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Hypervalent Iodine: New Reagents and Functionalization of Peptides

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par

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À ma famille,

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Abstract

Alkynes are found in a multitude of natural or synthetic bioactive compounds. In addition to the capacity of these chemical motifs to impact the physicochemical properties of a molecule of interest, the well-established reactivity of alkynes makes them ideal building blocks to access complex compounds. They have found applications in a variety of applied fields, including biochemistry and material sciences. The development of new alkynylation strategies is therefore of high interest.

The growing importance of peptide therapeutics led to a surge of interest for research focusing on their functionalization. In that regard, chemoselective late-stage chemical modifications of peptides are particularly attractive. Owing to their high functional group tolerance and biocompatibility, hypervalent iodine reagents have recently emerged as powerful tools for the functionalization of biomolecules.

The first objective of this Thesis was to develop new *N*-heterocyclic alkynyl hypervalent iodine reagents. The targeted scaffolds were based on amidine, benzylamine and sulfoximine with the initial goal of developing atom economical reactions. Their respective reactivities were compared to already established reagents and rationalized through the study of their X-ray structures and electronic density distributions. In particular, the new reagents exhibited valuable alkyne transfer properties towards strong nucleophiles. However, their efficiencies in metal-catalyzed or radical reactions were more limited. Their bioactivities for the inhibition of thiol-mediated uptake were assessed and showed either low activity or early onset of toxicity.

The second goal of this Thesis was to investigate the alkynylation of hydrazides with hypervalent iodine reagents in order to access functionalized azadipeptide derivatives. Using copper-catalysis we could access non-symmetrical ynehydrazides in moderate to excellent yields. Most functional groups naturally present in amino acids were tolerated in the reaction conditions and silyl, alkyl and aryl substituted alkynes were efficiently transferred to hydrazide nucleophiles. Benefiting from the rich chemistry of alkynes, we could further derivatize the obtained alkynylated azadipeptides.

Finally, we explored the decarboxylative functionalization of the C-Terminus of small peptides promoted by hypervalent iodine reagents. In a first project, we used photoredox-catalysis to access a variety of *N,O*-acetals from native small peptides up to tetramer. These reactive intermediates could be used for the diversification of peptide C-terminus through Friedel-Crafts reactions with phenols and indoles. Employing proteinogenic nucleophiles we could synthesize peptide derivatives bearing non-natural cross-links. Building upon a side-reaction observed in this project, we could develop a decarboxylative cyclization reaction

leading to aminal heterocycles from readily available dipeptide derivatives and commercially available hypervalent iodine reagent PIDA. A broad variety of fused ring sizes could be obtained and several functional groups were tolerated.

Keywords: alkynylation, hypervalent iodine reagents, azapeptides, copper catalysis, photoredox catalysis, decarboxylation, Friedel-Crafts, bioconjugation, aminal heterocycles, PIDA.

Résumé

Les alcynes sont présents dans une multitude de composés bioactifs naturels ou synthétiques. Outre la capacité de ces motifs chimiques à impacter les propriétés physicochimiques d'une molécule d'intérêt, la réactivité bien établie des alcynes en fait des blocs de construction idéaux pour accéder à des produits complexes. Ils ont également trouvé des applications dans divers domaines appliqués, notamment en biochimie et en chimie des matériaux. Le développement de nouvelles stratégies d'alcynation est donc d'un grand intérêt.

L'importance croissante des médicaments à base de peptides a entraîné un regain d'intérêt pour la recherche axée sur leur fonctionnalisation. À cet égard, les modifications chimiques sélectives des peptides sont particulièrement intéressantes. En raison de leur grande tolérance aux groupes fonctionnels et de leur biocompatibilité, les réactifs d'iode hypervalent sont récemment apparus comme des outils puissants pour la fonctionnalisation des biomolécules.

Le premier objectif de cette thèse était de développer de nouveaux réactifs d'iode hypervalent possédant une structure *N*-hétérocycliques et un alcyne. Les structures ciblées étaient basées sur une amidine, une benzylamine et une sulfoximine dans le but initial de développer des réactions économes en atomes. Leurs réactivités respectives ont été comparées à celles de réactifs déjà établis et rationalisées par l'étude de leurs structures aux rayons X et de leurs distributions de densité électronique. En particulier, les nouveaux réactifs ont montré de bonnes propriétés de transfert d'alcyne avec des nucléophiles forts. Cependant, leurs efficacités dans les réactions radicalaires ou catalysées par des métaux étaient plus limitées. Leurs bioactivités pour l'inhibition de l'absorption induite par les thiols ont été évaluées et ont montré soit une faible activité, soit un début précoce de toxicité.

Le second objectif de cette thèse était d'étudier l'alcynation des hydrazides avec des réactifs d'iode hypervalent afin d'accéder à des dérivés azadipeptidiques fonctionnalisés. En utilisant la catalyse au cuivre, nous avons pu accéder à des ynehydrazides non-symétriques avec des rendements de modérés à excellents. La plupart des groupes fonctionnels naturellement présents dans les acides aminés ont été tolérés dans les conditions de réaction et les alcynes substitués par des groupements silyles, alkyles et aryles ont été efficacement transférés à des hydrazides. En profitant de la riche chimie des alcynes, nous avons pu dériver davantage les azadipeptides alcynylés obtenus.

Enfin, nous avons exploré la fonctionnalisation *via* décarboxylation de l'extrémité C-terminale de petits peptides en utilisant des réactifs d'iode hypervalent. Dans un premier projet, nous avons utilisé la catalyse photoredox pour accéder à différents *N,O*-acétals à partir

de petits peptides natifs. Ces intermédiaires réactifs ont pu être utilisés pour la diversification de l'extrémité C-terminale de peptides par des réactions de Friedel-Crafts avec des phénols et des indoles. En utilisant des nucléophiles protéinogènes, nous avons pu synthétiser des dérivés peptidiques comportant des liaisons non naturelles. En s'appuyant sur une réaction secondaire observée dans ce projet, nous avons pu développer une réaction de cyclisation décarboxylative conduisant à des aminals hétérocycliques à partir de dérivés dipeptidiques facilement accessibles et du réactif d'iode hypervalent PIDA. Une grande diversité de tailles de cycles a pu être obtenue et plusieurs groupes fonctionnels ont été tolérés.

Mots clefs : alcynation, réactifs d'iode hypervalent, azapeptides, catalyse au cuivre, catalyse photoredox, décarboxylation, Friedel-Crafts, bioconjugaison, aminals hétérocycliques, PIDA.

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Abbreviations, Acronyms and Symbols

Å	Angström
AA	amino acid
Ac	acetyl
AcOBX	acetoxybenziodoxolone
Ala	alanine
APCI	atmospheric-pressure chemical ionization
aq	aqueous
Ar	aryl
Arg	arginine
Asn	asparagine
Asp	aspartic acid
atm	atmosphere
BHT	dibutylhydroxytoluene
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bisoxazoline
Bpin	pinacolboron
bpy	2,2'-bipyridine
br	broad
Bu	butyl
Bx	benziodoxole
BX	Benziodoxolone
Bz	benzoyl
BZ	benziodazolone
BZI	benziodazolimine
°C	degrees Celsius
3c-4e	3-center 4-electron bond
calcd	calculated
Cat.	catalyst
CBX	cyanobenziodoxolone
Cbz	benzyloxycarbonyl
cys	cysteine
4CzIPN	2,4,5,6-tetrakis(9*H*-carbazol-9-yl) isophthalonitrile
δ	NMR chemical shift in ppm
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl-sulfoxide
d.r.	diastereomeric ratio
DSC	*N,N'*-disuccinimidyl carbonate
dtbbpy	4,4′-di-tert-butyl-2,2′-dipyridine

EBS	ethynylbenziodosulfoximine
EBx	ethynylbenziodoxole
EBX	ethynylbenziodoxolone
EBz	ethynylbenziodazole
EBZ	ethynylbenziodazolone
EBZI	ethynylbenziodazolimine
EDA	ethyl diazoacetate
ee	enantiomeric excess
EI	electron impact ionization
El	electrophile
equiv.	equivalent
e.r.	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
ETP	epidithiodiketopiperazine
EWG	electron-withdrawing group
fac	facial
FITC	fluorescein isothiocyanate
g	gram
gem	geminal
Glu	glutamic acid
Gly	glycine
h	hour(s)
HAT	hydrogen atom transfer
HIR	hypervalent iodine reagent(s)
HIV	human immunodeficiency viruses
HMDS	hexamethyldisilizane
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IBX	2-iodoxybenzoic acid
*i*Pr	*iso*propyl
IR	infrared
IUPAC	international union of pure and applied chemistry
J	coupling constant
kcal	kilocalories
L	liter
LA	Lewis acid
LED	light emitting diode
Leu	leucine
Lys	lysine
m	multiplet
M	molarity
m/z	mass per electronic charge
MALDI	matrix assisted laser desorption ionization
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl

MEP	molecular electrostatic potential
Met	methionine
mg	milligram
MIC	minimal inhibition concentration
min	minute(s)
mL	milliliter
mmol	millimole
Mp	melting point
MS	molecular sieves
Mts	mesitylenesulfonyl
v	frequency (cm^{-1})
ND	not detected
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NR	no reaction
Nu	nucleophile
OTf	triflate
p	para
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Pbf	2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl
PIDA	phenyliodide diacetate
PIFA	phenyliodide ditrifluoroacetate
Pg	protecting group
Ph	phenyl
Phe	phenylalanine
ppm	parts per million
ppy	2-phenylpyridine
Pro	proline
PTC	phase transfer catalyst
PTSA	*para*-toluenesulfonic acid
Quant.	quantitative
RAE	redox-active ester
Rf	retention factor
rt	room temperature
s	singlet
sat.	saturated
SCE	saturated calomel electrode
Ser	serine
SET	single electron transfer
S_NAr	nucleophilic aromatic substitution
SPPS	solid-phase peptide synthesis
t	triplet
T	temperature
TBAF	tetra-*n*-butylammonium fluoride
t-Bu	*tert*-butyl
Tf	trifluoromethanesulfonyl

TFE	trifluoroethanol
THF	tetrahydrofuran
Thr	threonine
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMG	tetramethylguanidine
TMS	trimethylsilyl
Trp	tryptophan
Trt	trityl
Ts	tosyl
Tyr	tyrosine
µL	microliter
UUA	unnatural amino acids
Val	valine
VBX	vinylbenziodoxolone

Chapter 1:

Introduction

1. Introduction

Organic chemistry enables the synthesis of molecules and their modification to fine-tune their chemical, physical and biological properties. Multitude of scientific domains, from material science to biology, rely on easy access to complex molecules. The evolution of modern society goes together with an increasing demand in new and more complex molecular structures. Moreover, the increasing importance of developing more resource-efficient processes is challenging current synthesis methods. In this context, the development of new efficient and cost-effective strategies to access complex molecules is of the utmost importance for organic chemists.

Most often, chemical reactions involve the interaction between an electrophile and a nucleophile. This classical reactivity limits the possible disconnections of a targeted compound, relying on intrinsic nucleophilic and electrophilic synthons.[1] An alternative was proposed by Seebach who introduced the concept of inversion of polarity or Umpolung.[2] The strategy paved the way for new types of disconnections allowing to access valuable functionalities with a more straightforward approach compared to conventional methods.

In that regard, hypervalent iodine reagents have emerged as powerful tools for the Umpolung of inherently nucleophilic synthons.[3] In particular, the electrophilic transfer of valuable alkyne motifs could be successfully achieved using ethynylbenziodoxolone (EBX) reagents.[4] Our group devotes a significant part of its research towards the alkynylation of nucleophiles and the late-stage functionalization of complex molecules. Moreover, the combination of the high reactivity and biocompatibility of hypervalent iodine reagents made them ideal partner for the functionalization of biomolecules in polar and radical reactions.[5]

In this Thesis, our research on the development of new alkynylation hypervalent iodine reagents and on the functionalization of (aza)-peptides will be presented. The first chapter will provide a general introduction on hypervalent iodine reagents. Then, the different projects described in the Thesis will be discussed in three chapters with specific introductions and goal sections. In the first project (Chapter 3), the importance of alkynes and classical methods to access them will be highlighted. Then, an overview on the use of hypervalent iodine reagents

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[1] (a) E. J. Corey, *Chem Soc Rev* **1988**, *17*, 111–133. (b) E. J. Corey, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 455–465. (c) E. J. Corey, X.-M. Cheng, *Logic of Chemical Synthesis*, Wiley, New York, **1995**.
[2] Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239-258.
[3] A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328–3435.
[4] Hari, D. P.; Nicolai, S.; Waser, J. Alkynylations and Vinylations. In *PATAI'S Chemistry of Functional Groups*; Rappoport, Z., Ed.; John Wiley & Sons, Ltd: Chichester, UK, **2018**; 1-58.
[5] E. M. D. Allouche, E. Grinhagena, J. Waser, *Angew. Chem. Int. Ed.* **2022**, *61*, e202112287.

as alkynyl transfer reagents will be presented. Finally, our efforts towards the development and the study of the reactivity of new alkynyl hypervalent iodine reagents will be described. In the second project (Chapter 4), the classical approaches to access ynamides will be listed together with the current strategies for the alkynylation of hydrazides. Then, a short overview on azapeptides, which are hydrazide containing peptidomimetics, will be given. Next, our work towards the alkynylation of hydrazides for the synthesis of functionalized azadipeptides will be disclosed. In the last project (Chapter 5), the significance of decarboxylative couplings for peptide C-terminus bioconjugation and for the synthesis of aminal heterocycles will be detailed. Our efforts towards the decarboxylative arylation of small peptide C-termini and cyclization of dipeptide derivatives will then be described. Finally, a general conclusion will outline the main achievements of this Thesis and provide an outlook for future research (Chapter 6). The experimental and characterization data will be compiled in the final chapter (Chapter 7).

Chapter 2:

Introduction on Hypervalent Iodine Reagents

2. Introduction on Hypervalent Iodine Reagents

Iodine, like other halogen atoms, naturally occurs at different oxidation states, the most common being -I in monovalent iodocompounds or 0 in molecular iodine I_2.[1] However, being an element of the fifth row of the periodic table, iodine can break the octet rule and further oxidation states can be observed such as +III or +V. The serendipitous discovery of such hypervalent iodine compounds by Willgerodt in the late XIXth century,[2] paved the way for the development of new highly versatile organic reagents.

In this chapter, the key structural features and reactivity of hypervalent iodine reagents will be presented. The specific transformations relevant for this Thesis will be covered in the introductions of the following chapters.

2.1. Structure and Bonding in Hypervalent Iodine Reagents

Hypervalent Iodine Reagents (HIR) can be classified into two main categories depending on the oxidation state of the iodine, namely λ^3-iodane (+III) and λ^5-iodane (+V) according to IUPAC nomenclature. They can also be labeled with Martin-Arduengo N-X-L classification.[3] In this nomenclature, N designs the number of electrons in the valence shell around the central atom X and L describes the number of ligands around it (Figure 2.1). In this classification, λ^3-Iodanes can be described as 10-I-3, λ^3-Iodonium salts as 8-I-2 and λ^5-Iodanes as 12-I-5.

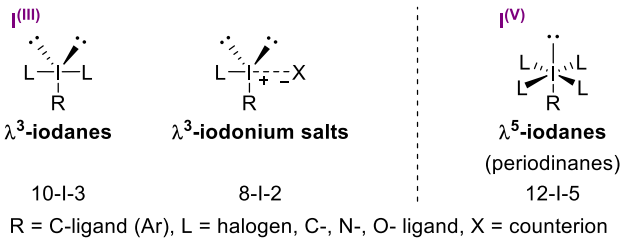

Figure 2.1. Structures of λ^3-iodanes, λ^3-iodonium salts and λ^5-iodanes.

λ^3-Iodanes are trivalent species, in which the iodine atom has 10 electrons in the valence shell and is in the oxidation state +III. They feature a distorted trigonal bipyramid geometry with the least electronegative ligand (usually an aryl group) and the two electron

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[1] We follow here, and in the rest of the thesis, the common convention that carbon is *less* electronegative than iodine. This convention does not take into account the hybridization of carbon. (χ(Csp) > χ(Csp^2)> χ(I) > χ(Csp^3), M. G. Brown, *J. Chem. Phys.* **1960**, *33*, 1881–1882).
[2] C. Willgerodt, *J. Prakt. Chem.* **1886**, *33*, 154–160.
[3] C. W. Perkins, J. C. Martin, A. J. Arduengo, W. Lau, A. Alegria, J. K. Kochi, *J. Am. Chem. Soc.* **1980**, *102*, 7753-7759.

pairs in equatorial positions. The two other ligands occupy the *trans* apical positions. Therefore, the three ligands are arranged in a T-shape manner with ideal angles L-I-L of 180° and L-I-R of 90° that have been confirmed by X-ray analysis. λ^3-Iodonium salts exhibit similar structures as λ^3-Iodanes. However, the less coordinating the counterion X, the more cationic the iodine complex is. This translates in the structures with longer I-X bonds and the formation of a pseudo-trigonal bipyramidal complex.[4]

λ^5-Iodanes or periodinanes are pentavalent species, in which the iodine atom has 12 electrons and is in the oxidation state +V. They adopt a distorted octahedral geometry with the least electronegative ligand (usually an aryl group) and the electron pair positioned in apical positions. The more electronegative ligands (usually heteroatoms) occupy the equatorial plane. These reagents are mostly known for their oxidizing properties. Notably, Dess-Martin Periodinane (DMP) and 2-iodoxybenzoic acid (IBX), are usually used as mild oxidants for alcohol.[5]

The unique structural properties of iodine (III) compounds are typically attributed to hypervalency, a bonding model initially proposed in the 1960s by Musher and later extended to hypervalent halogen derivatives by Martin.[6] In this model, only the electrons of nonhybridized 5p orbitals of the iodine atoms are engaged in the bonding. One electron of each axial L ligands is involved in a linear 3-center 4-electron (3c-4e) bond with the doubly occupied axial 5p orbital of iodine (Figure 2.2). This so-called *hypervalent bond* is longer, highly polarized towards the peripheral ligands and consequently weaker than a standard covalent bond leading to a higher electrophilic reactivity. The presence of two 3c-4e bonds in λ^5-iodanes explains their high electron deficiency and their use as oxidants.

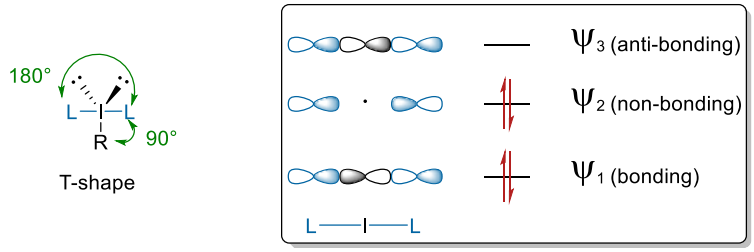

Figure 2.2. Molecular orbitals model for the L-I-L bond.

[4] This conception has been recently criticized. DFT calculations showed that the electron pairs would be better described as a 5s and a 5p orbitals. However, the computed structures still featured a T-shape. R. Robidas, D. Reinhard, S. M. Huber, C. Legault, *ChemPhysChem* **2022**, e202200634.
[5] (a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155-4156. (b) T. Wirth, *Angew. Chem. Int. Ed.* **2001**, *40*, 2812-2814.
[6] (a) J. I. Musher, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 54-68. (b) J. C. Martin, *Science* **1983**, *221*, 509-514.

It should be mentioned that some theoretical chemists have vividly questioned the concept of hypervalency. Notably, Gillespie and Silvi did not find fundamental difference in the bonding of hypervalent molecules and that of non-hypervalent molecules in their study of electron localization functions.[7] Moreover, this model does not explain the deviation in structure observed for diaryliodonium cations.[8] Nonetheless, the chemistry community has widely accepted the term “hypervalent” to describe the unusual structures and reactivity of hypercoordinated main-group elements.

Among λ^3-iodanes, compounds bearing an aryl group (R = Ar) in equatorial position are of particular interest. The possibility of conjugation between the π-system of the aryl and the lone pairs of the iodine center stabilizes the structure (Figure 2.3.A).[9] In fact, only such HIR are stable enough to be isolated and stored. Additional stability can be obtained by locking the iodine atom in an iodoheterocycle, resulting in a greater orbital overlapping. This restriction of the free rotation around the aryl-iodine bond is commonly achieved by tethering an amide, a carboxylic acid or a tertiary alcohol on the aryl ring. Moreover, the lone pairs of the heteroatom are then confined out of the 3c-4e plane which disfavors the reductive elimination between the axial ligands.[10] Finally, similarly to what is observed in metal complexes, a *trans*-effect can affect the 3c-4e bond. The higher the donating ability of a ligand, the longer the bond between iodine and the *trans* ligand will be (Figure 2.3.B). This effect can be used to modulate the reactivity and the stability of HIR.[11] Considering the most common cyclic λ^3-iodane scaffolds, amide-based ligands from benziodazolone (BZ) reagents have higher *trans* influence than benziodoxolones (BX) or benziodoxoles (Bx).

[7] R. Gillespie, B. Silvi, *Coord. Chem. Rev.* **2002**, *233-234*, 53-62.
[8] (a) V. V. Zhdankin, (**2014**), Hypervalent Iodine Chemistry: preparation, structure and synthetic applications of polyvalent iodine compounds, Wiley, Chichester. (b) S. S. Karandikar, A. Bhattacharjee, B. E. Metze, N. Javaly, E. J. Valente, T. M. McCormick, D. R. Stuart, *Chem. Sci.* **2022**, *13*, 6532–6540.
[9] V. V. Zhdankin, *Rev. Heteroat. Chem.* **1997**, *17*, 133-152.
[10] T.-Y. Sun, X. Wang, H. Geng, Y. Xie, Y.-D. Wu, X. Zhang, H. F. Schaefer III, *Chem. Commun.* **2016**, *52*, 5371-5374.
[11] (a) M. Ochiai, T. Sueda, K. Miyamoto, P. Kiprof, V. V. Zhdankin, *Angew. Chem. Int. Ed.* **2006**, *45*, 8203-8206. (b) P. K. Sajith, C. H. Suresh, *Inorg. Chem.* **2012**, *51*, 967–977. (c) P. K.Sajith, C. H. Suresh, *Inorg. Chem.* **2013**, *52*, 6046–6054.

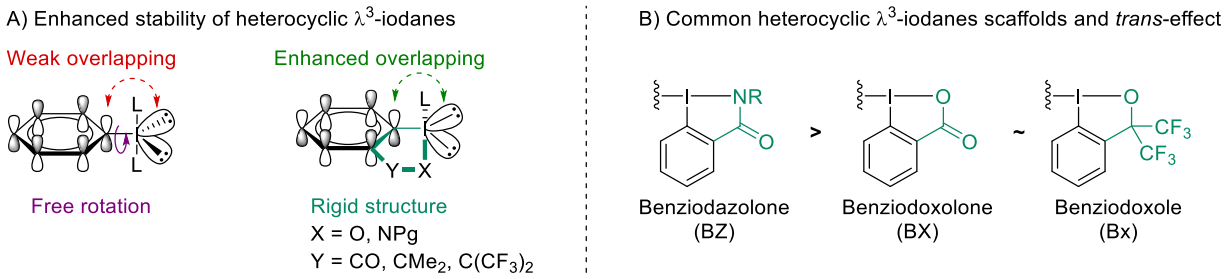

Figure 2.3. A) Enhanced stability of heterocyclic λ^3-iodanes, B) Common cyclic λ^3-iodanes scaffolds and *trans*-effect.

2.2. Reactivity of Hypervalent Iodine Reagents

Initially mostly studied for their peculiar structural features, polyvalent iodine reagents have gradually attracted the attention of chemists for their exceptional reactivity arising from the high-energy hypervalent bond.[12] They have been established as valuable alternatives to transition metals in oxidation and functional group transfer reactions because of their lower toxicity and impact on the environment.[13] The oxidative properties of λ^5-iodanes make them not suitable for group transfer reactions. Therefore, this class of reagents will not be further discussed.

In the context of functional group transfers, cyclic HIR and especially the benziodoxol(on)e (BX) class of reagents have been particularly studied (Figure 2.4). While the tethered ligand is usually used to stabilize and tune the reactivity of the electrophilic reagent, the other ligand is installed to be transferred onto a nucleophilic partner or to be exchanged. For instance, acetoxybenziodoxolone (AcOBX, **2.1**) is commonly used to activate nucleophilic substrate *via* ligand exchange which can then undergo further transformation (see Chapter 5 for more details). Other reagents have been designed for the electrophilic or radical transfer of heteroatoms such as aminations,[14] nitrooxylation[15] or azidation.[16] For the later, moving from the BX core to the benziodazolone (BZ) improved the safety profile of the reagents without

[12] For recent reviews see: (a) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299-5358. (b) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328-3435. (c) Jr. L. F. Silva, B. Olofsson, *Nat. Prod. Rep.* **2011**, *28*, 1722-1754.
[13] M. S. Yusubov, V. V. Zhdankin, *Resour. Effic. Technol.* **2015**, *1*, 49-67.
[14] Selected examples: (a) V. V. Zhdankin, M. McSherry, B. Mismash, J. T. Bolz, J. K. Woodward, R. M. Arbit, S. Erickson, *Tetrahedron Lett.* **1997**, *38*, 21–24. (b) K. Kiyokawa, T. Kosaka, T. Kojima, S. Minakata, *Angew. Chem. Int. Ed.* **2015**, *54*, 13719–13723. (c) D. L. Poeira, A. C. R. Negrão, H. Faustino, J. A. S. Coelho, C. S. B. Gomes, P. M. P. Gois, M. M. B. Marques, *Org. Lett.* **2022**, *24*, 776–781.
[15] R. Calvo, A. Le Tellier, T. Nauser, D. Rombach, D. Nater, D. Katayev, *Angew. Chem. Int. Ed.* **2020**, *59*, 17162–17168.
[16] For selected examples: (a) A. P. Krasutsky, C. J. Kuehl, V. V. Zhdankin, *Synlett* **1995**, *1995*, 1081–1082. (b) A. Sharma, J. F. Hartwig, *Nature* **2015**, *517*, 600–604. (c) S. Alazet, F. Le Vaillant, S. Nicolai, T. Courant, J. Waser, *Chem. Eur. J.* **2017**, *23*, 9501–9504.

impacting significantly the reactivity.[17] Similarly, trifluoromethylation (Togni reagent II, **2.6**),[18] cyanation,[19] or (hetero)arylation reagent have been developed.[20] Ethynylbenziodoxolone (EBX, **2.9**)[21] and vinylBX (VBX, **2.10**)[22] have recently emerged as versatile reagents for electrophilic or radical alkynylation and vinylation, respectively. Alkynylation using hypervalent iodine reagents being one of the main topics of this Thesis, it will be discussed in more details in the next chapter.

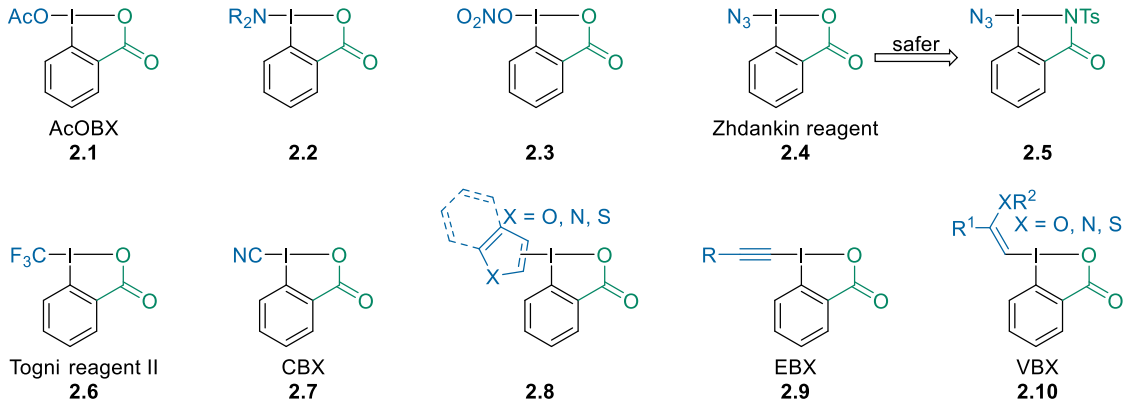

Figure 2.4. Common cyclic hypervalent iodine reagents.

We have presented here the reactivity of cyclic HIR because they are relatively stable reagents yet still highly reactive. It should be noted that for most of the reagents drawn, their acyclic iodonium equivalents exist and have been used in several transformations. It should also be mentioned that significant effort is being made to develop I(I)/I(III) catalytic transformations. However, they are so far limited to halogenation and oxidative transformations.[12b,23]

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[17] S. Alazet, J. Preindl, R. Simonet-Davin, S. Nicolai, A. Nanchen, T. Meyer, J. Waser, *J. Org. Chem.* **2018**, *83*, 12334–12356.
[18] (a) P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579–2586. (b) J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682.
[19] For selected examples: (a) V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, B. Mismash, J. K. Woodward, A. J. Simonsen, *Tetrahedron Lett.* **1995**, *36*, 7975–7978. (b) M. V. Vita, P. Caramenti, J. Waser, *Org. Lett.* **2015**, *17*, 5832–5835. (c) F. Le Vaillant, M. D. Wodrich, J. Waser, *Chem. Sci.* **2017**, *8*, 1790–1800.
[20] For selected examples: (a) M. S. Yusubov, R. Y. Yusubova, V. N. Nemykin, V. V. Zhdankin, *J. Org. Chem.* **2013**, *78*, 3767–3773. (b) P. Caramenti, S. Nicolai, J. Waser, *Chem. Eur. J.* **2017**, *23*, 14702–14706. (c) P. Caramenti, R. K. Nandi, J. Waser, *Chem. Eur. J.* **2018**, *24*, 10049–10053.
[21] (a) V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 6547–6551. (b) D. P. Hari, P. Caramenti, J. Waser, *Acc. Chem. Res.* **2018**, *51*, 3212–3225.
[22] (a) T. Kitamura, T. Fukuoka, Y. Fujiwara, *Synlett* **1996**, *1996*, 659–660. (b) N. Declas, G. Pisella, J. Waser, *Helv. Chim. Acta* **2020**, *103*, e2000191.
[23] T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073–2085.

2.3. References

1. We follow here, and in the rest of the thesis, the common convention that carbon is *less* electronegative than iodine. This convention does not take into account the hybridization of carbon. ($\chi(Csp) > \chi(Csp^2) > \chi(I) > \chi(Csp^3)$, M. G. Brown, *J. Chem. Phys.* **1960**, *33*, 1881–1882).
2. C. Willgerodt, *J. Prakt. Chem.* **1886**, *33*, 154–160.
3. C. W. Perkins, J. C. Martin, A. J. Arduengo, W. Lau, A. Alegria, J. K. Kochi, *J. Am. Chem. Soc.* **1980**, *102*, 7753-7759.
4. This conception has been recently criticized. DFT calculations showed that the electron pairs would be better described as a 5s and a 5p orbitals. However, the computed structures still featured a T-shape. R. Robidas, D. Reinhard, S. M. Huber, C. Legault, *ChemPhysChem* **2022**, e202200634.
5. (a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155-4156. (b) T. Wirth, *Angew. Chem. Int. Ed.* **2001**, *40*, 2812-2814.
6. (a) J. I. Musher, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 54-68. (b) J. C. Martin, *Science* **1983**, *221*, 509-514.
7. R. Gillespie, B. Silvi, *Coord. Chem. Rev.* **2002**, *233-234*, 53-62.
8. (a) V. V. Zhdankin, (**2014**), Hypervalent Iodine Chemistry: preparation, structure and synthetic applications of polyvalent iodine compounds, Wiley, Chichester. (b) S. S. Karandikar, A. Bhattacharjee, B. E. Metze, N. Javaly, E. J. Valente, T. M. McCormick, D. R. Stuart, *Chem. Sci.* **2022**, *13*, 6532–6540.
9. V. V. Zhdankin, *Rev. Heteroat. Chem.* **1997**, *17*, 133-152.
10. Sun, T.-Y., Wang, X., Geng, H., Xie, Y., Wu, Y.-D., Zhang, X., Schaefer III, H. F. *Chem. Commun.* **2016**, *52*, 5371-5374.
11. (a) M. Ochiai, T. Sueda, K. Miyamoto, P. Kiprof, V. V. Zhdankin, *Angew. Chem. Int. Ed.* **2006**, *45*, 8203-8206. (b) P. K. Sajith, C. H. Suresh, *Inorg. Chem.* **2012**, *51*, 967–977. (c) P. K.Sajith, C. H. Suresh, *Inorg. Chem.* **2013**, *52*, 6046–6054.
12. For recent reviews see: (a) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299-5358. (b) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328-3435. (c) Jr. L. F. Silva, B. Olofsson, *Nat. Prod. Rep.* **2011**, *28*, 1722-1754.
13. M. S. Yusubov, V. V. Zhdankin, *Resour. Effic. Technol.* **2015**, *1*, 49-67.
14. Selected examples: (a) V. V. Zhdankin, M. McSherry, B. Mismash, J. T. Bolz, J. K. Woodward, R. M. Arbit, S. Erickson, *Tetrahedron Lett.* **1997**, *38*, 21–24. (b) K. Kiyokawa, T. Kosaka, T. Kojima, S. Minakata, *Angew. Chem. Int. Ed.* **2015**, *54*, 13719–13723. (c) D. L. Poeira, A. C. R. Negrão, H. Faustino, J. A. S. Coelho, C. S. B. Gomes, P. M. P. Gois, M. M. B. Marques, *Org. Lett.* **2022**, *24*, 776–781.
15. R. Calvo, A. Le Tellier, T. Nauser, D. Rombach, D. Nater, D. Katayev, *Angew. Chem. Int. Ed.* **2020**, *59*, 17162–17168.
16. For selected examples: (a) A. P. Krasutsky, C. J. Kuehl, V. V. Zhdankin, *Synlett* **1995**, *1995*, 1081–1082. (b) A. Sharma, J. F. Hartwig, *Nature* **2015**, *517*, 600–604. (c) S. Alazet, F. Le Vaillant, S. Nicolai, T. Courant, J. Waser, *Chem. Eur. J.* **2017**, *23*, 9501–9504.
17. S. Alazet, J. Preindl, R. Simonet-Davin, S. Nicolai, A. Nanchen, T. Meyer, J. Waser, *J. Org. Chem.* **2018**, *83*, 12334–12356.
18. (a) P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579–2586. (b) J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682.
19. For selected examples: (a) V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, B. Mismash, J. K. Woodward, A. J. Simonsen, *Tetrahedron Lett.* **1995**, *36*, 7975–7978. (b) M. V. Vita, P. Caramenti, J. Waser, *Org. Lett.* **2015**, *17*, 5832–5835. (c) F. Le Vaillant, M. D. Wodrich, J. Waser, *Chem. Sci.* **2017**, *8*, 1790–1800.
20. For selected examples: (a) M. S. Yusubov, R. Y. Yusubova, V. N. Nemykin, V. V. Zhdankin, *J. Org. Chem.* **2013**, *78*, 3767–3773. (b) P. Caramenti, S. Nicolai, J. Waser, *Chem. Eur. J.* **2017**,

23, 14702–14706. (c) P. Caramenti, R. K. Nandi, J. Waser, *Chem. Eur. J.* **2018**, *24*, 10049–10053.

21. (a) V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 6547–6551. (b) D. P. Hari, P. Caramenti, J. Waser, *Acc. Chem. Res.* **2018**, *51*, 3212–3225.
22. (a) T. Kitamura, T. Fukuoka, Y. Fujiwara, *Synlett* **1996**, *1996*, 659–660. (b) N. Declas, G. Pisella, J. Waser, *Helv. Chim. Acta* **2020**, *103*, e2000191.
23. T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073–2085.

Chapter 3:

Development and Study of *N*-Heterocyclic Alkynyl Hypervalent Iodine Reagents

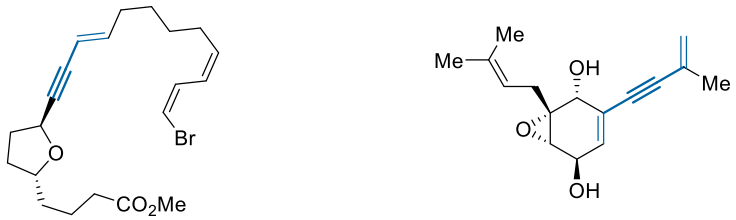
3. Development and Study of *N*-Heterocyclic Alkynyl Hypervalent Iodine Reagents

Despite being one of the smallest functional groups, alkynes are among the most versatile building blocks in organic chemistry with applications spanning from biochemistry to material sciences. Hypervalent iodine reagents have recently emerged as powerful tool allowing to transfer alkynes onto nucleophilic substrates. In this chapter our efforts towards the development of new cyclic alkynyl hypervalent iodine reagents will be described. Their reactivity will be studied and rationalized by analyzing their structural features and electronics.

3.1. Introduction

3.1.1. Alkynes: Importance and Transformation

Although not widely occurring in Nature, alkynes incorporated in natural products can be found and are usually embedded in π conjugated systems (Figure 3.1). For instance, mutafuran A (**3.1**), bearing an ene-yne 2,5-disubstituted tetrahydrofuran scaffolds, was isolated from the marine sponge *Xestospongia muta* and exhibited interesting antifungal activity.[1] The meroterpenoid Biscognienyne B (**3.2**) was isolated from the lichen *Usnea mutabilis* and showed cytotoxic activity against HeLa and SW480 cancer cell lines.[2]



mutafuran A
3.1

biscognienyne B
3.2

Figure 3.1. Examples of natural molecules bearing alkynes.

The acetylene group is a privileged function in medicinal chemistry and has been broadly exploited in drug discovery as it can be used to tune physicochemical properties, such as lipophilicity or metabolism resistance (Figure 3.2).[3] Linagliptin (**3.3**), containing a

[1] B. I. Morinaka, C. K. Skepper, T. F. Molinski, *Org. Lett.* **2007**, *9*, 1975–1978.
[2] H. Zhao, G.-D. Chen, J. Zou, R.-R. He, S.-Y. Qin, D. Hu, G.-Q. Li, L.-D. Guo, X.-S. Yao, H. Gao, *Org. Lett.* **2017**, *19*, 38–41.
[3] T. T. Talele, *J. Med. Chem.* **2020**, *63*, 5625–5663.

propargylamine, is a highly potent drug for the treatment of type 2 diabetes.[4] Systematic structural variations showed that the presence of the alkynyl moiety was essential to eliminate undesired interaction *in vivo*. Efavirenz (**3.4**), bearing a trifluoromethyl propargylic chiral center, has proven successful as antiretroviral medication against HIV.[5] Finally, ethynylestradiol (**3.5**) is one of the most common synthetic estrogen medications used in birth control pills.[6] Compared to natural estradiol, lacking the terminal alkyne, compound **3.5** exhibits improved bioavailability and increased resistance to metabolism.

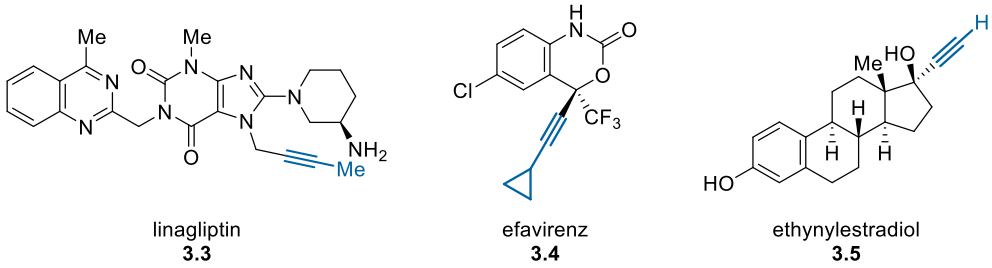


Figure 3.2. Examples of synthetic drug molecules bearing alkynes.

In addition to their interesting structural properties, alkynes are reactive moieties that can be used as handles for functionalization (Figure 3.3). Among the main transformations that alkynes can undergo, reduction of the triple bond has been particularly studied (A). Notably, the partial reduction of alkynes could lead selectively to either *E* or *Z* olefins depending on the catalyst used. Alkynes are also suitable partners in cross-coupling reactions such as in Suzuki or Sonogashira cross-coupling (B).[7] Recent development in alkyne metathesis revived the interest for this transformation and it is now well established and used for the total synthesis of complex molecules (B).[8] Similar to alkenes, the C-C bond can be cleaved under oxidative conditions leading to carboxylic acids (C).[9] In addition, the π-system can be activated by a Lewis or a Brønsted acid, which, in presence of water, gives access to carbonyl compounds (C).[10] Similar to alkenes, alkynes can be involved in cycloaddition reactions (D).[11] Among the possible cycloadditions, the 1,3-dipolar cycloaddition with organic

[4] M. Eckhardt, E. Langkopf, M. Mark, M. Tadayyon, L. Thomas, H. Nar, W. Pfrengle, B. Guth, R. Lotz, P. Sieger, H. Fuchs, F. Himmelsbach, *J. Med. Chem.* **2007**, *50*, 6450–6453.
[5] S. D. Young, S. F. Britcher, L. O. Tran, L. S. Payne, W. C. Lumma, T. A. Lyle, J. R. Huff, P. S. Anderson, D. B. Olsen, S. S. Carroll, *Antimicrob. Agents Chemother.* **1995**, *39*, 2602–2605.
[6] H. H. Inhoffen, W. Hohlweg, *Naturwissenschaften* **1938**, *26*, 96–96.
[7] (a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470. (b) Nobel Lecture: A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722–6737.
[8] A. Fürstner, *J. Am. Chem. Soc.* **2021**, *143*, 15538–15555.
[9] A. P. Y. Chan, A. G. Sergeev, *Coord. Chem. Rev.* **2020**, *413*, 213213.
[10] L. Hintermann, A. Labonne, *Synthesis* **2007**, *2007*, 1121–1150.
[11] (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.

azides, known as "Click Chemistry", is of paramount importance.[12] For examples, this reaction found applications in different fields of chemistry from the labelling of biomolecules to the functionalization of surfaces.[13] Alternatively, valuable vinyl organometallic compounds can be obtained through hydro- or carbometallation and used as versatile intermediates in follow-up reactions (E).[14] Finally, highly substituted olefins can be accessed *via* radical or nucleophilic additions, for which the selectivity can be controlled by metal catalysis.[15]

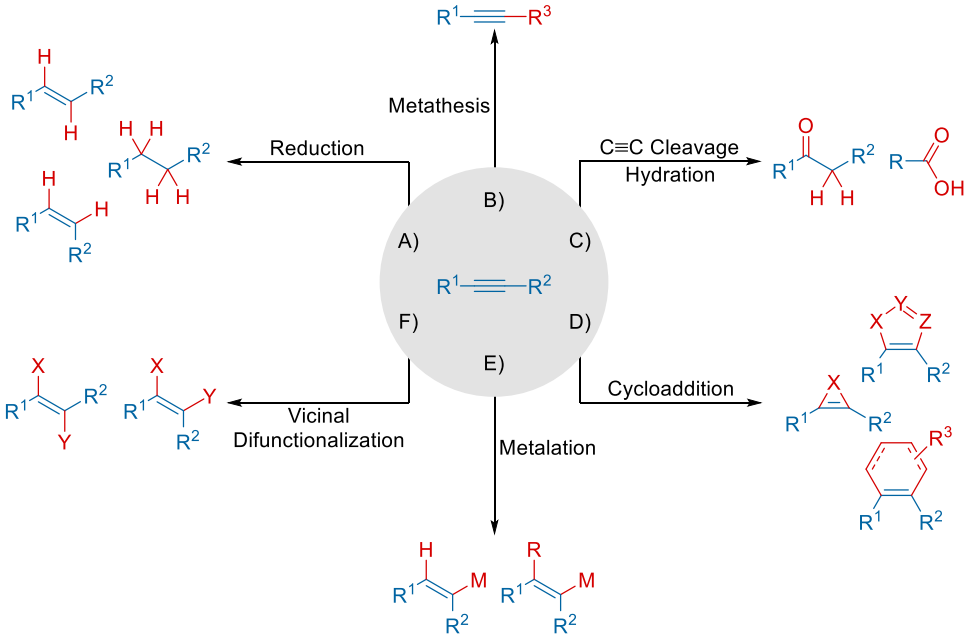


Figure 3.3. Selected transformations of alkynes.

3.1.2. Synthetic Strategies to Access Alkynes

As highlighted in the previous section, alkynes are of high interest for the scientific community, which led to the development of various efficient methods to construct or transfer alkynes. In order to construct a C-C triple bond, two main strategies can be followed (Scheme 3.1). Using strong base, single or double β-elimination from, respectively, vinyl halide or alkyl dihalides leads to the alkyne motif (A).[16] Starting from abundant carbonyl compounds and a diazo phosphonate reagent, the Seyferth-Gilbert homologation affords C-C triple bonds under

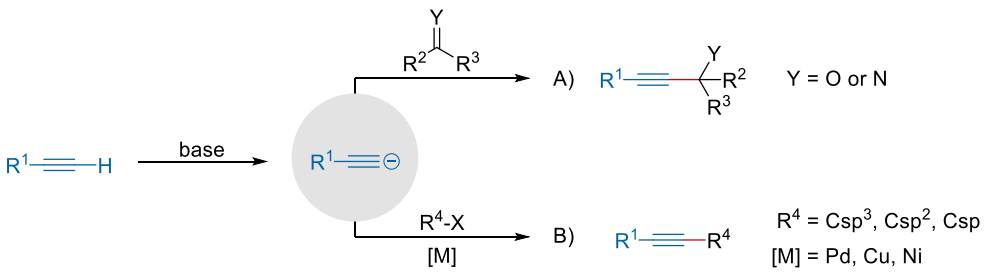
[12] M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952–3015.
[13] (a) J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev.* **2010**, *39*, 1272. (b) W. Xi, T. F. Scott, C. J. Kloxin, C. N. Bowman, *Adv. Funct. Mater.* **2014**, *24*, 2572–2590.
[14] (a) Z. Song, T. Takahashi, in *Compr. Org. Synth. II*, Elsevier, **2014**, pp. 838–876. (b) M. Zaidlewicz, A. Wolan, M. Budny, in *Compr. Org. Synth. II*, Elsevier, **2014**, pp. 877–963. (c) A. P. Dobbs, F. K. I. Chio, in *Compr. Org. Synth. II*, Elsevier, **2014**, pp. 964–998. (d) A. Ding, H. Guo, in *Compr. Org. Synth. II*, Elsevier, **2014**, pp. 891–938.
[15] (a) B. Gao, D. Deng, D. Huang, X. Sun, *Synthesis* **2021**, *53*, 3522–3534. (b) S. Ghosh, R. Chakrabortty, V. Ganesh, *ChemCatChem* **2021**, *13*, 4262–4298.
[16] R. Shaw, A. Elagamy, I. Althagafi, R. Pratap, *Org. Biomol. Chem.* **2020**, *18*, 3797–3817.

basic conditions (B).[17] Initially limited to ketones affording internal alkynes, the Ohira-Bestmann conditions allowed to access terminal alkynes starting from aldehydes.[18] A similar strategy, known as the Corey-Fuchs reaction, using carbon tetrabromide, as the carbene precursor, and triphenyl phosphine allows to access terminal alkynes.[19]

Scheme 3.1. Main strategies to synthesize alkynes.

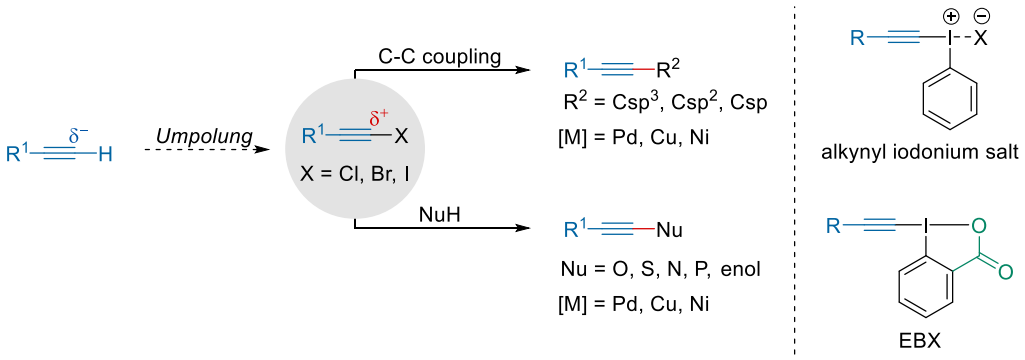
Terminal alkynes can be used in nucleophilic alkyne transfer reactions (Scheme 3.2). Acetylide intermediates are easily obtained upon deprotonation (pKa ~ 25) and can reacts with electrophiles. For instance, this strategy is widely used to synthesize propargyl alcohols or amines (A).[20] Acetylides can also be involved in cross-coupling reactions with various electrophiles under transition metal catalysis (B). For instance, the Sonogashira coupling involving a copper-acetylide and a palladium catalyst is a method of choice for the introduction of an alkyne in a molecule containing Csp^2 carbons.[7a] Copper catalysis can be used to generate diynes, either symmetrical *via* Glaser dimerization,[21] or, unsymmetrical *via* the Cadiot-Chodkiewicz reaction.[22] β-Elimination was a major limitation for the development of Csp-Csp^3 coupling but recent development in Ni-catalysis allowed to efficiently couple acetylides with alkyl halides.[23]

[17] (a) D. Seyferth, R. S. Marmor, P. Hilbert, *J. Org. Chem.* **1971**, *36*, 1379–1386. (b) J. C. Gilbert, U. Weerasooriya, *J. Org. Chem.* **1982**, *47*, 1837–1845.
[18] (a) S. Ohira, *Synth. Commun.* **1989**, *19*, 561–564. (b) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, *1996*, 521–522.
[19] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**,*13*, 3769–3772.
[20] For addition on carbonyl: (a) Y. Sempere, E. M. Carreira, in *Org. React.* (Ed.: John Wiley & Sons, Inc.), Wiley, **2019**, pp. 207–254. For addition on imine: (b) I. Jesin, G. C. Nandi, *Eur. J. Org. Chem.* **2019**, *2019*, 2704–2720.
[21] C. Glaser, *Berichte Dtsch. Chem. Ges.* **1869**, *2*, 422–424.
[22] (a) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes;* Viehe, H. G., ed.; Dekker: New York, **1969,** pp. 597-647. (b) J. J. Li, in *Name React.*, Springer International Publishing, Cham, **2021**, pp. 67–69.
[23] T. Iwasaki, N. Kambe, *Top. Curr. Chem.* **2016**, *374*, 66.



Scheme 3.2. Nucleophilic alkynylation strategies.

Although terminal alkynes are inherently nucleophilic, the installation of a electron-withdrawing leaving group at an extremity allows to couple alkynes with other nucleophiles by reversing its reactivity (Scheme 3.3).[24] The concept of reversal of reactivity was introduced by Seebach as Umpolung and originally applied to the reversal of the reactivity of aldehydes.[25] Initially, electrophilic alkynylation have been investigated using haloalkynes in carbon-carbon and heteroatom-carbon couplings.[26] The low reactivity of haloalkynes is hampering the direct alkynylation of nucleophiles, but the addition of transition metal catalysts allowed the development of electrophilic alkynylation strategies. Of particular interest for this Thesis, the alkynylation of nitrogen-based nucleophiles has been intensively studied and will be the subject of a more thorough overview in the next chapter. While iodoalkynes are rarely used because of their instability, their oxidized hypervalent iodine equivalents have been particularly prolific as electrophilic sources of alkynes and more details will be given in the next section.



Scheme 3.3. Electrophilic alkynylation strategies with haloalkynes.

Other strategies have been studied to transfer alkynes onto nucleophiles. For instance, *in-situ* oxidation of terminal alkynes with stoichiometric lead (IV) has been investigated for the alkynylation of soft carbon nucleophiles.[27] The high toxicity of the reagents used has limited the application of this strategy. Alternatively, alkynyl sulfones have been established as

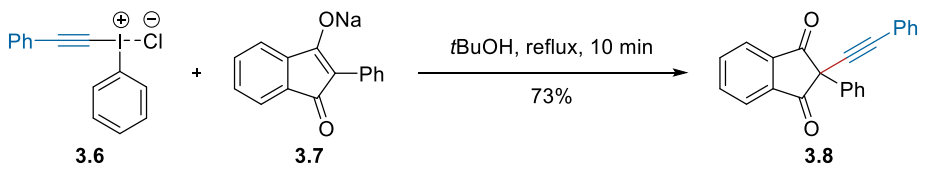
[24] J. P. Brand, J. Waser, *Chem. Soc. Rev.* **2012**, *41*, 4165.
[25] D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258.
[26] W. Wu, H. Jiang, *Acc. Chem. Res.* **2014**, *47*, 2483–2504.
[27] M. G. Moloney, J. T. Pinhey, E. G. Roche, *Tetrahedron Lett.* **1986**, *27*, 5025–5028.

suitable partners for the alkynylation of transient nucleophilic radicals.[28] The Alcarazo group recently reported the development of alkynyl sulfonium salt reagents reviving the interest for these peculiar reagents.[29] The development of alkynyl cationic equivalents and their use in alkynylation reactions is still the subject of numerous investigations, particularly with hypervalent iodine reagents.

3.1.3. Alkyne Transfer Using Hypervalent Iodine Reagents

3.1.3.1. Reactivity of Alkynyl Hypervalent Iodonium Salts

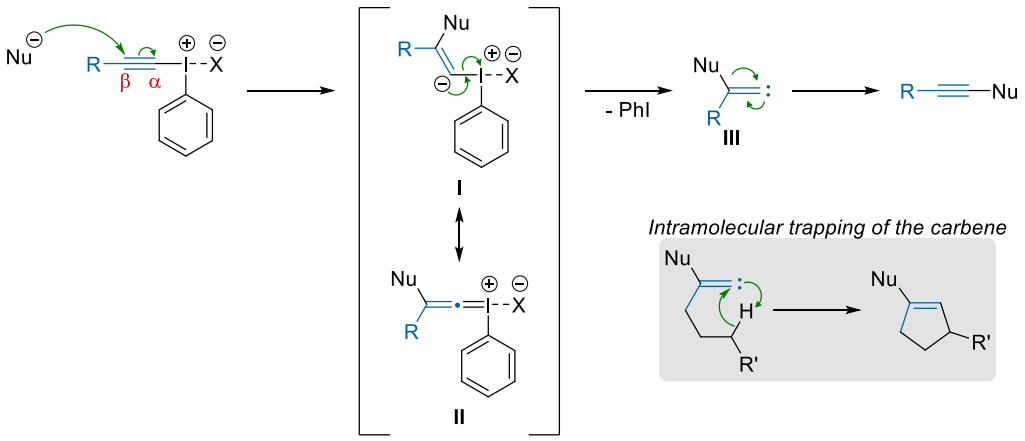
The first alkynylation using hypervalent iodine was reported by Beringer and Galton in 1965 using alkynyl iodonium salt **3.6**.[30] The hypervalent iodine reagent reacted with the soft enolate **3.7** to afford the α–alkynylated product **3.8** in good yield (Scheme 3.4). However, the reagent had a low stability and decomposed in few hours under inert conditions.



Scheme 3.4. First alkynylation with λ^3-iodonium salt.

A putative mechanism was proposed by the Ochiai group for the nucleophilic addition on alkynyl iodonium salts (Scheme 3.5).[31] Michael addition at the β-position on the iodonium salt would generate an unstable iodonium ylide (**I**), which possesses another resonance structure "iodo-allene" (**II**). In the absence of a proton source, elimination leading to alkylidene carbene (**III**) is favored due to the exceptional nucleofuge property of iodobenzene.[32] 1,2-Shift would provide the desired alkyne. The isolation of products derived from a 1,5-C-H insertion supports the involvement of a carbene intermediate. The migratory ability of the alkylidene substituents could be assessed by ^{13}C-labelling experiments.[33]

[28] D. Ge, X. Wang, X.-Q. Chu, *Org. Chem. Front.* **2021**, *8*, 5145–5164.
[29] (a) B. Waldecker, F. Kraft, C. Golz, M. Alcarazo, *Angew. Chem. Int. Ed.* **2018**, *57*, 12538–12542. For review: (b) S. I. Kozhushkov, M. Alcarazo, *Eur. J. Inorg. Chem.* **2020**, *2020*, 2486–2500.
[30] F. M. Beringer, S. A.Galton, *J. Org. Chem.* **1965**, *30*, 1930-1934.
[31] M. Ochiai, M. Kunishima, Y. Nagao, K. Fuji, M. Shiro, E. Fujita, *J. Am. Chem. Soc.* **1986**, *108*, 8281–8283.
[32] T. Okuyama, T. Takino, T. Sueda, M. Ochiai, *J. Am. Chem. Soc.* **1995**, *117*, 3360–3367.
[33] L. I. Dixon, M. A. Carroll, T. J. Gregson, G. J. Ellames, R. W. Harrington, W. Clegg, *Org. Biomol. Chem.* **2013**, *11*, 5877.



Scheme 3.5. Proposed mechanism for the nucleophilic addition on alkynyl HIR.

Alkynyl iodonium salt reagents are usually obtained from a λ^3-iodane precursor and the corresponding free,[34] silylated,[35] stannylated,[36] or borylated alkyne (Scheme 3.6).[37] The Olofsson group later developed one pot protocols to access these reagents directly from iodobenzene.[38] Together with the already mentioned alkynylation of 1,3-diketones,[30,31,39] C(sp^2)-,[40] N-,[41] O-,[42] S-,[43] and P-nucleophiles could be alkynylated with iodonium salts.[44]

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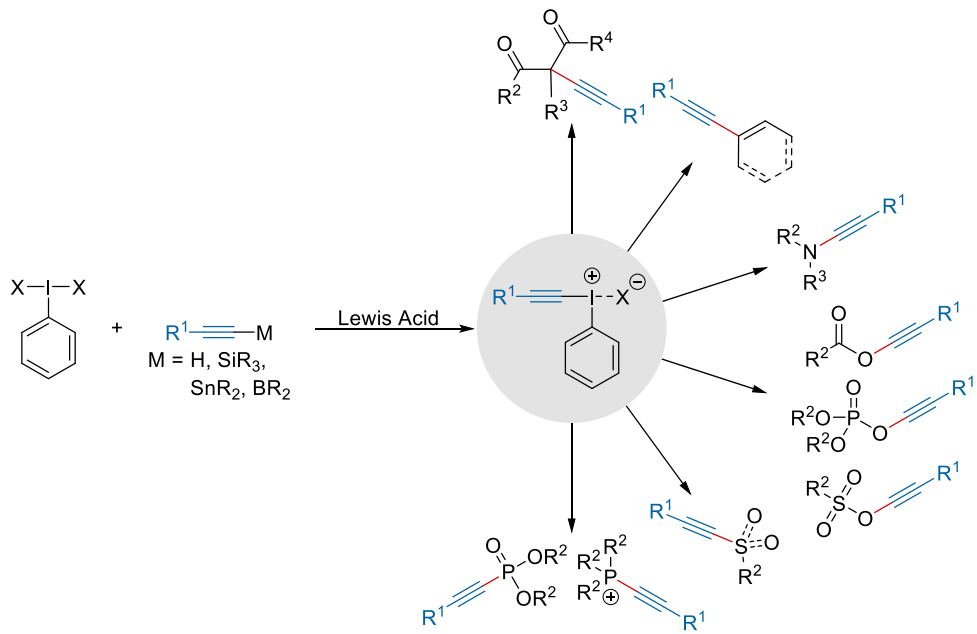
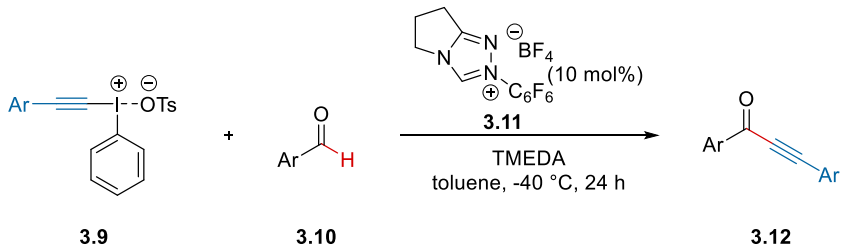
[34] (a) L. Rebrovic, G. F. Koser, *J. Org. Chem.* **1984**, *49*, 4700–4702. (b) P. J. Stang, B. W. Surber, Z. C. Chen, K. A. Roberts, A. G. Anderson, *J. Am. Chem. Soc.* **1987**, *109*, 228–235. (c) M. Yoshida, N. Nishimura, S. Hara, *Chem. Commun.* **2002**, 1014–1014.
[35] (a) M. Ochiai, M. Kunishima, K. Sumi, Y. Nagao, E. Fujita, M. Arimoto, H. Yamaguchi, *Tetrahedron Lett.* **1985**, *26*, 4501–4504. (b) T. Kitamura, P. J. Stang, *J. Org. Chem.* **1988**, *53*, 4105–4106. (c) T. Kitamura, *Synthesis* **1998**, *1998*, 1416–1418.
[36] (a) P. J. Stang, B. L. Williamson, V. V. Zhdankin, *J. Am. Chem. Soc.* **1991**, *113*, 5870–5871. (b) B. L. Williamson, P. J. Stang, A. M. Arif, *J. Am. Chem. Soc.* **1993**, *115*, 2590–2597.
[37] M. Yoshida, K. Osafune, S. Hara, *Synthesis* **2007**, *2007*, 1542–1546.
[38] (a) E. A. Merritt, B. Olofsson, *Eur. J. Org. Chem.* **2011**, *2011*, 3690–3694. (b) M. J. Bouma, B. Olofsson, *Chem. Eur. J.* **2012**, *18*, 14242–14245.
[39] M. D. Bachi, N. Bar-Ner, C. M. Crittell, P. J. Stang, B. L. Williamson, *J. Org. Chem.* **1991**, *56*, 3912–3915.
[40] (a) D.-Y. Yang, J. He, S. Miao, *Synth. Commun.* **2003**, *33*, 2695–2700. (b) C.-M. Yu, J.-H. Kweon, P.-S. Ho, S.-C. Kang, G. Y. Lee, *Synlett* **2005**, 2631–2634.
[41] See next chapter for more details on nitrogen alkynylation.
[42] (a) P. J. Stang, M. Boehshar, J. Lin, *J. Am. Chem. Soc.* **1986**, *108*, 7832–7834. (b) P. J. Stang, M. Boehshar, H. Wingert, T. Kitamura, *J. Am. Chem. Soc.* **1988**, *110*, 3272–3278. (c) P. J. Stang, T. Kitamura, M. Boehshar, H. Wingert, *J. Am. Chem. Soc.* **1989**, *111*, 2225–2230. (d) P. J. Stang, C. M. Crittell, A. M. Arif, M. Karni, Y. Apeloig, *J. Am. Chem. Soc.* **1991**, *113*, 7461–7470.
[43] (a) R. R. Tykwinski, B. L. Williamson, D. R. Fischer, P. J. Stang, A. M. Arif, *J. Org. Chem.* **1993**, *58*, 5235–5237. (b) K. Miyamoto, Y. Nishi, M. Ochiai, *Angew. Chem. Int. Ed.* **2005**, *44*, 6896–6899. (c) J.-B. Han, L. Yang, X. Chen, G.-F. Zha, C.-P. Zhang, *Adv. Synth. Catal.* **2016**, *358*, 4119–4124.
[44] (a) M. Ochiai, M. Kunishima, Y. Nagao, K. Fuji, E. Fujita, *J Chem Soc Chem Commun* **1987**, 1708–1709. (b) J.-L. Zhang, Z.-C. Chen, *Synth. Commun.* **1998**, *28*, 175–179.



Scheme 3.6. Synthesis and reactivity of alkynyl iodonium salt.

More recently, the Kalek group reported that using *N*-heterocyclic carbene (NHC, **3.11**) as catalyst, a broad range of alkynylated carbonyl compounds **3.12** could be accessed from aromatic aldehydes **3.10** and iodonium salts **3.9** as alkynyl sources (Scheme 3.7).[45] Surprisingly, experimental and computational mechanistic studies suggested that the reaction proceeds *via* a direct substitution at the α-acetylenic position and not *via* the commonly accepted addition at the β-carbon followed by 1,2-shift (*vide supra*).



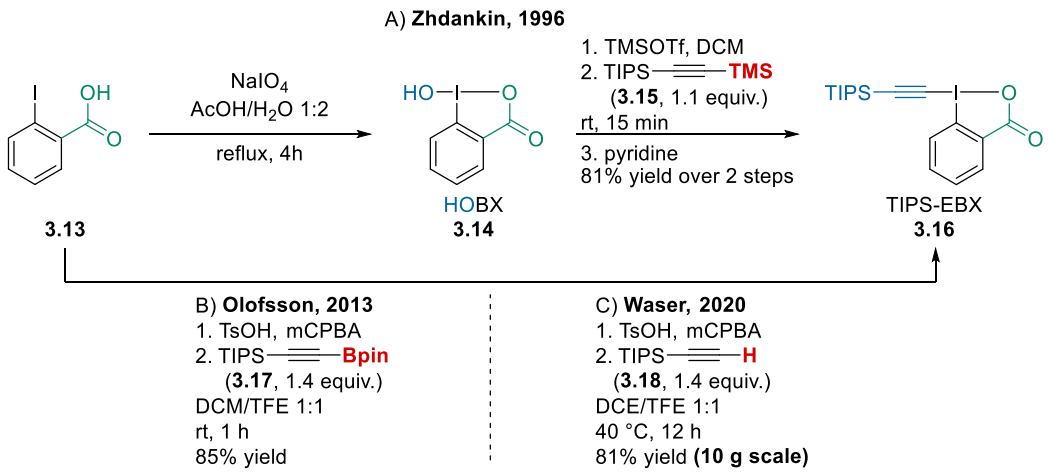
Scheme 3.7. NHC-catalyzed alkynylation of aldehydes **3.10** with iodonium salts **3.9**.

Despite being highly reactive, the instability of alkynyl iodonium salts remains a challenge. In this context, the development of the bench stable cyclic ethynylbenziodoxol(on)e (EBX) reagents renewed the interest for alkynyl hypervalent iodine reagents.

[45] A. A. Rajkiewicz, N. Wojciechowska, M. Kalek, *ACS Catal.* **2020**, *10*, 831–841.

3.1.3.2. Reactivity of EBX reagents

EBX reagents were discovered by the Ochiai group, which only reported their synthesis and structures.[46] Few years later, the Zhdankin group reported an improved two-step procedure allowing to access various alkyl-, aryl- and silyl-substituted EBX reagents (Scheme 3.8.A).[47] Initially, these reagents were merely studied as structural curiosity until our group and other started to investigate their reactivity.[48] With a renewed interest for EBX reagents, the Olofsson group developed a one-pot two-step procedure starting with the *in-situ* oxidation of 2-iodobenzoic acid (**3.13**) followed by reaction with pinacol alkynylboronates (Scheme 3.8.B).[38b] Building upon these protocols, our group reported a similar one-pot procedure but with a commercially available terminal alkyne for the synthesis of TIPS-EBX (**3.16**) up to 10 g scale (Scheme 3.8.C).[49] Lower yields are obtained with alkyl or aryl substituents with this protocol and the use of borylated or silylated alkynes are usually preferred to synthesize the corresponding reagents.



Scheme 3.8. Improvements in the synthesis EBX reagents (illustrated with TIPS-EBX).

Recently, our group reported a new protocol to access a broad range of alkyl-, aryl-or silyl-EBX starting from TsOBX (**3.19**) and alkynyltrifluoroborates (Scheme 3.9).[50] HIR **3.19** is easily accessed from **3.13** in two steps, similarly, BF_3K-salts are readily obtained from commercially available terminal alkynes. This reaction does not require any additive, tolerates various solvents and the reagents can be obtained in high purity without purification.

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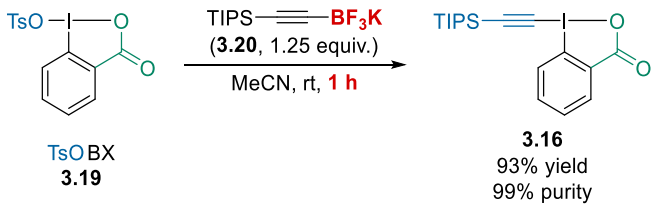
[46] M. Ochiai, Y. Masaki, M. Shiro, *J. Org. Chem.* **1991**, *56*, 5511–5513.
[47] V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 6547–6551.
[48] J. P. Brand, D. F. González, S. Nicolai, J. Waser, *Chem Commun* **2011**, *47*, 102–115.
[49] D. P. Hari, P. Caramenti, L. Schouwey, M. Chang, S. Nicolai, D. Bachert, T. Wright, C. Orella, J. Waser, *Org. Process Res. Dev.* **2020**, *24*, 106–110.
[50] J. Borrel, J. Waser, *Org. Lett.* **2022**, *24*, 142–146.



Scheme 3.9. Most recent progress in the synthesis of EBX (illustrated with TIPS-EBX).

In 2009, our group reported the first application of EBX reagents with the alkynylation of indole and pyrrole heterocycles under gold catalysis.[51] This pioneering work has sparked the interest of the chemistry community and EBX have rapidly emerged as versatile reagents for alkynyl transfer reactions. Several reviews highlighted the importance of these reagents and selected recent applications are given below (Figure 3.4).[52] π-Acid catalysts (Au and Pt) enabled the regioselective alkynylation of heterocycles such as indoles,[51,53] pyrroles,[51,53] thiophenes,[51,53] furans,[54] and benzofurans.[55] Similarly, anilines could be alkynylated in *para* position using TIPS-EBX (**3.16**) and gold catalysis.[56] Isoquinolones were also suitable substrates for regioselective alkynylations.[57] Interestingly, a rhodium catalyst promoted exclusively C8-alkynylation when Au provided C4-functionalized products. The difference of reactivity was explained by the way EBX interacted with the catalyst, as a Lewis acid for gold or as a Brønsted base for rhodium.[58] Pd-catalysis promoted the oxy- and aminoalkynylation of unactivated olefins.[59] More recently, the Hashmi group reported the CH functionalization of cyclopropenes using dual Au/Ag catalysis and ethynylbenziodoxole (X = $(CF_3)_2$) reagents.[60] Cyanocarbene intermediates can be formed by the reaction of $TMSN_3$ with EBX reagents and then trapped by [1.1.1]-propellane affording tetrasubstituted alkenyl nitriles.[61] The M. Waser

[51] J. Brand, J. Charpentier, J. Waser, *Angew. Chem. Int. Ed.* **2009**, *48*, 9346–9349.
[52] For recent reviews: (a) D. P. Hari, S. Nicolai, J. Waser, in *PATAIS Chem. Funct. Groups* (Ed.: Z. Rappoport), John Wiley & Sons, Ltd, Chichester, UK, **2018**, pp. 1–58. (b) D. P. Hari, P. Caramenti, J. Waser, *Acc. Chem. Res.* **2018**, *51*, 3212–3225.
[53] (a) J. P. Brand, C. Chevalley, R. Scopelliti, J. Waser, *Chem. Eur. J.* **2012**, *18*, 5655–5666. (b) G. L. Tolnai, S. Ganss, J. P. Brand, J. Waser, *Org. Lett.* **2013**, *15*, 112–115.
[54] Y. Li, J. P. Brand, J. Waser, *Angew. Chem. Int. Ed.* **2013**, *52*, 6743–6747.
[55] Y. Li, J. Waser, *Beilstein J. Org. Chem.* **2013**, *9*, 1763–1767.
[56] J. P. Brand, J. Waser, *Org. Lett.* **2012**, *14*, 744–747.
[57] A. C. Shaikh, D. R. Shinde, N. T. Patil, *Org. Lett.* **2016**, *18*, 1056–1059.
[58] F. Zhao, B. Xu, D. Ren, L. Han, Z. Yu, T. Liu, *Organometallics* **2018**, *37*, 1026–1033.
[59] (a) S. Nicolai, S. Erard, D. F. González, J. Waser, *Org. Lett.* **2010**, *12*, 384–387. (b) S. Nicolai, C. Piemontesi, J. Waser, *Angew. Chem. Int. Ed.* **2011**, *50*, 4680–4683.
[60] Y. Yang, P. Antoni, M. Zimmer, K. Sekine, F. F. Mulks, L. Hu, L. Zhang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2019**, *58*, 5129–5133.
[61] X. Jiang, Z. Zheng, Y. Gao, D. Lan, W. Xu, W. Zhang, G. Chen, *Org. Chem. Front.* **2022**, *9*, 2234–2239.

group developed a metal-free Cadiot-Chodkiewicz reaction allowing to access unsymmetrical 1,3-diynes.[62]

The recent surge of interest for photoredox catalysis prompted chemists to look at the reactivity of EBX under such conditions. The Xiao and our groups, simultaneously reported the decarboxylative alkynylation of carboxylic acids under photoredox conditions.[63] It should be mentioned that prior to these reports, the Li group disclosed a silver nitrate catalyzed decarboxylative alkynylation of aliphatic acids.[64] Since these seminal works, numerous applications of EBX reagents in radical reactions have been reported.[65] For instance, the Chen group developed a photoredox catalyzed alkynylation of donor-aminocyclopropanes using blue LEDs.[66] Interestingly, our group recently demonstrated that aryl-EBX reagents were able to absorb blue light and induce alkynylation reactions that had been previously reported requiring photocatalysts.[67]

The alkynylation of carbon nucleophiles has been explored using stabilized enolates.[68] Phase transfer catalysts (PTC) allowed to render these transformations enantioselective.[69] Using stabilized enolates, the Hashmi group reported a gold catalyzed cascade C(sp^3)-H alkynylation/oxyalkynylation reaction affording tetrasubstituted furans.[70] Following a similar strategy, the same group developed a new protocol to access indolizines from 2-substituted pyridine derivatives.[71] Additionally, under basic conditions hetereoatoms such as sulfur,[72] phosphorous,[73] or nitrogen can be alkynylated.[41]

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[62] J. Schörgenhumer, M. Waser, *Org. Biomol. Chem.* **2018**, *16*, 7561–7563. For prior examples using gold catalysis: (a) X. Li, X. Xie, N. Sun, Y. Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 6994–6998. (b) S. Banerjee, N. T. Patil, *Chem. Commun.* **2017**, *53*, 7937–7940.
[63] (a) Q.-Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199. (b) F. Le Vaillant, T. Courant, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204.
[64] X. Liu, Z. Wang, X. Cheng, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 14330–14333.
[65] F. Le Vaillant, J. Waser, *Chem. Sci.* **2019**, *10*, 8909–8923.
[66] Z. Liu, S. Wu, Y. Chen, *ACS Catal.* **2021**, *11*, 10565–10573.
[67] (a) S. G. E. Amos, D. Cavalli, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 23827–23834. (b) Tin. V. T. Nguyen, J. Waser, *ChemRxiv* **2022**, *ver. 1*, DOI 10.26434/chemrxiv-2022-vf5gm.
[68] (a) D. Fernández González, J. P. Brand, J. Waser, *Chem. Eur. J.* **2010**, *16*, 9457–9461. (b) D. Fernández González, J. P. Brand, R. Mondière, J. Waser, *Adv. Synth. Catal.* **2013**, *355*, 1631–1639.
[69] (a) X. Wu, S. Shirakawa, K. Maruoka, *Org Biomol Chem* **2014**, *12*, 5388–5392. (b) B. Meng, Q. Shi, Y. Meng, J. Chen, W. Cao, X. Wu, *Org. Biomol. Chem.* **2021**, *19*, 5087–5092.
[70] C. Han, X. Tian, L. Song, Y. Liu, A. S. K. Hashmi, *Org. Chem. Front.* **2021**, *8*, 6546–6552.
[71] C. Han, Y. Liu, X. Tian, F. Rominger, A. S. K. Hashmi, *Org. Lett.* **2021**, *23*, 9480–9484.
[72] For thiol: (a) R. Frei, J. Waser, *J. Am. Chem. Soc.* **2013**, *135*, 9620–9623. (b) R. Frei, M. D. Wodrich, D. P. Hari, P.-A. Borin, C. Chauvier, J. Waser, *J. Am. Chem. Soc.* **2014**, *136*, 16563–16573. (c) M. D. Wodrich, P. Caramenti, J. Waser, *Org. Lett.* **2016**, *18*, 60–63. For sulfenate: S. G. E. Amos, S. Nicolai, A. Gagnebin, F. Le Vaillant, J. Waser, *J. Org. Chem.* **2019**, *84*, 3687–3701. For sulfone: C. C. Chen, J. Waser, *Org. Lett.* **2015**, *17*, 736–739.
[73] C. C. Chen, J. Waser, *Chem Commun* **2014**, *50*, 12923–12926.

Finally, thanks to their high reactivity and biocompatibility HIR have recently been employed for the functionalization of biomolecules.[74] For instance, our group could extend the photoredox catalyzed decarboxylative alkynylation from organic molecules to small peptides.[75] Our group could also exploit the selective alkynylation of cysteines to develop tools for the labeling and stapling of peptides and small proteins.[76] In protic solvents, the alkynylation of thiols with EBX reagents is competing with the formation of vinylbenziodoxolone (VBX) reagents.[77] Benefiting from this reactivity, our group could, in collaboration with the Fierz group, develop a "doubly orthogonal" labeling based on the formation of S-VBX in physiological conditions.[78]

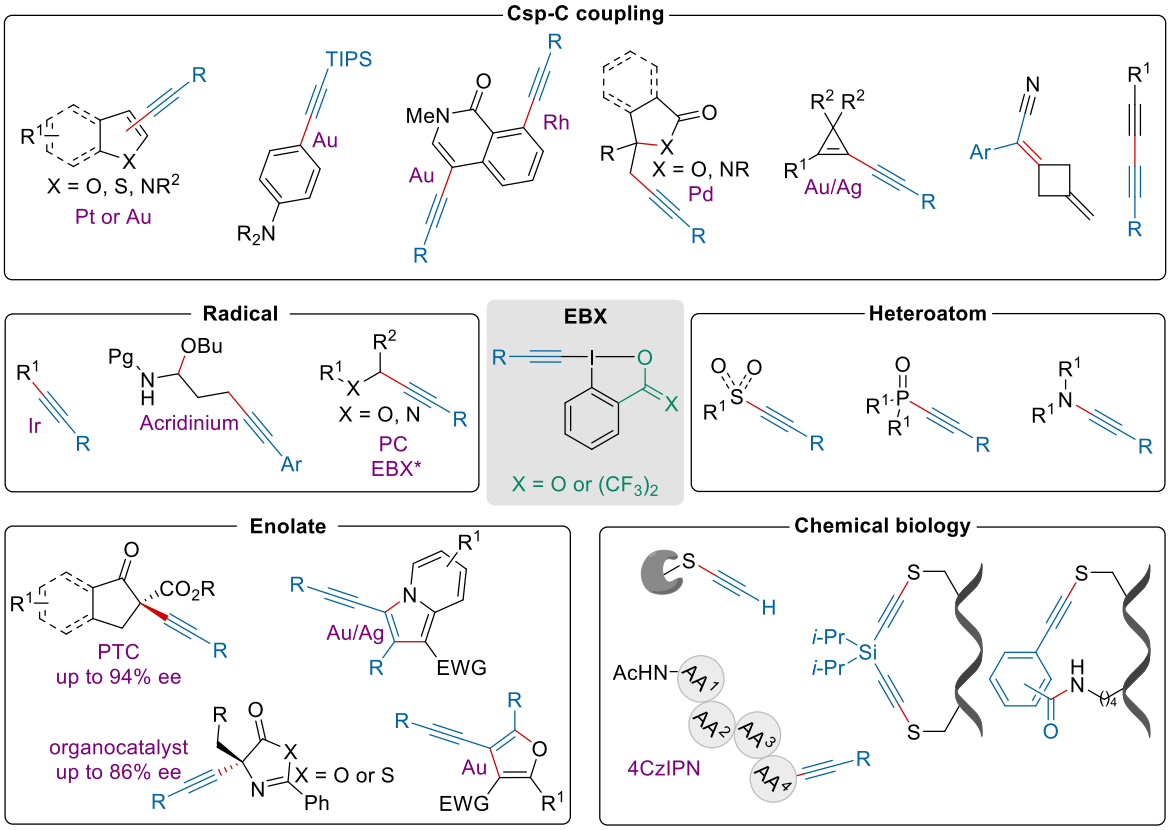
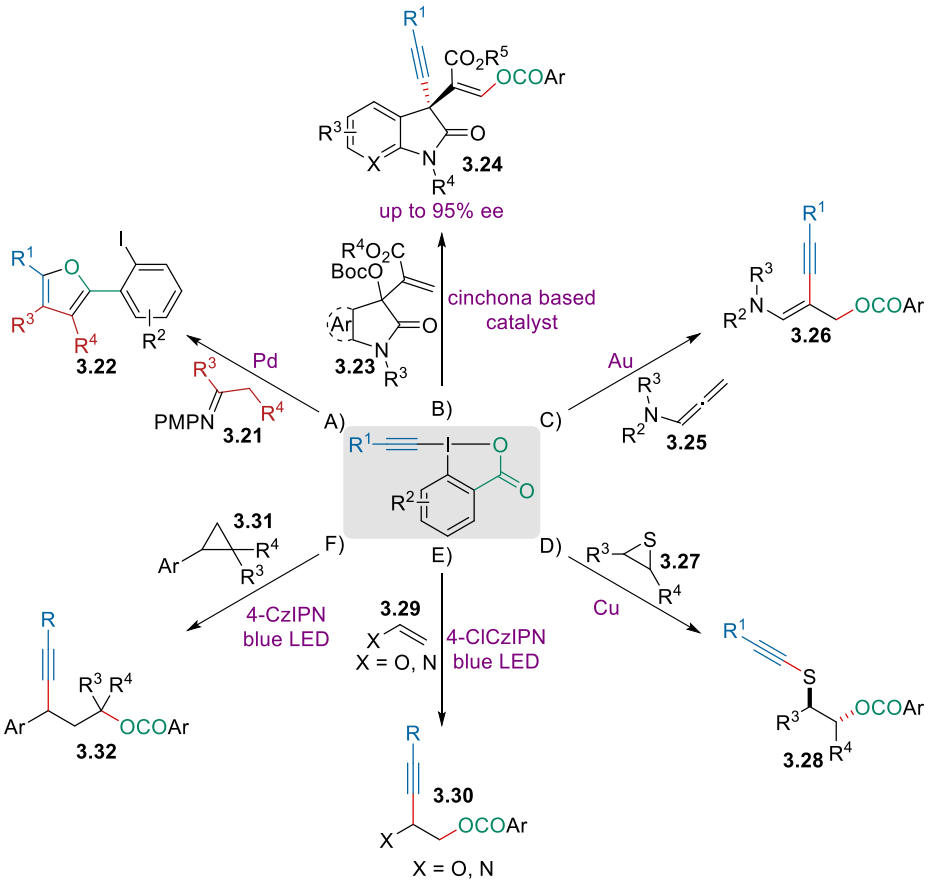


Figure 3.4. Selected applications of EBX.

[74] E. M. D. Allouche, E. Grinhagena, J. Waser, *Angew. Chem. Int. Ed.* **2022**, *61*, e202112287.
[75] M. Garreau, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2019**, *58*, 8182–8186.
[76] For labeling: (a) D. Abegg, R. Frei, L. Cerato, D. P. Hari, C. Wang, J. Waser, A. Adibekian, *Angew. Chem. Int. Ed.* **2015**, *54*, 10852–10857. (b) R. Tessier, R. K. Nandi, B. G. Dwyer, D. Abegg, C. Sornay, J. Ceballos, S. Erb, S. Cianférani, A. Wagner, G. Chaubet, A. Adibekian, J. Waser, *Angew. Chem. Int. Ed.* **2020**, *59*, 10961–10970. (c) A. K. Mishra, R. Tessier, D. P. Hari, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 17963–17968. For stapling: J. Ceballos, E. Grinhagena, G. Sangouard, C. Heinis, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 9022–9031.
[77] For a review on VBX reagents: N. Declas, G. Pisella, J. Waser, *Helv. Chim. Acta* **2020**, *103*, e2000191.
[78] R. Tessier, J. Ceballos, N. Guidotti, R. Simonet-Davin, B. Fierz, J. Waser, *Chem* **2019**, *5*, 2243–2263.

In the transformations described previously, the sole transfer of the alkynyl group from EBX reagents led to the formation of a stoichiometric amount of 2-iodobenzoic acid (**3.13**) as waste. The pursuit of higher efficiency in organic chemistry led to the development of atom economical reactions valorizing the by-product **3.13** (Scheme 3.10).[79] While attempting to synthesize pyrroles from imine (**3.21**) and EBX reagents, Yoshikai and coworkers observed the formation of furans (**3.22**), in which most of the reagent was introduced but with the loss of one carbon of the alkyne and one oxygen of the carboxylate (A).[80] The Chen group reported a highly regioselective and enantioselective 1,3-oxyalkynylation of isatin derivatives (**3.23**) using a cinchona derived organocatalyst to promote a Morita-Baylis-Hillman type reactivity (B).[81] A 1,2-oxyalkynylation of *N*-allenamides (**3.25**) catalyzed by gold was disclosed by the Patil group allowing to access valuable 1,3-enynes (**3.26**) (C).[82] Our group described a copper-catalyzed oxyalkynylation of thiiranes (**3.27**) with EBX reagents which provided β-hydroxy sulfide compounds (**3.28**) in moderate to good yields (D).[83] The oxyalkynylation of enol ethers and ene-carbamates (**3.29**) was enabled *via* the photocatalytic oxidation of the alkenes and led to the formation of valuable 1-alkynyl-1,2-amino alcohols and diols (**3.30**) (E).[84] Using similar conditions, the Studer group recently developed a photoredox catalyzed 1,3-oxyalkynylation of aryl cyclopropanes (**3.31**) (F).[85]

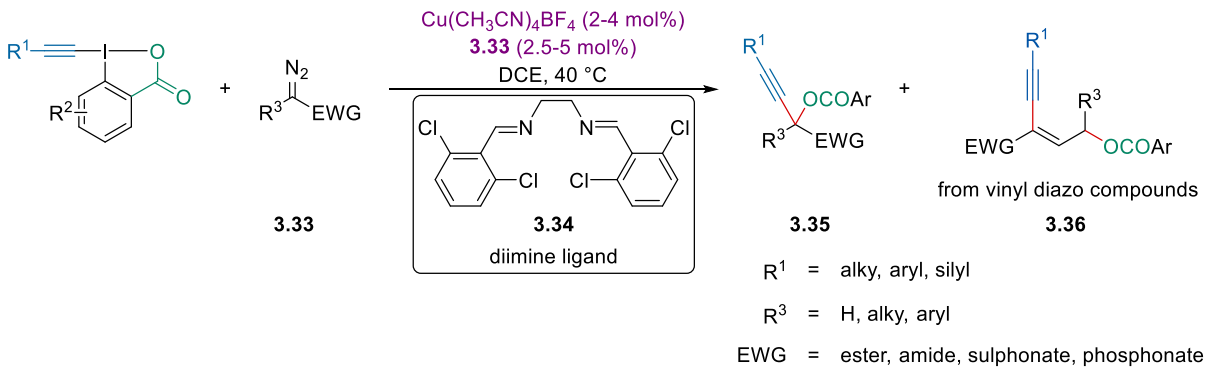
[79] For recent reviews on atom economical reaction with HIR: (a) A. Boelke, P. Finkbeiner, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2018**, *14*, 1263–1280. (b) G. Grelier, B. Darses, P. Dauban, *Beilstein J. Org. Chem.* **2018**, *14*, 1508–1528.
[80] A complex mechanism is proposed in the article for this unexpected reaction: B. Lu, J. Wu, N. Yoshikai, *J. Am. Chem. Soc.* **2014**, *136*, 11598–11601.
[81] Z.-C. Chen, P. Chen, Z. Chen, Q. Ouyang, H.-P. Liang, W. Du, Y.-C. Chen, *Org. Lett.* **2018**, *20*, 6279–6283.
[82] S. Banerjee, B. Senthilkumar, N. T. Patil, *Org. Lett.* **2019**, *21*, 180–184.
[83] J. Borrel, G. Pisella, J. Waser, *Org. Lett.* **2020**, *22*, 422–427.
[84] S. G. E. Amos, S. Nicolai, J. Waser, *Chem. Sci.* **2020**, *11*, 11274–11279.
[85] Z. Zuo, A. Studer, *Org. Lett.* **2022**, *24*, 949–954.



Scheme 3.10. Atom-economical transformations with EBX.

In addition, metal carbenes represent as well ideal reactive partners to develop atom economical reactions as they display both nucleophilic and electrophilic reactivity at the carbenic carbon.[86] Our group successfully applied the dual reactivity of metal carbenes, obtained by displacement of molecular nitrogen from diazo compounds (**3.33**) under copper-catalysis, for oxyalkynylation reactions (Scheme 3.11).[87] Using diimine ligand (**3.34**) and coper catalysis allowed the 1,1-functionalization of acceptor-diazo compounds (**3.35**) and the 1,3-functionnalization of vinyl diazo compounds (**3.36**). Later, our group disclosed an asymmetric version of this transformation using a chiral bisoxazoline (BOX) ligand.[88]

[86] (a) X. Guo, W. Hu, *Acc. Chem. Res.* **2013**, *46*, 2427–2440. (b) R. Zhao, L. Shi, *Angew. Chem. Int. Ed.* **2020**, *59*, 12282–12292.
[87] D. P. Hari, J. Waser, *J. Am. Chem. Soc.* **2016**, *138*, 2190–2193.
[88] D. P. Hari, J. Waser, *J. Am. Chem. Soc.* **2017**, *139*, 8420–8423.



Scheme 3.11. Oxyalkynylation of acceptor diazo compounds.

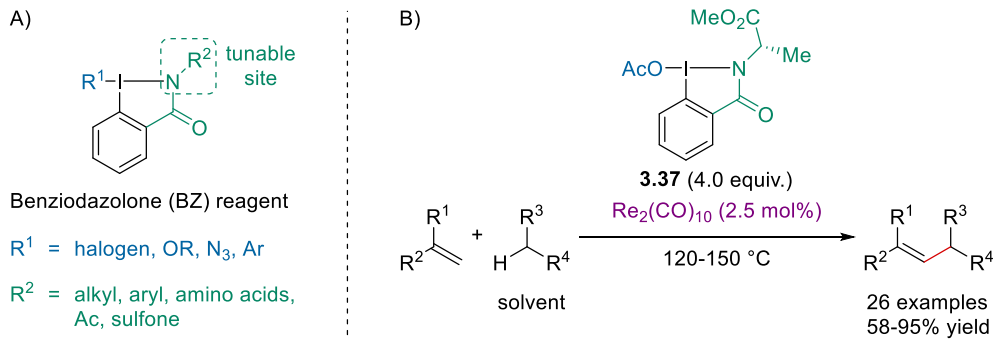
EBX reagents have been extensively studied in group transfer reactions. However, only the benzyl core could be modified to tune the reactivity of the reagents. Introducing a substituted nitrogen, instead of the oxygen in the iodoheterocycle, would allow to broaden the possibilities for structure and reactivity adjustment.

3.1.4. Development of *N*-Heterocyclic Hypervalent Iodine Reagents

The benziodazolone (BZ) class of reagent bearing a nitrogen atom in the iodoheterocycle was discovered more than 60 years ago (Scheme 3.12.A). These reagents have been studied by several researchers mainly for the determination and the study of their X-ray structures.[89] The first synthetic application of BZ reagents was reported in 2015 with the radical dehydrogenative olefination of Csp^3-H bonds developed by the Wang group (Scheme 3.12.B).[90] In this transformation, alanine derived benziodazolone **3.37** was used as a radical shuttle.

[89] (a) R. M. Keefer, L. J. Andrews, *J. Am. Chem. Soc.* **1959**, *81*, 5329–5333. (b) W. Wolf, L. Steinberg, *Chem. Commun. Lond.* **1965**, 449. (c) H. J. Barber, M. A. Henderson, *J. Chem. Soc. C Org.* **1970**, 862. (d) D. G. Naae, J. Z. Gougoutas, *J. Org. Chem.* **1975**, *40*, 2129–2131. (e) K. Prout, M. N. Stevens, A. Coda, V. Tazzoli, R. A. Shaw, T. Demir, *Z. Für Naturforschung B* **1976**, *31*, 687–688. (f) T. M. Balthazor, D. E. Godar, B. R. Stults, *J. Org. Chem.* **1979**, *44*, 1447–1449. (g) R. A. Moss, S. Chatterjee, B. Wilk, *J. Org. Chem.* **1986**, *51*, 4303–4307. (h) V. V. Zhdankin, R. M. Arbit, M. McSherry, B. Mismash, V. G. Young, *J. Am. Chem. Soc.* **1997**, *119*, 7408–7409. (i) V. V. Zhdankin, R. M. Arbit, B. J. Lynch, P. Kiprof, V. G. Young, *J. Org. Chem.* **1998**, *63*, 6590–6596. (j) V. V. Zhdankin, A. E. Koposov, J. T. Smart, R. R. Tykwinski, R. McDonald, A. Morales-Izquierdo, *J. Am. Chem. Soc.* **2001**, *123*, 4095–4096. (k) V. V. Zhdankin, A. Y. Koposov, L. Su, V. V. Boyarskikh, B. C. Netzel, V. G. Young, *Org. Lett.* **2003**, *5*, 1583–1586. (l) A. Yoshimura, M. T. Shea, C. L. Makitalo, M. E. Jarvi, G. T. Rohde, A. Saito, M. S. Yusubov, V. V. Zhdankin, *Beilstein J. Org. Chem.* **2018**, *14*, 1016–1020. (m) M. T. Shea, G. T. Rohde, Y. A. Vlasenko, P. S. Postnikov, M. S. Yusubov, V. V. Zhdankin, A. Saito, A. Yoshimura, *Molecules* **2021**, *26*, 7355.

[90] H. Gu, C. Wang, *Org. Biomol. Chem.* **2015**, *13*, 5880–5884.



Scheme 3.12. Benziodazolone class of reagents and first synthetic application.

While Togni reagent I (**3.38**) is a well-established trifluoromethylation hypervalent iodine reagent,[91] its trifluoromethylthiol equivalent (**3.39**) was initially thought to be a $I^{(III)}$-compound but intensive structural investigations showed that the iodine atom was monovalent (**3.40**) (Figure 3.5).[92] Computational studies concluded that due to unfavorable *trans*-effect the thioperoxide isomer (**3.40**) was favored compared to the hypervalent iodine form (**3.39**).[93] The Zhang group reasoned that using the benziodazolone core instead of the benziodoxol(on)e core they could synthesize a stable reagent.[94] The combination of matching *trans*-effect between the trifluoromethylthiol and N-acetylbenzamide ligands, and the introduction of an acetyl group allowing an intramolecular secondary I-O bonding enabled to make a stable reagent (**3.41**) bearing an I-SCF_3 bond. This study illustrated the impact of the design of the iodoheterocycle on the stability and reactivity of hypervalent iodine reagents.

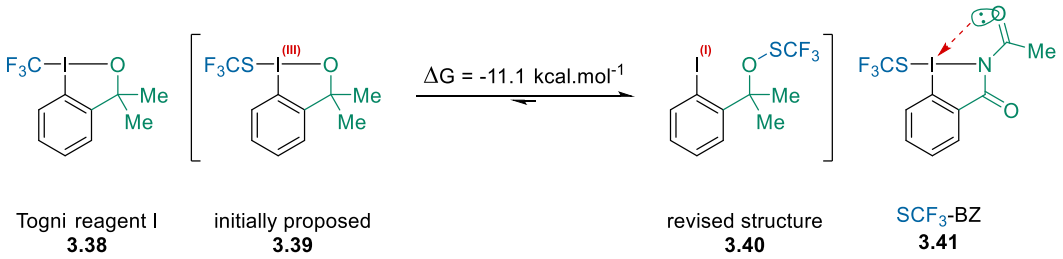
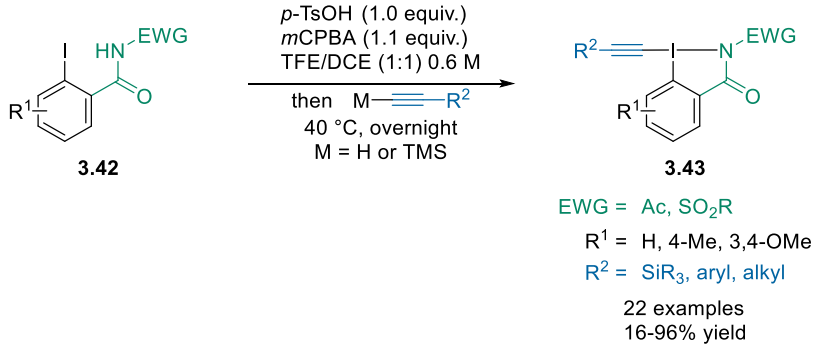


Figure 3.5. From Togni reagent to the first SCF_3-HIR.

Our group has been particularly interested in the use of hypervalent iodine reagents to develop alkynylation reactions, of particular interest was the possibility to transfer both ligands

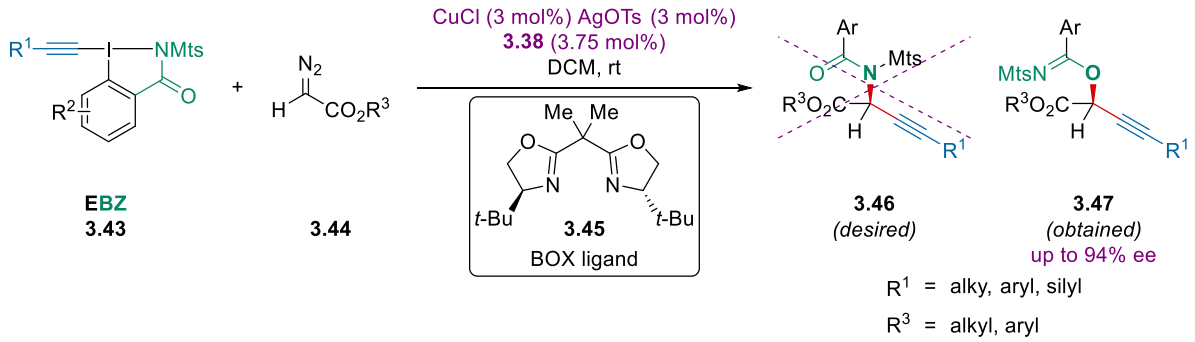
[91] J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682.
[92] For seminal paper: X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457–3460. For revision of the structure: (a) E. V. Vinogradova, P. Müller, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2014**, *53*, 3125–3128. (b) X. Shao, C. Xu, L. Lu, Q. Shen, *J. Org. Chem.* **2015**, *80*, 3012–3021.
[93] For *trans*-effect: M. Ochiai, T. Sueda, K. Miyamoto, P. Kiprof, V. V. Zhdankin, *Angew. Chem. Int. Ed.* **2006**, *45*, 8203–8206. For computations: T.-Y. Sun, X. Wang, H. Geng, Y. Xie, Y.-D. Wu, X. Zhang, H. F. Schaefer III, *Chem. Commun.* **2016**, *52*, 5371–5374.
[94] X.-G. Yang, K. Zheng, C. Zhang, *Org. Lett.* **2020**, *22*, 2026–2031.

of EBX reagents on metal carbenes (*vide supra*). Our group then wondered if using a similar strategy α-alkynyl amino acids derivatives could be obtained. For this purpose, our group successfully developed ethynylbenziodazolone (**3.43**, EBZ) reagents that could be obtained in one step from the corresponding iodobenzamide **3.42** (Scheme 3.13).[95]



Scheme 3.13. Synthesis of ethynylbenziodazolone (EBZ) reagents.

Unfortunately, while studying the aminoalkynylation of diazoacetates **3.44** the targeted α-alkynyl amino acids **3.46** were never detected. Nonetheless, our group could develop a highly efficient and selective oxyalkynylation of diazo compounds using copper catalysis and BOX ligand **3.45** leading to imidates **3.47** (Scheme 3.14).

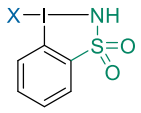


Scheme 3.14. Oxyalkynylation of acceptor diazo compounds with EBZ reagents.

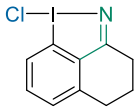
It should be noted that several other *N*-heterocyclic reagents have been developed with different scaffolds (Figure 3.6). For instance, benziodathiazole reagents **3.48** were reported by Jaffe and Leffler who studied only their structures and did not report any reactivity.[96] Reagent **3.49** was synthesized by the Yamaguchi group as the result of an undesired oxidation of the iodine atom.[97] More recently, the Togni and Magnier groups

[95] D. P. Hari, L. Schouwey, V. Barber, R. Scopelliti, F. Fadaei-Tirani, J. Waser, *Chem. Eur. J.* **2019**, *25*, 9522–9528.
[96] H. Jaffe, J. E. Leffler, *J. Org. Chem.* **1975**, *40*, 797–799.
[97] T. Ohwada, N. Tani, Y. Sakamaki, Y. Kabasawa, Y. Otani, M. Kawahata, K. Yamaguchi, *Proc. Natl. Acad. Sci.* **2013**, *110*, 4206–4211.

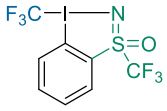
disclosed the synthesis of sulfoximine based reagent **3.50** which was shown to be an efficient trifluoromethylation reagent.[98] In addition, *N*-heterocyclic regents bearing two nitrogen atoms on the iodoheterocycle have also been investigated. For example, Braddock and coworkers reported the use of an amidine based reagent **3.51** for the bromolactonization of olefins.[99] However, the structure of the reagent was only postulated but not characterized. Recently the Zhdankin group disclosed the synthesis of benzimidazole-based reagent **3.52** from their iodonium salt equivalents.[100] Finally, Nachtsheim and coworkers investigated the synthesis and thermal stability of pseudo-cyclic reagents **3.53** as well as their reactivity as organocatalysts in oxidation reactions.[101]



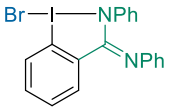
3.48
Leffler, **1975**
2 examples
reactivity not reported



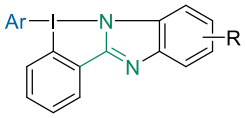
3.49
Yamaguchi, **2013**
1 example
undesired oxidation



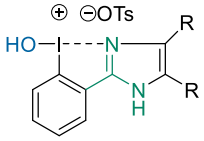
3.50
Togni and Magnier, **2019**
1 example
trifluoromethylation



3.51
Braddock, **2006**
only postulated
bromolactonization



3.52
Zhdankin, **2018**
18 examples
reactivity not reported



3.53
Nachtsheim, **2018/2020**
7 examples
organocatalysts for oxidation

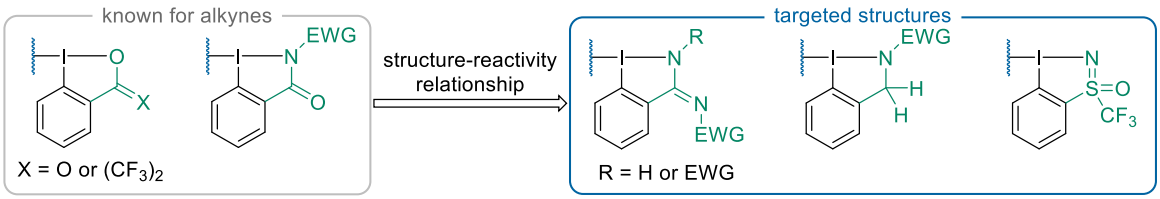
Figure 3.6. Other reported *N*-heterocyclic hypervalent iodine reagents.

