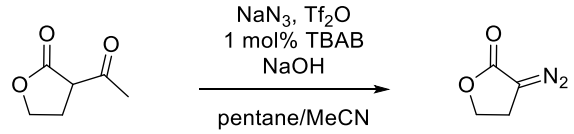
[413] O. A. Davis, R. A. Croft, J. A. Bull, *Chem. Commun.* **2015**, *51*, 15446.

[414] H. Keipour, T. Ollevier, *Org. Lett.* **2017**, *19*, 5736.

[415] T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 8834.

[416] L. Huang, W. D. Wulff *J. Am. Chem. Soc.* **2011**, *133*, 8892.

3-Diazodihydrofuran-2(3*H*)-one (6.6p)



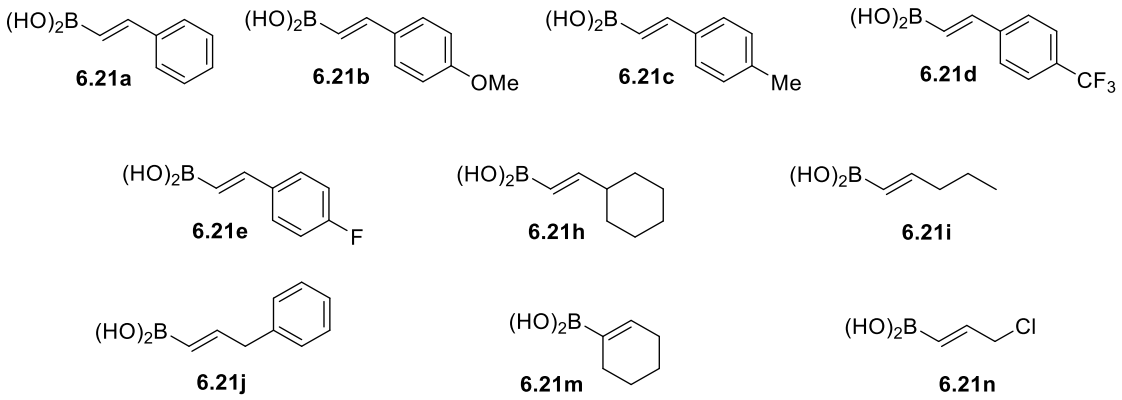
6.61 **6.6p**

Following a reported procedure,[417] sodium azide (2.42 g, 37.2 mmol, 4.00 equiv), sodium hydroxide (78 mL, 2 M in water), tetrabutylammonium bromide (30.0 mg, 0.09 mmol, 0.01 equiv) and pentane (40 mL) were mixed in a 250 mL round-bottom flask with magnetic stir bar open to the air and allowed to cool to 0 °C. With vigorous stirring, Tf_2O (3.10 mL, 18.6 mmol, 2.00 equiv) was added dropwise. After 10 min, a solution of 2-acetyl-butyrolactone (**6.61**) (1.00 mL, 9.30 mmol, 1.00 equiv) in MeCN (35 mL) was poured into the round-bottom flask through a funnel, followed by an additional MeCN (10 mL) to complete the transfer. The initially colorless reaction mixture immediately turned yellow. After allowing to stir for 30 min at 0 °C, the mixture was diluted with ice water (25 mL) and chilled EtOAc (25 mL) and transferred to a separatory funnel. After phase separation and removal of the organic layer, the aqueous layer was washed with cold EtOAc (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 50:50 as eluent to afford the corresponding 3-diazodihydrofuran-2(3*H*)-one (**6.6p**) as a bright yellow crystalline solid (0.32 g, 2.8 mmol, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (t, *J* = 8.0 Hz, 2H, C*H*$_2$), 3.36 (t, *J* = 8.0 Hz, 2H, C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 65.3, 49.4, 23.1. The values of the NMR spectra are in accordance with reported literature data.[417]

10.4.2. Preparation of VBX Reagents

10.4.2.1. Vinylboronic acid precursors

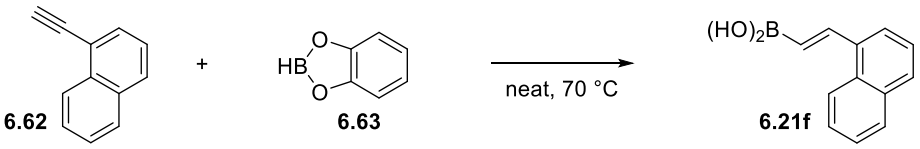
trans-2-Phenylvinylboronic acid (**6.21a**), *trans*-2-(4-Methoxyphenyl)vinylboronic acid (**6.21b**), *trans*-2-(4-Methylphenyl)vinylboronic acid (**6.21c**), *trans*-2-[4-(Trifluoromethyl)phenyl]vinylboronic acid (**6.21d**), *trans*-2-(4-Fluorophenyl)vinylboronic acid (**6.21e**), 2-Cyclohexylvinylboronic acid (**6.21h**), 1-Penten-1-ylboronic acid (**6.21i**), *trans*-3-Phenyl-1-propen-1-ylboronic acid (**6.21j**), 1-Cyclohexenylboronic acid (**6.21m**), and *trans*-2-Chloromethylvinylboronic acid (**6.21n**) were directly purchased from chemical suppliers.



[417] E. S. Sattely, S. J. Meek, S. J. Malcolmson, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 943.

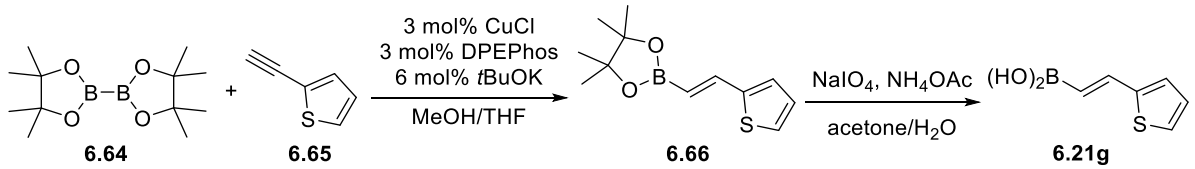
The ^{13}C NMR signal for carbons attached to boron was broad or did not appear in the collected spectra due to the quadrupolar splitting of ^{11}B.[418]
All boronic acids analyzed under electrospray ionization-MS analysis gave complex ionization pathways.[419] Faint signals could be obtained using APPI-MS.

(*E*)-(2-(Naphthalen-1-yl)vinyl)boronic acid (6.21f)



Following a reported procedure,[420] catecholborane (**6.63**) (640 µL, 6.00 mmol, 1.20 equiv) was added dropwise to stirring neat 1-ethynylnaphthalene (**6.62**) (711 µL, 5.00 mmol, 1.00 equiv) at 0 °C under inert atmosphere. The reaction mixture was stirred at room temperature until the gas evolution had ceased and, then was heated to 70 °C and stirred for 3 h. The resulting thick oil was dissolved in THF (8 mL) and then slowly added to an ice-cold mixture of Et_2O/water 1:1 (25 mL) and stirred for an additional 30 minutes. The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with water (5 x 15 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting crude residue was dissolved in boiling water (70 mL). The insoluble materials were discarded by hot filtration and the aqueous filtrate was allowed to cool to room temperature. The precipitate was collected by filtration to give (*E*)-(2-(naphthalen-1-yl)vinyl)boronic acid (**6.21f**) as a white solid (324 mg, 1.60 mmol, 33%). ^1H NMR (400 MHz, DMSO-d_6/D_2O 9:1) δ 8.21 (d, *J* = 8.3 Hz, 1H, Ar*H*), 8.09 (d, *J* = 18.2 Hz, 1H, BCHC*H*), 7.93 – 7.82 (m, 2H, Ar*H*), 7.73 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.62 – 7.44 (m, 3H, Ar*H*), 6.20 (d, *J* = 18.2 Hz, 1H, BC*H*CH); ^{13}C NMR (101 MHz, DMSO-d_6/D_2O 9:1) δ 143.5, 135.6, 134.0, 131.3, 129.4, 129.3, 127.3, 126.9, 126.6, 124.2, 124.0; ^{11}B NMR (128 MHz, DMSO-d_6/D_2O 9:1) δ 29.0. The ^{13}C NMR signal for the carbon attached to boron did not appear due to the quadrupolar splitting of ^{11}B. The values of the NMR spectra are in accordance with reported literature data.[420]

(*E*)-(2-(Thiophen-2-yl)vinyl)boronic acid (6.21g)



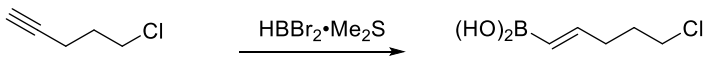
Following a reported procedure,[421] CuCl (15.0 mg, 0.150 mmol, 0.03 equiv), NaO*t*Bu (29.0 mg, 0.300 mmol, 0.06 equiv) and DPEPhos (81.0 mg, 0.150 mmol, 0.03 equiv) were dissolved in THF (5 mL) under argon. The reaction mixture was stirred for 30 min at room temperature and then, bis(pinacolato)diboron (**6.64**) (1.40 g, 5.50 mmol, 1.10 equiv) and THF (2.5 mL) were added and the reaction mixture was stirred for another 10 min and then 2-ethynylthiophene (**6.65**) (0.475 mL, 5.00 mmol, 1.00 equiv) was added, followed by MeOH (0.405 mL, 10.0 mmol, 2.00 equiv). The reactor wall was washed with THF (1.5 mL), sealed, and stirred for 4 h. The reaction mixture was filtered through a pad of Celite, washed with EtOAc and the solvent was removed under reduced pressure. The resulting

[418] B. Wrackmeyer, *Prog. Nucl. Magn. Reson. Spectrosc.* **1979**, *12*, 227.
[419] L. Wang, C. Dai, S. K. Burroughs, S. L. Wang, B. Wang, *Chem. Eur. J.* **2013**, *19*, 7587.
[420] T. Haddad, R. Gershman, R. Dilis, D. Labaree, R. B. Hochberg, R. N. Hanson, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5999.
[421] C. Feng, H. Wang, L. Xua, P. Li, *Org. Biomol. Chem.* **2015**, *13*, 7136.

oil was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford (*E*)-4,4,5,5-tetramethyl-2-(2-(thiophen-2-yl)vinyl)-1,3,2-dioxaborolane (**6.66**) as a clear yellow oil (1.07 g, 4.53 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 18.1 Hz, 1H, C*H*CHB), 7.24 (d, *J* = 5.1, 1H, Ar*H*), 7.11 – 7.05 (m, 1H, Ar*H*), 6.99 (dd, *J* = 5.1, 3.6 Hz, 1H, Ar*H*), 5.91 (d, *J* = 18.1 Hz, 1H, CHC*H*B), 1.30 (s, 12H, 4 x C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 141.9, 127.8, 127.8, 126.4, 83.5, 24.9. The ^{13}C NMR signal for the carbon attached to boron did not appear due to the quadrupolar splitting of ^{11}B. The values of the NMR spectra are in accordance with reported literature data.[421]

Following a reported procedure,[421] (*E*)-4,4,5,5-tetramethyl-2-(2-(thiophen-2-yl)vinyl)-1,3,2-dioxaborolane (**6.66**) (1.00 g, 4.23 mmol, 1.00 equiv), NH_4OAc (1.63 g, 21.2 mmol, 5.00 equiv), $NaIO_4$ (4.53 g, 21.2 mmol, 5.00 equiv) were suspended in a mixture acetone/water 1:1 (42 mL). The resulting slurry was stirred at room temperature for 16 h. It was then diluted with EtOAc (30 mL), washed successively with water (2 x 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude yellow oil was dissolved with diethyl ether (20 mL) then shaken 5 min with a basic aqueous solution of sorbitol (25 mL, 1 M sorbitol, 1 M Na_2CO_3), the aqueous layer was re-acidified with 4 M HCl (25 mL, pH = 2) and extracted with diethyl ether (35 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford (*E*)-(2-(thiophen-2-yl)vinyl)boronic acid (**6.21g**) as a clear yellow solid (0.416 g, 2.70 mmol, 64%). M.p. 118 – 120 °C; ^{1}H NMR (400 MHz, DMSO-d_6/D_2O 9:1) δ 7.47 (d, *J* = 5.1 Hz, 1H, Ar*H*), 7.36 (d, *J* = 18.1 Hz, 1H, C*H*CHB), 7.14 (m, 1H, Ar*H*), 7.04 (dd, *J* = 5.1, 3.5 Hz, 1H, Ar*H*), 5.80 (d, *J* = 18.1 Hz, 1H, CHC*H*B); ^{13}C NMR (101 MHz, DMSO-d_6/D_2O 9:1) δ 144.0, 138.8, 128.2, 127.6, 126.4, 122.6 (br); ^{11}B NMR (128 MHz, DMSO-d_6/D_2O 9:1) δ 28.5. The ^{13}C NMR signal for the carbon attached to boron was broad due to the quadrupolar splitting of ^{11}B. The values of the NMR spectra are in accordance with reported literature data.[422]

(*E*)-(5-Chloropent-1-en-1-yl)boronic acid (6.21k)

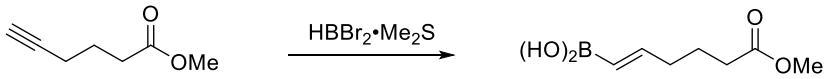


6.67 **6.21k**

A solution of 1 M dibromoborane dimethyl sulfide complex in DCM (6.00 mL, 6.00 mmol, 1.2 equiv) was added dropwise to neat 5-chloropent-1-yne (**6.67**) (0.523 mL, 5.00 mmol, 1.0 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature. After stirring for 4 h, the solution was transferred slowly to an ice-cooled mixture of diethyl ether/water 2:1 (18 mL) and stirred vigorously for 15 min. The mixture was diluted with diethyl ether (20 mL) and extracted with water (2 x 10 mL). The organic layer was then shaken 5 min with a basic aqueous solution of sorbitol (25 mL, 1 M sorbitol, 1 M Na_2CO_3), the aqueous layer was re-acidified with 4 M HCl (25 mL, pH = 2) and extracted with diethyl ether (35 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford (*E*)-(5-chloropent-1-en-1-yl)boronic acid (**6.21k**) as a light yellow oil (461 mg, 3.11 mmol, 62 %). ^{1}H NMR (400 MHz, DMSO-d_6/D_2O 9:1) δ 6.40 (dt, *J* = 17.9, 6.5 Hz, 1H, CHC*H*CH_2), 5.35 (dt, *J* = 17.9, 1.5 Hz, 1H, BC*H*CH), 3.60 (t, *J* = 6.5 Hz, 2H, C*H*$_2$Cl), 2.19 (dtd, *J* = 7.8, 6.6, 1.6 Hz, 2H, CHC*H*$_2$CH$_2$), 1.79 (dq, *J* = 8.4, 6.6 Hz, 2H, C*H*$_2$CH$_2$Cl); ^{13}C NMR (101 MHz, DMSO-d_6/D_2O 9:1) δ 149.0, 125.8 (br), 45.3, 32.4, 31.3; ^{11}B NMR (128 MHz, DMSO-d_6/D_2O 9:1) δ 27.3; IR (ν_{max}, cm^{-1}) 2961 (m), 2922 (w), 1634 (m), 1347 (s), 1305 (m), 1225 (m), 1051 (w), 998 (m), 691 (m), 652 (m); HRMS (APPI/LTQ-Orbitrap) Calcd for $C_5H_9BClO_2^-$ [M^-] 147.0390; found 147.0394. The ^{13}C NMR signal for the carbon attached to boron was broad due to the quadrupolar splitting of ^{11}B.

[422] S. Liu, L. S. Liebeskind, *J. Am. Chem. Soc.* **2008**, *130*, 6918.

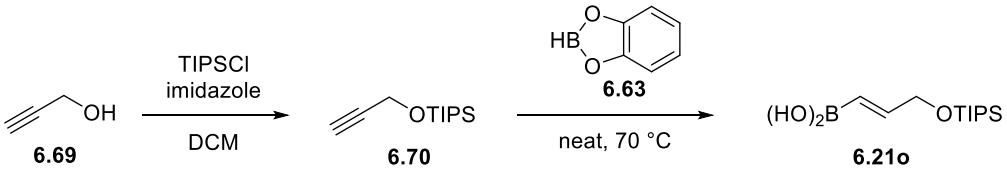
(*E*)-(6-Methoxy-6-oxohex-1-en-1-yl)boronic acid (6.21l)



6.68 **6.21l**

Following a reported procedure,[423] a solution of 1 M dibromoborane dimethyl sulfide complex in DCM (6.00 mL, 6.00 mmol, 1.2 equiv) was added dropwise to neat methyl hex-5-ynoate (**6.68**) (631 mg, 5.00 mmol, 1.00 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature. After stirring for 4 h, the solution was transferred slowly to an ice-cooled mixture of diethyl ether/water 2:1 (18 mL) and stirred vigorously for 15 min. The mixture was diluted with diethyl ether (20 mL) and extracted with water (2 x 10 mL). The organic layer was then shaken 5 min with a basic aqueous solution of sorbitol (25 mL, 1 M sorbitol, 1 M Na_2CO_3), the aqueous layer was re-acidified with 4 M HCl (25 mL, pH = 2) and extracted with diethyl ether (35 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford (*E*)-(6-methoxy-6-oxohex-1-en-1-yl)boronic acid (**6.21l**) as a light brown oil (517 mg, 3.01 mmol, 60 %). ^{1}H NMR (400 MHz, DMSO-d_6/D_2O 9:1) δ 6.38 (dt, *J* = 17.9, 6.4 Hz, 1H, CHC*H*CH_2), 5.30 (dt, *J* = 17.9, 1.6 Hz, 1H, BC*H*CH), 3.55 (s, 3H, OCH_3), 2.26 (t, *J* = 7.4 Hz, 2H, CH_2CO_2Me), 2.10 – 2.00 (m, 2H, CH_2BCC), 1.59 (p, *J* = 7.4 Hz, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (101 MHz, DMSO-d_6/D_2O 9:1) δ 174.4, 150.1, 125.2 (br), 51.8, 34.5, 33.0, 23.6. The ^{13}C NMR signal for the carbon attached to boron was broad due to the quadrupolar splitting of ^{11}B. The values of the NMR spectra are in accordance with reported literature data.[423]

(*E*)-(3-((Triisopropylsilyl)oxy)prop-1-en-1-yl)boronic acid (6.21o)



6.69 **6.70** **6.21o**

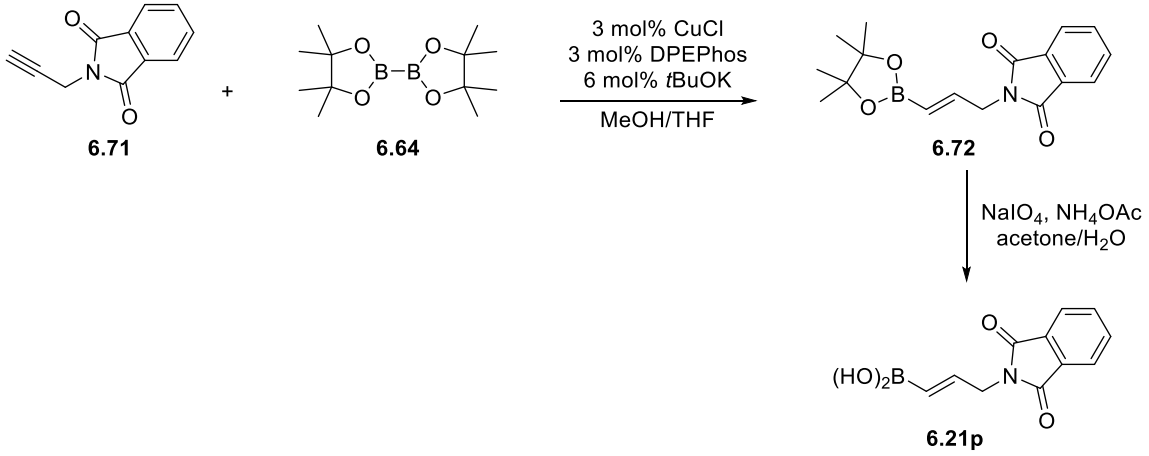
Following a reported procedure,[424] a solution of propargyl alcohol (**6.69**) (1.04 mL, 17.8 mmol, 1.00 equiv), imidazole (3.04 g, 44.7 mmol, 2.50 equiv), and triisopropylchlorosilane (5.73 mL, 26.8 mmol, 1.50 equiv) in DCM (30 mL) was stirred at room teperature for 16 h. The reaction mixture was diluted with DCM (30 mL) and quenched with water (10 mL). The aqueous layer was separated and extracted with DCM (2 × 15 mL). The combined organic layers were washed successively with water (2 × 15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using pentane as eluent providing triisopropyl(prop-2-yn-1-yloxy)silane (**6.70**) as a colorless oil (3.23 g, 15.2 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (d, *J* = 2.4 Hz, 2H, CH_2O), 2.39 (t, *J* = 2.4 Hz, 1H, CC*H*), 1.26 – 0.99 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.5, 72.7, 51.7, 17.8, 12.0. The values of the NMR spectra are in accordance with reported literature data.[424]

Catecholborane (**6.63**) (1.71 mL, 16.0 mmol, 1.05 equiv) was added dropwise to stirring neat triisopropyl(prop-2-yn-1-yloxy)silane (**6.70**) (3.23 g, 15.2 mmol, 1.00 equiv) at 0 °C under inert atmosphere. The reaction mixture was stirred at room temperature until the gas evolution had ceased and, then was heated to 70 °C and stirred for 4 h. After cooling to room temperature, the reaction mixture was diluted in Et_2O (150 mL) and 1 N NaOH (45 mL) was added. After vigorous stirring for 10

[423] D. Kontokosta, D. S. Mueller, H.-Y. Wang, L. L. Anderson, *Org. Lett.* **2013**, *15*, 4830.
[424] M. S. Oderinde, H. N. Hunter, M. G. Organ, *Chem. Eur. J.* **2012**, 18, 10817.

min, the mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with 1 N NaOH (60 mL), water (3 x 60 mL) and water/brine 1:1 (60 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using Et_2O/pentane 50:50 as eluent to afford (*E*)-(3-((triisopropylsilyl)oxy)prop-1-en-1-yl)boronic acid (**6.21o**) as a colorless oil (2.12 g, 8.21 mmol, 54%). Rf = 0.37 (Et_2O/pentane, 50:50), KMnO4; ^{1}H NMR (400 MHz, DMSO-d_6/D_2O 9:1) δ 6.46 (dt, *J* = 17.9, 3.7 Hz, 1H, C*H*CHB), 5.59 (dt, *J* = 17.9, 2.0 Hz, 1H, CHC*H*B), 4.22 (dd, *J* = 3.7, 2.0 Hz, 2H, CH_2O), 1.05 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, DMSO-d_6/D_2O 9:1) δ 149.6, 122.0 (br), 65.1, 18.5, 12.1; ^{11}B (128 MHz, DMSO-d_6/D_2O 9:1) δ 26.1; IR (ν_{max}, cm^{-1}) 2942 (m), 2895 (m), 2867 (m), 1638 (m), 1462 (m), 1372 (s), 1344 (s), 1291 (s), 1258 (m), 1131 (s), 1107 (s), 1055 (m), 1017 (m), 994 (m), 953 (m), 882 (s), 771 (m), 681 (s), 663 (s), 653 (s); HRMS (APPI/LTQ-Orbitrap) Calcd for $C_{12}H_{26}BO_3Si^-$ [M$^-$] 257.1750; found 257.1749. The ^{13}C NMR signal for the carbon attached to boron was broad due to the quadrupolar splitting of ^{11}B.

(*E*)-(3-(1,3-Dioxoisoindolin-2-yl)prop-1-en-1-yl)boronic acid (6.21p)



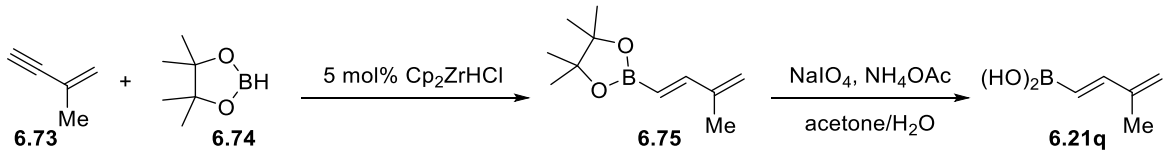
6.71 **6.64** **6.72** **6.21p**

Following a reported procedure,[421] CuCl (15.0 mg, 0.150 mmol, 0.03 equiv), NaO*t*Bu (29.0 mg, 0.300 mmol, 0.06 equiv) and DPEPhos (81.0 mg, 0.150 mmol, 0.03 equiv) were dissolved in THF (5 mL) under argon. The reaction mixture was stirred for 30 min at room temperature and then, bis(pinacolato)diboron (**6.64**) (1.40 g, 5.50 mmol, 1.10 equiv) and THF (2.5 mL) were added and the reaction mixture was stirred for another 10 min and then *N*-propargylphtalimide (**6.71**) (0.926 g, 5.00 mmol, 1.00 equiv) was added, followed by MeOH (0.405 mL, 10.0 mmol, 2.00 equiv). The reactor wall was washed with THF (1.5 mL), sealed, and stirred for 4 h. The reaction mixture was filtered through a pad of Celite, washed with EtOAc and the solvent was removed under reduced pressure. The resulting oil was purified by column chromatography using EtOAc/pentane 15:85 as eluent to afford (*E*)-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)isoindoline-1,3-dione (**6.72**) as a white solid (1.49 g, 4.75 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H, Ar*H*), 7.72 (dd, *J* = 5.5, 3.1 Hz, 2H, Ar*H*), 6.59 (dt, *J* = 18.0, 4.5 Hz, 1H, C*H*CHB), 5.48 (dt, *J* = 18.0, 1.9 Hz, 1H, CHC*H*B), 4.38 (dd, *J* = 4.6, 1.8 Hz, 2H, CH_2N), 1.22 (s, 12H, 4 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 145.4, 134.2, 132.2, 123.5, 83.5, 41.1, 24.9. The ^{13}C NMR signal for the carbon attached to boron did not appear due to the quadrupolar splitting of ^{11}B. The values of the NMR spectra are in accordance with reported literature data.[421]

Following a reported procedure,[421] (*E*)-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)isoindoline-1,3-dione (**6.72**) (1.49 g, 4.75 mmol), NH_4OAc (1.83 g, 23.7 mmol, 5.00 equiv), $NaIO_4$ (5.08 g, 23.7 mmol, 5.00 equiv) were suspended in a mixture acetone/water 1:1 (46 mL). The resulting

slurry was stirred at room temperature for 16 h. It was then diluted with EtOAc (30 mL), washed successively with water (2 x 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford (*E*)-(3-(1,3-dioxoisoindolin-2-yl)prop-1-en-1-yl)boronic acid (**6.21p**) as a white solid (0.805 g, 3.48 mmol, 73%). M.p. 145 – 147 °C; ^{1}H NMR (400 MHz, DMSO-d_6/D_2O 9:1) δ 7.95 – 7.77 (m, 4H, Ar*H*), 6.41 (dt, *J* = 18.0, 4.3 Hz, 1H, C*H*CHB), 5.24 (dt, *J* = 18.0, 1.9 Hz, 1H, CHC*H*B), 4.22 (dd, *J* = 4.3, 1.9 Hz, 2H, CH_2N); ^{13}C NMR (101 MHz, DMSO-d_6/D_2O 9:1) δ 168.2, 143.2, 135.2, 131.9, 124.4 (br), 123.7, 41.0; ^{11}B NMR (128 MHz, DMSO-d_6/D_2O 9:1) δ 26.8; IR (ν_{max}, cm^{-1}) 2985 (m), 2904 (m), 1773 (m), 1716 (s), 1427 (m), 1395 (s), 1343 (m), 1071 (s), 1055 (s), 726 (m); HRMS (APPI/LTQ-Orbitrap) Calcd for $C_{11}H_{11}BNO_4^+$ [M+H]$^+$ 232.0776; found 232.0775. The ^{13}C NMR signal for the carbon attached to boron was broad due to the quadrupolar splitting of ^{11}B.

(*E*)-(3-Methylbuta-1,3-dien-1-yl)boronic acid (6.21q)

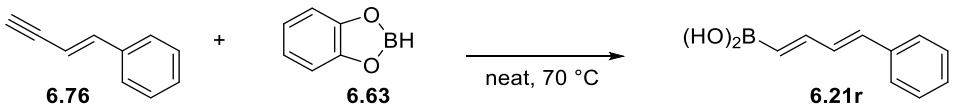


Following a reported procedure,[425] to a flask containing Cp_2ZrHCl (64.0 mg, 0.250 mmol, 0.05 equiv) at 0 °C under argon atmosphere was added pinacolborane (**6.74**) (0.798 mL, 5.50 mmol, 1.10 equiv) then dropwise 2-methylbut-1-en-3-yne (**6.73**) (0.485 mL, 5.00 mmol, 1.00 equiv). The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 24 h. The crude reaction was directly purified by column chromatography using EtOAc/pentane 2:98 as eluent to afford 4,4,5,5-tetramethyl-2-[(1*E*)-3-methylbuta-1,3-dien-1-yl]-1,3,2-dioxaborolane (**6.75**) as a colorless oil (789 mg, 4.05 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 18.2 Hz, 1H, C*H*CHB), 5.56 (d, *J* = 18.2 Hz, 1H, CHC*H*B), 5.21 – 5.13 (m, 2H, CCH_2), 1.85 (t, *J* = 1.1 Hz, 3H, CCH_3), 1.28 (s, 12H, 4 x CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 143.2, 120.3, 116.7 (br), 83.4, 24.9, 17.9. The ^{13}C NMR signal for the carbon attached to boron was broad due to the quadrupolar splitting of ^{11}B. The values of the NMR spectra are in accordance with reported literature data.[425]

Following a reported procedure,[425] to a stirred solution of 4,4,5,5-tetramethyl-2-[(1*E*)-3-methylbuta-1,3-dien-1-yl]-1,3,2-dioxaborolane (**6.75**) (772 mg, 3.98 mmol, 1.00 equiv) in acetone (125 mL) were added an aqueous solution of NH_4OAc (79 mL, 0.1 M, 1.50 equiv) and $NaIO_4$ (2.55 g, 11.9 mmol, 3.0 equiv). The cloudy mixture was stirred at room temperature for 24 h. After cautious acidification with aqueous 2 M HCl (pH = 2), the aqueous layer was extracted with AcOEt (2 x 80 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford (*E*)-(3-methylbuta-1,3-dien-1-yl)boronic acid (**6.21q**) as a light yellow solid (200 mg, 1.79 mmol, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 17.8 Hz, 1H, C*H*CHB), 5.68 (d, *J* = 17.9 Hz, 1H, CHC*H*B), 5.29 (s, 1H, CCH_2), 5.27 (s, 1H, CCH_2), 1.92 (s, 3H, CCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 143.2, 121.6, 120.0 (br), 18.1; ^{11}B NMR (128 MHz, DMSO-d_6/D_2O 9:1) δ 19.38. The ^{13}C NMR signal for the carbon attached to boron was broad due to the quadrupolar splitting of ^{11}B. The values of the NMR spectra are in accordance with reported data.[425]

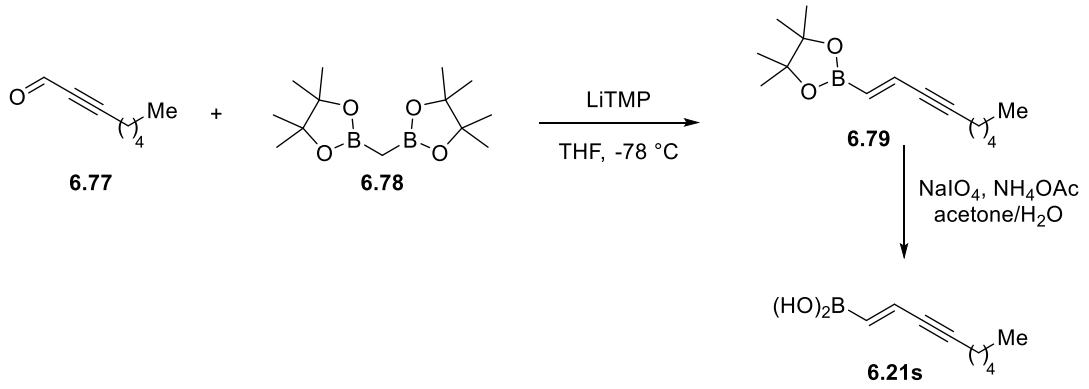
[425] A. Cannillo, S. Norsikian, P. Retailleau, M.-E. T. H. Dau, B. I. Iorga, J.-M. Beau, *Chem. Eur. J.* **2013**, *19*, 9127.

((1*E*,3*E*)-4-Phenylbuta-1,3-dien-1-yl)boronic acid (6.21r)



Catecholborane (**6.63**) (533 µl, 5.00 mmol, 1.00 equiv) was added dropwise to stirring neat (*E*)-but-1-en-3-yn-1-ylbenzene (**6.76**) (641 mg, 5.00 mmol, 1.00 equiv) at 0 °C under inert atmosphere. The reaction mixture was stirred at room temperature until the gas evolution had ceased and, then was heated to 70 °C and stirred for 1 h. The reaction was cooled to 0 °C and quenched by dropwise addition of water (3 mL). The solid was suspended in water (20 mL) and vigorously stirred at room temperature for 18 h. The mixture was extracted with diethyl ether (2 x 20 mL) and washed with water (5 x 20 mL). The organic layer was then shaken 5 min with a basic aqueous solution of sorbitol (25 mL, 1 M sorbitol, 1 M Na_2CO_3), the aqueous layer was re-acidified with 4 M HCl (25 mL, pH = 2) and extracted with diethyl ether (35 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford ((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)boronic acid (**6.21r**) as a off-white solid (461 mg, 3.11 mmol, 62 %). M.p. 110 – 112 °C; ^{1}H NMR (400 MHz, DMSO-d_6/D_2O 9:1) δ 7.54 – 7.48 (m, 2H), 7.38 – 7.30 (m, 2H), 7.30 – 7.22 (m, 1H), 7.08 – 6.87 (m, 2H), 6.69 (d, *J* = 15.4 Hz, 1H), 5.65 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6/D_2O 9:1) δ 146.9, 137.0, 134.7, 131.4, 129.1, 128.6 (br), 128.4, 127.0; ^{11}B NMR (128 MHz, DMSO-d_6/D_2O 9:1) δ 29.2; IR (ν_{max}, cm^{-1}) 2967 (m), 2912 (m), 1622 (m), 1427 (m), 1456 (s), 1082 (s), 1021 (s); HRMS (APPI/LTQ-Orbitrap) Calcd for $C_{10}H_{11}BO_2^+$ [M^+] 174.0847; found 174.0847. The ^{13}C NMR signal for the carbon attached to boron was broad due to the quadrupolar splitting of ^{11}B.

(*E*)-Non-1-en-3-yn-1-ylboronic acid (6.21s)



Following a reported procedure,[426] a 100 mL flask was charged with LiTMP (883 mg, 6.00 mmol, 1.20 equiv), sealed with a septum cap, and removed from the glovebox. The reaction flask was cooled to 0 °C, and dry THF (6 mL), followed by a solution of bis[(pinacolato)boryl]methane (**6.78**) (1.60 g, 6.00 mmo, 1.20 equiv) in THF (12 mL) were added. The reaction was stirred for 5 minutes at 0 °C and then was cooled to -78 °C, and a solution of oct-2-ynal (**6.77**) (0.735 mL, 5.00 mmol, 1.00 equiv) in THF (6.00 mL) was added slowly. The reaction was stirred at -78 °C for 4 h and the solvent was removed under reduced pressure. The crude reaction mixture was purified by column chromatography using EtOAc/pentane 2:98 as eluent to afford (*E*)-4,4,5,5-tetramethyl-2-(non-1-en-3-yn-1-yl)-1,3,2-dioxaborolane (**6.79**) as a clear yellow oil (805 mg, 3.24 mmol, 65 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (dt, *J* = 18.3, 2.1 Hz, 1H, C*H*CHB), 5.92 (dd, *J* = 18.3, 0.6 Hz, 1H, CHC*H*B), 2.32 (tdd, *J* = 7.2, 2.2, 0.6 Hz,

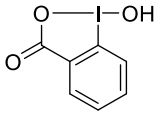
[426] J. R. Coombs, L. Zhang, J. P. Morken, *Org. Lett.* **2015**, 17, 1708.

2H, CCH_2), 1.56 – 1.48 (m, 2H, CH_2), 1.42 – 1.27 (m, 4H, 2 x CH_2), 1.26 (s, 12H, 4 x CH_3 pinacol), 0.89 (t, *J* = 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.5, 95.4, 83.6, 81.0, 31.2, 28.4, 24.9, 22.3, 19.7, 14.1. The ^{13}C NMR signal for the carbon attached to boron did not appear due to the quadrupolar splitting of ^{11}B. The values of the NMR spectra are in accordance with reported literature data.[426]

(*E*)-4,4,5,5-Tetramethyl-2-(non-1-en-3-yn-1-yl)-1,3,2-dioxaborolane (**6.79**) (0.805 g, 3.24 mmol, 1.00 equiv), NH_4OAc (1.250 g, 16.22 mmol, 5.00 equiv) and $NaIO_4$ (3.470 g, 16.22 mmol, 5.00 equiv) were suspended in a mixture acetone/water 1:1 (30 mL). The resulting slurry was stirred at room temperature for 16 h. It was then diluted with EtOAc (30 mL), washed successively with water (2 x 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting yellow oil was dissolved in diethyl ether (20 mL) then shaken 5 min with a basic aqueous solution of sorbitol (25 mL, 1 M sorbitol, 1 M Na_2CO_3), the aqueous layer was re-acidified with 4 M HCl (25 mL, pH = 2) and extracted with diethyl ether (35 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford (*E*)-non-1-en-3-yn-1-ylboronic acid (**6.21s**) as a yellow oil (0.365 g, 2.20 mmol, 68%). ^{1}H NMR (400 MHz, DMSO-d_6/D_2O 9:1) δ 6.27 (dt, *J* = 18.3, 2.1 Hz, 1H, C*H*CHB), 5.83 (d, *J* = 18.4 Hz, 1H, CHC*H*B), 2.32 (td, *J* = 7.0, 2.2 Hz, 2H, CCH_2), 1.46 (m, 2H, CH_2), 1.38 – 1.23 (m, 4H, 2 x CH_2), 0.86 (t, *J* = 7.0 Hz, 3H, CH_2CH_3); ^{13}C NMR (101 MHz, DMSO-d_6/D_2O 9:1) δ 136.6 (br), 126.6, 93.7, 81.2, 30.6, 27.9, 21.7, 18.7, 14.0; ^{11}B NMR (128 MHz, DMSO-d_6/D_2O 9:1) δ 27.2; IR (ν_{max}, cm^{-1}) 2985 (m), 2904 (m), 1773 (m), 1716 (s), 1427 (m), 1395 (s), 1343 (m), 1071 (s), 1055 (s), 726 (m); HRMS (APPI/LTQ-Orbitrap) m/z: $[M]^+$ Calcd for $C_9H_{15}BO_2^+$ 166.1160; found 166.1161. The ^{13}C NMR signal for the carbon attached to boron was broad due to the quadrupolar splitting of ^{11}B.

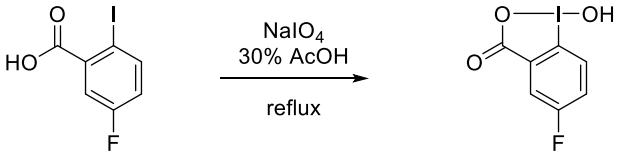
10.4.2.2. Synthesis of the VBX Reagents

The synthesis of 2-Iodosylbenzoic acid (**6.20a**) has been reported in section 10.2.2.



6.20a

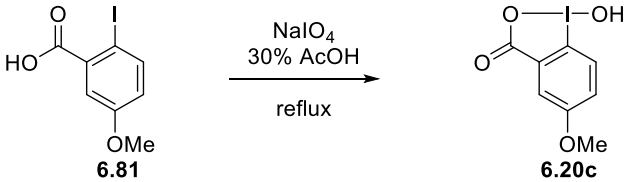
5-Fluoro-1-hydroxy-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.20b)



6.80 **6.20b**

Following a reported procedure,[427] $NaIO_4$ (2.25 g, 10.5 mmol, 1.05 equiv) and 5-fluoro-2-iodobenzoic acid (**6.80**) (2.70 g, 10.0 mmol, 1.00 equiv) were suspended in 30% (v/v) aq. AcOH (27 mL). The mixture was vigorously stirred under reflux for 4 h and allowed to cool to room temperature. The precipitate was collected by filtration, washed on the filter with ice water (3 x 8 mL) and acetone (3 x 6 mL), and air-dried in the dark to give 5-fluoro-1-hydroxy-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.20b**) as a white solid (2.62 g, 9.30 mmol, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H, Ar*H*), 7.89 – 7.78 (m, 2H, Ar*H*), 7.78 – 7.72 (m, 1H, Ar*H*); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 164.0 (d, *J* = 248.3 Hz), 134.2 (d, *J* = 7.3 Hz), 128.4 (d, *J* = 8.6 Hz), 121.8 (d, *J* = 24.0 Hz), 117.5 (d, J = 23.5 Hz), 114.3; ^{19}F NMR (376 MHz, DMSO-d_6) δ -112.7. The values of the NMR spectra are in accordance with reported literature data.[427]

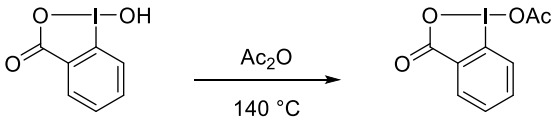
1-Hydroxy-5-methoxy-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.20c)



6.81 **6.20c**

Following a reported procedure,[427] $NaIO_4$ (2.25 g, 10.5 mmol, 1.05 equiv) and 2-iodo-5-methoxybenzoic acid (**6.81**) (2.78 g, 10.0 mmol, 1.00 equiv) were suspended in 30% (v/v) aq. AcOH (27 mL). The mixture was vigorously stirred under reflux for 4 h and allowed to cool to room temperature. The precipitate was collected by filtration, washed on the filter with ice water (3 x 8 mL) and acetone (3 x 6 mL), and air-dried in the dark to give 1-hydroxy-5-methoxy-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.20c**) as a white solid (2.31 g, 7.90 mmol, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H, Ar*H*), 7.72 – 7.61 (m, 1H, Ar*H*), 7.59 – 7.47 (m, 1H, Ar*H*), 3.88 (s, 3H, OCH_3); ^{13}C NMR (101MHz, DMSO-d_6) δ 167.9, 162.0, 133.5, 127.6, 122.0, 115.4, 109.5, 56.4. The values of the NMR spectra are in accordance with reported literature data.[427]

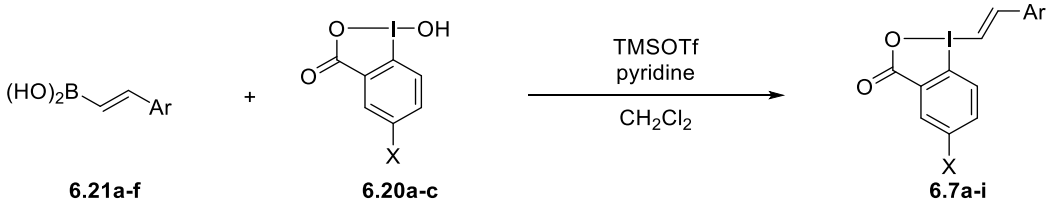
1-Acetoxy-1,2-benziodoxol-3-(1*H*)-one (6.22)



6.20a **6.22**

Following a reported procedure,[428] 2-iodosylbenzoic acid (**6.20a**) (20.8 g, 79.0 mmol, 1.00 equiv) was suspended in acetic anhydride (75.0 mL, 788 mmol, 10.0 equiv) and heated to reflux (140 °C) until complete dissolution (about 15 min). The resulting clear solution was allowed to cool to room temperature and then cooled to 5 °C overnight. The white crystals were filtered, washed with pentane (3 x 30 mL) and dried under reduced pressure to afford 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) as a white solid (22.3 g, 73.0 mmol, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar*H*), 8.00 (dd, *J* = 8.3, 1.0 Hz, 1H, Ar*H*), 7.92 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H, Ar*H*), 7.71 (td, *J* = 7.3, 1.1 Hz, 1H, Ar*H*), 2.25 (s, 3 H, COCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.5, 168.2, 136.2, 133.3, 131.4, 129.4, 129.1, 118.4, 20.4. The values of the NMR spectra are in accordance with reported literature data.[429]

General procedure A: Aryl-VBX synthesis



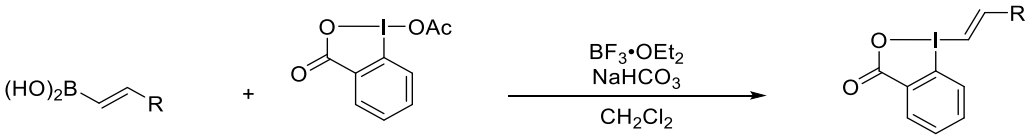
6.21a-f **6.20a-c** **6.7a-i**

To a suspension of 2-iodosylbenzoic acid (**6.20a-c**) (1.30 mmol, 1.00 equiv) in dry DCM (13 mL) was added TMSOTf (0.270 mL, 1.50 mmol, 1.15 equiv) dropwise over 10 min and stirred for 30 min at room temperature. Afterwards, the corresponding vinyl boronic acid (**6.21a-f**) (1.50 mmol, 1.15 equiv) was added and the reaction mixture was stirred until the reaction was completed (1 to 8 h, monitored by

[427] S. Bertho, R. Rey-Rodriguez, C. Colas, P. Retailleau, I. Gillaizeau, *Chem. Eur. J.* **2017**, *23*, 17674.
[428] P. Caramenti, S. Nicolai, J. Waser, *Chem. Eur. J.* **2017**, *23*, 14702.
[429] P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579.

TLC, MeOH/DCM 5:95). Pyridine (0.121 mL, 1.50 mmol, 1.15 equiv) was added and after further stirring for 10 min at room temperature, the solvent was removed under reduced pressure. The resulting solid was dissolved in DCM (20 mL) and washed with 1 M HCl (10 mL). The aqueous layer was extracted with DCM (3 x 20 mL). The organic layers were combined, washed successively with a saturated solution of $NaHCO_3$ (40 mL) and water (3 x 20 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting solid was dissolved again in DCM (minimum amount until dissolution) and precipitated in Et_2O (ca. 150 mL). After precipitation at 4 °C for 2 h, the solid was filtered and washed with Et_2O to afford the corresponding VBX reagent.

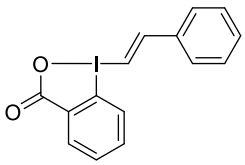
General procedure B: Alkyl-VBX synthesis



6.21h-s **6.22** **6.7j-u**

To a solution of the corresponding vinyl boronic acid (**6.21h-s**) (1.30 mmol, 1.00 equiv) in dry DCM (13 mL) was added BF_3•OEt_2 (0.198 mL, 1.56 mmol, 1.20 equiv) dropwise at 0 °C. After 15 minutes, 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol, 1.20 equiv) was added in one portion at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred until the reaction was completed (4 to 24 h, monitored by TLC using MeOH/DCM 5:95). The reaction was then quenched with a saturated solution of $NaHCO_3$ (13 mL) and stirred vigorously for 1 h. The resulting suspension was filtered and the filtrate was extracted with DCM (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting solid was dissolved in DCM (minimum amount until dissolution) and precipitated in Et_2O (ca. 150 mL). After precipitation at 4 °C for 2 h, the solid was filtered and washed with Et_2O to afford the corresponding VBX reagent.

(*E*)-1-Styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7a)

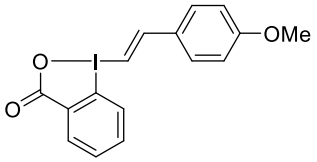


6.7a

Following general procedure **A**, starting from *trans*-2-phenylvinylboronic acid (**6.21a**) (221 mg, 1.50 mmol) and 2-iodosylbenzoic acid (**6.20a**) (343 mg, 1.30 mmol), afforded (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) as a white solid (351 mg, 1.00 mmol, 77%). ^{1}H NMR (400 MHz, MeOD) δ 8.32 – 8.25 (m, 1H, Ar*H*), 7.97 (d, *J* = 15.5 Hz, 1H, ICHC*H*Ph), 7.77 – 7.63 (m, 6H, Ar*H* and IC*H*CHPh), 7.54 – 7.45 (m, 3H, Ar*H*); ^{13}C NMR (101 MHz, MeOD) δ 170.1, 155.8, 136.7, 135.3, 134.5, 133.3, 132.1, 131.8, 130.2, 129.0, 129.0, 115.5, 100.0. The values of the NMR spectra are in accordance with reported literature data.[67]

The reaction was scaled up to *trans*-2-phenylvinylboronic acid (**6.21a**) (1.48 g, 10.0 mmol) and 2-iodosylbenzoic acid (**6.20a**) (2.30 g, 8.70 mmol) to afford (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (2.20 g, 6.30 mmol, 72%).

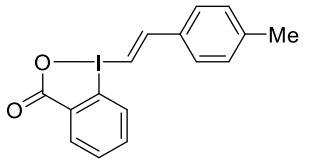
(*E*)-1-(4-Methoxystyryl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7b)



6.7b

Following general procedure **A**, starting from *trans*-2-(4-methoxyphenyl)vinylboronic acid (**6.21b**) (266 mg, 1.50 mmol) and 2-iodosylbenzoic acid (**6.20a**) (343 mg, 1.30 mmol), afforded (*E*)-1-(4-methoxystyryl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7b**) as a white solid (306 mg, 0.805 mmol, 62%). ^{1}H NMR (400 MHz, MeOD) δ 8.29 (dt, *J* = 5.8, 3.5 Hz, 1H, Ar*H*), 7.89 (d, *J* = 15.3 Hz, 1H, ICHC*H*Ph), 7.78 – 7.60 (m, 5H, Ar*H*), 7.45 (d, *J* = 15.4 Hz, 1H, IC*H*CHPh), 7.12 – 6.95 (m, 2H, Ar*H*), 3.87 (s, 3H, OC*H$_3$*); ^{13}C NMR (101 MHz, MeOD) δ 170.1, 163.7, 155.8, 135.2, 134.5, 133.3, 131.8, 130.8, 129.4, 128.9, 115.6, 115.5, 95.9, 56.0. The values of the NMR spectra are in accordance with reported literature data.[67]

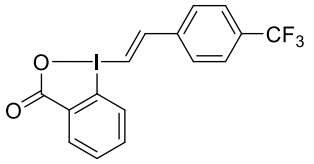
(*E*)-1-(4-Methylstyryl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7c)



6.7c

Following general procedure **A**, starting from *trans*-2-(4-methylphenyl)vinylboronic acid (**6.21c**) (242 mg, 1.50 mmol) and 2-iodosylbenzoic acid (**6.20a**) (343 mg, 1.30 mmol), afforded (*E*)-1-(4-methylstyryl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7c**) as a white solid (335 mg, 0.920 mmol, 71%). ^{1}H NMR (400 MHz, MeOD) δ 8.32 – 8.25 (m, 1H, Ar*H*), 7.92 (d, *J* = 15.4 Hz, 1H,ICHC*H*Ph), 7.76 – 7.64 (m, 3H, Ar*H*), 7.62 – 7.54 (m, 3H, Ar*H* and IC*H*CHPh), 7.31 (d, *J* = 7.9 Hz, 2H, Ar*H*), 2.42 (s, 3H, C*H$_3$*); ^{13}C NMR (101 MHz, MeOD) δ 169.9, 155.7, 142.8, 135.0, 134.3, 133.8, 133.1, 131.6, 130.6, 128.8, 128.7, 115.3, 98.1, 21.3. The values of the NMR spectra are in accordance with reported literature data.[67]

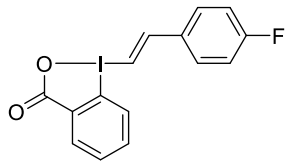
(*E*)-1-(4-(Trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7d)



6.7d

Following general procedure **A**, starting from *trans*-2-[4-(trifluoromethyl)phenylvinylboronic acid (**6.21d**) (323 mg, 1.50 mmol) and 2-iodosylbenzoic acid (**6.20a**) (343 mg, 1.30 mmol), afforded (*E*)-1-(4-(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7d**) as a white solid (275 mg, 0.658 mmol, 51%). ^{1}H NMR (400 MHz, MeOD) δ 8.30 (m, 1H, Ar*H*), 8.05 (d, *J* = 15.5 Hz, 1H, ICHC*H*Ph), 7.93 – 7.84 (m, 3H, Ar*H* and IC*H*CHPh), 7.81 (m, 2H, Ar*H*), 7.74 (m, 3H, Ar*H*); ^{13}C NMR (101 MHz, MeOD) δ 170.6, 154.1, 140.6, 136.0, 134.4, 133.8, 133.7 (q, *J* = 37.7 Hz), 132.4, 129.9, 129.7, 127.5 (q, *J* = 3.8 Hz), 125.8 (q, *J* = 271.5 Hz) 115.9, 104.1; ^{19}F NMR (376 MHz, MeOD) δ -64.4. The values of the NMR spectra are in accordance with reported literature data.[67]

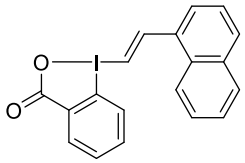
(*E*)-1-(4-Fluorostyryl)-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7e)



6.7e

Following general procedure **A**, starting from *trans*-2-(4-fluorophenyl)vinylboronic acid (**6.21e**) (248 mg, 1.50 mmol) and 2-iodosylbenzoic acid (**6.20a**) (343 mg, 1.30 mmol), afforded (*E*)-1-(4-fluoroystyryl)-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7e**) as a white solid (424 mg, 1.152 mmol, 89%). M.p. 146 – 148 °C; R_f = 0.11 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.38 – 8.31 (m, 1H, Ar*H*), 8.02 (d, *J* = 15.2 Hz, 1H, ICHC*H*Ph), 7.85 – 7.71 (m, 5H, Ar*H*), 7.66 (d, *J* = 15.3, 1H, IC*H*CHPh), 7.30 – 7.22 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, MeOD) δ 170.9, 166.4 (d, *J* = 251.2 Hz), 155.9, 137.0, 134.2, 133.3 (d, *J* = 3.0 Hz), 132.6, 132.2, 131.9 (d, *J* = 8.7 Hz), 130.4, 117.7 (d, *J* = 22.3 Hz), 115.7, 98.2; ^{19}F NMR (376 MHz, MeOD) δ -110.9; IR (ν_{max}, cm^{-1}) 3018 (s), 2946 (s), 2858 (m), 1750 (s), 1731 (s), 1542 (s), 1512 (s), 1319 (s), 1271 (s), 1243 (s), 1200 (s), 1165 (s), 1124 (s), 968 (s), 838 (m); HRMS (ESI) Calcd for $C_{15}H_{11}FIO_2^+$ $[M+H]^+$ 368.9782; found 368.9785.

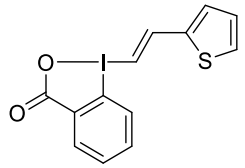
(*E*)-1-(2-(Naphthalen-1-yl)-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7f)



6.7f

Following general procedure **A**, starting from (*E*)-(2-(naphthalen-1-yl)vinyl)boronic acid (**6.21f**) (296 mg, 1.50 mmol) and 2-iodosylbenzoic acid (**6.20a**) (343 mg, 1.30 mmol), afforded (*E*)-1-(2-(naphthalen-1-yl)-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7f**) as a white solid (316 mg, 0.790 mmol, 61%). M.p. 164 – 166 °C; R_f = 0.20 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.79 (d, *J* = 15.1 Hz, 1H, ICHC*H*Ph), 8.33 – 8.28 (m, 1H, Ar*H*), 8.27 – 8.23 (m, 1H, Ar*H*), 8.05 – 7.89 (m, 3H, Ar*H*), 7.85 – 7.79 (m, 1H, Ar*H*), 7.74 – 7.66 (m, 3H, Ar*H* and IC*H*CHPh), 7.65 – 7.55 (m, 3H, Ar*H*); ^{13}C NMR (101 MHz, MeOD) δ 168.7, 151.7, 133.9, 133.8, 133.1, 132.6, 131.9, 131.0, 130.8, 130.4, 128.5, 127.7, 127.0, 126.2, 125.2, 122.8, 114.3, 101.2, 78.1; IR (ν_{max}, cm^{-1}) 2985 (s), 2906 (s), 1390 (m), 1247 (m), 1227 (m), 1065 (s), 1051 (s), 896 (m), 867 (m); HRMS (ESI) Calcd for $C_{19}H_{13}INaO_2^+$ $[M+Na]^+$ 422.9852; found 422.9851.

