Thèse n° 9481

Photochemical Alkynylations with Hypervalent Iodine Reagents

Présentée le 3 juin 2022

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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École
polytechnique
fédérale
de Lausanne

2022

To my parents and sister,

A mes amis

“One advantage of being disorderly is that one is constantly making exciting discoveries”

A. A. Milne

« On ne découvre pas de terre nouvelle sans consentir à perdre de vue,

d'abord et longtemps, tout rivage. »

André Gide

Acknowledgements

I would first like to thank my supervisor Professor Jerome Waser for the freedom, independence, and trust you have shown me over the past years, which has allowed me to grow as a chemist. I am very happy to have had the opportunity to draft my papers and have your keen eye to improve them. I would also like to thank you for your availability and willingness to discuss career opportunities, my doubts and fears, and also more philosophical moments about motivation or work/life balance. I am grateful to know that even when I felt all was falling down you would spend the time to make sure it would be rebuilt.

I would like to sincerely thank Professors Abigail Doyle, David J. Procter and Jieping Zhu for accepting to read and evaluate my research and I would like to extend my gratitude to Professor Kevin Sivula for accepting the role of president of the jury.

I would like to thank all of the people I collaborated with: Stefano (special mention for mentoring my masters and the crazy COVID submission of the *Chem. Sci.*), Franck (special mention for starting me off in the PhD), Artem, Alec, Basil (special mention for being the first student I supervised, thank you for being a great student), Luca, Marion, Antonin, Diana and Cédric.

J'aimerais remercier Dr. Anne-Sophie Chauvin pour les opportunités d'enseignement que tu m'as données et pour lesquelles tu m'as fait confiance. C'était un plaisir de travailler avec toi.

J'aimerais remercier les équipes du magasin (Gladys, Annelise et Benjamin, Maurizio, Florent et Kosta). J'aimerais aussi remercier l'équipe de spectroscopie RMN (Aurélien en particulier, toujours disponible pour me donner un coup de main). Merci à Dr. Daniel Ortiz, Francisco Sepulveda et Dr. Laure Menin pour leur assistance jamais défaillante en matière de spectroscopie de masse, je me souviendrais toujours des larmes de joie que j'ai versées en recevant « la dernière masse du projet ». Thibault et Lorenzo, l'équipe info au top, merci de m'avoir tolérée en tant qu'informaticienne expérimentale, merci pour le temps que vous avez passé avec moi et pour toutes les choses que vous m'avez apprises. Véronique, merci pour ton aide, ta joie et ta disponibilité. Anne-Lene merci pour ton aide au niveau administratif, une thèse sans toi serait compliquée. Thank you to Ophélie and Cristian (LCS) for letting me borrow the potentiostat and spectrophotometers, and more importantly the time you spent to help me learn and the fun times around a beer.

Alice and Jack, I am so happy to have been a PhD rep with you guys, we went through hard and fun times, thank you for being great people and helping me build my career drive. I don't know if a PhD rep committee has had so much love for beer, love you guys!

I would also like to thank the LCSO group for the great atmosphere even during these masked times. I am so glad to have met you all and I hope that you will continue to keep this alive in the upcoming years.

Elija, as I am writing this, I am dawned by the idea that this is the last Sunday that I can say you are my labmate. Sorry for the singing, thank you for your smile, tolerance, rational and the birthday surprises. Thank you for just being you, I don't think I could have had a better labmate. Javier, so wise, so reasonable, so just, I'm very lucky to have shared the lab (and a birthday) with you, te deseo el major para tu familia (Helena, Pablito y niñita Clara), gracias por todo. Diana, we've had our moments, but I also know some of them have been great, I wish you a good next three years. Abhaya and Raj thanks for being chill labmates and the superbe food.

Nina, merci pour tout, ta disponibilité, ton espoir et ton soutien, bisous. Juju, merci pour ton sourire éternel, tes discussions, ton soutien – toujours un plaisir de parler de tout avec toi. Marion, quoi d'autre à part merci pour ta philoso-folie Braaaaoooouuuuh! Bisous. Eliott, merci pour ta connaissance sans faille et de m'avoir introduite à Ricky Gervais. Merci d'avoir été, avec Nina, le noyau de début de thèse, comme toujours avec de l'eau, ce serait parfait – malheureusement rarement pour la chimie, haha. Pierre merci d'apporter ta joie et gentillesse partout où tu vas. Mikus, thanks for those times in COVID when we played games online, your honesty and fair judgement. Stefano, merci pour le temps que tu donnes au labo et tes conseils précieux, je te souhaite le meilleur. Vlad, well it wouldn't be a party if you weren't there, thanks for the discussions we had in chemistry and out and thanks for teaching me that dance! Emma, merci pour ta fraîcheur et ton sourire. Xingyu and Tin, thanks for your happiness, your calmness, and all the conversations we have had until now. For the more recent arrivals, Yuji, Alexandre and Christine, I wish you the best over the upcoming years.

Pour les anciens, Franck merci pour tout, je suis fière d'avoir hérité de ton projet, Bastian, merci pour ta sympathie, ta lucidité, ton soutien et ton respect (et ton gout pour une soirée bien réussie), Guillaume, merci pour ta franchise, ton rire communicatif, je suis fière d'être ta BFF. Erwann, Durga et Paola, it's cheesy to say "I wouldn't be here without you" but I know that you were all there when I needed help believing in myself, thank you for that in addition to the fun times. Phil, thanks for the long evening chats and bringing me a little bit of home. Mingming, I'm glad to have met such a hard-working, fun person, wish you the best in Germany. Ashis, thanks for being the smile of the LCSO, keep your sweetness.

Next, a PhD without reliable and partygoing postdocs wouldn't be fun: Luca, Thomas, Vincent, Johannes and Tobi – thank you guys for encouraging the fun, the coffee breaks, and the beers! Grand merci aussi à Emmanuelle pour le soutien que tu m'as apporté pour mon futur post-doc. Nieves, thanks for your smile and easygoing attitude it's always a pleasure to chat with you.

Finally, I would like to thank Dani (in the immortal words of ABBA: thank you for the music – not your style I know), Romain, Verity, Raphael, Alec, Xiandong, Najung and Seongmin for the times we have shared.

I would also like to mention and thank the LCSA and LSPN – it's always a pleasure to meet-up with you guys for parties, defences and MOMs. Merci Cédric pour la MOM, j'espère qu'on va la faire craquer cette molecule! Un grand merci à Laura pour avoir été la meilleure copine de paillasse; Dina, pour être ma plus grande supportrice, merci d'être toi: gentille, tolérante et dévouée; et à mon pioupiou adorée, parce que sans toi mon monde serait moins beau, merci pour tout. Piou piou pioooouuu! Piou piou.

Merci à Tristan (Pierjan et le reste de la troupe) pour les bonnes soirées à la montagne promis je te donne ma thèse et on en discutera. Merci aussi à Zoé et Cynthia pour les weekends heureux.

Il y a 6 ans, j'ai juré de le placer alors le voici: Niiiiih ! (Merci les gars de l'UCBL pour les rires)

Mummy, Daddy and Gen (and Robin) thank you for all the times I just needed a break and a helping hand.

Lausanne February 2022

Abstract

Over the past twenty years, photochemical transformations have gained in importance in organic chemistry. Indeed, the development of photocatalysts has allowed the use of visible light as an energy source for chemical transformations. More specifically, photoredox chemistry has emerged as a valuable tool for the generation of free radical intermediates, enabling the organic chemist to envisage new bond disconnections and bond formations.

For the organic chemist, the triple C≡C bond, or alkyne, is a versatile functional group. Alkynes are valuable building blocks for accessing more complex scaffolds. They also have multiple applications in medicinal chemistry, materials science, and chemical biology. Hence, the development of strategies that give access to alkynes is highly relevant. Due to the innate electronics of the alkyne, its transfer was initially limited to the alkynylation of electron-poor positions (electrophiles), however the development of alkyne transfer reagents have allowed the alkynylation of electron-rich positions (nucleophiles), and, more recently, the alkynylation of radicals. Specifically, ethynylbenziodoxolones (EBXs), hypervalent iodine (III) reagents bearing an alkyne, have frequently been used for the alkynylation of radicals. In combination with photochemical conditions they have enabled the activation of multiple functional groups (for example: carboxylates, potassium alkyl trifluoroborates salts, or α-oxo C-H bonds) for the introduction of an alkyne.

The first objective of this research was to enable the photochemical difunctionalisation of double bonds to allow the introduction of an alkyne and a second functional group using EBXs. Indeed, difunctionalisation strategies are highly valuable as they can allow a rapid increase in molecular complexity in a single step. We found that enamides and enol ethers could undergo an alkynylative difunctionalisation with EBXs in presence of a photocatalyst and a hypervalent iodine additive. This method gave access to 1-alkynyl-1,2-aminoalcohols and diols scaffolds, which can be selectively deprotected to deliver the free alcohol or free amine.

The second objective of this thesis was to develop a deoxyalkynylation strategy to allow the conversion of alcohols into alkynes. Starting from cesium oxalates, in presence of a photocatalyst and the EBX reagent, we could access a broad scope of aliphatic arylalkynes. Interestingly, the key to success for this project was found in the choice of light source: to ensure high yields, two high intensity blue LED lamps (440 nm, ca. 80 W) were required. During our mechanistic studies we discovered that this light source could also generate an excited state EBX species. We then decided to explore this discovery: we were delighted to find that the EBX alone under irradiation could promote the photomediated alkynylation of carboxylates, trifluoroborates, enamides, imines and α-oxo C-H bonds. Although the understanding of this process is still in the preliminary stages, we believe that the discovery of

the direct photoexcitation of EBXs will enable facile reaction discovery and complement photocatalysed strategies.

Keywords: Photochemistry, photoredox catalysis, direct photoexcitation, alkynes, 1,2-aminoalcohols, difunctionalisation, deoxygenation, alkynylation

Resumé

Lors des vingt dernières années, les transformations photochimiques ont gagné en importance en chimie organique. En effet, le développement de photocatalyseurs a permis l'utilisation de lumière visible pour l'activation de transformations chimiques. La photochimie est un outil de valeur pour la génération d'intermédiaires radicalaires et a permis au chimiste organicien d'envisager de nouvelles déconnexions et formations de liaisons chimiques.

Pour le chimiste organicien, la triple liaison C≡C, ou alcyne, est un groupement fonctionnel très important. Il est utile en tant que plateforme de synthèse donnant accès à des structures plus complexes. Les alcynes possèdent aussi de nombreuses applications en chimie pharmaceutique, chimie des matériaux et en chimie des biomolécules. Ainsi, les stratégies permettant l'introduction de ce groupement fonctionnel sont prisées. De part la polarisation électronique de l'alcyne, son transfert était limité à l'alcynation d'électrophiles. Cependant, le développement de réactifs pour le transfert d'alcyne permet aujourd'hui l'alcynation de nucléophiles et depuis quelques années l'alcynation de radicaux. En particulier, les ethynylbenziodoxolones (EBXs), des réactifs à l'iode (III) hypervalent substitués d'un alcyne, ont été fréquements utilisés pour l'alcynation de radicaux. En combinant avec des conditions photochimiques ces réactifs ont permis l'activation de nombreux groupements fonctionnels (par exemple : carboxylates, alkyl trifluoroborates de potassium, ou les liaisons α-oxo C-H) afin d'introduire un alcyne.

Le premier objectif de cette thèse était le développement d'une difonctionnalisation d'alcènes en vue d'introduire un alcyne sous conditions photochimiques. En effet, les difonctionnalisations sont très utiles vue qu'elles permettent de gagner en complexité chimique en une seule étape. Nous avons trouvé que les enamides ainsi que les éthers d'énol étaient des substrats de choix. En combinant un réactif à l'iode hypervalent : l'éthynylbenziodoxolone (EBX) avec un photocatalyseur, nous avons réussi à synthétiser une famille de 1-alcynyl-1,2-aminoalcools et diols. Ces derniers ont pu être déprotégés de manière sélective afin de donner accès à l'alcool et l'amine libres. La clé de l'optimisation de cette stratégie s'est trouvée dans la recristallisation de l'EBX et l'addition d'un deuxième réactif à l'iode hypervalent en quantités sous-stœchiométriques.

Le deuxième objectif de cette thèse était le développement d'une déoxygénation pour la synthèse d'alcynes. En utilisant des oxalates de césium, en présence d'un photocatalyseur, et un EBX, nous avons pu synthétiser de nombreux alcynes aliphatiques. La clé pour l'optimisation de cette stratégie était le choix de la source lumineuse: nous avons utilisé deux lampes à DEL (440 nm, ca. 80 W) afin d'obtenir de hauts rendements. Lors de nos études mécanistiques nous avons découvert la non-innocence de l'EBX avec cette source de lumière.

En effet, nous avons réussi générer un EBX à l'état excité. Ceci nous a permis de fixer un dernier objectif : le développement d'alcynations photochimiques en absence de photocatalyseur. Nous avons découvert que l'EBX seul pouvait promouvoir l'alcynation photomédiée de carboxylates, d'alkyl trifluoroborates de potassium, d'enamides, d'imines et de liaisons α-oxo C-H. Même si notre compréhension de ce phénomène reste à un stade préliminaire, nous sommes confiants que la découverte de la photoexcitation directe des EBX peut faciliter la découverte de nouvelles alcynations par voie photochimique et ainsi complémenter les stratégies photocatalysées.

Mots clés: Photochimie, catalyse photoredox, photoexcitation directe, alcyne, 1,2-aminoalcool, difonctionnalisation, deoxygénation, alcynation

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List of abbreviations

4-CzIPN	2,4,5,6-tetrakis-(*9H*-carbazol-9-yl) isophthalonitrile
Ac	acetyl
aq.	aqueous
Ar	aryl
AT	atom transfer
atm	atmosphere
BIOH	1-hydroxybenziodoxolone
BIOAc	1-acetoxybenziodoxolone
boc	*tert*butyloxycarbonyl
BP	benzophenone
bpy	2,2'-bipyridine
br	broad
brsm	based on recovered starting material
Bu	butyl
°C	degrees centigrade
c	concentration
ca.	circa
calcd	calculated
cat.	catalytic
CBX	CyanoBenziodoXolone
Cbz	carboxybenzyl
CFL	Compact Fluorescent Lightbulb
CV	Cyclic voltammetry
Cy	cyclohexyl
δ	NMR chemical shift in ppm
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DCA	9,10-dicyanoanthracene
DCE	dichloroethane
DIAD	di*iso*propyl azodicarboxylate
DIBALH	di*iso*butylaluminium hydride
DIPEA	di*iso*propylethylamine
DHP	1,4-dihydropyridine
DMAP	4-dimethylamino pyridine

DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dtbbpy	4,4'-ditertbuyl-2,2'-bipyridine
d.r.	diastereomeric ratio
DBHP	di-*tert*butylperoxide
EBX	ethynyl benziodoxolone
EDG	electron donating group
ee	enantiomeric excess
EI	electron impact ionization
EnT	Energy Transfer
eq.	equation
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EWG	electron withdrawing group
g	gram
h	hour(s)
HAT	Hydrogen atom transfer
HE	Hantzsch ester
HFIP	hexafluoro *iso*propanol
HIR	Hypervalent iodine reagent
HOMO	Highest occupied molecular orbital
HPLC	high pressure liquid chromatography
HTIB	hydroxy(tosyloxy iodo)benzene
Hz	hertz
i	iso
IC	internal conversión
ISC	intersystem crossing
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
kcal	kilocalories
KHMDS	potassium hexamethyldisilazane
kJ	kilojoule
L	liter
LG	leaving group

LUMO	lowest unoccupied molecular orbital
m	multiplet
m/z	mass per electronic charge
M	mol/L
Me	methyl
Mes	mesityl
mg	milligram
min	minute(s)
mixt.	mixture
mL	milliliter
MLCT	metal to ligand charge transfer
MTBE	methyl *tert*-butyl ether
µL	microliter
mmol	millimol
M.p.	melting point
MS	mass spectrometry
ν	frequency (cm^{-1})
N	normality
*n*BuLi	*n*-butyllithium
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
NPhth	*N*-phthalimidoyl
n.r.	no reaction
p	para
PC	photocatalyst
PCET	Proton Coupled Electron Transfer
PG	protecting group
PIDA	phenyliodide diacetate
PIFA	phenyliodide ditrifluoroacetate
Ph	phenyl
PhEBX	1-[phenylethynyl]-1,2-benziodoxol-3(1*H*)-one
Phen	phenathroline
PMP	paramethoxyphenyl
ppm	parts per million
Pr	propyl
q	quartet

quint.	quintet
quant.	quantitative
RAG	redox active group
R_f	retention factor
RT	room temperature
s	singlet
sat.	saturated
SCE	Satured calomel electrode
SET	single electron transfer
sol.	solution
t	triplet
T	temperature
TBA	tetrabutylammonium
TBADT	tetrabutylammonium decatungstate
TBAF	tetra-*n*-butylammonium fluoride
*t*Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	triflyl
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TIPSEBX	1-[(tri*iso*propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one
TLC	thin layer chromatography
TMACl	tetramethylammonium chloride
TMS	trimethylsilyl
Ts	tosyl
UV-Vis	ultraviolet and visible
V	Volt
XAT	X atom transfer (X = halogen)

Chapter 1: General introduction

1. General Introduction

Over the past centuries, chemistry has contributed to advances in numerous domains including medicine, electronics, materials science, energy, agriculture, and cosmetics. Major advances in chemistry have allowed the synthesis of more efficient medicines that can now treat what once was untreatable, more resistant or biodegradable materials, and bio-sourced fuels. For this reason, the development of chemical processes is of utmost interest. New methods can give access to new scaffolds or can improve the synthetic routes to access known compounds of interest. Developing new methods today can prove more complicated than before. The resources that we use in chemistry generally come from the petrochemical industry which is non-renewable. Consequently, the interest for developing efficient and alternative synthetic methods is growing. Sustainability of a chemical process can be improved by using renewable resources, and it's efficiency can increase by using less energy consuming conditions, or waste minimisation. For the latter, paying attention to atom and step economy is valuable, just as developing strategies that result in alternative or higher chemo- or regioselectivities. Although these principles have been known and applied for many years,[1] they are of utmost importance as the interest in sustainability increases in society. In this regard, fundamental research performed in an academic setting can help address the issues that entail from these principles as illustrated by the development of transition-metal catalysis or organocatalysis.

One approach for discovering sustainable strategies relies on the investigation of alternative bond disconnections. This approach can lead to the use of more abundant starting materials or can give access to a target scaffold in a single step, rather than several. In this regard, radical chemistry is an interesting approach. In comparison to ionic chemistry, radical chemistry has often been disregarded in the past due to the high reactivity of these open shell species, which limited the applications and tolerance of these strategies. Their reactivity has sometimes been difficult to control, their use can lead to undesired side reactivities, in particular when combined with a thermally activated radical initiator. Nevertheless, radical strategies offer different chemo- and regioselectivities when compared to their ionic equivalents and have been gaining in importance over the past century. Since the 1990s there has been an increase in interest toward radical chemistry as illustrated by the ratio of papers published with "radical" as a keyword: prior to 1990 the number of papers published represented less than 0.1% of all papers issued by the Journal of the American Chemical

[1] a. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford [England]; New York, 1998. b. Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301–312.

Society (Figure 1.1, black line).[2] Interestingly, the number of citations of the same publications has increased strongly over the past decades (grey bars). This suggests that even though the amount of work published in the field is relatively constant, the general interest towards these papers is growing. One specific way of generating radicals is through photomediated approaches. Since 1965, the ratio of publications issued with keywords associated to photochemistry[3] is variable. Although, since 2010, there is a continual increase in the ratio of papers published.

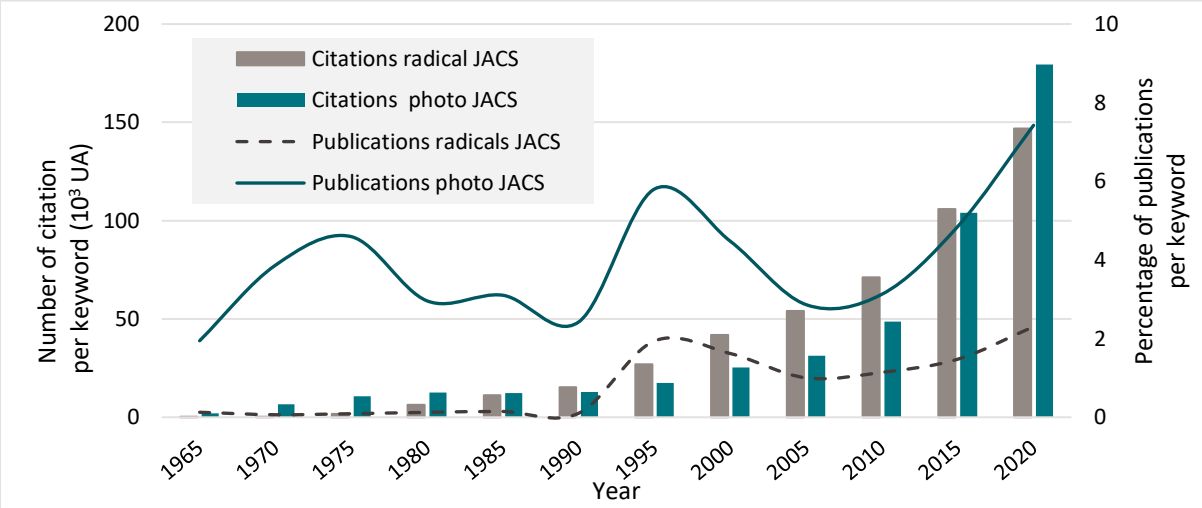

Figure 1.1. Number of publications and citations of publications per year per keyword (source Web of Science)[4]

Photochemistry is far from a new approach; it was first discussed by Ciamician as a promising area of research in the 1910s,[5] however in the 20th century it usually required the use of high-energy UV light. It has only recently emerged as a reliable activation strategy for chemical reactions. The development of photocatalysts has enabled the use of visible light as an energy source and brought photochemistry into the limelight. Using visible light and catalysis to generate highly reactive open-shell species allows radical chemistry to proceed at room temperature with a catalytic generation of the highly reactive intermediates. Consequently, photocatalysis overcomes the limitations associated to UV-light (personal protection, quartz

[2] As an illustrative example we have chosen the publications from the Journal of the American Chemical Society from 1960 to 2020. When regarding the overall publication rate of JACS, we can see a steady increase from 1960 to 2020 with no rapid increases or decreases that could have been associated to the creation of satellite journal such as organic letters or ACS catalysis for example. It's directed towards a general chemistry public which should therefore illustrate the trends in real time and we also compared these trends to that of the Journal of Organic Chemistry which also correlate the observation for JACS. Publications from Wiley and the Royal Chemical Society did not allow us to interpret the data due to major editorial changes over the past 20 years.
[3] "photochem*" OR "photocat*" OR "photomed*" OR "photoredox"
[4] This chart was extracted from: https://www.webofscience.com/
consulted on 10th January 2022. Search: TOPIC: *keywords* PUBLICATION: "Journal of the American Chemical society" Publication date range: "1950 – 2022". Keywords: "radical" or "photochem* OR photocat* OR photoredox* OR photomed*"
[5] Ciamician, G. *Science* **1912**, *36*, 385–394.

glassware). It can also alleviate the necessity for a strong radical chain process and limit the potential for side-reactivity which can sometimes occur with thermally activated radical reactions.

Alkynes are a versatile and attractive functional group. They are omnipresent in synthetic methods as targets, and they can also be considered as a versatile platform for further transformations.[6] They are stable enough to induce mechanical rigidity into a structure allowing them to have applications in materials science, chemical biology, or medicinal chemistry. From a synthetic perspective, they can undergo selective activation to deliver cyclic scaffolds, alkenes, allenes, or ketones. In this regard, the development of alkynylation reactions is highly relevant. Specifically, EthynylBenziodoXolones (EBXs), first synthesised by Ochiai and Zhdankin,[7] enable an *Umpolung*[8] of the alkyne. Various methods have allowed the alkynylation of nucleophiles,[9] and since 2012 their somophilic character has been illustrated with multiple reports on the alkynylation of radicals with EBXs and thus allowing them to be combined with photochemical transformations.[10] It is this area of research that my PhD was centred: developing photochemical alkynylations with hypervalent iodine reagents.

In this thesis, we shall first establish the background and significance of this research by initially discussing photophysics, the concept of photochemistry and its current scope of applications. We will then discuss the versatility of the alkyne functional group and the current strategies to access them with an accent on radical alkynylation strategies. To close the background and significance chapter, we will finally turn to the hypervalent iodine reagents and how they have been combined with photochemical strategies as both additives and an alkyne source. The third chapter of this thesis will establish the objectives and goal of this research. The three following chapters will discuss the findings of this research by covering: (1) a difunctionalisation strategy, (2) a deoxygenation strategy, and (3) our results associated to the direct photoexcitation of the EBX reagents. We shall then conclude the thesis and propose an outlook for future research. The final chapter will include the experimental and characterisation data for each of the projects presented.

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[6] a. Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations; Trost, B. M., Li, C.-J., Eds.; Wiley-VCH: Weinheim, 2015. b. Acetylene Chemistry: Chemistry, Biology, and Material Science; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim; [Great Britain], 2005.
[7] a. Ochiai, M.; Masaki, Y.; Shiro, M. *J. Org. Chem.* **1991**, *56*, 5511–5513. b. Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Simonsen, A. J. *J. Org. Chem.* **1996**, *61*, 6547–6551.
[8] Concept introduced by Seebach in 1979: Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258.
[9] Hari, D. P.; Nicolai, S.; Waser, J. Alkynylations and Vinylations. In *PATAI'S Chemistry of Functional Groups*; 2018; pp 1–58.
[10] a. Liu, X.; Wang, Z.; Cheng, X.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 14330–14333. b. Le Vaillant, F.; Waser, J. *Chem. Sci.* **2019**, *10*, 8909–8923.

Chapter 2: Background and significance

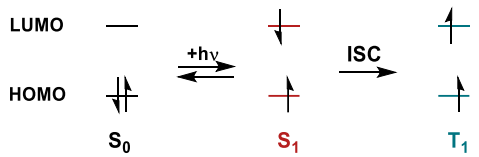
2. Background and Significance

2.1. Photochemistry

Using light as an energy source is an attractive way to overcome the activation energy associated to a chemical transformation. Until the turn of the century, the use of visible light in chemical transformations was relatively scarce. UV light was preferred due to the greater absorption for many molecules in the UV region. That being said, the higher energy of this light source could be impractical both from a reaction design standpoint (selectivity) and a technical perspective (specific glassware and personnel protection equipment). To use visible light, chemists developed photosensitizers and photocatalysts[1] that could be selectively photoexcited and then selectively activate the substrate of choice.[2,3]

2.1.1. Photophysics

Photochemical transformations rely on the fundamentals of photophysics, in a sense it is the consequence of the interaction of light with matter.[4] For a reaction to occur, the first step is the photoexcitation of a molecule. Upon absorption of a photon, an electron of the HOMO is promoted to the LUMO. The molecule, once in the ground state S_0, is now in the excited state S_1 (Scheme 2.1).[5] The promoted electron can then undergo inter system crossing (ISC) resulting in a generally longer-lived triplet state T_1.



Scheme 2.1. Frontier molecular orbital occupation in the ground state and the excited states.

It is important to note that each state (S_0, S_1 and T_1) of the molecule possess multiple vibrational modes following the degrees of freedom of the molecule (Figure 2.1). The

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[1] For simplicity reasons, from here on we will only use the word "photocatalyst" as defined by IUPAC: "Catalyst able to produce, upon absorption of light, chemical transformations of the reaction partners. The excited state of the photocatalyst repeatedly interacts with the reaction partners forming reaction intermediates and regenerates itself after each cycle of such interactions." Source: https://doi.org/10.1351/goldbook.PT07446

[2] Selected reviews on photocatalysis: a. Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2010**, *40*, 102–113. b. Ravelli, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev.* **2012**, *42*, 97–113. c. Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617–1622. d. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363. e. Fukuzumi, S.; Ohkubo, K. *Org. Biomol. Chem.* **2014**, *12*, 6059–6071. f. Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166. g. Arias-Rotondo, D. M.; McCusker, J. K. *Chem. Soc. Rev.* **2016**, *45*, 5803–5820. h. Amos, S. G. E.; Garreau, M.; Buzzetti, L.; Waser, J. *Beilstein J. Org. Chem.* **2020**, *16*, 1163–1187.

[3] Selected books on photocatalysis: a. Klán, P.; Wirz, J. *Photochemistry of Organic Compounds: From Concepts to Practice*; Wiley: Chichester, West Sussex, U.K, 2009. b. Wardle, B. *Principles and Applications of Photochemistry*; 2009. c. Balzani, V.; Ceroni, P.; Juris, A. *Photochemistry and Photophysics: Concepts, Research, Applications*; Wiley-VCH: Weinheim, 2014. d. Fagnoni, M.; Protti, S.; Ravelli, D. *Photoorganocatalysis in Organic Synthesis*; Catalytic Science Series; WORLD SCIENTIFIC (EUROPE), 2019; Vol. 18.

[4] Larsson, S. Photophysics and Photochemistry. In *Chemical Physics*; CRC Press, 2012.

[5] Triplet ground states also exist, for example: molecular oxygen.

absorption of a photon is a quick process, less than a femtosecond, so quick that the nuclei of the molecule are considered immobile. The Franck-Condon principle describes this by representing nuclear movement along the horizontal axis, hence the absorption of a photon is represented vertically. After excitation to one of the vibrational modes of the excited S_1 state, the molecule can relax through non-radiative transitions such as vibration ($S_n^* \rightarrow S_n$ or $T_n^* \rightarrow T_n$), internal conversion ($S_n \rightarrow S_m$ where n > m), intersystem crossing ($S_1 \rightarrow T_1$) , or non-radiative decay ($S_1 \rightarrow S_0$ or $T_1 \rightarrow S_0$) or through radiative processes such as fluorescence ($S_1 \rightarrow S_0$) or phosphorescence ($T_1 \rightarrow S_0$).

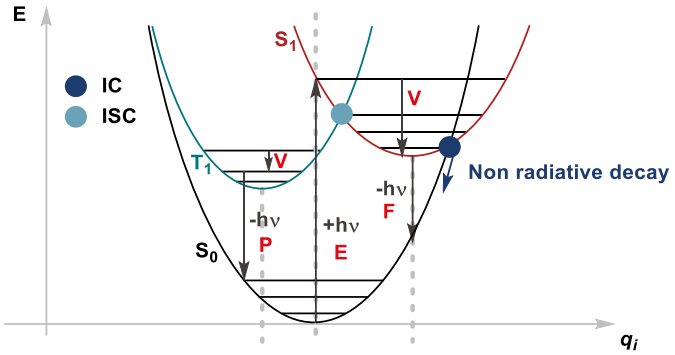


Figure 2.1. Illustrative potential energy surfaces for the ground state (S_0) and the excited states (S_1 and T_1) with different geometry. (IC = internal conversion, ISC = intersystem crossing, P = phosphorescence, V = vibration E = excitation, F = fluorescence).

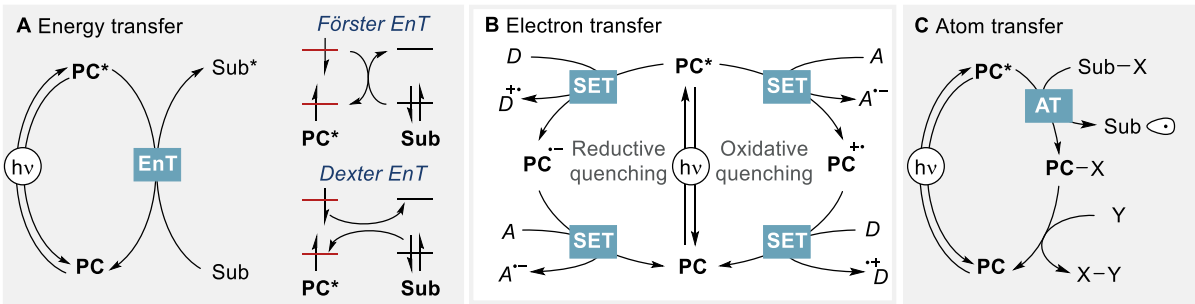
2.1.2. Photocatalysis

After excitation, most molecules will rapidly relax back down to the ground state S_0. In contrast, photocatalysts possess relatively long-lived excited states (scale: µs – ns). This allows them to interact with a second molecule and engage in energy transfer (EnT), single electron transfer (SET), or atom transfer (AT). It is important to note that even with a long-lived excited state, the excited photocatalyst is a transient species and therefore should essentially react with ground state or long-lived reaction intermediates.

2.1.2.1. Mechanisms in photocatalysis

Three main classes of activation can then occur (Scheme 2.2). A first mode of activation results in an energy transfer (EnT, A), where the excited state photocatalyst transfers its excited state energy to the substrate of choice generally through a non-radiative process (e.g., triplet sensitisation). Two common pathways for EnT are the Förster and Dexter EnT. The Förster EnT proceeds “through-space” where the excited PC* relaxes to the ground state in proximity to the substrate and transfers the energy to the substrate, resulting in the excited state substrate. The Dexter EnT proceeds “through-bond” and can be represented by two simultaneous electron transfers, this mechanism is generally more frequently encountered and requires orbital overlap for the EnT to occur.[2g] This results in the regeneration of the photocatalyst in the ground state and the excited state substrate. A second mode of activation

proceeds through a single electron transfer (SET, B). The excited state photocatalyst (with two unpaired electrons) can act as either an oxidant or a reductant. In a reductive quenching cycle, the excited state photocatalyst will first interact with an electron donor (***D***) resulting in an oxidised species (***D***$^{\bullet+}$) which can now react further, and the reduced photocatalyst (**PC**$^{\bullet-}$). To oxidise **PC**$^{\bullet-}$ back to the ground state, an electron acceptor (***A***) is needed. Inversely, in an oxidative quenching cycle the photocatalyst is first oxidised to **PC**$^{\bullet+}$ by an acceptor (***A***) then reduced by a donor (***D***). In both cycles, the substrate can occupy either role (***A*** or ***D***), in a redox neutral cycle both roles of ***A*** and ***D*** will be occupied by substrate and reagent, whereas in net reductive (or oxidative) cycles a stoichiometric sacrificial reductant (or oxidant) will be required to maintain the catalytic cycle. The third mode of activation is atom transfer (AT), in this case the excited state catalyst can abstract an atom (generally a hydrogen). To regenerate the ground state photocatalyst a second molecule needs to abstract the atom. In the case of hydrogen transfer, this can either occur through deprotonation then reoxidation or through HAT.



Scheme 2.2. General scheme for substrate activation with a photocatalyst.

In addition to these fundamental activation modes, other elemental steps can occur and further promote the EnT, SET, or AT. This can be protonation or deprotonation in the case of proton coupled electron transfer (PCET)[6] or Lewis acid promoted SETs,[7] and finally H-bonding to the photocatalyst or coordination to the metal centre of the photocatalyst for SET or EnT.[8]

2.1.2.2. Common photocatalysts

Over the past years, photocatalysis has been combined with organocatalysis,[9] metallaphotoredox,[10] or flow chemistry, the latter, allowing its application in an industrial

[6] Murray, P. R. D.; Cox, J. H.; Chiappini, N. D.; Roos, C. B.; McLoughlin, E. A.; Hejna, B. G.; Nguyen, S. T.; Ripberger, H. H.; Ganley, J. M.; Tsui, E.; Shin, N. Y.; Koronkiewicz, B.; Qiu, G.; Knowles, R. R. *Chem. Rev.* **2022**, *122*, 2017–2291
[7] Amador, A. G.; Sherbrook, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2016**, *138*, 4722–4725.
[8] Genzink, M. J.; Kidd, J. B.; Swords, W. B.; Yoon, T. P. *Chem. Rev.* **2022**, *122*, 1654–1716.
[9] Liu, Y.-Y.; Liu, J.; Lu, L.-Q.; Xiao, W.-J. *Top. Curr. Chem.* **2019**, *377*, 37.
[10] a. Twilton, J.; Le, C. (Chip); Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, *1*, 0052. b. Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. *Chem. Rev.* **2022**, *122*, 1485-1542.

setting.[11] It has also found applications with biomolecules[12] and has recently been merged with electrochemistry.[13] These advances have been established in parallel with the continual development of photocatalyst libraries to ensure longer lifetimes, increased redox windows, activation at different wavelengths, and greater photostability. Where there are many possible scaffolds that can be used, in organic chemistry, two frequently used classes stand out: (1) polypyridyl transition metal complexes and (2) organophotocatalysts or organic dyes (Figure 2.2). The organometallic complexes are often constituted with rare transition-metals (Ru or Ir, **PC.1** - **PC.3**) for the most common blue light absorbing catalysts and their ligands are generally *N-N* bidentate (often *bis*-pyridines (bpy)) or *C-N* bidentate (with phenylpyridines (ppy)). One of the most studied complexes is $Ru(bpy)_3^{2+}$ (**PC.1**).[2g] Upon absorption of a photon these complexes generally undergo metal to ligand charge transfer (MLCT). For an octahedral complex, the excited electron undergoes a $t_{2g} \rightarrow \pi^*$ transition. This occurs when the π^* is lower in energy than the e_g orbitals of the metal. This also means that the ligands directly influence the redox potentials for the excited, reduced, and oxidised states of the photocatalyst. Typically, the ligands can be tuned by introducing electron withdrawing groups resulting in an increased oxidative character of the complex, or by introducing bulky substituents on the positions prone to functionalisation during the reaction to prevent photocatalyst deactivation or side reactions (highlighted in blue). In addition to the rare metals Ru and Ir, more common earth abundant metals such as Cu are being explored inspired by $Cu(dap)_2Cl$ (**PC.4**).[14] Over the past decade, the most promising approach to sustainable and cheaper photocatalysts goes through the development of organic dyes (**PC.5** – **PC.9a**). Today, there are multiple dye families and many groups have focused on the tuning of their scaffolds to improve their photostability or modify their redox properties.[2f,h] For example, Eosin Y (**PC.5**), a member of the xanthene family, is commonly use in photoreductions, whereas 9-mesityl-10-methylacridiums ($MesAcr^+$, **PC.6**) and dicyanoanthracene (DCA, **PC.7**) are often used for excited state oxidations. Diarylketones, such as benzophenone (BP, **PC.8**), have been found highly efficient as HAT-photocatalysts. Finally, since 2017 the applications of aminated cyanoarenes have flourished, specifically 2,4,5,6-tetrakis-(*9H*-carbazol-9-yl) isophthalonitrile (4CzIPN, **PC.9a**). Originally developed as an OLED (organic light emitting diode),[15] it has one of the longest-lived excited states amidst commonly used photocatalysts

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[11] a. Sambiagio, C.; Noël, T. *Trends Chem.* **2020**, *2*, 92–106. b. Kayahan, E.; Jacobs, M.; Braeken, L.; Thomassen, L. C. J.; Kuhn, S.; Gerven, T. van; Leblebici, M. E. *Beilstein J. Org. Chem.* **2020**, *16*, 2484–2504.
[12] a. Bottecchia, C.; Noël, T. *Chem. – Eur. J.* **2019**, *25*, 26–42. b. Lechner, V. M.; Nappi, M.; Deneny, P. J.; Folliet, S.; Chu, J. C. K.; Gaunt, M. J. *Chem. Rev.* **2022**, *122*, 1752–1829.
[13] a. Liu, J.; Lu, L.; Wood, D.; Lin, S. *ACS Cent. Sci.* **2020**, *6*, 1317–1340. b. Tay, N. E. S.; Lehnherr, D.; Rovis, T. *Chem. Rev.* **2022**, *122*, 2487–2649.
[14] Minozzi, C.; Caron, A.; Grenier-Petel, J.; Santandrea, J.; Collins, S. K. *Angew. Chem. Int. Ed.* **2018**, *57*, 5477–5481.
[15] Uoyama, H.; Goushi, K.; Shizu, K.; Nomura, H.; Adachi, C. *Nature* **2012**, *492*, 234–238.

(5 µs). In addition, the HOMO (centred on the carbazoyl units) and LUMO (centred on the isophthalonitrile core) of 4CzIPN do not overlap, meaning that the excitation of this species results in a charge transfer from the carbazoles to the isophthalonitrile. This phenomenon is similar to the MLCT transitions of the organometallic photocatalysts,[16] and allows the same tuning strategies to be used for the redox potentials of the excited, oxidised, and reduced states of the photocatalyst,[17] but also the triplet energy for EnT type mechanisms.[18]

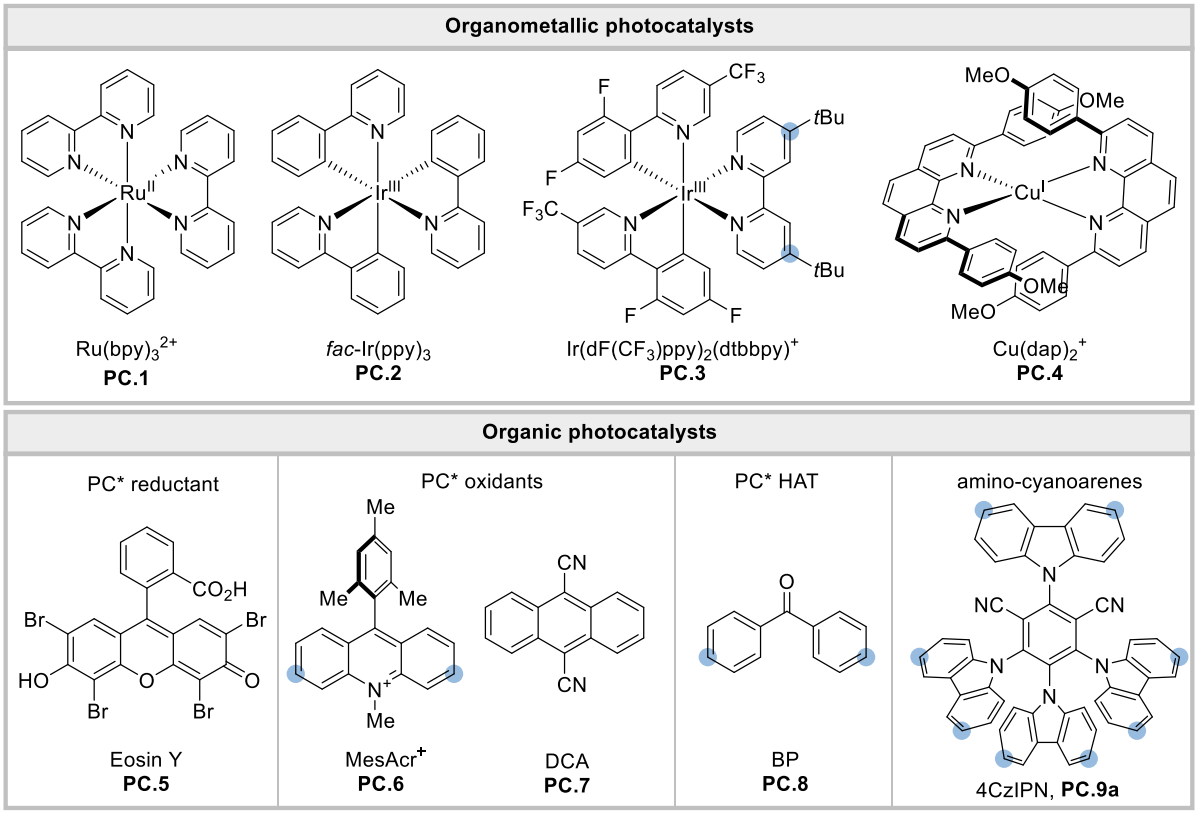


Figure 2.2. Common photocatalysts (highlighted in blue: common modification points, not exhaustive).

2.1.3. Photocatalyst-free strategies

In addition to the rapid development of photocatalytic strategies, particular attention has also been paid to strategies that do not use a photocatalyst. These strategies involve the direct photoexcitation of a single (or a pair of) substrate(s) or reactive intermediate(s).[19] One of the more traditional approaches is the direct excitation of individual reagents or substrates (Scheme 2.3, A1). Certain scaffolds (**Sub**) are prone to direct photoexcitation and can react in their excited state either directly with a partner (**R**), or after fragmentation to a free radical

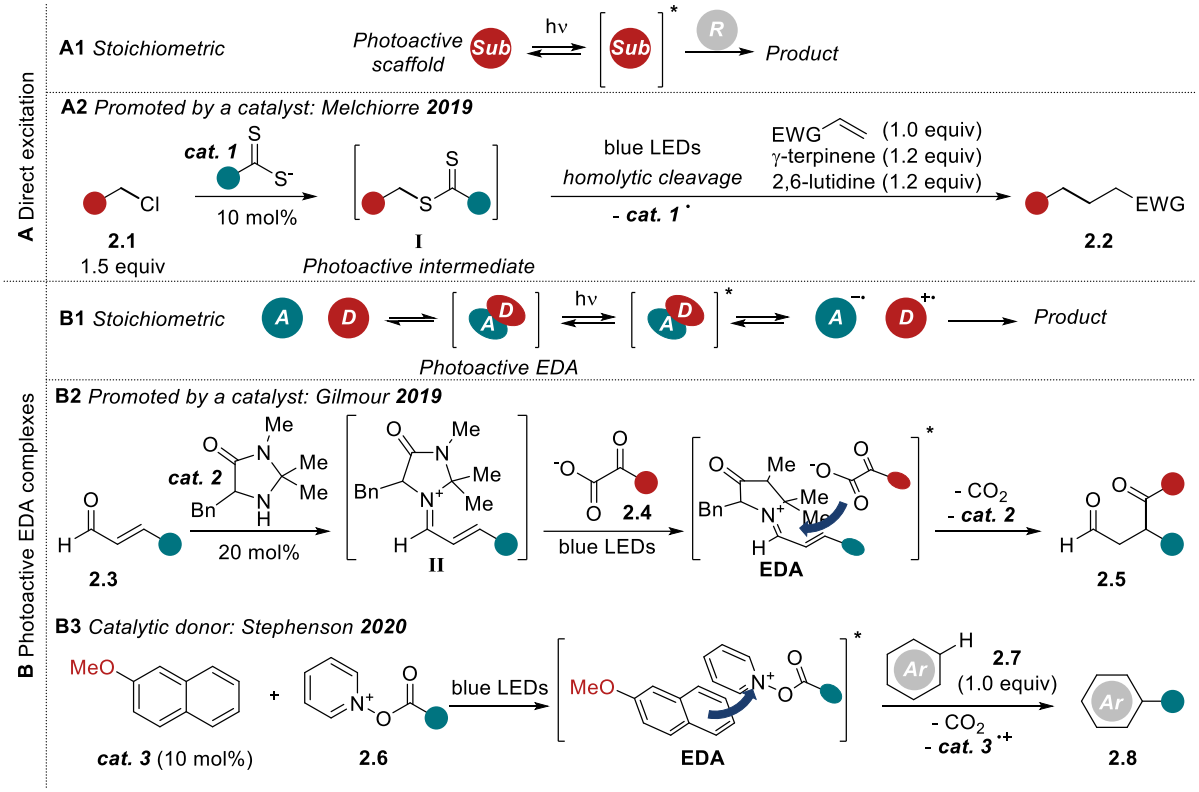
[16] Shang, T.-Y.; Lu, L.-H.; Cao, Z.; Liu, Y.; He, W.-M.; Yu, B. *Chem. Commun.* **2019**, *55*, 5408–5419.
[17] a. Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. *Chem. Sci.* **2018**, *9*, 5883–5889. b. Speckmeier, E.; Fischer, T. G.; Zeitler, K. *J. Am. Chem. Soc.* **2018**, *140*, 15353–15365. c. Garreau, M.; Le Vaillant, F.; Waser, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 8182–8186.
[18] Lu, J.; Pattengale, B.; Liu, Q.; Yang, S.; Shi, W.; Li, S.; Huang, J.; Zhang, J. *J. Am. Chem. Soc.* **2018**, *140*, 13719–13725.
[19] Wei, Y.; Zhou, Q.-Q.; Tan, F.; Lu, L.-Q.; Xiao, W.-J. *Synthesis* **2019**, *51*, 3021–3054.

species. Recently organocatalysts[20] have been combined with this approach.[21] In 2019, the Melchiorre group reported the dechloroalkylation of alkyl chloride with a nucleophilic organocatalyst (***cat. 1***, A2). Alkyl chlorides (**2.1**) are converted to the photoactive intermediate **I**. Under blue irradiation, the latter undergoes homolytic cleavage to an alkyl radical which can then be trapped by a Michael acceptor. The organocatalyst is regenerated in-situ along with the formation of the product (**2.2**) using γ-terpinene as a stoichiometric reductant. A second general approach involves photoactive electron donor acceptor complexes (EDAs, B1).[22] A photoactive EDA is composed of two molecules which, upon irradiation, transfer an electron from the donor (***D***) to the acceptor (***A***). This can lead to one or two free radical species which will then react further and ultimately deliver the desired product. In 2019, the Gilmour group reported the β-acylation of enals (**2.3**, B2) with α-ketoesters (**2.4**) in presence of an amine organocatalyst (***cat. 2***). **2.3** is converted to the iminium (**II**) which then forms an EDA complex with **2.4**. Following the electron transfer from **2.4** to **II**, decarboxylation affords an acyl radical which can then be alkylated by the enal derivative. This frees the organocatalyst ***cat. 2*** and delivers the final product **2.5**. Finally, Stephenson and co-workers reported a decarboxylative arylation starting from a pyridinium salt (**2.6**, B3) and electron poor aromatics (**2.7**) using 2-methoxynaphthalene (***cat. 3***) as a catalytic electron donor. In this case, a photoactive EDA forms between **2.6** and ***cat. 3*** and results in the reductive cleavage of **2.6** to an alkyl radical. The latter is trapped by an arene (**2.7**) which is then rearomatised to **2.8** by the oxidised ***cat. 3***$^{\bullet+}$.

[20] Book chapter: Holden, C. M.; Melchiorre, P. Photochemistry and Excited-State Reactivity of Organocatalytic Intermediates. In *Photochemistry*; Albini, A., Protti, S., Eds.; Royal Society of Chemistry: Cambridge, 2019; Vol. 47, pp 344–378.

[21] a. Mazzarella, D.; Crisenza, G. E. M.; Melchiorre, P. *J. Am. Chem. Soc.* **2018**, *140*, 8439–8443. b. Verrier, C.; Alandini, N.; Pezzetta, C.; Moliterno, M.; Buzzetti, L.; Hepburn, H. B.; Vega-Peñaloza, A.; Silvi, M.; Melchiorre, P. *ACS Catal.* **2018**, *8*, 1062–1066. c. Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem.* **2017**, *9*, 868–873. d. Schweitzer-Chaput, B.; Horwitz, M. A.; de Pedro Beato, E.; Melchiorre, P. *Nat. Chem.* **2019**, *11*, 129–135. e. Mazzarella, D.; Magagnano, G.; Schweitzer-Chaput, B.; Melchiorre, P. *ACS Catal.* **2019**, *9*, 5876–5880. f. Beato, E. de P.; Mazzarella, D.; Balletti, M.; Melchiorre, P. *Chem. Sci.* **2020**, *11*, 6312–6324.

[22] For a comprehensive review on photoactive EDA complexes: Crisenza, G. E. M.; Mazzarella, D.; Melchiorre, P. *J. Am. Chem. Soc.* **2020**, *142*, 5461–5476.



Scheme 2.3. Photocatalyst-free strategies for the generation of *C*-centred radicals.

2.1.4. Photocatalysed approaches for *C*-centred radical generation

The diversity of photocatalyst scaffolds and photomediated approaches have popularised the use of visible light as an energy source for the generation of radicals. This variety has brought particular attention on the formation of *C*-centred radicals. In addition to the complementary chemo- and regioselectivities, photocatalytic strategies have given easy access to C(sp^3) and C(sp^2) centred radicals.[2] Furthermore, the high energy of these intermediates can help circumvent steric effects allowing the synthesis of highly congested systems. In this paragraph, we will focus on the generation of *C*(sp^3)-centred radicals through redox active group fragmentation, atom abstraction, and from π-systems.

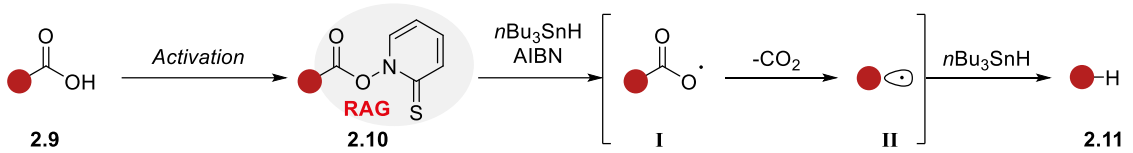
2.1.4.1. *C*(sp^3)-centred radicals from redox active group fragmentation

2.1.4.1.1. Overview

A very reliable way of generating a *C*-centred radical is through the fragmentation of a redox active group (RAG). In seminal works, decarboxylation had been used in the Kolbe electrolysis or the Hunsdiecker reaction.[23] Barton and co-workers, by their design of the Barton esters, illustrated further the concept of redox active group for selective activation in radical

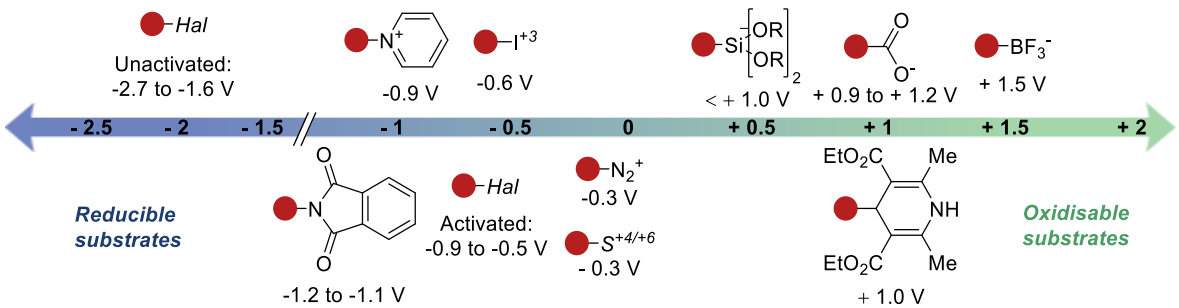
[23] a. Kolbe, H. *Ann. Chem. Pharm.* **1849**, *69*, 257–294. b. Vijh, A. K.; Conway, B. E. *Chem. Rev.* **1967**, *67*, 623–664. b. Hunsdiecker, H.; Hunsdiecker, Cl. *Ber. Dtsch. Chem. Ges. B Ser.* **1942**, *75*, 291–297.

decarboxylations (Scheme 2.4).[24] They initially chose thermal activation with tributyltin hydride and AIBN as an initiator for the reduction of the thiooxopyridinyl esters (**2.10**, obtained from the carboxylic acid **2.9**) to the hydrocarbon (**2.11**). They later found that the esters could undergo direct photoexcitation and fragmentation to the desired radical (**II**).[25]



Scheme 2.4. Reductive decarboxylation of thiooxopyridinyl esters.

Since this pioneering work, multiple RAGs have been used to generate *C*-centred radicals. Depending on the desired coupling partner, it is possible to chose substrates to oxidise such as carboxylates, dihydropyridines (DHP), trifluoroborates or silicates, and substrates to reduce such as *N*-phthalimidoyl esters, pyridiniums, halides, hypervalent iodine or sulfur species, or diazonium salts.[13b]



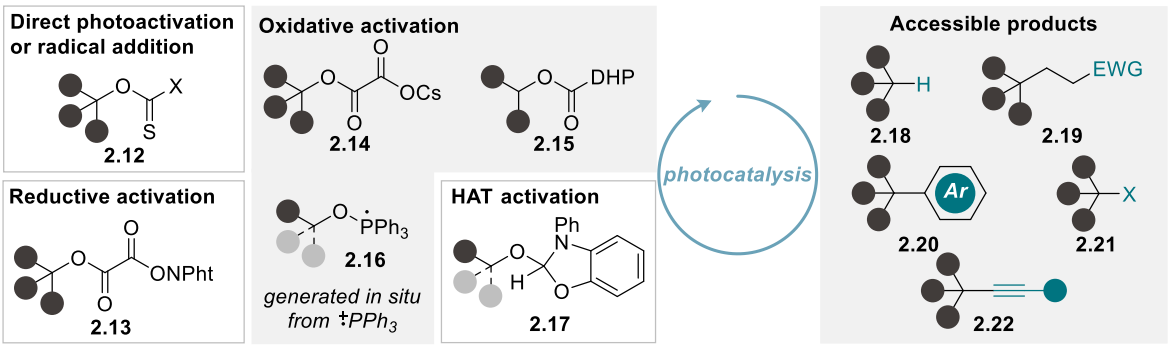
Scheme 2.5. Common RAGs for accessing *C*-centred radicals.

2.1.4.1.2. Alcohols as alkyl radical precursors

Due to the availability of alcohols, of late, they have attracted attention in refunctionalisation reactions. Multiple strategies have been applied allowing the generation of *C*-centred radicals from alcohols. Xanthates (Scheme 2.6, **2.12**) have been used in both direct excitation strategies and photoredox strategies. This has allowed the conversion of the alcohol to reduced and arylated products (**2.18** and **2.20**).[26] *N*-phthalimidoyl oxalates (**2.13**) can be reduced to the desired radical and have been used for alkylation (**2.19**) and alkynylation (**2.22**).[27] Oxalates, often cesium oxalates (**2.14**), can undergo oxidative fragmentation, and

[24] a. Barton, D. H. R.; Dowlatshahi, H. A.; Motherwell, W. B.; Villemin, D. *J. Chem. Soc. Chem. Commun.* **1980**, *15*, 732–733. b. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979–4982. c. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc. Chem. Commun.* **1983**, *17*, 939.
[25] Barton, D. H. R.; Ozbalik, N.; Schmitt, M. *Tetrahedron Lett.* **1989**, *30*, 3263–3266.
[26] a. Chenneberg, L.; Baralle, A.; Daniel, M.; Fensterbank, L.; Goddard, J.-P.; Ollivier, C. *Adv. Synth. Catal.* **2014**, *356*, 2756–2762. b. Vara, B. A.; Patel, N. R.; Molander, G. A. *ACS Catal.* **2017**, *7*, 3955–3959.
[27] a. Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342–15345. b. Gao, C.; Li, J.; Yu, J.; Yang, H.; Fu, H. *Chem. Commun.* **2016**, *52*, 7292–7294.

have been used for alkylation (**2.19**), arylation (**2.20**) and halogenation (**2.21**)[28] Recently DHP esters (**2.15**) have also been reported to undergo oxidative fragmentation for arylation (**2.20**).[29] In-situ activation of alcohols has also been performed with triphenyl phosphine which, after oxidation to the radical cation, can activate free alcohols through the formation of intermediate (**2.16**), this strategy has been essentially used for reduction but can also allow C-C bond formation.[30] Finally, HAT has been used to activate the NHC derivative **2.17** for the synthesis of arylated products (**2.20**).[31]



Scheme 2.6. Photomediated deoxyalkylation strategies.

2.1.4.2. *C*-centred radicals from atom abstraction

Another interesting approach for the generation of *C*-centred radicals is through the abstraction of an atom. The activation of C-H bonds is a longstanding goal in organic chemistry. In biological processes C-H activation often occurs through the abstraction of a hydrogen atom. For example, cytochrome P450 (CYP450), in presence of oxygen, can generate an iron-oxo intermediate capable of HAT.[32] More generally, atom abstraction only occurs for singly bonded atoms: hydrogens or halogens (Scheme 2.7). To perform a HAT an electrophilic radical is required (often *O*- or *N*-centred), and the BDE of the formed bond needs to be higher than the bond broken.[33] Inversely, performing a XAT (X atom transfer, X = halogen) requires a nucleophilic radical (such as an α-amino radical).[34] For HAT, many photocatalysts have been designed (generally of the diarylketone family). However, XAT, a more recent discovery, is performed with a trialkylamine combined with a photocatalyst.

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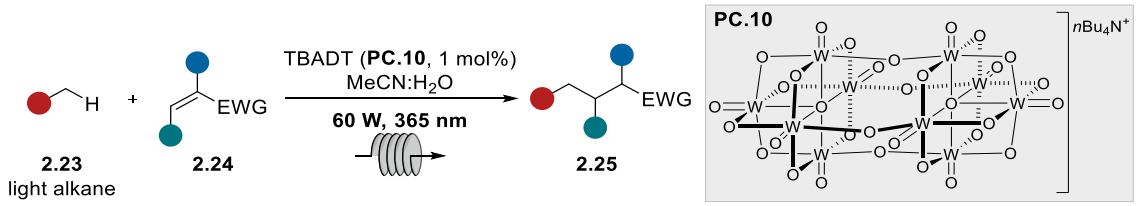
[28] a. Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273. b. Zhang, X.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 13862–13865. c. Abbas, S. Y.; Zhao, P.; Overman, L. E. *Org. Lett.* **2018**, *20*, 868–871. d. Su, J. Y.; Grünenfelder, D. C.; Takeuchi, K.; Reisman, S. E. *Org. Lett.* **2018**, *20*, 4912–4916.
[29] a. Wei, Y.; Ben-zvi, B.; Diao, T. *Angew. Chem. Int. Ed.* **2021**, *60*, 9433–9438. b. Wei, Y.; Lam, J.; Diao, T. *Chem. Sci.* **2021**, *12*, 11414–11419.
[30] Stache, E. E.; Ertel, A. B.; Rovis, T.; Doyle, A. G. *ACS Catal.* **2018**, *8*, 11134–11139.
[31] Dong, Z.; MacMillan, D. W. C. *Nature* **2021**, *598*, 451–456.
[32] P. B. Danielson. *Curr. Drug Metab.* **2002**, *3*, 561–597.
[33] a. Lai, W.; Li, C.; Chen, H.; Shaik, S. *Angew. Chem. Int. Ed.* **2012**, *51* (23), 5556–5578. b. Capaldo, L.; Ravelli, D.; Fagnoni, M. *Chem. Rev.* **2022**, *122*, 1875–1924. c. Chang, L.; An, Q.; Duan, L.; Feng, K.; Zuo, Z. *Chem. Rev.* **2022**, *122*, 2429–2486.
[34] Juliá, F.; Constantin, T.; Leonori, D. *Chem. Rev.* **2022**, *122*, 2292–2352.

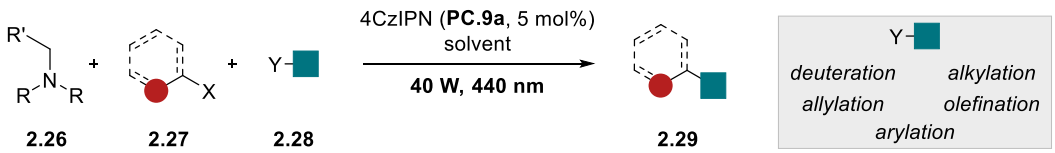
Scheme 2.7. Atom abstractions

In 2020, the Noel, Fagnoni and Sun groups collaborated towards a photocatalysed HAT functionalisation of light gaseous alkanes in flow (Scheme 2.8).[35] The excited state decatungstate (**PC.10***) performs a HAT on gaseous hydrocarbons (**2.23**), the resulting *C*-centred radical adds to the alkene (**2.24**) delivering the functionalised hydrocarbon (**2.25**).



Scheme 2.8. HAT functionalisation of gaseous alkanes

In 2020, Leonori and co-workers issued a general approach to halogen atom abstraction with α-amino radicals (Scheme 2.9).[36] Under blue LED irradiation **PC.9a*** oxidises the alkyl amine (**2.26**). Following deprotonation, the resulting *C*-centred radical abstracts a halogen (Br or I) from the substrate (**2.27**). Both C(sp^3) and C(sp^2) radicals can be generated with this strategy and successfully trapped by a radical trap (**2.28**) giving access to the final product (**2.29**). The intermediate radicals can undergo deuteration, Giese type additions, allylation, cobalt-mediated olefination and arylation.



Scheme 2.9. XAT functionalisation of alkyl and aryl halides

2.1.4.3. *C*-centred radicals from π-systems

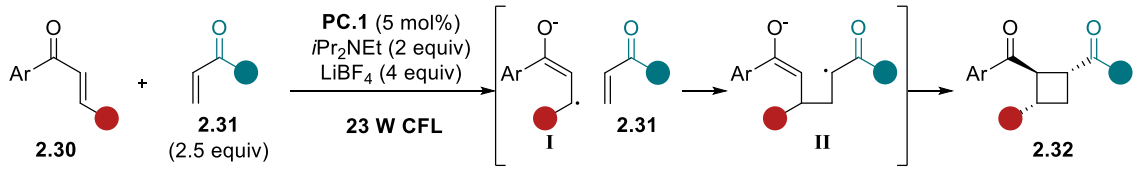
2.1.4.3.1. Radical additions to alkenes

A third strategy for the generation of *C*-centred radicals is through the addition of radicals to π-systems. Similarly to polar chemistry, the electronics of the alkene affect the type of radical it reacts with: (1) nucleophilic radicals, such as α-amino radicals, react well with electron-poor systems like Michael acceptors. (2) inversely, electrophilic radicals, for example, α-keto or trifluoromethyl radicals, prefer electron-rich systems like enamines, enamides, or enol ethers,

a. Radical addition to electron-poor alkenes

[35] Laudadio, G.; Deng, Y.; van der Wal, K.; Ravelli, D.; Nuño, M.; Fagnoni, M.; Guthrie, D.; Sun, Y.; Noël, T. *Science* **2020**, *369*, 92–96.
[36] Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Juliá, F.; Leonori, D. *Science* **2020**, *367*, 1021–1026.

The addition of a radical to an electron-poor alkene results in an electrophilic radical – such as an α-keto radical which is generally trapped by hydrogen atom or reduced and protonated. This strategy has been frequently used in alkynylation procedures with Michael acceptors as illustrated previously. In certain specific cases, the radical can in fact be intercepted to form a carbon-carbon bond (generally through a cyclisation process). This strategy was explored by the Yoon group in 2008 and 2009 for [2+2] cyclisations (Scheme 2.10).[37] Under irradiation by a CFL, they report the reduction of the aromatic enone (**2.30**) by the excited state photocatalyst (**PC.1***, $Ru(bpy)_3^{2+}$) to the intermediate **I**. This can now add to the unsubstituted enone (**2.31**) resulting in the α-keto radical **II**. The radical can then add intramolecularly to the enolate, which after oxidation affords the desired [2+2] product (**2.32**).



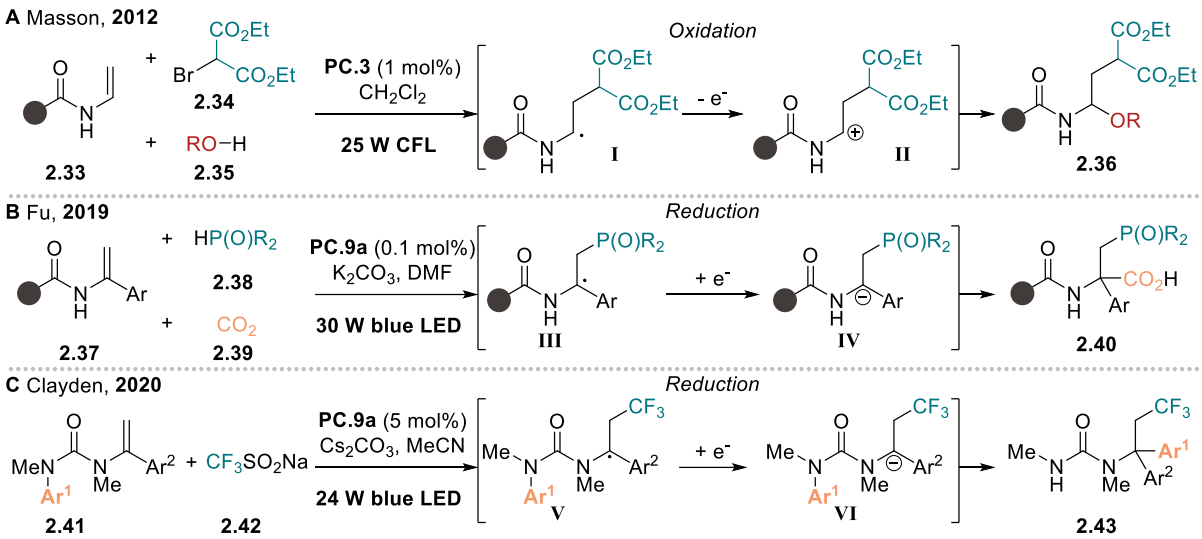
Scheme 2.10. Photocatalysed [2+2]-cycloaddition via radical addition to enones

b. Radical addition to electron-rich alkenes

When turning to electron-rich alkenes, enamides are substrates of choice: the mesomer donor effect of the amide polarises the bond to allow addition of electrophilic radicals to the β-position of the alkene. This addition results in an α-amino radical which can then be further functionalised.[38] In 2012, Courant and Masson reported a photocatalysed carboetherification of enamides and ene-carbamates (**2.33**, Scheme 2.11, A).[39] Under irradiation with a CFL, the bromomalonate (**2.34**) is reduced by the excited state photocatalyst (**PC.3***, $Ir(dF(CF_3)ppy)_2(dtbbpy)^+$) to the malonyl radical that could then add to the enamide (**2.33**). The ensuing α-amino radical (**I**) is then oxidised to the cation (**II**), then quenched with the alcohol (**2.35**) delivering the desired carboetherification product (**2.36**). This strategy has also been used with a trifluoromethyl radical source instead of the malonate (discussed in section 2.3.2.3.2. Photocatalysed SET reduction of λ3-iodanes). A variation to this type of photocatalysed enamide difunctionalisation is the reduction of the α-amino radical to form the final product.[40] In 2019, Fu and co-workers reported a phosphocarboxylation of enamide (**2.37**) with 4CzIPN (**PC.9a**) as a photocatalyst (B).[40a] Under blue LED irradiation, **PC.9a*** can oxidise the phosphine oxide (**2.38**) in presence of a base generating an electrophilic *P*-centred radical which can then add to **2.37**. The resulting α-amino radical (**III**) is then reduced to the anion

[37] a. Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887. b. Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604–14605.
[38] For a review: Courant, T.; Masson, G. *J. Org. Chem.* **2016**, *81*, 6945–6952.
[39] Courant, T.; Masson, G. *Chem. – Eur. J.* **2012**, *18*, 423–427.
[40] a. Fu, Q.; Bo, Z.-Y.; Ye, J.-H.; Ju, T.; Huang, H.; Liao, L.-L.; Yu, D.-G. *Nat. Commun.* **2019**, *10*, 3592. b. Abrams, R.; Clayden, J. *Angew. Chem. Int. Ed.* **2020**, *59*, 11600–11606.

(**IV**) and trapped by CO_2 to afford the desired difunctionalised product (**2.40**). This was later followed by a trifluoroarylation of vinyl-ureas (**2.41**) reported by Abrams and Clayden (C).[40b] Under blue LED irradiation the excited state photocatalyst (**PC.9a***) can oxidise **2.42** to generate a trifluoromethyl radical. The latter can then add to the vinyl-urea (**2.41**) generating an α-amino radical (**V**). The latter is reduced to the anion (**VI**) which then undergoes a Smiles-Truce rearrangement forming the trifluoroarylated product (**2.43**).



Scheme 2.11. Photocatalysed difunctionalisation of enamides and analogues by radical addition.

2.1.4.3.2. Activation of π-systems through oxidation or reduction

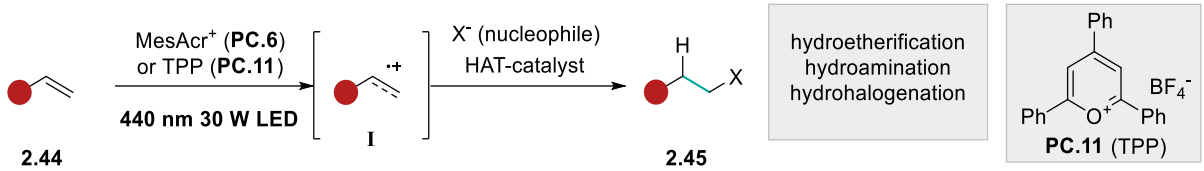
In addition to their reactivity with radicals π-systems can also undergo redox processes: (1) slightly electron-rich alkenes and arenes can undergo oxidation to radical cationic intermediates allowing them to react with nucleophiles, and (2) electron-poor π-systems such as imines, ketones, and enones can be reduced to the corresponding radical anionic intermediate, the latter can then fragment, undergo radical recombination, or protonation.

a. Oxidation

Since 2012, Nicewicz and co-workers have reported diverse hydrofunctionalisations of alkenes proceeding through the oxidation of the alkene (Scheme 2.12).[41] Under blue LED irradiation the excited state **PC.6*** (or **PC.11***) perform a single electron oxidation of the alkene (**2.44**). The resulting radical cation (**I**) is then trapped by an external nucleophile (*O*-, *N*-nucleophiles, or halides). The ensuing radical then abstracts a H-atom from the HAT-catalyst and afford the desired hydrofunctionalised product (**2.45**). In certain cases,

[41] Review article: a. Margrey, K. A.; Nicewicz, D. A. *Acc. Chem. Res.* **2016**, *49*, 1997–2006. For mechanistic studies: g. Romero, N. A.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 17024–17035.

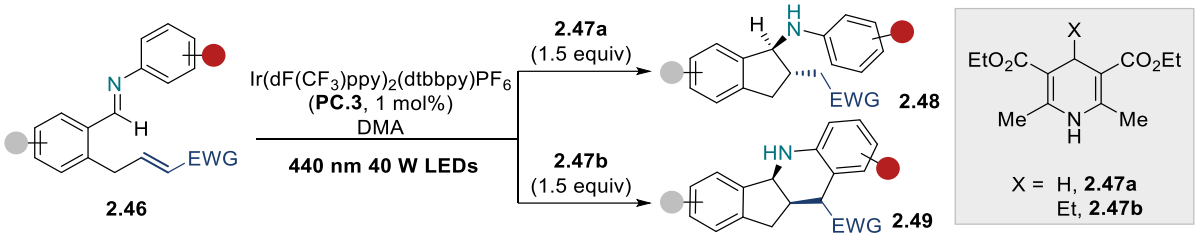
tandem 5-exo-trig cyclisation could also be combined to give a variety of heterocycles.[42] The anti-Markovnikov regioselectivity of these radical cations was first described by Arnold and co-workers, they propose that the radical cation will first undergo quenching by a nucleophile generating the most stable radical then radical quenching.[43]



Scheme 2.12. Photocatalysed hydrofunctionalisation of alkenes via alkenyl radical cations.

b. Reduction

In 2021, Dixon and co-workers reported a single electron reduction of aromatic imines (**2.46**) under blue LED irradiation (Scheme 2.13).[44] In presence of the photocatalyst (**PC.3***) and Hantzsch ester (**2.47a**), the aromatic imine (**2.46**) can be reduced to the α-amino radical, which can then cyclise to the desired product **2.48**. Interestingly, in presence of **2.47b** a second cyclisation occurs delivering the tricyclic product (**2.49**).



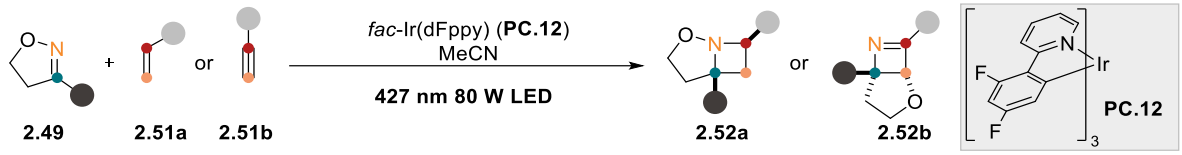
Scheme 2.13. Photocatalysed imine reduction for the generation of α-amino radicals for divergent cyclisations.

2.1.4.3.3. Energy transfer

Finally, *C*-centred radicals can also be generated from π-systems using an EnT approach. Traditionally used for alkene isomerisation or [2+2] cyclobutene synthesis,[45] this approach was extended to photomediated azetidine and azetine synthesis by the Schindler group in 2020 and 2021 (Scheme 2.14).[46] A carefully selected photocatalyst (**PC.12**) under blue LED

[42] a. Grandjean, J.-M. M.; Nicewicz, D. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 3967–3971. b. Zeller, M. A.; Riener, M.; Nicewicz, D. A. *Org. Lett.* **2014**, *16*, 4810–4813. c. Cavanaugh, C. L.; Nicewicz, D. A. *Org. Lett.* **2015**, *17*, 6082–6085. d. Gesmundo, N. J.; Grandjean, J.-M. M.; Nicewicz, D. A. *Org. Lett.* **2015**, *17*, 1316–1319.
[43] a. Arnold, D. R.; Du, X. *J. Am. Chem. Soc.* **1989**, *111*, 7666–7667. b. Arnold, D. R.; Chan, M. S. W.; McManus, K. A. *Can. J. Chem.* **1996**, *74*, 2143–2166. c. Mangion, D.; Arnold, D. R. *Acc. Chem. Res.* **2002**, *35*, 297–304.
[44] Maitland, J. A. P.; Leitch, J. A.; Yamazaki, K.; Christensen, K. E.; Cassar, D. J.; Hamlin, T. A.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2021**, *60*, 24116–24123.
[45] a. Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. *Chem. Soc. Rev.* **2018**, *47*, 7190–7202. b. Zhou, Q.-Q.; Zou, Y.-Q.; Lu, L.-Q.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2019**, *58*, 1586–1604.
[46] a. Becker, M. R.; Wearing, E. R.; Schindler, C. S. *Nat. Chem.* **2020**, *12*, 898–905. b. Wearing, E. R.; Blackmun, D. E.; Becker, M. R.; Schindler, C. S. *J. Am. Chem. Soc.* **2021**, *143*, 16235–16242.

irradiation could generate the triplet state of **2.50** which could then react with either an alkene (**2.51a**) to form the azetidine (**2.52a**) or an alkyne (**2.51b**) which resulted in the azetine (**2.52b**).



Scheme 2.14. Photocatalysed azetidine and azetine synthesis via the triplet sensitisation of isoxazolines.

2.1.5. Photochemistry – conclusive remarks

Over the past decades, photoredox chemistry helped develop the area of catalytic and non-catalytic photomediated transformations. As presented prior in this section, photochemical strategies are highly valuable for the generation of *C*-centred radicals. The current diversity of approaches to photocatalysis (energy transfer, electron transfer, and atom transfer) enables the activation of a variety of functional groups allowing deoxygenation, decarboxylation, deamination, dehalogenation, and the functionalisation of C-H bonds. When combined with the chemo- and regioselectivities (e.g. Markovnikov vs anti-Markovnikov regioselectivity) that radical chemistry provides, photochemistry can be considered as a highly valuable tool for the organic chemist when regarding the design of new transformations. In the following section of this chapter, we will discuss the synthesis and application of alkynes with a focus on the alkynylation of radicals.

2.2. Alkynes: reactivity and synthesis

2.2.1. Importance of alkynes

2.2.1.1. Alkyne-containing bioactive compounds

Alkynes are highly relevant structural motifs in medicinal chemistry (Figure 2.3).[47] One of the drugs for the treatment of mantle cell lymphoma is the ynone Acalabrutinib (**2.53**).[48] Tazarotene (**2.54**), a diaryl alkyne is used for the treatment of acne and psoriasis.[49] Turning to aliphatic alkynes and, in particular the propargyl motif, Efavirenz (**2.55**) has proven successful as an anti-HIV treatment,[50] oxybutynin (**2.56**) aides the treatment of overactive bladder syndrome,[51] and levonorgestrel (**2.57**) is one of the few contragestive drugs and is used as an emergency contraceptive.[52]

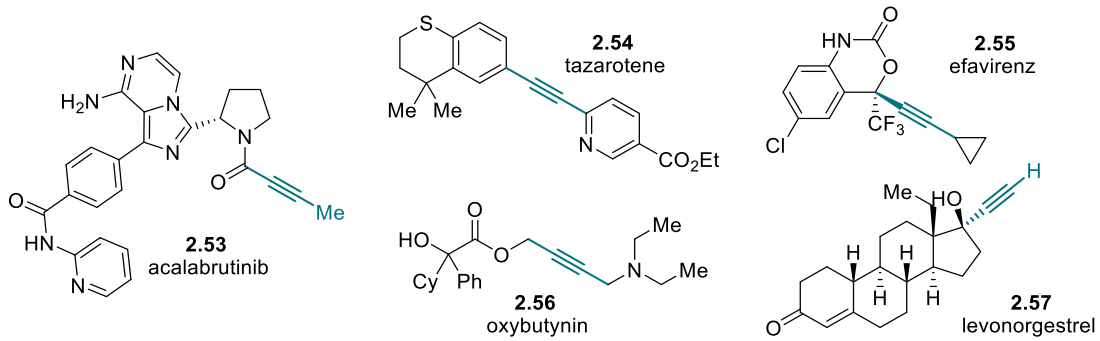


Figure 2.3. Examples of approved drugs containing aliphatic and internal alkynes.

In addition to medicinal chemistry, materials science values the alkyne for its unique rigidity and, therefore, its effect on a material's structure and physical properties.[53] These structural

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[47] Talele, T. T. *J. Med. Chem.* **2020**, *63*, 5625–5663.

[48] a. Barf, T. a; Jans, C. G. J. M.; Man, D. A. P. A.; Oubrie, A. a; Raaijmakers, H. C. a; Rewinkel, J. B. M.; Sterrenburg, J.-G.; Wijkmans, J. C. H. M. WO2013010868 (A1), January 24, **2013**. b. Budideti, S. R.; Konduri, S. K. M.; Sanapureddy, J. M. R.; Remella, R. K.; Thoota, S. K.; Kothamunireddygari, S.; Muddasani, P. R.; Nannapaneni, V. C. WO2021111465 (A1), June 10, **2021**. c. Barf, T.; Covey, T.; Izumi, R.; Kar, B. van de; Gulrajani, M.; Lith, B. van; Hoek, M. van; Zwart, E. de; Mittag, D.; Demont, D.; Verkaik, S.; Krantz, F.; Pearson, P. G.; Ulrich, R.; Kaptein, A. *J. Pharmacol. Exp. Ther.* **2017**, *363*, 240–252. d. Wang, M.; Rule, S.; Zinzani, P. L.; Goy, A.; Casasnovas, O.; Smith, S. D.; Damaj, G.; Doorduijn, J. K.; Lamy, T.; Morschhauser, F.; Panizo, C.; Shah, B.; Davies, A.; Eek, R.; Dupuis, J.; Jacobsen, E.; Kater, A. P.; Le Gouill, S.; Oberic, L.; Robak, T.; Jain, P.; Frigault, M. M.; Izumi, R.; Nguyen, D.; Patel, P.; Yin, M.; Długosz-Danecka, M. *Leukemia* **2019**, *33*, 2762–2766.

[49] a. Chandraratna, R. A. S. US5089509 (A), February 18, **1992**. b. Thacher, S. M.; Standeven, A. M.; Athanikar, J.; Kopper, S.; Castilleja, O.; Escobar, M.; Beard, R. L.; Chandraratna, R. A. S. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 528–534.

[50] a. Young, S. D.; Tran, L. O.; Britcher, S. F.; Lumma, W. C. J.; Payne, L. S. Benzoxazinones as Inhibitors of HIV Reverse Transcriptase. EP0582455 (A1), February 9, 1994. b. Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S. *Antimicrob. Agents Chemother.* **1995**.

[51] a. Lish, P. M.; Labudde, J. A.; Peters, E. L.; Robbins, S. I. *Arch. Int. Pharmacodyn. Ther.* **1965**, *156*, 467–488. b. Majewski, R. F.; Campbell, K. N.; Dykstra, S.; Covington, R.; Simms, J. C. *J. Med. Chem.* **1965**, *8*, 719–720.

[52] a. Ho, P. C.; Kwan, M. S. W. *Hum. Reprod.* **1993**, *8*, 389–392. b. Task Force on Postovulatory Methods of Fertility Regulation: World Health Organization. *The Lancet* **1998**, *352*, 428–433. c. Zadbuke, S. A.; Mehare, K. G.; Godbole, H. M.; Singh, G. P. An Improved Process for Preparation of Levonorgestrel. WO2012110947A1, August 23, **2012**.

[53] a. *Acetylene Chemistry: Chemistry, Biology, and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim; [Great Britain], 2005. b. Kijima, M. Polyyne-Type Materials. In *Polyynes*; CRC Press, 2005.

properties have also been applied in chemical biology with peptide stapling[54] and the intrinsic reactivity of the alkyne has opened the door to labelling by the means of the azide-alkyne click reaction.[55]

2.2.1.2. Alkyne occurrence in natural products

Alkynes are also found in natural products such as the caryoynencins (Figure 2.4, **2.58**), a member of the polyyne class,[56] or the ene-yne-ene biscongnienyne B (**2.59**).[57] A variety of peptidic molecules have also been isolated with the incorporation of an alkyne such as dragomabin A (**2.60**), which has antimalarial bioactivity.[58]

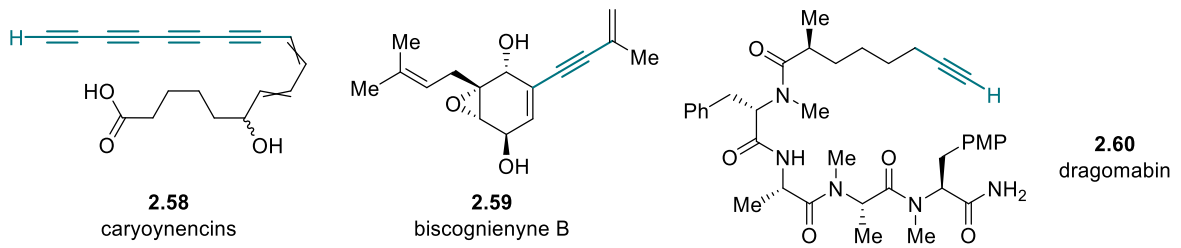

Figure 2.4. Examples of naturally occurring alkynes

2.2.1.3. Reactivity of alkynes

In addition to their intrinsic structural properties, alkynes can be subjected to a broad panel of transformations. They are relatively stable allowing them to be well tolerated in reactions involving thermal or photochemical activation. Due to the higher energy of the π-orbital, they can also undergo selective activation (Scheme 2.15). Common reactions include: (a) stereoselective reductions to either (*Z*) or (*E*) alkenes, (b) *cis*- or *trans*- metalation with organometallic intermediates,[59] (c) metathesis with alkynes and alkenes,[60] (d) Lewis acid activation allowing nucleophile incorporation,[61] and finally, (e) (2+3), [2+4], or [2+2+2] cyclisations.[62]

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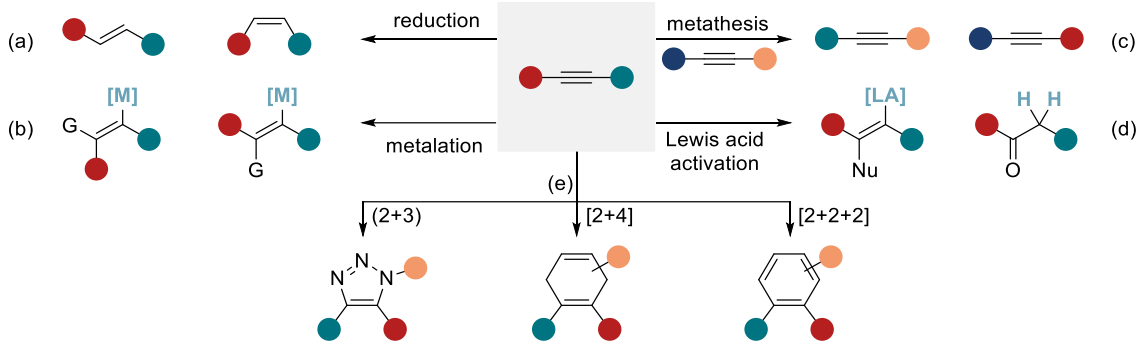
[54] Ceballos, J.; Grinhagena, E.; Sangouard, G.; Heinis, C.; Waser, J. *Angew. Chem. Int. Ed.* **2021**, *60*, 9022–9031.
[55] Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905–4979.
[56] a. Kusumi, T.; Ohtani, I.; Nishiyama, K.; Kakisawa, H. *Tetrahedron Lett.* **1987**, *28*, 3981–3984. b. Li, X.; Lv, J.-M.; Hu, D.; Abe, I. *RSC Chem. Biol.* **2021**, *2*, 166–180.
[57] Lv, J.-M.; Gao, Y.-H.; Zhao, H.; Awakawa, T.; Liu, L.; Chen, G.-D.; Yao, X.-S.; Hu, D.; Abe, I.; Gao, H. *Angew. Chem. Int. Ed.* **2020**, *59*, 13531–13536.
[58] a. McPhail, K. L.; Correa, J.; Linington, R. G.; González, J.; Ortega-Barría, E.; Capson, T. L.; Gerwick, W. H. *J. Nat. Prod.* **2007**, *70*, 984–988. b. Chai, Q.-Y.; Yang, Z.; Lin, H.-W.; Han, B.-N. *Mar. Drugs* **2016**, *14*, 216.
[59] Knochel, P. Carbometallation of Alkenes and Alkynes. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; pp 865–911.
[60] Fürstner, A. *J. Am. Chem. Soc.* **2021**, *143*, 15538–15555.
[61] Brenzovich Jr., W. E. *Angew. Chem. Int. Ed.* **2012**, *51*, 8933–8935.
[62] a. Regioselective Syntheses of Polysubstituted Benzenes Catalyzed by Transition Metal Complexes. In *Alkynes in Cycloadditions*; John Wiley & Sons, Ltd, 2013; pp 5–105. b. Selected Cycloaddition and Heterocyclization Reactions with Unusual Acetylenic and Allenic Starting Compounds. In *Alkynes in Cycloadditions*; John Wiley & Sons, Ltd, 2013; pp 233–247.

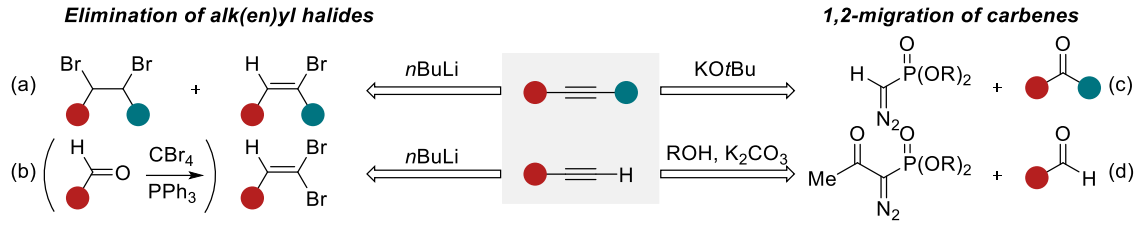


Scheme 2.15. Possible reaction pathways for alkynes.

2.2.2. Traditional alkynylation approaches

2.2.2.1. Alkyne construction

When turning to the synthesis of alkynes there are several possible strategies. One of the earliest approaches is the construction of the alkyne (Scheme 2.16). This can occur through the elimination of halogen groups (a). A specific example of this is the Corey-Fuchs reaction (b),[63] starting from an aldehyde, carbon tetrabromide in presence of triphenyl phosphine affords a *gem*-dibromoalkene which, upon treatment with *n*BuLi, provides the desired terminal alkyne. A second general approach consists in generating an alkenyl-carbene of which one of the substituents can undergo 1,2-migration resulting in the desired alkyne. This was first illustrated by Seyferth and Gilbert, later, Bestmann and Ohira proposed a modification allowing milder conditions.[64] Both approaches start from a carbonyl species and a diazophosphonate. Under the Seyferth-Gilbert conditions a strong base and ketones are required, allowing the synthesis of internal alkynes (c). The Ohira-Bestmann conditions allow milder activation with a nucleophilic alcohol and a carbonate base and extends this approach to aldehydes for the synthesis of terminal alkynes (d).



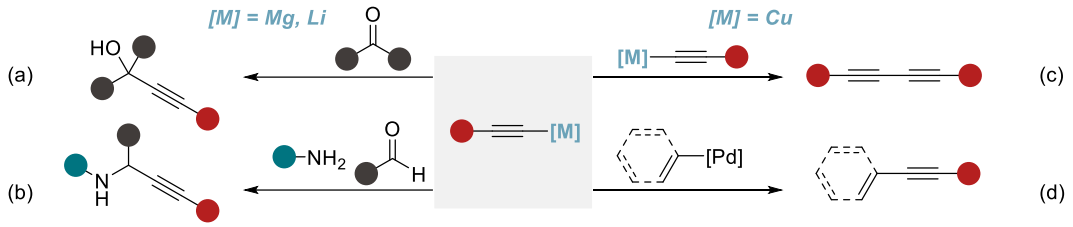
Scheme 2.16. Alkyne construction through elimination and carbene rearrangement

[63] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.
[64] a. Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379–1386. b. Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837–1845. c. Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *1996*, 521–522.

2.2.2.2. Alkyne transfer

2.2.2.2.1. Nucleophilic alkynylation

A second approach to the synthesis of alkynes exploits their nucleophilic character (Scheme 2.17). Acetylides can be easily obtained by deprotonation (pKa ≈ 29 in DMSO) and present good reactivity with carbonyls (a),[65] imines – as in the A^3 coupling reaction (b),[66] or with other organometallic species in the context of cross-coupling reactions (c and d). In 1869, Glaser discovered that free alkynes could undergo dimerisation in presence of copper.[67] Later, the works of Cadiot and Chodkiewicz demonstrated that a similar coupling could be performed by using a free-alkyne and an alkynyl halide in presence of copper, giving access to asymmetrical diynes.[68] Finally, Sonogashira and co-workers found that aryl-palladium species could react with copper acetylides and enabled the formation of C(sp^2)-C(sp) bonds.[69] To date, the Sonogashira coupling is one of the most commonly used strategies for the introduction of an alkyne to a molecule.



Scheme 2.17. Nucleophilic alkyne transfer with acetylides.

2.2.2.2.2. Electrophilic alkynylation

Over the past decades, organic chemists have investigated the *Umpolung* of reactivity.[70] In the case of the alkyne this consists in introducing an electron-withdrawing leaving group at an extremity of the alkyne. This had led to the use of alkynyl halides, alkynyl sulfones and hypervalent iodine reagents (Table 2.1).[71] Specifically, alkynyl halides enable the alkynylation of *C*(sp^3)- and *N*-nucleophiles. Alkynyl sulfones have been applied for the alkynylation of both *C*(sp^3)- and C(sp^2)-nucleophiles. Although alkynyl iodides are rarely used due to their instability, their oxidised counter-parts: iodonium salts or ethynylbenziodoxolones (EBXs)

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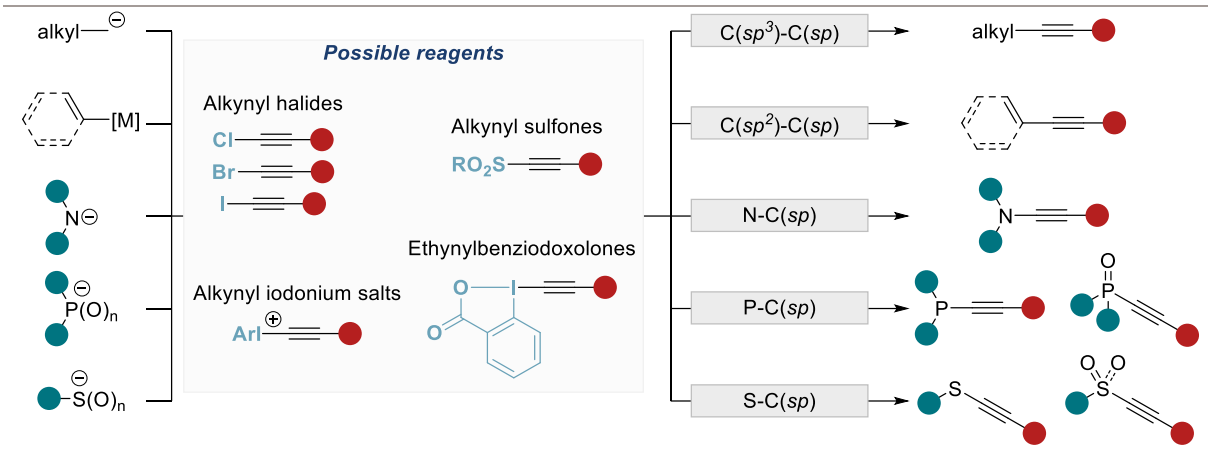
[65] a. Favorskii, A.E. *Zhurnal Russkago Fiziko-Khimicheskago Obshchestva*, **1905**, *37*, 643–645. b. Favorskii, A.E. *Bull. Soc. Chim. France* **1907**, *2*, 1087–1088.
[66] For reviews: a. Yoo, W.-J.; Zhao, L.; Li, C.-J. *Aldrichimica Acta* **2011**, *44*, 43–51. b. Peshkov, V. A.; Pereshivko, O. P.; Eycken, E. V. V. der. *Chem. Soc. Rev.* **2012**, *41*, 3790–3807. c. Jesin, I.; Nandi, G. C. *Eur. J. Org. Chem.* **2019**, *2019*, 2704–2720.
[67] a. Glaser, C. *Berichte Dtsch. Chem. Ges.* **1869**, *2*, 422–424. b. Glaser, C. *Justus Liebigs Ann. Chem.* **1870**, *154*, 137–171.
[68] a. Chodkiewicz, W. *Ann. Chim. Paris* **1957**, *2*, 819-869. b. Cadiot, P.; Chodkiewicz, W. *In* Chemistry of Acetylenes; Viehe, H. G., Ed.; Marcel Dekker: New York, **1969**, pp 597-647
[69] a. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470. b. Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46–49.
[70] Concept introduced by: Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258.
[71] Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165–4179.

have been frequently used in the alkynylation of both heteroatom-based nucleophiles and *C*(*sp*^{3})- or *C*(*sp*^{2})-nucleophiles.

Table 2.1. Electrophilic alkynylation of *C*-, *N*-, *P*- and *S*-nucleophile with electrophilic alkynylation reagents.



Alkyne source	C(*sp*^{3})-C(*sp*)	C(*sp*^{2})-C(*sp*)	N-C(*sp*)	P-C(*sp*)	S-C(*sp*)
Alkynyl halides	Yes	-	Yes	-	-
Alkynyl sulfones	Yes	Yes	-	-	-
Alkynyl iodonium salts	Yes	Yes	Yes	Yes	Yes
EBXs	Yes	Yes	Yes	Yes	Yes

2.2.3. Alkynylation of radicals

A final strategy for the synthesis of alkynylated compounds proceeds through the alkynylation of radicals.[72] Unlike *C*(*sp*^{3})- and *C*(*sp*^{2})-centred radicals the *C*(*sp*)-radical remains elusive. A seminal report from 1969 suggests that irradiation of phenylethynyl iodide could generate alkynyl radicals.[73] This method highlighted the potential photoactivation and reactivity of alkynyl iodides as a proof of concept. Since this report, the alkynyl radical has been poorly supported as an intermediate in organic chemistry as it is too energetic, although it has attracted some attention in physical chemistry.[74] The BDE of the C(*sp*)-H bond is calculated to be ca. 550 kJ.mol^{-1},[75] almost 100 kJ.mol^{-1} stronger than an O-H bond. This suggests that in the context of organic chemistry (generally in a solvent with a reactive partner and therefore in presence of many weaker C-H bonds) the use of an alkynyl radical for a functionalisation may be difficult to perform and control. Hence, most radical alkynylation strategies proceed

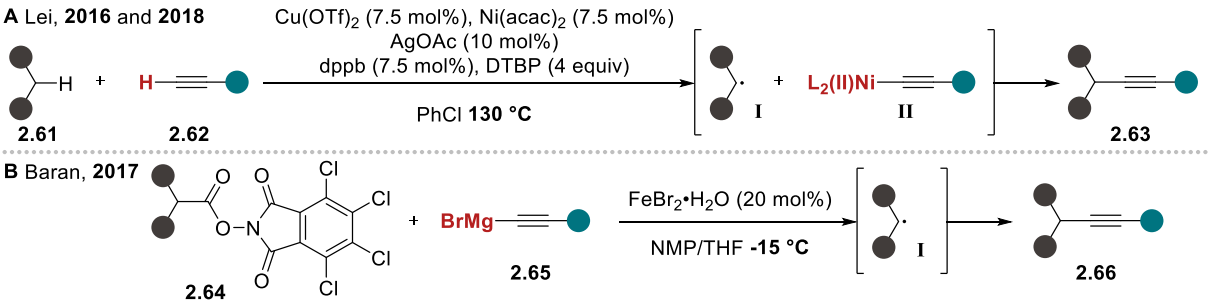
[72] Le Vaillant, F.; Waser, J. *Chem. Sci.* **2019**, *10*, 8909–8923.
[73] Martelli, G.; Spagnolo, P.; Tiecco, M. *J. Chem. Soc. Chem. Commun.* **1969**, No. 6, 282b–2283.
[74] a. Kaiser, R. I. *Chem. Rev.* **2002**, *102*, 1309–1358. b. Wheeler, S. E.; Robertson, K. A.; Allen, W. D.; Schaefer; Bomble, Y. J.; Stanton, J. F. *J. Phys. Chem. A* **2007**, *111*, 3819–3830. c. Crider, P. E.; Castiglioni, L.; Kautzman, K. E.; Neumark, D. M. *J. Chem. Phys.* **2009**, *130*, 044310.
[75] Reported between 130 and 135 kcal.mol^{-1} (1 kcal.mol^{-1} ≈ 4.1 kJ.mol^{-1}) in: a. Ervin, K. M.; Gronert, S.; Barlow, S. E.; Gilles, M. K.; Harrison, A. G.; Bierbaum, V. M.; DePuy, C. H.; Lineberger, W. C.; Ellison, G. B. *J. Am. Chem. Soc.* **1990**, *112*, 5750–5759. b. Bauschlicher, C. W.; Langhoff, S. R. *Chem. Phys. Lett.* **1992**, *193*, 380–385. c. Robinson, M. S.; Polak, M. L.; Bierbaum, V. M.; DePuy, C. H.; Lineberger, W. C. *J. Am. Chem. Soc.* **1995**, *117*, 6766–6778.

through the alkynylation of radicals rather than the generation of an alkynyl radical. Similarly to electrophilic alkynylation, various alkyne sources have been used: (1) free-alkynes, alkynyl halides and alkynyl silanes in combination with a transition metal, (2) alkynyl sulfones and (3) alkynyl hypervalent iodine species. Finally, the activation of propargylic alcohols under radical conditions can lead to an intramolecular alkyne migration from the α-oxo position to an alkene.

2.2.3.1. Alkynylation of radicals with metal acetylides

2.2.3.1.1. Organometallic redox strategies

In 2016 and 2018, the Lei group reported a multimetallic system for the alkynylation of alkyl radicals (Scheme 2.18, A).[76] Their strategy relies on the generation of an alkyl radical (**I**) from an alkane (**2.61**) with di(*tert*-butyl)peroxide (DTBP). **I** can then react with the in-situ generated Ni(II)acetylide (**II**) to form the desired alkyne (**2.63**). In 2017, the Weix and Baran groups both independently reported a decarboxylative alkynylation using similar multimetallic systems. In the report by the Baran group (B), they found that the perchloro *N*-phthalimidoyl esters (**2.64**) could generate alkyl radicals (**I**) and iron catalysis with magnesium acetylides (**2.65**) could furnish the desired internal alkynes (**2.66**).[77]



Scheme 2.18. Alkynylation of radicals with transition metal acetylides.

Over the past years copper acetylides have been frequently used for the radical difunctionalisation of alkenes.[78] Specifically, the Liu group has illustrated the powerful combination of alkynylsiloxanes and copper for asymmetric radical alkynylation (Scheme 2.19).[79] They report the difunctionalisation of styrenes (**2.67**) with **HIR.1** as a trifluoromethyl radical source and **2.68** as an alkyne source for the formation of products **2.70**.

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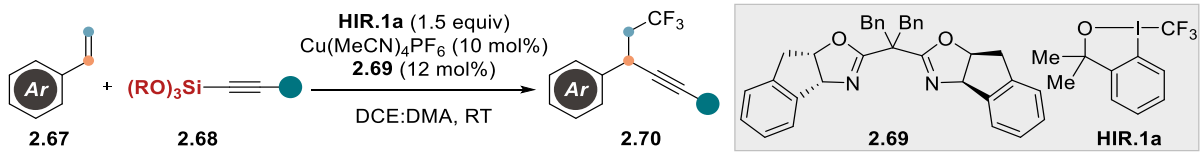
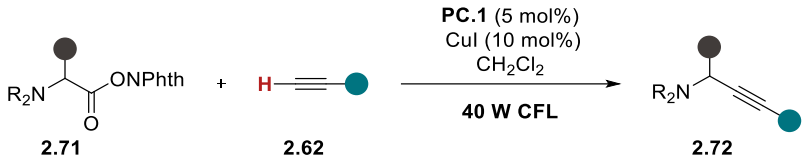
[76] a. Tang, S.; Wang, P.; Li, H.; Lei, A. *Nat. Commun.* **2016**, *7*, 11676. b. Tang, S.; Liu, Y.; Gao, X.; Wang, P.; Huang, P.; Lei, A. *J. Am. Chem. Soc.* **2018**, *140*, 6006–6013.
[77] a. Smith, J. M.; Qin, T.; Merchant, R. R.; Edwards, J. T.; Malins, L. R.; Liu, Z.; Che, G.; Shen, Z.; Shaw, S. A.; Eastgate, M. D.; Baran, P. S. *Angew. Chem. Int. Ed.* **2017**, *56*, 11906–11910. b. Huang, L.; Olivares, A. M.; Weix, D. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 11901–11905.
[78] a. Zhou, S.; Song, T.; Chen, H.; Liu, Z.; Shen, H.; Li, C. *Org. Lett.* **2017**, *19*, 698–701. b. Zhang, Y.; Zhang, D. *J. Org. Chem.* **2020**, *85*, 3213–3223. c. Hu, Z.; Fu, L.; Chen, P.; Cao, W.; Liu, G. *Org. Lett.* **2021**, *23*, 129–134.
[79] a. Fu, L.; Zhou, S.; Wan, X.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2018**, *140*, 10965–10969. b. Fu, L.; Zhang, Z.; Chen, P.; Lin, Z.; Liu, G. *J. Am. Chem. Soc.* **2020**, *142*, 12493–12500.



Scheme 2.19. Alkynylsiloxanes for radical difunctionalisation of alkenes using copper catalysis.

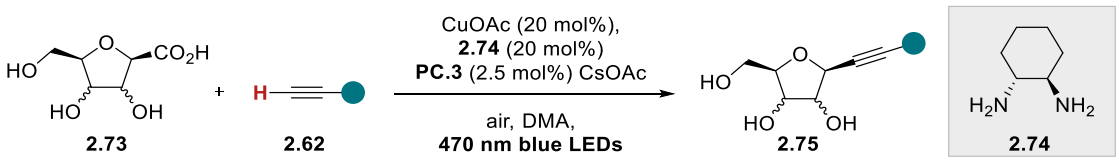
2.2.3.1.2. Photomediated strategies

Under photoredox catalysis, the Fu group reported the decarboxylative alkynylation of *N*-phthalimidoyl esters (**2.71**) with **PC.1** ($Ru(bpy)_3^{2+}$, Scheme 2.20).[80] Their strategy used free-alkynes (**2.63**) with copper iodide to give access to a variety of propargylic amines (**2.72**).



Scheme 2.20. Photocatalysed and copper catalysed decarboxylative alkynylation using free alkynes.

A more recent example of photoredox catalysis combined with copper acetylides is the decarboxylative synthesis of *C*-furanosides from Zhu and Messaoudi (Scheme 2.21).[81] Under blue LED irradiation, they could perform the oxidative decarboxylation of the furanoside (**2.73**) by the excited state photocatalyst **PC.3*** ($Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$), the resulting anomeric radical is then trapped by a Cu(II) acetylide formed in-situ from **2.62** and the active copper complex. Reductive elimination affords the alkynyl-furanoside **2.75**.



Scheme 2.21. Photomediated and copper-catalysed diastereoselective decarboxylative alkynylation of furanosides with free alkynes.

Finally, the direct photoexcitation of copper acetylides has been reported. In this regard, under light irradiation the Sonogashira cross-coupling can be performed with only copper catalysis (no palladium nor photocatalyst) and the Glaser coupling has been extended to heterocoupling.[82] In 2020, Mao and co-workers decided to investigate this phenomenon in the context of a decarboxylative alkynylation (Scheme 2.22).[83] Under irradiation at 460 nm, an excited state Cu(I)-acetylide-triethylamine complex can reduce the phthalimidoyl ester **2.76**,

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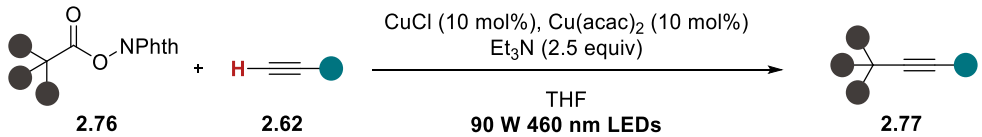
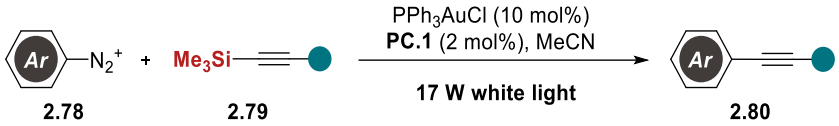
[80] Zhang, H.; Zhang, P.; Jiang, M.; Yang, H.; Fu, H. *Org. Lett.* **2017**, *19*, 1016–1019.
[81] Zhu, M.; Messaoudi, S. *ACS Catal.* **2021**, *11*, 6334–6342.
[82] a. Sagadevan, A.; Hwang, K. C. *Adv. Synth. Catal.* **2012**, *354*, 3421–3427. b. Sagadevan, A.; Lyu, P.-C.; Hwang, K. C. *Green Chem.* **2016**, *18*, 4526–4530. c. Sagadevan, A.; Charpe, V. P.; Hwang, K. C. *Catal. Sci. Technol.* **2016**, *6*, 7688–7692.
[83] a. Hazra, A.; Lee, M. T.; Chiu, J. F.; Lalic, G. *Angew. Chem.* **2018**, *130*, 5590–5594. b. Mao, Y.; Zhao, W.; Lu, S.; Yu, L.; Wang, Y.; Liang, Y.; Ni, S.; Pan, Y. *Chem. Sci.* **2020**, *11*, 4939–4947.

fragmentation of **2.76** results in a *C*-centred radical that is trapped by the Cu(II)-acetylide. The ensuing Cu(III) complex undergoes reductive elimination affording **2.77**.



Scheme 2.22. Decarboxylative alkynylation by direct excitation of copper acetylides.

Under photocatalysed conditions the Toste group reported the alkynylation of aryl radicals with TMS-acetylenes (TMS = trimethylsilyl) as an alkyne source (Scheme 2.23).[84] Under white light irradiation the excited state **PC.1*** ($Ru(bpy)_3^{2+}$) reduces the aryl diazonium salt (**2.78**) generating an aryl radical which can then add to the Au(I) catalyst. Transmetallation between the ensuing aryl-Au(III) intermediate and the TMS-acetylene (**2.79**) results in an alkynyl-aryl-Au(III) species which undergoes reductive elimination to product **2.80**. Glorius and co-workers also developed a method for dual gold/photoredox alkynylation of aryl radicals using free-alkynes.[85]



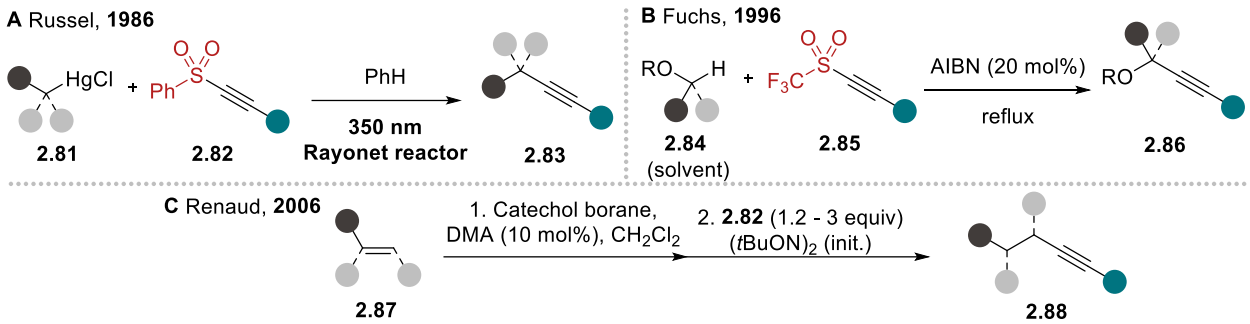
Scheme 2.23. Gold catalysed alkynylation of aryl radicals with TMS-acetylenes and aryl diazonium salts under photoredox catalysis.

2.2.3.2. Radical alkynylation with alkynyl sulfones

The use of alkynyl sulfones for the alkynylation of radicals[86] predates the applications of free-alkynes, metal acetylides and alkynylsilanes (Scheme 2.24).[87] In 1986, Russel and co-workers reported a photoinitiated generation of alkyl radicals from alkylmercury halides (**2.81**, A) and their trapping with alkynyl phenylsulfones (**2.82**) to form internal alkynes (**2.83**).[87a,b] Later in 1996, Fuchs and co-workers developed a C-H alkynylation of ethers (**2.84**, B) in presence of AIBN as a radical initiator. [87c,d] The ensuing α-oxoradicals could be trapped by trifluoromethyl alkynylsulfones (**2.85**) for the synthesis of **2.86**. Finally, Renaud and co-workers developed a two-step one-pot procedure for the alkynylation of alkenes (C). [88] The alkenes (**2.87**) first undergo hydroboration with catechol borane, then the borane can be

[84] Kim, S.; Rojas-Martin, J.; Toste, F. D. *Chem. Sci.* **2015**, *7*, 85–88.
[85] Tlahuext-Aca, A.; Hopkinson, M. N.; Sahoo, B.; Glorius, F. *Chem. Sci.* **2015**, *7*, 89–93.
[86] Ge, D.; Wang, X.; Chu, X.-Q. *Org. Chem. Front.* **2021**, *8*, 5145–5164.
[87] a. Russell, G. A.; Ngoviwatchai, P. *Tetrahedron Lett.* **1986**, *27*, 3479–3482. b. Russell, G. A.; Ngoviwatchai, P. *J. Org. Chem.* **1989**, *54*, 1836–1842. c. Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4486–4487. d. Xiang, J.; Jiang, W.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 6635–6638.
[88] Schaffner, A.-P.; Darmency, V.; Renaud, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 5847–5849.

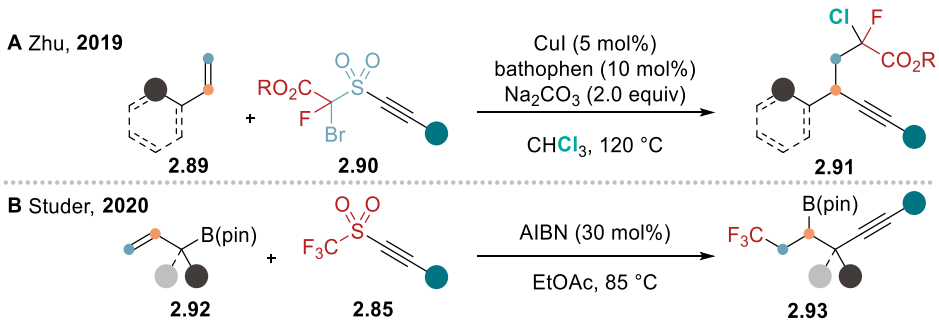
converted to the alkyne (**2.88**) using **2.82** as an alkyne source and *tert*-butyl hyponitrite as a radical initiator.



Scheme 2.24. Seminal reports of alkynylation of alkyl radicals with alkynyl sulfones.

Since these seminal reports, alkynyl sulfones have been used in radical alkynylation strategies involving thermally activated radical initiators,[89] metal-based redox transformations with manganese or iron,[90] photoredox catalysis and electrochemical strategies.

In 2019, Zhu and co-workers published an alkynylative difunctionalisation of alkenes (**2.89**, Scheme 2.25, A).[91] In this transformation, the tuned alkynyl sulfone **2.90** is reduced by the copper catalyst, cleaving the C-Br bond. The resulting α-F-α-keto radical then adds to the alkene (**2.89**), generating a benzylic radical. The latter is subject to an intramolecular alkyne transfer with leads to a sulfonyl radical that can then undergo desulfonylation-chlorination and deliver the final compound **2.91**. In 2020, the Studer group reported a radical 1,3-trifluoromethylalkynylation of allylboronanes under thermal activation (B).[92] Using AIBN as a radical initiator at 85 °C, they could convert the allylboranes (**2.92**) to the product **2.93** through a 1,2-boron shift with **2.85** as both a trifluoromethyl radical and an alkyne source.



Scheme 2.25. Desulfonylative alkynylation of alkyl radicals for alkene difunctionalisation.

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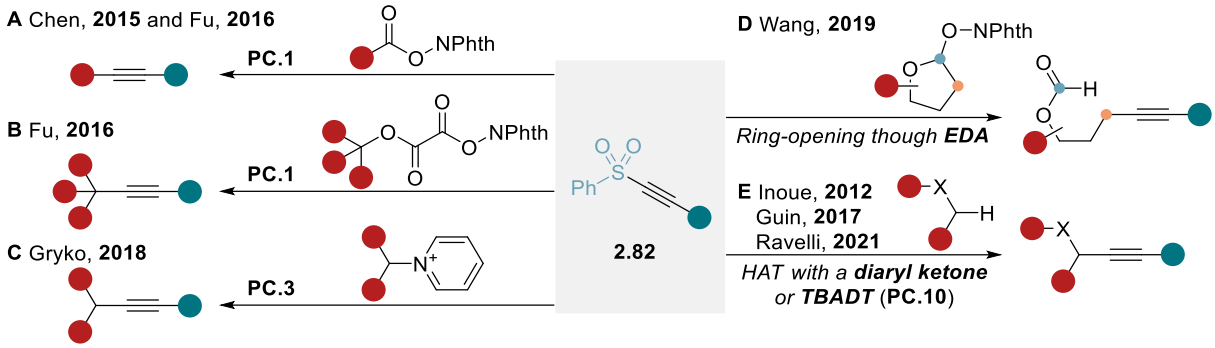
[89] a. Liautard, V.; Robert, F.; Landais, Y. *Org. Lett.* **2011**, *13*, 2658–2661. b. Xia, Y.; Studer, A. *Angew. Chem. Int. Ed.* **2019**, *58*, 9836–9840

[90] a. Ren, R.; Wu, Z.; Xu, Y.; Zhu, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 2866–2869. b. Guan, H.; Sun, S.; Mao, Y.; Chen, L.; Lu, R.; Huang, J.; Liu, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 11413–11417.

[91] Wang, M.; Zhang, H.; Liu, J.; Wu, X.; Zhu, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 17646–17650.

[92] Jana, K.; Bhunia, A.; Studer, A. *Chem* **2020**, *6*, 512–522.

Alkynyl sulfones have also several applications in photochemical activation, they have often been combined with reducible RAGs such as *N*-phthalimidoyl esters for decarboxylative alkynylation (Scheme 2.26, A)[93] or *N*-phthalimidoyl oxalates for deoxyalkynylation (B).[94] In 2018, the Gryko group developed a deaminative alkynylation with pyridinium salts (C).[95] Wang and co-workers reported a ring-opening of medium sized rings by reducing *N*-phthalimidoyl acetals through a photoactive EDA complex (D).[96] Multiple groups have approached HAT of ethers and amides using various HAT-type photocatalysts (E).[97] Inoue and co-workers could apply this strategy for the total synthesis of (+)-lactacystin[98] and also developed a chiral alkynyl sulfoximine for an enantioselective radical alkynylation.[99]



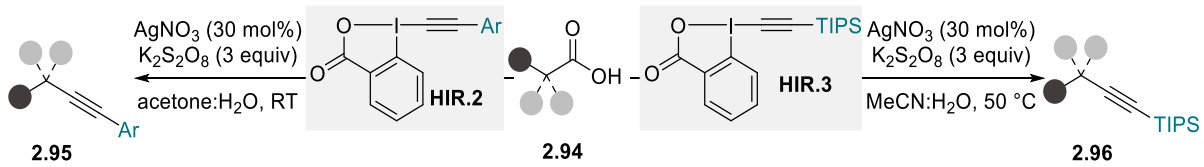
Scheme 2.26. Photochemical methods for defunctionalisation-alkynylation with alkynyl sulfones.

2.2.3.3. Hypervalent iodine reagents

Hypervalent iodine reagents and more specifically, the ethynybenziodoxolones (EBXs) have, over the past years, emerged as a reliable tool for the alkynylation of radicals as first described by Li and co-workers (Scheme 2.27).[100] They reported the oxidative decarboxylation of **2.94** using silver nitrate and sodium persulfate. The ensuing *C*-centred radical could then be trapped by the EBX (**HIR.2** or **HIR.3**) reagent to afford **2.95** and **2.96**. Interestingly, they observed a considerable difference between ArEBXs (**HIR.2**) and TIPS-EBX (TIPS = triisopropylsilyl, **HIR.3**). The transfer of a phenylacetylene fragment occurred at room temperature, whereas the decarboxylative alkynylation with TIPS-EBX required heating to 50 °C. Since this report, multiple photochemical strategies have been developed using the EBXs (this will be discussed in section 2.3.2.3.3). This method was later extended to

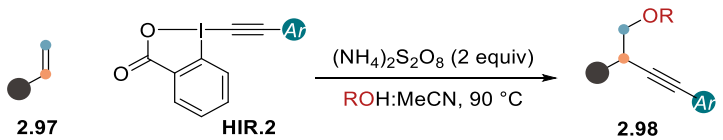
[93] a. Yang, J.; Zhang, J.; Qi, L.; Hu, C.; Chen, Y. *Chem. Commun.* **2015**, *51*, 5275–5278. b. Jiang, M.; Jin, Y.; Yang, H.; Fu, H. *Sci. Rep.* **2016**, *6*, 26161.
[94] Gao, C.; Li, J.; Yu, J.; Yang, H.; Fu, H. *Chem. Commun.* **2016**, *52*, 7292–7294. d. Schwarz, J.; König, B. *ChemPhotoChem* **2017**, *1*, 237–242.
[95] Ociepa, M.; Turkowska, J.; Gryko, D. *ACS Catal.* **2018**, *8*, 11362–11367.
[96] Shi, J.-L.; Wang, Z.; Zhang, R.; Wang, Y.; Wang, J. *Chem. – Eur. J.* **2019**, *25*, 8992–8995.
[97] a. Hoshikawa, T.; Kamijo, S.; Inoue, M. *Org. Biomol. Chem.* **2012**, *11*, 164–169. b. Paul, S.; Guin, J. *Green Chem.* **2017**, *19*, 2530–2534. c. Capaldo, L.; Ravelli, D. *Org. Lett.* **2021**, *23*, 2243–2247.
[98] Yoshioka, S.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2015**, *17*, 90–93.
[99] Nagatomo, M.; Yoshioka, S.; Inoue, M. *Chem. – Asian J.* **2015**, *10*, 120–123.
[100] Liu, X.; Wang, Z.; Cheng, X.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 14330–14333.

difluorocarboxylates by Hashmi and co-workers.[101] In addition to carboxylic acids, alkyl-DHPs and alkylated Meyer nitriles have also been used as alkyl radical sources in persulfate promoted radical alkynylations with EBXs.[102]



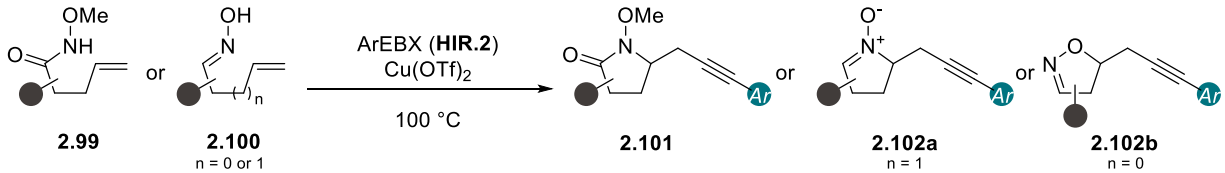
Scheme 2.27. Silver catalysed decarboxylative alkynylation with EBXs.

In 2018, Liu and co-workers reported the oxyalkynylation of alkenes using ammonium persulfate as an oxidant (Scheme 2.28).[103] The alkene (**2.97**) is first oxidised by the persulfate resulting in an alkene radical cation which can then be trapped by an external nucleophile – in this case the alcohol or water co-solvent. This generates a *C*-centred radical which can then be trapped by **HIR.2** and afford the desired difunctionalised product (**2.98**).



Scheme 2.28. Metal-free oxyalkynylation of styrenes and aliphatic alkenes with EBXs.

The EBXs have also been combined with copper catalysis for alkene difunctionalisation (Scheme 2.29).[104] This was illustrated by the Wang and Han groups for the cyclisation of Weinreb amides (**2.99**) and oximes (**2.100**) on to alkenes giving access to heterocyclic **2.101** and **2.102a** or **2.102b**. In the study by Han with the oximes, they proposed the oxidation of the oxime (**2.100**) to a radical intermediate which undergoes 5-exo-trig cyclisation. The resulting *C*-centred radical can then be trapped by the EBX reagent.



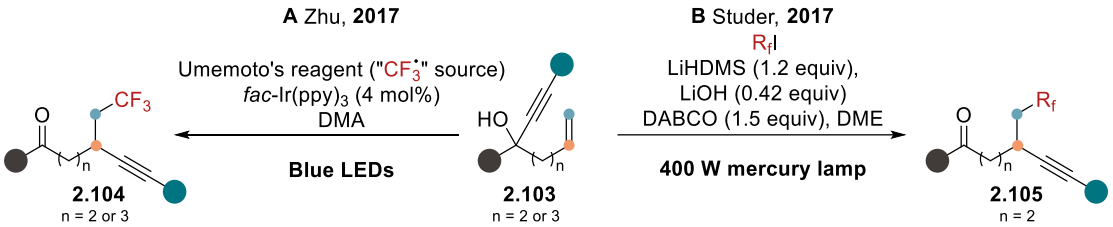
Scheme 2.29. Alkene difunctionalisation with EBXs and copper catalysis

2.2.3.4. Alkyne migration strategies for alkene difunctionalisation

Finally, alkyne migration has also been frequently used for the difunctionalisation of alkenes.[105] This approach was first developed in parallel by the independent works of the Zhu

[101] Chen, F.; Hashmi, A. S. K. *Org. Lett.* **2016**, *18*, 2880–2882.
[102] Liu, X.; Liu, R.; Dai, J.; Cheng, X.; Li, G. *Org. Lett.* **2018**, *20*, 6906–6909.
[103] Li, Y.; Lu, R.; Sun, S.; Liu, L. *Org. Lett.* **2018**, *20*, 6836–6839.
[104] a. Shen, K.; Wang, Q. *Chem. Sci.* **2017**, *8*, 8265–8270. b. Han, W.-J.; Wang, Y.-R.; Zhang, J.-W.; Chen, F.; Zhou, B.; Han, B. *Org. Lett.* **2018**, *20*, 2960–2963.
[105] Wu, X.; Zhu, C. *Acc. Chem. Res.* **2020**, *53*, 1620–1636.

and Studer groups (Scheme 2.30).[106] The Zhu group reported a photocatalysed strategy starting from **2.103** with Umemoto's reagent[107] and **PC.2** (*fac*-Ir(ppy)$_3$) under blue LED irradiation for the synthesis of trifluoromethylated alkynes (**2.104**).[106a] Studer on the other hand, used perfluoroalkyl iodides and a high intensity mercury lamp to access perfluoroalkylated alkynes (**2.105**).[106b] Since these seminal reports, this approach has been applied under thermal activation with radical initiators[108] and electrochemical activation.[109] The scope has been extended from perfluoroalkylation to sulfonation,[109] phosphonation[108b] and difluoroalkylation.[108a, c-d,110]



Scheme 2.30. Radical alkene difunctionalisation from propargylic alcohols via alkyne transfer.

2.2.4. Alkynes: reactivity and synthesis – conclusive remarks

In this section, we have discussed the importance of alkynes as targets and as reactive platforms for further transformations. It is apparent that the diversification of strategies allowing their incorporation is of utmost importance. We have focussed on the emergence of radical alkynylation and have briefly explored the possible disconnections and starting materials (e.g., carboxylates, alkenes, ethers) for alkynylation strategies. We were able to identify different reagents for the alkynylation of radicals. In this regard, the EBXs, a class of hypervalent iodine (**III**) species, have frequently been used for radical alkynylation. In the upcoming chapter we will discuss the reactivity of the EBXs in comparison to other hypervalent iodine (III) species with a particular attention to photochemical strategies.

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[106] a. Xu, Y.; Wu, Z.; Jiang, J.; Ke, Z.; Zhu, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 4545–4548. b. Tang, X.; Studer, A. *Chem. Sci.* **2017**, *8*, 6888–6892.
[107] *S*-trifluoromethyl dibenzothiophenium tetrafluoroborate.
[108] a. Li, M.; Zhu, X.-Y.; Qiu, Y.-F.; Han, Y.-P.; Xia, Y.; Wang, C.-T.; Li, X.-S.; Wei, W.-X.; Liang, Y.-M. *Adv. Synth. Catal.* **2019**, *361*, 2945–2950. b. Jin, S.; Sun, S.; Yu, J.-T.; Cheng, J. *J. Org. Chem.* **2019**, *84*, 11177–11185. c. Jin, S.; Chen, F.; Qian, P.; Cheng, J. *Org. Biomol. Chem.* **2021**, *19*, 2416–2419. d. Zhang, J.-J.; Chen, D.; Qin, Y.-Q.; Deng, W.; Luo, Y.-Y.; Xiang, J.-N. *Org. Biomol. Chem.* **2021**, *19*, 3154–3158.
[109] Gao, Y.; Mei, H.; Han, J.; Pan, Y. *Chem. – Eur. J.* **2018**, *24*, 17205–17209.
[110] Liu, J.; Li, W.; Xie, J.; Zhu, C. *Org. Chem. Front.* **2018**, *5*, 797–800.

2.3. Hypervalent iodine (III) reagents

2.3.1. From iodides to λ^3-iodanes

2.3.1.1. Discovery of (dichloroiodo)benzene

In the late XIXth century, Willgerodt found that by bubbling chlorine gas in a solution of iodobenzene he was able to synthesise and isolate (dichloroiodo)benzene (Figure 2.5, **HIR.4**).[111] Thirty years later, he had developed a library of over 500 organo-iodine (III) species including (diacetoxyiodo)benzene (**HIR.5**) and the first diaryl iodonium salt (**HIR.5**).[112]

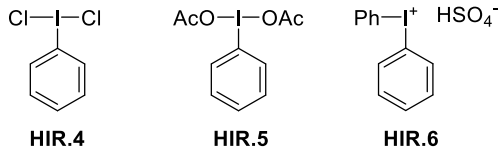

Figure 2.5. First examples of λ^3-iodanes species.

2.3.1.2. Hypervalent iodine compounds: structure and electronics

Iodine, element of the fifth row of the periodic table, has the following electronic configuration: $[Kr]5s^2 4d^{10} 5p^5$. Elemental iodine (I_2) is in the oxidation state 0, however iodine is often incorporated to organic molecules or salts as an iodide (oxidation state: - 1, Figure 2.6, A). As other elements of the third row and lower, iodine can break the octet rule and be found in oxidation states +III and +V, and in some rarer cases +VII. λ^5-Iodanes, such as DMP (Dess-Martin periodinane), have a distorted octahedral iodine centre resulting in a distorted square-based pyramid geometry[113] and are known for their oxidising character.[114] λ^3-Iodanes have a distorted trigonal bipyramid iodine centre (B).[115] The presence of three ligands and two doublets results in the characteristic T-shaped geometry of these scaffolds which can be explained by the "hypervalent bond" (C).[116] Specifically, for λ^3-iodanes a three-centre-four-electron (3c-4e$^-$) bond has been proposed.[117] The bonding electron pair is delocalised along three centres and the presence of the third ligand bound through the 5*p* orbital of the iodine centre leads to three orbitals: bonding (Ψ_1), non-bonding (Ψ_2) and anti-bonding (Ψ_3). The HOMO (Ψ_2) presents a nodal plane allowing the most electronegative

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[111] Willgerodt, C. *J. Prakt. Chem.* **1886**, *33*, 154–160.
[112] Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178.
[113] Schröckeneder, A.; Stichnoth, D.; Mayer, P.; Trauner, D. *Beilstein J. Org. Chem.* **2012**, *8*, 1523–1527.
[114] a. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. b. Wirth, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 2812–2814.
[115] Zhdankin, V. V. Introduction and General Overview of Polyvalent Iodine Compounds. In *Hypervalent Iodine Chemistry*; John Wiley & Sons, Ltd, 2013; pp 1–20.
[116] Hypervalency was first introduced by Musher, further discussed by Martin. The concept is still under discussion. a. Musher, J. I. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 54–68. b. Martin, J. C. *Science* **1983**, *221*, 509–514. c. Ivanov, A. S.; Popov, I. A.; Boldyrev, A. I.; Zhdankin, V. V. *Angew. Chem. Int. Ed.* **2014**, *53*, 9617–9621. d. Durrant, M. C. *Chem. Sci.* **2015**, *6*, 6614–6623.
[117] a. Pimentel, G. C. *J. Chem. Phys.* **1951**, *19*, 446–448. b. Hach, R. J.; Rundle, R. E. *J. Am. Chem. Soc.* **1951**, *73*, 4321–4324.

ligands to occupy the apical positions,[118] leaving the equatorial positions to the doublets and the third ligand – generally an aryl ring for greater stability due to orbital overlap.[119]

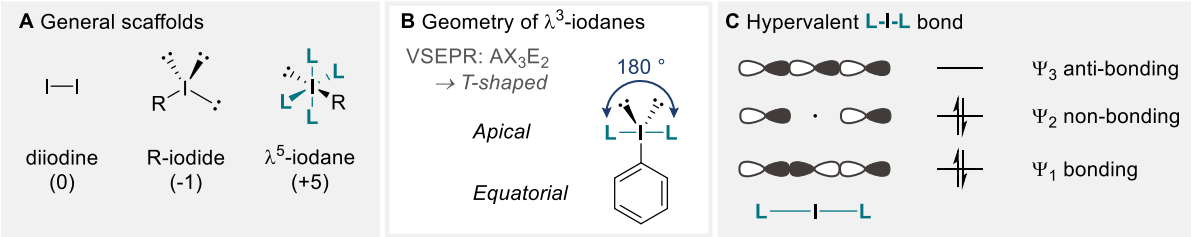

Figure 2.6. Iodanes: structure and electronics. A. Diiodine, R-iodide, and λ^5-iodane. B. Geometry of λ^3-iodanes. C. Hypervalent iodine bond.

2.3.1.3. Reactivity of λ^3-iodanes

λ^3-iodanes can be either oxidants or functional group transfer agents (Figure 2.7). The oxidant-type reagents are often acyclic and based on a difunctionalised iodobenzene scaffold (**HIR.7**) such as PIDA or PIFA, although they can also be found with cyclic forms (**HIR.8**). They generally have two heteroatom ligands (often *O*-based, Cl or N_3). For functional group transfer, the heterocyclic scaffold (**HIR.8**) and the iodonium salts (**HIR.9**) are preferred. The heterocyclic compounds (benziodoxoles) have found to be easier to use, bench and air stable, and tolerant to shock and friction (with some exceptions for the CF_3 and N_3 reagents).[120]

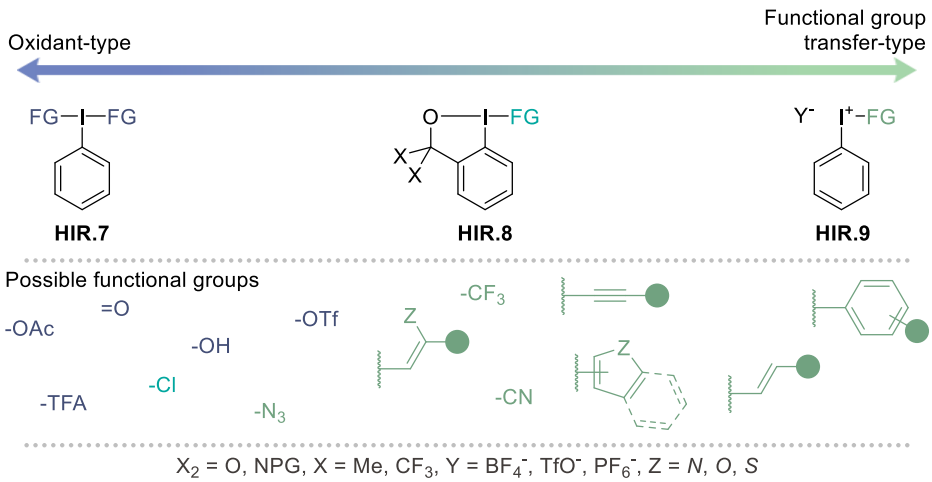

Figure 2.7. General structure of aryl substituted λ^3-iodanes.

λ^3-iodanes, and more specifically the benziodoxolones used for group transfer, generally tend to result in the *Umpolung* of reactivity of the transferable functional group. This is well illustrated by the EBXs (Scheme 2.31). Traditionally, the alkyne is nucleophilic and reacts as

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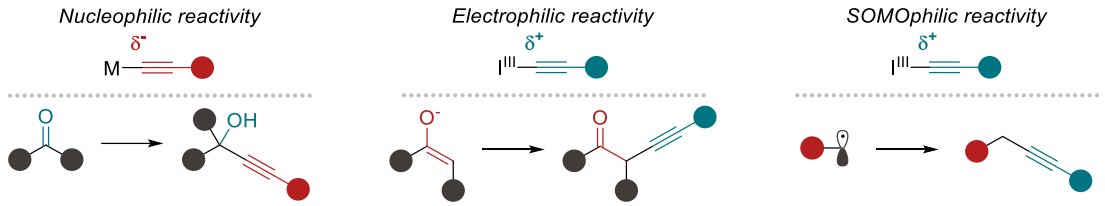
[118] a. Stang, P. J.; Zhdankin, V. V. *Chem. Rev. Soc.* **2008**, *108*, 5299–5358. b. Silva, L. F.; Olofsson, B. *Nat. Prod. Rep.*, **2011**, 28, 1722–1754.
[119] a. Zhdankin V. V. *Rev. Heteroat. Chem.* **1997**, *17*, 133–152. b. Sun, T.-Y.; Wang, X.; Geng, H.; Xie, Y.; Wu, Y.-D.; Zhang, X.; H. F. Schaefer III. *Chem. Commun.* **2016**, *52*, 5371–5374.
[120] a. Fiederling, N.; Haller, J.; Schramm, H. *Org. Process Res. Dev.* **2013**, *17*, 318–319. b. Alazet, S.; Preindl, J.; Simonet-Davin, R.; Nicolai, S.; Nanchen, A.; Meyer, T.; Waser, J. *J. Org. Chem.* **2018**, *83*, 12334–12356.

an acetylide attacking electrophilic centres. In the case of the EBXs, the hypervalent iodine causes an electron deficiency on the alkyne allowing the alkynylation of both two-electron and single-electron nucleophiles.[72,121]

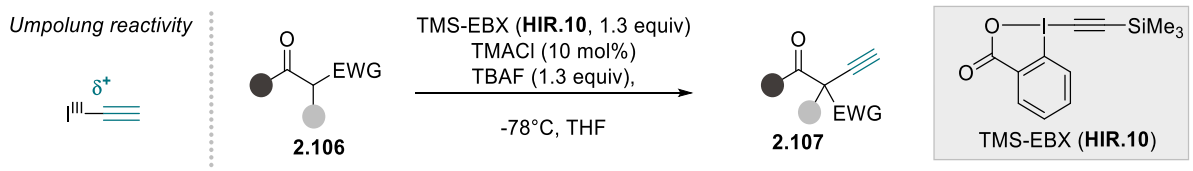


Scheme 2.31. Nucleophilic reactivity of acetylides and EBXs for electrophilic and SOMOphilic alkynylation.

This general *Umpolung* of reactivity has been used for trifluoromethylation,[122] cyanation,[123] azidation,[120b,124] (hetero)arylation,[125] and (hetero)alkenylation.[126]

2.3.1.4. Electrophilic functional group transfer with λ^3-iodanes

In 2010, our group illustrated the electrophilic nature of EBXs with an alkynylation of α-ketoesters (Scheme 2.32).[127] The α-ketoesters (**2.106**) could successfully be converted to the desired alkynylated (**2.107**) products using TMS-EBX (TMS = trimethylsilyl, **HIR.10**) as an alkyne source with TBAF. Since this report, EBXs have been used with various carbon and heteroatom nucleophiles.[128]



Scheme 2.32. α-ketoester alkynylation with TMS-EBX (HIR.10).

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[121] Waser, J. Alkynylation with Hypervalent Iodine Reagents. In *Hypervalent Iodine Chemistry*, 373; Wirth, T. Eds.; Top. Curr. Chem; Springer, Cham, 2016, pp 187-222.
[122] Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 754–757.
[123] a. Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J. *Tetrahedron Lett.* **1995**, *36*, 7975–7978. b. Vita, M. V.; Caramenti, P.; Waser, J. *Org. Lett.* **2015**, *17*, 5832–. c. Frei, R.; Courant, T.; Wodrich M. D.; Waser, J. *Chem. Eur. J.* **2015**, *21*, 2662–2668.
[124] a. Zhdankin, V. V.; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 5192. b. Vita, M. V.; Waser, J. *Org. Lett.* **2013**, *15*, 3246–3249. c. Alazet, S.; Le Vaillant, F.; Nicolai, S.; Courant, T.; Waser, J. *Chem. – Eur. J.* **2017**, *23*, 9501–9504.
[125] a. Yusubov, M. S.; Yusubova, R. Y.; Nemykin, V. N.; Zhdankin, V. V. *J. Org. Chem.* **2013**, *78*, 3767–3773. b. Caramenti, P.; Nicolai, S.; Waser, J. *Chem. Eur. J.* **2017**, *23*, 14702–14706. c. Grenet, E.; Das, A.; Caramenti, P.; Waser, J. *Beilstein J. Org. Chem.* **2018**, *14*, 1208–1214. d. Caramenti, P.; Nandi, R. K.; Waser, J. *Chem. Eur.J.* **2018**, 24, 10049–10053. e. Grenet, E.; Waser, J. *Org. Lett.* **2018**, *20*, 1473–1476.
[126] Stridfeldt, E.; Seemann, A.; Bouma, M. J.; Dey, C.; Ertan, A.; Olofsson, B. *Chem. Eur. J.* **2016**, *22*, 16066.
[127] a. Fernández González, D.; Brand, J. P.; Waser, J. *Chem. – Eur. J.* **2010**, *16*, 9457–9461. b. Fernández González, D.; Brand, J. P.; Mondière, R.; Waser, J. *Adv. Synth. Catal.* **2013**, *355*, 1631–1639.
[128] a. Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165–4179. b. Hari, D. P.; Caramenti, P.; Waser, J. *Acc. Chem. Res.* **2018**, *51*, 3212–3225. c. Hari, D. P.; Nicolai, S.; Waser, J. Alkynylations and Vinylations. In *PATAI'S Chemistry of Functional Groups*; 2018; pp 1–58.

Over the past decade, many groups have illustrated the ambiphilicity of these reagents through atom economical transformations (Scheme 2.33).[129] In 2012, the Szabó and Sodeoka groups independently developed an atom economical 1,2-oxytrifluoromethylation of styrenes (B).[130] Both strategies used copper catalysis under thermal activation and the Togni reagent (**HIR.1b**) to convert the alkenes (**2.108**) to the oxytrifluoromethylated products **2.109**. In 2016, our group developed a copper catalysed 1,1-oxyalkynylation of diazo compounds (**2.110**) with EBXs (**HIR.2** or **HIR.3**, B).[131] The method afforded a wide range of 1-alkynylalcohol scaffolds **2.11**. These methods could then be extended to 1,1-oxyvinylation and 1,1-aminoalkynylation.[132] Finally, copper catalysis enabled the ring-opening/oxyalkynylation of thiiranes using EBX reagents.[133] In 2019, an 1,2-oxyalkynylation of allenamides was designed by the Patil group (C).[134] The method involved gold catalysis for the activation of the allenamides (**2.112**) and an EBX (**HIR.2** or **HIR.3**) as alkyne and oxygen source. In 2017, Gillaizeau and co-workers issued an iron-catalysed 1,2-oxyazidation of enamides (**2.114**) using ABX (**HIR.11**) to afford the product **2.115** (D).[135] Interestingly, their mechanistic studies suggest that the reaction proceeds most likely through the addition of an *O*-centred radical to the alkene.[136]

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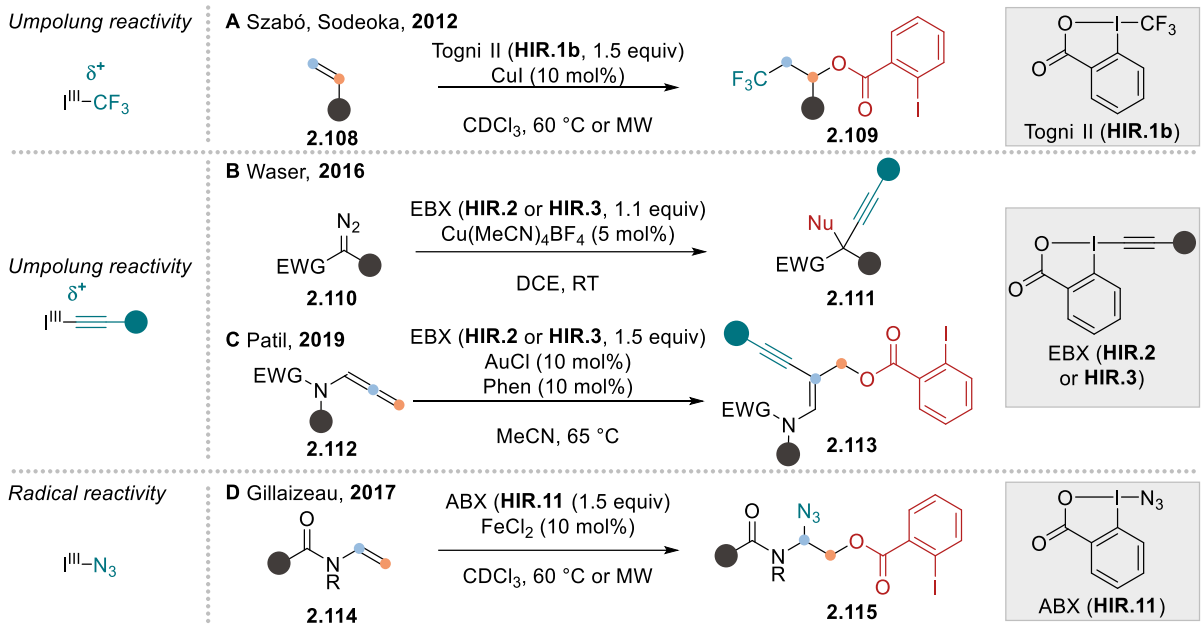
[129] Boelke, A.; Finkbeiner, P.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2018**, *14*, 1263–1280.
[130] a. Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882–2885. b. Egami, H.; Shimizu, R.; Sodeoka, M. *Tetrahedron Lett.* **2012**, *53*, 5503–5506. c. Egami, H.; Shimizu, R.; Usui, Y.; Sodeoka, M. *J. Fluor. Chem.* **2014**, *167*, 172–178.
[131] a. Hari, D. P.; Waser, J. *J. Am. Chem. Soc.* **2016**, *138*, 2190–2193. b. Hari, D. P.; Waser, J. *J. Am. Chem. Soc.* **2017**, *139*, 8420–8423.
[132] a. Pisella, G.; Gagnebin, A.; Waser, J. *Org. Lett.* **2020**, *22*, 3884–3889. b. Pisella, G.; Gagnebin, A.; Waser, J. *Chem. – Eur. J.* **2020**, *26*, 10199–10204. c. Ramirez, N. P.; Pisella, G.; Waser, J. *J. Org. Chem.* **2021**, *86*, 10928–10938.
[133] Borrel, J.; Pisella, G.; Waser, J. *Org. Lett.* **2020**, *22*, 422–427.
[134] Banerjee, S.; Senthilkumar, B.; Patil, N. T. *Org. Lett.* **2019**, *21*, 180–184.
[135] Bertho, S.; Rey-Rodriguez, R.; Colas, C.; Retailleau, P.; Gillaizeau, I. *Chem. – Eur. J.* **2017**, *23*, 17674–17677.
[136] Similar examples were described in section 2.1.4.3.1 Radical additions to alkenes



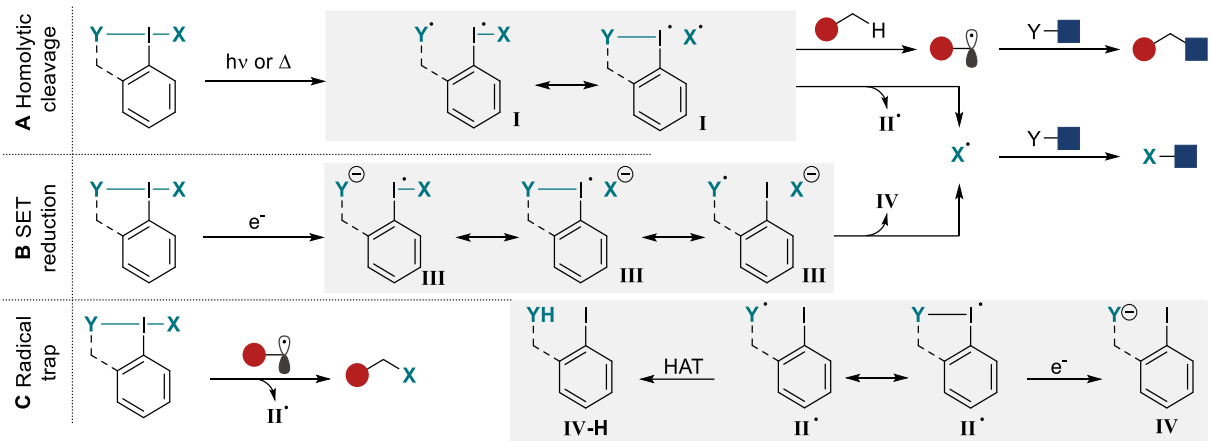
Scheme 2.33. HIRs for atom economical 1,2-difunctionalisations of alkenes and 1,1-difunctionalisations of diazo compounds.

2.3.2. λ³-iodanes in photochemistry

2.3.2.1. Overview of radical reaction pathways

Before discussing photochemical strategies, it is important to note that HIRs have been used in radical strategies using non-photomediated activation strategies.[137] They have been: (1) combined with radical initiators such as peroxides, BEt_3/air, or TEMPO•, (2) reduced by external reductants such as Fe(II) or Cu(I), and (3) reported to undergo homolytic cleavage induced by heating for select reagents. These methods allow us to distinguish three key mechanisms that HIRs follow in radical processes. The first pathway is the homolytic cleavage of a reagent (Scheme 2.34, A). This can occur under thermal or photochemical activation; it generally results in the cleavage of an apical ligand. The resulting radical **I** has been reported to perform HAT,[138] and, in the case where a ligand is detachable, this can generate a free radical **X•**, which can proceed in other radical processes, and the iodanyl radical **II•**. The second pathway involves the SET reduction of a reagent (B), this results in a reduced reagent **III** which can then fragment releasing a ligand as the free radical **X•** and the iodobenzoate **IV**. The last pathway occurs when the HIR acts as a radical trap (C), in this case, a free radical adds to the reagent and displaces the iodobenzoate fragment by releasing the iodanyl radical **II•**. Finally, SET reduction of the iodanyl radical **II•** will afford the iodobenzoate anion **IV**.

[137] Wang, X.; Studer, A. *Acc. Chem. Res.* **2017**, *50*, 1712–1724.
[138] a. Moteki, S. A.; Usui, A.; Zhang, T.; Solorio Alvarado, C. R.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 8657–8660. b. Amey, R. L.; Martin, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 3060–3065.



Scheme 2.34. General reaction pathways for λ³-iodanes under radical conditions

2.3.2.2. Oxidant-type λ³-iodanes

2.3.2.2.1. Direct excitation

The first example of direct photoexcitation of oxidant-type HIRs dates back to 1991: Togo and co-workers investigated a hypervalent iodine mediated deoxygenation (Scheme 2.35, A).[139] They reported the deoxygenation of (adamant-1-yl)-2-oxoacetate (**2.116**) for the functionalisation of lepidine (**2.117**) in presence of a PIDA analogue **HIR.12** under irradiation. They proposed the displacement of an acetate of **HIR.12** by the oxalate which could then undergo homolytic cleavage and deoxygenation. The resulting radical was trapped by **2.117**, affording **2.118** This principle has since been applied for the activation of carboxylic acids, alcohols, and amines.[140] In 2014, Maruoka and co-workers reported the use of a PIDA analogue **HIR.13** for the generation of acyl radicals (B).[141] The direct excitation of **HIR.13** resulted in an iodanyl radical that could perform a HAT on the aldehyde (**2.119**). The ensuing acyl radical could then be trapped by an electron-poor alkene (**2.120**) delivering **2.121**. In 2020, the Xuan group reported an alkylation of quinoxalinones.[142] Blue LED irradiation of the EDA complex between the DHP derivative (**2.122**) and **HIR.14** results in the oxidation of **2.122**. Subsequent fragmentation generates an alkyl radical which adds to the quinoxalinone (**2.123**) affording the product **2.124** after deprotonation.

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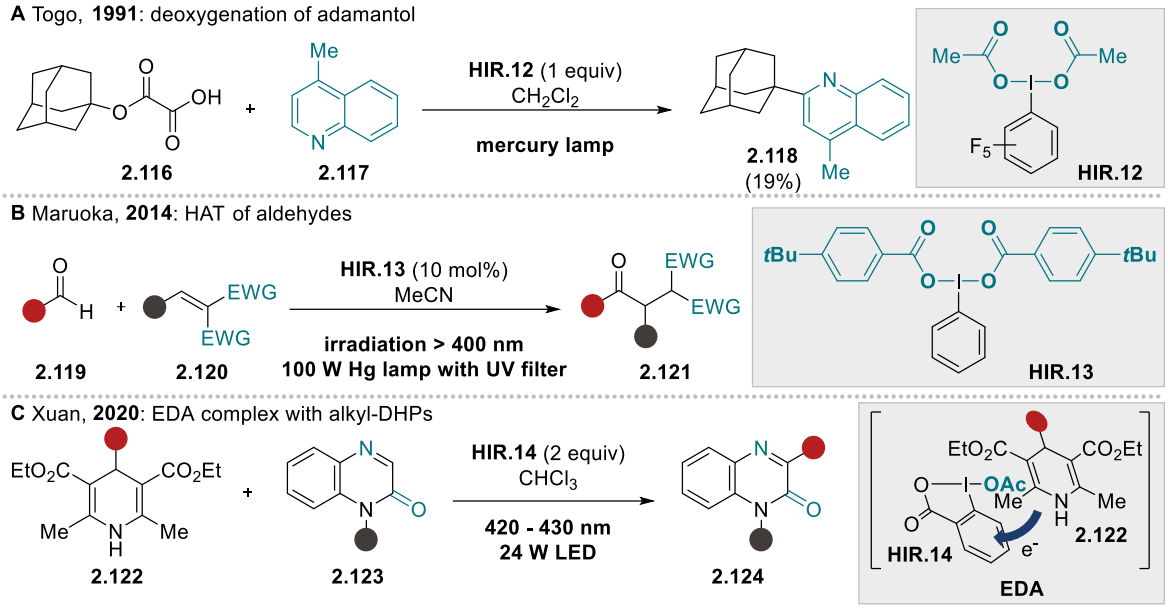
[139] Togo, H.; Aoki, M.; Yokoyama, M. *Chem. Lett.* **1991**, *20*, 1691–1694.
[140] Jia, K.; Chen, Y. Photochemistry of Hypervalent Iodine Compounds. In *PATAI'S Chemistry of Functional Groups*; American Chemical Society, 2018; pp 1–42.
[141] a. Moteki, S. A.; Usui, A.; Selvakumar, S.; Zhang, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2014**, *53*, 11060–11064. b. Selvakumar, S.; Sakamoto, R.; Maruoka, K. *Chem. – Eur. J.* **2016**, *22*, 6552–6555.
[142] He, X.-K.; Lu, J.; Zhang, A.-J.; Zhang, Q.-Q.; Xu, G.-Y.; Xuan, J. *Org. Lett.* **2020**, *22*, 5984–5989.



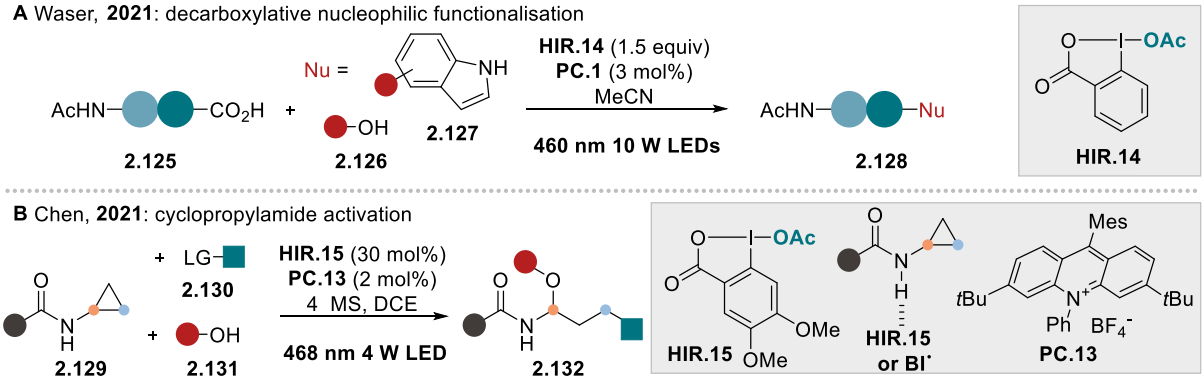
Scheme 2.35. Photocatalyst-free transformations mediated by the direct excitation of oxidant-type λ³-iodanes and derivatives.

2.3.2.2.2. Photocatalyst mediated approaches

Oxidant-type HIRs have also been used in combination with photocatalysis. Similarly to the photocatalyst-free methods, they have been used for the generation of iodanyl radicals for HAT [143] and or the activation of nucleophilic substrates.[144] In addition to these strategies they have also been used as co-oxidants. One recent example is the decarboxylative nucleophilic functionalisation of small peptides (Scheme 2.36, A).[145] The combination of **HIR.14** (BIOAc) with **PC.1** ($Ru(bpy)_3^{2+}$) enabled the generation of an α-amino cation equivalent from the peptides (**2.125**). The strategy allowed the incorporation of various nucleophiles (**2.126** or **2.127**) for the synthesis of functionalised peptides (**2.128**). This photocatalysis/HIR additive combination has also been used for the refunctionalisation of boronic acids and trifluoroborate salts.[146] Finally, Knowles found that TIPS-EBX (**HIR.3**) was an efficient external oxidant for the photocatalysed synthesis of pyrroloindolines.[147] In 2021, Chen and co-workers reported the first non-covalent substrate activation in the context of a cyclopropylamide difunctionalisation (B).[148] Under blue LED irradiation they performed a difunctionalisation of cyclopropylamides

[143] a. Li, G.-X.; Morales-Rivera, C. A.; Gao, F.; Wang, Y.; He, G.; Liu, P.; Chen, G. *Chem. Sci.* **2017**, *8*, 7180–7185. b. Li, G.-X.; Hu, X.; He, G.; Chen, G. *ACS Catal.* **2018**, *8*, 11847–11853.
[144] Wang, N.; Gu, Q.-S.; Li, Z.-L.; Li, Z.; Guo, Y.-L.; Guo, Z.; Liu, X.-Y. *Angew. Chem. Int. Ed.* **2018**, *57*, 14225–14229.
[145] Le Du, E.; Garreau, M.; Waser, J.; *Chem. Sci.* **2021**, *12*, 2467-2473.
[146] a. Huang, H.; Jia, K.; Chen, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 1881–1884. b. Dai, J.-J.; Zhang, W.-M.; Shu, Y.-J.; Sun, Y.-Y.; Xu, J.; Feng, Y.-S.; Xu, H.-J. *Chem. Commun.* **2016**, *52*, 6793–6796. c. Yang, B.; Xu, X.-H.; Qing, F.-L. *Org. Lett.* **2016**, *18*, 5956–5959. d. Li, G.-X.; Morales-Rivera, C. A.; Wang, Y.; Gao, F.; He, G.; Liu, P.; Chen, G. *Chem. Sci.* **2016**, *7*, 6407–6412. e. Li, X.; Han, M.-Y.; Wang, B.; Wang, L.; Wang, M. *Org. Biomol. Chem.* **2019**, *17*, 6612–6619. f. Li, P.; Zbieg, J. R.; Terrett, J. A. *Org. Lett.* **2021**, *23*, 9563–9568
[147] Gentry, E. C.; Rono, L. J.; Hale, M. E.; Matsuura, R.; Knowles, R. R. *J. Am. Chem. Soc.* **2018**, *140*, 3394–3402.
[148] Liu, Z.; Wu, S.; Chen, Y. *ACS Catal.* **2021**, *11*, 10565–10573.

(**2.129**) activated by **PC.13** and **HIR.15**. In presence of both a radical trap (**2.130**) and a nucleophile source (**2.131**) they could access complex 1,3-difunctionalised products (**2.132**). They found that **HIR.15** could activate the cyclopropylamide (**2.129**), through H-bonding allowing the oxidation of this substrate by the photocatalyst.



Scheme 2.36. Photocatalysed strategies using oxidant-type λ³-iodanes as an additive for decarboxylative and strain release ring-opening functionalisations.

2.3.2.3. Functional group transfer type λ³-iodanes

2.3.2.3.1. Direct excitation

The first report of direct excitation of HIRs for the transfer of a functional group is the example of Martin and co-workers in 1979 and their work on the direct chlorination and bromination of benzylic and allylic bonds (Scheme 2.37, A).[149] For example, irradiation of **HIR.16** with a mercury lamp in toluene (**2.133**) provided the chlorinated product (**2.134**) in 95% yield. Until very recently, this approach for functional transfer without photocatalyst had not been explored further.[150] In 2020, Nemoto and co-workers performed an extensive study on the photoactivity of iodine containing compounds in the visible light region (B).[151] This study investigated the absorption profiles of various HIRs; they found that **HIR.16** could undergo excitation at 400 nm and could be used for the difunctionalisation of styrene (**2.135**) delivering the chlorinated product **2.136**. They also performed the photoactivation at 450 nm of **HIR.11** for HAT functionalisation of **2.137** affording the azidated product **2.138**. Finally, in 2021, our group reported a synthesis of quinolines (C).[152] Direct excitation of **HIR.17** in presence of **HIR.14** and the cyclopropene (**2.139**) allowed the synthesis of quinolines (**2.140**). Preliminary studies showed that the combination of both HIRs resulted in an increased degradation of both species suggesting a cooperative effect between both reagents.

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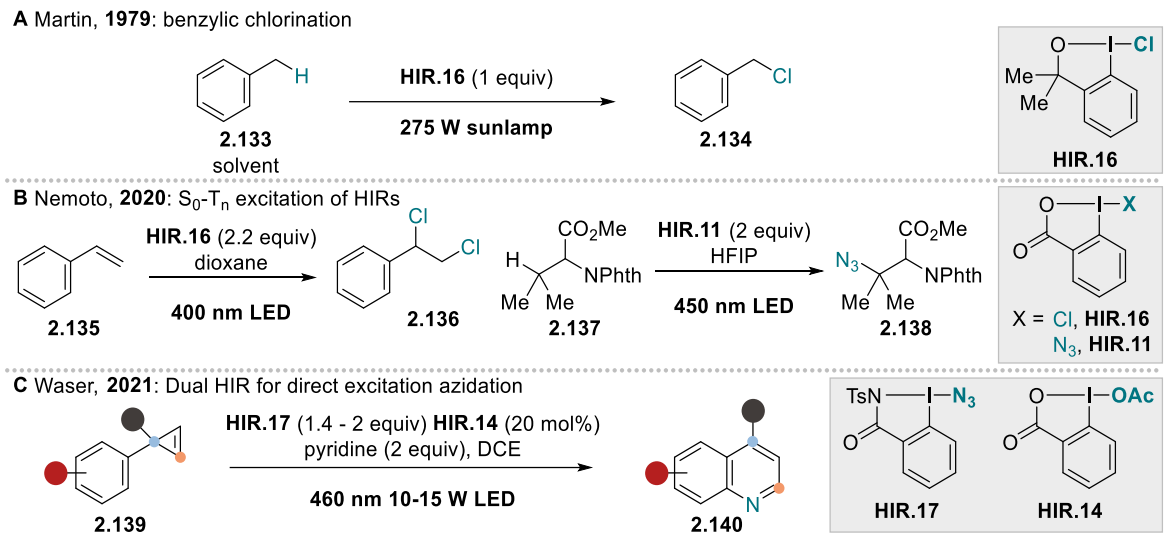
[149] a. Amey, R. L.; Martin, J. C. *J. Org. Chem.* **1979**, *44*, 1779–1784. b. Amey, R. L.; Martin, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 3060–3065.
[150] In 2018, the Chu group reported a possible EDA between DABCO and the Togni reagent: Chen, D.; Xu, L.; Long, T.; Zhu, S.; Yang, J.; Chu, L. *Chem. Sci.* **2018**, *9*, 9012–9017.
[151] Nakajima, M.; Nagasawa, S.; Matsumoto, K.; Kuribara, T.; Muranaka, A.; Uchiyama, M.; Nemoto, T. *Angew. Chem. Int. Ed.* **2020**, *59*, 6847–6852.
[152] Smyrnov, V.; Muriel, B.; Waser, J. *Org. Lett.* **2021**, *23*, 5435–5439.



Scheme 2.37. Direct excitation of HIRs for chlorination and azidation.

2.3.2.3.2. Photocatalysed SET reduction of λ³-iodanes

When turning to the photocatalytic approaches for functional group transfer with λ³-iodanes the reagents can be split into two categories: reducible reagents and radical traps. Generally speaking, reagents capable of being reduced generate the free radical of the desired transferable functional group. When combined with photocatalysis, this concept was illustrated by Zhu and co-workers with a SET reduction of the Togni reagent (**HIR.1b**, Scheme 2.38, A).[153,154] They report the trifluoromethylation of *N*-aryl acrylamides (**2.141**) under blue LED irradiation with **PC.14** and **HIR.1b** for the synthesis of oxindoles (**2.142**). The following year, Masson and co-workers reported a difunctionalisation strategy (B).[155] They combined **HIR.1b** with visible light photocatalysis (**PC.1**, $Ru(bpy)_3^{2+}$) for the difunctionalisation of enamides (**2.143**). They observed a radical polar cross-over (as described in section 2.1.4.3.1 b Radical addition to electron-rich alkenes) to an iminium intermediate that could then be trapped by a nucleophile to deliver **2.145** as the final product. In 2015, Greaney reported an oxyazidation of styrenes (C).[156] They combined **HIR.11** with **PC.4** ($Cu(dap)_2^{2+}$) under irradiation by a CFL for the conversion of styrenes (**2.146**) in presence of an alcohol (**2.147**) to the oxyazidated products **2.148**. A similar strategy was later applied in azidolactonisations.[120,157] In addition to the trifluoromethyl- and azido-reagents, halogenated reagents have also been used in a similar fashion.[158]

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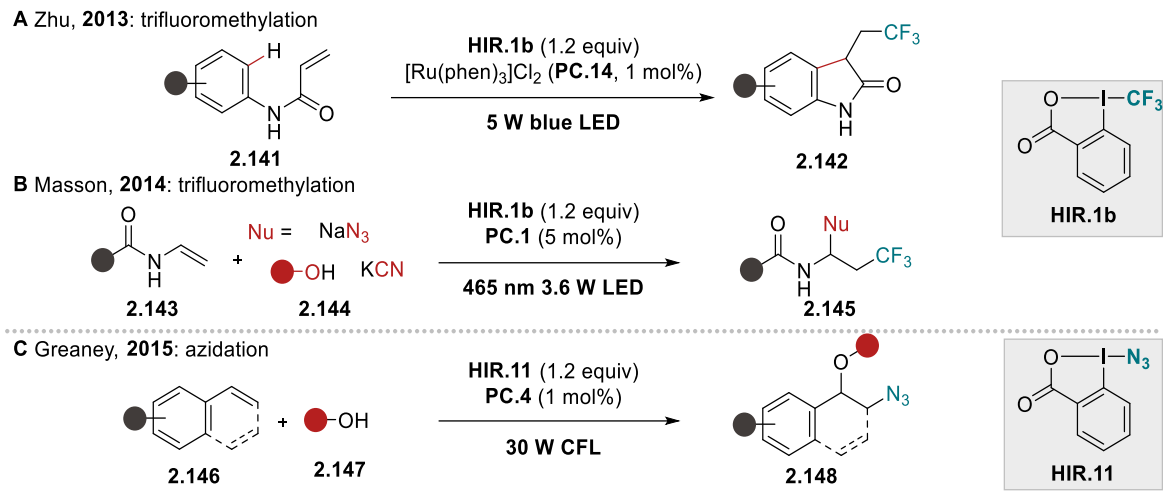
[153] Xu, P.; Xie, J.; Xue, Q.; Pan, C.; Cheng, Y.; Zhu, C. *Chem. – Eur. J.* **2013**, *19*, 14039–14042.
[154] It is important to note that the SET reduction of Togni reagents may not be limited to photoredox processes but could indeed be major in metal catalysed processes: Ling, L.; Liu, K.; Li, X.; Li, Y. *ACS Catal.* **2015**, *5*, 2458–2468.
[155] Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 1240–1243.
[156] Fumagalli, G.; Rabet, P. T. G.; Boyd, S.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2015**, *54*, 11481–11484.
[157] Alazet, S.; Le Vaillant, F.; Nicolai, S.; Courant, T.; Waser, J. *Chem. – Eur. J.* **2017**, *23*, 9501–9504.
[158] Wang, Y.; Li, G.-X.; Yang, G.; He, G.; Chen, G. *Chem. Sci.* **2016**, *7*, 2679–2683.

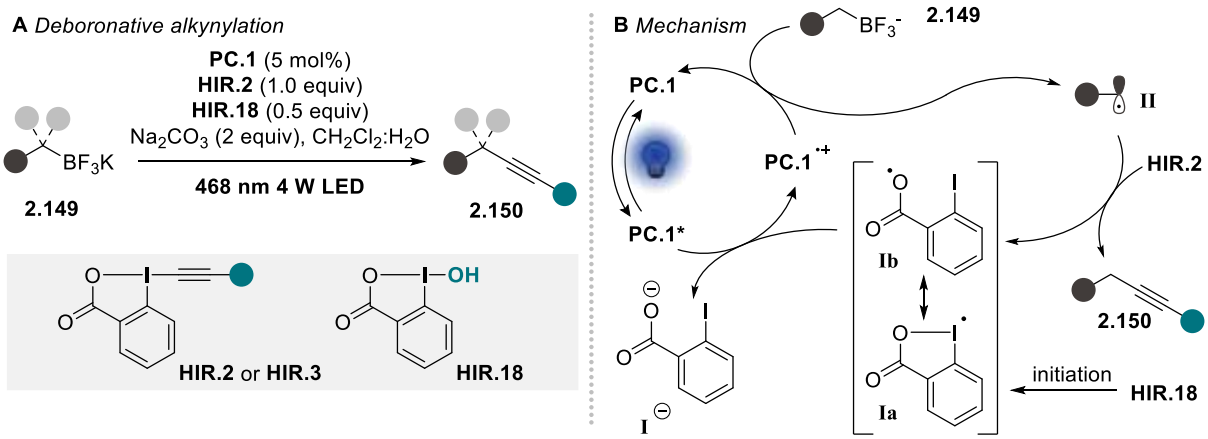


Scheme 2.38. Photocatalytic trifluoromethylation and azidation strategies via the SET reduction of λ³-iodanes

2.3.2.3.3. λ³-iodanes as radical traps under photocatalyst mediated conditions

a. Defunctionalisation alkynylation

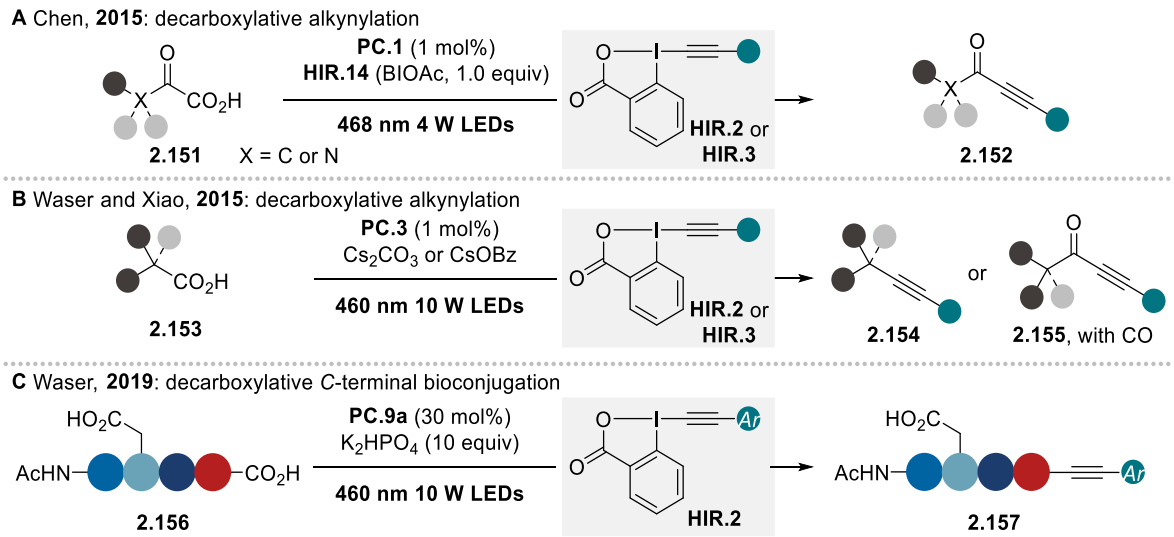
An early example of a photocatalysed alkynylation with EBXs was reported by the Chen group in 2014 (Scheme 2.39, A).[159] Under blue LED irradiation, they could convert trifluoroborate salts (**2.149**) to the corresponding alkynes (**2.150**) in presence of **PC.1** ($Ru(bpy)_3^{2+}$) and the additive (**HIR.18**). From a mechanistic standpoint, they propose an oxidative quenching cycle. The reaction is initiated by **HIR.18** generating the iodanyl radical **Ia** (in resonance with **Ib**). The excited state photocatalyst (**PC.1***) is then quenched by **Ia** generating the reduced iodobenzoate (**I**$^-$) and the oxidised photocatalyst (**PC.1**$^{\bullet+}$). The latter can now oxidise the alkyl-BF_3K salt (**2.149**), then fragments to the alkyl radical (**II**) and regenerating the ground state photocatalyst. **II** can then be trapped by the EBX (**HIR.2**) to afford the desired alkynylated product **2.150**. The trapping of **II** by **HIR.2** enables the generation of the iodanyl radical (**Ia**).



Scheme 2.39. Photocatalysed deboronative alkynylation with HIR.2 and proposed mechanism.

[159] Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. *J. Am. Chem. Soc.* **2014**, *136*, 2280–2283.

In 2015, the Chen group reported a decarboxylative alkynylation of α-ketoesters and α-amidoesters (**2.151**) using a hypervalent iodine oxidant (**HIR.14**) for substrate activation (Scheme 2.40, A).[160] The reaction proceeded in presence of **PC.1** ($Ru(bpy)_3^{2+}$) with an EBX (**HIR.2**) as a radical trap for the synthesis of ynones or ynamides (**2.152**). Later that year, the Xiao group and our group issued complementary photocatalysed decarboxylative alkynylations (B).[161] Both methods used **PC.3** under blue LED irradiation to oxidise the deprotonated carboxylic acid **2.153** and EBXs (**HIR.2** or **HIR.3**) as a radical trap to access the corresponding alkynes (**2.154**). Interestingly, the effect of the base seems to have a strong impact on the reaction time and the reagent compatibility. On the one hand, Xiao and co-workers used Cs_2CO_3, the reaction lasted 4 hours and presented a scope of arylalkynes with no example of a silyl alkyne transfer.[162] On the other hand, our group's method used cesium benzoate (CsOBz), the reaction took 24 hours to proceed, but the reagent scope included both TIPS-EBX (**HIR.3**) and Ar-EBXs (**HIR.2**). Xiao and co-workers could also access ynones by performing the reaction with a positive pressure of CO. This decarboxylative alkynylation strategy was later extended to small peptides by our group (C).[163] The peptides (**2.156**) could selectively undergo decarboxylation at the *C*-terminus to provide the desired alkynylated peptides (**2.157**) using **PC.9a** as an organic dye.

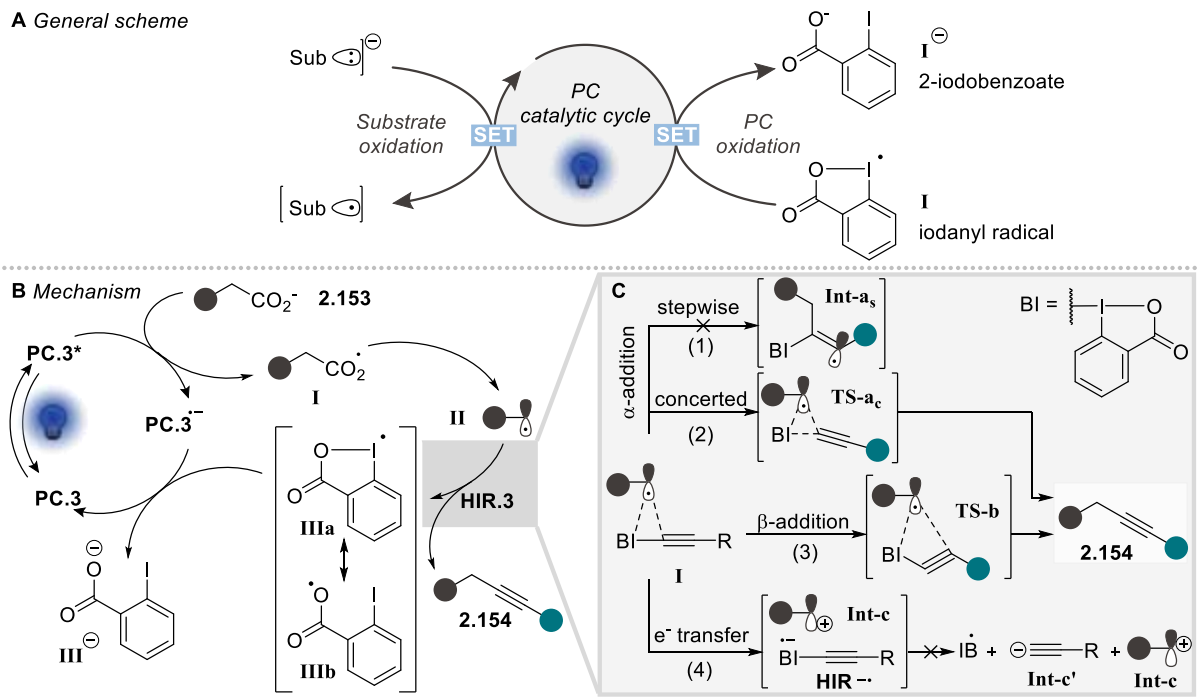


Scheme 2.40. Photoredox catalysed decarboxylative alkynylation with EBXs.

A general scheme can be envisaged for the mechanism of these transformations: the photocatalyst is responsible for the substrate oxidation and the iodanyl radical (**I**) is responsible for the photocatalyst oxidation (Scheme 2.41, A). In the case of the

[160] Huang, H.; Zhang, G.; Chen, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 7872–7876.
[161] a. Zhou, Q.; Guo, W.; Ding, W.; Wu, X.; Chen, X.; Lu, L.; Xiao, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199. b. Le Vaillant, F.; Courant, T.; Waser, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204.
[162] They were able to access one TIPS-alkyne in 56% yield for their scope of ynones with CO.
[163] Garreau, M.; Le Vaillant, F.; Waser, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 8182–8186.

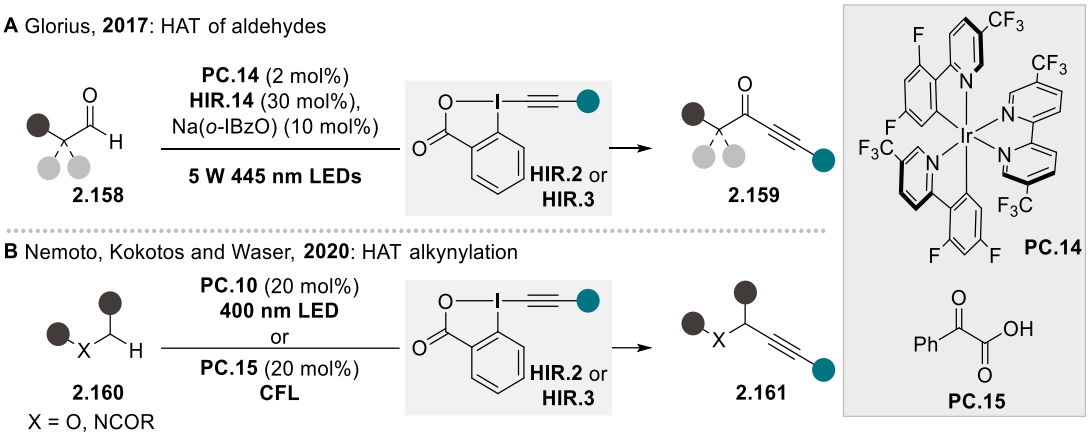
decarboxylative alkynylation with TIPS-EBX (**HIR.3**, B),[161] under blue light irradiation the photocatalyst (**PC.3**) absorbs a photon generating the excited state photocatalyst (**PC.3***, $E_{1/2}$(**PC.3***/**PC.3**$^{\bullet-}$) = + 1.21 V vs SCE). It can now perform a single electron oxidation of the carboxylate (**2.153**, + 0.9 V to + 1.2 V vs SCE), which generates a carboxyl radical (**I**). The latter undergoes rapid and irreversible β-fragmentation releasing $CO_{2(g)}$. The resulting alkyl radical (**II**) is then trapped by the EBX (**HIR.3**) forming the desired alkynylated product (**2.154**) and the iodanyl radical (**IIIa**), in resonance with the *O*-centred radical (**IIIb**). With a redox potential calculated to be + 0.25 V vs SCE for the couple **III**$^{\bullet+}$/**III**$^{-}$,[164] the iodanyl radical can be enable the reoxidation of the photocatalyst (**PC.3**$^{\bullet-}$, $E_{1/2}$(**PC.3**/**PC.3**$^{\bullet-}$) = - 1.37 V vs SCE) back down to the ground sate (**PC.3**). When turning specifically to the radical addition step (C), three main pathways were envisaged: (1) stepwise α-addition, (2) concerted α-addition (3) β-addition, and (4) electron transfer. For TIPS-EBX (**HIR.3**), DFT studies found that the intermediate resulting from the α-addition (1) was not calculable. This suggests that this pathway was unlikely to occur. The concerted α-addition (2) and the β-addition (2) pathways were accessible and due to the similar transition state energies (**TS-a**$_c$ and **TS-b**), both pathways may be occurring in parallel. Finally, the electron transfer pathway (3) seemed most likely unproductive: the electron transfer, albeit uphill, seemed feasible, however collapse to the acetylide and the iodanyl radical (IB$^{\bullet}$) was highly unfavourable.



Scheme 2.41. Photoredox catalysis with EBXs: mechanism of the decarboxylative alkynylation.

[164] Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* **2017**, *8*, 1790–1800.

As discussed previously, HAT is a valuable strategy for the photoredox generation of *C*-centred radicals. In 2017, Glorius reported a selective HAT-alkynylation of aldehydes (Scheme 2.42, A).[165] The aldehydes (**2.158**) undergo a photocatalysed HAT in presence of **HIR.14** and sodium 2-iodobenzoate (Na(*o*-IBzO)) with **PC.14**. The ensuing acyl radical is then trapped by **HIR.2** delivering the ynones (**2.159**). In 2020, the Kokotos group in collaboration with our group reported a photocatalysed HAT-alkynylation of ethers using glyoxylic acid as a photocatalyst, later that year Nemoto and co-workers reported a similar strategy using benzophenone (B).[166] In both cases the excited state photocatalysts **PC.10*** (benzophenone) or **PC.15** generate an electrophilic radical capable of HAT on **2.160**, the resulting α-oxo or α-amido radical can then be trapped by **HIR.2** affording **2.161**. In the report by Kokotos and co-workers, the mechanistic studies put in evidence the strong participation of a radical chain type mechanism to ensure high yields of the desired alkynylated product.



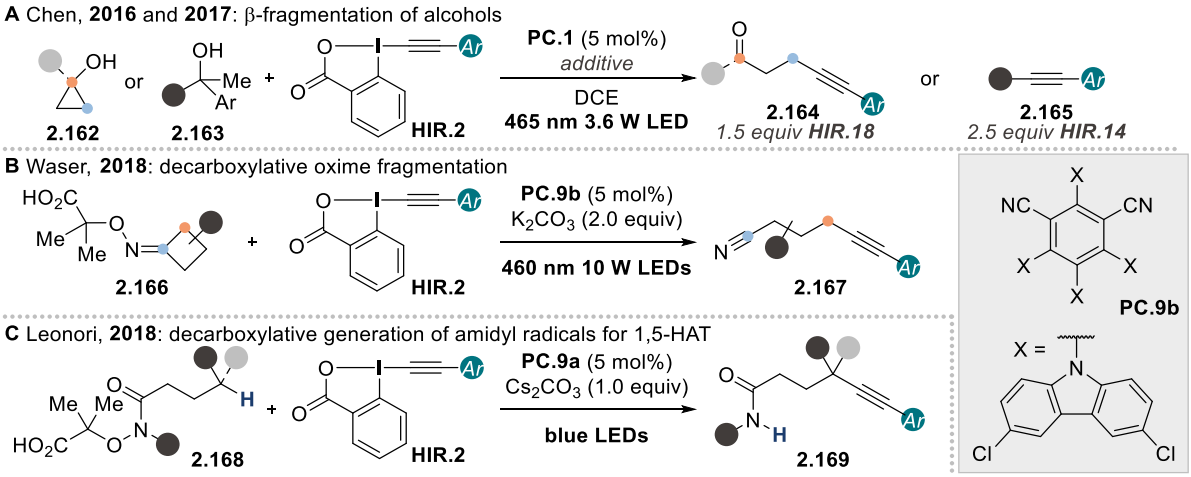
Scheme 2.42. Photomediated HAT of aldehydes and ether for alkynylation with EBXs.

b. Fragmentation cascades and remote functionalisation

In 2016, the Chen group investigated the β-fragmentation of alcohols for the ring-opening alkynylation of cyclopropyl alcohols, they could later generalise the β-fragmentation of alcohols (**2.162** or **2.163**) for the generation of acyl and phosphorus radicals (Scheme 2.43, A).[167] The alcohol can be activated by the additive (**HIR.14** or **HIR.18**) in presence of **PC.1** ($Ru(bpy)_3^{2+}$) under blue LED irradiation. β-fragmentation delivers the desired radical which can then be trapped by the EBX (**HIR.2**). In 2018, our group reported the oxidative fragmentation of oximes for the synthesis of alkynyl nitriles,[17a] using an oxime developed by the Leonori

[165] Mukherjee, S.; Garza-Sanchez, R. A.; Tlahuext-Aca, A.; Glorius, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 14723–14726.
[166] a. Voutyritsa, E.; Garreau, M.; Kokotou, M. G.; Triandafillidi, I.; Waser, J.; Kokotos, C. G. *Chem. – Eur. J.* **2020**, *26*, 14453–14460. b. Matsumoto, K.; Nakajima, M.; Nemoto, T. *J. Org. Chem.* **2020**, *85*, 11802–11811.
[167] a. Jia, K.; Zhang, F.; Huang, H.; Chen, Y. *J. Am. Chem. Soc.* **2016**, *138*, 1514–1517. b. Jia, K.; Pan, Y.; Chen, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 2478–2481. c. Jia, K.; Chen, Y. *Chem. Commun.* **2018**, *54*, 6105–6112. d. Jia, K.; Li, J.; Chen, Y. *Chem. – Eur. J.* **2018**, *24*, 3174–3177.

group (B).[168] Under blue LED irradiation, in presence of **PC.9b** (4ClCzIPN) the oxime (**2.166**) undergoes a decarboxylation fragmentation cascade. This entails ring-opening and the formation of a nitrile and a primary radical which can be alkynylated by **HIR.2** to form **2.167**. In the same year, Leonori used a similar redox active group this time as an amide to allow remote functionalisation of amides (C).[169] Similar to the example above, irradiation of **PC.9a** in presence of the redox active amide (**2.168**) promotes a fragmentation cascade. This leads to an amidyl radical which then performs a 1,5-HAT. The resulting *C*-centred radical was then trapped by **HIR.2**, affording **2.169**.



Scheme 2.43. Photocatalysed remote alkynylation via fragmentation cascades with EBXs.

Having explored a range of transformations using photoredox catalysis and HIRs as both alkyne source and substrate activators, the Chen group explored the effects of the HIR backbone (Figure 2.8).[170] They started by investigating the effect of the substitution of the reagent (**HIR.2b**) by introducing electron-withdrawing (F-atom, **HIR.19**) and electron-donating groups (-OMe, **HIR.20**). They studied three different alkynylation reactions: (1) a deboronation of trifluoroborate salts (**2.170a** - **2.170b**),[159] (2) the β-fragmentation of alcohols (**2.171a** and **2.171b**), [167a] and (3) the decarboxylation of a carboxylic acid (**2.172**).[160] Overall, the electron-rich substrate (**HIR.20**, in blue) affords the desired alkynylated products in the same or better yields when compared to the reference reagent **HIR.2b** (in black). The electron-poor scaffold (**HIR.19**, in red) performed variably depending on the reaction. In the deboronative alkynylation, it performs as well or better than the reference reagent **HIR.2b**, whereas for the β-fragmentation of alcohols and the decarboxylative alkynylation it leads to a drop in yield.

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[168] Dauncey, E. M.; Morcillo, S. P.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 744–748.
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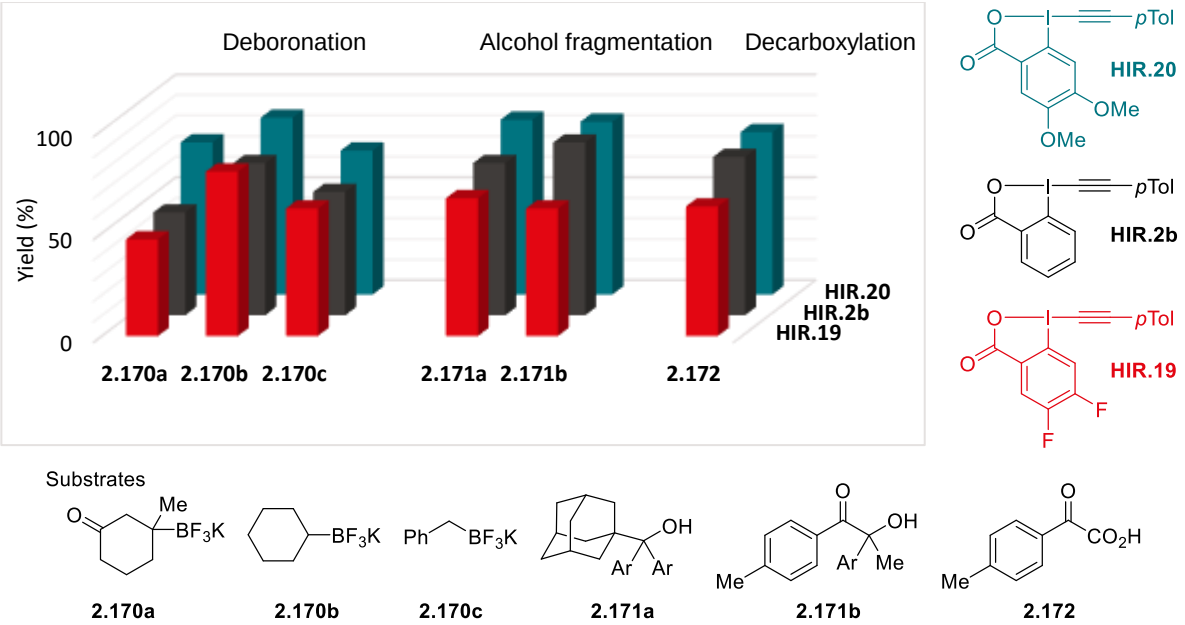

Figure 2.8. Effect of the core-modification of EBXs for a deboronative alkynylation, β-fragmentation of alcohols and decarboxylative alkynylation.

c. Alkene difunctionalisation

Like the oxime fragmentation and redox active amides seen in the previous paragraph, the α-aminooxy carboxylates have also been used for alkene difunctionalisation both in an intramolecular and an intermolecular fashion. In 2017, the Leonori group reported an intramolecular 1,2-iminoalkynylation of alkenes (Scheme 2.44, A).[171] Oxidation of the deprotonated **2.173** by the excited state photocatalyst **PC.6*** ($MesAcr^+$), resulting in an iminyl radical that then undergoes 5-exo-trig cyclisation. This results in a *C*-centred radical with can then be functionalised by **HIR.2** leading to the heterocyclic product **2.174**. In 2019, Studer and co-workers applied a similar strategy for an intermolecular 1,2-aminoalkynylation (B).[172] Under photoredox catalysis with **PC.9a** (4CzIPN), oxidative fragmentation of the *N*-Troc protected α-aminooxy carboxylate (**2.175**) resulted in an amidyl radical, which could then be intercepted by an alkene (**2.176**). This generates a *C*-centred radical, which was then trapped by **HIR.2** and delivered **2.177**.

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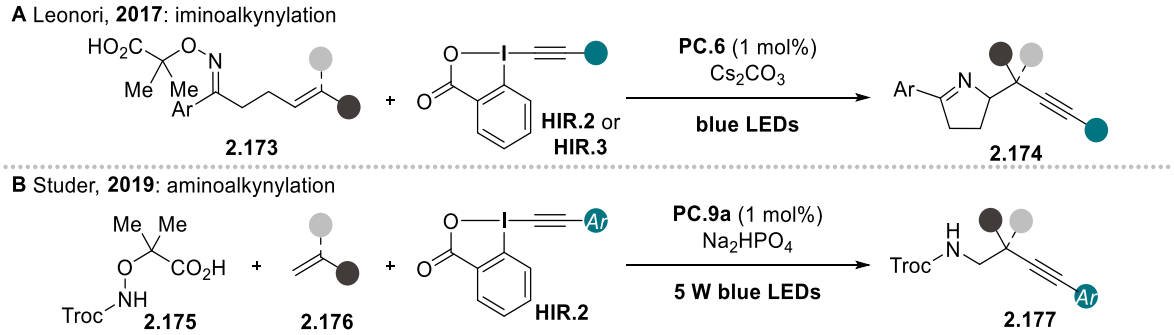

Scheme 2.44. Photomediated alkynylative difunctionalisation of alkenes with EBXs.

2.3.3. Hypervalent iodine (III) reagents – conclusive remarks

In this section, we discussed the electronics and the various scaffolds of hypervalent iodine (III) reagents and their reactivity in photochemical transformations. We could address the role of “oxidant-type” reagents and reagents employed for functional group transfer. The oxidant-type reagents have been often used as additives for substrate activation, as precursors for iodanyl radicals, and as external oxidants in photoredox catalysed transformations. Functional group transfer agents such as the trifluoromethyl- or the azido-reagents can be reduced to generate the trifluoromethyl- and azide radicals. In contrast, EBXs have been used exclusively as radical traps. EBXs have been frequently used for the alkynylation of radical resulting from the fragmentation of redox active groups and in some case the alkynylation of alkenes. However, to date, they have not been used in atom economical transformations. Finally, many of these hypervalent iodine reagents present photoactivity in the UV and visible region allowing them to be applied in both photocatalysed and non-photocatalysed transformations.

2.4. State of the art – conclusive remarks

In this chapter, after introducing frequently-used strategies in photochemistry today, it becomes apparent that photochemical transformations – including both photocatalysed and non-photocatalysed methods, are valuable for the generation of *C*-centred radicals. The use of free radical intermediates has often been disregarded due to the harsh conditions required for accessing these intermediates. In this regard, photochemical strategies have popularised the use of radical intermediates, which can now be generated in catalytic quantities at room-temperature. We then discussed the importance of alkynes for the synthetic chemist. Their synthesis can occur through four main strategies: (a) alkyne construction, (b) nucleophilic alkynylation (c) electrophilic alkynylation and (d) alkynylation of radicals. As the focus of this thesis is on photochemical strategies, this section focussed on the seminal reports of radical alkynylation in addition to recent advances in the field. Four main approaches for radical alkynylation were identified: (a) alkynylation with metal acetylides, (b) alkynylation with alkynyl sulfones, (c) alkynylation with EBX reagents, and (4) alkyne migrations. Finally, we turned to the role of hypervalent iodine reagents in photochemical transformations. After first discussing the role of “oxidant-type” hypervalent iodine reagents in photochemical transformations, the applications of functional group transfer reagents and more specifically EBXs was discussed. A variety of redox active groups can successfully be used in combination with EBXs for either direct or remote alkynylations. Despite the multiple applications of EBXs under photochemical activation, at the start of my thesis, there were no reports for a radical atom-economical alkynylative difunctionalisation.

2.5. References

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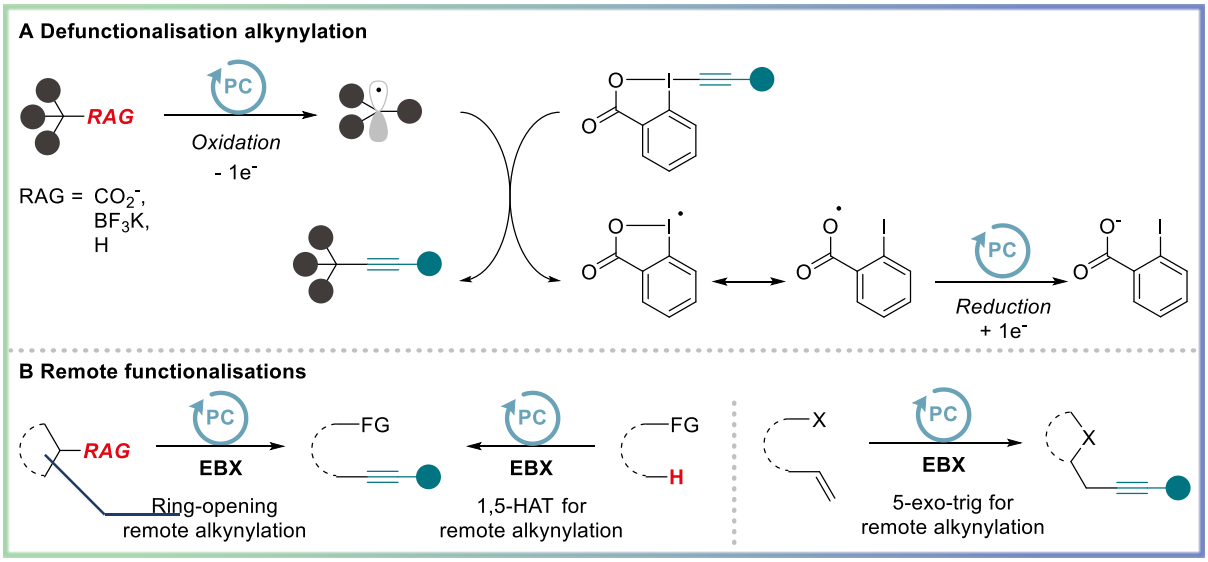
Chapter 3: Goals of the thesis

3. Goals of the thesis

The goal of this thesis is the study of photochemical alkynylations with hypervalent iodine reagents. As discussed previously, alkynes are versatile synthetic intermediates with applications from organic chemistry methodology to materials sciences and medicinal chemistry. In this regard, radical and photocatalytic alkynylations have enabled the synthesis of sterically demanding scaffolds. EBXs have been used for the defunctionalisation-alkynylation of carboxylates, alkyl trifluoroborates (not exhaustive) and the direct alkynylation of C-H bonds (Scheme 3.1). When using photocatalysis, the substrates generally pocess an oxidisable redox active group (resulting in a reduced photocatalyst species), as the iodanyl radical generally oxidises the photocatalyst. More recently, EBXs have been combined with remote alkynylation strategies that proceed either through ring-opening, 1,5-HAT or a 5-exo-trig cyclisation. At the start of my thesis, alcohols and amines had not been used as precursors for a defunctionalisation-alkynylation with EBXs, and there were no examples of alkene alkynylation strategies that did not involve a 5-exo-trig cyclisation. In this regard, we defined two main objectives: (1) the development of a photochemical difunctionalisation enabling the introduction of alkyne group and a second group; (2) the deoxyalkynylation of alcohols. Interesting while exploring this strategy, we discovered the photoactivity of EBXs and decided to explore this approach in photocatalyst free alkynylations.

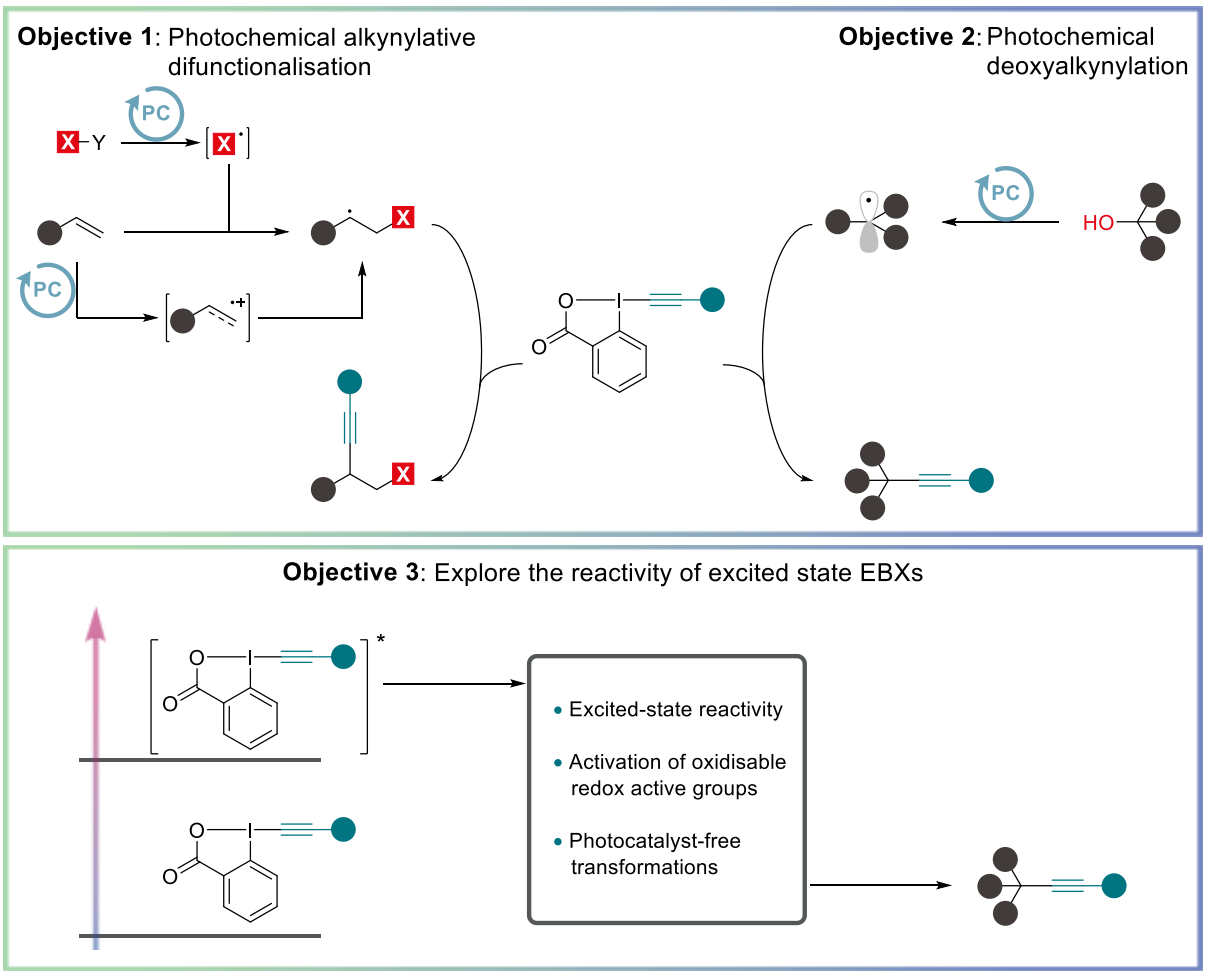


Scheme 3.1. Global state of the research: direct and remote photochemical alkynylations.

We first aimed to develop a difunctionalisation strategy (Scheme 3.2, **Objective 1**). Indeed, most photochemical alkynylations proceed following a defunctionalisation alkynylation strategy resulting in the replacement of functional group by an alkyne. The value of this approach is the selective activation of a specific functional group (e.g. carboxylate, trifluoroborate) and its replacement by a valuable alkyne group. Few examples, allow the

introduction of two functional groups, of which one is an alkyne. In the interest of step and atom economy, difunctionalisation strategies are highly relevant. Consequently, an alkynylative difunctionalisation strategy would enable the introduction of an alkyne and a second functional group in a single step. Amidst the many challenges that this type of strategy could entail, we hoped a photocatalytic approach could enable good chemoselectivity (alkene vs alkyne) and regioselectivity. Based on the literature precedence, two main approaches could be envisaged: (1) the addition of a free radical to the π-system generating a second radical that can allow the introduction of a second functional group; (2) the single electron oxidation of the π-system to generate a radical cationic intermediate followed by the addition of a nucleophile to provide a free radical that could then be functionalised. The first approach has been thoroughly explored using thermal and photochemical activation (see paragraphs: 2.1.4.3.1 Radical additions to alkenes and 2.3.2.3.2 Photocatalysed SET reduction of λ3-iodanes). The second approach has been poorly exploited with thermally activated radical initiators (see paragraph: 2.2.3.3 Hypervalent iodine reagents). Under photochemical activation, few reports include heteroatom substituted alkenes and the transformations were limited to hydrofunctionalisation and cyclisations (see paragraph: 2.1.4.3.2 Activation of π-systems through oxidation or reduction).

For our second objective, we aimed to investigate alcohols as precursors for alkyl radicals (Scheme 3.2, **Objective 2**). Indeed, alcohols are a frequently encountered functional group. Under radical conditions few procedures allow their conversion into alkynes (one example with *N*-phthalimidoyl oxalates is reported in paragraph 2.2.3.2. Radical alkynylation with alkynyl sulfones). However, the range of redox active groups for the generation of radicals from alcohols is relatively broad (references can be found in paragraph 2.1.4.1.2 Alcohols as alkyl radical precursors). In addition to the various activating groups, these strategies also allow the generation of tertiary radicals. Thanks to the high reactivity of these species, tertiary radicals are valuable intermediates for accessing quaternary carbon centres. Alcohols therefore seemed like ideal candidates for the construction of sterically demanding scaffolds. During our investigations, we discovered the photoactivity of EBXs, allowing us to define a third objective (**Objective 3**). Previous studies show the possible direct photoexcitation of hypervalent iodine species; however, these strategies generally involve the homolytic cleavage of an I^{III}-heteroatom bond (2.3.2.3.1, Direct excitation). The direct excitation and reactivity modes of an alkynyl-$I^{III}X$ type species, and more generally of carbon-$I^{III}X$, was unprecedented and worth exploring. We therefore sought to explore the excited state reactivity of the EBXs, its application in synthetic methodology and the limitations of the approach.



Scheme 3.2. Goals of the thesis.

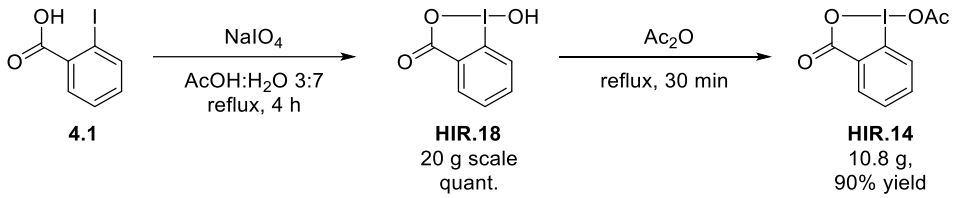
Chapter 4: Ene-Carbamate and Enol Ether Oxy-Alkynylation

4. Ene-Carbamate and Enol Ether Oxy-Alkynylation

4.1. Synthesis of the starting materials

4.1.1. Synthesis of hypervalent iodine precursors and additives (**HIR.18** and **HIR.14**)

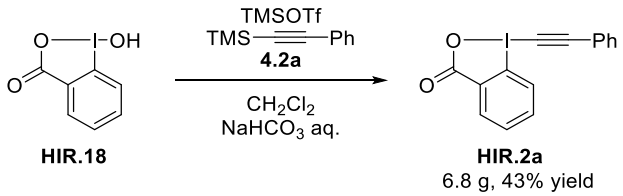
Starting from commercial *o*-iodobenzoic acid (**4.1**, Scheme 4.1) with sodium periodate as an oxidant,[1] **HIR.18** can be accessed in quantitative yield on 20-gram scale. **HIR.14** can then be synthesised by refluxing **HIR.18** in acetic anhydride affording the desired compound in 90% yield on 10-gram scale.[2]



Scheme 4.1. Synthesis of hypervalent precursors and additives (HIR.18 and HIR.14).

4.1.2. Model reagent: PhEBX (**HIR.2a**)

PhEBX (**HIR.2a**) was chosen as the model reagent for the optimisation studies as it has been reported to be a good radical trap (cf. introduction, sections 2.2.3.3. and 2.3.2.3.3).[3] It can be obtained in one step from **HIR.18** (Scheme 4.2).[4] **HIR.18** is activated by trimethylsilyl trifluromethane(sulfonate) followed by substitution with the alkyne **4.2**. The compound, **HIR.2a,** was reported to be purified by "boiling in acetonitrile" to afford a white solid. During this project, a second purification strategy was developed by recrystalising the crude solid in EtOAc:MeOH 2:1 to afford off-white to colourless needle-like crystals in 43% yield on gram scale.[5]



Scheme 4.2. Synthesis of PhEBX (HIR.2a).

4.1.3. Model substrate: *N*-vinyl oxazolidinone (**4.3a**)

N-vinyl oxazolidinone (**4.3a**) was selected for the optimisation of the reaction conditions based on previous reports as a model substrate for ene-carbamates with ATRA type

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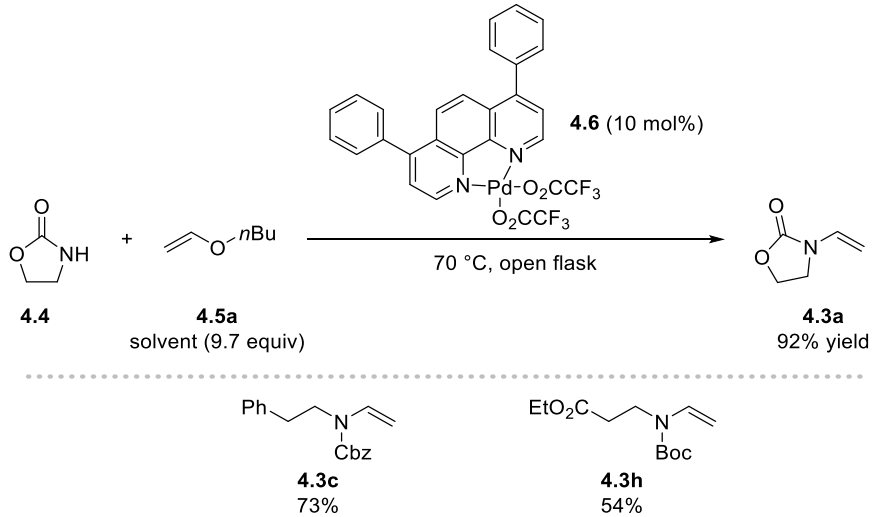
[1] Kraszkiewicz, L.; Skulski, L. *Arkivoc* **2003**, *2003*, 120–125.
[2] Eisenberger, P.; Gischig, S.; Togni, A. *Chem. - Eur. J.* **2006**, *12*, 2579–2586.
[3] a. Hari, D. P.; Nicolai, S.; Waser, J. Alkynylations and Vinylations. In *PATAI'S Chemistry of Functional Groups*; 2018; pp 1–58. b. Le Vaillant, F.; Waser, J. *Chem. Sci.* **2019**, *10*, 8909–8923.
[4] Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem. – Eur. J.* **2012**, *18*, 5655–5666.
[5] Amos, S. G. E.; Nicolai, S.; Waser, J.; **2020**, *11*, 11274-11279

transformations,[6] and for its absence of rotamers enabling facile ^{1}H NMR yield estimations. It can be obtained in one step through a palladium-catalysed cross coupling from commercial oxazolidinone (**4.4**) and *n*-butyl vinyl ether (**4.5a**) using the palladium catalyst (**4.6**, Scheme 4.3).[7] The corresponding ene-carbamate (**4.3a**) could be obtained in 92% yield. Although the palladium catalysed coupling with *n*-butyl vinyl ether was efficient for the synthesis of **4.3a**, due to the poor reproducibility for the synthesis of the catalyst (**4.6**),[8] this process was only applied for the synthesis of substrates **4.3c** and **4.3h**. We therefore investigated other strategies to access the desired scaffolds.



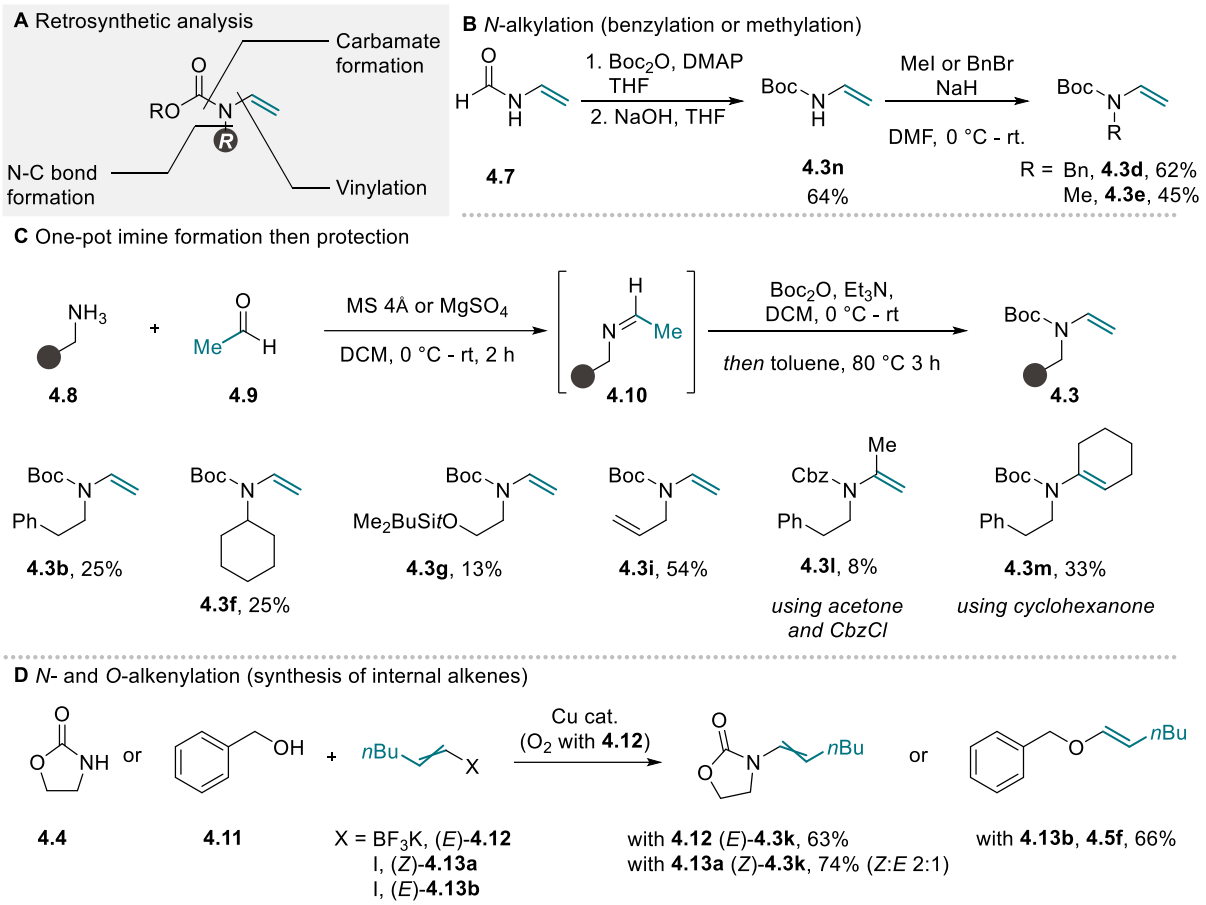
Scheme 4.3. Palladium catalysed vinylation of oxazolidinone: synthesis of *N*-vinyl oxazolidinone (4.3a), 4.3c and 4.3h.

4.1.4. General strategies for ene-carbamate synthesis

From a retrosynthetic point of view (Scheme 4.4, A), we can envisage the alkylation of a N-H vinyl carbamate, carbamate protection of the corresponding enamine, alkenylation of an N-H carbamate. The N-H vinyl carbamate (**4.3n**) could be obtained from commercial **4.7** in 64% yield (B). Alkylation of **4.3n** was successful for the synthesis of benzyl and methyl ene-carbamates (**4.3d**, 62% yield and **4.3e**, 45% yield).[9] For the synthesis of Boc protected ene-carbamates that could not be accessed by alkylation, we performed a one-pot imine formation, tautomerisation and Boc-protection (C).[10] Starting from an amine (**4.8**) in presence of acetaldehyde (**4.9**) and a desiccant, we could form the imine (**4.10**). The crude solution was then treated with a basic solution of Boc-anhydride, although the yields were not high (10-

[6] Poittevin, C.; Liautard, V.; Beniazza, R.; Robert, F.; Landais, Y. *Org. Lett.* **2013**, *15*, 2814–2817.
[7] Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845–1848.
[8] The precipitation of the catalyst **4.6** was biphasic which often led to decomplexation despite vigorous agitation rendering it's synthesis poor reproducible in our hands.
[9] a. Lefranc, J.; Fournier, A. M.; Mingat, G.; Herbert, S.; Marcelli, T.; Clayden, J. *J. Am. Chem. Soc.* **2012**, *134*, 7286–7289. b. De Simone, F.; Saget, T.; Benfatti, F.; Almeida, S.; Waser, J. *Chem. - Eur. J.* **2011**, *17*, 14527–14538. c. Liu, S.-Y.; Xu, S. WO/2015/126400, 2015, A1.
[10] Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216–12217.

30%), we could access the desired scaffolds (**4.3b**, **4.3f**, **4.3g** and **4.3i**) in synthetically relevant quantities (100 – 900 mg). This method also gave access to the Cbz-protected propen-2-yl scaffold **4.3l** in 8% yield, however, it did not work when attempting to access Cbz-protected vinyl carbamates.[11] The cyclohexenyl substrate **4.3m** could be accessed following this two-step protocol in 33% yield using cyclohexanone instead of acetaldehyde. Finally, the synthesis of internal ene-carbamates (**4.3k**, D) and enol ethers (**4.5f**) was possible from the corresponding carbamate (**4.4**) or alcohol (**4.11**) using copper catalysis with an alkene source (**4.12** or **4.13a** or **4.13b**).[12] (*E*)-4.3k could be obtained in 63% yield from **4.4** and (*E*)-**4.12**, (*Z*)-**4.3k** was obtained as a mixture of (*Z*) and (*E*) alkene (Z:E 2:1) in 74% overall yield using (Z)-**4.13a**. Finally, **4.5f** was obtained in 66% yield from **4.11** and (*E*)-**4.13b**.



Scheme 4.4. Synthesis of ene-carbamates and enol ether 4.5f.

4.1.5. Synthesis of the 4CzIPN-type photocatalysts (**PC.9a** and **PC.9b**)

The 4CzIPN catalysts are easily accessible in a single step from the corresponding commercial carbazole (**4.14a** or **4.14b**) and 2,4,5,6-tetrafluoroisophthalonitrile (**4.15**) with sodium hydride as a base. **PC.9a** was obtained in 73% yield and **PC.9b** in 87% yield.

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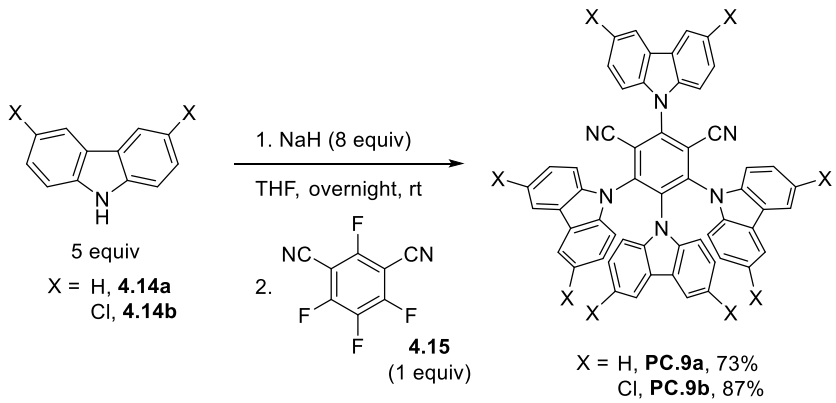
[11] We suspect this is due to the increased acidity of the media, which leads to the hydrolysis of the imine.
[12] Bolshan, Y.; Batey, R. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 2109–2112.



Scheme 4.5. Synthesis of the 4-CzIPN-type organic dyes.

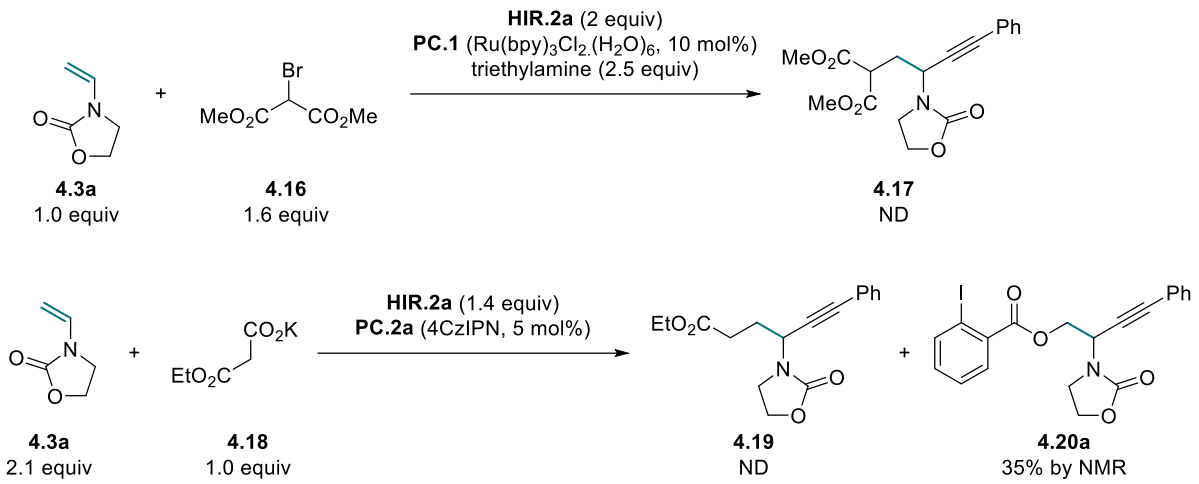
4.2. Optimisation of the reaction conditions

4.2.1. Preliminary results

These results were obtained by Dr. Stefano Nicolai.

Inspired by the work of Masson and Stephenson in the area of photomediated ATRA transformations,[13] we attempted a dicarbofunctionalisation of **4.3a** with bromomalonate **4.16** and **HIR.2a** (PhEBX) with **PC.1** ($Ru(bpy)_3^{2+}$) as a photocatalyst (Scheme.4.6). Unfortunately, the desired compound (**4.17**) was not observed and the reaction profile by ^{1}H NMR was messy. Considering the precedence of decarboxylative alkynylations with EBXs using photoredox catalysis,[14] we decided to use ethyl potassium malonate (**4.18**) to help generate the desired α-carbonyl radical with **PC.9a** (4CzIPN) an oxidising photocatalyst that can promote decarboxylations.[15] To our surprise, we did not observe the expected compound **4.19** but the incorporation of both parts of the EBX reagent resulting in the oxyalkynylated scaffold **4.20a** in 35% yield by ^{1}H NMR.

[13] For a review: Courant, T.; Masson, G. *J. Org. Chem.* **2016**, *81*, 6945–6952.
[14] a. Huang, H.; Zhang, G.; Chen, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 7872–7876. b. Zhou, Q.; Guo, W.; Ding, W.; Wu, X.; Chen, X.; Lu, L.; Xiao, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199. c. Le Vaillant, F.; Courant, T.; Waser, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204.
[15] Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. *Chem. Sci.* **2018**, *9*, 5883–5889.



Scheme.4.6. Discovery of the photocatalysed 1,2-oxyalkynylation of 4.3a with HIR.2a

We decided to proceed with the optimisation of the reaction conditions to promote the formation of compound **4.20a**.

4.2.2. Optimisation of the photocatalysed alkynylative difunctionalisation of **4.3a** with PhEBX (**HIR.2a**)

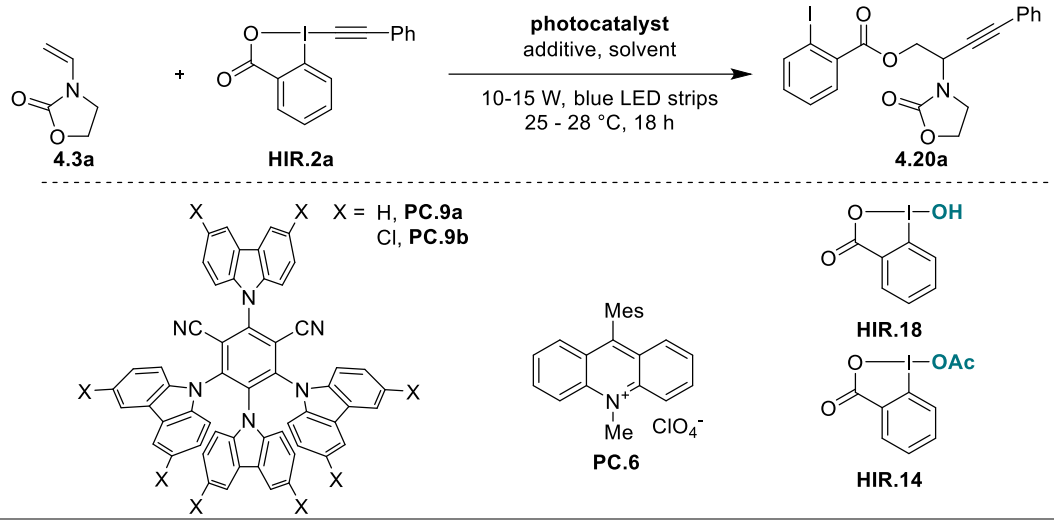
We soon realised that the malonate salt (**4.18**) was not playing a role in the transformation and speculated that we may be performing an oxidation of the ene-carbamate similarly to Nicewicz's alkene hydrofunctionalisations (cf. Introduction, paragraph 2.1.4.3.2. Activation of π-systems, a. Oxidations).[16] The redox potential of **4.3a** was measured to be +1.30 V vs SCE by cyclic voltammetry. We then proceeded to screen photocatalysts. With DCE as a solvent, **HIR.2a** as the limiting reagent and 1.5 equivalents of **4.3a**, 4CzIPN (**PC.9a***/**PC.9a**$^{\bullet-}$: +1.35 V vs SCE)[15] afforded the desired compound in 30% ^{1}H NMR yield (Table 4.1, entry 1). When moving to the slightly more oxidising photocatalyst 4ClCzIPN (**PC.9b***/**PC.9b**$^{\bullet-}$: +1.58 V)[15] the compound was obtained in 42% NMR yield (entry 2). Interestingly, MesAcr^{+} (**PC.6**$^{+}$*****/**PC.6**$^{\bullet}$: +2.06 V)[17] performed poorly: despite high conversion of **4.3a**, the desired product **4.20a** was obtained in 5% yield (entry 3). Upon repeating the reaction with **PC.9b**, we noticed that the yield varied depending on the batch of **HIR.2a** (entry 4). At this point, we turned to the synthetic procedure for the synthesis of **HIR.2a**. First, we decided to develop a recrystallisation procedure for **HIR.2a** to ensure higher purity. The recrystalised batch was then tested (**4.3a**, 1.5 equiv; **PC.9b**, 5 mol%, DCE) although the yield of **4.20a** was low (34%, entry 5) the result was reproducible (3 repetitions). When considering the use of oxidant-type HIRs as additives in photomediated transformations (cf. Chapter 2 paragraph 2.3.2.2. Oxidant-type λ^{3}-iodanes),

[16] Romero, N. A.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 17024–17035.
[17] Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166.

[18] we wondered if the addition of **HIR.14** or **HIR.18** could improve the yield. Furthermore, the lack of reproducible results depending on the batch of **HIR.2a** also suggested that an impurity may have been affecting the reaction yield, and it was indeed plausible that residual **HIR.18** may be a contaminant as it is the precursor for the synthesis of **HIR.2a**. When we performed the reaction with 1.5 equivalents of **HIR.18**, we observed a slight increase to 46% of **4.20a** (entry 6). We then decided to test the transformation with 1.5 equivalents of **HIR.14**, the desired oxyalkynylated product was obtained in 70% yield (entry 7). We then wondered if the **HIR.2a** was required as an alkyne source for the transformation. We tested the iodo-alkyne (**4.21**, 1 equiv) with **HIR.14** (1.5 equiv) and the desired compound was obtained in 20% yield (entry 8). We continued with **HIR.2a**, we found that the equivalents of **HIR.14** could be reduced to 0.5 equiv with no drop in yield (entries 9 and 10). However, with only 0.1 equiv of **HIR.14** we observed a slight decrease in yield (64%, entry 11) and decided to continue with 0.5 equiv. Both DMSO and CH_2Cl_2 could also be used as solvents (entries 12 and 13). Fine tuning of the reaction conditions were performed on scope scale (0.2 mmol): CH_2Cl_2 was used as solvent, the concentration was increased to 0.25 M, and the catalytic loading could be lowered to 2 mol% (entries 14 – 16) allowing formation of the desired compound in 80% yield. Interestingly, we found that with these conditions, **HIR.14** could be used in quantities as low as 0.05 equiv with no alteration to the yield (entry 17). At this stage, we were unsure of the role of **HIR.14**. As it could potentially be a source of iodanyl radical which could promote a radical chain process, we decided to keep 0.5 equiv of **HIR.14** for the final conditions.

[18] Jia, K.; Chen, Y. Photochemistry of Hypervalent Iodine Compounds. In *PATAI'S Chemistry of Functional Groups*; American Cancer Society, 2018; pp 1–42.

Table 4.1. Optimisation of the photocatalysed oxyalkynylation of ene-carbamate 4.3a with HIR.2a.



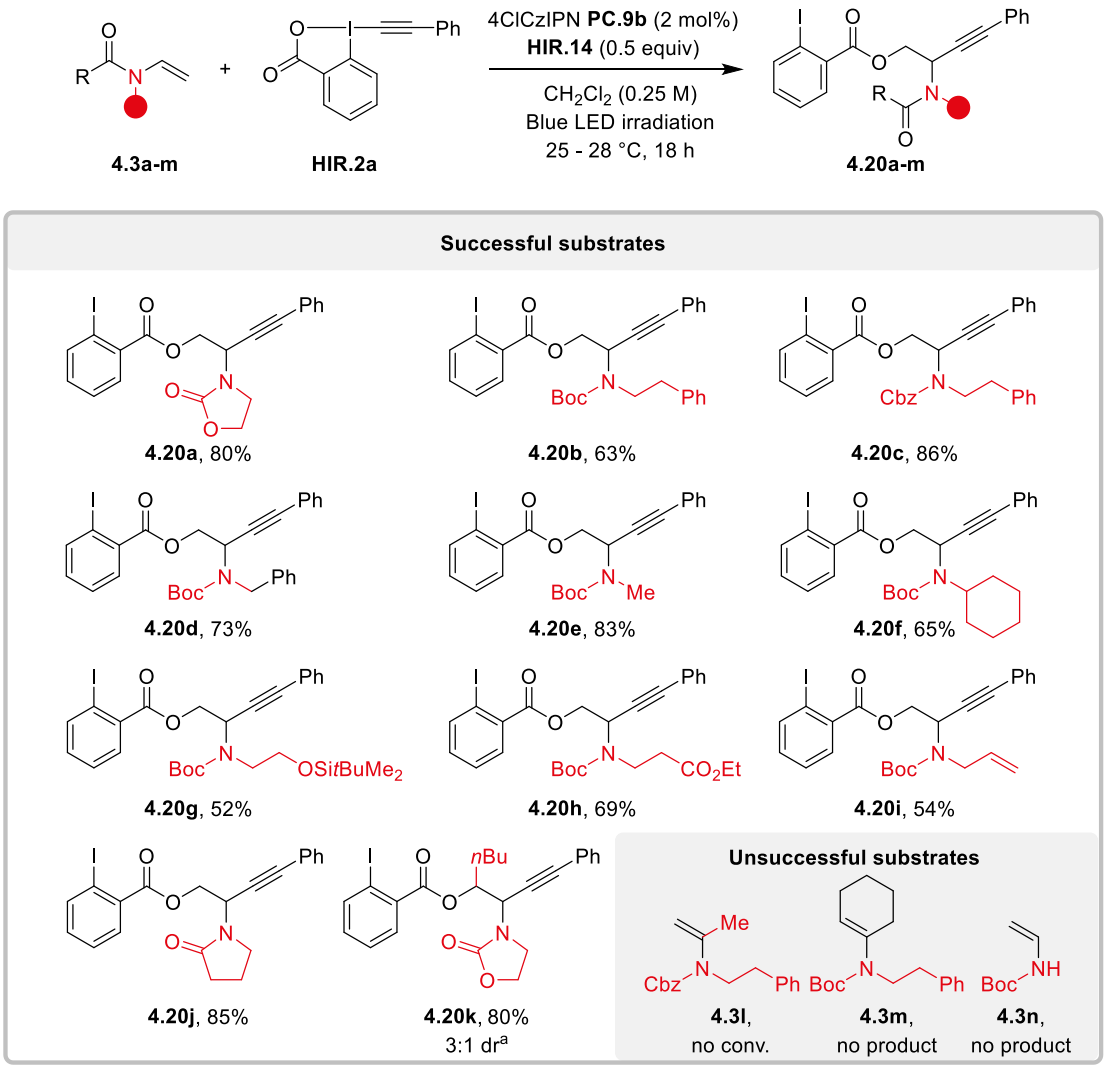
entry	PC	Additive (x equiv)	Solvent (M)	yield (%)
1	**PC.9a**	None	DCE	30
2	**PC.9b**	None	DCE	42
3	**PC.6**	None	DCE	5
4	**PC.9b**	None	DCE	36-65
5[b]	**PC.9b**	None	DCE	34
6[b]	**PC.9b**	**HIR.18** (1.5 equiv)	DCE (0.1 M)	46
7[b]	**PC.9b**	**HIR.14** (1.5 equiv)	DCE (0.1 M)	70
8[b,c]	**PC.9b**	**HIR.14** (1.5 equiv)	DCE (0.1 M)	20
9[b]	**PC.9b**	**HIR.14** (1.0 equiv)	DCE (0.1 M)	73
10[b]	**PC.9b**	**HIR.14** (0.5 equiv)	DCE (0.1 M)	75
11[b]	**PC.9b**	**HIR.14** (0.1 equiv)	DCE (0.1 M)	64
12[b]	**PC.9b**	**HIR.14** (0.5 equiv)	DMSO (0.1 M)	75
13[b]	**PC.9b**	**HIR.14** (0.5 equiv)	CH_2Cl_2 (0.1 M)	80
14[b]	**PC.9b**	**HIR.14** (0.5 equiv)	CH_2Cl_2 (0.25 M)	80
15[b]	**PC.9b**	**HIR.14** (0.5 equiv)	CH_2Cl_2 (0.5 M)	80
16[b,d]	**PC.9b**	**HIR.14** (0.5 equiv)	CH_2Cl_2 (0.25 M)	80
17[b,d]	**PC.9b**	**HIR.14** (0.05 equiv)	CH_2Cl_2 (0.25 M)	80

Reaction conditions: **4.3a** (0.15 mmol, 1.5 equiv), **HIR.2a** (0.1 mmol, 1.0 equiv), PC (5 mol%) in degassed solvent with additive when necessary. Bule LED irradiation (10 - 15 W, $\lambda_{max} \approx 460$ nm) for 18 h at rt. [a1]H NMR yield determined by addition of 1.0 equiv of CH_2Br_2 as an internal standard. [b]Recrystalised **HIR.2a**. [c]With 1-iodo-2-phenylacetylene instead of **HIR.2a**. [d]2 mol% of PC

4.3. Scope and application of the strategy

With the optimised reaction conditions in hand, we turned to the scope of the reaction (Scheme.4.7). The model substrate (**4.3a**), a cyclic ene-carbamate, afforded **4.20a** in 80% yield. Acyclic ene-carbamates with phenethyl substitution performed well, affording Boc- and Cbz-protected amines **4.20b** and **4.20c** in 63% and 86% yield. Boc-protected benzyl, methyl and cyclohexyl scaffolds delivered **4.20d**, **4.20e** and **4.20i** in 73%, 83% and 65% yield. A silylated alcohol and an ethyl ester were also well tolerated functionalities yielding the desired compounds **4.20g** and **4.20h** in 52% and 69% yield. An allyl ene-carbamate could be difunctionalised with no observable functionalisation of the allyl-double bond (**4.20f** in 54%

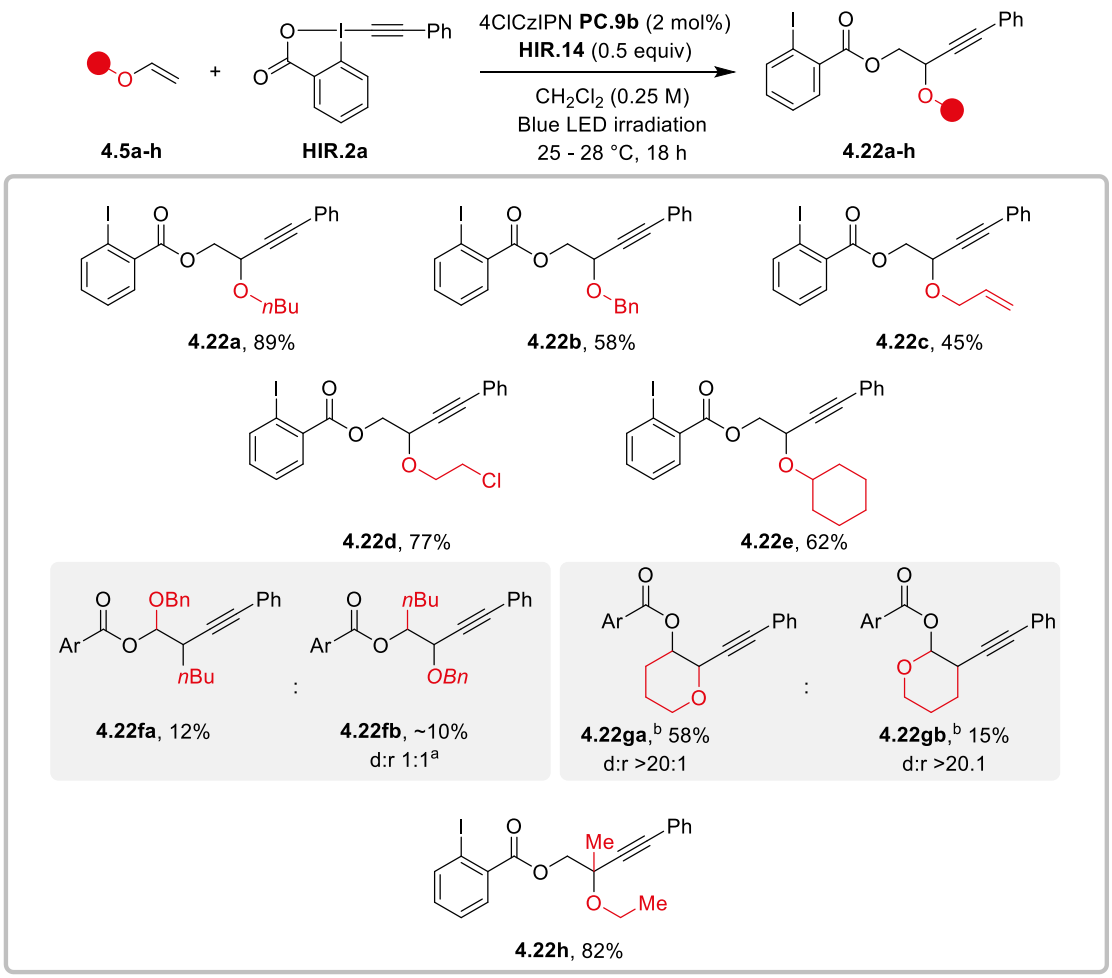
yield). This illustrated the possibility of selective functionalisation of ene-carbamates over alkenes. Commercial *N*-vinyl pyrrolidinone gave compound **4.20j** in 85% yield. We then tested this substrate on gram scale, which afforded 0.99 g of **4.20j** (74% yield). Finally, we explored the substitution pattern of the ene-carbamate. **4.20k** was obtained from β-substituted (*E*)-ene-carbamate as a mixture of diastereoisomers in 80% yield (3:1 dr.). Interestingly, the same result was obtained from the 2:1 mixture of (*Z*) and (*E*)-alkene suggesting that the conformation of the starting material does not impact the yield or the diastereoselectivity of the transformation. The scope did present some limitations: no conversion was observed with the α-methyl ene-carbamate (**4.3l**), despite observable conversion of the cycloxen-1-yl carbamate (**4.3m**) no product was detected by ^{1}H NMR analysis. Finally, the free N-H vinyl carbamate (**4.3n**) led to a very messy reaction mixture and no product formation.



Scheme.4.7. Scope of ene-carbamates for the photocatalysed alkynylative difunctionalisation. Reactions conditions: 0.20 - 0.25 mmol **HIR.2a** (1 equiv), alkene (1.2 - 1.5 equiv), **HIR.14** (0.5 equiv) and **PC.9b** (2 mol%) in CH_2Cl_2 0.25 M. Blue led irradiation (10 - 15 W, $\lambda_{max} \approx 460$ nm) for 18 h at rt.