[98] J. Kalim, T. Duhail, T.-N. Le, N. Vanthuyne, E. Anselmi, A. Togni, E. Magnier, *Chem. Sci.* **2019**, *10*, 10516–10523.
[99] D. C. Braddock, G. Cansell, S. A. Hermitage, *Chem. Commun.* **2006**, 2483-2485.
[100] Y. A. Vlasenko, P. S. Postnikov, M. E. Trusova, A. Shafir, V. V. Zhdankin, A. Yoshimura, M. S. Yusubov, *J. Org. Chem.* **2018**, *83*, 12056–12070.
[101] (a) A. Boelke, E. Lork, B. J. Nachtsheim, *Chem. Eur. J.* **2018**, *24*, 18653–18657. (b) A. Boelke, Y. A. Vlasenko, M. S. Yusubov, B. J. Nachtsheim, P. S. Postnikov, *Beilstein J. Org. Chem.* **2019**, *15*, 2311–2318. (c) A. Boelke, B. J. Nachtsheim, *Adv. Synth. Catal.* **2020**, *362*, 184–191.

3.2. Goals of the Project

As described previously, alkynes are versatile intermediates in organic chemistry with applications in various applied fields spanning from material sciences to chemical biology. Their synthesis has attracted a lot of attention and hypervalent iodine reagents have emerged as valuable tools for the installation of alkynes. Cyclic reagents rapidly replaced alkynyl iodonium salt reagents due to their higher stability and ease of handling. However, most effort focused on the benziodoxol(on)e scaffolds which offer limited possibility for structural modification. Our group later reported the synthesis of ethynylbenziodazolone reagents in which a nitrogen was inserted in the iodoheterocycle allowing an extra site for the tuning of the structure. While several hypervalent iodine reagent bearing a nitrogen bound to the iodine atom have been developed, their structure-reactivity relationships were not systematically investigated.

The first project of this Thesis aimed at synthesizing new *N*-heterocyclic alkynyl hypervalent iodine reagents (Scheme 3.15). The targeted structures are based on amidine, benzylamine and sulfoximine scaffolds with the objective of developing aminoalkynylation reactions. The study of their solid-state structures as well as electronic density distributions would offer important insights in order to rationalize their respective reactivity in different reactions.



Scheme 3.15. Development of new *N*-heterocyclic alkynyl hypervalent iodine reagents.

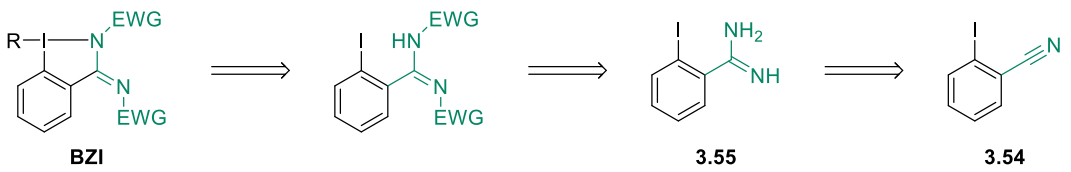
3.3. Results and Discussion

In this section, the results on the development of new hypervalent iodine reagents based on amidine, benzylamine and sulfoximine scaffolds will be presented.[102] Their solid-state structures and electron density distributions will be discussed.[103] Their reactivity in different classical reactions will be discussed. Finally, the new reagents were screened in a thiol-mediated uptake inhibition assay and the results will be presented.[104]

3.3.1. Synthesis of New *N*-Heterocyclic Alkynyl Hypervalent Iodine Reagents

3.3.1.1. Synthesis of Ethynylbenziodazolimine (EBZI) reagents

Commercially available 2-iodobenzonitrile (**3.54**) was chosen as starting material to access the benziodazolimine (BZI) reagents. Nucleophilic addition on the nitrile would lead to 2-iodobenzamidine (**3.55**). Protection of the amino and imino groups followed by oxidation would afford the amidine-based reagents (Scheme 3.16).

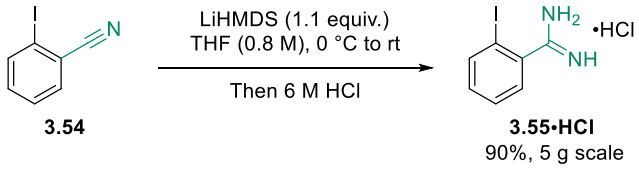


Scheme 3.16. Retrosynthetic approach towards amidine-based reagents.

In the forward sense, following a reported procedure,[105] 2-iodobenzonitrile (**3.54**) was treated with LiHMDS at 0 °C and then quenched by the addition of a 6 M solution of HCl affording the desired 2-iodobenzamidine in its hydrochloride salt form (**3.55·HCl**) in excellent yield on a 5 g scale (Scheme 3.17).[106]

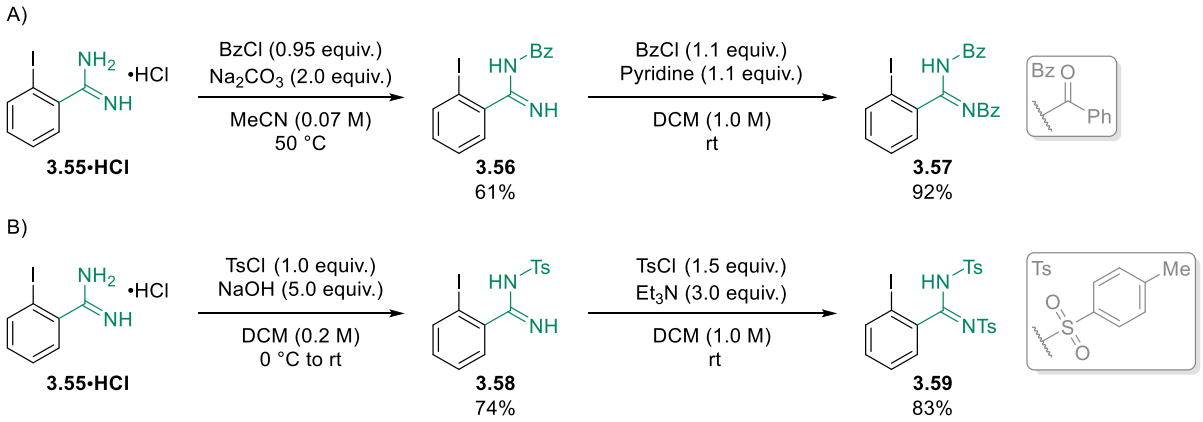
---

[102] The sulfoximine part was carried out as a collaborative work with Dr. Thibaut Duhail, Dr. Elsa Anselmi in the group of Dr. Emmanuel Magnier from the Institut Lavoisier de Versailles, France.
[103] The X-ray structures were determined by Dr. Rosario Scopelliti and Dr. Farzaneh Fadei-Tirani and the computations for the electron density distributions were performed by Dr. Matthew D. Wodrich from EPFL, Switzerland.
[104] The inhibition assays were carried out by Bumhee Lim, Yangyang Cheng and Dimitri Moreau in the group of Prof. Stefan Matile from the University of Geneva, Switzerland.
[105] S. Dalai, V. N. Belov, S. Nizamov, K. Rauch, D. Finsinger, A. de Meijere, *Eur. J. Org. Chem.* **2006**, *2006*, 2753–2765.
[106] The hydrochloride salt showed low solubility in standard organic solvents and it was partially soluble in alcohols. However, no attempt to isolate the pure 2-iodobenzamidine (**3.55**) was carried out, the hydrochloride salt was directly used as such for the next steps.



Scheme 3.17. Synthesis of 2-iodobenzamidine·HCl.

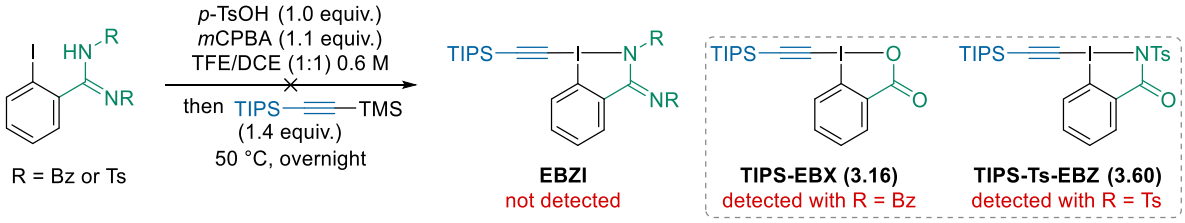
For the protection of amidine **3.55·HCl**, we selected benzoyl (Bz) and *p*-toluenesulfonyl (Ts) as model protecting groups. At the beginning of the project one-pot diprotection of amidine **3.55·HCl** was studied but we could only detect complex mixtures of isomers. Furthermore, in the perspective of fine tuning the properties of BZI reagents, it was expected that a stepwise protection procedure would be more versatile. Therefore, only the stepwise protection of 2-iodobenzamidine hydrochloride salt (**3.55·HCl**) will be discussed. For instance, bis-benzoylated amidine **3.57** could be obtained *via* sequential protection in 56% yield over two steps (Scheme 3.18.A).[107] Similarly, diprotected amidine **3.59** could be accessed after two successive tosylation steps affording the desired product in 61% over two steps (B).[107a]



Scheme 3.18. Synthesis of diprotected amidines **3.57** and **3.59**.

Having the amidine precursors in hand, we started to investigate the formation of alkynyl hypervalent iodine reagents following the one-pot oxidation-alkynylation protocol developed by our group for iodobenzamides (Scheme 3.19).[95] Unfortunately, with both protecting groups the desired ethynylbenziodazolimine (**EBZI**) reagents were not detected in the crude mixture. Analysis of the crude NMR showed the presence of products derived from first hydrolysis of the amidine followed by oxidation. For instance, TIPS-EBX (**3.16**) was found in the crude when starting with amidine **3.57** and TIPS-Ts-EBZ (**3.60**) was formed when **3.59** was subjected to the reaction conditions.

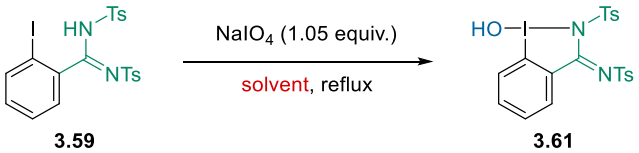
[107] (a) A. Guzmán, M. Romero, F. X. Talamás, R. Villena, R. Greenhouse, J. M. Muchowski, *J. Org. Chem.* **1996**, *61*, 2470–2483. (b) T. Yao, *Tetrahedron Lett.* **2015**, *56*, 4623–4626.



Scheme 3.19. Investigation of the one-pot protocol to access EBZI reagents.

Due to the higher sensitivity of the benzoyl protecting group towards hydrolysis, we decided to focus our attention on the oxidation of tosylated amidines. Moreover, the one-pot protocol being unsuccessful, we reasoned that a stepwise oxidation followed by alkynylation process would lead to the desired reagents. We started by investigating the transformation of amidine **3.59** into the HO-Ts-BZI (**3.61**) reagent (Table 3.1).[108] Starting with the standard conditions developed to oxidize 2-iodobenzoic acid,[109] a complex mixture was obtained but with poor conversion of the starting material (entry 1). Moving from water to DCE improved the solubility of **3.59** but no reaction occurred and the starting amidine could be recovered (entry 2). Going back to the water/acetic acid system but changing the ratio did not provide the desired reagent **3.61** (entries 3-4).

Table 3.1. Study of the oxidation of **3.59** to HO-Ts-BZI **3.61**.



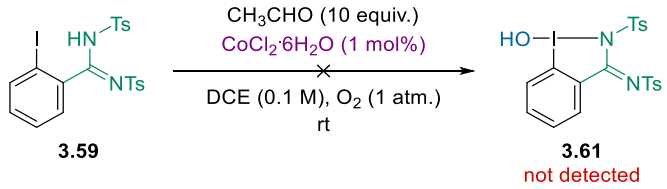
Entry	Solvent	Yield
1[a]	H_2O/AcOH (7:3)	Complex mixture
2[a]	DCE/AcOH (7:3)	NR
3[b]	H_2O/AcOH (4:1)	Complex mixture
4[b]	H_2O/AcOH (3:7)	Complex mixture

[a] Reaction conditions: 0.20 mmol of **3.59**, 0.21 mmol of $NaIO_4$, in solvent (0.40 M) at reflux. [b] Reaction conditions: 0.80 mmol of **3.59**, 0.84 mmol of $NaIO_4$, in solvent (0.40 M) at reflux.

In order to avoid hydrolysis, we decided to explore milder methods to oxidize compound **3.59**. In that regard, the aerobic oxidation procedure to generate hypervalent iodine reagents developed by Powers and coworkers seemed suitable.[110] However, when we applied

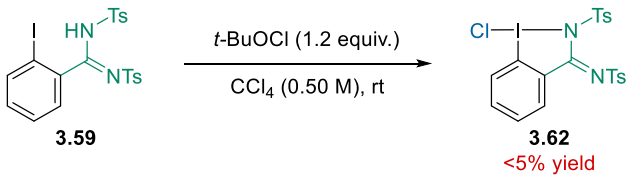
[108] For the nomenclature: HO-Ts-BZI = functional group bound to iodine – protecting groups on nitrogen – benziodazolimine.
[109] L. Kraszkiewicz, L. Skulski, *Arkivoc* **2003**, *2003*, 120–125.
[110] A. Maity, S.-M. Hyun, D. C. Powers, *Nat. Chem.* **2018**, *10*, 200–204.

the conditions to **3.59,** no reaction occurred and the starting material stayed mostly unaffected (Scheme 3.20).



Scheme 3.20. Aerobic oxidation of **3.59**.

Finally, we turned our attention towards water free oxidation conditions. Moreover, we wondered if the introduction of a ligand possessing a weaker *trans*-influence would facilitate the synthesis of BZI derivatives. For this purpose, we focused our attention on the introduction of a chlorine ligand.[93] Two procedures were selected to afford oxidative chlorination of **3.59**. The first one employed *tert*-butyl hypochlorite as reagent (Scheme 3.21).[111] The oxidant required to be prepared beforehand and used immediately as it degrades rapidly. The instability of *t*-BuOCl might explain why the desired product (**3.62**) was observed but only in traces amount and that around 80% of the starting material was recovered. Due to the high toxicity and restrictions to buy CCl_4, this method was not further investigated.

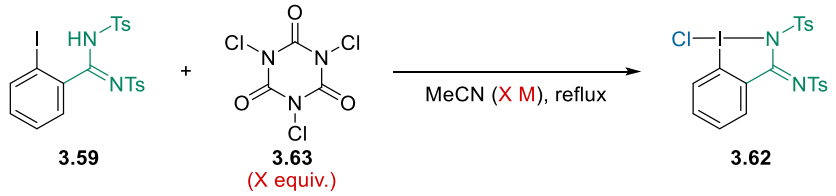


Scheme 3.21. Synthesis of Cl-Ts-BZI reagent **3.62**.

Then we studied the chlorination procedure developed by Togni and coworkers (Table 3.2).[112] Following the reported procedure, the desired product was not isolated (entry 1). Product **3.62** was most likely lost during filtration over Celite® pad due to low solubility in acetonitrile. Changing filtration conditions and slightly increasing the loading in oxidant **3.63** allowed to isolate **3.62** in moderate yield (entry 2). Moving to 0.40 equivalent of trichloroisocyanuric acid **3.63** with slightly more dilute conditions led to the formation of **3.62** in excellent yields (entries 3-4).

[111] R. L. Amey, J. C. Martin, *J. Org. Chem.* **1979**, *44*, 1779–1784.
[112] V. Matoušek, E. Pietrasiak, R. Schwenk, A. Togni, *J. Org. Chem.* **2013**, *78*, 6763–6768.

Table 3.2. Oxidative chlorination of amidine **3.59**.[a]

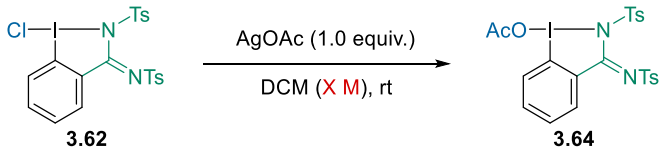


Entry	Equiv.	Concentration	Scale	Yield
1	0.27	0.30 M	0.20 mmol	-
2	0.34	0.30 M	0.80 mmol	53%
3	0.40	0.25 M	1.6 mmol	90%
4	0.40	0.25 M	2.0 mmol	93%

[a] Reaction conditions: X mmol of **3.59**, X equiv. of **3.63**, in dry MeCN (X M) at reflux.

Having **3.62** in hand, we were interested by ligand exchange reactions to access AcO-Ts-BZI reagent **3.64**. This type of hypervalent iodine has been shown to be a good precursor to alkynyl reagents.[47] Ligand exchange mediated by AgOAc allowed to synthesize **3.64** in very good yield following a procedure developed by Kita and coworkers (Table 3.3).[113] Decreasing the concentration to improve the solubility of the substrate and increasing the scale had limited impact on the reaction outcome and reagent **3.64** was obtained in excellent yield (entries 1-3).

Table 3.3. Synthesis of AcO-Ts-BZI **3.64**.[a]

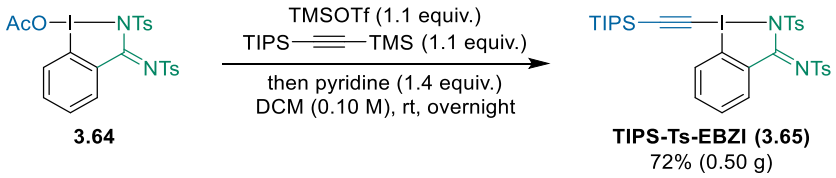


Entry	Concentration	Scale	Yield
1	0.35 M	0.17 mmol	95%
2	0.28 M	0.85 mmol	97%
3	0.21 M	1.7 mmol	Quant.

[a] Reaction conditions: X mmol of **3.62**, 1.0 equiv of AgOAc, in dry DCM (X M) at rt.

[113] Y. Kita, S. Akai, T. Okuno, M. Egi, T. Takada, H. Tohma, *Heterocycles* **1996**, *42*, 47–51.

Finally, following a slightly modified procedure developed by the Zhdankin group for the synthesis of EBX reagents,[47] TIPS-Ts-EBZI (**3.65**)[114] could be obtained in good yield on half a gram scale (Scheme 3.22).



Scheme 3.22. Synthesis of TIPS-Ts-EBZI **3.65**.

Good quality crystal of **3.65** could be obtained after recrystallization in ethyl acetate and the structure of TIPS-Ts-EBZI could be determined by X-ray diffraction (Figure 3.7). The key structural features of the reagent will be discussed in more details in the next section (3.3.2) and compared to already established alkynyl hypervalent iodine reagents.

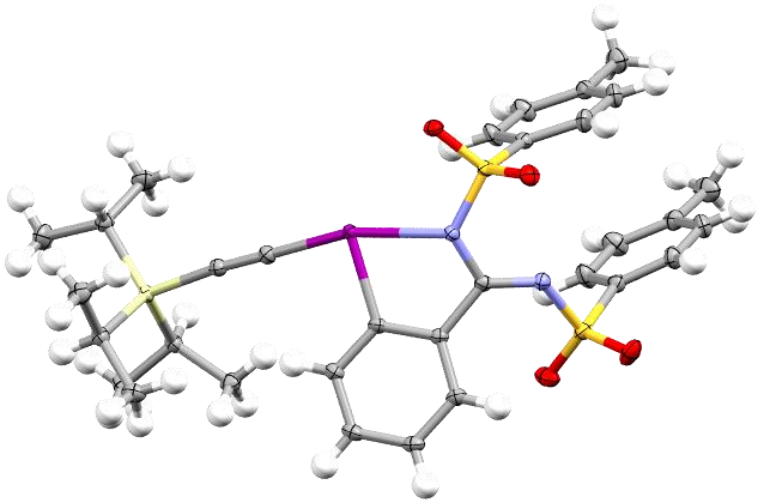
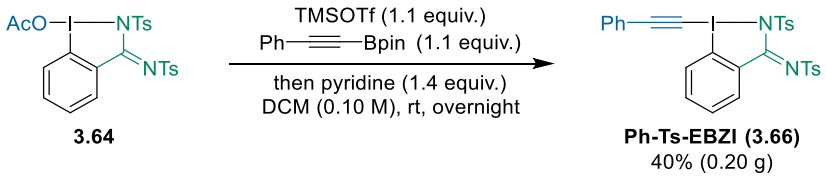


Figure 3.7. X-ray structure of TIPS-Ts-EBZI **3.65**.

Similarly, Ph-Ts-EBZI (**3.66**) could be obtained in moderate yield using a borylated instead of a silylated alkyne (Scheme 3.23).[38b]



Scheme 3.23. Synthesis of Ph-Ts-EBZI **3.66**.

[114] For the nomenclature: TIPS-Ts-EBZI = alkyne substituent – protecting groups – ethynylbenziodazolimine.

The structure of the reagent could also be determined by single crystal X-ray diffraction analysis (Figure 3.8).

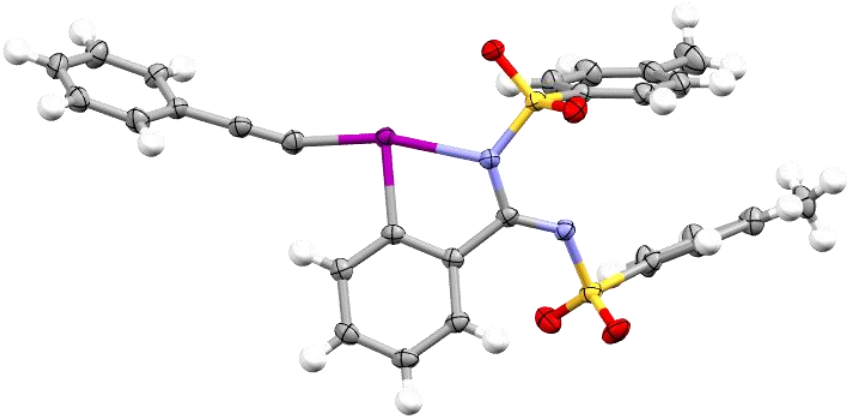
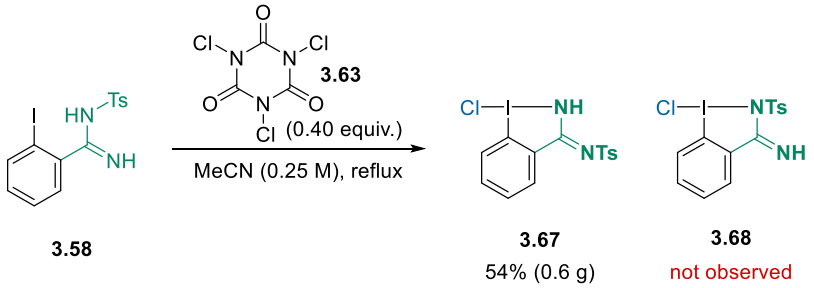


Figure 3.8. X-ray structure of Ph-Ts-EBZI **3.66**.

Having developed the alkynyl reagents with doubly protected amidine, we were curious to investigate the oxidation of mono-protected amidine **3.58**. When subjected to the previously developed chlorination procedure, **3.58** was converted into Cl-H,Ts-BZI (**3.67**) in moderate yield (Scheme 3.24).[115]



Scheme 3.24. Oxidative chlorination of amidine **3.58**.

X-ray diffraction allowed to confirm the structure of the obtained reagent (Figure 3.9), which is in accordance with the assumption that the isomer with the endocyclic free nitrogen atom (**3.67**) was more stable than the other one (**3.68**).[89i] It is worth noting that the corresponding NH-free amide reagent has been shown to be too unstable to be isolated,[89d] the presence of the sulfonyl group on the imino group might help to stabilize the compound *via* secondary interactions with the oxygen lone pairs (O-H = 2.127(2) Å).

[115] For the nomenclature: Cl-H,Ts-BZI = ligand bound to iodine – substituent on the nitrogen atom bound to iodine, substituent on imino group – benziodazolimine.

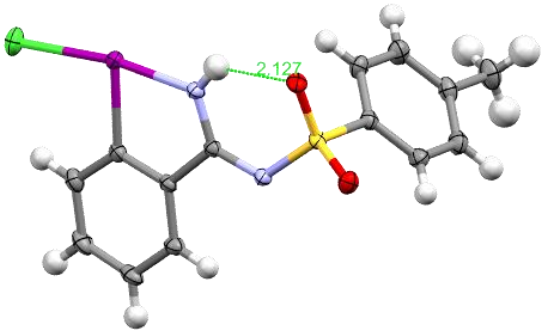
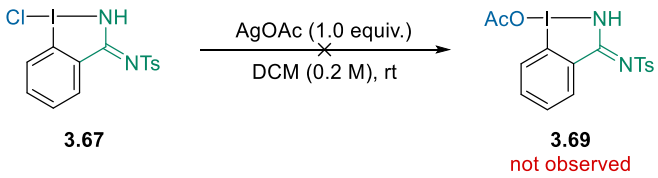


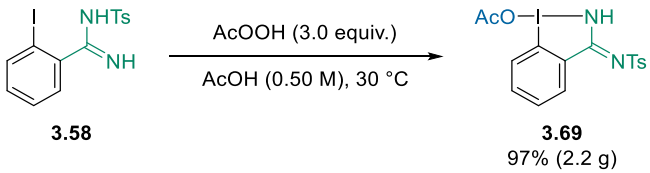
Figure 3.9. X-ray structure of Cl-H,Ts-BZI **3.67**.

Unfortunately, the ligand exchange using AgOAc for the synthesis of reagent **3.69** did not allow to isolate the desired compound (Scheme 3.25). A complex mixture of products was obtained. Moreover, due to low solubility in DCM, the desired compound might have been lost when filtering off AgCl.



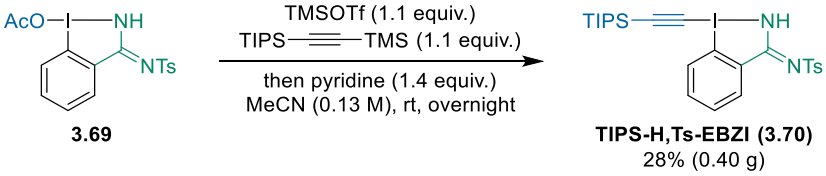
Scheme 3.25. Attempt to convert **3.67** into AcO-H,Ts-BZI **3.69**.

Interestingly, when subjected to peracetic acid in acetic acid, **3.58** was cleanly converted into AcO-H,Ts-BZI (**3.69**) in excellent yield up to 2.2-gram scale.[89i] When these conditions were applied to diprotected amidine **3.59**, only products arising from hydrolysis were obtained.



Scheme 3.26. Direct synthesis of AcO-H,Ts-BZI (**3.69**) from amidine **3.58**.

Due to low solubility of **3.69** in DCM, the previously used procedure for the synthesis of TIPS-Ts-EBZI **3.65** was slightly adapted and DCM was replaced by MeCN.[47] In contrast to the formation of diprotected reagent **3.65**, TIPS-H,Ts-EBZI **3.70** was obtained in moderate yield (Scheme 3.27).



Scheme 3.27. Synthesis of TIPS-H,Ts-EBZI **3.70**.

The structure of the reagent could also be unambiguously confirmed by single-crystal X-ray analysis (Figure 3.10).

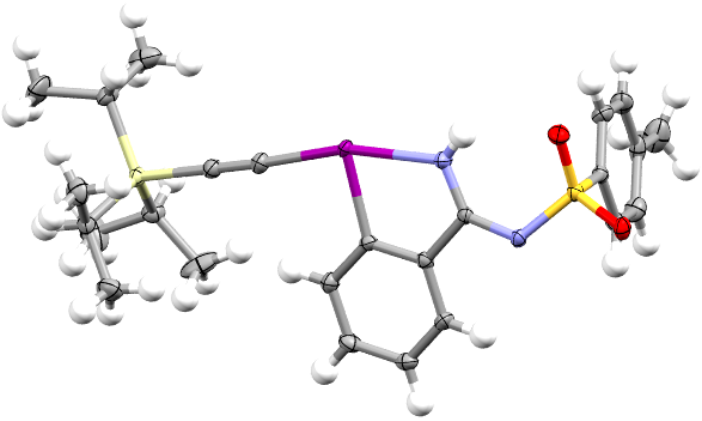
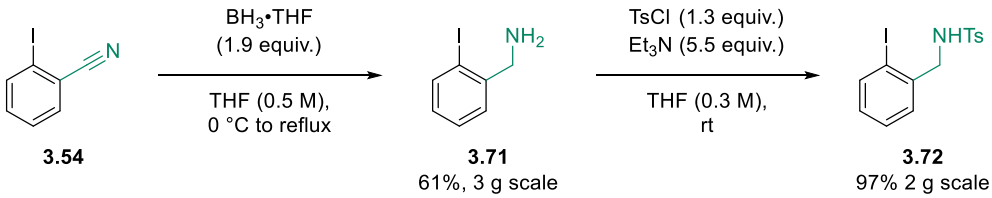


Figure 3.10. X-ray structure of TIPS-H,Ts-EBZI **3.70**.

3.3.1.2. Synthesis of Ethynylbenziodazole (EBz) reagents

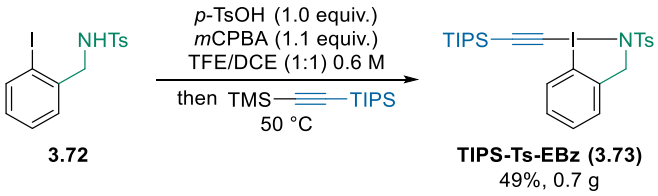
Starting from the same starting material **3.54** as for the amidine reagents, protected amine **3.72** could be obtained in 59% yield after two steps on multigram scales (Scheme 3.28). First reduction using BH_3·THF afforded the free amine **3.71** in 61% yield on a 3-gram scale without optimizing the reaction conditions.[116] Protection of the amine with tosyl chloride afforded the desired intermediate **3.72** in excellent yield on a 2-gram scale.[116]



Scheme 3.28. Synthesis of protected 2-iodobenzylamine **3.72** precursor.

[116] L. A. Aronica, G. Albano, L. Giannotti, E. Meucci, *Eur. J. Org. Chem.* **2017**, *2017*, 955–963.

To our delight, compound **3.72** could be directly transformed into the corresponding TIPS-Ts-EBz (**3.73**)[117] reagent using the one-pot protocol (Scheme 3.29).[95] The new alkynyl reagent could be isolated in 49% yield. Interestingly, no side-product arising from the direct oxidation of the amine group was isolated.



Scheme 3.29. Synthesis of TIPS-Ts-EBz **3.73**.

The structure of the reagent could be unambiguously determined through X-ray diffraction analysis (Figure 3.11).

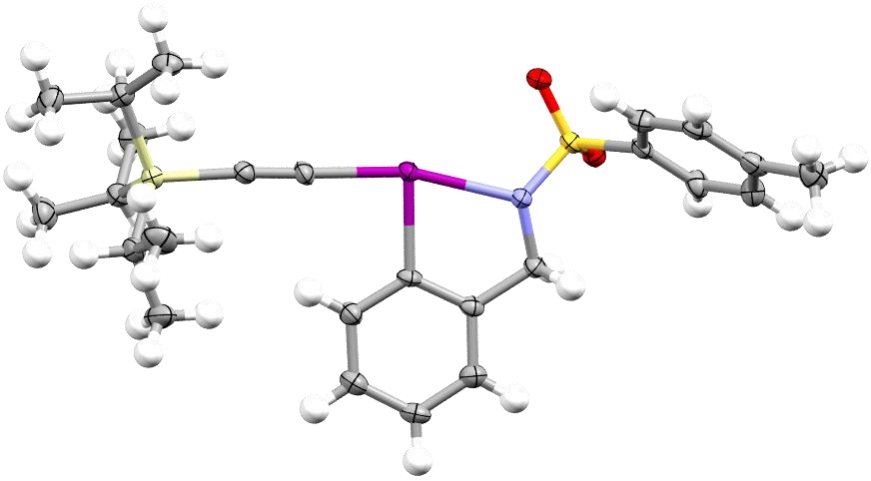


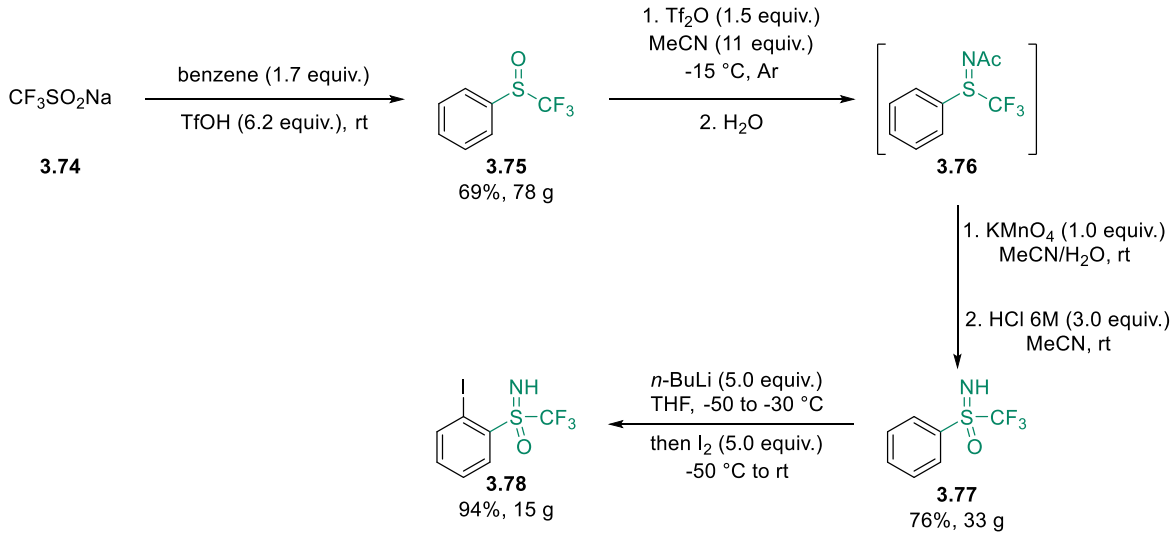
Figure 3.11. X-ray structure of TIPS-Ts-EBz **3.73**.

3.3.1.3. Synthesis of Ethynylbenziodosulfoximine (EBS) reagents

During our study on the development of new cyclic alkynyl hypervalent iodine reagent scaffolds, the Magnier and Togni groups reported a new sulfoximine based scaffold.[98] We decided to investigate this scaffold as well through a collaboration with the Magnier group. All the sulfoximine precursors presented below have been synthesized by Dr. Thibaut Duhail from the Magnier group.[102] Sulfinyl intermediate **3.75** could be obtained in large scale from benzene and Langlois reagent (Scheme 3.30).[118] A one-pot two steps procedure allowed to convert **3.75** into sulfoximine **3.77** in 76% yield over the two steps.[118] Finally, *ortho*-lithiation followed

[117] For the nomenclature: TIPS-Ts-EBz = Substituent on alkyne – Protecting group on the amine – Ethynylbenzidazole.
[118] A.-L. Barthelemy, V. Certal, G. Dagousset, E. Anselmi, L. Bertin, L. Fabien, B. Salgues, P. Courtes, C. Poma, Y. El-Ahmad, E. Magnier, *Org. Process Res. Dev.* **2020**, *24*, 704–712.

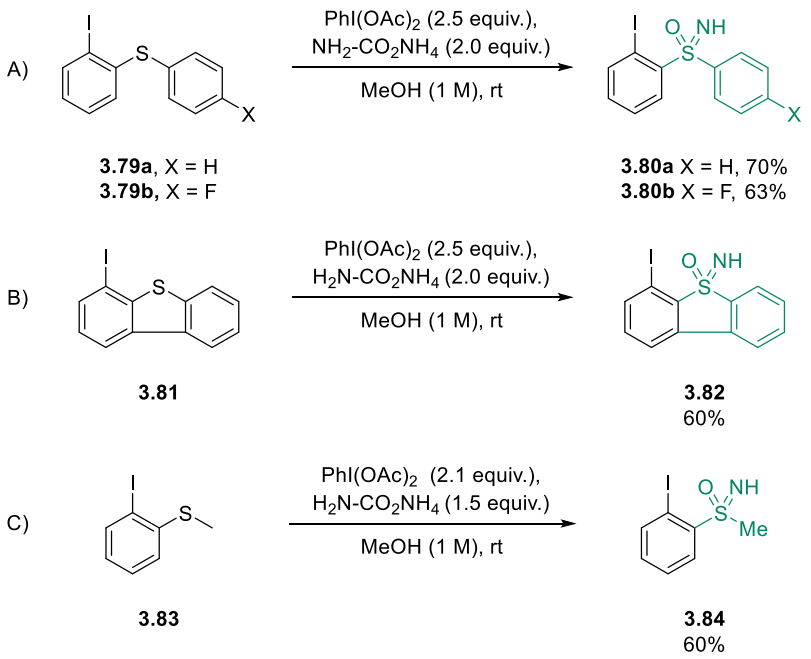
by iodination afforded the desired sulfoximine precursor **3.78** in excellent yield on a multigram scale.[98] Interestingly, the two enantiomers of **3.78** could be separated using preparative chiral HPLC.



Scheme 3.30. Synthesis of sulfoximine precursor **3.78**.

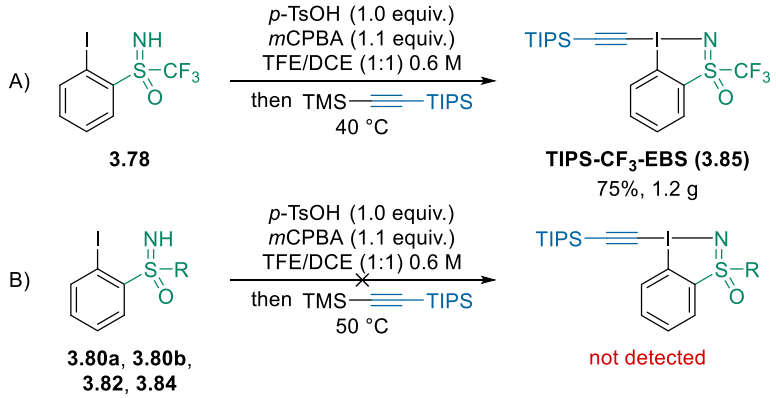
In addition to sulfoximine **3.78**, four other sulfoximines were prepared, in which the CF_3 group was replaced by an aryl or alkyl group (Scheme 3.31). Oxidation of diarylsulfides with PIDA in presence of ammonium carbamate led to the desired sulfoximine **3.80a** and **3.80b** in good yields (A).[119] Using the same strategy, thiophene **3.81** could be converted into **3.82** in 60% yield (B). Slightly changing the stoichiometry allowed to access sulfoximine **3.84** from sulfide **3.83** in 60% yield (C).

[119] A. Tota, M. Zenzola, S. J. Chawner, S. S. John-Campbell, C. Carlucci, G. Romanazzi, L. Degennaro, J. A. Bull, R. Luisi, *Chem. Commun.* **2017**, *53*, 348–351.



Scheme 3.31. Synthesis of other sulfoximine precursors.

The one-pot protocol could be successfully applied to sulfoximine **3.78** bearing a trifluoromethyl group and the desired TIPS-CF_3-EBS (**3.85**)[120] could be synthesized in good yield on a gram scale (Scheme 3.32.A).[95] It is worth noting that starting from enantiopure sulfoximine **3.78**, an enantiopure alkynyl hypervalent iodine reagent could be obtained with ee > 99%.[121] Unfortunately, none of the other sulfoximine precursors could be converted to hypervalent iodine reagents highlighting the importance of the CF_3 group on the sulfoximine, the same behavior had been already observed by the Magnier group.[98]



Scheme 3.32. Synthesis of ethynylbenziodosulfoximine reagents.

[120] For the nomenclature: TIPS-CF_3-EBS = substituent on alkyne – functional group on sulfoximine – ethynylbenziodosulfoximine.
[121] For another example of chiral alkynyl HIR: S. Companys, P. A. Peixoto, C. Bosset, S. Chassaing, K. Miqueu, J.-M. Sotiropoulos, L. Pouységu, S. Quideau, *Chem. Eur. J.* **2017**, *23*, 13309–13313.

The reagent **3.85** was obtained as a racemic mixture and was unambiguously characterized by single crystal X-ray diffraction as a cocrystal with water (Figure 3.12).

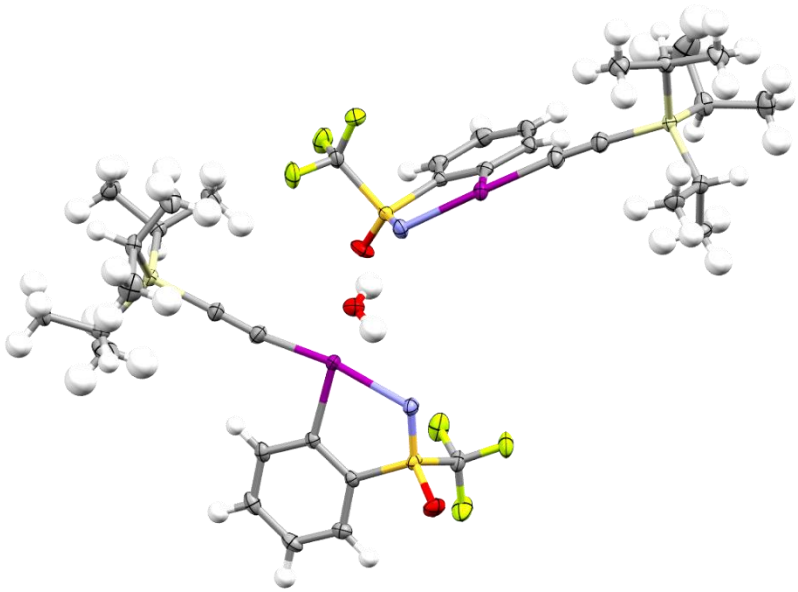


Figure 3.12. X-ray structure of the racemic reagent TIPS-CF_3-EBS **3.85**.

3.3.2. Solid-state Structures and Electron Density Distribution Comparison

Having a set of new reagents in hand, we decided to compare their structural features with already reported alkynyl hypervalent iodine reagents. We selected reagents bearing a TIPS substituent on the alkyne in order to compare the impact of the ligands on the structures. For instance, we analyzed the X-ray structures of reagents with various substituents on the aryl ring of EBX (reagents **3.86**, **3.16**, **3.87**, **3.88** and **3.90**)[53a], we also examined the benziodoxole reagent (**3.91**).[122] Finally, we added the recently developed EBZ reagent **3.60**[95] and the triazole-based reagent (**3.89**) reported by the Nachtsheim group (Table 3.4).[123]

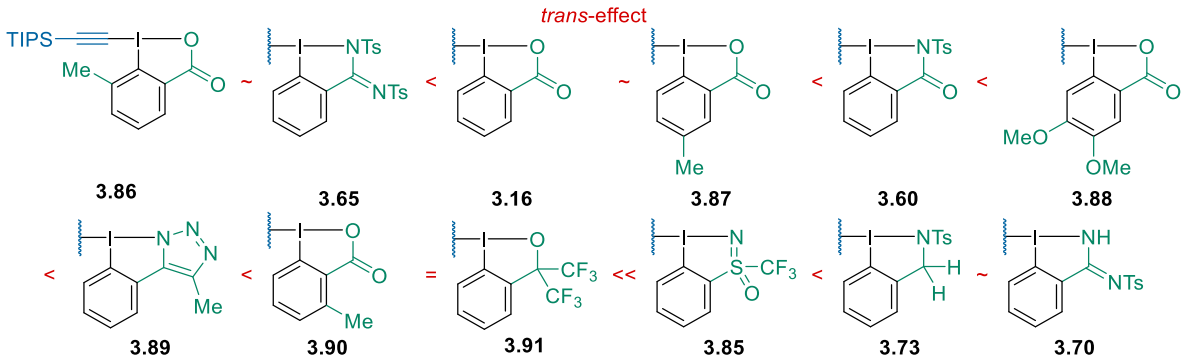
The comparison of the bond lengths between the iodine atom and the carbon from the alkyne allows to determine the relative *trans* effect of the substituents (see Chapter 2). The longer the bond length is, the higher the *trans* influence of the corresponding ligand is. From the data collected, we can conclude that iodobenzoate bearing a methyl *ortho* to the iodine (**3.86**) and diprotected amidine (**3.65**) are the ligands with the lower *trans* influence (entries 1-2). Iodobenzoate ligand and iodobenzoate with a methyl *para* to the iodine have similar *trans* influences (entries 3-4, I-C_{alkyne} = 2.054(2) vs 2.056(3) Å). An increase of the *trans* influence

[122] *Unpublished results.*
[123] T. J. Kuczmera, A. Boelke, B. J. Nachtsheim, *Eur. J. Org. Chem.* **2022**, *2022*, e202200276.

is observed moving from carboxylic acid to amide ligand (**3.60**, entry 5) or adding two methoxy groups on the aryl ring (**3.88**, entry 6). Changing the ligand to a triazole (**3.89**, entry 7, I-C_{alkyne} = 2.071(2) Å) or adding a methyl group *ortho* to the carboxylate (**3.90**, entry 8, I-C_{alkyne} = 2.073(1) Å) led to a slight increase in the *trans* influence. Similarly, benziodoxole based reagent **3.91** has a comparable *trans* effect (entry 9, I-C_{alkyne} = 2.073(2) Å). Finally, the higher *trans* effects were observed in the newly developed reagents (entries 10-12). The sulfoximine ligand (**3.85**, entry 10, I-C_{alkyne} = 2.089(3) Å) has a slightly lower effect than the benzylamine (**3.73**, entry 11, I-C_{alkyne} = 2.100(3) Å) and mono-protected amidine (**3.70**, entry 12, I-C_{alkyne} = 2.102(3) Å). The iodine-heteroatom bond length is similar for EBX (**3.16** and **3.87**), EBS (**3.85**) and EBz (**3.73**) (entries 3, 4, 10 and 11). For ligands **3.88**, **3.90**, **3.91** and **3.70** the bond is shorter (entries 6, 8, 9 and 12, I-X = 2.311(2), 2.309(1), 2.215(1) and 2.317(2) Å respectively) corresponding to a reduced ionic character of this bond. On the other hand, the iodine-heteroatom bond length is significantly longer for reagents **3.86**, **3.65**, **3.60** and **3.89** (entries 1, 2, 5 and 7, I-X = 2.385(4), 2.443(1), 2.387(6) and 2.431(1) Å respectively), this might be explained by increased steric hindrance in these reagents. As typically observed, the hypervalent bond was close to linearity in the reagents with X-I-C_{alkyne} angles ranging from 161.59(2)° for **3.86** (entry 1) to 171.23(1)° for **3.85** (entry 10). The typical T-shape structure is also observed with C_{Ar}-I-C_{alkyne} angle varying from 90.00(1)° for **3.70** (entry 12) to 95.23(2)° for **3.86** (entry 1). The torsion angle between the iodine-alkyne bond and the aryl showed that they are in most cases in the same plane with angles from -0.49(3)° for **3.73** (entry 11) to -8.33(2)° for **3.16** (entry 3). Due to higher steric hindrance, the torsion angle is significantly higher in reagents **3.86** (entry 1, 34.54(5)°), this hypervalent twist has been used to enhance the reactivity of hypervalent iodine reagents.[124] Interestingly, while it was shown that the hypervalent twist impacted significantly the torsion angle, it had little impact on the ligand-I bond length.[124b] The interaction between the tosyl groups in reagent **3.65** seems to induce a torsion between the iodine-alkyne bond and the aryl (entry 2, -16.56(1)°). Finally, the close proximity of one oxygen from the tosyl protecting groups and the iodine atom in reagents **3.65**, **3.60** and **3.73** (entries 2, 5 and 11, I-O = 3.319(1), 3.285(5) and 3.246(3) Å) might indicate potential secondary interactions.

[124] Selected examples: (a) J. T. Su, W. A. Goddard, *J. Am. Chem. Soc.* **2005**, *127*, 14146–14147. (b) A.-A. Guilbault, C. Y. Legault, *ACS Catal.* **2012**, *2*, 219–222.

Table 3.4. Comparison of bond lengths and bond angles in TIPS-substituted alkynyl hypervalent iodine reagents.



Entry	Reagent	I-C_{alkyne} [Å]	I-X [Å]	X-I-C_{alkyne} [°]	C_{Ar}-I-C_{alkyne} [°]	Torsion [°]	I-$O_{sulfonyl}$ [Å]
1[a]	**3.86**	2.043(6)	2.385(4)	161.59(2)	95.23(2)	34.54(5)	-
2	**3.65**	2.046(2)	2.443(1)	165.51(5)	93.03(6)	-16.56(1)	3.319(1)
3[a]	**3.16**	2.054(2)	2.338(1)	166.11(6)	91.37(7)	-8.33(2)	-
4[a]	**3.87**	2.056(3)	2.327(2)	166.97(9)	91.29(1)	1.09(2)	-
5[b]	**3.60**	2.060(9)	2.387(6)	165.79(3)	92.08(3)	-6.63(7)	3.285(5)
6[a]	**3.88**	2.065(2)	2.311(2)	167.49(7)	92.24(9)	-4.82(2)	-
7[c]	**3.89**	2.071(2)	2.431(1)	164.77(6)	91.04(6)	8.3(1)	-
8[a]	**3.90**	2.073(1)	2.309(1)	167.15(4)	91.58(5)	-0.72(1)	-
9	**3.91**	2.073(2)	2.215(1)	169.02(6)	92.18(7)	7.33(1)	-
10	**3.85**	2.089(3)	2.337(2)	171.23(1)	90.31(1)	2.85(2)	-
11	**3.73**	2.100(3)	2.333 (3)	165.99(1)	90.77(1)	-0.49(3)	3.246(3)
12	**3.70**	2.102(3)	2.317(2)	164.74(9)	90.00(1)	3.44(2)	-

X = O or N, the torsion angle corresponds to torsion angle between the I-C_{alkyne} and the aryl ring. [a] data taken from ref.[53a] [b] data taken from ref.[95] [c] data taken from ref.[123]

In order to better understand how the different substituents adjacent to the iodine atom impact the electronic properties of the reagents, Dr. M. D. Wodrich computed their molecular electrostatic potential (MEP) (Figure 3.13). In all the reagents, a strong polarization towards the heteroatom containing ligand can be observed. The calculated dipole moment is higher for TIPS-EBX (**3.16**, 8.30 D) followed by TIPS-EBZ (**3.60**, 8.03 D) and TIPS-H,Ts-EBZI (**3.70**, 7.97 D). The other reagents have lower calculated dipole moments ranging from 7.17 D for

compound **3.85** to 3.69 D for **3.92** which is the least polarized reagents. The MEP maps enabled to visualize the σ-hole regions of the different reagents. These positively charged region around the iodine atom contribute significantly to the directionality and the strength of reagent-substrate/solvent interactions.[125] Reagents **3.16**, **3.91**, **3.70** and **3.85** exhibit the most spatially extended σ-hole regions. On the other hand, reagents bearing a tosyl group on the nitrogen bound to the iodine atom (**3.60**, **3.65** and **3.73**) and the benziodoxole reagent **3.92** have less extended positive regions. The presence of a secondary interaction between the tosyl groups and the iodine atom in some reagents might reduce their σ-hole regions. In addition, local potential maximum ($V_{x,max}$) can be extracted from the MEP maps. In all the reagents, the $V_{I,max}$ are comparable ranging from + 0.032 for **3.92** and **3.73** to + 0.052 for TIPS-EBX (**3.16**). Interestingly, the structure of the iodoheterocycle seems to have a bigger effect on the spatial extension of the σ-hole regions than on the potential maximum at the iodine atom. While the electron density is significantly negative around the heteroatom bound to the iodine center in the benziodoxol(on)e reagents (**3.16**, **3.91** and **3.92**) and the sulfoximine based reagent (**3.85**), it is almost neutral for the other reagents. The electronic density seems actually to be located on the oxygens of the protecting groups in reagents **3.65** and **3.73** or on the exocyclic heteroatoms for **3.60** and **3.70**.

[125] H. Pinto de Magalhães, A. Togni, H. P. Lüthi, *J. Org. Chem.* **2017**, *82*, 11799–11805.

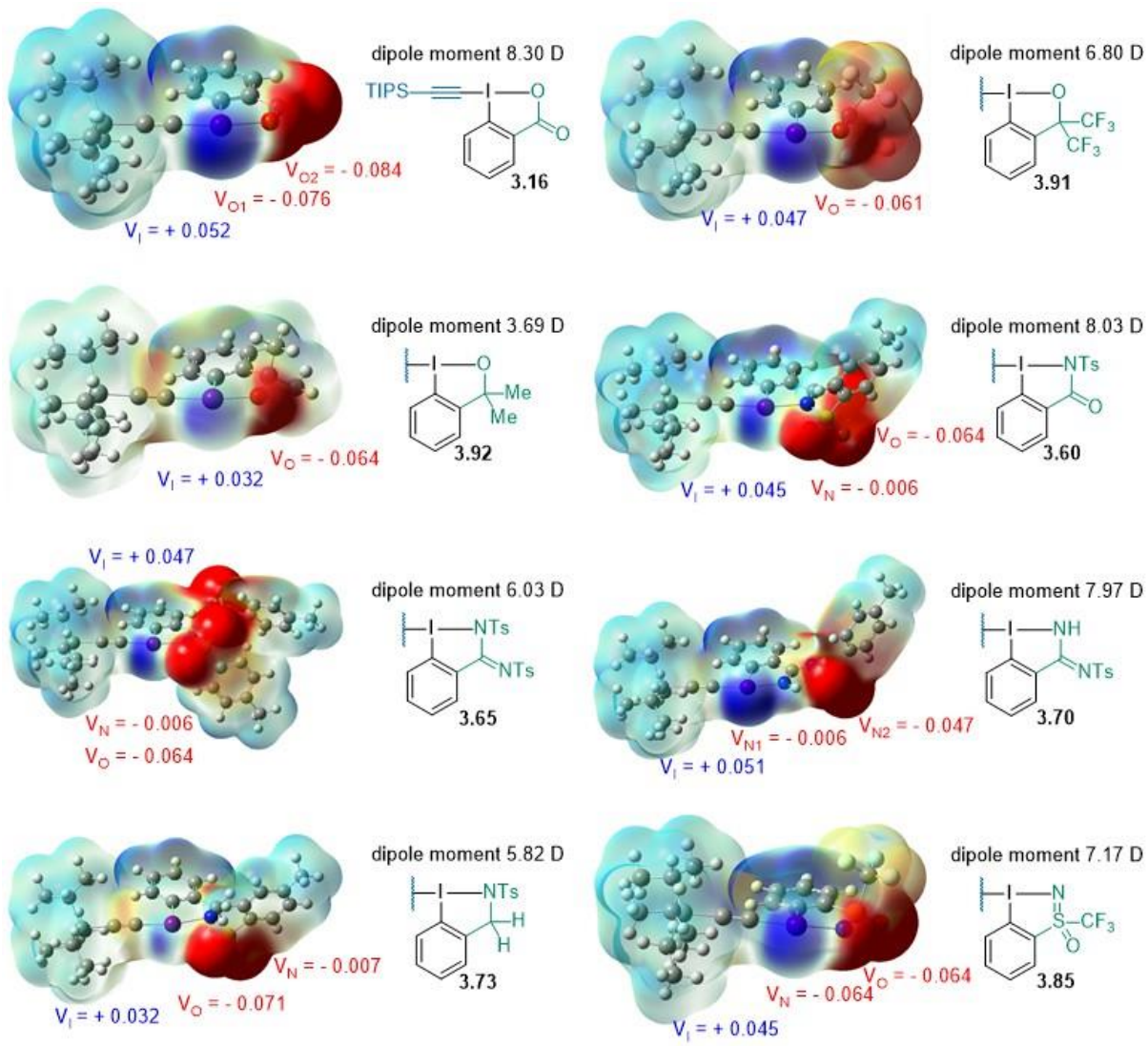


Figure 3.13. Molecular electrostatic potential (MEP) maps computed at the M06/def2-SVP levels. MEPs are mapped onto the 0.001 au isodensity surface. V_x corresponds to the potential maximum around the atom X and is give in au.

Overall, these results might imply that the major resonance structures of reagents **3.65**, **3.60**, **3.73** and **3.70** are ionic structures, in which the iodine would be positively charged and the ligand negatively charged with the charge delocalized on the protecting groups (Figure 3.14).

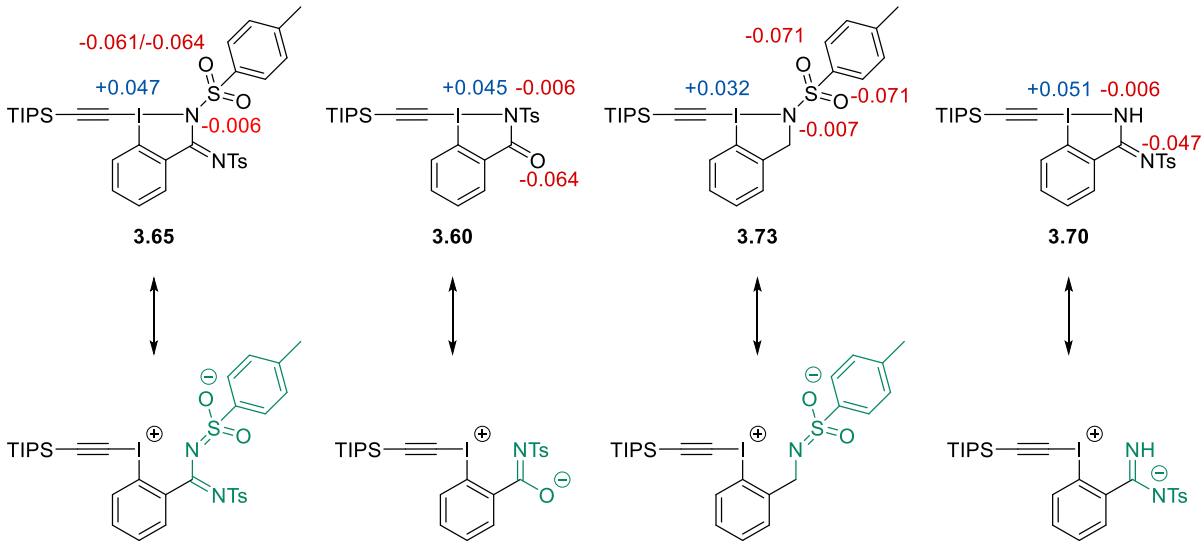


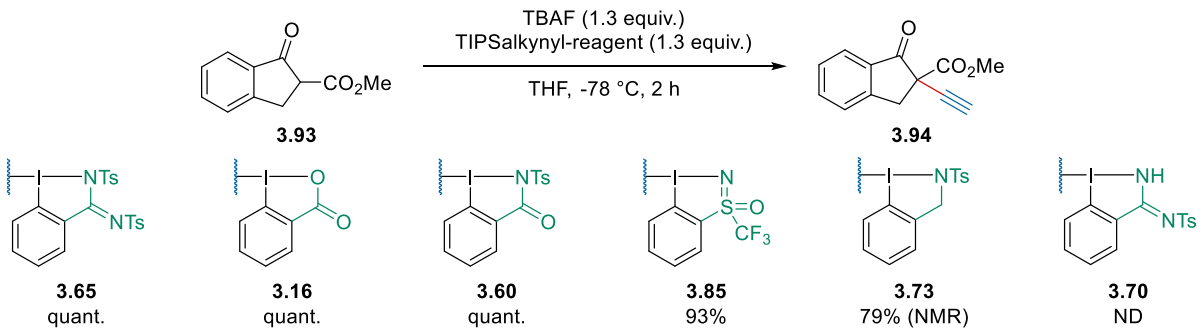
Figure 3.14. Potential major resonance structures of reagents **3.65**, **3.60**, **3.73** and **3.70**.

3.3.3. Reactivity Comparison

After describing the structural features, electronic distributions, we decided to compare the reactivity of the newly designed HIR in standard alkynylation reactions.

3.3.3.1. Alkynylation of β-Ketoesters

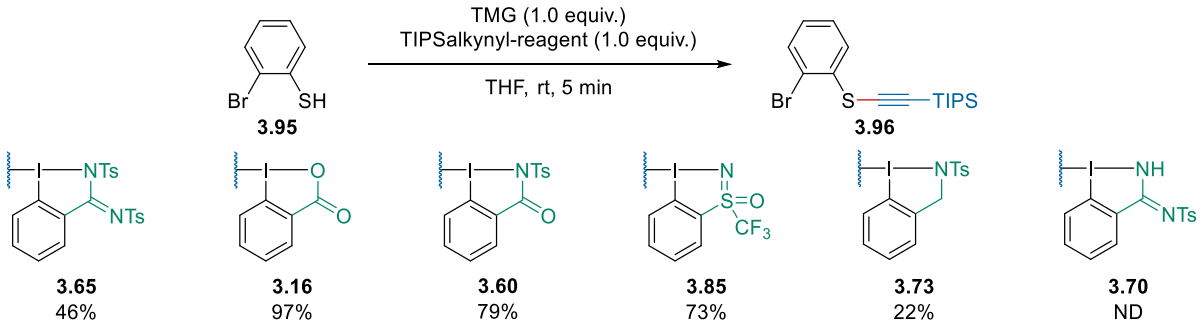
We started our investigation with the alkynylation of β-ketoester **3.93** (Scheme 3.33). The already established TIPS-EBX (**3.16**) and more recent TIPS-Ts-EBZ (**3.60**) have been shown to afford the alkynylated product **3.94** in quantitative yield in both cases.[68b,95] Interestingly, in the conditions optimized for TIPS-EBX (**3.16**), TIPS-Ts-EBZI (**3.65**) performed very well leading to the product **3.94** in quantitative yield as well. The sulfoximine reagent **3.85** was an efficient alkynyl transfer reagent and the desired product **3.93** was obtained in 93% yield, unfortunately when the chiral reagent was used no significant chiral induction was detected (<5% ee). We believe that the stereogenic center in the reagent and the reactive site on the alkyne are not close enough to promote any selectivity, a similar result had been previously observed by the Magnier group with their Togni-like reagent.[98] Reagent **3.73** was found to be an efficient alkynyl-transfer reagent as well and the alkynylated product **3.94** was formed in 79% NMR yield. However, the product could not be isolated pure due to coelution with *N*-(2-iodobenzyl)-4-methylbenzenesulfonamide (**3.72**) formed after transfer of the alkyne from reagent **3.73**. Finally, when using mono-protected amidine reagent **3.70**, only degradation of the reagent was observed.



Scheme 3.33. Alkynylation of β-ketoester **3.93**.

3.3.3.2. Alkynylation of Thiols

We then turned our attention to one of the benchmark reactions for EBX reagents, the alkynylation of thiols (Scheme 3.34).[72a] Computational mechanistic investigations showed that the accessibility of the σ-hole was essential for this reaction.[72b,c] For instance, reagents **3.16** and **3.85** having extended σ-hole regions were efficient alkynyl transfer reagents and afforded **3.96** in 97% and 73% yield, respectively. Reagents **3.60** and **3.65** have similar σ-hole regions, however **3.60** performed better in the reaction (79% vs 46% yield, respectively).[95] The difference of reactivity might be due to higher steric hindrance in the diprotected amidine reagent **3.65**. EBz reagent **3.73** reacted poorly in this transformation, which is in accordance with its relatively small σ-hole region. Finally, as observed previously, mono-protected amidine reagent **3.70** only decomposed in the reaction conditions and the desired thioalkyne **3.96** was not detected.

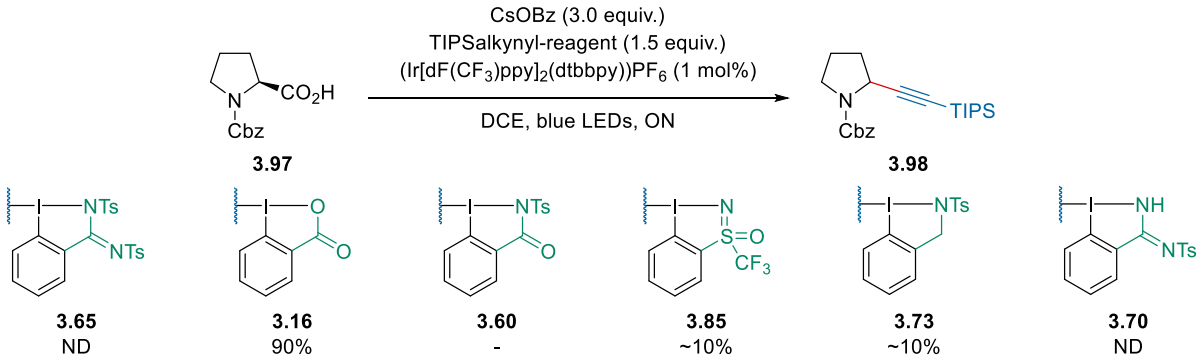


Scheme 3.34. Thioalkynylation reaction.

3.3.3.3. Photoredox-Catalyzed Decarboxylative Alkynylation

We were curious to investigate the reactivity of the new reagents in radical alkynylation reactions and selected the decarboxylative alkynylation of proline as model reaction (Scheme 3.35).[63b] Unfortunately the reaction conditions developed for EBX reagents, 90% yield for TIPS-EBX **3.16**, were not suitable for the other reagents. For instance, the amidine reagents **3.65** and **3.70** only decomposed during the reaction and the desired product **3.98** was not

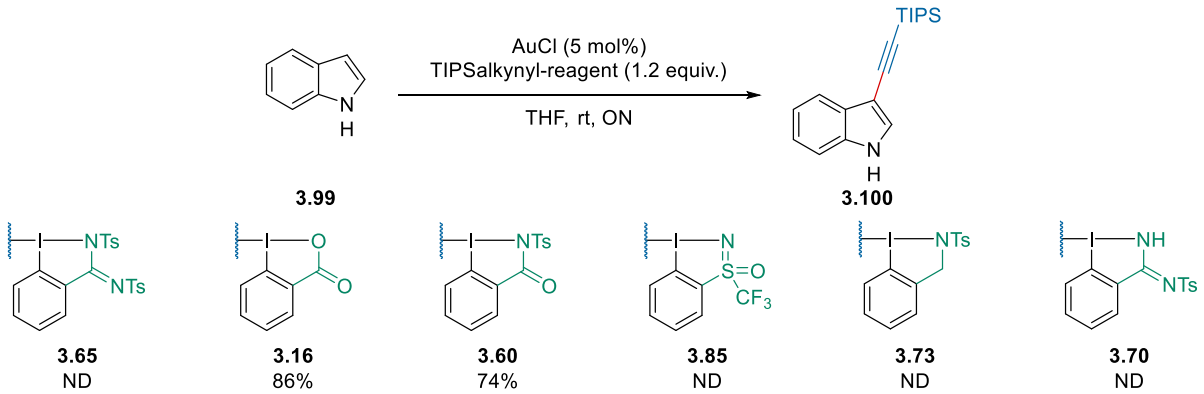
detected. However, TIPS-Ts-EBS (**3.85**) and TIPS-Ts-EBz (**3.73**) exhibited low reactivity affording the alkynylated product **3.98** in *ca.* 10% yield. This promising reactivity could imply that these two scaffolds could be valuable to develop new photoredox catalyzed transformations in the future.



Scheme 3.35. Decarboxylative alkynylation of Cbz-Pro-OH **3.97**.

3.3.3.4. Gold-catalyzed Alkynylation of Indoles

We then focused our attention on metal-catalyzed transformations and started to investigate the gold-catalyzed alkynylation of indoles that our group reported in 2009 (Scheme 3.36).[51] While the reaction worked well for TIPS-EBX (**3.16**)[51] and TIPS-Ts-EBZ (**3.60**)[95], none of the newly developed reagents gave promising results. Only degradation of the different reagents was observed, this lack of reactivity towards alkynylation might be due to a better coordination of the Nitrogen-based ligands to gold prohibiting the desired reaction to occur.[126]



Scheme 3.36. Gold-catalyzed alkynylation of indole **3.99**.

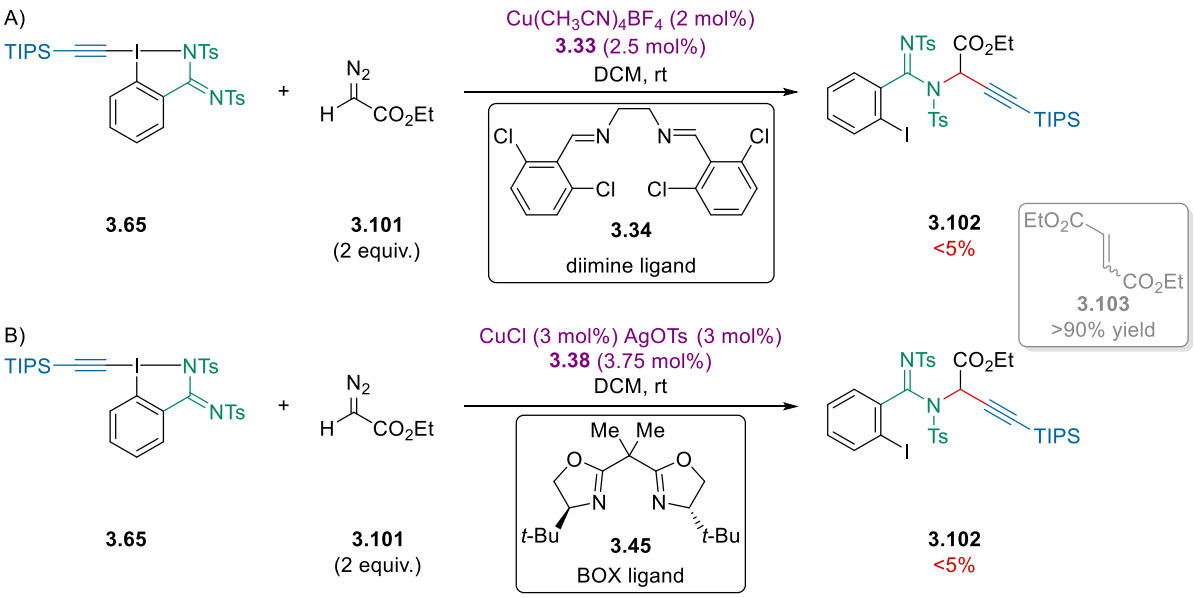
3.3.3.5. Aminoalkynylation of Diazo Compounds

One of the long-standing projects in the group was to develop an aminoalkynylation reaction with diazo compounds. Unfortunately, the ethynylbenziodazolone reagents

[126] A. Ariafard, *ACS Catal.* **2014**, *4*, 2896–2907.

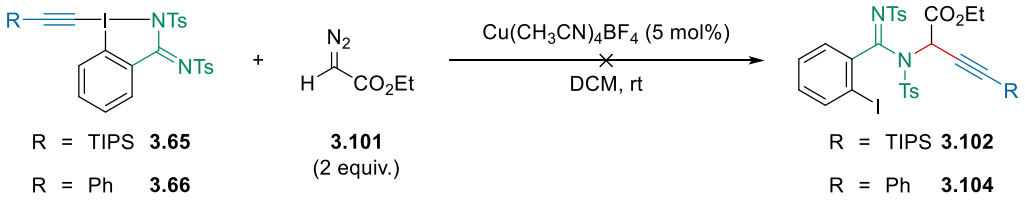
developed to reach this goal turned out to transfer the oxygen to the metal carbene instead of the nitrogen from the iodoheterocycle (see section 3.1.4).[95] We wondered if the new *N*-heterocyclic alkynyl hypervalent iodine reagents that we developed could be used in aminoalkynylation of diazo compounds.

We started to investigate the reactivity of TIPS-Ts-EBZI (**3.65**) with ethyl diazoacetate (EDA, **3.101**) under the conditions developed in our group for oxyalkynylation reactions (Scheme 3.37). First, we explored the transformation using $Cu(CH_3CN)_4BF_4$ as catalyst in presence of diimine ligand **3.34** (A).[87] The desired product **3.102** could only be detected by mass spectrometry but not clearly identified in the NMR spectrum of the crude mixture nor isolated by preparative thin-layer chromatography. Moreover, almost all the carbene precursor dimerized under the reaction conditions leading to **3.103** in more than 90% yield. The same reaction outcome was obtained when the conditions developed for amide-based reagents were used, namely CuCl (3 mol%), AgOTs (3 mol%) and BOX ligand **3.45** (B).[95]



Scheme 3.37. Initial aminoalkynylation attempts with EDA (**3.101**) and TIPS-Ts-EBZI (**3.65**).

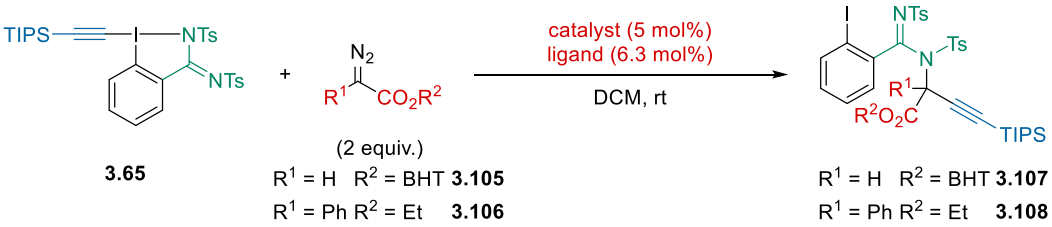
Next, we decided to screen conditions without ligands and study the impact of the substituent on the alkyne on the reactivity (Scheme 3.38). With both TIPS-(**3.65**) and Ph-Ts-EBZI (**3.66**) reagents, only degradation was observed and the dimerization products of EDA (**3.103**) were obtained as the major products.

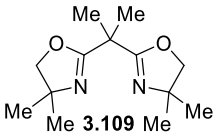


Scheme 3.38. Attempts with reagents **3.65** and **3.66**.

Dimerization of EDA (**3.101**) being the major side reaction occurring, we decided to investigate carbene precursors less prone to dimerization. For instance, bulky dibutylhydroxytoluene (BHT) diazo acetate (**3.105**) and donor-acceptor ethyl diazo phenylacetate (**3.106**) were investigated (Table 3.5). $Cu(CH_3CN)_4BF_4$ and $Rh_2(OAc)_4$ only allowed formation of traces amount of the targeted compound (entries 1-2). In contrast, no reaction occurred with $AuCl_3$ and $PdCl_2(PPh_3)_2$ and 62% or 70% of the starting EBZI (**3.65**) could be recovered (entries 3-4). Adding diimine ligand **3.34** did not improve the reaction outcome and no reaction occurred with BOX ligand **3.109** (entries 5-6). Moving from CuOAc to $Cu(OAc)_2$ with diimine ligand **3.34** had no impact on the reaction (entries 7-8). Finally, using a donor-acceptor diazo **3.106** did not provide the aminoalkynylation product and 80% of the starting reagent could be recovered after purification (entry 9).

Table 3.5. Screening of different diazo compounds, ligands and catalysts.[a]



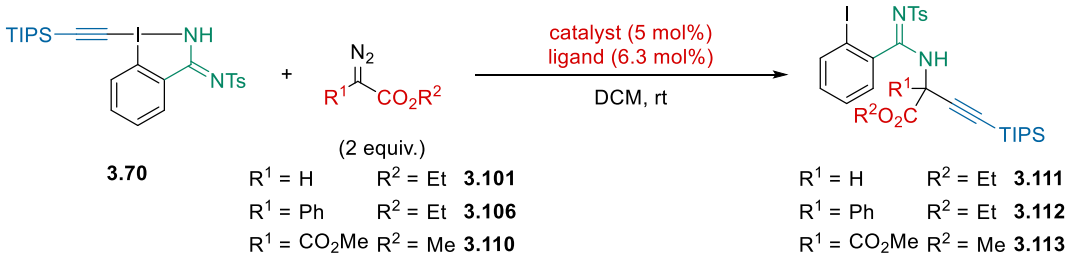
Entry	Diazo (R^1/R^2)	Cat.	Ligand	Yield
1	H/BHT	$Cu(CH_3CN)_4BF_4$	-	<5%
2	H/BHT	$Rh_2(OAc)_4$	-	<5%
3	H/BHT	$AuCl_3$	-	NR
4	H/BHT	$PdCl_2(PPh_3)_2$	-	NR
5	H/BHT	$Cu(CH_3CN)_4BF_4$	**3.34**	<5%
6	H/BHT	$Cu(CH_3CN)_4BF_4$	 **3.109**	NR
7	H/BHT	CuOAc	**3.34**	<5%
8	H/BHT	$CuOAc_2$	**3.34**	<5%
9	Ph/Et	$Cu(CH_3CN)_4BF_4$		NR

[a] Reaction conditions: 0.05 mmol of TIPS-Ts-EBZI (**3.65**), 5.0 mol% of catalyst, 6.3 mol% of ligand, 0.10 mmol of diazo compounds in dry DCM (0.05 M) at rt.

EBZI reagents bearing two nitrogen atoms protected by tosyl groups seemed not to be effective for the aminoalkynylation of diazo compounds. We were then curious about the reactivity of mono-protected amidine reagent **3.70** in this transformation (Table 3.6). As observed previously, with EDA the aminoalkynylation product **3.111** could only be detected by mass spectrometry when using $Cu(CH_3CN)_4BF_4$ as catalyst but only products of degradation of the reagent could be isolated (entry 1). In contrast, with Rh(II) catalyst only dimerization of the diazo compound occurred and most of the starting reagent **3.70** could be recovered (entry 2). The presence of a potentially acidic proton in the hypervalent iodine reagent motivated us

to investigate the effect of the addition of a base on the reaction (entries 3-4). Unfortunately, the addition of cesium carbonate only promoted the degradation of the reagent **3.70**. Addition of ligand **3.34** (entry 5), moving to donor-acceptor diazo compound **3.106** (entry 6) or to acceptor-acceptor diazo compound **3.110** (entry 7) did not allow to improve the outcome of the transformation.

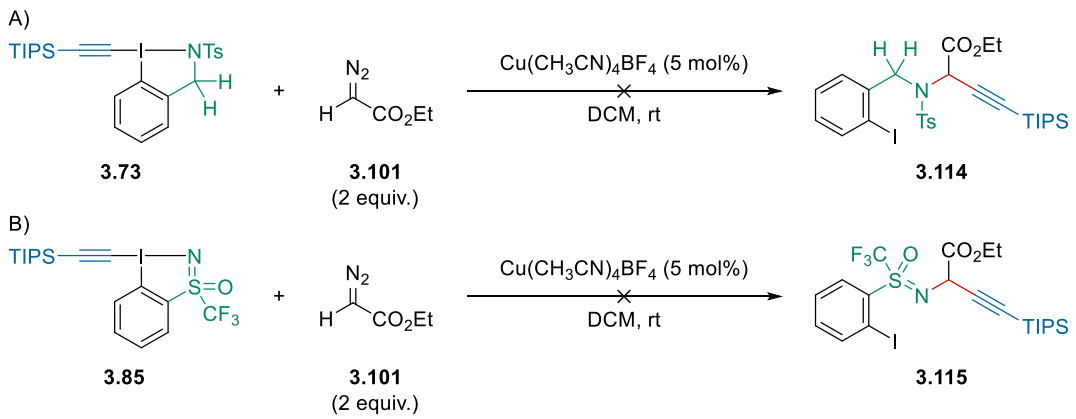
Table 3.6. Aminoalkynylation attempts with TIPS-H,Ts-EBZI (**3.70**).[a]



Entry	Diazo (R^1/R^2)	Cat.	Ligand	Additive	Yield
1	H/Et	$Cu(CH_3CN)_4BF_4$	-	-	<5%
2	H/Et	$Rh_2(OAc)_4$	-	-	NR
3	H/Et	$Cu(CH_3CN)_4BF_4$	-	Cs_2CO_3 (1 equiv.)	degradation
4	H/Et	$Rh_2(OAc)_4$	-	Cs_2CO_3 (1 equiv.)	degradation
5	H/Et	$Cu(CH_3CN)_4BF_4$	**3.34**	-	degradation
6	Ph/Et	$Cu(CH_3CN)_4BF_4$	-	-	degradation
7	CO_2Me/Me	$Cu(CH_3CN)_4BF_4$	-	-	degradation

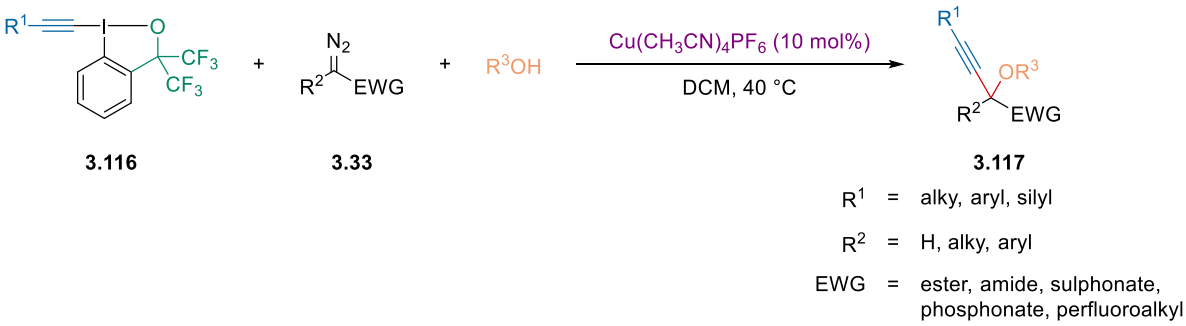
[a] Reaction conditions: 0.05 mmol of TIPS-H,Ts-EBZI (**3.70**), 5.0 mol% of catalyst, 6.3 mol% of ligand, 0.10 mmol of diazo compounds in dry DCM (0.05 M) at rt.

Finally, we started to investigate the reactivity of the reagents **3.73** and **3.85** with EDA (**3.101**) for the development of an aminoalkynylation reaction (Scheme 3.39). Unfortunately, when the reagent **3.73** was mixed with EDA in presence of a copper catalyst in DCM the formation of the desired product **3.114** was not observed (A). Similarly, compound **3.115** was not detected when using sulfoximine-based reagents **3.85** (B).



Scheme 3.39. Aminoalkynylation attempts with reagents **3.73** and **3.85**.

During the course of our studies on the development of aminoalkynylation reactions with hypervalent reagent, Dr. Guillaume Pisella, a former PhD student from our group, serendipitously discovered that when using EBx reagents **3.116** in the presence of an alcohol in the oxyalkynylation conditions, a three-component reaction was taking place leading to compounds **3.117** (Scheme 3.40).[127] During the optimization of the reaction, amines have been tested as well and showed promising results that were further studied.[128] Due to the lack of reactivity of our new reagents in the aminoalkynylation of diazo compounds we decided to stop our investigations on this transformation.



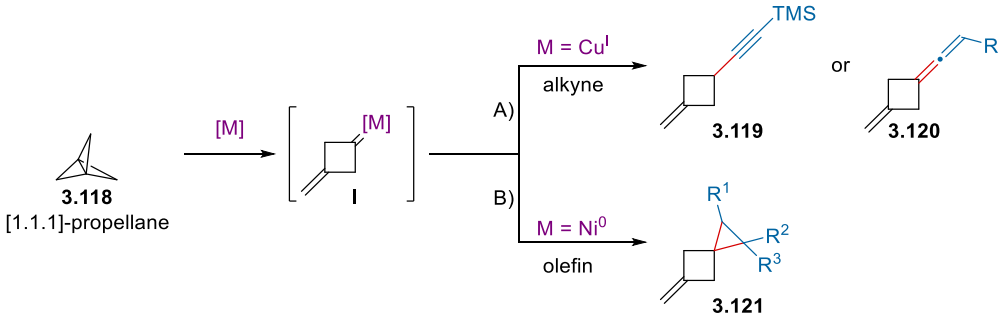
Scheme 3.40. Development of a three-component oxyalkynylation reaction.

3.3.3.6. Aminoalkynylation of [1.1.1]-propellane

The Aggarwal and Tolnai groups recently reported transition-metal catalyzed ring opening reactions of [1.1.1]-propellane (**3.118**) (Scheme 3.41). The reactions are believed to occur through the *in-situ* generation of a highly reactive non-stabilized metal carbene intermediate **I**. Using a copper-catalyst Tolnai and coworkers developed an efficient synthesis of alkynylcyclobutanes (**3.119**) and allenic cyclobutanes (**3.120**) (A).[129] The Aggarwal group

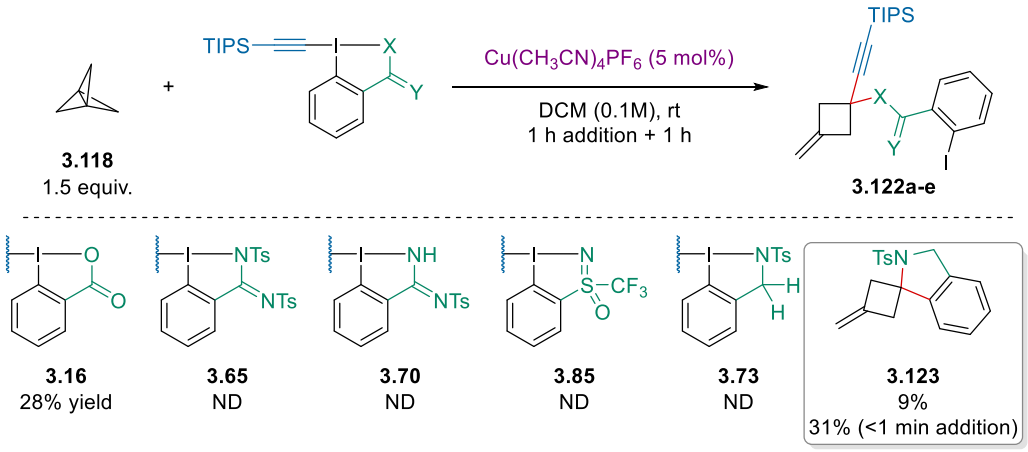
[127] G. Pisella, A. Gagnebin, J. Waser, *Chem. Eur. J.* **2020**, *26*, 10199–10204.
[128] N. P. Ramirez, G. Pisella, J. Waser, *J. Org. Chem.* **2021**, *86*, 10928–10938.
[129] D. Lasányi, G. L. Tolnai, *Org. Lett.* **2019**, *21*, 10057–10062.

studied the cyclopropanation of the carbene intermediate **I** under nickel catalysis (B).[130] Various spirocyclic compounds (**3.121**) could be obtained with yields up to 89%.



Scheme 3.41. Transition-metal catalyzed ring-opening of [1.1.1]-propellane **3.118**.

Initial study by Dr. Guillaume Pisella revealed that under copper catalysis, oxyalkynylation of carbene-precursor **3.118** afforded **3.122a** in a promising 28% yield with a dropwise addition of a solution of **3.118** in one hour (Scheme 3.42).[131] We were curious to investigate the reactivity of the new reagents with this non-stabilized carbene precursor. Unfortunately, the desired products of aminoalkynylation (**3.122b-e**) were not detected with the nitrogen-containing alkynyl HIR. However, in the case of reagent **3.73**, an interesting side-product (**3.123**) could be isolated in 9% yield. When the addition was done manually in less than one minute, product **3.123** could be obtained in a better yield (31%) probably due to less degradation of the starting material **3.118**.

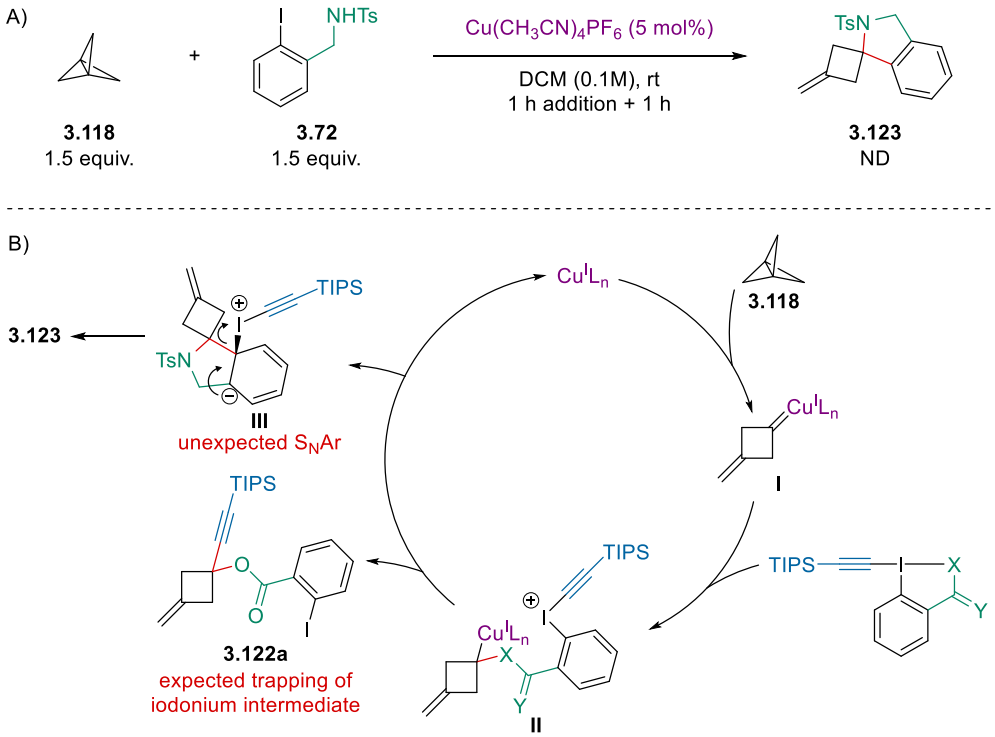


Scheme 3.42. Reactivity of alkynyl hypervalent iodine reagents with **3.118**.

Intrigued by the formation of the spirocyclic compound **3.123** we carried out a control experiment to determine if it came from the reaction between propellane **3.118** and the

[130] S. Yu, A. Noble, R. B. Bedford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2019**, *141*, 20325–20334.
[131] Dr. Guillaume Pisella, **2021**, *New Vinylation and Alkynylation Strategies with Hypervalent Iodine Reagents and Diazo Compounds*, PhD Thesis n°8727, EPFL, Lausanne.

hypervalent iodine reagent **3.73** or with **3.72** that could be generated in the reaction mixture if the alkyne is transferred (Scheme 3.43.A). The desired product was not formed and only polymerization of the starting propellane **3.118** was observed. The hypervalent bond seems to be required for the transformation to occur and based on previous work in our group we could propose a mechanism for this reaction (Scheme 3.43.B).[87,88,95,127-131] First, the copper catalyst would react with the propellane **3.118** affording the carbene intermediate **I**. Nucleophilic attack from the hypervalent iodine reagent heterocycle would lead to the iodonium intermediate **II**. Trapping of the alkynyl iodonium by the organocopper species would lead to the oxyalkynylation product in the case of TIPS-EBX **3.16**. For reagent **3.73** a nucleophilic aromatic substitution *via* intermediate **III** would account for the formation of compound **3.123**.

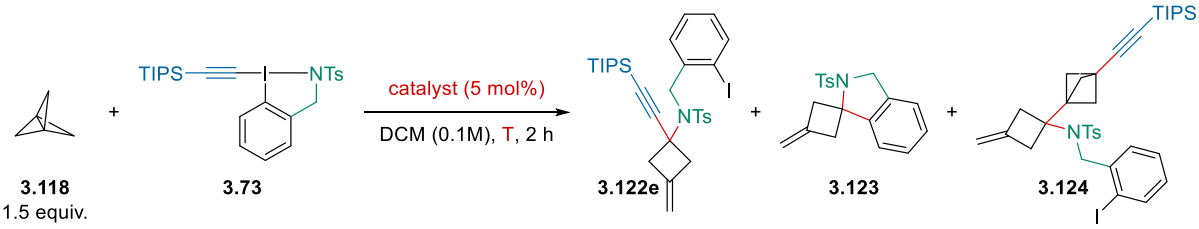


Scheme 3.43. A) control experiment. B) Proposed mechanism.

We set to study the reaction between [1.1.1]-propellane (**3.118**) and TIPS-Ts-EBz (**3.73**) by screening different copper catalysts and temperatures (Table 3.7). When the reaction was run at 0 °C, the aminoalkynylation product (**3.122e**) was only detected by Mass spectrometry (entry 1). On the other hand, the spirocyclic compound **3.123** could be isolated in the same yield as when the reaction was set up at room temperature but a new compound **3.124** could also be isolated in 12% yield. We believe that this product could arise from the trapping of a second molecule of propellane (**3.118**) by intermediate **II** (*vide supra*) followed by trapping of the alkynyl iodonium salt. When switching the catalyst to CuI (entry 2), **3.123** could be isolated in 31% yield and the two other products were not detected. Using a Cu(II)

catalyst was detrimental to the reaction as only degradation was observed (entry 3). Performing the addition of the propellane at -78 °C and letting the reaction warm up to room temperature only favored the formation of the spirocyclic compound **3.123** (entry 4). Changing the counterion of the catalyst from PF_6^- to BF_4^- promoted the formation of the dimeric amino-alkynylation product **3.124** that could be obtained in 27% yield (entry 5). Finally, increasing the concentration to 0.25 M and decreasing the reaction time to one hour allowed to access **3.124** in 69% yield (entry 6).

Table 3.7. Investigation of the aminoalkynylation of [1.1.1]-propellane (**3.118**).[a]



Entry	Catalyst	T	3.122e	3.123	3.124
1	$Cu(MeCN)_4PF_6$	0 °C	<5%	32%	12%
2	CuI	0 °C	-	31%	-
3	$CuCl_2$	0 °C	-	-	-
4	$Cu(MeCN)_4PF_6$	from -78 °C to rt	-	37%	-
5	$Cu(MeCN)_4BF_4$	0 °C	-	-	27%
6[b]	$Cu(MeCN)_4BF_4$	0 °C	-	-	69%

[a] Reaction conditions: 0.05 mmol of TIPS-Ts-EBz (**3.73**), 5.0 mol% of catalyst, 0.075 mmol of [1.1.1]-propellane (**3.118**) in dry DCM (0.1 M) at the indicated temperature for 2 h. Isolated yield after preparative TLC is given. [b] concentration 0.25 M, and 1 hour reaction time.

Although compound **3.124** represented the first example of aminoalkynylation using *N*-heterocyclic alkynyl hypervalent iodine reagent, we had to stop investigating this transformation. The results turned out to be highly dependent on the batch of propellane **3.118** that could only be obtained as a solution in diethyl ether together with bromobenzene and dibutyl ether.[130] Moreover, systematic determination of the concentration of the propellane solution prior to use showed a rapid decrease over time even when the compound was stored in a freezer at -20 °C under inert atmosphere and the solution became more and more turbid probably due to polymerization. Finally, even though the transformation is interesting on a reactivity level, its synthetic utility would be limited.

3.3.4. Inhibition of Thiol-Mediated Uptake Comparison

Thiol-mediated uptake, which corresponds to the capacity of oligochalcogenides to promote cell penetration, has attracted a lot of attention in the last decades due to its high efficiency.[132] The general mechanism governing this process is a dynamic covalent oligochalcogenide exchange with thiols and/or disulfides at the surface of cells often coupled with various uptake mechanisms such as direct translocation, endocytosis or fusion (Figure 3.15.A). However, this process can be hampered by irreversible covalent binding of the cell surface's thiols with inhibitors (Figure 3.15.B). Thiol-mediated uptake is used by several viruses to enter cells, notably HIV or some coronaviruses.[133] Inhibiting this process would therefore be of interest to prevent viral infections.

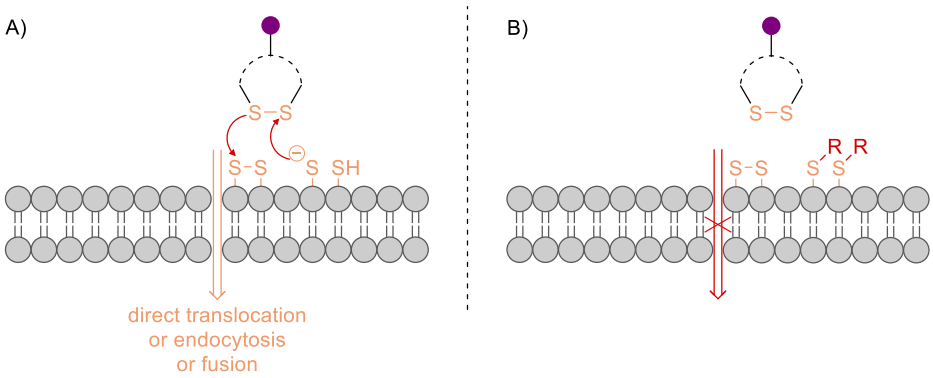


Figure 3.15. A) Thiol-mediated uptake *via* dynamic covalent chalcogen exchange cascades. B) General scheme for the inhibition of thiol-mediated uptake with covalent inhibitors.

The high reactivity of alkynyl hypervalent iodine reagents with thiols makes them good candidate for the covalent inhibition of thiol-mediated uptake. In order to test this hypothesis, we collaborated with the Matile group to perform the inhibition assays. The conjugate **3.125** containing an epidithiodiketopiperazine (ETP) and fluorescein (FITC) was selected as reporter. FITC-ETP **3.125** penetrates efficiently in HeLa cells and stains cytosol and nucleus.[134]

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[132] Q. Laurent, R. Martinent, B. Lim, A.-T. Pham, T. Kato, J. López-Andarias, N. Sakai, S. Matile, *JACS Au* **2021**, *1*, 710–728.
[133] (a) H. J.-P. Ryser, R. Flückiger, *Drug Discov. Today* **2005**, *10*, 1085–1094. (b) D. Lavillette, R. Barbouche, Y. Yao, B. Boson, F.-L. Cosset, I. M. Jones, E. Fenouillet, *J. Biol. Chem.* **2006**, *281*, 9200–9204. (b) E. Fenouillet, R. Barbouche, I. M. Jones, *Antioxid. Redox Signal.* **2007**, *9*, 1009–1034.
[134] L. Zong, E. Bartolami, D. Abegg, A. Adibekian, N. Sakai, S. Matile, *ACS Cent. Sci.* **2017**, *3*, 449–453.

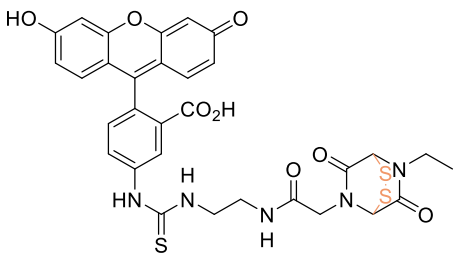
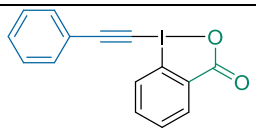
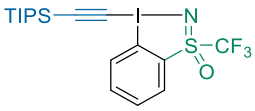
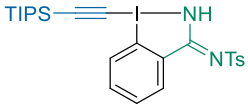
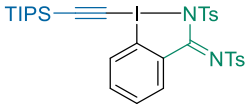
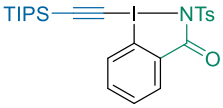
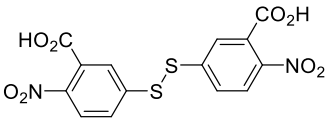
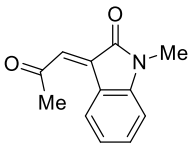


Figure 3.16. FITC-ETP receptor **3.125**.

The decrease of fluorescence of the cells allowed to determine the inhibition of thiol-mediated uptake. The efficiency of the inhibition was determined by the MIC, minimum inhibitory concentration needed to inhibit *ca.* 15% the thiol-mediated uptake. IC_{50}, concentration needed to reach 50% inhibition, is less favorable due to competing effects such as precipitation or toxicity at higher concentration. In this assay (Table 3.8, selected examples), Ph-EBX (**3.126**) showed a promising MIC < 2 μM, however it also exhibited an early onset of toxicity detrimental to the inhibition at concentration higher than the IC_{50} = 10 μM (entry 1). EBS reagent **3.85** showed as well a promising MIC < 2 μM but also an apparent concentration independent inhibition from MIC to the onset of toxicity (entry 2). This surprising behavior might be related to competing precipitation of the reagent. Amidine-based reagents (**3.70** and **3.65**) showed lower inhibition activity with MIC = 10 and 15 μM, respectively, and lower toxicity was observed for mono-protected amidine **3.70** (entries 3-4). Finally, TIPS-Ts-EBZ (**3.60**) was inactive in the thiol-mediated uptake inhibition of reporter **3.125** (entry 5). In this assay, other reagents have been investigated such as Ellman's reagent **3.127** which is one of the standard inhibitors to study thiol-mediated uptake but performed poorly (entry 6).[135] The best results were obtained for super-cinnamaldehyde **3.128** developed by the Patapoutian group with MIC < 1 μM and IC_{50} = 4 μM.[136] Overall, the newly developed reagent tested in this inhibition assay did not outperform the already established EBX class of reagents with only reagent **3.85** exhibiting high activity but with an undesirable dose-response curve.

[135] G. L. Ellman, *Arch. Biochem. Biophys.* **1959**, *82*, 70–77.
[136] L. J. Macpherson, A. E. Dubin, M. J. Evans, F. Marr, P. G. Schultz, B. F. Cravatt, A. Patapoutian, *Nature* **2007**, *445*, 541–545.

Table 3.8. Inhibition of thiol-mediated uptake of fluorescently-labeled FITC-ETP reporter **3.125**.

Entry	Reagent	MIC (μM)	IC_{50} (μM)
1	 Ph-EBX **3.126**	<2	10[t]
2	 **3.85**	<2	-[f]
3	 **3.70**	10	>50
4	 **3.65**	15	>50[t]
5	 **3.60**	>50	-
6	 **3.127**	500	-[t]
7	 **3.128**	<1	4

Conditions: 1 h pre-incubation of HeLa cells with inhibitors, followed by 30 min incubation with **3.125**. MIC: concentration needed to inhibit by *ca.* 15% the thiol-mediated uptake. IC_{50}: concentration needed to inhibit by *ca.* 50% the thiol-mediated uptake. [t] onset of toxicity. [f] "flat" dose-response curve.

3.4. Conclusion and Perspectives

In summary, we have developed four new *N*-heterocyclic alkynyl hypervalent iodine reagents and reagent **3.85** could be obtained as a single enantiomer (Figure 3.17). Their X-ray structures were analyzed and compared to already established reagents which allowed to extract valuable structural information such as the *trans*-effect of the different scaffolds. Likewise, we could study and compare the electronic density distributions of the different reagents, which helped to rationalize their difference of reactivity in some transformations. Their reactivity was studied and compared; however, the new reagents did not outperform the benchmark TIPS-EBX reagent in the reactions tested to date.[137] Finally, the bioactivity of the reagents was investigated in the inhibition of thiol-mediated uptake but they exhibited either low activity or early onset of toxicity.[138]

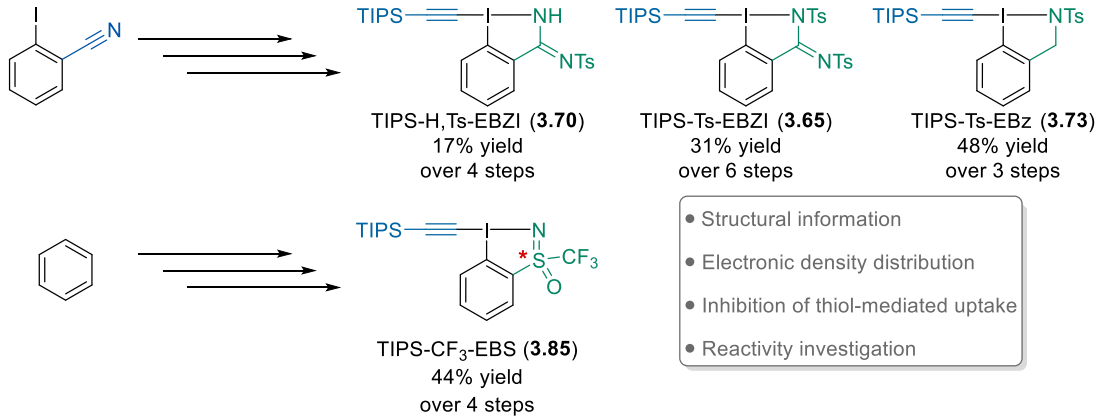


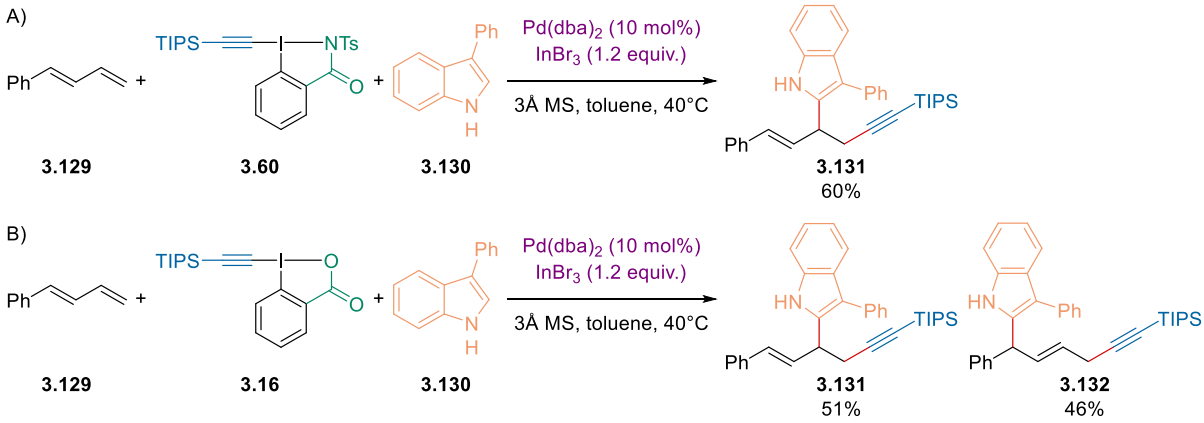
Figure 3.17. Summary of the study on *N*-heterocyclic alkynyl hypervalent iodine reagents.