(*E*)-1-(2-(Thiophen-2-yl)vinyl)-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7g)

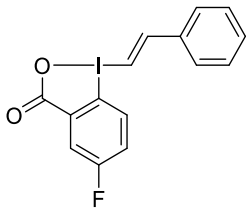


6.7g

Following general procedure **B**, with a final purification by column chromatography using MeOH/DCM 5:95 as eluent to obtain the titled compound in pure form. Starting from (*E*)-(2-(thiophen-2-yl)vinyl)boronic acid (**6.21g**) (169 mg, 1.10 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-1-(non-1-en-3-yn-1-yl)-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7g**)

as a beige solid (145 mg, 0.407 mmol, 37%). M.p. (dec.) 201 – 205 °C; R_f = 0.13 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD/CD_2Cl_2 9:1) δ 8.32 – 8.25 (m, 1H, Ar*H*), 8.04 (d, *J* = 15.3 Hz, 1H, ICHC*H*), 7.74 – 7.65 (m, 3H, Ar*H*), 7.62 (dt, *J* = 5.0, 0.9 Hz, 1H, Ar*H*), 7.43 (dd, *J* = 3.7, 1.1 Hz, 1H, Ar*H*), 7.29 (d, *J* = 15.3 Hz, 1H, IC*H*CH), 7.18 (dd, *J* = 5.1, 3.7 Hz, 1H, Ar*H*); ^{13}C NMR (101 MHz, MeOD/CD_2Cl_2 9:1) δ 169.8, 148.0, 140.9, 135.1, 134.2, 133.2, 132.3, 131.7, 130.7, 129.1, 128.5, 115.7, 96.3; IR (ν_{max}, cm^{-1}) 2987 (s), 2967 (s), 2907 (m), 1750 (m), 1735 (m), 1649 (m), 1573 (m), 1557 (m), 1540 (m), 1512 (m), 1452 (w), 1393 (m), 1251 (m), 1101 (w), 1068 (s), 1054 (s), 869 (m), 765 (m), 734 (m), 687 (m), 629 (s), 611 (s); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{10}IO_2S^+$ 356.9441; found 356.9442.

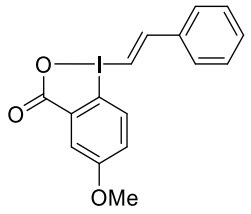
(*E*)-5-Fluoro-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7h)



6.7h

Following general procedure **A**, starting from (*E*)-styrylboronic acid (**6.21a**) (221 mg, 1.50 mmol) and 1-hydroxy-5-fluoro-1,2-benziodoxol-3(1H)-one (**6.20b**) (367 mg, 1.30 mmol), afforded (*E*)-5-fluoro-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7i**) as a white solid (278 mg, 0.760 mmol, 58%). M.p. 174 – 176 °C; R_f = 0.15 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.03 – 7.94 (m, 2H, Ar*H* and ICHC*H*Ph), 7.77 – 7.64 (m, 4H, Ar*H* and IC*H*CHPh), 7.55 – 7.44 (m, 4H, Ar*H*); ^{13}C NMR (101 MHz, MeOD) δ 168.7, 166.1 (d, *J* = 250.5 Hz), 156.1, 137.3, 136.6, 132.2, 131.0 (d, *J* = 8.4 Hz), 130.2, 129.0, 122.3 (d, *J* = 24.0 Hz), 119.8 (d, *J* = 23.9 Hz), 108.5, 99.7; ^{19}F NMR (376 MHz, MeOD) δ -113.5; IR (ν_{max}, cm^{-1}) 2987 (s), 2973 (s), 2905 (s), 1748 (m), 1737 (m), 1649 (m), 1559 (m), 1540 (m), 1512 (m), 1395 (m), 1255 (m), 1079 (s), 1054 (s), 863 (m); HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{10}FINaO_2^+$ 390.9602; Found 390.9595.

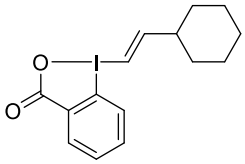
(*E*)-5-Methoxy-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7i)



6.7i

Following general procedure **A**, starting from (*E*)-styrylboronic acid (**6.21a**) (221 mg, 1.50 mmol) and 5-methoxy-1-hydroxy-1,2-benziodoxol-3-(1H)-one (**6.20c**) (382 mg, 1.30 mmol), afforded (*E*)-5-methoxy-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7h**) as a white solid (422 mg, 1.11 mmol, 85%). M.p. 167 – 168 °C; R_f = 0.13 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 7.95 (d, *J* = 15.4 Hz, 1H, ICHC*H*Ph), 7.82 (d, *J* = 3.0 Hz, 1H, Ar*H*), 7.74 – 7.61 (m, 3H, Ar*H* and IC*H*CHPh), 7.55 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.52 – 7.44 (m, 3H, Ar*H*), 7.25 (dd, *J* = 9.0, 3.1 Hz, 1H, Ar*H*), 3.88 (s, 3H, OC*H*$_3$); ^{13}C NMR (101 MHz, MeOD) δ 169.9, 163.7, 155.6, 136.7, 135.9, 132.1, 130.2, 129.7, 129.0, 121.7, 117.8, 103.6, 99.6, 56.4; IR (ν_{max}, cm^{-1}) 2977 (s), 2903 (m), 1617 (w), 1580 (w), 1411 (s), 1379 (s), 1259 (m), 1052 (s), 811 (m), 881 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{14}IO_3^+$ 380.9982; found 380.9980.

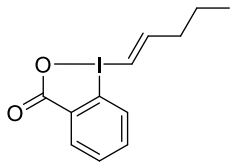
(*E*)-1-(2-Cyclohexylvinyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7j)



6.7j

Following general procedure **B**, starting from *trans*-2-cyclohexylvinyl)boronic acid (**6.21j**) (200 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-1-(2-cyclohexylvinyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7j**) as a white solid (274 mg, 0.769 mmol, 59%). M.p. 136 – 138 °C; R_f = 0.19 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.31 – 8.24 (m, 1H, Ar*H*), 7.75 – 7.65 (m, 3H, Ar*H*), 7.13 (dd, *J* = 15.1, 7.0 Hz, 1H, ICHC*H*cy), 6.84 (dd, *J* = 15.1, 1.2 Hz, 1H, IC*H*CHcy), 2.54 – 2.41 (m, 1H, cy-*H*), 1.99 – 1.90 (m, 2H, cy-*H*), 1.89 – 1.79 (m, 2H, cy-*H*), 1.78 – 1.69 (m, 1H, cy-*H*), 1.50 – 1.21 (m, 5H, cy-*H*); ^{13}C NMR (101 MHz, MeOD) δ 170.4, 166.0, 135.6, 134.9, 133.8, 132.2, 129.2, 115.2, 99.4, 46.2, 33.2, 27.3, 27.2. The values of the NMR spectra are in accordance with reported literature data.[67]

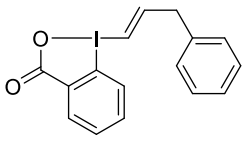
(*E*)-1-(Pent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7k)



6.7k

Following general procedure **B**, starting from *trans*-1-penten-1-yboronic acid (**6.21k**) (148 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-1-(pent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7k**) as a white solid (115 mg, 0.364 mmol, 28%). M.p. (dec.) 154 – 160 °C; R_f = 0.15 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.34 – 8.22 (m, 1H, Ar*H*), 7.80 – 7.63 (m, 3H, Ar*H*), 7.16 (dt, *J* = 14.9, 7.0 Hz, 1H, ICHC*H*CH_2), 6.87 (dt, *J* = 15.0, 1.4 Hz, 1H, IC*H*CHCH_2), 2.49 (qd, *J* = 7.2, 1.5 Hz, 2H, CHCH_2CH_2), 1.65 (h, *J* = 7.4 Hz, 2H, $CH_2CH_2CH_3$), 1.05 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (101 MHz, MeOD) δ 169.7, 160.4, 134.9, 133.1, 131.6, 128.7, 114.7, 100.1, 38.6, 22.2, 13.7; IR (ν_{max}, cm^{-1}) 2987 (s), 2973 (s), 2905 (s), 1748 (m), 1737 (m), 1649 (m), 1559 (m), 1540 (m), 1512 (m), 1395 (m), 1255 (m), 1079 (s), 1054 (s), 863 (m); HRMS (ESI) Calcd for $C_{12}H_{14}IO_2^+$ $[M+H]^+$ 317.0033; found 317.0033.

(*E*)-1-(3-Phenylprop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7l)

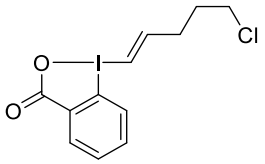


6.7l

Following general procedure **B**, starting from *trans*-3-Phenyl-1-propen-1-ylboronic acid (**6.21l**) (211 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-1-(3-phenylprop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7l**) as a white solid (332 mg, 0.912 mmol, 70%). M.p. 144 – 145 °C; R_f = 0.18 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.30 – 8.23 (m, 1H, Ar*H*), 7.72 – 7.64 (m, 3H, Ar*H*), 7.41 – 7.23 (m, 6H, Ar*H* and ICHC*H*Bn), 6.88 (dt, *J* = 14.9, 1.5 Hz,

1H, IC*H*CHPh), 3.83 (dd, *J* = 6.9, 1.4 Hz, 2H, C*H*$_2$Ph); ^{13}C NMR (101 MHz, MeOD) δ 170.0, 159.0, 138.4, 135.2, 134.2, 133.4, 131.8, 130.0, 130.0, 129.0, 128.1, 115.0, 101.2, 42.7; IR (ν_{max}, cm^{-1}) 2987 (s), 2973 (s), 2905 (s), 1748 (m), 1737 (m), 1649 (m), 1559 (m), 1540 (m), 1512 (m), 1395 (m), 1255 (m), 1079 (s), 1054 (s), 863 (m); HRMS (ESI) Calcd for $C_{16}H_{14}IO_2^+$ $[M+H]^+$ 365.0033; found 365.0033.

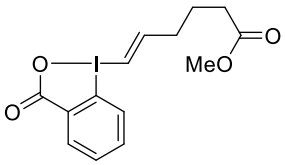
(*E*)-1-(5-Chloropent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7m)



6.7m

Following general procedure **B**, starting from (*E*)-(5-chloropent-1-en-1-yl)boronic acid (**6.21m**) (193 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-1-(5-chloropent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7m**) as a white solid (201 mg, 0.573 mmol, 44%). M.p. 133 – 135 °C; R_f = 0.19 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.34 – 8.24 (m, 1H, Ar*H*), 7.83 – 7.66 (m, 3H, Ar*H*), 7.19 (dt, *J* = 15.0, 6.9 Hz, 1H, ICHC*H*CH$_2$), 6.97 (dt, *J* = 15.0, 1.5 Hz, 1H, IC*H*CHCH$_2$), 3.70 (t, *J* = 6.4 Hz, 2H, C*H*$_2$Cl), 2.76 – 2.62 (m, 2H, CH$_2$C*H*$_2$CH), 2.09 (p, *J* = 6.7 Hz, 2H, C*H*$_2$CH$_2$Cl); ^{13}C NMR (101 MHz, MeOD) δ 168.6, 157.4, 133.8, 133.1, 131.9, 130.4, 127.6, 113.5, 100.1, 43.4, 32.5, 30.4; IR (ν_{max}, cm^{-1}) 2968 (m), 2897 (m), 1719 (w), 1596 (m), 1557 (m), 1346 (m), 1276 (m), 1261 (m), 1056 (m), 961 (m), 830 (m), 751 (s); HRMS (ESI) Calcd for $C_{12}H_{13}ClIO_2^+$ $[M+H]^+$ 350.9643; found 350.9645.

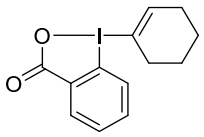
Methyl (*E*)-6-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(*3H*))-yl)hex-5-enoate (6.7n)



6.7n

Following general procedure **B**, starting from (E)-(6-methoxy-6-oxohex-1-en-1-yl)boronic acid (**6.21n**) (224 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded methyl (*E*)-6-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(*3H*))-yl)hex-5-enoate (**6.7n**) (210 mg, 0.561 mmol, 43%) as an off-white solid. M.p. 147 – 149 °C; R_f = 0.07 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.31 – 8.23 (m, 1H, Ar*H*), 7.78 – 7.64 (m, 3H, Ar*H*), 7.15 (dt, *J* = 15.0, 6.9 Hz, 1H, ICHC*H*), 6.90 (dt, *J* = 14.9, 1.4 Hz, 1H, IC*H*CH), 3.68 (s, 3H, OC*H*$_3$), 2.61 – 2.50 (m, 2H, C*H*$_2$CC), 2.46 (t, *J* = 7.3 Hz, 2H, C*H*$_2$CO$_2$Me), 1.91 (p, *J* = 7.4 Hz, 2H, CH$_2$C*H*$_2$CH$_2$); ^{13}C NMR (101 MHz, MeOD) δ 175.2, 170.0, 159.4, 135.2, 134.6, 133.3, 131.8, 129.0, 114.9, 101.1, 52.1, 35.9, 33.8, 24.3; IR (ν_{max}, cm^{-1}) 3443 (w), 3047 (w), 2958 (w), 2922 (w), 1731 (m), 1606 (s), 1557 (m), 1440 (m), 1363 (m), 1342 (m), 1294 (w), 1205 (m), 1184 (m), 1151 (m), 1005 (m), 961 (m), 830 (m); HRMS (ESI) Calcd for $C_{14}H_{16}IO_4^+$ $[M+H]^+$ 375.0088; found 375.0091.

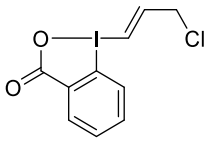
(*E*)-1-(Cyclohex-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7o)



6.7o

Following general procedure **B**, starting from 1-cyclohexenylboronic acid (**6.21o**) (164 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-1-(cyclohex-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7o**) as a white solid (213 mg, 0.649 mmol, 50%). M.p. 116 – 118 °C; R_f = 0.15 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.28 (dt, *J* = 7.2, 1.3 Hz, 1H, Ar*H*), 7.78 – 7.66 (m, 3H, Ar*H*), 7.07 (tt, *J* = 3.9, 1.8 Hz, 1H, ICC*H*), 2.73 – 2.68 (m, 2H, cy-*H*), 2.53 (tq, *J* = 6.0, 3.0 Hz, 2H, cy-*H*), 1.94 (pd, *J* = 6.0, 3.6 Hz, 2H, cy-*H*), 1.88 – 1.80 (m, 2H, cy-*H*); ^{13}C NMR (101 MHz, MeOD) δ 170.0, 152.3, 135.8, 133.8, 132.0, 129.0, 118.6, 113.5, 35.2, 30.1, 25.7, 21.5; IR (ν_{max}, cm^{-1}) 2976 (w), 2934 (w), 2906 (w), 1651 (m), 1600 (s), 1558 (m), 1435 (m), 1377 (m), 1346 (m), 1332 (m), 1107 (s), 905 (s), 853 (m), 826 (m), 748 (s); HRMS (ESI) Calcd for $C_{13}H_{14}IO_2^+$ $[M+H]^+$ 329.0033; found 329.0031. One carbone was not resolved at 101 MHz.

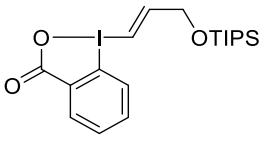
(*E*)-1-(3-Chloroprop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7p)



6.7p

Following general procedure **B**, with the addition of 2,2,2-trifluoroethanol (1.3 mL) after 3 h of reaction to dissolve the insoluble material. Starting from *trans*-2-chloromethylvinylboronic acid (**6.21p**) (156 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-1-(3-chloroprop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7p**) as a white solid (137 mg, 0.425 mmol, 46%). M.p. (dec.) 166 – 170 °C; R_f = 0.10 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.37 – 8.27 (m, 1H, Ar*H*), 7.84 – 7.70 (m, 3H, Ar*H* and IC*H*C*H*CH$_2$), 7.33 – 7.28 (m, 2H, Ar*H*), 4.53 – 4.46 (m, 2H, C*H*$_2$Cl); ^{13}C NMR (101 MHz, MeOD) δ 170.3, 153.6, 136.0, 133.6, 132.9, 132.1, 129.6, 115.0, 104.3, 45.2; IR (ν_{max}, cm^{-1}) 2987 (s), 2973 (s), 2905 (s), 1748 (m), 1737 (m), 1649 (m), 1559 (m), 1540 (m), 1512 (m), 1395 (m), 1255 (m), 1079 (s), 1054 (s), 863 (m); HRMS (ESI) Calcd for $C_{10}H_9ClIO_2^+$ $[M+H]^+$ 322.9330; found 322.9332.

(*E*)-1-(3-((Triisopropylsilyl)oxy)prop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(*1H*)-one (6.7q)

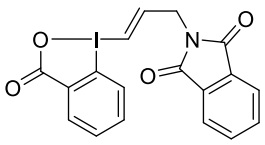


6.7q

Following general procedure **B**, starting from (*E*)-(3-((triisopropylsilyl)oxy)prop-1-en-1-yl)boronic acid (**6.21q**) (336 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-1-(3-((triisopropylsilyl)oxy)prop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(*1H*)-one (**6.7q**) (370 mg, 0.804 mmol, 62%) as a white solid. M.p. 157 – 159 °C; R_f = 0.20 (MeOH/DCM 5:95); ^{1}H NMR

(400 MHz, MeOD) δ 8.36 – 8.26 (m, 1H, Ar*H*), 7.73 (m, 3H, Ar*H*), 7.34 (dt, *J* = 14.7, 3.2 Hz, 1H, ICHC*H*), 7.08 (dt, *J* = 14.7, 2.2 Hz, 1H, IC*H*CH), 4.71 (dd, *J* = 3.2, 2.1 Hz, 2H, CH_2O), 1.31 – 1.10 (m, 21H, TIPS); ^{13}C NMR (101 MHz, MeOD) δ 170.3, 159.7, 135.7, 133.6, 132.9, 132.0, 129.3, 114.9, 98.7, 66.2, 18.5, 13.2; IR (ν_{max}, cm^{-1}) 3057 (w), 2944 (w), 2863 (w), 1644 (w), 1607 (w), 1264 (m), 1129 (w), 1014 (w), 943 (w), 914 (w), 734 (s), 701 (s); HRMS (ESI) Calcd for $C_{19}H_{30}IO_3Si^+$ $[M+H]^+$ 461.1003; found 461.1015.

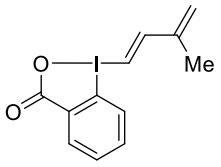
(*E*)-2-(3-(3-Oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)allyl)isoindoline-1,3-dione (6.7r)



6.7r

Following general procedure **B**, with the addition of 2,2,2-trifluoroethanol (1.3 mL) after 3 h of reaction to dissolve the insoluble material. Starting from (*E*)-(3-(1,3-dioxoisoindolin-2-yl)prop-1-en-1-yl)boronic acid (**6.21r**) (300 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-2-(3-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)allyl)isoindoline-1,3-dione (**6.7r**) as a white solid (417 mg, 0.963 mmol, 74%). M.p. (dec.) 163 – 167 °C; R_f = 0.12 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.40 – 8.34 (m, 1H, Ar*H*), 7.98 – 7.77 (m, 7H, Ar*H*), 7.35 (dt, *J* = 14.8, 4.8 Hz, 1H, ICHC*H*), 7.21 (dt, *J* = 14.8, 1.6 Hz, 1H, IC*H*CH), 4.75 (dd, *J* = 4.8, 1.6 Hz, 2H, CH_2N); ^{13}C NMR (101 MHz, MeOD) δ 171.0, 169.2, 154.8, 137.6, 135.7, 134.1, 133.4, 132.5, 131.1, 129.1, 124.5, 114.8, 100.4, 42.0; IR (ν_{max}, cm^{-1}) 2977 (s), 2917 (s), 1722 (m), 1483 (m), 1407 (s), 1374 (m), 1261 (m), 1329 (m), 1056 (s), 875 (w); HRMS (ESI) Calcd for $C_{18}H_{12}INNaO_4^+$ $[M+Na]^+$ 455.9703; found 455.9702.

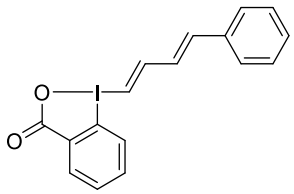
(*E*)-1-(3-Methylbuta-1,3-dien-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7s)



6.7s

Following general procedure **B**, starting from (*E*)-(3-methylbuta-1,3-dien-1-yl)boronic acid (**6.21s**) (146 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-1-(3-methylbuta-1,3-dien-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7s**) as a beige solid (225 mg, 0.716 mmol, 55%). M.p. (dec.) 70 – 72 °C; R_f = 0.11 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.31 – 8.26 (m, 1H, Ar*H*), 7.78 – 7.61 (m, 4H, Ar*H* and ICHC*H*C), 7.09 (d, *J* = 15.2 Hz, 1H, IC*H*CHC), 5.53 – 5.42 (m, 2H, CCH_2), 2.05 (t, *J* = 1.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, MeOD) δ 170.6, 158.7, 143.6, 135.9, 134.3, 133.8, 132.3, 129.5, 126.2, 115.5, 100.5, 18.3; IR (ν_{max}, cm^{-1}) 2987 (s), 2896 (m), 1632 (w), 1584 (m), 1570 (m), 1407 (m), 1381 (m), 1261 (m), 1230 (m), 1054 (s), 873 (m), 813 (m); HRMS (ESI) Calcd for $C_{12}H_{11}INaO_2^+$ $[M+Na]^+$ 336.9696; found 336.9695.

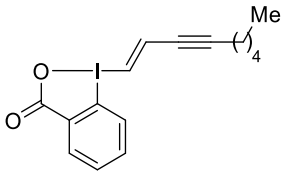
(*E*)-1-((1*E*,3*E*)-4-Phenylbuta-1,3-dien-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7t)



6.7t

Following general procedure **B**, starting from ((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)boronic acid (**6.21t**) (226 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-1-((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7t**) as a beige solid (196 mg, 0.520 mmol, 40%). M.p. (dec.) 169 – 173 °C; R_f = 0.17 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.35 – 8.27 (m, 1H, Ar*H*), 7.82 – 7.68 (m, 4H, Ar*H* and ICHC*H*), 7.62 – 7.56 (m, 2H, Ar*H*), 7.45 – 7.32 (m, 3H, Ar*H*), 7.22 (dd, *J* = 15.6, 10.6 Hz, 1H, C*H*CHPh), 7.13 (d, *J* = 14.7 Hz, 1H, IC*H*CH), 7.05 (d, *J* = 15.6 Hz, 1H, CHC*H*Ph); ^{13}C NMR (101 MHz, MeOD) δ 170.4, 156.9, 143.1, 137.2, 136.0, 133.7, 133.5, 132.2, 131.0, 130.2, 129.5, 128.9, 127.8, 115.7, 100.0; IR (ν_{max}, cm^{-1}) 2975 (s), 2911 (m), 1720 (m), 1448 (m), 1409 (s), 1381 (m), 1259 (m), 1056 (s), 873 (m), 809 (m), 782 (m); HRMS (ESI) Calcd for $C_{17}H_{13}INaO_2^+$ $[M+Na]^+$ 398.9852; found 398.9852.

(*E*)-1-(Non-1-en-3-yn-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6.7u)

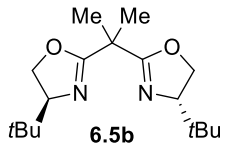


6.7u

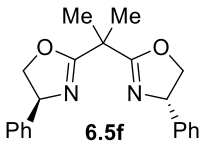
Following general procedure **B**, starting from (*E*)-non-1-en-3-yn-1-ylboronic acid (**6.21u**) (216 mg, 1.30 mmol) and 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**6.22**) (477 mg, 1.56 mmol), afforded (*E*)-1-(non-1-en-3-yn-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7u**) as a white solid (376 mg, 1.02 mmol, 79%). M.p. 139 – 141 °C; R_f = 0.26 (MeOH/DCM 5:95); ^{1}H NMR (400 MHz, MeOD) δ 8.30 – 8.22 (m, 1H, Ar*H*), 7.77 – 7.62 (m, 3H, Ar*H*), 7.33 (d, *J* = 15.5 Hz, 1H, ICHC*H*), 7.06 (dt, *J* = 15.5, 2.3 Hz, 1H, IC*H*CH), 2.47 (td, *J* = 7.0, 2.2 Hz, 2H, CC*H*$_2$CH$_2$), 1.66 – 1.56 (m, 2H, CCH$_2$C*H*$_2$), 1.51 – 1.31 (m, 4H, 2 x C*H*$_2$), 0.94 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, MeOD) δ 170.0, 136.3, 135.4, 134.3, 133.3, 131.9, 129.1, 115.5, 111.8, 101.4, 79.2, 32.2, 29.1, 23.2, 20.2, 14.3; IR (ν_{max}, cm^{-1}) 2975 (s), 2911 (m), 1720 (m), 1448 (m), 1409 (s), 1381 (m), 1259 (m), 1056 (s), 873 (m), 809 (m), 782 (m); HRMS (ESI) Calcd for $C_{16}H_{18}IO_2^+$ $[M+H]^+$ 369.0346; found 369.0340.

10.4.3. Preparation of Ligands

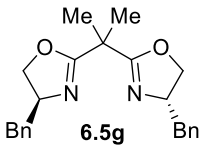
BOX ligands **6.5b**, **6.5f**, **6.5g** and **6.5j** were directly obtained from chemical suppliers.



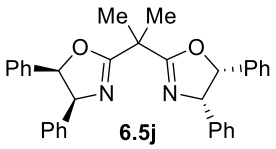
6.5b



6.5f

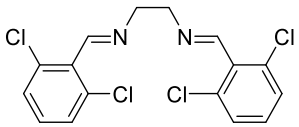


6.5g



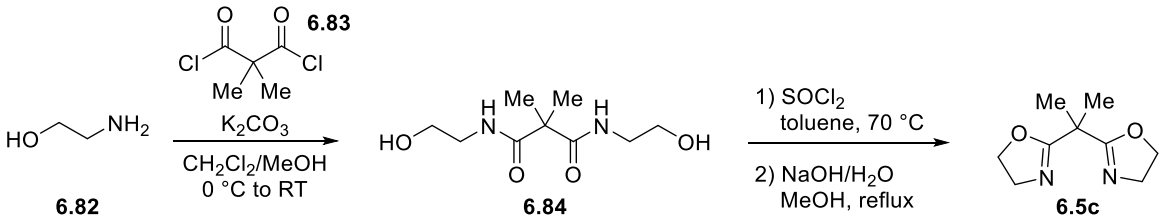
6.5j

The synthesis of ligand **6.5a** has been reported in section 10.2.



6.5a

2,2'-(Propane-2,2-diyl)bis(4,5-dihydrooxazole) (6.5c)



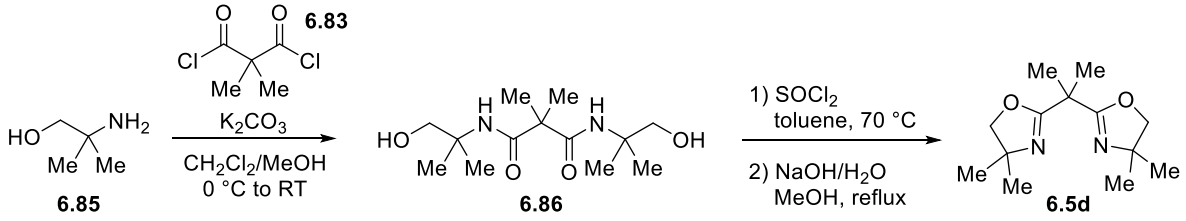
Following a reported procedure,[430] K_2CO_3 (2.76 g, 20.0 mmol, 4.0 equiv) was suspended in DCM (50 mL) at 0 °C under argon and then ethanolamine (**6.82**) (0.63 mL, 10.5 mmol, 2.1 equiv) was added. A solution of dimethylmalonyl dichloride (**6.83**) (0.660 mL, 5.00 mmol, 1.0 equiv) in DCM (10 mL) was added dropwise to the cold mixture. The mixture was allowed to warm to room temperature and stirred for 16 h. MeOH (50 mL) was added and the mixture was stirred for 2 h. The whole reaction mixture was filtered through Celite (5 g) and rinsed twice with MeOH (2 × 10 mL). The solvent was removed under reduce pressure. The crude *N*,*N*'-bis(2-hydroxyethyl)-2,2-dimethylmalonamide (**6.84**) was obtained as a white residue (1.12 g) and was used directly into the next step without further purification.

The crude bisamide **6.84** was dissolved in toluene (30 mL) and heated to 70 °C under argon. Thionyl chloride (1.46 mL, 20.0 mmol, 4.0 equiv) was added in one portion and the resulting mixture was stirred at 70 °C for 5 h. The reaction was cooled to 0 °C and quenched with a saturated $NaHCO_3$ solution (15 mL). The mixture was extracted with DCM (5 × 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to furnish a pale yellow oil. The residue was dissolved in 17.0 mL of a 5% methanolic NaOH solution (0.830 g of NaOH was completely dissolved in 0.850 mL H_2O and then diluted with 16.1 mL MeOH) and heated to reflux for 2 h under argon. The solvent was removed under reduced pressure and the resulting residue was partitioned between DCM (10 mL) and H_2O (10 mL). The aqueous phase was extracted with DCM (5 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to furnish afford 2,2'-(propane-2,2-diyl)bis(4,5-dihydrooxazole) (**6.5c**) as a pale yellow wax (412 mg, 2.26 mmol, 45 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (t, *J* = 9.5 Hz, 4H, 2 x

[430] L. Miao, I. Haque, M. R. Manzoni, W. S. Tham, S. R. Chemler, *Org. Lett.* **2010**, *12*, 4739.

CH_2O), 3.87 (t, *J* = 9.5 Hz, 4H, 2 x CH_2N), 1.51 (s, 6H, 2 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 68.2, 54.5, 38.8, 24.4. The values of the NMR spectra are in accordance with reported literature data.[430]

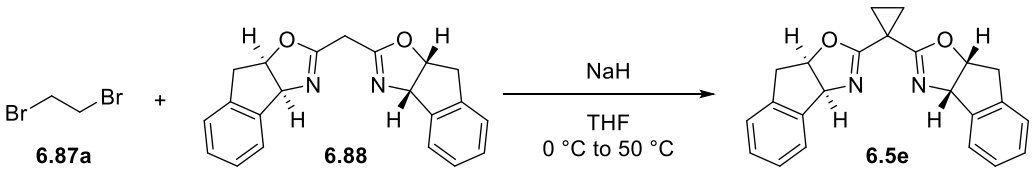
2,2'-(propane-2,2-diyl)bis(4,4-dimethyl-4,5-dihydrooxazole) (6.5d)



Following a reported procedure,[431] 2-amino-2-methylpropan-1-ol (**6.85**) (0.952 mL, 10.5 mmol, 2.1 equiv) was added to a suspension of K_2CO_3 (2.76 g, 20.0 mmol, 4.0 equiv) DCM (50 mL) at 0 °C under argon. A solution of dimethylmalonyl dichloride (**6.83**) (0.660 mL, 5.00 mmol, 1.0 equiv) in DCM (10 mL) was added dropwise to the cold mixture. The mixture was allowed to warm to room temperature and stirred for 16 h. MeOH (50 mL) was added and the mixture was stirred for 2 h. The whole reaction mixture was filtered through Celite (5 g) and rinsed twice with MeOH (2 × 10 mL). The solvent was removed under reduce pressure. The crude *N*,*N*'-bis(1-hydroxy-2-methylpropan-2-yl)-2,2-dimethylmalonamide (**6.86**) was obtained as a white residue (1.42 g) and was used directly into the next step without further purification.

The crude bisamide **6.86** was dissolved in toluene (30 mL) and heated to 70 °C under argon. Thionyl chloride (1.50 mL, 20.0 mmol, 4.0 equiv) was added in one portion and the resulting mixture was stirred at 70 °C for 5 h. The reaction was cooled to 0 °C and quenched with a saturated $NaHCO_3$ solution (15 mL). The mixture was extracted with DCM (5 × 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to furnish a pale yellow oil. The residue was dissolved in 17.0 mL of a 5% methanolic NaOH solution (0.830 g of NaOH was completely dissolved in 0.850 mL H_2O and then diluted with 16.1 mL MeOH) and heated to reflux for 2 h under argon. The solvent was removed under reduced pressure and the resulting residue was partitioned between DCM (10 mL) and H_2O (10 mL). The aqueous layer was extracted with DCM (5 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to furnish afford 2,2'-(propane-2,2-diyl)bis(4,4-dimethyl-4,5-dihydrooxazole) (**6.5d**) as a pale yellow wax (471 mg, 2.00 mmol, 40 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 4H, 2 x CH_2O), 1.49 (s, 6H, 2 x CH_3), 1.27 (s, 12H, 4 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 79.4, 67.0, 38.2, 28.0, 25.4. The values of the NMR spectra are in accordance with reported literature data.[432]

(3a*R*,3a'*R*,8a*S*,8a'*S*)-2,2'-(Cyclopropane-1,1-diyl)bis(8,8a-dihydro-3aH-indeno[1,2- d]oxazole) (6.5e)



Following a reported procedure,[433] to a solution of dihydrobisoxazoline **6.88** (330 mg, 1.00 mmol, 1.00 equiv) in THF (4 mL), was added NaH (60% in mineral oil, 120 mg, 3.00 mmol, 3.00 equiv) in portions at 0 °C. After complete addition, the mixture was stirred for 30 min at that temperature. A solution of dibromoethane (**6.87a**) (130 µL, 1.50 mmol, 1.50 equiv) in THF (1 mL) was then added dropwise at 0

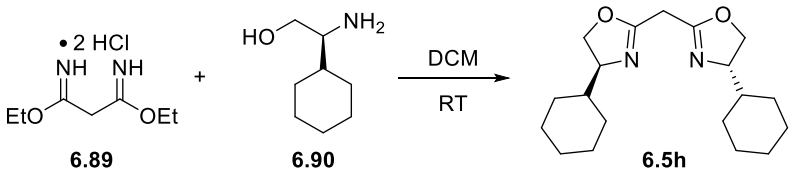
[431] M. C. Paderes, S. R. Chemler, *Eur. J. Org. Chem.* **2011**, *2011*, 3679.

[432] K. M. Partridge, I. A. Guzei, T. P. Yoon, *Angew. Chem. Int. Ed.* **2010**, *49*, 930.

[433] M. P. Sibi, M. Liu, *Org. Lett*. **2000**, *2*, 3393.

°C over 10 minutes. After the addition, the ice bath was removed and the reaction mixture was heated to 50 °C for an additional 2 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 25:75 as eluent to furnish (3a*R*,3a'*R*,8a*S*,8a'*S*)-2,2'-(cyclopropane-1,1-diyl)bis(8,8adihydro-3aH-indeno[1,2-d]oxazole) (**6.5e**) as a white solid (220 mg, 0.617 mmol, 62%). Rf = 0.50 (MeOH/EtOAc 1:9), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 2H, Ar*H*), 7.25 – 7.17 (m, 6H, Ar*H*), 5.52 (d, *J* = 7.9 Hz, 2H, 2 x N-C*H*), 5.41 – 5.23 (m, 2H, 2 x O-C*H*), 3.38 (dd, *J* = 17.9, 7.0 Hz, 2H, 2 x ArCH_a), 3.19 (dd, *J* = 17.9, 1.9 Hz, 2H, 2 x ArCH_b), 1.44 – 1.15 (m, 4H, CH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 141.9, 139.8, 128.5, 127.5, 125.7, 125.3, 83.5, 76.5, 39.8, 18.5, 16.0. The characterization data corresponded to the reported values.[434]

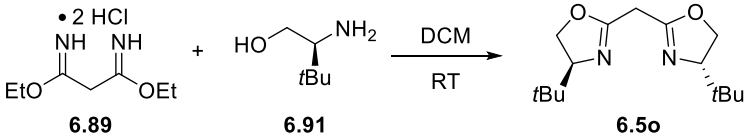
Bis((*S*)-4-cyclohexyl-4,5-dihydrooxazol-2-yl)methane (6.5h)



6.89 **6.90** **6.5h**

To a solution of (*R*)-2-amino-2-cyclohexylethanol (**6.90**) (0.260 g, 1.5 mmol, 2.0 equiv) in DCM (4.7 mL) was added diethyl malonimidate dihydrochloride (**6.89**) (0.173 g, 0.75 mmol, 1.0 equiv). The resulting cloudy solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (5 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography using MeOH/EtOAc/penatne 2:20:80 to afford bis((*S*)-4-cyclohexyl-4,5-dihydrooxazol-2-yl)methane (**6.5h**) as a white solid (0.100 g, 0.314 mmol, 42%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.23 (dd, *J* = 9.7, 8.3 Hz, 2H, 2 x OCH_a), 3.97 (t, *J* = 8.2 Hz, 2H, 2 x N-C*H*), 3.85 (ddd, *J* = 9.6, 8.1, 6.6 Hz, 2H, 2 x OCH_b), 3.23 (d, *J* = 1.2 Hz, 2H, O(C=N)CH_2), 1.90 – 0.82 (m, 22H, *cyclohexyl*). The values of the NMR spectra are in accordance with reported literature data.[435]

(4*S*,4'*S*)-2,2'-(Cyclopropane-1,1-diyl)bis(4-(tert-butyl)-4,5-dihydrooxazole) (6.5o)



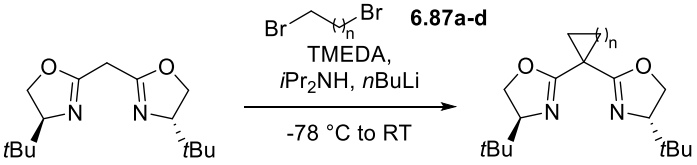
6.89 **6.91** **6.5o**

Following a reported procedure,[311] to a solution of (*S*)-*tert*-leucinol (**6.91**) (0.94 g, 8.0 mmol, 2.0 equiv) in DCM (40 mL) was added diethyl malonimidate dihydrochloride (**6.89**) (0.93 g, 4.0 mmol, 1.0 equiv). The resulting cloudy solution was stirred at room temperature for 36 h. The reaction mixture was diluted with water (8 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and concentrated. The resulting oily residue was distilled bulb-to-bulb (Kugelrohr distillation, 150 °C at 0.2 mbar) to afford bis((*S*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)methane (**6.5o**) as a white solid (0.600 g, 2.84 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (dd, *J* = 10.1, 8.7 Hz, 2H, 2 x OCH_a), 4.02 (dd, *J* = 8.7, 7.7 Hz, 2H, 2 x C(CH_3)$_3$C*H*), 3.81 (ddt, *J* = 10.1, 7.8, 1.1 Hz, 2H, 2 x OCH_b), 3.27 (t, *J* = 1.2 Hz, 2H, O(C=N)CH_2), 0.82 (s, 18H, 2 x C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 76.0, 69.1, 34.0, 28.4, 26.0. The values of the NMR spectra are in accordance with reported literature data.[311]

[434] A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc*. **2014**, *136*, 14365.

[435] T. Yong, H. Jianglin, X. Zuowei, K. Qikai, L. Qiongjie, C. Yujing (Shangai Inst Organic Chem), PCT Int. Appl. CN104926747 (A), **2015**.

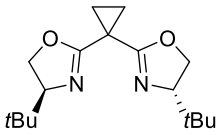
General procedure C: Synthesis of BOX ligands 6.5k-n[311]



6.5o **6.5k-n**

Following a reported procedure,[311] to a solution of bis((*S*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)methane (**6.5o**) (75 mg, 0.28 mmol, 1.0 equiv) in THF (5 mL) in a 20 mL microwave vial, was added TMEDA (85 µL, 0.56 mmol, 2.0 equiv) and *i*Pr_2NH (40 mL, 0.28 mmol, 1.0 equiv). The solution was cooled to -78 °C and *n*BuLi (0.38 mL, 1.5 M in hexane, 0.56 mmol, 2.0 equiv) was added. The reaction mixture was warmed to -20 °C and stirred at that temperature for 30 minutes. The solution was cooled back to -78 °C and dibromoalkane **6.87a-d** (0.28 mmol, 2.0 equiv) was added. After the addition, the cold bath was removed and the reaction mixture was allowed to stir at room temperature for an additional 16 h. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl (2.5 mL) and diluted with water (2 mL) to dissolve the resulting salts. The mixture was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated. The resulting oily residue was purified by column chromatography using EtOAc/pentane 1:2 to 1:1 as eluent to afford the corresponding spirocyclic BOX ligand **6.5k-n**.

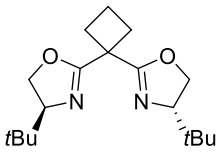
(4*S*,4'*S*)-2,2'-(Cyclopropane-1,1-diyl)bis(4-(*tert*-butyl)-4,5-dihydrooxazole) (6.5k)



6.5k

Following the general procedure **C**, **6.5k** was obtained as a white solid (42 mg, 0.14 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (dd, *J* = 10.0, 8.6 Hz, 2H, 2 x OCH_a), 4.10 (dd, *J* = 8.7, 7.3 Hz, 2H, 2 x C$(CH_3)_3$C*H*), 3.82 (dd, *J* = 10.0, 7.2 Hz, 2H, 2 x OCH_b), 1.52 – 1.47 (m, 2H, 2 x CH_a of CyP), 1.30 – 1.24 (m, 2H, 2 x CH_b of CyP), 0.86 (s, 18H, 2 x C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 75.2, 69.1, 33.8, 25.7, 18.2, 15.1. The values of the NMR spectra are in accordance with reported literature data.[311]

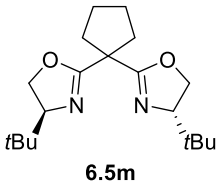
(4*S*,4'*S*)-2,2'-(Cyclobutane-1,1-diyl)bis(4-(*tert*-butyl)-4,5-dihydrooxazole) (6.5l)



6.5l

Following the general procedure **C**, **6.5l** was obtained as a white solid (30 mg, 0.10 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 – 4.07 (m, 4H, 2 x OCH_a *and* 2 x C$(CH_3)_3$C*H*), 3.82 (dd, *J* = 10.0, 7.2 Hz, 2H, 2 x OCH_b), 1.52 – 1.47 (m, 2H, *cyclobutyl*), 1.30 – 1.24 (m, 4H, *cyclobutyl*), 0.85 (s, 18H, 2 x C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 75.6, 69.5, 42.3, 34.1, 30.5, 25.9, 16.9. The values of the NMR spectra are in accordance with reported literature data.[311]

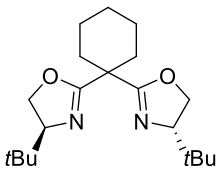
(4*S*,4'*S*)-2,2'-(Cyclopentane-1,1-diyl)bis(4-(*tert*-butyl)-4,5-dihydrooxazole) (6.5m)



6.5m

Following the general procedure **C**, **6.5m** was obtained as a white solid (54 mg, 0.17 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 – 4.00 (m, 4H, 2 x OCH_a *and* 2 x C$(CH_3)_3$C*H*), 3.85 (dd, *J* = 10.1, 7.1 Hz, 2H, 2 x OCH_b), 2.45 – 2.31 (m, 2H, 2 x C-CH_2), 2.18 – 2.07 (m, 2H, 2 x C-CH_2), 1.81 – 1.63 (m, 4H, CH_2-CH_2), 0.87 (s, 18H, 2 x C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 75.5, 69.2, 49.3, 35.6, 34.1, 25.9, 25.2. The values of the NMR spectra are in accordance with reported literature data.[311]

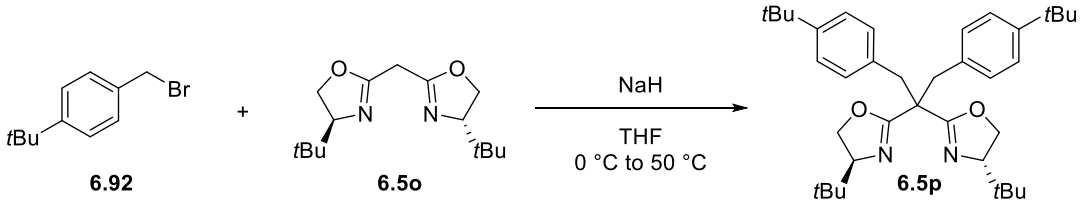
(4*S*,4'*S*)-2,2'-(Cyclohexane-1,1-diyl)bis(4-(*tert*-butyl)-4,5-dihydrooxazole) (6.5n)



6.5n

Following the general procedure **C**, **6.5n** was obtained as a white solid (50 mg, 0.15 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (dd, *J* = 10.2, 8.6 Hz, 2H, 2 x OC*H*$_a$), 4.05 (dd, J = 8.6, 7.2 Hz, 2H, C(CH$_3$)$_3$C*H*), 3.87 (dd, *J* = 10.2, 7.2 Hz, 2H, 2 x OC*H*$_b$), 2.11 (ddd, *J* = 12.7, 7.8, 3.8 Hz, 2H, *cyclohexyl*), 1.94 (ddd, *J* = 13.1, 8.1, 3.2 Hz, 2H, *cyclohexyl*), 1.74 – 1.59 (m, 2H, *cyclohexyl*), 1.54 – 1.39 (m, 4H, *cyclohexyl*), 0.88 (s, 18H, 2 x C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 75.7, 68.7, 43.3, 34.0, 32.7, 26.0, 25.6, 22.7.The values of the NMR spectra are in accordance with reported literature data.[311]

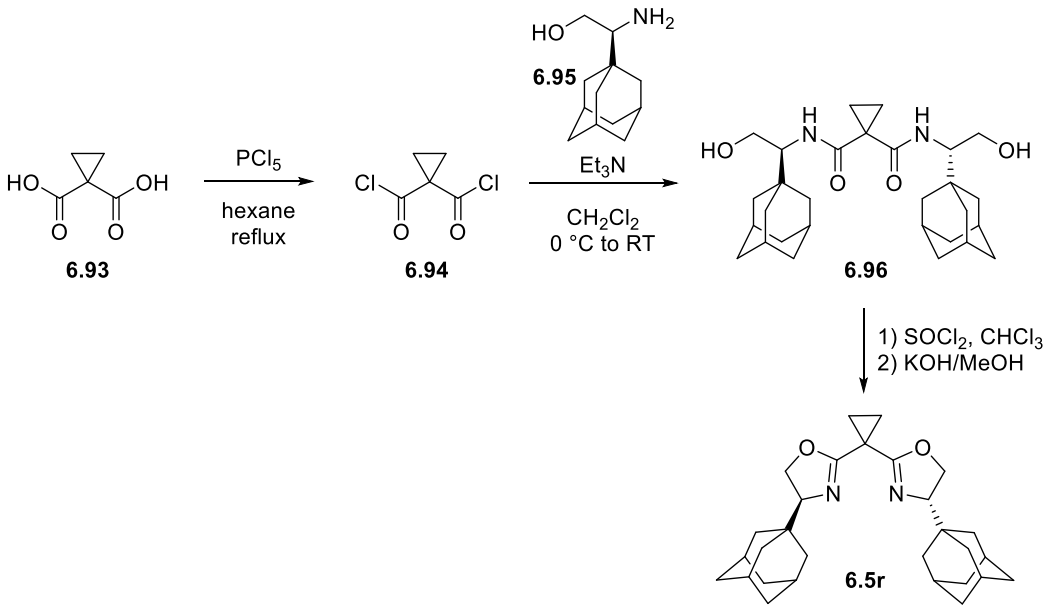
(4*S*,4'*S*)-2,2'-(1,3-bis(4-(*tert*-butyl)phenyl)propane-2,2-diyl)bis(4-(*tert*-butyl)-4,5-dihydrooxazole) (6.5p)



6.92 **6.5o** **6.5p**

To a solution of bis((*S*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)methane (**6.5o**) (87 mg, 0.325 mmol, 1.0 equiv) in THF (10 mL) in a 20 mL microwave vial, was added NaH (60% in mineral oil, 94mg, 2.340 mmol, 7.2 equiv) in portion. After 10 min, the reaction mixture was cooled to 0 °C and 1-(bromomethyl)-4-(*tert*-butyl)benzene (**6.92**) (0.300 mL, 1.625 mmol, 5.0 equiv) in THF (5 mL) was added dropwise. The resulting mixture was stirred for 6 h at 50 °C. The reaction was cooled to room temperature and quenched with sat. aq. NH_4Cl (10mL), then water (30mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 5:95 as eluent to furnish (4*S*,4'*S*)-2,2'-(1,3-bis(4-(*tert*-butyl)phenyl)propane-2,2-diyl)bis(4-(*tert*-butyl)-4,5-dihydrooxazole) (**6.5p**) as a colorless solid (127 mg, 0.227 mmol, 70%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.34 – 7.26 (m, 4H, Ar*H*), 7.22 – 7.14 (m, 4H, Ar*H*), 4.14 (dd, *J* = 10.2, 8.6 Hz, 2H, 2 x OC*H*$_a$), 3.98 (t, *J* = 8.5 Hz, 2H, C(CH$_3$)$_3$C*H*), 3.75 (dd, *J* = 10.1, 8.3 Hz, 2H, 2 x OC*H*$_b$), 3.32 (d, *J* = 14.1 Hz, 2H, C*H*$_2$-Ar), 3.05 (d, *J* = 14.1 Hz, 2H, C*H*$_2$-Ar), 1.31 (s, 18H, 2 x Ar-*t*Bu), 0.81 (s, 18H, 2 x CH-*t*Bu); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 166.6, 149.9, 134.7, 130.8, 125.4, 76.2, 68.9, 48.9, 38.6, 34.8, 34.2, 31.7, 26.1.The values of the NMR spectra are in accordance with reported literature data.[344]

(*S*,*S*,*S*,4*S*,4'*S*)-2,2'-(cyclopropane-1,1-diyl)bis(4-((3*S*,5*S*,7*S*)-adamantan-1-yl)-4,5-dihydrooxazole) (6.5r)



Following a reported procedure,[436] phosphorus pentachloride (4.2 g, 20.0 mmol, 4.0 equiv) was added in one portion to a solution of cyclopropane-1,1-dicarboxylic acid (**6.93**) (650 mg, 5.0 mmol, 1.0 equiv), in anhydrous hexane (20 mL). The mixture was stirred and heated at reflux for 12 h. Then, the reaction solution was cooled and concentrated under vacuum to remove the solvent and $POCl_3$ by-product. Anhydrous hexane was added to the residue and the resulting mixture was filtered and concentrated to afford cyclopropane-1,1-dicarbonyl dichloride (**6.94**) as a colorless oil (590 mg, 3.53 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 4H, 2 x C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 23.1, 21.5. The values of the NMR spectra are in accordance with reported literature data.[436]

A solution of cyclopropane-1,1-dicarbonyl dichloride (**6.94**) (41.7 mg, 0.250 mmol, 1.0 equiv) in dry CH_2Cl_2 (1.25 mL) was added dropwise to a solution of chiral (*S*)-2-((3*S*,5*S*,7*S*)-adamantan-1-yl)-2-aminoethanol (**6.95**) (98 mg, 0.5 mmol, 2.0 equiv) and triethylamine (87 µL, 0.625 mmol, 2.5 equiv) in dry CH_2Cl_2 (3.75 mL) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Then, the mixture was successively washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine, then dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using MeOH/CH_2Cl_2 5:95 as eluent to afford *N,N*'-bis((*S*)-1-((3*S*,5*S*,7*S*)-adamantan-1-yl)-2-hydroxyethyl)cyclopropane-1,1-dicarboxamide (**6.96**) as a white solid (82 mg, 0.169 mmol, 68%). R_f = 0.20 (MeOH/DCM) 5:95, *p*-anisaldehyde; M.p. 216 – 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 9.6 Hz, 2H, 2 x N*H*), 3.88 (dd, *J* = 11.2, 3.6 Hz, 2H, 2 x OCH_a), 3.74 (td, *J* = 9.3, 3.6 Hz, 2H, 2 x OCH_b), 3.56 (dd, *J* = 11.2, 9.0 Hz, 2H, 2 x HNC*H*), 2.62 (br s, 2H, 2 x O*H*), 2.04 – 1.91 (m, 6H, C-$H_{adamantyl}$), 1.80 – 1.47 (m, 26H, C-$H_{adamantyl\ +\ cyclopropyl}$), 1.24 (q, *J* = 4.2 Hz, 2H, C-$H_{cyclopropyl}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 61.5, 60.4, 39.2, 37.0, 35.7, 30.6, 28.4, 15.4; IR (ν_{max}, cm^{-1}) 3674 (w), 3310 (w), 2987 (s), 2971 (s), 2900 (s), 2359 (w), 2340 (w), 1661 (w), 1627 (m), 1542 (m), 1406 (m), 1394 (m), 1230 (w), 1196 (w), 1075 (s), 1066 (s), 1050 (s), 1030 (s), 896 (w), 732 (m), 655 (w); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{45}N_2O_4^+$ 485.3374; Found 485.3383.

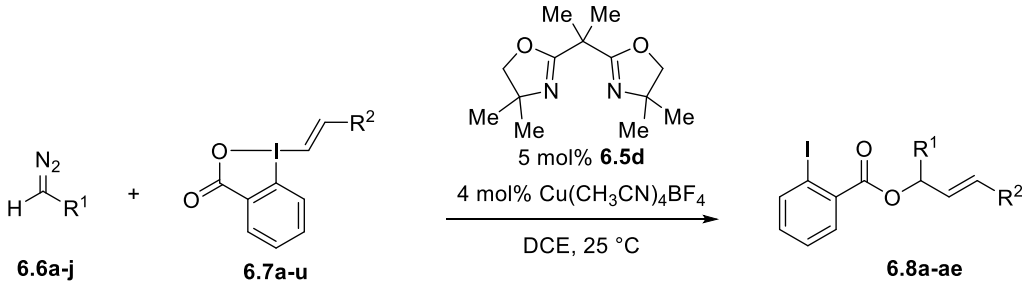
A solution of thionyl chloride (44 µL, 0.600 mmol, 4.0 equiv) in $CHCl_3$ (1.0 mL) was added dropwise to a solution of *N,N*'-bis((*S*)-1-((3*S*,5*S*,7*S*)-adamantan-1-yl)-2-hydroxyethyl)cyclopropane-1,1-

[436] H. Zheng, M. P. Doyle, *Angew. Chem. Int. Ed.* **2019**, *58*, 12502.

dicarboxamide (**6.96**) (72.7 mg, 0.15 mmol, 1.0 equiv) in $CHCl_3$ (1.0 mL) at 0 °C. The reaction mixture was stirred at 70 °C for 6 h, then cooled to room temperature. The reaction mixture was concentrated under reduced pressure to remove the $SOCl_2$ then dissolved in a solution of potassium hydroxide (84 mg, 1.50 mmol, 10 equiv) in MeOH (1.5 mL). The suspension was stirred at reflux for 6 h. Water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phase was washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/pentane 33:67 as eluent to furnish (*S*,*S*,*S*,4*S*,4'*S*)-2,2'-(cyclopropane-1,1-diyl)bis(4-((3*S*,5*S*,7*S*)-adamantan-1-yl)-4,5-dihydrooxazole) (**6.5r**) as a white solid (34 mg, 0.076 mmol, 51%). R_f = 0.23 (EtOAc/pentane 33:67), $KMnO_4$; M.p. 143 – 145 °C; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.19 – 4.12 (m, 2H, 2 x OCH_a), 4.07 (dd, *J* = 10.0, 8.6 Hz, 2H, 2 x N-C*H*), 3.61 (dd, *J* = 10.0, 7.6 Hz, 2H, 2 x OCH_b), 2.03 – 1.91 (m, 6H, C-$H_{adamantyl}$), 1.75 – 1.52 (m, 18H, C-$H_{adamantyl}$), 1.44 – 1.31 (m, 6H, C-$H_{adamantyl}$), 1.31 – 1.18 (m, 4H, 2 x C$H_{2cycloprpyl}$); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.4, 76.1, 68.1, 38.9, 37.7, 36.1, 30.0, 18.8, 14.9; IR (ν_{max}, cm^{-1}) 2900 (s), 2885 (s), 2846 (m), 1656 (s), 1449 (w), 1363 (m), 1348 (m), 1318 (w), 1278 (w), 1248 (w), 1171 (s), 1145 (w), 1117 (m), 1102 (m), 977 (m), 934 (m), 902 (m), 730 (w); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{41}N_2O_2^+$ 449.3163; Found 449.3157.