Having explored a scope of ene-carbamates, we wondered if our method could also be applied to enol ethers (Scheme.4.8). Similarly to ene-carbamates they present a redox potential that

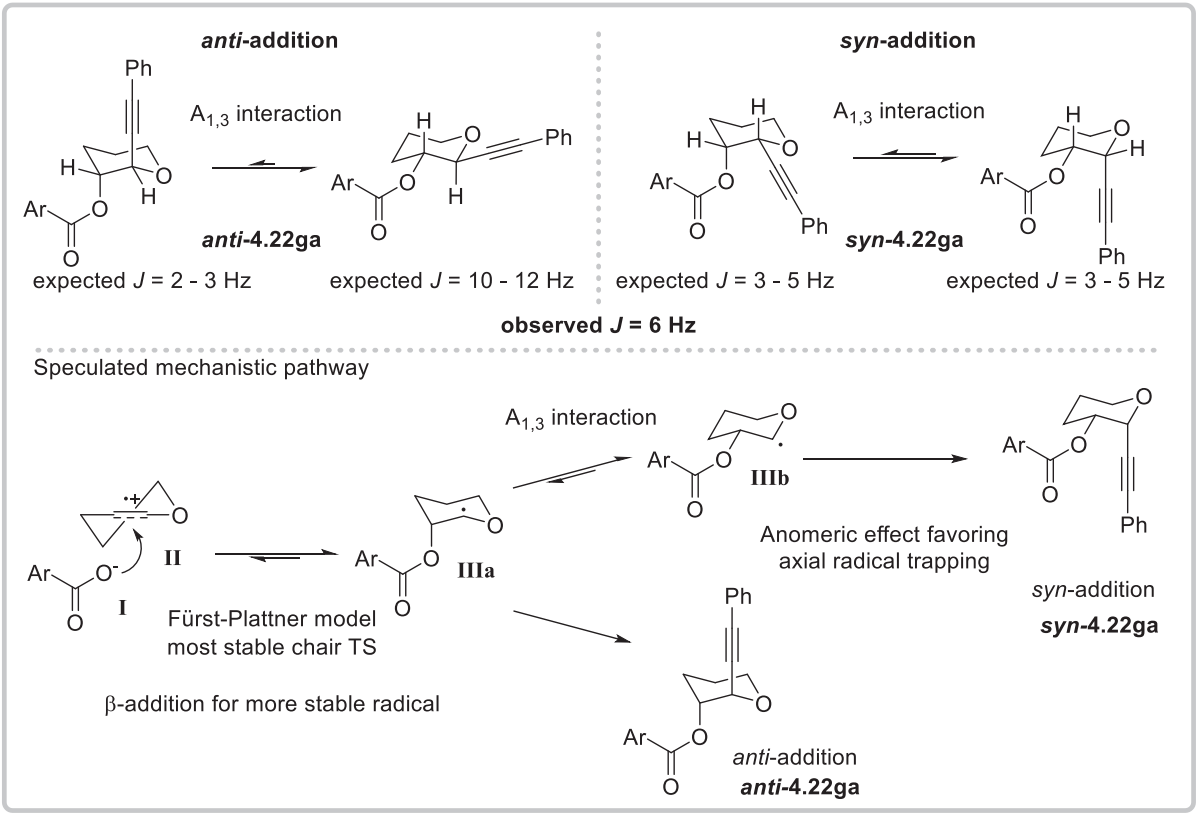
could allow their oxidation with **PC.9b** (e.g. dihydropyran (DHP, **4.5g**), + 1.51 V vs SCE,[19] *iso*-butyl *N*-vinyl ether, 1.46 vs SCE).[20] With no change to the reaction conditions, we were pleased to observe the difunctionalisation of aliphatic, benzylic and allylic ethers affording **4.22a**, **4.22b** and **4.22c** in 89%, 58% and 46% yield respectively. The method also gave access to the chlorinated product **4.22d** in 77% yield and cyclohexyl substituted enol ether **4.22e** in 62% yield. Interestingly, β-substitution resulted in a complex inseparable mixture of regio- and diasteroisomers. The acetal (**4.22fa**) was obtained in 12% yield (single diasteroeisomer by ^{1}H NMR), and the anti-Markovnikov product (**4.22fb**) was formed in 10% yield as a mixture of diastereoisomers. Similarly, DHP **4.5g** afforded two regioisomers: the anti-Markovnikov product (**4.22ga**) in 58% yield, and the Markovnikov product (**4.22gb**) in 15% yield. Both compounds were isolated together as single diastereoisomers based on ^{1}H NMR analysis. In contrast to our result with α-substituted ene-carbamates, α-substitution of enol-ethers was well tolerated, giving access to tertiary ether **4.22h** in 82% yield.



[19] Roth, H.; Romero, N.; Nicewicz, D. *Synlett* **2015**, *27*, 714–723.
[20] Michaudel, Q.; Chauviré, T.; Kottisch, V.; Supej, M. J.; Stawiasz, K. J.; Shen, L.; Zipfel, W. R.; Abruña, H. D.; Freed, J. H.; Fors, B. P. *J. Am. Chem. Soc.* **2017**, *139*, 15530–15538.

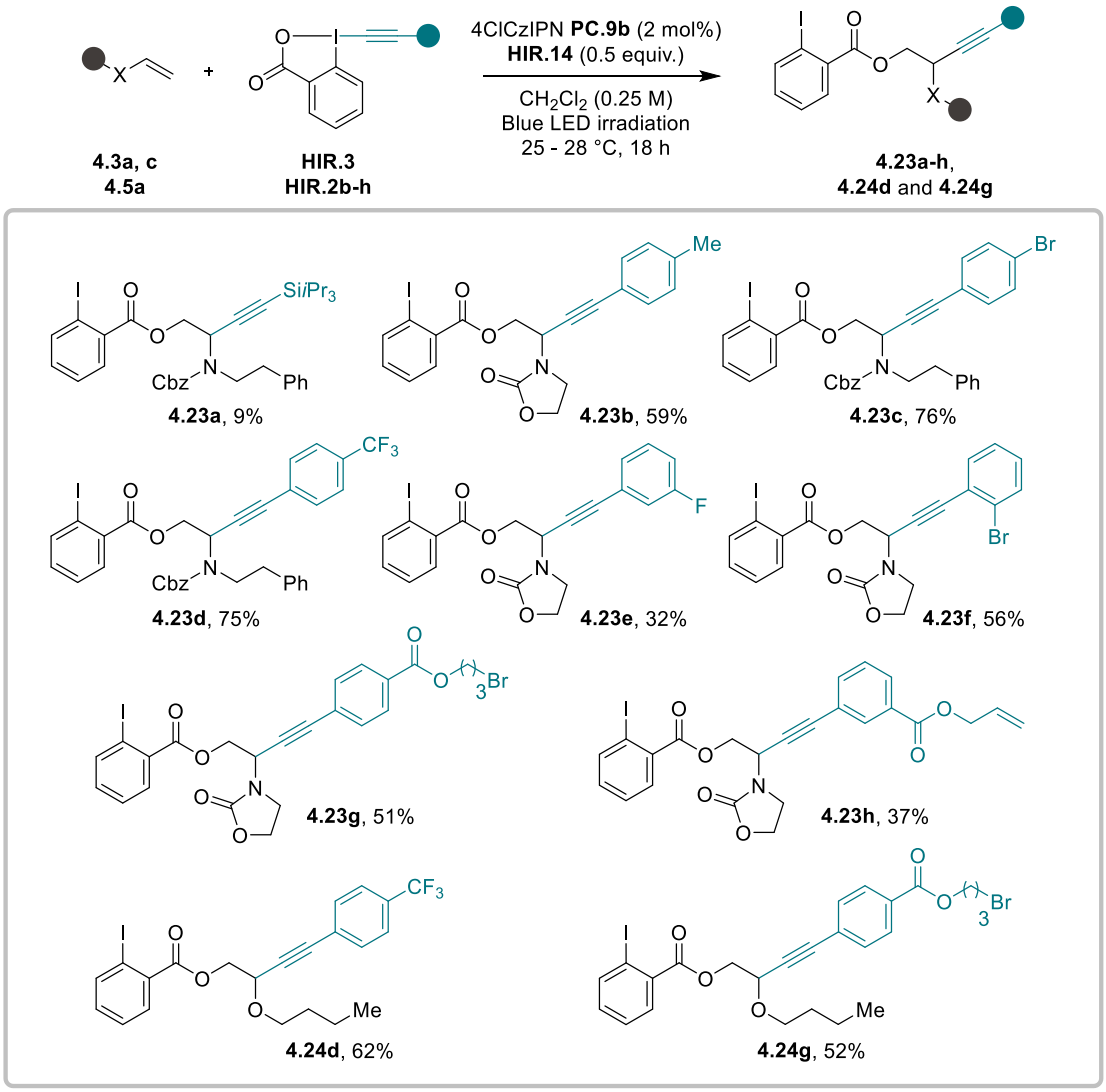
Scheme 4.8. Scope of enol ethers for the photocatalysed alkynylative difunctionalisation. Reactions conditions: 0.20 - 0.25 mmol **HIR.2a** (1 equiv), alkene (1.2 - 1.5 equiv), **HIR.14** (0.5 equiv) and **PC.9b** (2 mol%) in CH_2Cl_2 0.25 M. Blue led irradiation (10 - 15 W, $\lambda_{max} \approx 460$ nm) for 18 h at rt. [a]dr. was determined after isolation by ^{1}H NMR. [b]**4.22ga** and **4.22gb** were obtained as an inseparable mixture as single diastereoisomers

We then attempted to determine the structure of **4.22ga** (Scheme 4.9). The coupling constant between the α-oxo-hydrogens was found to be 6.0 Hz. The coupling constant that we would expect from an *anti*-addition (*anti*-**4.22ga**) would be around 2 – 3 Hz for the diaxial conformer and 10 – 12 Hz for the diequatorial conformer. For *syn*-**4.22ga**, we would expect a coupling constant around 3 – 5 Hz for both conformers. Based on our experimental value of 6.0 Hz, it is difficult to distinguish between the *anti*- or *syn*-products. To further understand whether a *syn*- or *anti*- addition would be favoured we decided to consider the mechanism. First, we would expect the addition of the carboxylate (**I**) to the oxidised enol ether (**II**) to occur in β to form the most stable radical. This addition would proceed through a Fürst-Plattner type model to give the most stable chair-like transition state. Due to the anomeric effect, the resulting radical (**IIIa**) could then react in axial to deliver *anti*-**4.22ga**. However **IIIa** is also subject to an $A_{1,3}$ interaction of the carboxylate group, we believe a rapid conformation change would convert **IIIa** to **IIIb** followed by trapping of the radical **IIIb** would give access to *syn*-**4.22ga**. Overall, we are not able to clearly define the relative configuration of the two centres.



Scheme 4.9. Structural analysis of the difunctionalisation product of dihydropyran (4.22ga)

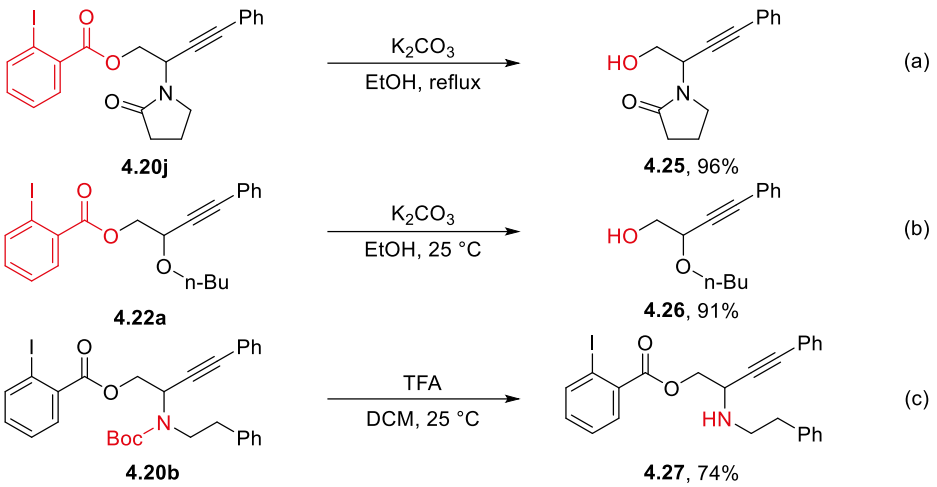
We then investigated the EBX reagents (Scheme.4.10). When using TIPS-EBX (**HIR.3**), the desired compound **4.23a** was obtained in only 9% yield. When turning to ArEBXs, slightly more electron rich *p*-tolylalkyne could be transferred in 59% yield (**4.23b**). A variety of halogenated arylalkynes were obtained in 32 - 76% yield (**4.23c** – **4.23f**). Interestingly, more complex EBXs were also tolerated with potentially redox sensitive groups affording **4.23g** and **4.23h** in 51% and 37% yield. Similarly, enol ethers were successful with **HIR.2d** and **HIR.2g** giving access to **4.24d** and **4.24g** in 62% and 52% yield.



Scheme.4.10. Scope EBX reagents for the photocatalysed alkynylative difunctionalisation. Reactions conditions: 0.25 mmol **HIR.3** or **HIR.2a-h** (1 equiv), alkene (1.5 equiv), **HIR.14** (0.5 equiv) and **PC.9b** (2 mol%) in CH_2Cl_2 0.25 M. Blue led irradiation (10 - 15 W, $\lambda_{max} \approx 460$ nm) for 18 h at rt.

Finally, having explored the scope of the transformation, we attempted the selective deprotection of the carbamates and esters to the corresponding amine and alcohols (Scheme 4.11). The ester moiety could be successfully saponified on both the 1,2-aminoalcohol and the 1,2-diol scaffolds affording **4.25** and **4.26** in 96% and 91% yield (a and b). To our delight,

Boc deprotection with TFA followed by a basic work-up afforded the dialkylamino ester **4.27** in 74% yield (c).



Scheme 4.11. Orthogonal deprotections of 4.20j, 4.22a and 4.20b to the free alcohols and amine.

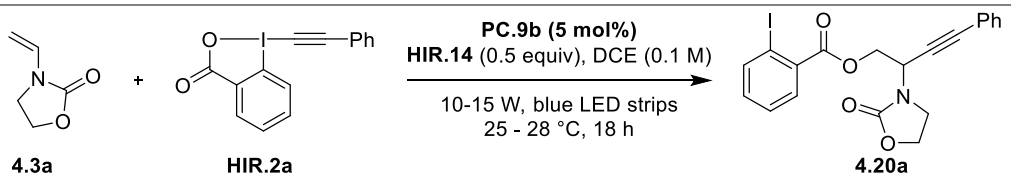
4.4. Mechanism of the transformation

4.4.1. Control reactions and radical chain hypothesis

4.4.1.1. Dark and photocatalyst-free reactions

When performing the reaction in absence of light and/or photocatalyst we did not observe product formation, thus confirming the photomediated process and the need for a photocatalyst (Table 4.2, entries 1 –3).

Table 4.2. Photocatalyst-free and dark experiments for the difunctionalisation of 4.3a with HIR.2a



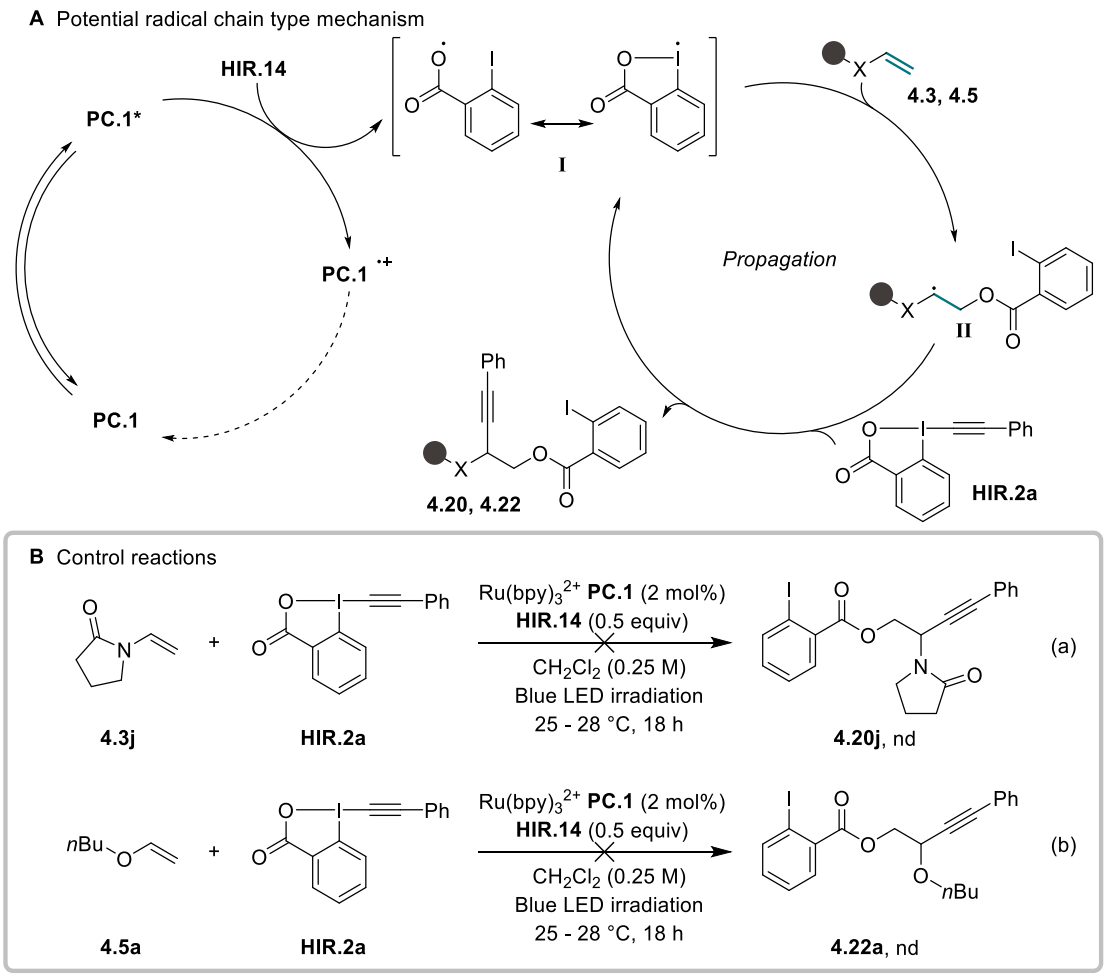
entry	variation to the conditions above	conversion	yield (%)
1	Dark	ND	ND
2	Without **PC.9b**	ND	ND
3	Dark, without **PC.9b**	ND	ND

Reaction conditions: **4.3a** (0.15 mmol, 1.5 equiv), **HIR.2a** (0.1 mmol, 1.0 equiv), **HIR.14** (0.05 mmol, 0.5 equiv), **PC.9b** (5 mol%) in degassed DCE. Blue LED irradiation (10 - 15 W, $\lambda_{max} \approx 460$ nm) for 18 h at rt.

4.4.1.2. Towards promoting a radical chain process

During our studies, we envisaged the possibility of a radical chain process sustained by the iodanyl radical **I** (Scheme.4.12, A). The excited state photocatalyst **PC.9b** would be capable of generating the iodanyl radical **I** upon reduction of **HIR.14** – the additive in our reaction conditions. The resulting radical **I**, inherently electrophilic, could then add to an electron rich π-system such as the enamide or enol ether generating the radical **II**. In turn, the latter would be trapped by the EBX reagent delivering a difunctionalised product **4.20**-**4.22** and the iodanyl

radical **I** allowing a radical chain type process to proceed. To understand if this was a major pathway, we performed several experiments to generate the iodanyl radical selectively. The Chen group reported a slow reduction of **HIR.14** with **PC.1** ($Ru(bpy)_3^{2+}$) allowing the generation of the iodanyl radical **I**.[21] With **PC.1** the oxidation of the enamide would be minimal due to the low oxidative capacity of this photocatalyst ($E_{1/2}(Ru^{II*}/Ru^{I})$ = + 0.7 V vs SCE). We therefore performed our reaction with **PC.1**; no product was detected for both enamide **4.3j** and enol ether **4.5a** and no other degradation products were detected by ^{1}H NMR (Scheme.4.12, B). Furthermore, no conversion was observed for **4.3j**.[22] In both cases, no residual **HIR.14** was detected, this suggests that the iodanyl radical (**I**) was most likely generated under our reaction conditions. The lack of conversion, product formation and observable degradation of the alkenes despite the conversion of **HIR.14** leads us to believe that the iodanyl radical (**I**) alone cannot sustain product formation. These results do not exclude the possibility of a radical chain type mechanism with **PC.9b**, although they do suggest that it may not be a major reaction pathway.



[21] Huang, H.; Zhang, G.; Chen, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 7872–7876.
[22] No residual **4.5a** was detected however this could be due to it's low boiling point (94 °C) and the fact that the crude reaction is concentrated in vacuo.

Scheme.4.12. First hypothetical radical chain process for the alkynylative difunctionalisation enamides and enol ethers and control reactions with PC.1.

In 2017, the Leonori group reported an imino-functionalisation of alkenes with **PC.6** (more details can be found in the introduction paragraph 2.3.2.3.3.c. Alkene difunctionalisation).[23] Interestingly, their experimental studies and in particular the high quantum yield (Φ = 4.8) show the presence of a radical chain process in the case of TIPS-EBX (**HIR.3**). Based on this precedence,[24] we envisaged that **PC.6** may also help us identify if a radical chain process is occurring under our conditions (Scheme.4.13, A). The radical chain process would be sustained by the iodanyl radical (**I**) as previously described, although the initiation step would be different: the excited state photocatalyst (**PC.6***) would first oxidise the electron-rich alkene (**4.3** or **4.5**) to the radical cationic intermediate (**II**). The latter could be trapped by a nucleophile generated in-situ (such as the iodobenzoate). This would result in an α-amino radical (**III**) that could react with **HIR.2** releasing a difunctionalised product **4.28** and the iodanyl radical (**I**) allowing the propagation stage to proceed. We therefore decided to test both substrates **4.3j** and **4.5a** with **PC.6** (B). For both the enamide (**4.3j**) and the enol ether (**4.5a**), we observed full conversion although only 10% formation of **4.20j** and 5% of **4.22a**. The 80% conversion the enamide[25] suggests the presence of a background process that would be more efficient than the desired difunctionalisation under these conditions. Based on the ^{1}H NMR, unfortunately no clear degradation products were identified, we suspect oligomerisation or polymerisation of the enamide may be one of the main degradation pathways. The presence of product formation suggests that the iodanyl radical (**I**) is indeed produced under our reaction conditions, however the poor quantities of product formation suggest that the envisaged radical chain propagation steps, if occurring, are insufficient to overcome the other degradation pathways. This strongly suggests that in presence of **PC.6** the role of the iodanyl radical (**I**) as a radical chain initiator is inadequate for both substrates **4.3j** and **4.5a**. When considering our experimental results with **PC.6b**, where the mass conservation was ensured and therefore the degradation processes were outcompeted, we therefore doubt the dominance of a radical chain process that would be sustained by the iodanyl radical (**I**) allowing the difunctionalisation to occur.

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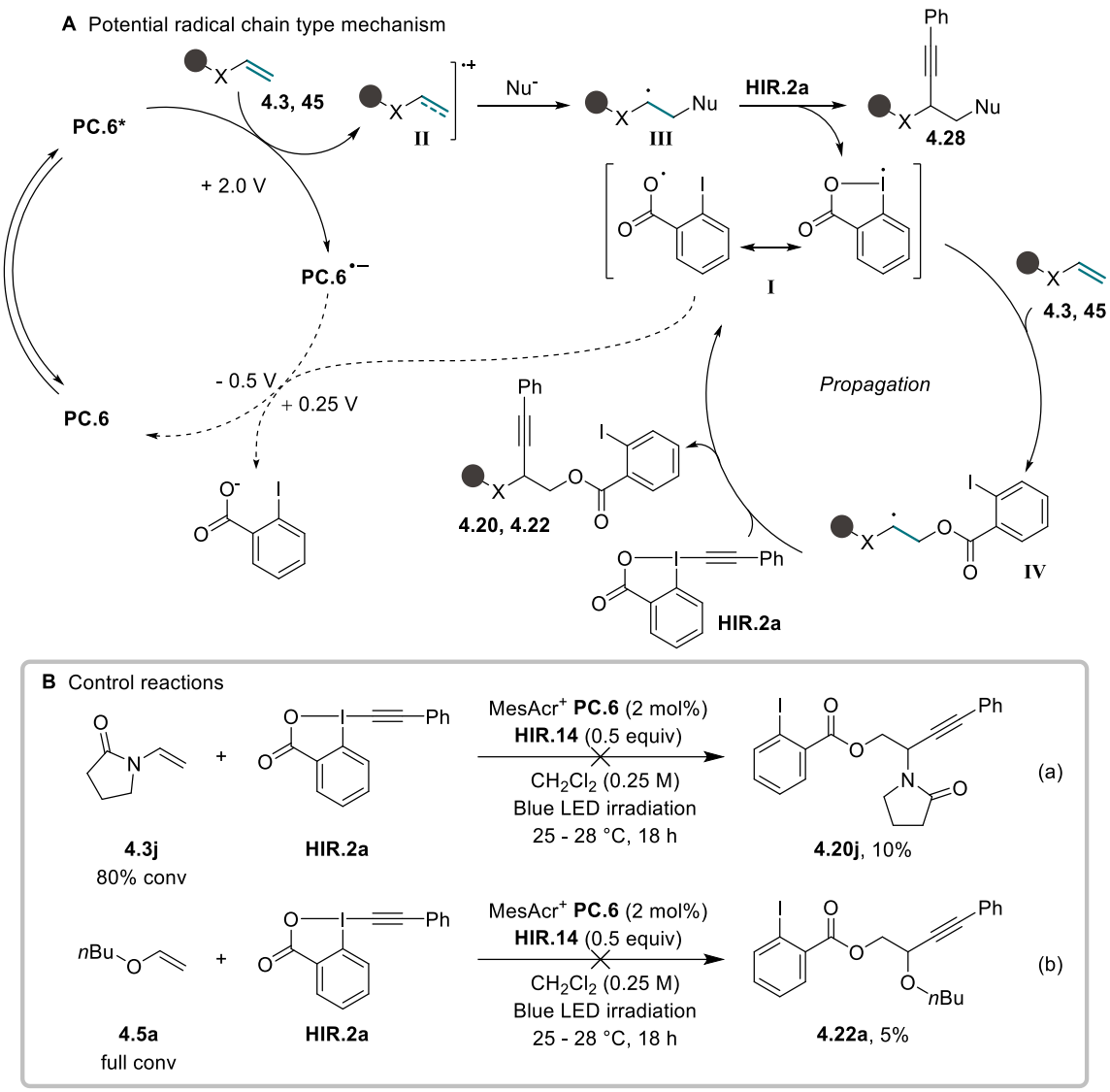
[23] Davies, J.; Sheikh, N. S.; Leonori, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 13361–13365.
[24] To the best of our knowledge, there are only two reports for the combination of EBXs with **PC.6**. Neither propose the reduction of the iodanyl radical by the acridine radical suggesting that this process may be inefficient despite it thermodynamic feasibility. Second literature example: Li, J.; Liu, Z.; Wu, S.; Chen, Y. *Org. Lett.* **2019**, *21*, 2077–2080.
[25] The full conversion of the enol ether cannot be interpreted as the compound has a low boiling point (94 °C) and can be explained by the loss of the starting material during concentration of the rude in vacuo.



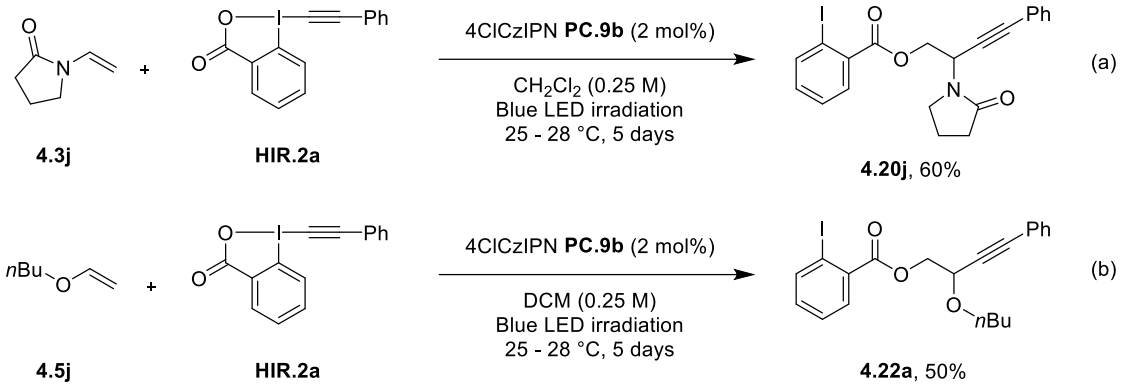
Scheme.4.13. Second hypothetical radical chain process for the alkynylative difunctionalisation of enamides and enol-ethers and control reactions with PC.6.

The use of different catalysts to try and promote a radical chain pathway resulted in very poor product formation suggesting that a radical chain process may be inefficient under our reaction conditions, although we cannot exclude this possibility entirely. However in each case, the additive **HIR.14** was fully consumed, this made us question the role of the additive.

4.4.1.3. The role of **HIR.14** as an additive

During our optimisation studies, we observed lower yields in the absence of **HIR.14** (Table 4.1, entry 5). We therefore decided to perform the reaction without the additive to identify if a longer reaction time could lead to higher yields (Scheme.4.14). Interestingly after 5 days (ca. 7 x the optimal reaction time), we can see 60% formation of **4.20j** (for **4.20a**, 18 hours without the additive provided 34% of difunctionalisation product). Similarly, the enol ether **4.5a** also provides the corresponding difunctionalised product **4.22a** in 50% yield without additive after 5 days of reaction. These results show that the additive **HIR.14** most likely plays a supportive

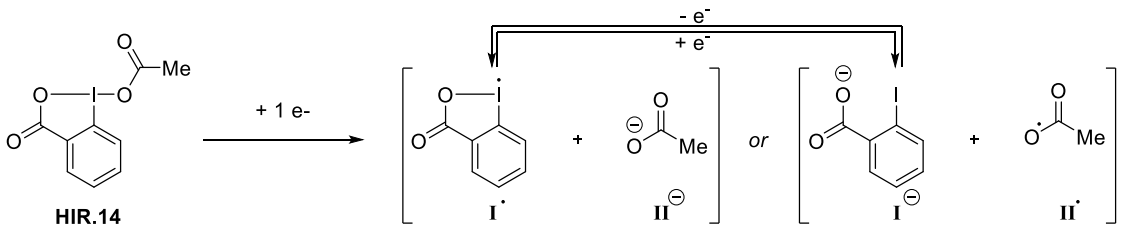
role. Its presence allows the reaction to proceed more quickly but is not necessary for the formation of the product in synthetically relevant yields.



Scheme.4.14. Photocatalysed oxyalkynylation of 4.3j and 4.5a in the absence of HIR.14.

HIR.14 can produce four possible intermediates upon reduction (Equation 4.1. Possible intermediates generated from the reduction of HIR.14.). Based on the redox potentials of each redox couple ($E_{1/2}$(**I**$^{\bullet}$/**I**$^{-}$) = + 0.25 V vs SCE,[26] $E_{1/2}$(**II**$^{\bullet}$/**II**$^{-}$) = + 1.47 V vs SCE),[19] the initial intermediates should be **I**$^{\bullet}$ and **II**$^{-}$, knowing that **I**$^{\bullet}$ could then be reduced to the iodobenzoate **I**$^{-}$. Under our conditions we observed no acetate incorporation suggesting that both **II**$^{\bullet}$ and **II**$^{-}$ do not play a role in the product formation. We can therefore envisage two possible roles of **HIR.14** under our reaction conditions: (1) **HIR.14** may indeed allow a radical chain type mechanism to occur, (2) it could simply improve the photocatalytic turnover as the iodanyl radical is a transient species whereas **HIR.14** is not.

Equation 4.1. Possible intermediates generated from the reduction of HIR.14.



4.4.1.4. Summary of the experimental observations

The reaction requires the presence of light and the photocatalyst **PC.9b** confirming the photomediated character of the transformation. When using **PC.1** ($Ru(bpy)_3^{2+}$), a photocatalyst that has been reported to generate the iodanyl radical from **HIR.14**, we did not observe any product formation and no conversion was observed for the enamide despite full conversion of the additive **HIR.14**. Furthermore, **PC.6** ($MesAcr^{+}$), which had been reported to promote a

[26] Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* **2017**, *8*, 1790–1800.

radical chain process in presence of an EBX reagent also performed poorly. High conversion of the alkenes was observed but only traces of the product was formed, suggesting that yet again that a radical chain relying on the iodanyl radical may be inefficient for the difunctionalisation. Both sets of experiments do not support a strong radical chain process, however we cannot exclude that this may be a background process occurring under our reaction conditions. We then investigated the role of **HIR.14**. Interestingly, we found that the reaction still proceeds in absence of **HIR.14** although the required reaction time is a lot longer to ensure synthetically relevant yields. This suggests that **HIR.14**, or an intermediate it produces under our reaction conditions, plays a key role in the mechanism of the reaction. As a strong radical chain type mechanism seemed unlikely, we decided to explore the possibility of a radical cation type mechanism.

4.4.2. Electrochemical investigation

We turned to cyclic voltammetry to probe the possibility of a radical cationic pathway. The model substrate (**4.3a**) presents a distinct irreversible oxidation wave allowing us to estimate the $E_{1/2}$(**4.3a**$^{+\bullet}$/**4.3a**) = + 1.30 V vs SCE. When turning to **4.3l**, we can see that the oxidation wave occurs at a higher potential. We estimate the redox potential to be $E_{1/2}$(**4.3l**$^{+\bullet}$/**4.3l**) ≈ + 1.86 V vs SCE. This correlates with the lack of conversion observed with this substrate. Finally, the cyclohexenyl substrate **4.3m** also presents an irreversible oxidation wave in the same range as **4.3a** ($E_{1/2}$(**4.3m**$^{+\bullet}$/**4.3m**) = + 1.40 V vs SCE). This correlates with our experimental observations where **4.3m** indeed degrades under our reaction conditions although no production formation was observed. Internal alkenes were tolerated for the enamide **4.3k**, which leads us to believe that it should also be possible for **4.3m**. However, the tertiary α-amino radical that would result from nucleophilic attack could be easier to oxidise to the cation in presence of both **PC.9b** and **HIR.14**.[27] This would prevent the alkynylation step from occurring. In addition, the resulting radical could be too sterically encumbered the alkynylation to proceed. Based on the ^{1}H NMR crude analysis it was difficult to identify any clearly distinguishable degradation products, we observed ca. 50% conversion of the EBX. Isolation of the crude did not allow us to identify the possible side products.

[27] **HIR.14** has been reported to promote the formation of iminiums under photoredox catalysis: Le Du, E.; Garreau, M.; Waser, J.; *Chem. Sci.* **2021**, *12*, 2467-2473.

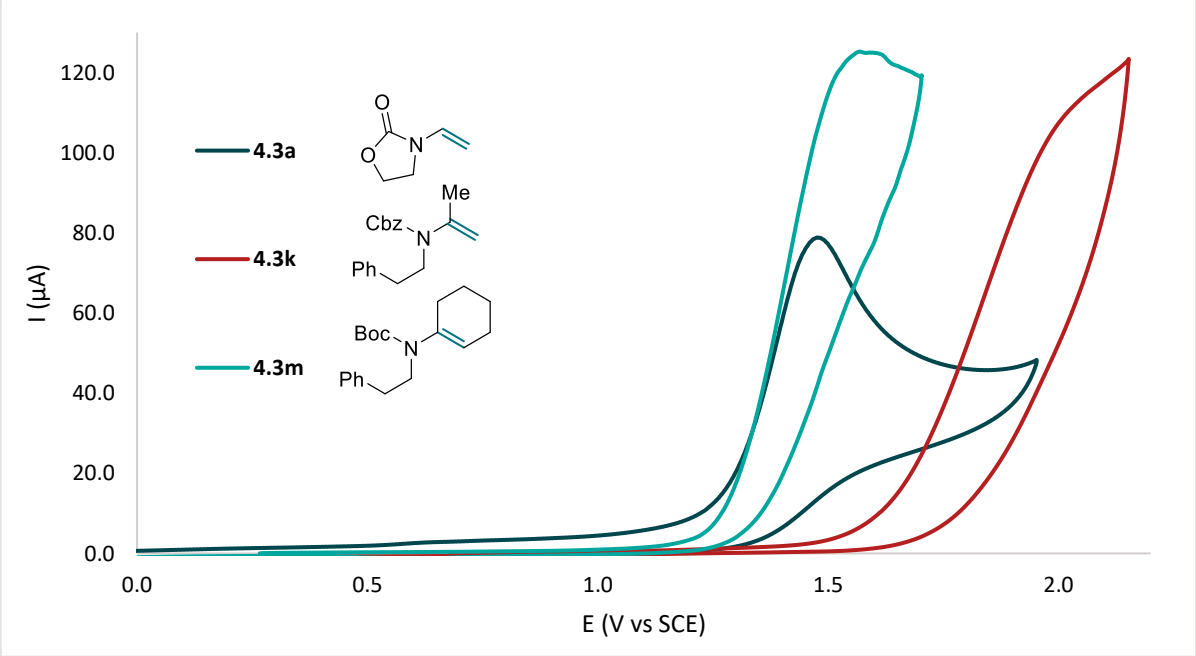


Figure 4.1. Cyclic voltammograms of 4.3a, 4.3l and 4.3m in MeCN, 0.10 mM.

Finally, we measured the CV of the acyclic ene-carbamate **4.3c**, although the oxidation wave was not as intense or as well defined as that observed for **4.3a**, we were able to estimate the redox potential to be $E_{1/2}$(**4.3c**$^{+\bullet}$/**4.3c**) = + 1.3 V vs SCE.

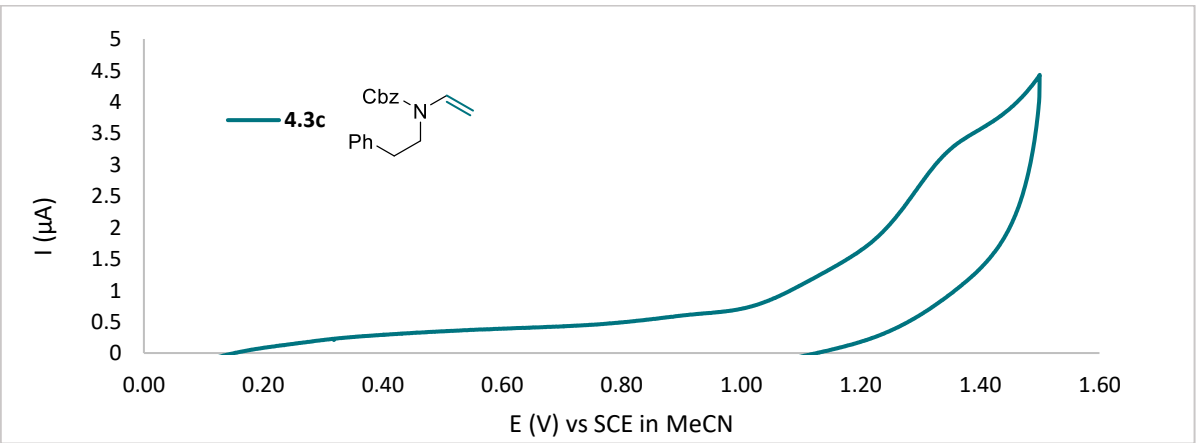


Figure 4.2. Cyclic voltammogram of 4.3c in MeCN, 0.10 mM.

When turning to the enol ethers, their redox potentials have already been reported and have been estimated to be $E_{1/2}$(**4.5**$^{+\bullet}$/**4.5**) = + 1.5 V vs SCE.[28]

4.4.3. Fluorescence quenching experiments and excited state reactivity

Following the cyclic voltammetry experiments confirming the thermodynamic feasibility of a SET oxidation of the ene-carbamates we proceeded to perform Stern-Volmer and

[28] + 1.46 V vs SCE for *iso*-butyl vinyl ether, taken from: Michaudel, Q.; Chauviré, T.; Kottisch, V.; Supej, M. J.; Stawiasz, K. J.; Shen, L.; Zipfel, W. R.; Abruña, H. D.; Freed, J. H.; Fors, B. P. *J. Am. Chem. Soc.* **2017**, *139*, 15530–15538. + 1.5 V vs SCE for DHP, taken from: 1. Roth, H.; Romero, N.; Nicewicz, D. *Synlett* **2015**, *27*, 714–723.

fluorescence quenching studies to evaluate which species was quenching the photocatalyst. With ene-carbamate **4.3a**, we indeed observed a linear quenching trend of the photocatalyst proportional to the amount of enamide.

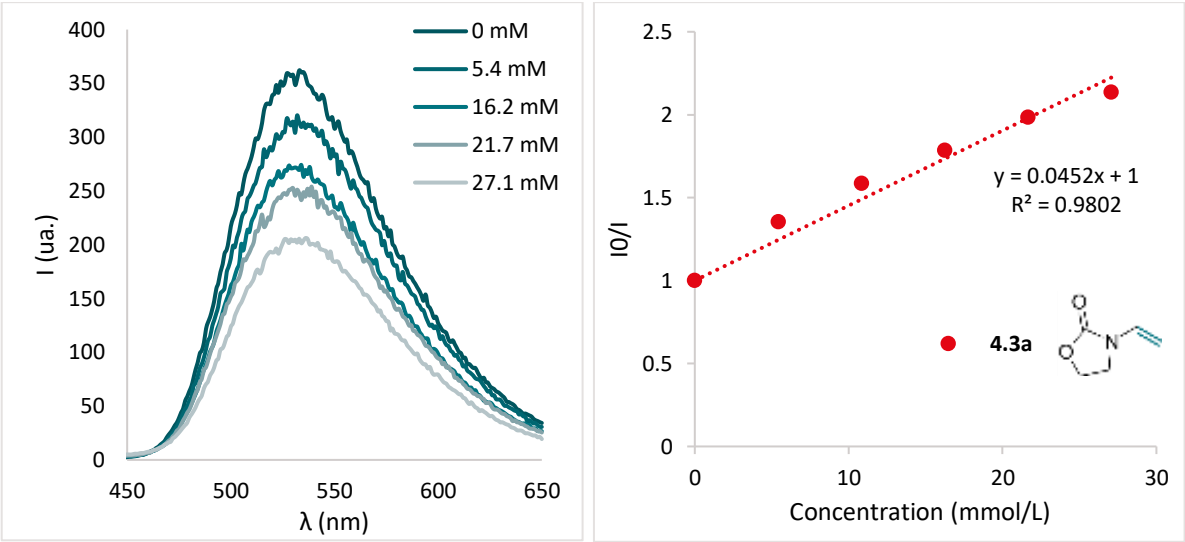
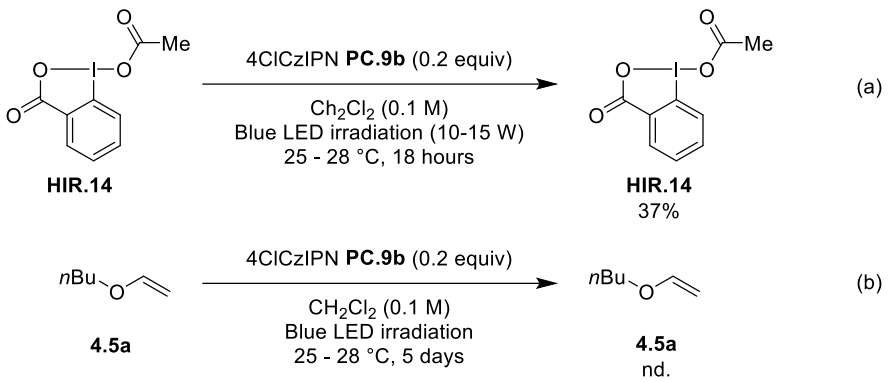


Figure 4.3. Fluorescence quenching studies and Stern-Volmer plot for 4.3a.

However, when turning to the enol ethers we did not observe a clear fluorescence quenching trend. When regarding the redox potentials, the enol ether **4.5g** has a redox potential of + 1.5 V vs SCE and the excited state photocatalyst is at +1.58 V vs SCE. Where the SET may be thermodynamically possible, the small difference between the redox potentials could indeed explain the lack of fluorescence quenching. Furthermore, the lack of fluorescence quenching suggests that the enol ethers may be subject to a different photocatalytic cycle.

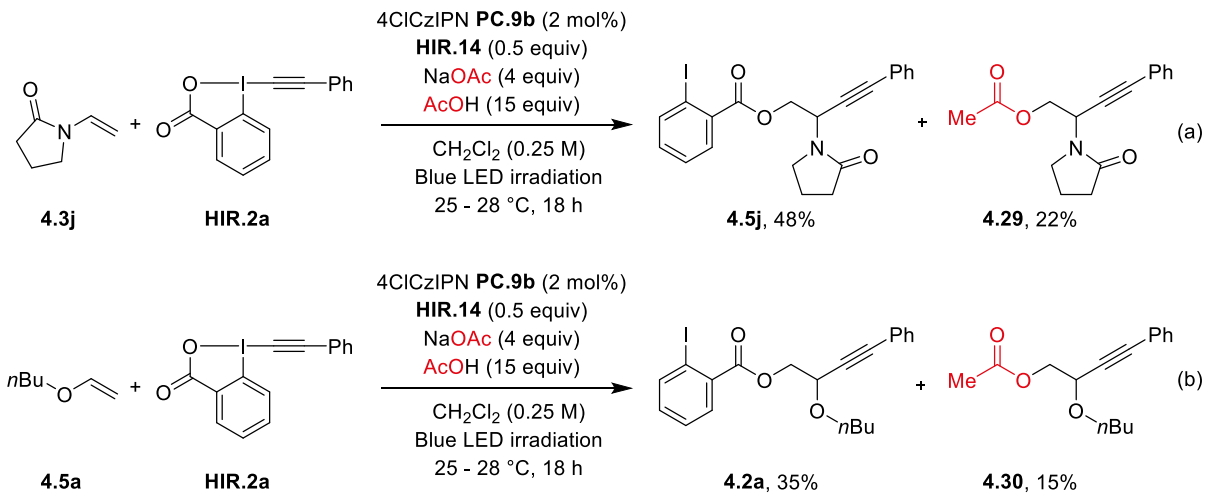
Then, we attempted the fluorescence quenching of **HIR.14**, unfortunately, the lack of solubility of the species in CH_2Cl_2 and DMSO led to non-conclusive results. We therefore performed a control experiment with **HIR.14** and 20 mol% of **PC.9b** under blue LED irradiation. We also subjected the enol ether **4.5a** to the same reaction conditions. Interestingly, **HIR.14** underwent 63% degradation and no residual **4.5a** was detected. This demonstrates **PC.9b*** can promote the degradation of both **HIR.14** and **4.5a**, this could indicate that **PC.9b*** may be capable of generating the iodanyl radical from **HIR.14** and the radical cation from **4.5a**.



Scheme.4.15. Photodegradation of HIR.14 and 4.5a in presence of PC.9b.

4.4.4. Radical cation intermediate and crossover experiments

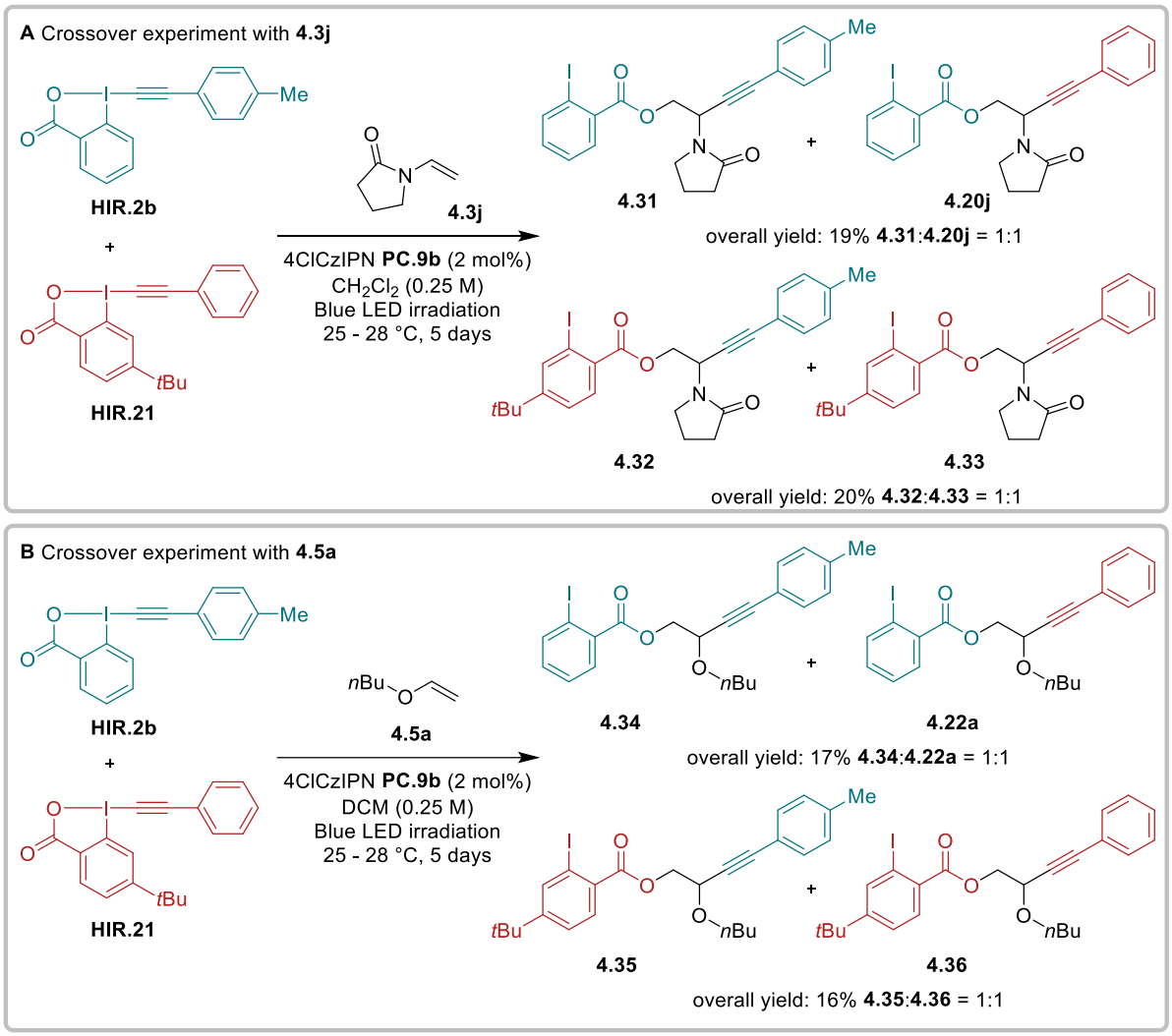
Our experimental data strongly corroborates the possibility of an oxidation of the enamides to a radical cationic intermediate. However, the results in relation to the enol ether are less conclusive. Hence, we wondered whether it would be possible to trap in-situ the radical cation with a different nucleophile than the iodobenzoate. We performed the reaction in presence of acetic acid and sodium acetate. To our delight, with enamide **4.3j** we could indeed incorporate the acetate moiety (**4.29**) in 22% ^{1}H NMR yield for 48% NMR yield of the 2-iodobenzoate product (Scheme.4.16, ratio 3:7). When performing the same reaction with the enol ether **4.5a** we also observed 15% acetate incorporation (**4.30**) for 34% iodobenzoate incorporation (ratio 3:7).



Scheme.4.16. Photocatalysed alkynylative 1,2-difunctionalisation of 4.3j and 4.5a with an acetate as an external nucleophile.

The incorporation of an external nucleophile further supports the radical cation pathway. However, our optimised reaction conditions do not include a typical nucleophilic species and 15 equivalents of acetate were needed to deliver only a 3:7 incorporation of acetate over the iodobenzoate. We therefore wondered if the alkyne and carboxylate incorporation were occurring in an intramolecular fashion. We turned to crossover experiments to help us understand this. We chose to use simplified reaction conditions: without **HIR.14** over 5 days.

We chose *p*Tol-EBX (**HIR.2b**) and the *tert*-butyl core modified **HIR.21** as both reagents present similar electronic effects (no additional resonance structures, both inductive donor) as this would limit the variations of nucleophilicity of the iodobenzoate or the somophilicity of the EBX. The enamide difunctionalisation resulted in an overall isolated yield of 39% for 40% ^{1}H NMR yield. The 4 products **4.31**, **4.20j**, **4.32** and **4.33** were isolated as two mixtures of alkynyl esters: **4.31** and **4.20j** were isolated together in 19% in a 1:1 ratio and **4.32** and **4.33** were obtained in 20% in 1:1 ratio. The same observations were made for the enol ether, **4.34** and **4.22a** were obtained as a 1:1 ratio in 17% yield, and a 1:1 ratio of **4.35** and **4.36** was isolated in 16% yield. Combined, the overall yield of enol ether difunctionalisation was 33% for 36% ^{1}H NMR yield. These results show that all four products were synthesised in a 1:1:1:1 ratio resulting in full scrambling of both parts of the reagent. On the premise that the reagents do not scramble prior to the difunctionalisation, these results confirm that the carboxylate and alkyne transfer are intermolecular events.

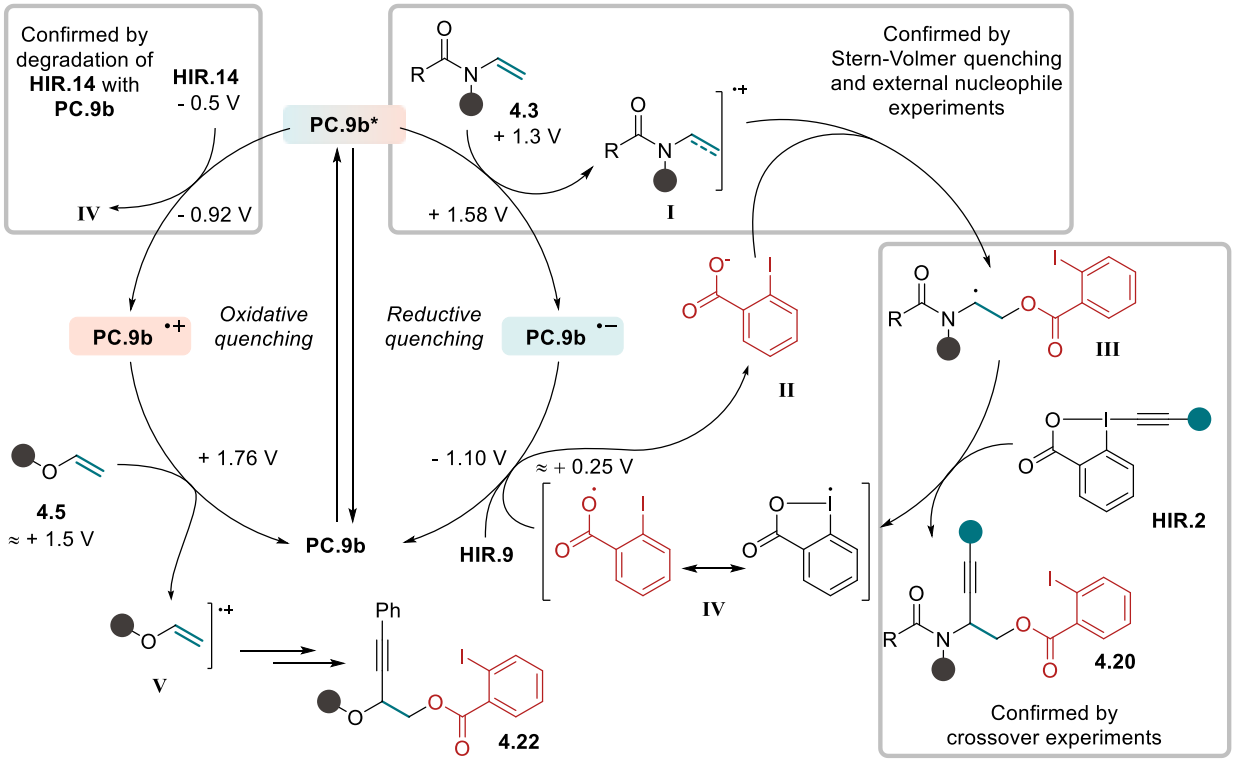


Scheme.4.17. Photocatalysed alkynylative difunctionalisation of 4.3j and 4.5a in presence of 2 different EBXs and in absence of HIR.14.

4.4.5. Mechanistic proposal

Based on our experimental data, we propose the following mechanism for the enamides and ene-carbamates (Scheme.4.18). Under blue LED irradiation, the excited state photocatalyst **PC.9b*** can undergo reductive quenching by the ene-carbamate (**4.3**) – as confirmed by the Stern-Volmer quenching experiment. This results in the generation of a radical cation (**I**) that can then be quenched by an external nucleophile such as the in-situ generated iodobenzoate (**II**). The ensuing α-amino radical **III** can then be trapped by the EBX reagent (**HIR.2**) delivering the final compound and releasing the iodanyl radical **IV**. The latter plays a key role in oxidising the photocatalyst back down to the ground state and generating the iodobenzoate **II**. When turning to the role of the additive **HIR.14**, our experimental data suggests that it plays a supporting role. We speculate that **PC.9b*** could undergo oxidative quenching by **HIR.14** helping generate more iodanyl radical that could help in the generation of the iodobenzoate **II**. The corresponding oxidative quenching cycle could then be closed by the enamide resulting in the radical cationic intermediate. Considering our data related to the enol ethers, and, in particular, the lack of fluorescence quenching of the photocatalyst by the enol ether, we can propose that the enol ethers are most likely going through essentially the oxidative quenching cycle. This would first be initiated by **HIR.14** and could potentially be sustained by the iodanyl radical (**IV**).[29] Although our control experiments do not suggest a substantial radical chain for the enol ethers either, the lack of clear quenching leads us to believe that a radical chain may be more predominant with these scaffolds.

[29] Although both the iodanyl radical (**II**) and **PC.9b*** are transient species, the lifetime of **PC.9b*** is relatively long (2 µs) which could allow an interaction between the two species. This would need to be compared to the lifetime of the iodanyl radical and its capacity to accumulate in the media, which has not yet been studied.



Scheme.4.18. Proposed mechanism for the photoctalysed alkynylative 1,2-difunctionalisation of ene-carbamates and enol ethers with ArEBXs, HIR.14 and PC.9b.

4.5. Conclusion

During this project, we were able to develop a method for the selective photocatalytic activation of *N*- and *O*-alkenes.[30] This difunctionalisation strategy ensures an anti-Markovnikov type selectivity and contributes formally to the Umpolung of the enamide and enol ether functional groups. Under blue LED irradiation, we found that 4ClCzIPN (**PC.9b**) in presence of an ArEBX species could convert a variety of ene-carbamates and enol ethers to 1-alkynyl-1,2-aminoalcohol and diol scaffolds. The addition of a substoichiometric quantity of BIOAc ensured high yields after 18 hours of reaction time. Mechanistic investigations suggest that the main reaction pathway proceeds through the photocatalysed oxidation of the ene-carbamate and enol ether to a radical cation. The latter can then be trapped by an external nucleophile before being alkynylated. Further mechanistic experiments suggest that the photocatalytic cycle may vary depending on the substrate. Fluorescence quenching experiments suggest that the enamide could quench the excited state leaving place for a reductive quenching cycle. Whereas enol ethers are most likely oxidised through the oxidative quenching cycle. **HIR.14** seems to play an important role on the speed of the reaction and may further promote an oxidative quenching type mechanism or participate in the initiation of radical chain processes.

[30] Amos, S. G. E.; Nicolai, S.; Waser, J. *Chem. Sci.* **2020**, *11*, 11274–11279.

4.6. References

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8. The precipitation of the catalyst was biphasic which often led to decomplexation despite vigorous agitation rendering it's synthesis poor reproducible in our hands.
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11. We suspect this is due to the increased acidity of the media which leads to the hydrolysis of the imine.
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19. Roth, H.; Romero, N.; Nicewicz, D. *Synlett* **2015**, *27*, 714–723.
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21. Huang, H.; Zhang, G.; Chen, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 7872–7876.
22. No residual **4.5a** was detected however this could be due to it's low boiling point (94 °C) and the fact that the crude reaction is concentrated in vacuo.
23. Davies, J.; Sheikh, N. S.; Leonori, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 13361–13365.
24. To the best of our knowledge, there are only two reports for the combination of EBXs with **PC.6**. Neither propose the reduction of the iodanyl radical by the acridine radical suggesting that this process may be inefficient despite it thermodynamic feasibility. Second literature example: Li, J.; Liu, Z.; Wu, S.; Chen, Y. *Org. Lett.* **2019**, *21*, 2077–2080.
25. The full conversion of the enol ether cannot be interpreted as the compound has a low boiling point (94 °C) and can be explained by the loss of the starting material during concentration of the rude in vacuo.
26. Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* **2017**, *8*, 1790–1800.
27. **HIR.14** has been reported to promote the formation of iminiums under photoredox catalysis: Le Du, E.; Garreau, M.; Waser, J.; *Chem. Sci.* **2021**, *12*, 2467-2473.
28. + 1.46 V vs SCE for *iso*-butyl vinyl ether, taken from: Michaudel, Q.; Chauviré, T.; Kottisch, V.; Supej, M. J.; Stawiasz, K. J.; Shen, L.; Zipfel, W. R.; Abruña, H. D.; Freed, J. H.; Fors, B. P. *J. Am. Chem. Soc.* **2017**, *139*, 15530–15538. + 1.5 V vs SCE for DHP, taken from: 1. Roth, H.; Romero, N.; Nicewicz, D. *Synlett* **2015**, *27*, 714–723.
29. Although both the iodanyl radical (**II**) and **PC.9b*** are both transient species, the lifetime of **PC.9b*** is relatively long (2 µs) which could allow and interaction between the two species. This of course would need to be compared to the lifetime of the iodanyl radical and its capacity to accumulate in the media, unfortunately we have not studied this.
30. Amos, S. G. E.; Nicolai, S.; Waser, J. *Chem. Sci.* **2020**, *11*, 11274–11279.

Chapter 5: Photocatalysed Studies Towards Deoxyalkynylation, Deoxycyanation, and Dethioalkynylation

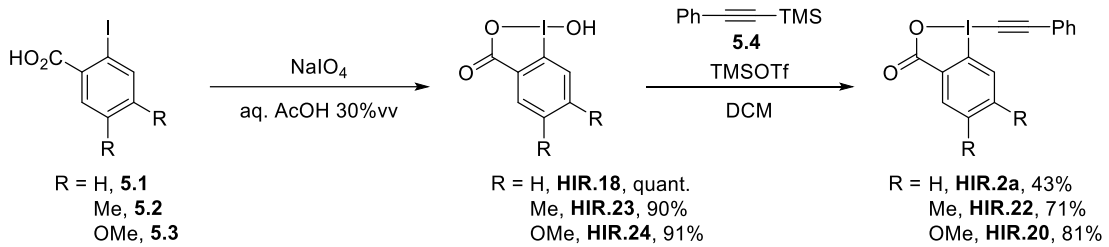
5. Photomediated Deoxyalkynylation, Deoxycyanation, and Dethioalkynylation

This project was performed with the contributions of Diana Cavalli and Dr. Franck Le Vaillant. Their specific contributions will be specified in the following paragraphs.

5.1. Synthesis of the starting materials

5.1.1. Synthesis of PhEBX (**HIR.2a**) and analogues (**HIR.22** and **HIR.20**)

PhEBX (**HIR.2a**) was selected as the model reagent for our investigations of the deoxyalkynylation strategy. During our studies we also investigated the core modifications of the reagent. The reagents were obtained following the same strategy as presented in chapter 4. Commercially available 2-iodobenzoic acids (**5.1**, **5.2** and **5.3**) were first oxidised to **HIR.18**, **HIR.23** and **HIR.24** in quantitative, 90% and 91% yield respectively.[1] The reagents **HIR.2a**, **HIR.22** and **HIR.20** were then obtained by activation of **HIR.18**, **HIR.23** and **HIR.15** with trimethylsilyl (trifluoromethane)sulfonate and substitution with the trimethylsilyl alkyne **5.4** in 43%, 71% and 81% yield (Scheme 5.1).[2]



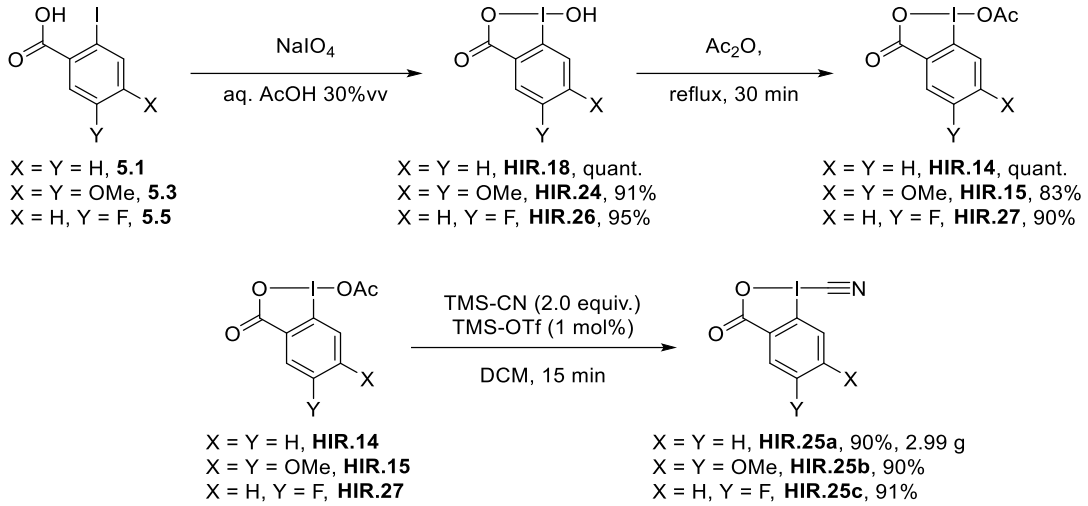
Scheme 5.1. Synthesis of PhEBX (HIR.2a) and analogues (HIR.20 and HIR.22).

5.1.2. Synthesis of CBX (**HIR.25a**) and analogues

For the deoxycyanation we chose CBX (**HIR.25a**) as a model reagent. As for the deoxyalkynylation, we were interested by the effect of the core substitutions of the HIR, so we synthesised the dimethoxy-CBX (**HIR.25b**) and the fluorinated-CBX (**HIR.25c**). All reagents could be accessed in three steps from the commercial *o*-iodobenzoic acids (Scheme 5.2).[3] As for the synthesis of the REBXs, the first step is the oxidation of the *o*-iodobenzoic acid (**5.1**, **5.3** or **5.5**) to **HIR.18**, **HIR.24** and **HIR.26** with sodium periodate (yield > 90%). **HIR.14**, **HIR.15** and **HIR.27** could then be obtained by refluxing **HIR.18**, **HIR.24** and **HIR.26** in acetic anhydride (yields > 80%). The CBX reagents were then obtained from the acetylated intermediates with

[1] Kraszkiewicz, L.; Skulski, L. *Arkivoc* **2003**, *2003*, 120–125.
[2] a. Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem. – Eur. J.* **2012**, *18*, 5655–5666. b. Pan, Y.; Jia, K.; Chen, Y.; Chen, Y. *Beilstein J. Org. Chem.* **2018**, *14*, 1215–1221.
[3] Eisenberger, P.; Gischig, S.; Togni, A. *Chem. - Eur. J.* **2006**, *12*, 2579–2586.

cyano(trimethyl)silane and a catalytic quantity of trimethylsilyl (trifluoromethane)sulfonate. **HIR.25a**, **HIR.25b** and **HIR.25c** were obtained in over 90% yield.

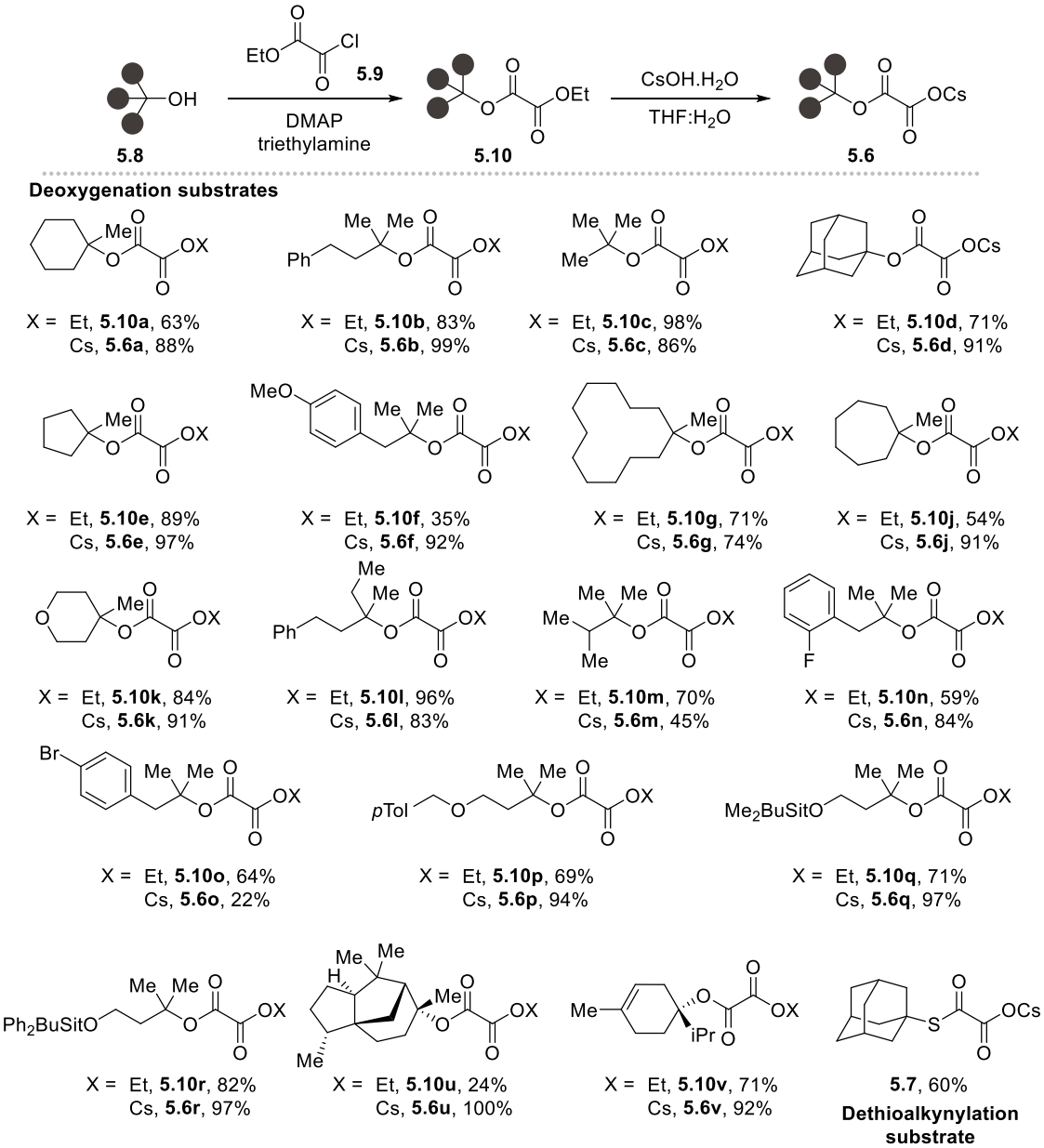


Scheme 5.2. Synthesis of CBX (HIR.25a) and analogues (HIR.25b and HIR.25c).

5.1.3. Synthesis of model cesium *tert*-alkyl oxalates (**5.6a** and **5.6b**) and cesium thiooxoacetate (**5.7**)

For the deoxyalkynylation and deoxycyanation strategy **5.6a** and **5.6b** were chosen as model substrates as they have previously been used in photomediated deoxygenation strategies and had also been used in the optimisations of these strategies.[4] The cesium *tert*-alkyl oxalates (**5.6**) can be obtained by acylation of the corresponding alcohol **5.8** with ethyl chlorooxoacetate (**5.9**), forming **5.10**, followed by selective saponification with cesium hydroxide to the desired cesium *tert*-alkyl oxalate (**5.6**). The model substrates were obtained from commercial 1-methylcyclohexanol (**5.8a**, Scheme 5.3) and 2-methyl-4-phenylbutan-2-ol (**5.8b**). Acylation of the alcohols to the ethyl *tert*-alkyl oxalate (**5.9a** and **5.9b**) proceeded in 63% and 83% yield respectively. Finally, saponification afforded the desired cesium oxalates (**5.6a** and **5.6b**) in 88% and 99% yield. Comparably, the remaining cesium oxalates were synthesised from the corresponding alcohols via the ethyl *tert*-alkyl oxalates (**5.8c-v**, 24 – 98% yield) and were obtained in 22% – quantitative yields (**5.6c-v**). To access cesium alkylthiooxo acetate **5.7,** we proceeded through the same strategy as for the cesium alkyl oxalates in a one-pot procedure. After acylation of 1-adamantane thiol, an aqueous work-up with 1 equivalent of 1 M cesium hydroxide afforded **5.7** in 60% yield.

[4] a. Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273. b. Su, J. Y.; Grünenfelder, D. C.; Takeuchi, K.; Reisman, S. E. *Org. Lett.* **2018**, *20*, 4912–4916.



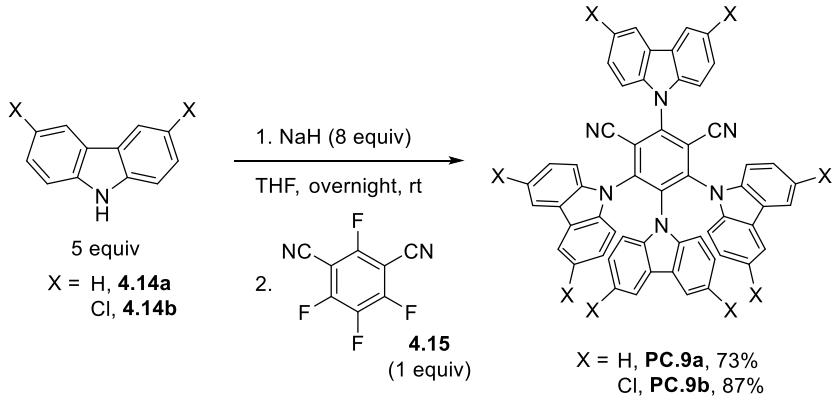
Scheme 5.3. Synthesis of cesium oxalates 5.6a-v and thio-oxoacetate 5.7.

In comparison to the previously reported decarboxylative alkynylations,[5] where the starting material is invariably the carboxylic acid, the use of oxalate salts proves to be a more practical option. Oxalic acids, particularly *tert*-alkyl oxalic acids, are not bench stable whereas cesium oxalates are bench stable. When starting from a salt, the screening of counter cation effect is integrated into the synthesis of the oxalate. During preliminary studies performed by Dr. Franck Le Vaillant, the cesium salts gave better results. This is in correlation with the observations of the MacMillan and Overman groups.[4a] In this chapter, we will focus on the use of cesium oxalates.

[5] a. Xuan, J.; Zhang, Z.-G.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2015**, *54*, 15632–15641. b. Le Vaillant, F.; Courant, T.; Waser, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204.

5.1.4. Synthesis of the 4CzIPN-type photocatalysts (**PC.9a** and **PC.9b**)

As described in chapter 4, the 4CzIPN catalysts are easily accessible in a single step from the corresponding commercial carbazole (**4.14a** or **4.14b**) and 2,4,5,6-tetrafluoroisophthalonitrile (**4.15**) with sodium hydride as a base (Scheme 5.4). **PC.9a** was obtained in 73% yield and **PC.9b** in 87% yield.



Scheme 5.4. Synthesis of the 4CzIPN-type organic dyes.

5.2. Photocatalysed deoxyalkynylation

5.2.1. Preliminary studies towards the deoxyalkynylation

These results were obtained in collaboration with Dr. Franck Le Vaillant.

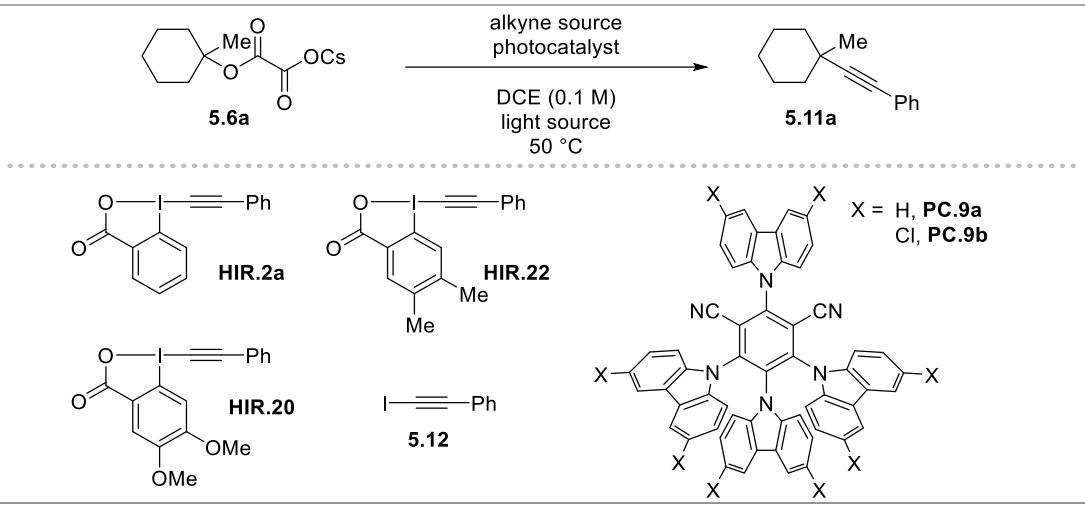
5.2.1.1. Initial optimisation studies for the photocatalysed deoxyalkynylation

We started our optimisation studies using the cyclohexyl substrate **5.6a** and **HIR.2a** as an alkyne source (Table 5.3). Under the irradiation of a Rayonet reactor (415 nm) with 1.5 equiv of **HIR.2a** and **PC.9a** as a photocatalyst in DCE we could obtain the desired deoxyalkynylated product **5.11a** in 55% yield (entry 1). We then turned to other solvents such as THF, DME or DMF. Where THF and DME resulted in a drop in yield of **5.11**(25% and 10%, entries 2 and 3), DMF provided the desired alkyne in 55% yield (entry 4). We wondered whether the solubility of the cesium salt could be improved in DCE by adding 10 equiv of water. Unfortunately, the desired alkyne was obtained in 20% yield (entry 5). Then we wondered if increasing the loading of EBX could improve the yield, however, even with 2.5 equiv we obtained only 61% yield of **5.11**(entry 6). This result fell in the same range as the 55% yield obtained with 1.5 equiv of **HIR.2a**. During our studies, Chen and co-workers reported a study on the impact of the core substitution of the EBX.[6] We were particularly interested in the electron-rich substitution of the core as it had often improved the transformations. We chose to investigate two scaffolds: first, the 4,5-dimethyl reagent **HIR.22** and, second, the 4,5-dimethoxy reagent

[6] Cf. Chapter 2: Background and significance, 2.3.2.3.3.b. Fragmentation cascades. Pan, Y.; Jia, K.; Chen, Y.; Chen, Y. *Beilstein J. Org. Chem.* **2018**, *14*, 1215–1221.

HIR.20. With **HIR.22** (1.5 equiv) we could obtain comparable yields to that of 2.5 equivalents of **HIR.2a** (61%, entry 7) and **HIR.20** gave an increase in yield of **5.11a**: 76% (entry 8). Increasing the loading of **HIR.20** to 2 equivalents or using **PC.9b** as a photocatalyst did not improve the yield of **5.11a** (76% and 70%, entries 9 and 10). Finally, we tested blue LED strips as a source of irradiation and the desired compound was obtained in 70% yield (entry 7). Due to the greater availability of blue LED strips, we proceeded to scope exploration with this light source.

Table 5.3. Initial optimisation of the photocatalysed deoxyalkynylation of 5.6a with EBXs.



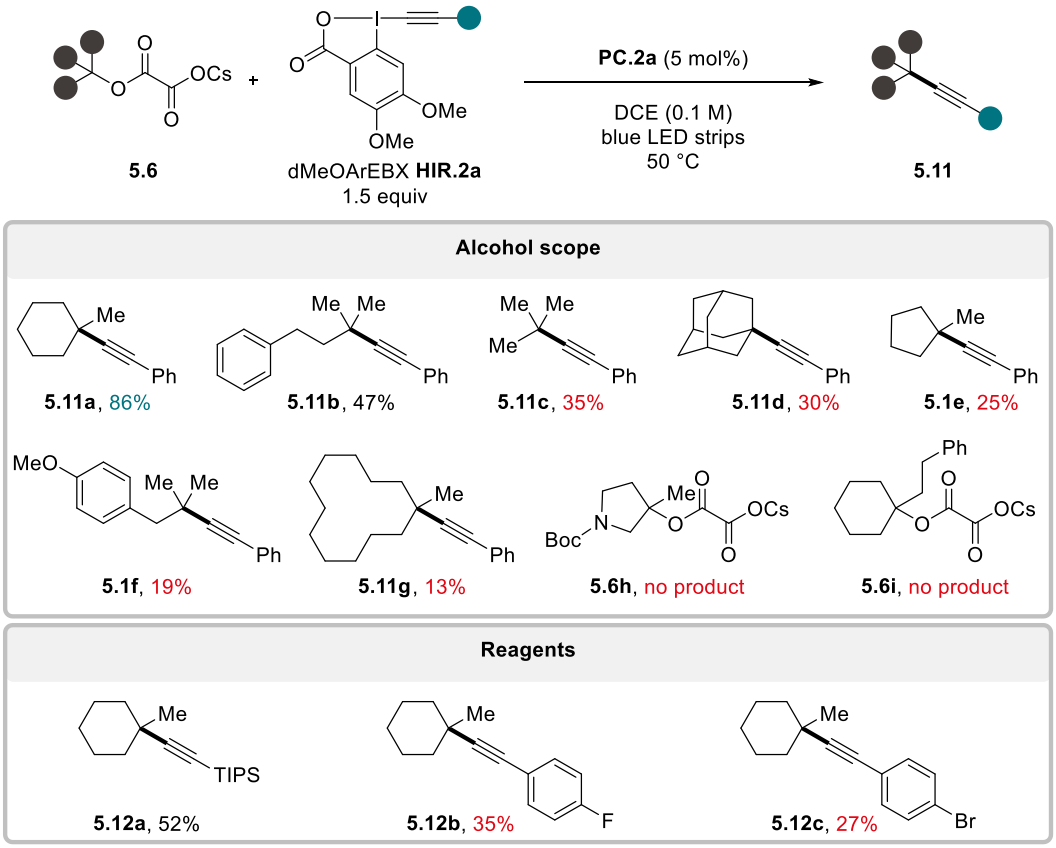
Entry	Reagent (equiv)	Photocatalyst	Solvent	Light source	Yield (%)
1	**HIR.2a** (1.5)	**PC.9a**	DCE	Rayonet	55
2	**HIR.2a** (1.5)	**PC.9a**	THF	Rayonet	25
3	**HIR.2a** (1.5)	**PC.9a**	DME	Rayonet	10
4	**HIR.2a** (1.5)	**PC.9a**	DMF	Rayonet	55
5[a]	**HIR.2a** (1.5)	**PC.9a**	DCE	Rayonet	20
6	**HIR.2a** (2.5)	**PC.9a**	DCE	Rayonet	61
7	**HIR.22** (1.5)	**PC.9a**	DCE	Rayonet	61
8	**HIR.20** (1.5)	**PC.9a**	DCE	Rayonet	76
9	**HIR.20** (2.0)	**PC.9a**	DCE	Rayonet	76
10	**HIR.20** (1.5)	**PC.9b**	DCE	Rayonet	70
11	**HIR.20 (1.5)**	**PC.9a**	**DCE**	**Blue LED strips**	**70**

Reaction conditions: **5.6a** (0.10 mmol, 1.0 equiv), EBX, PC (5 mol%) in degassed solvent. Irradiation for 18 hours at rt. Yields are isolated, margin of error: 1 mg of **5.11a** = 6% yield. [a]Reaction was performed with 10 equiv H_2O

5.2.1.2. Initial scope exploration

With the optimised conditions in hand, we turned to explore the scope of our reaction. Interestingly, on scope scale we observed an increase in yield for substrate **5.6a** (**5.11a**, 86%, Scheme 5.5). However, when turning to other substrates the method was less efficient. Compound **5.11b** was obtained in 47% yield and alkynes **5.11c**-**e** were obtained in 35 – 25%

yield. Finally, **5.11f** and **5.1g** could be accessed in less than 20% yields whereas as substrates **5.6h** and **5.6i** led to no product formation and a complex reaction mixture. Based on these results, it seemed that our optimal conditions lacked generality. Finally, we tested three other dimethoxy- core-modified EBX reagents. Interestingly, the TIPS alkyne **5.12a** could be obtained in 52% yield, whereas *p*-fluorophenyl and *p*-bromophenyl substitution provided **5.12b** and **5.12c** in 35% and 27% yield.



Scheme 5.5. Preliminary scope investigation of the deoxyalkynylation with HIR.20. Reaction conditions: The reactions were performed on 0.3 mmol scale with **HIR.20** (1.5 equiv) and **PC.9a** under blue LED strip (10-15 W) irradiation for 18 hours.

5.2.1.3. Deoxyalkynylation – conclusive remarks

Following our preliminary studies, it seemed our conditions lacked generality. Indeed, using the core modified **HIR.20** with **PC.9a** led to good yields in our initial optimisation with **5.6a**. However, different substrates led systematically to at least a 40% drop in yield of the desired deoxyalkynylated products. Furthermore, modification of the alkyne on the dimethoxy-modified reagents also led to lower yields even with the model substrate. We proceeded with a second round of optimisation with substrate **5.6b** as model substrate.

5.2.2. Second attempt towards a photocatalysed deoxyalkynylation

These results were obtained in collaboration with Diana Cavalli.

5.2.2.1. Optimisation of the photocatalysed deoxyalkynylation

5.2.2.1.1. Reagent and solvent screening for the photocatalysed deoxyalkynylation

For the second optimisation attempt of the photocatalysed deoxyalkynylation we chose **5.6b** for the model substrate. Upon careful analysis of reported literature,[4,7] we noted that the majority of deoxygenation strategies reported used high intensity blue LED lamps (30 – 40 W, λ_{max} = 440 nm). We envisaged that the intensity of the light irradiation may have played an important role in these strategies. To test our hypothesis, we started from the optimal conditions previously established: **PC.9a**, with 1.5 equiv of the EBX reagent in DCE (0.1 M, Table 5.4). We decided to test the optimal reagent (**HIR.20**) and the unmodified reagent (**HIR.2a**).[8] We performed both reactions under the irradiation of two blue LED lamps (440 nm, 2 x 40 W) and obtained 55% of **5.11b** with **HIR.20** and 67% yield of **5.11b** with **HIR.2a** (entries 1 and 2). This suggests that the core modification may not be necessary for optimal results. In addition to the formation of the desired deoxyalkynylated product (**5.11b**), we also observed the formation of 10% of **5.13a** resulting from the alkynylation of DCE with **HIR.2a**. We therefore proceeded to screen solvents to minimise the amount of solvent alkynylation. DMSO, MeCN and THF led to a considerable drop in yield (52%, 40% and 22%, entries 3 – 5). We then tried DME:DMF 9:1 to help solubilise the cesium salt **5.6b**. The desired compound was obtained in 70% yield (entry 6). We then wondered whether the addition of water to further promote the solubilisation of the cesium salt would be beneficial. Unfortunately, no improvement was observed (55%, entry 7). We then turned to CH_2Cl_2, for this we ensured that our reaction set-up could sustain the potential pressure by using a screw-cap vial.[9] To our delight, we observed a slight increase in yield (75%) and only traces of solvent alkynylation (**5.13b**, entry 8).

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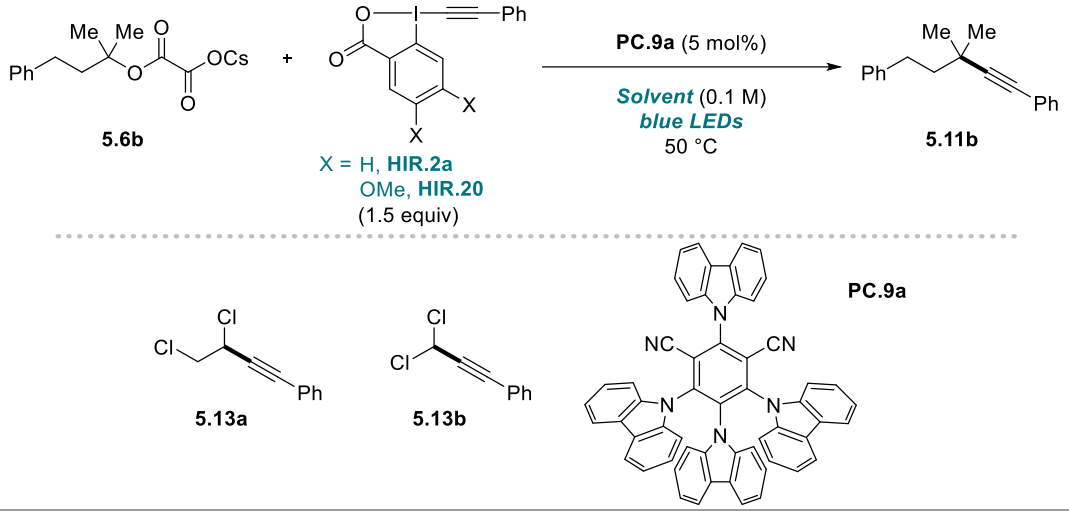
[7] a. Zhang, X.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 13862–13865. b. Su, J. Y.; Grünenfelder, D. C.; Takeuchi, K.; Reisman, S. E. *Org. Lett.* **2018**, *20*, 4912–4916.

[8] Using **HIR.2a** instead of a core-modified reagent would be more attractive from a cost perspective (from fluorochem: *o*-iodobenzoic acid: 0.64 CHF/g, 2-iodo-4,5-dimethoxybenzoic acid: 12 CHF/g, 2-iodo-4,5-dimethylbenzoic acid: 146 CHF/g).

[9] This set-up was also used for the screening of other solvents. We observed no loss of solvent overnight and the potential pressure build-up did not result in any experimental issues (similar vials have been reported to tolerate up to 10 bar). In our first studies we had been using a test-tube with a stopper which led every now and then to the stopper popping off and the loss of our inert atmosphere. The screw-cap set-up seems overall reliable.

Table 5.4. Optimisation of the photocatalysed deoxyalkynylation of 5.6b with EBXs.

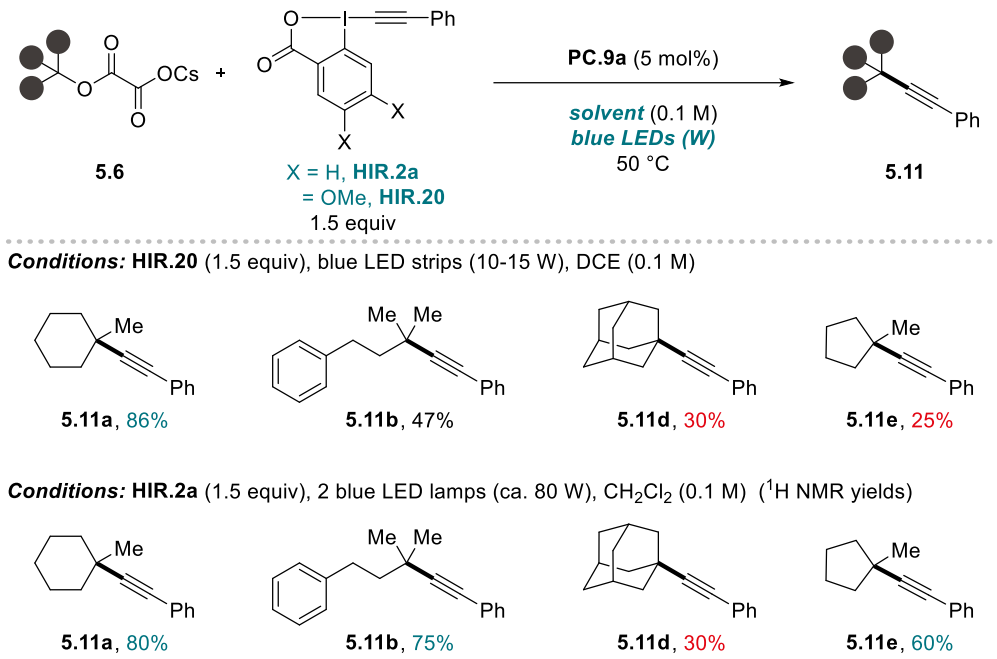


Entry	Reagent	Solvent (M)	^{1}H NMR yield (%)
1	**HIR.20**	DCE (0.1)	55
2	**HIR.2a**	DCE (0.1)	67
3	**HIR.2a**	DMSO (0.1)	52
4	**HIR.2a**	MeCN (0.1)	40
5	**HIR.2a**	THF (0.1)	22
6	**HIR.2a**	DME:DMF 9:1 0.1)	70
7	**HIR.2a**	DME:DMF 9:1 + 10 eq. H_2O (0.1)	55
8	**HIR.2a**	**CH_2Cl_2 (0.1)**	**75**

Reaction conditions: **5.6b** (0.10 mmol, 1.0 equiv), EBX (0.15 mmol, 1.5 equiv), **PC.9a** (5 mol%) in degassed solvent. Irradiation for 18 hours at rt (1 lamp 40 W, 2 lamps: 80 W, λ_{max} = 440 nm). ^{1}H NMR quantification was done using 1 equiv of CH_2Br_2 as an internal standard.

5.2.2.1.2. Preliminary scope exploration of the deoxyalkynylation

Considering our promising results, we performed a preliminary scope study to evaluate the generality of our optimised conditions (Scheme 5.6). To our delight, our new conditions seemed more efficient, compounds **5.11a**, **5.11b**, **5.11e** could be obtained in synthetically relevant yields (60 – 80%). Unfortunately, **5.11d** was obtained in the same 30% yield. Overall, these results were promising so we proceeded with final screening of the reaction conditions.



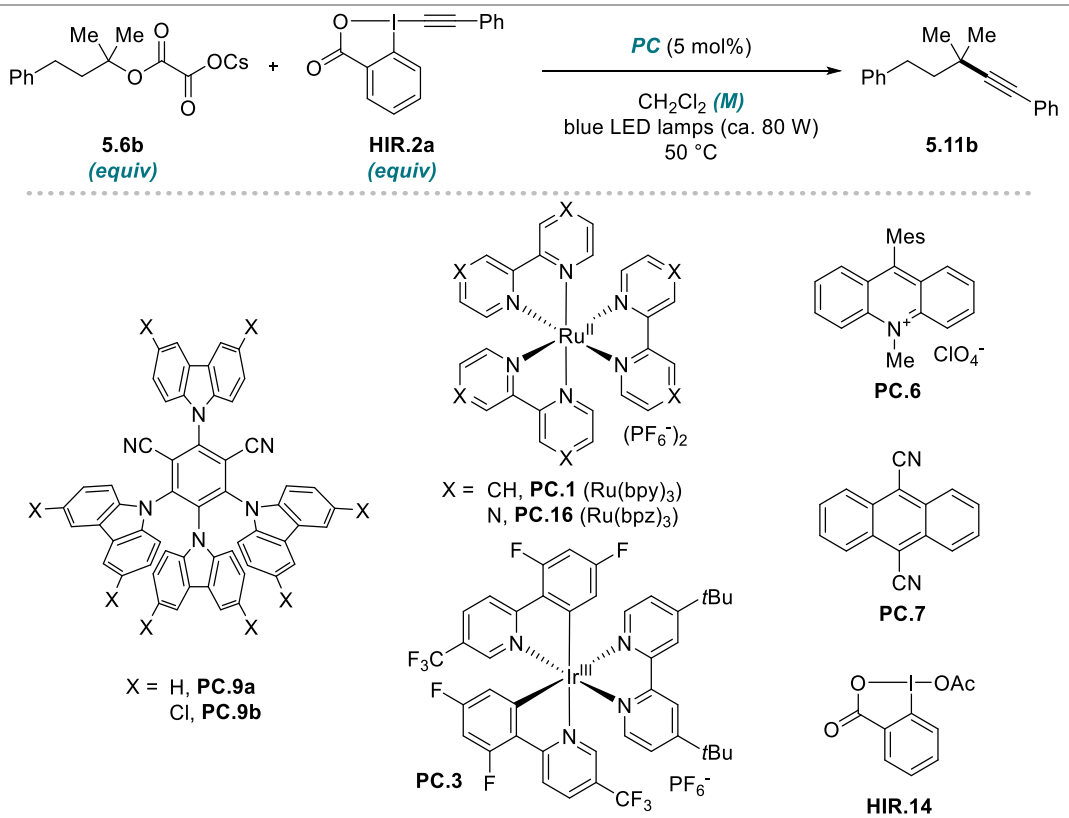
Scheme 5.6. Pre-scope investigation of the deoxyalkynylation of cesium oxalates with HIR.2a. Reaction conditions: The reactions were performed on 0.1 mmol scale, 5.6 (1 equiv), EBX (1.5 equiv), PC.9a (5 mol%) in degassed solvent using blue LED lamps unless specified elsewhere (1 lamp 40 W, 2 lamps: 80 W). ^{1}H NMR quantification was done using 1 equiv of CH_2Br_2 as an internal standard.

5.2.2.1.3. Fine-tuning of the deoxyalkynylation

We continued our optimisation studies by screening photocatalysts: **PC.9b** performed as well as **PC.9a** (75%, Table 5.5, entry 1). **PC.3** ($Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$), often used in previous deoxygenation studies,[4,7] afforded the desired alkyne **5.11b** in a lower 50% yield (entry 2). Other transition metal-based catalysts **PC.1** ($Ru(bpy)_3(PF_6)_2$) and **PC.16** ($Ru(bpz)_3(PF_6)_2$) were also less efficient affording the desired alkyne in poor yields (<10% and 20%, entries 3 and 4). Highly oxidising organic dyes **PC.6** ($MesAcr.BF_4$) and **PC.7** (DCA) were slightly less efficient than **PC.9a** and **PC.9b** (ca. 55% yield of **5.11b**, entries 5 and 6). We continued our studies with **PC.9a** and turned to the stoichiometry of the **5.6b** and **HIR.2a**. Inverting the stoichiometry to have 1.2 equiv of **5.6b** led to a considerable drop in yield (45%, entry 7). With a 1:1 ratio of **5.6b:HIR.2a** the compound was obtained in 64% yield (entry 8) whereas the ratio 1.2:1.0 was slightly less efficient but still in the same range (56%, entry 9). Increasing the equivalents of **HIR.2a** to 1.8 or 2.5 did not further improve the yield of the transformation (ca. 70%, entries 10 and 11). We then investigated the effect of the concentration of the reaction. At higher (0.5 M) and lower (0.05 M) concentrations the reaction proceeded similarly (ca. 75%, entries 12 and 13). However, when moving to a lower concentration (0.02 M), the yield dropped to 55% (entry 14). We continued with 0.1 M to ensure greater solubility of our cesium salts for the scope studies. We attempted the addition of **HIR.14** (BIOAc) as an additive. Unfortunately, this did not improve the reaction yields, delivering **5.11b** in 65% (entry 15). Finally, we wondered if the light source had indeed played a key role in the optimisation of the reaction conditions. Indeed, when the reaction was performed with the traditional blue LED

strips (ca. 10-15 W) we observed a low yield (27%, entry 16). Finally, we decided to test **HIR.20** instead of **HIR.2a**, however a slight drop in yield was observed (65%, entry 17).

Table 5.5. Fine-tuning of the reaction conditions for the deoxyalkynylation of cesium oxalate 5.6b with HIR.2a.



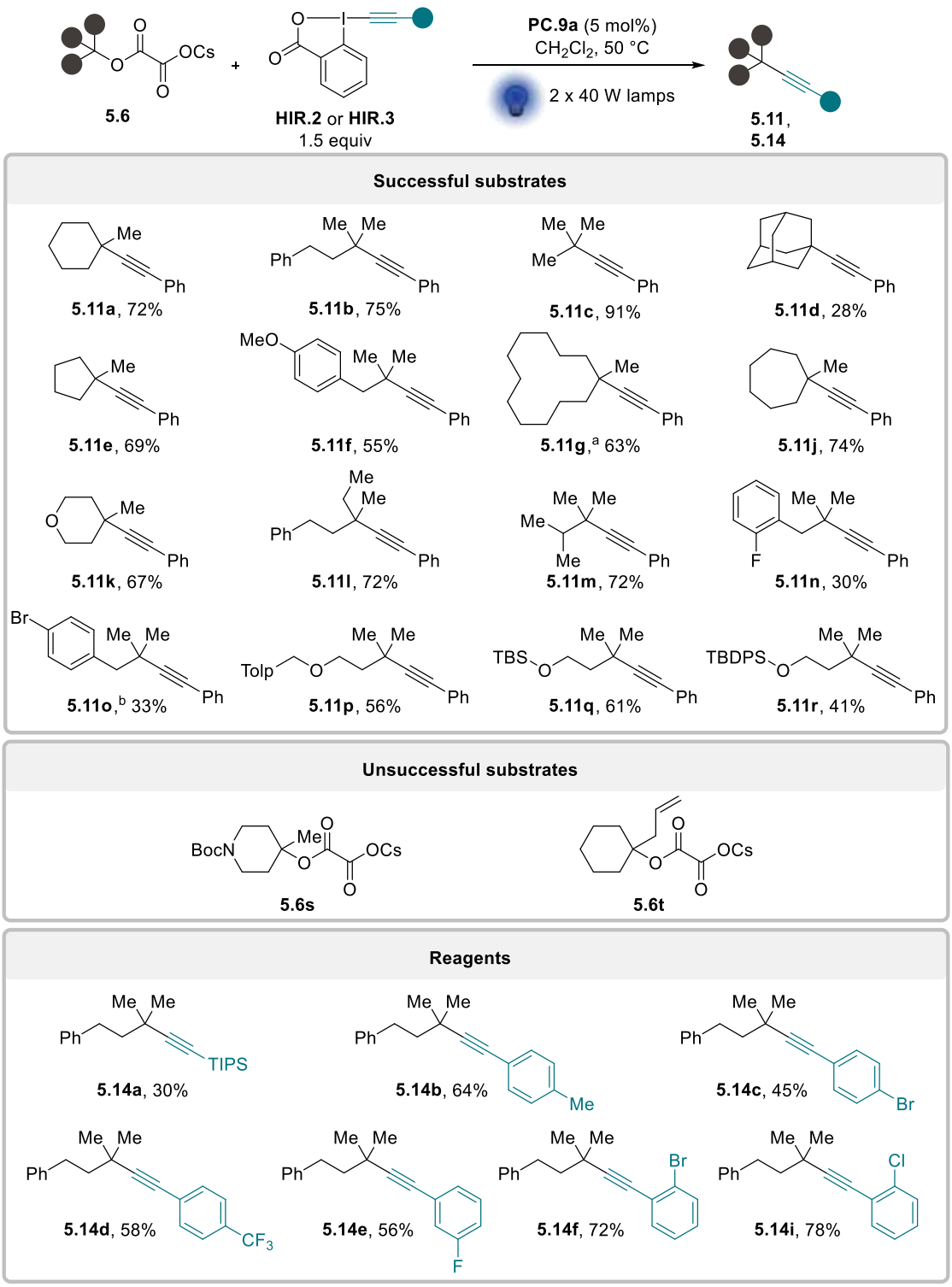
Entry	Concentration (M)	Photocatalyst	Stoichiometry 5.6b:HIR.2a	^{1}H NMR yield (%)
1	0.1	**PC.9b**	1:1.5	75
2	0.1	**PC.3**	1:1.5	50
3	0.1	**PC.1**	1:1.5	<10
4	0.1	**PC.16**	1:1.5	20
5	0.1	**PC.6**	1:1.5	53
6	0.1	**PC.7**	1:1.5	55
7	0.1	**PC.9a**	1.2:1	45
8	0.1	**PC.9a**	1:1	64
9	0.1	**PC.9a**	1:1.2	56
10	0.1	**PC.9a**	1:1.8	70
11	0.1	**PC.9a**	1:2.5	75
12	0.5	**PC.9a**	1:1.5	75
13	0.05	**PC.9a**	1:1.5	73
14	0.02	**PC.9a**	1:1.5	55
15[a]	0.1	**PC.9a**	1:1.5	65
16[b]	0.1	**PC.9a**	1:1.5	27
17[c]	0.1	**PC.9a**	1:1.5	65

Reaction conditions: **5.6b** (0.10 mmol, 1.0 equiv), **HIR.2a** (0.15 mmol, 1.5 equiv), PC (5 mol%) in degassed CH_2Cl_2. Irradiation for 18 hours at rt (1 lamp 40 W, 2 lamps: 80 W, λ_{max} = 440 nm). ^{1}H NMR quantification was done using 1 equiv of CH_2Br_2 as an internal standard. [a]The reaction was performed with 0.5 equiv of BIOAc (**HIR.14**) as an additive. [b]The reaction was performed with blue LED strips (10 -12 W, λ_{max} = 460 nm). [c]The reaction was performed with **HIR.20** instead of **HIR.2a**

5.2.2.2. Scope of the deoxyalkynylation

With the optimised conditions in hand, we proceeded by investigating the scope of the transformation (Scheme 5.7). In comparison to our first scope investigation (Scheme 5.5), most substrates afforded the desired alkynes in higher yields: **5.11a-c**, **5.11e** and **5.11f** were obtained in 55% to 91% yield. Unfortunately, the adamantyl alkyne **5.11d** was obtained in only 28% yield. This scaffold was also problematic in a deoxyalkylation from *N*-phthalimidoyl oxalates reported by Overman and co-workers.[10] We then explored other cyclic scaffolds, the cycloheptanyl alkyne **5.11j** was delivered in 74% yield and the tetrahydropyran derivative afforded **5.11k** in 64% yield. We then turned to more bulky scaffolds, **5.11l** and **5.11m** were both accessed in 72% yield. Other homo-benzylic alcohols were tested, affording the desired alkynes **5.11n** and **5.11o** in lower yields (ca. 30%). Finally, we tested some protected diols: both benzyl and silyl protecting groups were tolerated and all three alkynes (**5.11p-r**) were synthesised in 41 – 61% yield. During our studies, we encountered a limitation with substrate **5.6s**, we observed a messy reaction profile by TLC and we were unable to isolate any product from the reaction. Similarly, with the homo-allylic scaffold **5.6t** we were unable to isolate any product. We also tested primary and secondary alcohols in our preliminary scope investigation, despite conversion of both the oxalate and the reagent, we did not detect the desired deoxyalkynylated product by ^{1}H NMR. We then turned to the scope of reagents, when using **HIR.3**, we obtained 30% of the TIPS alkyne (**5.14a**). Substitution in *para* was overall tolerated with alkynes **5.14b**-**5.14d** in 45% - 64% yield. *meta*-fluoro substitution afforded **5.14e** in 56% yield. Interestingly, electron poor substitution in the *ortho* position led to high yields of alkynes **5.14f** and **5.14i** (72% and 78%). Unfortunately, alkyl-EBXs were unsuccessful proving unstable under the reaction conditions.

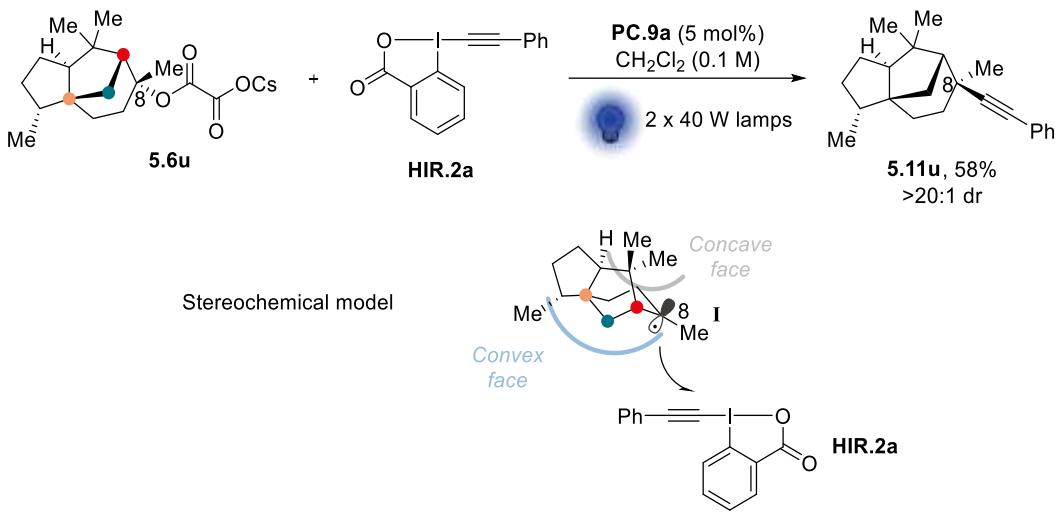
[10] Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342–15345.



Scheme 5.7. Scope of the photocatalysed deoxyalkynylation of cesium oxalates with EBXs. Reaction conditions: The reactions were performed on 0.3 mmol scale **5.6** (1.0 equiv), **HIR.2** or **HIR.3** (1.5 equiv) with **PC.9a** (5 mol%) in CH_2Cl_2 (0.1 M) using blue LED lamps (2 x 40 W, 440 nm)

5.2.2.3. Photocatalysed deoxyalkynylation of natural products

Finally, we applied our strategy to two natural products. We successfully performed the diastereoselective deoxyalkynylation of (-)-cedrol giving access to **5.11u** in 58% yield in over 20:1 dr (Scheme 5.8). Based on the structure of (-)-cedrol and the key radical intermediate (**I**), an attack from the convex face seemed probable.



Scheme 5.8. Photocatalysed deoxyalkynylation of (-)-cedrol with HIR.2a and stereochemical model.

The absolute stereochemistry of the C8 centre was determined by HMBC and NOESY NMR analyses and was found to be (*S*), which would result from an inversion of this stereocenter in relation to the alcohol precursor, thus confirming our stereochemical model (Figure 5.5.1).

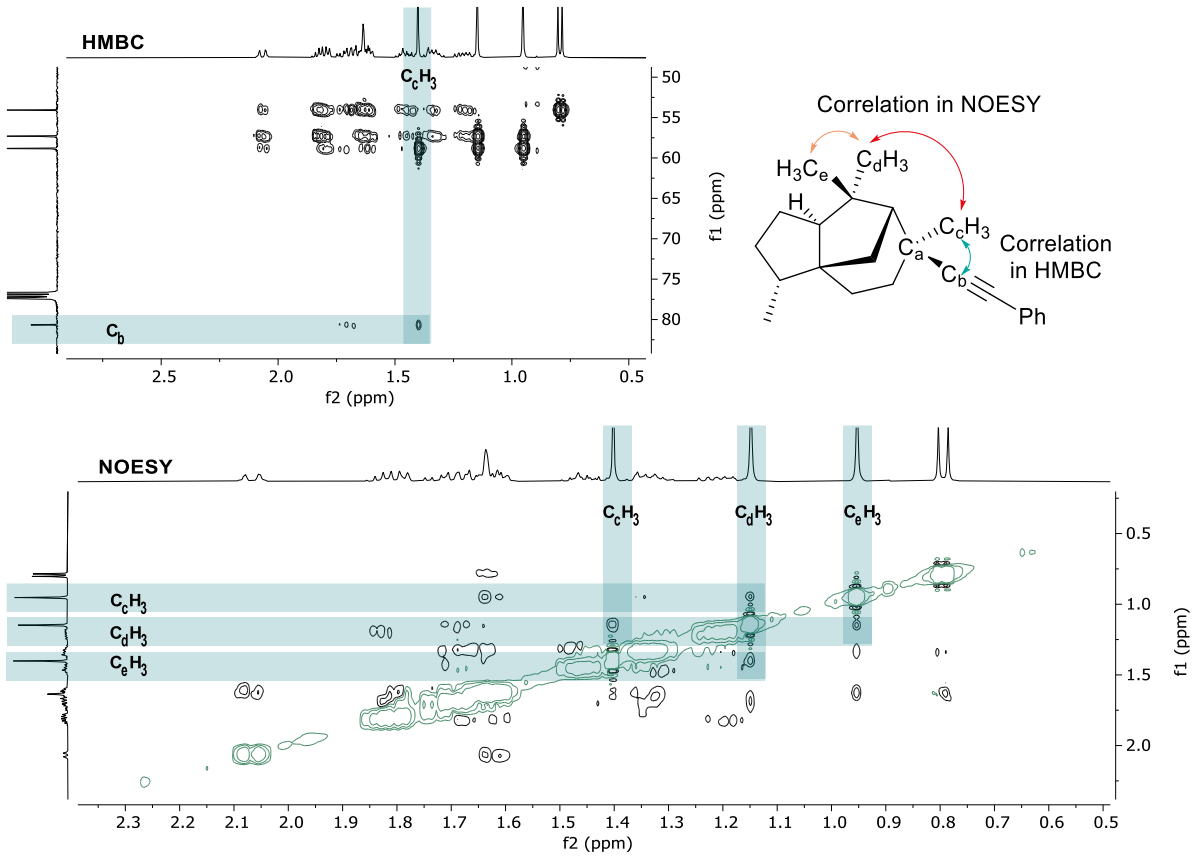
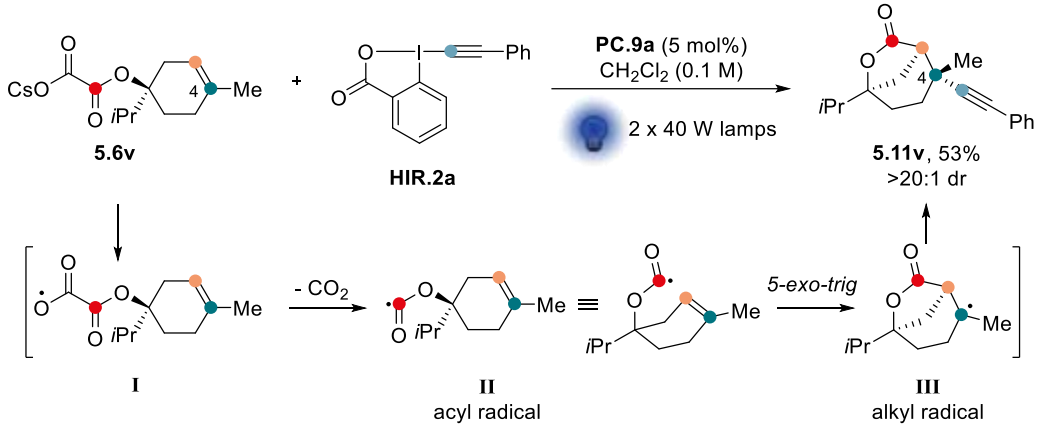


Figure 5.5.1. HMBC and NOESY NMR spectra allowing the structural determination of 5.11u.

When turning to (-)-terpinen-4-ol, we didn't observe the expected deoxyalkynylation product, however, we did observe the formation of **5.11v** in 53% yield in over 20:1 dr (Scheme 5.9). The formation of **5.11v** can be explained by the first decarboxylation of **I** to afford intermediate

acyl radical **II**. Then, instead of releasing a second molecule of CO_2, the acyl radical (**II**) undergoes 5-exo-trig cyclisation to the alkyl radical (**III**), which in turn is trapped by **HIR.2a** delivering **5.11v**.



Scheme 5.9. Photocatalysed remote alkynylation of (-)-terpinen-4-ol with HIR.2a.

Following COSY and NOESY NMR analyses, the C4 centre was found to be of (*R*) configuration (Figure 5.5.2).

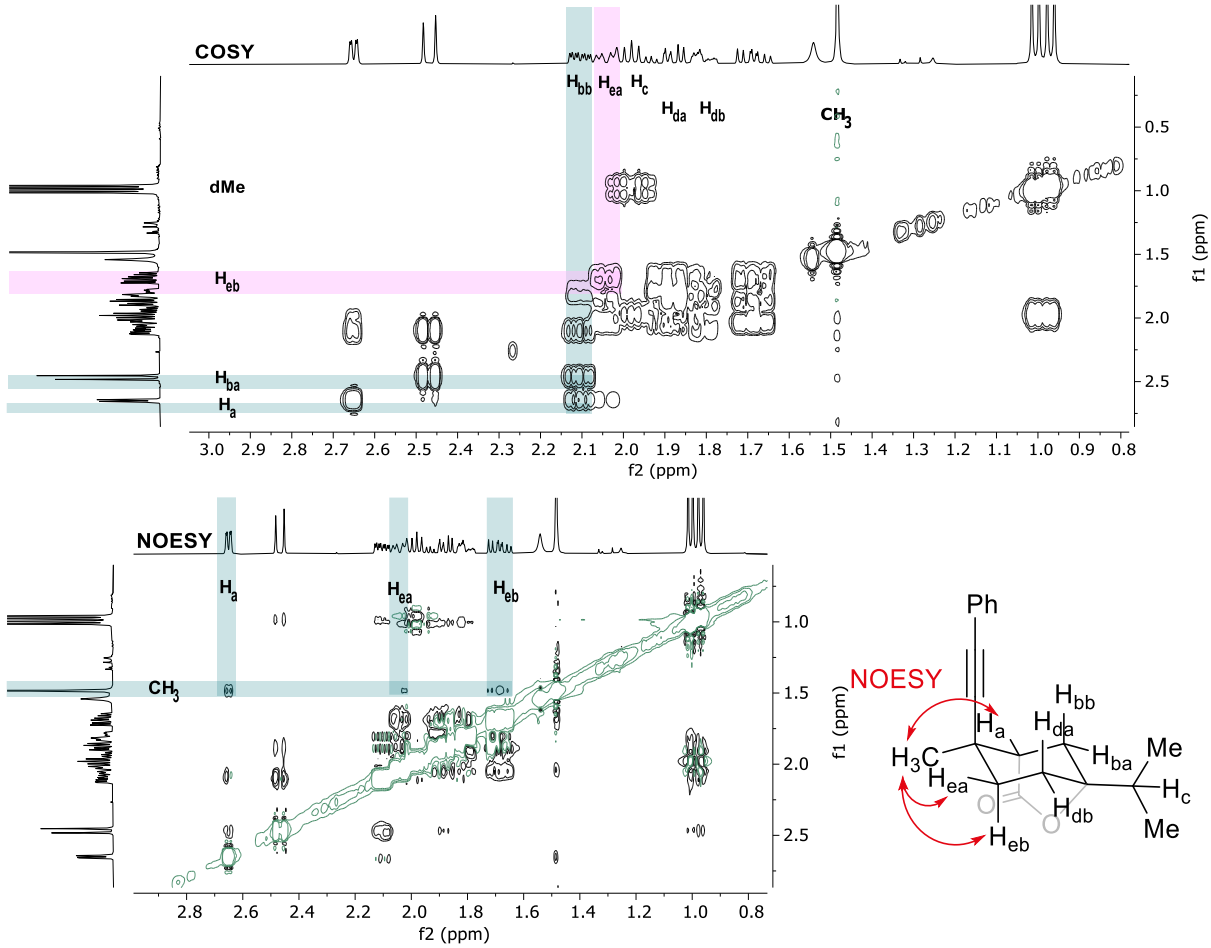
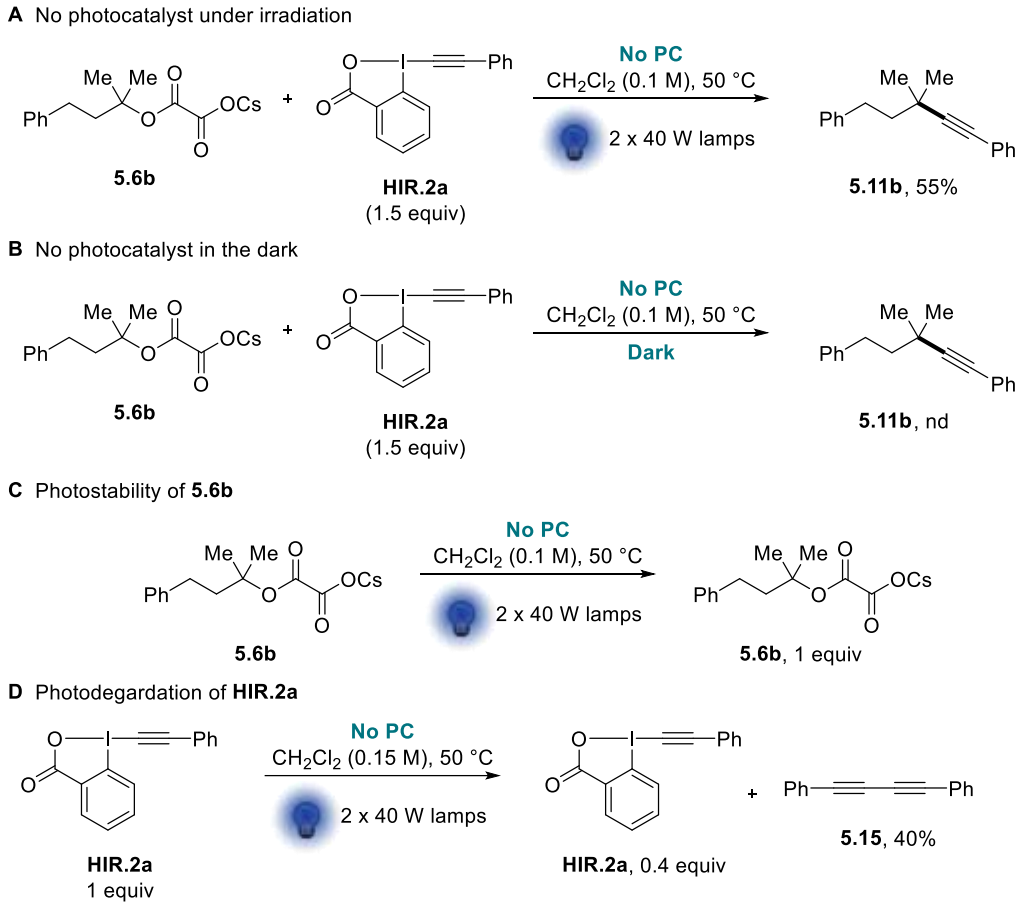


Figure 5.5.2. COSY and NOESY NMR spectra allowing the structural determination of 5.11v.

5.2.3. Initial mechanistic studies for the deoxyalkynylation

5.2.3.1. Control reactions for the deoxyalkynylation

We started our mechanistic investigation by establishing the photocatalytic nature of this process (Scheme 5.10). We started by performing the reaction without photocatalyst under blue LED irradiation (2 x 40 W lamps) (**A**). Contrary to our expectations based on known literature for photocatalysed alkynylations with **HIR.2a**, we obtained the desired alkyne **5.11b** in 55% yield suggesting that the photocatalyst was not necessary to access the alkyne but did improve the overall yield of the transformation. We then performed the reaction in the dark without photocatalyst (**B**): no **5.11b** was detected, confirming the photomediated nature of this transformation. Intrigued by these results, we wondered whether the starting materials were stable under irradiation with the two high intensity lamps. First, the cesium oxalate **5.6b** was stable under irradiation: in the absence of photocatalyst and **HIR.2a**, no degradation was observed (**C**). When turning to the reagent stability, only 0.4 equiv of **HIR.2a** could be recovered under irradiation (2 x 40 W blue LED lamps) in absence of the photocatalyst and the cesium salt. Furthermore, we observed the formation of diyne **5.15** in 40% yield based on ^{1}H NMR analysis (**D**). This result demonstrates that **HIR.2a** can undergo photodegradation, which could explain the 55% yield of **5.11b** in absence of a photocatalyst (**A**).

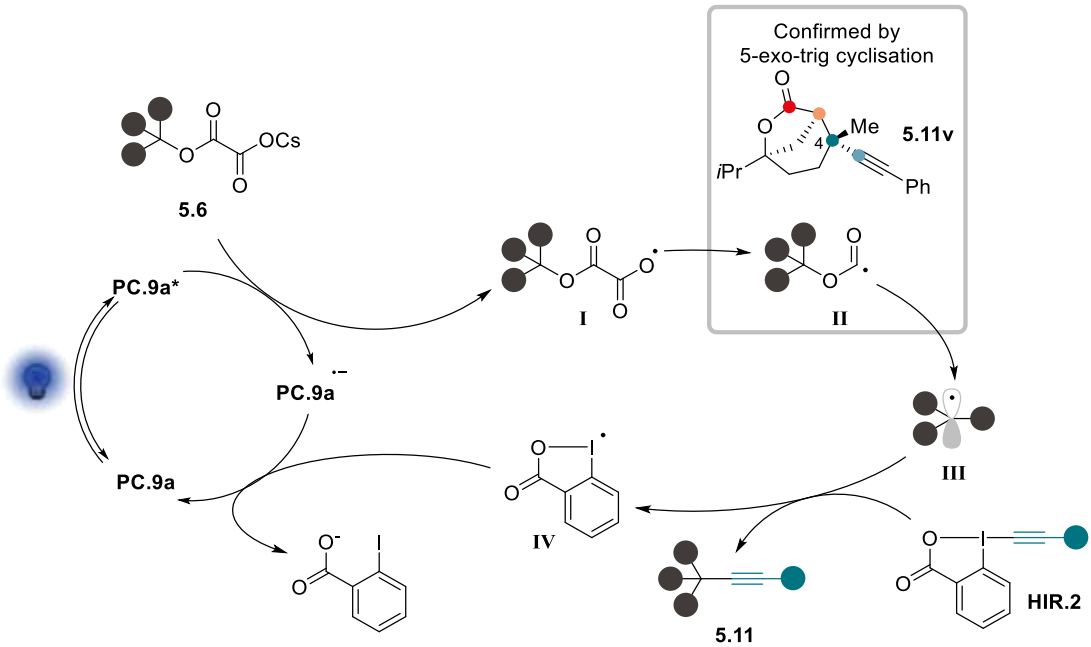


Scheme 5.10. Dark and photocatalyst-free experiments for the photocatalysed deoxyalkynylation of 5.6b with HIR.2a. Control reactions identifying the photostability of 5.6b and the photodegradation of HIR.2a.

5.2.3.2. Preliminary mechanistic proposal

Although we observed background reactivity in absence of the photocatalyst (**PC.9a**), the lower yield in absence of the photocatalyst strongly suggested that a photocatalytic cycle was still contributing to the reaction. Based on previous literature reports,[4,7] the excited state photocatalyst **PC.9a*** (+ 1.35 V vs SCE) can perform a single electron oxidation of **5.6** (+ 1.3 V Vs SCE for the cesium *tert*-butyl oxalate) affording the *O*-centred radical (**I**, Scheme 5.11). The latter undergoes a first rapid decarboxylation to the acyl radical (**II**), followed by a second slower decarboxylation to the alkyl radical (**III**).[11] The stepwise character of the deoxygenation process was confirmed by the 5-exo-trig cyclisation of the terpinene-4-ol derivative **5.11v**. For the unbiased substrates, the alkyl radical (**III**) can be trapped by **HIR.2** forming **5.11** and iodanyl radical (**IV**, $E_{1/2}$(**IV**$^{\bullet}$/**IV**$^{-}$) = + 0.25 V vs SCE). The latter can then close the photocatalytic cycle ($E_{1/2}$(**PC.9a**/**PC.9a**$^{\bullet-}$) = - 1.1 V vs SCE). The mechanism associated to the background photocatalyst-free transformation will be discussed in chapter 6.

[11] Simakov, P. A.; Martinez, F. N.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 1226–1232.



Scheme 5.11. Preliminary mechanistic proposal for the photocatalyst mediated deoxyalkynylation of 5.6 with HIR.2.

5.3. Towards a photocatalysed deoxycyanation and dethioalkynylation

These results were obtained in collaboration with Dr. Franck Le Vaillant. These transformations were envisaged as a complement to the deoxyalkynylation strategy. The majority of these experiments were performed in parallel with the first optimisation study of the deoxyalkynylation.

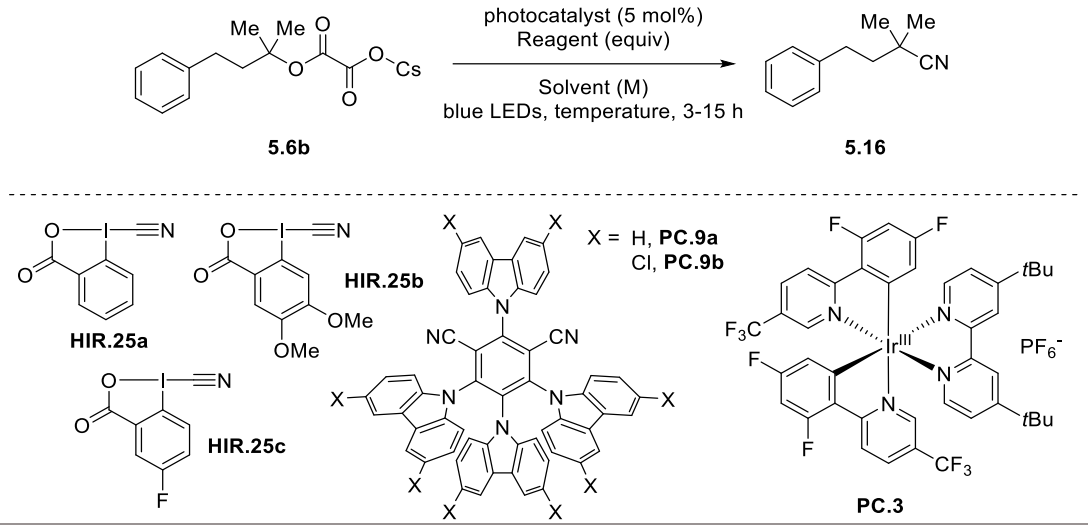
5.3.1. Photocatalysed deoxycyanation

5.3.1.1. Optimisation of the deoxycyanation

We started our optimisation with substrate **5.6b** to facilitate TLC analysis as the product is UV visible. We started with 2 equivalents of **HIR.25a** using **PC.9a** as a photocatalyst in DCE (0.05 M based on **5.6b**). The desired compound **5.16** was obtained in 23% yield (Table 5.6, entry 1). Other solvents were screened: 9:1 DCE:DMF, MeOH and acetone gave no improvement (entries 2 - 4). THF gave a slightly better yield (30% yield, entry 5), DME gave 39% yield and 1:3 DCE:THF gave 40% (entries 6 and 7, 47% brsm). For experimental simplicity we continued our studies in DME. We observed full conversion of the starting material **5.6b** in 3 hours affording **5.16** in 35% yield (entry 8). We then checked two alternative photocatalysts: **PC.9b** and **PC.3** ($Ir(dF(CF_3)ppy)_2(dtbbpy)^+$) both photocatalysts afforded **5.16** in a slightly lower yield (30% and 29%, entries 9 and 10). We investigated the effects of core-modification of the reagent, electron rich **HIR.25b** afforded traces of **5.16,** whereas electron poor **HIR.25c** delivered the desired compound in 21% yield (entries 11 and 12). Unfortunately, neither of the modified reagent performed better than **HIR.25a**. We then investigated the temperature of the reaction: increasing the temperature to 40 °C or 60 °C resulted in a drop in yield (entries 13 and 14). Decreasing the temperature to 8 - 14 °C over 4 hours[12] led to lower conversion of **5.6b** (60%), 28% yield of **5.16** (entry 15, 47% brsm). We attempted to change the set-up with an immerged glass rod illuminated with a blue LED. However, this change in light source led to lower yields over 24 hours at 10 °C and at 28 °C suggesting that the light source had a negative impact on the yield of **5.16** (entries 16 and 17). We then screened different concentrations (0.2 M, 0. 01 M, entries 18 and 19) and different loading of **HIR.25a** (5 equiv, 1.5 equiv) with no observable improvement (entries 20 and 21). Finally, considering the results from the deoxyalkynylation, we wondered if the high intensity blue LED lamps (2 x 40 W, λ_{max} = 440 nm) could improve the reaction yield, no improvement was observed with 1.5 equiv of **HIR.25a** (entry 22).

[12] The reaction was maintained at this temperature by refilling every 20 min a glass dish that was coated on the outside with the blue led strips, with 400 mL of water at 8 °C. Due to the safety hazard associated to the transfer of 400 mL of cold water to and from an electric LED bath the reaction was stopped after 4 hours despite incomplete conversion.

Table 5.6. Optimisation studies towards the photocatalysed deoxycyanation of 5.6b with CBX and analogues.

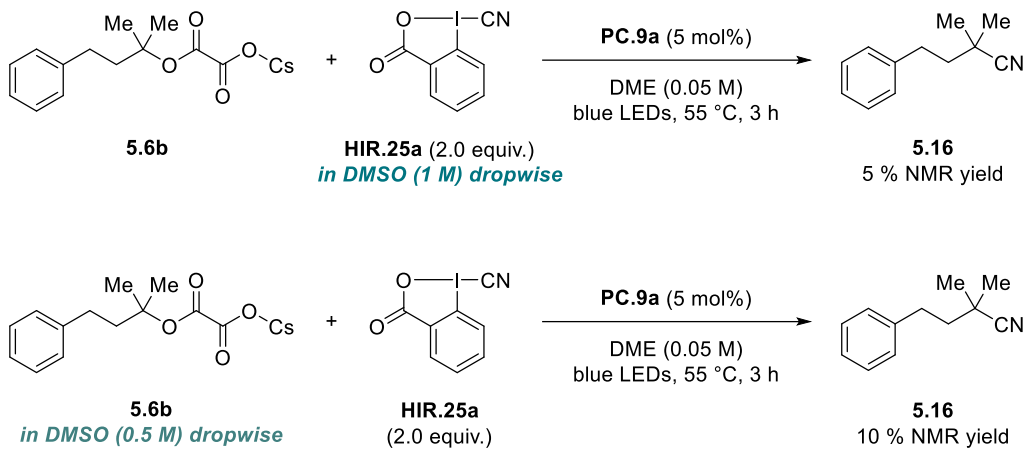


Entry	Solvent (M)	Photocatalyst	Reagent (equiv)	T (°C)	NMR yield (%)[b]
1	DCE (0.05)	**PC.9a**	**HIR.25a (2)**	28	23
2	9:1 DCE:DMF (0.05)	**PC.9a**	**HIR.25a (2)**	28	25
3	MeOH (0.05)	**PC.9a**	**HIR.25a (2)**	28	<5
4	Acetone (0.05)	**PC.9a**	**HIR.25a (2)**	28	15
5	THF (0.05)	**PC.9a**	**HIR.25a (2)**	28	30
6	DME (0.05)	**PC.9a**	**HIR.25a (2)**	28	39
7	1:3 DCE:THF (0.05)	**PC.9a**	**HIR.25a (2)**	28	40
8[a]	DME (0.05)	**PC.9a**	**HIR.25a (2)**	28	35
9[a]	DME (0.05)	**PC.9b**	**HIR.25a (2)**	28	30
10[a]	DME (0.05)	**PC.3**	**HIR.25a (2)**	28	29
11[a]	DME (0.05)	**PC.9a**	**HIR.25b (2)**	28	<5
12[a]	DME (0.05)	**PC.9a**	**HIR.25c (2)**	28	21
13[a]	DME (0.05)	**PC.9a**	**HIR.25a (2)**	40	16
14[a]	DME (0.05)	**PC.9a**	**HIR.25a (2)**	60	17
15[a]	DME (0.05)	**PC.9a**	**HIR.25a (2)**	8-14[b]	28
16	DME (0.05)	**PC.9a**	**HIR.25a (2)**	10[c,d]	5
17	DME (0.05)	**PC.9a**	**HIR.25a (2)**	28[c]	10
18[a]	DME (0.2)	**PC.9a**	**HIR.25a (2)**	28	<5
19[a]	DME (0.01)	**PC.9a**	**HIR.25a (2)**	28	15
20[a]	DME (0.05)	**PC.9a**	**HIR.25a (5)**	28	NR
21[a]	DME (0.05)	**PC.9a**	**HIR.25a (1.5)**	28	23
22[e]	DME (0.05)	**PC.9a**	**HIR.25a (1.5)**	28	16

Reaction conditions: The reactions were performed on 0.1 mmol scale **5.6b** (0.1 mmol, 1 equiv), **HIR.25**, PC (5 mol%) in degassed solvent under the irradiation of blue LED strips (10-15 W). ^{1}H NMR quantification was done using 1 equiv of CH_2Br_2 as an internal standard. [a]Reaction was run for 3 hours. [b]The reaction was maintained at this temperature with a cooled water bath that was renewed every 30 min [c]The reaction was irradiated by an immerged glass rod illuminated by a 420 nm blue LED 8 W. [d]The reaction was cooled down by use of a cryostat. [e]Reaction was irradiated using 2 blue LED lamps (2 x 40 W, λ_{max} = 440 nm)

5.3.1.2. Dropwise additions

Considering the rapid conversion of **5.6b** under our reaction conditions, we attempted performing the reaction with a dropwise addition of **5.6b** and **HIR.25a**. To ensure minimal solvent effects DMSO was the ideal solvent for the preparation of concentrated solutions of **5.6b** (0.5 M) and **HIR.25a** (1 M). The stock solutions were then added progressively over 3 hours to the corresponding reaction mixtures (Scheme 5.12). Unfortunately, **5.16** was obtained in lower yields in both cases.



Scheme 5.12. Attempts towards a photocatalysed deoxycyanation of 5.6b with HIR.25a with a dropwise addition of either HIR.25a or 5.6b.

5.3.1.3. Deoxycyanation – conclusive remarks

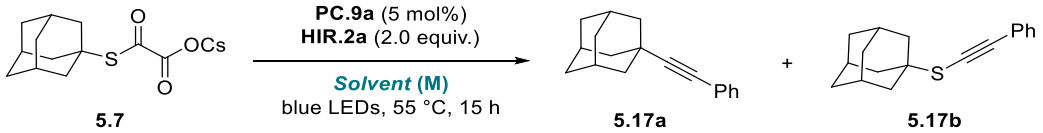
Our preliminary studies towards a deoxycyanation strategy have been hampered by the difficulty associated to following and identifying the mass balance of the cesium oxalate, indeed the conversion of **5.6b** is fast and complete in under 3 hours but the yield of **5.16** is around 35 - 40% with the optimal conditions. This suggests that there is one, or more, rapid degradation pathways for the cesium oxalate **5.6b**. Furthermore, the degradation products are not visible after concentration by ^{1}H NMR and HRMS analyses. This suggests that they may be volatile.

5.3.2. Photocatalysed dethioalkynylation of thio-oxoacetate **5.7**

5.3.2.1. Preliminary studies

We started our studies on the dethioalkynylation of **5.7** with **PC.9a** as a photocatalyst and 2 equivalents of **HIR.2a** in DCE (0.05 M based on **5.7**). Interestingly, this reaction afforded two products: the dethioalkynylated product **5.17a** and the thioalkyne **5.17b** in 20% and 50% yield respectively (Table 5.7, entry 1). We then proceeded to screen solvents: DME, THF and toluene did not help improve the yield of **5.17a** (<15% yield entries 2 - 4), DME and THF even increased the yield of thioalkyne **5.17b** (71 and 73%, entries 2 and 3). We then looked into the concentration of the reaction. At 0.03 M, we observed a decrease in yield for **5.17a** (15%) and the formation of **5.17b** was favoured (67%, entry 5). 0.05 M, 0.07 M, and 0.1 M gave comparable results (20-25% yield of **5.17a** and 50-55% yield of **5.17b** entries 1, 6 and 7). 0.2 M delivered **5.17a** in 20% yield and inhibited slightly the formation of **5.17b** (40% instead of 50%, entry 8). Finally, performing the reaction at 28 °C rather than 55 °C limited the formation of both products **5.17a** (10% yield) and **5.17b** (15% yield, entry 9).

Table 5.7. Preliminary optimisation studies towards a dethioalkynylation of 5.7 with HIR.2a and PC.9a.



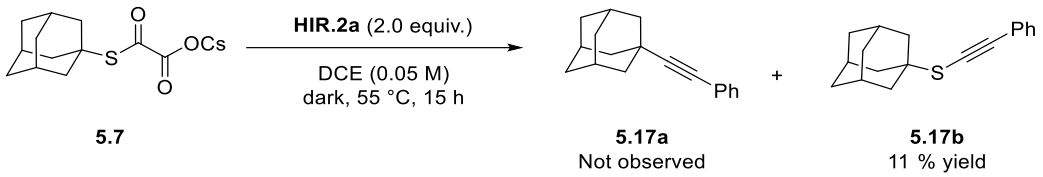
Entry	Solvent	(M)	NMR yield 5.17a (%)	NMR yield 5.17b (%)
1	DCE	0.05	20	50
2	DME	0.05	10	71
3	THF	0.05	15	73
4	PhMe	0.05	<5	<10
5	DCE	0.03	15	67
6	DCE	0.07	23	54
7	DCE	0.1	25	55
8	DCE	0.2	20	40
9[a]	DCE	0.05	10	15

Reaction conditions: The reactions were performed on 0.1 mmol scale **5.7** (0.1 mmol, 1.0 equiv), **HIR.2a** (0.2 mmol, 2.0 equiv), **PC.9a** (5 mol%) under the irradiation of blue LED strips (10-15 W). ^{1}H NMR quantification was done using 1 equiv of CH_2Br_2 as an internal standard. [a]Performed at 28°C

5.3.2.2. Dark experiments for the dethioalkynylation

To understand the nature of the competition between the formation of **5.17a** and **5.17b**, we performed the reaction in the dark in absence of a photocatalyst. **5.7** was heated to 55 °C in DCE (0.05 M) with 2 equivalents of **HIR.2a** (Equation 5.1). We did not observe formation of the product **5.17a**, confirming the photomediated character of this transformation. However, we did observe the formation of **5.17b** in 11% yield. This is far from the 50% observed under irradiation. This suggests that a thermal pathway can be envisaged for the formation of the

thioalkyne **5.17b**. However, the lower yield (11% instead of 50% under irradiation) suggests that the light irradiation may promote a second reaction pathway for the formation of **5.17b**.



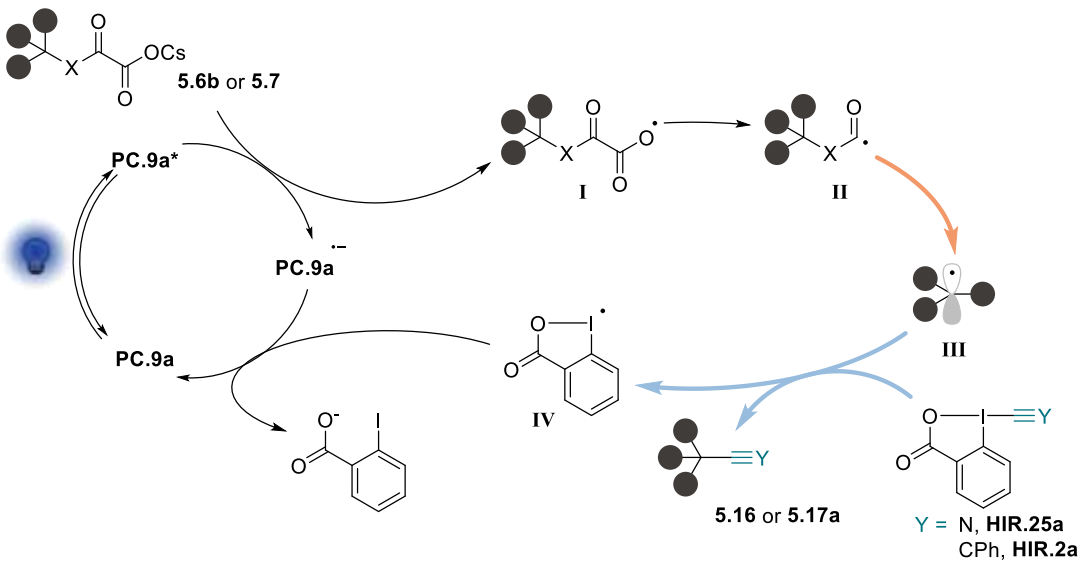
Equation 5.1. Dark experiment of the dethioalkynylation of 5.7 under thermal activation.

5.3.2.3. Dethioalkynylation – conclusive remarks

This project has stayed in a preliminary stage. Overall, there is a strong competition between dethioalkynylation and thioalkynylation affording the desired product **5.17a** in consistently lower yields than **5.17b**. As the abundance of tertiary thiols is low, we did not press further on this project.

5.3.3. Mechanistic analysis and assessment of the deoxycyanation and dethioalkynylation

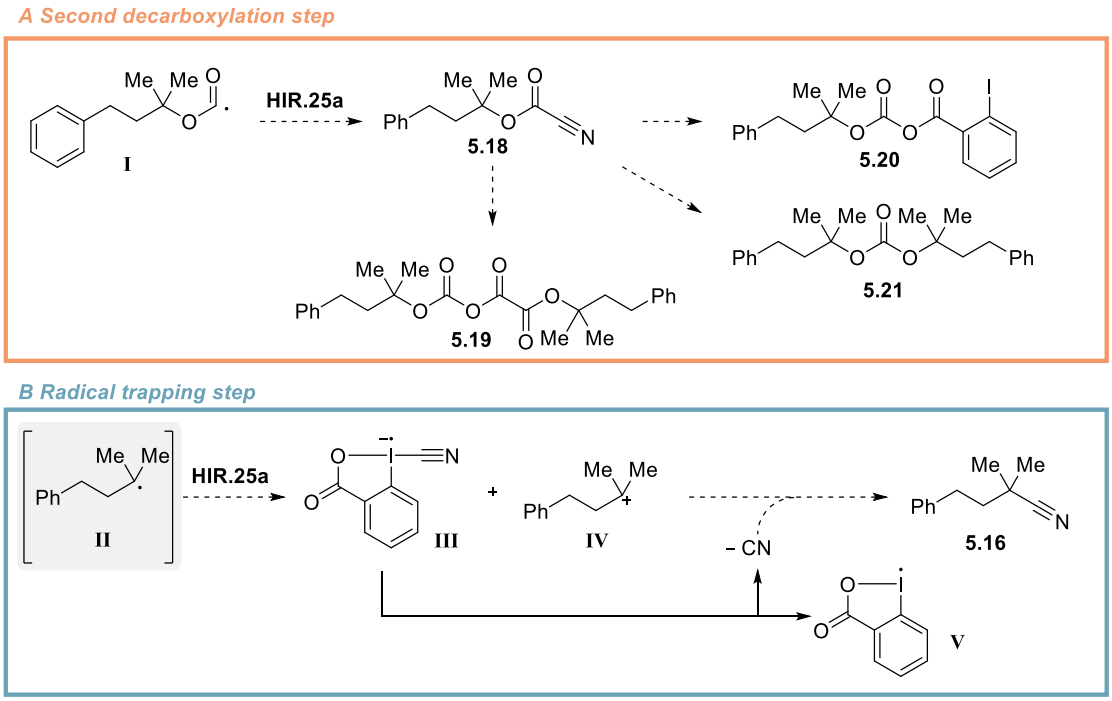
To address the issues related to the deoxycyanation and dethioalkynylation strategies, it is worthwhile exploring the potential mechanism and investigating the potential side reactivities related to these transformations. Based on literature precedence, the excited state photocatalyst would oxidise **5.6b** and **5.7**, then they would undergo a first decarboxylation to the radical intermediate (II). A second fragmentation should then occur releasing CO_2 for substrate **5.6b** and SCO for substrate **5.7**. The ensuing radical would be then trapped releasing the iodanyl radical which would turn over the photocatalytic cycle. Based on our unsuccessful attempts towards both the deoxycyanation and the dethioalkynylation, we wondered whether the second decarboxylation step (in orange) or the radical-trapping step (blue) may be problematic in these transformations.



Scheme 5.13. Plausible mechanistic basis for the deoxycyanation and the dethioalkynylation.

For the deoxycyanation, we investigated the possible side products resulting from a single decarboxylation (A). If the radical (**I**) was intercepted by **HIR.25a** we form the cyano formate **5.18**, which could then be susceptible to the other nucleophiles in the media such as **5.6b** or the ensuing iodobenzoate or even the starting alcohol affording compounds such as **5.19**, **5.20** or **5.21**. Signature signals of these scaffolds were detected by ^{1}H NMR, however these species were not isolated and characterised as a side product of the transformation. Radical interception of the acyl radical (**I**) could explain the low product formation and high conversion of the cesium oxalate. Considering the deoxyalkynylation of this substrate was possible and efficient, we can speculate that unless the radical (**I**) is intercepted, it should undergo

decarboxylation to radical (**II**, B).[13] We could also envisage a radical polar crossover where **HIR.25a** and the radical (**II**) could undergo a SET generating the cation (**IV**) and a reduced CBX intermediate (**III**). The latter could then collapse to the cyanide anion and the iodanyl radical (**V**). The cyanide could then intercept the cation **IV**. This reaction pathway was in fact favoured in the decarboxylative cyanation reported by our group which only tolerated α-amino and α-oxo acids.[14] If this was the case for our transformation we could try and promote the oxidation by introducing electron withdrawing groups on **HIR.25a**.

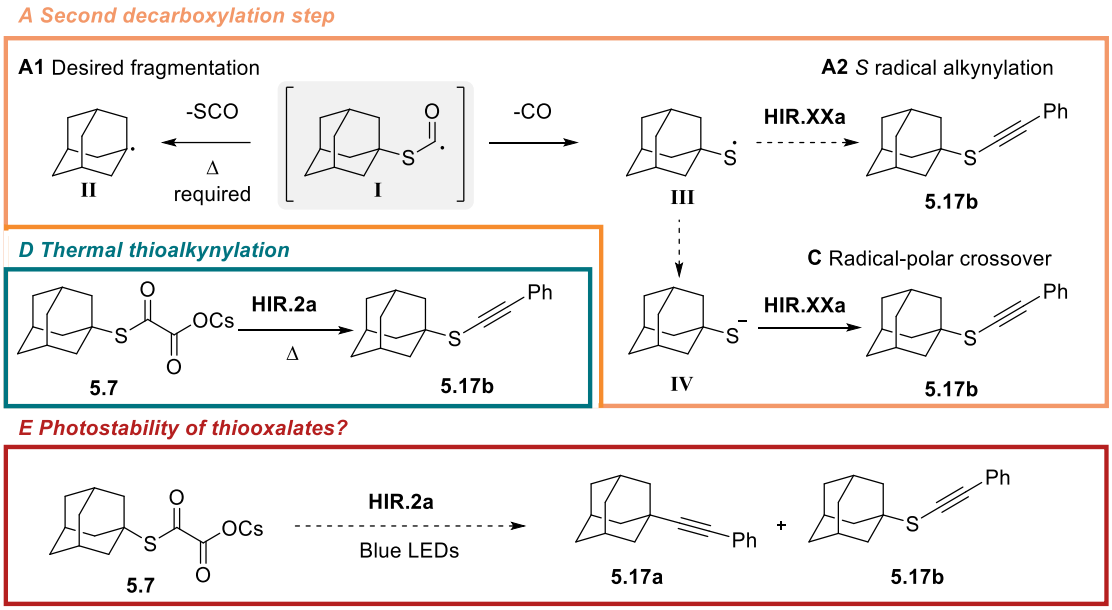


Scheme 5.14. Possible degradation pathways for the deoxycyanation and alternative mechanism for the formation of 5.16.

When turning to the dethioalkynylation process, after our initial investigation, we discovered that (1) the adamantyl derivative performed poorly in our deoxyalkynylation strategy and this was also the case for the deoxygenation,[10] (2) the desired fragmentation of thio oxo-acetates is in fact thermodynamically uphill.[15] These experimental and theoretical observations clearly suggest that the loss of SCO is disfavoured and can explain why a higher temperature led to a slight increase in yield of the dethioalkynylated product **5.17a** (10% at rt. 20% at 60 °C). When considering the mechanism (Scheme 5.15), the step that should convert **I** to **II** by loss of SCO is most likely highly inefficient (**A1**). However, the first decarboxylation can still occur. We can therefore envisage two pathways for the quenching of the intermediate radical (**I**). A decarbonylation could occur, which would result in the formation of the thiyl radical (**III**). The

[13] Gilbert, K. E. *J. Org. Chem.* **1984**, *49*, 6–10.
[14] Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* **2017**, *8*, 1790–1800.
[15] Morihovitis, T.; Schiesser, C. H.; Skidmore, M. A. *J. Chem. Soc. Perkin Trans. 2* **1999**, No. 10, 2041–2047.

latter could potentially be trapped by **HIR.2a** and deliver the thioalkyne **5.17b** or reduced to the thiolate (**IV**) before being trapped by the EBX reagent.[16] Under thermal activation in the dark, we also observed the formation of the thioalkyne **5.17b**, this could be due to residual thiol from the one pot-procedure used in the synthesis or the hydrolysis of the thio oxo-acetate. Finally, due to the higher yields of both **5.17a** and **5.17b** under irradiation, it would be interesting to determine if any background reactivity is observed upon irradiation in absence of the photocatalyst.



Scheme 5.15. Possible degradation pathways for the photocatalysed dethioalkynylation of 5.7.

5.4. Conclusion

During this project, we established that alkynylated quaternary centres could be accessed under blue LED irradiation starting from bench stable cesium oxalates.[17] We found that 4CzIPN proved to be an efficient photocatalyst for the oxidation of these substrates which was also found optimal in the work of Xie published in parallel to our studies.[18] We investigated the synthesis of cyanated quaternary centres, however we were unable to find satisfactory conditions allowing the formation of the desired nitriles in high yields. Our optimal conditions used 4CzIPN as a photocatalyst and CBX as a nitrile source in DME. Unfortunately, we were unable to identify the side products resulting from the rapid conversion of the cesium oxalate. We believe that investigating electron-poor reagents could be beneficial and may promote the oxidation of the alkyl radical to the cation, which would lead to a radical-polar crossover pathway that was previously established for the decarboxylative cyanation. As for the

[16] Hari, D. P.; Nicolai, S.; Waser, J. Alkynylations and Vinylations. In *PATAI'S Chemistry of Functional Groups*; 2018; pp 1–58.
[17] Amos, S. G. E.; Cavalli, D.; Le Vaillant, F.; Waser, J. *Angew. Chem. Int. Ed.* **2021**, *60*, 23827–23834.
[18] Li, M.; Liu, T.; Li, J.; He, H.; Dai, H.; Xie, J. *J. Org. Chem.* **2021**, *86*, 12386–12393.

dethioalkynylation, it seems that the competition between the formation of the desired compound and the thioalkyne is difficult to control. Before continuing this project, control reactions that would help identify the main pathway for the thioalkyne formation are necessary. Considering the uphill character of the C-S bond cleavage step we would need to envisage a reactor that would tolerate heating and irradiation or proceeding to traditional thermal radical initiators to allow this transformation to occur. Further assessment of the scope of this method would also need to be established as few tertiary thiols are available. More importantly, in this project we discovered that Ph-EBX can undergo photodegradation and the deoxyalkynylation can proceed in absence of a photocatalyst albeit with lower yields. This result will be discussed in the following chapter.

5.5. References

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6. Cf. Chapter 2: Background and significance, 2.3.2.3.3.b. Fragmentation cascades. Pan, Y.; Jia, K.; Chen, Y.; Chen, Y. *Beilstein J. Org. Chem.* **2018**, *14*, 1215–1221.
7. a. Zhang, X.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 13862–13865. b. Su, J. Y.; Grünenfelder, D. C.; Takeuchi, K.; Reisman, S. E. *Org. Lett.* **2018**, *20*, 4912–4916.
8. Using **HIR.2a** instead of a core-modified reagent would be more attractive from a cost perspective (from fluorochem: *o*-iodobenzoic acid: 0.64 CHF/g, 2-iodo-4,5-dimethoxybenzoic acid: 12 CHF/g, 2-iodo-4,5-dimethylbenzoic acid: 146 CHF/g).
9. This set-up was also used for the screening of other solvents. We observed no loss of solvent overnight and the potential pressure build-up did not result in any experimental issues (similar vials have been reported to tolerate up to 10 bar). In our first studies we had been using a test-tube with a stopper which led every now and then to the stopper popping off and the loss of our inert atmosphere. The screw-cap set-up seems overall reliable.
10. Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342–15345.
11. Simakov, P. A.; Martinez, F. N.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 1226–1232.
12. The reaction was maintained at this temperature by refilling every 20 min a glass dish that was coated on the outside with the blue led strips, with 400 mL of water at 8 °C. Due to the safety hazard associated to the transfer of 400 mL of cold water to and from an electric LED bath the reaction was stopped after 4 hours despite incomplete conversion.
13. Gilbert, K. E. *J. Org. Chem.* **1984**, *49*, 6–10.
14. Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* **2017**, *8*, 1790–1800.
15. Morihovitis, T.; Schiesser, C. H.; Skidmore, M. A. *J. Chem. Soc. Perkin Trans. 2* **1999**, No. 10, 2041–2047.
16. Hari, D. P.; Nicolai, S.; Waser, J. Alkynylations and Vinylations. In *PATAI'S Chemistry of Functional Groups*; 2018; pp 1–58.
17. Amos, S. G. E.; Cavalli, D.; Le Vaillant, F.; Waser, J. *Angew. Chem. Int. Ed.* **2021**, *60*, 23827–23834.
18. Li, M.; Liu, T.; Li, J.; He, H.; Dai, H.; Xie, J. *J. Org. Chem.* **2021**, *86*, 12386–12393.

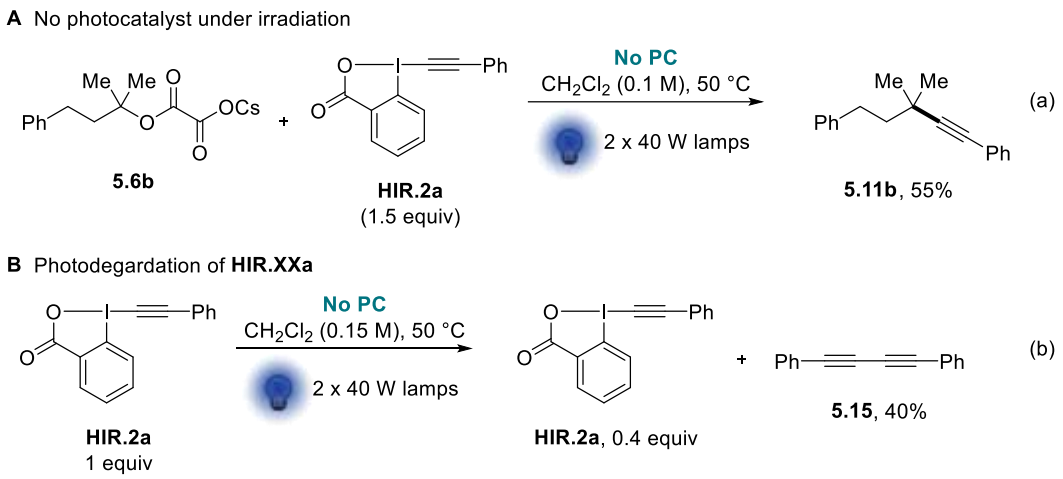
Chapter 6: Direct Excitation of ArEBXs for Deoxyalkynylation and Other Photocatalyst-free Alkynylations

6. Direct Excitation of ArEBXs for Deoxyalkynylation and Other Photocatalyst-free Alkynylations

These results were obtained in collaboration with Diana Cavalli.

6.1. Summary of previous results

In chapter 5, we developed a photocatalyst mediated deoxyalkynylation procedure. The key element to the optimisation was the choice of a high intensity blue LED irradiation. Interestingly, the control reactions indicated a strong background reaction resulting in the same deoxyalkynylated products (**5.11b**) in absence of the photocatalyst (Scheme 5.10, A). Intrigued by this result, we investigated the photostability of the cesium salt, which was stable, and **HIR.2a**, which resulted in the formation of diyne **5.15**. This suggested that **HIR.2a** may be responsible for this background reactivity with this new light source.



Scheme 6.1. Control reactions without photocatalyst for the deoxyalkynylation of 5.6b and the photodegradation of HIR.2a.

6.2. Optimisation of the photocatalyst free transformation

Our preliminary result showed that **5.6b** could be converted to **5.11b** in 55% yield with 1.5 equiv of **HIR.2a** in CH_2Cl_2 under irradiation (2 x 40 W 440 nm blue LED lamps) (entry 1). In addition to the previously mentioned diyne formation (**5.15**, Scheme 5.10, **B**), we observed the formation of two ketones **6.1** and **6.2** as side products in 14% and 11% yield. We first screened solvents: MeCN and DMSO afforded only traces of **5.11b** (entries 2 and 3). Interestingly, both solvents led to high consumption of **HIR.2a** and very low conversion of **5.6b** along with the formation of ketones **6.1** and **6.2** in non-negligeable yields (DMSO: **6.1**, 29%, **6.2**, 21%; MeCN: **6.1**, 36%, **6.2**, 16%). Then we tested methanol, which resulted in a complex reaction profile by ^{1}H NMR and a low yield of **5.11b** (17%, Table 6.8, entry 4). We wondered whether the ketones **6.1** and **6.2** could result from a thermal reaction pathway and attempted to reduce the reaction temperature to help improve the yield of **5.11b**. When reducing the

temperature of the reaction to 30 - 35 °C, we did not see an improvement of the yield of **5.11b**, however the reaction profile was cleaner with less ketone formation (entry 5). We then investigated the light source. We started by testing a UVA high intensity photoreactor (360 nm ca. 40 W), surprisingly, no **5.11b** was detected despite conversion of **HIR.2a** (entry 6). When we turned to the traditional blue LED strips (10 - 15 W), we observed no product formation,[1] but we did see formation of the ketones (**6.1**, 35%, **6.2** 22%, entry 7). We then turned to the stoichiometry of the reaction, with 2.0 and 2.5 equiv of **HIR.2a** we observed a slight increase in yield of **5.11b** to 58% and 57% and we observed more residual **HIR.2a** (entries 8 and 9). We decided to keep the 2.5 equiv of **HIR.2a** and run the reaction for 24 h instead 18 h.[2] We observed a slight increase in yield to 67%, full conversion of the cesium salt and the reaction profile seemed overall cleaner with less ketone formation (entry 10). We then decided to explore the effect of the wavelength of the light source. Due to technical limitations, we screened the wavelengths at 40 W intensity with a single lamp. With a single 40 W lamp with an irradiation centred around 440 nm we obtained **5.11b** in 41% yield, 20% and 25% of the ketones and we observed 0.35 equiv of residual **5.6b** and **HIR.2a** (entry 11). The 427 nm lamp resulted in overall similar results to the irradiation at 440 nm in terms of yield of **5.11b**, side product formation, and conversion (entry 12). Irradiation at 390 nm led to slightly lower yields and conversion (entry 13). Similarly, irradiation at a higher wavelength (467 nm) led to slighter lower product formation (34%), slightly higher **6.1** formation (30%), but considerably less conversion of **HIR.2a** (30%, entry 14). We then wondered if certain additives may promote the conversion of **5.11b**, we tested two bases (Cs_2CO_3 and CsOBz) to maintain the basic character of our reaction conditions. Unfortunately, this led to full consumption of **HIR.2a** with very poor yields of **5.11b** (entries 15 and 16). Similarly, we wondered if we could limit the formation of ketone **6.1** by preventing the accumulation of iodobenzoate in the reaction media. To do so, we thought that the addition of a non-acid H-atom source may help trap the iodanyl radical (**I**) that results from the addition of a radical on to **HIR.2a**. We tested our reaction with 2 equiv of THF and γ-terpinene (**6.3**). Interestingly, this had the opposite effect: **6.1** was formed in over 50% in both cases and no improvement was observed for the yield of **5.11b** (entries 17 and 18). Overall, using two 40 W 440 nm lamps with 2.5 equiv of **HIR.2a** proved the most efficient for the formation of **5.11b**.

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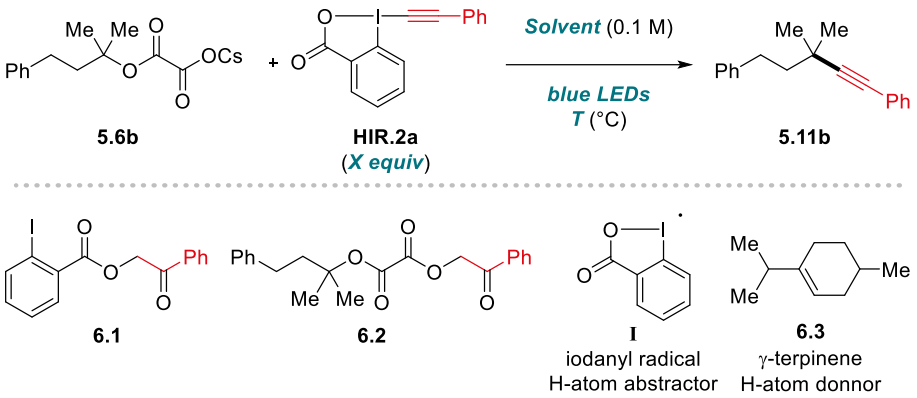
[1] This result is in accord with the reported literature procedures and their control reactions where the reaction does not proceed in absence of photocatalyst: a. Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. *J. Am. Chem. Soc.* **2014**, *136*, 2280–2283. b. Zhou, Q.; Guo, W.; Ding, W.; Wu, X.; Chen, X.; Lu, L.; Xiao, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199. c. Le Vaillant, F.; Courant, T.; Waser, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204. d. Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* **2017**, *8*, 1790–1800. e. Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. *Chem. Sci.* **2018**, *9*, 5883–5889. f. Garreau, M.; Le Vaillant, F.; Waser, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 8182–8186. g. Amos, S. G. E.; Nicolai, S.; Waser, J. *Chem. Sci.* **2020**, *11*, 11274–11279.

[2] Longer reaction times did not lead to any further increase in yield of **5.11b**

Table 6.8. Optimisation of the photocatalyst-free deoxyalkynylation of 5.6b with HIR.2a.



Conditions						Product formation 1H NMR yield			Residual starting material (equiv)	
Entry	X	solvent	**T** (°C)	**λ** (nm)	I (W)	5.11b (%)	**6.1** (equiv)	**6.2** (equiv)	5.6b	HIR.2a
1	1.5	CH_2Cl_2	50	440	80	55	0.14	0.11	0.25	traces
2	1.5	MeCN	50	440	80	4	0.29	0.21	0.80	nd
3	1.5	DMSO	50	440	80	4	0.36	0.16	0.64	nd
4	1.5	MeOH	50	440	80	17	-	-	-	nd
5	1.5	CH_2Cl_2	~35	440	80	50	0.10	0.20	0.12	0.20
6	1.5	CH_2Cl_2	~35	360[a]	40	nd	0.30	0.30	0.70	0.50
7	1.5	CH_2Cl_2	~35	460[b]	~12	nd	0.35	0.22	0.70	0.60
8	2.0	CH_2Cl_2	~35	440	80	58	0.25	0.30	0.10	0.25
9	2.5	CH_2Cl_2	~35	440	80	57	0.50	0.40	0.10	0.40
10[c]	2.5	CH_2Cl_2	~35	440	80	67	0.31	0.30	nd	0.20
11[c]	2.5	CH_2Cl_2	~35	440	40	41	0.25	0.20	0.35	0.34
12[c]	2.5	CH_2Cl_2	~35	427	40	43	0.25	0.13	0.30	0.41
13[c]	2.5	CH_2Cl_2	~35	390	40	34	0.19	0.13	0.44	0.49
14[c]	2.5	CH_2Cl_2	~35	467	40	34	0.30	0.20	0.35	0.75
15[c,d]	2.5	CH_2Cl_2	~35	440	80	20	0.54	0.18	0.35	nd
16[c,e]	2.5	CH_2Cl_2	~35	440	80	10	0.15	nd	0.63	traces
17[c,f]	2.5	CH_2Cl_2	~35	440	80	nd	0.56	0.44	0.50	traces
18[c,g]	2.5	CH_2Cl_2	~35	440	80	50	0.65	0.30	0.20	nd

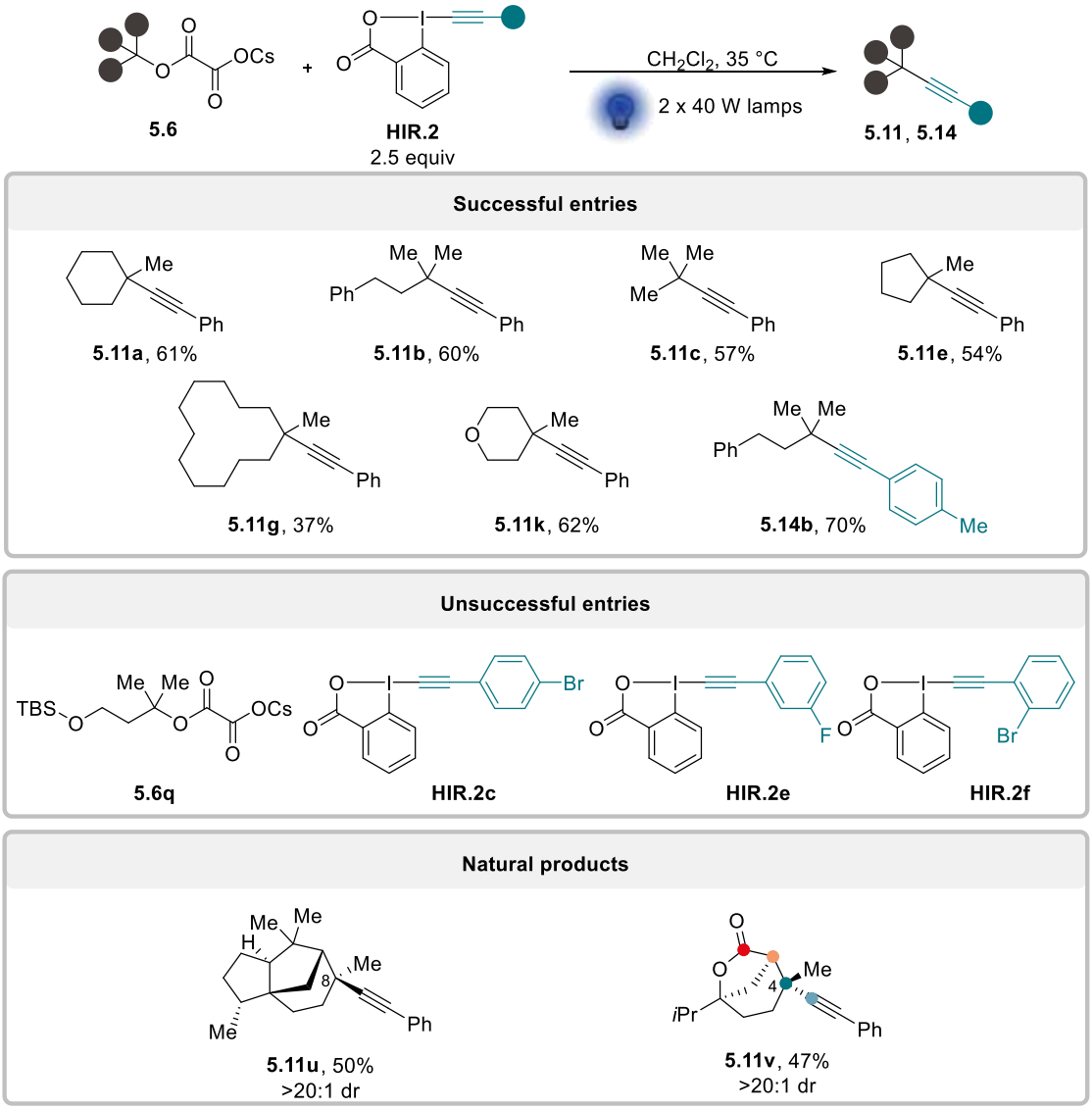
Reaction conditions: The reactions were performed on 0.1 mmol scale using blue LED lamps unless specified elsewhere (1 lamp 40 W, 2 lamps: 80 W). ^{1}H NMR quantification was done using 1 equiv of CH_2Br_2 as an internal standard. [a]Rayonet reactor was used. [b]Blue LED strips. [c]Reactions were run for 24 hours, [d]The reaction was performed with Cs_2CO_3 (0.5 equiv). [e]The reaction was performed with CsOBz (1 equiv). [f]The reaction was performed with THF (2 equiv). [g]The reaction was performed with **6.3** (2 equiv)

6.3. Scope of the photocatalyst-free deoxyalkynylation and scope of photocatalyst-free transformations with **HIR.2a**

6.3.1. Scope of the photocatalyst-free deoxyalkynylation

With the optimised conditions in hand, we proceeded with a small scope of substrates (Scheme 6.2). We could obtain **5.11a**, **5.11b** and **5.11n** within 10% of the yields of the photocatalyst mediated transformation (described in chapter 5). **5.11e**, **5.11h** and **5.11j** were obtained in lower yields (37 - 57%). Intriguingly, **HIR.2b** afforded the corresponding alkyne

5.14b in a slightly higher yield than the photocatalysed method (70% instead of 64%). Unfortunately, this method was less tolerant: in particular, the TBS-protected diol **5.6q** decomposed under these conditions and the desired deoxyalkynylated product was not formed. Furthermore, halogen substitution of the reagent (**HIR.2c**, **HIR.2e** and **HIR.2f**) led to very poor yields (<20% by NMR). Finally, we tested our strategy with (-)-cedrol and (-)-terpinen-4-ol derivatives, we could obtain **5.11u** in 50% yield and **5.11v** in 47% yield as single diastereoisomers (dr. >20:1).

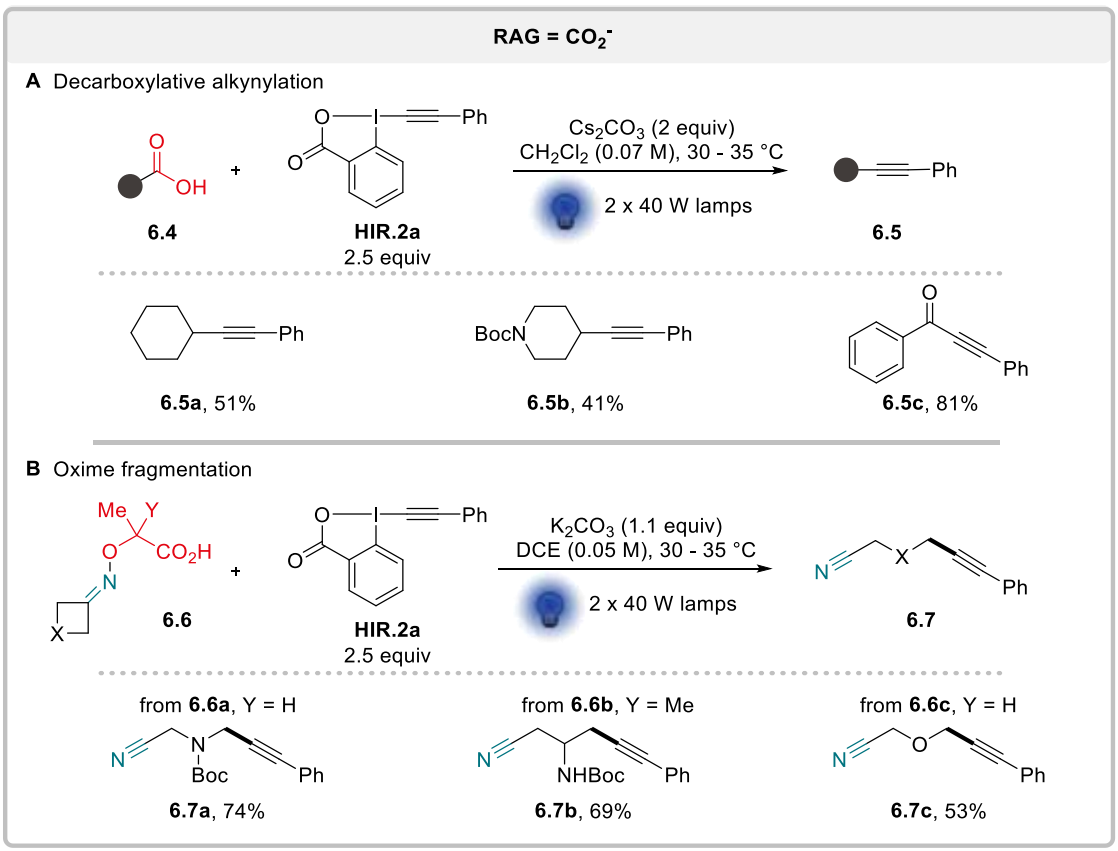


Scheme 6.2. Scope of the photocatalyst-free deoxyalkynylation of cesium oxalates with HIR.2. Reaction conditions: The reactions were performed on 0.3 mmol scale 5.6 (0.3 mmol, 1.0 equiv), PC.2 (2.5 equiv), CH_2Cl_2 (0.1 M) using blue LED lamps (2 x 40 W, 440 nm).

Despite the limitations of this method, the overall technical simplicity of this reaction is valuable. We wondered if this approach could help alleviate the need for a photocatalyst in other radical alkynylation strategies or help discover new reactions. We therefore screened different redox active groups (RAGs) to test with our photocatalyst-free conditions.

6.3.2. Decarboxylative alkynylation strategies

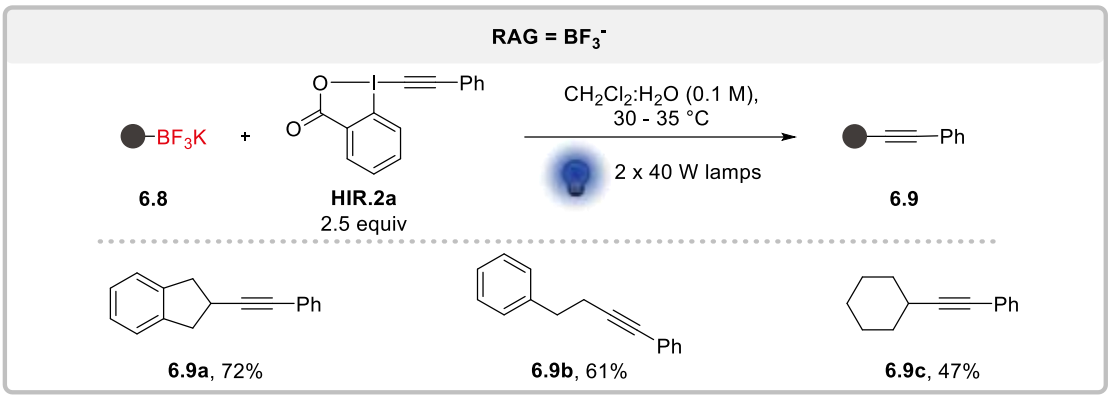
We first turned to the decarboxylative alkynylation developed by our group and the Xiao group.[1b,c] We found that the conditions of Xiao were closer to those of our deoxygenation strategy (CH_2Cl_2 as solvent and strong basic conditions with Cs_2CO_3). Under the irradiation of two blue LED lamps (440 nm, 2 x 40 W) we were able to perform the transformation without the reported photocatalyst (**PC.3**, $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$) by simply increasing the loading of **HIR.2a** from 1.5 to 2.5 equivalents (Scheme 6.3, **A**). We were able to successfully decarboxylate secondary carboxylic acids (**6.4a** and **6.4b**) to form **6.5a** and **6.5b** in 51% and 41% yield. We were also able to perform the reaction with an α-keto acid to form ynone **6.5c** in 81% yield. In addition to this decarboxylative alkynylation, we wondered if our previously reported oxime fragmentation[1e] could also proceed in absence of a photocatalyst. Similarly, changing only the light source (2 x 40 W 440 nm blue LED lamps) and increasing slightly the loading of **HIR.2a** from 2.0 to 2.5 equivalents the reaction proceeded well in absence of photocatalyst (Scheme 6.3, **B**). To our delight, three alkynyl nitriles (**6.7a-c**) could be accessed from the corresponding oximes in 53% to 74% yield.



Scheme 6.3. Photocatalyst-free activation of carboxylates for decarboxylative alkynylation and oxime fragmentation with HIR.2. Reaction conditions: The reactions were performed on 0.3 mmol scale using blue LED lamps (2 x 40 W, 440 nm)

6.3.3. Deboronative alkynylation

Having established that carboxylates were compatible with the photocatalyst free conditions we turned to other functional groups. When considering the redox potentials of the carboxylates (**6.4$^{\bullet}$/6.4^{-}**: ca. + 1.2 V vs SCE, **6.6$^{\bullet}$/6.6^{-}** : ca. + 1.5 V vs SCE),[1b,c,e] we wondered if trifluoroborate salts (**6.8$^{\bullet}$/6.8^{-}:** ca. 1.5 V vs SCE)[3] would also undergo activation in absence of a photocatalyst. Indeed, Chen and co-workers reported a deboronative alkynylation using **PC.1** ($Ru(bpy)_3^{2+}$).[1a,4] To our delight, irradiation of 2.5 equivalents of **HIR.2a** in presence of the alkyl trifluoroborate afforded the corresponding alkynes **6.9a** – **6.9c** in 47% to 72% yield (Scheme 6.4). Interestingly, these conditions not only enabled the reaction to proceed without photocatalyst (**PC.1**, ($Ru(bpy)_3PF_6$)) but also without the need for the additive BIOH (**HIR.18**), which was necessary to obtain high yields in the reported photocatalytic method. Furthermore, the reaction tolerated water as co-solvent just as the photocatalytic method did.



Scheme 6.4. Photocatalyst-free deboronative alkynylation with HIR.2. Reaction conditions: The reactions were performed on 0.3 mmol scale using blue LED lamps (2 x 40 W, 440 nm).

6.3.4. Oxyalkynylation of N-vinyl pyrrolidinone (**4.3j**) with **HIR.2a**

Having established that non-nucleophilic oxidisable trifluoroborate salts could be activated in absence of a photocatalyst, we wondered if π-systems could also be activated. First, we attempted the oxyalkynylation procedure previously developed (see Chapter 4, **4.3j$^{\bullet+}$/4.3j**: ≈ 1.3 V vs SCE).[1g] Pleasantly, we found that the new light source (2 x 40 W 440 nm blue LED lamps) could deliver the desired oxyalkynylated product **4.20j** in 35% yield with no changes to the previously established reaction conditions other than the removal of the photocatalyst (Scheme 6.5).

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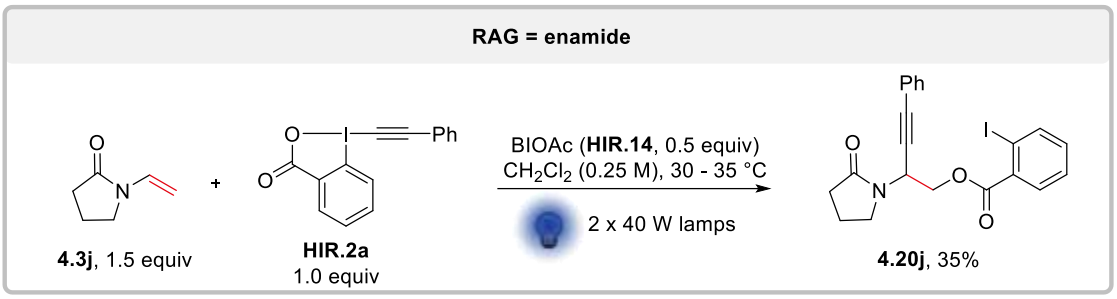
[3] Converted from V vs Fc to V vs SCE, taken from: Yasu, Y.; Koike, T.; Akita, M. *Adv. Synth. Catal.* **2012**, *354*, 3414–3420.
[4] Cf. Chapter 2. Background and significance; 2.3.2.3.3 λ^3-iodanes as radical traps under photocatalyst mediated conditions



Scheme 6.5. Photocatalyst-free oxyalkynylation of 4.3j with HIR.2a. Reaction conditions: The reaction was performed on 0.1 mmol scale using blue LED lamps (2 x 40 W, 440 nm).

6.3.5. Deaminative alkynylation of **6.10** with **HIR.2a**

It seemed clear that these photocatalyst-free conditions were well tolerated in a variety of reported radical alkynylation strategies. We therefore wondered if this could be used to discover new alkynylation transformations. To demonstrate this, we chose to investigate a deaminative alkynylation inspired by the deaminative alkylation reported by Rovis and co-workers.[5] Indeed, they measured the redox potential of this class of electron-rich imine to be 1.46 V vs SCE, putting it in the same range as the other successful scaffolds we had tested. We then subjected the imine **6.10** to similar conditions to those reported by Rovis:[6] DCE (0.05 M) as solvent, 20 mol% TMG, 2.5 equiv of **HIR.2a** instead of a Michael acceptor and we used the two 440 nm blue LED lamps (2 x 40 W). Unfortunately, we detected no product formation (Scheme 6.6, 20 mol% TMG). Upon reassessment of their reaction conditions, we realised that the deprotonation of the imine radical cation intermediate proposed by Rovis (**I**, pKa ≈ 15) was likely dependant on the regeneration of TMG: in their case, an alkylation reaction with a Michael acceptor, an enolate can be formed (pK_a ≈ 23) allowing the regeneration of the catalytic TMG base.[7] In our case, an alkynylation with **HIR.2a**, a carboxylate (pKa ≈ 4) can eventually be generated from the iodobenzoate part of **HIR.2a**. Considering the difference in pKa (TMG: pKa ≈ 23, **I**: pKa ≈ 15 and carboxylate: pKa ≈ 4) TMG would not be regenerated under our reaction conditions, **I** would not be deprotonated, which would hamper the reaction. We therefore performed a second test using 1.1 equivalents of Cs_2CO_3[8] to ensure the deprotonation of **I**. To our delight, this enabled the reaction to proceed affording 57% of the desired alkyne **6.11**. This specific example illustrates how the photocatalyst-free conditions can help discover new transformations.

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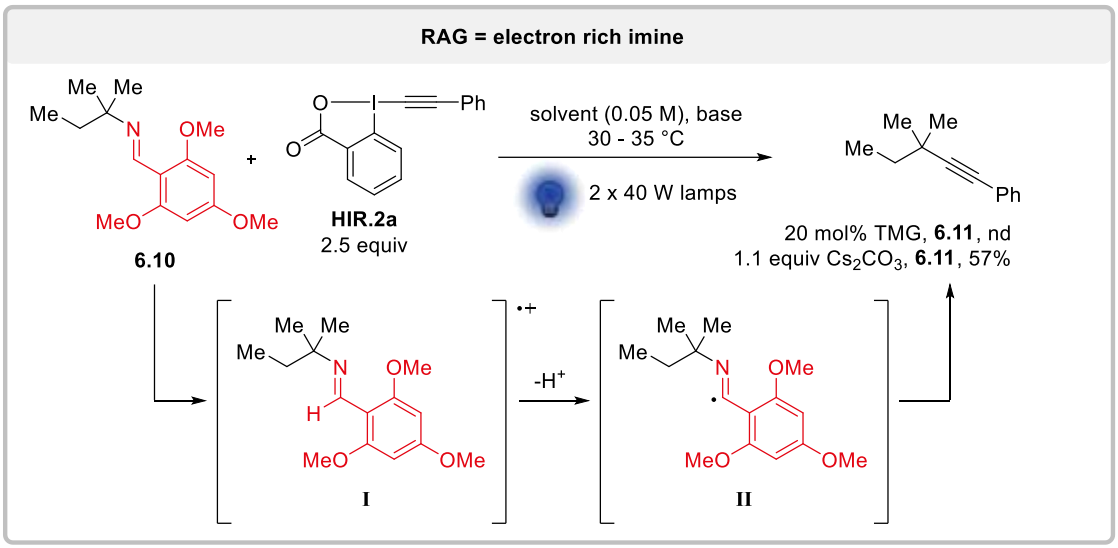
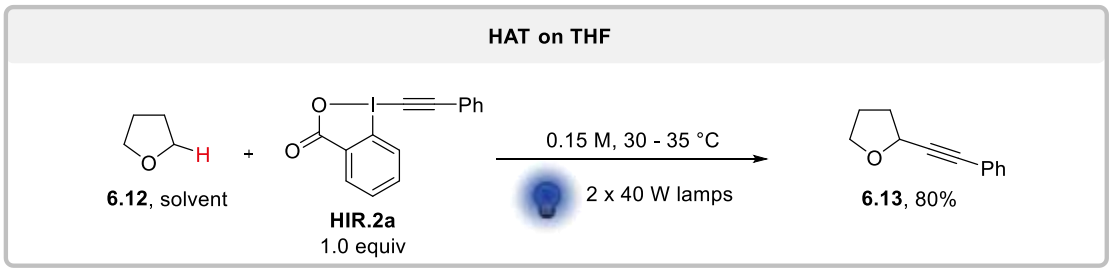
[5] Ashley, M. A.; Rovis, T. *J. Am. Chem. Soc.* **2020**, *142*, 18310–18316.
[6] The reported photocatalyst was **PC.3** ($Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$))
[7] In their report, they also discuss other mechanistic pathways such as PCET events involving the photocatalyst, however they were unable to distinguish between the two pathways.
[8] We chose Cs_2CO_3 over TMG as it had been successfully combined with the decarboxylative alkynylation photocatalyst-free conditions (see 6.3.2) and CH_2Cl_2 over DCE to limit solvent functionalisation (see 5.2.2.1)



Scheme 6.6. Photocatalyst-free deaminative alkynylation of 6.10 with HIR.2a. Reaction conditions: The reaction was performed on 0.3 mmol scale using blue LED lamps (2 x 40 W, 440 nm).

6.3.6. Alkynylation of THF through HAT

Having thoroughly explored a variety of oxidisable functional groups, we wondered if non-oxidisable functional groups could also be activated. In this regard, HAT of THF for alkynylation has been thoroughly reported with the EBXs, however it always requires the presence of a photocatalyst.[9] We decided to irradiate **HIR.2a** in THF with the two blue LED lamps (2 x 40 W, 440 nm) (Scheme 6.7). To our delight, we were able to access 80% of **6.13** demonstrating that with the correct light source the use of a photocatalyst in this type of reaction was not be necessary.



Scheme 6.7. Photocatalyst free alkynylation of THF with HIR.2a. Reaction conditions: The reactions were performed on 0.2 mmol scale using blue LED lamps (2 x 40 W, 440 nm).

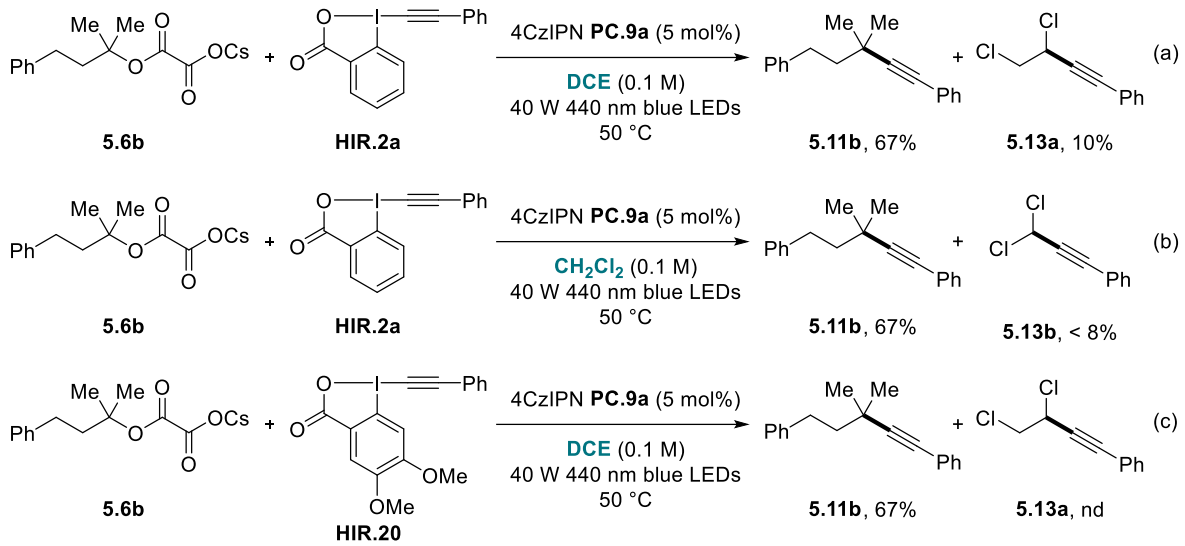
6.3.7. Alkynylation of 1,2-dichloroethane through HAT

6.3.7.1. Summary of key results and relevant literature examples

During our optimisation studies towards the deoxyalkynylation of cesium oxalates, we noticed the formation of compound **5.13a** in 10% yield resulting from the C-H alkynylation of DCE (Scheme 6.8, equation a). Similarly with CH_2Cl_2 as a solvent we observed compound **5.13b** in

[9] Cf. Chapter 2: Background and significance: 2.3.2.3. λ3-iodanes as radical traps under photocatalyst mediated conditions. a. Matsumoto, K.; Nakajima, M.; Nemoto, T. *J. Org. Chem.* **2020**, *85*, 11802–11811. b. Voutyritsa, E.; Garreau, M.; Kokotou, M. G.; Triandafillidi, I.; Waser, J.; Kokotos, C. G. *Chem. – Eur. J.* **2020**, *26*, 14453–14460.

under 8% yield (equation b). Finally, we observed no solvent functionalisation when using **HIR.20** (equation c), suggesting that the core scaffold of the HIR may be playing a key role in the functionalisation of the solvent.



Scheme 6.8. Preliminary results for the photocatalysed alkynylation of chlorinated solvents with EBXs.

When considering the C-H functionalisation of THF with EBXs, strong evidence suggests that the mechanism proceeds through a radical chain mechanism relying on the iodanyl radical,[10] we therefore envisaged that for chlorinated solvents this could be a possibility as well. Indeed, Fuchs reported the radical alkynylation of DCE with alkynyl triflones (**2.85**, Scheme 6.9, **A**),[11] and Liu and Tian reported the generation of α-dichloro radicals from CH_2Cl_2 using dicumylperoxide (DCP) as a HAT agent (B).[12] To the best of our knowledge, these are the only two examples of the functionalisation of an α-chloro radical. Alkyl and propargyl chlorides are valuable building blocks for alkylation. Alkyl chlorides are easily accessible and are often cheaper than alkyl bromide and iodides. Chlorination reactions are frequently used with complex scaffolds and chlorine substitution can be found in bioactive compounds.[13] In this regard, developing a strategy that would allow the functionalisation of a chlorine substituted carbon centre could give access to more complex alkyl and propargyl chlorides. Furthermore, the few reports using these radicals suggests that their reactivity is poorly understood, which led us to believe that exploring these radicals could be of interest from a fundamental research perspective.

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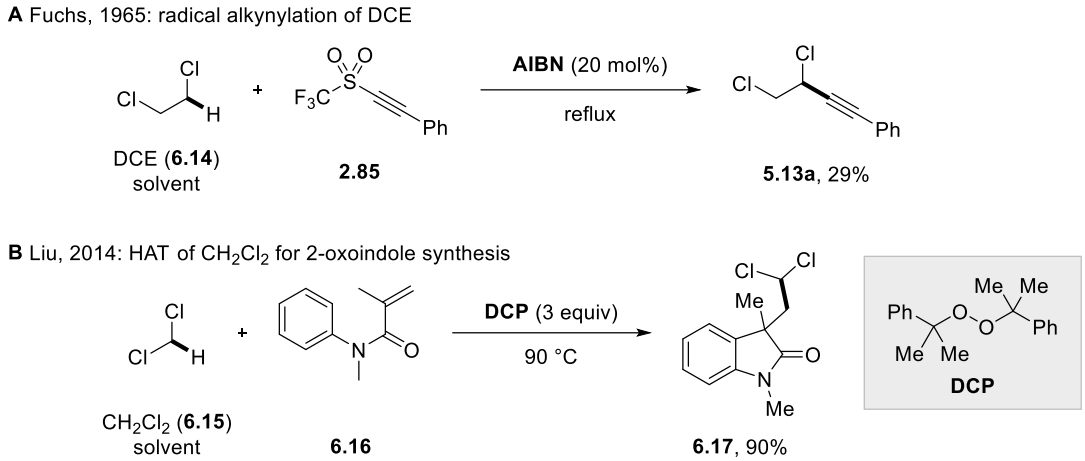
[10] Cf. chapter 2: Background and significance. paragraph: 2.3.2.3.3. a Defunctionalisation alkynylation. Selected examples: a. Matsumoto, K.; Nakajima, M.; Nemoto, T. *J. Org. Chem.* **2020**, *85*, 11802–11811. b. Voutyritsa, E.; Garreau, M.; Kokotou, M. G.; Triandafillidi, I.; Waser, J.; Kokotos, C. G. *Chem. – Eur. J.* **2020**, *26*, 14453–14460.
[11] Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4486–4487.
[12] Tian, Y.; Liu, Z.-Q. *RSC Adv.* **2014**, *4*, 64855–64859.
[13] Gál, B.; Bucher, C.; Burns, N. Z. *Mar. Drugs* **2016**, *14*, 206.



Scheme 6.9. Examples of α-chloro radical generation from DCE and CH_2Cl_2.

6.3.7.2. Preliminary studies towards the α-HAT of 1,2-dichloroethane

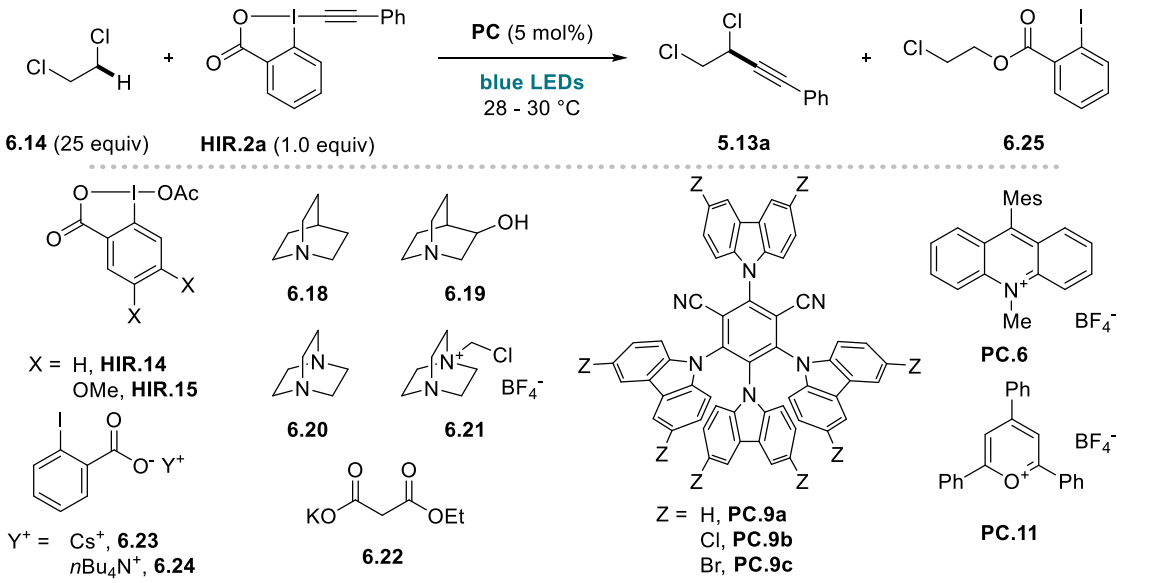
We started our studies with similar conditions to that of the deoxygenation: **HIR.2a** (1.0 equiv), **PC.9a** (5 mol%), DCE (0.5 M ≡ 25 equiv) using two 40 W 440 nm lamps as a light source (Table 6.9 , entry 1). The desired alkynylated product **5.13a** was obtained in 11% yield. We then wondered if the addition of **HIR.14** could help promote the reaction: using the same light source, we screened **PC.9a** and **PC.9b**,[14] however no improvement was observed (entries 2 and 3). We then wondered if the degradation of **HIR.2a** to the diyne was outcompeting the solvent functionalisation. To hamper this degradation process, we wondered if the reaction could proceed with a light source which did not lead to the direct photoexcitation of **HIR.2a**, we turned to the less intense and less energetic blue LED strips (λ_{max} ≈ 460 nm, I = 10 - 12 W). With 0.3 equiv of **HIR.14**, we observed a slight improvement: 14% formation of **5.13a** with **PC.9a** and 15% with **PC.9b** (entries 4 and 5). We decided to increase the loading of **HIR.14** to 1.0 equiv and prolong the reaction time to 2.7 days to see if the yield could improve, however we obtained the desired alkyne in the same yield (15%, entry 6). Considering the lack of improvement, we decided to investigate other additives as HAT agents, we then screened: **HIR.15** (4%, entry 7), quinuclidine (**6.18**), 3-hydroxyquinuclidine (**6.19**), and DABCO (**6.20**), however no product was detected (entries 8 - 10). We then tested the alkylated DABCO (**6.21**) as the cationic nature of the oxidation of **6.21** could lead to a possibly more reactive dicationic radical species. We screened **PC.9a** and more oxidising catalysts: **PC.9c**, **PC.6** and **PC.11** to hopefully oxidise **6.21**. Unfortunately, in all cases the desired compound was not observed (entries 11 - 14). This could be due to the potentially high redox potential of **6.21** or the nature of the ensuing radical dication. Overall, *N*-centred radicals did not seem to promote the desired reaction. We then wondered if a carbon centred radical would be more suited. As the EBXs

[14] In chapter 4 we observed full degradation of **HIR.14** in presence of **PC.9b**.

have been used for decarboxylative alkynylations,[15] we wondered if **6.22** could be used to generate an electrophilic *C*-centred radical capable of performing HAT (BDE ≈ 97 kcal.mol^{-1}).[16] With both **PC.9a** and **PC.9c**, no product was detected (entries 15 and 16). This could be related to the inefficient decarboxylation of **6.22** or the possibly higher BDE of DCE (approximate BDE ≈ 100 kcal.mol^{-1}).[17] Finally, we turned back to *O*-centred radicals and more specifically the iodanyl radical that may be responsible for the HAT of DCE: we decided to try an oxidative approach from 2-iodobenzoate for the generation of this radical.[18] We tested the cesium 2-iodobenzoate (**6.23**) and tetrabutylammonium 2-iodobenzoate (**6.24**) in presence of **PC.9a**. Unfortunately, we only observed traces of the desired compound **5.13a** in addition to a second compound (**6.25**) resulting most likely from the nucleophilic substitution of DCE by the iodobenzoate (entries 17 and 18). To confirm our hypothesis, we performed a control reaction in the dark with **6.24** in DCE and observed 100% formation of **6.25** (entry 19).

[15] Cf. Chapter 2: Background and significance, paragraph 2.3.2.3.3 λ3-iodanes as radical traps under photocatalyst mediated transformations, selected examples: a. Zhou, Q.; Guo, W.; Ding, W.; Wu, X.; Chen, X.; Lu, L.; Xiao, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199. b. Le Vaillant, F.; Courant, T.; Waser, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204.
[16] For methyl acetate: BDE(MeC(O)CH_2-H) = 97 kcal.mol^{-1}, taken from: Oyeyemi, V. B.; Keith, J. A.; Carter, E. A. *J. Phys. Chem. A* **2014**, *118*, 7392–7403.
[17] We have not found the specific BDE of DCE however the BDE of chloromethane and dichloromethane have been calculated: BDE(Cl_2CH-H) = 100 kcal.mol^{-1} and BDE($ClCH_2$-H) = 103 kcal.mol^{-1}. Taken from: Tschuikow-Roux, E.; Paddison, S. *Int. J. Chem. Kinet.* **1987**, *19*, 15–24.
[18] With **HIR.14** a reduction is required to generation the iodanyl radical

Table 6.9. Preliminary optimisation studies towards the α-chloro alkynylation of DCE with EBXs.



Entry	HAT agent (equiv)	PC	λ (nm)	I (W)	^{1}H NMR yield (%)
1	-	**PC.9a**	440	80	11
2	**HIR.14** (0.3)	**PC.9a**	440	80	9
3	**HIR.14** (0.3)	**PC.9b**	440	80	8
4	**HIR.14** (0.3)	**PC.9a**	460	10 - 12	14
5	**HIR.14** (0.3)	**PC.9b**	460	10 - 12	15
6[a]	**HIR.14** (1.0)	**PC.9a**	460	10 - 12	15
7	**HIR.15** (0.3)	**PC.9a**	460	10 - 12	7
8	**6.18** (0.3)	**PC.9a**	460	10 - 12	nd
9	**6.19** (0.3)	**PC.9a**	460	10 - 12	nd
10	**6.20** (0.3)	**PC.9a**	460	10 - 12	nd
11	**6.21** (0.3)	**PC.9a**	460	10 - 12	nd
12	**6.21** (0.3)	**PC.9c**	460	10 - 12	nd
13	**6.21** (0.3)	**PC.6**	460	10 - 12	nd
14	**6.21** (0.3)	**PC.11**	460	10 - 12	nd
15	**6.22** (0.3)	**PC.9a**	460	10 - 12	traces
16	**6.22** (0.3)	**PC.9c**	460	10 - 12	traces
17	**6.23** (0.3)	**PC.9a**	460	10 - 12	traces + 6% of **6.25**
18	**6.24** (0.3)	**PC.9a**	460	10 - 12	8% of **6.25**
19[b]	**6.24** (1.0)	**-**	460	10 - 12	nd; 100% **6.25**

Reaction conditions: EBX (0.1 mmol, 1 equiv), **PC** (5 mol%) with additive if needed in degassed DCE. Irradiation for 18 hours at rt (1 lamp 40 W, 2 lamps: 80 W, λ_{max} = 440 nm). ^{1}H NMR quantification was done using 1 equiv of CH_2Br_2 as an internal standard. [a]The reaction was run for 2.7 days. [b]The reaction was performed without **HIR.2a**.

6.3.7.3. α-chloro HAT of DCE: conclusive remarks

In the preliminary exploration of this project, we have identified that the functionalisation in α to a chlorine atom is possible and we speculate that it could occur through a HAT process. We have seen that electrophilic *N*-centred radical cations, frequently used for HAT processes, do not seem well suited for this type of transformation. Our best results involve the use of **HIR.14** as a HAT agent however we were unable to improve this result with higher loading and longer reaction time, which could suggest that: (1) the activation of the solvent is inefficient and is outcompeted by a degradation process involving the HAT agent, (2) the

functionalisation of the solvent with **HIR.2a** is inefficient. To improve the solvent activation, we can envisage other HAT-agents such as tuned iodanyl radicals or screen HAT-type photocatalysts such as TBADT and diarylketones. To improve the trapping of the radical, we could move towards an acrylamide as they have already been reported to trap this type of radical. Changing radical trap could help prevent the side reactivity we observe in presence of the 2-iodobenzoate. Finally, the philicity of this class of radical is unclear, although we have been able to trap it with **HIR.2a** (commonly used for nucleophilic radicals), the presence of the electron-poor chlorine atom, which can also be mesomer-donor, makes it difficult to predict the philicity of this radical. Hence, for further research, it would be worthwhile exploring the two potential sides of this radical and envisage using a nucleophilic radical as a HAT-agent from trialkylamino-borane complexes, as described by Ye and co-workers,[19] and also screen the electronics of the radical trap with, for example, acrylates, enamides and styrenes would help maximise the chances of success.

6.4. Mechanistic studies of the photocatalyst-free deoxyalkynylation

Preliminary control reactions showed that our alkynylating reagent **HIR.2a** could undergo photodegradation and may be responsible for the reactivity observed in absence of a photocatalyst. Furthermore, we found that a variety of RAGs could be activated under simple irradiation of the reaction mixture involving in all cases a substrate (oxalate, carboxylate, trifluoroborate salt, enamide, aryl imine or THF) and **HIR.2a**. Considering the generality of this approach, we decided to investigate the mechanism of the deoxyalkynylation reaction and further understand the reactivity of **HIR.2a** with our light source.

Based on literature precedence and our preliminary data, we formulated four main hypotheses to gain greater understanding on the mechanism of our photocatalyst-free strategy:

1. Presence of trace hypervalent iodine species as radical initiators
2. Ketones **6.1** or **6.2** as either photocatalysts or reaction intermediates
3. EDA complexes between **HIR.2a** and **5.6b**
4. Direct excitation of the starting materials **5.6b** or **HIR.2a**.

6.4.1. Mass balance of the deoxyalkynylation of **5.6b** with **HIR.2a** with and without photocatalyst

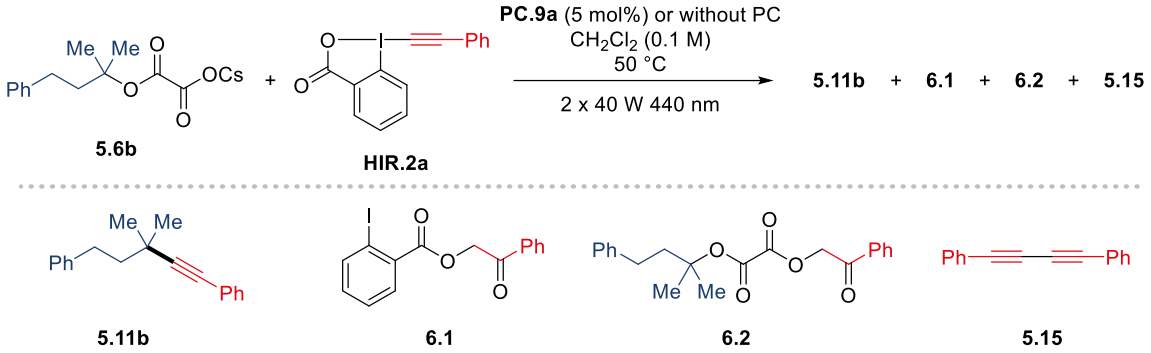
We started by analysing the mass balance of the reaction using ^{1}H NMR analysis. First, the photocatalyst mediated reaction resulted in a clean reaction profile after 18 hours of irradiation (Table 6.10, A). We detected 0.08 equiv of residual **5.6b** and 0.75 equiv of **5.11b**, leaving ca.

[19] Lei, G.; Xu, M.; Chang, R.; Funes-Ardoiz, I.; Ye, J. *J. Am. Chem. Soc.* **2021**, *143*, 11251–11261.

0.13 equiv of the 2-methyl-4-phenylbutan-2-yl fragment (highlighted in blue) unaccounted for. In addition, we observed 0.25 equiv **5.15**,[20] leaving 0.25 equiv of the 2-phenylethynyl fragment (highlighted in red) unaccounted for. Finally, we observed formation of 2-iodobenzoate. Unfortunately, this compound could not be quantified for two reasons: (1) the reaction crude needed to be filtered to ensure a homogeneous NMR sample in $CDCl_3$;[21] (2) when we did not filter the crude, we observed big shift changes (± 0.5 ppm) of the 2-iodobenzoate depending on its concentration making its quantification impractical. Overall, considering the traces of **6.1** and **6.2** and the error of the analysis, the mass balance of the reaction is conserved. We then analysed the reaction profile of the photocatalyst-free method after 24 hours of irradiation (Table 6.10, B). Full conversion of **5.6b** to 0.67 equiv of **5.11b** and 0.30 equiv of **6.2** account for 0.97 equiv of the 2-methyl-4-phenylbutan-2-yl fragment. When concerning the 2-phenylethynyl fragment, we observe 0.20 equiv of residual **HIR.2a**, 0.31 equiv of **6.1** and 0.5 equiv of **5.15**, amounting to ca. 2.2 equiv in total. Similarly, to the photocatalyst mediated reaction, the 2-iodobenzoate fragment was unquantifiable by ^{1}H NMR analysis. In the photocatalyst-free transformation, the reaction profile may be a little more complex with the formation of five different products in significant quantities, but the mass balance is overall maintained.

[20] Due to overlap with the other signal the error on this value is greater than the standard 5% of ^{1}H NMR.
[21] DMSO-d_6 could not be used du to the overlapping shifts of **6.1**, **6.2** and the traces of CH_2Cl_2.

Table 6.10. Initial and final stoichiometry for the deoxyalkynylation. A. Photocatalyst mediated method. B. Photocatalyst-free method.



A With **PC.9a** (5 mol%)

Compound / **Time**	**5.6b** (equiv)	**HIR.2a** (equiv)	**5.11b** (equiv)	**6.2** (equiv)	**6.2** (equiv)	**5.15** (equiv)
0	1.0	1.5	0	0	0	0
18 hours	0.08	traces	0.75	traces	traces	0.25

B Without **PC.9a** (5 mol%)

Compound / **Time**	**5.6b** (equiv)	**HIR.2a** (equiv)	**5.11b** (equiv)	**6.1** (equiv)	**6.2** (equiv)	**5.15** (equiv)
0	1.0	2.5	0	0	0	0
24 hours	nd	0.20	0.67	0.31	0.30	0.5

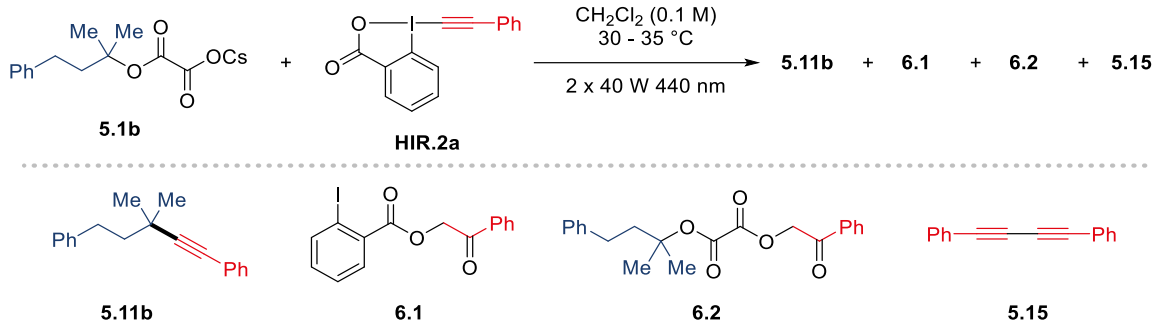
nd: not detected

We continued our studies on the mass balance of the transformation and performed ^{1}H NMR monitoring of the reaction (Table 6.11). To ensure the inert conditions of the reaction mixture, these experiments were set up as individual batches (7 different reaction vessels).[22] At 30 minutes of reaction time, we could observe the conversion of **5.6b** and **HIR.2a** to the desired deoxyalkynylated product **5.11b** (11%), the ketones (**6.1**, 6% and **6.2**, 7%) and the diyne (**5.15**, 18%). The formation of these compounds continues until 8 hours, where the conversion of **5.6b** is almost complete. After 16 hours of reaction, almost complete conversion of **HIR.2a** is observed and the yield of the side products is at a maximum. This data suggests that after 8 hours of reaction the optimal yield of **5.11b** is obtained, which conflicts with our optimisation studies where a slight increase of yield of **5.11b** was observed between 18 and 24 hours of reaction time (Table 6.8, entry 10). Additionally, we can see a variation up to 8% in **5.11b** from 8 hours to 32 hours of reaction therefore suggesting that this discrepancy may be related to individual batches and the intrinsic error of the NMR. Overall, the monitoring of the reaction suggests that we may have been able to obtain the same results in 8 hours instead of 24 hours. However, we observe no product degradation from 16 to 32 hours, which leads us to

[22] We tried to monitor the reaction by sampling a single reaction with an inert internal standard (trimethyl phenylsilane), however, after 4 hours of reaction time no conversion was observed.

believe that choosing 24 hours as a reaction time was not detrimental to the yield of the deoxyalkynylation.

Table 6.11. ^{1}H NMR monitoring of the photocatalyst-free deoxyalkynylation of 5.6b with HIR.2a with normalised ^{1}H NMR quantification[23] of 5.6b, HIR.2a, 5.11b, 5.15, 6.1 and 6.2 taken over 32 hours.



Time (h)	5.6b (%)	HIR.2a (%)	5.11b (%)	6.1 (%)	6.2 (%)	5.15 (%)	total alcohol fragment (%)	total alkyne fragment (%)
0	100	100	0	0	0	0	100	100
0.5	80	76	11	2	7	14	98	100
1	51	56	29	8	17	29	97	112
4	10	23	63	13	17	34	90	102
8	4	14	66	14	18	34	88	96
16	4	10	58	14	24	38	86	96
24	4	6	63	18	24	40	91	98
32	3	2	62	16	27	40	92	93

Having confirmed that the mass balance of the transformation was indeed conserved throughout the reaction, suggesting that the products were stable under our reaction conditions, we turned to each hypothesis and studied them independently.

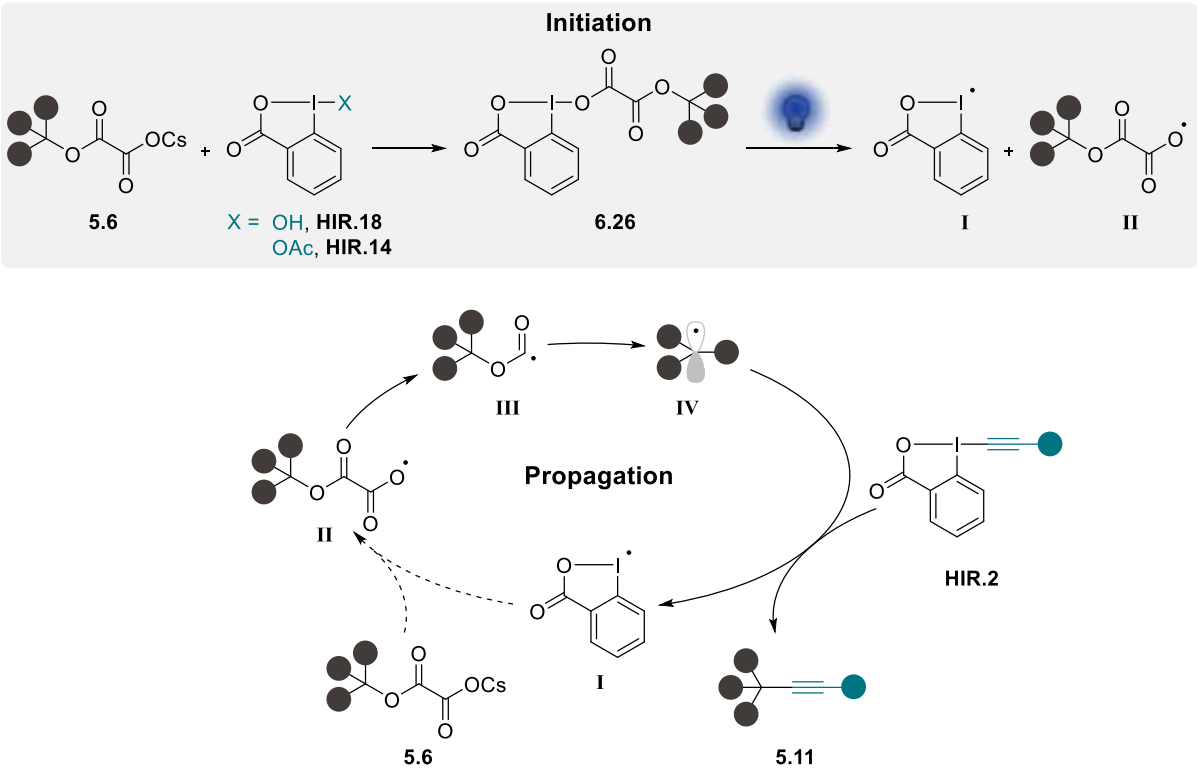
6.4.2. Hypothesis 1: Presence of trace hypervalent iodine species as radical initiators

In previous literature reports,[24] the use of **HIR.18** (BIOH) or **HIR.14** (BIOAc) has promoted reactions under visible light irradiation in absence of a photocatalyst by the formation of covalent adducts between the substrate, generally nucleophilic such as a carboxylate. In the case of our photocatalyst-free deoxyalkynylation, the following type of mechanism could proceed (Scheme 6.10). First, there would be an initiation stage where the nucleophilic substrate **5.6** would displace the leaving group X on either **HIR.18** or **HIR.14** resulting in the

[23] X_{norm} is the normalised quantity of the desired species and is calculated following: $X_{norm} = \frac{X}{X_{max}} \times 100$. where, X = equivalents of compound estimated by ^{1}H NMR, X_{max} = maximum number of equivalents

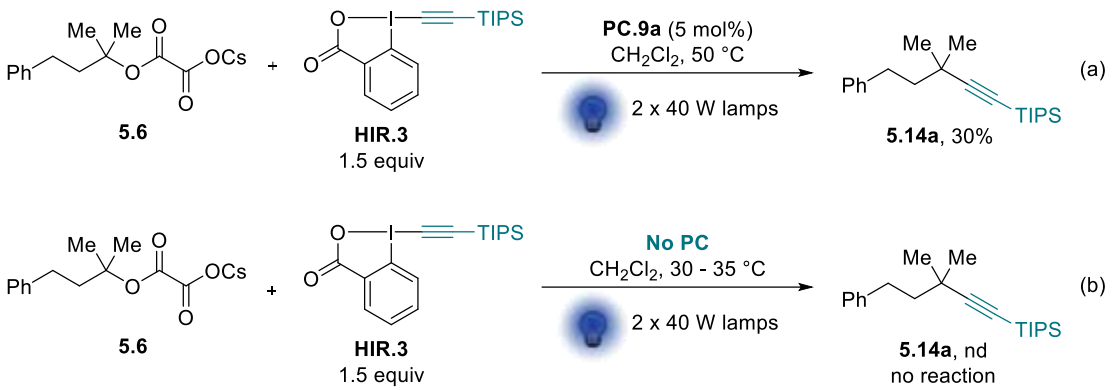
[24] Jia, K.; Chen, Y. Photochemistry of Hypervalent Iodine Compounds. In *PATAI'S Chemistry of Functional Groups*; American Cancer Society, 2018; pp 1–42.

formation of the covalent intermediate **6.26**. Then irradiation of the latter could provoke a homolytic cleavage of the I(III)-O bond to the iodanyl radical **I** and the oxalyl radical **II**. Then the propagation stage could ensue: radical **II** would undergo two subsequential decarboxylations to the tertiary radical **IV**, which in turn would be trapped by **HIR.2** to generate the desired deoxyalkynylated product **5.11** and the iodanyl radical **I**. For the propagation stage to be complete, the iodanyl radical **I** would need to be capable of oxidising the oxalate salt **5.6**. From a thermodynamic perspective, the redox potential of the iodanyl/iodobenzoate couple would be insufficient ($E_{1/2}$(**I**$^{\bullet}$/**I**$^{-}$) = + 0.25 V vs SCE) to oxidise the oxalate ($E_{1/2}$(**II**/**5.6**) ≈ 1.3 V vs SCE).



Scheme 6.10. Speculative mechanism for a photomediated deoxyalkynylation of 5.6 with HIR.2 with HIR.18 or HIR.14 as initiators.

To study this hypothesis, we wondered if we could find a similar reaction system which worked with **PC.9a** but did not present any background reactivity under simple irradiation of the two blue LED lamps in absence of a photocatalyst. To our delight, **HIR.3** (TIPS-EBX) worked sufficiently in presence of **PC.9a** (30% yield of **5.14a**) and no reactivity was observed in absence of **PC.9a** (Scheme 6.11). These results confirmed that we could use **HIR.3** as a radical trap in absence of a photocatalyst with the corresponding additives to see if they could promote the deoxyalkynylation.



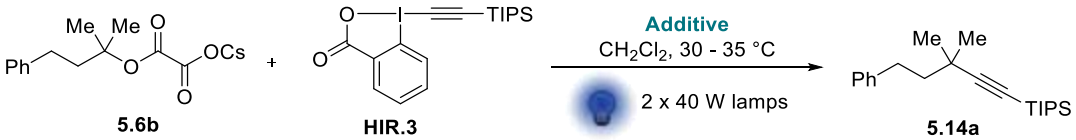
Scheme 6.11. Photocatalysed deoxyalkynylation of 5.6b with HIR.3 (TIPS-EBX) and control experiment in absence of PC.9a.

We proceeded with the control reactions by intentionally adding the potential trace hypervalent iodine precursor (**HIR.18** or **HIR.14**), using **HIR.3** as a radical alkynylating agent, **5.6b** as the model substrate and the same light source as used for the optimised methods (2 x 40 W 440 nm blue LED lamps) (Table 6.12). First, we investigated **HIR.18**. Indeed, it is the precursor for the synthesis of **HIR.2a** and therefore it is plausible that traces of **HIR.18** could be in our reaction media. However, upon addition of 0.2 equiv of **HIR.18** only 5% product formation was detected and 92% of **5.6b** was unreacted (entry 1).[25] Furthermore, we tried to force the formation and degradation of the suspected covalent intermediate **6.26** by irradiating a 1:1.5 ratio of **5.6b** and **HIR.18** however only 10% of oxalate consumption was observed (entry 2). This suggests that if a stoichiometric covalent adduct is formed then our light source may be poorly adapted to promote the homolytic cleavage. We then turned to **HIR.14**. As with BIOH, very little product formation was detected upon addition of 0.2 equiv of **HIR.14** to the reaction between **5.6b** and **HIR.3** (**5.14a**, 5%, entry 3). We then irradiated a 1:1.5 ratio of **5.6b** and **HIR.14** yet no conversion was observed (entry 4). Overall, these experiments suggest that even if we had traces of **HIR.18** or **HIR.14**, they do not enable considerable reaction to proceed in absence of a photocatalyst. Only, traces of the desired deoxyalkynylated product were obtained even with a loading of 20 mol%, ie. well higher than the potential traces in the reagent **HIR.2a** as neither of these compounds are observed in the purified batch of **HIR.2a** by ^{1}H NMR. Furthermore, RAGs that do not posses a strongly nucleophilic lone pair (trifluoroborate salts, enamide, imine, THF) can be activated under our photocatalyst-free conditions where a covalent adduct would be difficult to imagine with these substrates. Additionally, we observe little to no reactivity with halogen substituted ArEBXs in absence of a photocatalyst whereas these radical traps worked well in presence of the photocatalyst. These reagents are

[25] This result is not surprising: 30 mol% of BIOH has been used to activate α-ketoesters under sunlight irradiation in presence of bromoalkynes. The authors propose the in-situ formation of bromobenziodoxolone (an analogue of **HIR.18**), which allows the reaction to proceed with a substoichiometric quantity of BIOH. It therefore seems logical that our oxalates could undergo a similar activation. Tan, H.; Li, H.; Ji, W.; Wang, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 8374–8377.

synthesised and purified in the same fashion, if there was an impurity in our batch of **HIR.2a** it should also be present in the other ArEBXs. Hence, the potential impurities are most likely not promoting the photocatalyst-free transformation.

Table 6.12. Photomediated deoxyalkynylation of 5.6b with HIR.18 and HIR.14 as initiators and HIR.3 as a radical trap.



Entry	HIR.3 (equiv)	Additive (equiv)	5.6b (%)	5.14a (%)
1	1.5	**HIR.18** (0.2)	92	5
2	-	**HIR.18** (1.5)	90	-
3	1.5	**HIR.14** (0.2)	92	5
4	-	**HIR.14** (1.5)	100	-

Reaction conditions: The reactions were performed on 0.1 mmol scale using blue LED lamps (2 x 40 W, 440 nm). 1 equiv of CH_2Br_2 was added as an internal standard and DMSO-d_6 was used as solvent to ensure full solubilisation of the crude.

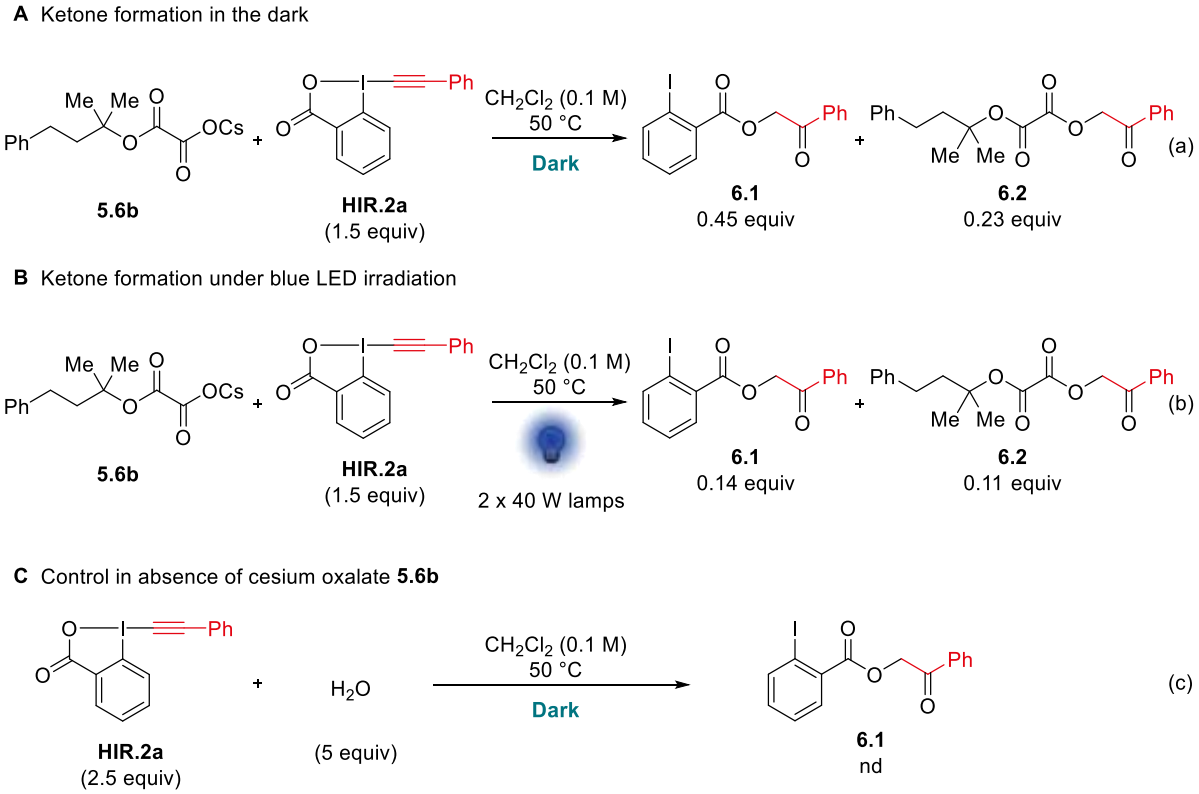
6.4.3. Hypothesis 2: Ketones **6.1** or **6.2** as either photocatalysts or reaction intermediates

6.4.3.1. Formation of the ketone side products

We were intrigued by the formation of the side products ketones **6.1** and **6.2**. **6.1** had already been observed previously with photoredox catalysis and transition metal mediated transformations,[26] however, to the best of our knowledge, the formation of **6.2**, or analogues, from EBXs had not yet been reported. To understand how this reaction was proceeding we decided to perform some control reactions in the dark at 50 °C. When turning back to our second control reaction performed with **5.6b** and 1.5 equiv of **HIR.2a** at 50 °C in CH_2Cl_2, we saw no deoxyalkynylated product **5.11b** and no diyne formation, but we did see the formation of ketones **6.1** (0.45 equiv) and **6.2** (0.23 equiv) (Scheme 6.12, **A**). In comparison, the same reaction when performed under irradiation of two blue LED lamps (2 x 40 W; 440 nm) led to 0.14 equiv of **6.1** and 0.11 equiv of **6.2** (Scheme 6.12, **B**). Both ketones were obtained in higher yields without irradiation; this suggests that their formation can proceed through a thermal pathway and may be outcompeted by the formation of desired deoxyalkynylated product (**5.11b**). The formation of **6.1** and **6.2** from **HIR.2a** requires an additional equivalent of H_2O, we suspect that there are traces of water from the synthesis of the cesium salts. Interestingly, we did not observe the formation of **6.1** in the absence of the cesium salt even

[26] See supporting information of these references: a. Wu, J.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 11107–11111. b. Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. *Chem. Sci.* **2018**, *9*, 5883–5889.

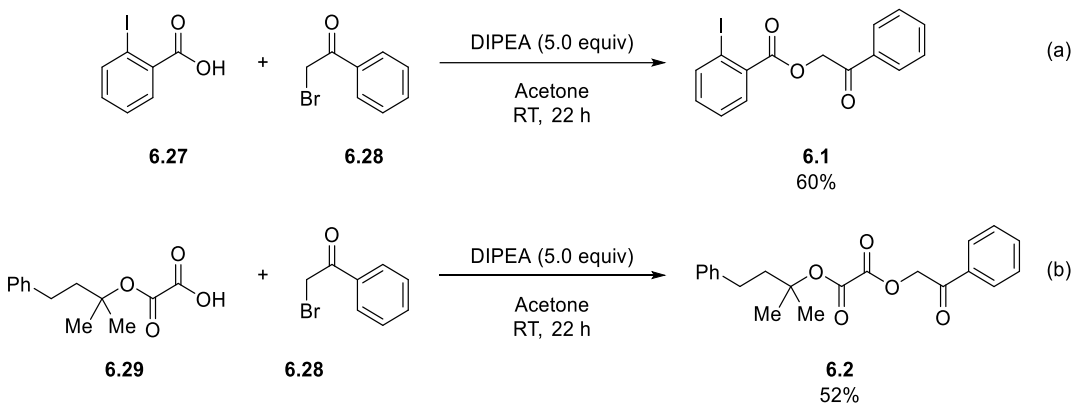
in presence of H_2O (Scheme 6.12, **C**). We believe this may be due to the poor miscibility of H_2O and CH_2Cl_2 and the relatively low nucleophilicity of H_2O in comparison to a carboxylate or an oxalate.



Scheme 6.12. Dark experiment and control reactions for the generation of the ketone side-products 6.1 and 6.2.

6.4.3.2. Synthesis of ketones 6.1 and 6.2

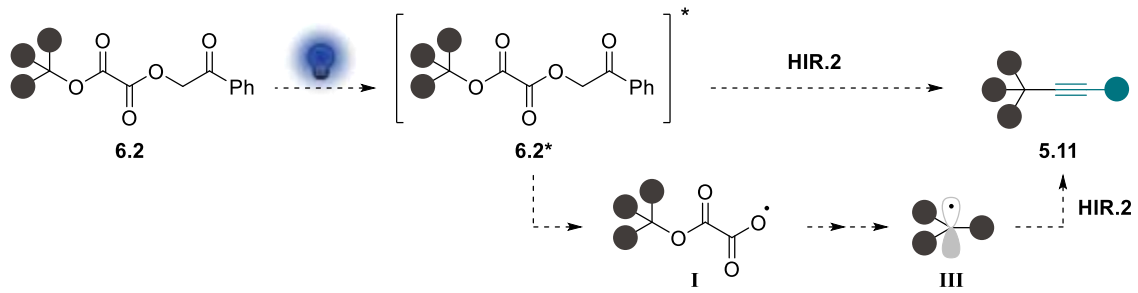
To guarantee the purity of the ketones we synthesised them from the corresponding nucleophile (**6.27** or **6.29**) and phenacyl bromide (**6.28**, Scheme 6.13).



Scheme 6.13. Synthesis of the ketone side products 6.1 and 6.2

6.4.3.3. Control reactions for the deoxyalkynylation of **5.6b** with **6.1** and **6.2**

Considering the photosensitivity of aromatic ketones,[27] we wondered if **6.1** or **6.2** could be acting as a photocatalyst generated in-situ. We then envisaged that **6.2** could, in fact, be an intermediate towards the synthesis of **5.11b**, although purely speculative, we could imagine that its excited state could result in the formation of radical **III** that could then be trapped by **HIR.2** to form **5.11b** (Scheme 6.14).

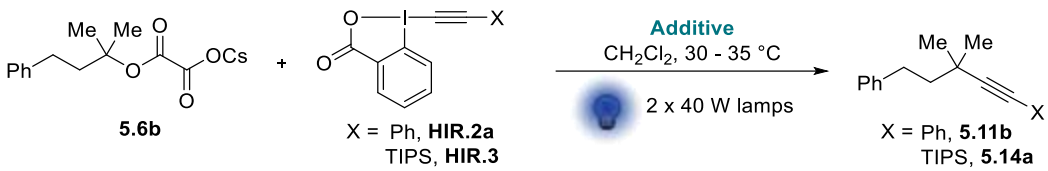


Scheme 6.14. Possible mechanism for the conversion of 6.2 to 5.11b under irradiation.

First, we explored the role of **6.1**. A CH_2Cl_2 solution of **5.6b**, **HIR.3** (1.5 equiv) and **6.1** (0.2 equiv) was irradiated (2 x 40 W, 440 nm) (Table 6.13). Only traces of the alkyne **5.14a** could be detected and practically no conversion of **5.6b** was observed (entry 1). Furthermore, when we irradiated a 1:1 ratio of **5.6b** and **6.1** no conversion or degradation was observed (entry 2). These results suggest that ketone **6.1** plays little to no role in the photocatalyst-free transformation and presents considerable photostability. Second, **6.2** (0.7 equiv) was subjected to the model system, similarly, only 5% of **5.14a** was detected and only 8% conversion of **5.6b** was observed (entry 3). Upon irradiation of a 1:1 ratio of **5.6b** and **6.2**, no conversion was observed (entry 4). Finally, we tested our hypothesis where **6.2** would be a reactive intermediate. We attempted to convert **6.2** to **5.11b** in presence of **HIR.2a**, however no conversion of **6.2** was noted and no alkyne formation was observed (entry 5). These results are consistent with the report literature data: diaryl ketones generally absorb in the UVB region (360 - 400 nm) and **6.1** and **6.2** are mono-aryl ketones and should absorb at lower wavelengths than a diaryl ketones and our light source is centred around 440 nm. Furthermore, when we use UVB irradiation we see no product formation despite the presence of the ketones **6.1** and **6.2** in the reaction media (see Table 6.8). Overall, our data suggest that the ketones **6.1** and **6.2** are thermal side products that compete with the deoxyalkynylation pathway but most likely do not promote it.

Table 6.13. Photomediated deoxyalkynylation of 5.6b with ketones 6.1 and 6.2 as photocatalysts and HIR.3 as a radical trap.

[27] Pérez-Prieto, J.; Galian, R. E.; Miranda, M. A. Diaryl Ketones as Photoactivators. In *Mini-Reviews in Organic Chemistry*; 2006; Vol. 3, pp 117–135.

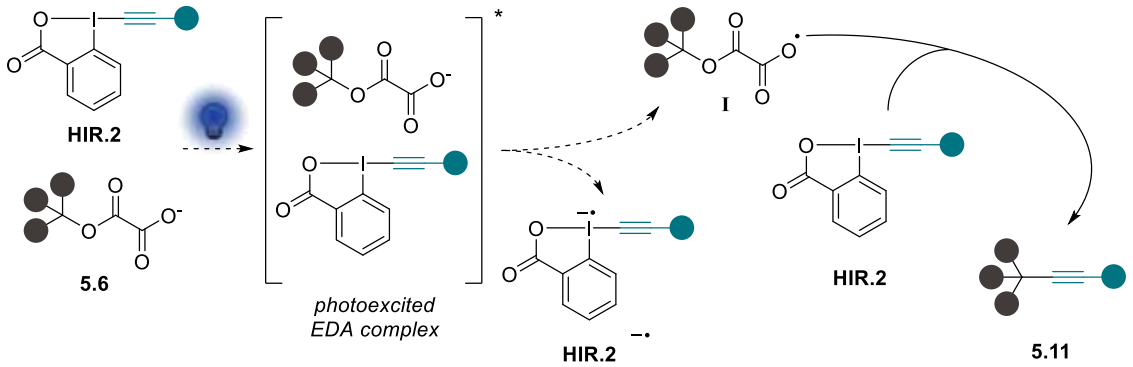


Entry	EBX (equiv)	Additive (equiv)	**5.6b** (%)	**5.14a** (%)
1	**HIR.3** (1.5)	**6.1** (0.2)	98	2
2	-	**6.1** (1.0)	100	-
3	**HIR.3** (1.5)	**6.2** (0.7)	92	5
4	-	**6.2** (1.0)	100	-
5	**HIR.2a** (1.5)	**6.2** (1.0)	-	**5.11b**: nd

Reaction conditions: The reactions were performed on 0.1 mmol scale using blue LED lamps (2 x 40 W, 440 nm).

6.4.4. Hypothesis 3: EDA complexes between **HIR.2a** and **5.6b**

Having established that neither trace impurities nor ketones were promoting the reaction, it seemed clear that the photoexcitation of either or both **HIR.2** and **5.6** was mostly likely responsible for the deoxygenation of **5.6**. First, we envisaged the possibility of a photosensitive EDA complex (Scheme 6.15). If **HIR.2** and **5.6** formed a photoactive EDA complex their photoexcitation would result in a SET from **5.6** to **HIR.2** resulting in **I** and **HIR.2**$^{\bullet-}$. **I** could then deliver the desired alkyl radical and the product, as described previously.



Scheme 6.15. Possible EDA complex between HIR.2 and 5.6 that could lead to the formation of 5.11 under irradiation.

We turned to UV-Vis analysis to identify the presence or not of an EDA complex (Figure 6.1). First, the spectra of **5.6b** and **HIR.2a** present absorption bands in the UV region (270 nm for **5.6b**, and 340 nm for **HIR.2a**) and present low absorption with no clear band in the visible region (> 400 nm) (spectra **A** and **B**). When both compounds were analysed in a 1:1 ratio at the same concentrations and the difference between the absorption of the 1:1 ratio and the absorption of each species (**5.6b** and **HIR.2a**) clearly shows no new absorption band (spectra **C**). Based on this result, we can conclude that **5.6b** and **HIR.2a** do not form a photoactive EDA complex.