Up to now, only TIPS-Ts-EBz (**3.73**) exhibited a promising reactivity with [1.1.1]-propellane (**3.118**) as for the first time we were able to observe an aminoalkynylation reaction with a nitrogen-containing hypervalent iodine reagent. However, the lack of reproducibility and the limited potential scope of the transformation prompted us to stop the investigations. More studies towards the development of atom-economical transformations with this reagent would be highly valuable.

During the writing of this Thesis, Chen and coworkers reported a regioselective palladium-catalyzed 1,2-alkynyl-carbonalization of conjugated dienes with indoles and TIPS-Ts-EBZ (**3.60**) (Scheme 3.44.A).[139] Interestingly, in this transformation EBZ reagents were

[137] E. Le Du, T. Duhail, M. D. Wodrich, R. Scopelliti, F. Fadaei-Tirani, E. Anselmi, E. Magnier, J. Waser, *Chem. Eur. J.* **2021**, *27*, 10979–10986.
[138] B. Lim, Y. Cheng, T. Kato, A. Pham, E. Le Du, A. K. Mishra, E. Grinhagena, D. Moreau, N. Sakai, J. Waser, S. Matile, *Helv. Chim. Acta* **2021**, *104*, e2100085.
[139] J. Huang, L.-L. Chen, Z.-M. Chen, *Org. Lett.* **2022**, *24*, 5777–5781.

superior to EBX reagents as they avoided the formation of the side-product **3.132** arising from a competitive 1,4-functionalization (Scheme 3.44.B).



Scheme 3.44. Palladium-catalyzed 1,2-alkynyl-carbonalization of conjugated dienes.

This recent application of EBZ might encourage the chemistry community to systematically investigate the reactivity of *N*-heterocyclic alkynyl hypervalent iodine reagents in addition to the classical EBX reagents.

3.5. References

1. B. I. Morinaka, C. K. Skepper, T. F. Molinski, *Org. Lett.* **2007**, *9*, 1975–1978.
2. H. Zhao, G.-D. Chen, J. Zou, R.-R. He, S.-Y. Qin, D. Hu, G.-Q. Li, L.-D. Guo, X.-S. Yao, H. Gao, *Org. Lett.* **2017**, *19*, 38–41.
3. T. T. Talele, *J. Med. Chem.* **2020**, *63*, 5625–5663.
4. M. Eckhardt, E. Langkopf, M. Mark, M. Tadayyon, L. Thomas, H. Nar, W. Pfrengle, B. Guth, R. Lotz, P. Sieger, H. Fuchs, F. Himmelsbach, *J. Med. Chem.* **2007**, *50*, 6450–6453.
5. S. D. Young, S. F. Britcher, L. O. Tran, L. S. Payne, W. C. Lumma, T. A. Lyle, J. R. Huff, P. S. Anderson, D. B. Olsen, S. S. Carroll, *Antimicrob. Agents Chemother.* **1995**, *39*, 2602–2605.
6. H. H. Inhoffen, W. Hohlweg, *Naturwissenschaften* **1938**, *26*, 96–96.
7. (a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470. (b) Nobel Lecture: A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722–6737.
8. A. Fürstner, *J. Am. Chem. Soc.* **2021**, *143*, 15538–15555.
9. A. P. Y. Chan, A. G. Sergeev, *Coord. Chem. Rev.* **2020**, *413*, 213213.
10. L. Hintermann, A. Labonne, *Synthesis* **2007**, *2007*, 1121–1150.
11. (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.
12. M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952–3015.
13. (a) J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev.* **2010**, *39*, 1272. (b) W. Xi, T. F. Scott, C. J. Kloxin, C. N. Bowman, *Adv. Funct. Mater.* **2014**, *24*, 2572–2590.
14. (a) Z. Song, T. Takahashi, in *Compr. Org. Synth. II*, Elsevier, **2014**, pp. 838–876. (b) M. Zaidlewicz, A. Wolan, M. Budny, in *Compr. Org. Synth. II*, Elsevier, **2014**, pp. 877–963. (c) A. P. Dobbs, F. K. I. Chio, in *Compr. Org. Synth. II*, Elsevier, **2014**, pp. 964–998. (d) A. Ding, H. Guo, in *Compr. Org. Synth. II*, Elsevier, **2014**, pp. 891–938.
15. (a) B. Gao, D. Deng, D. Huang, X. Sun, *Synthesis* **2021**, *53*, 3522–3534. (b) S. Ghosh, R. Chakrabortty, V. Ganesh, *ChemCatChem* **2021**, *13*, 4262–4298.
16. R. Shaw, A. Elagamy, I. Althagafi, R. Pratap, *Org. Biomol. Chem.* **2020**, *18*, 3797–3817.
17. (a) D. Seyferth, R. S. Marmor, P. Hilbert, *J. Org. Chem.* **1971**, *36*, 1379–1386. (b) J. C. Gilbert, U. Weerasooriya, *J. Org. Chem.* **1982**, *47*, 1837–1845.
18. (a) S. Ohira, *Synth. Commun.* **1989**, *19*, 561–564. (b) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, *1996*, 521–522.
19. E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**,*13*, 3769–3772.
20. For addition on carbonyl: (a) Y. Sempere, E. M. Carreira, in *Org. React.* (Ed.: John Wiley & Sons, Inc.), Wiley, **2019**, pp. 207–254. For addition on imine: (b) I. Jesin, G. C. Nandi, *Eur. J. Org. Chem.* **2019**, *2019*, 2704–2720.
21. C. Glaser, *Berichte Dtsch. Chem. Ges.* **1869**, *2*, 422–424.
22. (a) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes;* Viehe, H. G., ed.; Dekker: New York, **1969,** pp. 597-647. (b) J. J. Li, in *Name React.*, Springer International Publishing, Cham, **2021**, pp. 67–69.
23. T. Iwasaki, N. Kambe, *Top. Curr. Chem.* **2016**, *374*, 66.
24. J. P. Brand, J. Waser, *Chem. Soc. Rev.* **2012**, *41*, 4165.
25. D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258.
26. W. Wu, H. Jiang, *Acc. Chem. Res.* **2014**, *47*, 2483–2504.
27. M. G. Moloney, J. T. Pinhey, E. G. Roche, *Tetrahedron Lett.* **1986**, *27*, 5025–5028.
28. D. Ge, X. Wang, X.-Q. Chu, *Org. Chem. Front.* **2021**, *8*, 5145–5164.
29. (a) B. Waldecker, F. Kraft, C. Golz, M. Alcarazo, *Angew. Chem. Int. Ed.* **2018**, *57*, 12538–12542. For review: (b) S. I. Kozhushkov, M. Alcarazo, *Eur. J. Inorg. Chem.* **2020**, *2020*, 2486–2500.
30. F. M. Beringer, S. A.Galton, *J. Org. Chem.* **1965**, *30*, 1930-1934.

31. M. Ochiai, M. Kunishima, Y. Nagao, K. Fuji, M. Shiro, E. Fujita, *J. Am. Chem. Soc.* **1986**, *108*, 8281–8283.
32. T. Okuyama, T. Takino, T. Sueda, M. Ochiai, *J. Am. Chem. Soc.* **1995**, *117*, 3360–3367.
33. L. I. Dixon, M. A. Carroll, T. J. Gregson, G. J. Ellames, R. W. Harrington, W. Clegg, *Org. Biomol. Chem.* **2013**, *11*, 5877.
34. (a) L. Rebrovic, G. F. Koser, *J. Org. Chem.* **1984**, *49*, 4700–4702. (b) P. J. Stang, B. W. Surber, Z. C. Chen, K. A. Roberts, A. G. Anderson, *J. Am. Chem. Soc.* **1987**, *109*, 228–235. (c) M. Yoshida, N. Nishimura, S. Hara, *Chem. Commun.* **2002**, 1014–1014.
35. (a) M. Ochiai, M. Kunishima, K. Sumi, Y. Nagao, E. Fujita, M. Arimoto, H. Yamaguchi, *Tetrahedron Lett.* **1985**, *26*, 4501–4504. (b) T. Kitamura, P. J. Stang, *J. Org. Chem.* **1988**, *53*, 4105–4106. (c) T. Kitamura, *Synthesis* **1998**, *1998*, 1416–1418.
36. (a) P. J. Stang, B. L. Williamson, V. V. Zhdankin, *J. Am. Chem. Soc.* **1991**, *113*, 5870–5871. (b) B. L. Williamson, P. J. Stang, A. M. Arif, *J. Am. Chem. Soc.* **1993**, *115*, 2590–2597.
37. M. Yoshida, K. Osafune, S. Hara, *Synthesis* **2007**, *2007*, 1542–1546.
38. (a) E. A. Merritt, B. Olofsson, *Eur. J. Org. Chem.* **2011**, *2011*, 3690–3694. (b) M. J. Bouma, B. Olofsson, *Chem. Eur. J.* **2012**, *18*, 14242–14245.
39. M. D. Bachi, N. Bar-Ner, C. M. Crittell, P. J. Stang, B. L. Williamson, *J. Org. Chem.* **1991**, *56*, 3912–3915.
40. (a) D.-Y. Yang, J. He, S. Miao, *Synth. Commun.* **2003**, *33*, 2695–2700. (b) C.-M. Yu, J.-H. Kweon, P.-S. Ho, S.-C. Kang, G. Y. Lee, *Synlett* **2005**, 2631–2634.
41. See next chapter for more details on nitrogen alkynylation.
42. (a) P. J. Stang, M. Boehshar, J. Lin, *J. Am. Chem. Soc.* **1986**, *108*, 7832–7834. (b) P. J. Stang, M. Boehshar, H. Wingert, T. Kitamura, *J. Am. Chem. Soc.* **1988**, *110*, 3272–3278. (c) P. J. Stang, T. Kitamura, M. Boehshar, H. Wingert, *J. Am. Chem. Soc.* **1989**, *111*, 2225–2230. (d) P. J. Stang, C. M. Crittell, A. M. Arif, M. Karni, Y. Apeloig, *J. Am. Chem. Soc.* **1991**, *113*, 7461–7470.
43. (a) R. R. Tykwinski, B. L. Williamson, D. R. Fischer, P. J. Stang, A. M. Arif, *J. Org. Chem.* **1993**, *58*, 5235–5237. (b) K. Miyamoto, Y. Nishi, M. Ochiai, *Angew. Chem. Int. Ed.* **2005**, *44*, 6896–6899. (c) J.-B. Han, L. Yang, X. Chen, G.-F. Zha, C.-P. Zhang, *Adv. Synth. Catal.* **2016**, *358*, 4119–4124.
44. (a) M. Ochiai, M. Kunishima, Y. Nagao, K. Fuji, E. Fujita, *J Chem Soc Chem Commun* **1987**, 1708–1709. (b) J.-L. Zhang, Z.-C. Chen, *Synth. Commun.* **1998**, *28*, 175–179.
45. A. A. Rajkiewicz, N. Wojciechowska, M. Kalek, *ACS Catal.* **2020**, *10*, 831–841.
46. M. Ochiai, Y. Masaki, M. Shiro, *J. Org. Chem.* **1991**, *56*, 5511–5513.
47. V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 6547–6551.
48. J. P. Brand, D. F. González, S. Nicolai, J. Waser, *Chem Commun* **2011**, *47*, 102–115.
49. D. P. Hari, P. Caramenti, L. Schouwey, M. Chang, S. Nicolai, D. Bachert, T. Wright, C. Orella, J. Waser, *Org. Process Res. Dev.* **2020**, *24*, 106–110.
50. J. Borrel, J. Waser, *Org. Lett.* **2022**, *24*, 142–146.
51. J. Brand, J. Charpentier, J. Waser, *Angew. Chem. Int. Ed.* **2009**, *48*, 9346–9349.
52. For recent reviews: (a) D. P. Hari, S. Nicolai, J. Waser, in *PATAIS Chem. Funct. Groups* (Ed.: Z. Rappoport), John Wiley & Sons, Ltd, Chichester, UK, **2018**, pp. 1–58. (b) D. P. Hari, P. Caramenti, J. Waser, *Acc. Chem. Res.* **2018**, *51*, 3212–3225.
53. (a) J. P. Brand, C. Chevalley, R. Scopelliti, J. Waser, *Chem. Eur. J.* **2012**, *18*, 5655–5666. (b) G. L. Tolnai, S. Ganss, J. P. Brand, J. Waser, *Org. Lett.* **2013**, *15*, 112–115.
54. Y. Li, J. P. Brand, J. Waser, *Angew. Chem. Int. Ed.* **2013**, *52*, 6743–6747.
55. Y. Li, J. Waser, *Beilstein J. Org. Chem.* **2013**, *9*, 1763–1767.
56. J. P. Brand, J. Waser, *Org. Lett.* **2012**, *14*, 744–747.
57. A. C. Shaikh, D. R. Shinde, N. T. Patil, *Org. Lett.* **2016**, *18*, 1056–1059.
58. F. Zhao, B. Xu, D. Ren, L. Han, Z. Yu, T. Liu, *Organometallics* **2018**, *37*, 1026–1033.

59. (a) S. Nicolai, S. Erard, D. F. González, J. Waser, *Org. Lett.* **2010**, *12*, 384–387. (b) S. Nicolai, C. Piemontesi, J. Waser, *Angew. Chem. Int. Ed.* **2011**, *50*, 4680–4683.
60. Y. Yang, P. Antoni, M. Zimmer, K. Sekine, F. F. Mulks, L. Hu, L. Zhang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2019**, *58*, 5129–5133.
61. X. Jiang, Z. Zheng, Y. Gao, D. Lan, W. Xu, W. Zhang, G. Chen, *Org. Chem. Front.* **2022**, *9*, 2234–2239.
62. J. Schörgenhumer, M. Waser, *Org. Biomol. Chem.* **2018**, *16*, 7561–7563. For prior examples using gold catalysis: (a) X. Li, X. Xie, N. Sun, Y. Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 6994–6998. (b) S. Banerjee, N. T. Patil, *Chem. Commun.* **2017**, *53*, 7937–7940.
63. (a) Q.-Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199. (b) F. Le Vaillant, T. Courant, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204.
64. X. Liu, Z. Wang, X. Cheng, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 14330–14333.
65. F. Le Vaillant, J. Waser, *Chem. Sci.* **2019**, *10*, 8909–8923.
66. Z. Liu, S. Wu, Y. Chen, *ACS Catal.* **2021**, *11*, 10565–10573.
67. (a) S. G. E. Amos, D. Cavalli, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 23827–23834. (b) Tin. V. T. Nguyen, J. Waser, *ChemRxiv* **2022**, *ver. 1*, DOI 10.26434/chemrxiv-2022-vf5gm.
68. (a) D. Fernández González, J. P. Brand, J. Waser, *Chem. Eur. J.* **2010**, *16*, 9457–9461. (b) D. Fernández González, J. P. Brand, R. Mondière, J. Waser, *Adv. Synth. Catal.* **2013**, *355*, 1631–1639.
69. (a) X. Wu, S. Shirakawa, K. Maruoka, *Org Biomol Chem* **2014**, *12*, 5388–5392. (b) B. Meng, Q. Shi, Y. Meng, J. Chen, W. Cao, X. Wu, *Org. Biomol. Chem.* **2021**, *19*, 5087–5092.
70. C. Han, X. Tian, L. Song, Y. Liu, A. S. K. Hashmi, *Org. Chem. Front.* **2021**, *8*, 6546–6552.
71. C. Han, Y. Liu, X. Tian, F. Rominger, A. S. K. Hashmi, *Org. Lett.* **2021**, *23*, 9480–9484.
72. For thiol: (a) R. Frei, J. Waser, *J. Am. Chem. Soc.* **2013**, *135*, 9620–9623. (b) R. Frei, M. D. Wodrich, D. P. Hari, P.-A. Borin, C. Chauvier, J. Waser, *J. Am. Chem. Soc.* **2014**, *136*, 16563–16573. (c) M. D. Wodrich, P. Caramenti, J. Waser, *Org. Lett.* **2016**, *18*, 60–63. For sulfenate: S. G. E. Amos, S. Nicolai, A. Gagnebin, F. Le Vaillant, J. Waser, *J. Org. Chem.* **2019**, *84*, 3687–3701. For sulfone: C. C. Chen, J. Waser, *Org. Lett.* **2015**, *17*, 736–739.
73. C. C. Chen, J. Waser, *Chem Commun* **2014**, *50*, 12923–12926.
74. E. M. D. Allouche, E. Grinhagena, J. Waser, *Angew. Chem. Int. Ed.* **2022**, *61*, e202112287.
75. M. Garreau, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2019**, *58*, 8182–8186.
76. For labeling: (a) D. Abegg, R. Frei, L. Cerato, D. P. Hari, C. Wang, J. Waser, A. Adibekian, *Angew. Chem. Int. Ed.* **2015**, *54*, 10852–10857. (b) R. Tessier, R. K. Nandi, B. G. Dwyer, D. Abegg, C. Sornay, J. Ceballos, S. Erb, S. Cianférani, A. Wagner, G. Chaubet, A. Adibekian, J. Waser, *Angew. Chem. Int. Ed.* **2020**, *59*, 10961–10970. (c) A. K. Mishra, R. Tessier, D. P. Hari, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 17963–17968. For stapling: J. Ceballos, E. Grinhagena, G. Sangouard, C. Heinis, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 9022–9031.
77. For a review on VBX reagents: N. Declas, G. Pisella, J. Waser, *Helv. Chim. Acta* **2020**, *103*, e2000191.
78. R. Tessier, J. Ceballos, N. Guidotti, R. Simonet-Davin, B. Fierz, J. Waser, *Chem* **2019**, *5*, 2243–2263.
79. For recent reviews on atom economical reaction with HIR: (a) A. Boelke, P. Finkbeiner, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2018**, *14*, 1263–1280. (b) G. Grelier, B. Darses, P. Dauban, *Beilstein J. Org. Chem.* **2018**, *14*, 1508–1528.
80. A complex mechanism is proposed in the article for this unexpected reaction: B. Lu, J. Wu, N. Yoshikai, *J. Am. Chem. Soc.* **2014**, *136*, 11598–11601.
81. Z.-C. Chen, P. Chen, Z. Chen, Q. Ouyang, H.-P. Liang, W. Du, Y.-C. Chen, *Org. Lett.* **2018**, *20*, 6279–6283.
82. S. Banerjee, B. Senthilkumar, N. T. Patil, *Org. Lett.* **2019**, *21*, 180–184.
83. J. Borrel, G. Pisella, J. Waser, *Org. Lett.* **2020**, *22*, 422–427.

84. S. G. E. Amos, S. Nicolai, J. Waser, *Chem. Sci.* **2020**, *11*, 11274–11279.
85. Z. Zuo, A. Studer, *Org. Lett.* **2022**, *24*, 949–954.
86. (a) X. Guo, W. Hu, *Acc. Chem. Res.* **2013**, *46*, 2427–2440. (b) R. Zhao, L. Shi, *Angew. Chem. Int. Ed.* **2020**, *59*, 12282–12292.
87. D. P. Hari, J. Waser, *J. Am. Chem. Soc.* **2016**, *138*, 2190–2193.
88. D. P. Hari, J. Waser, *J. Am. Chem. Soc.* **2017**, *139*, 8420–8423.
89. (a) R. M. Keefer, L. J. Andrews, *J. Am. Chem. Soc.* **1959**, *81*, 5329–5333. (b) W. Wolf, L. Steinberg, *Chem. Commun. Lond.* **1965**, 449. (c) H. J. Barber, M. A. Henderson, *J. Chem. Soc. C Org.* **1970**, 862. (d) D. G. Naae, J. Z. Gougoutas, *J. Org. Chem.* **1975**, *40*, 2129–2131. (e) K. Prout, M. N. Stevens, A. Coda, V. Tazzoli, R. A. Shaw, T. Demir, *Z. Für Naturforschung B* **1976**, *31*, 687–688. (f) T. M. Balthazor, D. E. Godar, B. R. Stults, *J. Org. Chem.* **1979**, *44*, 1447–1449. (g) R. A. Moss, S. Chatterjee, B. Wilk, *J. Org. Chem.* **1986**, *51*, 4303–4307. (h) V. V. Zhdankin, R. M. Arbit, M. McSherry, B. Mismash, V. G. Young, *J. Am. Chem. Soc.* **1997**, *119*, 7408–7409. (i) V. V. Zhdankin, R. M. Arbit, B. J. Lynch, P. Kiprof, V. G. Young, *J. Org. Chem.* **1998**, *63*, 6590–6596. (j) V. V. Zhdankin, A. E. Koposov, J. T. Smart, R. R. Tykwinski, R. McDonald, A. Morales-Izquierdo, *J. Am. Chem. Soc.* **2001**, *123*, 4095–4096. (k) V. V. Zhdankin, A. Y. Koposov, L. Su, V. V. Boyarskikh, B. C. Netzel, V. G. Young, *Org. Lett.* **2003**, *5*, 1583–1586. (l) A. Yoshimura, M. T. Shea, C. L. Makitalo, M. E. Jarvi, G. T. Rohde, A. Saito, M. S. Yusubov, V. V. Zhdankin, *Beilstein J. Org. Chem.* **2018**, *14*, 1016–1020. (m) M. T. Shea, G. T. Rohde, Y. A. Vlasenko, P. S. Postnikov, M. S. Yusubov, V. V. Zhdankin, A. Saito, A. Yoshimura, *Molecules* **2021**, *26*, 7355.
90. H. Gu, C. Wang, *Org. Biomol. Chem.* **2015**, *13*, 5880–5884.
91. J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682.
92. For seminal paper: X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457–3460. For revision of the structure: (a) E. V. Vinogradova, P. Müller, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2014**, *53*, 3125–3128. (b) X. Shao, C. Xu, L. Lu, Q. Shen, *J. Org. Chem.* **2015**, *80*, 3012–3021.
93. For *trans*-effect: M. Ochiai, T. Sueda, K. Miyamoto, P. Kiprof, V. V. Zhdankin, *Angew. Chem. Int. Ed.* **2006**, *45*, 8203–8206. For computations: T.-Y. Sun, X. Wang, H. Geng, Y. Xie, Y.-D. Wu, X. Zhang, H. F. Schaefer III, *Chem. Commun.* **2016**, *52*, 5371–5374.
94. X.-G. Yang, K. Zheng, C. Zhang, *Org. Lett.* **2020**, *22*, 2026–2031.
95. D. P. Hari, L. Schouwey, V. Barber, R. Scopelliti, F. Fadaei-Tirani, J. Waser, *Chem. Eur. J.* **2019**, *25*, 9522–9528.
96. H. Jaffe, J. E. Leffler, *J. Org. Chem.* **1975**, *40*, 797–799
97. T. Ohwada, N. Tani, Y. Sakamaki, Y. Kabasawa, Y. Otani, M. Kawahata, K. Yamaguchi, *Proc. Natl. Acad. Sci.* **2013**, *110*, 4206–4211.
98. J. Kalim, T. Duhail, T.-N. Le, N. Vanthuyne, E. Anselmi, A. Togni, E. Magnier, *Chem. Sci.* **2019**, *10*, 10516–10523.
99. D. C. Braddock, G. Cansell, S. A. Hermitage, *Chem. Commun.* **2006**, 2483-2485.
100. Y. A. Vlasenko, P. S. Postnikov, M. E. Trusova, A. Shafir, V. V. Zhdankin, A. Yoshimura, M. S. Yusubov, *J. Org. Chem.* **2018**, *83*, 12056–12070.
101. (a) A. Boelke, E. Lork, B. J. Nachtsheim, *Chem. Eur. J.* **2018**, *24*, 18653–18657. (b) A. Boelke, Y. A. Vlasenko, M. S. Yusubov, B. J. Nachtsheim, P. S. Postnikov, *Beilstein J. Org. Chem.* **2019**, *15*, 2311–2318. (c) A. Boelke, B. J. Nachtsheim, *Adv. Synth. Catal.* **2020**, *362*, 184–191.
102. The sulfoximine part was carried out as a collaborative work with Dr. Thibaut Duhail, Dr. Elsa Anselmi in the group of Dr. Emmanuel Magnier from the Institut Lavoisier de Versailles, France.
103. The X-ray structures were determined by Dr. Rosario Scopelliti and Dr. Farzaneh Fadei-Tirani and the computations for the electron density distributions were performed by Dr. Matthew D. Wodrich from EPFL, Switzerland.
104. The inhibition essay was carried out by Bumhee Lim, Yangyang Cheng and Dimitri Moreau in the group of Prof. Stefan Matile from the University of Geneva, Switzerland.

105. S. Dalai, V. N. Belov, S. Nizamov, K. Rauch, D. Finsinger, A. de Meijere, *Eur. J. Org. Chem.* **2006**, *2006*, 2753–2765.
106. The hydrochloride salt showed low solubility in standard organic solvents and it was partially soluble in alcohols. However, no attempt to isolate the pure 2-iodobenzamidine (**3.46**) was carried out, the hydrochloride salt was directly used as such for the next steps.
107. (a) A. Guzmán, M. Romero, F. X. Talamás, R. Villena, R. Greenhouse, J. M. Muchowski, *J. Org. Chem.* **1996**, *61*, 2470–2483. (b) T. Yao, *Tetrahedron Lett.* **2015**, *56*, 4623–4626.
108. For the nomenclature: HO-Ts-BZI = functional group bound to iodine – protecting groups on nitrogen – benziodazolimine.
109. L. Kraszkiewicz, L. Skulski, *Arkivoc* **2003**, *2003*, 120–125.
110. A. Maity, S.-M. Hyun, D. C. Powers, *Nat. Chem.* **2018**, *10*, 200–204.
111. R. L. Amey, J. C. Martin, *J. Org. Chem.* **1979**, *44*, 1779–1784.
112. V. Matoušek, E. Pietrasiak, R. Schwenk, A. Togni, *J. Org. Chem.* **2013**, *78*, 6763–6768.
113. Y. Kita, S. Akai, T. Okuno, M. Egi, T. Takada, H. Tohma, *Heterocycles* **1996**, *42*, 47–51.
114. For the nomenclature: TIPS-Ts-EBZI = alkyne substituent – protecting groups – ethynylbenziodazolimine.
115. For the nomenclature: Cl-H,Ts-BZI = ligand bound to iodine – substituent on the nitrogen atom bound to iodine, substituent on imino group – benziodazolimine.
116. L. A. Aronica, G. Albano, L. Giannotti, E. Meucci, *Eur. J. Org. Chem.* **2017**, *2017*, 955–963.
117. For the nomenclature: TIPS-Ts-EBz = Substituent on alkyne – Protecting group on the amine – Ethynylbenzidazole.
118. A.-L. Barthelemy, V. Certal, G. Dagousset, E. Anselmi, L. Bertin, L. Fabien, B. Salgues, P. Courtes, C. Poma, Y. El-Ahmad, E. Magnier, *Org. Process Res. Dev.* **2020**, *24*, 704–712.
119. A. Tota, M. Zenzola, S. J. Chawner, S. S. John-Campbell, C. Carlucci, G. Romanazzi, L. Degennaro, J. A. Bull, R. Luisi, *Chem. Commun.* **2017**, *53*, 348–351.
120. For the nomenclature: TIPS-CF_3-EBS = substituent on alkyne – functional group on sulfoximine – ethynylbenziodosulfoximine.
121. For another example of chiral alkynyl hypervalent iodine reagent: S. Companys, P. A. Peixoto, C. Bosset, S. Chassaing, K. Miqueu, J.-M. Sotiropoulos, L. Pouységu, S. Quideau, *Chem. Eur. J.* **2017**, *23*, 13309–13313.
122. Unpublished results.
123. T. J. Kuczmera, A. Boelke, B. J. Nachtsheim, *Eur. J. Org. Chem.* **2022**, *2022*, e202200276.
124. Selected examples: (a) J. T. Su, W. A. Goddard, *J. Am. Chem. Soc.* **2005**, *127*, 14146–14147. (b) A.-A. Guilbault, C. Y. Legault, *ACS Catal.* **2012**, *2*, 219–222.
125. H. Pinto de Magalhães, A. Togni, H. P. Lüthi, *J. Org. Chem.* **2017**, *82*, 11799–11805.
126. A. Ariafard, *ACS Catal.* **2014**, *4*, 2896–2907.
127. G. Pisella, A. Gagnebin, J. Waser, *Chem. Eur. J.* **2020**, *26*, 10199–10204.
128. N. P. Ramirez, G. Pisella, J. Waser, *J. Org. Chem.* **2021**, *86*, 10928–10938.
129. D. Lasányi, G. L. Tolnai, *Org. Lett.* **2019**, *21*, 10057–10062.
130. S. Yu, A. Noble, R. B. Bedford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2019**, *141*, 20325–20334.
131. Dr. Guillaume Pisella, **2021**, *New Vinylation and Alkynylation Strategies with Hypervalent Iodine Reagents and Diazo Compounds*, PhD Thesis n°8727, EPFL, Lausanne.
132. Q. Laurent, R. Martinent, B. Lim, A.-T. Pham, T. Kato, J. López-Andarias, N. Sakai, S. Matile, *JACS Au* **2021**, *1*, 710–728.
133. (a) H. J.-P. Ryser, R. Flückiger, *Drug Discov. Today* **2005**, *10*, 1085–1094. (b) D. Lavillette, R. Barbouche, Y. Yao, B. Boson, F.-L. Cosset, I. M. Jones, E. Fenouillet, *J. Biol. Chem.* **2006**, *281*, 9200–9204. (b) E. Fenouillet, R. Barbouche, I. M. Jones, *Antioxid. Redox Signal.* **2007**, *9*, 1009–1034.
134. L. Zong, E. Bartolami, D. Abegg, A. Adibekian, N. Sakai, S. Matile, *ACS Cent. Sci.* **2017**, *3*, 449–453.
135. G. L. Ellman, *Arch. Biochem. Biophys.* **1959**, *82*, 70–77.

136. L. J. Macpherson, A. E. Dubin, M. J. Evans, F. Marr, P. G. Schultz, B. F. Cravatt, A. Patapoutian, *Nature* **2007**, *445*, 541–545.
137. E. Le Du, T. Duhail, M. D. Wodrich, R. Scopelliti, F. Fadaei-Tirani, E. Anselmi, E. Magnier, J. Waser, *Chem. Eur. J.* **2021**, *27*, 10979–10986.
138. B. Lim, Y. Cheng, T. Kato, A. Pham, E. Le Du, A. K. Mishra, E. Grinhagena, D. Moreau, N. Sakai, J. Waser, S. Matile, *Helv. Chim. Acta* **2021**, *104*, e2100085.
139. J. Huang, L.-L. Chen, Z.-M. Chen, *Org. Lett.* **2022**, *24*, 5777–5781.

Chapter 4:

Copper-Catalyzed Alkynylation of Hydrazides for the Synthesis of Functionalized Azadipeptides

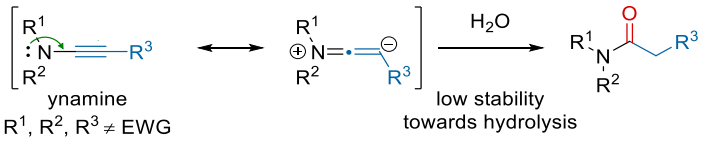
4. Copper-Catalyzed Alkynylation of Hydrazides for the Synthesis of Functionalized Azadipeptides

The formation of N-Csp bond has been the focus of intensive research in the last decades owing to the versatility of the resulting ynamides products. Hypervalent iodine reagents have been particularly successful to achieve this transformation. In this chapter, our efforts and developments towards the alkynylation of hydrazides using EBX reagents will be presented. This transformation would allow for an easy access to valuable functionalized azadipeptides.

4.1. Introduction

4.1.1. Ynamides: Structure and Synthesis

Although alkynes have been broadly studied for their remarkable reactivity in the last century, heteroatom-substituted alkynes have been comparably less investigated due to their instability and the difficulty to synthesize them. For instance, ynamines were first characterized in 1958 and 1960 and a practical synthesis was reported only a few years later.[1-3] Their inherent high reactivity due to the delocalization of the nitrogen lone pair in the π-system of the alkyne made them highly sensitive towards protonation and hydrolysis (Scheme 4.1). This limitation might explain why their synthetic uses have been scarce.[4]

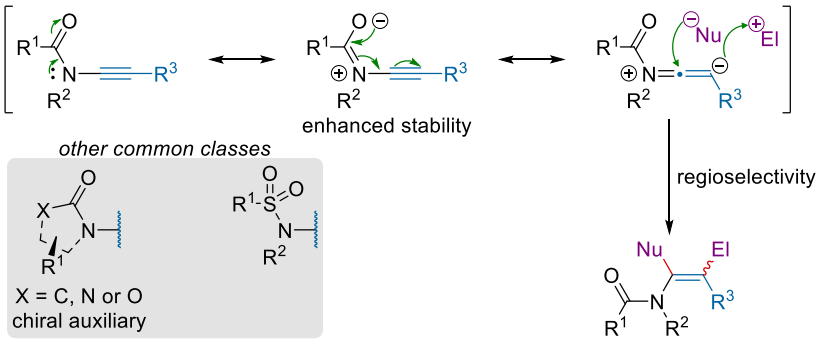


Scheme 4.1. Ynamine hydrolysis.

The high reactivity of ynamines could be tamed by introducing an electron-withdrawing group on the nitrogen. The reduction of the electron density *via* extra delocalization of the nitrogen's lone pair allowed to access bench stable ynamide compounds (Scheme 4.2). The strong polarization of the alkyne is maintained allowing the regioselective functionalization of

[1] H. Zaugg, L. Swett, G. Stone, *J. Org. Chem.* **1958**, *23*, 1389–1390.
[2] V. Wolf, F. Kowitz, *Justus Liebigs Ann. Chem.* **1960**, *638*, 33–42.
[3] H. G. Viehe, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 477–477.
[4] For review: (a) H. G. Viehe, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 767–778. (b) J. Ficini, *Tetrahedron* **1976**, *32*, 1449–1486. (c) C. A. Zificsak, J. A. Mulder, R. P. Hsung, C. Rameshkumar, L.-L. Wei, *Tetrahedron* **2001**, *57*, 7575–7606. (d) A. R. Katritzky, R. Jiang, S. K. Singh, *Heterocycles* **2004**, *63*, 1455-1475.

these reagents. Although discovered in 1972,[5] the rich chemistry of ynamides was only intensively investigated in the last two decades with the development of efficient syntheses to access them.[6] Ynamides are highly versatile building blocks that can be involved in cycloaddition reactions.[7] Moreover, they can react either as electrophiles or nucleophiles in ionic reactions.[8] Although less developed, ynamides have been shown to be valuable reactive partners in radical reactions.[9]



Scheme 4.2. Most common classes of ynamides and reactivity.

The first synthesis of ynamides reported by the Viehe group relied on an elimination reaction from halo-enamides (Scheme 4.3.A).[5] In the early 2000s, this strategy became the standard for the synthesis of ynamides from bromo-enamides.[10] Moreover, the use of β,β-chloro-enamides (X = R^2 = Cl) allowed to access chloro-ynamides that could be involved in cross-coupling reactions to access a broad variety of internal alkynes.[11] However, this strategy was somewhat limited by the difficult synthesis of halo-enamides. Recent advances by the

[5] Z. Janousek, J. Collard, H. G. Viehe, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 917–918.
[6] For recent reviews: (a) G. Evano, A. Coste, K. Jouvin, *Angew. Chem. Int. Ed.* **2010**, *49*, 2840–2859. (b) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2010**, *110*, 5064–5106. (c) G. Evano, K. Jouvin, A. Coste, *Synthesis* **2012**, *45*, 17–26. (d) A. M. Cook, C. Wolf, *Tetrahedron Lett.* **2015**, *56*, 2377–2392. (e) G. Evano, N. Blanchard, G. Compain, A. Coste, C. S. Demmer, W. Gati, C. Guissart, J. Heimburger, N. Henry, K. Jouvin, G. Karthikeyan, A. Laouiti, M. Lecomte, A. Martin-Mingot, B. Métayer, B. Michelet, A. Nitelet, C. Theunissen, S. Thibaudeau, J. Wang, M. Zarca, C. Zhang, *Chem. Lett.* **2016**, *45*, 574–585.
[7] (a) G. Duret, V. Le Fouler, P. Bisseret, V. Bizet, N. Blanchard, *Eur. J. Org. Chem.* **2017**, *2017*, 6816–6830. (b) F.-L. Hong, L.-W. Ye, *Acc. Chem. Res.* **2020**, *53*, 2003–2019.
[8] For electrophilic reactivity: (a) G. Evano, M. Lecomte, P. Thilmany, C. Theunissen, *Synthesis* **2017**, *49*, 3183–3214. (b) Y.-B. Chen, P.-C. Qian, L.-W. Ye, *Chem. Soc. Rev.* **2020**, *49*, 8897–8909. For nucleophilic reactivity: G. Evano, B. Michelet, C. Zhang, *Comptes Rendus Chim.* **2017**, *20*, 648–664.
[9] C. Mahe, K. Cariou, *Adv. Synth. Catal.* **2020**, *362*, 4820–4832.
[10] L.-L. Wei, J. A. Mulder, H. Xiong, C. A. Zificsak, C. J. Douglas, R. P. Hsung, *Tetrahedron* **2001**, *57*, 459–466.
[11] Selected examples: (a) D. Brückner, *Synlett* **2000**, *2000*, 1402–1404. (b) D. Rodríguez, L. Castedo, C. Saá, *Synlett* **2004**, 783–786. (c) S. Couty, M. Barbazanges, C. Meyer, J. Cossy, *Synlett* **2005**, *2005*, 905–910. (d) D. Brückner, *Tetrahedron* **2006**, 3809–3814. (e) M. F. Martínez-Esperón, D. Rodríguez, L. Castedo, C. Saá, *Tetrahedron* **2006**, 3843–3855. (f) D. Rodríguez, M. Martínez-Esperón, L. Castedo, C. Saá, *Synlett* **2007**, *2007*, 1963–1965.

Evano group,[12] using copper-catalysis and *gem*-dibromoalkenes, and the Anderson group,[13] involving the use of inexpensive trichloroethene as a C_2 synthon, allowed to broaden the scope of ynamides accessible through this strategy. Another classical way to access ynamides involved propargylation of amines followed by isomerization of the alkyne (B). Initially discovered by Zaugg and coworkers,[14] and later investigated by the Galy and Katritzky groups,[15] this transformation was limited in application and by the formation of the corresponding allenamides. Nonetheless, Hsung and coworkers could develop an efficient synthesis of chiral ynamides using only 20 mol% of *t*-BuOK and chiral propargylamines.[16]

The renewal of interest for copper-catalysis in the last 20 years led to important breakthroughs, notably for the formation of C-N bonds.[17] For instance, the first general approach to access ynamides from nitrogen nucleophiles and bromoalkynes using copper-catalysis was reported in 2003 by the Hsung group (C).[18] However, the required high temperature (110 °C) limited the scope of the reaction. Danheiser and coworkers could increase the scope of the transformation by using stoichiometric amount of copper and KHMDS, which allowed the reaction to take place at room temperature.[19] Finally, the Hsung group could further improve the process by using $CuSO_4$ as catalyst, a bipyridine ligand and potassium phosphate as base.[20] Although, this protocol is still one of the most efficient way to access ynamides, the use of bromoalkynes, which have strong lachrymatory properties when volatiles, can limit its application. In this context, copper-catalyzed oxidative amidation strategies have been developed (D). Building upon old reports from the Peterson and Balsamo groups,[21] Stahl and coworkers reported a direct copper-catalyzed aerobic oxidative amidation of terminal alkynes.[22] However, in order to avoid dimerization of the alkynes, a large excess

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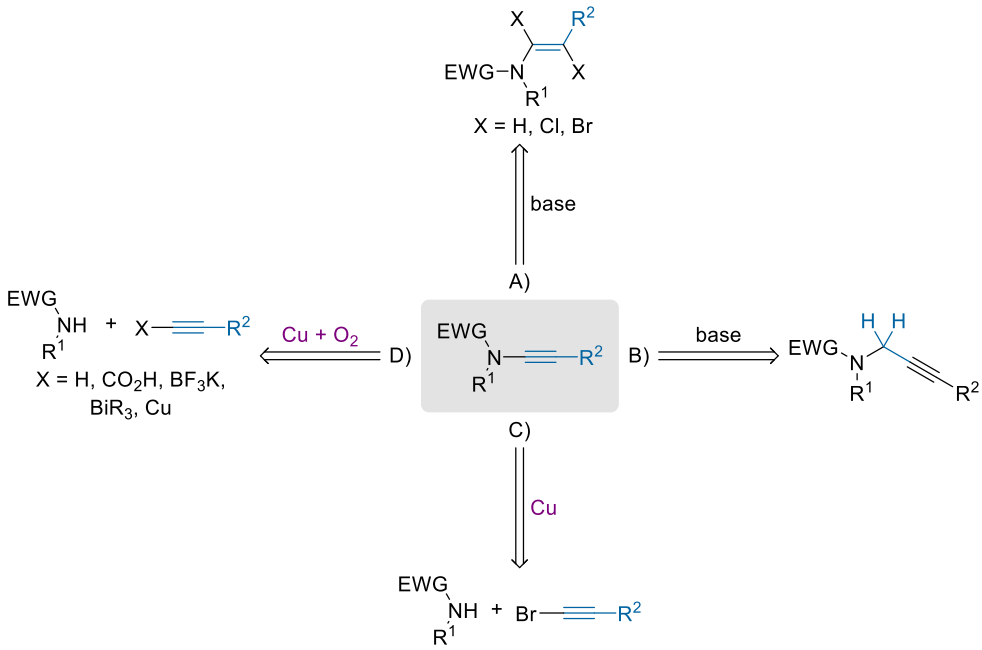
[12] Selected examples: (a) A. Coste, G. Karthikeyan, F. Couty, G. Evano, *Angew. Chem. Int. Ed.* **2009**, *48*, 4381–4385. (b) A. Coste, F. Couty, G. Evano, *Org. Lett.* **2009**, *11*, 4454–4457. (c) K. Jouvin, A. Coste, A. Bayle, F. Legrand, G. Karthikeyan, K. Tadiparthi, G. Evano, *Organometallics* **2012**, *31*, 7933–7947.
[13] Selected examples: (a) S. J. Mansfield, C. D. Campbell, M. W. Jones, E. A. Anderson, *Chem. Commun.* **2015**, *51*, 3316–3319. (b) S. J. Mansfield, R. C. Smith, J. R. J. Yong, O. L. Garry, E. A. Anderson, *Org. Lett.* **2019**, *21*, 2918–2922.
[14] H. Zaugg, L. Swett, G. Stone, *J. Org. Chem.* **1958**, *23*, 1389–1390.
[15] (a) J. P. Galy, J. Elguero, E. J. Vincent, A. M. Galy, J. Barbe, *Synthesis* **1979**, *1979*, 944–946. (b) A. Mahamoud, J. P. Galy, E. J. Vincent, J. Barbe, *Synthesis* **1981**, *1981*, 917–918. (c) A. R. Katritzky, W. H. Ramer, *J. Org. Chem.* **1985**, *50*, 852–856.
[16] J. Huang, H. Xiong, R. P. Hsung, C. Rameshkumar, J. A. Mulder, T. P. Grebe, *Org Lett* **2002**, *4*, 2417–2420.
[17] G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054–3131.
[18] M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, J. Huang, K. C. M. Kurtz, L. Shen, C. J. Douglas, *J. Am. Chem. Soc.* **2003**, *125*, 2368–2369.
[19] J. R. Dunetz, R. L. Danheiser, *Org. Lett.* **2003**, *5*, 4011–4014.
[20] Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* **2004**, *6*, 1151–1154.
[21] (a) L. I. Peterson, E. C. Britton, *Tetrahedron Lett.* **1968**, *9*, 5357–5360. (b) A. Balsamo, B. Macchia, F. Macchia, A. Rossello, P. Domiano, *Tetrahedron Lett.* **1985**, *26*, 4141–4144.
[22] T. Hamada, X. Ye, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 833–835.

of the corresponding amide was needed. Similar transformations were later developed replacing the free alkyne with CO_2H-,[23] BF_3K-,[24] BiR_3-,[25] and Cu-substituted alkynes.[26]

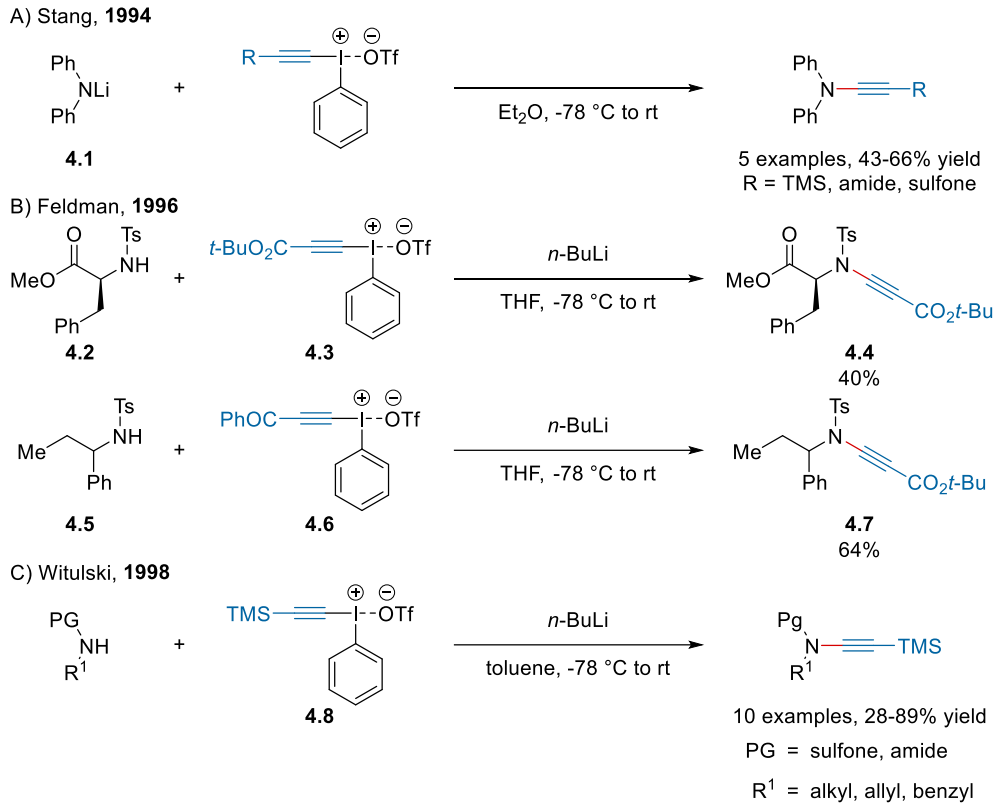


Scheme 4.3. General strategies to access ynamides.

Before the development of copper-catalyzed amidation, alkynyl iodonium salts have been particularly successful reagents for the alkynylation of nucleophilic amides (Scheme 4.4). For instance, the seminal work from the Stang group disclosed the reaction of TMS-, amide- and sulfone-substituted alkynyl iodonium triflate salts with lithiated diphenyl amine (**4.1**) (A).[27] Although limited in scope, this transformation set the way for the development of more efficient syntheses of ynamides. Starting from tosylated secondary amines and using *n*-BuLi as a base, Feldman and coworkers could access ynamides **4.4** and **4.7** bearing electron-withdrawing groups on the alkynes with moderate yields (B).[28] Using a similar strategy, the Witulski group developed an alkynylation of amides and sulfonamides using TMS-substituted alkynyl iodonium triflate **4.8** (C).[29] A variety of ynamides were obtained in moderate to good yields, the TMS substituent could be easily removed using tetrabutylammonium fluoride. Despite the need for strong bases and the use of iodonium salts that cannot be stored for a prolonged

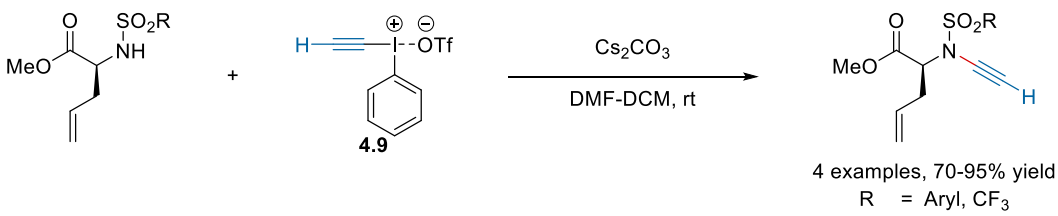
[23] W. Jia, N. Jiao, *Org. Lett.* **2010**, *12*, 2000–2003.
[24] K. Jouvin, F. Couty, G. Evano, *Org. Lett.* **2010**, *12*, 3272–3275.
[25] T. Sueda, A. Oshima, N. Teno, *Org. Lett.* **2011**, *13*, 3996–3999.
[26] K. Jouvin, J. Heimburger, G. Evano, *Chem Sci* **2012**, *3*, 756–760.
[27] P. Murch, B. L. Williamson, P. J. Stang, *Synthesis* **1994**, *1994*, 1255–1256.
[28] K. S. Feldman, M. M. Bruendl, K. Schildknegt, A. C. Bohnstedt, *J. Org. Chem.* **1996**, *61*, 5440–5452.
[29] B. Witulski, T. Stengel, *Angew. Chem. Int. Ed.* **1998**, *37*, 489–492.

time, these strategies have been shown to be valuable alternatives for bulky nitrogen nucleophiles reacting poorly in copper-catalyzed transformations.[30]



Scheme 4.4. Ynamide synthesis with alkynyl iodonium salts.

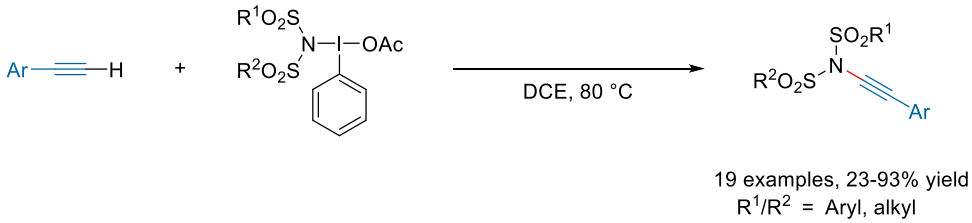
In order to access *N*-(ethynyl)allylglycine derivatives, the Witulski group developed an efficient alkynylation reaction using reagent **4.9** bearing no substituent on the alkyne, which allowed the use of a mild base Cs_2CO_3 (Scheme 4.5).[31] The alkyne and allyl moieties could then be used in highly stereoselective intramolecular Pauson-Khand reactions leading to functionalized proline derivatives.



Scheme 4.5. Synthesis of terminal ynamides from reagent **4.9** and allyl glycine derivatives.

[30] Selected examples: (a) J. D. Rainier, J. E. Imbriglio, *Org. Lett.* **1999**, *1*, 2037–2039. (b) B. Witulski, T. Stengel, *Angew. Chem. Int. Ed.* **1999**, *38*, 2426–2430. (c) J. D. Rainier, J. E. Imbriglio, *J. Org. Chem.* **2000**, *65*, 7272–7276. (d) B. Witulski, M. Gößmann, *Synlett* **2000**, *2000*, 1793–1797. (e) B. Witulski, C. Alayrac, *Angew. Chem. Int. Ed.* **2002**, *41*, 3281–3284.
[31] B. Witulski, M. Gößmann, *Chem. Commun.* **1999**, 1879–1880.

More recently, the Muñiz group proposed an elegant alternative based on nitrogen containing HIR and nucleophilic aryl substituted alkynes (Scheme 4.6).[32] Various bissulfonylated ynamides could be accessed in moderate to excellent yields from commercially available acetylene compounds. The hypervalent iodine reagent was readily accessible by mixing commercially available PIDA and the corresponding amine. The proposed mechanism involved the displacement of the nitrogen ligand by acetylene followed by classical addition of a nucleophile on alkynyl hypervalent iodine reagents (see section 3.1.3). One drawback of this reaction lied in the limited choice of electron-poor amines to be able to synthesize the corresponding HIR.

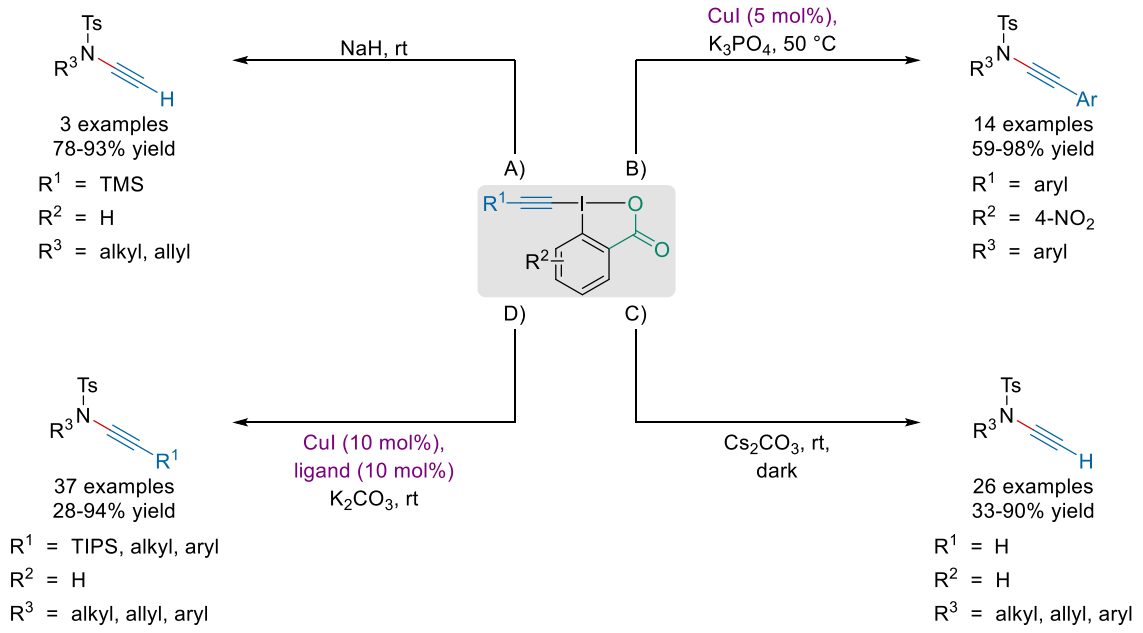


Scheme 4.6. Amidation of alkynes with hypervalent iodine reagents.

As discussed in the previous chapter, the development of cyclic EBX reagents was followed with progress in alkynylation transformations and notably for the synthesis of ynamides (Scheme 4.7). For instance, the Cossy group reported the synthesis of three terminal ynamides in excellent yields at room temperature using NaH to deprotonate the corresponding amines (A).[33] Amides and carbamates failed to afford ynamides under these reaction conditions. A year later, Ohno, Fujii and coworkers disclosed an efficient CuI catalyzed amidation using aryl-EBX reagents and relatively mild reaction conditions (K_3PO_4 as base and 50 °C) (B).[34] The highly functionalized ynamides obtained *via* this method were further used to access indoloquinolines. More recently, the Itoh and Tada groups developed a stable ethynylBX-MeCN complex (R^1 = H) which was successfully involved in the ethynylation of amines (C).[35] Only sulfones as protecting groups were tolerated in the transformation and tosylated amino acids were successfully converted into terminal ynamides. Although the reaction conditions are mild, the instability of the EBX reagent required the reaction to be set up in the dark. Finally in 2021, the same groups extended the procedure to substituted alkynyl-EBX reagents using CuI as catalyst and either dibenzoylmethane or a 2,2'-bipyridine ligand (D).[36] This procedure allowed to access a broad range of tosyl-ynamides in

[32] J. A. Souto, P. Becker, Á. Iglesias, K. Muñiz, *J. Am. Chem. Soc.* **2012**, *134*, 15505–15511.
[33] T. Aubineau, J. Cossy, *Chem. Commun.* **2013**, *49*, 3303–3305.
[34] Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2014**, *16*, 3138–3141.
[35] M. Yudasaka, D. Shimbo, T. Maruyama, N. Tada, A. Itoh, *Org. Lett.* **2019**, *21*, 1098–1102.
[36] R. Takai, D. Shimbo, N. Tada, A. Itoh, *J. Org. Chem.* **2021**, *86*, 4699–4713.

moderate to excellent yields under mild conditions. While EBX reagents have been particularly efficient for the formation of Csp-N bonds, they are, so far, limited to the alkynylation of sulfonyl protected amines.



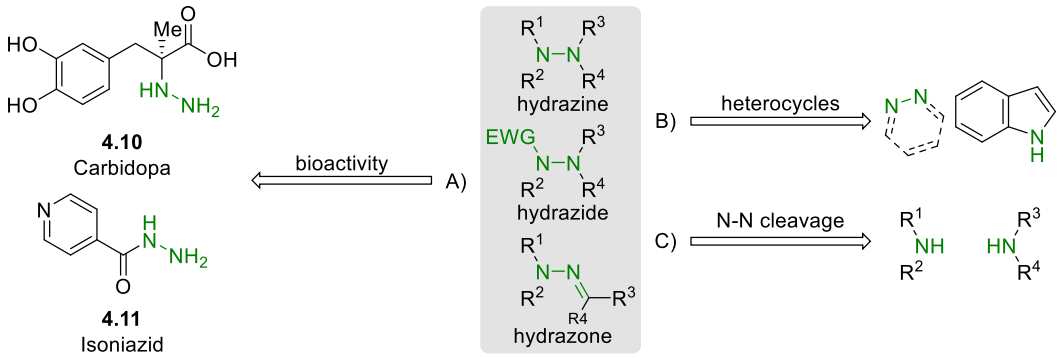
Scheme 4.7. Ynamide synthesis with EBX reagents.

4.1.2. Ynehydrazides: an Underdeveloped Class of Ynamides

Hydrazine and its derivatives, hydrazide (bearing an electron-withdrawing group) and hydrazone (one nitrogen embedded in an imine), are versatile functional groups in drug discovery and organic chemistry (Scheme 4.8).[37] Molecules bearing these functional groups have been shown to have interesting bioactivities (A).[38] For instance, Carbidopa (**4.10**), a derivative of L-DOPA bearing a free hydrazine, is used in the treatment of Parkinson's disease.[39] Isoniazid (**4.11**) is used for its antibiotic activity in the treatment of tuberculosis.[40] Concerning their reactivity, hydrazines and their derivatives have been particularly used for the synthesis of heterocycles (B).[41] In addition to the exceptional reactivity of these building

[37] E. W. Schmidt, *Hydrazine and Its Derivatives: Preparation, Properties, Applications*, 2nd ed.; John Wiley & Sons: New York, **2001**.
[38] For review: (a) S. Rollas, S. Küçükgüzel, *Molecules* **2007**, *12*, 1910–1939. (b) Ł. Popiołek, *Med. Chem. Res.* **2017**, *26*, 287–301.
[39] M. Sletzinger, J. M. Chemerda, F. W. Bollinger, *J. Med. Chem.* **1963**, *6*, 101–103.
[40] C. Vilchèze, W. R. Jacobs, Jr., *Annu. Rev. Microbiol.* **2007**, *61*, 35–50.
[41] For review: (a) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911. (b) A. Moulin, M. Bibian, A.-L. Blayo, S. El Habnouni, J. Martinez, J.-A. Fehrentz, *Chem. Rev.* **2010**, *110*, 1809–1827. (c) A. A. Hassan, A. M. Shawky, *J. Heterocycl. Chem.* **2010**, *47*, 745–763.

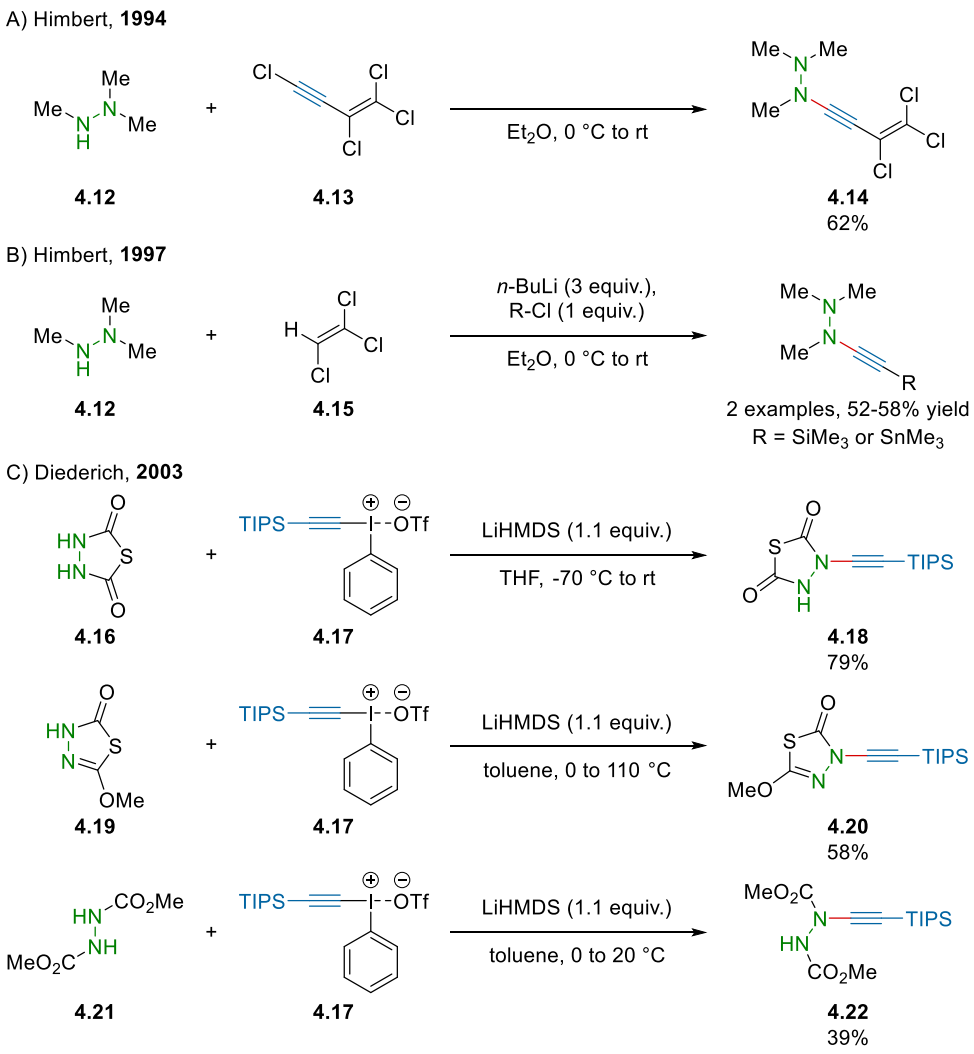
blocks, the cleavage of the N-N bond leads to amines or amides and, hence, hydrazine could be seen as protecting groups for nitrogen.[42]



Scheme 4.8. Significance of hydrazines and their derivatives.

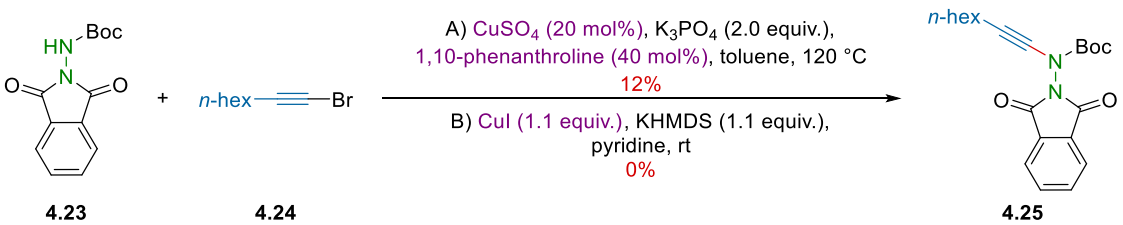
Although the combination of the rich chemistry of alkynes with that of hydrazine derivatives would be worth thorough investigations, examples of the corresponding ynehydrazides are scarce in the literature. The lack of general methods to access them has limited their studies. The Himbert group reported the first synthesis of ynehydrazines *via* the addition of highly nucleophilic trimethylhydrazine (**4.12**) onto highly reactive perchlorobutenyne (**4.13**) (Scheme 4.9.A).[43] Compound **4.14** could be obtained in 62% yield and the trichloroethene motif could be used for further functionalization of the molecule. The same group reported the synthesis of two other TMS or $SnMe_3$ substituted ynehydrazines through the reaction of **4.12** with trichloroethene (**4.15**) and 3 equivalents of *n*-BuLi (B).[44] Using alkynyl iodonium salt **4.17** and LiHMDS as a base, Diederich and coworkers could synthesize the first ynehydrazides in moderate to good yields (C).[45] In their quest for azoacetylenes, a second alkynylation of compounds **4.18** and **4.22** was attempted with the same method but failed to afford dialkynylated products.

[42] Selected examples: Zn/AcOH (a) Y. Leblanc, R. Zamboni, M. A. Bernstein, *J. Org. Chem.* **1991**, *56*, 1971–1972. Li/NH_3 (b) M. A. Brimble, C. H. Heathcock, *J. Org. Chem.* **1993**, *58*, 5261–5263. H_2/Pd$(OH)_2$ (c) Y. H. Kim, J. Y. Choi, *Tetrahedron Lett.* **1996**, *37*, 5543–5546. Oxidative cleavage (d) R. Fernández, A. Ferrete, J. M. Llera, A. Magriz, E. Martín-Zamora, E. Díez, J. M. Lassaletta, *Chem. Eur. J.* **2004**, *10*, 737–745. SmI_2 (e) H. Ding, G. K. Friestad, *Org. Lett.* **2004**, *6*, 637–640. Raney Ni (f) P. Sinha, C. C. Kofink, P. Knochel, *Org. Lett.* **2006**, *8*, 3741–3744. Photochemical cleavage (g) S. Lebrun, A. Couture, E. Deniau, P. Grandclaudon, *Synlett* **2009**, *2009*, 2621–2624.
[43] A. Löffler, G. Himbert, *Synthesis* **1994**, *1994*, 383–386.
[44] G. Himbert, H. Naßhan, O. Gerulat, *Synthesis* **1997**, *1997*, 293–294.
[45] F. Denonne, P. Seiler, F. Diederich, *Helv. Chim. Acta* **2003**, *86*, 3096–3117.



Scheme 4.9. First syntheses of ynehydrazines and ynehydrazides.

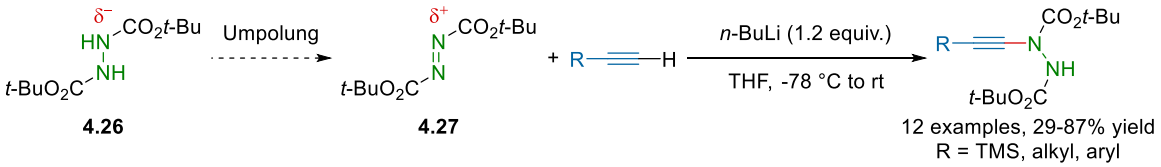
A decade later, the Batey group reinvestigated the synthesis of ynehydrazides in order to access precursors of heterocycles.[46] They first tried the typical conditions to synthesize ynamides developed by the Hsung group (conditions A)[20] or the Danheiser group (conditions B)[19] but did not obtain the desired product **4.25** in satisfactory yield (Scheme 4.10).



Scheme 4.10. Initial attempts with Cu-mediated Csp-N bond formation.

[46] R. E. Beveridge, R. A. Batey, *Org. Lett.* **2012**, *14*, 540–543.

In order to access ynehydrazides, they reasoned that inversing the reactivity of the coupling partners could lead to better results (Scheme 4.11). Therefore, they studied the alkynylation of di-*tert*-butyl azodicarboxylate (**4.27**) which could be seen as an electrophilic equivalent of hydrazide **4.26**. Using *n*-BuLi to deprotonate free alkynes, a variety of ynehydrazides substituted by an alkyl chain, an aryl or a TMS group could be obtained in moderate to good yields.



Scheme 4.11. Lithium acetylides addition to azodicarboxylate **4.27**.

Since the development of this method, several applications of ynehydrazides have been disclosed for the total synthesis of natural products,[47] for the synthesis of heterocycles,[48] and azo-photoswitches.[49] However, this protocol lacks generality due to the use of symmetrical azodicarboxylates as hydrazide precursors and the strong base required to deprotonate acetylenes limits the functional group tolerance of the transformation.

4.1.3. Azapeptides: Importance of Hydrazide Containing Peptides

Designing functionalized peptidomimetics, which can be easily synthesized, has gained interest in recent decades as a result of the rising development of peptide-based drugs.[50] In this context, the introduction of azaamino acids, in which the α-carbon is replaced by a nitrogen atom (Figure 4.1), allowed to improve the structural and conformational characteristics of several bioactive peptides.[51] Although azaamino acids, also known as carbazic acid esters, have been known since the beginning of the 20th century,[52] the first incorporation of such subunit in a native peptide was reported in 1963 by Laubach and

[47] R. E. Beveridge, R. A. Batey, *Org. Lett.* **2013**, *15*, 3086–3089.
[48] Selected examples: (a) P. R. Walker, C. D. Campbell, A. Suleman, G. Carr, E. A. Anderson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9139–9143. (b) V. Palani, J. Chen, T. R. Hoye, *Org. Lett.* **2016**, *18*, 6312–6315. (c) J. Chen, V. Palani, T. R. Hoye, *J. Am. Chem. Soc.* **2016**, *138*, 4318–4321. (d) R. Diana-Rivero, B. Halsvik, F. García Tellado, D. Tejedor, *Org. Lett.* **2021**, *23*, 4078–4082.
[49] J. R. Tuck, R. J. Tombari, N. Yardeny, D. E. Olson, *Org. Lett.* **2021**, *23*, 4305–4310.
[50] A. Henninot, J. C. Collins, J. M. Nuss, *J. Med. Chem.* **2018**, *61*, 1382–1414.
[51] For reviews: (a) J. Gante, *Synthesis* **1989**, *21*, 405–413. (b) C. Proulx, D. Sabatino, R. Hopewell, J. Spiegel, Y. Garcia-Ramos, W. D. Lubell, *Future Med. Chem.* **2011**, *3*, 1139–1164. (c) R. Chingle, C. Proulx, W. D. Lubell, *Acc. Chem. Res.* **2017**, *50*, 1541–1556. (d) C. Proulx, J. Zhang, D. Sabatino, S. Chemtob, H. Ong, W. D. Lubell, *Biomedicines* **2020**, *8*, 241.
[52] (a) R. Stollé, *Berichte Dtsch. Chem. Ges.* **1910**, *43*, 2468–2470. (b) O. Diels, *Berichte Dtsch. Chem. Ges.* **1914**, *47*, 2183–2195. (c) K. Ronco, B. Prijs, H. Erlenmeyer, *Helv. Chim. Acta* **1956**, *39*, 1253–1257. (d) K. Ronco, H. Erlenmeyer, *Helv. Chim. Acta* **1956**, *39*, 1045–1051.

coworkers with the synthesis of [azaVal[3]]-angiotensin II (**4.28**).[53] While the bioactivity of the analogue to bovine angiotensin II was preserved, the duration of activity was increased probably due to a greater protease stability provided by the incorporation of an azaamino acid residue.[54]

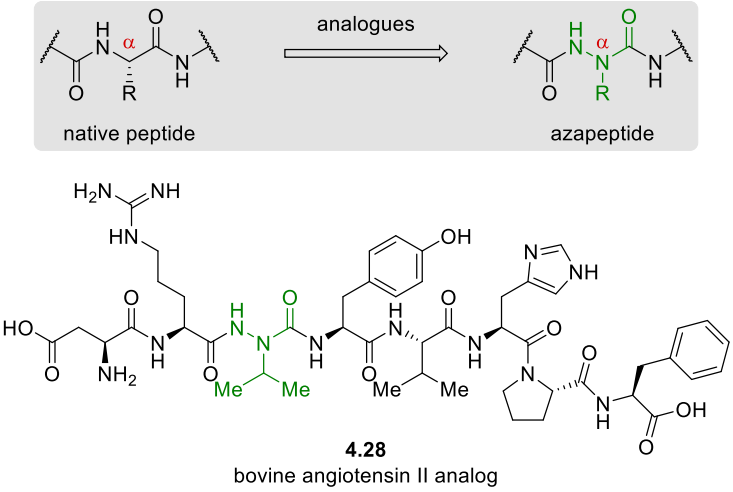


Figure 4.1. Azapeptides and [azaVal[3]]-angiotensin II (**4.28**).

By switching the α-carbon for a nitrogen, the aza-residue does no longer possess a chiral center. However, the α-center in azaamino acids can be considered as being configurationally flexible but with preferred geometries.[55] For instance, the incorporation of azaglycine residues provides additional H-bond donor which improves the self-assembly of the corresponding azapeptides and their stability (R = H, Figure 4.1).[56] In addition, the planarity of urea coupled to the repulsion of the hydrazine nitrogen lone pairs tends to favor the formation of internal H-bond inducing β-turn conformations characterized by restricted backbone dihedral value ranges (φ = 90 ± 30° or -90 ± 30° and ψ = 0 ± 30° or 180 ± 30°, Figure 4.2).[57]

[53] H.-J. Hess, W. T. Moreland, G. D. Laubach, *J. Am. Chem. Soc.* **1963**, *85*, 4040–4041.
[54] Anand. S. Dutta, M. B. Giles, *J. Chem. Soc., Perkin Trans. 1* **1976**, 244–248.
[55] M. Thormann, H.-J. Hofmann, *J. Mol. Struct. (Theochem)* **1999**, *469*, 63–76.
[56] (a) Y. Zhang, R. M. Malamakal, D. M. Chenoweth, *J. Am. Chem. Soc.* **2015**, *137*, 12422–12425. (b) Y. Zhang, M. Herling, D. M. Chenoweth, *J. Am. Chem. Soc.* **2016**, *138*, 9751–9754. (c) A. J. Kasznel, Y. Zhang, Y. Hai, D. M. Chenoweth, *J. Am. Chem. Soc.* **2017**, *139*, 9427–9430. (d) K. Baruah, B. Sahariah, S. S. Sakpal, J. K. R. Deka, A. K. Bar, S. Bagchi, B. K. Sarma, *Org. Lett.* **2021**, *23*, 4949–4954.
[57] (a) Z. Benatalah, A. Aubry, G. Boussard, M. Marraud, *Int. J. Pept. Protein Res.* **1991**, *38*, 603–605. (b) M. Thormann, H.-J. Hofmann, *J. Mol. Struct. (Theochem)* **1999**, *469*, 63–76. (c) H.-J. Lee, K.-H. Choi, I.-A. Ahn, S. Ro, H. G. Jang, Y.-S. Choi, K.-B. Lee, *J. Mol. Struct.* **2001**, *569*, 43–54. (d) D. Sabatino, C. Proulx, P. Pohankova, H. Ong, W. D. Lubell, *J. Am. Chem. Soc.* **2011**, *133*, 12493–12506.

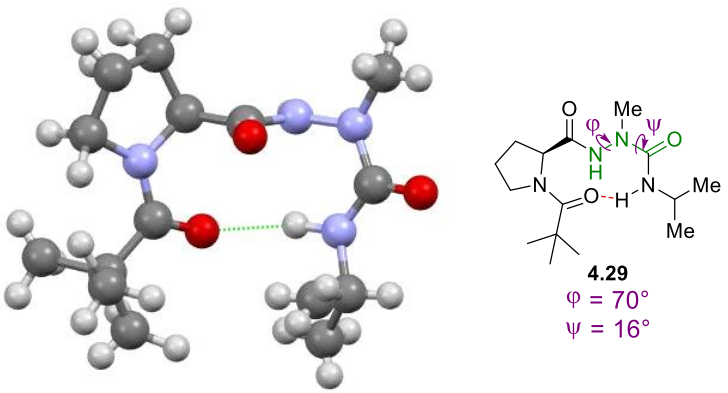
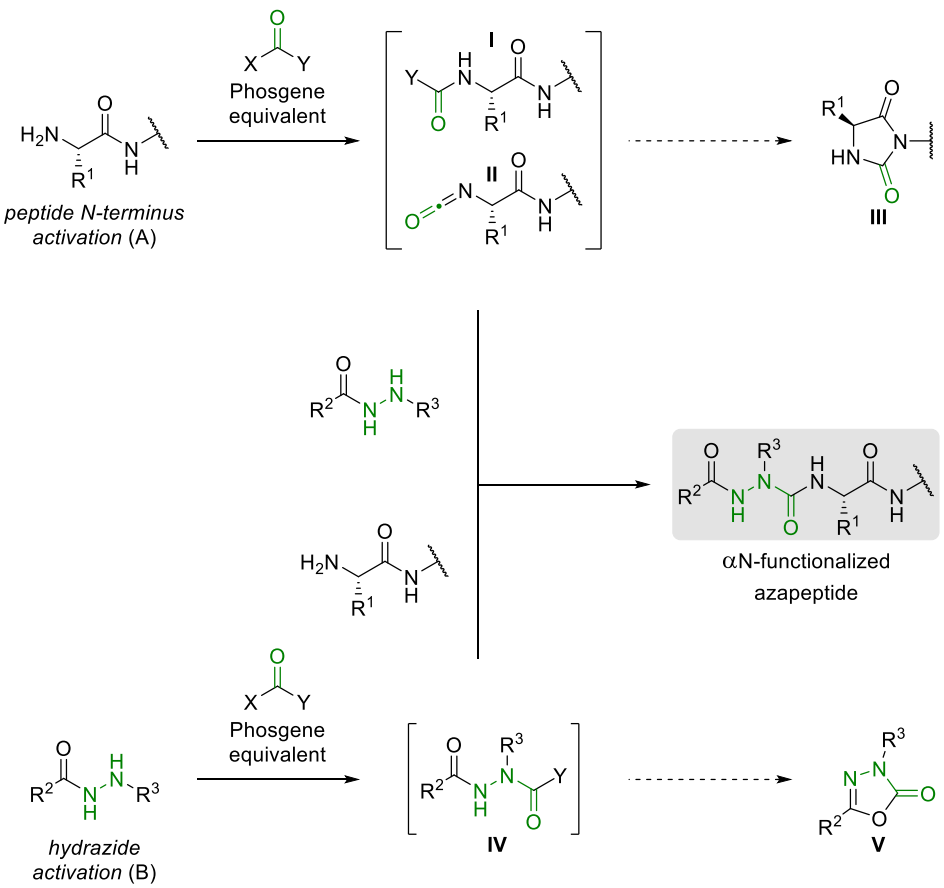


Figure 4.2. Example of β-turn with azapeptide **4.29**. X-ray taken from ref. 57a.

Regarding the synthesis of azapeptides, two strategies are usually followed (Scheme 4.12). The first strategy involves the activation of the corresponding peptide N-terminus (A).[58] This strategy requires the use of phosgene equivalents to introduce the carbonyl, which leads to the formation of activated carbamate (**I**) or isocyanate (**II**) intermediates that can then be trapped by the desired substituted hydrazide. The main drawback of the method is the formation of hydantoin side-products (**III**) when the peptide part contains more than one amino acid. The second strategy is based on the activation of the corresponding hydrazide using phosgene equivalents leading to intermediate (**IV**) that can then react with the desired peptidic part (B).[59] The limitation of this strategy lies in the cyclization of intermediate **IV** generating oxadiazolone side-products (**V**). Although both strategies allowed to synthesize azapeptides, the need to use pre-functionalized hydrazides is not ideal if a library of compounds needs to be built with variation only at the α-nitrogen.

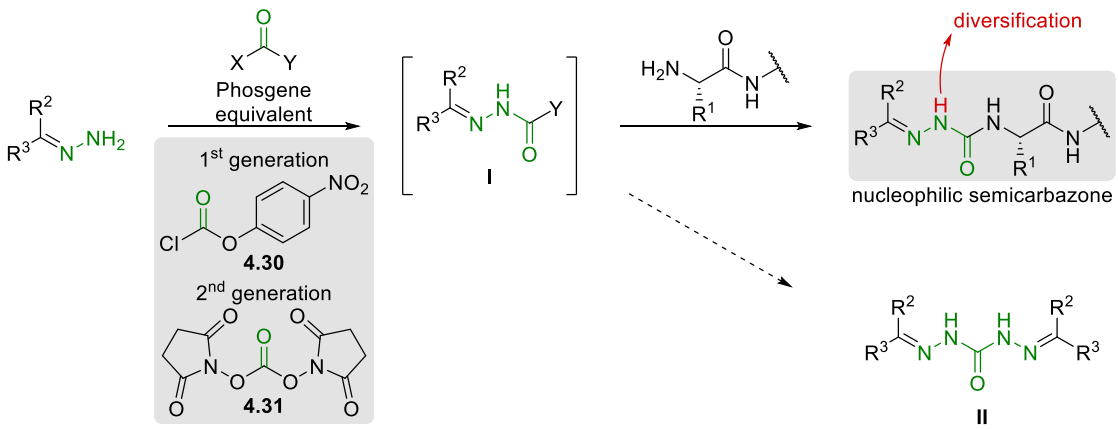
[58] Selected examples: (a) I.-A. Ahn, S. Woong Kim, S. Ro, *Mol. Divers.* **1998**, *4*, 23–24. (b) S. H. L. Verhelst, M. D. Witte, S. Arastu-Kapur, M. Fonovic, M. Bogyo, *ChemBioChem* **2006**, *7*, 943–950. (c) C. J. Gray, M. Quibell, N. Baggett, T. Hammerle, *Int. J. Pept. Protein Res.* **2009**, *40*, 351–362.
[59] Selected examples: (a) H. Han, K. D. Janda, *J. Am. Chem. Soc.* **1996**, *118*, 2539–2544. (b) C. Frochot, R. Vanderesse, A. Driou, G. Linden, M. Marraud, M. T. Cung, *Lett. Pept. Sci.* **1997**, *4*, 219–225. (c) C. Gibson, S. L. Goodman, D. Hahn, G. Hölzemann, H. Kessler, *J. Org. Chem.* **1999**, *64*, 7388–7394. (d) E. Wieczerzak, P. Drabik, L. Łankiewicz, S. Ołdziej, Z. Grzonka, M. Abrahamson, A. Grubb, D. Brömme, *J. Med. Chem.* **2002**, *45*, 4202–4211. (e) R. E. Melendez, W. D. Lubell, *J. Am. Chem. Soc.* **2004**, *126*, 6759–6764.



Scheme 4.12. Initial strategies to access functionalized azapeptides.

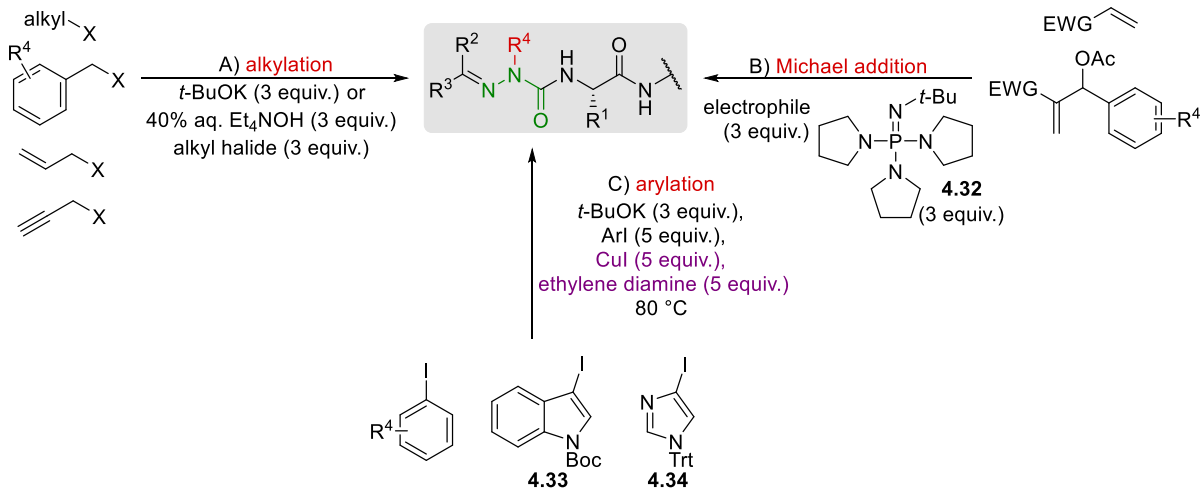
The Lubell group later developed a new approach for the synthesis of azapeptides (Scheme 4.13). The strategy is based on the coupling of a hydrazone with the desired peptidic chain using phosgene equivalents. The first generation involved the use of *p*-nitrophenyl chloroformate (**4.30**) which allowed to reduce the formation of hydrazone dimerization product (**II**) compared to classical phosgene equivalents.[60] However, due to the difficulty to remove *p*-nitrophenol generated during the reaction, the transformation was further improved by using *N,N'*-disuccinimidyl carbonate (DSC, **4.31**).[61] The main advantage of the approach lies in the greater acidity of the semicarbazone nitrogen (proton highlighted in red, Scheme 4.13) compared to the other nitrogen of the azapeptides. Selective functionalization of semicarbazone nitrogen is then possible under basic conditions and the cleavage of the hydrazone protecting groups allows to further grow the azapeptides.

[60] D. Sabatino, C. Proulx, S. Klocek, C. B. Bourguet, D. Boeglin, H. Ong, W. D. Lubell, *Org. Lett.* **2009**, *11*, 3650–3653.
[61] (a) Y. Garcia-Ramos, W. D. Lubell, *J. Pept. Sci.* **2013**, *19*, 725–729. (b) M. Bowles, C. Proulx, in *Methods Enzymol.*, Elsevier, **2021**, pp. 169–190.



Scheme 4.13. Lubell group's strategy for the synthesis of azapeptide derivatives.

In their initial report, Lubell and coworkers demonstrated that the alkylation of semicarbazones was possible under basic conditions using *t*-BuOK (Scheme 4.14.A).[60] It was later shown that using a 40% aqueous solution of tetrabutylammonium hydroxide reduced the risk of epimerization.[61a,62] Non-nucleophilic phosphazene base **4.32** enabled the functionalization of azapeptides with Michael acceptors and allylic acetates (B).[57d] Finally, *N*-(hetero)arylation could also be performed with stoichiometric amount of CuI and ethylene diamine (C).[63]



Scheme 4.14. Functionalization of semicarbazones.

Semicarbazones have emerged as valuable precursors for functionalized azapeptides, however their reactivity has been scarcely studied. For instance, to the best of our knowledge no alkynylation of semicarbazones had been reported at the onset of this project.

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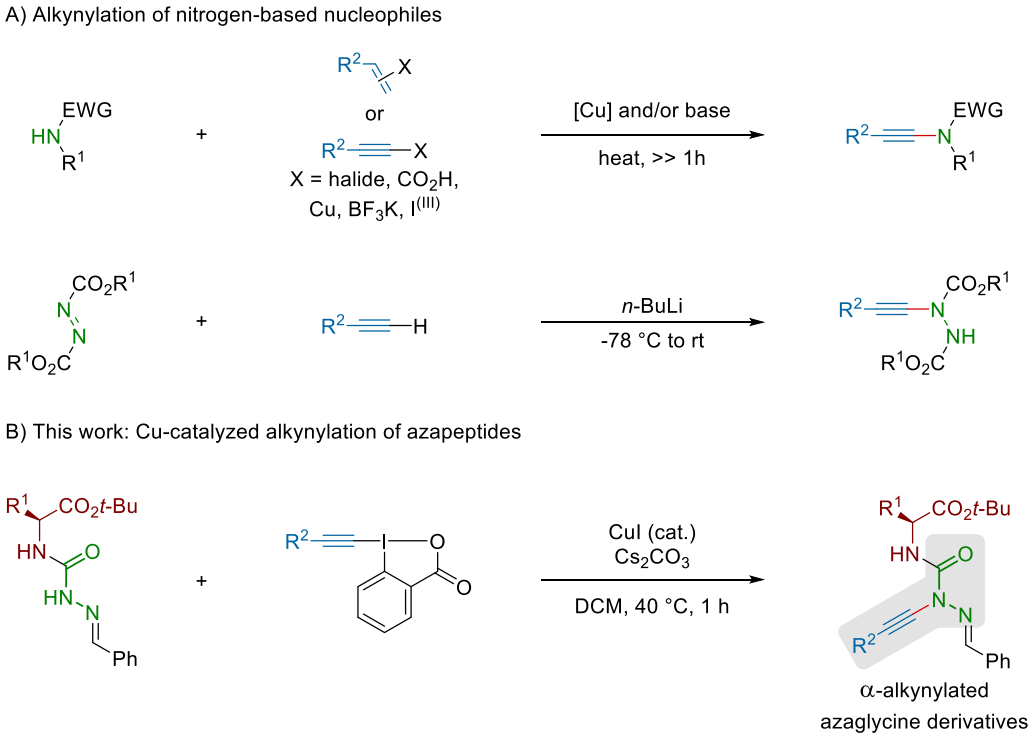
[62] Selected examples: (a) N.-D. Doan, R. Hopewell, W. D. Lubell, *Org. Lett.* **2014**, *16*, 2232–2235. (b) J. Zhang, C. Proulx, A. Tomberg, W. D. Lubell, *Org. Lett.* **2014**, *16*, 298–301. (c) M. Traoré, M. Gignac, N.-D. Doan, F. Hof, W. D. Lubell, *J. Pept. Sci.* **2017**, *23*, 266–271.
[63] C. Proulx, W. D. Lubell, *Org. Lett.* **2010**, *12*, 2916–2919.

4.2. Goals of the Project

As discussed in the previous sections, the formation of Csp-N bond has been broadly studied and notably for the formation of ynamides (Scheme 4.15.A). The synthesis of ynehydrazides is currently relying on the addition of acetylides onto azodicarboxylates. The use of strong bases and symmetrical hydrazide precursors is, however, restricting the potential application of ynehydrazides.

The serendipitous discovery of a hydrazone alkynylation reaction, led us to study the copper-catalyzed alkynylation of semicarbazones with alkynyl hypervalent iodine reagents (Scheme 4.15.B). The mild reaction conditions would allow to tolerate more functional groups and broaden the scope of non-symmetrical ynehydrazides accessible. In addition, the introduction of an alkynyl on the α-nitrogen of azapeptides could serve as a handle for further functionalization. The obtained α-alkynylated azaglycine derivatives could be valuable analogues of bioactive and synthetically useful α-alkynyl amino acids.[64]



Scheme 4.15. A) Overview of current alkynylation of nitrogen-based nucleophiles approaches. B) Our approach towards the alkynylation of azapeptides.

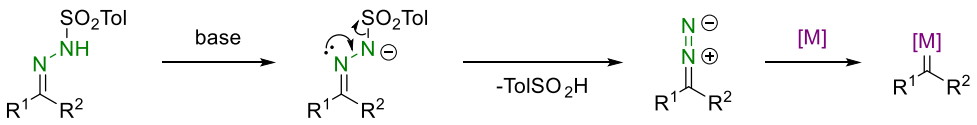
[64] (a) P. Meffre, F. Le Goffic, *Amino Acids* **1996**, *11*, 313–328. (b) J. Bolsakova, A. Jirgensons, *Eur. J. Org. Chem.* **2016**, *2016*, 4591–4602.

4.3. Results and Discussion

In this section, our efforts on the development of a copper-catalyzed alkynylation of azadipeptide derivatives will be presented. This project was realized in collaboration with Julien Borrel and his specific contributions will be highlighted in the following sections.

4.3.1. Serendipitous Reaction Discovery and Optimization

The last reactivity investigated in the previous chapter (see section 3.3.3.6) showed that alkynyl hypervalent iodine reagents could also react with non-stabilized carbenes and form oxyalkynylated products. In order to further study this reactivity, we decided to investigate tosyl-hydrazones as carbene precursors. Bamford and Stevens showed that under basic conditions tosyl-hydrazones could be converted to the corresponding diazo compounds *via* the loss of toluenesulfinic acid (Scheme 4.16).[65] Barluenga and coworkers later demonstrated that the *in-situ* formed diazo compound could be used as a metal carbene precursor for cross-coupling reactions.[66] Since this seminal work, sulfonyl hydrazones have emerged as ideal carbene precursors due to their ease of synthesis, by condensation of sulfonyl hydrazine with the corresponding ketones or aldehydes, and their improved stability and safety profile compared to diazo compounds.[67]



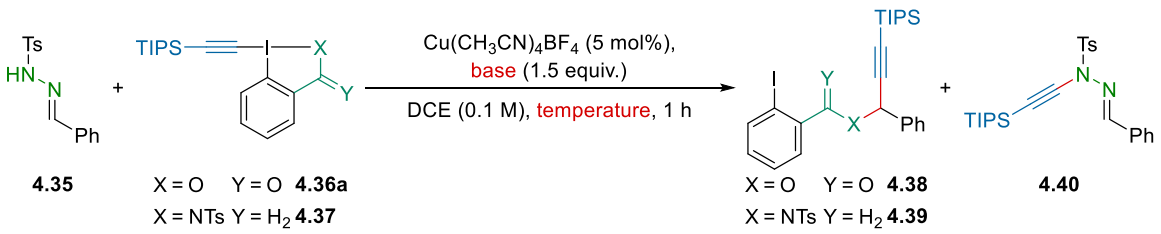
Scheme 4.16. Bamford-Stevens reaction to access metal carbenes.

As aryl sulfonyl-hydrazones usually require lower temperature to undergo the Bamford-Stevens reaction, we decided to investigate the reactivity of the tosyl-hydrazone derived from benzaldehyde **4.35** (Table 4.1). First, we studied the formation of product **4.38** and **4.39** using $Cu(CH_3CN)_4BF_4$ as catalyst and Cs_2CO_3 as base (entries 1-2). However, at 60 °C only alkynylation of hydrazone **4.35** was observed and **4.40** was obtained in 48% yield from **4.36a** and 26% from **4.37**. With these results in hand, we decided to shift our goal to the alkynylation of hydrazones after having discovered a mild procedure to access non-symmetrical ynehydrazides. In the absence of base, no reaction occurred and both starting materials could be recovered (entry 3). Lowering the temperature to 40 °C was beneficial for

[65] W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, 4735–4740.
[66] J. Barluenga, P. Moriel, C. Valdés, F. Aznar, *Angew. Chem. Int. Ed.* **2007**, *46*, 5587–5590.
[67] For reviews: (a) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236–247. (b) M. Jia, S. Ma, *Angew. Chem. Int. Ed.* **2016**, *55*, 9134–9166. (c) Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* **2017**, *117*, 13810–13889.

the transformation and **4.40** could be isolated in 75% yield (entry 4). However, no reaction was observed when lowering the temperature to room temperature (entry 5). Changing the base to *t*-BuOLi, often used to deprotonate sulfonyl hydrazones, only afforded **4.40** in reduced yield (entry 6). Finally, performing the reaction not under inert atmosphere was tolerated and compound **4.40** could be isolated in 79% yield (entry 7).

Table 4.1. Reactivity investigation between hydrazone **4.35** and HIR **4.36a** and **4.37**.[a]

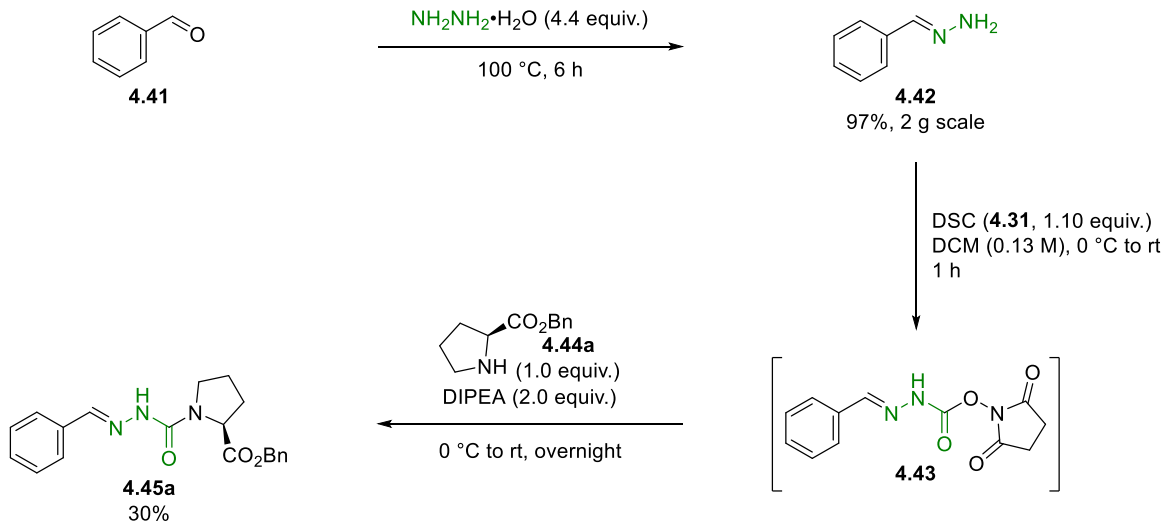


Entry	HIR	Base	Temperature	4.38/4.39	4.40
1	**4.36a**	Cs_2CO_3	60 °C	-	48%
2	**4.37**	Cs_2CO_3	60 °C	-	26%
3	**4.36a**	none	60 °C	-	-
4	**4.36a**	Cs_2CO_3	40 °C	-	75%
5	**4.36a**	Cs_2CO_3	rt	-	-
6	**4.36a**	*t*-BuOLi	40 °C	-	62%
7[b]	**4.36a**	Cs_2CO_3	40 °C	-	79%

[a] Reaction conditions: **4.35** (0.05 mmol), HIR (0.05 mmol), $Cu(CH_3CN)_4BF_4$ (2.50 µmol), base (75.0 µmol) in 0.50 mL of dry DCE under N_2 at the indicated temperature for 1 hour. Isolated yield after preparative TLC is given. [b] reaction flask opened to air.

Having established the possibility to alkynylate tosyl hydrazones, we wondered if semicarbazones would be suitable substrates in the transformation allowing to access alkynylated azapeptides. For this purpose, we selected semicarbazone **4.45a** derived from proline as model substrate. We believed that investigating the transformation with **4.45a** would be facilitated by the absence of other nucleophilic nitrogen on the semicarbazone. Its synthesis was performed in two steps (Scheme 4.17). First, the free hydrazone **4.42** was obtained by the condensation of hydrazine monohydrate with benzaldehyde **4.41**.[68] The compound was obtained in excellent yield on a 2-gram scale, as decomposition of the compound was observed upon storage in a freezer at -20 °C we did not perform the reaction on bigger scale. Then following the 2nd generation submonomer strategy developed by the Lubell group,[61] semicarbazone **4.45a** could be obtained in 30% yield.

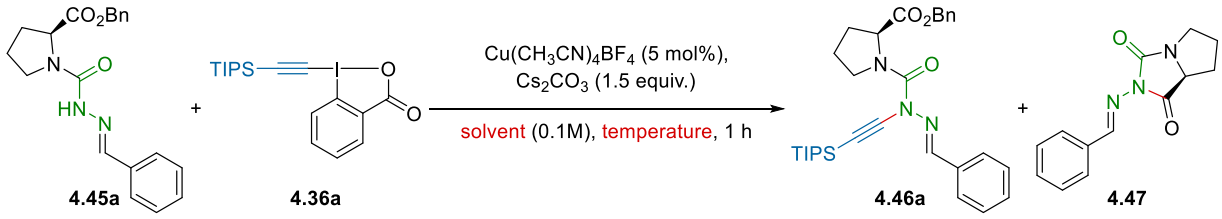
[68] A. J. Wommack, D. C. Moebius, A. L. Travis, J. S. Kingsbury, *Org. Lett.* **2009**, *11*, 3202–3205.



Scheme 4.17. Synthesis of hydrazone **4.42** and semicarbazone **4.45a**.

Having semicarbazone **4.45a** in hand, we decided to investigate its reactivity in alkynylation reactions with TIPS-EBX (**4.36a**) (Table 4.2). Starting with the conditions for tosyl hydrazone **4.35**, full conversion of **4.45a** was observed but alkynylated product **4.46a** could not be detected (entry 1). At that time, the main side product of the reaction was not isolated but according to the NMR of the crude mixture it corresponded to the cyclization product **4.47**. In absence of copper catalyst, semicarbazone **4.45a** was fully converted under the reaction conditions but **4.46a** was not observed (entry 2). A control experiment without base showed that compound **4.45a** is stable under copper catalysis in presence of TIPS-EBX but no reaction occurred (entry 3). Lowering the temperature and switching for more polar solvent did not improve the reaction outcome (entries 4-5). However, a more careful purification of the crude mixture allowed to confirm the structure of the side-product to be the bicyclic compound **4.47** (entry 5).

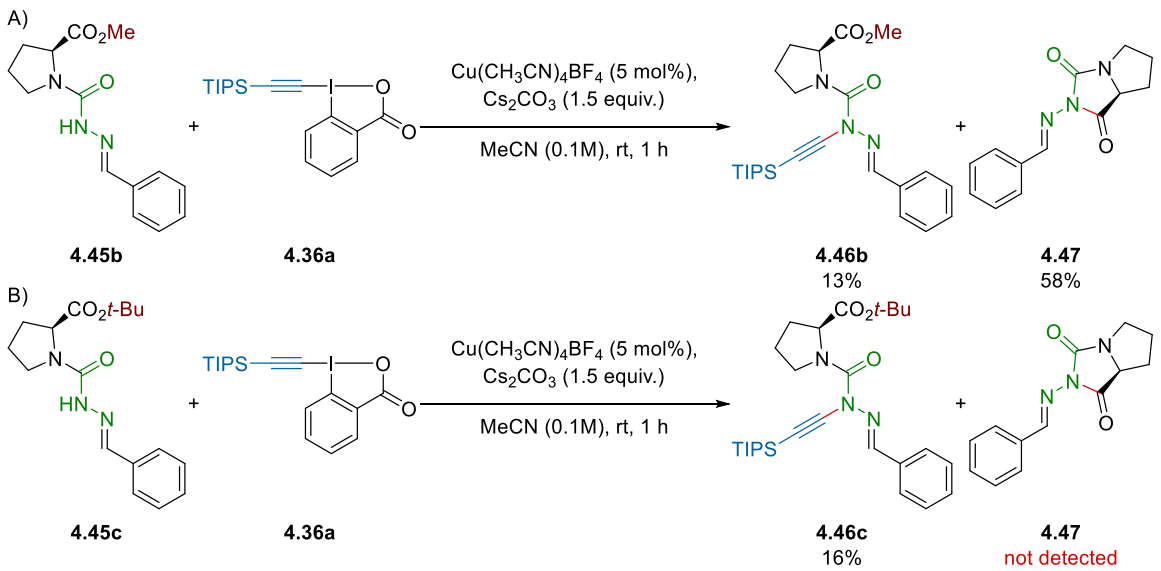
Table 4.2. Investigation of the alkynylation of semicarbazone **4.45a** with TIPS-EBX (**4.36a**).[a]



Entry	Solvent	Temperature	4.46a	4.47
1	DCE	40 °C	ND	-
2[b]	DCE	40 °C	ND	-
3[c]	DCE	40 °C	NR	NR
4	THF	rt	ND	-
5	MeCN	rt	ND	82%

[a] Reaction conditions: **4.45a** (0.05 mmol), **4.36a** (0.05 mmol), Cs_2CO_3 (75 µmol), $Cu(CH_3CN)_4BF_4$ (2.5 µmol) in dry solvent (0.5 mL) at the indicated temperature under air for 1 hour. Isolated yield after preparative TLC is given. [b] no catalyst. [c] no base.