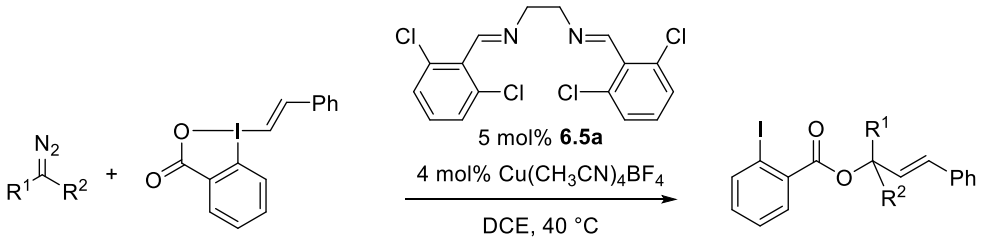
10.4.4. Oxy-Vinylation Reaction

General procedure D: Oxy-vinylation of unsubstituted diazo compound



Under inert atmosphere, a catalytic solution was prepared by mixing $Cu(CH_3CN)_4BF_4$ (12.6 mg, 40.0 µmol) and 2,2'-(propane-2,2-diyl)bis(4,4-dimethyl-4,5-dihydrooxazole) (**6.5d**) (11.9 mg, 50.0 µmol) in DCE (5.0 mL) at 25 °C for 1 h. 1.0 mL of the catalytic solution was then added to a suspension of VBX (**6.7a-u**) (0.200 mmol, 1.00 equiv) and diazo compound (**6.6a-j**) (0.400 mmol, 2.00 equiv) in DCE (4.0 mL). The reaction mixture was stirred at 25 °C. After the reaction was completed (monitored by TLC, EtOAc/pentane 5:95 and MeOH/DCM 5:95), the solvent was removed under reduced pressure and the resulting crude oil was purified by column chromatography (EtOAc/pentane) directly without further work-up to afford the corresponding product (**6.8a-ae**).

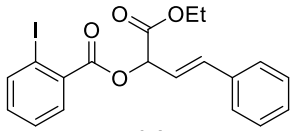
General procedure E: Oxy-vinylation of substituted diazo compound



6.6m-q **6.7a** **6.8af-ai**

Under inert atmosphere, a catalytic solution was prepared by mixing $Cu(CH_3CN)_4BF_4$ (12.6 mg, 40.0 µmol) and (1*E*,1'*E*)-*N*,*N*'-(ethane-1,2-diyl)bis(1-(2,6-dichlorophenyl)methanimine) (**6.5a**) (18.7 mg, 50.0 µmol) in DCE (5.0 mL) at 25 °C for 1 h. 1.0 mL of the catalytic solution was then added to a suspension of Ph-VBX (**6.7a**) (0.200 mmol, 1.00 equiv) and diazo compound (**6.8af-ai**) (0.400 mmol, 2.00 equiv) in DCE (4.0 mL). The reaction mixture was stirred at 40 °C. After the reaction was completed (monitored by TLC, EtOAc/pentane 5:95 and MeOH/DCM 5:95), the solvent was removed under reduced pressure and the resulting crude oil was purified by column chromatography (EtOAc/pentane, ratio indicated in the R_f measurement) directly without further work-up to afford the corresponding product (**6.8af-ai**).

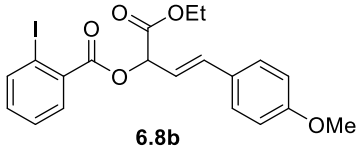
(*E*)-1-Ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (6.8a)



6.8a

Following general procedure **D**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8a**) as a colorless oil (83 mg, 0.19 mmol, 95%). R_f = 0.24 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (ddd, *J* = 10.8, 7.9, 1.4 Hz, 2H, Ar*H*), 7.49 – 7.41 (m, 3H, Ar*H*), 7.38 – 7.27 (m, 3H, Ar*H*), 7.19 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H, Ar*H*), 6.93 (dd, *J* = 15.9, 1.2 Hz, 1H, CHC*H*Ph), 6.38 (dd, *J* = 15.9, 7.1 Hz, 1H, C*H*CHPh), 5.87 (dd, *J* = 7.1, 1.3 Hz, 1H, OC*H*CC), 4.29 (qd, *J* = 7.1, 2.4 Hz, 2H, OCH_2CH_3), 1.32 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 165.6, 141.6, 135.8, 135.7, 134.2, 133.2, 131.7, 128.8, 128.8, 128.1, 127.0, 120.7, 94.6, 74.3, 62.2, 14.3; IR (ν_{max}, cm^{-1}) 2978 (m), 2902 (m), 1735 (s), 1582 (w), 1451 (m), 1395 (m), 1369 (m), 1278 (s), 1258 (s), 1199 (m), 1129 (m), 1098 (s), 1044 (s), 1016 (s), 966 (m), 863 (m), 764 (s), 750 (s); HRMS (ESI) Calcd for $C_{19}H_{17}INaO_4^+$ $[M+Na]^+$ 459.0064; found 459.0070.

(*E*)-1-Ethoxy-4-(4-methoxyphenyl)-1-oxobut-3-en-2-yl 2-iodobenzoate (6.8b)

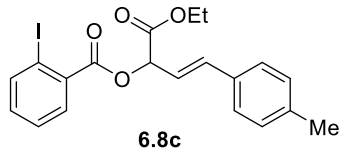


6.8b

Following general procedure **D**, starting from (*E*)-1-(4-methoxystyryl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7b**) (76.0 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-4-(4-methoxyphenyl)-1-oxobut-3-en-2-yl 2-iodobenzoate (**6.8b**) as a colorless oil (76 mg, 0.16 mmol, 81%). R_f = 0.12 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.95 (m, 2H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.40 – 7.34 (m, 2H, Ar*H*), 7.18 (ddd, *J* = 7.9, 7.4,

1.7 Hz, 1H, Ar*H*), 6.90 – 6.82 (m, 3H, Ar*H* and CHC*H*Ph), 6.23 (dd, *J* = 15.9, 7.4 Hz, 1H, C*H*CHPh), 5.83 (dd, *J* = 7.4, 1.2 Hz, 1H, OC*H*CC), 4.28 (qd, *J* = 7.1, 3.0 Hz, 2H, OC*H*$_2$CH$_3$), 3.81 (s, 3H, ArOC*H*$_3$), 1.31 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 165.7, 160.1, 141.6, 135.6, 134.2, 133.2, 131.7, 128.4, 128.3, 128.1, 118.3, 114.2, 94.5, 74.6, 62.1, 55.5, 14.3; IR (ν_{max}, cm^{-1}) 2933 (m), 2862 (w), 2091 (w), 1731 (s), 1607 (m), 1582 (w), 1511 (s), 1465 (m), 1288 (m), 1248 (s), 1194 (m), 1175 (s), 1128 (m), 1096 (s), 1015 (s), 969 (m), 824 (m); HRMS (ESI) Calcd for $C_{20}H_{19}INaO_5^+$ [M+Na]$^+$ 489.0169; found 489.0169.

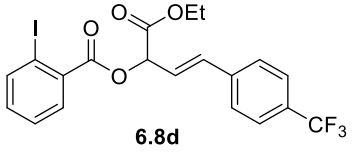
(*E*)-1-Ethoxy-1-oxo-4-(*p*-tolyl)but-3-en-2-yl 2-iodobenzoate (6.8c)



6.8c

Following general procedure **D**, starting from (*E*)-1-(4-methylstyryl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7c**) (72.8 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxo-4-(*p*-tolyl)but-3-en-2-yl 2-iodobenzoate (**6.8c**) as a colorless oil (83 mg, 0.18 mmol, 92%). R_f = 0.26 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (ddd, *J* = 9.7, 7.9, 1.4 Hz, 2H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.37 – 7.29 (m, 2H, Ar*H*), 7.23 – 7.12 (m, 3H, Ar*H*), 6.93 – 6.85 (m, 1H, CHC*H*Ph), 6.32 (dd, *J* = 15.9, 7.2 Hz, 1H, C*H*CHPh), 5.85 (dd, *J* = 7.2, 1.3 Hz, 1H, OC*H*CC), 4.28 (qd, *J* = 7.1, 2.2 Hz, 2H, OC*H*$_2$CH$_3$), 2.35 (s, 3H, ArC*H*$_3$), 1.31 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 165.6, 141.6, 138.8, 135.8, 134.2, 133.2, 132.9, 131.7, 129.5, 128.1, 126.9, 119.6, 94.5, 74.5, 62.1, 21.4, 14.3; IR (ν_{max}, cm^{-1}) 2979 (m), 2906 (m), 1732 (s), 1462 (m), 1429 (m), 1372 (m), 1294 (s), 1239 (s), 1198 (s), 1127 (s), 1098 (s), 1041 (s), 1014 (s), 965 (s), 855 (m), 810 (m), 740 (s); HRMS (ESI) Calcd for $C_{20}H_{19}INaO_4^+$ [M+Na]$^+$ 473.0220; found 473.0220.

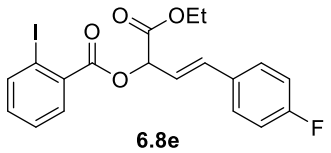
(*E*)-1-Ethoxy-1-oxo-4-(4-(trifluoromethyl)phenyl)but-3-en-2-yl 2-iodobenzoate (6.8d)



6.8d

Following general procedure **D**, starting from (*E*)-1-(4-(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7d**) (84.0 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxo-4-(4-(trifluoromethyl)phenyl)but-3-en-2-yl 2-iodobenzoate (**6.8d**) as a colorless oil (73 mg, 0.15 mmol, 72%). R_f = 0.22 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (ddd, *J* = 15.1, 7.9, 1.4 Hz, 2H, Ar*H*), 7.60 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.53 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.46 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.24 – 7.17 (m, 1H, Ar*H*), 6.96 (dd, *J* = 16.0, 1.4 Hz, 1H, CHC*H*Ph), 6.48 (dd, *J* = 16.0, 6.6 Hz, 1H, C*H*CHPh), 5.91 (dd, *J* = 6.7, 1.4 Hz, 1H, OC*H*CC), 4.30 (qd, *J* = 7.1, 2.3 Hz, 2H, OC*H*$_2$CH$_3$), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 165.5, 141.7, 139.2, 134.0, 133.9, 133.4, 131.7, 130.5 (q, *J* = 32.6 Hz), 128.2, 127.2, 125.8 (q, *J* = 3.9 Hz), 124.1 (q, *J* = 272.0 Hz), 123.5, 94.6, 73.8, 62.4, 14.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7; IR (ν_{max}, cm^{-1}) 2979 (m), 2914 (m), 1732 (m), 1466 (w), 1415 (m), 1374 (w), 1325 (s), 1243 (s), 1196 (m), 1166 (m), 1108 (s), 1067 (s), 1047 (s), 1014 (s), 969 (m), 857 (m), 822 (m), 742 (s); HRMS (ESI) Calcd for $C_{20}H_{16}F_3INaO_4^+$ [M+Na]$^+$ 526.9938; found 526.9951.

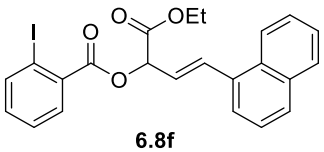
(*E*)-1-Ethoxy-4-(4-fluorophenyl)-1-oxobut-3-en-2-yl 2-iodobenzoate (6.8e)



6.8e

Following general procedure **D**, starting from (*E*)-1-(4-fluorostyryl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7e**) (73.6 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-4-(4-fluorophenyl)-1-oxobut-3-en-2-yl 2-iodobenzoate (**6.8e**) as a colorless oil (60 mg, 0.13 mmol, 66%). R_f = 0.22 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.99 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar*H*), 7.50 – 7.36 (m, 3H, Ar*H*), 7.19 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.08 – 6.99 (m, 2H, Ar*H*), 6.93 – 6.84 (m, 1H, CHC*H*Ph), 6.30 (dd, *J* = 15.9, 7.1 Hz, 1H, C*H*CHPh), 5.85 (dd, *J* = 7.1, 1.3 Hz, 1H, OC*H*CC), 4.28 (qd, *J* = 7.1, 3.2 Hz, 2H, OCH_2CH_3), 1.32 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 165.6, 163.0 (d, *J* = 248.5 Hz), 141.6, 134.6, 134.1, 133.3, 131.9 (d, *J* = 3.3 Hz), 131.7, 128.7 (d, *J* = 8.2 Hz), 128.2, 120.5 (d, *J* = 2.2 Hz), 115.8 (d, *J* = 21.7 Hz), 94.5, 74.2, 62.2, 14.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.7; IR (ν_{max}, cm^{-1}) 2981 (m), 2932 (w), 1734 (s), 1601 (m), 1585 (m), 1509 (s), 1466 (m), 1423 (m), 1376 (m), 1290 (s), 1211 (s), 1131 (s), 1104 (s), 1016 (s), 967 (m), 859 (m), 826 (m), 740 (s), 716 (m); HRMS (ESI) Calcd for $C_{19}H_{16}FINaO_4^+$ $[M+Na]^+$ 476.9970; found 476.9971.

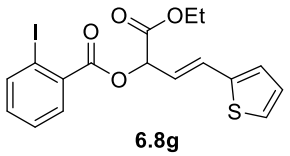
(*E*)-1-Ethoxy-4-(naphthalen-1-yl)-1-oxobut-3-en-2-yl 2-iodobenzoate (6.8f)



6.8f

Following general procedure **D**, starting from (*E*)-1-(2-(naphthalen-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7f**) (80.0 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-4-(naphthalen-1-yl)-1-oxobut-3-en-2-yl 2-iodobenzoate (**6.8f**) as a white solid (79 mg, 0.16 mmol, 81%). M.p. 59 – 61 °C; R_f = 0.18 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.09 (m, 1H, Ar*H*), 8.04 (dt, *J* = 7.8, 1.4 Hz, 2H, Ar*H*), 7.91 – 7.78 (m, 2H, Ar*H*), 7.71 (d, *J* = 15.7 Hz, 1H, CHC*H*Ph), 7.64 (dt, *J* = 7.2, 1.0 Hz, 1H, Ar*H*), 7.58 – 7.42 (m, 4H, Ar*H*), 7.20 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H, Ar*H*), 6.44 (dd, *J* = 15.7, 6.9 Hz, 1H, C*H*CHPh), 6.01 (dd, *J* = 6.9, 1.4 Hz, 1H, OC*H*CC), 4.33 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 1.35 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 165.7, 141.6, 134.2, 133.7, 133.5, 133.3, 133.1, 131.7, 131.2, 129.0, 128.7, 128.2, 126.5, 126.1, 125.7, 124.5, 123.9, 123.8, 94.5, 74.4, 62.2, 14.3; IR (ν_{max}, cm^{-1}) 3057 (w), 2985 (m), 2904 (m), 1732 (s), 1583 (m), 1464 (m), 1429 (m), 1395 (m), 1370 (m), 1335 (m), 1284 (s), 1241 (s), 1192 (s), 1131 (s), 1094 (s), 1016 (s), 967 (s), 859 (m), 775 (s), 736 (s); HRMS (ESI) Calcd for $C_{23}H_{19}INaO_4^+$ $[M+Na]^+$ 509.0220; found 509.0233.

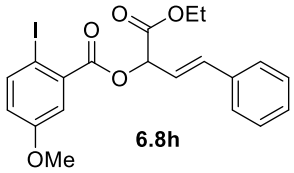
(*E*)-1-Ethoxy-1-oxo-4-(thiophen-2-yl)but-3-en-2-yl 2-iodobenzoate (6.8g)



6.8g

Following general procedure **D**, starting from (*E*)-1-(2-(thiophen-2-yl)vinyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7g**) (71.2 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 mL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxo-4-(thiophen-2-yl)but-3-en-2-yl 2-iodobenzoate (**6.8g**) as a clear yellow oil (67 mg, 0.15 mmol, 76%). R_f = 0.24 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.95 (m, 2H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.24 (dt, *J* = 5.0, 0.9 Hz, 1H, Ar*H*), 7.19 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H, Ar*H*), 7.08 – 7.00 (m, 2H, Ar*H* and CHC*H*Ph), 6.99 (dd, *J* = 5.1, 3.6 Hz, 1H, Ar*H*), 6.20 (dd, *J* = 15.7, 7.2 Hz, 1H, C*H*CHPh), 5.82 (dd, *J* = 7.2, 1.3 Hz, 1H, OC*H*CC), 4.28 (qq, *J* = 7.1, 3.6 Hz, 2H, OC*H*$_2$CH$_3$), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 165.6, 141.6, 140.6, 134.1, 133.3, 131.7, 128.9, 128.2, 127.7, 127.6, 125.8, 119.9, 94.6, 74.1, 62.2, 14.3; IR (ν_{max}, cm^{-1}) 3057 (w), 2985 (m), 2904 (m), 1732 (s), 1583 (m), 1464 (m), 1429 (m), 1395 (m), 1370 (m), 1335 (m), 1284 (s), 1241 (s), 1192 (s), 1131 (s), 1094 (s), 1016 (s), 967 (s), 859 (m), 775 (s), 736 (s); HRMS (ESI) Calcd for $C_{17}H_{15}IO_4S$ [M$^+$] 441.9730; found 441.9733.

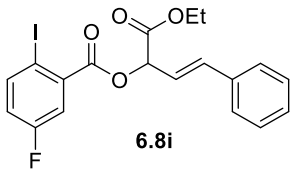
(*E*)-1-Ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodo-5-methoxybenzoate (6.8h)



6.8h

Following general procedure **D**, starting from (*E*)-5-methoxy-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7h**) (76.0 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodo-5-methoxybenzoate (**6.8h**) as a colorless oil (78 mg, 0.17 mmol, 84%). R_f = 0.14 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.7 Hz, 1H, Ar*H*), 7.52 (d, *J* = 3.1 Hz, 1H, Ar*H*), 7.48 – 7.41 (m, 2H, Ar*H*), 7.39 – 7.27 (m, 3H, Ar*H*), 6.93 (dd, *J* = 16.0, 1.2 Hz, 1H, CHC*H*Ph), 6.79 (dd, *J* = 8.7, 3.1 Hz, 1H, Ar*H*), 6.38 (dd, *J* = 15.9, 7.1 Hz, 1H, C*H*CHPh), 5.85 (dd, *J* = 7.1, 1.3 Hz, 1H, OC*H*CC), 4.29 (qd, *J* = 7.1, 2.8 Hz, 2H, OC*H*$_2$CH$_3$), 3.84 (s, 3H, ArOC*H*$_3$), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 165.5, 159.7, 142.1, 135.8, 135.7, 135.0, 128.8, 128.8, 127.0, 120.7, 119.8, 117.2, 82.8, 74.4, 62.1, 55.7, 14.3; IR (ν_{max}, cm^{-1}) 2986 (w), 2937 (w), 1736 (s), 1590 (m), 1565 (m), 1469 (m), 1449 (m), 1394 (m), 1368 (m), 1313 (m), 1284 (s), 1241 (s), 1213 (s), 1184 (s), 1092 (s), 1046 (s), 1029 (s), 1009 (s), 966 (s), 911 (m), 811 (m), 777 (m), 732 (s), 693 (s); HRMS (ESI) Calcd for $C_{20}H_{19}IO_5$ [M$^+$] 466.0272; found 466.0276.

(*E*)-1-Ethoxy-1-oxo-4-phenylbut-3-en-2-yl 5-fluoro-2-iodobenzoate (6.8i)

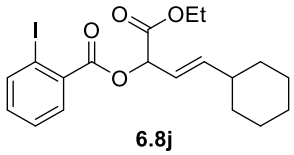


6.8i

Following general procedure **D**, starting from (*E*)-5-fluoro-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7i**) (73.6 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl 5-fluoro-2-iodobenzoate (**6.8i**) as a

colorless oil (77 mg, 0.17 mmol, 85%). R_f = 0.34 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.7, 5.3 Hz, 1H, Ar*H*), 7.73 (dd, *J* = 8.9, 3.1 Hz, 1H, Ar*H*), 7.48 – 7.41 (m, 2H, Ar*H*), 7.39 – 7.28 (m, 3H, Ar*H*), 7.01 – 6.88 (m, 2H, Ar*H* and CHC*H*Ph), 6.37 (dd, *J* = 15.9, 7.2 Hz, 1H, C*H*CHPh), 5.85 (dd, *J* = 7.2, 1.3 Hz, 1H, OC*H*CC), 4.29 (qd, *J* = 7.1, 3.3 Hz, 2H, OC*H*$_2$CH$_3$), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 164.5 (d, *J* = 2.6 Hz), 162.5 (d, *J* = 249.7 Hz), 143.0 (d, *J* = 7.3 Hz), 136.1, 135.6 (d, *J* = 7.3 Hz), 135.6, 128.9, 127.0, 120.9 (d, *J* = 21.4 Hz), 120.4, 119.2 (d, *J* = 24.2 Hz), 87.6 (d, *J* = 3.6 Hz), 74.6, 62.3, 14.3; ^{19}F NMR (376 MHz, CDCl3) δ -113.0; IR (ν_{max}, cm^{-1}) 1736 (s), 1575 (m), 1465 (m), 1449 (m), 1394 (m), 1370 (m), 1296 (m), 1264 (s), 1241 (s), 1188 (s), 1127 (m), 1084 (m), 1017 (s), 964 (m), 819 (m), 777 (m), 734 (s), 691 (m); HRMS (ESI) Calcd for $C_{19}H_{16}FIO_4$ [M$^+$] 454.0072; found 454.0074. One carbon was not resolved at 101 MHz.

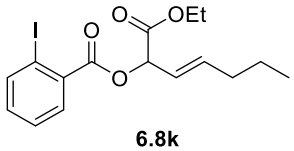
(*E*)-4-Cyclohexyl-1-ethoxy-1-oxobut-3-en-2-yl 2-iodobenzoate (6.8j)



6.8j

Following general procedure **D**, starting from (*E*)-1-(2-cyclohexylvinyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7j**) (71.2 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxo-5-phenylpent-3-en-2-yl 2-iodobenzoate (**6.8j**) as a colorless oil (88 mg, 0.20 mmol, 99%). R_f = 0.37 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.17 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H, Ar*H*), 6.04 – 5.94 (m, 1H, CHC*H*cy), 5.66 – 5.57 (m, 2H, C*H*CHy and OC*H*CC), 4.24 (qd, *J* = 7.1, 2.7 Hz, 2H, OC*H*$_2$CH$_3$), 2.98 (m, 1H, cy-*H*), 1.80 – 1.69 (m, 4H, cy-*H*), 1.69 – 1.61 (m, 1H, cy-*H*), 1.34 – 1.03 (m, 8H, cy-*H* and OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 165.7, 143.9, 141.5, 134.3, 133.1, 131.7, 128.1, 119.4, 94.5, 74.6, 61.8, 40.6, 32.5 – 32.3 (2 s, rotamer), 32.5, 32.4, 26.2, 26.0, 14.3; IR (ν_{max}, cm^{-1}) 2977 (m), 2920 (m), 2848 (m), 1736 (s), 1579 (m), 1450 (m), 1286 (s), 1239 (s), 1190 (s), 1133 (s), 1100 (s), 1014 (s), 965 (s), 740 (s); HRMS (ESI) Calcd for $C_{19}H_{23}INaO_4^+$ [M+Na]$^+$ 465.0533; found 465.0542.

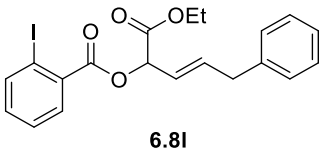
(*E*)-1-Ethoxy-1-oxohept-3-en-2-yl 2-iodobenzoate (6.8k)



6.8k

Following general procedure **D**, starting from (*E*)-1-(1-(pent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7k**) (63.2 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxohept-3-en-2-yl 2-iodobenzoate (**6.8k**) as a colorless oil (76 mg, 0.19 mmol, 94%). R_f = 0.37 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.95 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 – 7.12 (m, 1H, Ar*H*), 6.10 – 5.99 (m, 1H, CHC*H*CH$_2$), 5.72 – 5.60 (m, 2H, C*H*CHCH$_2$ and OC*H*CC), 4.25 (td, *J* = 7.2, 6.7 Hz, 2H, OC*H*$_2$CH$_3$), 2.15 – 2.05 (m, 2H, CHC*H*$_2$CH$_2$), 1.45 (h, *J* = 7.3 Hz, 2H, CH$_2$C*H*$_2$CH$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 0.91 (t, *J* = 7.4 Hz, 3H, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 165.7, 141.6, 138.4, 134.3, 133.1, 131.7, 128.1, 121.9, 94.5, 74.5, 61.8, 34.5, 21.9, 14.3, 13.7; IR (ν_{max}, cm^{-1}) 2959 (m), 2928 (m), 2867 (m), 1732 (s), 1591 (m), 1464 (m), 1431 (m), 1368 (m), 1284 (s), 1239 (s), 1192 (s), 1131 (s), 1096 (s), 1014 (s), 965 (s), 740 (s); HRMS (ESI) Calcd for $C_{16}H_{19}INaO_4^+$ [M+Na]$^+$ 425.0220; found 425.0232.

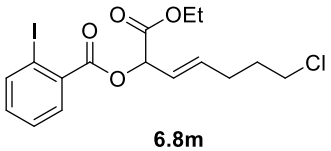
(*E*)-1-Ethoxy-1-oxo-5-phenylpent-3-en-2-yl 2-iodobenzoate (6.8l)



6.8l

Following general procedure **D**, starting from (*E*)-1-(3-phenylprop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7l**) (72.8 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxo-5-phenylpent-3-en-2-yl 2-iodobenzoate (**6.8l**) as a colorless oil (81 mg, 0.18 mmol, 90%). R_f = 0.26 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.35 – 7.27 (m, 2H, Ar*H*), 7.25 – 7.13 (m, 4H, Ar*H*), 6.22 (dtd, *J* = 14.7, 6.8, 0.8 Hz, 1H, CHC*H*Bn), 5.80 – 5.66 (m, 2H, C*H*CHBn and OC*H*CC), 4.26 (qd, *J* = 7.1, 2.4 Hz, 2H, OCH_2CH$_3$), 3.50 – 3.43 (m, 2H, CHCH_2Ph), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 165.5, 141.4, 138.9, 136.3, 134.1, 133.0, 131.5, 128.6, 128.6, 128.0, 126.4, 123.1, 94.4, 74.0, 61.8, 38.6, 14.2; IR (ν_{max}, cm^{-1}) 2981 (w), 2918 (m), 1732 (s), 1456 (m), 1429 (m), 1288 (s), 1237 (s), 1200 (s), 1129 (s), 1098 (s), 1016 (s), 973 (s), 742 (s), 699 (s); HRMS (ESI) Calcd for $C_{20}H_{19}INaO_4^+$ $[M+Na]^+$ 473.0220; found 473.0223.

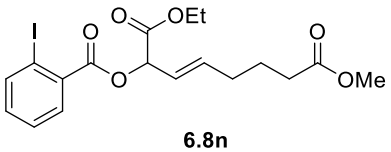
(*E*)-7-Chloro-1-ethoxy-1-oxohept-3-en-2-yl 2-iodobenzoate (6.8m)



6.8m

Following general procedure **D**, starting from (*E*)-1-(5-chloropent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7m**) (70.1 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-7-chloro-1-ethoxy-1-oxohept-3-en-2-yl 2-iodobenzoate (**6.8m**) as a colorless oil (82 mg, 0.19 mmol, 94%). R_f = 0.20 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar*H*), 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.18 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.02 (dtd, *J* = 15.1, 6.9, 1.1 Hz, 1H, CHC*H*CH$_2$), 5.75 (ddt, *J* = 15.3, 7.1, 1.4 Hz, 1H, C*H*CHCH$_2$), 5.66 (dd, *J* = 7.1, 1.0 Hz, 1H, OC*H*CC), 4.25 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 3.54 (t, *J* = 6.5 Hz, 2H, CH$_2$CH_2Cl), 2.35 – 2.24 (m, 2H, CHCH_2CH$_2$), 1.96 – 1.85 (m, 2H, CH$_2$CH_2CH$_2$Cl), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 165.6, 141.6, 136.1, 134.2, 133.2, 131.6, 128.1, 123.3, 94.5, 74.1, 62.0, 44.2, 31.4, 29.5, 14.3; IR (ν_{max}, cm^{-1}) 2977 (m), 2920 (m), 2848 (m), 1736 (s), 1579 (m), 1450 (m), 1286 (s), 1239 (s), 1190 (s), 1133 (s), 1100 (s), 1014 (s), 965 (s), 740 (s); HRMS (ESI) Calcd for $C_{16}H_{18}ClINaO_4^+$ $[M+Na]^+$ 458.9831; found 458.9835.

(*E*)-1-Ethyl 8-methyl 2-((2-iodobenzoyl)oxy)oct-3-enedioate (6.8n)

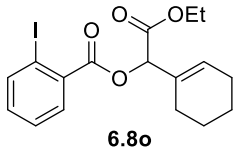


6.8n

Following general procedure **D**, starting from methyl (*E*)-6-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-one (**6.7n**) (74.8 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethyl 8-methyl 2-((2-iodobenzoyl)oxy)oct-3-enedioate (**6.8n**) as a colorless oil (77 mg, 0.17 mmol, 84%). R_f = 0.13 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.0,

1.1 Hz, 1H, Ar*H*), 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.21 – 7.14 (m, 1H, Ar*H*), 6.01 (dtd, *J* = 14.8, 6.8, 0.8 Hz, 1H, CHC*H*CH_2), 5.75 – 5.60 (m, 2H, OC*H*CC and *CH*CHCH$_2$), 4.24 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 3.66 (s, 3H, OCH_3), 2.32 (t, *J* = 7.5 Hz, 2H, CH_2CO$_2$Me), 2.21 – 2.12 (m, 2H, CHCH_2CH$_2$), 1.76 (p, *J* = 7.3 Hz, 2H, CH$_2$CH_2CH$_2$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 168.7, 165.6, 141.5, 136.9, 134.2, 133.1, 131.6, 128.1, 122.8, 94.5, 74.2, 61.9, 51.7, 33.3, 31.7, 23.9, 14.3; IR (ν_{max}, cm^{-1}) 2956 (w), 1735 (s), 1606 (s), 1436 (m), 1367 (w), 1344 (m), 1292 (m), 1238 (m), 1209 (m), 1157 (m), 1096 (m), 1017 (s), 965 (m), 834 (m); HRMS (ESI) Calcd for $C_{18}H_{21}INaO_6^+$ [M+Na]$^+$ 483.0275; found 483.0280.

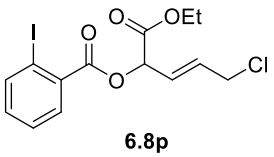
1-(Cyclohex-1-en-1-yl)-2-ethoxy-2-oxoethyl 2-iodobenzoate (6.8o)



6.8o

Following general procedure **D**, starting from (*E*)-1-(cyclohex-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7o**) (65.6 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded 1-(cyclohex-1-en-1-yl)-2-ethoxy-2-oxoethyl 2-iodobenzoate (**6.8o**) as a colorless oil (80 mg, 0.19 mmol, 97%). R_f = 0.36 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.20 – 7.14 (m, 1H, Ar*H*), 6.04 – 5.99 (m, 1H, CC*H*CH$_2$), 5.55 (d, *J* = 1.0 Hz, 1H, OC*H*CC), 4.25 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 2.30 – 1.18 (m, 1H, cy-*H*), 2.16 – 1.96 (m, 3H, cy-*H*), 1.74 – 1.58 (m, 4H, cy-*H*), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 165.9, 141.6, 134.4, 133.1, 131.7, 131.1, 130.5, 128.1, 94.5, 78.1, 61.7, 25.4, 24.9, 22.4, 22.0, 14.3; IR (ν_{max}, cm^{-1}) 2959 (m), 2928 (m), 2867 (m), 1732 (s), 1591 (m), 1464 (m), 1431 (m), 1368 (m), 1284 (s), 1239 (s), 1192 (s), 1131 (s), 1096 (s), 1014 (s), 965 (s), 740 (s); HRMS (ESI) Calcd for $C_{17}H_{19}INaO_4^+$ [M+Na]$^+$ 437.0220; found 437.0225.

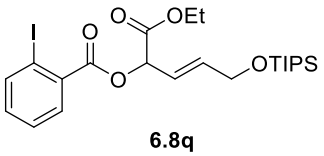
(*E*)-5-Chloro-1-ethoxy-1-oxopent-3-en-2-yl 2-iodobenzoate (6.8p)



6.8p

Following general procedure **D**, starting from (*E*)-1-(3-chloroprop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7p**) (64.5 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-5-chloro-1-ethoxy-1-oxopent-3-en-2-yl 2-iodobenzoate (**6.8p**) as a colorless oil (26.0 mg, 0.06 mmol, 32%). R_f = 0.19 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.96 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.20 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H, Ar*H*), 6.20 (dtd, *J* = 15.3, 6.4, 1.4 Hz, 1H, CHC*H*CH$_2$Cl), 6.04 (ddt, *J* = 15.3, 6.0, 1.3 Hz, 1H, C*H*CHCH$_2$Cl), 5.76 (dq, *J* = 5.9, 1.1 Hz, 1H, OC*H*CC), 4.27 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 4.11 (dt, *J* = 6.4, 1.1 Hz, 2H, CH_2Cl), 1.31 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 165.4, 141.7, 133.9, 133.3, 131.7, 131.3, 128.2, 126.0, 94.6, 72.9, 62.3, 43.6, 14.3; IR (ν_{max}, cm^{-1}) 2959 (m), 2928 (m), 2867 (m), 1732 (s), 1591 (m), 1464 (m), 1431 (m), 1368 (m), 1284 (s), 1239 (s), 1192 (s), 1131 (s), 1096 (s), 1014 (s), 965 (s), 740 (s); HRMS (ESI) Calcd for $C_{14}H_{14}ClINaO_4^+$ [M+Na]$^+$ 430.9518; found 430.9521.

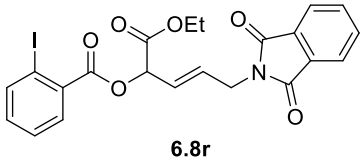
(*E*)-1-Ethoxy-1-oxo-5-((triisopropylsilyl)oxy)pent-3-en-2-yl 2-iodobenzoate (6.8q)



6.8q

Following general procedure **D**, starting from (*E*)-1-(3-((triisopropylsilyl)oxy)prop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7q**) (92.0 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxo-5-((triisopropylsilyl)oxy)pent-3-en-2-yl 2-iodobenzoate (**6.8q**) as a colorless oil (94 mg, 0.17 mmol, 86%). R_f = 0.54 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.96 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.17 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.14 (dtd, *J* = 15.4, 3.7, 1.2 Hz, 1H, CHC*H*CH$_2$O), 6.02 (ddt, *J* = 15.4, 6.5, 2.0 Hz, 1H, C*H*CHCH$_2$O), 5.74 (dq, *J* = 6.5, 1.3 Hz, 1H, OC*H*CC), 4.33 (dt, *J* = 3.6, 1.7 Hz, 2H, C*H*$_2$OTIPS), 4.25 (qd, *J* = 7.1, 1.2 Hz, 2H, OC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.17 – 1.02 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 165.6, 141.6, 136.0, 134.2, 133.2, 131.7, 128.1, 120.8, 94.5, 73.8, 62.8, 61.9, 18.1, 14.3, 12.1; IR (ν_{max}, cm^{-1}) 2960 (m), 2941 (s), 2866 (s), 2727 (w), 1736 (s), 1463 (m), 1378 (w), 1284 (m), 1248 (s), 1200 (m), 1124 (s), 1044 (s), 1017 (s), 967 (m), 880 (s); HRMS (ESI) Calcd for $C_{23}H_{35}INaO_5Si^+$ $[M+Na]^+$ 569.1191; found 569.1197.

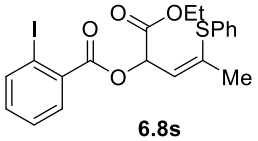
(*E*)-5-(1,3-Dioxoisoindolin-2-yl)-1-ethoxy-1-oxopent-3-en-2-yl 2-iodobenzoate (6.8r)



6.8r

Following general procedure **D**, starting from (*E*)-2-(3-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)allyl)isoindoline-1,3-dione (**6.7r**) (87.0 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-5-(1,3-dioxoisoindolin-2-yl)-1-ethoxy-1-oxopent-3-en-2-yl 2-iodobenzoate (**6.8r**) as a white sticky solid (31.0 mg, 0.06 mmol, 30%). M.p. 77 – 78 °C; R_f = 0.31 (EtOAc/pentane 25:75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.89 – 7.81 (m, 2H, Ar*H*), 7.77 – 7.69 (m, 2H, Ar*H*), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.17 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.12 (dtd, *J* = 15.5, 5.9, 1.4 Hz, 1H, CHC*H*CH$_2$N), 5.96 (ddt, *J* = 15.5, 6.0, 1.4 Hz, 1H, C*H*CHCH$_2$N), 5.71 (dd, *J* = 6.0, 1.3 Hz, 1H, OC*H*CC), 4.36 (dt, *J* = 5.9, 1.2 Hz, 2H, C*H*$_2$NPhth), 4.24 (qd, *J* = 7.1, 0.9 Hz, 2H, OC*H*$_2$CH$_3$), 1.28 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 167.9, 165.4, 141.6, 134.3, 133.9, 133.2, 132.2, 131.7, 129.3, 128.1, 125.7, 123.6, 94.5, 73.1, 62.2, 38.9, 14.2; IR (ν_{max}, cm^{-1}) 3463 (w), 3053 (w), 2985 (w), 2922 (m), 2854 (w), 1733 (m), 1709 (s), 1582 (w), 1467 (m), 1430 (m), 1392 (s), 1288 (m), 1244 (m), 1200 (m), 1130 (m), 1101 (m), 1046 (m), 1017 (s), 944 (m); HRMS (ESI) Calcd for $C_{22}H_{18}INNaO_6^+$ $[M+Na]^+$ 542.0071; found 542.0082.

(*Z*)-1-ethoxy-1-oxo-4-(phenylthio)pent-3-en-2-yl 2-iodobenzoate (6.8s)

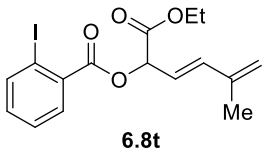


6.8s

Following general procedure **D**, starting from (*Z*)-1-(2-(phenylthio)prop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7v**) (79.0 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*Z*)-1-ethoxy-1-oxo-4-(phenylthio)pent-3-en-2-yl 2-

iodobenzoate (**6.8s**) as a colorless oil (57.0 mg, 0.118 mmol, 59%). R_f = 0.10 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (ddd, *J* = 7.9, 3.5, 1.2 Hz, 1H, Ar*H*), 7.96 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.46 – 7.39 (m, 3H, Ar*H*), 7.35 – 7.26 (m, 3H, Ar*H*), 7.18 (tdd, *J* = 7.6, 4.0, 1.7 Hz, 1H, Ar*H*), 6.40 (d, *J* = 8.9 Hz, 1H, C=C*H*), 5.91 (dq, *J* = 8.8, 1.3 Hz, 1H, OC*H*CC), 4.28 (qd, *J* = 7.1, 4.5 Hz, 2H, OCH_2CH$_3$), 1.95 (d, *J* = 1.3 Hz, 3H, CH_3), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); 168.7, 165.5, 141.5, 141.2, 134.4, 133.1, 132.8, 132.6, 131.6, 129.2, 128.1, 127.9, 123.6, 94.5, 72.2, 62.1, 24.2, 14.3; HRMS (ESI) Calcd for $C_{20}H_{19}INaO_4S$+ [M+Na]+ 504.9941; found 504.9950.

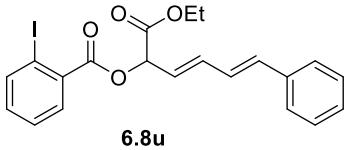
(*E*)-1-Ethoxy-5-methyl-1-oxohexa-3,5-dien-2-yl 2-iodobenzoate (6.8t)



6.8t

Following general procedure **D**, starting from (*E*)-1-(3-methylbuta-1,3-dien-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7s**) (62.8 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-5-methyl-1-oxohexa-3,5-dien-2-yl 2-iodobenzoate (**6.8t**) as a colorless oil (66 mg, 0.17 mmol, 82%). R_f = 0.33 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.97 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.18 (ddd, *J* = 8.0, 7.5, 1.7 Hz, 1H, Ar*H*), 6.63 (d, *J* = 15.3 Hz, 1H, CHC*H*C), 5.85 – 5.73 (m, 2H, C*H*CHC and OC*H*CC), 5.14 – 5.09 (m, 2H, CCH_2), 4.27 (qd, *J* = 7.1, 1.7 Hz, 2H, OCH_2CH$_3$), 1.88 (t, *J* = 1.0 Hz, 3H, CCH_3), 1.31 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 165.6, 141.6, 140.8, 138.5, 134.2, 133.2, 131.7, 128.1, 120.7, 119.6, 94.5, 74.3, 62.1, 18.5, 14.3; IR (ν_{max}, cm^{-1}) 2959 (m), 2928 (m), 2867 (m), 1732 (s), 1591 (m), 1464 (m), 1431 (m), 1368 (m), 1284 (s), 1239 (s), 1192 (s), 1131 (s), 1096 (s), 1014 (s), 965 (s), 740 (s); HRMS (ESI) Calcd for $C_{16}H_{17}INaO_4^+$ [M+Na]$^+$ 423.0064; found 423.0065.

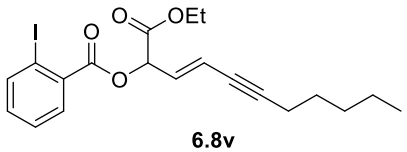
(3*E*,5*E*)-1-Ethoxy-1-oxo-6-phenylhexa-3,5-dien-2-yl 2-iodobenzoate (6.8u)



6.8u

Following general procedure **D**, starting from (*E*)-1-((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7t**) (75.0 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (3*E*,5*E*)-1-ethoxy-1-oxo-6-phenylhexa-3,5-dien-2-yl 2-iodobenzoate (**6.8u**) as a colorless oil (84 mg, 0.18 mmol, 91%). R_f = 0.23 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar*H*), 7.98 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.49 – 7.38 (m, 3H, Ar*H*), 7.37 – 7.30 (m, 2H, Ar*H*), 7.29 – 7.22 (m, 1H, Ar*H*), 7.19 (td, *J* = 7.7, 1.8 Hz, 1H, Ar*H*), 6.80 (dd, *J* = 15.4, 10.3 Hz, 1H, CHCHC*H*CHPh), 6.75 – 6.64 (m, 2H, CHC*H*CHC*H*Ph), 6.01 – 5.93 (m, 1H, C*H*CHCHCHPh), 5.79 (dd, *J* = 7.0, 1.1 Hz, 1H, OC*H*CC), 4.28 (qd, *J* = 7.1, 0.9 Hz, 2H, OCH_2CH$_3$), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 165.6, 141.6, 136.8, 136.0, 135.5, 134.1, 133.2, 131.7, 128.8, 128.3, 128.1, 127.2, 126.8, 124.0, 94.6, 74.1, 62.1, 14.3; IR (ν_{max}, cm^{-1}) 2985 (w), 2918 (w), 1732 (s), 1583 (w), 1466 (w), 1284 (m), 1243 (s), 1129 (m), 1100 (m), 1014 (s), 988 (m), 738 (s), 689 (s); HRMS (ESI) Calcd for $C_{21}H_{19}INaO_4^+$ [M+Na]$^+$ 485.0220; found 485.0216.

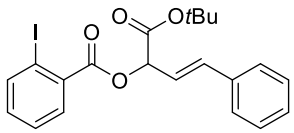
(*E*)-1-Ethoxy-1-oxoundec-3-en-5-yn-2-yl 2-iodobenzoate (6.8v)



6.8v

Following general procedure **D**, starting from (*E*)-1-(non-1-en-3-yn-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7u**) (73.6 mg, 0.200 mmol) and ethyl 2-diazoacetate (**6.6a**) (48.0 µL, 87% wt in DCM, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxoundec-3-en-5-yn-2-yl 2-iodobenzoate (**6.8v**) as a colorless oil (88 mg, 0.19 mmol, 97%). R_f = 0.40 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar*H*), 7.95 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.18 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H, Ar*H*), 6.17 (ddt, *J* = 15.8, 6.5, 0.7 Hz, 1H, C*H*CHCC), 6.02 (dtd, *J* = 15.8, 2.1, 1.4 Hz, 1H, CHC*H*CC), 5.72 (dd, *J* = 6.6, 1.4 Hz, 1H, OC*H*CC), 4.25 (qd, *J* = 7.1, 2.2 Hz, 2H, OCH_2CH$_3$), 2.31 (td, *J* = 7.1, 2.2 Hz, 2H, CCH_2CH$_2$), 1.57 – 1.48 (m, 2H, CCH$_2$CH_2), 1.42 – 1.21 (m, 7H, pentyl-*H* and OCH$_2$CH_3), 0.90 (t, *J* = 7.1 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 165.2, 141.5, 133.7, 133.2, 131.8, 131.6, 128.0 116.1, 94.5, 94.2, 77.5, 73.4, 62.1, 31.1, 28.2, 22.2, 19.4, 14.1, 14.0; IR (ν_{max}, cm^{-1}) 2957 (m), 2935 (m), 2859 (w), 2219 (w), 1738 (s), 1584 (m), 1465 (m), 1429 (m), 1370 (m), 1284 (m), 1241 (s), 1196 (s), 1131 (s), 1096 (s), 1043 (m), 1027 (s), 1017 (s), 954 (s), 738 (s); HRMS (ESI) Calcd for $C_{20}H_{24}IO_4^+$ $[M+H]^+$ 455.0714; found 455.0720.

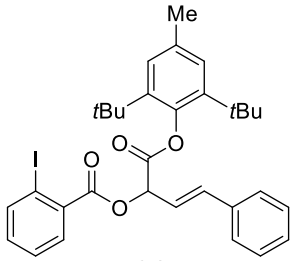
(*E*)-1-(*tert*-Butoxy)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (6.8w)



6.8w

Following general procedure **D**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and *tert*-butyl 2-diazoacetate (**6.6b**) (65.0 µL, 85% wt in DCM, 0.400 mmol), afforded (*E*)-1-(*tert*-butoxy)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8w**) as a white solid (90 mg, 0.19 mmol, 97%). M.p. 62 – 64 °C; R_f = 0.36 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (td, *J* = 7.9, 1.4 Hz, 2H, Ar*H*), 7.47 – 7.40 (m, 3H, Ar*H*), 7.38 – 7.32 (m, 2H, Ar*H*), 7.32 – 7.27 (m, 1H, Ar*H*), 7.19 (ddd, *J* = 7.9, 7.4, 1.8 Hz, 1H, Ar*H*), 6.90 (dd, *J* = 15.9, 1.4 Hz, 1H, CHC*H*Ph), 6.37 (dd, *J* = 16.0, 6.9 Hz, 1H, C*H*CHPh), 5.75 (dd, *J* = 6.9, 1.4 Hz, 1H, OC*H*CC), 1.51 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 165.7, 141.6, 135.9, 135.2, 134.4, 133.1, 131.7, 128.8, 128.6, 128.1, 127.0, 121.2, 94.5, 83.1, 74.8, 28.2; IR (ν_{max}, cm^{-1}) 2978 (m), 2902 (m), 1735 (s), 1582 (w), 1451 (m), 1395 (m), 1369 (m), 1278 (s), 1258 (s), 1199 (m), 1129 (m), 1098 (s), 1044 (s), 1016 (s), 966 (m), 863 (m), 764 (s), 750 (s); HRMS (ESI) Calcd for $C_{21}H_{21}INaO_4^+$ $[M+Na]^+$ 487.0377; found 487.0382.

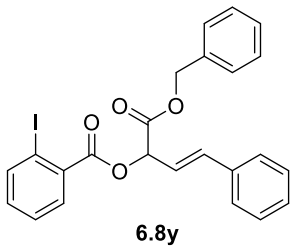
(*E*)-1-(2,6-di-*tert*-Butyl-4-methylphenoxy)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (6.8x)



6.8x

Following general procedure **D**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**6.6c**) (115 mg, 0.400 mmol), afforded (*E*)-1-(2,6-di-*tert*-butyl-4-methylphenoxy)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8x**) as a white solid (123 mg, 0.200 mmol, 100%). R_f = 0.45 (EtOAc/pentane 5:95); M.p. 151 – 153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (ddd, *J* = 7.8, 4.5, 1.4 Hz, 2H, Ar*H*), 7.51 – 7.45 (m, 2H, Ar*H*), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.40 – 7.29 (m, 3H, Ar*H*), 7.23 – 7.16 (m, 1H, Ar*H*), 7.16 – 7.10 (m, 2H, Ar*H*), 7.02 (d, *J* = 14.9 Hz, 1H, CHC*H*Ph), 6.62 – 6.52 (m, 2H, C*H*CHPh and OC*H*CC), 2.32 (s, 3H, ArC*H*$_3$), 1.38 (s, 9H, C(C*H*$_3$)$_3$), 1.31 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 165.0, 145.8, 142.2, 142.1, 141.6, 136.2, 135.7, 135.2, 134.4, 133.2, 131.6, 128.9, 128.8, 128.1, 127.5, 127.2, 127.0, 120.7, 94.6, 74.1, 35.5, 35.5, 31.8, 31.4, 21.6; IR (ν_{max}, cm^{-1}) 2961 (m), 2922 (m), 1769 (s), 1742 (s), 1468 (m), 1425 (m), 1270 (s), 1247 (s), 1196 (s), 1180 (s), 1129 (s), 1100 (s), 1016 (s), 969 (m), 742 (s); HRMS (ESI) Calcd for $C_{32}H_{35}INaO_4^+$ $[M+Na]^+$ 633.1472; found 633.1474; The structure of **6.8x** was confirmed by X-ray analysis. Crystals were grown by dissolving 10 mg of pure **6.8x** in a minimum amount of benzene (100 µL) at room temperature. Slow evaporation over one week provided suitable crystals. Supplementary crystallographic data for this compound have been deposited at Cambridge Crystallographic Data Centre (CCDC 1897009) and can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/

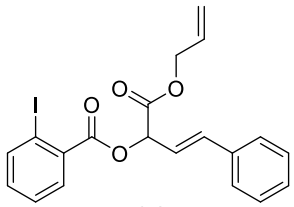
(*E*)-1-(Benzyloxy)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (6.8y)



6.8y

Following general procedure **D**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and benzyl 2-diazoacetate (**6.6d**) (88.0 µL, 90% wt in DCM, 0.400 mmol), afforded (*E*)-1-(Benzyloxy)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8y**) as a colorless oil (92.0 mg, 0.19 mmol, 92%). R_f = 0.26 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.96 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.46 – 7.27 (m, 11H, Ar*H*), 7.19 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.90 (dd, *J* = 16.0, 1.3 Hz, 1H, CHC*H*Ph), 6.37 (dd, *J* = 15.9, 7.1 Hz, 1H, C*H*CHPh), 5.93 (dd, *J* = 7.1, 1.3 Hz, 1H, OC*H*CC), 5.26 (s, 2H, OC*H*$_2$Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 165.6, 141.6, 136.0, 135.7, 135.3, 134.1, 133.3, 131.7, 128.8, 128.8, 128.8, 128.6, 128.4, 128.1, 127.0, 120.5, 94.5, 74.3, 67.7; IR (ν_{max}, cm^{-1}) 2978 (m), 2902 (m), 1735 (s), 1582 (w), 1451 (m), 1395 (m), 1369 (m), 1278 (s), 1258 (s), 1199 (m), 1129 (m), 1098 (s), 1044 (s), 1016 (s), 966 (m), 863 (m), 764 (s), 750 (s); HRMS (ESI) Calcd for $C_{24}H_{19}INaO_4^+$ $[M+Na]^+$ 521.0220; found 521.0235.

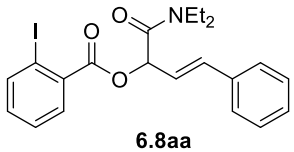
(*E*)-1-(Allyloxy)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (6.8z)



6.8z

Following general procedure **D**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and allyl 2-diazoacetate (**6.6e**) (50.4 mg, 0.400 mmol), afforded (*E*)-1-(allyloxy)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8z**) as a colorless oil (82 mg, 0.18 mmol, 91%). R_f = 0.24 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (ddd, *J* = 10.7, 7.9, 1.4 Hz, 2H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 3H, Ar*H*), 7.39 – 7.27 (m, 3H, Ar*H*), 7.19 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.94 (dd, *J* = 16.0, 1.2 Hz, 1H, CHC*H*Ph), 6.39 (dd, *J* = 15.9, 7.1 Hz, 1H, C*H*CHPh), 6.00 – 5.87 (m, 2H, OC*H*CC and OCH_2CHCH_2), 5.36 (dq, *J* = 17.2, 1.5 Hz, 1H, $CHCH_2$), 5.26 (dq, *J* = 10.5, 1.3 Hz, 1H, $CHCH_2$), 4.72 (dt, *J* = 5.8, 1.4 Hz, 2H, OCH_2CHCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 165.6, 141.6, 136.0, 135.7, 134.1, 133.3, 131.7, 131.5, 128.9, 128.8, 128.1, 127.0, 120.6, 119.1, 94.6, 74.3, 66.5; IR (ν_{max}, cm^{-1}) 3063 (w), 3026 (w), 2946 (w), 1736 (s), 1585 (m), 1427 (w), 1290 (m), 1239 (s), 1188 (s), 1133 (s), 1096 (s), 1043 (m), 1014 (s), 963 (s), 937 (m), 742 (s), 689 (s); HRMS (ESI) Calcd for $C_{20}H_{17}INaO_4^+$ $[M+Na]^+$ 471.0064; found 471.0063.

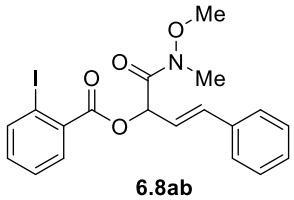
(*E*)-1-(Diethylamino)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (6.8aa)



6.8aa

Following general procedure **D**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and 2-diazo-*N*,*N*-diethylacetamide (**6.6f**) (56.5 mg, 0.400 mmol), afforded (*E*)-1-(diethylamino)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8aa**) as a white solid (87 mg, 0.19 mmol, 94%). R_f = 0.24 (EtOAc/pentane 20:80); M.p. 113 – 115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.98 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar*H*), 7.46 – 7.38 (m, 3H, Ar*H*), 7.38 – 7.27 (m, 3H, Ar*H*), 7.15 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.88 (d, *J* = 16.0 Hz, 1H, CHC*H*Ph), 6.43 (dd, *J* = 16.0, 7.9 Hz, 1H, C*H*CHPh), 6.12 (dd, *J* = 7.9, 0.9 Hz, 1H, OC*H*CC), 3.59 – 3.30 (m, 4H, $N(CH_2CH_3)_2$), 1.31 (t, *J* = 7.2 Hz, 3H, $N(CH_2CH_3)_2$), 1.17 (t, *J* = 7.1 Hz, 3H, $N(CH_2CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 166.1, 141.3, 136.9, 135.7, 134.5, 133.0, 132.1, 128.9 (2 C), 128.1, 127.1, 122.0, 94.4, 72.9, 41.9, 41.0, 14.5, 13.0; IR (ν_{max}, cm^{-1}) 3063 (w), 3026 (w), 2946 (w), 1736 (s), 1585 (m), 1427 (w), 1290 (m), 1239 (s), 1188 (s), 1133 (s), 1096 (s), 1043 (m), 1014 (s), 963 (s), 937 (m), 742 (s), 689 (s); HRMS (ESI) Calcd for $C_{21}H_{22}INNaO_3^+$ $[M+Na]^+$ 486.0537; found 486.0535.