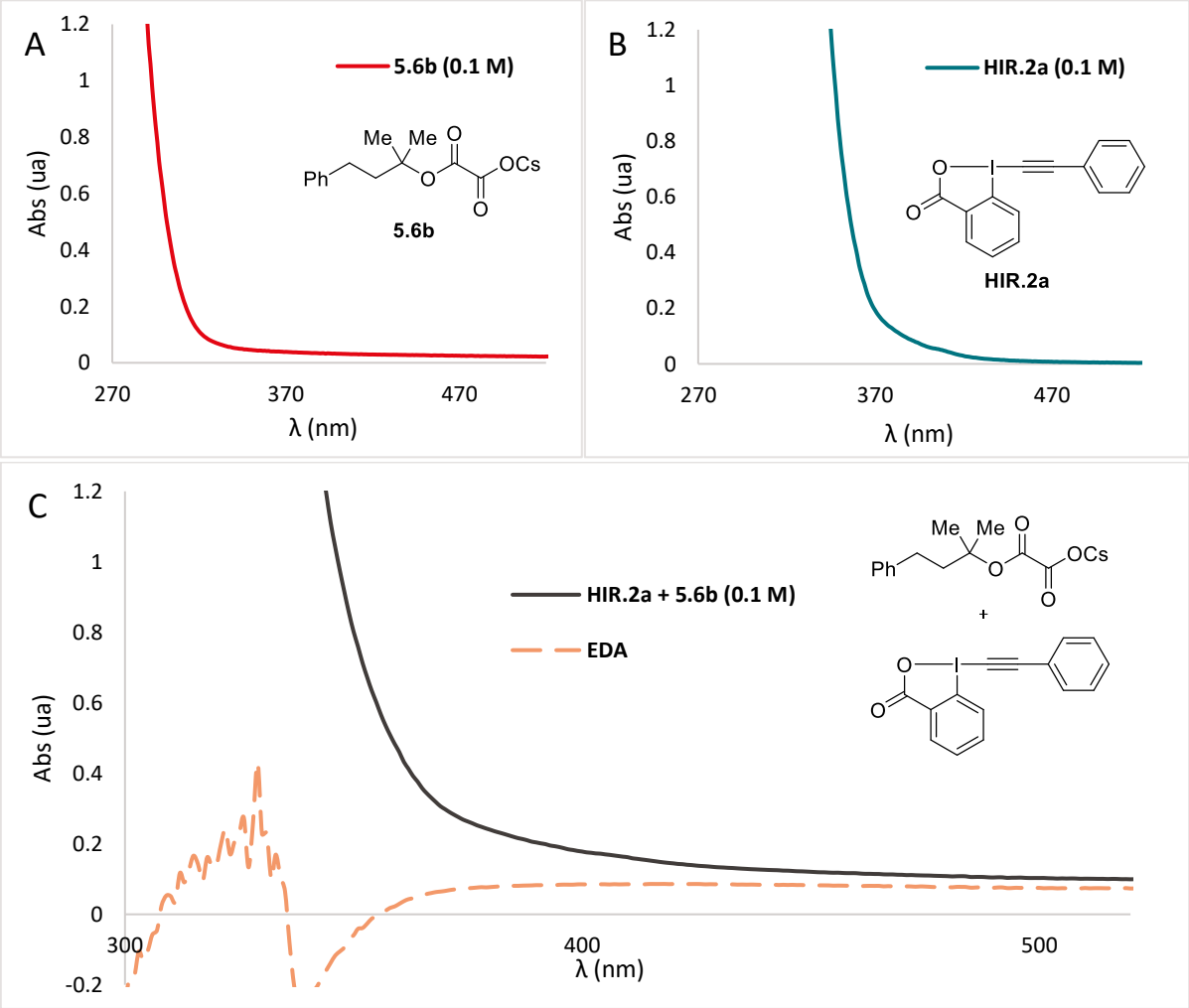


Figure 6.1. UV-Vis absorption spectra. A Abs(**5.6b**) 0.1 M in DMSO, **B** Abs(**HIR.2a**) 0.1 M in DMSO, **C** Abs(**5.6b**:**HIR.2a** 1:1) 0.1 M in DMSO (black line) and the corresponding EDA trace (orange dash line, Abs(**5.6b**:**HIR.2a** 1:1) – [Abs(**5.6b**) + Abs(**HIR.2a**)])

6.4.5. Hypothesis 4: Direct excitation of the **HIR.2a**

6.4.5.1. UV-Vis spectrometry

Having refuted the other hypotheses, we wondered if the hypervalent iodine reagent was photoactive. At the time of our studies, ArEBXs had not been reported to undergo direct excitation under visible light irradiation; although, other hypervalent iodine reagents have been reported to undergo $S_0 \rightarrow T_n$ transitions under visible light irradiation.[28] When exploring the possibility of an EDA complex, we measured the UV-Vis spectrum of **HIR.2a**, we did not observe a clear band in the visible region for **HIR.2a**, however the absorption clearly tails off into the visible region in comparison to **5.6b**. We decided to explore this further (Figure 6.2, blue dashed trace). Having already measured the absorption of **HIR.2a**, we then measured the fluorescence emission spectrum of **HIR.2a** following an excitation at 390 nm. We were

[28] Nakajima, M.; Nagasawa, S.; Matsumoto, K.; Kuribara, T.; Muranaka, A.; Uchiyama, M.; Nemoto, T. *Angew. Chem. Int. Ed.* **2020**, *59*, 6847–6852.

pleased to see a broad fluorescence band λ_{max} = 485nm (red dashed trace). At this point, we wondered if we could measure a fluorescence excitation spectrum for an emission at 485 nm. This approach could help indicate whether one or more absorption bands are responsible for the emission at 485 nm. Interestingly, we observed two bands a first band: λ_{max} = 360 nm and a second band λ_{max} = 430 nm (black dotted trace). The presence of the second band indicates that irradiation at 440 nm can result in fluorescence at 485 nm, thus confirming the possibility of an excited state resulting from the irradiation of **HIR.2a** with our light source (light blue line, λ_{max} = 440 nm).

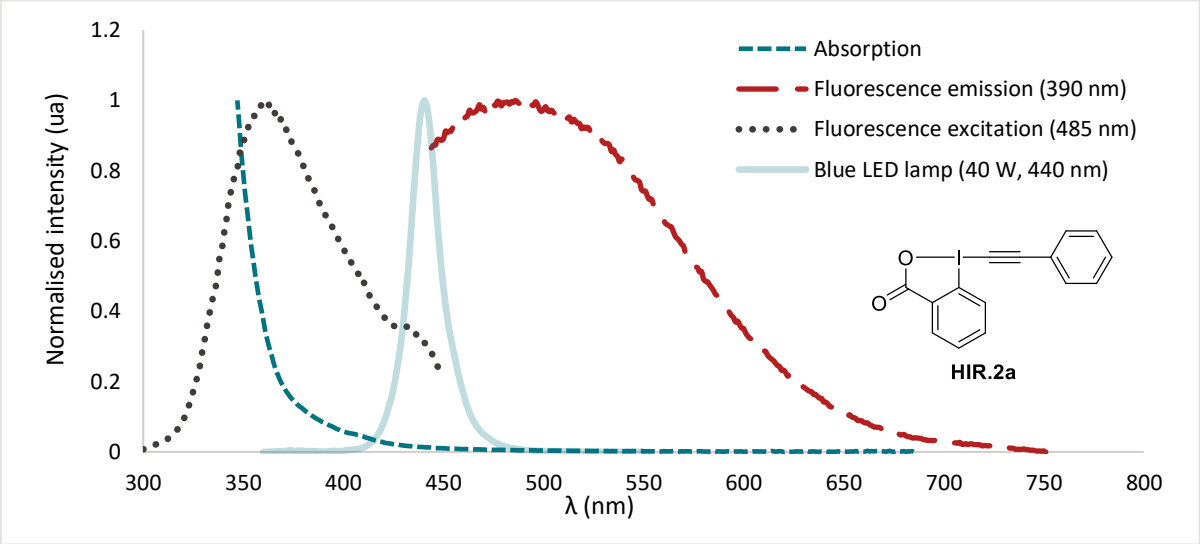


Figure 6.2. Normalised UV-Vis absorption, fluorescence emission and fluorescence excitation spectra of HIR.2a.

These observations correlate well with our prior experimental observations: (1) multiple classes and scaffolds of starting materials are compatible with our photocatalyst free conditions; (2) few hypervalent iodine reagents are compatible suggesting that the reagent may play a key role in the photocatalyst-free conditions. We then calculated the extinction coefficient of **HIR.2a** with a Beer-Lambert linear regression (Figure 6.3). We indeed saw a linear regression following the Beer-Lambert law from 0.014 M to 0.14 M of **HIR.2a** in DMSO at 420 nm, 440 nm and 460 nm. This confirmed that despite the high concentration (0.1 M) of our analysis, there were no observable aggregate effects thus confirming our observations. It also allowed us to calculate the extinction coefficient at all three wavelengths: λ = 420 nm, 0.54 $L.mol^{-1}.cm^{-1}$, λ = 420 nm, 0.33 $L.mol^{-1}.cm^{-1}$, λ = 460 nm, 0.23 $L.mol^{-1}.cm^{-1}$. These extinction coefficients are considerably low and could suggest that the transition they characterise is forbidden.[29]

[29] For hypervalent iodine species ε_{max} ($S_0 \rightarrow T_n$) < 30 $L.mol^{-1}.cm^{-1}$ taken from Nakajima, M.; Nagasawa, S.; Matsumoto, K.; Kuribara, T.; Muranaka, A.; Uchiyama, M.; Nemoto, T. *Angew. Chem. Int. Ed.* **2020**, *59*, 6847–6852.

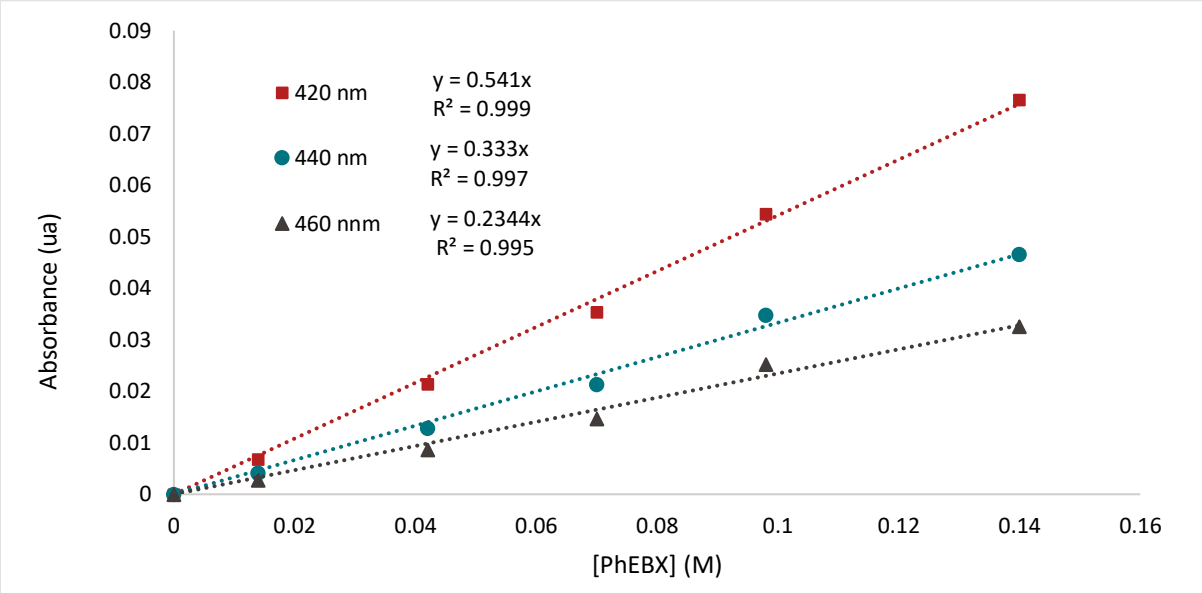


Figure 6.3. Linear regression of the absorbance of HIR.2a at different concentrations from 0.02 to 0.14 M at 420 nm (red), 440 nm (blue) and 460 nm (black).

We then wondered if the absorption data of other reagents could give us an insight on the variations between reagents. We measured the absorption spectra of **HIR.2b**, **HIR.2e** and **HIR.3** to compare to **HIR.2a** (Figure 6.4). All four compounds present very similar absorption profiles. **HIR.2b** (yielding 70% of deoxyalkynylated product) presents a bathochromic shift when compared to **HIR.2a** (60% of product) whereas **HIR.2e** (less than 20% product formation) overlays almost perfectly with **HIR.2a**. Finally, **HIR.3** (no conversion, no reactivity) presents a hypsochromic shift although still seems to absorb slightly in the visible region. This hypsochromic shift could explain the lack of reactivity of **HIR.3** in absence of a photocatalyst. However, these analyses do not allow us to understand the difference in reactivity between **HIR.2a** and **HIR.2e**.

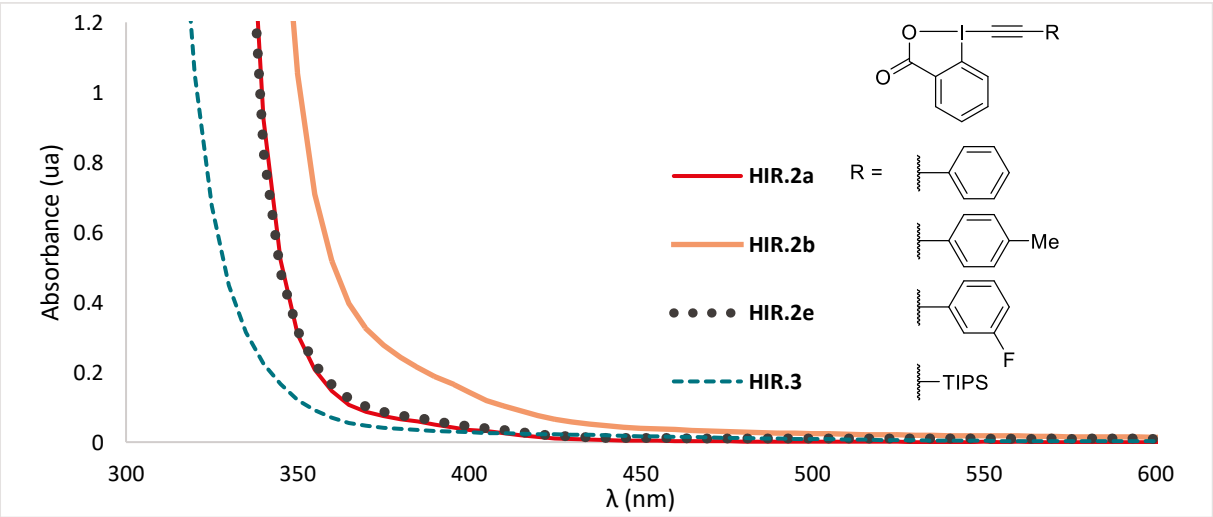


Figure 6.4. UV-Vis spectra of HIR.2a (reference, red line), HIR.2b (small orange dash), HIR.2e (grey dotted line) and HIR.3 (big blue dash).

6.4.5.1.1. Cyclic voltammetry

Having established that **HIR.2a** and other ArEBXs absorb in the visible region we aimed to gain a greater understanding of the redox properties of these species in the excited state. Indeed, multiple oxidisable substrates could be converted under this direct excitation of ArEBXs approach, it therefore seemed coherent to envisage the excited state **HIR.2a*** as a photooxidant. We measured the cyclic voltammogram of **HIR.2a** and estimated the ground state redox potential of the couple **HIR.2a**$^{\bullet-}$/**HIR.2a** to be - 0.87 V vs SCE (Figure 6.5).

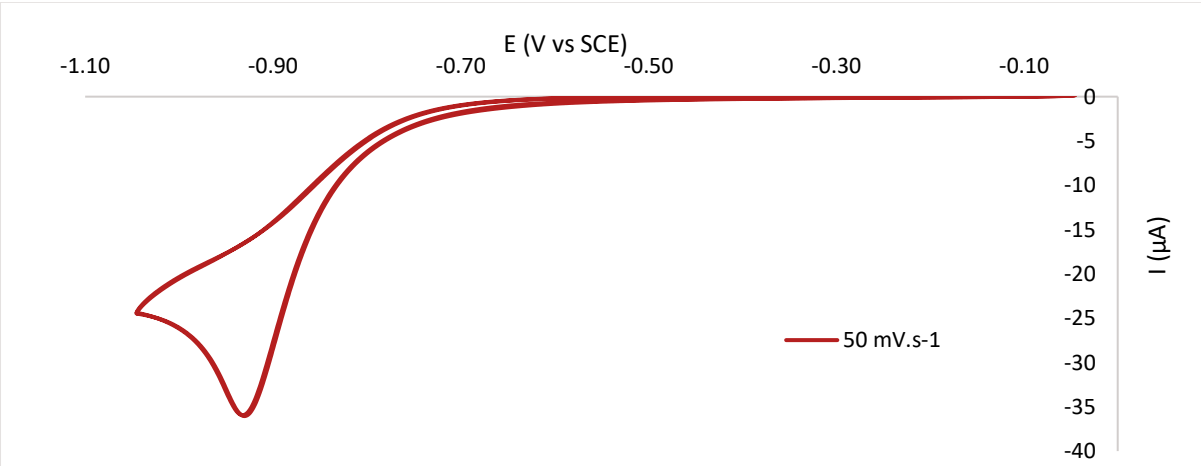


Figure 6.5. Cyclic voltammogram of HIR.2a 0.1 mM in MeCN.

With the redox potential of **HIR.2a**/**HIR.2a**$^{\bullet-}$ in the ground state and the absorption spectra we could then estimate the redox potential in the excited state following this equation:

$E_{1/2}$(**HIR.2a***/**HIR.2a**$^{\bullet-}$) = $E_{0\text{-}0}$ + $E_{1/2}$(**HIR.2a**/**HIR.2a**$^{\bullet-}$).

Where $E_{1/2}$(**HIR.2a**/**HIR.2a**$^{\bullet-}$) is the redox potential of **HIR.2a** in the ground state and $E_{0\text{-}0}$ is the energy of the vibronic 0-0 transition. It was determined experimentally by position of the long wavelength tail of the absorption spectrum at 460 nm (Figure 6.2):[30]

$$E=\frac{hc}{\lambda} \leftrightarrow E_{0\text{-}0}=\frac{1240}{460}= 2.7 \text{ eV}$$

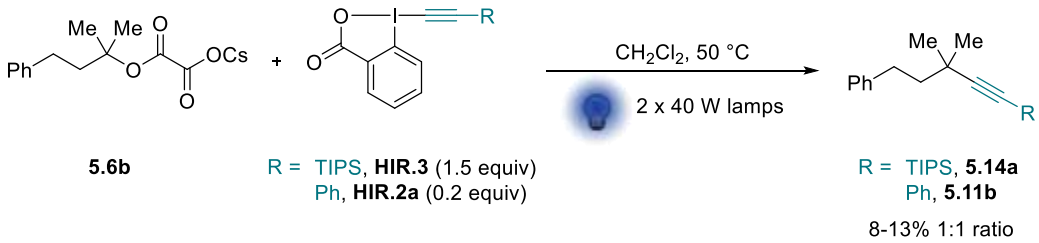
$E_{1/2}$(**HIR.2a***/**HIR.2a**$^{\bullet-}$) = $E_{0\text{-}0}$ + $E_{1/2}$(**HIR.2a**/**HIR.2a**$^{\bullet-}$) = <u>+ 1.8 V vs SCE</u>

[30] This value was determined in an approximative fashion by observing the flattening of the curve (it gives an underestimation of the real value). This value should be close to the vibronic 0-0 transition of what we believe to be the triplet state, which is normally calculated from the phosphorescence trace. Unfortunately we were unable to perform the phosphorescence analysis, further work is being performed in this direction confirming our initial approximation. The 0-0 vibronic transition of the singlet state seems to be approximately around 390 nm (determined by the intercept of the absorption trace and the fluorescence trace).

This result suggests that the excited state **HIR.2a*** is a strong oxidant and could be capable of oxidising the substrates that we could activate under photocatalyst-free conditions (+ 1.2 < $E_{1/2}$(**sub•⁺/sub**) < +1.5 V vs SCE).[31]

Finally, we wondered if we could further confirm our hypothesis that **HIR.2a** may be a photooxidant by performing a crossover experiment using **HIR.2a** as an additive and **HIR.3** as a non-photosensitive radical alkynylating agent (Equation 6.1). When we used 0.2 equiv of **HIR.2a** to promote the reaction between **HIR.3** and **5.6b** in absence of a photocatalyst under the irradiation of two blue LED lamps (2 x 40 W, 440 nm), we observed 20% conversion of the substrate **5.6b** and 8 – 13% yield of the TIPS- and Ph-alkynes **5.14a** and **5.6b** in a 1:1 ratio. This result suggests that **HIR.2a** was indeed capable of activating the substrate **5.6b** under simple irradiation. **HIR.2a** could act as a photooxidant allowing the deoxygenation of **5.6b** to occur for it then to be trapped by either **HIR.2a** or **HIR.3**. This result also explains the need for a higher loading (2.5 equiv) of the reagent to obtain synthetically relevant yields. Indeed, we think that 1 equiv of **HIR.2a** would be needed to perform the oxidation, and 1 equiv would serve as a radical trap.

Equation 6.1. HIR.2a promoted photometdiated deoxyalkynation of 5.6b with HIR.3 as a radical trap.



6.4.6. Mechanistic overview

Based on previous reports for deoxygenative strategies with oxalates and our experimental data, we propose the following mechanism to explain the photocatalyst free deoxyalkynylation (Scheme 6.16). First, **HIR.2** undergoes direct photoexcitation to **HIR.2*** under the irradiation of two 40 W 440 nm lamps. This step was confirmed by our experimental data: diyne **5.15** formation upon sole irradiation of **HIR.2a** and our UV-Vis spectroscopic studies. Then, the excited state **HIR.2*** (+ 1.8 V Vs SCE), can perform a single electron oxidation of the oxalate **5.6** (+ 1.3 V vs SCE) resulting in the formation of the reduced **HIR.2**$^{\bullet-}$ and *O*-centred radical **I**. The latter can then undergo two decarboxylations going through the acyl radical **II** and deliver

[31] Unfortunately due to the unavailability of the potentiostat normally used for our electrochemical analyses, the CVs of the other reagents (**HIR.2b**, **HIR.2e** and **HIR.3**) have not been measured precisely. Using an IKA ElectraSyn we have a rough estimation of their redox potentials in the excited state:
$E_{1/2}$(**HIR.2b*/HIR.2b**) ≈ + 1.7 ± 0.1 V vs SCE; $E_{1/2}$(**HIR.2e*/HIR.2e**) ≈ + 2.0 ± 0.1 V vs SCE and $E_{1/2}$(**HIR.3*/HIR.3**) > + 2 V vs SCE.

the alkyl radical **III**. A second molecule of **HIR.2** can then trap the alkyl radical **III** affording the desired deoxyalkynylated product **5.11** and iodanyl radical **IV**. For now, the reactivity of **HIR.2**$^{\bullet-}$ is not well understood. Based on its structure, we believe it is most likely a very reactive species. As it is a radical anion, it could be a source of acetylide. However, we have not observed the formation of the free alkyne which could be expected if a free acetylide was generated. Furthermore, the collapse of the TIPS-EBX radical anion (**HIR.3**$^{\bullet-}$) to the corresponding acetylide has already been calculated,[32] the transition state was found to be highly energetic, which suggests that the collapse to the acetylide and the iodanyl radical would be unlikely. The collapse to the iodobenzoate and the alkynyl radical seems also unlikely due to the high energy of the alkynyl radical. However, we do observe formation of the diyne, we could envisage that **HIR.2**$^{\bullet-}$ could be trapped by a second molecule of **HIR.2** delivering the diyne **5.15**, generating an iodobenzoate (**V**) and an iodanyl radical (**IV**). In addition to the reactivity of **HIR.2**$^{\bullet-}$, it is difficult to establish how the iodanyl radical (**IV**) reacts under our reaction conditions. In a traditional, photoredox catalysed processes, it often intervenes in the oxidation of the photocatalyst ensuring a closed photocatalytic cycle. However, in absence of a photocatalyst, it may, under our conditions, be accumulating to a certain extent in the media. Based on literature, this radical is a potent H-atom abstractor, we observed the C-H alkynylation of CH_2Cl_2 under our reaction conditions, which suggests that this could indeed be a plausible pathway.[33] When considering other ground state species (such as the starting material or the products) it seems unlikely the iodanyl radical would be able to oxidise them considering its low redox potential ($E_{1/2}$(**IV**/**V**) = + 0.25 V vs SCE), however it could react with **HIR.2**. Although **HIR.2** have only been reported to trap nucleophilic radicals, if left with no choice, an electrophilic radical could potentially be trapped this could potentially lead to the ketone side product after hydration (**6.1**). That being said, the ketone formation under thermal activation is efficient and it seems unlikely that a second process would contribute to the formation of **6.1**. Finally, if the iodanyl radical (**IV**) can indeed accumulate at least partially in the media, we could also envisage it's quench by more transient species such as **HIR.2*** or **HIR.2**$^{\bullet-}$. Specifically, reacting with the latter could enable the regeneration of **HIR.2** and the formation of more stable **V**. Reacting with the radical anion could also regenerate the ground state **HIR.2** and the iodobenzoate (**V**). More studies need to be conducted on these species to have a better understanding of their reactivity. This mechanistic proposal can then be extended to the other redox groups we have studied (carboxylates, alkyl trifluoroborates, enamides, and electron-rich imines).

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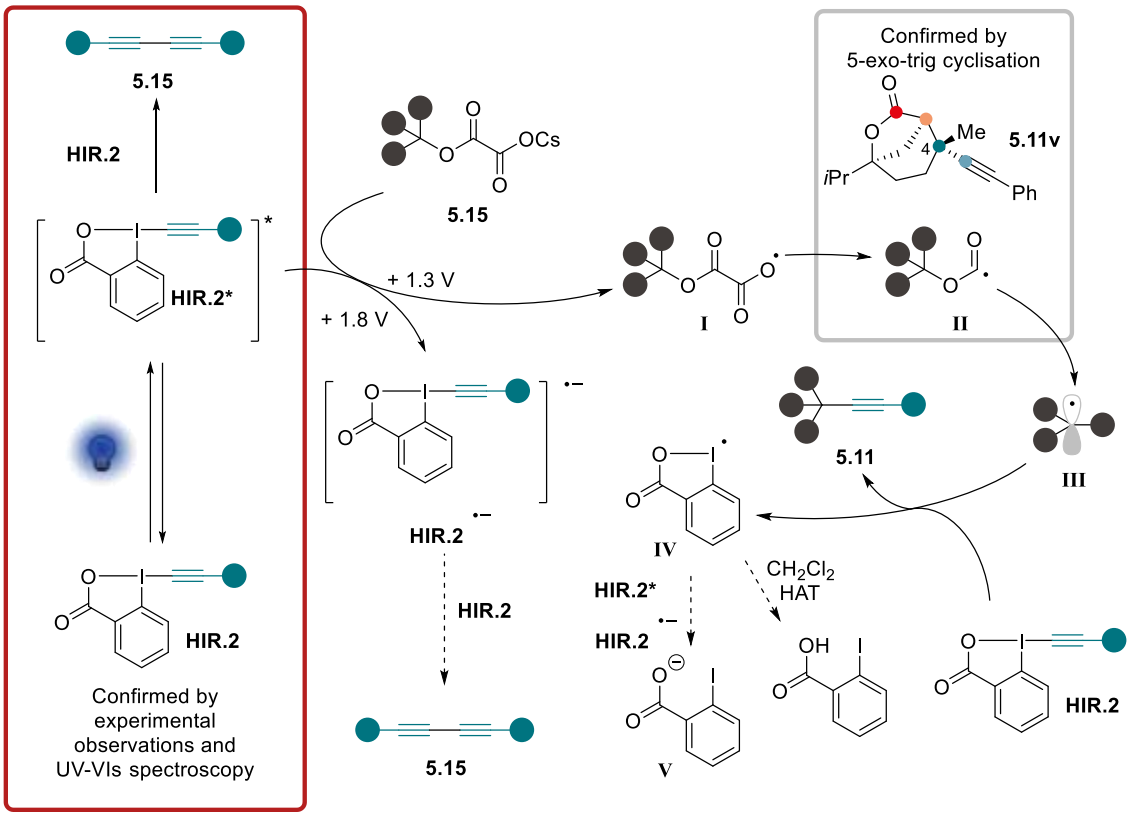
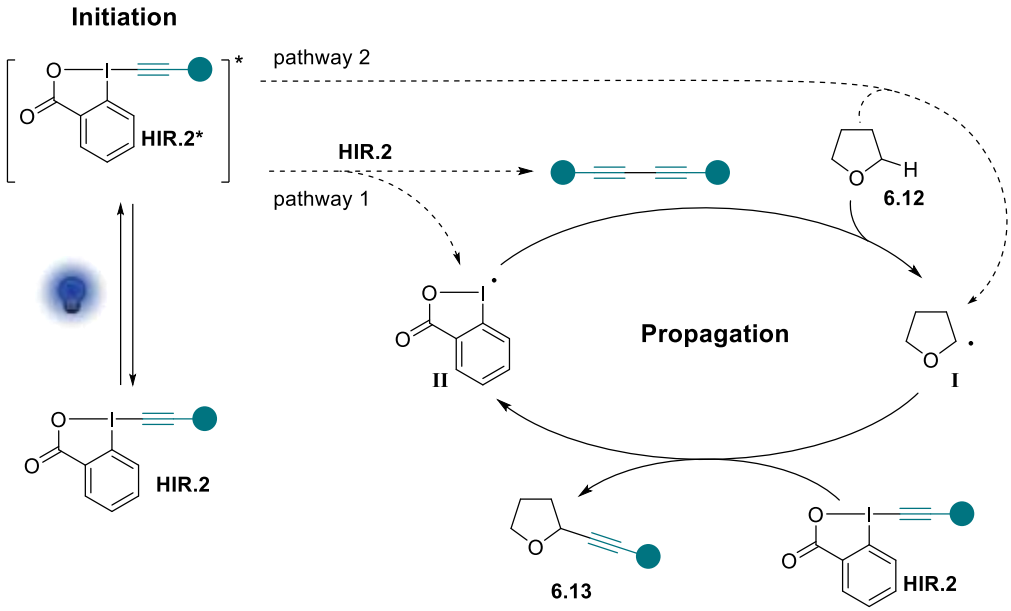
[32] Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* **2017**, *8*, 1790–1800.
[33] 6% of Cl_2CH-alkyne were obtained with the optimised conditions



Scheme 6.16. Mechanistic proposal for the direct excitation of HIR.2 and the photocatalyst-free deoxyalkynylation of 5.6.

Based on previous literature reports, the alkynylation of THF proceeds through a radical chain type mechanism sustained by the iodanyl radical as a HAT agent (Φ = 1.93 with **HIR.3**).[34] In our case, following the direct excitation of **HIR.2** to **HIR.2***, two options could initiate the radical chain (Scheme 6.17): (1) **HIR.2*** could react with a second molecule of **HIR.2** resulting potentially in the formation of diyne **5.15** and the iodanyl radical **II**. The iodanyl radical could then perform a HAT on THF resulting in **I** and eventually **6.13**; (2) **HIR.2*** could perform directly a HAT on THF to generate radical **I**. The latter would then be trapped by **HIR.2** to form alkyne **6.13** and iodanyl radical (**II**), which would then be able to propagate by performing a HAT on THF.

[34] Voutyritsa, E.; Garreau, M.; Kokotou, M. G.; Triandafillidi, I.; Waser, J.; Kokotos, C. G. *Chem. – Eur. J.* **2020**, *26*, 14453–14460.



Scheme 6.17. Mechanistic proposal for the H-atom abstraction and functionalisation of THF by the direct excitation of HIR.2.

6.5. Conclusion and prospects

In this chapter, we have discussed the direct excitation of ArEBXs and their application as photooxidants. We found that 2.5 equiv of **HIR.2** under the irradiation of two 40 W 440 nm lamps was necessary for the deoxyalkynylation to proceed in absence of a photocatalyst. Then, we were able to extend this strategy to the activation of multiple oxidisable groups (carboxylates, alkyl trifluoroborates and enamides) with potentials ranging from + 1.2 – + 1.5 V vs SCE for alkynylations previously reported with photocatalysts. We were also able to develop the first deaminative alkynylation strategy using an electron-rich imine, which underlines the relevance of photoactive reagents for reaction discovery. Based on literature reports and our experimental data, we have been able to propose a plausible mechanism for the photocatalyst-free reactions involving the direct excitation of **HIR.2**. It helps explain why the light source (two 40 W 440 nm lamps) were required to promote this photocatalyst-free transformation and why this discovery has not been made sooner as previous reports use blue LED strips (10 – 12 W, 460 nm). It also helps us understand why 2.5 equiv of reagent were required for optimal results, as 1 equivalent could be required for the oxidation and a second equivalent would act as a radical trap. The mechanistic proposal is still speculative: the reactivity of the reduced reagent **HIR.2**$^{\bullet-}$ and the iodanyl radical is poorly understood under our reaction conditions. The main drawbacks associated to this method are associated to the substitution of the ArEBX. Indeed, even a small change in electronics (halogen substitution) led to a drop in yield. Electrochemical studies of the unsuccessful reagent need to be performed to see if there is a correlation between the scaffold and the redox potential in the excited state. It would be worthwhile to gain knowledge on the nature (S or T) and the lifetime

of the excited state **HIR.2*** as this could help us understand further the mechanism of the reaction. Furthermore, fluorescence quenching studies would also help understand the reactivity of **HIR.2***. Indeed, we could attempt to quench **HIR.2*** with **HIR.3**, an oxidisable substrate, or THF.

6.6. References

1. This result is in accord with the reported literature procedures and their control reactions where the reaction does not proceed in absence of photocatalyst: a. Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. *J. Am. Chem. Soc.* **2014**, *136*, 2280–2283. b. Zhou, Q.; Guo, W.; Ding, W.; Wu, X.; Chen, X.; Lu, L.; Xiao, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199. c. Le Vaillant, F.; Courant, T.; Waser, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204. d. Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* **2017**, *8*, 1790–1800. e. Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. *Chem. Sci.* **2018**, *9*, 5883–5889. f. Garreau, M.; Le Vaillant, F.; Waser, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 8182–8186. g. Amos, S. G. E.; Nicolai, S.; Waser, J. *Chem. Sci.* **2020**, *11*, 11274–11279.
2. Longer reaction times did not lead to any further increase in yield of **5.11b**
3. Converted from V vs Fc to V vs SCE, taken from: Yasu, Y.; Koike, T.; Akita, M. *Adv. Synth. Catal.* **2012**, *354*, 3414–3420.
4. Cf. Chapter 2. Background and significance; 2.3.2.3.3 λ^3-iodanes as radical traps under photocatalyst mediated conditions
5. Ashley, M. A.; Rovis, T. *J. Am. Chem. Soc.* **2020**, *142*, 18310–18316.
6. The reported photocatalyst was **PC.3** ($Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$))
7. In their report, they also discuss other mechanistic pathways such as PCET events involving the photocatalyst, however they were unable to distinguish between the two pathways.
8. We chose Cs_2CO_3 over TMG as it had been successfully combined with the decarboxylative alkynylation photocatalyst-free conditions (see 6.3.2) and CH_2Cl_2 over DCE to limit solvent functionalisation (see 5.2.2.1)
9. Cf. Chapter 2: Background and significance: 2.3.2.3. λ3-iodanes as radical traps under photocatalyst mediated conditions. a. Matsumoto, K.; Nakajima, M.; Nemoto, T. *J. Org. Chem.* **2020**, *85*, 11802–11811. b. Voutyritsa, E.; Garreau, M.; Kokotou, M. G.; Triandafillidi, I.; Waser, J.; Kokotos, C. G. *Chem. – Eur. J.* **2020**, *26*, 14453–14460.
10. Cf. chapter 2: Background and significance. paragraph: 2.3.2.3.3. a Defunctionalisation alkynylation. Selected examples: a. Matsumoto, K.; Nakajima, M.; Nemoto, T. *J. Org. Chem.* **2020**, *85*, 11802–11811. b. Voutyritsa, E.; Garreau, M.; Kokotou, M. G.; Triandafillidi, I.; Waser, J.; Kokotos, C. G. *Chem. – Eur. J.* **2020**, *26*, 14453–14460.
11. Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4486–4487.
12. Tian, Y.; Liu, Z.-Q. *RSC Adv.* **2014**, *4*, 64855–64859.
13. Gál, B.; Bucher, C.; Burns, N. Z. *Mar. Drugs* **2016**, *14*, 206.
14. In chapter 4 we observed full degradation of **HIR.14** in presence of **PC.9b**.
15. Cf. Chapter 2: Background and significance, paragraph 2.3.2.3.3 λ3-iodanes as radical traps under photocatalyst mediated transformations, selected examples: a. Zhou, Q.; Guo, W.; Ding, W.; Wu, X.; Chen, X.; Lu, L.; Xiao, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199. b. Le Vaillant, F.; Courant, T.; Waser, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204.
16. For methyl acetate: BDE($MeC(O)CH_2$-H) = 97 kcal.mol^{-1}, taken from: Oyeyemi, V. B.; Keith, J. A.; Carter, E. A. *J. Phys. Chem. A* **2014**, *118*, 7392–7403.
17. We have not found the specific BDE of DCE however the BDE of chloromethane and dichloromethane have been calculated: BDE(Cl_2CH-H) = 100 kcal.mol^{-1} and BDE($ClCH_2$-H) = 103 kcal.mol^{-1}. Taken from: Tschuikow-Roux, E.; Paddison, S. *Int. J. Chem. Kinet.* **1987**, *19*, 15–24.
18. With **HIR.14** a reduction is required to generation the iodanyl radical
19. Lei, G.; Xu, M.; Chang, R.; Funes-Ardoiz, I.; Ye, J. *J. Am. Chem. Soc.* **2021**, *143*, 11251–11261.
20. Due to overlap with the other signal the error on this value is greater than the standard 5% of ^{1}H NMR.
21. DMSO-d_6 could not be used du to the overlapping shifts of **6.1**, **6.2** and the traces of CH_2Cl_2.
22. We tried to monitor the reaction by sampling a single reaction with an inert internal standard (trimethyl phenylsilane), however, after4 hours of reaction time no conversion was observed.
23. X_{norm} is the normalised quantity of the desired species and is calculated following: $X_{norm} = \frac{X}{X_{max}} \times 100$. where, X = equivalents of compound estimated by ^{1}H NMR, X_{max} = maximum number of equivalents
24. Jia, K.; Chen, Y. Photochemistry of Hypervalent Iodine Compounds. In *PATAI'S Chemistry of Functional Groups*; American Cancer Society, 2018; pp 1–42.
25. This result is not surprising: 30 mol% of BIOH has been used to activate α-ketoesters under sunlight irradiation in presence of bromoalkynes. The authors propose the in-situ formation of bromobenziodoxolone (an analogue of **HIR.18**), which allows the reaction to proceed with a substoichiometric quantity of BIOH. It therefore seems logical that our oxalates could undergo a similar activation. Tan, H.; Li, H.; Ji, W.; Wang, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 8374–8377.
26. See supporting information of these references: a. Wu, J.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 11107–11111. b. Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. *Chem. Sci.* **2018**, *9*, 5883–5889.
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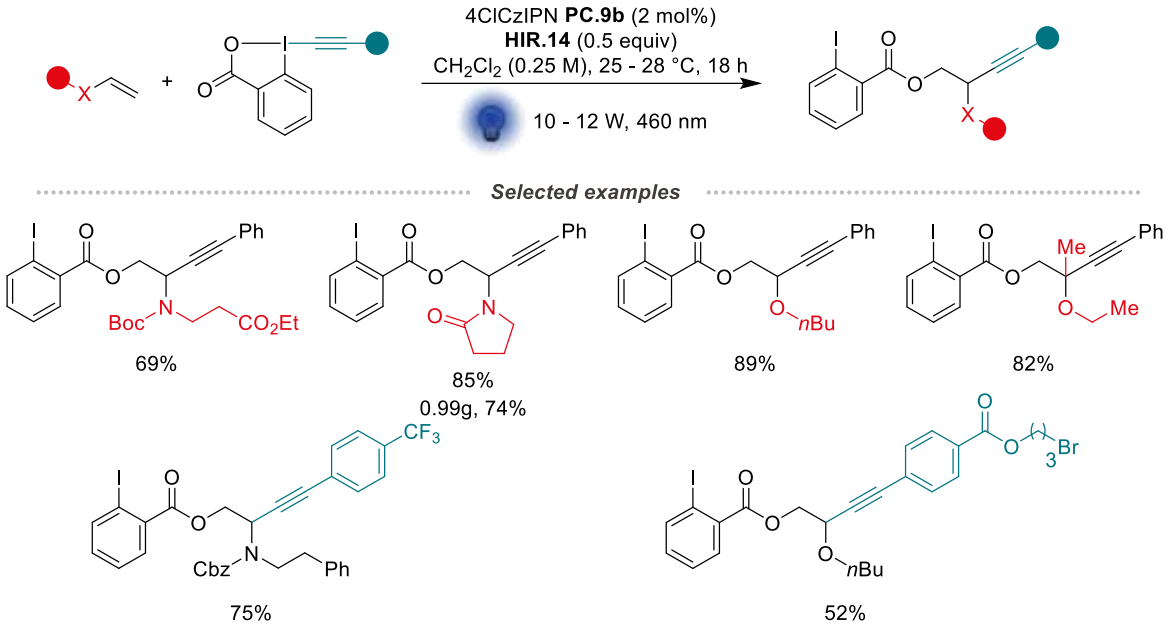
29. For hypervalent iodine species ε_{max} ($S_0 \rightarrow T_n$) < 30 $L.mol^{-1}.cm^{-1}$ taken from Nakajima, M.; Nagasawa, S.; Matsumoto, K.; Kuribara, T.; Muranaka, A.; Uchiyama, M.; Nemoto, T. *Angew. Chem. Int. Ed.* **2020**, *59*, 6847–6852.
30. This value was determined in an approximative fashion by observing the flattening of the curve (it gives an underestimation of the real value). This value should be close to the vibronic 0-0 transition of what we believe to be the triplet state, which is normally calculated from the phosphorescence trace. Unfortunately we were unable to perform the phosphorescence analysis, further work is being performed in this direction confirming our initial approximation. The 0-0 vibronic transition of the singlet state seems to be approximately around 390 nm (determined by the intercept of the absorption trace and the estimated prolongation of the fluorescence trace).
31. Unfortunately due to the unavailability of the potentiostat normally used for our electrochemical analyses, the CVs of the other reagents (**HIR.2b**, **HIR.2e** and **HIR.3**) have not been measured precisely. Using an IKA ElectraSyn we have a rough estimation of their redox potentials in the excited state:
$E_{1/2}$(**HIR.2b*/HIR.2b**) ≈ + 1.7 ± 0.1 V vs SCE; $E_{1/2}$(**HIR.2e*/HIR.2e**) ≈ + 2.0 ± 0.1 V vs SCE and $E_{1/2}$(**HIR.3*/HIR.3**) > + 2 V vs SCE.
32. Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* **2017**, *8*, 1790–1800.
33. 6% of Cl_2CH-alkyne were obtained with the optimised conditions
34. Voutyritsa, E.; Garreau, M.; Kokotou, M. G.; Triandafillidi, I.; Waser, J.; Kokotos, C. G. *Chem. – Eur. J.* **2020**, *26*, 14453–14460.

Chapter 7: Conclusions and Outlook

7. General conclusion and Outlook

The research projects discussed in this thesis aimed to develop alkynylation strategies with EBX reagents under photochemical activation. When considering the state of the art in the field, we had identified two initial objectives: (1) an alkynylative difunctionalisation of alkenes and (2) the conversion of alcohols into alkynes.

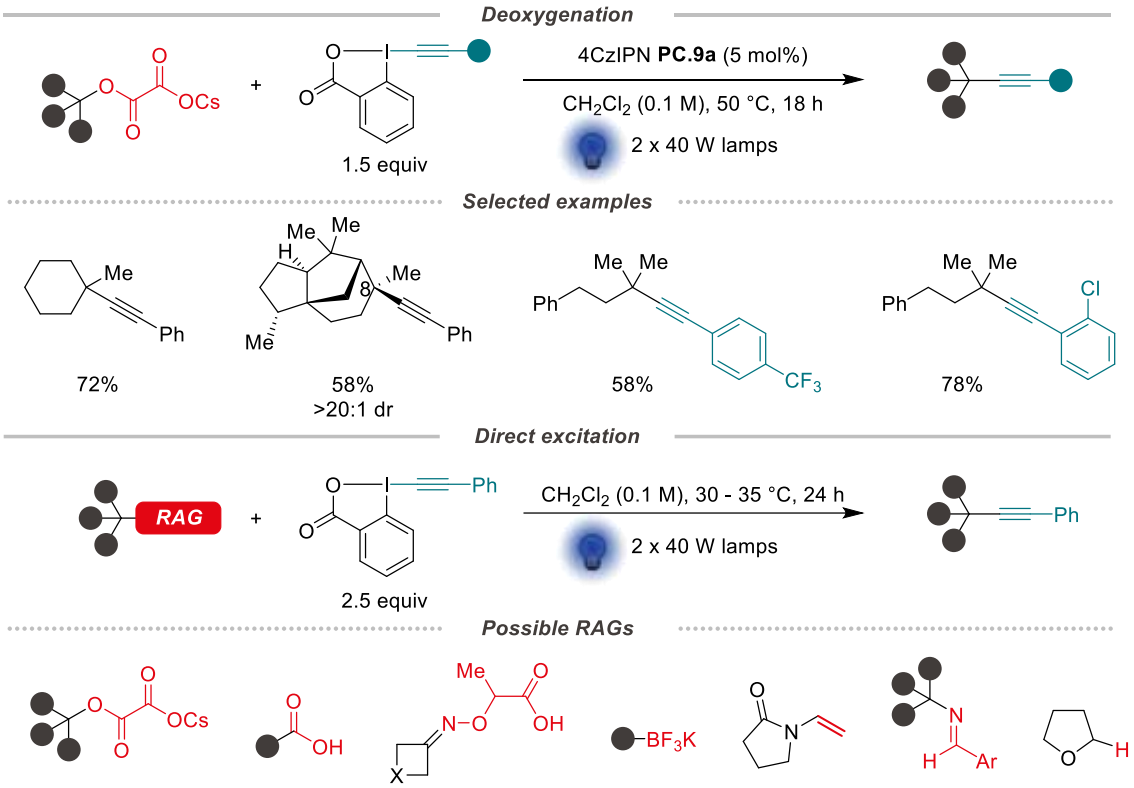
With the first project, we were able to develop an atom-economical oxyalkynylation of ene-carbamates and enol ethers to access 1-alkynyl-1,2-amino alcohol and diol scaffolds (Scheme 7.1). Our strategy tolerated a variety of ArEBXs and used 4ClCzIPN as an organic dye and **HIR.14** as an additive. Our mechanistic studies suggested that the reaction was proceeding through the oxidation of the alkene to the radical cation intermediate, although a radical chain process could still be occurring in the background. Interestingly, our data suggested that the difunctionalisation of the ene-carbamates was most likely associated to a reductive quenching cycle, in contrast to the enol ethers, which most likely were difunctionalised through an oxidative quenching cycle.



Scheme 7.1. Alkynylative difunctionalisation of ene-carbamates and enol ethers.

In our second project, we developed a deoxyalkynylation strategy of cesium oxalates that can be easily accessed from tertiary alcohols. Our optimised conditions used 4CzIPN as a photocatalyst and a variety of ArEBX as an alkyne source (Scheme 7.2). The key element to the success of this reaction lied in the choice of the light source: we had to use two 40 W 440 nm lamps to ensure high yields and generality of the method. We attempted to extend the deoxyalkynylation to deoxycyanation and dethioalkynylation, however, the preliminary investigations of both transformations did not lead to synthetically relevant yields of the desired products. During the investigation of the deoxyalkynylation, we discovered the photoactivity of

PhEBX using two 40 W 440 nm lamps. We decided to explore this for the development of photocatalyst-free EBX-mediated alkynylations. We found that by using 2.5 equiv of the EBX, we can perform a deoxyalkynylation of cesium oxalates, a decarboxylative alkynylation, a decarboxylation-alkynylation ring-opening cascade, a deboronative alkynylation, a difunctionalisation of an enamide and the alkynylation of THF – transformations that had previously required a photocatalyst to proceed. It also allowed us to discover a deaminative alkynylation strategy using an electron-rich imine. Our mechanistic studies suggest that the excited state EBX reagent can act as photooxidant, and in the case of the alkynylation of THF it could initiate a radical chain process proceeding through HAT.



Scheme 7.2. Photocatalyst-meditation deoxyalkynylation and direct excitation of PhEBX for redox active group activation.

Based on the advances made with these projects, we can envisage further research towards the introduction of alkynes under photochemical activation and the use of excited state hypervalent iodine reagents.

1. The development of a multicomponent alkynylative difunctionalisation of enamides would be highly relevant: the incorporation of diverse nucleophiles, such as amines or phosphines, for example, could give access to 1,2-diamines or 1,2-phosphinoamines which could be interesting for the development of new bidentate ligands. In this regard, the development of an asymmetric strategy would be undeniably valuable. Considering the recent advances in copper chemistry, this strategy seems very promising. In particular, the

decarboxylative alkynylation from Zhu and Messaoudi[1] demonstrates that copper catalysis can be combined with the oxidation of a substrate under photoredox catalysis.

2. The investigation of C-N cleavage for alkynylation is of high interest: with our preliminary data associated to a deaminative alkynylation, we could envisage the development of this strategy using either the direct excitation of EBXs or by developing a photocatalysed process. Where the use of these imines on small molecules would only be an extension to the pre-existing strategies for alkylation and arylation,[2] its application to biomolecules would be a highly valuable strategy. Indeed, *N*-terminus selective bioconjugation strategies are scarce.[3] Furthermore, the EBXs have frequently been used under biocompatible conditions and for bioconjugation.[4] This type of strategy could also enable a lysine selective bioconjugation strategy.

3. Gaining greater understanding on the photophysical processes associated to the direct photoexcitation of EBXs would be useful. The nature of the excited state EBX is currently ongoing photophysical investigation to further understand how it can promote reactions in absence of a photocatalyst. With this data, we could then envisage reagent tuning to: (1) ensure greater functional group tolerance by lowering the redox potential of the excited state or (2) activate more challenging substrates by increasing its redox potential. These reagents could in theory be tuned by the addition of electron-poor or electron-rich substituents to their core. Despite the synthetic simplicity and practicality of using a single reagent for the activation and functionalisation of a substrate, the cost associate to this type of strategy is still high. Indeed, 2.5 equiv of EBX were required for this strategy to work. Investigating, methods to regenerate the EBX reagent in-situ would be highly valuable to allow a lower loading of the reagent. Furthermore, we could also envisage different polyaromatic scaffolds that would ensure greater stability of an iodine (III) species that would be unreactive as a radical trap. This could enable the development of hypervalent iodine based photocatalysts. Finally, we can also envisage the application of the direct excitation of EBXs for the activation of other substrates, our group has recently applied this strategy for a 1,3-difucntionalisation of cyclopropanes and the C-H alkynylation of cyclopropanes.[5]

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[1] Zhu, M.; Messaoudi, S. *ACS Catal.* **2021**, *11*, 6334–6342.
[2] a. Ashley, M. A.; Rovis, T. *J. Am. Chem. Soc.* **2020**, *142*, 18310–18316. b. Dorsheimer, J. R.; Ashley, M. A.; Rovis, T. *J. Am. Chem. Soc.* **2021**, *143*, 19294–19299.
[3] Boutureira, O.; Bernardes, G. J. L. *Chem. Rev.* **2015**, *115*, 2174–2195.
[4] a. Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. *J. Am. Chem. Soc.* **2014**, *136*, 2280–2283. b. Tessier, R.; Ceballos, J.; Guidotti, N.; Simonet-Davin, R.; Fierz, B.; Waser, J. *Chem* **2019**, *5*, 2243–2263. c. Garreau, M.; Le Vaillant, F.; Waser, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 8182–8186. d. Ceballos, J.; Grinhagena, E.; Sangouard, G.; Heinis, C.; Waser, J. *Angew. Chem. Int. Ed.* **2021**, *60*, 9022–9031.
[5] Preprint available online: Nguyen, T. V. T.; Waser, J. ChemRXiv, **2022**, DOI:10.26434/chemrxiv-2022-vf5gm

Chapter 8: Experimental procedures and characterisation data

8. Experimental procedures and characterisation data

8.1. General methods

All reactions that were carried out in oven dried glassware and under an atmosphere of nitrogen is stated at the start of the reaction conditions. For flash chromatography, distilled technical grade solvents were used. THF, CH_3CN, toluene, Et_2O 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, Fluka, VWR, TCI, 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 glass plates and visualized with UV light and *p*-anisaldehyde stain (EtOH:H2SO4:AcOH:*p*-anisaldehyde 135:5:1.5:3.7 V:V:V:V).

^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-*d*, acetonitrile-d^3 CD_3OD, DMSO-d_6 or acetone-d_6, all signals Are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal acetonitrile signal at 1.94 ppm, the internal methanol signal at 3.30 ppm, the internal DMSO signal at 2.50 ppm or the internal acetone signal at 2.05 ppm as standard. The data is 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-*d*ecoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-*d*, acetonitrile-d^3 CD_3OD, DMSO-d_6 or acetone-d_6, all signals Are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal acetonitrile signal at 1.3 ppm the internal methanol signal at 49.0 ppm, the internal DMSO signal at 39.5 ppm or the internal acetone signals at 29.84 and 206.26 ppm as standard.

Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and is 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.

UV/Vis spectroscopy was performed on an Agilent Cary 60 UV-Vis and steady-state luminescence spectroscopy was recorded on a Varian Cary Eclipse spectrophotometer.

Cyclic voltammetry experiments were performed on a Biologic SP-150 Potentiostat, with a three-electrode cell configuration: a glassy carbon electrode as the working electrode, Pt wire as a counter electrode and an Ag/AgCl (KCl, 3M) electrode as the reference electrode. Bu_4NPF_6 was employed as the electrolyte (0.1 M).

All photochemical reactions were carried out in oven dried glassware and under inert atmosphere (freeze pump thaw solvent stored on molecular sieves and under argon for maximum one week) unless specified otherwise. All reactions were performed under the irradiation of blue LED strips (ca. 12 W, $\lambda_{max} \approx 460$ nm), Kessil lamps (40 W per lamp, 390, 427, 440, 467 nm) or a Rayonet reactor (for 360 nm).

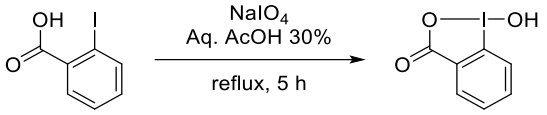
For the blue LED strips: the reactions were performed in 1.5 - 2.5 mL screw-cap vials which were stuck to the base of a crystallization dish. To the crystallization dish (a straight sided 15 cm diameter pyrex dish) were attached the blue LEDs (RUBAN LED 5MÈTRES - 60LED/M - 3528 BLEU - IP65 with Transformateur pour Ruban LED 24W/2A/12V, bought directly on RubanLED.com: 4.8 W/m: for 1 crystallisation dish: 2.5 meters were required total wattage: 12 W). The distance between the LEDs and the test tubes was approximatively 3 cm for all vials and test tubes. In order to keep the temperature as constant as possible all reactions were ventilated by use of an over-head ventilator (desk fan). Long irradiation resulted in temperature increasing up to 27°C during overnight reactions. Without cooling the temperature could rise to 60 °C by covering the dish with aluminium foil.

For the Kessil lamps: the reactions were performed in 2.5 -7.5 mL screw-cap vials, which were stuck to a glass plate, the two Kessil lamps were placed on each side of the vials. In the absence of cooling the reactions would heat up to 50 °C. With cooling by an over-head ventilator the reactions still warmed to 30 - 35 °C.

8.2. Synthesis of hypervalent iodine reagents

The synthesis of reagents **HIR.2a-l**, **HIR.3**, **HIR.14**, **HIR.18** and **HIR.25a** had already been described before by our group. The procedures are taken from the indicated publications. The work-up and purification has been modified for the synthesis of **HIR.2a-i**, the data has been appropriately attributed to the synthetic procedures.

1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (**HIR.18**)

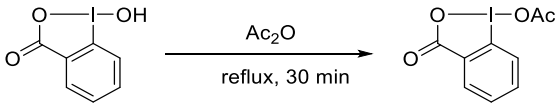


4.1 **HIR.18**

Following a reported procedure,[1] $NaIO_4$ (40.5 g, 189 mmol, 1.05 equiv) and 2-iodobenzoic acid (**4.1**) (44.8 g, 180 mmol, 1.0 equiv) were suspended in 30% (v:v) aq. AcOH (350 mL). The mixture was vigorously stirred and refluxed for 5 h. The reaction mixture was then diluted with cold water (250 mL) and allowed to cool to rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 150 mL) and acetone (3 x 150 mL), and air-*d*ried in the dark overnight to afford 1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (**HIR.18**) (44.3 g, 168 mmol, 93% yield) as a white solid.

^{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, Ar*H*). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4. Consistent with reported data.[1]

1-Acetoxy-1,2-benziodoxol-3-(1H)-one (**HIR.14**)



HIR.18 **HIR.14**

Following a reported procedure,[2] compound **HIR.18** (3.00 g, 11.3 mmol, 1.00 equiv) was heated in Ac_2O (10 mL) to reflux until the solution turned clear (without suspension, ca. 30 min). The mixture was then left to cool down and white crystals started to form. The crystallization was continued at -18 °C. The crystals were then collected and dried overnight under high vacuum to give compound **HIR.14** (3.06 g, 10.0 mmol, 86% yield).

^{1}H NMR (400 MHz, Chloroform-d_3) δ 8.25 (dd, 1 H, J = 7.6, 1.4 Hz, Ar*H*), 8.00 (dd, 1 H, J = 8.3, 0.5 Hz, Ar*H*), 7.92 (dt, 1 H, J = 7.0, 1.7 Hz, Ar*H*), 7.71 (td, 1 H, J = 7.6, 0.9 Hz, Ar*H*), 2.25 (s, 3 H, COCH_3). NMR data correspond to the reported values.[2]

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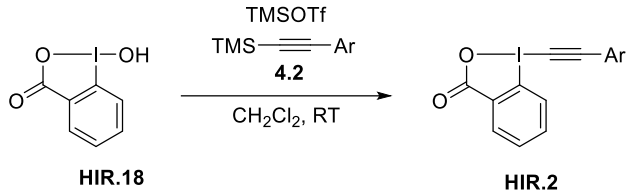
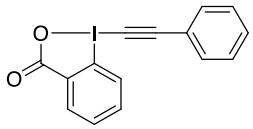
[1] Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem. Eur. J.* **2012**, *18*, 5655.
[2] Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *12*, 2579.

GP1: ArEBX synthesis (**HIR.2a-i**)



Following a reported procedure,[1,3],[4 5] trimethylsilyltriflate (1.1 equiv) was added dropwise to a suspension of 2-iodosylbenzoic acid (**HIR.14**) (1.0 equiv) in CH_2Cl_2 (0.38 ML) at 0 °C. The mixture was stirred for 1 h, followed by the dropwise addition of trimethyl(arylethynyl)silane (**4.2**) (1.1 equiv) (slightly exothermic). The resulting suspension was stirred for 6 h at RT, during this time a white solid was formed. A saturated solution of $NaHCO_3$ (40% of CH_2Cl_2 volume) was added and the mixture was stirred vigorously for 30 min resulting in a biphasic suspension. The suspension was diluted with $CHCl_3$ and water, the solid aggregates could be further dissolved with MeOH (1-5%). The mixture was extracted twice with $CHCl_3$. The combined organic layers were washed 3 times with "water:aq. sat. $NaHCO_3$" (1:1 v:v), and brine. The orgaic layer was then dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting mixture was combined with the solid obtained by recrystallisation in MeCN or EtOAc:MeOH (2:1, ca. 28 mL/g). Filtration at high temperature The mixture was cooled down, filtered and dried under high vacuum to afford ArEBX.

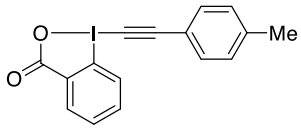
1-(Phenylethynyl)-1,2-benziodoxol-3(1*H*)-one (**HIR.2a**)



Following **GP1**: with **HIR.18** (12.1 g, 45.8 mmol, 1.0 equiv) trimethylsilyltriflate (9.1 mL, 50 mmol, 1.1 equiv), and trimethyl(phenylethynyl)silane (8.8 mL, 50 mmol, 1.1 equiv).
Recrystalization: EtOAc:MeOH (2:1, 30 mL/g) afforded PhEBX **HIR.2a** (6.8 g, 20 mmol, 43%)

Colourless to off-white needle like crystals.
Mp (Dec.) 155 – 160 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) 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** (101 MHz, Chloroform-*d*) 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. Consistent with reported data.[1]

1-[4-Methylphenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**HIR.2b**)



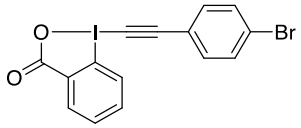
Following **GP1**: with **HIR.18** (1.32 g, 5.00 mmol, 1.00 equiv) trimethylsilyltriflate (1.0 mL, 5.5 mmol, 1.1 equiv), and trimethyl(phenylethynyl)silane (1.04 g, 5.50 mmol, 1.10 equiv).
Recrystalization: EtOAc:MeOH (2:1, 30 mL/g) afforded: **HIR.2b** (0.540 g, 1.49 mmol, 30% yield)

Off-white needle like crystals.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.43 (dd, *J* = 6.1, 2.9 Hz, 1H, Ar*H*), 8.30– 8.14 (m, 1H, Ar*H*), 7.77 (dd, *J* = 6.9, 3.1 Hz, 2H, Ar*H*), 7.50 (d, *J* = 7.8 Hz, 2H, Ar*H*), 7.25 (d, *J* = 7.6 Hz, 2H, Ar*H*), 2.43 (s, 3H, ArC*H*$_3$); **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.6, 141.5, 134.9, 132.8, 132.5, 131.6, 131.3,

[3] Lu, B.; Wu, J.; Yoshikai, N. *J. Am. Chem. Soc.* **2014**, *136*, 11598.
[4] Jia, K.; Zhang, F.; Huang, H.; Chen, Y. *J. Am. Chem. Soc* **2016**, *138*, 1514.
[5] Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. *J. Am. Chem. Soc.* **2014**, *136*, 2280.

129.5, 126.2, 117.4, 116.2, 107.25, 49.1, 21.7. The characterization data corresponded to the reported values.[5]

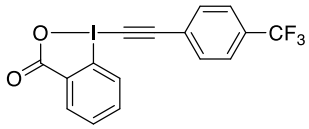
1-[4-Bromophenylethynyl]-1,2-benziodoxol-3(1H)-one (**HIR.2c**)



Following **GP1**: with **HIR.18** (1.3 g, 5.0 mmol, 1.0 equiv) trimethylsilyltriflate (1.0 mL, 5.5 mmol, 1.1 equiv), and trimethyl((4-bromophenyl)ethynyl)silane (1.2 g, 5.5 mmol, 1.1 equiv). Recrystalization: EtOAc:MeOH (3:1, 30 mL/g) afforded: **HIR.2c** (1.4 g, 3.3 mmol, 66%)

Colourless fine needles.
Mp (Dec.) 158-163 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) 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, 2 H, *J* = 8.5 Hz, Ar*H*). **^{13}C NMR** (101 MHz, Chloroform-*d*) 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. Consistent with reported data. [6]

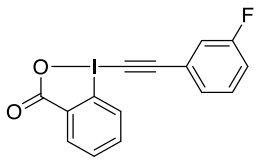
1-[4-Trifluoromethylphenylethynyl]-1,2-benziodoxol-3(1H)-one (**HIR.2d**)



Following **GP1**: with **HIR.18** (1.3 g, 5.0 mmol, 1.0 equiv) trimethylsilyltriflate (1.0 mL, 5.5 mmol, 1.1 equiv), and trimethyl((4-(trifluoromethyl)phenyl)ethynyl)silane (1.3 mL, 5.5 mmol, 1.1 equiv). Recrystalization: MeCN (30 mL/g) affording: **HIR.2d** (1.3 g, 3.2 mmol, 64%)

Colourless needle like crystals.
^{1}H NMR (400 MHz, Chloroform-*d*) 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** (101 MHz, Chloroform-*d*) 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. Consistent with reported data.[3]

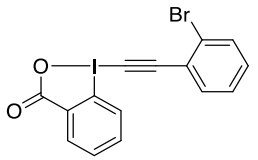
1-[3-Fluorophenylethynyl]-1,2-benziodoxol-3(1H)-one (**HIR.2e**)



Following **GP1**: with **HIR.2e** (1.3 g, 5.0 mmol, 1.0 equiv) trimethylsilyltriflate (1.0 mL, 5.5 mmol, 1.1 equiv), and trimethyl((3-fluorophenyl)ethynyl)silane (1.1 mL, 5.5 mmol, 1.1 equiv). Recrystallisation: EtOAc:MeOH (9:1, 20 mL/g) afforded: **HIR.2e** (787 mg, 2.15 mmol, 43% yield)

Colourless fine needles.
^{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) 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. One carbon is not resolved. **^{19}F NMR** (376 MHz, DMSO-d_6) δ -111.7. Consistent with reported data.[6]

1-[2-Bromophenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**HIR.2f**)

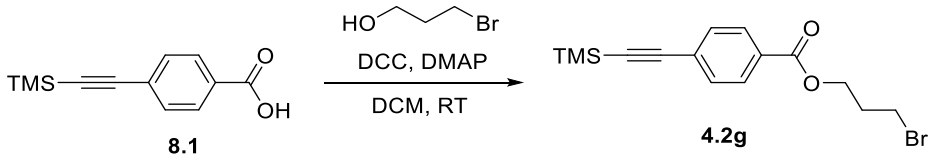


Following **GP1**: with **HIR.18** (1.3 g, 5.0 mmol, 1.0 equiv) trimethylsilyltriflate (1.0 mL, 5.5 mmol, 1.1 equiv), and trimethyl((2-bromophenyl)ethynyl)silane (1.2 g, 5.5 mmol, 1.1 equiv). Recrystallisation: EtOAc:MeOH (3:1, 30 mL/g) afforded: **HIR.2f** (1.5 g, 3.5 mmol, 70%)

[6] Garreau, M.; Le Vaillant, F.; Waser, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 8182.

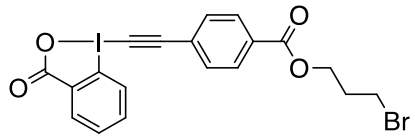
Colourless fine needles.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (td, *J* = 7.3, 2.1 Hz, 2 H, Ar*H*), 7.84 – 7.74 (m, 2 H, Ar*H*), 7.68 (d, *J* = 1.1 Hz, 1 H, Ar*H*), 7.61 (dd, *J* = 7.6, 1.7 Hz, 1 H,*ArH*), 7.36 (m, 2 H, Ar*H*).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.6, 135.2, 134.7, 133.0, 132.7 , 131.8, 131.3, 127.6, 126.8, 126.4, 123.2, 116.5, 104.3, 55.4. Consistent with reported data.[6]

1-[(4-(3-Bromoprop-1-yl-benzoate)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**HIR.2g**)



Following a reported procedure,[6] 4-(dimethylamino)-pyridine (67 mg, 0.55 mmol, 12 mol%) was added to a stirred reaction mixture of 4-((trimethylsilyl)ethynyl)benzoic acid (**8.1**) (1.0 g, 4.6 mmol, 1.0 equiv), dicyclohexylcarbodiimide (1.0 g, 5.0 mmol, 1.1 equiv), 3-bromopropan-1-ol (0.62 mL, 6.9 mmol, 1.5 equiv) in dry CH_2Cl_2 (15 mL) at room temperature. The reaction mixture was filtered after 15 h and the solid was rinsed with dichloromethane (2 x 10 mL). The combined filtrates were concentrated under vacuum. Purification by column chromatography pentane:ethyl acetate 9:1 afforded 3-bromopropyl 4-((trimethylsilyl)ethynyl)benzoate (**4.2g**) (1.3 g, 3.8 mmol, 82 % yield) as a white solid.

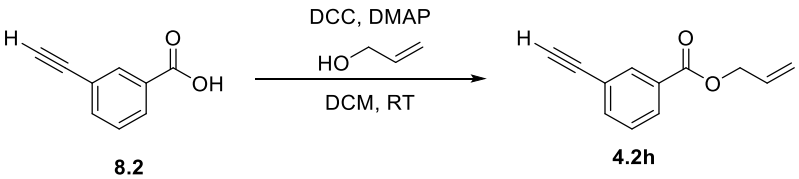
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.52 (d, *J* = 8.7 Hz, 2H, Ar*H*), 4.46 (t, *J* = 6.0 Hz, 2H, OCH_2), 3.54 (t, *J* = 6.6 Hz, 2H, BrCH_2), 2.32 (p, *J* = 6.4 Hz, 2H, CH_2CH_2), 0.26 (s, 9H, TMS). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 165.8, 131.9, 129.5, 129.4, 127.9, 104.0, 97.9, 62.9, 31.8, 29.4, -0.2. The characterisation data corresponds to the reported literature values.[6]



Following **GP1**: with **HIR.18** (0.354 g, 1.34 mmol, 1.00 equiv) trimethylsilyltriflate (0.28 mL, 1.5 mmol, 1.1 equiv), and 3-bromopropyl 4-((trimethylsilyl)ethynyl)benzoate (**4.2g**, 0.500 g, 1.47 mmol).
Recrystallisation: MeCN (40 mL/g) affording: **HIR.2g** (0.430 g, 0.838 mmol, 63% yield)

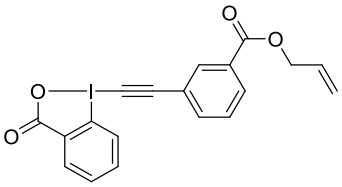
Off-white partially crystalline solid.
Mp (dec) = 152 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.51 – 8.35 (m, 1H, Ar*H*), 8.25 (dd, *J* = 7.5, 1.6 Hz, 1H, Ar*H*), 8.14 – 7.95 (m, 2H, Ar*H*), 7.88 – 7.74 (m, 2H, Ar*H*), 7.74 – 7.52 (m, 2H, Ar*H*), 4.51 (t, *J* = 6.0 Hz, 2H, OCH_2), 3.56 (t, *J* = 6.5 Hz, 2H, CH_2Br), 2.35 (p_{app}, *J* = 6.3 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.5, 165.3, 135.1, 132.8, 132.6, 131.8, 131.6, 131.3, 129.8, 126.3, 125.1, 116.1, 105.0, 63.3, 54.1, 31.7, 29.2. **IR** (ν_{max}, cm^{-1}) 3017 (m), 2987 (m), 2971 (m), 2912 (m), 2902 (m), 2154 (m), 1710 (m), 1619 (s), 1600 (s), 1553 (m), 1437 (m), 1392 (m), 1330 (s), 1272 (s), 1258 (s), 1210 (m), 1178 (m), 1102 (s), 1083 (s), 1076 (s), 1016 (m). **HRMS** (ESI/QTOF) m/z $[M + H]^+$ Calcd for $C_{19}H_{14}{}^{79}BrIO_4{}^+$ 512.9193; Found 512.9208 Calcd for $C_{19}H_{14}{}^{81}BrIO_4{}^+$ 514.9195; Found 514.9191.

1-[(3-(Prop-2-en-1-yl-benzoate)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**HIR.2h**)



N,N-dimethylpyridin-4-amine (0.050 g, 0.41 mmol) was added to a stirred reaction mixture of 3-ethynylbenzoic acid (**8.2**, 0.500 g, 3.42 mmol), *N,N'*-methanediylidenedicyclohexanamine (0.777 g, 3.76 mmol) and prop-2-en-1-ol (0.349 mL, 5.13 mmol) in dry CH_2Cl_2 (14 mL) at RT The reaction mixture was filtered after 15 h and the solid was rinsed with dichloromethane (2 x 5 mL). The combined filtrates were concentrated under vacuum. Purification by column chromatography with pentane:ethyl acetate 10:0 to 9:1 afforded prop-2-en-1-yl 3-(ethynyl)benzoate (**4.2h**, 0.570 g, 3.06 mmol, 89% yield) as a colorless oil.

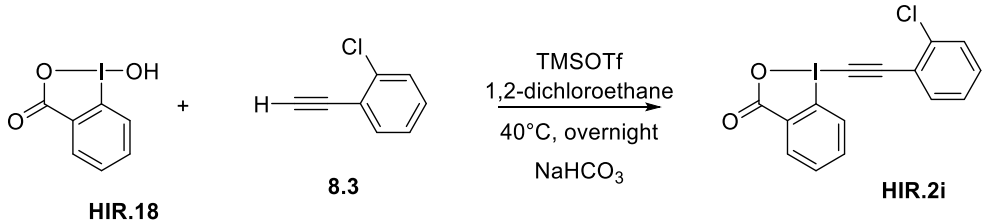
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (t, *J* = 1.7 Hz, 1H, Ar*H*), 8.04 (dt, *J* = 7.9, 1.5 Hz, 1H, Ar*H*), 7.67 (dt, *J* = 7.7, 1.5 Hz, 1H, Ar*H*), 7.41 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.04 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H, C*H*=CH_2), 5.42 (dq, *J* = 17.2, 1.5 Hz, 1H, CH=CH_2), 5.30 (dq, *J* = 10.5, 1.3 Hz, 1H, CH=CH_2), 4.83 (dt, *J* = 5.7, 1.4 Hz, 2H, CH_2-CH=CH_2), 3.13 (s, 1H, aklynyl*H*). Compound was used directly in next step with no further analysis.



Following **GP1**: with **HIR.18** (0.500 g, 1.89 mmol, 1.00 equiv) trimethylsilyltriflate (0.4 mL, 2 mmol, 1.1 equiv), and allyl 3-ethynylbenzoate (4**.2h**, 0.388 g, 2.08 mmol, 1.10 equiv). Crystallization from CH_2Cl_2:heptane (3:1 total volume 40 mL), fridge for 1h then RT for 4 hours, filtration washing with ether affording: **HIR.2h** (0.312 g, 0.722 mmol, 38% yield)

Off-white partially crystalline solid
Mp (dec.) = 60 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.48 – 8.34 (m, 1H, Ar*H*), 8.29 (d, *J* = 1.8 Hz, 1H, Ar*H*), 8.29 – 8.21 (m, 1H, Ar*H*), 8.17 (dt, *J* = 7.9, 1.5 Hz, 1H, Ar*H*), 7.85 – 7.72 (m, 3H, Ar*H*), 7.54 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.05 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H, C*H*=CH_2), 5.44 (dq, *J* = 17.2, 1.5 Hz, 1H, CH=CH_2), 5.33 (dq, *J* = 10.3, 1.3 Hz, 1H, CH=CH_2), 4.86 (dt, *J* = 5.7, 1.4 Hz, 2H, CH_2-CH=CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.5, 165.0, 136.8, 135.1, 134.0, 132.6, 131.8, 131.8, 131.7, 131.3, 131.0, 129.0, 126.3, 121.1, 118.9, 116.1, 105.1, 66.1, 51.9. **IR** (ν_{max}, cm^{-1}) 2986 (s), 2973 (s), 2900 (s), 2196 (w), 1717 (s), 1599 (m), 1407 (m), 1271 (s), 1241 (s), 1066 (s). **HRMS** (ESI/QTOF) m/z $[M + H]^+$ Calcd for $C_{19}H_{14}IO_4^+$ 432.9931; Found 432.9934.

1-[2-Chlorophenylethynyl]-1,2-benziodoxol-3(1H)-one (**HIR.2i**)

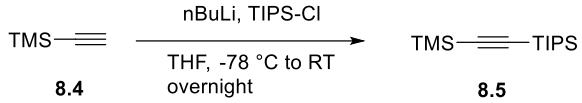


Following a slightly modified reported procedure, trimethylsilyl triflate (0.40 mL, 2.2 mmol, 1.2 equiv) was added to a suspension of 2-iodosylbenzoic acid (**HIR.18**, 0.548 g, 2.08 mmol, 1.1 equiv) in DCE (5.8 mL) at RT The resulting suspension was stirred for 1 h, followed by the drop wise addition of (2-chlorophenyl)acetylene (**8.3**, 0.26 mL, 0.19 mmol, 1.0 equiv). The resulting suspension was stirred for 15 h at 40 °C A saturated solution of $NaHCO_3$ (20 mL) was then added and the mixture was stirred vigorously for 30 minutes resulting in a persistent emulsion/suspension. Water (5 mL) was added, followed by chloroform (15 mL) and MeOH (ca. 0.5 mL) resulting in 2 clear layers. The two layers were seperated and the organic layer was washed with sat. $NaHCO_3$ (5 mL), dried over Na_2SO_4, filtered and evaporated under

reduced pressure. The resulting solid was recrystallized from EtOAc:MeOH (7:3 v:v, ca. 10 mL). The mixture was cooled down overnight in the freezer (-20 °C), filtered and washed with Et_2O to afford **HIR.2i** (0.217 g, 0.567 mmol, 30% yield) as a white crystalline solid.

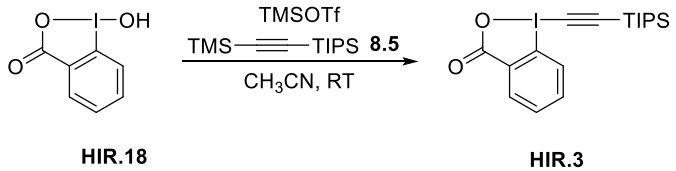
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.46 – 8.38 (m, 2H, Ar*H*), 7.84 – 7.73 (m, 2H, Ar*H*), 7.62 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar*H*), 7.50 (dt, *J* = 8.2, 1.2 Hz, 1H, Ar*H*), 7.46 – 7.37 (m, 1H, Ar*H*), 7.33 (td, *J* = 7.6, 1.3 Hz, 1H, Ar*H*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.6, 137.2, 135.2, 134.5, 132.7, 131.8, 131.7, 131.3, 129.9, 127.0, 126.7, 121.0, 116.4, 102.7, 56.0. Consistent with reported data[7]

1-[(Tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **HIR.3**)[8]



Following a reported procedure,[9] *n*-butyllithium (2.5 M in hexanes, 28 mL, 70 mmol, 0.98 equiv) was added dropwise to a stirred solution of ethynyltrimethylsilane (**8.4**) (7.0 g, 71 mmol, 1.0 equiv) in THF (100 mL) at -78 °C. The mixture was warmed to 0 °C and stirred for 5 min. The mixture was then cooled back to -78 °C and chlorotri*iso*propylsilane (15 mL, 71 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 (100 mL) was added, and the reaction mixture was extracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with water and brine, then dried over MgSO4, filtered and concentrated under reduced pressure to obtain a colorless liquid which was further purified by filtration on silica eluting with pentane (500 mL) to yield **8.5** (16 g, 64 mmol, 90% yield) as a colorless liquid.

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 1.08 (m, 21H, TIPS), 0.18 (s, 9H, TMS). Consistent with reported data.[9]



Following a reported procedure,[10] 2-iodosylbenzoic acid (**HIR.18**) (8.0 g, 30 mmol, 1.0 equiv) was charged in an oven-*d*ried round-bottomed 250 mL flask equipped with a magnetic stirrer. The solid was placed under a nitrogen atmosphere and anhydrous acetonitrile (100 mL) was added. The mixture was cooled to 0 °C. Trimethylsilyltriflate (6.0 mL, 33 mmol, 1.1 equiv) was

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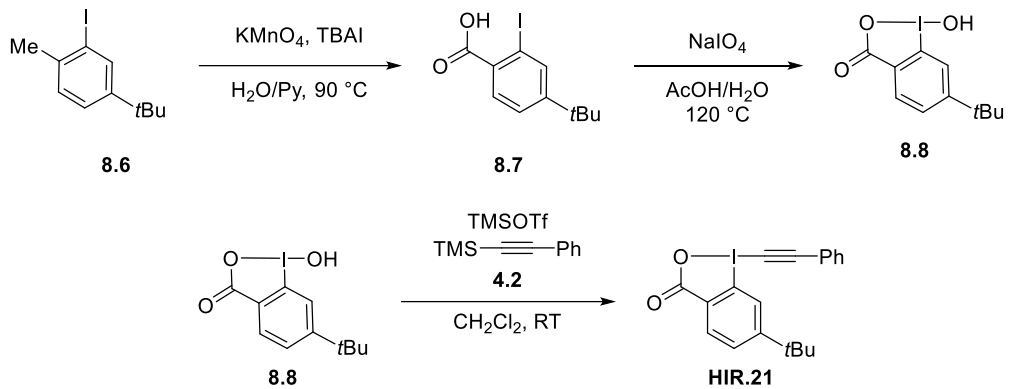
[7] Li, M.; Li, W.; Lin, C.-D.; Wang, J.-H.; Wen, L.-R. *J. Org. Chem.* **2019**, *84* (11), 6904–6915.
[8] In this methodology TIPS-EBX (**HIR.3**) was obtained using its previous synthetic strategy however recently we have developed a one-pot proceedure: Hari, D. P.; Caramenti, P.; Schouwey, L.; Chang, M.; Nicolai, S.; Bachert, D.; Wright, T.; Orella, C.; Jerome Waser, J. *Org. Process Res. Dev.* **2020**, *24*, 106.
[9] Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938.
[10] Brand, J. P.; Waser, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 7304.

added dropwise. After 15 min, (trimethylsilyl)(tri*iso*propylsilyl)acetylene (**8.5**, 8.5 g, 33 mmol, 1.1 equiv) was added dropwise. After 30 min, the suspension became an orange solution. Pyridine (2.7 mL, 33 mmol, 1.1 equiv) was added dropwise. After 15 min, the reaction mixture was transferred in a one-neck 500 mL flask and concentrated under vacuum to afford a yellow solid. The solid was dissolved in CH_2Cl_2 (100 mL) and transferred in a 500 mL separatory funnel. The organic layer was washed with a 1 M HCl solution (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (2 x 100 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (40 mL) afforded TIPS-EBX (**HIR.3**) (9.2 g, 21.5 mmol, 71% yield) as colorless crystals.

Mp (Dec.) 170-176 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) *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, Chloroform-*d*) δ 166.4, 134.6, 132.3, 131.4, 131.4, 126.1, 115.6, 114.1, 64.6, 18.4, 11.1. **IR** v 2943 (m), 2865 (m), 1716 (m), 1618 (m), 1604 (s), 1584 (m), 1557 (m), 1465 (m), 1439 (w), 1349 (m), 1291 (m), 1270 (w), 1244 (m), 1140 (m), 1016 (m), 999 (m), 883 (m), 833 (m), 742 (m), 702 (s), 636 (m). Consistent with reported data.[10]

4-tert-butyl-1-[phenylethynyl]-1,2-benziodoxol-3(1H)-one (**HIR.21**)



From a modification of known procedures,[11] to the solution of 4-*tert*-butyl-2-iodo-1-methylbenzene **8.6** (6.8 g, 25 mmol, 1 equiv) in H_2O/pyridine (85 mL : 106 mL), was added $KMnO_4$ (15.6 g, 99.0 mmol, 4 equiv) and $nBuN_4I$ (137 mg, 0.371 mmol, 1.5 mol %). The purple mixture was heated to reflux for 4 days. It was then allowed to cool down to room temperature and the solids were filtered off through a pad of celite, which was then washed with aq. NaOH (2.0 M). Most of the pyridine was removed from the filtrate by evaporation under reduced pressure. The aqueous residue was washed with diethyl ether (3 x 100 mL) and it then acidified until pH < 2 by careful addition of aq. HCl (37% v/v). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic extracts were dried over $MgSO_4$, filtered

[11] Declas, N.; Le Vaillant, F.; Waser. J.; *Org. Lett.* **2019**, 21, 524–528.

and concentrated under vacuum to provide the 4-(*tert*-butyl)-2-iodobenzoic acid **8.7** (3.88 g, 12.8 mmol, 52%) as a yellowish solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 1.8Hz, 1H, Ar*H*), 7.97 (d, *J* = 8.2Hz, 1H, Ar*H*), 7.45 (dd, *J* = 8.2, 1.8Hz, 1H, Ar*H*), 1.31 (s, 9H, C*H*$_3$). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 171.6, 158.0, 139.6, 132.3, 130.2, 125.5, 95.5, 35.1, 31.1. The compound was used directly in the next step with no further analysis.

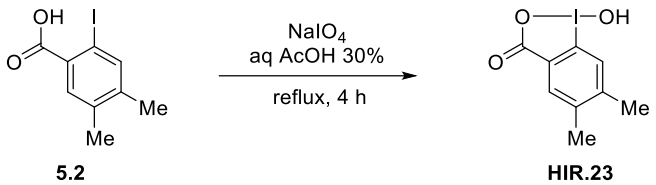
Following a reported procedure,[11] $NaIO_4$ (2.67 g, 12.5 mmol, 1.05 equiv) and 4-(*tert*-butyl)-2-iodobenzoic acid (**8.7**) (3.80 g, 12.5 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (24 mL). The mixture was vigorously stirred and refluxed (140 °C) for 4 h. The reaction mixture was then allowed to cool to room temperature, protecting it from light. The bottom of the flask was scratched with a spatual in order to induce the crystallization. The flask was then cooled to -18 °C (by transferring it into a freezer) and kept at this temperature for 3 hours. The precipitated white crystalline solid was then collected by filtration and washed with several portions of pentane to provide **8.8** (3.47 g, 10.8 mmol, 87%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (s, 1H, O*H*), 7.92 (d, *J* = 7.8Hz, 1H, Ar*H*), 7.81 (s, 1H, Ar*H*), 7.74 (d, *J* = 7.8Hz, 1H, Ar*H*), 1.35 (s, 9H, C*H*$_3$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 168.6, 158.8, 131.8, 130.0, 128.8, 123.3, 121.5, 36.5, 31.8. The compound was used directly in the next step with no further analysis.

Following a odified reported procedure,[1] in an oven dried flask **8.8** (7.32 g, 27.7 mmol, 1.0 equiv) was suspended in CH_2Cl_2 (anhydrous; 8.5 mL). At room temperature, TMSOTf (0.62 mL, 3.4 mmol, 1.1 equiv) was added dropwise to the mixture, resulting in the formation of a clear green solution that rapidly became dark yellow and finally a pale yellow suspension (after 15 minutes from the reaction starting). The latter was stirred for 1 hour at room temperature and then trimethyl(phenylethynyl)silane (0.68 mL, 3.4 mmol, 1.1 equiv) was also added dropwise. The mixture turned into a pale yellow/brown clear solution, which then became an off-white suspension and was stirred at room temperature for 6 hours. After this time, sat. aq. $NaHCO_3$ (8.5 mL) was added and the mixture was vigorously stirred for 15 minutes, becoming a thicker yellow suspension. The solid was filtered off. The two-layer liquid filtrate was separated and the organic layer was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The previously collected solid was dissolved in CH_2Cl_2 (+ a 10% v/v portion of EtOAc to achieve complete dissolution) and the resulting solution was further washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$. The solution was combined with the previous part of the crude product and concentrated. The resulting solid was combined with the the solid obtained from the previous filtration and boiled in acetonitrile (75 mL) for 15 minutes. The suspension was allowed to cool down to room temperature. The precipitated solid was collected by filtation and washed with MeCN and pentane affording **HIR.21** as a colorless solid (0.842 g, 2.08 mmol, 67 % yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (dd, *J* = 4.7, 3.2 Hz, 2H, Ar*H*), 7.76 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar*H*), 7.63 – 7.52 (m, 2H, Ar*H*), 7.52 – 7.36 (m, 3H, Ar*H*), 1.38 (s, 9H, *t*Bu). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.7, 159.5, 132.5, 132.0, 130.7, 129.1, 128.8, 128.7, 122.8, 120.6, 116.7, 106.5, 36.0, 31.2. One carbon is not resolved. **HRMS** (ESI/QTOF) m/z [M + H]$^{+}$ Calcd for $C_{19}H_{17}IO_2^{+}$ 405.0346; Found 405.0345.

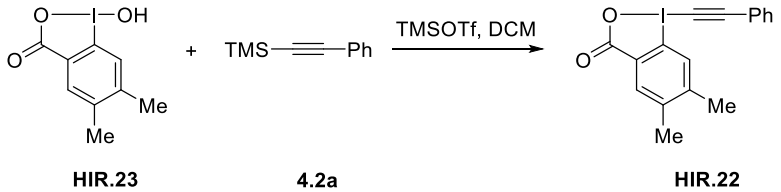
4,5-Dimethyl-1-hydroxy-1,2-benziodoxol-3-(1H)-one (**HIR.23**)



Following a reported procedure,[1] $NaIO_4$ (0.81 g, 3.8 mmol, 1.05 equiv) and 2-iodo-4,5-dimethylbenzoic acid (**5.2**) (1.00 g, 3.62 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (4.8 mL). The mixture was vigorously stirred and refluxed for 3 h30. The reaction mixture was then diluted with cold water (8 mL) and allowed to cool to rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 5 mL) and acetone:water (1:1) (5 mL), and N_2-dried in the dark to give the pure product **HIR.23** (1.00 g, 3.25 mmol, 90%) as a colorless solid (95% purity by ^{1}H NMR).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H, O*H*), 7.78 (s, 1H, Ar*H*), 7.54 (s, 1H, Ar*H*), 2.38 (s, 3H, *Me*), 2.37 (s, 3H, *Me*).**^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.9, 144.2, 139.4, 131.8, 129.2, 126.3, 117.0, 20.1, 18.9. **HRMS (ESI)** calcd for $C_9H_{10}IO_3^{+}$ [M+H]$^{+}$ 292.9669; found 292.9667

4,5-Dimethyl-1-[phenylethynyl]-1,2-benziodoxol-3(1H)-one (**HIR.22**)

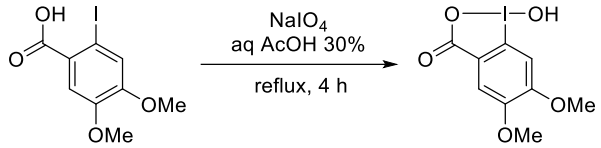


Following a modified reported procedure,[1] trimethylsilyltriflate (0.64 mL, 3.5 mmol, 1.1 eq.) was added dropwise to a stirred solution of 4,5-dimethyl-2-iodosylbenzoic **16b** (0.94 g, 3.2 mmol, 1 equiv) in CH_2Cl_2 (16 mL) at RT. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of trimethyl(phenylethynyl)silane (**50**) (0.69 mL, 3.5 mmol, 1.1 equiv) (slightly exothermic). The resulting suspension was stirred for 6 h at RT, during this time a white solid was formed. A saturated solution of $NaHCO_3$ (10 mL) was then added and the mixture was stirred vigorously. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was recrystallized in CH_3CN (40 mL) to afford the expected reagent (758 mg, 2.02 mmol, 63%) as a colorless solid. The mother liquors was condensed then reflux in CH_3CN (4 mL), filtered and washed with cold CH_3CN

and pentane and dried under high vacuum to afford the reagent **27b** (100 mg, 0.266 mmol, 8.3%, not pure) as a colorless solid. Combined yield: 71%.

Mp (Dec.) 159.9 – 160.8 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.16 (s, 1H, Ar*H*), 7.90 (s, 1H, Ar*H*), 7.72 – 7.57 (m, 2H, Ar*H*), 7.57 – 7.40 (m, 3H, Ar*H*), 2.41 (d, *J* = 7.3 Hz, 6H, 2 x C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.1, 145.2, 141.2, 133.2, 132.8, 130.7, 128.9, 128.8, 126.5, 120.7, 112.6, 106.2, 20.7, 19.4. (1C not resolved) **IR** (ν_{max}, cm^{-1}) 3052 (m), 2900 (m), 2130 (s), 1648 (s), 1469 (s), 1382 (s), 1277 (s), 1073 (s). **HRMS** (ESI/QTOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{14}IO_2^+$ 377.0033; Found 377.0031.

4,5-Dimethoxy-1-hydroxy-1,2-benziodoxol-3-(1H)-one (**HIR.24**)

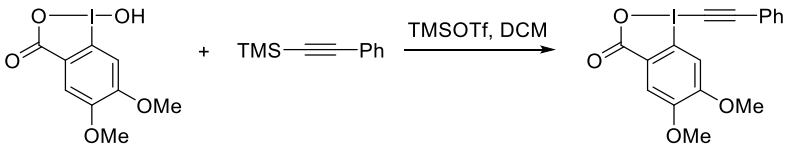


5.3 **HIR.24**

Following a reported procedure,[12] $NaIO_4$ (840 mg, 3.95 mmol, 1.05 equiv) and 4,5-dimethoxy-2-iodobenzoic acid (**5.3**) (1.16 g, 3.76 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (1.8 mL in 4.5mL of H_2O). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (20 mL) and allowed to cool to rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 10 mL) and acetone (3 x 10 mL), and air-dried in the dark to give the pure product **HIR.24** (1.22 g, 3.76 mmol, >99%) as a colorless solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 7.99 (bs, 1 H, O*H*), 7.44 (s, 1 H, Ar*H*), 7.22 (s, 1 H, Ar*H*), 3.88 (bs, 6 H, OC*H*$_3$); **^{13}C NMR** (100 MHz, DMSO-d6) δ 168.6, 154.1, 150.8, 124.3, 112.5, 110.9, 107.5, 56.2, 56.0. The compound was used directly in next steps with no further analysis.

4,5-Dimethoxy-1-[phenylethynyl]-1,2-benziodoxol-3(1H)-one (**HIR.20**)



HIR.24 **4.2a** **HIR.20**

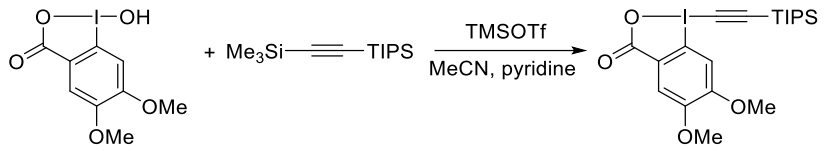
Following a reported procedure,[13] trimethylsilyl triflate (1.47 mL, 8.15 mmol, 1.10 equiv) was added to a suspension of **HIR.24** (2.40 g, 7.41 mmol, 1.00 equiv) in CH_2Cl_2 (37 mL) at RT. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of trimethyl(phenylethynyl)silane (1.60 mL, 8.15 mmol, 1.10 equiv). The resulting suspension was stirred for 6 h at RT, during this time a yellow suspension was formed. A saturated solution of $NaHCO_3$ (25 mL) was then added. The two layers were separated and the aqueous layer

[12] Chen, M.; Huang, Z.-T.; Zheng, Q.-Y. *Org. Biomol. Chem.* **2015**, *13*, 8812
[13] Pan, Y.; Jia, K.; Chen, Y.; Chen, Y. *Beilstein J. Org. Chem.* **2018**, *14*, 1215–1221.

was extracted with CH_2Cl_2 (25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was recrystallized in CH_3CN (50 mL) and a few EtOH to afford the reagent (2.41 mg, 5.90 mmol, 80%) as a colorless solid. The mother liquors was reflux in CH_3CN (4 mL), filtered and washed with cold CH_3CN and pentane and dried under high vacuum to afford the reagent **HIR.20** (100 mg, 0.245 mmol, 3.3%) as a colorless solid. Combined yield: 81%.

Mp (Dec.) 176-179 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) 7.89 (s, 1 H; Ar*H*), 7.70 (s, 1 H; Ar*H*), 7.60 (m, 2 H; Ar*H*), 7.50 (m, 3 H; Ar*H*), 4.05 (s, 3 H; C*H*$_3$), 3.98 (s, 3 H; C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) 166.8, 154.9, 152.2, 132.6, 130.8, 128.9, 124.4, 120.5, 113.3, 107.6, 106.3, 105.3, 56.7, 56.4, 51.2. **IR** 3079 (w), 2935 (w), 2854 (w), 2147 (w), 1742 (w), 1623 (s), 1569 (m), 1497 (s), 1442 (m), 1396 (s), 1300 (m), 1272 (s), 1215 (s), 1167 (m), 1128 (w), 1023 (m), 906 (w), 781 (m), 735 (s), 656 (w), 635 (s). **HRMS** (ESI) calcd for $C_{17}H_{14}O_4I^+$ (M+H) 408.9937, found 408.9949.

4,5-Dimethoxy-1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (**HIR.26**)

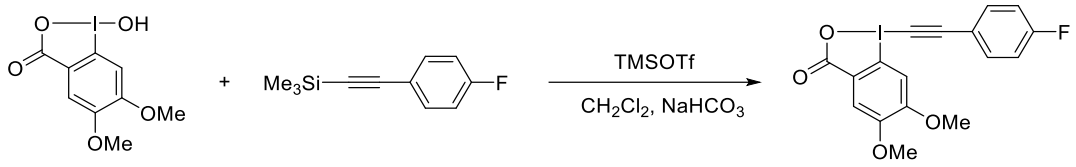


HIR.24 **8.5** **HIR.XX 26?**

Following a modified procedure,[13] trimethylsilyltriflate (400 µL, 2.20 mmol, 1.1 equiv, freshly distilled) was added dropwise to a stirred solution of **16c** (648 mg, 2.00 mmol, 1.0 equiv) in acetonitrile (10 mL). After 2 min, (trimethylsilyl)(tri*iso*-propylsilyl)acetylene (**17**) (560 mg, 2.20 mmol, 1.1 equiv) was added dropwise, followed, after 20 min, by the addition of pyridine (180 µL, 2.20 mmol, 1.1 equiv). The mixture was stirred 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 saturated solution of $NaHCO_3$ (40 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (*ca* 8 mL) and wash with hexanes afforded **5c** (575 mg, 1.18 mmol, 59%) as colorless cristals.

Mp (Dec.) 180-183°C. **^{1}H NMR** (400 MHz, Chloroform-*d*) 7.83 (s, 1 H, Ar*H*), 7.61 (s, 1 H, Ar*H*), 3.99 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 1.14 (m, 21 H, TIPS). **^{13}C NMR** (101 MHz, Chloroform-*d*) 166.7, 154.9, 152.2, 124.5, 113.8, 113.2, 107.8, 104.7, 66.0, 56.7, 56.5, 18.5, 11.2. **IR** 2945 (w), 1616 (m), 1569 (w), 1497 (m), 1464 (w), 1396 (m), 1317 (w), 1269 (m), 1215 (m), 1181 (w), 1129 (w), 1026 (w), 921 (w), 884 (w), 778 (w), 734 (m), 708 (m), 639 (s). **HRMS** (ESI) calcd for $C_{20}H_{30}O_4ISi^+$ (M+H) 489.0958, found 489.0950.

4,5-Dimethoxy-1-[(4-fluorophenyl)ethynyl]-1,2-benziodoxol-3(1H)-one (**HIR.28**)

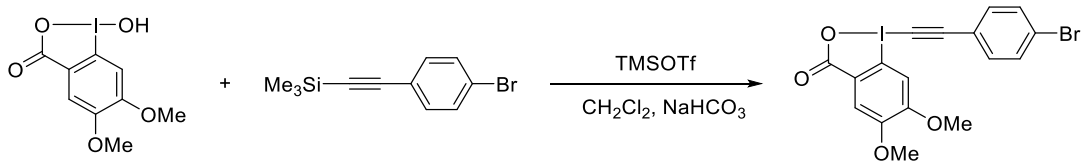


HIR.24 **8.10** **HIR.28**

Following a modified procedure,[13] trimethylsilyl trifluoromethanesulfonate (0.398 mL, 2.200 mmol, 1.10 equiv) was added to a suspension of **HIR.24** (0.648 g, 2.00 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) at RT. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of ((4-fluorophenyl)ethynyl)trimethylsilane (0.446 mL, 2.20 mmol, 1.10 equiv). The resulting suspension was stirred for 6 h at RT, during this time a yellow suspension was formed. A saturated solution of $NaHCO_3$ (5 mL) was then added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was recrystallized in CH_3CN (10 mL) and to afford **HIR.28** (570 mg, 1.33 mmol, 67%) as a colorless solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (s, 1H, Ar*H*), 7.62 (s, 1H, Ar*H*), 7.62 – 7.48 (m, 2H, Ar*H*), 7.24 – 7.05 (m, 2H, Ar*H*), 4.29 – 3.69 (m, 6H, dMeO). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 164.0 (d, *J* = 253.7 Hz) 155.0, 152.3, 134.9 (d, *J* = 8.8 Hz), 124.4, 116.5 (d, *J* = 22.4 Hz), 113.3, 107.6, 105.2 (d, *J* = 13.4 Hz), 56.7, 56.4. The reagent was tested without further analysis.

4,5-Dimethoxy-1-[(4-bromophenyl)ethynyl]-1,2-benziodoxol-3(1H)-one (**HIR.29**)

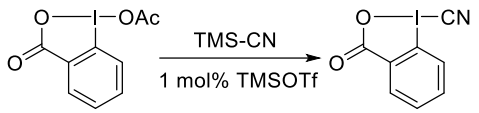


HIR.24 **4.2c** **HIR.29**

Following a modified procedure,[13] trimethylsilyl trifluoromethanesulfonate (0.40 mL, 2.2 mmol, 1.1 equiv) was added to a suspension of **HIR.24** (0.648 g, 2.00 mmol, 1.00 equiv) in CH_2Cl_2 (37 mL) at RT. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of ((4-bromophenyl)ethynyl)trimethylsilane (0.557 g, 2.200 mmol) (solution in 1 mL CH_2Cl_2, rinced with 0.5 mL). The resulting suspension was stirred for 6 h at RT, during this time a yellow suspension was formed. A saturated solution of $NaHCO_3$ (25 mL) was then added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was recrystallized in CH_3CN (50 mL) and a few drops EtOH to afford the reagent **HIR.29** (800 mg, 1.64mmol,82%) as a colorless solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (s, 1H, Ar*H*), 7.70 – 7.52 (m, 3H, Ar*H*), 7.52 – 7.37 (m, 2H, Ar*H*), 4.16 – 3.67 (m, 6H, dMeO). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.8, 155.0, 152.3, 133.9, 132.3, 125.6, 124.4, 113.3, 107.6, 105.2, 104.9, 56.7, 56.5. 2 carbons are not resolved. The reagent was tested without further analysis.

1-Cyano-1,2-benziodoxol-3-(1H)-one (**HIR.25a**)

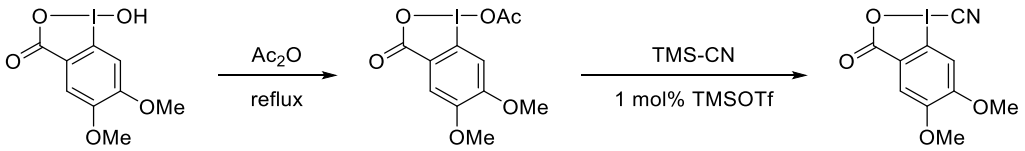


HIR.14 **HIR.25**

Following a reported procedure,[12] **HIR.14** (3.50 g, 11.4 mmol, 1.00 equiv.) was dissolved under nitrogen in dry CH_2Cl_2 (60 mL, 0.19 M). To the clear colourless solution was added via syringe trimethylsilyl cyanide (TMSCN, 3.0 mL, 23 mmol, 2.00 equiv.) over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMSOTf, 21 μL, 0.11 mmol, 0.01 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried *in vacuo* affording **HIR.25a** (96%, 2.99 g, 11.0 mmol).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 (d, J = 8.3 Hz, 1 H, Ar*H*), 8.13 (dd, *J* = 7.4, 1.7 Hz, 1 H, Ar*H*), 8.06-7.97 (m, 1 H, Ar*H*), 7.88 (t, *J* = 7.3 Hz, 1 H, Ar*H*). **^{13}C NMR** (101 MHz, DMSO-d6) δ 166.7, 136.5, 132.0, 131.9, 130.2, 127.8, 117.5, 87.9. The data correspond to those reported in literature.[12]

4,5-Dimethoxy-1-Cyano-1,2-benziodoxol-3-(1H)-one (**HIR.25b**)



HIR.24 **HIR.15** **HIR.25b**

Following a reported procedure,[2] 4,5-dimethoxyl-1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (**HIR.24**, 115 mg, 0.355 mmol, 1.00 eq.) was suspended in acetic anhydride (1.0 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 5 mL) and dried *in vacuo* affording **HIR.15** (108 mg, 0.295 mmol, 83 %) as a white solid.

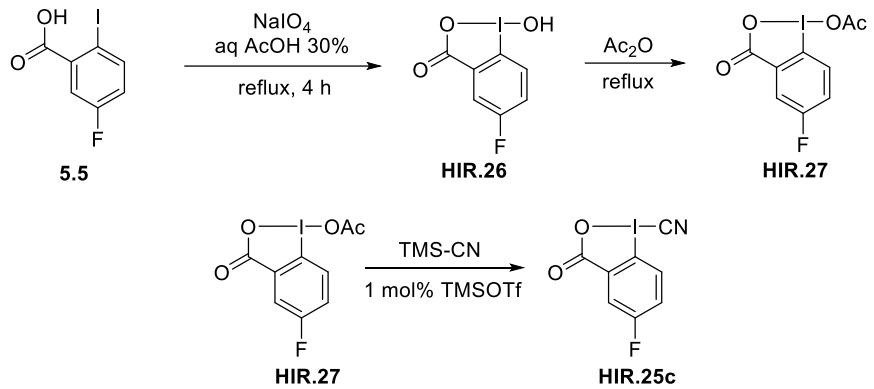
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (s, 1H, Ar*H*), 7.19 (s, 1H, Ar*H*), 3.92 (s, 3H, O*Me*), 3.90 (s, 3H, O*Me*), 2.25 (s, 3H, OC(O)*Me*). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 174. 5, 167.7, 155.3, 151.2, 122.0, 112.9, 110.6, 109.2, 56.2, 56.1, 20.0. The values of the NMR spectra are in accordance with reported literature data.[12]

Following a reported procedure,[12] 4,5-dimethoxy-1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**HIR.15**, 92 mg, 0.251 mmol, 1.00 equiv.) was dissolved under nitrogen in dry

dichloromethane (2 mL). To the clear colorless solution was added *via* syringe trimethylsilyl cyanide (TMS-CN, 67 μL, 0.50 mmol, 2.00 equiv.) over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 0.90 μL, 5.03 μmol, 0.02 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried *in vacuo* affording **HIR.25b** (75 mg, 0.225 mmol, 90 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (s, 1H, Ar*H*), 7.53 (s, 1H, Ar*H*), 3.93 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.6, 155.2, 151.9, 123.1, 112.7, 109.2, 107.0, 88.7, 56.2, 55.0. The characterization data is in accordance with reported literature values.[12]

5-Fluoro-1-Cyano-1,2-benziodoxol-3-(1H)-one (**HIR.25c**)



Following a reported procedure,[2] $NaIO_4$ (760 mg, 3.55 mmol, 1.05 equiv) and 5-fluoro-2-iodobenzoic acid (**5.5**) (900 mg, 3.38 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (1.8 mL) / H_2O (4.5 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 rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 10 mL) and acetone (3 x 10 mL), and air-dried in the dark to give the pure product **HIR.26** (908 mg, 3.22 mmol, 95%) as a colorless solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (bs, 1 H, O*H*), 7.90 – 7.78 (m, 2 H, Ar*H*), 7.75 (dd, *J* = 8.4, 2.5 Hz, 1 H, Ar*H*). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.7 (d, *J* = 2.6 Hz), 164.0 (d, *J* = 248.3 Hz), 134.2 (d, *J* = 7.5 Hz), 128.5 (d, *J* = 8.7 Hz), 121.98 (d, *J* = 23.9 Hz), 117.4 (d, *J* = 23.6 Hz), 114.4. The compound was used in the next step with no further analysis.

Following a reported procedure,[2] hypervalent iodine precursor **HIR.26** (800 mg, 2.84 mmol, 1.00 equiv.) was suspended in acetic anhydride (2.80 mL, 29.7 mmol, 10.5 equiv) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to cool down to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again

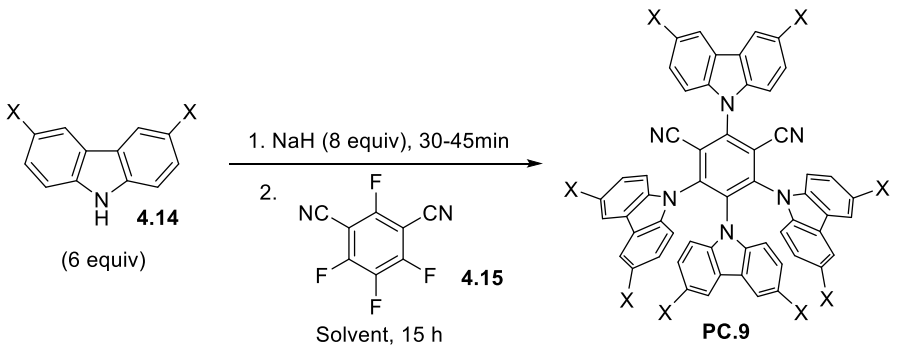
filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried in vacuo affording **HIR.27** (825 mg, 2.55 mmol, 90%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.93 (m, 2H, Ar*H*), 7.64 (ddd, *J* = 9.1, 7.7, 2.9 Hz, 1H, Ar*H*), 2.26 (s, 3H, OC(O)*Me*). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 176.4, 166.7 (d, *J* = 2.9 Hz), 165.0 (d, *J* = 254.5 Hz), 131.7 (d, *J* = 8.0 Hz), 131.0 (d, *J* = 8.1 Hz), 123.7 (d, *J* = 24.0 Hz), 120.0 (d, *J* = 24.3 Hz), 111.2 (d, *J* = 2.3 Hz), 20.2. The compound was used in the next step with no further analysis.

Following a reported procedure,[12] **HIR.27** (750 g, 2.31 mmol, 1.00 equiv.) was dissolved under nitrogen in dry dichloromethane (15 mL). To the clear colorless solution was added *via* syringe trimethylsilyl cyanide (TMS-CN, 0.62 mL, 4.6 mmol, 2.0 equiv.), over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 4.2 μL, 23 μmol, 0.010 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried *in vacuo* affording **HIR.25c** (610 mg, 2.10 mmol, 91 %) as a white solid.

Mp. 181.1 – 184.1°C (decomp). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.25 (dd, *J* = 8.9, 4.2 Hz, 1H, Ar*H*), 7.99 – 7.75 (m, 2H, Ar*H*). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.3 (d, *J* = 2.4 Hz), 164.6 (d, *J* = 251.5 Hz), 133.1 (d, *J* = 7.7 Hz), 130.1 (d, *J* = 8.9 Hz), 123.8 (d, *J* = 24.5 Hz), 118.4 (d, *J* = 24.1 Hz), 111.4, 87.4. **IR** (solid) 3870 (s), 3740 (s), 3686 (s), 3620 (m), 3435 (w), 3335 (w), 3227 (w), 3109 (w), 2988 (w), 2914 (w), 2360 (m), 2162 (w), 2005 (w), 1926 (w), 1865 (w), 1739 (m), 1702 (m), 1647 (m), 1518 (s), 1457 (m), 1419 (m), 1306 (m), 1141 (w), 1025 (s), 823 (w). **HRMS** (ESI) calcd for $C_8H_4FINO_2^+$ $[M+H]^+$ 291.9265; found 291.9270.

8.3. GP2: Synthesis of the photocatalysts

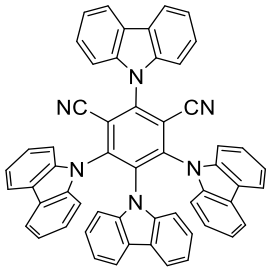


Following a reported procedure,[14] Sodium hydride (60% suspension in mineral oil, 8.0 equiv) was added slowly to a stirred solution of substituted-carbazole **4.14** (5.0 equiv) in dry THF (0.05 M) under a nitrogen atmosphere at RT After 30 min, 2,4,5,6-tetrafluoroisophthalonitrile **4.15** (1.0 mmol, 1.0 equiv) was added. After stirring at RT for 15 h, 2 mL water was added to the reaction mixture to quench the excess of NaH. The resulting mixture was then

[14] Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. *Chem. Sci.* **2018**, *9*, 5883–5889.

concentrated under reduced pressure. The crude product was purified by recrystallization from hexane:CH_2Cl_2 then filtered. The brown liquid filtrate was concentrated and recrystallized as before. The combined solids were then purified by column chromatography on silica gel with CH_2Cl_2:Hexane.

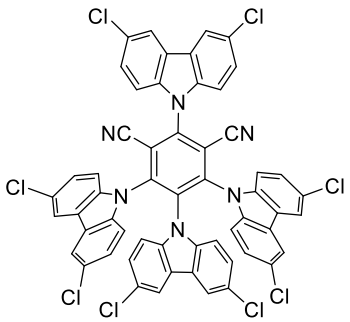
2,4,5,6-Tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN, **PC.9a**)



Following **GP2** and starting from 9*H*-carbazole **4.14a** (X = H, 1.67 g, 10.0 mmol, 5.00 equiv), sodium hydride (0.60 g, 15 mmol, 7.5 equiv) and 2,4,5,6-tetrafluoroisophthalonitrile **4.15** (0.40 g, 2.0 mmol) in 40 mL of THF. Recrystallisation (Hexanes:CH_2Cl_2 (1:1, 90 mL)) afforded the crude product as a yellow powder. Column chromatography afforded 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (**PC.9a**) as a bright yellow crystalline solid (1.14 g, 1.45 mmol, 73 % yield).

Rf (Hexane;CH_2Cl_2 1:1) = 0.29. (yellow spot on TLC). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.2 (d, *J* = 7.7 Hz, 2H, Ar*H*), 7.8 – 7.6 (m, 8H, Ar*H*), 7.5 (ddd, *J* = 8.0, 6.6, 1.6 Hz, 2H, Ar*H*), 7.3 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.2 (dd, *J* = 8.4, 1.5 Hz, 4H, Ar*H*), 7.2 – 7.0 (m, 8H, Ar*H*), 6.8 (t, *J* = 7.8 Hz, 4H, Ar*H*), 6.6 (td, *J* = 7.6, 1.2 Hz, 2H, Ar*H*).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 145.2, 144.6, 140.0, 138.2, 136.9, 134.7, 127.0, 125.8, 124.9, 124.7, 124.5, 123.8, 122.4, 121.9, 121.4, 121.0, 120.4, 119.6, 116.3, 111.6, 109.9, 109.5, 109.4. ^{1}H NMR shift in Chloroform-*d* are consistent with reported data.[15]

(2r,4s,5r)-2,4,5,6-Tetrakis(3,6-dichloro-9*H*-carbazol-9-yl)isophthalonitrile (4ClCzIPN, **PC.9b**)

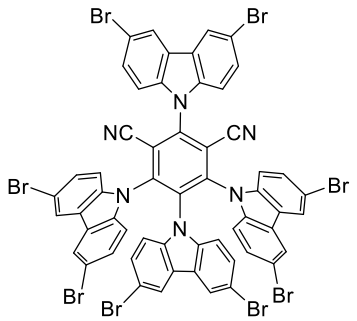


Following **GP2** and starting from 3,6-*d*ichloro-9*H*-carbazole **4.14b** (X = Cl, 1.96 g, 6.00 mmol, 6.0 equiv), sodium hydride (320 mg, 8.00 mmol, 8.0 equiv) and 2,4,5,6-tetrafluoroisophthalonitrile **4.15** (200 mg, 1.00 mmol) in 20 mL of THF. Recrystallization (Hexanes:CH_2Cl_2 (1:2, 80 mL)) gave 900 mg of yellow powder, then second recrystallization gave 325 mg of brown powder. Column chromatography of the combined solid afforded (2r,4s,5r)-2,4,5,6-tetrakis(3,6-*d*ichloro-9H-carbazol-9-yl)isophthalonitrile (**PC.9b**) as a bright yellow crystalline solid (830 mg, 0.780 mmol, 87 % yield).

Rf (Hexane:CH_2Cl_2 1:1) 0.25. (yellow spot on TLC). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.60 (d, *J* = 2.1 Hz, 2H, Ar*H*), 8.15 (d, *J* = 2.1 Hz, 4H, Ar*H*), 8.08 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.87 (dd, *J* = 8.8, 2.1 Hz, 2H, Ar*H*), 7.80 (d, *J* = 2.2 Hz, 2H, Ar*H*), 7.69 (d, *J* = 8.8 Hz, 4H, Ar*H*), 7.46 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.32 (dd, *J* = 8.8, 2.2 Hz, 4H, Ar*H*), 6.93 (dd, *J* = 8.8, 2.2 Hz, 2H, Ar*H*). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 145.0, 144.5, 138.5, 137.4, 136.5, 135.8, 134.5, 127.8, 127.0, 126.4, 125.7, 125.3, 124.2, 123.8, 123.3, 121.6, 120.9, 120.3, 116.8, 112.6, 112.5, 112.3, 111.7. **HRMS** (ESI) calcd for $C_{56}H_{24}Cl_8N_6$ [M+] 1059.9565; found 1059.9573.

[15] Uoyama, H.; Goushi, K.; Shizu, K.; Nomura, H.; Adachi, C. *Nature* **2012**, *492*, 234.

(2r,4s,5r)-2,4,5,6-Tetrakis(3,6-dibromo-9*H*-carbazol-9-yl)isophthalonitrile (4ClCzIPN, **PC.9c**)



Following **GP2** and starting from 3,6-*d*ichloro-9*H*-carbazole **4.14c** (X = Br, 1.00 g, 3.08 mmol, 5.0 equiv), sodium hydride (197 mg, 8.00 mmol, 8.0 equiv) and 2,4,5,6-tetrafluoroisophthalonitrile **4.15** (123 mg, 1.00 mmol) in 20 mL of THF. Recrystallization (Acetone, 15 mL) afforded (2r,4s,5r)-2,4,5,6-tetrakis(3,6-*d*ichloro-9H-carbazol-9-yl)isophthalonitrile (**PC.9b**) as a bright yellow crystalline solid (962 mg, 0.396 mmol, 64 % yield).

Rf (Hexane/ CH_2Cl_2 1/1) = 0.43. (yellow spot on TLC). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 1.8 Hz, 2H, Ar*H*), 8.30 (d, *J* = 2.0 Hz, 4H, Ar*H*), 8.04 – 7.99 (m, 4H, Ar*H*), 7.96 (dd, *J* = 8.6, 1.9 Hz, 2H, Ar*H*), 7.64 (d, *J* = 8.8 Hz, 4H, Ar*H*), 7.47 – 7.35 (m, 6H, Ar*H*), 7.05 (dd, *J* = 8.8, 2.0 Hz, 2H, Ar*H*). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 145.0, 144.5, 138.6, 137.7, 136.8, 135.9, 130.4, 129.1, 128.0, 124.7, 124.2, 123.9, 123.8, 116.8, 115.0, 114.4, 113.6, 112.9, 112.7, 111.7. **HRMS** (ESI/QTOF) m/z: [M + K]+ Calcd for $C_{56}H_{32}Br_8KN_6^+$ 1458.5787; Found 1458.5812.

8.4. Ene-carbamate and enol ether oxy-alkynylation

Synthesis of electron rich alkenes (**4.3a-n** and **4.5f**)

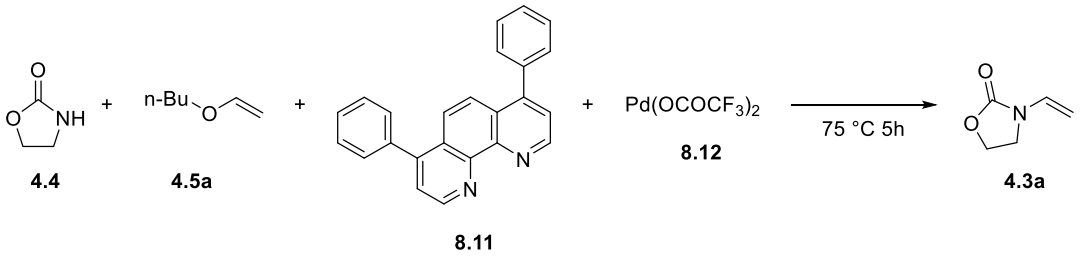
General note on commercial alkenes:

N-vinyl pyrrolidinone (sodium hydroxide as inhibitor) (**4.3j**) and 2-chloroethyl vinyl ether (triethanolamine as stabiliser) (**4.5d**) were purchased from Sigma Aldrich. *n*Butyl vinyl ether (**4.5a**) and 3,4-dihydro-2H-pyran (**4.5g**) were purchased from Acros. ((Vinyloxy)methyl benzene (**4.5b**) and 2-ethoxy prop-1-ene (**4.5h**) were purchased from Fluorochem. Allyl vinyl ether (**4.5c**) was purchased from abcr. Cyclohexyl vinyl ether (stabilized with KOH) (**4.5e**) was purchased from TCI. All commercial alkenes were filtered over basic alumina before use and were used within 15 min without direct light exposition.

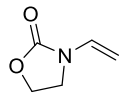
General note on synthesised alkenes:

All alkenes were used within 6 months of synthesis, stored at 4 °C and hidden from light. Some degradation (coloration) could be observed although it was not detrimental for the reaction yield.

N-vinyloxazolidin-2-one (**4.3a**)

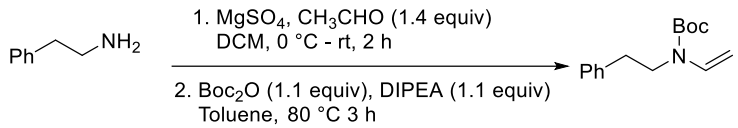


Following a modified reported procedure,[16] in a 25 mL round bottomed flask equipped with magnetic stirrer, bathophenanthroline (**8.11**, 0.015 g, 0.045 mmol, 0.05 equiv), $Pd(OCOCF_3)_2$ (**8.12**, 0.015 g. 0.045 mmol, 0.05 equiv) and oxazolidinone (**4.4**, 0.077 g 0.904 mmol, 1.0 equiv) were dissolved in *n*butyl vinyl ether (**4.5a**, 1.0 mL, 7.8 mmol, 8.6 equiv). The flask was closed with a septum and then opened to the atmosphere by means of a needle (1.2 x 40 mm). The yellow suspension was then stirred at 75 °C for 2 hours. At this time, the mixture cooled down to room temperature. With no further treatment, the crude oil was then submitted directly to column chromatography (SiO_2; Pent:EtOAc 98:2 to 8:2)[17] affording **4.3a** as a colorless oil (0.095 g, 0.84 mmol, 92% yield).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.88 (dd, *J* = 15.8, 9.0 Hz, 1H, NC*H*=CH_2), 4.51 – 4.38 (m, 3H, cyclic-CH_2 + CH=CH_2), 4.29 (dd, *J* = 15.8, 1.3 Hz, 1H, NCH=CH_2), 3.79 – 3.64 (m, 2H, cyclic-CH_2). The values of the ^{1}H NMR spectrum are in accordance with reported literature data.[16]

Tert-butyl phenethyl(vinyl)carbamate (**4.3b**)

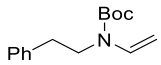


4.8b **4.3b**

A flame-*d*ried, 50 mL round-bottomed, two-necked flask was charged with anhydrous $MgSO_4$ (stored in the glove box; 4.5 g), closed, evacuated, and backfilled with nitrogen. CH_2Cl_2 (dry; 10 mL) was added followed by 2-phenylethanamine (**4.8a**, 1.3 mL, 10 mmol, 1.0 equiv). The resulting suspension was cooled down to 0 °C (ice/water bath). Acetaldehyde (0.80 mL, 14 mmol, 1.4 equiv) was then added. The mixture was stirred and allowed to warm to room temperature over a period of 1 hour, and then stirred at room temperature for one additional hour. The solids were then removed through rapid filtration. CH_2Cl_2 was then distilled off (1 atm, 50 °C). To the crude imine was added a solution of di-*tert*-butyl dicarbonate (2.40 g, 11.0 mmol, 1.1 equiv) in toluene (dry; 5.0 mL), followed by DIPEA (freshly distilled over KOH; 1.8 mL, 11 mmol, 1.1 equiv). The resulting yellow solution was stirred at 70 °C for 3 hours. The reaction was stopped and the volatiles were removed under reduced pressure. The resulting crude yellow-orange oil was submitted to column chromatography (Biotage, 40 g SiO_2; EtOAc in pentane, 0 to 8%). The desired product was obtained as a mixture with unreacted Boc_2O. The excess Boc_2O was removed as following: the eluate was dissolved in EtOH (5 mL) and imidazole (300 mg) and DMAP (54.0 mg, 0.1 eq compared to imidazole) were added. The

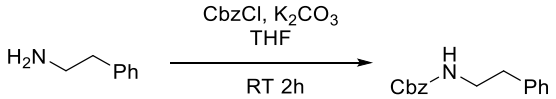
[16] Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845–1848.
[17] Pentane:EtOAc 95:5 needs to be run for at least 5 column volumes due to remove all the excess butyl vinyl ether.

resulting mixture was stirred at room temperature for 10 minutes. It was then concentrated under reduced pressure. The crude oil was submitted to column chromatography (Biotage, 24 g SiO_2; EtOAc in pentane, 0 to 10%) to furnish pure *tert*-butyl phenethyl(vinyl)carbamate **4.3b** as a pale yellow oil (0.607 g, 2.45 mmol, 25% yield).



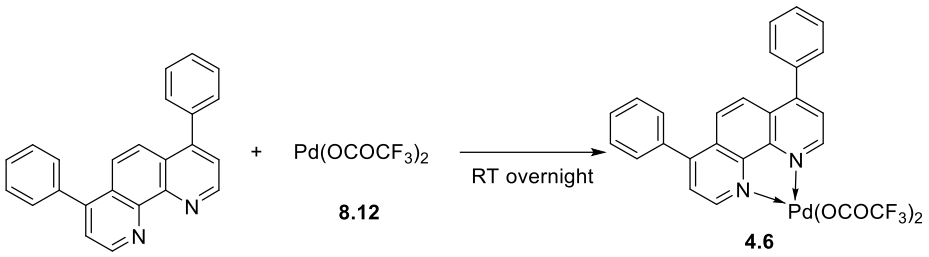
Rf (pentane:Et_2O 95:5) = 0.5.
^{1}H NMR (400 MHz, Acetonitrile-*d*3) δ 7.30 (dd, *J* = 8.0, 6.7 Hz, 2H, Ph*H*), 7.26 - 7.18 (m, 3H, Ph*H*), 7.06 (br s, 1H, -*CH*=CH_2), 4.43 (d, *J* = 16.2 Hz, 1H, -CH=CH_2), 4.25 (br s, 1H, -CH=CH_2), 3.75 - 3.64 (m, 2H, CH_2), 2.88 - 2.76 (m, 2H, CH_2), 1.41 (br s, 9H, C(CH_3)$_3$ in Boc).
^{13}C NMR (101 MHz, Acetonitrile-*d*3) δ 153.7, 140.3, 133.4, 129.9, 129.4, 127.2, 91.4, 81.6, 45.4, 33.7, 28.2. **IR** (ν_{max}, cm^{-1}) 3372 (m), 2969 (m), 2924 (m), 2880 (m), 1704 (w), 1614 (m), 1595 (s), 1557 (m), 1493 (m), 1352 (s), 1148 (s), 1231 (m), 1052 (m), 880 (m), 828 (m), 765 (m), 745 (s), 694 (m). **HRMS** (ESI/QTOF) m/z $[M + Na]^+$ Calcd for $C_{15}H_{21}NNaO_2^+$ 270.1464; Found 270.1464.

Benzyl phenethyl(vinyl)carbamate (**4.3c**)



4.8a **8.13**

To a flame dried flask and under argon, 2-phenethylamine (**4.8a**, 4.0 mL, 32 mmol, 1 equiv) and powered K_2CO_3 were suspended in anhydrous THF (125 mL, 0.25 M). Benzyl chloroformate (5.0 mL, 35 mmol, 1.1 equiv) was added dropwise to the suspension. The reaction was stirred at room temperature for 2 h. The solution was quenched with sat. aq. $NaHCO_3$ (40 mL) and the product was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 x 40 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (SiO_2, Pentane : EtOAc 1 : 4) affording pure benzyl phenethylcarbamate (**8.13**, 8.0 g, 31 mmol, 99% yield). The compound was used directly in next step.

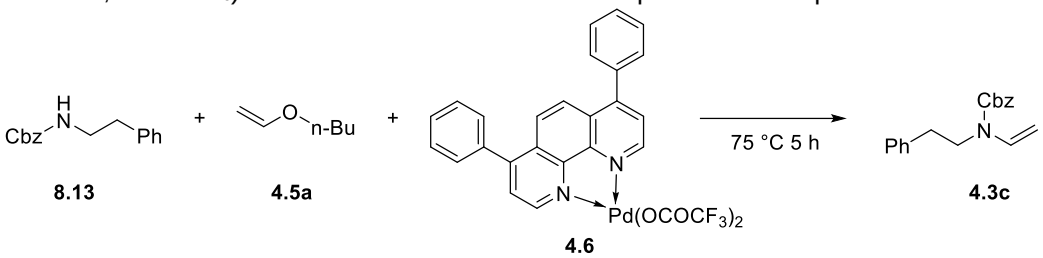


8.11 **8.12** **4.6**

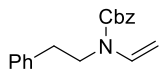
In a 25 mL flask palladium trifluoroacetate (**8.12**, 0.415 g, 1.21 mmol) was dissolved in MeCN (29.9 mL). The flask was put under nitrogen and stirred at RT. A solution of 4,7-diphenyl-1,10-phenanthroline (**8.11**, 0.402 g, 1.21 mmol) in CH_2Cl_2 (Ratio: 1.000, Volume: 14.95 mL) was added. The dark brown solution was stirred overnight.

n-Hexane was added slowly under vigorous stirring (ca. 40 mL). The mixture was left to precipitate slowly over 30 min at rt. The suspension was cooled to 0 °C with an ice bath and the reaction was filtered and washed with pentane. 0.100 g of yellow complex was recovered. The filtrate was concentrated under reduced pressure, redisoved in a minimum of CH_2Cl_2 (ca. 5 mL) and precipitated out with n-hexane. the suspension was cooled to 0 °C with an ice bath and was filtered a second time affording 0.563 g of yellow complex. The two batches were further dried on the high vaccum affording BphenPd$(O_2C_2F_3)_2$ (**4.6**, 0.595 g, 0.895 mmol, 73.9 % yield) (0.095 of first batch and 0.500 g of second batch). *This complexation is quite sensitive to scale and the purity of the palladium and phenathroline these compounds were purchased from Acros and were used with no further purification. Yields were variable between different bottles of the same supplier. Hexane proved more efficient than pentane for the precipitation, but in some cases precipitation was not observed and couldn't be induced.*

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 2H, Ar*H*), 8.27 – 8.04 (m, 4H, Ar*H*), 7.69 (s, 10H, Ar*H*).**^{19}F NMR** (376 MHz, DMSO-d_6) δ -73.3. The ^{1}H NMR data corresponds to the reported literature data.[18]



A 5 mL round-bottomed test tube was charged with BphenPd$(O_2CCF_3)_2$ (**4.6**, 39.0 mg, 0.0590 mmol, 7.5 mol%). *n*Butyl vinyl ether (**4.5a**, 1.2 mL, 9.4 mmol, 12 equiv) was added, followed by benzyl phenethylcarbamate (**8.13**, 0.200 g, 0.783 mmol, 1.0 equiv). The vial was sealed with a PTFE septum, which was then pierced with a needle (gauge 18 - "pink needle") in order to ensure exposure to air. The resulting brown-orange suspension was stirred at 80 °C for 3 hours. After this time, TLC analysis showed complete conversion of the starting material. The reaction mixture was then allowed to cool down to room temperature and was subsequently submitted to column chromatography (Biotage, 25 g SiO_2; EtOAc in pentane, 2 to 20% - 3 CV used to elute the butyl vinyl ether off). Pure benzyl phenethyl(vinyl)carbamate **4.3c** (0.160 g, 0.569 mmol, 73% yield) was obtained as a colorless oil.

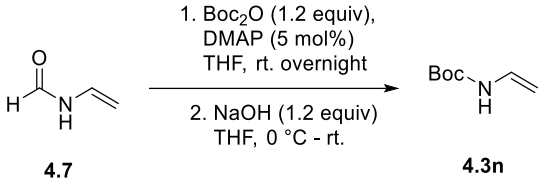


Rf (pentane :EtOAc 9 :1) 0.60. **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 7.43 - 7.31 (m, 5H, Ph*H*), 7.27 (d, *J* = 7.1 Hz, 3H, Ph*H*), 7.24 - 7.15 (m, 2H, Ph*H*), 7.08 (dd, *J* = 16.0, 9.4 Hz, 1H, -*CH*=CH_2), 5.09 (br s, 2H, PhCH_2O), 4.52 (d, *J* = 16.1 Hz, 1H, -CH=CH_2), 4.32 (br s, 1H, -*CH*=CH_2), 3.75 (t, *J* = 7.7 Hz, 2H, CH_2CH_2), 2.84 (dd, *J* = 8.8, 6.6 Hz, 2H, CH_2CH_2).
^{13}C NMR (101 MHz, Acetonitrile-d_3, 2 carbons are not resolved) δ 154.2, 140.0, 137.6, 133.4, 129.8, 129.5, 129.4, 129.1, 128.9, 127.3, 92.7, 68.4, 45.5, 33.9. **IR** (v_{max}, cm^{-1}) 3027 (w), 3065 (w), 3090 (w), 2964 (w), 1707 (s), 1631 (s), 1389 (s), 1421 (m), 1453 (m), 1345 (m), 1180 (s), 1275 (m), 1104

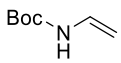
[18]Milani, B.; Alessio, E.; Mestroni, G.; Sommazzi, A.; Garbassi, F.; Zangrando, E.;Bresciani-Pahor, N.; Randaccio, L. *J. Chem. Soc., Dalton Trans.*, **1994**, 1903-1911

(m), 837 (m), 748 (s), 698 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{18}H_{19}NNaO_2^+$ 304.1308; Found 304.1313.

Tert-butyl benzyl(vinyl)carbamate (**4.3n**)



Following a reported procedure,[19] in a 250 mL, three-necked, round-bottomed flask, *N*-vinylformamide (**4.7**, 2.7 mL, 38 mmol, 1.0 equiv) was dissolved in THF (dry; ca. 130 mL). To the resulting pale yellow solution, di-*tert*-butyl dicarbonate (10.1 g, 46.2 mmol, 1.2 equiv) and DMAP (0.235 g, 1.93 mmol, 5 mol%) were added under nitrogen. The mixture, which rapidly became bright yellow, was then stirred at room temperature overnight. After 16 hours, it was concentrated under reduced pressured. The orange crude oil was then submitted to column chromatography (Biotage, 80 g SiO_2; EtOAc in pentane, 5 to 50%) to afford *tert*-butyl formyl(vinyl)carbamate (4.70 g, 27.5 mmol, 71% yield) as a yellow oil. The compound was used directly in next step, in a 100 mL one-necked, round-bottomed flask, *tert*-butyl formyl(vinyl)carbamate (4.60 g, 26.9 mmol, 1.0 equiv) was dissolved in THF (16 mL). The solution was cooled to 0 °C (ice water bath). Aq. NaOH (2.0 M; 16 mL, 32 mmol, 1.2 equiv) was added drop-wise, over a period of 20 minutes (syringe pump). Once the addition was complete, stirring was continued at 0 °C for another 15 minutes. The suspension was then allowed to warm to room temperature and stirred for additional 3 hours. Water (30 mL) was then added and the aqueous layer was extracted with MeO*t*Bu (4 x 30 mL). The combined organic extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude solid was dissolved in pentane at room temperature (in order to reduce the volume of pentane, the dissolution was done under ultrasound irradiation). The solution was then allow to stand at -20 °C (freezer) overnight. The precipitate was then collected by filtration and washed with a minimal amount of ice-cold pentane. *tert*-Butyl vinylcarbamate (**4.3n**, 2.45 g, 17.1 mmol, 64% yield) was obtained as a crystalline, colorless solid.

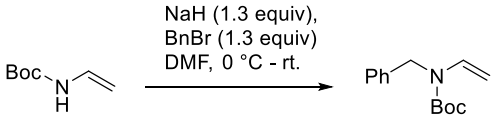


^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 7.31 (s, 1H, -*CH*=CH_2), 6.60 (ddd, *J* = 15.8, 10.8, 8.9 Hz, 1H, -CH=CH_2), 4.47 (d, *J* = 15.8 Hz, 1H, -CH=CH_2), 4.14 (d, *J* = 8.9 Hz, 1H, N*H*), 1.43 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 153.9, 131.4, 92.3, 80.5, 28.4.

[19] Kassir, A. F.; Ragab, S. S.; Nguyen, T. A. M.; Charnay-Pouget, F.; Guillot, R.; Scherrmann, M. C.; Boddaert, T.; Aitken, D. J. *J. Org. Chem.* **2016**, *81*, 9983.

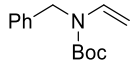
Compound was used directly in next step with no further analysis.

Tert-butyl benzyl(vinyl)carbamate (**4.3d**)



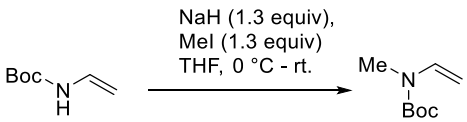
4.3n **4.3d**

Following a reported procedure,[20] in a 100 mL, two-necked, round-bottomed flask, *tert*-butyl vinylcarbamate (**4.3n**, 0.773 g, 5.40 mmol, 1.0 equiv) was dissolved in DMF (dry; 12.6 mL). The colorless solution was cooled to 0 °C (ice-water bath) and sodium hydride (60% dispersion in paraffin; 0.281 g, 7.02 mmol, 1.3 equiv) was added in single portion. Bubbling was immediately observed. The suspension was stirred at 0 °C for 30 minutes and at room temperature for another 30 minutes. The mixture looked, at this point, like a yellow-grey turbid solution. Benzyl bromide (0.84 mL, 7.0 mmol, 1.3 equiv) was then added drop-wise, followed by a catalytic amount of TBAI (tip of a spatula). The mixture was stirred at room temperature for 3 hours. After this time, full conversion of the starting material was observed based on TLC analysis (pentane:EtOAc 97:3). The reaction was quenched by cautious addition of water (12 mL), followed by sat. aq. NH_4Cl (12 mL). The aqueous layer was then extracted with ether (4 x 20 mL). The combined organic extracts were washed with water (30 mL), brine (2 x 30 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting yellow crude oil was submitted to column chromatography (Biotage, 40 g SiO_2; EtOAc in pentane, 0 to 7%) to provide *tert*-butyl benzyl(vinyl)carbamate **4.3d** (95% pure; 0.822 g, 3.35 mmol, 62% yield) as a yellow oil.



Rf(pentane:EtOAc 9:1) = 0.5.
^{1}H NMR (400 MHz, DMSO-d_6, undefined rotameric mixture) δ 7.48 – 7.27 (m, 3H, Ph*H*), 7.30 – 7.15 (m, 2H, Ph*H*), 7.06 (bs, 1H, C*H*=CH_2), 4.69 (s, 2H, PhCH_2), 4.29 (bs, 1H, CH=CH_2), 4.19 (bs, 1H, CH=CH_2), 1.44 (bs, 9H, C(CH_3)$_3$). **^{13}C NMR** (101 MHz, DMSO-d_6, undefined rotameric mixture) δ 153.0, 138.8, 138.0, 133.1, 128.9, 128.8, 128.7, 128.0, 127.9, 127.3, 126.8, 93.0, 81.5, 71.9. The ^{1}H NMR characterisation data are in accordance to the reported literature data.[21]

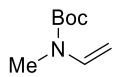
T*ert*-butyl methyl(vinyl)carbamate (**4.6e**)



4.3n **4.3e**

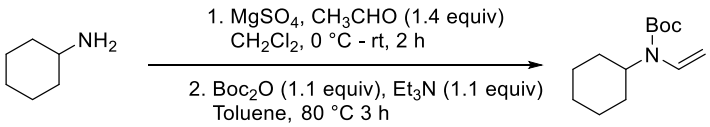
[20] Liu, S.-Y.; Xu, S. WO2015/126400, 2015, A1.
[21] Bach, T. and Schröder, J. *Liebigs Ann./Recl.*, **1997**, *1997*, 2226

Following a reported procedure,[22] A 100 mL, two-necked, round-bottomed flask was charged with NaH (60% w/w dispersion in mineral oil; 0.192 g, 4.80 mmol, 1.2 equiv). The flask was evacuated, and backfilled with nitrogen (3 times). THF (dry; 30 mL) was then added. The resulting suspension was cooled to 0 °C (ice - water bath) and a solution of *t*-butyl N-vinyl carbamate (**4.3n**, 0.572 g, 4.00 mmol, 1.0 equiv) in THF (dry; 10 mL) was added slowly, by syringe at the same temperature. Immediately, moderate gas bubbling was observed. The resulting pale yellow mixture was stirred at 0 °C for 30 minutes. Methyl iodide (0.39 mL, 6.4 mmol, 1.6 equiv) was then added. The cooling bath was removed and stirring was continued under Ar (balloon) overnight. The reaction was then quenched by addition of sat. aq. NH_4Cl (30 mL). The aqueous layer was separated and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was submitted to column chromatography (SiO_2; EtOAc:pentane 0:100 to 25 / 75) to give *tert*-butyl *N*-methyl *N*-vinyl carbamate (**4.3e**, 0.282 g, 1.70 mmol, 45% yield) as a colorless oil.



Although this compound is known,[23] no NMR data has been reported at RT.
Rf(pentane:EtOAc = 9:1) = 0.55.
^{1}H NMR (400 MHz, Acetonitrile-d3) δ 7.15 (m, 1H, -*CH*=CH_2), 4.27 (d, *J* = 15.8 Hz, 1H, -CH=CH_2), 4.18 (m, 1H, -CH=CH_2), 2.96 (s, 3H, CH_3), 1.47 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 153.3, 134.7, 90.7, 81.2, 29.6, 28.0.
IR (ν_{max}, cm^{-1}) 3116 (w), 2978 (w), 1708 (s), 1626 (s), 1479 (m), 1459 (w), 1436 (m), 1410 (m), 1352 (s), 1318 (s), 1290 (m), 1254 (w), 1145 (s), 1060 (m), 979 (w), 865 (m), 835 (m), 768 (m), 659 (w).
HRMS (APPI/LTQ-Orbitrap) m/z $[M + Na]^+$ Calcd for $C_8H_{15}NNaO_2^+$ 180.0995; Found 180.0998.

Tert-butyl cyclohexenyl(vinyl)carbamate (**4.3f**)

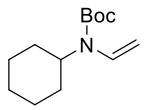


4.8f **4.3f**

A flame-*d*ried, 100 mL round-bottomed, two-necked flask was charged with anhydrous $MgSO_4$ (stored in the glove box; 4.5 g), closed, evacuated, and backfilled with nitrogen. CH_2Cl_2 (dry; 10 mL) was added followed by cyclohexanamine (**4.8b**, 1.2 mL, 10 mmol, 1.0 equiv). The resulting suspension was cooled down to 0 °C (ice/water bath). Acetaldehyde (0.80 mL, 14 mmol, 1.4 equiv) was then added. The mixture was stirred and allowed to warm to room temperature over a period of 1 hours, and then stirred at room temperature for 1 additional hour. The solids were then removed through rapid filtration. CH_2Cl_2 was then distilled off (rotary evaporator). The crude imine was used directly in the next step with no further

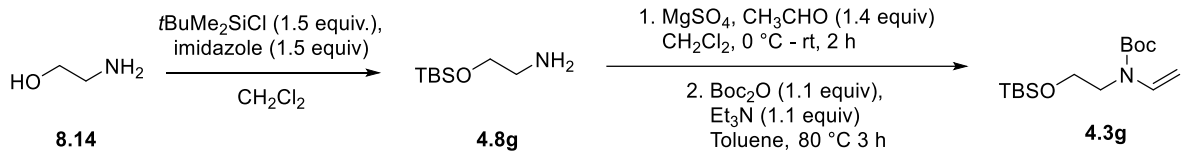
[22] Boyington, A. J.; Seath, C. P.; Zearfoss, A. M.; Xu, Z.; Jui, N. T. *J. Am. Chem. Soc.* **2019**, *141*, 4147.
[23] Chu, S.; Münster, N.; Balan, T.; Smith, M. D. *Angew. Chem. Int. Ed.* **2016**, *55*,14306.

purification. To the crude imine was added a solution of di-*tert*-butyl dicarbonate (2.40 g, 11.0 mmol, 1.1 equiv) in toluene (dry; 5.0 mL), followed by triethylamine (1.5 mL, 11 mmol, 1.1 equiv). The resulting yellow solution was stirred at 80 °C for 3 hours. The reaction was stopped and the volatiles were removed under reduced pressure. The resulting crude yellow-orange oil was submitted to column chromatography (SiO_2; Pentane/Et_2O 248/2 to 24/1). The desired product was obtained as a mixture with unreacted Boc_2O. The exceeding Boc_2O was removed as following: the eluate was dissolved in EtOH (5 mL) and imidazole (300 mg) and DMAP (54.0 mg, 0.1 eq compared to imidazole) were added. The resulting mixture was stirred at room temperature for 10 minutes. It was then concentrated under reduced pressure. The crude oil was submitted to column chromatography (Biotage, 24 g SiO_2; Et_2O in pentane, 1 to 5%) to furnish pure *tert*-butyl cyclohexyl(vinyl)carbamate **4.3f** as a pale yellow oil (0.607 g, 2.45 mmol, 25% yield).

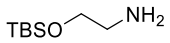


Rf (pentane/Et_2O 95/5) 0.5.
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 6.82 (dd, J = 16.1, 9.6 Hz, 1H, -*CH*=CH_2), 4.59 (d, J = 16.1 Hz, 1H, -CH=CH_2), 4.26 (d, J = 9.6 Hz, 1H, -CH=CH_2), 3.65 (m, 1H, N*CH*), 2.01 (dd, J = 12.6, 3.7 Hz, 2H, *Cy*), 1.84 – 1.74 (m, 2H, *Cy*), 1.68 – 1.57 (m, 3H, *Cy*), 1.46 (s, 9H, $C(CH_3)_3$), 1.33 (qt, J = 12.9, 3.7 Hz, 2H, *Cy*), 1.13 (qt, J = 13.0, 3.6 Hz, 1H, *Cy*).
^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 153.6, 134.1, 93.2, 81.1, 55.9, 30.2, 28.1, 26.7, 25.9. **IR** (ν_{max}, cm^{-1}) 2979 (m), 2930 (m), 1704 (s), 1622 (s), 1171 (s), 1146 (s). **HRMS** (APCI/QTOF) m/z [M + Na]+ Calcd for $C_{13}H_{23}NNaO_2^+$ 248.1621; Found 248.1621.

Tert-butyl (2-*tert*-butyldimethylsilyl)oxy)ethyl)(vinyl)carbamate (**4.3g**)

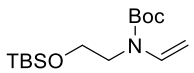


Under standard silylating conditions: in a 50 mL single-necked, round bottomed flask, a solution of *tert*-butyldimethylchlorosilane (2.41, 16.0 mmol, 1.5 equiv) in dichloromethane (7.0 mL) was added drop-wise over a period of 3 min to a stirred solution of ethanolamine (**8.14**, 0.80 mL, 13 mmol, 1.0 equiv) and imidazole (1.36 g, 20.0 mmol, 1.5 equiv) in dichloromethane (14 mL) at room temperature. The resulting mixture initially looked like a milky solution that became clear and colorless after being stirred at room temperature for 1 hour. Water (20 mL) was then added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 2-((*tert*-butyldimethylsilyl)oxy)ethanamine (**4.8g**, 2.05 g, 11.7 mmol, 88% yield) as pale yellow oil, which was used directly in next step with no further analysis.



^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.62 (t, *J* = 5.3 Hz, 2H, *CH₂*), 2.77 (t, *J* = 5.3 Hz, 2H, *CH₂*), 1.74 (s, 2H, *NH₂*), 0.89 (s, 9H, C(*CH₃*)₃), 0.06 (s, 6H, *CH₃*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 65.1, 44.3, 25.9, 18.3, -5.3.

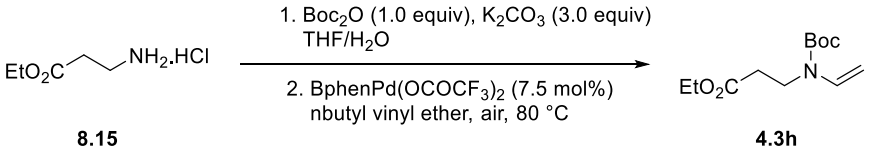
A flame-*d*ried, 100 mL round-bottomed, two-necked flask was charged with anhydrous $MgSO_4$ (stored in the glove box; 4.5 g), closed, evacuated, and backfilled with nitrogen. CH_2Cl_2 (dry; 10 mL) was added, followed by 2-((*tert*-butyldimethylsilyl)oxy)ethanamine (1.75 g, 10.0 mmol, 1.0 equiv). The resulting suspension was cooled down to 0 °C (ice/water bath). Acetaldehyde (0.80 mL, 14 mmol, 1.4 equiv) was then added. The mixture was stirred at 0 ° for 45 minutes, and then at room temperature for additional 45 minutes. The solids were then removed through rapid filtration. CH_2Cl_2 was then distilled off (rotary evaporator) to give a red crude imine. To the crude imine was added a solution of di-*tert*-butyl dicarbonate (2.40 g, 11.0 mmol, 1.1 equiv) in toluene (dry; 5.0 mL), followed by triethylamine (1.5 mL, 11 mmol, 1.1 equiv). The resulting orange suspension was stirred at 80 °C for 5 hours, slowly becoming a dark orange solution. The reaction was stopped and the volatiles were removed under reduced pressure. The resulting crude yellow-orange oil was submitted to column chromatography (SiO_2; Pentane:Et_2O 248:2 to 24:1). The desired product was obtained as a mixture with unreacted Boc_2O. The excess Boc_2O was removed as following: the eluate was dissolved in EtOH (5 mL) and imidazole (300 mg) and DMAP (54.0 mg, 0.1 eq compared to imidazole) were added. The resulting mixture was stirred at room temperature for 10 minutes. It was then concentrated under reduced pressure. The crude oil was submitted to column chromatography (Biotage, 24 g SiO_2; EtOAc in pentane, 1 to 5%) to furnish pure *tert*-butyl (2-((*tert*-butyldimethylsilyl)oxy)ethyl)(vinyl)carbamate **4.3g** (0.379 g, 1.26 mmol, 13% yield) as a colorless oil.



Rf (pentane:Et_2O 95:5) = 0.63.

^{1}H NMR (400 MHz, Acetonitrile-*d₃*) δ 7.03 (m, 1H, -*CH*=CH_2), 4.40 (d, *J* = 16.0 Hz, 1H, -CH=*CH₂*), 4.20 (br s, 1H, -CH=*CH₂*), 3.72 (td, *J* = 6.1, 0.8 Hz, 2H, *CH₂*), 3.60 (t, *J* = 6.2 Hz, 2H, *CH₂*), 1.46 (s, 9H, C(*CH₃*)₃), 0.88 (s, 9H, C(*CH₃*)₃), 0.04 (s, 6H, *CH₃* in TBS). **^{13}C NMR** (101 MHz, Acetonitrile-*d₃*) δ 153.8, 134.2, 91.7, 81.7, 60.4, 45.9, 28.4, 26.2, 18.9, -5.2. **IR** (ν_{max}, cm^{-1}) 2957 (m), 2862 (w), 1707 (s), 1631 (m), 1466 (m), 1358 (s), 1250 (m), 1142 (s), 1117 (s), 831 (s), 780 (s), 926 (w), 977 (w). **HRMS** (ESI/QTOF) m/z $[M + Na]^+$ Calcd for $C_{15}H_{31}NNaO_3Si^+$ 324.1965; Found 324.1966.

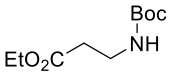
Ethyl 3-((*tert*-butoxycarbonyl)(vinyl)amino)propanoate (**4.3h**)



8.15 **4.3h**

In a 50 mL single-necked, round-bottomed flask, ethyl 3-aminobutanoate hydrochloride (**8.15**, 0.550 g, 3.58 mmol, 1.0 equiv), Boc_2O (0.781 g, 3.58 mmol, 1.0 equiv) and K_2CO_3 (1.49 g,

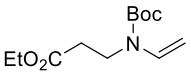
10.7 mmol, 2.5 equiv) were suspended in a mixture of THF:H_2O (10 mL, 1 : 1). The mixture was stirred at room temperature for 4 hours. It was then diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give pure ethyl 3-((*tert*-butoxycarbonyl)amino)propanoate (**8.16**, 0.707 g, 3.25 mmol, 91% yield) as a colorless oil.



8.16

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 5.37 (s, 1H, N*H*), 4.09 (q, *J* = 7.1 Hz, 2H, O$CH_2$$CH_3$), 3.26 (q, *J* = 6.5 Hz, 2H, CH_2), 2.43 (t, *J* = 6.6 Hz, 2H, CH_2), 1.39 (s, 9H, C(CH_3)$_3$ in Boc), 1.21 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).**^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 172.7, 156.7, 79.3, 61.1, 37.1, 35.4, 28.5, 14.5. The compound was used directly in next step with no further analysis.

Following an adapted reported procedure,[24] a 5 mL round-bottomed test tube was charged with (dpp)Pd(O_2CCF_3)$_2$ (**4.6**, 31.0 mg, 0.0460 mmol, 5 mol%). nButyl vinyl ether (**4.5a**, 1.5 mL, 11 mmol, 12 equiv) was added, followed by ethyl 3-((*tert*-butoxycarbonyl)amino)propanoate (**8.16**, 0.200 g, 0.921 mmol, 1.0 equiv). The vial was sealed with a PTFE septum, which was then pierced with a needle (gauge 18 - "pink needle") in order to ensure exposure to air. The resulting brown-orange suspension was stirred at 80 °C for 2 hours. After this time, the mixture looked like a clear orange solution. According to TLC analysis, the starting material was still present after this time, with no further progress upon stirring the mixture at the same temperature for additional 60 minutes. A further amount of catalyst (16.0 mg, 0.0260 mmol, 2.5 mol%; overall 7.5 mol%) was therefore added and stirring was continued at 80 °C for 2 hours. The reaction mixture was then allowed to cool down to room temperature and was subsequently submitted to column chromatography (Biotage, 25 g SiO_2; EtOAc in pentane, 2 to 20%).[17] Pure ethyl 3-((*tert*-butoxycarbonyl)(vinyl)amino)propanoate **4.3h** (0.121 g, 0.499 mmol, 54% yield) was obtained as a colorless oil.

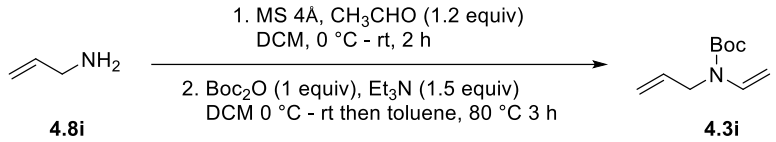


Rf (pentane:EtOAc 9:1) = 0.60.

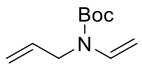
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 7.00 (dd, *J* = 16.1, 9.6 Hz, 1H, -CH=CH_2), 4.36 (d, *J* = 16.1 Hz, 1H, -CH=CH_2), 4.21 (d, *J* = 9.5 Hz, 1H, -CH=CH_2), 4.08 (q, *J* = 7.1 Hz, 2H, O$CH_2$$CH_3$), 3.81 - 3.68 (m, 2H, CH_2), 2.49 (dd, *J* = 8.4, 6.5 Hz, 2H, CH_2), 1.46 (s, 9H, C(CH_3)$_3$ in Boc), 1.21 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 171.8, 153.0, 132.9, 91.0, 81.7, 60.8, 39.3, 32.3, 27.9, 14.1. **IR** (v_{max}, cm^{-1}) 3382 (w), 2976 (w), 1732 (m), 1688 (m), 1516 (m), 1370 (m), 1415 (w), 1447 (w), 1282 (m), 1250 (s), 1167 (s), 1072 (m), 1021 (m), 977 (m), 856 (m), 787 (m), 647 (m). **HRMS** (ESI/QTOF) m/z $[M + Na]^+$ Calcd for $C_{12}H_{21}NNaO_4^+$ 266.1363; Found 266.1362.

[24] Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845–1848.

T*ert*-butyl allyl(vinyl)carbamate (**4.3i**)

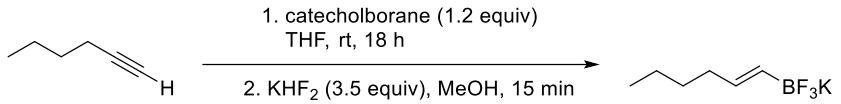


Following a modified reported procedure,[25] to a mixture of allylamine (**4.8i**, 1.5 mL, 20.1 mmol, 1.0 equiv) and 4 Å mol sieves (2 g) in CH_2Cl_2 (25 mL) at 0 °C was added acetaldehyde (1.4 mL, 24 mmol, 1.2 equiv) dropwise. The solution was warmed to rt over 1 h, stirred for an additional 1 h, and decanted. To the resultant solution at 0 °C, triethylamine (3.90 mL, 30.1 mmol, 1.5 equiv) and di-*tert*-butyl dicarbonate (4.37 g, 20.1 mmol, 1.0 equiv) were added. The mixture was warmed to rt and stirred for 15 h. The solution was concentrated, and toluene (30 mL) was added. The solution was heated at 70 °C for 3 h and then concentrated. Purification by silica-gel chromatography (SiO_2-Et_3N deactivated; Pent:Et_2O 98:2) afforded *tert*-butyl allyl(vinyl)carbamate **4.3i** (0.5496 g, 3.00 mmol, 15 % yield) as a colorless oil.



Rf (pentane:Et_2O 95:5) = 0.4.
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 7.06 (dd, *J* = 15.8, 9.4 Hz, 1H, N*CH*=CH_2), 5.78 (ddt, *J* = 17.2, 10.3, 5.0 Hz, 1H, *CH*=CH_2), 5.17 – 4.94 (m, 2H, *CH*=CH_2), 4.30 (d, *J* = 16.0 Hz, 1H, NCH=CH_2), 4.18 (d, 9.6 Hz, 1H, *CH*=CH_2), 4.13 (d, *J* = 5.0 Hz, 2H, CH_2), 1.46 (s, 9H, C(CH_3)$_3$).
^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 152.7, 133.5, 133.3, 115.7, 91.4, 81.4, 45.7, 27.9. **IR** (ν_{max}, cm^{-1}) 3006 (s), 2985 (s), 2942 (s), 2924 (s), 2909 (s), 2883 (s), 1723 (s), 1703 (s), 1633 (s), 1626 (s), 1618 (s), 1419 (s), 1364 (s), 1239 (s), 1146 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M + H]$^+$ Calcd for $C_{10}H_{18}NO_2^+$ 184.1332; Found 184.1327.

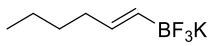
(*E*)-3-(hex-1-en-1-yl)oxazolidine-2-one ((*E*)-**4.3k**)



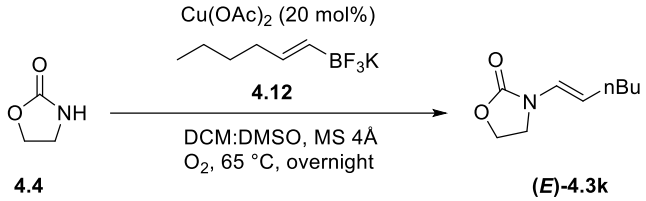
Following a modified reported procedure,[26] in sealed 20 mL, round-bottomed vial, 1-hexyne (**8.17**, 0.70 mL, 5.9 mmol, 1.0 equiv) and catecholborane (0.77 mL, 7.1 mmol, 1 .20 equiv) were dissolved in THF (dry; 19 mL) and the mixture was stirred under reflux for 18 hours. After this time, the pale yellow solution was allowed to cool down to room temperature, transfered into a 25 mL, round bottomed flask and concentrated under reduced pressure. Water (0.8 mL) was added to the residue, with immediate formation of a colorless solid. The suspension was vigorously stirred for 4 hours at room temperature. The solid was collected by filtration and washed with water. (*E*)-Hex-1-en-1-ylboronic acid (0.469 g, 3.66 mmol, 62% yield) was obtained as a colorless solid, which was directly submitted to the following step. Following a

[25] Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216–12217.
[26] Perner, R. J.; Lee, C.-H.; Jiang, M., Gu, Y.-G., DiDomenico, S.; Bayburt, E. K.; Alexander, K. M.; Kohlhaas, K. L.; Jarvis, M. F.; Kowaluk, E., L.; Bhagwat, S. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2803.

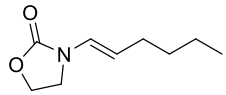
reported procedure,[27] in a 25 mL, round bottomed flask, (*E*)-hex-1-en-1-ylboronic acid (0.469 g, 3.66 mmol, 1.0 equiv) was dissolved in the minimal volume of MeOH (1.2 mL). A solution of KHF_2 (1.00 g, 12.8 mmol, 3.5 equiv) in water (2.9 mL; 4.5 M) was added slowly, causing the rapid precipitation of a colorless solid. The suspension was stirred at room temperature for 15 minutes. The solid (potassium (*E*)-trifluoro(hex-1-en-1-yl)borate (**4.12**, 0.244 g, 1.28 mmol, 35% yield) was then collected by filtration and dried under vacuum.



^{1}H NMR (400 MHz, Acetonitrile-*d*$_3$) δ 5.62 (dq, *J* = 12.6, 6.0 Hz, 1H, BCH=*CH*), 5.30 (dqd, *J* = 17.6, 3.7, 1.8 Hz, 1H, B*CH*=CH), 1.99 – 1.94 (m, 2H, CH-C*H*$_2$), 1.37 - 1.24 (m, 4H, *CH*$_2$*CH*$_2$), 0.89 (m, 3H, *CH*$_3$). The ^{1}H NMR data corresponds to the reported literature data.[27]



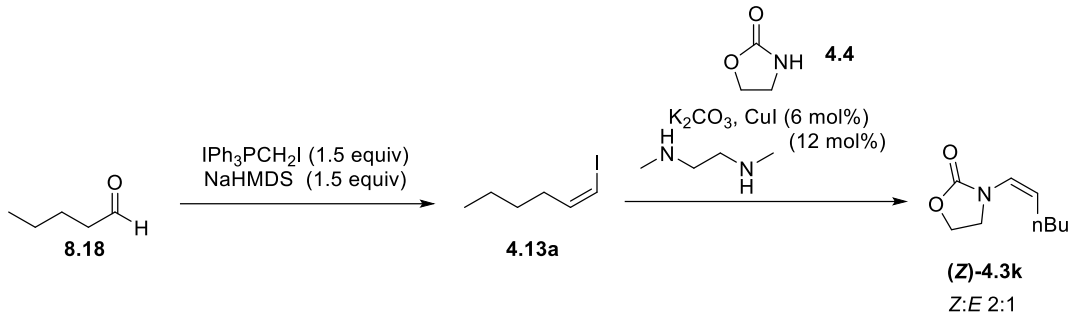
Following a reported procedure,[28] in a sealed 5.0 mL round bottomed test tube, potassium (*E*)-trifluoro(hex-1-en-1-yl)borate **4.12** (0.244 g, 1.28 mmol, 1.7 equiv), oxazolidin-2-one (0.066 g, 0.76 mmol, 1.0 equiv), and copper(II) acetate (0.027 g, 0.15 mmol, 0.20 equiv) were dissolved in a mixture of CH_2Cl_2 (dry; 1.5 mL) and DMSO (dry; 1.5 mL) in the presence of MS (4Å; 0.60 g). The resulting blue suspension was stirred overnight at 65 °C under an atmosphere of oxygen (balloon). After 20 hours, it was allowed to cool down to room temperature and filtered through a plug of celite, which was then washed with several portions of EtOAc. The resulting filtrate was concentrated under reduced pressure and submitted to column chromatography (still retaining DMSO) (SiO_2; EtOAc in pentane 5 to 20%). (*E*)-3-(Hex-1-en-1-yl)oxazolidin-2-one ((*E*)-**4.3k**, 0.081 g, 0.48 mmol, 63% yield) was obtained as a colorless oil.



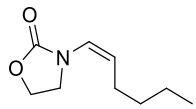
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.64 (d, *J* = 14.3 Hz, 1H, N*CH*=CH-), 4.80 (dt, *J* = 14.2, 7.1 Hz, 1H, NCH=*CH*-), 4.42 (m, 2H, *CH*$_2$ in the oxazolidinone cycle), 3.72 - 3.60 (m, 2H, *CH*$_2$ in the oxazolidinone cycle), 2.06 (qd, *J* = 7.1, 1.4 Hz, 2H, CH=CH*CH*$_2$), 1.44 - 1.26 (m, 4H, *CH*$_2$*CH*$_2$), 0.90 (t, *J* = 7.1 Hz, 3H, CH_3).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.4, 123.8, 111.4, 62.1, 42.6, 32.2, 29.4, 22.1, 13.9.
The characterisation data corresponds to the reported literature data.[28]

[27] Batey R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683.
[28] Bolshan, Y.; Batey, R. *Angew. Chem. Int. Ed.* **2008**, *47*, 2109.

(*Z*)-3-(hex-1-en-1-yl)oxazolidine-2-one ((*Z*)-**4.3k**)



Following a reported procedure,[29] under nitrogen atmosphere, iodo(iodomethyl)triphenylphosphorane (5.16 g, 9.25 mmol) was suspended in THF (13 mL). At room temperature, sodium bis(trimethylsilyl)amide (2 M in THF, 4.6 mL, 9.3 mmol, 1.5 equiv) was added dropwise over 5 min. The reaction was stirred for 30 min then cooled to -78 °C. A solution of valeraldehyde (**8.18**, 0.658 mL, 6.16 mmol, 1.0 equiv) in THF (13 mL) was added dropwise over 15 min. The reaction was then stirred at -78 °C for 1 h then quenched with ammonium chloride (0.561 g, 10.5 mmol) dissolved in 10 mL water then warmed to RT. The crude was diluted with Et_2O (20 mL) and brine:water (1:1, 20 mL). The layers were separated, the aqueous layers were extracted with Et_2O (5x30 mL). The organic layer was washed with $NaHCO_3$ sat (2*20 mL), then brine (20 mL). The organic layers were combined and concentrated under reduced pressure. The compound was purified by column chromatography: SiO_2 using pentane affording (*Z*)-1-iodohex-1-ene (**4.12a**, 0.830 g, 3.95 mmol, 64 % yield). The later was used directly in the next step. Following a reported literature procedure, an oven-dried pointed 2 mL microwave vial was charged with oxazolidin-2-one (**4.4,** 0.237 g, 2.72 mmol, 1 equiv) and potassium carbonate (0.414 g, 2.99 mmol, 1.2 equiv). Under the inert atmosphere of a glove box copper(I) iodide (0.036 g, 0.19 mmol, 6 mol%) was added and the vial was sealed. *N*,*N*'-dimethylethylenediamine (0.041 mL, 0.38 mmol, 12 mol%) and a solution of (*Z*)-1-iodohex-1-ene (0.80 g, 3.8 mmol, 1.4 equiv) in anhydrous toluene (0.9 mL) were added *via* syringe. The resulting greenish suspension was stirred at 110-115 °C for 20 hours. The solution colored a darkish orange. The crude was filtered over a celite pad and washed with CH_2Cl_2. The crude oil was submitted to column chromatography (SiO_2; EtOAc in pentane, 24/1 to 80/20) to afford 3-(hex-1-en-1-yl)oxazolidin-2-one as a mixture of Z and E isomers ((*Z*)-**4.3k** and (*E*)-**4.3k**, 0.340 g, 0.200 mmol, 74% yield, Z:E ratio 2:1)

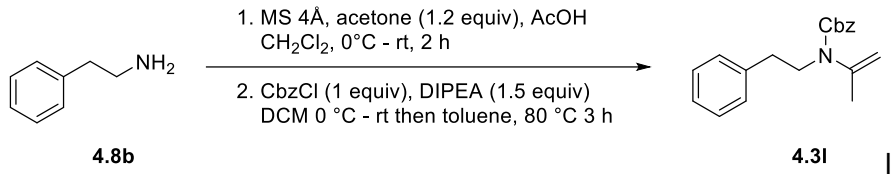


Characterisation of the Z :E mixture :

[29] Selter, L. Harms, K.; Koert, U. *Eur. J. Org. Chem.* **2017**, 1215.

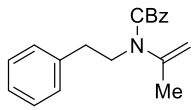
Rf (pentane :EtOAc 6 :4) = 0.4.
^{1}H NMR (400 MHz, Benzene-d_6, 2 :1 mixture of (*Z*) in **bold** and (*E*) alkene in *italic*) δ *7.01 – 6.78* (m, 0.5H, RC*H*=CHR, (*E*)-isomer), **6.44** (dt, *J* = 9.7, 1.6 Hz, 1H, RC*H*=CHR, (*Z*)-isomer), **4.46** (dt, *J* = 9.7, 7.6 Hz, 1H, RC*H*=CHR, (*Z*)-isomer), *4.32* (dd, *J* = 14.3, 7.1 Hz, 0.5H, RC*H*=CHR, (*E*)-isomer), ***3.48 – 3.01*** (m, 3H, cyclic-CH_2, (*E*)-isomer + (*Z*)-isomer), **2.85 – 2.58** (m, 2H, cyclic-CH_2, (*Z*)-isomer), *2.45 – 2.28* (m, 1H, cyclic-CH_2, (*E*)-isomer), *1.87* (tdt, *J* = 7.1, 4.4, 1.5 Hz, 1H, allylic-CH_2, (*E*)-isomer), **1.81** (tdt, *J* = 7.4, 5.8, 1.7 Hz, 2H, allylic-CH_2, (*Z*)-isomer), *1.30 – 1.20* (m, 2H, CH_2-CH_2-CH_3, (*E*)-isomer), **1.19** (m, 4H, CH_2-CH_2-CH_3, (*Z*)-isomer), ***0.93 – 0.81*** (m, 2+3H, CH_3, (*E*)-isomer + (*Z*)-isomer). **^{13}C NMR** (101 MHz, Benzene-d_6, the C=O of (*E*)-isomer is not resolved) δ 156.9, 125.5, 123.9, 113.3, 110.3, 61.9, 61.8, 45.3, 42.4, 33.4, 33.4, 30.3, 26.8, 23.1, 23.0, 14.7. **IR** (ν_{max}, cm^{-1}) 2959 (m), 2931 (m), 2871 (m), 1752 (s), 1415 (s), 1243 (m), 1094 (s), 1075 (s), 1040 (m). **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z [M + H]$^+$ Calcd for $C_9H_{16}NO_2^+$ 170.1176; Found 170.1177.

Benzyl phenethyl(propen-2-yl)carbamate (**4.3l**)



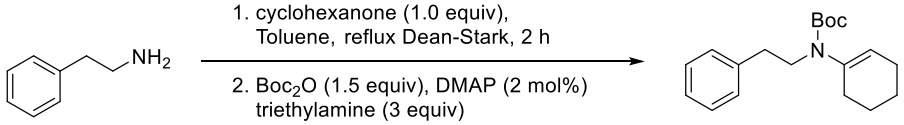
4.8b **4.3l**

Based on a modified reported procedure, to a solution of 2-phenylethanamine (**4.8b**, 1.6 mL, 13 mmol, 1 equiv), acetic acid (0.14 mL, 2.5 mmol, 0.2 equiv) and 4 Å mol sieves (2.8 g) in CH_2Cl_2 (16 mL) at 0 °C was added propan-2-one (1.0 mL, 14 mmol, 1.2 equiv) dropwise. The solution was warmed to RT and stirred for 14 h and decanted. To the resulting solution at 0 °C were added CH_2Cl_2 (10 mL), benzyl chloroformate (1.9 mL, 13 mmol, 1 equiv) and *N*-ethyl-*N*-*iso*propylpropan-2-amine (3.0 mL, 18 mmol, 1.5 equiv). The reaction mixture was warmed to RT and stirred for 18 h. The solution was concentrated and toluene (10 mL) was added. The solution was heated to 80 °C for 36 h and then concentrated. The crude oil was purified by column chromatography (SiO_2, pentane:Et_2O, 100:0 to 90:10) affording **4.8l** as a colorless oil (0.351 g, 1.20 mmol, 90% purity, 8% yield).



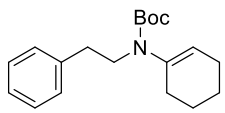
Rf (pentane:EtOAc 9:1) = 0.7.
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 7.49 – 7.27 (m, 7H, Ph*H*), 7.28 – 7.19 (m, 3H, Ph*H*), 5.12 (s, 2H, OCH_2Ph), 4.93 (q, *J* = 1.3 Hz, 1H, C=CH_2), 4.83 (m, 1H, C=CH_2), 3.77 – 3.62 (m, 2H, CH_2), 3.02 – 2.86 (m, 2H, CH_2), 1.88 (s, 3H, CH_3).
^{13}C NMR (101 MHz, Acetonitrile-d_3, as a not fully resolved mixture of rotamers) δ 154.9, 145.7, 139.8, 137.7, 129.4, 129.4, 129.2, 129.0, 129.0, 128.8, 128.8, 128.7, 128.5, 128.3, 128.1, 128.1, 127.8, 126.8, 126.8, 110.9, 90.5, 67.2, 67.1, 64.6, 51.1, 46.8, 36.9, 35.2, 27.0, 21.1. **IR** (ν_{max}, cm^{-1}) 2987 (s), 2972 (s), 2959 (s), 2900 (s), 1760 (s), 1699 (s), 1685 (s), 1649 (s), 1403 (s), 1304 (s), 1099 (s), 1067 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M + H]$^+$ Calcd for $C_{19}H_{22}NO_2^+$ 296.1645; Found 296.1636.

Tert-butyl cyclohex-1-en-1-yl(phenethyl)carbamate (**4.3m**)



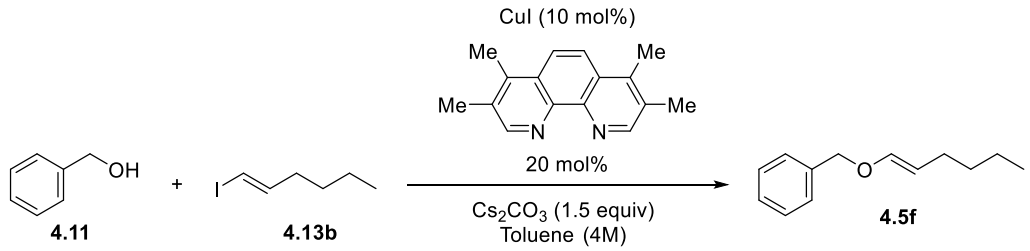
4.8b **4.3m**

2-phenylethanamine (**4.8b** 1.2 mL, 9.8 mmol, 1 equiv) and cyclohexanone (1.0 mL, 9.7 mmol, 1.0 equiv) were dissolved in toluene (50 mL) then refluxed for 3h with a Dean-Stark apparatus. The reaction was cooled to room temperature then concentrated to half the initial volume by rotary evaporation. The resulting solution was cooled to 0 °C and a solution of Boc_2O (3.16 g, 14.47 mmol) and DMAP (0.024 g, 0.193 mmol) in toluene (50 mL) was added dropwise to the reaction mixture (30 min). The reaction was stirred at 0°C for 2h. After stirring for 2 h at this temperature, triethylamine (2.97 g, 30.0 mmol) was added dropwise to the reaction mixture, and stirring was continued for another 2 h at 0 °C then left overnight at rt. The reaction mixture was then washed with saturated $NaHCO_3$ (2 x 50 mL), NH_4Cl (3 x 70 mL) and sat. aq. NaCl (2 x 70 mL) solutions, dried over $MgSO_4$, filtered and concentrated in vaccuo. The crude yellow oil was submitted to column chromatography: Pent:Et2O (24:1) resuting in one pure fraction (40 mg) and 5 other Boc_2O contaminated fractions. The Boc_2O contaminated fractions were conentrated then solubilised in 50 mL CH_2Cl_2. Imidazole work-up was attempted: 1H-imidazole (0.788 g, 11.58 mmol) were added after consumtion of Boc_2O (TLC analysis PAN stain blue spot Rf = 0.7, Pent.EtOAc 9:1). The organic layer was washed with aq. AcOH 30% was added dried over Na_2SO_4, filtered and concentrated under reduced pressure resulting in pure *tert*-butyl cyclohex-1-en-1-yl(phenethyl)carbamate **4.3m** (0.950 g, 3.15 mmol, 32.7 % yield)



Rf (pentane:Et_2O 9:1) = 0.6.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 – 7.17 (m, 2H, Ph), 7.15 – 7.09 (m, 3H, Ph), 5.45 (s, 1H, RC*H*=CNR), 3.51 – 3.42 (m, 2H, NCH_2-CH_2Ph), 2.82 – 2.74 (m, 2H, NCH_2-CH_2Ph), 2.06 – 1.94 (m, 4H, cyclic-CH_2), 1.64 – 1.54 (m, 2H, cyclic-CH_2), 1.49 (qd, *J* = 5.9, 2.5 Hz, 2H, cyclic-CH_2), 1.37 (s, 9H, *t*Bu). **^{13}C NMR** (101 MHz, Chloroform-*d*, as a mixture of rotamers) δ 155.9, 154.5, 139.7, 139.4, 128.9, 128.4, 126.4, 126.2, 123.5, 79.4, 50.7, 42.0, 35.5, 28.4, 27.0, 24.7, 23.0, 21.9. **HRMS** (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{27}NNaO_2^+$ 324.1934; Found 324.1935.

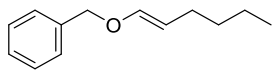
(*E*)-((hex-1-en-1-yloxy)methyl)benzene (**4.5f**)



Following a slightly modified reported procedure,[30] inside a glove box, a 5 mL test tube was charged with CuI (0.038 g, 0.10 mmol, 10 mol%), 3,4,7,8-tetramethyl-1,10-phenanthroline (0.94.6 mg, 0.200 mmol, 20 mol%) and Cs_2CO_3 (0.977 g, 3.00 mmol, 1.5 equiv). The tube was sealed and withdrawn from the glovebox. Toluene (dry, 1.0 mL), followed by benzyl alcohol (**4.11**, 0.41 mL, 2.0 mmol, 2 equiv) and *E*-1-iodohexene (**4.13b**, 0.210 g, 1.00 mmol, 1 equiv)

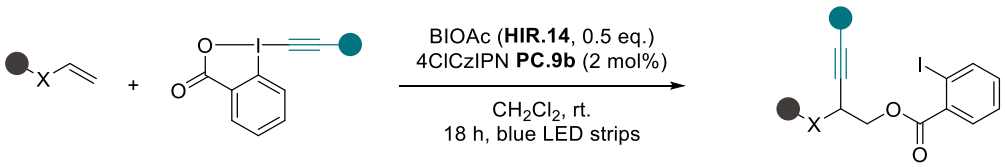
[30]Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978.

were then added via syringe. The reaction mixture was heated to 80 ºC for 8 hours. After this time TLC analysis showed full consumption of the iodo-alkene. The reaction was stopped, the now brown suspension was allowed to cool down to room temperature, and the solids were then filtered off through a short pad of SiO_2, which was washed with several portions of CH_2Cl_2. The resulting brown-orange solution was concentrated under reduced pressure. The so obtained brown crude oil was submitted to column chromatography (Biotage, 12 g SiO_2; CH_2Cl_2 in pentane, 1 to 10%) to afford (*E*)-((hex-1-en-1-yloxy)methyl)benzene (**4.5f**, 0.253 g, 1.32 mmol, 66% yield) as a colorless oil.



Rf (pentane: CH_2Cl_2 96:4) = 0.6.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.34 (m, 4H, Ph*H*), 7.31 (m, 1H, Ph*H*), 6.34 (dt, *J* = 12.5, 1.4 Hz, 1H, O*CH*=CH-), 4.90 (dt, *J* = 12.5, 7.3 Hz, 1H, OCH=*CH*-), 4.72 (s, 2H, Ph*CH$_2$*O), 1.94 (dtt, *J* = 8.5, 7.2, 1.4 Hz, 2H, CH=CH*CH$_2$*), 1.40 – 1.25 (m, 4H, *CH$_2$CH$_2$*), 0.90 (m, 3H, *CH$_3$*).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 145.8, 137.4, 128.5, 127.8, 127.6, 105.3, 71.1, 32.8, 27.4, 22.1, 13.9. **IR** (ν_{max}, cm^{-1}) 3011 (m), 2998 (m), 2970 (s), 2955 (s), 2923 (s), 2902 (s), 2850 (m), 1672 (m), 1455 (m), 1380 (m), 1258 (m), 1213 (s), 1153 (s), 1124 (s), 1075 (s), 1046 (s), 1038 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M + H]$^+$ Calcd for $C_{13}H_{19}O^+$ 191.1430; Found 191.1433.

GP3: oxyalkynylation of ene-carbamates and enol ethers



4.3 **4.5** **HIR.2** **HIR.3** **4.20** **4.22** **4.23**

An oven-dried flat-bottomed screw-cap vial equipped with a magnetic stirrer was charged with R-EBX (**HIR.2**, 0.25 mmol, 1.0 equiv), BIOAc (**HIR.14**, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%). The reaction vessel was sealed with a rubber septum. Following three vacuum/nitrogen cycles, dry, degassed (*via* freeze-pump-thaw technique) CH_2Cl_2 (0.25 M based on R-EBX, 1.0 mL) was then added. The substrate (0.38 mmol, 1.5 equiv)[31] was then added *via* syringe. The rubber septum was replaced with the corresponding screw-cap under a flux of Argon. The reaction was irradiated overnight (15 h-18 h) with blue LED strips under ventilation (T = 25°C) and stirring. The volatiles were evaporated off. The crude was then dissolved in CH_2Cl_2 with 0.2 mL of Et_3N. A solid deposit for flash chromatography was prepared with SiO_2 (ca. 3g). The crude was then purified though flash

[31] Some reactions were performed on 0.2 mmol scale of PhEBX with 1.2 equiv of alkene.

chromatography (Et_3N deactivated SiO_2 ca. 40 g or biotage : SiO_2 25 g, Pentane:Et_2O or Pentane:EtOAc)[32] affording the desired difunctionalised product.

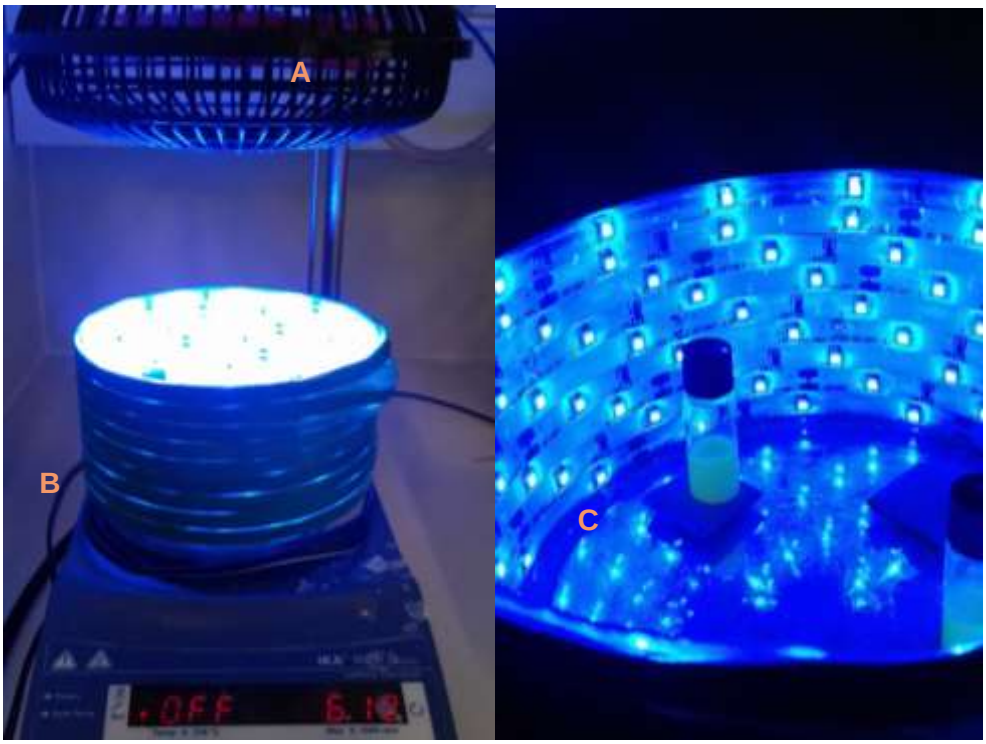
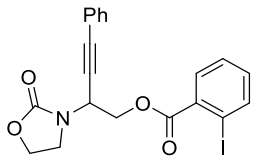


Figure 8.1. Experimental set-up. A: Overtop ventilation, B: crystallisation bowl wrapped with LEDs. C flask stuck to bottom of crystallisation bowl ca. 3 cm away from LEDs. The whole set up is concealed from the external light sources with a reflective shield.

2-(2-Oxooxazolidin-3-yl)-4-phenylbut-3-yn-1-yl 2-iodo benzoate (**4.20a**)

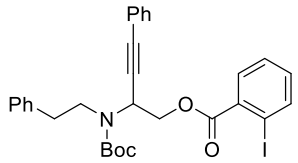


Performed on 0.2 mmol scale.
Following **GP3**: Obtained from *N*-vinyloxazolidin-2-one (**4.3a**, 0.027 g, 0.24 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.070 g, 0.20 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.031 g, 0.10 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 4 mg, 4 µmol, 2 mol%); CH_2Cl_2 (0.8 mL, 0.25 M) after 18 hours.
Column: Pentane:EtOAc, 9:1 to 8:2. Yield 80% (0.074 g, 0.16 mmol). Yellow oil with residual grease.

Rf (Pentane:EtOAc 8:2) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.84 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.44 (dd, *J* = 7.9, 1.8 Hz, 2H, Ph*H*), 7.41 (dd, *J* = 7.7, 1.2 Hz, 1H, Ar*H*), 7.38 - 7.31 (m, 3H, Ph*H*), 7.17 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H, Ar*H*), 5.37 (dd, *J* = 9.0, 4.4 Hz, 1H, NC*H*), 4.77 (dd, *J* = 11.5, 9.0 Hz, 1H, OCH_2), 4.47 (dd, *J* = 11.5, 4.4 Hz, 1H, OCH_2), 4.44 - 4.33 (m, 2H, CH_2), 3.85 (dt, *J* = 9.2, 8.1 Hz, 1H, CH_2), 3.78 (td, *J* = 8.6, 5.6 Hz, 1H, CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 165.9, 158.0, 141.4, 134.2, 133.1, 131.9, 131.3, 129.2, 128.5, 128.2, 121.5, 94.3, 87.5, 80.9, 63.8, 62.4, 46.2, 41.2. **IR** (ν_{max}, cm^{-1}) 3060 (w), 2993 (w), 2920 (w), 2851 (w), 2229 (w), 1750 (s), 1487 (m), 1422 (m), 1249 (s). **HRMS** (ESI) calcd for $C_{20}H_{17}INO_4^+$ $[M+H]^+$ 462.0197; found 462.0206.

[32] Coelution of residual alkene was often observed hence the greater quantities of SiO_2. The corresponding dilution can lead to poor detection of the compound by TLC (both UV and p-anisaldehyde stains should be combined).

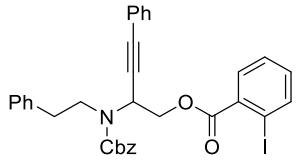
2-((T*ert*-butoxycarbonyl)(phenethyl)amino)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.20b**)



Performed on 0.2 mmol scale.
Following **GP3**: Obtained from *tert*-butyl phenethyl(vinyl)carbamate (**4.3b**, 0.054 g, 0.24 mmol, 1.2 equiv); PhEBX (**2**, 0.070 g, 0.20 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.031 g, 0.10 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 4 mg, 4 µmol, 2 mol%), CH_2Cl_2 (0.8 mL, 0.25 M) after 18 hours.
Column: Pentane:EtOAc, 1:0 to 9:1. Yield 63% (0.074 g, 0.12 mmol). Pale yellow oil.

Rf (Pent.:EtOAc 9:1) = 0.25
^{1}H NMR (400 MHz, Acetonitrile-d_3, 7:3 mixture of rotamers) δ 8.06 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.85 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.56 – 7.37 (m, 6H, Ph*H* + Ar*H*), 7.33 – 7.19 (m, 6H, Ph*H* + Ar*H*), 5.64 (bs, 0.7H, major, NC*H*), 5.37 (bs, 0.3H, minor, NC*H*), 4.55 (d, *J* = 6.9 Hz, 2H, OCH_2), 3.66 – 3.43 (m, 2H, CH_2), 3.01 (dq, *J* = 12.5, 7.5, 6.9 Hz, 2H, CH_2), 1.46 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of rotamers, signals not fully resolved) δ 172.0, 166.2, 142.0, 135.3, 133.7, 132.2, 131.6, 129.6, 129.2, 128.8, 122.5, 94.0, 81.1, 65.0, 60.8, 47.6, 40.9, 35.1, 28.0, 14.1. **IR** (ν_{max}, cm^{-1}) 2977 (s), 2952 (m), 1733 (s), 1692 (s), 1403 (s), 1366 (s), 1247 (s), 1159 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{30}H_{30}INNaO_4^+$ 618.1112; Found 618.1109.

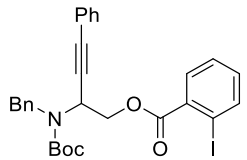
2-(((Benzyloxy)carbonyl)(phenethyl)amino)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.20c**)



Performed on 0.2 mmol scale.
Following **GP3**: Obtained from benzyl phenethyl(vinyl)carbamate (**4.3c**, 0.068 g, 0.24 mmol, 1.2 equiv); PhEBX (**HIR.2a**, 0.070 g, 0.2 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.031 g, 0.1 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 4 mg, 4 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 10:0 to 9:1. Yield 86% (0.108 g, 0.172 mmol). Pale yellow oil.

Rf (Pent.:EtOAc 9:1) = 0.25.
^{1}H NMR (400 MHz, Acetonitrile-d_3, 6:4 mixture of rotamers) δ 8.01 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.75 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.61 – 7.07 (m, 12H, Ph*H*), 5.62 (bs, 0.6H, major, N*CH*), 5.48 (bs, 0.4H minor, N*CH*)., 5.12 (d, *J* = 3.7 Hz, 2H, O*CH$_2$*Ph), 4.58 – 4.51 (m, 2H, CH*CH$_2$*O), 3.72 – 3.47 (m, 2H, CH_2CH_2), 3.12 – 2.90 (m, 2H, CH_2CH_2). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of rotamers, signals not fully resolved) δ 166.7, 156.8, 142.2, 140.2, 137.7, 134.0, 132.6, 131.8, 130.0, 129.7, 129.6, 129.4, 129.3, 128.9, 122.8, 94.3, 86.8, 84.5, 68.2, 65.5, 49.0, 47.4, 36.9, 35.9. **IR** (ν_{max}, cm^{-1}) 3033 (m), 3071 (m), 2951 (m), 2862 (m), 1732 (s), 1700 (s), 1586 (m), 1491 (m), 1453 (s), 1409 (s), 1370 (m), 1282 (s), 1250 (s), 1174 (m), 1129 (s), 1104 (s), 1047 (m), 1015 (s), 977 (m), 742 (s), 685 (m), 691 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{33}H_{28}INNaO_4^+$ 652.0955; Found 652.0961.

2-(Benzyl(*tert*-butoxycarbonyl)amino)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.20d**)

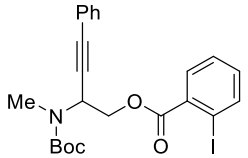


Performed on 0.2 mmol scale.
Following **GP3**: Obtained from *tert*-butyl benzyl(vinyl)carbamate (**4.3d**, 0.056 g, 0.24 mmol, 1.2 equiv); PhEBX (**HIR.2a**, 0.070 g, 0.2 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.031 g, 0.1 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 4 mg, 4 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 10:0 to 9:1. Yield 73% (0.085 g, 0.146 mmol). Pale yellow oil.

Rf (Pent.:EtOAc 9:1) = 0.25.
^{1}H NMR (400 MHz, Acetonitrile-d_3, 6:4 mixture of rotamers) δ 8.06 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.83 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.49 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.45 – 7.21 (m, 11H, Ar*H* + Ph*H*), 5.78 (m, 0.6H, major, NC*H*), 5.45 (m, 0.4H, minor, NC*H*), 4.71 (d, *J* = 16.3 Hz, 1H, PhC*H$_2$*), 4.60 (d, *J* = 16.3 Hz, 1H, PhC*H$_2$*), 4.52 (dd, *J* = 11.2, 5.5 Hz, 1H, OC*H$_2$*), 4.46 (dd, *J* = 11.2, 8.4 Hz, 1H, OC*H$_2$*), 1.62 – 1.16 (m, 9H, C(*CH$_3$*)$_3$). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of rotamers, signals not fully resolved) δ 166.1, 155.7, 141.9, 140.4, 135.1, 133.7, 132.1, 131.6, 129.4, 129.1, 128.9, 128.8, 128.7, 127.5, 127.3, 122.5, 94.1, 86.6, 84.4, 81.0, 65.2, 48.2, 48.1, 28.0. **IR** (ν_{max}, cm^{-1}) 3062 (w), 3029 (w), 2976 (m), 2930 (w), 1733 (m), 1704 (s), 1685 (s), 1392 (s), 1366 (m), 1287 (m), 1242

(s), 1162 (s), 1131 (m), 1119 (s), 1101 (s), 1016 (m). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{29}H_{28}INNaO_4^+$ 604.0955; Found 604.0957.

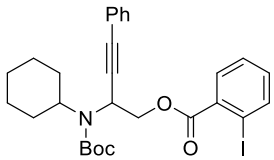
2-(Methyl(*tert*-butoxycarbonyl)amino)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.20e**)



Performed on 0.2 mmol scale
Following **GP3**: Obtained from *tert*-butyl methyl(vinyl)carbamate (**4.3e**, 0.059 g, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.2 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 10:0 to 9:1. Yield 83% (0.105 g, 0.208 mmol). Colorless oil.

Rf (Pent.:EtOAc 9:1) = 0.25.
^{1}H NMR (400 MHz, Acetonitrile-d_3, 7 : 3 mixture of rotamers) δ 8.06 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.83 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.54 – 7.42 (m, 3H, Ar*H* + Ph*H*), 7.46 – 7.35 (m, 3H, Ph*H*), 7.26 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.70 (bs, 0.7H, major, N*CH*), 5.54 (bs, 0.3H, minor, N*CH*), 4.64 – 4.44 (m, 2H, OCH_2), 2.98 (s, 3H, NCH_3), 1.40 (bs, *J* = 9.8 Hz, 9H, C(CH_3)$_3$). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of rotamers, signals not fully resolved) δ 166.6, 156.3, 155.3, 142.3, 135.7, 134.1, 132.6, 132.0, 129.9, 129.6, 129.2, 122.9, 94.5, 94.4, 86.7, 84.1, 80.9, 64.4, 49.1, 47.9, 30.2, 28.4. **IR** (ν_{max}, cm^{-1}) 3059 (w), 2976 (m), 2932 (w), 2875 (w), 1733 (m), 1685 (s), 1388 (s), 1245 (s), 1147 (s), 741 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{23}H_{24}INNaO_4^+$ 528.0642; Found 528.0651.

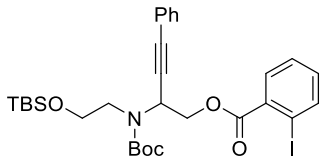
2-((*Tert*-butoxycarbonyl)(cyclohexyl)amino)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.20f**)



Performed on 0.2 mmol scale
Following **GP3**: Obtained from cyclohexyl(vinyl)carbamate (**4.3f**, 0.068 g, 0.24 mmol, 1.2 equiv); PhEBX (**HIR.2a**, 0.070 g, 0.2 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.031 g, 0.1 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 4 mg, 4 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 10:0 to 9:1. Yield 65% (0.074 g, 0.13 mmol). Pale yellow oil.

Rf (Pent.:EtOAc 9:1) = 0.3.
^{1}H NMR (400 MHz, Acetonitrile-d_3, 1:1 mixture of rotamers) δ 8.04 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.82 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.50 – 7.41 (m, 3H, Ar*H* and Ph*H*), 7.41 – 7.32 (m, 3H, Ar*H* and Ph*H*), 7.24 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.49 (bs, 0.5H, N-*CH*-alkyne), 5.01 (bs, 0.5H, N*CH*-alkyne), 4.59 (bs, 1H, OCH_2), 4.50 (bs, 1H, OCH_2) 3.70 (bs, 0.5H, Cy*H*-N), 3.44 (bs, 0.5H, Cy*H*-N), 1.88 – 1.69 (m, 4H, *Cy*), 1.70 – 1.53 (m, 2H, *Cy*), 1.44 (s, 9H, C(CH_3)$_3$), 1.37 – 1.22 (m, 2H, *Cy*), 1.12 (ddt, *J* = 16.3, 12.7, 3.4 Hz, 2H, *Cy*). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of rotamers, signals not fully resolved) δ 166.4, 141.9, 135.5, 133.7, 132.0, 131.5, 129.3, 129.2, 128.8, 122.9, 94.0, 80.6, 65.7, 65.4, 56.6, 33.6, 31.5, 28.2, 26.6, 25.9, 25.4. **IR** (ν_{max}, cm^{-1}) 2987 (s), 2972 (s), 2960 (s), 2901 (s), 1733 (s), 1705 (s), 1698 (s), 1686 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{28}H_{32}INNaO_4^+$ 596.1268; Found 596.1270.

2-((*Tert*-butoxycarbonyl)(2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.20g**)

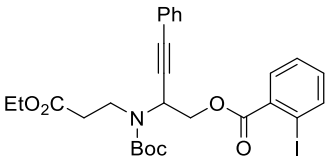


Performed on 0.2 mmol scale
Following **GP3**: Obtained from *tert*-butyl (2-((*tert*-butyldimethylsilyl)oxy)ethyl)(vinyl)carbamate (**4.3g**, 0.072 g, 0.24 mmol, 1.2 equiv); PhEBX (**HIR.HIR.2aa**, 0.070 g, 0.2 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.031 g, 0.1 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 4 mg, 4 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 10:0 to 9:1. Yield 52% (0.068 g, 0.11 mmol). Pale yellow oil.

Rf (Pent.:EtOAc 9:1) = 0.4.
^{1}H NMR (400 MHz, Acetonitrile-d_3, 7:3 mixture of rotamers) δ 8.05 – 7.98 (m, 1H, Ar*H*), 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.48 – 7.38 (m, 3H, Ar*H* + Ph*H*), 7.41 – 7.29 (m, 3H, Ph*H*), 7.21 (td, *J* = 7.7,

1.8 Hz, 1H, , Ar*H*), 5.53 (bs, 0.6H, major, NC*H*), 5.24 (s, 0.4H, minor, NC*H*), 4.65 – 4.35 (m, 2H, CH_2), 3.82 – 3.74 (m, 2H, CH_2), 3.44 (d, *J* = 6.9 Hz, 2H, CH_2), 1.38 (s, 9H, C(CH_3)$_3$), 0.83 (s, 9H, C(CH_3)$_3$), 0.00 (s, 6H, Me_2). **^{13}C NMR** (101 MHz, Acetonitrile-*d*$_3$, mixture of rotamers, signals not fully resolved) δ 166.7, 142.3, 135.9, 134.1, 132.6, 132.0, 129.9, 129.6, 129.2, 94.4, 81.3, 65.7, 62.5, 48.7, 48.3, 47.5, 28.5, 26.3, 26.3, 18.9, -5.1. **IR** (v_{max}, cm^{-1}) 2986 (s), 2900 (s), 1735 (s), 1698 (s), 1405 (s), 1250 (s), 1050 (s). **HRMS** (ESI/QTOF) m/z [M + H]$^+$ Calcd for $C_{30}H_{41}INO_5Si^+$ 650.1793; Found 650.1791.

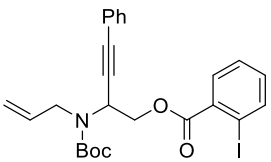
2-((*Tert*-butoxycarbonyl)(3-ethoxy-3-oxopropyl)amino)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.20h**)



Performed on 0.2 mmol scale
Following **GP3**: Obtained from ethyl 3-((*tert*-butoxycarbonyl)(vinyl)amino)propanoate (**4.3h**, 0.058 g, 0.24 mmol, 1.2 equiv); PhEBX (**HIR.2a**, 0.070 g, 0.2 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.031 g, 0.1 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 4 mg, 4 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 10:0 to 9:1. Yield 69% (0.082 g, 0.14 mmol). Pale yellow oil.

Rf (Pent.:EtOAc 9:1) = 0.35.
^{1}H NMR (400 MHz, Acetonitrile-*d*$_3$, 7:3 mixture of rotamers) δ 8.05 – 7.98 (m, 1H, Ar*H*), 7.80 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.48 – 7.41 (m, 3H, Ar*H* and Ph*H*), 7.41 – 7.30 (m, 3H, Ar*H* and Ph*H*), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.53 (bs, 0.7H, major, N*CH*), 5.31 (bs, 0.3H, minor, N*CH*), 4.50 (d, *J* = 7.0 Hz, 2H, O*CH*$_2$-CHN), 4.02 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$*CH*$_3$), 3.60 (m, 2H, *CH*$_2$), 2.68 (d, *J* = 8.7 Hz, 2H, *CH*$_2$), 1.37 (s, 9H, C(*CH*$_3$)$_3$), 1.13 (t, *J* = 7.1 Hz, 3H, OCH$_2$*CH*$_3$). **^{13}C NMR** (101 MHz, Acetonitrile-*d*$_3$, mixture of rotamers, signals not fully resolved) δ 172.0, 166.2, 142.0, 135.3, 133.7, 132.2, 131.6, 129.6, 129.2, 128.8, 122.5, 94.0, 81.1, 65.0, 60.8, 47.6, 35.1, 28.0, 14.1. **IR** (v_{max}, cm^{-1}) 3009 (s), 3004 (s), 2974 (s), 2943 (s), 2928 (s), 2883 (s), 1739 (s), 1726 (s), 1716 (s), 1705 (s), 1696 (s), 1685 (s), 1678 (s), 1406 (s), 1248 (s), 1159 (s), 1046 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{27}H_{30}INNaO_6^+$ 614.1010; Found 614.1011.

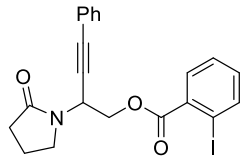
2-(Allyl(*tert*-butoxycarbonyl)amino)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.20i**)



Performed on 0.25 mmol scale
Following **GP3**: Obtained from *tert*-butyl allyyl(vinyl)carbamate (**4.3i**, 0.069 g, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 10:0 to 9:1. Yield 54% (0.072 g, 0.14 mmol). Pale yellow oil.

Rf (Pent.:Et_2O 9:1) = 0.2.
^{1}H NMR (400 MHz, Acetonitrile-*d*$_3$, 6:4 mixture of rotamers) δ 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.83 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.52 – 7.43 (m, 3H, Ar*H* + Ph*H*), 7.43 – 7.33 (m, 3H, Ph*H*), 7.24 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 6.08 – 5.90 (m, 1H, R-C*H*=CH$_2$), 5.63 (bs, 0.6H, NC*H*), 5.33 (bs, 0.4H, NC*H*), 5.28 – 5.19 (m, 1H, CH=C*H*$_2$), 5.19 – 5.06 (m, 1H, CH=C*H*$_2$), 4.49 (m, 2H, C*H*$_2$), 4.09 – 3.89 (m, 2H, C*H*$_2$), 1.39 (s, 9H, C(C*H*$_3$)$_3$). **^{13}C NMR** (101 MHz, Acetonitrile-d3) δ 166.2, 155.6, 141.9, 136.3, 136.0, 135.3, 134.2, 133.7, 132.1, 131.6, 130.4, 129.5, 129.2, 128.8, 128.4, 122.6, 116.2, 114.8, 94.0, 80.8, 65.0, 28.2, 28.0. **IR** (v_{max}, cm^{-1}) 3377 (w), 3073 (w), 2977 (w), 2933 (w), 1733 (m), 1691 (s), 1583 (w), 1449 (m), 1395 (s), 1368 (m), 1322 (m), 1284 (m), 1247 (s), 1168 (s), 1139 (s), 1103 (m), 1043 (w), 1014 (m), 989 (m), 920 (w), 862 (w), 743 (s), 692 (m). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{25}H_{26}INNaO_4^+$ 554.0799; Found 554.0809.

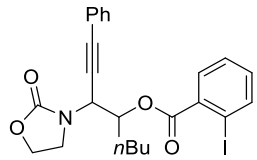
2-(2-oxopyrrolidin-1-yl)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.20j**)



Performed on 0.25 mmol scale
Following **GP3**: Obtained from *N*-vinyl pyrrolidinone (**4.3j**, 0.042 g, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.031 g, 0.1 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 4 mg, 4 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 9:1 to 8:2. Yield 85% (0.098 g, 0.21 mmol). Pale yellow oil.

Rf (Pent.:EtOAc 9:1) = 0.25.
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.06 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.81 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.58 – 7.47 (m, 3H, Ar*H* and Ph*H*), 7.47 – 7.33 (m, 3H, Ph*H*), 7.27 (td, *J* = 7.7, 1.8 Hz, 1H, Ar*H*), 5.53 (dd, *J* = 8.6, 4.8 Hz, 1H, N*CH*CH_2O), 4.64 (dd, *J* = 11.3, 8.6 Hz, 1H, NCH*CH_2*O), 4.50 (dd, *J* = 11.2, 4.8 Hz, 1H, NCH*CH_2*O), 3.75 – 3.52 (m, 2H, *CH_2*), 2.39 – 2.30 (m, 2H, *CH_2*), 2.12 – 2.02 (m, 2H, *CH_2*). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 175.4, 166.5, 141.8, 135.6, 133.7, 132.3, 131.4, 129.6, 129.2, 129.1, 128.9, 122.4, 93.8, 86.0, 83.1, 64.4, 43.9, 31.1, 18.2. **IR** (ν_{max}, cm^{-1}) 3054 (s), 2972 (s), 2894 (s), 1732 (s), 1686 (s), 1417 (s), 1284 (s), 1246 (s), 1132 (s), 1104 (s). **HRMS** (ESI/QTOF) m/z [M + H]$^+$ Calcd for $C_{21}H_{19}INO_3^+$ 460.0404; Found 460.0414

3-(2-Oxooxazolidin-3-yl)-1-phenyloct-1-yn-4-yl 2-iodobenzoate (**4.20k**)



Performed on 0.25 mmol scale
Following **GP3**: Obtained from (*E*)-3-(Hex-1-en-1-yl)oxazolidin-2-one ((*E*)-**4.3k**, 0.064 g, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv);
BIOAc (**HIR.14**, 0.038 g, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 19:1 to 8:2. Isolated separately as two diastereoisomers (0.076 g, 60% and 0.027 g, 20% yield) as 2 colorless oils. Overall yield 80% (0.103 g, 0.199 mmol, dr: 3:1).

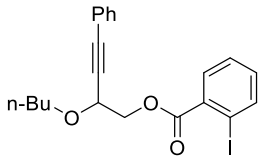
OR Obtained from the 2:1 mixture of (*Z*)-3-(Hex-1-en-1-yl)oxazolidin-2-one and (*E*)-isomer ((*Z*:*E*)-**4.3k**, 0.064 g, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv);
BIOAc (**HIR.14**, 0.038 g, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 19:1 to 8:2. Isolated separately as two diastereoisomers (0.079 g, 61% yield and 0.025 g, 19% yield) as 2 colorless oils.. Overall yield 80% (0.104g, 0.201 mmol, dr: 3:1).

Major diastereoisomer:
Rf (Pent:EtOAc 7:3) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.78 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.45 - 7.42 (m, 2H, Ph*H*), 7.40 (dd, *J* = 7.6, 1.3 Hz, 1H, Ar*H*), 7.38 - 7.30 (m, 3H, Ph*H*), 7.16 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.43 (td, *J* = 8.7, 3.4 Hz, 1H, OC*H*), 5.11 (d, *J* = 8.5 Hz, 1H, NC*H*), 4.37 (td, *J* = 8.1, 6.0 Hz, 1H, C*H_2*), 4.30 (q, *J* = 8.8 Hz, 1H, C*H_2*), 3.86 - 3.76 (m, 2H, C*H_2*), 2.02 (m, 1H, C*H_2*), 1.86 (dtd, *J* = 14.4, 8.8, 5.8 Hz, 1H, C*H_2*), 1.59 - 1.27 (m, 4H C*H_2*- C*H_2*- CH_3), 0.92 (t, *J* = 7.2 Hz, 3H, C*H_3*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.3, 158.3, 141.3, 134.8, 132.9, 131.9, 130.9, 129.1, 128.5, 128.2, 121.6, 94.1, 87.8, 81.6, 73.8, 62.5, 50.5, 41.6, 31.1, 27.2, 22.4, 13.9. **IR** (ν_{max}, cm^{-1}) 2960 (w), 2929 (w), 2862 (w), 2252 (w), 1742 (m), 1736 (m), 1420 (m), 1286 (m), 1249 (m), 907 (s), 727 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{24}H_{24}INNaO_4^+$ 540.0642; Found 540.0640.

Minor diastereoisomer:
Rf (Pent:EtOAc 7:3) = 0.35.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.78 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.50 – 7.30 (m, 6H, Ph*H* + Ar*H*), 7.16 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 5.43 (td, *J* = 8.7, 3.4 Hz, 1H OC*H*), 5.11 (d, *J* = 8.5 Hz, 1H, NC*H*), 4.52 – 4.24 (m, 2H, C*H_2*), 3.91 – 3.77 (m, 2H, C*H_2*), 2.05 (m, 1H, C*H_2*), 1.86 (m, 5.7 Hz, 1H, C*H_2*), 1.56 – 1.21 (m, 4H, C*H_2*-C*H_2*-CH_3), 0.90 (dt, *J* = 18.0, 7.2 Hz, 3H, CH_2-CH_2-C*H_3*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 165.7, 158.2, 141.7, 134.7, 133.1, 132.0, 131.3, 129.1, 128.5, 128.2, 122.0, 94.5, 87.7, 81.7, 75.8, 62.6, 50.2, 42.7, 31.3, 27.5, 22.6, 14.1. **IR** (ν_{max}, cm^{-1}) 2957 (m), 2925 (m), 2871 (m), 1743 (s), 1727 (s), 1490 (m), 1417 (m), 1246 (s),

1133 (s), 759 (s), 741 (s). **HRMS** (ESI/QTOF) m/z [M + H]$^+$ Calcd for $C_{24}H_{25}INO_4^+$ 518.0823; Found 518.0830.

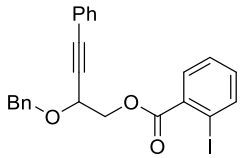
2-Butoxy-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.22a**)



Performed on 0.25 mmol scale
Following **GP3**: Obtained from *n*butyl vinyl ether (**4.5a**, 0.048 mL, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.1 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:Et_2O, 100:0 to 95:5. Yield 89% (0.100 g, 0.223 mmol). Colorless oil.

Rf (Pentane:Et_2O 95:5) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (dd, *J* = 7.9, 1.3 Hz, 1H, Ar*H*), 7.88 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.48 – 7.41 (m, 2H, Ph*H*), 7.39 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.36 – 7.27 (m, 3H, Ph*H*), 7.15 (td, *J* = 7.7, 1.8 Hz, 1H, Ar*H*), 4.68 (dd, *J* = 6.8, 4.8 Hz, 1H, O*CH*CH_2), 4.57 (d, *J* = 5.2 Hz, 2H, CH_2), 3.86 (dt, *J* = 9.1, 6.6 Hz, 1H, CH_2), 3.55 (dt, *J* = 9.1, 6.5 Hz, 1H, CH_2), 1.63 (dq, *J* = 8.3, 6.6 Hz, 2H, CH_2), 1.49 – 1.35 (m, 2H, CH_2), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.2, 141.5, 134.8, 132.9, 132.0, 131.4, 128.8, 128.4, 128.0, 122.4, 94.4, 87.1, 84.9, 69.2, 68.3, 66.8, 31.8, 19.4, 14.0. **IR** (ν_{max}, cm^{-1}) 2987 (s), 2978 (s), 2934 (s), 2912 (s), 2901 (s), 2855 (s), 1756 (s), 1465 (s), 1428 (s), 1378 (s), 1269 (s), 1103 (s), 1076 (s), 1057 (s), 1027 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{21}H_{21}INaO_3^+$ 471.0428; Found 471.0438.

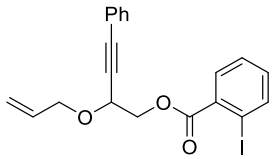
2-Benzyloxy-4-phenylbut-1-yn-4-yl 2-iodobenzoate (**4.22b**)



Performed on 0.25 mmol scale
Following **GP3**: Obtained from ((vinyloxy)methyl)benzene (**4.5b**, 50 µl, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.2 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.1 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 4 mg, 4 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 9:1 to 8:2. Yield 58% (70 mg, 0.15 mmol). Yellow oil.

Rf (Pent:EtOAc = 9:1) = 0.4.
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.03 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.79 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.58 – 7.44 (m, 3H, Ph*H* + Ar*H*), 7.45 – 7.26 (m, 8H, Ph*H*), 7.24 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 4.87 (d, *J* = 11.7 Hz, 1H, PhCH_2), 4.77 (dd, *J* = 6.6, 4.2 Hz, 1H, OC*H*), 4.66 (d, *J* = 11.7 Hz, 1H, PhCH_2), 4.64 – 4.50 (m, 2H, OCH_2). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 166.6, 141.8, 138.4, 135.9, 133.6, 132.3, 131.3, 129.6, 129.2, 129.0, 128.9, 128.7, 128.4, 122.5, 93.8, 87.5, 85.1, 71.2, 68.1, 66.8. **IR** (ν_{max}, cm^{-1}) 2987 (s), 2972 (s), 2959 (s), 2920 (s), 2909 (s), 2901 (s), 2884 (s), 1726 (s), 1394 (s), 1375 (s), 1286 (s), 1265 (s), 1243 (s), 1135 (s), 1076 (s), 1038 (s), 1016 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M + H]$^+$ Calcd for $C_{24}H_{20}IO_3^+$ 483.0452; Found 483.0435.

2-(Allyloxy)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.22c**)

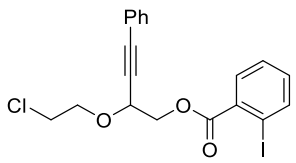


Performed on 0.25 mmol scale
Following **GP3**: Obtained from (allyloxy)ethene (**4.5c**, 0.039 mL, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:Et_2O, 95:5 to 90:10. Some fractions were not pure and were purified by preparative TLC (Pentane:Et_2O 93:7). Combined yield 46% (0.050 g, 0.12 mmol). Colorless oil.

Rf (Pent:Et_2O = 9:1) = 0.5.
^{1}H NMR (400 MHz, Acetonitrile-d3) δ 8.03 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar*H*), 7.82 (d, *J* = 1.7 Hz, 1H, Ar*H*), 7.53 – 7.43 (m, 3H, Ph*H* + Ar*H*), 7.42 – 7.32 (m, 3H, Ph*H*), 7.25 (ddd, *J* = 8.0, 7.5, 1.7 Hz, 1H, Ar*H*), 5.97 (dddd, *J* = 17.2, 10.4, 6.0, 5.2 Hz, 1H, C*H*=CH_2), 5.35 (dq, *J* = 17.3, 1.7 Hz, 1H, CH=CH_2), 5.22 – 5.18 (m, 1H, CH=CH_2), 4.75 (dd, *J* = 6.3, 4.4 Hz, 1H, OC*H*), 4.62 – 4.47 (m, 2H, OCH_2), 4.33

(ddt, *J* = 12.7, 5.2, 1.5 Hz, 1H, OC*H*$_2$), 4.13 (ddt, *J* = 12.7, 6.0, 1.4 Hz, 1H, OC*H*$_2$). **^{13}C NMR** (101 MHz, Acetonitrile-*d*$_3$) δ 166.7, 141.7, 136.0, 135.0, 133.6, 132.2, 131.2, 129.5, 129.2, 128.9, 122.5, 117.4, 93.7, 87.2, 85.2, 70.2, 68.0, 66.8. **IR** (ν_{max}, cm^{-1}) 3078 (m), 2987 (s), 2972 (s), 2900 (s), 1732 (s), 1286 (s), 1243 (s), 1134 (s), 1097 (s), 1079 (s), 1045 (s), 1016 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M]$^+$ Calcd for $C_{20}H_{17}IO_3^+$ 432.0217; Found 432.0210.

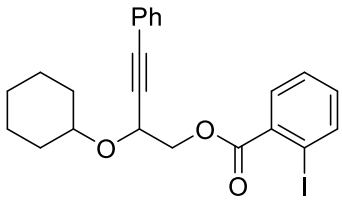
2-(2-Chloroethoxy)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.22d**)



Performed on 0.25 mmol scale
Following **GP3**: Obtained from (2-chloroethoxy)ethene (**4.5d**, 0.038 mL, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:Et$_2$O, 95:5 to 90:10. Some fractions were not pure and were purified by preparative TLC (Pentane:Et$_2$O 93:7). Combined yield 77% (0.088 g, 0.19 mmol, > 90% pure). Pale yellow oil with residual grease.

Rf (Pentane:EtOac 9:1) = 0.7.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.90 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.48 – 7.43 (m, 2H, Ph*H*), 7.43 – 7.37 (m, 1H, Ar*H*), 7.36 – 7.30 (m, 3H, Ph*H*), 7.17 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 4.79 (dd, *J* = 6.2, 5.3 Hz, 1H, OC*H*), 4.69 – 4.53 (m, 2H, OC*H*$_2$), 4.11 (dt, *J* = 10.5, 5.7 Hz, 1H, OC*H*$_2$), 3.85 (ddd, *J* = 10.5, 6.5, 5.6 Hz, 1H, OC*H*$_2$), 3.78 – 3.66 (m, 2H, C*H*$_2$Cl). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.0, 141.4, 134.5, 132.9, 131.9, 131.4, 128.9, 128.4, 128.0, 121.9, 94.3, 87.9, 83.6, 69.1, 68.7, 66.4, 42.6. **IR** (ν_{max}, cm^{-1}) 2958 (m), 2925 (m), 2853 (m), 1728 (s), 1286 (s), 1267 (s), 1249 (s), 1120 (s), 1102 (s), 1015 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{19}H_{16}ClINaO_3^+$ 476.9725; Found 476.9733.

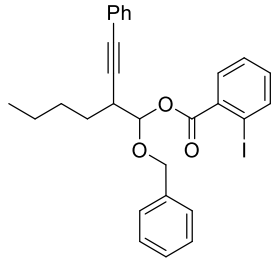
2-Cyclohexyloxy-4-phenylbut-1-yn-4-yl 2-iodobenzoate (**4.22e**)



Performed on 0.25 mmol scale
Following **GP3**: Obtained from cyclohexyl(vinyl)ether (**4.5e**, 0.053 mL, 0.047 g, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.52 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 100:0 95:5 to 8:2. Yield 62% (0.073 g, 0.15 mmol). Colorless oil.

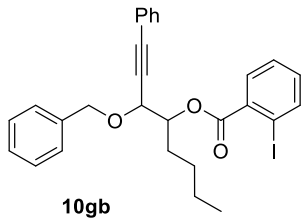
Rf (Pentane:EtOac 9:1) = 0.7.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.89 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.47 – 7.43 (m, 2H, Ph*H*), 7.42 – 7.36 (m, 1H, Ar*H*), 7.36 – 7.28 (m, 3H, Ph*H*), 7.16 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H, Ar*H*), 4.80 (dd, *J* = 7.4, 4.5 Hz, 1H, OC*H*), 4.61 – 4.46 (m, 2H, OC*H*$_2$), 3.70 (tt, *J* = 9.3, 3.8 Hz, 1H, Cy*H*), 2.06 – 1.84 (m, 2H, Cy*H*), 1.84 – 1.65 (m, 2H, Cy*H*), 1.62 – 1.40 (m, 2H, Cy*H*), 1.40 – 1.17 (m, 4H, Cy*H*). **^{13}C NMR** (101 MHz, Chloroform-d) δ 166.1, 141.4, 134.7, 132.8, 131.8, 131.3, 128.6, 128.3, 127.9, 122.4, 94.4, 86.2, 85.6, 67.2, 65.4, 33.2, 31.5, 25.7, 24.0. **IR** (ν_{max}, cm^{-1}) 2997 (s), 2987 (s), 2971 (s), 2933 (s), 2901 (s), 1725 (s), 1287 (s), 1243 (s), 1133 (s), 1098 (s), 1075 (s), 1038 (s), 1016 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{23}H_{23}INaO_3^+$ 497.0584; Found 497.0592.

1-(Benzyloxy)-2-(phenylethynyl)hexyl 2-iodobenzoate (**4.22fa**) and 3-(benzyloxy)-1-phenyloct-1-yn-4-yl 2-iodobenzoate (**4.22fb**)



Performed on 0.25 mmol scale
Following **GP3**: Obtained from (E)-((hex-1-en-1-yloxy)methyl)benzene (**4.5f**, 0.071 g, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 4 mg, 4 µmol, 2 mol%) after 18 hours.
First column: Pentane:EtOAc, 100:0 to 90:10, then second column: Pentane:EtOAc 98:2 to 92:8. Fraction 1: **4.22fa** (0.015 g, 0.028 mmol, 11% yield). Pale yellow oil. Fraction 2 (based on 1H NMR analysis) **4.22fb** (85 mol% and wt%) **4.22fa** (15 mol% and wt%) overall mass 0.014 g, 0.026 mmol. Pale yellow oil.
Overall yields:
4.22fa: 0.015 g + 0.002 g = 0.017 g, 0.032 mmol, 13% yield.
4.22fb: 0.015 g – 0.002 g = 0.013 g, 0.024 mmol, 10% yield

Major product **4.22fa** as a 1:1 mixture of diastereoisomers based on OC*H*$_2$Ph signals: 4.72 ppm and 4.69 ppm:
^{1}H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of diastereoisomers) δ 7.94 (ddd, *J* = 7.8, 6.5, 1.3 Hz, 1H, Ar*H*), 7.79 (ddd, *J* = 7.9, 6.8, 1.8 Hz, 1H, Ar*H*), 7.37 – 7.16 (m, 11H, Ph*H* + Ar*H*), 7.09 (tdd, *J* = 7.9, 6.2, 1.8 Hz, 1H, Ar*H*), 6.18 (m, 1H, O$_2$C*H*), 4.86 (d, *J* = 6.7 Hz, 0.5H, OC*H*$_2$Ph), 4.83 (d, *J* = 6.6 Hz, 0.5H, OC*H*$_2$Ph), 4.72 (d, *J* = 7.2 Hz, 0.5H, OC*H*$_2$Ph), 4.69 (d, *J* = 7.1 Hz, 0.5H, OC*H*$_2$Ph), 3.04 (dt$_{app}$, *J* = 9.9, 5.0 Hz, 1H, C*H*R-alkyne), 1.77 – 1.45 (m, 2H, C*H*$_2$-CH$_2$-CH$_2$-CH$_3$), 1.43 – 1.13 (m, 4H, CH$_2$-C*H*$_2$-C*H*$_2$-CH$_3$), 0.84 (t, *J* = 7.2 Hz, 3H, CH$_2$-CH$_2$-CH$_2$-C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of diasteroisomers, not all carbons are resolved) δ 166.2, 166.1, 141.5, 141.3, 137.1, 137.0, 134.8, 134.6, 132.9, 132.8, 131.8, 131.7, 131.2, 131.2, 128.5, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 123.5, 123.4, 98.9, 98.6, 88.0, 87.9, 83.5, 72.0, 72.0, 38.3, 38.1, 29.7, 29.4, 29.4, 29.1, 22.5, 22.5, 14.0. **IR** (ν_{max}, cm^{-1}) 3076 (w), 2986 (s), 2972 (s), 2931 (m), 2917 (s), 2893 (m), 1728 (m), 1454 (m), 1402 (m), 1271 (m), 1242 (m), 1090 (s), 1064 (s), 1050 (s). **HRMS** (ESI/QTOF) m/z [M + K]$^+$ Calcd for $C_{28}H_{27}IKO_3^+$ 577.0636; Found 577.0647.

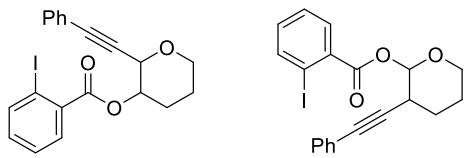


10gb

Minor product **4.22fb** as a 1:1 mixture of diastereoisomers based on peak at 4.90 ppm, isolated with 15% of **4.22fa**.
For ease of interpretation: the ^{1}H NMR data is reported without the signals corresponding to **4.22fa**; the ^{13}C NMR data is reported as measured.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar*H*), 7.83 (ddd, *J* = 9.7, 7.8, 1.8 Hz, 1H, Ar*H*), 7.47 – 7.43 (m, 2H, Ph*H*), 7.40 – 7.24 (m, 9H, Ph*H* + Ar*H*), 7.14 (tt, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 5.43 (tdd, *J* = 8.5, 6.0, 4.3 Hz, 1H, OC*H*), 4.90 (d, 0.5H, 1 diastereoisomer, OCH$_2$Ph) , 4.90 (d, 0.5H, 1 diastereoisomer, OCH$_2$Ph), 4.65 (d, *J* = 12.0 Hz, 1H, OC*H*$_2$Ph), 4.59 – 4.53 (m, 1H, OC*H*), 2.04 – 1.86 (m, 1H, C*H*$_2$-CH$_2$-CH$_2$-CH$_3$), 1.47 – 1.30 (m, 3H, C*H*$_2$-C*H*$_2$-CH$_2$-CH$_3$), 0.95 – 0.82 (m, 5H, CH$_2$-CH$_2$-C*H*$_2$-C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.1, 166.0, 141.5, 141.3, 137.6, 135.4, 135.2, 134.6, 132.9, 132.6, 132.5, 131.9, 131.8, 131.2, 131.1, 131.1, 128.7, 128.6, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 125.5, 122.4, 122.4, 98.6, 94.2, 94.2, 87.7, 87.5, 84.8, 76.0, 75.6, 72.0, 70.9, 70.7, 70.5, 66.7, 38.8, 38.1, 34.5, 31.9, 30.4, 30.3, 29.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.2, 28.9, 27.7, 27.5, 25.1, 23.8, 23.0, 22.7, 22.6, 22.5, 14.1, 14.1, 14.0, 11.0. **IR** (ν_{max}, cm^{-1}) 3009 (m), 2996 (m), 2931 (m), 2916 (s), 2908 (m), 2892 (m), 1732 (m), 1394 (m), 1089 (m), 1076 (s), 1062 (s), 1024 (m). **HRMS** (ESI/QTOF) m/z [M + K]$^+$ Calcd for $C_{28}H_{27}IKO_3^+$ 577.0636; Found 577.0646.

2-(Phenylethynyl)tetrahydro-2H-pyran-3-yl 2-iodobenzoate (**4.22ga**) 3-(phenylethynyl)tetrahydro-2H-pyran-2-yl 2-iodobenzoate (**4.22gb**); 4:1 regioisomeric mixture

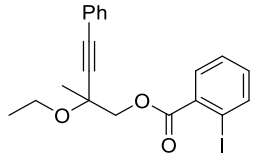


58% : 15%

Performed on 0.25 mmol scale
Following **GP3**:
Obtained from 2,3-dihydropyran (**4.5g**, 34 µL, 0.38 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.114 g, 0.1 mmol, 1.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 9:1 to 8:2. Yield 73% (0.076 g, 0.17 mmol). Yellow oil.

Rf (pentane:EtOAc 9:1) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*, 8:2 mixture of regioisomers major in **bold**, minor in *italic* those corresponding to both are both ***bold and italic***) δ *8.02* (dd, *J* = 7.6, 1.2 Hz, 0.2H, minor, Ar*H*), **8.00** (dd, *J* = 7.9, 1.2 Hz, 0.8H, major, Ar*H*), *7.91* (dd, *J* = 7.8, 1.7 Hz, 0.2H, minor, Ar*H*), **7.86** (dd, *J* = 7.8, 1.7 Hz, 0.8H, major, Ar*H*), ***7.48 – 7.36*** (m, 3H, Ph*H*), ***7.37 – 7.26*** (m, 3H, Ph*H* + Ar*H*), ***7.20 – 7.12*** (m, 1H, Ar*H*), *6.19* (d, *J* = 4.4 Hz, 0.2H, minor, ArCO_2-C*H*R-OR), **5.24 – 5.14** (m, 0.8H, major, alkynyl-C*H*R-OR), **4.74** (d, *J* = 5.3 Hz, 0.8H, major, ArCO_2-C*H*R_2), *4.11* (ddd, *J* = 11.6, 7.7, 3.5 Hz, 1H, RO-CH_2R), ***3.70*** (ddd, *J* = 11.1, 6.3, 3.7 Hz, 1H, RO-CH_2R), *3.06* (dt, *J* = 6.5, 4.5 Hz, 0.2H, alkynyl-C*H*R_2, minor), ***2.36*** (ddd, *J* = 13.1, 8.8, 4.2 Hz, 1H, CH_2), ***2.06 – 1.85*** (m, 2H, CH_2), ***1.69*** (dtt, *J* = 13.3, 6.9, 3.8 Hz, 1H, CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of regioisomers some carbons are not resolved) δ 165.7, 141.5, 141.3, 135.0, 133.0, 132.8, 131.9, 131.8, 131.4, 131.1, 128.7, 128.3, 128.2, 128.1, 128.0, 122.2, 95.3, 94.2, 87.8, 87.6, 84.6, 72.0, 69.0, 64.9, 64.4, 32.4, 29.7, 26.2, 25.8, 22.5, 22.3. **IR** (ν_{max}, cm^{-1}) 3060 (m), 2987 (s), 2901 (s), 1725 (m), 1428 (m), 1379 (m), 1249 (s), 1078 (s), 1044 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{20}H_{17}INaO_3^+$ 455.0115; Found 455.0122.

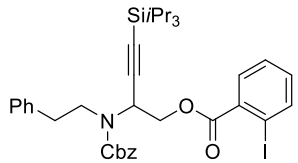
2-Ethoxy-2-methyl-4-phenylbut-1-yn-4-yl 2-iodobenzoate (**4.22h**)



Performed on 0.25 mmol scale
Following **GP3**: Obtained from 2-ethoxypro-1-ene (**4.5h**, 42 µL, 0.37 mmol, 1.5 equiv); PhEBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.15 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 9:1 to 7:3. Yield 82% (0.089 g, 0.21 mmol). Colorless oil.

Rf (Pentane:EtOAc 9:1) = 0.2.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.82 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.38 – 7.26 (m, 3H, Ar*H* + Ph*H*), 7.26 – 7.19 (m, 3H, Ph*H*), 7.06 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H, Ar*H*), 4.51 (d, *J* = 11.2 Hz, 1H, OCH_2), 4.35 (d, *J* = 11.2 Hz, 1H, OCH_2), 3.74 – 3.64 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 1.57 (s, 3H, Me), 1.17 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.0, 141.4, 134.8, 132.8, 131.8, 131.3, 128.6, 128.3, 127.9, 122.3, 94.4, 87.7, 86.6, 72.3, 69.0, 60.2, 24.8, 15.8. **IR** (ν_{max}, cm^{-1}) 3004 (s), 2987 (s), 2972 (s), 2911 (s), 2901 (s), 2883 (s), 1732 (s), 1379 (s), 1288 (s), 1243 (s), 1125 (s), 1099 (s), 1066 (s), 1046 (s), 1016 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{20}H_{19}INaO_3^+$ 457.0271; Found 457.0272.

2-(((Benzyloxy)carbonyl)(phenethyl)amino)-4-(triisopropylsilyl)but-3-yn-1-yl 2-iodobenzoate (**4.23a**)

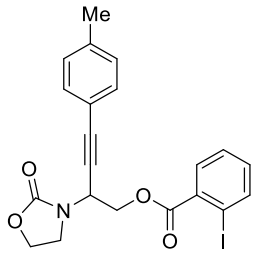


Performed on 0.25 mmol scale
Following **GP3**: from benzyl phenethyl(vinyl)carbamate (**4.3c**, 0.106 g, 0.375 mmol, 1.5 equiv); **HIR.3** (0.107 g, 0.25 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.15 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 93:7 to 9:1. Yield 9% (0.007 g, 0.03 mmol). Colorless oil.

Rf (pentane:EtOAc 8:2) = 0.15.

^{1}H NMR (400 MHz, Acetonitrile-d_3, 6:3 mixture of rotamers) δ 8.02 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.75 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.43 (dd, *J* = 8.4, 7.2 Hz, 1H, Ar*H*), 7.34 (d, *J* = 11.1 Hz, 6H, Ph*H* + Ar*H*), 7.29 – 7.14 (m, 4H, Ph*H*), 7.13 – 7.09 (m, 1H, Ar*H*), 5.45 (s, 0.6H, NC*H*), 5.35 (s, 0.3H, NC*H*), 5.14 (d, *J* = 12.4 Hz, 1H, PhCH_2), 5.09 (s, 1H, PhCH_2), 4.44 (dd, *J* = 6.2, 3.6 Hz, 2H, OCH_2), 3.59 (dd, *J* = 10.2, 6.8 Hz, 2H, PhCH_2-CH_2), 3.01 (ddd, *J* = 13.0, 9.5, 6.3 Hz, 1H, NCH_2), 2.93 (s, 1H, NCH_2), 1.05 (d, *J* = 2.3 Hz, 18H, Si*i*Pr$_3$). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 166.2, 156.2, 141.9, 139.8, 137.4, 135.3, 133.7, 131.5, 129.4, 129.2, 129.1, 129.0, 128.8, 128.8, 128.6, 127.0, 126.9, 102.4, 94.1, 88.4, 68.9, 67.8, 65.5, 48.8, 46.9, 42.4, 36.4, 34.5, 32.2, 29.9, 23.0, 18.5, 18.4, 18.3, 18.2, 17.9, 14.0, 12.8, 11.9, 11.5, 11.2. **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{36}H_{44}INNaO_4Si^+$ 732.1977; Found 732.1976.
Unfortunately, insufficient quantities of compound **4.23a** was obtained to allow interpretable IR analysis.

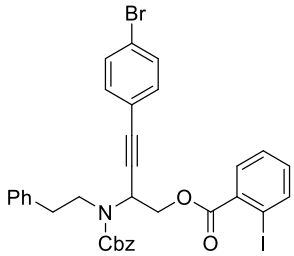
4-(4-Methylphenyl)-2-(2-oxooxazolidin-3-yl)but-3-yn-1-yl 2-iodobenzoate (**4.23b**)



Performed on 0.5 mmol scale
Following **GP3**: Obtained from *N*-vinyloxazolidin-2-one (**4.3a**, 0.042 g, 0.37 mmol, 1.5 equiv); *p*TolEBX (**HIR.2b**, 0.91 g, 0.25 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.15 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 8:2 to 5:5. Yield 59% (0.070 g, 0.15 mmol). Yellow oil.

Rf (Pent:EtOAc 8:2) = 0.3.
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.49 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.41 – 7.33 (m, 2H, Ar*H*), 7.25 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H, Ar*H*), 7.22 – 7.16 (m, 2H, Ar*H*), 5.23 (dd, *J* = 8.6, 4.6 Hz, 1H, NC*H*), 4.65 (dd, *J* = 11.4, 8.6 Hz, 1H, CH_2), 4.49 (dd, *J* = 11.4, 4.6 Hz, 1H, CH_2), 4.41 – 4.27 (m, 2H, CH_2), 3.86 – 3.70 (m, 2H, CH_2), 2.34 (s, 3H, Me). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 166.5, 158.5, 141.8, 140.2, 135.6, 133.7, 132.2, 131.4, 129.8, 128.9, 119.2, 93.8, 87.2, 81.4, 64.5, 63.2, 46.3, 41.7, 21.1. **IR** (ν_{max}, cm^{-1}) 2998 (s), 2972 (s), 2943 (s), 2901 (s), 1748 (s), 1481 (s), 1408 (s), 1377 (s), 1286 (s), 1248 (s), 1075 (s), 1066 (s), 1038 (s), 1016 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{21}H_{18}INNaO_4^+$ 498.0173; Found 498.0182.

2-(((Benzyloxy)carbonyl)(phenethyl)amino)-4-(4-bromophenyl)but-3-yn-1-yl 2-iodobenzoate (**4.23c**)



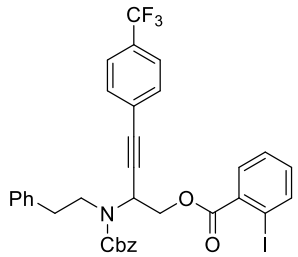
Performed on 0.5 mmol scale
Following **GP3**: Obtained from benzyl phenethyl(vinyl)carbamate (**4.3c**, 0.106 g, 0.375 mmol, 1.2 equiv); *p*BrPhEBX (**HIR.2c**, 0.107 g, 0.250 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 4 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 10:0 to 9:1. Yield 76% (0.191 g, 0.135 mmol). Pale yellow oil.

Rf (Pent.:EtOAc 9:1) = 0.25.
^{1}H NMR (400 MHz, Acetonitrile-d_3, 9:1 mixture of rotamers)[33] δ 8.05 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.80 – 7.73 (m, 1H, Ar*H*), 7.61 – 7.53 (m, 2H, Ar*H* or Ph*H*), 7.47 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.43 – 7.25 (m, 7H, Ph*H* + Ar*H*), 7.29 – 7.16 (m, 5H, Ar*H*), 7.16 – 7.11 (m, 1H, Ar*H*), 5.61- (bs, "0.7H", major, NC*H*), 5.48 (bs, "0.3H", minor, NC*H*), 5.15 (m, 2H, PhCH_2O), 4.56 (q, *J* = 5.4, 4.3 Hz, 2H, OCH_2), 3.64 (dq, *J* = 17.8, 7.6, 7.2 Hz, 1.8H, major, CH_2), 3.36 (q, *J* = 6.8 Hz, 0.2H, minor, CH_2), 3.00 (t, *J* = 8.6 Hz, 1.8H, major, CH_2), 2.80 (t, *J* = 7.2 Hz, 0.2H, minor, CH_2). **^{13}C NMR** (101 MHz,

[33] The rotamer ratio was based on the signals at 3.00 and 2.80 ppm as they are better defined; the proton signals associated to the NC*H* (5.61 and 5.48 ppm) are broad signals therefore precise integration cannot be guaranteed.

Acetonitrile-d_3, mixture of rotamers, not all peaks are resolved) δ 166.4, 156.4, 141.9, 139.8, 137.4, 135.5, 133.9, 133.7, 132.4, 132.1, 131.4, 129.3, 129.1, 129.0, 128.9, 128.9, 128.6, 126.9, 123.3, 121.7, 93.9, 85.5, 85.3, 67.8, 65.1, 48.7, 47.1, 36.5. **IR** (ν_{max}, cm^{-1}) 2987 (s), 2972 (s), 2901 (s), 1749 (s), 1470 (s), 1419 (s), 1376 (s), 1286 (s), 1242 (s), 1133 (s), 1076 (s), 1048 (s), 1017 (s). **HRMS** (ESI/QTOF) m/z $[M + Na]^+$ Calcd for $C_{20}H_{15}{}^{79}BrINNaO_4{}^+$ 561.9121; Found 561.9118.

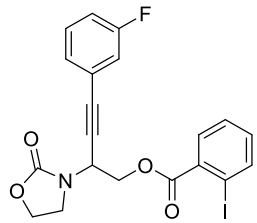
2-(((Benzyloxy)carbonyl)(phenethyl)amino)-4-(4-(trifluoromethyl)phenyl)but-3-yn-1-yl 2-iodobenzoate (**4.23d**)



Performed on 0.5 mmol scale
Following **GP3**: Obtained from benzyl phenethyl(vinyl)carbamate (**4.3c**, 0.106 g, 0.375 mmol, 1.5 equiv); *p*CF_3PhEBX (**HIR.2d**, 0.105 g, 0.250 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 10:0 to 9:1. Yield 75% (0.130 g, 0.186 mmol). Pale yellow oil.

Rf (Pent.:EtOAc 9:1) = 0.25.
^{1}H NMR (400 MHz, Acetonitrile-d_3, 6:4 mixture of rotamers) δ 8.02 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.88 - 7.72 (m, 1H, Ar*H*), 7.72 - 7.56 (m, 5H, Ph*H* + Ar*H*), 7.50 - 7.06 (m, 11H, Ph*H* + Ar*H*), 5.65 (bs, 0.6H, major, NC*H*), 5.50 (bs, 0.4H, minor, NC*H*), 5.13 (m, 2H, PhCH_2O), 4.72 - 4.41 (m, 2H, OCH_2), 3.62 (t, *J* = 8.1 Hz, 2H, CH_2), 3.17 - 2.85 (m, 2H, CH_2). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of rotamers, 2 carbons not resolved) δ 166.4, 156.4, 141.9, 139.7, 137.3, 135.5, 133.7, 132.8, 131.4, 130.41 (q, *J* = 32.6 Hz), 129.3, 129.1, 129.0, 128.9, 128.76 - 128.28 (m), 126.9, 126.6, (q, *J* = 4.0 Hz), 123.3, 93.9, 86.9, 85.0, 67.8, 65.0, 48.7, 47.2, 36.5. **^{19}F NMR** (376 MHz, Acetonitrile-d_3) δ -63.4. **IR** (ν_{max}, cm^{-1}) 2986 (s), 2970 (s), 2961 (s), 2934 (s), 2901 (s), 1733 (s), 1715 (s), 1705 (s), 1699 (s), 1685 (s), 1410 (s), 1322 (s), 1247 (s). **HRMS** (ESI/QTOF) m/z $[M + H]^+$ Calcd for $C_{34}H_{28}F_3INO_4{}^+$ 698.1010; Found 698.1006.

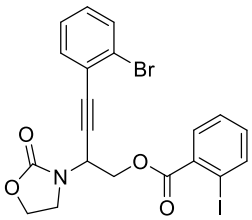
4-(3-Fluorophenyl)-2-(2-oxooxazolidin-3-yl)but-3-yn-1-yl 2-iodobenzoate (**4.23e**)



Performed on 0.5 mmol scale
Following **GP3**: Obtained from *N*-vinyloxazolidin-2-one (**4.3a**, 0.042 g, 0.37 mmol, 1.5 equiv); *m*FPhEBX (**HIR.2e**, 0.092 g, 0.25 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.15 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 8:2 to 5:5. Yield 32% (0.038 g, 0,079 mmol). Yellow oil.

Rf (Pent:EtOAc 8:2) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.76 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.34 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.28 – 7.18 (m, 1H, Ar*H*), 7.15 (dt, *J* = 7.7, 1.2 Hz, 1H, Ar*H*), 7.14 – 7.02 (m, 2H, Ar*H*), 7.00 (tdd, *J* = 8.4, 2.6, 1.1 Hz, 1H, Ar*H*), 5.30 (dd, *J* = 8.9, 4.4 Hz, 1H, NC*H*), 4.69 (dd, *J* = 11.5, 8.9 Hz, 1H, CH_2), 4.44 – 4.25 (m, 3H, CH_2), 3.81 – 3.71 (m, 1H, CH_2), 3.75 – 3.66 (m, 1H, CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 165.9, 162.3 (d, *J* = 247.3 Hz), 157.9, 141.5, 134.1, 133.1, 131.3, 130.2 (d, *J* = 8.5 Hz), 128.2, 127.9 (d, *J* = 3.1 Hz), 123.3 (d, *J* = 9.3 Hz), 118.8 (d, *J* = 23.0 Hz), 116.6 (d, *J* = 21.0 Hz), 94.3, 86.1 (d, *J* = 3.3 Hz), 81.9, 63.6, 62.4, 46.1, 41.3. **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -112.3. **IR** (ν_{max}, cm^{-1}) 2973 (s), 2932 (m), 2889 (m), 1734 (s), 1581 (s), 1485 (s), 1419 (s), 1376 (s), 1286 (s), 1246 (s), 1226 (s), 1172 (s), 1152 (s), 1133 (s), 1093 (s), 1045 (s), 1016 (s). **HRMS** (ESI/QTOF) m/z $[M + H]^+$ Calcd for $C_{20}H_{16}FINO_4{}^+$ 480.0103; Found 480.0098.

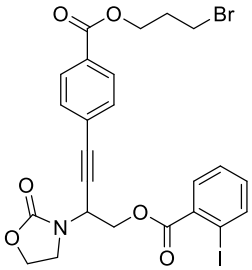
4-(2-Bromophenyl)-2-(2-oxooxazolidin-3-yl)but-3-yn-1-yl 2-iodobenzoate (**4.23f**)



Performed on 0.5 mmol scale
Following **GP3**: Obtained from *N*-vinyloxazolidin-2-one (**4.3a**, 0.042 g, 0.37 mmol, 1.5 equiv); *o*BrPhEBX (**HIR.2f**, 0.107 g, 0.250 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.15 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 8:2 to 5:5. Yield 56% (0.080 g, 0.14 mmol). Yellow oil.

Rf (Pent:EtOAc 8:2) = 0.25
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.86 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.60 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar*H*), 7.47 (dd, *J* = 7.7, 1.8 Hz, 1H, Ar*H*), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.29 (td, *J* = 7.6, 1.3 Hz, 1H, Ar*H*), 7.20 (dtd, *J* = 20.1, 7.8, 1.8 Hz, 2H, Ar*H*), 5.41 (dd, *J* = 8.8, 4.3 Hz, 1H, NC*H*), 4.80 (dd, *J* = 11.5, 8.8 Hz, 1H, CH_2), 4.51 (dd, *J* = 11.5, 4.3 Hz, 1H, CH_2), 4.48 – 4.33 (m, 2H, CH_2), 3.96 (dt, *J* = 9.4, 8.1 Hz, 1H, CH_2), 3.81 (td, *J* = 8.6, 5.6 Hz, 1H, CH_2). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 166.4, 158.5, 141.9, 135.5, 134.3, 133.7, 133.1, 131.5, 131.2, 128.9, 128.2, 125.6, 124.2, 93.9, 87.1, 85.4, 64.5, 63.2, 46.4, 42.0. **IR** (ν_{max}, cm^{-1}) 2987 (s), 2972 (s), 2901 (s), 1749 (s), 1470 (s), 1419 (s), 1376 (s), 1286 (s), 1242 (s), 1133 (s), 1076 (s), 1048 (s), 1017 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{20}H_{15}{}^{79}BrINNaO_4{}^+$ 561.9121; Found 561.9118.