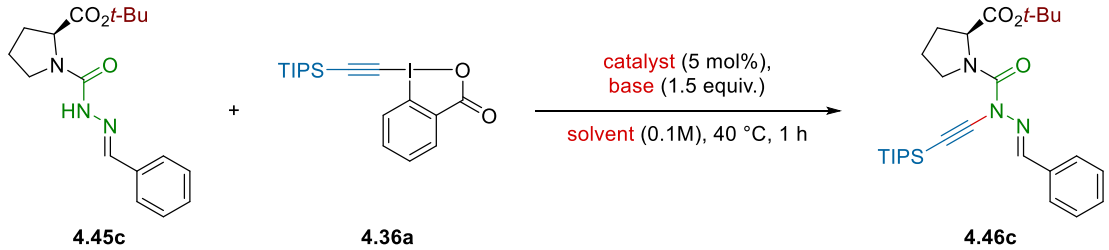
The cyclization of semicarbazone **4.45a** being the main reaction taking place, we decided to investigate the effect of different protecting group at the C-terminus position of the proline on the reaction (Scheme 4.18). Semicarbazone protected at the C-terminus position as a methyl ester **4.45b** and as a *tert*-butyl ester **4.45c** were synthesized as described previously and obtained in 33% and 63% yield respectively. When **4.45b** was subjected to the reaction conditions ($Cu(CH_3CN)_4BF_4$ (5 mol%), Cs_2CO_3 (1.5 equiv.) in MeCN at room temperature for 1 hour), we could isolate the desired alkynylated product **4.46b** in 13% but also **4.47** as major product (A). Finally, the bulkier *tert*-butyl ester hampered the cyclization and alkynylated product **4.46c** could be isolated in 16% yield but with poor conversion of both starting materials (B).



Scheme 4.18. Impact of the C-terminus ester on the alkynylation reaction.

Having established that **4.45c** was not prone to cyclization, we set to optimize the alkynylation with this compound as model substrate (Table 4.3). Repeating the reaction in MeCN but at 40 °C led to an increase in yield and **4.46c** could be isolated in 32% yield (entry 1). *i*-PrOH and DCE were screened as solvent and **4.46c** was obtained in 48% and 60% yield respectively (entries 2-3). The alkynylated product **4.46c** was formed in lower yield when changing the catalyst for CuCl (entry 4). However, $CuCl_2$ and CuI performed better in the reaction and afforded the desired product in 68% yield and 76% yield (entries 5-6). Changing the base to Na_2CO_3 or K_2CO_3 was detrimental to the reaction (entries 7-8). The role of cesium to promote the reaction is not clearly understood but it might be linked to the precipitation of 2-iodobenzoate-cesium salt during the reaction, which would be a driving force for the reaction. Increasing the stoichiometry of TIPS-EBX (**4.36a**) from 1.0 equivalent to 1.5 equivalents did not lead to an improvement of the reaction (entry 9). Finally, switching the solvent from DCE to DCM as a cheaper and less regulated alternative led to similar results and **4.46c** could be isolated in 72% yield (entry 10). Interestingly, even when not dry DCM was used in the reaction, the alkynylated product was formed, albeit with a lower 48% yield (entry 11). Control experiments showed that in absence of CuI (entry 12) or in absence of Cs_2CO_3 (entry 13) compound **4.46c** was not formed.

Table 4.3. Investigation of the alkynylation of semicarbazone **4.45c** with TIPS-EBX (**4.36a**).[a]



4.45c **4.36a** **4.46c**

Entry	Catalyst (5 mol%)	Base (1.5 equiv.)	Solvent	Yield
1	$Cu(CH_3CN)_4BF_4$	Cs_2CO_3	MeCN	32%
2	$Cu(CH_3CN)_4BF_4$	Cs_2CO_3	*i*-PrOH	48%
3	$Cu(CH_3CN)_4BF_4$	Cs_2CO_3	DCE	60%
4	CuCl	Cs_2CO_3	DCE	36%
5	$CuCl_2$	Cs_2CO_3	DCE	68%
6	CuI	Cs_2CO_3	DCE	76%
7	CuI	Na_2CO_3	DCE	8%
8	CuI	K_2CO_3	DCE	12%
9[b]	CuI	Cs_2CO_3	DCE	72%
10	CuI	Cs_2CO_3	DCM	72%
11[c]	CuI	Cs_2CO_3	DCM	48%
12	None	Cs_2CO_3	DCM	-
13	CuI	None	DCM	-

[a] Reaction conditions: **4.45c** (0.05 mmol), **4.36a** (0.05 mmol), base (75 μmol), catalyst (2.5 μmol) in dry solvent (0.5 mL) at 40 °C under air for 1 hour. Isolated yield after preparative TLC is given. [b] 1.5 equiv. of **4.36a**. [c] not dry DCM.

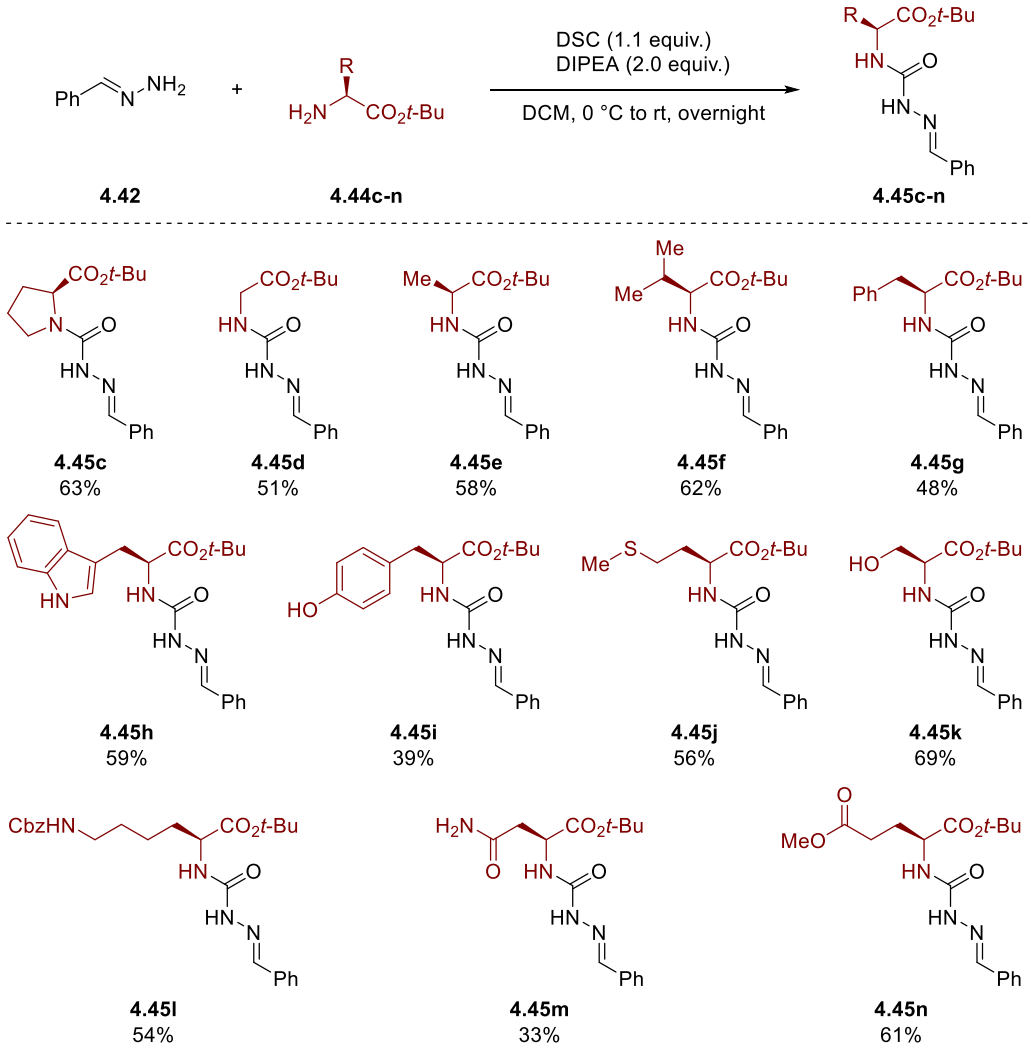
4.3.2. Scope and Limitations

Having optimized the reaction conditions for the copper-catalyzed alkynylation of azadipeptide derivatives, we decided to explore the scope and limitations of the transformation.

4.3.2.1. Scope of Semicarbazones

In order to investigate the functional group tolerance of the transformation, we synthesized various semicarbazones starting from commercially available amino acids (Scheme 4.19). As already discussed, the semicarbazone derived from proline (**4.45 c**) could be obtained in good yield. Azadipeptide derivatives with aliphatic side chains derived from glycine (**4.45d**), alanine (**4.45e**) and valine (**4.45f**) were accessed in, respectively, 51%, 58% and 62% yield. Aromatic residues on the side chains were tolerated and compounds **4.45g**,

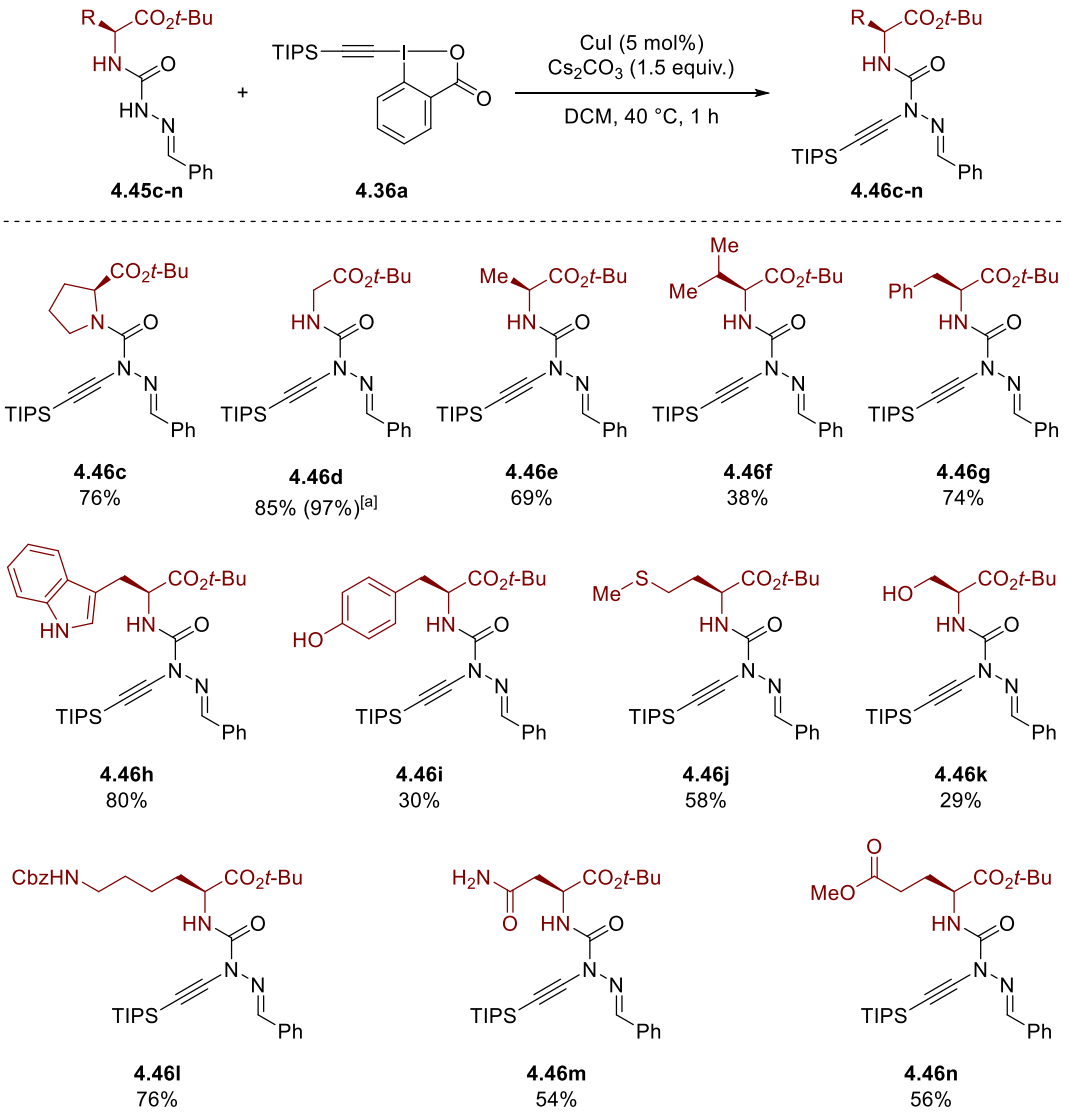
4.45h and **4.45i** could be synthesized in moderate to good yields. Semicarbazones derived from methionine (**4.45j**) and serine (**4.45k**) were obtained in 56% and 69% yield respectively. Azapeptides containing a nitrogen on the side chains embedded in a carbamate (**4.45l**) or an amide (**4.45m**) could also be accessed in moderate yields. Finally, protected glutamic acid containing semicarbazone **4.45n** was synthesized in 61% yield.



Scheme 4.19. Synthesis of semicarbazones **4.45c-n**.

With the azapeptide derivatives in hand, we investigated the scope of the transformation, which was performed on a 0.3 mmol scale (Scheme 4.20). The model substrate **4.45c** afforded alkynylated product **4.46c** in 76% yield similar to the result obtained on optimization scale (0.05 mmol). Glycine derived semicarbazone **4.45d** worked well in the transformation leading to **4.46d** in 85% yield on scope scale and 97% yield on a 1 mmol scale. Aliphatic side chains were tolerated under the reaction conditions, although a lower yield was obtained for **4.45f** containing a bulkier isopropyl group compared to **4.45e** bearing a methyl on the side-chain. Semicarbazones **4.45g** and **4.45h** afforded the corresponding alkynylated

products **4.46g** and **4.46h** bearing aromatic groups on the side chains in, respectively, 74% and 80% yield. Unfortunately, alkynylated azapeptide derivative **4.46i** was obtained only in 30% yield probably due to the presence of the free hydroxyl group from the tyrosine. Methionine containing semicarbazone **4.45j** led to **4.46j** in 58% with no side reactivity observed between the sulfide and EBX reagent **4.36a**.[69] An alcohol on the side chain of serine containing azapeptide derivative **4.45k** was tolerated and the corresponding alkynylated product **4.46k** was isolated in 29% yield. On the other hand, protected nitrogen on the side chains were well tolerated with **4.45l** and **4.45m** affording the alkynylated semicarbazones **4.46l** and **4.46m** in 76% and 54% yield respectively. Finally, protected glutamic acid derived alkynylated product **4.46n** could be accessed in 56% yield.

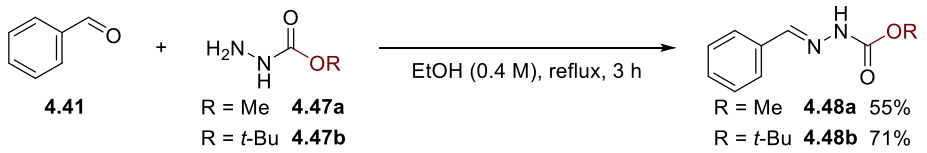


[a] reaction performed on 1 mmol scale.

Scheme 4.20. Scope of amino acids on a 0.3 mmol scale.

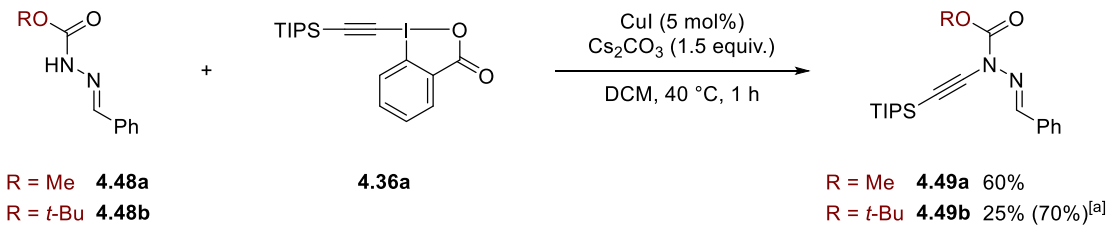
[69] J. Borrel, G. Pisella, J. Waser, *Org. Lett.* **2020**, *22*, 422–427.

We then wondered if the developed procedure would also work on simple azaglycine derivatives. For this purpose, we synthesized semicarbazones **4.48a** and **4.48b** *via* the condensation of methyl (**4.47a**) or *tert*-butylcarbazate (**4.47b**) onto benzaldehyde (**4.41**) (Scheme 4.21).[70]



Scheme 4.21. Synthesis of azaglycine derivatives **4.48a** and **4.48b**.

Using the previously developed conditions, semicarbazone **4.48a** was efficiently alkynylated and product **4.49a** was obtained in 60% yield (Scheme 4.22). On the other hand, **4.49b** was only obtained in 25% yield with CuI. Using the conditions developed for tosyl hydrazone **4.35** (Table 4.1), with $Cu(CH_3CN)_4BF_4$, higher yield could be reached.



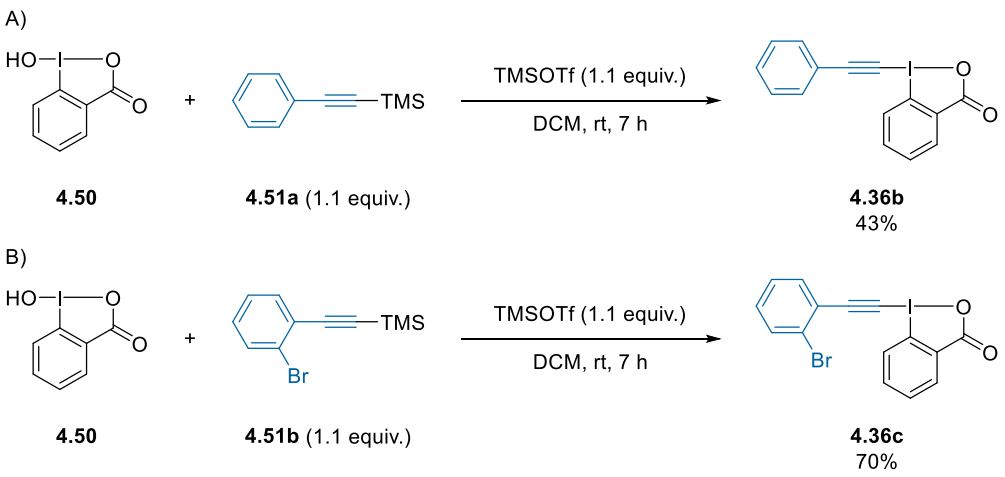
[a] $Cu(CH_3CN)_4BF_4$ (5 mol%)

Scheme 4.22. Alkynylation of azaglycine derivatives **4.48a** and **4.48b** on a 0.3 mmol scale.

4.3.2.2. Scope of EBX reagents

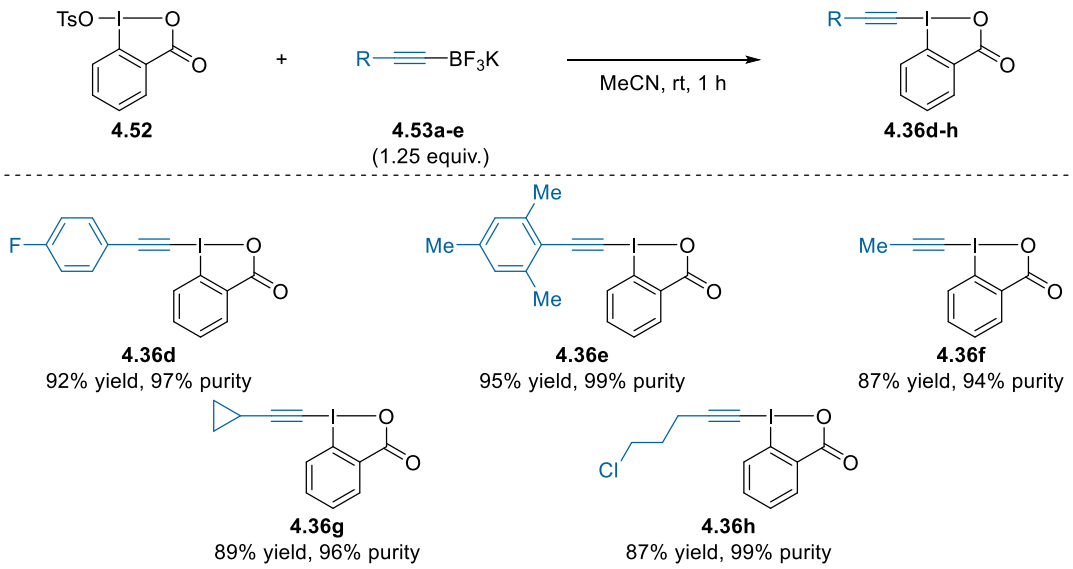
For the investigation of the scope of EBX reagents, Ph-EBX (**4.36b**) was synthesized following an established procedure starting from HO-BX (**4.50**) and TMS substituted phenyl acetylene (**4.51a**) and obtained in 43% yield (Scheme 4.23.A).[71] Following the same strategy, reagent **4.36c** bearing a bromine in *ortho* position could be accessed in 70% yield (B).[72]

[70] M. S. Santos, A. Nortcliffe, W. Lewis, T. D. Bradshaw, C. J. Moody, *Chem. Eur. J.* **2018**, *24*, 8325–8330.
[71] S. G. E. Amos, D. Cavalli, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 23827–23834.
[72] T. Nguyen is acknowledged for providing **4.36c**.



Scheme 4.23. Synthesis of EBX **4.36b** and **4.36c**.

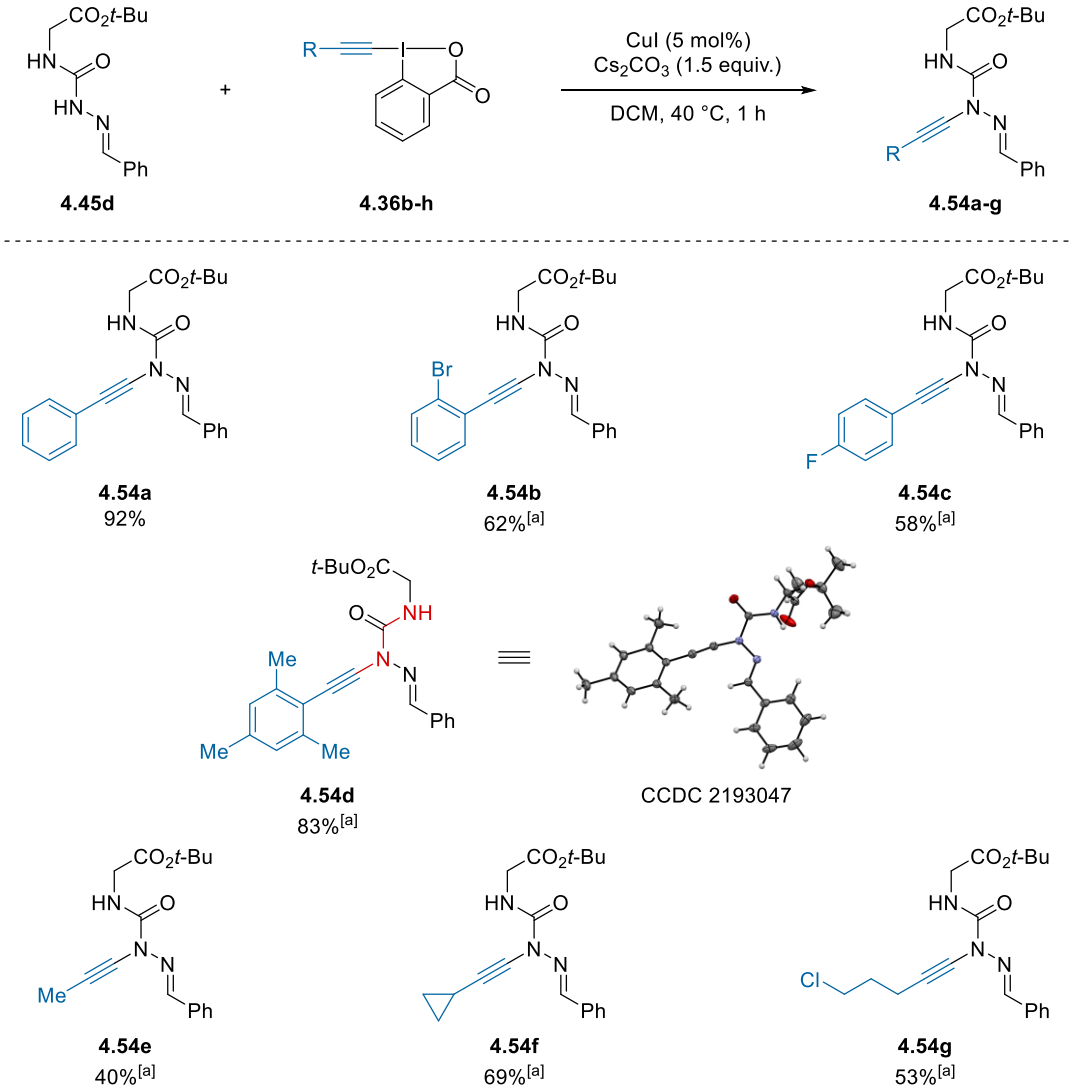
The following EBX reagents were synthesized by Julien Borrel using the procedure he recently developed in our group (Scheme 4.24).[73] As described in the previous chapter (see section 3.1.3), various EBX reagents could be obtained in one hour from readily available TsOBX (**4.52**) and alkynyl trifluoroborates (**4.53a-e**) without the addition of additives and no purification was required. Two different aryl-EBX reagents could be obtained in excellent yields and purities (determined by ^{1}H NMR) with either a fluorine in *para*-position (**4.36d**) or as a mesityl (**4.36e**). Alkyl-EBX could also be synthesized, albeit with a slightly lower yield. For instance, **4.36f** bearing a methyl group, **4.36g** bearing a cyclopropyl group and **4.36h** bearing a chloropropyl group were formed in, respectively, 87%, 89% and 87% yield with purity higher than 94%.



Scheme 4.24. Synthesis of reagents **4.36d-h**.

[73] J. Borrel, J. Waser, *Org Lett* **2022**, *24*, 142–146.

Having various EBX reagents in hand, we moved on to explore the scope of the reaction using azadipeptide derivative **4.45d** as model substrate (Scheme 4.25). Ph-EBX was well tolerated in the transformation leading to alkynylated product **4.54a** in 92% yield. Aryl acetylene bearing electron-withdrawing groups could be transferred to **4.45d**. Products **4.54b** bearing a bromine in *ortho* position and **4.54c** with a fluorine in *para* position were obtained respectively in 62% and 58% yield. Mesityl containing EBX **4.36e** afforded product **4.54d** in 83% yield. The structure of **4.54d** was confirmed by single crystal X-ray diffraction and exhibited, in the solid state, a *trans*-amide geometry. Alkyl acetylenes could also be transferred to semicarbazone **4.45d** and compounds bearing a methyl (**4.54e**), a cyclopropyl (**4.54f**) and a chloropropyl group (**4.54g**) were obtained in moderate to good yields.



[a] Reaction performed by Julien Borrel.

Scheme 4.25. Scope of EBX reagents on a 0.3 mmol scale.

4.3.2.3. Limitations

During the scope of amino acids, all the semicarbazones tested afforded the desired alkynylated product in moderate to good yields. However, during the scope of EBX reagents we encountered some limitations (Figure 4.3).[74] When using regents bearing a nitro (**4.36i**) or a methyl ester group (**4.36j**) in *para* position the corresponding alkynylated products could be obtained only in less than 10% yield. Similarly, alkyl reagents bearing a free hydroxyl (**4.36k**) or an azide group (**4.36l**) were not suitable alkynyl transfer reagents in this transformation. Full conversion of the EBX reagents and poor conversion of semicarbazone **4.45d** was observed, which suggested that those reagents were not stable under the reaction conditions.

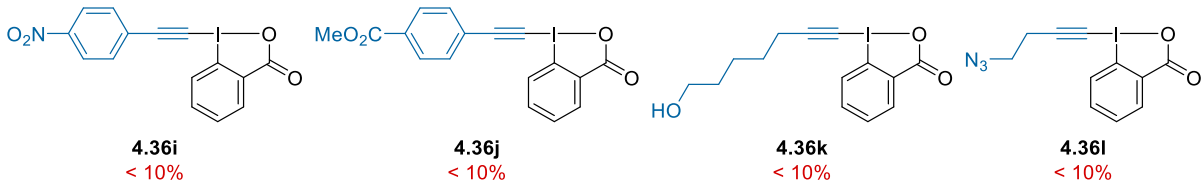
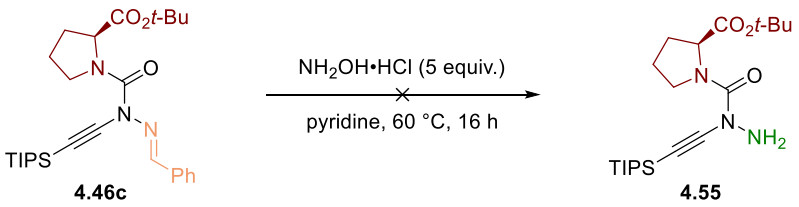


Figure 4.3. Unsuccessful substrates.

4.3.3. Product Modifications

4.3.3.1. Semicarbazone deprotection

As first product modification, we studied the deprotection of the semicarbazone **4.46c** using hydroxylamine hydrochloride in pyridine (Scheme 4.26).[75] Unfortunately, poor conversion of the starting material was observed and the desired compound **4.55** was not detected in the crude mixture.



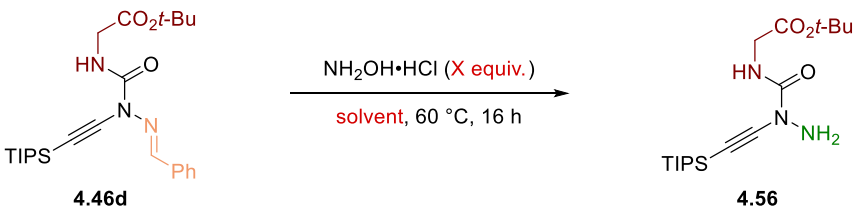
Scheme 4.26. Unsuccessful attempt to deprotect the semicarbazone **4.46c**.

For ease of analysis, we moved to study the deprotection of semicarbazone **4.46d** having a more defined ^{1}H-NMR spectrum (Table 4.4). Using the same conditions as previously mentioned did not lead to the formation of **4.56** and almost no conversion of starting material was observed (entry 1). Increasing the amount of hydroxylamine hydrochloride to 30

[74] J. Borrel and N. Declas are acknowledged for providing EBX **4.37i-l**.
[75] C. B. Bourguet, P.-L. Boulay, A. Claing, W. D. Lubell, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3361–3365.

equivalents had no effect on the reaction and most of **4.46d** could be recovered at the end of the reaction (entry 2). We wondered if pyridine was a suitable solvent for the deprotection of our substrate and tested different solvent systems. Using an ethanol/water 10:1 mixture full conversion of the semicarbazone **4.46d** was observed but only a complex mixture was obtained at the end of the reaction (entry 3). Finally, no conversion was observed with the solvent system ethyl acetate/water 4:1 (entry 4).[76]

Table 4.4. Deprotection attempts on semicarbazone **4.46d**.[a]

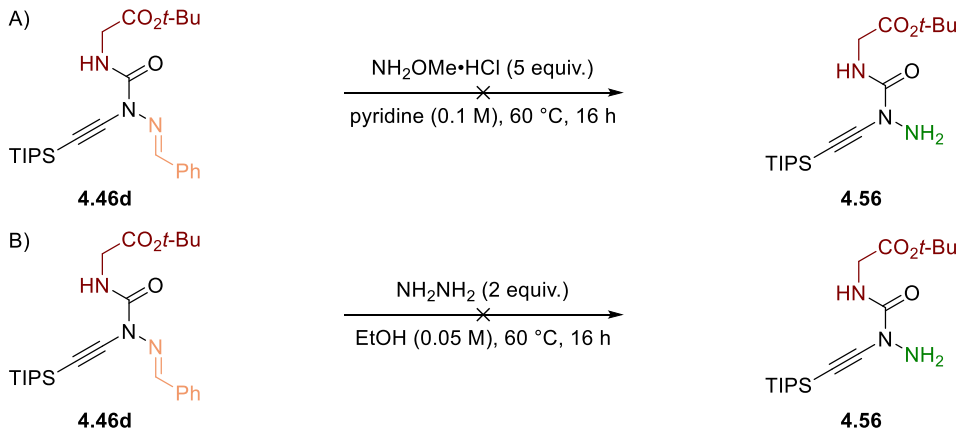


Entry	Solvent	X equiv.	4.56
1	pyridine (0.05 M)	5 equiv.	NR
2	pyridine (0.05 M)	30 equiv.	NR
3	EtOH/H_2O 10:1 (0.05 M)	5 equiv.	complex mixture
4	EtOAc/H_2O 4:1 (0.10 M)	5 equiv.	NR

[a] Reaction conditions: **4.46d** (0.05 mmol), $NH_2OH{\cdot}HCl$ (X equiv.) in indicated solvent at 60 °C overnight.

Hydroxylamine hydrochloride being ineffective for the deprotection of our substrate, we decided to investigate other deprotection methods for semicarbazones (Scheme 4.27). First, we tried to deprotect compound **4.46d** using more nucleophilic methoxamine hydrochloride but no reaction was observed (A).[77] When attempting to deprotect **4.46d** with hydrazine, the starting material was fully consumed but only a complex mixture was obtained and the desired product **4.56** was not detected (B).[78]

[76] U. Huynh, Md. N. Uddin, S. E. Wengryniuk, S. L. McDonald, D. M. Coltart, *Tetrahedron Lett.* **2016**, *57*, 4799–4802.
[77] Y. Shen, G. K. Friestad, *J. Org. Chem.* **2002**, *67*, 6236–6239.
[78] A. Aboelmagd, E. M. S. Salem, I. A. I. Ali, M. S. Gomaa, *Arkivoc* **2019**, *2019*, 27–42.

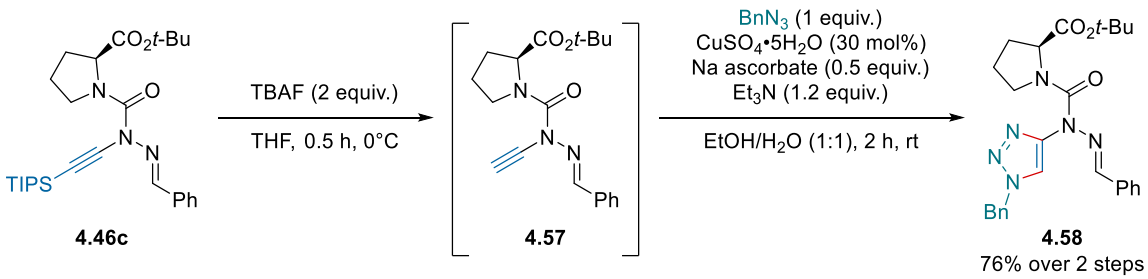


Scheme 4.27. Other deprotection attempts on semicarbazone **4.46d**.

The presence of a TIPS and a *tert*-butyl group on the molecule might shield the hydrazone part of the molecule and hamper the deprotection of compounds **4.46c** or **4.46d**. Therefore, we decided to investigate the deprotection of the silylated alkyne prior to the removal of the hydrazone part.

4.3.3.2. TIPS-alkyne Deprotection

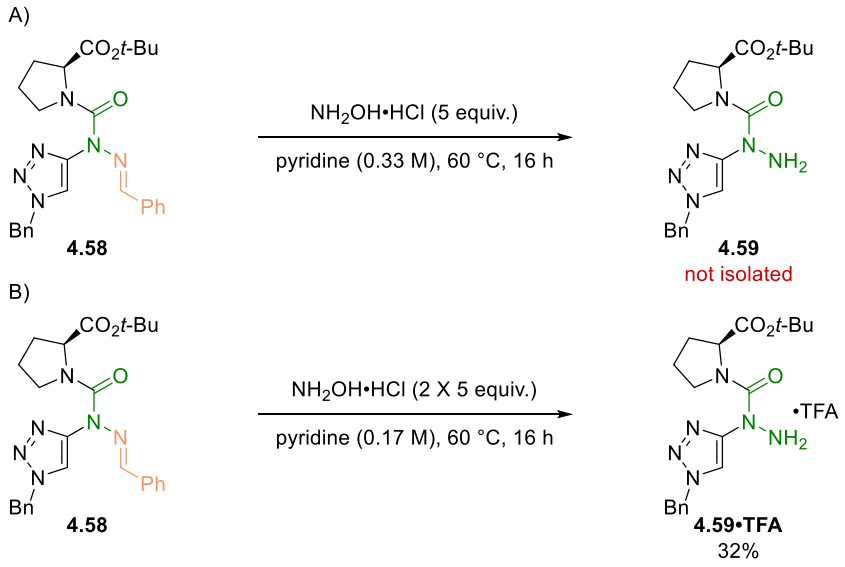
Deprotection of the silylated alkyne in compound **4.46c** was first investigated as the presence of a nucleophilic nitrogen in **4.46d** could induce cyclization side-reactions (Scheme 4.28). Two equivalents of tetrabutyl ammonium fluoride led to the full conversion of **4.46c** to **4.57** as determined by ^{1}H-NMR.[49] However, the free alkyne **4.57** could not be isolated due to degradation while attempting to purify it. We then decided to telescope the deprotection of the silylated alkyne with a Huisgen [3+2] cycloaddition to afford **4.58**. At the end of the silyl removal step, an aqueous work-up was performed quickly to remove the unreacted TBAF. To the crude mixture, a copper sulfate catalyst, sodium ascorbate as a ligand, triethylamine and benzyl azide were added.[79] After two hours at room temperature, triazole containing compound **4.58** could be isolated in 76% yield over two steps.



Scheme 4.28. TBAF deprotection followed by Click chemistry on **4.46c**.

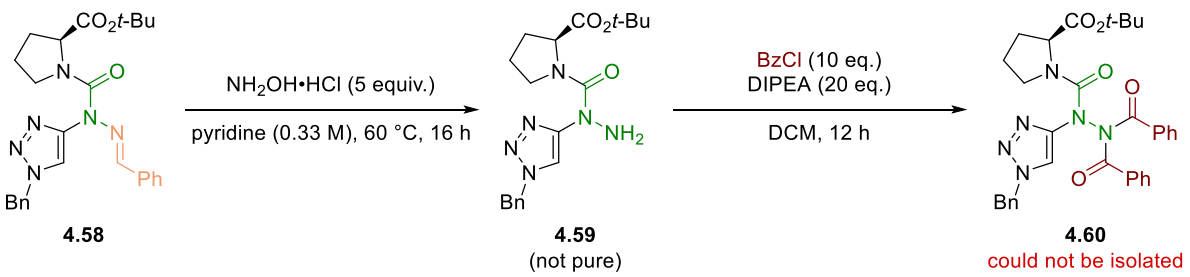
[79] H. Erhardt, F. Mohr, S. F. Kirsch, *Chem. Commun.* **2016**, *52*, 545–548.

Having compound **4.58** in hand, we wondered if the semicarbazone could be deprotected now that the TIPS substituent was removed from the molecule (Scheme 4.29). Using a 1.5 M solution of hydroxylamine hydrochloride in pyridine, we could detect the formation of the deprotected hydrazide **4.59** by ^{1}H NMR (A). However, the compound could never be isolated pure using standard silica-based purification techniques. In order to push the reaction to completion, Julien Borrel added sequentially twice a 1.5 M solution of hydroxylamine hydrochloride in pyridine and let the reaction stirred overnight at 60 °C. The crude mixture was concentrated and purified by reverse-phase HPLC which allowed to isolate the free hydrazide **4.59** as a TFA salt in 32% yield (B).



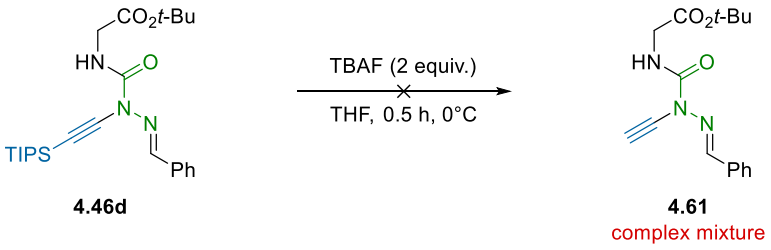
Scheme 4.29. Deprotection of semicarbazone **4.58**.

Before discovering that the free hydrazide **4.59** needed to be purified by RP-HPLC, we attempted to trap it with benzoyl chloride (Scheme 4.30). The deprotection was attempted with hydroxylamine hydrochloride in pyridine, the crude mixture was concentrated under reduced pressure and then used in the next step. ^{1}H NMR and mass spectrometry confirmed the formation of the desired diacylated product **4.60**. However, it could not be isolated using standard silica-based techniques.



Scheme 4.30. *In-situ* trapping attempt of free hydrazide **4.59** with BzCl.

After showing that the alkyne in proline derived semicarbazone **4.46c** could be deprotected using TBAF, we wondered if the same could be done on the glycine derived semicarbazone **4.46d** (Scheme 4.31). However, a complex mixture was obtained and the desired free ynehydrazide **4.61** could not be clearly identified in the crude mixture. This result seemed to confirm our initial assumption that the presence of a nucleophilic nitrogen on the molecule might induce side-reactions with the free alkyne if formed.



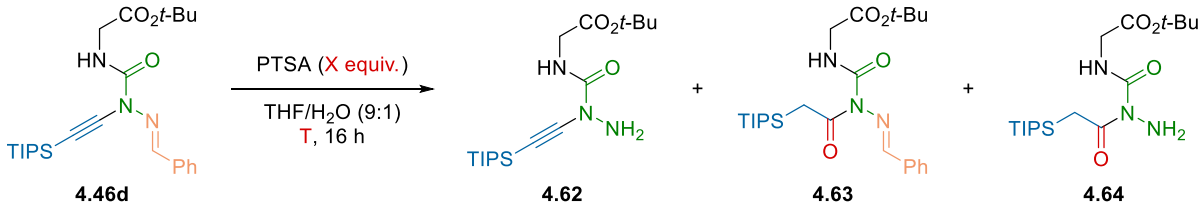
Scheme 4.31. TBAF deprotection of **4.46d**.

4.3.3.3. Ynehydrazide Hydration

While attempting to deprotect semicarbazone **4.46d** under acidic conditions, we observed the hydration of the alkyne moiety and decided to investigate the transformation (Table 4.5). Treatment of compound **4.46d** with 7 equivalents of PTSA at room temperature overnight did not provide the targeted product **4.62** (entry 1). However, from the crude mixture we could isolate hydrated product **4.63** in 42% yield and hydrated-deprotected product **4.64** could be obtained but not as a pure product. To the best of our knowledge, compound **4.63** represents the first example of acylation of azaglycine derivative. For instance, it has been reported that chloroacetyl chloride reacted preferentially with the hydrazone C=N bond to form azetidinones.[80] Julien Borrel could reproduce the results and screened additional conditions. Lowering the stoichiometry of PTSA resulted in a diminished yield for **4.63** and **4.64** (entry 2). Similarly, increasing the temperature proved detrimental for the formation of **4.63**, although **4.64** was formed in similar yields as at room temperature (entry 3).

[80] Selected examples: (a) A. Rajasekaran, K. S. Devi, *Med. Chem. Res.* **2013**, *22*, 2578–2588. (b) S. Jamal Gilani, Mohd. Zaheen Hassan, S. Sarim Imam, C. Kala, S. Prakash Dixit, *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1825–1830.

Table 4.5. Hydration of ynehydrazide **4.46d**.[a]

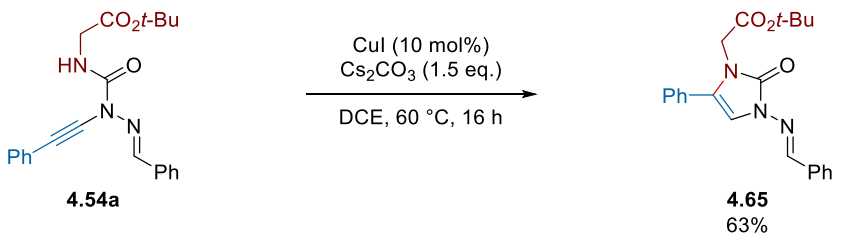


Entry	Temperature	X equiv.	4.62	4.63	4.64
1	rt	7 equiv.	-	42%	<19%
2[b]	rt	2 equiv.	-	13%	<5%
3[b]	50 °C	7 equiv.	-	12%	<19%

[a] Reaction conditions: **4.46d** (0.05 mmol), PTSA (X equiv.) in THF/H_2O (9:1, 0.05 M) at the indicated temperature overnight. Isolated yield after preparative TLC is given. [b] performed by Julien Borrel.

4.3.3.4. 5-endo-dig Cyclization

During the investigation of the scope of the transformation with EBX reagents (Scheme 4.25), traces amount of 5-endo-dig cyclization product could be observed in some cases. Julien Borrel could show that under the alkynylation reaction conditions but at higher temperature (60 °C) alkynylated product **4.54a** could be cleanly converted to the *N*-amino-imidazolin-2-one compound **4.65** in 63% yield (Scheme 4.32). The incorporation of this type of scaffolds in peptide mimics has been reported to favor β-turn conformations.[81]

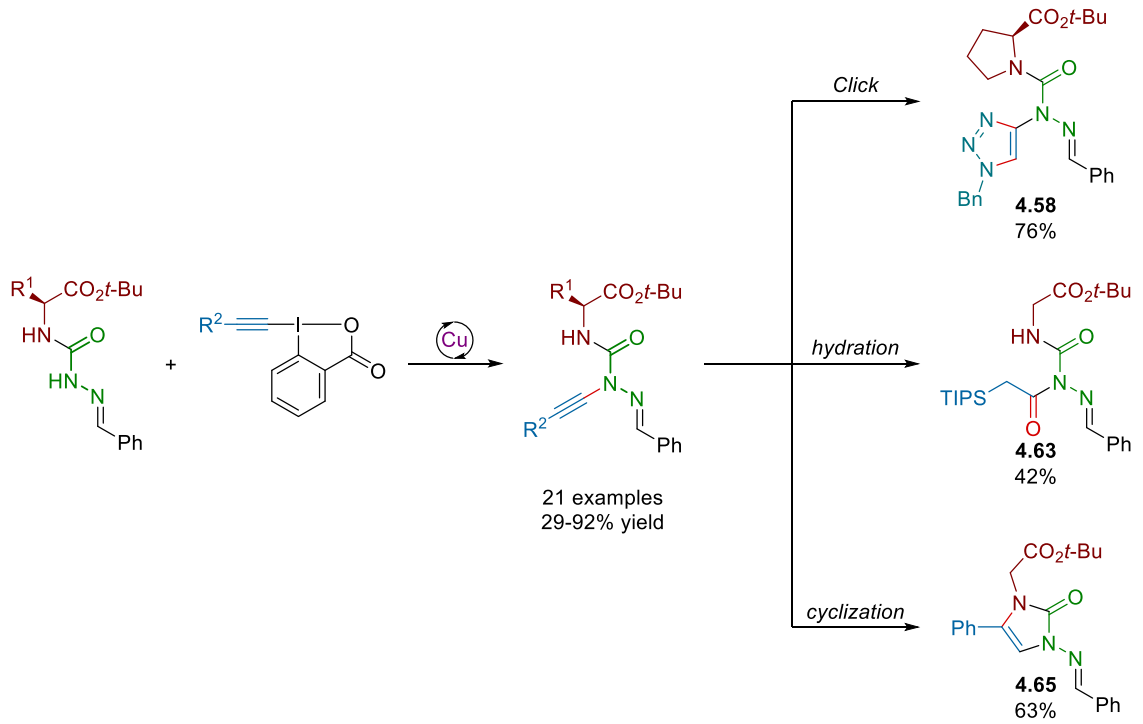


Scheme 4.32. 5-endo-dig cyclization of **4.54a**.

[81] C. Proulx, W. D. Lubell, *Org. Lett.* **2012**, *14*, 4552–4555.

4.4. Conclusions and Perspectives

To conclude, we have developed an efficient copper-catalyzed alkynylation of azadipeptide derivatives using EBX reagents (Scheme 4.33).[82] This methodology allowed to access non-symmetrical ynehydrazides in moderate to excellent yields using semicarbazones as nucleophiles. Most functional groups naturally occurring in amino acids were tolerated in the transformation and silyl, alkyl and aryl substituted alkynes could be transferred onto hydrazide nucleophiles. The obtained alkynylated azadipeptide derivatives could be further functionalized by taking advantage of the reactivity of the installed alkynes.



Scheme 4.33. Summary of the project on the copper-catalyzed alkynylation of azadipeptide derivatives with EBX reagents.

The extension of this strategy to semicarbazones on solid support would be highly valuable to access larger functionalized azapeptides. Moreover, it would facilitate the incorporation of amino acids bearing functional groups that could not be tested in this project due to the difficulty to prepare the corresponding semicarbazones in solution.

[82] E. Le Du, J. Borrel, J. Waser, *Org. Lett.* **2022**, *24*, 6614–6618.

4.5. References

1. H. Zaugg, L. Swett, G. Stone, *J. Org. Chem.* **1958**, *23*, 1389–1390.
2. V. Wolf, F. Kowitz, *Justus Liebigs Ann. Chem.* **1960**, *638*, 33–42.
3. H. G. Viehe, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 477–477.
4. For review: (a) H. G. Viehe, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 767–778. (b) J. Ficini, *Tetrahedron* **1976**, *32*, 1449–1486. (c) C. A. Zificsak, J. A. Mulder, R. P. Hsung, C. Rameshkumar, L.-L. Wei, *Tetrahedron* **2001**, *57*, 7575–7606. (d) A. R. Katritzky, R. Jiang, S. K. Singh, *Heterocycles* **2004**, *63*, 1455-1475.
5. Z. Janousek, J. Collard, H. G. Viehe, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 917–918.
6. For recent review: (a) G. Evano, A. Coste, K. Jouvin, *Angew. Chem. Int. Ed.* **2010**, *49*, 2840–2859. (b) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2010**, *110*, 5064–5106. (c) G. Evano, K. Jouvin, A. Coste, *Synthesis* **2012**, *45*, 17–26. (d) A. M. Cook, C. Wolf, *Tetrahedron Lett.* **2015**, *56*, 2377–2392. (e) G. Evano, N. Blanchard, G. Compain, A. Coste, C. S. Demmer, W. Gati, C. Guissart, J. Heimburger, N. Henry, K. Jouvin, G. Karthikeyan, A. Laouiti, M. Lecomte, A. Martin-Mingot, B. Métayer, B. Michelet, A. Nitelet, C. Theunissen, S. Thibaudeau, J. Wang, M. Zarca, C. Zhang, *Chem. Lett.* **2016**, *45*, 574–585.
7. (a) G. Duret, V. Le Fouler, P. Bisseret, V. Bizet, N. Blanchard, *Eur. J. Org. Chem.* **2017**, *2017*, 6816–6830. (b) F.-L. Hong, L.-W. Ye, *Acc. Chem. Res.* **2020**, *53*, 2003–2019.
8. For electrophilic reactivity: (a) G. Evano, M. Lecomte, P. Thilmany, C. Theunissen, *Synthesis* **2017**, *49*, 3183–3214. (b) Y.-B. Chen, P.-C. Qian, L.-W. Ye, *Chem. Soc. Rev.* **2020**, *49*, 8897–8909. For nucleophilic reactivity: G. Evano, B. Michelet, C. Zhang, *Comptes Rendus Chim.* **2017**, *20*, 648–664.
9. C. Mahe, K. Cariou, *Adv. Synth. Catal.* **2020**, *362*, 4820–4832.
10. L.-L. Wei, J. A. Mulder, H. Xiong, C. A. Zificsak, C. J. Douglas, R. P. Hsung, *Tetrahedron* **2001**, *57*, 459–466.
11. Selected examples: (a) D. Brückner, *Synlett* **2000**, *2000*, 1402–1404. (b) D. Rodríguez, L. Castedo, C. Saá, *Synlett* **2004**, 783–786. (c) S. Couty, M. Barbazanges, C. Meyer, J. Cossy, *Synlett* **2005**, *2005*, 905–910. (d) D. Brückner, *Tetrahedron* **2006**, 3809–3814. (e) M. F. Martínez-Esperón, D. Rodríguez, L. Castedo, C. Saá, *Tetrahedron* **2006**, 3843–3855. (f) D. Rodríguez, M. Martínez-Esperón, L. Castedo, C. Saá, *Synlett* **2007**, *2007*, 1963–1965.
12. Selected examples: (a) A. Coste, G. Karthikeyan, F. Couty, G. Evano, *Angew. Chem. Int. Ed.* **2009**, *48*, 4381–4385. (b) A. Coste, F. Couty, G. Evano, *Org. Lett.* **2009**, *11*, 4454–4457. (c) K. Jouvin, A. Coste, A. Bayle, F. Legrand, G. Karthikeyan, K. Tadiparthi, G. Evano, *Organometallics* **2012**, *31*, 7933–7947.
13. Selected examples: (a) S. J. Mansfield, C. D. Campbell, M. W. Jones, E. A. Anderson, *Chem. Commun.* **2015**, *51*, 3316–3319. (b) S. J. Mansfield, R. C. Smith, J. R. J. Yong, O. L. Garry, E. A. Anderson, *Org. Lett.* **2019**, *21*, 2918–2922.
14. H. Zaugg, L. Swett, G. Stone, *J. Org. Chem.* **1958**, *23*, 1389–1390.
15. (a) J. P. Galy, J. Elguero, E. J. Vincent, A. M. Galy, J. Barbe, *Synthesis* **1979**, *1979*, 944–946. (b) A. Mahamoud, J. P. Galy, E. J. Vincent, J. Barbe, *Synthesis* **1981**, *1981*, 917–918. (c) A. R. Katritzky, W. H. Ramer, *J. Org. Chem.* **1985**, *50*, 852–856.
16. J. Huang, H. Xiong, R. P. Hsung, C. Rameshkumar, J. A. Mulder, T. P. Grebe, *Org Lett* **2002**, *4*, 2417–2420.
17. G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054–3131.
18. (a) M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, J. Huang, K. C. M. Kurtz, L. Shen, C. J. Douglas, *J. Am. Chem. Soc.* **2003**, *125*, 2368–2369.
19. J. R. Dunetz, R. L. Danheiser, *Org. Lett.* **2003**, *5*, 4011–4014.
20. Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* **2004**, *6*, 1151–1154.
21. (a) L. I. Peterson, E. C. Britton, *Tetrahedron Lett.* **1968**, *9*, 5357–5360. (b) A. Balsamo, B. Macchia, F. Macchia, A. Rossello, P. Domiano, *Tetrahedron Lett.* **1985**, *26*, 4141–4144.
22. T. Hamada, X. Ye, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 833–835.

23. W. Jia, N. Jiao, *Org. Lett.* **2010**, *12*, 2000–2003.
24. K. Jouvin, F. Couty, G. Evano, *Org. Lett.* **2010**, *12*, 3272–3275.
25. T. Sueda, A. Oshima, N. Teno, *Org. Lett.* **2011**, *13*, 3996–3999.
26. K. Jouvin, J. Heimburger, G. Evano, *Chem Sci* **2012**, *3*, 756–760.
27. P. Murch, B. L. Williamson, P. J. Stang, *Synthesis* **1994**, *1994*, 1255–1256.
28. K. S. Feldman, M. M. Bruendl, K. Schildknegt, A. C. Bohnstedt, *J. Org. Chem.* **1996**, *61*, 5440–5452.
29. B. Witulski, T. Stengel, *Angew. Chem. Int. Ed.* **1998**, *37*, 489–492.
30. Selected examples: (a) J. D. Rainier, J. E. Imbriglio, *Org. Lett.* **1999**, *1*, 2037–2039. (b) B. Witulski, T. Stengel, *Angew. Chem. Int. Ed.* **1999**, *38*, 2426–2430. (c) J. D. Rainier, J. E. Imbriglio, *J. Org. Chem.* **2000**, *65*, 7272–7276. (d) B. Witulski, M. Gößmann, *Synlett* **2000**, *2000*, 1793–1797. (e) B. Witulski, C. Alayrac, *Angew. Chem. Int. Ed.* **2002**, *41*, 3281–3284.
31. B. Witulski, M. Gößmann, *Chem. Commun.* **1999**, 1879–1880.
32. J. A. Souto, P. Becker, Á. Iglesias, K. Muñiz, *J. Am. Chem. Soc.* **2012**, *134*, 15505–15511.
33. T. Aubineau, J. Cossy, *Chem. Commun.* **2013**, *49*, 3303–3305.
34. Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2014**, *16*, 3138–3141.
35. M. Yudasaka, D. Shimbo, T. Maruyama, N. Tada, A. Itoh, *Org. Lett.* **2019**, *21*, 1098–1102.
36. R. Takai, D. Shimbo, N. Tada, A. Itoh, *J. Org. Chem.* **2021**, *86*, 4699–4713.
37. E. W. Schmidt, Hydrazine and Its Derivatives: Preparation, Properties, Applications, 2nd ed.; John Wiley & Sons: New York, **2001**.
38. For review: (a) S. Rollas, S. Küçükgüzel, *Molecules* **2007**, *12*, 1910–1939. (b) Ł. Popiołek, *Med. Chem. Res.* **2017**, *26*, 287–301.
39. M. Sletzinger, J. M. Chemerda, F. W. Bollinger, *J. Med. Chem.* **1963**, *6*, 101–103.
40. C. Vilchèze, W. R. Jacobs, Jr., *Annu. Rev. Microbiol.* **2007**, *61*, 35–50.
41. For review: (a) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911. (b) A. Moulin, M. Bibian, A.-L. Blayo, S. El Habnouni, J. Martinez, J.-A. Fehrentz, *Chem. Rev.* **2010**, *110*, 1809–1827. (c) A. A. Hassan, A. M. Shawky, *J. Heterocycl. Chem.* **2010**, *47*, 745–763.
42. Selected examples: Zn/AcOH (a) Y. Leblanc, R. Zamboni, M. A. Bernstein, *J. Org. Chem.* **1991**, *56*, 1971–1972. Li/NH_3 (b) M. A. Brimble, C. H. Heathcock, *J. Org. Chem.* **1993**, *58*, 5261–5263. H_2/$Pd(OH)_2$ (c) Y. H. Kim, J. Y. Choi, *Tetrahedron Lett.* **1996**, *37*, 5543–5546. Oxidative cleavage (d) R. Fernández, A. Ferrete, J. M. Llera, A. Magriz, E. Martín-Zamora, E. Díez, J. M. Lassaletta, *Chem. Eur. J.* **2004**, *10*, 737–745. SmI_2 (e) H. Ding, G. K. Friestad, *Org. Lett.* **2004**, *6*, 637–640. Raney Ni (f) P. Sinha, C. C. Kofink, P. Knochel, *Org. Lett.* **2006**, *8*, 3741–3744. Photochemical cleavage (g) S. Lebrun, A. Couture, E. Deniau, P. Grandclaudon, *Synlett* **2009**, *2009*, 2621–2624.
43. A. Löffler, G. Himbert, *Synthesis* **1994**, *1994*, 383–386.
44. G. Himbert, H. Naßhan, O. Gerulat, *Synthesis* **1997**, *1997*, 293–294.
45. F. Denonne, P. Seiler, F. Diederich, *Helv. Chim. Acta* **2003**, *86*, 3096–3117.
46. R. E. Beveridge, R. A. Batey, *Org. Lett.* **2012**, *14*, 540–543.
47. R. E. Beveridge, R. A. Batey, *Org. Lett.* **2013**, *15*, 3086–3089.
48. Selected examples: (a) P. R. Walker, C. D. Campbell, A. Suleman, G. Carr, E. A. Anderson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9139–9143. (b) V. Palani, J. Chen, T. R. Hoye, *Org. Lett.* **2016**, *18*, 6312–6315. (c) J. Chen, V. Palani, T. R. Hoye, *J. Am. Chem. Soc.* **2016**, *138*, 4318–4321. (d) R. Diana-Rivero, B. Halsvik, F. García Tellado, D. Tejedor, *Org. Lett.* **2021**, *23*, 4078–4082.
49. J. R. Tuck, R. J. Tombari, N. Yardeny, D. E. Olson, *Org. Lett.* **2021**, *23*, 4305–4310.
50. A. Henninot, J. C. Collins, J. M. Nuss, *J. Med. Chem.* **2018**, *61*, 1382–1414.
51. For reviews: (a) J. Gante, *Synthesis* **1989**, *21*, 405–413. (b) C. Proulx, D. Sabatino, R. Hopewell, J. Spiegel, Y. Garcia-Ramos, W. D. Lubell, *Future Med. Chem.* **2011**, *3*, 1139–1164. (c) R. Chingle, C. Proulx, W. D. Lubell, *Acc. Chem. Res.* **2017**, *50*, 1541–1556. (d) C. Proulx, J. Zhang, D. Sabatino, S. Chemtob, H. Ong, W. D. Lubell, *Biomedicines* **2020**, *8*, 241.

52. (a) R. Stollé, *Berichte Dtsch. Chem. Ges.* **1910**, *43*, 2468–2470. (b) O. Diels, *Berichte Dtsch. Chem. Ges.* **1914**, *47*, 2183–2195. (c) K. Ronco, B. Prijs, H. Erlenmeyer, *Helv. Chim. Acta* **1956**, *39*, 1253–1257. (d) K. Ronco, H. Erlenmeyer, *Helv. Chim. Acta* **1956**, *39*, 1045–1051.
53. H.-J. Hess, W. T. Moreland, G. D. Laubach, *J. Am. Chem. Soc.* **1963**, *85*, 4040–4041.
54. Anand. S. Dutta, M. B. Giles, *J. Chem. Soc., Perkin Trans. 1* **1976**, 244–248.
55. M. Thormann, H.-J. Hofmann, *J. Mol. Struct. (Theochem)* **1999**, *469*, 63–76.
56. (a) Y. Zhang, R. M. Malamakal, D. M. Chenoweth, *J. Am. Chem. Soc.* **2015**, *137*, 12422–12425. (b) Y. Zhang, M. Herling, D. M. Chenoweth, *J. Am. Chem. Soc.* **2016**, *138*, 9751–9754. (c) A. J. Kasznel, Y. Zhang, Y. Hai, D. M. Chenoweth, *J. Am. Chem. Soc.* **2017**, *139*, 9427–9430. (d) K. Baruah, B. Sahariah, S. S. Sakpal, J. K. R. Deka, A. K. Bar, S. Bagchi, B. K. Sarma, *Org. Lett.* **2021**, *23*, 4949–4954.
57. (a) Z. Benatalah, A. Aubry, G. Boussard, M. Marraud, *Int. J. Pept. Protein Res.* **1991**, *38*, 603–605. (b) M. Thormann, H.-J. Hofmann, *J. Mol. Struct. (Theochem)* **1999**, *469*, 63–76. (c) H.-J. Lee, K.-H. Choi, I.-A. Ahn, S. Ro, H. G. Jang, Y.-S. Choi, K.-B. Lee, *J. Mol. Struct.* **2001**, *569*, 43–54. (d) D. Sabatino, C. Proulx, P. Pohankova, H. Ong, W. D. Lubell, *J. Am. Chem. Soc.* **2011**, *133*, 12493–12506.
58. Selected examples: (a) I.-A. Ahn, S. Woong Kim, S. Ro, *Mol. Divers.* **1998**, *4*, 23–24. (b) S. H. L. Verhelst, M. D. Witte, S. Arastu-Kapur, M. Fonovic, M. Bogyo, *ChemBioChem* **2006**, *7*, 943–950. (c) C. J. Gray, M. Quibell, N. Baggett, T. Hammerle, *Int. J. Pept. Protein Res.* **2009**, *40*, 351–362.
59. Selected examples: (a) H. Han, K. D. Janda, *J. Am. Chem. Soc.* **1996**, *118*, 2539–2544. (b) C. Frochot, R. Vanderesse, A. Driou, G. Linden, M. Marraud, M. T. Cung, *Lett. Pept. Sci.* **1997**, *4*, 219–225. (c) C. Gibson, S. L. Goodman, D. Hahn, G. Hölzemann, H. Kessler, *J. Org. Chem.* **1999**, *64*, 7388–7394. (d) E. Wieczerzak, P. Drabik, L. Łankiewicz, S. Ołdziej, Z. Grzonka, M. Abrahamson, A. Grubb, D. Brömme, *J. Med. Chem.* **2002**, *45*, 4202–4211. (e) R. E. Melendez, W. D. Lubell, *J. Am. Chem. Soc.* **2004**, *126*, 6759–6764.
60. D. Sabatino, C. Proulx, S. Klocek, C. B. Bourguet, D. Boeglin, H. Ong, W. D. Lubell, *Org. Lett.* **2009**, *11*, 3650–3653.
61. (a) Y. Garcia-Ramos, W. D. Lubell, *J. Pept. Sci.* **2013**, *19*, 725–729. (b) (b) M. Bowles, C. Proulx, in *Methods Enzymol.*, Elsevier, **2021**, pp. 169–190.
62. Selected examples: (a) N.-D. Doan, R. Hopewell, W. D. Lubell, *Org. Lett.* **2014**, *16*, 2232–2235. (b) J. Zhang, C. Proulx, A. Tomberg, W. D. Lubell, *Org. Lett.* **2014**, *16*, 298–301. (c) M. Traoré, M. Gignac, N.-D. Doan, F. Hof, W. D. Lubell, *J. Pept. Sci.* **2017**, *23*, 266–271.
63. C. Proulx, W. D. Lubell, *Org. Lett.* **2010**, *12*, 2916–2919.
64. (a) P. Meffre, F. Le Goffic, *Amino Acids* **1996**, *11*, 313–328. (b) J. Bolsakova, A. Jirgensons, *Eur. J. Org. Chem.* **2016**, *2016*, 4591–4602.
65. W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, 4735–4740.
66. J. Barluenga, P. Moriel, C. Valdés, F. Aznar, *Angew. Chem. Int. Ed.* **2007**, *46*, 5587–5590.
67. For reviews: (a) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236–247. (b) M. Jia, S. Ma, *Angew. Chem. Int. Ed.* **2016**, *55*, 9134–9166. (c) Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* **2017**, *117*, 13810–13889.
68. A. J. Wommack, D. C. Moebius, A. L. Travis, J. S. Kingsbury, *Org. Lett.* **2009**, *11*, 3202–3205.
69. J. Borrel, G. Pisella, J. Waser, *Org. Lett.* **2020**, *22*, 422–427.
70. M. S. Santos, A. Nortcliffe, W. Lewis, T. D. Bradshaw, C. J. Moody, *Chem. Eur. J.* **2018**, *24*, 8325–8330.
71. S. G. E. Amos, D. Cavalli, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 23827–23834.
72. T. Nguyen is acknowledged for the synthesis of **4.37c**.
73. J. Borrel, J. Waser, *Org Lett* **2022**, *24*, 142–146.
74. J. Borrel and N. Declas are acknowledged for providing EBX **4.37i-l**.
75. C. B. Bourguet, P.-L. Boulay, A. Claing, W. D. Lubell, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3361–3365.

76. U. Huynh, Md. N. Uddin, S. E. Wengryniuk, S. L. McDonald, D. M. Coltart, *Tetrahedron Lett.* **2016**, *57*, 4799–4802.
77. Y. Shen, G. K. Friestad, *J. Org. Chem.* **2002**, *67*, 6236–6239.
78. A. Aboelmagd, E. M. S. Salem, I. A. I. Ali, M. S. Gomaa, *Arkivoc* **2019**, *2019*, 27–42.
79. H. Erhardt, F. Mohr, S. F. Kirsch, *Chem. Commun.* **2016**, *52*, 545–548.
80. Selected examples: (a) A. Rajasekaran, K. S. Devi, *Med. Chem. Res.* **2013**, *22*, 2578–2588. (b) S. Jamal Gilani, Mohd. Zaheen Hassan, S. Sarim Imam, C. Kala, S. Prakash Dixit, *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1825–1830.
81. C. Proulx, W. D. Lubell, *Org. Lett.* **2012**, *14*, 4552–4555.
82. E. Le Du, J. Borrel, J. Waser, *Org. Lett.* **2022**, *24*, 6614–6618.

Chapter 5:

Decarboxylative Functionalization of Small Peptides with Hypervalent Iodine Reagents

5. Decarboxylative Functionalization of Small Peptides with Hypervalent Iodine Reagents

The functionalization of peptides has been the focus of intensive research in the last decades due to the growing importance of peptide therapeutics. In this chapter, our efforts and developments towards the decarboxylative functionalization of small peptides using hypervalent iodine reagents will be presented. This strategy provided an easy access to valuable functionalized small peptides and new types of peptide cross-linking. The extension of this strategy to the synthesis of valuable aminal heterocycles will be described as well.

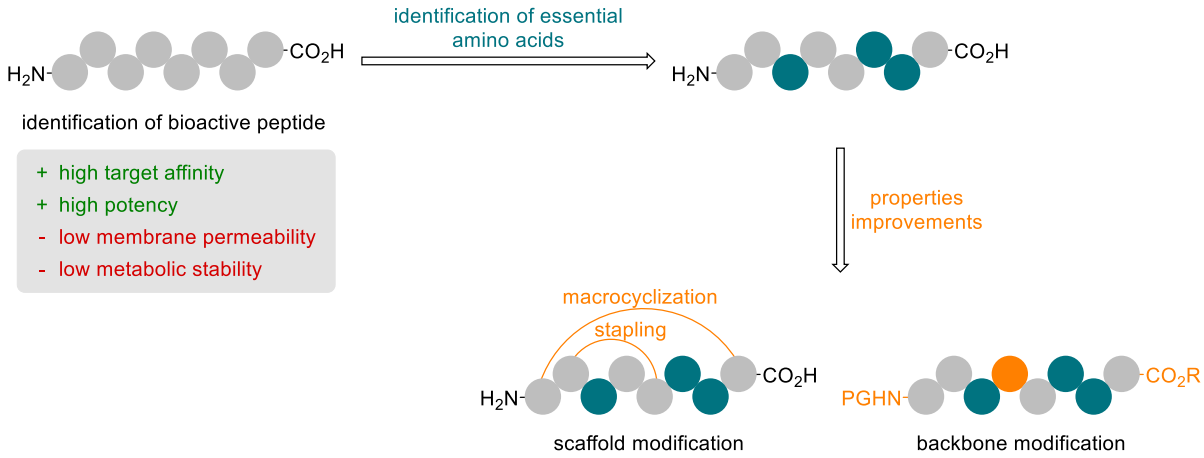
5.1. Introduction

5.1.1. Significance of C-Terminal Bioconjugation

In the last decades, bioactive peptides have received a lot of interest for their potential therapeutic use as they are able to interact with receptors and prevent interaction between proteins of interest.[1] Peptide therapeutics benefit from higher target affinities than small molecules, which is often related to higher potency and lower off-target side-effects. However, they suffer from low membrane permeability and low metabolic stability. In this context, several strategies have been developed to improve the properties of peptides after having identified the amino acids essential for the bioactivity (Scheme 5.1). These strategies can be classified either as modification of the peptide scaffold or modification of the peptide backbone. In order to increase metabolic stability, rigidifying the peptide scaffold has emerged has an efficient strategy. Macrocyclization,[2] or peptide stapling,[3] in which two amino acids on the same side of an α-helix are connected by a linker, have been developed in order to constrain peptide conformations and enhance their stability towards proteases. Alternatively, the backbone of peptides can be modified by incorporating, during their synthesis, unnatural amino acids (UUA) less prone to proteolytic degradation.[1] In addition, the late-stage functionalization of native peptides allows to easily diversify the backbone and introduce small organic

[1] For reviews: (a) K. Fosgerau, T. Hoffmann, *Drug Discov. Today* **2015**, *20*, 122–128. (b) T. Dang, R. D. Süssmuth, *Acc. Chem. Res.* **2017**, *50*, 1566–1576. (c) I. W. Hamley, *Chem. Rev.* **2017**, *117*, 14015–14041. (d) A. Henninot, J. C. Collins, J. M. Nuss, *J. Med. Chem.* **2018**, *61*, 1382–1414.
[2] For reviews: (a) J. S. Davies, *J. Pept. Sci.* **2003**, *9*, 471–501. (b) P. G. Dougherty, A. Sahni, D. Pei, *Chem. Rev.* **2019**, *119*, 10241–10287. (c) V. Sarojini, A. J. Cameron, K. G. Varnava, W. A. Denny, G. Sanjayan, *Chem Rev* **2019**, *119*, 10318–10359.
[3] For reviews: (a) Y. H. Lau, P. de Andrade, Y. Wu, D. R. Spring, *Chem. Soc. Rev.* **2015**, *44*, 91–102. (b) X. Xie, L. Gao, A. Y. Shull, Y. Teng, *Future Med. Chem.* **2016**, *8*, 1969–1980. (c) M. Moiola, M. G. Memeo, P. Quadrelli, *Molecules* **2019**, *24*, 3654.

molecules.[4] The generated bioconjugates could combine the advantages of bioactive peptides with the one of small molecules such as enhanced membrane permeability and metabolic stability.[5]



Scheme 5.1. General strategies for peptide bioactivity improvement.

Despite intensive research in the field, the modification of peptide backbones still suffers from some limitations. For instance, the late-stage functionalization of peptides usually relies on nucleophilic residues, mainly cysteine or lysine, or aromatic residues, such as phenylalanine, tyrosine or tryptophan, which are not always accessible depending on the folding of the peptides.[6] On the other hand, most native peptides possess a carboxylic acid at the C-terminus which is often solvent exposed and plays an important role on the bioactivity of peptides.[7] Although targeting this position would offer a general and selective method for the structural modification of peptides, C-terminus functionalization remains relatively underdeveloped.

Proteinogenic carboxylic acids from the side-chain of aspartic acid and glutamic acid or from the peptide C-terminus have been scarcely studied as handles for functionalization due to the difficulty to differentiate them. Progress in solid-phase peptide synthesis (SPPS) and the introduction of orthogonal protecting groups allowed to develop selective functionalization of either the side-chains or the C-terminus. The transformations, however,

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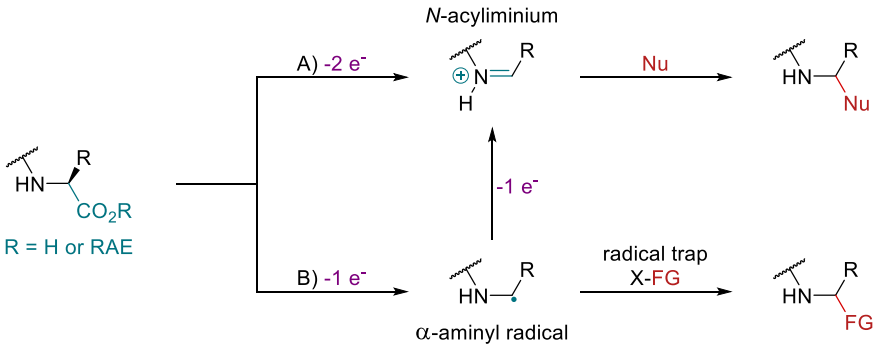
[4] For reviews: (a) D. J. Craik, D. P. Fairlie, S. Liras, D. Price, *Chem. Biol. Drug Des.* **2013**, *81*, 136–147. (b) S.-B. Yang, N. Banik, B. Han, D.-N. Lee, J. Park, *Pharmaceutics* **2022**, *14*, 1378.
[5] For reviews: (a) T. Ueda, *Biochim. Biophys. Acta BBA - Proteins Proteomics* **2014**, *1844*, 2053–2057. (b) P. M. Drake, D. Rabuka, *Curr. Opin. Chem. Biol.* **2015**, *28*, 174–180. For selected example: D. T. Cohen, C. Zhang, C. M. Fadzen, A. J. Mijalis, L. Hie, K. D. Johnson, Z. Shriver, O. Plante, S. J. Miller, S. L. Buchwald, B. L. Pentelute, *Nat. Chem.* **2019**, *11*, 78–85.
[6] J. N. deGruyter, L. R. Malins, P. S. Baran, *Biochemistry* **2017**, *56*, 3863–3873.
[7] For reviews: (a) J.-J. Chung, S. Shikano, Y. Hanyu, M. Li, *Trends Cell Biol.* **2002**, *12*, 146–150. (b) G. Marino, U. Eckhard, C. M. Overall, *ACS Chem. Biol.* **2015**, *10*, 1754–1764. (c) S. Sharma, M. R. Schiller, *Crit. Rev. Biochem. Mol. Biol.* **2019**, *54*, 85–102.

were mostly limited to amidation or esterification.[6,8] The recent developments in decarboxylative couplings on small molecules have led to a surge of interest in the functionalization of peptide carboxylic acids.[9] In the following parts we will focus on decarboxylative couplings applied to peptides. Only selected examples applied to amino acids and relevant to this Thesis will be presented.

5.1.2. Decarboxylative Couplings from Native Peptides and Redox-Active Esters

5.1.2.1. Overview of Decarboxylative Couplings

Decarboxylative coupling has recently emerged as a strategic tool to diversify the C-terminus of native (R = H) or activated peptides (R = redox-active ester (RAE)) (Scheme 5.2).[10] Decarboxylative strategies can be classified in two categories: (A) 2-electron oxidation leading to a *N*-acyliminium that can be trapped by nucleophiles or (B) 1-electron oxidation leading to an α-aminyl radical that can either react with a radical trap or, less common, be further oxidized to form a *N*-acyliminium intermediate.



Scheme 5.2. Overview of decarboxylative coupling strategies from native peptides and RAE.

5.1.2.2. Decarboxylative Couplings via 2-electron Processes

Carboxylic acids are ubiquitous in chemistry, their stability, availability and ease of handling have made them ideal functional groups to develop coupling reactions notably *via* decarboxylation. Building upon seminal works from Faraday and Kolbe on electrochemical oxidative decarboxylation (Scheme 5.3.A),[11] Hofer and Moest reported the first

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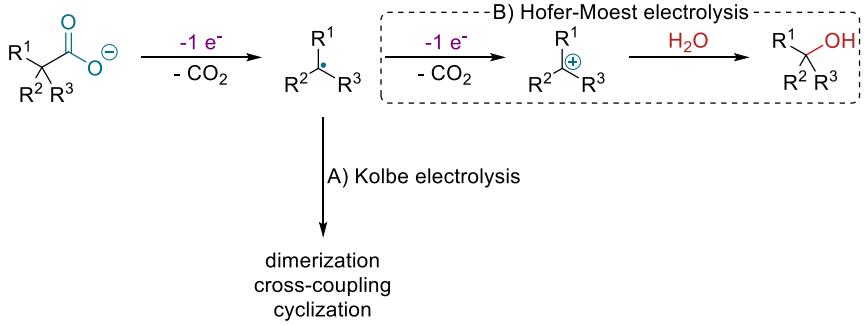
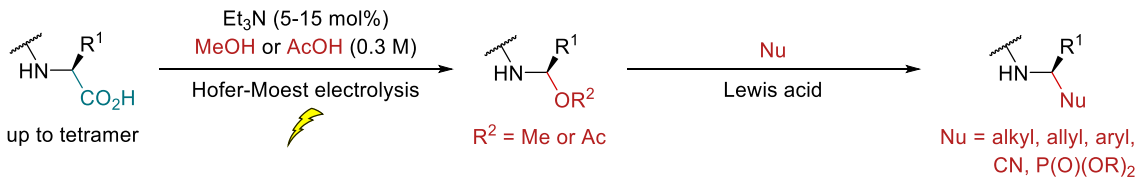
[8] For reviews: (a) J. Alsina, F. Albericio, *Biopolymers* **2003**, *71*, 454–477. (b) E. Baslé, N. Joubert, M. Pucheault, *Chem. Biol.* **2010**, *17*, 213–227.
[9] For reviews on decarboxylative couplings: (a) Z.-L. Wang, *Adv. Synth. Catal.* **2013**, *355*, 2745–2755. (b) T. Patra, D. Maiti, *Chem. Eur. J.* **2017**, *23*, 7382–7401.
[10] L. R. Malins, *Pept. Sci.* **2018**, *110*, e24049.
[11] (a) M. Faraday, *Ann. Phys. Chem.* **1834**, *109*, 433–451. (b) H. Kolbe, *Ann. Chem. Pharm.* **1849**, *69*, 257–294.

decarboxylative coupling of carboxylic acids *via* a 2-electron oxidation leading to alcohols in presence of water (B).[12] The main limitation of this process lies in the required high current densities which reduce the functional group tolerance.[13]



Scheme 5.3. Kolbe and Hofer-Moest electrolyses.

Although the applications of electrochemistry on small organic molecules are rapidly expanding, its application to the modification of peptides remains scarce.[14] Seebach and coworkers pioneered the application of the Hofer-Moest electrolysis to amino acids and small peptides up to tetramers (Scheme 5.4).[15] Electrolysis in presence of methanol or acetic acid led to the formation of *N,O*-acetals, which are masked *N*-acyliminiums.[16] Activation of the *N,O*-acetals using Lewis acids enabled the incorporation of various nucleophiles such as Grignard reagents, allyl silanes, TMSCN or phosphites.



Scheme 5.4. Electrochemical peptide C-terminus diversification.

More recently, the Malins group improved the conditions and could reduce the stoichiometry of the alcohol or carboxylic acid in the first step from use as solvent to 3 equivalents (Scheme 5.5.A). It allowed them to study the ease of formation of the corresponding *N*-acyliminiums depending on the leaving group. They then could incorporate

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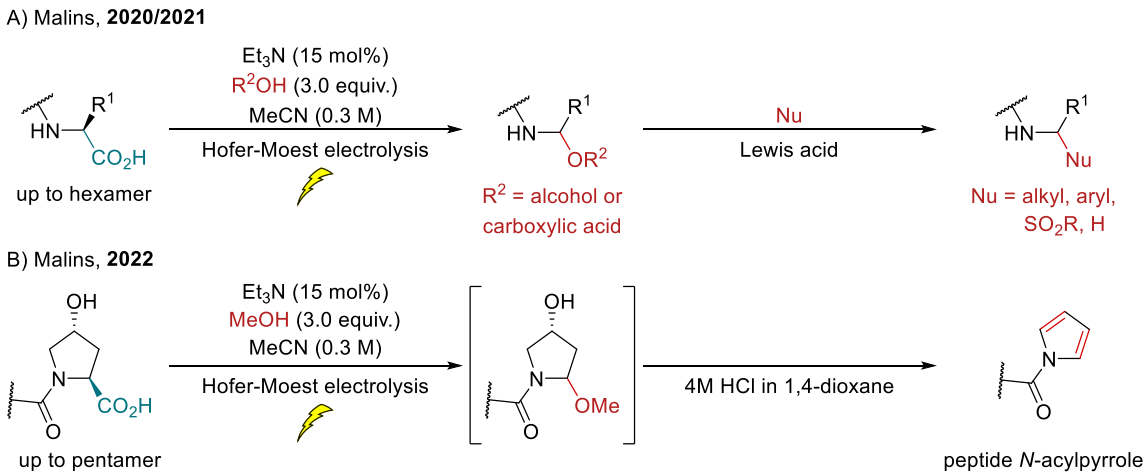
[12] H. Hofer, M. Moest, *Justus Liebigs Ann. Chem.* **1902**, *323*, 284–323.
[13] A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619.
[14] A. S. Mackay, R. J. Payne, L. R. Malins, *J. Am. Chem. Soc.* **2022**, *144*, 23–41.
[15] (a) P. Renaud, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 843–844. (b) D. Seebach, R. Charczuk, C. Gerber, P. Renaud, H. Berner, H. Schneider, *Helv. Chim. Acta* **1989**, *72*, 401–425. (c) C. Gerber, D. Seebach, *Helv. Chim. Acta* **1991**, *74*, 1373–1385.
[16] For reviews on *N*-acyliminiums: (a) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817–3856. (b) M. G. Vinogradov, O. V. Turova, S. G. Zlotin, *Russ. Chem. Rev.* **2017**, *86*, 1–17. (c) P. Wu, T. E. Nielsen, *Chem. Rev.* **2017**, *117*, 7811–7856.

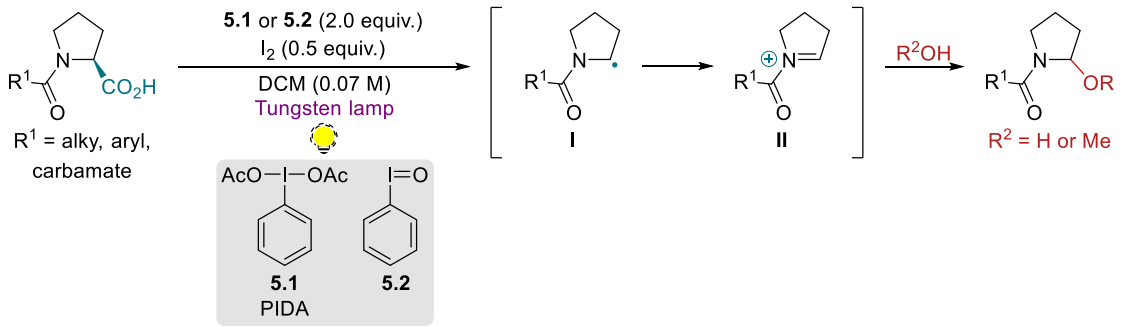
different nucleophiles, in particular they could access natural product analogues using aryls in the Friedel-Crafts step and designer peptide α-amides using silanes.[17] From hydroxyproline containing peptides, they could access peptide C-terminal *N*-acylpyrroles in a one-pot two-step process *via* aromatization of *N,O*-acetals under acidic conditions (Scheme 5.5.B).[18]



Scheme 5.5. Recent applications of the Hofer-Moest electrolysis by the Malins group.

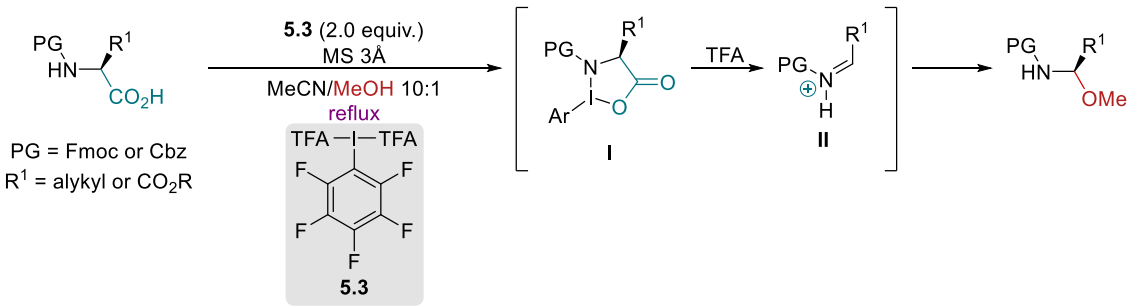
Alternatively, the Suárez group demonstrated that *N,O*-acetals could be formed *via* oxidative decarboxylation using hypervalent iodine oxidants (**5.1** or **5.2**) in presence of elemental iodine and under visible light irradiation (Scheme 5.6).[19] The reaction is presumed to involve two successive 1-electron oxidation steps first generating α-aminyl radical **I** then *N*-acyliminium intermediate **II**. As previously described, the *N,O*-acetals could be activated using $BF_3{\cdot}Et_2O$ as a Lewis acid to introduce allylsilanes and silyl enol ethers. Originally limited to proline, this strategy could be later expanded to the functionalization of various amino acids and small peptides.[20]

[17] (a) Y. Lin, L. R. Malins, *Chem. Sci.* **2020**, *11*, 10752–10758. (b) Y. Lin, L. R. Malins, *J. Am. Chem. Soc.* **2021**, *143*, 11811–11819.
[18] Y. Lin, L. R. Malins, *Synthesis* **2022**, *54*, 3558–3567.
[19] (a) A. Boto, R. Hernández, E. Suárez, *Tetrahedron Lett.* **1999**, *40*, 5945–5948. (b) A. Boto, R. Hernández, E. Suárez, *J. Org. Chem.* **2000**, *65*, 4930–4937.
[20] Selected examples: (a) A. Boto, J. A. Gallardo, R. Hernández, C. J. Saavedra, *Tetrahedron Lett.* **2005**, *46*, 7807–7811. (b) C. J. Saavedra, R. Hernández, A. Boto, E. Álvarez, *Tetrahedron Lett.* **2006**, *47*, 8757–8760. (c) R. Fan, W. Li, B. Wang, *Org. Biomol. Chem.* **2008**, *6*, 4615-4621. (d) D. Hernández, A. Boto, D. Guzmán, E. Alvarez, *Org. Biomol. Chem.* **2017**, *15*, 7736–7742. (e) D. Hernández, C. Carro, A. Boto, *J. Org. Chem.* **2021**, *86*, 2796–2809.



Scheme 5.6. *N,O*-acetal formation using hypervalent iodine under visible light irradiation.

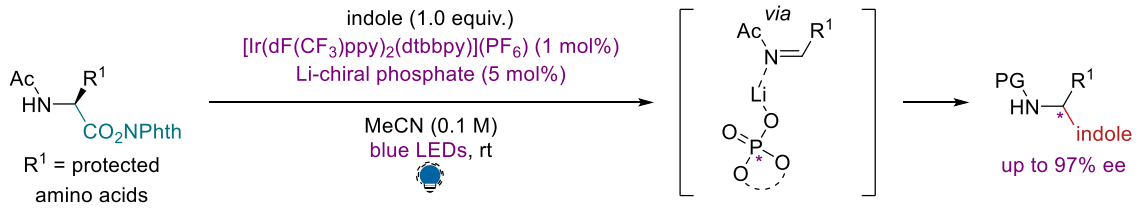
Similarly, Kita and coworkers reported the generation of *N,O*-acetals from non-cyclic amino acids using HIR **5.3** and heating at reflux to initiate the decarboxylation.[21] As no signal was observed by ESR spectroscopy, the authors proposed a mechanism involving the generation of hypervalent iodine intermediate **I** which would collapse to generate *N*-acyliminium **II** that could then be trapped by methanol.



Scheme 5.7. *N,O*-acetal formation using hypervalent iodine at elevated temperature.

In addition, decarboxylative coupling can be induced using photoredox catalysis and more details will be given in the next section as it is usually used to generate an α-aminyl radical that is then directly trapped. However, the Wang group reported an *in-situ* formation of *N*-acylimine under photoredox and chiral phosphate catalysis, the intermediate could then be engaged in Friedel-Crafts reactions with indoles (Scheme 5.8).[22] The proposed mechanism involved two successive single electron transfers (SET) leading to a *N*-acyliminium that could be deprotonated by a chiral phosphate catalyst to generate a *N*-acylimine which then could react with indoles.

[21] Y. Harayama, M. Yoshida, D. Kamimura, Y. Wada, Y. Kita, *Chem. Eur. J.* **2006**, *12*, 4893–4899.
[22] M.-L. Shen, Y. Shen, P.-S. Wang, *Org. Lett.* **2019**, *21*, 2993–2997.



Scheme 5.8. Asymmetric Friedel-Crafts reaction *via in-situ* generated *N*-acylimine.

Finally, metal catalyzed decarboxylative coupling of amino acids proceeding through *N*-acyliminiums have been reported.[23] However, due to the elevated temperatures usually required (> 100 °C), these strategies have been limited to unfunctionalized amino acids and were not extended to peptides.

5.1.2.3. Decarboxylative Couplings via 1-electron Processes

In parallel to the development of the Kolbe electrolysis, researchers have been interested in chemical decarboxylation reactions involving 1-electron processes with the goal to intercept the generated radical (Scheme 5.9). For instance, the Borodin-Hunsdiecker reaction allows to access alkyl, vinyl or alkynyl halides from the corresponding silver-carboxylate salts (A).[24] As an alternative to the use of silver salts, Barton and coworkers developed a radical decarboxylation reaction by activating carboxylic acids with *N*-hydroxypyridine-2-thione and using tin hydride reagents or thiols (B).[25] Okada, Oda and coworkers later reported a photosensitized alternative to the Barton decarboxylation with *N*-acyloxyphthalimides and the reaction could proceed in high yields under aqueous conditions (C).[26]

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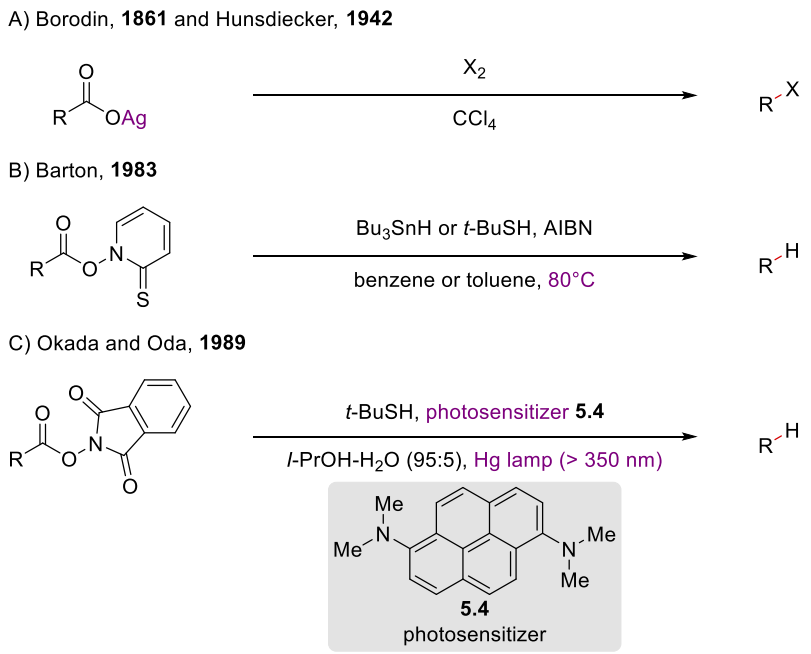
[23] Selected examples: (a) H.-P. Bi, L. Zhao, Y.-M. Liang, C.-J. Li, *Angew. Chem. Int. Ed.* **2009**, *48*, 792–795. (b) H.-P. Bi, W.-W. Chen, Y.-M. Liang, C.-J. Li, *Org. Lett.* **2009**, *11*, 3246–3249. (c) J. Guo, Y. Xie, Q.-L. Wu, W.-T. Zeng, A. S. C. Chan, J. Weng, G. Lu, *RSC Adv.* **2018**, *8*, 16202–16206.
[24] (a) A. Borodine, *Ann. Chem. Pharm.* **1861**, *119*, 121–123. (b) H. Hunsdiecker, Cl. Hunsdiecker, *Berichte Dtsch. Chem. Ges. B Ser.* **1942**, *75*, 291–297. (c) J. J. Li, in *Name React.*, Springer International Publishing, Cham, **2014**, pp. 327–328.
[25] (a) D. H. R. Barton, D. Crich, W. B. Motherwell, *J. Chem. Soc. Chem. Commun.* **1983**, 939-941. (b) D. H. R. Barton, D. Crich, W. B. Motherwell, *Tetrahedron Lett.* **1983**, *24*, 4979–4982. (c) M. F. Saraiva, M. R. C. Couri, M. Le Hyaric, M. V. de Almeida, *Tetrahedron* **2009**, *65*, 3563–3572.
[26] (a) K. Okada, K. Okamoto, M. Oda, *J. Am. Chem. Soc.* **1988**, *110*, 8736–8738. (b) K. Okada, K. Okubo, N. Morita, M. Oda, *Tetrahedron Lett.* **1992**, *33*, 7377–7380.



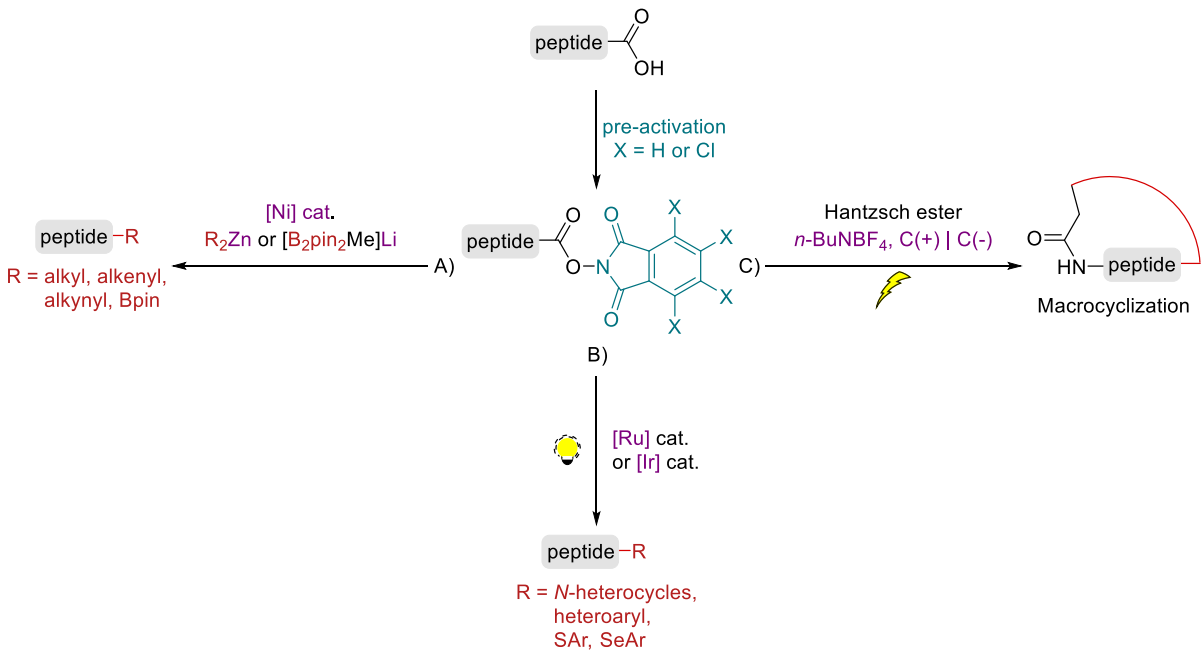
Scheme 5.9. Seminal works on radical decarboxylation of redox-active esters.

Okada and Oda groups later expanded their strategy to chlorination,[27] Giese reaction,[28] and phenylselenation from *N*-acyloxyphthalimides using photoredox conditions.[29] The Overmann group could showcase the synthetic utility of the transformation in the total synthesis (-)-Aplyviolene,[30] and by applying it to form quaternary carbons.[31]

In the last decade, the activation of carboxylic acids with *N*-acyloxyphthalimides has been particularly investigated for the development decarboxylative couplings for peptides (Scheme 5.10). The Baran and Weix groups concurrently reported that a Ni(I) catalyst could engage in SET with redox active esters leading to decarboxylation, the formed radical could then recombine with the Ni catalyst and be involved in cross-coupling reactions.[32] Baran and coworkers could then exploit this reactivity to functionalize the side-chains of amino acids and

[27] K. Okada, K. Okamoto, M. Oda, *J. Chem. Soc. Chem. Commun.* **1989**, 1636-1637.
[28] K. Okada, K. Okamoto, N. Morita, K. Okubo, M. Oda, *J. Am. Chem. Soc.* **1991**, *113*, 9401–9402.
[29] K. Okada, K. Okubo, N. Morita, M. Oda, *Chem. Lett.* **1993**, *22*, 2021–2024.
[30] M. J. Schnermann, L. E. Overman, *Angew. Chem. Int. Ed.* **2012**, *51*, 9576–9580.
[31] G. Pratsch, G. L. Lackner, L. E. Overman, *J. Org. Chem.* **2015**, *80*, 6025–6036.
[32] (a) J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C.-M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 2174–2177. (b) K. M. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. G. Ackerman, D. J. Weix, *J. Am. Chem. Soc.* **2016**, *138*, 5016–5019.

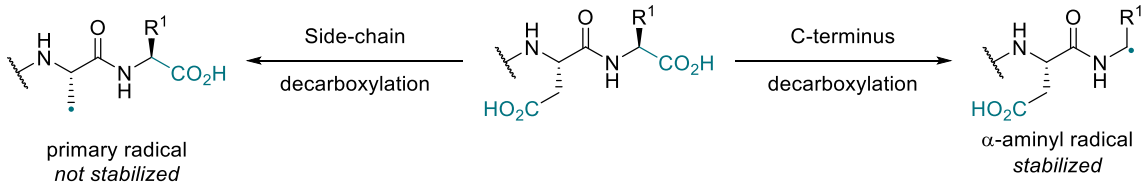
peptides *via* decarboxylative alkylation,[33] alkenylation,[34] or alkynylation (A).[35] The same group showed that the reductive decarboxylation of redox-active esters could be followed by Giese reactions and the transformation was suitable for the functionalization and the macrocyclization of resin-bound peptides.[36] The concept could also be extended to the decarboxylative borylation of peptide C-termini.[37] Building on the work of Okada and Oda (*vide supra*), the H. Fu group could install *N*-heterocycles and phenanthridine on peptides using a ruthenium based photocatalyst (B).[38] Similarly, Y. Fu and coworkers could introduce *N*-heteroarenes using an iridium based photocatalyst.[39] Visible light promoted thioarylation[40] and selenoarylation were reported as well.[41] Finally, the Wang group showed that *N*-acyloxyphthalimides could undergo cathodic reduction generating a nucleophilic radical that could react intramolecularly in a Giese type macrocyclization reaction (C).[42]



Scheme 5.10. Decarboxylative couplings on peptides using redox active esters.

[33] T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate, P. S. Baran, *Science* **2016**, *352*, 801–805.
[34] J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D.-H. Bao, F.-L. Wei, T. Zhou, M. D. Eastgate, P. S. Baran, *Nature* **2017**, *545*, 213–218.
[35] J. M. Smith, T. Qin, R. R. Merchant, J. T. Edwards, L. R. Malins, Z. Liu, G. Che, Z. Shen, S. A. Shaw, M. D. Eastgate, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 11906–11910.
[36] T. Qin, L. R. Malins, J. T. Edwards, R. R. Merchant, A. J. E. Novak, J. Z. Zhong, R. B. Mills, M. Yan, C. Yuan, M. D. Eastgate, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 260–265.
[37] C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan, P. S. Baran, *Science* **2017**, *356*, eaam7355.
[38] Y. Jin, M. Jiang, H. Wang, H. Fu, *Sci. Rep.* **2016**, *6*, 20068.
[39] W.-M. Cheng, R. Shang, Y. Fu, *ACS Catal.* **2017**, *7*, 907–911.
[40] Y. Jin, H. Yang, H. Fu, *Chem. Commun.* **2016**, *52*, 12909–12912.
[41] M. Jiang, H. Yang, H. Fu, *Org. Lett.* **2016**, *18*, 1968–1971.
[42] X. Chen, X. Luo, X. Peng, J. Guo, J. Zai, P. Wang, *Chem. Eur. J.* **2020**, *26*, 3226–3230.