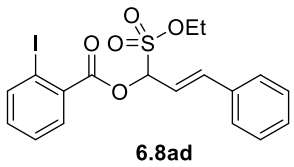
(*E*)-1-(Methoxy(methyl)amino)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (6.8ab)



6.8ab

Following general procedure **D**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and 2-diazo-*N*-methoxy-*N*-methylacetamide (**6.6g**) (51.6 mg, 0.400 mmol), afforded (*E*)-1-(methoxy(methyl)amino)-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**5g**) as a white solid (89 mg, 0.20 mmol, 99%). R_f = 0.27 (EtOAc/pentane 20:80); M.p. 90 – 92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 8.00 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar*H*), 7.45 – 7.40 (m, 3H, Ar*H*), 7.37 – 7.26 (m, 3H, Ar*H*), 7.17 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.93 (d, *J* = 15.9 Hz, 1H, CHC*H*Ph), 6.41 (dd, *J* = 15.9, 7.5 Hz, 1H, C*H*CHPh), 6.27 (d, *J* = 7.5 Hz, 1H, OC*H*CC), 3.87 (s, 3H, OCH_3), 3.27 (s, 3H, NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 166.0, 141.4, 136.0, 136.0, 134.4, 133.1, 132.0, 128.8, 128.7, 128.1, 127.0, 121.0, 94.4, 72.9, 61.7, 32.5; IR (ν_{max}, cm^{-1}) 3055 (w), 3020 (w), 2973 (w), 2942 (w), 1728 (s), 1681 (s), 1466 (m), 1431 (m), 1284 (m), 1251 (s), 1133 (s), 1102 (s), 1016 (m), 969 (s), 738 (s); HRMS (ESI) Calcd for $C_{19}H_{18}INNaO_4^+$ $[M+Na]^+$ 474.0173; found 474.0175.

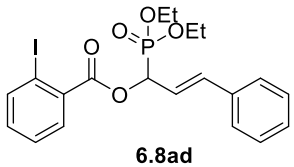
(*E*)-1-(Ethoxysulfonyl)-3-phenylallyl 2-iodobenzoate (6.8ac)



6.8ad

Following general procedure **D**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and ethyl diazomethanesulfonate (**6.6h**) (60.1 mg, 0.400 mmol), afforded (*E*)-1-(ethoxysulfonyl)-3-phenylallyl 2-iodobenzoate (**6.8ac**) as a colorless oil (96 mg, 0.20 mmol, 100%). R_f = 0.12 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 8.01 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.51 – 7.44 (m, 3H, Ar*H*), 7.40 – 7.30 (m, 3H, Ar*H*), 7.27 – 7.21 (m, 1H, Ar*H*), 7.12 – 7.03 (m, 1H, CHC*H*Ph), 6.70 (dd, *J* = 7.5, 1.1 Hz, 1H, OC*H*CC), 6.40 (dd, *J* = 15.9, 7.5 Hz, 1H, C*H*CHPh), 4.43 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 1.40 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 142.1, 140.0, 134.8, 134.0, 132.6, 132.0, 129.6, 129.0, 128.4, 127.4, 116.0, 95.1, 84.1 69.8, 15.5; IR (ν_{max}, cm^{-1}) 2975 (w), 2924 (w), 1742 (m), 1675 (s), 1624 (m), 1581 (m), 1364 (m), 1291 (m), 1237 (s), 1174 (s), 1129 (s), 1088 (s), 1015 (s), 968 (s), 919 (s), 739 (s), 688 (s); HRMS (ESI) Calcd for $C_{18}H_{17}INaO_5S^+$ $[M+Na]^+$ 494.9734; found 494.9730.

(*E*)-1-(Diethoxyphosphoryl)-3-phenylallyl 2-iodobenzoate (6.8ad)

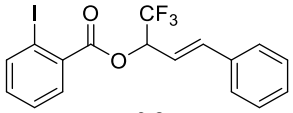


6.8ad

Following general procedure **D**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and diethyl (diazomethyl)phosphonate (**6.6i**) (71.3 mg, 0.400 mmol), afforded (*E*)-1-(diethoxyphosphoryl)-3-phenylallyl 2-iodobenzoate (**6.8ad**) as a colorless oil (97 mg, 0.19 mmol,

97%). R_f = 0.28 (EtOAc/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.47 – 7.40 (m, 3H, Ar*H*), 7.36 – 7.27 (m, 3H, Ar*H*), 7.22 – 7.16 (m, 1H, Ar*H*), 6.91 – 6.83 (m, 1H, CHC*H*Ph), 6.37 (ddd, *J* = 15.9, 7.6, 5.8 Hz, 1H, C*H*CHPh), 6.09 (ddd, *J* = 13.5, 7.6, 1.3 Hz, 1H, OC*H*CC), 4.27 – 4.16 (m, 4H, (O)P(OC*H*$_2$CH$_3$)$_2$), 1.33 (t, *J* = 7.1 Hz, 6H, (O)P(OCH$_2$C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9 (d, *J* = 7.9 Hz), 141.7, 136.0, 135.9 (d, *J* = 3.1 Hz), 134.1, 133.3, 131.5, 128.8, 128.6, 128.2, 127.0, 120.0 (d, *J* = 4.5 Hz), 94.7, 70.6 (d, *J* = 170.7 Hz), 63.6 (dd, *J* = 9.0, 6.8 Hz), 16.7 (t, *J* = 5.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.4; IR (ν_{max}, cm^{-1}) 3057 (w), 2981 (w), 2930 (w), 2901 (w), 1734 (m), 1288 (m), 1241 (s), 1131 (m), 1096 (m), 1014 (s), 967 (s), 793 (m), 738 (s), 691 (m); HRMS (ESI) Calcd for $C_{20}H_{22}INaO_5P^+$ $[M+Na]^+$ 523.0142; found 523.0154.

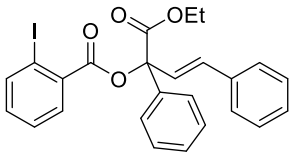
(*E*)-1,1,1-Trifluoro-4-phenylbut-3-en-2-yl 2-iodobenzoate (6.8ae)



6.8ae

Following general procedure **D**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and 2-diazo-1,1,1-trifluoroethane (**6.6j**) (1.08 mL, 0.37 M in DCM, 0.400 mmol), afforded (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8ae**) as a colorless oil (88 mg, 0.20 mmol, 100%). R_f = 0.52 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.45 (dtd, *J* = 7.7, 4.1, 1.9 Hz, 3H, Ar*H*), 7.40 – 7.29 (m, 3H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.00 (d, *J* = 15.9 Hz, 1H, CHC*H*Ph), 6.24 (dd, *J* = 15.9, 7.9 Hz, 1H, C*H*CHPh), 6.12 – 6.02 (m, 1H, OC*H*CC); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 141.9, 139.6, 135.1, 133.6, 133.3, 131.6, 129.3, 128.9, 128.2, 127.2, 123.3 (q, *J* = 280.6 Hz), 117.0 (d, *J* = 1.7 Hz), 94.8, 72.4 (q, *J* = 33.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.9; HRMS (ESI) Calcd for $C_{17}H_{12}F_3IO_2$ $[M^+]$ 431.9829; found 431.9846.

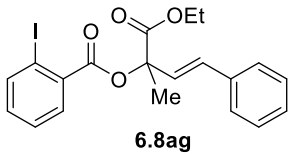
(*E*)-1-Ethoxy-1-oxo-2,4-diphenylbut-3-en-2-yl 2-iodobenzoate (6.8af)



6.8af

Following general procedure **E**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and ethyl 2-diazo-2-phenylacetate (**6.6m**) (76.0 mg, 0.400 mmol), afforded (*E*)-1-ethoxy-1-oxo-2,4-diphenylbut-3-en-2-yl 2-iodobenzoate (**6.8af**) as a colorless oil (73 mg, 0.14 mmol, 71%). R_f = 0.40 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.95 (dd, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.76 – 7.64 (m, 2H, Ar*H*), 7.52 – 7.14 (m, 11H, Ar*H* and CHC*H*Ph), 6.53 (d, *J* = 16.3 Hz, 1H, C*H*CHPh), 4.41 – 4.15 (m, 2H, OC*H*$_2$CH$_3$), 1.26 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 165.2, 141.5, 138.2, 136.2, 135.2, 133.9, 133.0, 131.2, 128.7, 128.6, 128.6, 128.4, 128.2, 127.1, 126.6, 94.1, 84.2, 62.4, 14.2; IR (ν_{max}, cm^{-1}) 2974 (m), 2900 (m), 1735 (s), 1495 (m), 1449 (m), 1431 (m), 1276 (s), 1256 (s), 1092 (s), 1042 (s), 1016 (s), 974 (m), 764 (s), 750 (s); HRMS (ESI) Calcd for $C_{24}H_{19}INaO_4^+$ $[M+Na]^+$ 521.0220; found 521.0227. One carbon was not resolved at 101 MHz.

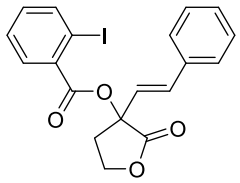
(*E*)-1-Ethoxy-2-methyl-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (6.8ag)



6.8ag

Following general procedure **E**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and ethyl 2-diazopropanoate (**6.6n**) (51.3 mg, 0.400 mmol), afforded (*E*)-1-ethoxy-2-methyl-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8ag**) as a colorless oil (80 mg, 0.18 mmol, 89%). R_f = 0.26 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.85 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.45 – 7.39 (m, 3H, Ar*H*), 7.35 – 7.29 (m, 2H, Ar*H*), 7.28 – 7.23 (m, 1H, Ar*H*), 7.16 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H, Ar*H*), 6.80 (d, *J* = 16.3 Hz, 1H, CHC*H*Ph), 6.62 (d, *J* = 16.2 Hz, 1H, C*H*CHPh), 4.27 (qd, *J* = 7.1, 2.6 Hz, 2H, OC*H*$_2$CH$_3$), 1.92 (s, 3H, CC*H*$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 165.4, 141.4, 136.1, 135.3, 132.9, 131.4, 131.2, 128.8, 128.4, 128.1, 127.8, 126.9, 94.0, 81.4, 62.1, 23.2, 14.2; IR (ν_{max}, cm^{-1}) 2963 (w), 2920 (m), 2856 (w), 1744 (m), 1345 (w), 1274 (m), 1241 (s), 1180 (s), 1131 (s), 1092 (s), 1043 (m), 1016 (s), 965 (m), 914 (m), 736 (s), 691 (s); HRMS (ESI) Calcd for $C_{20}H_{19}INaO_4^+$ $[M+Na]^+$ 473.0220; found 473.0213.

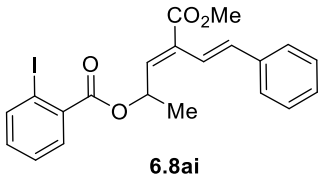
(*E*)-2-Oxo-3-styryltetrahydrofuran-3-yl 2-iodobenzoate (6.8ah)



6.8ah

Following general procedure **E**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and 3-diazodihydrofuran-2(3*H*)-one (**6.6p**) (44.8 mg, 0.400 mmol), afforded (*E*)-2-oxo-3-styryltetrahydrofuran-3-yl 2-iodobenzoate (**6.8ah**) as a thick colorless oil (78 mg, 0.18 mmol, 90%). R_f = 0.31 (EtOAc/pentane 20:80); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar*H*), 7.91 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.50 – 7.39 (m, 3H, Ar*H*), 7.39 – 7.28 (m, 3H, Ar*H*), 7.18 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.95 (d, *J* = 16.2 Hz, 1H, CHC*H*Ph), 6.48 (d, *J* = 16.2 Hz, 1H, C*H*CHPh), 4.65 (td, *J* = 9.2, 2.4 Hz, 1H, OCH_2^1), 4.36 (td, *J* = 9.4, 7.0 Hz, 1H, OCH_2^2), 3.10 (dt, *J* = 13.4, 9.4 Hz, 1H, CCH_2^1), 2.90 (ddd, *J* = 13.4, 7.0, 2.5 Hz, 1H, CCH_2^2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 165.2, 141.6, 135.1, 134.6, 133.9, 133.4, 131.6, 129.1, 128.9, 128.2, 127.2, 123.1, 94.3, 80.4, 65.0, 33.4; IR (ν_{max}, cm^{-1}) 2974 (m), 2900 (m), 1735 (s), 1495 (m), 1449 (m), 1431 (m), 1276 (s), 1256 (s), 1092 (s), 1127 (m), 1042 (s), 1016 (s), 974 (m), 764 (s), 750 (s); HRMS (ESI) Calcd for $C_{19}H_{15}INaO_4^+$ $[M+Na]^+$ 456.9907; found 456.9906.

(3*E*,5*E*)-4-(Methoxycarbonyl)-6-phenylhexa-3,5-dien-2-yl 2-iodobenzoate (6.8ai)

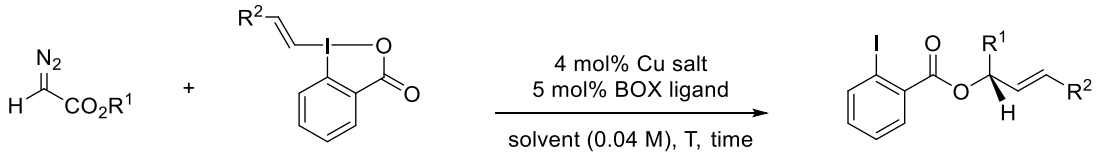


6.8ai

Following general procedure **E**, starting from (*E*)-1-styryl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6.7a**) (70.0 mg, 0.200 mmol) and (*E*)-methyl 2-diazopent-3-enoate (**6.6q**) (0.400 mL, 1.0 M in pentane, 0.400 mmol), afforded (3*E*,5*E*)-4-(methoxycarbonyl)-6-phenylhexa-3,5-dien-2-yl 2-iodobenzoate (**6.8ai**) as a

colorless oil (58 mg, 0.13 mmol, 63%). R_f = 0.22 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.79 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.53 – 7.46 (m, 2H, Ar*H*), 7.43 – 7.31 (m, 3H, Ar*H*), 7.31 – 7.27 (m, 1H, Ar*H*), 7.15 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.09 (d, *J* = 16.3 Hz, 1H, CHC*H*Ph), 6.97 (d, *J* = 16.0 Hz, 1H, C*H*CHPh), 6.71 (d, *J* = 8.7 Hz, 1H, CH_3CHCH), 6.15 (dq, *J* = 8.3, 6.5 Hz, 1H, OC*H*CH_3), 3.83 (s, 3H, OCH_3), 1.59 (d, *J* = 6.5 Hz, 3H, OCHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 165.9, 141.5, 139.3, 136.9, 135.7, 135.2, 132.8, 131.7, 131.1, 128.8, 128.5, 128.1, 127.1, 120.2, 94.2, 68.9, 52.4, 20.5; IR (ν_{max}, cm^{-1}) 2948 (w), 2995 (w), 2844 (w), 1789 (w), 1718 (s), 1583 (m), 1436 (m), 1282 (m), 1241 (s), 1156 (m), 1129 (s), 1098 (s), 1039 (s), 1015 (s), 968 (m), 739 (s), 694 (s); HRMS (ESI) Calcd for $C_{21}H_{19}INaO_4^+$ [M+Na]$^+$ 485.0220; found 485.0219.

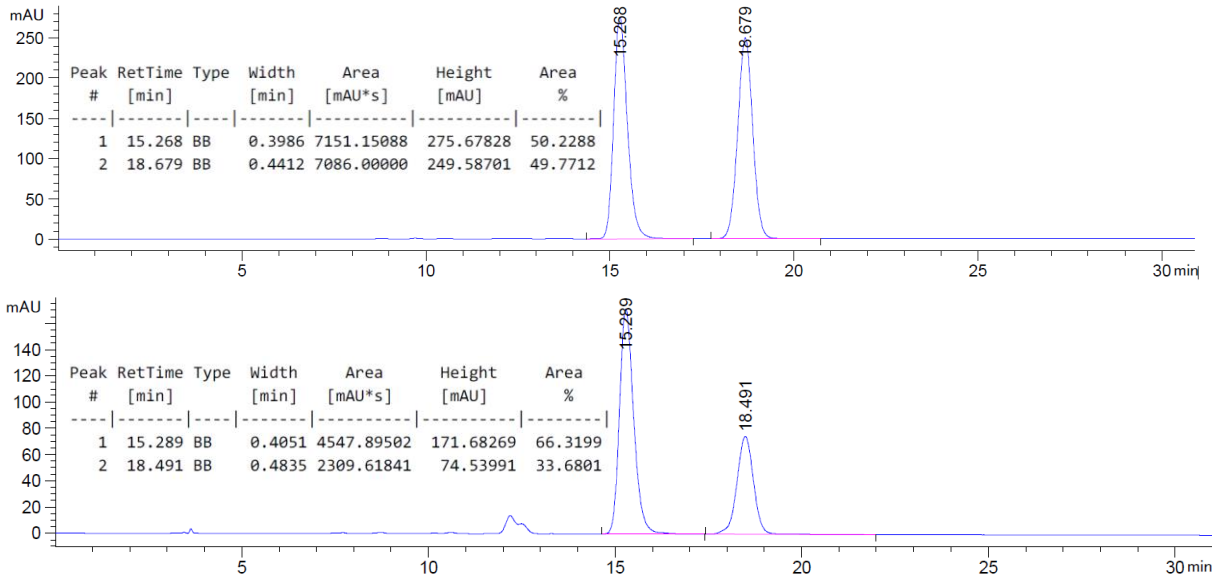
10.4.5. Enantioselective transformation



Under inert atmosphere, a catalytic solution was prepared by mixing the copper salt (4.00 µmol, 0.08 equiv), and BOX ligand (**6.5b-r**) (5.00 µmol, 0.10 equiv) in the solvent (0.500 mL) at 25 °C for 1 h. 0.250 mL of the catalytic solution was then added to a stirring suspension of VBX (0.05 mmol, 1.00 equiv) and diazo compound (0.10 mmol, 2.00 equiv) in the solvent (1.0 mL). The reaction mixture was stirred at the indicated temperature and time (monitored by TLC (EtOAc/pentane 5:95 and MeOH/DCM 5:95)) and the solvent was removed under reduced pressure. The resulting crude oil was purified by PTLC (EtOAc/pentane) directly without further work-up to afford the corresponding allylic ester product.

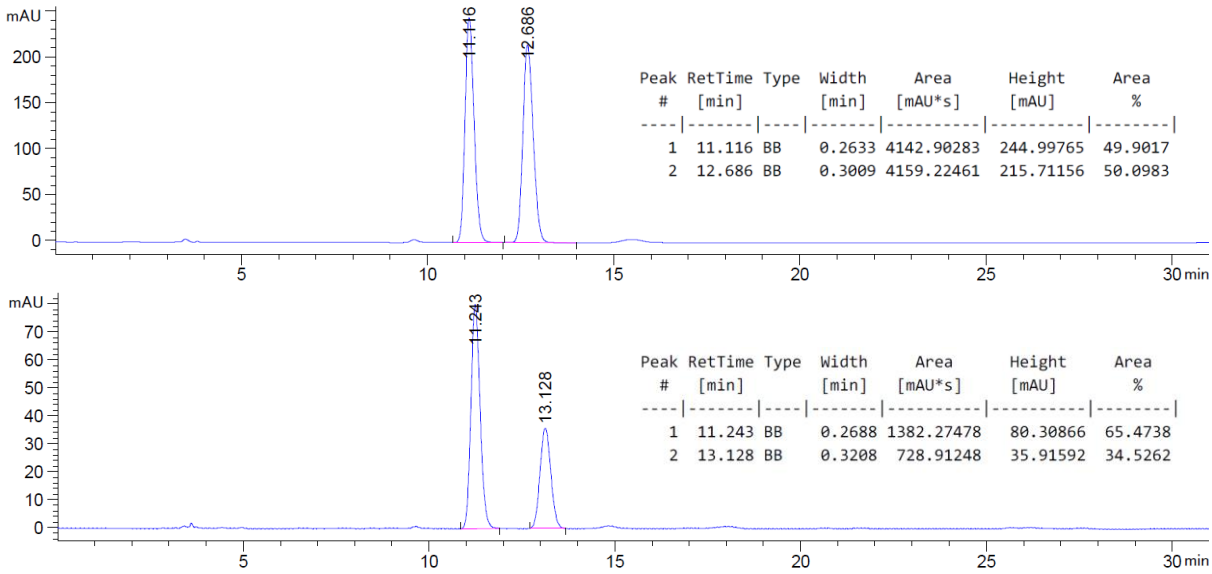
HPLC trace of compound **6.8a**

Chiral HPLC conditions: Chiralpak IC 95:5 Hexane/*i*PrOH, 1 mL/min, 30 min. λ = 254 cm^{-1}.



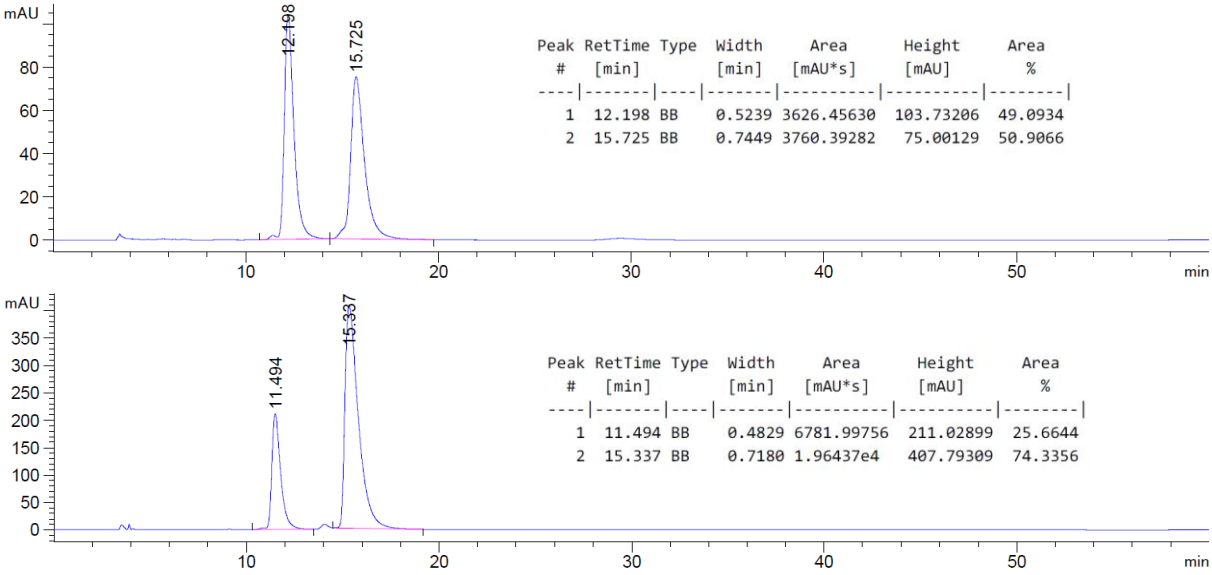
HPLC of trace compound **6.8j**

Chiral HPLC conditions: Chiralpak IC 95:5 Hexane/*i*PrOH, 1 mL/min, 30 min. λ = 254 cm^{-1}.



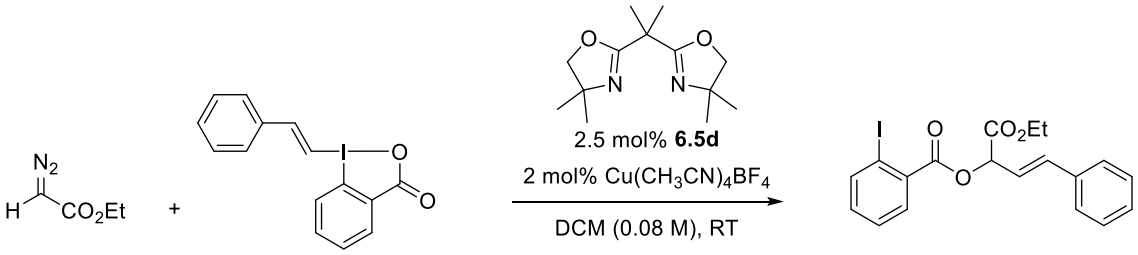
HPLC trace of compound **6.8x**

Chiral HPLC conditions: Chiralpak IC 99.50:0.50 Hexane/*i*PrOH, 1 mL/min, 60 min. λ = 254 cm^{-1}.



10.4.6. Product Modifications

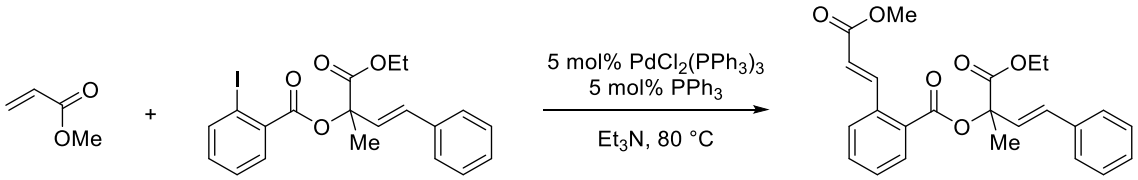
Scale-up synthesis of 6.5d using DCM as solvent and using a lower catalyst loading



6.6a **6.7a** **6.8a**

A catalytic solution was prepared by mixing $Cu(CH_3CN)_4BF_4$ (12.6 mg, 40.0 µmol) and 2,2'-(propane-2,2-diyl)bis(4,4-dimethyl-4,5-dihydrooxazole) (**6.5d**) (11.9 mg, 50.0 µmol) in DCM (5.0 mL) at 25 °C for 1 h. The catalyst solution was then added to a stirring suspension of Ph-VBX (**6.7a**) (700 mg, 2.00 mmol, 1.00 equiv) and ethyl 2-diazoacetate (**6.6a**) (0.484 mL, 4.00 mmol, 2.00 equiv) in DCM (20.0 mL). The reaction mixture was stirred at 25 °C for 2 h, then the solvent was removed under reduced pressure and the resulting crude oil was purified by column chromatography using EtOAc/pentane 5:95 as mobile phase to afford (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**4a**) as a colorless oil (562 mg, 1.29 mmol, 64%).

(*E*)-1-Ethoxy-2-methyl-1-oxo-4-phenylbut-3-en-2-yl 2-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)benzoate (6.33)

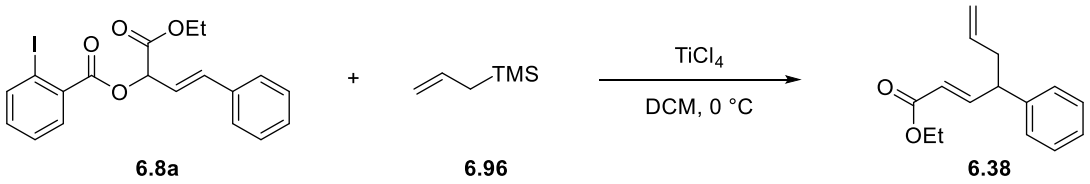


6.32 **6.8ag** **6.33**

A flame dried 8 mL microwave vial was charged with (*E*)-1-ethoxy-2-methyl-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8ag**) (45.0 mg, 0.100 mmol, 1.00 equiv), bis(triphenylphosphine)palladium (II) chloride (3.51 mg, 5.00 µmol, 0.05 equiv), triphenylphosphine (1.31 mg, 5.00 µmol, 0.05 equiv) and trimethylamine (0.5 mL). The resulting reaction mixture was degassed by "pump-freeze-thaw" cycles (3 times) *via* a syringe needle and then methyl acrylate (**6.32**) (45.0 µL, 0.500 mmol, 5.00 equiv) was added by syringe and the reaction mixture was stirred at 80 °C for 24 h. The solvent was removed under reduced pressure and the product was purified by column chromatography using EtOAc/pentane 15:85 as eluent to afford (*E*)-1-ethoxy-2-methyl-1-oxo-4-phenylbut-3-en-2-yl 2-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)benzoate (**6.33**) as a thick colorless oil (27.0 mg, 66.1 µmol, 66%). R_f = 0.32 (EtOAc/pentane 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 15.9 Hz, 1H, ArC*H*CHCO$_2$Me), 7.99 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar*H*), 7.66 – 7.59 (m, 1H, Ar*H*), 7.59 – 7.54 (m, 1H, Ar*H*), 7.47 (td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.44 – 7.39 (m, 2H, Ar*H*), 7.37 – 7.30 (m, 2H, Ar*H*), 7.29 – 7.22 (m, 1H, Ar*H*), 6.77 (d, *J* = 16.2 Hz, 1H, CHC*H*Ph), 6.65 (d, *J* = 16.2 Hz, 1H, C*H*CHPh), 6.34 (d, *J* = 15.9 Hz, 1H, ArCHC*H*CO$_2$Me), 4.28 (qd, *J* = 7.1, 1.9 Hz, 2H, OC*H*$_2$CH$_3$), 3.74 (s, 3H, OC*H*$_3$), 1.93 (s, 3H, CC*H*$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 167.0, 165.8, 144.0, 136.3, 136.1, 132.7, 131.4, 131.0, 130.3, 129.6, 128.8, 128.4, 128.0, 127.9, 127.0, 120.8, 81.3, 62.1, 51.9, 23.2, 14.2; IR (ν_{max}, cm^{-1}) 2991 (m), 2956 (m), 2926 (m), 1715 (s), 1636 (w), 1479 (w), 1448 (m), 1377 (w), 1315 (m), 1269 (s), 1196 (m), 1173 (m),

1121 (m), 1071 (s), 1044 (m), 1021 (m), 972 (m), 865 (m); HRMS (ESI) Calcd for $C_{24}H_{24}NaO_6^+$ [M+Na]$^+$ 431.1465; found 431.1472.

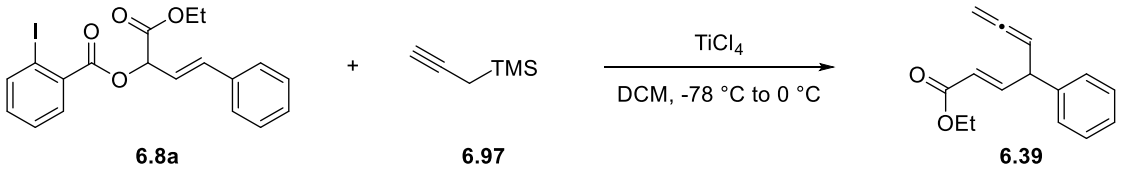
(*E*)-ethyl 4-phenylhepta-2,6-dienoate (6.38)



6.8a **6.96** **6.38**

To a solution of (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8a**) (87.2 mg, 0.200 mmol, 1.00 equiv) and allyltrimethylsilane (**6.96**) (48.0 µL, 0.300 mmol, 1.50 equiv) in dry DCM (2.0 mL) was added $TiCl_4$ (23.0 µL, 0.210 mmol, 1.05 equiv) dropwise at 0 °C under N_2. The reaction was stirred 15 minutes at 0 °C and then quenched with a saturated solution of $NaHCO_3$ (2.0 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using DCM/pentane 10:90 as eluent to afford (*E*)-ethyl 4-phenylhepta-2,6-dienoate (**6.38**) as a colorless oil (38.0 mg, 0.165 mmol, 83 %). R_f = 0.50 (DCM/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H, Ar*H*), 7.27 – 7.15 (m, 3H, Ar*H*), 7.09 (dd, *J* = 15.7, 7.5 Hz, 1H, C*H*CHCO$_2$Et), 5.78 (dd, *J* = 15.7, 1.4 Hz, 1H, CHC*H*CO$_2$Et), 5.69 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 1H, CHC*H*$_2$), 5.10 – 4.96 (m, 2H, C*H*C*H*$_2$), 4.17 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 3.50 (qd, *J* = 7.5, 1.3 Hz, 1H, PhC*H*CH$_2$), 2.56 (tt, *J* = 7.1, 1.3 Hz, 2H, PhCHC*H*$_2$), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 151.0, 141.7, 135.7, 128.8, 128.0, 127.0, 121.3, 117.2, 60.5, 48.4, 39.3, 14.4; IR (ν_{max}, cm^{-1}) 2975 (m), 2924 (m), 1718 (s), 1650 (m), 1456 (w), 1368 (m), 1311 (m), 1270 (m), 1233 (m), 1168 (s), 1045 (m), 981 (m), 916 (m), 759 (m), 699 (s); HRMS (ESI) Calcd for $C_{15}H_{19}O_2^+$ [M+H]$^+$ 231.1380; found 231.1377.

(*E*)-Ethyl 4-phenylhepta-2,5,6-trienoate (6.39)

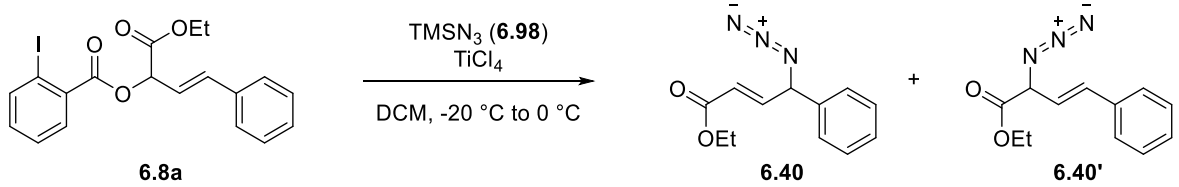


6.8a **6.97** **6.39**

To a solution of (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8a**) (87.2 mg, 0.200 mmol, 1.00 equiv) and propargyltrimethylsilane (**6.97**) (60.0 µL, 0.400 mmol, 2.00 equiv) in dry DCM (2.0 mL) was added $TiCl_4$ (23.0 µL, 0.210 mmol, 1.05 equiv) dropwise at -78 °C under N_2. The reaction was allowed to warm slowly to 0 °C and then quenched with a saturated solution of $NaHCO_3$ (2.0 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 2:98 as eluent to afford afford (*E*)-ethyl 4-phenylhepta-2,5,6-trienoate (**6.39**) as a colorless oil (27.0 mg, 0.118 mmol, 59 %). R_f = 0.54 (DCM/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H, Ar*H*), 7.29 – 7.20 (m, 3H, Ar*H*), 7.13 (dd, *J* = 15.6, 7.0 Hz, 1H, C*H*CHCO$_2$Et), 5.84 (dd, *J* = 15.6, 1.5 Hz, 1H, CHC*H*CO$_2$Et), 5.37 (q, *J* = 6.8 Hz, 1H, C*H*CCH$_2$), 4.82 (dd, *J* = 6.6, 2.7 Hz, 2H, CHCC*H*$_2$), 4.18 (q, *J* = 7.1 Hz, 3H, PhC*H* and OC*H*$_2$CH$_3$), 1.28 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6, 166.6, 149.4, 140.9, 128.9, 128.1, 127.3, 121.9, 91.9, 77.2, 60.5, 47.4, 14.4; IR (ν_{max}, cm^{-1}) 2982 (m), 2924 (m), 2853 (w), 1958 (w), 1715 (s), 1650 (m), 1454 (m), 1367 (m), 1307 (m), 1269 (m), 1232

(m), 1169 (s), 1071 (m), 1040 (s), 982 (m), 853 (m); HRMS (ESI) Calcd for $C_{15}H_{17}O_2^+$ $[M+H]^+$ 229.1223; found 229.1220.

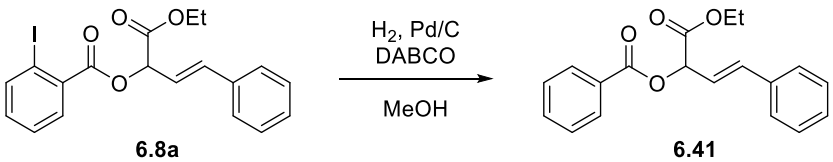
(*E*)-Ethyl 4-azido-4-phenylbut-2-enoate (6.40) and (*E*)-Ethyl 2-azido-4-phenylbut-3-enoate (6.40')



6.8a **6.40** **6.40'**

To a solution of (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8a**) (87.2 mg, 0.200 mmol, 1.00 equiv) and azidotrimethylsilane (**6.98**) (40.0 µL, 0.300 mmol, 1.50 equiv) in dry DCM (2.0 mL) was added $TiCl_4$ (23.0 µL, 0.210 mmol, 1.05 equiv) dropwise at -20 °C under N_2. The reaction was allowed to warm to room temperature and then quenched with a saturated solution of $NaHCO_3$ (2.0 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using DCM/pentane 10:90 as eluent to afford an isomeric mixture of (*E*)-ethyl 4-azido-4-phenylbut-2-enoate (**6.40**) and (*E*)-ethyl 2-azido-4-phenylbut-3-enoate (**6.40'**) as a colorless oil, 70:30 mixture of **6.40** and **6.40'** (40 mg, 0.17 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 5H, Ar*H*), 6.94 (dd, *J* = 15.5, 5.7 Hz, 1H, C*H*CHCO$_2$Et), 6.14 (dd, *J* = 15.5, 1.6 Hz, 1H, CHC*H*CO$_2$Et), 5.18 (dd, *J* = 5.7, 1.6 Hz, 1H, N$_3$C*H*CC), 4.33 – 4.18 (m, 2H, OC*H*$_2$CH$_3$), 1.34 – 1.28 (m, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 144.0, 129.3, 129.1, 127.6, 127.0, 123.0, 65.6, 60.9, 14.4 for γ-azidated ester (**6.40**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 5H, Ar*H*), 6.77 (dd, *J* = 15.8 Hz, 1.2 Hz, 1H, PhC*H*CH), 6.27 (dd, *J* = 15.8, 7.5 Hz, 1H, PhCHC*H*), 4.54 (dd, *J* = 7.5, 1.3 Hz, 1H, N$_3$C*H*CO$_2$Et), 4.33 – 4.18 (m, 2H, OC*H*$_2$CH$_3$), 1.34 – 1.28 (m, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 136.6, 136.0, 135.5, 128.9, 128.9, 120.8, 63.9, 62.4, 14.3 for α-azidated ester (**6.40'**). The values of the NMR spectra are in accordance with reported literature data.[437]

(*E*)-1-Ethoxy-1-oxo-4-phenylbut-3-en-2-yl benzoate (6.41)



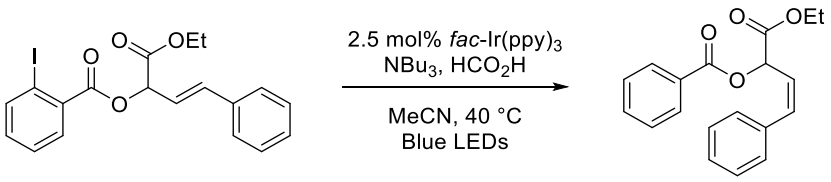
6.8a **6.41**

Following a reported procedure,[319] in a 20 mL Schlenk flask, (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8a**) (43.6 mg, 0.100 mmol, 1.00 equiv), DABCO (112 mg, 1.00 mmol, 10.0 equiv) and Pd/C (5.0 mg) were suspended in MeOH (10 mL). The reaction flask was evacuated and backfilled with argon (3 times) before being evacuated and backfilled with H_2 (1 atm). The reaction was stirred 10 min at room temperature, then the hydrogen was evacuated and replaced with argon. The reaction mixture was filtered through a pad of celite and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 95:5 as eluent to afford (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl benzoate (**6.41**) as a colorless oil (24.0 mg, 77.0 µmol, 77 %). R_f = 0.29 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.10 (m, 2H, Ar*H*), 7.65 – 7.55 (m, 1H, Ar*H*), 7.53 – 7.41 (m, 4H, Ar*H*), 7.40 – 7.27 (m, 3H, Ar*H*), 6.92 (dd, *J* = 16.0, 1.3 Hz, 1H,

[437] Y. Sawama, S. Nagata, Y. Yabe, K. Morita, Y. Monguchi, H. Sajiki, *Chem. Eur. J.* **2012**, *18*, 16608.

CHC*H*Ph), 6.41 (dd, *J* = 15.9, 7.0 Hz, 1H, C*H*CHPh), 5.85 (dd, *J* = 7.0, 1.3 Hz, 1H, OC*H*CC), 4.27 (qd, *J* = 7.1, 5.1 Hz, 2H, OC*H*$_2$CH$_3$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 165.9, 135.8, 135.4, 133.6, 130.1, 129.5, 128.8, 128.7, 128.6, 127.0, 121.2, 73.8, 62.0, 14.3; IR (ν_{max}, cm^{-1}) 3057 (w), 3030 (w), 1748 (m), 1724 (s), 1452 (m), 1315 (w), 1272 (s), 1251 (m), 1196 (m), 1106 (s), 1069 (m), 1024 (m), 965 (m), 738 (m), 712 (s), 689 (s); HRMS (ESI) Calcd for $C_{19}H_{18}NaO_4^+$ [M+Na]$^+$ 333.1097; found 333.1099.

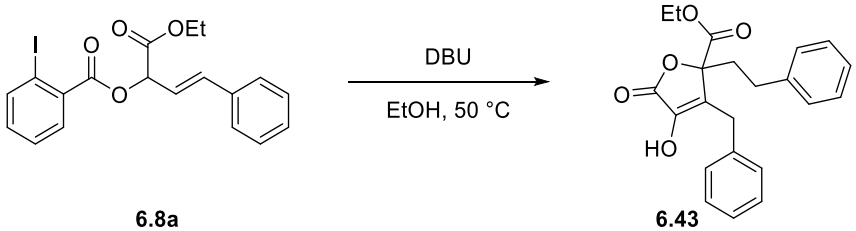
(*Z*)-1-Ethoxy-1-oxo-4-phenylbut-3-en-2-yl benzoate (6.42)



6.8a **6.42**

Following a reported procedure,[320] a flame dried 8 mL microwave vial with a rubber septum and magnetic stirring bar was charged with (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8a**) (43.6 mg, 0.100 mmol, 1.00 equiv), MeCN (1.0 mL), tributylamine (240 µL, 1.00 mmol, 10.0 equiv), formic acid (38 µL, 1.00 mmol, 10.0 equiv) and *fac*-Ir(ppy)$_3$ (1.64 mg, 2.50 µmol, 0.025 equiv). The resulting reaction mixture was degassed by "pump-freeze-thaw" cycles (3 times) *via* a syringe needle and placed in a 250 mL beaker with blue LEDs wrapped inside. The reaction mixture was stirred at 40 °C for 18 h. The solvent was removed under reduced pressure and the product was purified by column chromatography using DCM/pentane 50:50 as eluent to afford (*Z*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl benzoate (**6.42**) as a white solid (25.2 mg, 82.0 µmol, 82%). M.p. 76 – 78 °C; R_f = (DCM/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.03 (m, 2H, Ar*H*), 8.60 – 7.54 (m, 1H, Ar*H*), 7.51 – 7.28 (m, 7H, Ar*H*), 6.94 (d, *J* = 11.4 Hz, 1H, CHC*H*Ph), 6.05 (dd, *J* = 9.8, 0.9 Hz, 1H, OC*H*CC), 5.91 (dd, *J* = 11.4, 9.9 Hz, 1H, C*H*CHPh), 4.28 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 165.8, 136.8, 135.4, 133.5, 130.1, 129.5, 129.0, 128.7, 128.5, 128.3, 123.0, 70.3, 62.0, 14.2; IR (ν_{max}, cm^{-1}) 3065 (w), 3024 (w), 2981 (w), 1750 (s), 1722 (s), 1452 (m), 1370 (w), 1333 (w), 1315 (m), 1278 (s), 1258 (s), 1194 (m), 1100 (s), 1069 (s), 1026 (s), 814 (m), 773 (m), 710 (s); HRMS (ESI) Calcd for $C_{19}H_{18}NaO_4^+$ [M+Na]$^+$ 333.1097; found 333.1106.

Ethyl 3-benzyl-4-hydroxy-5-oxo-2-phenethyl-2,5-dihydrofuran-2-carboxylate (6.43)

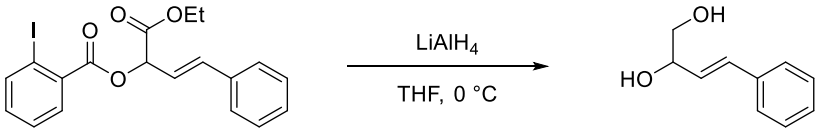


6.8a **6.43**

DBU (0.151 mL, 1.00 mmol, 10.0 equiv) was added to a solution of (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8a**) (43.6 mg, 0.100 mmol, 1.00 equiv) in ethanol (1 mL). The resulting solution was stirred 6 h at 50 °C. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography using MeOH/DCM 2:98 as eluent to afford ethyl 3-benzyl-4-hydroxy-5-oxo-2-phenethyl-2,5-dihydrofuran-2-carboxylate (**6.43**) as a white solid (17 mg, 0.046 mmol, 93%). M.p. 111 – 113 °C; R_f = 0.55 (MeOH/DCM 3:97); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H, Ar*H*), 7.27 – 7.21 (m, 5H, Ar*H*), 7.20 – 7.14 (m, 1H, Ar*H*), 7.01 – 6.94 (m, 2H, Ar*H*),

5.78 (br s, 1H, O*H*), 3.95 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.67 (s, 2H, CC*H*$_2$Ph), 2.55 – 2.32 (m, 3H, C*H*$_2$), 2.19 – 2.05 (m, 1H, C*H*$_2$), 1.15 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 168.0, 140.4, 139.1, 136.2, 130.9, 129.1, 128.9, 128.6, 128.5, 127.2, 126.4, 87.2, 62.6, 36.0, 30.2, 29.3, 14.0; IR (ν_{max}, cm^{-1}) 2919 (w), 1739 (s), 1292 (m), 1249 (m), 1218 (m), 1136 (m), 1105 (m), 1017 (m), 748 (s), 691 (m), 668 (s); HRMS (ESI) Calcd for $C_{22f}H_{23}O_5^+$ $[M+H]^+$ 367.1540; found $[M+H]^+$ 367.1549.

(*E*)-4-Phenylbut-3-ene-1,2-diol (6.44)



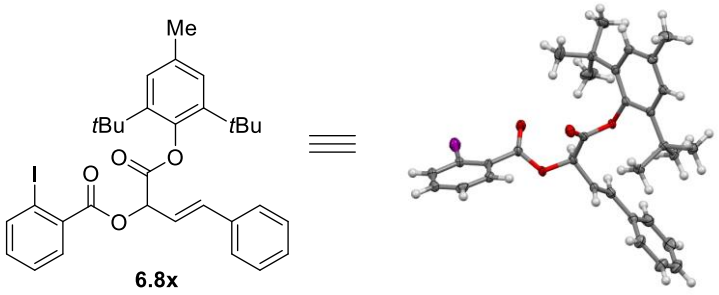
6.8a **6.44**

Following a reported procedure,[229] (*E*)-1-ethoxy-1-oxo-4-phenylbut-3-en-2-yl 2-iodobenzoate (**6.8a**) (87.2 mg, 0.200 mmol, 1.00 equiv) was dissolved in anhydrous THF (2.00 mL) in a 5 mL microwave vial. Then $LiAlH_4$ (2.4 M in THF, 0.300 mL, 0.600 mmol, 3.00 equiv) was added at 0 °C and stirred for 1 h. The resulting solution was quenched by the addition of saturated aqueous potassium sodium tartrate (2.00 mL) and the biphasic mixture was stirred for 1 h at room temperature. Then the reaction mixture was diluted with water (2.0 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 50:50 as eluent to afford (*E*)-4-phenylbut-3-ene-1,2-diol (**6.44**) as a white solid (30.0 mg, 0.183 mmol, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.18 (m, 5H, Ar*H*), 6.70 (dd, *J* = 16.0, 1.3 Hz, 1H, CHC*H*Ph), 6.21 (dd, *J* = 16.0, 6.3 Hz, 1H, C*H*CHPh), 4.44 (m, 1H, HOC*H*CC), 3.76 (dd, *J* = 11.2, 3.6 Hz, 1H, C*H*$_2$OH), 3.61 (dd, *J* = 11.2, 7.3 Hz, 1H, C*H*$_2$OH), 2.09 (br s, 2H, 2 x O*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 132.4, 128.8, 128.1, 127.8, 126.7, 73.3, 66.6. The values of the NMR spectra are in accordance with reported literature data.[438]

[438] T. Saravanan, R. Selvakumar, M. Doble, A. Chadha, *Tetrahedron: Asymmetry*, **2012**, *23*, 1360.

10.4.7. Crystal Structure

CCDC 1897009



6.8x

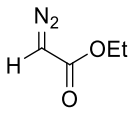
The ORTEP picture has been obtained by using a probability level of 50% for the ellipsoid display.

Empirical formula	$C_{32}H_{35}IO_4$	
Formula weight	610.50	
Temperature	101(1) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	*P*-1	
Unit cell dimensions	a = 10.8114(6) Å	α = 81.599(4)°.
	b = 10.9975(5) Å	β = 82.906(5)°.
	c = 12.6115(7) Å	γ = 78.119(4)°.
Volume	1444.84(13) $Å^3$	
Z	2	
Density (calculated)	1.403 Mg/m^3	
Absorption coefficient	8.972 mm^{-1}	
F(000)	624	
Crystal size	0.635 x 0.181 x 0.049 mm^3	
Theta range for data collection	3.559 to 75.162°.	
Index ranges	-13 ≤ h ≤ 13, -13 ≤ k ≤ 10, -15 ≤ l ≤ 15	
Reflections collected	10366	
Independent reflections	5771 [R_{int} = 0.0382]	
Completeness to theta = 67.684°	99.9 %	
Absorption correction	Analytical	
Max. and min. transmission	0.675 and 0.116	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5771 / 0 / 341	
Goodness-of-fit on F^2	1.039	
Final R indices [I > 2sigma(I)]	R_1 = 0.0400, wR_2 = 0.1027	
R indices (all data)	R_1 = 0.0464, wR_2 = 0.1072	
Largest diff. peak and hole	0.919 and -1.211 e.$Å^{-3}$	

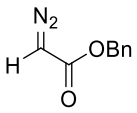
10.5. Three-Component Reaction for the Synthesis of Highly Functionalized Propargyl- and Allyl-Ethers

10.5.1. Preparation of Diazo Compounds

Ethyl 2-diazoacetate (**7.2c**) and benzyl 2-diazoacetate (**7.2d**) were directly purchased from chemical suppliers

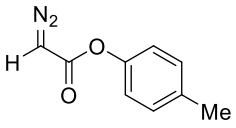


7.2c

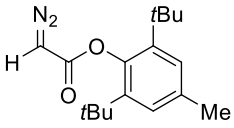


7.2d

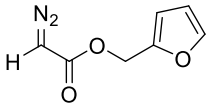
The synthesis of *p*-tolyl 2-diazoacetate (**7.2e**), 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**7.2f**) and furan-2-ylmethyl 2-diazoacetate (**7.2g**) has been reported in section 10.2.1. The synthesis of diethyl (diazomethyl)phosphonate (**7.2i**), ethyl diazomethanesulfonate (**7.2j**), 2,2,2-trifluorodiazoethane (**7.2k**), ethyl 2-diazopropanoate (**7.2p**) and 3-Diazodihydrofuran-2(3*H*)-one (**7.2r**) have been reported in section 10.4.1.



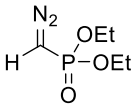
7.2e



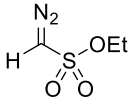
7.2f



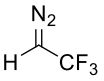
7.2g



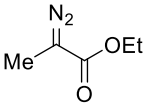
7.2i



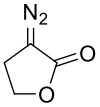
7.2j



7.2k



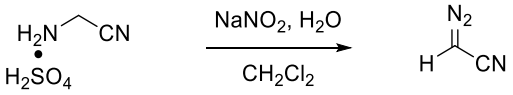
7.2p



7.2r

2-Diazoacetonitrile (7.2h)

CAUTION: This diazo compound is reported to be explosive at high concentration.

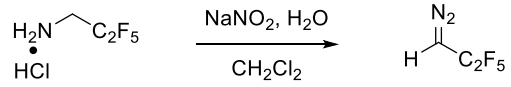


7.49 **7.2h**

Following a reported procedure,[439] to a suspension of 2-aminoacetonitrile sulfate (**7.49**) (3.70 g, 24.0 mmol, 1.00 equiv) in DCM (28 mL) at -10 °C was cautiously added dropwise an aqueous solution of sodium nitrite (4.97 g, 72.0 mmol, 3.00 equiv) in distilled water (22 mL) at such a rate that the temperature of the reaction did not rise above 0 °C. During the addition effervescence was observed. After the complete addition, the reaction was allowed to stir for 30 min at 0 °C. The organic layer was separated and the aqueous layer further extracted with DCM (20 mL). The combined organic layers were washed with 1% aqueous $NaHCO_3$ solution (10 mL), dried over $MgSO_4$, filtered and stored at -18 °C. The concentration of the solution was assumed to be 0.5 M of diazoacetonitrile (**7.2h**) in DCM and was used immediately without further purification.

[439] J. Dunn, A. P. Dobbs, *Tetrahedron* **2015**, *71*, 7386.

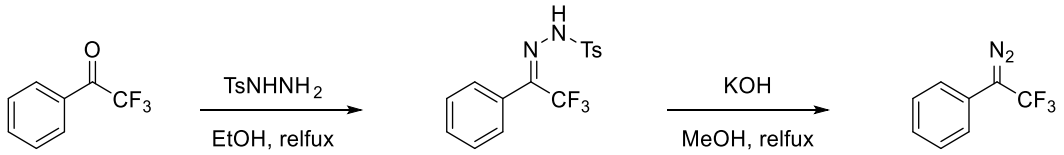
3-Diazo-1,1,1,2,2-pentafluoropropane (7.2l)



7.50 **7.2l**

Under argon, 2,2,2-trifluoroethanamine hydrochloride (**7.50**) (0.928 g, 5.00 mmol, 1.00 equiv) and sodium nitrite (0.379 g, 5.50 mmol, 1.10 equiv) were dissolved in degassed CH_2Cl_2 (10 mL). Degassed water (1.00 mL, 55.5 mmol, 11.1 equiv) was added slowly at 0 °C. The solution was stirred for 2 h at 0 °C and 1 h at room temperature. The organic layer was isolated, dried over $MgSO_4$, transferred into a vial, sealed and stored at -18 °C. The concentration of the obtained solution was determined to be 0.36 M by ^{19}F NMR analysis (according to an internal reference, $PhCF_3$). ^{19}F NMR (377 MHz, CH_2Cl_2) δ -88.96 – -89.01 (m), -110.98 – -111.03 (m).

(1-Diazo-2,2,2-trifluoroethyl)benzene (7.2q)

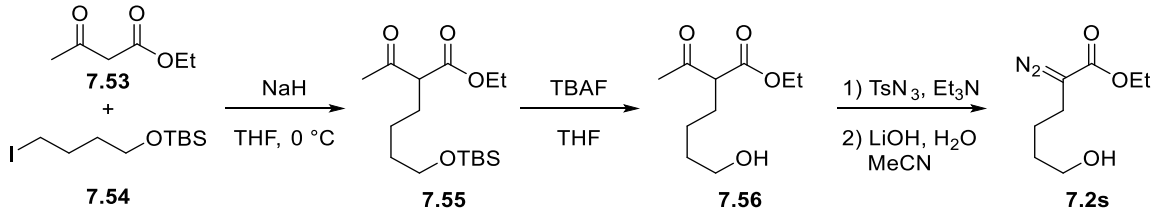


7.51 **7.52** **7.2q**

2,2,2-Trifluoroacetophenone (**7.51**) (702 µL, 5.00 mmol, 1.05 equiv) was added to EtOH (18.8 mL) at room temperature followed by *p*-toluenesulfonylhydrazide (880 mg, 4.76 mmol, 1.00 equiv) in one portion. A condenser was then attached and the contents were heated to reflux for 12 h. After this time, the solvent was removed under reduced pressure until the beginning of the formation of a solid. Then, pentane (100 mL) was added and the precipitate was collected by filtration and washed with pentane. The solid obtained was used in the next step without purification.