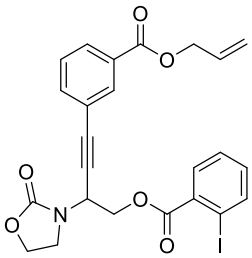
4-(4-((3-Bromopropoxy)carbonyl)phenyl)-2-(2-oxooxazolidin-3-yl)but-3-yn-1-yl 2-iodobenzoate (**4.23g**)



Performed on 0.5 mmol scale
Following **GP3**: Obtained from *N*-vinyloxazolidin-2-one (**4.3a**, 0.042 g, 0.37 mmol, 1.5 equiv); **HIR.2g** (0.124 g, 0.250 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.15 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 8:2 to 5:5. Yield 51% (0.077 g, 0.12 mmol). Yellow oil.

Rf (pentane:EtOAc 8:2) = 0.15.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.96 (m, 3, Ar*H*), 7.83 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.55 – 7.47 (m, 2H, Ar*H*), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.18 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H, Ar*H*), 5.40 (dd, *J* = 8.8, 4.4 Hz, 1H, NC*H*), 4.78 (dd, *J* = 11.5, 8.9 Hz, 1H, OCH_2), 4.54 – 4.34 (m, 5H, CH_2 + CO_2CH_2), 3.92 – 3.74 (m, 2H, CH_2), 3.55 (t, *J* = 6.5 Hz, 2H, CH_2Br), 2.33 (p_{app}, *J* = 6.3 Hz, 2H, CH_2-CH_2Br). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 165.9, 165.6, 157.9, 141.5, 134.1, 133.2, 131.9, 131.3, 130.3, 129.6, 128.2, 126.3, 94.3, 86.5, 84.0, 63.6, 63.0, 62.4, 46.2, 41.3, 31.7, 29.3. **IR** (ν_{max}, cm^{-1}) 2987 (s), 2972 (s), 2920 (s), 2900 (s), 1749 (s), 1715 (s), 1480 (s), 1407 (s), 1382 (s), 1268 (s), 1249 (s), 1104 (s), 1045 (s), 1017 (s). **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z [M + Na]$^+$ Calcd for $C_{24}H_{21}{}^{79}BrINNaO_6{}^+$ 647.9489; Found 647.9478.

4-(4-((Allyloxy)carbonyl)phenyl)-2-(2-oxooxazolidin-3-yl)but-3-yn-1-yl 2-iodobenzoate (**4.23h**)

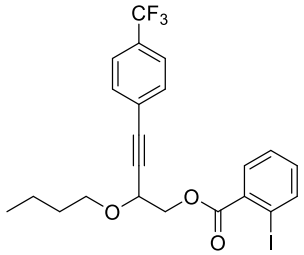


Performed on 0.5 mmol scale
Following **GP3**: Obtained from *N*-vinyloxazolidin-2-one (**4.3a**, 0.042 g, 0.37 mmol, 1.5 equiv); **HIR.2h** (0.108 g, 0.250 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.15 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 8:2 to 5:5. Yield 37% (0.047 g, 0.093 mmol). Clear oil.

Rf (pentane:EtOAc 8:2) = 0.15.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (td, *J* = 1.7, 0.6 Hz, 1H, Ar*H*), 8.09 – 8.03 (m, 1H, Ar*H*), 8.00 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.84 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.63 (dt, *J* = 7.7, 1.4 Hz, 1H, Ar*H*), 7.43 (tdd, *J* = 7.7, 2.7, 0.9 Hz, 2H, Ar*H*), 7.18 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H, Ar*H*), 6.05 (ddt, *J*

= 17.2, 10.4, 5.7 Hz, 1H, C*H*=CH_2), 5.45 (q, *J* = 1.5 Hz, 1H, NC*H*), 5.38 (d, *J* = 4.4 Hz, 1H, CH=CH_2), 5.33 (q, *J* = 1.3 Hz, 1H, CH_2-CH=CH_2), 4.84 (dt, *J* = 5.7, 1.4 Hz, 2H, CH=CH_2), 4.78 (dd, *J* = 11.5, 8.9 Hz, 1H, CH_2), 4.53 – 4.33 (m, 3H, CH_2), 3.91 – 3.74 (m, 2H, CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 165.9, 165.3, 157.9, 141.4, 136.1, 134.1, 133.1, 133.1, 131.9, 131.3, 130.6, 130.2, 128.7, 128.2, 122.0, 118.7, 94.3, 86.3, 81.9, 66.0, 63.7, 62.4, 46.2, 41.3. **IR** (ν_{max}, cm^{-1}) 3004 (s), 2986 (s), 2972 (s), 2911 (s), 2900 (s), 2883 (s), 1732 (s), 1487 (s), 1419 (s), 1376 (s), 1285 (s), 1242 (s), 1226 (s), 1133 (s), 1101 (s), 1080 (s), 1038 (s), 1028 (s). **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z [M + Na]$^+$ Calcd for $C_{24}H_{20}INNaO_6^+$ 568.0228; Found 568.0211.

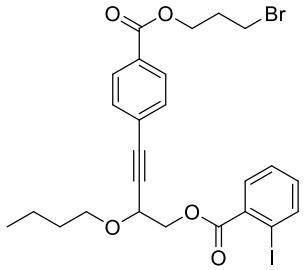
2-Butoxy-4-(4-(trifluoromethyl)phenyl)but-3-yn-1-yl 2-iodobenzoate (**4.24d**)



Performed on 0.5 mmol scale
Following **GP3**: Obtained from *n*butyl vinyl ether (**4.5a**, 0.048 mL, 0.38 mmol, 1.5 equiv); **HIR.2d** (0.104 g, 0.250 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.15 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 8:2 to 5:5. Yield 62% (0.082 g, 0.15 mmol). Yellow oil.

Rf (pentane:EtOAc 9:1) = 0.55.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.88 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.67 – 7.47 (m, 4H, Ar*H*), 7.40 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.16 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 4.69 (dd, *J* = 6.8, 4.8 Hz, 1H, OC*H*), 4.63 – 4.49 (m, 2H, OCH_2), 3.85 (dt, *J* = 9.2, 6.6 Hz, 1H, OCH_2), 3.56 (dt, *J* = 9.2, 6.5 Hz, 1H, OCH_2), 1.70 – 1.58 (m, 2H, CH_2-CH_2-CH_3), 1.55 – 1.33 (m, 2H, CH_2-CH_2-CH_3), 0.93 (t, *J* = 7.4 Hz, 3H, CH_2-CH_2-CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.0, 141.5, 134.6, 132.9, 132.1, 131.3, 130.4 (q, *J* = 33.0 Hz), 127.9, 126.0, 125.3 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 272.3 Hz), 94.3, 87.4, 85.5, 69.4, 68.2, 66.5, 31.6, 19.3, 13.9. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -62.9. **IR** (ν_{max}, cm^{-1}) 1732 (s), 1321 (s), 1286 (s), 1243 (s), 1167 (s), 1125 (s), 1104 (s), 1092 (s), 1086 (s), 1066 (s), 1044 (s), 1016 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{22}H_{20}F_3INaO_3^+$ 539.0301; Found 539.0306.

4-(4-((3-Bromopropoxy)carbonyl)phenyl)-2-butoxybut-3-yn-1-yl 2-iodobenzoate (**4.24g**)

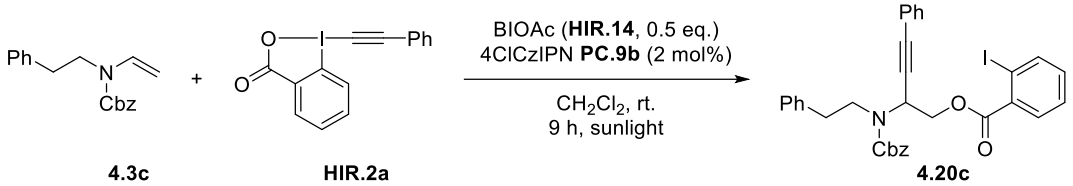


Performed on 0.5 mmol scale
Following **GP3**: Obtained from *n*butyl vinyl ether (**4.5a**, 0.048 mL, 0.38 mmol, 1.5 equiv); **HIR.2g** (0.124 g, 0.250 mmol, 1.0 equiv); BIOAc (**HIR.14**, 0.038 g, 0.15 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%) after 18 hours.
Column: Pentane:EtOAc, 98:2 to 90:10. Yield 52% (0.079 g, 0.13 mmol). Yellow oil.

Rf (pentane:EtOAc 9:1) = 0.5
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.87 (m, 3H, Ar*H*), 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.49 – 7.40 (m, 2H, Ar*H*), 7.33 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.09 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 4.62 (dd, *J* = 6.7, 4.8 Hz, 1H, OC*H*), 4.57 – 4.47 (m, 2H, CH_2), 4.40 (t, *J* = 6.0 Hz, 2H, CH_2), 3.78 (dt, *J* = 9.2, 6.6 Hz, 1H, CH_2), 3.48 (dt, *J* = 9.8, 6.5 Hz, 3H, CH_2), 2.25 (p_{app}, *J* = 6.3 Hz, 2H, CH_2-CH_2Br), 1.65 – 1.49 (m, 2H, CH_2-CH_2-CH_3), 1.49 – 1.28 (m, 2H, CH_2-CH_2-CH_3), 0.85 (t, *J* = 7.4 Hz, 2H, CH_2-CH_2-CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.0, 165.7, 141.4, 134.6, 132.9, 131.8, 131.3, 129.8, 129.5, 129.4, 127.9, 127.1, 94.3, 88.0, 86.1, 69.4, 68.2, 66.5, 62.9, 31.8, 31.6, 29.4, 19.3, 13.9. **IR** (ν_{max}, cm^{-1}) 2997 (s), 2987 (s), 2977 (s), 2971 (s), 2901 (s), 2892 (s), 1732 (m), 1394 (m), 1266 (s), 1242 (s), 1088 (s), 1066 (s), 1040 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{25}H_{26}BrINaO_5^+$ 634.9901; Found 634.9907

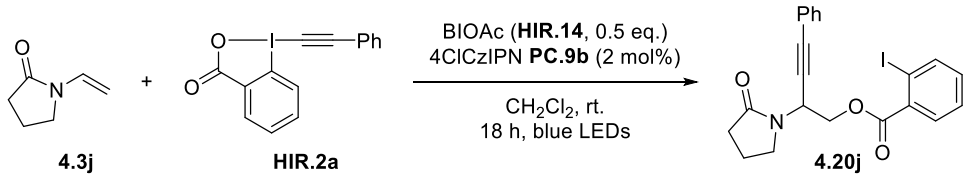
Gram scale synthesis and product modification

Sunlight experiment



An oven-dried flat-bottomed 2 mL screw-cap vial equipped with a magnetic stirrer was charged with Ph-EBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv), BIOAc (**HIR.14**, 0.038 g, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%). The reaction vessel was sealed with a rubber septum. Following three vacuum/nitrogen cycles, the vial was refilled with argon. Then, dry, degassed (*via* freeze-pump-thaw technique) CH_2Cl_2 (10.0 mL, 0.29 M) was added. Benzyl phenethyl(vinyl) carbamate (**4.3c**, 0.106 g, 0.375 mmol, 1.5 equiv) was then added *via* syringe. The reaction was placed in direct sunlight for 5 h under stirring then 4 h without stirring. A deactivated solid deposit for flash chromatography was prepared: a slurry of SiO_2 (ca. 3 g) and ca. 0.2 mL of Et_3N was prepared and then combined with the crude reaction mixture before concentration. The crude was then purified though flash chromatography (biotage: SiO_2 25 g, Pentane:EtOAc 0% to 15%) affording **4.20c** (0.107 g, 0.170 mmol, 68% yield). Weather report:[34] sunny with partial clouds temperature from 23-30 °C.

Gram scale synthesis of **4.20j**

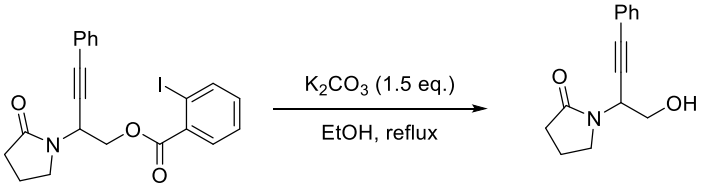


An oven-dried flat-bottomed 10 mL snap-cap vial equipped with a magnetic stirrer was charged with Ph-EBX (**HIR.2a**, 1.00 g, 2.87 mmol, 1.0 equiv), BIOAc (**7**, 0.440 g, 2.87 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 61 mg, 57 µmol, 2 mol%). The reaction vessel was sealed with a rubber septum. Following three vacuum/nitrogen cycles, the vial was refilled with argon. Then, dry, degassed (*via* freeze-pump-thaw technique) CH_2Cl_2 (10.0 mL, 0.29 M) was added. *N*-vinyl pyrrolidinone (**4.3j**, 0.46 mL, 4.3 mmol, 1.5 equiv) was then added *via* syringe. The reaction was irradiated overnight (18 h) with blue LED strips under ventilation (T = ca. 25°C) and stirring. A deactivated solid deposit for flash chromatography was prepared: a slurry of SiO_2 (ca. 20 g) and ca. 1 mL of Et_3N was prepared and then combined with the crude reaction mixture before concentration. The crude was then purified though flash chromatography

[34] https://www.historique-meteo.net/europe/suisse/lausanne/2019/07/24/ consulted on the 02.06.2020

(biotage : SiO_2 120 g, Pentane:EtOAc 20% to 50%) affording **4.20j** (0.998 g, 1.83 mmol, 64% yield).

1-(1-Hydroxy-4-phenylbut-3-yn-2-yl)pyrrolidin-2-one (**4.25**)

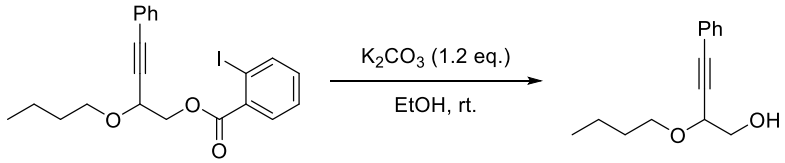


4.3j **4.25**

Following a modified reported procedure,[35] a flame dried 5 mL microwave vial with a rubber septum and magnetic stirring bar was charged with **4.3j** (100.0 mg, 217.0 µmol, 1.00 equiv), potassium;carbonate (0.045 mg, 0.32 mmol, 1.50 equiv) and ethanol (2 mL). The vial was sealed and stirred at reflux for 2h. At this time TLC showed full conversion of the starting material. The solvent was evaporated on top a silica plug then submitted to flash chromatography (Biotage SiO_2 12 g: CH_2Cl_2:AcOEt:MeOH 80:20:0, 60:40:0, 80:0:20) to afford 1-(1-hydroxy-4-phenylbut-3-yn-2-yl)pyrrolidin-2-one (**4.25**, 0.048 g, 0.21 mmol, 96% yield) as a yellowish oil.

Rf (CH_2Cl_2:MeOH 8:2) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 (dd, *J* = 7.4, 2.1 Hz, 2H, Ar*H*), 7.34 (td, *J* = 4.8, 2.3 Hz, 3H, Ar*H*), 5.27 (dd, *J* = 8.1, 4.8 Hz, 1H, N-C*H*R_2), 3.92 (dd, *J* = 11.4, 4.7 Hz, 1H, O-CH_2R), 3.82 (dd, *J* = 11.4, 8.1 Hz, 1H, O-CH_2R), 3.74 – 3.65 (m, 1H, cyclic-CH_2-N), 3.60 (dt, *J* = 9.5, 7.0 Hz, 1H, cyclic-CH_2-N), 3.05 (bs, 1H, OH), 2.54 – 2.44 (m, 2H, cyclic-CO-CH_2), 2.17 – 2.05 (m, 2H, cyclic-CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 175.8, 131.9, 128.7, 128.4, 122.1, 86.0, 83.0, 63.7, 47.0, 44.4, 31.3, 17.9. **IR** (v_{max}, cm^{-1}) 3373 (w), 2938 (w), 2879 (w), 1662 (s), 1420 (m), 1287 (m), 1069 (m). **HRMS** (ESI/QTOF) m/z $[M + Na]^+$ Calcd for $C_{14}H_{15}NNaO_2^+$ 252.0995; Found 252.1001.

2-Butoxy-4-phenylbut-3-yn-1-ol (**4.26**)



4.22a **4.26**

Following a slightly modified reported procedure,[35] a flame dried 5 mL microwave vial with a rubber septum and magnetic stirring bar was charged with **4.22a** (26.0 mg, 58.0 µmol, 1.00 equiv), potassium;carbonate (9.62 mg, 69.6 µmol, 1.20 equiv) and ethanol (600 µL). The mixture was stirred at room temperature for 60 h, then the solvent was evaporated and submitted to flash chromatography (SiO_2, CH_2Cl_2: EtOAc) to afford (**4.26**, 11.5 mg, 52.7 mmol, 91% yield).

Rf (CH_2Cl_2) = 0.3.

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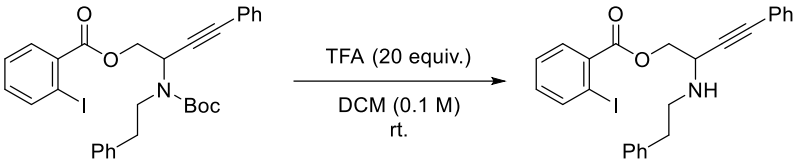
[35]Hari, D. P. and Waser, J. *J. Am. Chem. Soc.* **2016**, *138*, 2190

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.41 (m, 2H, Ph*H*), 7.36 – 7.27 (m, 3H, Ph*H*), 4.36 (dd, *J* = 6.2, 5.5 Hz, 1H, OC*H*), 3.87 (dt, *J* = 9.3, 6.6 Hz, 1H, OCH_2), 3.80 (t, *J* = 5.1 Hz, 2H, OCH_2), 3.51 (dt, *J* = 9.2, 6.6 Hz, 1H, OCH_2), 2.26 (d, *J* = 18.6 Hz, 1H, OH), 1.70 – 1.58 (m, 2H, CH_2-CH_2-CH_3), 1.49 – 1.35 (m, 2H, CH_2-CH_2-CH_3), 0.95 (t, *J* = 7.4 Hz, 3H, CH_2-CH_2-CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.8, 128.6, 128.3, 122.3, 86.8, 85.2, 70.9, 69.3, 65.4, 31.7, 19.3, 13.9. **IR** (ν_{max}, cm^{-1}) 3426 (m), 3006 (s), 2987 (s), 2958 (s), 2892 (s), 2867 (s), 1382 (m), 1103 (s), 1066 (s), 1047 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{14}H_{18}NaO_2^+$ 241.1199; Found 241.1195.

2-(Phenethylamino)-4-phenylbut-3-yn-1-yl 2-iodobenzoate (**4.27**)



4.20b **4.27**

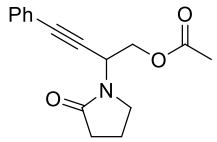
To a 5 mL vial equipped with a magnetic stirrer, **4.20b** (0.047 g, 0.078 mmol, 1 equiv) were dissolved in CH_2Cl_2 (0.8 mL), trifluoroacetic acid (130 µL, 1.90 mmol, 25 equiv) was added dropwise at room temperature. The reaction was stirred for 1h 30 min. At this time, TLC showed full conversion of **4.20b**. TFA and CH_2Cl_2 were evaporated off. The crude was diluted with Et_2O (1 mL) and basified with Na_2CO_3 aq. sat. (0.5 mL) until ph > 11. The aqueous layer was extracted a second time with Et_2O (1.5 mL). The combined organic layers were combined, dried over $MgSO_4$, then passed through a short plug of deactivated silica. The plug was then washed through with EtOAc. Upon concentration pure **4.27** was obtained as a colorless oil (0.029 g, 0.059, 74% yield).

Rf (CH_2Cl_2) = 0.15.
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.02 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.74 (dd, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.47 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.43 – 7.36 (m, 2H, Ph*H*), 7.39 – 7.30 (m, 3H, Ph*H*), 7.30 – 7.21 (m, 5H, Ph*H*), 7.24 – 7.10 (m, 1H, Ar*H*), 4.68 – 4.31 (m, 2H, O-CH_2), 4.16 – 3.99 (m, 1H, N-C*H*R), 3.17 (dt, *J* = 11.2, 7.2 Hz, 1H, N-CH_2R), 2.96 (ddd, *J* = 11.3, 7.6, 6.1 Hz, 1H, N-CH_2R), 2.91 – 2.67 (m, 2H, Ph-CH_2R), 2.26 – 2.00 (m, 1H, R_2N*H*). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 166.8, 141.7, 141.0, 136.2, 133.5, 132.1, 131.4, 129.3, 129.1, 129.0, 128.9, 128.9, 126.6, 123.3, 93.7, 88.3, 84.7, 67.4, 50.0, 48.9, 36.5. **IR** (ν_{max}, cm^{-1}) 3312 (w), 3060 (w), 3025 (w), 2955 (m), 2899 (m), 2847 (w), 1949 (w), 1730 (s), 1583 (m), 1490 (m), 1442 (m), 1285 (s), 1247 (s), 1132 (s), 1099 (s), 1015 (s). **HRMS** (ESI/QTOF) m/z [M + H]$^+$ Calcd for $C_{25}H_{23}INO_2^+$ 496.0768; Found 496.0769.

Acetate incorporation experiments

Following the general procedure for difunctionalisation (**GP3**), an oven dried 1.5 mL screw cap vial, equipped with a magnetic stirrer was charged with, PhEBX (**HIR.2a**, 0.035 g, 0.10 mmol, 1.00 equiv), BIOAc (**7**, 0.015 g, 0.050 mmol, 0.5 equiv), sodium acetate (0.003 g, 0.004 mmol, 0.4 equiv) and 4ClCzIPN (**PC.9b**, 2 mg, 2 µmol, 2 mol%). The vial was sealed with a septum and flushed with Ar for 5 min. Degassed CH_2Cl_2 (0.4 mL, 2.5 M) was added followed by acetic acid (86 µL, 1.5 mmol, 15.0 equiv) and *N*-vinyl pyrolidinone (**4.3j**, 16 µL, 0.015 mmol, 1.50 equiv). The reaction was irradiated with Blue LED strips for 15 h under agitation. The reaction was concentrated under vaccum, solubilised in Chloroform-*d* and 1 equiv of CH_2Br_2 was added (7 uL) to determine the crude ^{1}H NMR ratio of **4.20j** and **4.29** (**4.20j**:**4.29** 7:3 ^{1}H NMR). A

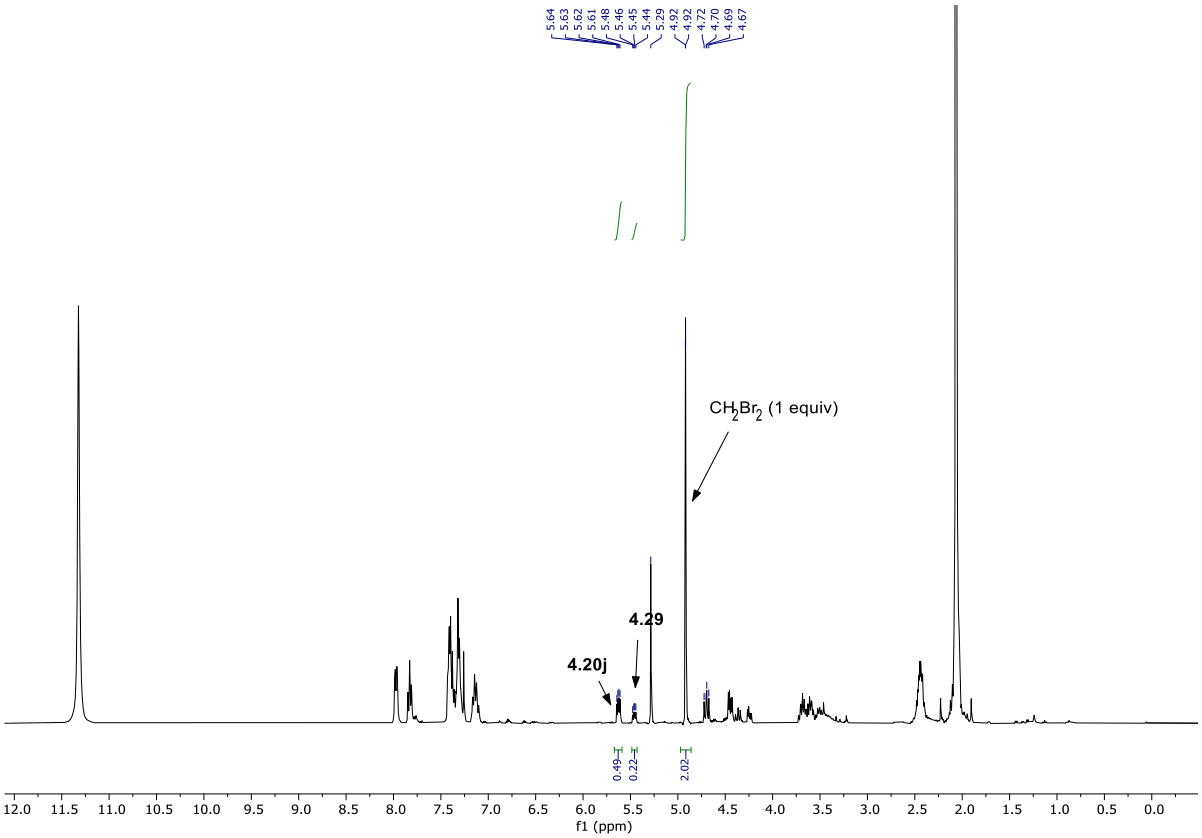
triethylamine deactivated silica solid deposit of the crude was prepared and the latter was submitted to column chromatography (SiO_2, 15 g) pentane:EtOAc 7:3 to 4:6.affording **4.20j** (0.016 g, 0.035 mmol, 35% yield) and **4.29** (0.009 g, 60% purity, 0.02 mmol, 22% yield) as pale yellow oils.



4.29 characterised as a mixture of iodobenzoic acid, **4.20j** and residual starting material **4.3j**. Purity 60%.

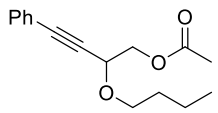
Rf (pentane:EtOAc 1:1) =0.3. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.46 – 7.37 (m, 2H, Ph), 7.37 – 7.28 (m, 3H, Ph), 5.46 (dd, *J* = 8.6, 4.8 Hz, 1H, N-C*H*), 4.37 (dd, *J* = 11.3, 8.6 Hz, 1H, O-CH_2), 4.25 (dd, *J* = 11.3, 4.8 Hz, 1H, O-CH_2), 3.65 (ddd, *J* = 9.4, 7.8, 6.4 Hz, 1H, N-CH_2), 3.59 – 3.46 (m, 1H, N-CH_2), 2.47 – 2.38 (m, 2H, cyclic-CH_2), 2.11-2.03 (m, 5H, COCH_3 + cyclic-CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 175.0, 170.6, 141.5, 131.9, 128.8, 128.4, 86.0, 82.2, 63.0, 43.6, 43.5, 31.0, 20.8, 18.0. **IR** (ν_{max}, cm^{-1}) 2983 (s), 2958 (s), 2925 (s), 2853 (s), 1745 (s), 1692 (s), 1491 (s), 1462 (s), 1420 (s), 1268 (s), 1229 (s), 1044 (s), 913 (s). **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z $[M + H]^+$ Calcd for $C_{16}H_{18}NO_3^+$ 272.1281; Found 272.1286.

^{1}H NMR (400 MHz) of the crude mixture:



Following the general procedure for difunctionalisation (**GP3**), an oven dried 1.5 mL screw cap vial, equipped with a magnetic stirrer was charged with, PhEBX (**HIR.2a**, 0.087 g, 0.25 mmol, 1.0 equiv), BIOAc (**HIR.14**, 0.039 g, 0.13 mmol, 0.5 equiv), sodium acetate (0.008 g, 0.009 mmol, 0.4 equiv) and 4ClCzIPN (**PC.9b**, 2 mg, 2 μmol, 2 mol%). The vial was sealed with a septum and flushed with Ar for 5 min. Degassed CH_2Cl_2 (1 mL, 2.5 M) was added followed by

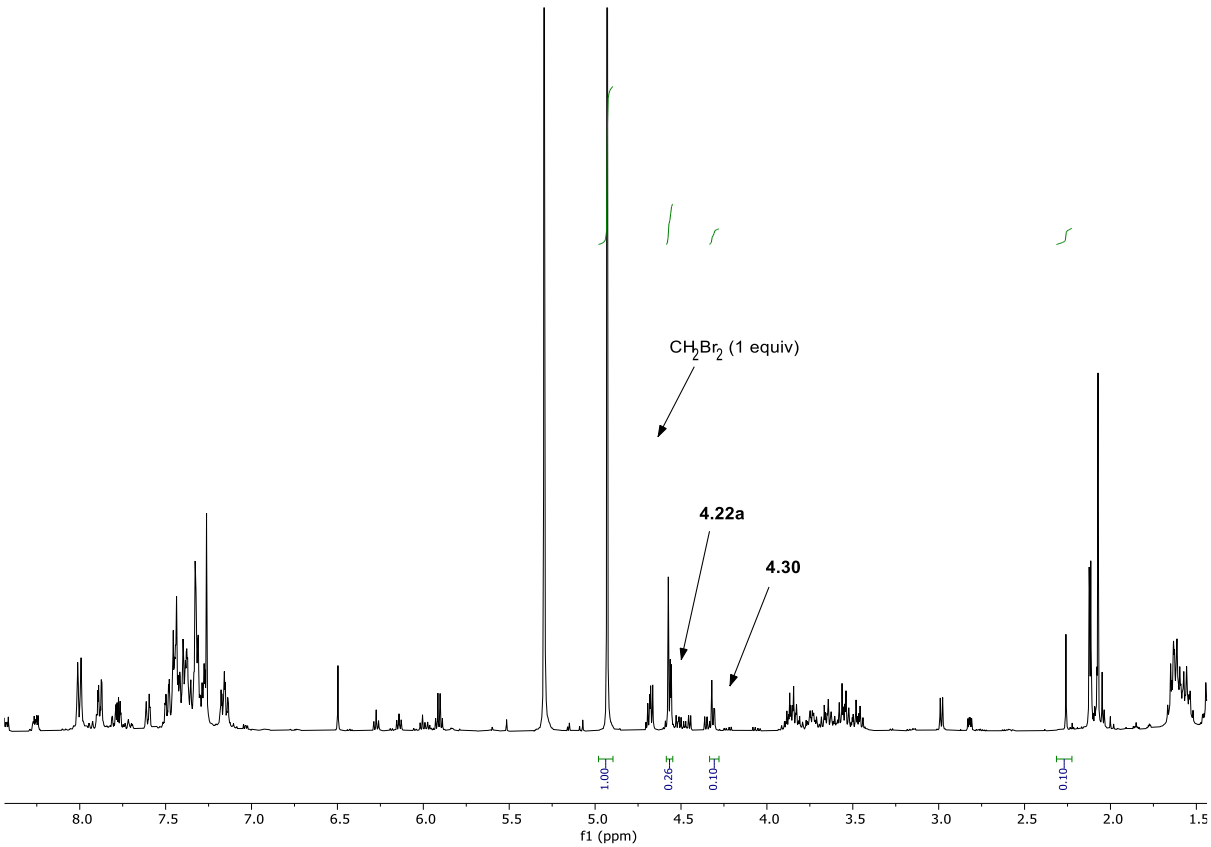
acetic acid (214 µL, 3.75 mmol, 15.0 equiv) and *n*butyl vinyl ether (**4.5a**, 38 µL, 0.38 mmol, 1.5 equiv). The reaction was irradiated with Blue LED strips for 15 h under agitation. The reaction was concentrated under vaccum, solubilised in Chloroform-*d* and 1 equiv of CH_2Br_2 was added (17.5 uL) to determine the crude ^{1}H NMR ratio of **4.22a** and **4.30** (**4.22a**:**4.30** 7:3 ^{1}H NMR). A triethylamine deactivated silica solid deposit of the crude was prepared and the latter was submitted to column chromatography (SiO_2, 15 g) pentane:EtOAc 7:3 to 4:6.affording **4.22a** (0.013 g, 0.035 mmol, 35% yield) and **4.30** (0.004 g, 60% purity, 0.02 mmol, 22% yield) as pale yellow oils.



4.30 characterised as a mixture of **4.22a** and residual starting material **4.5a**. Purity 40%.

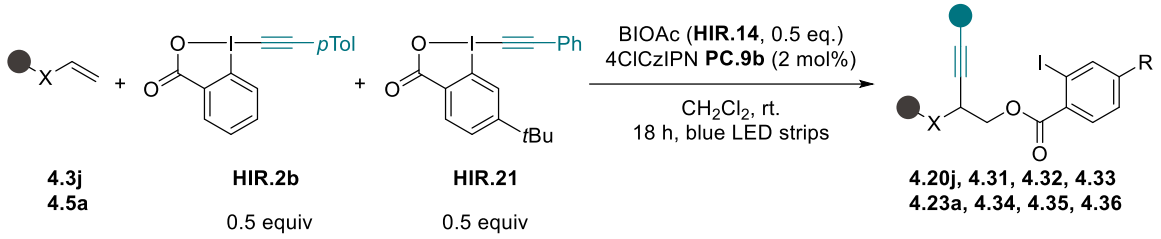
Rf (pentane:EtOAc 9:1) =0.5.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.25 (m, 5H, Ph), 4.51 (dd, *J* = 6.7, 4.8 Hz, 1H, OC*H*R$_2$), 4.34 – 4.28 (m, 2H, OC*H*$_2$R), 3.85 – 3.69 (m, 1H, C*H*$_2$), 2.82 (dd, *J* = 5.6, 3.2 Hz, 1H, C*H*$_2$), 2.12 (s, 3H), 1.69 – 1.58 (m, 2H, C*H*$_2$), 1.49 – 1.35 (m, 2H, C*H*$_2$), 0.93 (td, *J* = 7.3, 5.2 Hz, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.1, 131.8, 131.3, 127.9, 122.3, 96.1, 84.7, 69.1, 68.1, 65.8, 31.6, 19.3, 19.1, 13.8. **HRMS** (APPI/LTQ-Orbitrap) m/z: $[M]^+$ Calcd for $C_{16}H_{20}O_3^+$ 260.1407; Found 260.1406.

^{1}H NMR (400 MHz) of the crude mixture:



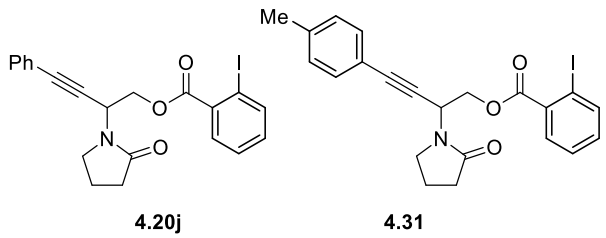
Crossover experiments

Following GP3:



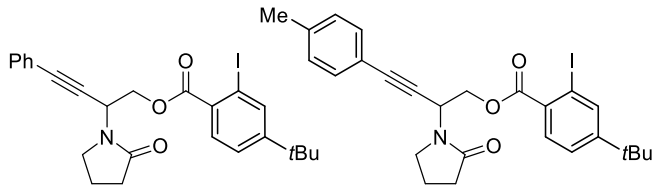
An oven-dried flat-bottomed screw-cap vial equipped with a magnetic stirrer was charged with **HIR.2b** (45 mg, 0.13 mmol, 0.5 equiv) and **HIR.21** (50 mg, 0.13 mmol, 0.5 equiv) and 4ClCzIPN (**PC.9b**, 5 mg, 5 µmol, 2 mol%). The reaction vessel was sealed with a rubber septum. Following three vacuum/nitrogen cycles, dry, degassed (*via* freeze-pump-thaw technique) CH_2Cl_2 (1 mL) was then added. The substrate (0.15 mmol, 1.5 equiv) was then added *via* syringe. The rubber septum was replaced with the corresponding screw-cap under a flux of Argon. The reaction was irradiated for 5 days with blue LED strips under ventilation (T = 25°C) and stirring. The volatiles were evaporated off. The crude was then analysed by ^{1}H NMR with CH_2Br_2 as an internal standard, then purified by preparative TLC (Si_2O, Heptane:EtOAc).

Reaction with **4.3j** (40 µL, 0.375 mmol, 1.5 equiv). Total ^{1}H NMR yield: 40%; isolated: 39%



4.20j and **4.31** were obtained as a 1:1 ratio (24 mg, 0.051 mmol, 20% yield). The ratio was determined by ^{1}H NMR after purification using the signal at 2.35 ppm.

Rf (Heptane:EtOAc 7:3) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of **4.20j** and **4.31,** the characteristic signal of **4.31** is highlighted in **bold**) δ 7.99 (dt, *J* = 8.0, 1.2 Hz, 2H, Ar*H*), 7.84 (ddd, *J* = 7.8, 1.9, 0.7 Hz, 2H, Ar*H*), 7.47 – 7.37 (m, 4H, ArH), 7.37 – 7.27 (m, 5H, Ar*H*), 7.20 – 7.09 (m, 4H, Ar*H*), 5.62 (ddd, *J* = 8.8, 6.4, 4.6 Hz, 2H, N-C*H*), 4.71 (ddd, *J* = 11.3, 8.8, 3.6 Hz, 2H, O-CH_2), 4.45 (ddd, *J* = 11.3, 5.3, 4.6 Hz, 2H, O-CH_2), 3.74 – 3.63 (m, 2H, N-CH_2), 3.59 (dddd, *J* = 9.7, 7.6, 6.2, 4.0 Hz, 2H, N-CH_2), 2.41 (dddd, *J* = 9.8, 6.7, 4.3, 2.6 Hz, 4H, cyclic-CH_2), **2.35** (s, 3H, ArCH_3), 2.13 – 2.00 (m, 4H, cyclic-CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*, 1:1 mixture of **4.20j** and **4.31**) δ 165.8, 160.3, 148.5, 141.4, 134.1, 133.0, 131.9, 131.8, 131.3, 129.1, 128.9, 128.4, 128.2, 121.9, 94.3, 82.0, 63.9, 45.9, 43.7, 42.1, 32.2, 31.2, 29.7, 21.5, 17.9, 8.7. Due to the overlapping signals 16 carbons are not resolved.
4.20j: HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}INO_3^+$ 460.0404; Found 460.0407.
4.31: HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}INO_3^+$ 474.0561; Found 474.0564.

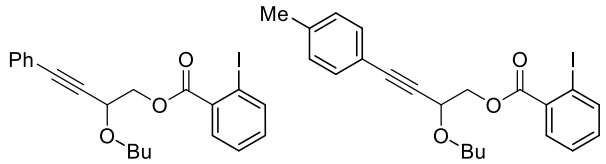


4.32 **4.33**

4.32 and **4.33** were obtained as a 1 :1 ratio (24 mg, 0.047 mmol, 19% yield). The ratio was determined by ^{1}H NMR after purification using the signal at 2.35 ppm.

Rf (heptane:EtOAc 7:3) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of **4.32** and **4.33**, the charcateristic signal of **4.33** is highlilghted in bold) δ 7.98 (dd, *J* = 1.9, 1.3 Hz, 2H, Ar*H*), 7.80 (dd, *J* = 8.2, 0.9 Hz, 2H, Ar*H*), 7.47 – 7.38 (m, 4H, Ar*H*), 7.37 – 7.28 (m, 5H, Ar*H*), 7.16 – 7.09 (m, 2H, Ar*H*), 5.61 (ddd, *J* = 8.8, 6.4, 4.6 Hz, 2H, N-C*H*), 4.70 (ddd, *J* = 11.3, 8.9, 3.7 Hz, 2H, OCH_2), 4.42 (ddd, *J* = 11.3, 5.3, 4.5 Hz, 2H, OCH_2), 3.74 – 3.64 (m, 2H, NCH_2), 3.64 – 3.48 (m, 2H, NCH_2), 2.41 (ddt, *J* = 8.2, 7.1, 2.5 Hz, 4H, cyclic-CH_2), **2.35** (s, 3H, ArCH_3), 2.13 – 2.01 (m, 4H, cyclic-CH_2), 1.33 – 1.28 (m, 18H, *t*Bu). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 165.8, 160.3, 148.5, 141.4, 134.1, 133.0, 131.9, 131.8, 131.3, 129.1, 128.9, 128.4, 128.2, 121.9, 94.3, 82.0, 63.9, 45.9, 43.7, 29.7, 21.5, 17.9, 8.7. Due to the overlapping signals 24 carbons are not resolved.
4.32: HRMS (ESI/QTOF) m/z: [M + Na]$^{+}$ Calcd for $C_{26}H_{28}INNaO_3^{+}$ 552.1006; Found 552.1019
4.33: HRMS (ESI/QTOF) m/z: [M + Na]$^{+}$ Calcd for $C_{25}H_{26}INNaO_3^{+}$ 538.0850; Found 538.0860

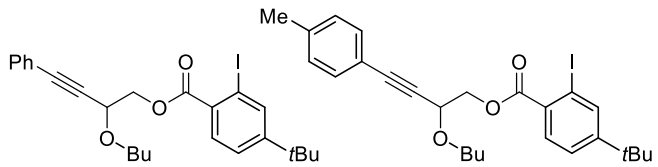
Reaction with **4.5a** (49 µL, 0.375 mmol, 1.5 equiv)



4.23a **4.34**

4.23a and **4.34** were obtained as a 1 :1 ratio (20 mg, 0.043 mmol, 17% yield). The ratio was determined by ^{1}H NMR after purification using the signal at 2.35 ppm.

Rf (pentane:EtOAc 9:1) = 0.5.
^{1}H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of **4.23a** and **4.34**, the charcateristic signal of **4.34** is highlilghted in bold) δ 8.00 (dt, *J* = 8.0, 1.3 Hz, 2H, Ar*H*), 7.88 (dt, *J* = 7.8, 1.5 Hz, 2H, Ar*H*), 7.49 – 7.42 (m, 2H, Ar*H*), 7.40 (tt, *J* = 7.7, 1.3 Hz, 2H, Ar*H*), 7.37 – 7.28 (m, 5H, Ar*H*), 7.20 – 7.09 (m, 4H, Ar*H*), 4.67 (dt, *J* = 6.9, 4.6 Hz, 2H, OC*H*), 4.62 – 4.53 (m, 4H, OCH_2), 3.85 (dtd, *J* = 9.5, 6.6, 2.9 Hz, 2H, OCH_2), 3.60 – 3.49 (m, 2H, OCH_2), **2.35** (s, 3H, ArCH_3), 1.69 – 1.57 (m, 4H, butyl-CH_2), 1.47 – 1.23 (m, 8H, butyl-CH_2), 0.92 (td, *J* = 7.4, 1.8 Hz, 6H, butyl-CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*, 1:1 mixture of **4.23a** and **4.34**) δ ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.9, 156.8, 138.8, 131.9, 131.8, 131.4, 131.2, 129.1, 128.6, 128.3, 125.1, 122.3, 119.2, 94.8, 84.9, 84.1, 69.1, 69.1, 68.3, 66.6, 66.6, 34.8, 31.7, 31.0, 21.5, 19.3, 13.9. Due to the overlapping signals 16 carbons are not resolved.
4.23a: HRMS (ESI/QTOF) m/z: [M + Na]$^{+}$ Calcd for $C_{21}H_{21}INaO_3^{+}$ 471.0428; Found 471.0434.
4.34: HRMS (ESI/QTOF) m/z: [M + Na]$^{+}$ Calcd for $C_{22}H_{23}INaO_3^{+}$ 485.0584; Found 485.0589.



4.35 **4.36**

4.35 and **4.36** were obtained as a 1 :1 ratio (24 mg, 0.041 mmol, 17% yield). The ratio was determined by ^{1}H NMR after purification using the signal at 2.35 ppm.

Rf (pentane:EtOAc 9:1) = 0.6.
^{1}H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of **4.35** and **4.36**, the charcateristic signal of **4.34** is highlilghted in bold) δ 7.99 (dd, *J* = 1.9, 1.2 Hz, 2H, Ar*H*), 7.84 (dd, *J* = 8.2, 1.4 Hz, 2H, Ar*H*), 7.48 – 7.43 (m, 2H, Ar*H*), 7.40 (ddd, *J* = 8.2, 1.9, 1.3 Hz, 2H, Ar*H*), 7.37 – 7.29 (m, 5H, Ar*H*), 7.16 – 7.09 (m, 2H, Ar*H*), 4.66 (dt, *J* = 7.2, 4.6 Hz, 2H, OC*H*), 4.60 – 4.48 (m, 4H, OCH_2), 3.85 (dtd, *J* = 9.5, 6.6, 3.0 Hz, 2H, OCH_2), 3.60 – 3.49 (m, 2H, OCH_2), **2.35** (s, 3H, ArCH_3), 1.63 (dddd, *J* = 8.8, 7.8, 6.7, 4.2 Hz, 4H, butyl-CH_2), 1.48 – 1.35 (m, 4H, butyl-CH_2), 1.31 (s, 18H, *t*Bu), 0.92 (td, *J* = 7.3, 1.9 Hz, 3H, butyl-CH_3). ^{13}C NMR (101 MHz, Chloroform-*d,* 1:1 mixture of **4.35** and **4.36**) δ 166.1, 141.4, 141.4, 138.8, 134.7, 132.8, 131.9, 131.8, 131.3, 129.1, 128.7, 128.3, 127.9, 122.3, 119.2, 94.3, 86.9, 84.7, 84.0, 77.4, 77.0, 76.7, 69.2, 69.1, 68.2, 66.8, 66.7, 62.8, 34.9, 31.6, 30.9, 21.5, 19.3, 13.9. Due to the overlapping signals 13 carbons are not resolved.
4.35: HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{25}H_{29}INaO_3^+$ 527.1054; Found 527.1072.
4.36: HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{26}H_{31}INaO_3^+$ 541.1210; Found 541.1227.

Electrochemical experiments

An Autolab potentiostat with a 3 electrode cell configuration: glassy carbon (working electrode), Pt wire as (control electrode), and Ag/AgCl (KCl, 3M aq.) as (reference electrode) was used for the measures. Tetrabutyl ammonium hexafluorophosphhate (TBAP, 0.1M in MeCN) was used as an electrolyte. The sample (0.01 mmol) was dissolved in a stock solution of TBAP (0.1 M, 10 mL in MeCN) and was degassed by bubbling Argon directly before measure. The redox couple E(alkene$^{+\bullet}$/alkene) is defined as the potential E measured for $\frac{I_{max}}{2}$.

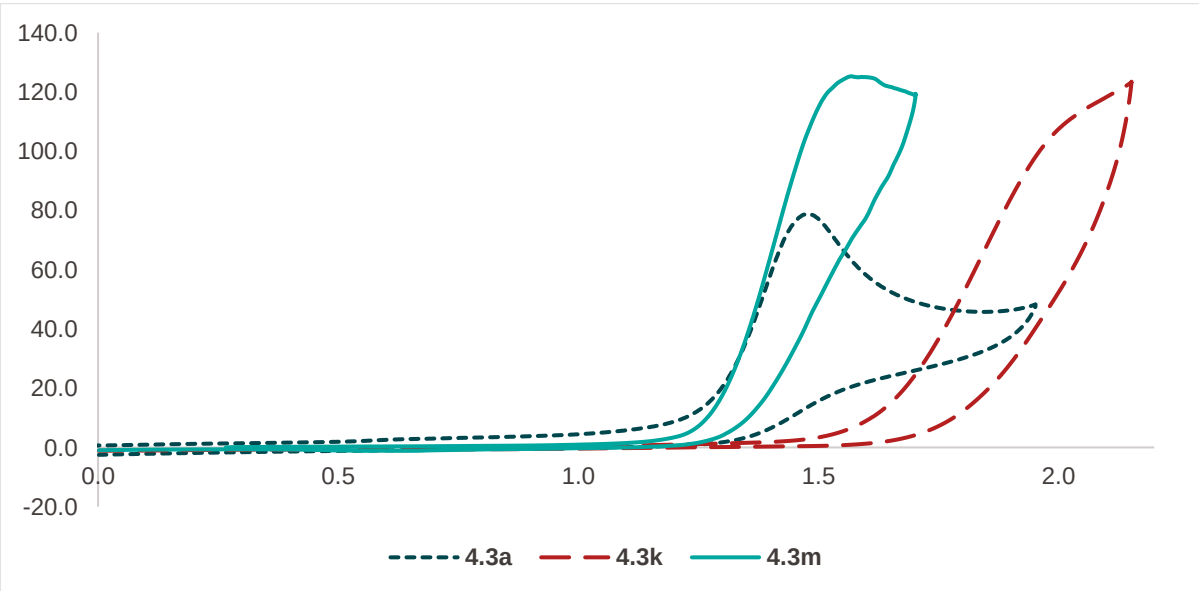


Figure 8.2. Cyclic voltagram of 4.3a (blue short dash), 4.3l (red long dash) and 4.3m (light blue plain line)

4.2a

$$I_{max} = 78\ \mu A;\ \frac{I_{max}}{2} = 39\ \mu A\ ;\ E = 1.30\ V \text{ so that } I = 39\ \mu A$$

E(**4.3a**$^{+\bullet}$/**4.3a**) = +1.30 V

4.33l

$$I_{max} \approx 110\ \mu A;\ \frac{I_{max}}{2} \approx 55\ \mu A\ ;\ E = 1.86\ V \text{ so that } I = 55\ \mu A$$

E(**4.3l**$^{+\bullet}$/**4.3l**) ≈ +1.86 V

4.3m

$$I_{max} = 120\ \mu A;\ \frac{I_{max}}{2} = 60\ \mu A\ ;\ E = 1.40\ V \text{ so that } I = 60\ \mu A$$

E(**4.3m**$^{+\bullet}$/**4.3m**) = +1.40 V

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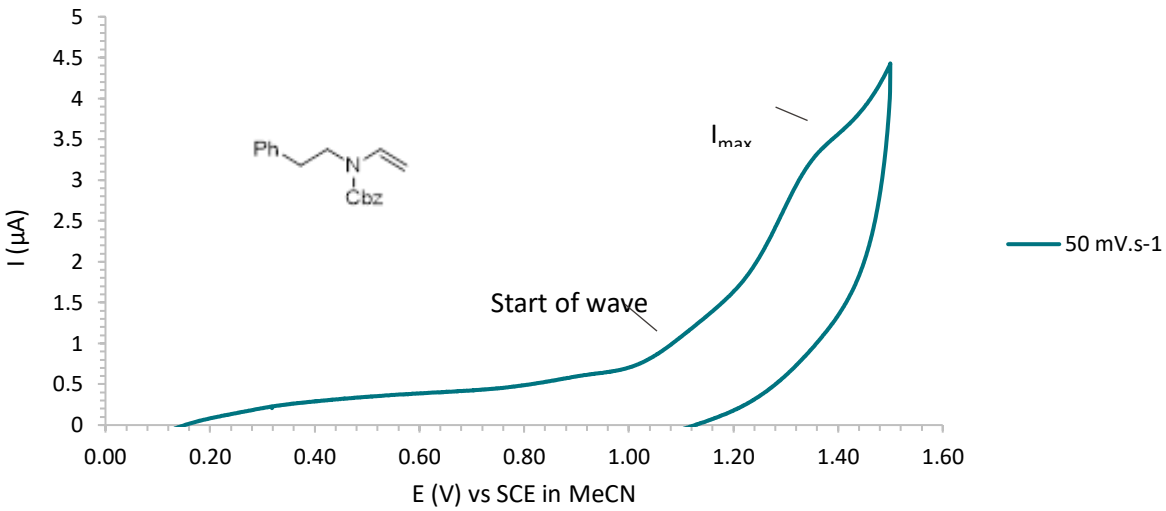


Figure 8.3. Cyclic voltagram of 4.3c

$$I_{max} = 3.24\ \mu A;\ I_{start\ of\ wave} = 0.78\ \mu A;\ \frac{I_{max} - I_{start\ of\ wave}}{2} = 2.46\ \mu A;$$

$$E = 1.28\ V \text{ so that } I = 2.46\ \mu A$$

E(**4.3c**$^{+\bullet}$/**4.3c**) = +1.28 V

Fluorescence quenching experiments and Stern-Volmer plot

Stern-Volmer fluorescence quenching experiments were conducted on a Varian Cary Eclipse machine.

A degassed stock solution of 48 µM of photocatalyst **PC.9b** in CH_2Cl_2 was prepared. 0.5 mL of this solution was placed in a 0.5 mL fluorimeter cuvette. Progressively, the quencher **4.3a** or **4.3l** was added via Hamilton syringe in portions of 5 µL or 10 µL between each addition the fluorescence spectra was measured.

The emission intensity was recorded at 527 nm.

Important note: Pre-prepared stock solutions of quencher and photocatalyst gave poorly reproducible results, it was found that the fluorescence spectra were the most reproducible when adding pure **4.3a** or **4.3l**, for this reason (in addition to the poor solubility of BIOAc) the fluorescence quenching spectra for **7** were not measured. The concentrations for the Stern-Volmer plots were calculated based on approximate volumetric masses of **4.3a** and **4.3l** at RT and ambient pressure. 40 µL of **4.3a** weigh 49 µg at RT and ambient pressure. Approximated volumetric mass was estimated to be 1.2 g/mL. 40 µL of **4.3l** weigh 42 µg Approximated volumetric mass was estimated to be 1.1 g/mL.

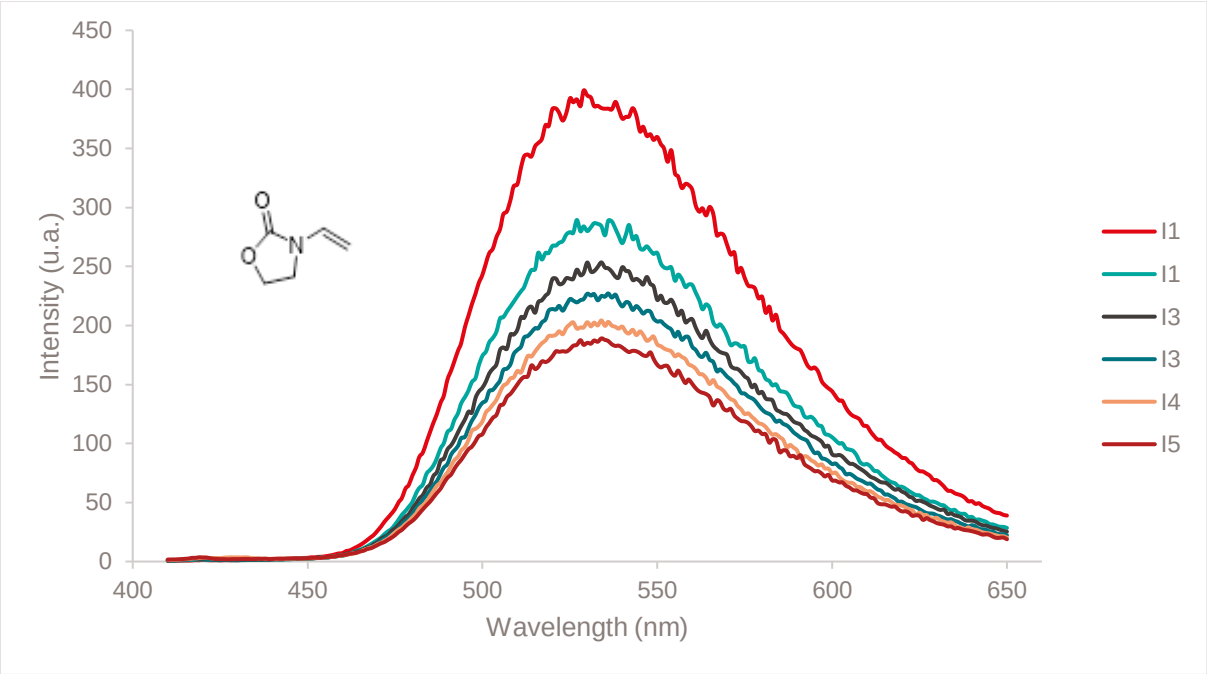


Figure 8.4. Fluorescence emission spectra of PC.9b: fluorescence quenching by 4.3a.

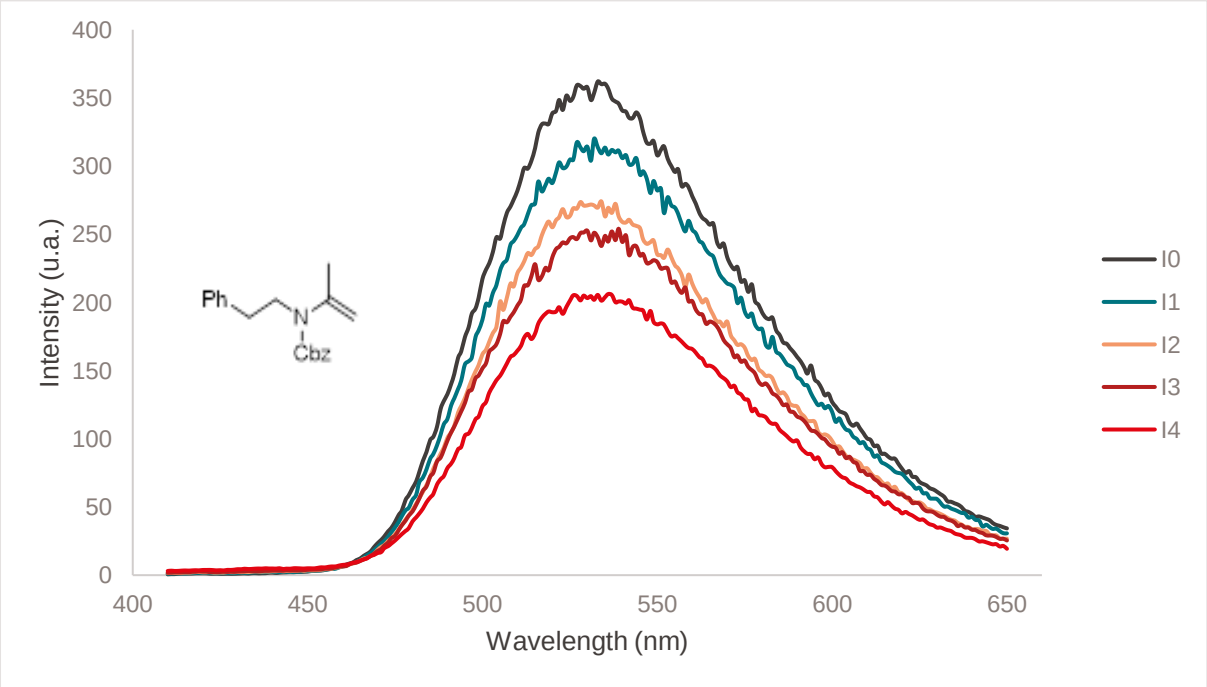


Figure 8.5. Fluorescence emission spectra of PC.9b: fluorescence quenching by 4.3l.

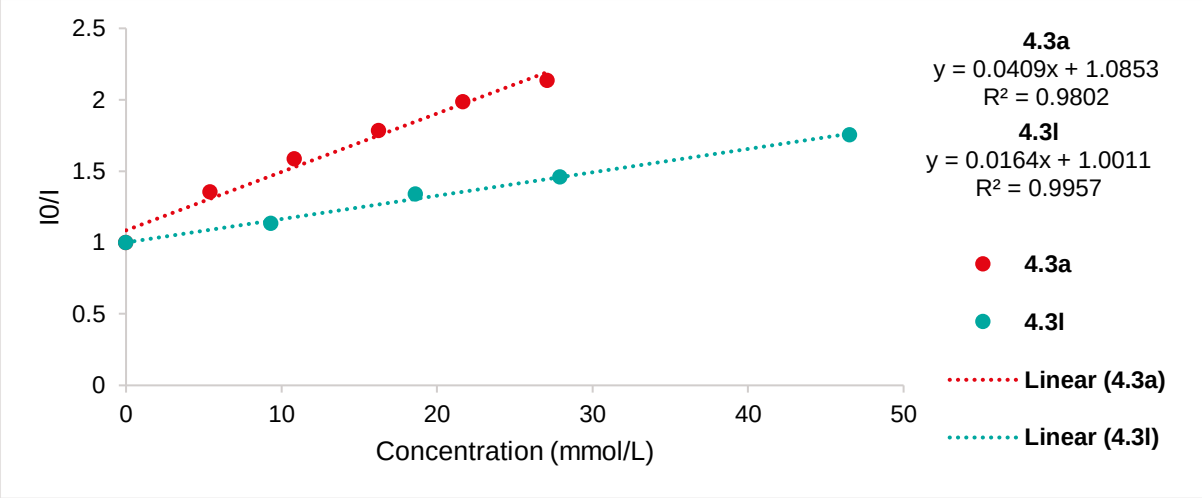


Figure 8.6. Stern-Volmer plot for 4.3a and 4.3l.

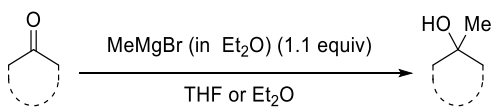
Interestingly **4.3l** also quenches the photocatalyst however the process is non-productive (no conv. with **4.3l**).

8.5. Deoxyalkynylation

Synthesis of tertiary alcohols

Alcohols for substrates **5.6a-d**, **5.6j-m**, **5.6u**, and **5.6v** were purchased from commercial sources (Sigma-Aldrich, Acros, TCI, abcr) and used directly without prior purification.

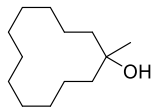
GP4: Synthesis of tertiary alcohols from ketones



8.19 **5.8**

An oven dried two-necked flask, equipped with a magnetic stirrer, was charged with the ketone **8.19** (1.0 equiv) and dissolved in anhydrous THF or Et_2O (0.2 M). The reaction was cooled to 0 °C with an ice bath. The methylmagnesium bromide solution (3.0 M in Et_2O) was diluted to 1 M and added dropwise to the cooled solution *via* a dropping funnel. The reaction was stirred at room temperature overnight (15 to 18 h) at this time the reaction was quenched with sat. aq. NH_4Cl, followed by the addition of water and EtOAc. The layers were separated, the aqueous layer was extracted 3 times with EtOAc then the combined organic layers were washed with sat. aq. NaCl. The organic layer was then dried on $MgSO_4$, filtered and concentrated under reduced pressure. The compound was purified by column chromatography (SiO_2, pentane:EtOAc, *p*-Anisaldehyde stain) affording the desired alcohol **5.8**.

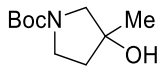
Methylcyclododecan-1-ol (**5.8g**)



Following **GP4**: from cyclododecanone (**8.19g**, 1.00 g, 5.49 mmol, 1.0 equiv) in Et_2O (25 mL, 0.2 M) using methylmagnesium bromide (3.0 M in Et_2O, 2.0 mL, 6.00 mmol, 1.1 equiv) diluted with THF (4.0 mL).
Column chromatography (SiO_2, 10% EtOAC in Pentane) afforded methylcyclododecan-1-ol **5.8g** (609 mg, 3.07 mmol, 56 %) as a white amorphous solid. The NMR data was collected and the compound was used in the next step without further analysis.

Rf (pentane:EtOAc 9:1) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.59 – 1.52 (m, 2 H, C*H*$_2$), 1.45 – 1.25 (m, 20 H, C*H*$_2$), 1.17 (s, 3 H, C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 73.8, 36.3, 29.2, 26.6, 26.2, 22.7, 22.2, 20.1.

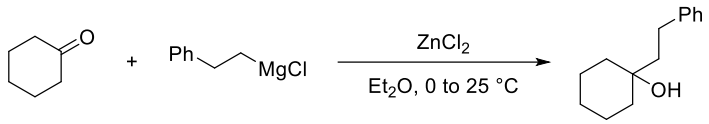
N-Boc-3-hydroxy-3-methyl pyrrolidine (**5.8h**)



Following **GP4**: *N*-Boc pyrrolidin-3-one (**8.19h**, 2.04 g, 11.01 mmol, 1.0 equiv.) in anhydrous Et_2O (20 mL, 0.55 M) using methylmagnesium bromide (3.0 M in Et_2O, 3.7 mL, 11 mmol, 1.1 equiv).
Column chromatography (SiO_2, hexanes:EtOAc 1:1 ratio) afforded *N*-Boc-3-hydroxy-3-methyl pyrrolidine (**5.8h**, 604 mg, 5.20 mmol, 52 %) as a colourless oil. The NMR data was collected and the compound was used in the next step without further analysis.

Rf (hexanes:EtOAc 1:1) = 0.5.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.53 – 3.43 (m, 2H), 3.37 (dd, *J* = 11.4, 1.6 Hz, 1H), 3.22 (d, *J* = 11.5 Hz, 1H), 1.93 – 1.73 (m, 2H), 1.45 (s, 9H), 1.40 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 154.7, 79.3, 58.8, 44.8, 39.2, 28.5, 28.4, 25.4.

1-phenethylcyclohexanol (**5.8i**)



8.19i **8.20** **5.8i**

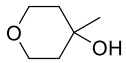
Following a modified reported procedure,[36] a 20 mL round-bottomed test tube was charged with zinc(II) chloride (0.263 g, 1.93 mmol, 25 mol%), sealed, and evacuated. Diethyl ether (dry; 10 mL) was then added via syringe, followed by cyclohexanone **8.19i** (0.80 mL, 7.7 mmol, 1.0 equiv.). The solution was cooled to 0 °C (ice-water bath) and phenethylmagnesium chloride **8.20** (1.0 M in THF; 9.3 mL, 9.3 mmol, 1.2 equiv.) was then added drop-wise. Stirring was continued at 0 °C for 2 hours. The mixture was then warmed to room temperature and stirred overnight. After 20 hours, the initially grey solution converted into a pale grey suspension. At this point, the reaction was quenched by cautious addition of sat. aq. NH_4Cl (20 mL). The aqueous layer was extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting crude oil was submitted to column chromatography (Biotage, 40 g SiO2; EtOAc

[36] Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998.

in pentane, 5 to 20%) to furnish 1-phenethylcyclohexanol **5.8i** (0.423 g, 2.07 mmol, 27% yield) as a colourless solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 - 7.23 (m, 2H), 7.24 - 7.14 (m, 3H), 2.77 - 2.63 (m, 2H), 1.84 - 1.70 (m, 2H), 1.67 - 1.55 (m, 5H), 1.55 - 1.42 (m, 2H), 1.39 - 1.17 (m, 1H), 1.24 (br s, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 142.9, 128.4, 128.4, 125.7, 71.4, 44.3, 37.5, 29.4, 25.8, 22.3. The values of the NMR spectrum are in accordance with reported literature data.[37]

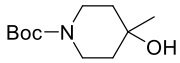
4-Methyltetrahydro-2*H*-pyran-4-ol (**5.8k**)



Following **GP4**: from tetrahydro-4*H*-pyran-4-one (**8.19k**, 0.94 mL, 10 mmol, 1.0 equiv) in THF (50 mL, 0.2 M) using methylmagnesium bromide (3.0 M in Et_2O, 3.7 mL, 11 mmol, 1.1 equiv) diluted with THF (7.3 mL).
Column chromatography (SiO_2, 25% EtOAc in Pentane) afforded 4-methyltetrahydro-2*H*-pyran-4-ol **5.8k** (604 mg, 5.20 mmol, 52 %) as a colourless oil. The NMR data was collected and the compound was used in the next step without further analysis.

Rf (pentane:EtOAc 3:1) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.81 – 3.75 (m, 2H, OCH_2), 3.72 – 3.76 (m, 2H, OCH_2), 1.77 – 1.62 (m, 2H, CH_2), 1.58 – 1.48 (m, 2H, CH_2), 1.28 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 67.5, 64.4, 39.6, 30.3.

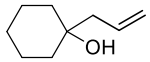
tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (**5.8s**)



Following **GP4**: from tert-butyl 4-oxopiperidine-1-carboxylate (**8.19s**, 1.00 g, 5.02 mmol, 1.0 equiv) in Et_2O (25 mL, 0.2 M) using methylmagnesium bromide (3.0 M in Et_2O, 3.7 mL, 11 mmol, 1.1 equiv).
Column chromatography (SiO_2, 30% EtOAc in Pentane) afforded **5.8s** (893 mg, 4.15 mmol, 83% yield) as a colourless oil. The NMR data was collected and the compound was used in the next step without further analysis.

Rf (pentane:EtOAc 3:1) = 0.2.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.74 – 3.64 (m, 2H, cyclic-CH_2), 3.23 (ddd, *J* = 14.0, 8.2, 6.4 Hz, 2H, cyclic-CH_2), 1.57 – 1.47 (m, 4H, cyclic-CH_2), 1.45 (s, 9H, *t*Bu), 1.25 (s, 3H, CH_3).

1-allylcyclohexanol (**5.8t**)



Following **GP4**: from cyclohexanone (**8.19i**, 1.1 mL, 10 mmol, 1.0 equiv) in Et_2O (50 mL, 0.2 M) using allylmagnesium bromide (1.0 M in Et_2O, 3.7 mL, 11 mmol, 1.1 equiv).
Column chromatography (SiO_2, 25% EtOAc in Pentane) afforded **5.8t** (971 mg, 6.92 mmol, 68% yield) as a colourless oil. The NMR data was collected and the compound was used in the next step without further analysis.

Rf (pentane:EtOAc 3:1) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.82 (ddt, *J* = 17.0, 10.2, 7.5 Hz, 1H, C*H*=CH_2), 5.12 – 5.04 (m, 1H, CH=CH_2), 5.08 – 4.99 (m, 1H, CH=CH_2), 2.15 (dt, *J* = 7.5, 1.1 Hz, 2H, CH_2-CH=CH_2), 1.60 – 1.46 – 1.15 (m, 10H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 133.7, 118.7, 71.0, 46.7, 37.4, 25.8, 22.2.

GP5: Synthesis of tertiary alcohols from esters

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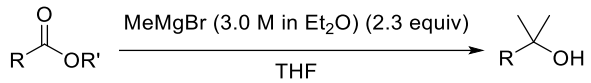
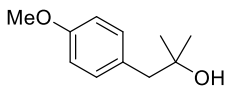
[37] Yus, M.; Martínez, P.; Guijarro, D. *Tetrahedron* **2001**, *57*, 10119.



8.21 **5.8**

An oven dried two necked flask, equipped with a magnetic stirrer, was charged with the ester **8.21** (1.0 equiv) and dissolved in anhydrous THF (1.0 M). The reaction was cooled to 0 °C with an ice bath. The methyl magnesium bromide solution was diluted to 1 M with THF and added dropwise to the cooled solution *via* syringe. The reaction was left to stir at room temperature overnight (15 to 18 h) at this time the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted 3 times with EtOAc then the combined organic layers were washed with sat. aq. NaCl. The organic layers were then dried on $MgSO_4$, filtered and concentrated under reduced pressure. The compound was purified by column chromatography (SiO_2, pentane:EtOAc 9:1, 4:1, *p*-Anisaldehyde stain blue to purple and black spots) affording the desired alcohol.

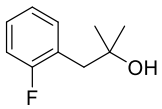
1-(4-Methoxyphenyl)-2-methylpropan-2-ol (**5.8f**)



Following **GP5**: from methyl 2-(4-methoxyphenyl)acetate (**8.21f** ,1.0 mL, 6.3 mmol, 1.0 equiv) in THF (60 mL, 0.1 M) and methyl magnesium bromide (3 M in Et_2O) (4.8 mL, 14 mmol, 2.3 equiv) diluted with 10 mL of THF.
Column chromatography (SiO_2 ca. 40 g, pentane:EtOAc 9:1 to 8:2) afforded 1-(4-methoxyphenyl)-2-methylpropan-2-ol **5.8f** (0.898 g, 4.98 mmol, 79%).

Rf (pentane:EtOAc 9:1) = 0.3
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 7.11 (m, 2H, Ar*H*), 6.88 – 6.83 (m, 2H, Ar*H*), 3.80 (s, 3H, OMe), 2.71 (s, 2H, ArCH_2), 1.21 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.5, 131.5, 129.9, 113.8, 70.9, 55.4, 48.9, 29.2.
The reported NMR data are consitant with the reported data.[38]

1-(2-Fluorophenyl)-2-methylpropan-2-ol (**5.8n**)

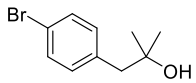


Following **GP5:** from methyl 2-(2-fluorophenyl)acetate (**8.21n**, 1.0 mL, 6.8 mmol, 1.0 equiv) in THF (60 mL, 0.1 M) and methyl magnesium bromide (3 M in Et_2O) (5.2 mL, 16 mmol, 2.3 equiv) diluted with 10 mL of THF.
Column chromatography (SiO_2 ca. 40g, pentane:EtOAc 9:1 to 8:2) afforded 1-(2-fluorophenyl)-2-methylpropan-2-ol **5.8n** (0.723 g, 4.30 mmol, 63%).

Rf (pentane:EtOAc 9:1) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 – 7.18 (m, 2H, Ar*H*), 7.13 – 7.00 (m, 2H, Ar*H*), 2.83 (d, J = 1.5 Hz, 2H, CH_2), 1.48 (s, 1H, O*H*), 1.25 (d, J = 0.9 Hz, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 161.5 (d, *J* = 244.7 Hz), 132.8 (d, *J* = 4.7 Hz), 128.3 (d, *J* = 8.2 Hz), 124.9 (d, *J* = 16.0 Hz), 123.8 (d, *J* = 3.5 Hz), 115.4 (d, *J* = 23.0 Hz), 71.3, 42.3, 29.1. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -116.1. **IR** (ν_{max}, cm^{-1}) 3420 (m), 3061 (m), 2975 (m), 2963 (m), 2936 (m), 1583 (m), 1493 (s), 1455 (s), 1228 (s), 1184 (s), 1134 (s), 753 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z $[M]^+$ Calcd for $C_{10}H_{12}F^+$ 151.0918; Found 151.0921.

[38] Okamura, T.; Egoshi, S.; Dodo, K.; Sodeoka, M.; Iwabuchi, Y.; Kanoh, N. *Chem. – Eur. J.* **2019**, *25*, 16002–16006.

1-(4-bromophenyl)-2-methylpropan-2-ol (**5.8o**)

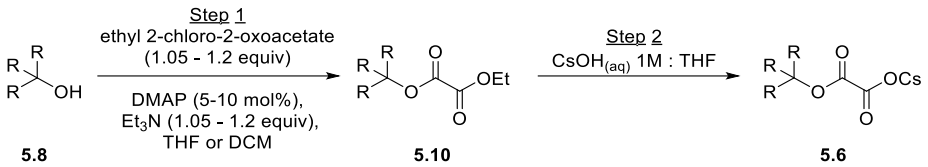


Following **GP5**: from ethyl 2-(4-bromophenyl)acetate (**8.21o**, 1.00 g, 4.11 mmol, 1.0 equiv) in THF (40 mL, 0.1 M) and methyl magnesium bromide (3 M in Et_2O) (3.2 mL, 9.46 mmol, 2.3 equiv) diluted with 6 mL of THF.
Column chromatography (SiO_2 ca. 40 g, pentane:EtOAc 9:1 to 8:2) afforded 1-(4-bromophenyl)-2-methylpropan-2-ol **5.8o** (0.781 g, 3.41 mmol, 83%).

Rf (pentane:EtOAc 9:1) = 0.3
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.39 (m, 2H, Ar*H*), 7.13 – 7.06 (m, 2H, Ar*H*), 2.72 (s, 2H, CH_2), 1.38 (s, 1H, O*H*), 1.21 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 136.8, 132.2, 131.2, 120.5, 70.7, 49.1, 29.2. **IR** (ν_{max}, cm^{-1}) 3668 (m), 2972 (s), 2901 (s), 1488 (s), 1406 (s), 1377 (s), 1229 (s), 1075 (s), 1056 (s), 1012 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M]$^+$ Calcd for $C_{10}H_{12}{}^{79}Br^+$ 211.0117; Found 211.0122.

Synthesis of cesium salts

GP6: Synthesis of cesium salts from tertiary alcohols



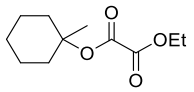
Step 1: Following a modified reported procedure,[39] a two necked round bottomed flask, equipped with a magnetic stirrer, was charged with THF or CH_2Cl_2 (0.1 or 0.2 M),[40] DMAP (0.15 mmol, 5 mol%), the tertiary alcohol **5.8** (3.00 mmol, 1.00 equiv) and triethylamine (1.05 - 1.2 equiv) were then added. Ethyl 2-chloro-2-oxoacetate (1.05 - 1.2 equiv) was then added dropwise and giving a yellowish solution. The reaction was then stirred for 1 h – 2 h at room temperature. Upon full conversion of the alcohol, indicated by TLC analysis, the reactions were quenched with sat. aq. NH_4Cl. The layers were then separated and the organic layer was then washed twice with brine (ca. 10 mL). The organic layer was then dried over Na_2SO_4 and filtered. A solid deposit for flash chromatography was prepared: (ca. 5-7 g SiO_2) concentrated under reduced pressure. The compound was purified by flash chromatography (SiO_2, pentane:EtOAc 9:1, 4:1, *p*-Anisaldehyde stain blue, green or purple spots) affording the desired alkyl ethyl oxalate **5.10**.

Step 2: Following a modified reported procedure,[13] a round-bottom flask was charged with ethyl oxoacetate **5.10** (1.75 mmol, 1.00 equiv) followed by the addition of THF (1 M). To this solution, a 1 M stock solution of aq. CsOH (1.7 mmol, 1.00 equiv) was added dropwise (ca. 2 min). The mixture was stirred vigorously for 5 min at room temperature, then concentrated

[39] Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273.
[40] We have not noticed particular changes of reactivity between THF and CH_2Cl_2 or between 0.1 M or 0.2 M, use of CH_2Cl_2 simplifies extraction.

immediately under reduced pressure (T = 55°C - 60 °C: P = 300 mbar to 20 mbar).[41] The resulting solid was then dried under high vacuum for at least 4 hours affording a dry (rarely hygroscopic, some are soap-like) cesium salt **5.6**.

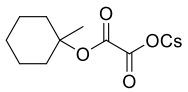
Ethyl 2-(1-methylcyclohex-1-yl)oxy-2-oxoacetate (**5.10a**)



5.10a was synthesized following step 1 of **GP6** in THF (90 mL, 0.1 M) using 1-methylcyclohexan-1-ol (**5.8a**, 1.1 mL, 8.8 mmol, 1.0 equiv), DMAP (107 mg, 0.876 mmol, 0.1 equiv) triethylamine (1.50 mL, 10.5 mmol, 1.2 equiv) and ethyl chloro-oxoacetate (1.20 mL, 10.5 mmol, 1.2 equiv).
Column chromatography (SiO_2, 2% EtOAc in Pentane) afforded ethyl (1-methylcyclohexyl) oxalate (**5.10a**, 1.18 g, 5.51 mmol, 63%) as a pale yellow oil.

Rf (pentane:EtOAc 98:2) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.30 (q, *J* = 7.12 Hz, 2H, CO_2CH_2), 2.21 – 2.18 (m, 2H, CH_2), 1.58 – 1.44 (m, 8 H, CH_2), 1.55 (s, 3H, CH_3), 1.35 (t, *J* = 7.12 Hz, 3 H, $CO_2CH_2CH_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.8, 157.2, 86.7, 62.8, 36.4, 25.3, 25.1, 22.1, 14.1. **IR** (ν_{max}, cm^{-1}) 2979 (w), 2938 (m), 2864 (w), 1743 (s), 1454 (w), 1326 (m), 1192 (s), 1146 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{11}H_{18}NaO_4^+$ 237.1097; found 237.1094

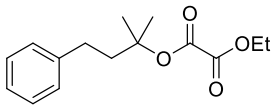
Cesium 2-(1-methylcyclohex-1-yl)oxy-2-oxoacetate (**5.6a**)



5.6a was synthesized following step 2 of **GP6** in THF (5.0 mL, 0.1 M) using ethyl (1-methylcyclohexyl) oxalate (**5.10a**, 1.07 g, 5.00 mmol, 1.0 equiv) and 1 M aq. CsOH (5.0 mL, 5.0 mmol, 1.0 equiv). Affording cesium 2-((1-methylcyclohexyl)oxy)-2-oxoacetate (**5.6a**, 1.4 g, 4.4 mmol, 88%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.08 – 1.96 (m, 2H, CH_2), 1.56 – 1.43 (m, 3H, CH_2), 1.43 – 1.29 (m, 7H, CH_2 + CH_3), 1.27 – 1.18 (m, 1H, CH_2). **^{13}C NMR** (101 MHz, DMSO) δ 167.7, 163.6, 79.2, 36.2, 25.3, 25.0, 21.5. **HRMS** (ESI/QTOF) m/z [M - Cs]$^-$ Calcd for $C_9H_{13}O_4^-$ 185.0819; Found 185.0819.

Ethyl 2-(2-methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.10b**)

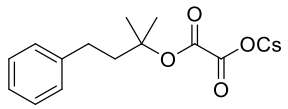


5.10a was synthesized following step 1 of **GP6** in THF (90 mL, 0.1 M) using 2-methyl-4-phenylbutan-2-ol (**5.8a**, 1.6 mL, 9.1 mmol, 1 equiv), DMAP (0.055 g, 0.46 mmol, 5 mol%), triethylamine (1.3 mL, 9.6 mmol, 1.05 equiv) and ethyl chloro-oxoacetate (1.1 mL, 9.6 mmol, 1.05 equiv).
Column chromatography (SiO_2, pentane:EtOAc 85:15) afforded ethyl (2-methyl-4-phenylbutan-2-yl) oxalate (**5.10a**, 2.00 g, 7.57 mmol, 83%) as a colorless oil.

Rf (pentane:EtOAc 9:1) = 0.5
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.29 (m, 2H, Ar*H*), 7.25 (d, *J* = 7.1 Hz, 3H, Ar*H*), 4.38 (q, *J* = 7.1 Hz, 2H, OCH_2-CH_3), 2.79 – 2.71 (m, 2H, Ph-CH_2), 2.25 – 2.16 (m, 2H, CH_2), 1.66 (s, 6H, d*Me*), 1.43 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.6, 157.1, 141.6, 128.5, 128.4, 126.0, 86.6, 62.8, 42.5, 30.2, 25.7, 14.0. **IR** (vmax, cm-1) 3087 (w), 3062 (w), 3029 (m), 2983 (m), 2949 (m), 2872 (w), 1761 (s), 1737 (s), 1327 (m), 1188 (s), 1163 (s), 1118 (s), 912 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{15}H_{20}NaO_4^+$ 287.1254; Found 287.1256.

[41] Other hydrolysis products have been observed when the reaction is left longer or triturated in diethyl ether to attempt purification.

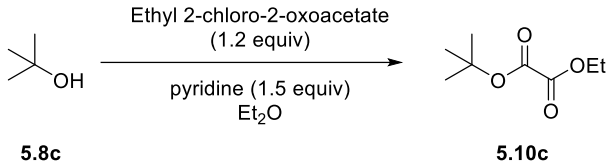
Cesium 2-(2-methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.6b**)



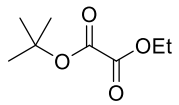
5.6b was synthesized following step 2 of **GP6** in THF (6.5 mL, 0.1 M) using ethyl (2-methyl-4-phenylbutan-2-yl) oxalate (**5.10b**, 1.70 g, 6.43 mmol, 1.0 equiv) and 1 M aq. CsOH (6.4 mL, 6.4 mmol, 1.0 equiv), affording cesium 2-(2-methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.6b**, 2.34 g, 6.36 mmol, 99%) as an off-white amorphous solid.

^{1}H NMR (400 MHz, D_2O) δ 7.31 (m, 5H, Ar*H*), 2.73 – 2.64 (m, 2H, ArCH_2), 2.20 – 2.11 (m, 2H, CH_2), 1.55 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, D_2O) δ 165.2, 164.1, 142.5, 128.7, 128.5, 126.0, 86.0, 41.3, 29.7, 25.4. **HRMS** (ESI/QTOF) m/z [M - Cs]$^-$ Calcd for $C_{13}H_{15}O_4^-$ 235.0976; Found 235.0979.

Ethyl (tert-butyl)oxy-2-oxoacetate (**5.10c**)

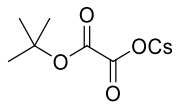


Following a reported procedure,[42] ethyl 2-chloro-2-oxoacetate (3.6 mL, 32 mmol, 1.2 equiv) was added to a solution of *tert*-butanol (**5.8c**, 2.0 g, 27 mmol, 1.0 equiv) and pyridine (3.26 mL, 40.5 mmol) in Et_2O (100 mL) and the resulting yellow solution was stirred at room temperature for 4 hours. The organic layer was washed with water (2 x 50 mL) and sat. aq. $NaHCO_3$ solution (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on a short column of silica gel (1:20 Et_2O:pentane) to give *tert*-butyl ethyl oxalate (**5.10c**, 4.4 g, 25 mmol, 98%) as a colorless oil.



^{1}H NMR (400 MHz, Chloroform-d) δ 4.31 (q, J = 7.1 Hz, 2H, OCH_2), 1.55 (s, 9H, tBu), 1.36 (t, J = 7.1 Hz, 3H, CH_2CH_3). **^{13}C NMR** (101 MHz, Chloroform-d) δ 158.8, 157.3, 85.0, 62.9, 27.9, 14.1. The NMR data obtained are consistent with the reported literature data.[16]

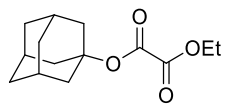
Cesium (tert-butyl)oxy-2-oxoacetate (**5.6c**)



5.6c was synthesized following step 2 of **GP6** in THF (2.1 mL, 0.1 M) using *tert*-butyl ethyl oxalate (**5.10c**, 0.366 g, 2.10 mmol, 1.0 equiv) and 1 M aq. CsOH (2.1 mL, 2.1 mmol, 1.0 equiv), affording cesium (*tert*-butyl)oxy-2-oxoacetate (**5.6c,** 0.505 g, 1.82 mmol, 86%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.5, 163.5, 78.0, 27.9. **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_6H_9CsNaO_4^+$ 300.9448; Found 300.9451.

Ethyl 2-(((1S,3S)-adamantan-1-yl)oxy)-2-oxoacetate (**5.10d**)



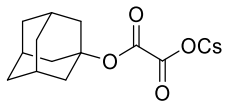
5.10d was synthesized following step 1 of **GP6** in CH_2Cl_2 (25 mL, 0.1 M) using adamant-1-ol (**5.8d**, 378 mg, 2.48 mmol, 1.0 equiv), DMAP (30.4 mg, 248 mmol, 10 mol%), triethylamine (0.41 mL, 3.0 mmol, 1.2 equiv) and ethyl chloro-oxoacetate (0.34 mL, 3.0 mmol, 1.2 equiv).

[42] Xu, Y.; McLaughlin, M.; Bolton, E. N.; Reamer, R. A. *J. Org. Chem.* **2010**, *75*, 8666–8669.

Column chromatography (SiO_2, 15% EtOAc in Pentane) afforded ethyl 2-(((1S,3S)-adamantan-1-yl)oxy)-2-oxoacetate (**5.10d**, 442 mg, 1.75 mmol, 71 %) as a pale yellow oil.

Rf (pentane:EtOac 9:1) = 0.5.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.31 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 2.19 (d, *J* = 2.7 Hz, 9H, ad-C*H*$_x$), 1.76 – 1.55 (m, 6H, ad-C*H*$_x$), 1.36 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.8, 156.8, 85.1, 62.9, 41.0, 36.1, 31.1, 14.1. **IR** (ν_{max}, cm^{-1}) 2911 (m), 2854 (w), 1760 (s), 1733 (s), 1176 (s), 1155 (s), 1044 (m). **HRMS** (APPI/LTQ-Orbitrap) m/z [M + Na]$^+$ Calcd for $C_{14}H_{20}NaO_4^+$ 275.1254; Found 275.1256.

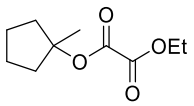
Cesium 2-(((1S,3S)-adamantan-1-yl)oxy)-2-oxoacetate (**5.6d**)



5.6d was synthesized following step 2 of **GP6** in THF (2.5 mL, 0.1 M) using ethyl 2-(((1*S*,3*S*)-adamantan-1-yl)oxy)-2-oxalate (**5.10d**, 252 mg, 1.00 mmol, 1.0 equiv) and 1 M aq. CsOH (2.5 mL, 2.5 mmol, 1.0 equiv). cesium 2-(((1*S*,3*S*)-adamantan-1-yl)oxy)-2-oxoacetate (**5.6d**, 0.32 g, 0.91 mmol, 91%) was obtained as an off-white amorphous solid.

^{1}H NMR (400 MHz, DMSO) δ 2.12 – 2.07 (m, 3H, C*H*), 2.06 – 1.99 (m, 6H, C*H*$_2$), 1.64 – 1.59 (m, 6H, C*H*$_2$). **^{13}C NMR** (101 MHz, DMSO) δ 167.3, 163.4, 78.0, 41.0, 35.8, 30.2. **HRMS** (ESI/QTOF) m/z [M - Cs]$^-$ Calcd for $C_{12}H_{15}O_4^-$ 223.0976; Found 223.0974.

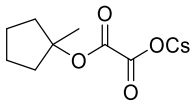
Ethyl 2-(1-methylcyclopent-1-yl)oxy-2-oxoacetate (**5.10e**)



5.10e was synthesized following step 1 of **GP6** in THF (16 mL, 0.2 M) using 1-methylcyclopentan-1-ol (**5.8e**, 337 mg, 3.36 mmol, 1.0 equiv), DMAP (21 mg, 0.17 mmol, 5 mol%), triethylamine (0.56 mL, 11 mmol, 1.2 equiv) and ethyl chloro-oxoacetate (0.45 mL, 11 mmol, 1.2 equiv).
Column chromatography (SiO_2, pentane:EtOAc 9:1 to 8:2) afforded ethyl (1-methylcyclopentan-1-yl) oxalate (**5.10e**, 596 mg, 2.98 mmol, 89%).

Rf (pentane:EtOAc 9:1) = 0.5.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.31 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 2.21 (ttd, *J* = 10.4, 4.8, 2.4 Hz, 2H, C*H*$_2$), 1.83 – 1.71 (m, 4H, C*H*$_2$), 1.71 – 1.58 (m, 5H, C*H*$_2$ + C*H*$_3$), 1.36 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.8, 157.5, 94.2, 62.9, 39.0, 24.1, 23.8, 14.1. **IR** (ν_{max}, cm^{-1}) 2984 (m), 2942 (m), 2910 (w), 1762 (s), 1737 (s), 1370 (m), 1324 (m), 1201 (s), 1139 (s), 1017 (m), 846 (m). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{10}H_{16}NaO_4^+$ 223.0941; Found 223.0935.

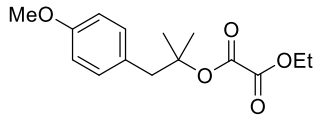
Cesium 2-(1-methylcyclopent-1-yl)oxy-2-oxoacetate (**5.6e**)



5.6e was synthesized following step 2 of **GP6** in THF (1.2 mL, 0.1 M) using ethyl (1-methylcyclopent-1-yl) oxalate (**5.10e**, 0.37 g, 1.8 mmol, 1.0 equiv) and 1 M aq. CsOH (1.8 mL, 1.8 mmol, 1.0 equiv), affording cesium 2-(1-methylcyclopent-1-yl)oxy-2-oxoacetate (**5.6e** 0.541 g, 1.78 mmol, 97%).

^{1}H NMR (400 MHz, DMSO) δ 1.97 (dddt, *J* = 7.1, 5.3, 3.0, 1.8 Hz, 2H, C*H*$_2$), 1.72 – 1.49 (m, 6H, C*H*$_2$), 1.46 (s, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, DMSO) δ 167.5, 163.5, 87.3, 24.3, 23.3, 14.2. Consistent with reported data.[39]

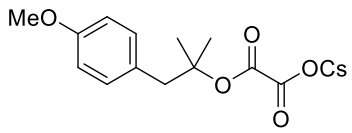
Ethyl (1-(4-methoxyphenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate (**5.10f**)



5.10f was synthesized following step 1 of **GP6** in CH_2Cl_2 (30 mL, 0.1 M) using 1-(4-methoxyphenyl)-2-methylpropan-2-ol (**5.8f**, 500 mg, 2.77 mmol, 1.0 equiv), DMAP (33 mg, 0.28 mmol, 10 mol%), triethylamine (0.40 mL, 2.9 mmol, 1.05 equiv) and ethyl chloro-oxoacetate (0.30 mL, 2.9 mmol, 1.05 equiv).
Column chromatography (SiO_2, pentane:EtOAc 4:1) afforded ethyl (1-(4-methoxyphenyl)-2-methylpropan-2-yl) oxalate (**5.10f**, 270 mg, 0.963 mmol, 35%) as a pale-yellow oil.

Rf (pentane:EtOAc 4:1) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 7.12 (m, 2H, Ar*H*), 6.87 – 6.79 (m, 2H, Ar*H*), 4.32 (q, *J* = 7.2 Hz, 2H, OCH_2CH$_3$), 3.79 (s, 3H, OCH_3), 3.03 (s, 2H, ArCH_2), 1.53 (s, 6H (CH_3)$_2$), 1.38 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.6, 158.6, 157.2, 131.8, 128.5, 113.6, 86.8, 62.9, 55.3, 46.1, 25.4, 14.1. **IR** (ν_{max}, cm^{-1}) 2995 (m), 2985 (m), 2953 (m), 2937 (m), 2909 (m), 2837 (m), 1761 (s), 1738 (s), 1612 (m), 1513 (s), 1465 (m), 1370 (m), 1321 (s), 1247 (s), 1189 (s), 1177 (s), 1164 (s), 1034 (s), 1019 (s), 851 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{15}H_{20}NaO_5^+$ 303.1203; Found 303.1206.

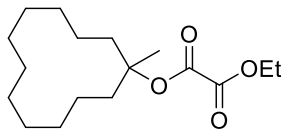
Cesium (1-(4-methoxyphenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate (**5.6f**)



5.6f was synthesized following step 2 of **GP6** in THF (0.7 mL, 0.1 M) using ethyl (1-(4-methoxyphenyl)-2-methylpropan-2-yl) oxalate (**5.10f**, 0.20 g, 0.71 mmol, 1.0 equiv) and 1 M aq. CsOH (0.7 mL, 0.7 mmol, 1.0 equiv), affording cesium (1-(4-methoxyphenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate (**5.6f**, 251 mg, 0.653 mmol, 92%) as a coloroless amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18 – 7.11 (m, 2H, Ar*H*), 6.85 – 6.78 (m, 2H, Ar*H*), 3.72 (s, 3H, OCH_3), 2.95 (s, 2H, ArCH_2), 1.31 (s, 6H, (CH_3)$_2$). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.7, 163.3, 157.7, 131.5, 129.3, 113.2, 80.2, 54.9, 44.5, 25.8. **HRMS** (ESI/QTOF) m/z [M - Cs]$^-$ Calcd for $C_{13}H_{15}O_5^-$ 251.0925; Found 251.0936.

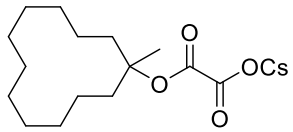
Ethyl (1-methylcyclododecyl) oxalate (**5.10g**)



5.10g was synthesized following step 1 of **GP6** in THF (25 mL, 0.1 M) using 1-methylcyclododecan-1-ol (**5.8g**, 500 mg, 2.52 mmol, 1.0 equiv), DMAP (31 mg, 0.25 mmol, 10 mol%), triethylamine (0.42 mL, 3.0 mmol, 1.2 equiv) and ethyl chloro-oxoacetate (0.34 mL, 3.0 mmol, 1.2 equiv).
Column chromatography (SiO_2, 20% EtOAc in Pentane) afforded ethyl (1-methylcyclododecyl) oxalate (**5.10g**, 1.08 g, 4.25 mmol, 71 %) as an off-white amorphous solid.

Rf (pentane:EtOAc 4:1) = 0.5.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.31 (q, *J* = 7.2 Hz, 2H, CO$_2$CH_2), 2.10 – 1.98 (m, 2H, CH_2), 1.74 – 1.61 (m, 2H, CH_2), 1.55 (s, 3H, CH_3), 1.49 – 1.23 (m, 21H, CH_2 + CH$_2$CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.9, 157.1, 90.8, 62.9, 32.9, 26.2, 26.2, 24.0, 22.5, 22.0, 19.5, 14.1. **IR** (ν_{max}, cm^{-1}) 2939 (s), 2861 (m), 1744 (s), 1467 (m), 1375 (m), 1325 (m), 1190 (s), 1152 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{17}H_{30}NaO_4^+$ 321.2036; Found 321.2037.

Cesium 2-((1-methylcyclododecyl)oxy)-2-oxoacetate (**5.6g**)

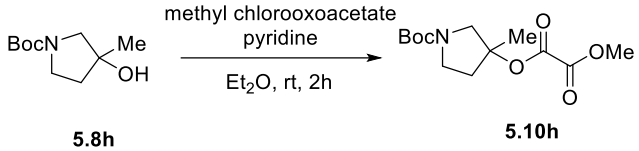


5.6g was synthesized following step 2 of **GP6** in THF (1.0 mL, 0.1 M) using ethyl (1-methylcyclododecyl) oxalate (**5.10g**, 300 mg, 1.00 mmol, 1.0 equiv) and 1 M aq. CsOH (1.0 mL, 1.00 mmol, 1.0 equiv). Cesium 2-((1-methylcyclododecyl)oxy)-2-oxoacetate (**5.6g**, 300 mg, 0.745 mmol, 74 %) was obtained as an off-white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.90 – 1.77 (m, 2H, CH_2), 1.56 – 1.42 (m, 2H, CH_2), 1.38 (s, 3H, CH_3), 1.34 – 1.18 (m, 18H, CH_2). **^{13}C NMR** (101 MHz, DMSO) δ 168.1, 164.0, 83.4, 33.21 26.3, 26.2, 24.4,

22.3, 22.0, 19.2. **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{15}H_{25}CsNaO_4^+$ 425.0700; Found 425.0695.

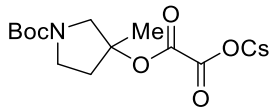
1-(tert-butoxycarbonyl)-3-methylpyrrolidin-3-yl methyl oxalate (**5.6h**)



Following a modified reported procedure,[42] methyl chlorooxoacetate (1.00 mL, 10.9 mmol, 2.0 equiv.) was added to a solution of **5.8h** (1.1 g, 5.47 mmol, 1.0 equiv.) and pyridine (0.88 mL, 11 mmol, 2.0 equiv.) in Et_2O (100 mL, 0.25 M) and the resulting yellow solution was stirred at room temperature for 4 hours. The organic phase was washed with water (2 x 25 mL) and an aqueous saturated solution of $NaHCO_3$ (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on a short column of silica gel (1:19 - 1:9 Et2O:hexanes) to give the product **5.10h** as a colorless oil (1.5 g, 5.2 mmol, 96%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.87 (s, 4H), 3.52 – 3.36 (m, 3H), 2.47 (s, 1H), 2.01 (d, *J* = 15.1 Hz, 1H), 1.69 (s, 3H), 1.44 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) mixture of rotamers δ 158.3, 156.8, 154.3, 89.5, 88.8, 79.8, 60.4, 56.0, 53.5, 44.2, 43.8, 36.6, 28.5, 21.3, 21.1, 14.2. The values of the NMR spectra are in accordance with reported literature data.[39]

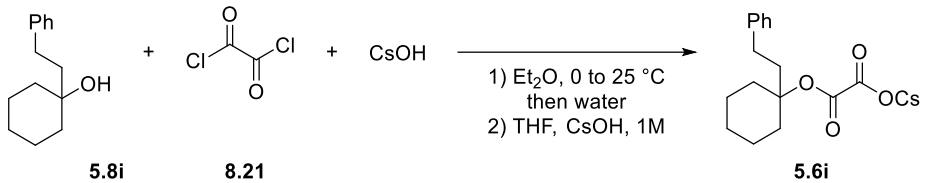
Cesium 2-((1-(tert-butoxycarbonyl)-3-methylpyrrolidin-3-yl)oxy)-2-oxoacetate (**5.6h**)



5.6h was synthesized following step 2 of **GP6** in THF (51 mL, 0.1 M) using ethyl (1-(tert-butoxycarbonyl)-3-methylpyrrolidin-3-yl) oxalate (**5.10h**, 1.5 g, 5.1 mmol, 1.0 equiv) and 1 M aq. CsOH (1.0 mL, 1.0 mmol, 1.0 equiv). Cesium 2-((1-(tert-butoxycarbonyl)-3-methylpyrrolidin-3-yl)oxy)-2-oxoacetate (**5.6h**, 1.9 g, 4.7 mmol, 92%) was obtained as an off-white solid.

^{1}H NMR (400 MHz, Deuterium Oxide) δ 3.77 (d, *J* = 32.2 Hz, 2H), 3.65 – 3.20 (m, 3H), 2.41 (dt, *J* = 12.0, 5.5 Hz, 1H), 2.02 (dt, *J* = 13.6, 8.7 Hz, 1H), 1.58 (s, 3H), 1.38 (s, 8H). The values of the ^{1}H NMR spectrum are in accordance with reported literature data.[39]

Cesium (1-phenyleth-2-yl)cyclohexan-1-yl)oxy)-2-oxoacetate (**5.6i**)



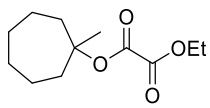
Following a modified reported procedure,[43] 1-phenethylcyclohexanol **5.8i** (0.200 g, 0.979 mmol, 1.0 equiv.) was dissolved in diethyl ether (dry; 4.9 mL), and the resulting colourless solution was cooled to 0 °C (ice-water bath). A solution of oxalyl chloride (0.14 mL, 1.7 mmol,

[43] Su, J. Y.; Grünenfelder, D. C.; Takehuchi, K.; Reisman, S. E.; *Org. Lett.* **2018**, *20*, 4912–4916.

1.7 equiv.) in diethyl ether (dry; 3.0 mL) was then added by syringe drop-wise at the same temperature. Stirring was continued at 0 °C for 2 hours. The pale yellow mixture was then warmed to room temperature and, after 1 hour, an additional amount of oxalyl chloride (0.90 mL, 1.1 equiv.) was added. Stirring was further continued at room temperature for 2 days, checking the consumption of the starting material by TLC analysis (pentane/EtOAc 9/1). After this time, the volatiles were removed under reduced pressure to furnish a greyish oil. The latter was dissolved in diethyl ether (10 mL) and treated by drop-wise addition of water (10 mL). After stirring for 5 minutes, the aqueous layer was separated and extracted with diethyl ether (3 x 10 mL). The combined ethereal extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, to afford a pale yellow oil (0.263 g). The latter was dissolved in THF (5.0 mL) and water (0.5 mL), and aq. CsOH (1.0 M; 0.90 mL, 0.90 mmol, 0.92 equiv.) was added slowly under vigorous stirring. After stirring for 5 minutes, the solution was submitted to low pressure distillation in order to remove the THF. The resulting pale yellow aqueous solution was then washed with a 1:1 mixture of pentane/diethyl ether (3 x 15 mL). It was then concentrated under reduced pressure and co-evaporated with toluene. The resulting off-white solid was then dried under high vacuum overnight. Caesium 2-oxo-2-((1-phenethylcyclohexyl)oxy)acetate **5.6i** (0.346 g, 0.848 mmol) was obtained in 87% yield.

^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ 7.23 (dd, *J* = 7.9, 6.9 Hz, 2H, Ph), 7.20 - 7.16 (m, 2H, Ph), 7.15 - 7.10 (m, 1H, Ph), 2.68 - 2.61 (m, 2H, PhC*H*$_2$), 2.33 (dt, *J* = 15.3, 3.7 Hz, 2H, PhCH$_2$-C*H*$_2$), 2.24 - 2.18 (m, 2H, cyclic-C*H*$_2$), 1.73 - 1.58 (m, 4H, cyclic-C*H*$_2$), 1.58 - 1.47 (m, 4H, cyclic-C*H*$_2$). **^{13}C NMR** (101 MHz, Methanol-*d*$_4$) δ 166.7, 166.4, 143.8, 129.4, 126.7, 86.4, 41.1, 35.6, 30.5, 26.7, 22.9. RMS (ESI/QTOF) m/z: $[M]^-$ Calcd for $C_{16}H_{19}O_4^-$ 275.1289; Found 275.1289.

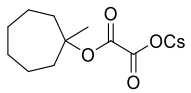
Ethyl 2-(1-methylcycloheptan-1-yl)oxy-2-oxoacetate (**5.10j**)



5.10j was synthesized following <u>step 1</u> of **GP6** in CH_2Cl_2 (35 mL, 0.1 M) using 1-methylcycloheptan-1-ol (**5.8j**, 0.30 mL, 3.4 mmol, 1 equiv), DMAP (42 mg, 0.34 mmol, 10 mol%), triethylamine (0.52 mL, 3.7 mmol, 1.1 equiv) and ethyl chloro-oxoacetate (0.42 mL, 3.8 mmol, 1.1 equiv).
Column chromatography (SiO_2, pentane:EtOAc 9:1) afforded ethyl (1-methylcycloheptan-1-yl) oxalate (**5.10j**, 0.373 g, 1.84 mmol, 54%).

Rf (pentane:EtOAc 9:1) = 0.5.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.30 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 2.20 (ddd, *J* = 14.9, 8.6, 1.7 Hz, 2H, cyclic-C*H*$_2$), 1.82 (ddd, *J* = 14.7, 9.8, 1.8 Hz, 2H, cyclic-C*H*$_2$), 1.70 – 1.39 (m, 11H, cyclic-(C*H*$_2$))$_4$ + CH$_3$, 1.35 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.9, 157.3, 91.1, 62.8, 40.0, 29.5, 26.6, 22.6, 14.1. **IR** (ν_{max}, cm^{-1}) 3005 (w), 2929 (m), 2858 (m), 1760 (s), 1736 (s), 1459 (m), 1446 (m), 1371 (m), 1323 (m), 1205 (s), 1186 (s), 1159 (s), 1128 (s), 861 (m). **HRMS** (ESI/QTOF) m/z $[M + Na]^+$ Calcd for $C_{12}H_{20}NaO_4^+$ 251.1254; Found 251.1259.

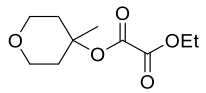
Cesium 2-(1-methylcycloheptan-1-yl)oxy-2-oxoacetate (**5.6j**)



5.6j was synthesized following step 2 of **GP6** in THF (1.1 mL, 0.1 M) using ethyl (1-methylcycloheptan-1-yl) oxalate (**5.10j**, 0.250 g, 1.10 mmol, 1.0 equiv) and 1 M aq. CsOH (1.1 mL, 1.1 mmol, 1.0 equiv), affording cesium 2-(1-methylcycloheptan-1-yl)oxy-2-oxoacetate (**5.6j**, 0.332 g, 1.00 mmol, 91%). Amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.02 (ddd, J = 14.3, 8.6, 1.6 Hz, 2H, cyclic-CH_2), 1.67 (ddd, J = 14.4, 9.9, 1.9 Hz, 2H, cyclic-CH_2), 1.60 – 1.42 (m, 6H, cyclic-CH_2), 1.41 (s, 3H, CH_3), 1.40 – 1.28 (m, 2H, cyclic-CH_2). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.2, 164.1, 83.9, 29.3, 27.2, 22.5. 1 carbon is unresolved.

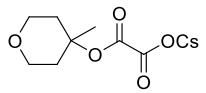
Ethyl (4-methyltetrahydro-2H-pyran-4-yl) oxalate (**5.10k**)



5.10k was synthesized following step 1 of **GP6** in THF (45 mL, 0.1 M) using 4-methyloxan-4-ol (**5.8k**, 500 mg, 4.30 mmol, 1.0 equiv), DMAP (53 mg, 0.43 mmol, 10 mol%), triethylamine (0.72 mL, 5.2 mmol, 1.2 equiv) and ethyl chloro-oxoacetate (0.58 mL, 5.2 mmol, 1.2 equiv).
Column chromatography (SiO_2, 15% EtOAc in Pentane) afforded ethyl (4-methyltetrahydro-2*H*-pyran-4-yl) oxalate (**5.10k**, 785 mg, 3.63 mmol, 84 %) as a pale yellow oil.

Rf (pentane:EtOAc 85:15) = 0.5.
^{1}H NMR (400 MHz, Chloroform-d) δ 4.33 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.83 – 3.59 (m, 4H, OCH_2), 2.27 – 2.17 (m, 2H, CH_2), 1.78 (ddd, J = 14.6, 10.1, 5.0 Hz, 2H, CH_2), 1.62 (s, 3H, CH_3), 1.37 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$). **^{13}C NMR** (101 MHz, Chloroform-d) δ 158.4, 157.1, 83.2, 63.7, 63.1, 36.6, 25.0, 14.1. **IR** (ν_{max}, cm^{-1}) 2968 (w), 2864 (w), 1744 (s), 1462 (w), 1324 (m), 1192 (s), 1134 (s), 1023 (m). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{10}H_{16}NaO_5^+$ 239.0890; Found 239.0894.

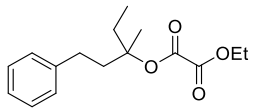
cesium (4-methyltetrahydro-2H-pyran-4-yl) oxalate (**5.6k**)



5.6k was synthesized following step 2 of **GP6** in THF (2.5 mL, 0.1 M) using ethyl (4-methyltetrahydro-2*H*-pyran-4-yl) oxalate (**5.10k**, 541 mg, 2.50 mmol, 1.0 equiv) and 1 M aq. CsOH (2.5 mL, 2.50 mmol, 1.0 equiv). Cesium 2-((3-methyl-1-phenylpentan-3-yl)oxy)-2-oxoacetate (**5.6k**, 725 mg, 2.27 mmol, 91%) was obtained as an off-white amorphous solid.

^{1}H NMR (400 MHz, DMSO) δ 3.66 – 3.49 (m, 4H, OCH_2), 2.04 – 1.93 (m, 2H, CH_2), 1.67 – 1.53 (m, 2H, CH_2), 1.45 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.6, 163.2, 76.5, 62.9, 36.6, 24.9. **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_8H_{11}CsNaO_5^+$ 342.9553; Found 342.9553.

Ethyl (3-methyl-1-phenylpentan-3-yl) oxalate (**5.10l**)

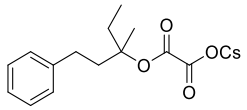


5.10l was synthesized following step 1 of **GP6** in THF (60 mL, 0.1 M) using 3-methyl-1-phenylpentan-3-ol (**5.8l,** 1.1 g, 6.0 mmol, 1.0 equiv), DMAP (73 mg, 0.60 mmol, 10 mol%), triethylamine (1.0 mL, 7.2 mmol, 1.2 equiv) and ethyl chloro-oxoacetate (0.80 mL, 7.2 mmol, 1.2 equiv). Column chromatography (SiO_2, 2% EtOAC in Pentane) afforded ethyl (3-methyl-1-phenylpentan-3-yl) oxalate (**5.10l**, 1.61 g, 5.78 mmol, 96 %) as a colourless oil.

Rf (pentane:EtOAc 98:2) = 0.4.
^{1}H NMR (400 MHz, Chloroform-d) δ 7.33 – 7.24 (m, 2H, ArH), 7.23 – 7.16 (m, 3H, ArH), 4.32 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 2.72 – 2.59 (m, 2H, ArCH_2), 2.30 – 2.18 (m, 1H, CH_2), 2.17 – 1.99 (m, 2H, CH_2), 1.97 – 1.85 (m, 1H, CH_2), 1.57 (s, 3H, CH_3), 1.37 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.95 (t, J = 7.5 Hz, 3H, CH_2CH_3). **^{13}C NMR** (101 MHz, Chloroform-d) δ 158.7, 157.2, 141.8, 128.6, 128.5, 126.1, 89.6, 62.9, 39.7, 30.9, 30.1, 23.1, 14.1, 8.1. **IR** (ν_{max}, cm^{-1}) 2979 (m), 2943 (w), 1739 (s), 1458 (m),

1323 (m), 1185 (s), 1115 (m), 1019 (m). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{16}H_{22}NaO_4^+$ 301.1410; Found 301.1412.

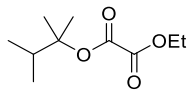
Cesium 2-((3-methyl-1-phenylpentan-3-yl)oxy)-2-oxoacetate (**5.6l**)



5.6l was synthesized following step 2 of **GP6** in THF (3.0 mL, 0.1 M) using ethyl (3-methyl-1-phenylpentan-3-yl) oxalate (**5.10l**, 835 mg, 3.00 mmol, 1.0 equiv) and 1 M aq. CsOH (3.0 mL, 3.00 mmol, 1.0 equiv). Cesium 2-((3-methyl-1-phenylpentan-3-yl)oxy)-2-oxoacetate (**5.6l**, 951 mg, 2.49 mmol, 83%) was obtained as an off-white amorphous solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.29 – 7.24 (m, 2H, Ar*H*), 7.19 – 7.14 (m, 3H, Ar*H*), 2.59 – 2.54 (m, 2H, Ar-C*H*$_2$), 2.11 – 2.03 (m, 1H, C*H*$_2$), 1.97 – 1.84 (m, 2H, C*H*$_2$), 1.76 – 1.67 (m, 1H, C*H*$_2$), 1.36 (s, 3H, C*H*$_3$), 0.84 (t, *J* = 7.53 Hz, 3H, CH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, DMSO-d$_6$) δ 167.7, 163.5, 142.3, 128.3, 128.2, 125.6, 82.3, 64.8, 30.6, 29.3, 23.2, 7.8. **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{14}H_{17}CsNaO_4^+$ 405.0074; Found 405.0075.

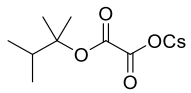
Ethyl (2,3-dimethylbutan-2-yl)oxy-2-oxoacetate (**5.10m**)



5.10m was synthesized following step 1 of **GP6** in CH_2Cl_2 (24 mL, 0.1 M) using 2,3-dimethyl-2-butanol (**5.8m**, 0.30 mL, 2.4 mmol, 1.0 equiv), DMAP (30 mg, 0.24 mmol, 10 mol%), triethylamine (0.35 mL, 2.5 mmol, 1.05 equiv) and ethyl chloro-oxoacetate (0.3 mL, 2.5 mmol, 1.05 equiv).
Column chromatography (SiO_2, pentane:EtOAc 9:1) afforded ethyl (2,3-dimethylbutan-2-yl) oxalate (**5.10m**, 0.340 g, 1.68 mmol, 70%).

Rf (pentane:EtOAc 9:1) = 0.5.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.30 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 2.27 (hept, *J* = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 1.49 (s, 6H, OC(C*H*$_3$)$_2$), 1.35 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 0.94 (d, *J* = 6.9 Hz, 6H, CH(C*H*$_3$)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.9, 157.3, 90.4, 62.8, 36.3, 22.5, 17.4, 14.1. **IR** (ν_{max}, cm^{-1}) 2995 (m), 2983 (m), 2962 (w), 2946 (w), 2891 (w), 2878 (w), 2840 (w), 1763 (s), 1737 (s), 1467 (m), 1371 (m), 1324 (s), 1191 (s), 1130 (s), 1094 (s), 1017 (m). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{10}H_{18}NaO_4^+$ 225.1097; Found 225.1099.

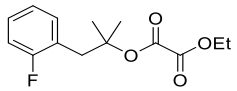
Cesium (2,3-dimethylbutan-2-yl)oxy-2-oxoacetate (**5.6m**)



5.6m was synthesized following step 2 of **GP6** in THF (1.0 mL, 0.1 M) using ethyl (2,3-dimethylbutan-2-yl) oxalate (**5.10m**, 0.200 g, 0.989 mmol, 1.0 equiv) and 1 M aq. CsOH (0.99 mL, 0.99 mmol, 1.0 equiv), affording cesium (2,3-dimethylbutan-2-yl)oxy-2-oxoacetate (**5.6m**, 137 mg, 0.447 mmol, 45%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 2.22 (hept, *J* = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 1.30 (s, 6H, OC(C*H*$_3$)$_2$), 0.84 (d, *J* = 6.9 Hz, 6H, CH(C*H*$_3$)$_2$). **^{13}C NMR** (101 MHz, DMSO-*d*$_6$) δ 167.6, 163.6, 83.0, 35.3, 22.7, 17.1. **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_8H_{13}CsNaO_4^+$ 328.9761; Found 328.9768.

Ethyl (1-(2-fluorophenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate (**5.10n**)

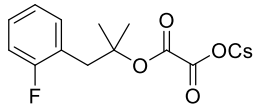


5.10n was synthesized following step 1 of **GP6** in CH_2Cl_2 (30 mL, 0.1 M) using 1-(2-fluorophenyl)-2-methylpropan-2-ol (**5.8n**, 500 mg, 2.97 mmol, 1.0 equiv), DMAP (36 mg, 0.30 mmol, 10 mol%), triethylamine (0.44 mL, 3.1 mmol, 1.05 equiv) and ethyl chloro-oxoacetate (0.35 mL, 3.1 mmol, 1.05 equiv).
Column chromatography (SiO_2, pentane:EtOAc 9:1 to 8:2) afforded ethyl (1-(4-fluorophenyl)-2-methylpropan-2-yl) oxalate (**5.10n**, 467 mg, 1.74 mmol, 59%) as a colorless oil.

Rf (pentane:EtOAc 9:1) = 0.35.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (td, *J* = 7.6, 1.8 Hz, 1H, Ar*H*), 7.26 – 7.20 (m, 1H, Ar*H*), 7.12 – 6.99 (m, 2H, Ar*H*), 4.32 (q, *J* = 7.2 Hz, 2H, OCH_2CH$_3$), 3.16 (d, *J* = 1.4 Hz, 2H, ArCH_2), 1.57 (d, *J* = 1.0 Hz, 6H, (CH_3)$_2$), 1.38 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.8, 160.4, 157.8 (d, *J* = 141.6 Hz), 133.2 (d, *J* = 4.4 Hz), 128.8 (d, *J* = 8.2 Hz), 123.9 (d, *J* = 3.5 Hz), 123.5 (d, *J* = 15.7 Hz), 115.4 (d, *J* = 23.0 Hz), 86.6, 62.9, 39.3, 25.4, 14.1. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -115.9. **IR** (v_{max}, cm^{-1}) 3004 (m), 2989 (m), 2965 (w), 2938 (m), 2899 (w), 1764 (s), 1737 (s), 1495 (m), 1456 (m), 1372 (m), 1319 (m), 1233 (s), 1190 (s), 1172 (s), 1120 (s), 759 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{14}H_{17}FNaO_4^+$ 291.1003; Found 291.1002.

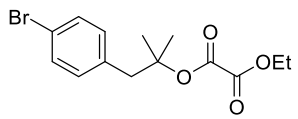
Cesium (1-(2-fluorophenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate (**5.6n**)



5.6n was synthesized following step 2 of **GP6** in THF (1.5 mL, 0.1 M) using ethyl (1-(2-fluorophenyl)-2-methylpropan-2-yl) oxalate (**5.10n**, 0.40 g, 1.5 mmol, 1.0 equiv) and 1 M aq. CsOH (1.5 mL, 1.5 mmol, 1.0 equiv), affording cesium (1-(2-fluorophenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate (**5.6n**, 469 mg, 1.26 mmol, 84%) as a coloroless amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (td, *J* = 7.7, 1.9 Hz, 1H, Ar*H*), 7.33 – 7.23 (m, 1H, Ar*H*), 7.19 – 7.06 (m, 2H, Ar*H*), 3.08 (s, 2H, ArCH_2), 1.34 (d, *J* = 1.0 Hz, 6H, (CH_3)$_2$). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.6, 163.1, 160.9 (d, *J* = 243.4 Hz), 133.1 (d, *J* = 4.4 Hz), 128.5 (d, *J* = 8.2 Hz), 124.0 (d, *J* = 4.0 Hz), 124.0, 114.9 (d, *J* = 22.9 Hz), 80.0, 37.5, 25.7. **^{19}F NMR** (376 MHz, DMSO-d_6) δ -116.6. **HRMS** (ESI/QTOF) m/z [M - Cs]$^-$ Calcd for $C_{12}H_{12}FO_4^-$ 239.0725; Found 239.0719.

Ethyl (1-(4-bromophenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate (**5.10o)**

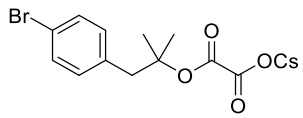


5.10o was synthesized following step 1 of general *procedure X* in CH_2Cl_2 (20 mL, 0.1 M) using 1-(4-bromophenyl)-2-methylpropan-2-ol (**5.8o,** 500 mg, 2.18 mmol, 1.0 equiv), DMAP (27 mg, 0.22 mmol, 10 mol%), triethylamine (0.3 mL, 2.4 mmol, 1.1 equiv) and ethyl chloro-oxoacetate (0.3 mL, 2.4 mmol, 1.1 equiv).
Column chromatography (SiO_2, pentane:EtOAc 9:1 to 8:2) afforded ethyl (1-(4-bromophenyl)-2-methylpropan-2-yl) oxalate **5.10o** (461 mg, 1.40 mmol, 64%).

Rf (pentane:EtOAc 4:1) = 0.4

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.38 (m, 2H, Ar*H*), 7.16 – 7.09 (m, 2H, Ar*H*), 4.32 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 3.03 (s, 2H, ArCH_2), 1.53 (s, 6H, (CH_3)$_2$), 1.38 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.4, 157.0, 135.4, 132.5, 131.3, 121.0, 86.1, 63.0, 46.5, 25.4, 14.1. **IR** (v_{max}, cm^{-1}) 3015 (w), 3002 (w), 2977 (w), 2934 (w), 2844 (w), 1760 (s), 1738 (s), 1490 (m), 1321 (m), 1188 (s), 1160 (s), 1115 (s), 1073 (m), 1012 (s), 796 (m). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{14}H_{17}{}^{79}BrNaO_4^+$ 351.0202; Found 351.0199

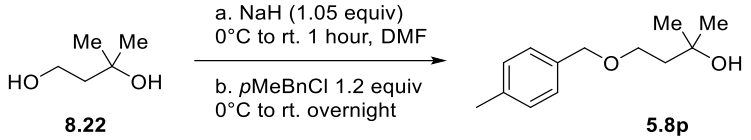
Cesium (1-(4-bromophenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate (**5.6o**)



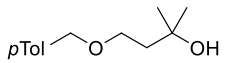
5.6o was synthesized following step 2 of general *procedure X* in THF (0.94 mL, 0.1 M) using ethyl (1-(4-bromophenyl)-2-methylpropan-2-yl) oxalate (**5.10o**, 310 mg, 0.941 mmol, 1.0 equiv) and 1 M aq. CsOH (0.94 mL, 0.94 mmol, 1.0 equiv), affording cesium (1-(4-bromophenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate (**5.6o**, 89 mg, 0.205 mmol, 22%) as an amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 – 7.32 (m, 2H, Ar*H*), 7.32 – 7.10 (m, 2H, Ar*H*), 3.01 (s, 2H, ArCH_2), 1.32 (s, 6H, (CH_3)$_2$). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.7, 163.1, 136.9, 132.8, 130.6, 119.5, 79.7, 44.5, 25.9. **HRMS** (ESI/QTOF) m/z [M - Cs]$^-$ Calcd for $C_{12}H_{12}{}^{79}BrO_4^-$ 298.9924; Found 298.9914.

4-Methylbenzylation of 3-methylbutane-1,3-diol (**5.8p**)

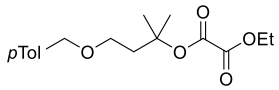


An oven dried 25 mL flask, equipped with a magnetic stirring bar, was flushed with nitrogen then charged with 3-methylbutane-1,3-diol (**8.22**, 0.26 mL, 2.4 mmol, 1.0 equiv) and anhydrous DMF (12.5 mL, 0.2 M). The solution was cooled to 0 °C and NaH (60% oil dispersion, 102 mg, 2.56 mmol, 1.05 equiv) was added portion-wise under nitrogen. The latter solution was stirred for 1 h at room temperature. The solution was cooled back down to 0 °C and 1-(chloromethyl)-4-methylbenzene (411 mg, 2.92 mmol, 1.2 equiv) was added under nitrogen. The reaction was left to warm up to RT slowly and was stirred overnight. The reaction was quenched with sat. aq. NH_4Cl (5 mL) then diluted with water (10 mL) and CH_2Cl_2 (15 mL). The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (15 mL). The organic layers were combined and washed with a (sat. aq. NaCl)water (1:1) solution (15 mL) three times. The organic layers were then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography (SiO_2, pentane:EtOAc 9:1 to 8:2) affording 2-methyl-4-((4-methylbenzyl)oxy)butan-2-ol (**5.8p**, 297 mg, 1.43 mmol, 59%) as a colorless oil with some trace impurities. After ^{1}H NMR and HRMS confirmation, the compound was used directly in next step with no further purification or analyses.



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.15 (d, *J* = 7.8 Hz, 2H, Ar*H*), 4.48 (s, 2H, ArC*H*$_2$), 3.70 (t, *J* = 5.9 Hz, 2H, C*H*$_2$), 3.14 (bs, 1H, OH), 2.34 (s, 3H, ArC*H*$_3$), 1.79 (t, *J* = 5.9 Hz, 2H, C*H*$_2$), 1.23 (s, 6H, (C*H*$_3$)$_2$). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{13}H_{20}NaO_2^+$ 231.1356; Found 231.1358.

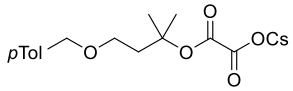
Ethyl (2-methyl-4-((4-methylbenzyl)oxy)butan-2-yl)oxy-2-oxoacetate (**5.10p**)



5.10p was synthesized following <u>step 1</u> of **GP6** in THF (11 mL, 0.1 M) using 2-methyl-4-((4-methylbenzyl)oxy)butan-2-ol (**5.8p**, 220 mg, 1.06 mmol, 1.0 equiv), DMAP (13 mg, 0.11 mmol, 10 mol%), triethylamine (0.16 mL, 1.2 mmol, 1.1 equiv) and ethyl chloro-oxoacetate (0.16 mL, 1.2 mmol, 1.1 equiv).
Column chromatography (SiO_2, pentane:EtOAc 9:1 to 8:2) afforded ethyl (2-methyl-4-((4-methylbenzyl)oxy)butan-2-yl) oxalate (**5.10p**, 224 mg, 0.726 mmol, 69%).

Rf (pentane:EtOAc 9:1) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.18 – 7.11 (m, 2H, Ar*H*), 4.44 (s, 2H, ArC*H*$_2$), 4.28 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.59 (t, *J* = 6.6 Hz, 2H, C*H*$_2$), 2.34 (s, 3H, ArC*H*$_3$), 2.19 (t, *J* = 6.6 Hz, 2H, C*H*$_2$), 1.57 (s, 6H, (C*H*$_3$)$_2$), 1.34 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.6, 157.2, 137.4, 135.3, 129.2, 127.8, 86.1, 73.0, 66.0, 62.9, 39.9, 26.3, 21.3, 14.1. **IR** (ν_{max}, cm^{-1}) 3048 (m), 3016 (m), 2991 (m), 2929 (m), 2876 (m), 2860 (m), 1760 (m), 1737 (s), 1370 (m), 1325 (m), 1187 (s), 1134 (s), 1112 (s), 1096 (s), 1018 (m), 802 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{17}H_{24}NaO_5^+$ 331.1516; Found 331.1518.

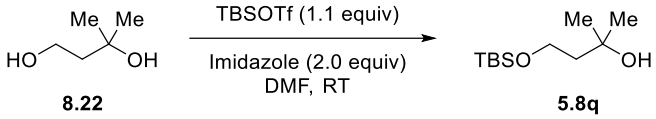
Cesium (2-methyl-4-((4-methylbenzyl)oxy)butan-2-yl)oxy-2-oxoacetate (**5.6p**)



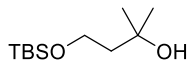
5.6p was synthesized following step 2 of **GP6** in THF (0.6 mL, 0.1 M) using ethyl (2-methyl-4-((4-methylbenzyl)oxy)butan-2-yl) oxalate (**5.10p**, 0.19 g, 0.60 mmol, 1.0 equiv) and 1 M aq. CsOH (0.6 mL, 0.6 mmol, 1.0 equiv), affording cesium (2-methyl-4-((4-methylbenzyl)oxy)butan-2-yl)oxy-2-oxoacetate (**5.6p**, 233 mg, 0.565 mmol, 94%) as a coloroless amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 – 7.17 (m, 2H, Ar*H*), 7.14 (d, *J* = 7.9 Hz, 2H, Ar*H*), 4.38 (s, 2H, ArCH_2), 3.54 – 3.45 (m, 2H, CH_2), 2.28 (s, 3H, ArCH_3), 2.01 (t, *J* = 7.1 Hz, 2H, CH_2), 1.37 (s, 6H, (CH_3)$_2$). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.0, 163.7, 136.9, 136.0, 129.3, 128.0, 79.6, 72.3, 66.3, 30.2 26.9, 21.2. **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{15}H_{19}CsNaO_5^+$ 435.0179; Found 435.0183.

4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-ol (**5.8q**)

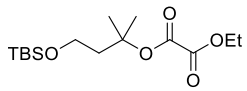


To a solution of 3-methylbutane-1,3-diol (**8.22**, 500 mg, 4.80 mmol, 1.00 equiv) and 1H-imidazole (654 mg, 9.60 mmol, 2.00 equiv) in *N,N*-dimethylformamide (25 mL), TBSOTf (1.4 g, 1.2 mL, 5.3 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at room temperature until TLC showed full conversion of the starting material. CH_2Cl_2 and a 1:1 solution of brine and water were added, the layers were separated and the organic layer was washed with half brine (2x), dried over MgSO4 and solvent removed *in vacuo*. The crude was purified by flash chromatography (SiO_2, 5% EtOAc in pentane) affording 4-((*tert*-butyldimethylsilyl)oxy)-2-methylbutan-2-ol (**5.8q**, 950 mg, 4.35 mmol, 91% yield) as a pale yellow oil. The NMR data was collected and the compound was used in the next step without further analyses.



Rf (pentane:EtOAc 95:5) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.91 (t, *J* = 5.8 Hz, 2H, OCH_2), 3.83 (bs, 1H, O*H*), 1.70 (t, *J* = 5.8 Hz , 2H, CH_2), 1.24 (s, 6H, C(CH_3)$_2$), 0.90 (s, 9H, C(CH_3)$_3$), 0.09 (s, 6H, Si(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 71.0, 61.1, 43.0, 29.4, 26.0, 18.2, -5.5.

4-((tert-Butyldimethylsilyl)oxy)-2-methylbutan-2-yl ethyl oxalate (**5.10q**)

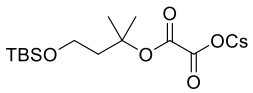


5.10q was synthesized following step 1 of **GP6** in THF (25 mL, 0.1 M) using 4-((*tert*-butyldimethylsilyl)oxy)-2-methylbutan-2-ol (**5.8q**, 500 mg, 2.30 mmol, 1.0 equiv), DMAP (28 mg, 0.23 mmol, 10 mol%), triethylamine (0.40 mL, 2.8 mmol, 1.2 equiv) and ethyl chloro-oxoacetate (0.30 mL, 2.8 mmol, 1.2 equiv).
Column chromatography (SiO_2, 2% EtOAc in Pentane) afforded 4-((*tert*-butyldimethylsilyl)oxy)-2-methylbutan-2-yl ethyl oxalate (**5.10q**, 517 mg, 1.62 mmol, 71 %) as a yellow oil.

Rf (pentane:EtOAc 98:2) = 0.2.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.31 (q, *J* = 7.2 Hz, 2H, COOCH_2), 3.75 (t, *J* = 6.7 Hz, 2H, OCH_2), 2.09 (t, *J* = 6.7 Hz, 2H, CH_2), 1.57 (s, 6H, C(CH_3)$_2$), 1.36 (t, *J* = 7.2 Hz, 3H, COOCH_3), 0.88 (s, 9H, C(CH_3)$_3$), 0.05 (s, 6H, Si(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.7, 157.1, 86.4, 62.9, 59.0, 43.0, 26.3, 26.0, 18.4, 14.1, -5.3. **IR** (v_{max}, cm^{-1}) 2944 (m), 2891 (m), 2863 (m), 1744 (s), 1468 (m),

1323 (m), 1256 (m), 1190 (s), 1133 (s), 1098 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{15}H_{30}NaO_5Si^+$ 341.1755; Found 341.1752.

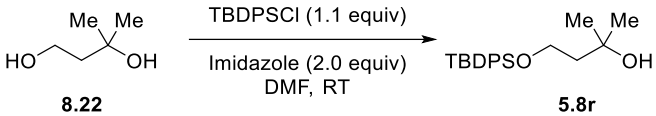
Cesium 2-((4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)oxy)-2-oxoacetate (**5.6q**)



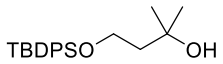
5.6q was synthesized following step 2 of **GP6** in THF (1.1 mL, 0.1 M) using 4-((*tert*-butyldimethylsilyl)oxy)-2-methylbutan-2-yl ethyl oxalate (**5.10q**, 350 mg, 1.10 mmol, 1.0 equiv) and 1 M aq. CsOH (1.1 mL, 1.1 mmol, 1.0 equiv). Cesium 2-((4-((*tert*-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)oxy)-2-oxoacetate (**5.6q**, 450 mg, 1.07 mmol, 97 %) was obtained as an off-white amorphous solid.

^{1}H NMR (400 MHz, DMSO) δ 3.65 (t, *J* = 7.2 Hz, 2H, OC*H*$_2$), 1.94 (t, *J* = 7.2 Hz, 2H, C*H*$_2$), 1.37 (s, 6H, C(C*H*$_3$)$_2$), 0.85 (s, 9H, C(C*H*$_3$)$_3$), 0.03 (s, 6H, Si(C*H*$_3$)$_2$). **^{13}C NMR** (101 MHz, DMSO) δ 167.5, 163.3, 79.1, 58.7, 42.7, 26.5, 25.8, 17.8, -5.3. **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{13}H_{25}CsNaO_5Si^+$ 445.0418; Found 445.0418.

4-((tert-butyldiphenylsilyl)oxy)-2-methylbutan-2-ol (**5.8r**)

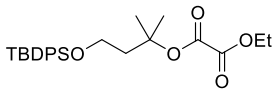


To a solution of 3-methylbutane-1,3-diol (**8.22**, 500 mg, 4.80 mmol, 1.00 equiv) and 1H-imidazole (654 mg, 9.60 mmol, 2.00 equiv) in *N,N*-dimethylformamide (25.0 mL), TBDPSCl (1.45 g, 1.37 mL, 5.28 mmol, 1.10 equiv) was added dropwise. The reaction mixture was stirred at room temperature until TLC showed full conversion of the starting material. CH_2Cl_2 and half brine were added, the layers were separated and the organic layer was washed with half brine (2x), dried over $MgSO_4$ and solvent removed under vacuo. The crude product was purified by flash chromatography (SiO_2, 5% EtOAc in pentane) affording 4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-2-ol (**5.8r**, 1.64 g, 4.80 mmol, 100% yield) as a fain yellow oil. The NMR data was collected and the compound was used in the next step without further analyses.



Rf (pentane:EtOAc 95:5) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.72 – 7.65 (m, 4H, Ar*H*), 7.47 – 7.36 (m, 6H, Ar*H*), 3.90 (t, J = 5.8 Hz, 2H, OC*H*$_2$), 3.74 (bs, 1H, O*H*), 1.75 (t, J = 5.7 Hz, 2H, C*H*$_2$), 1.27 (s, 6H, C(C*H*$_3$)$_2$OH), 1.05 (s, 9H, C(C*H*$_3$)$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 135.7, 132.9, 130.03, 128.0, 71.1, 62.2, 43.2, 29.5, 26.9, 19.1.

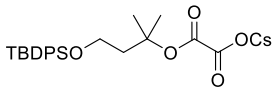
4-((tert-Butyldiphenylsilyl)oxy)-2-methylbutan-2-yl ethyl oxalate (**5.10r**)



5.10r was synthesized following step 1 of **GP6** in THF (30 mL, 0.1 M) using 4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-2-ol (**5.8r**, 1.00 g, 2.92 mmol, 1.0 equiv), DMAP (36 mg, 0.29 mmol, 10 mol%), triethylamine (0.50 mL, 3.5 mmol, 1.2 equiv) and ethyl chloro-oxoacetate (0.40 mL, 3.5 mmol, 1.2 equiv).
Column chromatography (SiO_2, 2% EtOAc in Pentane) afforded 4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-2-yl ethyl oxalate (**5.10r**, 1.06g, 2.40 mmol, 82 %) as a pale yellow oil.

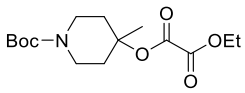
Rf (pentane:EtOAc 98:2) = 0.15.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.64 (m, 4H, Ar*H*), 7.43 – 7.35 (m, 6H, Ar*H*), 4.27 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.78 (t, *J* = 6.7 Hz, 2H, OCH_2), 2.16 (t, *J* = 6.7 Hz, 2H, CH_2), 1.55 (s, 6H, $C(CH_3)_2$), 1.32 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.04 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.5, 157.0, 135.6, 133.6, 129.7, 127.7, 86.2, 62.8, 59.8, 42.6, 26.8, 26.2, 19.1, 13.9. **IR** (ν_{max}, cm^{-1}) 3064 (w), 2939 (m), 2862 (m), 1743 (s), 1323 (m), 1190 (s), 1104 (s), 823 (m). **HRMS** (ESI/QTOF) m/z $[M + Na]^+$ Calcd for $C_{25}H_{34}NaO_5Si^+$ 465.2068; Found 465.2076.

Cesium 2-((4-((tert-butyldiphenylsilyl)oxy)-2-methylbutan-2-yl)oxy)-2-oxoacetate (**5.6r**)



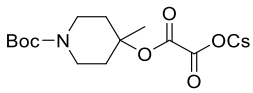
5.6r was synthesized following step 2 of **GP6** in THF (1.1 mL, 0.1 M) using 4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-2-yl ethyl oxalate (**5.10r**, 500 mg, 1.13 mmol, 1.0 equiv) and 1 M aq. CsOH (1.1 mL, 1.1 mmol, 1.0 equiv). Cesium 2-((4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-2-yl)oxy)-2-oxoacetate (**5.6r**, 600 mg, 1.10 mmol, 97 %) was obtained as an off-white amorphous solid.
^{1}H NMR (400 MHz, DMSO) δ 7.65 – 7.58 (m, 4H, Ar*H*), 7.48 – 7.41 (m, 6H, Ar*H*), 3.74 (t, *J* = 7.1 Hz, 2H, OCH_2), 2.03 (t, *J* = 7.1 Hz, 2H, CH_2), 1.34 (s, 6H, CH_3), 0.99 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (101 MHz, DMSO) δ 167.5, 163.2, 135.0, 133.2, 129.8, 127.9, 79.1, 59.9, 42.7, 26.7, 26.4, 18.7. **HRMS** (ESI/QTOF) m/z $[M + H]^+$ Calcd for $C_{23}H_{30}CsO_5Si^+$ 547.0912; Found 547.0908.

1-(*tert*-butoxycarbonyl)-4-methylpiperidin-4-yl ethyl oxalate (**5.10s**)



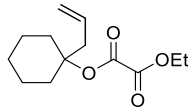
5.10s was synthesized following step 1 of **GP6** in THF (30 mL, 0.1 M) using tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (**5.8s**, 0.500 g, 2.32 mmol, 1.0 equiv), DMAP (28 mg, 0.23 mmol, 10 mol%), triethylamine (0.4 mL, 3 mmol, 1.2 equiv) and ethyl chloro-oxoacetate (0.30 mL, 2.8 mmol, 1.2 equiv).
Column chromatography (SiO_2, 2% EtOAc in Pentane) afforded 4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-2-yl ethyl oxalate (**5.10r**, 1.06g, 2.40 mmol, 82 %) as a pale yellow oil.
Rf (pentane:EtOAc 98:2) = 0.2.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.33 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.81 (dd, *J* = 13.7, 4.3 Hz, 2H, cyclic-CH_2), 3.10 (ddd, *J* = 14.0, 11.3, 3.0 Hz, 2H, cyclic-CH_2), 2.30 – 2.21 (m, 2H, cyclic-CH_2), 1.70 – 1.55 (m, 2H, , cyclic-CH_2), 1.61 (s, 3H, CH_3), 1.45 (s, 9H, *t*Bu), 1.37 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.3, 156.9, 154.7, 83.8, 79.7, 63.0, 39.6, 35.6, 28.4, 24.7, 14.0 **HRMS** (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{25}NNaO_6^+$ 338.1574; Found 338.1581.

Cesium 2-((1-(tert-butoxycarbonyl)-4-methylpiperidin-4-yl)oxy)-2-oxoacetate (**5.6s**)



5.6s was synthesized following step 2 of **GP6** in THF (1.1 mL, 0.1 M) using **5.10r** (315 mg, 1.00 mmol, 1.0 equiv) and 1 M aq. CsOH (1.0 mL, 1.0 mmol, 1.0 equiv). **5.6s** (410 mg, 978 µmol, 98% yield) was obtained as an off-white amorphous solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 3.60 (d, *J* = 13.4 Hz, 2H, cyclic-CH_2), 3.00 (m, 2H, cyclic-CH_2), 2.03 (d, *J* = 13.6 Hz, 2H, cyclic-CH_2), 1.51 – 1.39 (m, 2H, cyclic-CH_2), 1.43 (s, 3H, CH_3), 1.39 (d, *J* = 4.5 Hz, 9H, *t*Bu). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.0, 163.6, 154.5, 108.8, 79.1, 77.4, 35.8, 28.6, 25.2. **HRMS** (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{20}CsNNaO_6^+$ 442.0237; Found 442.0239.

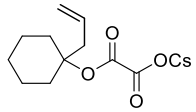
2-((1-allyl-cyclohexan-1-yl) ethyl oxalate (**5.10s**)



5.10t was synthesized following step 1 of **GP6** in THF (30 mL, 0.1 M) using **5.8t**, (500 mg, 3.57 mmol, 1.00 equiv), DMAP (44 mg, 34 µmol, 10 mol%) triethylamine (0.6 mL, 4 mmol, 1.2 equiv) and ethyl chloro-oxoacetate (0.5 µL, 4 mmol, 1.20 equiv).
Column chromatography (SiO_2, 2% EtOAc in Pentane) afforded **5.10t** (557 mg, 2.32 mmol, 65%) as a pale yellow oil.

Rf (pentane:EtOAc 98:2) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.76 (ddt, *J* = 15.9, 11.1, 7.4 Hz, 1H, C*H*=CH_2), 5.45 – 4.94 (m, 2H, CH=CH_2), 4.31 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 2.71 (dt, *J* = 7.4, 1.2 Hz, 2H, CH_2-CH=CH_2), 2.27 (dtt, *J* = 12.8, 3.1, 1.7 Hz, 2H, cyclic-CH_2), 1.80 – 1.48 (m, 6H, cyclic-CH_2), 1.36 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.32 – 1.19 (m, 2H, cyclic-CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.6, 156.9, 132.0, 118.9, 88.0, 62.7, 41.7, 34.1, 25.2, 21.7, 14.0. **HRMS** (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{20}NaO_4^+$ 263.1254; Found 263.1262.

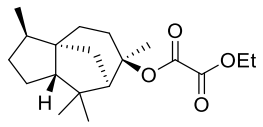
Cesium 2-((1-(allyl)-cyclohexan-1-yl)oxy)-2-oxoacetate (**5.6t**)



5.6t was synthesized following step 2 of **GP6** in THF (1.1 mL, 0.1 M) using **5.10t** (481 mg, 2.00 mmol, 1.00 equiv) and 1 M aq. CsOH (2.0 mL, 2.0 mmol, 1.0 equiv). **5.6t** (613 mg, 1.78 mmol, 89% yield) was obtained as an off-white amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.74 (ddt, *J* = 15.8, 11.4, 7.3 Hz, 1H, C*H*=CH_2), 5.11 – 4.94 (m, 2H, CH=CH_2), 2.59 (dt, *J* = 7.3, 1.3 Hz, 2H, CH_2-CH=CH_2), 2.20 – 1.97 (m, 2H, cyclic-CH_2), 1.62 – 1.10 (m, 8H, cyclic-CH_2). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.1, 163.8, 134.1, 118.2, 81.2, 42.1, 34.5, 25.5, 21.6. **HRMS** (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{11}H_{15}CsNaO_4^+$ 366.9917; Found 366.9914.

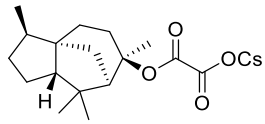
Ethyl (2-methyl-4-((4-methylbenzyl)oxy)butan-2-yl) oxalate (**5.10u**)



5.10u was synthesized following step 1 of **GP6** in CH_2Cl_2 (50 mL, 0.1 M) using (-)-cedrol (**5.8u**, 1.00 g, 4.46 mmol, 1.0 equiv), DMAP (0.054 g, 0.45 mmol, 10 mol%), triethylamine (0.68 mL, 4.9 mmol, 1.1 equiv) and ethyl chloro-oxoacetate (0.55 mL, 4.9 mmol, 1.1 equiv).
Column chromatography (SiO_2, pentane:EtOAc 9:1 to 8:2) afforded ethyl (2-methyl-4-((4-methylbenzyl)oxy)butan-2-yl) oxalate (**5.10u**, 0.343 g, 0.1.06 mmol, 24%).

Rf (pentane:EtOAc 9:1) = 0.45.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.30 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.46 – 2.40 (m, 1H, aliphatic-C*H* or CH_2), 2.17 (ddt, *J* = 13.6, 5.8, 1.7 Hz, 1H, aliphatic-C*H* or CH_2), 2.13 – 2.00 (m, 1H, aliphatic-C*H* or CH_2), 1.94 – 1.78 (m, 2H, aliphatic-C*H* or CH_2), 1.74 – 1.64 (m, 2H, aliphatic-C*H* or CH_2), 1.62 (d, *J* = 1.0 Hz, 3H, CH_3), 1.59 – 1.47 (m, 2H, aliphatic-C*H* or CH_2), 1.46 – 1.33 (m, 6H, aliphatic-C*H* or CH_2 + OCH_2CH_3), 1.32 – 1.23 (m, 1H, aliphatic-C*H* or CH_2), 1.18 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.84 (d, *J* = 7.1 Hz, 3H, CH_2CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.8, 157.1, 91.2, 62.8, 57.0, 56.8, 54.0, 43.7, 41.4, 41.2, 37.1, 33.0, 31.4, 28.5, 27.1, 25.5, 25.4, 15.6, 14.1. **IR** (ν_{max}, cm^{-1}) 2990 (w), 2939 (w), 2876 (w), 1738 (s), 1373 (s), 1236 (s), 1186 (m), 1044 (s). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{19}H_{30}NaO_4^+$ 345.2036; Found 345.2029.

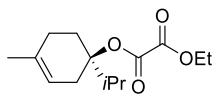
(-)-Cedrol derived cesium oxalate: cesium (2-methyl-4-((4-methylbenzyl)oxy)butan-2-yl)oxy-2-oxoacetate (**5.6u**)



5.6u was synthesized following step 2 of **GP6** in THF (0.78 mL, 0.1 M) using ethyl (2-methyl-4-((4-methylbenzyl)oxy)butan-2-yl) oxalate (**5.10u**, 0.250 g, 0.775 mmol, 1.0 equiv) and 1 M aq. CsOH (0.78 mL, 0.78 mmol, 1.0 equiv), affording cesium (2-methyl-4-((4-methylbenzyl)oxy)butan-2-yl)oxy-2-oxoacetate (**5.6u**, 0.330 g, 0.774 mmol, 100%). Amorphous white amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (d, J = 5.1 Hz, 1H, aliphatic-CH), 1.90 – 1.71 (m, 4H, aliphatic-CH), 1.68 – 1.54 (m, 2H, aliphatic-CH or CH2), 1.45 (s, 4H, aliphatic-CH or CH2 + CH_3), 1.42 – 1.19 (m, 5H, aliphatic-CH or CH2), 1.16 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.81 (d, J = 7.1 Hz, 3H, CHCH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.3, 163.5, 83.8, 56.4, 56.2, 53.6, 43.0, 40.7, 40.3, 36.4, 33.0, 30.6, 28.4, 27.3, 25.7, 24.9, 15.5. **HRMS** (ESI/QTOF) m/z [M - Cs]$^-$ Calcd for $C_{17}H_{25}O_4^-$ 293.1758; Found 293.1751.

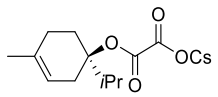
(R)-Ethyl (1-isopropyl-4-methylcyclohex-3-en-1-yl) oxalate (**5.10v**)



5.10v was synthesized following <u>step 1</u> of **GP6** in THF (60 mL, 0.1 M) using (-)-terpinen-4-ol (**5.8v**, 1.00 mL, 6.00 mmol, 1.0 equiv), DMAP (73 mg, 0.60 mmol, 10 mol%), triethylamine (1.00 mL, 7.20 mmol, 1.2 equiv) and ethyl chloro-oxoacetate (0.80 mL, 7.2 mmol, 1.2 equiv).
Column chromatography (SiO_2, 2% EtOAc in Pentane) afforded (*R*)-ethyl (1-isopropyl-4-methylcyclohex-3-en-1-yl) oxalate (**5.10v**, 1.08 g, 4.25 mmol, 71 %) as a pale yellow oil.

Rf (pentane:EtOAc 98:2) = 0.4.
^{1}H NMR (400 MHz, Chloroform-d) δ 5.29 – 5.21 (m, 1H, C=CH), 4.29 (q, J = 7.1 Hz, 2H, CO_2CH_2), 2.71 (hept, J = 6.9 Hz, 1H, CH(CH_3)$_2$), 2.54 – 2.43 (m, 2H, CH_2), 2.29 – 2.19 (m, 1H, CH_2), 2.11 – 1.98 (m, 1H, CH_2), 1.97 – 1.87 (m, 1H, CH_2), 1.78 – 1.68 (m, 1H, CH_2), 1.73 – 1.62 (m, 3H, CH_3), 1.34 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.95 (d, J = 6.9 Hz, 3H, CH(CH_3)$_2$), 0.94 (d, J = 6.9 Hz, 3H, CH(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-d) δ 158.9, 157.6, 133.8, 117.2, 91.1, 62.7, 32.7, 29.9, 27.9, 27.3, 23.3, 17.7, 17.2, 14.1. **IR** (ν_{max}, cm^{-1}) 2973 (m), 2933 (m), 1738 (s), 1444 (m), 1380 (m), 1324 (m), 1180 (s), 1014 (m). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{14}H_{22}NaO_4^+$ 277.1410; Found 277.1415.

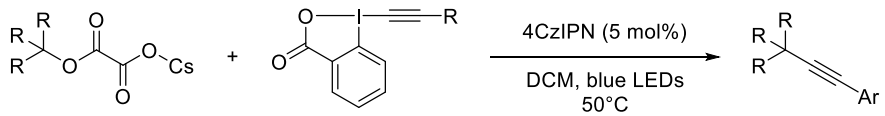
(-)Terpinen-4-ol derived cesium oxalate: cesium (R)-2-((1-isopropyl-4-methylcyclohex-3-en-1-yl)oxy)-2-oxoacetate (**5.6v**)



5.6v was synthesized following <u>step 2</u> of **GP6** in THF (2.0 mL, 0.1 M) using (*R*)-ethyl (1-isopropyl-4-methylcyclohex-3-en-1-yl) oxalate (**5.10v**, 509 mg, 2.00 mmol, 1.0 equiv) and 1 M aq. CsOH (2.0 mL, 2.0 mmol, 1.0 equiv). Cesium (*R*)-2-((1-isopropyl-4-methylcyclohex-3-en-1-yl)oxy)-2-oxoacetate (**5.6v**, 661 mg, 1.85 mmol, 92 %) was obtained as an off-white amorphous solid.

^{1}H NMR (400 MHz, DMSO) δ 5.20 – 5.16 (m, 1H, C=CH), 2.66 (p, J = 7.0 Hz, 1H, CH(CH_3)$_2$), 2.40 – 2.31 (m, 1H, CH_2), 2.23 – 2.04 (m, 2H, CH_2), 2.04 – 1.90 (m, 1H, CH_2), 1.86 – 1.71 (m, 1H, CH_2), 1.60 (s, 3H, CH_3), 1.59 – 1.50 (m, 1H, CH_2), 0.86 (d, J = 7.0 Hz, 3H, CH(CH_3)$_2$), 0.84 (d, J = 7.0 Hz, 3H), CH(CH_3)$_2$). **^{13}C NMR** (101 MHz, DMSO) δ 168.1, 163.5, 132.8, 117.9, 83.3, 32.0, 29.5, 27.7, 26.7, 23.2, 17.4, 16.7. **HRMS** (ESI/QTOF) m/z [M + H]$^+$ Calcd for $C_{12}H_{18}CsO_4^+$ 359.0254; Found 359.0260.

<u>GP7: 4CzIPN catalysed deoxyalkynylation:</u>



5.6 **HIR.2** **HIR.3** **5.11** **5.14**

An oven dried (7.5 mL) dram vial equipped with a magnetic stirrer was charged with the cesium salt **5.6** (0.30 mmol, 1.00 equiv), the EBX reagent (**HIR.2** or **HIR.3**, 1.5 mmol, 1.5 equiv) and 4CzIPN (**PC.9a**, 0.015 mmol, 5 mol%). The reaction vial was sealed with a septum. After 3 vacuum/N2 cycles (backfilling with Ar on the last cycle), dichloromethane (3.00 mL) was added

and the septums were replaced with a screw cap under a flux of Ar then the seal was wrapped with parafilm. The reactions were placed between 2 x 440 nm Kessil lamps at ca. 10 cm distance from both lamps (no ventilation, T = ca. 50 °C)[44] and stirred under irradiation for 15-18 hours. The reaction was filtered through a small celite plug which was washed with CH_2Cl_2. A solid deposit was prepared (ca. 2g SiO_2). The compound was purified by column chromatography (pentane:EtOAc).

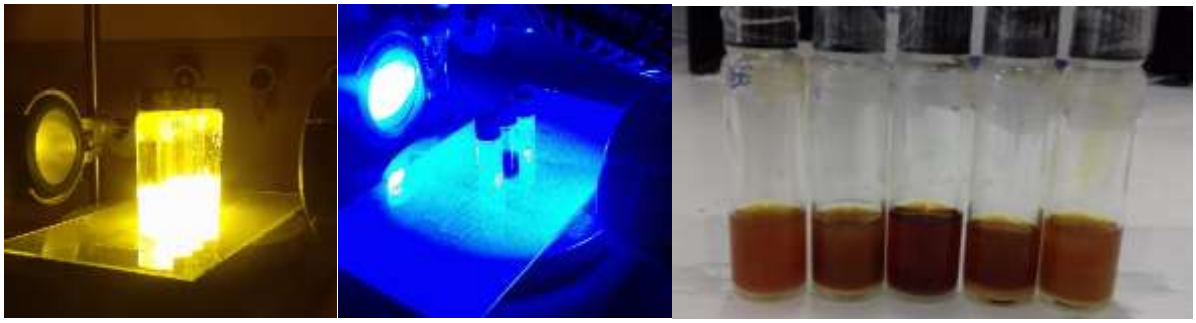
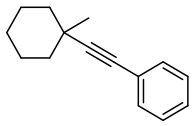


Figure 8.7. Experimental set-up. Left: Scope scale reactions (photo taken with a filter applied to it). Middle: optimization scale. Right: Scope scale reactions after irradiation (with PC, same appearance for PC-free reactions without)

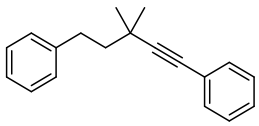
2-(1-Methylcyclohexyl)ethynylbenzene (**5.11a**)



5.11a was synthesized following **GP7** using cesium 2-(1-methylcyclohexan-1-yl)oxy-2-oxoacetate (**5.6a**, 0.095 g, 0.30 mmol, 1 equiv), PhEBX (**HIR.2a**, 0.157 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded (1-methylcyclohexyl)enthynylbenzene (**5.11a**, 0.053 g (80% purity), 0.22 mmol, 72%) as a colorless oil. The compound could be partially purified from 1,4-diphenylbuta-1,4-diyne (major impurity) by preparative TLC (SiO_2, glass plate, Heptane) allowing full characterisation of **5.11a**.

Rf (pentane) = 0.7.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.37 (m, 2H, Ar*H*), 7.32 – 7.22 (m, 3H, Ar*H*), 1.84 – 1.55 (m, 8H, CH_2), 1.28 (s, 3H, CH_3), 1.27 – 1.09 (m, 2H, CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.3, 127.5, 124.4, 96.9, 81.9, 39.7, 33.3, 30.4, 26.1, 23.6. Consistent with the reported NMR data.[45]

(3,3-dimethylpent-1-yne-1,5-diyl)dibenzene (**5.11b**)



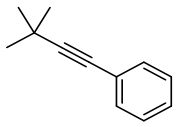
5.11b was synthesized following **GP7** using cesium 2-(methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.6b**, 0.110 g, 0.300 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 0.157 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded (3,3-dimethylpent-1-yne-1,5-diyl)dibenzene (**5.11b**, 0.056 g, 0.23 mmol, 75%) as a slightly yellow oil.

Rf (pentane) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.39 (m, 2H, Ar*H*), 7.33 – 7.27 (m, 5H, Ar*H*), 7.26 – 7.16 (m, 3H, Ar*H*), 2.95 – 2.79 (m, 2H, ArCH_2), 1.86 – 1.75 (m, 2H, ArCH_2CH_2), 1.36 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 142.9, 131.7, 128.6, 128.5, 128.3, 127.6, 125.8, 124.1, 97.0, 81.0,

[44] The reaction temperature was measured with an internal thermometer on a model system using 5 mol% 4CzIPN in CH_2Cl_2.
[45] Gao, C.; Li, J.; Yu, J.; Yang, H.; Fu, H. *Chem. Commun.* **2016**, *52*, 7292–7294.

45.7, 32.3, 32.0, 29.4. **IR** (ν_{max}, cm^{-1}) 3084 (m), 3060 (m), 3027 (m), 2968 (m), 2945 (m), 2910 (m), 2866 (m), 2224 (m), 1946 (m), 1878 (m), 1804 (m), 1748 (m), 1491 (m), 1265 (m), 1070 (m), 755 (s), 740 (s), 690 (s). **HRMS** (ESI/QTOF) m/z $[M + Ag]^+$ Calcd for $C_{19}H_{20}Ag^+$ 355.0610; Found 355.0615.

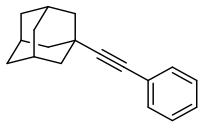
(3,3-Dimethylbut-1-yn-1-yl)benzene (**5.11c**)



5.11c was synthesized following **GP7** using cesium *tert*-butoxyl-2-oxoacetate (**5.6c**, 0.083 g, 0.30 mmol, 1 equiv), PhEBX (**HIR.2a**, 0.157 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M). Column chromatography (SiO_2, pentane) afforded (3,3-dimethylbut-1-yn-1-yl)benzene (**5.11c**, 0.051 g, 85% purity, 0.27 mmol, 91%) as a colorless oil. The compound could be partially purified from 1,4-diphenylbuta-1,4-diyne (major impurity) by preparative TLC (SiO_2, glass plate, Heptane) allowing full characterization of **5.11c**.

Rf (pentane) = 0.8.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.33 (m, 2H, Ar*H*), 7.32 – 7.20 (m, 3H, Ar*H*), 1.32 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.3, 127.5, 124.2, 98.7, 79.1, 31.2, 28.1. **IR** (ν_{max}, cm^{-1}) 3084 (m), 3054 (m), 2971 (m), 2903 (m), 2871 (m), 1780 (m), 1723 (m), 909 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z $[M]^+$ Calcd for $C_{12}H_{14}^+$ 158.1090; Found 158.1093.

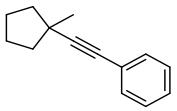
1-(Phenylethynyl)adamantane (**5.11d**)



5.11d was synthesized following the **GP7** using cesium 2-(((1*S*,3*S*)-adamantan-1-yl)oxy)-2-oxoacetate (**5.11d**, 107 mg, 0.300 mmol, 1.00 equiv), PhEBX (**HIR.2a**, 157 mg, 0.450 mmol, 1.50 equiv) and 4CzIPN (**PC.9a**, 12 mg, 0.015 mmol, 5 mol%).
Column chromatography (SiO_2, Pentane) afforded 1-(phenylethynyl)adamantane (**5.11d**, 20 mg, 0.080 mmol, 28%) as a pale yellow oil.

Rf (pentane) = 0.5.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.32 (m, 2H, Ar*H*), 7.32 – 7.19 (m, 3H, Ar*H*), 2.07 – 1.97 (m, 3H, C*H*), 1.97 – 1.92 (m, 6H, CH_2), 1.75 – 1.69 (m, 6H, CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.8, 128.2, 127.5, 124.2, 98.6, 79.5, 43.0, 36.6, 30.2, 28.2. **IR** (ν_{max}, cm^{-1}) 3060 (w), 2912 (s), 2853 (m), 1491 (m), 1450 (m). **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z $[M]^+$ Calcd for $C_{18}H_{20}^+$ 236.1560; Found 236.1561.

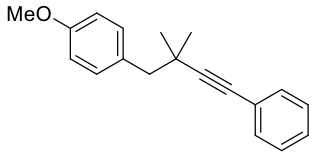
((1-Methylcyclopentyl)ethynyl)benzene (**5.11e**)



5.11e was synthesized following the **GP7** using cesium 2-((1-methylcyclopentyl)oxy)-2-oxoacetate (**5.6c**, 91 mg, 0.30 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 157 mg, 0.450 mmol, 1.50 equiv) and 4CzIPN (**PC.9a**, 12 mg, 0.015 mmol, 5 mol%).
Column chromatography (SiO_2, Pentane) afforded ((1-methylcyclopentyl)ethynyl)benzene (**5.11e**, 39 mg, 0.20 mmol, 69%) as a pale yellow oil.

Rf (pentane) = 0.6.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 - 7.36 (m, 2H, Ar*H*), 7.29 - 7.23 (m, 3H, Ar*H*), 2.01 - 1.95 (m, 2H, CH_2), 1.90 - 1.80 (m, 2H, CH_2) 1.75 - 1.66 (m, 2H, CH_2), 1.62 - 1.51 (m, 2H, CH_2), 1.35 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.3, 127.4, 124.4, 98.6, 79.6, 41.8, 38.5, 27.6, 24.5. **IR** (ν_{max}, cm^{-1}) 3060 (m), 2960 (s), 2869 (m), 1742 (m), 1488 (m), 1451 (m), 1322 (m), 1186 (m). **HRMS** (APPI/LTQ-Orbitrap) m/z $[M]^+$ Calcd for $C_{14}H_{16}^+$ 184.1247; Found 184.1248.

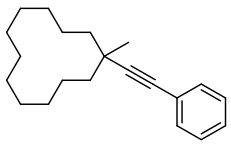
1-(2,2-Dimethyl-4-phenylbut-3-yn-1-yl)-4-methoxybenzene (**5.11f**)



5.11f was synthesized following **GP7** using cesium (1-(4-methoxyphenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate (**5.6f**, 0.115 g, 0.300 mmol, 1.00 equiv), PhEBX (**HIR.2a**, 0.157 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane:EtOAc 100:0 to 90:10) afforded 1-(2,2-dimethyl-4-phenylbut-3-yn-1-yl)-4-methoxybenzene (**5.11f**, 0.044 g, 0.17 mmol, 55%).

Rf (pentane:EtOAc 9:1) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.33 (m, 2H, Ar*H*), 7.31 – 7.21 (m, 5H, Ar*H*), 6.88 – 6.81 (m, 2H, Ar*H*), 3.80 (s, 3H, OC*H*$_3$), 2.74 (s, 2H, ArC*H*$_2$), 1.28 (s, 6H, (C*H*$_3$)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.4, 131.7, 131.6, 130.7, 128.3, 127.6, 124.2, 113.2, 97.2, 81.7, 55.4, 48.4, 33.1, 29.1. **IR** (ν_{max}, cm^{-1}) 3057 (m), 3034 (m), 2961 (m), 2933 (m), 2835 (m), 1786 (m), 1611 (m), 1512 (s), 1465 (m), 1302 (m), 1246 (s), 1177 (s), 1037 (s), 757 (s), 739 (s). **HRMS** (ESI/QTOF) m/z [M + Ag]$^+$ Calcd for $C_{19}H_{20}AgO^+$ 371.0560; Found 371.0552.

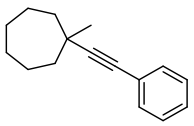
1-Methyl-1-(phenylethynyl)cyclododecane (**5.11g**)



5.11g was synthesized following the **GP7** using cesium 2-((1-methylcyclododecyl)oxy)-2-oxoacetate (**5.6g**, 121 mg (purity 80%), 0.240 mmol, 1.00 equiv), PhEBX (**HIR.2a**, 157 mg, 0.450 mmol, 1.9 equiv) and 4CzIPN (**PC.9a**, 12 mg, 0.015 mmol, 6 mol%).
Column chromatography (SiO_2, Pentane) afforded 1-methyl-1-(phenylethynyl)cyclododecane (**5.11g**, 43 mg, 0.15 mmol, 63%) as a pale yellow oil.

Rf (pentane) = 0.6.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.36 (m, 3H, Ar*H*), 7.29 – 7.23 (m, 2H, Ar*H*), 1.46 – 1.29 (m, 22H, C*H*$_2$), 1.23 (s, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.2, 127.4, 124.4, 98.4, 80.6, 35.0, 34.4, 27.5, 26.6, 26.3, 22.7, 22.3, 19.9. **IR** (ν_{max}, cm^{-1}) 3058 (w), 2936 (s), 2859 (m), 2226 (w), 1597 (w), 1479 (m), 1449 (m), 1273 (w). **HRMS** (ESI/QTOF) m/z [M + Ag]$^+$ Calcd for $C_{21}H_{30}Ag^+$ 389.1393; Found 389.1390.

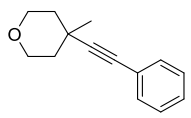
1-Methyl-1-(phenylethynyl)cycloheptane (**5.11j**)



5.11j was synthesized following **GP7** using cesium 2-(1-methylcycloheptan-1-yl)oxy-2-oxoacetate (**5.6j**, 0.110 g, 0.300 mmol, 1.00 equiv), PhEBX (**HJR.2a**, 0.157 g, 0.450 mmol, 1.5 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded (3,3-dimethylpent-1-yne-1,5-diyl)dibenzene (**5.11j**, 0.068 g, 75% purity 0.22 mmol, 74%) as a colorless oil. The compound could be partially purified from 1,4-diphenylbuta-1,4-diyne (major impurity) by preparative TLC (SiO_2, glass plate, Heptane) allowing full characterisation of **5.11j**.

Rf (pentane) = 0.7.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.39 (m, 2H, Ar*H*), 7.31 – 7.24 (m, 3H, Ar*H*), 1.95 – 1.84 (m, 2H, C*H*$_2$), 1.82 – 1.64 (m, 4H, C*H*$_2$), 1.64 – 1.56 (m, 2H, C*H*$_2$), 1.55 – 1.44 (m, 4H, C*H*$_2$), 1.29 (s, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.3, 127.4, 124.5, 98.1, 81.1, 42.3, 36.1, 31.5, 28.4, 24.0. **IR** (ν_{max}, cm^{-1}) 3081 (w), 3054 (w), 2961 (m), 2925 (s), 2855 (m), 1598 (m), 1491 (m), 1460 (m), 1231 (m), 912 (m), 755 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M]$^+$ Calcd for $C_{16}H_{20}^+$ 212.1560; Found 212.1558.

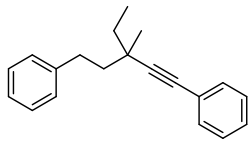
4-Methyl-4-(phenylethynyl)tetrahydro-2*H*-pyran (**5.11k**)



5.11k was synthesized following the **GP7** using ethyl (4-methyltetrahydro-2H-pyran-4-yl) oxalate (**5.6k**, 96 mg, 0.30 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 157 mg, 0.450 mmol, 1.50 equiv) and 4CzIPN (**PC.9a**, 12 mg, 0.015 mmol, 5 mol%).
Column chromatography (SiO_2, 1% to 5% EtOAc in Pentane) afforded, 4-methyl-4-(phenylethynyl)tetrahydro-2*H*-pyran (**5.11k**, 40 mg, purity: 94%, 0.19 mmol, 67%) as a colorless oil.

Rf (pentane:EtOAc 95:5) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.39 (m, 2H, Ar*H*), 7.32 – 7.27 (m, 3H, Ar*H*), 3.90 – 3.77 (m, 4H, OCH_2), 1.76 – 1.68 (m, 2H, CH_2), 1.61 (ddd, *J* = 13.2, 11.2, 5.0 Hz, 2H, CH_2), 1.35 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.4, 127.9, 123.8, 94.7, 83.0, 65.4, 39.4, 31.1, 30.2. **IR** (ν_{max}, cm^{-1}) 3058 (m), 2959 (s), 2857 (m), 1746 (m), 1492 (m), 1448 (m), 1174 (s), 1107 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M + H]$^+$ Calcd for $C_{14}H_{17}O^+$ 201.1274; Found 201.1273.

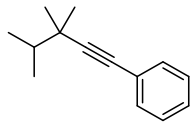
(3-Ethyl-3-methylpent-1-yne-1,5-diyl)dibenzene (**5.11l**)



5.11l was synthesized following the **GP7** using cesium 2-((3-methyl-1-phenylpentan-3-yl)oxy)-2-oxoacetate (**5.6l**, 115 mg, 0.300 mmol, 1.00 equiv), PhEBX (**HIR.2a**, 157 mg, 0.450 mmol, 1.50 equiv) and 4CzIPN (**PC.9a**, 12 mg, 0.015 mmol, 5 mol%).
Column chromatography (SiO_2, Pentane) affording (3-ethyl-3-methylpent-1-yne-1,5-diyl)dibenzene (**5.11l**, 57 mg, 0.22 mmol, 72%) as a pale yellow oil.

Rf (pentane) = 0.3
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.41 (m, 2H, Ar*H*), 7.32 – 7.27 (m, 5H, Ar*H*), 7.25 – 7.22 (m, 2H, Ar*H*), 7.21 – 7.17 (m, 1H, Ar*H*), 2.90 – 2.77 (m, 2H, ArCH_2), 1.90 – 1.82 (m, 1H, CH_2), 1.76 – 1.63 (m, 2H, CH_2), 1.59 – 1.50 (m, 1H, CH_2), 1.30 (s, 3H, CH_3), 1.07 (t, *J* = 7.40 Hz, 3H, CH_2CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 143.1, 131.8, 128.6, 128.5, 128.3, 127.6, 125.8, 124.3, 96.1, 82.2, 43.7, 36.2, 34.5, 31.9, 26.0, 9.5. **IR** (ν_{max}, cm^{-1}) 3062 (w), 3031 (m), 2969 (m), 2929 (m), 2858 (w), 1599 (m), 1493 (m), 1454 (m). **HRMS** (APPI/LTQ-Orbitrap) m/z [M]$^+$ Calcd for $C_{20}H_{22}^+$ 262.1716; Found 262.1716.

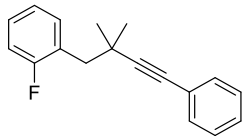
(3,3,4-trimethylpent-1yn-1-yl)benzene (**5.11m**)



5.11m was synthesized following **GP7** using cesium (2,3-dimethylbutan-2-yl)oxy-2-oxoacetate (**5.6m**, 0.092 g, 0.30 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 0.157 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded (3,3,4-trimethylpent-1-yn-1-yl)benzene (**5.11m**, 0.053 g, 85% purity, 0.21 mmol, 72%) as a colorless oil. The compound could be partially purified from 1,4-diphenylbuta-1,4-diyne (major impurity) by preparative TLC (SiO_2, glass plate, Heptane) allowing full characterisation of **5.11m**.

Rf (pentane) = 0.75.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.35 (m, 2H, Ar*H*), 7.32 – 7.22 (m, 3H, Ar*H*), 1.64 (hept, *J* = 6.8 Hz, 1H, C*H*(CH_3)$_2$), 1.25 (s, 6H, C(CH_3)$_2$), 1.03 (d, *J* = 6.8 Hz, 6H, CH(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.3, 127.4, 124.4, 97.0, 81.0, 38.0, 35.6, 27.1, 18.5. **IR** (ν_{max}, cm^{-1}) 3083 (m), 3055 (m), 2971 (s), 2939 (m), 2874 (m), 2228 (m), 1599 (m), 1489 (m), 1460 (m), 1369 (m), 1157 (m), 1061 (m), 911 (m), 755 (s), 691 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M]$^+$ Calcd for $C_{14}H_{18}^+$ 186.1403; Found 186.1403.

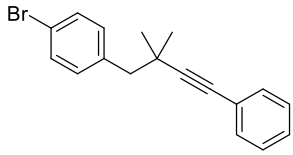
1-(2,2-Dimethyl-4-phenylbut-3-yn-1-yl)-2-fluorobenzene (**5.11n**)



5.11n was synthesized following **GP7** using cesium (1-(2-fluorophenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate (**5.6n**, 0.112 g, 0.300 mmol, 1.00 equiv), PhEBX (**HIR.2a**, 0.157 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded 1-(2,2-dimethyl-4-phenylbut-3-yn-1-yl)-2-fluorobenzene (**5.11n**, 0.023 g, 0.091 mmol, 30%).

Rf (pentane) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (td, *J* = 7.6, 1.9 Hz, 1H, Ar*H*), 7.38 – 7.36 (m, 1H, Ar*H*), 7.35 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.30 – 7.25 (m, 3H, Ar*H*), 7.25 – 7.17 (m, 1H, Ar*H*), 7.13 – 6.99 (m, 2H, Ar*H*), 2.87 (d, *J* = 1.5 Hz, 2H, ArCH_2), 1.33 (d, *J* = 1.0 Hz, 6H, C(CH_3)$_2$). **^{1}H NMR {^{19}F}** δ 7.42 (dd, *J* = 7.6, 1.8 Hz, 1H, Ar*H*), 7.39 – 7.32 (m, 2H, Ar*H*), 7.31 – 7.18 (m, 4H, Ar*H*), 7.13 – 7.01 (m, 2H, Ar*H*), 2.87 (s, 2H, ArCH_2), 1.33 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 161.7 (d, *J* = 245 Hz), 133.1 (d, *J* = 5 Hz), 131.6, 128.3 (d, *J* = 8 Hz), 128.3, 127.7, 125.5 (d, *J* = 16 Hz), 124.1, 123.5 (d, *J* = 4 Hz), 115.2 (d, *J* = 23 Hz), 96.7, 81.5, 41.3, 33.3, 29.1. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -116.1. **IR** (ν_{max}, cm^{-1}) 3061 (w), 2969 (w), 2925 (w), 1489 (m), 1488 (m), 1467 (m), 1280 (m), 1183 (m), 752 (s), 721 (m). **HRMS** (APPI/LTQ-Orbitrap) m/z [M]$^+$ Calcd for $C_{18}H_{17}F^+$ 252.1309; Found 252.1308.

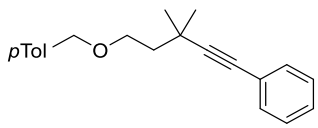
1-(2,2-dimethyl-4-phenylbut-3-yn-1-yl)-4-bromobenzene (**5.11o)**



5.11o was synthesized following *general procedure X* using cesium (1-(4-bromophenyl)-2-methylpropan-2-yl)oxy-2-oxoacetate **5.6o** (0.087 g, 0.2 mmol, 1 equiv), PhEBX (**HIR.2a,** 0.105 g, 0.3 mmol, 1.5 equiv), 4CzIPN (**PC.9a**, 0.008 g, 1.0 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.067 M).
Column chromatography (SiO_2, pentane) afforded 1-(2,2-dimethyl-4-phenylbut-3-yn-1-yl)-4-bromobenzene (**5.11o**, 0.021 g, 0.067 mmol, 33%).

Rf (pentane) = 0.35
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.39 (m, 2H, Ar*H*), 7.38 – 7.31 (m, 2H, Ar*H*), 7.32 – 7.25 (m, 3H, Ar*H*), 7.23 – 7.17 (m, 2H, Ar*H*), 2.74 (s, 2H, ArCH_2), 1.29 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 137.5, 132.4, 131.6, 130.9, 128.3, 127.8, 123.9, 120.6, 96.5, 82.1, 48.6, 32.9, 29.2. **IR** (ν_{max}, cm^{-1}) 3080 (m), 3060 (m), 3033 (m), 2967 (m), 2921 (m), 2863 (m), 1763 (m), 1737 (m), 1598 (m), 1489 (s), 1443 (m), 1384 (m), 1277 (m), 1187 (m), 1072 (s), 1048 (m), 1013 (s), 912 (s), 841 (s), 756 (s), 741 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M]$^+$ Calcd for $C_{18}H_{17}{}^{79}Br^+$ 312.0508; Found 312.0508

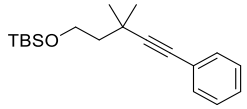
1-(((3,3-Dimethyl-5-phenylpent-4-yn-1-yl)oxy)methyl)-4-methylbenzene (**5.11p**)



5.11p was synthesized following **GP7** using cesium (2-methyl-4-((4-methylbenzyl)oxy)butan-2-yl)oxy-2-oxoacetate (**5.6p**, 0.124 g, 0.300 mmol, 1.00 equiv), PhEBX (**HIR.2a**, 0.157 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane:EtOAc 100:0 to 80:20) afforded 1-(((3,3-dimethyl-5-phenylpent-4-yn-1-yl)oxy)methyl)-4-methylbenzene (**5.11p**, 0.049 g, 0.17 mmol, 56%).

Rf(pentane:EtOAc 8:2) = 0.5.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.29 (m, 2H, Ar*H*), 7.30 – 7.21 (m, 5H, Ar*H*), 7.17 – 7.11 (m, 2H, Ar*H*), 4.50 (s, 2H, ArCH_2), 3.74 (dd, *J* = 7.6, 6.9 Hz, 2H, CH_2), 2.34 (s, 3H, ArCH_3), 1.89 – 1.81 (m, 2H, CH_2), 1.32 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 137.3, 135.6, 131.7, 129.2, 128.3, 127.9, 127.6, 124.0, 96.7, 80.8, 73.0, 68.2, 42.6, 30.6, 29.9, 21.3. **IR** (ν_{max}, cm^{-1}) 3052 (m), 3033 (m), 2969 (m), 2907 (m), 2863 (m), 1960 (w), 1900 (w), 1715 (w), 1598 (m), 1490 (m), 1443 (m), 1361 (m), 1096 (s), 802 (s), 754 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M]$^+$ Calcd for $C_{21}H_{24}O^+$ 292.1822; Found 292.1818.

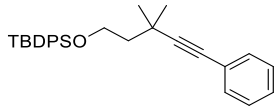
tert-Butyl((3,3-dimethyl-5-phenylpent-4-yn-1-yl)oxy)dimethylsilane (**5.11q**)



5.11q was synthesized following the **GP7** using cesium 2-((4-((*tert*-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)oxy)-2-oxoacetate (**5.6q**, 127 mg, 0.300 mmol, 1.00 equiv), PhEBX (**HIR.2a**, 157 mg, 0.450 mmol, 1.50 equiv) and 4CzIPN (**PC.9a**, 12 mg, 0.015 mmol, 5 mol%). Column chromatography (SiO_2, 5% CH_2Cl_2 in Pentane) afforded (3-*tert*-butyl((3,3-dimethyl-5-phenylpent-4-yn-1-yl)oxy)dimethylsilane (**5.11q**, 55 mg, 0.18 mmol, 61%) as a yellow oil.

Rf (pentane: CH_2Cl_2 95:5) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.34 (m, 2H, Ar*H*), 7.30 – 7.25 (m, 3H, Ar*H*), 3.90 (t, *J* = 7.5 Hz, 2H, OC*H*$_2$), 1.76 (t, *J* = 7.5 Hz, 2H, C*H*$_2$), 1.31 (s, 6H, C(C*H*$_3$)$_2$), 0.91 (s, 9H, C(C*H*$_3$)$_3$), 0.08 (s, 6H, Si(C*H*$_3$)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.3, 127.6, 124.1, 96.8, 80.7, 61.1, 45.8, 30.5, 29.9, 26.1, 18.5, -5.1. **IR** (ν_{max}, cm^{-1}) 3668 (w), 2962 (s), 2901 (s), 1467 (m), 1393 (m), 1254 (m), 1092 (s), 1057 (s). **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z [M + H]$^+$ Calcd for $C_{19}H_{31}OSi^+$ 303.2139; Found 303.2137.

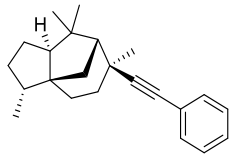
tert-Butyl((3,3-dimethyl-5-phenylpent-4-yn-1-yl)oxy)diphenylsilane (**5.11r**)



5.11r was synthesized following the **GP7** using cesium 2-((4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-2-yl)oxy)-2-oxoacetate (**5.6r**, 164 mg, 0.300 mmol, 1.00 equiv), PhEBX (**HIR.2a**, 157 mg, 0.450 mmol, 1.50 equiv) and 4CzIPN (**PC.9a**, 12 mg, 0.015 mmol, 5 mol%). Column chromatography (SiO_2, 5% CH_2Cl_2 in Pentane) afforded *tert*-butyl((3,3-dimethyl-5-phenylpent-4-yn-1-yl)oxy)diphenylsilane (**5.11r**, 53 mg, 0.12 mmol, 41%) as a yellow oil.

Rf (pentane: CH_2Cl_2, 95:5) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 – 7.64 (m, 4H, Ar*H*), 7.44 – 7.31 (m, 6H, Ar*H*), 7.29 – 7.21 (m, 5H, Ar*H*), 3.96 (dd, *J* = 7.6, 6.8 Hz, 2H, OC*H*$_2$), 1.82 (dd, *J* = 7.6, 6.8 Hz, 2H, C*H*$_2$), 1.27 (s, 6H, C(C*H*$_3$)$_2$), 1.05 (s, 9H, C(C*H*$_3$)$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 135.7, 134.1, 131.7, 129.7, 128.2, 127.8, 127.6, 124.0, 96.7, 80.8, 62.0, 45.5, 30.5, 30.0, 27.0, 19.3. **IR** (ν_{max}, cm^{-1}) 3668 (m), 3061 (m), 2966 (s), 2935 (s), 1478 (m), 1392 (m), 1258 (m), 1084 (s). **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z [M + Na]$^+$ Calcd for $C_{29}H_{34}NaOSi^+$ 449.2271; Found 449.2269.

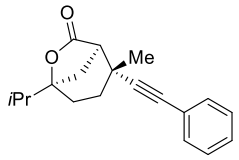
(3*R*,3a*S*,6*S*,7*R*,8a*S*)-3,6,8,8-tetramethyl-6-(phenylethynyl)octahydro-1H-3a,7-methanoazulene (**5.11u**)



5.11u was synthesized following **GP7** using cedrol derived cesium oxalate **5.6u** (0.128 g, 0.300 mmol, 1 equiv), PhEBX (**HIR.2a**, 0.157 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded (3*R*,3a*S*,6*S*,7*R*,8a*S*)-3,6,8,8-tetramethyl-6-(phenylethynyl)octahydro-1H-3a,7-methanoazulene (**5.11u**) as a single diasteroisomer (0.075 g (70% purity), dr > 20:1, 0.17 mmol, 58%). The compound could be partially purified from 1,4-diphenylbuta-1,4-diyne (major impurity) by preparative TLC (SiO_2, glass plate, Heptane) allowing full characterisation of **5.11u**.

Rf (pentane) = 0.6.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.35 (m, 2H, Ar*H*), 7.32 – 7.20 (m, 3H, Ar*H*), 2.18 – 2.10 (m, 1H, aliphatic-C*H* or C*H*$_2$), 1.95 – 1.83 (m, 2H, aliphatic-C*H* or C*H*$_2$), 1.85 – 1.76 (m, 1H, aliphatic-C*H* or C*H*$_2$), 1.79 – 1.65 (m, 5H, aliphatic-C*H* or C*H*$_2$), 1.60 – 1.50 (m, 1H, aliphatic-C*H* or C*H*$_2$), 1.48 (s, 3H, C*H*$_3$), 1.46 – 1.34 (m, 2H, aliphatic-C*H* or C*H*$_2$), 1.28 (dtd, *J* = 11.8, 7.7, 6.0 Hz, 1H, aliphatic-C*H* or C*H*$_2$), 1.22 (s, 3H, C*H*$_3$), 1.03 (s, 3H, C*H*$_3$), 0.87 (d, *J* = 7.1 Hz, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.6, 128.3, 127.3, 124.6, 100.0, 80.8, 59.0, 57.4, 54.2, 44.4, 44.0, 42.0, 39.1, 37.1, 34.9, 31.9, 29.8, 29.0, 28.5, 25.6, 15.7. **IR** (ν_{max}, cm^{-1}) 3055 (m), 3010 (m), 2950 (m), 2870 (m), 2851 (m), 1648 (m), 1474 (m), 1442 (m), 1246 (m), 755 (s), 724 (m), 690 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z [M]$^+$ Calcd for $C_{23}H_{30}^+$ 306.2342; Found 306.2342.

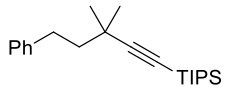
(1*R*,2*R*,5*R*)-5-isopropyl-2-methyl-2-(phenylethynyl)-6-oxabicyclo[3.2.1]octan-7-one (**5.11v**)



5.11v was synthesized following the **GP7** using cesium (*R*)-2-((1-isopropyl-4-methylcyclohex-3-en-1-yl)oxy)-2-oxoacetate (**5.11v**, 107 mg, 0.300 mmol, 1.00 equiv), PhEBX (**HIR.2a**, 157 mg, 0.450 mmol, 1.50 equiv) and 4CzIPN (**PC.9a**, 12 mg, 0.015 mmol, 5 mol%).
Column chromatography (SiO_2, 5% EtOAc in Pentane) afforded (1*R*,2*R*,5*R*)-5-isopropyl-2-methyl-2-(phenylethynyl)-6-oxabicyclo[3.2.1]octan-7-one (**5.11v**, 45 mg, dr > 20:1, 0.16 mmol, 53%) as a colorless oil.

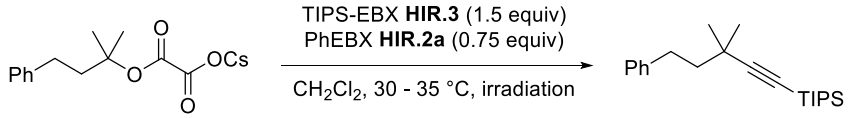
Rf (pentane:EtOAc 95:5) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.37 (m, 2H, Ar*H*), 7.35 – 7.28 (m, 3H, Ar*H*), 2.65 (dd, *J* = 5.6, 1.7 Hz, 1H, C*H*CO_2), 2.47 (d, *J* = 11.9 Hz, 1H, CO_2CHCH_{ax}), 2.15 – 2.08 (m, 1H, CO_2CHCH_{eq}), 2.07 – 2.00 (m, 1H, CCH_3CH_{ax}), 2.00 – 1.91 (m, 1H, $C(CH_3)_2H$), 1.91 – 1.85 (m, 1H, $COCH_{ax}$), 1.84 – 1.77 (m, 1H, $COCH_{eq}$), 1.74 – 1.63 (m, 1H, CCH_3CH_{eq}), 1.48 (s, 3H, CH_3), 1.01 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.97 (d, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 176.3, 131.8, 128.5, 128.3, 123.2, 93.1, 90.1, 82.6, 51.0, 37.4, 35.3, 34.7, 34.3, 27.3, 26.8, 17.2, 16.8. **IR** (ν_{max}, cm^{-1}) 3059 (w), 2967 (m), 2881 (m), 1773 (s), 1593 (w), 1461 (m), 1171 (m), 930 (m). **HRMS** (APPI/LTQ-Orbitrap) m/z $[M + Na]^+$ Calcd for $C_{19}H_{22}NaO_2^+$ 305.1512; Found 305.1512.

(3,3-Dimethyl-5-phenylpent-1-yn-1-yl)triisopropylsilane (**5.14a**)



5.14a was synthesized following the **GP7** using cesium (*R*)-2-((1-isopropyl-4-methylcyclohex-3-en-1-yl)oxy)-2-oxoacetate (**5.6b**, 37 mg, 0.10 mmol, 1.0 equiv), TIPS-EBX (**HIR.3**, 64 mg, 0.150 mmol, 1.50 equiv) and 4CzIPN (**PC.9a**, 4 mg, 0.005 mmol, 5 mol%). Yield was determined by ^{1}H NMR using CH_2Br_2 (7.0 µL, 0.10 mmol, 1.0 equiv) as an internal standard.

Characterisation data was obtained from the following transformation:

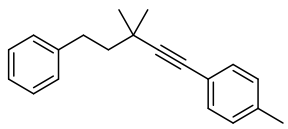


5.6b **5.14a**

An oven dried dram vial (2 mL), equipped with a magnetic stirrer, was charged with cesium oxalate (**5.6b**, 0.036 g, 0.10 mmol, 1 equiv), TIPS-EBX (**HIR.3**, 0.064 g, 0.15 mmol, 1.5 equiv) and PhEBX (**HIR.2a**, 0.026 g, 0.075 mmol, 0.75 equiv). The reaction vial was sealed with a septum. After 3 vacuum/N2 cycles (backfilling with Ar on the last cycle), dry degassed (freeze pump thaw) CH_2Cl_2 was added and the septum was replaced with a screw cap under a flux of Ar. The reactions were placed between 2 x 440 nm Kessil lamps at ca. 10 cm distance from both lamps (with ventilation T = ca. 30-35°C as specified) and stirred under irradiation for 18 hours. The reaction was filtered through a small celite plug which was washed with CH_2Cl_2. The reaction crude was concentrated *in vacuo*, and purified by preparative TLC (SiO2, heptane), affording (3,3-dimethyl-5-phenylpent-1-yn-1-yl)triisopropylsilane (**5.14a**, 2 mg, 0.006 mmol, 6% yield)

Rf (pentane) = 0.55
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.23 – 7.14 (m, 3H, Ar*H*), 2.85 – 2.75 (m, 2H, $PhCH_2$), 1.72 – 1.65 (m, 2H, CH_2), 1.26 (s, 6H, $C(CH_3)_2$), 1.13 – 0.98 (m, 22H, TIPS). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 143.0, 128.4, 128.4, 125.6, 116.2, 79.4, 45.8, 32.2, 29.7, 29.4, 18.7, 11.3. **HRMS** (APPI/LTQ-Orbitrap) m/z $[M + Na]^+$ Calcd for $C_{22}H_{36}NaSi^+$ 351.2478; Found 351.2485.

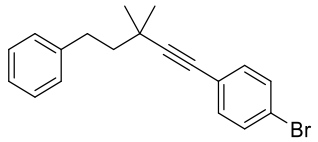
1-(3,3-Dimethyl-5-phenylpent-1-yn-1-yl)-4-methylbenzene (**5.14b**)



5.14b was synthesized following **GP7** using cesium 2-(methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.6a**, 0.110 g, 0.300 mmol, 1.0 equiv), **HIR.2b** (0.163 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded (3,3-dimethylpent-1-yne-1,5-diyl)dibenzene (**5.14b**, 0.050 g, 0.19 mmol, 64%) as a colorless oil.

Rf (pentane) = 0.4
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.26 (m, 4H, Ar*H*), 7.25 –7.15 (m, 3H, Ar*H*), 7.12 – 7.07 (m, 2H, Ar*H*), 2.96 – 2.76 (m, 2H, PhCH_2), 2.34 (s, 3H, ArCH_3), 1.85 – 1.74 (m, 2H, PhCH_2CH_2), 1.35 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 143.0, 137.6, 131.6, 129.1, 128.6, 128.5, 125.8, 121.1, 96.2, 81.0, 45.8, 32.3, 32.0, 29.4, 21.6. **IR** (v_{max}, cm^{-1}) 2858 (m), 2924 (s), 2970 (s), 3028 (m), 1508 (s), 1454 (s), 818 (s), 741 (s). **HRMS** (ESI/QTOF) m/z [M + H]$^+$ Calcd for $C_{20}H_{23}^+$ 263.1794; Found 263.1793.

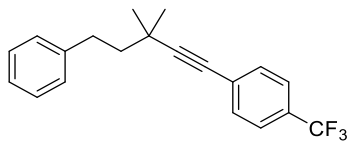
1-(3,3-Dimethyl-5-phenylpent-1-yn-1-yl)-4-bromobenzene (**5.14c**)



5.14c was synthesized following **GP7** using cesium 2-(methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.6a**, 0.110 g, 0.300 mmol, 1.00 equiv), **HIR.2c** (0.192 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded 1-(3,3-dimethyl-5-phenylpent-1-yn-1-yl)-4-bromobenzene (**5.14c**, 0.044 g, 0.13 mmol, 45%).

Rf (pentane) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.38 (m, 2H, Ar*H*), 7.33 – 7.25 (m, 2H, Ar*H*), 7.29 – 7.21 (m, 3H, Ar*H*), 7.25 – 7.14 (m, 2H, Ar*H*), 2.87 – 2.78 (m, 2H, ArCH_2), 1.83 – 1.74 (m, 2H, CH_2), 1.34 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 142.8, 133.2, 131.5, 128.5, 125.9, 123.1, 121.7, 98.3, 80.1, 45.5, 32.3, 32.1, 29.3. 1 carbon is not resolved. **IR** (v_{max}, cm^{-1}) 3086 (m), 3062 (m), 3026 (m), 2968 (m), 2920 (m), 2861 (m), 1485 (s), 1469 (m), 1312 (m), 1265 (m), 1070 (s), 1011 (s), 823 (s), 745 (s), 700 (s). **HRMS** (ESI/QTOF) m/z [M + Ag]$^+$ Calcd for $C_{19}H_{19}Ag^{79}Br^+$ 432.9716; Found 432.9707.

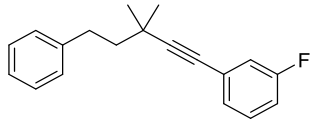
1-(3,3-Dimethyl-5-phenylpent-1-yn-1-yl)-4-(trifluoromethyl)benzene (**5.14d**)



5.14d was synthesized following **GP7** using cesium 2-(methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.6a**, 0.110 g, 0.300 mmol, 1 equiv), **HIR.2d** (0.187 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded 1-(3,3-dimethyl-5-phenylpent-1-yn-1-yl)-4-(trifluoromethyl)benzene (**5.14d**, 0.055 g, 0.17 mmol, 58%).

Rf (pentane) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.46 (m, 4H, Ar*H*), 7.34 – 7.17 (m, 5H, Ar*H*), 2.88 – 2.79 (m, 2H, ArCH_2), 1.85 – 1.77 (m, 2H, CH_2), 1.36 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 142.7, 132.0, 128.5 (m), 125.9, 125.2 (d, *J* = 3.9 Hz), 99.8, 80.0, 45.5, 32.3, 32.1, 29.2. 4 carbons not resolved. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -62.7. **IR** (v_{max}, cm^{-1}) 3028 (w), 2975 (w), 2940 (m), 2859 (m), 2822 (w), 2239 (w), 1617 (m), 1505 (m), 1324 (s), 1168 (m), 1130 (s), 1066 (s), 910 (s), 766 (m), 743 (s). **HRMS** (ESI/QTOF) m/z [M + Ag]$^+$ Calcd for $C_{20}H_{19}AgF_3^+$ 423.0484; Found 423.0479.

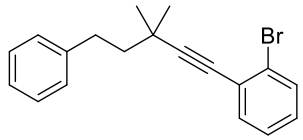
1-(3,3-Dimethyl-5-phenylpent-1-yn-1-yl)-3-fluorobenzene (**5.14e**)



5.14e was synthesized following **GP7** using cesium 2-(methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.6a**, 0.110 g, 0.300 mmol, 1 equiv), **HIR.2e** (0.164 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M). Column chromatography (SiO_2, pentane) afforded 1-(3,3-dimethyl-5-phenylpent-1-yn-1-yl)-3-fluorobenzene (**5.14e**, 0.045 g, 0.17 mmol, 56%).

Rf (pentane) = 0.5.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.15 (m, 7H, Ar*H*), 7.10 (ddd, *J* = 9.6, 2.7, 1.4 Hz, 1H, Ar*H*), 6.98 (tdd, *J* = 8.3, 2.7, 1.2 Hz, 1H, Ar*H*), 2.87 – 2.79 (m, 2H, ArCH_2), 1.84 – 1.75 (m, 2H, CH_2), 1.35 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.4 (d, *J* = 245.8 Hz), 142.6, 129.7 (d, *J* = 8.7 Hz), 128.4, 127.5 (d, *J* = 2.9 Hz), 126.1 – 125.3 (m), 118.4 (d, *J* = 22.5 Hz), 114.8 (d, *J* = 21.1 Hz), 98.0, 79.8, 45.4, 32.1, 31.9, 29.1. 2 carbons are not resolved. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -113.5 (d, *J* = 4.5 Hz). **IR** (v_{max}, cm^{-1}) 3087 (m), 3062 (m), 2972 (s), 2937 (s), 2911 (s), 1608 (s), 1580 (s), 1075 (s), 1056 (s), 909 (s), 873 (s), 784 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z $[M]^+$ Calcd for $C_{19}H_{19}F^+$ 266.1465; Found 266.1473.

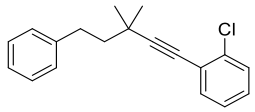
1-(3,3-dimethyl-5-phenylpent-1-yn-1-yl)-2-bromobenzene (**5.14f**)



5.14f was synthesized following **GP7** using cesium 2-(methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.6a**, 0.110 g, 0.300 mmol, 1.00 equiv), **HIR.2f** (0.192 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded (3,3-dimethylpent-1-yne-1,5-diyl)dibenzene (**5.14f**, 0.071 g, 0.22 mmol, 72%).

Rf (pentane) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.45 (dd, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.33 – 7.18 (m, 5H, Ar*H*), 7.22 – 7.14 (m, 1H, Ar*H*), 7.12 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 2.96 – 2.87 (m, 2H, ArCH_2), 1.87 – 1.78 (m, 2H, CH_2), 1.38 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 142.8, 133.2, 132.3, 128.7, 128.5, 128.4, 126.9, 126.0, 125.7, 101.9, 79.7, 45.5, 32.3, 32.2, 29.1. 1 carbon is not resolved. **IR** (v_{max}, cm^{-1}) 3062 (m), 3026 (m), 2968 (s), 2925 (m), 2865 (m), 2226 (m), 1466 (s), 1058 (m), 1047 (s), 1027 (s), 753 (s), 700 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z $[M]^+$ Calcd for $C_{19}H_{19}{}^{79}Br^+$ 326.0665; Found 326.0676.

1-(3,3-Dimethyl-5-phenylpent-1-yn-1-yl)-4-chlorobenzene (**5.14i**)

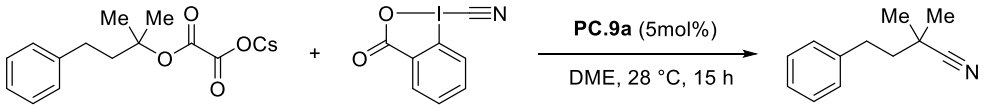


5.14i was synthesized following **GP7** using cesium 2-(methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.6a**, 0.110 g, 0.300 mmol, 1.00 equiv), **HIR.2i** (0.172 g, 0.450 mmol, 1.50 equiv), 4CzIPN (**PC.9a**, 0.012 g, 1.5 µmol, 5 mol%) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded 1-(3,3-dimethyl-5-phenylpent-1-yn-1-yl)-4-chlorobenzene (**5.14i**, 0.066 g, 0.23 mmol, 78%).

Rf (pentane) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.35 (m, 2H, Ar*H*), 7.33 – 7.14 (m, 7H, Ar*H*), 2.95 – 2.86 (m, 2H, ArCH_2), 1.86 – 1.77 (m, 2H, CH_2), 1.38 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 143.0, 136.0, 133.3, 129.3, 128.7, 128.6, 128.5, 126.4, 125.8, 123.9, 102.7, 78.0, 45.7, 32.4, 32.3, 29.3. **IR** (v_{max}, cm^{-1}) 2972 (m), 2901 (m), 1495 (w), 1406 (m), 1229 (m), 1075 (s), 905 (s), 729 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z $[M]^+$ Calcd for $C_{19}H_{19}{}^{35}Cl^+$ 282.1170; Found 282.1178.

Compounds **5.12a**, **5.12b**, **5.12c** were obtained using HIR.26, HIR.27 and HIR.28 respectively the products were not isolated. The yields were determined by ^{1}H NMR based on the structure of the analogue **5.11a**.

8.6. Deoxygenation-cyanation: synthesis of **5.16**



5.6b **HIR.25a** 2.0 equiv. **5.16**

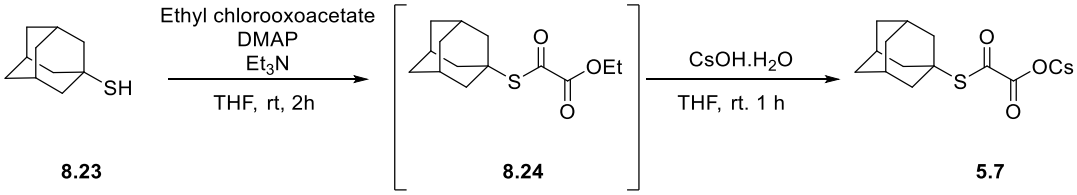
To an oven-dried 5 mL test-tube was charged **5.6b** (0.037 g, 0.10 mmol, 1.0 equiv.), **HIR.25a** (0.055 g, 0.20 mmol, 2.0 equiv.) and 4CzIPN (**PC.9a**, 3.9 mg, 5.0 μmol, 5 mol%). After three vacuum/N_2 cycles, DME (2 mL, 0.05 M) was added the reaction was degassed for 5 min by a balloon of Ar. The reaction was irradiated under ventilation with blue LEDs at 28 °C for 4 hours. The reaction was filtered over a celite pad and washed with acetone and concentrated under reduced pressure. Crude was purified by prep TLC (9:1 Hept:EtOAc) affording **5.16** (7 mg, 0.04 mmol, 39%).

For ^{1}H NMR yield calculations: CH_2Br_2 (6.0 μL, 0.086 mmol, 0.85 equiv.) was added as internal standard after work-up and concentration. The crude was immediately solubilised in Chloroform-*d* after addition. 6H singlet at 1.41 ppm for **5.16** was used for the calculation.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.28 (m, 2H, Ar*H*), 7.24 – 7.19 (m, 3H, Ar*H*), 2.86 – 2.76 (m, 2H, Ar-CH_2), 1.86 – 1.80 (m, 2H, Ar-CH_2-CH_2), 1.41 (s, 6H, (CH_3)$_2$). The results reported correspond to those in literature.[46]

8.7. Dethioalkynylation: synthesis of **5.17a** and **5.17b**

Synthesis of caesium 2-((3S,5S,7S)-adamant-1-ylthio)oxo-2-acetate (**5.7**)



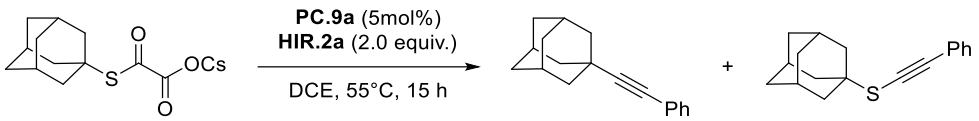
8.23 **8.24** **5.7**

(3S,5S,7S)-adamantane-1-thiol (**8.23**, 1.2 g, 7.13 mmol, 1.00 equiv.) was charged into a two necked round-bottomed flask with THF (35.7 mL, 0.2 M) equipped with a magnetic stirrer. Triethylamine (1.1 mL, 7.5 mmol, 1.1 equiv.) and DMAP (0.044 g, 0.36 mmol, 10 mol%) were then added. Ethyl 2-chloro-2-oxoacetate (0.84 mL, 7.5 mmol, 1.1 equiv.) was then added dropwise. The reaction was then stirred for 1 hour at room temperature. The reaction was quenched with sat. aq. NaCl (15 mL), then washed with 50%vv sat. aq. NaCl (2 x 6 mL). Caesium hydroxide hydrate (1.19 g, 7.06 mmol) with water (7 mL) was added to organic phase. The latter was agitated for 5 min. Hexane (25 mL) was added. Aqueous phase was

[46] Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2011**, *13*, 1622.

separated. Organic phase was back extracted with water (2 x 10 mL). The aqueous phases combined were then concentrated under reduced pressure. The resulting salt was dried overnight under reduced pressure by means of a desiccator (drying agent: SiO_2). Crude was suspended in Et_2O for 1h, washed and dried in desiccator (drying agent: SiO_2) affording **5.7** (1.6 g, 4.30 mmol, 60.3 % yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) 2.00 (bs, 6H, adamantyl-C*H*$_2$), 1.97 (bs, 3H, adamantyl-C*H*), 1.71-1.64 (m, 6H, adamantyl-C*H*$_2$). **^{13}C NMR** (101 MHz, DMSO-d$_6$) δ 197.2, 162.5, 47.6, 41.9, 36.5, 29.5. **IR** (ν_{max}, cm^{-1}) 2908 (m), 2855 (w), 1667 (s), 1642 (s), 1580 (s), 1354 (m), 1300 (m), 984 (m), 778 (s), 758 (m). **HRMS** (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{12}H_{15}CsNaO_3S^+$ 394.9689; Found 394.9686.



5.7 **5.17a** **5.17b**

To an oven-dried 5 mL test-tube was charged **5.7** (0.037 g, 0.10 mmol, 1.0 equiv.), PhEBX (**HIR.2a**, 0.070 g, 0.20 mmol, 2.0 equiv.) and 4CzIPN (**PC.9a**, 3.9 mg, 5.0 μmol, 5 mol%). After three vacuum/N_2 cycles, DCE (1 mL, 0.1 M) was added the reaction was degassed for 5 min by a balloon of Ar. The reaction was irradiated with blue LEDs at 55 °C for 15 hours. The reaction was filtered over a celite pad and washed with acetone and concentrated under reduced pressure. Crude was purified by prep TLC (Heptane) affording **5.17a** and **5.17b** as impure fractions.

For ^{1}H NMR yield calculations: CH_2Br_2 (6.0 μL, 0.086 mmol, 0.85 equiv.) was added as internal standard after work-up and concentration. The crude was immediately solubilised in Chloroform-*d* after addition. The 6H massif at 1.94-1.96 ppm for **5.17a** and the 3H broad singlet at 2.11-2.13 ppm for **5.17b** were used for the calculation.

5.17a: **^{1}H NMR** (400 MHz, chloroform-d) δ 2.00-1.98 (bs, 3H, adamantyl-C*H*), 1.96-1.94 (m, 6H, adamantyl-C*H*$_2$), 1.73-1.71 (m, 6H, adamantyl-C*H*$_2$). Consistent with the data found for **5.17d** with **GP7**.

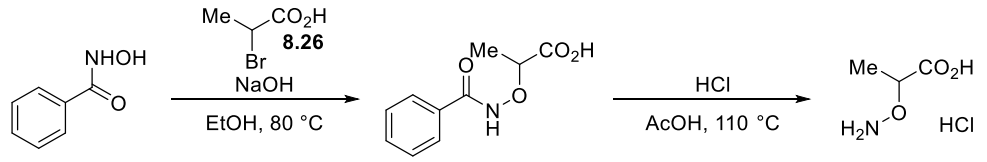
5.17b: **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.45 – 7.42 (m, 2H, Ar*H*), 7.31 – 7.28 (m, 2H, Ar*H*), 2.12 (t, *J* = 3.2 Hz, 3H, adamantyl-C*H*), 2.03 (d, *J* = 2.9 Hz, 6H, adamantyl-C*H*$_2$), 1.72 (t, *J* = 2.3 Hz, 6H, adamantyl-C*H*$_2$). HRMS (ESI$^+$) calcd. for [M+H]$^+$ 269.1364. Found 269.1358.

8.8. Direct excitation of ArEBXs

Synthesis of oximes

2-(Aminooxy)-2-methylpropanoic acid hydrochloride was purchased from commercial sources (ABCR)

2-(Aminooxy)propanoic acid hydrochloride (**8.28**)



8.25 **8.27** **8.28a**

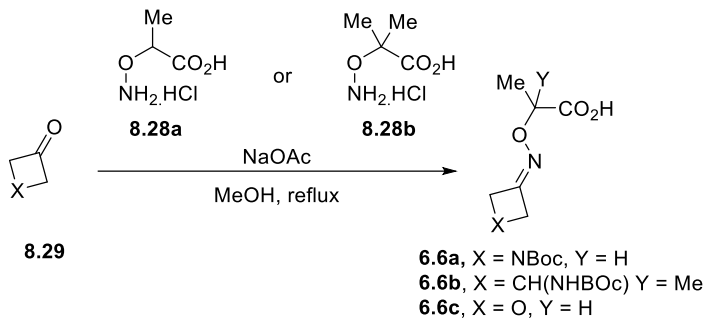
Following a reported procedure,[47] N-hydroxybenzamide (**8.25**) (6.08 g, 44.3 mmol, 1.0 equiv) and finely ground NaOH (5.32 g, 133 mmol, 3.0 equiv) were suspended in absolute EtOH (66 mL). To the resulting thick, off-white suspension, 2-bromopropanoic acid (**8.26**) (4.1 mL, 44 mmol, 1.0 equiv) was added slowly via syringe under stirring. This resulted in the conversion of the homogeneous suspension into a pale brown solution, which was then heated to 80 °C. Once this temperature was reached, the mixture looked again as a homogeneous, off-white suspension, which was stirred overnight. The mixture was then concentrated under reduced pressure to provide a solid residue, which was dissolved in water (90 mL). The resulting aqueous solution was washed once with diethyl ether (100 mL) and then acidified by careful addition of aq. HCl (37 % w/w) until pH = 1. It was then extracted with EtOAc (3 x 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to provide an off-white solid. Recrystallization from hexane (50 mL) and EtOAc (100 mL) afforded 2-(benzamidooxy)propanoic acid (**8.27**) (7.08 g, 33.9 mmol, 76% yield) as a colorless solid. The compound was used directly in next step with no further analyses.

2-(Benzamidooxy)propanoic acid (**8.27**) (7.08 g, 33.8 mmol, 1.0 equiv) was suspended in acetic acid (20.5 mL). Aq. HCl (5.0 M; 68 mL, 34 mmol, 10 equiv) was then added and the mixture was heated to reflux (110 °C), which resulted in the formation of a pale yellow, clear solution. The latter was refluxed for 18 hours. It was then allowed to cool down to room temperature. This led to the precipitation of a crystalline solid (benzoic acid), which was filtered off. The resulting solution was stored at 4 °C overnight, which permitted the precipitation of a further amount of benzoic acid. Upon removal of the latter (4.13 g, 33.8 mmol, 100% yield) through filtration, the so-obtained clear solution was concentrated under vacuum. The resulting wet solid was further dried under vacuum at 60 °C for 3 hours. It was then refluxed in a mixture of EtOAc (30 mL) and EtOH (1.5 mL) for 20 minutes, filtered, washed with pentane, and dried in the air. 2-(Aminooxy)propanoic acid hydrochloride (**8.28a**) was obtained as a colorless solid (4.15 g, 29.3 mmol, 87% yield). The compound was used directly in next step with no further analyses.

[47] H. Jiang, A. Studer, *Angew. Chem. Int. Ed.* **2017**, *56*, 12273–12276.

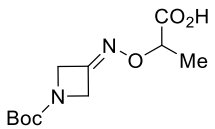
2-(Aminooxy)-2-methylpropanoic acid hydrochloride (**8.28b**) and cyclobutanones were commercially available and purchased.

GP8: Oxime synthesis



Following a reported procedure,[48] a solution of cyclobutanone (**8.29**) (1.0 equiv) in MeOH (0.20 M) was treated with hydroxylamine **8.28a** or **8.28b** (1.2 equiv), sodium acetate (2.4 equiv) and heated to reflux until complete by TLC analysis (4.5 – 6.0 hours). The mixture was then allowed to cool to room temperature and aq. Na_2CO_3 (2.0 M) was added. In some cases, the addition of a small volume of water was necessary to achieve the complete dissolution of the solids. The resulting aqueous solution was extracted once with Et_2O and the organic layer was washed with aq. Na_2CO_3 (2.0 M; 2 x). The combined aqueous extracts were then acidified by careful addition of aq. HCl solution (30% v/v) until pH < 2, and extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to provide the pure product.

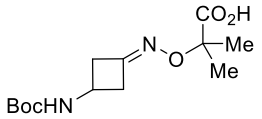
2-(((1-(Tert-butoxycarbonyl)azetidin-3-ylidene)amino)oxy)propanoic acid (**6.6a**)



6.6a was synthesized following **GP8** using *tert*-butyl 3-oxoazetidine-1-carboxylate (**8.29a**, 342 mg, 2.00 mmol, 1.0 equiv) and 2-(aminooxy)propanoic acid hydrochloride (**8.28a**, 340 mg, 2.40 mmol, 1.2 equiv) and NaOAc (394 mg, 4.80 mmol, 2.4 equiv). 2-(((1-(tert-butoxycarbonyl)azetidin-3-ylidene)amino)oxy)propanoic acid (**6.6a**, 517 mg, 2.00 mmol, 100%) was obtained as an off-white amorphous solid. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.70 (bs, 1H, CO_2H) 4.72 – 4.58 (m, 5H, C*H*$_2$-N + C*H*-O), 1.50 – 1.47 (m, 3H, Me), 1.45 (bs, 9H, *t*Bu).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 177.3, 156.3, 149.9, 80.9, 77.3, 58.3, 28.3, 16.6. **IR** (ν_{max}, cm^{-1}) 3700 – 2800 (broad), 2981 (m), 2939 (m), 1705 (s), 1396 (s), 1134 (s), 1250 (m), 1828 (w), 960 (m). **HRMS** (ESI/QTOF) m/z [M + Na]$^+$ Calcd for $C_{11}H_{18}N_2NaO_5^+$ 281.1108; Found 281.1112.

[48] E. M. Dauncey, S. P. Morcillo, J. J. Douglas, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2018**, *57*, 744–748.

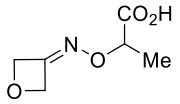
2-(((3-((tert-Butoxycarbonyl)amino)cyclobutylidene)amino)oxy)-2-methylpropanoic acid (**6.6b**)



6.6b was synthesized following **GP8** using *tert*-butyl (3-oxocyclobutyl)carbamate (**8.29b**) (250 g, 1.28 mmol, 1.0 equiv) and 2-(aminooxy)-2-methylpropanoic acid hydrochloride (**8.28b**, 252 mg, 1.62 mmol, 1.2 equiv) and NaOAc (266 mg, 3.24 mmol, 2.4 equiv). 2--(((3-((*tert*-Butoxycarbonyl)amino)cyclobutylidene)amino)oxy)-2-methylpropanoic acid (**6.6b**, 360 mg, 1.23 mmol, 98%) was obtained as an white amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H, CO_2H), 7.38 (d, J = 7.4 Hz, 1H, N*H*), 4.03 (q, J = 7.4 Hz, 1H, C*H*NHBoc), 3.19 – 2.98 (m, 2H, CH_2), 2.83 – 2.66 (m, 2H, CH_2), 1.39 (s, 9H, *t*Bu), 1.36 (s, 3H, CMe_2), 1.35 (s, 3H, CMe_2).**^{13}C NMR** (101 MHz, DMSO-d_6) δ 175.0, 154.7, 153.3, 80.1, 78.0, 38.8, 28.2, 24.0. 1 carbon is not resolved. Corresponds to literature data.[49]

2-(((Oxetan-3-ylidene)amino)oxy)propanoic acid (**6.6c**)



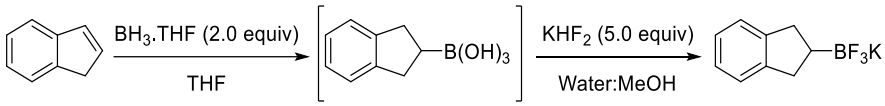
6.6c was synthesized following **GP8** using 3-oxetanone (**8.29c**, 72 mg, 1.0 mmol, 1.0 equiv) and 2-(aminooxy)propanoic acid hydrochloride (**8.29a**, 170 mg, 1.20 mmol, 1.2 equiv) and NaOAc (197 mg, 2.40 mmol, 2.4 equiv). 2-(((oxetan-3-ylidene)amino)oxy)propanoic acid (**6.6c**, 66 mg, purety 90%, 0.37 mmol, 37%) was obtained as an off-white amorphous solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.53 – 5.15 (m, 4H, OCH_2), 4.70 (q, J = 7.1 Hz, 1H, OC*H*Me), 1.50 (d, J = 7.1 Hz, 3H, Me). CO_2H is not detected. **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 176.9, 155.1, 79.2, 78.8, 29.9, 16.8, 0.1.**IR** (ν_{max}, cm^{-1}) 3556 – 2573 (broad), 3066 (w), 2939 (w), 2858 (w), 1720 (s), 1643 (w), 1442 (w), 1250 (m), 1300 (m), 1203 (m), 1138 (m), 1095 (m), 1041 (m), 976 (s), 864 (s).**HRMS** (ESI/QTOF) m/z $[M + H_{-1}]^-$ Calcd for $C_6H_8NO_4^-$ 158.0459; Found 158.0456.

Synthesis of potassium trifluoroboronates

potassium 2-phenyleth-1-yl-trifluoroborate (**6.8b**) was purchased from Sigma Aldrich.

potassium 2,3-dihydro-1H-inden-2-yl-trifluoroborate (**6.8a**)



8.30 **8.31** **6.8a**

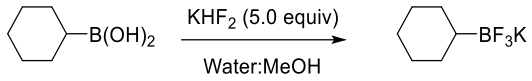
Following a reported procedure,[50] a flame dried round bottom flask containing a solution of BH_3.THF (34.0 mL, 34.0 mmol, 1.00M, 2.00 equiv) in THF was cooled to 0 °C. A solution of 1H-indene (**8.30**) (1.98 mL, 17.0 mmol, 1.00 equiv) in tetrahydrofuran (3.40 mL) was added and the mixture was warm to rt and stirred for 2 h. Water (3.40 mL) was added dropwise and the mixture was stirred for 3 h at rt. The mixture was concentrated in vacuo to remove the solvents except water. Ethyl acetate (50 mL) was added to the suspension and the mixture was washed with a sat. sol. of $NaHCO_3$ (50 mL) and brine (50 mL). The organic layers were combined, dried over $MgSO_4.(H_2O)_2$ and concentrated in vacuo. The crude oil was used

[49] Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. *Chem. Sci.* **2018**, *9*, 5883–5889.
[50] Weng, W.-Z.; Liang, H.; Zhang, B. *Org. Lett.* **2018**, *20* (16), 4979–4983.

directly in next step. To a round bottom flask (PFA) containing a solution of potassium hydrogen fluoride (6.64 g, 85.0 mmol, 5.00 equiv) in water (25.0 mL) were added the crude boronic acid (**8.31**) and methanol (34.0 mL). The mixture was stirred at rt open to air for 2 h. The mixture was concentrated in vacuo, the wet solid obtained was further dried by co-evaporation with acetone (3 times). The resulting solid was diluted with acetone (30 mL) and was put on the rotavap at P_{atm} with the bath at 45 °C for 10 minutes. The solution was filtered with care to leave the remaining insoluble solid in the flask. This process was repeated 2 more times, the solution of acetone was concentrated in vacuo to 1/3 of the initial volume. The solution was left to cool to rt then Et_2O was added to induce precipitation (~40 mL). The solution was cooled to 0 °C and left for 15 min standing at this temperature. The solid was filtered, washed with Et2O and dried in vacuo to afford potassium 2,3-dihydro-1*H*-inden-2-yl-trifluoroborate (**6.8a**) (1.38 g, 6.14 mmol, 36% yield) as a white solid.

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.07 (dd, *J* = 5.3, 3.3 Hz, 2H, Ar*H*), 6.95 (dd, *J* = 5.5, 3.1 Hz, 2H, Ar*H*), 2.75 (dd, *J* = 9.9, 3.6 Hz, 4H, CH_2), 1.29 (m, 1H, C*H*B). **^{13}C NMR** (101 MHz, Acetone-d_6) δ 148.3, 125.6, 124.6, 36.8. One carbon is not resolved. **^{19}F NMR** (376 MHz, Acetone-d_6) δ -146.34 (d, *J* = 95.0 Hz). Corresponds to the reported literature data.[51]

Potassium cyclohexyl-trifluoroborate (**6.8c**)

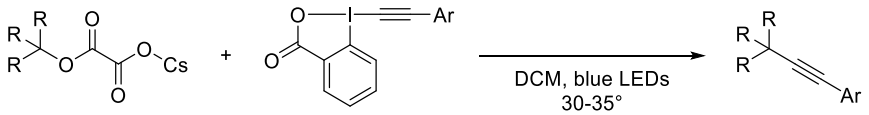


8.32 **6.8c**

Following a reported procedure,[52] in a round bottom flask (PFA), cyclohexyl boronic acid (**8.32**, 5.00 g, 39.1 mmol, 1.00 equiv) was dissolved in methanol (100 mL). Aqueous potassium hydrogen fluoride (50 mL, 4.5 M, 225 mmol) was then added. The resulting white slurry was stirred at room temperature for 30 min, concentrated in vacuo and dissolved in hot acetone. The mixture was filtered, the filtrate was concentrated in vacuo and the residue recrystallized from a minimal amount of ether, to afford potassium cyclohexyl trifluoroborate (**6.8c**, 1.20 g, 6.3 mmol, 16%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.63 – 1.51 (m, 3H, cyclic-CH_2), 1.51 – 1.40 (m, 2H, cyclic-CH_2), 1.19 – 0.95 (m, 3H, cyclic-CH_2), 0.88 (q, *J* = 12.4 Hz, 2H, cyclic-CH_2), -0.02 (bs, 1H, cyclic-C*H*-BF_3^-). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 31.2, 29.4, 28.7, 28.0. Corresponds to reported literature data.[52]

GP9: Direct excitation for deoxyalkynylation

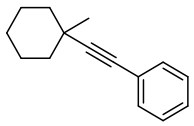


5.6 **HIR.2** **5.11**
5.14

[51] Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. *J. Am. Chem. Soc.* **2014**, *136* (6), 2280–2283.
[52] Cazorla, C.; Métay, E.; Lemaire, M. *Tetrahedron* **2011**, *67*, 8615–8621.

An oven dried (7.5 mL) dram vial equipped with a magnetic stirrer was charged with the cesium salt **5.6** (0.30 mmol, 1.00 equiv) and ArEBX (**HIR.2**, 2.5 mmol, 2.5 equiv). The reaction vial was sealed with a septum. After 3 vacuum/N2 cycles (backfilling with Ar on the last cycle), dichloromethane (3.00 mL) was added and the septums were replaced with a screw cap under a flux of Ar. The reactions were placed between 2 x 440 nm Kessil lamps at ca. 10 cm distance from both lamps (with ventilation, T = 30-35 °C) and stirred under irradiation for 24 hours. The reaction was filtered through a small celite plug which was washed with CH_2Cl_2. A solid deposit was prepared (ca. 2g SiO_2). The compound was purified by column chromatography (SiO_2, pentane:EtOAc).

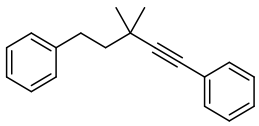
2-(1-Methylcyclohexyl)ethynylbenzene (**5.11a**)



5.11a was synthesized following **GP9** using cesium 2-(1-methylcyclohexan-1-yl)oxy-2-oxoacetate (**5.6a** 95 mg, 0.30 mmol, 1.0 equiv) and PhEBX (**HIR.2a**, 0.261 g, 0.750 mmol, 2.50 equiv) in degassed CH_2Cl_2 (3.0 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded ((1-methylcyclohexyl)ethynyl)benzene (**5.11a**, 0.063 mg (55% purity), 0.18 mmol, 61%) with major impurity 1,4-diphenylbutadiyne.

Rf (pentane) = 0.7.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.37 (m, 2H, Ar*H*), 7.32 – 7.22 (m, 3H, Ar*H*), 1.84 – 1.55 (m, 8H, C*H*$_2$), 1.28 (s, 3H, C*H*$_3$), 1.27 – 1.09 (m, 2H, C*H*$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.3, 127.5, 124.4, 96.9, 81.9, 39.7, 33.3, 30.4, 26.1, 23.6. Consistent with the reported NMR data.[53]

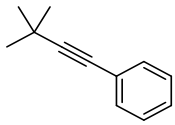
(3,3-dimethylpent-1-yne-1,5-diyl)dibenzene (**5.11b**)



5.11b was synthesized following **GP9** using cesium 2-(methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.6b**, 0.110 g, 0.300 mmol, 1.00 equiv) and PhEBX (**HIR.2a**, 0.261 g, 0.750 mmol, 2.50 equiv) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded (3,3-dimethylpent-1-yne-1,5-diyl)dibenzene (**5.11b**, 0.045 g, 0.18 mmol, 60%) as a slightly yellow oil.

Rf (pentane) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.39 (m, 2H, Ar*H*), 7.33 – 7.27 (m, 5H, Ar*H*), 7.26 – 7.16 (m, 3H, Ar*H*), 2.95 – 2.79 (m, 2H, ArC*H*$_2$), 1.86 – 1.75 (m, 2H, ArCH$_2$C*H*$_2$), 1.36 (s, 6H, C(C*H*$_3$)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 142.9, 131.7, 128.6, 128.5, 128.3, 127.6, 125.8, 124.1, 97.0, 81.0, 45.7, 32.3, 32.0, 29.4. Consistent with the data found for **5.11b** with **GP7**.

(3,3-Dimethylbut-1-yn-1-yl)benzene (**5.11c**)



5.11c was synthesized following **GP9** using cesium (*tert*-butyl)oxy-2-oxoacetate (**5.6c**, 0.083 g, 0.30 mmol, 1 equiv) and PhEBX (**HIR.2a**, 0.261 g, 0.750 mmol, 2.50 equiv) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded (3,3-dimethylbut-1-yne-1-yl)benzene (**5.11c**, 0.067 g, 49% purity 0.17 mmol, 57%) as a slightly yellow oil.

Rf (pentane) = 0.8.

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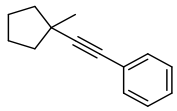
[53] Gao, C.; Li, J.; Yu, J.; Yang, H.; Fu, H. *Chem. Commun.* **2016**, *52*, 7292–7294.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.33 (m, 2H, Ar*H*), 7.32 – 7.20 (m, 3H, Ar*H*), 1.32 (s, 9H, C(C*H*$_3$)$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.3, 127.5, 124.2, 98.7, 79.1, 31.2, 28.1. Consistent with the data found for **5.11c** with **GP7**.

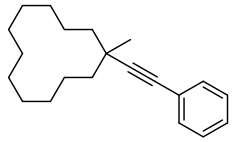
((1-Methylcyclopentyl)ethynyl)benzene (**5.11e**)



5.11e was synthesized following **GP9** using cesium 2-((1-methylcyclopentyl)oxy)-2-oxoacetate (**5.6e**, 91 mg, 0.30 mmol, 1.0 equiv) and PhEBX (**HIR.2a**, 0.261 g, 0.75 mmol, 2.50 equiv) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded ((1-methylcyclopentyl)ethynyl)benzene (**5.11e**, 57 mg, 42% purity, 0.16 mmol, 54%) with major impurity 1,4-diphenylbutadiyne.

Rf (pentane) = 0.6.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 - 7.36 (m, 2H, Ar*H*), 7.29 - 7.23 (m, 3H, Ar*H*), 2.01 - 1.95 (m, 2H, C*H*$_2$), 1.90 - 1.80 (m, 2H, C*H*$_2$) 1.75 - 1.66 (m, 2H, C*H*$_2$), 1.62 - 1.51 (m, 2H, C*H*$_2$), 1.35 (s, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.3, 127.4, 124.4, 98.6, 79.6, 41.8, 38.5, 27.6, 24.5. Consistent with the data found for **5.11e** with **GP7**.

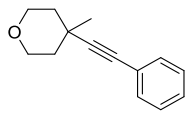
1-Methyl-1-(phenylethynyl)cyclododecane (**5.11g**)



5.11g was synthesized following **GP9** using cesium 2-(1-methylcyclododecan-1-yl)oxy-2-oxoacetate (**5.6g**, 151 mg (purity 80%), 0.300 mmol, 1.00 equiv) and PhEBX (**HIR.2a**, 0.261 g, 0.750 mmol, 2.50 equiv) in degassed CH_2Cl_2 (3.0 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded ((1-methylcyclododecyl)ethynyl)benzene (**5.11g**, 0.062 mg (47% purity), 0.11 mmol, 37%) with major impurity 1,4-diphenylbutadiyne.

Rf (pentane) = 0.6.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.36 (m, 3H, Ar*H*), 7.29 – 7.23 (m, 2H, Ar*H*), 1.46 – 1.29 (m, 22H, C*H*$_2$), 1.23 (s, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.2, 127.4, 124.4, 98.4, 80.6, 35.0, 34.4, 27.5, 26.6, 26.3, 22.7, 22.3, 19.9. Consistent with the data found for **5.11g** with **GP7**.

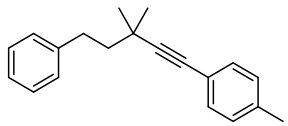
4-Methyl-4-(phenylethynyl)tetrahydro-2*H*-pyran (**5.11k**)



5.11k was synthesized following **GP9** using ethyl (4-methyltetrahydro-2*H*-pyran-4-yl) oxalate (**5.6k**, 0.096 g, 0.30 mmol, 1.0 equiv) and PhEBX (**HIR.2a**, 0.261 g, 0.750 mmol, 2.50 equiv) in degassed CH_2Cl_2 (3.0 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded 4-methyl-4-(phenylethynyl)tetrahydro-2*H*-pyran (**5.11k**, 0.040 g (93% purity), 0.19 mmol, 62%).

Rf (pentane:EtOAc 95:5) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.39 (m, 2H, Ar*H*), 7.32 – 7.27 (m, 3H, Ar*H*), 3.90 – 3.77 (m, 4H, OC*H*$_2$), 1.76 – 1.68 (m, 2H, C*H*$_2$), 1.61 (ddd, *J* = 13.2, 11.2, 5.0 Hz, 2H, C*H*$_2$), 1.35 (s, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.4, 127.9, 123.8, 94.7, 83.0, 65.4, 39.4, 31.1, 30.2. Consistent with the data found for **5.11k** with **GP7**.

1-(3,3-Dimethyl-5-phenylpent-1-yn-1-yl)-4-methylbenzene (**5.14b**)

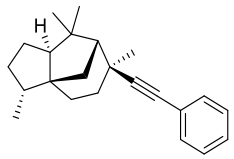


5.14b was synthesized following **GP9** using cesium 2-(methyl-4-phenylbutan-2-yl)oxy-2-oxoacetate (**5.6b**, 0.110 g, 0.300 mmol, 1.00 equiv) and **HIR.2b** (0.271 g, 0.750 mmol, 2.50 equiv) in degassed CH_2Cl_2 (3 mL, 0.1 M).

Column chromatography (SiO_2, pentane) afforded (3,3-dimethylpent-1-yne-1,5-diyl)dibenzene (**5.14b**, 0.055 g, 0.21 mmol, 70%) as a slightly yellow oil.

Rf (pentane) = 0.4
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.26 (m, 4H, Ar*H*), 7.25 –7.15 (m, 3H, Ar*H*), 7.12 – 7.07 (m, 2H, Ar*H*), 2.96 – 2.76 (m, 2H, PhCH_2), 2.34 (s, 3H, ArCH_3), 1.85 – 1.74 (m, 2H, PhCH_2CH_2), 1.35 (s, 6H, C(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 143.0, 137.6, 131.6, 129.1, 128.6, 128.5, 125.8, 121.1, 96.2, 81.0, 45.8, 32.3, 32.0, 29.4, 21.6. Consistent with the data found for **5.14b** with **GP7**.

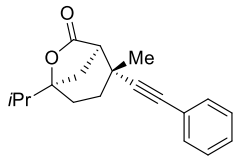
(3*R*,3a*S*,6*S*,7*R*,8a*S*)-3,6,8,8-tetramethyl-6-(phenylethynyl)octahydro-1H-3a,7-methanoazulene (**5.11u**)



5.11u was synthesized following **GP9** using cedrol derived cesium oxalate (**5.6u**, 0.128 g, 0.300 mmol, 1 equiv) and PhEBX (**HIR.2a**, 0.261 g, 0.750 mmol, 2.50 equiv) in degassed CH_2Cl_2 (3 mL, 0.1 M).
Column chromatography (SiO_2, pentane) afforded (3*R*,3a*S*,6*S*,7*R*,8a*S*)-3,6,8,8-tetramethyl-6-(phenylethynyl)octahydro-1H-3a,7-methanoazulene (**5.11u**) as a single diasteroisomer (0.077 g (48% purity), dr > 20:1, 0.15 mmol, 50%).

Rf (pentane) = 0.6.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.35 (m, 2H, Ar*H*), 7.32 – 7.20 (m, 3H, Ar*H*), 2.18 – 2.10 (m, 1H, aliphatic-C*H* or CH_2), 1.95 – 1.83 (m, 2H, aliphatic-C*H* or CH_2), 1.85 – 1.76 (m, 1H, aliphatic-C*H* or CH_2), 1.79 – 1.65 (m, 5H, aliphatic-C*H* or CH_2), 1.60 – 1.50 (m, 1H, aliphatic-C*H* or CH_2), 1.48 (s, 3H, CH_3), 1.46 – 1.34 (m, 2H, aliphatic-C*H* or CH_2), 1.28 (dtd, *J* = 11.8, 7.7, 6.0 Hz, 1H, aliphatic-C*H* or CH_2), 1.22 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.87 (d, *J* = 7.1 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.6, 128.3, 127.3, 124.6, 100.0, 80.8, 59.0, 57.4, 54.2, 44.4, 44.0, 42.0, 39.1, 37.1, 34.9, 31.9, 29.8, 29.0, 28.5, 25.6, 15.7. Consistent with the data found for **5.11u** with **GP7**.

(1*R*,2*R*,5*R*)-5-isopropyl-2-methyl-2-(phenylethynyl)-6-oxabicyclo[3.2.1]octan-7-one (**5.11v**)

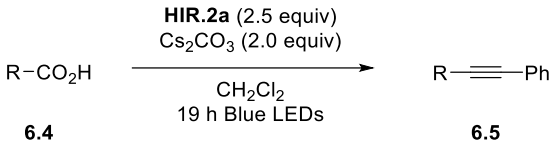


5.11v was synthesized following the **GP9** using cesium (*R*)-2-((1-isopropyl-4-methylcyclohex-3-en-1-yl)oxy)-2-oxoacetate (**5.6v**, 107 mg, 0.300 mmol, 1.00 equiv) and PhEBX (**HIR.2a**, 261 mg, 0.750 mmol, 2.5 equiv).
Column chromatography (SiO_2, 5% EtOAc in Pentane) afforded (1*R*,2*R*,5*R*)-5-isopropyl-2-methyl-2-(phenylethynyl)-6-oxabicyclo[3.2.1]octan-7-one (**5.11v**, 40 mg, dr > 20:1, 0.16 mmol, 47%) as a colorless oil.

Rf (pentane:EtOAc 95:5) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.37 (m, 2H, Ar*H*), 7.35 – 7.28 (m, 3H, Ar*H*), 2.65 (dd, *J* = 5.6, 1.7 Hz, 1H, C*H*CO_2), 2.47 (d, *J* = 11.9 Hz, 1H, CO_2CHCH_{ax}), 2.15 – 2.08 (m, 1H, CO_2CHCH_{eq}), 2.07 – 2.00 (m, 1H, CCH_3CH_{ax}), 2.00 – 1.91 (m, 1H, C(CH_3)$_2$*H*), 1.91 – 1.85 (m, 1H, COCH_{ax}), 1.84 – 1.77 (m, 1H, COCH_{eq}), 1.74 – 1.63 (m, 1H, CCH_3CH_{eq}), 1.48 (s, 3H, CH_3), 1.01 (d, *J* = 6.8 Hz, 3H, CH(CH_3)$_2$), 0.97 (d, *J* = 6.9 Hz, 1H, CH(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 176.3, 131.8, 128.5, 128.3, 123.2, 93.1, 90.1, 82.6, 51.0, 37.4, 35.3, 34.7, 34.3, 27.3, 26.8, 17.2, 16.8. Consistent with the data found for **5.11v** with **GP7**.

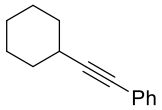
GP10: Direct excitation for decarboxylation alkynylation

All carboxylic acids were commercial, bought from commercial sources and used as such in the reactions.



Following a modified reported procedure,[54] a dram vial, equipped with a magnetic stirring bar, was charged with **HIR.2a** (261 mg, 0.750 mmol, 2.50 equiv), **6.4** (0.300 mmol, 1.00 equiv) and cesium carbonate (196 mg, 0.600 mmol, 2.00 equiv). After 3 vacuum/nitrogen cycles, refilling with argon upon the last cycle, dichloromethane (4.5 mL, degassed by freeze-pump-thaw) was then added and the reaction was irradiated for 21 hours with 2 Kessil lamps PR160 440 nm. A solid deposit was then prepared of the crude on SiO_2 and was purified by column chromatography (SiO_2, Pentane:EtOAc).

2-Cyclohexylethynylbenzene (**6.5a**)

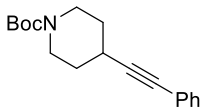


6.5a was synthesized following **GP10** using cyclohexanecarboxylic acid (**6.4a**, 38 mg, 0.30 µmol, 1.0 equiv), PhEBX (**HIR.2a**, 261 mg, 750 µmol, 2.50 equiv), Cs_2CO_3 (195 mg, 600 µmol, 2.0 equiv) in degassed CH_2Cl_2 (6 mL, 0.05 M). Column chromatography (SiO_2, pentane) afforded 1,3-diphenylprop-2-yn-1-one (**6.5a**, 35 mg, 0.15 mmol, 51%) as a yellow solid.

Rf (pentane) = 0.7.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (ddd, *J* = 8.0, 3.3, 1.4 Hz, 2H, Ar*H*), 7.28 – 7.25 (m, 3H, Ar*H*), 2.59 (tt, *J* = 9.3, 3.7 Hz, 1H, C*H*-alkyne), 1.89 (ddd, *J* = 15.6, 7.0, 3.3 Hz, 2H, cyclic-CH_2), 1.76 (dtd, *J* = 12.2, 6.1, 2.3 Hz, 2H, cyclic-CH_2), 1.62 – 1.47 (m, 4H, cyclic-CH_2), 1.44 – 1.29 (m, 2H, cyclic-CH_2).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.3, 127.5, 124.3, 94.6, 80.6, 32.9, 29.2, 26.1, 25.1.Corresponds to reported literature data.[54]

Tert-butyl 4-(phenylethynyl)piperidine-1-carboxylate (**6.5b**)

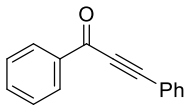


6.5b was synthesized following **GP10** using 1-Boc-piperidine-4-carboxylic acid (**6.4b**, 38 mg, 0.30 µmol, 1.0 equiv), PhEBX (**HIR.2a**, 261 mg, 750 µmol, 2.50 equiv), Cs_2CO_3 (195 mg, 600 µmol, 2.0 equiv) in degassed CH_2Cl_2 (6 mL, 0.05 M).
Column chromatography (SiO_2, pentane) afforded 1,3-diphenylprop-2-yn-1-one (**6.5b**, 35 mg, 0.12 mmol, 41%) as a yellow solid.

Rf (pentane:EtOAc 9:1) = 0.4

^{1}H NMR δ 7.46 – 7.36 (m, 2H, Ar*H*), 7.28 (dt, *J* = 4.6, 2.9 Hz, 3H, Ar*H*), 3.74 (ddd, *J* = 13.5, 6.7, 3.7 Hz, 2H, N(CH_2)$_2$), 3.25 (ddd, *J* = 13.5, 8.4, 3.5 Hz, 2H, N(CH_2)$_2$), 2.80 (tt, *J* = 8.0, 4.0 Hz, 1H, C*H*-alkyne), 1.85 (ddt, *J* = 13.7, 6.9, 3.6 Hz, 2H, cyclic-CH_2), 1.67 (dtd, *J* = 15.1, 7.3, 3.3 Hz, 2H, cyclic-CH_2), 1.47 (s, 9H, *t*Bu). Corresponds to reported literature data.[55]

1,3-Diphenylprop-2-yn-1-one (**6.5c**)



6.5c was synthesized following **GP10** using phenyglyoxylic acid (**6.4c**, 45 mg, 0.30 µmol, 1.0 equiv), PhEBX (**HIR.2a**, 261 mg, 750 µmol, 2.50 equiv), Cs_2CO_3 (195 mg, 600 µmol, 2.0 equiv) in degassed CH_2Cl_2 (6 mL, 0.05 M). Column chromatography (SiO_2, pentane:EtOAc 95:5) afforded 1,3-diphenylprop-2-yn-1-one (**6.5c**, 50 mg, 0.24 mmol, 81%) as a yellow solid.

Rf (pentane:EtOac 95:5) = 0.5.

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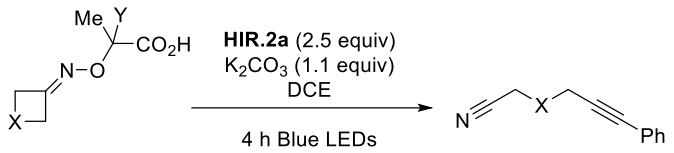
[54] Zhou, Q.; Guo, W.; Ding, W.; Wu, X.; Chen, X.; Lu, L.; Xiao, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199.
[55] Liu, X.-G.; Zhou, C.-J.; Lin, E.; Han, X.-L.; Zhang, S.-S.; Li, Q.; Wang, H. *Angew. Chem. Int. Ed.* **2018**, *57*, 13096–13100.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 – 8.21 (m, 2H, Ar*H*), 7.72 – 7.68 (m, 2H, Ar*H*), 7.67 – 7.60 (m, 1H, Ar*H*), 7.56 – 7.47 (m, 3H, Ar*H*), 7.46 – 7.39 (m, 2H, Ar*H*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 178.2, 137.0, 134.3, 133.2, 130.9, 129.7, 128.8, 128.8, 120.3, 93.3, 87.0. Corresponds to reported literature data.[54]

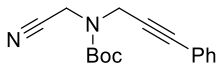
GP11: Direct exciation for alkynylative oxime fragmentation



6.6 **6.7**

Following a modified reported procedure,[56] a dram vial, equipped with a magnetic stirring bar, was charged with **HIR.2a** (261 mg, 750 µmol, 2.50 equiv), **6.6** (0.300 mmol, 1.00 equiv) and potassium carbonate (46 mg, 0.33 mmol, 1.10 equiv). After 3 vacuum/nitrogen cycles, refilling with argon upon the last cycle, 1,2-dichloroethane (2.00 mL, degassed by bubbling Ar) was then added and the reaction was irradiated for 3 h 50 min to 4 hours. A solid deposite of the crude was prepared and the compound was purified by column chromatography (SiO_2, pentane:EtOAc).