The redox-active ester approach requires a step of pre-functionalization of the peptides and discrimination between carboxylic acids on the side-chains or at the C-terminus is tedious. Photoredox catalyzed decarboxylation of native peptides has allowed to circumvent these issues. Starting from native peptides, the C-terminus decarboxylation is favored as it leads to a stabilized α-aminyl radical while the decarboxylation from the side-chain would provide a non-stabilized primary radical (Scheme 5.11).

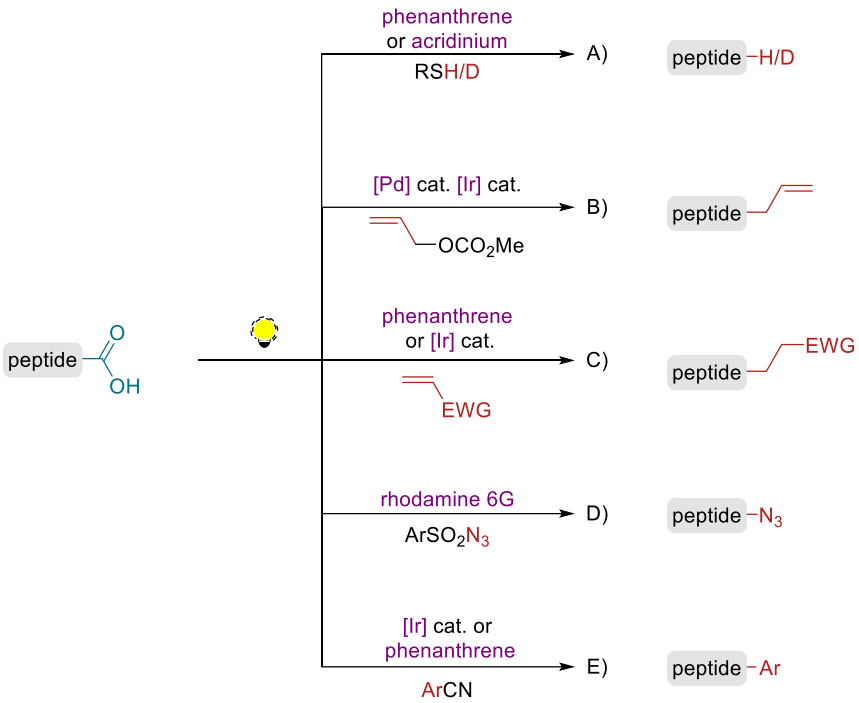


Scheme 5.11. Side-chain versus C-terminus decarboxylation.

Some examples of photoredox catalyzed decarboxylative couplings will be presented in the following paragraph (Scheme 5.12). Yoshimi, Itou and coworkers reported a photochemical decarboxylative deuteration of small peptides using phenanthrene (A).[43] The Wallentin group later described a photoredox catalyzed decarboxylative reduction of small peptide C-terminus using an acridinium dye (A).[44] The Tunge group developed a palladium/photoredox dual catalytic system for the decarboxylative allylation of amino acids and small peptides (B).[45] The MacMillan group investigated the Giese reaction *via* the photoredox catalyzed decarboxylation of amino acids and dipeptides (C).[46] Using an iridium based photocatalyst they could apply the strategy to the macrocyclization of larger peptides by installing acrylamide at the N-terminus. Showcasing the chemoselectivity for the decarboxylation of the C-terminus acid with photoredox catalysis, a peptide containing a glutamic acid was tolerated in the transformation.[47] Moving to a flavin-based photocatalyst, they were able to extend their methodology to the functionalization of native proteins.[48] Azide being a versatile functional group in organic chemistry, the Leonori group studied its incorporation in amino acid derivatives and dipeptides *via* decarboxylative coupling (D).[49] Using rhodamine 6G as photocatalyst they could induce a decarboxylative azidation, but the

[43] T. Itou, Y. Yoshimi, K. Nishikawa, T. Morita, Y. Okada, N. Ichinose, M. Hatanaka, *Chem. Commun.* **2010**, *46*, 6177–6179.
[44] C. Cassani, G. Bergonzini, C.-J. Wallentin, *Org. Lett.* **2014**, *16*, 4228–4231.
[45] S. B. Lang, K. M. O'Nele, J. T. Douglas, J. A. Tunge, *Chem. Eur. J.* **2015**, *21*, 18589–18593.
[46] L. Chu, C. Ohta, Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 10886–10889.
[47] S. J. McCarver, J. X. Qiao, J. Carpenter, R. M. Borzilleri, M. A. Poss, M. D. Eastgate, M. M. Miller, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2017**, *56*, 728–732.
[48] S. Bloom, C. Liu, D. K. Kölmel, J. X. Qiao, Y. Zhang, M. A. Poss, W. R. Ewing, D. W. C. MacMillan, *Nat. Chem.* **2018**, *10*, 205–211.
[49] D. C. Marcote, R. Street-Jeakings, E. Dauncey, J. J. Douglas, A. Ruffoni, D. Leonori, *Org. Biomol. Chem.* **2019**, *17*, 1839–1842.

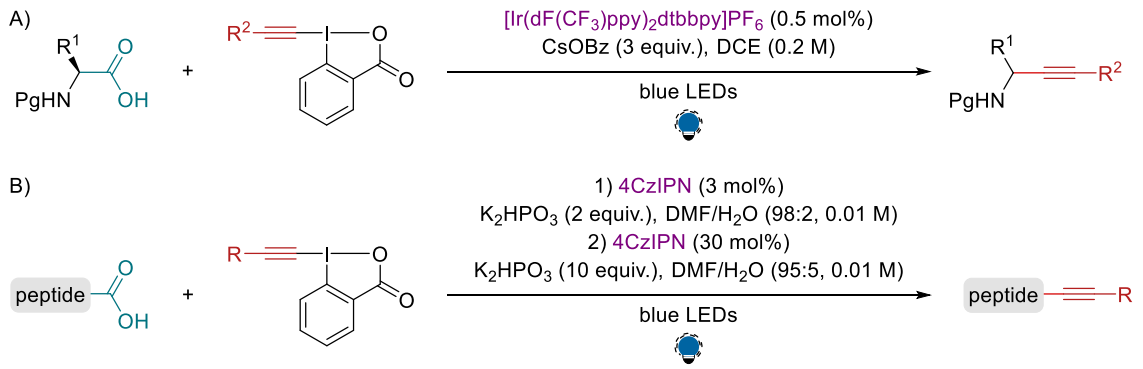
transformation required to have a proline at the C-terminus. Finally, the MacMillan group reported a decarboxylative arylation of amino acids using an iridium based photocatalyst and cyanoarenes (E).[50] This process was later extended by Yoshimi and coworkers to the decarboxylative arylation of tripeptides using phenanthrene as photosensitizer and aqueous conditions.[51]



Scheme 5.12. Decarboxylative couplings from native peptides.

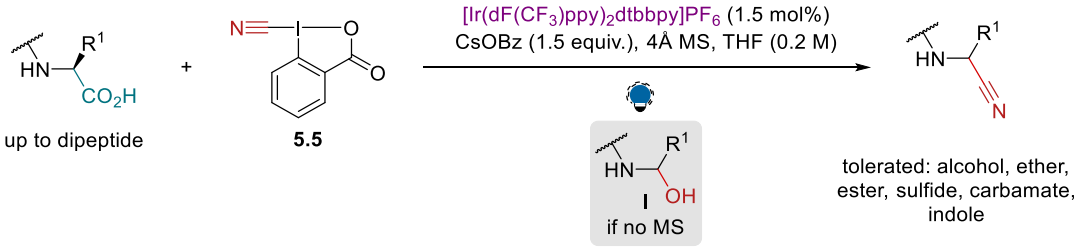
Our group, being particularly interested in alkynylation reactions, started to investigate decarboxylative transformations using photoredox conditions (Scheme 5.13). Using an iridium photocatalyst, our group developed a decarboxylative alkynylation of α-amino acids using EBX reagents (A).[52] Changing the photocatalyst to an organic dye and using aqueous conditions, our group could apply the transformation to dipeptides (Scheme 5.13.B, conditions 1) and to larger peptides up to hexapeptides (conditions 2).[53]

[50] Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 5257–5260.
[51] K. Maeda, H. Saito, K. Osaka, K. Nishikawa, M. Sugie, T. Morita, I. Takahashi, Y. Yoshimi, *Tetrahedron* **2015**, *71*, 1117–1123.
[52] F. Le Vaillant, T. Courant, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204. A similar strategy was concurrently reported: Q.-Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199.
[53] M. Garreau, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2019**, *58*, 8182–8186.



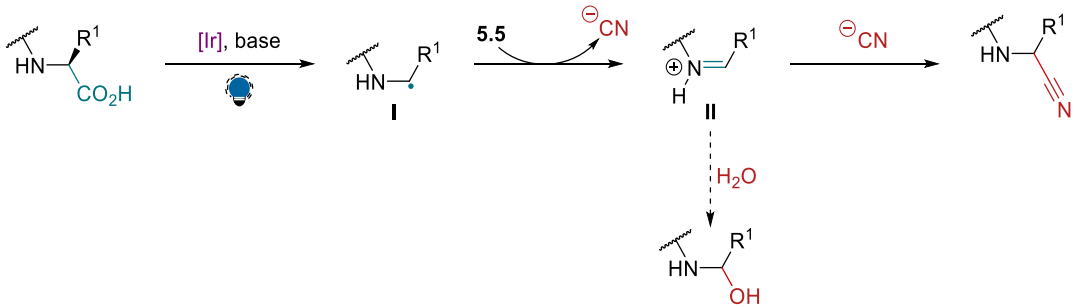
Scheme 5.13. Photoredox catalyzed decarboxylative alkynylation of amino acids and peptides with EBX.

Interestingly, similar conditions could be used for the decarboxylative cyanation of amino acids and dipeptides using cyanobenziodoxolone reagent (CBX, **5.5**) (Scheme 5.14).[54] However, in this case, the use of molecular sieves was required to reach high yields of cyanated products. In the absence of a drying agent, *N,O*-acetals **I** could be isolated.



Scheme 5.14. Photoredox catalyzed decarboxylative cyanation with CBX **5.5**.

Computational mechanistic investigations showed that the α-aminyl radical **I** formed *via* decarboxylation was further oxidized by HIR **5.5** leading to a *N*-acyliminium intermediate **II** (Scheme 5.15). This intermediate could then be trapped by cyanide or water in the absence of molecular sieves.



Scheme 5.15. Proposed mechanism for the decarboxylative cyanation with **5.5**.

As discussed in this section, the generation of *N,O*-acetals *via* 2-electron decarboxylation processes allows to access a versatile intermediate that can be used as a

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

platform to functionalize the C-terminus of native peptides with various nucleophiles. However, their application has been limited due to the low functional group tolerance of these processes. On the other hand, 1-electron photoredox catalyzed decarboxylative functionalization of native peptide C-termini has been shown to tolerate most of the proteinogenic functional groups. However, each functional group introduced required a specific set of conditions, which is not ideal in the optic of rapidly diversifying the C-terminus of a peptide of interest. Therefore, a combination of both approaches for which *N,O*-acetals would be generated under photoredox conditions would be valuable. It should be noted that examples of photoredox catalyzed decarboxylative C-O bond formation are scarce and frequently associated with overoxidation.[55]

5.1.3. Decarboxylative Approaches Towards Polycyclic Aminal Heterocycles

Heterocycles containing nitrogen atoms are ubiquitous in natural bioactive molecules.[56] Drawing inspiration from Nature, medicinal chemists have frequently used these building blocks to develop pharmaceutical compounds.[57] Of particular interest for this Thesis are polycyclic aminal heterocycles that can be found in natural and synthetic bioactive compounds (Figure 5.1). For instance, (+)-tryptoquivaline (**5.6**) bearing a [5,5] fused bicyclic aminal scaffold exhibited antiviral activity against Influenza A virus.[58] Tetraponerine T5 (**5.7**) was isolated from the paralyzing venom of pseudomyrmecine ants.[59] Kifunensine (**5.8**), which has a [6,5] fused bicyclic aminal structure, exhibits inhibitory activity against mannosidase I enzyme.[60] Finally, the alkaloid (±)-penicamide A (**5.9**) displays anti-inflammatory activity.[61]

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[55] Selected recent examples: (a) S. Inuki, K. Sato, Y. Fujimoto, *Tetrahedron Lett.* **2015**, *56*, 5787–5790. (b) S. N. Khan, M. K. Zaman, R. Li, Z. Sun, *J. Org. Chem.* **2020**, *85*, 5019–5026. (c) S. Shirase, S. Tamaki, K. Shinohara, K. Hirosawa, H. Tsurugi, T. Satoh, K. Mashima, *J. Am. Chem. Soc.* **2020**, *142*, 5668–5675. (d) T. M. Faraggi, W. Li, D. W. C. MacMillan, *Isr. J. Chem.* **2020**, *60*, 410–415.
[56] C. T. Walsh, *Tetrahedron Lett.* **2015**, *56*, 3075–3081.
[57] (a) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859. (b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J Med Chem* **2014**, *57*, 10257–10274.
[58] J. Peng, T. Lin, W. Wang, Z. Xin, T. Zhu, Q. Gu, D. Li, *J. Nat. Prod.* **2013**, *76*, 1133–1140.
[59] P. Merlin, J. C. Braekman, D. Daloze, J. M. Pasteels, *J. Chem. Ecol.* **1988**, *14*, 517–527.
[60] A. D. Elbein, J. E. Tropea, M. Mitchell, G. P. Kaushal, *J. Biol. Chem.* **1990**, *265*, 15599–15605.
[61] S. Chen, M. Jiang, B. Chen, J. Salaenoi, S.-I. Niaz, J. He, L. Liu, *Mar. Drugs* **2019**, *17*, 522.

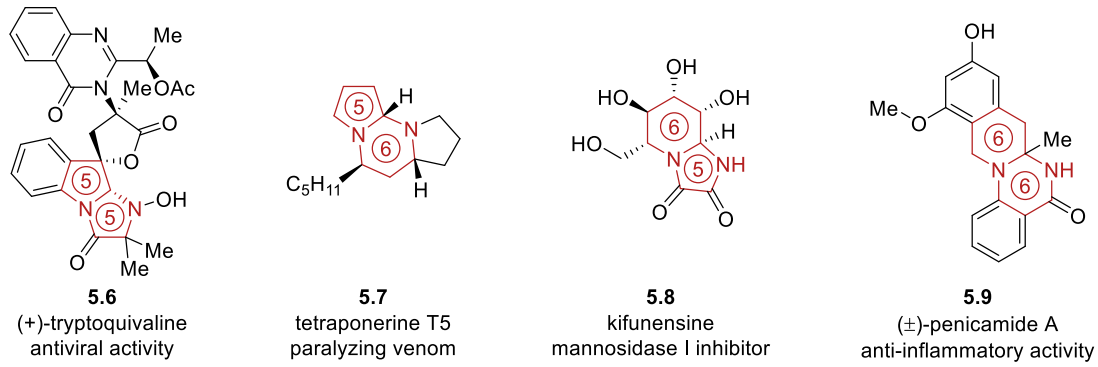
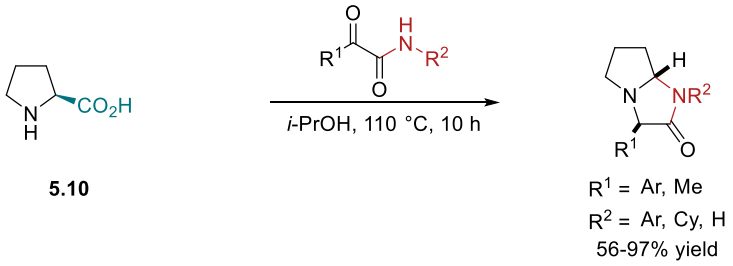


Figure 5.1. Examples of bioactive polycyclic aminal heterocycles.

Different strategies have been developed to access heterocyclic aminal compounds such as condensation of diamines with carbonyl compounds, ring expansions or contractions.[62] Of particular interest for this Thesis, polycyclic aminals can be obtained *via* the addition of tethered amines onto *N*-acyliminium.[63] However, only few examples have been reported involving the formation of *N*-acyliminium intermediates through decarboxylation. For instance, the Chen group developed a decarboxylative cyclization reaction between proline (**5.10**) and α-ketoamides (Scheme 5.16).[64] The reaction is proposed to involve first the condensation of proline (**5.10**) onto α-ketoamides followed by thermal decarboxylation and intramolecular trapping of a *N*-acyliminium intermediate.

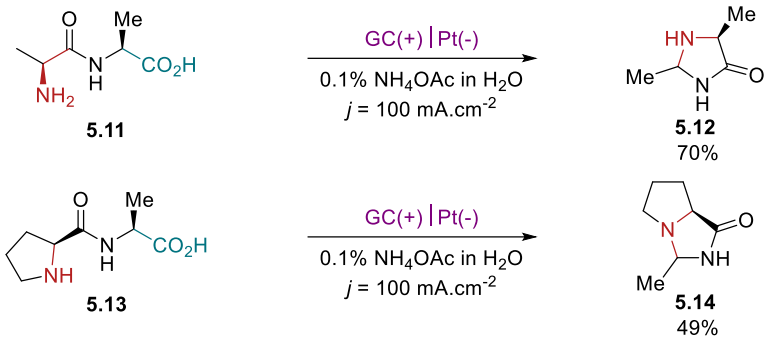


Scheme 5.16. Decarboxylative bicyclic aminal heterocycles synthesis by the Chen group.

During their study of the Hofer-Moest electrolysis applied to amino acids and small peptides, Seebach and coworkers submitted non-protected dipeptides to their reaction conditions and observed the formation of aminal heterocycles (Scheme 5.17).[15b] More

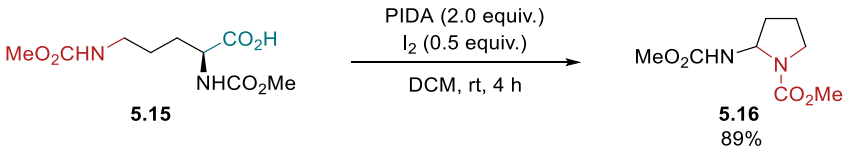
[62] T. R. Blackmore, P. E. Thompson, *Heterocycles* **2011**, *83*, 1953–1975.
[63] Selected recent examples: (a) X. Ren, J. A. O'Hanlon, M. Morris, J. Robertson, L. L. Wong, *ACS Catal.* **2016**, *6*, 6833–6837. (b) A. Bertamino, G. Lauro, C. Ostacolo, V. Di Sarno, S. Musella, T. Ciaglia, P. Campiglia, G. Bifulco, I. M. Gomez-Monterrey, *J. Org. Chem.* **2017**, *82*, 12014–12027. (c) Z. Zhu, X. Lv, J. E. Anesini, D. Seidel, *Org. Lett.* **2017**, *19*, 6424–6427. (d) Y. Yoshida, K. Omori, T. Hiroshige, T. Mino, M. Sakamoto, *Chem. Asian J.* **2019**, *14*, 2737–2743. (e) S. Biswas, B. Porashar, P. J. Arandhara, A. K. Saikia, *Chem. Commun.* **2021**, *57*, 11701–11704.
[64] J. Wu, H. Jiang, J. Yang, Z. Jin, D. Chen, *Tetrahedron Lett.* **2017**, *58*, 546–551.

specifically, imidazolidinone **5.12** could be obtained in 70% yield from alanine-alanine (**5.11**) and bicyclic aminal **5.14** was accessed in 49% yield from proline-alanine (**5.13**).



Scheme 5.17. Decarboxylative aminal heterocycles synthesis by Seebach and coworkers.

While investigating the formation of *N,O*-acetals *via* the decarboxylation of amino acids using hypervalent iodine oxidants, the Suárez group discovered that when ornithine **5.15** was subjected to a mixture of PIDA and I_2 it was cleanly converted to aminal **5.16** (Scheme 5.18).[19a] To the best of our knowledge, this transformation was not further investigated nor applied to the construction of polycyclic aminal compounds.



Scheme 5.18. Decarboxylative synthesis of aminal heterocycle **5.16** by the Suárez group.

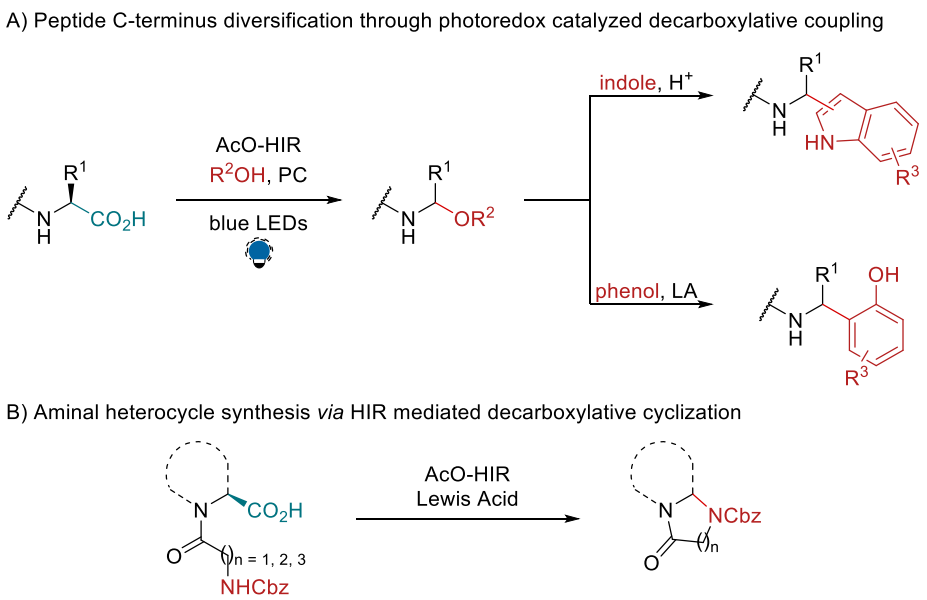
Although dipeptides derived from α-amino acids are readily accessible from cheap and abundant starting material, they have been scarcely used for the formation of polycyclic aminal compounds. Moreover, the previously described decarboxylative approach to aminal heterocycles lack generality and have only focused on the formation of [5,5]-fused bicycles.

5.2. Goals of the Project

As described previously, decarboxylative coupling strategies applied to peptides can be divided in two classes either involving 1-electron or 2-electron processes. In the first case, an α-aminyl radical is formed and reacted with electrophilic radical traps. Although the reaction conditions are usually mild and applicable to functionalized peptides, they lack generality and are often specific to one particular radical trap. On the other hand, 2-electron decarboxylative strategies require harsher conditions but allow to access *N*-acyliminium intermediates, which can be trapped by nucleophiles leading to complementary types of bond formation.

The first goal of this project aimed at combining both approaches by accessing *N,O*-acetals using photoredox catalysis (Scheme 5.19.A). The masked *N*-acyliminium intermediates would enable the diversification of peptide C-termini with different nucleophiles. Our investigation particularly focused on alcohol, indole and phenol nucleophiles, which are naturally occurring in amino acids.

The second objective of this project arose from the isolation of a cyclization side product while studying the scope of phenol nucleophiles. Using a hypervalent iodine reagent in combination with a Lewis acid, we aimed to develop a decarboxylative cyclization reaction to access aminal heterocycles from dipeptide derivatives (Scheme 5.19.B).



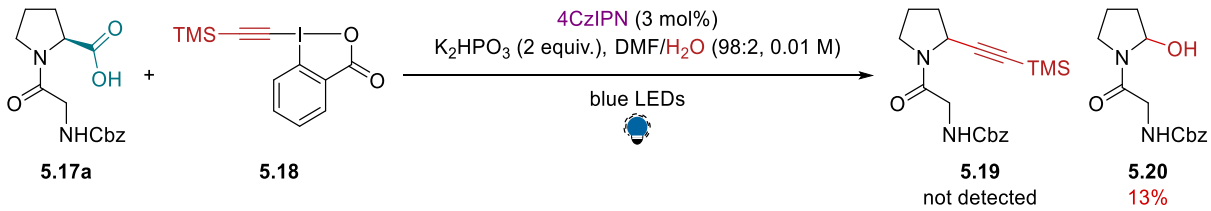
Scheme 5.19. Decarboxylative arylation and cyclization of small peptides.

5.3. C-Terminal Oxidative Decarboxylative Arylation of Small Peptides

In this section, our efforts towards the development of small peptide C-terminal diversifications *via* photoredox catalyzed decarboxylative couplings will be described. The project was initiated in our group by Dr. Marion Garreau and her specific contribution will be highlighted in the following sections.

5.3.1. Reaction Discovery and Optimization[65]

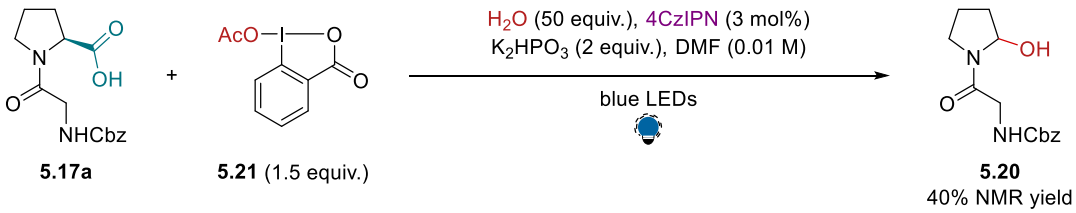
During her investigation on the decarboxylative alkynylation of peptides,[53] Dr. Marion Garreau observed the formation of hemiaminal **5.20** (Scheme 5.20).[66] In this example, the targeted alkynylated product **5.19**, arising from the photoredox catalyzed decarboxylative alkynylation of dipeptide **5.17a** with TMS-EBX (**5.18**), was not detected.



Scheme 5.20. Serendipitous discovery of a photoredox catalyzed decarboxylative hydroxylation of dipeptide **5.17a**.

It was hypothesized that compound **5.20** would be formed *via* two successive SETs as observed for the decarboxylative cyanation of amino acids described previously (Scheme 5.15). However, computational studies showed that this mechanism was unlikely with EBX reagents.[54] It was therefore believed that the reaction might be promoted by a hypervalent iodine oxidant impurity in the EBX reagent. Due to the recent application of AcO-BX (**5.21**) in decarboxylative reactions, it was selected as oxidant to further study the reaction (Scheme 5.21).[67] Replacing TMS-EBX (**5.18**) by AcO-BX (**5.21**) in the previous reaction conditions and adding 50 equivalents of water, compound **5.20** was formed in 40% NMR yield.

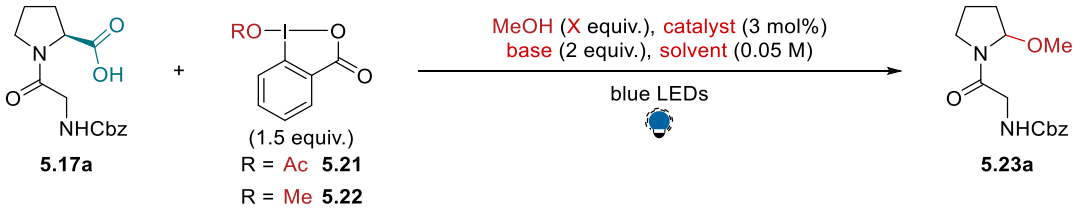
[65] This work was performed by Dr. M. Garreau.
[66] Dr. Marion Garreau, **2020**, *Development of Photocatalysts towards the Visible-Light driven C-Terminal Bioconjugation of Peptides and Proteins*, PhD Thesis n°10420, EPFL, Lausanne.
[67] Selected examples: (a) H. Huang, G. Zhang, Y. Chen, *Angew. Chem. Int. Ed.* **2015**, *54*, 7872–7876. (b) G.-X. Li, X. Hu, G. He, G. Chen, *ACS Catal.* **2018**, *8*, 11847–11853.



Scheme 5.21. Investigation of the decarboxylative hydroxylation of dipeptide **5.17a** with AcO-BX (**5.21**).

Due to the difficulty to isolate hemiaminal **5.20**, methanol was chosen for the optimization as it was shown to form *N,O*-acetals in previous works (see 5.1.2.2). The optimization of the oxidative decarboxylation of dipeptide **5.17a** was then investigated using reverse-phase HPLC to monitor the conversion of starting material and formation of *N,O*-acetal **5.23a** (Table 5.1). Using the conditions previously described, **5.23a** was formed in 46% HPLC yield and 18% isolated yield (entry 1). Although silica was deactivated using triethylamine, degradation of the *N,O*-acetal during the purification could not be completely avoided. Changing the photocatalyst from an organic dye to $Ru(bpy)_3Cl_2$ led to a slight increase in yield (entry 2). Reducing the stoichiometry of methanol from 50 equivalents to 10 equivalents was beneficial for the reaction (entry 3). Increasing the concentration to 0.05 M allowed to access **5.23a** in 82% HPLC yield. Full conversion of **5.17a** was observed when decreasing the quantity of methanol to 5 and 2 equivalents (entries 5-6). However, for practical reasons the rest of the optimization was investigated with 5 equivalents. Other photocatalysts were screened to achieve a metal-free transformation (entries 7-9). However, Eosin Y, Rhodamine B or Rose Bengal were not suitable for the reaction and degraded under the reaction conditions. Initial attempts to functionalize the obtained *N,O*-acetals showed that DMF was not ideal as solvent for the transformation. Changing DMF to MeCN allowed to observe full conversion of **5.17a** to **5.23a** (entry 10). Interestingly, a control experiment without K_2HPO_4 demonstrated that no base was required for the reaction and **5.23a** could be isolated in 68% on a 0.3 mmol scale (entry 11). DCE was tolerated as solvent and full conversion of **5.17a** could be observed by HPLC (entry 12). Finally, removing methanol and using MeO-BX (**5.22**) allowed to access **5.23a** in a slightly higher 75% isolated yield (entry 13). However, for more complex alcohols, the need to synthesize the alcohol-containing HIR prior to the reaction would not be desirable. Control experiments without light or photocatalyst only afforded traces amount of the targeted *N,O*-acetal **5.23a**.

Table 5.1. Optimization of the oxidative decarboxylation of dipeptides.[a]



Entry	Solvent	Catalyst	X	Base	HPLC Yield[b]
1[c]	DMF	4CzIPN	50	K_2HPO_4	46% (18%)[d]
2[c]	DMF	$Ru(bpy)_3Cl_2$	50	K_2HPO_4	59%
3[c]	DMF	$Ru(bpy)_3Cl_2$	10	K_2HPO_4	78%
4	DMF	$Ru(bpy)_3Cl_2$	10	K_2HPO_4	82%
5	DMF	$Ru(bpy)_3Cl_2$	5	K_2HPO_4	>95%
6	DMF	$Ru(bpy)_3Cl_2$	2	K_2HPO_4	>95%
7	DMF	Eosin Y	5	K_2HPO_4	17%
8[e]	DMF	Rhodamine B	5	K_2HPO_4	27%
9[e]	DMF	Rose Bengal	5	K_2HPO_4	35%
10	MeCN	$Ru(bpy)_3Cl_2$	5	K_2HPO_4	>95%
11	MeCN	$Ru(bpy)_3Cl_2$	5	none	>95% (68%)[d]
12	DCE	$Ru(bpy)_3Cl_2$	5	none	>95%
13[f]	MeCN	$Ru(bpy)_3Cl_2$	0	none	>95% (75%)[d]

[a] Reaction conditions: **5.17a** (0.10 mmol), **5.21** (0.15 mmol), MeOH (X equiv.), base (2.0 equiv.), catalyst (3.0 µmol) in dry degassed solvent under N_2 at room temperature for 15 hours. [b] Ratio of integration at 214 nm by RP-HPLC. [c] Concentration 0.01 M. [d] Isolated yield on 0.3 mmol. [e] Green LEDs. [f] **5.22** instead.

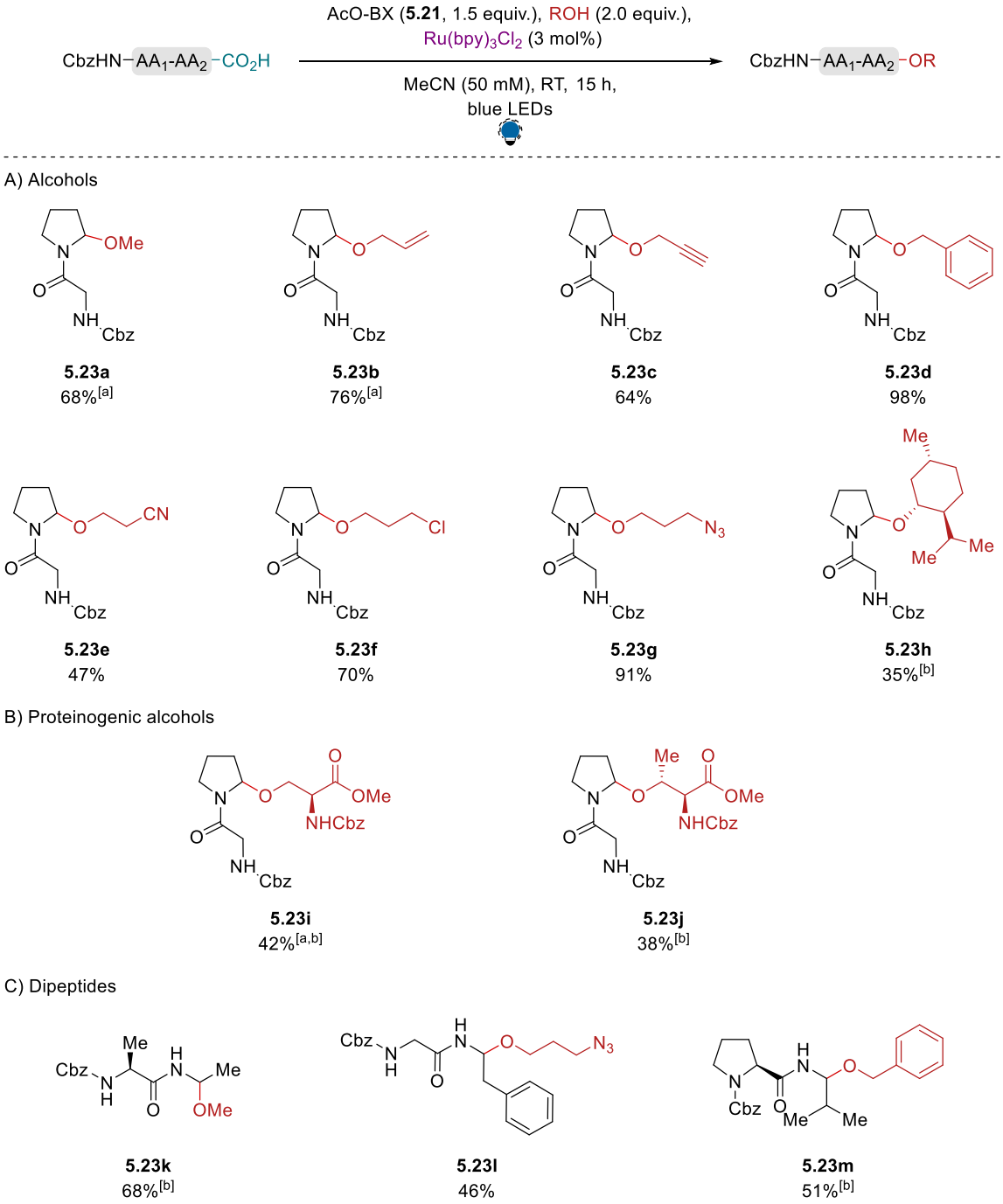
5.3.2. Scope and Limitations

Having the optimized reaction conditions for the photoredox catalyzed oxidative decarboxylation of dipeptides leading to *N,O*-acetals, we decided to explore the scope and limitations of the transformation. The scope of dipeptides was investigated with commercially available starting materials, the tetrapeptides were synthesized *via* SPPS.

5.3.2.1. Scope of N,O-Acetals

We started to examine the scope of alcohols that could be introduced onto dipeptide **5.17a** (Scheme 5.22.A). As described previously, using AcO-BX (**5.21**) and 2 equivalents of methanol, **5.17a** could be converted into **5.23a** with an isolated yield of 68%. Similarly, allyl, propargyl and benzyl alcohols provided access to the corresponding *N,O*-acetals **5.23b-d** in good to excellent yields. Alcohols bearing functional groups such as cyanide, chloride and azide were tolerated in the reaction conditions and afforded the corresponding *N,O*-acetals

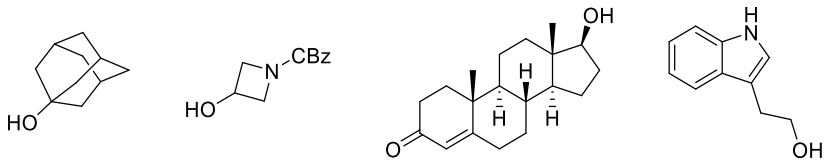
5.23e-g in 47%, 70% and 91% yield respectively. Additionally, *N,O*-acetal **5.23h** derived from sterically hindered secondary alcohol (L)-menthol could be obtained in 35% isolated yield. Interestingly, proteinogenic alcohols from serine and threonine allowed to access **5.23i** and **5.23j** in 42% and 38% yield respectively (B). These two *N,O*-acetals represent a new type of peptide cross-linking. Finally, different alcohols could be added to dipeptides Cbz-Ala-Ala (**5.17b**), Cbz-Gly-Phe (**5.17c**) and Cbz-Pro-Val (**5.17d**) leading to **5.23k-m** in yields ranging from 46% to 68% (C).



[a] reaction performed by Dr. Marion Garreau and reproduced with similar yields [b] Diastereoselectivity not determined due to the presence of rotamers.

Scheme 5.22. Scope of *N,O*-acetals on a 0.3 mmol scale.

During the investigation of the scope of the transformation, several alcohols were found to be ineffective (Figure 5.2). For instance, 1-Adamantanol **5.24**, Cbz-protected 3-hydroxyazetidine **5.25**, testosterone **5.26** and tryptophol **5.27** only afforded traces amount of the corresponding *N,O*-acetals with dipeptide **5.17a**. A complex mixture was obtained with all these substrates and the targeted compounds were found by mass spectrometry, but could not be clearly identified in the crude mixture. Additions of alcohols **5.24-26** might have been disfavored due to steric hindrances. Finally, **5.27** bearing an indole might have been oxidized under the reaction conditions.



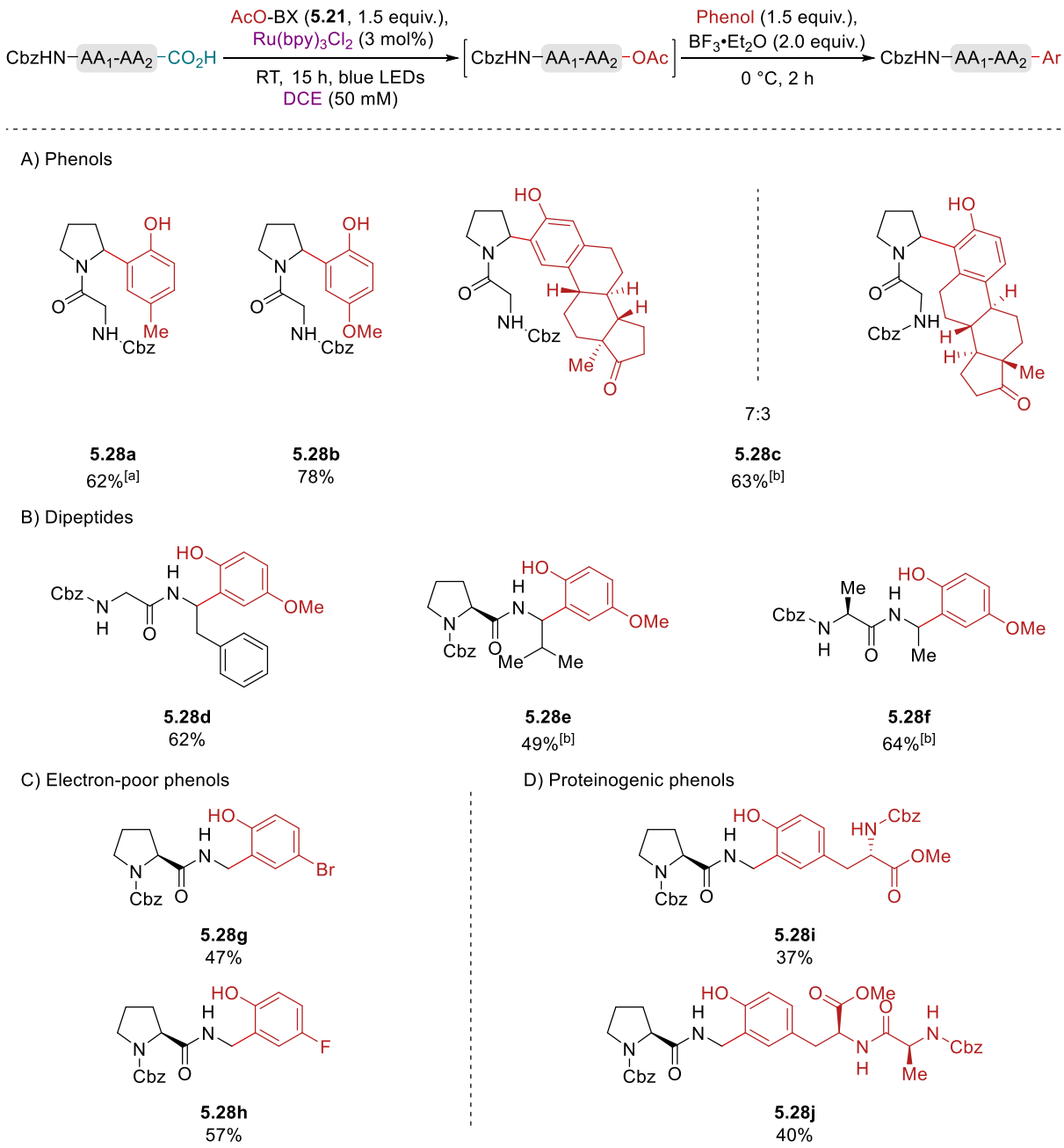
5.24 < 5% **5.25** < 5% **5.26** < 5% **5.27** < 5%

Figure 5.2. Unsuccessful alcohols.

5.3.2.2. Friedel-Crafts Scope with Phenols

While studying the formation of *N,O*-acetals, Dr. Marion Garreau noticed that when the reaction was set up without alcohol, the decarboxylation was still occurring and *N,OAc*-acetals were produced. These compounds were too unstable to be isolated and we wondered if we could benefit from their high reactivity to introduce other nucleophiles. Following the work from the White group,[68] we first investigated the addition of phenols using $BF_3{\cdot}Et_2O$ as Lewis acid (Scheme 5.23). While a complex mixture was obtained when the reaction was run in MeCN, **5.17a** was converted to **5.28a** with *para*-cresol in DCE (A). Electron-rich *para*-methoxyphenol was successfully involved in the Friedel-Crafts reaction leading to **5.28b** in 78% isolated yield. Interestingly, estrone could also be added to **5.17a** and afforded a 7:3 mixture of two regioisomers of **5.28c** in 63% yield. As expected, reaction with the position in *para* to the alkyl donating group was preferred. *para*-Methoxyphenol could be added to different dipeptides **5.17b-d** leading to **5.28d-f** in moderate yields (B). Electron-poor phenols could also be involved in the reaction with Cbz-Pro-Gly (**5.17e**) giving access to **5.28g**, with a bromine in *para* position, and **5.28h,** with a fluorine in *para* position, in 47% and 57% yield respectively (C). Finally, proteinogenic phenols embedded in tyrosine amino acids could also be used in the Friedel-Crafts reaction. For instance, tripeptide **5.28i** and tetrapeptide **5.28j** bearing an unnatural carbon-aryl amino acids cross-link could be obtained in moderate yields (D).

[68] T. J. Osberger, D. C. Rogness, J. T. Kohrt, A. F. Stepan, M. C. White, *Nature* **2016**, *537*, 214–219.



[a] reaction performed by Dr. Marion Garreau and reproduced with similar yields [b] Diastereoselectivity not determined due to the presence of rotamers.

Scheme 5.23. Scope of Friedel-Crafts reactions with phenols on a 0.3 mmol scale.

During our study of the scope of the reaction, we found that electron poor phenols **5.29**, **5.30** and **5.31** were not able to trap the *in-situ* formed *N*-acyliminium from **5.17a** (Figure 5.3). While the desired arylated products were not observed, we could identify the main side-product as the bicyclic aminal **5.32a**. This compound would be formed by intramolecular trapping of the *N*-acyliminium with the N-terminal of the second amino acid. Control experiment in absence of external nucleophile showed that this compound could be obtained in 70% yield (see section 5.4 for more details).

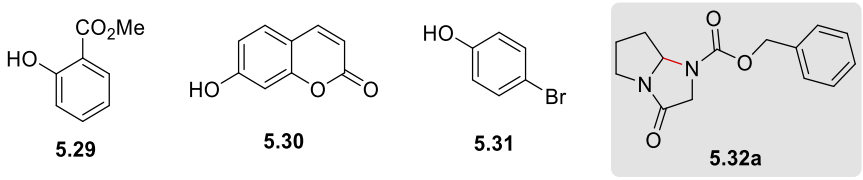
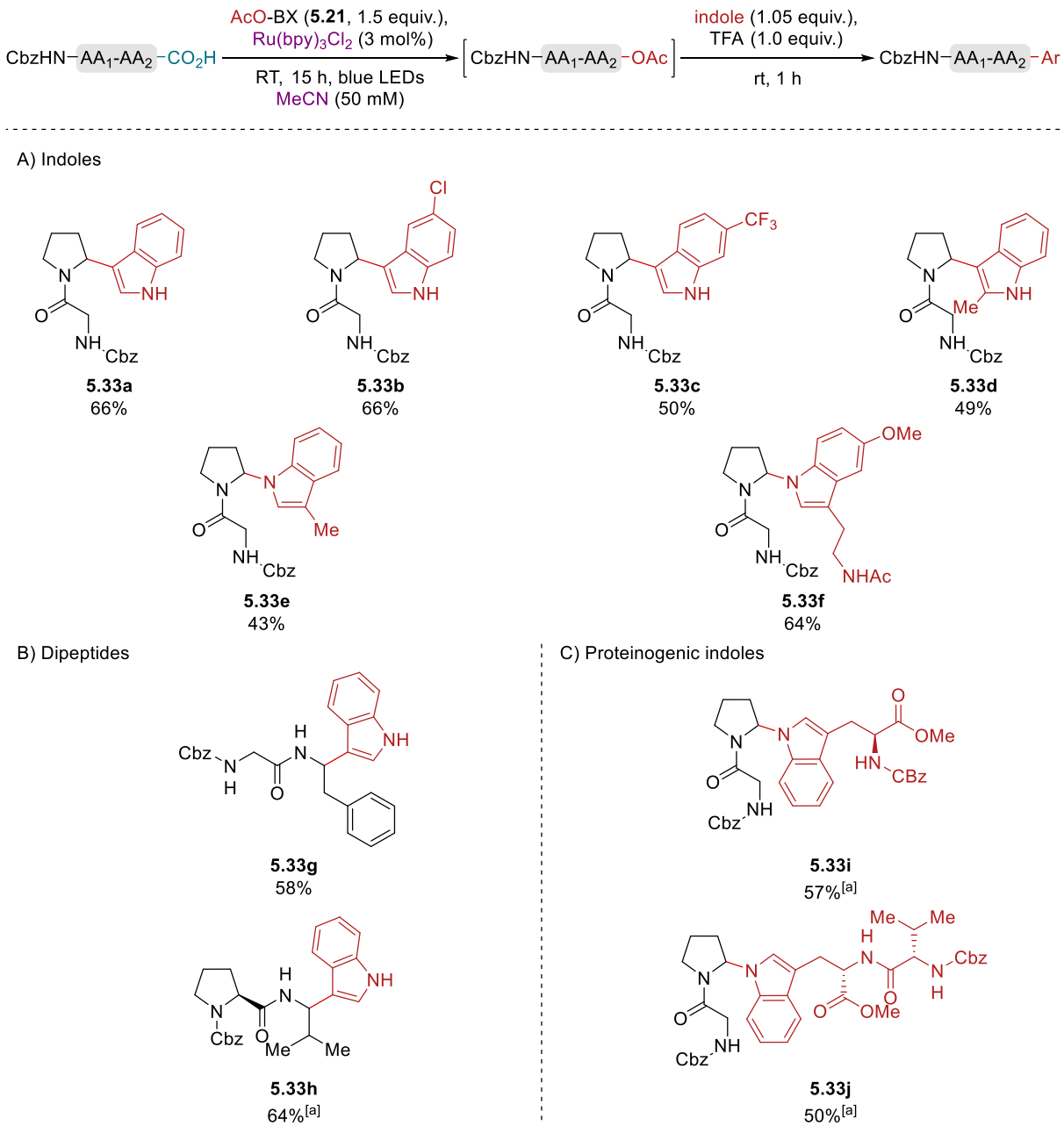


Figure 5.3. Unsuccessful phenols for the arylation of **5.17a** and side-product observed.

5.3.2.3. Friedel-Crafts Scope with Indoles

We then focused on the addition of indoles, a class of nucleophiles also naturally occurring on the side chain of tryptophan. Building upon conditions reported by our group,[69] we could access arylated dipeptide C-termini using a slight excess of indoles and 1 equivalent of TFA (Scheme 5.24). Starting from dipeptide **5.17a**, 1*H*-indole could be added leading to arylated compound **5.33a** in 66% isolated yield with complete selectivity for the C3-position (A). Indoles bearing a chlorine atom in C5 position or a trifluoromethyl substituent in C6 position afforded the corresponding products **5.33b** and **5.33c** in, respectively, 66% and 50% yield. C2-substituted indole led to the formation of **5.33d** in 49% yield. For C3-substituted indoles, a competition between C2 and N-addition was observed with the latter being favored. When 3-methylindole was used, N-addition product **5.33e** could be isolated in 43% yield and the C2-addition product could also be observed in the crude mixture but could not be isolated in pure form (ratio N/C2-addition 2:1 determined by ^{1}H NMR on the crude mixture). Melatonin, a bioactive C3-substituted indole, was tolerated under the reaction conditions and afforded **5.33f** in 64% yield, the C2-addition product was not observed in the crude mixture. *1H*-indole could also be used for the arylation of dipeptides **5.17c** and **5.17d** giving access to **5.33g** and **5.33h** in 58% and 64% yield respectively (B). Similarly, to what was observed with tyrosine, tryptophan could be used as a nucleophile in this transformation (C). For instance, unnatural tri- and tetrapeptides bearing an unprecedented carbon-nitrogen(indole) amino acid cross-link **5.33i** and **5.33j** could be obtained in 57% and 50% yield respectively.

[69] M. Wang, J. Waser, *Angew. Chem. Int. Ed.* **2019**, *58*, 13880–13884.



[a] Diastereoselectivity not determined due to the presence of rotamers.

Scheme 5.24. Scope of Friedel-Crafts reactions with indoles on a 0.3 mmol scale.

In order to try to favor the C2-addition of melatonin to dipeptide **5.17a**, we studied the reactivity of N-protected melatonin **5.34** and **5.35** (Figure 5.4). Unfortunately, none of them provided the desired arylated product probably due to the steric hindrance of the C2-position. The poor nucleophilicity of **5.34** could also be explained by the electron-withdrawing protecting group on the indole.

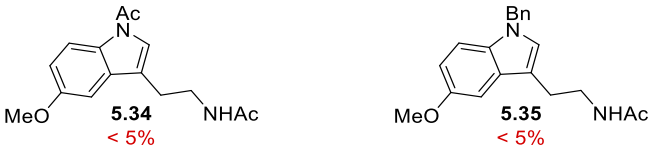
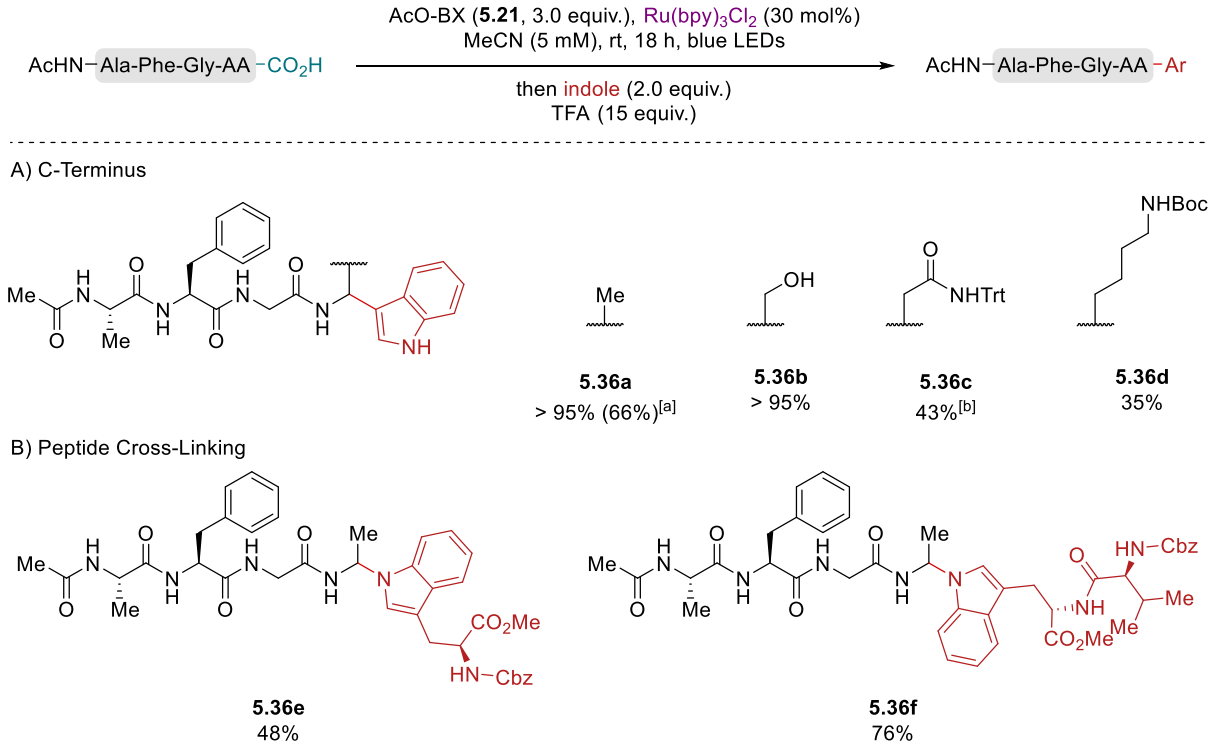


Figure 5.4. Unsuccessful substrates for the arylation of **5.17a**.

5.3.2.4. Application of the Strategy to Tetrapeptides

Finally, we decided to investigate the extension of the strategy to tetrapeptides. Unfortunately, the conditions for the addition of phenols were not tolerated and we could never observe arylation products presumably due to incompatibility of larger peptides with $BF_3 \cdot Et_2O$. On the other hand, for indoles, increasing the stoichiometry of the different reagents and decreasing the concentration for better solubility of the tetrapeptides allowed to access arylated compounds (Scheme 5.25). Full conversion towards the arylated products **5.36a-b** was observed with tetrapeptides bearing an alanine or a serine at the C-terminus. A calibration curve was established and used to determine that **5.36a** was formed in 66% yield. Arylated tetrapeptides **5.36c** and **5.36d** bearing respectively a protected amide and a protected amine at the C-terminus were formed in moderate HPLC ratios. Interestingly, tryptophan could still be used as nucleophile and unnatural pentapeptide **5.36e** and hexapeptide **5.36f** could be formed in moderate to good HPLC ratios.



Relative HPLC ratios of the area of the product over remaining starting material and peptide side-products at 214 nm are given averaged on 3 independent trials. [a] Calibrated yield. [b]. Compound **5.36c** could not be fully separated from a side-product by HPLC.

Scheme 5.25. Scope of decarboxylative arylation of tetrapeptides on a 1 µmol scale.

When the reaction conditions were applied to tetrapeptides bearing a protected aspartic acid, histidine or arginine at the C-terminus, the corresponding arylated product **5.36g-i** could be detected but with lower HPLC ratios (Figure 5.5).

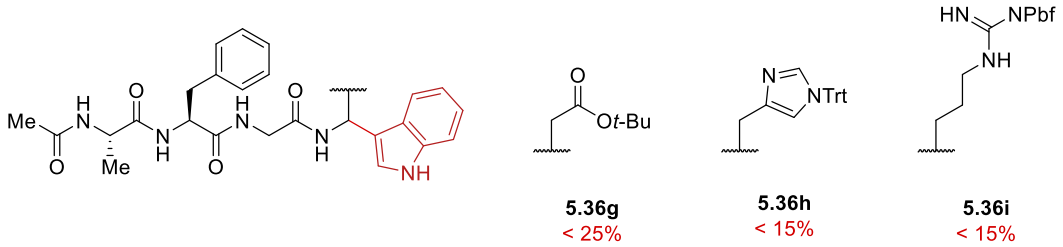
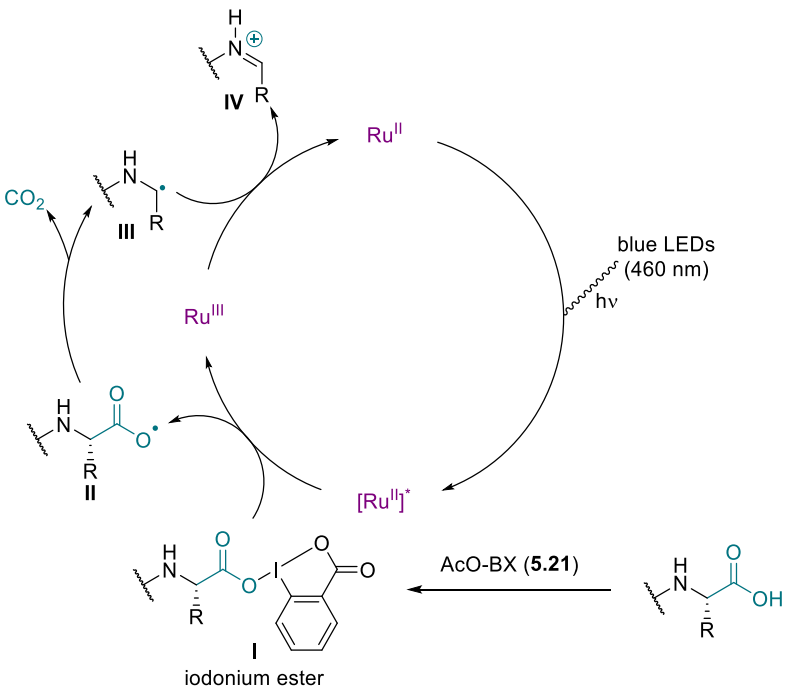


Figure 5.5. Less successful substrates for the decarboxylative arylation on tetrapeptides.

5.3.3. Proposed Mechanism

A first possible mechanism for the oxidative decarboxylation of peptide C-terminus could involve the formation of iodonium ester intermediate **I** (Scheme 5.26).[67a,70] Blue light excitation of $Ru(bpy)_3Cl_2$ would lead to a highly reducing $[Ru^{II}]^*$ species ($E_{1/2}(Ru^{III}/[Ru^{II}]^*)$ = -0.87 V vs SCE)[71] that has been proposed to be able to reduce iodonium ester leading to a carboxylate radical **II** and a Ru^{III} species.[67a,70] Decarboxylation would lead to α-aminyl radical intermediate **III** that could be oxidized by a Ru^{III} species to close the catalytic cycle ($E_{1/2}(Ru^{III}/Ru^{II})$ = +1.26 V vs SCE).[71,72] Although iodonium esters have been proposed as intermediates in different transformations,[67a,70] to the best of our knowledge no redox potentials have been reported. Unfortunately, in our hands, all attempts to synthesize iodonium esters failed to afford the desired intermediates and we could not study their redox properties. In addition, methanol could compete with dipeptide C-terminus for the ligand exchange with AcO-BX reagent (**5.21**) and promote side-reactions.[73] The fact that lower yields in *N,O*-acetals were obtained when large excesses of methanol were used in the optimization could be an indication that the first step of the mechanism involves the formation of iodonium ester intermediate **I** (see 5.3.1).

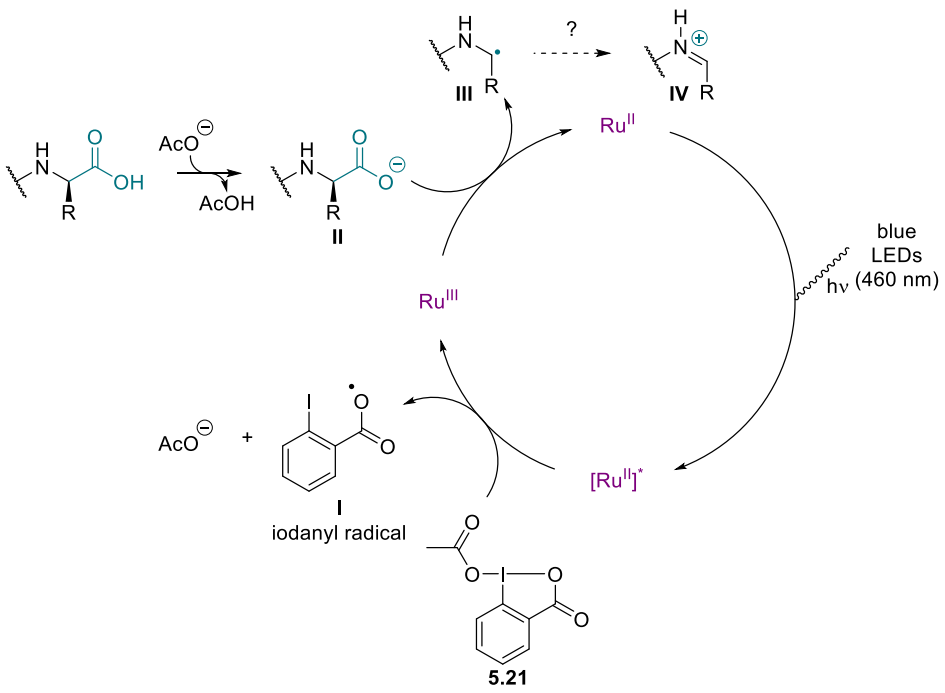
[70] Selected examples proposing the involvement of iodonium ester in decarboxylative coupling: (a) Y. Sakakibara, E. Ito, T. Fukushima, K. Murakami, K. Itami, *Chem. Eur. J.* **2018**, *24*, 9254–9258. (b) B. Maeda, Y. Sakakibara, K. Murakami, K. Itami, *Org. Lett.* **2021**, *23*, 5113–5117. (c) P. Li, J. R. Zbieg, J. A. Terrett, *ACS Catal.* **2021**, *11*, 10997–11004.
[71] J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617–1622.
[72] (a) D. D. M. Wayner, J. J. Dannenberg, D. Griller, *Chem. Phys. Lett.* **1986**, *131*, 189–191. (b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.
[73] G.-X. Li, X. Hu, G. He, G. Chen, *Chem. Sci.* **2019**, *10*, 688–693.



Scheme 5.26. Proposed mechanism for the oxidative decarboxylation *via* iodonium ester **I**.

Another alternative could involve the reduction of HIR **5.21** by the excited photocatalyst generating an iodanyl radical.[74,67] Oxidation of the carboxylate intermediate **II** by a Ru^{III} species would lead to intermediate **III** and close the catalytic cycle. The oxidation of α-aminyl radical **III** into *N*-acyliminium **IV** is not entirely understood. It could involve a second catalytic cycle in which the iodanyl radical **I** would be reduced by excited $[Ru^{II}]^*$ species and intermediate **III** would be oxidized to close the second catalytic cycle and produce the targeted *N*-acyliminium **IV**. However, the second catalytic cycle would involve the reaction of unstable intermediates $[Ru^{II}]^*$ and **III** present in low concentration. A second possibility could involve the oxidation of α-aminyl radical **III** ($E_{1/2}$(**IV**/**III**) ~ -1.0 V vs SCE)[72a] by iodanyl radical **I** ($E_{1/2}$(**I**/**I**$^-$) = + 0.25 V vs SCE)[54] leading to acyliminium **IV** and 2-iodobenzoate. We never observed the formation of a *N,O*-acetal bearing a 2-iodobenzoate moiety which should rule out the direct recombination of radicals **III** and **I**.

[74] G.-X. Li, C. A. Morales-Rivera, Y. Wang, F. Gao, G. He, P. Liu, G. Chen, *Chem. Sci.* **2016**, *7*, 6407–6412.

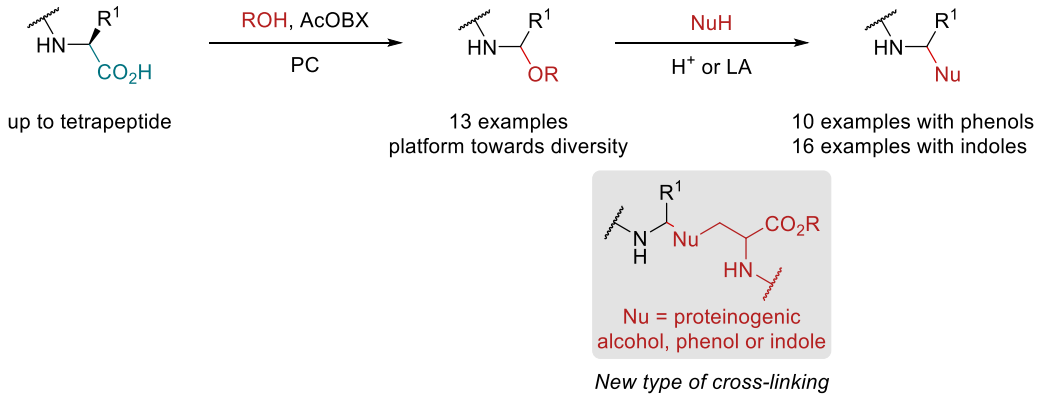


Scheme 5.27. Proposed mechanism for the oxidative decarboxylation *via* reduction of **5.21**.

Future mechanistic investigations should focus on the synthesis of relevant iodonium esters to be able to study their redox properties and have potential insight on the reaction mechanism.

5.3.4. Conclusions and Perspectives

To conclude, we have developed photoredox catalyzed conditions to access various *N,O*-acetals from native small peptides up to tetramers. These reactive intermediates could be used as a platform for the arylation of peptide C-terminus with phenols and indoles (Scheme 5.28).[75] The procedure for the introduction of indoles could be applied to several tetrapeptides bearing functional groups on the side chains. Interestingly, proteinogenic nucleophiles such as serine, threonine, tyrosine and tryptophan were tolerated under the reaction conditions and afforded cross-linked peptides.



Scheme 5.28. Overview of the C-terminal oxidative decarboxylative diversification of small peptides.

The successful addition of bioactive estrone and melatonin to small peptides showed that this strategy could be valuable for the development of peptide bioconjugates. However, the conditions should be improved to broaden the functional group tolerance and for application on larger native peptides or proteins.

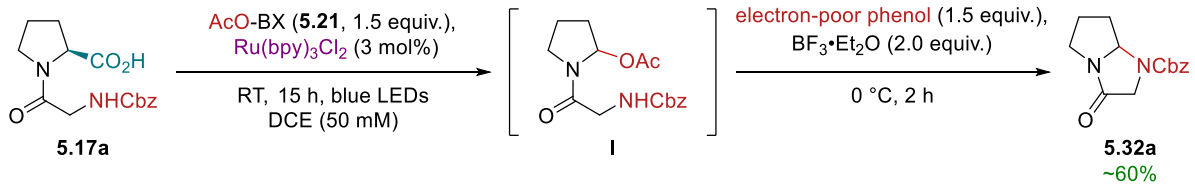
[75] E. Le Du, M. Garreau, J. Waser, *Chem. Sci.* **2021**, *12*, 2467–2473.

5.4. Decarboxylative Cyclization of Dipeptide Derivatives

In this section, our efforts towards the decarboxylative cyclization of dipeptide derivatives to access aminal heterocycles will be described. The project was performed by Emma Robert during her Master Thesis in our group, under the supervision of Prof. Jérôme Waser and myself.

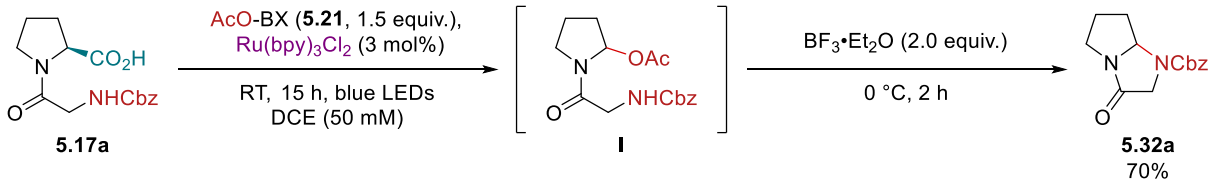
5.4.1. Reaction Discovery and Optimization

As described in the previous section, during the investigation of the scope of phenols in the decarboxylative arylation project, we observed the formation of bicyclic aminal **5.32a** in around 60% yield from dipeptide **5.17a** with electron-poor phenols (Scheme 5.29). The reaction is believed to go through *N,O*-acetal intermediate **I** then formation of an *N*-acyliminium intermediate followed by a competition between the addition of an external nucleophile or cyclization with the N-terminal nucleophile.



Scheme 5.29. Side-reaction observed with electron-poor phenols in the previous project.

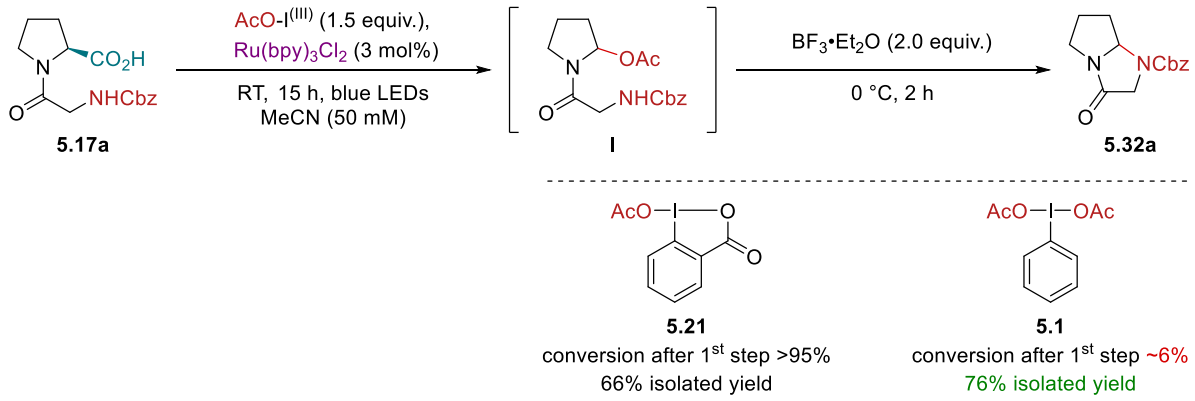
As a control experiment, the reaction was set-up without phenol and we were pleased to see the formation of **5.32a** in 70% isolated yield.



Scheme 5.30. Control experiment without phenol.

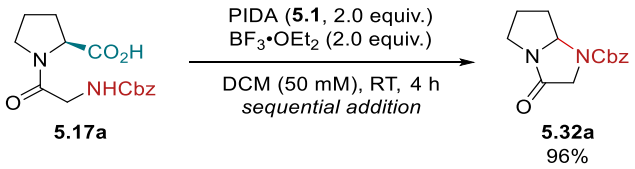
At this point Emma Robert joined our group for her Master Thesis with the goal to investigate this transformation. As most of the work has been performed by her, only a short overview of the key discoveries will be presented. First, the reaction was repeated but this time monitoring the conversion of starting material **5.17a** after the decarboxylation step and then the formation of cyclized product **5.32a** (Scheme 5.31). In the case of AcO-BX (**5.21**), full conversion of **5.17a** towards intermediate **I** was observed and **5.32a** could then be isolated in 66% yield after the addition of the Lewis acid. Inspired by the works of Suárez and Boto groups,[19,20] we investigated the impact of changing the HIR **5.21** to commercially available

PIDA (**5.1**). To our surprise almost no conversion of the dipeptide **5.17a** was observed after the first step but after the addition of $BF_3{\cdot}Et_2O$, **5.32a** could be isolated in 76% yield.



Scheme 5.31. Key discovery for the decarboxylative cyclization of dipeptide **5.17a**.

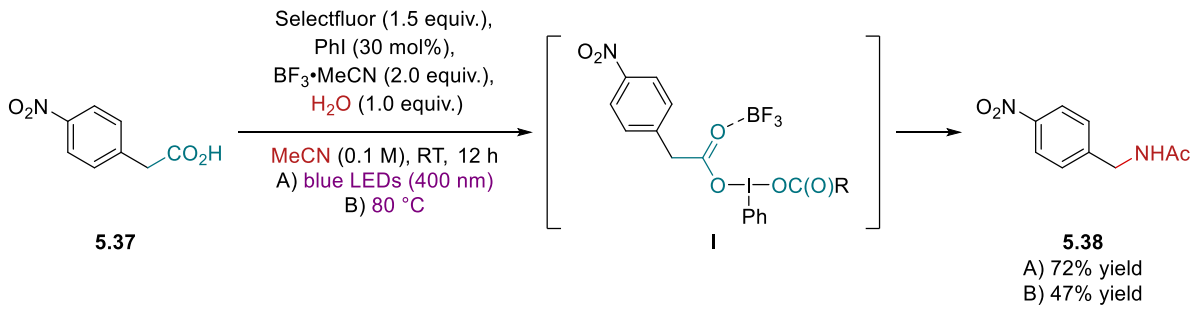
A short optimization showed that the photoredox catalyzed step was not necessary with PIDA and just activation of the HIR with $BF_3{\cdot}Et_2O$ was enough to promote the decarboxylative cyclization reaction.[76] Further fine tuning of reaction conditions showed that by proceeding *via* the sequential addition of 1 equivalent of PIDA and $BF_3{\cdot}Et_2O$ and a second equivalent of each reagent after 2 h would allow to access **5.32a** in almost quantitative yield (Scheme 5.32).



Scheme 5.32. Optimized conditions for the decarboxylative cyclization of **5.17a**.

Interestingly, during our investigation on the PIDA-$BF_3{\cdot}Et_2O$ mediated decarboxylative cyclization of dipeptide derivatives, König and coworkers reported a decarboxylative Ritter-type amination of benzylic and aliphatic carboxylic acids.[77] The reaction involved the *in-situ* generation of iodine (III) intermediate that would be activated by BF_3. However, during the optimization of the reaction with substrate **5.37** they found that the decarboxylation to access **5.38** required light irradiation, thermal activation afforded lower yield (Scheme 5.33).

[76] For activation of HIR with $BF_3{\cdot}Et_2O$: (a) S. Izquierdo, S. Essafi, I. del Rosal, P. Vidossich, R. Pleixats, A. Vallribera, G. Ujaque, A. Lledós, A. Shafir, *J. Am. Chem. Soc.* **2016**, *138*, 12747–12750. (b) A. Dasgupta, C. Thiehoff, P. D. Newman, T. Wirth, R. L. Melen, *Org. Biomol. Chem.* **2021**, *19*, 4852–4865.
[77] R. Narobe, K. Murugesan, S. Schmid, B. König, *ACS Catal.* **2022**, *12*, 809–817.

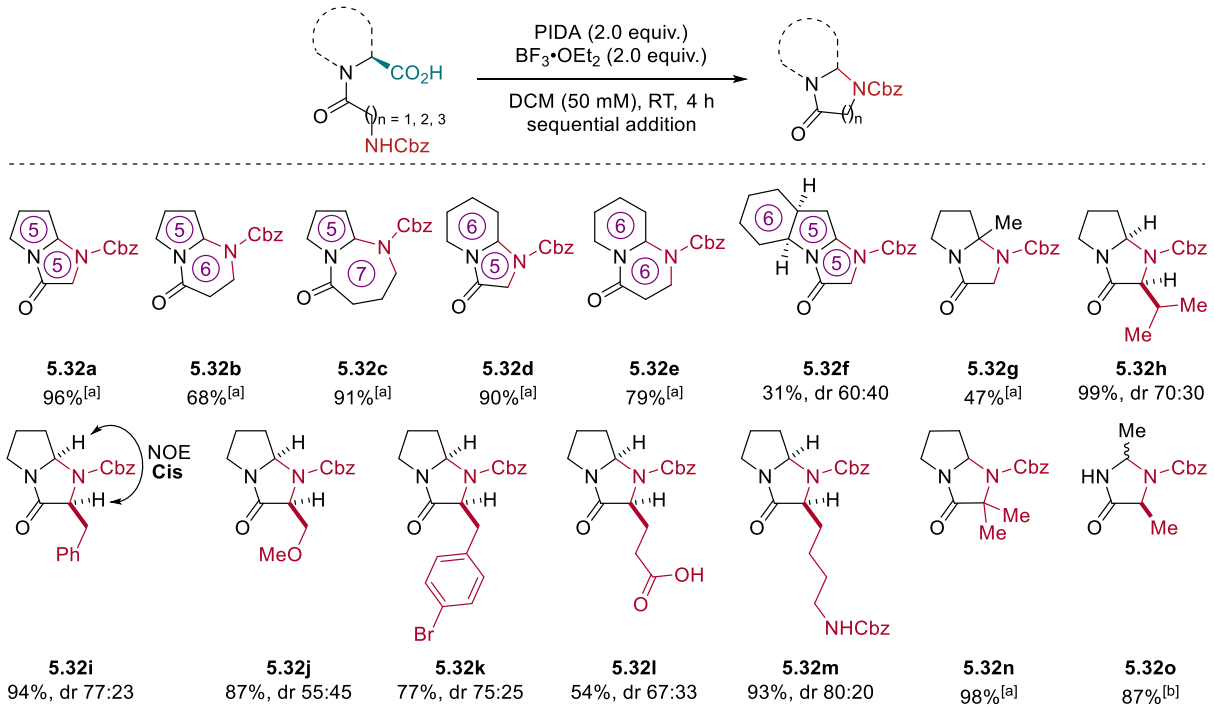


Scheme 5.33. Decarboxylative Ritter-type amination by the König group.

5.4.2. Scope and Limitations[78]

Having the optimized conditions in hand, the scope of the transformation was investigated (Scheme 5.34). Unlike what has been reported in the literature (see 5.1.3), our decarboxylative approach could be used for the synthesis of 5,5- (**5.32a**), 5,6- (**5.32b**), 5,7- (**5.32c**), 6,5- (**5.32d**) and 6,6- (**5.32e**) bicyclic aminals in yields ranging from 68% to 96%. Tricyclic compound **5.32f** could also be accessed albeit with lower yield and with low diastereoselectivity. A tertiary carboxylic acid was tolerated in the transformation and afforded **5.32g** in 47% yield. Modification of the N-terminal amino acid was possible and for example changing glycine to valine allowed to access **5.32h** in 99% yield with a moderate dr of 70:30. Similarly, with phenyl alanine, **5.32i** could be obtained in 94% yield with 77:23 diastereomeric ratio, NOE experiment allowed to determine that the major diastereomer had a *cis*-configuration. Functional groups on the N-terminal amino acid were tolerated such as protected serine (**5.32j**, 87%, dr = 55:45), *para*-bromophenyl alanine (**5.32k**, 77%, dr = 75:25), unprotected glutamic acid (**5.32l**, 54%, dr = 67:30) or protected lysine (**5.32m**, 93%, dr = 80:20). Dipeptide containing aminoisobutyric acid at the N-terminus afforded compound **5.32n** in excellent yield. Finally, non-cyclic dipeptide Cbz-alanine-alanine **5.17b** could also be involved in the decarboxylative cyclization reaction and led to compound **5.32o** in 87% yield.

[78] This work was performed by Emma Robert.



[a] racemic mixture. [b] dr could not be determined.

Scheme 5.34. Scope of decarboxylative cyclization of dipeptide derivatives on a 0.3 mmol scale

During the investigation of the scope of the transformation, several compounds were found to be unsuccessful in the decarboxylative cyclization reaction (Figure 5.6). When compound **5.39** was subjected to the reaction conditions a complex mixture was obtained. Full conversion of the starting material was observed but the desired product could not be clearly identified in the crude mixture. The generation of a highly reactive glycine derived *N*-acyliminium might have induced undesired side reactions. No conversion was observed in the case of compound **5.40** presumably due to the presence of a free amine at the N-terminus. When protected ornithine **5.41** was used only a complex mixture was obtained. Similarly, dipeptide derivative **5.42** did not allow to access the targeted 5,8-bicyclic compound and only a complex mixture was obtained.

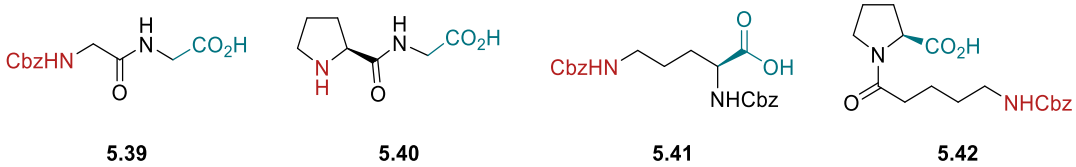
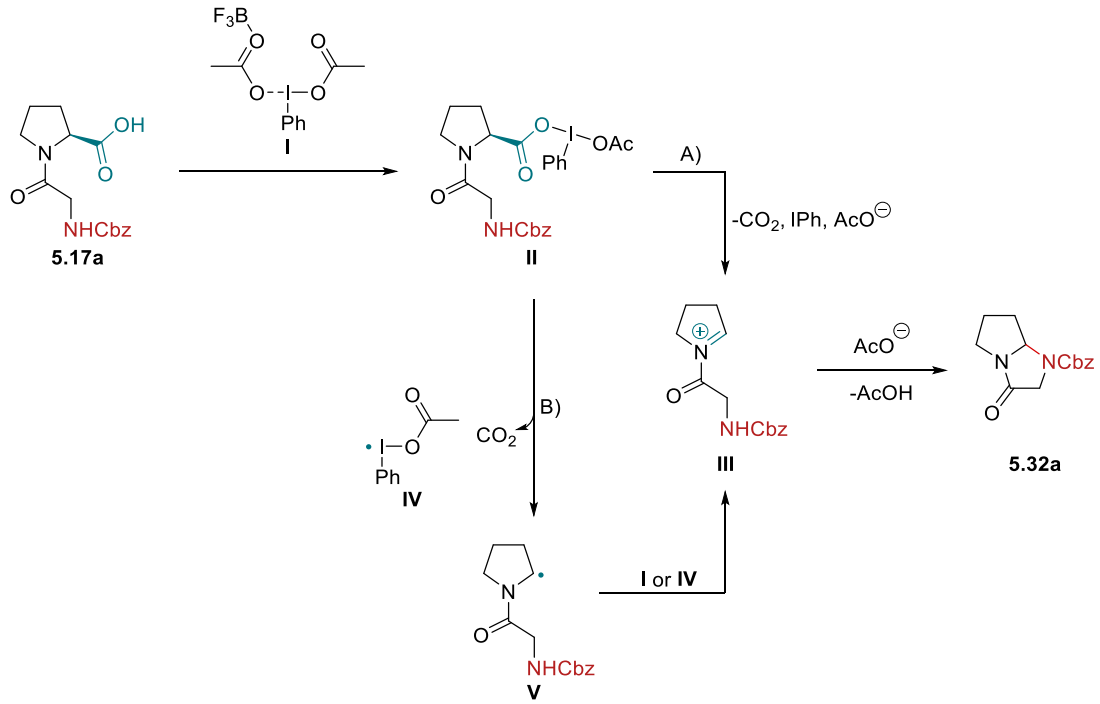


Figure 5.6. Unsuccessful substrate in the decarboxylative cyclization reaction.

5.4.3. Proposed Mechanism

Based on literature precedence, we could propose two different pathways for the decarboxylative cyclization reaction (Scheme 5.35).[76,77] Both would involve the formation of

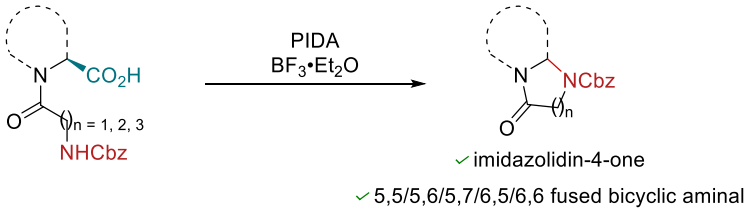
HIR intermediate **II** from activated PIDA-BF_3 species **I**. First a polar pathway would lead to *N*-acyliminium intermediate **III** *via* a fragmentation cascade of intermediate **II** (A). A second possibility would be a heterolytic cleavage of the I-O bond in intermediate **I** followed by decarboxylation leading to iodanyl radical **IV** and α-aminyl radical **V** (B). SET from **I** or **IV** would lead to *N*-acyliminium intermediate **III**, which upon intramolecular trapping would lead to the desired compound **5.32a**. However, as the reaction does not require external activation (heat or light) the pathway B is probably less favored.[77] More mechanistic investigation would be required to differentiate the two pathways.



Scheme 5.35. Proposed mechanisms for the decarboxylative cyclization of dipeptide derivatives illustrated for substrate **5.17a**.

5.4.4. Conclusions and Perspectives

To conclude, we have developed a decarboxylative cyclization reaction allowing to access aminal heterocycles from readily available dipeptide derivatives and a commercially available hypervalent iodine reagent.[79] A broad range of polycyclic aminals with different ring sizes could be accessed. Under the reaction conditions, some functional groups were tolerated such as an ether, a carbamate and, interestingly, a free primary carboxylic acid. The reaction is believed to proceed *via* a 2-electron process. In contrast to reported decarboxylation involving a PIDA-BF_3,[19-21,77] our method did not require additional additive, heating or light irradiation.



Scheme 5.36. Overview of the decarboxylative cyclization of dipeptide derivatives.

We have focused on the cyclization of dipeptide derivatives by exploiting the nucleophilicity of the N-terminal, but several follow-up investigations could be considered. First, other internal nucleophiles could be explored in the transformation to access more diverse cyclic scaffolds. The development of an asymmetric decarboxylative cyclization could be attempted by adding, for example, a chiral phosphate catalyst to the reaction. Finally, the implementation of the strategy for intermolecular reactions could be envisioned.

[79] E. G. L. Robert, E. Le Du, J. Waser, *Chem. Commun.* **2022**, *58*, 3473–3476.

5.5. References

1. For reviews: (a) K. Fosgerau, T. Hoffmann, *Drug Discov. Today* **2015**, *20*, 122–128. (b) T. Dang, R. D. Süssmuth, *Acc. Chem. Res.* **2017**, *50*, 1566–1576. (c) I. W. Hamley, *Chem. Rev.* **2017**, *117*, 14015–14041. (d) A. Henninot, J. C. Collins, J. M. Nuss, *J. Med. Chem.* **2018**, *61*, 1382–1414.
2. For reviews: (a) J. S. Davies, *J. Pept. Sci.* **2003**, *9*, 471–501. (b) P. G. Dougherty, A. Sahni, D. Pei, *Chem. Rev.* **2019**, *119*, 10241–10287. (c) V. Sarojini, A. J. Cameron, K. G. Varnava, W. A. Denny, G. Sanjayan, *Chem Rev* **2019**, *119*, 10318–10359.
3. For reviews: (a) Y. H. Lau, P. de Andrade, Y. Wu, D. R. Spring, *Chem. Soc. Rev.* **2015**, *44*, 91–102. (b) X. Xie, L. Gao, A. Y. Shull, Y. Teng, *Future Med. Chem.* **2016**, *8*, 1969–1980. (c) M. Moiola, M. G. Memeo, P. Quadrelli, *Molecules* **2019**, *24*, 3654.
4. For reviews: (a) D. J. Craik, D. P. Fairlie, S. Liras, D. Price, *Chem. Biol. Drug Des.* **2013**, *81*, 136–147. (b) S.-B. Yang, N. Banik, B. Han, D.-N. Lee, J. Park, *Pharmaceutics* **2022**, *14*, 1378.
5. For reviews: (a) T. Ueda, *Biochim. Biophys. Acta BBA - Proteins Proteomics* **2014**, *1844*, 2053–2057. (b) P. M. Drake, D. Rabuka, *Curr. Opin. Chem. Biol.* **2015**, *28*, 174–180. For selected example: D. T. Cohen, C. Zhang, C. M. Fadzen, A. J. Mijalis, L. Hie, K. D. Johnson, Z. Shriver, O. Plante, S. J. Miller, S. L. Buchwald, B. L. Pentelute, *Nat. Chem.* **2019**, *11*, 78–85.
6. J. N. deGruyter, L. R. Malins, P. S. Baran, *Biochemistry* **2017**, *56*, 3863–3873.
7. For reviews: (a) J.-J. Chung, S. Shikano, Y. Hanyu, M. Li, *Trends Cell Biol.* **2002**, *12*, 146–150. (b) G. Marino, U. Eckhard, C. M. Overall, *ACS Chem. Biol.* **2015**, *10*, 1754–1764. (c) S. Sharma, M. R. Schiller, *Crit. Rev. Biochem. Mol. Biol.* **2019**, *54*, 85–102.
8. For reviews: (a) J. Alsina, F. Albericio, *Biopolymers* **2003**, *71*, 454–477. (b) E. Baslé, N. Joubert, M. Pucheault, *Chem. Biol.* **2010**, *17*, 213–227.
9. For reviews on decarboxylative couplings: (a) Z.-L. Wang, *Adv. Synth. Catal.* **2013**, *355*, 2745–2755. (b) T. Patra, D. Maiti, *Chem. Eur. J.* **2017**, *23*, 7382–7401.
10. L. R. Malins, *Pept. Sci.* **2018**, *110*, e24049.
11. (a) M. Faraday, *Ann. Phys. Chem.* **1834**, *109*, 433–451. (b) H. Kolbe, *Ann. Chem. Pharm.* **1849**, *69*, 257–294.
12. H. Hofer, M. Moest, *Justus Liebigs Ann. Chem.* **1902**, *323*, 284–323.
13. A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619.
14. A. S. Mackay, R. J. Payne, L. R. Malins, *J. Am. Chem. Soc.* **2022**, *144*, 23–41.
15. (a) P. Renaud, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 843–844. (b) D. Seebach, R. Charczuk, C. Gerber, P. Renaud, H. Berner, H. Schneider, *Helv. Chim. Acta* **1989**, *72*, 401–425. (c) C. Gerber, D. Seebach, *Helv. Chim. Acta* **1991**, *74*, 1373–1385.
16. For reviews on *N*-acyliminiums: (a) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817–3856. (b) M. G. Vinogradov, O. V. Turova, S. G. Zlotin, *Russ. Chem. Rev.* **2017**, *86*, 1–17. (c) P. Wu, T. E. Nielsen, *Chem. Rev.* **2017**, *117*, 7811–7856.
17. (a) Y. Lin, L. R. Malins, *Chem. Sci.* **2020**, *11*, 10752–10758. (b) Y. Lin, L. R. Malins, *J. Am. Chem. Soc.* **2021**, *143*, 11811–11819.
18. Y. Lin, L. R. Malins, *Synthesis* **2022**, *54*, 3558–3567.
19. (a) A. Boto, R. Hernández, E. Suárez, *Tetrahedron Lett.* **1999**, *40*, 5945–5948. (b) A. Boto, R. Hernández, E. Suárez, *J. Org. Chem.* **2000**, *65*, 4930–4937.
20. Selected examples: (a) A. Boto, J. A. Gallardo, R. Hernández, C. J. Saavedra, *Tetrahedron Lett.* **2005**, *46*, 7807–7811. (b) C. J. Saavedra, R. Hernández, A. Boto, E. Álvarez, *Tetrahedron Lett.* **2006**, *47*, 8757–8760. (c) R. Fan, W. Li, B. Wang, *Org. Biomol. Chem.* **2008**, *6*, 4615-4621. (d) D. Hernández, A. Boto, D. Guzmán, E. Alvarez, *Org. Biomol. Chem.* **2017**, *15*, 7736–7742. (e) D. Hernández, C. Carro, A. Boto, *J. Org. Chem.* **2021**, *86*, 2796–2809.
21. Y. Harayama, M. Yoshida, D. Kamimura, Y. Wada, Y. Kita, *Chem. Eur. J.* **2006**, *12*, 4893–4899.
22. M.-L. Shen, Y. Shen, P.-S. Wang, *Org. Lett.* **2019**, *21*, 2993–2997.

23. Selected examples: (a) H.-P. Bi, L. Zhao, Y.-M. Liang, C.-J. Li, *Angew. Chem. Int. Ed.* **2009**, *48*, 792–795. (b) H.-P. Bi, W.-W. Chen, Y.-M. Liang, C.-J. Li, *Org. Lett.* **2009**, *11*, 3246–3249. (c) J. Guo, Y. Xie, Q.-L. Wu, W.-T. Zeng, A. S. C. Chan, J. Weng, G. Lu, *RSC Adv.* **2018**, *8*, 16202–16206.
24. (a) A. Borodine, *Ann. Chem. Pharm.* **1861**, *119*, 121–123. (b) H. Hunsdiecker, Cl. Hunsdiecker, *Berichte Dtsch. Chem. Ges. B Ser.* **1942**, *75*, 291–297. (c) J. J. Li, in *Name React.*, Springer International Publishing, Cham, **2014**, pp. 327–328.
25. (a) D. H. R. Barton, D. Crich, W. B. Motherwell, *J. Chem. Soc. Chem. Commun.* **1983**, 939-941. (b) D. H. R. Barton, D. Crich, W. B. Motherwell, *Tetrahedron Lett.* **1983**, *24*, 4979–4982. (c) M. F. Saraiva, M. R. C. Couri, M. Le Hyaric, M. V. de Almeida, *Tetrahedron* **2009**, *65*, 3563–3572.
26. K. Okada, K. Okamoto, M. Oda, *J. Am. Chem. Soc.* **1988**, *110*, 8736–8738.
27. K. Okada, K. Okamoto, M. Oda, *J. Chem. Soc. Chem. Commun.* **1989**, 1636-1637.
28. K. Okada, K. Okamoto, N. Morita, K. Okubo, M. Oda, *J. Am. Chem. Soc.* **1991**, *113*, 9401–9402.
29. K. Okada, K. Okubo, N. Morita, M. Oda, *Chem. Lett.* **1993**, *22*, 2021–2024.
30. M. J. Schnermann, L. E. Overman, *Angew. Chem. Int. Ed.* **2012**, *51*, 9576–9580.
31. G. Pratsch, G. L. Lackner, L. E. Overman, *J. Org. Chem.* **2015**, *80*, 6025–6036.
32. (a) J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C.-M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 2174–2177. (b) K. M. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. G. Ackerman, D. J. Weix, *J. Am. Chem. Soc.* **2016**, *138*, 5016–5019.
33. T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate, P. S. Baran, *Science* **2016**, *352*, 801–805.
34. J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D.-H. Bao, F.-L. Wei, T. Zhou, M. D. Eastgate, P. S. Baran, *Nature* **2017**, *545*, 213–218.
35. J. M. Smith, T. Qin, R. R. Merchant, J. T. Edwards, L. R. Malins, Z. Liu, G. Che, Z. Shen, S. A. Shaw, M. D. Eastgate, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 11906–11910.
36. T. Qin, L. R. Malins, J. T. Edwards, R. R. Merchant, A. J. E. Novak, J. Z. Zhong, R. B. Mills, M. Yan, C. Yuan, M. D. Eastgate, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 260–265.
37. C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan, P. S. Baran, *Science* **2017**, *356*, eaam7355.
38. Y. Jin, M. Jiang, H. Wang, H. Fu, *Sci. Rep.* **2016**, *6*, 20068.
39. W.-M. Cheng, R. Shang, Y. Fu, *ACS Catal.* **2017**, *7*, 907–911.
40. Y. Jin, H. Yang, H. Fu, *Chem. Commun.* **2016**, *52*, 12909–12912.
41. M. Jiang, H. Yang, H. Fu, *Org. Lett.* **2016**, *18*, 1968–1971.
42. X. Chen, X. Luo, X. Peng, J. Guo, J. Zai, P. Wang, *Chem. Eur. J.* **2020**, *26*, 3226–3230.
43. T. Itou, Y. Yoshimi, K. Nishikawa, T. Morita, Y. Okada, N. Ichinose, M. Hatanaka, *Chem. Commun.* **2010**, *46*, 6177–6179.
44. C. Cassani, G. Bergonzini, C.-J. Wallentin, *Org. Lett.* **2014**, *16*, 4228–4231.
45. S. B. Lang, K. M. O'Nele, J. T. Douglas, J. A. Tunge, *Chem. Eur. J.* **2015**, *21*, 18589–18593.
46. L. Chu, C. Ohta, Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 10886–10889.
47. S. J. McCarver, J. X. Qiao, J. Carpenter, R. M. Borzilleri, M. A. Poss, M. D. Eastgate, M. M. Miller, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2017**, *56*, 728–732.
48. S. Bloom, C. Liu, D. K. Kölmel, J. X. Qiao, Y. Zhang, M. A. Poss, W. R. Ewing, D. W. C. MacMillan, *Nat. Chem.* **2018**, *10*, 205–211.
49. D. C. Marcote, R. Street-Jeakings, E. Dauncey, J. J. Douglas, A. Ruffoni, D. Leonori, *Org. Biomol. Chem.* **2019**, *17*, 1839–1842.
50. Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 5257–5260.
51. K. Maeda, H. Saito, K. Osaka, K. Nishikawa, M. Sugie, T. Morita, I. Takahashi, Y. Yoshimi, *Tetrahedron* **2015**, *71*, 1117–1123.

52. F. Le Vaillant, T. Courant, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204. A similar strategy was concurrently reported: Q.-Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199.
53. M. Garreau, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2019**, *58*, 8182–8186.
54. F. Le Vaillant, M. D. Wodrich, J. Waser, *Chem. Sci.* **2017**, *8*, 1790–1800.
55. Selected examples: (a) S. Inuki, K. Sato, Y. Fujimoto, *Tetrahedron Lett.* **2015**, *56*, 5787–5790. (b) S. N. Khan, M. K. Zaman, R. Li, Z. Sun, *J. Org. Chem.* **2020**, *85*, 5019–5026. (c) S. Shirase, S. Tamaki, K. Shinohara, K. Hirosawa, H. Tsurugi, T. Satoh, K. Mashima, *J. Am. Chem. Soc.* **2020**, *142*, 5668–5675. (d) T. M. Faraggi, W. Li, D. W. C. MacMillan, *Isr. J. Chem.* **2020**, *60*, 410–415.
56. C. T. Walsh, *Tetrahedron Lett.* **2015**, *56*, 3075–3081.
57. (a) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859. (b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J Med Chem* **2014**, *57*, 10257–10274.
58. J. Peng, T. Lin, W. Wang, Z. Xin, T. Zhu, Q. Gu, D. Li, *J. Nat. Prod.* **2013**, *76*, 1133–1140.
59. P. Merlin, J. C. Braekman, D. Daloze, J. M. Pasteels, *J. Chem. Ecol.* **1988**, *14*, 517–527.
60. A. D. Elbein, J. E. Tropea, M. Mitchell, G. P. Kaushal, *J. Biol. Chem.* **1990**, *265*, 15599–15605.
61. S. Chen, M. Jiang, B. Chen, J. Salaenoi, S.-I. Niaz, J. He, L. Liu, *Mar. Drugs* **2019**, *17*, 522.
62. T. R. Blackmore, P. E. Thompson, *Heterocycles* **2011**, *83*, 1953–1975.
63. Selected recent examples: (a) X. Ren, J. A. O'Hanlon, M. Morris, J. Robertson, L. L. Wong, *ACS Catal.* **2016**, *6*, 6833–6837. (b) A. Bertamino, G. Lauro, C. Ostacolo, V. Di Sarno, S. Musella, T. Ciaglia, P. Campiglia, G. Bifulco, I. M. Gomez-Monterrey, *J. Org. Chem.* **2017**, *82*, 12014–12027. (c) Z. Zhu, X. Lv, J. E. Anesini, D. Seidel, *Org. Lett.* **2017**, *19*, 6424–6427. (d) Y. Yoshida, K. Omori, T. Hiroshige, T. Mino, M. Sakamoto, *Chem. Asian J.* **2019**, *14*, 2737–2743. (e) S. Biswas, B. Porashar, P. J. Arandhara, A. K. Saikia, *Chem. Commun.* **2021**, *57*, 11701–11704.
64. J. Wu, H. Jiang, J. Yang, Z. Jin, D. Chen, *Tetrahedron Lett.* **2017**, *58*, 546–551.
65. This work was performed by Dr. M. Garreau.
66. Dr. Marion Garreau, **2020**, *Development of Photocatalysts towards the Visible-Light driven C-Terminal Bioconjugation of Peptides and Proteins*, PhD Thesis n°10420, EPFL, Lausanne.
67. Selected examples: (a) H. Huang, G. Zhang, Y. Chen, *Angew. Chem. Int. Ed.* **2015**, *54*, 7872–7876. (b) G.-X. Li, X. Hu, G. He, G. Chen, *ACS Catal.* **2018**, *8*, 11847–11853.
68. T. J. Osberger, D. C. Rogness, J. T. Kohrt, A. F. Stepan, M. C. White, *Nature* **2016**, *537*, 214–219.
69. M. Wang, J. Waser, *Angew. Chem. Int. Ed.* **2019**, *58*, 13880–13884.
70. Selected examples proposing the involvement of iodonium ester in decarboxylative coupling: (a) Y. Sakakibara, E. Ito, T. Fukushima, K. Murakami, K. Itami, *Chem. Eur. J.* **2018**, *24*, 9254–9258. (b) B. Maeda, Y. Sakakibara, K. Murakami, K. Itami, *Org. Lett.* **2021**, *23*, 5113–5117. (c) P. Li, J. R. Zbieg, J. A. Terrett, *ACS Catal.* **2021**, *11*, 10997–11004.
71. J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617–1622.
72. (a) D. D. M. Wayner, J. J. Dannenberg, D. Griller, *Chem. Phys. Lett.* **1986**, *131*, 189–191. (b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.
73. G.-X. Li, X. Hu, G. He, G. Chen, *Chem. Sci.* **2019**, *10*, 688–693.
74. G.-X. Li, C. A. Morales-Rivera, Y. Wang, F. Gao, G. He, P. Liu, G. Chen, *Chem. Sci.* **2016**, *7*, 6407–6412.
75. E. Le Du, M. Garreau, J. Waser, *Chem. Sci.* **2021**, *12*, 2467–2473.
76. For activation of HIR with $BF_3 \cdot Et_2O$: (a) S. Izquierdo, S. Essafi, I. del Rosal, P. Vidossich, R. Pleixats, A. Vallribera, G. Ujaque, A. Lledós, A. Shafir, *J. Am. Chem. Soc.* **2016**, *138*, 12747–12750. (b) A. Dasgupta, C. Thiehoff, P. D. Newman, T. Wirth, R. L. Melen, *Org. Biomol. Chem.* **2021**, *19*, 4852–4865.
77. R. Narobe, K. Murugesan, S. Schmid, B. König, *ACS Catal.* **2022**, *12*, 809–817.
78. This work was performed by Emma Robert.
79. E. G. L. Robert, E. Le Du, J. Waser, *Chem. Commun.* **2022**, *58*, 3473–3476.