Following a reported procedure,[223a] 4-methyl-N'-(2,2,2-trifluoro-1-phenylethylidene)benzenesulfonohydrazide (**7.52**) was disolved in a 0.4 M solution of potassium hydroxide (561 mg, 5.00 mmol, 2.00 equiv) in MeOH (25.0 mL). A condenser was attached and the reaction mixture was stirred at reflux for 0.5 h. Then, the reaction was cooled to room temperature and diluted with water (15 mL). The crude product was extracted with pentane (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography using pentane as eluent to afford (1-diazo-2,2,2-trifluoroethyl)benzene (**7.2q**) as a volatile orange oil (344 mg, 1.85 mmol, 37%). The compound was kept as a 0.6 M solution in DCM at -18 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 2H, Ar*H*), 7.23 – 7.17 (m, 1H, Ar*H*), 7.13 – 7.05 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.6, 126.1, 125.8 (q, *J* = 269.4 Hz), 123.7, 122.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.4. One carbon was not resolved at 101 MHz. The values of the NMR spectra are in accordance with reported literature data.[223a]

Ethyl 2-diazo-6-hydroxyhexanoate (7.2s)



Adapted from a reported procedure,[440] ethyl acetoacetate (**7.53**) (3.79 mL, 30.0 mmol, 2.00 equiv) was added dropwise to a stirred suspension of sodium hydride (60 % dispersion in mineral oil, 900 mg, 22.5 mmol, 1.50 equiv) in dry THF (35.7 mL) at 0 °C. After 30 min, *tert*-butyl(4-iodobutoxy)dimethylsilane (**7.54**) (3.88 mL, 15.0 mmol, 1.00 equiv) was added slowly at ambient temperature, and the reaction was refluxed for 24 h. Saturated aqueous NH_4Cl (50 mL) was added, the two layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO4 and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford ethyl 2-acetyl-6-((*tert*-butyldimethylsilyl)oxy)hexanoate (**7.55**) as a colorless oil (3.66 g, 11.6 mmol, 77%). R_f = 0.30 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.59 (t, *J* = 6.3 Hz, 2H, C*H*$_2$OTBS), 3.40 (t, *J* = 7.4 Hz, 1H, C(O)C*H*C(O)), 2.22 (s, 3H, C(O)C*H*$_3$), 1.95 – 1.76 (m, 2H, CHC*H*$_2$), 1.57 – 1.48 (m, 2H, C*H*$_2$CH$_2$OTBS), 1.38 – 1.23 (m, 5H, OCH$_2$C*H*$_3$ and C*H*$_2$CH$_2$CH), 0.88 (s, 9H, Si-*tBu*), 0.03 (s, 6H, 2 x Si-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4, 170.0, 62.9, 61.5, 60.1, 32.6, 28.9, 28.2, 26.1, 24.0, 18.5, 14.3, -5.2; IR (ν_{max}, cm^{-1}) 2954 (m), 2930 (m), 2857 (m), 1741 (m), 1716 (s), 1360 (m), 1251 (m), 1150 (m), 1097 (s), 835 (s), 774 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{32}NaO_4Si^+$ 339.1962; Found 339.1961.

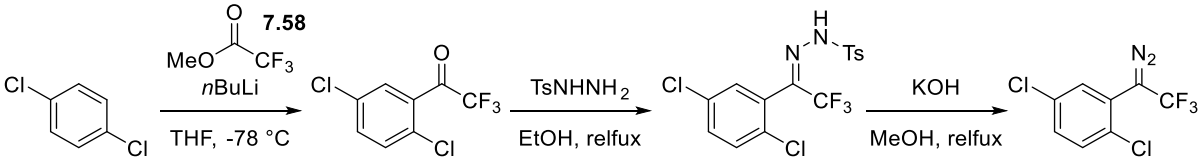
To a solution of ethyl 2-acetyl-6-((*tert*-butyldimethylsilyl)oxy)hexanoate (**7.55**) (3.17 g, 10.0 mmol, 1.00 equiv) in THF (20 mL) was added TBAF (11.0 mL, 11.0 mmol, 1.10 equiv, 1.0 M in THF) slowly and the mixture was stirred overnight at room temperature. After this time, the reaction was quechend by a saturated aqueous NH_4Cl solution (20 mL) and diluted with diethyl ether (20 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography using EtOAc/pentane 50:50 as eluent to afford ethyl 2-acetyl-6-hydroxyhexanoate (**7.56**) as a colorless oil (1.51 g, 7.49 mmol, 75%). R_f = 0.35 (EtOAc/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (qd, *J* = 7.1, 0.9 Hz, 2H, OC*H*$_2$CH$_3$), 3.64 (t, *J* = 6.4 Hz, 2H, C*H*$_2$OH), 3.42 (t, *J* = 7.3 Hz, 1H, C(O)C*H*C(O)), 2.23 (s, 3H, C(O)C*H*$_3$), 1.93 – 1.80 (m, 2H, CHC*H*$_2$), 1.64 – 1.53 (m, 3H, C*H*$_2$CH$_2$OH and O*H*), 1.42 – 1.31 (m, 2H, C*H*$_2$CH$_2$CH), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3, 170.0, 62.5, 61.5, 59.9, 32.4, 29.0, 27.9, 23.8, 14.3; IR (ν_{max}, cm^{-1}) 3436 (w), 2938 (m), 2869 (w), 1736 (s), 1711 (s), 1361 (m), 1201 (s), 1149 (s), 1056 (m), 1032 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{18}NaO_4^+$ 225.1097; Found 225.1101.

Adapted from a reported procedure,[440] a 1.0 M solution of tosylazide (2.07 g, 10.5 mmol, 1.50 equiv) in MeCN (10.5 mL) was added dropwise to a solution of 2-acetyl-6-hydroxyhexanoate (**7.56**) (1.46 g, 7.00 mmol, 1.00 equiv) and triethylamine (1.46 mL, 10.5 mmol, 1.50 equiv) in MeCN (21.2 mL) at ambient temperature. After stirring for 12 h, a solution of LiOH (0.84 g, 35 mmol, 5.0 equiv) in water (12.7 mL) was added and the mixture was stirred for another 12 h. Brine was added, the two layers were separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The

[440] S.-F. Zhu, X.-G. Song, Y. Li, Y. Cai, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 16374.

residue was purified by flash column chromatography using EtOAc/pentane 25:75 as eluent to afford ethyl 2-diazo-6-hydroxyhexanoate (**7.2s**) as a bright yellow oil (0.95 g, 5.1 mmol, 73%). R_f = 0.31 (EtOAc/pentane 25:75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.77 – 3.61 (m, 2H, C*H*$_2$OH), 2.43 – 2.30 (m, 2H, C*H*$_2$CN$_2$), 1.69 – 1.54 (m, 4H, C*H*$_2$C*H*$_2$), 1.51 (br s, 1H, O*H*), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 62.5, 60.9, 31.7, 24.2, 23.1, 14.7; IR (ν_{max}, cm^{-1}) 3437 (w), 2939 (w), 2868 (w), 2079 (s), 1686 (s), 1371 (s), 1328 (m), 1305 (s), 1276 (m), 1171 (s), 1119 (s), 1057 (m), 1024 (m), 740 (s); HRMS (APPI/LTQ-Orbitrap) m/z: $[M-N_2]^+$ Calcd. for $C_8H_{14}O_3^+$ 158.0937; Found 158.0937. One carbon was not resolved at 101 MHz.

1,4-Dichloro-2-(1-diazo-2,2,2-trifluoroethyl)benzene (7.2t)



Following a modified reported procedure,[441] a solution of 1,4-dichlorobenzene (**7.57**) (10.0 g, 68.0 mmol, 1.00 equiv) in anhydrous THF (150 mL) was cooled to -78 °C. Then, a 2.5 M solution of *n*-butyllithium (30.0 mL, 74.8 mmol, 1.10 equiv) in hexanes was added dropwise. The mixture was stirred for 1 h, followed by the dropwise addition of methyl 2,2,2-trifluoroacetate (**7.58**) (7.66 mL, 76.0 mmol, 1.12 equiv) in 30 min. The mixture was allowed to warm up to 0 °C, stirred for 2 h and then quenched with saturated aqueous ammonium chloride solution (50 mL). Diethyl ether (50 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation to afford 1-(2,5-dichloro-phenyl)-2,2,2-trifluoroethanone (**7.59**) as a colorless oil (12.2 g, 50.4 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H, Ar*H*), 7.49 – 7.54 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.8 (q, *J* = 37.6 Hz), 134.0, 133.1, 132.7, 132.1, 131.8, 129.6 (q, *J* = 2.2 Hz), 115.5 (q, *J* = 287.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.4. The values of the NMR spectra are in accordance with reported literature data.[441]

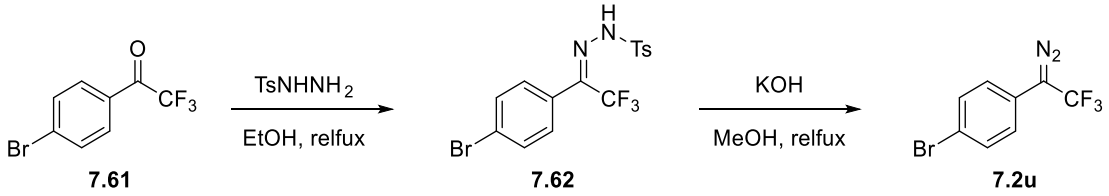
Adapted from a reported procedure,[223a] 1-(2,5-dichlorophenyl)-2,2,2-trifluoroethanone (**7.59**) (7.29 g, 30.0 mmol, 1.05 equiv) was added to EtOH (19 mL) at room temperature followed by *p*-toluenesulfonylhydrazide (5.32 g, 28.6 mmol, 1.00 equiv) in one portion. A condenser was then attached and the contents were heated to reflux for 12 h. After this time, the solvent was removed under reduced pressure until the beginning of the formation of a solid. Then, pentane (200 mL) was added and the precipitate was collected by filtration and washed with pentane. The solid obtained was used in the next step without purification.

Adapted from a reported procedure,[223a] *N*'-(1-(2,5-dichlorophenyl)-2,2,2-trifluoroethylidene)-4-methylbenzenesulfonohydrazide (**7.60**) was disolved in a 0.4 M solution of potassium hydroxide (3.37 g, 60.0 mmol, 2.00 equiv) in MeOH (17.5 mL). A condenser was attached and the reaction mixture was stirred at reflux for 0.5 h. Then, the reaction was cooled to room temperature and diluted with water (20 mL). The product was extracted with Et_2O (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography using pentane as eluent to afford 1,4-dichloro-2-(1-diazo-2,2,2-trifluoroethyl)benzene (**7.2t**) as a orange oil (1.69 g, 6.09 mmol, 20%). The compound was kept as a 0.6 M solution in DCM at -18 °C. R_f = 0.95 (pentane); ^{1}H NMR

[441] A. S. Golubev, A. F. Shidlovskii, A. S. Peregudov, N. D. Kagramanov, *Russ Chem Bull.* **2014**, *63*, 2264.

(400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H, Ar*H*), 7.30 – 7.25 (m, 1H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.7, 132.0, 131.8, 129.8, 129.5, 125.7 (q, *J* = 269.5 Hz), 123.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.8; IR (ν_{max}, cm^{-1}) 2096 (s), 1583 (m), 1470 (m), 1320 (s), 1251 (m), 1176 (s), 1149 (s), 1107 (s), 1060 (m), 977 (s), 815 (m), 795 (m), 729 (m); HRMS (APPI/LTQ-Orbitrap) m/z: $[M]^+$ Calcd. for $C_8H_3Cl_2F_3^+$ 225.9558; Found 225.9565. One carbon was not resolved at 101 MHz.

1-Bromo-4-(1-diazo-2,2,2-trifluoroethyl)benzene (7.2u)

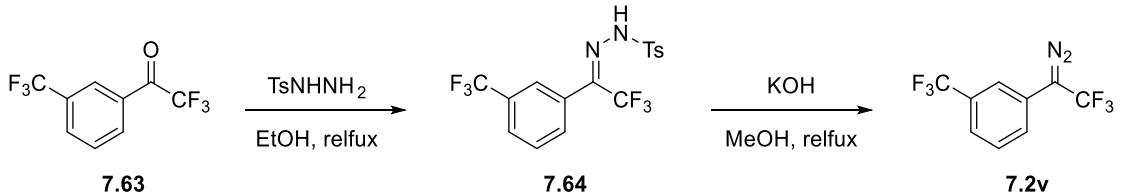


7.61 **7.62** **7.2u**

1-(4-Bromophenyl)-2,2,2-trifluoroethanone (**7.61**) (633 mg, 2.50 mmol, 1.05 equiv) was added to EtOH (4.7 mL) at room temperature followed by *p*-toluenesulfonylhydrazide (0.443 g, 2.38 mmol, 1.00 equiv) in one portion. A condenser was then attached and the contents were heated to reflux for 12 h. After this time, the solvent was removed under reduced pressure until the beginning of the formation of a solid. Then, pentane (100 mL) was added and the precipitate was collected by filtration and washed with pentane. The solid obtained was used in the next step without purification.

Following a reported procedure,[223a] N'-(1-(4-bromophenyl)-2,2,2-trifluoroethylidene)-4-methylbenzenesulfonohydrazide (**7.62**) was disolved in a 0.4 M solution of potassium hydroxide (281 mg, 5.00 mmol, 2.00 equiv) in MeOH (12.5 mL). A condenser was attached and the reaction mixture was stirred at reflux for 0.5 h. Then, the reaction was cooled to room temperature and diluted with water (15 mL). The crude product was extracted with pentane (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography using pentane as eluent to afford 1-bromo-4-(1-diazo-2,2,2-trifluoroethyl)benzene (**7.2u**) as a orange oil (146 mg, 0.551 mmol, 22%). The compound was kept as a 0.6 M solution in DCM at -18 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 2H, Ar*H*), 7.01 – 6.91 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.8, 125.7 (q, *J* = 270.3 Hz), 124.0, 123.0, 119.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.5. One carbon was not resolved at 101 MHz. The values of the NMR spectra are in accordance with reported literature data.[223a]

1-(1-Diazo-2,2,2-trifluoroethyl)-3-(trifluoromethyl)benzene (7.2v)

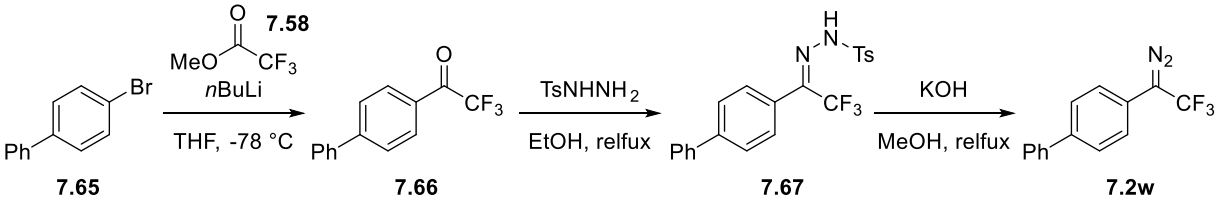


7.63 **7.64** **7.2v**

2,2,2-Trifluoro-1-(3-(trifluoromethyl)phenyl)ethanone (**7.63**) (0.605 g, 2.50 mmol, 1.05 equiv) was added to EtOH (4.7 mL) at room temperature followed by *p*-toluenesulfonylhydrazide (0.443 g, 2.38 mmol, 1.00 equiv) in one portion. A condenser was then attached and the contents were heated to reflux for 12 h. After this time, the solvent was removed under reduced pressure until the beginning of the formation of a solid. Then, pentane (100 mL) was added and the precipitate was collected by filtration and washed with pentane. The solid obtained was used in the next step without purification.

Adapted from a reported procedure,[223a] 4-methyl-N'-(2,2,2-trifluoro-1-(3(trifluoromethyl)phenyl)ethylidene)benzenesulfonohydrazide (**7.64**) was disolved in a 0.4 M solution of potassium hydroxide (281 mg, 5.00 mmol, 2.00 equiv) in MeOH (6.25 mL). A condenser was attached and the reaction mixture was stirred at reflux for 0.5 h. Then, the reaction was cooled to room temperature and diluted with water (15 mL). The crude product was extracted with pentane (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography using EtOAc/pentane 1:99 as eluent to afford 1-(1-diazo-2,2,2-trifluoroethyl)-3-(trifluoromethyl)benzene (**7.2v**) as a volatile orange oil (233 mg, 0.834 mmol, 33%, contains 10 wt. % of eluent). The compound was kept as a 0.6 M solution in DCM at -18 °C. R_f = 0.95 (EtOAc/pentane 1:99); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (tt, *J* = 7.8, 0.8 Hz, 1H, Ar*H*), 7.49 – 7.41 (m, 1H, Ar*H*), 7.33 – 7.23 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.2 (q, *J* = 32.6 Hz), 130.1, 125.3, 125.3 (q, *J* = 269.6 Hz), 125.2, 123.8 (q, *J* = 272.5 Hz), 122.7 (q, *J* = 3.8 Hz), 118.9 – 118.6 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.4, -63.1; IR (ν_{max}, cm^{-1}) 2089 (s), 1616 (w), 1591 (w), 1496 (w), 1455 (m), 1362 (m), 1338 (s), 1312 (s), 1273 (m), 1168 (s), 1111 (s), 1076 (s), 977 (m), 795 (s), 692 (s); HRMS (ESI/QTOF) m/z: $[M-N_2+H]^+$ Calcd. for $C_9H_5F_6^+$ 227.0290; Found 227.0291. One carbon was not resolved at 101 MHz.

4-(1-Diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl (7.2w)



A solution of 4-bromo-biphenyl (**7.65**) (4.66 g, 20.0 mmol, 1.00 equiv) in anhydrous THF (100 mL) was cooled to -78 °C. Then, a 2.5 M solution of *n*-butyllithium (9.60 mL, 24.0 mmol, 1.20 equiv) in hexanes was added dropwise. The mixture was stirred for 1 h, followed by the dropwise addition of methyl 2,2,2-trifluoroacetate (**7.58**) (2.21 mL, 22.0 mmol, 1.10 equiv) in 30 min. The mixture was allowed to warm up to room temperature, stirred for 18 h and then quenched with saturated aqueous ammonium chloride solution (50 mL). Diethyl ether (50 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by silica gel chromatography using pentane/EtOAc 90:10 as eluent to afford 1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethanone (**7.66**) as a slight yellow oil (3.37 g, 13.5 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.10 (m, 2H, Ar*H*), 7.81 – 7.74 (m, 2H, Ar*H*), 7.68 – 7.62 (m, 2H, Ar*H*), 7.54 – 7.41 (m, 3H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3 (q, *J* = 34.8 Hz), 148.4, 139.3, 130.9 (q, *J* = 2.2 Hz), 129.3, 129.1, 128.7, 127.8, 127.5, 116.9 (q, *J* = 291.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -71.32. The values of the NMR spectra are in accordance with reported literature data.[223a]

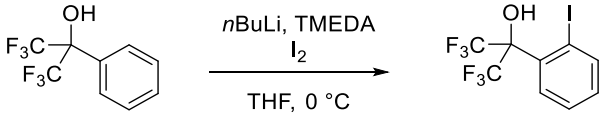
Following a reported procedure,[223a] 1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethanone (**7.66**) (3.36 g, 13.5 mmol, 1.05 equiv) was added to EtOH (9 mL) at room temperature followed by *p*-toluenesulfonylhydrazide (2.40 g, 12.9 mmol, 1.00 equiv) in one portion. A condenser was then attached and the contents were heated to reflux for 12 h. After this time, the solvent was removed under reduced pressure until the beginning of the formation of a solid. Then, pentane (200 mL) was added and the precipitate was collected by filtration and washed with pentane. The solid obtained was used in the next step without purification.

Following a reported procedure,[223a] *N*'-(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethylidene)-4-methylbenzenesulfonohydrazide (**7.67**) was disolved in a 0.4 M solution of potassium hydroxide (3.37

g, 60.0 mmol, 2.00 equiv) in MeOH (17.5 mL). A condenser was attached and the reaction mixture was stirred at reflux for 0.5 h. Then, the reaction was cooled to room temperature and diluted with water (20 mL). The product was extracted with Et_2O (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography using pentane as eluent to afford 4-(1-Diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl (**7.2w**) as a red solid (1.42 g, 5.44 mmol, 50%). The compound was kept at -18 °C. R_f = 0.70 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 2H, Ar*H*), 7.62 – 7.55 (m, 2H, Ar*H*), 7.45 (dd, *J* = 8.4, 6.9 Hz, 2H, Ar*H*), 7.41 – 7.34 (m, 1H, Ar*H*), 7.17 (d, *J* = 8.2 Hz, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 139.0, 129.1, 128.2, 127.7, 127.0, 125.8 (q, *J* = 269.6 Hz), 122.7, 122.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.32. One carbon was not resolved at 101 MHz. The values of the NMR spectra are in accordance with reported literature data.[223a]

10.5.2. Preparation of the Benziodoxole EBX' and VBX' Reagents

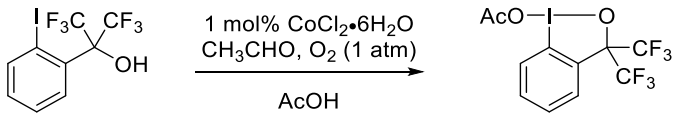
1,1,1,3,3,3-Hexafluoro-2-(2-iodophenyl)propan-2-ol (7.31)



7.68 **7.31**

Following a reported procedure,[442] TMEDA (1.27 mL, 8.40 mmol, 0.20 equiv) was added to a solution of *n*-BuLi (37.0 mL, 92.0 mmol, 2.20 equiv, 2.5 M in hexanes). After 15 min, the cloudy solution was cooled to 0 °C and 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol (**7.68**) (7.07 mL, 42.0 mmol, 1.00 equiv) in THF (6.0 mL) was added dropwise. The reaction was stirred 30 min at 0 °C and then 18 h at room temperature. Then, THF (30.0 mL) was added, followed by the portionwise addition of I_2 (11.3 g, 44.5 mmol, 1.05 equiv) at 0 °C and the mixture was stirred at 0 °C for 30 min and 4 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 3:97 as eluent to afford 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**7.31**) as a colorless oil (13.9 g, 37.5 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.9, 1.4 Hz, 1H, Ar*H*), 7.63 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.43 (dt, *J* = 8.4, 1.4 Hz, 1H, Ar*H*), 7.11 (dt, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 4.23 (s, 1H, O*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 131.4, 130.0, 129.7, 128.0, 122.6 (q, *J* = 291.4 Hz), 90.6, 78.9 (q, *J* = 32.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.4. The values of the NMR spectra are in accordance with reported literature data.[442]

3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (7.28)



7.31 **7.28**

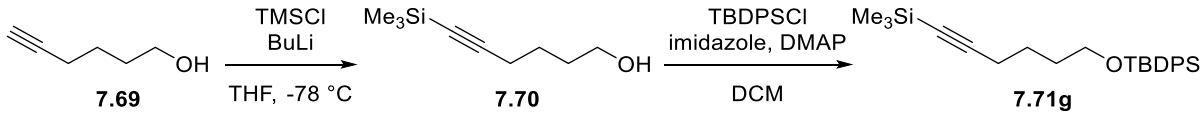
Following a slightly modified procedure,[443] a 500 mL flsak was charged with glacial acetic acid (188 mL), 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**7.31**) (13.9 g, 37.5 mmol, 1.00 equiv) and cobalt(II) chloride hexahydrate (89.0 g, 0.375 mmol, 0.01 equiv). The reaction vessel was purged with O_2 for 5 min before acetaldehyde (21.4 mL, 379 mmol, 10.0 equiv) was added in one portion. The

[442] J. Cvengroš, D. Stolz, A. Togni, *Synthesis* **2009**, 2818.

[443] A. Maity, S.-M. Hyun, D. C. Powers, *Nat. Chem.* **2018**, *10*, 200.

reaction mixture was stirred under 1 atm of O_2, delivered by inflated balloon, at room temperature for 12 h. Acetaldehyde (21.4 mL, 379 mmol, 10.00 equiv) was added and the reaction continue for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in DCM. The organic layer was washed with distilled water (50 mL) and extracted with DCM (3 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained residue was triturated in pentane for 0.5 h, filtered and washed with pentane (operation repeated 2 times) to afford 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) as a white solid (9.91 g, 23.2 mmol, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H, Ar*H*), 7.85 – 7.69 (m, 3H, Ar*H*), 2.19 (s, 3H, (O)CC*H*$_3$); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.4, 134.2, 131.4, 131.0, 130.8, 129.5 – 129.0 (m), 123.1 (q, *J* = 289.5 Hz), 116.1, 84.5 – 83.7 (m), 20.0; ^{19}F NMR (376 MHz, DMSO-d_6) δ -75.1. The values of the NMR spectra are in accordance with reported literature data.[429]

***Tert*-butyldiphenyl((6-(trimethylsilyl)hex-5-yn-1-yl)oxy)silane (7.71g)**



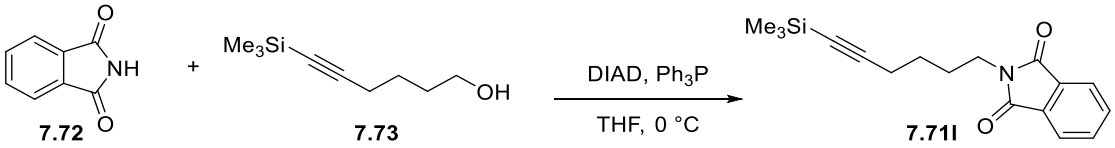
Following a reported procedure,[444] butyllithium (17.6 mL, 44.0 mmol, 2.20 equiv, 2.5 M in hexanes) was added dropwise to a stirring solution of 5-hexyn-1-ol (**7.69**) (2.20 mL, 20.0 mmol, 1.00 equiv) in THF (40.0 mL) at -78 °C. Stirring was continued for 1 h, then chlorotrimethylsilane (5.58 mL, 44.0 mmol, 2.20 equiv) was added at -78 °C. After 1 h, the reaction mixture was warmed to 0 °C. Aqueous 1M HCl (30 mL) was added dropwise and stirring was continued for 30 min at room temperature. The reaction mixture was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with water (30 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude oil was purified by column chromatography using Et_2O/pentane 20:80 as eluent to afford 6-(trimethylsilyl)hex-5-yn-1-ol (**7.70**) as a colorless oil (2.12 g, 14.2 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 – 3.62 (m, 2H, C*H*$_2$OH), 2.27 (t, *J* = 6.8 Hz, 2H, C≡CC*H*$_2$), 1.80 – 1.52 (m, 4H, C*H*$_2$C*H*$_2$), 1.13 (br s, 1H, O*H*), 0.14 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 107.3, 84.9, 62.6, 32.0, 25.0, 19.8, 0.3. The values of the NMR spectra are in accordance with reported literature data.[444]

Following a reported procedure,[445] under an atmosphere of nitrogen, 6-(trimethylsilyl)hex-5-yn-1-ol (**7.70**) (511 mg, 3.00 mmol, 1.00 equiv) was dissolved in DCM (10.00 mL). The alcohol was then treated, in succession, with imidazole (306 mg, 4.50 mmol, 1.50 equiv), DMAP (110 mg, 0.900 mmol, 0.3 equiv), and *tert*-butylchlorodiphenylsilane (1.17 mL, 4.50 mmol, 1.50 equiv). The reaction was stirred at room temperature. After 1 hour, the reaction was diluted with 30 mL of water then extracted with DCM (2 x 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude oil was purified by column chromatography using EtOAc/pentane 2:98 as eluent to afford tert-butyldiphenyl((6-(trimethylsilyl)hex-5-yn-1-yl)oxy)silane (**7.71g**) as a colorless oil (1.21 g, 2.95 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H, Ar*H*), 7.45 – 7.34 (m, 6H, Ar*H*), 3.67 (t, *J* = 5.9 Hz, 2H, C*H*$_2$O), 2.23 (t, *J* = 6.6 Hz, 2H, C≡CC*H*$_2$), 1.72 – 1.56 (m, 4H, C*H*$_2$C*H*$_2$), 1.05 (s, 9H, tBu), 0.14 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 134.2, 129.7, 127.8, 107.6, 84.6, 63.6, 31.8, 27.0, 25.3, 19.8, 19.4, 0.3. The values of the NMR spectra are in accordance with reported literature data.[445]

[444] M. Gersch, F. Gut, V. S. Korotkov, J. Lehmann, T. Böttcher, M. Rusch, C. Hedberg, H. Waldmann, G. Klebe, S. A. Sieber, *Angew. Chem. Int. Ed.* **2013**, *52*, 3009.

[445] E. C. McLaughlin, M. P. Doyle, *J. Org. Chem.* **2008**, *73*, 4317.

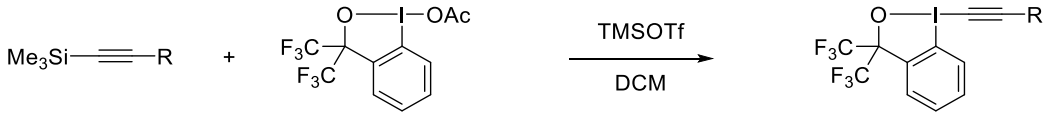
2-(6-(Trimethylsilyl)hex-5-yn-1-yl)isoindoline-1,3-dione (7.71l)



7.72 **7.73** **7.71l**

To a stirring solution of 6-(trimethylsilyl)hex-5-yn-1-ol (**7.72**) (852 mg, 5.00 mmol, 1.00 equiv) in THF (16.7 mL) was added triphenylphosphine (1.44 g, 5.50 mmol, 1.10 equiv) and DIAD (1.15 mL, 5.50 mmol, 1.10 equiv) at 0 °C. The reaction mixture was stirred at this temperature for 15 min and then, phthalimide (**7.73**) (750 mg, 5.10 mmol, 1.02 equiv) was added. The reaction was continued at room temperature for 5 h, then cold water (20 mL) was added and the product was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using Et_2O/pentane 10:90 as eluent to furnish 2-(6-(trimethylsilyl)hex-5-yn-1-yl)isoindoline-1,3-dione (**7.71l**) as a white solid (1.37 g, 4.58 mmol, 92%). M.p. 68 – 70 °C; R_f = 0.26 (Et_2O/pentane 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H, Ar*H*), 7.70 (dd, *J* = 5.4, 3.1 Hz, 2H, Ar*H*), 3.70 (t, *J* = 7.0 Hz, 2H, CH_2NPhth), 2.27 (t, *J* = 7.1 Hz, 2H, C≡CCH_2), 1.85 – 1.74 (m, 2H, CH_2), 1.61 – 1.49 (m, 2H, CH_2), 0.12 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 134.0, 132.3, 123.3, 106.7, 85.1, 37.6, 27.8, 25.9, 19.6, 0.3; IR (ν_{max}, cm^{-1}) 2955 (w), 2931 (w), 2170 (w), 1770 (w), 1705 (m), 1440 (w), 1390 (s), 1352 (m), 1324 (m), 1247 (m), 1035 (m), 904 (m), 841 (s), 761 (s), 718 (s), 638 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{22}NO_2Si^+$ 300.1414; Found 300.1413.

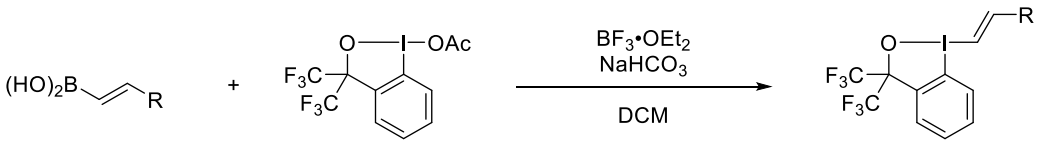
General procedure A: Synthesis of EBX' reagents



7.71a-n **7.28** **7.10a-n**

To a solution of 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (1.00 equiv) in dry DCM (*c* = 0.2 M) was added trimethylsilyl trifluoromethanesulfonate (1.10 equiv) dropwise at room temperature and the reaction mixture was stirred for 1 h. After this time, the corresponding trimethylethynylsilane (**7.71a-n**) (1.10 equiv) was added and the mixture was stirred for 6 h at room temperature. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane (3 times). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc/pentane as eluent to give the corresponding EBX' reagent (**7.10a-n**).

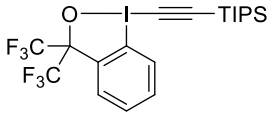
General procedure B: Synthesis of VBX' reagents



7.27a-f **7.28** **7.29a-f**

To a solution of the corresponding vinyl boronic acid (**7.27a-f**) (1.00 mmol, 1.00 equiv) in dry DCM (10 mL) was added BF_3•OEt_2 (0.152 mL, 1.20 mmol, 1.20 equiv) dropwise at 0 °C. After 15 minutes, 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (514 mg, 1.20 mmol, 1.20 equiv) was added in one portion at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane (3 times). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc/pentane as eluent to give the corresponding VBX' reagent.

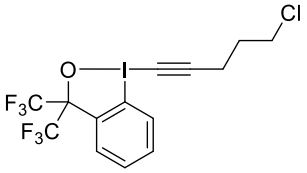
((3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (7.10a)



7.10a

Following general procedure A, starting from triisopropyl((trimethylsilyl)ethynyl)silane (**7.71a**) (2.80 g, 11.0 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (4.28 g, 10.0 mmol), afforded ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) as a white solid (5.33 g, 9.68 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar*H*), 7.88 – 7.81 (m, 1H, Ar*H*), 7.74 – 7.62 (m, 2H, Ar*H*), 1.23 – 1.07 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 131.3, 130.1, 130.2 – 130.0 (m), 128.3, 123.7 (q, *J* = 290.4 Hz), 112.3, 111.0, 81.6 (p, *J* = 29.5 Hz), 69.9, 18.7, 11.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[142]

1-(5-Chloropent-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (7.10b)

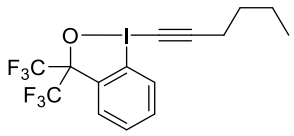


7.10b

Following general procedure A, starting from (5-chloropent-1-yn-1-yl)trimethylsilane (**7.71b**) (197 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (428 mg, 1.00 mmol), afforded 1-(5-chloropent-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10b**) as a white solid (273 mg, 0.580 mmol, 58%). M.p. 113 – 115 °C; R_f = 0.47 (EtOAc/pentane 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.17 (m, 1H, Ar*H*), 7.87 – 7.78 (m, 1H, Ar*H*), 7.73 – 7.64 (m, 2H, Ar*H*), 3.70 (t, *J* = 6.1 Hz, 2H, CH_2Cl), 2.74 (t, *J* = 6.9 Hz, 2H, CH_2C≡C), 2.07 (p, *J* = 6.6 Hz, 2H, CH_2CH_2Cl); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.0, 131.3, 130.1, 130.1 – 129.9 (m), 128.3, 123.7 (q, *J* = 290.5 Hz), 111.0, 105.5, 81.7 (p, *J* = 29.6 Hz), 45.2, 43.5, 31.0, 17.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2; IR (ν_{max}, cm^{-1}) 2158 (w), 1441 (w), 1427 (w), 1263 (s), 1178 (s), 1145 (s), 966 (s), 946 (s),

768 (s), 753 (s), 729 (s), 660 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{14}H_{11}ClF_6IO^+$ 470.9442; Found 470.9446.

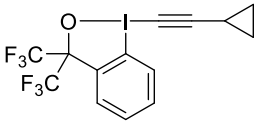
1-(Hex-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (7.10c)



7.10c

Following general procedure A, starting from hex-1-yn-1-yltrimethylsilane (**7.71c**) (222 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (428 mg, 1.00 mmol), afforded 1-(hex-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (**7.10c**) as a white solid (285 mg, 0.630 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.18 (m, 1H, Ar*H*), 7.86 – 7.79 (m, 1H, Ar*H*), 7.73 – 7.64 (m, 2H, Ar*H*), 2.53 (t, *J* = 7.0 Hz, 2H, C*H*$_2$C≡C), 1.67 – 1.56 (m, 2H, C*H*$_2$CH$_2$C≡C), 1.53 – 1.42 (m, 2H, C*H*$_2$CH$_3$), 0.96 (t, *J* = 7.3 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 131.2, 130.2, 130.0 – 129.8 (m), 128.3, 123.8 (q, *J* = 290.7 Hz), 111.1, 108.1, 81.7 (p, *J* = 29.4 Hz), 43.5, 30.6, 22.2, 20.2, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[446]

1-(Cyclopropylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (7.10d)

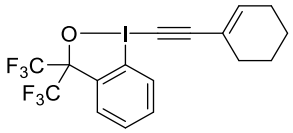


7.10d

Following general procedure A, starting from (cyclopropylethynyl)trimethylsilane (**7.71d**) (995 µL, 5.50 mmol) and 3,3-bis(trifluoromethyl)-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (2.14 g, 5.00 mmol), afforded 1-(cyclopropylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (**7.10d**) as an off-white solid (873 mg, 2.01 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.14 (m, 1H, Ar*H*), 7.88 – 7.74 (m, 1H, Ar*H*), 7.74 – 7.59 (m, 2H, Ar*H*), 1.54 (tt, J = 8.2, 5.0 Hz, 1H, C*H*C≡C), 1.00 – 0.91 (m, 2H, C*H*$_2$-cyclopropyl), 0.91 – 0.85 (m, 2H, C*H*$_2$-cyclopropyl); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 131.2, 130.2, 130.0, 129.8, 128.2, 123.8 (q, *J* = 290.8 Hz), 81.7 (p, *J* = 29.5 Hz), 39.4, 9.5, 1.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.3. The values of the NMR spectra are in accordance with reported literature data.[71a]

[446] X. Li, X. Xie, N. Sun, Y. Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 6994.

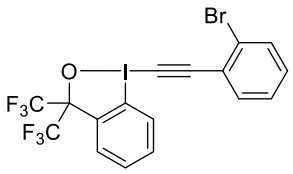
1-(Cyclohex-1-en-1-ylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (7.10e)



7.10e

Following general procedure A, starting from (cyclohex-1-en-1-ylethynyl)trimethylsilane (**7.71e**) (196 mg, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (428 mg, 1.00 mmol), afforded 1-(cyclohex-1-en-1-ylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10e**) as an off-white solid (213 mg, 0.450 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.13 (m, 1H, Ar*H*), 7.91 – 7.78 (m, 1H, Ar*H*), 7.73 – 7.60 (m, 2H, Ar*H*), 6.36 (p, *J* = 2.2 Hz, 1H, C=C*H*), 2.28 – 2.13 (m, 4H, 2 x CH_2C=C), 1.75 – 1.54 (m, 4H, CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 132.9, 129.8, 129.6, 128.1, 127.8, 123.4 (q, *J* = 290.3 Hz), 119.8, 111.2, 107.7, 81.3 (p, *J* = 29.6 Hz), 50.5, 28.7, 25.7, 21.9, 20.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[137]

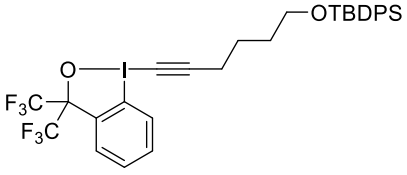
1-((2-Bromophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (7.10f)



7.10f

Following general procedure A, starting from ((2-bromophenyl)ethynyl)trimethylsilane (**7.71f**) (234 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (428 mg, 1.00 mmol), afforded 1-((2-bromophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10f**) as a white solid (535 mg, 0.970 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 – 8.43 (m, 1H, Ar*H*), 7.90 – 7.81 (m, 1H, Ar*H*), 7.76 – 7.68 (m, 2H, Ar*H*), 7.66 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.57 (dd, *J* = 7.6, 1.8 Hz, 1H, Ar*H*), 7.35 (td, *J* = 7.6, 1.3 Hz, 1H, Ar*H*), 7.32 – 7.24 (m, 1H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 133.2, 132.9, 131.4, 131.2, 130.2 – 129.9 (m), 130.0, 128.9, 127.5, 126.2, 123.9, 123.7 (q, *J* = 290.6 Hz), 111.6, 103.0, 81.8 (p, *J* = 29.8 Hz), 59.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.1. The values of the NMR spectra are in accordance with reported literature data.[145]

((6-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3H)-yl)hex-5-yn-1-yl)oxy)(tert-butyl)diphenylsilane (7.10g)

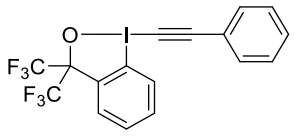


7.10g

Following general procedure A, starting from tert-butyldiphenyl((6-(trimethylsilyl)hex-5-yn-1-yl)oxy)silane (**7.71g**) (450 mg, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (428 mg, 1.00 mmol), afforded ((6-(3,3-bis(trifluoromethyl)-1λ^3-

benzo[*d*][1,2]iodaoxol-1(3H)-yl)hex-5-yn-1-yl)oxy)(tert-butyl)diphenylsilane (**7.10g**) as a white solid (355 mg, 0.500 mmol, 50%). M.p. 110 – 112 °C; R_f = 0.40 (EtOAc/pentane 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar*H*), 7.86 -7.78 (m, 1H, Ar*H*), 7.72 – 7.58 (m, 6H, Ar*H*), 7.46 – 7.32 (m, 6H, Ar*H*), 3.77 – 3.66 (m, 2H, C*H*$_2$OTBDPS), 2.59 – 2.49 (m, 2H, C*H*$_2$C≡C), 1.80 – 1.65 (m, 4H, C*H*$_2$C*H*$_2$CH$_2$O), 1.06 (s, 9H, *tBu*-Si); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 133.8, 132.7, 131.1, 130.0, 129.9 – 129.7 (m), 129.7, 128.1, 127.7, 123.6 (q, *J* = 290.4 Hz), 110.9, 107.7, 81.5 (p, *J* = 29.5 Hz), 63.2, 43.7, 31.6, 26.9, 25.0, 20.2, 19.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2; IR (ν_{max}, cm^{-1}) 2934 (w), 2855 (w), 2155 (w), 2071 (m), 1695 (w), 1427 (m), 1266 (m), 1257 (m), 1181 (s), 1151 (s), 1107 (m), 966 (s), 946 (s), 762 (s), 732 (s), 701 (s); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{31}H_{32}F_6IO_2Si^+$ 705.1115; Found 705.1114.

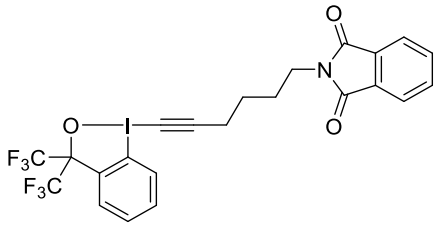
1-(Phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (7.10h)



7.10h

Following general procedure A, starting from trimethyl(phenylethynyl)silane (**7.71h**) (192 mg, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (428 mg, 1.00 mmol), afforded 1-(phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10h**) as a white solid (395 mg, 0.840 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.24 (m, 1H, Ar*H*), 7.86 (ddt, *J* = 7.4, 3.2, 1.4 Hz, 1H, Ar*H*), 7.75 – 7.66 (m, 2H, Ar*H*), 7.59 – 7.53 (m, 2H, Ar*H*), 7.48 – 7.37 (m, 3H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1, 132.8, 131.4, 130.3, 130.1, 130.0, 128.8, 128.5, 123.7 (q, *J* = 289.8 Hz), 121.4, 111.6, 105.4, 82.5 – 81.1 (m), 54.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[149c]

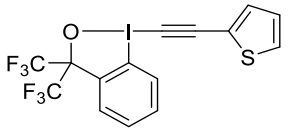
2-(6-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3H)-yl)hex-5-yn-1-yl)isoindoline-1,3-dione (7.10l)



7.10l

Following general procedure A, starting from 2-(6-(trimethylsilyl)hex-5-yn-1-yl)isoindoline-1,3-dione (**7.71l**) (330 mg, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (428 mg, 1.00 mmol), afforded 2-(6-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3H)-yl)hex-5-yn-1-yl)isoindoline-1,3-dione (**7.10l**) as a white solid (590 mg, 0.990 mmol, 99%). M.p. 139 – 141 °C; R_f = 0.13 (EtOAc/pentane 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.15 (m, 1H, Ar*H*), 7.89 – 7.78 (m, 3H, Ar*H*), 7.77 – 7.65 (m, 4H, Ar*H*), 3.75 (t, *J* = 7.0 Hz, 2H, C*H*$_2$NPhth), 2.59 (t, *J* = 7.0 Hz, 2H, C*H*$_2$C≡C), 1.87 (tt, *J* = 7.7, 6.4 Hz, 2H, C*H*$_2$CH$_2$N), 1.73 – 1.62 (m, 2H, C*H*$_2$CH$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 134.2, 133.0, 132.2, 131.2, 130.1, 130.0 – 129.8 (m), 128.4, 123.7 (q, *J* = 290.4 Hz), 123.4, 111.0, 106.9, 81.7 (p, *J* = 29.4 Hz), 44.6, 37.4, 27.8, 25.6, 20.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2; IR (ν_{max}, cm^{-1}) 2355 (w), 2164 (w), 2099 (w), 1707 (m), 1393 (m), 1264 (m), 1180 (s), 1154 (s), 965 (m), 947 (s), 767 (s), 751 (s), 714 (s) HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{23}H_{17}F_6INO_3^+$ 596.0152; Found 596.0157.

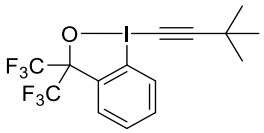
1-(Thiophen-2-ylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (7.10m)



7.10m

Following general procedure A, starting from trimethyl(thiophen-2-ylethynyl)silane (**7.71m**) (182 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (428 mg, 1.00 mmol), afforded 1-(thiophen-2-ylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (**7.10m**) as an off-white solid (403 mg, 0.850 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.19 (m, 1H, Ar*H*), 7.89 – 7.80 (m, 1H, Ar*H*), 7.76 – 7.66 (m, 2H, Ar*H*), 7.44 – 7.38 (m, 2H, Ar*H*), 7.07 (dd, J = 5.1, 3.7 Hz, 1H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 133.2, 131.4, 130.2, 123.0, 129.9, 128.5, 127.5, 123.7 (q, *J* = 291.2 Hz), 121.3, 111.8, 98.4, 81.8 (p, *J* = 29.7 Hz), 59.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[149c]

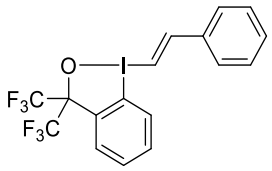
1-(3,3-Dimethylbut-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (7.10n)



7.10n

Following general procedure A, starting from (3,3-dimethylbut-1-yn-1-yl)trimethylsilane (**7.71n**) (229 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (428 mg, 1.00 mmol), afforded 1-(3,3-dimethylbut-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (**7.10n**) as a white solid (350 mg, 0.780 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.14 (m, 1H, Ar*H*), 7.89 – 7.78 (m, 1H, Ar*H*), 7.74 – 7.64 (m, 2H, Ar*H*), 1.34 (s, 9H, *tBu*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.7, 131.1, 130.3, 130.0, 128.0, 123.9 (q, *J* = 290.3 Hz), 116.1, 111.2, 81.9 (p, *J* = 29.6 Hz), 42.0, 30.8, 29.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[137]

(*E*)-1-Styryl-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (7.29a)



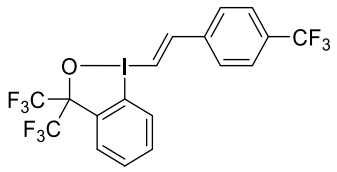
7.29a

Following general procedure B, starting from *trans*-2-phenylvinylboronic acid (**7.27a**) (148 mg, 1.00 mmol) and 3,3-bis(trifluoromethyl)-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (514 mg, 1.20 mmol), afforded (*E*)-1-styryl-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (**7.29a**) as a white solid (450 mg, 0.950 mmol, 95%). M.p. 167 – 168 °C; R_f = 0.57 (EtOAc/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 1H, Ar*H*), 7.66 – 7.57 (m, 2H, Ar*H* and ICHC*H*Ph), 7.57 – 7.42 (m, 7H, Ar*H*), 7.22 (d, *J* = 16.1 Hz, 1H, IC*H*CHPh); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 135.5, 132.2, 131.1, 130.8, 130.6, 130.6, 129.3, 127.5, 127.4, 124.2 (q, *J* = 291.4 Hz), 111.3, 104.8, 81.4 (p, *J* = 29.9 Hz); ^{19}F

NMR (376 MHz, $CDCl_3$) δ -76.1; IR (ν_{max}, cm^{-1}) 3675 (w), 2987 (s), 2900 (s), 1407 (m), 1394 (m), 1260 (s), 1174 (s), 1147 (s), 1050 (s), 959 (m), 939 (s), 741 (s), 729 (s), 691 (s); HRMS (APPI/LTQ-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{17}H_{12}F_6IO^+$ 472.9832; Found 472.9827; The structure of **7.29a** was confirmed by X-ray analysis. Crystals were grown by dissolving 10 mg of pure **7.29a** in $CDCl_3$ (500 µL) at room temperature. Slow evaporation over one week provided suitable crystals. Supplementary crystallographic data for this compound have been deposited at Cambridge Crystallographic Data Centre (CCDC 1993681) and can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/

The reaction was scaled up to *trans*-2-phenylvinylboronic acid (**7.27a**) (0.740 g, 5.00 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (2.57 g, 6.00 mmol), affording (*E*)-1-styryl-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.29a**) (2.20 g, 4.65 mmol, 93%).

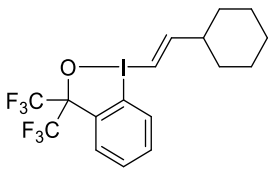
(*E*)-3,3-Bis(trifluoromethyl)-1-(4-(trifluoromethyl)styryl)-1,3-dihydro-benzo[*d*][1,2]iodaoxole (7.29b)



7.29b

Following general procedure B, starting from *trans*-2-[4-(trifluoromethyl)phenylvinylboronic acid (**7.27b**) (216 mg, 1.00 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (514 mg, 1.20 mmol), afforded (*E*)-3,3-bis(trifluoromethyl)-1-(4-(trifluoromethyl)styryl)-1,3-dihydro-benzo[*d*][1,2]iodaoxole (**7.29b**) as a white solid (455 mg, 0.840 mmol, 84%). M.p. 188 – 187 °C; R_f = 0.73 (EtOAc/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.84 (m, 1H, Ar*H*), 7.76 – 7.59 (m, 6H, Ar*H* and ICHC*H*Ph), 7.59 – 7.51 (m, 1H, Ar*H*), 7.51 – 7.45 (m, 1H, Ar*H*), 7.38 (d, *J* = 16.2 Hz, 1H, IC*H*CHPh); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 138.7, 132.3, 132.3 (q, *J* = 32.8 Hz), 131.0, 130.8, 130.9 – 130.6 (m), 127.7, 127.4, 126.3 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 291.6 Hz), 123.8 (q, *J* = 272.2 Hz), 111.2, 108.7, 81.4 (p, *J* = 28.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9, -76.1; IR (ν_{max}, cm^{-1}) 2987 (m), 2900 (m), 1323 (m), 1261 (s), 1183 (s), 1152 (s), 1119 (s), 1065 (s), 945 (s), 763 (s), 731 (s), 692 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{11}F_9IO^+$ 540.9705; Found 540.9708.

(*E*)-1-(2-Cyclohexylvinyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzobenzo[*d*][1,2]iodaoxole (7.29c)

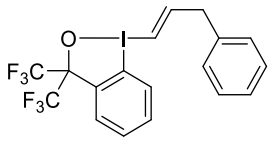


7.29c

Following general procedure B, starting from *trans*-2-cyclohexylvinyl)boronic acid (**7.27c**) (154 mg, 1.00 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (514 mg, 1.20 mmol), afforded (*E*)-1-(2-cyclohexylvinyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzobenzo[*d*][1,2]iodaoxole (**7.29c**) as a white solid (263 mg, 0.550 mmol, 55%). M.p. 170 °C; R_f = 0.55 (EtOAc/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dq, *J* = 7.7, 1.5 Hz, 1H, Ar*H*), 7.65 – 7.44

(m, 3H, Ar*H*), 6.80 (dd, *J* = 15.7, 6.7 Hz, 1H, CH=C*H*CH), 6.44 (dd, *J* = 15.7, 1.3 Hz, 1H, IC*H*=CH), 2.36 – 2.22 (m, 1H, C*H*$_{\text{-cyclohexyl}}$), 1.92 – 1.76 (m, 4H, C*H*$_{\text{-cyclohexyl}}$), 1.76 – 1.64 (m, 1H, C*H*$_{\text{-cyclohexyl}}$), 1.45 – 1.13 (m, 5H, C*H*$_{\text{-cyclohexyl}}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 131.9, 131.2, 130.6 – 130.5 (m), 130.4, 127.1, 124.3 (q, *J* = 292.1 Hz), 110.9, 103.1, 81.4 (p, *J* = 28.7 Hz), 44.4, 32.0, 25.9, 25.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.14; IR (ν_{max}, cm^{-1}) 2925 (w), 1256 (m), 1178 (s), 1149 (s), 1126 (m), 960 (m), 943 (s), 761 (s), 730 (s), 692 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}F_6IO^+$ 479.0301; Found 479.0309.

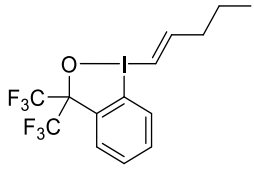
(*E*)-1-(3-Phenylprop-1-en-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzobenzo[*d*][1,2]iodaoxole (7.29d)



7.29d

Following general procedure B, starting from *trans*-3-Phenyl-1-propen-1-ylboronic acid (**7.27d**) (162 mg, 1.00 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (514 mg, 1.20 mmol), afforded (*E*)-1-(3-phenylprop-1-en-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzobenzo[*d*][1,2]iodaoxole (**7.29d**) as a white solid (416 mg, 0.860 mmol, 86%). M.p. 125 – 126 °C; R_f = 0.36 (EtOAc/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 1H, Ar*H*), 7.58 (td, *J* = 7.4, 1.3 Hz, 1H, Ar*H*), 7.52 (ddd, *J* = 8.6, 7.0, 1.6 Hz, 1H, Ar*H*), 7.44 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar*H*), 7.41 – 7.34 (m, 2H, Ar*H*), 7.33 – 7.27 (m, 1H, Ar*H*), 7.25 – 7.20 (m, 2H, Ar*H*), 7.01 (dt, *J* = 15.6, 6.5 Hz, 1H, CH_2C*H*=CH), 6.50 (dt, *J* = 15.6, 1.5 Hz, 1H, IC*H*=CH), 3.69 (dd, *J* = 6.5, 1.5 Hz, 2H, C*H*$_2$Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 136.9, 132.0, 131.1, 130.6 – 130.4 (m), 130.5, 129.2, 128.8, 127.3, 127.28, 124.2 (q, *J* = 291.9 Hz), 111.0, 106.8, 81.3 (p, *J* = 28.9 Hz), 42.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.1; IR (ν_{max}, cm^{-1}) 3674 (m), 2972 (s), 2901 (s), 1394 (m), 1258 (s), 1212 (m), 1173 (s), 1144 (s), 1121 (m), 1049 (s), 961 (m), 942 (s), 767 (s), 750 (s), 707 (s), 693 (s), 679 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{14}F_6IO^+$ 486.9988; Found 486.9994.

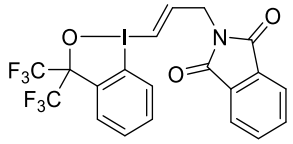
(*E*)-1-(Pent-1-en-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzobenzo[*d*][1,2]iodaoxole (7.29e)



7.29e

Following general procedure B, starting from *trans*-1-penten-1-yboronic acid (**7.27e**) (114 mg, 1.00 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**71**) (514 mg, 1.20 mmol), afforded (*E*)-1-(pent-1-en-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzobenzo[*d*][1,2]iodaoxole (**7.29e**) as a white solid (350 mg, 0.800 mmol, 80%). M.p. 150 – 151 °C; R_f = 0.39 (EtOAc/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.64 – 7.49 (m, 3H, Ar*H*), 6.87 (dt, *J* = 15.4, 6.7 Hz, 1H, CH=C*H*CH$_2$), 6.52 (d, *J* = 15.4 Hz, 1H, IC*H*=CH), 2.37 (q, *J* = 7.1 Hz, 2H, CHC*H*$_2$), 1.59 (h, *J* = 7.4 Hz, 2H, CH_2C*H*$_2$$CH_3$), 1.02 (t, *J* = 7.3 Hz, 3H, CH_2C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 132.0, 131.3, 130.6, 130.5, 127.3, 124.3 (q, *J* = 291.9 Hz), 111.0, 105.1, 82.5 – 80.7 (m), 38.1, 21.6, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.1; IR (ν_{max}, cm^{-1}) 3669 (w), 2987 (s), 2972 (s), 2908 (s), 2851 (m), 1755 (m), 1734 (m), 1450 (m), 1250 (m), 1153 (m), 1104 (m), 1078 (s), 1057 (s), 966 (m), 739 (m); HRMS (APPI/LTQ-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{14}H_{14}F_6IO^+$ 438.9988; Found 438.9992.