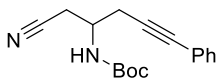
Tert-butyl (cyanomethyl)(3-phenylprop-2-yn-1-yl)carbamate (**6.7a**)



6.7a was synthesized following **GP11** using **6.6a** (77 mg, 0.30 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 261 mg, 750 µmol, 2.50 equiv), K_2CO_3 (46 mg, 0.33 mmol, 1.1 equiv) in degassed CH_2Cl_2 (6 mL, 0.05 M).
Column chromatography (SiO_2, pentane:EtOAc 20:1) afforded *tert*-butyl (cyanomethyl)(3-phenylprop-2-yn-1-yl)carbamate (**6.7a**, 60 mg, 0.22 mmol, 74%) as a yellow oil.

Rf (pentane:EtOac 20:1) = 0.35.
^{1}H NMR H NMR (400 MHz, Acetonitrile-d_3) δ 7.46 (m, 2H, Ph*H*), 7.37 (m, 3H, Ph*H*), 4.34 (s, 2H, CH_2), 4.27 (s, 2H, CH_2), 1.49 (s, 9H, Boc). **^{13}C NMR** (101 MHz, CD_3CN) δ 154.9, 132.4, 129.7, 129.5, 128.7, 123.3, 117.6, 85.1, 84.5, 82.7, 36.1, 28.3. Corresponds to reported literature data.[56]

Tert-butyl (1-cyano-5-phenylpent-4-yn-2-yl)carbamate (**6.7b**)

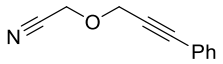


6.7b was synthesized following **GP11** using **6.6b** (86 mg, 0.30 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 261 mg, 750 µmol, 2.50 equiv), K_2CO_3 (46 mg, 0.33 mmol, 1.1 equiv) in degassed CH_2Cl_2 (6 mL, 0.05 M).
Column chromatography (SiO_2, pentane:EtOAc 9:1 to 8:2) afforded *tert*-butyl (1-cyano-5-phenylpent-4-yn-2-yl)carbamate (**6.7b**, 59 mg, 0.21 mmol, 69%) as a yellow solid.

Rf (pentane:EtOac 8:2) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 – 7.38 (m, 2H, Ar*H*), 7.39 – 7.28 (m, 3H, Ar*H*), 4.92 (m, 1H, N*H*), 4.14 (m, 1H, C*H*NHBoc), 2.90 – 2.69 (m, 4H, CH_2), 1.46 (s, 9H, *t*Bu). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 154.7, 131.6, 128.4, 128.3, 122.5, 116.9, 84.3, 83.3, 80.5, 46.3, 28.2, 24.5, 22.5. Corresponds to reported literature data.[56]

[56] Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. *Chem. Sci.* **2018**, *9*, 5883-5889.

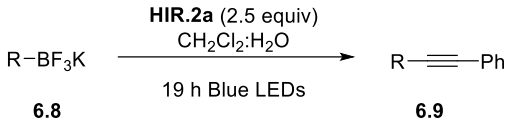
2-((3-Phenylprop-2-yn-1-yl)oxy)acetonitrile (**6.7c**)



6.7c was synthesized following **GP11** using **6.6c** (50 mg, 0.30 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 261 mg, 750 µmol, 2.50 equiv), K_2CO_3 (46 mg, 0.33 mmol, 1.1 equiv) in degassed CH_2Cl_2 (6 mL, 0.05 M).
Column chromatography (SiO_2, pentane:EtOAc 95:5) afforded 2--((3-phenylprop-2-yn-1-yl)oxy)acetonitrile (**6.7c**, 27 mg, 0.16 mmol, 53%) as an off-white oil.

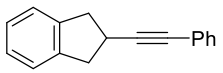
Rf (pentane:EtOac 95:5) = 0.3.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 – 7.39 (m, 2H, Ar*H*), 7.39 – 7.30 (m, 3H, Ar*H*), 4.55 (s, 2H, C*H*$_2$), 4.44 (s, 2H, C*H*$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.9, 129.1, 128.4, 121.8, 115.6, 88.7, 82.1, 59.0, 54.1. Corresponds to reported literature data.[56]

GP12: Direct excitation for deboronative alkynylation



Following a modified reported procedure,[51] an oven-dried (7.5 mL) dram vial equipped with a magnetic stirrer was charged with alkyl trifluoroborate (**6.8**, 0.30 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 261 mg, 0.750 mmol, 2.50 equiv) and Na_2CO_3 (64 mg, 0.60 mmol, 2.0 equiv). The vial was sealed with a septum. After 3 vacuum/N_2 cycles, CH_2Cl_2 (1.5 mL) and water (1.5 mL) were added and the septum was replaced with a screw cap. The reaction was placed between 2 x 440 nm Kessil lamps at ca. 7 cm distance from both lamps with a fan and stirred under irradiation for 19 h. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash chromatography (SiO_2,pentane:EtOAc) affording the corresponding alkyne.

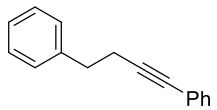
2-(Phenylethynyl)-2,3-dihydro-1H-indene (**6.9a**)



6.9a was synthesized following *general procedure I* using potassium 2,3-dihydro-1*H*-indenyl trifluoroborate (**6.8a**, 67 mg, 0.30 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 261 mg, 0.750 mmol, 2.50 equiv), Na_2CO_3 (64 mg, 0.60 mmol, 2.0 equiv) in degassed CH_2Cl_2:water (1:1) (3 mL, 0.1 M).
Column chromatography (SiO_2, 0 to 2% EtOAc in Pentane) afforded 2-(phenylethynyl)-2,3-dihydro-1*H*-indene (**6.9a,** 47 mg, 0.22 mmol, 72%) as a pale yellow solid.

Rf (pentane) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.40 (m, 2H Ar*H*), 7.30 – 7.27 (m, 3H, Ar*H*), 7.25 – 7.21 (m, 2H, Ar*H*), 7.19 – 7.16 (m, 2H, Ar*H*), 3.49 – 3.40 (m, 1H, C*H*), 3.35 – 3.29 (m, 2H, C*H*$_2$), 3.13 (dd, *J* = 15.2, 8.7 Hz, 2H, C*H*$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 142.2 131.8, 128.3, 127.8, 126.7, 124.5, 123.9, 93.2, 80.7, 40.5, 30.9. Corresponds to reported literature data. [51]

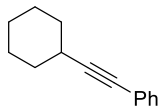
But-1-yne-1,4-diyldibenzene (**6.9b**)



6.9b was synthesized following **GP12** using potassium 2-phenylethyl trifluoroborate (**6.6b**, 64 mg, 0.30 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 261 mg, 0.750 mmol, 2.50 equiv), Na_2CO_3 (64 mg, 0.60 mmol, 2.0 equiv) in degassed CH_2Cl_2:water (1:1) (3 mL, 0.1 M).
Column chromatography (SiO_2, 0 to 2% EtOAc in Pentane) afforded but-1-yne-1,4-diyldibenzene (**6.9b**, 38 mg, 0.18 mmol, 61%) as a pale yellow oil.

Rf (pentane) = 0.4.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.36 (m, 2H, Ar*H*), 7.33 – 7.30 (m, 2H, Ar*H*), 7.31 – 7.27 (m, 5H, Ar*H*), 7.25 – 7.21 (m, 1H, Ar*H*), 2.93 (t, *J* = 7.5 Hz, 2H, CH_2), 2.70 (t, *J* = 7.5 Hz, 2H, CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 142.2, 131.2, 128.3, 127.8, 126.7, 124.5, 123.9, 93.2, 80.7, 40.5, 30.9. 1 carbon is not resolved. Corresponds to reported literature data. [51]

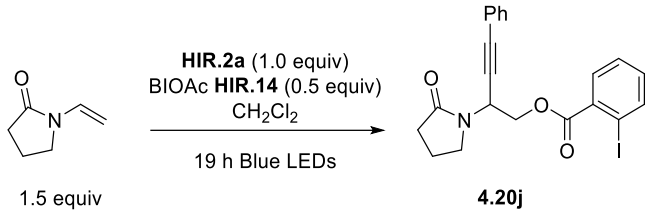
2-Cyclohexylethynylbenzene (**6.9c** same structure as **6.5a**)



6.9c was synthesized following **GP12** using potassium cyclohexyl trifluoroborate (**6.8c**, 57 mg, 0.30 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 261 mg, 750 µmol, 2.50 equiv), Na_2CO_3 (64 mg, 0.60 mmol, 2.0 equiv) in degassed CH_2Cl_2 (6 mL, 0.05 M).
Column chromatography (SiO_2, pentane) afforded 2-cyclohexylethynylbenzene (**6.9c**, 26 mg, 0.14 mmol, 47%) as a yellow solid.

Rf (pentane) = 0.7.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (ddd, *J* = 8.0, 3.3, 1.4 Hz, 2H, Ar*H*), 7.28 – 7.25 (m, 3H, Ar*H*), 2.59 (tt, *J* = 9.3, 3.7 Hz, 1H, C*H*-alkyne), 1.89 (ddd, *J* = 15.6, 7.0, 3.3 Hz, 2H, cyclic-CH_2), 1.76 (dtd, *J* = 12.2, 6.1, 2.3 Hz, 2H, cyclic-CH_2), 1.62 – 1.47 (m, 4H, cyclic-CH_2), 1.38 – 1.25 (m, 2H, cyclic-CH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.3, 127.5, 124.3, 94.6, 80.6, 32.9, 29.2, 26.1, 25.1. Corresponds to reported literature data.[51]

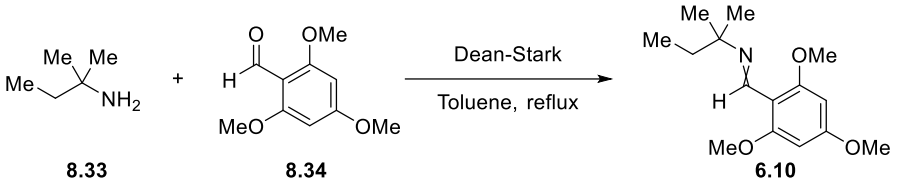
Direct excitation for the oxyalkynylation of *N*-vinyl pyrrolidinone

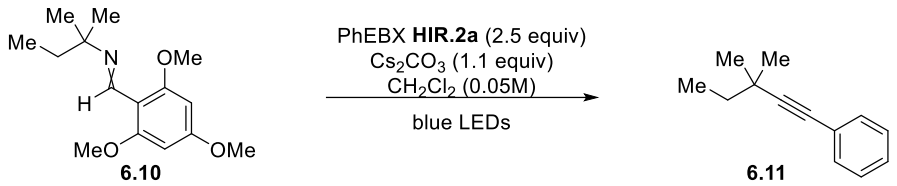


Following a modified reported procedure,[57] an oven dried dram vial, equipped with a magnetic stir bar was charged with **HIR.2a** (35 mg, 0.10 mmol, 1.0 equiv) and **HIR.14** (15 mg, 0.050 mmol, 0.50 equiv). After 3 vacum/nitrogen cycles refilling with Ar on the last cycle, degassed CH_2Cl_2 (0.40 mL) was added followed by *N*-vinylpyrolidinone **4.3j** (16.7 mg, 16.0 µL, 150 µmol, 1.50 equiv). The reaction was irradiated for 19 hours with 2 x 440 nm Kessil lamps. The reaction was concentrated in vacuo. An NMR sample of the crude was prepared with 1 equiv of CH_2Br_2 (7.0 µL, 0.10 mmol, 1 equiv) in CD_3CN. The ^{1}H NMR yield of **4.20j** was determined using the signal at 5.53 ppm (dd, *J* = 8.6, 4.8 Hz, 1H, NC*H*CH_2O) 35%

[57] Amos, S. G. E.; Nicolai, S.; Waser, J. *Chem. Sci.* **2020**, *11*, 11274-11279

Direct excitation for a deaminative alkynylation



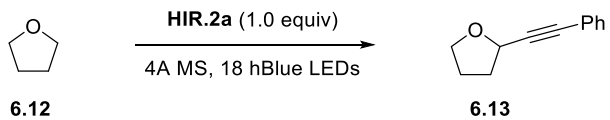


Following a slightly modified reported procedure,[58] a mixture of 2,4,6-trimethoxybenzaldehyde (**8.34**, 196 mg, 1.00 mmol, 1.00 equiv) and *tert*-amyl amine (**8.33**, 0.30 mL, 2.6 mmol, 2.6 equiv) in toluene (10 mL, 0.1 M) was heated in a Dean-Stark apparatus to reflux overnight. The reaction was then cooled, dried with Na_2SO_4, filtered, and evaporated affording crude imine *N-tert*-amyl-1-(2,4,6-trimethoxyphenyl)methanimine (**6.10**, 220 mg, 0.580 mmol, 85% pure, 71%) as a light yellow solid used directly in the next step.

An oven dried dram vial (7.5 mL) equipped with a magnetic stirrer was charged with crude imine **6.10** (80 mg, 85%wt 0.26 mmol, 1.0 equiv), PhEBX (**HIR.2a**, 261 mg, 0.750 mmol, 2.9 equiv) and cesium carbonate (108 mg, 0.330 mmol, 1.3 equiv). After 3 vacuum/N_2 cycles CH_2Cl_2 (6.0 mL) was added and the reaction was sealed with a screw cap under a flux of Ar. The reaction was then irradiated for 24 hours with 2 Kessil lamps (440 nm). The crude was purified by preparative TLC heptane:cyclohexane (1:1) affording 3,3-dimethylpent-1-ynylbenzene (**6.11**, 25.0 mg, 145 µmol, 57% yield) isolated with 2.25 eq of CH_2Cl_2 and traces of 1,3-diphenylbutadiene.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.27 (m, 5H, Ar*H*), 1.52 (q, *J* = 7.5 Hz, 2H, C*H*$_2$CH$_3$), 1.26 (s, 6H, C(C*H*$_3$)$_2$), 1.05 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 131.7, 128.9, 128.3, 127.5, 97.5, 80.5, 36.2, 32.2, 28.9, 9.9. **IR** (ν_{max}, cm^{-1}) 2924 (m), 2970 (m), 3055 (m), 3105 (m), 2858 (m), 3101 (m), 1361 (m), 1323 (m), 1041 (m). **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z [M + H]$^+$ Calcd for $C_{13}H_{17}^+$ 173.1325; Found 173.1324.

Direct excitation for HAT of THF



[58] Ashley, M. A.; Rovis, T. *J. Am. Chem. Soc.* **2020**, *142*, 18310–18316.

Following a modified reported procedure,[59] an oven dried (7.5 mL) dram vial equipped with a magnetic stirrer was charged with MS 4Å (20 mg) and PhEBX (**HIR.2a**, 70 mg, 0.20 mmol, 1.0 equiv). The reaction vial was sealed with a septum. After 3 vacuum/N2 cycles (backfilling with Ar on the last cycle), THF (**6.12**, 4.00 mL) was added and the septum is replaced with a screw cap under a flux of Ar. The reactions were placed between 2 x 460 nm Kessil lamps at ca. 10 cm distance from both lamps (no ventilation, T = ca. 50 °C) and stirred under irradiation for 18 hours. The reaction was filtered through a small celite plug which was washed with CH_2Cl_2. The reaction crude was concentrated in vacuo. An NMR sample of the crude was prepared with 1 equiv of CH_2Br_2 (14.0 µL, 0.200 mmol, 1 equiv) in Chloroform-*d*. The ^{1}H NMR yield of **6.13** was determined using the signal at 4.81 (dd, *J* = 7.2, 5.2 Hz, 1H, C*H*$_x$O) 80%.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45−7.41 (m, 2H, Ar*H*), 7.31−7.28 (m, 3H, Ar*H*), 4.81 (dd, *J* = 7.2, 5.2 Hz, 1H, C*H*$_x$O), 4.04−3.99 (m, 1H, C*H*$_x$O), 3.89−3.83 (m, 1H, C*H*$_x$O), 2.29−2.19 (m, 1H, C*H*$_x$), 2.15−2.04 (m, 2H, C*H*$_x$), 1.99−1.90 (m, 1H, C*H*$_x$). Corresponds to the reported literature data.[59]

8.9. α-chloro alkynylation of DCE

A flame dried screw-cap vial, equiped with a magnetic stir bar was charged with **HIR.2a** (87.0 mg, 250 µmol, 1.00 equiv), 4CzIPN (1 mg. 1 µmol, 2 mol%)and **HIR.14** (21 mg, 68 µmol, 0.28 equiv). The reaction was evacuated then backfilled with Ar. 1,2-dichloroethane (0.50 mL, 6.3 mmol, 25 equiv) was then added and the reaction was irradiated with blue lED strips under stirring for 2 days 14 hours 51 minutes. The crude was concetrated then purified by preparative TLC (SiO2, heptane) affording **5.13a** (8 mg, 0.04 mmol, 15%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.14 (m, 5H), 4.90 (t, *J* = 6.7 Hz, 1H), 3.99 – 3.78 (m, 3H). Corresponds to the reported literature data.[60]

[59] Matsumoto, K.; Nakajima, M.; Nemoto, T. *J. Org. Chem.* **2020**, *85* (18), 11802–11811.
[60] Xiang, J.; Jiang, W.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 6635–6638.

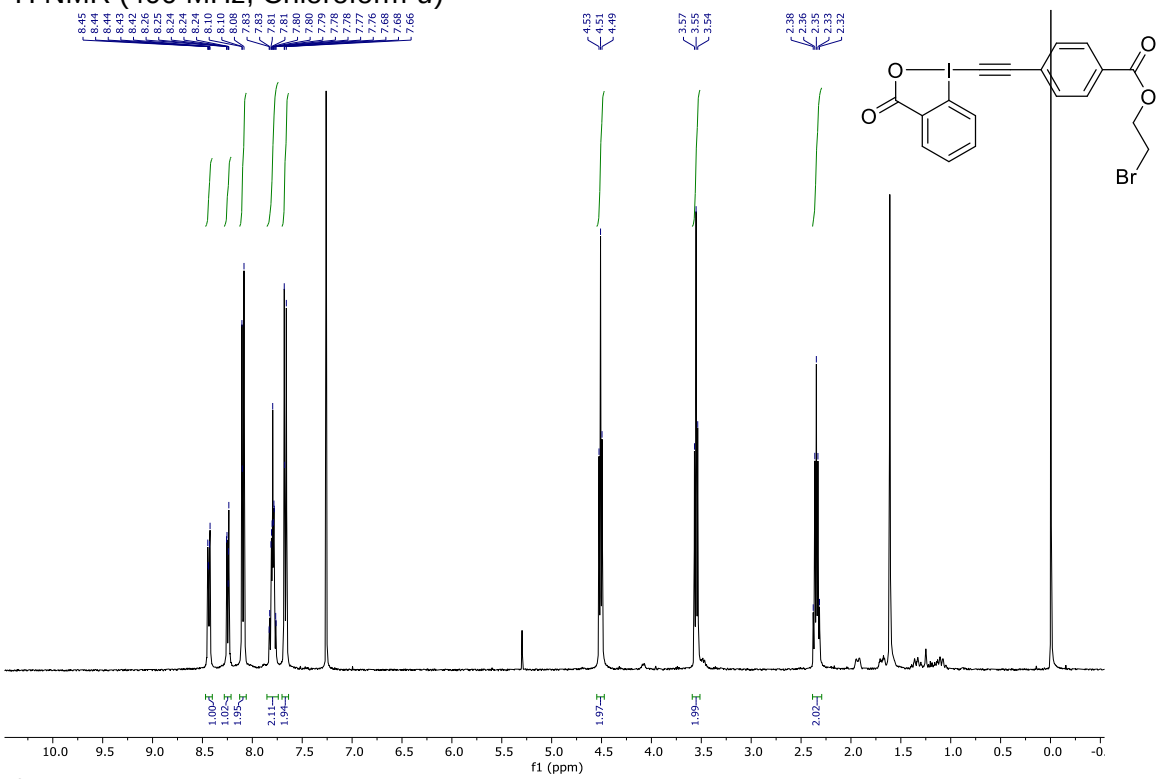
Chapter 9: Annexes

9. Annexes

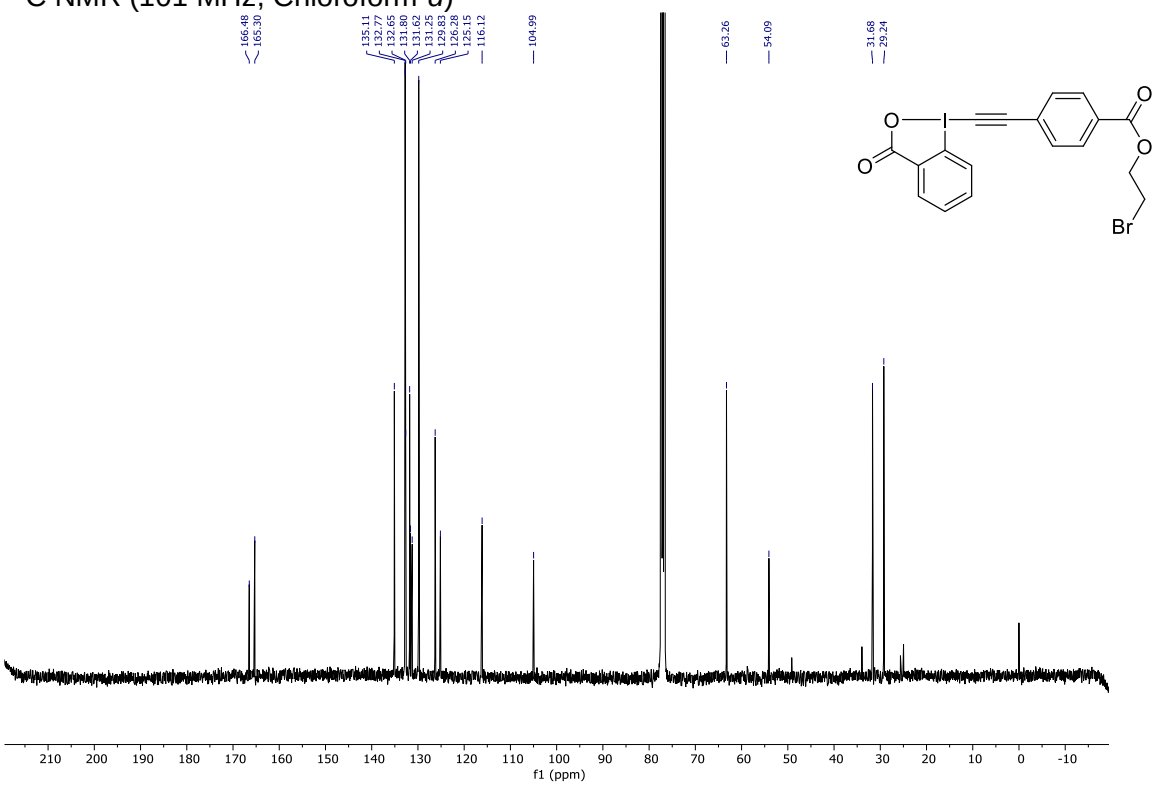
9.1. NMR spectra of new compounds

HIR.2g

^{1}H NMR (400 MHz, Chloroform-*d*)

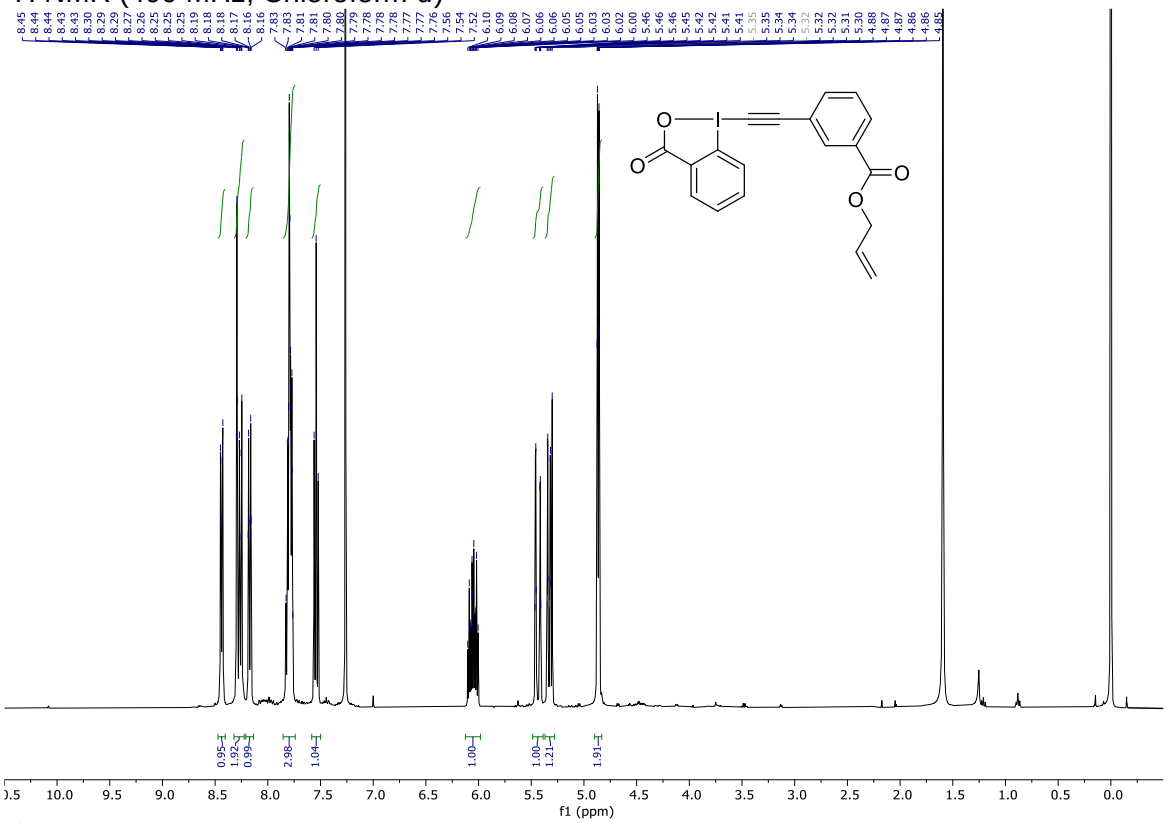


^{13}C NMR (101 MHz, Chloroform-*d*)

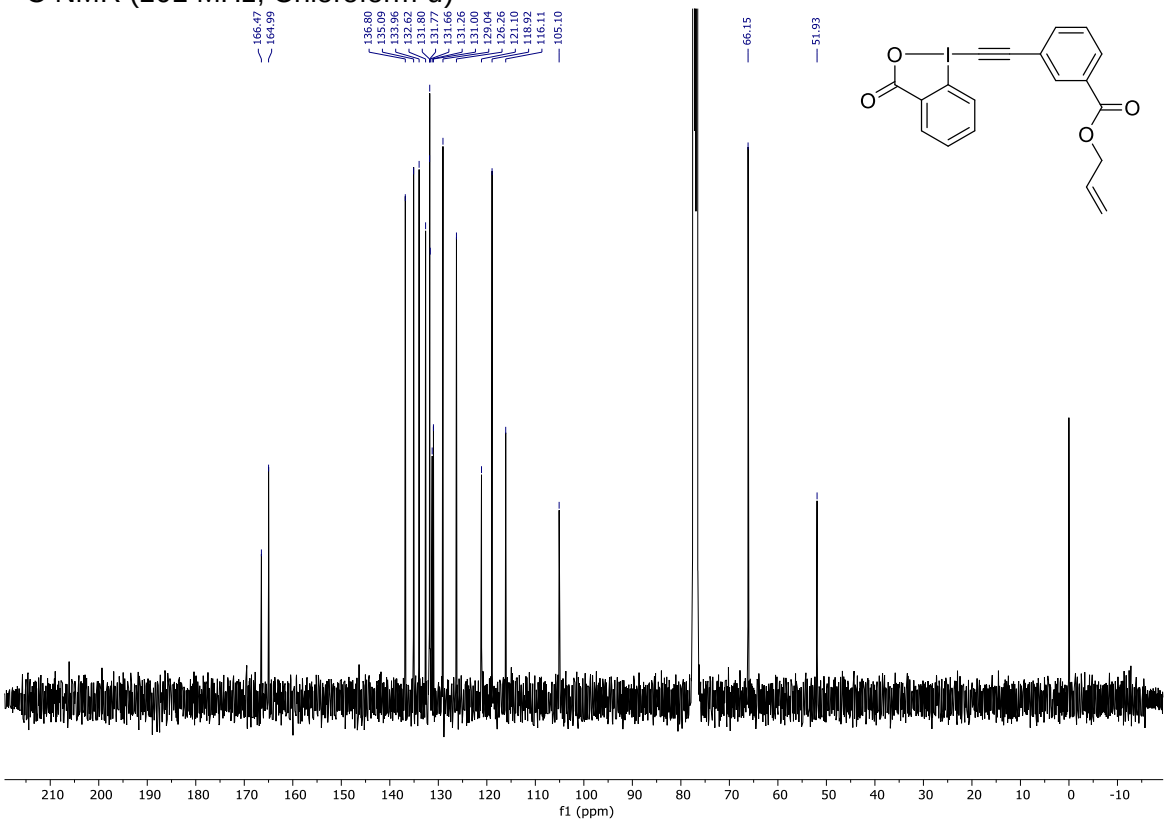


HIR.2h

^{1}H NMR (400 MHz, Chloroform-*d*)

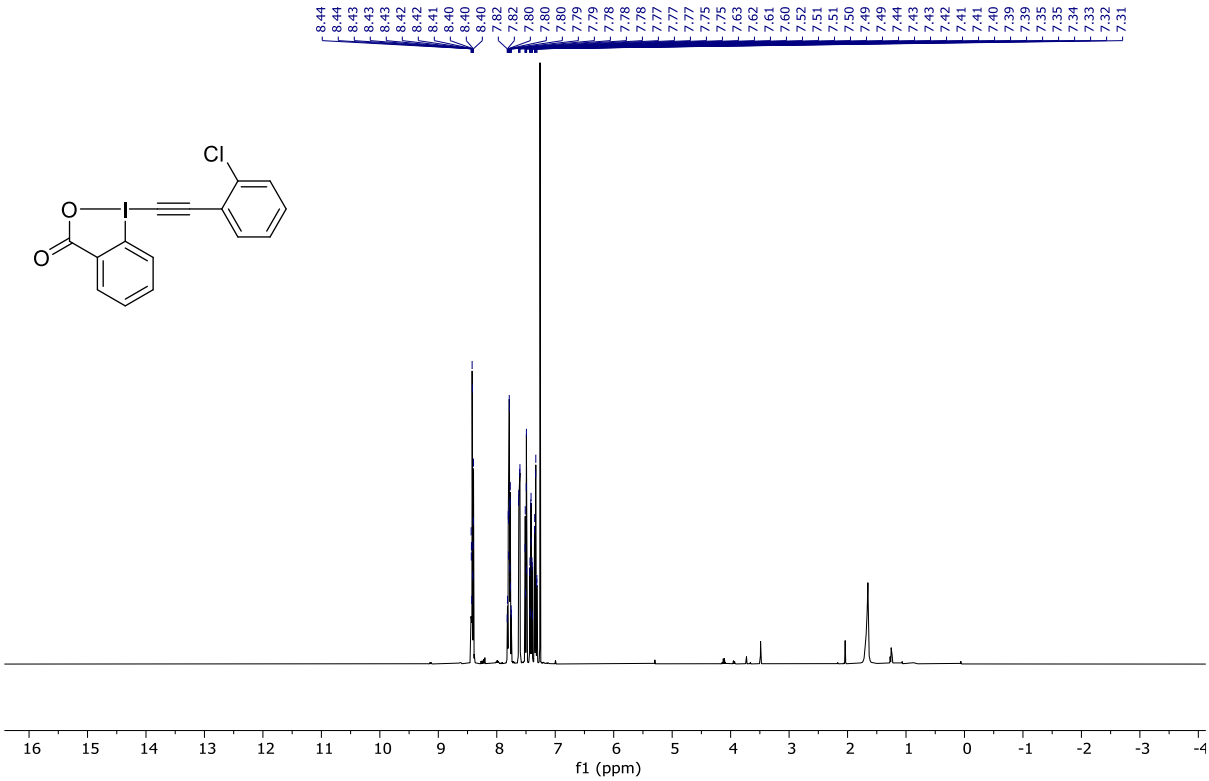


^{13}C NMR (101 MHz, Chloroform-*d*)

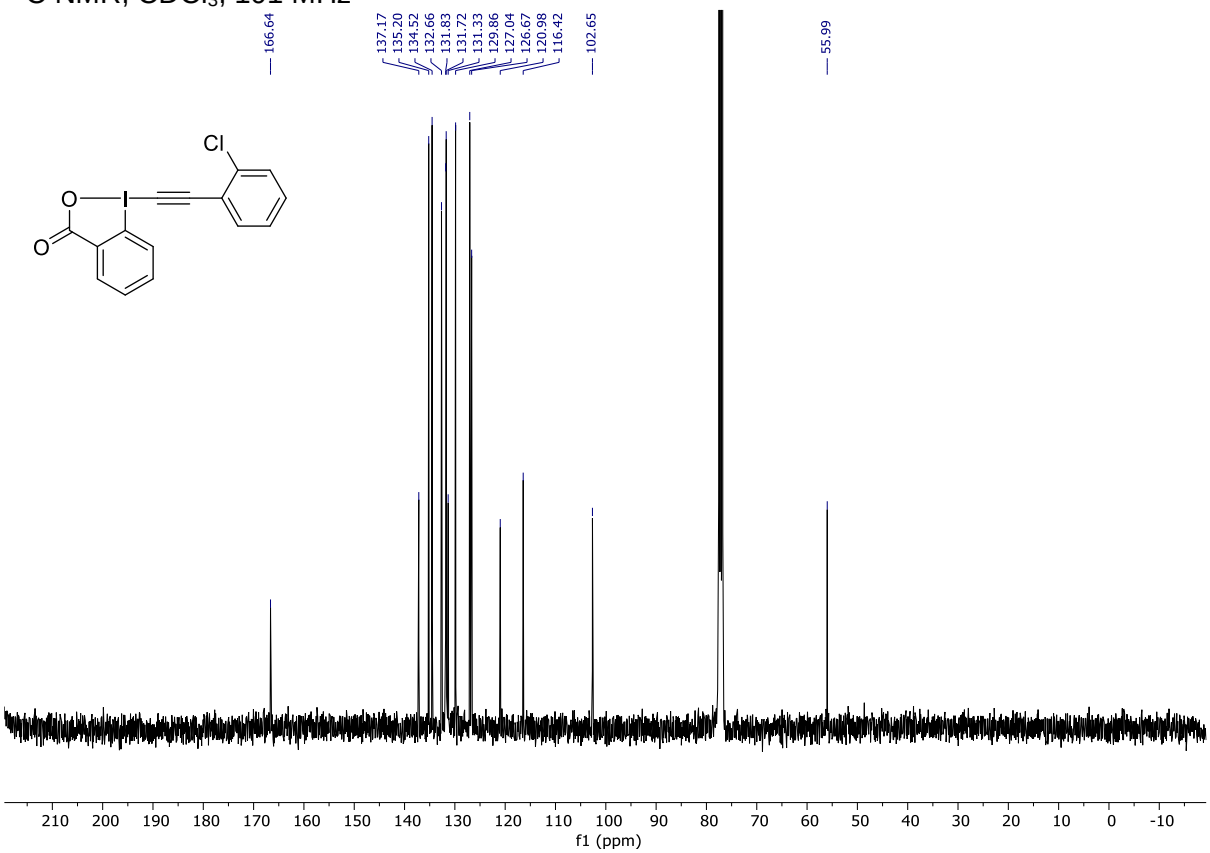


HIR.2i

^{1}H NMR, $CDCl_3$, 400 MHz

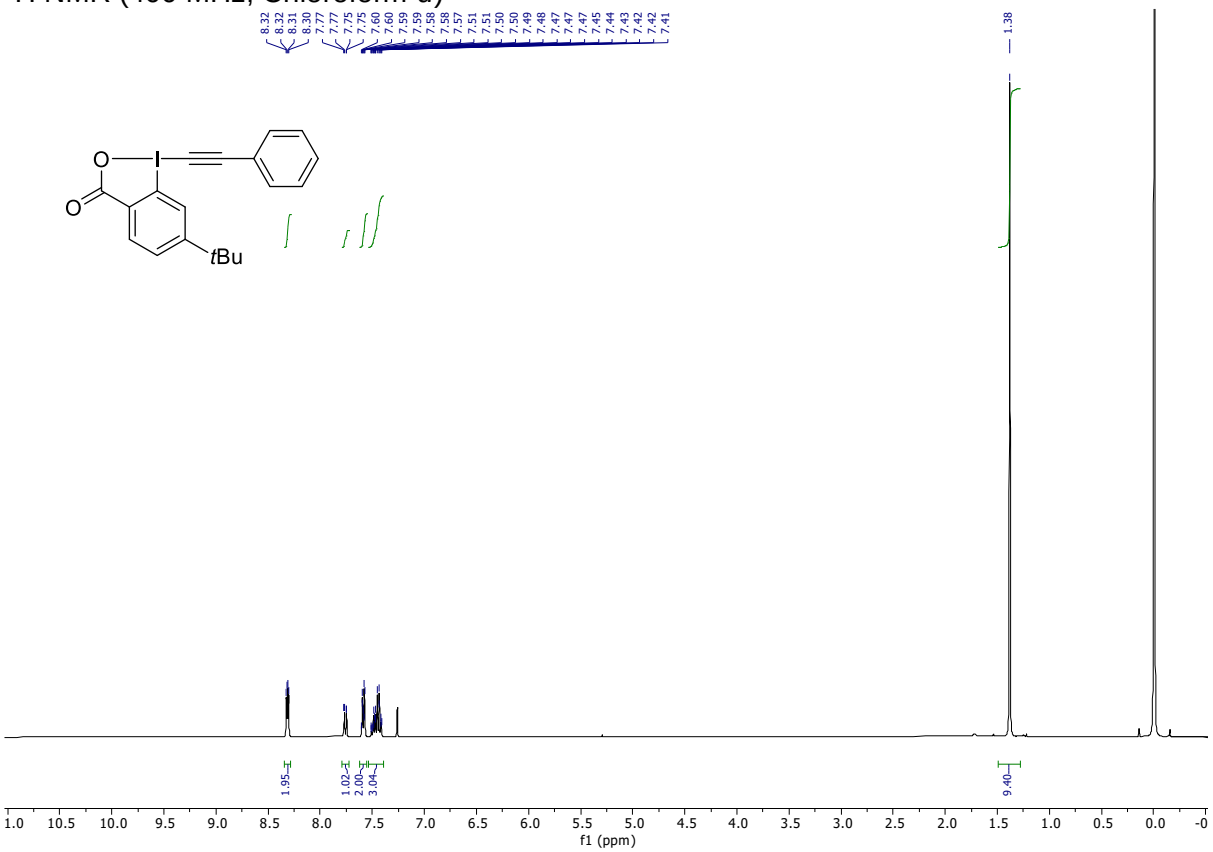


^{13}C NMR, $CDCl_3$, 101 MHz

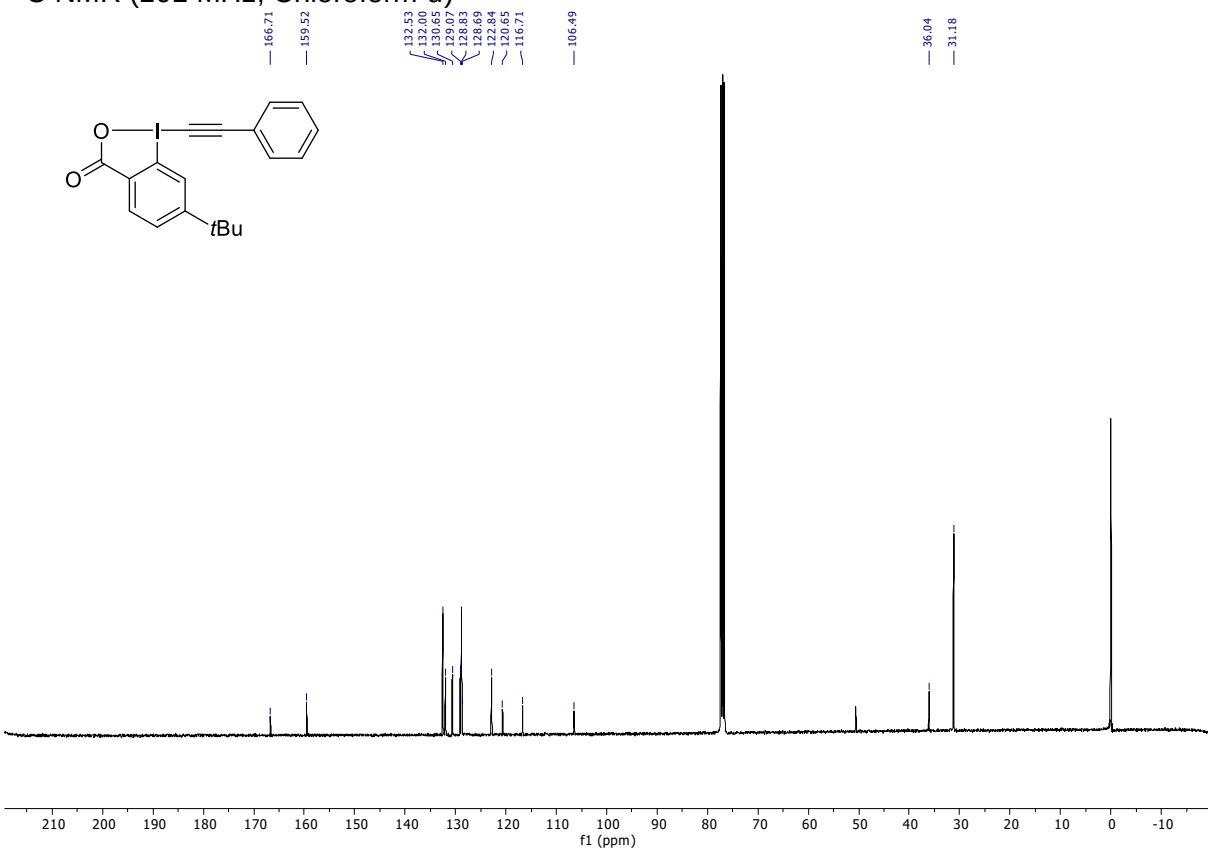


HIR.21

^{1}H NMR (400 MHz, Chloroform-*d*)

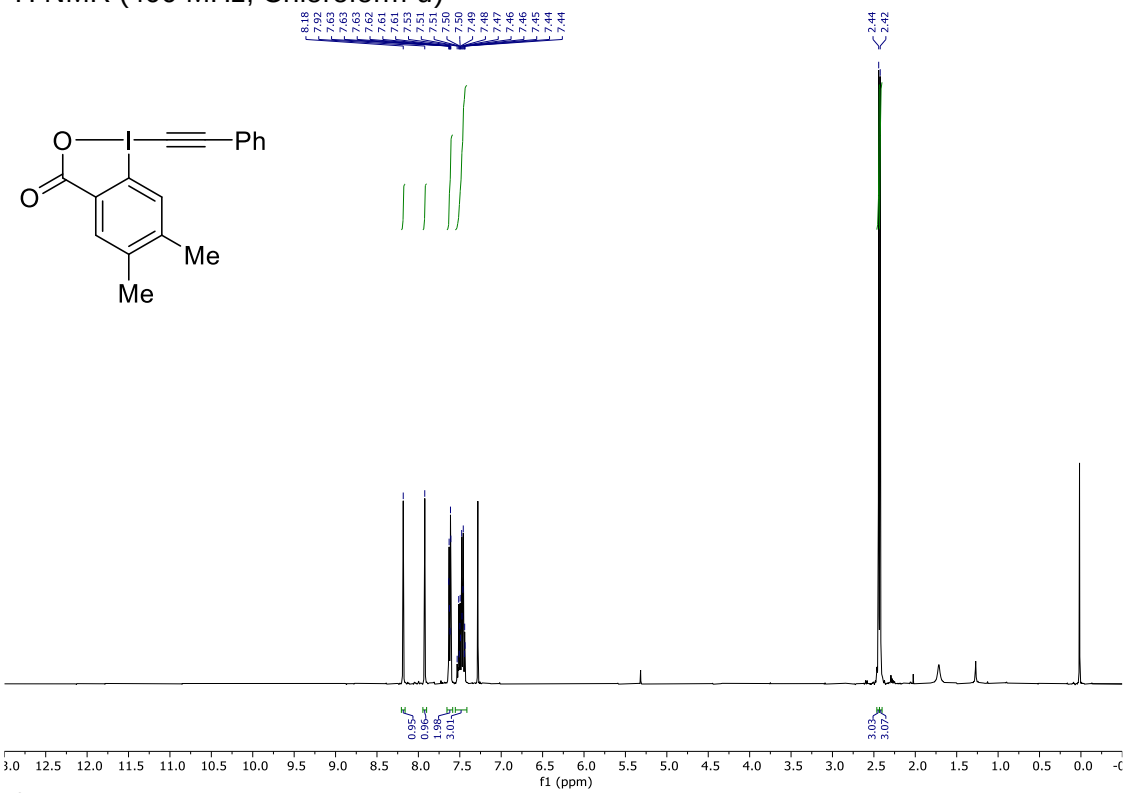


^{13}C NMR (101 MHz, Chloroform-*d*)

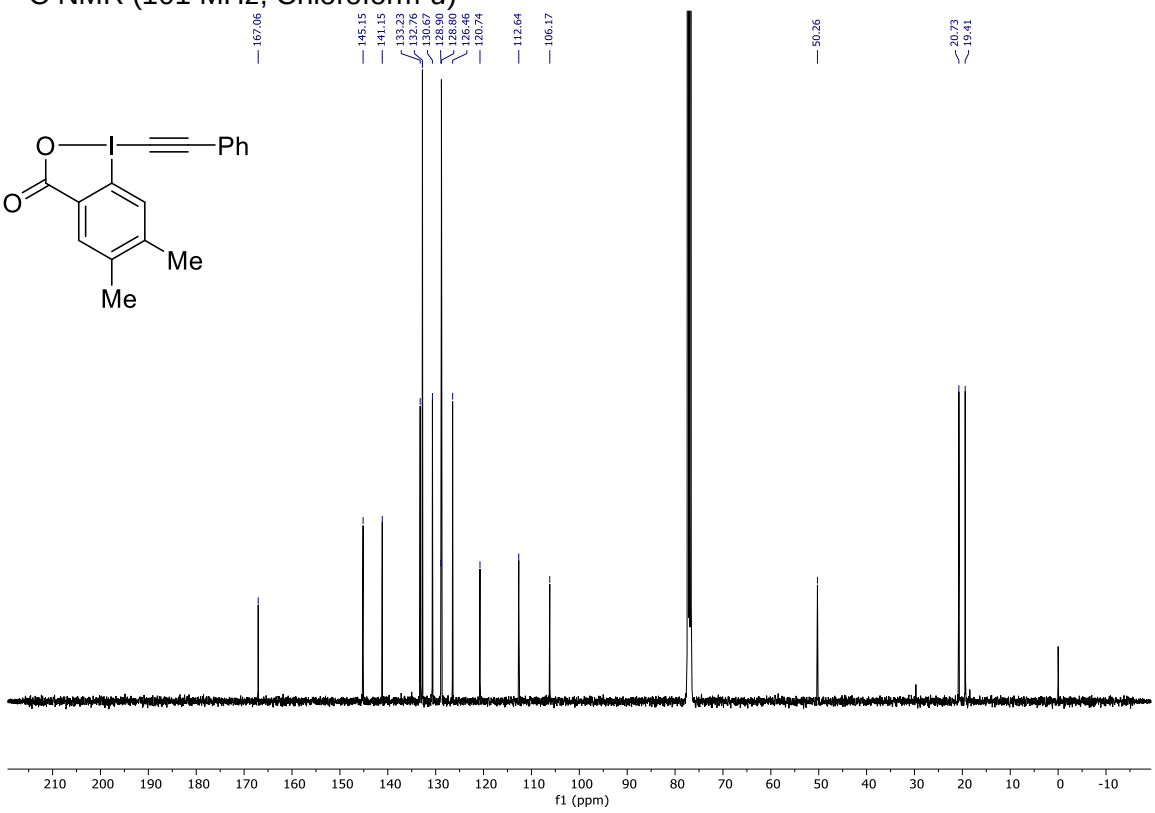


HIR.22

^{1}H NMR (400 MHz, Chloroform-*d*)

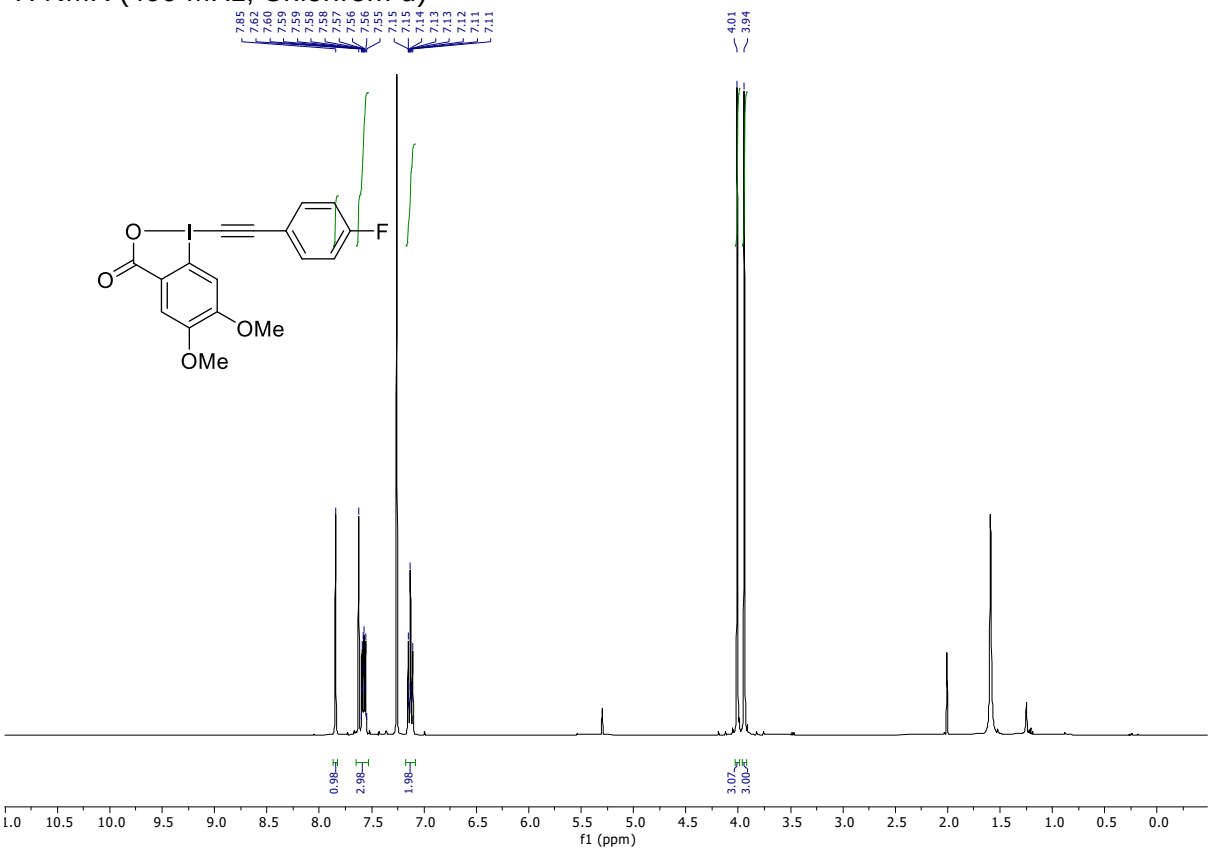


^{13}C NMR (101 MHz, Chloroform-*d*)

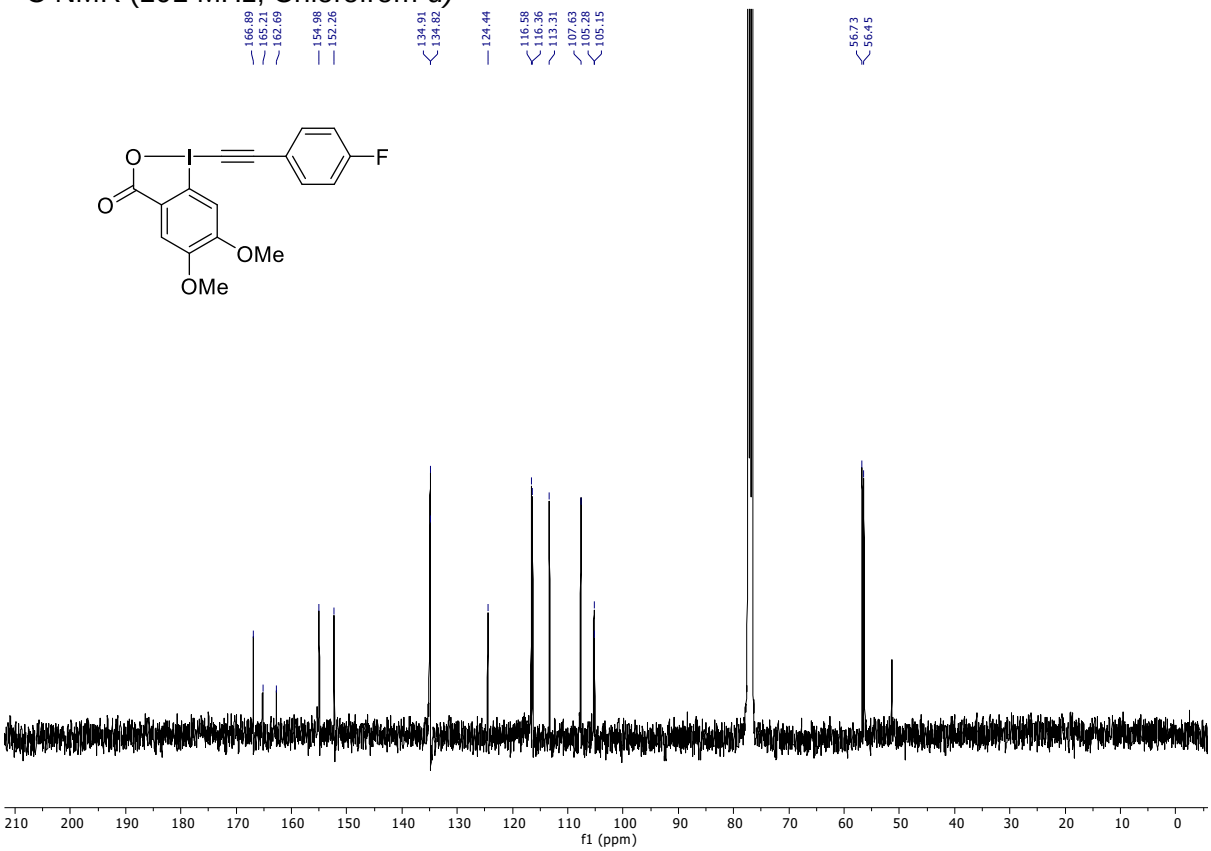


HIR.28

^{1}H NMR (400 MHz, Chlorfrom-*d*)

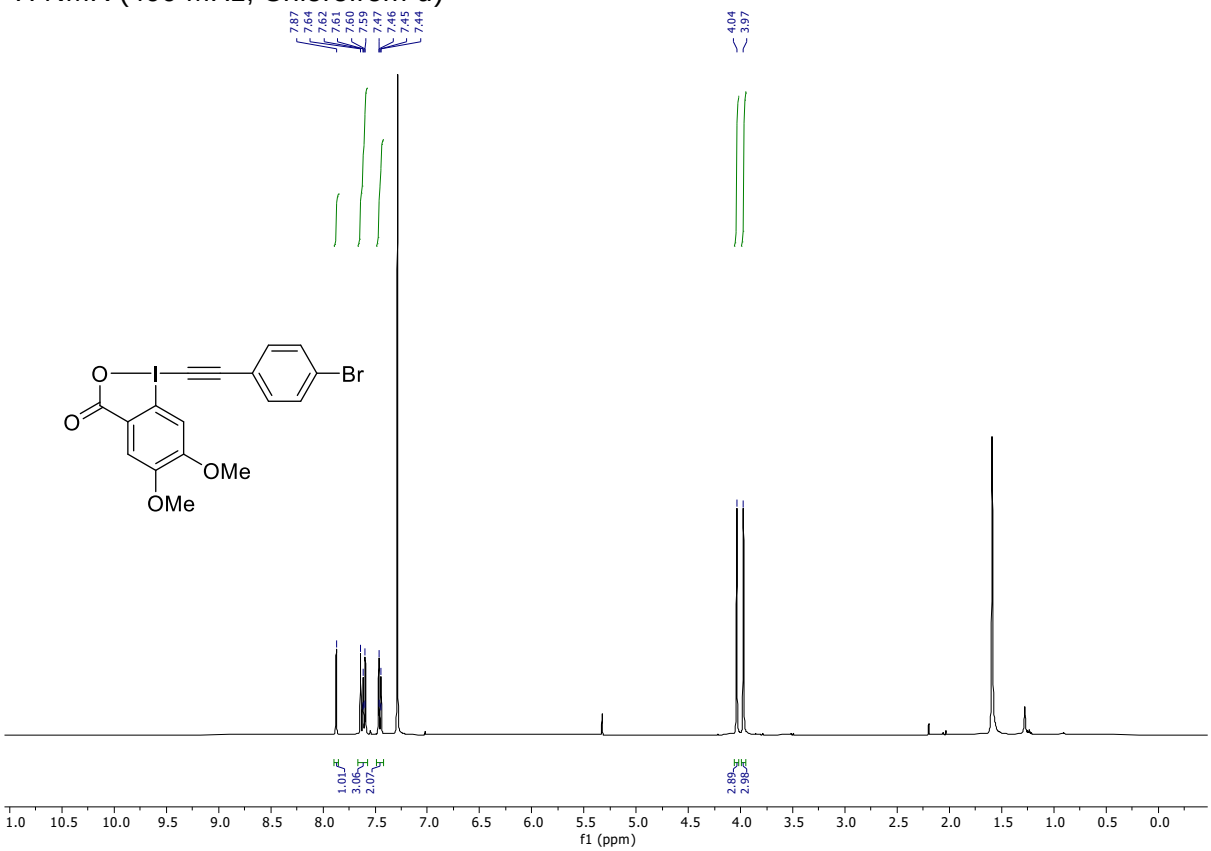


^{13}C NMR (101 MHz, Chlorofrom-*d)*

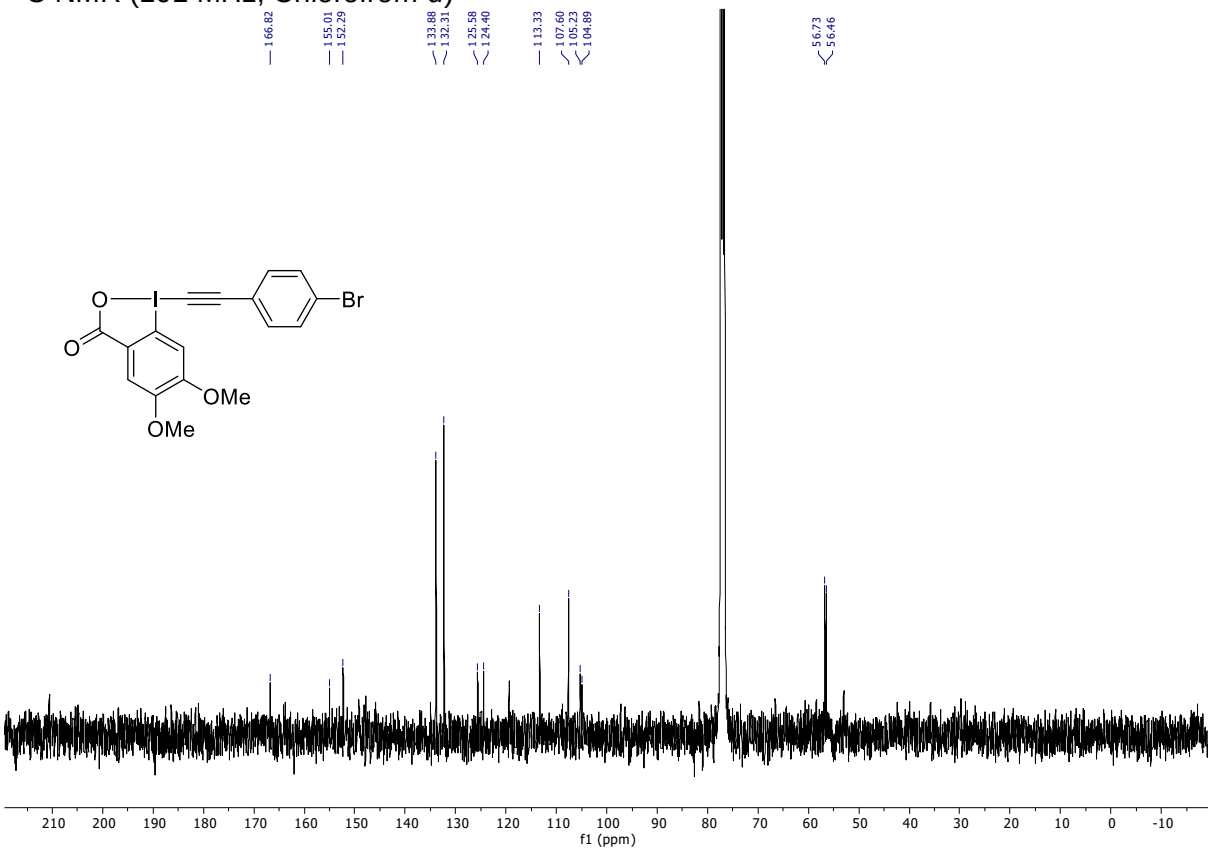


HIR.29

^{1}H NMR (400 MHz, Chlorofrom-*d*)

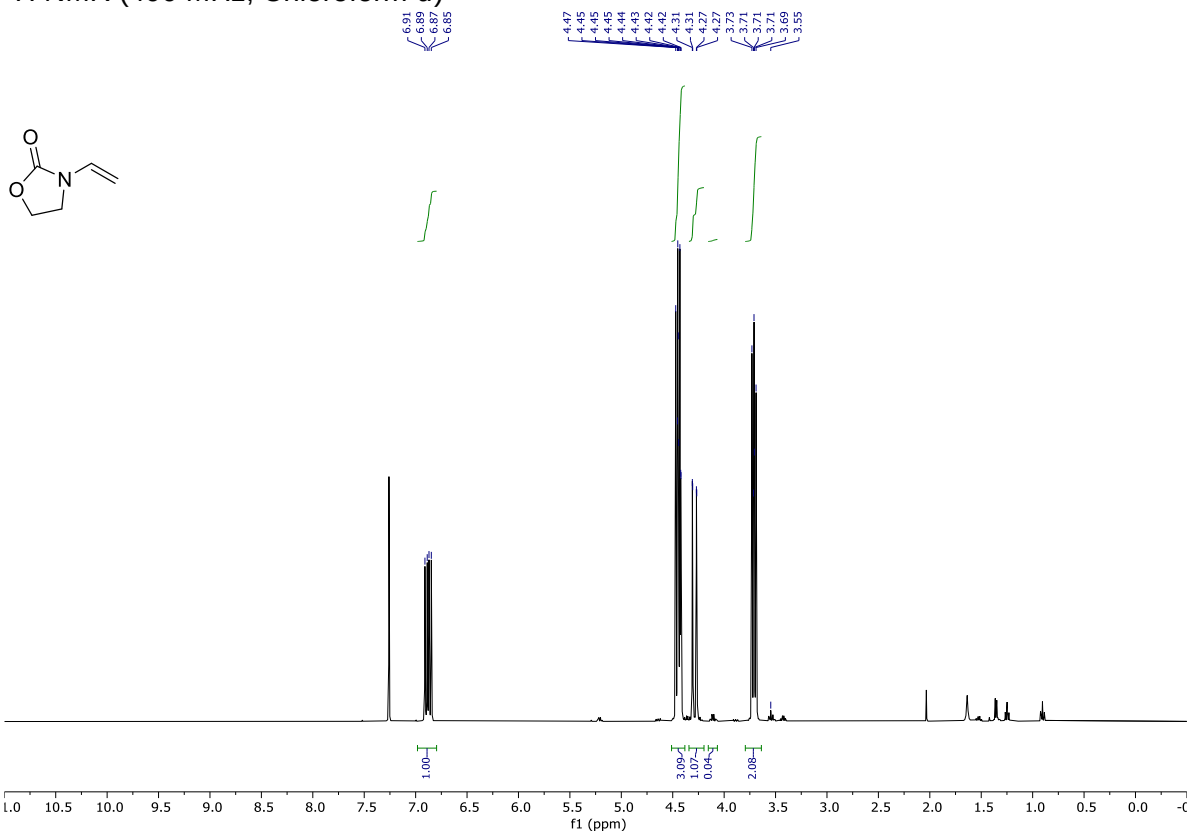


^{13}C NMR (101 MHz, Chlorofrom-*d*)



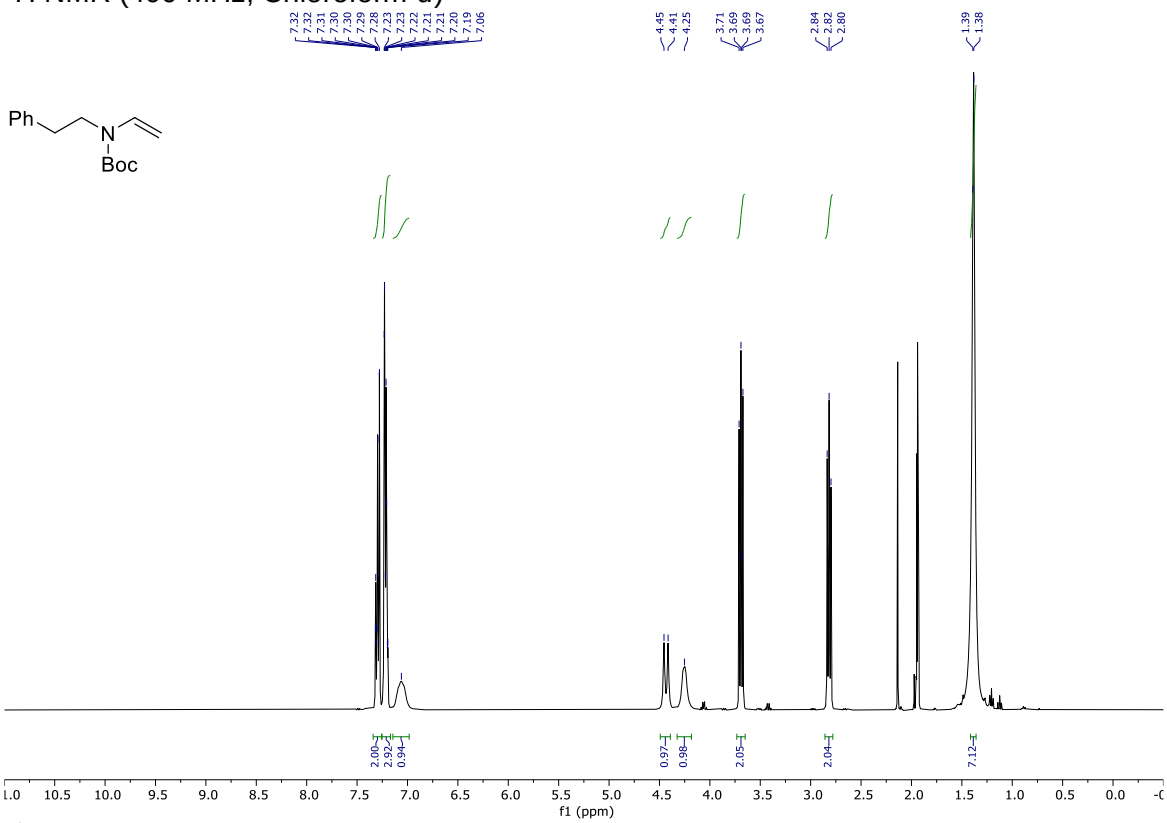
4.3a

^{1}H NMR (400 MHz, Chloroform-*d*)

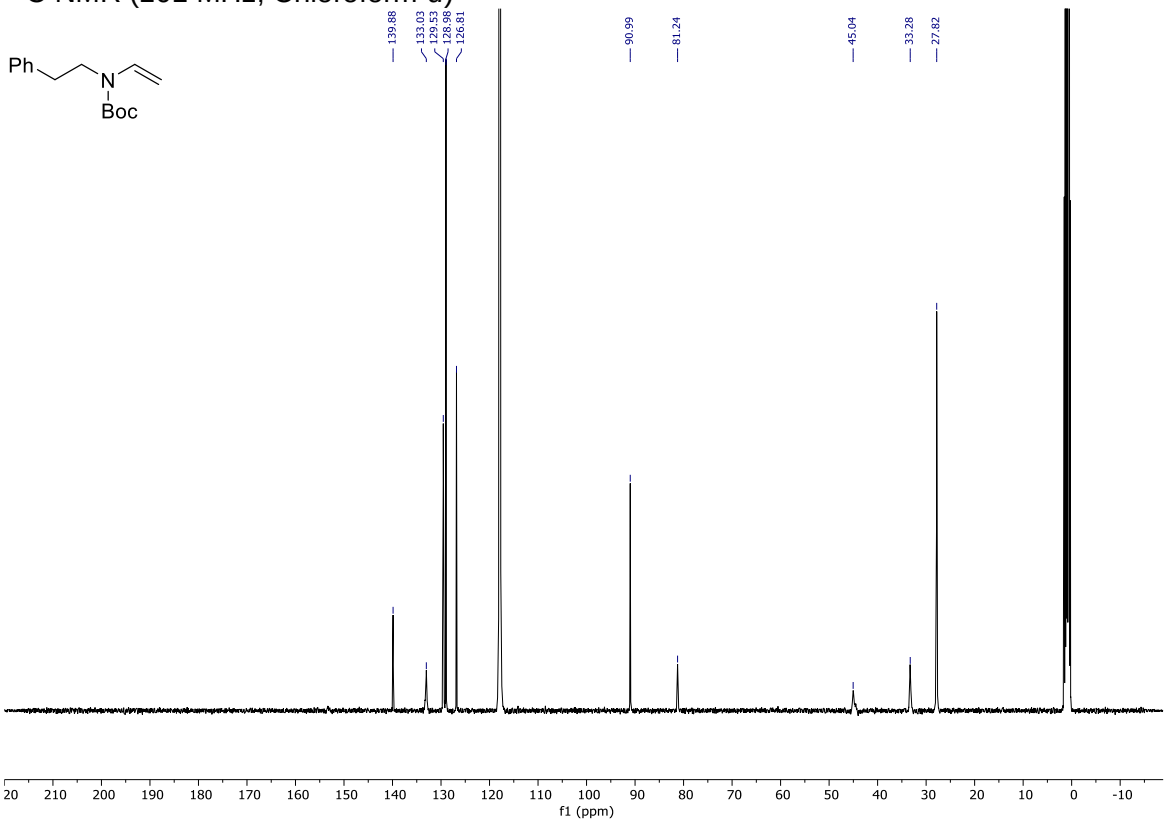


4.3b

^{1}H NMR (400 MHz, Chloroform-*d*)

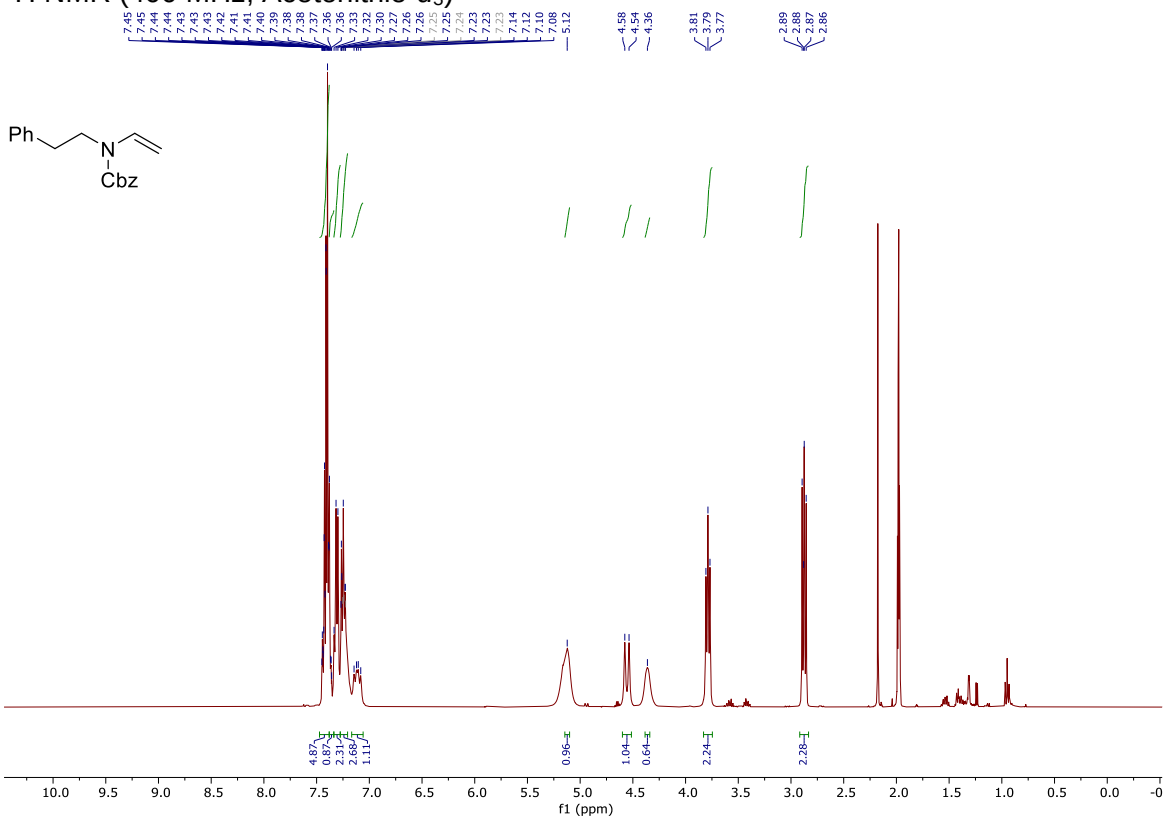


^{13}C NMR (101 MHz, Chloroform-*d*)

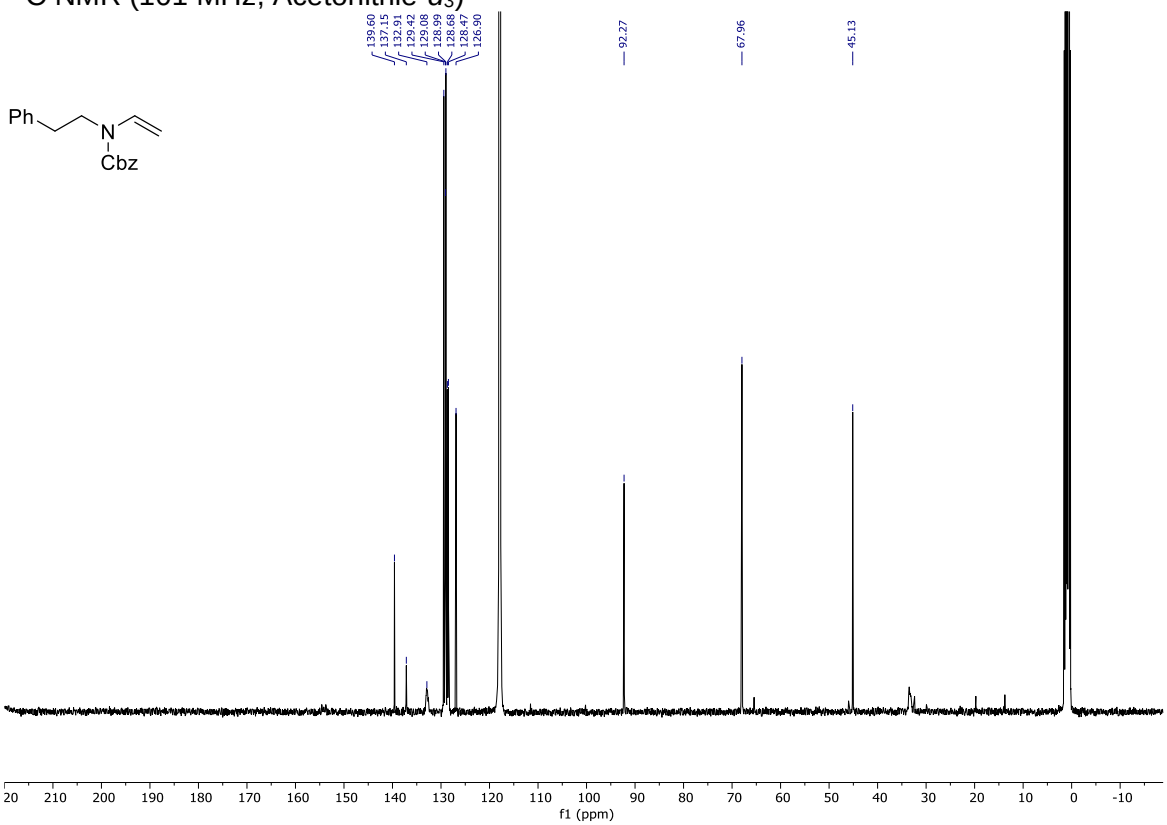


4.3c

^{1}H NMR (400 MHz, Acetonitrile-d_3)

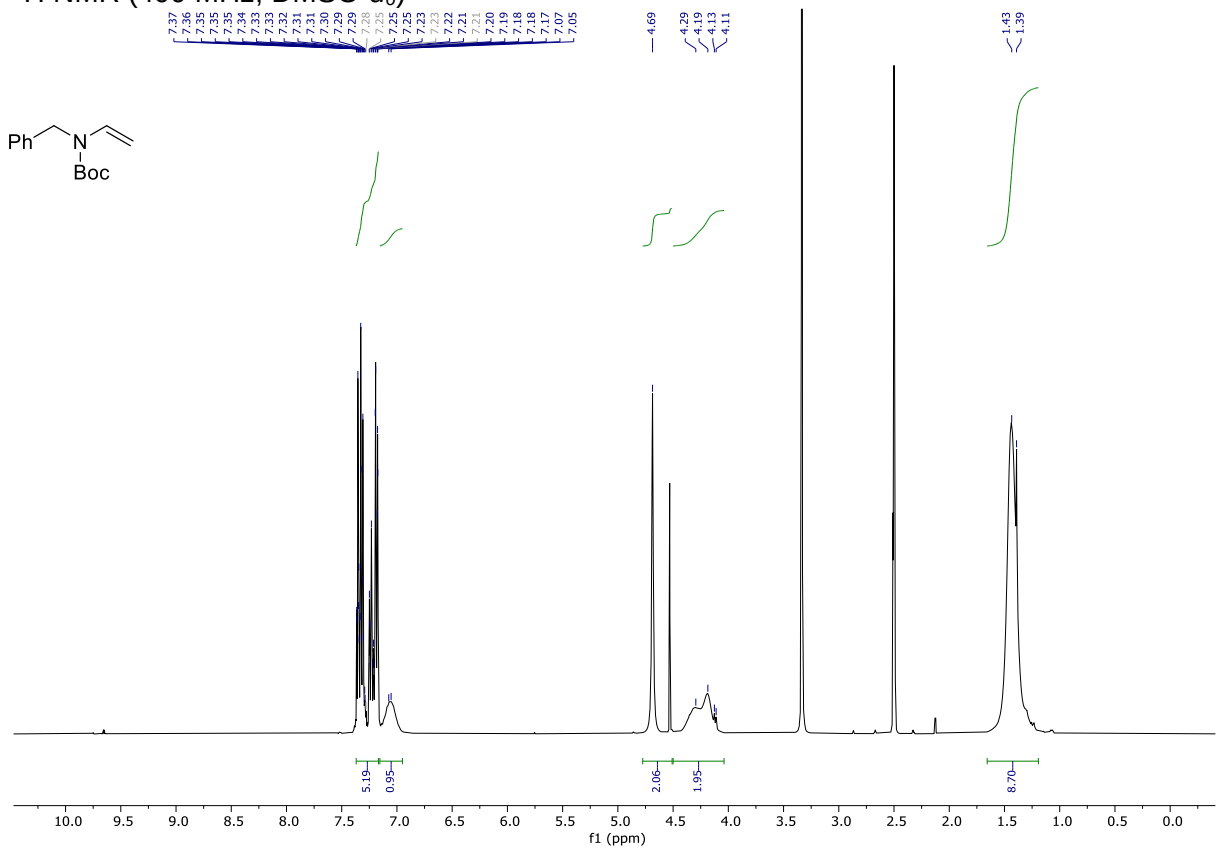


^{13}C NMR (101 MHz, Acetonitrile-d_3)



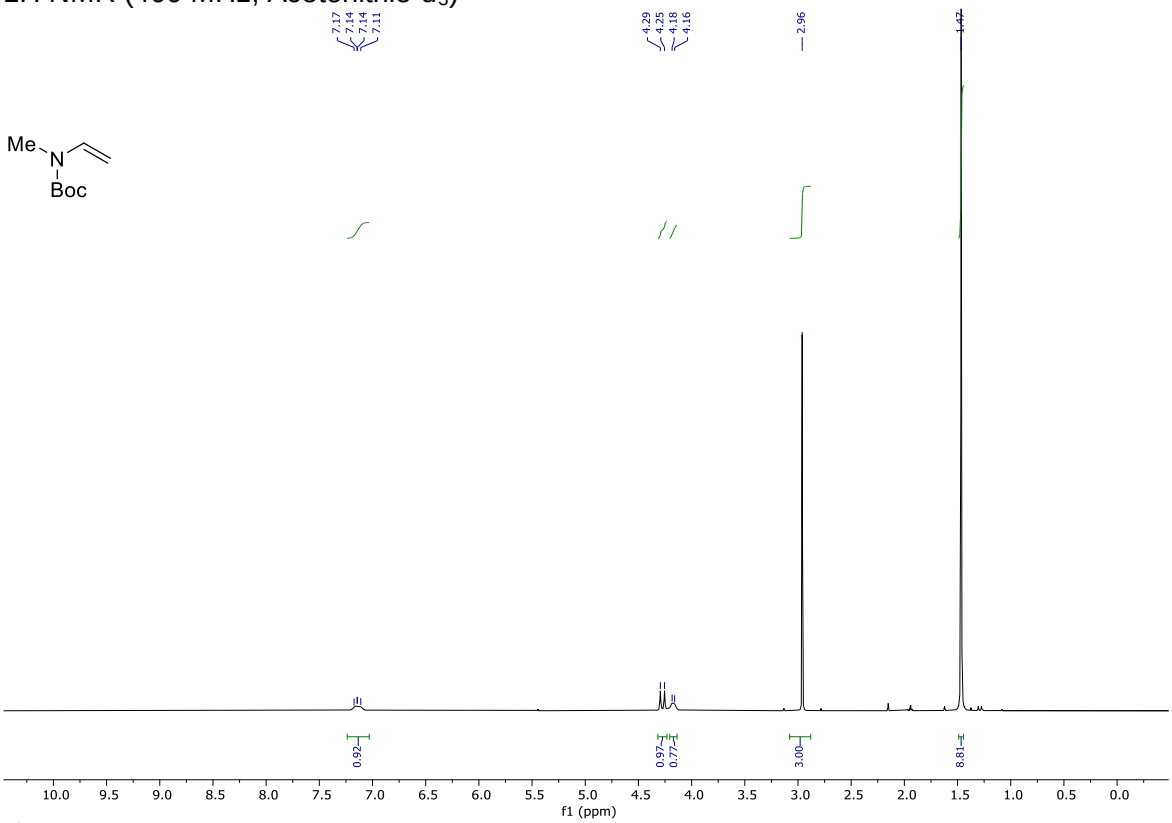
4.3d

^{1}H NMR (400 MHz, DMSO-d_6)

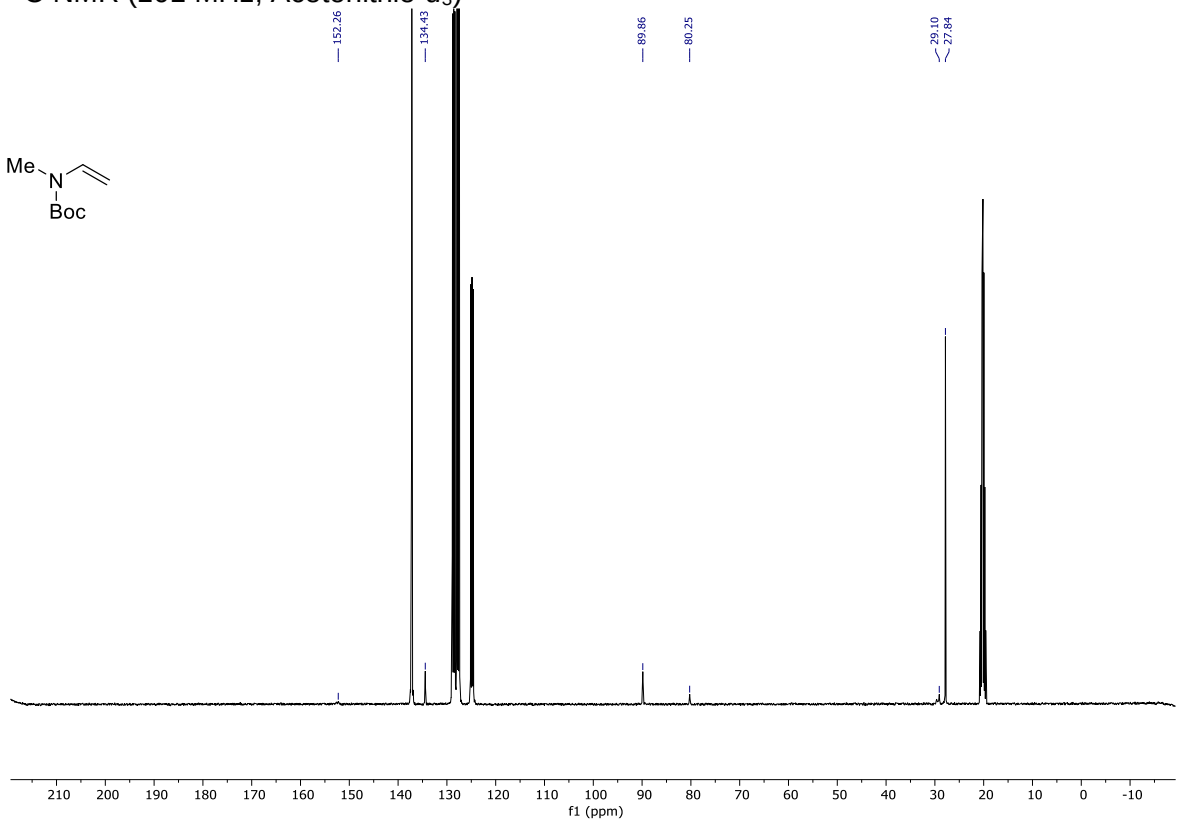


4.3e

1H NMR (400 MHz, Acetonitrile-d_3)

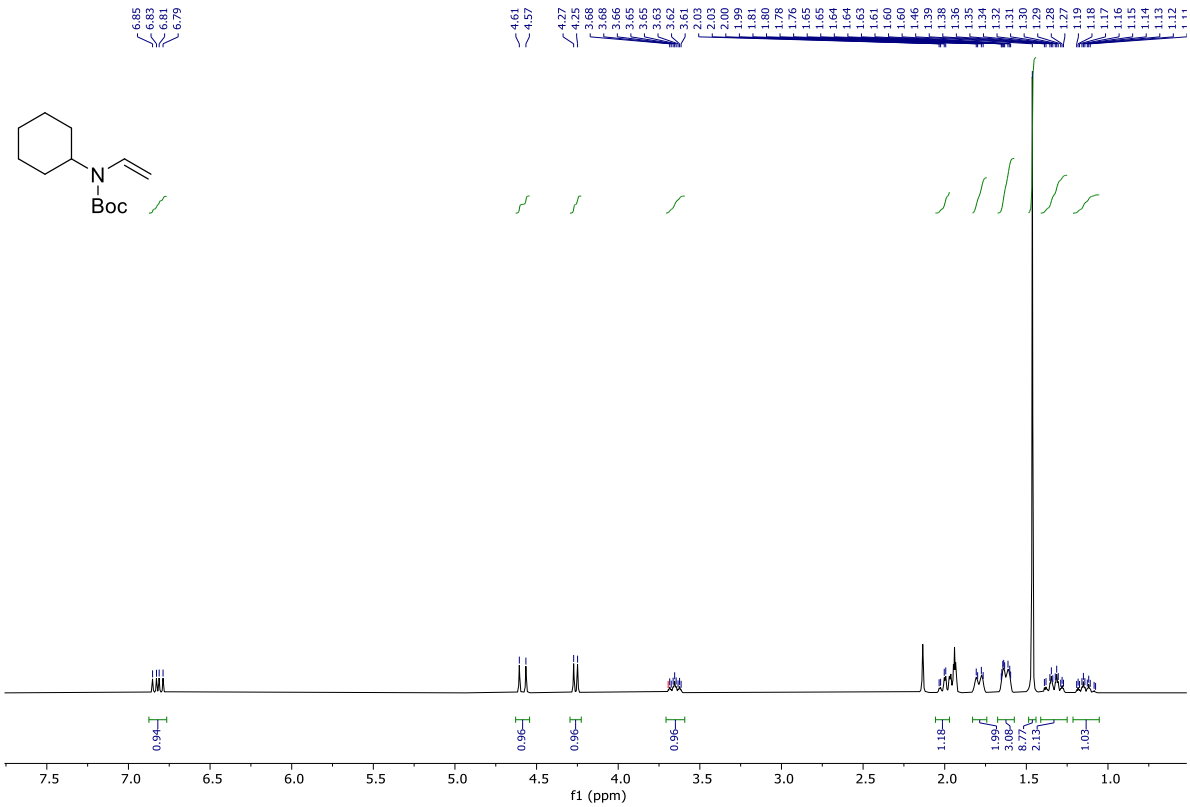


^{13}C NMR (101 MHz, Acetonitrile-d_3)

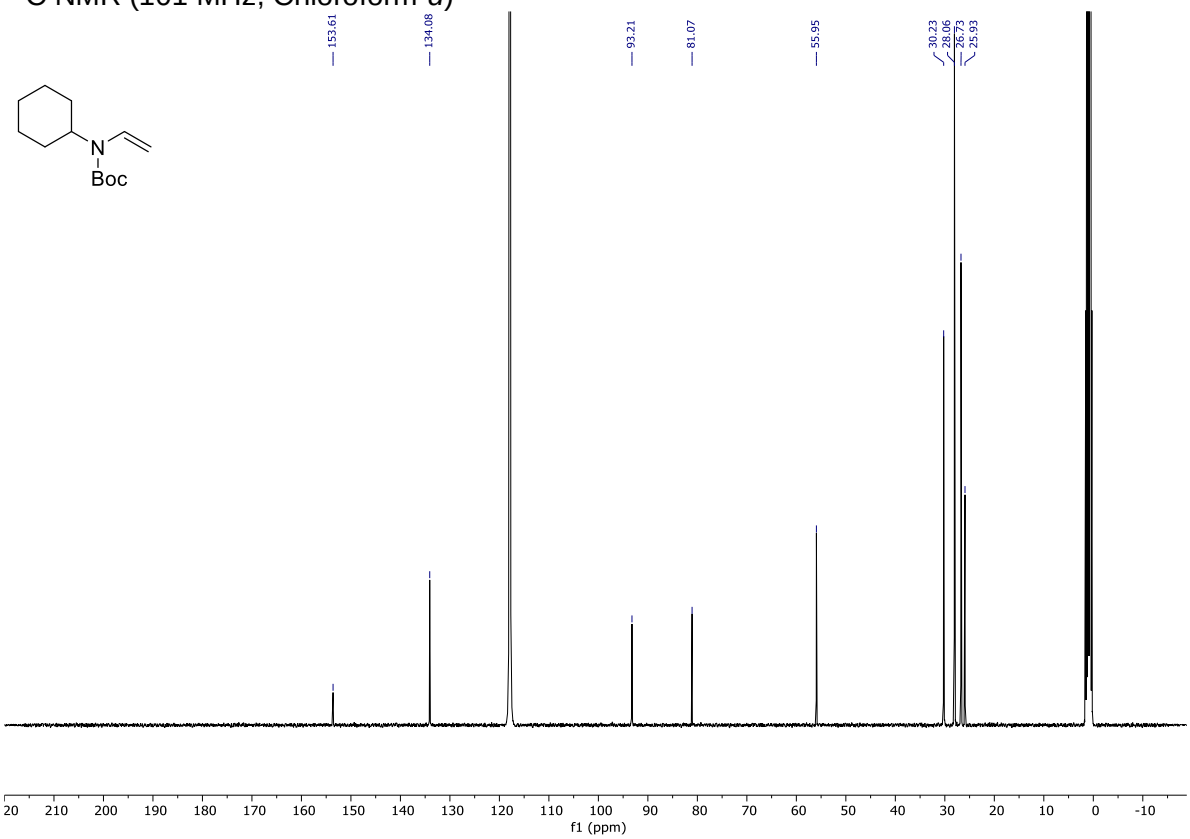


4.3f

^{1}H NMR (400 MHz, Chloroform-*d*)

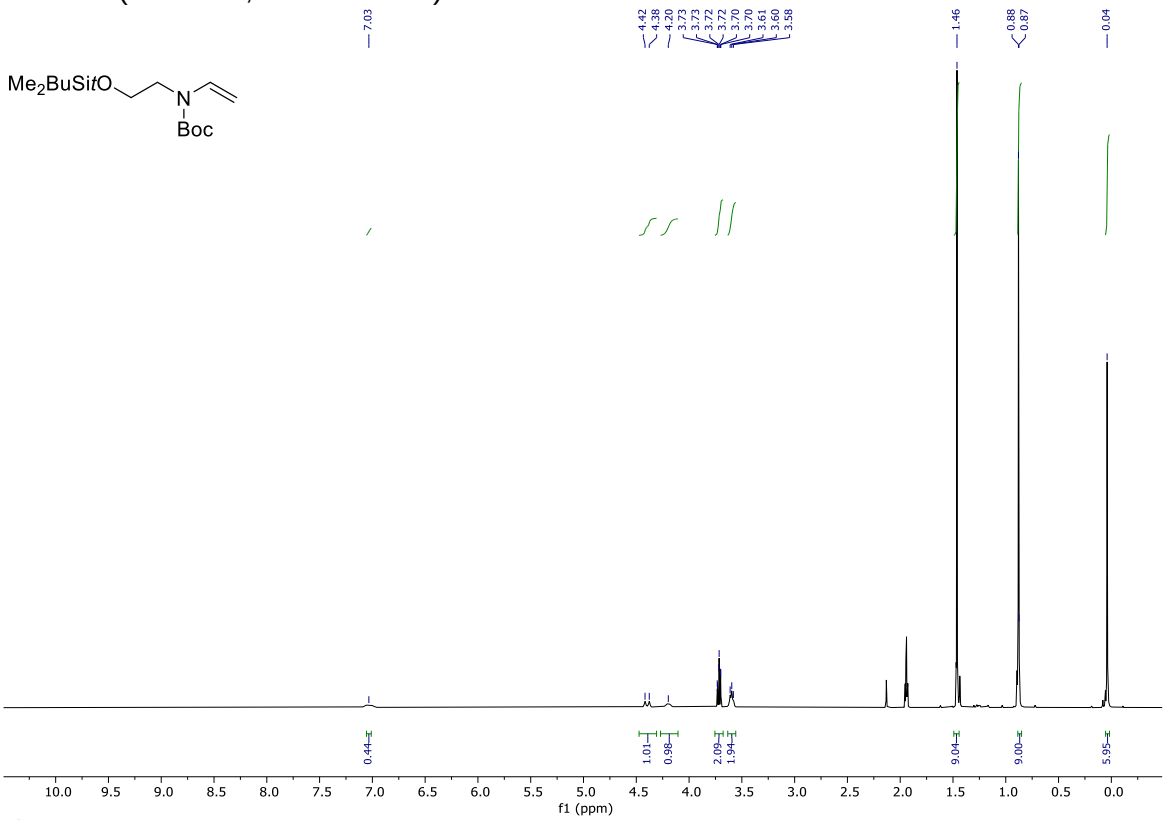


^{13}C NMR (101 MHz, Chloroform-*d*)

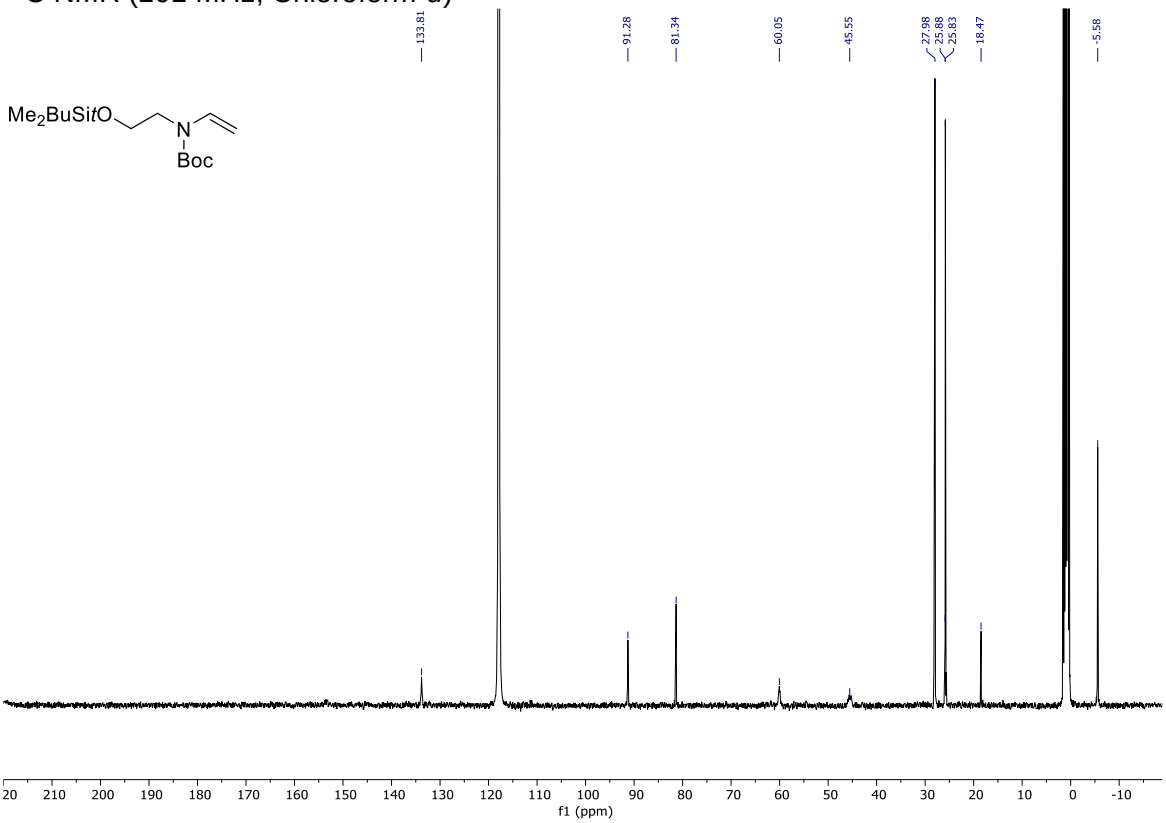


4.3g

^{1}H NMR (400 MHz, Chloroform-*d*)

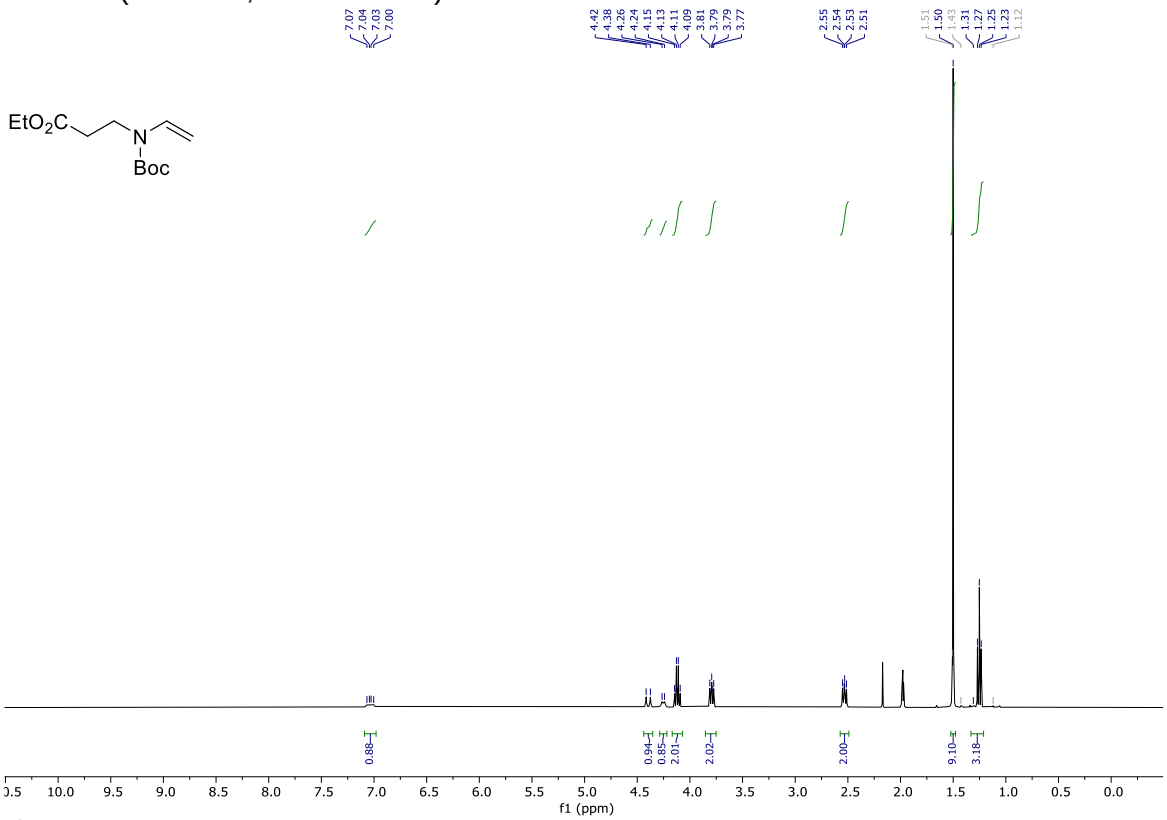


^{13}C NMR (101 MHz, Chloroform-*d*)

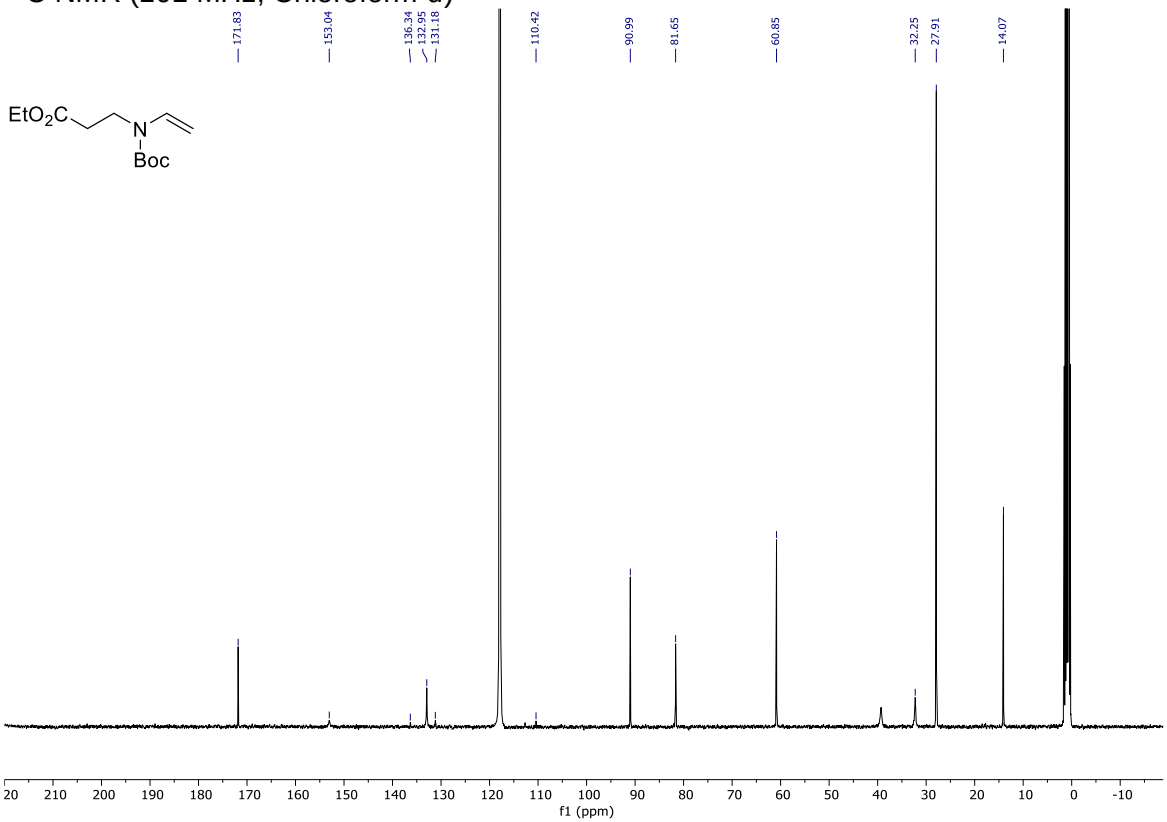


4.3h

^{1}H NMR (400 MHz, Chloroform-*d*)

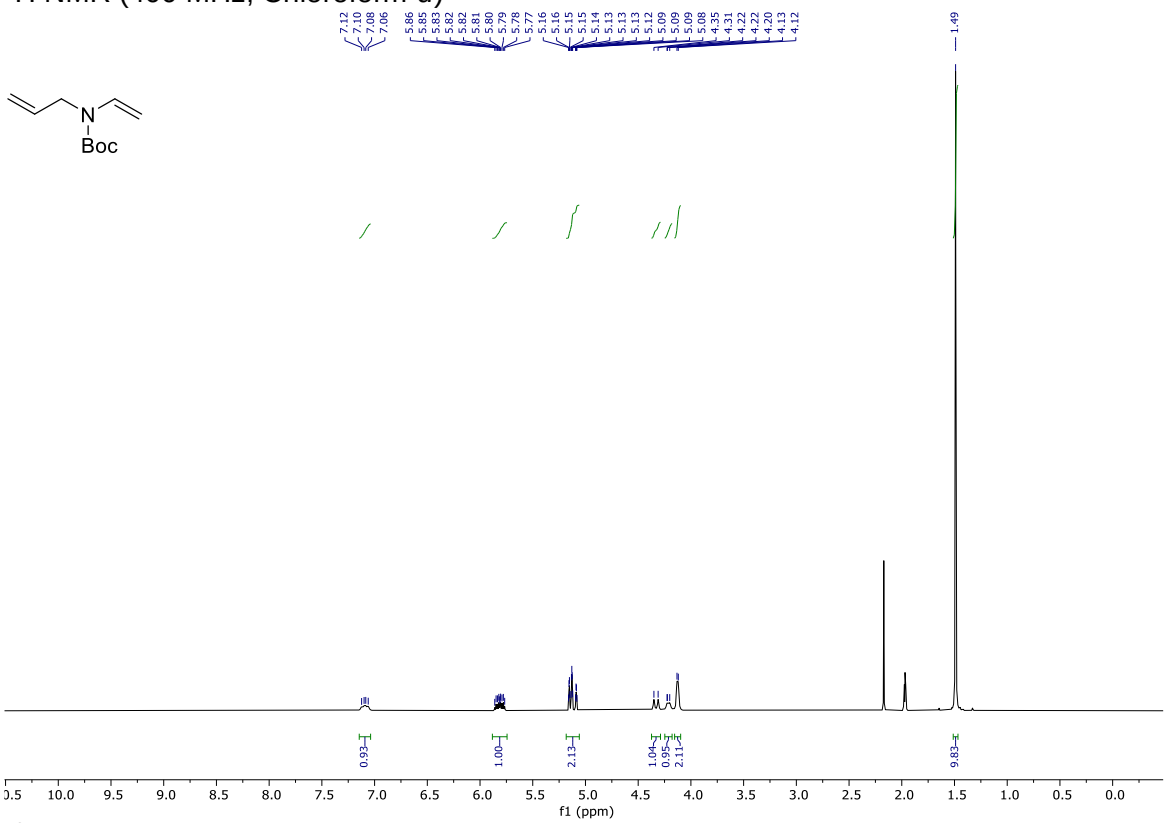


^{13}C NMR (101 MHz, Chloroform-*d*)

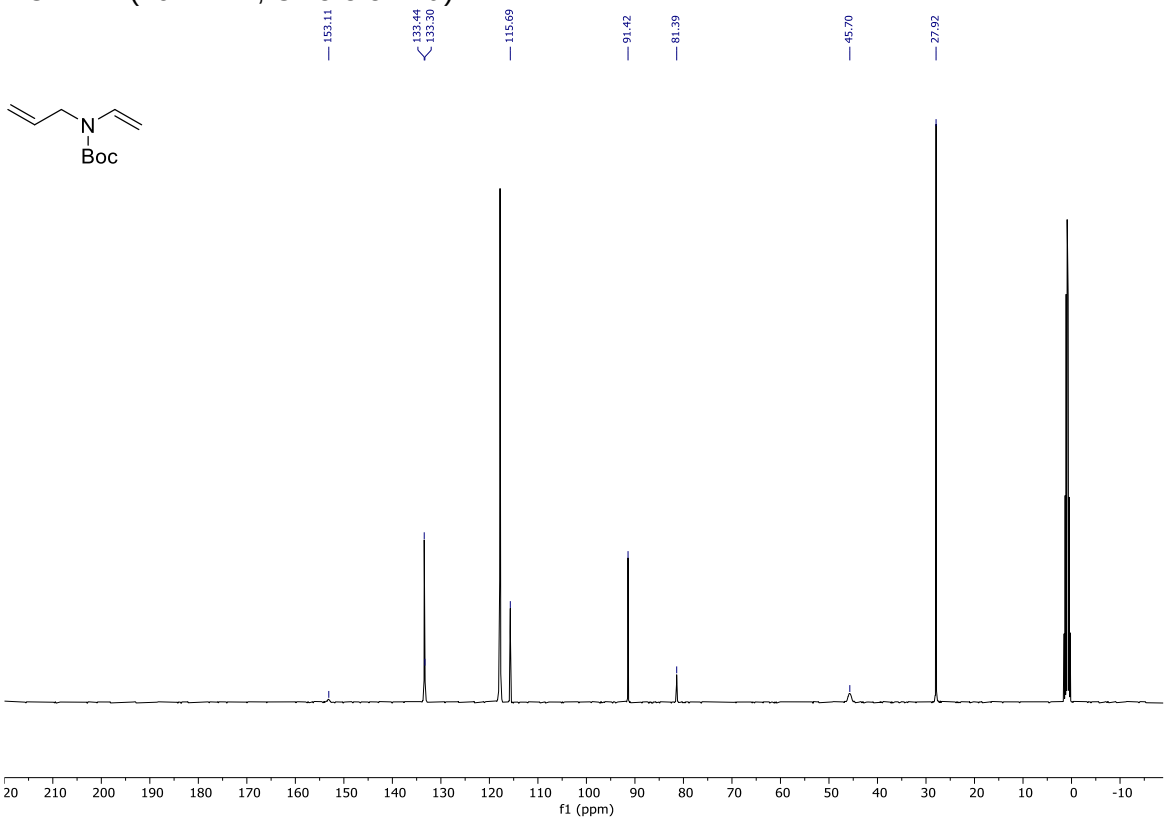


4.3i

^{1}H NMR (400 MHz, Chloroform-*d*)

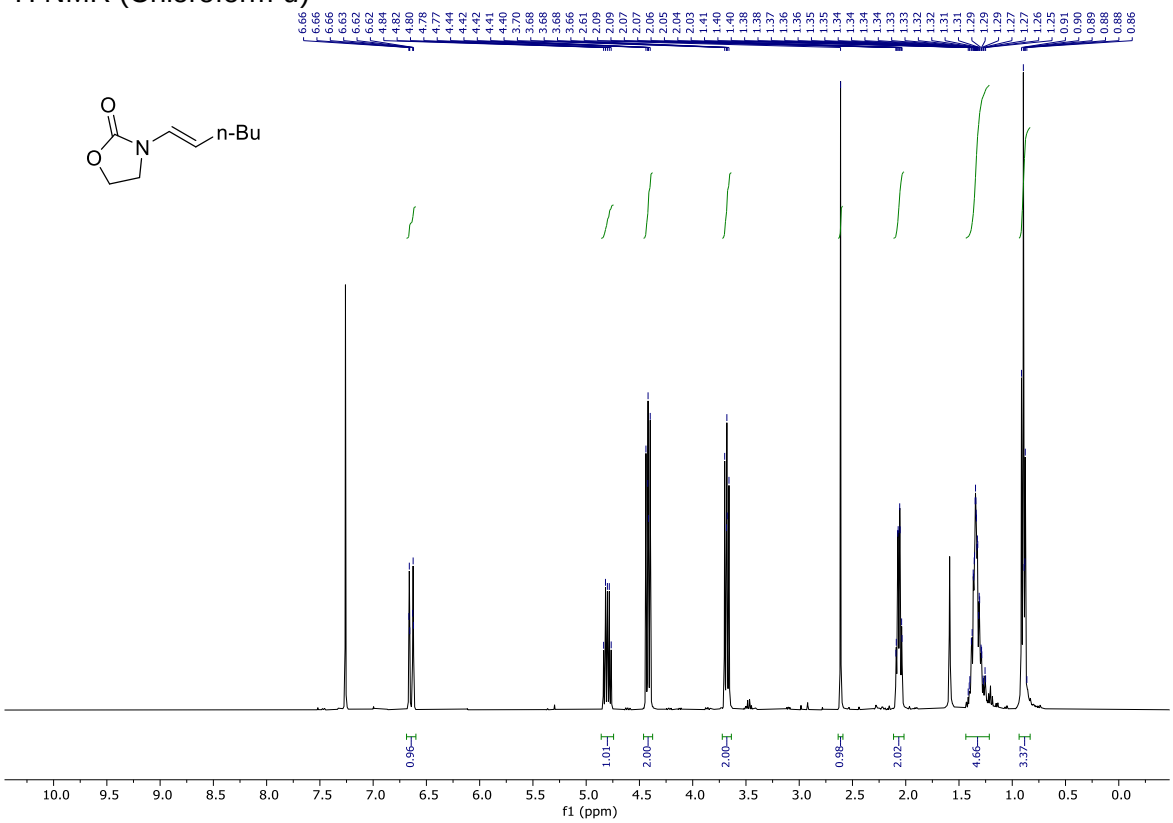


^{13}C NMR (101 MHz, Chloroform-*d*)



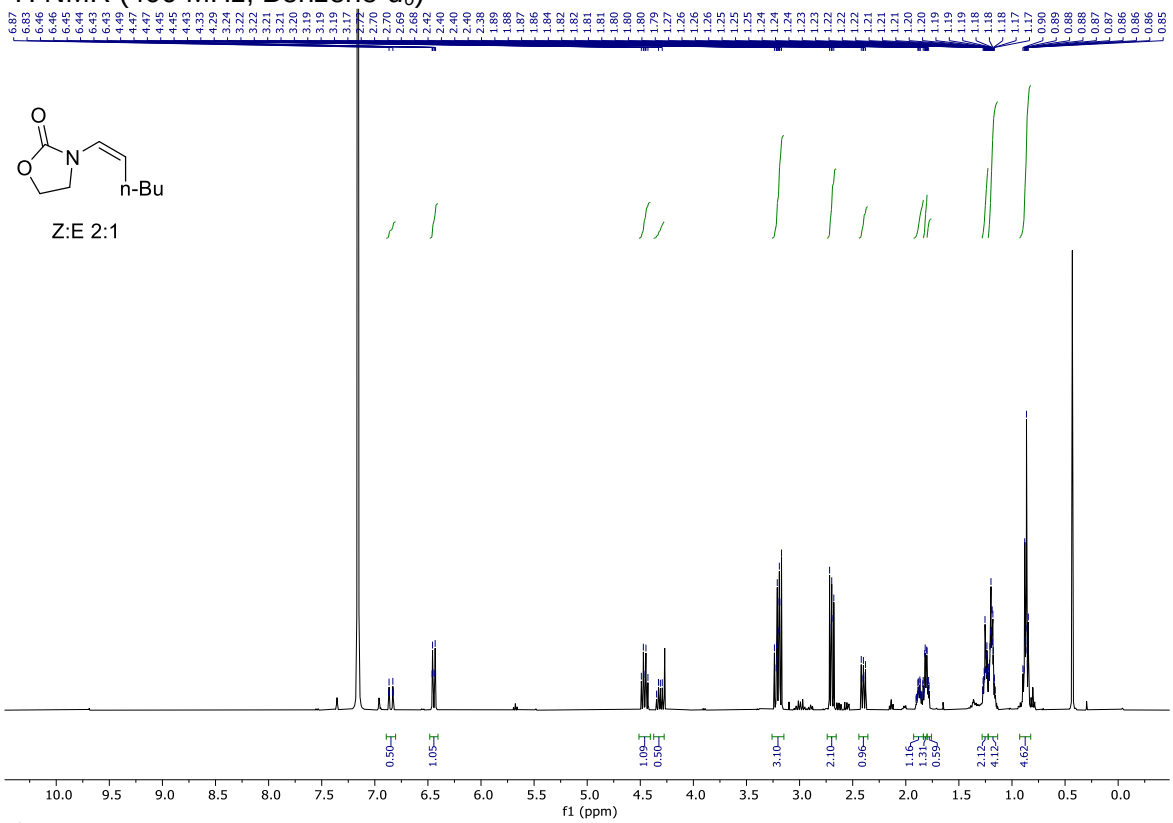
(*E*)-4.3k

^{1}H NMR (Chloroform-*d*)

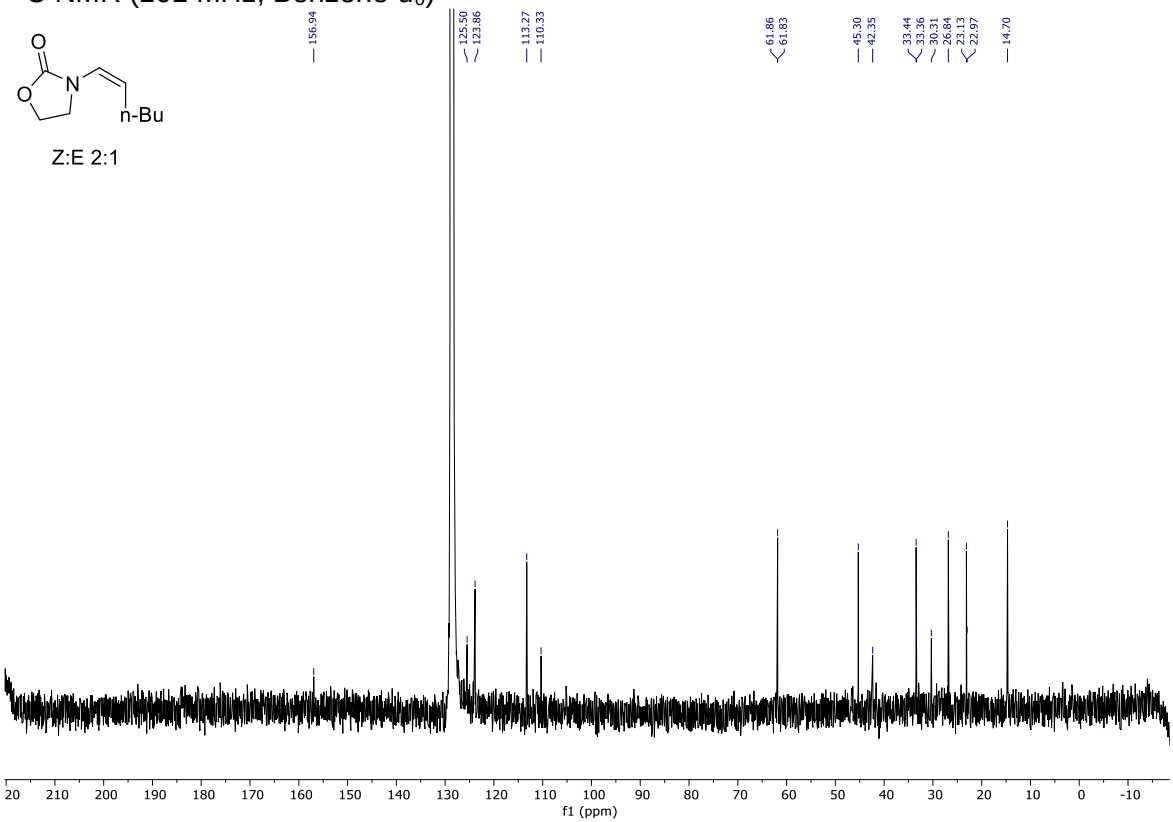


(*Z*)-4.3k + (*E*)-4.3k – (*Z*:*E*) 2:1

^{1}H NMR (400 MHz, Benzene-d_6)

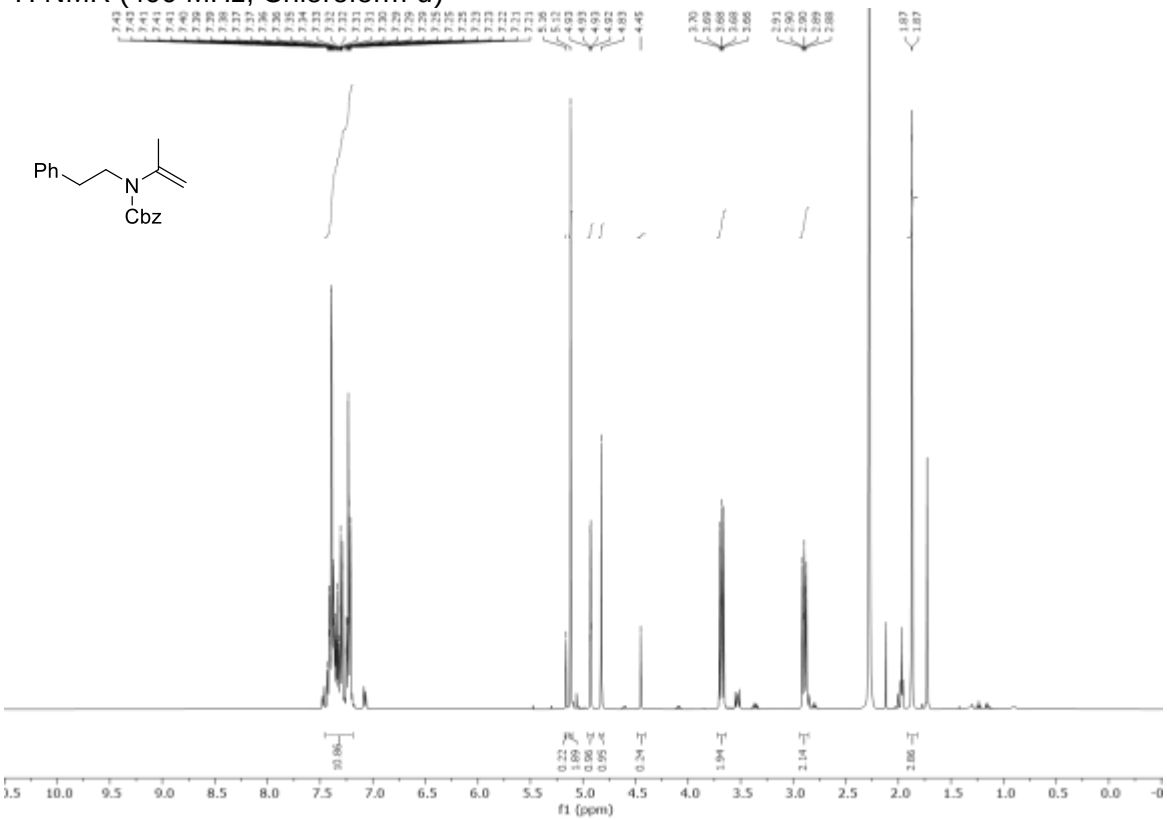


^{13}C NMR (101 MHz, Benzene-d_6)

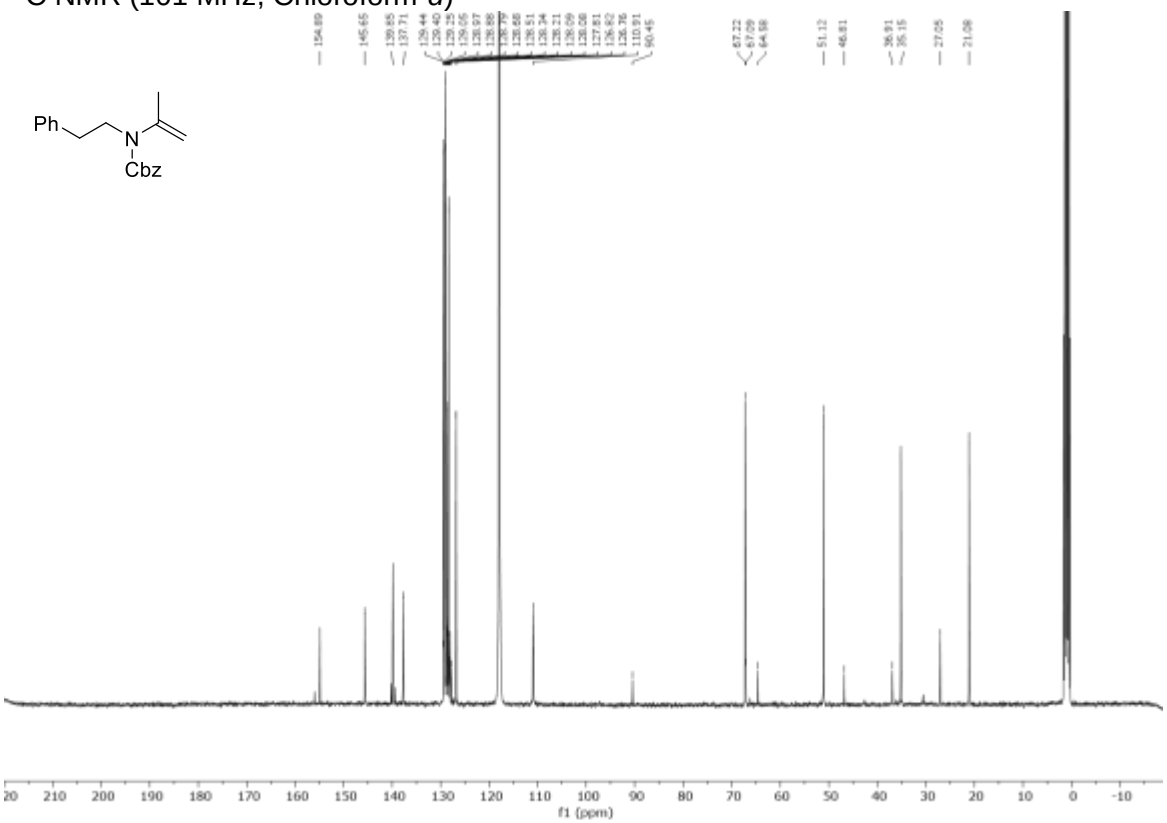


4.3l

^{1}H NMR (400 MHz, Chloroform-*d*)

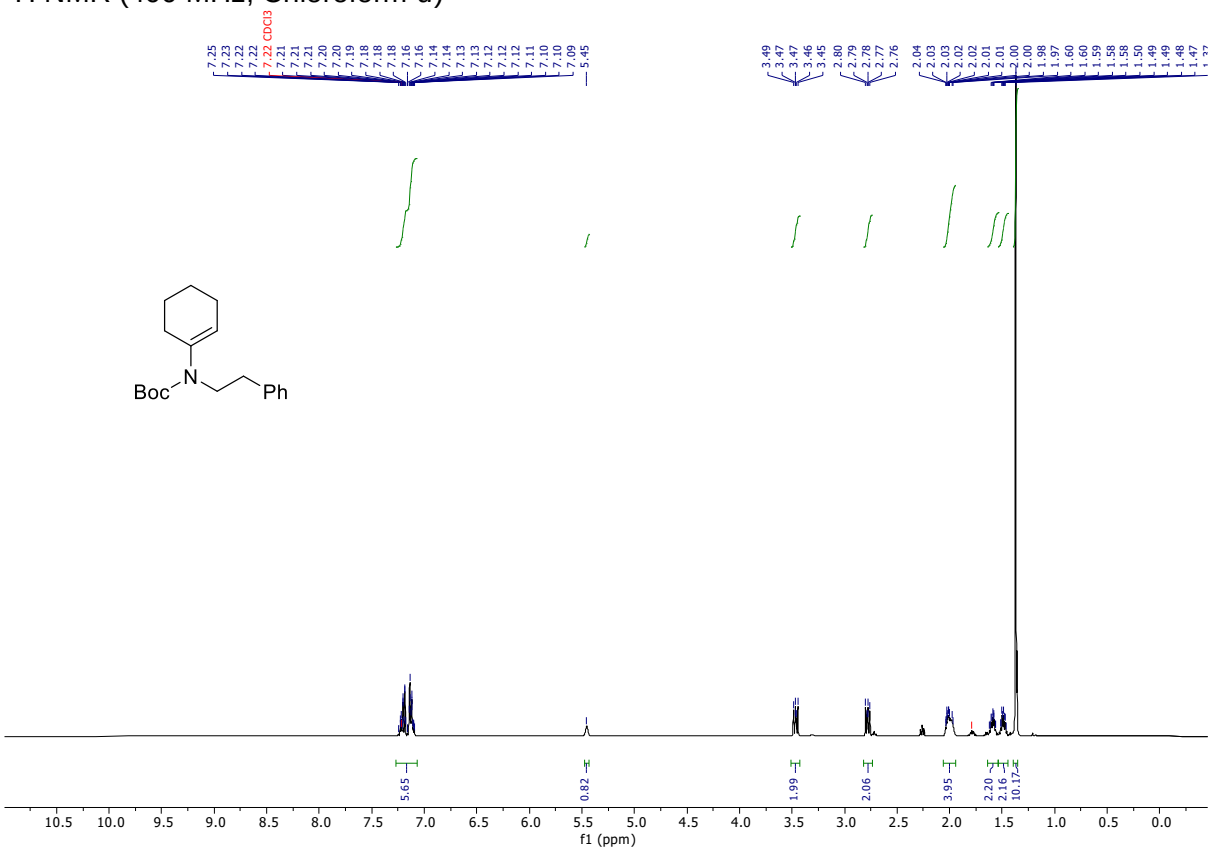


^{13}C NMR (101 MHz, Chloroform-*d*)

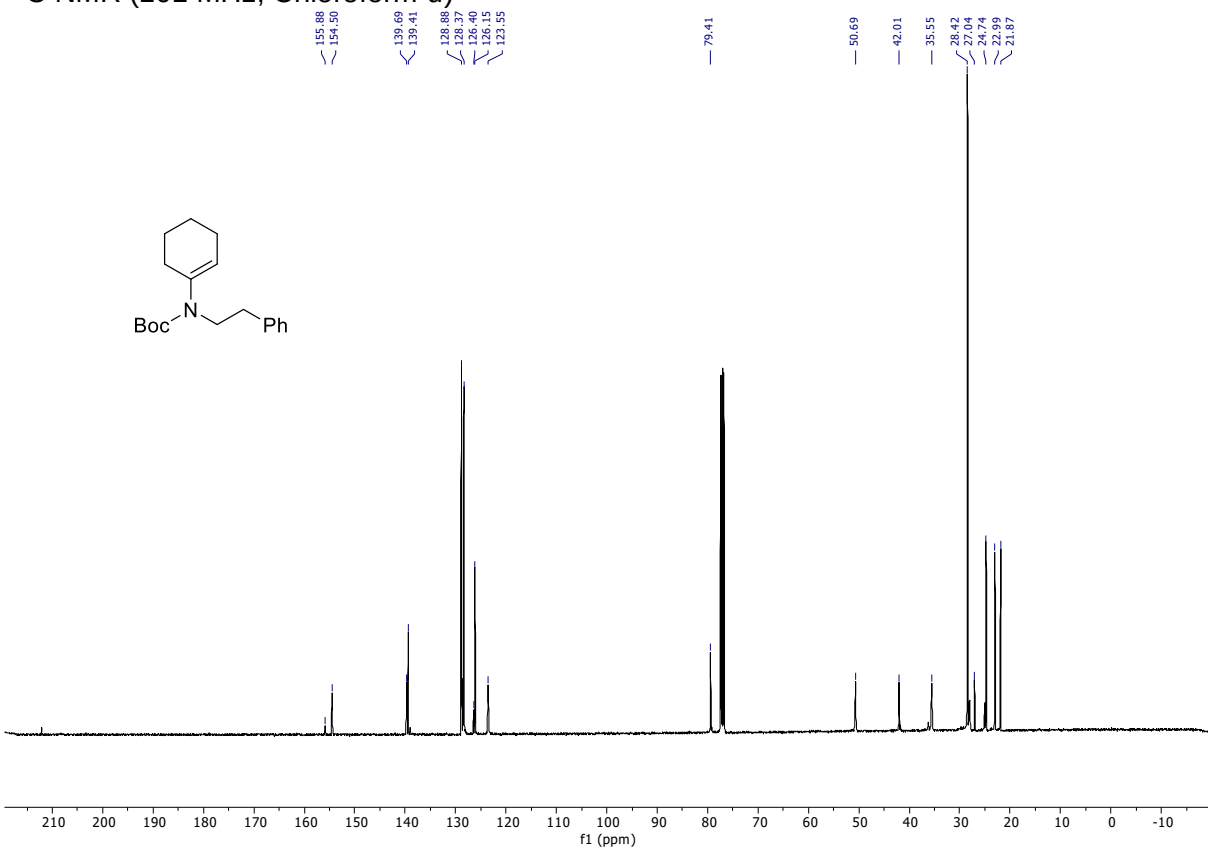


4.3m

^{1}H NMR (400 MHz, Chloroform-*d*)

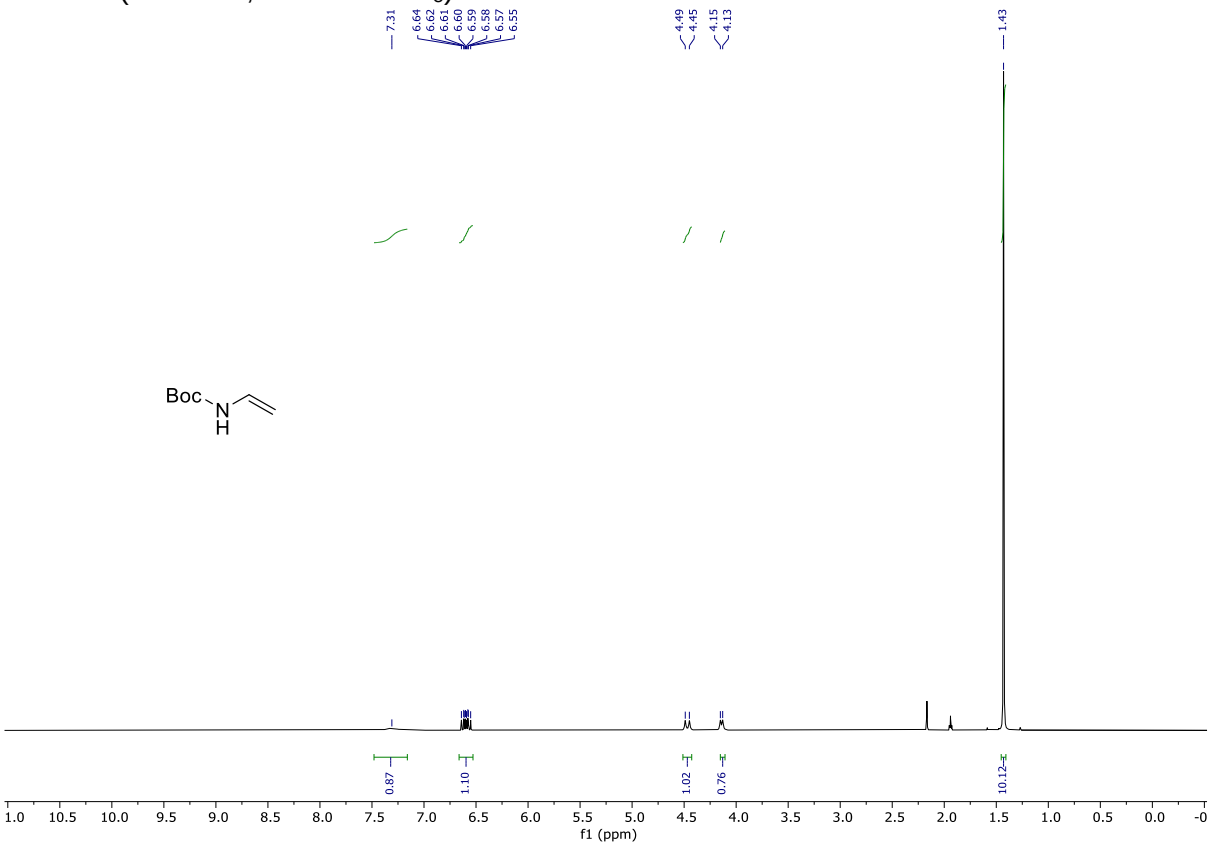


^{13}C NMR (101 MHz, Chloroform-*d*)

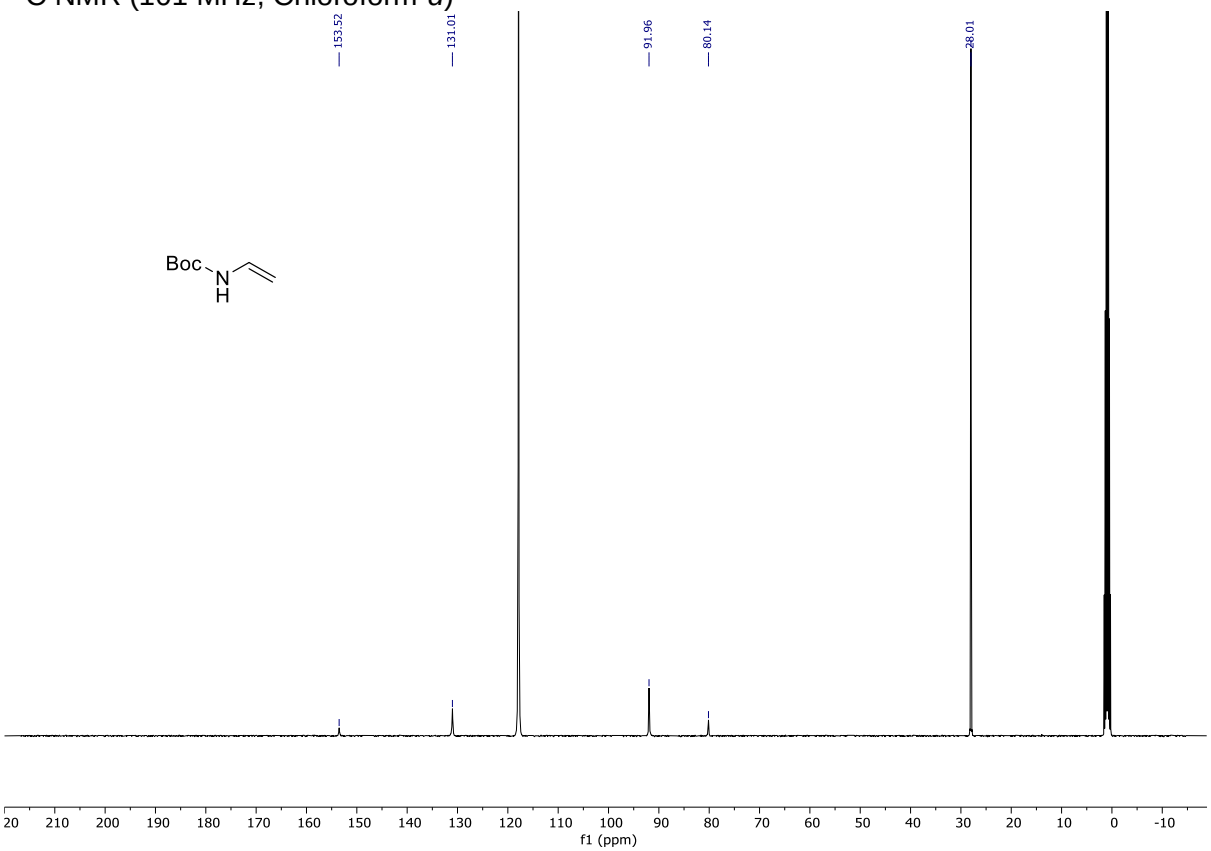


4.3n

^{1}H NMR (400 MHz, Acetonitrile-d_3)

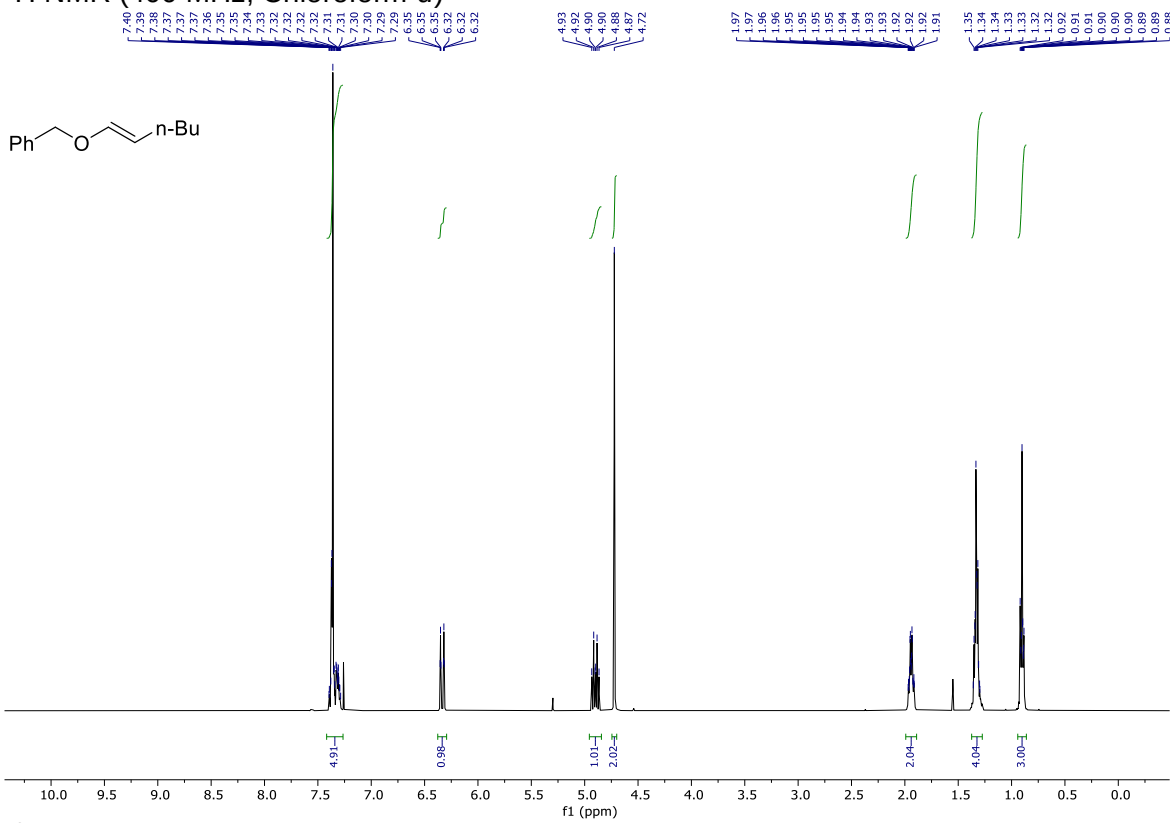


^{13}C NMR (101 MHz, Chloroform-d)

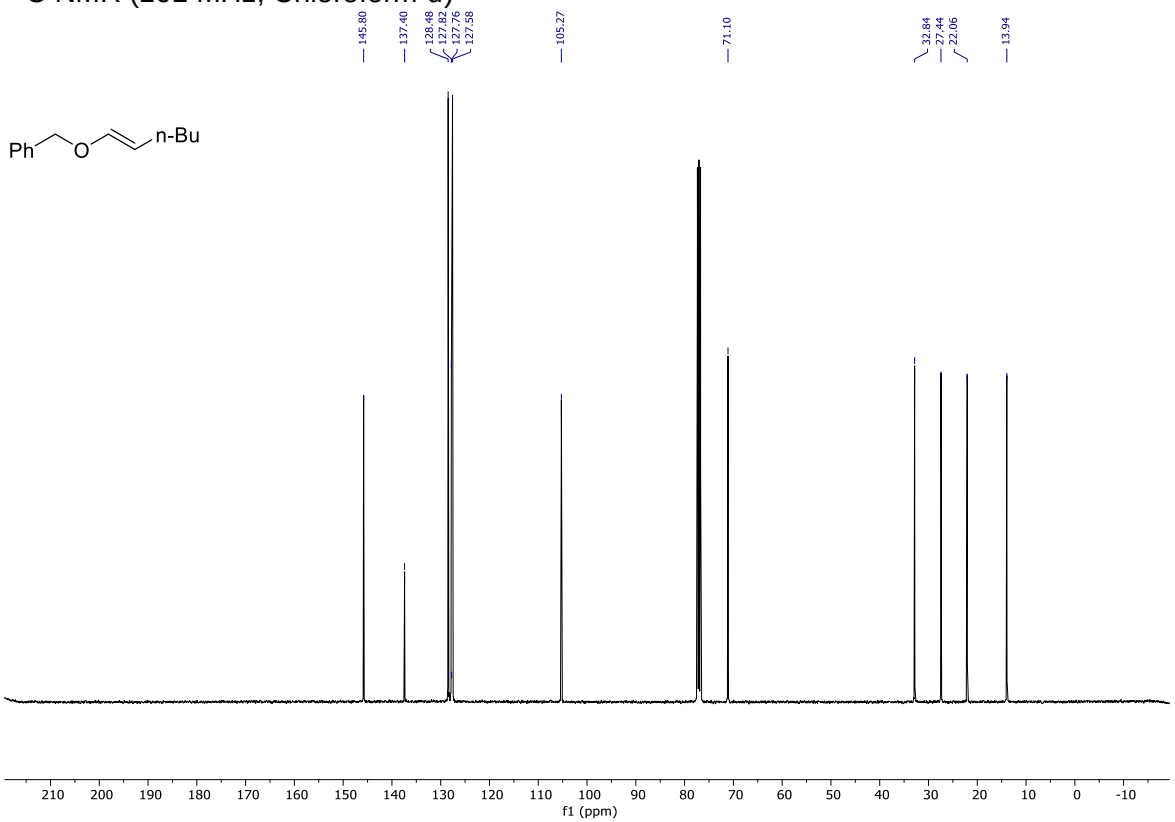


4.5f

^{1}H NMR (400 MHz, Chloroform-*d*)

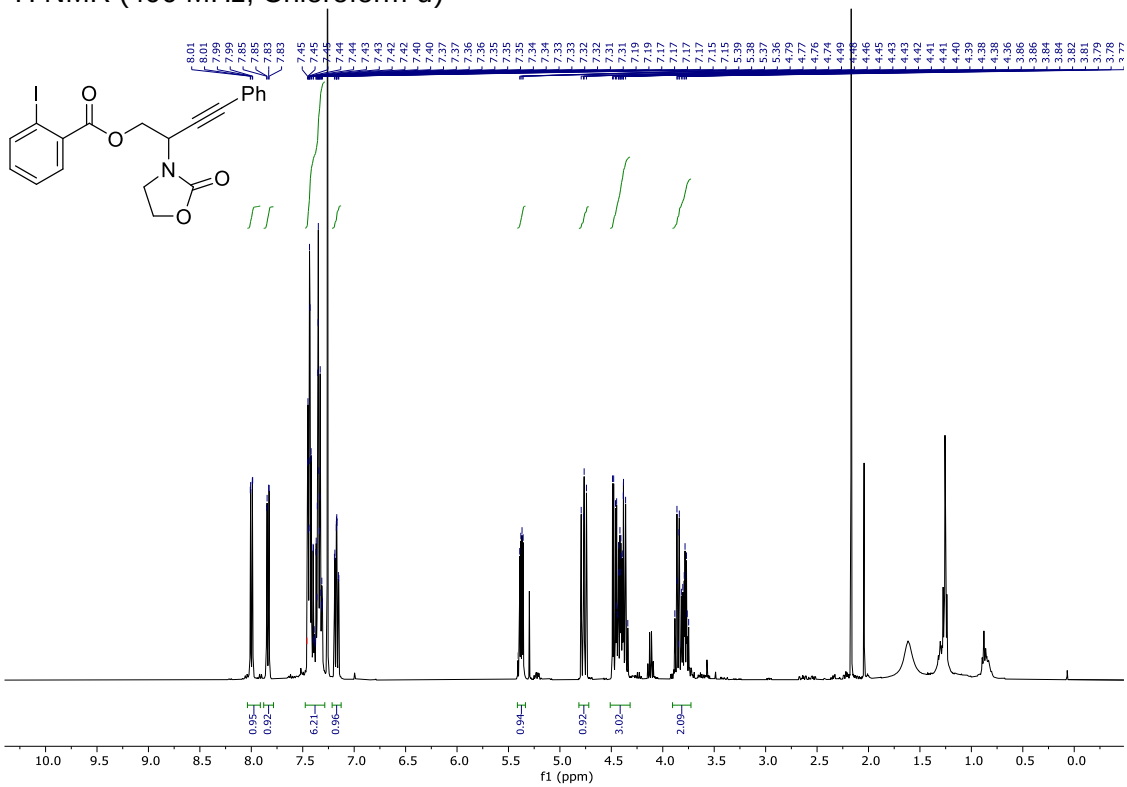


^{13}C NMR (101 MHz, Chloroform-*d*)

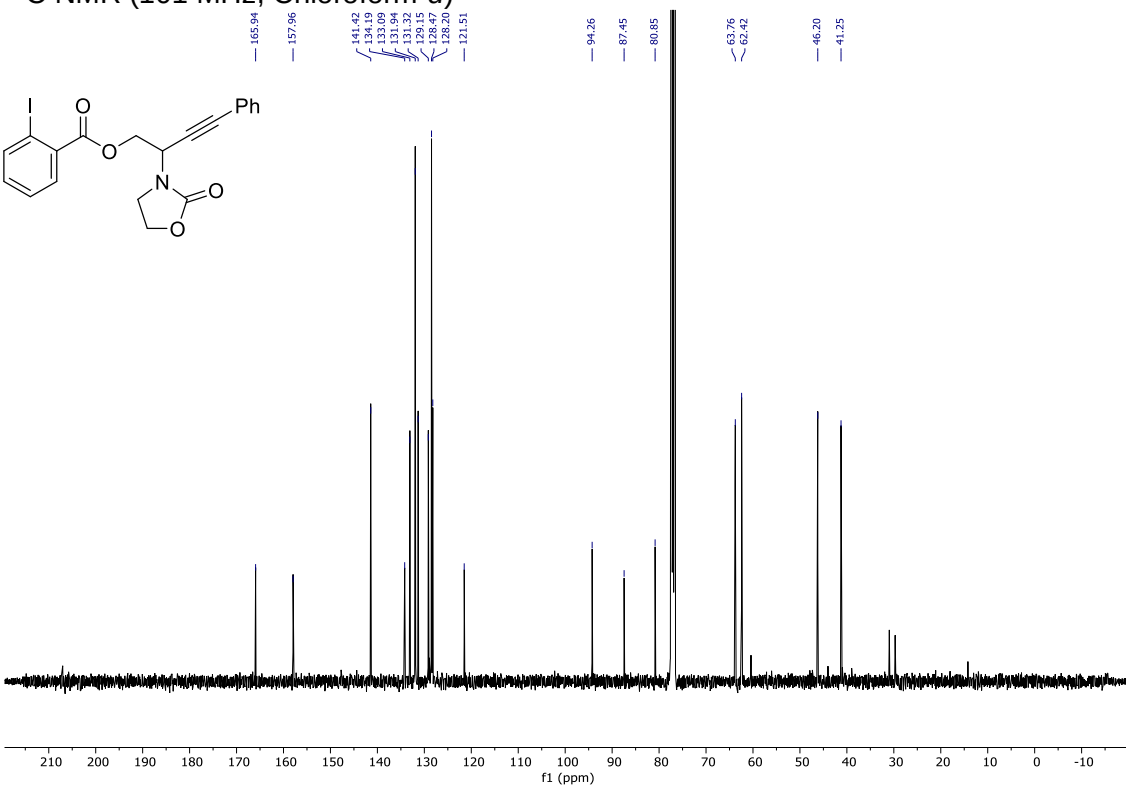


4.20a (traces of ethyl acetate)

^{1}H NMR (400 MHz, Chloroform-*d*)

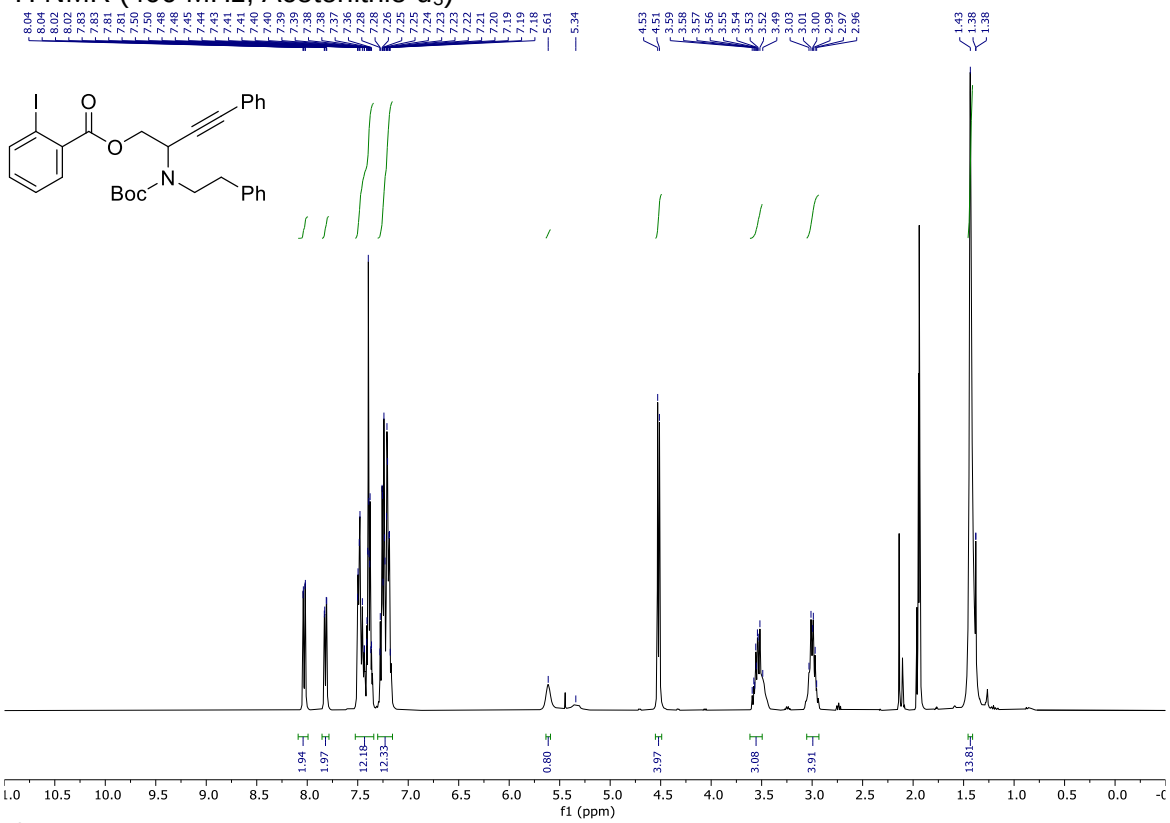


^{13}C NMR (101 MHz, Chloroform-*d*)

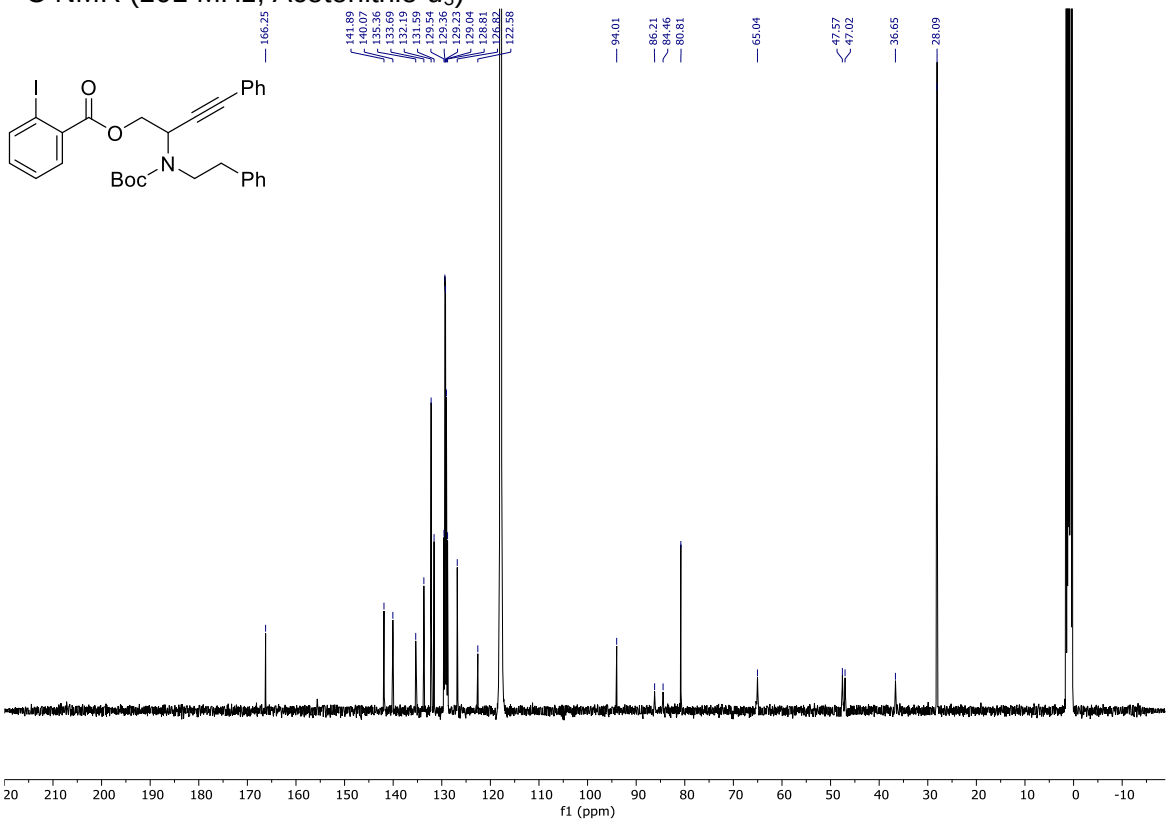


4.20b

^{1}H NMR (400 MHz, Acetonitrile-d_3)

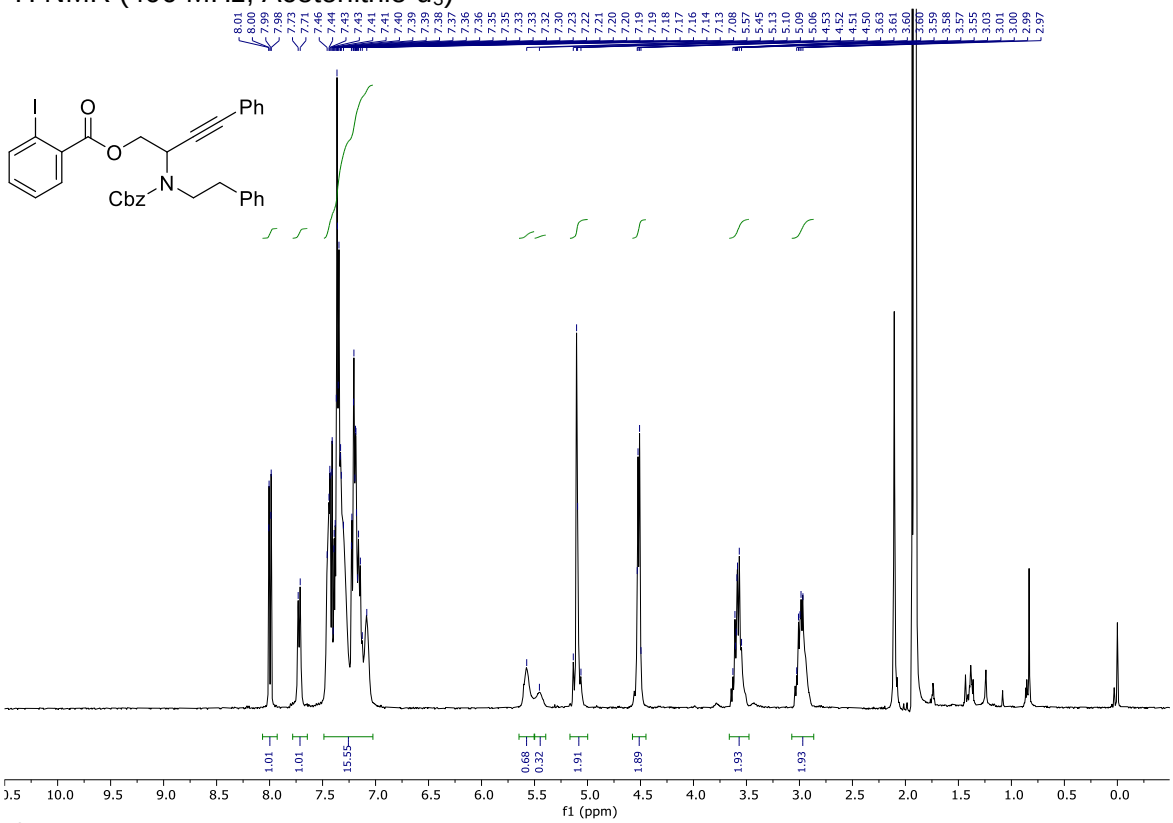


^{13}C NMR (101 MHz, Acetonitrile-d_3)

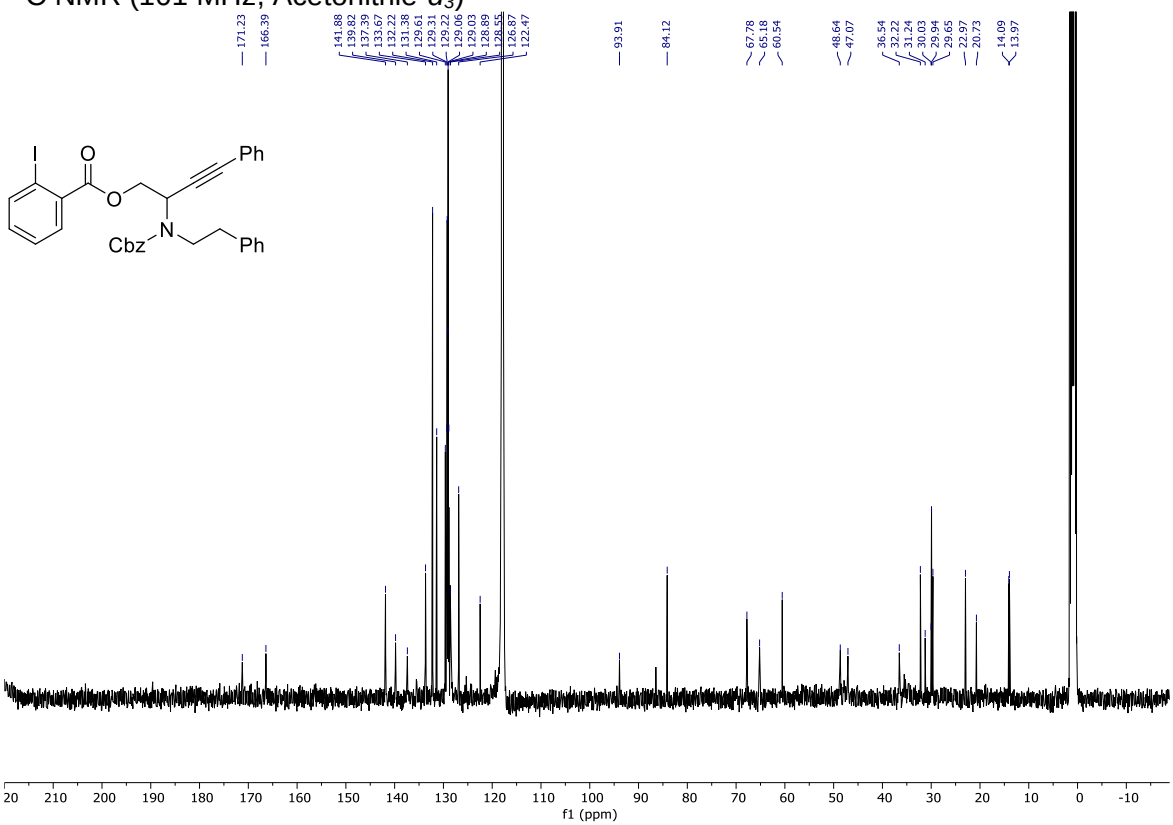


4.20c

^{1}H NMR (400 MHz, Acetonitrile-d_3)

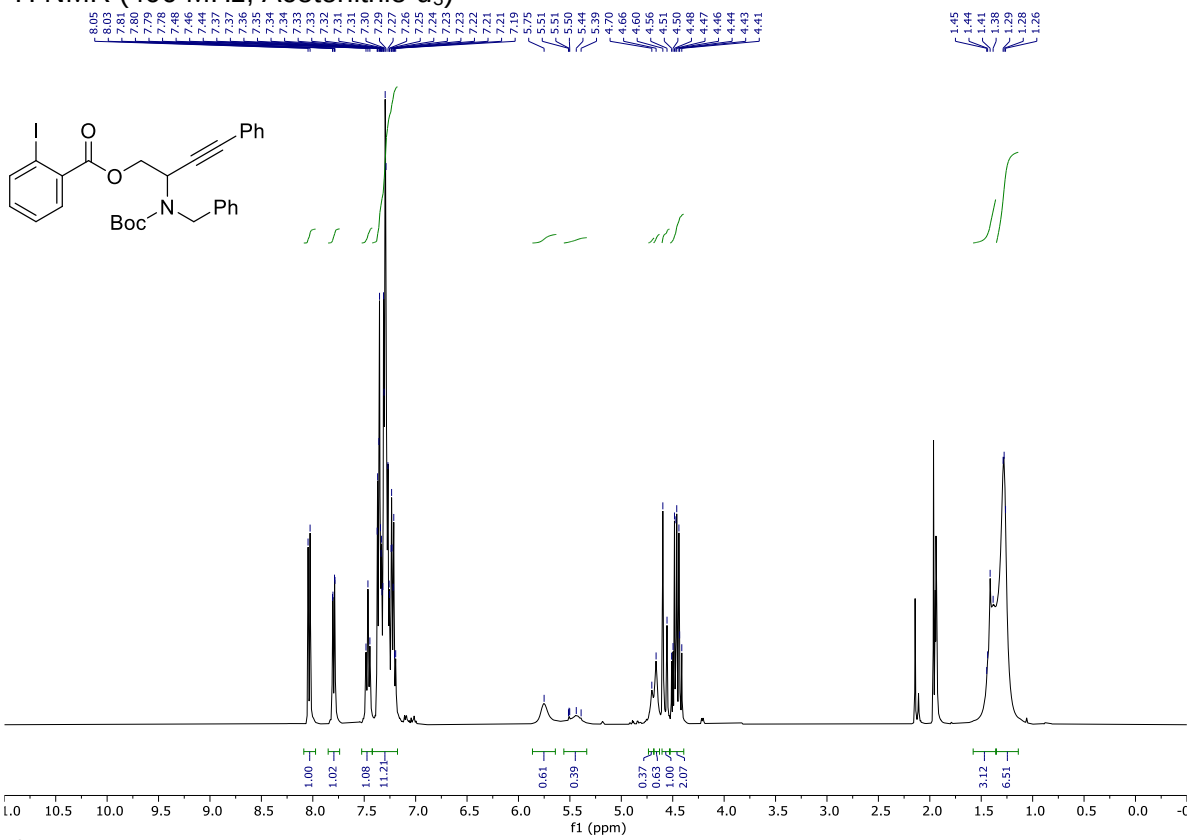


^{13}C NMR (101 MHz, Acetonitrile-d_3)

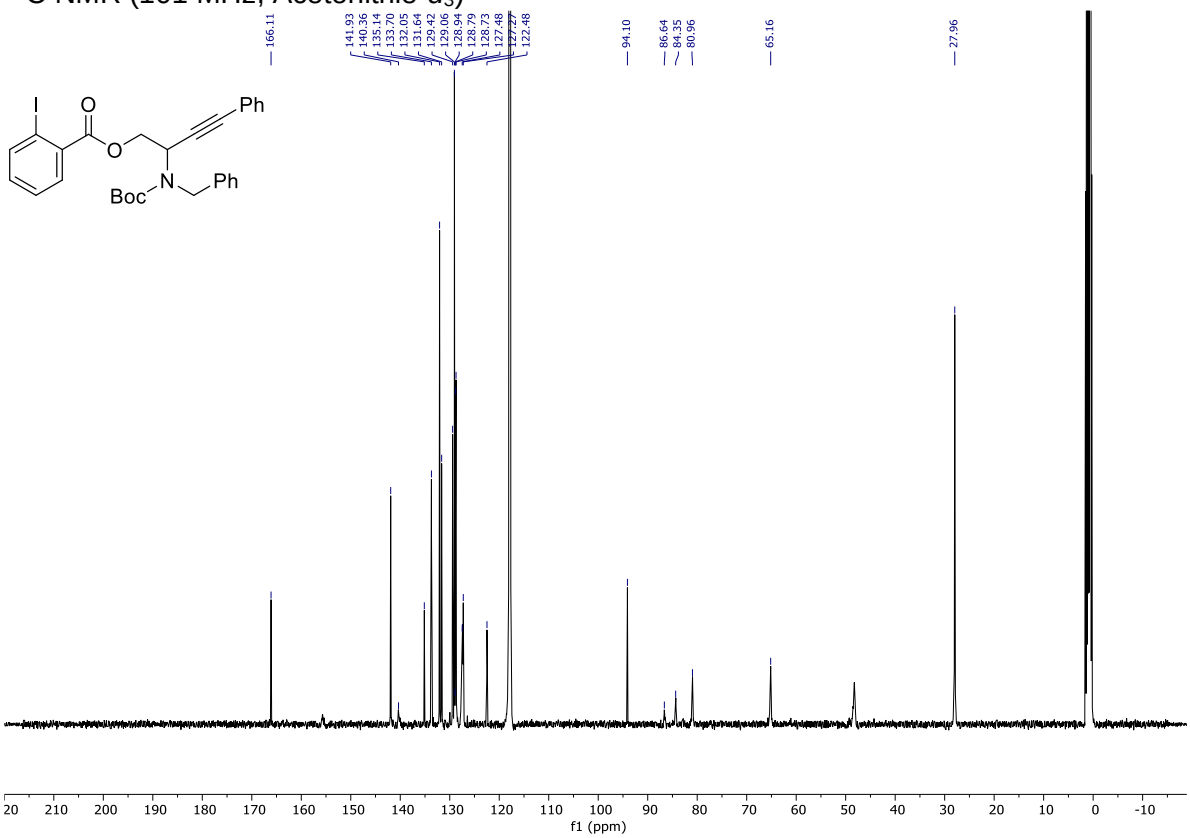


4.20d

^{1}H NMR (400 MHz, Acetonitrile-d_3)

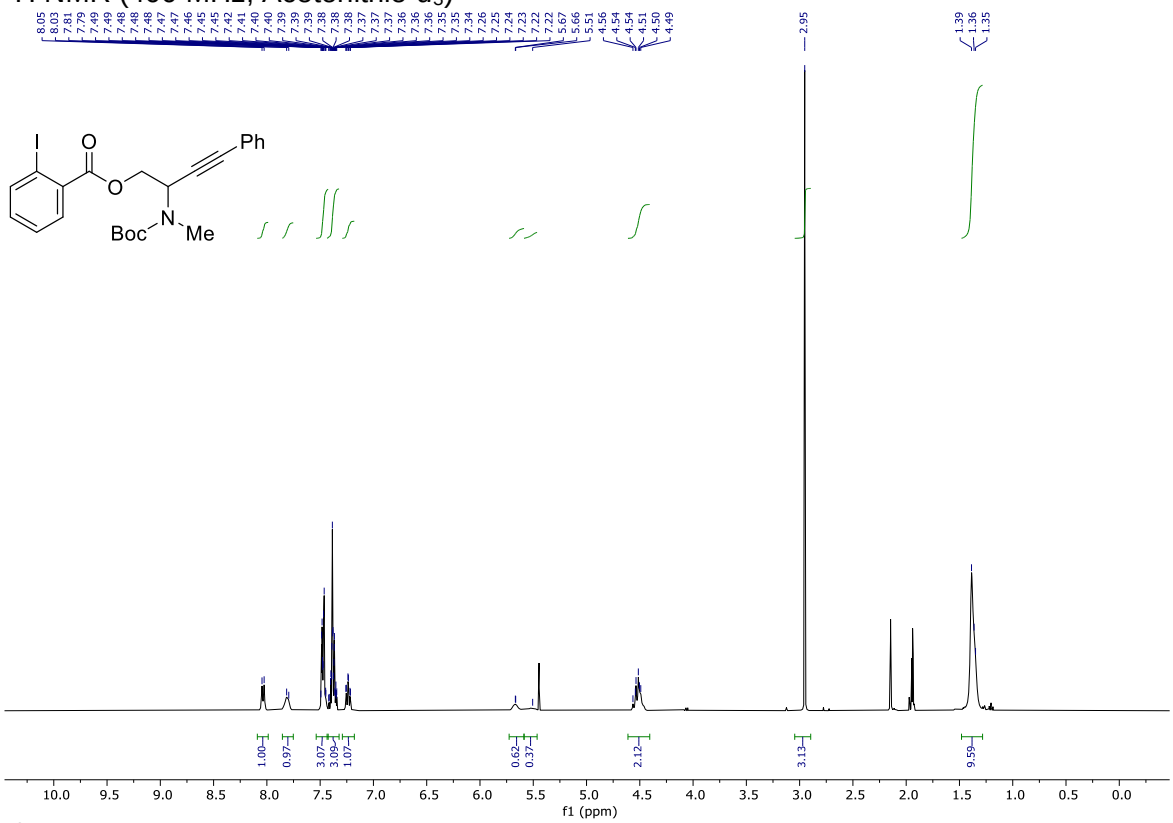


^{13}C NMR (101 MHz, Acetonitrile-d_3)

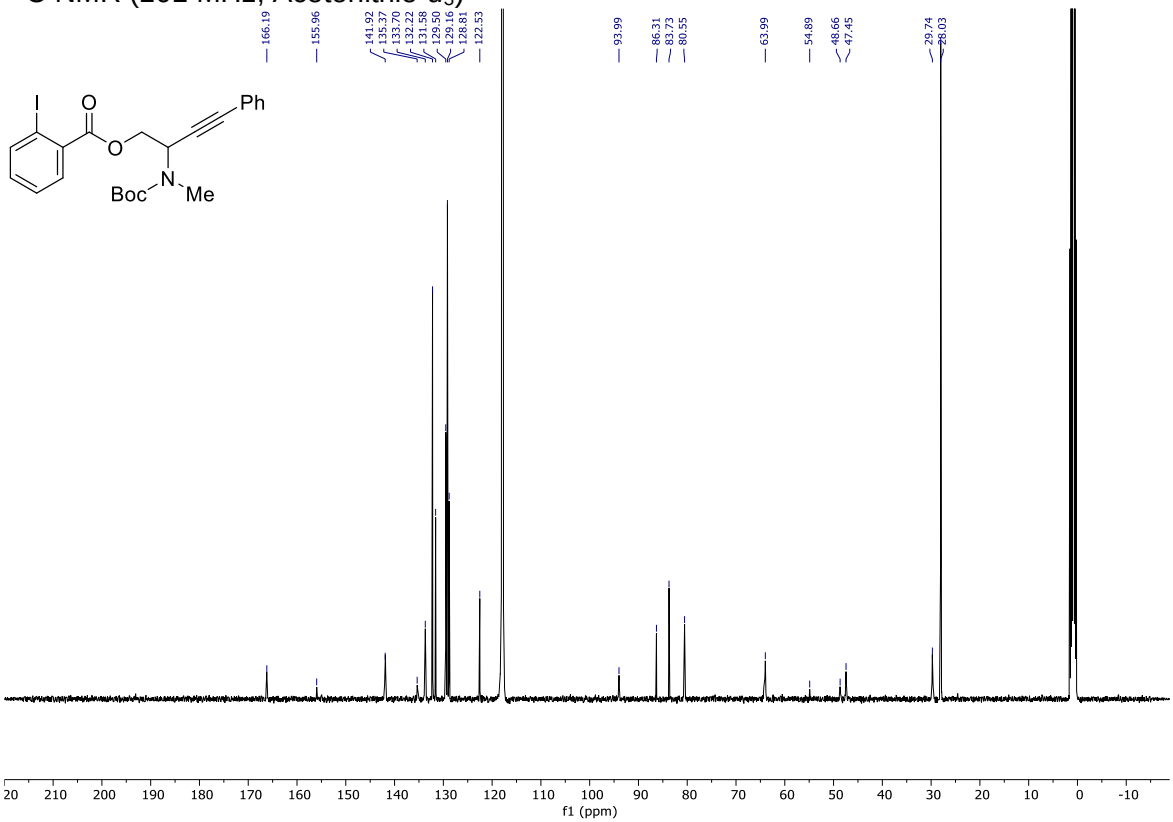


4.20e

^{1}H NMR (400 MHz, Acetonitrile-d_3)

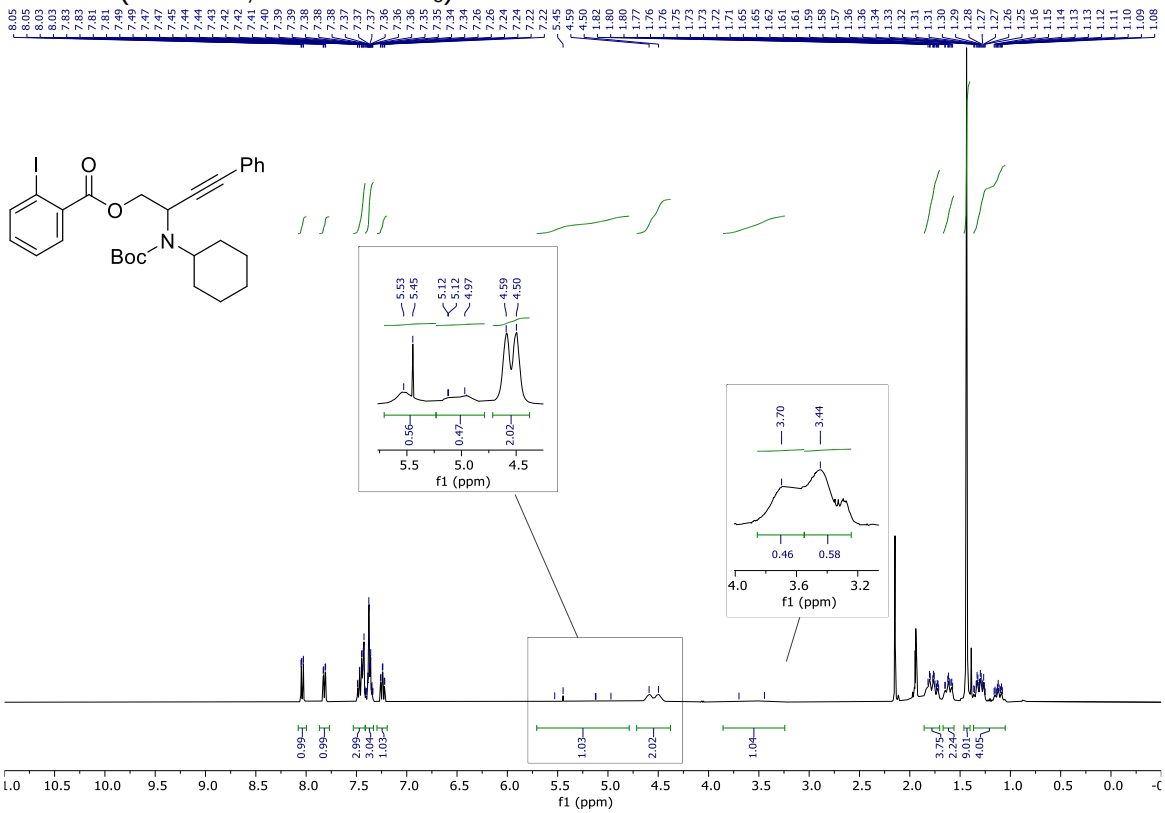


^{13}C NMR (101 MHz, Acetonitrile-d_3)

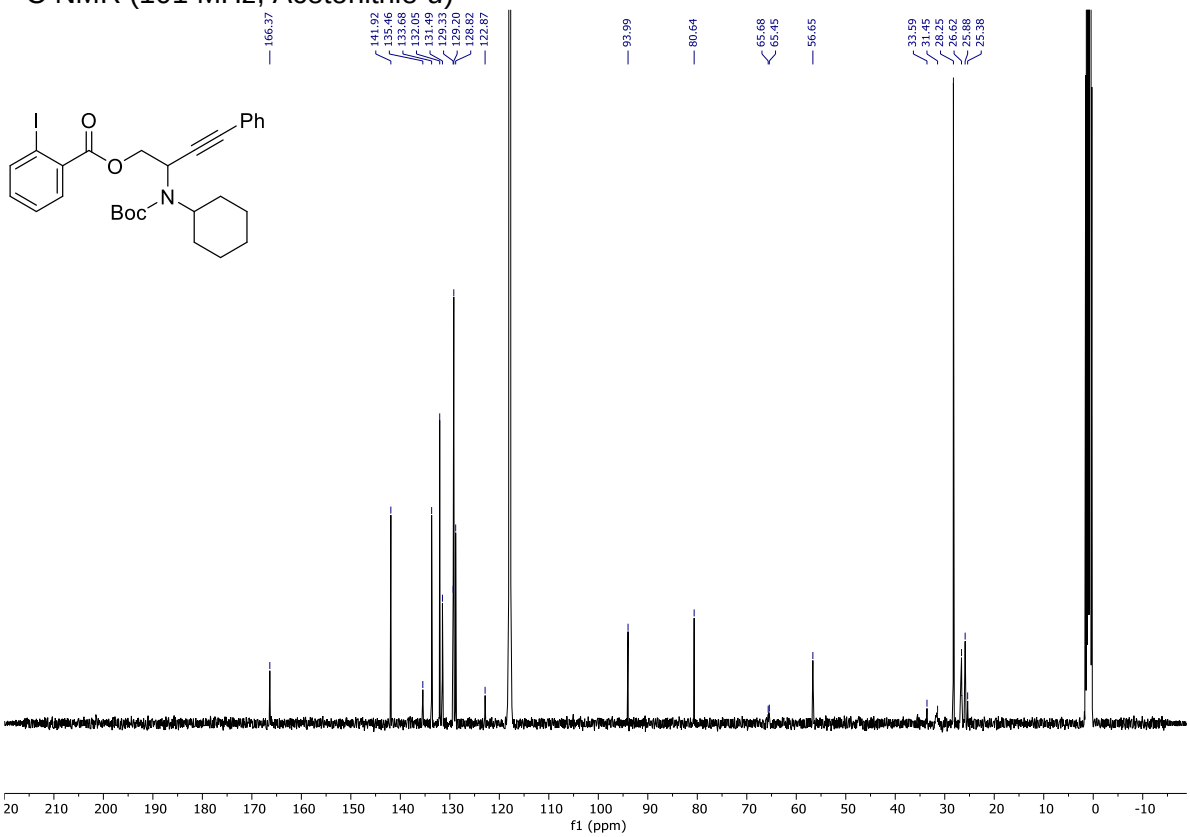


4.20f

^{1}H NMR (400 MHz, Acetonitrile-d_3)

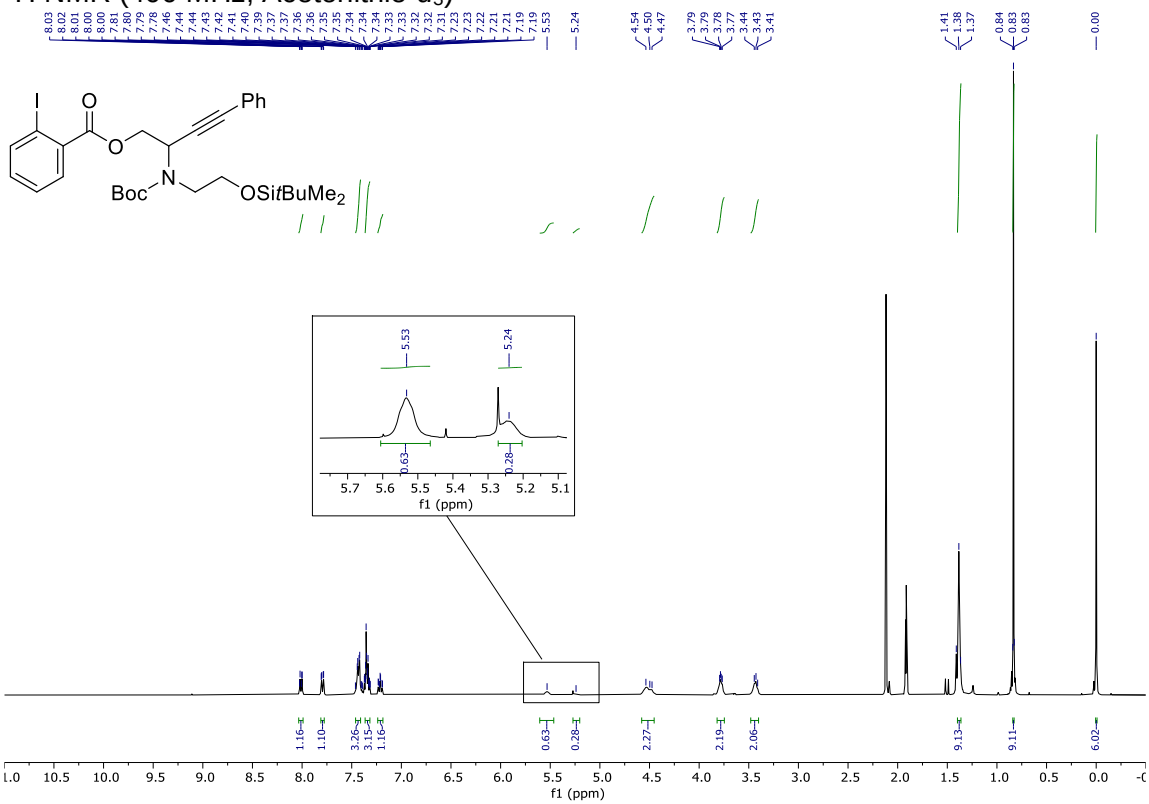


^{13}C NMR (101 MHz, Acetonitrile-d)

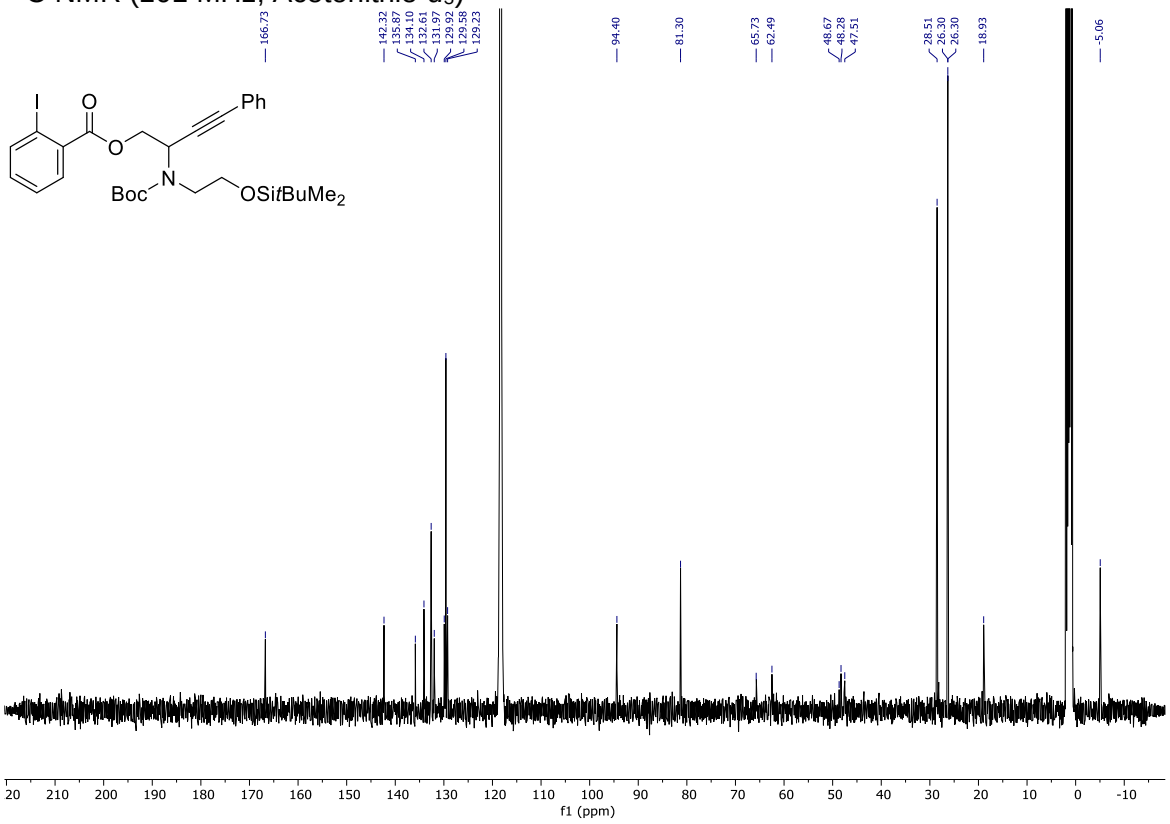


4.20g

^{1}H NMR (400 MHz, Acetonitrile-d_3)

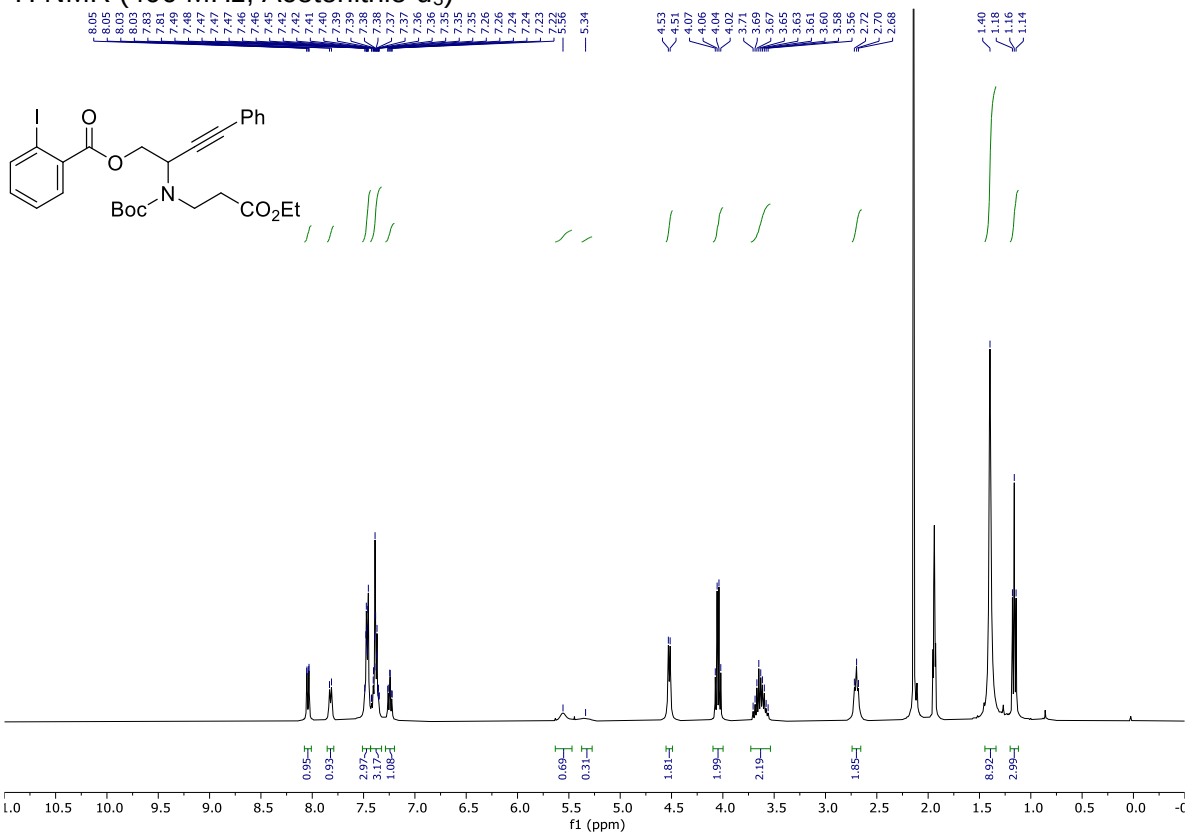


^{13}C NMR (101 MHz, Acetonitrile-d_3)

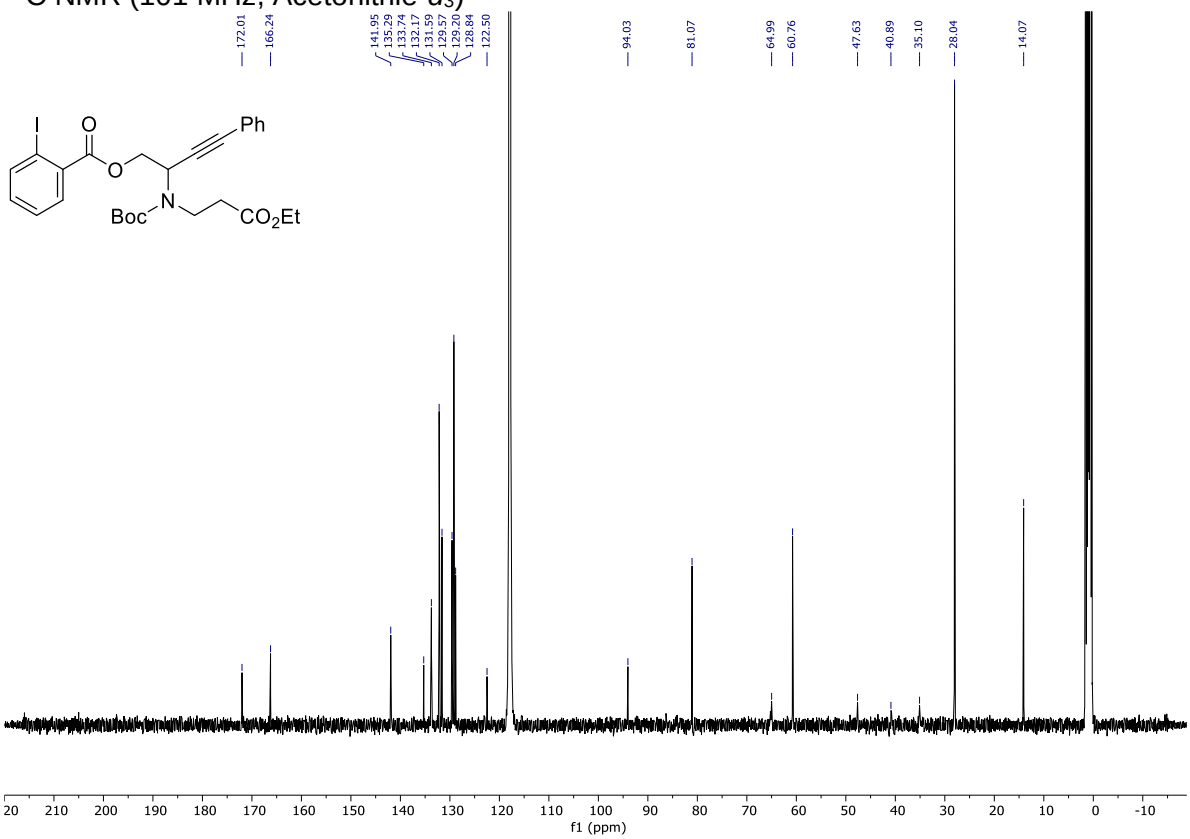


4.20h

^{1}H NMR (400 MHz, Acetonitrile-d_3)

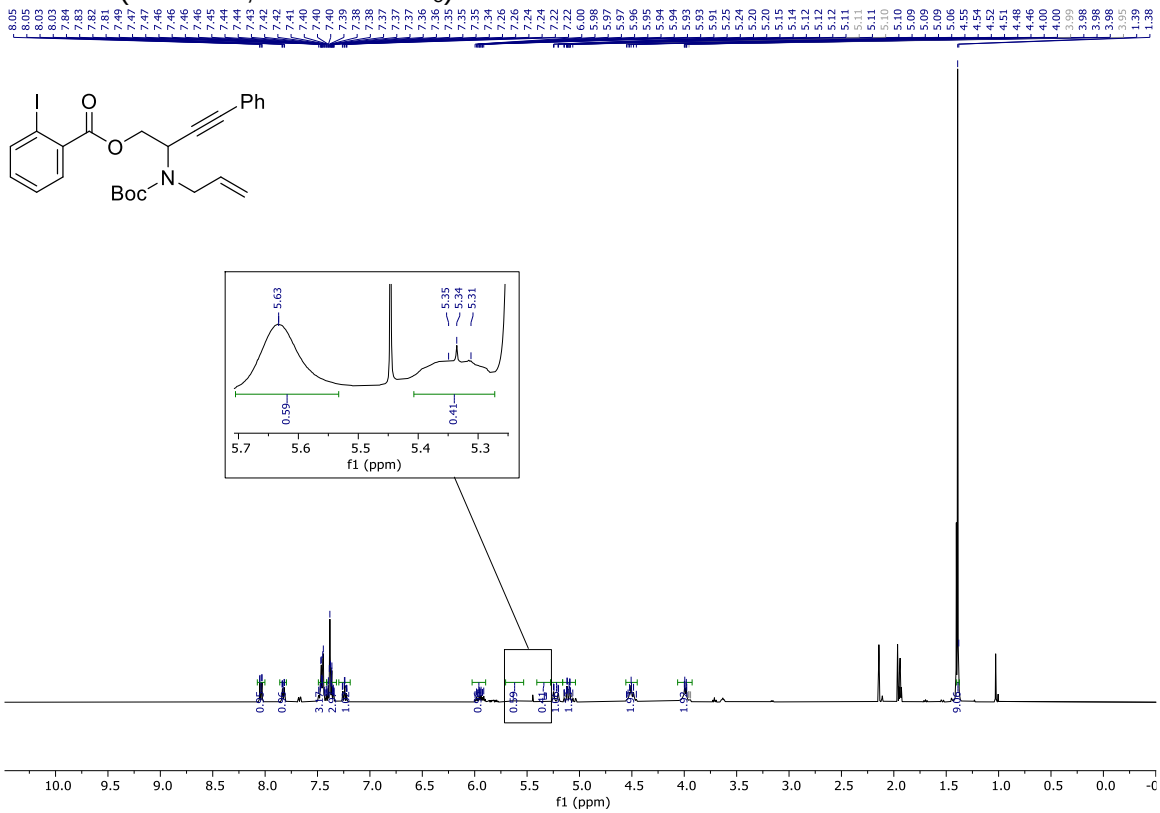


^{13}C NMR (101 MHz, Acetonitrile-d_3)

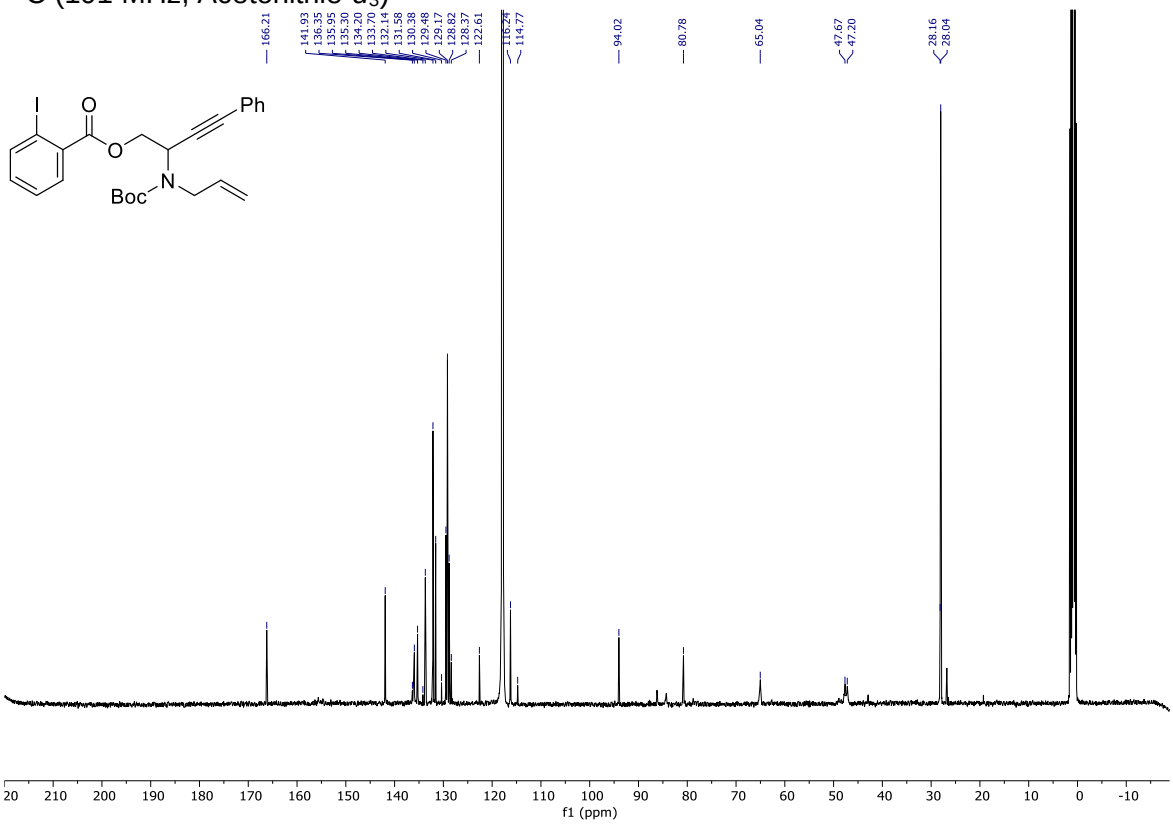


4.20i

^{1}H NMR (400 MHz, Acetonitrile-d_3)

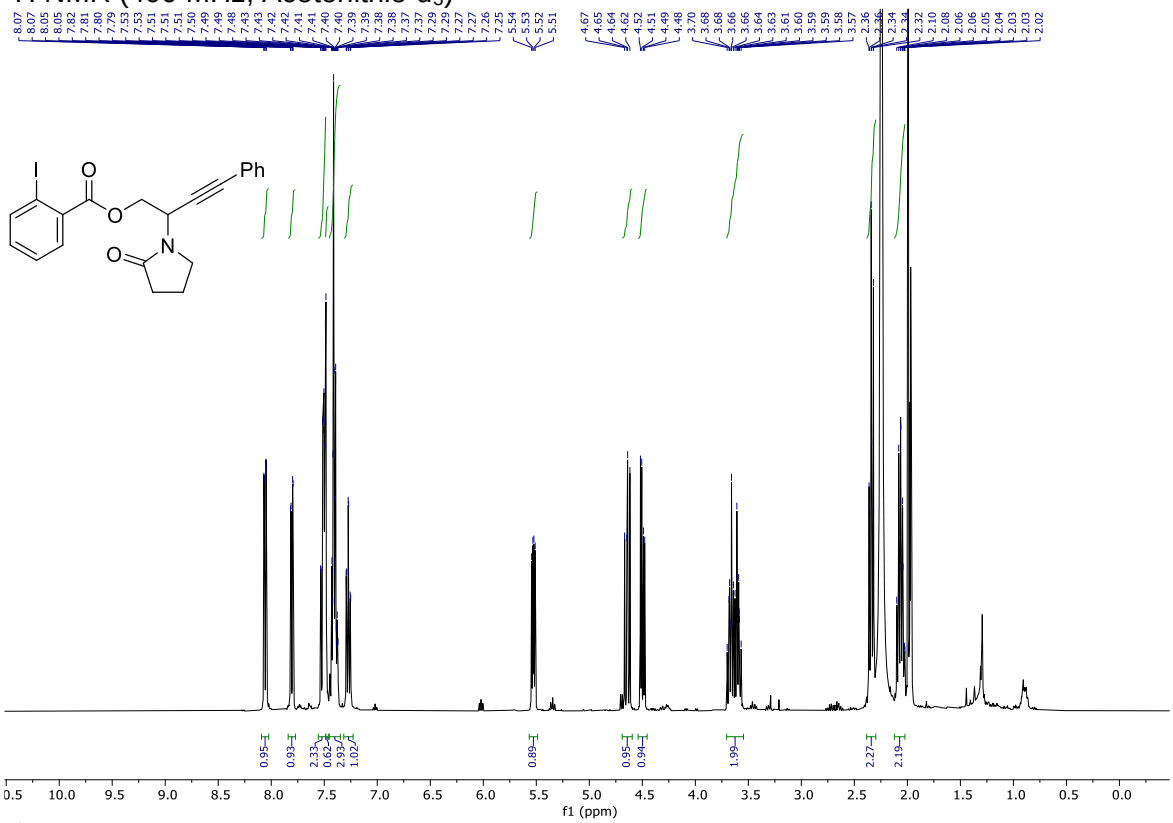


^{13}C (101 MHz, Acetonitrile-d_3)

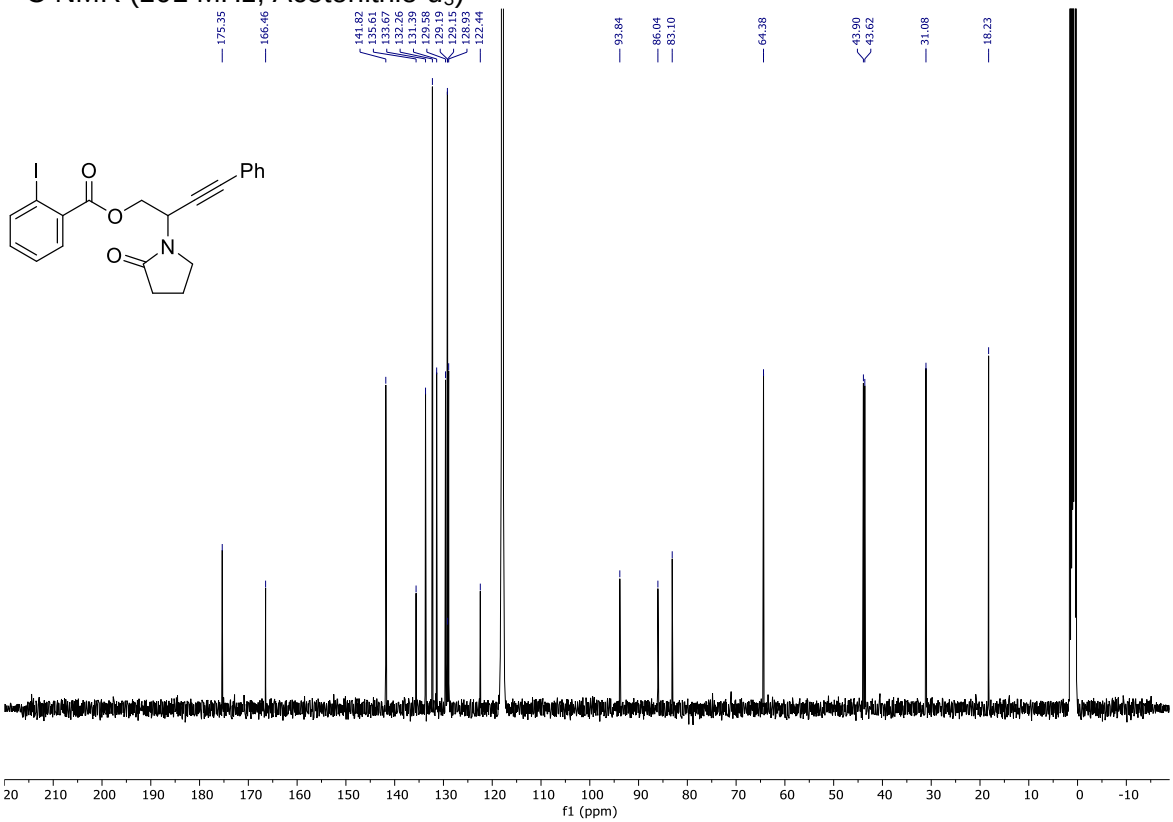


4.20j

^{1}H NMR (400 MHz, Acetonitrile-d_3)

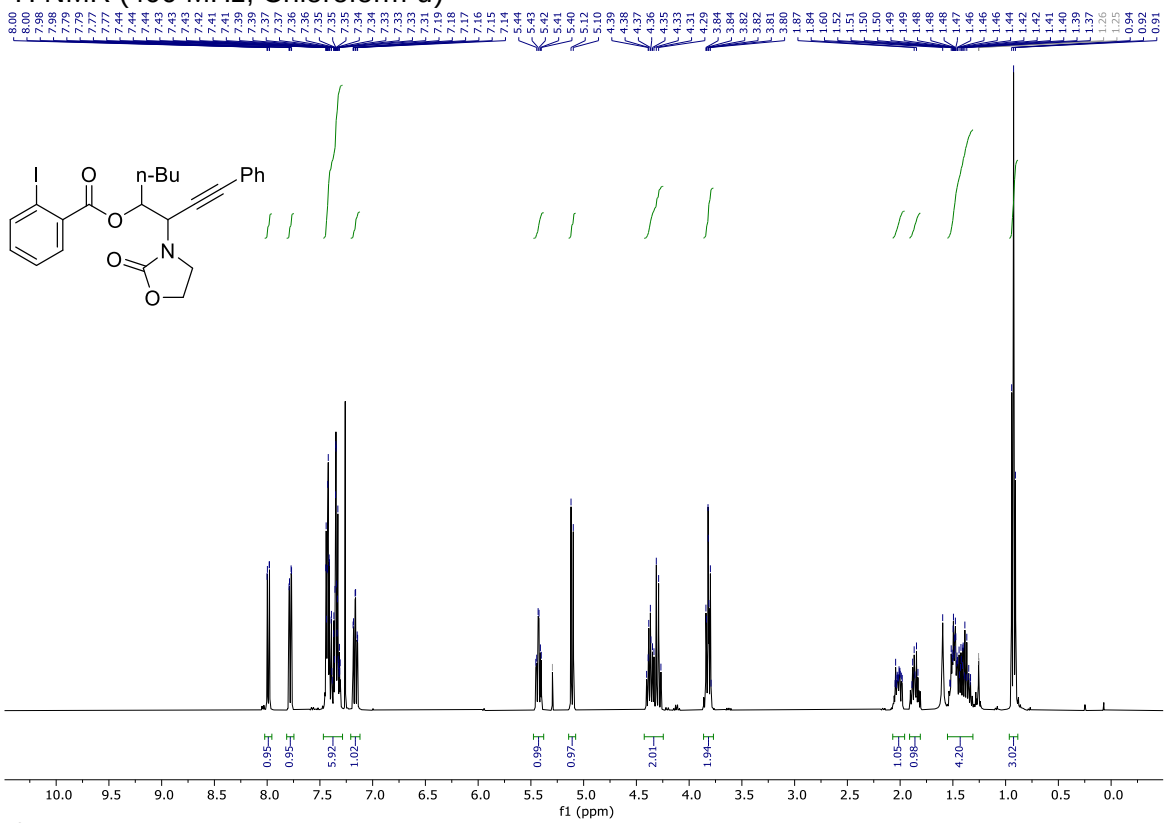


^{13}C NMR (101 MHz, Acetonitrile-d_3)

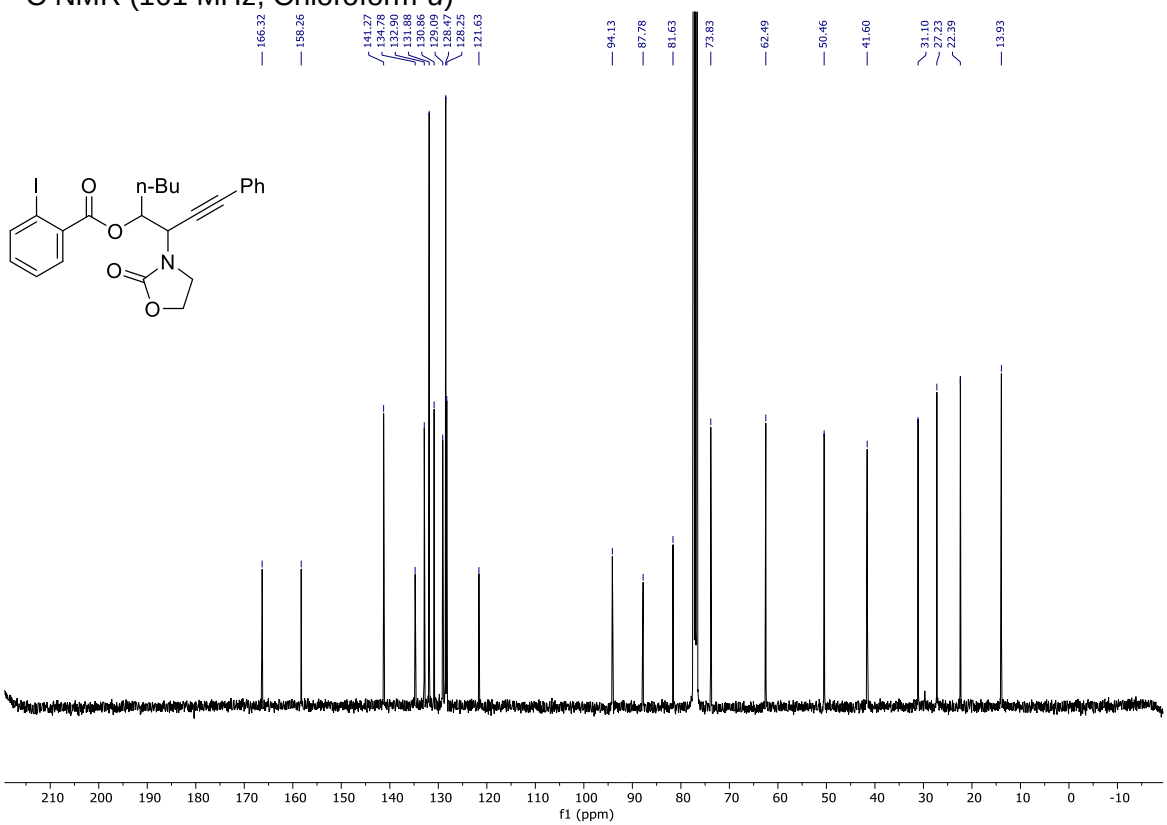


4.20k (major diastereoisomer)

^{1}H NMR (400 MHz, Chloroform-*d*)

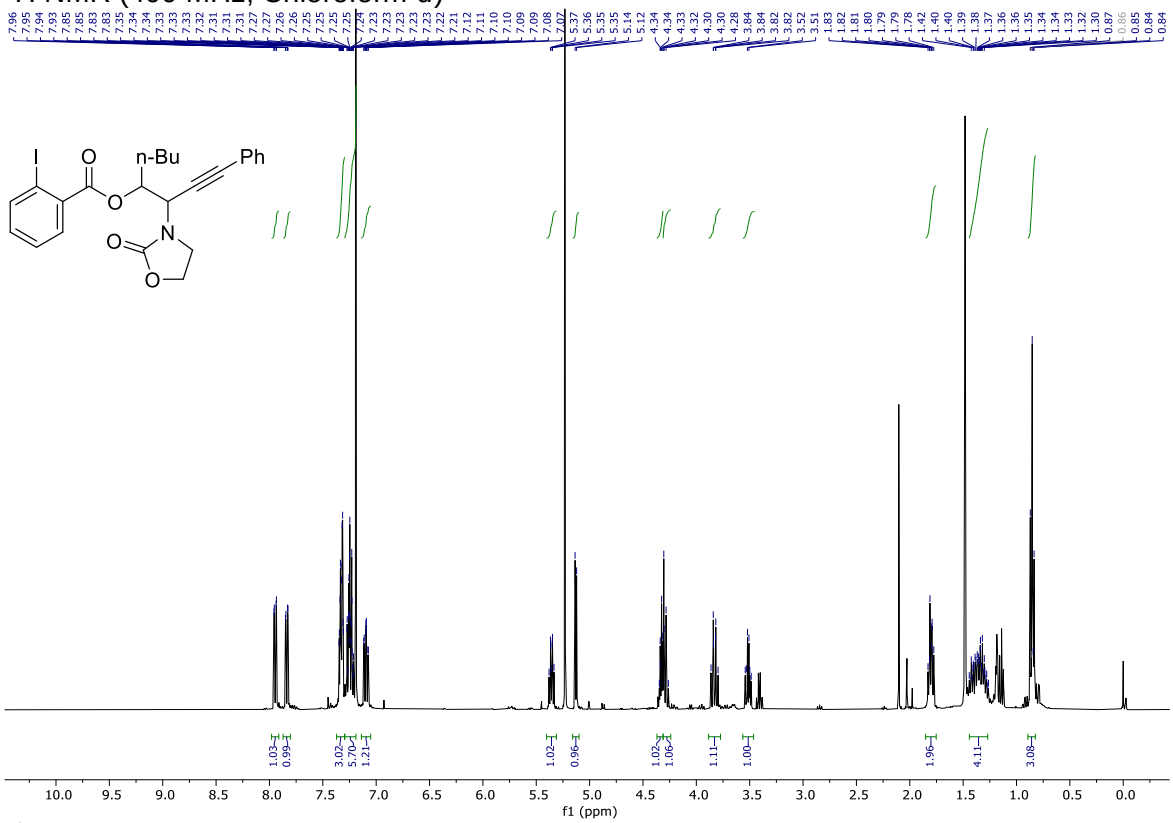


^{13}C NMR (101 MHz, Chloroform-*d*)

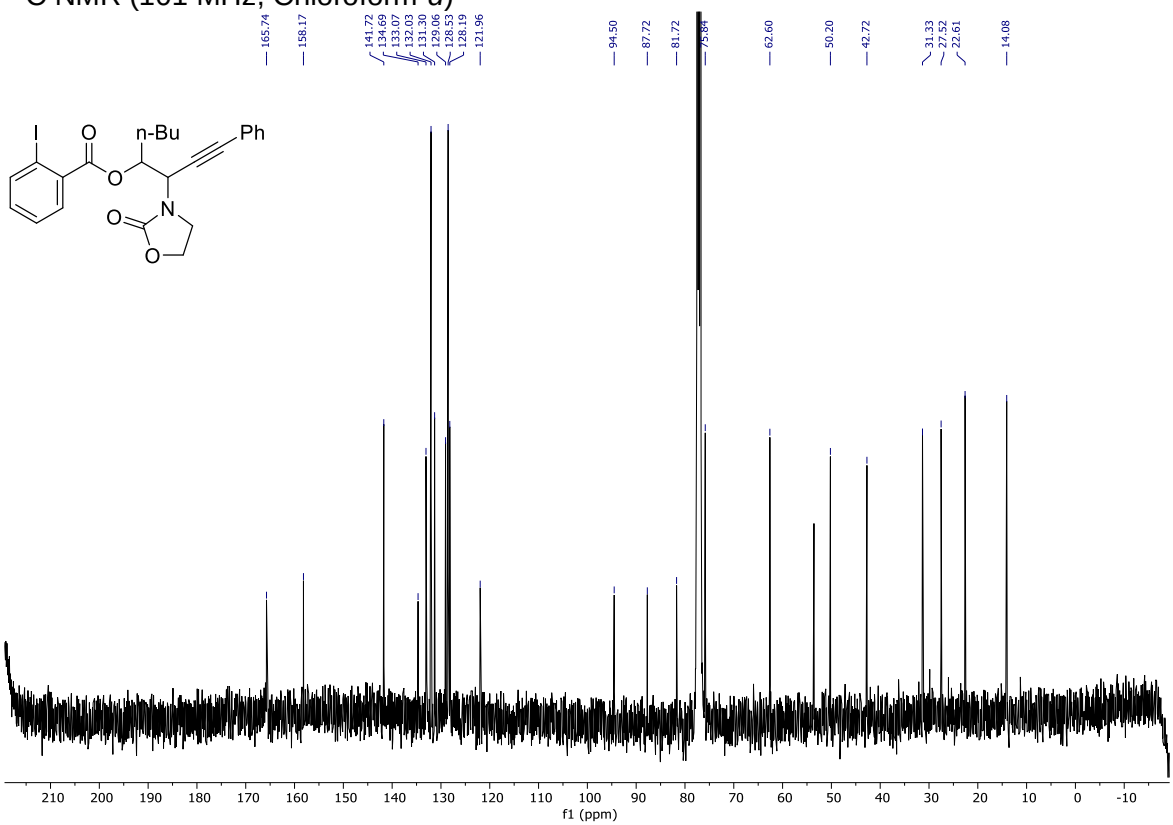


4.20k (minor diastereoisomer) (traces of DCM)

^{1}H NMR (400 MHz, Chloroform-*d*)

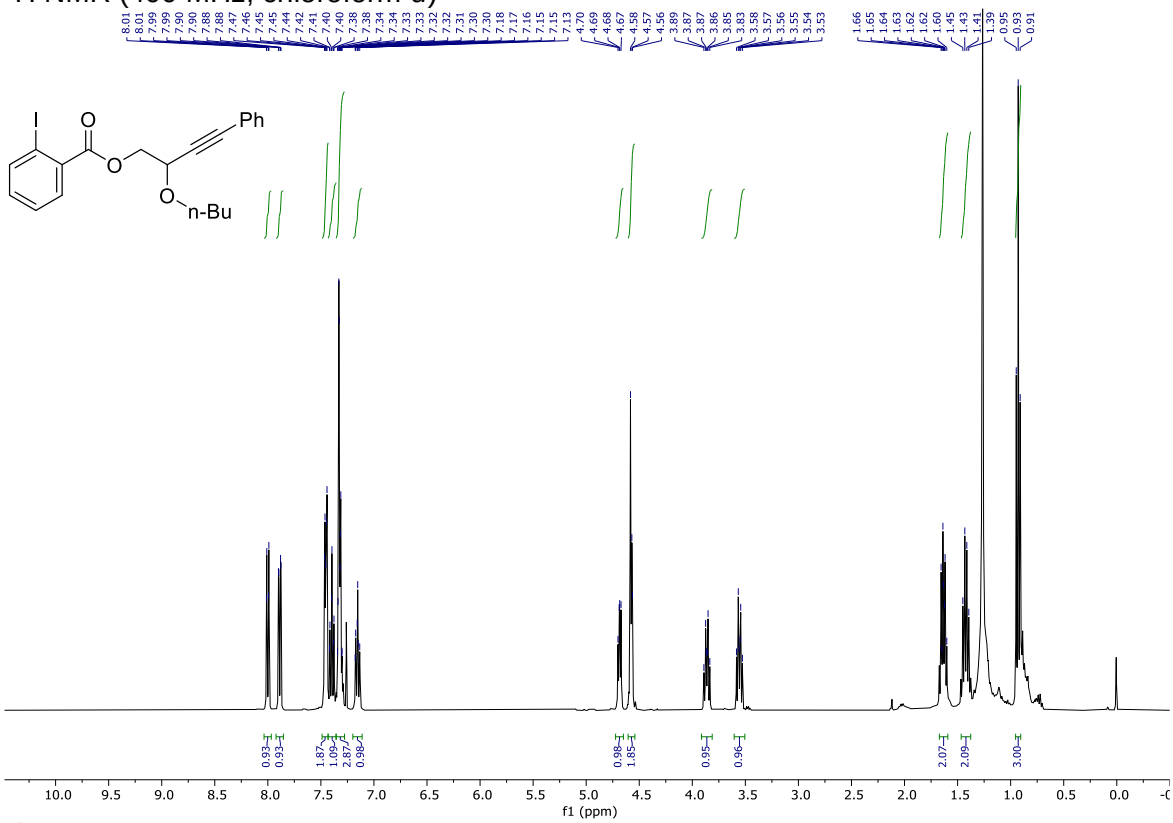


^{13}C NMR (101 MHz, Chloroform-*d*)

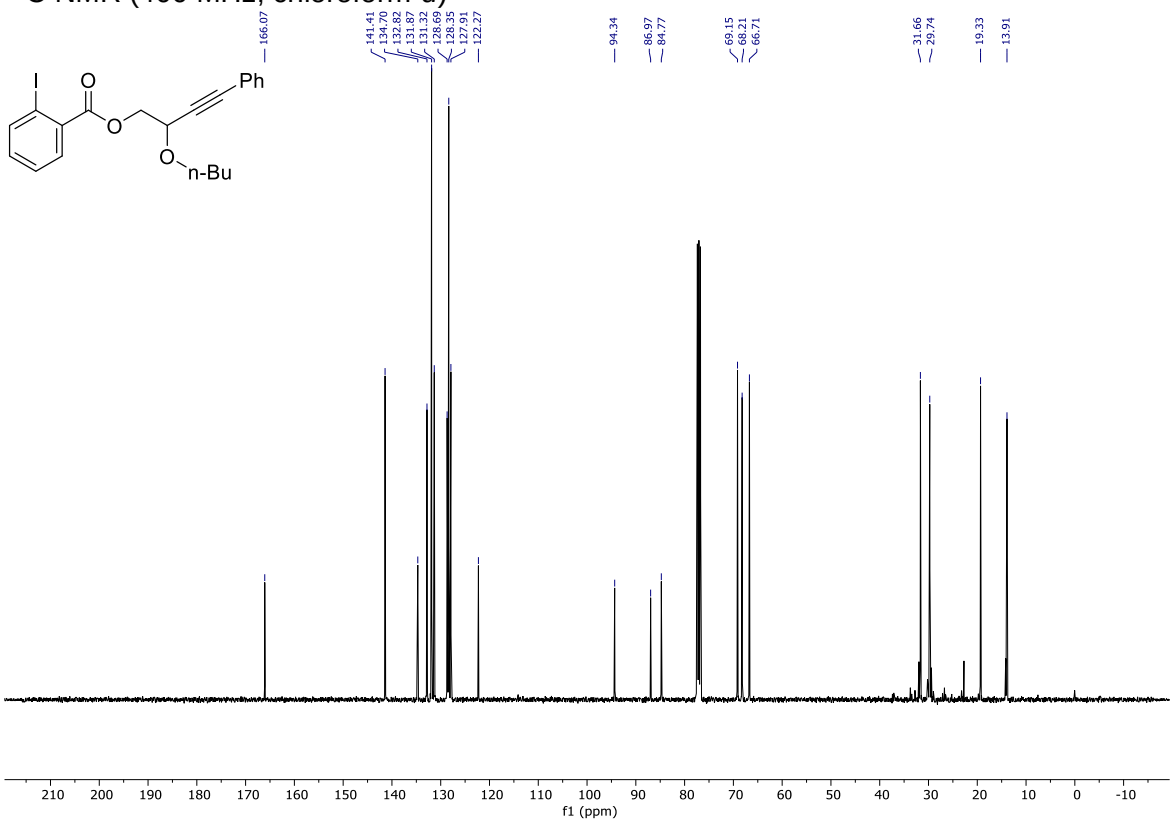


4.22a

^{1}H NMR (400 MHz, chloroform-*d*)

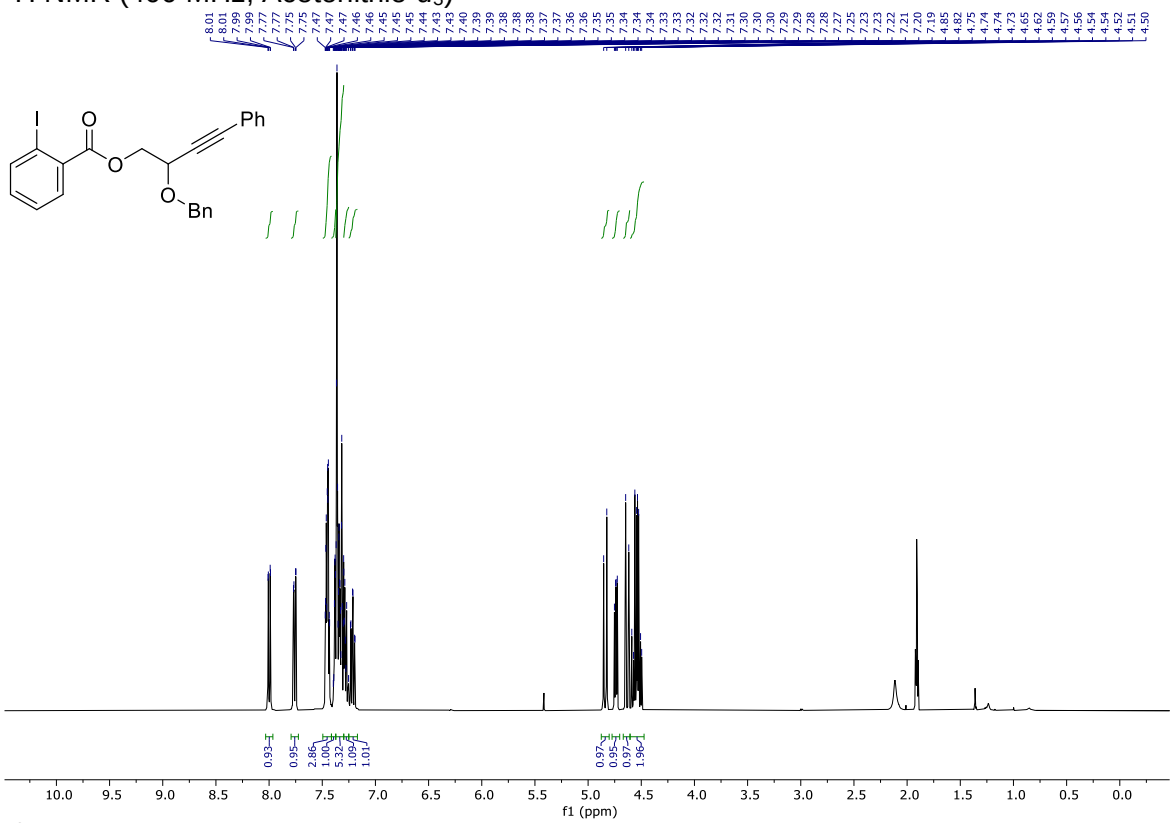


^{13}C NMR (400 MHz, chloroform-*d*)

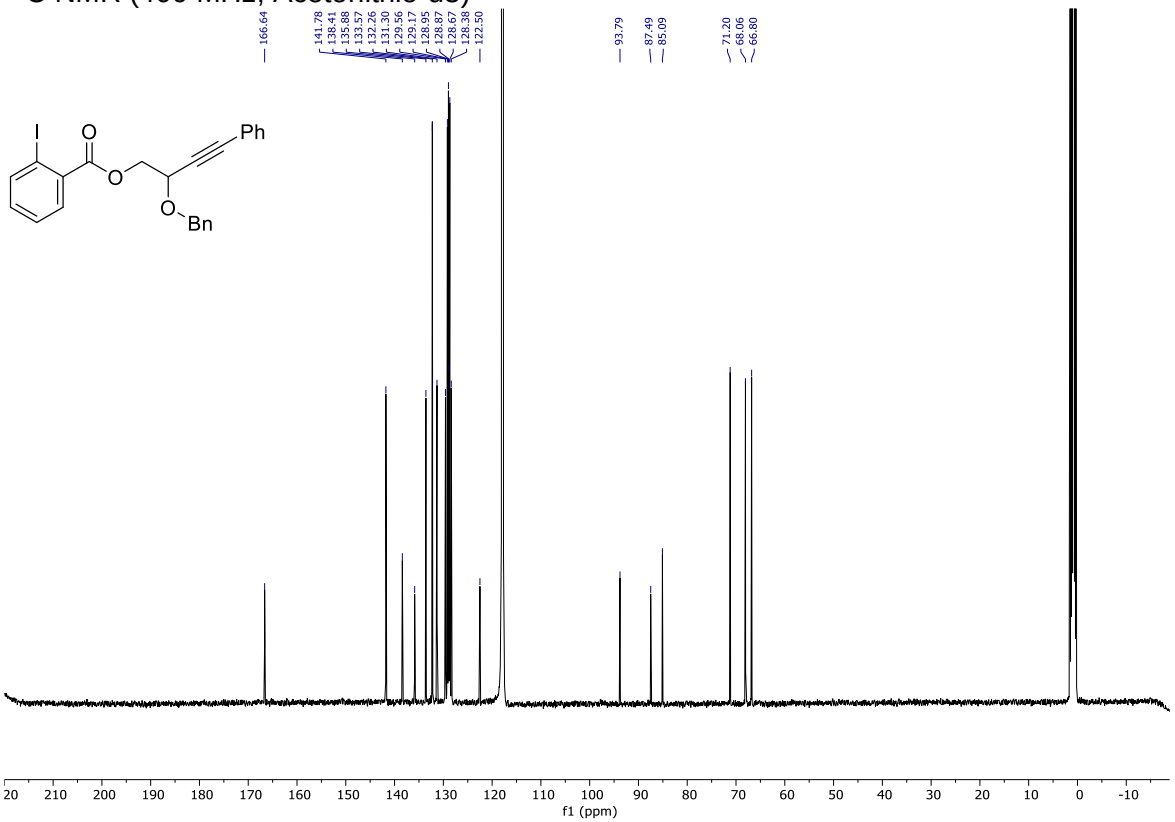


4.22b

^{1}H NMR (400 MHz, Acetonitrile-d_3)

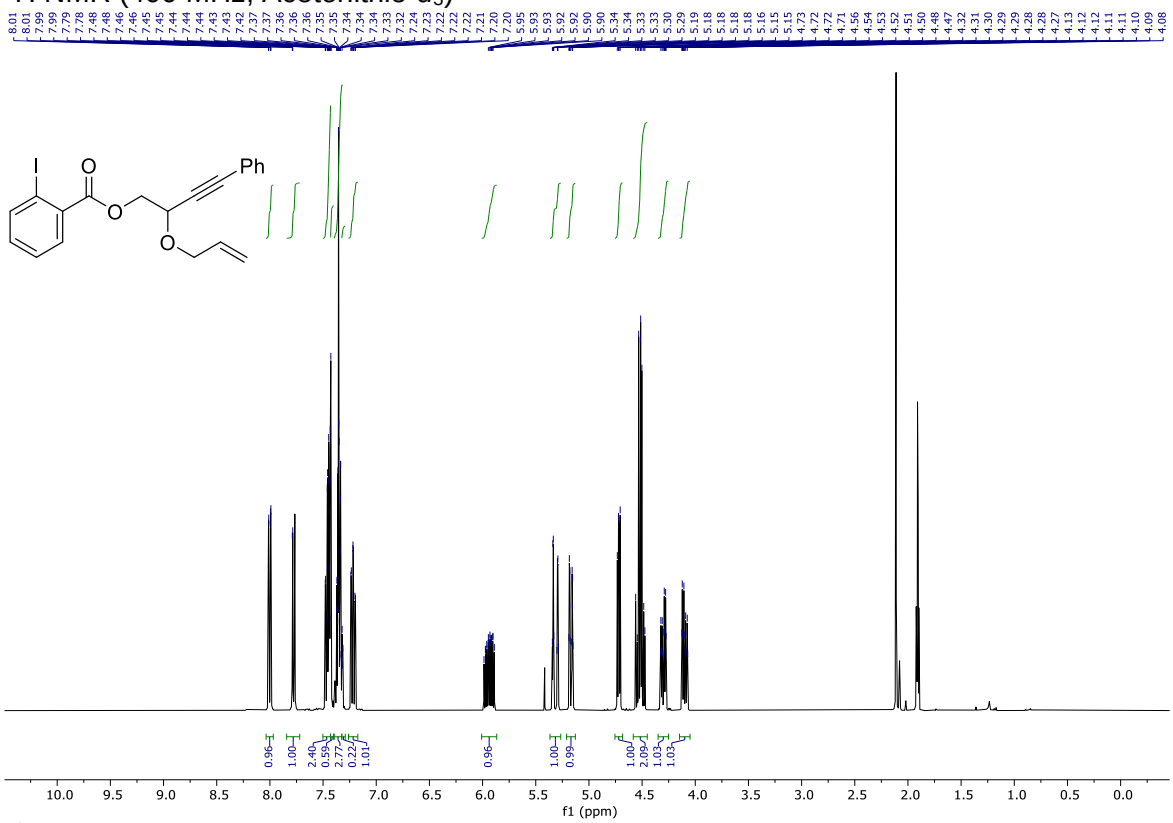


^{13}C NMR (400 MHz, Acetonitrile-d3)

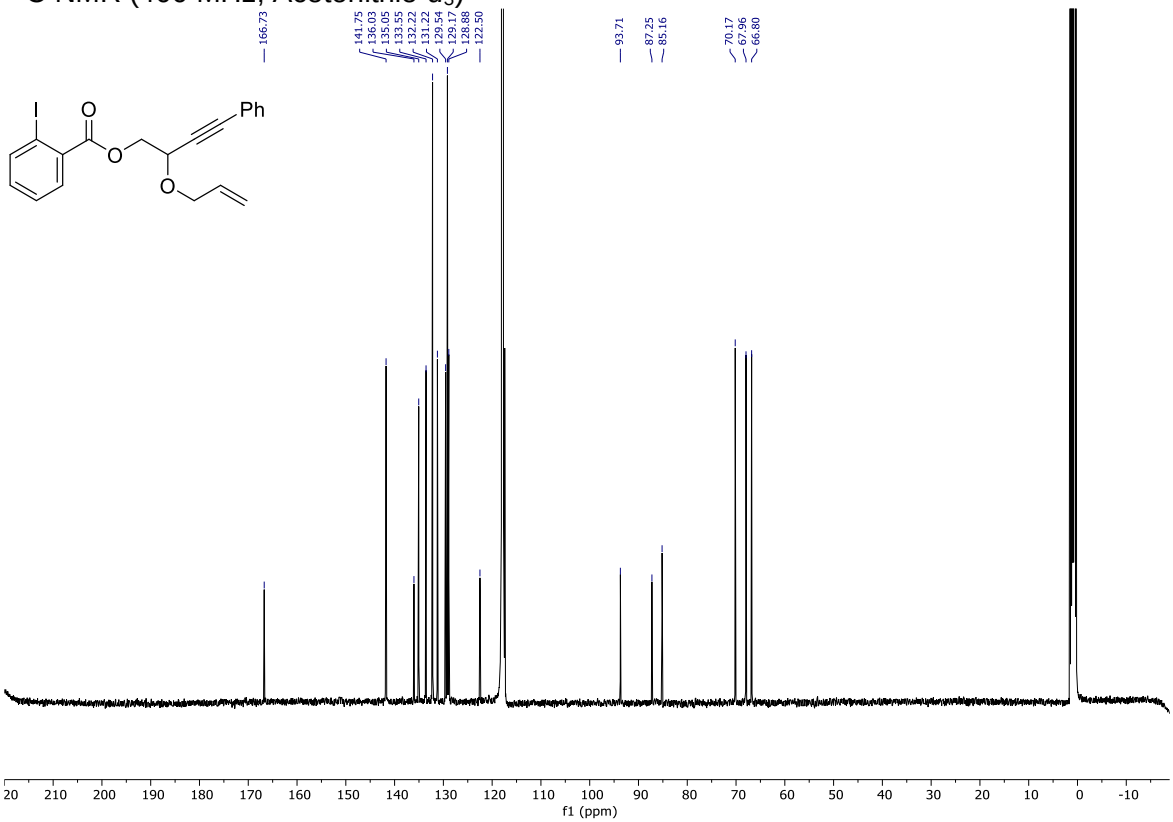


4.22c

^{1}H NMR (400 MHz, Acetonitrile-d_3)

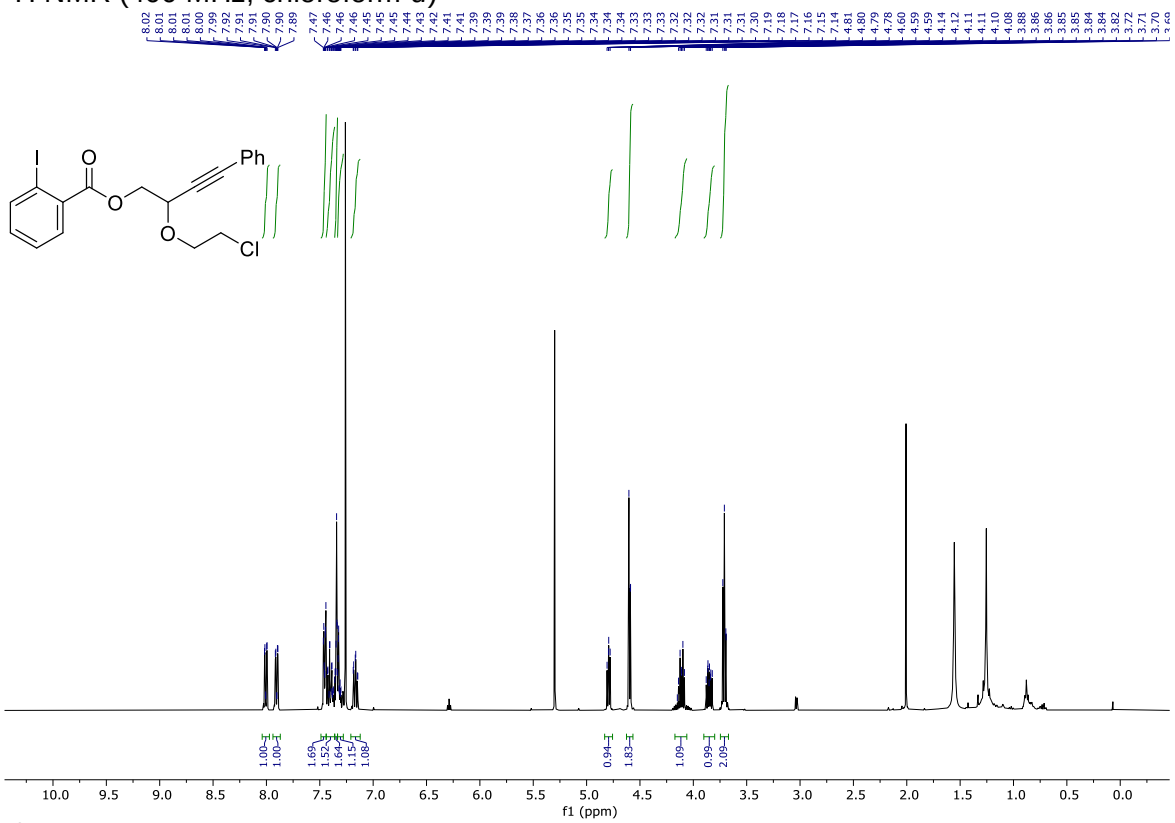


^{13}C NMR (400 MHz, Acetonitrile-d_3)