Chapter 6:

General Conclusion and Outlook

6. General Conclusion and Outlook

6.1. General Conclusion

The research projects presented in this Thesis aimed to develop new alkynyl hypervalent iodine reagents and to functionalize (aza)peptides. In the first project, we described the synthesis of four new *N*-heterocyclic alkynyl hypervalent iodine reagents (Figure 6.1). The reactivity of the new reagents was assessed and compared to already established reagents. The difference in reactivity between the reagents was analyzed taking into account their key structural features, determined by X-ray diffraction analysis, and their computed electronic density distributions. In addition, their bioactivity in the inhibition of thiol-mediated uptake was investigated but did not show promising results.

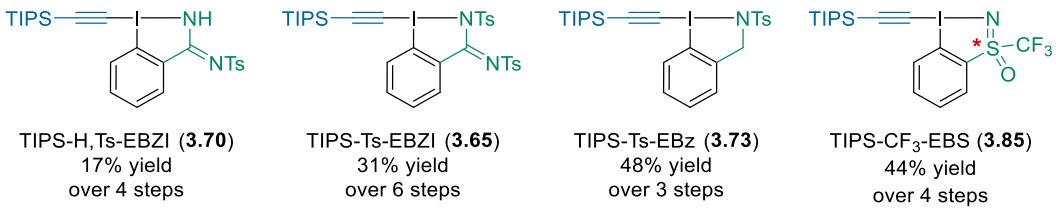
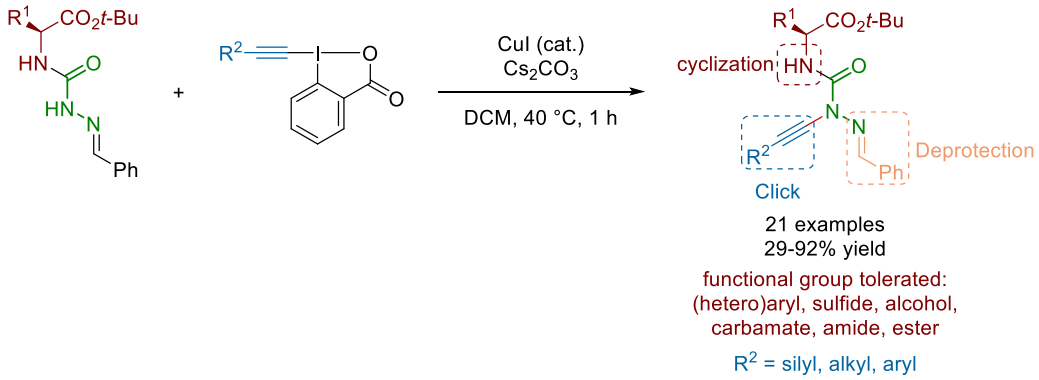


Figure 6.1. New *N*-heterocyclic alkynyl hypervalent iodine reagents developed.

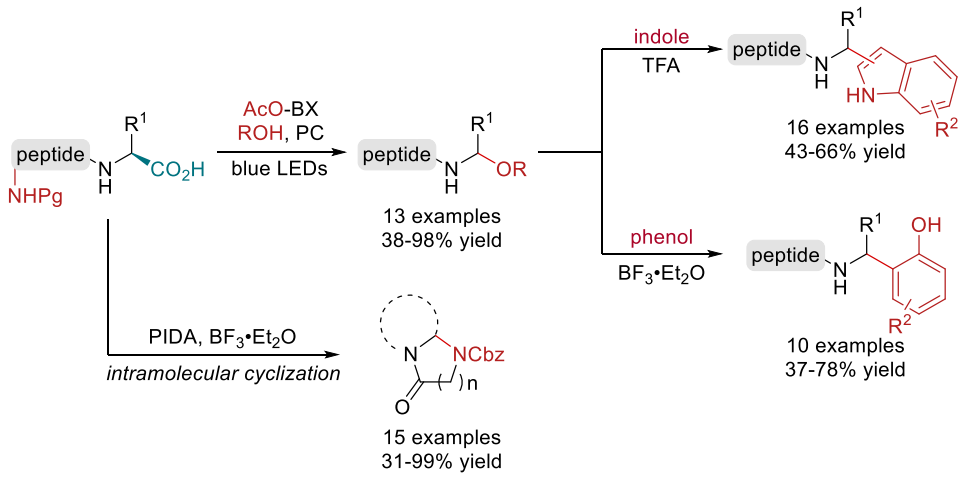
Next, we explored the alkynylation of hydrazides with alkynyl hypervalent iodine reagents. In collaboration with Julien Borrel, we developed a copper-catalyzed alkynylation of azadipeptide derivatives using EBX reagents (Scheme 6.1). Silyl-, alkyl- and aryl-substituted alkynes could be transferred and most proteinogenic functional groups were tolerated in the transformation. Functionalized azadipeptides could be obtained by nucleophilic attack or cycloaddition on the triple bond of the obtained α-alkynyl azaglycine derivatives.



Scheme 6.1. Copper-catalyzed alkynylation of azadipeptide derivatives.

Finally, we investigated the decarboxylative functionalization of small peptide C-termini with hypervalent iodine reagents (Scheme 6.2). First, in collaboration with Dr. Marion Garreau,

we developed a photoredox-catalyzed hydroxylation of small peptides allowing to access *N,O*-acetals, which could be used for the diversification of peptide C-termini *via* Friedel-Crafts arylation with indoles and phenols. New types of peptide cross-linking were formed when proteinogenic nucleophiles were used. Then, in collaboration with Emma Robert, a decarboxylative cyclization strategy to access aminal heterocycles from dipeptide derivatives and PIDA was discovered and optimized. Several functional groups were tolerated and a library of aminals with different ring sizes could be accessed.



Scheme 6.2. Decarboxylative functionalization of small peptides C-terminus with hypervalent iodine reagents.

6.2. Outlook

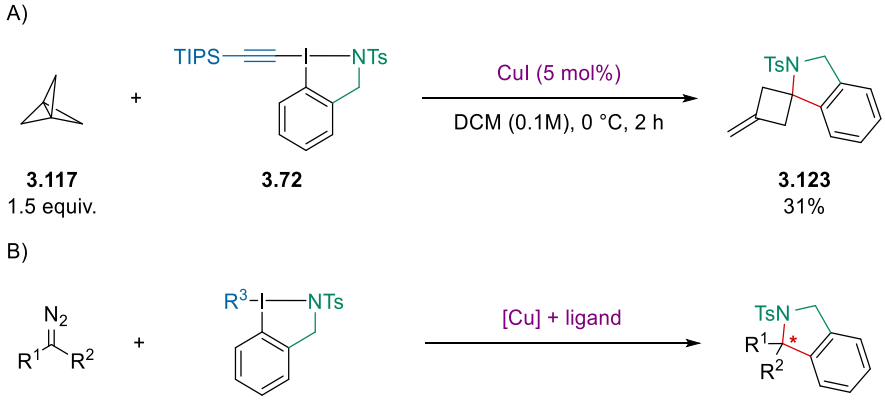
Building upon the results presented in this Thesis, several further research projects could be envisaged and will be discussed in the following sections.

6.2.1. *N*-Heterocyclic Alkynyl Hypervalent Iodine Reagents

During our investigation on the reactivity of reagents **3.72** with [1.1.1]-propellane (**3.117**), we isolated isoindoline **3.123** in 31% yield using CuI as catalyst (Scheme 6.3.A). The isoindoline moiety is found in numerous bioactive compounds and developing new strategies to access this scaffold would be desirable.[1] The serendipitously discovered transformation could be used to develop an enantioselective synthesis of isoindoline (B). Instead of using **3.117** as carbene precursors, more common diazo compounds could be investigated. We have shown that the reaction seems to require a hypervalent iodine bond (see section 3.3.3.6), several reagents could be investigated to establish which ligand on the hypervalent iodine

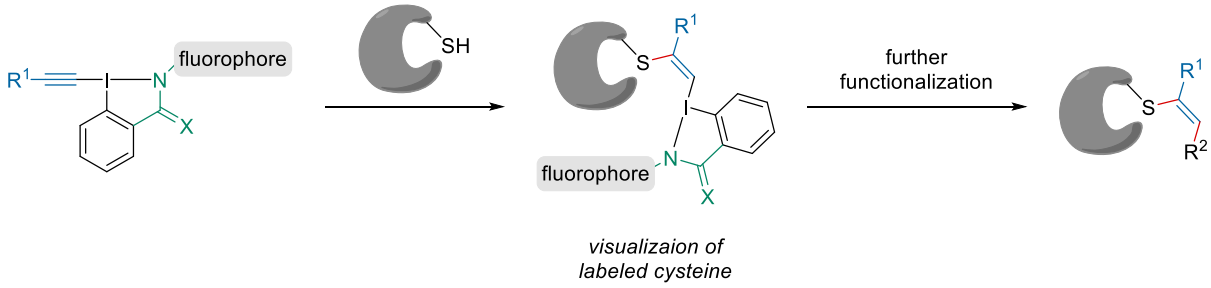
[1]For reviews: (a) K. Speck, T. Magauer, *Beilstein J. Org. Chem.* **2013**, *9*, 2048–2078. (b) R. Bhatia, *Curr. Top. Med. Chem.* **2016**, *17*, 189–207.

reagent would be more suitable for the transformation. A compromise between reaction efficiency and atom economy should be kept in mind as only one part of the hypervalent iodine reagent is transferred. Finally, adding a ligand to the reaction mixture could allow to develop an enantioselective synthesis of isoindoline.



Scheme 6.3. Synthesis of isoindoline compounds from hypervalent iodine reagents.

As discussed in the Thesis (see Chapter 3), *N*-heterocyclic hypervalent iodine reagents offer additional possibilities for the functionalization of their scaffolds. One could think about decorating such reagents with fluorophores (Scheme 6.4). Cysteine labeling could then be investigated,[2] the introduction of a fluorophore would allow to visualize the labeled cysteines. Moreover, the functionalization of the formed S-VBX could then potentially be monitored thanks to the loss of the fluorophore from the cysteine-containing peptides.



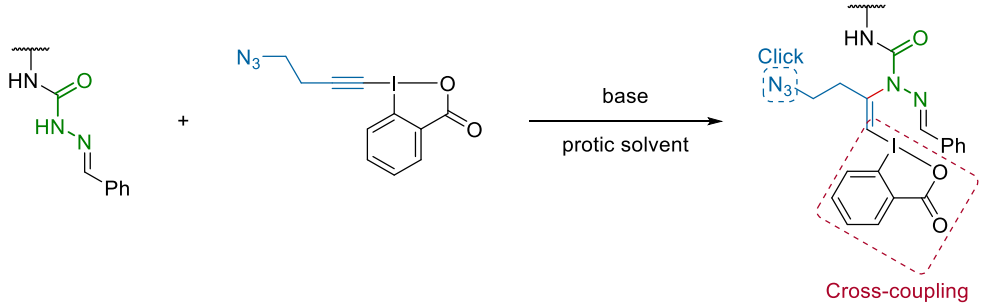
Scheme 6.4. Cysteine labeling with fluorophore-decorated hypervalent iodine reagents.

6.2.2. Azapeptides

Building upon what has been developed in our group for the functionalization of peptides, on could think of adapting some transformations for azapeptides. For example, during the exploration of the reactivity of azadipeptides with EBX reagents, an attempt to synthesize VBX was made. Although the desired product could not be isolated, signals in the

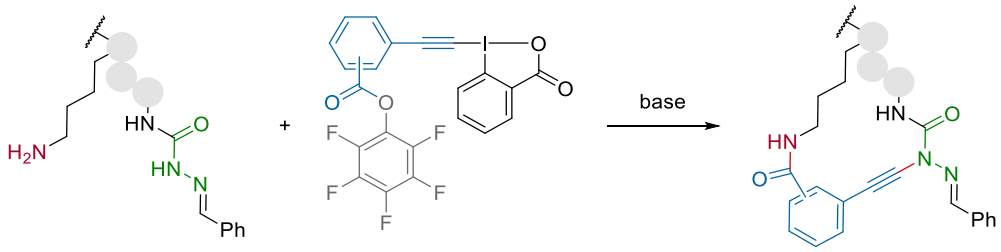
[2] R. Tessier, J. Ceballos, N. Guidotti, R. Simonet-Davin, B. Fierz, J. Waser, *Chem* **2019**, *5*, 2243–2263.

crude NMR spectrum as well as mass spectrometry confirmed the formation of a VBX intermediate. One could optimize this transformation and develop a “doubly orthogonal” labeling of azapeptides (Scheme 6.5).



Scheme 6.5. “Doubly orthogonal” labeling of azapeptides.

Alternatively, an azaglycine-lysine stapling could be developed similarly to what our group reported for cysteine-lysine stapling.[3] In this case, the α-nitrogen of the azaglycine residue would react with the alkyne part and the lysine with the activated ester (Scheme 6.6).

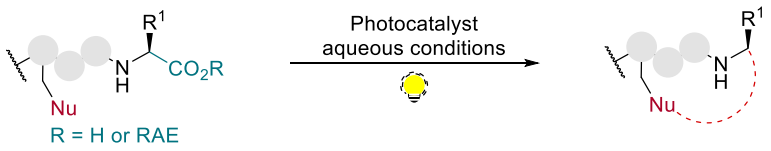


Scheme 6.6. Azaglycine-lysine stapling.

6.2.3. Decarboxylative Functionalization of Peptides

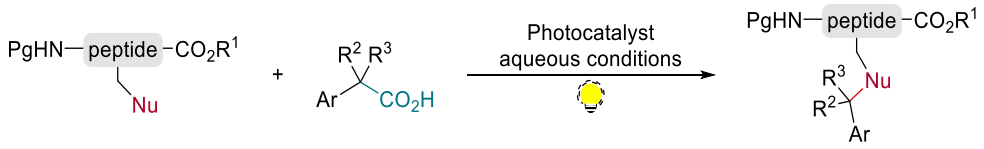
Having established that masked *N*-acyliminiums could be generated under photoredox conditions, one could think of leveraging these reactive intermediates to access macrocyclic peptides (Scheme 6.7). The reaction could be developed from native peptides and different proteinogenic nucleophiles could be investigated in the transformation. Redox active esters could also be tested in this reaction, Aggarwal and coworkers have recently disclosed a photoredox catalyzed decarboxylative phosphorylation of amino acid redox-active esters involving the generation of *N*-acyliminium intermediates.[4]

[3] J. Ceballos, E. Grinhagena, G. Sangouard, C. Heinis, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 9022–9031.
[4] D. Reich, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2022**, *61*, e202207063.



Scheme 6.7. Macrocyclization of peptides through a decarboxylative cyclization strategy.

We have demonstrated that some proteinogenic nucleophiles could be used to trap *N*-acyliminiums leading to new types of peptide cross-linking. The Itami and Terrett groups recently reported hypervalent iodine mediated photoredox catalyzed decarboxylation of benzylic carboxylic acids proceeding *via* benzylic carbocations.[5] As the reaction conditions are similar to those we reported for small peptides, one could think of combining both approaches to functionalize nucleophilic side-chains of peptides (Scheme 6.8). The use of bioactive carboxylic acid would allow to access potentially valuable bioconjugates.



Scheme 6.8. Decarboxylative functionalization of nucleophilic peptide residues.

[5] (a) B. Maeda, Y. Sakakibara, K. Murakami, K. Itami, *Org. Lett.* **2021**, *23*, 5113–5117. (b) P. Li, J. R. Zbieg, J. A. Terrett, *ACS Catal.* **2021**, *11*, 10997–11004.

Chapter 7:

Experimental Part

7. Experimental Part

7.1. General Methods

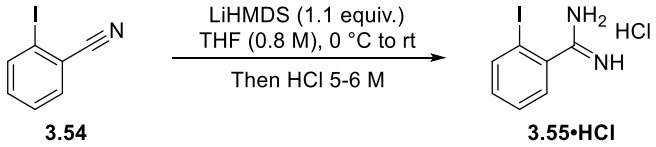
All reactions were carried out under air unless stated otherwise. Reactions requiring heating were carried out using DrySyn heating block. For flash chromatography, distilled technical grade solvents were used. THF, toluene, Et_2O and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content <10 ppm, Karl-Fischer titration). Solvents were degassed by bubbling with a balloon of argon or by Freeze-Pump-Thaw when mentioned. All chemicals were purchased from Acros, Aldrich, Combi-blocks, Fluka, Fluorochem, Merck, TCI or VWR and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Silicycle silica 40-63 µm (230-400 mesh), using the solvents indicated as eluent with 0.1-0.5 bar pressure or using Biotage Isolera Spektra One with pre-packaged silica cartridges purchased from Buchi, models: Sepacore or GraceResolve (4 g, 12 g, 25 g, 40g, 80g, 120g). TLC was performed on Merck silica gel 60 F254 TLC glass plates and visualized with UV light and potassium permanganate, *p*-anisaldehyde or ninhydrin stain. ^{1}H-NMR spectra were recorded on a Bruker DPX-400 400 MHz spectrometer in chloroform-d, DMSO-d_6, acetonitrile-d_3, methylene chloride-d_2, acetone-d_6 or methanol-d_4. All signals are reported in ppm using the residual solvent signal as internal reference (chloroform-d: 7.26 ppm, DMSO-d_6: 2.50 ppm, acetonitrile-d_3: 1.94 ppm, methylene chloride-d_2: 5.32 ppm, acetone-d_6: 2.06 ppm, methanol-d_4: 3.31 ppm). The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration, assignment). ^{13}C-NMR spectra were recorded with {^{1}H} decoupling on a Bruker DPX-400 101 MHz spectrometer in chloroform-d, DMSO-d_6, acetonitrile-d_3, methylene chloride-d_2, acetone-d_6 or methanol-d_4. All signals are reported in ppm using the residual solvent signal as internal reference (chloroform-d: 77.0 ppm, DMSO-d_6: 39.5 ppm, acetonitrile-d_3: 118.3 and 1.3 ppm, methylene chloride-d_2: 53.8 ppm or acetone-d_6: 206.3 and 29.8 ppm, methanol-d_4: 49.1 ppm). ^{19}F-NMR spectra were recorded with {^{1}H} decoupling on a Bruker DPX-400 376 MHz spectrometer in chloroform-d, DMSO-d_6 or acetone-d_6. ^{11}B-NMR spectra were recorded on a Bruker DPX-400 128 MHz spectrometer in DMSO-d_6 or acetone-d_6. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL. Electrospray-ionization HRMS data were acquired on a Q-Tof Ultima mass spectrometer (Waters) or a Q-Tof 6530 Accurate mass spectrometer (Agilent) operated in the positive ionization mode and fitted with a standard Z-spray ion source equipped with the Lock-Spray interface. Data from the Lock-Spray were used to calculate a correction factor for the mass scale and provide accurate mass information of the analyte. Data were processed using the MassLynx 4.1 software.

Atmospheric pressure photo-ionization (APPI) HRMS measurements were done on a LTQ Orbitrap Elite instrument (Thermofisher) operated in the positive ionization mode. The raw data obtained from the Q-TOF Waters instrument does not take into account the mass of the electron for the ion, the obtained raw data has been corrected by removing (positive ionization) or adding (negative ionization) the mass of the electron (0.5 mDa). Determination of enantiomeric purity was performed by HPLC analysis on chiral stationary phase on an Agilent Acquity instrument using a Daicel CHIRALPAK IB chiral column. The exact conditions for the analyses are specified within the characterization section. Optical rotations were measured on a polarimeter using a 10 cm cell with a Na 589 nm filter. The specific solvents and concentrations (in g/100 mL) are indicated. RP-HPLC was carried out on an Agilent 1260 HPLC system with a G2260A 1260 Prep ALS Autosampler, a G1361a 1260 Prep Pump, a G1365C 1260 MWD detector and a G1364B 1260 FC-PS collector, coupled with a Waters XBridge semi-preparative C18 column (19 x 150 mm, 5 µm). Water (solvent A) and water:acetonitrile 5:95 (solvent B), each containing 0.1% TFA, were used as the mobile phase at a flow rate of 20 $mL.min^{-1}$. The following method was used: 100% A to 100% B in 20 minutes. Photoredox catalyzed reactions were performed in test tubes (5 and 10 mL), which were hold using a rack for test tubes placed at the center of a crystallization flask. On this flask 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). The distance between the LEDs and the test tubes was approximatively 2 cm for the test tubes and 5 cm for the Schlenk flasks. Long irradiation resulted in temperature increasing up to 37°C during overnight reactions. Tetrapeptides were synthesized by solid phase peptide synthesis using a Multipep RSi Intavis.

7.2. Development and Study of N-Heterocyclic Alkynyl Hypervalent Iodine Reagents

7.2.1. Preparation of Precursors

2-Iodobenzamidine hydrochloride (3.55·HCl)

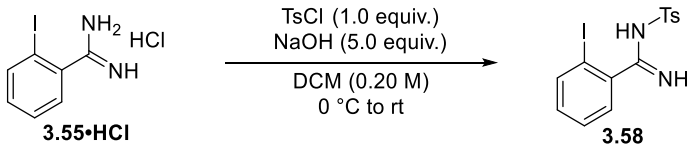


Following a reported procedure,[1] an oven-dried 250 mL flask was charged with LiHMDS (22 mL, 22 mmol, 1.1 equiv.) and cooled to 0 °C and a solution of 2-iodobenzonitrile (**3.54**) (4.6 g, 20 mmol, 1.0 equiv.) in 2.5 mL of dry THF was added dropwise and the reaction mixture was stirred at this temperature for 15 min. The reaction mixture was then stirred at room temperature for 4h. After cooling the reaction mixture to 0 °C, HCl (5 M in isopropanol, 12 mL, 60 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C and let warm up to rt. The precipitated product was filtered, washed with Et_2O and dry on the filter for 1 h to afford the title compound (**3.55·HCl**) as a white solid (5.1 g, 18 mmol, 90% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (br s, 4H, N*H*$_2$), 8.01 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.63-7.49 (m, 2H, Ar*H*), 7.35 (ddd, *J* = 7.9, 7.2, 2.0 Hz,1H, Ar*H*). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.7, 139.4, 136.0, 132.9, 129.0, 128.4, 94.9.

The characterization data corresponded to the reported values.[2]

2-Iodo-N-tosylbenzimidamide (3.58)



Following a slightly modified reported procedure,[3] a round bottom flask was loaded with 2-iodobenzimidamide·HCl (**3.55·HCl**) (2.1 g, 7.4 mmol, 1.0 equiv.), *p*-toluenesulfonyl chloride (1.4 g, 7.4 mmol, 1.0 equiv.) and DCM (37 mL). Subsequently, the solution was cooled down to 0 °C and a 10 M aqueous solution of NaOH (3.7 ml, 37 mmol, 5.0 equiv.) was added slowly. The reaction mixture was stirred for 5 h at room temperature. The mixture was washed with HCl 1M (3X20 mL), the organic layer was dried over MgSO4 and concentrated under vacuum. The crude mixture was purified by flash column chromatography (Pentane/EtOAc 1:2 to 1:1) to afford the title compound (**3.58**) as a white solid (2.2 g, 5.5 mmol, 74% yield)

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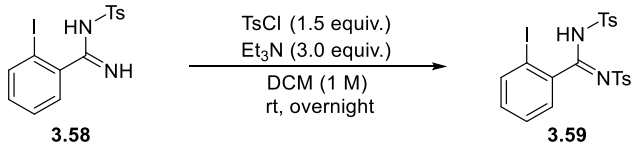
[1] S. Dalai, V. N. Belov, S. Nizamov, K. Rauch, D. Finsinger, A. de Meijere, *European Journal of Organic Chemistry* **2006**, *2006*, 2753–2765.
[2] T. Yao, *Tetrahedron Letters* **2015**, *56*, 4623–4626.
[3] M. Baeten, B. U. W. Maes, *Adv. Synth. Catal.* **2016**, *358*, 826–833.

R_f = 0.3 (Pentane/EtOAc 2:1). Mp: 136-138 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.37 (br s, 1H, *H*NTs), 7.88 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.81 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.37 (qd, *J* = 7.7, 1.5 Hz, 2H, Ar*H*), 7.29 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.13-7.06 (m, 1H, Ar*H*), 6.05 (br s, 1H, C=N*H*), 2.41 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 165.1, 143.4, 140.2, 139.9, 138.4, 131.9, 129.5, 128.9, 128.5, 127.1, 92.9, 21.7. **IR** (ν_{max}, cm^{-1}) 3369 (w), 3284 (w), 3121 (w), 3057 (w), 1629 (m), 1535 (m), 1416 (w), 1297 (m), 1142 (s), 1082 (s), 1018 (w), 835 (m), 806 (m), 788 (m), 751 (s), 716 (s), 685 (s), 656 (s). **HRMS** (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{14}H_{13}IN_2NaO_2S^+$ 422.9635; Found 422.9641.

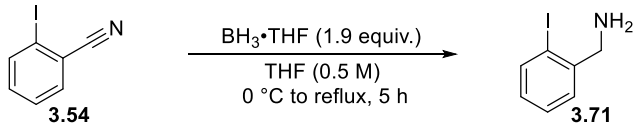
2-Iodo-N,N'-ditosylbenzimidamide (3.59)



Following a slightly modified procedure,[4] an oven-dried 10 mL microwave vial was charged with 2-iodo-N-tosylbenzimidamide (**3.58**) (1.5 g, 3.8 mmol, 1.0 equiv) and triethylamine (0.80 mL, 5.6 mmol, 1.5 equiv) and 1.9 mL of dry DCM. After 10mins a solution of *p*-toluenesulfonyl chloride (1.1 g, 5.6 mmol, 1.50 equiv) and triethylamine (0.80 mL, 5.6 mmol, 1.5 equiv) in 1.9 mL of dry DCM was added dropwise to the reaction mixture. The reaction mixture was stirred at rt overnight. The reaction mixture was then diluted with DCM (10 mL), and the mixture was washed 1M HCL (3X 10 mL). The organic phase was combined with a dichloromethane extract of the aqueous phase, dried (MgSO4), and concentrated under vacuum. The crude mixture was purified by flash column chromatography using DCM/MeOH 2% as mobile phase to afford the title compound as a yellowish solid (**3.59**) (1.7 g, 3.1 mmol, 83% yield).

R_f = 0.27 (DCM/MeOH 4%). **Mp**: 185-187 °C. **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 9.36 (s, 1H, N*H*), 7.84 (dd, *J* = 8.0, 0.7 Hz, 1H, Ar*H*), 7.62 (br s, 4H, Ar*H*), 7.47 (td, *J* = 7.6, 1.1 Hz, 1H, Ar*H*), 7.36-7.12 (m, 6H), 2.43 (s, 6H, CH_3). **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ 161.8, 139.8, 138.6, 132.7, 130.3, 129.8, 128.8, 128.0, 94.1, 21.7.[5] **IR** (ν_{max}, cm^{-1}) 3667 (w), 2978 (m), 2902 (m), 1603 (m), 1454 (m), 1352 (m), 1311 (m), 1168 (s), 1146 (s), 1083 (s), 932 (m), 818 (m), 768 (m), 720 (s), 682 (s). **HRMS** (APPI/LTQ-Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{21}H_{20}IN_2O_4S_2^+$ 554.9904; Found 554.9902.

2-Iodobenzylamine (3.71)



Following a slightly modified procedure,[6] in an oven dried round-bottom flask 2-iodobenzonitrile (**3.54**) (5.0 g, 22 mmol, 1.0 equiv.) and dry THF (44 mL) were mixed together, then borane-THF complex (41 ml, 41 mmol, 1.9 equiv.) was added dropwise to the solution at 0 °C. The mixture was refluxed under stirring for 5 h, then it was hydrolyzed at 0 °C with HCl

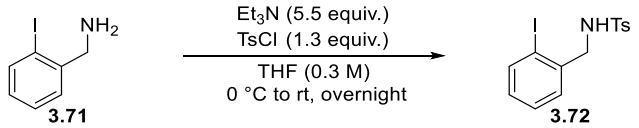
[4] A. Guzmán, M. Romero, F. X. Talamás, R. Villena, R. Greenhouse, J. M. Muchowski, *J. Org. Chem.* **1996**, *61*, 2470–2483.
[5] 2 carbons were not resolved by ^{13}C in acetonitrile-d_3
[6] L. A. Aronica, G. Albano, L. Giannotti, E. Meucci, *Eur. J. Org. Chem.* **2017**, *2017*, 955–963.

6 N until pH ~ 1; after, it was made basic with KOH until pH ~ 13 and extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under vacuum. The crude mixture was purified by flash column chromatography (DCM to DCM/MeOH 20:1) to afford the title compound as green oil (**3.71**) (3.1 g, 13 mmol, 61% yield)

Rf = 0.36 (DCM/MeOH 9:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.42-7.28 (m, 2H, Ar*H*), 6.95 (td, *J* = 7.7, 1.9 Hz, 1H, Ar*H*), 3.87 (s, 2H, ArCH_2NH_2), 1.64 (s, 2H, NH_2). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 145.2, 139.6, 128.8, 128.7, 128.6, 99.1, 51.5.

The characterization data corresponded to the reported values.[7]

N-(2-iodobenzyl)-4-methylbenzenesulfonamide (3.72)

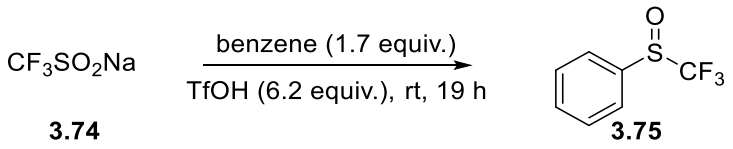


Following a slightly modified procedure,[6] in an oven dried round-bottom flask 2-iodobenzylamine (**3.71**) (1.0 g, 4.3 mmol, 1.0 equiv.) triethylamine (3.3 ml, 24 mmol, 5.5 equiv.) and dry THF (14 mL) were mixed together, then *p*-toluenesulfonyl chloride (1.1 g, 5.6 mmol, 1.3 equiv.) was added to the solution at 0 °C. The solution was left under stirring overnight at room temperature, then it was extracted with EtOAc. The combined organic phases were washed with H_2O and brine, dried over $MgSO_4$ and the solvent was removed under vacuum. The crude mixture was purified by flash column chromatography (Pentane/EtOAc 10:1) to afford the title compound as a white solid (**3.72**) (1.6 g, 4.2 mmol, 97% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75-7.70 (m, 3H, Ar*H*), 7.32-7.22 (m, 4H, Ar*H*), 6.94 (td, *J* = 7.6, 1.9 Hz, 1H, Ar*H*), 4.90 (t, *J* = 6.4 Hz, 1H, N*H*), 4.18 (d, *J* = 6.5 Hz, 2H, ArCH_2NHTs), 2.41 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 143.6, 139.6, 138.7, 137.0, 130.2, 129.8(3C), 128.7, 127.3, 98.9, 51.9, 21.7.

The characterization data corresponded to the reported values.[6]

((Trifluoromethyl)sulfinyl)benzene (3.75)



A dry 1 L, three-necked, round-bottomed flask equipped with a thermometer and a mechanical stirrer was charged with sodium trifluoromethanesulfinate (**3.74**) (90 g, 0.58 mol, 1.0 equiv.) and dried under vacuum for 24 h prior to use. The flask is placed in a cold-water bath and trifluoromethanesulfonic acid (0.32 L, 3.6 mol, 6.2 equiv.) is added, under argon, in three portions with vigorous stirring (around 100 mL each), in order to keep the temperature under 50 °C. After the addition, the reaction is stirred for 20−30 min until the temperature decreases to room temperature. Then, benzene (90 mL, 1.0 mol, 1.7 equiv.) is added in one portion and

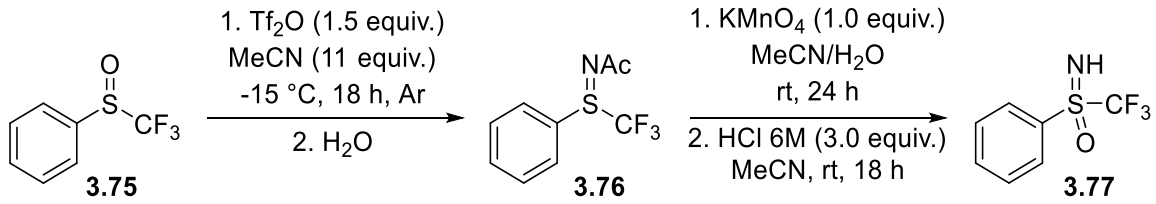
[7] T. Fukuyama, T. Bando, I. Ryu, *Synthesis* **2018**, *50*, 3015–3021.

the solution is stirred at room temperature for 19 h under an inert atmosphere. The reaction is quenched by pouring the reaction medium on ice (900 g), extracted with dichloromethane (3 × 100 mL), and washed with a saturated solution of $NaHCO_3$ (3 × 60 mL). The organic phase is dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product is purified by distillation under reduced pressure (78−80 °C at 15 mmHg) to afford the title compound as a colorless oil (**3.75**) (78 g, 0.40 mol, 69% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.4 Hz, 2H, Ar*H*), 7.70−7.49 (m, 3H, Ar*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.6 (q, *J* = 1.7 Hz), 133.6, 129.6, 125.9, 124.7 (q, *J* = 335 Hz, CF_3). **^{19}F** NMR (282 MHz, $CDCl_3$) δ −75.0 (s, 3F).

The characterization data corresponded to the reported values.[8]

(S-(trifluoromethyl)sulfonimidoyl)benzene (3.77)



In a dry 500 mL two-necked round-bottomed flask equipped with a dropping-funnel and a thermometer, a solution of phenyl trifluoromethyl sulfoxide (**3.75**) (40.0 g, 206 mmol, 1.00 equiv.) in dry acetonitrile (120 mL, 2.28 mol, 11.0 equiv.) is cooled to −15 °C under argon. Tf_2O (52.0 mL, 309 mmol, 1.50 equiv.) is introduced into the dropping-funnel and added dropwise to the solution, keeping the temperature around −15 °C. The solution is then left at −15 °C for 18 h under argon in a freezer. The reaction is quenched by pouring the reaction media on ice (400 g), extracted with dichloromethane (3 × 80 mL), and washed with a saturated solution of NaHCO3 (3 × 40 mL). The organic phase is dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To a solution of this crude product in acetonitrile (160 mL) and water (40 mL) is added $KMnO_4$ (32.6 g, 206 mmol, 1.00 equiv.) portion-wise. The reaction is stirred at room temperature for 18 h and diluted with H2O (150 mL), and a saturated solution of $Na_2S_2O_4$ is added until complete discoloration of the solution. The product is extracted with dichloromethane (3 × 70 mL), and the organic phase is dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product is dissolved in acetonitrile (184 mL), and HCl 6 M (67.2 mL) is added. The reaction is stirred at room temperature for 18 h. Then, water (100 mL) is added and the organic phase is extracted with dichloromethane (3 × 50 mL), washed with a solution of saturated NaHCO3 (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product is filtered on silica (200 g) using petroleum ether/ethyl acetate 8/2 as eluent to afford the title compound as a white solid (**3.77**) (32.8 g, 157 mmol, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.84−7.72 (m, 1H, Ar*H*), 7.63 (dd, *J* = 8.5, 7.1 Hz, 2H, Ar*H*), 3.53 (s, br s, 1H, N*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.6, 131.6, 130.7, 129.6, 121.0 (q, *J* = 333 Hz, CF_3). **^{19}F NMR** (282 MHz, $CDCl_3$) δ −79.3 (s, 3F).

The characterization data corresponded to the reported values.[8]

1-iodo-2-(*S*-(trifluoromethyl)sulfonimidoyl)benzene (3.78)

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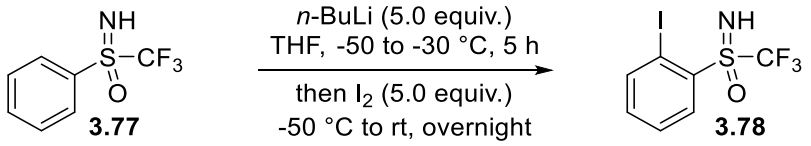
[8] A.-L. Barthelemy, V. Certal, G. Dagousset, E. Anselmi, L. Bertin, L. Fabien, B. Salgues, P. Courtes, C. Poma, Y. El-Ahmad, E. Magnier, *Org. Process Res. Dev.* **2020**, *24*, 704–712.



A solution of 2.5 M *n*-BuLi in hexane (96 mL, 0.24 mol, 5.0 equiv.) was added dropwise to a solution of (S-(trifluoromethyl)sulfonimidoyl)benzene (**3.77**) (10 g, 48 mmol, 1.0 equiv.) in freshly distilled THF (300 mL) at -50 °C. The reaction temperature was slowly increased to -30°C over 5 h. The reaction mixture was cooled to -50 °C, and solid I_2 (61 g, 0.24 mol, 5.0 equiv.) was added portion-wise. The reaction mixture was allowed to warm to room temperature overnight and subsequently quenched with a saturated aqueous NH_4Cl solution (200 mL). The aqueous layer was extracted with Et_2O (3 x 200 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography using toluene/MeOH (98/2) as eluent to give the title compound as a pale yellow solid (**3.78**) (15 g, 45 mmol, 94% yield).

^{1}H NMR (300 MHz, CD_3CN, 298 K): δ 8.40 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar*H*), 8.32 (dd, *J* = 7.9, 0.9 Hz, 1H, Ar*H*), 7.72-7.67 (m, 1H, Ar*H*), 7.43 (td, *J* = 7.7, 1.5 Hz, 1H, Ar*H*), 4.98 (br. s, 1H, N*H*). **^{13}C NMR** (75 MHz, CD_3CN, 298 K): δ 145.8, 137.2, 135.5, 135.2, 130.5, 121.8 (q, *J* = 333 Hz), 95.0. **^{19}F NMR** (282 MHz, CD_3CN, 298 K): δ -75.4.

The characterization data corresponded to the reported values.[9]

<u>Semi-preparative separation of **3.78**:</u>

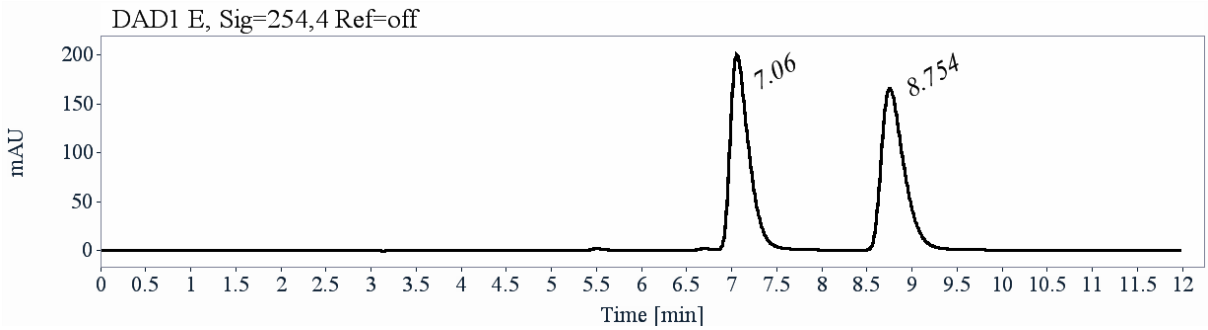


Figure S1: HPLC trace of racemic 3.78. Chromatographic conditions: Chiralpak AS-H (250 x 10 mm), n-hexane/isopropanol (80/20) as mobile phase, flow-rate = 5 mL/min, UV detection at 270 nm. Retention times: 7.06 min [(+)-3.78], 8.75 min [(–)-3.78].

RT [min]	Area	Area%
7.06	2830	49.46
8.75	2891	50.54

[9] J. Kalim, T. Duhail, T.-N. Le, N. Vanthuyne, E. Anselmi, A. Togni, E. Magnier, *Chem. Sci.* **2019**, *10*, 10516–10523.

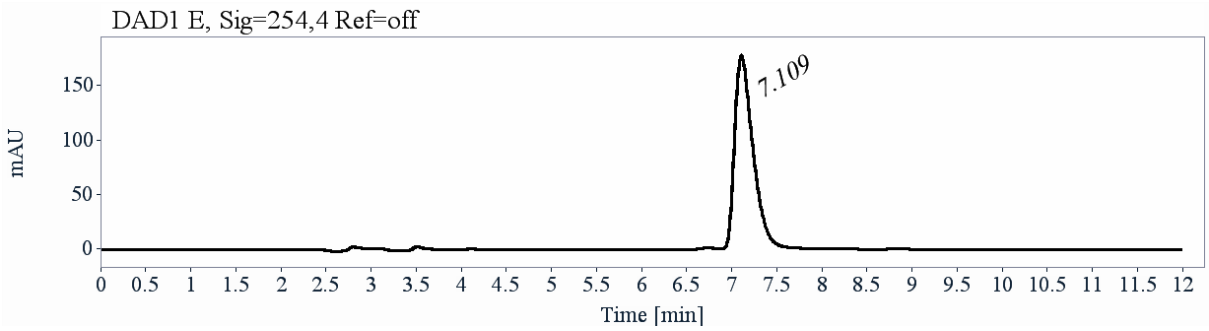


Figure S2: HPLC trace of enantiopure (+)-3.78. Chromatographic conditions: Chiralpak AS-H (250 x 10 mm), n-hexane/isopropanol (80/20) as mobile phase, flow-rate = 5 mL/min, UV detection at 270 nm.

RT [min]	Area	Area%
7.11	2474	100.00

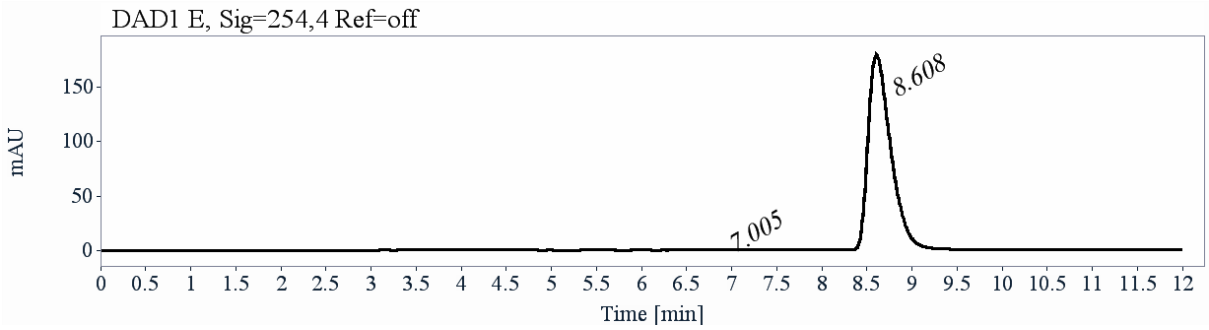
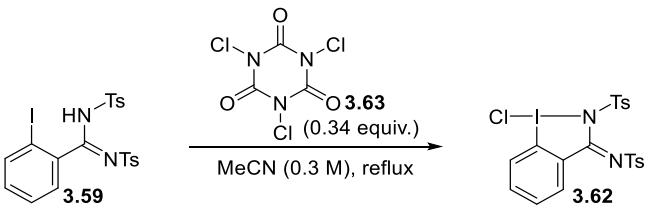


Figure S3: HPLC trace of enantiopure (–)-3.78. Chromatographic conditions: Chiralpak AS-H (250 x 10 mm), n-hexane/isopropanol (80/20) as mobile phase, flow-rate = 5 mL/min, UV detection at 270 nm

RT [min]	Area	Area%
7.00	7	0.23
8.61	3159	99.77

7.2.2. Preparation of Hypervalent Iodine Reagents

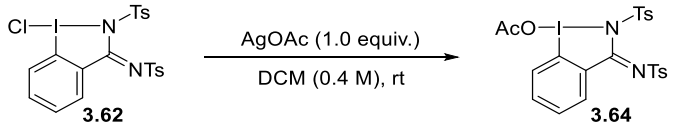
N-(1-chloro-2-tosyl-1,2-dihydro-3H-1λ^3-benzo[d][1,2]iodazol-3-ylidene)-4-methyl--benzenesulfonamide (Cl-Ts-BZI, 3.62)



Following a reported procedure,[10] an oven-dried round-bottom flask equipped with magnetic stirring bar was charged under Ar with solid 2-iodo-N,N'-ditosylbenzimidamide (**3.59**) (1.1 g, 2.0 mmol, 1.0 equiv.) and anhydrous MeCN (7.0 mL) was added. The resulting stirred suspension was heated to 75 °C. A solution of trichloroisocyanuric acid (**3.63**) (0.19 g, 0.80 mmol, 0.40 equiv, 1.2 equiv. in "Cl") in 1.0 mL of anhydrous MeCN was added dropwise. After addition was complete, the reaction mixture was refluxed for an additional 15 min. The reaction mixture was vacuum-filtered over a sintered-glass funnel and the precipitate was rinsed with additional hot MeCN (10−20 mL), the precipitate was air-dried. Then the precipitate was washed on a filter with DCM until only isocyanuric acid was left on the filter. The filtrate was concentrated under vacuum to afford the title compound (**3.62**) as a yellowish solid (1.1 g, 1.9 mmol, 93 %yield).

Mp > 223 °C (decomposition). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.36 (dd, *J* = 7.4, 2.1 Hz, 1H, Ar*H*), 8.45-8.36 (m, 1H, Ar*H*), 7.88 (ddd, *J* = 6.8, 4.6, 1.7 Hz, 2H, Ar*H*), 7.84 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.40 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.32 (d, *J* = 8.3 Hz, 2H, Ar*H*), 6.94 (d, *J* = 8.1 Hz, 2H, Ar*H*), 2.53 (s, 3H, CH_3), 2.35 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 153.5, 145.3, 143.3, 140.0, 136.7, 136.6, 134.0, 132.2, 130.7, 129.5, 129.4, 129.1, 128.5, 127.0, 114.9, 21.9, 21.8**. IR** (ν_{max}, cm^{-1}) 3086 (w), 1553 (m), 1444 (w), 1303 (m), 1256 (w), 1151 (m), 1082 (m), 1002 (w), 951 (w), 837 (m), 809 (m), 714 (s), 656 (m). Despite many attempts, the mass of the compound was not found by HRMS.

2-Tosyl-3-(tosylimino)-2,3-dihydro-1H-1λ^3-benzo[d][1,2]iodazol-1-yl acetate (AcO-Ts-BZI, 3.64)



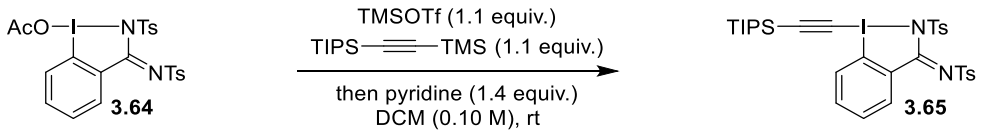
Following a reported procedure,[11] an oven-dried round-bottom flask equipped with magnetic stirring bar was charged under N_2 with N-(1-chloro-2-tosyl-1,2-dihydro-3H-1λ^3-benzo[d][1,2]iodazol-3-ylidene)-4-methylbenzenesulfonamide (**3.62**) (1.0 g, 1.7 mmol, 1.0 equiv.) and 8.0 mL of dry DCM was added. The flask was covered with aluminum foil to protect it from light. Silver acetate (0.28 g, 1.7 mmol, 1.0 equiv.) was added in one portion and the reaction mixture was stirred at rt for 22 h. The solution was filtered over a sintered-glass funnel and washed with DCM. The filtrate was concentrated under vacuum to afford the title compound (**3.64**) as a white solid (1.0 g,1.7 mmol, quant. yield).

Mp > 190 °C (decomposition). **^{1}H NMR** (400 MHz, Methylene Chloride-d_2) δ 9.28 (dd, *J* = 8.0, 1.6 Hz, 1H, Ar*H*), 8.14 (dd, *J* = 8.3, 1.1 Hz, 1H, Ar*H*), 7.87 (td, *J* = 8.4, 7.9, 1.6 Hz, 1H, Ar*H*), 7.83-7.78 (m, 1H, Ar*H*), 7.75 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.41 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.33 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.97 (d, *J* = 8.1 Hz, 2H, Ar*H*), 2.53 (s, 3H, ArCH_3), 2.36 (s, 3H, ArCH_3), 2.25 (s, 3H, OCCH_3). **^{13}C NMR** (101 MHz, Methylene Chloride-d_2) δ 176.7, 155.0, 145.7, 143.8, 140.7, 136.8, 136.7, 134.7, 131.8, 131.2, 130.9, 129.8(X2), 129.3, 127.1, 117.5, 22.0, 21.9, 21.0. **IR** (ν_{max}, cm^{-1}) 3076 (w), 2924 (w), 2751 (w), 1700 (w), 1540 (m), 1447 (w), 1326

[10] V. Matoušek, E. Pietrasiak, R. Schwenk, A. Togni, *J. Org. Chem.* **2013**, *78*, 6763–6768.
[11] Y. Kita, S. Akai, T. Okuno, M. Egi, T. Takada, H. Tohma, *HETEROCYCLES* **1996**, *42*, 47.

(m), 1257 (m), 1209 (m), 1149 (m), 1081 (m), 955 (w), 832 (m), 727 (s), 663 (s) **HRMS** (APPI/LTQ-Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{23}H_{22}IN_2O_6S_2^+$ 612.9959; Found 612.9946.

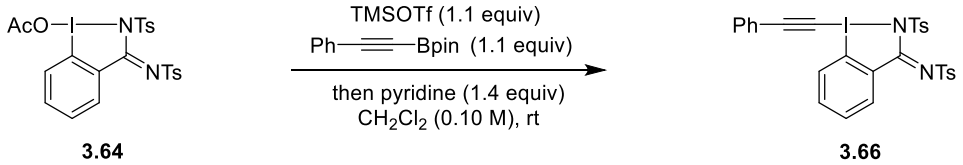
4-Methyl-N-(2-tosyl-1-((triisopropylsilyl)ethynyl)-1,2-dihydro-3H-1λ^3-benzo[d][1,2] iodazol-3-ylidene)benzenesulfonamide (TIPS-Ts-EBZI, 3.65)



Following a reported procedure,[12] an oven-dried round-bottom flask equipped with magnetic stirring bar was charged with AcO-Ts-BZI (**3.64**) (0.61 g, 1.0 mmol, 1.0 equiv.) and DCM (7.7 mL). TMS-OTf (0.20 mL, 1.1 mmol, 1.1 equiv.) was added to the solution and the resulting mixture was stirred at rt for 1 h. Then triisopropyl((trimethylsilyl)ethynyl)silane (0.28 g, 1.1 mmol, 1.1 equiv.) was added to the reaction mixture. After stirring at rt for 3 h, pyridine (0.11 mL, 1.4 mmol, 1.4 equiv.) was added and the reaction mixture was stirred vigorously for 30 min. The crude mixture was filtered and the precipitate washed with DCM. The filtrate was concentrated under vacuum and purified by flash column chromatography using DCM/MeOH 99.5:0.5 as mobile phase to afford the title compound as a white solid (**3.65**) (0.53 g, 0.72 mmol, 72% yield).

R$_f$ = 0.32 (DCM/MeOH 1%). **Mp** > 192 °C (decomposition). **^{1}H NMR** (400 MHz, Chloroform-d) δ 9.31 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar*H*), 8.49 (dd, *J* = 8.4, 0.9 Hz, 1H, Ar*H*), 7.86-7.67 (m, 4H, Ar*H*), 7.35 (br d, *J* = 27.6 Hz, 4H, Ar*H*), 6.86 (br s, 2H, Ar*H*), 2.48 (br s, 3H, ArC*H*$_3$), 2.30 (br s, 3H, ArC*H*$_3$), 1.27-1.10 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, Chloroform-d) δ 153.0, 142.1, 141.1, 139.8, 135.6, 135.1, 134.3, 130.6, 130.5, 127.9 (X2), 127.2 (X2), 125.6, 114.3, 114.2, 67.8, 20.6 (X2), 17.5, 10.2. **IR** (vmax, cm^{-1}) 2949 (w), 2866 (w), 1523 (m), 1456 (w), 1351 (w), 1279 (m), 1147 (m), 1079 (s), 945 (w), 845 (m), 690 (s). **HRMS** (ESI/QTOF) m/z: [M + H]$^+$ Calcd for $C_{32}H_{40}IN_2O_4S_2Si^+$ 735.1238; Found 735.1248.

4-Methyl-*N*-(1-(phenylethynyl)-2-tosyl-1,2-dihydro-3*H*-1λ^3-benzo[d][1,2] iodazol-3-ylidene)benzenesulfonamide (Ph-Ts-EBZI, 3.66).



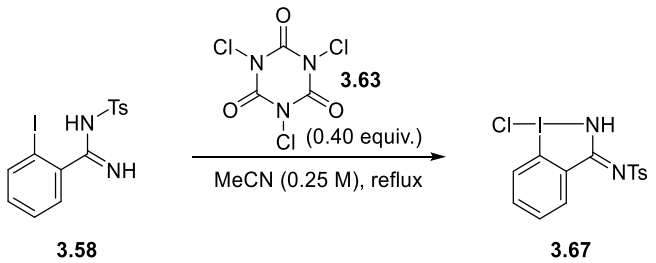
Following a reported procedure, [S12] an oven-dried round-bottom flask equipped with a magnetic stirring bar was charged with AcO-Ts-BZI (**3.64**) (0.40 g, 0.65 mmol, 1.0 equiv) and CH_2Cl_2 (5.0 mL). TMSOTf (0.13 mL, 0.72 mmol, 1.1 equiv) was added to the solution and the resulting mixture was stirred at rt for 1 h. Then 2-phenyl-1-ethynylboronic acid pinacol ester (0.18 g, 0.72 mmol, 1.1 equiv) was added to the reaction mixture. After stirring at rt for 2 h, pyridine (74 µL, 0.91 mmol, 1.4 equiv) was added and the reaction mixture was stirred vigorously for 1 h. The crude mixture was filtered and the precipitate washed with CH_2Cl_2. The filtrate was concentrated under vacuum and purified by flash column chromatography using

[12] V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 6547–6551.

CH_2Cl_2/MeOH 99.5:0.5 as mobile phase. Recrystallization in EtOAc afforded the Ph-Ts-EBZI (**3.66**) as a white solid (0.17 g, 0.26 mmol, 40% yield).

R_f = 0.30 (CH_2Cl_2/MeOH 1%); **Mp** > 190 °C (decomposition); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.33 (dd, *J* = 7.88, 1.43 Hz, 1H, Ar*H*), 8.44 (d, *J* = 7.73 Hz, 1H, Ar*H*), 7.88-7.69 (br m, 5H, Ar*H*), 7.64-7.56 (m, 2H, Ar*H*), 7.51 (dd, *J* = 8.50, 6.31 Hz, 1H, Ar*H*), 7.44 (t, *J* = 7.32 Hz, 2H, Ar*H*), 7.41-7.28 (br m, 3H, Ar*H*), 6.87 (br s, 2H, Ar*H*), 2.49 (br s, 3H), 2.33 (br s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.1, 143.4, 142.2, 141.0, 136.7, 136.1, 135.7, 133.1, 131.8, 131.5, 131.1, 129.0, 128.9, 128.5, 128.4, 126.8, 120.4, 115.8, 107.6, 55.1, 21.7 (×2); **IR** (vmax, cm^{-1}) 3065 (w), 2983 (w), 2915 (w), 2144 (w), 1736 (w), 1524 (m), 1447 (w), 1350 (w), 1282 (m), 1146 (m), 1079 (s), 949 (w), 847 (m), 806 (m), 715 (s), 653 (s); **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{24}IN_2O_4S_2^+$ 655.0217; Found 655.0229.

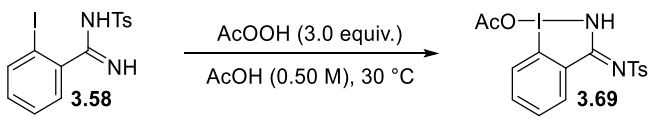
((E)-N-(1-chloro-1,2-dihydro-3H-1λ^3-benzo[d][1,2]iodazol-3-ylidene)-4-methylbenzene sulfonamide (Cl-H,Ts-BZI, 3.67)



A flame-dried round bottom flask equipped with magnetic stirring bar was charged under Ar with solid 2-iodo-N-tosylbenzimidamide (**3.58**) (1.0 g, 2.5 mmol, 1.0 equiv.) and anhydrous MeCN (8.0 mL) was added. The resulting mixture was heated to 75 °C. A solution of trichloroisocyanuric acid (0.23 g, 1.0 mmol, 0.4 equiv., 1.2 equiv. in "Cl") in 2.0 mL of anhydrous MeCN was added dropwise. During the addition of the trichloroisocyanuric acid solution, formation of insoluble isocyanuric acid became apparent. After addition was complete, the reaction mixture was refluxed for an additional 5 min. The reaction mixture was vacuum-filtered over a sintered-glass funnel and the precipitate was rinsed with additional MeCN (10−20 mL). The filtrate was concentrated under vacuum. Recrystallization in DCM afforded the title compound as a slightly yellow solid (**3.67**) (0.58 g, 1.3 mmol, 54% yield).

Mp > 194 °C (decomposition). **^{1}H NMR** (400 MHz, Acetone-d_6) δ 9.44 (s, 1H, N*H*), 8.45 (d, *J* = 8.45 Hz, 1H, Ar*H*), 8.24 (d, *J* = 7.62 Hz, 1H, Ar*H*), 8.05 (t, *J* = 7.77 Hz, 1H, Ar*H*), 7.88 (t, *J* = 7.45 Hz, 1H, Ar*H*), 7.84 (d, *J* = 8.09 Hz, 2H, Ar*H*), 7.34 (d, *J* = 8.03 Hz, 2H, Ar*H*), 2.38 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, Acetone-d_6) δ 160.7, 142.7, 140.5, 135. 5, 134.2, 131.3, 131.0, 129.2, 128.4, 126.3, 118.2, 20.5. **IR** (vmax, cm^{-1}) 3322 (w), 3065 (w), 2915 (w), 1577 (m), 1520 (s), 1428 (m), 1272 (m), 1192 (w), 1121 (m), 1070 (m), 1007 (w), 871 (s), 769 (s), 672 (s) **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}ClIN_2O_2S^+$ 434.9425; Found 434.9434.

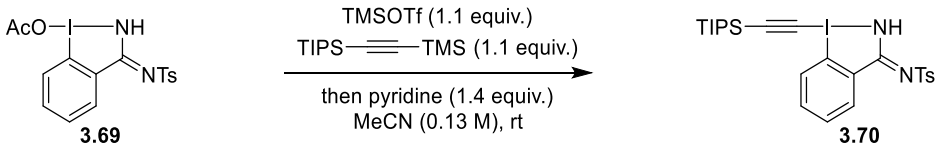
3-(Tosylimino)-2,3-dihydro-1H-1λ^3-benzo[d][1,2]iodazol-1-yl acetate (AcO-H,Ts-BZI, 3.69)



Following a slightly modified reported procedure,[13] in a round bottom flask, 2-iodo-N-tosylbenzimidamide (**3.58**) (2.0 g, 5.0 mmol, 1.0 equiv.) was dissolved in acetic acid (10 mL). The reaction mixture was cooled to 0 °C and peracetic acid (39% in acetic acid, 2.6 mL, 15 mmol, 3.0 equiv) was added dropwise to the aluminum foil covered flask. The reaction mixture was stirred at 30 °C for 2 h. The reaction was quenched by the addition of water (5 mL) and the precipitate was filtrated and washed with cold water (4X 5 mL) and with cold Et_2O (3X 5 mL). The precipitate was dried under vacuum and afforded the title compound as a white solid (**3.69**) (2.2 g, 4.8 mmol, 97% yield).

Mp > 166 °C (decomposition). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.97 (s, 1H, N*H*), 8.00 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.86-7.81 (m, 2H, Ar*H*), 7.73 (d, *J* = 8.2 Hz, 3H, Ar*H*), 7.22 (d, *J* = 8.0 Hz, 2H, Ar*H*), 2.32 (s, 3H, ArCH_3), 1.91 (s, 3H, OCCH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 172.1, 169.0, 144.2, 142.5, 140.1, 132.3, 131.9, 129.6, 129.0, 128.5, 126.5, 121.0, 21.1, 20.9. **IR** (vmax, cm^{-1}) 3336 (w), 3064 (w), 2979 (w), 2920 (w), 1611 (w), 1576 (m), 1516 (s), 1363 (m), 1318 (s), 1158 (m), 1136 (s), 1082 (s), 1016 (m), 873 (s), 781 (s), 734 (m), 660 (s). **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{16}H_{16}IN_2O_4S^+$ 458.9870; Found 458.9854.

4-Methyl-N-(1-((triisopropylsilyl)ethynyl)-1,2-dihydro-3H-1λ^3-benzo[d][1,2]iodazol-3-ylidene)benzenesulfonamide (TIPS-H,Ts-EBZI, 3.70)

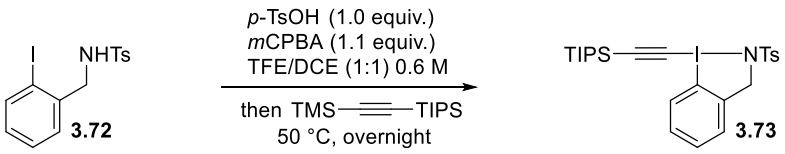


Following a reported procedure,[12] an oven-dried round-bottom flask equipped with magnetic stirring bar was charged with AcO-H,Ts-BZI (**3.69**) (1.0 g, 2.2 mmol, 1.0 equiv.) and MeCN (17 mL). TMS-OTf (0.43 mL, 2.4 mmol, 1.1 equiv.) was added to the solution and the resulting mixture was stirred at rt for 1 h. Then triisopropyl((trimethylsilyl)ethynyl)silane (0.61 g, 2.4 mmol, 1.1 equiv.) was added to the reaction mixture. After stirring at rt for 18 h, pyridine (0.25 mL, 3.1 mmol, 1.4 equiv.) was added and the reaction mixture was stirred vigorously for 1 h. The crude mixture was filtered and the precipitate washed with MeCN. The filtrate was concentrated under vacuum and purified by flash column chromatography using DCM/MeOH 99:1 as mobile phase to afford the title compound as a white solid (**3.70**) (0.36 g, 0.61 mmol, 28% yield).

R_f = 0.20 (DCM/MeOH 1%). **Mp** > 162 °C (decomposition). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.55 (dd, *J* = 5.8, 3.2 Hz, 2H, N*H* and Ar*H*), 8.48-8.41 (m, 1H, Ar*H*), 7.86 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.71 (q, *J* = 5.2, 3.5 Hz, 2H, Ar*H*), 7.21 (d, *J* = 8.0 Hz, 2H, Ar*H*), 2.36 (s, 3H, CH_3), 1.13 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 159.9, 142.0, 141.0, 134.1, 133.1, 131.4, 131.3, 129.2, 127.2, 126.4, 113.8, 110.2, 78.1, 21.6, 18.7, 11.4. **IR** (vmax, cm-1) 3329 (w), 2948 (w), 2870 (w), 1579 (w), 1517 (m), 1375 (m), 1271 (m), 1167 (w), 1135 (m), 1078 (m), 1002 (w), 876 (m), 812 (m), 773 (m), 662 (s). **HRMS** (ESI/QTOF) m/z: [M + H]$^+$ Calcd for $C_{25}H_{34}IN_2O_2SSi^+$ 581.1149; Found 581.1148.

[13] V. V. Zhdankin, R. M. Arbit, B. J. Lynch, P. Kiprof, V. G. Young, *J. Org. Chem.* **1998**, *63*, 6590–6596.

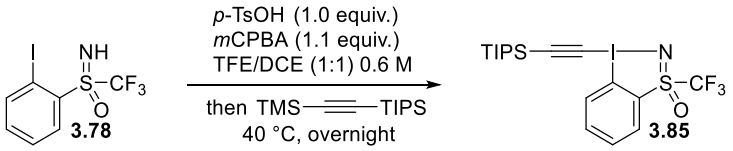
2-Tosyl-1-((triisopropylsilyl)ethynyl)-2,3-dihydro-1H-1λ³-benzo[d][1,2]iodazole (TIPS-Ts-EBz, 3.73)



Following a slightly modified reported procedure,[14] in a sealed tube, N-(2-iodobenzyl)-4-methyl-benzenesulfonamide (**3.72**) (1.0 g, 2.6 mmol, 1.0 equiv.), *p*-TsOH (0.49 g, 2.6 mmol, 1.0 equiv.) and *m*CPBA (0.64 g, 2.8 mmol, 1.1 equiv) were suspended in DCE:TFE (Ratio: 1:1, Volume: 4.4 mL) and heated up to 50 °C for 60 min. Triisopropyl(2-trimethylsilylethynyl)silane (0.92 g, 3.6 mmol, 1.4 equiv) was added at this temperature. The reaction mixture was stirred at this temperature overnight. The reaction mixture was concentrated under vacuum. The crude mixture was dissolved in 5 mL of DCM and washed with sat. $NaHCO_3$ (3 X 5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$ and the solvent were evaporated under vacuum. The crude mixture was purified by flash column chromatography using DCM/MeOH 99.5:0.5 as mobile phase to afford the title compound as a white solid (**3.73**) (0.71 g, 1.3 mmol, 49% yield).

R_f = 0.29 (DCM/MeOH 1%). **Mp** > 133 °C (decomposition). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.31-8.25 (m, 1H, Ar*H*), 7.78-7.73 (m, 2H, Ar*H*), 7.49 (td, *J* = 7.3, 1.0 Hz, 1H, Ar*H*), 7.40-7.33 (m, 1H, Ar*H*), 7.25-7.17 (m, 3H, Ar*H*), 4.32 (s, 2H, ArCH_2N), 2.37 (s, 3H, ArCH_3), 1.13 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 141.7, 139.1, 138.3, 130.8, 130.2, 129.7, 129.4, 128.8, 127.0, 111.3, 109.9, 75.8, 46.5, 21.6, 18.7, 11.4. **IR** (ν_{max}, cm^{-1}) 2940 (m), 2864 (m), 1461 (m), 1273 (s), 1253 (m), 1151 (s), 1135 (s), 1087 (s), 999 (m), 915 (s), 883 (m), 811 (m), 747 (s), 674 (s). **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{35}INO_2SSi^+$ 568.1197; Found 568.1202.

3-(Trifluoromethyl)-1-((triisopropylsilyl)ethynyl)-1H-1λ³,3λ⁴-benzo[d][1,3,2]iodathiazole 3-oxide (TIPS-CF_3-EBS, 3.85)



Following a slightly modified reported procedure,[14] in a sealed tube 1-iodo-2-(S-(trifluoromethyl)sulfonimidoyl)benzene (**3.78**) (1.0 g, 3.0 mmol, 1.0 equiv.), *p*-TsOH (0.57 g, 3.0 mmol, 1.0 equiv.) and *m*CPBA (0.74 g, 3.3 mmol, 1.1 equiv.) were suspended in DCE:TFE (Ratio: 1:1, Volume: 5.0 mL) and heated up to 40 °C for 60 min. Triisopropyl((trimethylsilyl)ethynyl)silane (1.1 g, 4.2 mmol, 1.4 equiv.) was added at this temperature. The reaction mixture was stirred at this temperature overnight. pyridine (0.34 mL, 4.2 mmol, 1.4 equiv.) was added and the mixture was stirred vigorously for 10 min. The reaction mixture was concentrated under vacuum. The crude mixture was dissolved in 5 mL of DCM and washed with sat. $NaHCO_3$ (3 X 5 mL) and brine (5 mL). The organic layer was

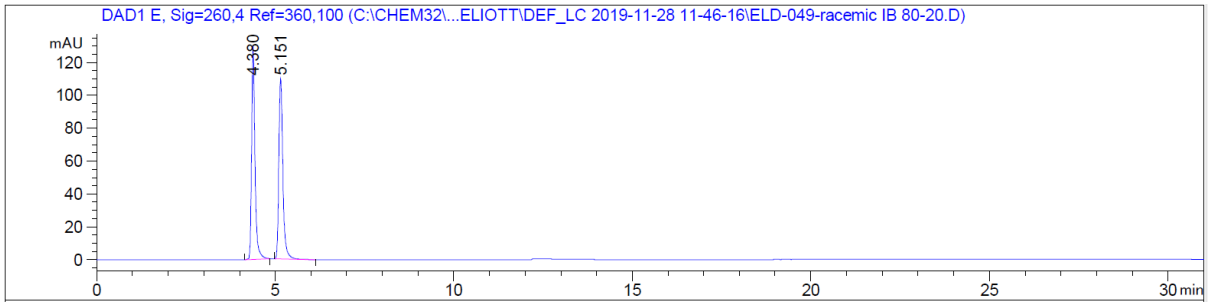
[14] D. P. Hari, P. Caramenti, L. Schouwey, M. Chang, S. Nicolai, D. Bachert, T. Wright, C. Orella, J. Waser, *Org. Process Res. Dev.* **2020**, *24*, 106–110.

dried over $MgSO_4$ and the solvent were evaporated under vacuum. The crude mixture was purified by flash column chromatography using DCM/MeOH 99:1 as mobile phase to afford the title compound as a slightly yellow solid (**3.85**) (1.2 g, 2.2 mmol, 75 % yield).

R_f = 0.21 (DCM/MeOH 1%). **Mp** > 125 °C (decomposition). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.79-8.74 (m, 1H, Ar*H*), 8.22 (d, *J* = 7.3 Hz, 1H, Ar*H*), 7.95-7.84 (m, 2H, Ar*H*), 1.15 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 135.5, 132.4, 131.4, 129.9, 129.0, 122.6 (q, *J* = 337.2 Hz), 120.9, 110.8, 76.1, 18.7, 11.4. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -77.8. **IR** (ν_{max}, cm^{-1}) 3076 (m), 2945 (m), 2867 (m), 1559 (m), 1464 (m), 1434 (m), 1301 (s), 1254 (m), 1189 (s), 1169 (s), 1096 (m), 1063 (s), 883 (m), 690 (s). **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{26}F_3INOSSi^+$ 516.0496; Found 516.0494.

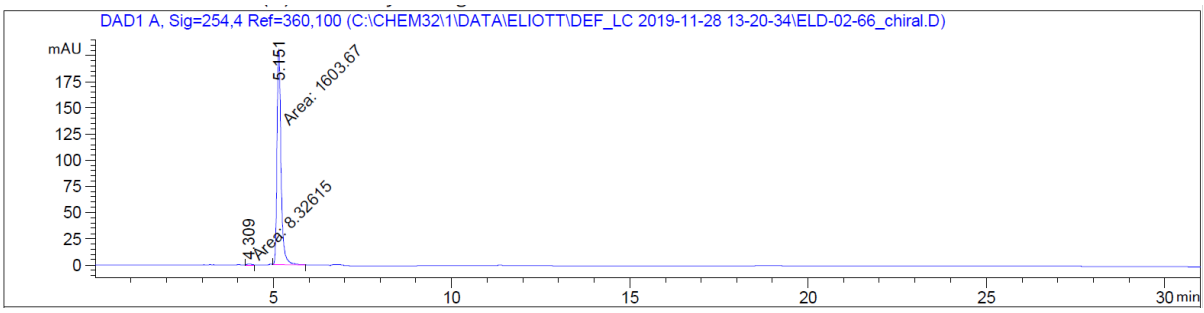
For the enantiomer **3.85** prepared from (-)-**3.78**: $[\alpha]_\lambda^{20}$ ($CHCl_3$, c = 0.5, λ = 589 nm): +12

HPLC trace of racemic **3.85**, Chiralpak IB 80:20 Hexane/i-PrOH, 1.0 ml/min, 31 min



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.380	BB	0.0987	858.55957	130.60844	49.9553
2	5.151	BB	0.1197	860.09583	109.41880	50.0447

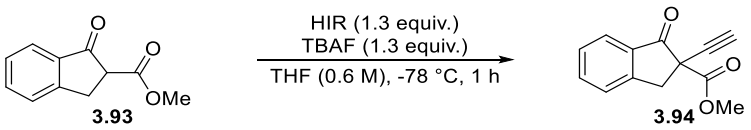
HPLC trace of enantiopure (+)-**3.85** obtained from (-)-**3.78**, Chiralpak IB 80:20 Hexane/i-PrOH, 1.0 ml/min, 31 min



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.309	MM	0.1568	8.32615	8.84966e-1	0.5165
2	5.151	MM	0.1303	1603.67468	205.11935	99.4835

7.2.3. Reactivity Investigation

Alkynylation of β-ketoesters



Following a reported procedure,[15] a solution of methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3.93**) (20 mg, 0.10 mmol, 1.0 equiv.) and hypervalent iodine reagent (0.13 mmol, 1.30 equiv.) in dry THF (1.7 mL) was stirred at -78 °C for 5 min under nitrogen. After this period of time, TBAF (0.13 mL, 0.13 mmol, 1.3 equiv.) was added and the mixture was vigorously stirred at -78 °C. The reaction was monitored by TLC analysis (Pentane/EtOAc, 4:1, UV and p-anisaldehyde) and was complete at -78 °C in 1 hour. The reaction was quenched by addition of water at rt and aqueous layer was extracted with DCM. The combined layers were dried over MgSO4 and concentrated under vacuum. The crude mixture was purified by PrepTLC (Pentane/EtOAc 5/1) to afford the title compound **3.94** as a yellow oil.

Starting from TIPS-H,Ts-EBZI **3.70** (75 mg, 0.13 mmol, 1.3 equiv.), **3.94** was not observed.

Starting from TIPS-Ts-EBz **3.73** (74 mg, 0.13 mmol, 1.3 equiv.), **3.94** could not be isolated from the degradation products of **3.73** (79% NMR yield using CH_2Br_2 as internal standard).

Starting from racemic TIPS-EBS **3.85** (67 mg, 0.13 mmol, 1.3 equiv.), **3.94** (20 mg, 90 µmol, 90% yield) was obtained as a racemic mixture.

Starting from enantiopure TIPS-EBS **(+)-3.85** (67 mg, 0.13 mmol, 1.3 equiv.), **3.94** (20 mg, 90 µmol, 90% yield) was obtained as a racemic mixture.

Starting from TIPS-EBX **3.16** (56 mg, 0.13 mmol, 1.3 equiv.), **3.94** (21 mg, 0.10 mmol, quant. Yield) was obtained.

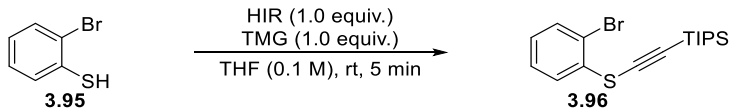
Starting from TIPS-Ts-EBZI **3.65** (96 mg, 0.13 mmol, 1.3 equiv.), **3.94** (21 mg, 0.10 mmol, quant. Yield) was obtained.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.70-7.64 (m, 1H, Ar*H*), 7.50 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.47-7.41 (m, 1H, Ar*H*), 3.94 (d, *J* = 17.1 Hz, 1H, ArCH_2), 3.80 (s, 3H, OCH_3), 3.52 (d, *J* = 17.1 Hz, 1H, ArCH_2), 2.42 (s, 1H, C*H*).

[15] D. Fernández González, J. P. Brand, R. Mondière, J. Waser, *Advanced Synthesis & Catalysis* **2013**, *355*, 1631–1639.

The ^{1}H NMR data corresponds to literature data.[15]

Alkynylation of thiol



Following a reported procedure,[16] a 5 mL microwave vial was charged with a magnetic stir bar, 2-bromobenzenethiol (**3.95**) (12 µL, 0.10 mmol, 1.0 equiv.), 1,1,3,3-tetramethylguanidine (13 µL, 0.10 mmol, 1.0 equiv.) and THF (1.0 mL). After stirring the resulting solution for 5 minutes at room temperature, hypervalent iodine reagent (0.10 mmol, 1.0 equiv.) was added as a solid in one portion. The resulting reaction mixture was stirred with an open flask for 5 minutes at room temperature. Next, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The reaction mixture was purified by PrepTLC using pentane as mobile phase affording **3.96** as a clear colorless oil.

Starting from TIPS-H,Ts-EBZI **3.70** (58 mg, 0.10 mmol, 1.0 equiv.), **3.96** was not observed.

Starting from TIPS-Ts-EBz **3.73** (57 mg, 0.10 mmol, 1.0 equiv.), **3.96** (8 mg, 2 µmol, 22% yield)

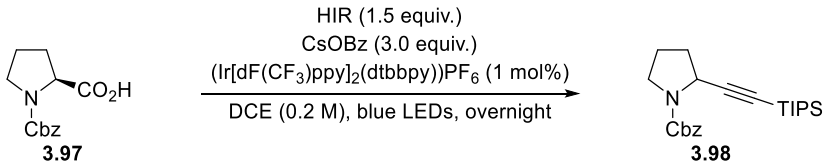
Starting from racemic TIPS-EBS **3.85** (52 mg, 0.10 mmol, 1.0 equiv.), **3.96** (27 mg, 73 µmol, 73% yield) was obtained.

Starting from TIPS-Ts-EBZI **3.65** (74 mg, 0.10 mmol, 1.0 equiv.), **3.96** (17 mg, 46 µmol, 46% yield) was obtained.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.51-7.47 (m, 1H, Ar*H*), 7.40-7.31 (m, 1H, Ar*H*), 7.08 (td, *J* = 7.9, 1.3 Hz, 1H, Ar*H*), 1.13 (m, 21H, TIPS).

The ^{1}H NMR data corresponds to literature data.[16]

Decarboxylative-alkynylation of proline



Following a reported procedure,[17] dry degassed DCE (0.50 mL) was added in a flame dried 1.5 mL test tube containing a Teflon coated stirring bar, Cbz-Pro-OH (**3.97**) (25 mg, 0.10 mmol, 1.0 equiv.), hypervalent iodine reagent (0.15 mmol, 1.5 equiv.), CsOBz (76 mg, 0.30 mmol, 3.0 equiv.) and $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (1.1 mg, 1.0 µmol, 0.01 equiv.) under N_2. The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 22 h at rt. The reaction mixture was filtered over celite, eluting with ethyl acetate, and evaporated under reduced pressure. The crude

[16] R. Frei, J. Waser, *J. Am. Chem. Soc.* **2013**, *135*, 9620–9623.
[17] F. Le Vaillant, T. Courant, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204.

product was purified by preparative TLC (Pentane/Ethyl Acetate 8/2) directly without any further work-up.

Starting from TIPS-H,Ts-EBZI **3.70** (87 mg, 0.15 mmol, 1.5 equiv.), **3.98** was not observed.

Starting from TIPS-Ts-EBz **3.73** (85 mg, 0.15 mmol, 1.5 equiv.), **3.98** (4 mg, 10 µmol, 10% yield)

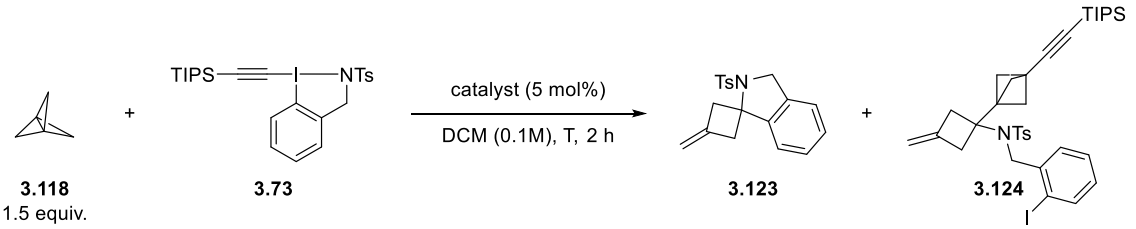
Starting from racemic TIPS-EBS **3.85** (77 mg, 0.15 mmol, 1.5 equiv.), **3.98** (4 mg, 10 µmol, 10% yield) was obtained.

Starting from TIPS-Ts-EBZI **3.65** (110 mg, 0.150 mmol, 1.5 equiv.), **3.98** was not observed.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45-7.27 (m, 5H, Ar*H*), 5.17 (s, 2H, OCH_2Ph), 4.66-4.52 (m, 1H, CbzNC*H*CC), 3.63-3.49 (m, 1H, CbzNCH_2), 3.48-3.29 (m, 1H, CbzNCH_2), 2.24-1.86 (m, 4H, CbzNCH$_2$CH_2CH_2CH), 1.03 (s, 21H, TIPS).

The ^{1}H NMR data corresponds to literature data.[17]

Aminoalkynylation of [1.1.1]-propellane



A solution of [1.1.1]-propellane (**3.118**) (concentration determined prior to use by NMR, 75.0 µmol, 0.700 M, 1.50 equiv) in Et_2O was added dropwise to a solution of TIPS-Ts-EBz (**3.73**) (28.4 mg, 50.0 µmol, 1.00 equiv) and catalyst (2.50 µmol, 0.0500 equiv) in DCM (Volume: 500 µl) at the indicated temperature. At the end of the addition, the reaction was stirred for 2 h at this temperature. The solvent was removed under reduced pressure and the crude product was purified by Prep-TLC (EtOAc/pentane 97:3).

3-Methylene-2'-tosylspiro[cyclobutane-1,1'-isoindoline] (3.123)

Using CuI (0.48 mg, 2.5 µmol, 0.050 equiv), **3.123** (5.0 mg, 0.015 mmol, 31% yield) was obtained as a colorless oil.

R_f = 0.15 (Pentane/EtOAc 97:3). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 2H, Ar*H*), 7.54 – 7.50 (m, 1H, Ar*H*), 7.33 – 7.26 (m, 3H, Ar*H*), 7.26 – 7.23 (m, 1H, Ar*H*), 7.16 – 7.12 (m, 1H, Ar*H*), 5.08 – 5.01 (m, 2H, C=CH_2), 4.65 (s, 2H, ArCH_2), 4.15 – 4.05 (m, 2H, CCH_2), 2.98 – 2.88 (m, 2H, CCH_2), 2.41 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.2, 143.3, 140.8, 137.7, 133.2, 129.7, 128.5, 127.9, 127.0, 121.8, 120.8, 107.3, 66.9, 53.9, 48.2, 21.5, 18.7. **HRMS** (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{19}NNaO_2S^+$ 348.1029; Found 348.1032.

N-(2-Iodobenzyl)-4-methyl-N-(3-methylene-1-(3-((triisopropylsilyl)ethynyl)bicyclo[1.1.1]pentan-1-yl)cyclobutyl)benzenesulfonamide (3.124)

Using $Cu(CH_3CN)_4BF_4$ (0.80 mg, 2.5 µmol, 0.050 equiv), **3.124** (18 mg, 0.026 mmol, 69% yield) was obtained as a colorless oil.

R_f = 0.36 (Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 – 7.73 (m, 3H, Ar*H*), 7.64 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.40 – 7.37 (m, 1H, Ar*H*), 7.37 – 7.31 (m, 2H, Ar*H*), 6.97 (td, *J* = 7.5, 1.7 Hz, 1H, Ar*H*), 4.78 – 4.71 (m, 2H, C=CH_2), 4.48 (s, 2H, ArCH_2), 2.85 – 2.75 (m, 2H, CCH_2), 2.67 – 2.57 (m, 2H, CCH_2), 2.45 (s, 3H, CH_3), 1.75 (s, 6H, 3 X CH_2 bicyclobutane), 1.10 – 0.95 (m, 21H, TIPS).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6, 142.7, 139.6, 139.2, 138.2, 129.9, 129.2, 128.8, 128.6, 127.3, 111.5, 108.1, 97.2, 81.8, 56.5, 50.8, 50.3, 42.0, 40.5, 31.8, 21.7, 18.8, 11.3. **HRMS** (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{46}INNaO_2SSi^+$ 722.1961; Found 722.1981.

7.2.4. X-ray Crystallographic Data

*7.2.4.1. Single Crystal X-Ray Diffraction for the compound **3.65***

Crystals of the compound **3.65** were obtained from slow evaporation of a DCM solution.

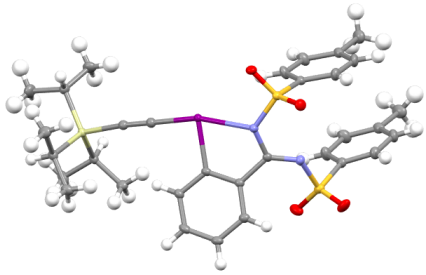


Table 1. Crystal data and structure refinement for **3.65**.

Identification code	CCDC 2072274	
Empirical formula	$C_{32}H_{39}IN_2O_4S_2Si$	
Formula weight	734.76	
Temperature	100.01(11) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*-1	
Unit cell dimensions	a = 11.3588(3) Å	α= 112.064(3)°.
	b = 11.8051(3) Å	β= 98.385(2)°.
	c = 14.2418(4) Å	γ = 105.326(2)°.
Volume	1641.46(8) $Å^3$	
Z	2	
Density (calculated)	1.487 Mg/m^3	
Absorption coefficient	1.178 mm^{-1}	
F(000)	752	
Crystal size	0.545 x 0.213 x 0.093 mm^3	
Θ range for data collection	2.553 to 32.959°.	
Index ranges	$-15 \leq h \leq 16$, $-17 \leq k \leq 13$, $-15 \leq l \leq 20$	
Reflections collected	19613	
Independent reflections	10888 [R_{int} = 0.0177]	
Completeness to θ = 25.242°	99.9 %	
Absorption correction	Gaussian	
Max. and min. transmission	1.000 and 0.407	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10888 / 0 / 387	
Goodness-of-fit on F^2	1.052	
Final R indices [I > 2σ(I)]	R_1 = 0.0244, wR_2 = 0.0561	
R indices (all data)	R_1 = 0.0276, wR_2 = 0.0576	
Largest diff. peak and hole	0.617 and -0.488 e.$Å^{-3}$	

*7.2.4.2. Single Crystal X-Ray Diffraction for the compound **3.70***

Crystals of the compound **3.70** were obtained from slow evaporation of a DCM solution.

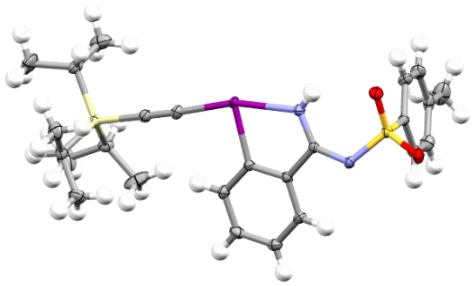
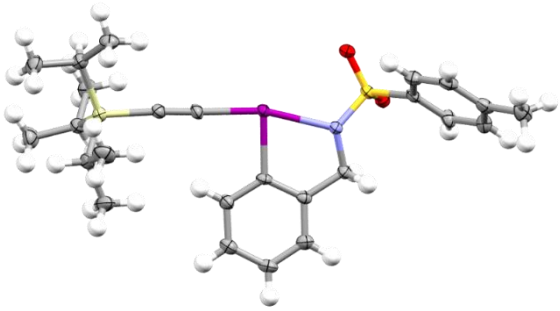


Table 1. Crystal data and structure refinement for **3.70.**

Identification code	CCDC 2072273	
Empirical formula	$C_{25}H_{33}IN_2O_2SSi$	
Formula weight	580.58	
Temperature	140.02(18) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 11.6983(5) Å	α= 90°.
	b = 16.7909(6) Å	β= 99.201(3)°.
	c = 13.5441(4) Å	γ = 90°.
Volume	2626.17(17) $Å^3$	
Z	4	
Density (calculated)	1.468 Mg/m^3	
Absorption coefficient	1.368 mm^{-1}	
F(000)	1184	
Crystal size	0.297 x 0.108 x 0.044 mm^3	
Θ range for data collection	2.426 to 32.970°.	
Index ranges	$-17 \leq h \leq 17$, $-25 \leq k \leq 25$, $-20 \leq l \leq 20$	
Reflections collected	15787	
Independent reflections	15787	
Completeness to θ = 25.242°	99.2 %	
Absorption correction	Gaussian	
Max. and min. transmission	1.000 and 0.698	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	15787 / 0 / 303	
Goodness-of-fit on F^2	0.924	
Final R indices [I > 2σ(I)]	R_1 = 0.0417, wR_2 = 0.0763	
R indices (all data)	R_1 = 0.0646, wR_2 = 0.0802	
Largest diff. peak and hole	1.534 and -0.833 e.$Å^{-3}$	

*7.2.4.3. Single Crystal X-Ray Diffraction for the compound **3.73***

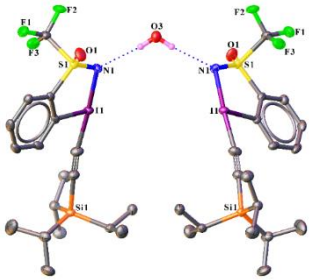
Crystals of the compound **3.73** were obtained from slow evaporation of a DCM solution.



Compound	**TIPS-Ts-EBz**
Identification code	CCDC 2072275
Formula	$C_{25}H_{34}INO_2SSi$
$D_{calc.}$/ g cm^{-3}	1.476
μ/mm^{-1}	11.226
Formula Weight	567.58
Color	clear colorless
Shape	plate
Size/mm^3	0.75×0.30×0.07
T/K	100.00(10)
Crystal System	triclinic
Space Group	$P\bar{1}$
a/Å	8.3150(5)
b/Å	9.5571(4)
c/Å	16.2727(8)
α/°	95.596(4)
β/°	91.566(5)
γ/°	96.709(4)
V/Å^3	1277.18(11)
Z	2
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu $K\alpha$
Θ_{min}/°	2.731
Θ_{max}/°	76.215
Measured Refl's.	10120
Ind't Refl's	5160
Refl's with I > 2(I)	5087
R_{int}	0.0292
Parameters	288
Restraints	0
Largest Peak/e Å^{-3}	2.075
Deepest Hole/e Å^{-3}	-1.586
GooF	1.085
wR_2 (all data)	0.1245
wR_2	0.1242
R_1 (all data)	0.0444
R_1	0.0442

*7.2.4.4. Single Crystal X-Ray Diffraction for the compound **3.85***

Crystals of the compound **3.85** were obtained from slow evaporation of a DCM solution.



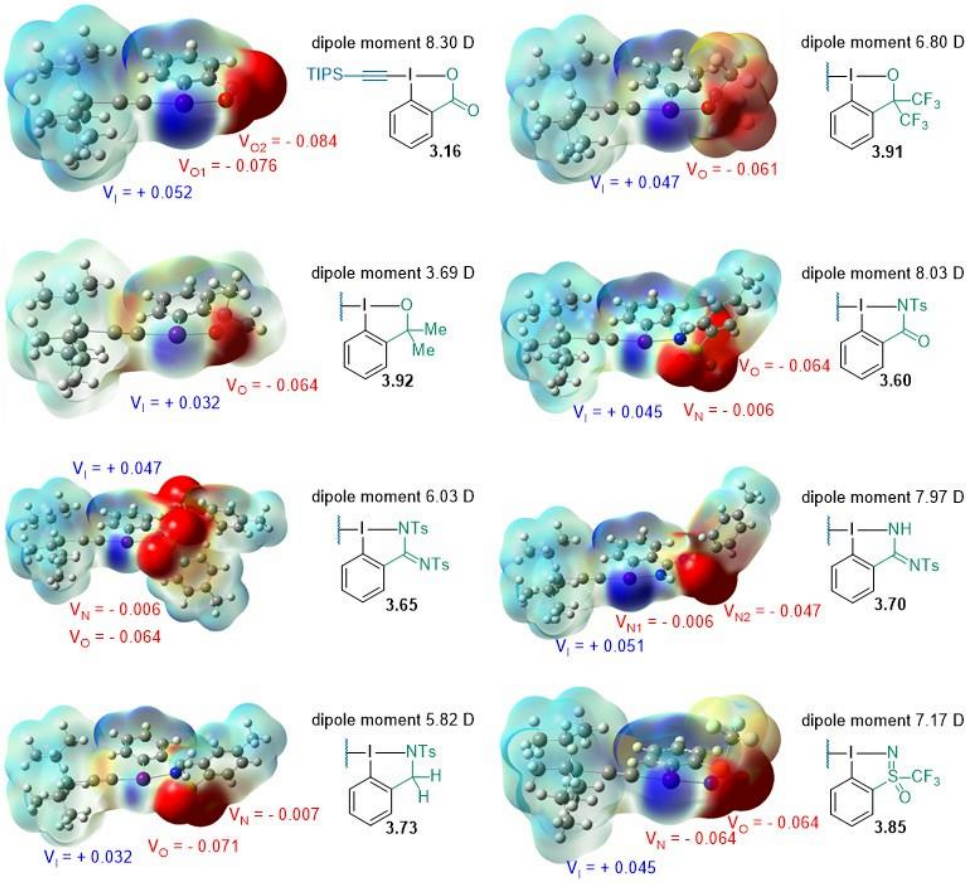
Compound	**TIPS-CF$_3$-EBS**
Identification code	CCDC 2072276
Formula	$C_{72}H_{102}F_{12}I_4N_4O_5S_4Si_4$
$D_{calc.}$/ g cm^{-3}	1.610
μ/mm^{-1}	1.681
Formula Weight	2079.77
Color	clear colorless
Shape	prism
Size/mm^3	0.79×0.39×0.29
T/K	140.00(10)
Crystal System	tetragonal
Flack Parameter	-0.003(5)
Space Group	$I4_1$
a/Å	19.07771(12)
b/Å	19.07771(12)
c/Å	23.5685(2)
α/°	90
β/°	90
γ/°	90
V/Å^3	8577.97(14)
Z	4
Z'	0.5
Wavelength/Å	0.71073
Radiation type	Mo $K\alpha$
Θ_{min}/°	2.539
Θ_{max}/°	32.974
Measured Refl's.	52957
Ind't Refl's	14808
Refl's with I > 2(I)	13940
R_{int}	0.0271
Parameters	490
Restraints	1
Largest Peak/e Å^{-3}	0.412
Deepest Hole/e Å^{-3}	-0.496
GooF	1.022
wR_2 (all data)	0.0478
wR_2	0.0465
R_1 (all data)	0.0263
R_1	0.0228

7.2.5. DFT Calculations and Coordinates

Geometries of the hypervalent iodine reagents were first optimized at the M06/def2-SVP level in Gaussian09.[18] Electrostatic potential maps and corresponding surface values were obtained using GaussView 5.0.9 via mapping onto the isodensity surface at 0.001au.[19] Reported dipole moments were obtained from the M06/def2-SVP computations on the optimized structures.

[18] (a) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241. (b) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Acc. Chem. Res.* **2008**, *41*, 157–167. (c) Weigend, F.; Ahlrichs, R. Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305. (d) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian09, Revision D.01*; Gaussian, Inc.: Wallingford CT, 2016.

[19] Dennington, R.; Keith, T. A.; Millam, J. M. *GaussView 5.0.9*; Semichem Inc.: Shawnee Mission, KS, 2009.


dipole moment 8.30 D
TIPS
3.16
V_{O2} = - 0.084
V_{O1} = - 0.076
V_I = + 0.052
dipole moment 6.80 D
CF_3
CF_3
3.91
V_I = + 0.047
V_O = - 0.061
dipole moment 3.69 D
Me
Me
3.92
V_O = - 0.064
V_I = + 0.032
dipole moment 8.03 D
NTs
3.60
V_O = - 0.064
V_I = + 0.045
V_N = - 0.006
V_I = + 0.047
dipole moment 6.03 D
NTs
NTs
3.65
V_N = - 0.006
V_O = - 0.064
dipole moment 7.97 D
NH
NTs
3.70
V_{N1} = - 0.006
V_{N2} = - 0.047
V_I = + 0.051
dipole moment 5.82 D
NTs
H
H
3.73
V_N = - 0.007
V_I = + 0.032
V_O = - 0.071
dipole moment 7.17 D
N
S
CF_3
O
3.85
V_O = - 0.064
V_N = - 0.064
V_I = + 0.045

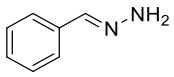
7.3. Copper-Catalyzed Alkynylation of Hydrazides for the Synthesis of Functionalized Azadipeptides

7.3.1. Preparation of Azapeptides

H-Pro-O*t*Bu, H-Gly-O*t*Bu, H-Tyr-O*t*Bu, H-Trp-O*t*Bu, H-Asn-O*t*Bu, H-Lys(Z)-O*t*Bu·HCl, H-Met-O*t*Bu·HCl, H-Glu(OMe)-O*t*Bu·HCl, H-Val-O*t*Bu·HCl, H-Phe-O*t*Bu·HCl, H-Ser-O*t*Bu·HCl, H-Ala-O*t*Bu·HCl, phenylacetylene, 2-ethynyl-1,3,5-trimethylbenzene, ethynyltriisopropylsilane, ethynylcyclopropane, 5-chloropent-1-yne, 1-ethynyl-3-methoxybenzene, 1-ethynyl-4-fluorobenzene and 2-bromo-1-(trimethylsilylethynyl)benzene were commercially available and used as received.

General procedures for azapeptides synthesis

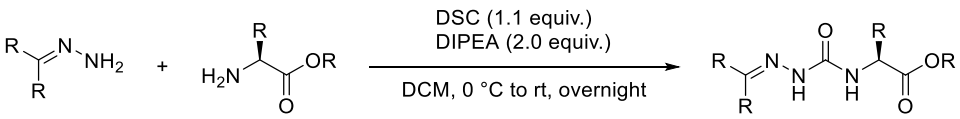
(*E*)-benzylidenehydrazine (4.42)



Following a reported procedure,[1] a microwave vial was charged under N_2 with hydrazine monohydrate (4.00 mL, 82.5 mmol, 4.38 equiv) and benzaldehyde (1.92 mL, 18.8 mmol, 1.00 equiv) was added dropwise at 0 °C. The reaction mixture was vigorously stirred at 100 °C for 6 h. The reaction was cooled to rt and the product was extracted with 3 X 2 mL of DCM. The combined extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. (*E*)-Benzylidenehydrazine (**4.42**) (2.19 g, 18.2 mmol, 97% yield) was obtained as a yellowish oil and was used without further purification.[2]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H, *H*C=N), 7.59-7.51 (m, 2H, Ar*H*), 7.38-7.27 (m, 3H, Ar*H*), 5.53 (br s, 2H, NH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3, 135.2, 128.8, 128.7, 126.3. Spectroscopic data was consistent with the values reported in the literature.1

General procedure A for the coupling of hydrazine with amino acids

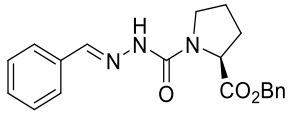


Using a slightly modified literature procedure,[3] in a flame-dried round-bottom flask, at 0 °C, a solution of *N,N'*-disuccinimidyl carbonate (DSC) (1.10 equiv.) in dry DCM (0.35 M) was treated dropwise over 20 min with a solution of the corresponding hydrazone (1.00 equiv.) in dry DCM

[1] Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. *Org. Lett.* **2009**, *11* (15), 3202–3205.
[2] For long term storage, the hydrazine was kept under N_2 in a -20 °C freezer in which it solidified. When needed the solid was let thawing before using it.
[3] Y. Garcia-Ramos, W. D. Lubell, *J. Pept. Sci.* **2013**, *19*, 725–729.

(0.23 M). The ice bath was removed, and the reaction mixture was allowed to warm to room temperature. After stirring for 1 h, the mixture was cooled to 0 °C and treated dropwise with a premixed solution of the corresponding amino acid (1.00 equiv.) and DIPEA (2.00 equiv.) in DCM (0.8 M). The ice bath was removed. The reaction mixture was allowed to warm to room temperature and stirred overnight. The crude mixture was diluted with 20 mL of sat. $NaHCO_3$, extracted with DCM (3 x 30 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The volatiles were evaporated, and the crude was purified on a column of silica gel using flash chromatography.

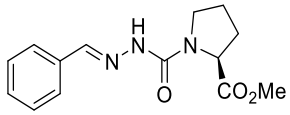
Benzyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (4.45a)



Following general procedure A and starting with DSC (581 mg, 2.20 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (240 mg, 2.00 mmol, 1.00 equiv.), H-Pro-OBn HCl (483 mg, 2.00 mmol, 1.00 equiv.), DIPEA (697 µL, 4.00 mmol, 2.00 equiv.) and 17.6 mL of dry DCM, benzyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (**4.45a**) (211 mg, 600 µmol, 30% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 200:1).

Rf (DCM/MeOH 20:1): 0.31. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (s, 1H, N*H*), 7.70 (s, 1H, *H*C=N), 7.62 – 7.52 (m, 2H, Ar*H*), 7.36 – 7.27 (m, 8H, Ar*H*), 5.19 (d, *J* = 12.4 Hz, 1H, CH_2Ph), 5.09 (d, *J* = 12.3 Hz, 1H, CH_2Ph), 4.82 (dd, *J* = 8.6, 3.7 Hz, 1H, NC*H*CO_2Bn), 3.88 – 3.69 (m, 2H, NCH_2), 2.31 – 2.17 (m, 1H, NCHCH_2), 2.16 – 1.87 (m, 3H, NCHCH_2 and NCH_2CH_2).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8, 154.8, 142.5, 135.7, 134.4, 129.6, 128.7, 128.7, 128.4, 128.2, 127.1, 67.0, 60.5, 48.4, 30.3, 24.0. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{20}H_{21}N_3NaO_3^+$ 374.1475; Found 374.1474.

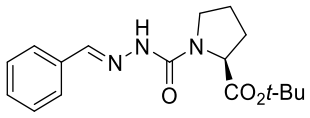
Methyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (4.45b)



Following general procedure A and starting with DSC (581 mg, 2.20 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (240 mg, 2.00 mmol, 1.00 equiv.), H-Pro-OMe HCl (331 mg, 2.00 mmol, 1.00 equiv.), DIPEA (697 µL, 4.00 mmol, 2.00 equiv.) and 17.6 mL of dry DCM, methyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (**4.45b**) (184 mg, 668 µmol, 33% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 100:1).

Rf (DCM/MeOH 20:1): 0.25. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.81 (s, 1H, N*H*), 7.79 (s, 1H, *H*C=N), 7.65 – 7.55 (m, 2H, Ar*H*), 7.44 – 7.28 (m, 3H, Ar*H*), 4.76 (dd, *J* = 8.8, 3.6 Hz, 1H, NC*H*CO_2Me), 3.86 – 3.71 (m, 2H, NCH_2), 3.69 (s, 3H, OCH_3), 2.32 – 2.15 (m, 1H, NCHCH_2), 2.11 – 1.90 (m, 3H, NCHCH_2 and NCH_2CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.6, 154.8, 142.5, 134.4, 129.6, 128.7, 127.1, 60.4, 52.3, 48.3, 30.3, 24.0. **HRMS (nanochip-ESI/LTQ-Orbitrap)** m/z: $[M + Na]^+$ Calcd for $C_{14}H_{17}N_3NaO_3^+$ 298.1162; Found 298.1168.

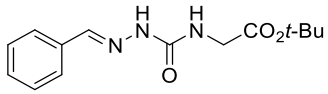
***tert*-Butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (4.45c)**



Following general procedure A and starting with DSC (581 mg, 2.20 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (240 mg, 2.00 mmol, 1.00 equiv.), H-Pro-OtBu (361 mg, 2.00 mmol, 1.00 equiv.), DIPEA (697 µL, 4.00 mmol, 2.00 equiv.) and 17.6 mL of dry DCM, *tert*-Butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (**4.45c**) (400 mg, 1.26 mmol, 63% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 200:1).

Rf (DCM/MeOH 20:1): 0.35. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (s, 1H, N*H*), 7.76 (s, 1H, *H*C=N), 7.62 (dt, *J* = 8.4, 2.2 Hz, 2H, Ar*H*), 7.43-7.28 (m, 3H, Ar*H*), 4.73-4.65 (m, 1H, NC*H*CO_2tBu), 3.84-3.66 (m, 2H, NCH_2), 2.22 (dq, *J* = 12.3, 8.5 Hz, 1H, NCHCH_2), 2.12-1.85 (m, 3H, NCHCH_2 and NCH_2CH_2), 1.41 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.1, 154.6, 142.0, 134.5, 129.5, 128.7, 127.2, 81.6, 61.0, 48.4, 30.5, 28.1, 23.7. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{23}N_3NaO_3^+$ 340.1632; Found 340.1632. **IR** (v_{max}, cm^{-1}) 3230 (w), 2979 (m), 2882 (w), 1737 (s), 1650 (m), 1549 (m), 1395 (s), 1365 (s), 1207 (m), 1145 (s), 1080 (m), 911 (m), 737 (s). $[\alpha]_D^{25}$ = -83.4 (c = 0.57, $CHCl_3$).