(*E*)-2-(3-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)allyl)isoindoline-1,3-dione (7.29f)

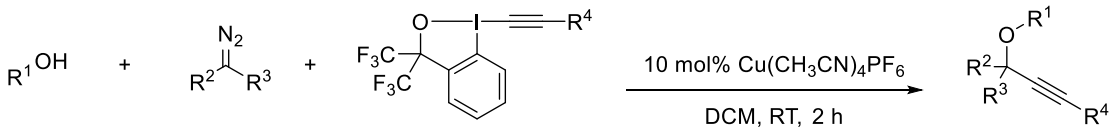


7.29f

Following general procedure B, starting from (*E*)-(3-(1,3-dioxoisoindolin-2-yl)prop-1-en-1-yl)boronic acid (**7.27f**) (231 mg, 1.00 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**7.28**) (514 mg, 1.20 mmol), afforded (*E*)-2-(3-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)allyl)isoindoline-1,3-dione (**7.29f**) as a white solid (422 mg, 0.760 mmol, 76%). M.p. 179 – 180 °C; R_f = 0.18 (EtOAc/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 5.5, 3.0 Hz, 2H, Ar*H*), 7.86 – 7.74 (m, 3H, Ar*H*), 7.64 – 7.56 (m, 2H, Ar*H*), 7.56 – 7.48 (m, 1H, Ar*H*), 6.83 (dt, *J* = 15.8, 5.0 Hz, 1H, CH_2CH=CH), 6.72 (dt, *J* = 15.8, 1.4 Hz, 1H, CH=C*H*I), 4.56 (dd, *J* = 5.0, 1.4 Hz, 2H, NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 146.9, 134.7, 132.5, 131.9, 130.8, 130.6, 130.6 – 130.4 (m), 127.9, 124.1 (q, *J* = 291.5 Hz), 123.9, 111.1, 109.3, 81.2 (*p*, *J* = 29.2 Hz), 41.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.1; IR (ν_{max}, cm^{-1}) 3674 (m), 2973 (s), 2900 (s), 1771 (m), 1720 (s), 1421 (m), 1392 (s), 1260 (s), 1211 (m), 1173 (s), 1156 (s), 1048 (s), 978 (w), 962 (m), 944 (s), 930 (s), 761 (m), 718 (s), 693 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{13}F_6INO_3^+$ 555.9839; Found 555.9839.

10.5.3. Three-Component Reaction of Alcohols, Diazo Compounds and Hypervalent Iodine Reagents

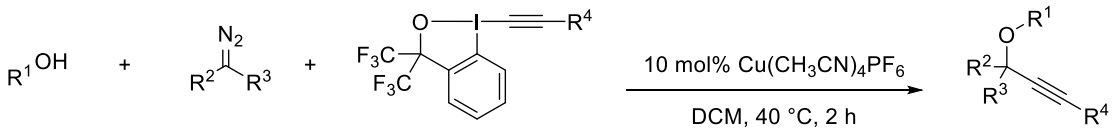
General procedure C: Three-component reaction at 25 °C



7.1 **7.2** **7.10** **7.4**

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (11.2 mg, 30.0 µmol, 0.10 equiv), EBX reagent **7.10** (0.30 mmol, 1.00 equiv) and alcohol **7.1** (1.20 mmol, 4.00 equiv), if solid. The vial was capped, removed from the glovebox and dry DCM (2.0 mL) was added. The alcohol was added at this point if liquid. To the resulting solution was added a 0.6 M solution of diazo compound **7.2** (0.60 mmol, 2.00 equiv) in dry DCM in 1 h *via* seringe pump at 25 °C. The system was mainted isobaric with a filled balloon with N_2. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography using EtOAc/pentane as eluent (the solvent ratio indicated in the R_f measurement was used), directly without further work-up to afford the corresponding product **7.4**.

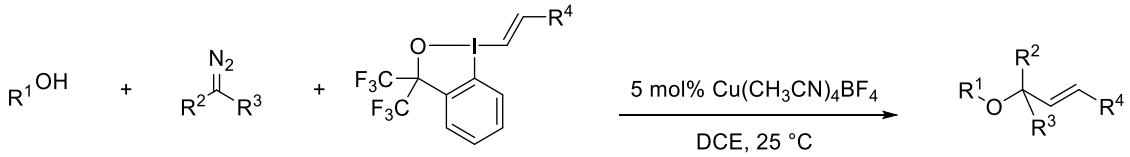
General procedure D: Three-component reaction at 40 °C



7.1 **7.2** **7.10** **7.4**

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (11.2 mg, 30.0 µmol, 0.10 equiv), EBX reagent **7.10** (0.30 mmol, 1.00 equiv) and alcohol **7.1** (1.20 mmol, 4.00 equiv), if solid. The vial was capped, removed from the glovebox and dry DCM (2.0 mL) was added. The alcohol was added at this point if liquid. To the resulting solution was added a 0.6 M solution of diazo compound **7.2** (0.60 mmol, 2.00 equiv) in dry DCM in 1 h *via* seringe pump at 40 °C. The system was mainted isobaric with a filled balloon with N_2. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography using EtOAc/pentane as eluent (the solvent ratio indicated in the R_f measurement was used), directly without further work-up to afford the corresponding product **7.4**.

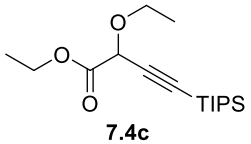
General procedure E: Three-component reaction with VBX reagents



7.1 **7.2** **7.29** **7.17**

An oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4BF_4$ (4.72 mg, 15.0 µmol, 0.05 equiv), VBX reagent **7.29** (0.30 mmol, 1.00 equiv) and alcohol **7.1** (0.90 mmol, 3.00 equiv), if solid. The vial was capped, removed from the glovebox and dry DCM (3.0 mL) was added. The alcohol was added at this point if liquid. To the resulting solution was added a 0.6 M solution of diazo compound **7.2** (0.60 mmol, 2.00 equiv) in dry DCM (1.0 mL) in 1 h *via* seringe pump at 25 °C. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography using EtOAc/pentane as eluent (the solvent ratio indicated in the Rf measurement was used), directly without further work-up to afford the corresponding product **7.17**.

Ethyl 2-ethoxy-4-(triisopropylsilyl)but-3-ynoate (7.4c)

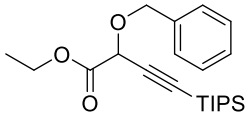


7.4c

Following general procedure C, starting from ethanol (**7.1b**) (70.0 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4c**) as a colorless oil (87 mg, 0.28 mmol, 93%). R_f = 0.29 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (s, 1H, *H*CC≡C), 4.35 – 4.17 (m, 2H, C*H*$_2$OC(O)), 3.79 (dq, *J* = 9.1, 7.0 Hz, 1H, OC*H*$_2$CH$_3$), 3.65 (dq, *J* = 9.2, 7.0 Hz, 1H, OC*H*$_2$CH$_3$), 1.29 (m, 6H, 2 x OCH$_2$C*H*$_3$), 1.13 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 100.4, 89.2, 69.2, 64.6, 62.0, 18.7, 15.2, 14.2, 11.2; IR (ν_{max}, cm^{-1}) 2943 (m), 2867 (m), 2175 (w), 1759 (s), 1464 (m), 1281 (m), 1192 (m), 1116 (s),

1032 (s), 882 (s), 677 (s), 661 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{17}H_{32}NaO_3Si^+$ 335.2013; Found 335.2009.

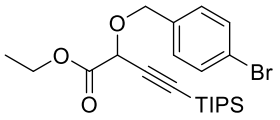
Ethyl 2-(benzyloxy)-4-(triisopropylsilyl)but-3-ynoate (7.4d)



7.4d

Following general procedure C, starting from benzyl alcohol (**7.1a**) (124 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4d**) as a colorless oil (85 mg, 0.23 mmol, 76%). R_f = 0.33 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H, ArH), 4.86 – 4.79 (m, 1H, OC*H*$_2$Ph), 4.79 – 4.69 (m, 2H, OC*H*$_2$Ph and *H*CC≡C), 4.35 – 4.16 (m, 2H, OC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.13 – 0.97 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 136.9, 128.7, 128.6, 128.2, 100.0, 90.0, 70.4, 68.1, 62.0, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (m), 2175 (w), 1756 (s), 1463 (m), 1275 (m), 1192 (s), 1111 (s), 1031 (s), 882 (s), 739 (m), 697 (s), 677 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{22}H_{34}NaO_3Si^+$ 397.2169; Found 397.2172.

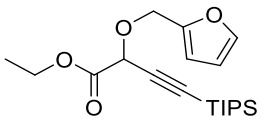
Ethyl 2-((4-bromobenzyl)oxy)-4-(triisopropylsilyl)but-3-ynoate (7.4e)



7.4e

Following general procedure C, starting from 4-bromobenzyl alcohol (**7.1c**) (224 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4e**) as a colorless oil (99 mg, 0.22 mmol, 73%). R_f = 0.29 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H, Ar*H*), 7.32 – 7.24 (m, 2H, Ar*H*), 4.80 – 4.72 (m, 2H, OC*H*$_2$Ar and *H*CC≡C), 4.68 (m, 1H, OC*H*$_2$Ar), 4.35 – 4.16 (m, 2H, OC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 – 0.96 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 136.1, 131.7, 130.2, 122.2, 99.7, 90.4, 69.6, 68.2, 62.1, 18.7, 14.2, 11.2; IR (ν_{max}, cm^{-1}) 2943 (m), 2892 (m), 2866 (m), 1755 (s), 1489 (m), 1463 (m), 1367 (m), 1279 (m), 1194 (s), 1112 (s), 1070 (s), 1039 (s), 1012 (s), 882 (s), 801 (s), 677 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{22}H_{33}BrNaO_3Si^+$ 475.1275; Found 475.1279.

Ethyl 2-(furan-2-ylmethoxy)-4-(triisopropylsilyl)but-3-ynoate (7.4f)

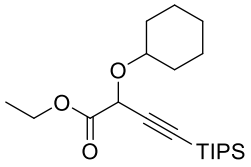


7.4f

Following general procedure C, starting from furfuryl alcohol (**7.1d**) (104 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4f**) as a colorless oil (69 mg, 0.19 mmol, 63%). R_f = 0.28 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 1.9, 0.8 Hz, 1H, Ar*H*), 6.39 (dd, *J* = 3.2, 0.8 Hz, 1H, Ar*H*), 6.34 (dd, *J* = 3.2, 1.9 Hz, 1H, Ar*H*), 4.81 – 4.67 (m, 3H, *H*CC≡C and C*H*$_2$Ar), 4.33 – 4.16 (m, 2H,

OC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 – 0.96 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 150.5, 143.4, 110.8, 110.5, 99.6, 90.4, 67.8, 62.1, 61.9, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (s), 2866 (s), 2174 (w), 1756 (s), 1464 (m), 1277 (m), 1193 (s), 1151 (s), 1097 (s), 1043 (s), 1015 (s), 921 (m), 883 (s), 737 (s), 676 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{20}H_{32}NaO_4Si^+$ 387.1962; Found 387.1974.

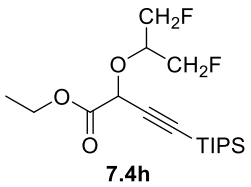
Ethyl 2-(cyclohexyloxy)-4-(triisopropylsilyl)but-3-ynoate (7.4g)



7.4g

Following general procedure C, starting from cyclohexanol (**7.1e**) (127 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4g**) as a colorless oil (99 mg, 0.27 mmol, 90%). R_f = 0.33 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 1H, *H*CC≡C), 4.36 – 4.15 (m, 2H, OC*H*$_2$CH$_3$), 3.65 (tt, *J* = 9.6, 3.9 Hz, 1H, O-C*H*-$_{cyclohexyl}$), 2.04 – 1.90 (m, 2H, 2 x C*H*-$_{cyclohexyl}$), 1.82 – 1.69 (m, 2H, 2 x C*H*-$_{cyclohexyl}$), 1.56 – 1.12 (m, 9H, 2 x C*H*$_2$-$_{cyclohexyl}$ and OCH$_2$C*H*$_3$), 1.11 – 0.93 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 101.3, 88.6, 77.1, 67.2, 61.9, 32.9, 31.9, 25.8, 24.5, 24.3, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (m), 2175 (w), 1756 (s), 1463 (m), 1275 (m), 1192 (s), 1111 (s), 1040 (s), 882 (s), 739 (m), 697 (s), 676 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{21}H_{38}NaO_3Si^+$ 389.2482; Found 389.2487.

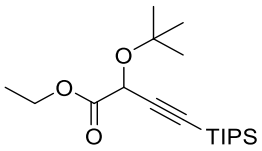
Ethyl 2-((1,3-difluoropropan-2-yl)oxy)-4-(triisopropylsilyl)but-3-ynoate (7.4h)



7.4h

Following general procedure C, starting from 1,2-difluoro-2-propanol (**7.1f**) (93.0 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4**) as a colorless oil (68 mg, 0.19 mmol, 63%). R_f = 0.27 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (s, 1H, *H*CC≡C), 4.78 – 4.64 (m, 2H, 2 x C*H*$_2$F), 4.64 – 4.52 (m, 2H, 2 x C*H*$_2$F), 4.36 – 4.17 (m, 3H, OC*H* and OC*H*$_2$CH$_3$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 – 0.95 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 99.4, 90.9, 81.5 (ddd, *J* = 171.5, 15.9, 6.5 Hz), 74.6 (t, *J* = 20.6 Hz), 69.2, 62.2, 18.6, 14.2, 11.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2; IR (ν_{max}, cm^{-1}) 2945 (m), 2894 (m), 2867 (m), 2176 (w), 1755 (s), 1464 (m), 1282 (m), 1200 (s), 1121 (s), 1091 (s), 1028 (s), 970 (m), 882 (s), 677 (s), 660 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{18}H_{32}F_2NaO_3Si^+$ 385.1981; Found 385.1987.

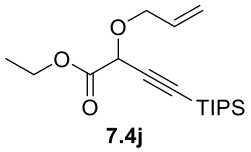
Ethyl 2-(tert-butoxy)-4-(triisopropylsilyl)but-3-ynoate (7.4i)



7.4i

Following general procedure C, starting from *tert*-butanol (**7.1g**) (115 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4i**) as a colorless oil (70 mg, 0.21 mmol, 69%). R_f = 0.40 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (s, 1H, *H*CC≡C), 4.34 – 4.15 (m, 2H, OC*H*$_2$CH$_3$), 1.31 – 1.26 (m, 12H, *t*Bu and OCH$_2$C*H*$_3$), 1.10 – 0.93 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 103.6, 87.3, 76.5, 63.2, 61.9, 28.1, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2961 (m), 2943 (m), 2866 (m), 2177 (w), 1766 (s), 1741 (m), 1464 (m), 1367 (s), 1275 (m), 1254 (m), 1188 (s), 1096 (s), 1033 (s), 882 (s), 750 (m), 677 (s); HRMS (ESI/QTOF) m/z: [M+Na]$^+$ Calcd. for $C_{19}H_{36}NaO_3Si^+$ 363.2326; Found 363.2329.

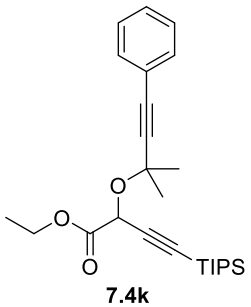
Ethyl 2-(allyloxy)-4-(triisopropylsilyl)but-3-ynoate (7.4j)



7.4j

Following general procedure D, starting from allyl alcohol (**7.1h**) (115 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4j**) as a colorless oil (45 mg, 0.14 mmol, 46%). R_f = 0.31 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (dddd, *J* = 17.0, 10.3, 6.5, 5.4 Hz, 1H, C*H*=CH$_2$), 5.34 (dq, *J* = 17.2, 1.6 Hz, 1H, CH=C*H*$_2$), 5.25 (dq, *J* = 10.4, 1.2 Hz, 1H, CH=C*H*$_2$), 4.79 (s, 1H, *H*CC≡C), 4.36 – 4.12 (m, 4H, OC*H*$_2$CH and OC*H*$_2$CH$_3$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 133.6, 118.9, 100.1, 89.7, 69.7, 68.2, 62.0, 18.7, 14.2, 11.2; IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (s), 2175 (w), 1758 (s), 1464 (m), 1270 (m), 1189 (s), 1111 (s), 1038 (s), 996 (s), 921 (m), 882 (s), 676 (s); HRMS (ESI/QTOF) m/z: [M+Na]$^+$ Calcd. for $C_{18}H_{32}NaO_3Si^+$ 347.2013; Found 347.2008.

Ethyl 2-((2-methyl-4-phenylbut-3-yn-2-yl)oxy)-4-(triisopropylsilyl)but-3-ynoate (7.4k)

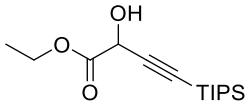


7.4k

Following general procedure D, starting from 4-phenyl-2-methyl-3-butyn-2-ol (**7.1i**) (192 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4k**) as a colorless oil (54 mg, 0.13 mmol, 42%). R_f = 0.38 (EtOAc/pentane

3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H, Ar*H*), 7.33 – 7.27 (m, 3H, Ar*H*), 5.20 (s, 1H, *H*CC≡C), 4.35 – 4.12 (m, 2H, OC*H*$_2$CH$_3$), 1.68 (s, 3H, C(C*H*$_3$)$_2$), 1.62 (s, 3H, C(C*H*$_3$)$_2$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.09 – 0.93 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 131.9, 128.6, 128.4, 122.5, 102.8, 90.1, 88.0, 85.8, 73.7, 65.4, 61.9, 30.0, 29.4, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (m), 2178 (w), 1765 (s), 1741 (m), 1464 (m), 1283 (m), 1269 (m), 1184 (s), 1152 (s), 1091 (s), 1038 (s), 882 (s), 756 (s), 690 (s), 677 (s), 661 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{26}H_{38}NaO_3Si^+$ 449.2482; Found 449.2485.

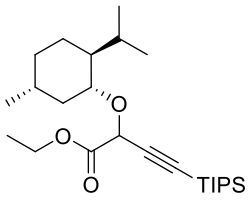
Ethyl 2-hydroxy-4-(triisopropylsilyl)but-3-ynoate (7.4l)



7.4l

Adapted from general procedure C, starting from water (**7.1j**) (54 µL, 3.0 mmol, 10.0 equiv), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol, 1.00 equiv), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM, 2.00 equiv), afforded the title compound (**7.4l**) as a colorless oil (28 mg, 0.10 mmol, 33%). R_f = 0.11 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (d, *J* = 5.2 Hz, 1H, *H*CC≡C), 4.41 – 4.20 (m, 2H, OC*H*$_2$CH$_3$), 3.00 (br d, *J* = 7.0 Hz, 1H, O*H*), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.09 – 1.02 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 102.3, 87.4, 62.8, 62.1, 18.6, 14.2, 11.2; IR (ν_{max}, cm^{-1}) 3469 (br w), 2943 (s), 2866 (s), 2177 (w), 2099 (m), 1745 (s), 1465 (m), 1301 (m), 1259 (m), 1202 (m), 1093 (s), 1028 (s), 882 (s), 677 (s), 661 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{15}H_{28}NaO_3Si^+$ 307.1700; Found 307.1700.

Ethyl 2-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-4-(triisopropylsilyl)but-3-ynoate (7.4m)

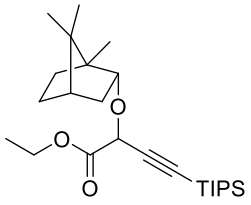


7.4m + 7.4m'

Following general procedure C, starting from (-)-menthol (**7.1k**) (188 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4m/m'**) (50:50 *dr* in the crude ^{1}H NMR) as a colorless oil (107 mg, 0.25 mmol, 84%). A pure analytical sample of each diastereoisomer was isolated by PTLC using EtOAc/pentane 4:96 as eluent. Diaster **7.4m**: R_f = 0.35 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 1H, *H*CC≡C), 4.36 – 4.12 (m, 2H, OC*H*$_2$CH$_3$), 3.51 (td, *J* = 10.6, 4.2 Hz, 1H, OC*H*-$_{cyclohexyl}$), 2.31 (pd, *J* = 7.0, 2.8 Hz, 1H, C*H*-$_{cyclohexyl}$), 2.09 – 2.00 (m, 1H, C*H*-$_{cyclohexyl}$), 1.70 – 1.58 (m, 2H, C*H*-$_{cyclohexyl}$), 1.40 – 1.24 (m, 6H, C*H*-$_{isopropyl}$, C*H*-$_{cyclohexyl}$ and OCH$_2$C*H*$_3$), 1.11 – 1.03 (m, 22H, C*H*-$_{cyclohexyl}$ and TIPS), 0.90 (m, 7H, C*H*-$_{cyclohexyl}$ and 2 x C*H*$_3$-$_{isopropyl}$), 0.82 (d, *J* = 7.0 Hz, 3H, C*H*$_3$-$_{methyl}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 101.0, 88.8, 78.4, 67.1, 61.9, 47.8, 39.8, 34.6, 31.7, 25.7, 23.7, 22.4, 21.0, 18.7, 16.6, 14.2, 11.3; Diaster **7.4m'**: R_f = 0.36 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (s, 1H, *H*CC≡C), 4.16 – 4.00 (m, 2H, OC*H*$_2$CH$_3$), 3.21 (td, *J* = 10.6, 4.4 Hz, 1H, OC*H*-$_{cyclohexyl}$), 2.10 (m, 2H, C*H*-$_{cyclohexyl}$), 1.51 – 1.42 (m, 2H, C*H*-$_{cyclohexyl}$), 1.24 – 1.05 (m, 6H, C*H*-$_{isopropyl}$, C*H*-$_{cyclohexyl}$ and OC*H*$_2$CH$_3$), 0.90 (s, 22H, C*H*-$_{cyclohexyl}$ and TIPS), 0.73 (m, 7H, C*H*-$_{cyclohexyl}$ and 2 x C*H*$_3$-$_{isopropyl}$), 0.60 (d, *J* = 6.9 Hz, 3H, C*H*$_3$-$_{methyl}$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 102.1, 88.6, 80.9, 69.1, 61.9, 48.3, 41.7, 34.4, 31.8, 25.5, 23.4, 22.3, 21.1, 18.7,

16.3, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2952 (s), 2925 (s), 2867 (s), 1766 (s), 1744 (m), 1463 (m), 1367 (m), 1274 (m), 1186 (s), 1107 (s), 1038 (s), 882 (s), 677 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{25}H_{46}NaO_3Si^+$ 445.3108; Found 445.3116.

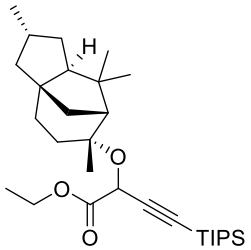
Ethyl 4-(triisopropylsilyl)-2-(((2*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)but-3-ynoate (7.4n)



7.4n

Following general procedure C, starting from (-)-borneol (**7.1l**) (185 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4n**) (55:45 *dr* in the crude ^{1}H NMR) as a colorless oil (110 mg, 0.260 mmol, 87%). R_f = 0.45 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 and 4.68 (2 x s, 1H, *H*CC≡C), 4.33 – 4.15 (m, 2H, OC*H*$_2$CH$_3$), 4.06 – 3.92 (m, 1H, OC*H*), 2.25 – 1.99 (m, 2H, CH-$_{bicyclo[2.2.1]heptan-2-yl}$), 1.77 – 1.59 (m, 2H, CH-$_{bicyclo[2.2.1]heptan-2-yl}$), 1.34 – 1.15 (m, 6H, CH-$_{bicyclo[2.2.1]heptan-2-yl}$ and OCH$_2$C*H*$_3$), 1.12 – 0.94 (m, 21H, TIPS), 0.92- 0.88 (m, 3H, CH$_3$), 0.87 – 0.81 (m, 6H, 2 x CH$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 168.0, 101.7, 101.5, 88.9, 88.5, 84.6, 83.7, 69.6, 68.7, 61.8, 61.7, 49.6, 49.5, 48.0, 45.2, 36.7, 36.0, 28.3, 28.2, 26.8, 26.7, 19.9, 19.0, 18.9, 18.7, 14.2, 14.0, 13.7, 11.3; IR (ν_{max}, cm^{-1}) 2943 (m), 2891 (m), 2866 (m), 2178 (w), 1765 (s), 1741 (m), 1464 (m), 1269 (m), 1184 (s), 1152 (s), 1091 (s), 1038 (s), 882 (s), 756 (s), 690 (s), 677 (s), 661 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{25}H_{44}NaO_3Si^+$ 443.2952; Found 443.2966.

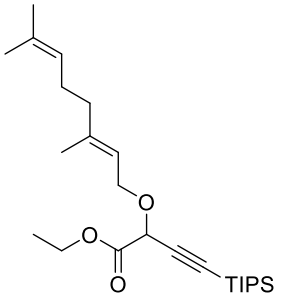
Ethyl 2-(((2*R*,3a*R*,6*R*,7*R*,8a*R*)-2,6,8,8-tetramethyloctahydro-1*H*-3a,7-methanoazulen-6-yl)oxy)-4-(triisopropylsilyl)but-3-ynoate (7.4o)



7.4o

Following general procedure C, starting from (+)-cedrol (**7.1m**) (267 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4o**) (50:50 *dr* in the crude ^{1}H NMR) as a colorless oil (88 mg, 0.18 mmol, 60%). R_f = 0.36 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 and 4.82 (2 x s, 1H, *H*CC≡C), 4.31 – 4.15 (m, 2H, OC*H*$_2$CH$_3$), 2.12 – 1.17 (m, 22H, C*H*-$_{alphatic}$ and OCH$_2$C*H*$_3$), 1.10 – 0.93 (m, 24H, C*H*$_3$ and TIPS), 0.83 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 168.9, 103.7, 103.1, 87.9, 87.3, 82.3, 82.3, 62.6, 62.2, 61.8, 61.7, 57.7, 57.1, 57.1, 57.0, 54.1, 54.1, 43.5, 43.4, 41.5, 41.4, 41.3, 37.2, 37.2, 32.9, 32.3, 31.5, 31.4, 29.1, 29.0, 27.7, 27.6, 25.5, 25.3, 25.0, 18.7, 15.8, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (m), 2178 (w), 1765 (s), 1741 (m), 1464 (m), 1283 (m), 1269 (m), 1184 (s), 1152 (s), 1091 (s), 1038 (s), 882 (s), 756 (s), 690 (s), 677 (s), 661 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{30}H_{52}NaO_3Si^+$ 511.3578; Found 511.3582.

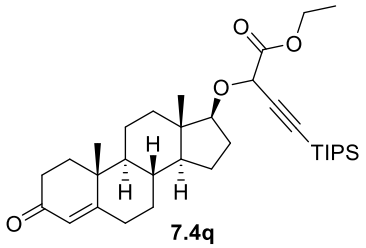
(*E*)-Ethyl 2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-4-(triisopropylsilyl)but-3-ynoate (7.4p)



7.4p

Following general procedure D, starting from geraniol (**7.1n**) (211 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4p**) as a colorless oil (72 mg, 0.17 mmol, 57%). R_f = 0.38 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (ddt, *J* = 8.3, 7.0, 1.3 Hz, 1H, C*H*CH$_2$O), 5.08 (ddp, *J* = 7.0, 5.8, 1.4 Hz, 1H, (H$_3$C)$_2$C=C*H*), 4.77 and 4.68 (2 x s, 1H, *H*CC≡C), 4.34 – 4.18 (m, 4H, CHC*H$_2$*O and OC*H$_2$*CH$_3$), 2.16 – 2.01 (m, 4H, C*H$_2$*C*H$_2$*), 1.69 (m, 6H, 2 x C*H$_3$*), 1.60 (d, *J* = 1.4 Hz, 3H, C*H$_3$*), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H$_3$*), 1.13 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 142.5, 132.0, 124.0, 119.6, 100.6, 89.2, 67.7, 64.9, 62.0, 39.8, 26.4, 25.8, 18.7, 17.8, 16.6, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2959 (s), 2942 (s), 2893 (m), 2866 (s), 2174 (w), 1758 (s), 1463 (m), 1271 (m), 1189 (s), 1103 (s), 1040 (s), 883 (s), 677 (s), 662 (s); HRMS (ESI/QTOF) m/z: [M+Na]$^+$ Calcd. for $C_{25}H_{44}NaO_3Si^+$ 443.2952; Found 443.2953.

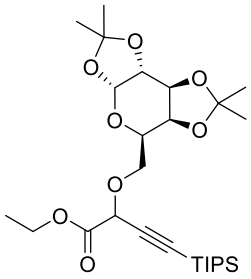
Ethyl 2-(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)oxy)-4-(triisopropylsilyl)but-3-ynoate (7.4q)



7.4q

Adapted from general procedure C, starting from testosterone (**7.1o**) (260 mg, 0.900 mmol, 3 equiv), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol, 1.00 equiv), and ethyl 2-diazoacetate (**7.2c**) (1.00 mL, 0.60 mmol, 0.6 M in DCM, 2.00 equiv), afforded the title compound (**7.4q**) (55:45 *dr* in the crude ^{1}H NMR) as a thick colorless oil (88 mg, 0.16 mmol, 53%). R_f = 0.45 (EtOAc/pentane 20:80), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H, *H*C=C), 4.76 – 4.65 (m, 1H, *H*CC≡C), 4.34 – 4.14 (m, 2H, OC*H$_2$*CH$_3$), 3.77 – 3.60 (m, 1H, OC*H*), 2.50 – 2.16 (m, 4H, C*H*-$_{alkyl}$), 2.13 – 1.90 (m, 3H, C*H*-$_{alkyl}$), 1.88 – 1.77 (m, 1H, C*H*-$_{alkyl}$), 1.76 – 1.50 (m, 5H, C*H*-$_{alkyl}$), 1.50 – 0.77 (m, 36H, C*H*-$_{alkyl}$, C*H$_3$*, C*H$_3$*, OCH$_2$C*H$_3$* and TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 199.7, 171.4, 171.3, 168.0, 167.8, 124.0, 101.4, 101.3, 89.0, 88.6, 88.2, 88.2, 87.7, 69.2, 68.9, 61.9, 61.8, 54.0, 54.0, 50.7, 50.6, 43.1, 43.0, 38.8, 38.8, 37.6, 37.1, 35.9, 35.6, 34.1, 32.9, 31.7, 31.6, 28.2, 27.7, 23.5, 20.8, 20.7, 18.7, 17.5, 14.2, 11.8, 11.7, 11.3; IR (ν_{max}, cm^{-1}) 2919 (s), 2850 (m), 1759 (m), 1672 (m), 1659 (m), 1464 (m), 1268 (m), 1230 (m), 1188 (m), 1158 (m), 1115 (s), 1101 (s), 1016 (m), 882 (s), 779 (m), 679 (s); HRMS (ESI/LTQ-Orbitrap) m/z: [M+H]$^+$ Calcd. for $C_{34}H_{55}O_4Si^+$ 555.3864; Found 555.3859.

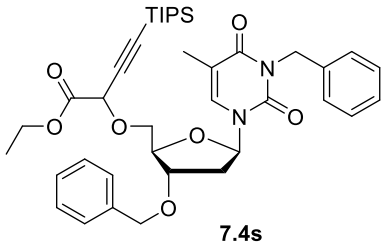
Ethyl 2-(((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-d]pyran-5-yl)methoxy)-4-(triisopropylsilyl)but-3-ynoate (7.4r)



7.4r

Following general procedure C, starting from 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose (**7.1p**) (312 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4r**) (58:42 *dr* in the crude ^{1}H NMR) as a colorless oil (88 mg, 0.17 mmol, 56%). R_f = 0.62 (EtOAc/pentane 20:80), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (d, *J* = 5.0 Hz, 1H, OC*H*$_{anomer}$), 4.94 and 4.89 (2 x s, 1H, *H*CC≡C), 4.60 (ddd, *J* = 8.0, 3.7, 2.4 Hz, 1H, OC*H*), 4.34 – 4.15 (m, 4H, 2 x OC*H* and OC*H*$_2$CH$_3$), 4.11 – 3.96 (m, 1H, OC*H*), 3.96 – 3.79 (m, 2H, OC*H*$_2$), 1.56 – 1.52 (m, 3H, C(C*H*$_3$)$_2$), 1.45 – 1.41 (m, 3H, C(C*H*$_3$)$_2$), 1.35 – 1.31 (m, 6H, C(C*H*$_3$)$_2$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 167.6, 109.4, 109.4, 108.8, 108.7, 100.1, 100.0, 96.5, 96.4, 89.7, 89.7, 71.4, 71.0, 70.8, 70.6, 69.6, 69.3, 67.5, 67.5, 67.0, 66.5, 62.0, 61.9, 29.7, 26.2, 26.1, 25.1, 24.7, 24.6, 18.7, 14.2, 11.2; IR (ν_{max}, cm^{-1}) 2941 (m), 2867 (w), 1757 (m), 1463 (w), 1382 (m), 1371 (m), 1255 (m), 1211 (s), 1169 (m), 1109 (s), 1069 (s), 1003 (s), 919 (m), 884 (m), 866 (m), 677 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{27}H_{46}NaO_8Si^+$ 549.2854; Found 549.2855.

Ethyl 2-(((2*R*,3*S*,5*R*)-5-(3-benzyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-(benzyloxy)tetrahydrofuran-2-yl)methoxy)-4-(triisopropylsilyl)but-3-ynoate (7.4s)

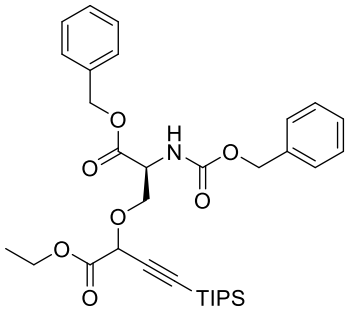


7.4s

Following general procedure D, starting from 3-benzyl-1-((2R,4S,5R)-4-(benzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**7.1q**) (507 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4s**) (53:47 *dr* in the crude ^{1}H NMR) as a thick colorless oil (89 mg, 0.13 mmol, 43%). R_f = 0.38 (EtOAc/pentane 20:80), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 and 7.73 (2 x d, *J* = 1.4 Hz, 1H, *H*C=C), 7.52 – 7.44 (m, 2H, Ar*H*), 7.41 – 7.20 (m, 8H, Ar*H*), 6.48 (td, *J* = 8.2, 5.6 Hz, 1H, OC*H*N), 5.12 (s, 2H, NC*H*$_2$Ar), 4.78 (s, 1H, *H*CC≡C), 4.57 (dd, *J* = 11.7, 4.1 Hz, 1H, OC*H*$_2$Ar), 4.49 (d, *J* = 11.7 Hz, 1H, OC*H*$_2$Ar), 4.37 – 4.16 (m, 4H, OC*H*$_2$CH$_3$, BnOC*H* and OC*H*$_2$CH), 4.09 – 4.01 (m, 0.5H, OC*H*$_2$CH), 3.94 – 3.80 (m, 1H, OCH$_2$C*H*), 3.70 – 3.61 (m, 0.5H, OC*H*$_2$CH), 2.46 (dddd, *J* = 13.4, 5.5, 3.9, 1.7 Hz, 1H, C*H*$_2$-$_{cyclic}$), 2.22 – 2.07 (m, 1H, C*H*$_2$-$_{cyclic}$), 1.93 (dd, *J* = 3.7, 1.2 Hz, 3H, C*H*$_3$), 1.29 (td, *J* = 7.1, 1.4 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 – 0.91 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 166.9, 163.7,

163.7, 151.3, 151.3, 137.7, 137.7, 137.2, 137.2, 134.6, 134.4, 129.3, 129.3, 128.6, 128.5, 128.0, 127.7, 127.6, 127.6, 110.6, 110.4, 99.2, 99.0, 91.1, 90.5, 86.0, 85.9, 83.6, 83.6, 80.4, 80.1, 71.4, 71.3, 69.2, 69.1, 68.8, 68.7, 62.2, 44.6, 44.6, 37.6, 37.6, 18.7, 18.6, 14.2, 13.3, 13.2, 11.2; IR (ν_{max}, cm^{-1}) 2947 (m), 2867 (m), 2175 (w), 1754 (m), 1701 (s), 1649 (s), 1458 (s), 1273 (m), 1200 (s), 1084 (s), 921 (m), 885 (m), 739 (m), 690 (s), 672 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{39}H_{52}N_2NaO_7Si+$ 711.3436; Found 711.3433.

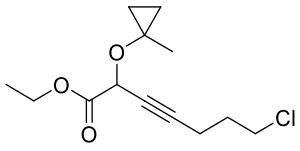
Ethyl 2-((S)-3-(benzyloxy)-2-(((benzyloxy)carbonyl)amino)-3-oxopropoxy)-4-(triisopropylsilyl)but-3-ynoate (7.4t)



7.4t

Following general procedure D, starting from *N*-carbobenzoxy-L-serine benzyl ester (**7.1r**) (395 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4t**) (53:47 *dr* in the crude ^{1}H NMR) as a colorless oil (65 mg, 0.11 mmol, 36%). R_f = 0.55 (EtOAc/pentane 20:80), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 10H, Ar*H*), 6.03 and 5.83 (2 x d, 8.4 Hz, 1H, N*H*), 5.28 – 5.05 (m, 4H, 2 x CH_2OAr), 4.85 – 4.76 (m, 1H, *H*CC≡C), 4.63 – 4.54 (m, 1H, NC*H*), 4.33 – 4.08 (m, 3H, OCH_2CH and OCH_2CH$_3$), 4.00 – 3.96 (m, 1H, OCH_2CH), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.09 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 170.0, 167.5, 167.3, 156.3, 156.2, 136.5, 136.4, 135.6, 135.5, 128.7, 128.7, 128.6, 128.6, 128.4, 128.4, 128.2, 128.2, 128.2, 128.2, 128.1, 98.8, 98.6, 91.1, 91.0, 69.0, 68.8, 68.0, 67.5, 67.4, 67.2, 67.1, 62.2, 62.1, 54.5, 54.5, 18.7, 14.2, 11.2; IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (m), 1746 (s), 1727 (s), 1509 (m), 1457 (m), 1336 (m), 1289 (m), 1197 (s), 1120 (s), 1053 (s), 882 (m), 735 (m), 696 (s), 677 (s), 664 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{33}H_{45}NNaO_7Si^+$ 618.2858; Found 618.2863.

Ethyl 7-chloro-2-(1-methylcyclopropoxy)hept-3-ynoate (7.4u)

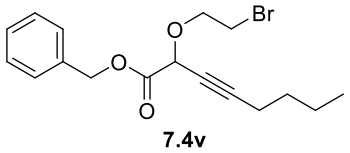


7.4u

Following general procedure C, starting from 1-methylcyclopropanol (**7.1s**) (68.0 µL, 1.20 mmol), 1-(5-chloropent-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10b**) (141 mg, 0.300 mmol), and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**7.4u**) as a colorless oil (27 mg, 0.10 mmol, 35%). R_f = 0.11 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (t, *J* = 2.2 Hz, 1H, *H*CC≡C), 4.25 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 3.63 (t, *J* = 6.4 Hz, 2H, CH_2Cl), 2.42 (td, *J* = 6.8, 2.2 Hz, 2H, C≡CCH_2), 1.96 (p, *J* = 6.6 Hz, 2H, CH_2CH$_2$Cl), 1.43 (s, 3H, CH_3), 1.31 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.07 – 1.00 (m, 1H, C*H*-$_{cyclopropyl}$), 0.93 – 0.85 (m, 1H, C*H*-$_{cyclopropyl}$), 0.49 – 0.37 (m, 2H, C*H*-$_{cyclopropyl}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 85.8, 76.4, 67.5, 62.1, 60.2, 43.6, 31.1, 21.2, 16.4, 14.2, 13.9, 13.5; IR (ν_{max}, cm^{-1}) 2963 (w), 2236 (w), 1759

(s), 1739 (s), 1445 (m), 1388 (m), 1291 (m), 1251 (s), 1187 (s), 1110 (m), 1075 (s), 1022 (s), 857 (m), 727 (m), 658 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{13}H_{19}ClNaO_3^+$ 281.0915; Found 281.0917.

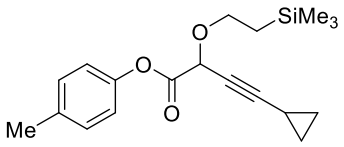
Benzyl 2-(2-bromoethoxy)oct-3-ynoate (7.4v)



7.4v

Following general procedure C, starting from 2-bromoethanol (**7.1t**) (85.0 µL, 1.20 mmol), 1-(hex-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10c**) (135 mg, 0.300 mmol), and benzyl 2-diazoacetate (**7.2d**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4v**) as a colorless oil (92 mg, 0.26 mmol, 87%). R_f = 0.21 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.28 (m, 5H, Ar*H*), 5.31 – 5.18 (m, 2H, C*H*$_2$Ar), 4.85 (t, *J* = 2.2 Hz, 1H, *H*CC≡C), 4.04 – 3.87 (m, 2H, OC*H*$_2$CH$_2$Br), 3.50 (t, *J* = 6.5 Hz, 2H, C*H*$_2$Br), 2.24 (td, *J* = 7.0, 2.2 Hz, 2H, C≡CC*H*$_2$), 1.55 – 1.44 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 1.44 – 1.27 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 0.89 (t, *J* = 7.3 Hz, 3H, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 135.3, 128.7, 128.6, 128.3, 89.7, 72.8, 69.1, 68.4, 67.5, 30.4, 29.8, 22.0, 18.6, 13.7; IR (ν_{max}, cm^{-1}) 2959 (w), 2933 (w), 1742 (m), 1256 (s), 1213 (s), 1180 (s), 1148 (s), 1110 (s), 963 (m), 947 (m), 926 (m), 756 (s), 729 (s), 698 (s), 680 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{17}H_{21}BrNaO_3^+$ 375.0566; Found 375.0571.

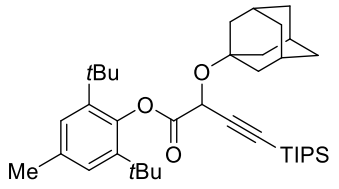
***p*-Tolyl 4-cyclopropyl-2-(2-(trimethylsilyl)ethoxy)but-3-ynoate (7.4w)**



7.4w

Following general procedure C, starting from 2-(trimethylsilyl)ethanol (**7.1u**) (172 µL, 1.20 mmol), 1-(cyclopropylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10d**) (130 mg, 0.300 mmol), and *p*-tolyl 2-diazoacetate (**7.2e**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**7.4w**) as a colorless oil (67 mg, 0.20 mmol, 68%). R_f = 0.34 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 2H, Ar*H*), 7.05 – 6.98 (m, 2H, Ar*H*), 4.85 (d, *J* = 2.0 Hz, 1H, *H*CC≡C), 3.84 – 3.75 (m, 1H, OC*H*$_2$), 3.75 – 3.66 (m, 1H, OC*H*$_2$), 2.34 (s, 3H, ArC*H*$_3$), 1.37 – 1.27 (m, 1H, C*H*-$_{cyclopropyl}$), 1.09 – 1.00 (m, 2H, C*H*$_2$TMS), 0.86 – 0.72 (m, 4H, C*H*-$_{cyclopropyl}$), 0.04 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 148.4, 135.9, 130.1, 121.0, 91.8, 68.8, 68.6, 66.8, 21.0, 18.2, 8.5, 8.5, -0.3, -1.3; IR (ν_{max}, cm^{-1}) 2953 (w), 2895 (w), 2238 (w), 1775 (m), 1507 (m), 1248 (m), 1195 (s), 1166 (s), 1095 (s), 857 (s), 835 (s), 695 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{19}H_{26}NaO_3Si^+$ 353.1543; Found 353.1543.

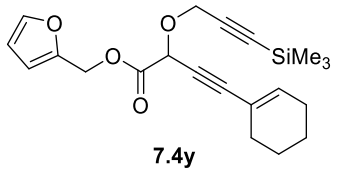
2,6-Di-tert-butyl-4-methylphenyl 2-((3s,5s,7s)-adamantan-1-yloxy)-4-(triisopropylsilyl)but-3-ynoate (7.4x)



7.4x

Following general procedure C, starting from 1-adamantanol (**7.1v**) (183 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and 1,3-di-*tert*-butyl-2-(diazomethyl)-5-methylbenzene (**7.2f**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**7.4x**) as a viscous colorless oil (132 mg, 0.220 mmol, 74%). R_f = 0.43 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2H, Ar*H*), 5.18 (s, 1H, *H*CC≡C), 2.31 (s, 3H, C*H*$_3$), 2.24 – 2.15 (m, 3H, 3 x C*H*), 2.01 – 1.87 (m, 6H, C(C*H*$_2$)$_3$), 1.73 – 1.59 (m, 6H, 3 x C*H*$_2$), 1.35 (m, 18H, 2 x *tBu*), 1.08 (s, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 146.4, 142.3, 142.1, 134.8, 127.1, 127.1, 103.8, 89.0, 76.2, 62.5, 42.3, 36.4, 35.5, 35.5, 31.8, 31.7, 30.9, 21.7, 18.7, 18.7, 11.4; IR (ν_{max}, cm^{-1}) 2912 (m), 2865 (m), 2251 (w), 2176 (w), 1760 (m), 1462 (m), 1421 (m), 1364 (m), 1271 (m), 1200 (m), 1183 (m), 1144 (m), 1104 (s), 1074 (s), 1018 (m), 909 (s), 883 (m), 733 (s), 677 (s); HRMS (ESI/QTOF) m/z: $[M+K]^+$ Calcd. for $C_{38}H_{60}KO_3Si^+$ 631.3943; Found 631.3958.

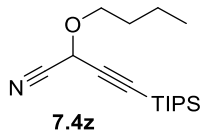
Furan-2-ylmethyl 4-(cyclohex-1-en-1-yl)-2-((3-(trimethylsilyl)prop-2-yn-1-yl)oxy)but-3-ynoate (7.4y)



7.4y

Following general procedure D, starting from 3-trimethylsilyl-2-propyn-1-ol (**7.1w**) (148 µL, 1.20 mmol), 1-(cyclohex-1-en-1-ylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10e**) (119 mg, 0.300 mmol), and furan-2-ylmethyl 2-diazoacetate (**7.2g**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**7.4y**) as a viscous colorless oil (36 mg, 0.10 mmol, 39%). R_f = 0.21 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 1.9, 0.9 Hz, 1H, Ar*H*), 6.49 – 6.42 (m, 1H, Ar*H*), 6.36 (dd, *J* = 3.3, 1.9 Hz, 1H, Ar*H*), 6.16 (p, *J* = 2.1 Hz, 1H, C=C*H*), 5.25 – 5.13 (m, 2H, OC*H*$_2$Ar), 5.08 (s, 1H, *H*CC≡C), 4.37 (s, 2H, OC*H*$_2$C≡C), 2.14 – 2.04 (m, 4H, C*H*-$_{cyclohexenyl}$), 1.68 – 1.51 (m, 4H, C*H*-$_{cyclohexenyl}$), 0.16 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 148.8, 143.6, 137.6, 119.7, 111.4, 110.8, 100.0, 92.9, 90.0, 78.7, 67.5, 59.5, 56.7, 28.9, 25.8, 22.3, 21.5, -0.1; IR (ν_{max}, cm^{-1}) 2934 (m), 2862 (w), 1753 (m), 1444 (w), 1251 (m), 1181 (m), 1090 (s), 1009 (m), 846 (s), 753 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{21}H_{26}NaO_4Si^+$ 393.1493; Found 393.1491.

2-Butoxy-4-(triisopropylsilyl)but-3-ynenitrile (7.4z)

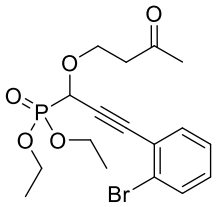


7.4z

Following general procedure C, starting from 1-butanol (**7.1x**) (110 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and 2-diazoacetonitrile (**7.2h**) (1.20 mL, 0.600 mmol, 0.50 M in DCM), afforded the title

compound (**7.4z**) as a colorless oil (57 mg, 0.19 mmol, 65%). R_f = 0.14 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (s, 1H, *H*CC≡C), 3.82 – 3.72 (m, 1H, OC*H*$_2$), 3.69 – 3.61 (m, 1H, OC*H*$_2$), 1.63 (tt, *J* = 8.3, 6.3 Hz, 2H, OCH$_2$C*H*$_2$), 1.47 – 1.35 (m, 2H, C*H*$_2$CH$_3$), 1.14 – 0.97 (m, 21H, TIPS), 0.93 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 114.9, 96.3, 91.8, 68.3, 58.0, 31.3, 19.3, 18.6, 13.9, 11.1; IR (ν_{max}, cm^{-1}) 2945 (m), 2867 (m), 1740 (m), 1717 (m), 1464 (m), 1253 (m), 1091 (s), 1029 (m), 882 (s), 836 (m), 776 (m), 678 (s), 662 (s); HRMS (APCI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{32}NOSi^+$ 294.2248; Found 294.2251.

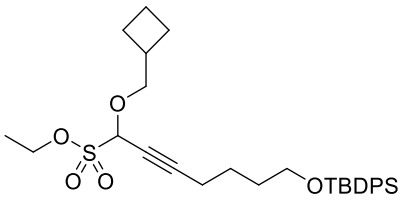
Diethyl (3-(2-bromophenyl)-1-(3-oxobutoxy)prop-2-yn-1-yl)phosphonate (7.4aa)



7.4aa

Following general procedure C, starting from 4-hydroxy-2-butanone (**7.1y**) (103 µL, 1.20 mmol), 1-((2-bromophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10f**) (165 mg, 0.300 mmol) and diethyl (diazomethyl)phosphonate (**7.2i**) (1.00 mL, 0.600 mmol, 0.60 M in DCM), afforded the title compound (**7.4aa**) as a colorless oil (95 mg, 0.23 mmol, 76%). R_f = 0.17 (EtOAc/pentane 20:80), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar*H*), 7.50 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar*H*), 7.30 – 7.23 (m, 1H, Ar*H*), 7.20 (td, *J* = 7.7, 1.8 Hz, 1H, Ar*H*), 4.73 (d, *J* = 19.4 Hz, 1H, *H*CC≡C), 4.34 – 4.18 (m, 5H, 2 x POC*H*$_2$CH$_3$ and OC*H*$_2$), 3.92 (ddd, *J* = 9.6, 6.8, 5.9 Hz, 1H, OC*H*$_2$), 2.88 – 2.70 (m, 2H, C*H*$_2$COCH$_3$), 2.20 (s, 3H, COC*H*$_3$), 1.36 (tt, *J* = 7.0, 1.0 Hz, 6H, 2 x POCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7, 133.9 (d, *J* = 2.8 Hz), 132.6, 130.2, 127.2, 125.7 (d, *J* = 3.1 Hz), 124.3 (d, *J* = 3.6 Hz), 87.7 (d, *J* = 10.0 Hz), 86.1 (d, *J* = 5.2 Hz), 67.1 (d, *J* = 175.3 Hz), 66.0 (d, *J* = 12.5 Hz), 64.1 (dd, *J* = 11.1, 6.7 Hz), 43.6, 30.5, 16.7 (dd, *J* = 5.7, 3.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.3; IR (ν_{max}, cm^{-1}) 2917 (w), 2849 (w), 1715 (m), 1469 (w), 1236 (m), 1165 (w), 1097 (m), 1021 (s), 977 (m), 756 (m); HRMS (APPI/LTQ-Orbitrap) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{23}BrO_5P^+$ 417.0461; Found 417.0455.

Ethyl 7-((tert-butyldiphenylsilyl)oxy)-1-(cyclobutylmethoxy)hept-2-yne-1-sulfonate (7.4ab)

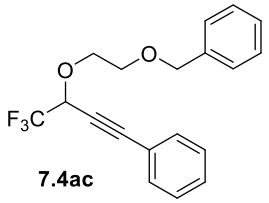


7.4ab

Following general procedure C, starting from cyclobutanemethanol (**7.1z**) (113 µL, 1.20 mmol), ((6-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)hex-5-yn-1-yl)oxy)(tert-butyl)diphenylsilane (**7.10g**) (211 mg, 0.300 mmol), and ethyl diazomethanesulfonate (**7.2j**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**7.4ab**) as a colorless oil (132 mg, 0.240 mmol, 81%). R_f = 0.35 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H, Ar*H*), 7.49 – 7.33 (m, 6H, Ar*H*), 5.25 (t, *J* = 1.6 Hz, 1H, *H*CC≡C), 3.80 – 3.45 (m, 6H, 3 x OC*H*$_2$), 2.58 (hept, *J* = 7.4 Hz, 1H, OCH$_2$C*H*), 2.31 – 2.21 (m, 2H, C*H*$_2$-$_{aliphatic}$), 2.13 – 2.00 (m, 2H, C*H*$_2$-$_{aliphatic}$), 1.98 – 1.80 (m, 2H, C*H*$_2$-$_{aliphatic}$), 1.80 – 1.59 (m, 6H, C*H*$_2$-$_{aliphatic}$), 1.23 (t, *J* = 7.1 Hz, 3H, OC*H*$_2$CH$_3$), 1.05 (s, 9H, tBu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 134.1, 129.7, 127.8, 91.7, 86.5, 76.0, 69.4, 63.4, 61.0, 35.0, 31.9, 27.0, 25.3, 25.2, 25.0, 19.4, 18.7, 18.6, 15.2; IR (ν_{max}, cm^{-1}) 2931 (m), 2859 (m), 2245 (w), 1428

(m), 1389 (w), 1359 (m), 1148 (m), 1108 (s), 1041 (s), 1008 (m), 740 (m), 701 (s), 613 (m); HRMS (APPI/LTQO) m/z: $[M\text{-}C_2H_5O_3S]^+$ Calcd. for $C_{28}H_{37}O_2Si^+$ 433.2557; Found 433.2543.

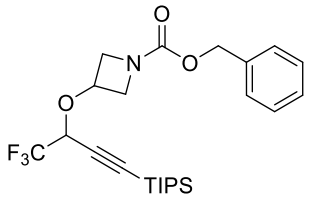
(3-(2-(Benzyloxy)ethoxy)-4,4,4-trifluorobut-1-yn-1-yl)benzene (7.4ac)



7.4ac

Following general procedure C, starting from 2-(benzyloxy)ethanol (**7.1aa**) (171 µL, 1.20 mmol), 1-(phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10h**) (141 mg, 0.300 mmol), and 2,2,2-trifluorodiazoethane (**7.2k**) (1.62 mL, 0.600 mmol, 0.37 M in DCM), afforded the title compound (**7.4ac**) as a colorless oil (73 mg, 0.22 mmol, 73%). R_f = 0.27 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H, Ar*H*), 7.41 – 7.26 (m, 8H, Ar*H*), 4.90 (q, *J* = 5.9 Hz, 1H, *H*CC≡C), 4.60 (s, 2H, CH_2Ar), 4.06 – 3.98 (m, 1H, OCH_2), 3.98 – 3.90 (m, 1H, OCH_2), 3.80 – 3.66 (m, 2H, CH_2OBn); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 132.2, 129.5, 128.6, 128.5, 127.9, 127.8, 122.7 (q, *J* = 281.8 Hz), 121.3, 88.8, 79.3 (q, *J* = 2.4 Hz), 73.5, 69.8 (q, *J* = 35.1 Hz), 69.4, 69.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.8; IR (ν_{max}, cm^{-1}) 2871 (w), 1720 (w), 1703 (w), 1491 (w), 1454 (w), 1362 (w), 1272 (s), 1184 (s), 1141 (s), 1095 (s), 1028 (m), 756 (s), 690 (s); HRMS (APPI/LTQ-Orbitrap) m/z: $[M]^+$ Calcd. for $C_{19}H_{17}F_3O_2^+$ 334.1175; Found 334.1173.