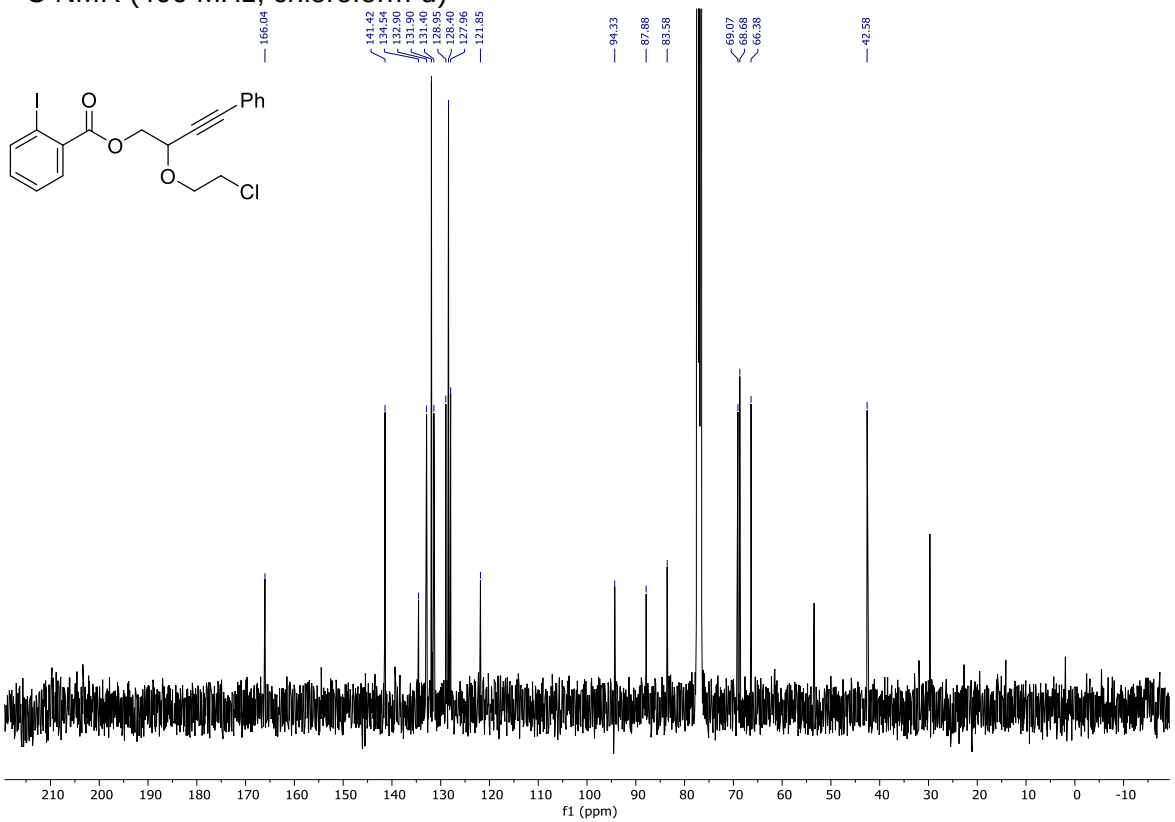


4.22d

^{1}H NMR (400 MHz, chloroform-*d*)

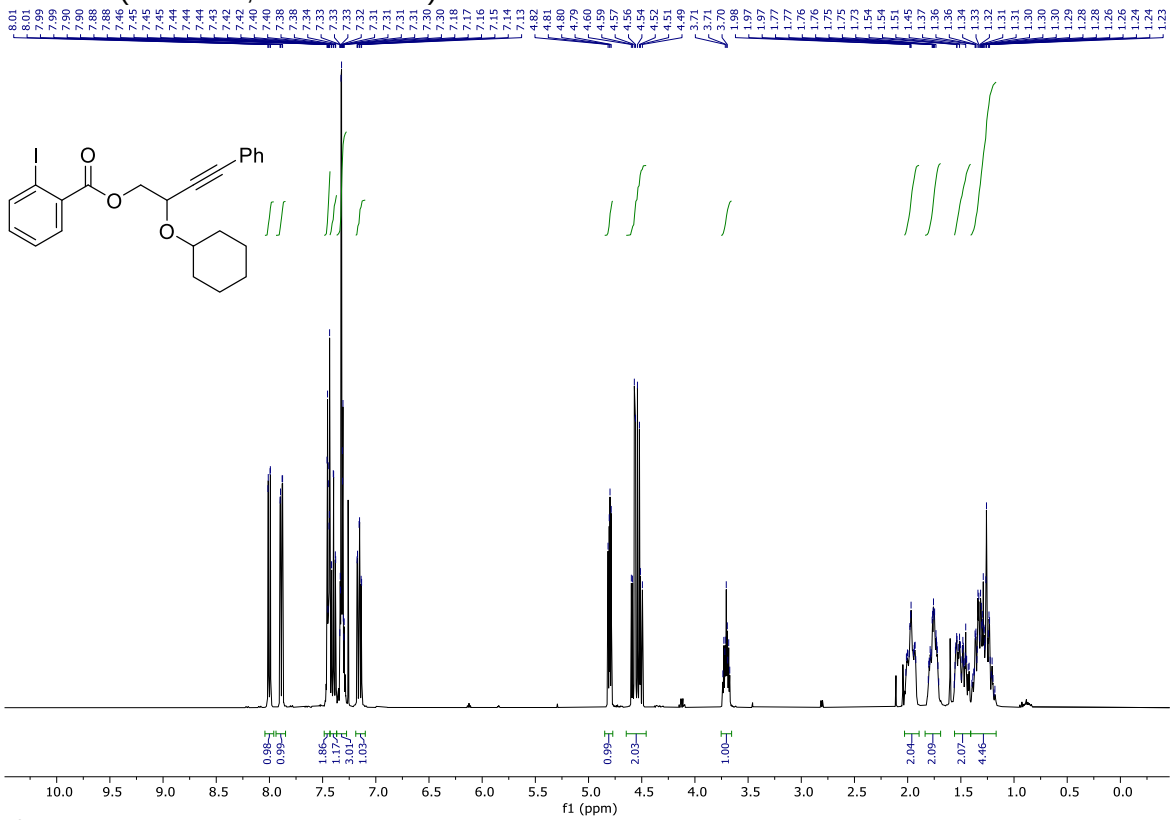


^{13}C NMR (400 MHz, chloroform-*d*)

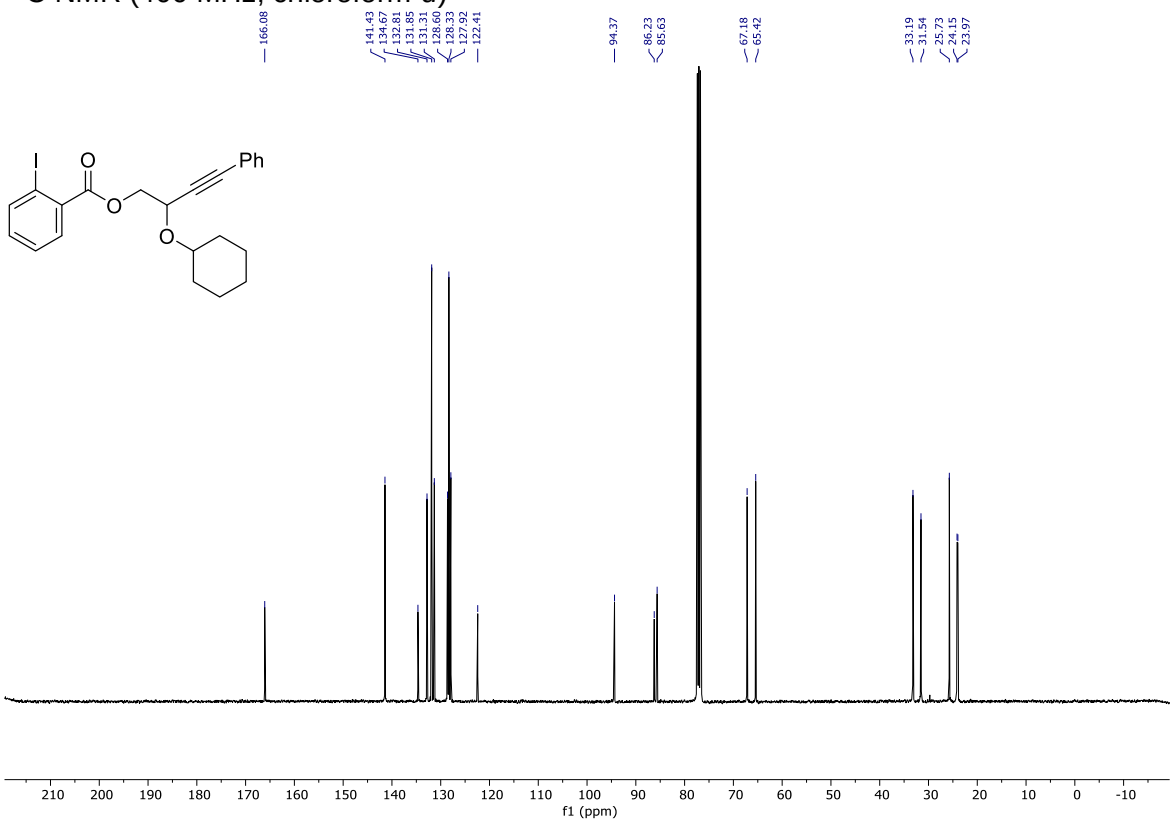


4.22e

^{1}H NMR (400 MHz, chloroform-*d*)

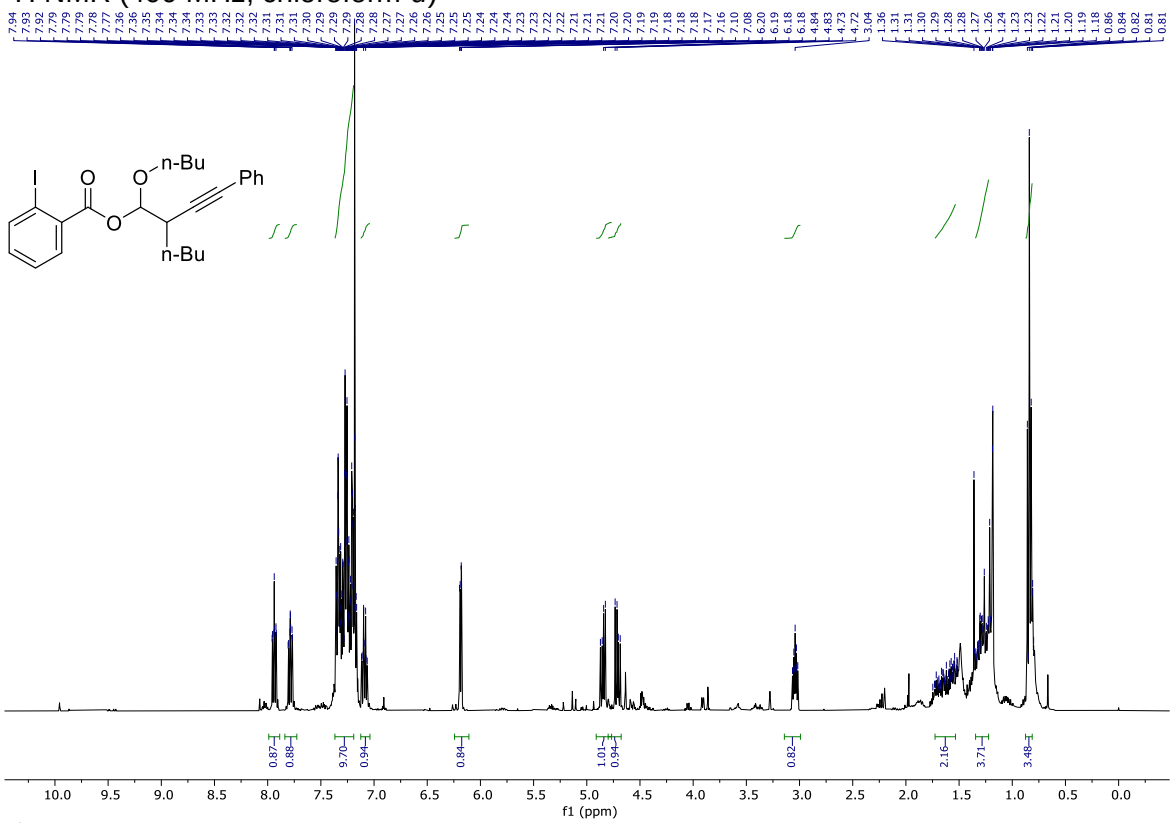


^{13}C NMR (400 MHz, chloroform-*d*)

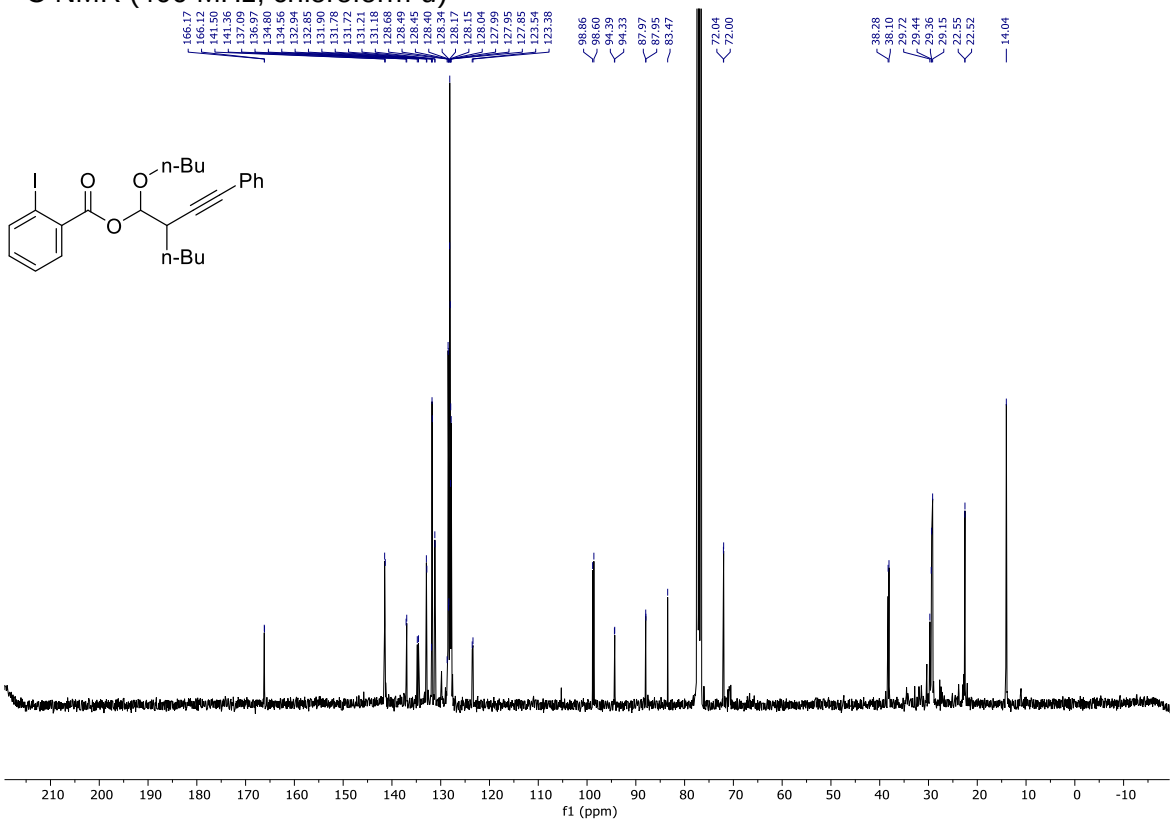


4.22fa

^{1}H NMR (400 MHz, chloroform-*d*)

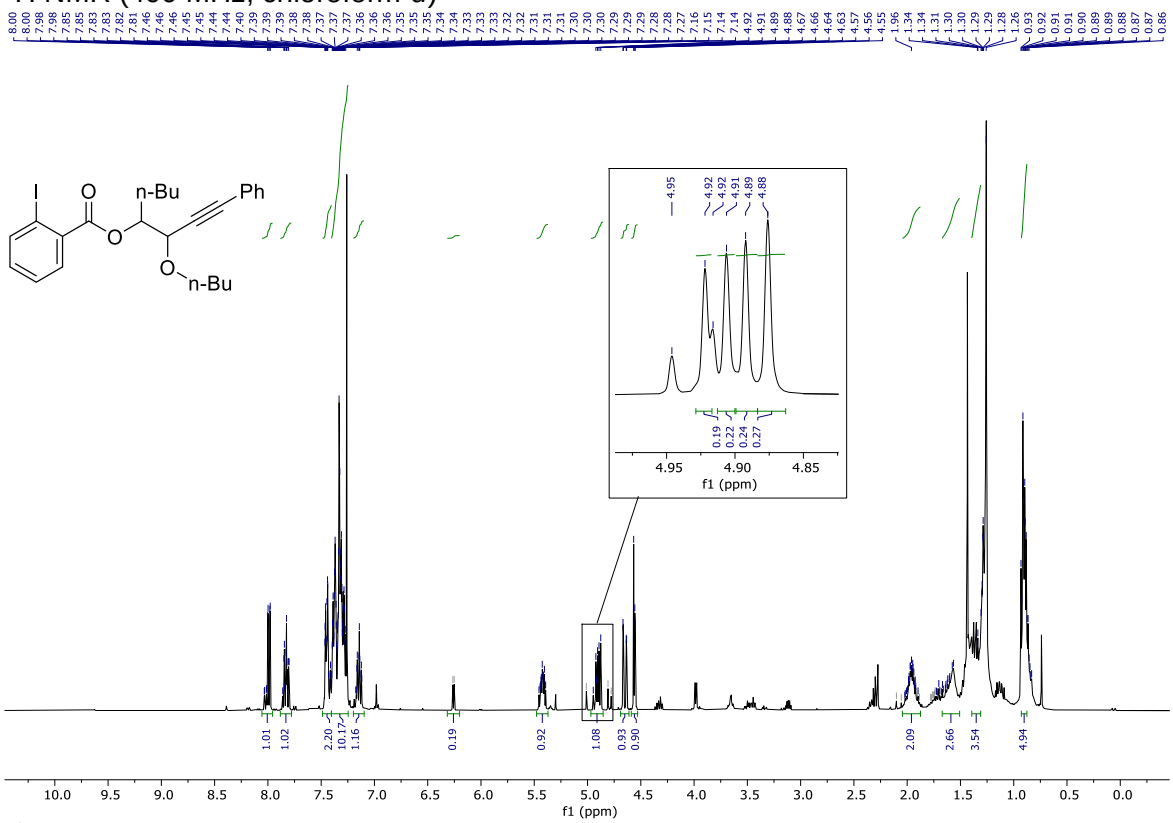


^{13}C NMR (400 MHz, chloroform-*d*)

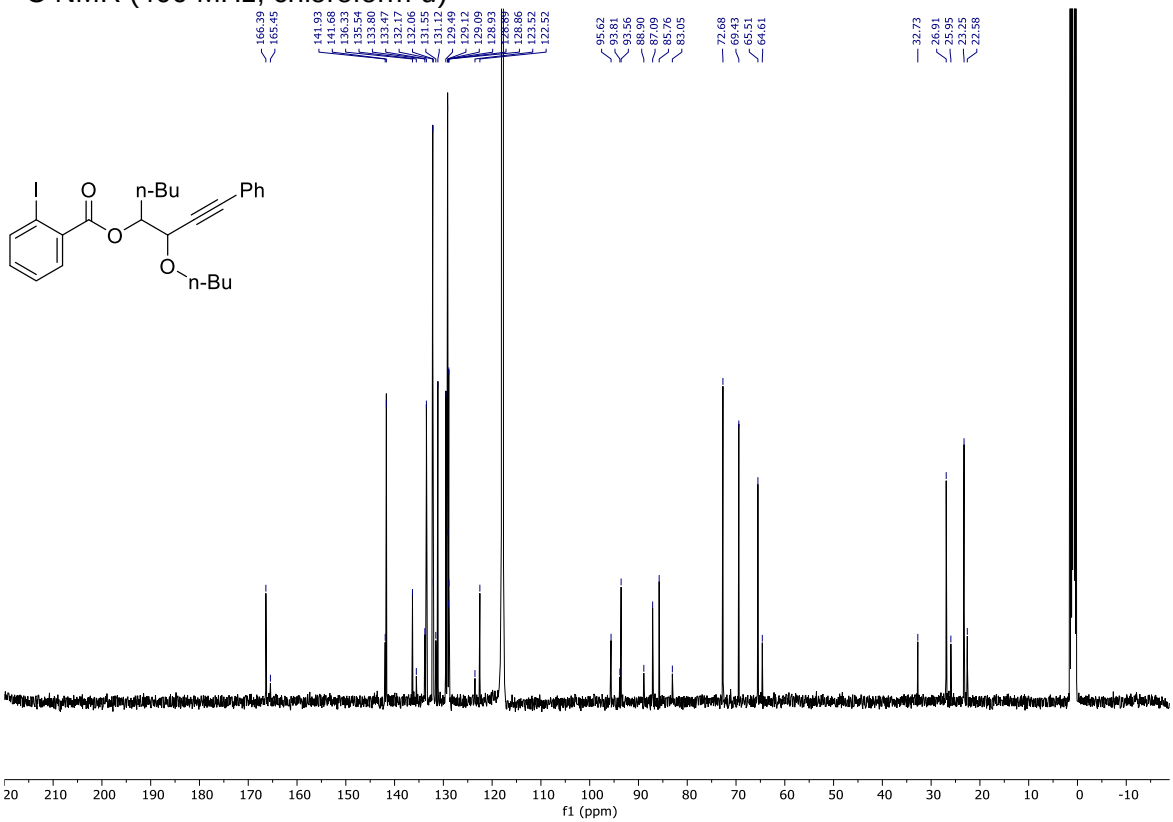


4.22fb

^{1}H NMR (400 MHz, chloroform-*d*)

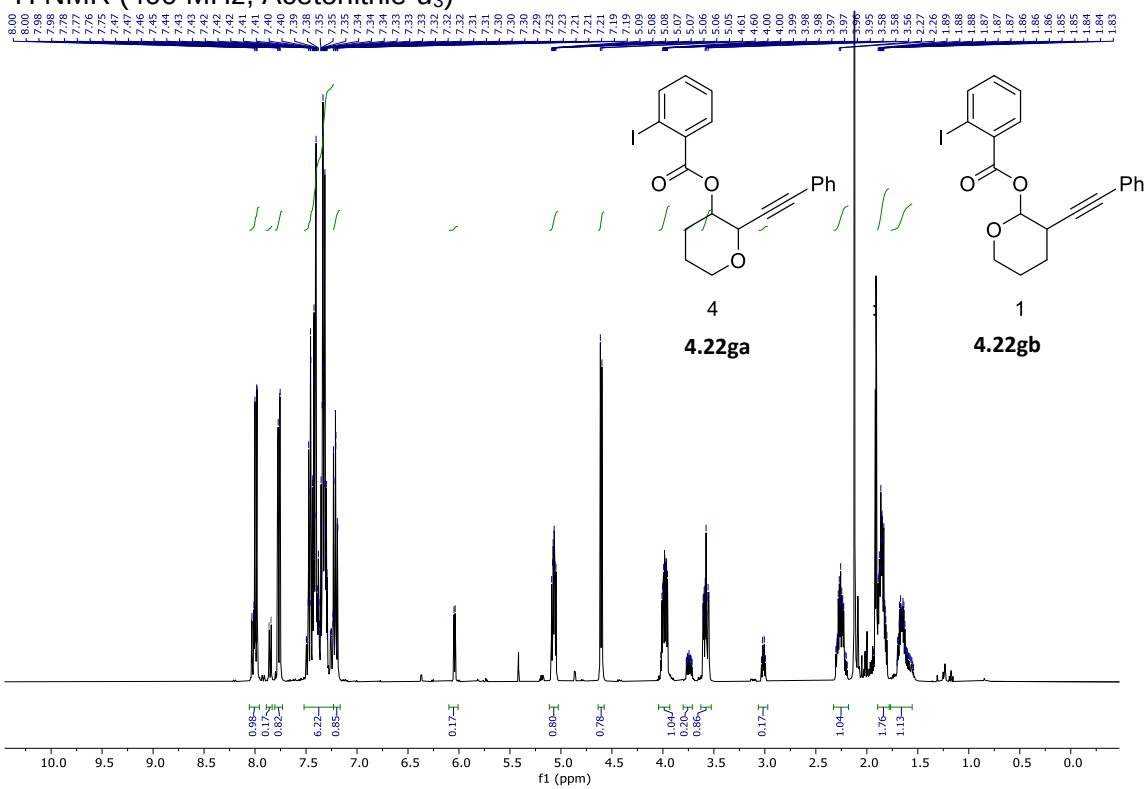


^{13}C NMR (400 MHz, chloroform-*d*)

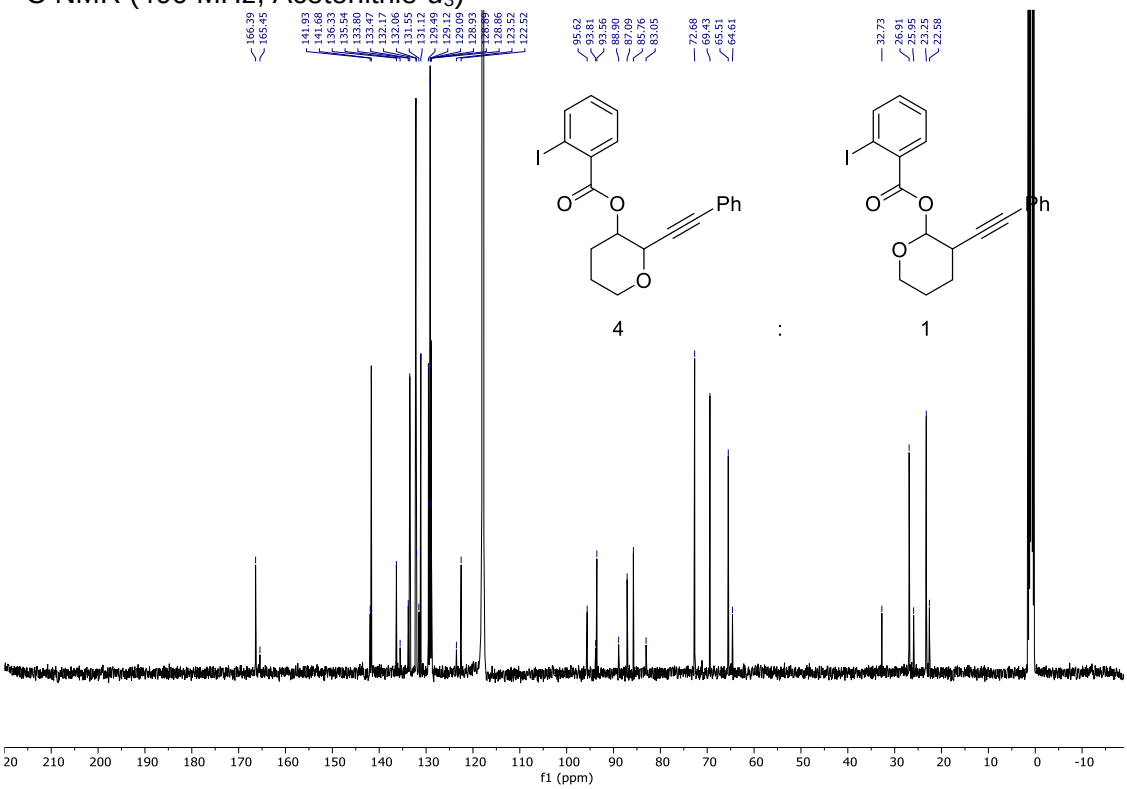


4.22ga + 4.22gb – 4:1 regioisomeric mixture

^{1}H NMR (400 MHz, Acetonitrile-d_3)

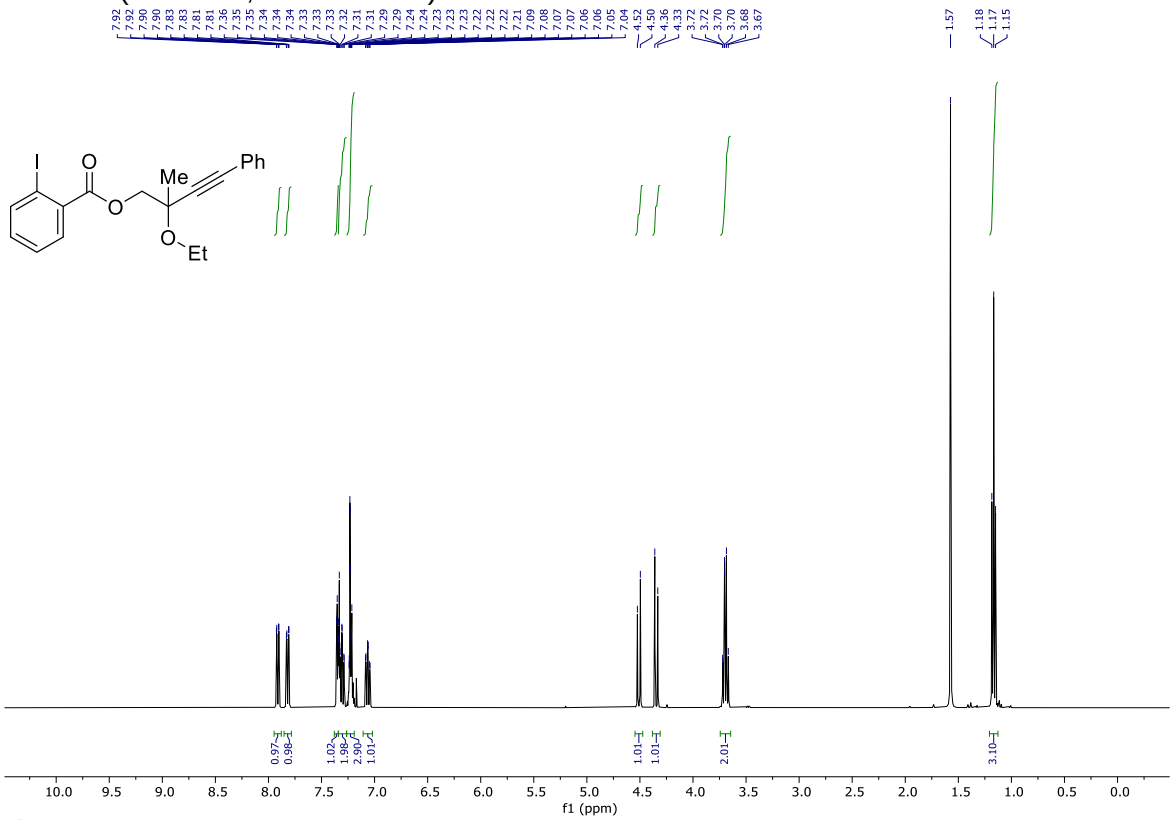


^{13}C NMR (400 MHz, Acetonitrile-d_3)

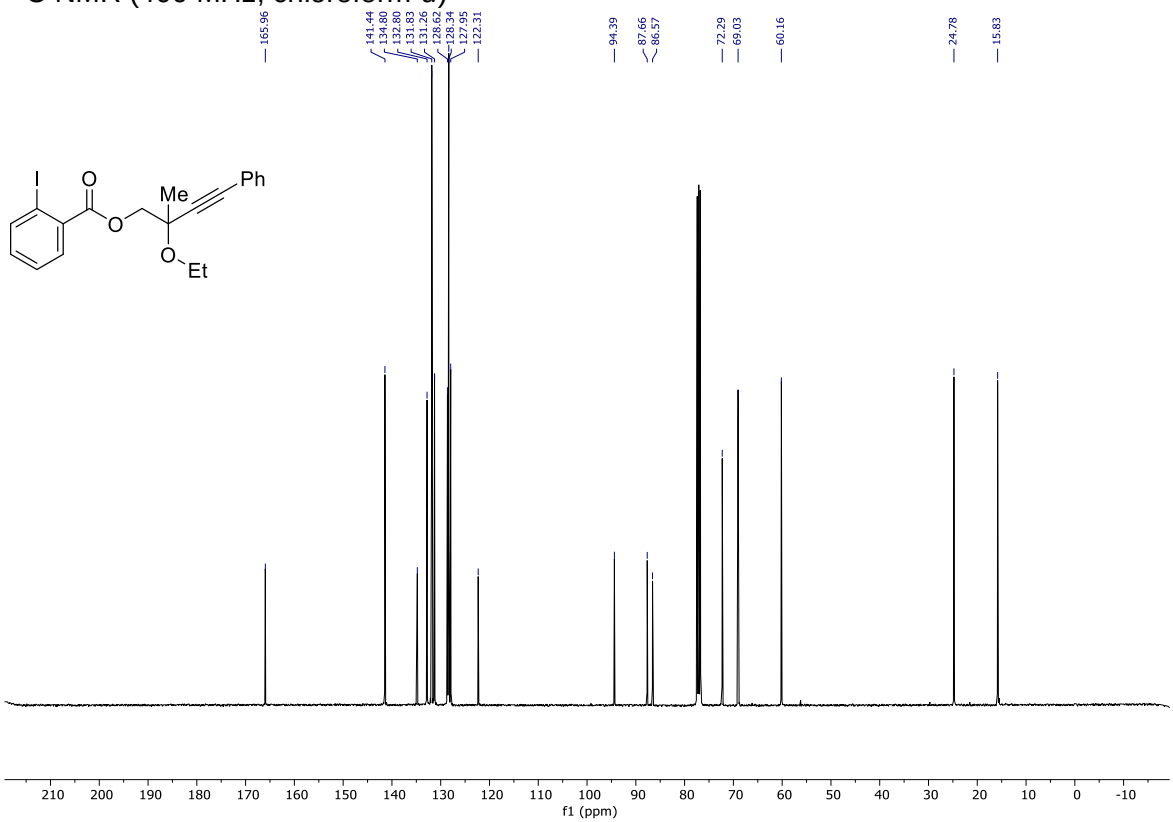


4.22h

^{1}H NMR (400 MHz, chloroform-*d*)

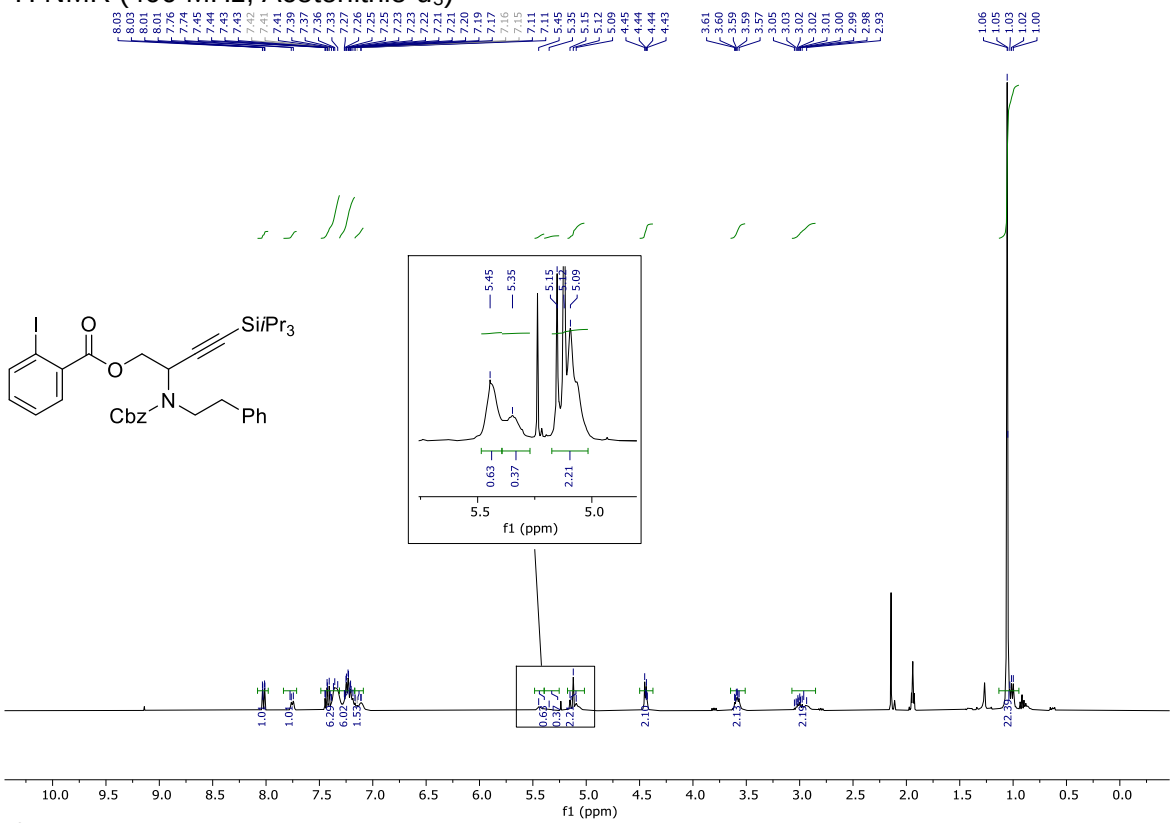


^{13}C NMR (400 MHz, chloroform-*d*)

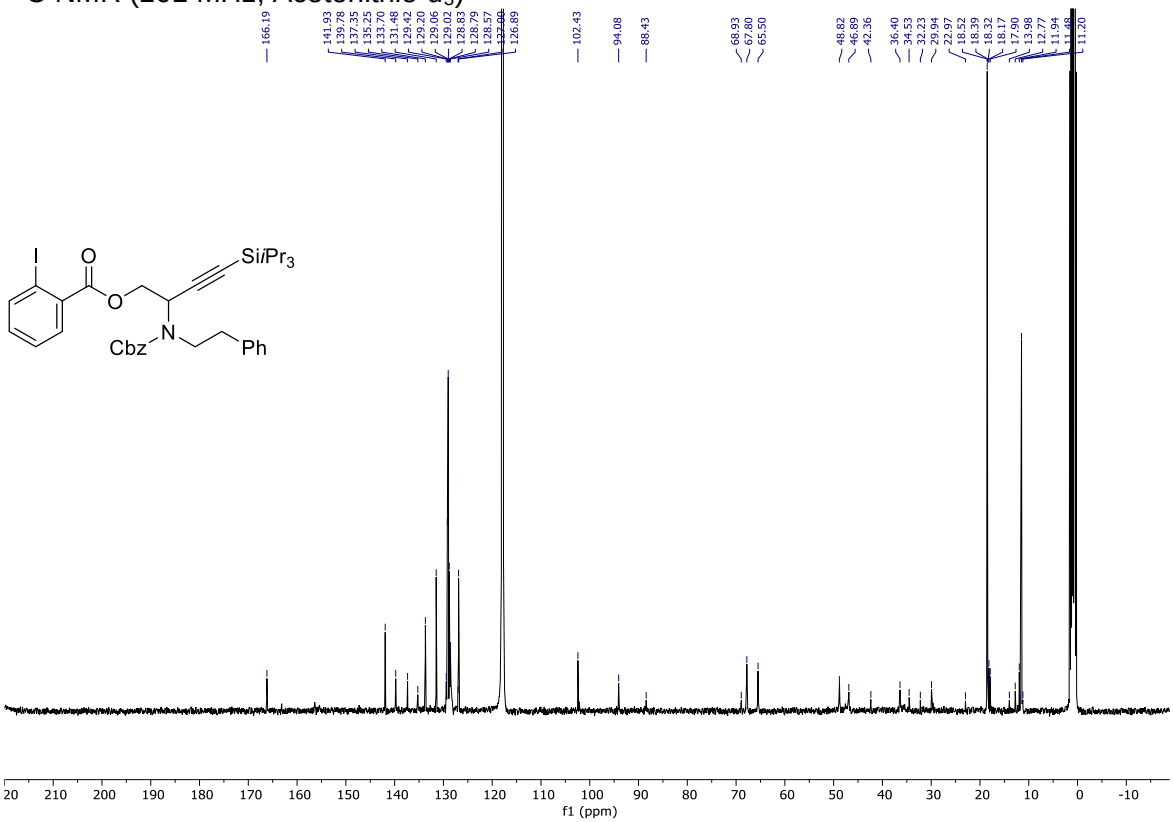


4.23a

^{1}H NMR (400 MHz, Acetonitrile-d_3)

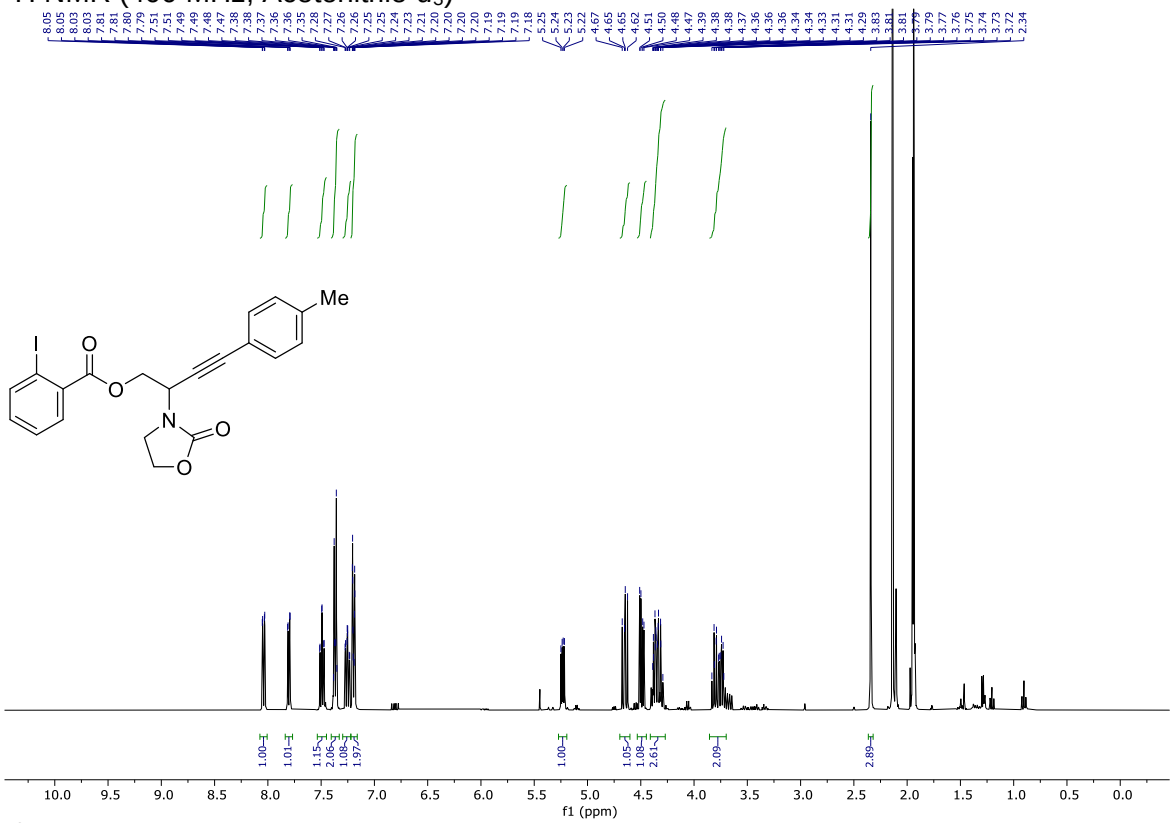


^{13}C NMR (101 MHz, Acetonitrile-d_3)

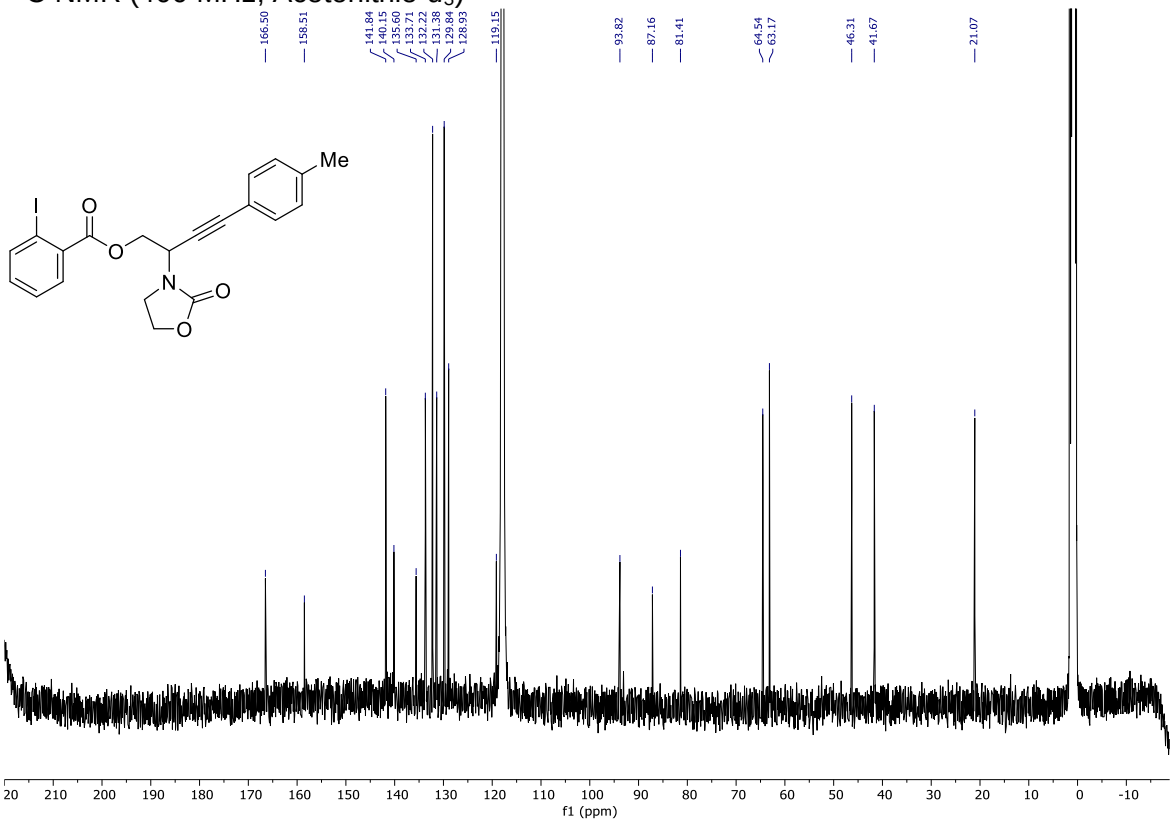


4.23b

^{1}H NMR (400 MHz, Acetonitrile-d_3)

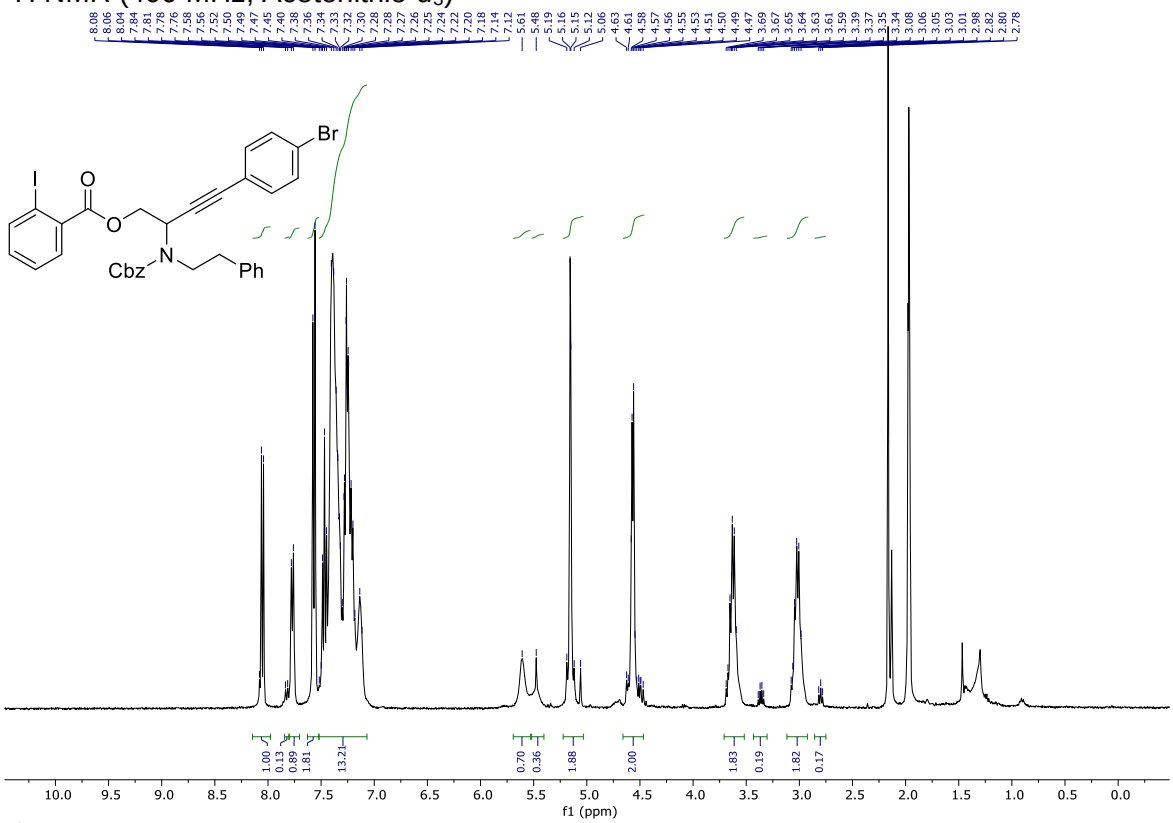


^{13}C NMR (400 MHz, Acetonitrile-d_3)

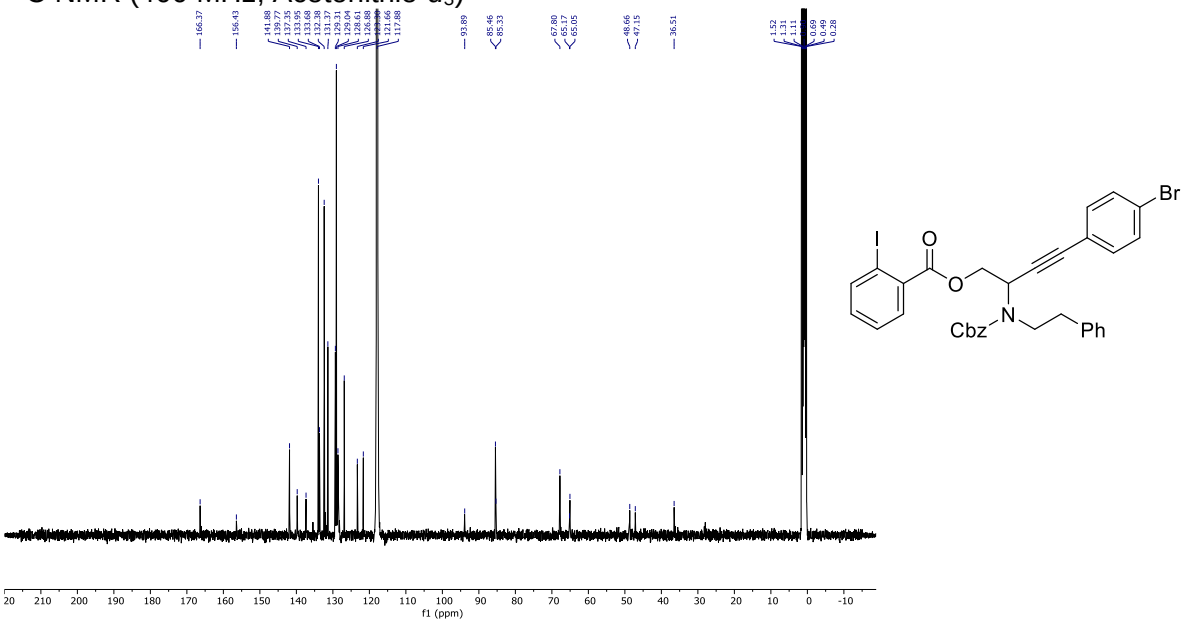


4.23c

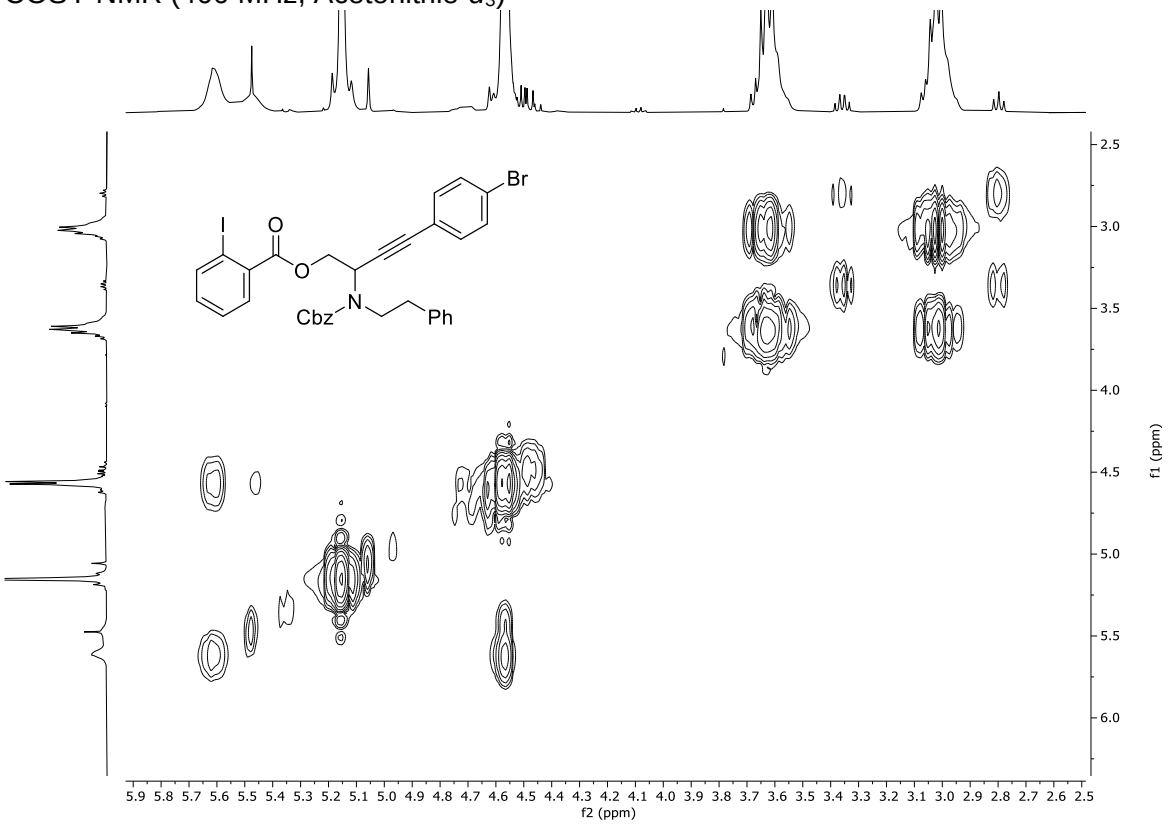
^{1}H NMR (400 MHz, Acetonitrile-d_3)



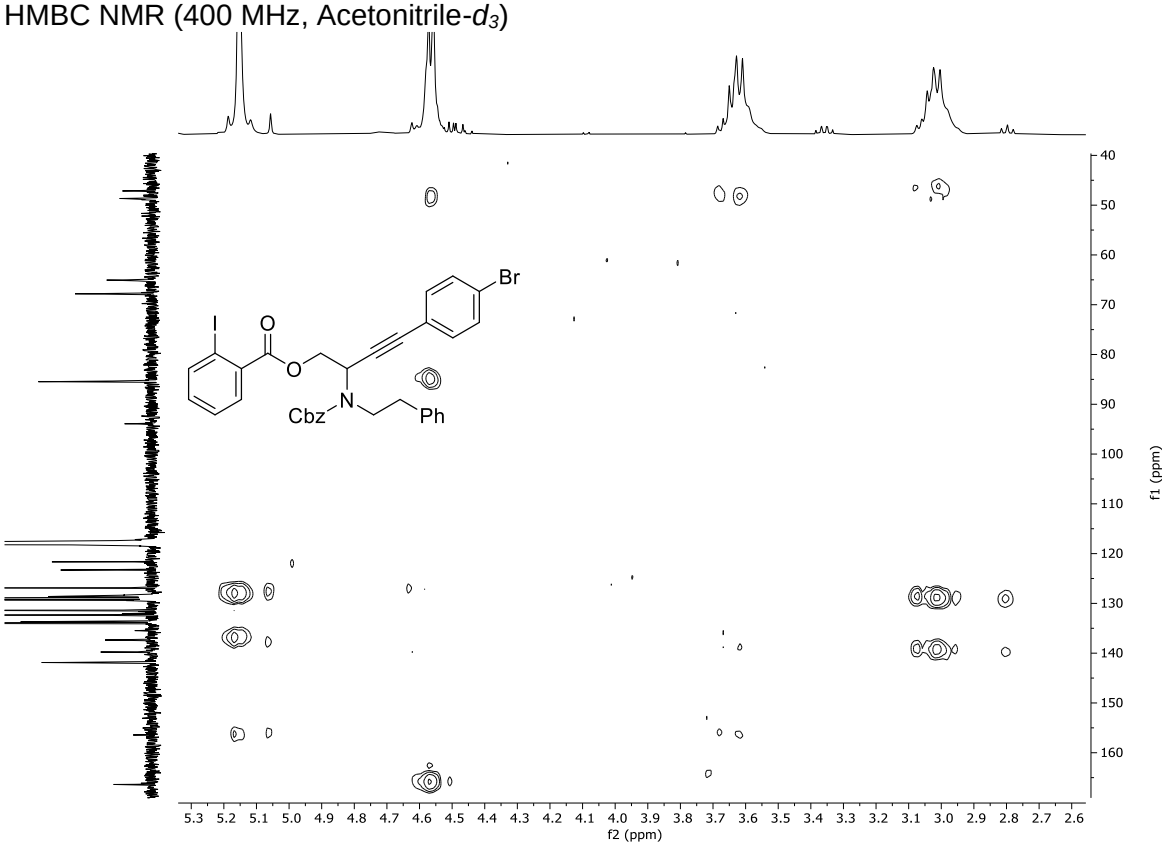
^{13}C NMR (400 MHz, Acetonitrile-d_3)



COSY NMR (400 MHz, Acetonitrile-d_3)

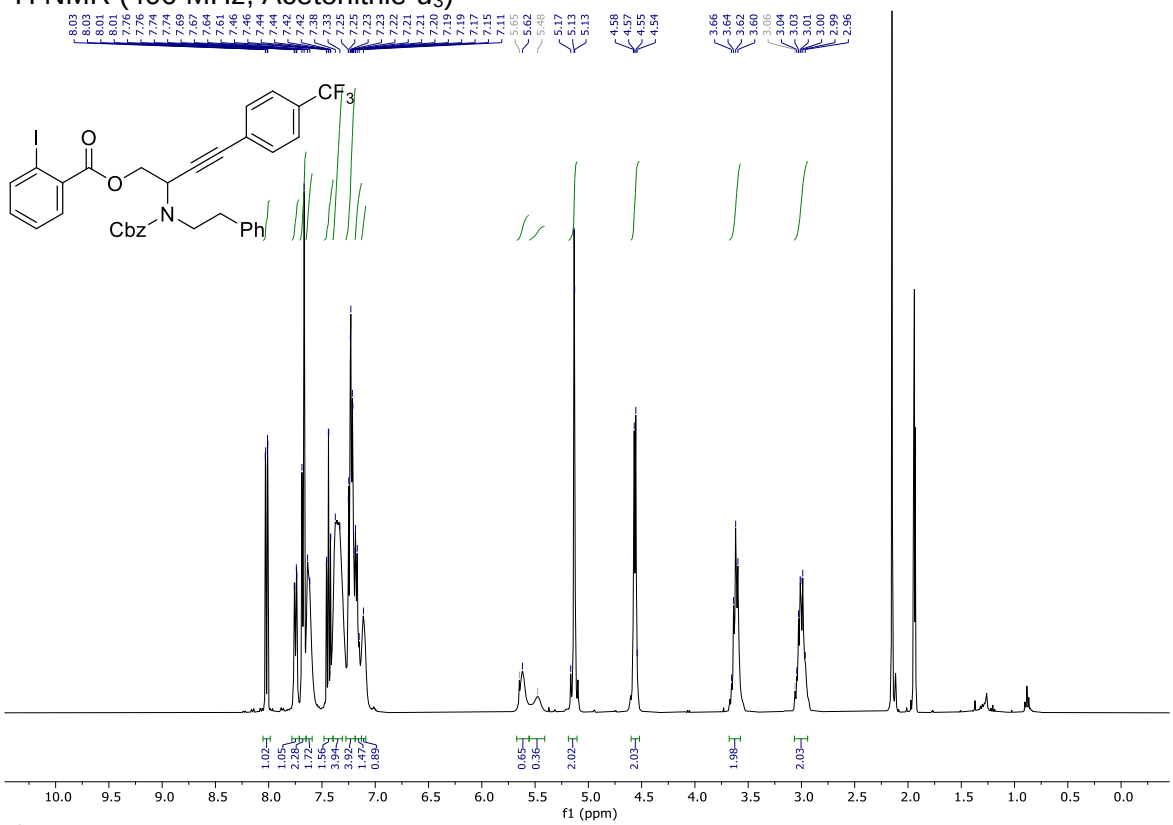


HMBC NMR (400 MHz, Acetonitrile-d_3)

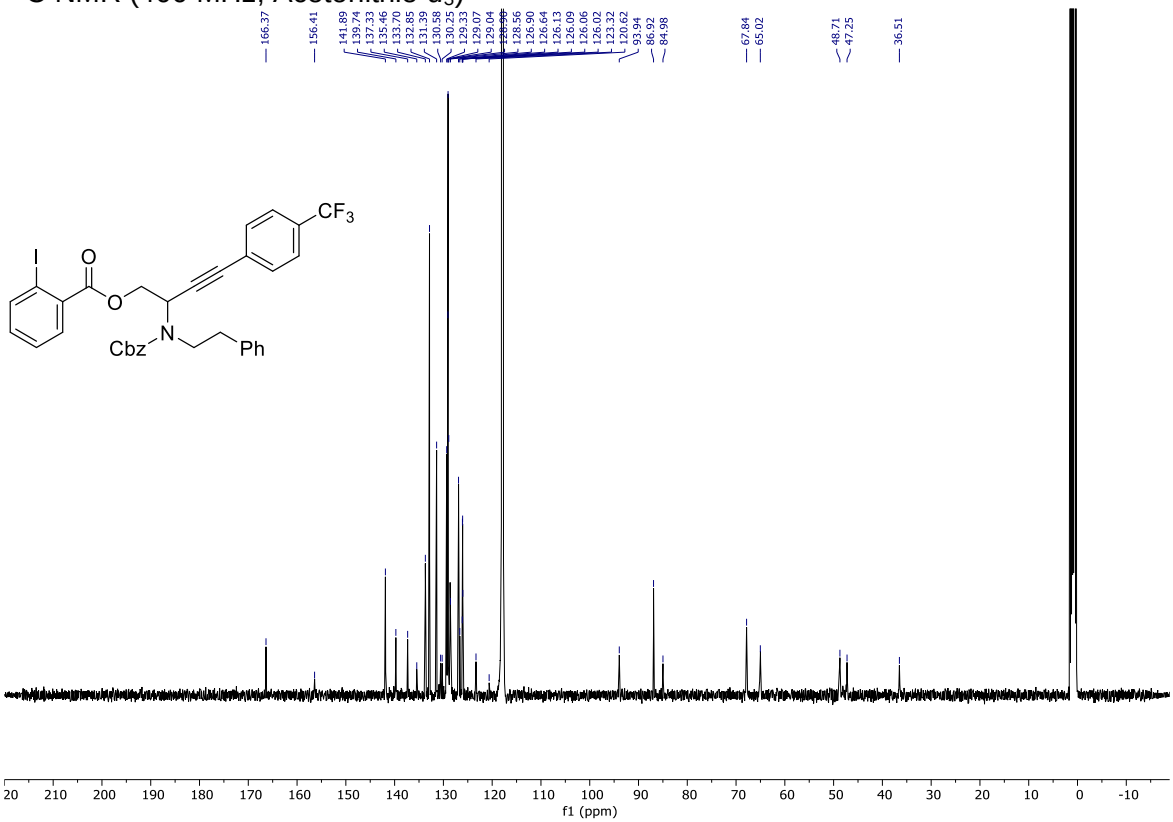


4.23d

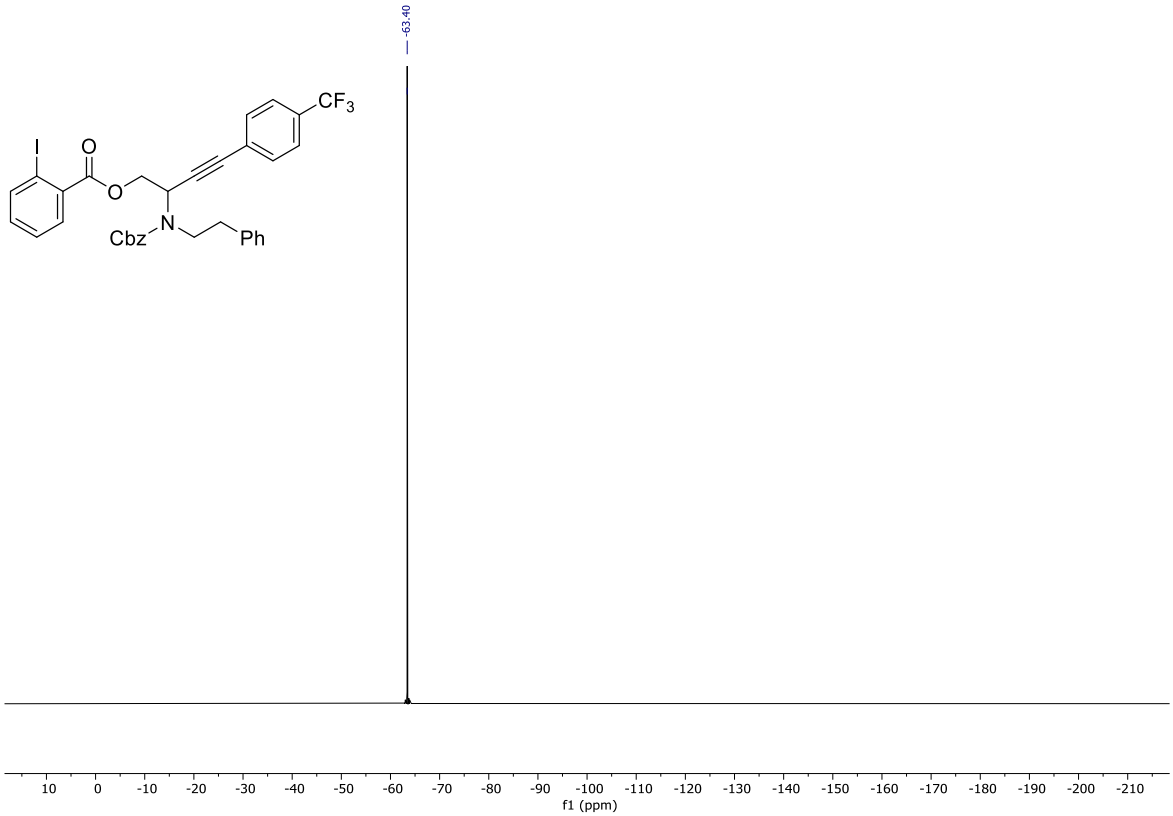
^{1}H NMR (400 MHz, Acetonitrile-d_3)



^{13}C NMR (400 MHz, Acetonitrile-d_3)

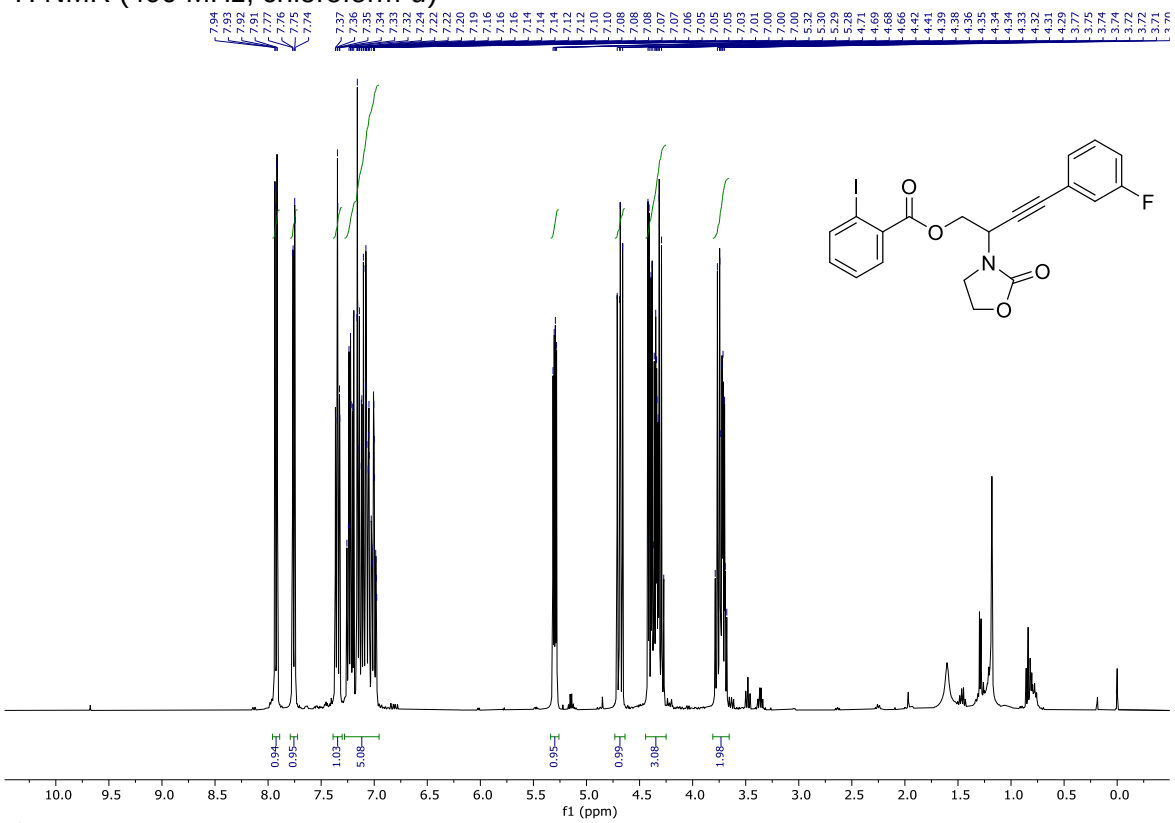


^{19}F NMR (376 MHz, Acetonitrile-d_3)

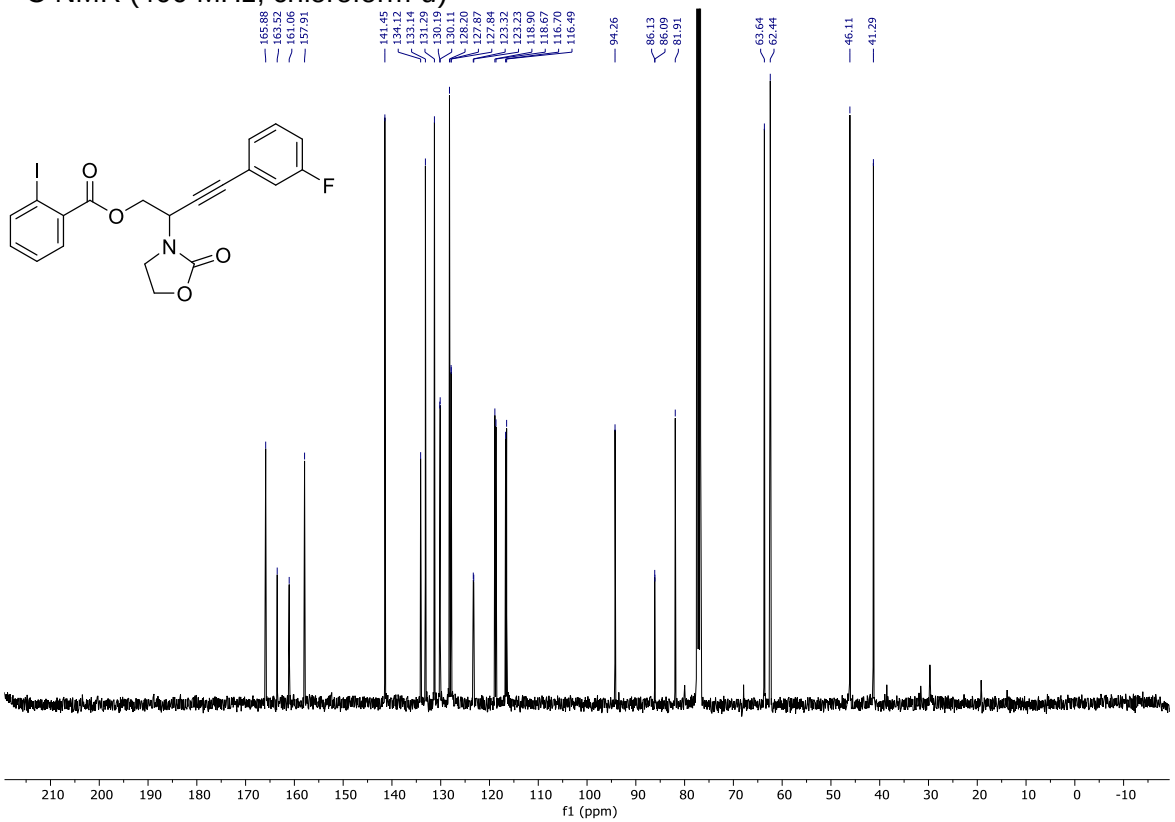

-63.40
CF3
I
O
O
N
Cbz
Ph
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

4.23e

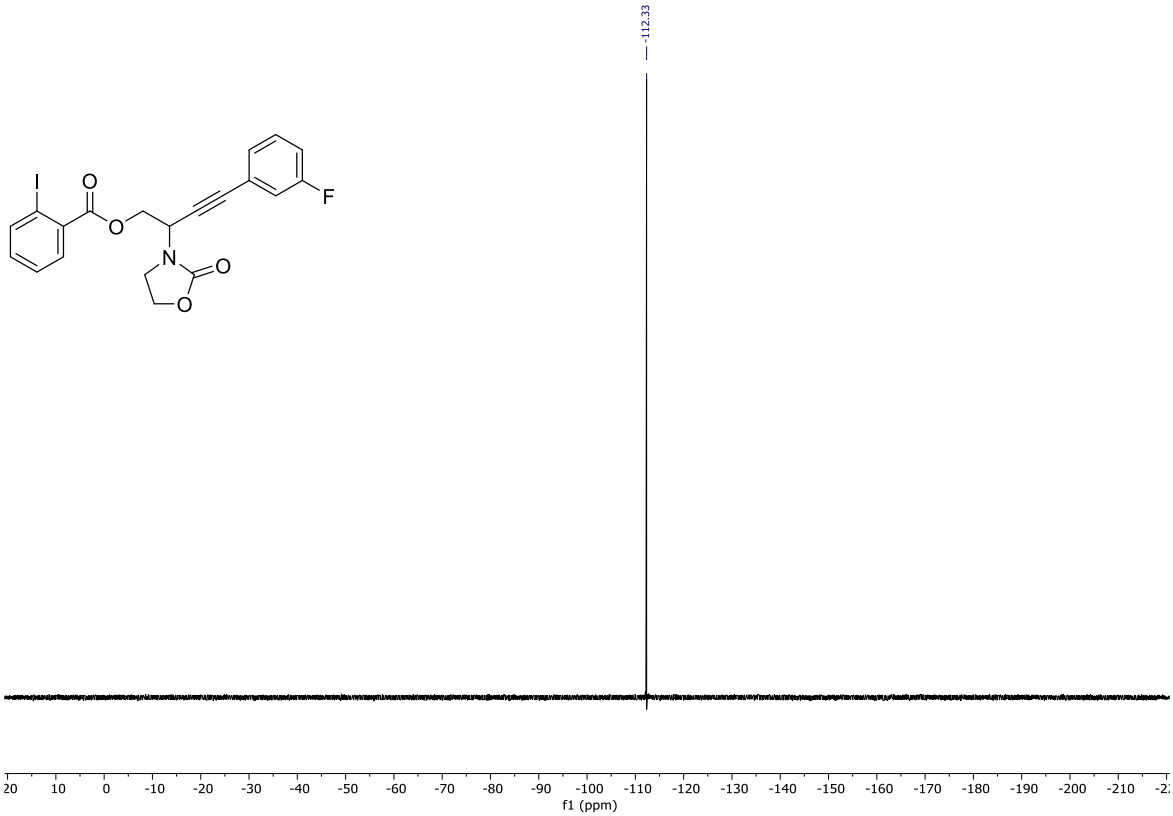
^{1}H NMR (400 MHz, chloroform-*d*)



^{13}C NMR (400 MHz, chloroform-*d*)



^{19}F NMR (376 MHz, Chloroform-d_3)


-112.33
I
O
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N
O
O
F
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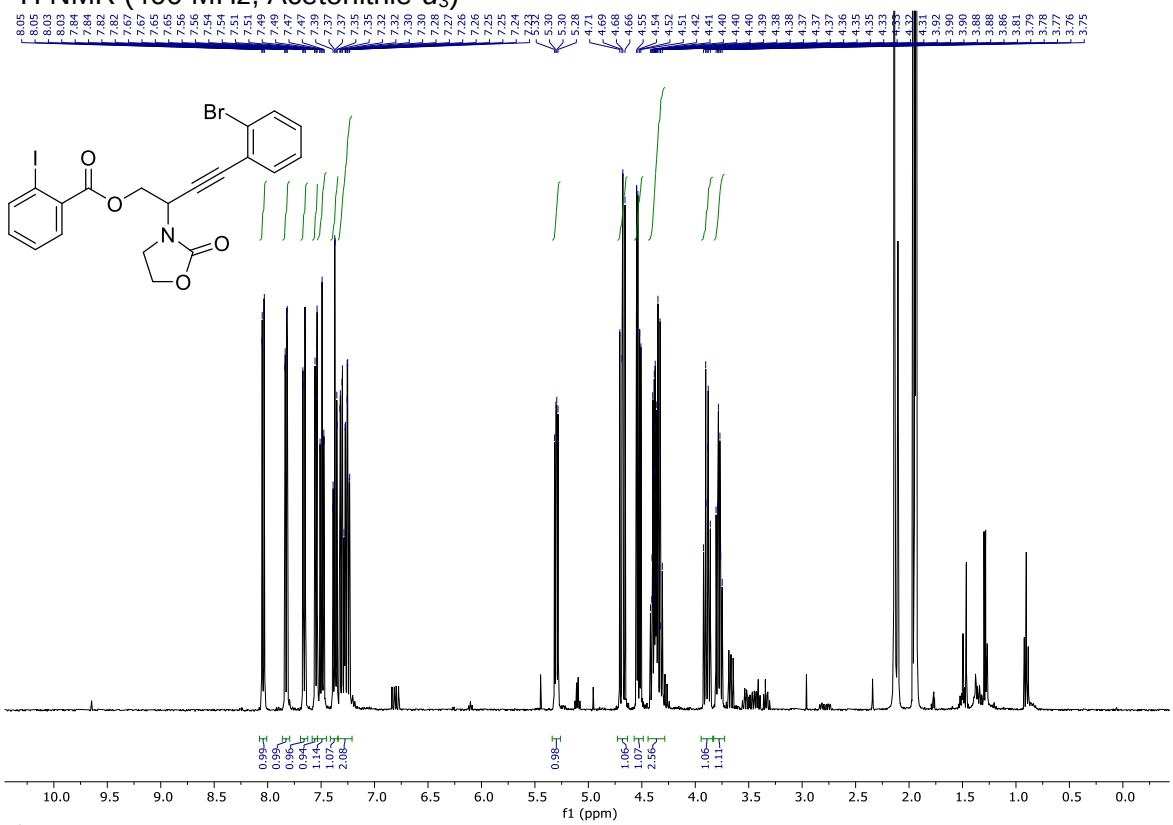
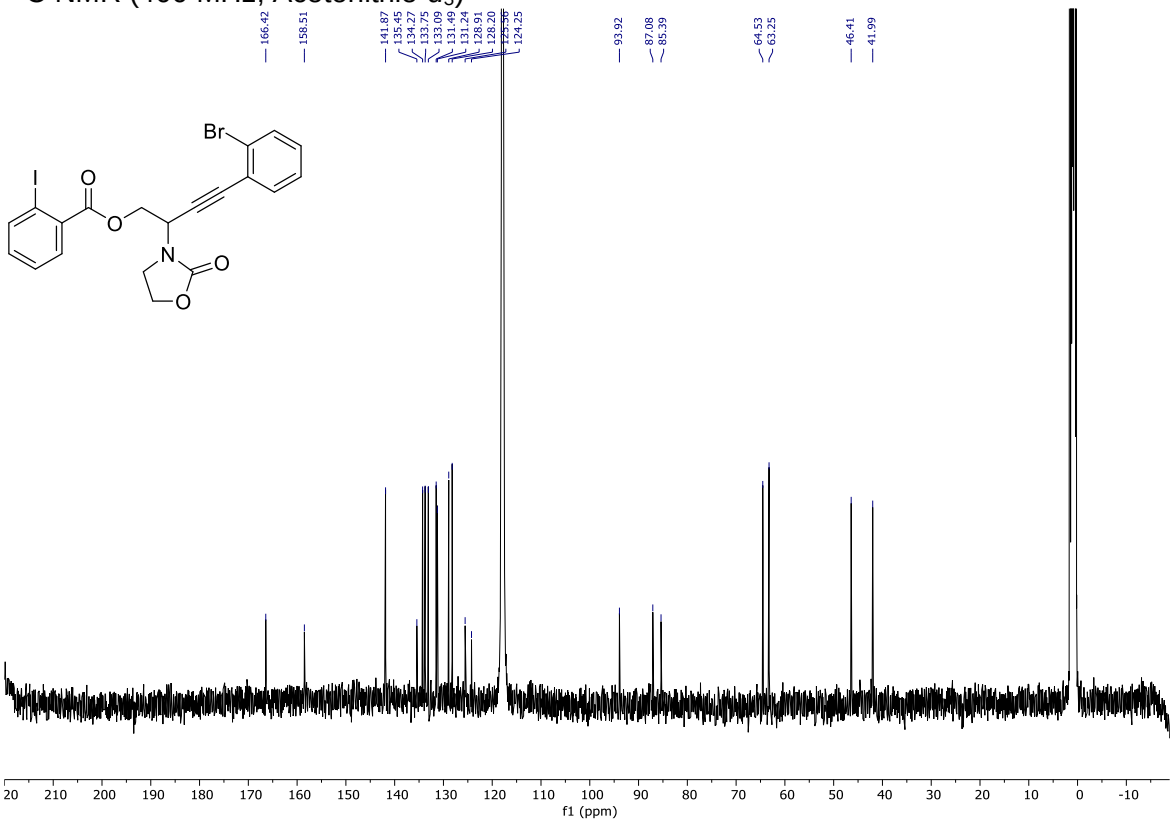
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

4.23f

^{1}H NMR (400 MHz, Acetonitrile-d_3)

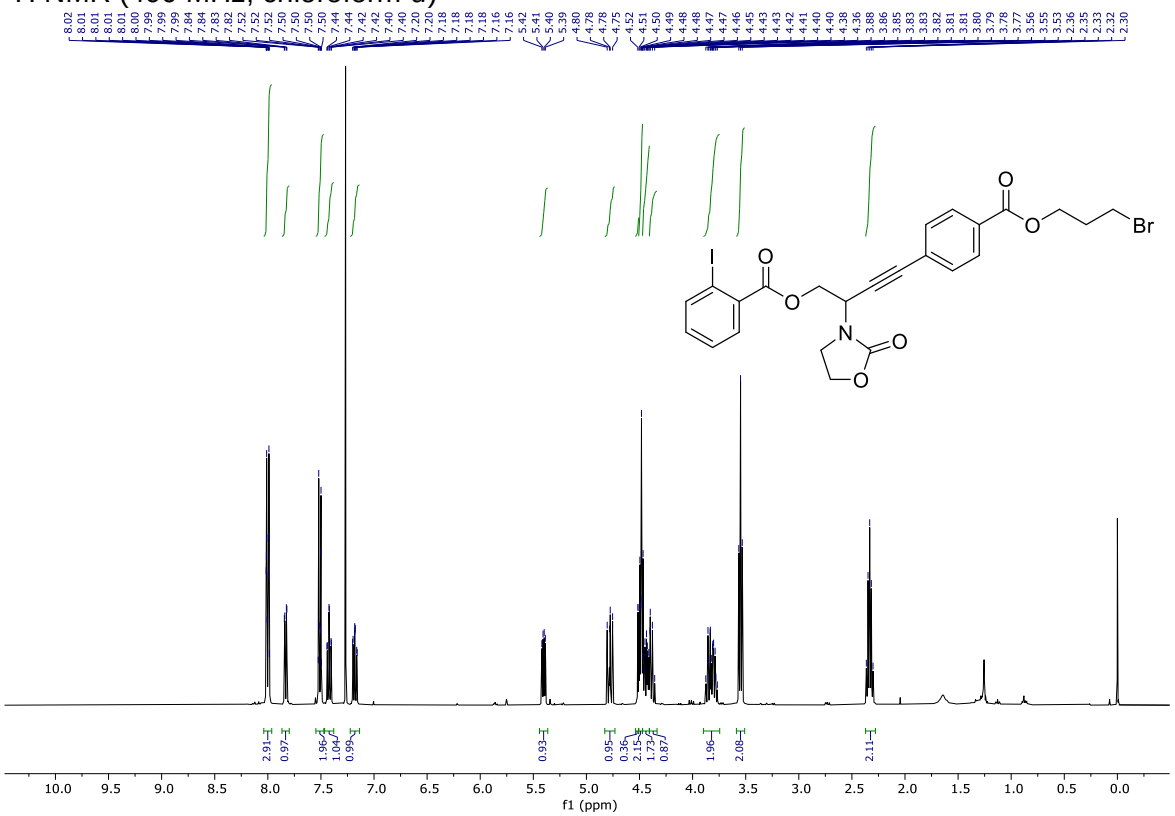


^{13}C NMR (400 MHz, Acetonitrile-d_3)

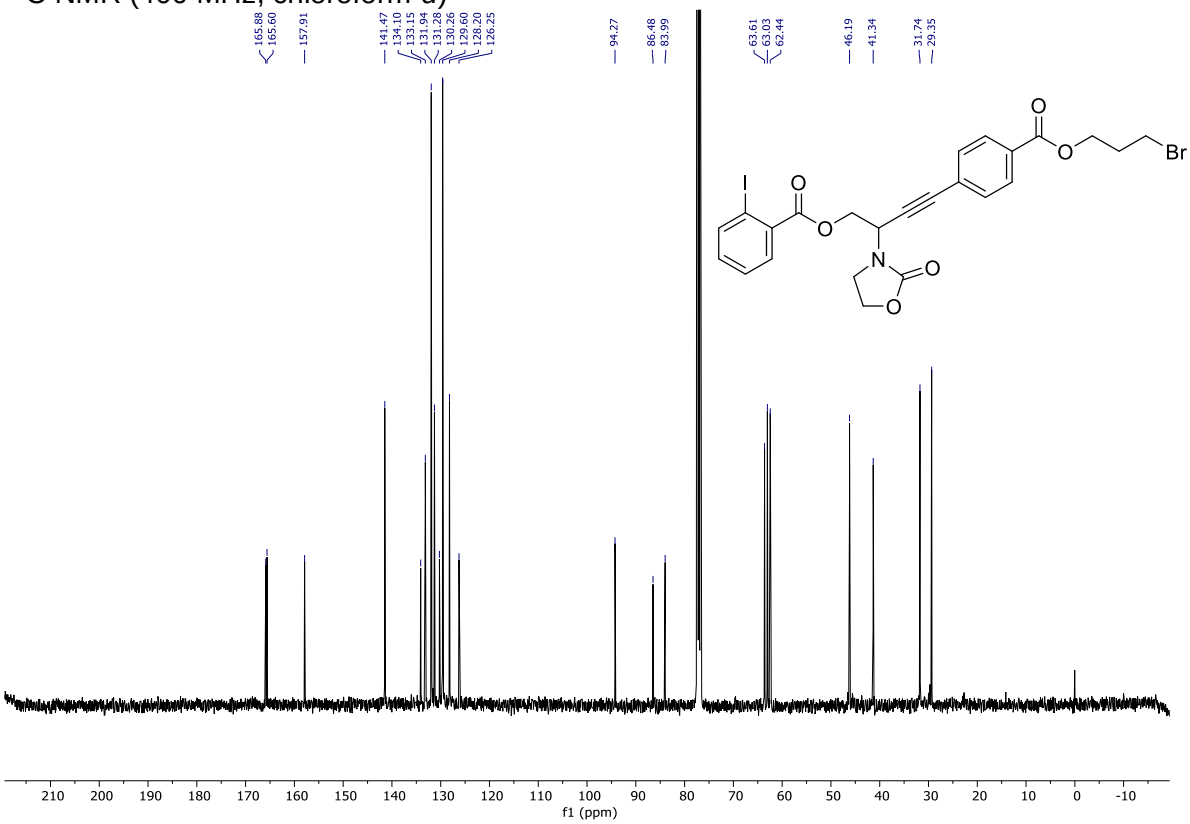


4.23g

^{1}H NMR (400 MHz, chloroform-*d*)

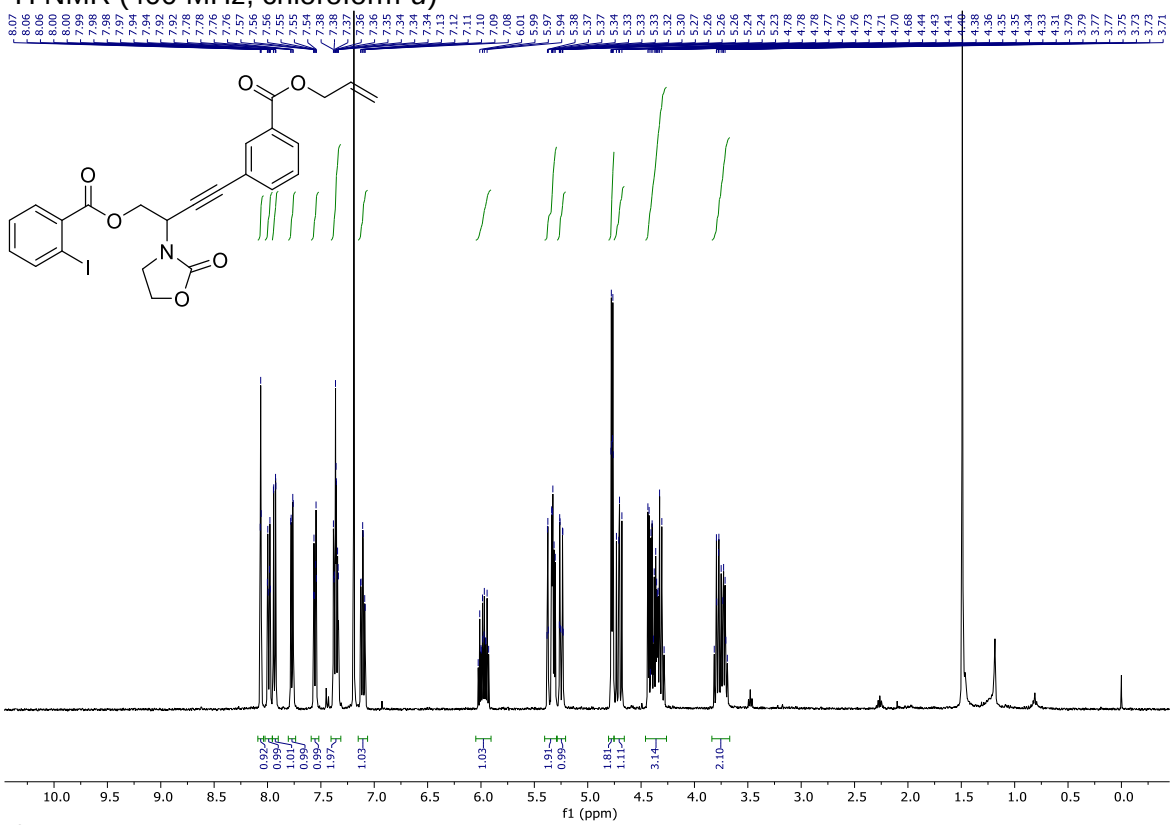


^{13}C NMR (400 MHz, chloroform-*d*)

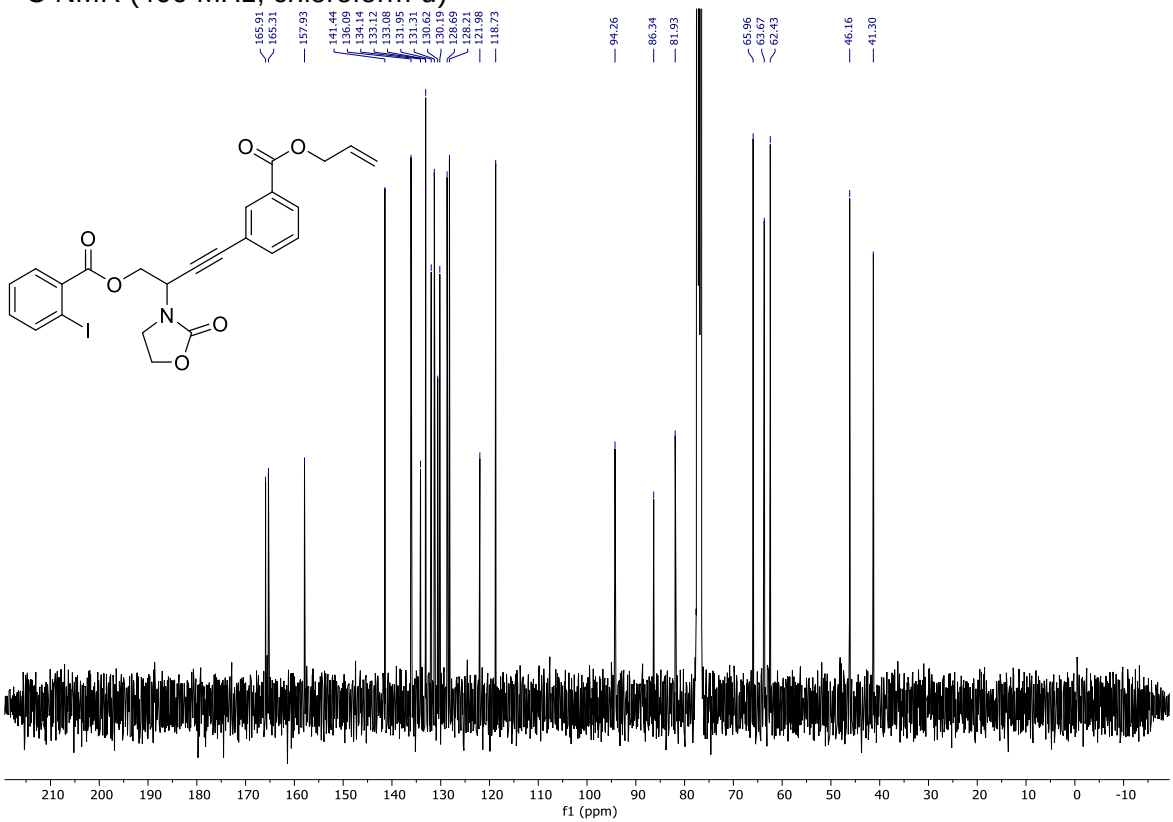


4.23h

^{1}H NMR (400 MHz, chloroform-*d*)

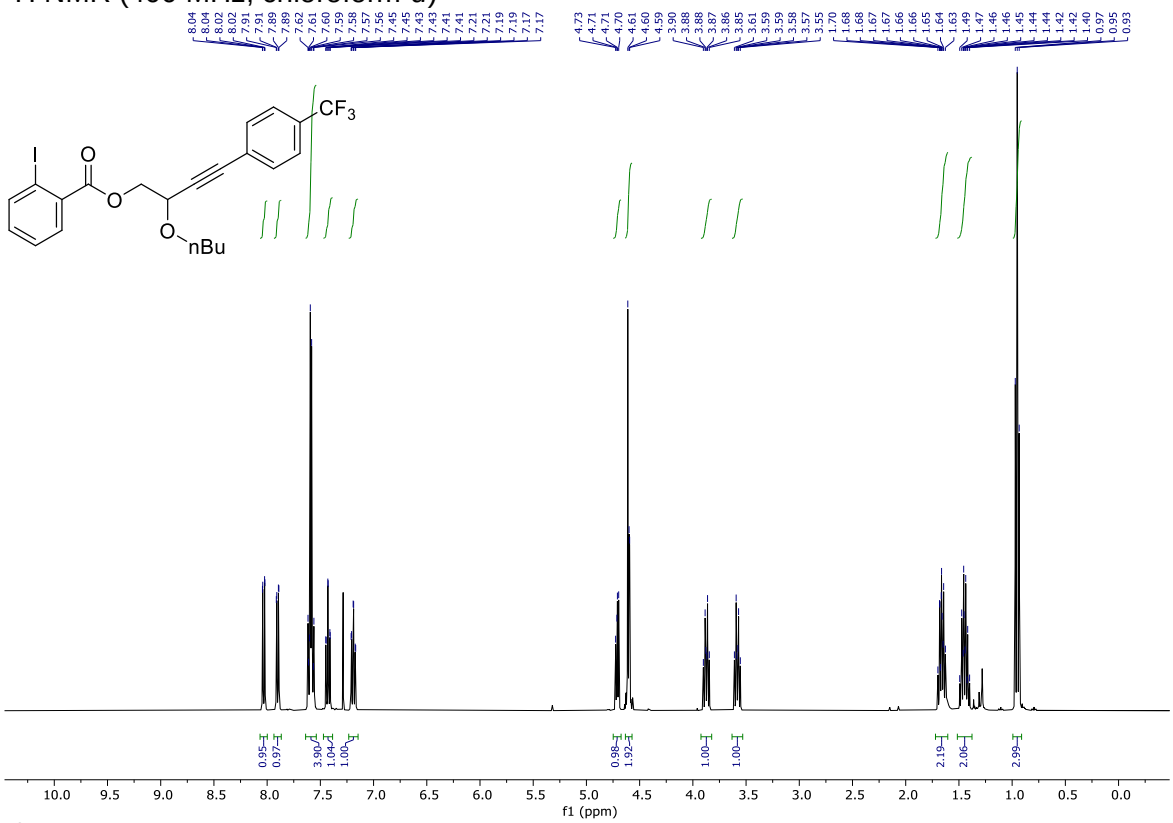


^{13}C NMR (400 MHz, chloroform-*d*)

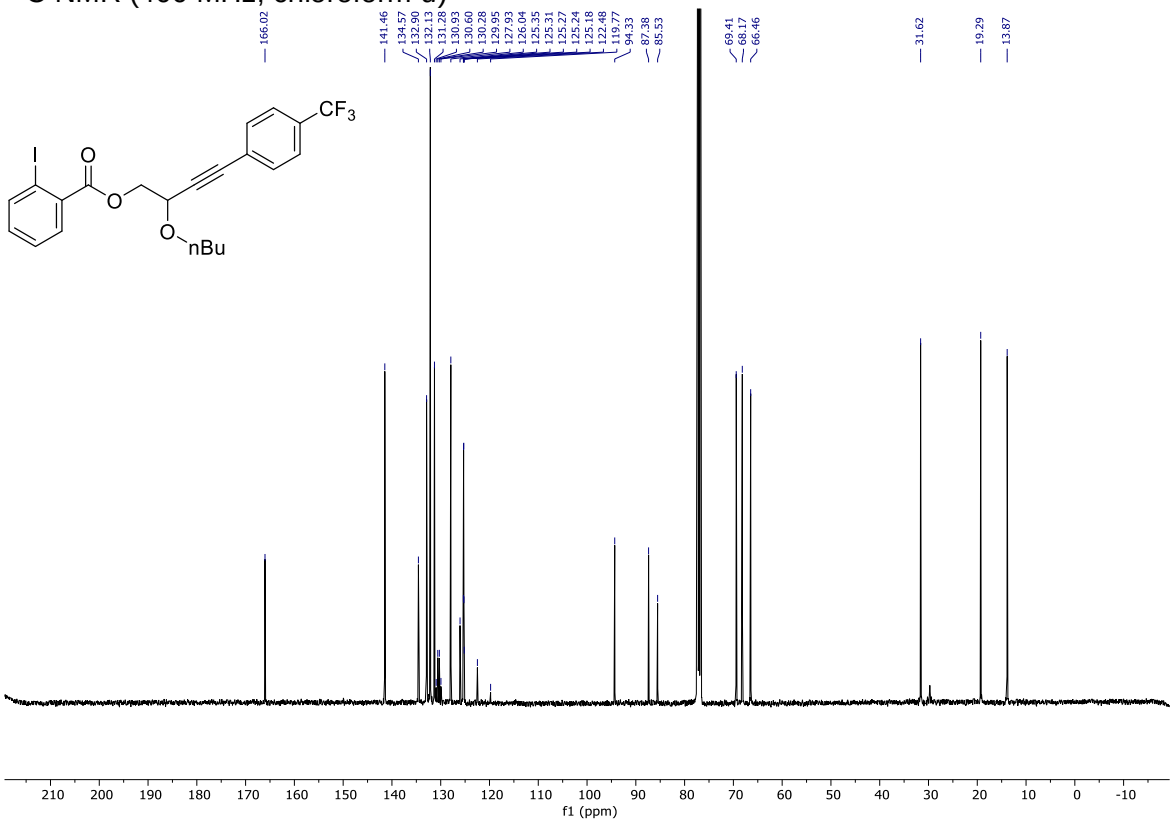


4.24d

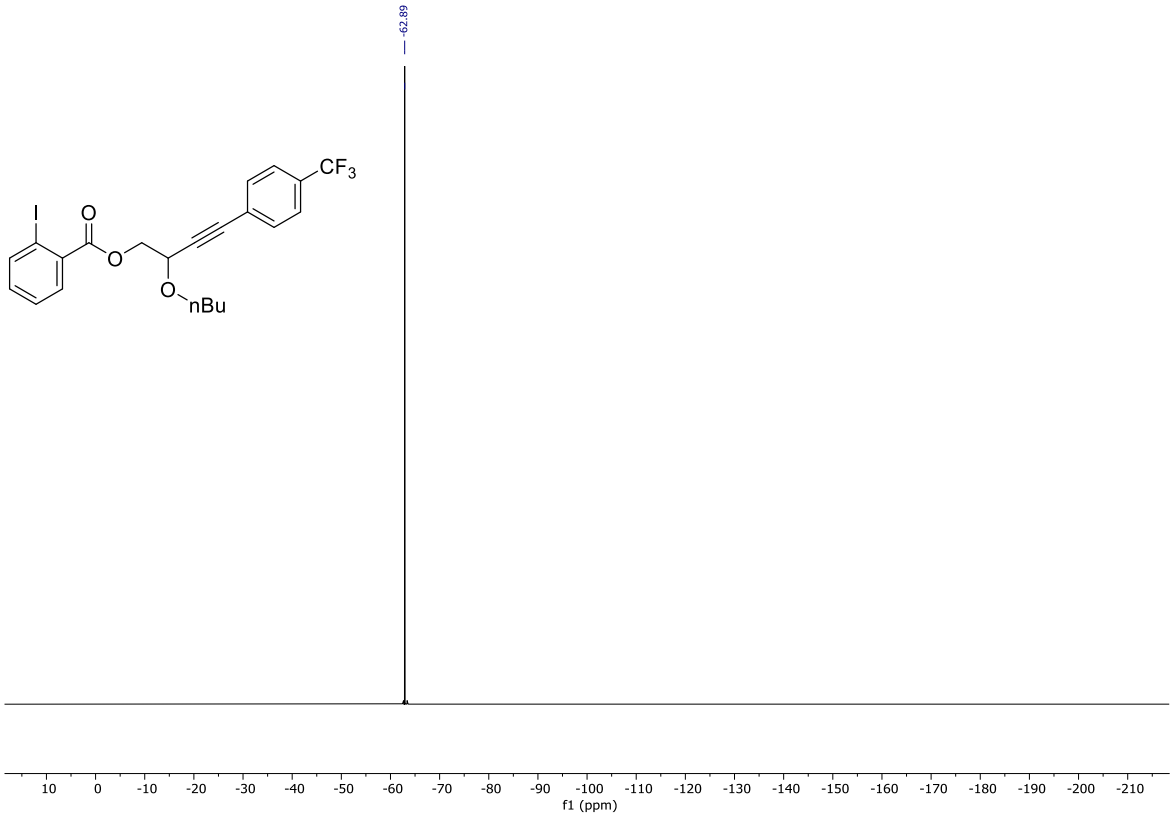
^{1}H NMR (400 MHz, chloroform-*d*)



^{13}C NMR (400 MHz, chloroform-*d*)



^{19}F NMR (376 MHz, Chloroform-*d*)


-62.89
CF3
I
O
O
O
nBu
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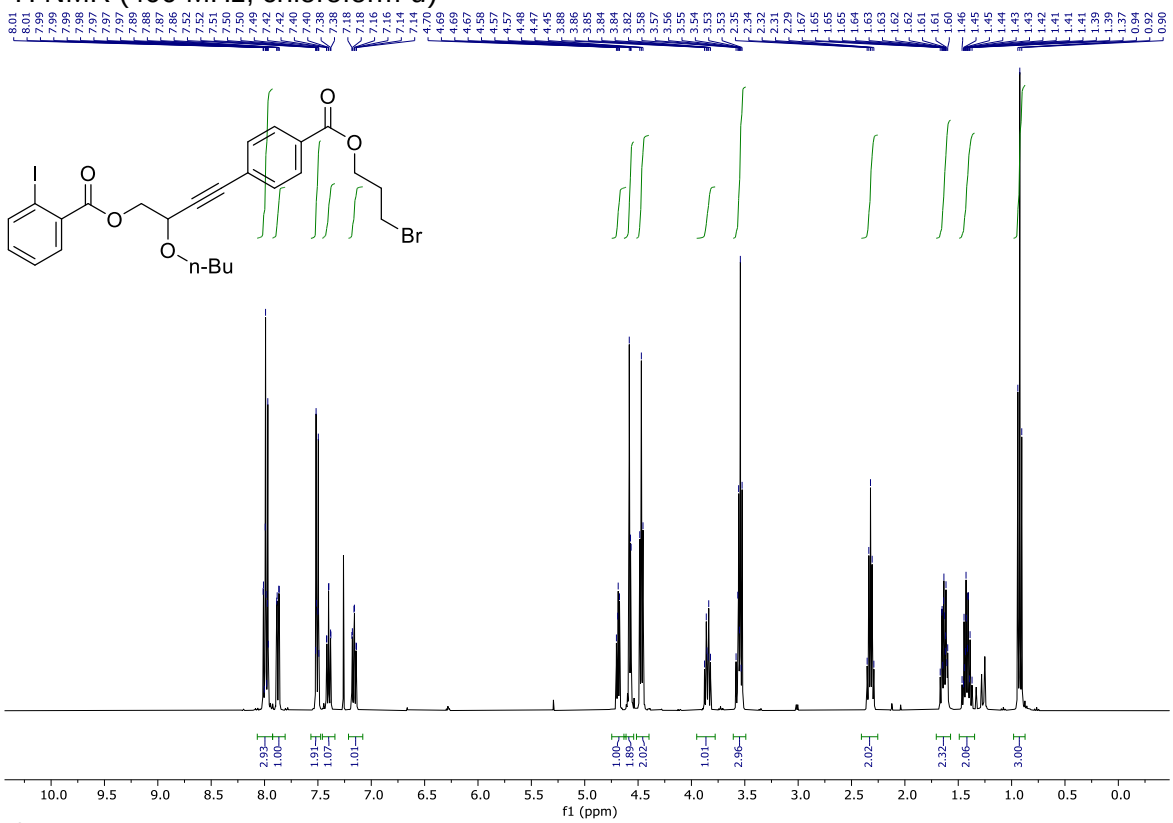
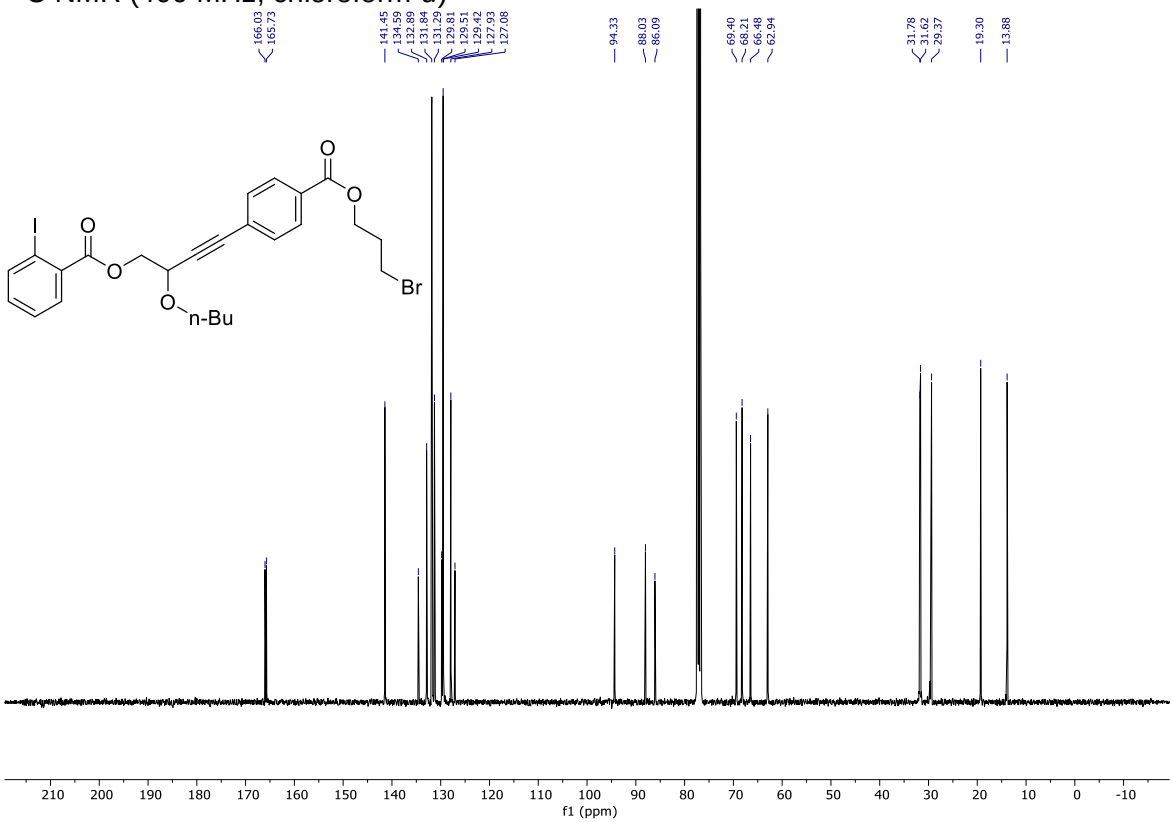
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

4.24g

^{1}H NMR (400 MHz, chloroform-*d*)

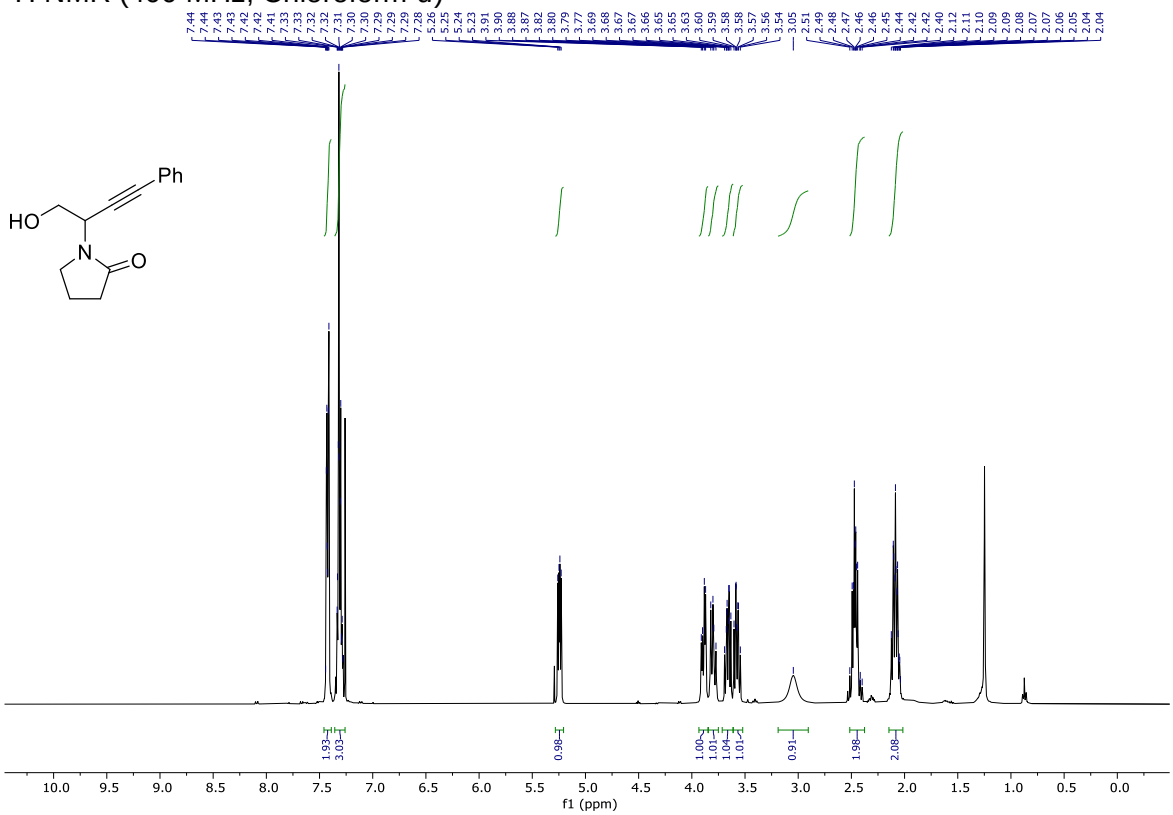


^{13}C NMR (400 MHz, chloroform-*d*)

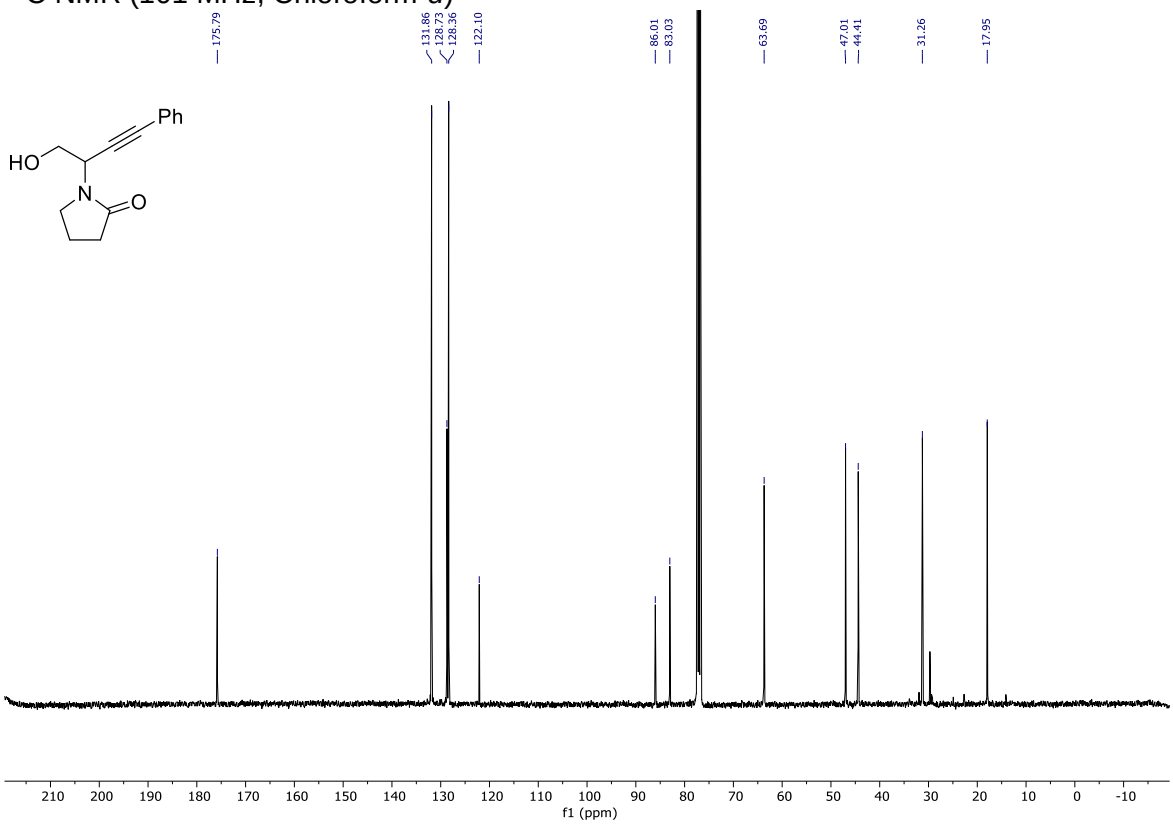


4.25

^{1}H NMR (400 MHz, Chloroform-*d*)

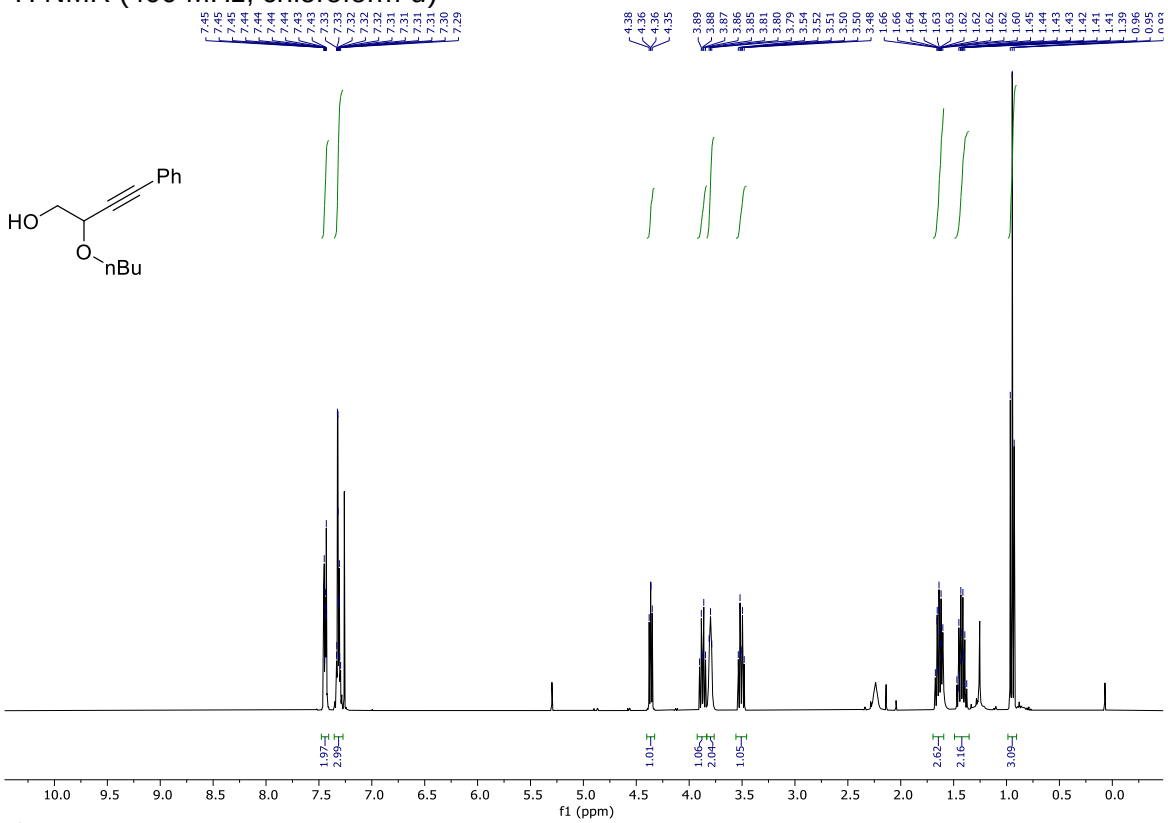


^{13}C NMR (101 MHz, Chloroform-*d*)

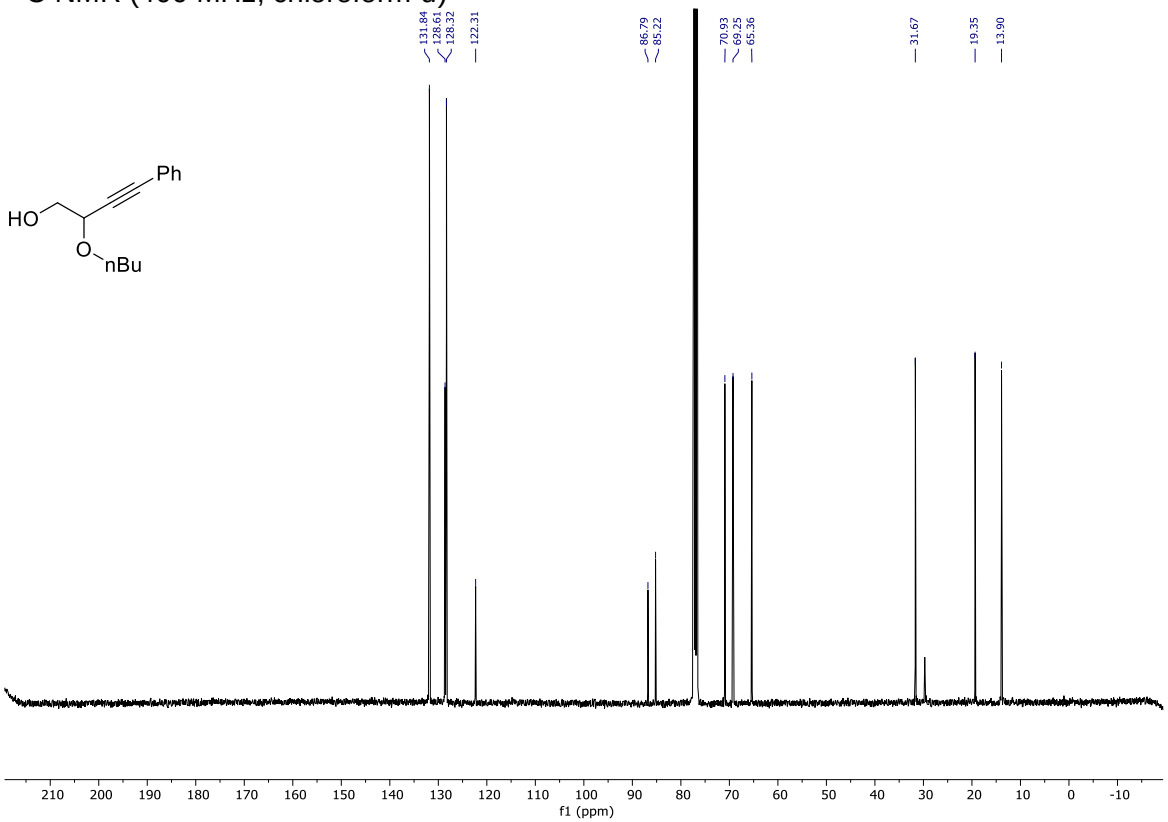


4.26

^{1}H NMR (400 MHz, chloroform-*d*)

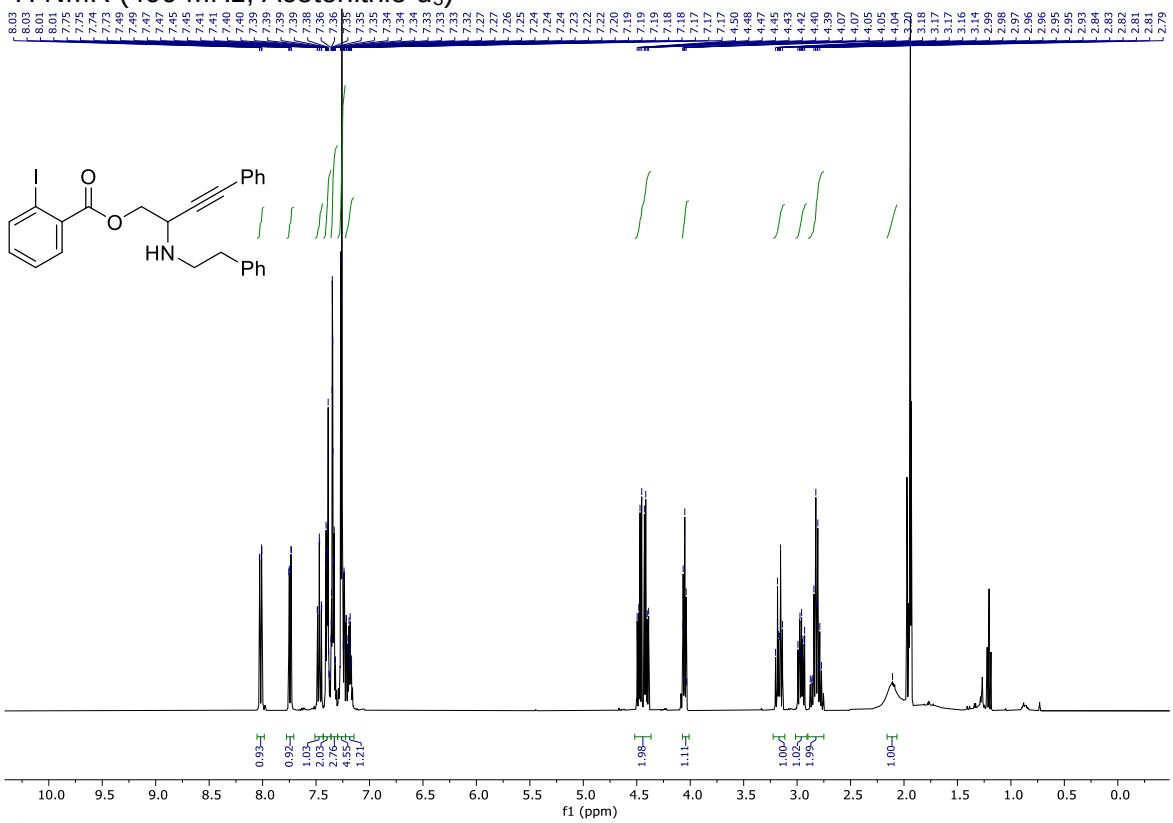


^{13}C NMR (400 MHz, chloroform-*d*)

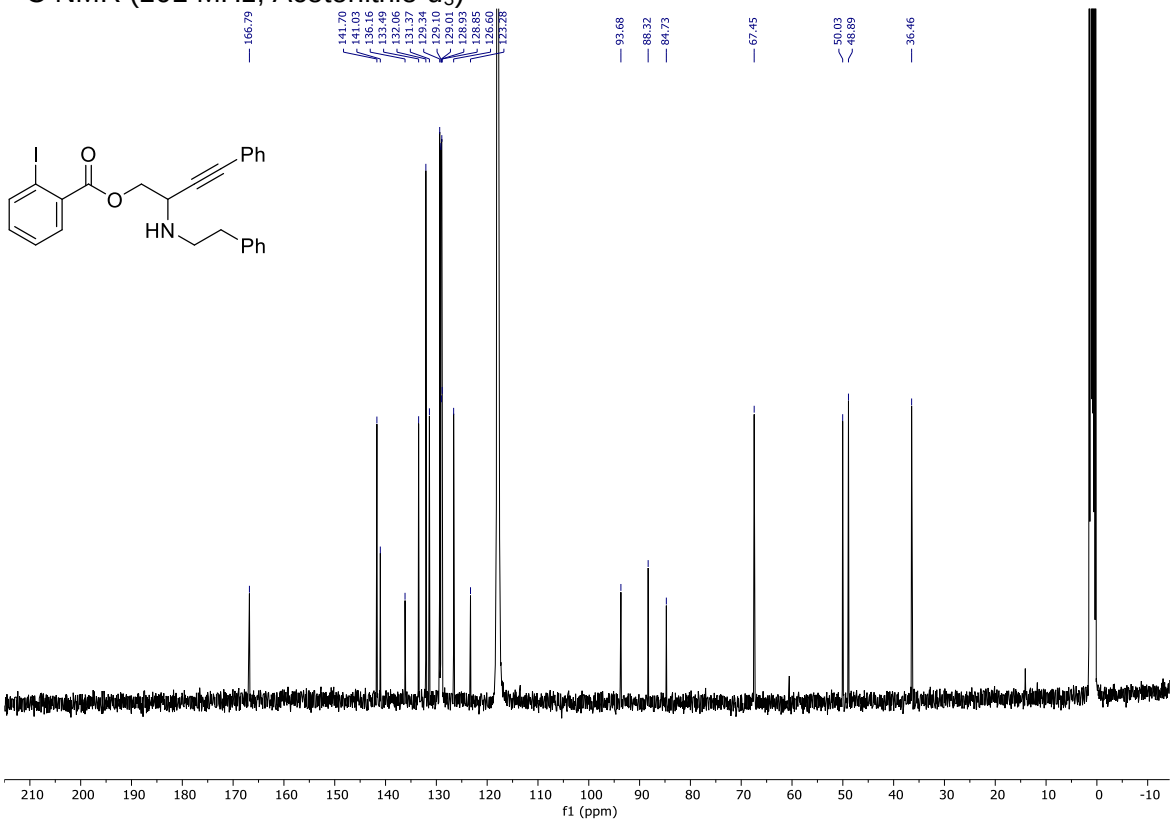


4.27

^{1}H NMR (400 MHz, Acetonitrile-d_3)

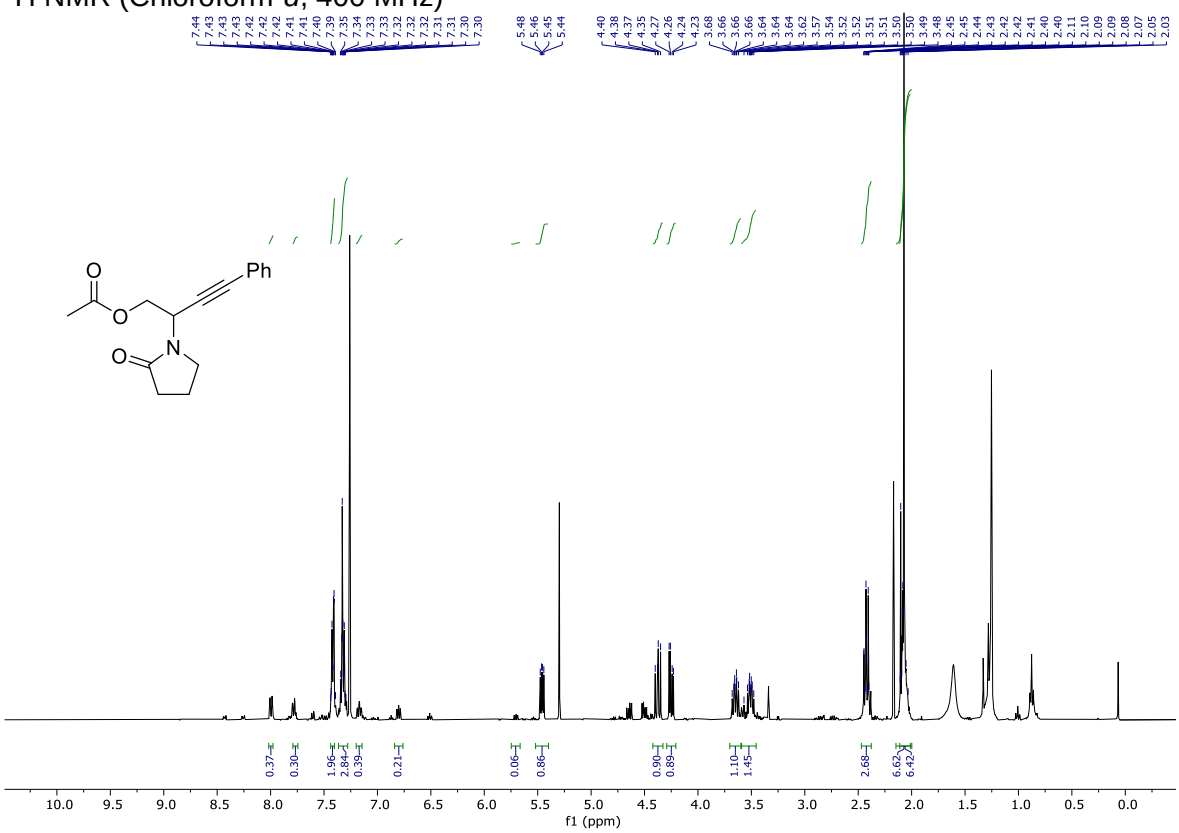


^{13}C NMR (101 MHz, Acetonitrile-d_3)

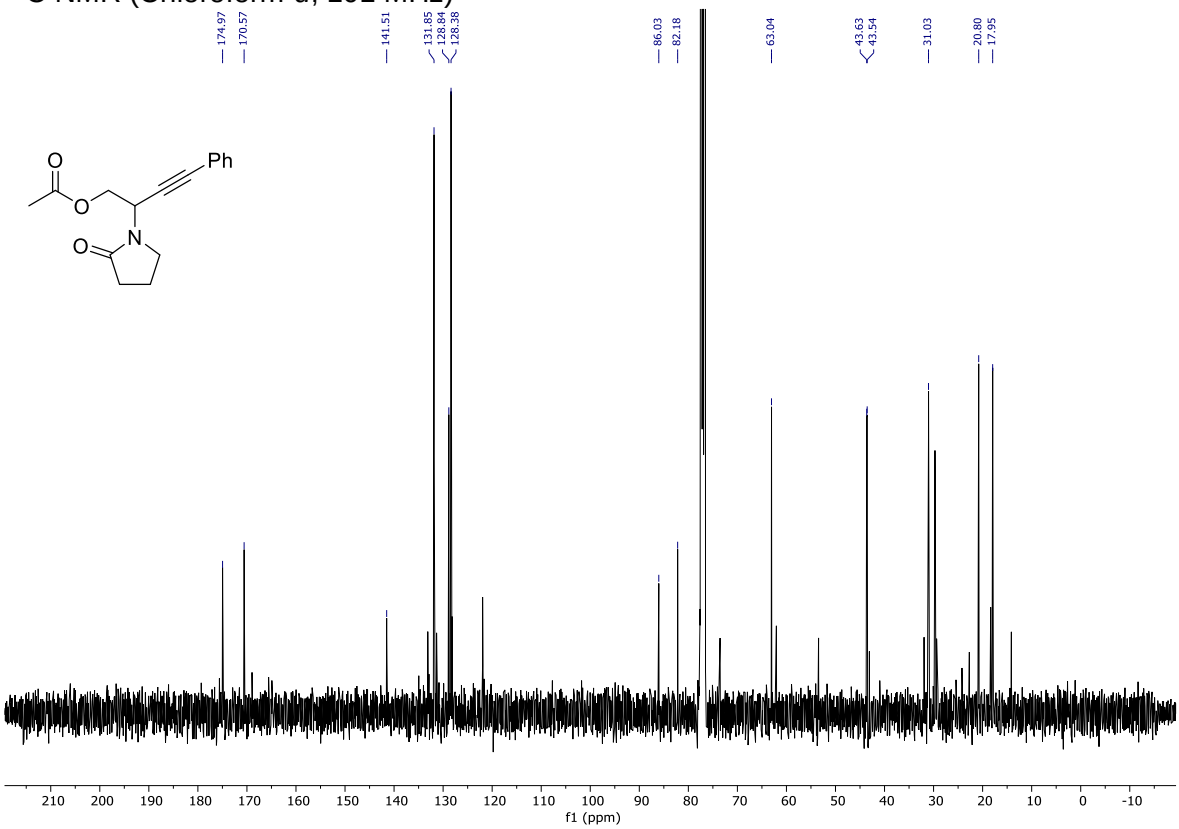


4.29

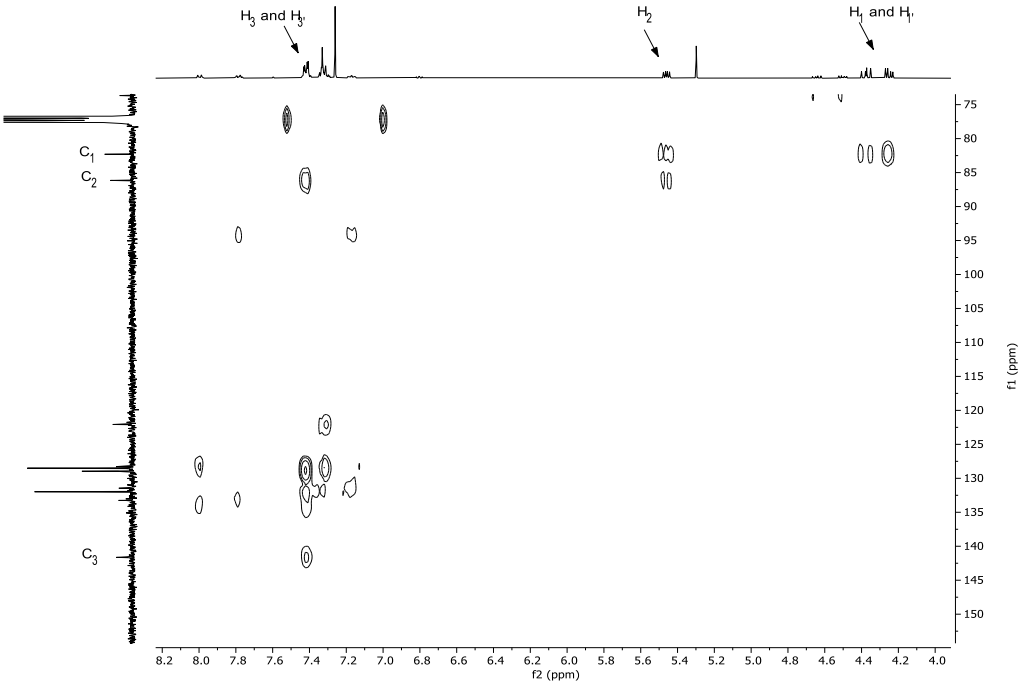
^{1}H NMR (Chloroform-*d*, 400 MHz)

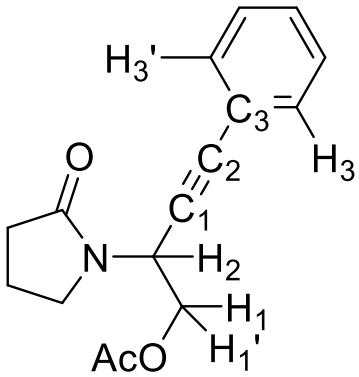


^{13}C NMR (Chloroform-*d*, 101 MHz)



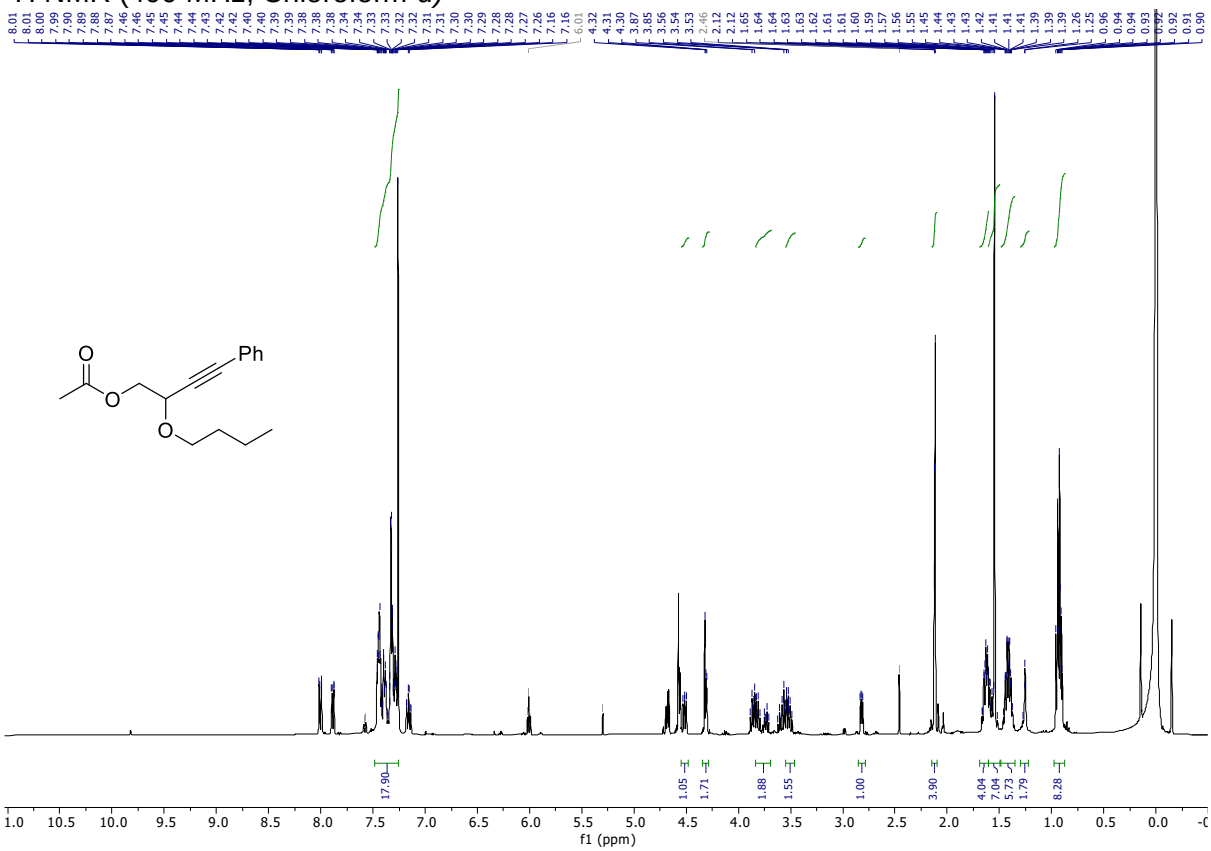
HMBC (Chloroform-*d*) zoom on aromatic/alkyne regions for attribution of the quaternary carbons



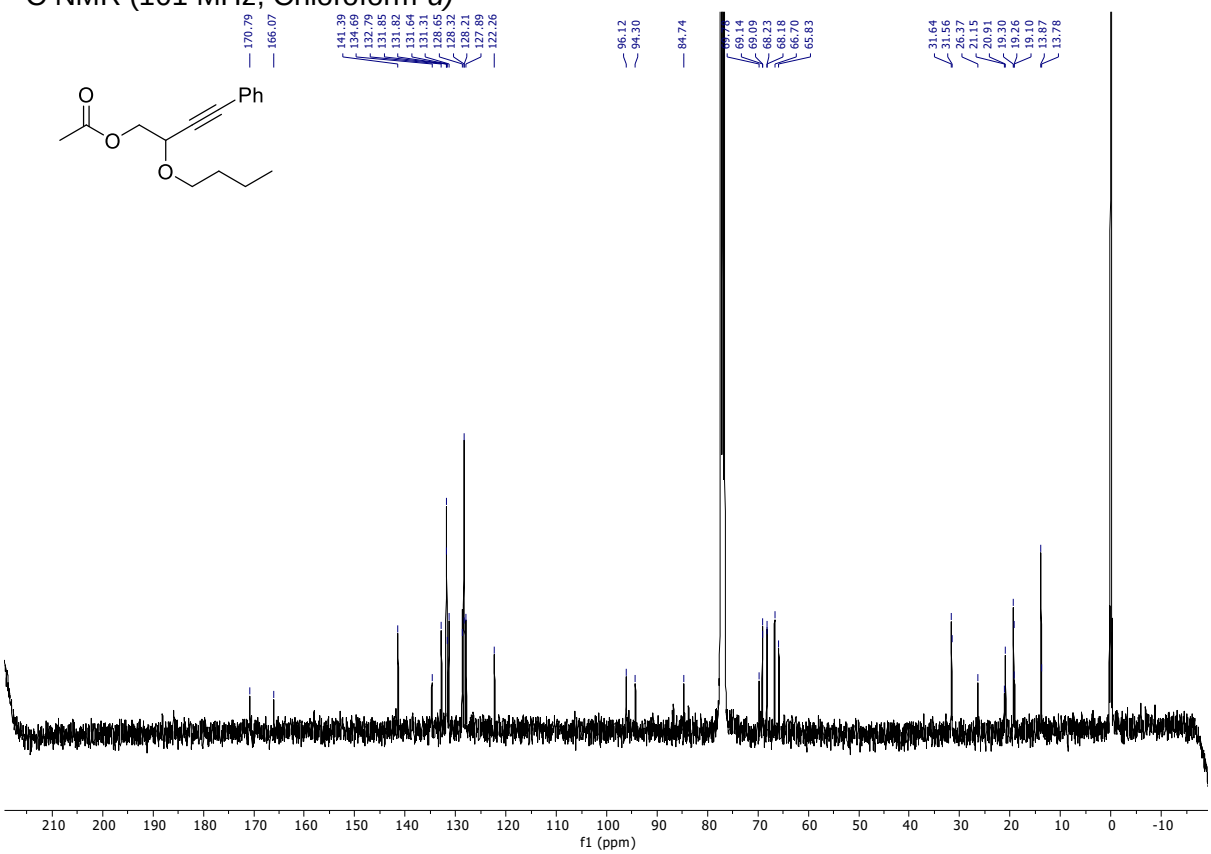


4.30

^{1}H NMR (400 MHz, Chloroform-*d)*

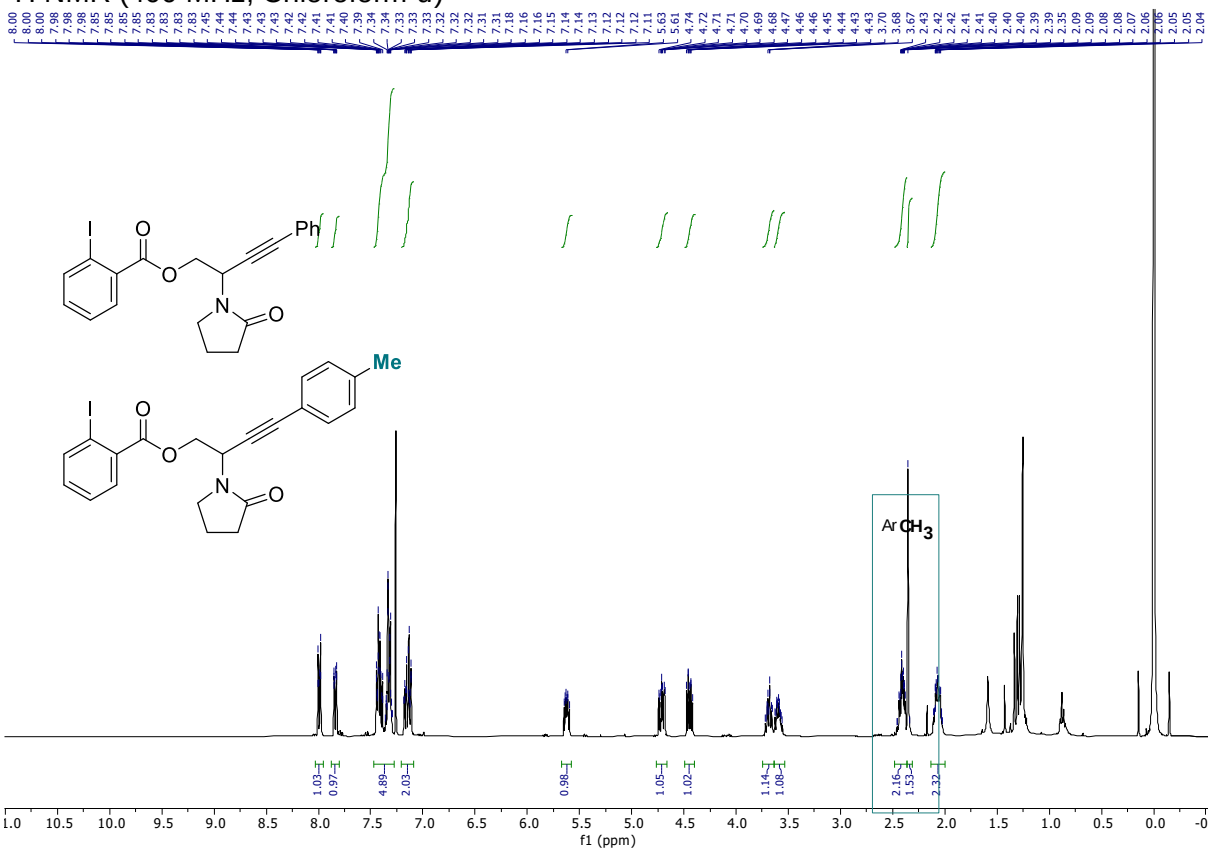


^{13}C NMR (101 MHz, Chloroform-*d)*

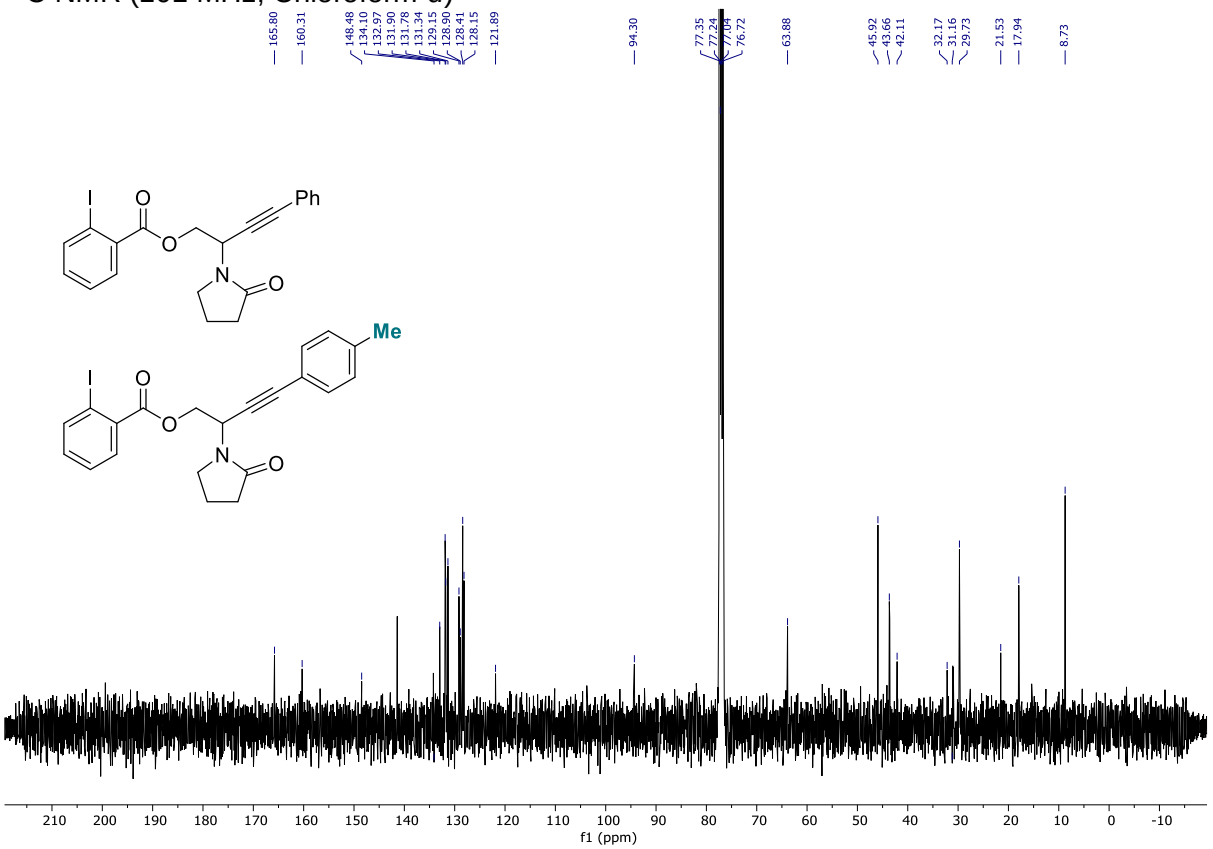


4.23b:4.31(1:1)

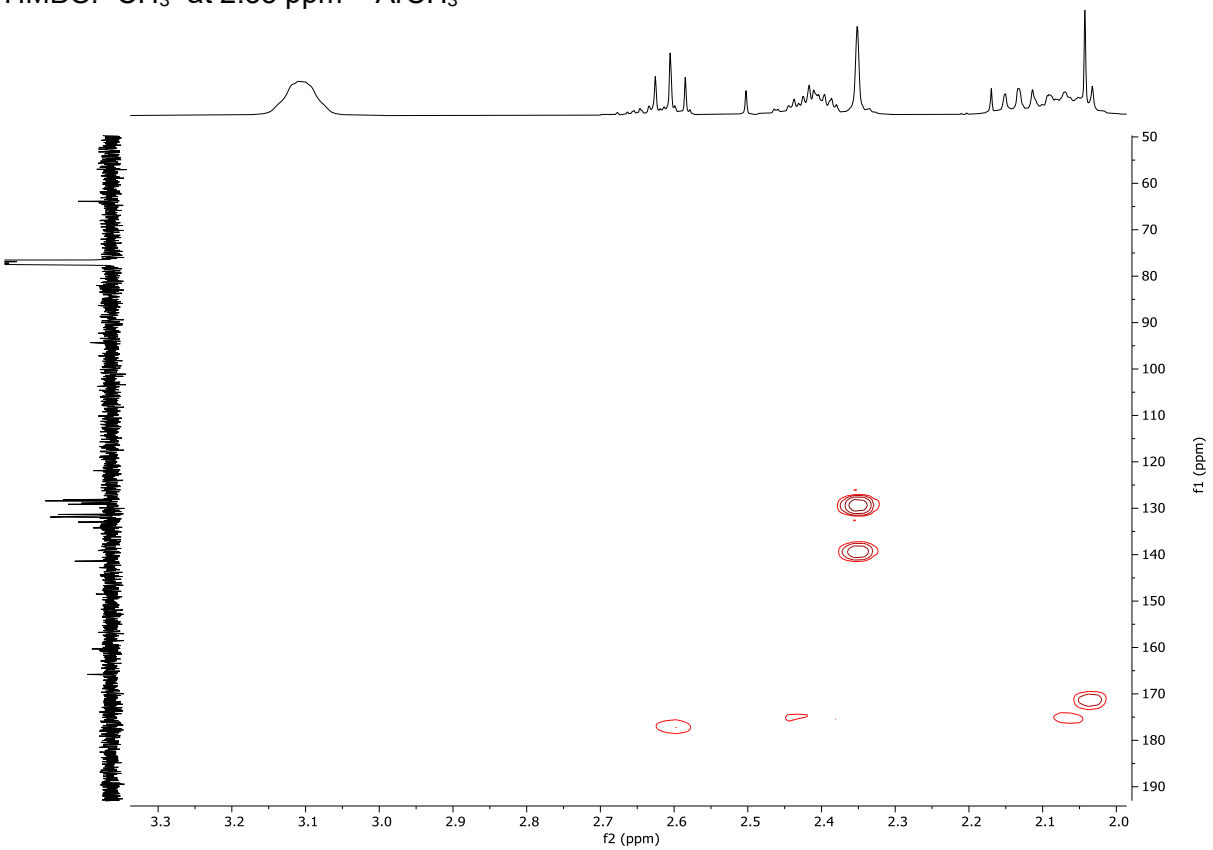
^{1}H NMR (400 MHz, Chloroform-*d*)



^{13}C NMR (101 MHz, Chloroform-*d*)

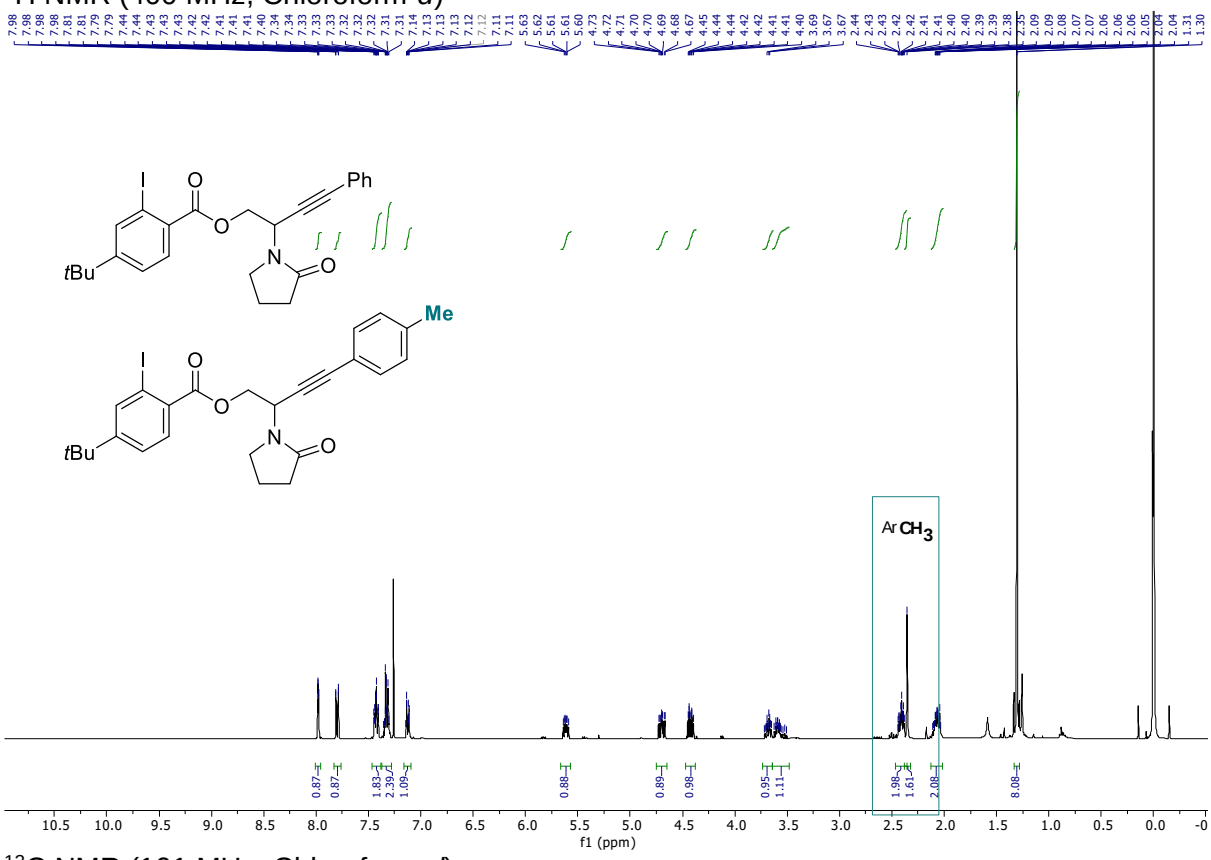


HMBC: “CH_3” at 2.35 ppm = $ArCH_3$

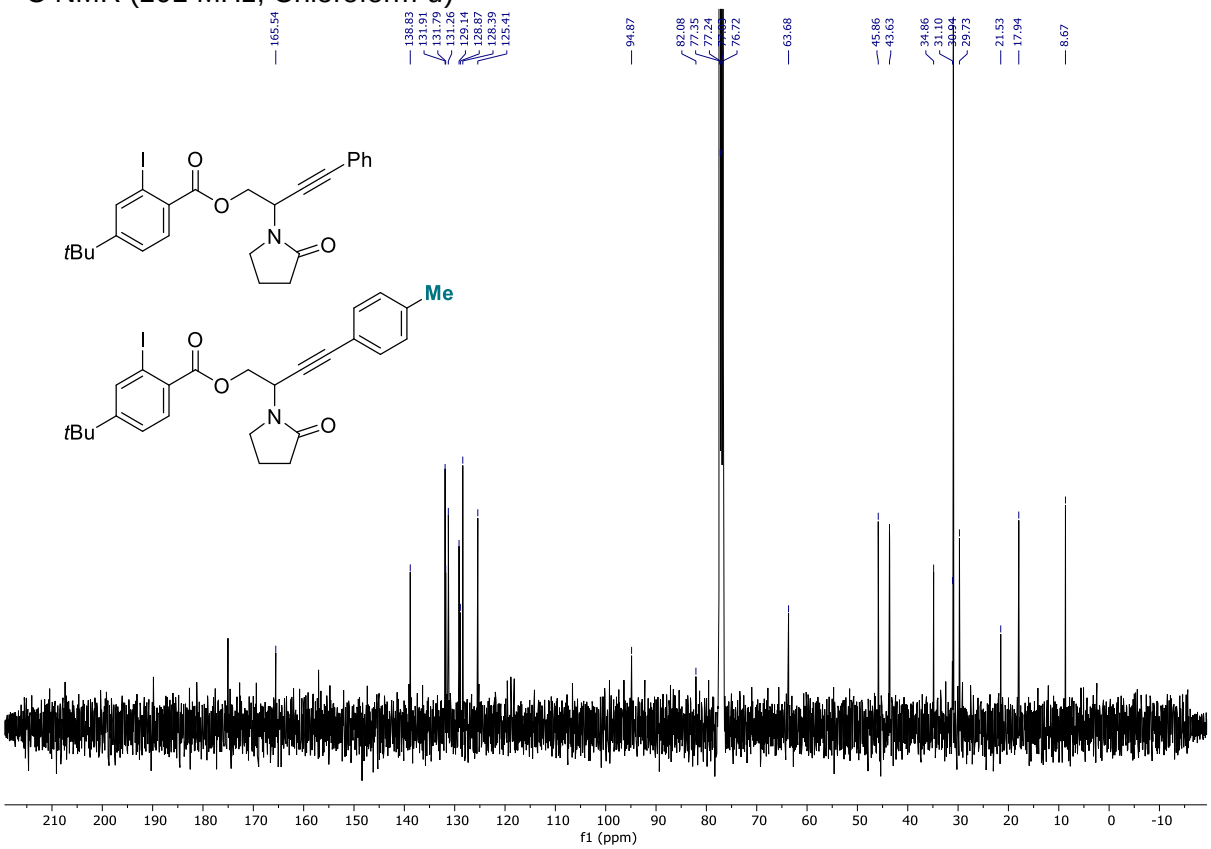


4.32:4.33 (1:1)

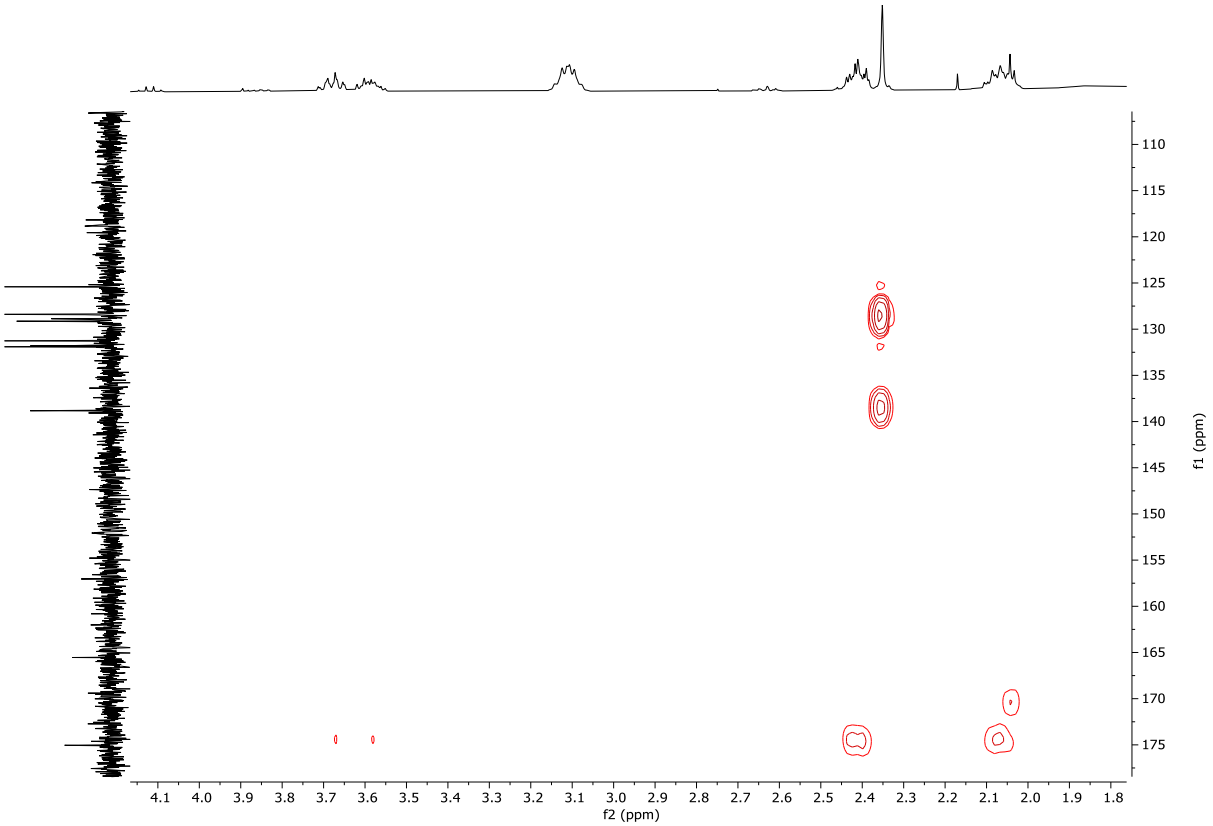
^{1}H NMR (400 MHz, Chloroform-*d*)



^{13}C NMR (101 MHz, Chloroform-*d*)

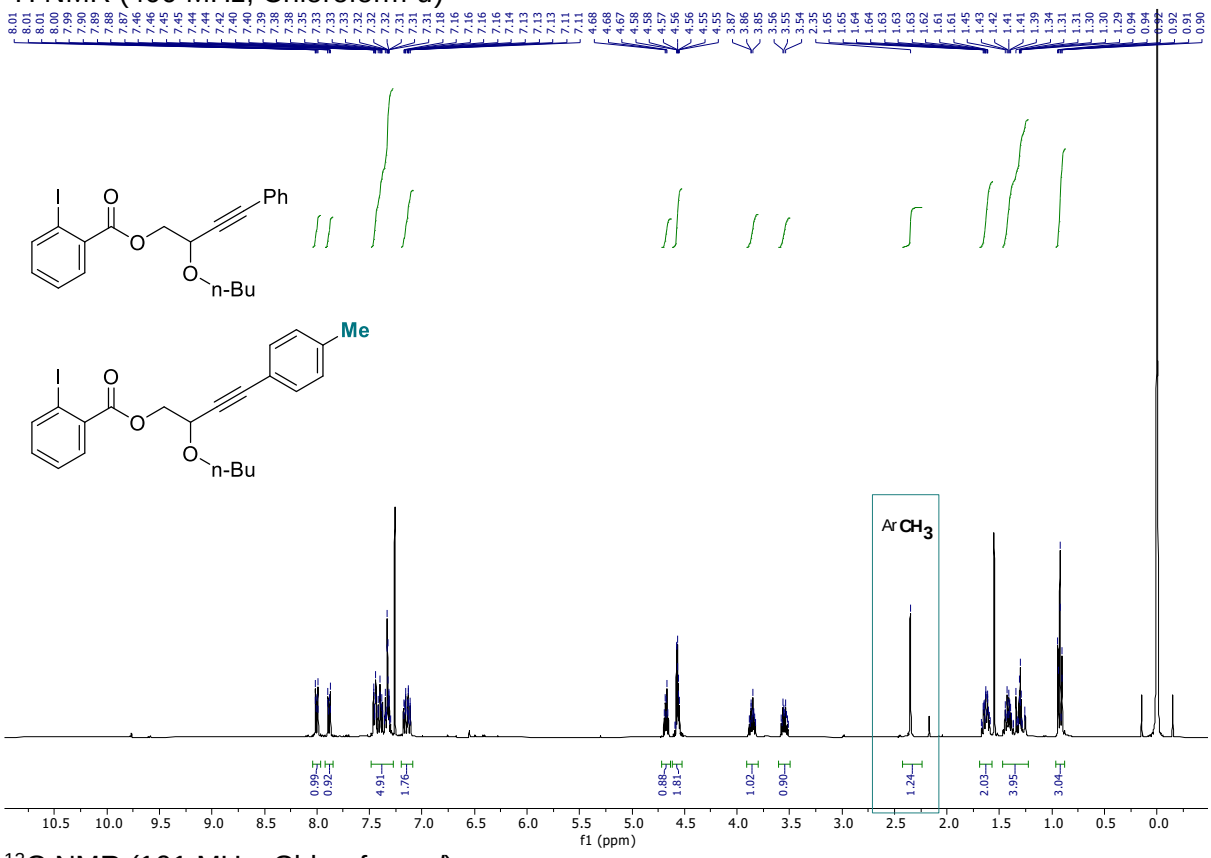


HMBC: “CH_3” at 2.35 ppm = $ArCH_3$

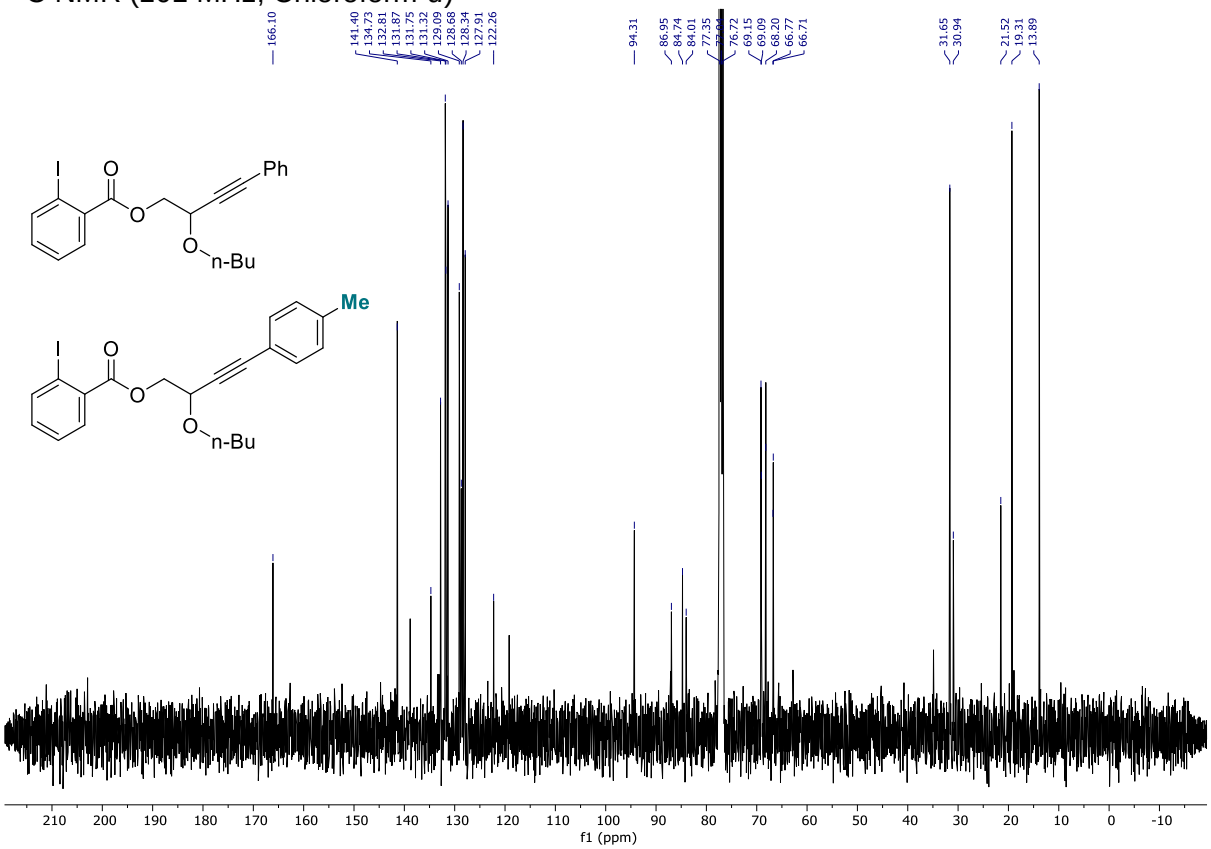


4.34:4.22a (1:1)

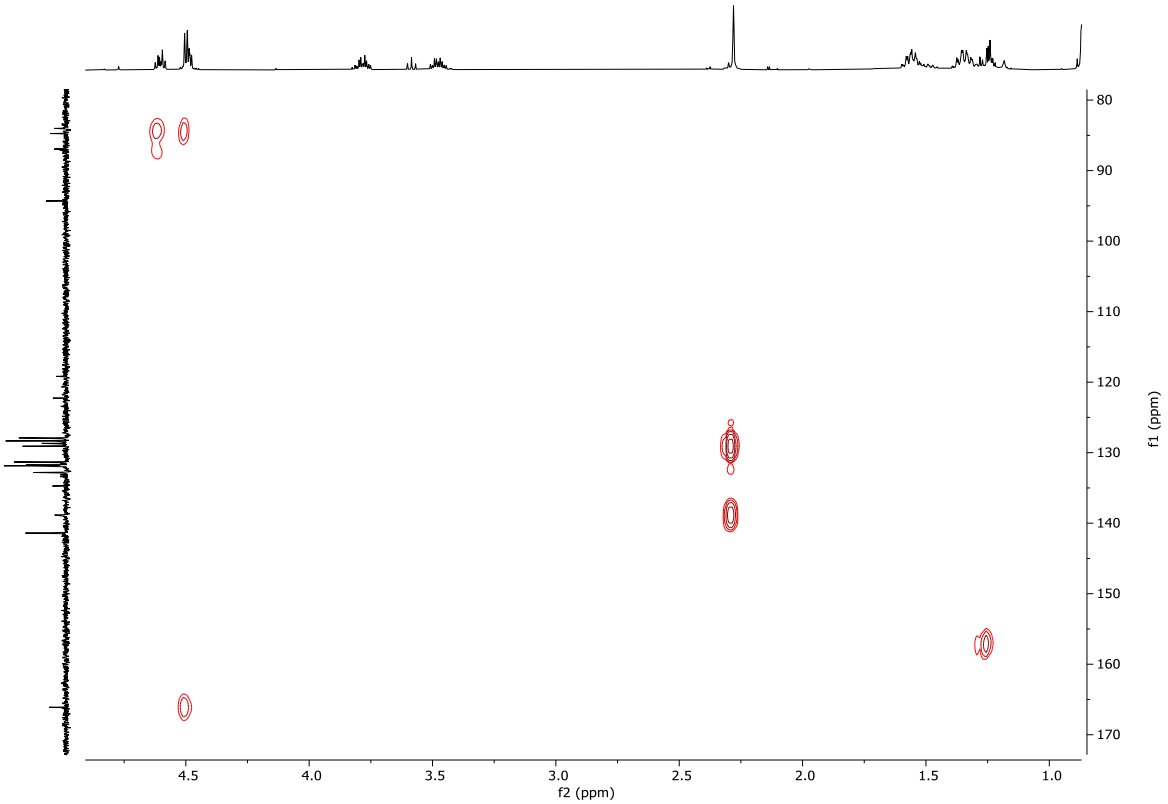
^{1}H NMR (400 MHz, Chloroform-*d*)



^{13}C NMR (101 MHz, Chloroform-*d*)

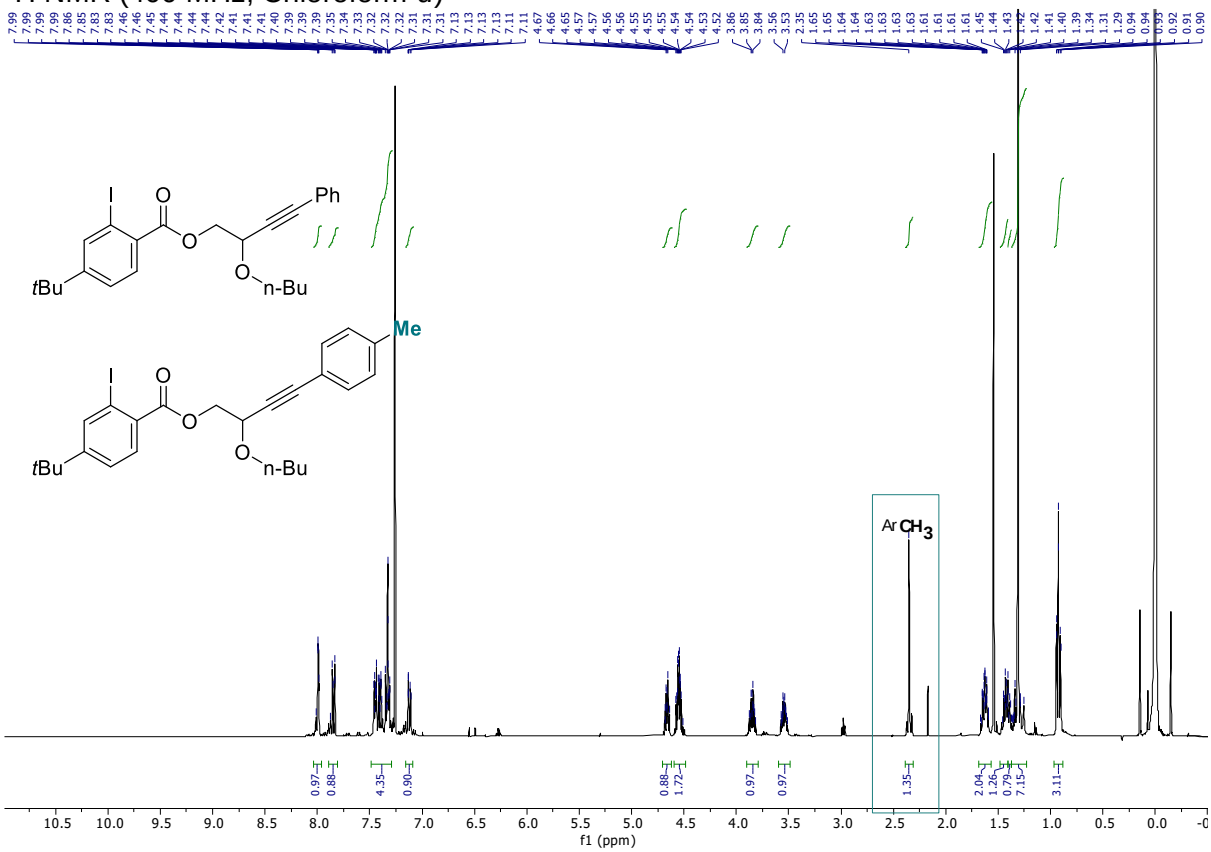


HMBC: “CH_3” at 2.35 ppm = $ArCH_3$

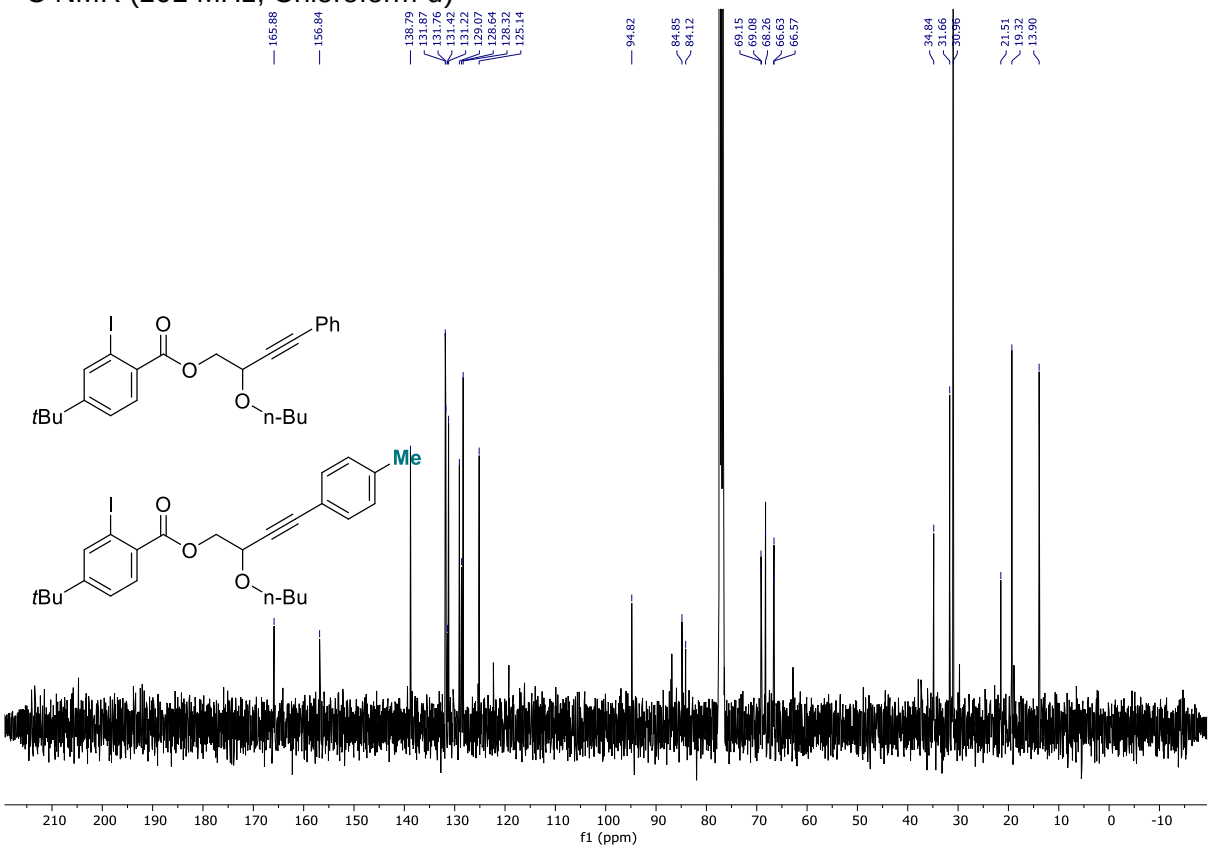


4.35:4.36 (1:1)

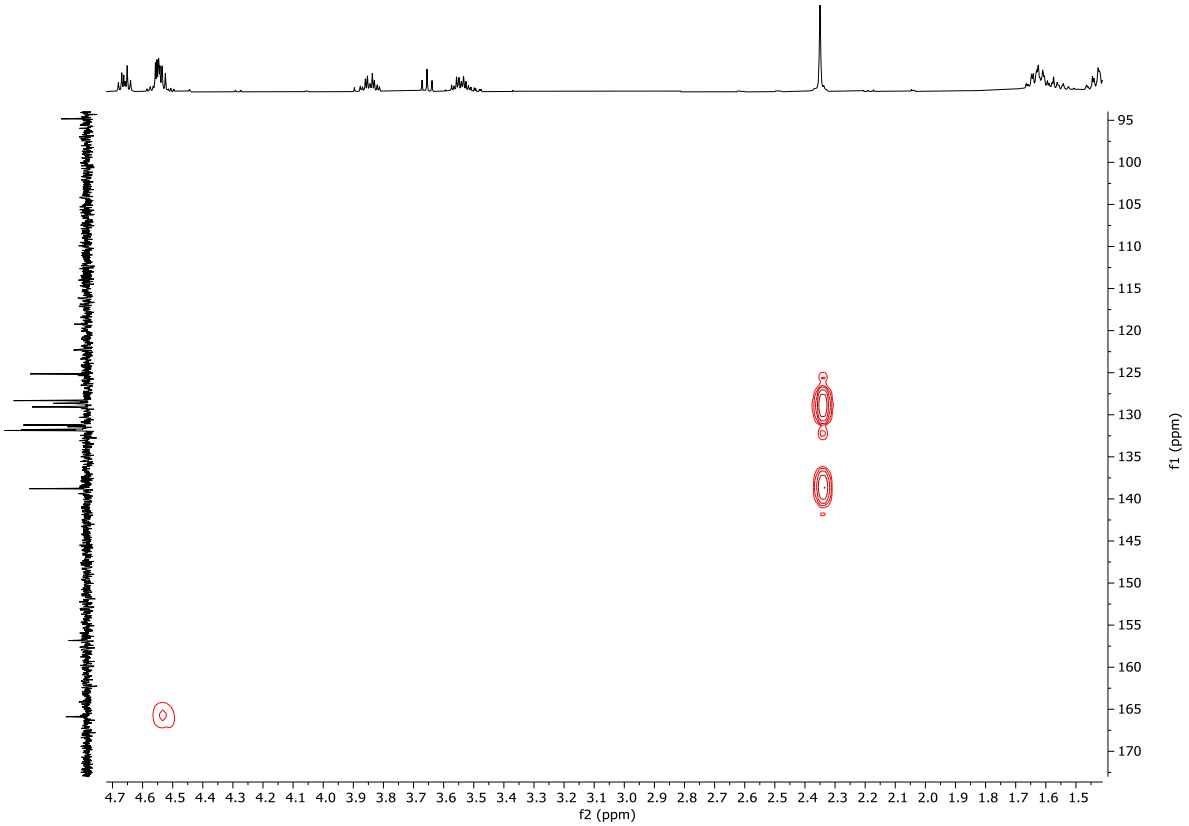
^{1}H NMR (400 MHz, Chloroform-*d*)



^{13}C NMR (101 MHz, Chloroform-*d*)

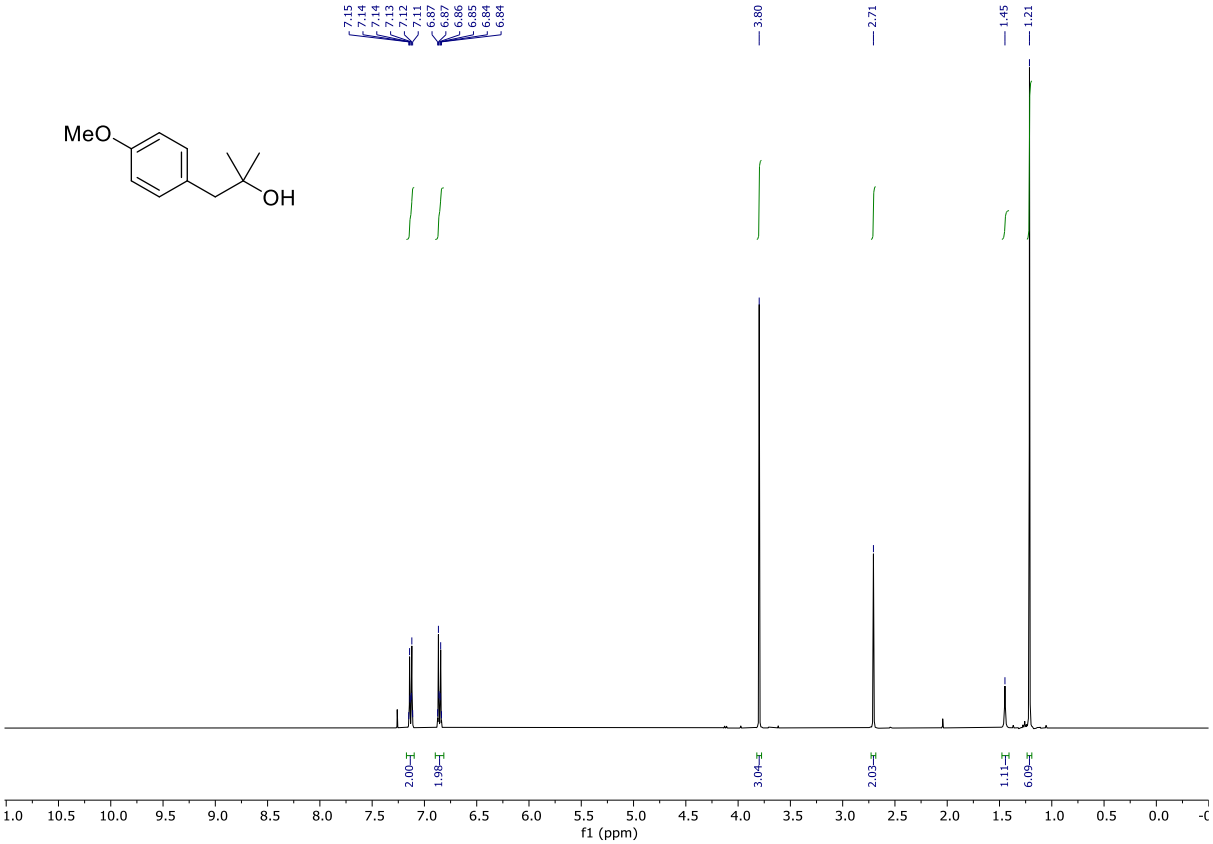


HMBC: “CH_3” at 2.35 ppm = $ArCH_3$

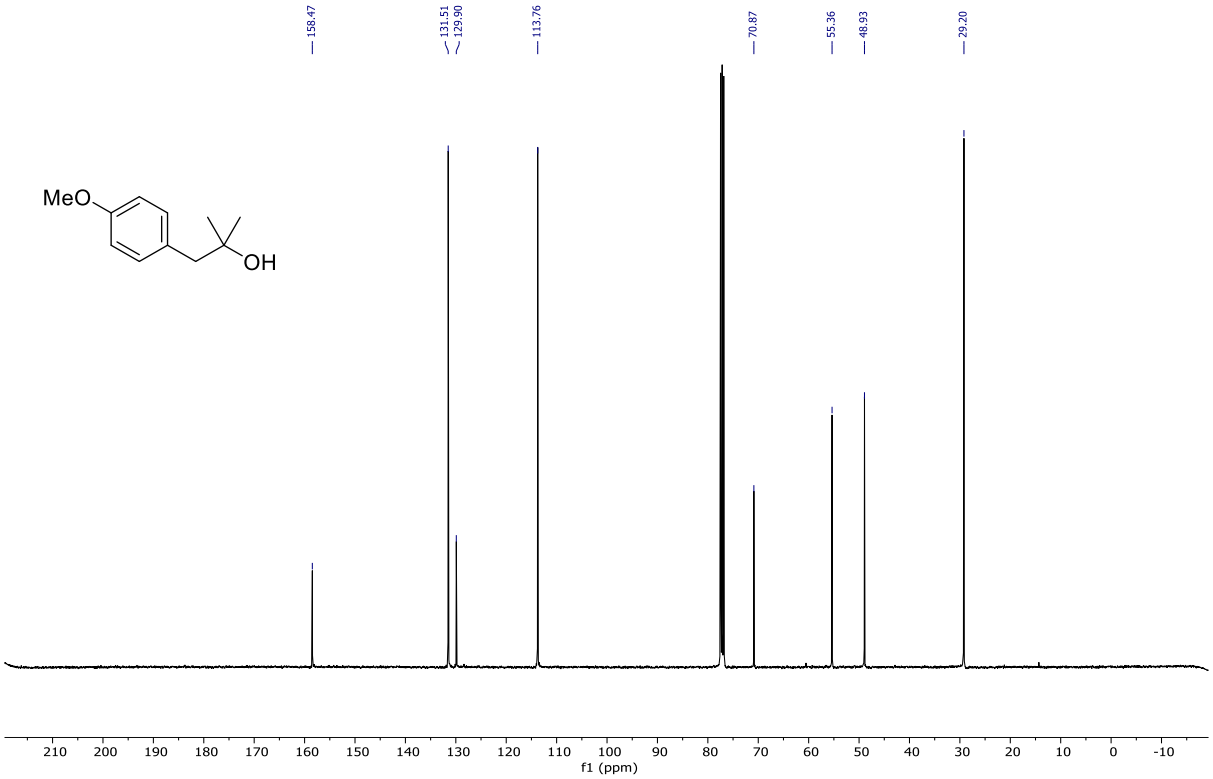


5.8f

^{1}H NMR, $CDCl_3$, 400 MHz

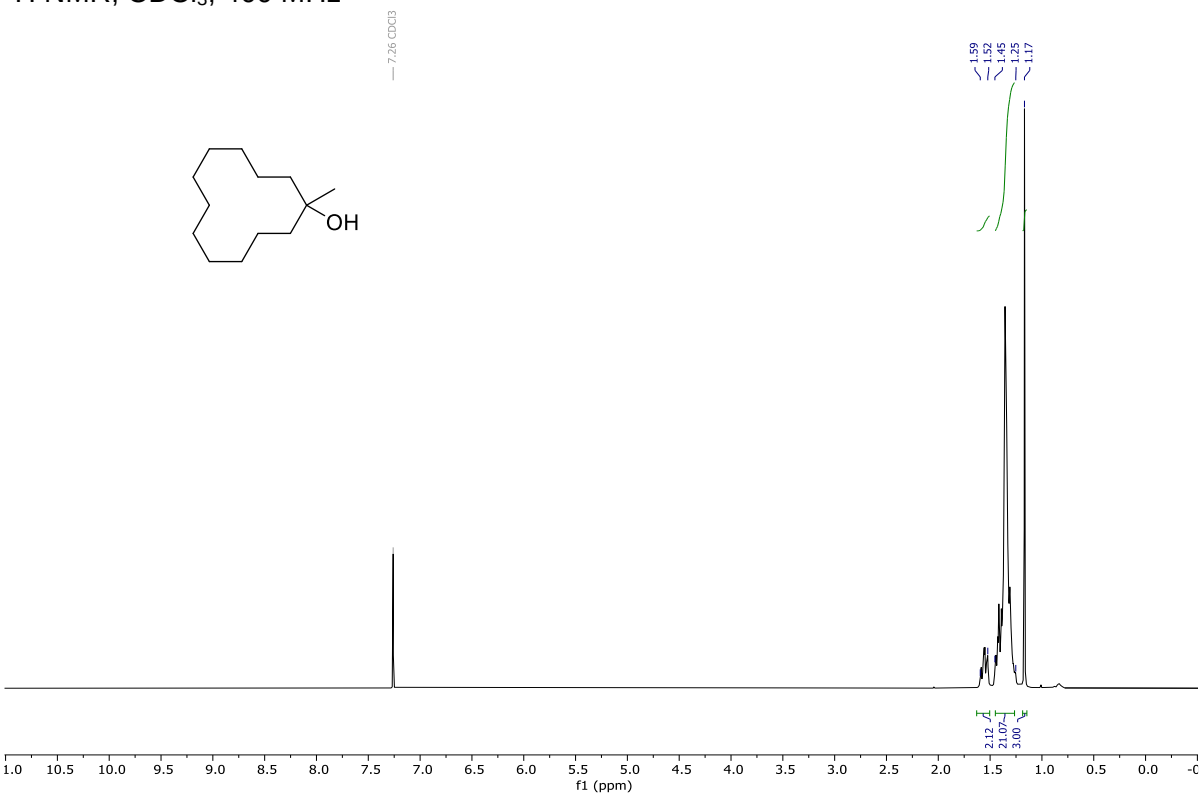


^{13}C NMR, $CDCl_3$, 101 MHz

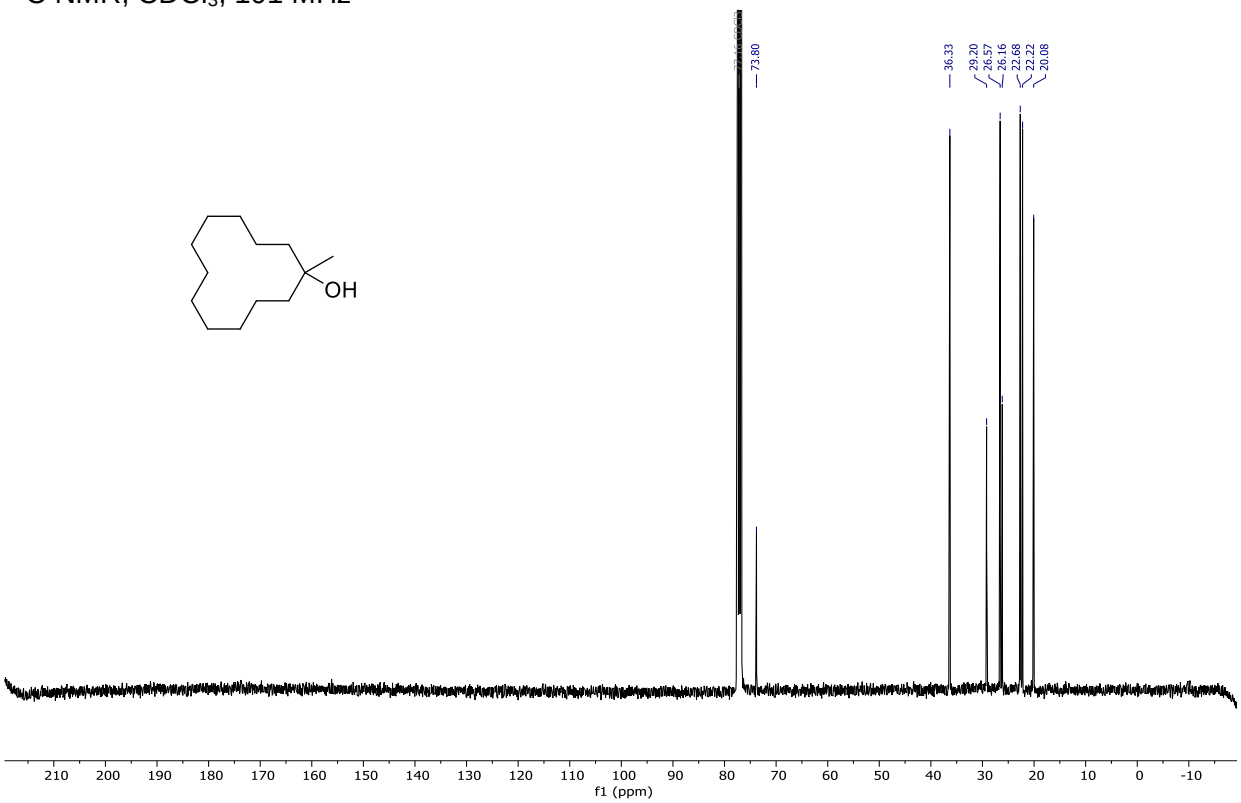


5.8g

^{1}H NMR, $CDCl_3$, 400 MHz

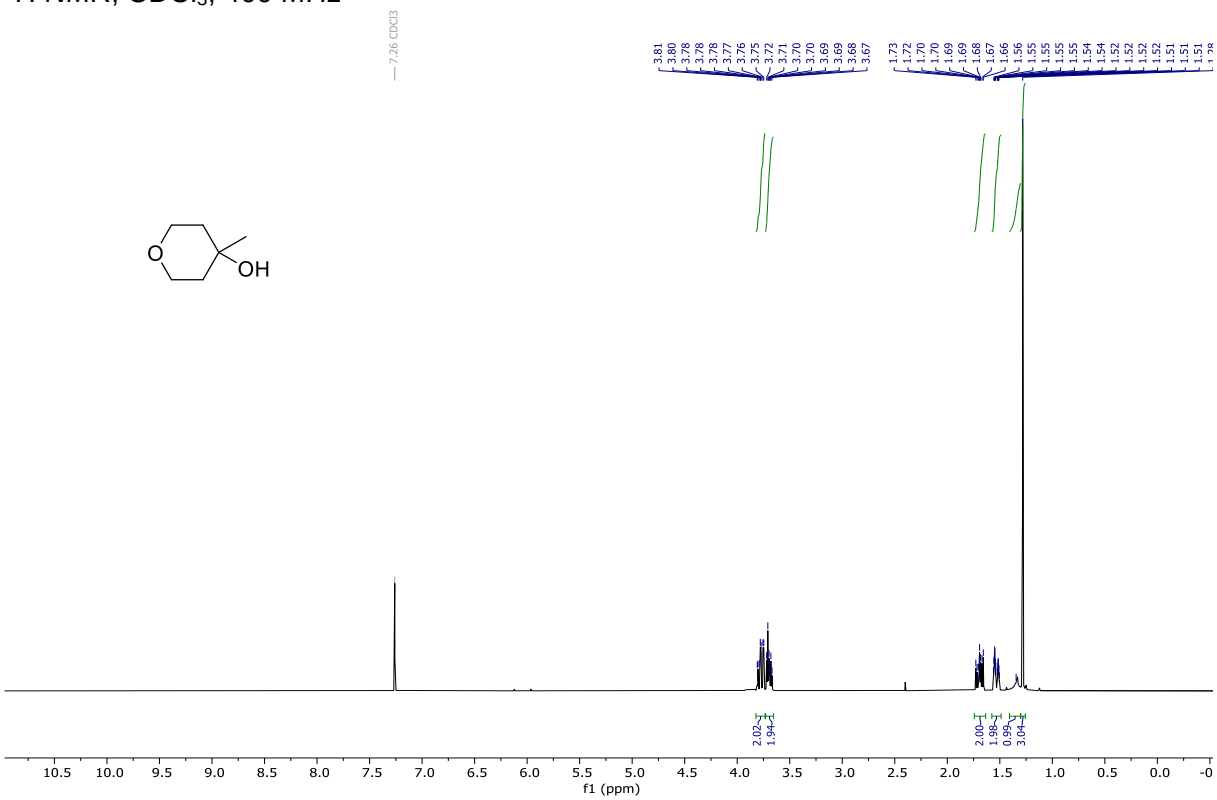


^{13}C NMR, $CDCl_3$, 101 MHz

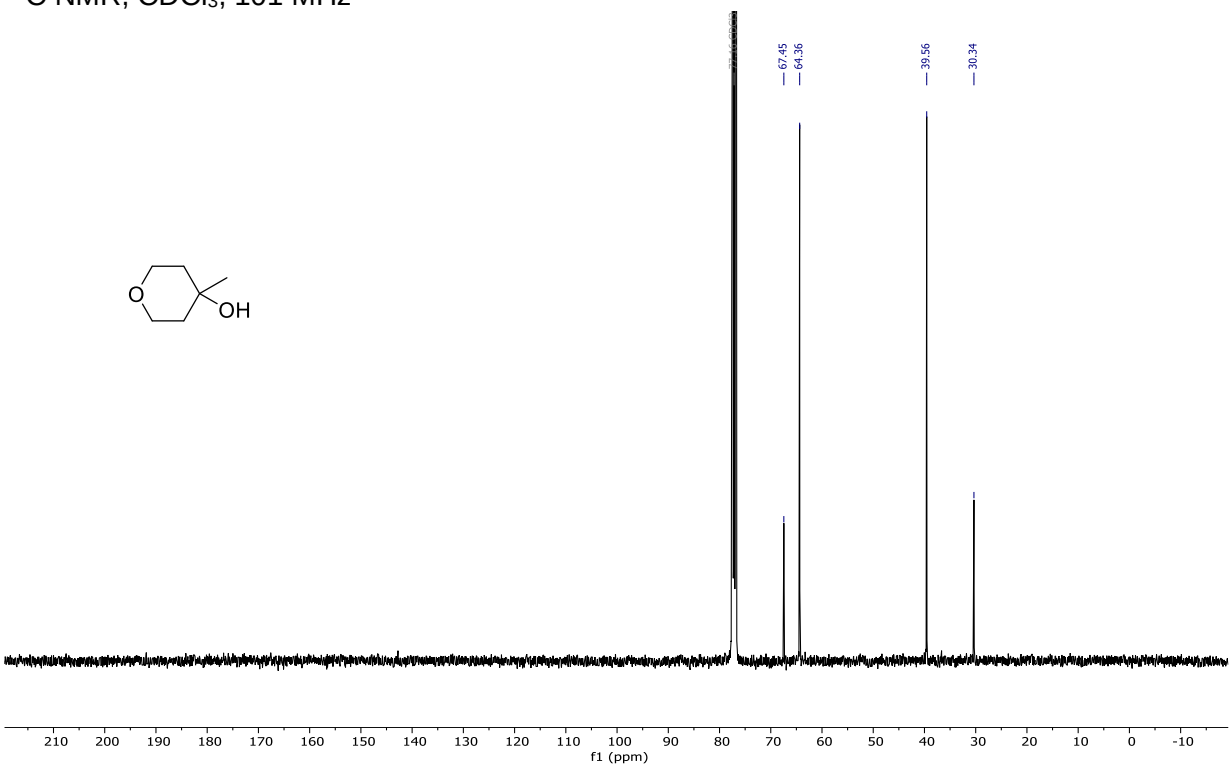


5.8k

^{1}H NMR, $CDCl_3$, 400 MHz

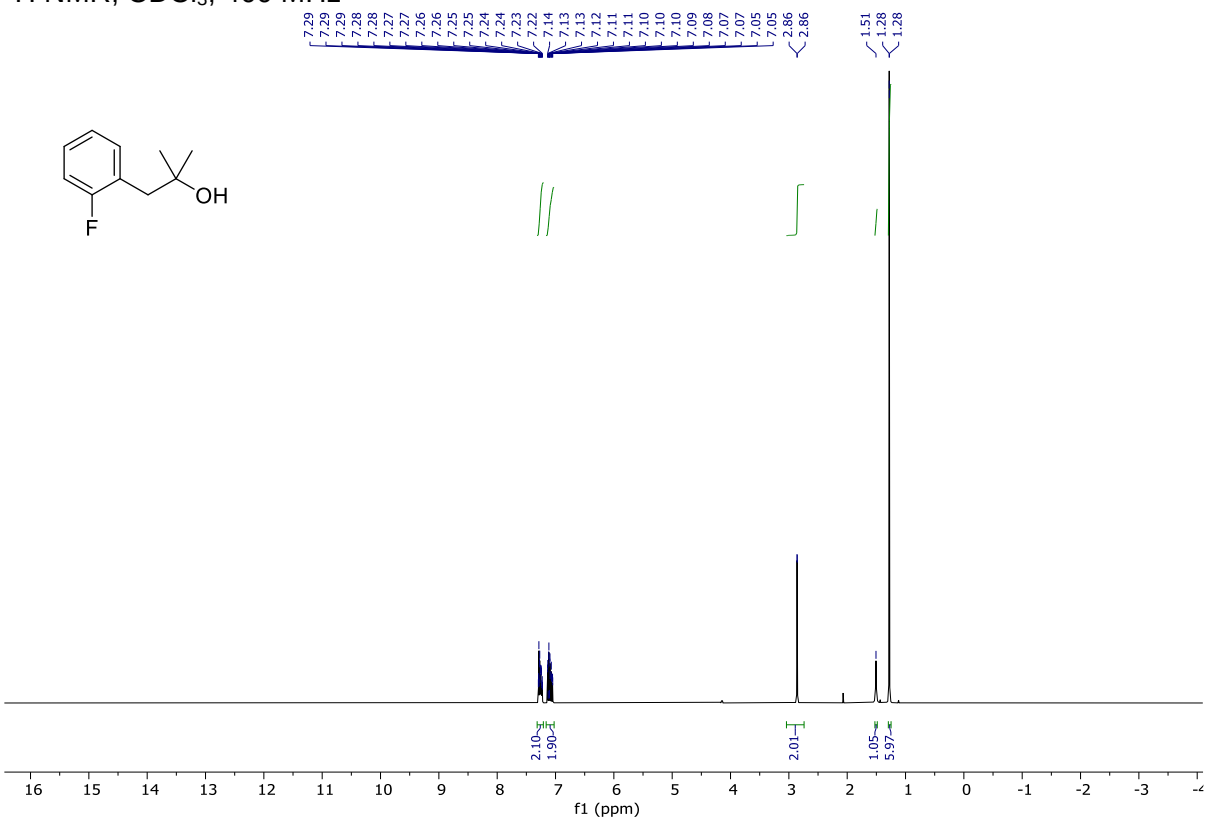


^{13}C NMR, $CDCl_3$, 101 MHz

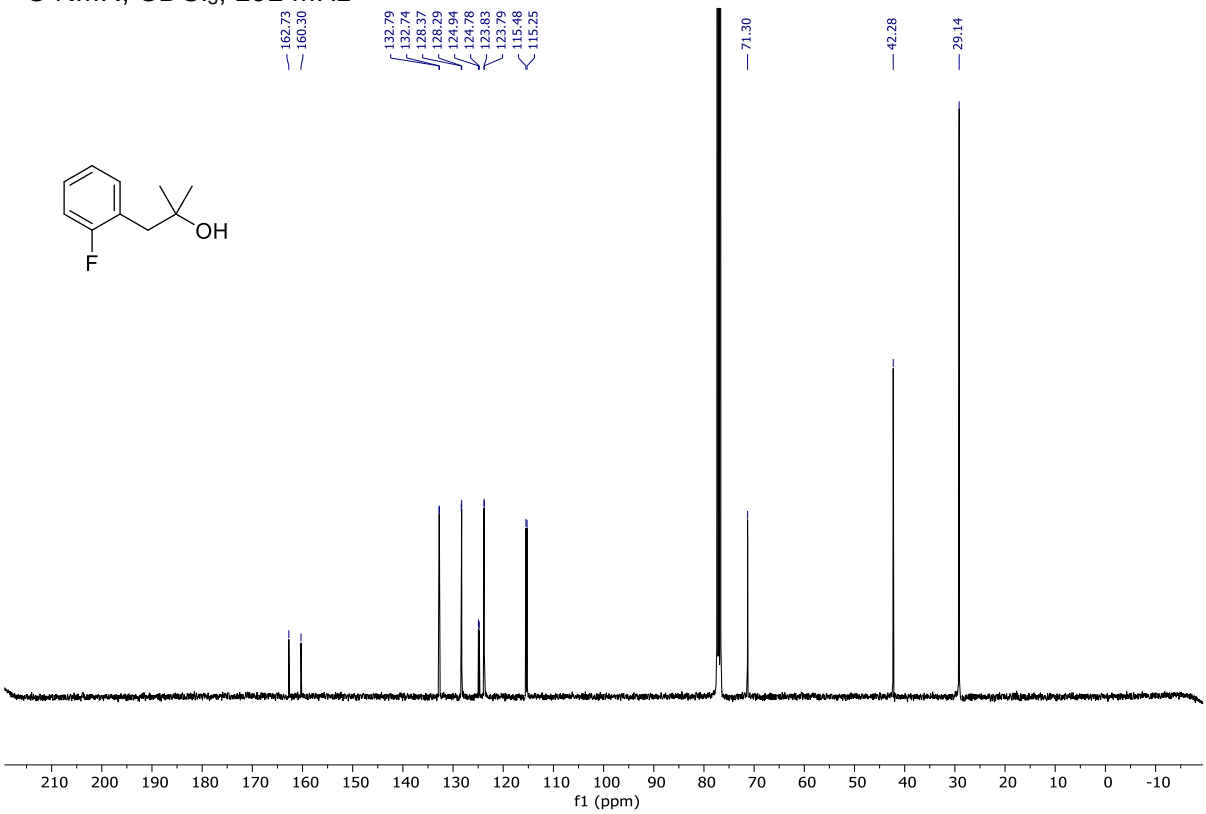


5.8n

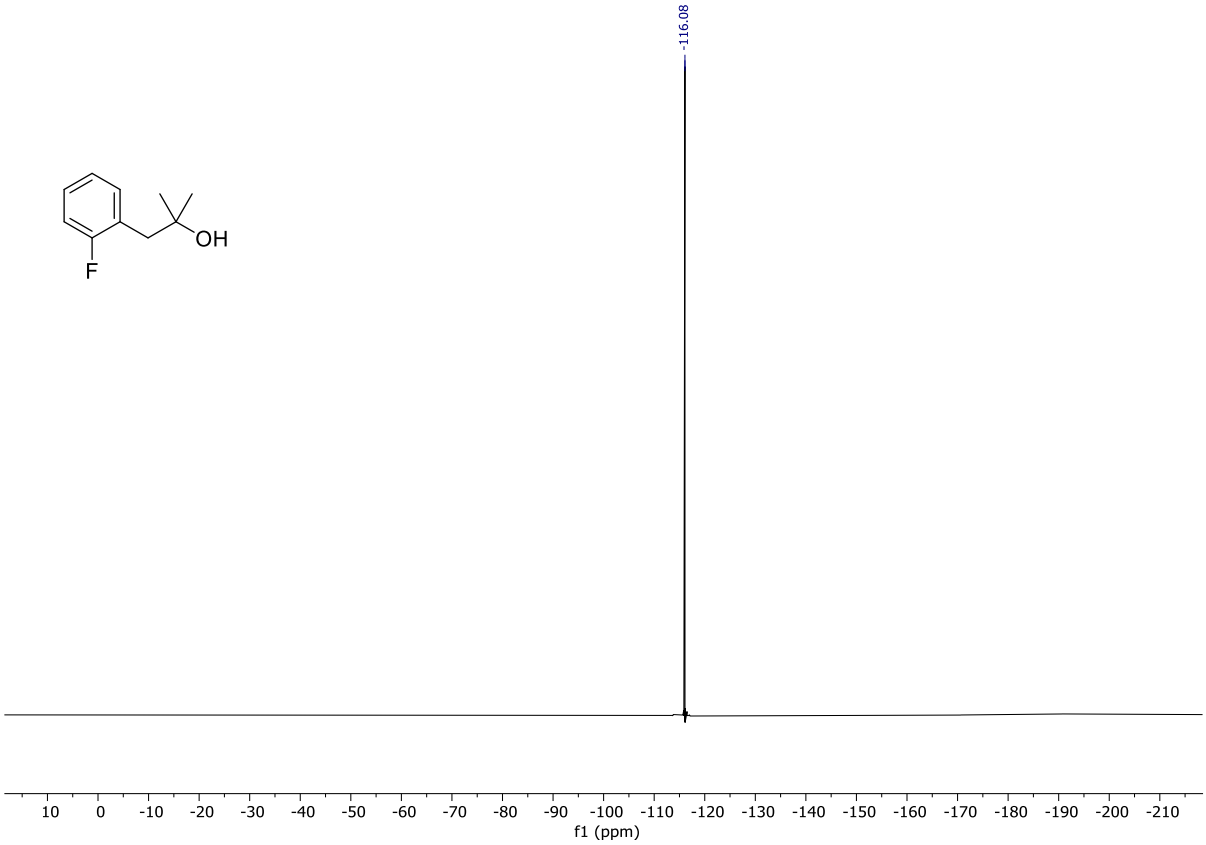
^{1}H NMR, $CDCl_3$, 400 MHz



^{13}C NMR, $CDCl_3$, 101 MHz

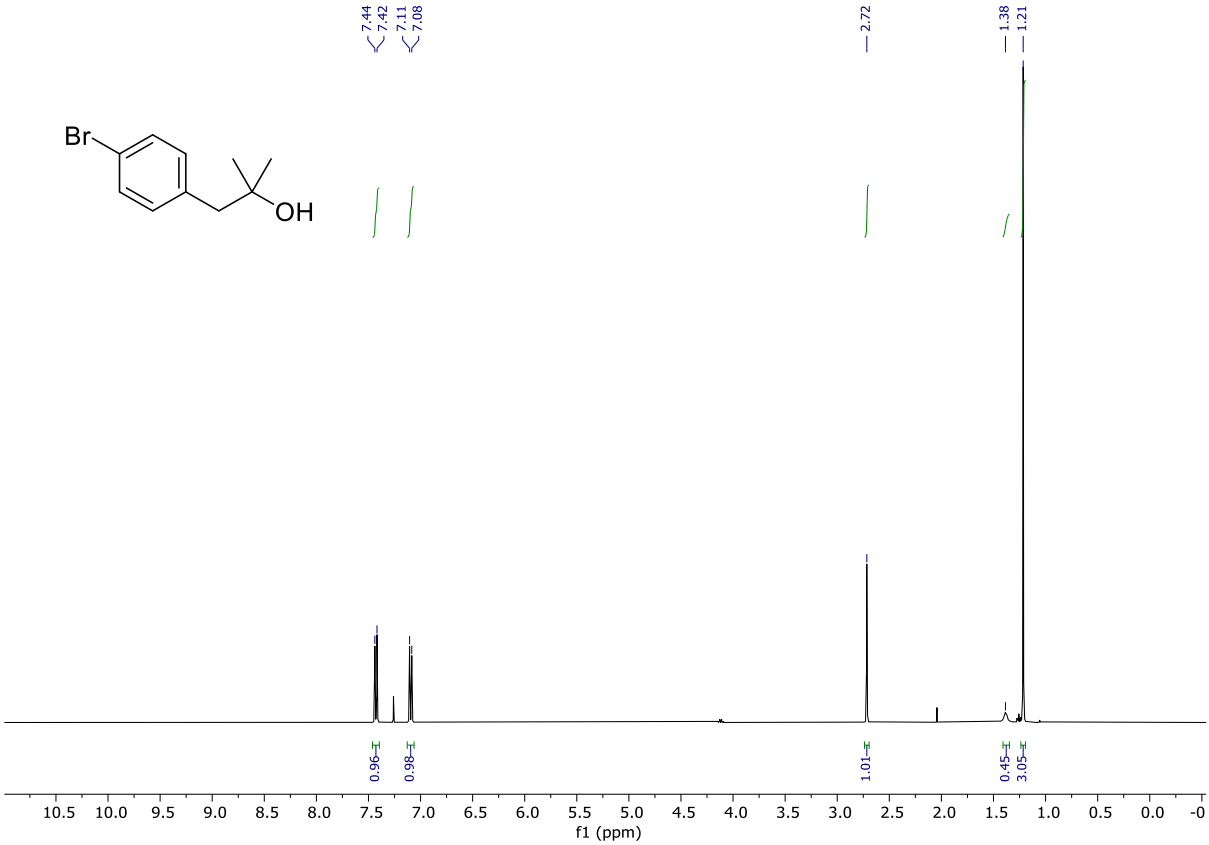


^{19}F NMR, $CDCl_3$, 376 MHz

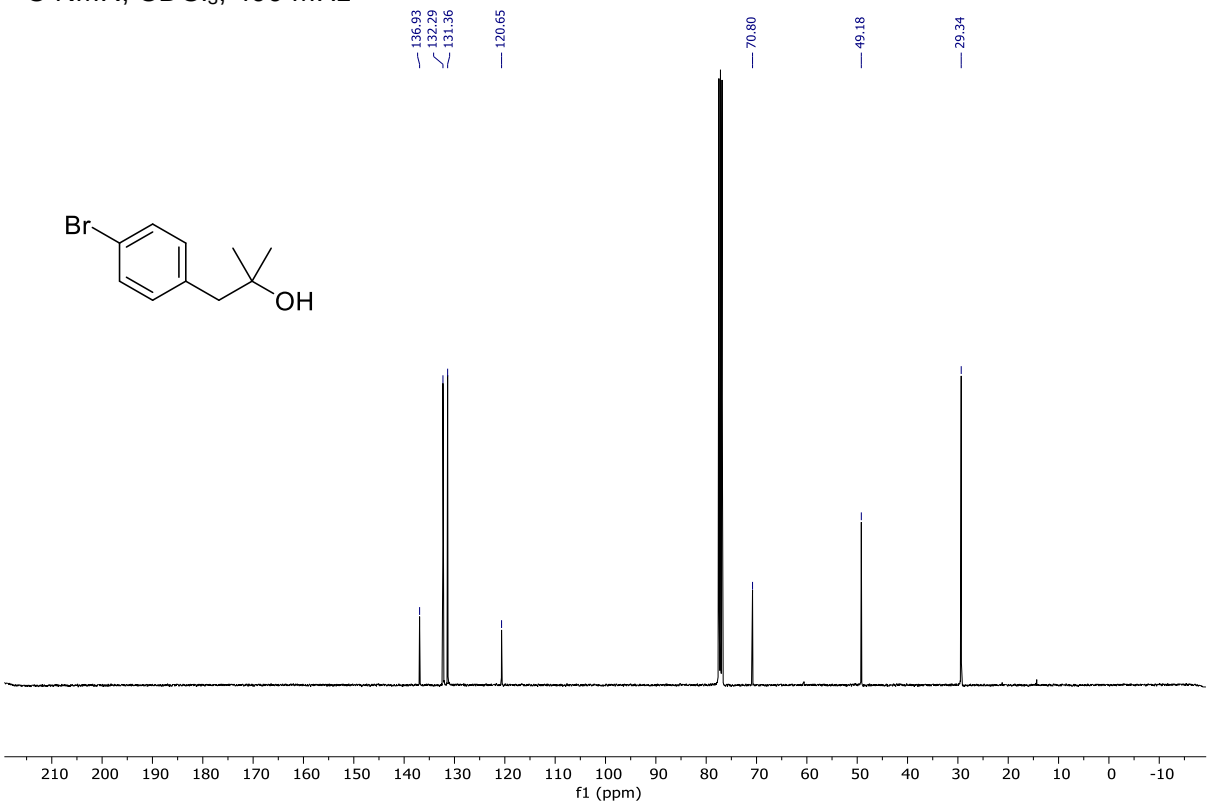


5.8o

^{1}H NMR, $CDCl_3$, 400 MHz

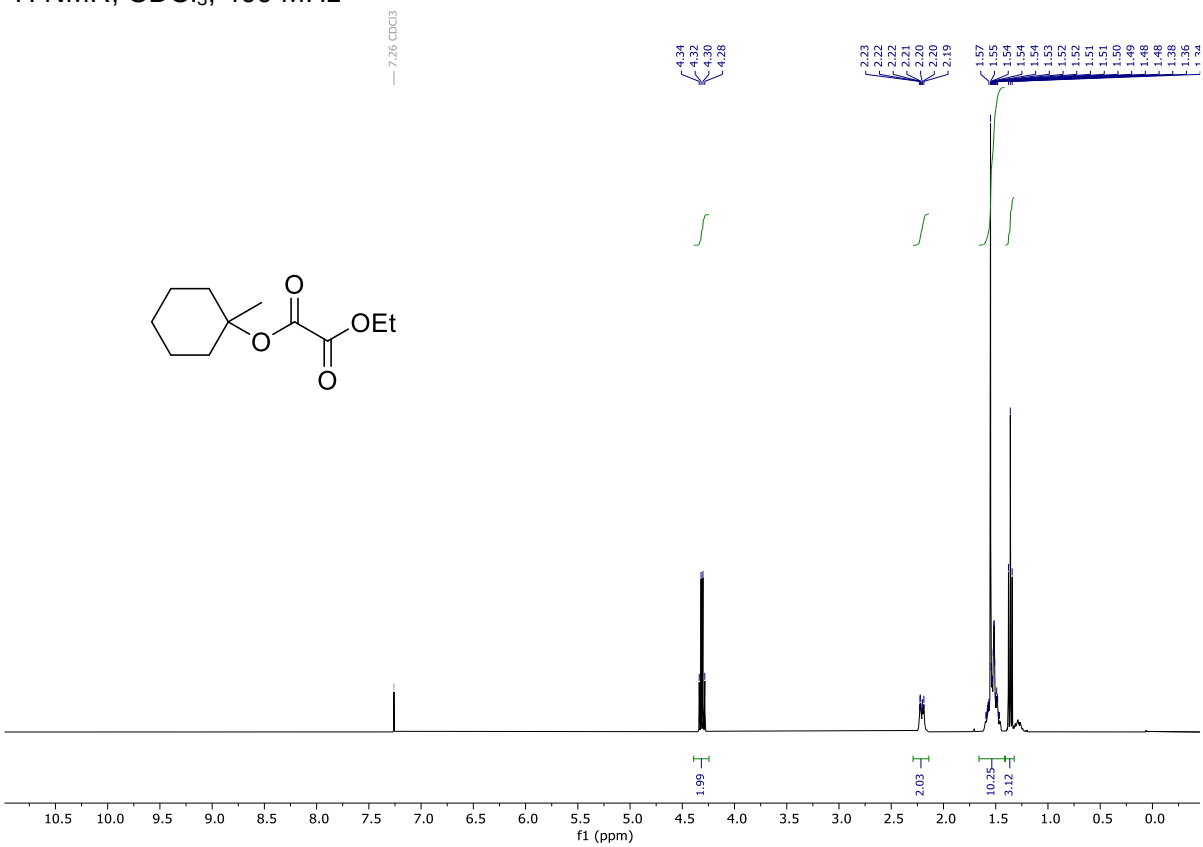


^{13}C NMR, $CDCl_3$, 400 MHz

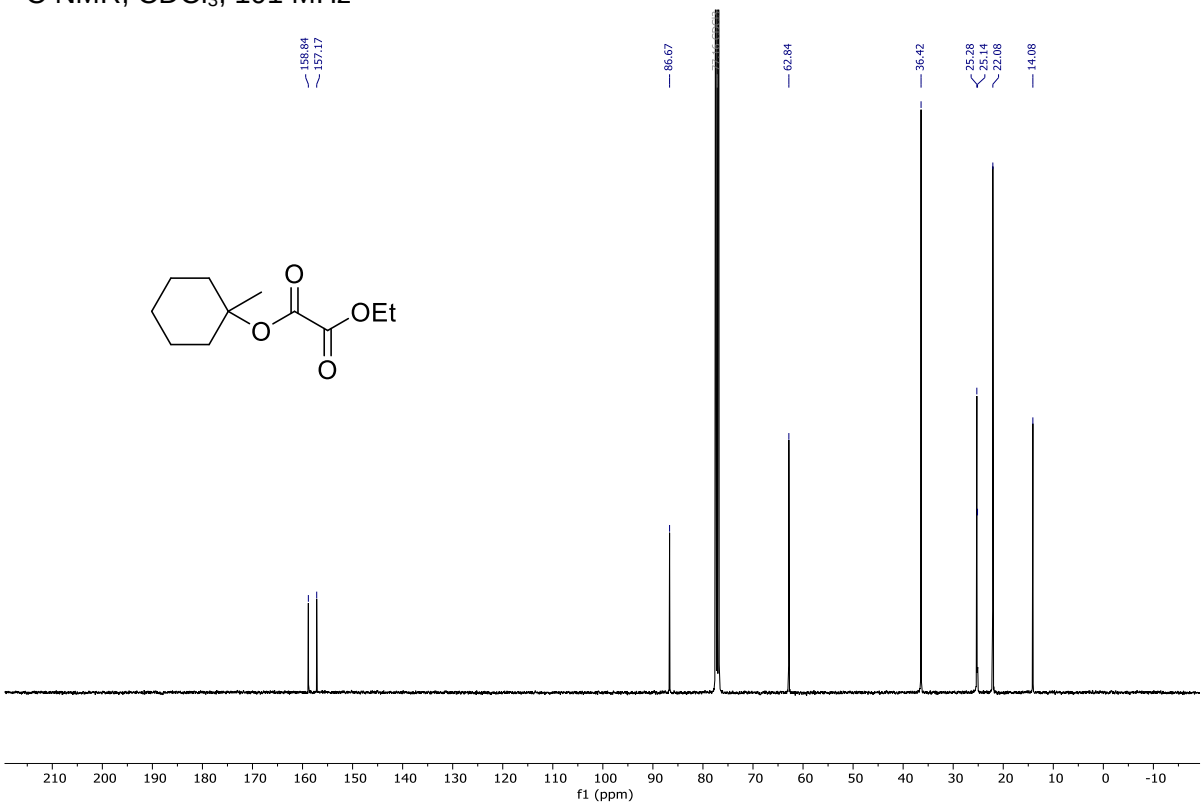


5.10a

^{1}H NMR, $CDCl_3$, 400 MHz

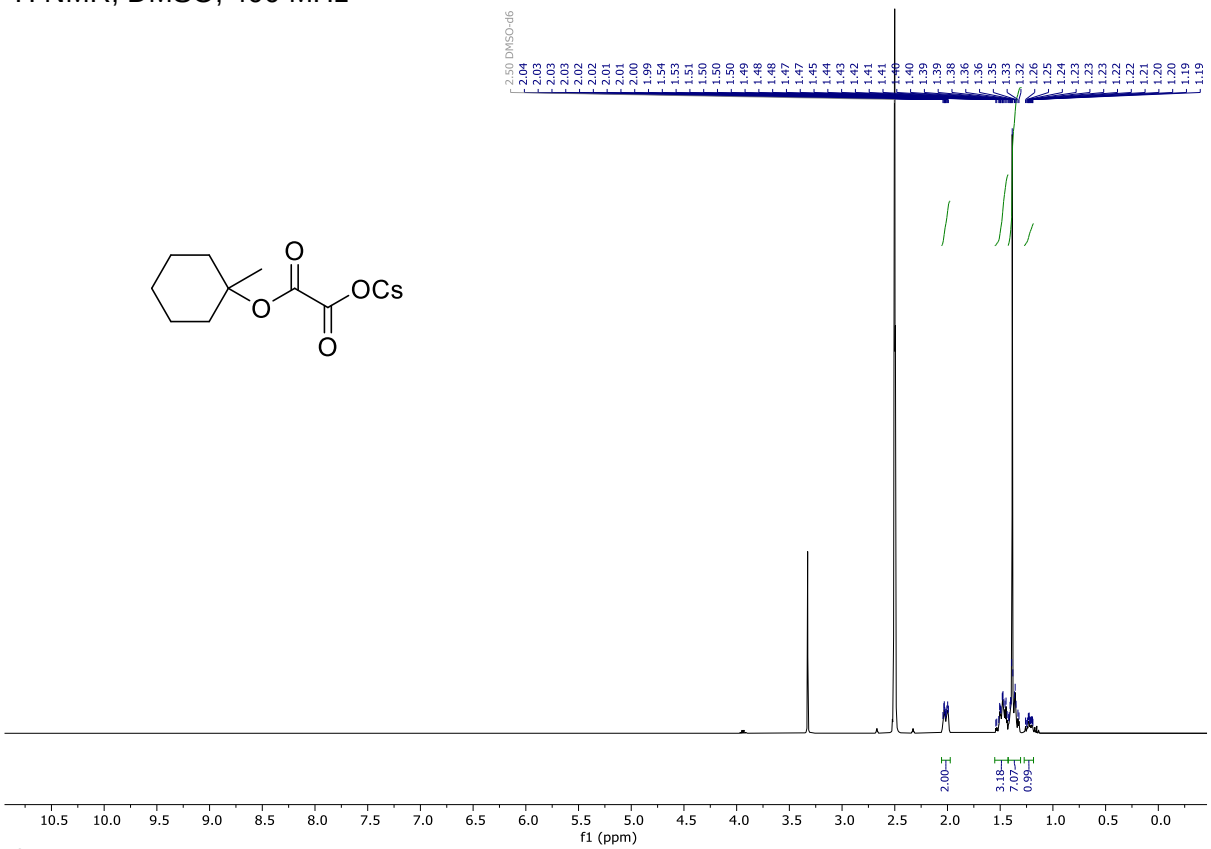


^{13}C NMR, $CDCl_3$, 101 MHz

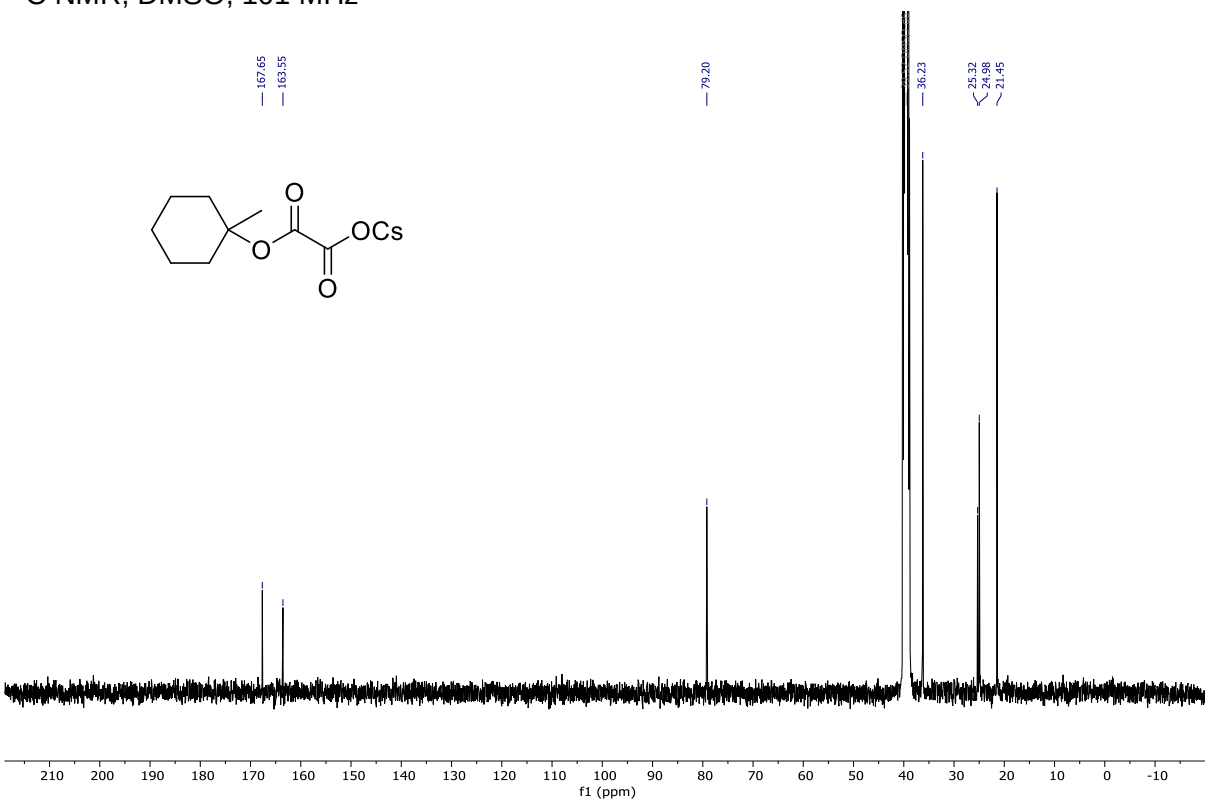


5.6a

^{1}H NMR, DMSO, 400 MHz

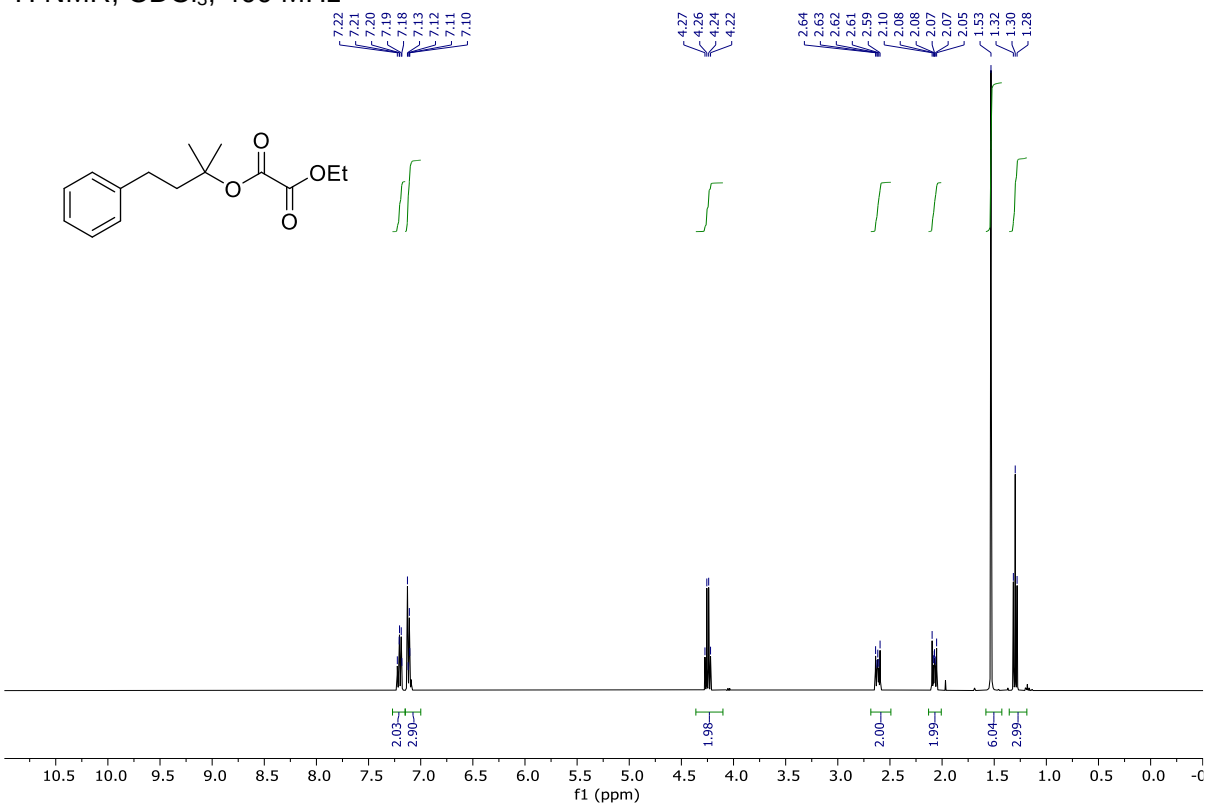


^{13}C NMR, DMSO, 101 MHz

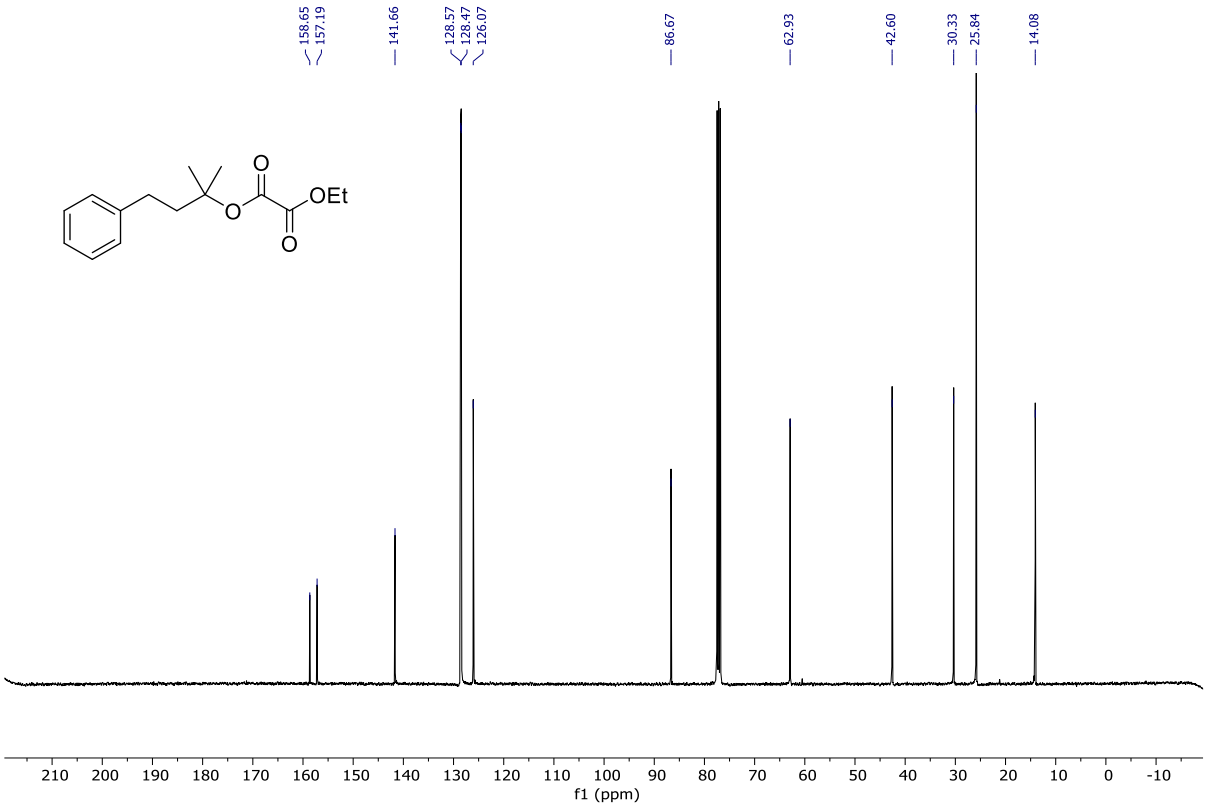


5.10b

^{1}H NMR, $CDCl_3$, 400 MHz

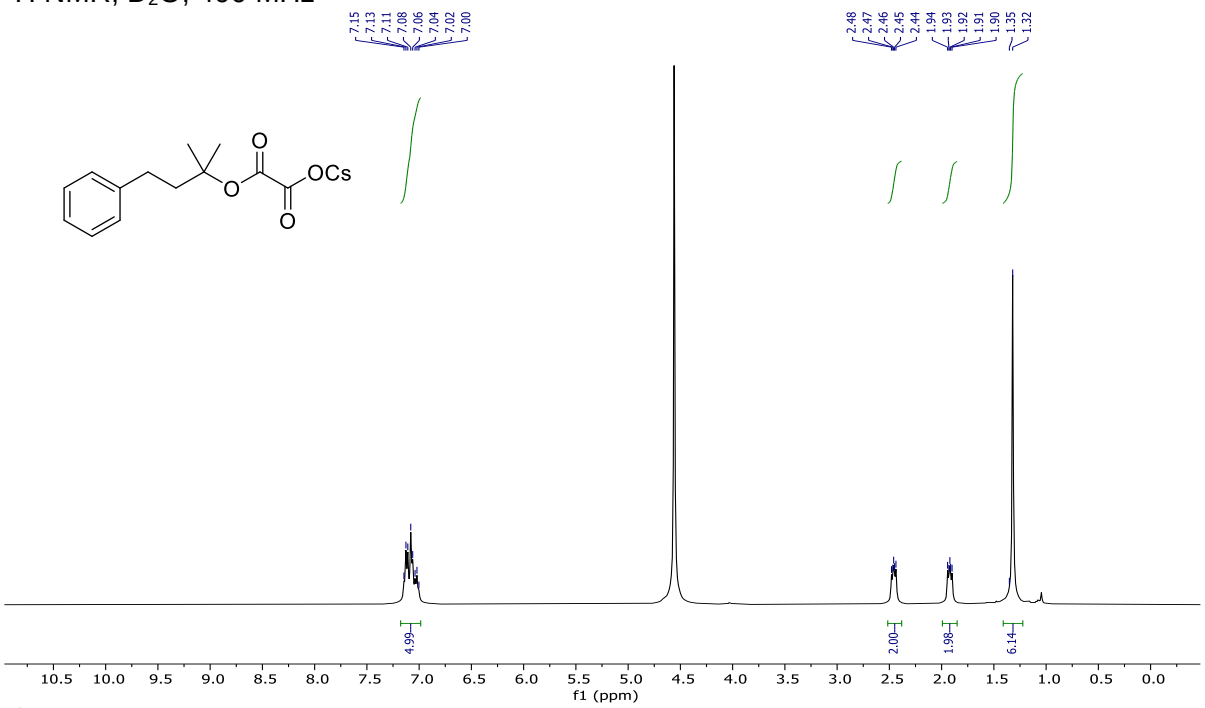


^{13}C NMR, $CDCl_3$, 400 MHz

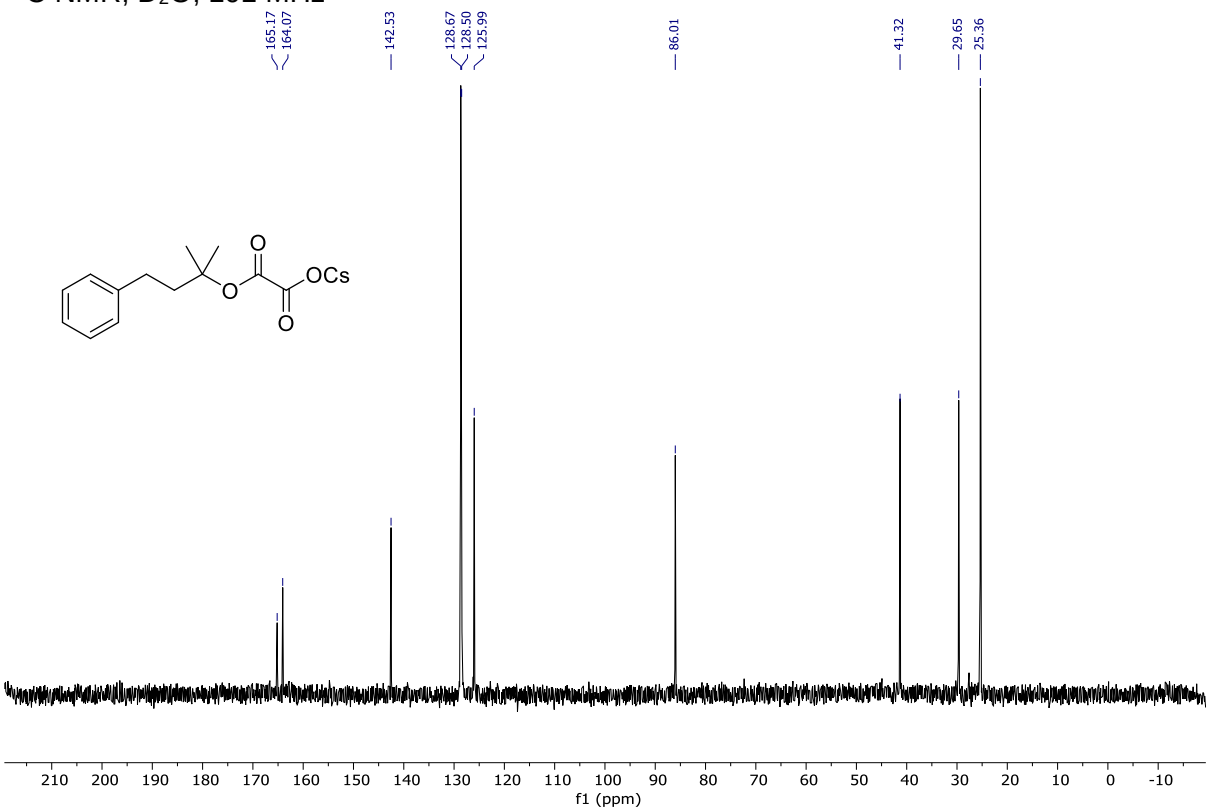


5.6b

^{1}H NMR, D_2O, 400 MHz

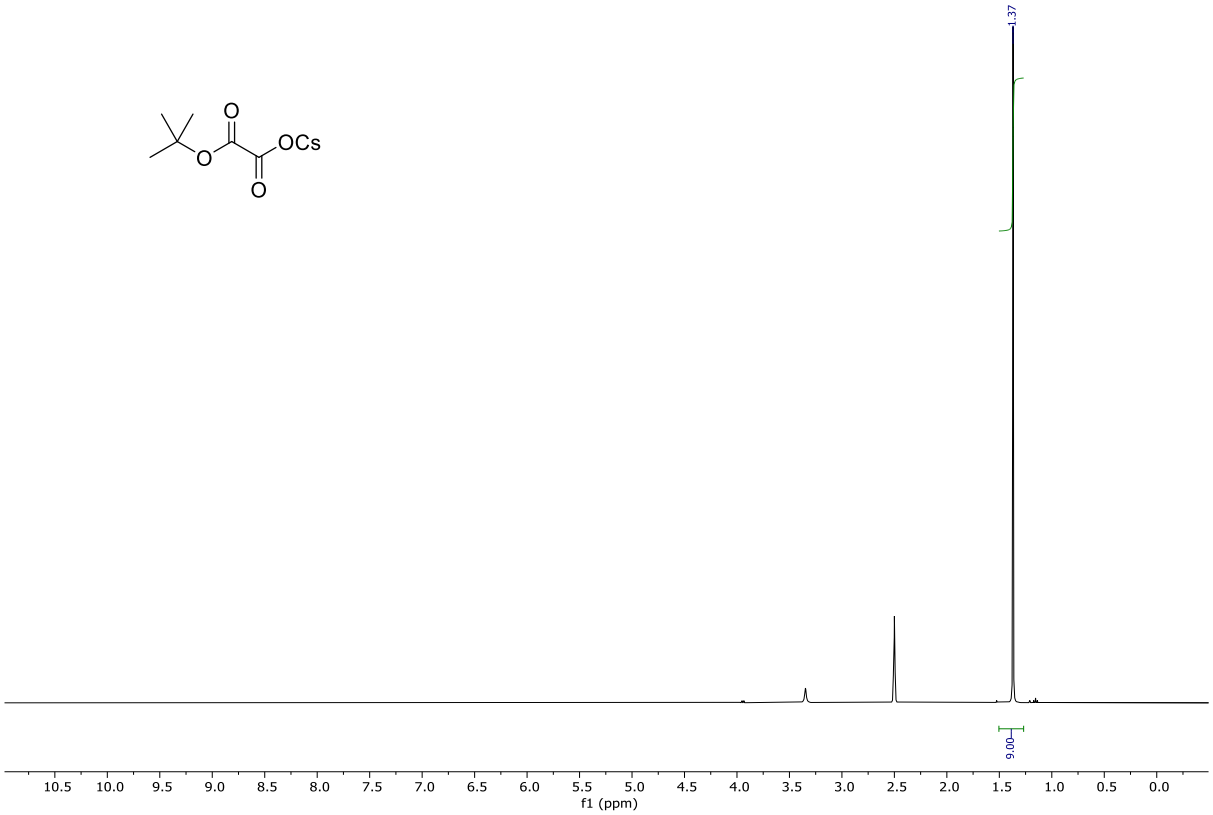


^{13}C NMR, D_2O, 101 MHz

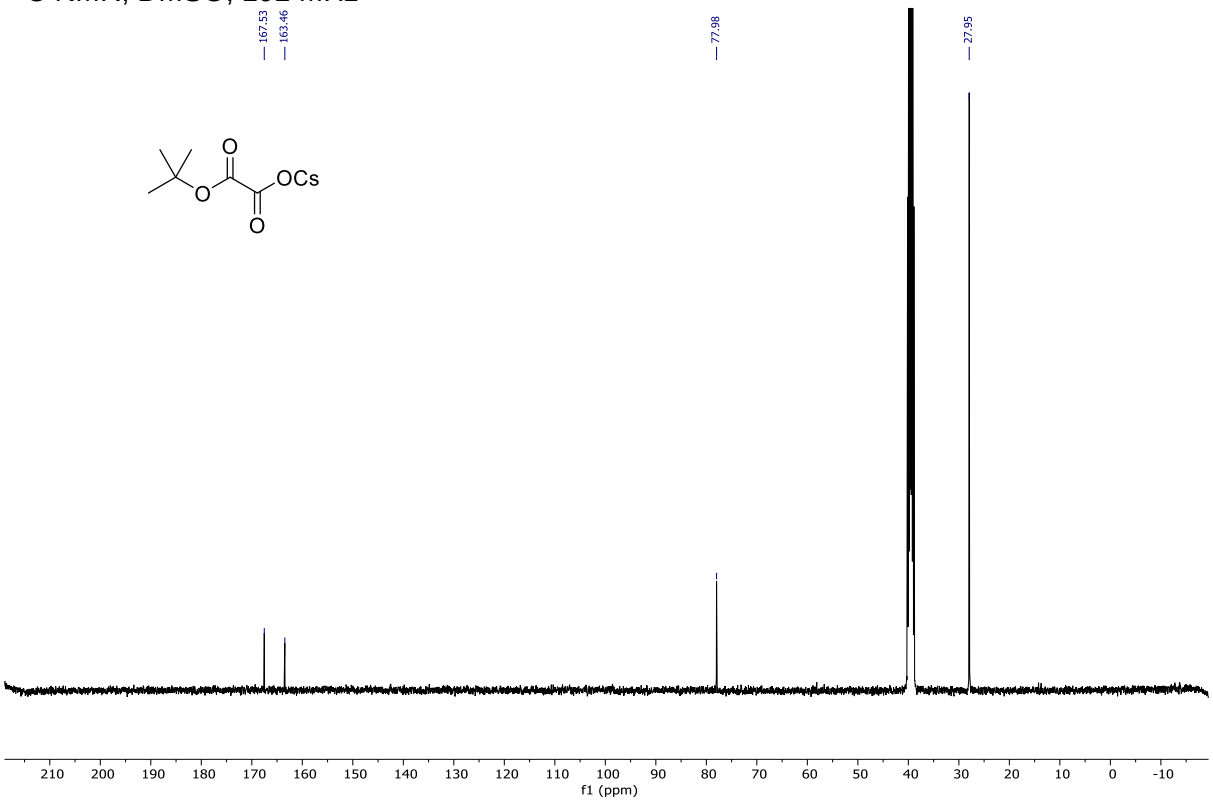


5.6c

^{1}H NMR, DMSO, 400 MHz

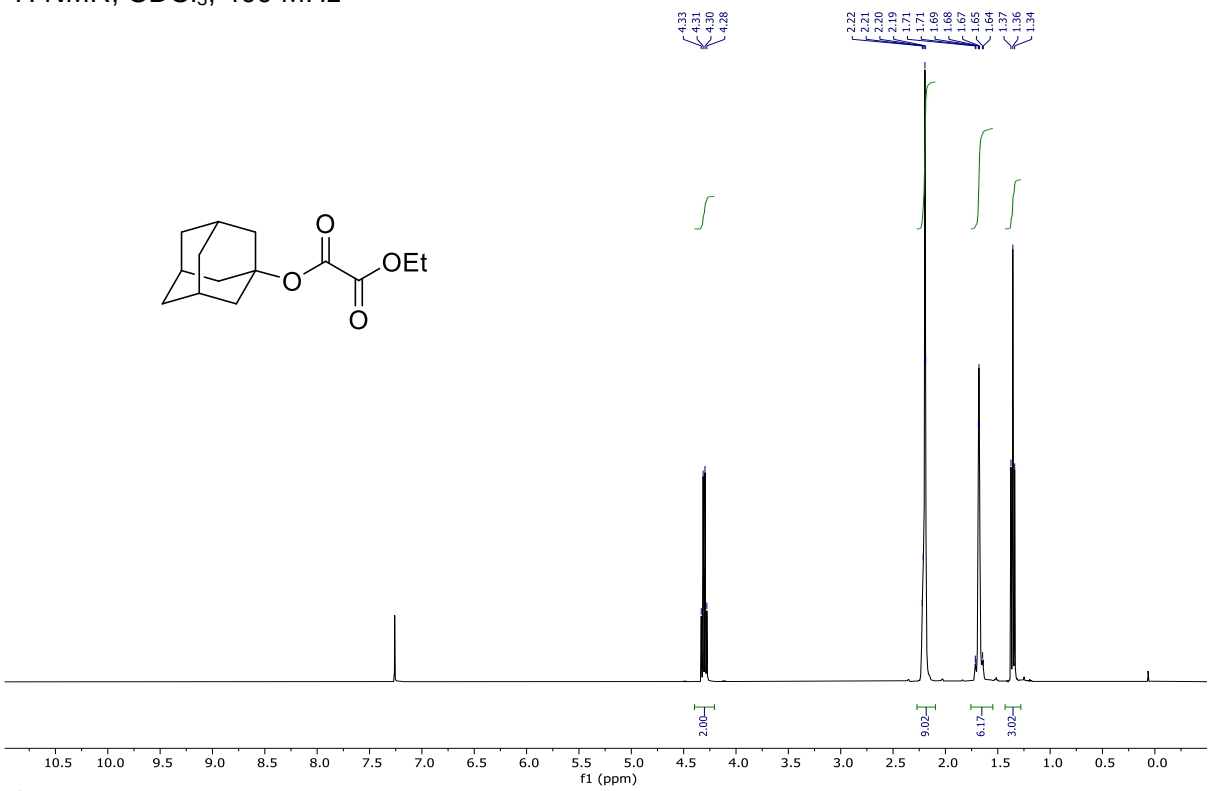


^{13}C NMR, DMSO, 101 MHz

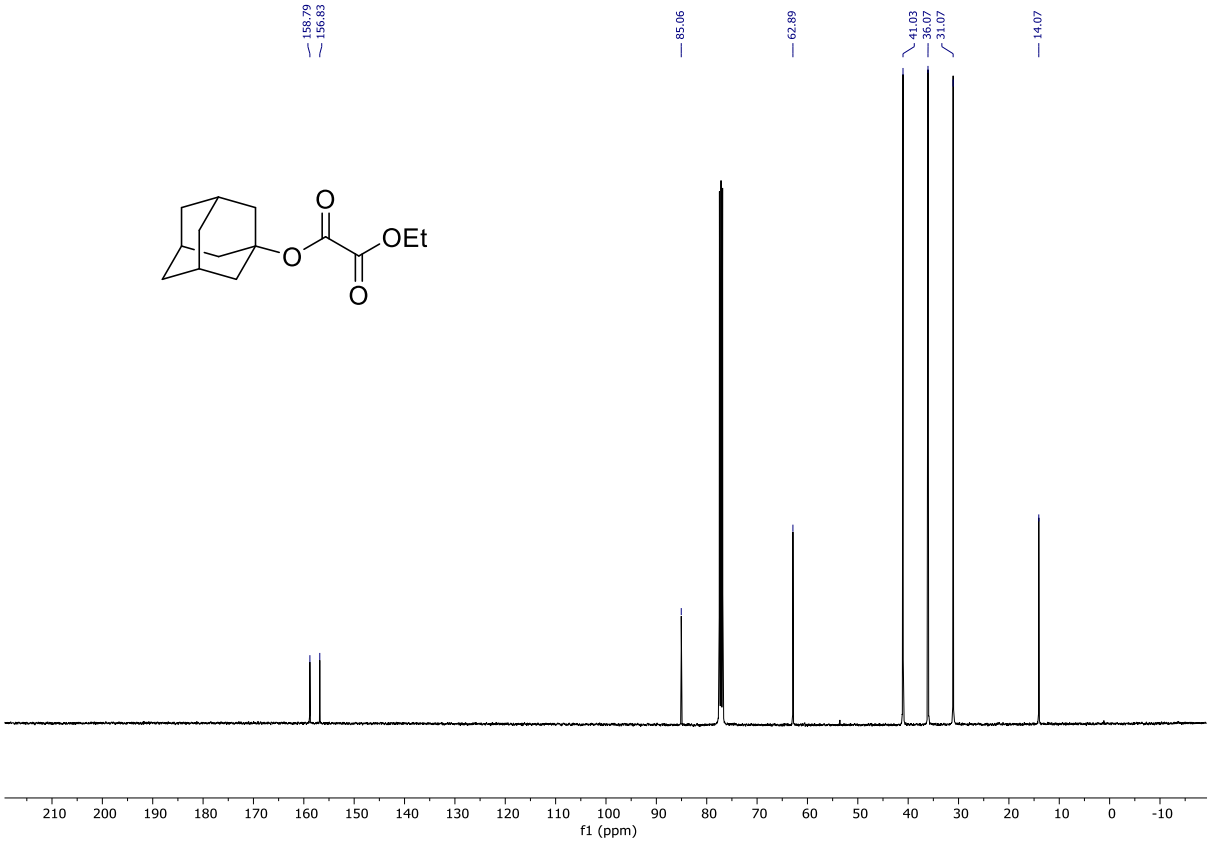


5.10d

^{1}H NMR, $CDCl_3$, 400 MHz

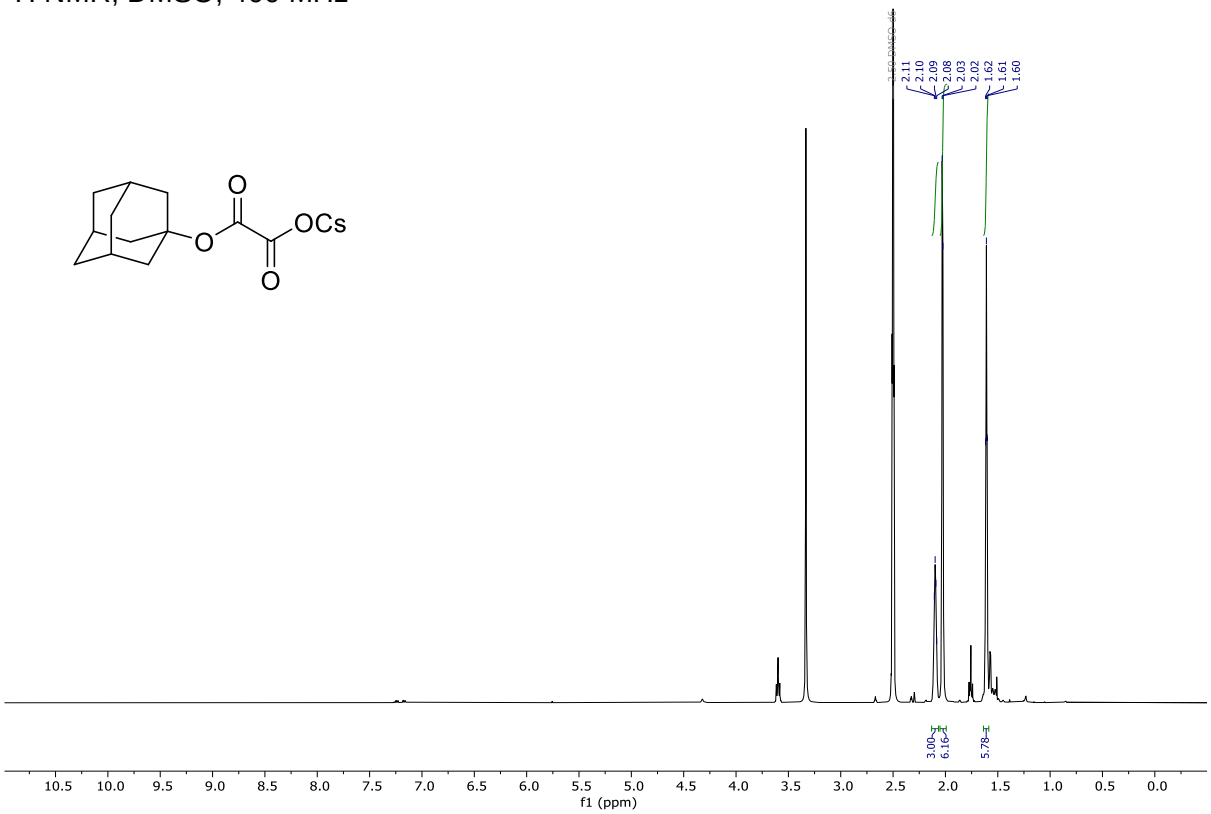


^{13}C NMR, $CDCl_3$, 101 MHz

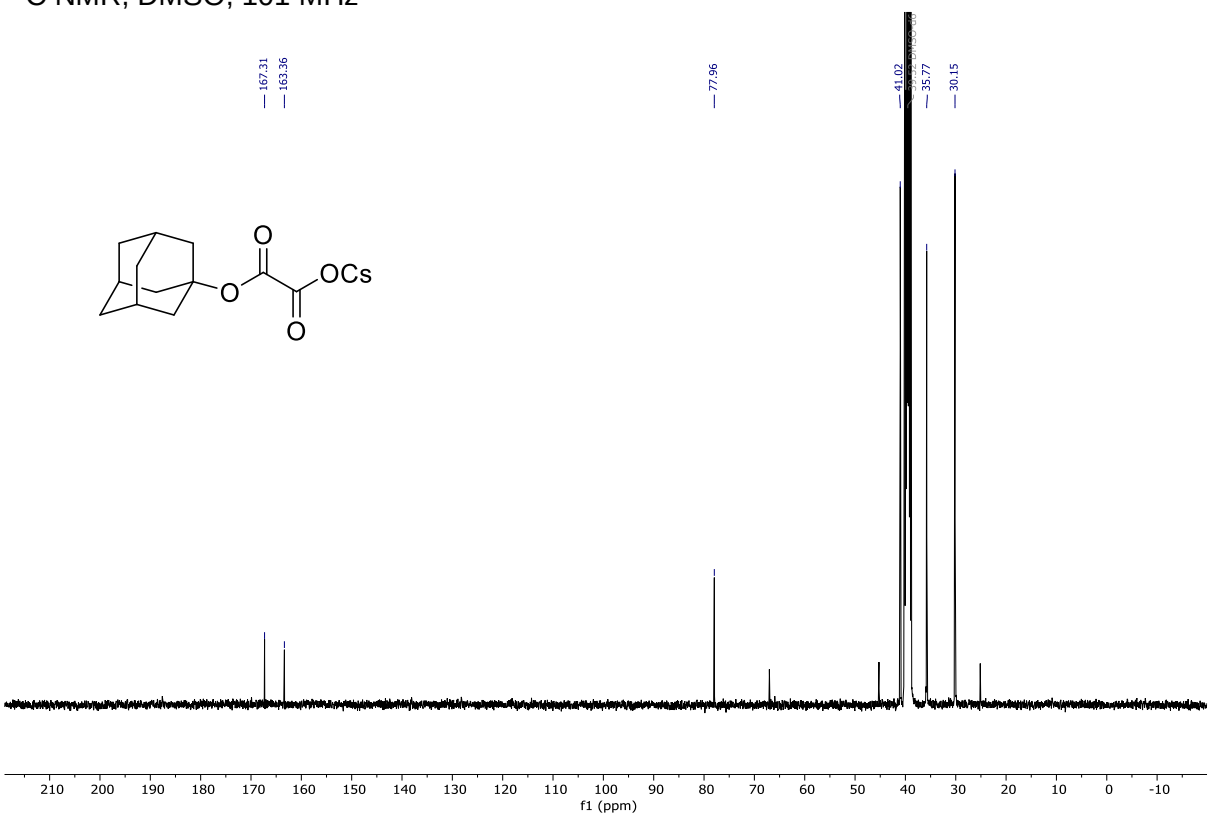


5.6d (with 25% 5.10d)