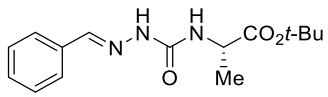
***tert*-Butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (4.45d)**



Following general procedure A and starting with DSC (1.45 g, 5.50 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (601 mg, 5.00 mmol, 1.00 equiv.), H-Gly-OtBu (690 mg, 5.00 mmol, 1.00 equiv.), DIPEA (1.74 mL, 10.0 mmol, 2.00 equiv.) and 44 mL of dry DCM, *tert*-Butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**4.45d**) (712 mg, 2.57 mmol, 51% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 100:1).

Rf (DCM/MeOH 20:1): 0.23. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.51 (s, 1H, NN*H*), 7.76 (s, 1H, *H*C=N), 7.64 (dd, *J* = 7.6, 1.9 Hz, 2H, Ar*H*), 7.44-7.31 (m, 3H, Ar*H*), 6.64 (t, *J* = 5.4 Hz, 1H, N*H*), 4.06 (d, *J* = 5.5 Hz, 2H, CH_2), 1.51 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.6, 156.4, 141.7, 134.1, 129.8, 128.8, 127.0, 82.2, 42.6, 28.2. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{14}H_{19}N_3NaO_3^+$ 300.1319; Found 300.1318. **IR** (v_{max}, cm^{-1}) 3345 (w), 2988 (w), 1783 (m), 1733 (s), 1675 (m), 1539 (s), 1369 (s), 1224 (s), 1152 (s), 1069 (m), 757 (m).

***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-alaninate (4.45e)**

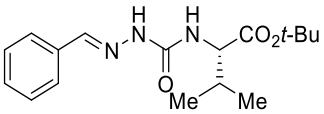


Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Ala-O*t*Bu HCl (275 mg, 1.50

mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-alaninate (**4.45e**) (254 mg, 0.872 mmol, 58% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM/MeOH 50:1).

Rf (DCM/MeOH 50:1): 0.15. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.29 (s, 1H, NN*H*), 7.75 (s, 1H, *H*C=N), 7.68-7.61 (m, 2H, Ar*H*), 7.43-7.31 (m, 3H, Ar*H*), 6.70 (d, *J* = 7.8 Hz, 1H, N*H*CH), 4.51 (p, *J* = 7.2 Hz, 1H, NHC*H*), 1.55-1.42 (m, 12H, CH_3 and *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7, 155.8, 141.4, 134.1, 129.8, 128.8, 127.0, 81.9, 49.3, 28.2, 19.5. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{15}H_{21}N_3NaO_3^+$ 314.1475; Found 314.1474. **IR** (ν_{max}, cm^{-1}) 3400 (w), 3189 (w), 3071 (m), 2988 (m), 1737 (m), 1668 (s), 1524 (s), 1369 (s), 1141 (s), 911 (m), 846 (m), 757 (m), 732 (s). $[\alpha]_D^{25}$ = +58.8 (c = 0.55, $CHCl_3$).

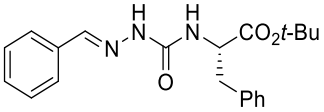
***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-valinate (4.45f)**



Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Val-O*t*Bu HCl (321 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-valinate (**4.45f**) (295 mg, 0.924 mmol, 62% yield) was obtained as a colorless oil after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 100:1).

Rf (DCM/MeOH 50:1): 0.21. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.33 (s, 1H, NN*H*), 7.76 (s, 1H, *H*C=N), 7.63 (m, 2H, Ar*H*), 7.43-7.32 (m, 3H, Ar*H*), 6.69 (d, *J* = 9.1 Hz, 1H, N*H*CH), 4.44 (dd, *J* = 9.1, 4.6 Hz, 1H, NHC*H*), 2.30-2.16 (m, 1H, NHCHC*H*), 1.50 (s, 9H, *t*-Bu), 1.02 (d, *J* = 6.9 Hz, 3H, CH_3), 0.99 (d, *J* = 6.9 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.5, 156.3, 141.4, 134.2, 129.8, 128.8, 127.0, 81.9, 58.2, 31.9, 28.2, 19.2, 17.8. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{17}H_{25}N_3NaO_3^+$ 342.1788; Found 342.1781. **IR** (ν_{max}, cm^{-1}) 3428 (w), 3215 (w), 2966 (m), 1729 (s), 1683 (s), 1524 (s), 1369 (s), 1217 (m), 1136 (s), 944 (w), 842 (m), 752 (s). $[\alpha]_D^{25}$ = +54.3 (c = 0.81, $CHCl_3$).

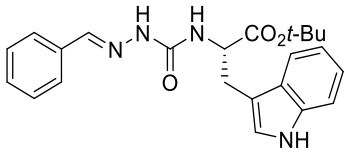
***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-phenylalaninate (4.45g)**



Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Phe-O*t*Bu HCl (391 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-phenylalaninate (**4.45g**) (262 mg, 0.713 mmol, 48% yield) was obtained as a colorless oil after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 100:1).

Rf (DCM/MeOH 50:1): 0.23. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.08 (s, 1H, NN*H*), 7.70 (s, 1H, *H*C=N), 7.61-7.52 (m, 2H, Ar*H*), 7.37 (m, 3H, Ar*H*), 7.33-7.28 (m, 2H, Ar*H*), 7.27 (m, 1H, Ar*H*), 7.26-7.23 (m, 2H, Ar*H*), 6.65 (d, *J* = 8.4 Hz, 1H, N*H*CH), 4.77 (dt, *J* = 8.4, 6.0 Hz, 1H, NHC*H*), 3.26-3.09 (m, 2H, NHCHCH_2), 1.42 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 155.7, 141.2, 136.5, 134.1, 129.8, 129.8, 128.8, 128.5, 127.1, 127.0, 82.2, 54.2, 39.0, 28.1. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{21}H_{25}N_3NaO_3^+$ 390.1788; Found 390.1786. **IR** (v_{max}, cm^{-1}) 3403 (w), 3087 (m), 2981 (m), 1740 (m), 1686 (s), 1527 (s), 1365 (s), 1163 (s), 1134 (s), 910 (m), 846 (m), 733 (s). $[\alpha]_D^{25}$ = +14.7 (c = 0.60, $CHCl_3$).

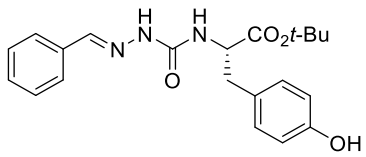
***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-tryptophanate (4.45h)**



Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Trp-O*t*Bu (445 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-tryptophanate (**4.45h**) (362 mg, 0.891 mmol, 59% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 50:1).

Rf (DCM/MeOH 50:1): 0.16. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.16 (s, 1H, NN*H*), 8.18 (s, 1H, N*H*), 7.69 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.60 (s, 1H, *H*C=N), 7.44-7.26 (m, 6H, Ar*H*), 7.21-7.13 (m, 1H, Ar*H*), 7.11-7.06 (m, 2H, Ar*H*), 6.71 (d, *J* = 8.4 Hz, 1H, N*H*CH), 4.85 (dt, *J* = 8.4, 5.7 Hz, 1H, NHC*H*), 3.36 (d, *J* = 5.7 Hz, 2H, NHCHCH_2), 1.40 (s, 9H, *t*-Bu).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.6, 156.0, 141.2, 136.2, 134.1, 129.6, 128.7, 128.0, 127.0, 122.9, 122.2, 119.8, 119.1, 111.2, 110.7, 82.0, 54.1, 28.3, 28.1. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{23}H_{26}N_4NaO_3^+$ 429.1897; Found 429.1894. **IR** (v_{max}, cm^{-1}) 3247 (w), 2974 (w), 1729 (w), 1661 (m), 1535 (m), 1515 (m), 1369 (m), 1231 (w), 1156 (m), 1131 (m), 907 (s), 727 (s). $[\alpha]_D^{25}$ = -54.6 (c = 0.54, $CHCl_3$).

***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-tyrosinate (4.45i)**

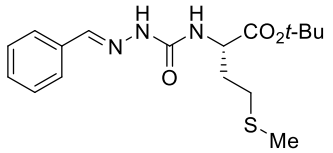


Following general procedure A and starting with DSC (581 mg, 2.20 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (240 mg, 2.00 mmol, 1.00 equiv.), H-Tyr-O*t*Bu (484 mg, 2.00 mmol, 1.00 equiv.), DIPEA (696 µL, 4.00 mmol, 2.00 equiv.) and 17.6 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-tyrosinate (**4.45i**) (300 mg, 0.782 mmol, 39% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 50:1).

Rf (DCM/MeOH 20:1): 0.17. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.85 (s, 1H, NN*H*), 7.64 (s, 1H, *H*C=N), 7.57-7.51 (m, 2H, Ar*H*), 7.41-7.29 (m, 3H, Ar*H*), 7.05 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.73

(dd, *J* = 9.0, 2.4 Hz, 2H, Ar*H*), 6.65 (d, *J* = 8.5 Hz, 1H, N*H*CH), 6.33 (s, 1H, O*H*), 4.71 (dt, *J* = 8.5, 6.1 Hz, 1H, NHC*H*), 3.13-2.97 (m, 2H, NCHCH_2), 1.44 (s, 9H, *t*-Bu).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.3, 155.7, 155.2, 141.6, 134.0, 130.8, 129.9, 128.8, 127.9, 127.1, 115.5, 82.4, 54.4, 38.1, 28.2. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{21}H_{25}N_3NaO_4^+$ 406.1737; Found 406.1735. **IR** (v_{max}, cm^{-1}) 3294 (w), 2978 (w), 1725 (w), 1672 (m), 1532 (m), 1369 (m), 1231 (w), 1156 (m), 907 (s), 730 (s). $[\alpha]_D^{25}$ = -5.4 (c = 0.54, $CHCl_3$).

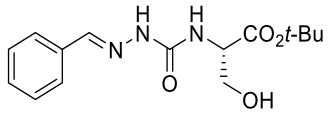
***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-methioninate (4.45j)**



Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Met-O*t*Bu HCl (382 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-methioninate (**4.45j**) (294 mg, 0.837 mmol, 56% yield) was obtained as a colorless oil after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 50:1).

Rf (DCM/MeOH 50:1): 0.13. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.32 (s, 1H, NN*H*), 7.76 (s, 1H, *H*C=N), 7.65 (m, 2H, Ar*H*), 7.45-7.31 (m, 3H, Ar*H*), 6.79 (d, *J* = 8.2 Hz, 1H, N*H*CH), 4.63 (td, *J* = 7.7, 5.0 Hz, 1H, NHC*H*), 2.70-2.52 (m, 2H, SCH_2), 2.22 (m, 1H, NHCHCH_2), 2.12 (s, 3H, SCH_3), 2.11 (m, 1H, NHCHCH_2), 1.50 (s, 9H, *t*-Bu).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.4, 156.0, 141.6, 134.1, 129.9, 128.8, 127.0, 82.2, 52.8, 33.0, 30.2, 28.2, 15.6. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{17}H_{25}N_3NaO_3S^+$ 374.1509; Found 374.1502. **IR** (v_{max}, cm^{-1}) 3414 (w), 3202 (m), 3100 (m), 2974 (m), 1730 (m), 1668 (s), 1531 (s), 1369 (s), 1145 (s), 950 (w), 849 (w), 759 (m). $[\alpha]_D^{25}$ = -8.4 (c = 0.24, $CHCl_3$).

***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-serinate (4.45k)**

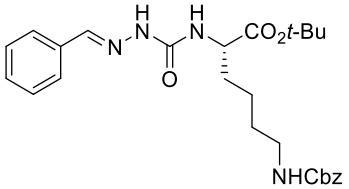


Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Ser-O*t*Bu HCl (312 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-serinate (**4.45k**) (316 mg, 1.03 mmol, 69% yield) was obtained as a colorless oil after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 50:1).

Rf (DCM/MeOH 20:1): 0.20. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.38 (s, 1H, NN*H*), 7.74 (s, 1H, *H*C=N), 7.68-7.58 (m, 2H, Ar*H*), 7.43-7.31 (m, 3H, Ar*H*), 7.07 (d, *J* = 6.8 Hz, 1H, N*H*CH), 4.56 (ddd, *J* = 6.9, 4.8, 3.4 Hz, 1H, NHC*H*), 4.04 (ddd, *J* = 11.1, 6.0, 3.4 Hz, 1H, NHCHCH_2), 3.96 (ddd, *J* = 11.1, 6.2, 4.9 Hz, 1H, NHCHCH_2), 3.12 (t, *J* = 6.2 Hz, 1H, O*H*), 1.52 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.7, 156.7, 142.1, 133.9, 130.0, 128.8, 127.1, 83.0, 64.8, 56.4, 28.2. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{15}H_{21}N_3NaO_4^+$ 330.1424; Found

330.1422. **IR** (v_{max}, cm^{-1}) 3407 (w), 2985 (w), 1732 (m), 1658 (m), 1527 (m), 1368 (m), 1156 (m), 1131 (m), 907 (s), 727 (s). $[\alpha]_D^{25}$ = +56.8 (c = 0.47, $CHCl_3$).

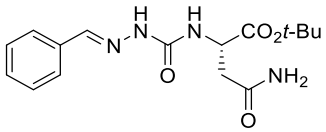
***tert*-Butyl *(E)*-N^2-(2-benzylidenehydrazine-1-carbonyl)-N^6-((benzyloxy)carbonyl)-*L*-lysinate (4.45l)**



Following general procedure A and starting with DSC (291 mg, 1.10 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (120 mg, 1.00 mmol, 1.00 equiv.), H-Lys(Z)-O*t*Bu HCl (393 mg, 1.00 mmol, 1.00 equiv.), DIPEA (348 µL, 2.00 mmol, 2.00 equiv.) and 8.80 mL of dry DCM, *tert*-butyl *(E)*-N^2-(2-benzylidenehydrazine-1-carbonyl)-N^6-((benzyloxy)carbonyl)-*L*-lysinate (**4.45l**) (260 mg, 0.539 mmol, 54% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 100:1).

Rf (DCM/MeOH 50:1): 0.15. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (s, 1H, NN*H*), 7.68 (s, 1H, *H*C=N), 7.63 (dd, *J* = 7.6, 1.9 Hz, 2H, Ar*H*), 7.41-7.27 (m, 8H, Ar*H*), 6.66 (d, *J* = 8.4 Hz, 1H, N*H*CH), 5.07 (s, 2H, OCH_2Ph), 4.90 (t, *J* = 5.0 Hz, 1H, N*H*Cbz), 4.50 (td, *J* = 7.9, 5.1 Hz, 1H, NHC*H*), 3.20 (q, *J* = 6.5 Hz, 2H, CH_2NHCbz), 1.96-1.85 (m, 1H, NHCHCH_2), 1.80-1.70 (m, 1H, NHCHCH_2), 1.64-1.52 (m, 2H, CH_2CH$_2$NHCbz), 1.50-1.40 (m, 11H, NHCHCH$_2$CH_2 and *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.9, 156.5, 155.8, 141.5, 136.8, 134.0, 129.9, 128.8, 128.6, 128.2, 127.0, 82.1, 66.7, 53.1, 40.9, 33.1, 29.5, 28.2, 22.5. One aromatic ^{13}C is not resolved. **HRMS (nanochip-ESI/LTQ-Orbitrap)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{34}N_4NaO_5^+$ 505.2421; Found 505.2415. **IR** (v_{max}, cm^{-1}) 3367 (w), 2978 (m), 2934 (m), 2862 (w), 1675 (s), 1526 (s), 1368 (m), 1251 (s), 1155 (s), 1134 (s), 1023 (w), 755 (s). $[\alpha]_D^{25}$ = +1.6 (c = 0.42, $CHCl_3$).

***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-asparaginate (4.45m)**

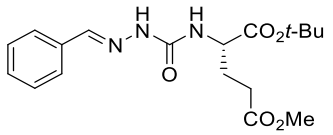


Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Asn-O*t*Bu (436 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-asparaginate (**4.45m**) (166 mg, 0.497 mmol, 33% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 50:1 to DCM/MeOH 20:1).

Rf (DCM/MeOH 20:1): 0.23. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.38 (s, 1H, NN*H*), 7.75 (s, 1H, *H*C=N), 7.64-7.57 (m, 2H, Ar*H*), 7.38-7.29 (m, 3H, Ar*H*), 7.19 (d, *J* = 8.1 Hz, 1H, N*H*CH), 6.21 (br s, 1H, C(O)NH_2), 5.99 (br s, 1H, C(O)NH_2), 4.71 (dt, *J* = 8.2, 5.1 Hz, 1H, NHC*H*), 2.94-2.81 (m, 2H, NHCHCH_2), 1.49 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7, 170.4, 156.4,

142.0, 134.0, 129.9, 128.8, 127.1, 82.7, 50.4, 38.7, 28.1. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{16}H_{22}N_4NaO_4^+$ 357.1533; Found 357.1525. **IR** (v_{max}, cm^{-1}) 3379 (m), 3168 (w), 2960 (w), 1731 (m), 1669 (s), 1520 (s), 1361 (m), 1159 (s), 1127 (s), 914 (m), 730 (s). $[\alpha]_D^{25}$ = +30.6 (c = 0.51, $CHCl_3$).

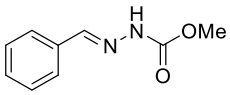
1-(*tert*-Butyl) 5-methyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-glutamate (4.45n)



Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Glu(OMe)-O*t*Bu HCl (401 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, 1-(*tert*-butyl) 5-methyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-glutamate (**4.45n**) (332 mg, 0.914 mmol, 61% yield) was obtained as a colorless oil after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 50:1).

Rf (DCM/MeOH 50:1): 0.10. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.07 (s, 1H, NN*H*), 7.73 (s, 1H, *H*C=N), 7.66 (m, 2H, Ar*H*), 7.44-7.32 (m, 3H, Ar*H*), 6.75 (d, *J* = 8.2 Hz, 1H, N*H*CH), 4.54 (td, *J* = 8.2, 4.9 Hz, 1H, NHC*H*), 3.66 (s, 3H, OCH_3), 2.58-2.37 (m, 2H, CH_2CO$_2$Me), 2.34-2.25 (m, 1H, NHCHCH_2), 2.07 (m, 1H, NHCHCH_2), 1.50 (s, 9H, *t*-Bu).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.6, 171.4, 155.9, 141.5, 134.0, 129.9, 128.8, 127.1, 82.4, 52.9, 51.9, 30.4, 28.4, 28.2. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{18}H_{25}N_3NaO_5^+$ 386.1686; Found 386.1680. **IR** (v_{max}, cm^{-1}) 3375 (w), 3201 (w), 3094 (w), 2959 (m), 1737 (s), 1672 (s), 1531 (s), 1368 (s), 1226 (m), 1153 (s), 917 (w), 849 (w), 757 (m). $[\alpha]_D^{25}$ = +11.7 (c = 0.32, $CHCl_3$).

Methyl (*E*)-2-benzylidenehydrazine-1-carboxylate (4.48a)



Following a reported procedure,[4] to a solution of methyl *N*-aminocarbamate (866 mg, 9.42 mmol, 1.00 equiv) in ethanol (23.5 mL) was added benzaldehyde (962 µL, 9.42 mmol, 1.00 equiv). The reaction mixture was stirred under reflux for 3 h. The solution was cooled to room temperature and the precipitate filtered (washed with hexane) under vacuum. Methyl (*E*)-2-benzylidenehydrazine-1-carboxylate (**4.48a**) (925 mg, 5.19 mmol, 55% yield) was collected as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52-8.19 (m, 1H, NN*H*), 7.87 (s, 1H, *H*C=N), 7.73-7.61 (m, 2H, Ar*H*), 7.43-7.32 (m, 3H, Ar*H*), 3.86 (s, 3H, OCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.6, 144.9, 133.7, 129.9, 128.5, 127.2, 52.8. Spectroscopic data was consistent with the values reported in the literature.[5]

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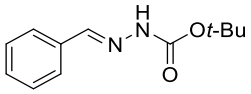
[4] Santos, M. S.; Nortcliffe, A.; Lewis, W.; Bradshaw, T. D.; Moody, C. J. *Chem. Eur. J.* **2018**, *24* (33), 8325–8330.
[5] He, R.; Lam, Y. *Org. Biomol. Chem.* **2008**, *6* (12), 2182-2186.

tert-Butyl (_E_)-2-benzylidenehydrazine-1-carboxylate (4.48b)



Following a reported procedure,4 to a solution of *tert*-butylcarbazate (1.27 g, 9.42 mmol, 1.00 equiv) in ethanol (23.5 mL) was added benzaldehyde (962 µL, 9.42 mmol, 1.00 equiv). The reaction mixture was stirred under reflux for 3 h. The solution was cooled to room temperature and the precipitate filtered (washed with hexane) under vacuum. *tert*-Butyl (*E*)-2-benzylidenehydrazine-1-carboxylate (**4.48b**) (1.47 g, 6.67 mmol, 71% yield) was collected as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H, NN*H*), 7.83 (s, 1H, *H*C=N), 7.70-7.66 (m, 2H, Ar*H*), 7.40-7.32 (m, 3H, Ar*H*), 1.54 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.4, 143.7, 134.0, 130.0, 128.7, 127.3, 81.6, 28.4. Spectroscopic data was consistent with the values reported in the literature.[6]

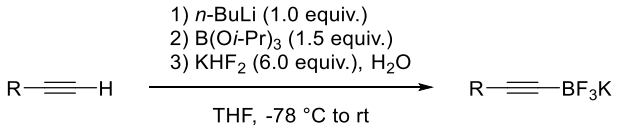
7.3.2. Procedures for the synthesis of EBX

The preparation of the following BF_3K-alyknes and EBX reagents had been already described before. The procedures are taken here from the indicated publications to facilitate reproduction of the results by having all the data in the same file.

Synthesis of Potassium Trifluoroborate Salts

General note: It is known that carbons linked to the boron atom are difficult to be observed by ^{13}C NMR due to a broadening of the signal caused by the quadrupole moment of ^{11}B nuclei. This implies that the two carbons of the alkyne (in alkynyl-BF_3K) are too broad to be properly visible.[7] Therefore, they are not listed in the characterization data.

General procedure B:



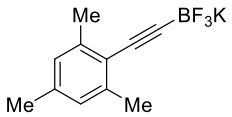
Following a reported procedure.[8] An oven-dried round-bottom flask (PFA), charged with alkyne (1.0 equiv.) if solid, was evacuated and backfilled with N_2 (3x). Then, alkyne (if liquid) and dry THF (0.3 M) were added. The mixture was cooled to -78 °C and a solution of *n*-BuLi (2.5 M, 1.0 equiv.) in hexane was added dropwise under N_2. The reaction was stirred at -78 °C for 1 h and B(O*i*-Pr)$_3$ (1.5 equiv.) was added quickly. The reaction was stirred 10 min at -78 °C then 2 h at rt. The mixture was cooled to 0 °C and a saturated solution of KHF_2 (6.0 equiv.) in water (40% of THF volume + additional 40% to rinse the remaining solid) was added. The reaction was stirred at rt open to air for 2 h then concentrated *in vacuo*. The wet solid

[6] Löser, R.; Schilling, K.; Dimmig, E.; Gütschow, M. *J. Med. Chem.* **2005**, *48* (24), 7688–7707.
[7] R. A. Oliveira, R. O. Silva, G. A. Molander, P. H. Menezes, *Magn. Reson. Chem.* **2009**, *47*, 873–878.
[8] J. Borrel, J. Waser, *Org. Lett.* **2022**, *24*, 142–146.

obtained was further dried by co-evaporation with acetone. To the dry solid was added acetone (~50 mL) and the resulting mixture was placed on a rotary evaporator and rotated rapidly at atmospheric pressure with the bath set at 45 °C for 15 minutes. The flask was removed and the mixture carefully filtered taking care to leave the insoluble material in the reaction flask. Acetone was once again added and the process (heating for 15 min then collection of the liquid) was repeated 2 more times. The combined acetone filtrates were concentrated *in vacuo* to approximately 1/3 of the initial volume. Et_2O (~60 mL) was added causing a white solid to precipitate. The mixture was cooled to 0 °C for 10 min then filtered. The solid obtained was washed with Et_2O and dried in vacuo to afford the desired potassium alkynyltrifluoroborate.

Note: This purification procedure usually affords the pure desired product. If it is not the case a more classical recrystallization from acetone followed by precipitation with Et_2O can be performed.

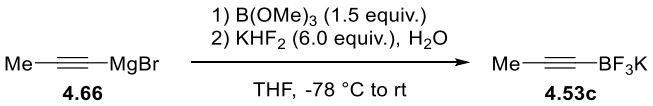
Potassium trifluoro(mesitylethynyl)borate (4.53b):



Synthesized following general procedure B, starting from 2-ethynyl-1,3,5-trimethylbenzene (0.950 g, 1.03 mL, 6.3 mmol). Potassium trifluoro(mesitylethynyl)borate (**4.53b**) (1.23 g, 4.94 mmol, 78%) was obtained as a white solid.

^{1}H NMR (400 MHz, acetone-d_6) δ 6.79 (s, 2H, Ar*H*), 2.34 (s, 6H, C*H₃*), 2.20 (s, 3H, C*H₃*). **^{13}C NMR** (101 MHz, acetone-d_6) δ 140.0, 135.9, 127.9, 124.0, 21.3, 21.2. **^{19}F NMR** (377 MHz, acetone-d_6) δ -134.3. **^{11}B NMR** (128 MHz, acetone-d_6) δ -1.0 (q, *J* = 37.3 Hz). Spectroscopic data was consistent with the values reported in the literature.8

Potassium trifluoro(prop-1-yn-1-yl)borate (4.53c)

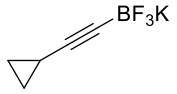


Following a reported procedure.8 An oven-dried round-bottom flask (PFA) was evacuated and backfilled with N_2 (3x). Then, a solution of 1-propynylmagnesium bromide (**4.66**) (15 mL, 7.5 mmol, 0.5 M, 1.0 equiv.) in THF and dry THF (15 mL) were added. The solution was cooled to -78 °C and $B(OMe)_3$ (1.25 mL, 11.3 mmol, 1.5 equiv.) was added quickly under N_2. The reaction was stirred 1 h at -78 °C then 1.5 h at -20 °C. A saturated solution of KHF_2 (3.5 g, 45 mmol, 6.0 equiv.) in water (10 mL + additional 10 mL to rinse the remaining solid) was added. The reaction was stirred at rt open air for 2 h then concentrated *in vacuo*. The wet solid obtained was further dried by co-evaporation with acetone. To the dry solid was added acetone (~30 mL) and the resulting mixture was placed on a rotary evaporator and rotated rapidly at atmospheric pressure with the bath set at 45 °C for 15 minutes. The flask was removed and the mixture carefully filtered taking care to leave the insoluble material in the reaction flask. Acetone was once again added and the process (heating for 15 min then collection of the liquid) was repeated 2 more times. The combined acetone filtrates were concentrated *in vacuo* to approximately 1/3 of the initial volume. Et_2O (~30 mL) was added causing a white solid to precipitate. The mixture was cooled to 0 °C for 10 min then filtered.

The solid obtained was washed with Et_2O and dried in vacuo to afford potassium trifluoro(prop-1-yn-1-yl)borate (**4.53c**) (0.95 g, 6.5 mmol, 87%) as a white solid.

^{1}H NMR (400 MHz, acetone-d_6) δ 1.64 – 1.58 (m, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, acetone-d_6) δ 4.0. **^{19}F NMR** (376 MHz, acetone-d_6) δ -134.7 (dd, *J* = 76.0, 37.4 Hz). **^{11}B NMR** (128 MHz, acetone-d_6) δ -1.7 (q, *J* = 38.2 Hz). Spectroscopic data was consistent with the values reported in the literature.8

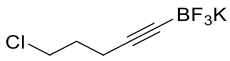
Potassium (cyclopropylethynyl)trifluoroborate (4.53d)



Synthesized following general procedure B, starting from ethynylcyclopropane (0.50 g, 0.64 mL, 7.5 mmol). Potassium (cyclopropylethynyl)trifluoroborate (**4.53d**) (0.86 g, 5.0 mmol, 67%) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 – 1.01 (m, 1H, C*H*CH$_2$), 0.61 – 0.54 (m, 2H, CHC*H*$_2$), 0.42 – 0.36 (m, 2H, CHC*H*$_2$). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 7.4, 0.1. **^{19}F NMR** (377 MHz, DMSO-d_6) δ -131.1. **^{11}B NMR** (128 MHz, DMSO-d_6) δ -2.1 (q, *J* = 37.5 Hz). Spectroscopic data was consistent with the values reported in the literature.8

Potassium (5-chloropent-1-yn-1-yl)trifluoroborate (4.53e)

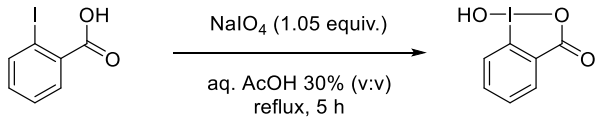


Synthesized following general procedure B, starting from 5-chloropent-1-yne (0.77 g, 0.80 mL, 7.5 mmol). Potassium (5-chloropent-1-yn-1-yl)trifluoroborate (**4.53e**) (1.28 g, 6.14 mmol, 82%) was obtained as a white solid.

^{1}H NMR (400 MHz, acetone-d_6) δ 3.70 (t, *J* = 6.6 Hz, 2H, ClC*H*$_2$CH$_2$), 2.24 – 2.17 (m, 2H, C≡CC*H*$_2$CH$_2$), 1.85 (p, *J* = 6.7 Hz, 2H, CH$_2$C*H*$_2$CH$_2$). **^{13}C NMR** (101 MHz, acetone-d_6) δ 44.9, 33.1, 17.3. **^{19}F NMR** (376 MHz, acetone-d_6) δ -134.6. Spectroscopic data was consistent with the values reported in the literature.[9]

Procedures for the synthesis of EBX

1-[Hydroxy]-1,2-benziodoxol-3-(1*H*)-one (4.50)



4.67 **4.50**

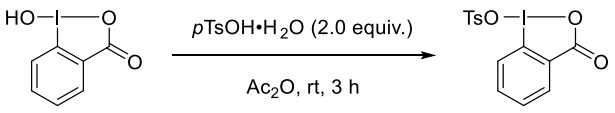
Following a reported procedure.8 $NaIO_4$ (18.1 g, 84.7 mmol, 1.05 equiv) and 2-iodobenzoic acid (**4.67**) (20.0 g, 80.6 mmol, 1.00 equiv) were suspended in a mixture of AcOH (36 mL) and water (84 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (100 mL) and allowed to cool to room temperature protected from light. The crude product was collected by filtration, washed on the filter with ice water (3

[9] G. A. Molander, B. W. Katona, F. Machrouhi, *J. Org. Chem.* **2002**, *67*, 8416–8423.

x 50 mL) and acetone (3 x 50 mL), and air-dried in the dark to give the pure product **4.50** (20.0 g, 75.7 mmol, 94%) 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. Spectroscopic data was consistent with the values reported in the literature.8

1-[*p*-Methylbenzenesulfonyloxy]-1,2-benziodoxol-3-(1*H*)-one (4.52)



4.50 **4.52**

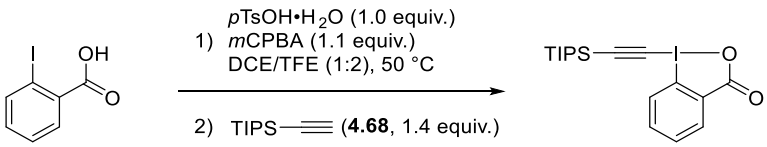
Following a reported procedure.8 *p*TsOH•H_2O (5.71 g, 30.0 mmol, 2.0 equiv.) was added portion-wise to an oven-dried flask containing a suspension of 1-[Hydroxy]-1,2-benziodoxol-3-(1*H*)-one (**4.50**) (3.96 g, 15.0 mmol, 1.0 equiv.) in acetic anhydride (15 mL). After 5 min, a slightly exothermic reaction began and the mixture turned into a clear slightly yellow solution. The reaction was stirred at rt under N_2 for 3 h. During the course of the reaction precipitation of the product as a white solid might occur. Dry Et_2O (40 mL) was added and the mixture was cooled to 0 °C for 10 min. At this point precipitation of the product should have occurred. The solid was filtered and washed with dry Et_2O (4 x 40 mL) then dried in vacuo to afford 1-[*p*-methylbenzenesulfonyloxy]-1,2-benziodoxol-3-(1*H*)-one (**4.52**) (4.75 g, 11.4 mmol, 76%) as a white solid.

Note: The product is slightly hygroscopic, when filtering it using vacuum filtration it is advised to avoid extensive drying on the frit. Just removing the ether is enough to collect it properly and further drying can be carried in vacuo.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.98 – 7.93 (m, 1H, Ar*H*), 7.83 (dd, *J* = 8.1, 0.9 Hz, 1H, Ar*H*), 7.70 (td, *J* = 7.4, 1.0 Hz, 1H, Ar*H*), 7.51 – 7.46 (m, 2H, Ar*H*), 7.15 – 7.10 (m, 2H, Ar*H*), 2.28 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.9, 145.2, 138.1, 134.6, 131.5, 131.2, 130.5, 128.3, 126.4, 125.6, 120.5, 20.9. Spectroscopic data was consistent with the values reported in the literature.[10]

Note: We observed a slow solubilization of **4.52** if dry DMSO is used. We think water present in DMSO help the solubilization and that when dry DMSO is used the solubilization happen after a couple of minutes (~5min) due to the progressive absorption of the water present in the air by the solvent.

1-[(Triisopropylsilyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (4.36a)



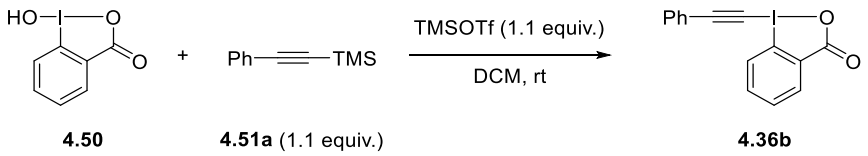
4.67 **4.36a**

[10] M. Nappi, C. He, W. G. Whitehurst, B. G. N. Chappell, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2018**, *57*, 3178–3182.

Following a reported procedure,[11] a 250 mL, three-necked, round-bottomed flask was equipped with a Teflon-coated magnetic stirrer (2 cm), a Liebig reflux condenser (open to air), and a septum. The septum was removed, and the flask was charged with *o*-iodobenzoic acid (**4.67**) (6.00 g, 24.2 mmol, 1.00 equiv), *p*-toluenesulfonic acid monohydrate (4.60 g, 24.2 mmol, 1.00 equiv), 1,2-dichloroethane (36.3 mL), and trifluoroethanol (36.3 mL). The resulting white suspension was stirred (600 rpm) at room temperature. *m*CPBA (≤77% purity; 5.96 g, 26.6 mmol, ≤1.10 equiv) was added in portions over a period of 10 min. During the addition, the suspension slightly darkened, becoming beige. After the addition of *m*CPBA, the septum was replaced, and the flask was placed in dry-sin preheated to 55 °C and stirred (600 rpm). The mixture turned from a white suspension to a clear yellow color solution over a period of 5 min. After 1.5 h, (triisopropylsilyl)acetylene (**4.68**) (7.60 mL, 33.9 mmol, 1.40 equiv) was added dropwise via a 10 mL syringe over a period of 5 min and stirring was continued at 55 °C for another 24 h. After this time, the pale-yellow solution was allowed to cool down to room temperature. Saturated aq. $NaHCO_3$ (120 mL) was then added: a pinkish mixture was formed with significant bubbling. This biphasic mixture was stirred (1000 rpm) at room temperature for 1 h. The mixture was transferred to a 250 mL separatory funnel, and the reaction flask was rinsed with dichloromethane (12 mL). The two layers were separated, and the aqueous layer was extracted with additional portions of dichloromethane (3 × 40 mL). The combined organic layers were washed with water (3 × 50 mL), prior to being dried over $MgSO_4$ (ca. 3.0 g), filtered into a 250 mL round-bottomed flask, and concentrated via rotary evaporation, to provide an off-white solid. The latter was purified by recrystallization from acetonitrile (12 mL) to provide 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (**4.36a**) (8.36 g, 19.5 mmol, 81% yield) as a crystalline, white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 5.9, 3.2 Hz, 1H, Ar*H*), 8.34−8.25 (m, 1H, Ar*H*), 7.80−7.72 (m, 2H, Ar*H*), 1.27−1.06 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.5, 134.6, 132.3, 131.4, 131.4, 126.1, 115. 6, 114.0, 64.6, 18.4, 11.1. Spectroscopic data was consistent with the values reported in the literature.11

1-[Phenylethynyl]-1,2-benziodoxol-3-(1*H*)-one (4.36b)



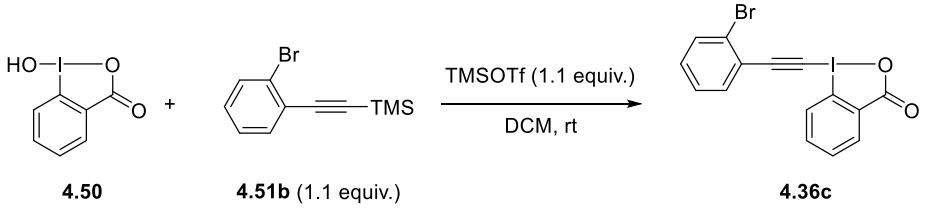
Following a reported procedure.[12] Trimethylsilyltriflate (9.1 mL, 50 mmol, 1.1 equiv) was added dropwise to a suspension of 1-[hydroxy]-1,2-benziodoxol-3-(1*H*)-one (**4.50**) (12.1 g, 45.8 mmol, 1.0 equiv) in CH_2Cl_2 (120 mL) at 0 °C. The mixture was stirred for 1 h, followed by the dropwise addition of trimethyl(phenylethynyl)silane (**4.51a**) (8.8 mL, 50 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 $NaHCO_3$ (120 mL) was added and the mixture was stirred vigorously for 30 min. The two layers of the mother liquors were separated and the organic layer was washed with sat. $NaHCO_3$ (2x50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was recrystalized in EtOAc:MeOH

[11] D. P. Hari, P. Caramenti, L. Schouwey, M. Chang, S. Nicolai, D. Bachert, T. Wright, C. Orella, J. Waser, *Org. Process Res. Dev.* **2020**, *24*, 106–110.
[12] S. G. E. Amos, D. Cavalli, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 23827–23834.

(7:3 v:v) (ca. 20 mL). The solution was left to cool to rt then in the freezer overnight, filtered and dried under high vacuum to afford 1-[phenylethynyl]-1,2-benziodoxol-3-(1*H*)-one (**4.36b**) (6.8 g, 25 mmol, 43% yield) as colorless crystals.

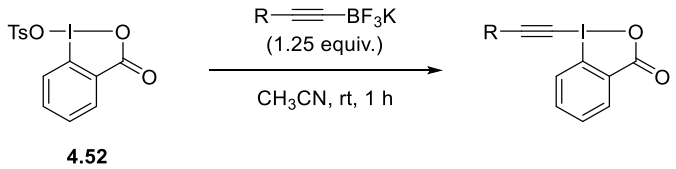
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (m, 1H, Ar*H*), 8.28 (m, 1H, Ar*H*), 7.80 (m, 2H, Ar*H*), 7.63 (m, 2H, Ar*H*), 7.48 (m, 3H, Ar*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9, 134.9, 132.9, 132.5, 131.6, 131.3. 130.8, 128.8, 126.2, 120.5, 116.2, 106.6, 50.2. Spectroscopic data was consistent with the values reported in the literature.12

1-[(2-Bromophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (4.36c)



Following a reported procedure.12 Trimethylsilyl triflate (0.42 mL, 2.4 mmol, 1.1 equiv) was added to a suspension of 1-[hydroxy]-1,2-benziodoxol-3-(1*H*)-one (**4.50**) (0.562 g, 2.13 mmol, 1.00 equiv) in CH_2Cl_2 (6 mL) at rt. The resulting suspension was stirred for 1 h, followed by the drop wise addition of ((2-bromophenyl)ethynyl)trimethylsilane (**4.51b**) (0.50 mL, 2.4 mmol, 1.1 equiv). The resulting suspension was stirred for 6 h at rt. A saturated solution of $NaHCO_3$ (10 mL) was then added and the mixture was stirred vigorously for 1 h resulting in a persistent emulsion/suspension. The mixture was diluted with $CHCl_3$ (10 mL), water (5 mL) and MeOH (ca. 2 mL) to afford 2 distinct layers. The two layers were separated, 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 in EtOAc:MeOH (7:3 v:v) (ca. 20 mL). The solution was left to cool to rt then was placed in the freezer (-20 °C) overnight. The crystals were filtered and washed with Et_2O to afford 1-[(2-bromophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (**4.36c**) (1.50 g, 3.51 mmol, 70% yield) as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) 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, Ar*H*), 7.36 (m, 2 H, Ar*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.6, 135.2, 134.7, 133.0, 132.7, 131.8, 131.3, 127.6, 126.8, 126.4, 123.2, 116.5, 104.3, 55.4. Spectroscopic data was consistent with the values reported in the literature.12



General procedure C for the purification-free synthesis of EBX reagents on 0.4 mmol scales

Following a reported procedure.8 A capped oven dried microwave vial charged with 1-(*p*-methylbenzenesulfonyloxy)-1,2-benziodoxol-3-(1*H*)-one (**4.52**) (167 mg, 0.400 mmol, 1.0 equiv.) and potassium alkynyltrifluoroborate (0.50 mmol, 1.25 equiv.) was evacuated and backfilled with N_2 (3x). Dry acetonitrile (4 mL) was added under N_2 and the reaction was stirred at rt for 1 h. To the mixture was added a sat. sol. of $NaHCO_3$ (8 mL) and the mixture was

vigorously stirred open to air for 1 h. Water (10 mL) was added and the mixture was extracted with 3 x 20 mL of DCM, the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude EBX was triturated in pentane, which induced precipitation if it was an oil. The pentane layer was discarded with care to leave the solid in the flask. This process was repeated 2 more times then the solid was dried *in vacuo* to afford the desired compounds.

Note: Purity of the product obtained was determined using ^{1}H NMR by dissolving the entirety of the compound in $CDCl_3$ (~4 mL) and adding CH_2Br_2 (14.0 µL, 0.1975 mmol, 0.49 equiv.) as internal standard.

Purity is determined based on the signal of CH_2Br_2 (4.93 ppm) normalize at I = 1 and an aromatic signal of the EBX corresponding to 1 H:

$$n(EBX)_{eff} = \frac{\frac{I_{EBX}}{N_{EBX}} * n_{std} * N_{std}}{I_{std}} = \frac{\frac{I_{EBX}}{1} * 0.1975 * 2}{1} = I_{EBX} * 0.3950$$

$$p_{EBX} = \frac{n(EBX)_{eff}}{n(EBX)_{theo}} = \frac{n(EBX)_{eff}}{\frac{m_{EBX}}{MW_{EBX}}}$$

$n(EBX)_{eff}$: moles of EBX determined by NMR (in mmol).

$n(EBX)_{theo}$: moles of EBX calculated from the mass obtained if 100% pure (in mmol).

I_{EBX}: Integral of the EBX signal.

I_{std}: Integral of the standard (CH_2Br_2) signal.

N_{EBX}: Number of protons corresponding the EBX signal.

N_{std}: Number of protons corresponding the standard (CH_2Br_2) signal.

m_{EBX}: mass of EBX obtained at the end of the reaction (in mg).

MW_{EBX}: Molecular weight of the EBX (in mg/mmol)

p_{EBX}: purity of the EBX

General procedure D for the purification-free synthesis of EBX reagents on 0.5 mmol scales

Following an adapted version of a reported procedure.8 A capped oven dried microwave vial charged with 1-(*p*-methylbenzenesulfonyloxy)-1,2-benziodoxol-3-(1*H*)-one (**4.52**) (209 mg, 0.500 mmol, 1.0 equiv.) and potassium alkynyltrifluoroborate (0.625 mmol, 1.25 equiv.) was evacuated and backfilled with N_2 (3x). Dry acetonitrile (5 mL) was added under N_2 and the reaction was stirred at rt for 1 h. To the mixture was added a sat. sol. of $NaHCO_3$ (8 mL) and the mixture was vigorously stirred open to air for 1 h. Water (10 mL) was added and the mixture was extracted with 3 x 20 mL of DCM, the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude EBX was triturated in pentane, which induced precipitation if it was an oil. The pentane layer was discarded with care to leave the solid in the flask. This process was repeated 2 more times then the solid was dried *in vacuo* to afford the desired compounds.

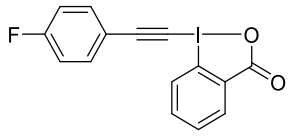
Note: Purity of the product obtained was determined using ^{1}H NMR by dissolving the entirety of the compound in $CDCl_3$ (~4 mL) and adding CH_2Br_2 (17.5 µL, 0.2469 mmol, 0.49 equiv.) as internal standard.

Purity is determined based on the signal of CH_2Br_2 (4.93 ppm) normalize at I = 1 and an aromatic signal of the EBX corresponding to 1 H:

$$n(EBX)_{eff} = \frac{\frac{I_{EBX}}{N_{EBX}} * n_{std} * N_{std}}{I_{std}} = \frac{\frac{I_{EBX}}{1} * 0.2469 * 2}{1} = I_{EBX} * 0.4938$$

$$p_{EBX} = \frac{n(EBX)_{eff}}{n(EBX)_{theo}} = \frac{n(EBX)_{eff}}{\frac{m_{EBX}}{MW_{EBX}}}$$

1-[(4-Fluorophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (4.36d)



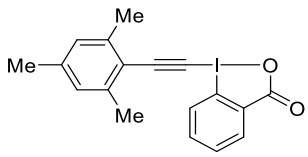
Synthesized following general procedure D, starting from potassium trifluoro((4-fluorophenyl)ethynyl)borate (141 mg, 0.625 mmol). 1-[(4-Fluorophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (**4.36d**) (172.4 mg, 0.4592 mmol, 92%, 97% purity) was obtained as a white solid. Spectroscopic data was consistent with the values reported in the literature.[13]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.36 (m, 1H, Ar*H*), 8.25 – 8.18 (m, 1H, Ar*H*), 7.81 – 7.70 (m, 2H, Ar*H*), 7.64 – 7.56 (m, 2H, Ar*H*), 7.16 – 7.08 (m, 2H, Ar*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.8, 164.0 (d, *J* = 253.8 Hz), 135.2 (d, *J* = 8.9 Hz), 135.0, 132.6, 131.7, 131.5, 126.5, 116.9 (d, *J* = 3.7 Hz), 116.4 (d, *J* = 22.4 Hz), 116.3, 105.5, 50.4 (d, *J* = 2.0 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -106.0.

$$n(EBX)_{eff} = 0.93 * 0.4938 = 0.4592\ mmol$$

$$p_{EBX} = \frac{0.4592}{\frac{172.4}{366.13}} = 0.9752 = 97\%\ purity$$

1-[Mesitylethynyl]-1,2-benziodoxol-3-(1*H*)-one (4.36e)



Synthesized following general procedure C, starting from potassium trifluoro(mesitylethynyl)borate (**4.53b**) (125 mg, 0.500 mmol). The reaction was stirred at rt for 2 h. 1-[Mesitylethynyl]-1,2-benziodoxol-3-(1*H*)-one (**4.36e**) (148.2 mg, 0.3792 mmol, 95%, 99% purity) was obtained as a white solid.

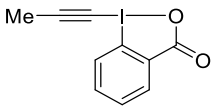
[13] D. P. Hari, G. Pisella, M. D. Wodrich, A. V. Tsymbal, F. F. Tirani, R. Scopelliti, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 5475–5481.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.38 (m, 1H, Ar*H*), 8.33 – 8.25 (m, 1H, Ar*H*), 7.79 – 7.71 (m, 2H, Ar*H*), 6.95 (s, 2H, Ar*H*), 2.47 (s, 6H, ArCH_3), 2.34 (s, 3H, ArCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.7, 142.4, 141.0, 134.9, 132.7, 131.7, 131.6, 128.3, 126.2, 117.6, 116.7, 105.6, 55.7, 21.7, 21.3. Spectroscopic data was consistent with the values reported in the literature.[14]

$$n(EBX)_{eff} = 0.96 * 0.3950 = 0.3792\ mmol$$

$$p_{EBX} = \frac{0.3792}{\frac{148.2}{390.21}} = 0.9984 = 99\%\ purity$$

1-[Prop-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (4.36f)



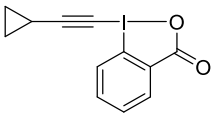
Synthesized following general procedure C, starting from potassium trifluoro(prop-1-yn-1-yl)borate (**4.53c**) (73.0 mg, 0.500 mmol). 1-[Prop-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (**4.36f**) (105.9 mg, 0.3476 mmol, 87%, 94% purity) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.33 (m, 1H, Ar*H*), 8.22 – 8.13 (m, 1H, Ar*H*), 7.79 – 7.67 (m, 2H, Ar*H*), 2.26 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$)[15] δ 166.6, 134.8, 132.5, 131.6, 126.3, 115.6, 105.1, 39.0, 5.7. Spectroscopic data was consistent with the values reported in the literature.14

$$n(EBX)_{eff} = 0.88 * 0.3950 = 0.3476\ mmol$$

$$p_{EBX} = \frac{0.3476}{\frac{105.9}{286.07}} = 0.9390 = 94\%\ purity$$

1-[Cyclopropylethynyl]-1,2-benziodoxol-3-(1*H*)-one (4.36g)



Synthesized following general procedure C, starting from potassium (cyclopropylethynyl)trifluoroborate (**4.53d**) (86.0 mg, 0.500 mmol). 1-[Cyclopropylethynyl]-1,2-benziodoxol-3-(1*H*)-one (**4.36g**) (115.7 mg, 0.3555 mmol, 89%, 96% purity) was obtained as a white solid.

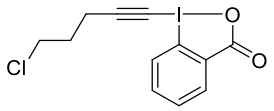
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 – 8.34 (m, 1H, Ar*H*), 8.18 – 8.12 (m, 1H, Ar*H*), 7.79 – 7.68 (m, 2H, Ar*H*), 1.65 – 1.56 (m, 1H, C*H*CH_2), 1.05 – 0.97 (m, 2H, CHCH_2), 0.97 – 0.91 (m, 2H, CHCH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.7, 134.7, 132.4, 131.6, 131.5, 126.2, 115.9, 113.4, 35.1, 9.8, 1.1. Spectroscopic data was consistent with the values reported in the literature.14

$$n(EBX)_{eff} = 0.90 * 0.3950 = 0.3555\ mmol$$

[14] R. Frei, M. D. Wodrich, D. P. Hari, P. A. Borin, C. Chauvier, J. Waser, *J. Am. Chem. Soc.* **2014**, *136*, 16563–16573.
[15] One aromatic carbon signal was not resolved, consistent with literature.

$$p_{EBX} = \frac{0.3555}{\frac{115.7}{312.10}} = 0.9590 = 96\%\ purity$$

1-[5-Chloropent-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (4.36h)



Synthesized following general procedure D, starting from potassium (5-chloropent-1-yn-1-yl)trifluoroborate (**4.53e**) (130 mg, 0.625 mmol). 1-[5-Chloropent-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (**4.36h**) (152.3 mg, 0.4345 mmol, 87%, 99% purity) was obtained as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.0, 2.2 Hz, 1H, Ar*H*), 8.22 – 8.11 (m, 1H, Ar*H*), 7.79 – 7.66 (m, 2H, Ar*H*), 3.70 (t, *J* = 6.1 Hz, 2H, ClC*H*$_2$CH$_2$), 2.81 (t, *J* = 6.9 Hz, 2H, C≡CC*H*$_2$CH$_2$), 2.10 (p, *J* = 6.6 Hz, 2H, CH$_2$C*H*$_2$CH$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.0, 134.8, 132.4, 131.6, 131.5, 126.5, 115.8, 107.0, 43.4, 41.1, 30.7, 17.9. Spectroscopic data was consistent with the values reported in the literature.14

$$n(EBX)_{eff} = 0.88 * 0.4938 = 0.4345\ mmol$$

$$p_{EBX} = \frac{0.4345}{\frac{152.3}{348.56}} = 0.9944 = 99\%\ purity$$

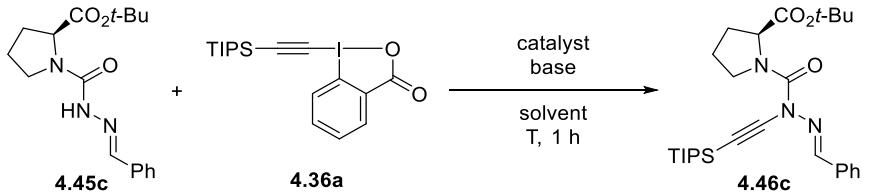
7.3.3. Optimization of the alkynylation of azapeptides

tert-Butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate **4.45c** was chosen as substrate on a 0.05 mmol scale.

General method for the optimization of the reaction

An oven-dried 5 mL microwave vial equipped with a magnetic stirring bar was charged under air with TIPS-EBX (**4.36a**) (21.4 mg, 50.0 µmol, 1.00 equiv.), the corresponding base (75.0 µmol, 1.50 equiv.), *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (**4.45c**) (15.9 mg, 50.0 µmol, 1.00 equiv.) and the corresponding catalyst (2.50 µmol, 5 mol%). The vial was capped and 500 µL of dry solvent was added. The heterogeneous mixture was vigorously stirred at the indicated temperature for 1 hour. After this time, the reaction was cooled down to room temperature, and the mixture was filtered over a pad of Celite® using DCM to rinse (≈ 10 mL) and concentrated under reduced pressure. The crude residue was then purified by preparative thin-layer chromatography (DCM/MeOH 100:1).

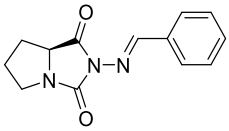
Table S1. Optimization of the azapeptide alkynylation.



entry	base	T	solvent	catalyst	yield
1	*t*-BuOK	rt	CH_3CN	$Cu(CH_3CN)_4BF_4$	20%
2	Cs_2CO_3	rt	CH_3CN	$Cu(CH_3CN)_4BF_4$	16%
3	Cs_2CO_3	40 °C	CH_3CN	$Cu(CH_3CN)_4BF_4$	32%
4	Cs_2CO_3	40 °C	*i*-PrOH	$Cu(CH_3CN)_4BF_4$	48%
5	Cs_2CO_3	40 °C	DCE	$Cu(CH_3CN)_4BF_4$	60%
6	Cs_2CO_3	40 °C	DCE	CuCl	36%
7	Cs_2CO_3	40 °C	DCE	$CuCl_2$	68%
8	Cs_2CO_3	40 °C	DCE	CuI	76%
9[a]	Cs_2CO_3	40 °C	DCE	CuI	72%
10	Na_2CO_3	40 °C	DCE	CuI	8%
11	K_2CO_3	40 °C	DCE	CuI	12%
12	-	40 °C	DCE	CuI	-[b]
13	Cs_2CO_3	40 °C	DCE	-	-[c]
14	**Cs_2CO_3**	**40 °C**	**DCM**	**CuI**	**72%**
15	Cs_2CO_3	40 °C	DCM (not dry)	CuI	48%

[a] TIPS-EBX (1.5 equiv.). [b] No conversion of both starting materials. [c] decomposition of **2a**.

(*S*,*E*)-2-(Benzylideneamino)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (4.47)

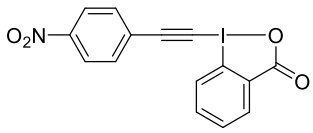


This compound was obtained as the main side product when the reaction was run with **4.46a** or **4.46b**

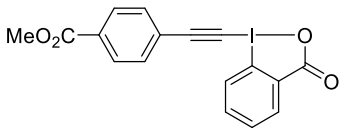
Rf (DCM): 0.40 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.33 (s, 1H, *H*C=N), 7.87 – 7.80 (m, 2H, Ar*H*), 7.51 – 7.38 (m, 3H, Ar*H*), 4.16 (dd, *J* = 9.2, 7.5 Hz, 1H, NC*H*C(O)), 3.77 (dt, *J* = 11.3, 7.8 Hz, 1H, NCH_2), 3.35 (ddd, *J* = 11.3, 8.3, 4.5 Hz, 1H, NCH_2), 2.35 (dtd, *J* = 12.6, 7.2, 3.6 Hz, 1H NCHCH_2), 2.24 – 2.04 (m, 2H, NCH_2CH_2), 1.82 (dtd, *J* = 12.6, 9.4, 8.2 Hz, 1H, NCHCH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.3, 158.6, 157.7, 133.5, 131.9, 128.8, 128.6, 61.6, 45.9, 27.9, 26.7. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}N_3O_2^+$ 244.1081; Found 244.1085.

7.3.4. Scope of the reaction

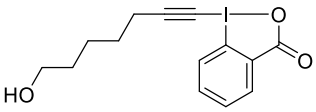
Unsucessful EBX reagents:



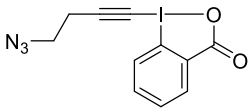
4.36i



4.36j



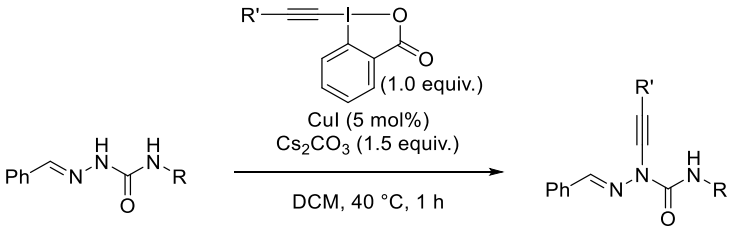
4.36k



4.36l

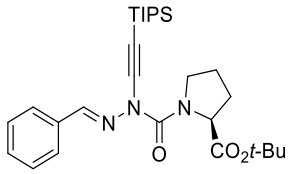
Figure S1. List of unsuccessful EBX reagents tested.

General procedure E for the alkynylation reaction done on 0.3 mmol scale



An oven-dried 5 mL microwave vial equipped with a magnetic stirring bar was charged under air with the corresponding EBX (0.300 mmol, 1.00 equiv.), Cs_2CO_3 (147 mg, 0.450 mmol, 1.50 equiv.), the chosen substrate (0.300 mmol, 1.00 equiv.) and CuI (2.90 mg, 15.0 µmol, 5 mol%). The vial was capped and 3.00 mL of dry DCM was added. The heterogeneous mixture was vigorously stirred at 40 °C for 1 hour. After this time, the reaction was cooled down to room temperature, and the mixture was filtered over a pad of Celite® using DCM to rinse (≈ 50 mL) and concentrated under reduced pressure. The crude residue was then purified by column chromatography on silica gel.

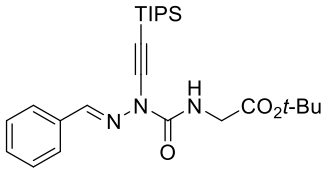
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-prolinate (4.46c)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (**4.45c**) (95.0 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *t*ert-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-prolinate (**4.46c**) (113 mg, 0.227 mmol, 76% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM/MeOH 200:1).

Rf (DCM/MeOH 100:1): 0.45. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.68-7.61 (m, 2H, Ar*H*), 7.48-7.34 (m, 3H, Ar*H*), 5.24-4.39 (br s, 1H, NC*H*), 4.06-3.58 (br s, 2H, NCH_2), 2.47-2.19 (br s, 1H, NCHCH_2), 2.09-1.81 (br s, 3H, NCHCH_2 and NCH_2CH_2), 1.54-1.23 (br s, 9H, *t*-Bu), 1.21-1.04 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.4, 153.6, 144.2, 133.8, 130.2, 128.9, 127.9, 90.0, 84.2, 81.5, 62.2, 50.5, 27.9, 18.9, 11.5. (2 C not resolved)**. HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{28}H_{44}N_3O_3Si^+$ 498.3146; Found 498.3150. **IR** (v_{max}, cm^{-1}) 2960 (m), 2866 (m), 2156 (m), 1740 (s), 1686 (s), 1462 (m), 1404 (s), 1361 (s), 1149 (s), 882 (m), 752 (m). $[\alpha]_D^{25}$ = -66.4 (c = 0.53, $CHCl_3$).

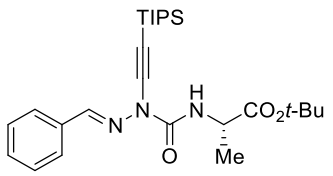
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)glycinate (4.46d)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**4.45d**) (83.2 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *t*ert-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)glycinate (**4.46d**) (117 mg, 0.256 mmol, 85% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).
The reaction was also carried out on 1 mmol scale affording **4.46d** (445 mg, 0.972 mmol, 97% yield).

Rf (DCM): 0.5. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.73-7.64 (m, 2H, Ar*H*), 7.47-7.40 (m, 3H, Ar*H*), 7.09 (t, *J* = 5.2 Hz, 1H, N*H*), 4.08 (d, *J* = 5.3 Hz, 2H, CH_2), 1.50 (s, 9H, *t*-Bu), 1.15 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1, 153.2, 145.0, 133.1, 130.7, 129.0, 127.9, 88.4, 85.1, 82.5, 43.1, 28.2, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{25}H_{39}N_3NaO_3Si^+$ 480.2653; Found 480.2657. **IR** (v_{max}, cm^{-1}) 3407 (w), 2949 (m), 2865 (m), 2152 (m), 1740 (m), 1712 (s), 1513 (s), 1369 (s), 1241 (m), 1167 (s), 1004 (w), 883 (m), 759 (s).

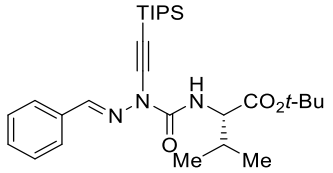
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-alaninate (4.46e)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-alaninate (**4.45e**) (87.4 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-alaninate (**4.46e**) (97.0 mg, 0.206 mmol, 69% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

Rf (DCM): 0.61. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (s, 1H, *H*C=N), 7.73-7.64 (m, 2H, Ar*H*), 7.49-7.38 (m, 3H, Ar*H*), 7.24 (d, *J* = 7.5 Hz, 1H, N*H*CH), 4.52 (p, *J* = 7.2 Hz, 1H, NHC*H*), 1.53-1.46 (m, 12H, CH_3 and *t*-Bu), 1.24-1.09 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.2, 152.5, 144.8, 133.2, 130.7, 129.0, 127.9, 88.6, 85.1, 82.2, 49.9, 28.1, 19.4, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{26}H_{41}N_3NaO_3Si^+$ 494.2809; Found 494.2806. **IR** (ν_{max}, cm^{-1}) 3408 (w), 2949 (m), 2858 (m), 2158 (m), 1719 (s), 1498 (s), 1452 (s), 1347 (m), 1227 (m), 1156 (s), 1109 (m), 947 (m), 871 (s), 735 (s). $[\alpha]_D^{25}$ = +38.9 (c = 0.46, $CHCl_3$).

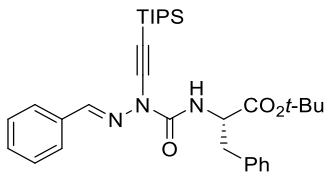
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-valinate (4.46f)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-valinate (**4.45f**) (96.0 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-valinate (**4.46f**) (57.0 mg, 0.114 mmol, 38% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

Rf (DCM): 0.59. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.67 (m, 2H, Ar*H*), 7.49-7.40 (m, 3H, Ar*H*), 7.19 (d, *J* = 8.9 Hz, 1H, N*H*CH), 4.45 (dd, *J* = 9.0, 4.4 Hz, 1H, NHC*H*), 2.26 (pd, *J* = 6.9, 4.5 Hz, 1H, NHCHC*H*), 1.49 (s, 9H, *t*-Bu), 1.15 (m, 21H, TIPS), 0.95 (d, *J* = 6.9 Hz, 3H, CH_3), 0.92 (d, *J* = 6.9 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 153.0, 144.7, 133.2, 130.7, 129.1, 127.8, 88.6, 85.2, 82.2, 58.9, 31.9, 28.2, 19.0, 18.9, 17.9, 11.5. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{28}H_{45}N_3NaO_3Si^+$ 522.3122; Found 522.3123. **IR** (ν_{max}, cm^{-1}) 3405 (w), 2956 (m), 2869 (m), 2152 (m), 1719 (s), 1501 (s), 1369 (s), 1315 (m), 1156 (s), 1116 (s), 910 (m), 878 (s), 737 (s). $[\alpha]_D^{25}$ = +39.7 (c = 0.41, $CHCl_3$).

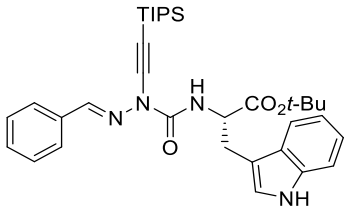
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-phenylalaninate (4.46g)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-phenylalaninate (**4.45g**) (110 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-phenylalaninate (**4.46g**) (121 mg, 0.221 mmol, 74% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

Rf (DCM): 0.55. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (s, 1H, *H*C=N), 7.62-7.53 (m, 2H, Ar*H*), 7.46-7.36 (m, 3H, Ar*H*), 7.33-7.26 (m, 3H, Ar*H*), 7.24-7.20 (m, 2H, Ar*H*), 7.12 (d, *J* = 8.4 Hz, 1H, N*H*CH), 4.81 (ddd, *J* = 8.4, 6.5, 5.1 Hz, 1H, NHC*H*), 3.26 (dd, *J* = 13.8, 5.0 Hz, 1H, NHCHCH_2), 3.13 (dd, *J* = 13.8, 6.5 Hz, 1H, NHCHCH_2), 1.41 (s, 9H, *t*-Bu), 1.16 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5, 152.6, 144.7, 136.2, 133.1, 130.7, 129.8, 129.0, 128.6, 127.8, 127.1, 88.5, 85.2, 82.5, 54.6, 38.8, 28.1, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{32}H_{45}N_3NaO_3Si^+$ 570.3122; Found 570.3138. **IR** (v_{max}, cm^{-1}) 3410 (w), 2956 (m), 2866 (m), 2162 (m), 1737 (s), 1497 (s), 1369 (m), 1156 (s), 1105 (m), 882 (m), 755 (s). $[\alpha]_D^{25}$ = +11.8 (c = 0.53, $CHCl_3$).

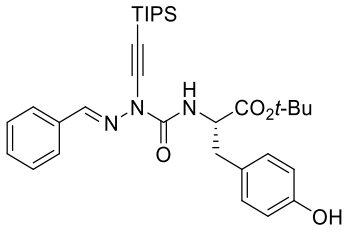
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-tryptophanate (4.46h)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-tryptophanate (**4.45h**) (122 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-tryptophanate (**4.46h**) (140 mg, 0.239 mmol, 80% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

Rf (DCM): 0.41. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (s, 1H, *H*C=N), 8.10 (s, 1H, N*H*), 7.65 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.43-7.29 (m, 6H, Ar*H*), 7.22-7.12 (m, 2H, Ar*H* and N*H*CHCH_2), 7.10-7.00 (m, 2H, Ar*H*), 4.90 (dt, *J* = 8.5, 5.5 Hz, 1H, NHC*H*CH_2), 3.46-3.30 (m, 2H, NHCHCH_2), 1.37 (s, 9H, *t*-Bu), 1.15 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 152.8, 144.7, 136.2, 133.1, 130.5, 128.9, 128.0, 127.9, 122.9, 122.3, 119.9, 119.2, 111.1, 110.5, 88.6, 85.1, 82.2, 54.6, 28.2, 28.1, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{34}H_{46}N_4NaO_3Si^+$ 609.3231; Found 609.3232. **IR** (v_{max}, cm^{-1}) 3385 (w), 2952 (m), 2865 (m), 2156 (m), 1704 (m), 1502 (s), 1367 (m), 1153 (s), 1102 (m), 910 (m), 734 (s). $[\alpha]_D^{25}$ = -33.5 (c = 0.52, $CHCl_3$).

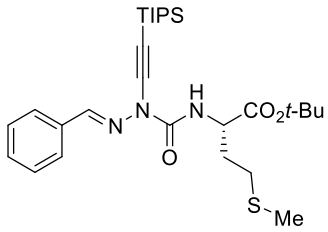
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-tyrosinate (4.46i)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-tyrosinate (**4.45i**) (115 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-tyrosinate (**4.46i**) (50.0 mg, 89.0 µmol, 30% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM to DCM/MeOH 100:1).

Rf (DCM/MeOH 100:1): 0.17. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (s, 1H, *H*C=N), 7.63-7.54 (m, 2H, Ar*H*), 7.47-7.37 (m, 3H, Ar*H*), 7.11 (d, *J* = 8.5 Hz, 1H, N*H*CH), 7.08-7.04 (m, 2H, Ar*H*), 6.79-6.71 (m, 2H, Ar*H*), 5.19 (s, 1H, O*H*), 4.80-4.71 (m, 1H, NHC*H*), 3.16 (dd, *J* = 14.0, 5.1 Hz, 1H, NHCHCH_2), 3.06 (dd, *J* = 14.0, 6.3 Hz, 1H, NHCHCH_2), 1.43 (s, 9H, *t*-Bu), 1.23-1.08 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7, 155.0, 152.7, 144.8, 133.1, 130.9, 130.7, 129.0, 128.0, 127.9, 115.5, 88.4, 85.3, 82.5, 54.7, 37.9, 28.2, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{32}H_{45}N_3NaO_4Si^+$ 586.3072; Found 586.3088. **IR** (ν_{max}, cm^{-1}) 3389 (m), 2941 (m), 2862 (m), 2152 (m), 1704 (m), 1618 (w), 1502 (s), 1369 (m), 1228 (m), 1156 (s), 907 (m), 732 (s). $[\alpha]_D^{25}$ = +3.7 (c = 0.31, $CHCl_3$).

***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-methioninate (4.46j)**

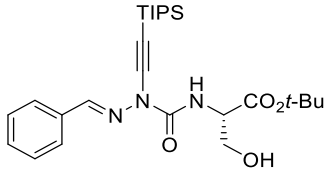


Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-methioninate (**4.45j**) (105 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-methioninate (**4.46j**) (92.0 mg, 0.173 mmol, 58% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

Rf (DCM): 0.62. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.74-7.65 (m, 2H, Ar*H*), 7.49-7.39 (m, 3H, Ar*H*), 7.34 (d, *J* = 8.0 Hz, 1H, N*H*CH), 4.62 (ddd, *J* = 7.9, 7.0, 5.1 Hz, 1H, NHC*H*), 2.67-2.50 (m, 2H, SCH_2), 2.24 (m, 1H, NHCHCH_2), 2.14-2.02 (m, 4H, SCH_3 and NHCHCH_2), 1.50 (s, 9H, *t*-Bu), 1.15 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.9, 152.9, 144.9, 133.1, 130.7, 129.1, 127.9, 88.5, 85.3, 82.7, 53.6, 32.7, 30.0, 28.2, 18.9, 15.7, 11.5. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{28}H_{45}N_3NaO_3SSi^+$ 554.2843; Found

554.2840. **IR** (ν_{max}, cm^{-1}) 3412 (w), 2938 (m), 2862 (m), 2158 (m), 1717 (s), 1502 (s), 1361 (m), 1153 (s), 1109 (m), 912 (m), 875 (m), 734 (s). $[\alpha]_D^{25}$ = +9.9 (c = 0.57, $CHCl_3$).

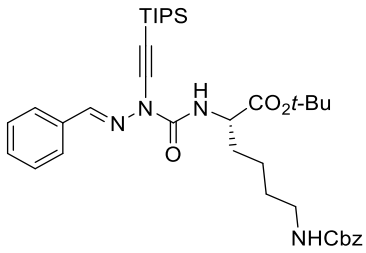
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-serinate (4.46k)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-serinate (**4.45k**) (92.0 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-serinate (**4.46k**) (43.0 mg, 88.0 µmol, 29% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM to DCM/MeOH 100:1).

Rf (DCM/MeOH 50:1): 0.31. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.74-7.65 (m, 2H, Ar*H*), 7.53 (d, *J* = 6.7 Hz, 1H, N*H*CH), 7.48-7.40 (m, 3H, Ar*H*), 4.56 (dt, *J* = 7.1, 3.7 Hz, 1H, NHC*H*), 4.11-3.96 (m, 2H, NHCHCH_2), 2.36 (br s, 1H, O*H*), 1.52 (s, 9H, *t*-Bu), 1.15 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3, 153.5, 145.2, 133.0, 130.8, 129.1, 128.0, 88.2, 85.4, 83.2, 64.3, 56.7, 28.2, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{41}N_3NaO_4Si^+$ 510.2759; Found 510.2750. **IR** (ν_{max}, cm^{-1}) 3444 (w), 2943 (m), 2862 (m), 2158 (m), 1708 (m), 1504 (s), 1347 (m), 1163 (m), 1113 (m), 1073 (m), 909 (s), 871 (m), 732 (s). $[\alpha]_D^{25}$ = +24.3 (c = 0.29, $CHCl_3$).

***tert*-Butyl (*E*)-N^2-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-N^6-((benzyloxy)carbonyl)-*L*-lysinate (4.46l)**

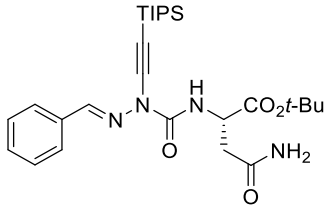


Synthesized from *tert*-butyl (*E*)-N^2-(2-benzylidenehydrazine-1-carbonyl)-N^6-((benzyloxy)carbonyl)-*L*-lysinate (**4.45l**) (145 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-N^2-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-N^6-((benzyloxy)carbonyl)-*L*-lysinate (**4.46l**) (152 mg, 0.229 mmol, 76% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM to DCM/MeOH 100:1).

Rf (DCM): 0.12. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.68 (dq, *J* = 4.8, 3.0 Hz, 2H, Ar*H*), 7.49-7.39 (m, 3H, Ar*H*), 7.39-7.24 (m, 5H, Ar*H*), 7.20 (d, *J* = 8.1 Hz, 1H, N*H*CH), 5.07 (s, 2H, OCH_2Ph), 4.81-4.72 (m, 1H, N*H*Cbz), 4.56-4.47 (m, 1H, NHC*H*), 3.20 (q, *J* = 6.5 Hz, 2H, CH_2NHCbz), 2.00-1.88 (m, 1H, NHCHCH_2), 1.83-1.72 (m, 1H, NHCHCH_2), 1.58-1.40 (m, 13H, CH_2CH$_2$NHCbz, NHCHCH$_2$CH_2 and *t*-Bu), 1.24-1.10 (m, 21H, TIPS). **^{13}C NMR** (101

MHz, $CDCl_3$) δ 171.5, 156.5, 152.8, 144.9, 136.8, 133.1, 130.7, 129.1, 128.6, 128.2, 127.9, 88.5, 85.2, 82.5, 66.7, 53.9, 41.0, 33.0, 29.7, 28.2, 22.5, 18.9, 11.5. One aromatic ^{13}C is not resolved. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{37}H_{54}N_4NaO_5Si^+$ 685.3756; Found 685.3767. **IR** (ν_{max}, cm^{-1}) 3411 (m), 2949 (m), 2862 (m), 2155 (m), 1712 (s), 1495 (s), 1365 (m), 1246 (s), 1159 (s), 910 (m), 875 (m), 734 (s). $[\alpha]_D^{25}$ = +10.1 (c = 0.62, $CHCl_3$).

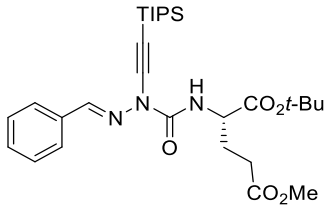
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-asparaginate (4.46m)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-asparaginate (**4.45m**) (100 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-asparaginate (**4.46m**) (84.0 mg, 0.163 mmol, 54% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM/MeOH 100:1 to DCM/MeOH 20:1).

Rf (DCM/MeOH 20:1): 0.27. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (s, 1H, *H*C=N), 7.77 (d, *J* = 7.9 Hz, 1H, N*H*CH), 7.71-7.66 (m, 2H, Ar*H*), 7.45-7.39 (m, 3H, Ar*H*), 5.90 (s, 1H, C(O)NH_2), 5.53 (s, 1H, C(O)NH_2), 4.68 (dt, *J* = 8.0, 4.6 Hz, 1H, NHC*H*), 3.02-2.85 (m, 2H, NHCHCH_2), 1.49 (s, 9H, *t*-Bu), 1.15 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.1, 169.8, 153.4, 145.1, 133.0, 130.7, 129.0, 128.0, 88.4, 85.1, 82.8, 51.0, 37.9, 28.0, 18.8, 11.4. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{27}H_{42}N_4NaO_4Si^+$ 537.2868; Found 537.2865. **IR** (ν_{max}, cm^{-1}) 3425 (m), 3266 (w), 2942 (m), 2866 (m), 2152 (m), 1738 (m), 1700 (s), 1672 (s), 1520 (s), 1358 (m), 1254 (m), 1152 (s), 914 (m), 733 (s). $[\alpha]_D^{25}$ = +14.7 (c = 0.32, $CHCl_3$).

1-(*tert*-Butyl) 5-methyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-glutamate (4.46n)

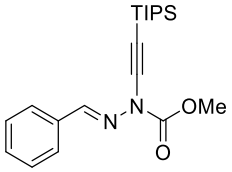


Synthesized from 1-(*tert*-butyl) 5-methyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-glutamate (**4.45n**) (109 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. 1-(*tert*-Butyl) 5-methyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-glutamate (**4.46n**) (92.0 mg, 0.169 mmol, 56% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

Rf (DCM): 0.45. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (s, 1H, *H*C=N), 7.76-7.67 (m, 2H, Ar*H*), 7.44 (m, 3H, Ar*H*), 7.30-7.26 (m, 1H, N*H*CH), 4.54 (td, *J* = 7.9, 5.0 Hz, 1H, NHC*H*), 3.65 (s, 3H, OCH_3), 2.56-2.37 (m, 2H, CH_2CO$_2$Me), 2.34-2.24 (m, 1H, NHCHCH_2), 2.10 (m, 1H,

NHCHC*H*$_2$), 1.49 (s, 9H, *t*-Bu), 1.15 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.5, 170.9, 153.0, 145.0, 133.1, 130.7, 129.0, 128.0, 88.4, 85.2, 82.7, 53.6, 51.9, 30.3, 28.2 (X2), 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{29}H_{45}N_3NaO_5Si^+$ 566.3021; Found 566.3030. **IR** (v_{max}, cm^{-1}) 3403 (w), 2944 (m), 2866 (m), 2152 (m), 1722 (s), 1502 (s), 1369 (m), 1153 (s), 1109 (m), 1011 (m), 882 (m), 733 (s). $[\alpha]_D^{25}$ = +9.2 (c = 0.49, $CHCl_3$).

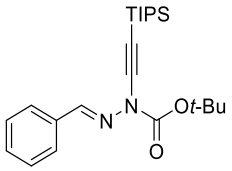
Methyl (*E*)-2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carboxylate (4.49a)



Synthesized from methyl (*E*)-2-benzylidenehydrazine-1-carboxylate (**4.48a**) (53.5 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. Methyl (*E*)-2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carboxylate (**4.49a**) (65.0 mg, 0.181 mmol, 60% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

Rf (DCM): 0.67. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (s, 1H, *H*C=N), 7.79-7.70 (m, 2H, Ar*H*), 7.47-7.38 (m, 3H, Ar*H*), 3.97 (s, 3H, C*H*$_3$), 1.25-1.09 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5, 147.3, 133.2, 130.8, 128.9, 128.2, 88.3, 85.1, 54.8, 18.8, 11.4. **HRMS (ESI/QTOF)** m/z: [M + H]$^+$ Calcd for $C_{20}H_{31}N_2O_2Si^+$ 359.2149; Found 359.2149. **IR** (v_{max}, cm^{-1}) 2941 (s), 2862 (m), 2162 (m), 1767 (s), 1747 (s), 1441 (s), 1386 (m), 1325 (s), 1282 (s), 1228 (s), 952 (m), 882 (m), 755 (s).

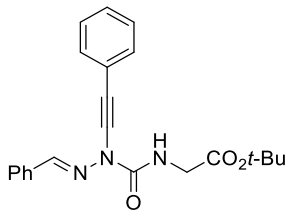
***tert*-Butyl (*E*)-2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carboxylate (4.49b)**



Synthesized from *tert*-Butyl (*E*)-2-benzylidenehydrazine-1-carboxylate (**4.48b**) (66.0 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**4.36a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carboxylate (**4.49b**) (30.0 mg, 75.0 µmol, 25% yield) was obtained as a yellowish oil after purification by column chromatography on silica (Pentane/DCM 10:1).

Rf (Pentane/DCM 10:1): 0.15. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (s, 1H, *H*C=N), 7.78-7.70 (m, 2H, Ar*H*), 7.46-7.36 (m, 3H, Ar*H*), 1.59 (s, 9H, *t*-Bu), 1.23-1.08 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.1, 146.7, 133.5, 130.5, 128.8, 128.1, 88.9, 84.8, 84.1, 28.2, 18.8, 11.5. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{23}H_{36}N_2NaO_2Si^+$ 423.2438; Found 423.2434. **IR** (v_{max}, cm^{-1}) 2941 (m), 2869 (m), 2162 (m), 1763 (s), 1737 (m), 1462 (m), 1370 (m), 1282 (m), 1235 (s), 1152 (s), 852 (m), 755 (m).

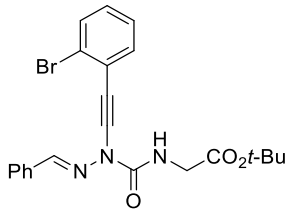
***tert*-Butyl (*E*)-(2-benzylidene-1-(phenylethynyl)hydrazine-1-carbonyl)glycinate (4.54a)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**4.45d**) (83.2 mg, 0.300 mmol, 1.00 equiv.) and Ph-EBX (**4.36b**) (104 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *t*ert-Butyl (*E*)-(2-benzylidene-1-(phenylethynyl)hydrazine-1-carbonyl)glycinate (**4.54a**) (104 mg, 0.276 mmol, 92% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

Rf (DCM): 0.57. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (s, 1H, *H*C=N), 7.78-7.69 (m, 2H, Ar*H*), 7.60-7.51 (m, 2H, Ar*H*), 7.45-7.41 (m, 3H, Ar*H*), 7.38-7.34 (m, 3H, Ar*H*), 7.18 (t, *J* = 5.1 Hz, 1H, N*H*CH_2), 4.11 (d, *J* = 5.3 Hz, 2H, NHCH_2), 1.52 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0, 153.3, 144.5, 133.0, 131.9, 130.7, 129.0, 128.7, 128.5, 128.0, 122.3, 85.3, 82.6, 75.1, 43.2, 28.2. **HRMS (ESI/QTOF)** m/z: [M + H]$^+$ Calcd for $C_{22}H_{24}N_3O_3^+$ 378.1812; Found 378.1819. **IR** (v_{max}, cm^{-1}) 3419 (w), 2979 (w), 2931 (w), 2224 (w), 1712 (s), 1508 (s), 1365 (m), 1216 (m), 1152 (s), 1113 (m), 945 (w), 846 (w), 753 (s).

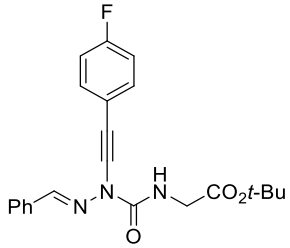
***tert*-Butyl (*E*)-(2-benzylidene-1-((2-bromophenyl)ethynyl)hydrazine-1-carbonyl)glycinate (4.54b)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**4.45d**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[(2-bromophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (**4.36c**) (128 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((2-bromophenyl)ethynyl)hydrazine-1-carbonyl)glycinate (**4.54b**) (84.4 mg, 0.185 mmol, 62%) was obtained as a yellow amorphous solid after purification by column chromatography on silica (Pentane/EtOAc, 95:5 to 85:15).

Rf (Pentane/EtOAc, 85:15): 0.27. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 (s, 1H, *H*C=N), 7.78 – 7.72 (m, 2H, Ar*H*), 7.65-7.56 (m, 2H, Ar*H*), 7.48 – 7.41 (m, 3H, Ar*H*), 7.31 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.23 – 7.14 (m, 2H, Ar*H* + N*H*), 4.11 (d, *J* = 5.3 Hz, 2H, NHCH_2), 1.52 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9, 153.1, 145.5, 133.1, 132.8, 132.5, 130.8, 129.2, 129.0, 128.1, 127.3, 125.0, 124.2, 84.2, 82.6, 79.8, 43.2, 28.2. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{22}H_{22}BrN_3NaO_3^+$ 478.0737; Found 478.0741. **IR** (v_{max}, cm^{-1}) 3405 (w), 2979 (w), 2226 (m), 1712 (s), 1503 (s), 1366 (m), 1216 (m), 1148 (s), 1112 (s), 1024 (m), 949 (m), 845 (m).

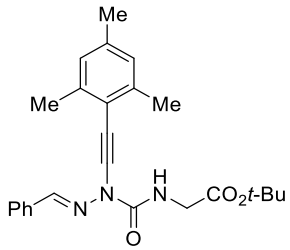
***tert*-Butyl (*E*)-(2-benzylidene-1-((4-fluorophenyl)ethynyl)hydrazine-1-carbonyl)glycinate (4.54c)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**4.45d**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[(4-fluorophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (**4.36d**) (113 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((4-fluorophenyl)ethynyl)hydrazine-1-carbonyl)glycinate (**4.54c**) (68.4 mg, 0.173 mmol, 58%) was obtained as a yellow oil after purification by column chromatography on silica (Pentane/EtOAc, 95:5 to 85:15).

Rf (Pentane/EtOAc, 85:15): 0.35. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (s, 1H, *H*C=N), 7.77 – 7.69 (m, 2H, Ar*H*), 7.56 – 7.49 (m, 2H, Ar*H*), 7.47 – 7.39 (m, 3H, Ar*H*), 7.18 (t, *J* = 5.3 Hz, 1H, N*H*), 7.10 – 7.01 (m, 2H, Ar*H*), 4.10 (d, *J* = 5.3 Hz, 2H, NHCH_2), 1.51 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0, 162.9 (d, *J* = 250.1 Hz), 153.3, 144.5, 134.1 (d, *J* = 8.5 Hz), 132.9, 130.7, 129.0, 127.9, 118.3 (d, *J* = 3.6 Hz), 115.8 (d, *J* = 22.1 Hz), 84.1, 82.5, 74.7, 43.2, 28.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.4. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}FN_3O_3^+$ 396.1718; Found 396.1712. **IR** (v_{max}, cm^{-1}) 3406 (w), 2980 (w), 2228 (w), 1711 (s), 1504 (s), 1366 (m), 1216 (s), 1113 (s), 836 (s), 755 (m).

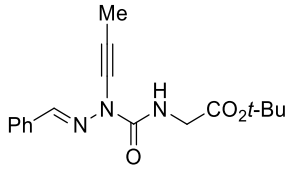
***tert*-Butyl (*E*)-(2-benzylidene-1-(mesitylethynyl)hydrazine-1-carbonyl)glycinate (4.54d)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**4.45d**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[mesitylethynyl]-1,2-benziodoxol-3-(1*H*)-one (**4.36e**) (118 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-(mesitylethynyl)hydrazine-1-carbonyl)glycinate (**4.54d**) (104 mg, 0.249 mmol, 83%) was obtained as a yellow solid after purification by column chromatography on silica (DCM).

Rf (Pentane/EtOAc, 85:15): 0.46. **Mp**: 148 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (s, 1H, *H*C=N), 7.76 – 7.68 (m, 2H, Ar*H*), 7.48 – 7.41 (m, 3H, Ar*H*), 7.22 (t, *J* = 5.3 Hz, 1H, N*H*), 6.92 (s, 2H, Ar*H*), 4.13 (d, *J* = 5.3 Hz, 2H, NHCH_2), 2.50 (s, 6H, ArCH_3), 2.31 (s, 3H, ArCH_3), 1.53 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0, 153.3, 144.1, 139.5, 137.8, 133.0, 130.5, 128.9, 127.8, 127.7, 119.2, 82.9, 82.4, 82.3, 43.1, 28.1, 21.4, 21.3. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{25}H_{29}N_3NaO_3^+$ 442.2101; Found 442.2091. **IR** (v_{max}, cm^{-1}) 3421 (m), 2979 (m), 2920 (m), 2236 (w), 2224 (w), 1714 (s), 1502 (s), 1366 (s), 1213 (m), 1152 (s), 1113 (s), 942 (m), 852 (m), 752 (s)

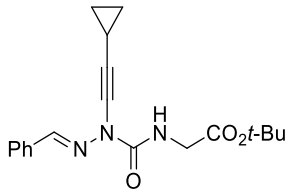
***tert*-Butyl (*E*)-(2-benzylidene-1-(prop-1-yn-1-yl)hydrazine-1-carbonyl)glycinate (4.54e)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**4.45d**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[Prop-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (**4.36f**) (91.3 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-(prop-1-yn-1-yl)hydrazine-1-carbonyl)glycinate (**4.54e**) (38.1 mg, 0.121 mmol, 40%) was obtained as a colorless oil after purification by column chromatography on silica (Pentane/EtOAc, 85:15 to 80:20) followed by preparative TLC (DCM/MeOH, 98:2).

Rf (Pentane/EtOAc, 75:25): 0.33. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (s, 1H, *H*C=N), 7.74 – 7.67 (m, 2H, Ar*H*), 7.45 – 7.38 (m, 3H, Ar*H*), 7.07 (t, *J* = 5.3 Hz, 1H, N*H*), 4.06 (d, *J* = 5.3 Hz, 2H, NHCH_2), 2.19 (s, 3H, CH_3), 1.50 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1, 153.9, 143.4, 133.2, 130.4, 128.9, 127.8, 82.4, 81.1, 65.5, 43.2, 28.2, 4.1. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}N_3O_3^+$ 316.1656; Found 316.1647. **IR** (ν_{max}, cm^{-1}) 3409 (w), 2979 (m), 2248 (w), 1740 (m), 1707 (s), 1509 (s), 1393 (m), 1367 (m), 1226 (m), 1152 (s), 849 (m), 753 (s), 730 (m).

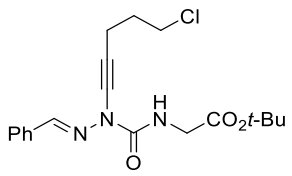
***tert*-Butyl (*E*)-(2-benzylidene-1-(cyclopropylethynyl)hydrazine-1-carbonyl)glycinate (4.54f)**



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**4.45d**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[cyclopropylethynyl]-1,2-benziodoxol-3-(1*H*)-one (**4.36g**) (97.5 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-(cyclopropylethynyl)hydrazine-1-carbonyl)glycinate (**4.54f**) (71.0 mg, 0.208 mmol, 69%) was obtained as a yellow oil after purification by column chromatography on silica (Pentane/EtOAc, 95:5 to 80:20).

Rf (Pentane/EtOAc, 75:25): 0.5. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (s, 1H, *H*C=N), 7.74 – 7.66 (m, 2H, Ar*H*), 7.46 – 7.38 (m, 3H, Ar*H*), 7.07 (t, *J* = 5.3 Hz, 1H, N*H*), 4.05 (d, *J* = 5.3 Hz, 2H, NHCH_2), 1.61 – 1.53 (m, 1H, C*H*CH_2), 1.49 (s, 9H, *t*-Bu), 0.97 – 0.90 (m, 2H, CHCH_2), 0.89 – 0.82 (m, 2H, CHCH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1, 153.9, 143.5, 133.2, 130.4, 128.9, 127.8, 90.0, 82.4, 61.7, 43.2, 28.2, 9.5, -0.2. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{19}H_{24}N_3O_3^+$ 342.1812; Found 342.1807. **IR** (ν_{max}, cm^{-1}) 3408 (w), 2980 (m), 2246 (w), 1743 (m), 1707 (s), 1506 (s), 1367 (s), 1227 (m), 1152 (s), 1110 (m), 945 (m), 849 (m), 757 (m).

***tert*-Butyl (E)-(2-benzylidene-1-(5-chloropent-1-yn-1-yl)hydrazine-1-carbonyl)glycinate (4.54g)**

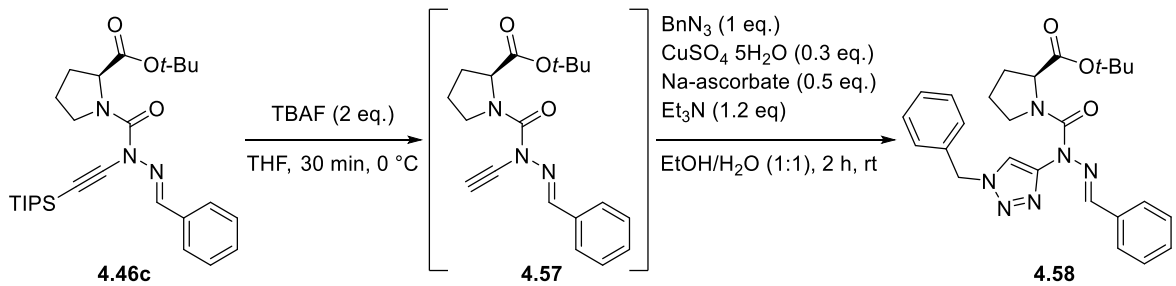


Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**4.45d**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[5-Chloropent-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (**4.36h**) (106 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-(5-chloropent-1-yn-1-yl)hydrazine-1-carbonyl)glycinate (**4.54g**) (60.2 mg, 159 µmol, 53% yield) was obtained as a colorless oil after purification by column chromatography on silica (Pentane/EtOAc, 85:15 to 80:20) followed by preparative TLC (DCM/MeOH, 98:2).

Rf (Pentane/EtOAc, 85:15): 0.27. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (s, 1H, *H*C=N), 7.74 – 7.68 (m, 2H, Ar*H*), 7.46 – 7.39 (m, 3H, Ar*H*), 7.09 (t, *J* = 5.3 Hz, 1H, N*H*), 4.06 (d, *J* = 5.3 Hz, 2H, NHCH_2), 3.74 (t, *J* = 6.2 Hz, 2H, ClCH_2CH$_2$), 2.78 (t, *J* = 6.7 Hz, 2H, C≡CCH_2CH$_2$), 2.08 (p, *J* = 6.6 Hz, 2H,CH$_2$CH_2CH$_2$), 1.50 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0, 153.7, 143.8, 133.1, 130.6, 129.0, 127.9, 83.5, 82.5, 67.5, 43.8, 43.2, 31.3, 28.2, 16.6. **HRMS (ESI/QTOF)** m/z: [M + H]$^+$ Calcd for $C_{19}H_{25}ClN_3O_3^+$ 378.1579; Found 378.1578. **IR** (ν_{max}, cm^{-1}) 3404 (w), 2979 (w), 2251 (w), 1743 (m), 1708 (s), 1514 (s), 1367 (m), 1227 (m), 1153 (s), 852 (w), 754 (m).

7.3.5. Post-functionalizations

Huisgen [3+2]-cycloadditions



To a 0°C cooled solution of *tert*-butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl) ethynyl)hydrazine-1-carbonyl)-*L*-prolinate (**4.46c**) (199 mg, 0.400 mmol, 1.00 equiv) in THF (4.00 mL) was added TBAF (1 M in THF, 800 µL, 0.800 mmol, 2.00 equiv) dropwise, and the reaction was stirred for 30 min. The solution was warmed to ambient temperature, poured into H_2O (20 mL), and extracted with EtOAc (3 x 30 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was pure enough to be used in the next step without further purification.[16]

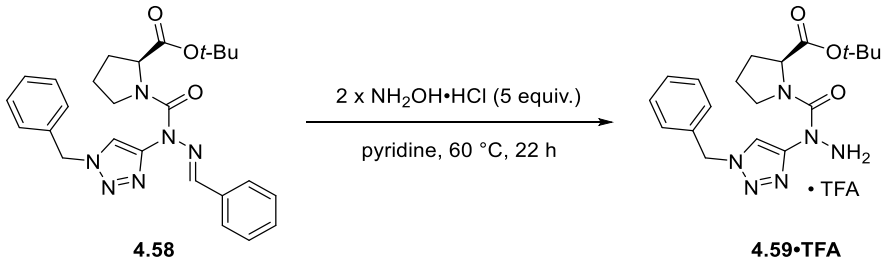
Following a reported procedure,[17] to a solution of *tert*-butyl (*E*)-(2-benzylidene-1-ethynylhydrazine-1-carbonyl)-*L*-prolinate (**4.57**) (137 mg, 0.400 mmol, 1.00 equiv), benzyl

[16] ^{1}H NMR of the crude mixture showed full conversion of the starting material. The desired deprotected compound was not isolated as initial attempts led to decomposition of the product overtime.
[17] Tuck, J. R.; Tombari, R. J.; Yardeny, N.; Olson, D. E. *Org. Lett.* **2021**, *23* (11), 4305–4310.

azide (50.0 µL, 0.400 mmol, 1.00 equiv), triethylamine (67.0 µL, 0.480 mmol, 1.20 equiv) in EtOH (0.48 mL) and H_2O (0.48 mL), $CuSO_4 \cdot 5H_2O$ (30.0 mg, 0.120 mmol, 0.300 equiv) and sodium *L*-ascorbate (40.0 mg, 0.200 mmol, 0.500 equiv) were added. The mixture was allowed to stir at rt for 2 h under N_2 and concentrated. Then the mixture was diluted with water and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated at reduced pressure. *tert*-Butyl (*E*)-(1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (**4.58**) (145 mg, 0.306 mmol, 76% yield) was isolated as a brownish amorphous solid after purification by column chromatography on silica (DCM/MeOH 100:1).

Rf (Pentane/DCM 50:1): 0.19. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (s, 1H, *H*C=C), 7.61-7.48 (m, 3H, *H*C=N and Ar*H*), 7.44-7.28 (m, 8H, Ar*H*), 5.56 (s, 2H, CH_2Ph), 5.29-4.26 (br s, 1H, NC*H*CO_2*t*-Bu), 4.15-3.52 (br s, 2H, NCH_2), 2.46-2.18 (br s, 1H, $NCH_2CH_2CH_2$), 2.07-1.79 (br s, 3H, $NCH_2CH_2CH_2$ and $NCH_2CH_2CH_2$), 1.52-1.19 (br s, 9H, *t*-Bu).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.9, 141.6, 141.4, 134.6, 134.2, 129.6, 129.4, 129.1, 128.7, 128.4, 127.4, 122.0, 81.2, 62.2, 55.1, 50.6, 28.0 (3 C were not fully resolved). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{30}N_6NaO_3^+$ 497.2272; Found 497.2277. **IR** (v_{max}, cm^{-1}) 3147 (w), 2978 (m), 2916 (w), 1737 (m), 1654 (s), 1603 (w), 1415 (s), 1358 (m), 1227 (m), 1152 (s), 911 (s), 730 (s). $[\alpha]_D^{25}$ = -61.1 (c = 0.50, $CHCl_3$).

Hydrazone deprotection



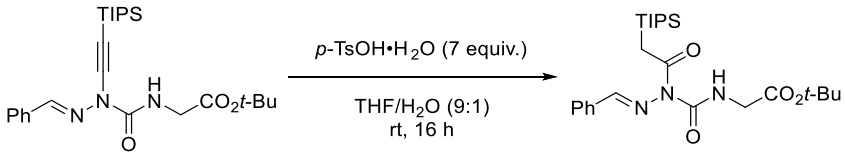
A capped oven dried microwave vial charged with *tert*-Butyl (*E*)-(1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (**4.58**) (47.5 mg, 0.100 mmol, 1.0 equiv.) was evacuated and backfilled with N_2 (3x). Then, a pre-stirred solution of $NH_2OH \cdot HCl$ (34.7 mg, 0.500 mmol, 5.0 equiv.) in dry pyridine (0.3 mL) was added under N_2. The reaction was stirred at 60 °C for 6 h, then, a freshly prepared solution of $NH_2OH \cdot HCl$ (34.7 mg, 0.500 mmol, 5.0 equiv.) in dry pyridine (0.3 mL) was added under N_2. The reaction was further stirred at 60 °C for 16 h. The volatiles were evaporated *in vacuo* and the crude oil was co-evaporated with ethyl acetate to help removing pyridine. The crude compound was purified by preparative RP-HPLC (t_R: 11.5 min) to afford *tert*-butyl (1-(1-benzyl-1H-1,2,3-triazol-4-yl)hydrazine-1-carbonyl)-*L*-prolinate trifluoroacetic acid salt (**4.59·TFA**) (16.0 mg, 32.0 µmol, 32%) as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H, *H*C=C), 7.39 – 7.32 (m, 3H, Ar*H*), 7.31 – 7.26 (m, 2H, Ar*H*), 5.46 (s, 2H, CH_2Ph), 5.16 (s, 3H, NH_3^+), 4.63 – 4.55 (m, 1H, NC*H*CO_2*t*-Bu), 3.62 (t, *J* = 6.7 Hz, 2H, NCH_2), 2.23 – 2.12 (m, 1H, $NCH_2CH_2CH_2$), 2.00 – 1.78 (m, 3H, $NCH_2CH_2CH_2$), 1.43 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$)[18] δ 172.7, 159.5 (q, *J* = 41.1 Hz), 156.5, 149.5, 134.3, 129.2, 129.0, 128.3, 114.2, 81.3, 62.2, 55.1, 49.8, 30.8, 28.1, 23.5. **HRMS (ESI/QTOF)**

[18] The CF_3 carbon from the TFA was not resolved.

m/z: [M + Na]$^+$ Calcd for $C_{19}H_{26}N_6NaO_3^+$ 409.1959; Found 409.1952. **IR** (ν_{max}, cm^{-1}) 2984 (w), 1737 (m), 1644 (m), 1416 (s), 1368 (s), 1202 (s), 1155 (s), 982 (m), 763 (m). $[\alpha]_D^{25}$ = -24.9 (c = 0.53, $CHCl_3$).

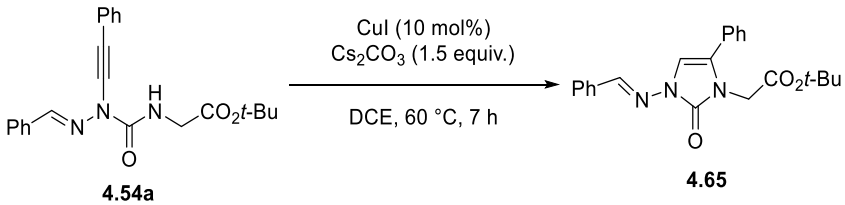
Hydration



To a microwave vial containing a solution of *tert*-butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-glycinate (**4.46d**) (46 mg, 0.050 mmol, 1.0 equiv.) in a mixture of THF (1.8 mL) and H_2O (0.2 mL) was added *p*TsOH•H_2O (0.13 g, 0.35 mmol, 7.0 equiv.). The reaction was stirred at rt open to air for 16 h. The mixture was diluted with DCM (5 mL) and quenched with the addition of a 1 M aq. Sol. Of NaOH (10 mL). The mixture was extracted with 3 x 10 mL of DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by preparative TLC (DCM) to afford *tert*-butyl (*E*)-(2-benzylidene-1-(2-(triisopropylsilyl)acetyl)hydrazine-1-carbonyl)glycinate (**4.63**) (20 mg, 0.042 mmol, 42%) as a colorless oil.