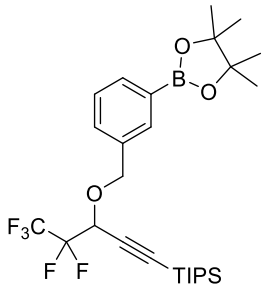
Benzyl 3-((1,1,1-trifluoro-4-(triisopropylsilyl)but-3-yn-2-yl)oxy)azetidine-1-carboxylate (7.4ad)



7.4ad

Following general procedure D, starting from benzyl 3-hydroxyazetidine-1-carboxylate (**7.1ab**) (249 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and 2,2,2-trifluorodiazoethane (**7.2k**) (1.67 mL, 0.600 mmol, 0.36 M in DCM), afforded the title compound (**7.4ad**) as a colorless oil (86 mg, 0.18 mmol, 61%). R_f = 0.09 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H, Ar*H*), 5.10 (s, 2H, OCH_2Ar), 4.73 – 4.63 (m, 1H, OC*H*), 4.55 (q, *J* = 5.8 Hz, 1H, *H*CC≡C), 4.30 – 4.16 (m, 2H, NCH_2), 4.11 (ddd, *J* = 9.7, 4.4, 1.1 Hz, 1H, NCH_2), 4.01 (ddd, *J* = 9.8, 4.4, 1.2 Hz, 1H, NCH_2), 1.14 – 0.95 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 136.6, 128.6, 128.2, 128.1, 122.1 (q, *J* = 281.9 Hz), 95.7, 93.5, 68.2 (q, *J* = 35.5 Hz), 67.7, 67.0, 57.9 – 56.3 (m), 18.6, 11.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -77.0; IR (ν_{max}, cm^{-1}) 2946 (m), 2867 (m), 1713 (s), 1456 (m), 1418 (s), 1352 (m), 1272 (m), 1181 (s), 1146 (s), 1093 (s), 1039 (m), 1001 (m), 882 (m), 736 (m), 697 (m), 680 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{34}F_3NNaO_3Si_+$ 492.2152; Found 492.2164.

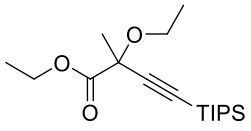
Triisopropyl(4,4,5,5,5-pentafluoro-3-((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)pent-1-yn-1-yl)silane (7.4ae)



7.4ae

Following general procedure C, starting from (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (**7.1ac**) (281 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.2l**) (165 mg, 0.300 mmol), and 3-diazo-1,1,1,2,2-pentafluoropropane (**3j**) (1.67 mL, 0.600 mmol, 0.36 M in DCM), afforded the title compound (**7.4ae**) as a colorless oil (128 mg, 0.234 mmol, 78%). R_f = 0.40 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.73 (m, 2H, Ar*H*), 7.49 (dt, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.44 – 7.34 (m, 1H, Ar*H*), 4.88 (d, *J* = 11.7 Hz, 1H, CH_2O), 4.77 – 4.66 (m, 1H, CH_2O), 4.66 – 4.54 (m, 1H, *H*CC≡C), 1.35 (s, 12H, 4 x CH_3), 1.19 – 0.96 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3, 134.9, 134.9, 131.4, 129.4 (br s), 128.2, 118.8 (tq, *J* = 287.0, 35.0 Hz), 111.8 (qdd, *J* = 256.8, 36.3, 5.0 Hz), 95.9, 93.3, 84.0, 71.0, 67.3 (dd, *J* = 29.5, 24.8 Hz), 25.01 (d, *J* = 4.7 Hz), 18.6, 11.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.1, -119.9 (d, *J* = 273.9 Hz), -125.3 (d, *J* = 274.2 Hz); IR (ν_{max}, cm^{-1}) 2945 (m), 2868 (m), 2181 (w), 1464 (w), 1434 (w), 1358 (s), 1321 (m), 1216 (s), 1198 (s), 1144 (s), 1099 (m), 1079 (m), 988 (m), 965 (m), 883 (m), 853 (m), 743 (m), 708 (s), 672 (s); HRMS (APCI/QTOF) m/z: $[M+NH_4]^+$ Calcd. for $C_{27}H_{44}BF_5NO_3Si^+$ 564.3098; Found 564.3115.

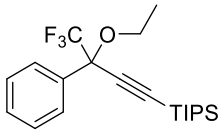
Ethyl 2-ethoxy-2-methyl-4-(triisopropylsilyl)but-3-ynoate (7.4af)



7.4af

Following general procedure D, starting from ethanol (**7.1b**) (70.0 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and ethyl 2-diazopropanoate (**7.2p**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4af**) as a colorless oil (42 mg, 0.13 mmol, 43%). R_f = 0.37 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 – 4.12 (m, 2H, (O)COCH_2), 3.81 (dq, *J* = 8.7, 7.1 Hz, 1H, OCH_2CH$_3$), 3.59 (dq, *J* = 8.9, 7.0 Hz, 1H, OCH_2CH$_3$), 1.67 (s, 3H, CH_3), 1.29 (t, *J* = 7.1 Hz, 3H, (O)COCH$_2$CH_3), 1.25 (t, *J* = 7.0 Hz, 3H, OCH_2CH$_3$), 1.08 (s, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 104.4, 87.9, 75.0, 62.4, 61.9, 27.7, 18.7, 15.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (m), 2868 (m), 1748 (s), 1460 (m), 1247 (m), 1196 (m), 1124 (s), 1065 (m), 881 (m), 670 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{18}H_{34}NaO_3Si^+$ 349.2169; Found 349.2172.

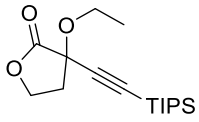
(3-Ethoxy-4,4,4-trifluoro-3-phenylbut-1-yn-1-yl)triisopropylsilane (7.4ag)



7.4ag

Following general procedure D, starting from ethanol (**7.1b**) (70.0 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and (1-diazo-2,2,2-trifluoroethyl)benzene (**7.2q**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4ag**) as a colorless oil (66 mg, 0.17 mmol, 57%). R_f = 0.65 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H, Ar*H*), 7.45 – 7.37 (m, 3H, Ar*H*), 3.83 (dq, *J* = 8.9, 7.0 Hz, 1H, OC*H*$_2$CH$_3$), 3.44 (dq, *J* = 9.0, 7.0 Hz, 1H, OC*H*$_2$CH$_3$), 1.28 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$), 1.21 – 0.95 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4, 129.6, 128.3, 128.3, 123.1 (q, *J* = 285.2 Hz), 99.5, 93.2, 79.5 (q, *J* = 31.1 Hz), 61.7, 18.7, 15.4, 11.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.7; IR (ν_{max}, cm^{-1}) 2947 (m), 2869 (m), 1460 (m), 1272 (m), 1180 (s), 1120 (m), 1068 (s), 952 (m), 884 (m), 763 (m), 708 (m), 672 (s); HRMS (ESI/QTOF) m/z: $[M+Ag]^+$ Calcd. for $C_{21}H_{31}AgF_3OSi^+$ 491.1142; Found 491.1136.

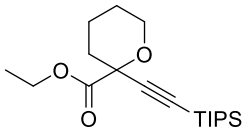
3-Ethoxy-3-((triisopropylsilyl)ethynyl)dihydrofuran-2(3*H*)-one (7.4ah)



7.4ah

Following general procedure D, starting from ethanol (**7.1b**) (70.0 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol), and 3-diazodihydrofuran-2(3*H*)-one (**7.2r**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4ah**) as a colorless oil (44 mg, 0.14 mmol, 47%). R_f = 0.26 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 – 4.27 (m, 2H, OC*H*$_2$CH$_2$), 3.99 – 3.81 (m, 2H, OC*H*$_2$CH$_3$), 2.66 – 2.46 (m, 2H, OCH$_2$C*H*$_2$), 1.23 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$), 1.13 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 100.7, 91.9, 73.4, 65.4, 62.4, 38.9, 18.7, 15.5, 11.2; IR (ν_{max}, cm^{-1}) 2944 (s), 2867 (m), 2170 (w), 1787 (s), 1463 (m), 1377 (m), 1224 (m), 1155 (s), 1060 (s), 1026 (s), 884 (m), 764 (m), 671 (s); HRMS (APCI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{31}O_3Si^+$ 311.2037; Found 311.2030.

Ethyl 2-((triisopropylsilyl)ethynyl)tetrahydro-2*H*-pyran-2-carboxylate (7.4ai)

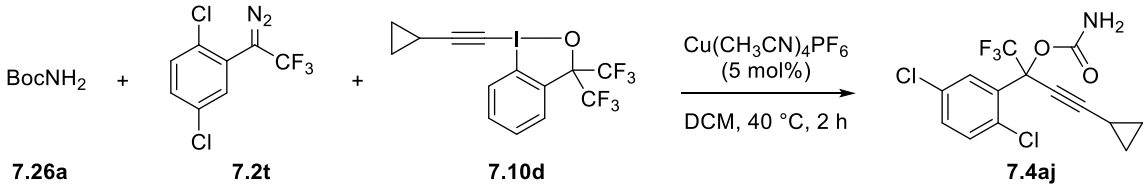


7.4ai

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (11.2 mg, 30.0 µmol, 0.10 equiv) and ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (165 mg, 0.300 mmol). To the resulting solution was added a 0.6 M solution of ethyl 2-diazo-6-hydroxyhexanoate (**7.2s**) (0.60 mmol, 2.00 equiv) in dry DCM in 1 h via seringe pump at 25 °C. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography (EtOAc/pentane) directly without further work-up, affording the title compound (**7.4ai**) as a colorless oil (21 mg, 62 µmol, 21%). R_f = 0.17 (EtOAc/pentane 3:97), *p*-

anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (qq, *J* = 7.1, 3.6 Hz, 2H, OC*H*$_2$CH$_3$), 4.09 – 3.96 (m, 1H, OC*H*$_2$), 3.96 – 3.85 (m, 1H, OC*H*$_2$), 2.09 – 2.00 (m, 1H, C*H*-$_{aliphatic}$), 2.00 – 1.69 (m, 3H, C*H*-$_{aliphatic}$), 1.67 – 1.39 (m, 2H, C*H*-$_{aliphatic}$), 1.29 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.16 – 0.84 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 102.9, 89.4, 74.4, 64.3, 62.0, 34.6, 25.0, 20.0, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (s), 2865 (s), 2166 (w), 1762 (s), 1742 (s), 1464 (m), 1289 (m), 1255 (s), 1203 (s), 1149 (s), 1095 (m), 1066 (s), 1018 (s), 920 (m), 882 (s), 759 (m), 676 (s), 660 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{19}H_{34}NaO_3Si^+$ 361.2169; Found 361.2174.

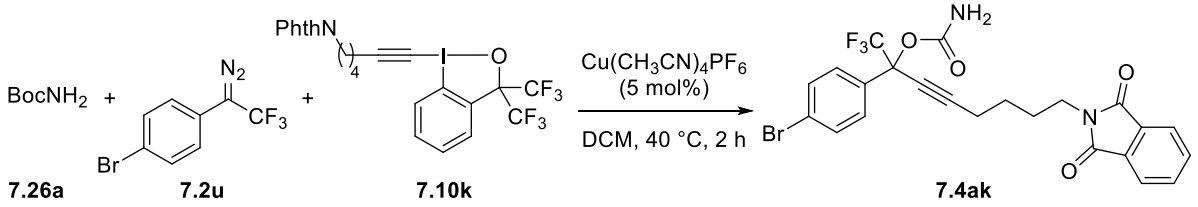
2-(4-Bromophenyl)-8-(1,3-dioxoisoindolin-2-yl)-1,1,1-trifluorooct-3-yn-2-yl carbamate (7.4aj)



7.26a **7.2t** **7.10d** **7.4aj**

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (5.59 mg, 15.0 µmol, 0.05 equiv), 1-(cyclopropylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10d**) (130 mg, 0.300 mmol, 1.00 equiv) and *tert*-butyl carbamate (**7.26a**) (45.7 mg, 0.390 mmol, 1.30 equiv). The vial was capped, removed from the glovebox and dry DCM (5.35 mL) was added. To the resulting solution was added a 0.6 M solution of 1,4-dichloro-2-(1-diazo-2,2,2-trifluoroethyl)benzene (**7.2t**) (0.65 mL, 0.39 mmol, 1.30 equiv) in dry DCM in 1 h via seringe pump at 25 °C. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography, using DCM as eluent, directly without further work-up affording the title compound (**7.4aj**) as a white solid (65 mg, 0.19 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 2.3 Hz, 1H, Ar*H*), 7.33 – 7.29 (m, 1H, Ar*H*), 7.29 – 7.24 (m, 1H, Ar*H*), 4.88 (br s, 2H, N*H*$_2$), 1.42 (tt, *J* = 8.2, 5.2 Hz, 1H, C*H*-$_{cyclopropyl}$), 0.94 – 0.83 (m, 4H, C*H*-$_{cyclopropyl}$); ^{13}C NMR (101 MHz, $CDCl_3$) 152.5, 133.3, 132.8, 132.1, 131.9, 131.1, 130.7, 122.5 (q, *J* = 285.8 Hz), 95.3, 77.9 (q, *J* = 33.3 Hz), 67.1, 8.8, 8.7, -0.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -77.5. The values of the NMR spectra are in accordance with reported literature data.[330]

2-(4-Bromophenyl)-8-(1,3-dioxoisoindolin-2-yl)-1,1,1-trifluorooct-3-yn-2-yl carbamate (7.4ak)

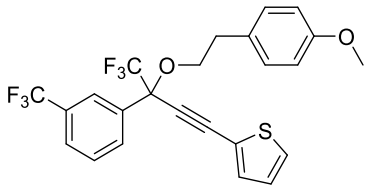


7.26a **7.2u** **7.10k** **7.4ak**

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (5.59 mg, 15.0 µmol, 0.05 equiv), 2-(6-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3H)-yl)hex-5-yn-1-yl)isoindoline-1,3-dione (**7.10k**) (179 mg, 0.300 mmol, 1.00 equiv) and *tert*-butyl carbamate (**7.26a**) (45.7 mg, 0.390 mmol, 1.30 equiv). The vial was capped, removed from the glovebox and dry DCM (2.35 mL) was added. To the resulting solution was added a 0.6 M solution of 1-bromo-4-(1-diazo-2,2,2-trifluoroethyl)benzene (**7.2u**) (0.65 mL, 0.39 mmol, 1.30 equiv) in dry DCM in 1 h via seringe pump at 40 °C. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography, using EtOAc/pentane 33:67 as eluent, directly without further work-up affording the title compound (**7.4ak**) as a white solid (49 mg, 90 µmol, 31%). M.p. 117 – 118 °C; R_f = 0.54 (EtOAc/pentane 50:50), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.79 (m, 2H, Ar*H*), 7.75

– 7.67 (m, 2H, Ar*H*), 7.56 – 7.45 (m, 4H, Ar*H*), 5.00 (br s, 2H, NH_2), 3.72 (t, *J* = 7.0 Hz, 2H, CH_2N), 2.44 (t, *J* = 6.9 Hz, 2H, CH_2C≡C), 1.92 – 1.79 (m, 2H, CH_2), 1.74 – 1.61 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 152.4, 134.1, 133.1, 132.2, 131.7, 128.8, 124.1, 123.4, 122.2 (q, *J* = 284.2 Hz), 91.1, 72.7, 72.2 (q, *J* = 32.4 Hz), 37.5, 27.8, 25.4, 18.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -77.5; IR (ν_{max}, cm^{-1}) 2945 (m), 2870 (m), 2358 (w), 1461 (m), 1273 (m), 1180 (s), 1117 (s), 1068 (s), 763 (m), 711 (m), 674 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{18}BrF_3N_2NaO_4^+$ 545.0294; Found 545.0284.

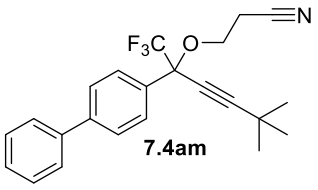
2-(4,4,4-Trifluoro-3-(4-methoxyphenethoxy)-3-(3-(trifluoromethyl)phenyl)but-1-yn-1-yl)thiophene (7.4al)



7.4al

Following general procedure D, starting from 4-methoxyphenethyl alcohol (**7.1ag**) (183 mg, 1.20 mmol), 1-(thiophen-2-ylethynyl)-3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10i**) (143 mg, 0.300 mmol), and 1-(1-diazo-2,2,2-trifluoroethyl)-3-(trifluoromethyl)benzene (**7.2v**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**7.4al**) as an unseparable mixture with the corresponding O-H insertion product. The yield was estimated to be 73% by ^{19}F NMR spectroscopy. A pure analytical sample was isolated by PTLC using toluene/acetone 95:5 as eluent. R_f = 0.31 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H, Ar*H*), 7.75 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.69 – 7.63 (m, 1H, Ar*H*), 7.48 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.41 – 7.36 (m, 2H, Ar*H*) , Ar*H*, 7.16 – 7.10 (m, 2H, Ar*H*), 7.05 (dd, *J* = 5.1, 3.7 Hz, 1H, Ar*H*), 6.86 – 6.80 (m, 2H, Ar*H*), 4.04 – 3.95 (m, 1H, OCH_2), 3.79 (s, 3H, OCH_3), 3.59 – 3.51 (m, 1H, OCH_2), 2.94 (t, *J* = 6.9 Hz, 2H, CH_2Ar); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 135.4, 134.2, 131.7, 131.0 (q, *J* = 32.7 Hz), 130.4, 130.2, 129.1, 129.0, 127.4, 126.7 (q, *J* = 3.1 Hz), 125.2 (q, *J* = 3.5 Hz), 123.9 (q, *J* = 272.3 Hz), 122.8 (q, *J* = 285.9 Hz), 120.5, 114.0, 84.8, 84.7, 79.5 (q, *J* = 31.7 Hz), 67.6, 55.4, 35.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6, -78.2; IR (ν_{max}, cm^{-1}) 2931 (w), 2226 (w), 1515 (m), 1329 (m), 1252 (m), 1178 (s), 1130 (s), 1082 (m), 1039 (m), 910 (w), 815 (w), 713 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{24}H_{19}F_6O_2S^+$ 485.1004; Found 485.1006.

3-((2-([1,1'-Biphenyl]-4-yl)-1,1,1-trifluoro-5,5-dimethylhex-3-yn-2-yl)oxy)propanenitrile (7.4am)

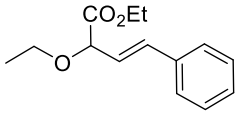


7.4am

Following general procedure D, starting from 3-hydroxypropionitrile (**7.1ah**) (81.0 µL, 1.20 mmol), 1-(3,3-dimethylbut-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.10j**) (135 mg, 0.300 mmol), and 4-(1-diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl (**7.2w**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**7.4am**) as a colorless oil (68 mg, 0.18 mmol, 59%). R_f = 0.24 (EtOAc/pentane 5:95), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.75 (m, 2H, Ar*H*), 7.69 – 7.57 (m, 4H, Ar*H*), 7.51 – 7.43 (m, 2H, Ar*H*), 7.42 – 7.35 (m, 1H, Ar*H*), 3.96 (dt, *J* = 9.4, 6.1 Hz, 1H, OCH_2), 3.67 (ddd, *J* = 9.4, 7.5, 6.1 Hz, 1H, OCH_2), 2.83 – 2.63 (m, 2H, CH_2CN), 1.37 (s, 9H, *t*Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 140.3, 132.7, 129.0, 128.7, 127.9, 127.3, 127.3, 122.9 (q, *J* = 285.0 Hz), 117.4, 101.4, 79.4 (q, *J* = 31.8 Hz), 70.8, 60.4, 30.7, 28.0, 19.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.84; IR (ν_{max}, cm^{-1}) 2975 (w), 2251 (w), 1487 (m), 1290 (m), 1255 (m), 1175 (s), 1090 (s), 1007 (m), 943 (m), 884 (m), 836

(m), 766 (s), 738 (s), 697 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{22}F_3NNaO^+$ 408.1546; Found 408.1546.

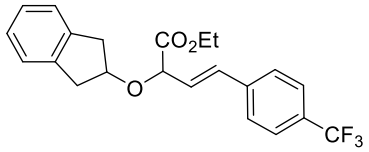
(*E*)-Ethyl 2-ethoxy-4-phenylbut-3-enoate (7.17b)



7.17b

Following general procedure E, starting from ethanol (**7.1b**) (52.5 µL, 0.900 mmol), (*E*)-1-styryl-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**7.29a**) (142 mg, 0.300 mmol) and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded (*E*)-ethyl 2-ethoxy-4-phenylbut-3-enoate (**7.17b**) as a colorless oil (28 mg, 0.12 mmol, 40%). R_f = 0.26 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H, Ar*H*), 7.35 – 7.29 (m, 2H, Ar*H*), 7.29 – 7.23 (m, 1H, Ar*H*), 6.77 (dd, *J* = 16.0, 1.3 Hz, 1H, HC=C*H*Ph), 6.23 (dd, *J* = 15.9, 6.8 Hz, 1H, *H*C=CHPh), 4.51 (dd, *J* = 6.8, 1.4 Hz, 1H, OC*H*C), 4.31 – 4.18 (m, 2H, C(O)OCH_2CH$_3$), 3.61 (qq, *J* = 9.1, 7.0 Hz, 2H, OCH_2CH$_3$), 1.30 (t, *J* = 7.1 Hz, 6H, 2 x OCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 136.2, 134.0, 128.7, 128.3, 126.9, 124.3, 79.9, 65.5, 61.4, 15.3, 14.4; IR (ν_{max}, cm^{-1}) 2980 (m), 2937 (w), 1738 (s), 1636 (m), 1451 (m), 1371 (m), 1313 (s), 1268 (s), 1189 (s), 1159 (s), 1091 (s), 1023 (s), 699 (s); HRMS (ESI) calcd for $C_{14}H_{18}NaO_3^+$ $[M+Na]^+$ 257.1148; found 257.1146.

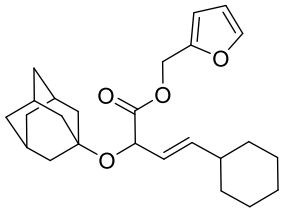
(*E*)-Ethyl 2-((2,3-dihydro-1*H*-inden-2-yl)oxy)-4-(4-(trifluoromethyl)phenyl)but-3-enoate (7.17c)



7.17c

Following general procedure E, starting from 2-indanol (**7.1ai**) (161 mg, 0.900 mmol), (*E*)-3,3-bis(trifluoromethyl)-1-(4-(trifluoromethyl)styryl)-1,3-dihydro-benzo[*d*][1,2]iodaoxole (**7.29b**) (162 mg, 0.300 mmol) and ethyl 2-diazoacetate (**7.2c**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded (*E*)-ethyl 2-((2,3-dihydro-1*H*-inden-2-yl)oxy)-4-(4-(trifluoromethyl)phenyl)but-3-enoate (**7.17c**) as a colorless oil (52 mg, 0.13 mmol, 44%). R_f = 0.12 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.46 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.25 – 7.12 (m, 4H, Ar*H*), 6.78 (dd, *J* = 16.0, 1.5 Hz, 1H, HC=C*H*Ar), 6.37 (dd, *J* = 15.9, 6.0 Hz, 1H, *H*C=CHAr), 4.70 (dd, *J* = 6.1, 1.5 Hz, 1H, OC*H*C), 4.54 (tt, *J* = 6.6, 5.1 Hz, 1H, OC*H*(CH$_2$)$_2$), 4.27 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 3.29 – 3.03 (m, 4H, 2 x CH_2Ar), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 140.7, 140.4, 139.7, 132.0, 130.0 (q, *J* = 32.6 Hz), 127.2, 127.0, 126.9, 126.8, 125.7 (q, *J* = 3.8 Hz), 124.8, 124.2 (q, *J* = 272.1 Hz), 80.3, 78.3, 61.7, 39.7, 39.3, 14.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6; IR (ν_{max}, cm^{-1}) 2932 (w), 2359 (w), 1743 (m), 1614 (w), 1324 (s), 1261 (m), 1168 (s), 1116 (s), 1067 (s), 1024 (m), 972 (m), 831 (m), 742 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{21}F_3NaO_3^+$ 413.1335; Found 413.1342.

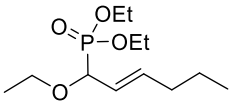
(*E*)-Furan-2-ylmethyl 2-adamantan-1-yloxy)-4-cyclohexylbut-3-enoate (7.17d)



7.17d

Following general procedure E, starting from 1-adamantanol (**7.1v**) (161 mg, 0.90 mmol), (*E*)-1-(2-cyclohexylvinyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzobenzo[*d*][1,2]iodaoxole (**7.29c**) (143 mg, 0.300 mmol) and furan-2-ylmethyl 2-diazoacetate (**7.2g**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded (*E*)-furan-2-ylmethyl 2-adamantan-1-yloxy)-4-cyclohexylbut-3-enoate (**7.17d**) as a colorless oil (47 mg, 0.12 mmol, 39%). R_f = 0.21 (EtOAc/pentane 2:98), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 1H, Ar*H*), 6.40 (d, *J* = 3.2 Hz, 1H, Ar*H*), 6.34 (dd, *J* = 3.3, 1.8 Hz, 1H, Ar*H*), 5.72 (ddd, *J* = 15.6, 6.6, 1.4 Hz, 1H, HC=C*H*-cHex), 5.43 (ddd, *J* = 15.6, 5.9, 1.4 Hz, 1H, *H*C=CH-cHex), 5.12 (q, *J* = 13.1 Hz, 2H, C*H*$_2$Ar), 4.65 (dt, *J* = 5.9, 1.1 Hz, 1H, OC*H*C), 2.10 (p, *J* = 3.3 Hz, 3H,C*H*-$_{aliphatic}$), 1.93 (dtd, *J* = 11.1, 7.4, 3.2 Hz, 1H, C*H*-$_{aliphatic}$), 1.80 – 1.50 (m, 17H,C*H*-$_{aliphatic}$), 1.33 – 0.95 (m, 5H,C*H*-$_{aliphatic}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 149.5, 143.2, 139.8, 124.1, 111.0, 110.7, 74.7, 70.8, 58.3, 41.8, 40.4, 36.4, 32.6, 32.5, 30.7, 26.3, 26.1; IR (ν_{max}, cm^{-1}) 3669 (w), 2972 (s), 2908 (s), 2851 (m), 1755 (m), 1734 (m), 1450 (m), 1250 (m), 1153 (m), 1104 (m), 1078 (s), 966 (m), 739 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{35}O_4^+$ 399.2530; Found 399.2536.

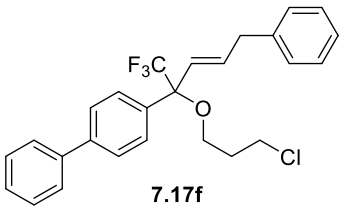
(*E*)-Diethyl (1-ethoxyhex-2-en-1-yl)phosphonate (7.17e)



7.17e

Following general procedure E, starting from ethanol (**7.1b**) (52.5 µL, 0.900 mmol), (*E*)-1-(pent-1-en-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzobenzo[*d*][1,2]iodaoxole (**7.29e**) (131 mg, 0.300 mmol) and diethyl (diazomethyl)phosphonate (**7.2i**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded (*E*)-diethyl (1-ethoxyhex-2-en-1-yl)phosphonate (**7.17e**) as a colorless oil (18 mg, 70 µmol, 23%). R_f = 0.22 (EtOAc/pentane 50:50), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 – 5.75 (m, 1H, HC=C*H*-*n*Pr), 5.49 (dddt, *J* = 15.5, 7.8, 4.8, 1.5 Hz, 1H, *H*C=CH-*n*Pr), 4.22 – 4.11 (m, 4H, 2 x P(O)OC*H*$_2$CH$_3$), 4.05 (ddd, *J* = 14.7, 7.8, 1.0 Hz, 1H, OC*H*C), 3.66 (dq, *J* = 9.3, 7.0 Hz, 1H, OC*H*$_2$CH$_3$), 3.49 (dq, *J* = 9.3, 6.9 Hz, 1H, OC*H*$_2$CH$_3$), 2.13 – 2.02 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 1.43 (h, *J* = 7.3 Hz, 2H, CH$_2$C*H*$_2$CH$_3$), 1.32 (td, *J* = 7.1, 1.2 Hz, 6H, 2 x P(O)OCH$_2$C*H*$_3$), 1.21 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$), 0.91 (t, *J* = 7.4 Hz, 3H, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.0 (d, *J* = 13.5 Hz), 123.6 (d, *J* = 3.6 Hz), 77.3 (d, *J* = 169.8 Hz), 66.0 (d, *J* = 12.6 Hz), 62.9 (dd, *J* = 25.4, 6.9 Hz), 34.6, 22.3 (d, *J* = 2.9 Hz), 16.7 (t, *J* = 5.0 Hz), 15.3, 13.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.49; IR (ν_{max}, cm^{-1}) 2968 (m), 2930 (m), 2872 (w), 1393 (w), 1251 (m), 1099 (m), 1051 (s), 1024 (s), 967 (s), 790 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{25}NaO_4P^+$ 287.1383; Found 287.1391.

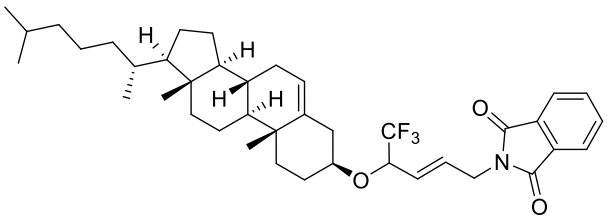
(*E*)-4-(2-(3-Chloropropoxy)-1,1,1-trifluoro-5-phenylpent-3-en-2-yl)-1,1'-biphenyl (7.17f)



7.17f

Following general procedure E, starting from 3-chloro-1-propanol, (**7.1aj**) (75 µL, 0.90 mmol), (*E*)-1-(3-phenylprop-1-en-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzobenzo[*d*][1,2]iodaoxole (**7.29d**) (146 mg, 0.300 mmol) and 4-(1-diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl (**7.2w**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded (*E*)-4-(2-(3-chloropropoxy)-1,1,1-trifluoro-5-phenylpent-3-en-2-yl)-1,1'-biphenyl (**7.17f**) as a colorless oil (96 mg, 0.22 mmol, 72%). R_f = 0.45 (EtOAc/pentane 2:98); ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.58 (m, 6H, Ar*H*), 7.53 – 7.43 (m, 2H, Ar*H*), 7.43 – 7.31 (m, 3H, Ar*H*), 7.30 – 7.20 (m, 3H, Ar*H*), 6.21 (dt, *J* = 15.9, 6.8 Hz, 1H, HC=C*H*-CH_2Ph), 5.95 – 5.82 (m, 1H, *H*C=CH-CH_2Ph), 3.72 (t, *J* = 6.4 Hz, 2H, CH_2Cl), 3.66 (t, *J* = 5.9 Hz, 2H, CH_2O), 3.59 (dd, *J* = 6.9, 1.5 Hz, 2H, CH_2Ph), 2.10 (p, *J* = 6.1 Hz, 2H, C$H_2$$CH_2$Cl); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 140.5, 139.1, 137.6, 134.5, 129.0, 129.0, 128.8, 128.7, 127.7, 127.3, 127.0, 126.6, 125.9, 125.0 (q, *J* = 287.5 Hz), 81.9 (q, *J* = 27.4 Hz), 61.2, 41.8, 39.3, 33.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.9; IR (ν_{max}, cm^{-1}) 3668 (w), 2987 (m), 2971 (m), 2910 (m), 1487 (w), 1262 (m), 1163 (s), 1075 (s), 840 (m), 766 (m), 737 (s), 696 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{24}ClF_3NaO^+$ 467.1360; Found 467.1366.

2-((*E*)-4-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy)-5,5,5-trifluoropent-2-en-1-yl)isoindoline-1,3-dione (7.17g)



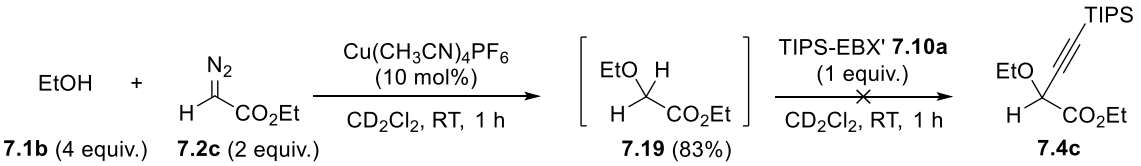
7.17g

Following general procedure E, starting from cholesterol (**7.1ak**) (348 mg, 0.900 mmol), (*E*)-2-(3-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)allyl)isoindoline-1,3-dione (**7.29f**) (167 mg, 0.300 mmol) and 2-diazo-1,1,1-trifluoroethane (**7.2k**) (1.67 mL, 0.600 mmol, 0.36 M in DCM), afforded 2-((*E*)-4-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy)-5,5,5-trifluoropent-2-en-1-yl)isoindoline-1,3-dione (**7.17g**) (55:45 *dr* in the crude ^{19}F NMR) as a white solid (120 mg, 0.180 mmol, 61%). M.p. 158 °C; R_f = 0.23 (EtOAc/pentane 5:95), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 2H, Ar*H*), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H, Ar*H*), 6.08 – 5.96 (m, 1H, HC=C*H*-CH_2N), 5.75 – 5.63 (m, 1H, *H*C=CH-CH_2N), 5.34 – 5.26 (m, 1H, *H*C=C(C)$_2$), 4.34 (dt, *J* = 6.0, 1.8 Hz, 2H, CH_2N), 4.24 – 4.15 (m, 1H, C*H*CF_3), 3.36 – 3.23 (m, 1H, C*H*O), 2.36 – 2.19 (m, 2H, C*H*-$_{aliphatic}$), 2.03 – 1.73 (m, 5H, C*H*-$_{aliphatic}$), 1.62 – 0.79 (m, 33H, C*H*-$_{aliphatic}$), 0.66 (s, 3H, C*H*-$_{aliphatic}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 140.4, 140.3, 134.2, 132.2, 130.5, 130.5, 126.0, 125.9, 124.0 (q, *J* = 281.9 Hz), 124.0 (q, *J* = 281.9 Hz), 123.6, 122.3, 122.3, 80.0, 79.9, 75.5 (q, *J* = 31.1 Hz), 75.5 (q, *J* = 31.1 Hz), 56.9, 56.3, 50.2, 42.4, 39.9, 39.7, 39.5, 38.9, 38.8, 37.2, 37.1, 36.8, 36.8, 36.3, 35.9, 32.0, 32.0, 29.0, 28.4, 28.2, 24.4, 24.0, 23.0, 22.7, 21.2, 19.5, 18.9, 12.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -77.26, -77.28; IR (ν_{max}, cm^{-1}) 2949 (m), 1775 (w), 1711 (s), 1468 (w), 1429 (m), 1399 (m), 1275 (m), 1181 (m), 1150 (m), 1121 (s), 1078 (m),

944 (m), 727 (s), 714 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{40}H_{54}F_3NNaO_3^+$ 676.3948; Found 676.3954.

10.5.4. Control Experiments and Mechanistic Studies

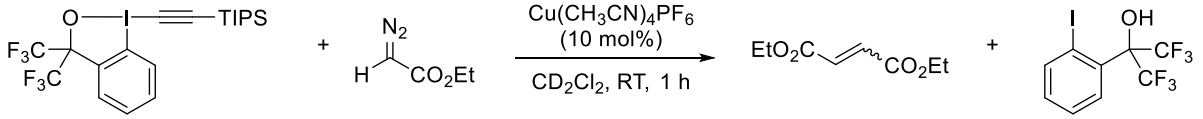
a) Sequential addition of the alcohol and the EBX' reagent (Figure 20, section 7.4.):



7.1b (4 equiv.) **7.2c** (2 equiv.) **7.19** (83%) **7.4c**

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (3.0 mg, 8.0 µmol, 0.20 equiv). The vial was capped, removed from the glovebox and CD_2Cl_2 (0.80 mL) was added, followed by EtOH (**7.1b**) (19 µL, 0.32 mmol, 8.00 equiv). Ethyl diazoacetate (**7.2c**) (19 µL, 0.16 mmol, 4.00 equiv, 87%wt in DCM) was added dropwise and the resulting reaction mixture was stirred at room temperature for 1 h. After this time, an aliquot of the solution (0.40 mL) was taken and a ^1H NMR spectrum of the reaction mixture was recorded **(C)**. A solution of TIPS-EBX' (**7.10a**) (22.0 mg, 40.0 µmol, 1.00 equiv) in CD_2Cl_2 (0.40 mL) was added to the first solution and the reaction was continued for 1 h at room temperature. A ^1H NMR spectrum was recoreded **(D)**.

b) EBX' reagent and diazo compound in presence of copper catalyst (Figure 21, section 7.4.):

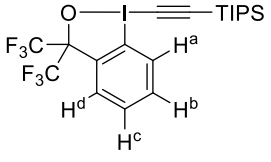


7.10a (1 equiv.) **7.2c** (2 equiv.) **7.30** **7.31**

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (3.0 mg, 8.0 µmol, 0.10 equiv) and TIPS-EBX' **7.10a** (44 mg, 80 µmol, 1.00 equiv). The vial was capped, removed from the glovebox and CD_2Cl_2 (0.80 mL) was added, followed by the dropwise addition of ethyl diazoacetate (**7.2c**) (19 µL, 0.16 mmol, 4.00 equiv, 87%wt in DCM). Rapid evolution of nitrogen was observed to occur. The reaction was continued for 1 h at room temperature. A ^1H NMR spectrum was recorded **(C)**.

c) ^1H and ^{19}F NMR titration of EBX' reagent with $Cu(CH_3CN)_4PF_6$:

In a N_2 filled glovebox, two differents oven-dried 10 mL microwave vials were prepared with the following solutions:
(1): 0.1 M solution of TIPS-EBX' (**7.10a**) (110 mg, 2.00 mmol) in CD_2Cl_2 (2.0 mL).
(2): 0.1 M solution of $Cu(CH_3CN)_4PF_6$ (74.5 mg, 2.00 mmol) in CD_2Cl_2 (2.0 mL).
TIPS-EBX' (**7.10a**) (200 µL of solution (1), 0.02 mmol, 1.00 equiv) was then stirred for 1h at room temperature with differents equivalent of $Cu(CH_3CN)_4PF_6$ (gradient from 0 µL of solution (2), 0.00 mmol, 0.00 equiv to 600 µL of solution (2), 0.06 mmol, 3.00 equiv) All solutions were adjusted with CD_2Cl_2 (600 µL to 0 µL) before the addition of the solution (2) to have V_{tot} = 800 µL.



7.10a

$^1H^a$: δ 8.43 - 8.36 (m, 1H)
$^1H^{b+c}$: δ 7.76 - 7.66 (m, 2H)
$^1H^d$: δ 7.86 - 7.79 (m, 1H)
^{19}F : δ 76.5

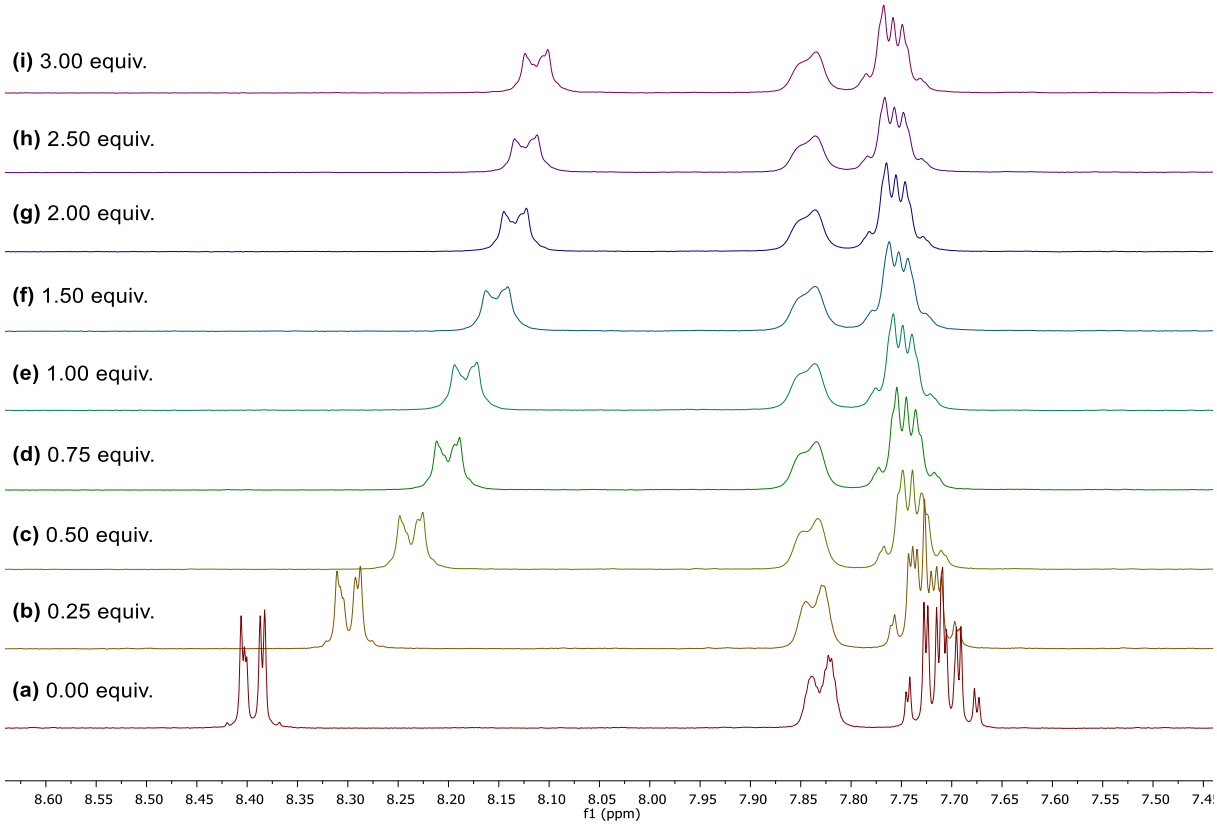


Figure S2: ^{1}H NMR titration of the EBX' reagent **7.10a** with $Cu(CH_3CN)_4PF_6$.

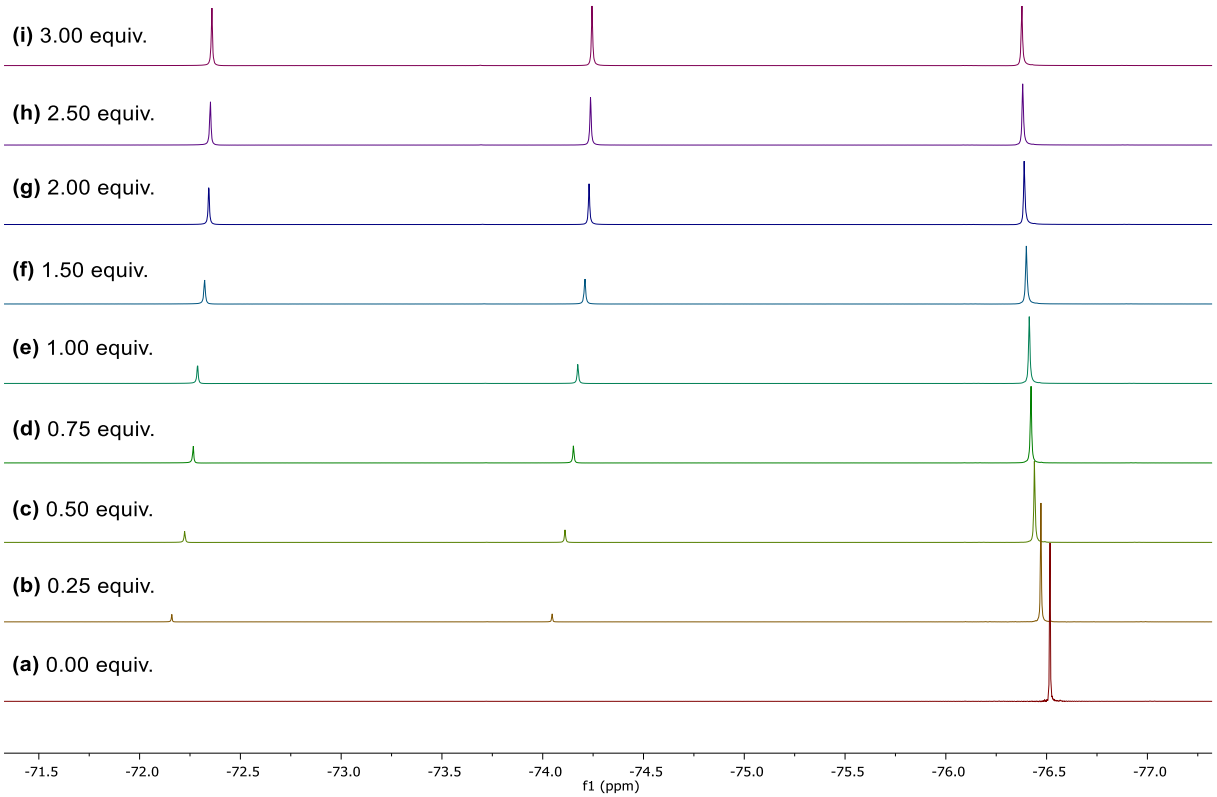


Figure S3: ^{19}F NMR titration of the EBX' reagent **7.10a** with $Cu(CH_3CN)_4PF_6$.

Progressive shifts of the aromatic $^{1}H^{a}$ were observed upon addition of the copper salt, with a significant diminution after one equivalent. Others ^{1}H signals were less influenced by the presence of the Cu salt. Minor shift of ^{19}F signal of **7.10a** was observed.

d) ^{13}C NMR spectrum of the complexation of the EBX' reagent with $Cu(CH_3CN)_4PF_6$ (Figure 23, section 7.4.):

Samples **(a)** (0.00 equiv) and **(e)** (1.00 equiv) from the titration experiment were submitted to ^{13}C NMR analysis.

e) Mixing EtOH with $Cu(CH_3CN)_4PF_6$:

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (30 mg, 0.080 mmol, 1.00 equiv). The vial was capped, removed from the glovebox and CD_2Cl_2 (0.80 mL) was added, followed by the addition of EtOH (**7.1b**) (19 µL, 0.32 mmol, 4.00 equiv). The resulting reaction mixture was stirred at room temperature for 1 h. A ^{1}H NMR spectrum was recoreded **(c)**. The solvent was then removed under reduced pressure and a new ^{1}H NMR spectrum was recorded in CD_2Cl_2 **(d)**.

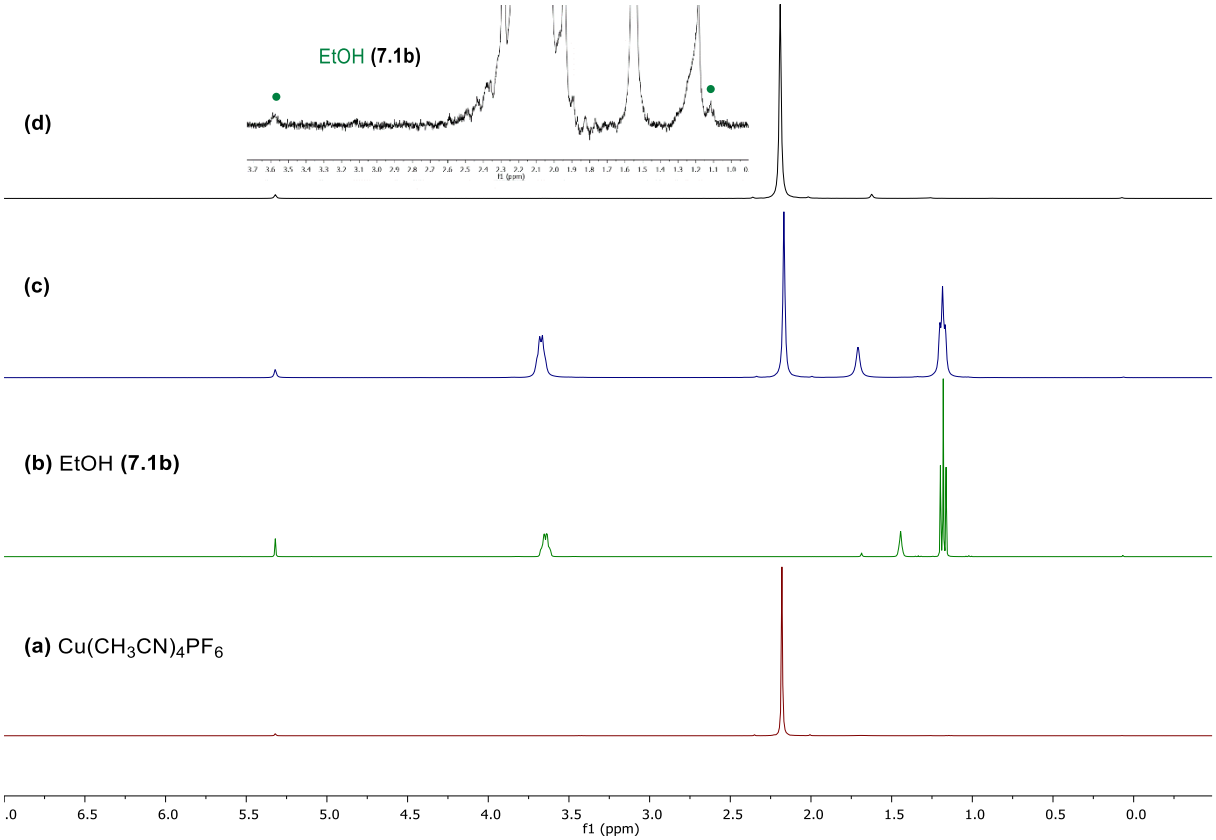
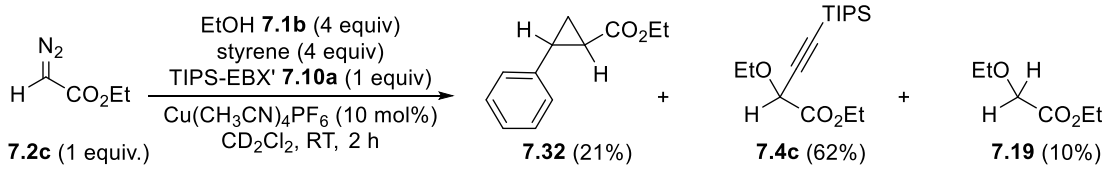


Figure S4: ^{1}H NMR spectrum of the complexation of EtOH and $Cu(CH_3CN)_4PF_6$.

No shift of ^{1}H signals of ethanol or $Cu(CH_3CN)_4PF_6$ were observed. When the reaction mixture was evaporated, the initial copper salt was recovered.

f) Cu-carbene trapping through cyclopropanation (Scheme 98, section 7.4.):



In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (3.0 mg, 8.0 µmol, 0.10 equiv) and TIPS-EBX' **7.10a** (44 mg, 80 µmol, 1.00 equiv). The vial was capped, removed from the glovebox and CD_2Cl_2 (0.80 mL) was added, followed by the addition of ethanol (**7.1b**) (19 µL, 0.32 mmol, 4.00 equiv) and styrene (37 µL, 0.32 mmol, 4.00 equiv). A solution of ethyl diazoacetate (**7.2c**) in DCM (133 µL, 80 µmol, 1.00 equiv, 0.6 M) was slowly added in 1 h via seringe pump. At the end of the addition, the reaction was continued 1 h at room temperature. ^{1}H NMR spectrum of the reaction mixture was recoreded (**d**). For comparison, control experiments missing the EBX reagent (spectrum (**c**)), ethanol (spectrum (**b**)) and EBX + ethanol (spectrum (**a**)) were done.

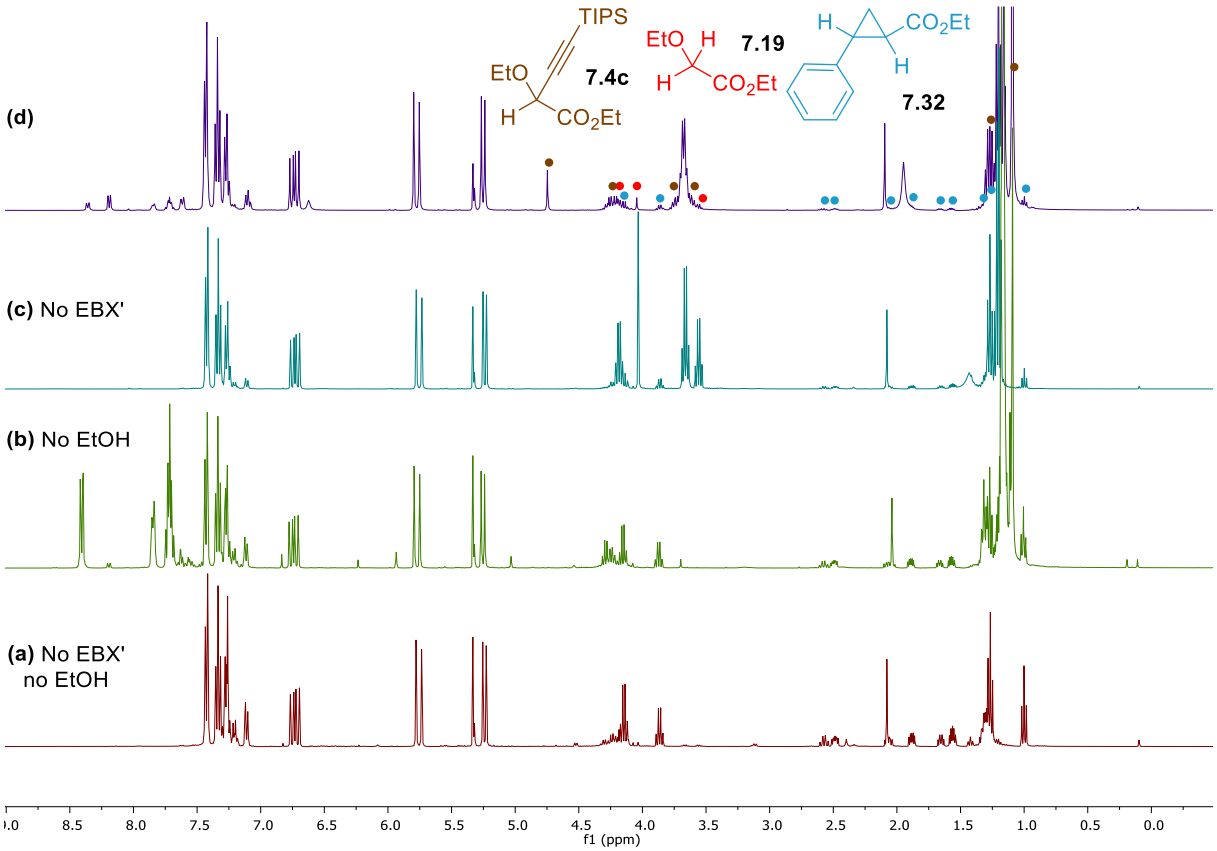
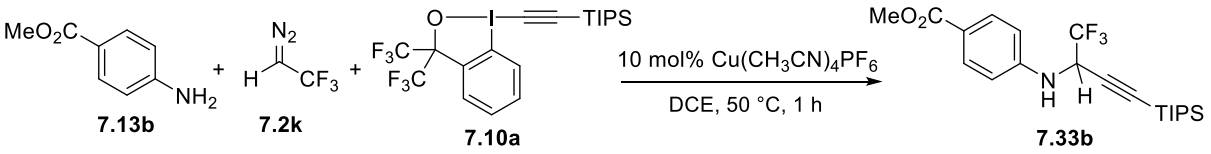


Figure S5: ^{1}H NMR spectrum of the competitive cyclopropanation with styrene.

The three-component product **7.4c** was the major product observed (62%). The conversion of TIPS-EBX' (**7.10a**) was 62%. A detectable amount of cyclopropane **7.31** was observed (21%). The O-H insertion product **7.19** was also detected (10%). In absence of EtOH, cyclopropane **7.32** was the major product formed (spectrum (**a**) and (**b**)). The O-H insertion product **7.19** was predominant (83%) over the cyclopropane **7.31** (16%) when EtOH (4.00 equiv) and styrene (4.00 equiv) were in competition (spectrum (**c**)).