^{1}H NMR, DMSO, 400 MHz

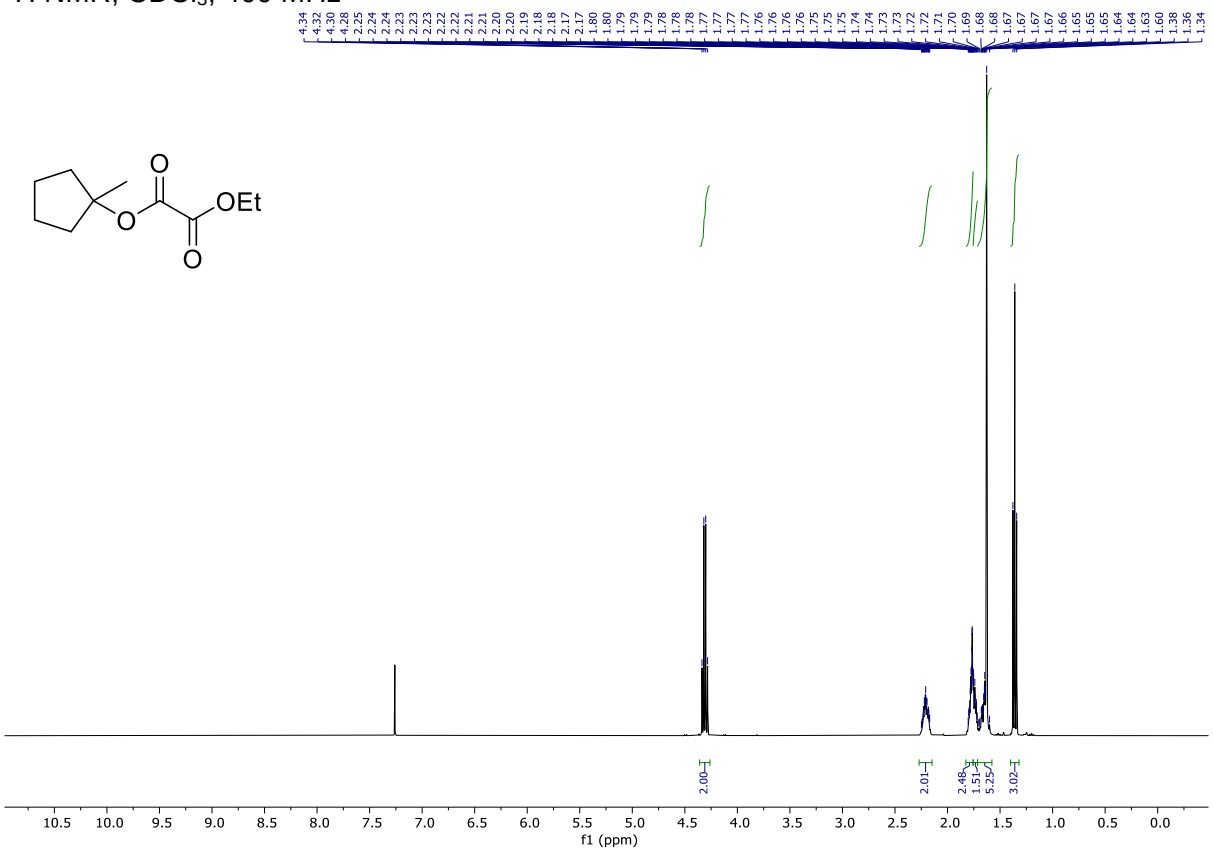


^{13}C NMR, DMSO, 101 MHz

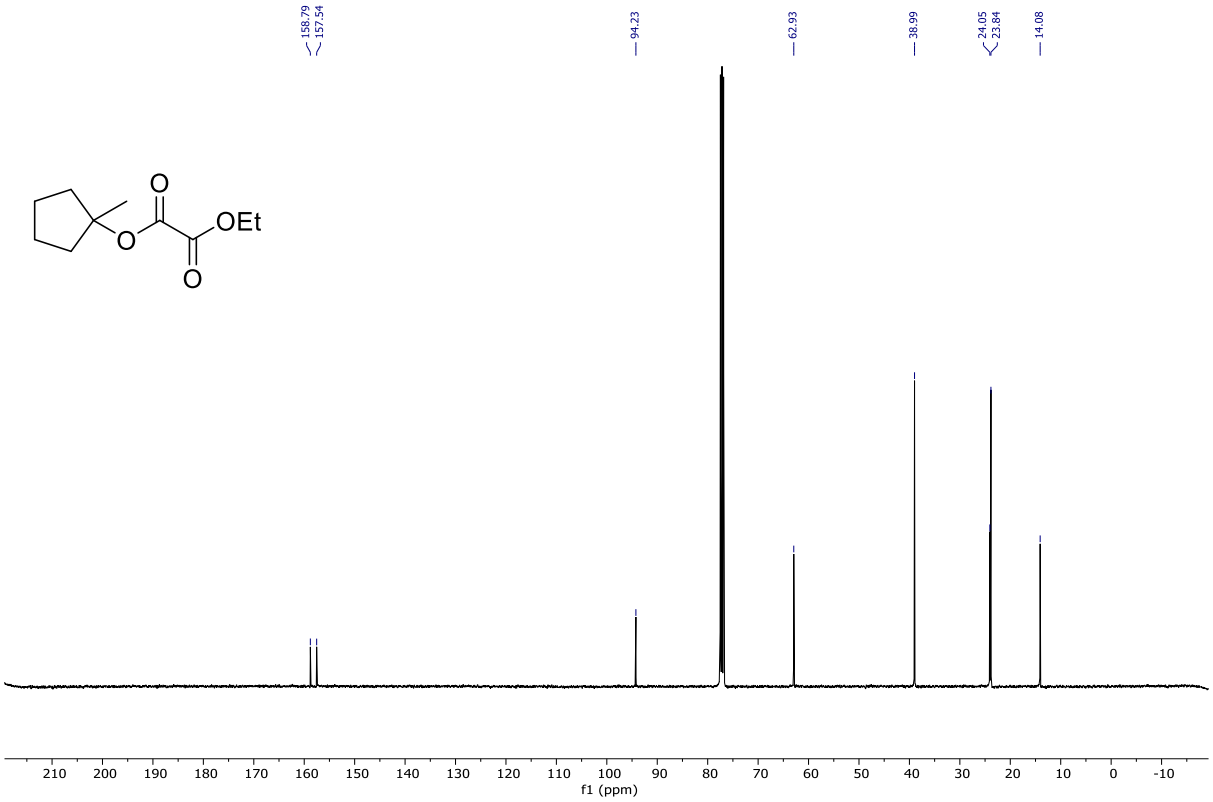


5.10e

^{1}H NMR, $CDCl_3$, 400 MHz

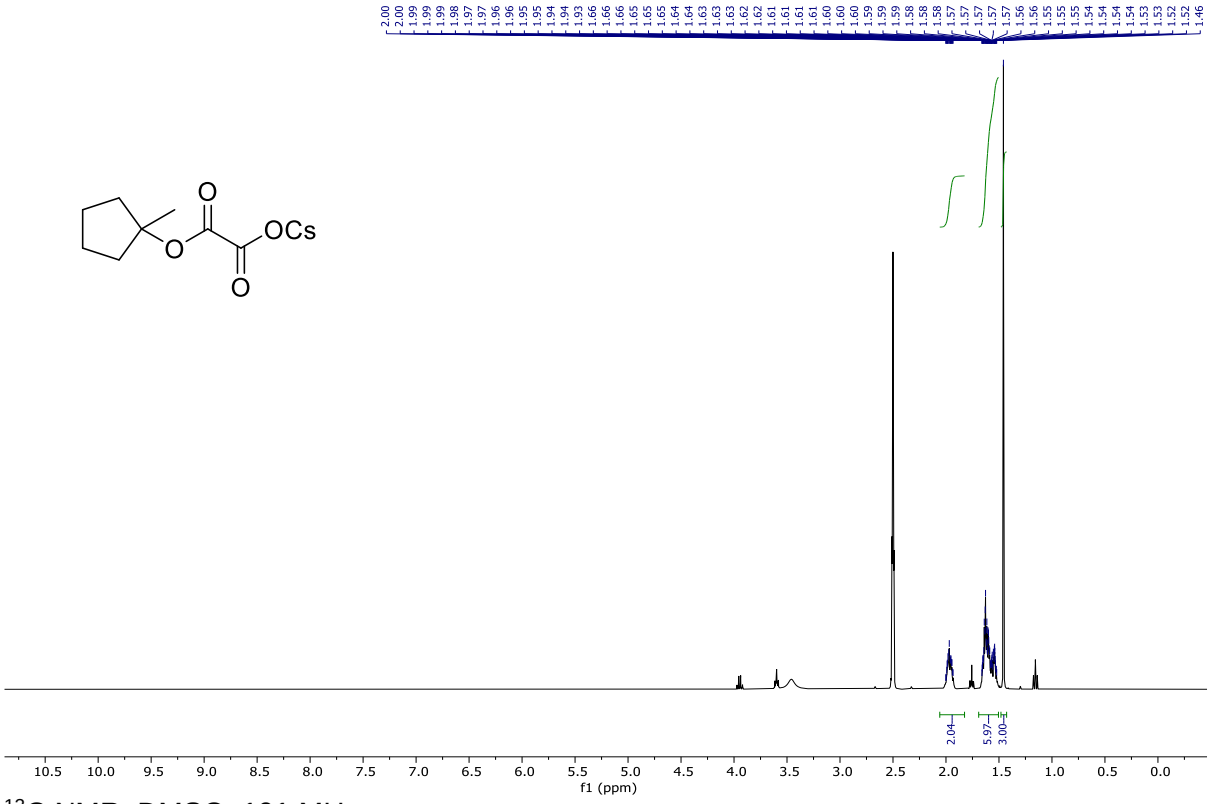


^{13}C NMR, $CDCl_3$, 101 MHz

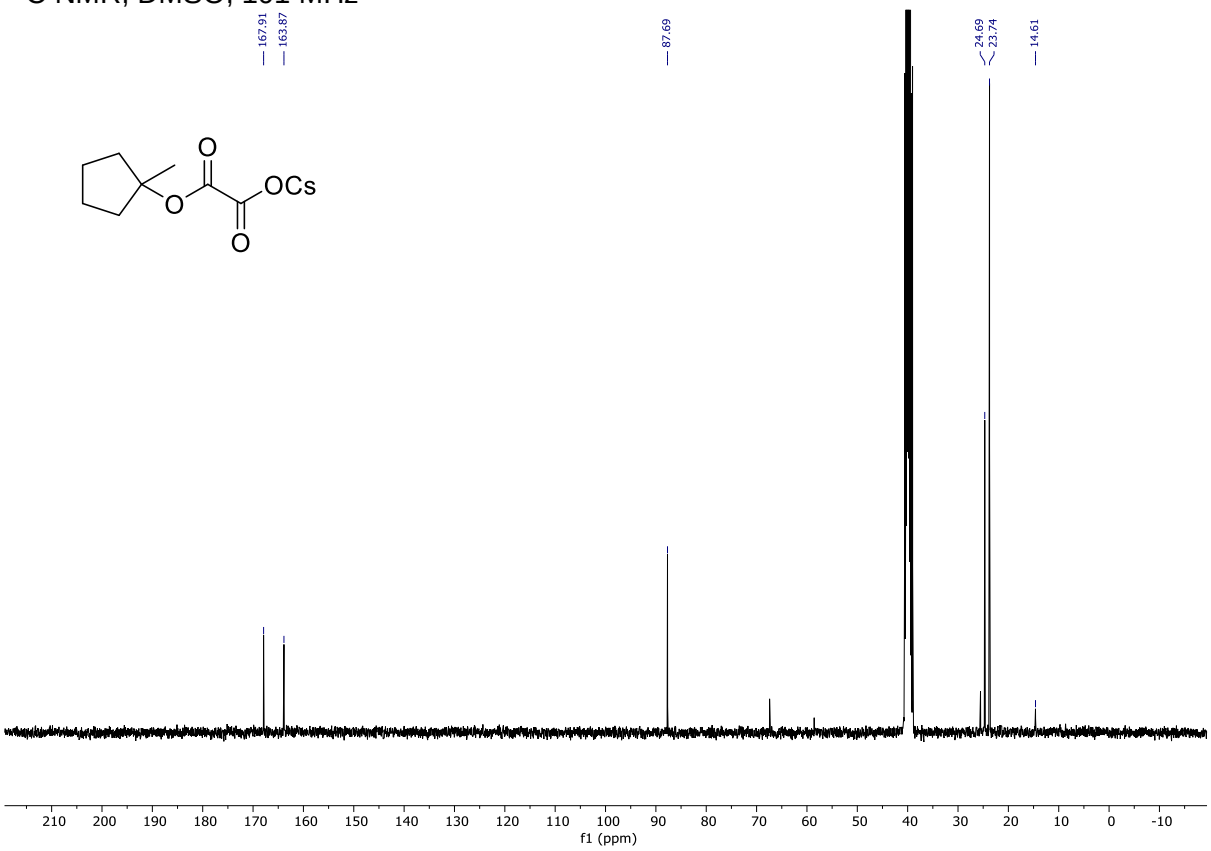


5.6e

^{1}H NMR, DMSO, 400 MHz

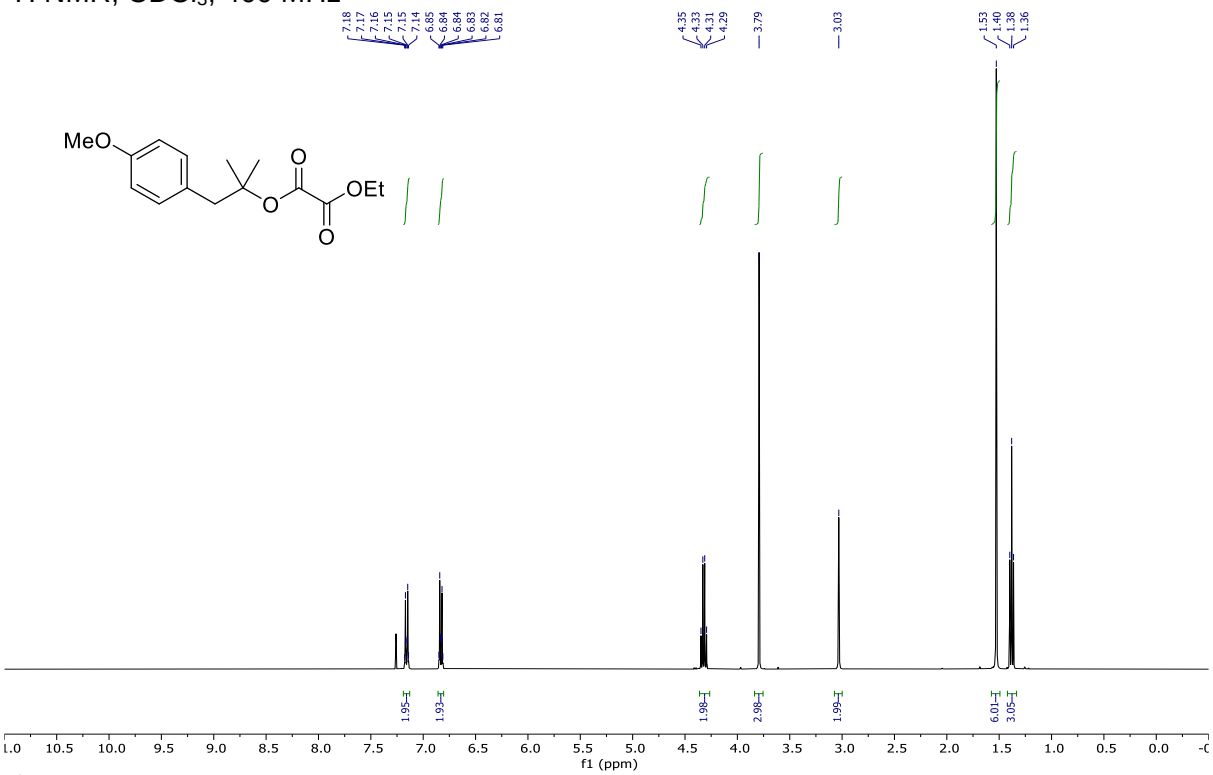


^{13}C NMR, DMSO, 101 MHz

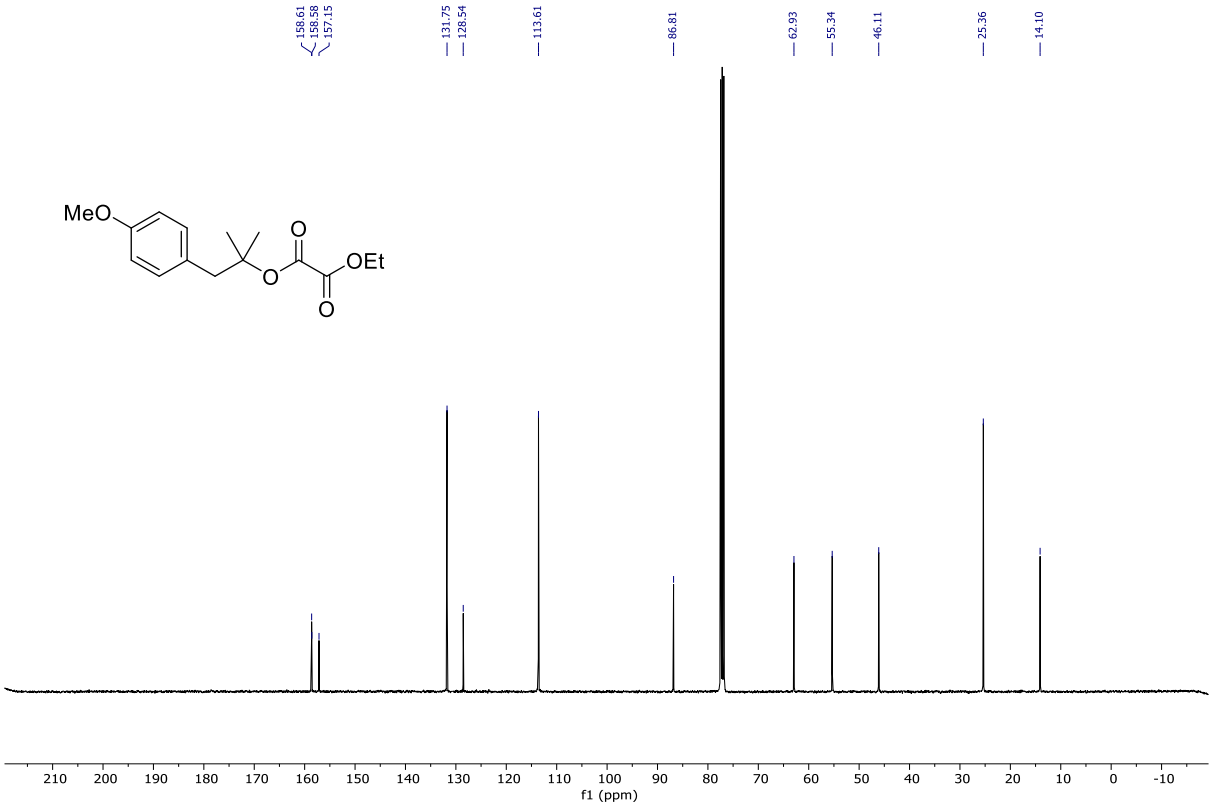


5.10f

^{1}H NMR, $CDCl_3$, 400 MHz

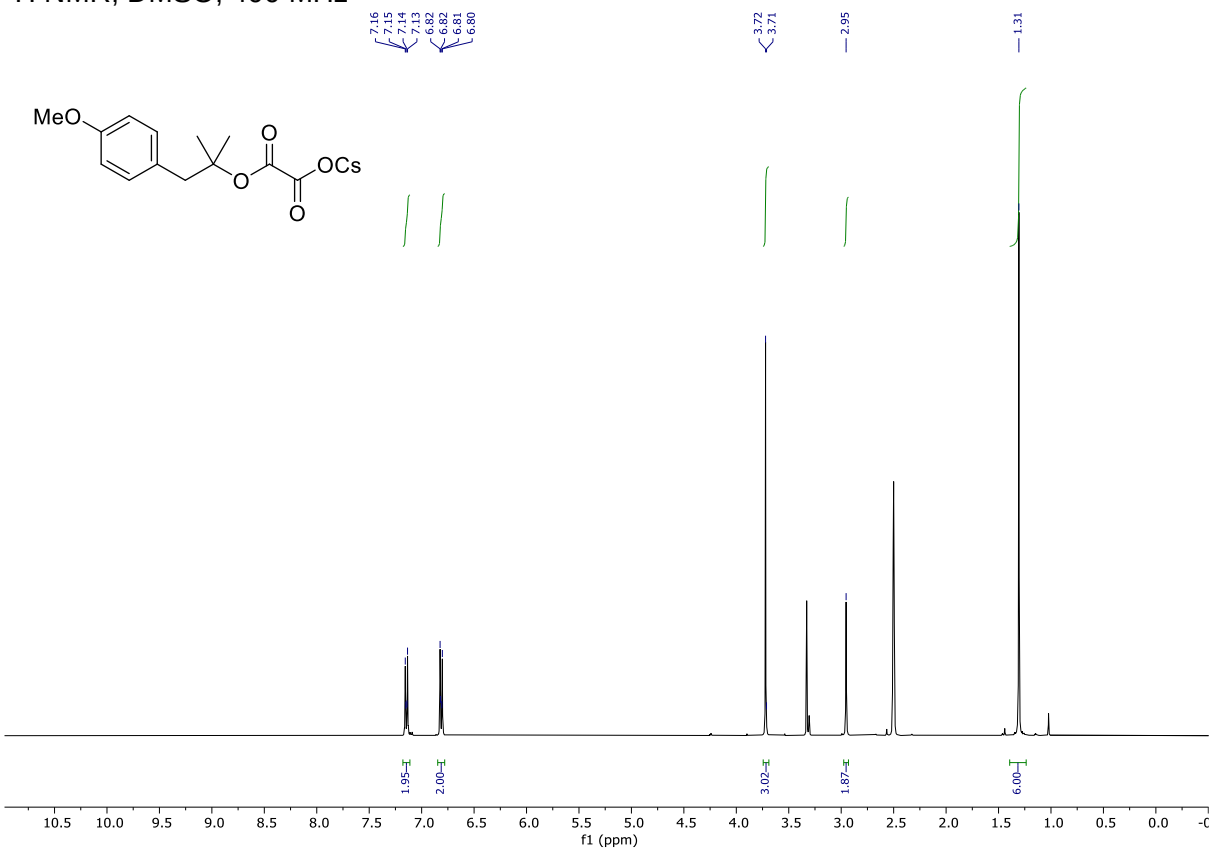


^{13}C NMR, $CDCl_3$, 101 MHz

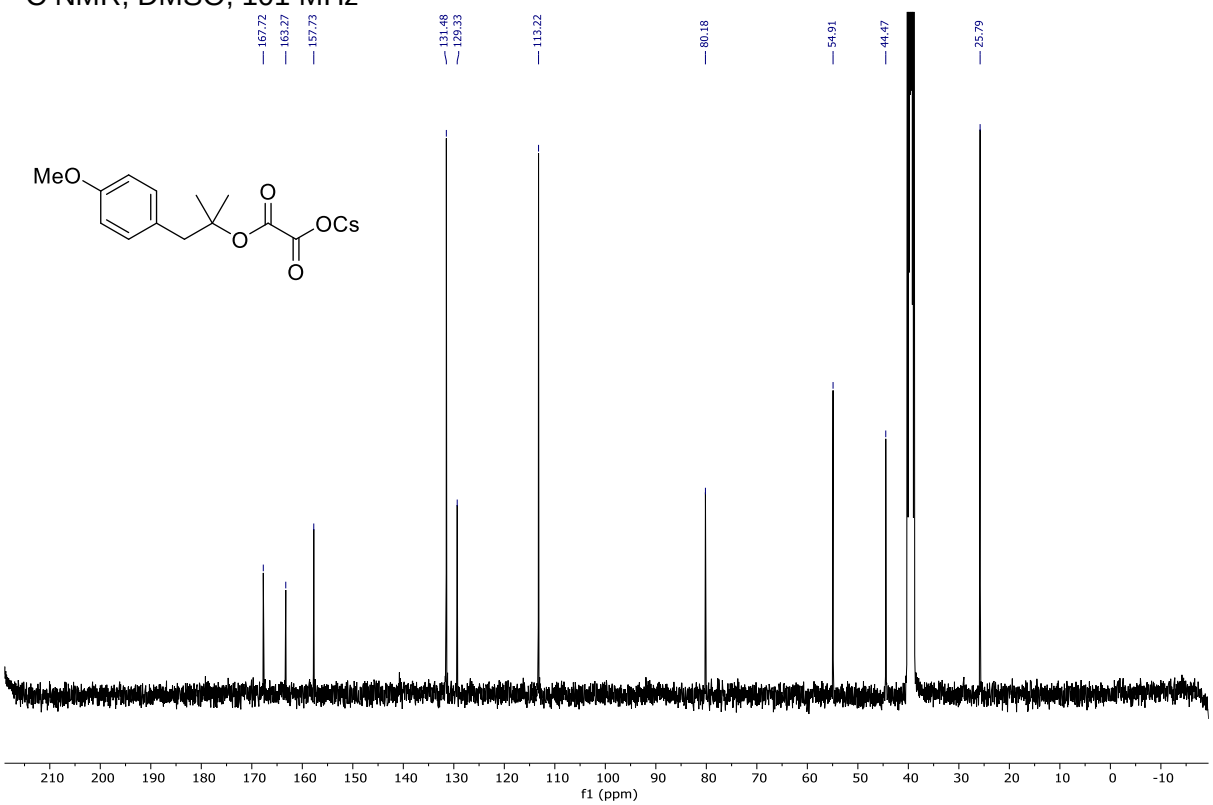


5.6f

^{1}H NMR, DMSO, 400 MHz

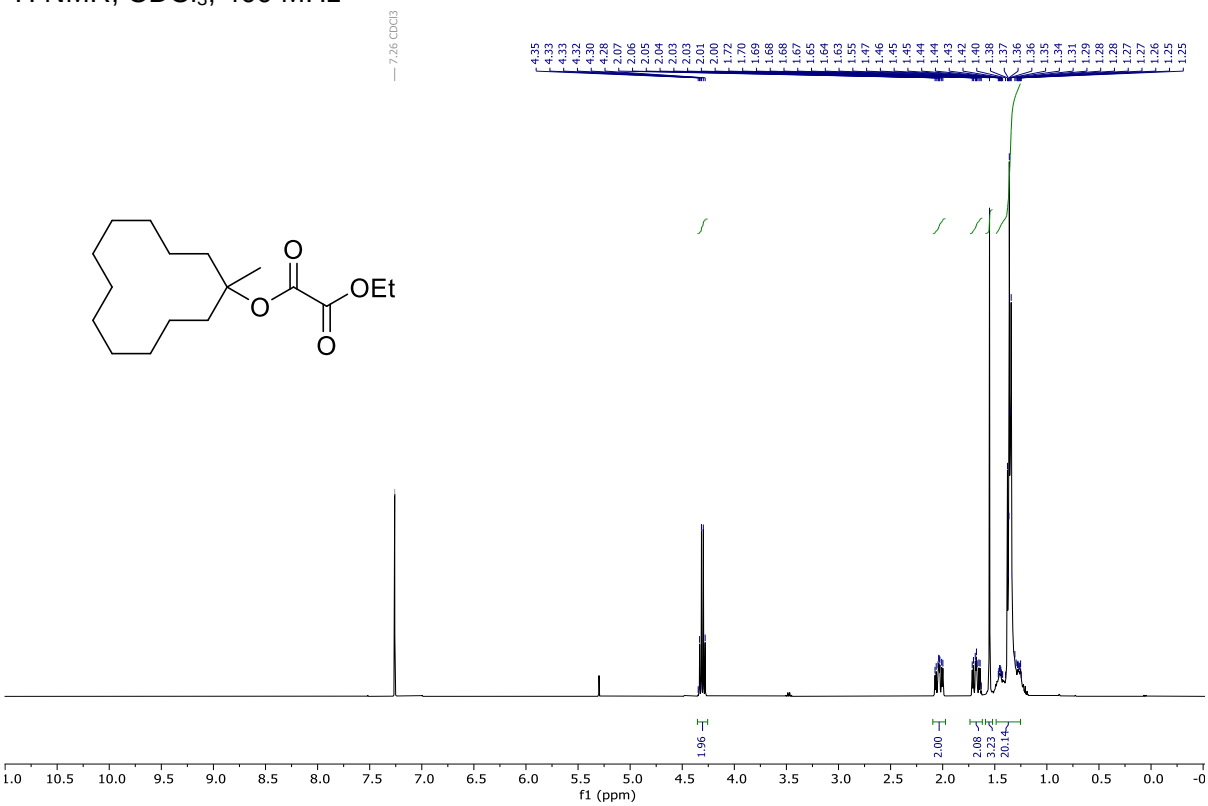


^{13}C NMR, DMSO, 101 MHz

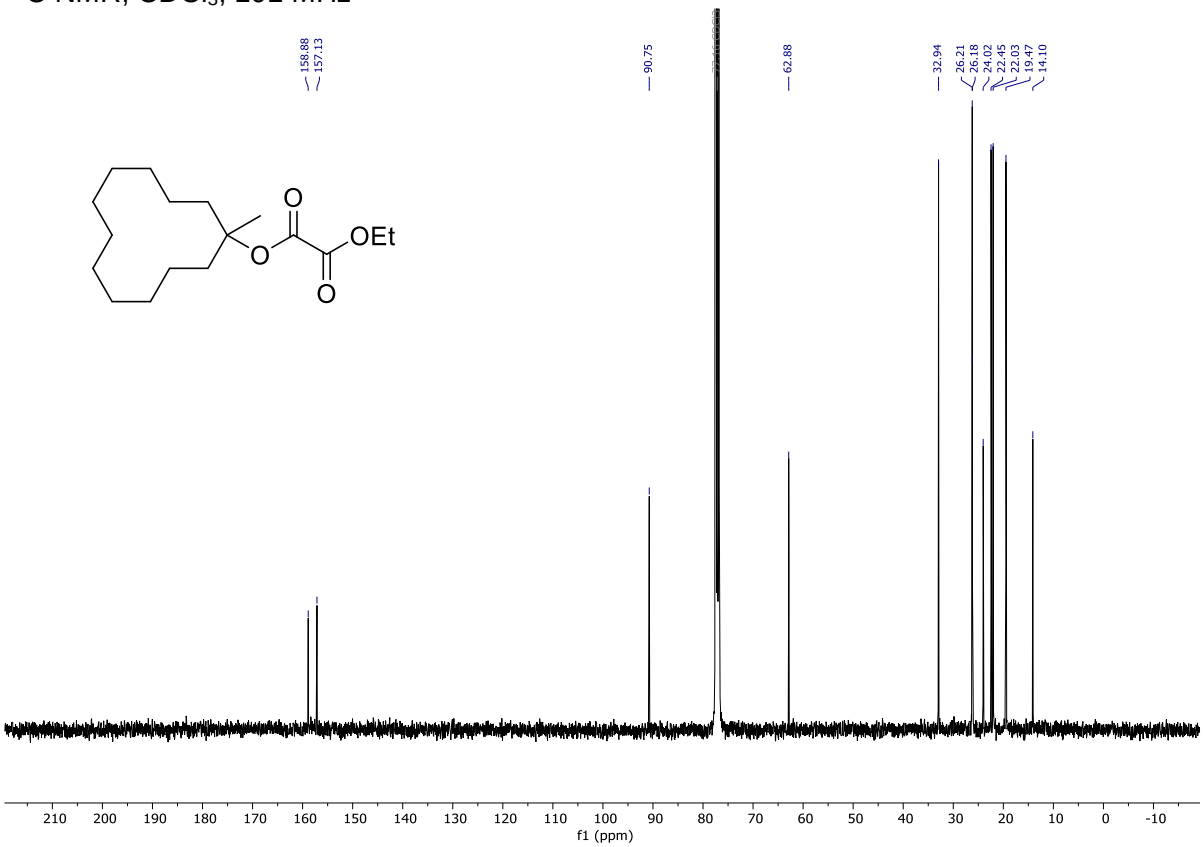


5.10g

^{1}H NMR, $CDCl_3$, 400 MHz

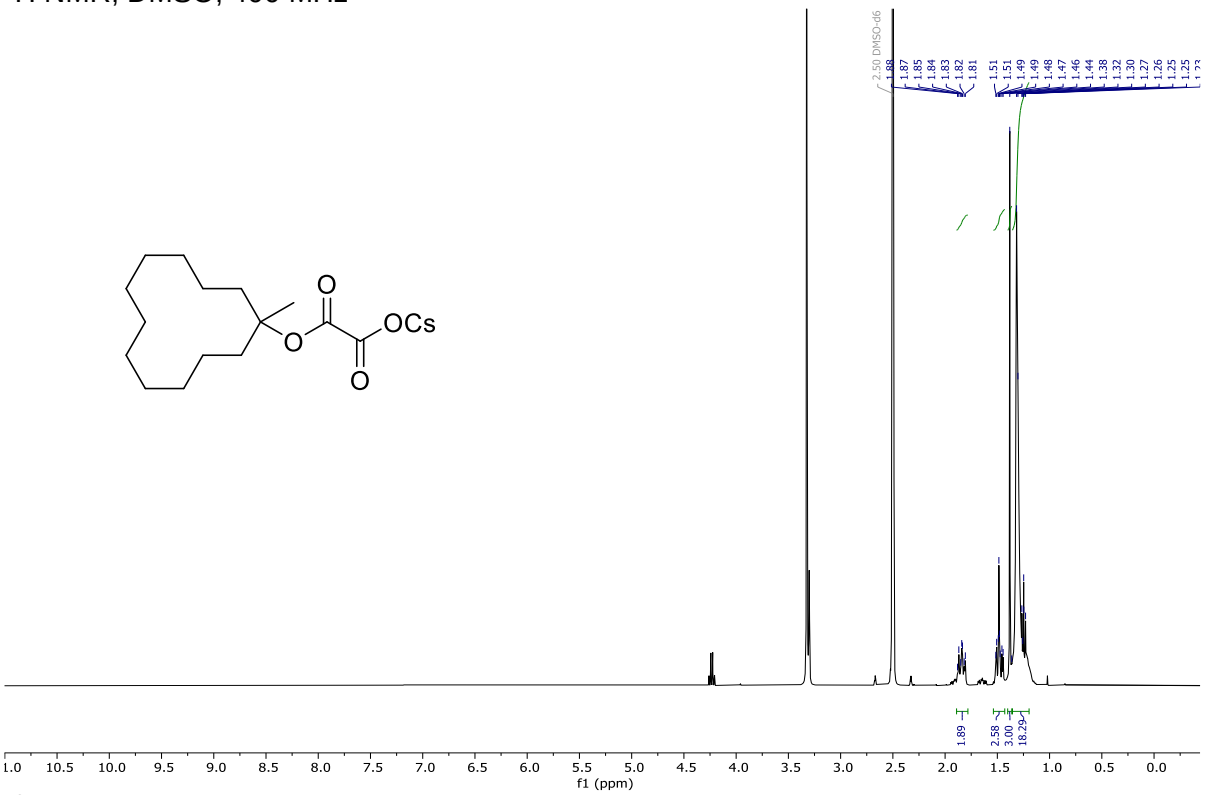


^{13}C NMR, $CDCl_3$, 101 MHz

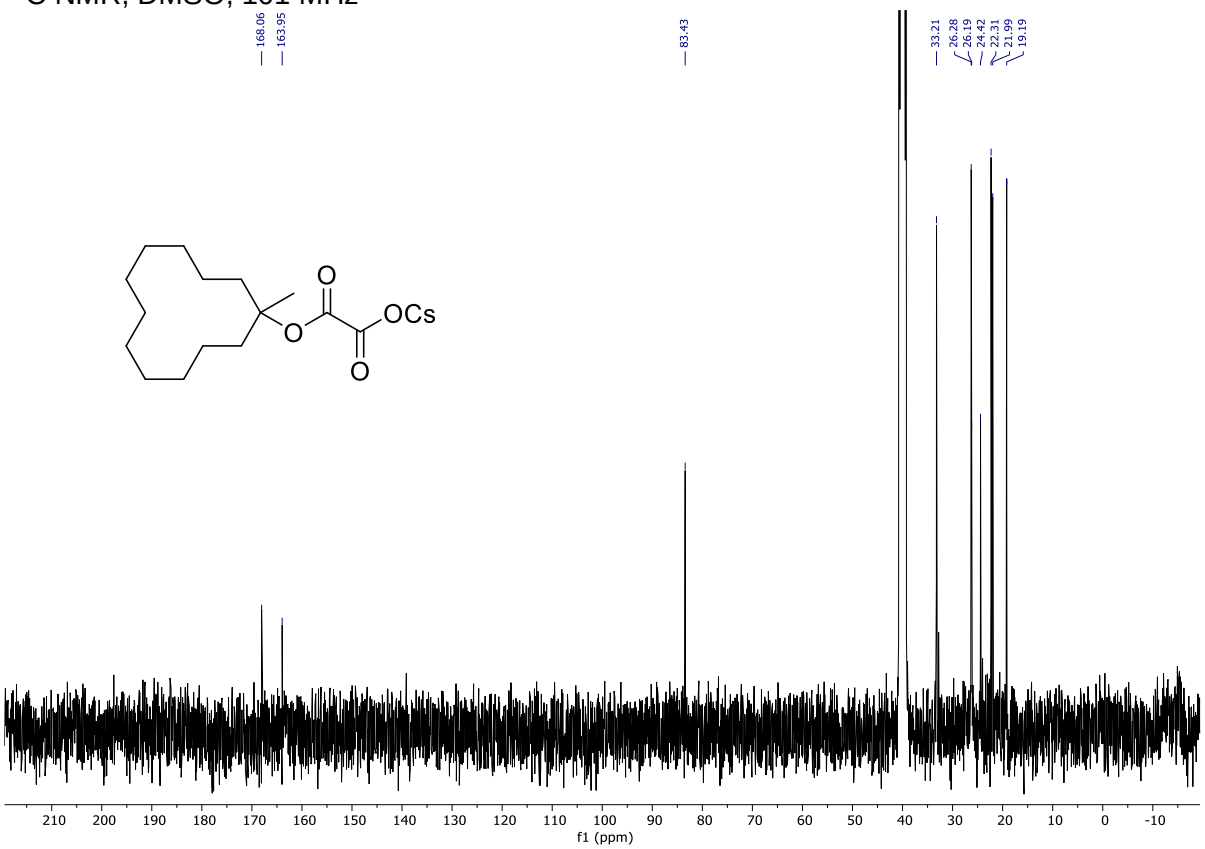


5.6g

^{1}H NMR, DMSO, 400 MHz

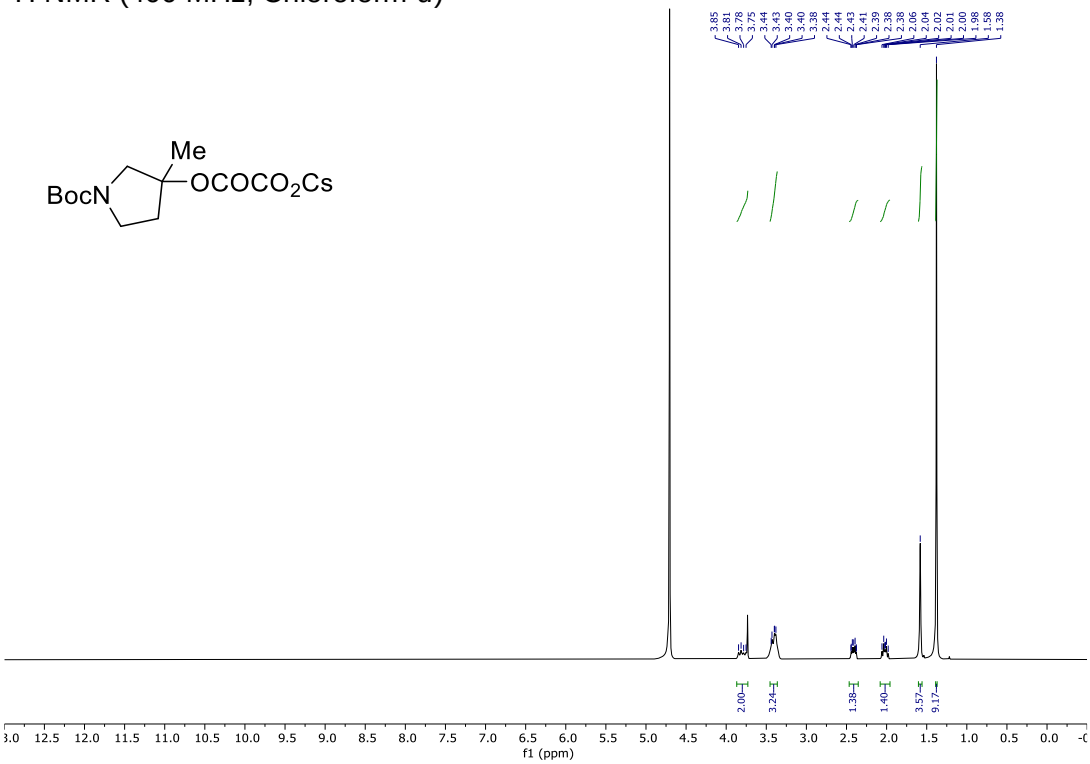


^{13}C NMR, DMSO, 101 MHz



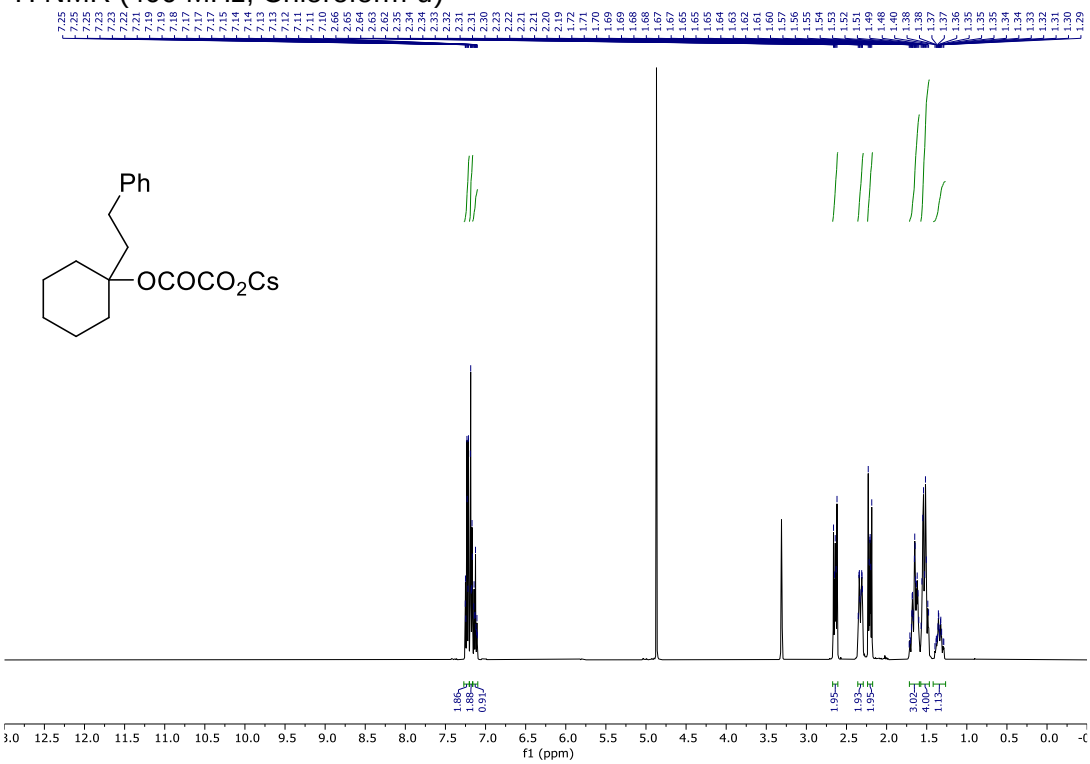
5.6h

^{1}H NMR (400 MHz, Chloroform-*d*)

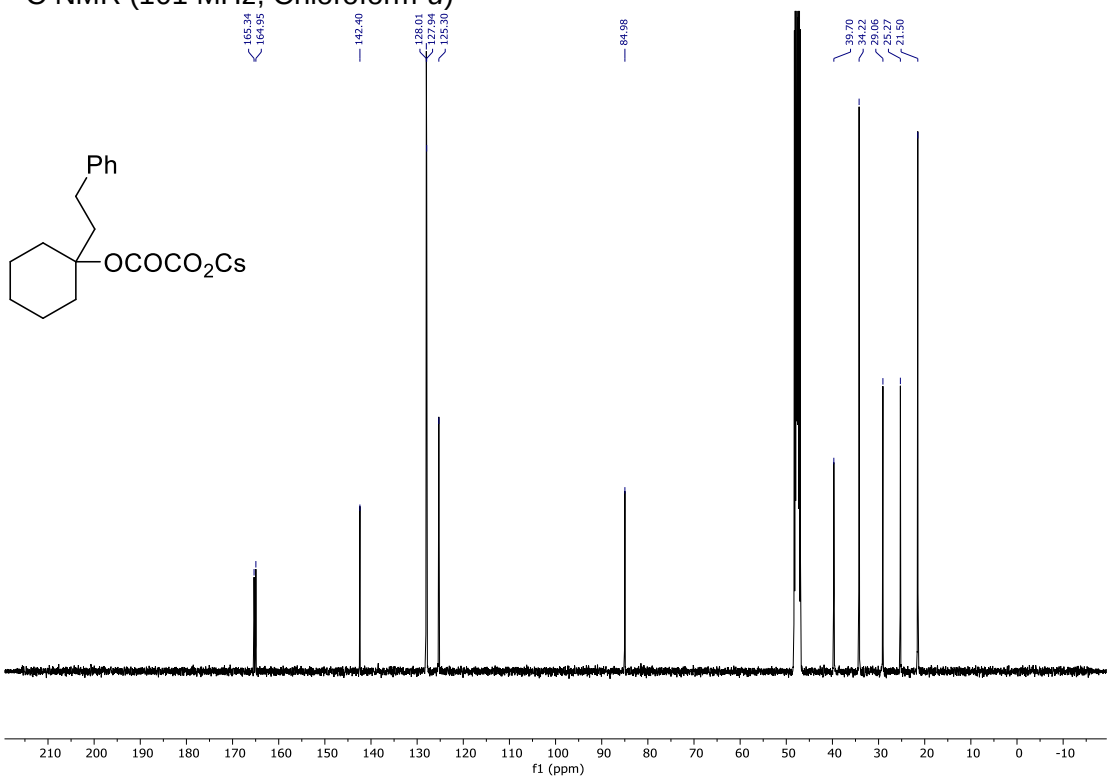


5.6i

^{1}H NMR (400 MHz, Chloroform-*d*)

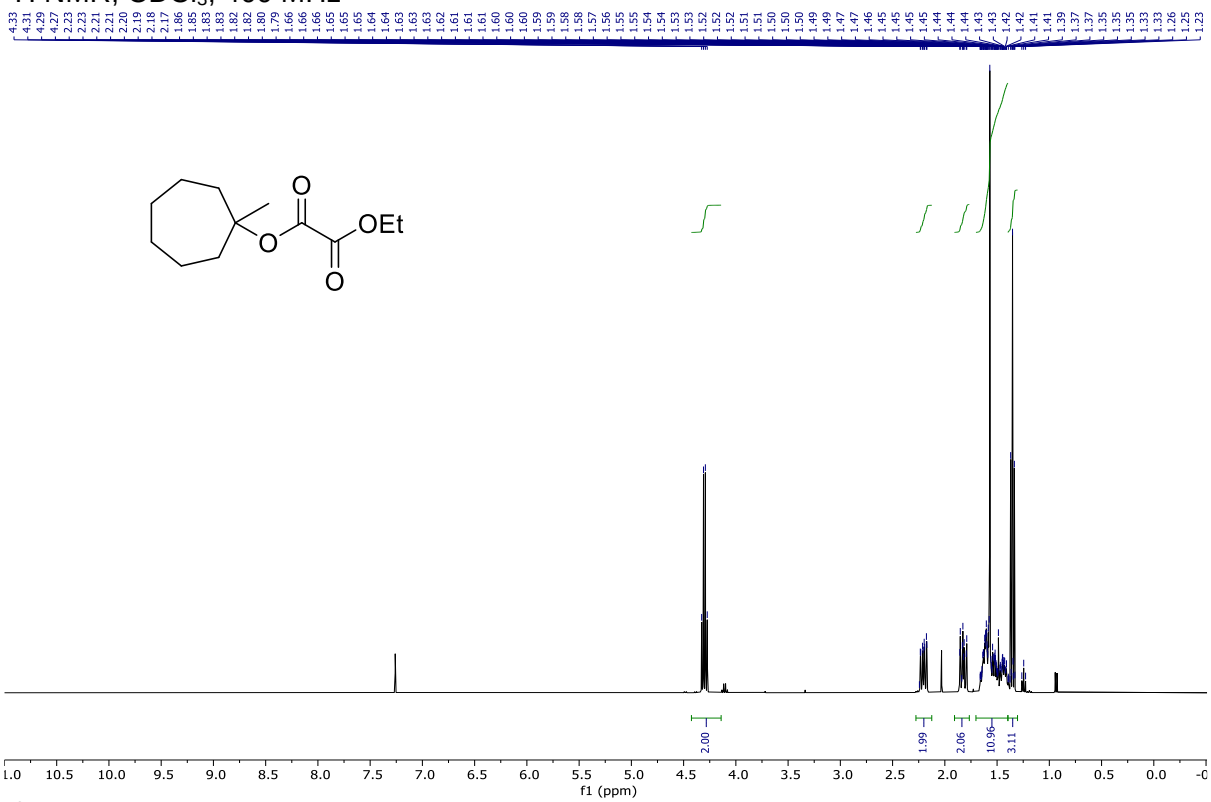


^{13}C NMR (101 MHz, Chloroform-*d*)

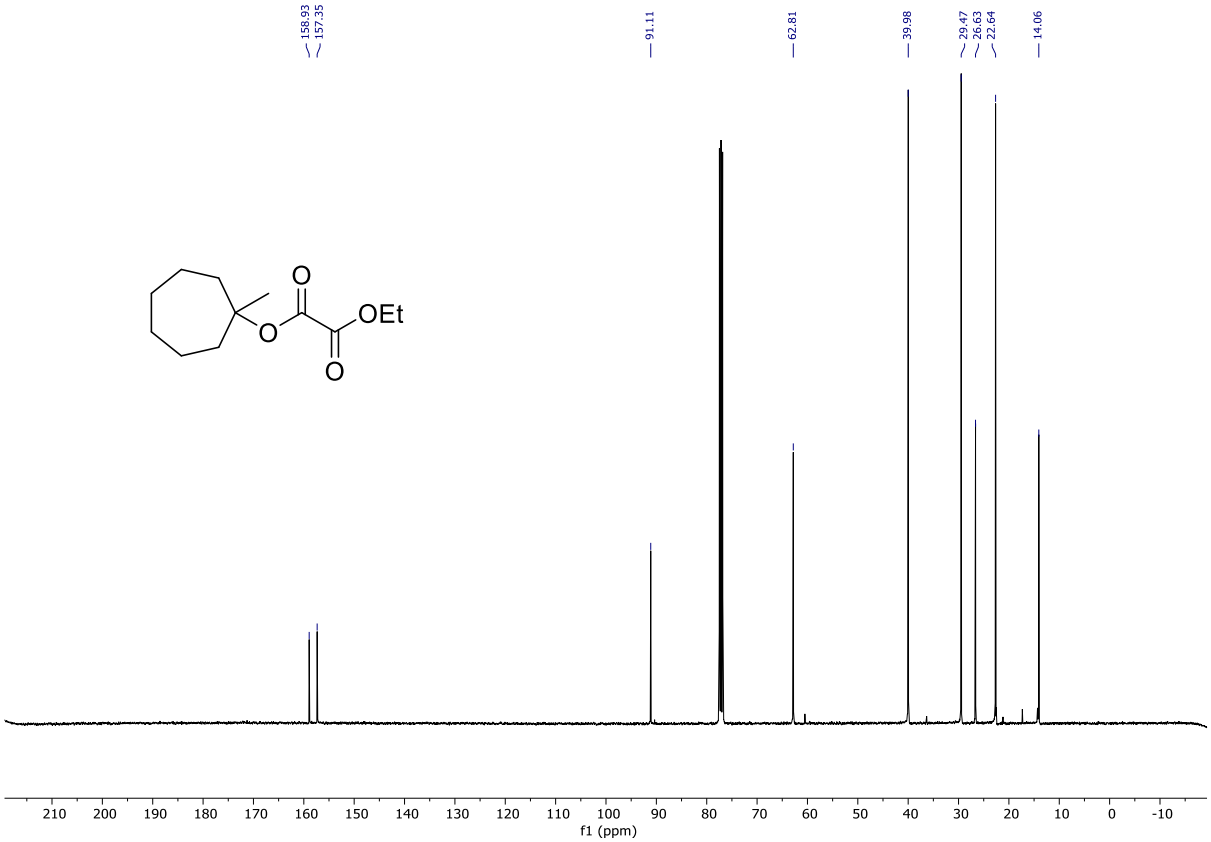


5.10j

^{1}H NMR, $CDCl_3$, 400 MHz

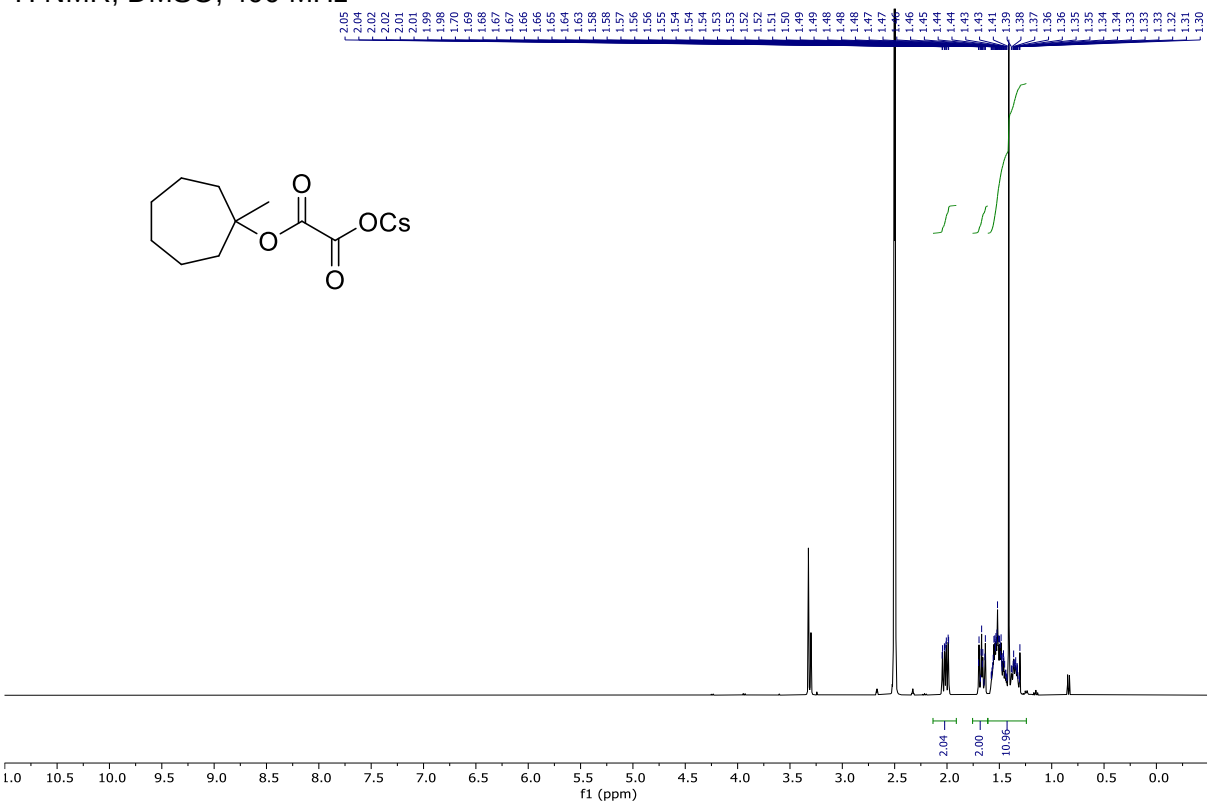


^{13}C NMR, $CDCl_3$, 101 MHz

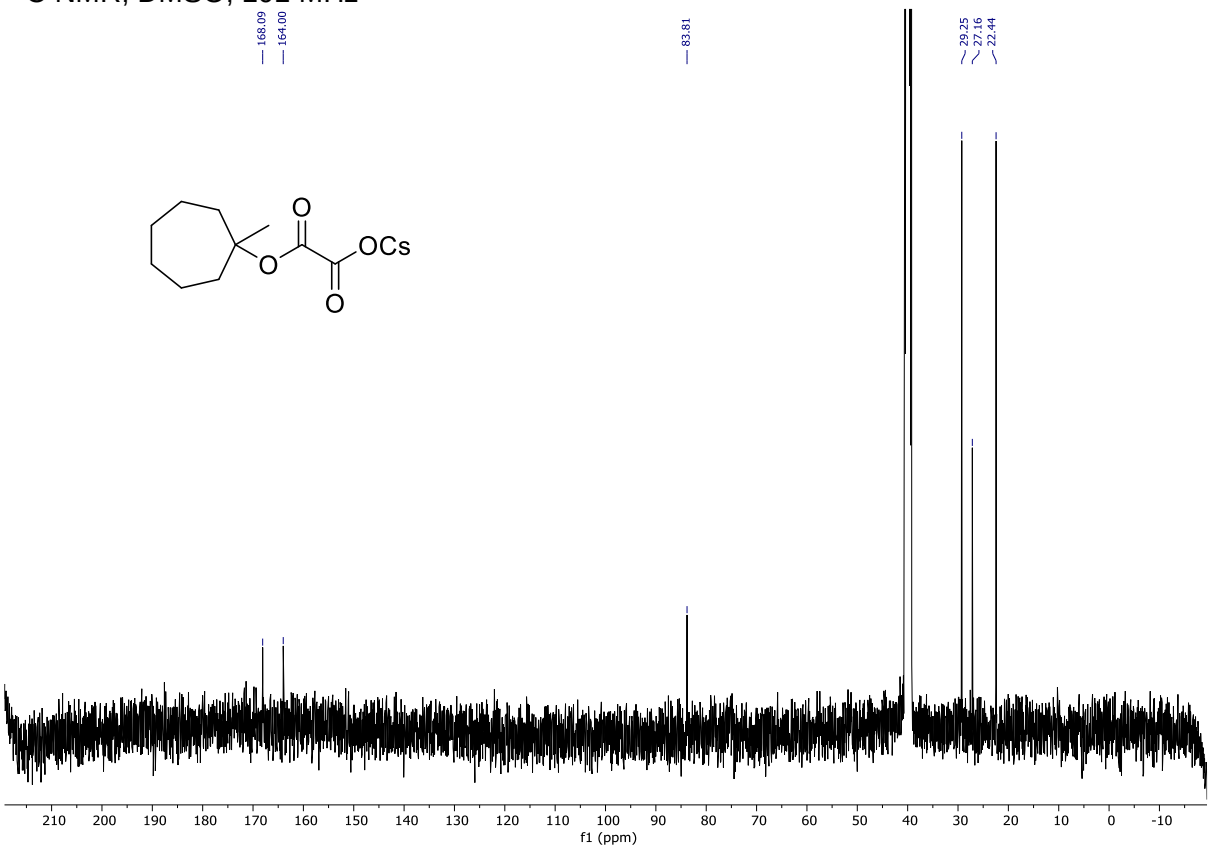


5.6j

^{1}H NMR, DMSO, 400 MHz

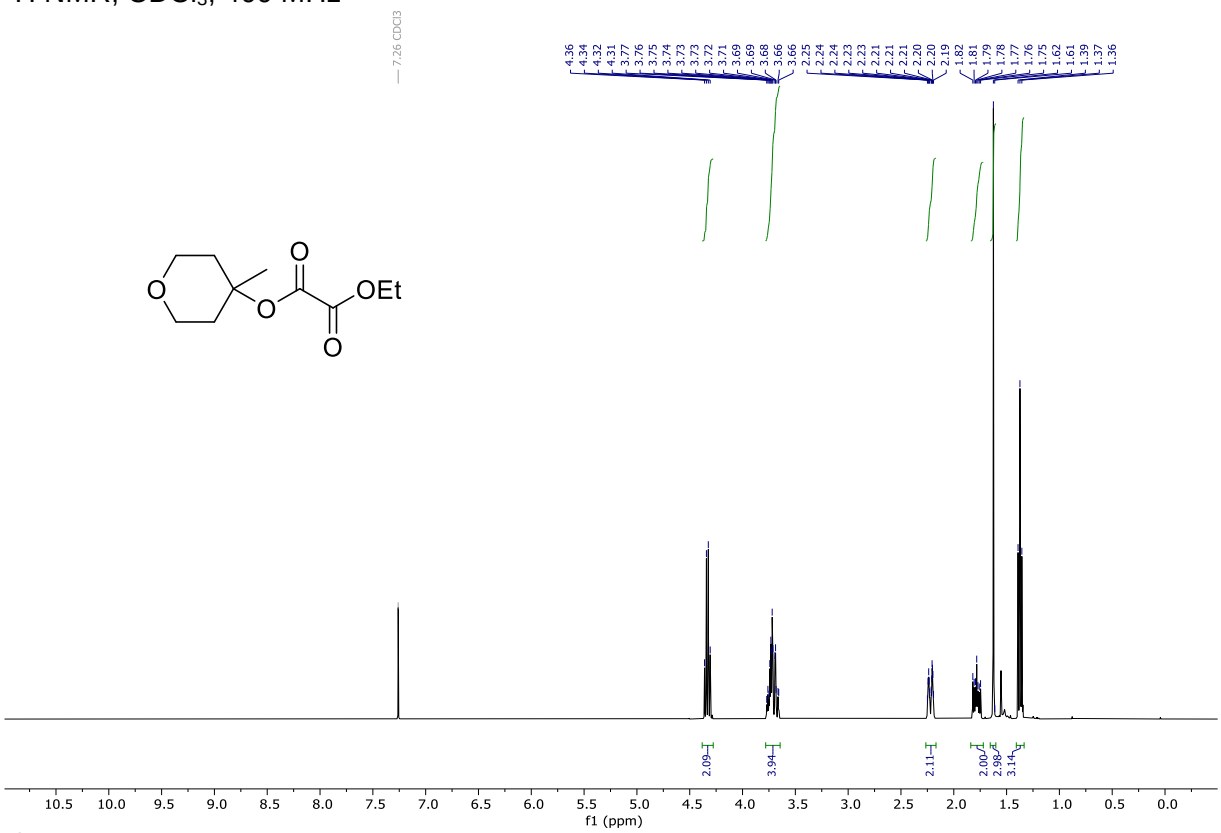


^{13}C NMR, DMSO, 101 MHz

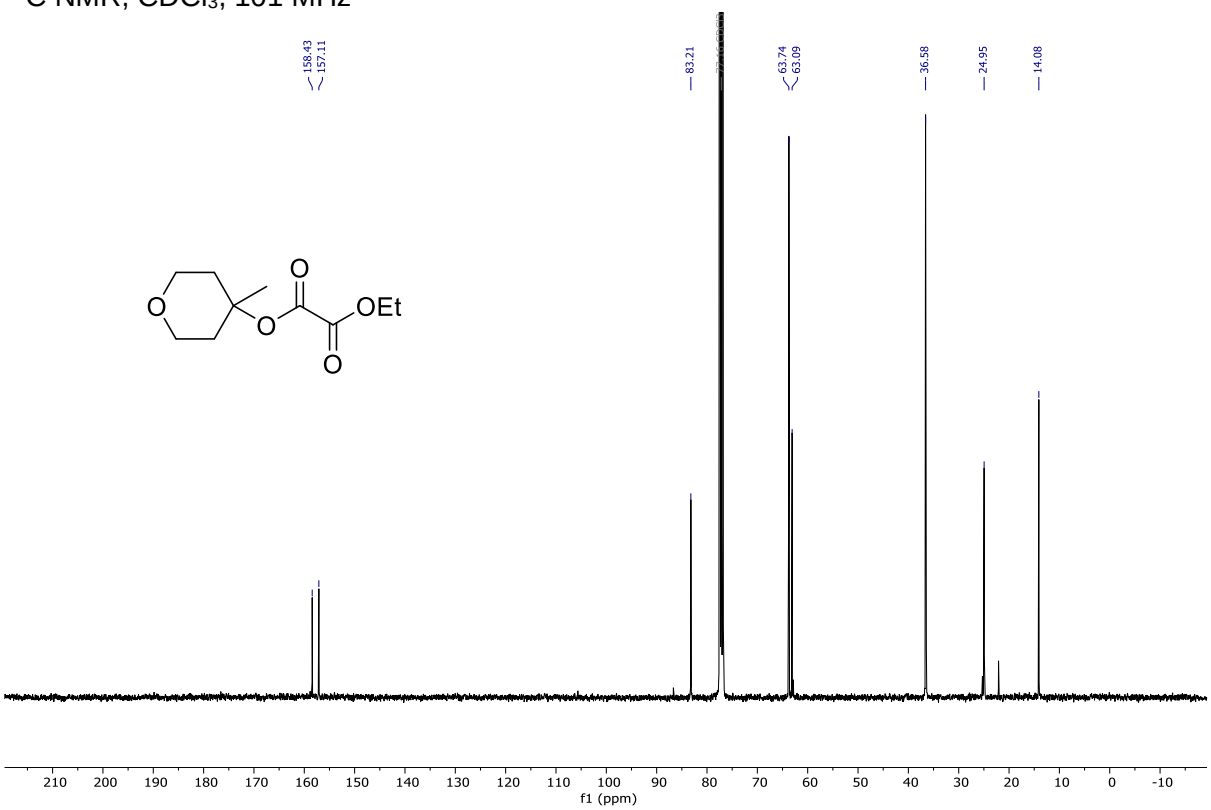


5.10k

^{1}H NMR, $CDCl_3$, 400 MHz

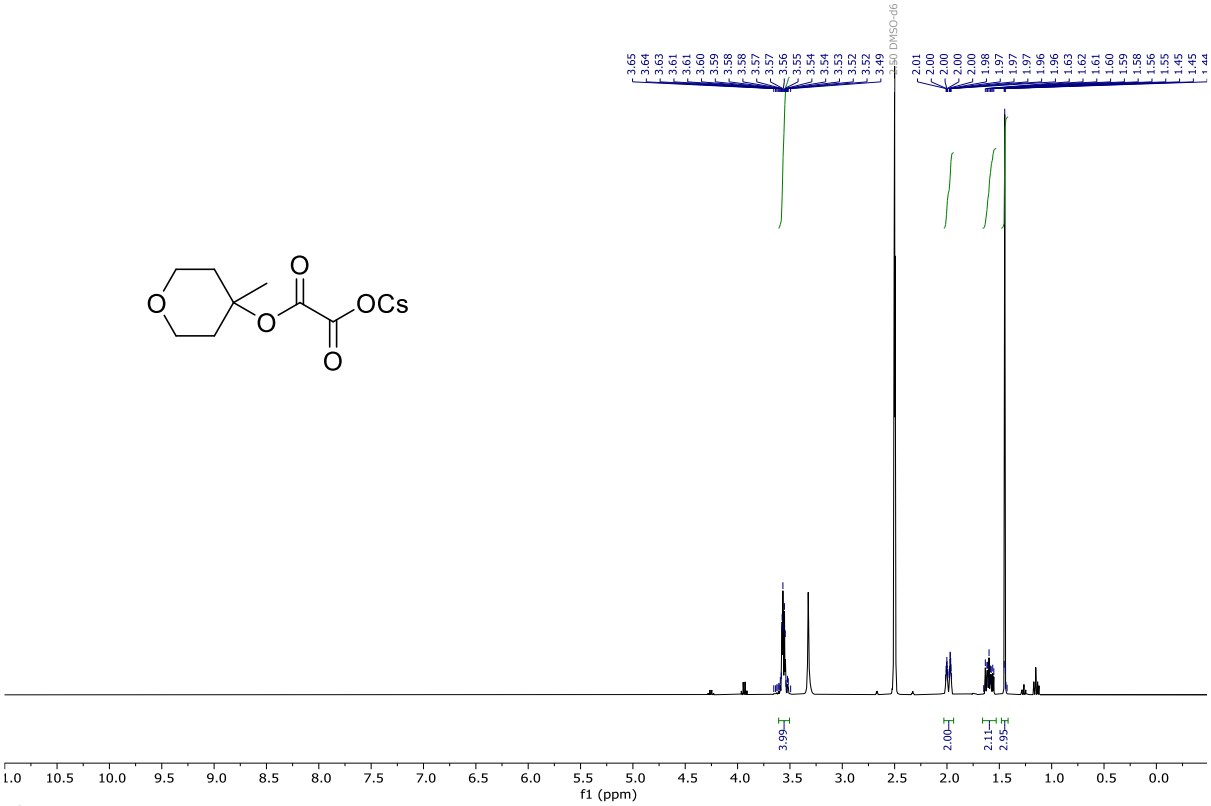


^{13}C NMR, $CDCl_3$, 101 MHz

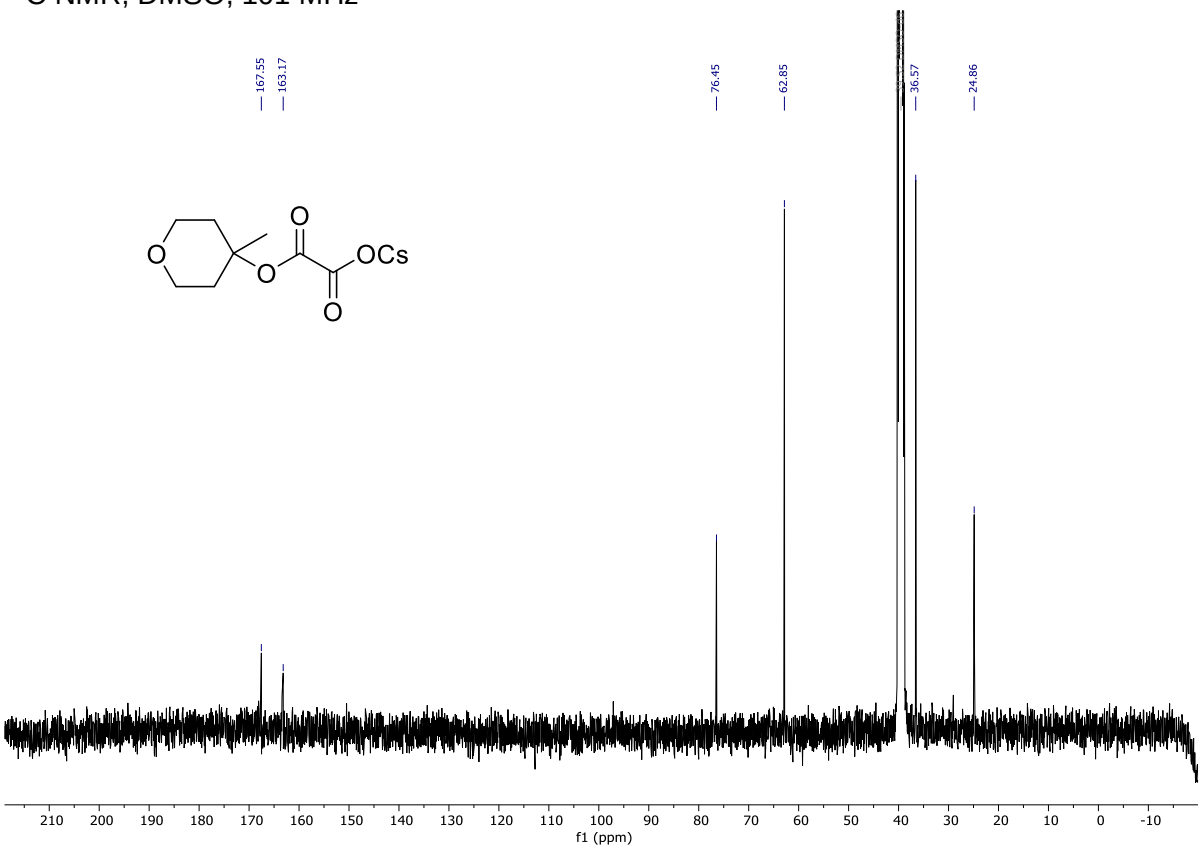


5.6k

^{1}H NMR, DMSO, 400 MHz

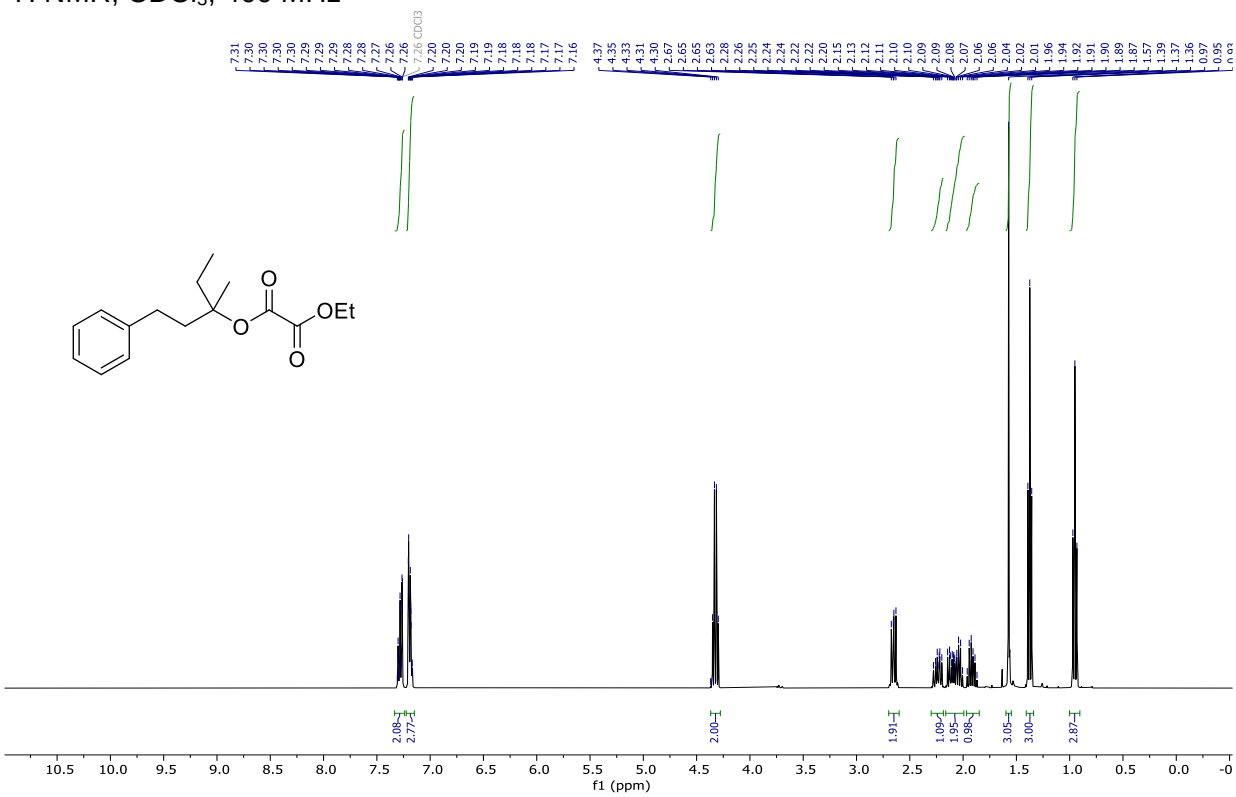


^{13}C NMR, DMSO, 101 MHz

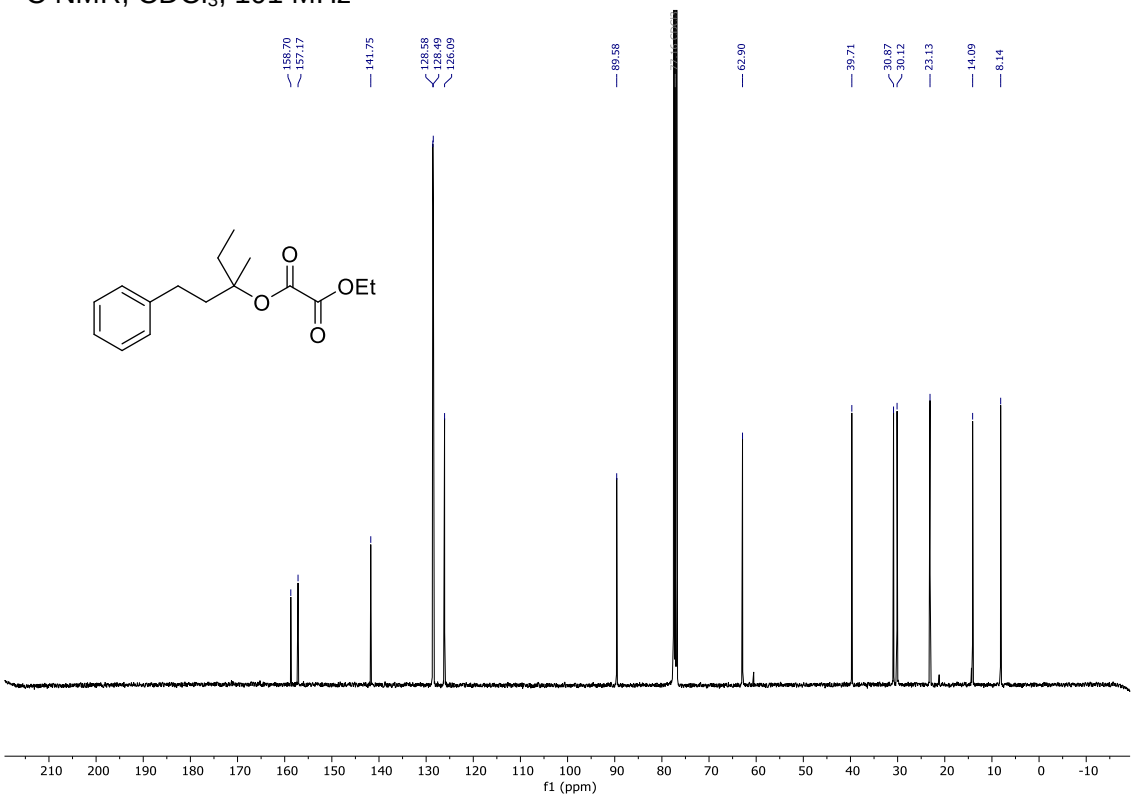


5.10l

^{1}H NMR, $CDCl_3$, 400 MHz

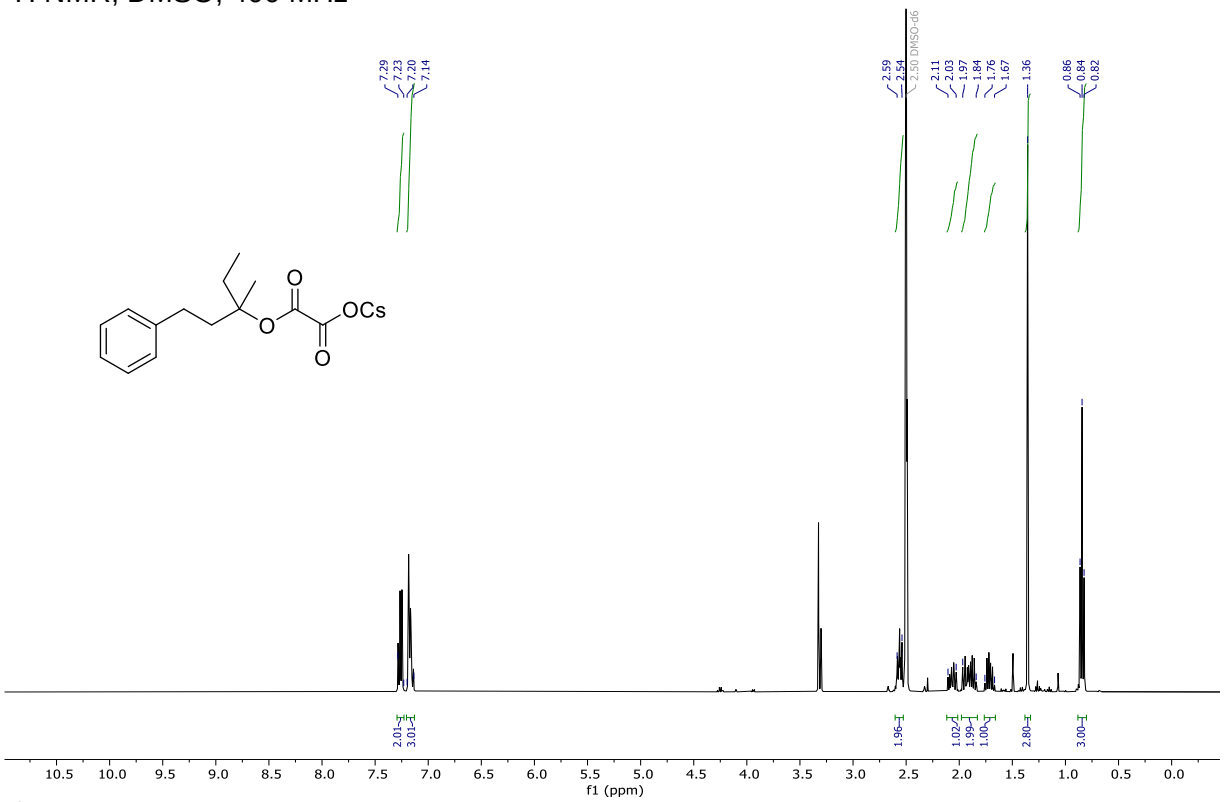


^{13}C NMR, $CDCl_3$, 101 MHz

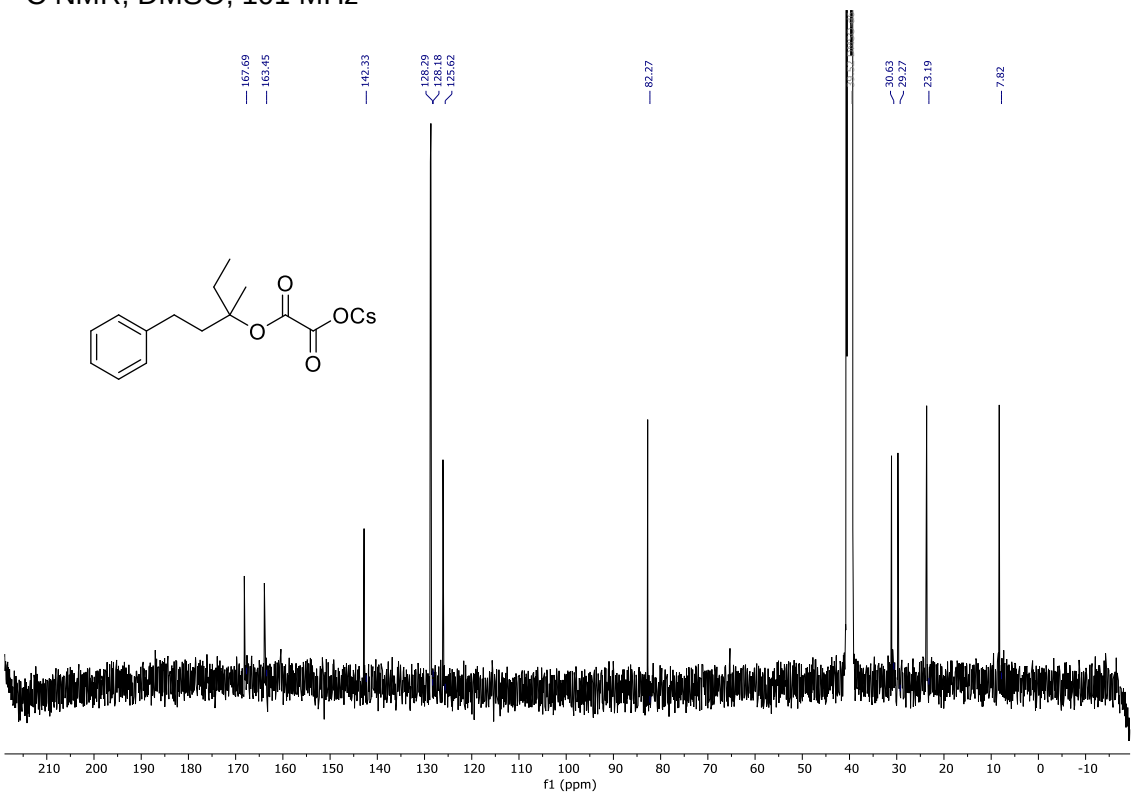


5.6l

^{1}H NMR, DMSO, 400 MHz

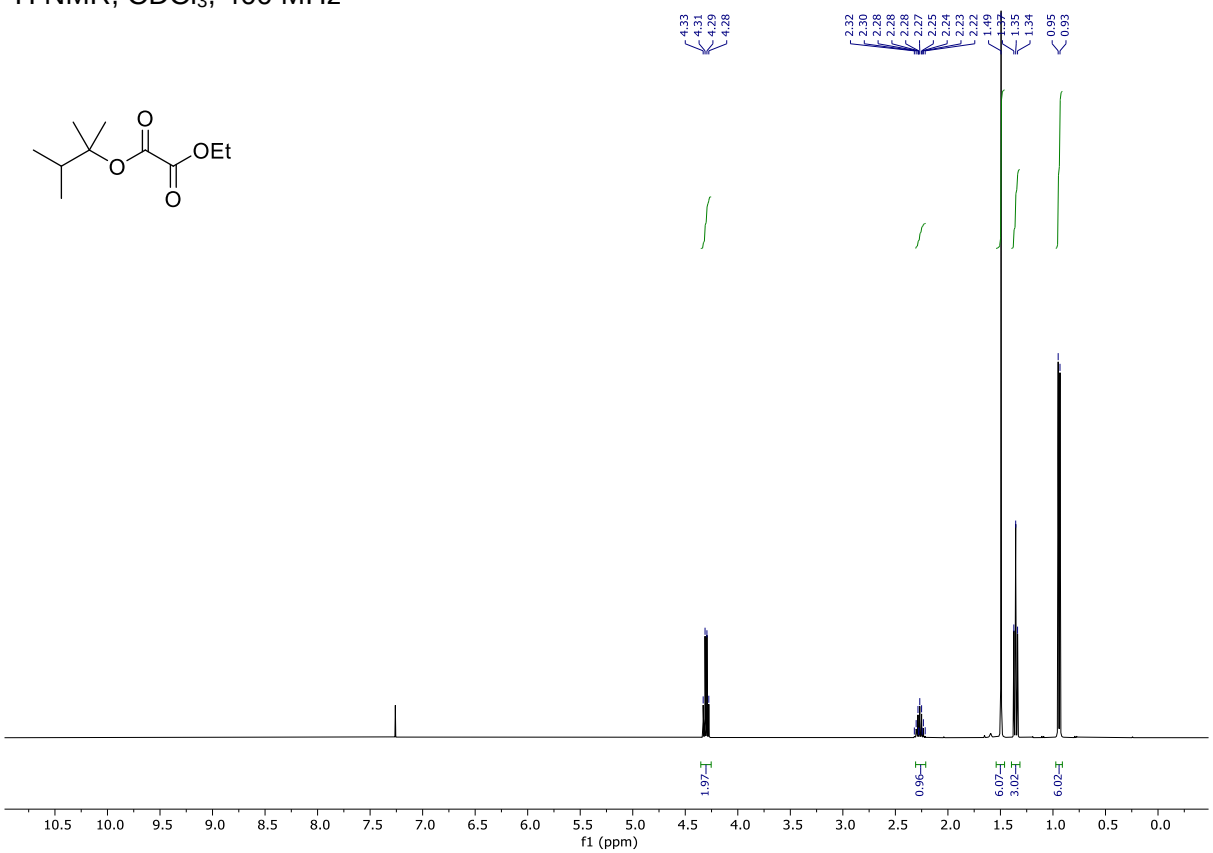


^{13}C NMR, DMSO, 101 MHz

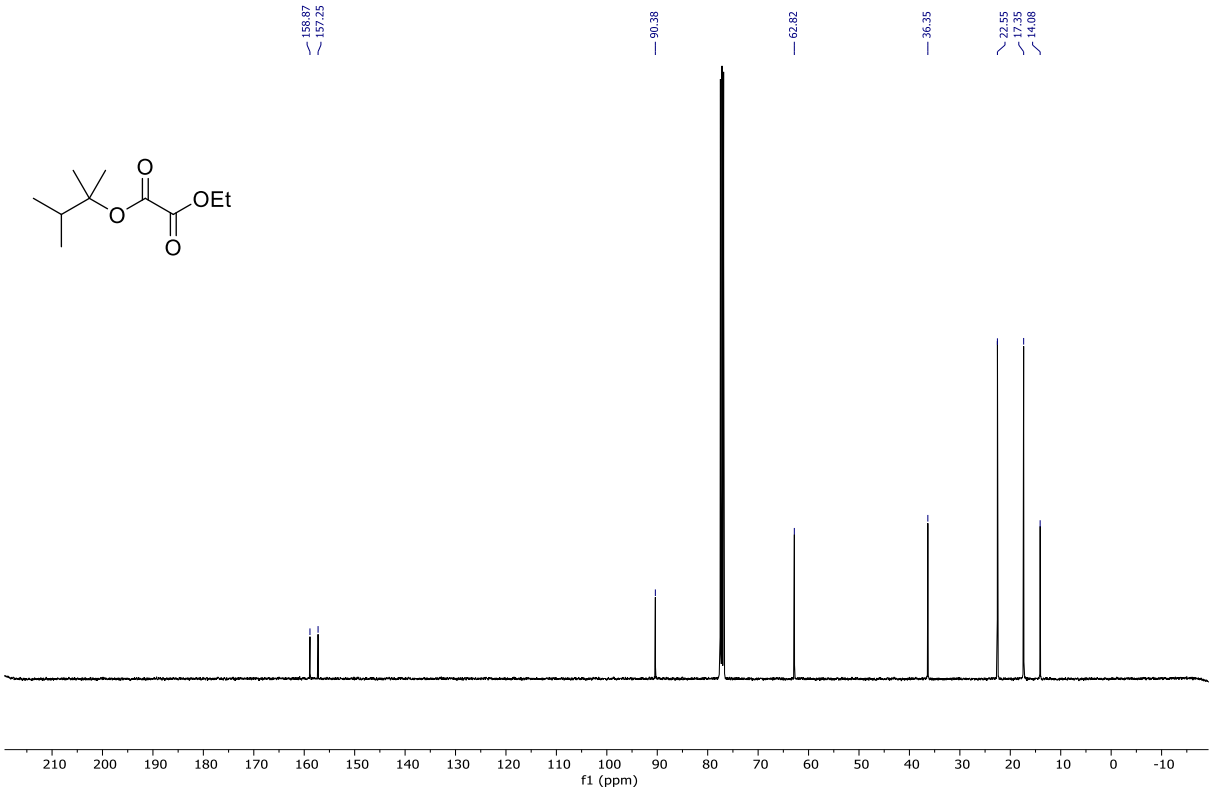


5.10m

^{1}H NMR, $CDCl_3$, 400 MHz

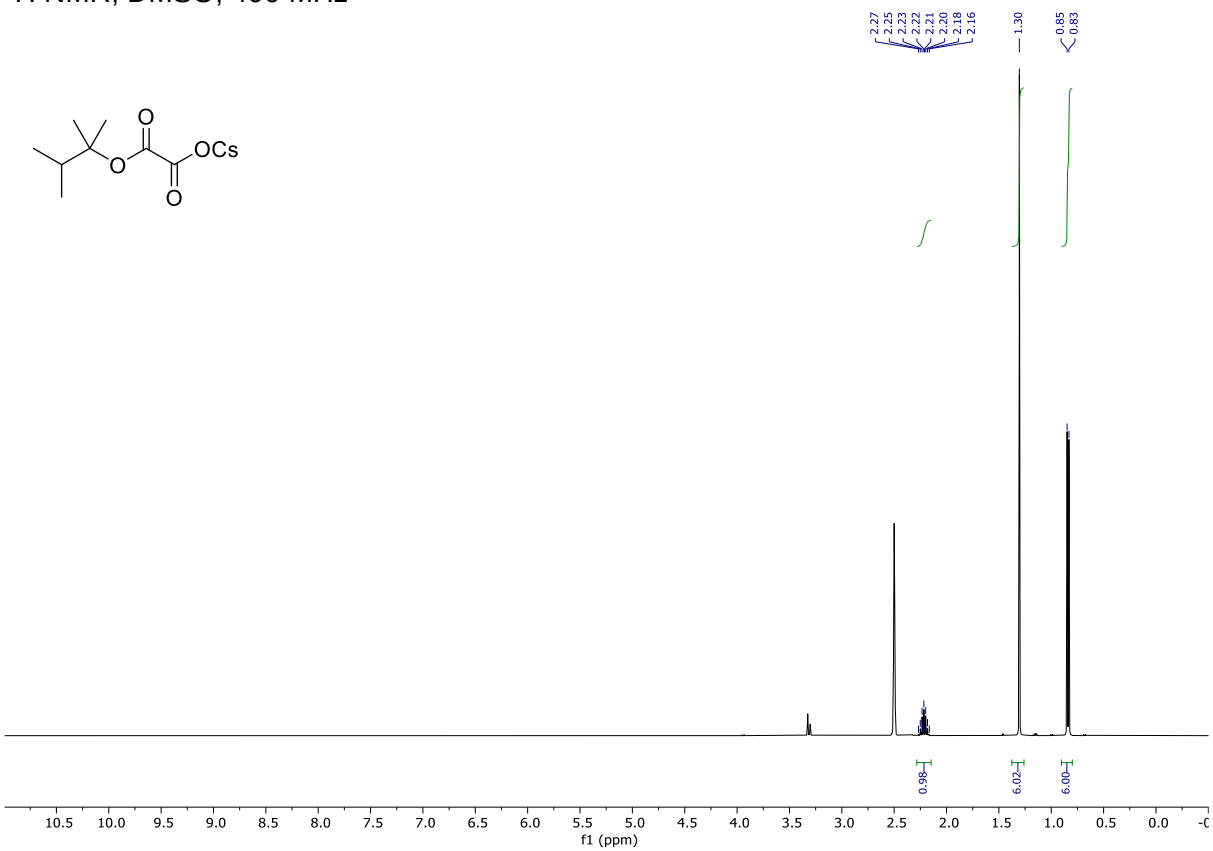


^{13}C NMR, $CDCl_3$, 101 MHz

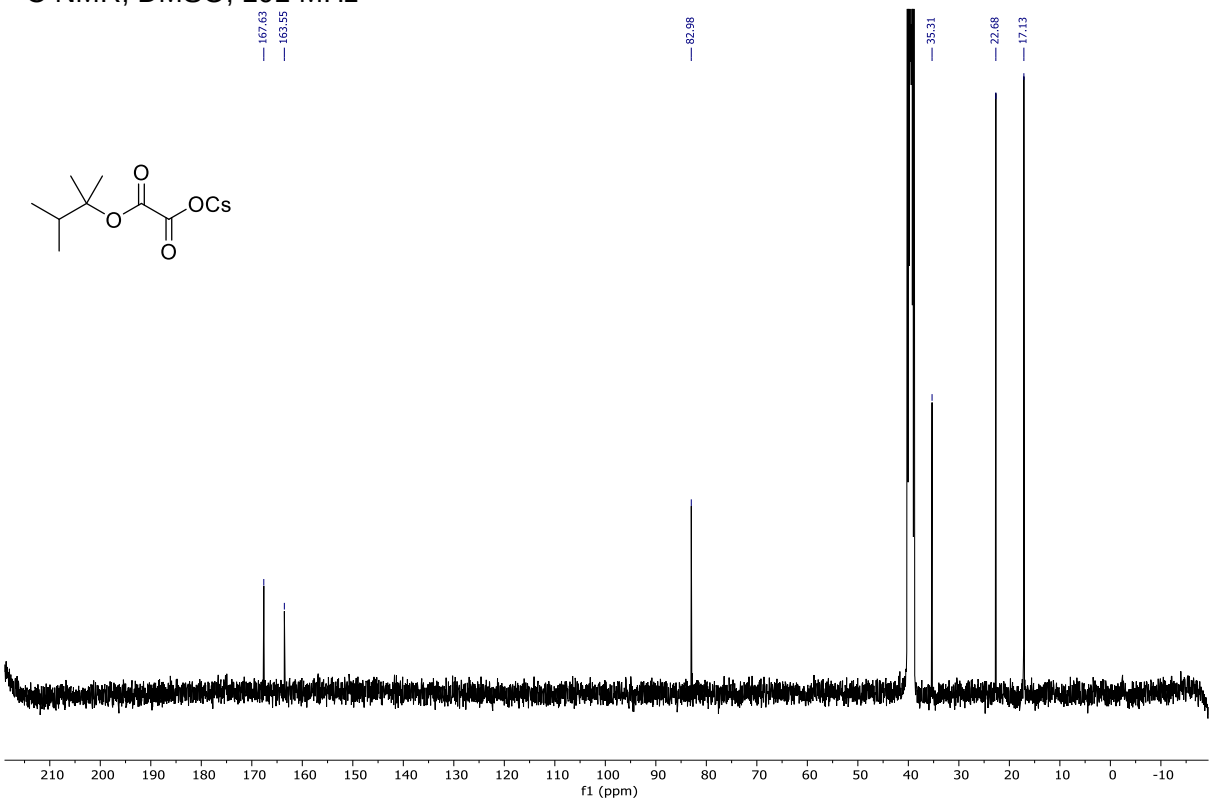


5.6m

^{1}H NMR, DMSO, 400 MHz

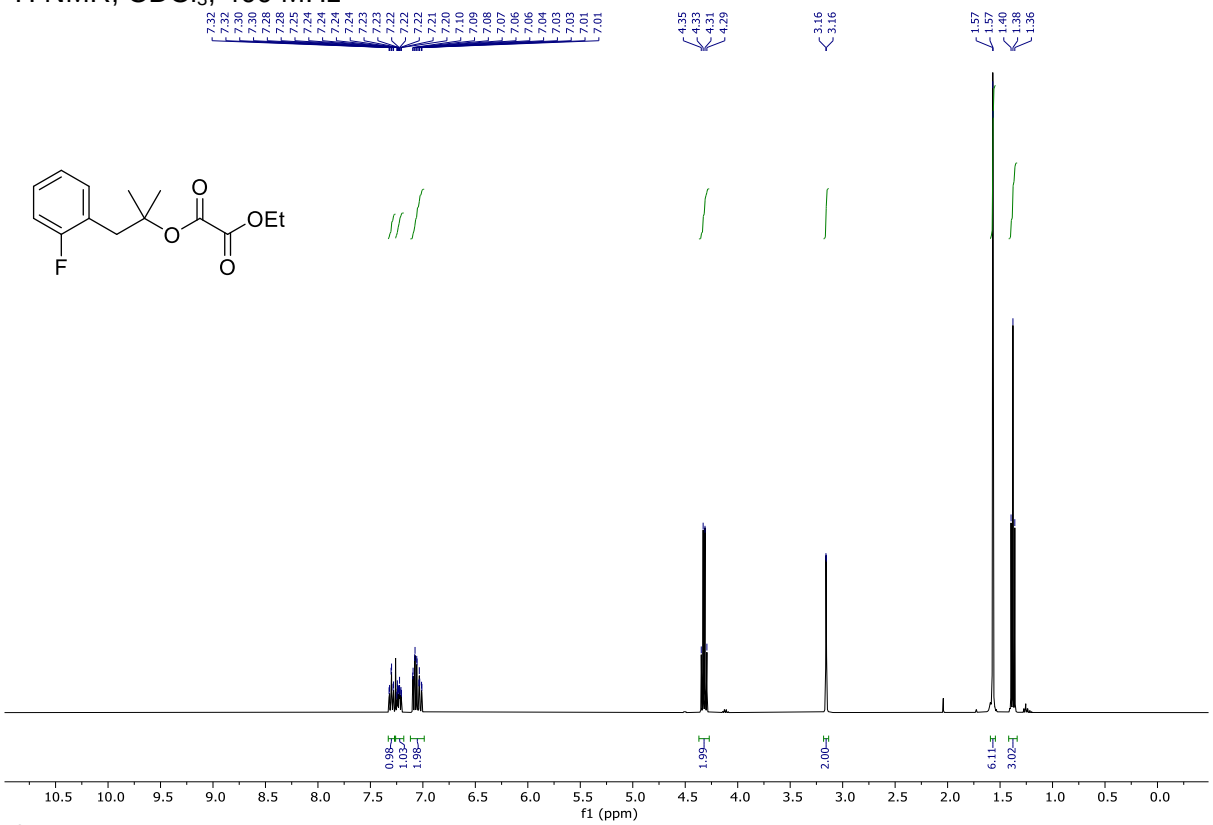


^{13}C NMR, DMSO, 101 MHz

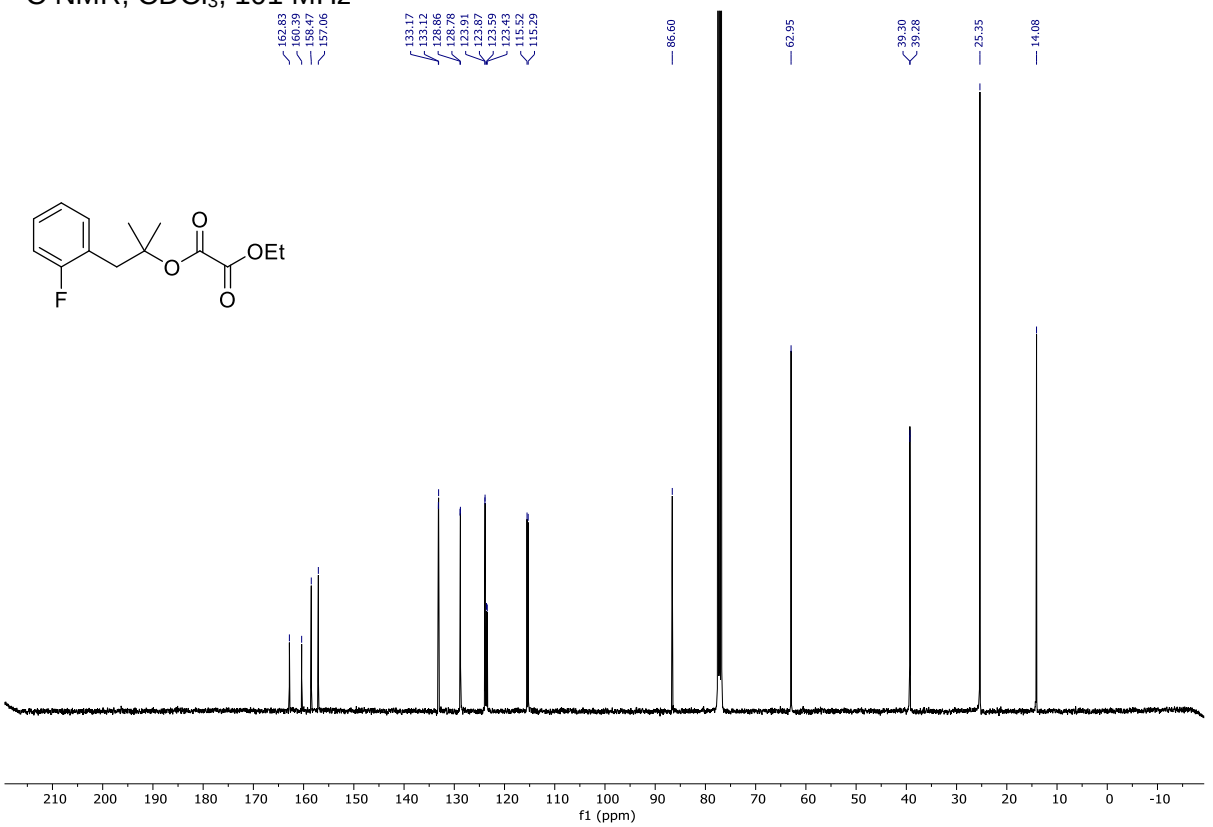


5.10n

^{1}H NMR, $CDCl_3$, 400 MHz



^{13}C NMR, $CDCl_3$, 101 MHz

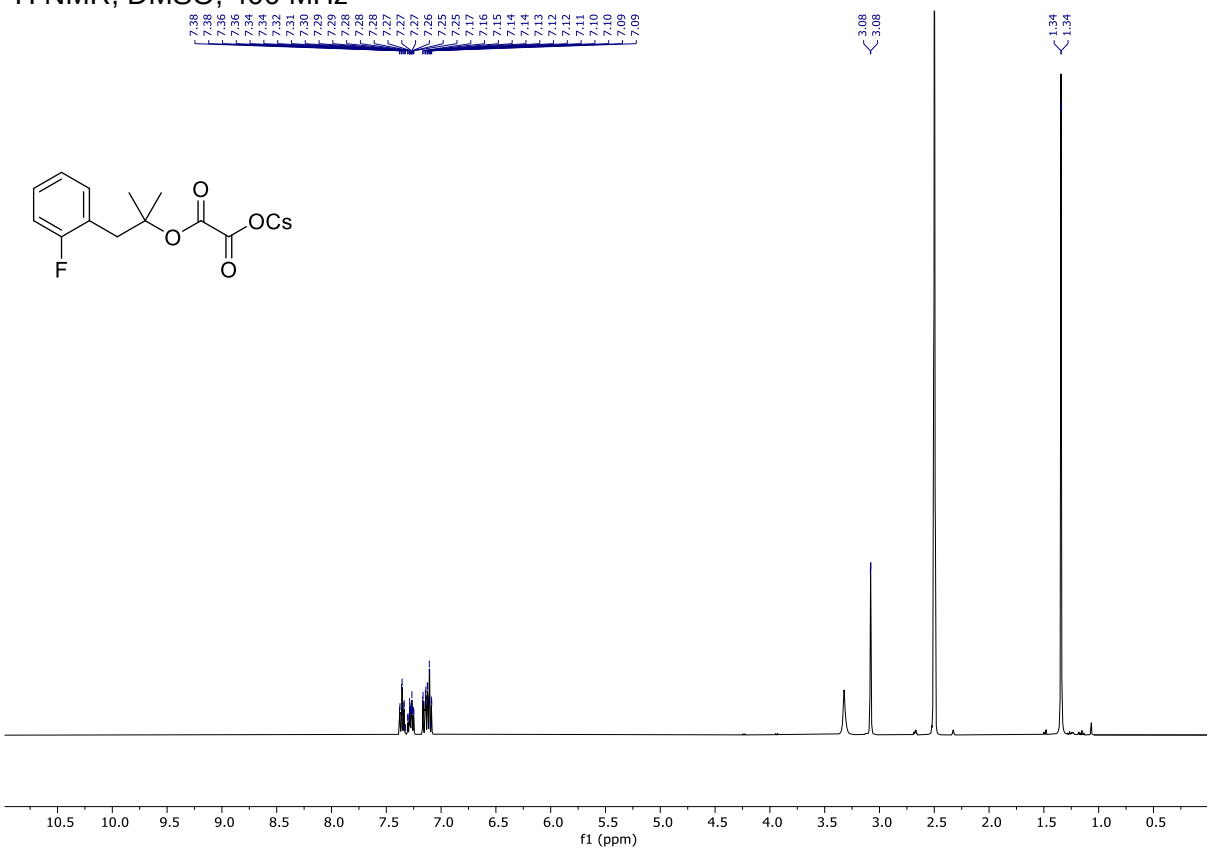


^{19}F NMR, $CDCl_3$, 376 MHz

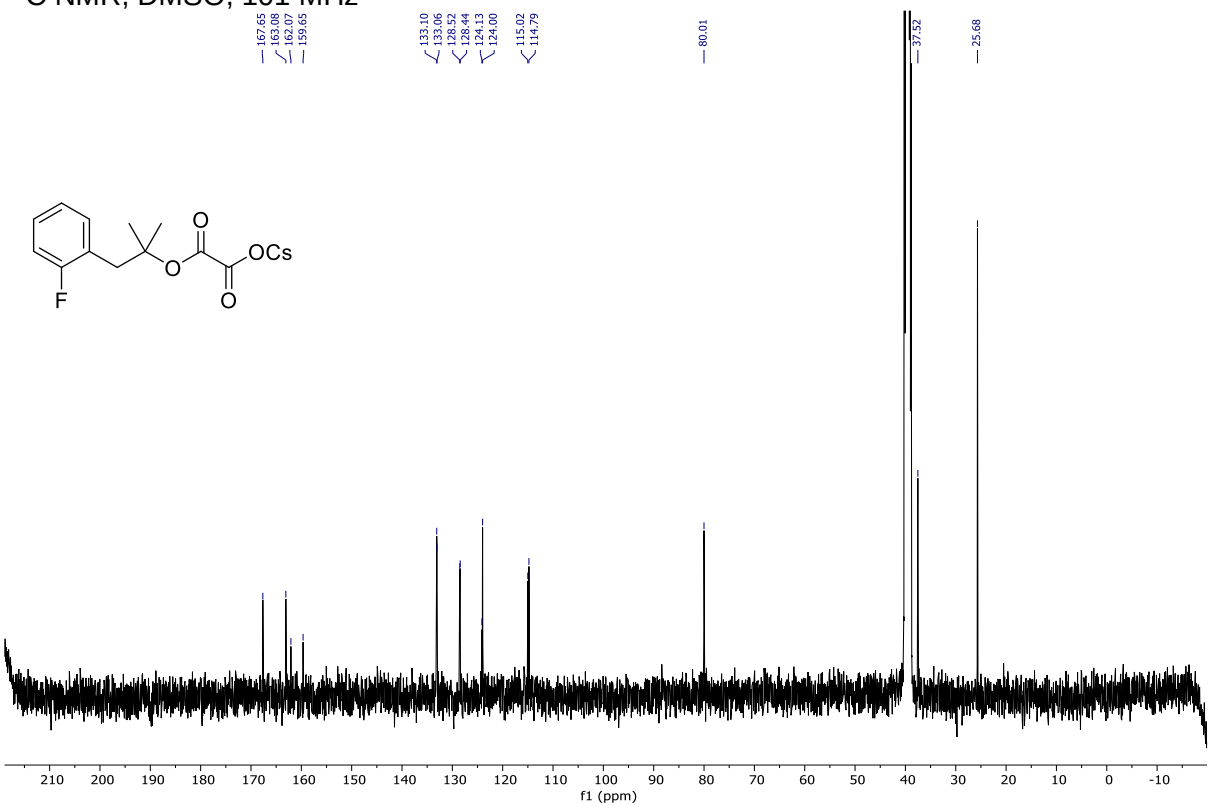
-115.86
O
OEt
O
O
F
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

5.6n

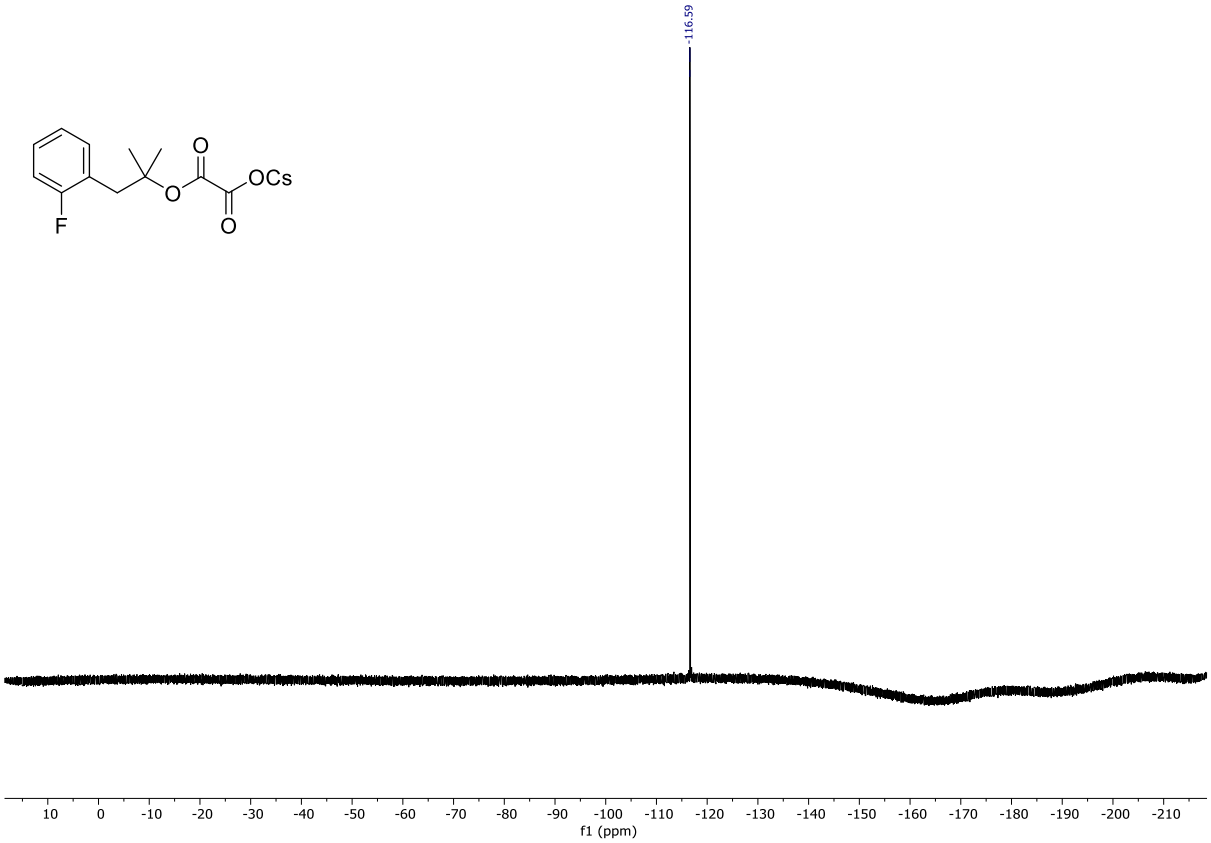
^{1}H NMR, DMSO, 400 MHz



^{13}C NMR, DMSO, 101 MHz

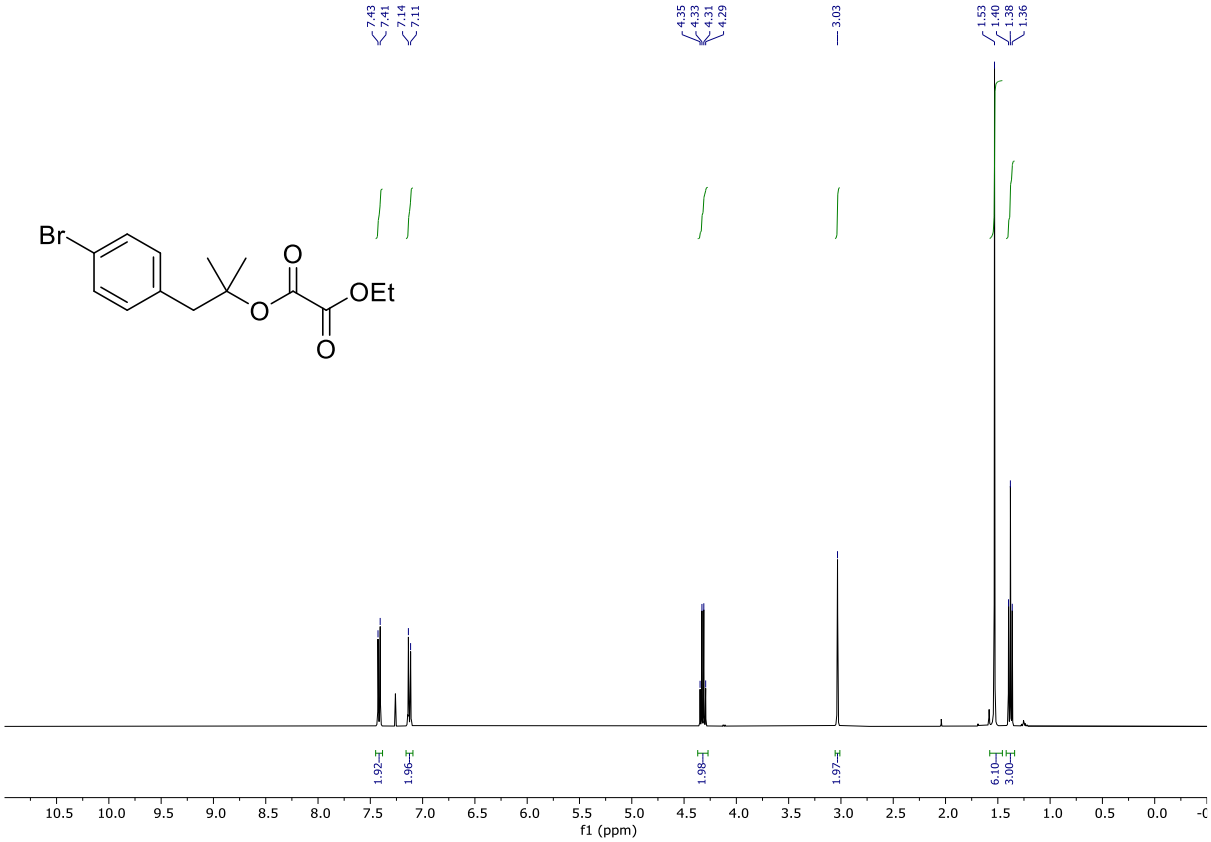


^{19}F NMR, DMSO, 376 MHz

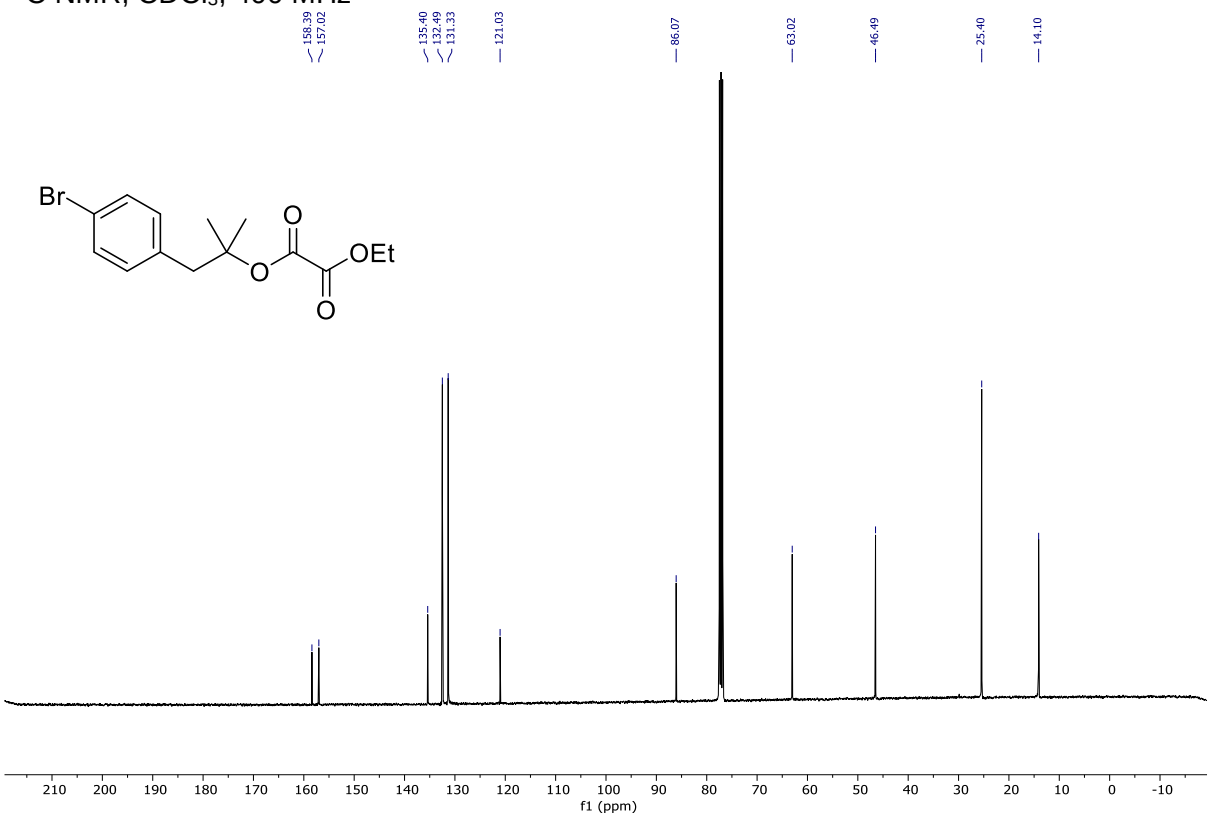

-116.59
O
OCs
O
O
F
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

5.10o

^{1}H NMR, $CDCl_3$, 400 MHz

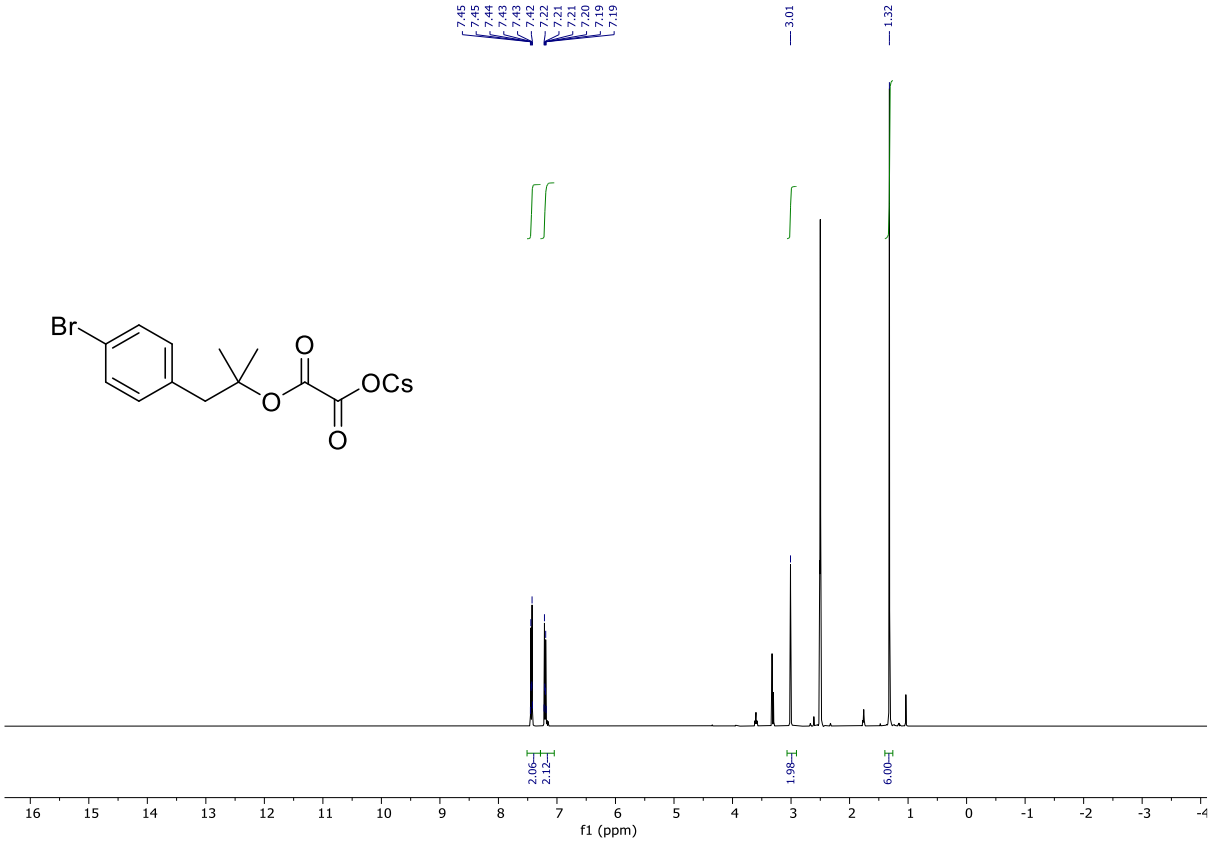


^{13}C NMR, $CDCl_3$, 400 MHz

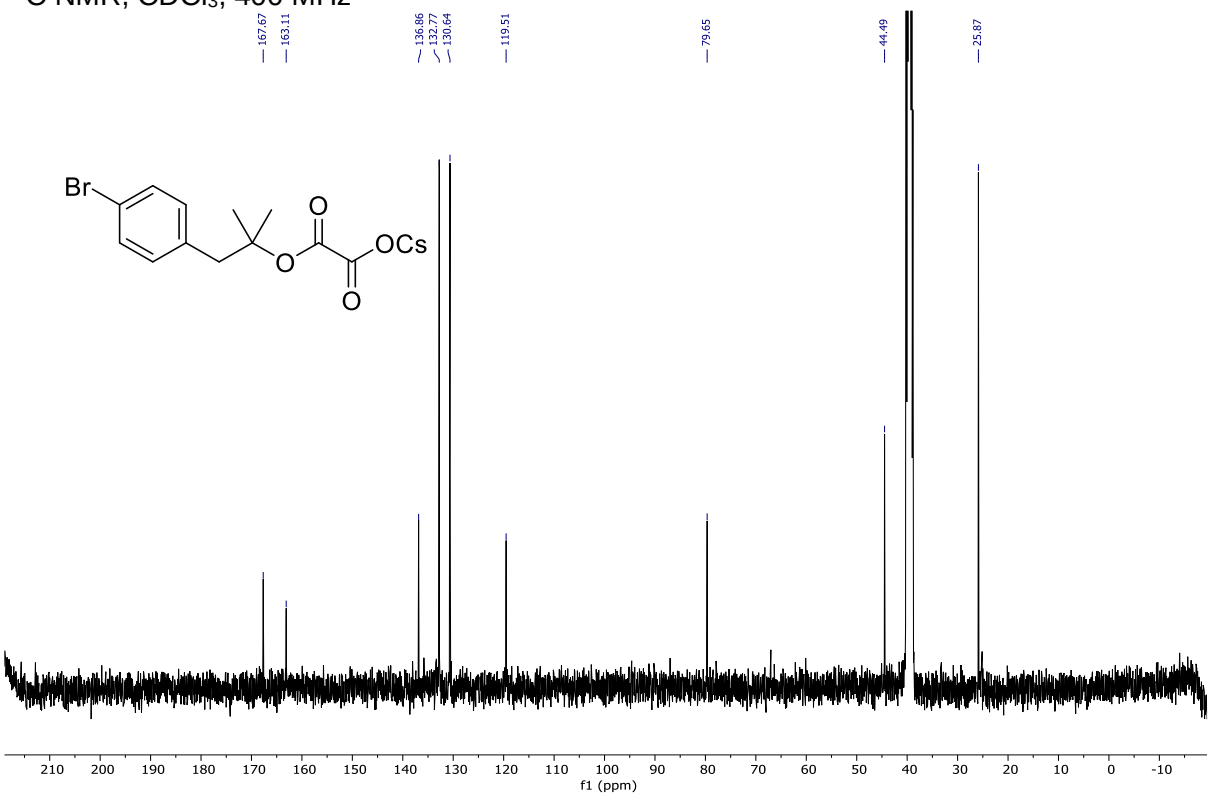


5.6o

^{1}H NMR, $CDCl_3$, 400 MHz

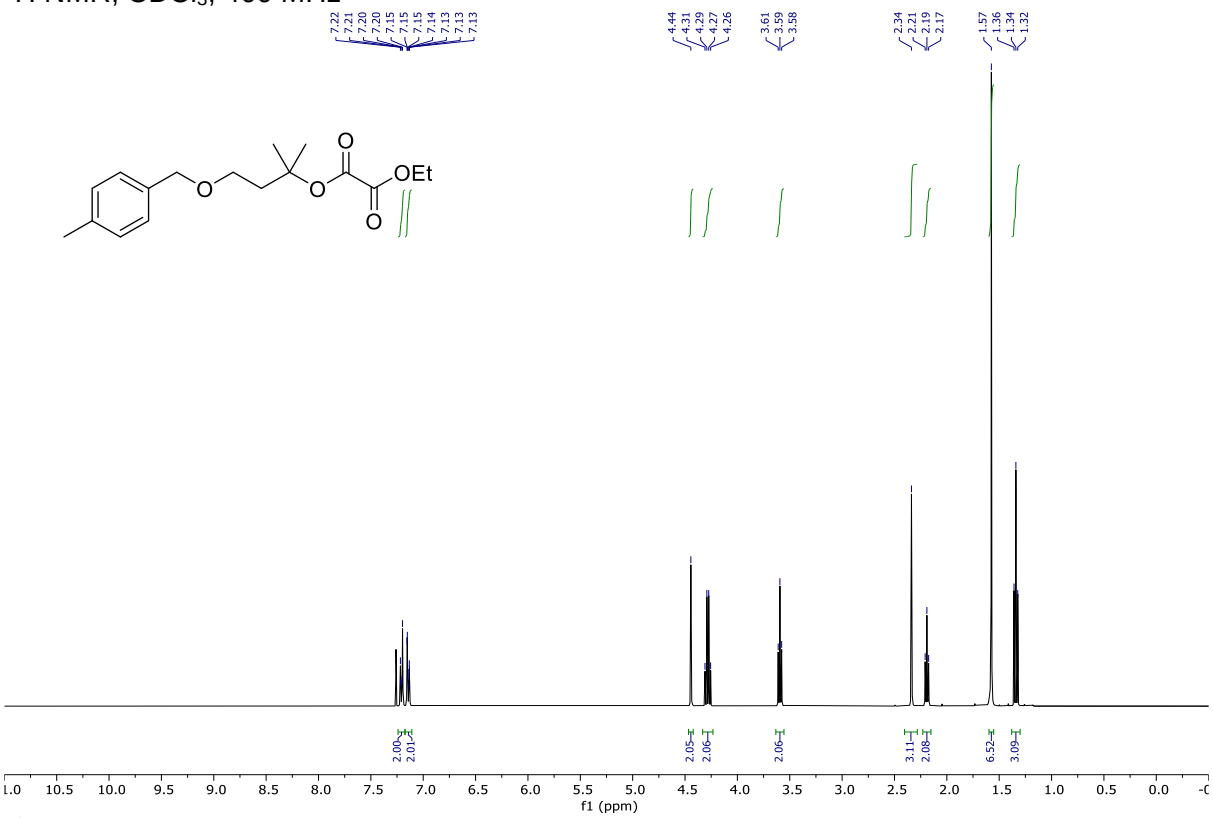


^{13}C NMR, $CDCl_3$, 400 MHz

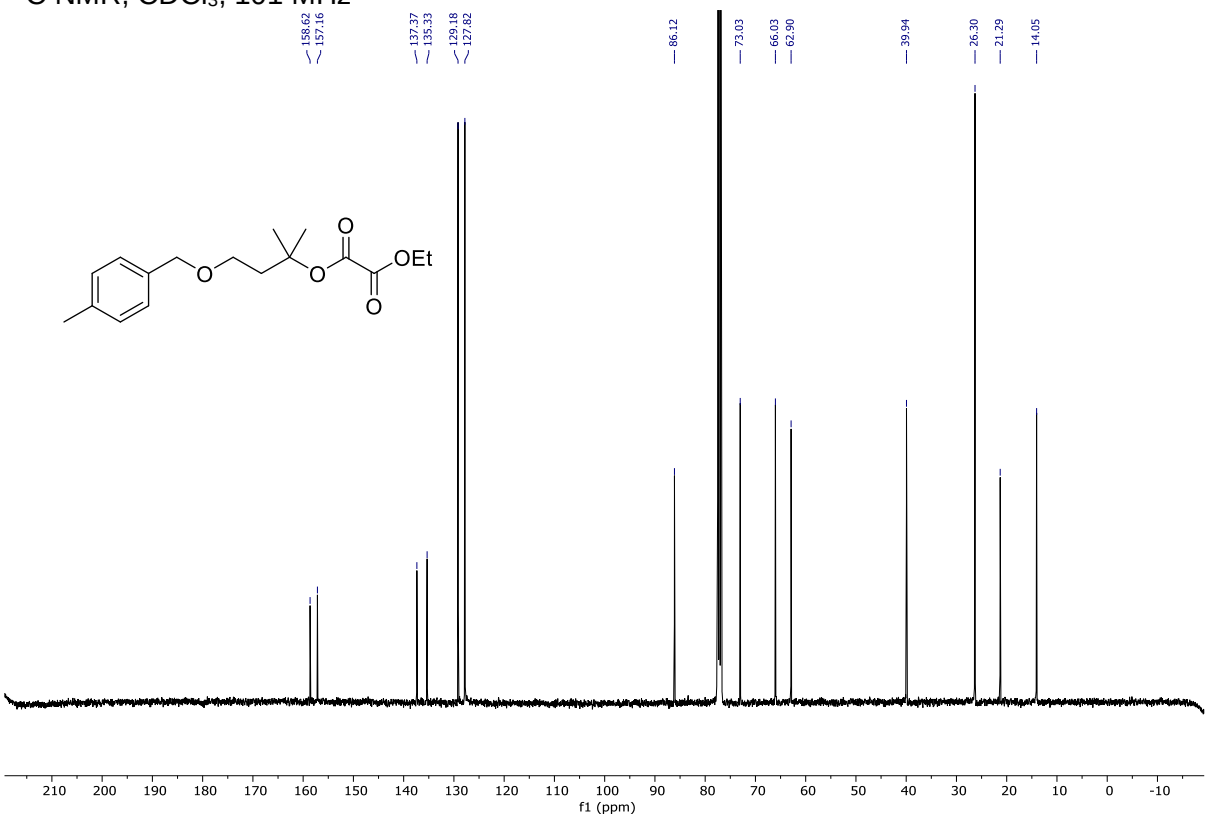


5.10p

^{1}H NMR, $CDCl_3$, 400 MHz

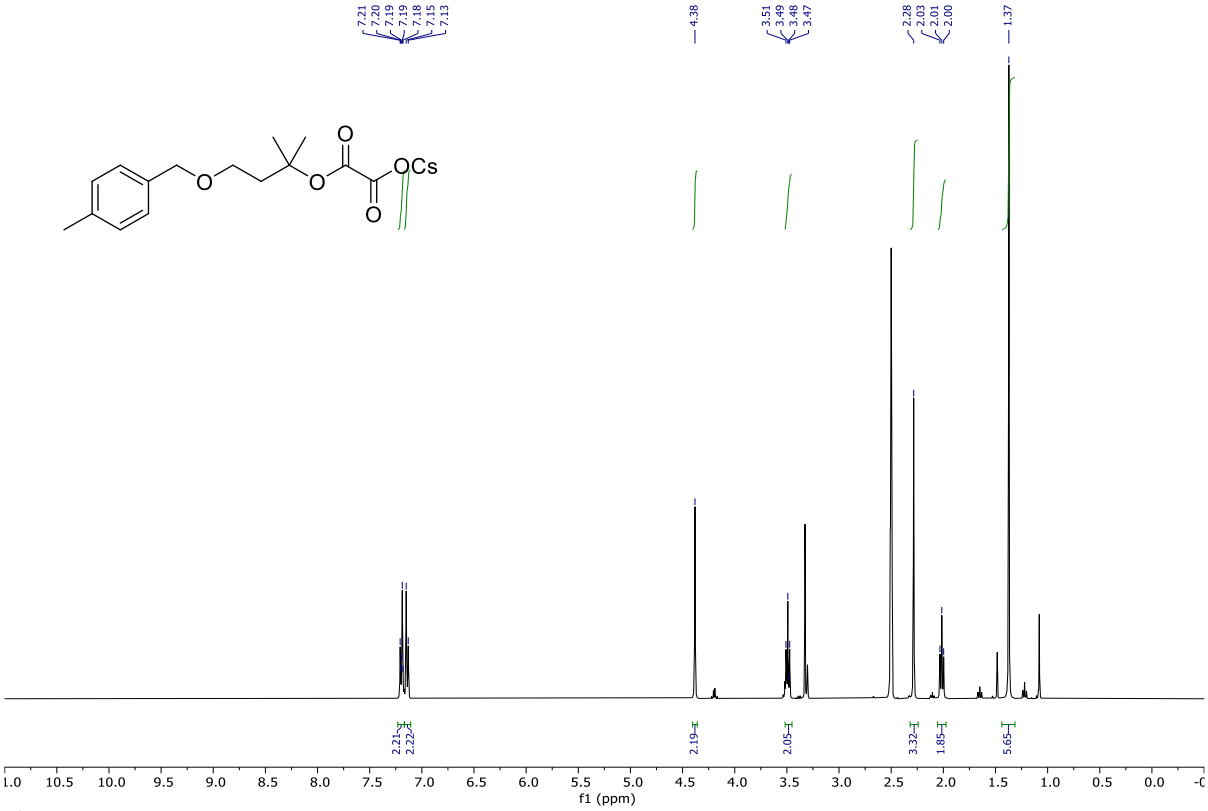


^{13}C NMR, $CDCl_3$, 101 MHz

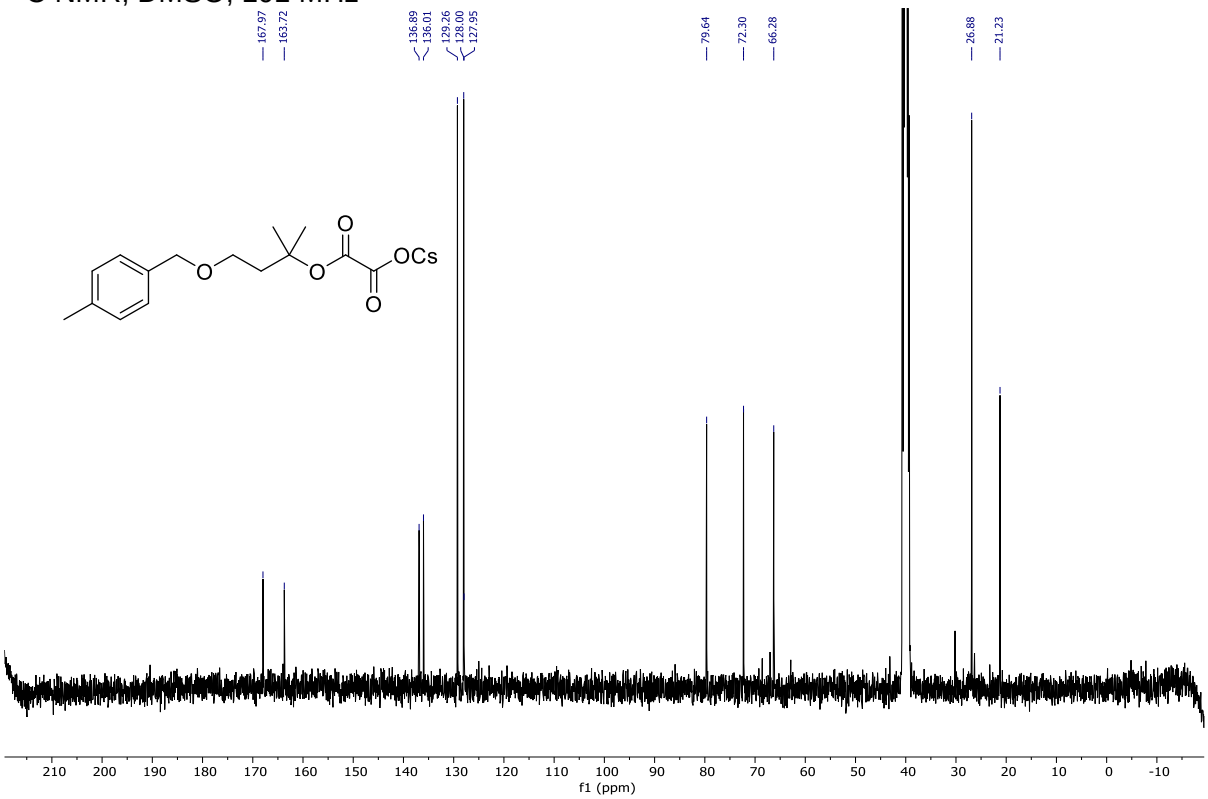


5.6p

^{1}H NMR, DMSO, 400 MHz

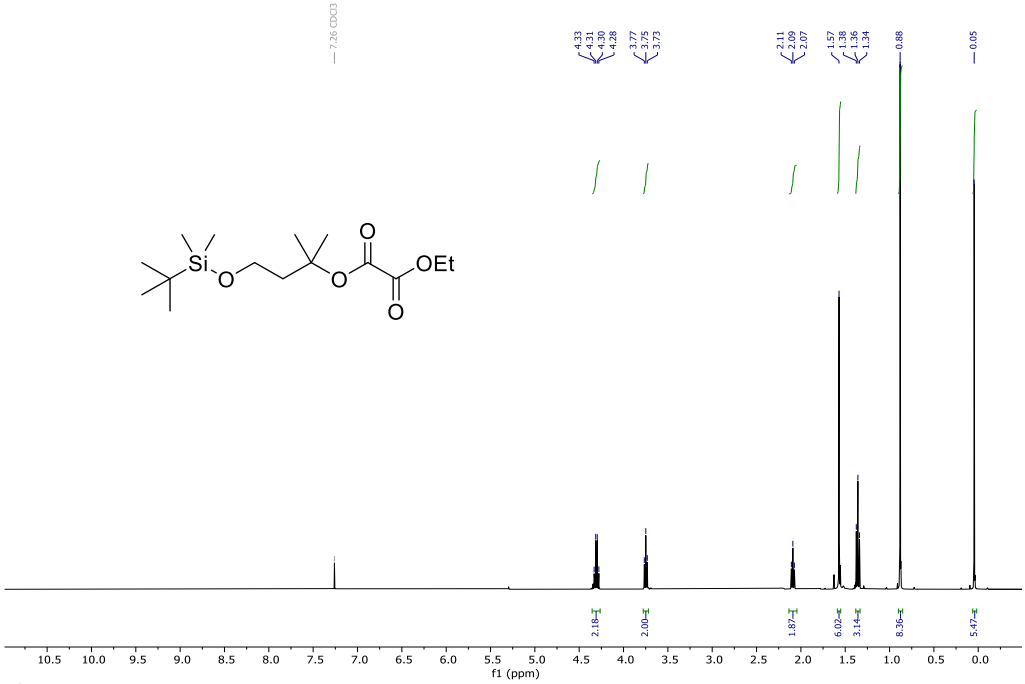


^{13}C NMR, DMSO, 101 MHz

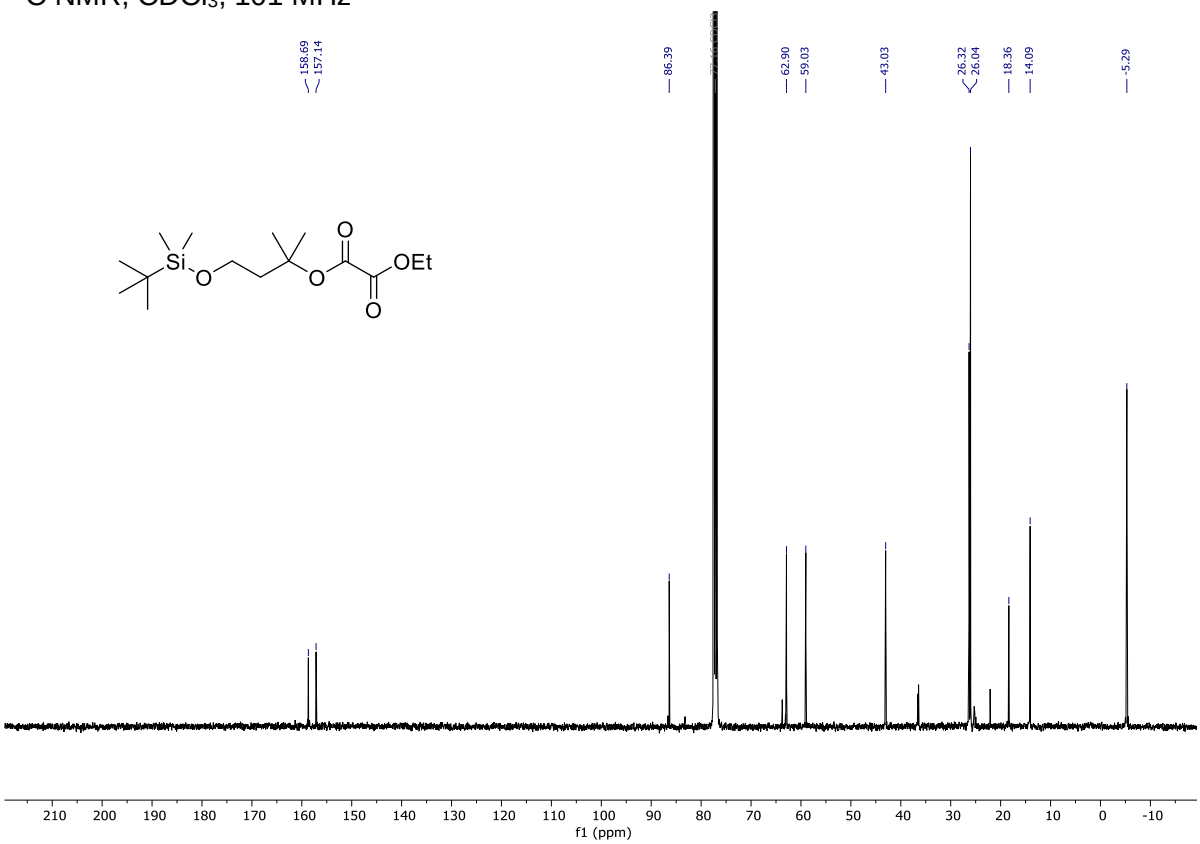


5.10q

^{1}H NMR, $CDCl_3$, 400 MHz

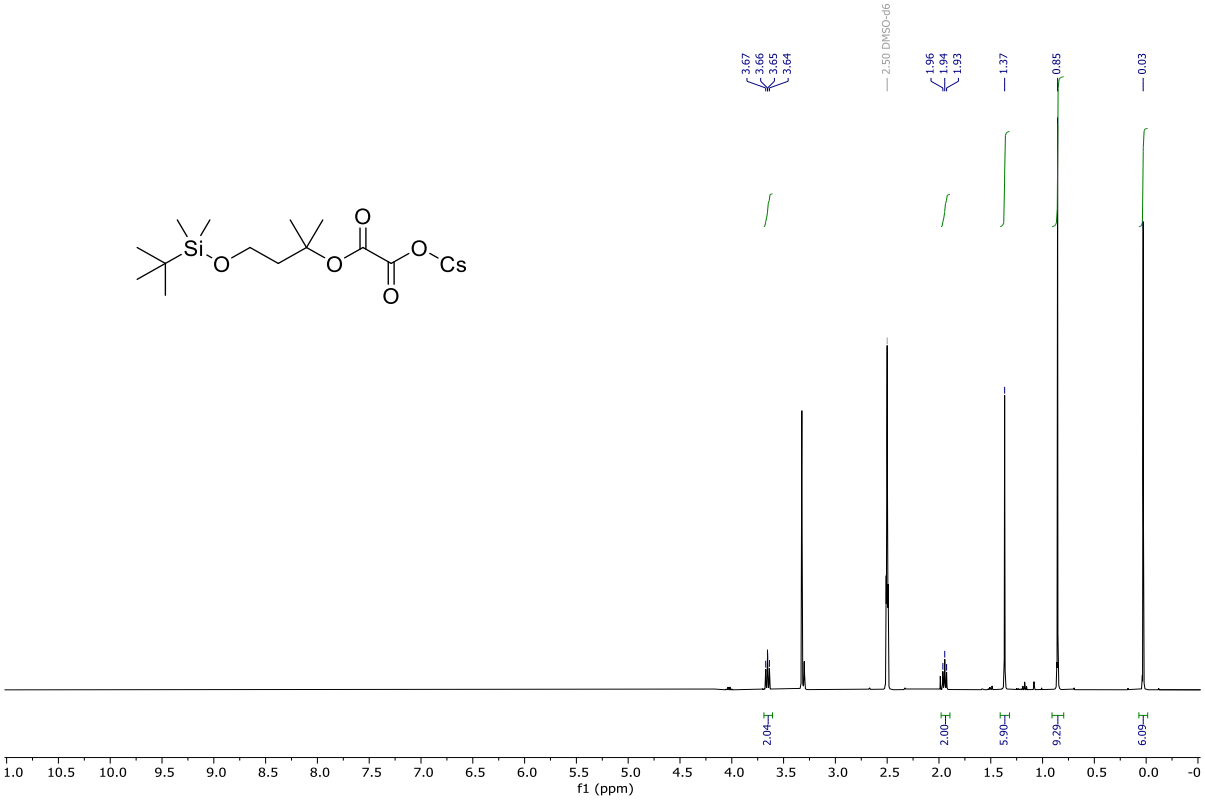


^{13}C NMR, $CDCl_3$, 101 MHz

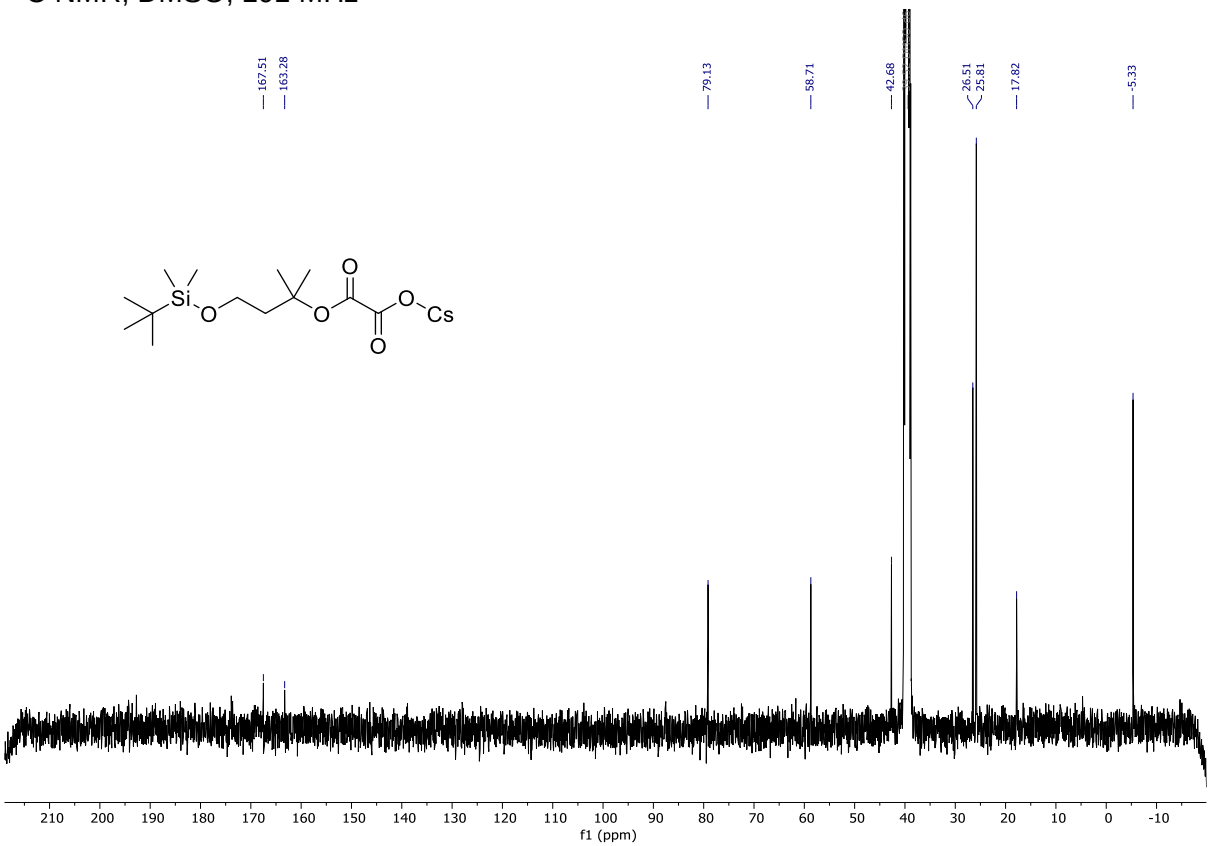


5.6q

^{1}H NMR, DMSO, 400 MHz

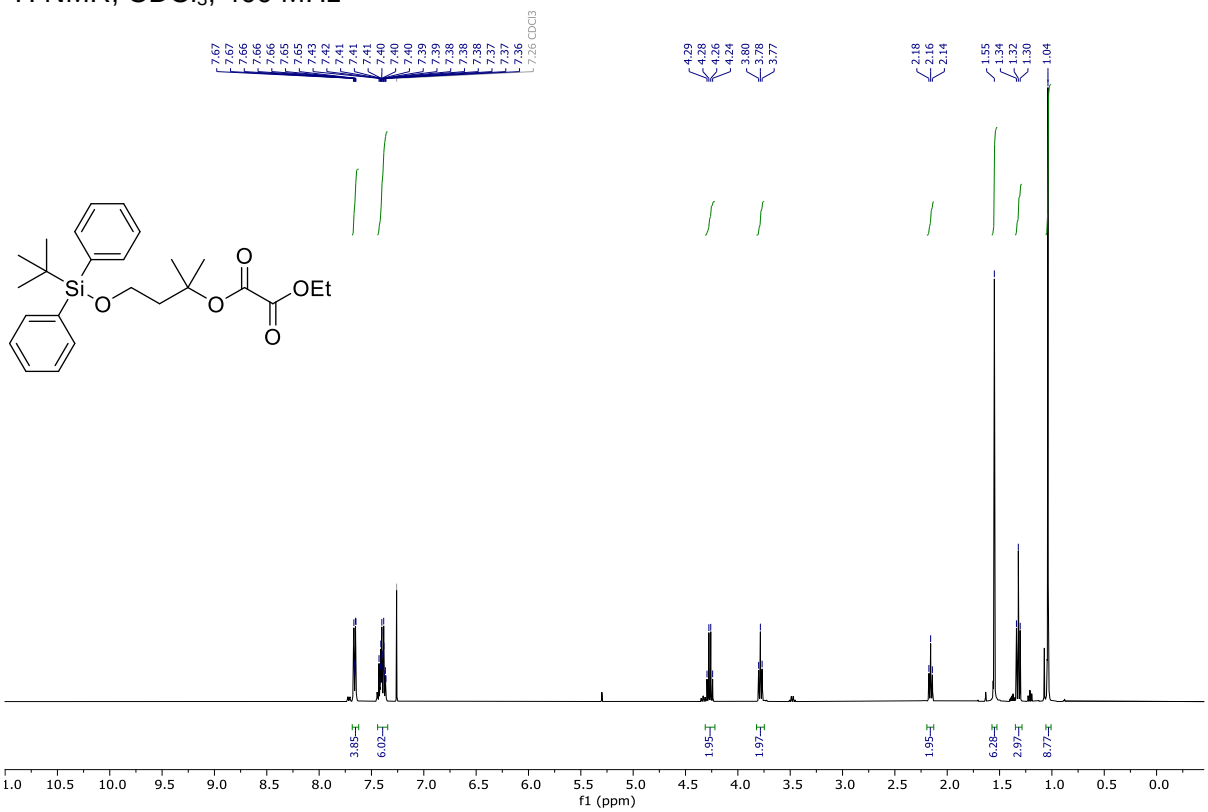


^{13}C NMR, DMSO, 101 MHz

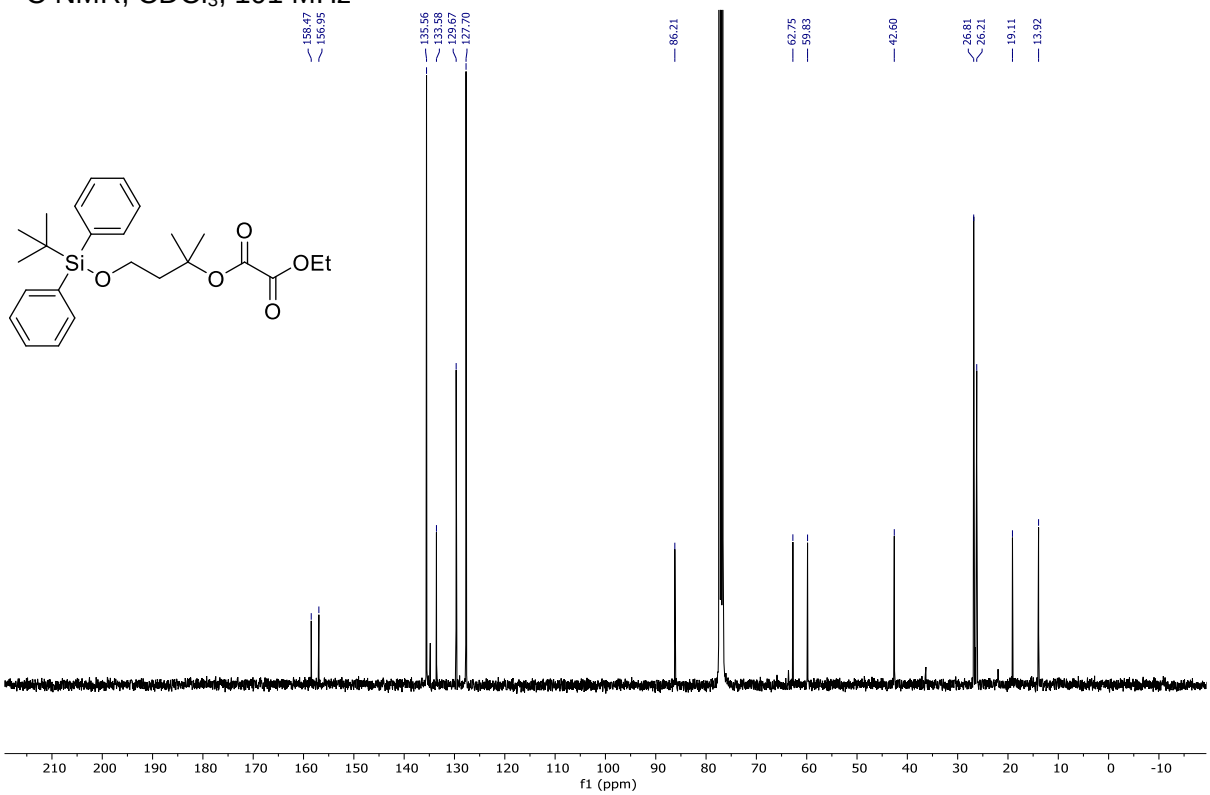


5.10r

^{1}H NMR, $CDCl_3$, 400 MHz

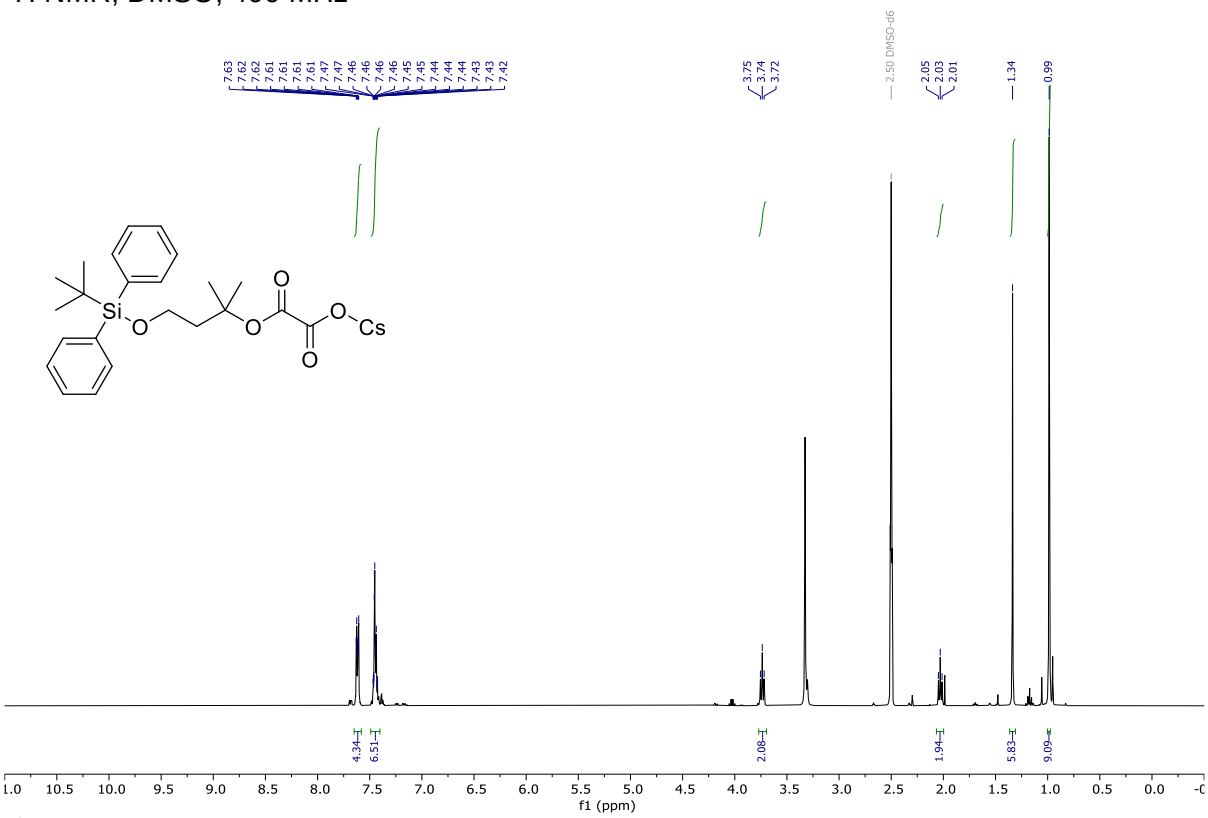


^{13}C NMR, $CDCl_3$, 101 MHz

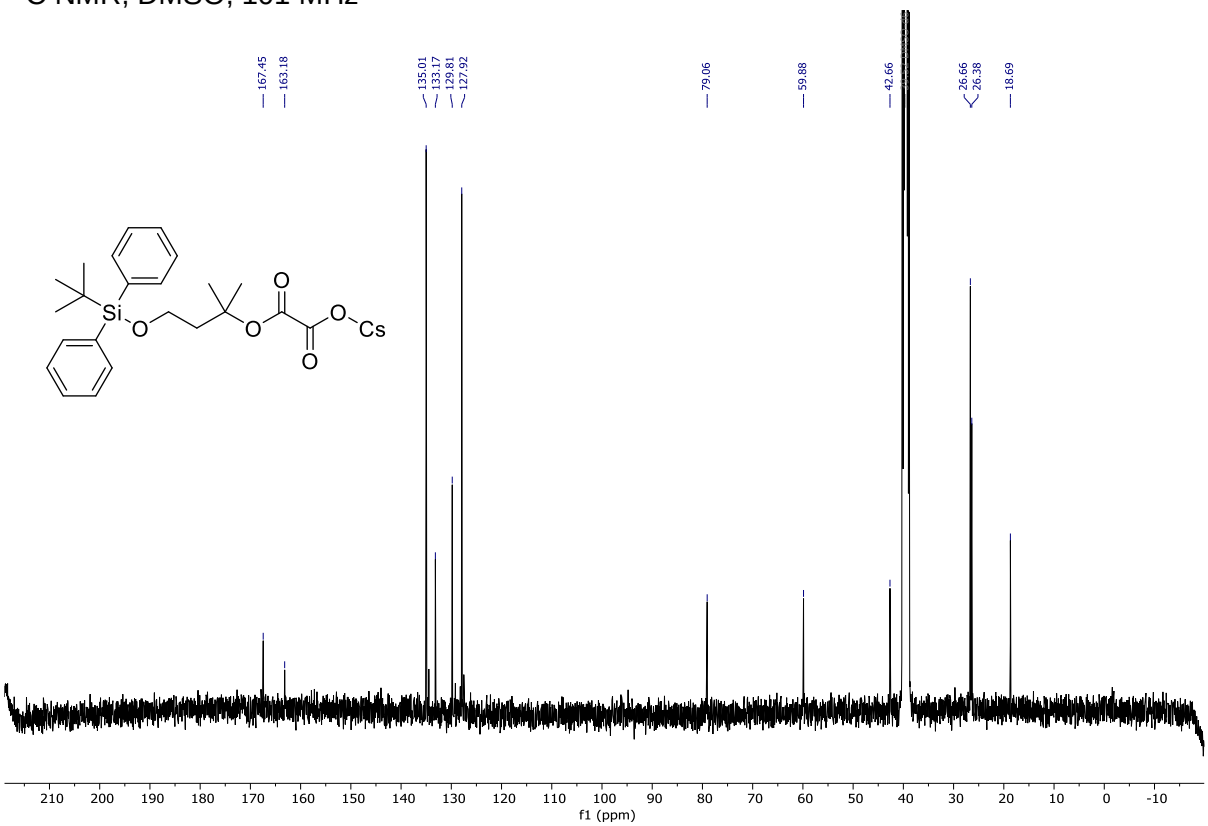


5.6r

^{1}H NMR, DMSO, 400 MHz

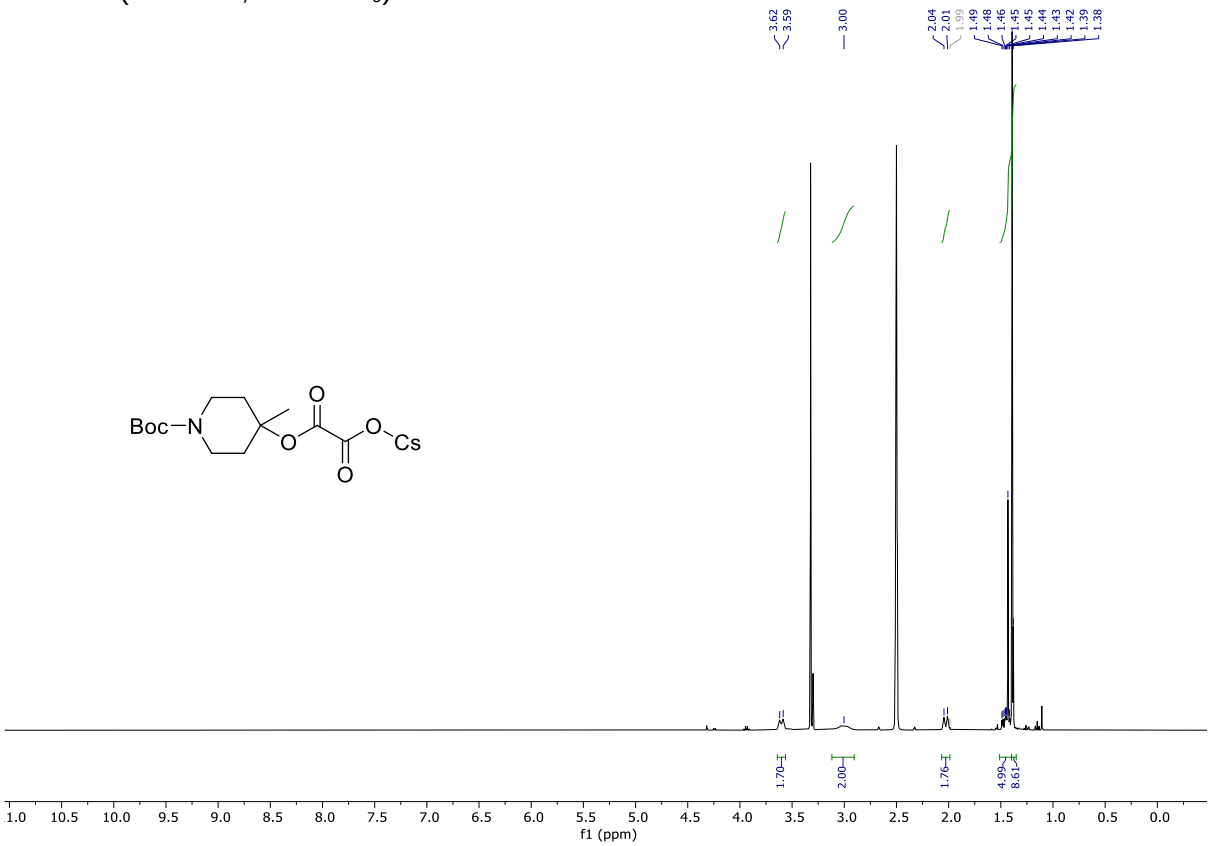


^{13}C NMR, DMSO, 101 MHz

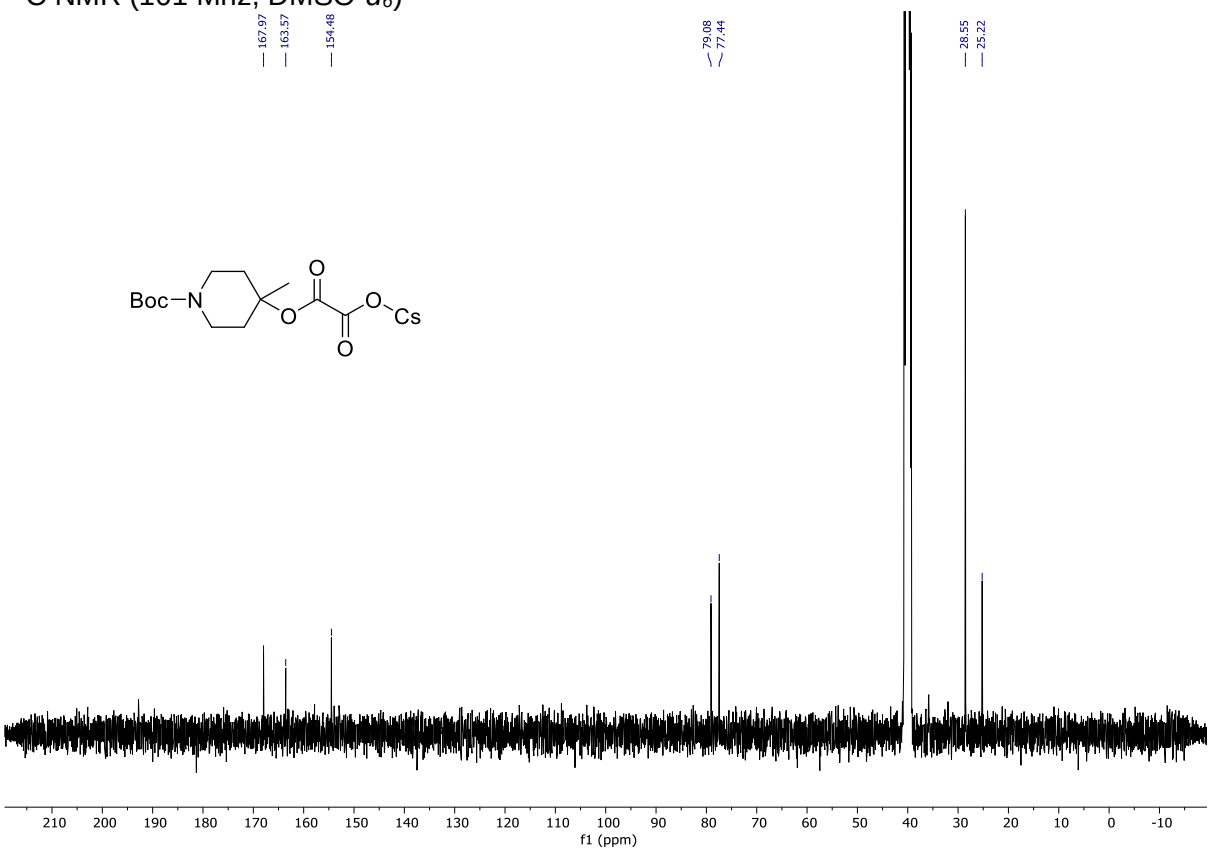


5.6s

^{1}H NMR (400 Mhz, DMSO-d_6)

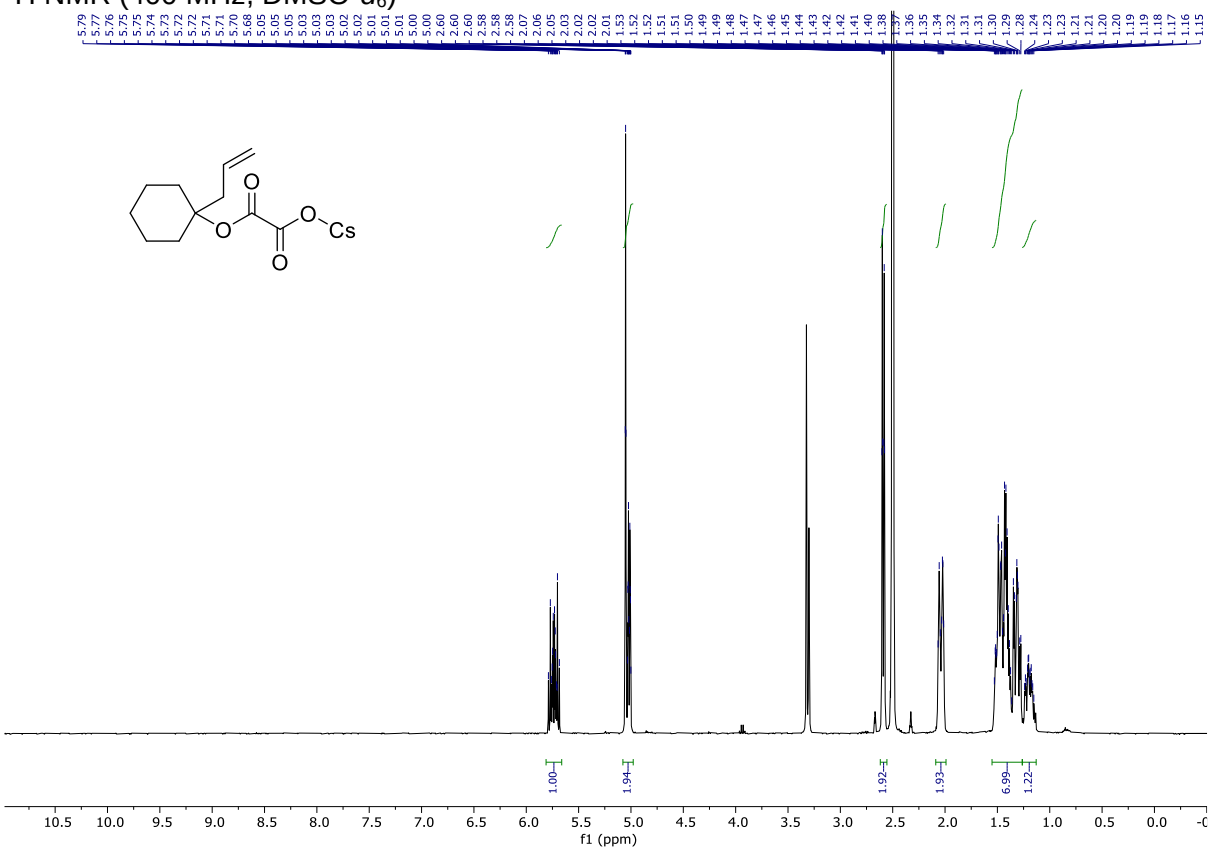


^{13}C NMR (101 Mhz, DMSO-d_6)

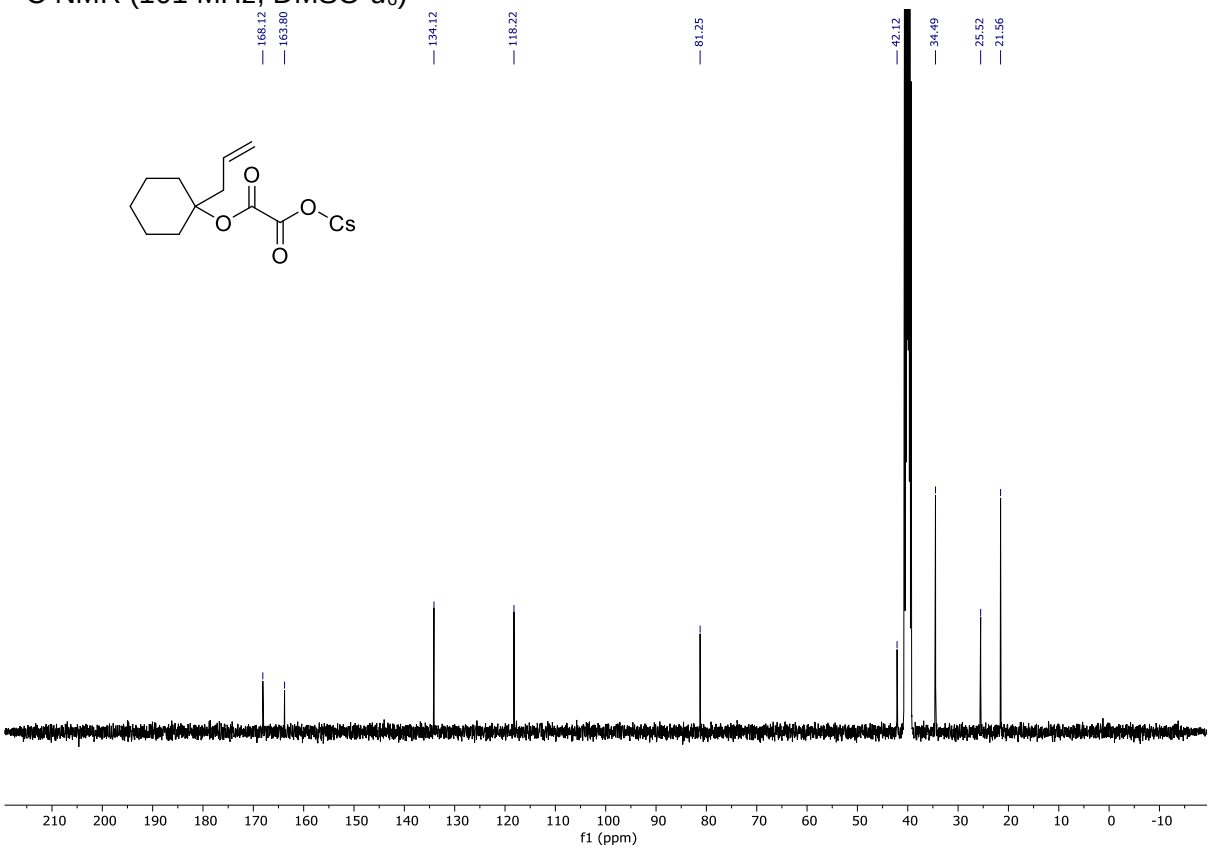


5.6t

^{1}H NMR (400 MHz, DMSO-d_6)

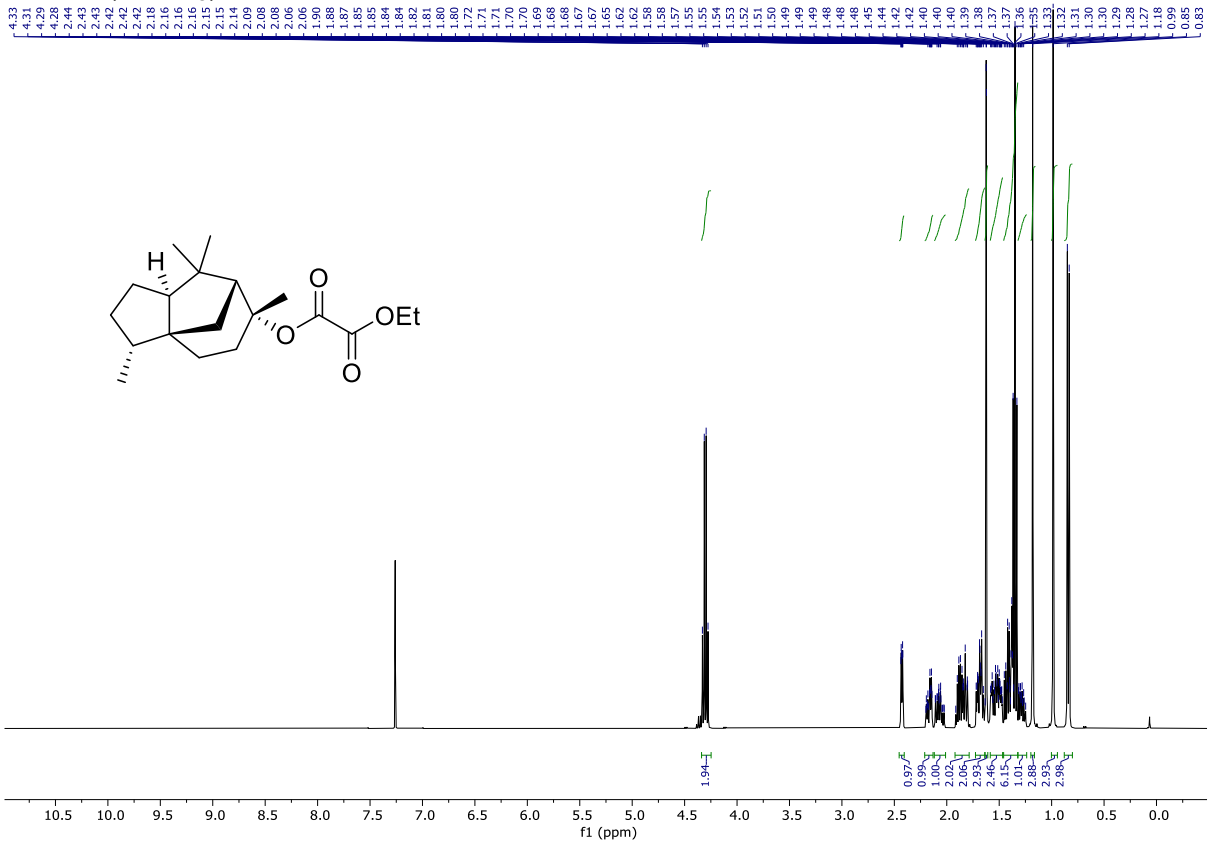


^{13}C NMR (101 MHz, DMSO-d_6)

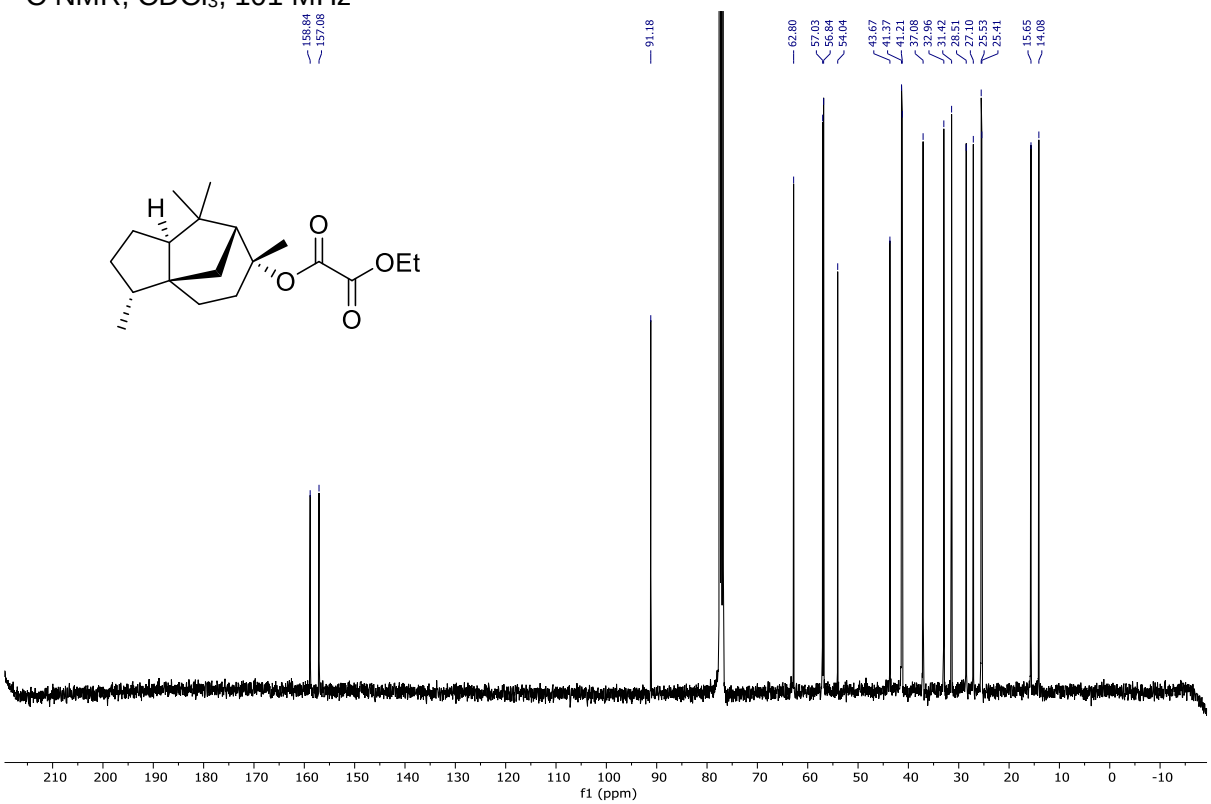


5.10u

^{1}H NMR, $CDCl_3$, 400 MHz

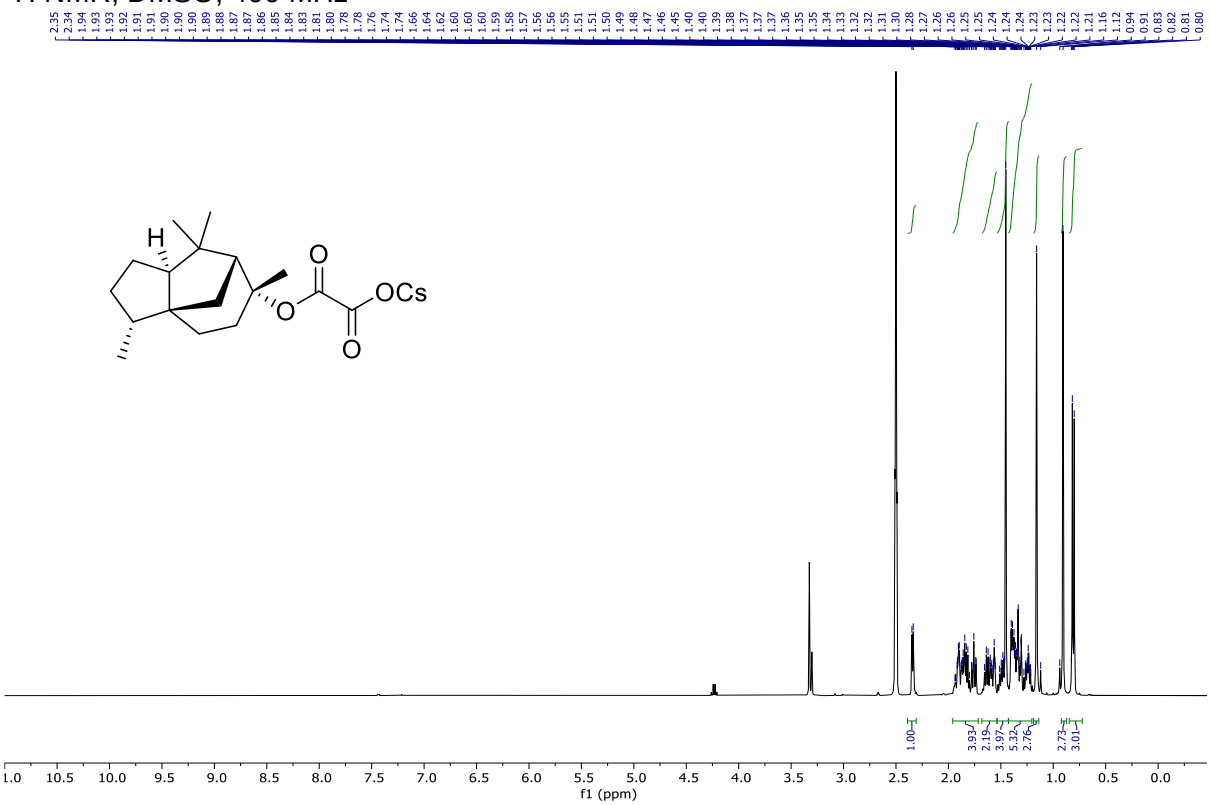


^{13}C NMR, $CDCl_3$, 101 MHz

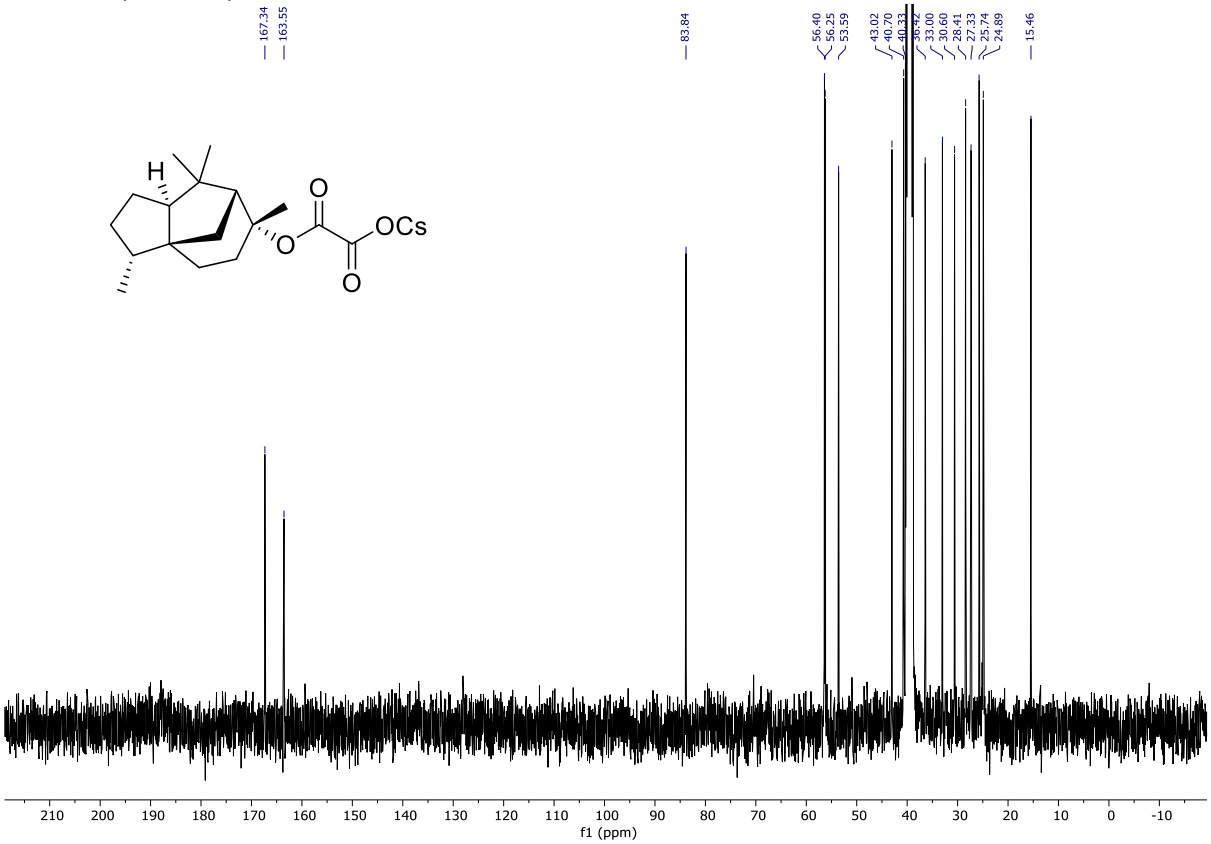


5.10u

^{1}H NMR, DMSO, 400 MHz

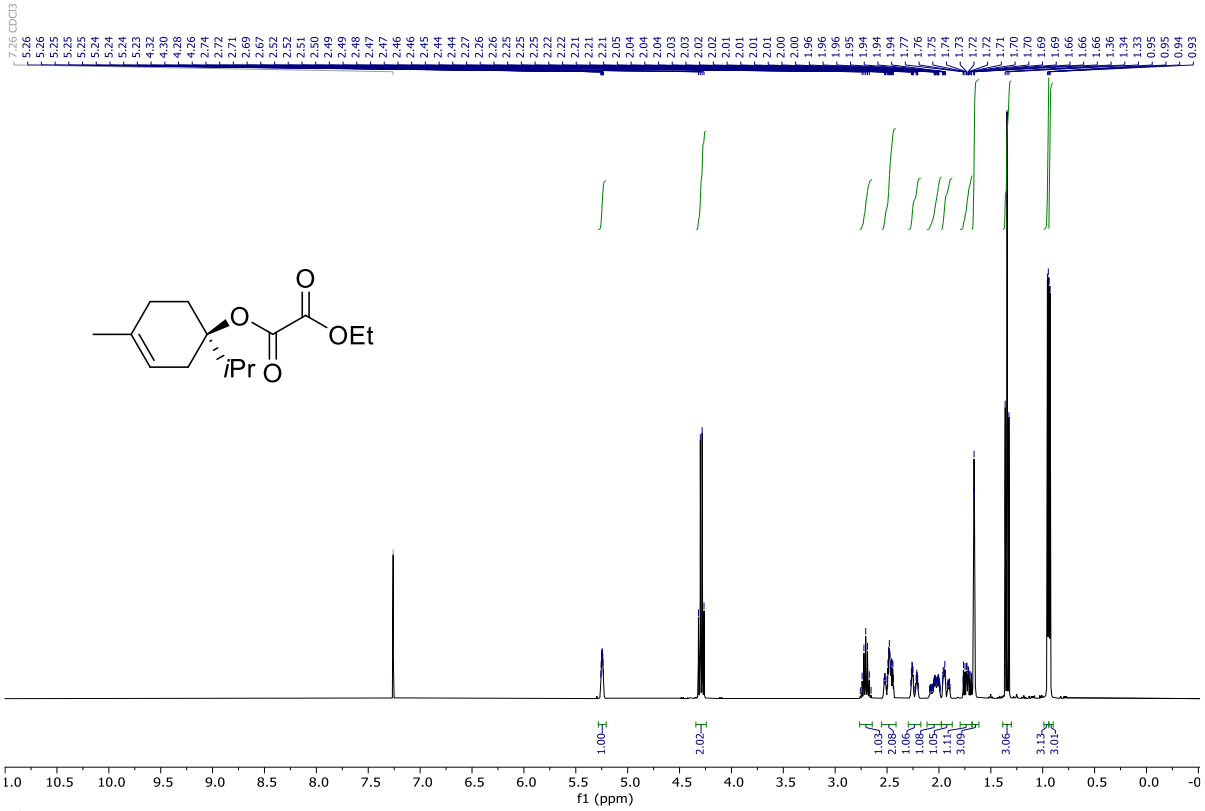


^{13}C NMR, DMSO, 101 MHz

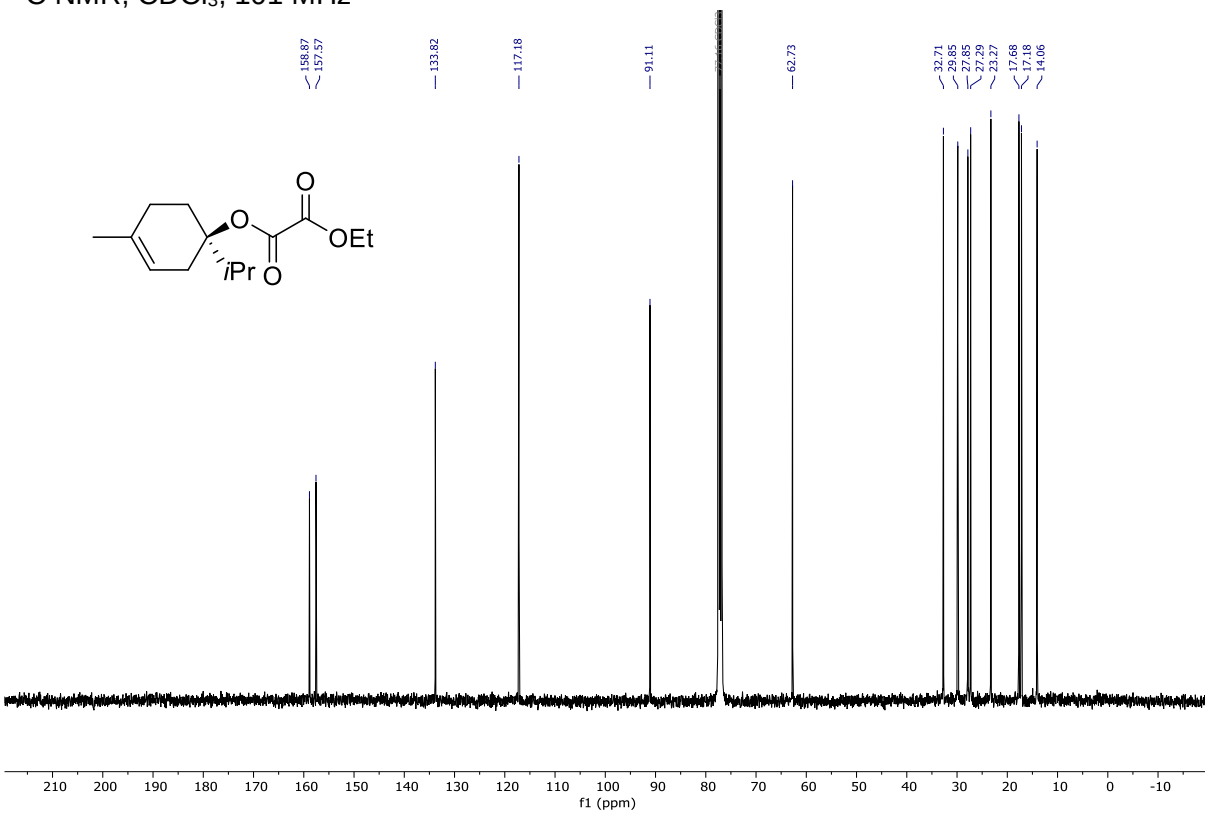


5.10v

^{1}H NMR, $CDCl_3$, 400 MHz

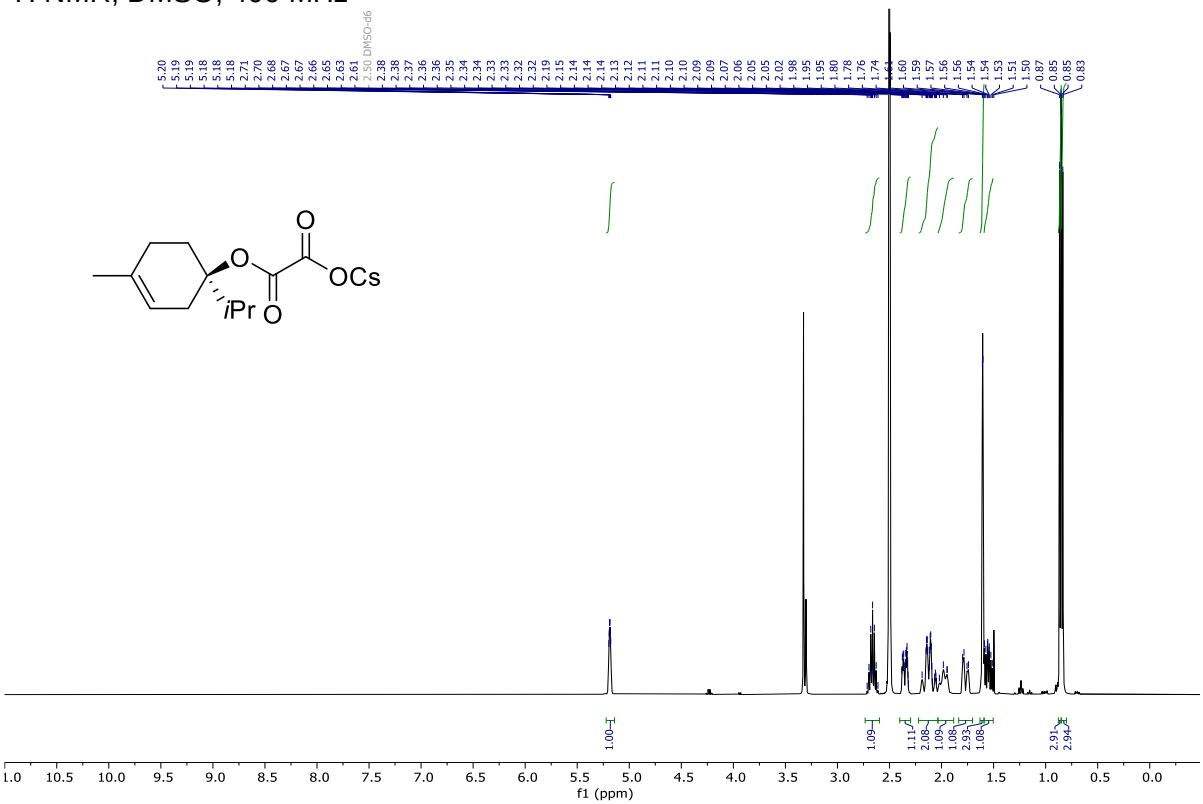


^{13}C NMR, $CDCl_3$, 101 MHz

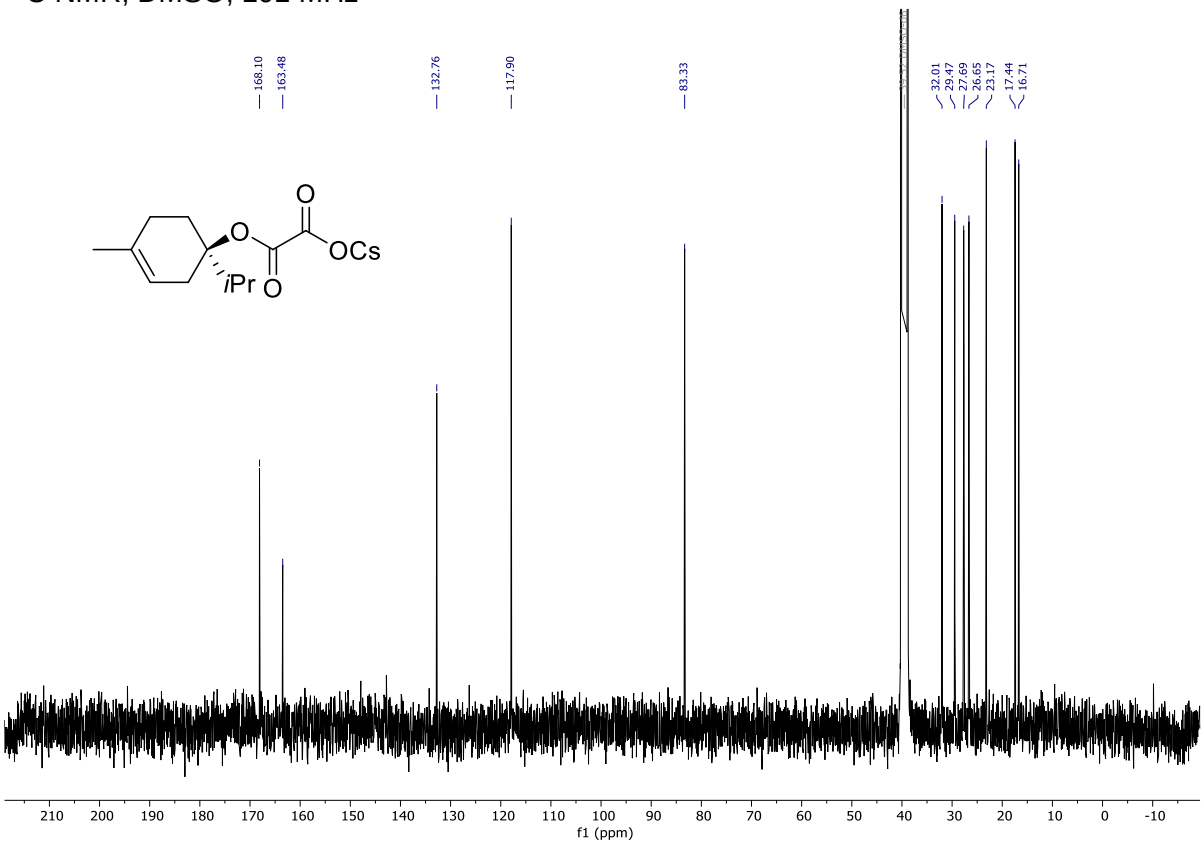


5.6v

^{1}H NMR, DMSO, 400 MHz

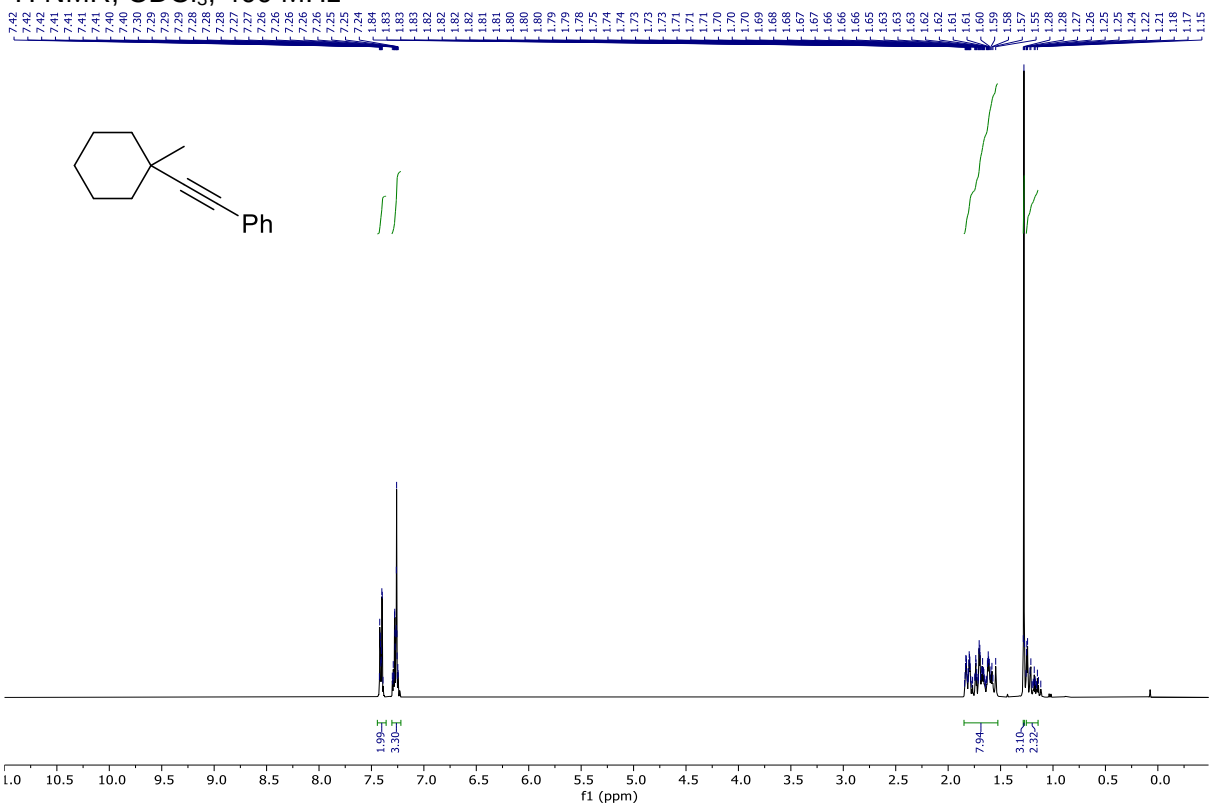


^{13}C NMR, DMSO, 101 MHz

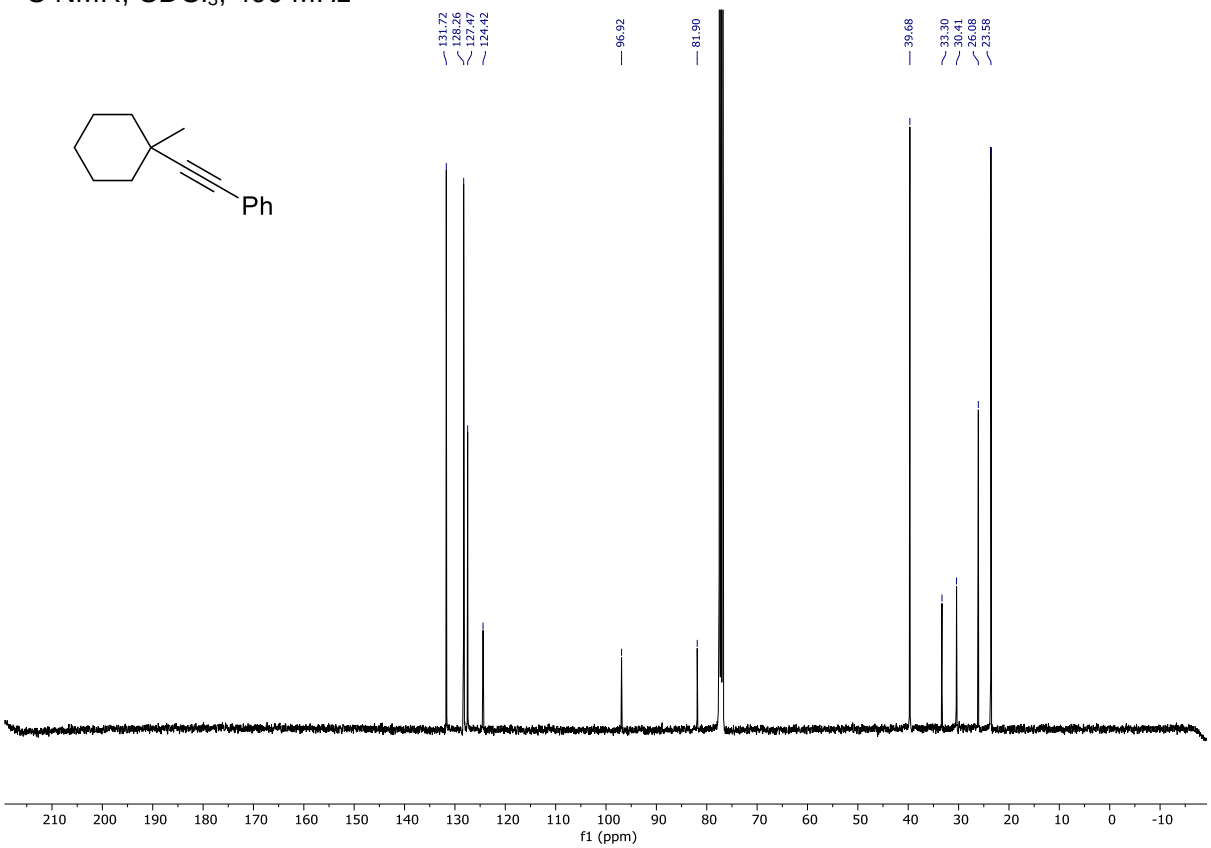


5.11a

^{1}H NMR, $CDCl_3$, 400 MHz

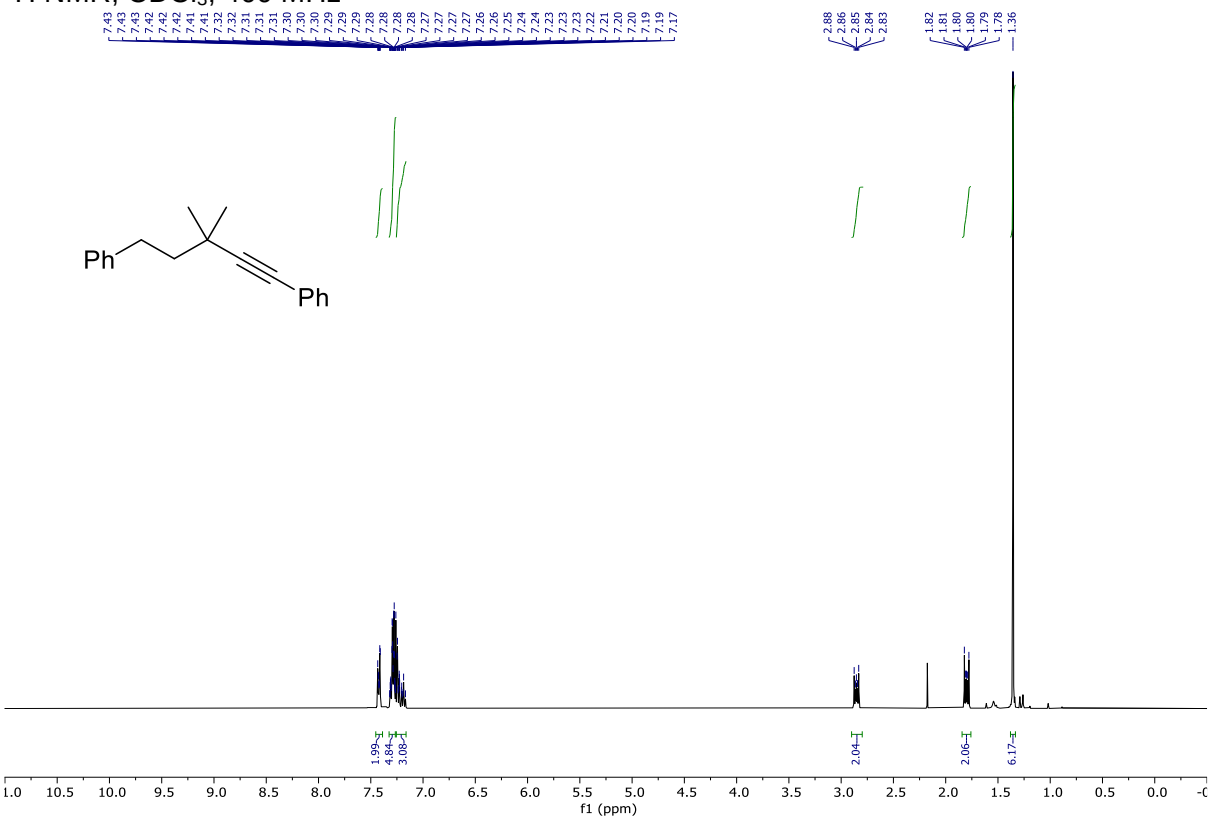


^{13}C NMR, $CDCl_3$, 400 MHz

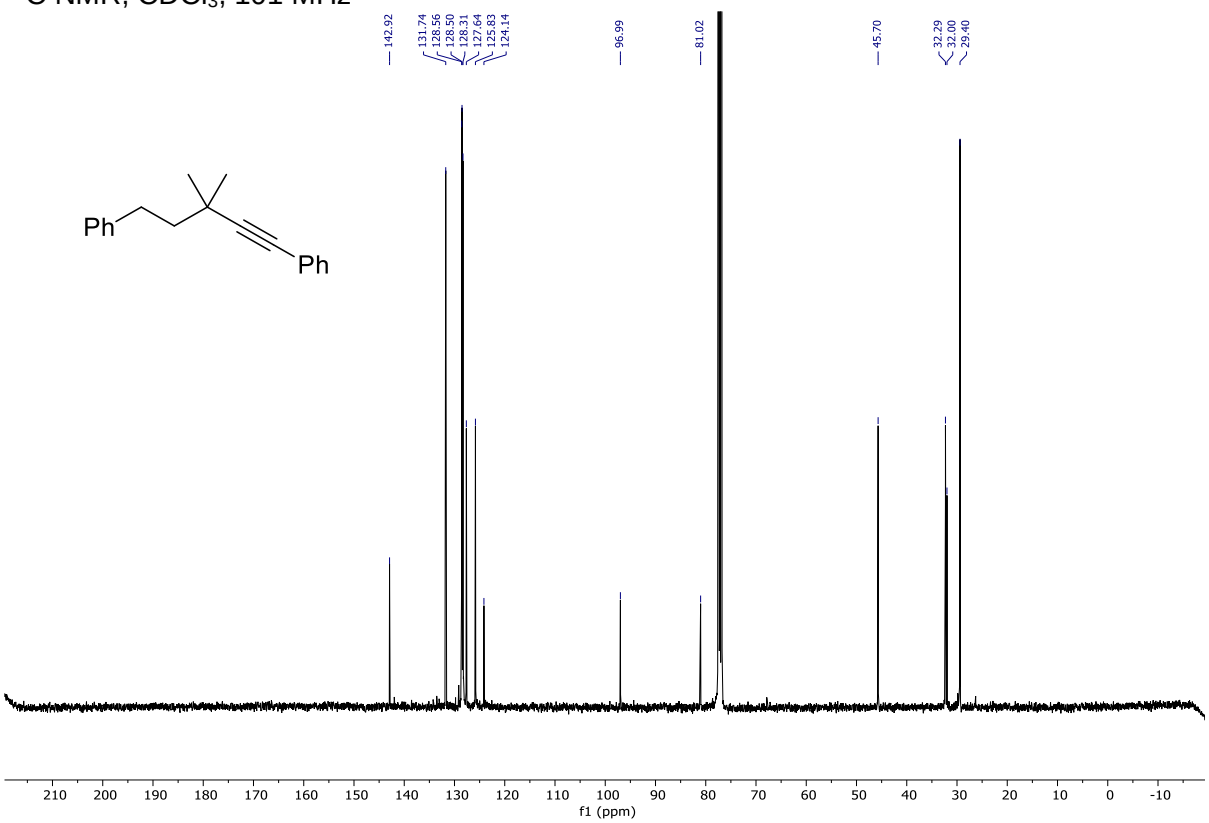


5.11b

^{1}H NMR, $CDCl_3$, 400 MHz

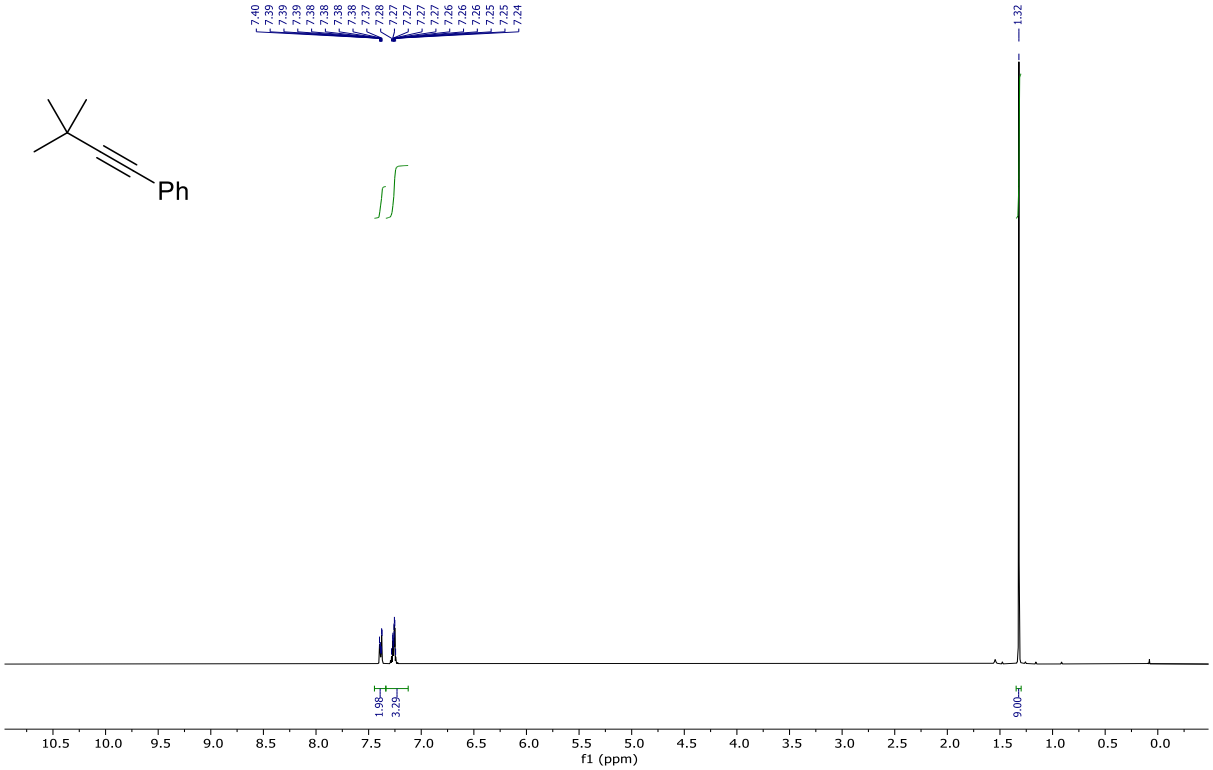


^{13}C NMR, $CDCl_3$, 101 MHz

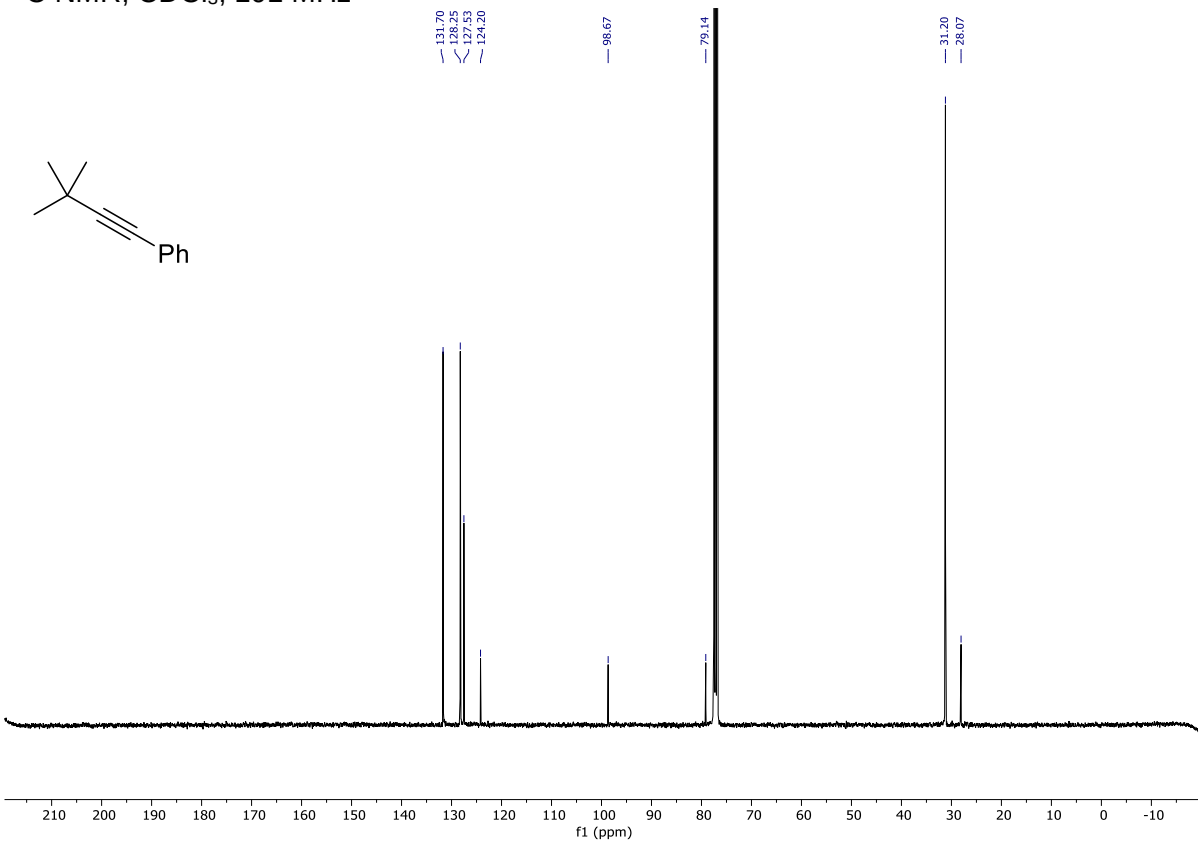


5.11c

^{1}H NMR, $CDCl_3$, 400 MHz

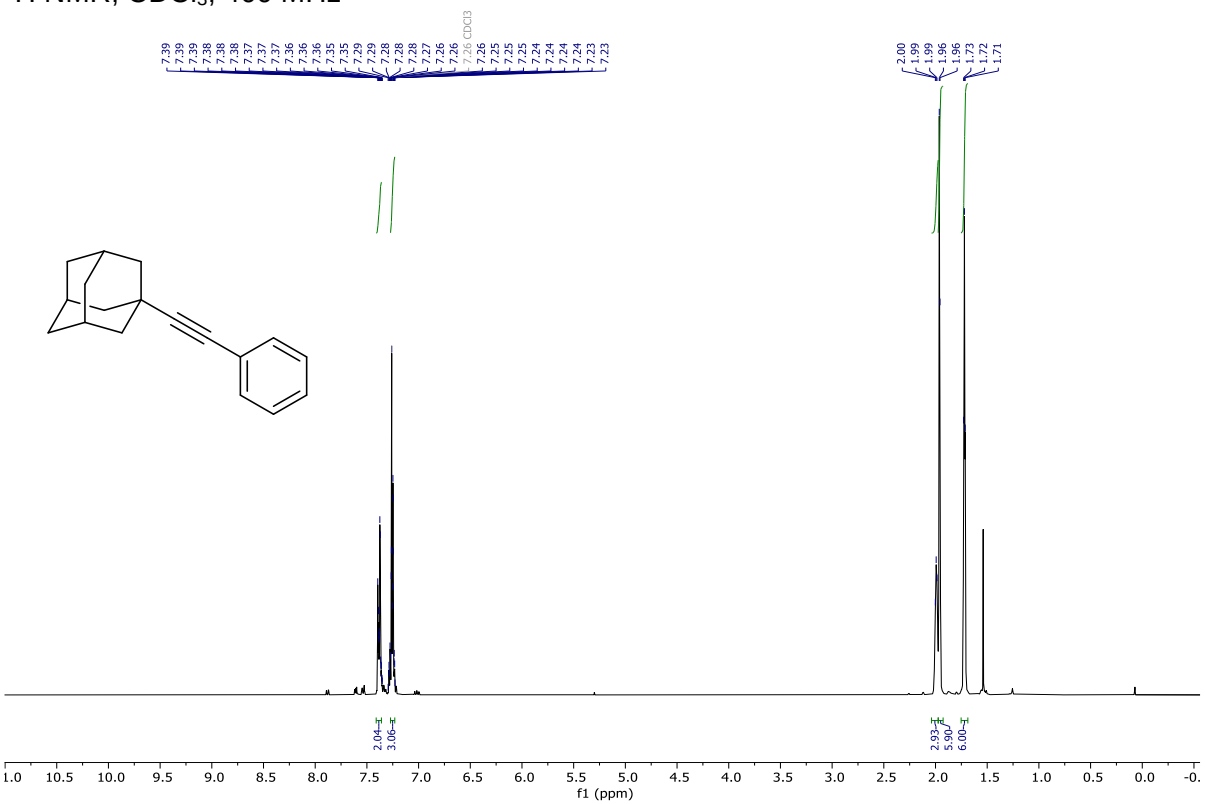


^{13}C NMR, $CDCl_3$, 101 MHz

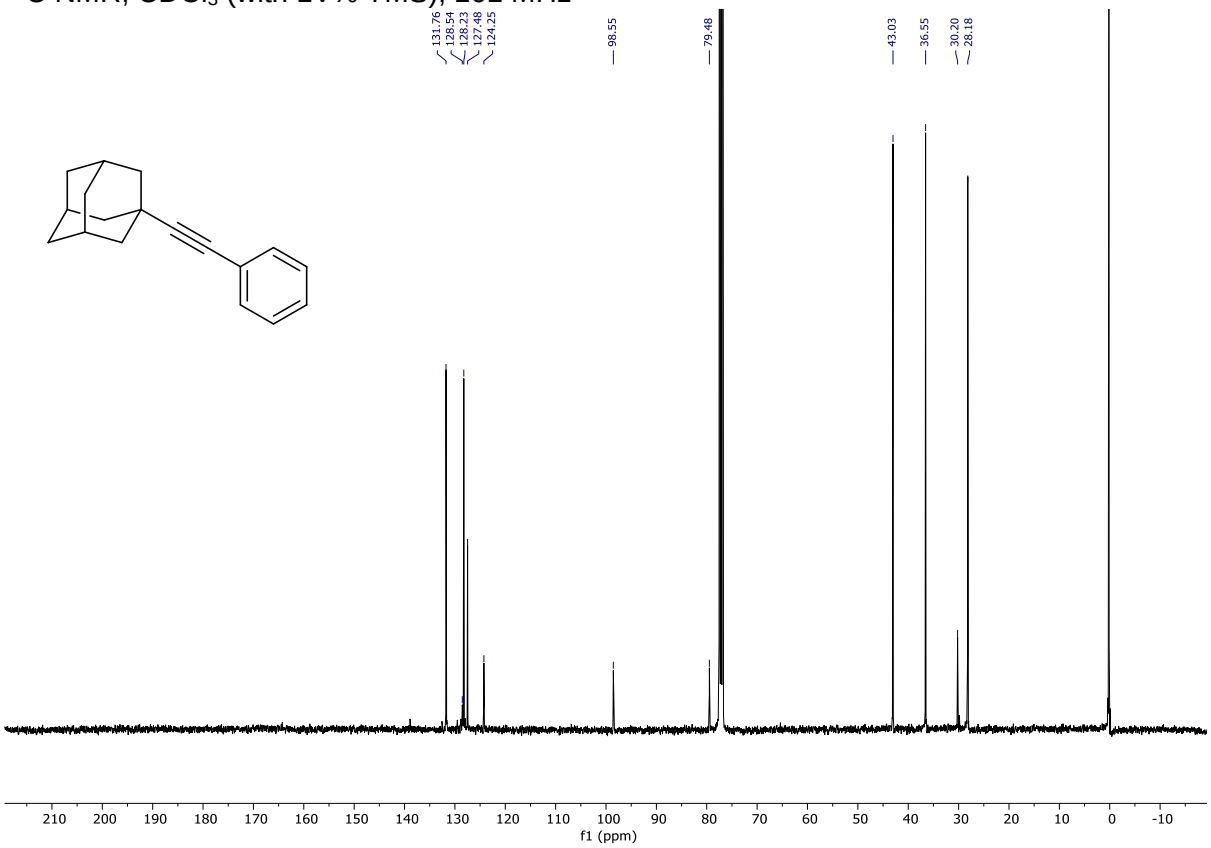


5.11d

^{1}H NMR, $CDCl_3$, 400 MHz

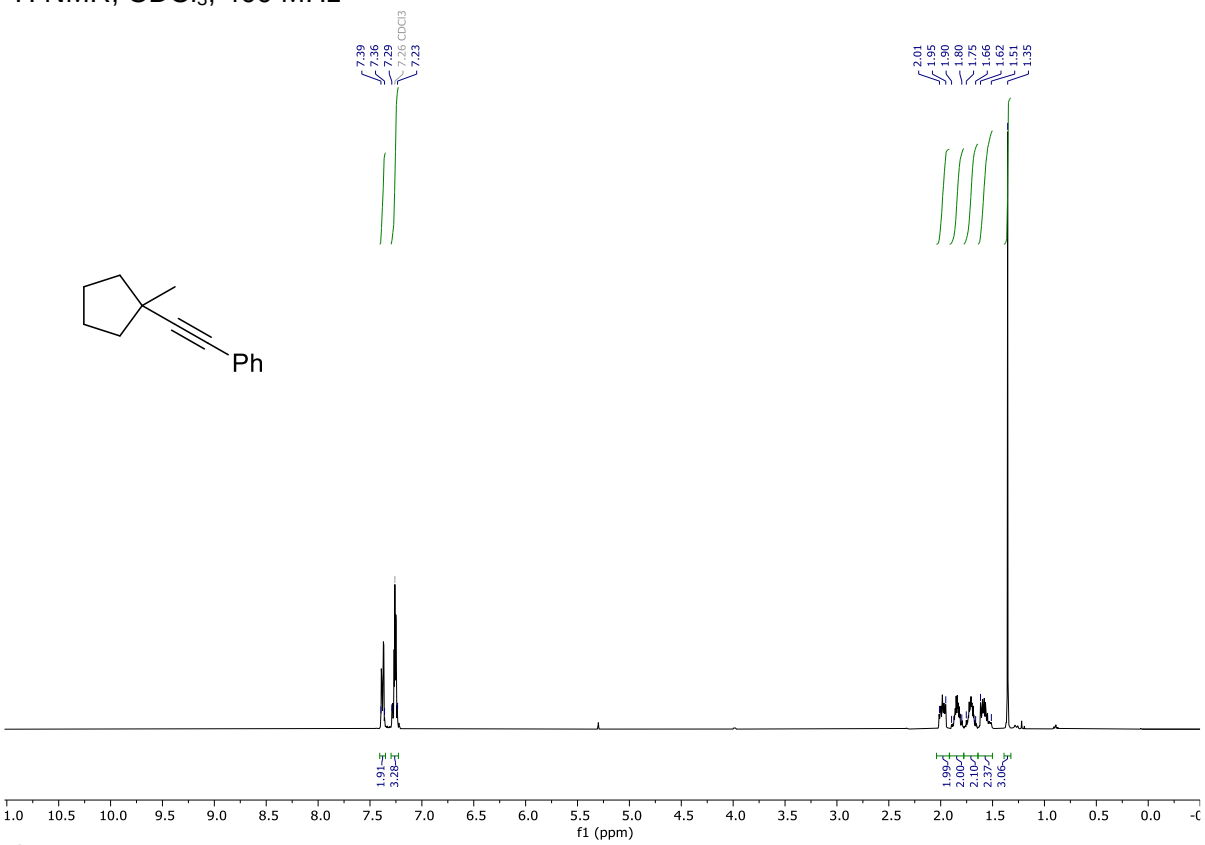


^{13}C NMR, $CDCl_3$ (with 1V% TMS), 101 MHz

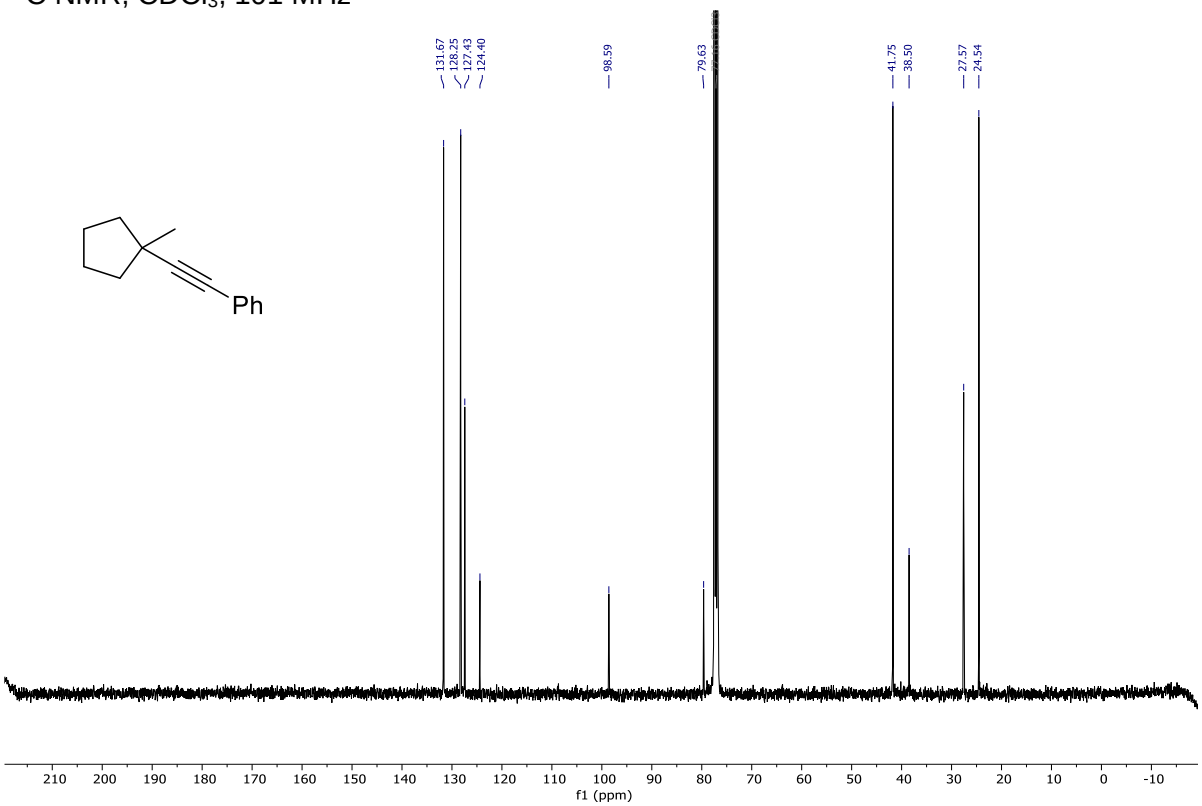


5.11e

^{1}H NMR, $CDCl_3$, 400 MHz

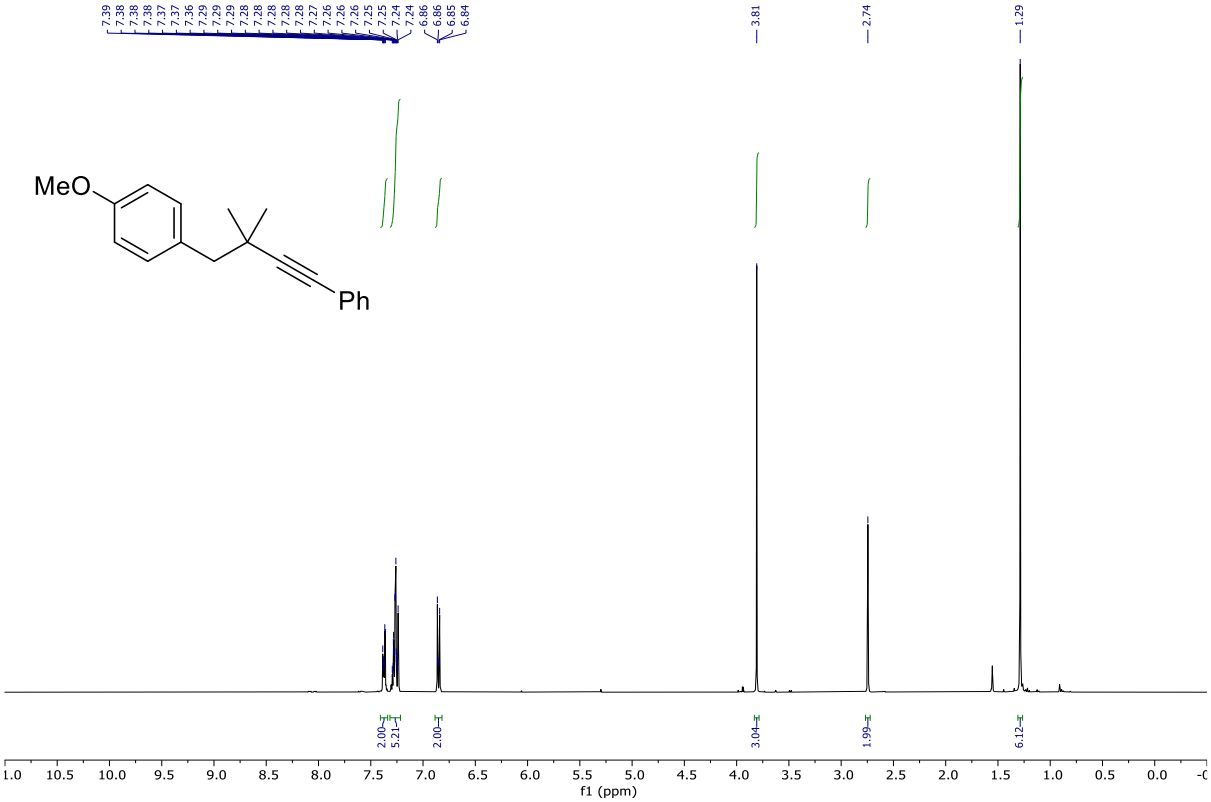


^{13}C NMR, $CDCl_3$, 101 MHz

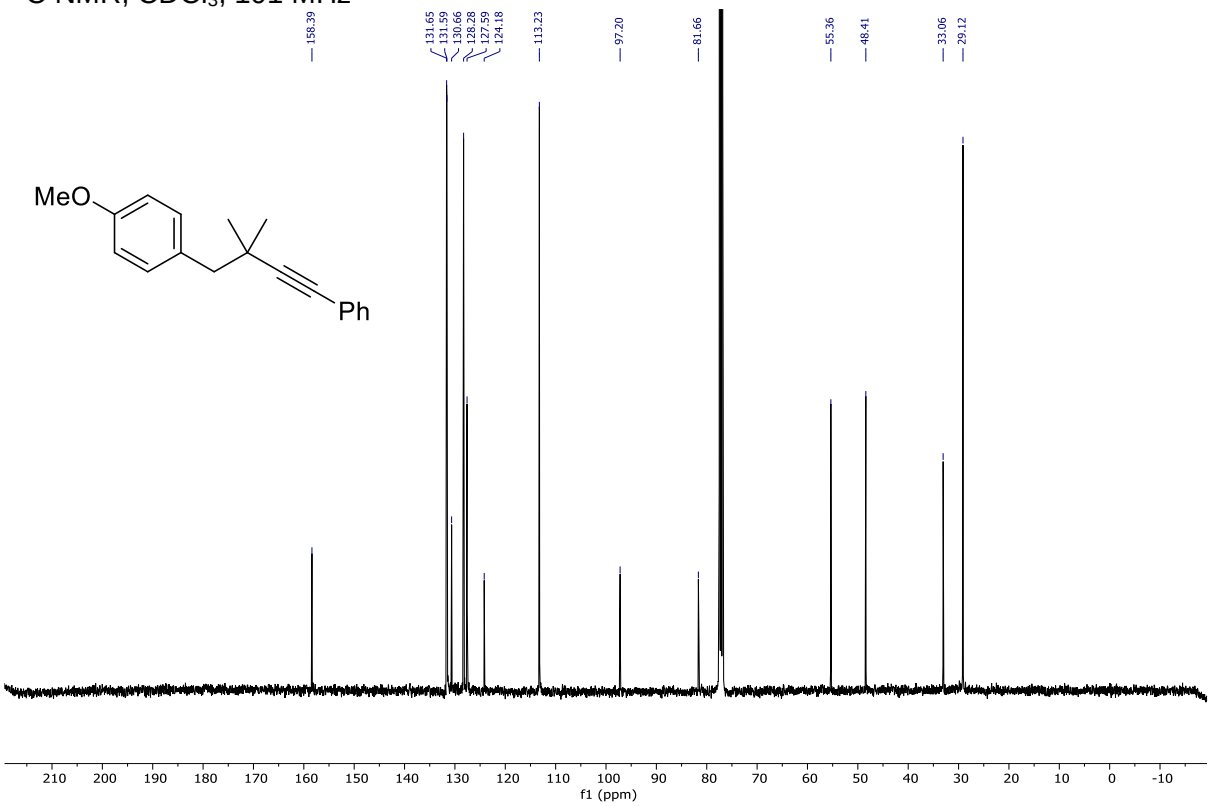


5.11f

^{1}H NMR, $CDCl_3$, 400 MHz

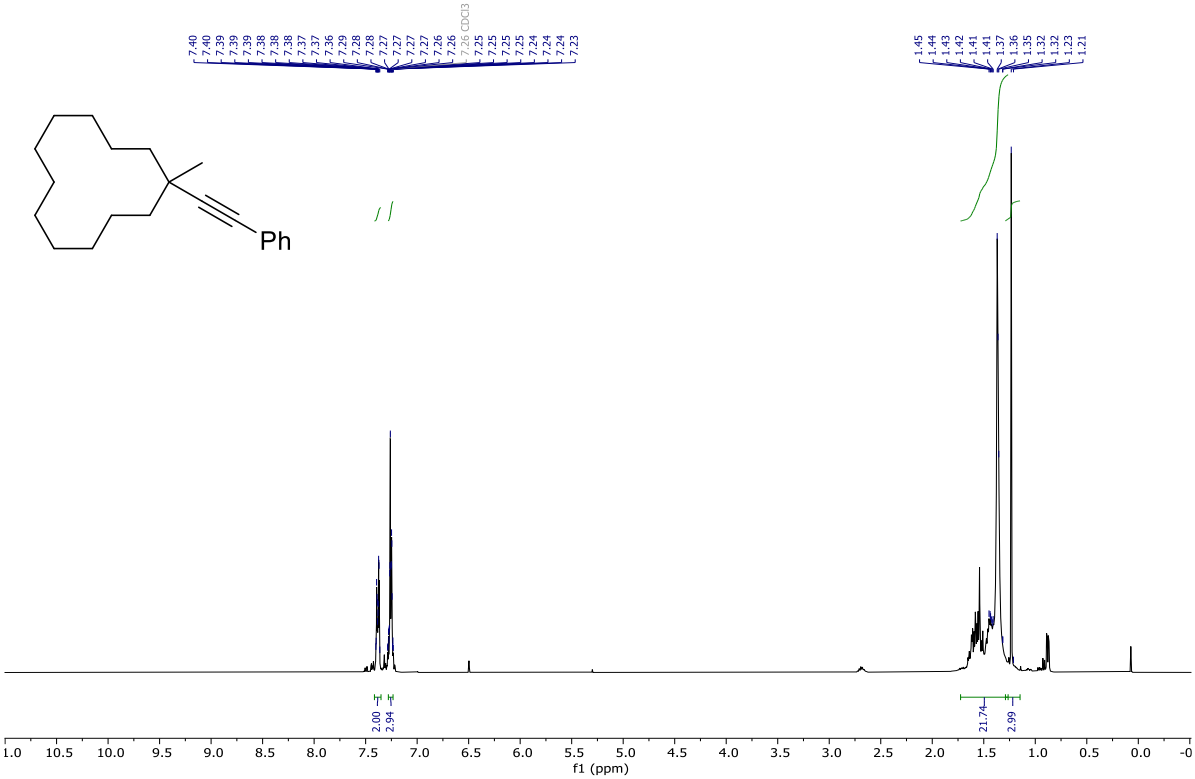


^{13}C NMR, $CDCl_3$, 101 MHz

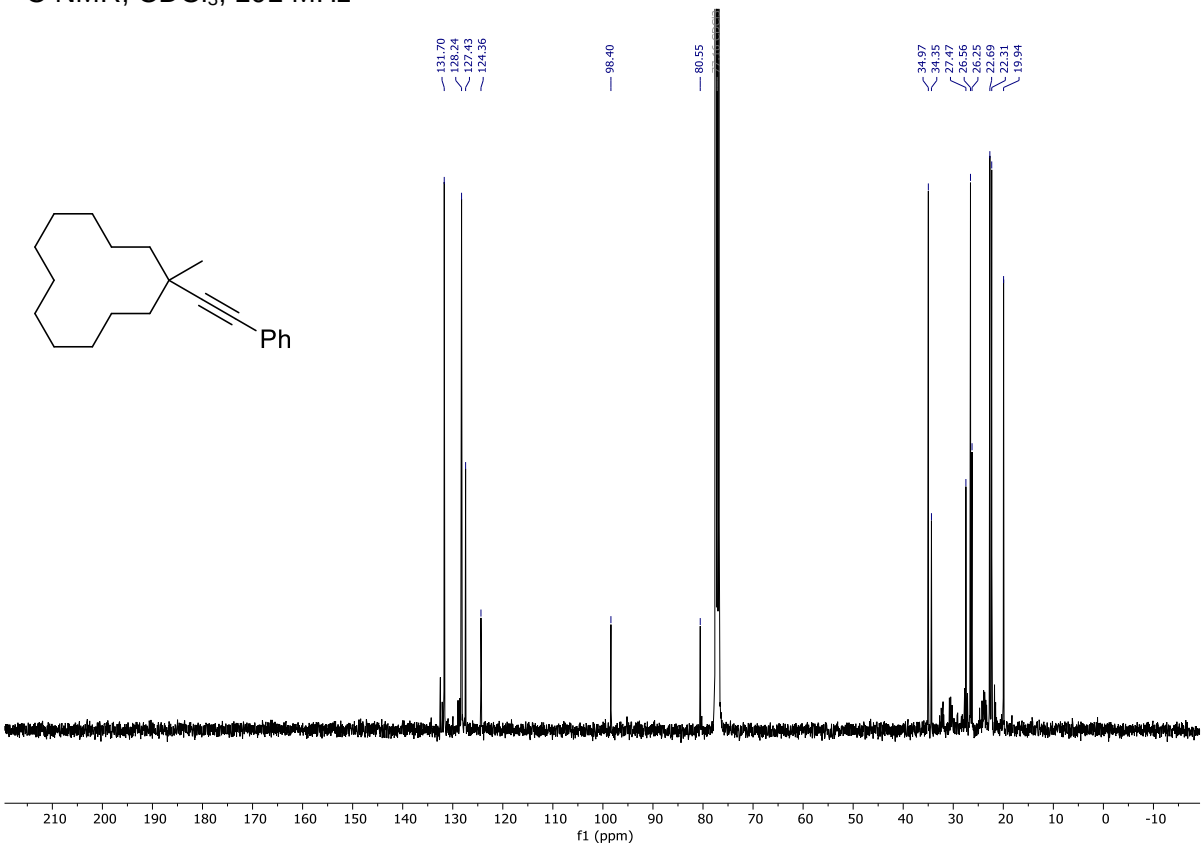


5.11g

^{1}H NMR, $CDCl_3$, 400 MHz

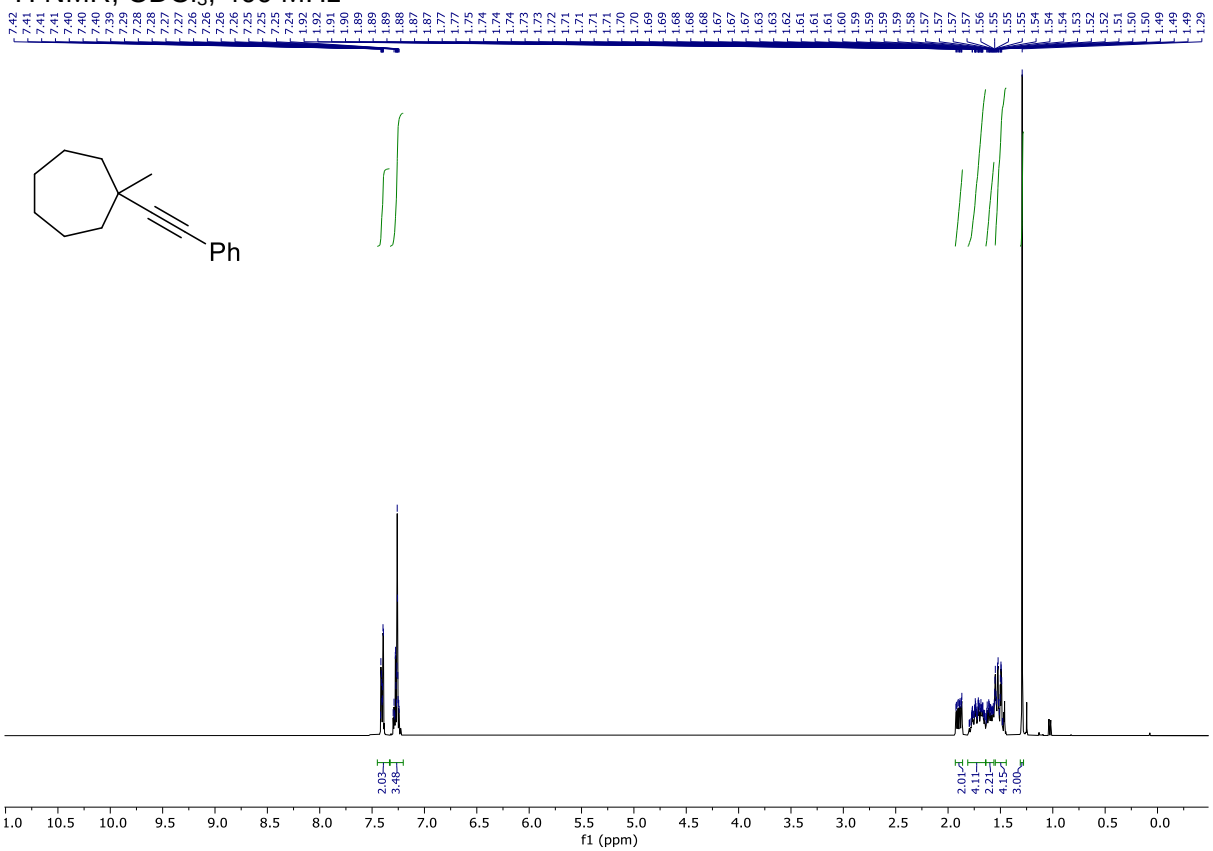


^{13}C NMR, $CDCl_3$, 101 MHz

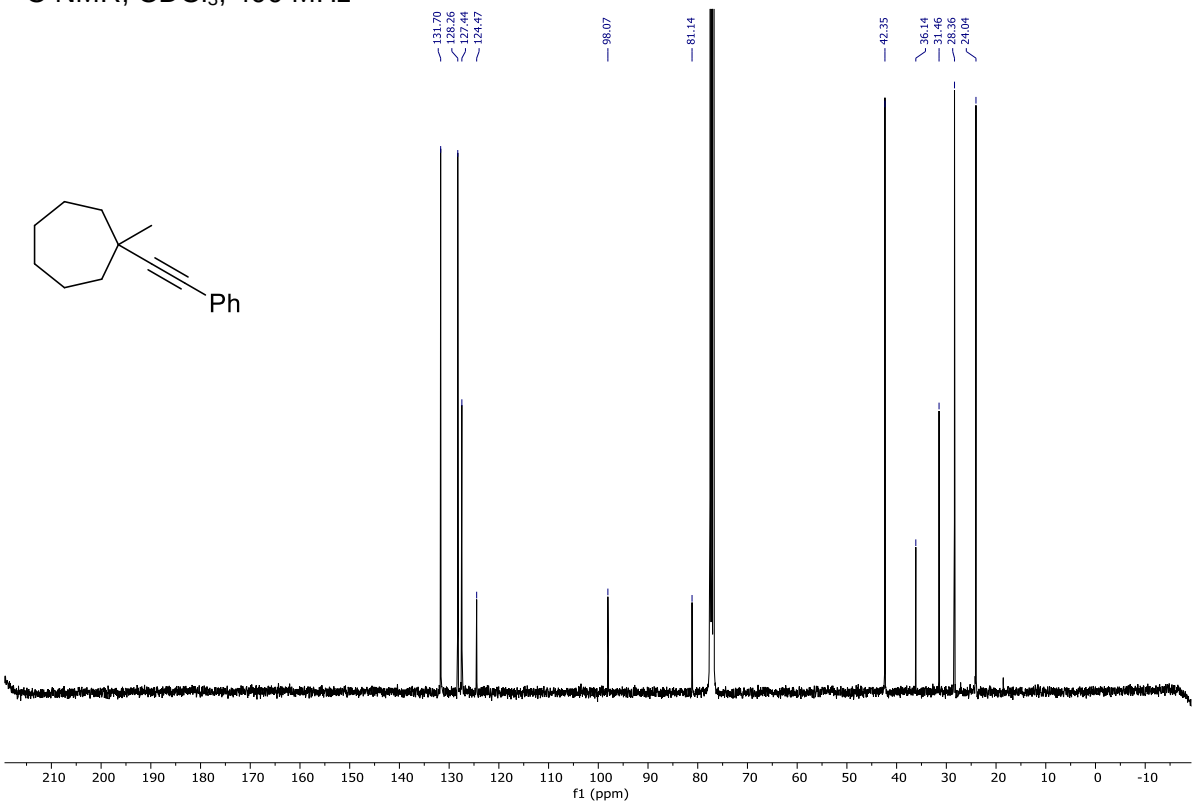


5.11j

^{1}H NMR, $CDCl_3$, 400 MHz

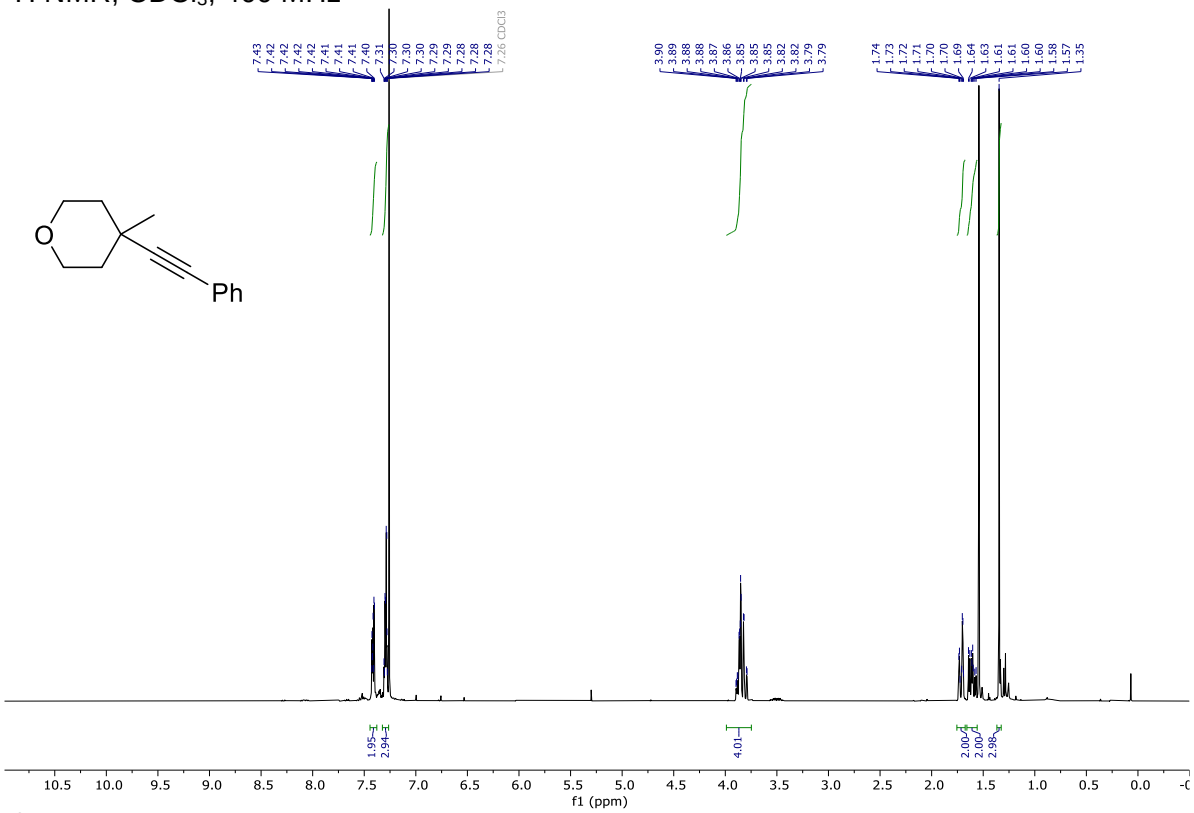


^{13}C NMR, $CDCl_3$, 400 MHz

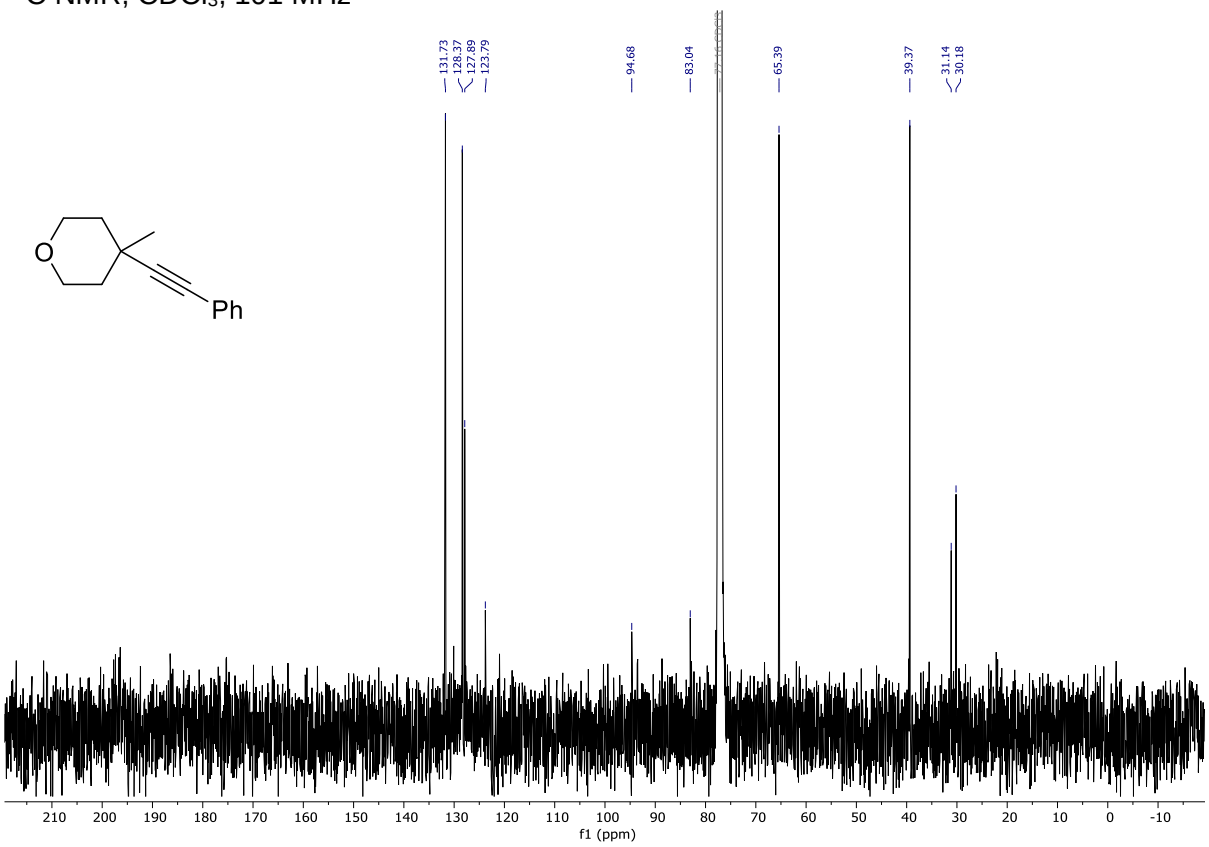


5.11k

^{1}H NMR, $CDCl_3$, 400 MHz

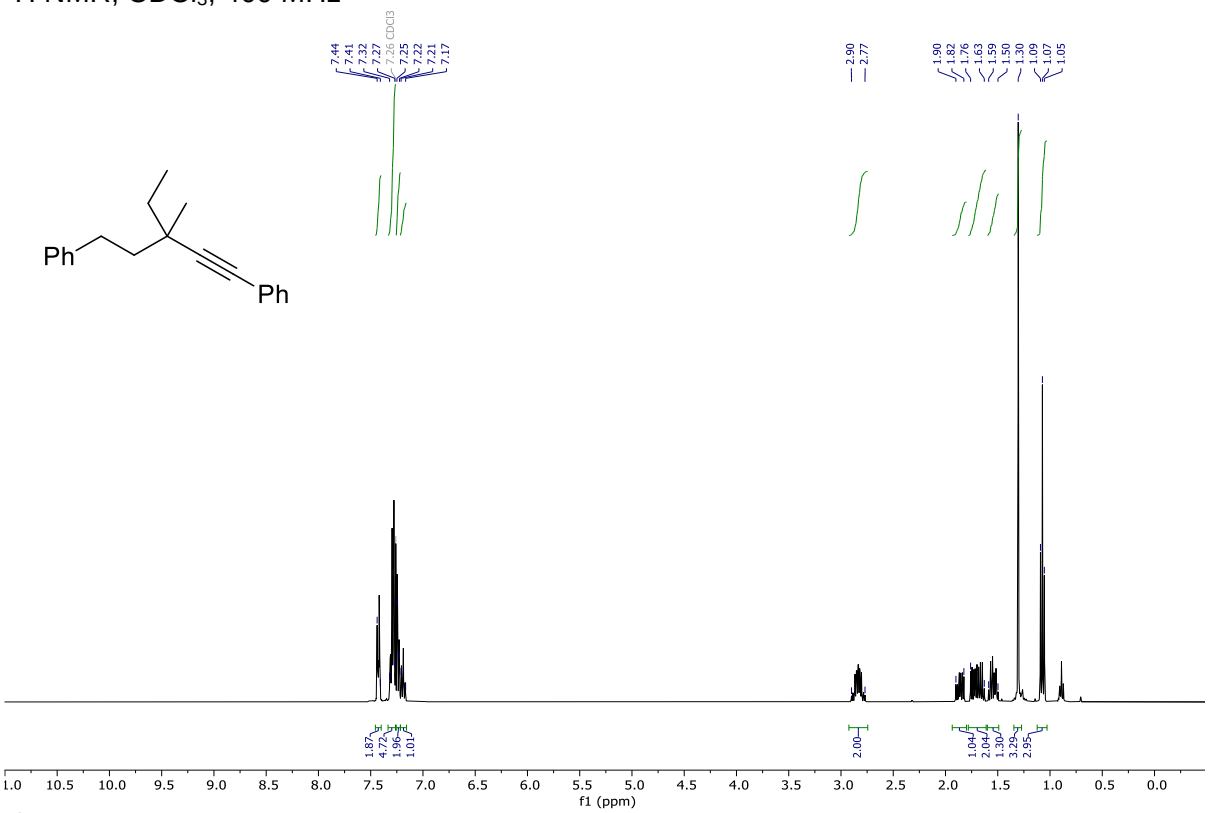


^{13}C NMR, $CDCl_3$, 101 MHz

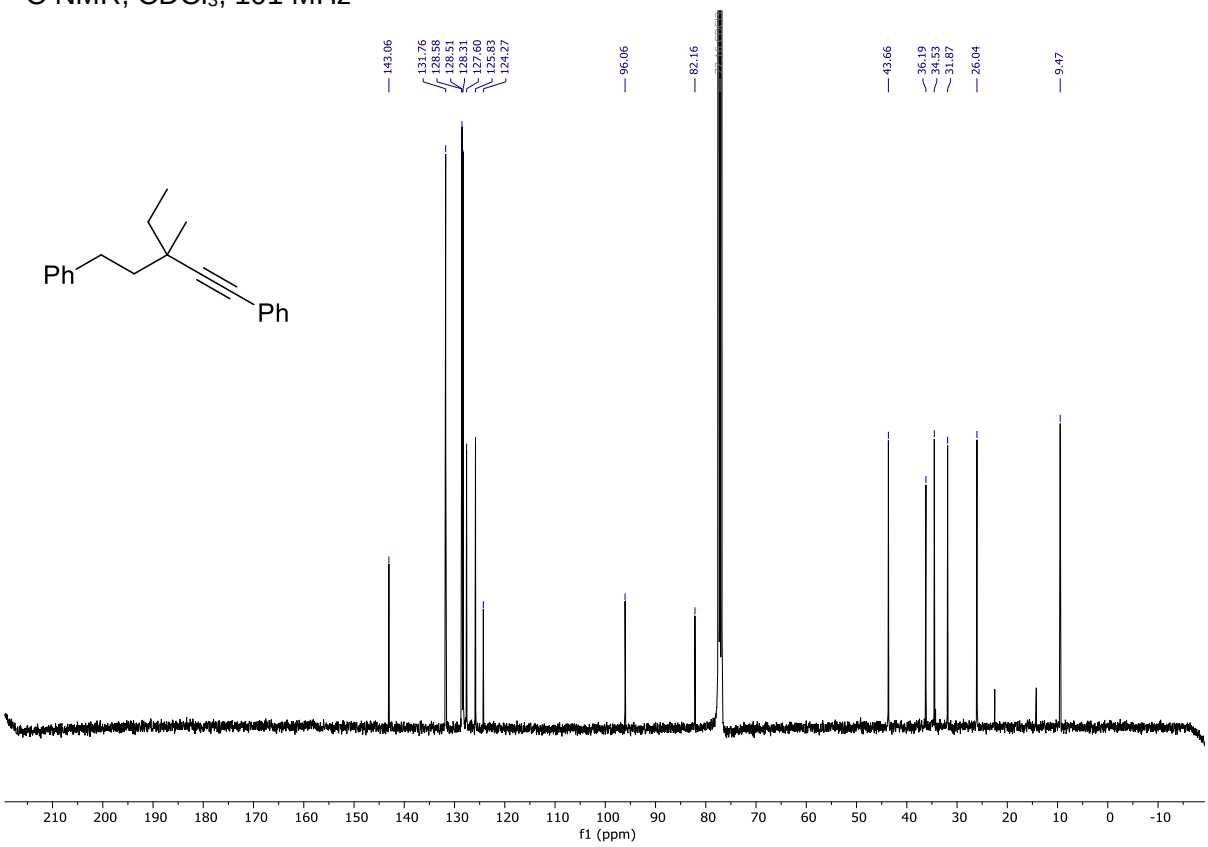


5.11l

^{1}H NMR, $CDCl_3$, 400 MHz

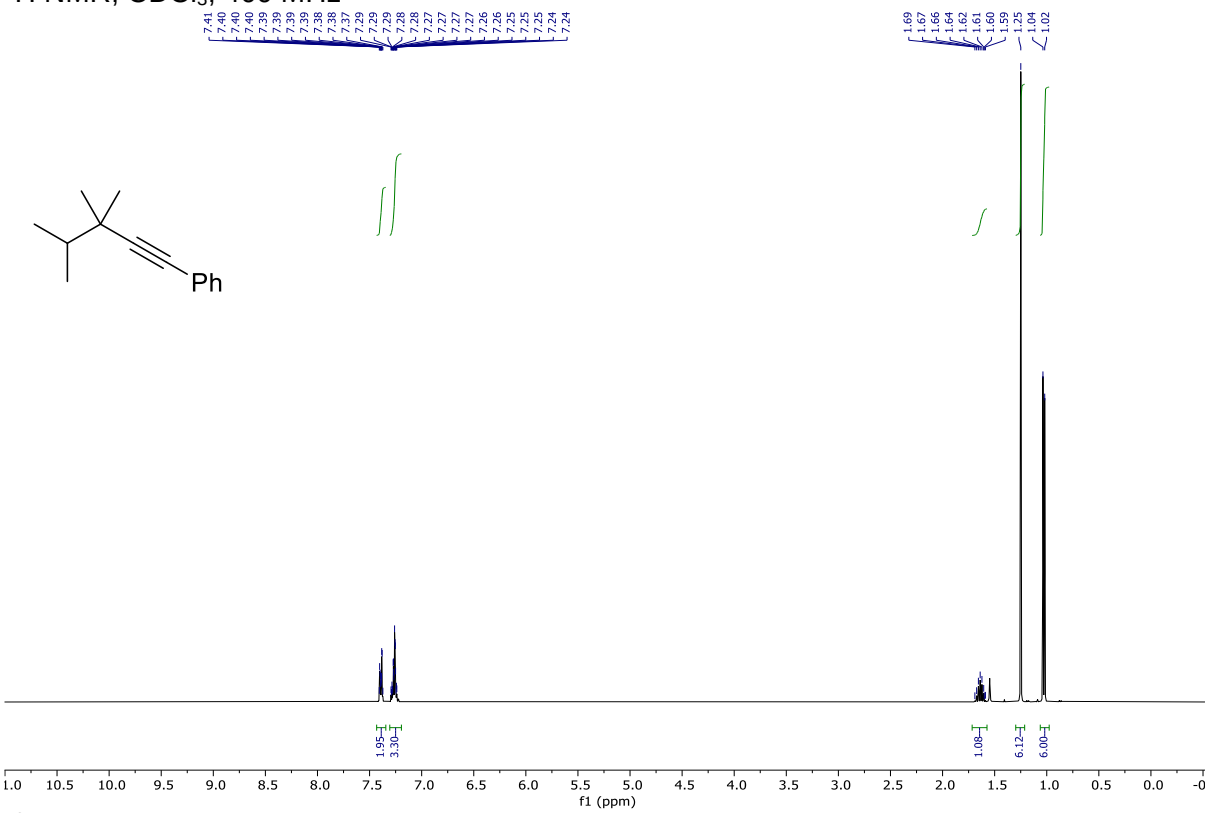


^{13}C NMR, $CDCl_3$, 101 MHz

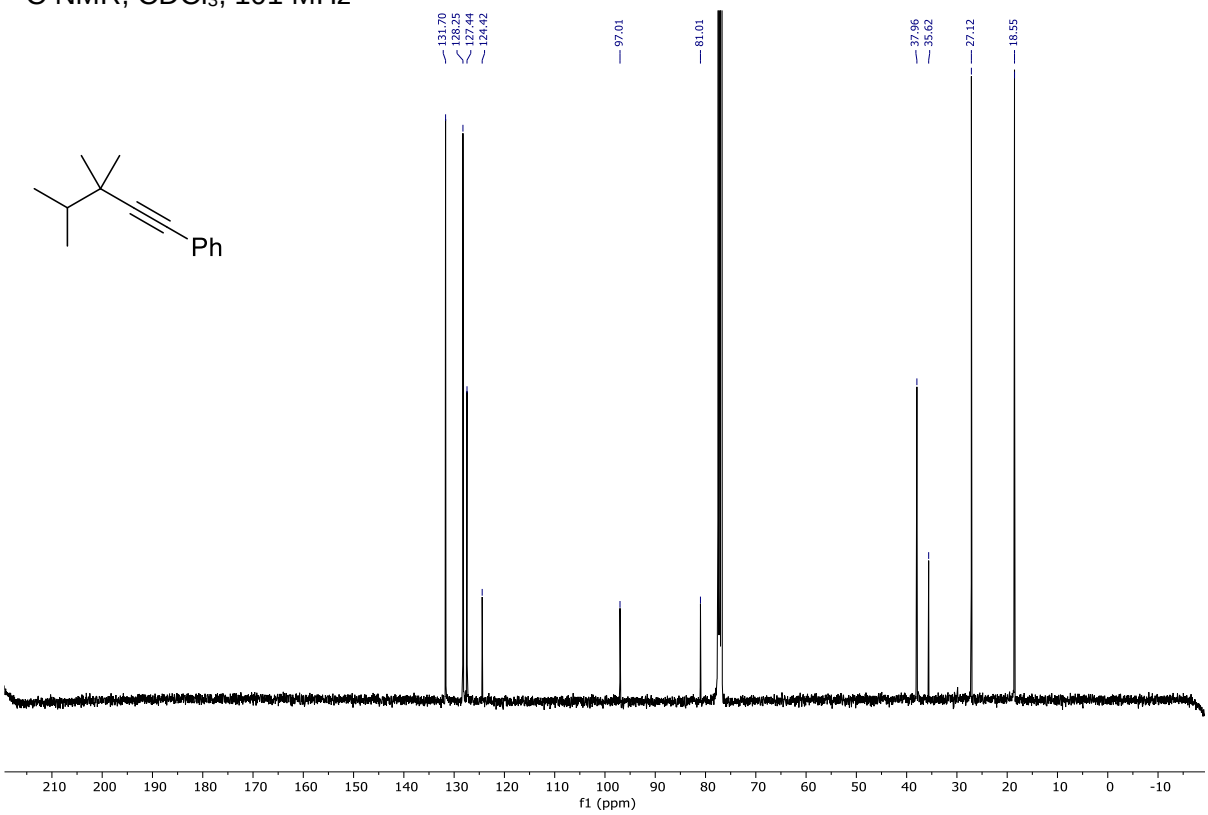


5.11m

^{1}H NMR, $CDCl_3$, 400 MHz

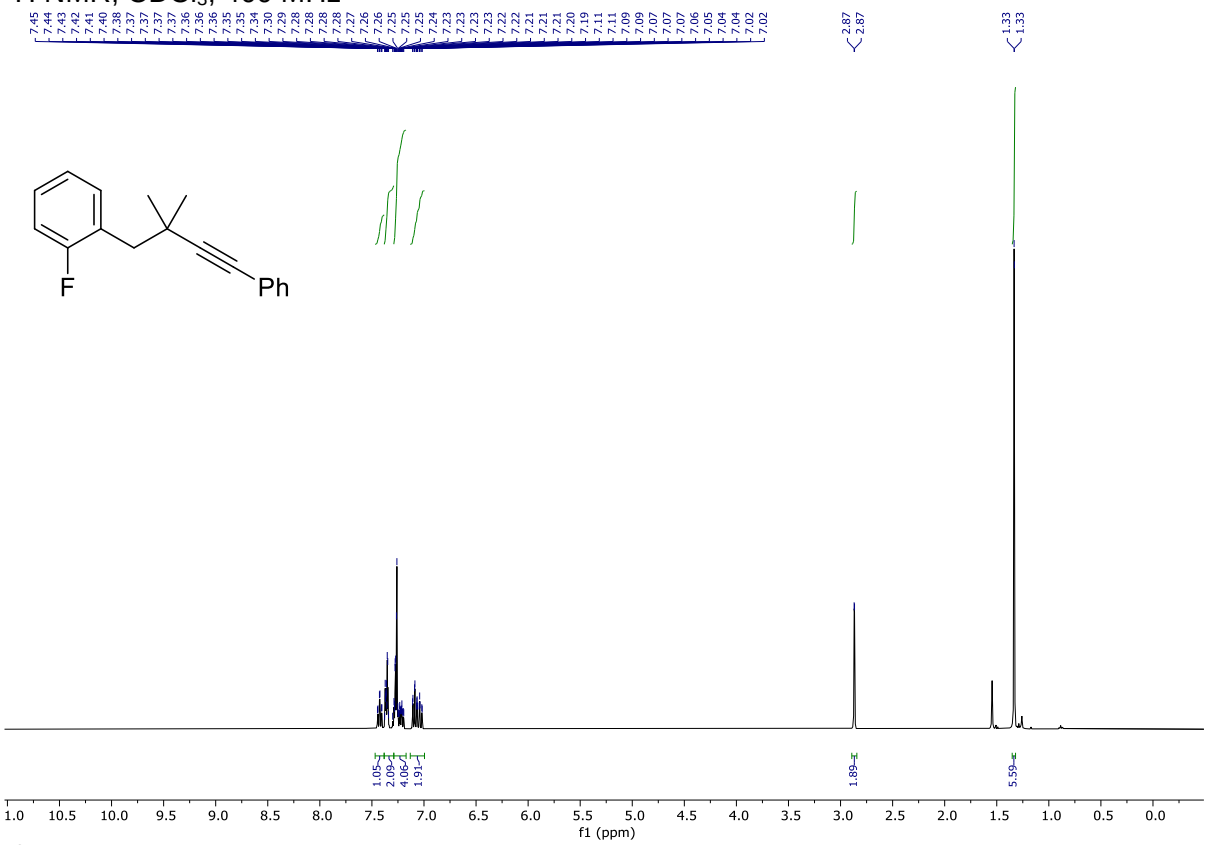


^{13}C NMR, $CDCl_3$, 101 MHz

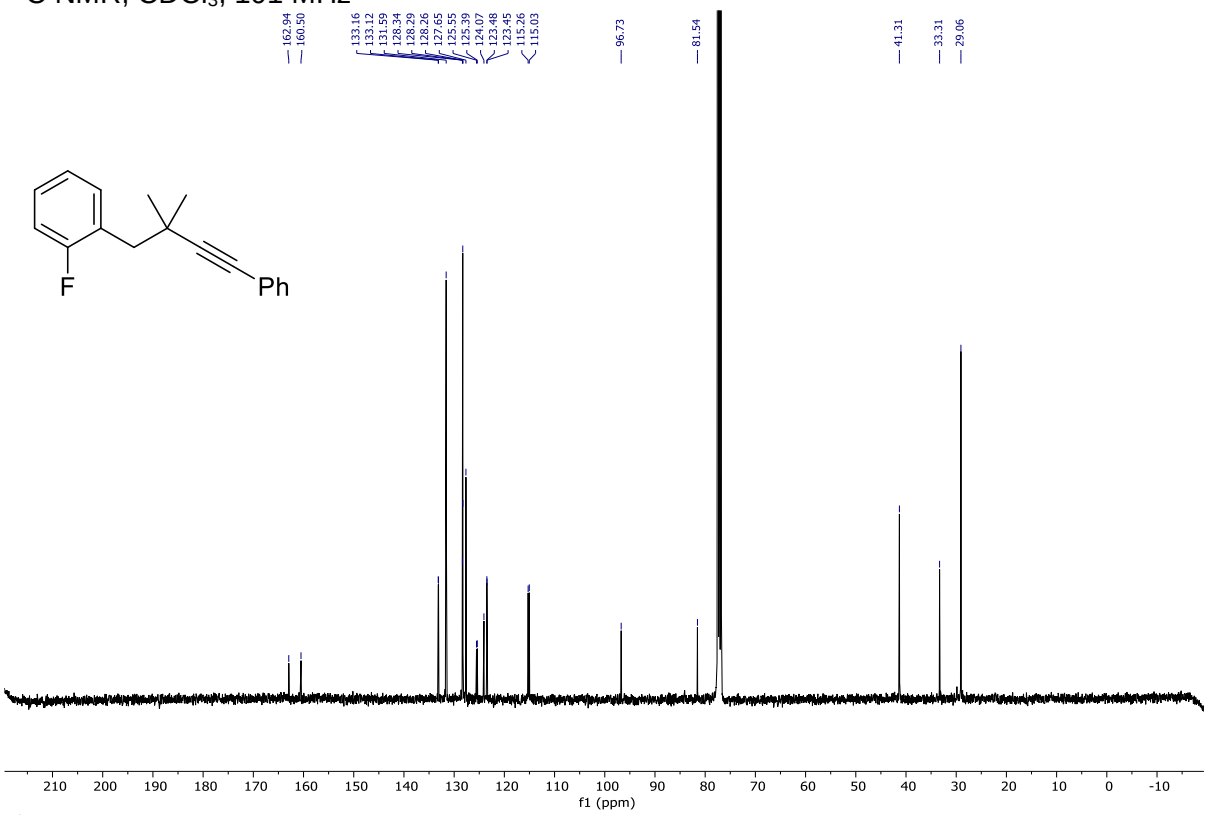


5.11n

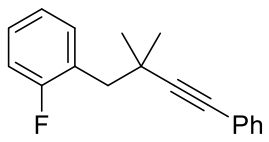
^{1}H NMR, $CDCl_3$, 400 MHz

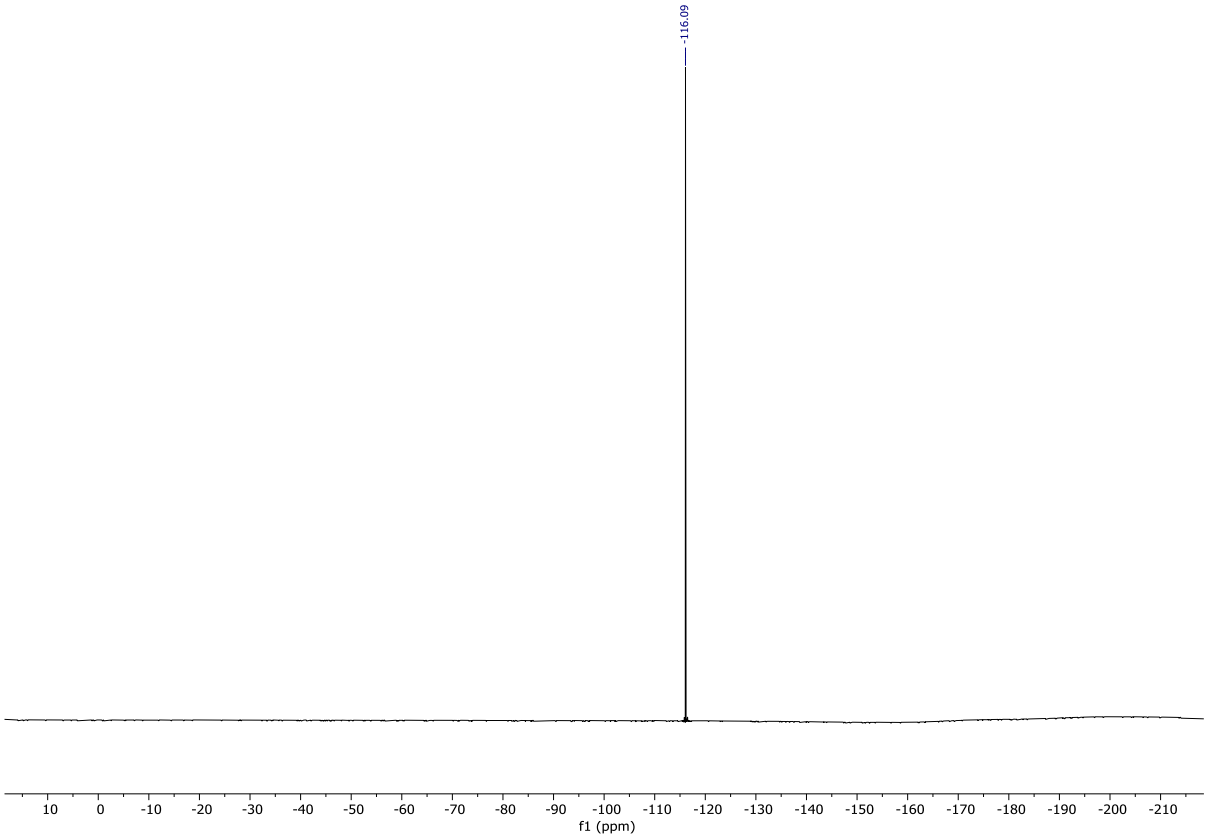


^{13}C NMR, $CDCl_3$, 101 MHz



^{19}F NMR, $CDCl_3$, 376 MHz

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-100
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-130
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-150
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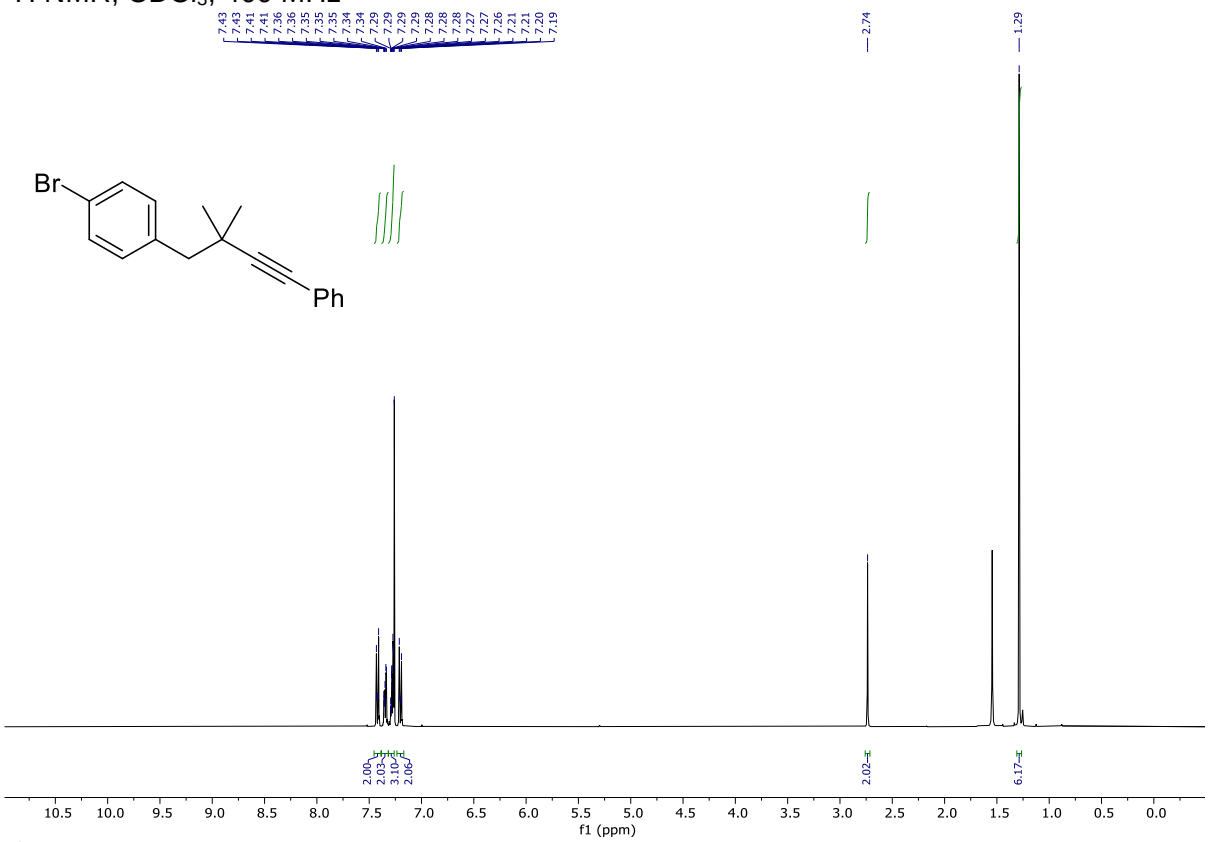
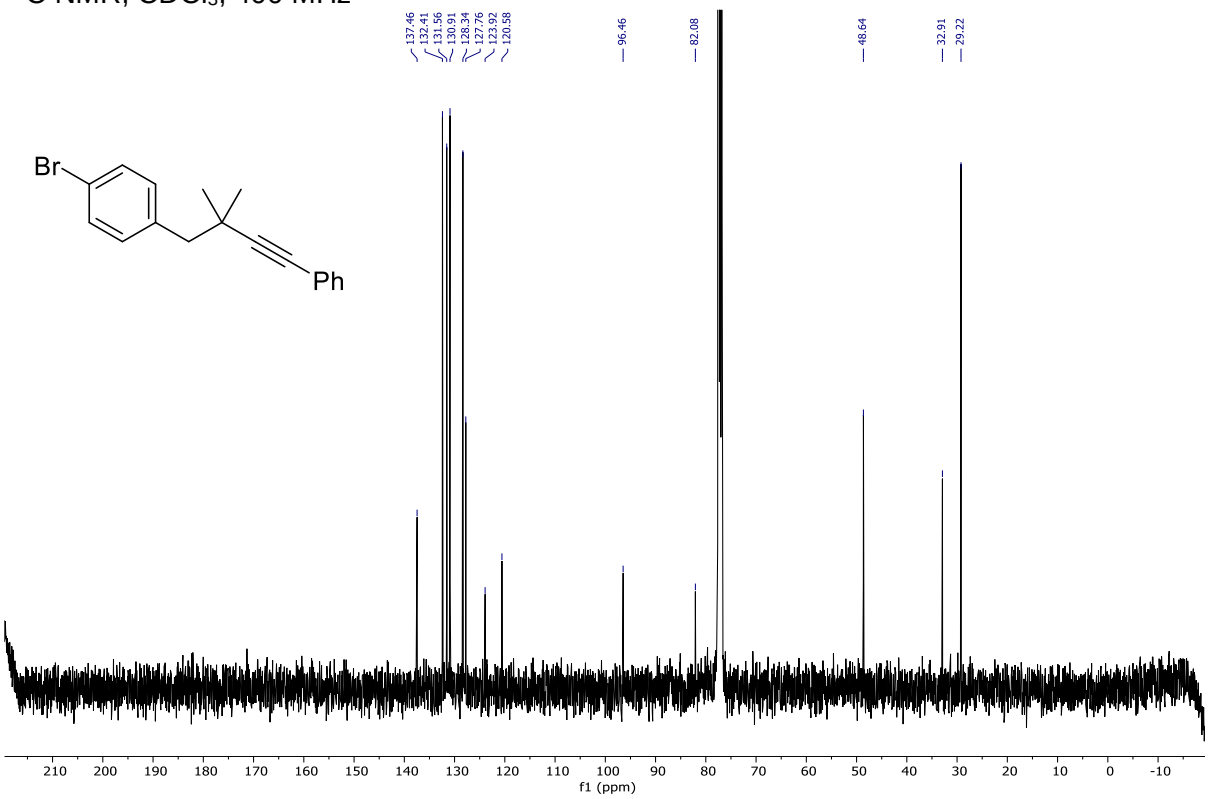
-170
-180
-190
-200
-210
f1 (ppm)

5.11o

^{1}H NMR, $CDCl_3$, 400 MHz

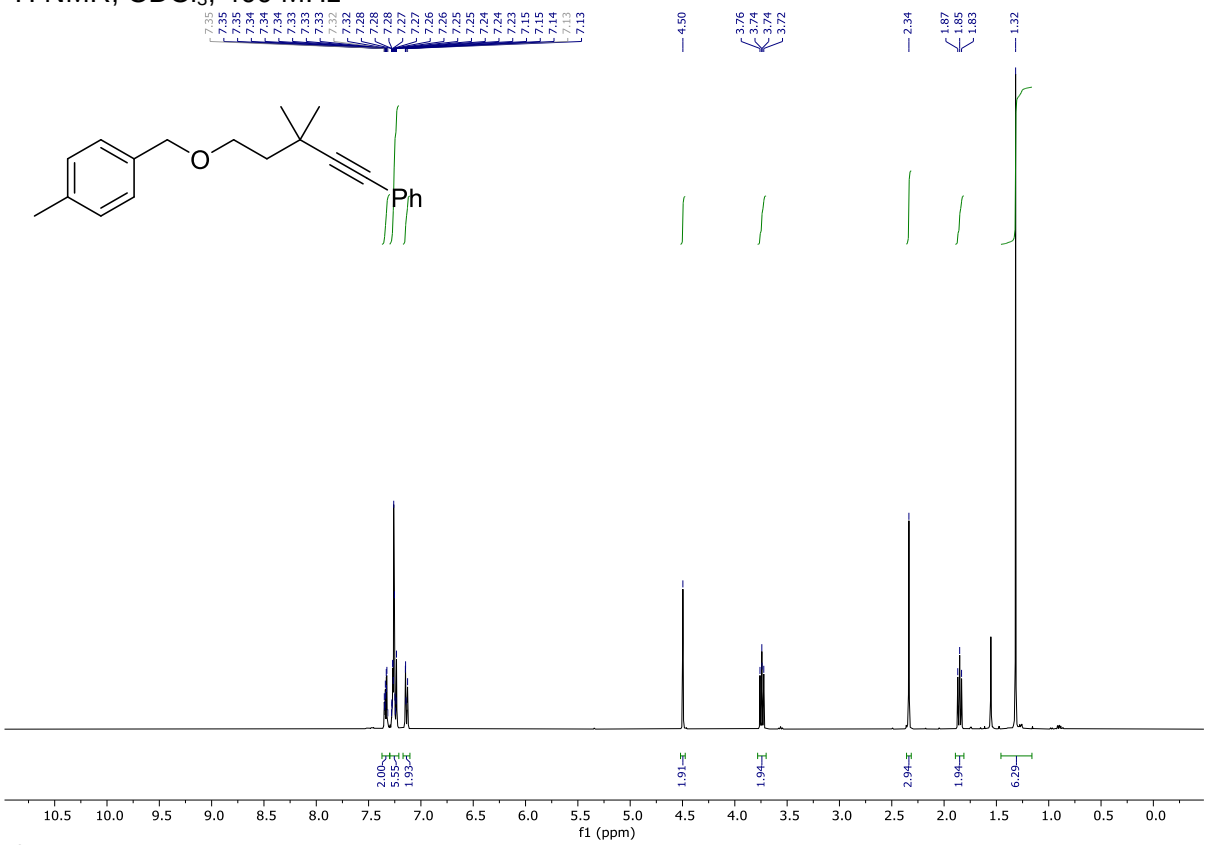


^{13}C NMR, $CDCl_3$, 400 MHz

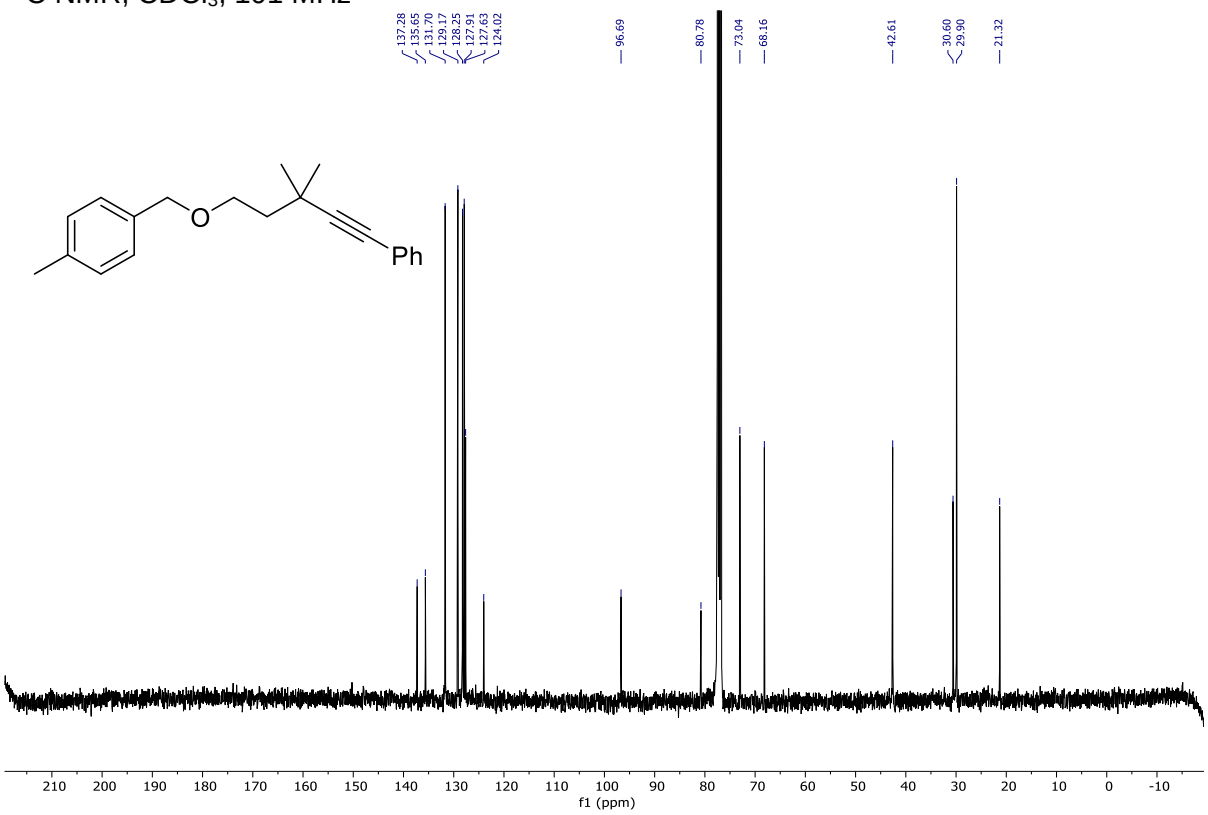


5.11p

^{1}H NMR, $CDCl_3$, 400 MHz

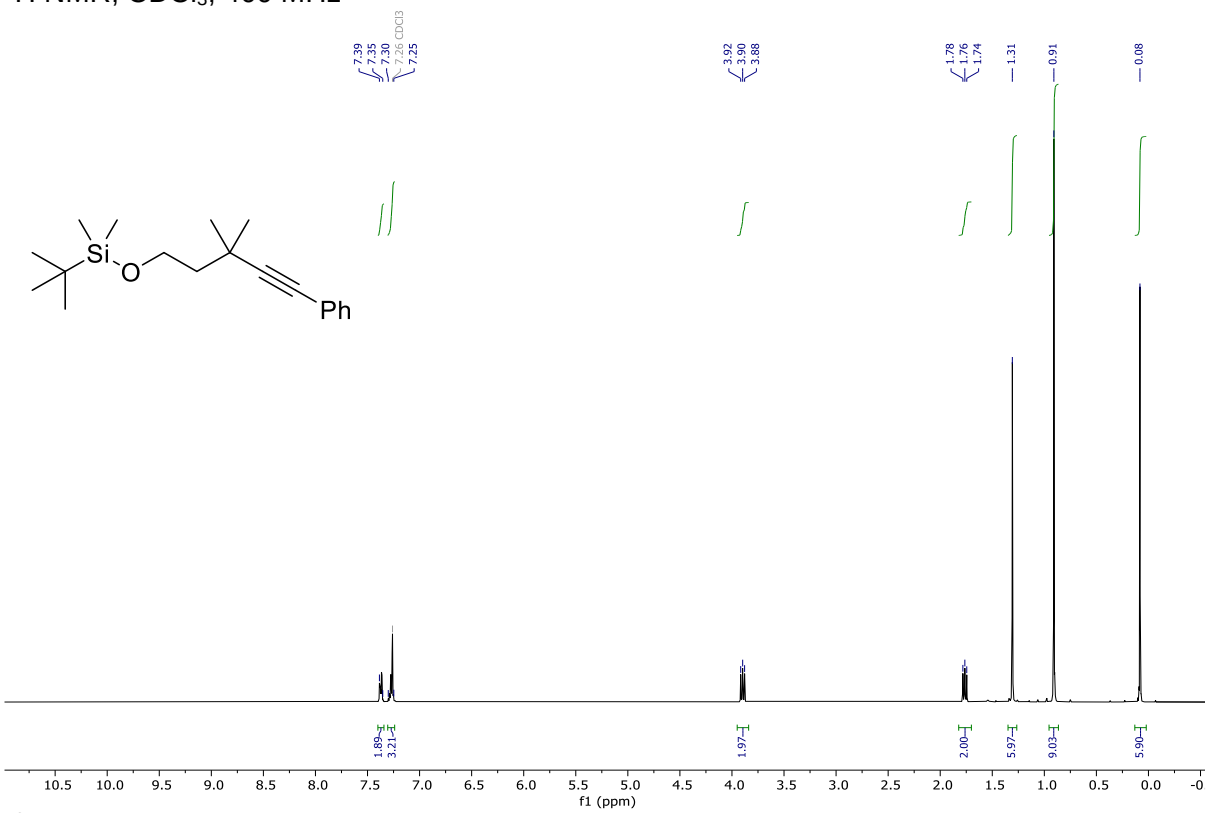


^{13}C NMR, $CDCl_3$, 101 MHz

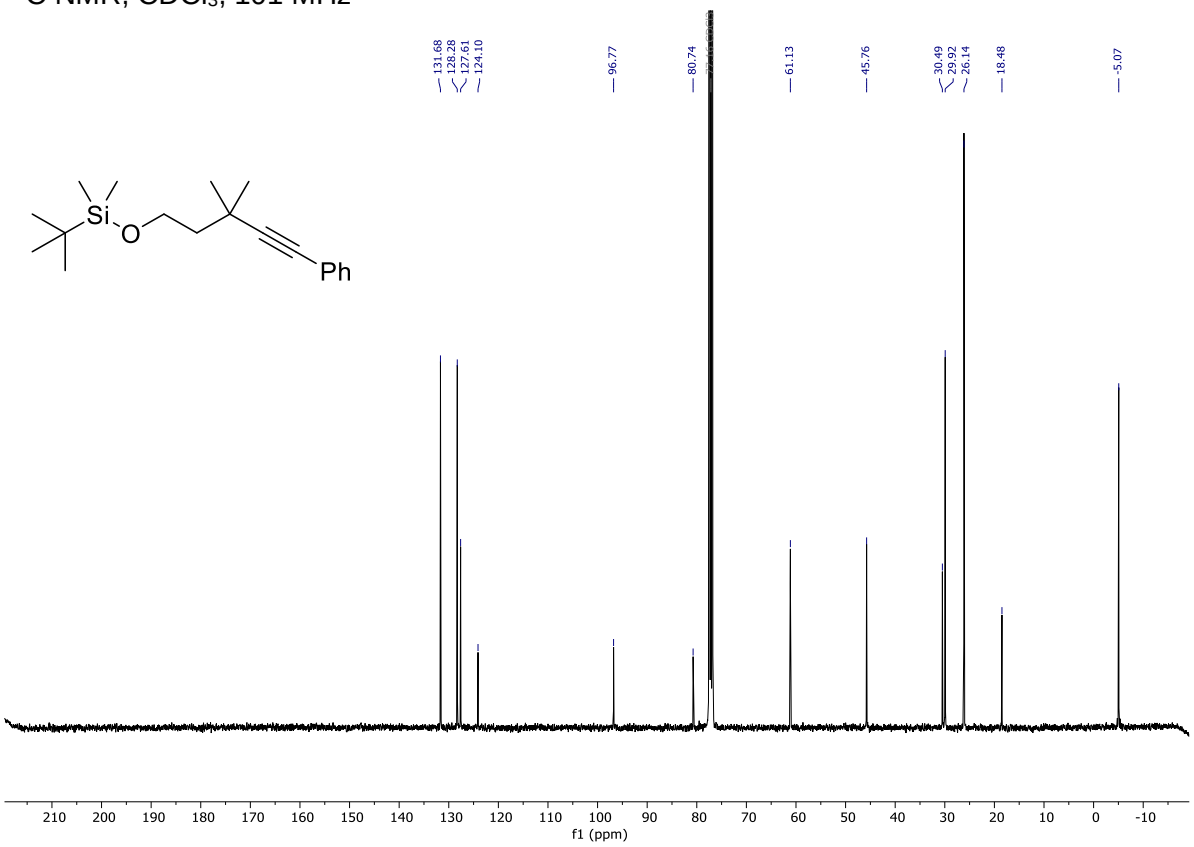


5.11q

^{1}H NMR, $CDCl_3$, 400 MHz

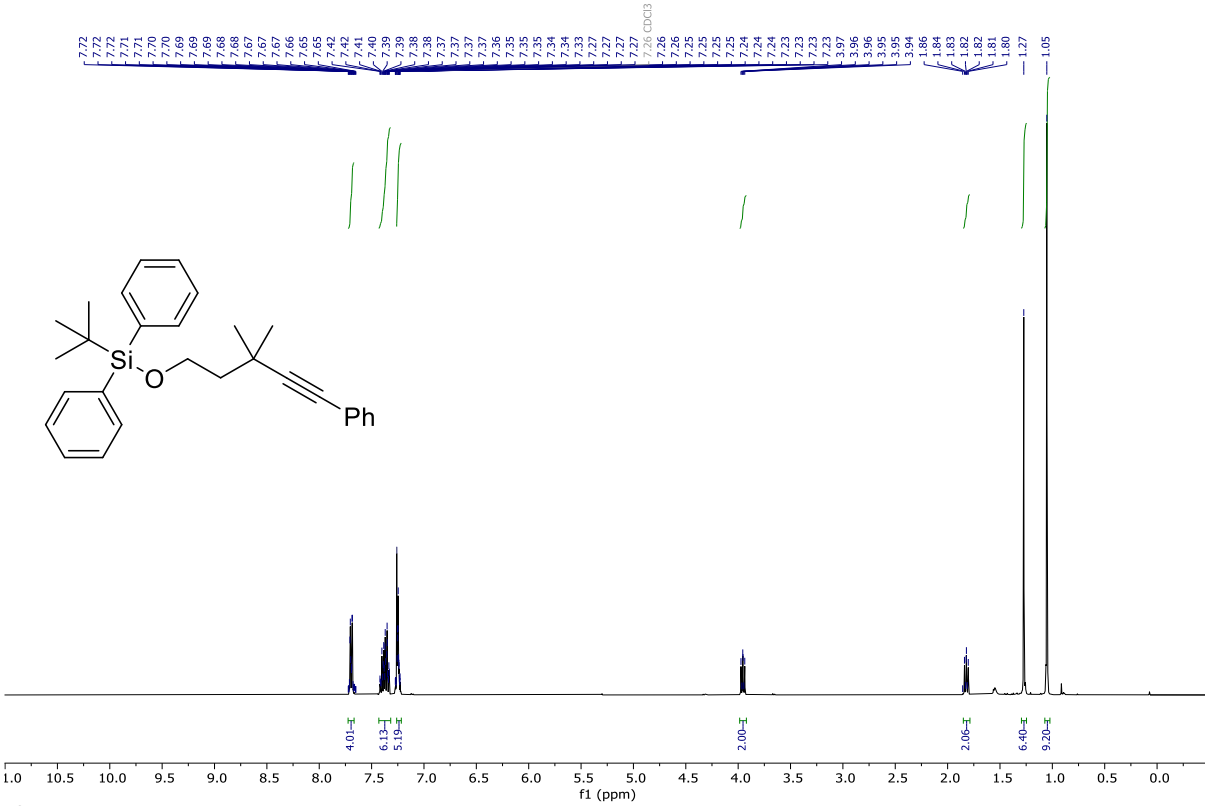


^{13}C NMR, $CDCl_3$, 101 MHz

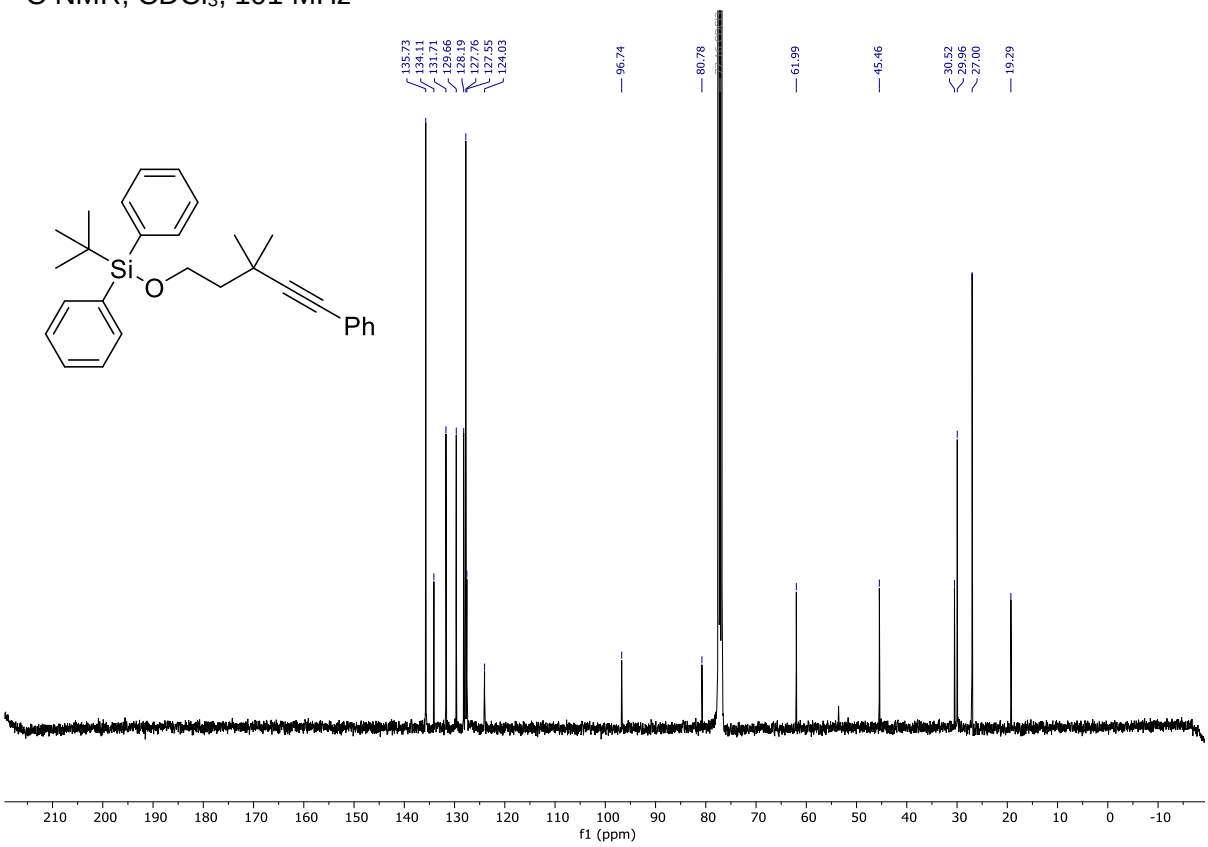


5.11r

^{1}H NMR, $CDCl_3$, 400 MHz

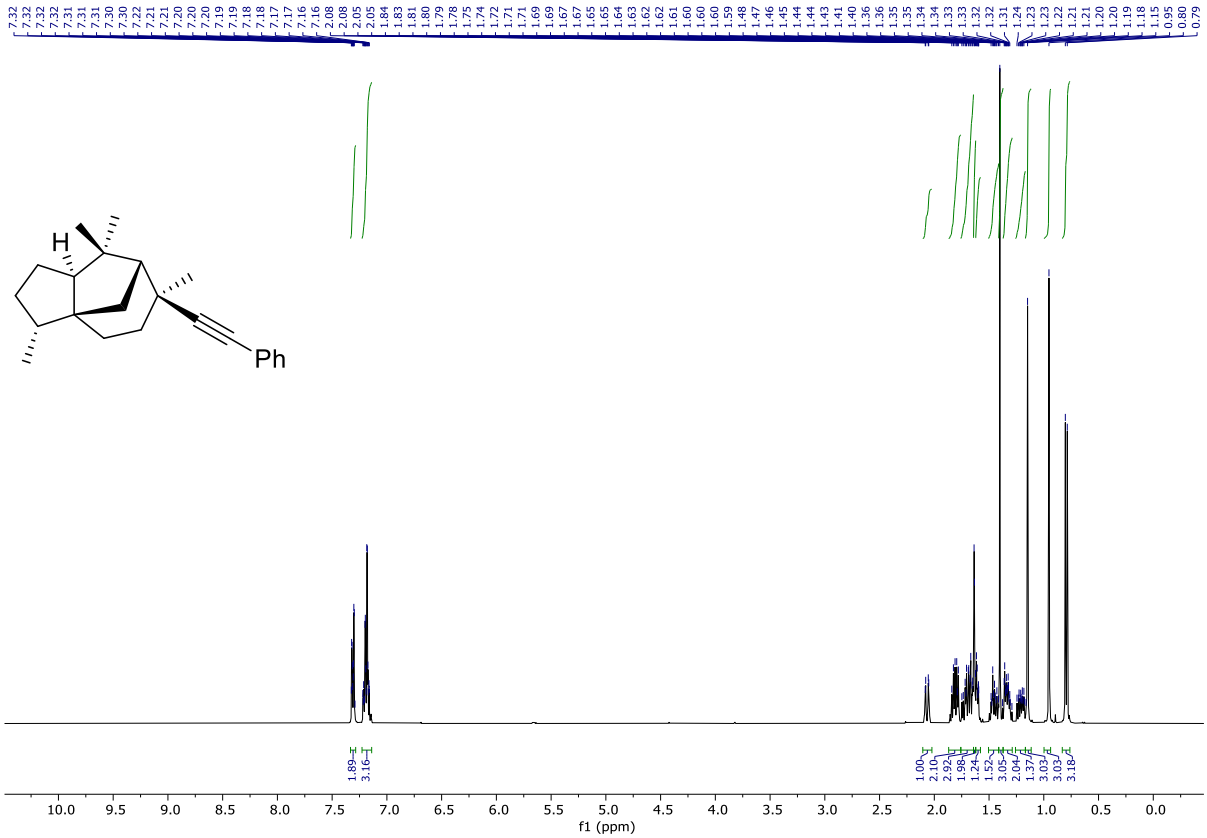


^{13}C NMR, $CDCl_3$, 101 MHz

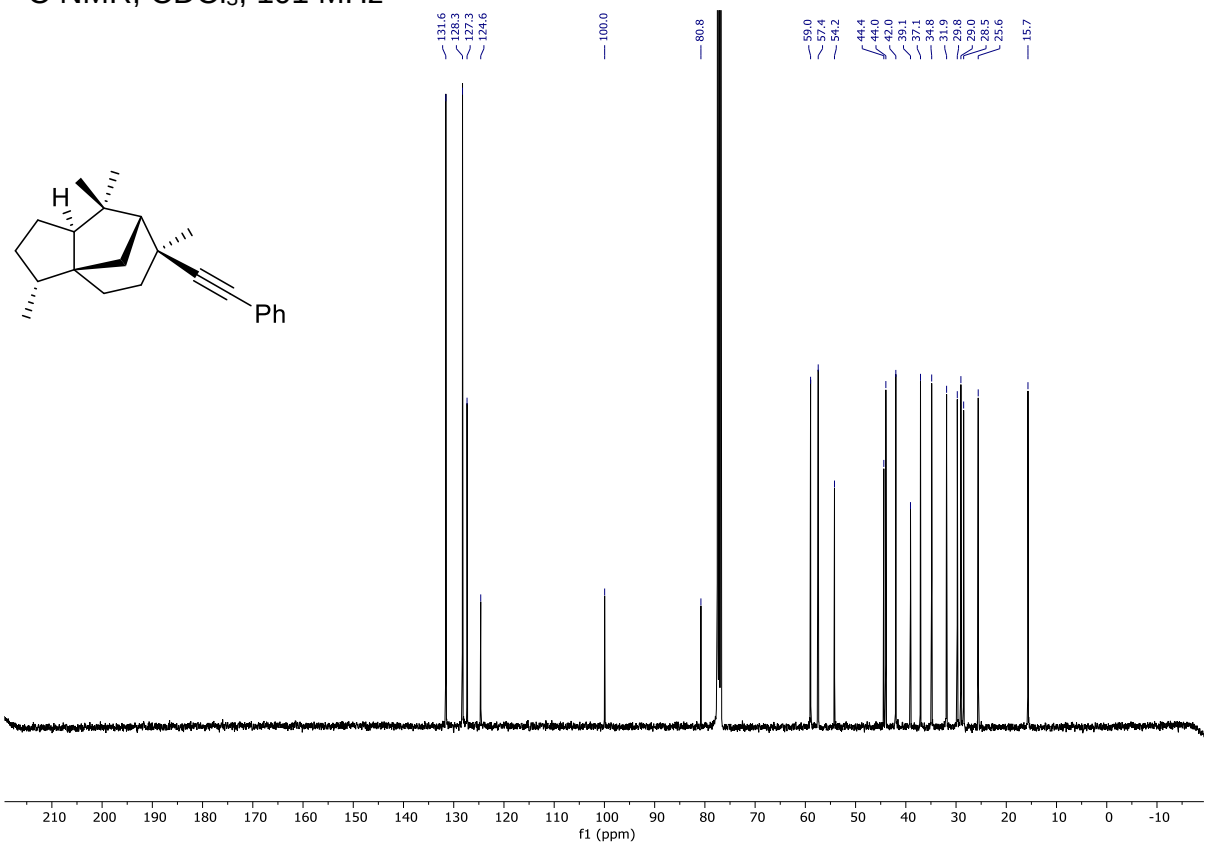


5.11u

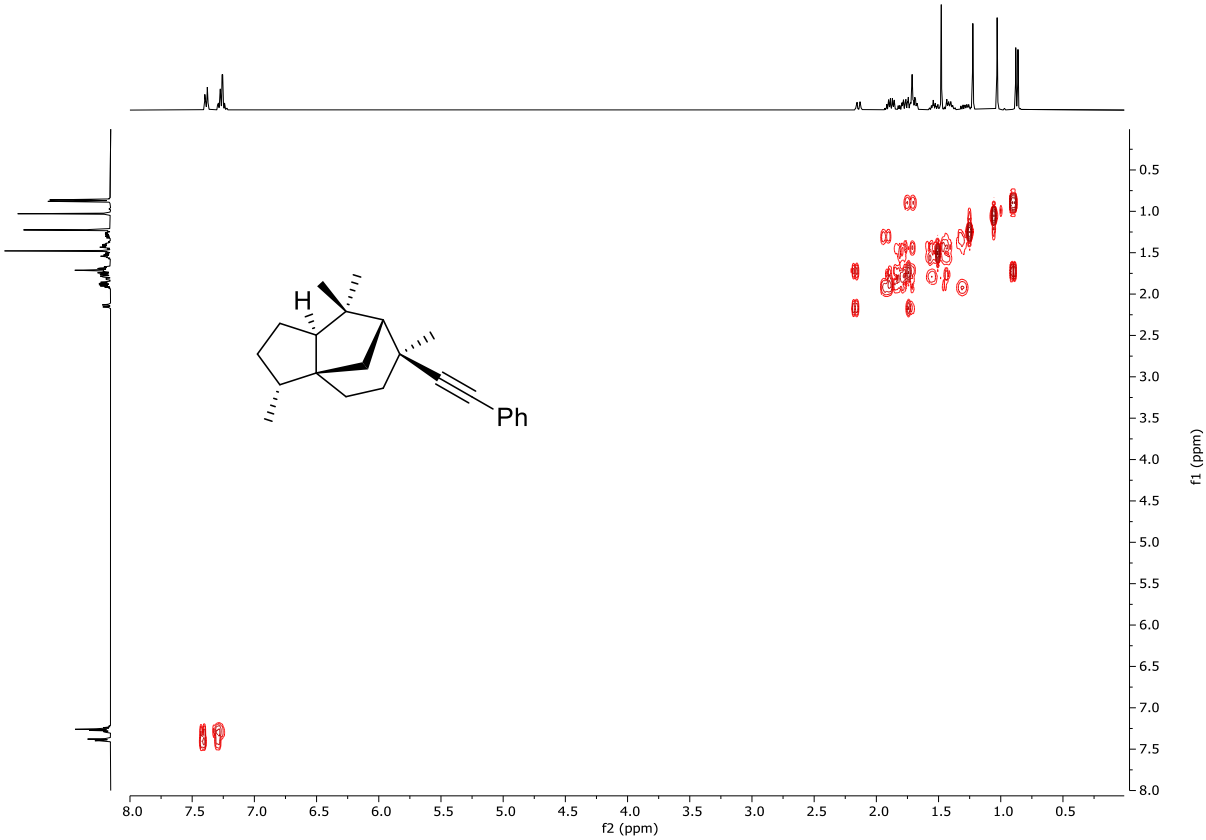
^{1}H NMR, $CDCl_3$,400 MHz



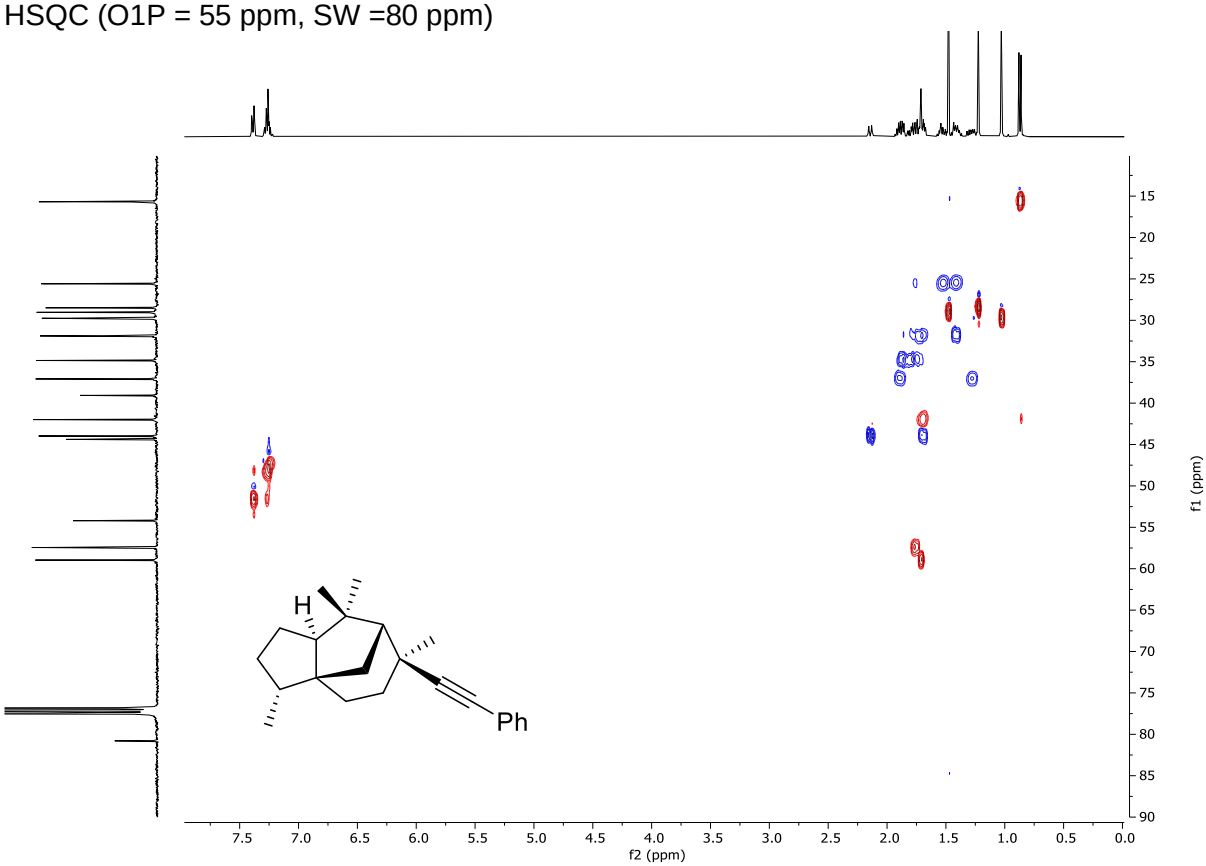
^{13}C NMR, $CDCl_3$, 101 MHz



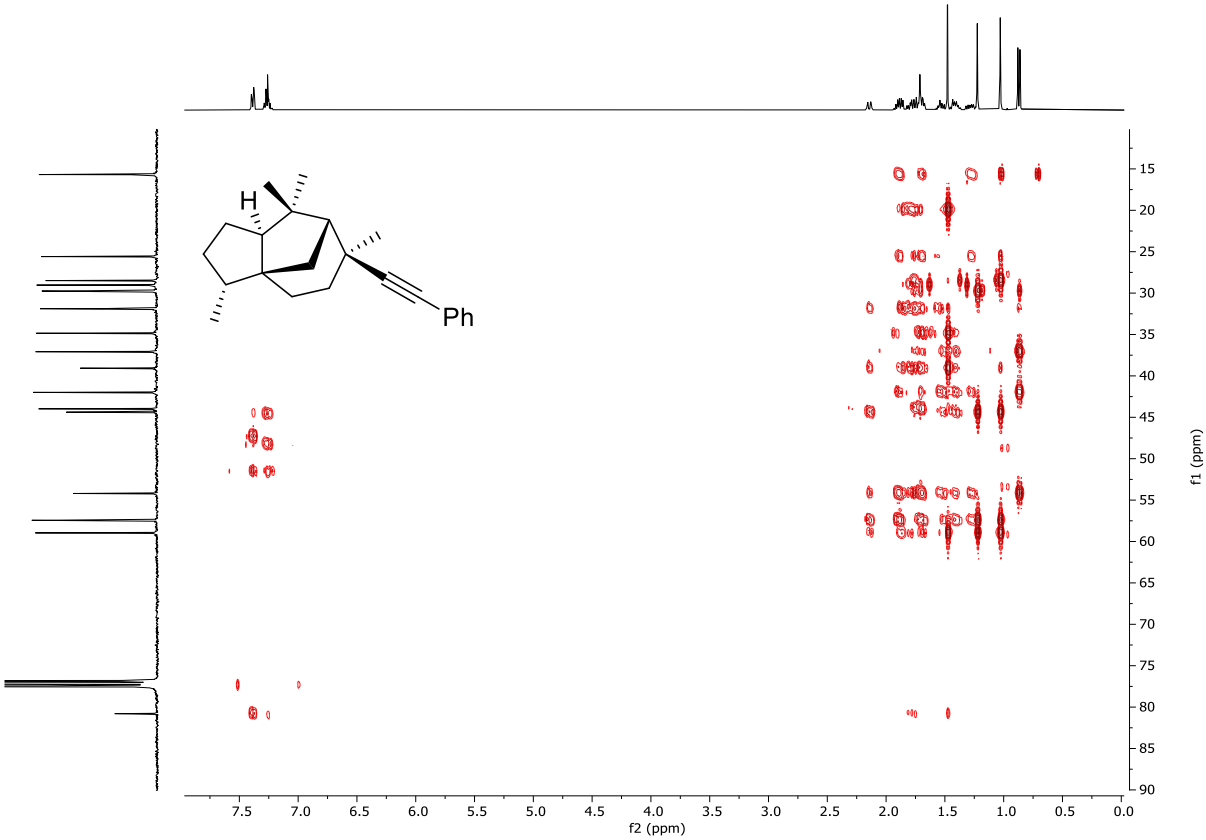
COSY



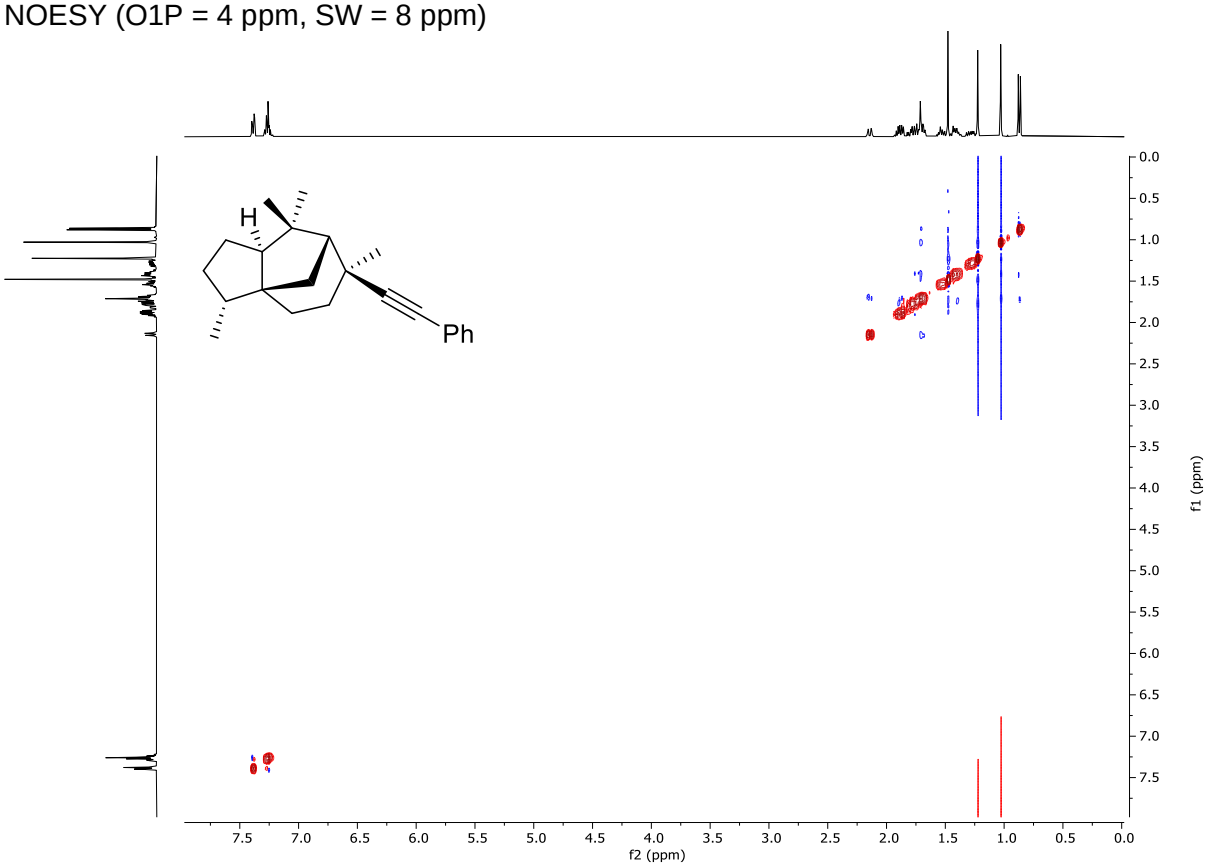
HSQC (O1P = 55 ppm, SW =80 ppm)



HMBC (O1P = 55 ppm; SW = 80 ppm)

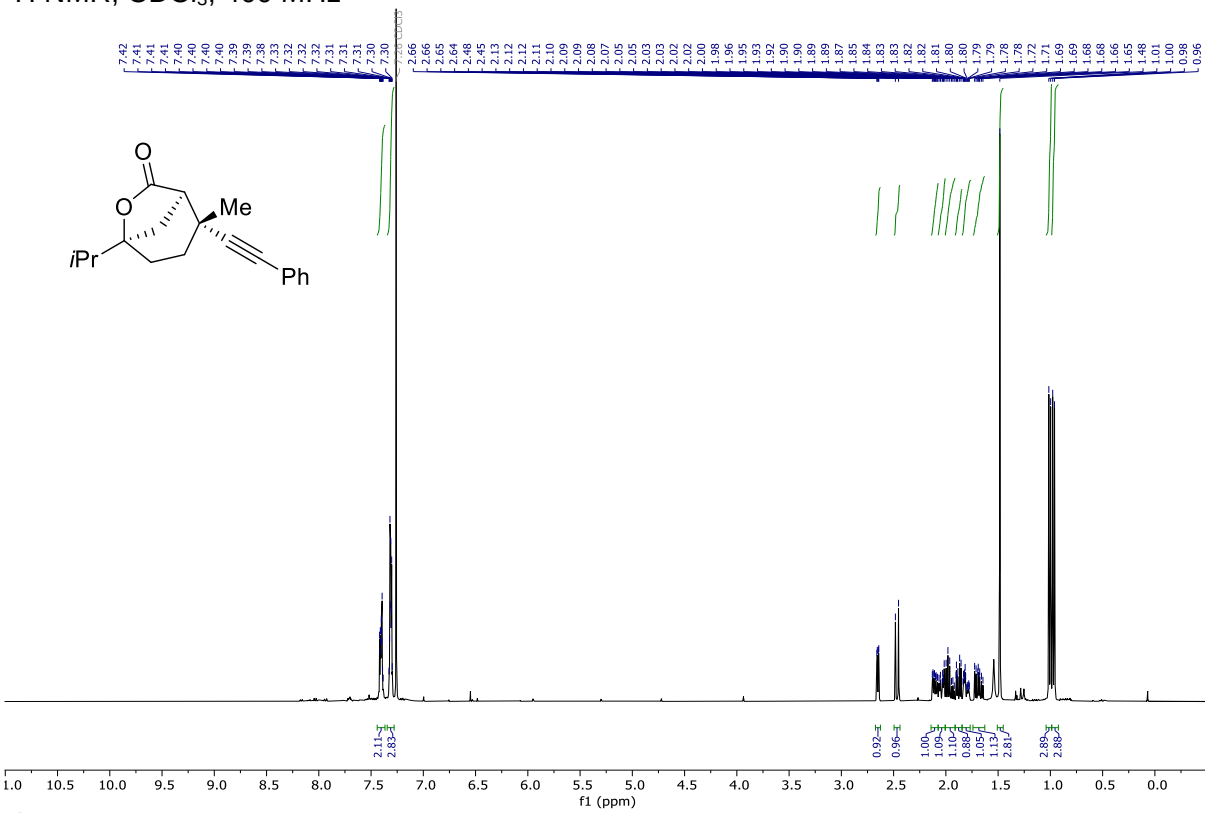


NOESY (O1P = 4 ppm, SW = 8 ppm)

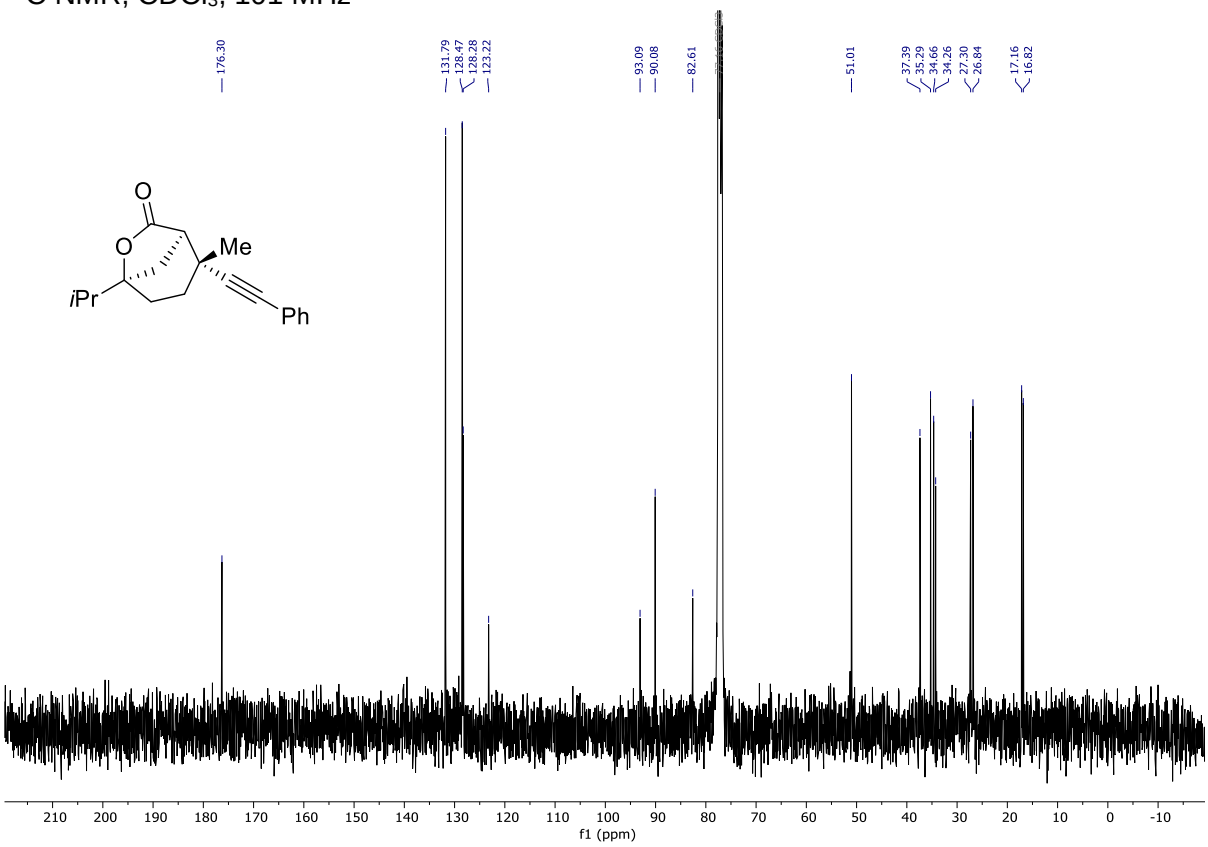


5.11v

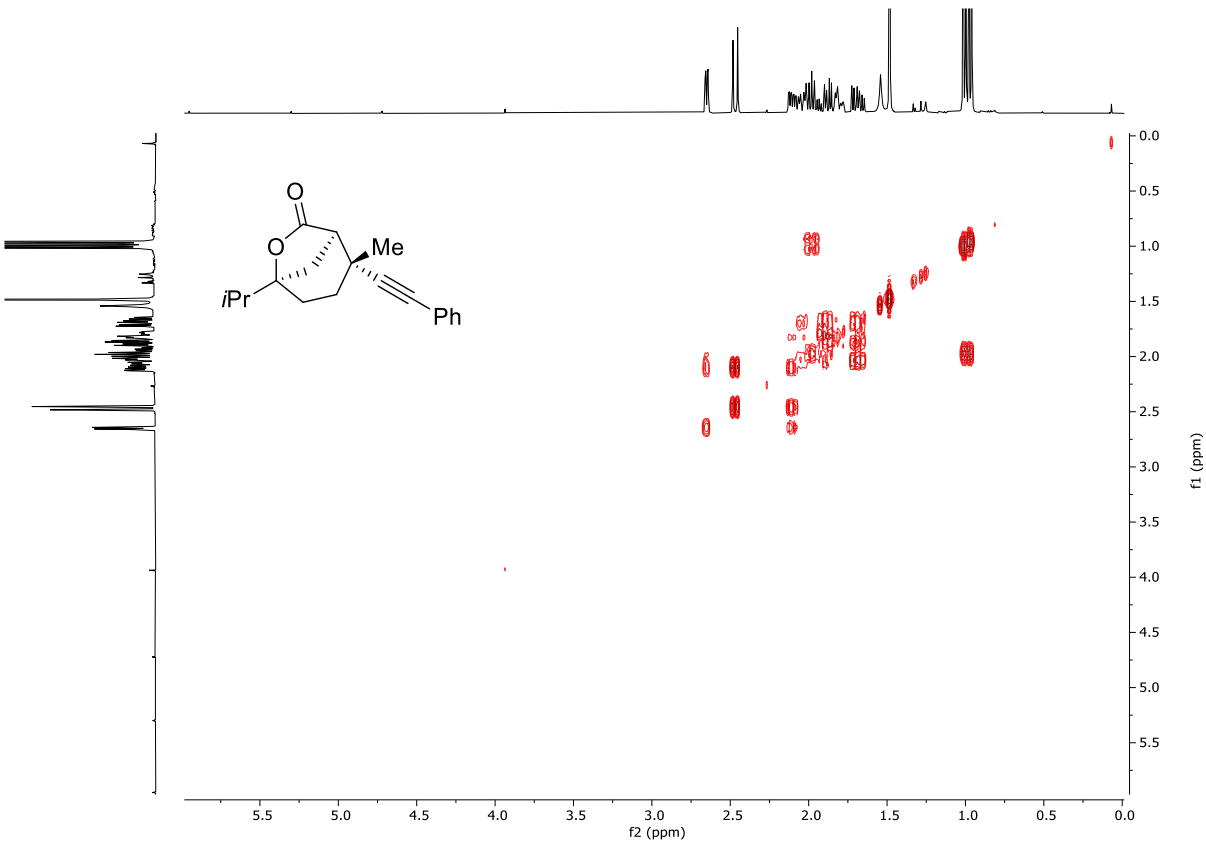
^{1}H NMR, $CDCl_3$, 400 MHz



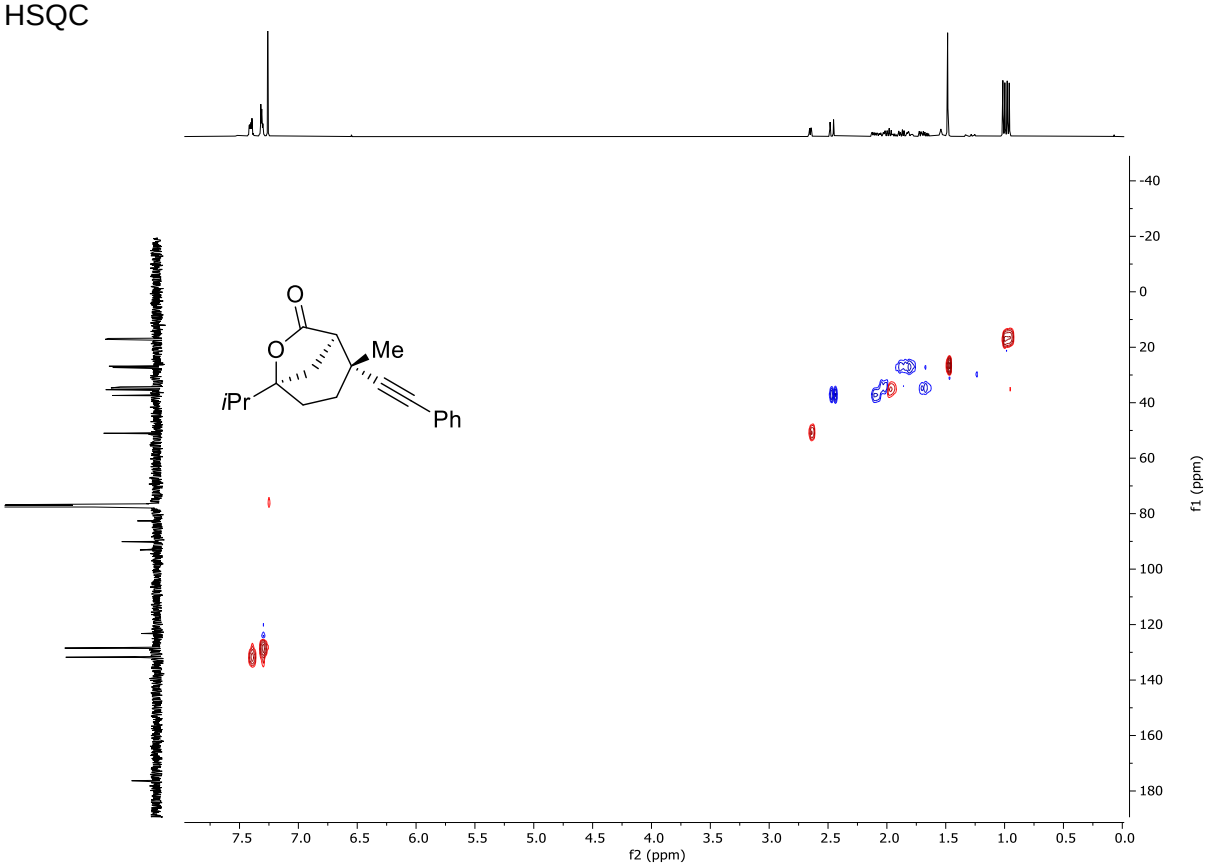
^{13}C NMR, $CDCl_3$, 101 MHz



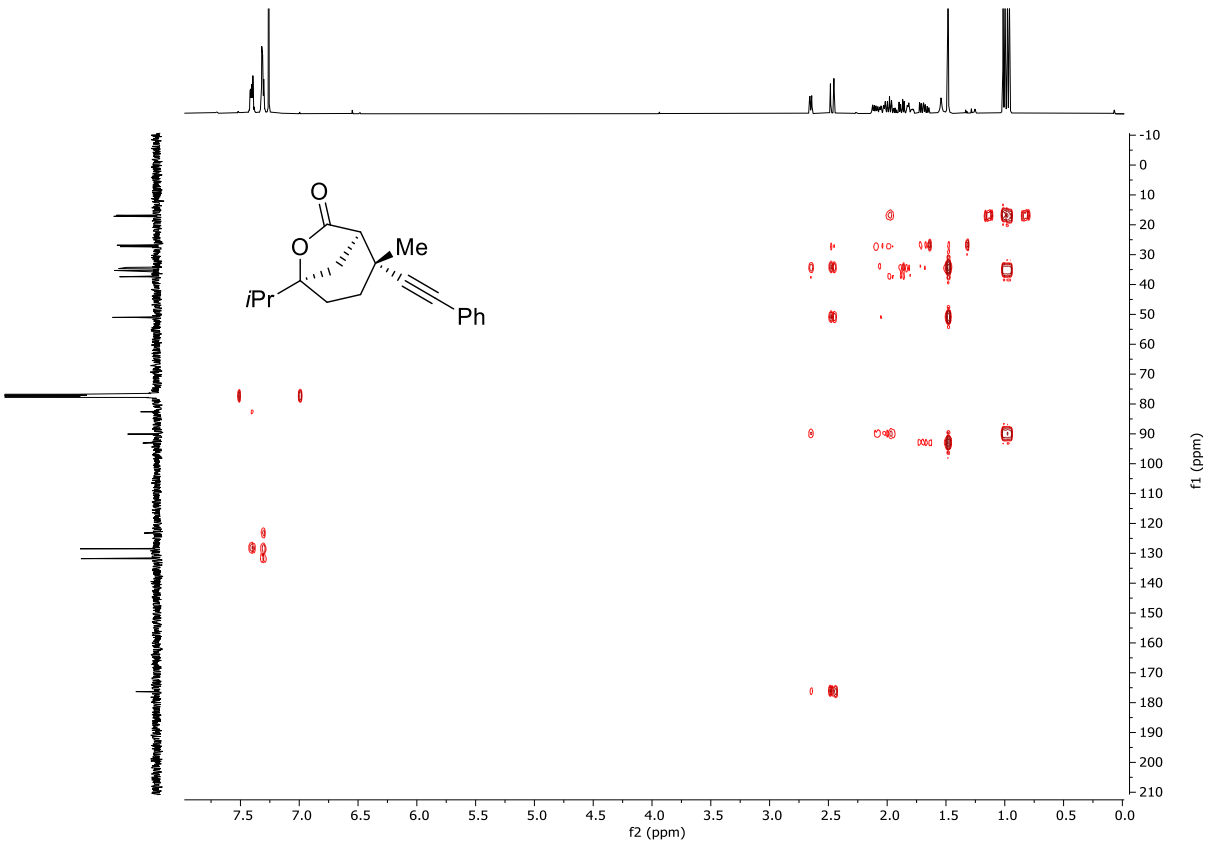
COSY (O1P = 3 ppm; SW = 6 ppm)



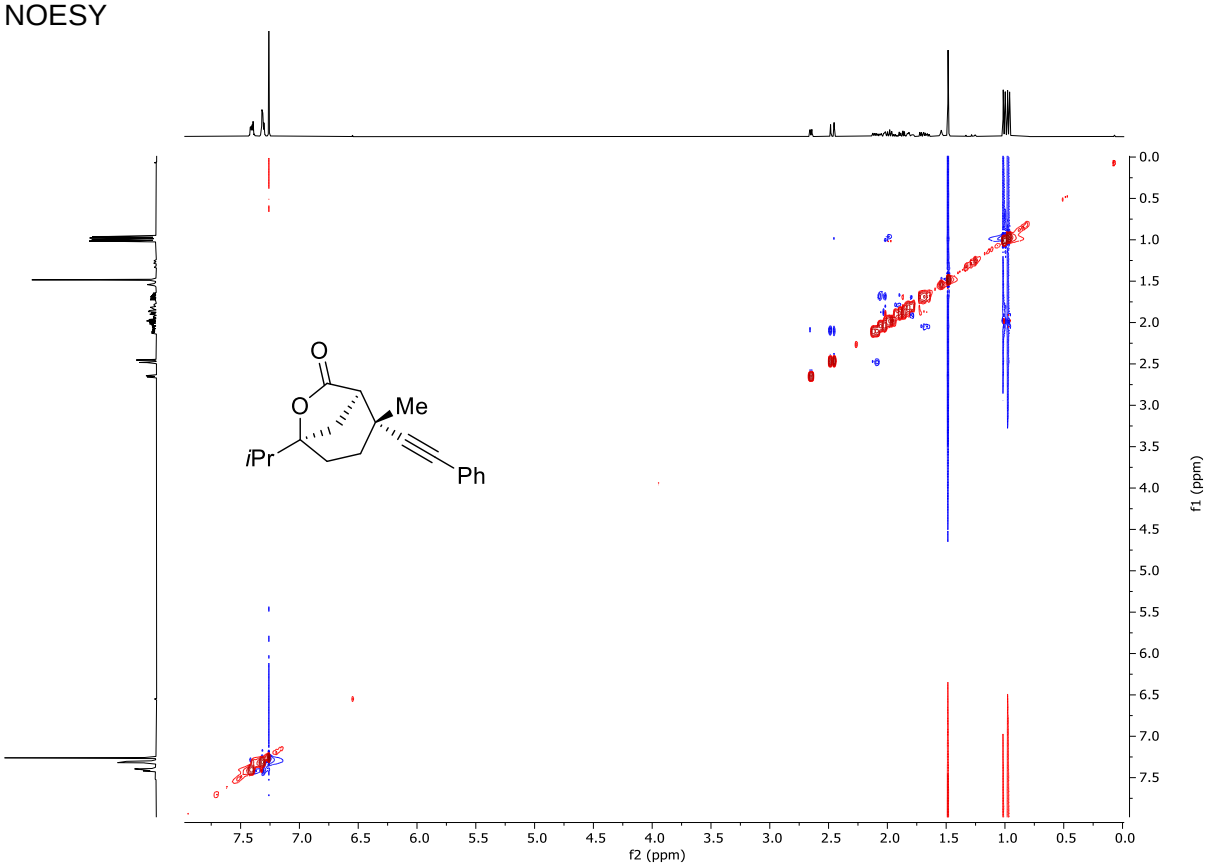
HSQC



HMBC

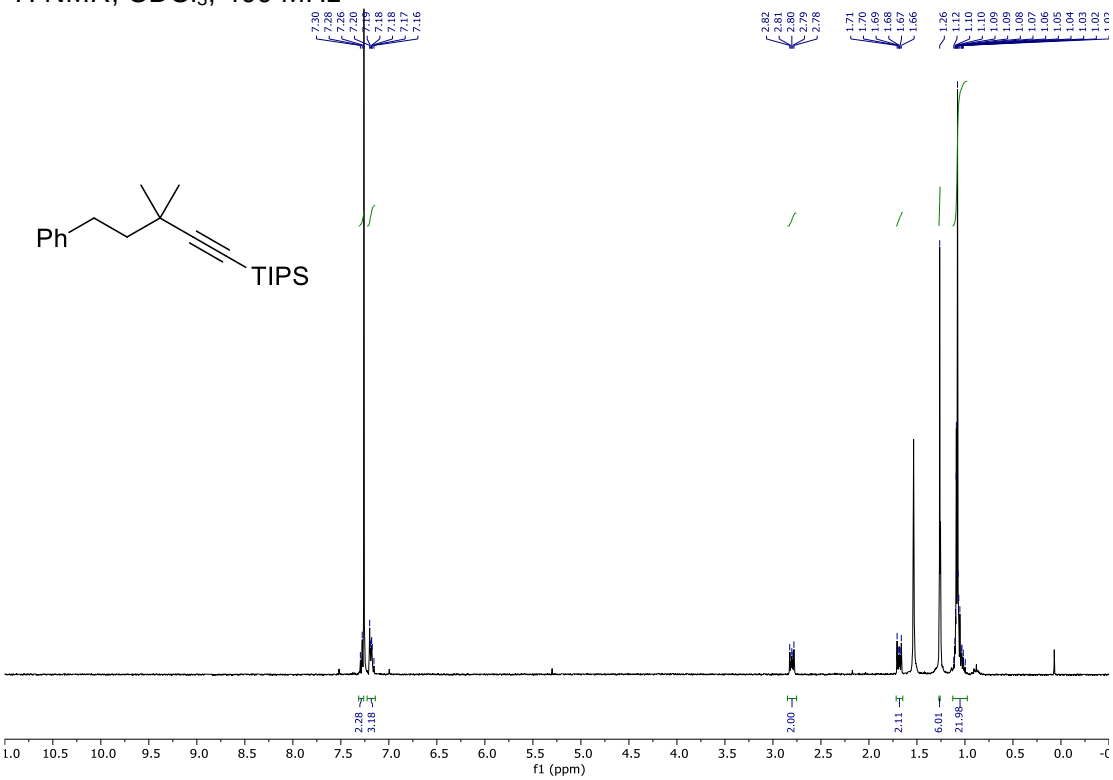


NOESY

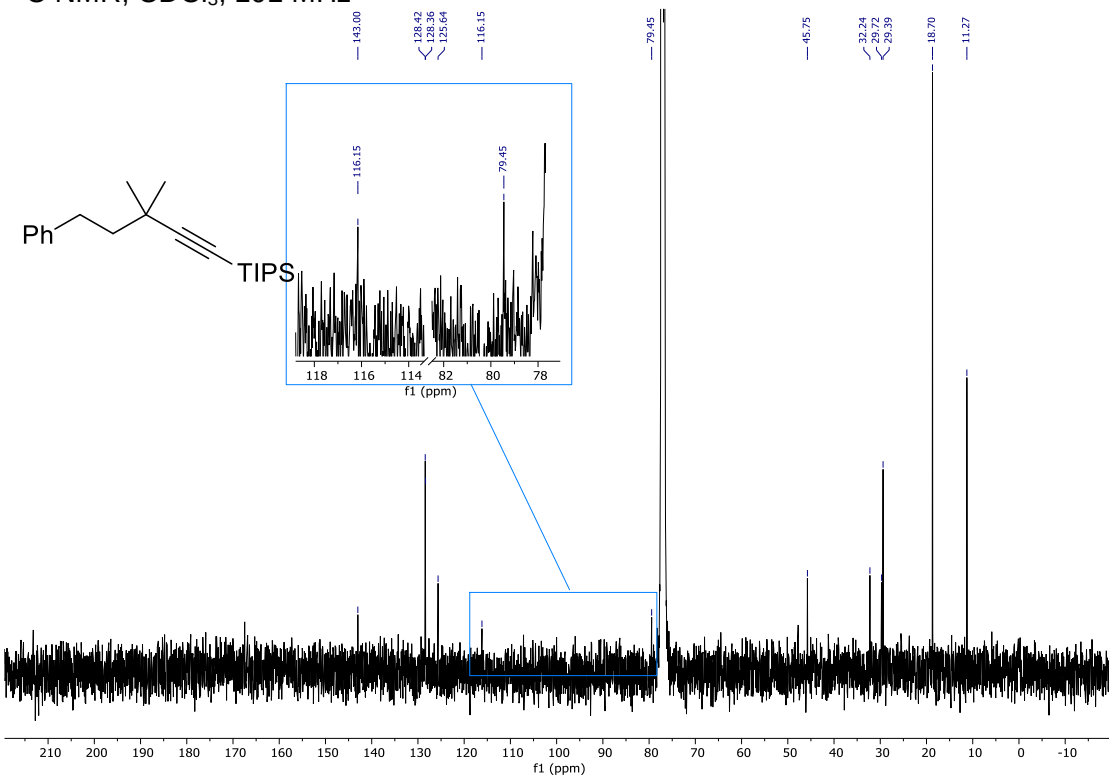


5.14a

^{1}H NMR, $CDCl_3$, 400 MHz

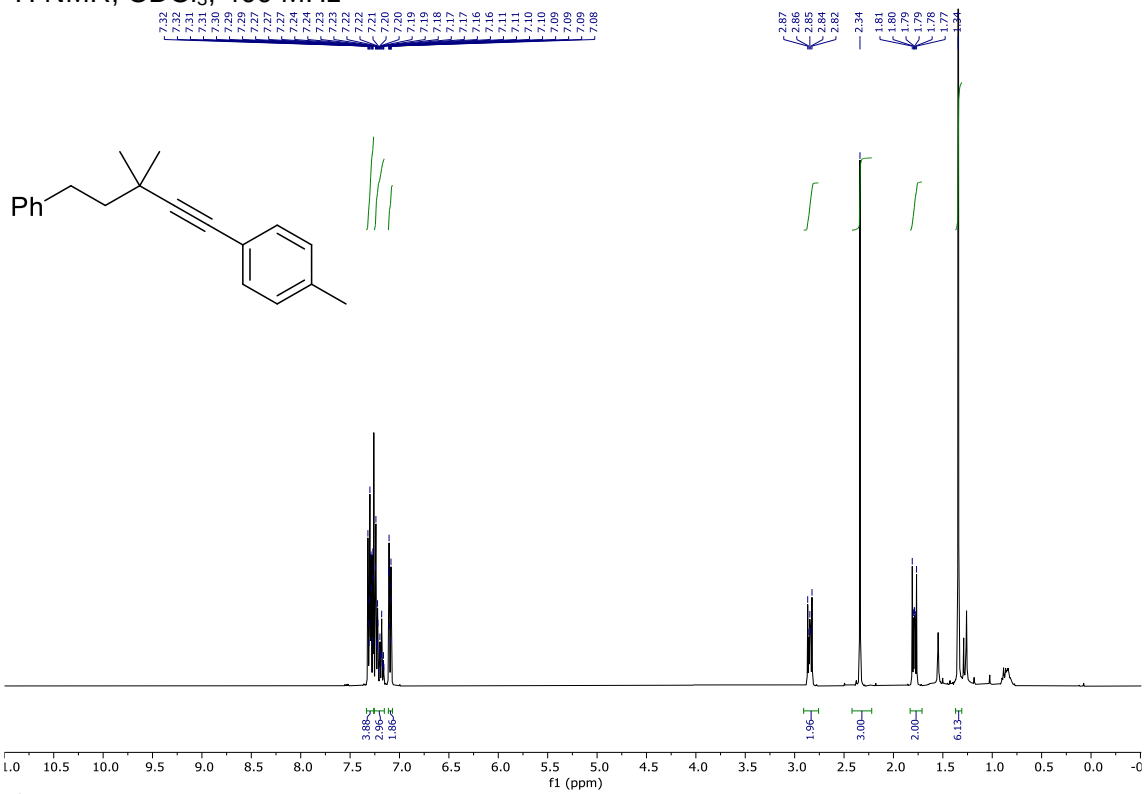


^{13}C NMR, $CDCl_3$, 101 MHz

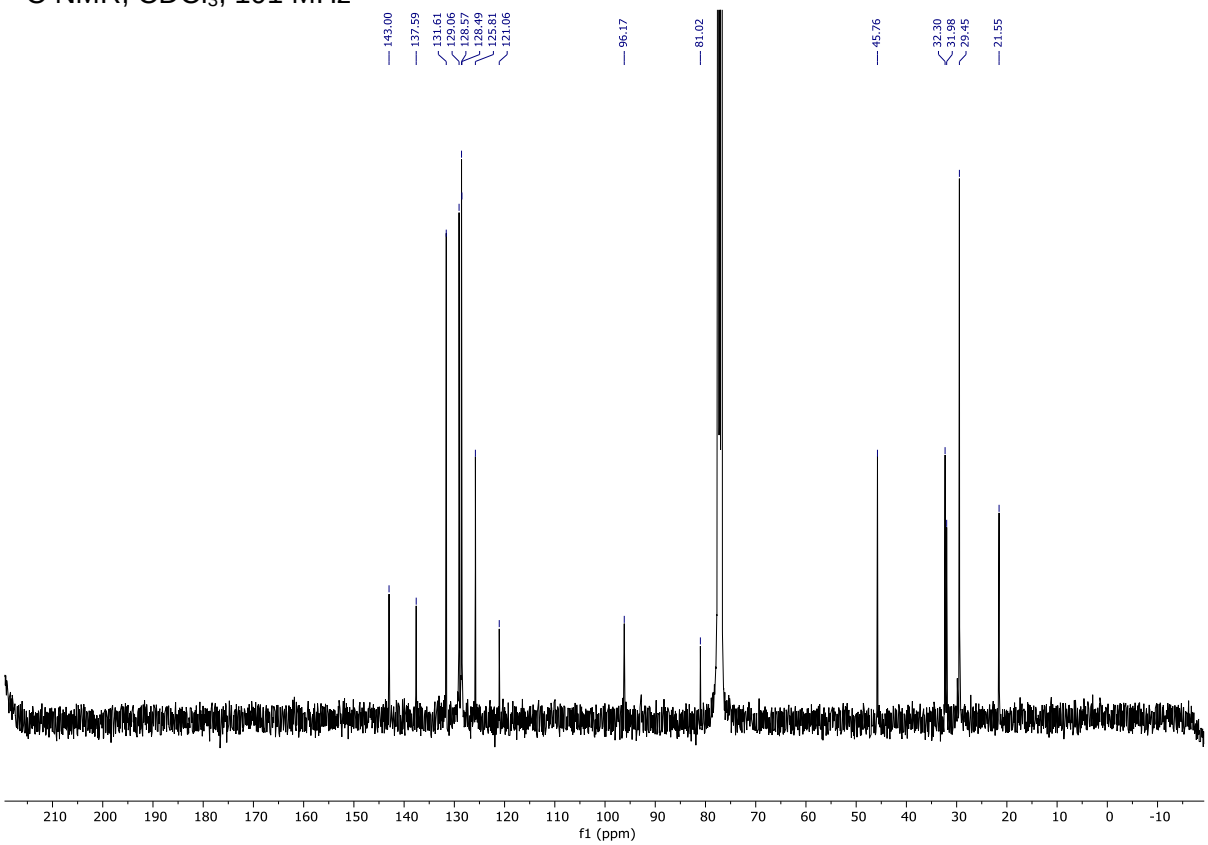


5.14b

^{1}H NMR, $CDCl_3$, 400 MHz

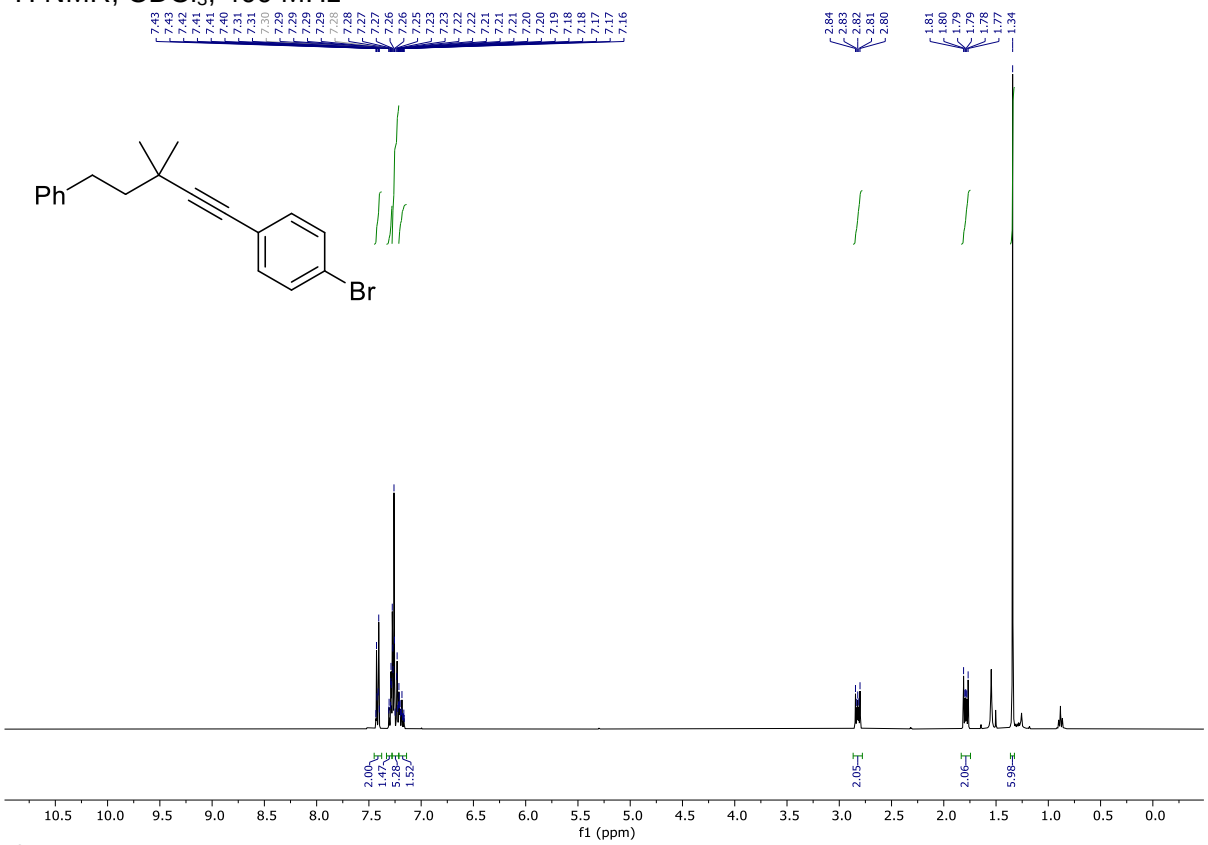


^{13}C NMR, $CDCl_3$, 101 MHz

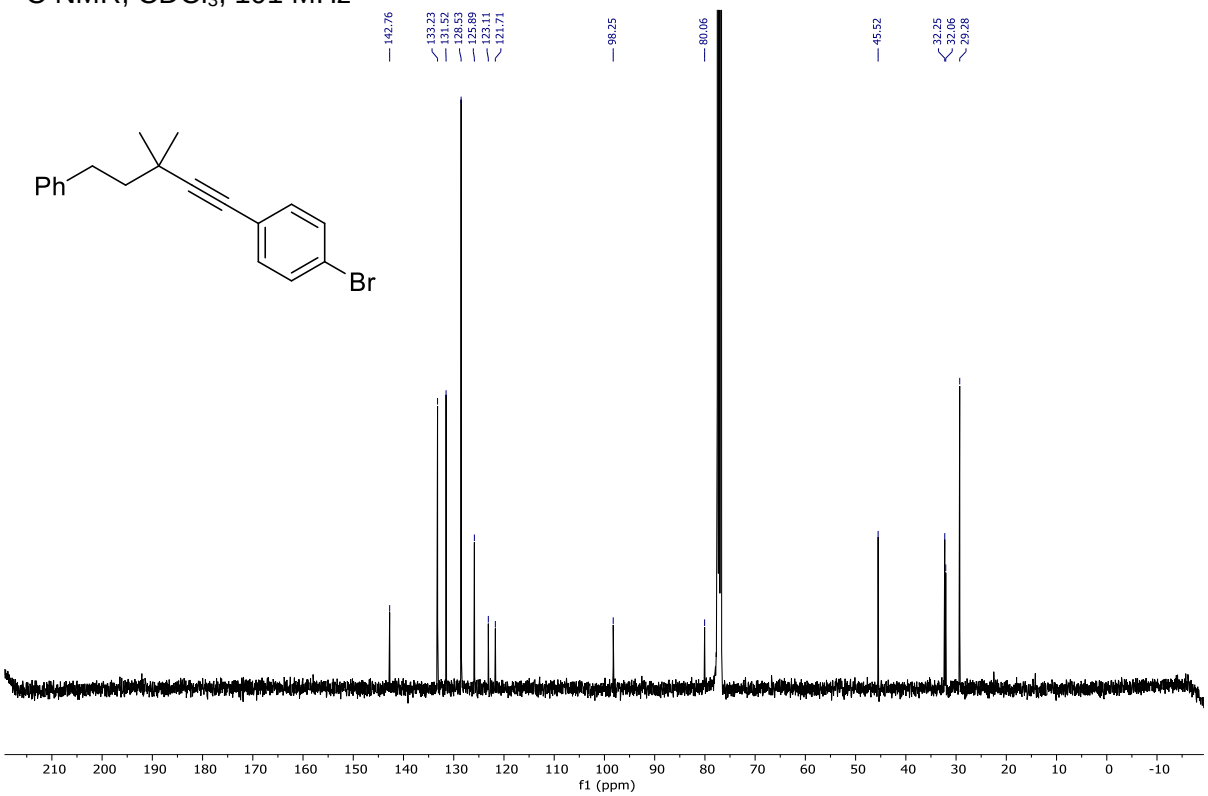


5.14c

^{1}H NMR, $CDCl_3$, 400 MHz

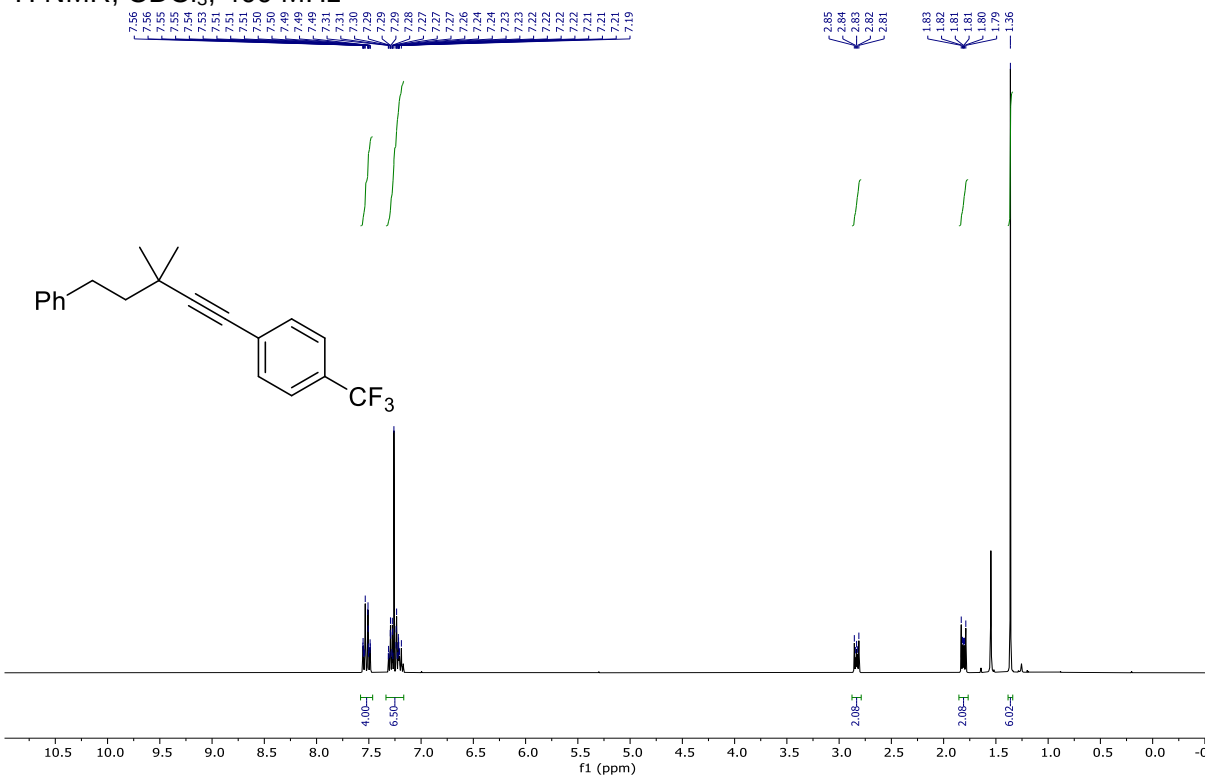


^{13}C NMR, $CDCl_3$, 101 MHz

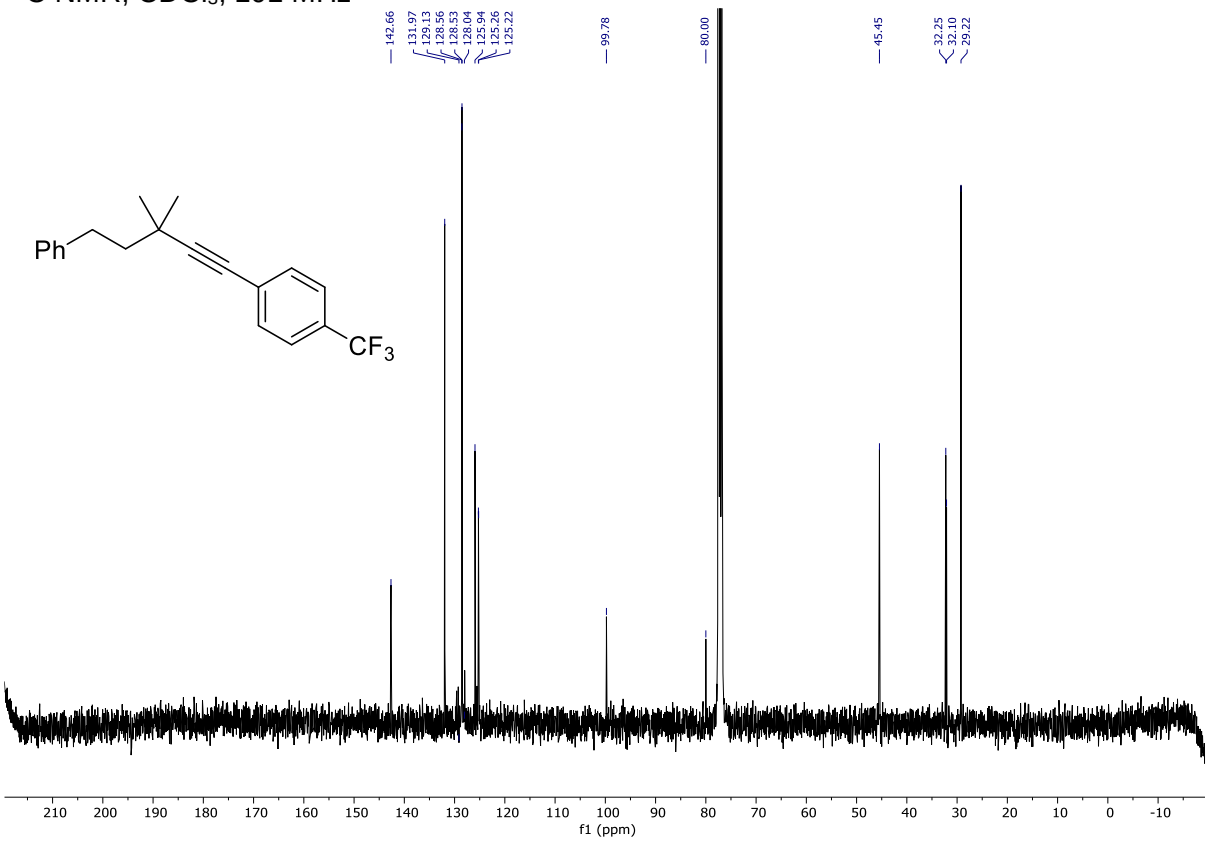


5.14d

^{1}H NMR, $CDCl_3$, 400 MHz



^{13}C NMR, $CDCl_3$, 101 MHz

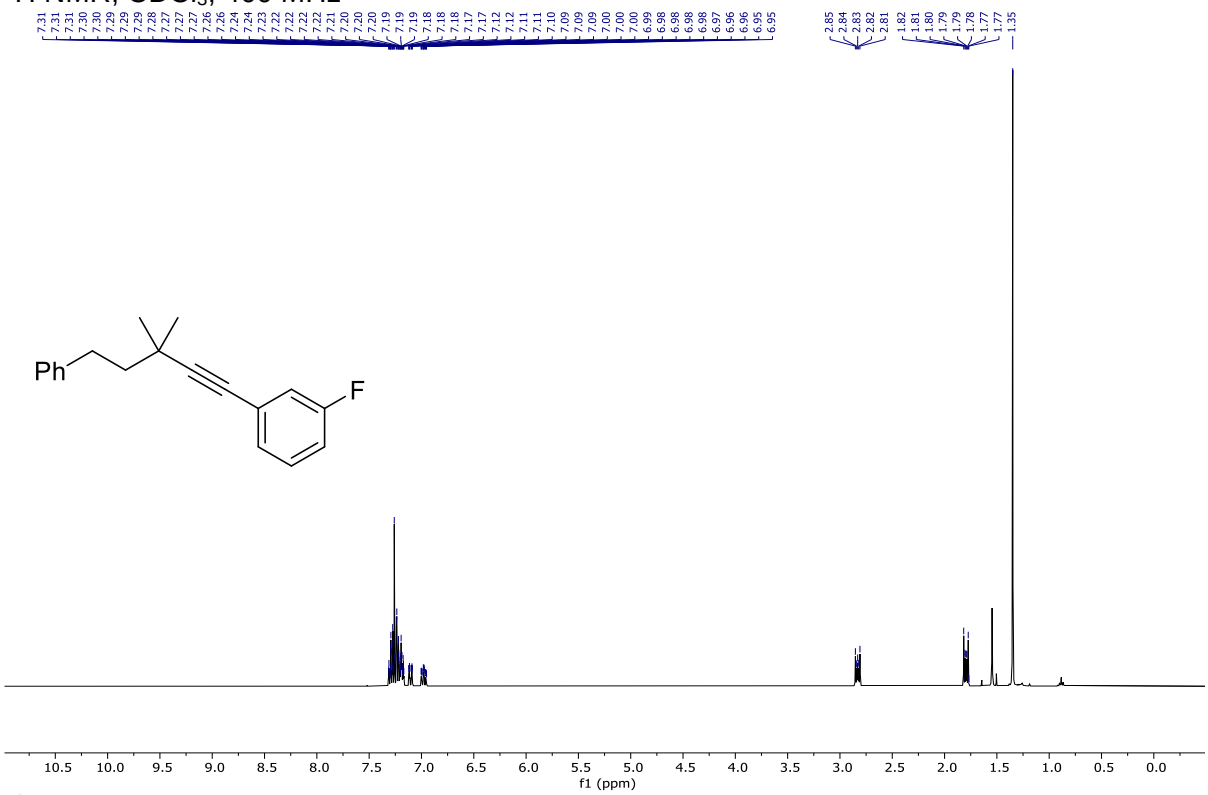


^{19}F NMR, $CDCl_3$, 376 MHz,

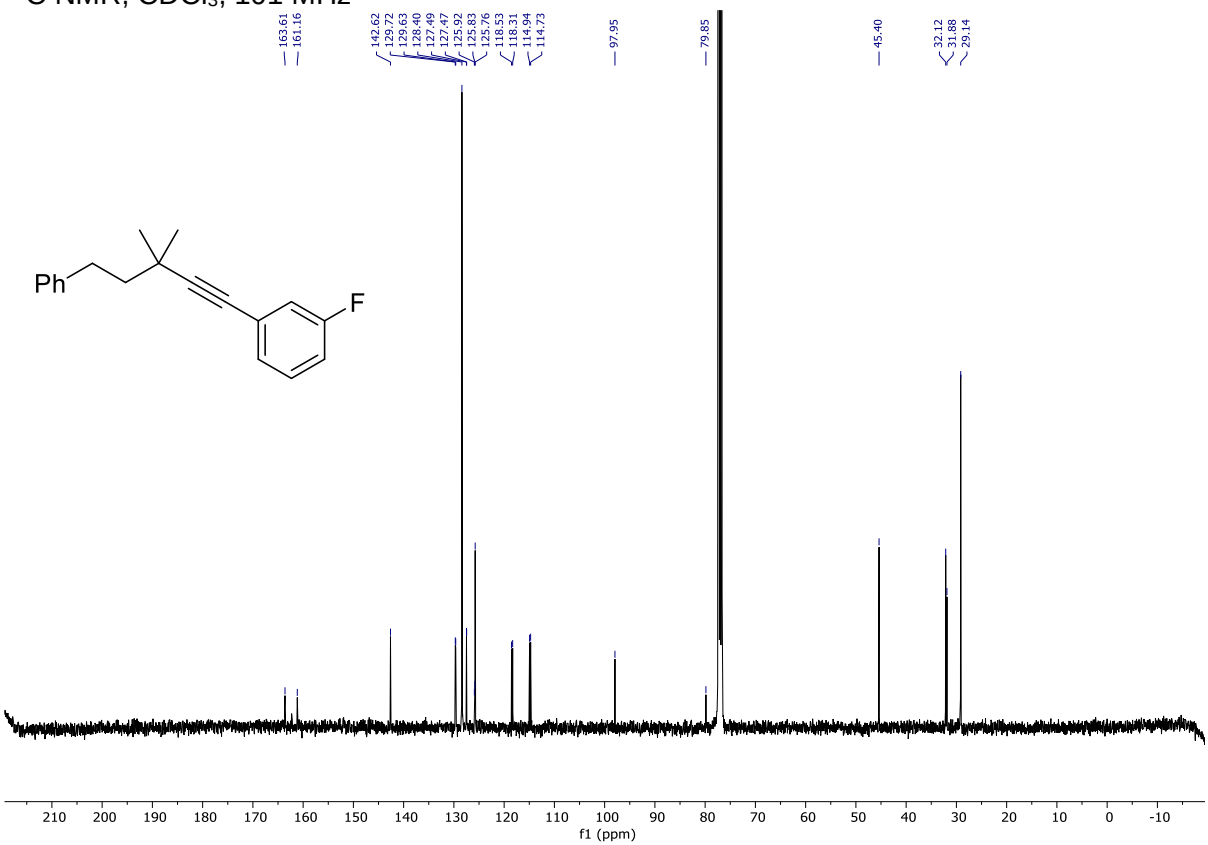
-62.70
Ph
CF3
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

5.14e

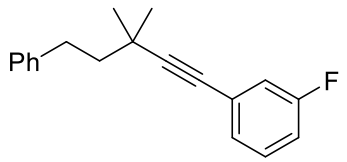
^{1}H NMR, $CDCl_3$, 400 MHz



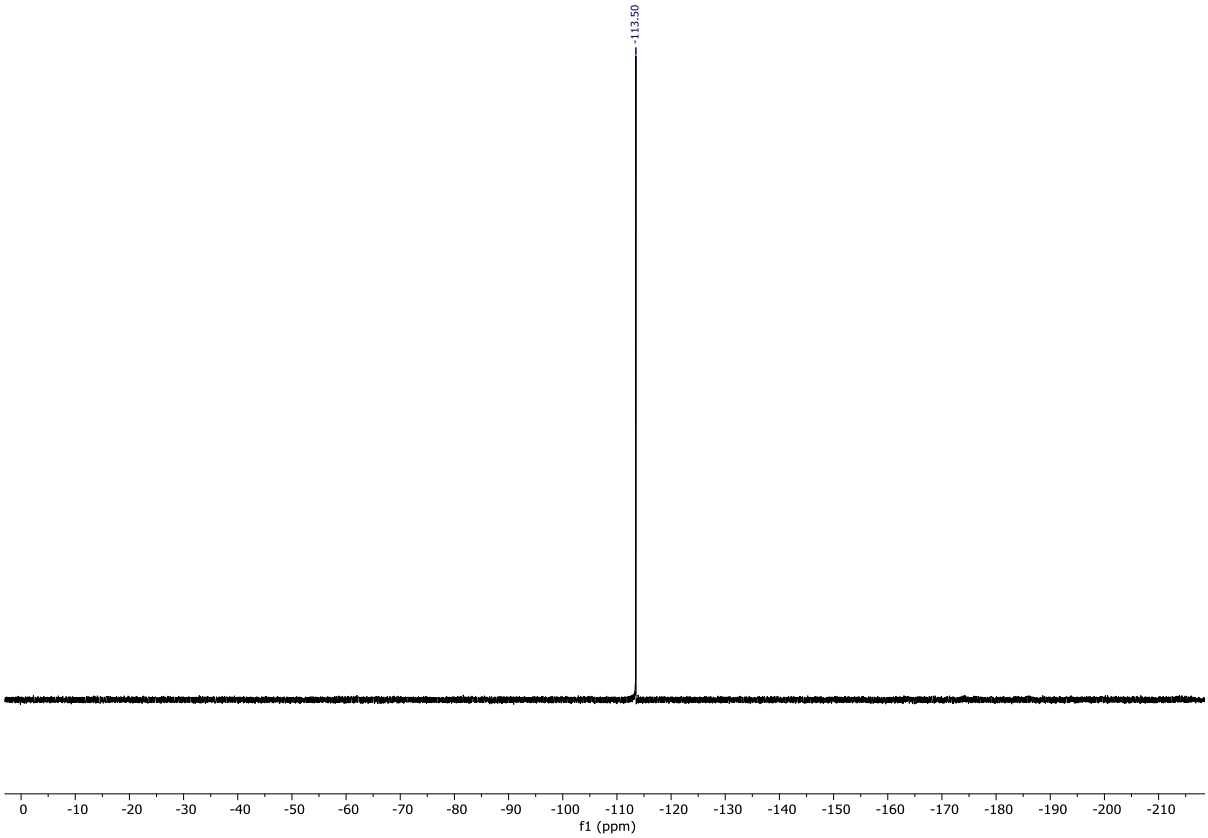
^{13}C NMR, $CDCl_3$, 101 MHz



^{19}F NMR, $CDCl_3$, 376 MHz

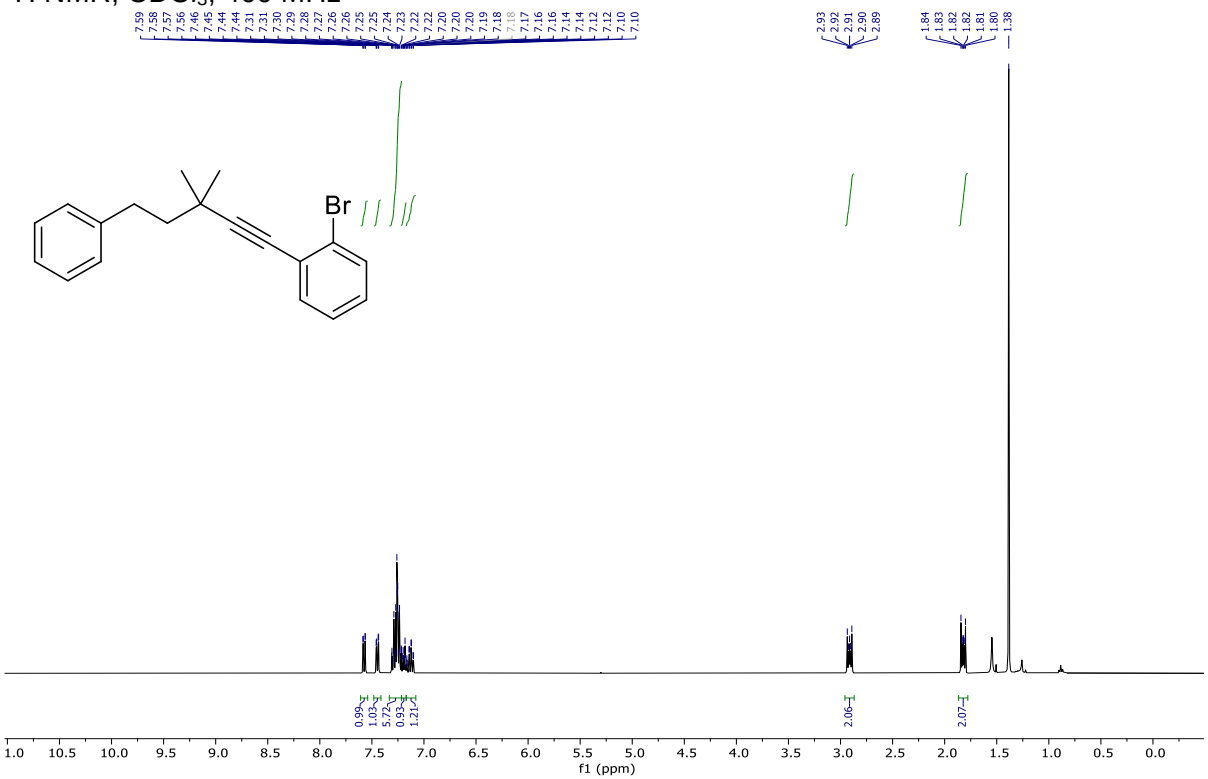


9.147

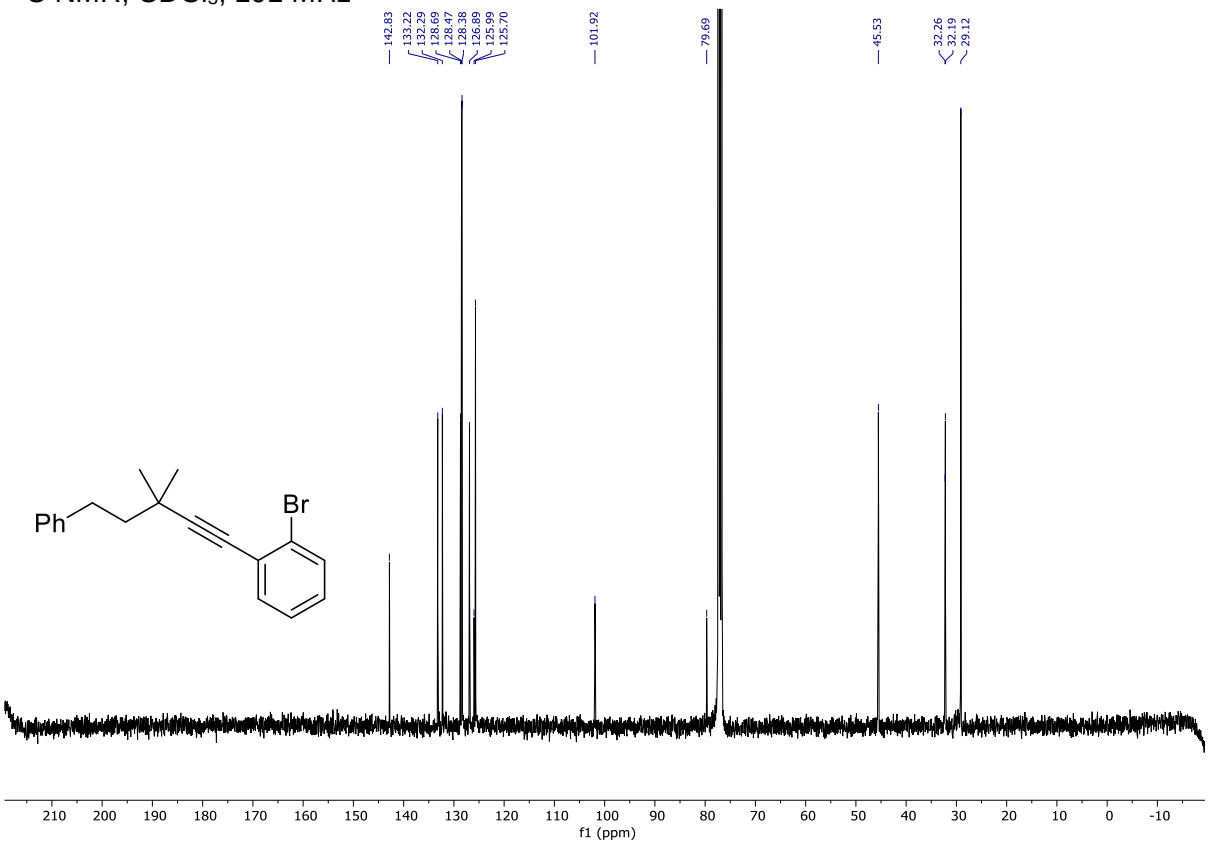

-113.50
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

5.14f

^{1}H NMR, $CDCl_3$, 400 MHz

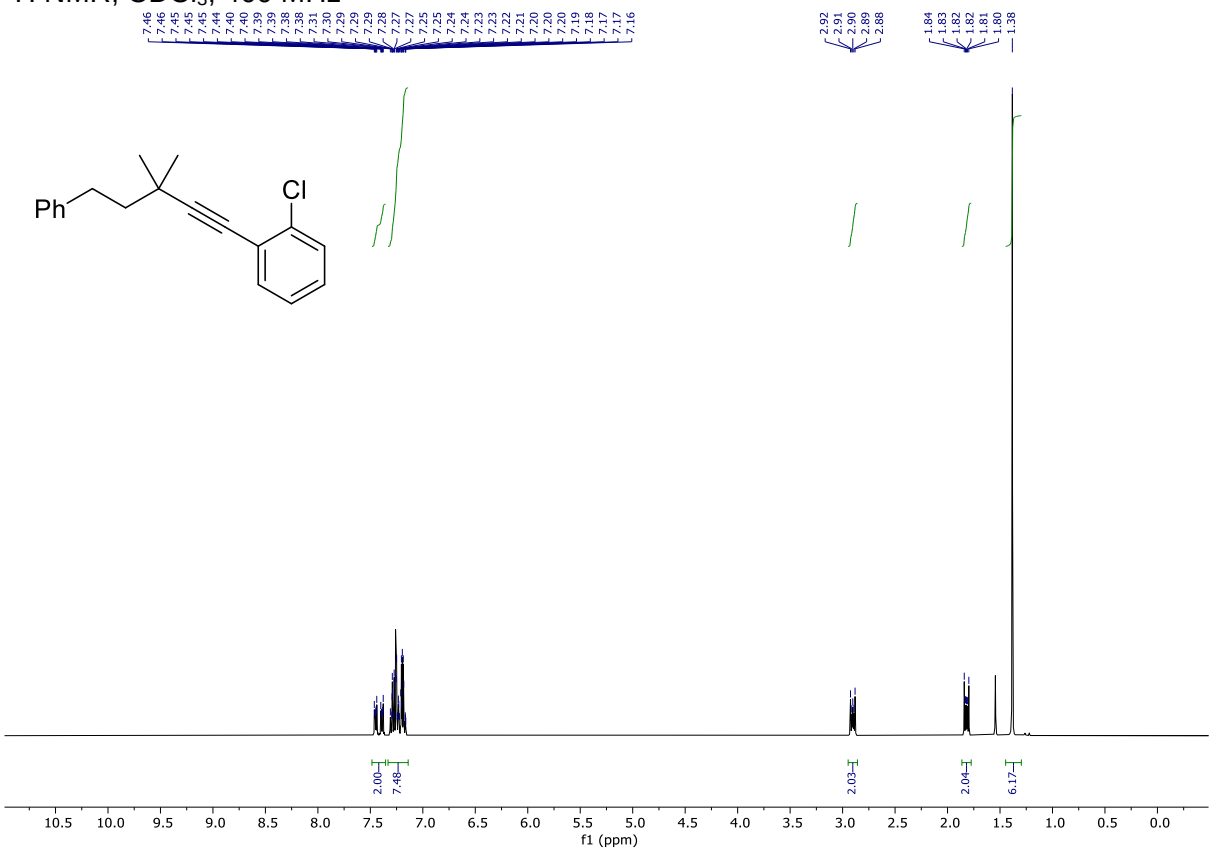


^{13}C NMR, $CDCl_3$, 101 MHz

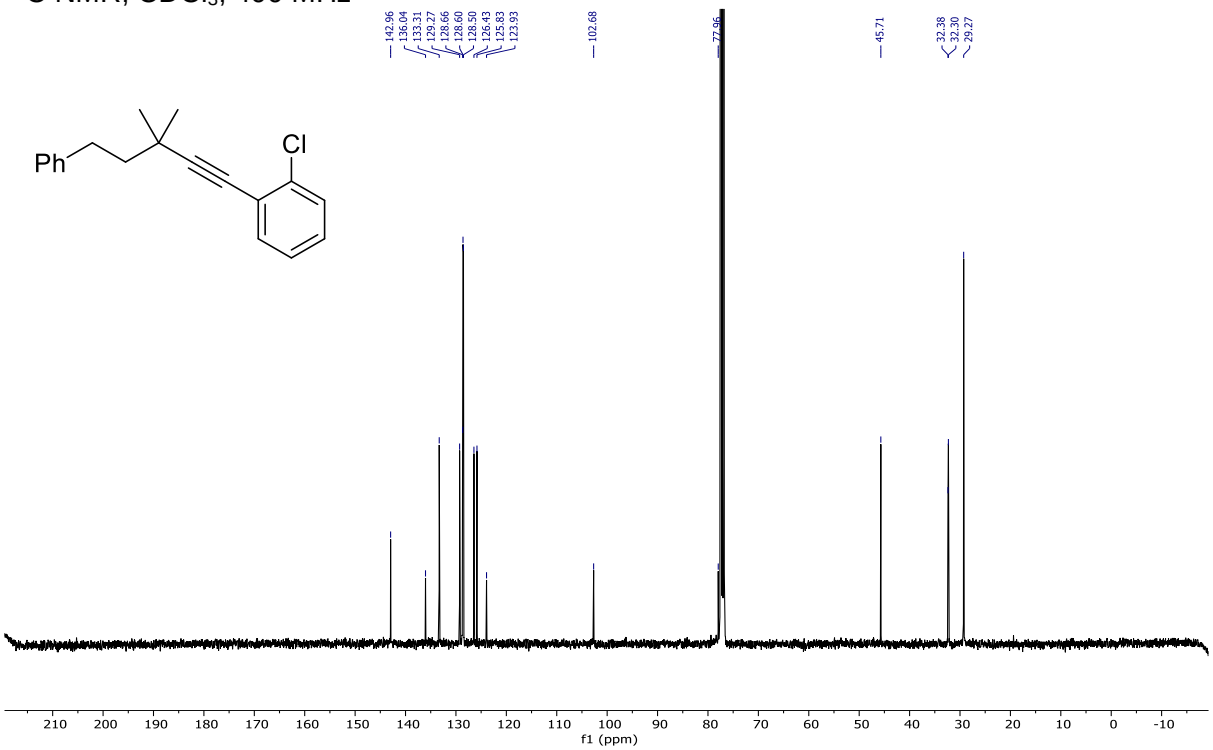


5.14i

^{1}H NMR, $CDCl_3$, 400 MHz

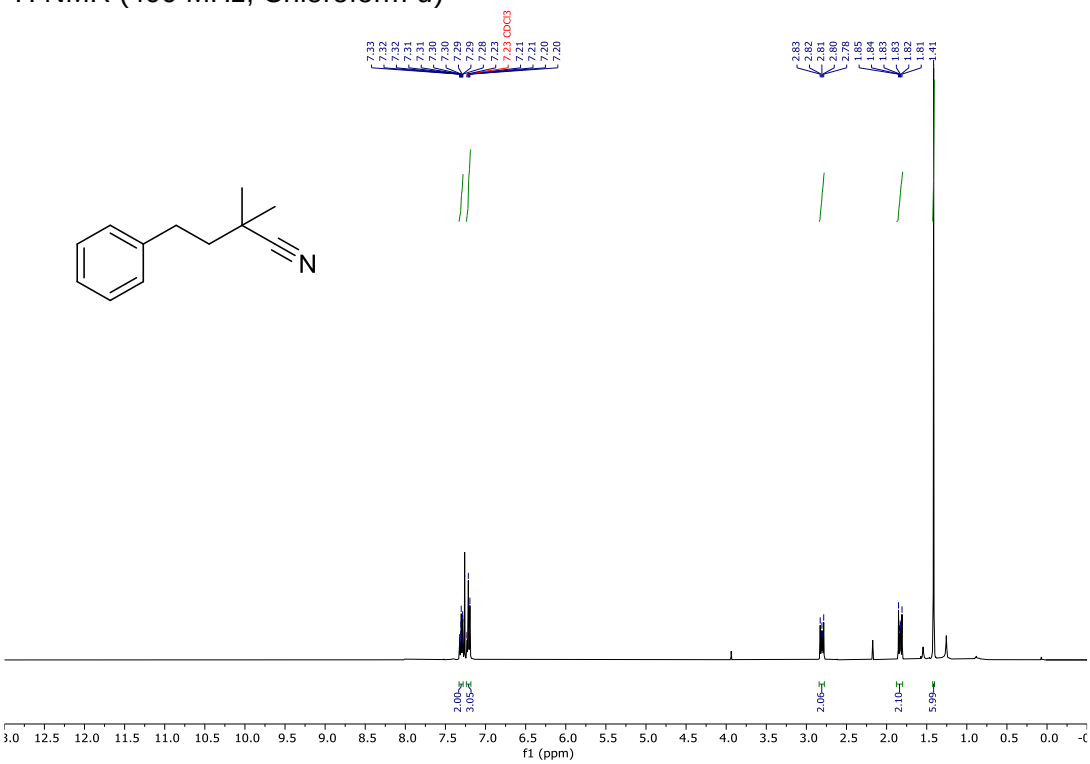


^{13}C NMR, $CDCl_3$, 400 MHz

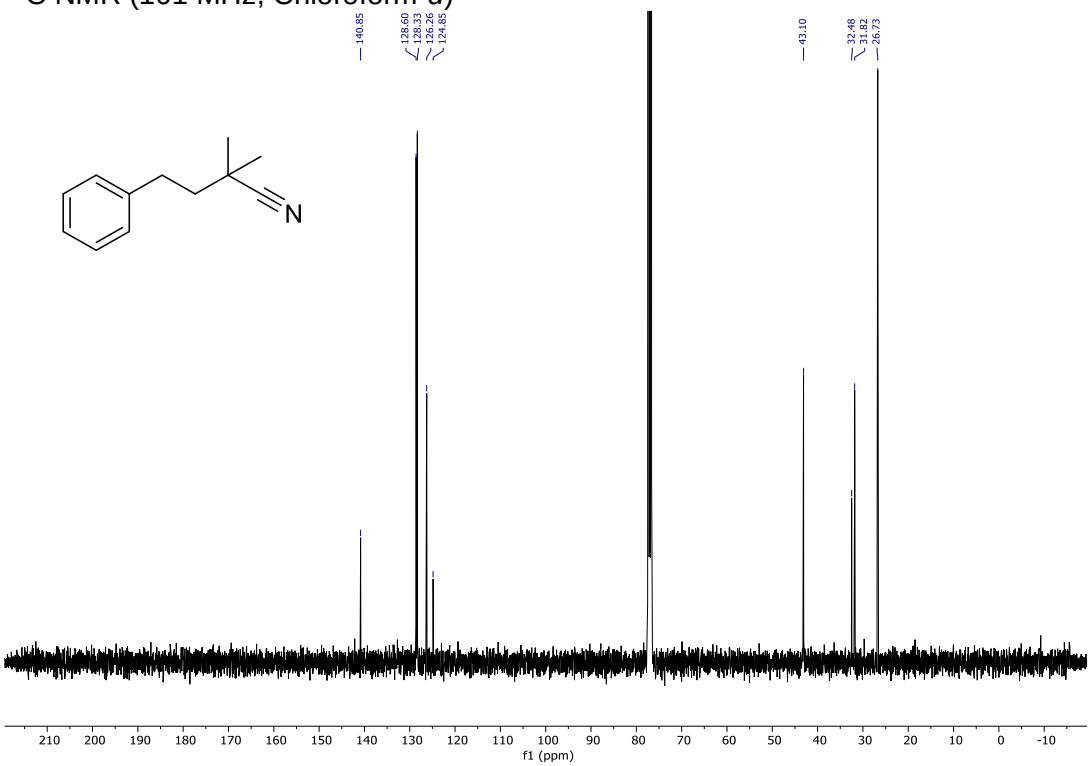


5.16

^{1}H NMR (400 MHz, Chloroform-*d*)

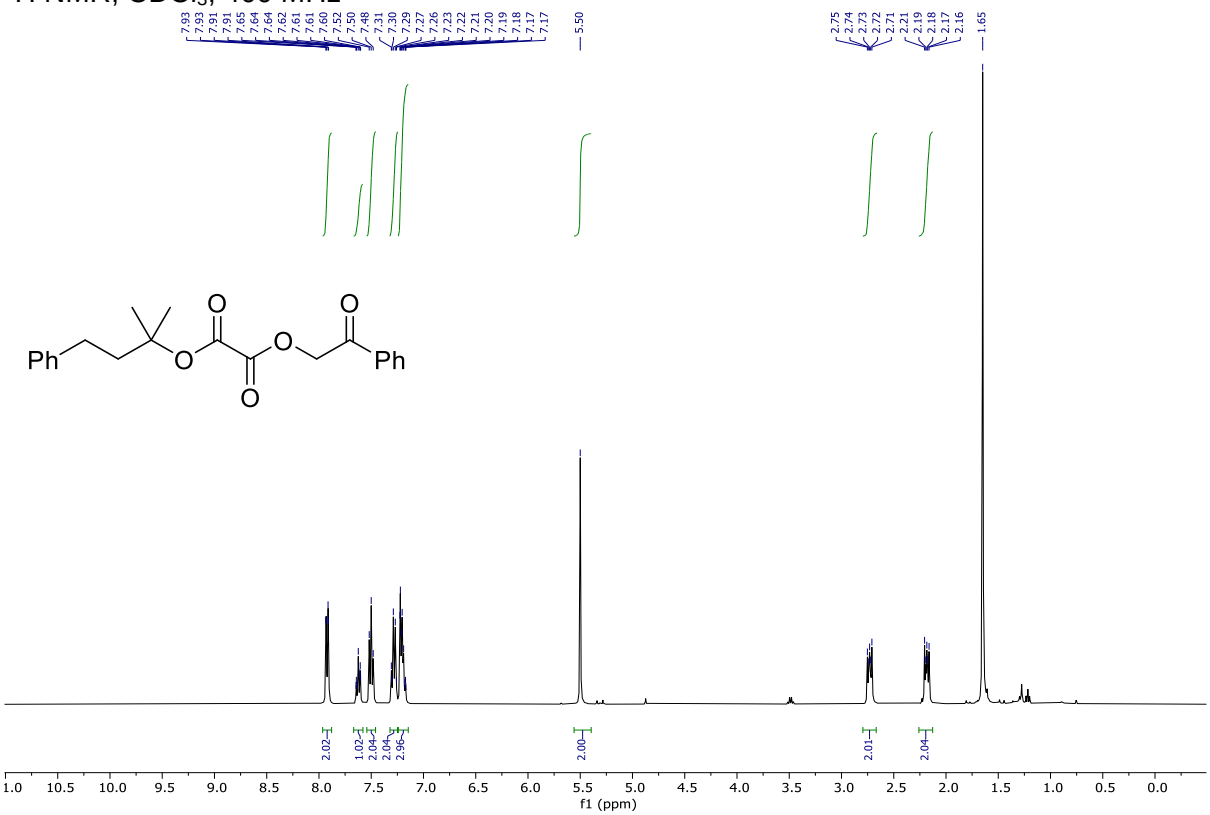


^{13}C NMR (101 MHz, Chloroform-*d*)

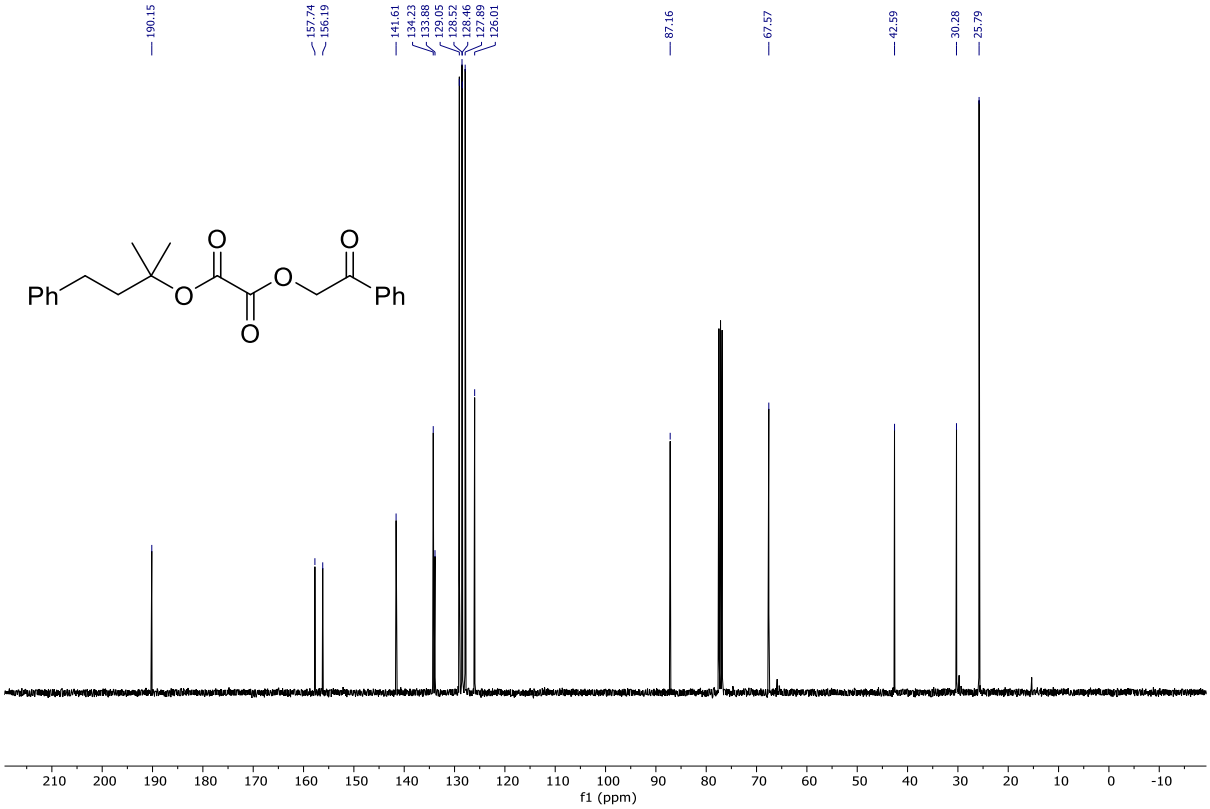


6.2

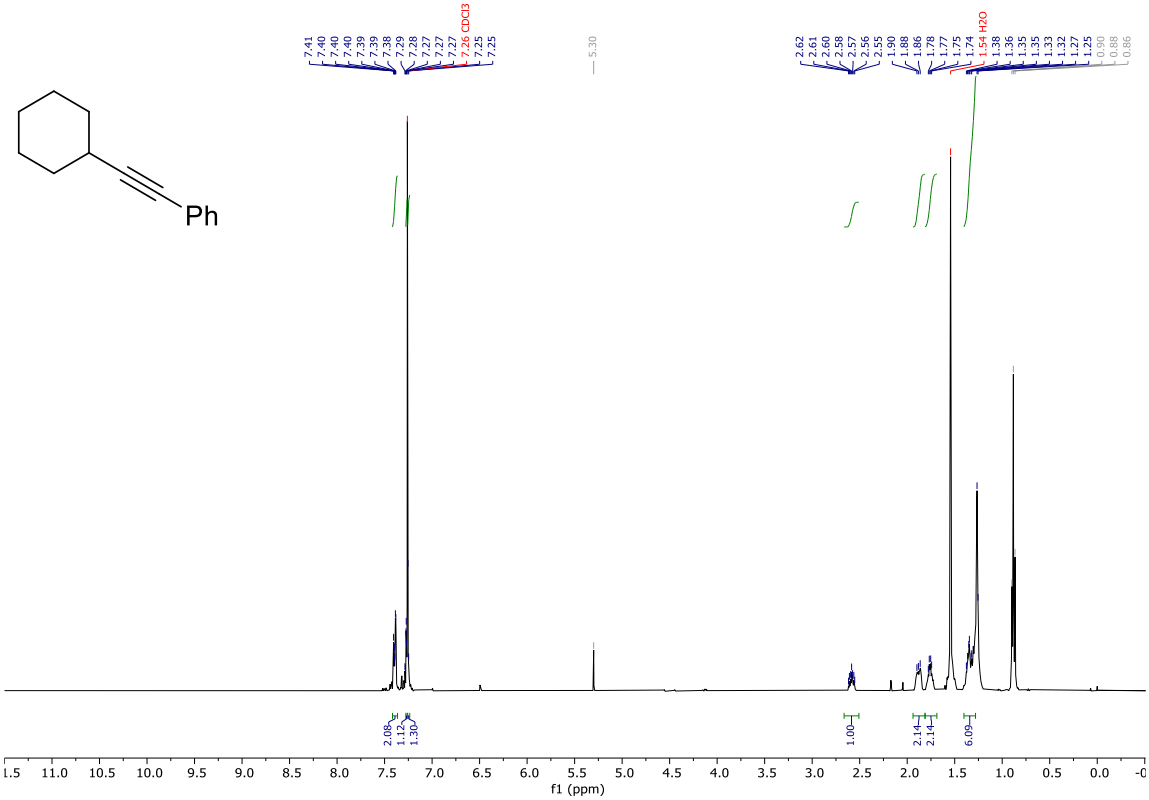
^{1}H NMR, $CDCl_3$, 400 MHz



^{13}C NMR, $CDCl_3$, 101 MHz

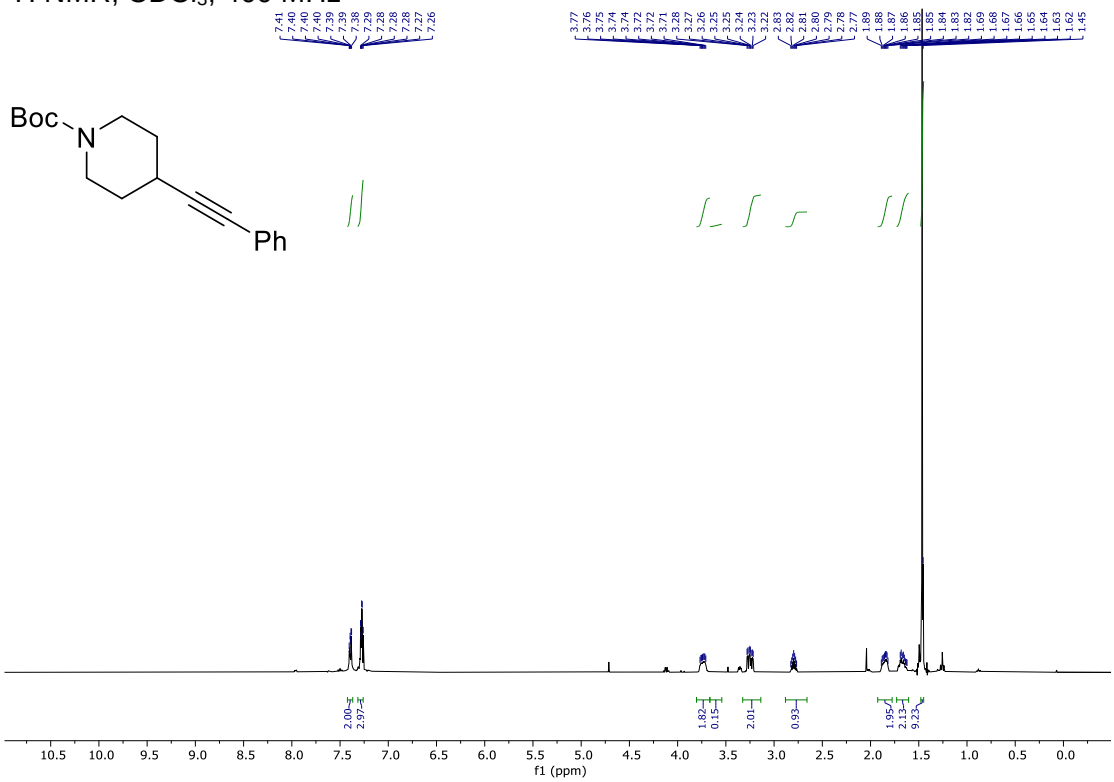


6.4a (also 6.9c)
^{1}H NMR, $CDCl_3$, 400 MHz



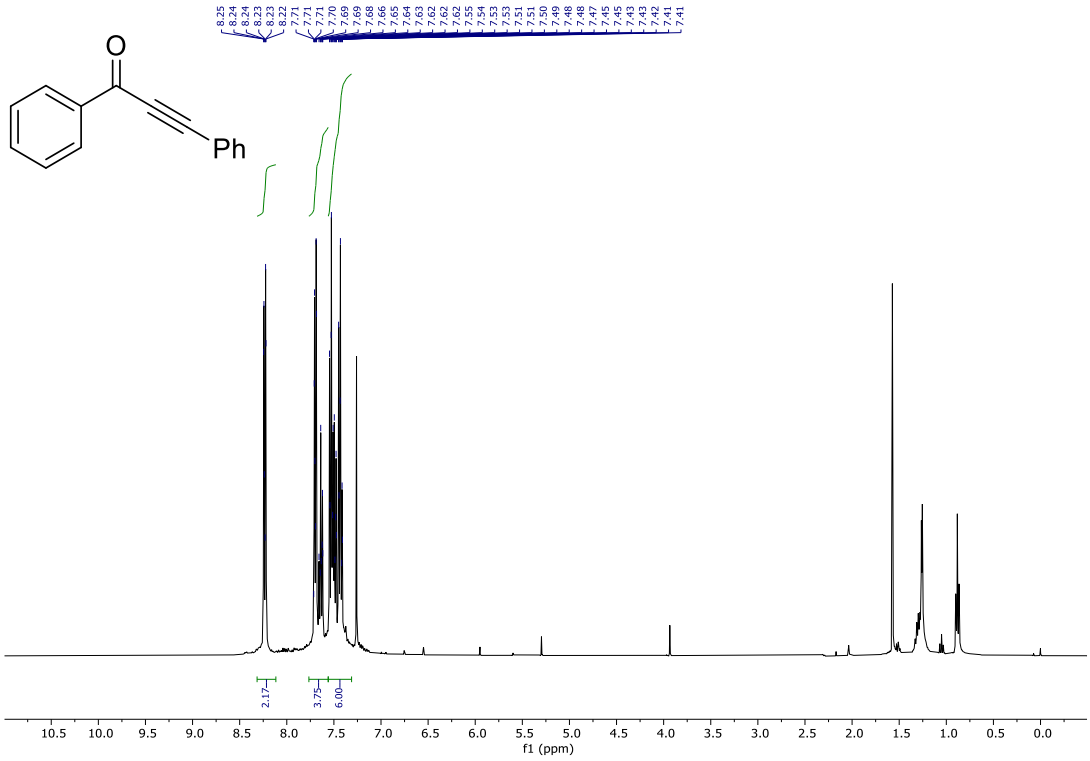
6.4b

^{1}H NMR, $CDCl_3$, 400 MHz



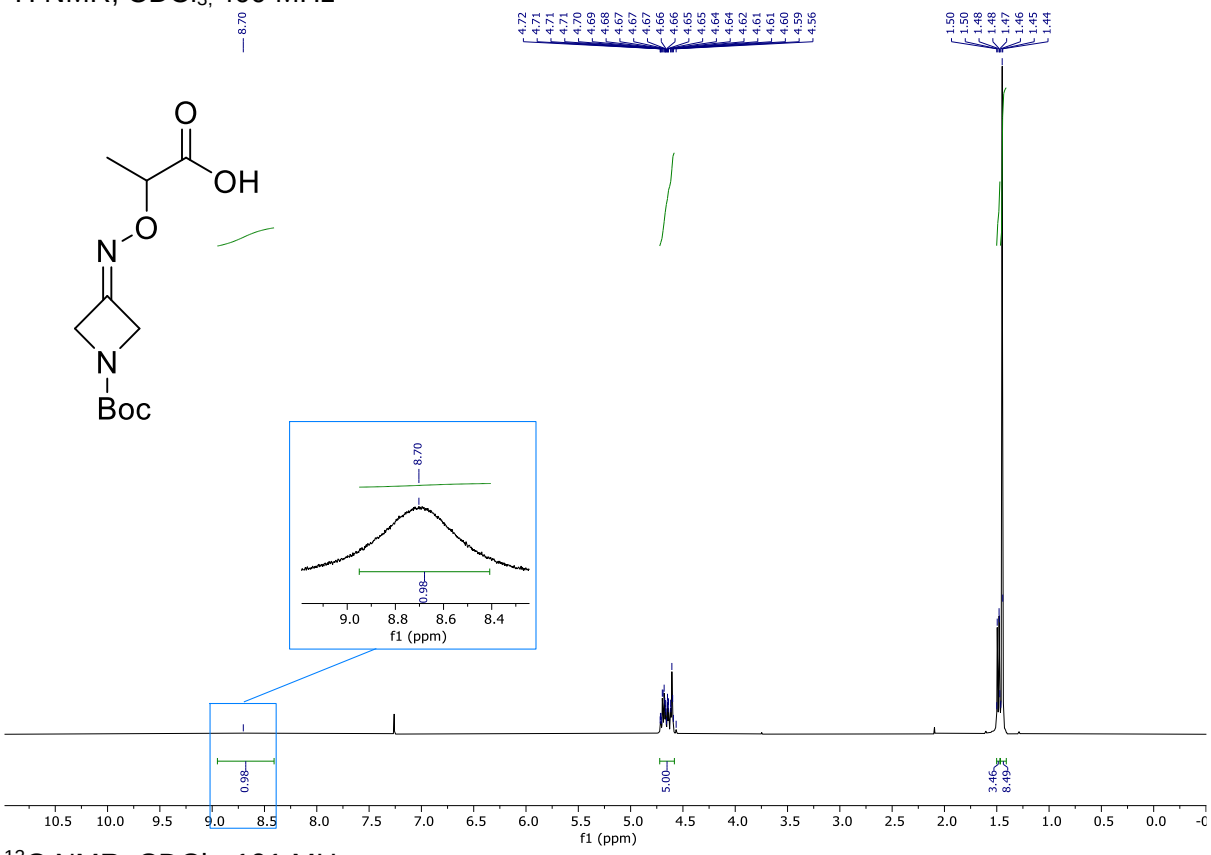
6.4c

^{1}H NMR, $CDCl_3$, 400 MHz

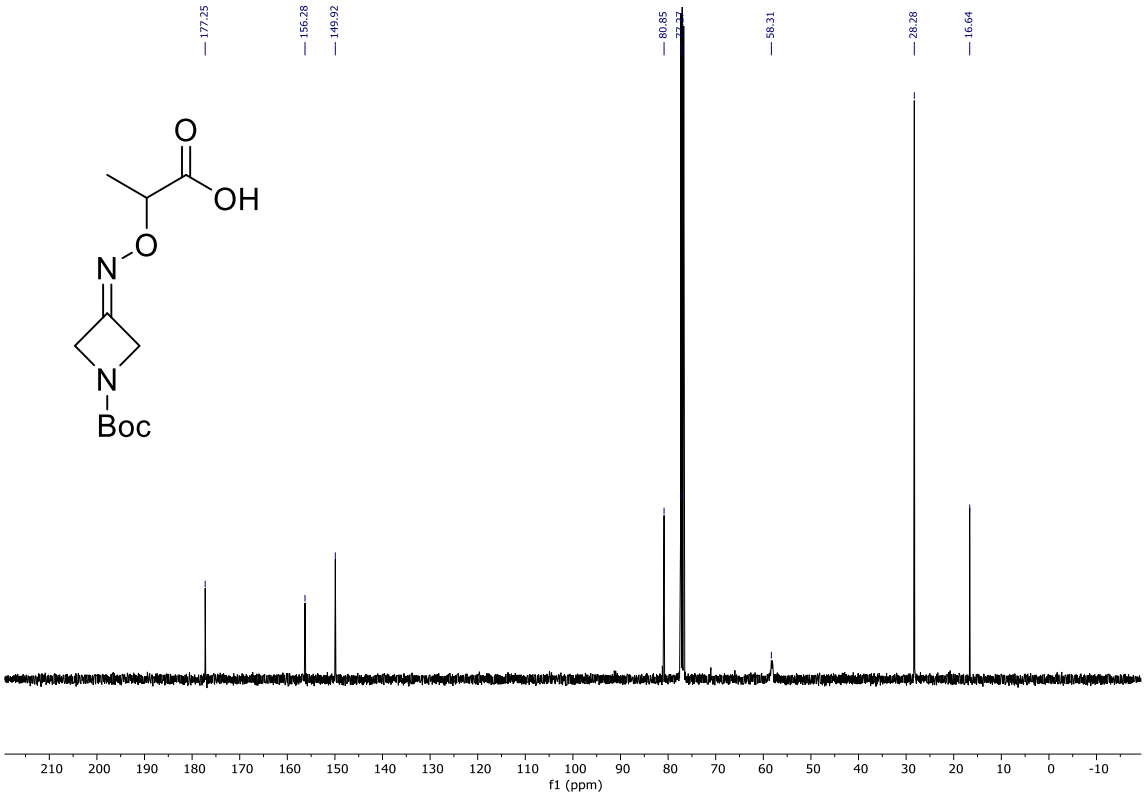


6.6a

^{1}H NMR, $CDCl_3$, 400 MHz

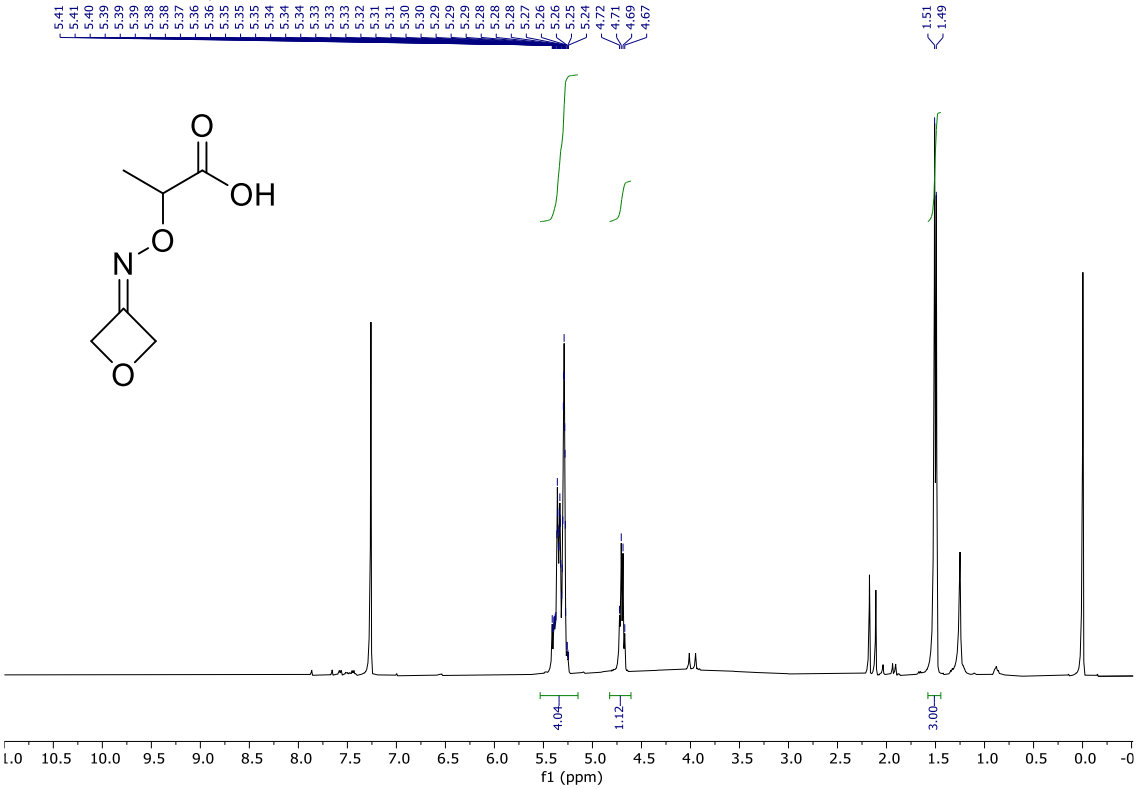


^{13}C NMR, $CDCl_3$, 101 MHz

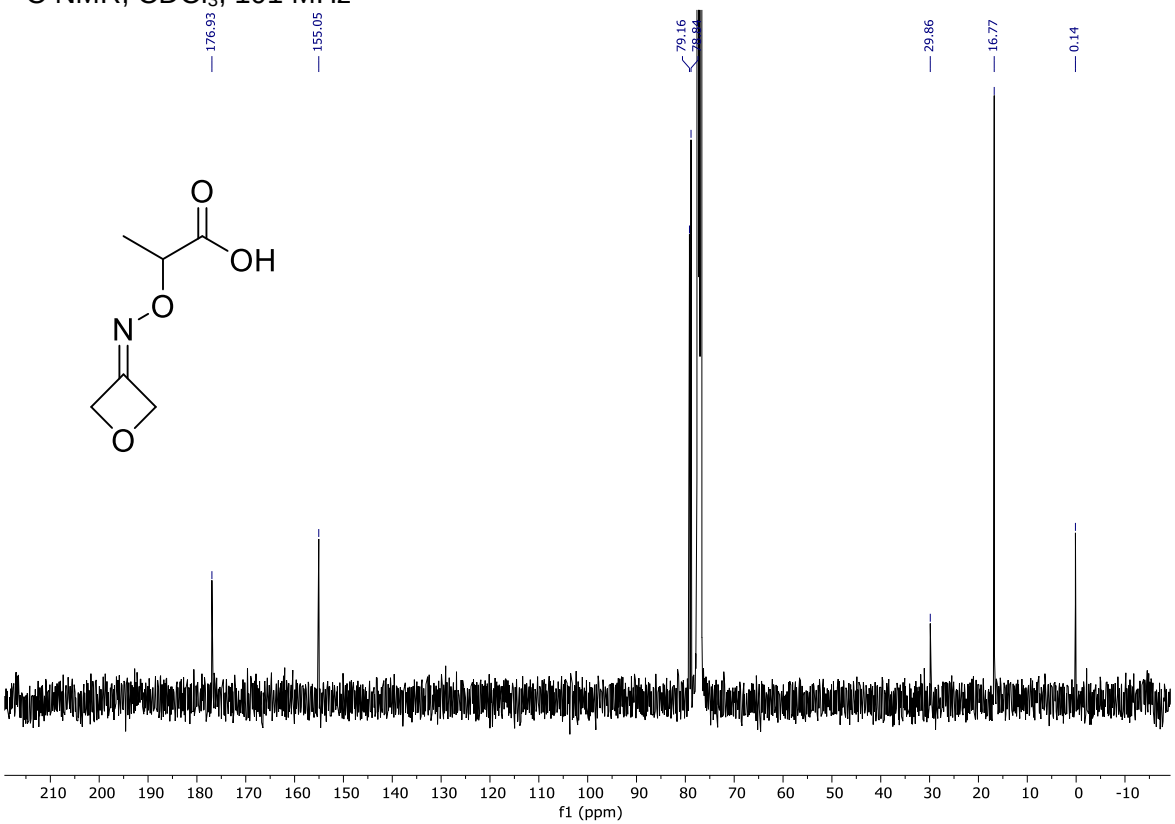


6.6c

^{1}H NMR, $CDCl_3$, 400 MHz

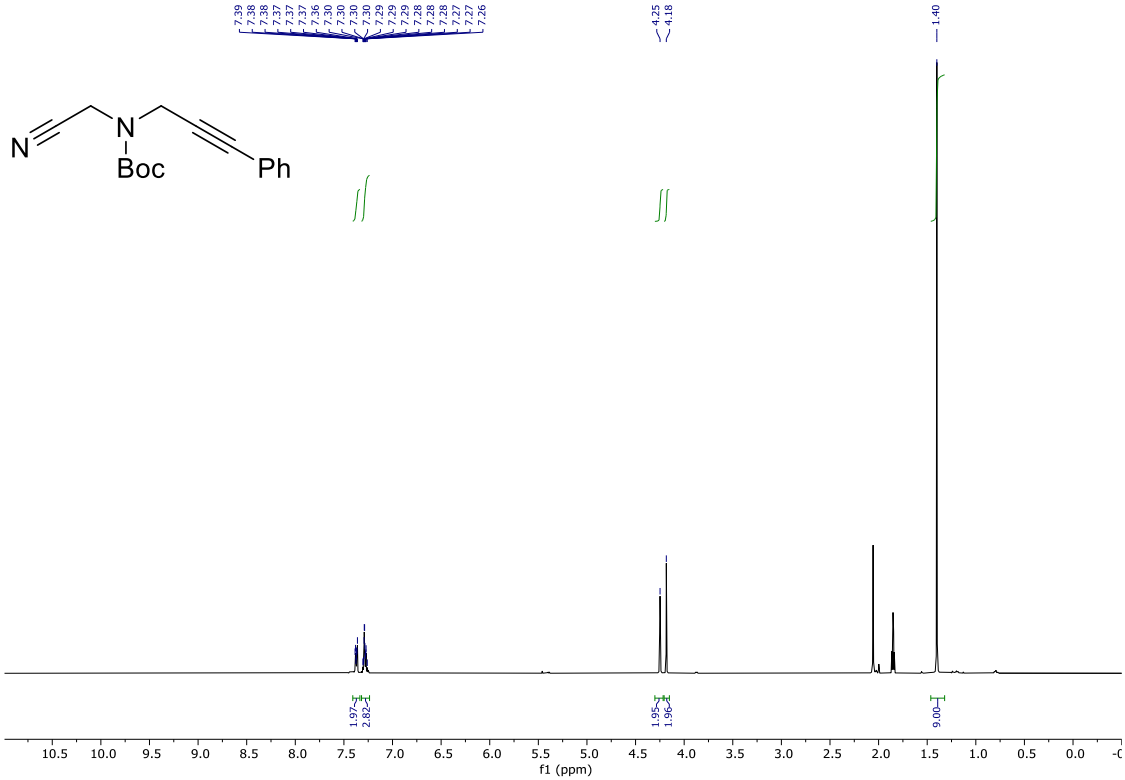


^{13}C NMR, $CDCl_3$, 101 MHz



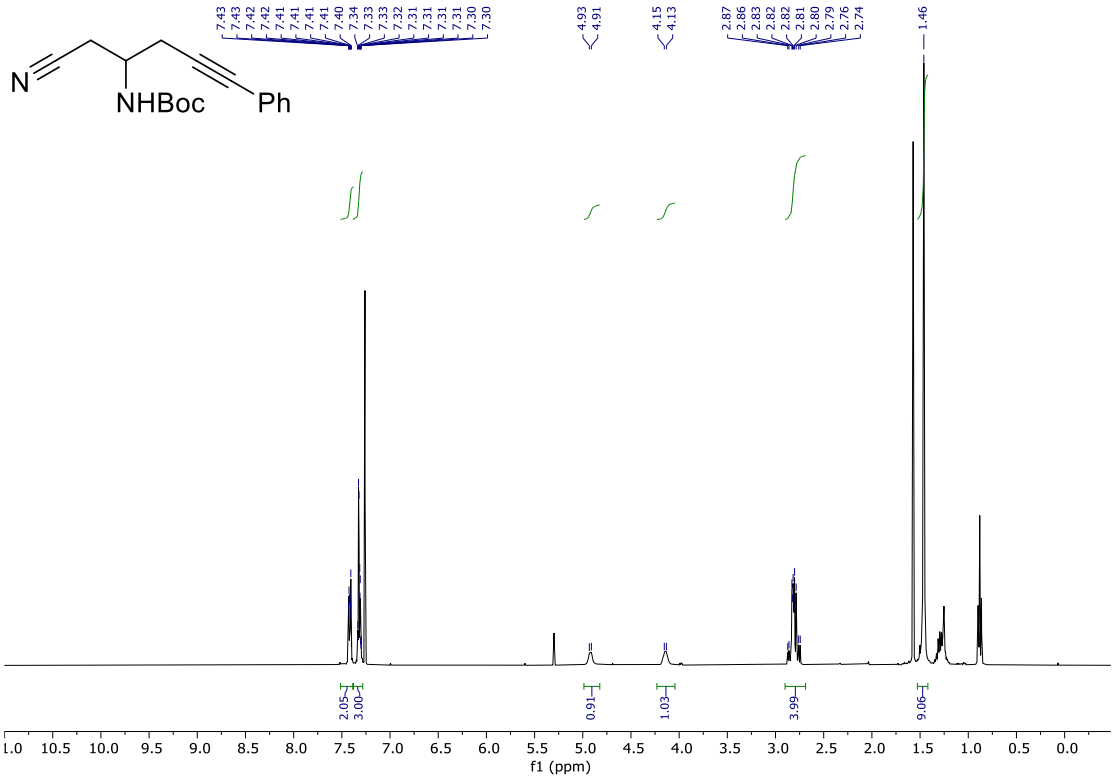
6.7a

^{1}H NMR, CD_3CN, 400 MHz



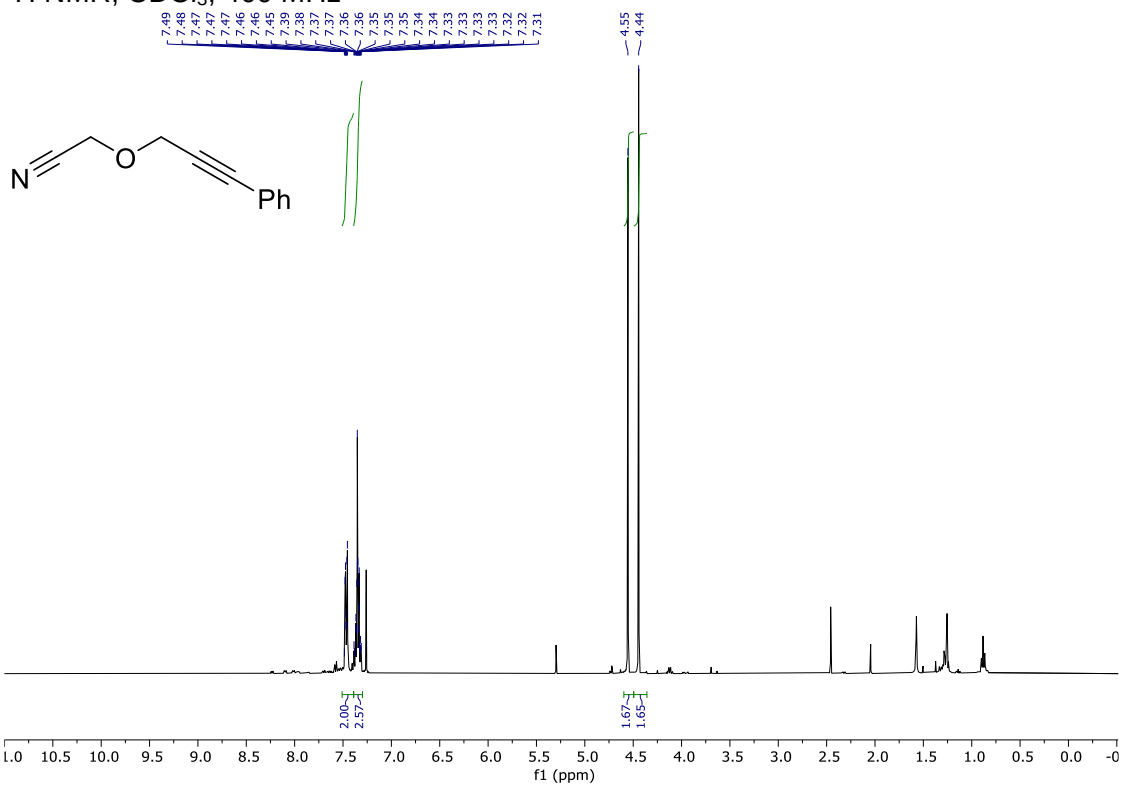
6.7b

^{1}H NMR, $CDCl_3$, 400 MHz



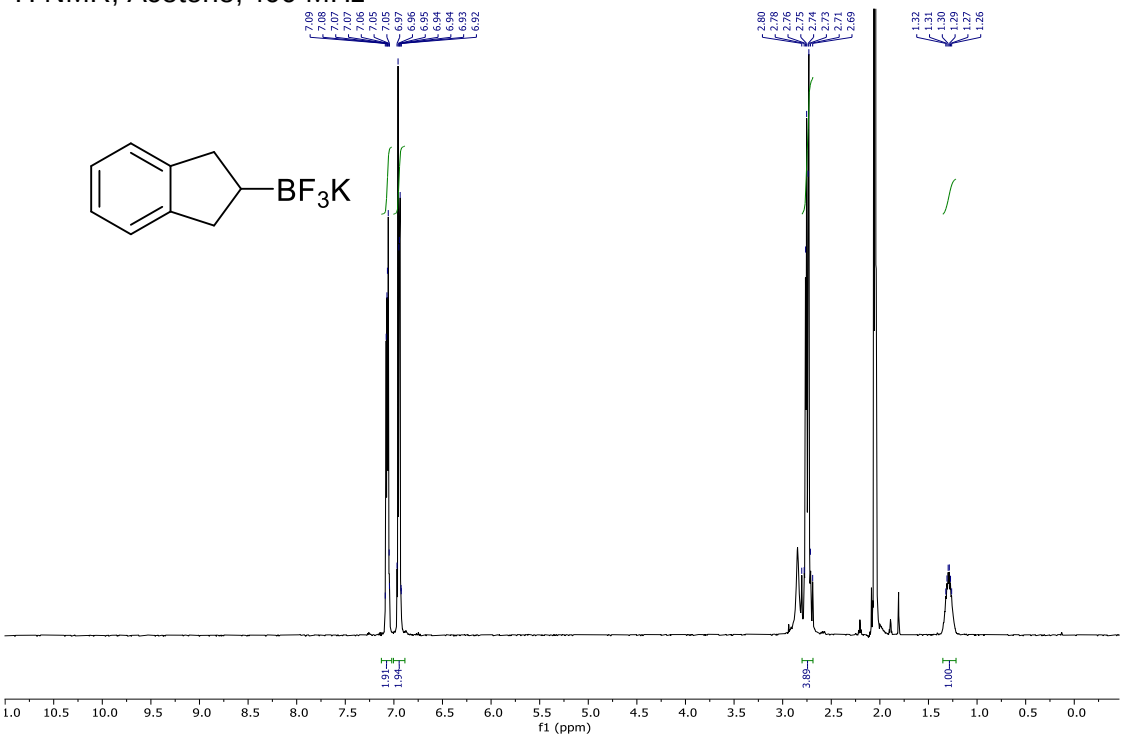
6.7c

^{1}H NMR, $CDCl_3$, 400 MHz



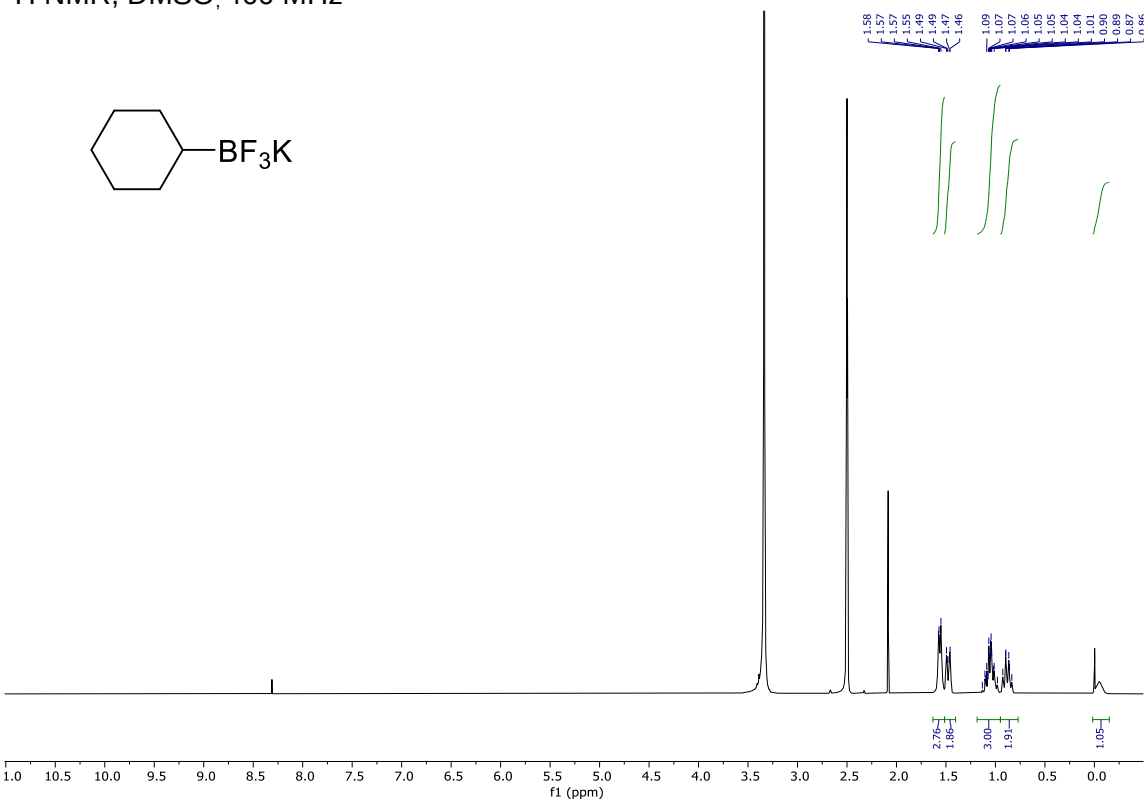
6.8a

^{1}H NMR, Acetone, 400 MHz



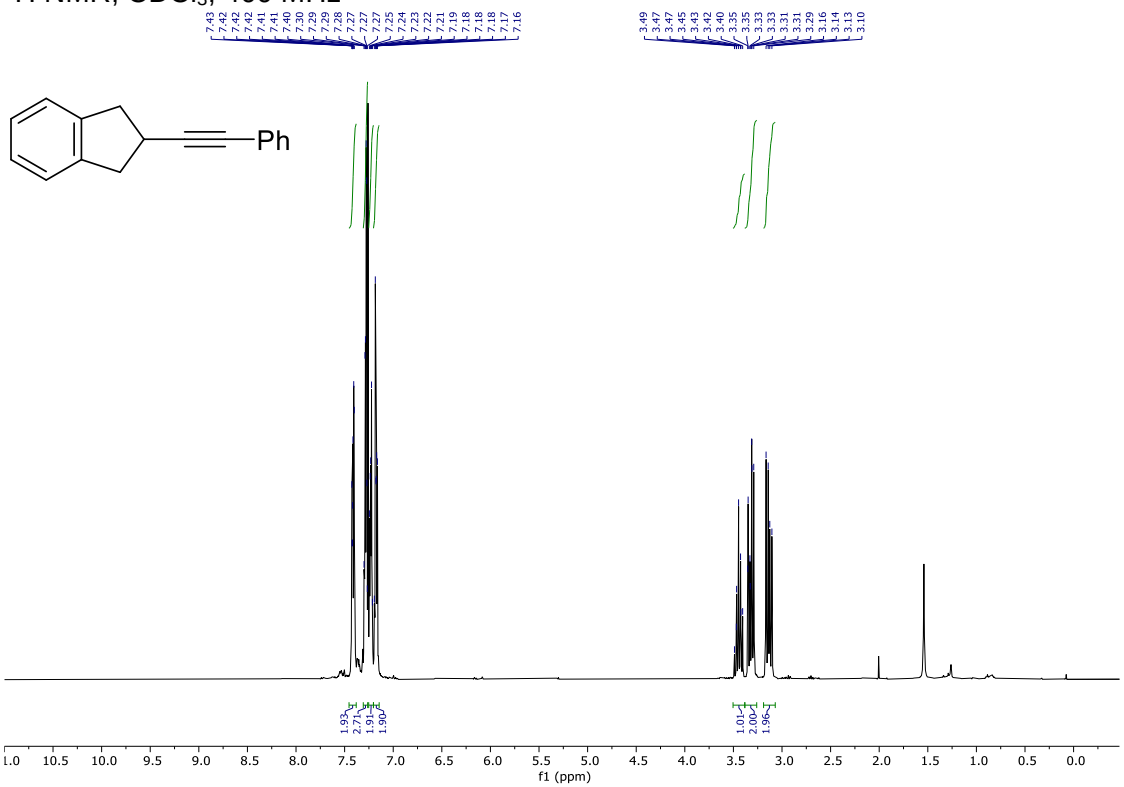
6.8c

^{1}H NMR, DMSO, 400 MHz



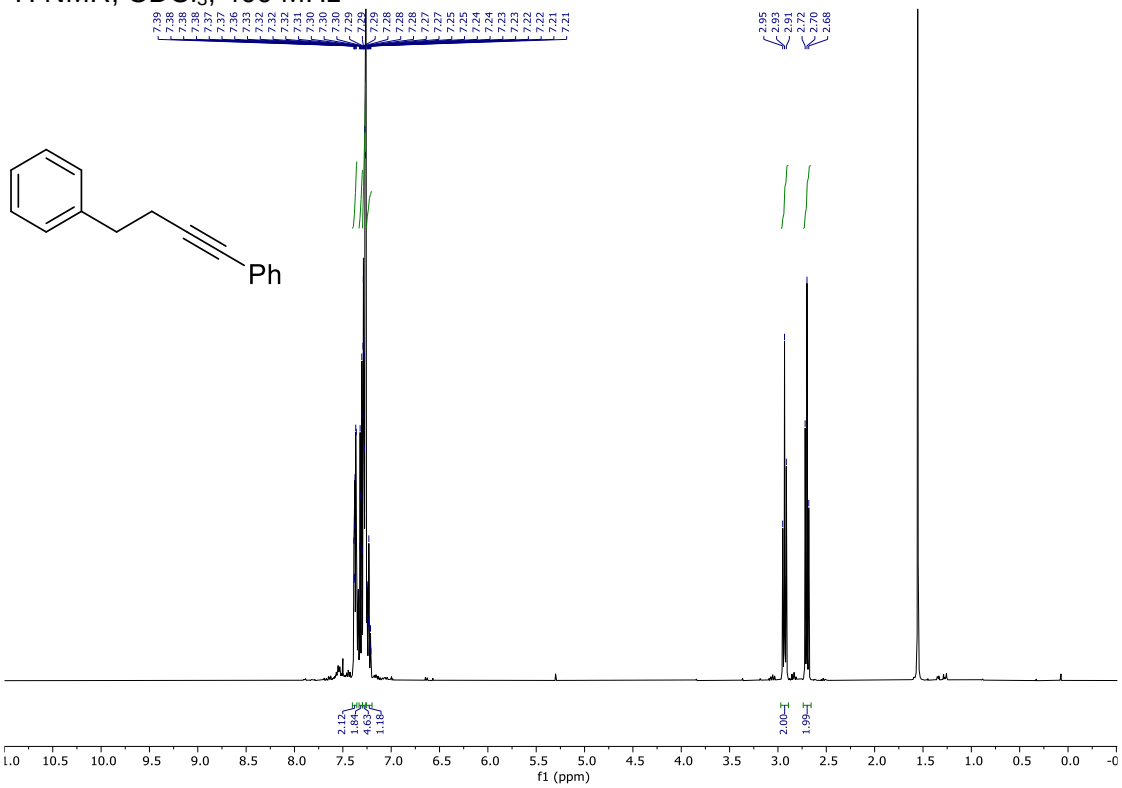
6.9a

^{1}H NMR, $CDCl_3$, 400 MHz



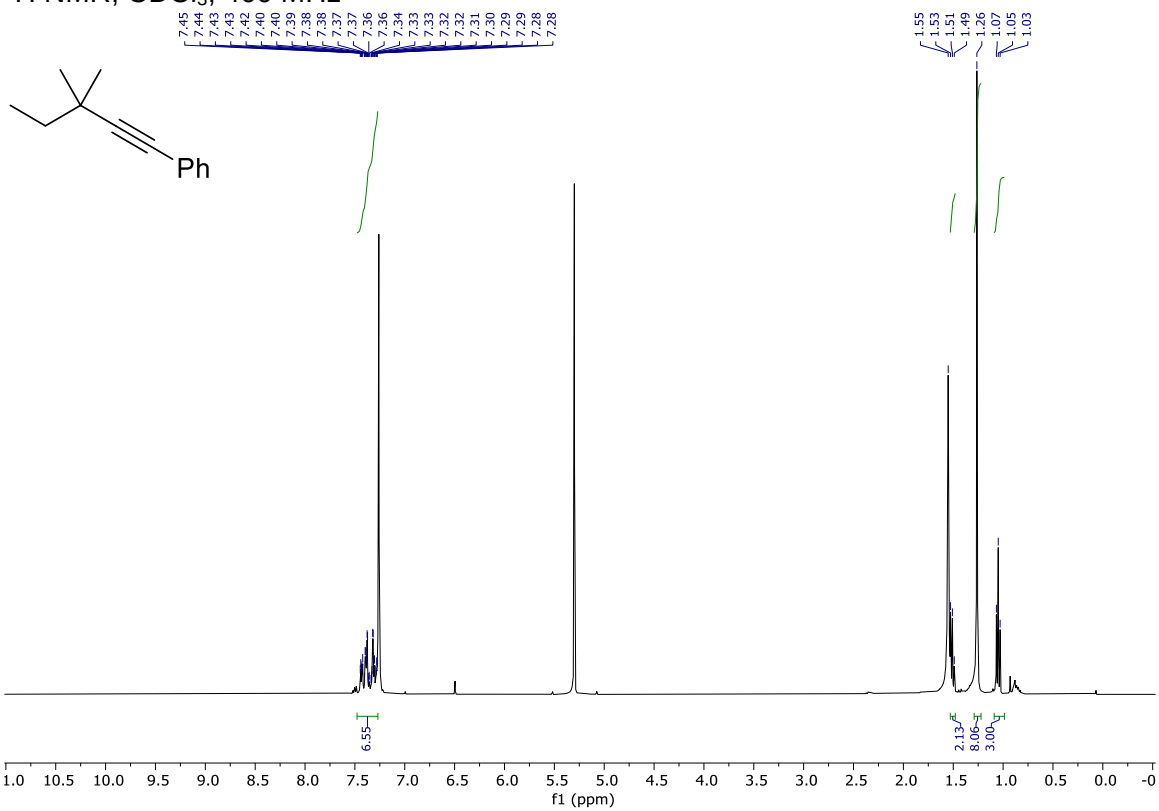
6.9b

^{1}H NMR, $CDCl_3$, 400 MHz

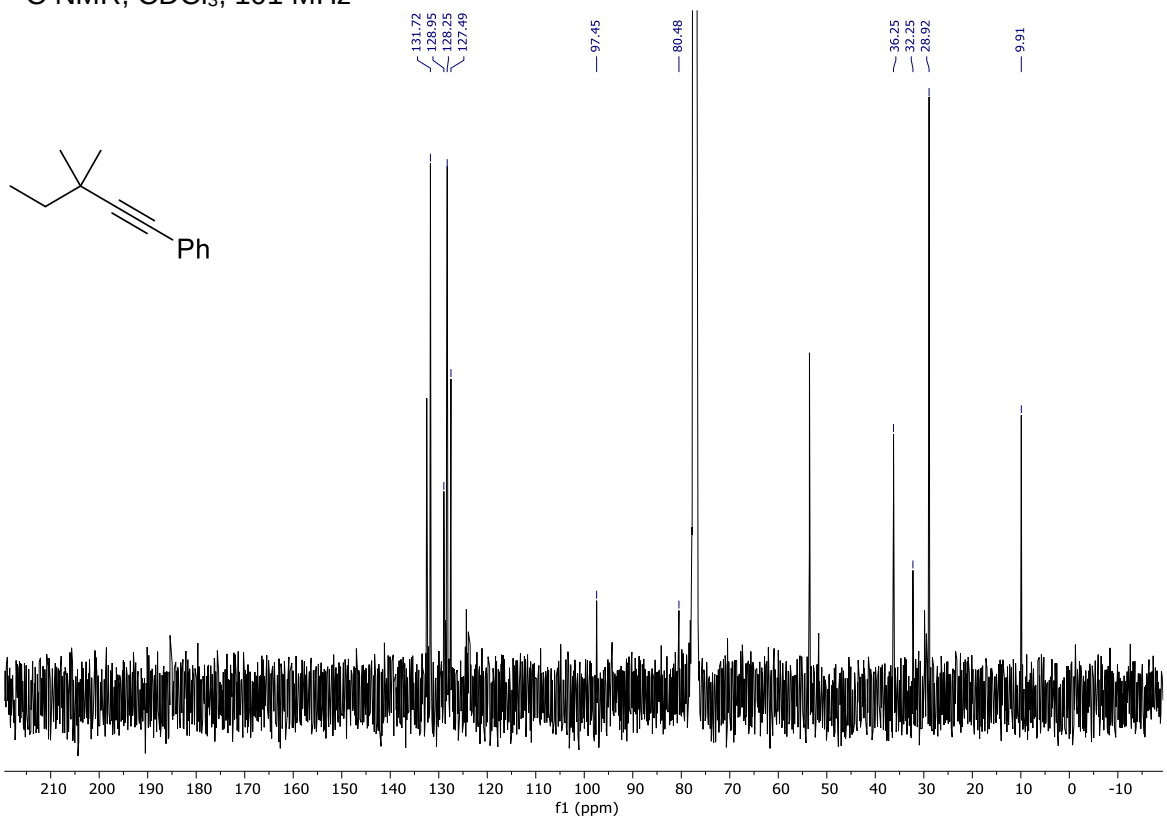


6.11

^{1}H NMR, $CDCl_3$, 400 MHz



^{13}C NMR, $CDCl_3$, 101 MHz



9.2. Complete curriculum vitae

Contact information

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September 26th 1993
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LinkedIn: https://www.linkedin.com/in/stephanie-amos-a9a080105/

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1007 Lausanne
Switzerland

Education

January 2017 – April 2022: PhD in Organic chemistry – Ecole Polytechinque Fédérale de Lausanne – "*Photoredox catalysis for alkynylation.*" Supervisor: Prof. Dr. Jerome Waser

September 2015 – July 2017: MSc: Organic synthesis and chemistry of bioactive molecules – University Claude Bernard Lyon 1, France.

September 2012 – July 2015: BSc in Chemistry – University Claude Bernard Lyon 1, France

Employment

January 2018 – April 2022: PhD student – Ecole Polytechinque Fédéreale de Lausanne – Laboratory of Catalysis and Organic Synthesis – "Photochemical alkynylations with hypervalent iodine reagents" Under the supervision of Prof. Dr. Jerome Waser.

February – July 2017: Master intern – Ecole Polytechinque Fédéreale de Lausanne – Laboratory of Catalysis and Organic Synthesis – "Sulfenate Alkynylation with EBX reagents" Under the supervision of Dr. Stefano Nicolai and Prof. Dr. Jerome Waser

April – July 2016: Master intern – University Claude Bernard of Lyon 1 – "Vinylation of amides and valorisation of levullinic acid." Supervisor: Prof. Dr. Bruno Andrioletti

Institutional responsibilities

October 2018 – October 2020: PhD student representative for the doctoral school.

Approved research projects

2021: Swiss National Science Foundation Postdoc.Mobility Research Grant, number: N° 500PN_206476 "Sustainable-metal catalysis: Inventing novel acylations."

Teaching duties

January 2017 – June 2021: Teaching assistant at EPFL and UNIL: Bachelor organic chemistry lectures and experimental chemistry courses.

September 2020 – January 2021: Supervision of a MSc student in the group of Prof. Dr. Jerome Waser.

June 2019 – September 2019: Supervision of a BSc summer intern.

Active memberships in scientific societies

Swiss Chemical Society since 2018

American Chemical Society since 2021

Prizes and awards

2021: SCS-Metrohm Best Oral presentation award at the SCS Fall meeting 2021

2021: FBM-UNIL*"Special award for outstanding dedication in practical teaching"*

2020: SCGC-EPFL: "*Teaching excellency for assistantship*"

Languages and soft skills

English: Native speaker; French: Native speaker; Spanish: Basic knowledge

Spring 2019: Successfully completed a Scientific writing in English course.

January 2018 – January 2022: IT referent for LCSO: Installation of a web server on Linux, PC installation, hardware/software debugging. Efforts recognized with an award.

Presentations

Oral presentations

1. "Ethynylbenziodoxolones: Photocatalysis and Direct Excitation for Difunctionalisation and Deoxyalkynylation" S. G. E. Amos, Diana Cavalli, Franck Le Vaillant, Stefano Nicolai, Jerome Waser. SCS Fall meeting 2021, https://fm21.scg.ch, Switzerland (online), 10 September 2021. Recognized by the SCS-Metrohm Best Oral Presentation Award.

2. "Photocatalysis for enamide and enol ether oxyalkynylation and alcohol deoxyalkynylation." S. G. E. Amos, Diana Cavalli, Franck Le Vaillant, Stefano Nicolai, Jerome Waser. ACS Spring meeting, https://www.acs.org/content/acs/en/meetings.html, San Francisco USA (online), 16 April 2021.

Poster communications

3. "Anti-Markovnikov Oxyalkynylation of Ene-carbamates and Enol-ethers under Photoredox Catalysis." S. G. E. Amos, Stefano Nicolai, Jerome Waser. SCS Fall meeting 2020, https://fm20.chemistrycongresses.ch/en/, Switzerland (online), 25.08.2020.

4. "Anti-Markovnikov Difunctionalization of N- and O- substituted alkenes." S. G. E. Amos, Stefano Nicolai, Jerome Waser. EWOC 2020, https://ewochem.org/ewoc-2020/, USA (online), 13-14.08.2020.

5. "Photomediated Oxyalkynylation of Ene-carbamates and Enol Ethers with Benziodoxolone Reagents." S. G. E. Amos, Stefano Nicolai, Jerome Waser. IsySyCat 2019, http://www.isysycat2019.eventos.chemistry.pt, Evora Portugal, 3-6.09.2019.

6. "Photomediated Oxyalkynylation of Ene-carbamates and Enol Ethers with Benziodoxolone Reagents." S. G. E. Amos, Stefano Nicolai, Jerome Waser. SCS Summer School, https://sem19-1.chemistrycongresses.ch/en/, 18-22.08.2019.

7. "Use of Benziodoxolones in Photoredox-catalysed Decarboxylative Alkynylation and Cyanation Reactions." S. G. E. Amos, Franck Le Vaillant, Jerome Waser. IASOC 2018, http://www.iasoc.it/home/, Naples Italy, 22-25.09.2018.

8. "Photoredox-catalysed Decarboxylative Alkynylation and Cyanation Using Hypervalent Iodine Reagents." S. G. E. Amos, Franck Le Vaillant, Jerome Waser. SCS Fall meeting, 2018, https://fm18.chemistrycongresses.ch/index.php?option=com_content&view=category&layout=blog&id=8&Itemid=101&lang=en, Lausanne Switzerland, 07.09.2018.

9. "Metal-free Valorisation of Levullinic Acid: Synthesis of Lactams." S. G. E. Amos, Florian Geyer, Audrey Ledoux, Eric Framery, Bruno Andrioletti. SCF Section Rhone Alpes Spring meeting, https://new.societechimiquedefrance.fr/Events/, Grenoble, 09.06.2016.

9.3. List of publications

Research articles:

5. S. G. E. Amos,‡ D. Cavalli,‡ F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.*, **2021**, *60*, 23827-23834. "Direct Photoexcitation of Ethynylbenziodoxolones: An Alternative to Photocatalysis for Alkynylation Reactions". Previous version as a preprint available at: https://chemrxiv.org/engage/chemrxiv/article-details/60e7f14c9ab06e66064ccfbe "From Photoredox Catalysis to the Direct Excitation of EthynylBenziodoXolones: Accessing Alkynylated Quaternary Carbons from Alcohols via Oxalates".

4. S. G. E. Amos, S. Nicolai, J. Waser, *Chem. Sci.*, **2020**, *11*, 11274-11279. "Photocatalytic Umpolung of N- and O- Substituted Alkenes for the Synthesis of 1,2-Amino Alcohols and Diols". Previous version as a preprint available at: https://chemrxiv.org/engage/chemrxiv/article-details/60c74c32567dfeb869ec50da, "Accessing 1,2-Amino Alcohols and Diols through Photocatalytic Anti-Markovnikov Difunctionalisation of Ene-Carbamates and Enol Ethers"

3. S. G. E. Amos, S. Nicolai, A. Gagnebin, F. Le Vaillant, J. Waser, *J. Org. Chem.*, **2019**, *84*, 3687. "Metal-Free Electrophilic Alkynylation of Sulfenate Anions with Ethynylbenziodoxolone Reagents".

Review articles:

2. Invited article: S. G. E. Amos, J. Waser, *Chimia*, **2022**, manuscript accepted. "Radical Alkynylations with EthynylBenziodoXolones: from Photocatalysis to Direct Excitation"

1. S. G. E. Amos,‡ M. Garreau,‡ L. Buzzetti,‡ J. Waser, *Beilstein J. Org. Chem.*, **2020**, *16*, 1163. Review: "Photocatalysis with organic dyes: facile access to reactive intermediates for synthesis".

‡: These authors contributed equally to the work.