10.5.5. Extension to Anilines

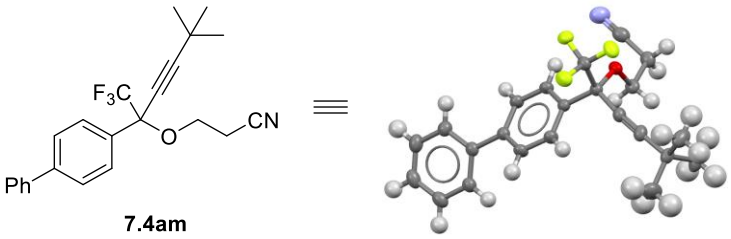
Methyl 4-((1,1,1-trifluoro-4-(triisopropylsilyl)but-3-yn-2-yl)amino)benzoate (7.33b)



In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (11.2 mg, 30.0 µmol, 0.10 equiv), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**7.10a**) (27 mg, 0.50 mmol, 1.00 equiv) and methyl 4-aminobenzoate (**7.13b**) (30.2 mg, 0.200 mmol, 4.00 equiv). The vial was capped, removed from the glovebox, dry DCE (0.725 mL) was added and the reaction was heated to 50 °C. To the resulting solution was added a 0.36 M solution of 2,2,2-trifluorodiazoethane (**7.2k**) (0.278 mL, 0.100 mmol, 2.00 equiv) in dry DCM in 30 min *via* seringe pump. The system was mainted isobaric with a filled balloon with N_2. At the end of the addition, the reaction was continued for 30 min at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by preparative TLC using EtOAc/pentane 8:92 as eluent to afford methyl 4-((1,1,1-trifluoro-4-(triisopropylsilyl)but-3-yn-2-yl)amino)benzoate as a colorless solid (**7.33b**) (13 mg, 0.031 mmol, 63%). R_f = 0.29 (EtOAc/pentane 10:90), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 2H, Ar*H*), 6.72 (dd, *J* = 9.0, 2.4 Hz, 2H, Ar*H*), 4.82 (dq, *J* = 9.2, 5.9 Hz, 1H, C*H*CF_3), 4.33 (d, *J* = 9.1 Hz, 1H, N*H*), 3.87 (s, 3H, OC*H*$_3$), 1.12 – 0.85 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 148.9, 131.6, 123.5 (q, *J* = 282.3 Hz), 121.5, 113.2, 97.3, 89.8, 51.9, 49.8 (q, *J* = 34.8 Hz), 18.6, 11.1; ^{19}F NMR 376 MHz, $CDCl_3$) δ -75.7; HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{21}H_{31}F_3NO_2Si^+$ 414.2071; Found 414.2074.

10.5.6. Crystal Structures

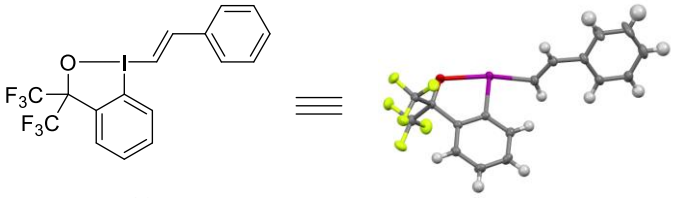
CCDC 1985456



7.4am

Empirical formula	$C_{23}H_{22}F_3NO$	
Formula weight	385.41	
Temperature	140.00(10) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	*Pbca*	
Unit cell dimensions	a = 8.81133(9) Å	α = 90°.
	b = 20.9653(2) Å	β = 90°.
	c = 22.3585(3) Å	γ = 90°.
Volume	4130.33(8) $Å^3$	
Z	8	
Density (calculated)	1.240 Mg/m^3	
Absorption coefficient	0.785 mm^{-1}	
F(000)	1616	
Crystal size	0.440 x 0.151 x 0.120 mm^3	
Theta range for data collection	3.954 to 72.795°.	
Index ranges	-10 ≤ h ≤ 10, -25 ≤ k ≤ 25, -27 ≤ l ≤ 27	
Reflections collected	32007	
Independent reflections	4078 [R_{int} = 0.0354]	
Completeness to theta = 67.684°	99.8 %	
Absorption correction	Gaussian	
Max. and min. transmission	1.000 and 0.548	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4078 / 133 / 349	
Goodness-of-fit on F^2	1.053	
Final R indices [I > 2sigma (I)]	R_1 = 0.0308, wR_2 = 0.0838	
R indices (all data)	R_1 = 0.0374, wR_2 = 0.0864	
Extinction coefficient	0.00022(6)	
Largest diff. peak and hole	0.275 and -0.189 e.$Å^{-3}$	

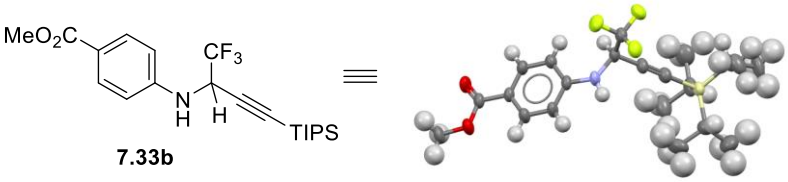
CCDC 1993681



7.29a

Empirical formula	$C_{17}H_{11}F_6IO$	
Formula weight	472.16	
Temperature	100.00(10) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 11.1353(5) Å	α = 90°.
	b = 15.0180(6) Å	β = 106.691(5)°.
	c = 10.6385(5) Å	γ = 90°.
Volume	1704.12(14) $Å^3$	
Z	4	
Density (calculated)	1.840 Mg/m^3	
Absorption coefficient	1.942 mm^{-1}	
F(000)	912	
Crystal size	0.514 x 0.114 x 0.098 mm^3	
Theta range for data collection	2.415 to 33.022°.	
Index ranges	-16 ≤ h ≤ 16, -22 ≤ k ≤ 21, -16 ≤ l ≤ 15	
Reflections collected	7694	
Independent reflections	7694	
Completeness to q = 25.242°	99.9 %	
Absorption correction	Gaussian	
Max. and min. transmission	1.000 and 0.696	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7694 / 0 / 227	
Goodness-of-fit on F^2	0.914	
Final R indices [I > 2sigma(I)]	R_1 = 0.0264, wR_2 = 0.0545	
R indices (all data)	R_1 = 0.0419, wR_2 = 0.0568	
Largest diff. peak and hole	1.621 and -0.734 $e.Å^{-3}$	

Not registered in CCDC – 7.33b



7.33b

Empirical formula	$C_{21}H_{30}F_3NO_2Si$	
Formula weight	413.55	
Temperature	130(1) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	*P*-1	
Unit cell dimensions	a = 7.9513(9) Å	α = 89.560(10)°.
	b = 9.7717(10) Å	β = 75.444(11)°.
	c = 15.144(2) Å	γ = 84.693(9)°.
Volume	1133.9(2) $Å^3$	
Z	2	
Density (calculated)	1.211 Mg/m^3	
Absorption coefficient	1.262 mm^{-1}	
F(000)	440	
Crystal size	0.621 x 0.137 x 0.078 mm^3	
Theta range for data collection	4.545 to 72.494°.	
Index ranges	$-9 \le h \le 5$, $-11 \le k \le 11$, $-18 \le l \le 18$	
Reflections collected	7816	
Independent reflections	4275 [R_{int} = 0.0525]	
Completeness to theta = 67.684°	98.6 %	
Absorption correction	Analytical	
Max. and min. transmission	0.930 and 0.680	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4275 / 0 / 264	
Goodness-of-fit on F^2	1.026	
Final R indices [I > 2sigma(I)]	R_1 = 0.0676, wR_2 = 0.1745	
R indices (all data)	R_1 = 0.0962, wR_2 = 0.2061	
Largest diff. peak and hole	0.546 and -0.320 $e.Å^{-3}$	

10.6. Mechanistic Studies on the Two-Component Oxy-Alkynylation Reaction

10.6.1. Computational Details

The geometries of all structures were optimized at the M06[447]/def2-SVP[448] level in implicit dichloromethane solvent using the SMD solvation model[449] as implemented in Gaussian 09.[450] The "Ultrafine" integration grid was used throughout to remove known problems related to grid size with the M06 family of functionals.[451] Final reported free energies include single points on the M06 geometries at the PBE0[452]-dDsC[453]/TZ2P level, solvation corrections using the COSMO-RS solvation model[454] obtained using ADF,[455] and M06 free energy corrections obtained using the rigid-rotor harmonic oscillator proposed by Grimme[456] as implemented in GoodVibes.[457]

10.6.2. Other Experiments

10.6.2.1. Preparation of the Starting Materials

Ethyl 2-diazoacetate (**8.1b**) was directly purchased from Sigma Aldrich. The synthesis of (1*E*,1'*E*)-*N,N*'-(ethane-1,2-diyl)bis(1-(2,6-dichlorophenyl)methanimine) (**8.5e**), 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**8.10**), TIPS-EBX (**8.2b**), Ph-EBX (**8.2c**) have been reported in section 10.2. The synthesis of ethyl 2-diazopropanoate (**8.1d**) and 2,2'-(propane-2,2-diyl)bis(4,4-dimethyl-4,5-dihydrooxazole) (**8.5d**) have been reported in section 10.4.

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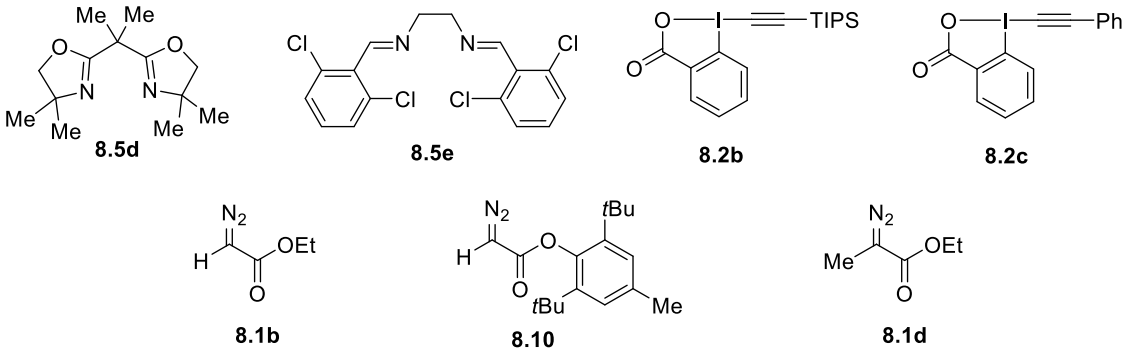
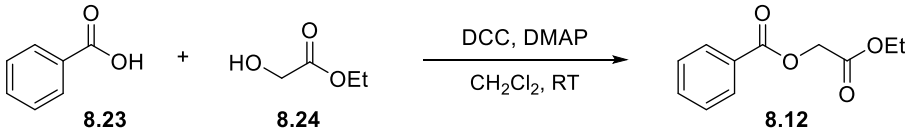
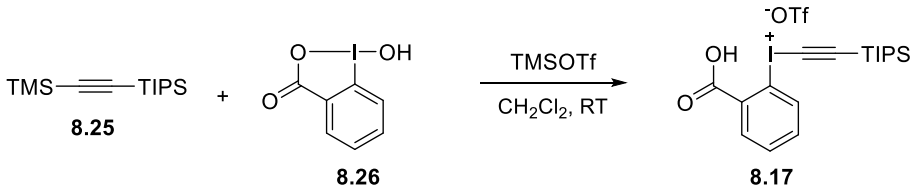


2-Ethoxy-2-oxoethyl benzoate (8.12)



To a stirred solution of benzoic acid (**8.23**) (672 mg, 5.50 mmol, 1.1 equiv) in DCM (50 mL) is added DMAP (0.061 g, 0.50 mmol, 0.10 equiv) and ethyl glycolate (**8.24**) (475 µL, 5.00 mmol, 1.0 equiv). Finally, DCC (1.14 g, 5.50 mmol, 1.10 equiv) is added to the reaction mixture and the reaction was stirred at room temperature for 4 h. The white precipitate was filtered-off and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford **8.12** as a colorless oil (958 mg, 4.60 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 8.19 (m, 2H, Ar*H*), 7.54 – 7.67 (m, 1H, Ar*H*), 7.40 – 7.52 (m, 2H, Ar*H*), 4.84 (s, 2H, OCH_2CO), 4.27 (q, *J* = 7.2 Hz, 2H, O$CH_2$$CH_3$), 1.32 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 165.5, 133.1, 129.7, 128.9, 128.2, 61.1, 60.9, 13.9. The values of the NMR spectra are in accordance with reported literature data.[458]

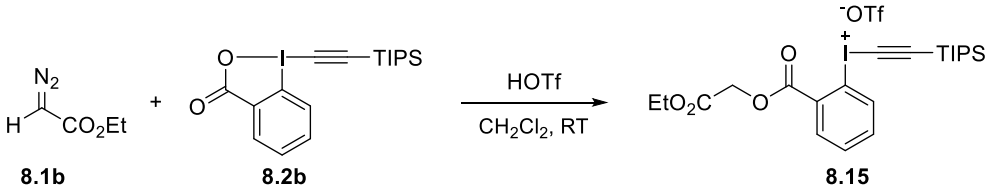
(2-Carboxyphenyl)((triisopropylsilyl)ethynyl)iodonium triflate (8.17)



Following a reported procedure,[140b] trimethylsilyltriflate (300 µL, 1.65 mmol, 1.1 equiv) was added dropwise to a stirred solution of 2-iodosylbenzoic acid (**8.26**) (396 mg, 1.50 mmol, 1.0 equiv) in DCM (5.0 mL). After 1 h, triisopropyl((trimethylsilyl)ethynyl)silane (**8.25**) (420 mg, 1.65 mmol, 1.1 equiv) was added dropwise. The mixture was stirred 5 h at room temperature and then the solvent was then removed under reduced pressure. The yellow crude oil was crystallized in Et_2O/hexane 1:1 to afford **8.17** as a white solid (810 mg, 1.40 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 7.1 Hz, 1H, Ar*H*), 8.37 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.90 (dt, *J* = 21.1, 7.6 Hz, 2H, Ar*H*), 5.36 (br s, 1H, O*H*), 1.38 – 1.06 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 137.7, 133.6, 132.3, 128.8, 125.9, 121.9, 120.0 (q, *J* = 319 Hz), 114.5, 48.2, 18.4, 11.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.16. The values of the NMR spectra are in accordance with reported literature data.[140b]

[458] R. N. Reddi, P. K. Prasad, A. Sudalai, *Org. Lett.* **2014**, *16*, 5674.

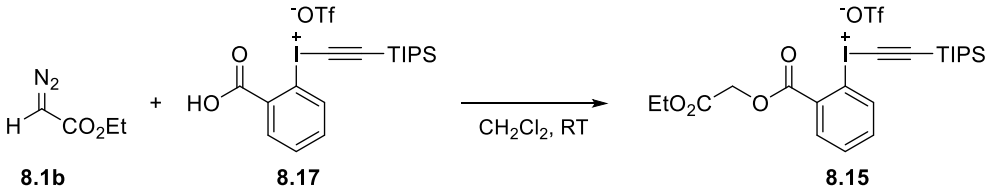
(2-((2-Ethoxy-2-oxoethoxy)carbonyl)phenyl)((triisopropylsilyl)ethynyl)iodonium triflate (8.15)



8.1b **8.2b** **8.15**

Trifluoromethanesulfonic acid (139 µL, 1.58 mmol, 1.05 equiv) was added dropwise to a stirred solution of TIPS-EBX (**8.2b**) (643 mg, 1.50 mmol, 1.00 equiv) in DCM (5.0 mL). The mixture was stirred for 1 h at room temperature and then ethyl 2-diazoacetate (**8.1b**) (181 µL, 87% wt in DCM, 1.50 mmol, 1.05 equiv) was added dropwise in 15 minutes. Strong nitrogen evolution was observed and the resulting reaction mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum and the crude solid was dissolved in DCM (2 mL) and then Et_2O (12 mL) was added. The precipitate was collected and the crystalization procedure was repeated one more time to afford **8.15** as a colorless crystalline powder (702 mg, 1.06 mmol, 70%). R_f = 0.30 (MeOH/CH_2Cl_2 5:95); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.47 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar*H*), 8.41 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.98 (td, *J* = 7.8, 1.8 Hz, 1H, Ar*H*), 7.91 (t, *J* = 7.5 Hz, 1H, Ar*H*), 5.09 (s, 2H, OC*H*$_2$CO), 4.28 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 1.31 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.26 (q, *J* = 6.3 Hz, TIPS), 1.22-1.16 (m, 18H, TIPS); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 170.0, 166.2, 139.1, 134.1, 133.0, 130.5, 125.6, 124.3, 121.2 (q, *J* = 320.6 Hz), 115.8, 64.7, 63.0, 45.8, 18.7, 14.4, 11.8; ^{19}F NMR (377 MHz, CD_2Cl_2) δ -78.8; HRMS (ESI/QTOF) m/z: [M-TfO$^-$]$^+$ Calcd for $C_{22}H_{32}IO_4Si^+$ 515.1109; Found 515.1120.

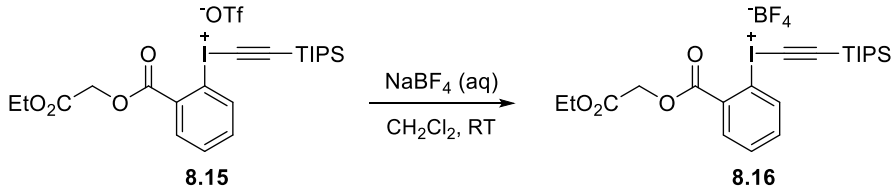
Alternatively, (2-((2-ethoxy-2-oxoethoxy)carbonyl)phenyl)((triisopropylsilyl)ethynyl)iodonium triflate (**8.15**) was prepared from **8.17**:



8.1b **8.17** **8.15**

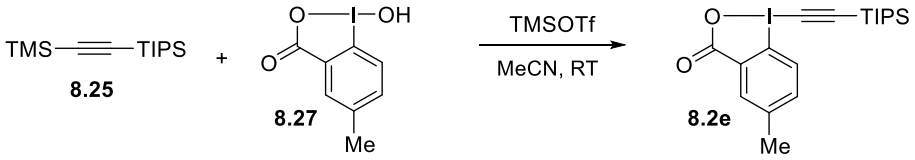
Ethyl 2-diazoacetate (**8.1b**) (29 µL, 87% wt in DCM, 0.240 mmol, 1.2 equiv) was added dropwise to a stirred solution of (2-carboxyphenyl)((triisopropylsilyl)ethynyl)iodonium triflate (**8.17**) (116 mg, 0.200 mmol, 1.0 equiv) in DCM (0.8 mL). The mixture was stirred at room temperature for 1 h and the solvent was removed under vacuum. The crude solid was dissolved in DCM and then Et_2O (5 volumes) was added. The precipitate was collected and the crystalization procedure was repeated one more time to afford **8.15** as a colorless crystalline powder (116 mg, 0.175 mmol, 87%).

(2-((2-Ethoxy-2-oxoethoxy)carbonyl)phenyl)((triisopropylsilyl)ethynyl)iodonium tetrafluoroborate (8.16)



Following a reported procedure,[459] (2-((2-ethoxy-2-oxoethoxy)carbonyl)phenyl)((triisopropylsilyl)ethynyl)iodonium triflate (**8.15**) (665 mg, 1.00 mmol, 1.00 equiv) was disolved in DCM (10 mL) and was thorougly extracted with a 1 M $NaBF_4$ aqueous solution (10 mL, 5 extractions). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **8.16** as a white solid (385 mg, 0.640 mmol, 64%). R_f = 0.30 (MeOH/CH_2Cl_2 5:95); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.50 (dd, *J* = 7.6, 1.8 Hz, 1H, Ar*H*), 8.37 (dd, *J* = 8.4, 1.0 Hz, 1H, Ar*H*), 8.03 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H, Ar*H*), 7.95 (td, *J* = 7.5, 1.0 Hz, 1H, Ar*H*), 5.11 (s, 2H, OC*H*$_2$CO), 4.28 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 1.31 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.27 (m, 3H, TIPS), 1.19 (d, *J* = 6.6 Hz, 18H, TIPS); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 170.0, 166.1, 139.4, 134.3, 133.4, 129.8, 126.2, 125.2, 114.5, 65.0, 63.0, 44.8, 18.8, 14.4, 11.8; ^{19}F NMR (377 MHz, CD_2Cl_2) δ -148.9, -148.9 – -149.0 (m); HRMS (ESI/QTOF) m/z: $[M\text{-}BF_4^-]^+$ Calcd for $C_{22}H_{32}IO_4Si^+$ 515.1109; Found 515.1113.

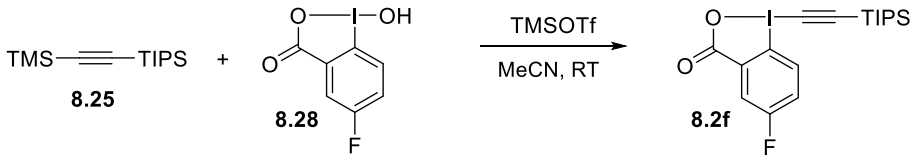
5-Methyl-1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (8.2e)



Following a reported procedure,[140b] timethylsilyltriflate (400 µL, 2.20 mmol, 1.1 equiv) was added dropwise to a stirred solution of 1-hydroxy-5-methyl-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**8.27**) (556 mg, 2.00 mmol, 1.0 equiv) in acetonitrile (10 mL). After 20 min, triisopropyl((trimethylsilyl)ethynyl)silane (**8.25**) (560 mg, 2.20 mmol, 1.1 equiv) was then added dropwise. After 1 h, pyridine (180 µL, 2.20 mmol, 1.1 equiv) was added and the mixture was stirred for 20 min. The solvent was then removed under reduced pressure and the yellow crude oil was dissolved in dichloromethane (20 mL). The organic layer was washed with 1 M HCl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The organic layers were combined, washed with a sat. aq. solution of $NaHCO_3$ (40 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (ca 25 mL) and wash with hexanes afforded **8.2e** as colorless crystals (559 mg, 1.26 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, 1H, *J* = 1.5 Hz, Ar*H*), 8.12 (d, 1H, J = 8.5 Hz, Ar*H*), 7.57 (dd, 1H, *J* = 8.5, 1.8 Hz, Ar*H*), 2.51 (s, 3H, C*H*$_3$), 1.16 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 142.5, 135.6, 133.0, 131.2, 125.8, 113.8, 111.8, 64.6, 20.7, 18.5, 11.2. The values of the NMR spectra are in accordance with reported literature data.[140b]

[459] M. Reitti, P. Villo, B. Olofsson, *Angew. Chem. Int. Ed.* **2016**, *55*, 8928.

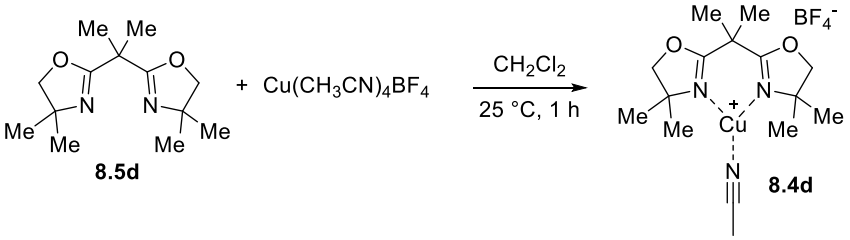
5-Fluoro-1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (8.2f)



Following a reported procedure,[140b] timethylsilyltriflate (247 µL, 1.36 mmol, 1.1 equiv) was added dropwise to a stirred solution of 1-hydroxy-5-fluoro-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**8.28**) (350 mg, 1.24 mmol, 1.0 equiv) in acetonitrile (5 mL). After 20 min, triisopropyl((trimethylsilyl)ethynyl)silane (**8.25**) (347 mg, 1.36 mmol, 1.1 equiv) was then added dropwise. After 1 h, pyridine (110 µL, 1.36 mmol, 1.1 equiv) was added and the mixture was stirred for 20 min. The solvent was then removed under reduced pressure. The crude product was purified by column chromatography using EtOAc as eluent to afford **8.2f** as a white solid (324 mg, 1.12 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, 1H, *J* = 9.0, 4.2 Hz, Ar*H*), 8.10 (dd, 1H, *J* = 7.9, 2.9 Hz, Ar*H*), 7.48 (m, 1H, Ar*H*), 1.16 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6 (d, *J* = 254 Hz), 165.2 (d, *J* = 7 Hz), 134.2 (d, *J* = 7 Hz), 127.8 (d, *J* = 8 Hz), 122.2 (d, *J* = 24 Hz), 119.4 (d, *J* = 24 Hz), 115.0 (s), 108.0 (d, *J* = 1 Hz), 64.0 (s), 18.5 (s), 11.2 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.7. The values of the NMR spectra are in accordance with reported literature data.[140b]

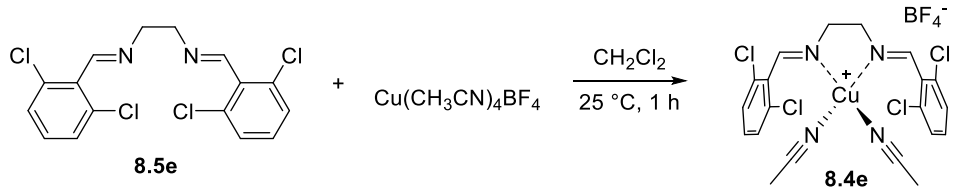
10.6.2.2. Mechanistic Studies

Preparation of [BOX•Cu(CH$_3$CN)]BF$_4$ (8.4d)



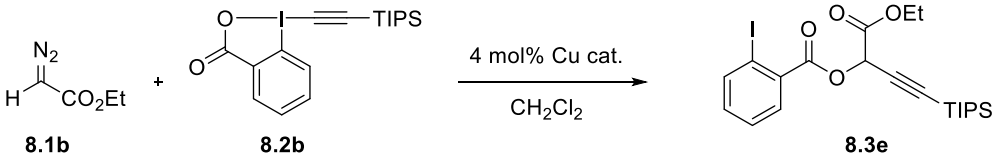
In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with terakis(acetonitrile)copper(I)tetrafluoroborate (157 mg, 0.50 mmol, 1.0 equiv). The vial was capped, removed from the glovebox and a solution of 2,2'-(propane-2,2-diyl)bis(4,4-dimethyl-4,5-dihydrooxazole) (**8.5d**) (119 mg, 0.50 mmol, 1.0 equiv) in degassed and dry DCM (4.0 mL) was added in one portion and under an argon atmosphere. The resulting colorless homogeneous solution was stirred for 1 h at room temperature. The solvent was removed under the Schlenk-line and then dried overnight to afford **8.4d** as a white solid (175 mg, 0.407 mmol, 81%). The complex was storred in the glovebox. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.19 (s, 4H, 2 x OC*H$_2$*), 2.24 (s, 3H, C*H$_3$*CN), 1.57 (s, 6H, 2 x C*H$_3$*), 1.37 (s, 12H, 4 x C*H$_3$*); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 171.7, 118.8, 79.9, 68.6, 40.0, 28.4, 25.2, 3.1; HRMS (ESI/QTOF) m/z: [M-BF_4^-]$^+$ Calcd for $C_{15}H_{25}CuN_3O_2^+$ 342.1237; Found 342.1241. The structure of **8.4d** was confirmed by X-ray analysis. Crystals were grown by dissolving 20 mg of pure **8.4d** in CH_2Cl_2 (50 µL) and layering with Et_2O (200 µL) at room temperature. Slow diffusion over one week provided suitable crystals.

Preparation of [diimine•Cu(CH$_3$CN)$_2$]BF$_4$ (8.4e)



In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with terakis(acetonitrile)copper(I)tetrafluoroborate (157 mg, 0.50 mmol, 1.0 equiv). The vial was capped, removed from the glovebox and a solution of (*NE*,*N'E*)-*N*,*N*'-bis(2,6-dichlorobenzylidene)ethane-1,2-diamine (**8.5e**) (187 mg, 0.50 mmol, 1.0 equiv) in degassed and dry DCM (4.0 mL) was added in one portion and under an argon atmosphere. The resulting yellow solution was stirred for 1 h at room temperature. The solvent was removed under the Schlenk-line and then dried overnight to afford **8.4e** as a yellow solid (301 mg, 0.496 mmol, 99%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.66 (s, 2H, NC*H*), 7.59 – 7.38 (m, 6H, Ar*H*), 4.13 (s, 4H, 2 x CH_2), 1.96 (s, 6H, 2 x CH_3CN); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 163.8, 134.5, 132.9, 132.3, 129.4, 61.0, 2.5; HRMS (ESI/QTOF) m/z: [M-BF_4^--2 x MeCN]$^+$ Calcd for $C_{16}H_{12}Cl_4CuN_2^+$ 434.9045; Found 434.9034. The sp carbon of the acetonitrile was not resolved at 101 MHz.

Comparison of the copper complexes activity



In a N_2 filled glovebox, catalytic solutions of copper were prepared:

(A) [BOX•Cu(CH$_3$CN)]BF$_4$ (**8.4d**) (3.40 mg, 8.00 µmol, 0.08 equiv) in CH_2Cl_2 (1.0 mL)

(B) [diimine•Cu(CH$_3$CN)$_2$]BF$_4$ (**8.4e**) (4.90 mg, 8.00 µmol, 0.08 equiv) in CH_2Cl_2 (1.0 mL)

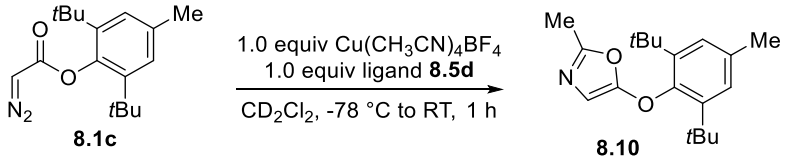
(C) Cu(CH$_3$CN)$_4$BF$_4$ (**8.6**) (2.50 mg, 8.00 µmol, 0.08 equiv) in CH_2Cl_2 (1.0mL)

Then, 500 µL of each solutions were injected into three different 10 mL micro-wave vials containing a solution of TIPS-EBX (**8.2b**) (43.0 mg, 0.10 mmol, 1.0 equiv) and ethyl 2-diazoacetate (**8.1b**) (25.0 µL, 87% wt in DCM, 0.20 mmol, 2.0 equiv). The reactions were stirred at room temperature for 1 h and then 40 °C for catalysts (B) and (C). At the end of the reaction, the solvent was removed under reduced pressure and CH_2Br_2 (70 µL, 0.1 M in $CDCl_3$, 0.10 mmol, 1.0 equiv) was added as internal standard and the crude reaction mixtures were analyzed by ^{1}H NMR.

Stochiometric mixture of [BOX•Cu(CH$_3$CN)]BF$_4$ (8.4d) and TIPS-EBX (8.2b) and ^{13}C NMR analysis

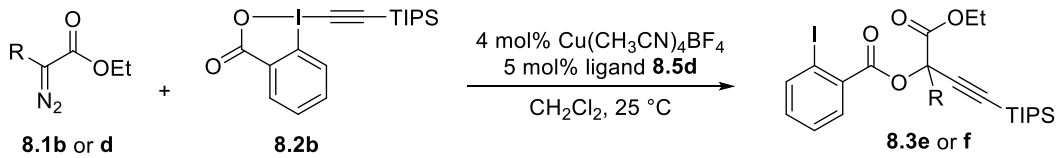
In a N_2 filled glovebox, a solution of TIPS-EBX (**8.2b**) (21.0 mg, 0.05 mmol, 1.0 equiv) in degassed and dry CD_2Cl_2 (0.5 mL) and a solution of BOX•Cu(CH$_3$CN)]BF$_4$ (**8.4d**) (27.0 mg, 0.625 mmol, 1.25 equiv) in degassed and dry CD_2Cl_2 (0.625 mL) were prepared. Then, 500 µL of the copper solution was injected in the EBX solution under stirring at room temperature. After 2 min, an aliquot of ca. 500 µL was taken and analyzed by ^{13}C NMR.

5-(2,6-Di-*tert*-butyl-4-methylphenoxy)-2-methyloxazole (8.10)



2,2'-(Propane-2,2-diyl)bis(4,4-dimethyl-4,5-dihydrooxazole) (**8.5d**) (36.0 mg, 0.150 mmol, 1.0 equiv) was weighted in a schlenk tube and CD_2Cl_2 (0.750 mL) was added. The solution was degassed by freeze-pump-thaw cycles (3 times). $Cu(CH_3CN)_4BF_4$ (31.5 mg, 0.100 mmol, 1.0 equiv) was weighted in the glovebox in an oven-dried microwave tube and inert Argon atmosphere was built. 500 µL of the BOX ligand solution was added to the copper salt and the reaction mixture was stirred at room tempeature for 1 h before being cooled to -78 °C. Meanwhile, a solution of 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**8.1c**) (43.5 mg, 0.150 mmol, 1.0 equiv) in dry CD_2Cl_2 (1.5 mL) was prepared in a schlenk tube and degassed by freeze-pump-thaw. The tube was cooled to -78 °C. Then, 500 µL of the diazo solution was added to the copper solution at -78 °C. A purple solution formed. The solution is stable at this temperature and the diazo was not decomposed after 1h (TLC). 750 µL of the resulting solution was quickly injected in a dry, inert and pre-cooled NMR tube, capped with a septum. ^{13}C VT NMR was recorded form -78 °C to +20 °C with gradient of +10 °C (NS/10 °C = 100; O1P = 200; SW = 400). At the end of the experiment, ^{13}C and ^{1}H NMR of the final reaction mixture were recorded at +25 °C. A quantitative formation to **8.10** was observed. The mixture in the NMR tube was direclty purified by preparative TLC using EtOAc/pentane 5:95 as eluent to afford **8.10** as a white solid (18 mg, 0.060 mmol, 60%). R_f = 0.33; EtOAc/pentane 5:95; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.13 (d, *J* = 0.7 Hz, 2H, Ar*H*), 5.37 (s, 1H, Ar*H*), 2.32 (t, J = 0.7 Hz, 3H, C*H*$_3$), 2.30 (s, 3H, C*H*$_3$), 1.29 (s, 18H, 2 x *t*Bu); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 160.9, 151.8, 149.6, 143.1, 135.4, 128.2, 100.6, 36.1, 32.0, 21.7, 14.3; HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{28}NO_2^+$ 302.2115; Found 302.2121. The structure of **8.10** was confirmed by X-ray analysis. Crystals were grown by slow evaporation of CD_2Cl_2.

Reactivity comparison between diazo substrates 8.1b and 8.1d



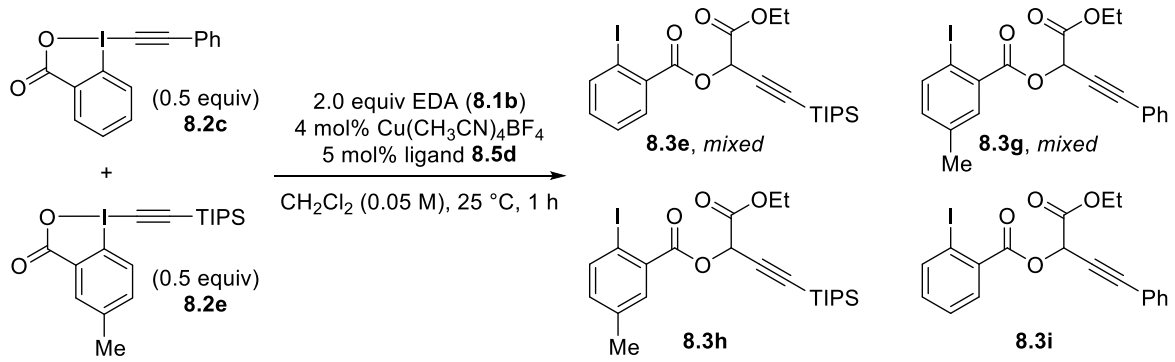
In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN_4)BF_4$ (10.0 mg, 16.0 µmol, 0.16 equiv) and in 2,2'-(propane-2,2-diyl)bis(4,4-dimethyl-4,5-dihydrooxazole) (**8.5d**) (9.52 mg, 20.0 mmol, 0.20 equiv). The vial was capped, removed from the glovebox, dry DCM (4.0 mL) was added and the solution was stirred at room temperature for 1 h. Then, 1.0 mL of the solution was added to micro-wave vials containing the following solutions at room temperature:

(A) ethyl 2-diazoacetate (**8.1d**) (51 µL, 87% wt in DCM, 0.40 mmol, 2.0 equiv) and TIPS-EBX (**8.2b**) (86 mg, 0.200 mmol, 1.0 equiv) in DCM (3.0 mL)

(B) ethyl 2-diazopropanoate (**8.1d**) (51 mg, 0.40 mmol, 2.0 equiv) and TIPS-EBX (**8.2b**) (86 mg, 0.20 mmol, 1.0 equiv) in DCM (3.0 mL)

The reaction were monitored by TLC (EtOAc/pentane 5:95). After disappearance of the diazo substrate, the solvent was removed under reduced pressure and CH_2Br_2 (140 µL, 0.1 M in $CDCl_3$, 0.20 mmol, 1.0 equiv) was added as internal standard and the crude reaction mixtures were analyzed by ^{1}H NMR.

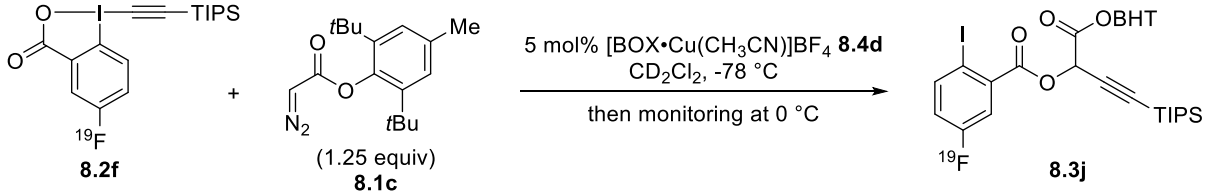
Competitive experiment



A catalytic solution of $Cu(CH_3CN)_4BF_4$ (6.30 mg, 20.0 µmol, 0.08 equiv) and 2,2'-(propane-2,2-diyl)bis(4,4-dimethyl-4,5-dihydrooxazole) (**8.5d**) (5.96 mg, 23.0 µmol, 0.10) were mixed together in CH_2Cl_2 (4.0 mL) for 1 h at room temperature. A flame dried 10 mL microwave vial was successively charged under nitrogen with Ph-EBX (**8.2c**) (52.0 mg, 0.15 mmol, 0.5 equiv), and 5-methyl-1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**8.2e**) (66.0 g, 0.15 mmol, 0.5 equiv), dry DCE (4.0 mL) and ethyl 2-diazoacetate (**8.1b**) (73 µL, 87% wt in DCM, 0.60 mmol, 2.0 equiv). 2.0 mL of catalytic solution was then slowly added to the resulting mixture and stirred at room temperature for 1 h and then evaporated under reduced pressure. Dibromomethane (0.012 mL, 0.150 mmol, 0.5 equiv) was added to the crude product, dissolved in $CDCl_3$ and analyzed by ^1H NMR. The ratio of product was determined as follow: **8.3e**/**8.3g**/**8.3h**/**8.3i** = 0.40:0.57:1.0:0.75. The crude NMR yields were determined as follow: **8.3e** = 28%; **8.3g** = 30%; **8.3h** = 54%; **8.3i** = 53%.

10.6.3. Kinetic Studies

Representative experiment at [EBX **8.2f**] = 0.050 M, [diazo **8.1c**] = 0.0625 M and [cat **8.4d**] = 0.0025 M.



Catalytic solution: [BOX•Cu(CH₃CN)]BF₄ (**8.4d**) (7.518 mg, 17.50 µmol) was dissolved in CD_2Cl_2 (1.75 mL). The solution was cooled to -78 °C. Stock solution for 7 reactions.

Reagents solution: 5-Fluoro-1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (**8.2f**) (154 mg, 0.35 mmol, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**8.1c**) (126 mg, 0.44 mmol, 1.25 equiv) were dissolved in CD_2Cl_2 (5.25 mL). The solution was cooled to -78 °C. Stock solution for 7 reactions.

Reaction: 250 µL of the catalytic solution (-78 °C) was quickly added to a microwave tube containing 750 µL of a stirring reagents solution (-78 °C). Then, an aliquot of 500µL of the reaction mixture was quickly syringed and introduced in a pre-cooled (-78 °C) NMR tube. The tube can be kept at this temperature for long period. Cat. loading = 5 mol%, C = 0.05 M.

Analysis: The NMR tube was quickly transferred into the NMR machine with the cryo-probe being set to -20°C. Lock, atma and shim were done after stabilization of the temperature at -20 °C. Then, the cryo-probe was set-up to 0 °C and FID was recorded (1 spectrum/min, 35 scans/spectrum).

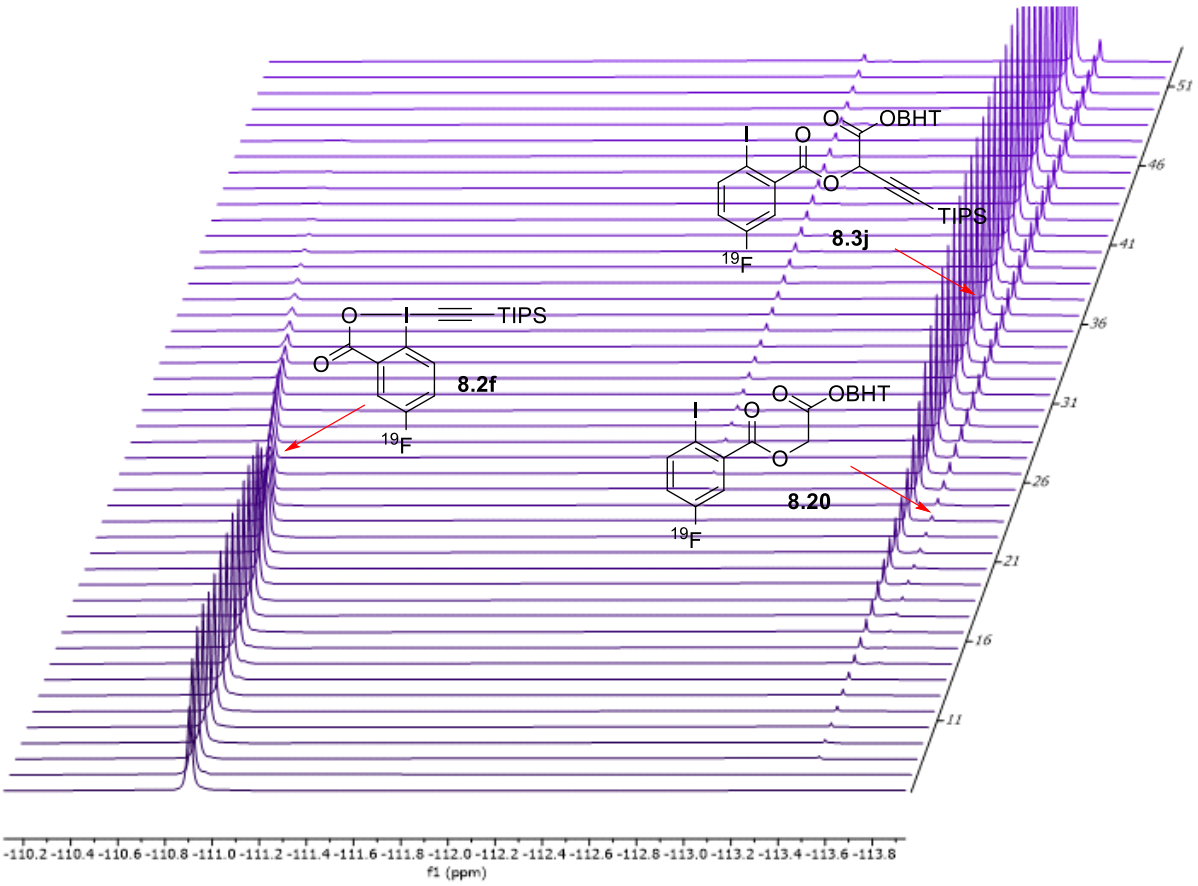


Figure S6: *In situ* ^{19}F NMR reaction progress analysis.

Calibration curve: The standard curve between the concentration of product **8.2f** and EBX **8.3j** and the ^{19}F NMR spectrum integration values of **8.2f** and **8.3j** was established.

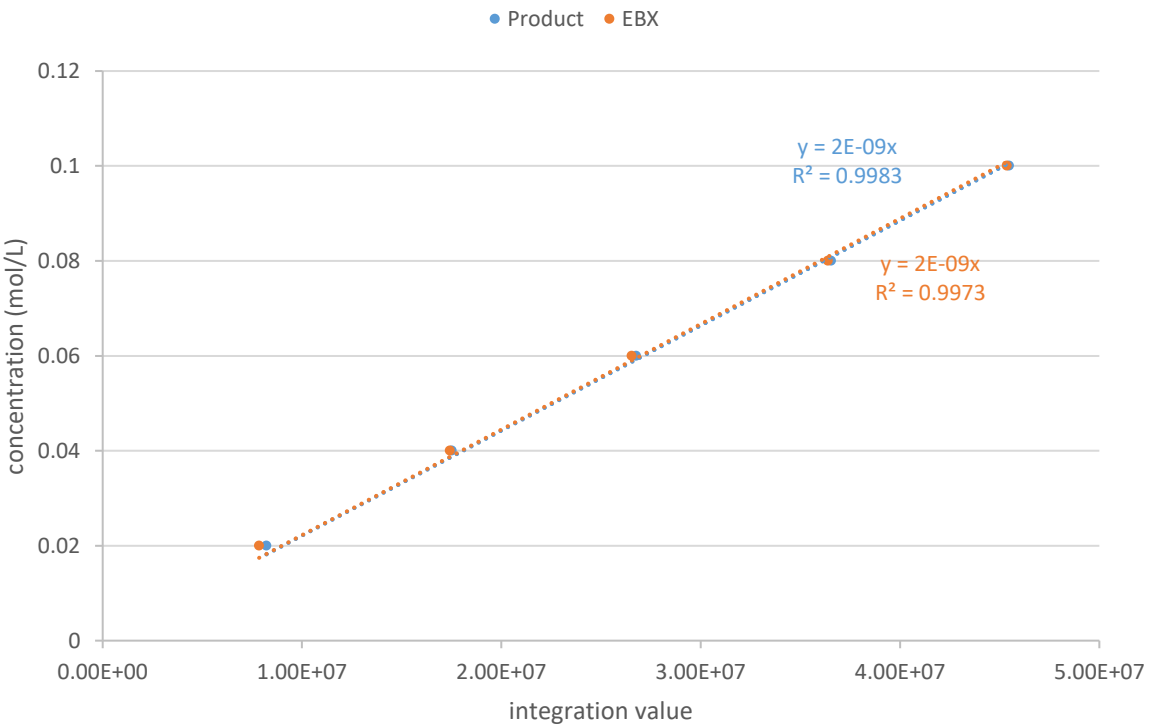
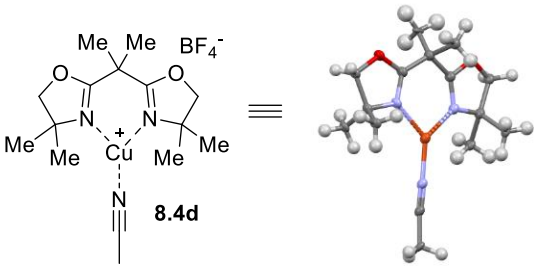


Figure S7: Standard curves between the concentration of product **8.2f** and EBX **8.3f** and the integration values of the ^{19}F NMR spectrum.

10.6.4. Crystal Structures

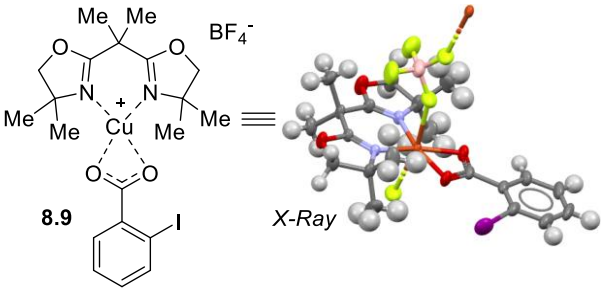
Not registered in CCDC – 8.4d



The tetrafluoroborate anion could not be refined.

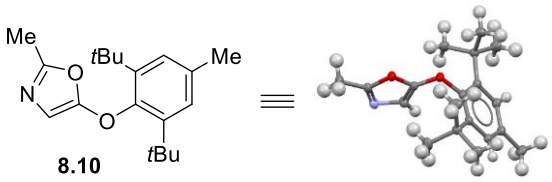
Formula	$C_{15}H_{25}CuN_3O_2$
$D_{calc.}$/ g cm^{-3}	0.574
m/mm^{-1}	0.803
Formula Weight	342.92
Colour	colourless
Shape	plate
Size/mm^3	0.41×0.34×0.10
T/K	140.00(10)
Crystal System	orthorhombic
Flack Parameter	0.47(5)
Space Group	$Pmc2_1$
a/Å	12.01173(12)
b/Å	14.46253(13)
c/Å	22.8374(2)
a/°	90
b/°	90
g/°	90
V/Å^3	3967.31(7)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu$K\alpha$
Q_{min}/°	3.056
Q_{max}/°	75.882
Measured Refl's.	43113
Indep't Refl's	8164
Refl's I≥2s(I)	7962
R_{int}	0.0356
Parameters	387
Restraints	693
Largest Peak/e Å^{-3}	4.263
Deepest Hole/e Å^{-3}	-1.049
GooF	1.806
wR_2 (all data)	0.3511
wR_2	0.3373
R_1 (all data)	0.1165
R_1	0.1141

Not registered in CCDC – Compound 8.9



Formula	$C_{20}H_{26}BCuF_4IN_2O_4$
$D_{calc.}$/ g cm^{-3}	1.734
□/mm^{-1}	2.224
Formula Weight	635.68
Colour	clear intense blue
Shape	plate
Size/mm^3	0.38×0.21×0.04
T/K	140.00(10)
Crystal System	orthorhombic
Space Group	*Pnma*
a/Å	17.7517(6)
b/Å	7.1447(3)
c/Å	19.2000(7)
□/°	90
□/°	90
□/°	90
V/Å^3	2435.15(15)
Z	4
Z'	0.5
Wavelength/Å	0.71073
Radiation type	Mo*Kα*
□$_{min}$/°	3.042
□$_{max}$/°	30.505
Measured Refl's.	22755
Indep't Refl's	3990
Refl's I≥2□(I)	3040
R_{int}	0.0335
Parameters	226
Restraints	225
Largest Peak/e Å^{-3}	0.662
Deepest Hole/e Å^{-3}	-0.755
GooF	1.049
wR_2 (all data)	0.0932
wR_2	0.0841
R_1 (all data)	0.0572
R_1	0.0383

Not registered in CCDC – 8.10



8.10

Formula	$C_{19}H_{27}NO_2$
$D_{calc.}$/ g cm^{-3}	1.149
m/mm^{-1}	0.576
Formula Weight	301.41
Colour	colourless
Shape	irregular
Size/mm^3	0.31×0.13×0.07
T/K	140.00(10)
Crystal System	triclinic
Space Group	$P\bar{1}$
a/Å	8.7749(3)
b/Å	9.2983(4)
c/Å	12.5161(5)
a/°	90.139(3)
b/°	106.343(3)
g/°	116.050(4)
V/Å^3	870.94(6)
Z	2
Z'	1
Wavelength/Å	1.54184
Radiation type	CuKa
Q_{min}/°	3.720
Q_{max}/°	75.901
Measured Refl's.	7825
Indep't Refl's	3529
Refl's I≥2s(I)	3313
R_{int}	0.0128
Parameters	208
Restraints	0
Largest Peak/e Å^{-3}	0.310
Deepest Hole/e Å^{-3}	-0.220
GooF	1.094
wR_2 (all data)	0.1178
wR_2	0.1160
R_1 (all data)	0.0453
R_1	0.0430

11

Annexes

11. Annexes

11.1. Spectra of New Compounds

See USB stick for spectra.

11.2. Curriculum Vitae

Guillaume Pisella

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Date of birth: 05 May 1992
Google Scholar: Guillaume Pisella
ORCID: 0000-0003-0258-4874

Education

Since 2017 **PhD in Organic Chemistry** (EPFL, Switzerland)
Supervisor: Prof. Jérôme Waser (LCSO research group)

2014 – 2016 **Chemical Engineer** (ENSCP, France) and **Master of Science** (UPMC, France)
Major: Molecular and Biological Chemistry

2013 – 2014 **1st year Master of Science** (Paris-Saclay University, France)
Organic Chemistry

2012 – 2013 **Apprenticeship** (Paris-Saclay University, France)
Synthetic and Medicinal Chemistry

Professional Experience

Since 2017 **PhD in Organic Chemistry – 4 years, Waser Group (LCSO), EPFL, Switzerland**
New Vinylation and Alkynylation Strategies with Hypervalent Iodine Reagents and Diazo Compounds.
Copper catalysis, carbene chemistry, multi-component reactions, design and synthesis of new hypervalent iodine reagents, target-oriented applications, mechanistic and kinetic studies, enantioselective synthesis, chiral ligand synthesis, organometallic chemistry, air-free techniques, episulfide chemistry, scientific writing and oral communication.

2016 **Master thesis – 6 months, Lautens Group, University of Toronto, Canada**
Tandem Ruthenium/Palladium-Catalyzed Asymmetric Synthesis of Oxindoles.
Palladium and rhodium catalysis, asymmetric synthesis, oxindoles chemistry.

2015 **Engineer internship – 5 months, Roche pRED, Basel, Switzerland**
New Linker Technology for Antibody Drug Conjugates.
Medicinal chemistry, ADC, heterocyclic chemistry, peptide synthesis.

2014 **Master internship – 5 months, Syngenta, Stein, Switzerland**
New Enantioselective Approaches to Aryldione Herbicides.
Process research, asymmetric hydrogenation, large-scale synthesis, optimizations.

2012 – 2013 **Apprenticeship – 1 year, Sanofi R&D, Chilly-Mazarin, France**
Synthesis and Study of Amphiphilic Fluorescent Heterocycles.
Click chemistry, cross-coupling reactions, nucleotides chemistry, lipids chemistry, amphiphiles, biomaterials, hydrogels, supramolecular chemistry.

Diploma, reference letters and work certificates are available on demand.

Skills and Languages

Teaching	Formation of a laboratory technician – 1 year, from Laboratoire-Ecole of EPFL. Mentorship of a master student – 6 months. Teaching assistant at the bachelor level, practical and theoretical courses (600 hours).
Software	MS Office (PowerPoint, Word, Excel), ChemDraw, NMR (MestreNova, Topspin), Electronic laboratory notebook (E-Notebook, Symyx Notebook), bibliographic research (Reaxys, SciFinder), literature management (Zotero, Mendeley, EndNote, Inoreader).
Chemistry	NMR spectroscopy (1D, 2D, low temperature), mass spectrometry (LC-MS, GC-MS, MALDI-TOF), chromatography (HPLC, chiral, GC), spectroscopy (IR, UV-Vis, fluorescence), automated preparative chromatography (CombiFlash), high-pressure reaction (autoclave, H-Cube), microwave reaction, peptide synthesis.
Additional	Biochemistry, Chemical Engineering, Materials Chemistry and Polymers, Theoretical Chemistry, Radioactivity and Nuclear Energy, Computational Chemistry and Molecular Modelling, Computer programming (C language), Quantic Mechanic, Experimental Design (DOE), Communication Techniques, Management, Entrepreneurship, Marketing, Risk Management.
Languages	English: fluent, French: native, German: notions.

Scientific Communications

Publications

D. P. Hari,† G. Pisella,† M. D. Wodrich, A. V. Tsymbal, F. Fadaei Tirani, R. Scopelliti, J. Waser, Low-Temperature Intramolecular [4+2] Cycloaddition of Allenes with Arenes for the Synthesis of Diene Ligands. *Angew. Chem. Int. Ed.* **2021**, *60*, 5475.

N. Declas,† G. Pisella,† J. Waser, Vinylbenziodoxol(on)es: Synthetic Methods and Applications. *Helv. Chim. Acta* **2020**, *103*, e2000191.

G. Pisella, A. Gagnebin, J. Waser, Copper-Catalyzed Oxyvinylation of Diazo Compounds. *Org. Lett.* **2020**, *22*, 3884.

G. Pisella, A. Gagnebin, J. Waser, Three-Component Reaction for the Synthesis of Highly Functionalized Propargyl Ethers. *Chem. Eur. J.* **2020**, *26*, 10199.
Highlighted in *Chimia* **2020**, *74*, 504.

J. Borrel,† G. Pisella,† J. Waser, Copper-Catalyzed Oxyalkynylation of C–S Bonds in Thiiranes and Thiethanes with Hypervalent Iodine Reagents. *Org. Lett.* **2020**, *22*, 422.
Highlighted in *Synfacts* **2020**, *16*, 309.

K. Yamamoto, Z. Qureshi, J. Tsoung, G. Pisella, M. Lautens, Combining Ru-Catalyzed C–H Functionalization with Pd-Catalyzed Asymmetric Allylic Alkylation: Synthesis of 3-Allyl-3-aryl Oxindole Derivatives from Aryl α-Diazoamides. *Org. Lett.* **2016**, *18*, 4954.

Conferences

Swiss Chemical Society Fall Meetings, Switzerland, 2017, 2018, 2019, 2020.

Markovnikov Congress on Organic Chemistry, Moscow – Kazan, Russia, 2019.

6th International Conference on Hypervalent Iodine Chemistry, Cardiff, UK, 2018.

Summer School – Trends in Organic Synthesis, Villars-sur-Ollon, Switzerland, 2017.