Rf (DCM): 0.62. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.35 (t, *J* = 5.4 Hz, 1H, N*H*), 8.50 (s, 1H, *H*C=N), 7.79 – 7.74 (m, 2H, Ar*H*), 7.50 – 7.39 (m, 3H, Ar*H*), 4.00 (d, *J* = 5.3 Hz, 2H, NHCH_2), 2.55 (s, 2H, C(O)CH_2TIPS), 1.48 (s, 9H, *t*-Bu), 1.22 – 1.02 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.8, 168.6, 162.9, 153.1, 133.5, 131.6, 128.8, 128.5, 82.2, 43.3, 28.2, 21.1, 18.5, 11.6. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{25}H_{41}N_3NaO_4Si^+$ 498.2759; Found 498.2763. **IR** (ν_{max}, cm^{-1}) 3274 (w), 2943 (m), 2867 (m), 2254 (w), 1745 (m), 1708 (s), 1657 (m), 1512 (m), 1367 (s), 1224 (s), 1154 (s), 883 (m), 769 (m), 755 (m).

5-*endo-dig* Cyclization



A capped oven dried microwave vial charged with *tert*-Butyl (*E*)-(2-benzylidene-1-(phenylethynyl)hydrazine-1-carbonyl)glycinate (**4.54a**) (18.8 mg, 50.0 µmol, 1.0 equiv.), CuI (1.0 mg, 5.0 µmol, 0.1 equiv.) and Cs_2CO_3 (24.4 mg, 75.0 µmol, 1.5 equiv.) was evacuated and backfilled with N_2 (3x). Then, dry DCE (0.5 mL) was added and the reaction was stirred at 60 °C for 6 h. The mixture was filtered over a pad of Celite® using DCM to rinse (≈ 10 mL). The solution was concentrated in vacuo and the crude oil was purified by preparative TLC (Pentane/EtOAc, 85:15) to afford *tert*-butyl (*E*)-2-(3-(benzylideneamino)-2-oxo-5-phenyl-2,3-dihydro-1H-imidazol-1-yl)acetate (**4.65**) (11.8 mg, 31.3 µmol, 63%) as a yellow oil.

Rf (DCM): 0.59. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77 (s, 1H, *H*C=N), 7.81 – 7.72 (m, 2H, Ar*H*), 7.49 – 7.44 (m, 2H, Ar*H*), 7.43 – 7.35 (m, 5H, Ar*H*), 7.33 (s, 1H, *H*C=C), 7.31 – 7.27 (m, 1H,

Ar*H*), 4.26 (s, 2H, NC*H*$_2$), 1.52 (s, 9H, *t*-Bu). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.6, 150.1, 148.8, 138.6, 134.7, 130.3, 128.9, 128.7, 128.2, 127.6, 127.3, 123.0, 111.7, 81.1, 49.6, 28.3. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}N_3O_3^+$ 378.1812; Found 378.1813. **IR** (ν_{max}, cm^{-1}) 2978 (w), 2256 (w), 1743 (s), 1693 (s), 1651 (m), 1450 (m), 1405 (m), 1368 (m), 1218 (m), 1153 (s), 1022 (m), 912 (m), 754 (m).

7.3.6. Crystal structure of *tert*-butyl (*E*)-(2-benzylidene-1-(mesitylethynylhydrazine-1-carbonyl)glycinate

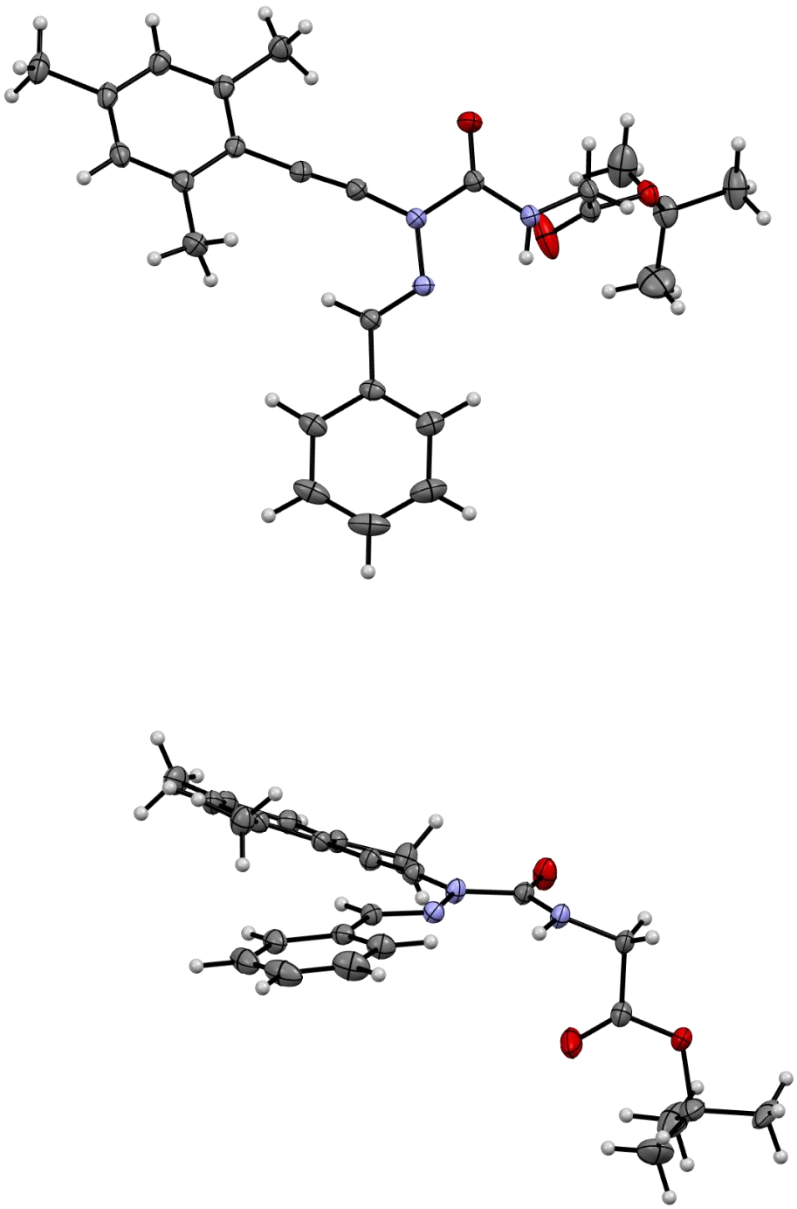


Figure S1: Ellipsoid plot (probability level 50%) of **4.54d**

Compound	**4.54d**
Formula	$C_{25}H_{29}N_3O_3$
$D_{calc.}$/ g cm^{-3}	1.214
μ/mm^{-1}	0.080
Formula Weight	419.51
Color	clear pale colorless
Shape	prism-shaped
Size/mm^3	0.95×0.28×0.21
T/K	140.00(10)
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	9.8053(3)
b/Å	25.9739(6)
c/Å	9.6703(4)
α/°	90
β/°	111.234(4)
γ/°	90
V/Å^3	2295.64(14)
Z	4
Z'	1
Wavelength/Å	0.71073
Radiation type	Mo K$_\alpha$
Θ_{min}/°	2.751
Θ_{max}/°	32.745
Measured Refl's.	35274
Indep't Refl's	7912
Refl's I≥2 σ(I)	6089
R_{int}	0.0271
Parameters	384
Restraints	255
Largest Peak	0.300
Deepest Hole	-0.233
GooF	1.034
wR_2 (all data)	0.1235
wR_2	0.1126
R_1 (all data)	0.0648
R_1	0.0458

Crystals were grown by preparing a solution of **4.54d** in Et_2O, adding hexane and leaving the solution slowly evaporate over 3-4 days.

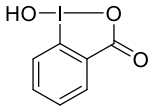
Analysis of the crystal: A suitable crystal with dimensions 0.95 × 0.28 × 0.21 mm^3 was selected and mounted on a SuperNova, Dual, Cu at home/near, AtlasS2 diffractometer. The crystal was kept at a steady T = 140.00(10) K during data collection. The structure was solved with the **ShelXT** 2018/2 (Sheldrick, 2018) solution program using dual methods and by using **Olex2** 1.5 (Dolomanov et al., 2009) as the graphical interface. The model was refined with **ShelXL** 2018/3 (Sheldrick, 2015) using full matrix least squares minimization on F^2.

Supplementary crystallographic data for this compound have been deposited at Cambridge Crystallographic Data Centre (CCDC 2193047) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif

7.4. C-Terminal Oxidative Decarboxylative Arylation of Small Peptides

7.4.1. Preparation of Reagents and Catalysts

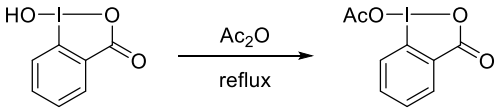
1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (5.43)



5.43

See procedure for compound **4.50**.

1-Acetoxy-1,2-benziodoxol-3-(1H)-one (AcO-BX, 5.21)

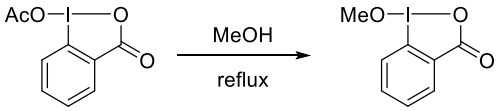


5.43 **5.21**

Following a reported procedure,[1] 1-hydroxy-1,2-benziodoxol-3-(1H)-one (**5.43**, 10.3 g, 39.1 mmol, 1.00 equiv) was suspended in acetic anhydride (35 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 20 mL) and dried in vacuo affording **5.21** (10.8 g, 35.3 mmol, 90%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (dd, 1H, *J* = 7.6, 1.6 Hz, Ar*H*), 8.00 (dd, 1H, *J* = 8.3, 1.0 Hz, Ar*H*), 7.92 (ddd, 1H, *J* = 8.4, 7.2, 1.6 Hz, Ar*H*), 7.71 (td, 1H, *J* = 7.3, 1.1 Hz, Ar*H*), 2.25 (s, 3H, COCH_3). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 176.5, 168.2, 136.2, 133.3, 131.4, 129.4, 129.1, 118.4, 20.4. The values of the NMR spectra are in accordance with reported literature data.[1]

1-Metoxy-1,2-benziodoxol-3-(1H)-one (MeO-BX, 5.22)



5.21 **5.22**

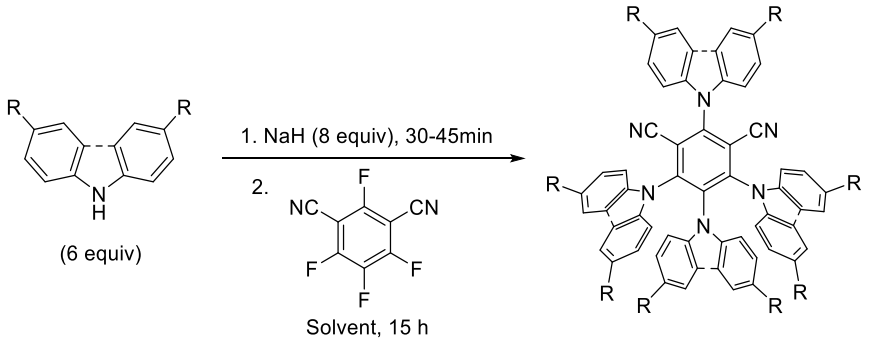
Following a reported procedure,[2] AcO-BX (**5.21**, 1.0 g, 3.3 mmol, 1.0 equiv) was refluxed in MeOH (10 mL) for 15 min until a clear, colorless solution was obtained. The mixture was cooled to room temperature and then to -20°C. The precipitate was filtered, washed with a

[1] J. P. Brand, C. Chevalley, R. Scopelliti, J. Waser, *Chem. Eur. J.* **2012**, *18*, 5655–5666.
[2] J. Hu, T. Lan, Y. Sun, H. Chen, J. Yao, Y. Rao, *Chem. Commun.* **2015**, *51*, 14929–14932.

minimal amount of MeOH, and dried under vacuum. **5.22** (0.69 g, 2.5 mmol, 76%) was obtained as white crystals.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar*H*), 7.90 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H, Ar*H*), 7.76 (dd, *J* = 8.3, 1.0 Hz, 1H, Ar*H*), 7.69 (td, *J* = 7.4, 1.0 Hz, 1H, Ar*H*), 4.27 (s, 3H, O*Me*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 168.1, 135.2, 133.0, 131.1, 130.7, 126.0, 118.6, 62.4. The values of the NMR spectra are in accordance with reported literature data.[2]

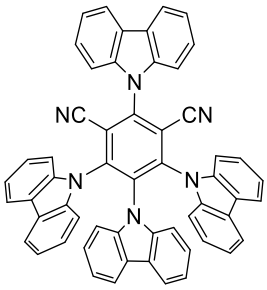
Preparation of catalysts



General procedure A:

Sodium hydride (60% suspension in mineral oil, 8.0 equiv) was added slowly to a stirred solution of substituted-carbazole (5.0 equiv) in dry THF (0.05 M) under a nitrogen atmosphere at RT. After 30 min, 2,4,5,6-tetrafluoroisophthalonitrile (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 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 DCM/Hexane.

2,4,5,6-Tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN, 5.46)



Following the general procedure A and starting from 9H-carbazole **5.44** (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 **5.45** (0.40 g, 2.0 mmol) in 40 mL of THF. Recrystallization (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 (**5.46**) as a bright yellow crystalline solid (1.14 g, 1.45 mmol, 73 % yield).

Rf (Hexane/DCM 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. The values of the NMR spectra are in accordance with reported literature data.[3]

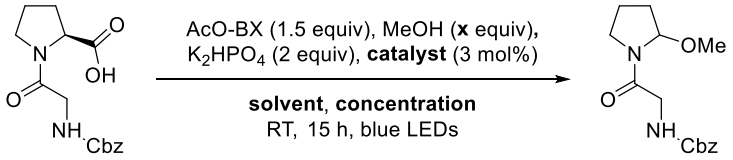
7.4.2. Peptide Synthesis

The used dipeptides were commercially available. All peptide tetramers were synthesized by solid phase peptide synthesis using a 2-chlorotrityl chloride resin (1.0-1.6 mmol/g, 100-200 mesh). The first amino acid was loaded on the resin by incubation of the Fmoc-protected monomer (3 equiv of the number of active sites on the resin), DIPEA (4 equiv) in dichloromethane for 2 h. A cycle consisted first of the deprotection, achieved by stirring for 20 min with a 20% solution of piperidine in DMF, twice. Then the resin was washed with DMF (7x). Double couplings were performed by adding the Fmoc-protected monomer (4 equiv), HBTU (4 equiv), HOBt (4 equiv), NMM (4 equiv) and stirring for 45 min. Capping was carried out at the end of each cycle, followed by a DMF wash (7x). Acetylation of the N-terminal was achieved by incubating the resin with an Acetic Anhydride/DIPEA/DMF 10/15/75 solution for 30 min, twice. Cleavage of peptides with no protecting groups on the side-chains was performed by stirring the resin in a 20% solution of HFIP in dichloromethane for 30 min. In the presence of protecting groups, a TFA/water/triisopropylsilane 95/2.5/2.5 was used instead and the stirring time increased to 2 h. The cleavage mixture was poured into cold diethyl ether and precipitated peptides were recovered. The crude peptides were purified by preparative RP-HPLC using a gradient water-95% acetonitrile in 20 min. Pure peptides were analyzed by RP-HPLC and HRMS.

[3] H. Uoyama, K. Goushi, K. Shizu, H. Nomura, C. Adachi, *Nature* **2012**, *492*, 234–238.

7.4.3. Optimization

Optimization of the oxidative decarboxylation



Degassed solvent was added in a 10 mL test tube containing a Teflon coated stirring bar, Z-Gly-Pro (**5.17a**) (31 mg, 0.10 mmol, 1.0 equiv), AcO-BX (**5.21**) (0.15 mmol, 1.5 equiv), the base and the catalyst under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs at RT.

Procedure for HPLC yields:

The reaction was monitored by dilution of 50 µL of the crude with 950 µL of acetonitrile. The yield was estimated by the absorbance of product in comparison to the overall absorbance of product, unreacted starting material and side-products if any.

Procedure for isolated yields:

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by preparative TLC (DCM/ethyl acetate 7:3).

Table S2. Optimization of the oxidative decarboxylation on dipeptides

Entry	Solvent	Concentration (mM)	Catalyst	Base (equiv)	Alcohol (equiv)	HPLC yield (%)[a]
1	DMF	10	4CzIPN (**3a**)	K_2HPO_4 (2)	MeOH (50)	46
2	DMF	10	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (50)	59
3	DMF	10	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (10)	78
4	DMF	50	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (10)	82
5	DMF	50	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (5)	>95
6	DMF	50	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (2)	>95
7	DMF	50	Eosin Y	K_2HPO_4 (2)	MeOH (5)	17
8[b]	DMF	50	Rhodamine B	K_2HPO_4 (2)	MeOH (5)	27
9[b]	DMF	50	Rose Bengal	K_2HPO_4 (2)	MeOH (5)	35
10[b]	DMF	50	4DPAIPN (**3b**)	K_2HPO_4 (2)	MeOH (5)	45
11	MeCN	50	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (5)	>95

12	MeCN	50	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	-	MeOH (5)	>95 (68)[c]
13	DCE	50	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	-	MeOH (5)	>95

[a] Ratio of integration at 214 nm by RP-HPLC, [b] green LEDs, [c] isolated yield.

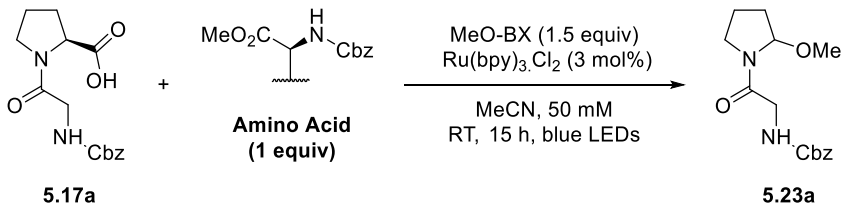
Control experiments were carried out and only traces of the desired product were observed in the absence of light or catalyst.

Robustness experiments

Degassed MeCN (2 mL) was added in a 5 mL test tube containing Cbz-Gly-Pro (**5.17a**) (31 mg, 0.10 mmol, 1.0 equiv), the protected amino acid (0.1 mmol, 1 equiv), MeO-BX (**5.22**) (42 mg, 0.45 mmol, 1.5 equiv) and $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2.3 mg, 3.00 μmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs for 15 h at RT.

The reaction was monitored by dilution of 50 μL of the crude with 950 μL of acetonitrile. The yield was estimated by the absorbance of product in comparison to the overall absorbance of product, unreacted starting material and side-products if any.

Table S3. Robustness experiments



Entry	Amino acid (1 equiv)	HPLC yield (%)
1	Cbz-Met-OMe	15
2	Cbz-Ser-OMe	90[a]
3	Cbz-His-OMe	25
4	Cbz-Arg-OMe	>95
5	Cbz-Tyr-OMe	<5
6	Cbz-Trp-OMe	<5
7	Cbz-Gln-OMe	36
8	Cbz-Lys-OMe	<5
9	Cbz-Asp-OMe	>95
10	Cbz-Cys-OMe	62

[a] + 10% of Serine addition on Z-Gly-Pro (**5.17a**).

7.4.4. Scope on Dipeptides

General procedure 1 for the oxidative decarboxylation of dipeptides

Degassed MeCN (6 mL) was added in a 10 mL test tube containing the corresponding dipeptide (0.30 mmol, 1.0 equiv), MeO-BX (**5.22**) (125 mg, 0.450 mmol, 1.50 equiv) and $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (6.8 mg, 9.0 µmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs for 15 h at RT.

A solution obtained by dilution of 50 µL of the crude with 950 µL of acetonitrile was injected into the HPLC to monitor the conversion of the starting material.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography DCM to DCM/ethyl acetate on triethylamine deactivated silica (5 vol% in DCM).

General procedure 2 for the oxidative decarboxylation of dipeptides

Degassed MeCN (6 mL) was added in a 10 mL test tube containing the corresponding dipeptide (0.30 mmol, 1.0 equiv), AcO-BX (**5.21**) (138 mg, 0.450 mmol, 1.50 equiv), the alcohol (0.60 mmol, 2.0 equiv) and $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (6.8 mg, 9.0 µmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs for 15 h at RT.

A solution obtained by dilution of 50 µL of the crude with 950 µL of acetonitrile was injected into the HPLC to monitor the conversion of the starting material.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography DCM to DCM/ethyl acetate on triethylamine deactivated silica (5 vol% in DCM).

General procedure 3 for the decarboxylative arylation of dipeptides

Degassed DCE (6 mL) was added in a 10 mL test tube containing the corresponding dipeptide (0.30 mmol, 1.0 equiv), AcO-BX (**5.21**) (138 mg, 0.450 mmol, 1.50 equiv) and $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (6.8 mg, 9.0 µmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs for 15 h at RT.

A solution obtained by dilution of 50 µL of the crude with 950 µL of acetonitrile was injected into the HPLC to monitor the conversion of the starting material.

The phenol (0.45 mmol, 1.5 equiv) was added and the reaction mixture degassed by Ar bubbling before cooling at 0 °C. $BF_3 \cdot OEt_2$ (158 µL, 0.600 mmol, 2.00 equiv) was added dropwise and the mixture stirred for 2 h at 0 °C.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography DCM to DCM/ethyl acetate on triethylamine deactivated silica (5 vol% in DCM).

General procedure 4 for the decarboxylative arylation of dipeptides

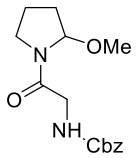
Degassed MeCN (6 mL) was added in a 10 mL test tube containing the corresponding dipeptide (0.30 mmol, 1.0 equiv), AcO-BX (**5.21**) (138 mg, 0.450 mmol, 1.50 equiv) and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (6.8 mg, 9.0 µmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs for 15 h at RT.

A solution obtained by dilution of 50 µL of the crude with 950 µL of acetonitrile was injected into the HPLC to monitor the conversion of the starting material.

The indole (0.306 mmol, 1.02 equiv) was added and TFA (23 µL, 0.30 mmol, 1.0 equiv) was added dropwise and the mixture stirred for 1 h at RT.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography DCM to DCM/ethyl acetate on triethylamine deactivated silica (5 vol% in DCM).

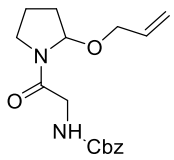
Benzyl (2-(2-methoxypyrrolidin-1-yl)-2-oxoethyl)carbamate (5.23a)



Following General Procedure 1 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv), **5.23a** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a pale yellow oil (66 mg, 0.23 mmol, 75%).

Rf (DCM/ethyl acetate 7:3): 0.3. **^{1}H NMR** (400 MHz, Chloroform-*d*, 1:1 mixture of rotamers (R^1/R^2)) δ 7.40-7.26 (m, 5H, Ar*H* (R^1+R^2)), 5.70 (s, 1H, N*H* (R^1+R^2)), 5.43 (d, *J* = 4.9 Hz, 0.5H, NC*H*COMe (R^1)), 5.12 (s, 2H, OCH_2Ph (R^1+R^2)), 4.96 (d, *J* = 4.5 Hz, 0.5H, NC*H*COMe (R^2)), 4.18-4.05 (m, 1H, NC(O)CH_2NHCbz (R^1)), 4.05-3.91 (m, 1H, NC(O)CH_2NHCbz (R^2)), 3.67 (ddd, *J* = 11.3, 8.4, 2.3 Hz, 0.5H, C(O)NCH_2 (R^1)), 3.58-3.48 (m, 0.5H, C(O)NCH_2 (R^2)), 3.38 (s, 1.5H, OCH_3 (R^1)), 3.43-3.32 (m, 1H, C(O)NCH_2 (R^1+R^2)), 3.31 (s, 1.5H, OCH_3 (R^2)), 2.24-1.66 (m, 4H, $NCH_2CH_2CH_2CH$ (R^1+R^2)). **^{13}C NMR** (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) δ 168.3, 168.2, 156.2, 156.2, 136.4, 136.3, 128.4, 128.0, 127.9, 88.2, 87.5, 66.8, 66.8, 56.6, 54.2, 45.8, 44.8, 43.4, 42.9, 31.2, 30.7, 22.7, 20.7. **IR** (ν_{max}, cm^{-1}) 3324 (m), 2980 (m), 2886 (m), 2339 (w), 1718 (s), 1655 (s), 1520 (m), 1451 (m), 1246 (s), 1170 (m), 1055 (s), 914 (m), 826 (w), 741 (m), 699 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{15}H_{20}N_2NaO_4^+$ 315.1315; Found 315.1315.

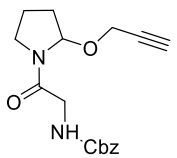
Benzyl (2-(2-(allyloxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.23b)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and allyl alcohol (41 µL, 0.60 mmol, 2.0 equiv), **5.23b** was obtained after column chromatography DCM to DCM/ethyl acetate 9:1 as a pale yellow oil (73 mg, 0.23 mmol, 76%).

Rf (DCM/ethyl acetate 7:3): 0.35. **^{1}H NMR** (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers (major/minor)) δ 7.42-7.27 (m, 5H, Ar*H* (major+minor)), 5.97-5.81 (m, 1H, CH_2C*H*=CH_2 (major+minor)), 5.72 (br s, 1H, N*H* (major+minor)), 5.56 (d, *J* = 4.9 Hz, 0.6H, C(O)NC*H* (major)), 5.37-5.20 (m, 1.2H, CH_2CH=CH_2 (major)), 5.17-5.06 (m, 3.2H, CH_2CH=CH_2 (minor), OCH_2Ph (major+minor) and C(O)NC*H* (minor)), 4.22-3.86 (m, 4H, CH_2CH=CH_2 and C(O)CH_2NHCbz (major+minor)), 3.68 (ddd, *J* = 11.3, 8.6, 2.0 Hz, 0.4H, C(O)NCH_2 (minor)), 3.57-3.48 (m, 0.6H, C(O)NCH_2 (major)), 3.44-3.25 (m, 1H, C(O)NCH_2 (major+minor)), 2.30-1.64 (m, 4H, $NCH_2CH_2CH_2CH$ (major+minor)). **^{13}C NMR** (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) δ 168.2, 168.1, 156.2, 156.2, 136.4, 136.4, 136.3, 134.7, 133.5, 128.4, 128.0, 127.9, 117.9, 116.6, 86.8, 86.1, 70.2, 68.0, 66.9, 66.8, 66.8, 45.9, 44.9, 43.4, 43.1, 31.7, 31.5, 22.8, 20.7. **IR** (ν_{max}, cm^{-1}) 3331 (m), 2982 (m), 2898 (m), 1720 (s), 1657 (s), 1538 (m), 1451 (m), 1247 (s), 1171 (m), 1052 (s), 915 (m), 740 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaO_4^+$ 341.1472; Found 341.1476.

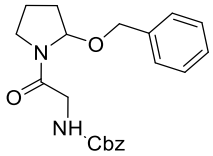
Benzyl (2-oxo-2-(2-(prop-2-yn-1-yloxy)pyrrolidin-1-yl)ethyl)carbamate (5.23c)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and propargyl alcohol (36 µL, 0.60 mmol, 2.0 equiv), **5.23c** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (61 mg, 0.19 mmol, 64%).

Rf (DCM/ethyl acetate 7:3): 0.33. **^{1}H NMR** (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers (major/minor)) *δ* 7.39-7.28 (m, 5H, Ar*H* (major+minor)), 5.69 (br s, 1H, N*H* (major+minor)), 5.66 (d, *J* = 4.9 Hz, 0.6H, C(O)NC*H* (major)), 5.31 (d, *J* = 4.1 Hz, 0.4H, C(O)NC*H*O (minor)), 5.12 (s, 2H, OCH_2Ph (major+minor)), 4.30 (qd, *J* = 15.7, 2.4 Hz, 1.2H, OCH_2CCH (major)), 4.23-4.07 (m, 1.4H, OCH_2CCH (minor) and C(O)CH_2NHCbz (major)), 4.05-3.90 (m, 1.4H, C(O)CH_2NHCbz (major+minor)), 3.71-3.63 (m, 0.4H, C(O)NCH_2 (minor)), 3.53 (t, *J* = 8.8 Hz, 0.6H, C(O)NCH_2 (major)), 3.36 (dq, *J* = 27.4, 9.7, 8.7 Hz, 1H, C(O)NCH_2 (major+minor)), 2.58 (m, 0.4H, OCH_2CC*H* (minor)), 2.42 (t, *J* = 2.36 Hz, 0.6H, OCH_2CC*H* (major)), 2.30-1.70 (m, 4H, $NCH_2CH_2CH_2CH$ (major+minor)). **^{13}C NMR** (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) *δ* 168.7, 168.3, 156.4, 136.6, 136.5, 128.6, 128.2, 128.1, 86.3, 86.1, 80.3, 78.7, 75.9, 73.9, 67.1, 57.1, 54.5, 46.1, 45.1, 43.6, 43.5, 32.0, 31.5, 22.9, 20.8. **IR** (vmax, cm^{-1}) 3416 (w), 3299 (m), 2973 (w), 2889 (w), 2116 (w), 1720 (s), 1662 (s), 1524 (m), 1430 (s), 1254 (s), 1172 (m), 1058 (s), 911 (m), 737 (s), 700 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}N_2NaO_4^+$ 339.1315; Found 339.1315.

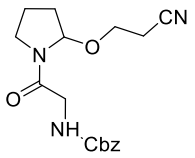
Benzyl (2-(2-(benzyloxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.23d)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and benzyl alcohol (65 µL, 0.60 mmol, 2.0 equiv), **5.23d** was obtained after column chromatography DCM to DCM/ethyl acetate 20:1 as a pale yellow oil (108 mg, 0.293 mmol, 98%).

Rf (DCM/ethyl acetate 7:3): 0.41. **^{1}H NMR** (400 MHz, Chloroform-*d,* 6:4 mixture of rotamers (major/minor)) *δ* 7.40-7.27 (m, 10H, Ar*H* (major+minor)), 5.74-5.63 (m, 1.6H, N*H* (major+minor) and C(O)NC*H* (major)), 5.20 (d, *J* = 4.1 Hz, 0.4H, C(O)NC*H* (minor)), 5.13 (d, *J* = 2.5 Hz, 2H, C(O)OCH_2Ph (major+minor)), 4.70 (br s, 0.6H, NCHOCH_2Ph (major)), 4.67 (d, *J* = 3.0 Hz, 0.6H, NCHOCH_2Ph (major)), 4.56-4.46 (m, 0.8H, NCHOCH_2Ph (minor)), 4.09 (qd, *J* = 17.0, 4.6 Hz, 0.8H, C(O)CH_2NHCbz (minor)), 3.91 (m, 1.2H, C(O)CH_2NHCbz (major)), 3.74-3.65 (m, 0.4H, C(O)NCH_2 (minor)), 3.49 (t, *J* = 8.9 Hz, 0.6H, C(O)NCH_2 (major)), 3.41 (td, *J* = 11.2, 10.5, 7.0 Hz, 0.4H, C(O)NCH_2 (minor)), 3.31 (q, *J* = 9.6 Hz, 0.6H, C(O)NCH_2 (major)), 2.34-1.67 (m, 4H, $NCH_2CH_2CH_2CH$ (major+minor)). **^{13}C NMR** (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) *δ* 168.4, 168.3, 156.4, 156.3, 149.3, 141.0, 138.7, 137.0, 136.6, 136.5, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.1, 87.2, 86.5, 71.3, 69.5, 67.1, 67.0, 65.5, 46.1, 45.0, 43.6, 43.3, 32.0, 31.7, 23.0, 21.0. **IR** (ν_{max}, cm^{-1}) 3418 (w), 3329 (w), 2979 (w), 2881 (w), 1721 (s), 1659 (s), 1524 (m), 1452 (m), 1347 (w), 1253 (m), 1172 (m), 1107 (m), 1054 (s), 914 (m), 740 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{21}H_{24}N_2NaO_4^+$ 391.1628; Found 391.1633.

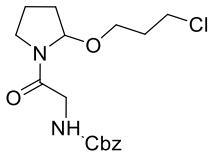
Benzyl (2-(2-(2-cyanoethoxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.23e)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and 3-hydroxypropionitrile (41 µL, 0.60 mmol, 2.0 equiv), **5.23e** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (47 mg, 0.14 mmol, 47%).

Rf (DCM/ethyl acetate 7:3): 0.24. **^{1}H NMR** (400 MHz, Chloroform-*d,* 8:2 mixture of rotamers (major/minor)) *δ* 7.39-7.28 (m, 5H, Ar*H* (major+minor)), 5.63 (br s, 1H (major+minor)), 5.55 (d, *J* = 4.9 Hz, 0.8H, C(O)NC*H* (major)), 5.12 (m, 2.2H, OCH_2Ph (major+minor) and C(O)NC*H* (minor)), 4.10 (qd, *J* = 16.9, 4.8 Hz, 0.4H, C(O)CH_2NHCbz (minor)), 4.01-3.91 (m, 1.6H, C(O)CH_2NHCbz (major)), 3.83 (tq, *J* = 7.4, 4.0 Hz, 1.6H, OCH_2CH_2CN (major)), 3.69 (dq, *J* = 12.9, 5.3, 3.9 Hz, 0.4H, OCH_2CH_2CN (minor)), 3.65-3.61 (m, 0.2H, C(O)NCH_2 (minor)), 3.56 (t, *J* = 9.0 Hz, 0.8H, C(O)NCH_2 (major)), 3.45-3.38 (m, 0.2H, C(O)NCH_2 (minor)), 3.34 (q, *J* = 9.8 Hz, 0.8H, C(O)NCH_2 (major)), 2.63 (t, *J* = 6.4 Hz, 0.4H, OCH_2CH_2CN (minor)), 2.55 (m, 1.6H, OCH_2CH_2CN (major)), 2.31-1.68 (m, 4H, $NCH_2CH_2CH_2CHO$ (major+minor)). **^{13}C NMR** (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) *δ* 169.0, 168.3, 156.5, 156.4, 136.5, 128.7, 128.3, 128.2, 118.1, 117.5, 87.5, 86.7, 67.1, 63.9, 61.5, 46.1, 45.9, 45.3, 43.6, 43.2, 32.0, 31.7, 23.0, 20.9, 19.3, 19.2. **IR** (ν_{max}, cm^{-1}) 3407 (w), 3329 (w), 2959 (w), 2887 (w), 2251 (w), 1720 (s), 1660 (s), 1525 (m), 1429 (s), 1336 (m), 1254 (s), 1172 (m), 1085 (s), 1060 (s), 914 (m), 739 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{17}H_{21}N_3NaO_4^+$ 354.1424; Found 354.1422.

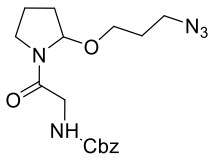
Benzyl (2-(2-(3-chloropropoxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.23f)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and 3-chloropropan-1-ol (25 µL, 0.60 mmol, 2.0 equiv), **5.23f** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (74 mg, 0.21 mmol, 70%).

Rf (DCM/ethyl acetate 7:3): 0.29. **^{1}H NMR** (400 MHz, Chloroform-*d,* 6:4 mixture of rotamers (major/minor)) *δ* 7.38-7.28 (m, 5H, Ar*H* (major+minor)), 5.75-5.63 (m, 1H, N*H* (major+minor)), 5.51 (d, *J* = 4.86 Hz, 0.6H, C(O)NC*H* (major)), 5.12 (s, 2H, OCH_2Ph (major+minor)), 5.07 (d, *J* = 4.2 Hz, 0.4H C(O)NC*H* (minor)), 4.18-4.01 (m, 1H, C(O)CH_2NHCbz (major+minor)), 3.96 (dt, *J* = 17.4, 4.5 Hz, 1H, C(O)CH_2NHCbz (major+minor)), 3.72-3.49 (m, 5H, $OCH_2CH_2CH_2Cl$, $OCH_2CH_2CH_2Cl$ and C(O)NCH_2, (major+minor)), 3.34 (dq, *J* = 26.5, 9.7, 8.6 Hz, 1H, C(O)NCH_2 (major+minor)), 2.33-1.55 (m, 6H, $NCH_2CH_2CH_2CH$ and $OCH_2CH_2CH_2Cl$ (major+minor)). **^{13}CNMR** (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) *δ* 168.4, 168.3, 156.4, 136.5, 128.6, 128.2, 128.1, 87.2, 86.5, 67.0, 65.2, 62.9, 46.1, 45.1, 43.6, 43.2, 42.0, 41.7, 32.7, 32.3, 31.7, 31.6, 23.0, 21.0. **IR** (ν_{max}, cm^{-1}) 3415 (w), 3319 (w), 2959 (m), 2882 (w), 1721 (s), 1660 (s), 1524 (m), 1430 (s), 1246 (m), 1171 (m), 1059 (s), 996 (m), 911 (m), 738 (s), 701 (m). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{17}H_{23}ClN_2NaO_4^+$ 377.1239; Found 377.1232.

Benzyl (2-(2-(3-azidopropoxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.23g)

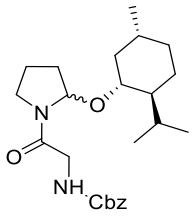


Following General Procedure 2 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and 3-azidopropan-1-ol (600 µL, 1M in DCM, 0.60 mmol, 2.0 equiv), **5.23g** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (99 mg, 0.27 mmol, 91%).

Rf (DCM/ethyl acetate 7:3): 0.38. **^{1}H NMR** (400 MHz, Chloroform-*d,* 6:4 mixture of rotamers (major/minor)) *δ* 7.38-7.28 (m, 5H, Ar*H* (major+minor)), 5.75-5.63 (m, 1H, N*H* (major+minor)), 5.50 (d, *J* = 4.9 Hz, 0.6H, C(O)NC*H* (major)), 5.12 (s, 2H, OCH_2Ph (major+minor)), 5.05 (d, *J* = 4.2 Hz, 0.4H, C(O)NC*H*O (minor)), 4.16-4.01 (m, 0.8H, C(O)CH_2NHCbz (minor)), 4.01-3.91 (m, 1.2H, C(O)CH_2NHCbz (major)), 3.76 (t, *J* = 4.7 Hz, 0.8H, $OCH_2CH_2CH_2N_3$ (minor)), 3.65 (qd, *J* = 6.1, 5.1, 1.8 Hz, 1.2H, $OCH_2CH_2CH_2N_3$ (major)), 3.56-3.26 (m, 4H, $OCH_2CH_2CH_2N_3$ and (CO)NCH_2 (major+minor)), 2.24-1.66 (m, 6H, $NCH_2CH_2CH_2CHO$ and $OCH_2CH_2CH_2N_3$ (major+minor)). **^{13}C NMR** (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) *δ* 168.4, 168.2, 156.4, 136.5, 128.6, 128.2, 128.1, 87.3, 86.6, 67.0, 65.7, 63.4, 60.1, 48.6, 48.5, 48.4, 46.0, 45.1, 43.6, 43.2, 31.8, 31.6, 31.5, 29.4, 29.2, 23.0, 21.0. **IR** (ν_{max}, cm^{-1}) 3418 (w), 3318 (w), 2952 (m), 2881 (m), 2097 (s), 1721 (s), 1661 (s), 1523 (m), 1452 (s), 1256 (s), 1172 (m), 1056 (s), 912 (m), 739 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for

$C_{17}H_{23}N_5NaO_4^+$ 384.1642; Found 384.1646.

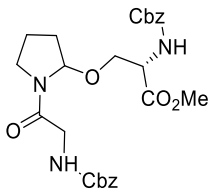
Benzyl (2-(2-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.23h)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and (1R,2S,5R)-(-)-menthol (94 mg, 0.60 mmol, 2.0 equiv), **5.23h** was obtained after column chromatography DCM to DCM/ethyl acetate 15:1 as a pale yellow oil as an unresolved mixture of diastereomers (44 mg, 0.11 mmol, 35%).

Rf (DCM/ethyl acetate 7:3): 0.63. **^{1}H NMR** (400 MHz, Chloroform-*d*, unresolved mixture of diastereomers and rotamers) *δ* 7.39-7.28 (m, 5H, Ar*H*), 5.79-5.71 (m, 0.7H, N*H* and C(O)NC*H*), 5.66 (br s, 0.4H, N*H*), 5.58 (m, 0.5H, N*H* and C(O)NC*H*), 5.26 (d, *J* = 4.16 Hz, 0.4H, C(O)NC*H*), 5.19-5.07 (m, 2H, OCH_2Ph), 4.22-3.82 (m, 2H, C(O)CH_2NHCbz), 3.69 (t, *J* = 9.3 Hz, 0.3H, C(O)NCH_2), 3.54 (t, *J* = 9.3 Hz, 0.3H, C(O)NCH_2), 3.51-3.19 (m, 2H, C(O)NCH_2 and NCHOC*H*), 3.12 (tt, *J* = 11.5, 5.7 Hz, 0.3H, C(O)NCH_2), 2.32-1.83 (m, 6H, NCH_2CH_2CH_2CH and *H*menthol), 1.79-1.61 (m, 4H, NCH_2CH_2CH_2CH and *H*menthol), 1.43-1.07 (m, 3H, *H*menthol), 1.06-0.61 (m, 13H, *H*menthol).**^{13}C NMR** (101 MHz, Chloroform-*d,* mixture of diastereomers and rotamers, signals not fully resolved) *δ* 168.3, 168.0, 167.7, 156.5, 156.4, 156.3, 136.6, 136.5, 128.6, 128.2, 128.1, 128.0, 85.7, 83.2, 82.8, 77.8, 75.7, 74.9, 67.0, 66.9, 48.8, 48.3, 48.1, 46.0, 45.0, 44.7, 43.7, 43.5, 43.4, 41.8, 41.7, 40.8, 39.7, 34.7, 34.6, 34.4, 32.5, 31.8, 31.7, 31.6, 31.5, 31.4, 25.7, 25.5, 25.2, 25.1, 23.3, 23.2, 23.1, 22.9, 22.5, 22.4, 21.4, 21.3, 21.1, 20.8, 16.2, 16.1, 15.9. **IR** (ν_{max}, cm^{-1}) 3417 (w), 3315 (w), 2954 (m), 2871 (m), 1724 (s), 1661 (s), 1523 (m), 1428 (s), 1242 (m), 1173 (m), 1095 (m), 1049 (s), 915 (m), 736 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{24}H_{36}N_2NaO_4^+$ 439.2567; Found 439.2567.

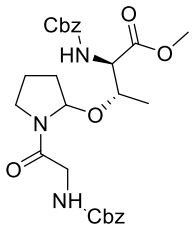
(2S)-Methyl 2-(((benzyloxy)carbonyl)amino)-3-((1-(2-(((benzyloxy)carbonyl)amino)acetyl)pyrrolidin-2-yl)oxy)propanoate (5.23i)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and Cbz-Ser-OMe (114 mg, 0.450 mmol, 1.50 equiv), **5.23i** was obtained after column chromatography DCM to DCM/ethyl acetate 1:1 as a pale yellow oil and a mixture of diastereomers (65 mg, 0.13 mmol, 42%).

Rf (DCM/ethyl acetate 7:3): 0.3. **^{1}H NMR** (400 MHz, Chloroform-*d*, mixture of rotamers of diastereomers)[4] δ 7.40-7.25 (m, 10H, Ar*H*), 6.05 (d, 0.3H, N*H* Ser), 5.93 (d, *J* = 8.4 Hz, 0.1H, N*H* Ser), 5.72 (br s, 1H, N*H* Gly), 5.65 (s, 0.4H, N*H* Ser), 5.47 (d, *J* = 4.8 Hz, 0.3H, C(O)NC*H* Pro), 5.41 (d, *J* = 4.9 Hz, 0.4H, C(O)NC*H* Pro), 5.12 (s, 4H, OCH_2Ph Gly+Ser), 5.09-5.05 (m, 0.3H, C(O)NC*H* Pro), 4.59-4.49 (m, 0.3H, NHC*H* Ser), 4.51-4.41 (m, 0.7H, NHC*H* Ser), 4.12-3.78 (m, 4H, OCH_2 Ser and C(O)CH_2NHCbz Gly), 3.77-3.62 (m, 3H, CO_2CH_3 Ser), 3.59-3.19 (m, 2H, C(O)NCH_2 Pro), 2.19-1.61 (m, 4H, $NCH_2CH_2CH_2CH$ Pro). **^{13}C NMR** (101 MHz, Chloroform-*d,* mixture of rotamers of diastereomers, signals not fully resolved) δ 170.8, 170.7, 170.2, 168.5, 168.2, 156.2, 155.9, 136.3, 136.3, 136.2, 128.5, 128.4, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 87.6, 87.2, 87.0, 86.7, 68.9, 68.6, 67.1, 67.0, 66.9, 66.3, 66.2, 54.6, 54.4, 54.3, 54.0, 52.8, 52.7, 52.5, 52.4, 45.9, 45.1, 44.9, 43.4, 43.4, 42.9, 42.8, 33.7, 31.5, 31.4, 31.1, 31.1, 22.7, 22.7, 20.7, 20.6, 20.4. **IR** (v_{max}, cm^{-1}) 3324 (m), 2979 (m), 2885 (w), 1718 (s), 1658 (s), 1518 (m), 1436 (m), 1242 (m), 1054 (s), 914 (m), 738 (s), 699 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{31}N_3NaO_8^+$ 536.2003; Found 536.2014.

(2S,3R)-methyl 2-(((benzyloxy)carbonyl)amino)-3-((1-(2-(((benzyloxy)carbonyl)amino) acetyl)pyrrolidin-2-yl)oxy)butanoate (5.23j)

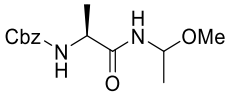


Following General Procedure 2 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and Cbz-Thr-OMe (160 mg, 0.450 mmol, 1.50 equiv), **5.23j** was obtained after column chromatography DCM to DCM/ethyl acetate 1:1 as a pale yellow oil and a mixture of diastereomers (60 mg, 0.11 mmol, 38%).

Rf (DCM/ethyl acetate 7:3): 0.36. **^{1}H NMR** (400 MHz, Chloroform-*d*, mixture of rotamers of diastereomers)[4] δ 7.40-7.28 (m, 10H, Ar*H*), 5.67 (d, *J* = 14.7 Hz, 1H, N*H* Gly), 5.60 (d, *J* = 9.4 Hz, 0.5H, N*H* Thr), 5.55 (d, *J* = 4.7 Hz, 0.6H, C(O)NC*H* Pro), 5.54-5.48 (m, 0.25H, N*H* Thr), 5.43 (d, *J* = 9.7 Hz, 0.25H, N*H* Thr), 5.40 (d, *J* = 4.7 Hz, 0.4H, C(O)NC*H* Pro), 5.17-5.06 (m, 4H, OCH_2Ph Gly and Ser), 4.54-4.37 (m, 0.5H, OC*H* and NHC*H* Thr), 4.37-4.22 (m, 1.2H, OC*H* and NHC*H* Thr), 4.22-4.11 (m, 0.3H, OC*H* and NHC*H* Thr), 3.96 (m, 2H, C(O)CH_2NHCbz Gly), 3.78-3.58 (m, 3H, OCH_3 Thr), 3.47 (dq, *J* = 16.4, 9.5, 8.9 Hz, 0.5H, C(O)NCH_2 Pro), 3.40-3.19 (m, 1.5H, C(O)NCH_2 Pro), 2.15-1.68 (m, 4H, $NCH_2CH_2CH_2CH$ Pro), 1.39-1.16 (m, 3H, OCHCH_3 Thr). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 171.6, 171.4, 168.7, 168.0, 156.8, 156.7, 156.3, 136.5, 136.4, 136.3, 128.7, 128.6, 128.3, 128.2, 128.1, 86.7, 84.4, 83.9, 74.7, 72.3, 71.3, 67.4, 67.3, 67.2, 67.1, 59.1, 59.0, 52.7, 52.5, 52.4, 46.1, 45.7, 45.0, 44.8, 43.6, 43.5, 43.2, 32.2, 32.1, 31.7, 31.3, 22.9, 22.8, 20.5, 20.4, 17.8, 16.9, 16.0. **IR** (v_{max}, cm^{-1}) 3365 (w), 2979 (w), 2890 (w), 2099 (w), 1719 (s), 1663 (m), 1523 (m), 1436 (m), 1318 (m), 1256 (m), 1173 (m), 1065 (s), 1002 (m), 911 (m), 739 (s). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{27}H_{33}N_3NaO_8^+$ 550.2160; Found 550.2161.

[4] Due to the complexity of the mixture, signals were not attributed to each rotamer and diastereomer.

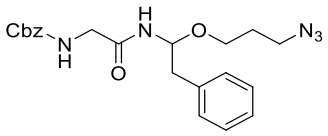
Benzyl ((2S)-1-((1-methoxyethyl)amino)-1-oxopropan-2-yl)carbamate (5.23k)



Following General Procedure 1 and starting with Cbz-Ala-Ala (**5.17b**) (88 mg, 0.30 mmol, 1.0 equiv), **5.23k** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a white amorphous solid (57 mg, 0.20 mmol, 68%) and as a mixture of unresolved diastereomers.

Rf (DCM/ethyl acetate 7:3): 0.25. **^{1}H NMR** (400 MHz, Chloroform-*d*, mixture of diastereomers and rotamers) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H, Ar*H*), 6.30 (br s, 1H, N*H*), 5.33 (s, 1H, N*H*Cbz), 5.24 (dqd, *J* = 9.2, 5.9, 3.3 Hz, 1H, C(O)NC*H*COMe), 5.12 (s, 2H, OCH_2Ph), 4.22 (q, *J* = 6.8 Hz, 1H, CbzNC*H*Me), 3.30 (s, 1H, OCH_3), 3.27 (s, 2H, OCH_3), 1.40 (t, *J* = 7.3 Hz, 3H, CbzNCHCH_3), 1.30 (d, *J* = 5.9 Hz, 3H, C(O)NHCHCH_3). **^{13}C NMR** (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) δ 172.3, 156.0, 136.0, 128.6, 128.3, 128.1, 78.4, 67.2, 55.6, 50.7, 28.9, 21.5, 18.7, 18.3. **IR** (ν_{max}, cm^{-1}) 3286 (m), 2981 (w), 1688 (s), 1651 (s), 1540 (s), 1453 (m), 1382 (w), 1324 (m), 1261 (s), 1135 (m), 1070 (m), 914 (m), 738 (s), 699 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{14}H_{20}N_2NaO_4^+$ 303.1315; Found 303.1315.

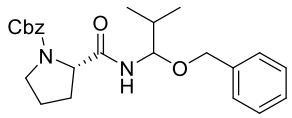
Benzyl (2-((1-(3-azidopropoxy)-2-phenylethyl)amino)-2-oxoethyl)carbamate (5.23l)



Following General Procedure 2 and starting with Cbz-Gly-Phe (**5.17c**) (107 mg, 0.30 mmol, 1.0 equiv) and 3-azidopropan-1-ol (600 µL, 1M in DCM, 0.60 mmol, 2.0 equiv), **5.23l** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a colorless oil (57 mg, 0.14 mmol, 46%).

Rf (DCM/ethyl acetate 7:3): 0.52. **^{1}H NMR** (400 MHz, Acetonitrile-d_3, 75:25 mixture of rotamers (major/minor)) δ 7.41-7.21 (m, 10H, Ar*H* (major+minor)), 6.88 (d, *J* = 9.4 Hz, 1H, N*H* Phe (major+minor)), 6.02 (m, 0.25H, N*H* Gly (minor)), 5.90 (m, 0.75H, N*H* Gly (major)), 5.28 (dt, *J* = 9.6, 6.3 Hz, 1H, NHC*H* Phe (major+minor)), 5.09 (d, *J* = 9.8 Hz, 2H, OCH_2Ph (major+minor)), 3.81 (d, *J* = 6.1 Hz, 0.5H, NHCH_2 Gly (minor)), 3.66 (dd, *J* = 6.1, 2.8 Hz, 1.5H, NHCH_2 Gly (major)), 3.60-3.51 (m, 1H, OCH_2CH$_2$CH$_2$N$_3$ (major+minor)), 3.42-3.35 (m, 1.5H, OCH_2CH$_2$CH$_2$N$_3$ (major+minor) and OCH$_2$CH$_2$CH_2N$_3$ (minor)), 3.23 (t, *J* = 6.7 Hz, 1.5H, OCH$_2$CH$_2$CH_2N$_3$ (major)), 2.94 (dd, *J* = 13.8, 6.2 Hz, 1H, NHCHCH_2 Phe (major+minor)), 2.83 (dd, *J* = 13.7, 6.3 Hz, 1H, NHCHCH_2 Phe (major+minor)), 1.77-1.63 (m, 2H, OCH$_2$CH$_2$CH_2N$_3$ (major+minor)). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of rotamers, signals not fully resolved) δ 170.5, 168.2, 157.6, 138.1, 138.0, 137.5, 130.6, 129.6, 129.5, 129.2, 128.9, 128.8, 127.4, 126.4, 123.6, 113.5, 81.1, 67.4, 67.3, 65.2, 59.4, 49.1, 44.8, 41.9, 32.4, 29.6. **IR** (ν_{max}, cm^{-1}) 3347 (m), 3064 (m), 2935 (m), 2880 (m), 2097 (s), 1708 (s), 1664 (s), 1517 (s), 1455 (m), 1257 (s), 1155 (m), 1050 (s), 909 (m), 738 (s), 699 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{21}H_{25}N_5NaO_4^+$ 434.1799; Found 434.1801

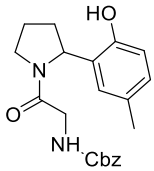
Benzyl (2S)-2-((1-(benzyloxy)-2-methylpropyl)carbamoyl)pyrrolidine-1-carboxylate (5.23m)



Following General Procedure 2 and starting with Cbz-Pro-Val (**5.17d**) (105 mg, 0.30 mmol, 1.0 equiv) and benzyl alcohol (65 µL, 0.60 mmol, 2.0 equiv), **5.23m** was obtained after column chromatography DCM to DCM/ethyl acetate 15:1 as a colorless oil (63 mg, 0.15 mmol, 51%).

Rf (DCM/ethyl acetate 7:3): 0.71. **^{1}H NMR** (400 MHz, Acetonitrile-*d*$_3$, mixture of rotamers of diastereomers) δ 7.45-7.16 (m, 10H, Ar*H*), 6.97-6.70 (m, 1H, N*H*), 5.18-5.05 (m, 1.5H, OC*H*$_2$Ph Cbz), 4.99 (d, *J* = 13.3 Hz, 0.5H, OC*H*$_2$Ph Cbz), 4.91 (m, 1H, NHC*H* Val), 4.54 (m, 0.5H, OC*H*$_2$Ph Val), 4.49-4.33 (m, 1H, OC*H*$_2$Ph Val), 4.26 (m, 1.5H, OC*H*$_2$Ph Val and CbzNC*H* Pro), 3.59-3.40 (m, 2H, CbzNC*H*$_2$ Pro), 2.33-2.19 (m, 1H, CbzNCH$_2$C*H*$_2$C*H*$_2$CH Pro), 2.05-1.95 (m, 1H, CbzNCH$_2$C*H*$_2$C*H*$_2$CH Pro), 1.92-1.73 (m, 3H, CbzNCH$_2$C*H*$_2$C*H*$_2$CH Pro and NHCHC*H* Val), 0.98-0.72 (m, 6H, C*H*$_3$ Val). **^{13}C NMR** (101 MHz, Acetonitrile-*d*$_3$, mixture of rotamers of diastereomers, signals not fully resolved) δ 174.1, 173.8, 173.7, 156.2, 155.5, 139.8, 139.7, 138.1, 129.4, 129.3, 129.2, 128.9, 128.7, 128.6, 128.4, 128.3, 84.5, 84.3, 70.1, 67.5, 67.4, 62.1, 62.0, 61.6, 61.4, 48.3, 47.8, 33.7, 32.5, 30.8, 25.3, 24.3, 18.6, 18.0, 17.9, 17.8. **IR** (ν_{max}, cm^{-1}) 3338 (m), 3063 (m), 2929 (m), 1672 (s), 1529 (s), 1417 (s), 1356 (s), 1231 (m), 1119 (s), 1089 (m), 1039 (m), 912 (m), 737 (s), 697 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{24}H_{30}N_2NaO_4^+$ 433.2098; Found 433.2090.

Benzyl (2-(2-(2-hydroxy-5-methylphenyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.28a)

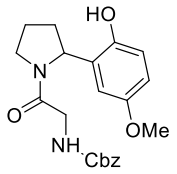


Following General Procedure 3 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and *p*-cresol (49 mg, 0.45 mmol, 1.5 equiv), **5.28a** was obtained after column chromatography DCM to DCM/ethyl acetate 7:3 as a pale yellow amorphous solid (68 mg, 0.19 mmol, 62%).

Rf (DCM/ethyl acetate 7:3): 0.4. **^{1}H NMR** (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 8.94 (s, 1H, O*H* (major+minor)), 7.33 (dt, *J* = 9.1, 4.6 Hz, 5H, Ar*H* (major+minor)), 6.94 (d, *J* = 8.1 Hz, 0.7H, Ar*H* (major)), 6.89 (s, 0.7H, Ar*H* (major)), 6.82 (d, *J* = 7.6 Hz, 0.3H, Ar*H* (minor)), 6.76 (d, *J* = 8.1 Hz, 0.7H, Ar*H* (major)), 6.66 (s, 0.3H, Ar*H* (minor)), 6.51 (d, *J* = 8.0 Hz, 0.3H, Ar*H* (minor)), 5.79 (br s, 0.3H, N*H* (minor)), 5.67 (br s, 0.7H, N*H* (major)), 5.39 (dd, *J* = 7.5, 3.0 Hz, 0.7H, C(O)NC*H* (major)), 5.17 (d, *J* = 7.7 Hz, 0.3H, C(O)NC*H* (minor)), 5.11 (s, 1.4H, OC*H*$_2$Ph (major)), 5.07 (s, 0.6H, OC*H*$_2$Ph (minor)), 4.07 (td, *J* = 20.3, 18.9, 4.6 Hz, 1H, C(O)C*H*$_2$NHCbz (major+minor)), 3.92 (dd, *J* = 17.4, 4.0 Hz, 0.7H, C(O)C*H*$_2$NHCbz (major)), 3.79 (d, *J* = 6.0 Hz, 0.3H, C(O)NC*H*$_2$ (minor)), 3.73 (d, *J* = 8.1 Hz, 0.3H, C(O)NC*H*$_2$ (minor)), 3.67-3.51 (m, 1.4H, C(O)NC*H*$_2$ (major)), 3.43 (dd, *J* = 17.2, 3.3 Hz, 0.3H, C(O)C*H*$_2$NHCbz (minor)), 2.43-2.14 (m, 6H, NCH$_2$C*H*$_2$C*H*$_2$CH and C*H*$_3$ (major+minor)), 1.98-1.82 (m, 1H, NCH$_2$C*H*$_2$C*H*$_2$CH (major+minor)). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.4, 156.6, 156.4, 153.1, 150.7, 136.4, 129.9, 129.6, 129.0, 128.6, 128.3, 128.1, 127.8, 127.4, 126.5, 125.9, 118.4, 115.6, 67.1, 55.9, 55.2, 47.5, 46.2, 43.6, 43.3, 34.4, 31.2, 30.5, 25.2, 21.8, 21.0, 20.9. **IR** (ν_{max}, cm^{-1}) 3313 (w), 2978 (m), 2899 (w), 2360 (w), 1714 (s), 1640 (s), 1510 (m), 1436 (m), 1269 (m), 1055 (m),

738 (m), 699 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{21}H_{22}N_2NaO_4^+$ 389.1472; Found 389.1472.

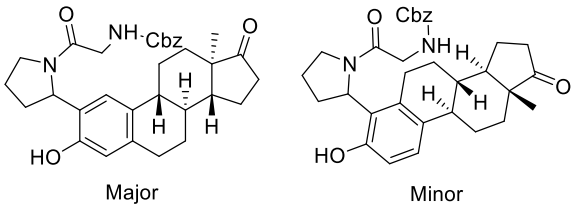
Benzyl (2-(2-(2-hydroxy-5-methoxyphenyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.28b)



Following General Procedure 3 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and 4-methoxyphenol (56 mg, 0.45 mmol, 1.5 equiv), **5.28b** was obtained after column chromatography DCM to DCM/ethyl acetate 7:3 as a pale yellow oil (90 mg, 0.23 mmol, 78%).

Rf (DCM/ethyl acetate 7:3): 0.35. **^{1}H NMR** (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 8.73 (s, 1H, O*H* (major+minor)), 7.38-7.28 (m, 5H, Ar*H* (major+minor)), 6.78 (d, *J* = 8.7 Hz, 0.7H, Ar*H* (major)), 6.68 (dd, *J* = 8.7, 2.9 Hz, 0.7H, Ar*H* (major)), 6.65 (d, *J* = 2.8 Hz, 0.7H Ar*H* (major)), 6.57-6.50 (m, 0.6H, Ar*H* (minor)), 6.45 (d, *J* = 2.1 Hz, 0.3H,Ar*H* (minor)), 5.81 (s, 0.3H, N*H* (minor)), 5.66 (s, 0.7H, N*H* (major)), 5.41-5.35 (m, 0.7H, C(O)NC*H* (major)), 5.16 (d, *J* = 7.1 Hz, 0.3H, C(O)NC*H* (minor)), 5.11 (s, 1.4H, OCH_2Ph (major)), 5.08 (s, 0.6H, OCH_2Ph (minor)), 4.16-4.00 (m, 1H, C(O)CH_2NHCbz (major+minor)), 3.93 (dd, *J* = 17.4, 4.2 Hz, 0.7H, C(O)CH_2NHCbz (major)), 3.74 (s, 2.1H, OCH_3 (major)), 3.70 (s, 0.9H, OCH_3 (minor)), 3.62 (dd, *J* = 11.1, 7.1 Hz, 1H, C(O)NCH_2 (major+minor)), 3.59-3.53 (m, 1H, C(O)NCH_2 (major+minor)), 3.46 (dd, *J* = 17.1, 3.6 Hz, 0.3H, C(O)CH_2NHCbz (minor)), 2.40-2.11 (m, 3H, $NCH_2CH_2CH_2CH$ (major+minor)), 1.99-1.82 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 168.0, 167.2, 156.5, 156.3, 153.5, 153.4, 149.2, 147.0, 136.4, 129.2, 128.7, 128.6, 128.3, 128.1, 118.9, 116.3, 113.4, 112.7, 112.6, 111.8, 67.1, 56.0, 55.9, 55.4, 47.5, 46.3, 43.6, 43.3, 34.3, 31.2, 25.1, 21.7. **IR** (v_{max}, cm^{-1}) 3671 (m), 3320 (m), 2987 (s), 2899 (m), 1717 (s), 1638 (s), 1507 (s), 1453 (s), 1434 (s), 1350 (m), 1286 (s), 1207 (s), 1045 (s), 815 (m), 740 (m). **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{21}H_{25}N_2O_5^+$ 385.1758; Found 385.1747.

and Benzyl (2-(2-((8S,9R,13R,14R)-3-hydroxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-2-yl)pyrrolidin-1-yl)-2-oxoethyl) carbamate and Benzyl (2-(2-((8S,9R,13R,14R)-3-hydroxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-4-yl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.28c)



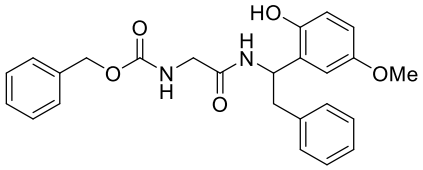
Following General Procedure 3 and starting with Cbz-Pro-Gly (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and estrone (122 mg, 0.450 mmol, 1.50 equiv), **5.28c** was obtained after column chromatography DCM to DCM/ethyl acetate 7:3 as a pale yellow amorphous solid (100 mg, 0.188 mmol, 63%, ratio major/minor 7:3).

Rf (DCM/ethyl acetate 7:3): 0.32.

Major**: ^{1}H NMR** (400 MHz, Acetonitrile-d_3, unresolved mixture of rotamers of diastereomers) δ 7.31 (m, 5H, Ar*H*), 7.23-7.10 (m, 0.4H, O*H*), 7.10-6.95 (m, 1H, Ar*H*), 6.89-6.73 (m, 0.6H, O*H*), 6.68-6.48 (m, 1H, Ar*H*), 5.89-5.59 (m, 1H, N*H* Gly), 5.17 (m, 1H, C(O)NC*H*), 5.01 (m, 2H, OCH_2Ph), 4.00-3.40 (m, 4H, C(O)CH_2NHCbz and C(O)NCH_2), 3.29-2.97 (m, 1H, ArCH_2 estrone), 2.90-2.60 (m, 1H ArCH_2 estrone), 2.48-2.26 (m, 3H), 2.04 (m, 5H), 1.90-1.73 (m, 2H), 1.67-1.25 (m, 7H), 0.86 (m, 3H, CH_3). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of rotamers of diastereomers, signals not fully resolved) δ 166.8, 157.1, 153.2, 153.0, 138.2, 136.5, 132.5, 129.4, 128.8, 128.7, 127.3, 126.4, 125.7, 125.5, 114.8, 114.6, 79.3, 78.6, 67.1, 67.0, 56.8, 56.5, 51.2, 48.7, 48.5, 48.1, 47.3, 47.1, 45.3, 45.1, 44.9, 43.9, 43.8, 43.2, 39.4, 38.3, 36.4, 34.0, 32.6, 32.4, 31.4, 30.4, 29.8, 27.6, 27.4, 27.2, 27.1, 26.8, 26.6, 25.0, 24.8, 22.1, 14.3, 14.2. **IR** (ν_{max}, cm^{-1}) 3305 (m), 2929 (m), 2867 (m), 1726 (s), 1633 (s), 1509 (s), 1451 (s), 1372 (m), 1281 (s), 1257 (s), 1056 (s), 831 (m), 741 (m), 698 (s). **HRMS (nanochip-ESI/LTQ-Orbitrap)** m/z: [M + H]$^+$ Calcd for $C_{32}H_{39}N_2O_5^+$ 531.2853; Found 531.2840

Minor: **^{1}H NMR** (400 MHz, Acetonitrile-d_3, unresolved mixture of rotamers of diastereomers) δ 8.26-8.17 (m, 0.2H, O*H*), 8.04-7.93 (m, 0.4H, O*H*), 7.32 (m, 5H Ar*H*), 6.99-6.90 (m, 0.6H, Ar*H*), 6.82 (s, 0.4H, Ar*H*), 6.58-6.45 (m, 1H, Ar*H*), 5.89-5.59 (m, 1H, N*H* Gly), 5.27-5.09 (m, 1H, C(O)NC*H*), 5.03 (m, 2H, OCH_2Ph), 4.00-3.85 (m, 1.6H, C(O)CH_2NHCbz), 3.84-3.74 (m, 0.4H, C(O)CH_2NHCbz), 3.73-3.46 (m, 2H,C(O)NCH_2), 2.88-2.66 (m, 2H, ArCH_2 estrone), 2.47-2.25 (m, 3H), 2.13-1.97 (m, 5H), 1.87-1.72 (m, 2H), 1.67-1.33 (m, 7H), 0.88 (m, 3H, CH_3). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of rotamers of diastereomers, signals not fully resolved) δ 174.0, 168.6, 153.0, 152.0, 138.3, 137.8, 132.2, 129.4, 129.3, 128.8, 128.7, 127.3, 127.1, 124.1, 123.8, 116.3, 67.1, 56.4, 51.1, 48.7, 47.9, 47.0, 44.9, 44.8, 44.0, 43.8, 39.7, 39.4, 39.2, 36.3, 35.0, 34.5, 32.6, 32.3, 32.1, 31.1, 29.8, 29.6, 27.3, 26.9, 26.8, 25.2, 25.1, 24.5, 23.7, 22.3, 22.2, 14.3, 14.2, 11.3. **IR** (ν_{max}, cm^{-1}) 3337 (m), 2951 (s), 2872 (m), 1733 (s), 1638 (s), 1509 (s), 1454 (s), 1426 (s), 1284 (s), 1254 (s), 1055 (s), 775 (m), 699 (m). **HRMS (nanochip-ESI/LTQ-Orbitrap)** m/z: [M + H]$^+$ Calcd for $C_{32}H_{39}N_2O_5^+$ 531.2853; Found 531.2838

Benzyl (2-((1-(2-hydroxy-5-methoxyphenyl)-2-phenylethyl)amino)-2-oxoethyl) carbamate (5.28d)

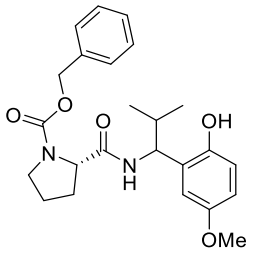


Following General Procedure 3 and starting with Cbz-Gly-Phe (**5.17c**) (107 mg, 0.300 mmol, 1.00 equiv) and 4-methoxyphenol (56 mg, 0.45 mmol, 1.50 equiv), **5.28d** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a colorless oil (81 mg, 0.19 mmol, 62%).

Rf (DCM/ethyl acetate 7:3): 0.31. **^{1}H NMR** (400 MHz, Chloroform-*d,* unresolved mixture of rotamers) δ 7.98-7.49 (br s, 1H, O*H*), 7.34 (m, 5H, Ar*H*), 7.19 (dq, *J* = 14.2, 7.0 Hz, 4H, Ar*H*), 7.10 (d, *J* = 6.7 Hz, 2H, Ar*H*), 6.78 (d, *J* = 8.7 Hz, 1H, Ar*H*), 6.68 (dd, *J* = 8.7, 2.9 Hz, 1H, Ar*H*), 6.64 (s, 1H, N*H* Phe), 5.40 (s, 1H, N*H* Gly), 5.28 (q, *J* = 8.48 Hz, 1H, NHC*H*Ar), 5.09 (s, 2H, OCH_2Ph), 3.69 (d, *J* = 7.47 Hz, 5H, OCH_3 and NHCH_2), 3.20-3.05 (m, 2H, NHCHCH_2Ph). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 169.8, 156.8, 153.5, 148.4, 137.7, 136.1, 129.2, 128.8, 128.6, 128.5, 128.3, 128.1, 126.8, 118.4, 114.0, 113.4, 67.5, 55.9, 51.1, 44. 6, 40.1. **IR** (ν_{max}, cm^{-1}) 3402 (m), 3065 (m), 2935 (m), 2836 (w),

1707 (s), 1655 (s), 1524 (s), 1455 (m), 1350 (m), 1260 (s), 1211 (s), 1154 (s), 1032 (m), 910 (s), 735 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{25}H_{26}N_2NaO_5^+$ 457.1734; Found 457.1738.

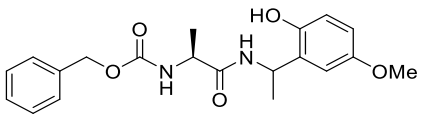
Benzyl (2S)-2-((1-(2-hydroxy-5-methoxyphenyl)-2-methylpropyl)carbamoyl)pyrrolidine-1-carboxylate (5.28e)



Following General Procedure 3 and starting with Cbz-Pro-Val (**5.17d**) (105 mg, 0.300 mmol, 1.00 equiv) and 4-methoxyphenol (56 mg, 0.45 mmol, 1.50 equiv), **5.28e** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a colorless oil (63 mg, 0.15 mmol, 49%).

Rf (DCM/ethyl acetate 7:3): 0.32. **^{1}H NMR** (400 MHz, Chloroform-*d*, mixture of rotamers and diastereomers) δ 8.08-7.51 (m, 1H, O*H*), 7.33 (m, 4H, Ar*H*), 7.22 (m, 1H, Ar*H*), 7.09-6.90 (m, 1H, N*H*), 6.78 (d, *J* = 3.7 Hz, 1H, Ar*H*), 6.72-6.59 (m, 2H, Ar*H*), 5.31-4.88 (m, 2H, OCH_2Ph), 4.60 (t, *J* = 8.8 Hz, 1H, NHC*H*Ar), 4.34 (m, 1H, NC*H*C(O)), 3.74 (m, 3H, OCH_3), 3.63-3.32 (m, 2H, CH_2NCbz), 2.38-1.55 (m, 5H, NCH$_2$CH_2CH_2CH and NHCHC*H*), 1.09-0.69 (m, 6H, CH(CH_3)$_2$). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 172.7, 172.6, 156.4, 155.6, 153.7, 153.5, 149.9, 148.9, 128.7, 128.4, 128.0, 116.2, 114.9, 113.7, 113.4, 67.7, 60.6, 55.9, 55.8, 47.6, 31.1, 24.7, 24.6, 20.4, 20.0. **IR** (ν_{max}, cm^{-1}) 3330 (m), 2958 (m), 2873 (m), 1685 (s), 1530 (s), 1508 (s), 1432 (s), 1356 (s), 1207 (s), 1119 (s), 1040 (m), 911 (s), 735 (s). **HRMS (ESI/QTOF)** m/z: [M + H]$^+$ Calcd for $C_{24}H_{31}N_2O_5^+$ 427.2227; Found 427.2229.

Benzyl ((2S)-1-((1-(2-hydroxy-5-methoxyphenyl)ethyl)amino)-1-oxopropan-2-yl) carbamate (5.28f)

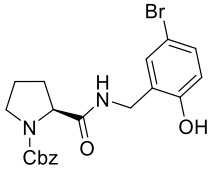


Following General Procedure 3 and starting with Cbz-Ala-Ala (**5.17b**) (88 mg, 0.30 mmol, 1.0 equiv) and 4-methoxyphenol (56 mg, 0.45 mmol, 1.50 equiv), **5.28f** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a colorless oil (71 mg, 0.19 mmol, 64%).

Rf (DCM/ethyl acetate 7:3): 0.34. **^{1}H NMR** (400 MHz, Chloroform-*d*, mixture of rotamers and diastereomers) δ 8.23 (br s, 1H, OH), 7.41-7.27 (m, 5H, Ar*H*), 7.07-6.90 (br s, 1H, ArCHN*H*), 6.82 (dd, *J* = 8.7, 4.7 Hz, 1H, Ar*H*), 6.71 (ddd, *J* = 11.6, 6.2, 3.2 Hz, 2H, Ar*H*), 5.50-5.28 (m, 1H, CbzN*H*), 5.17 (dt, *J* = 15.0, 7.2 Hz, 1H, ArC*H*NH), 5.08 (m, 2H, OCH_2Ph), 4.17 (m, 1H, CbzNHC*H*), 3.73 (m, 3H, OCH_3), 1.49 (dd, *J* = 16.9, 6.2 Hz, 3H, ArCHCH_3), 1.37-1.27 (m, 3H, CbzNHCHCH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 173.0, 172.9, 156.2, 156.0, 153.4, 148.5, 135.9, 129.4, 128.6, 128.3, 128.1, 118.6, 118.5, 113.7, 112.3, 67.2, 55.8, 50.4, 50.3, 44.1, 19.6, 18.6, 18.0. **IR**

(v_{max}, cm^{-1}) 3327 (m), 3079 (m), 2936 (m), 2834 (m), 1705 (s), 1651 (s), 1508 (s), 1453 (s), 1258 (s), 1207 (s), 1030 (m), 910 (m), 734 (s), 699 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{20}H_{24}N_2NaO_5^+$ 395.1577; Found 395.1582.

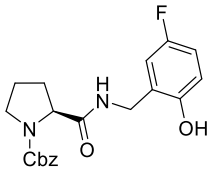
Benzyl (S)-2-((5-bromo-2-hydroxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (5.28g)



Following General Procedure 3 and starting with Cbz-Pro-Gly (**5.17e**) (92 mg, 0.30 mmol, 1.0 equiv) and 4-bromophenol (78 mg, 0.45 mmol, 1.5 equiv), **5.28g** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a white amorphous solid (61 mg, 0.14 mmol, 47%).

Rf (DCM/ethyl acetate 7:3): 0.5. **^{1}H NMR** (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 9.33 (br s, 1H, O*H* (major+minor)), 7.83 (br m, 0.7H, N*H* (major)), 7.44-7.27 (br m, 5H, Ar*H* (major+minor)), 7.19 (br m, 2H, Ar*H* (major+minor)), 7.04-6.91 (br m, 0.3H, N*H* (minor)), 6.80 (d, *J* = 8.6 Hz, 1H, Ar*H* (major+minor)), 5.09 (br m, 2H, OCH_2Ph (major+minor)), 4.44-4.05 (br m, 3H, NC*H*C(O), NHCH_2Ar (major+minor)), 3.46 (br m, 2H, CH_2NCbz (major+minor)), 2.13 (br m, 4H, $NCH_2CH_2CH_2CH$ (major+minor)). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 175.0, 174.4, 156.7, 155.2, 136.1, 133.4, 132.8, 128.8, 128.5, 128.1, 126.3, 120.0, 111.5, 67.8, 60.7, 60.2, 47.7, 47.4, 40.2, 28.1, 24.7, 23.9. **IR** (v_{max}, cm^{-1}) 3291 (m), 3055 (m), 2933 (w), 1682 (s), 1542 (s), 1481 (s), 1419 (s), 1355 (s), 1275 (s), 1173 (s), 1092 (m), 909 (s), 732 (s). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{20}H_{21}{}^{(79)}BrN_2NaO_4^+$ 455.0577; Found 455.0579.

Benzyl (S)-2-((5-fluoro-2-hydroxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (5.28h)

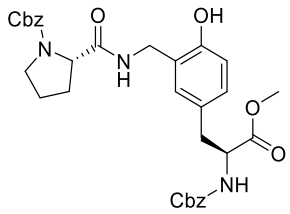


Following General Procedure 3 and starting with Cbz-Pro-Gly (**5.17e**) (92 mg, 0.30 mmol, 1.0 equiv) and 4-fluorophenol (50 mg, 0.45 mmol, 1.5 equiv), **5.28h** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (64 mg, 0.17 mmol, 57%).

Rf (DCM/ethyl acetate 7:3): 0.48. **^{1}H NMR** (400 MHz, Chloroform-*d*, 1:1 mixture of rotamers (R^1/R^2)) δ 9.02 (br s, 1H, O*H* (R^1+R^2)), 7.82 (br m, 0.5H, N*H* (R^1)), 7.30 (br m, 5H, Ar*H* (R^1+R^2)), 7.18 (br m, 0.5H, N*H* (R^2)), 6.87 (qd, *J* = 8.8, 5.5 Hz, 2H, Ar*H* (R^1+R^2)), 6.72 (br m, 1H, Ar*H* (R^1+R^2)), 5.23-4.91 (br s, 2H, OCH_2Ph (R^1+R^2)), 4.44-4.08 (br m, 3H, NC*H*C(O), NHCH_2Ar (R^1+R^2)), 3.46 (br m, 2H, CH_2NCbz (R^1+R^2)), 2.47-1.79 (br m, 4H, $NCH_2CH_2CH_2CH$ (R^1+R^2)). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 174.3, 156.7, 156.3 (d, *J* = 236.7 Hz), 151.9 (d, *J* = 2.0 Hz), 136.2, 128.8, 128.5, 128.1, 125.2, 119.0 (d, *J* = 7.9 Hz), 116.8 (d, *J* = 23.1 Hz), 116.4 (d, *J* = 23.2 Hz), 67.8, 60.2, 59.5, 47.3, 47.0, 40.3, 28.0, 24.7, 23.9, 22.8. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -124.92, -125.08. **IR** (v_{max}, cm^{-1}) 3314 (m), 2925 (m), 2853 (m), 1684 (s), 1536 (m), 1508 (s), 1444 (s), 1356 (s), 1256 (s),

1188 (s), 1122 (s), 909 (s), 733 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{20}H_{21}BrN_2NaO_4^+$ 455.0577; Found 455.0579.

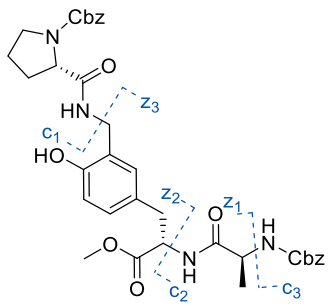
Benzyl(S)-2-((5-((S)-2-(((benzyloxy)carbonyl)amino)-3-methoxy-3-oxopropyl)-2-hydroxy benzyl)carbamoyl)pyrrolidine-1-carboxylate (5.28i)



Following General Procedure 3 and starting with Cbz-Pro-Gly (**5.17e**) (92 mg, 0.30 mmol, 1.0 equiv) and Cbz-Tyr-OMe (148 mg, 0.450 mmol, 1.50 equiv), **5.28i** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a white amorphous solid (65 mg, 0.11 mmol, 37%).

Rf (DCM/ethyl acetate 7:3): 0.32. **^{1}H NMR** (400 MHz, Chloroform-*d*, complex mixture of rotamers) δ 9.05 (br s, 1H, O*H*), 7.68 (br m, 0.5H, N*H* Gly), 7.43-7.27 (m, 10H, Ar*H*), 7.19 (br m, 0.5H, N*H* Gly), 6.91 (dd, *J* = 8.3, 2.2 Hz, 1H, Ar*H*), 6.81 (d, J = 8.2 Hz, 2H, Ar*H*), 5.10 (m, 5H, OCH_2Ph Pro+Tyr and N*H* Tyr), 4.59 (q, *J* = 5.9 Hz, 0.8H, NHC*H* Tyr), 4.46 (br s, 0.2H, NHC*H* Tyr), 4.33 (br m, 1H, NC*H*C(O) Pro), 4.25 (br m, 0.5H, NHCH_2Ar Gly), 4.14 (dt, *J* = 12.1, 6.1 Hz, 1.5H, NHCH_2Ar Gly), 3.71 (s, 3H, OCH_3 Tyr), 3.44 (br m, 2H, CH_2NCbz Pro), 2.99 (qd, *J* = 14.0, 5.9 Hz, 2H, NHCHCH_2 Tyr), 2.44-1.73 (br m, 4H, NCH$_2$CH_2CH_2CH Pro). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 174.1, 172.2, 156.6, 155.8, 155.1, 136.4, 136.2, 131.8, 130.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.0, 124.2, 118.2, 67.7, 67.1, 60.3, 55.1, 52.5, 47.3, 40.5, 37.4, 28.1, 24.7. **IR** (ν_{max}, cm^{-1}) 3317 (m), 3065 (m), 2949 (m), 1693 (s), 1533 (s), 1436 (s), 1355 (s), 1262 (s), 1213 (s), 1121 (m), 911 (s), 732 (s**). HRMS (ESI/QTOF)** m/z: [M + H]$^+$ Calcd for $C_{32}H_{36}N_3O_8^+$ 590.2497; Found 590.2490.

Benzyl (S)-2-((5-((S)-2-((S)-2-(((benzyloxy)carbonyl)amino)propanamido)-3-methoxy-3-oxopropyl)-2-hydroxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (5.28j)



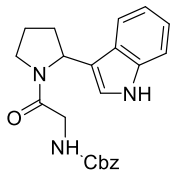
Following General Procedure 3 and starting with Cbz-Pro-Gly (**5.17e**) (92 mg, 0.30 mmol, 1.0 equiv) and Cbz-Ala-Tyr-OMe (180 mg, 0.450 mmol, 1.50 equiv), **5.28j** was obtained after column chromatography DCM to DCM/ethyl acetate 7:3 as a white amorphous solid (80 mg, 0.12 mmol, 40%).

Rf (DCM/ethyl acetate 7:3): 0.16. **^{1}H NMR** (400 MHz, Acetonitrile-d_3, complex mixture of rotamers) δ 9.07 (s, 0.3H, O*H*), 8.54 (s, 0.4H, O*H*), 7.74 (s, 1H, N*H* Gly), 7.42-7.23 (m, 9H, Ar*H*), 7.16 (d, *J* = 5.8 Hz, 1H, Ar*H*), 6.99-6.83 (m, 3H, Ar*H* and N*H* Tyr), 6.71 (d, *J* = 8.1 Hz,

1H, Ar*H*), 6.18-6.06 (m, 0.7H, N*H* Ala), 5.89 (s, 0.3H, N*H* Ala), 5.19-4.87 (m, 4H, OCH_2Ph Pro+Ala), 4.57 (ddt, *J* = 10.3, 7.9, 4.0 Hz, 1H, NHC*H* Tyr), 4.31-4.01 (m, 4H, NC*H* Pro, NHCH_2 Gly and NHC*H* Ala), 3.66 (d, *J* = 3.3 Hz, 3H, OCH_3 Tyr), 3.46 (m, 2H, NCH_2 Pro), 3.07-2.96 (m, 1H, NCHCH_2 Tyr), 2.85 (m, 1H, NCHCH_2 Tyr), 2.15-2.01 (m, 1H, $NCH_2CH_2CH_2CH$ Pro), 1.91-1.72 (m, 3H, $NCH_2CH_2CH_2CH$ Pro), 1.20 (dd, *J* = 16.9, 7.1 Hz, 3H, CH_3 Ala). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of rotamers, signals not fully resolved) δ 176.2, 175.5, 173.4, 173.3, 172.8, 172.7, 172.6, 157.1, 156.9, 156.2, 155.6, 155.5, 155.0, 152.2, 138.1, 138.0, 137.9, 133.0, 132.4, 131.5, 131.1, 130.5, 130.4, 130.1, 129.5, 129.4, 128.9, 128.7, 128.6, 128.4, 125.7, 120.6, 117.4, 117.3, 67.7, 67.5, 67.3, 67.1, 61.9, 61.4, 54.6, 54.4, 52.8, 51.5, 48.2, 47.8, 40.2, 39.6, 37.0, 36.9, 32.1, 30.9, 25.1, 24.3, 18.5, 18.3. **IR** (v_{max}, cm^{-1}) 3317 (s), 2954 (m), 1661 (s), 1535 (s), 1448 (s), 1358 (s), 1256 (s), 1213 (s), 1120 (m), 1059 (m), 910 (s), 773 (m), 735 (s), 698 (s). **HRMS (nanochip-ESI/LTQ-Orbitrap)** m/z: $[M + H]^+$ Calcd for $C_{35}H_{41}N_4O_9^+$ 661.2868; Found 661.2883. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 661.2883. Measured c and z ions are reported in the table below

	G	**Y**	**A**
N-terminal	1	2	3
c	249.12	-	-
C-terminal	3	2	1
z	413.17	-	510.22

Benzyl (2-(2-(1H-indol-3-yl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.33a)

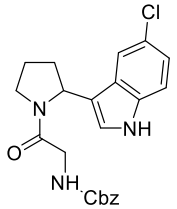


Following General Procedure 4 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and 1H-indole (36 mg, 0.31 mmol, 1.02 equiv), **5.33a** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow amorphous solid (75 mg, 0.20 mmol, 66%).

Rf (DCM/ethyl acetate 7:3): 0.25. **^{1}H NMR** (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers(major/minor)) δ 8.42 (s, 0.3H, N*H* indole (minor)), 8.35 (s, 0.7H, N*H* indole (major)), 7.58 (d, *J* = 7.9 Hz, 0.3H, Ar*H* (minor)), 7.50 (d, *J* = 7.9 Hz, 0.7H, Ar*H* (major)), 7.39-7.27 (m, 6H, Ar*H* (major+minor)), 7.24-7.17 (m, 1H, Ar*H* (major+minor)), 7.17-7.09 (m, 1H, Ar*H* (major+minor)), 6.88-6.80 (m, 1H, Ar*H* (major+minor)), 5.80 (s, 0.3H, N*H* Gly (minor)), 5.66 (s, 0.7H, N*H* Gly (major)), 5.59 (dd, *J* = 7.1, 2.7 Hz, 0.3H, C(O)NC*H* (minor)), 5.23-5.14 (m, 0.7H, C(O)NC*H* (major)), 5.11 (s, 0.6H, OCH_2Ph (minor)), 5.04 (s, 1.4H, OCH_2Ph (major)), 4.04 (dd, *J* = 15.8, 4.6 Hz, 1.3H, C(O)CH_2NHCbz (major+minor)), 3.81 (dt, *J* = 12.0, 5.8 Hz, 0.7H, C(O)NCH_2 (major)), 3.69 (m, 1.7H, C(O)CH_2NHCbz (major) and C(O)NCH_2 (major+minor)), 3.53 (q, *J* = 8.1 Hz, 0.3H, C(O)NCH_2 (minor)), 2.36-1.85 (m, 4H, $NCH_2CH_2CH_2CH$ (major+minor)).**^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.7, 166.7, 156.5, 156.3, 137.0, 136.6, 128.6, 128.2, 128.1, 125.3, 124.8, 122.7, 122.2, 121.4, 121.3, 120.0, 119.6, 119.0, 118.7, 116.8, 116.7, 111.8, 111.6, 67.0, 66.9, 55.0, 54.9, 46.9, 46.0, 45.9, 43.7, 43.4, 34.5, 32.1, 24.2, 22.2. **IR** (v_{max}, cm^{-1}) 3311 (m), 3046 (w),

2977 (m), 2876 (w), 1710 (s), 1638 (s), 1521 (m), 1455 (s), 1252 (s), 1165 (m), 1055 (m), 910 (m), 737 (s) **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{22}H_{23}N_3NaO_3^+$ 400.1632; Found 400.1629.

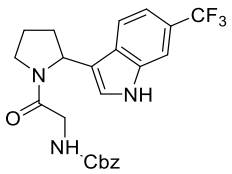
Benzyl (2-(2-(5-chloro-1H-indol-3-yl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.33b)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and 5-Chloro-1H-indole (46 mg, 0.31 mmol, 1.02 equiv), **5.33b** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (82 mg, 0.20 mmol, 66%).

Rf (DCM/ethyl acetate 7:3): 0.36. **^{1}H NMR** (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers(major/minor)) δ 8.72 (s, 0.4H, N*H* indole (minor)), 8.59 (s, 0.6H, N*H* indole (major)), 7.51 (d, *J* = 1.7 Hz, 0.4H, Ar*H* (minor)), 7.47-7.41 (m, 0.6H, Ar*H* (major)), 7.36-7.27 (m, 5H, Ar*H* (major+minor)), 7.22 (dd, *J* = 14.1, 8.7 Hz, 1H, Ar*H* (major+minor)), 7.11 (td, *J* = 8.7, 8.0, 1.7 Hz, 1H, Ar*H* (major+minor)), 6.82 (d, *J* = 1.9 Hz, 0.4H, Ar*H* (minor)), 6.73 (d, *J* = 2.4 Hz, 0.6H, Ar*H* (minor)), 5.75 (s, 0.4H, N*H* Gly (minor)), 5.68 (s, 0.6H, N*H* Gly (major)), 5.53-5.47 (m, 0.4H, C(O)NC*H* (minor)), 5.15-4.99 (m, 2.6H, C(O)NC*H* (major) and OCH_2Ph (major+minor)), 4.13-3.93 (m, 1.4H, C(O)CH_2NHCbz (major+minor)), 3.81-3.68 (m, 1.6H, C(O)NCH_2 (major+minor)), 3.64 (dd, *J* = 17.4, 4.5 Hz, 0.6H, C(O)CH_2NHCbz (major)), 3.53 (q, *J* = 7.8 Hz, 0.4H, C(O)NCH_2 (minor)), 2.35-2.16 (m, 1H, NCH$_2$CH_2CH_2CH (major+minor)), 2.06 (dtd, *J* = 17.1, 8.2, 3.7 Hz, 2H, NCH$_2$CH_2CH_2CH (major+minor)), 1.96-1.84 (m, 1H, NCH$_2$CH_2CH_2CH (major+minor)). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.6, 166.9, 156.4, 156.3, 136.4, 135.3, 135.2, 128.5, 128.4, 128.1, 128.1, 128.0, 127.9, 126.1, 125.6, 125.5, 125.1, 122.9, 122.7, 122.3, 118.2, 118.0, 116.3, 116.2, 112.8, 112.6, 67.0, 66.9, 54.8, 54.6, 46.8, 46.0, 43.6, 43.3, 34.4, 32.1, 24.0, 22.1. **IR** (ν_{max}, cm^{-1}) 3308 (m), 2927 (m), 1710 (s), 1638 (s), 1520 (m), 1454 (s), 1254 (s), 1173 (m), 1055 (m), 909 (s), 733 (s). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{22}H_{22}ClN_3NaO_3^+$ 434.1242; Found 434.1253.

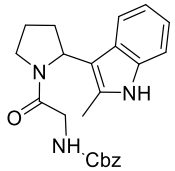
Benzyl (2-oxo-2-(2-(6-(trifluoromethyl)-1H-indol-3-yl)pyrrolidin-1-yl)ethyl)carbamate (5.33c)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and 6-trifluoromethyl-1H-indole (57 mg, 0.31 mmol, 1.02 equiv), **5.33c** was obtained after column chromatography DCM to DCM/ethyl acetate 7:3 as a pale yellow oil (67 mg, 0.15 mmol, 50%).

Rf (DCM/ethyl acetate 7:3): 0.35. **^{1}H NMR** (400 MHz, Acetonitrile-*d*$_3$, 1:1 mixture of rotamers, (R^1/R^2)) δ 9.69 (s, 0.5H, N*H* indole (R^1)), 9.52 (s, 0.5H, N*H* indole (R^2)), 7.79-7.73 (m, 1H, Ar*H* (R^1+R^2)), 7.73-7.66 (m, 1H, Ar*H* (R^1+R^2)), 7.39-7.26 (m, 5H, Ar*H* (R^1+R^2)), 7.26-7.21 (m, 1H, Ar*H* (R^1+R^2)), 7.19-7.09 (m, 1H, Ar*H* (R^1+R^2)), 5.84 (s, 0.5H, N*H* Gly (R^1)), 5.72 (s, 0.5H, N*H* Gly (R^2)), 5.47-5.39 (m, 0.5H, C(O)NC*H* (R^1)), 5.29 (d, *J* = 5.4 Hz, 0.5H, C(O)NC*H* (R^2)), 5.05 (s, 1H, OC*H*$_2$Ph (R^1)), 4.98 (s, 1H, OC*H*$_2$Ph (R^2)), 3.96 (d, *J* = 5.3 Hz, 1H, C(O)C*H*$_2$NHCbz (R^1+R^2)), 3.89 (dd, *J* = 17.2, 5.3 Hz, 0.5H, NC(O)C*H*$_2$NHCbz (R^1)), 3.72 (dt, *J* = 11.7, 6.3 Hz, 1H, C(O)NC*H*$_2$ (R^1+R^2)), 3.57 (m, 1H, C(O)NC*H*$_2$ (R^1+R^2)), 3.44 (dd, *J* = 17.0, 5.5 Hz, 0.5H, C(O)C*H*$_2$NHCbz (R^2)), 2.39-2.13 (m, 2H, NCH$_2$C*H*$_2$C*H*$_2$CH (R^1+R^2)), 2.03-1.97 (m, 1H, NCH$_2$C*H*$_2$C*H*$_2$CH (R^1+R^2)), 1.91-1.82 (m, 1H, NCH$_2$C*H*$_2$C*H*$_2$CH (R^1+R^2)). **^{13}C NMR** (101 MHz, Acetonitrile-*d*$_3$, mixture of rotamers, signals not fully resolved) δ 168.5, 167.8, 157.3 (d, *J* = 12.25 Hz), 138.2, 136.7, 136.4, 129.4, 129.3, 128.8, 128.7, 128.3, 127.8, 126.3, 125.9, 125.1, 124.3, 124.0, 123.8, 123.5, 120.28 (d, *J* = 13.93 Hz), 118.8, 116.4 (dd, *J* = 36.31, 3.45 Hz), 110.12 (dd, *J* = 28.22, 4.43 Hz), 67.1, 67.0, 55.0, 54.8, 47.4, 46.6, 44.1, 43.8, 35.5, 33.0, 30.3, 24.7, 22.8. **IR** (v_{max}, cm^{-1}) 3365 (s), 3032 (m), 2930 (m), 1710 (s), 1642 (s), 1509 (s), 1454 (s), 1336 (s), 1257 (s), 1157 (s), 1111 (s), 1053 (s), 961 (m), 878 (m), 816 (s), 698 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{23}H_{22}F_3N_3NaO_3^+$ 468.1505; Found 468.1513.

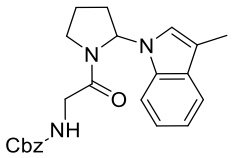
Benzyl (2-(2-(2-methyl-1H-indol-3-yl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.33d)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and 2-Methyl-1H-indole (40 mg, 0.31 mmol, 1.02 equiv), **5.33d** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a brown amorphous solid (58 mg, 0.15 mmol, 49%).

Rf (DCM/ethyl acetate 7:3): 0.36. **^{1}H NMR** (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 8.25 (s, 0.3H, N*H* indole (minor)), 8.18 (s, 0.7H, N*H* indole (major)), 7.34-7.22 (m, 7H, Ar*H* (major+minor)), 7.16-7.08 (m, 1H, Ar*H* (major+minor)), 7.04 (dd, *J* = 9.3, 6.6 Hz, 1H, Ar*H* (major+minor)), 5.65 (s, 1H, N*H* Gly (major+minor)), 5.32 (t, *J* = 6.9 Hz, 0.3H, C(O)NC*H* (minor)), 5.10-4.98 (m, 2.7H, C(O)NC*H* (major) and OC*H*$_2$Ph (major+minor)), 4.10 (dd, *J* = 17.0, 4.5 Hz, 0.3H, C(O)C*H*$_2$NHCbz (minor)), 4.00-3.90 (m, 1.7H, C(O)C*H*$_2$NHCbz (major+minor) and C(O)NC*H*$_2$ (major)), 3.79 (dt, *J* = 12.8, 7.2 Hz, 1H, C(O)NC*H*$_2$ (major+minor)), 3.69 (td, *J* = 10.1, 8.0, 5.6 Hz, 0.3H, C(O)NC*H*$_2$ (minor)), 3.30 (dd, *J* = 17.3, 3.2 Hz, 0.7H, C(O)C*H*$_2$NHCbz (major)), 2.40-2.28 (m, 4H, C*H*$_3$ and NCH$_2$C*H*$_2$C*H*$_2$CH (major+minor)), 2.22-1.84 (m, 3H, NCH$_2$C*H*$_2$C*H*$_2$CH (major+minor)).**^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.8, 166.4, 156.3, 156.2, 136.6, 135.5, 131.9, 131.3, 128.6, 128.1, 128.0, 126.2, 125.7, 121.6, 120.9, 119.9, 119.4, 118.1, 117.7, 111.6, 111.1, 110.9, 66.9, 66.8, 55.1, 54.8, 47.8, 47.1, 43.7, 43.3, 35.6, 32.7, 25.4, 23.7, 12.0, 11.8. **IR** (v_{max}, cm^{-1}) 3393 (m), 3299 (m), 3060 (m), 2965 (m), 2875 (m), 1710 (s), 1637 (s), 1510 (m), 1459 (s), 1237 (m), 910 (m), 737 (s). **HRMS (ESI/QTOF)** m/z: [M + H]$^+$ Calcd for $C_{23}H_{26}N_3O_3^+$ 392.1969; Found 392.1977

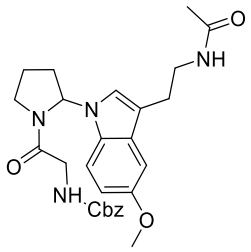
Benzyl (2-(2-(3-methyl-1H-indol-1-yl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5.33e)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and 3-Methyl-1H-indole (40 mg, 0.31 mmol, 1.02 equiv), **5.33e** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a white amorphous solid (50 mg, 0.13 mmol, 43%).

Rf (DCM/ethyl acetate 7:3): 0.58. **^{1}H NMR** (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers (major/minor)) δ 7.55 (dd, *J* = 17.6, 7.8 Hz, 1H, Ar*H* (major+minor)), 7.43 (d, *J* = 8.2 Hz, 0.4H, Ar*H* (minor)), 7.31 (*t*, J = 7.3 Hz, 6H, Ar*H* (major+minor)), 7.24-7.08 (m, 1.6H, Ar*H* (major+minor)), 6.76 (d, *J* = 11.0 Hz, 1H, Ar*H* (major+minor)), 6.52-6.45 (m, 0.4H, C(O)NC*H* (minor)), 6.21 (d, *J* = 5.2 Hz, 0.6H, C(O)NC*H* (major)), 5.65 (br s, 0.4H, N*H* (minor)), 5.43 (br s, 0.6H, N*H* (major)), 5.18-4.93 (m, 2H, OCH_2Ph (major+minor)), 4.13 (ddt, *J* = 13.9, 10.6, 5.0 Hz, 1H, C(O)CH_2NHCbz (major+minor)), 3.96 (ddd, *J* = 16.3, 10.9, 4.2 Hz, 1H, C(O)CH_2NHCbz (minor) and C(O)NCH_2 (major)), 3.84 (d, *J* = 10.2 Hz, 0.4H, C(O)NCH_2 (minor)), 3.73 (dt, *J* = 11.6, 8.1 Hz, 0.6H, C(O)NCH_2 (major)), 3.60 (dt, *J* = 18.4, 9.4 Hz, 0.4H, C(O)NCH_2 (minor)), 3.20 (dd, *J* = 17.4, 3.3 Hz, 0.6H,NC(O)CH_2NHCbz (major)), 2.47-2.23 (m, 4H, CH_3 and NCH$_2$CH_2CH_2CH (major+minor)), 2.23-1.96 (m, 3H, NCH$_2$CH_2CH_2CH (major+minor)).**^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 168.8, 167.8, 156.4, 156.3, 136.5, 134.9, 129.7, 129.2, 128.7, 128.6, 128.2, 128.1, 128.0, 122.6, 122.0, 121.5, 121.1, 119.9, 119.7, 119.3, 119.2, 112.8, 111.8, 109.8, 109.2, 68.7, 68.1, 67.0, 47.2, 46.1, 43.8, 43.1, 34.8, 32.3, 23.9, 21.7, 9.9. **IR** (v_{max}, cm^{-1}) 3415 (m), 3053 (m), 2935 (w), 2145 (w), 1714 (s), 1662 (s), 1510 (m), 1432 (m), 1350 (m), 1193 (m), 985 (m), 910 (s), 736 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{23}H_{25}N_3NaO_3^+$ 414.1788; Found 414.1797.

Benzyl (2-(2-(3-(2-acetamidoethyl)-5-methoxy-1H-indol-1-yl)pyrrolidin-1-yl)-2-oxoethyl) carbamate (5.33f)

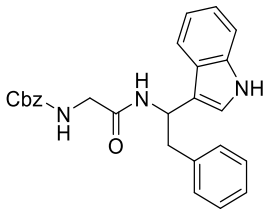


Following General Procedure 4 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and melatonin (71 mg, 0.31 mmol, 1.02 equiv), **5.33f** was obtained after column chromatography DCM to ethyl acetate as a colorless oil (95 mg, 0.19 mmol, 64% yield).

Rf (DCM/ethyl acetate 7:3): 0.13. **^{1}H NMR** (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 7.38-7.27 (m, 5.3H, Ar*H* (major+minor)), 7.19 (d, *J* = 8.9 Hz, 0.7H, Ar*H* (major)), 7.03 (d, *J* = 2.3 Hz, 0.7H, Ar*H* (major)), 6.98 (d, *J* = 2.3 Hz, 0.3H, Ar*H* (minor)), 6.90 (dt, *J* = 8.8, 2.9 Hz, 1H, Ar*H* (major+minor)), 6.86 (s, 0.3H, Ar*H* (minor)), 6.82 (s, 0.7H, Ar*H* (major)), 6.40 (d, *J* = 5.3 Hz, 0.3H, C(O)NC*H* (minor)), 6.28 (s, 0.7H, AcN*H* (major)), 6.08 (dd, *J* = 6.0, 2.8 Hz, 0.7H, C(O)NC*H* (major)), 5.65 (s, 0.6H, AcN*H* and CbzN*H* (minor)), 5.48 (s, 0.7H, CbzN*H* (major)), 5.09 (s, 0.6H, OCH_2Ph (minor)), 5.00 (d, *J* = 2.8 Hz, 1.4H, OCH_2Ph

(major)), 4.15-3.89 (m, 1.7H, C(O)C*H*$_2$NHCbz (major+minor) and C(O)NC*H*$_2$ (major)), 3.89-3.70 (m, 4.3H, OC*H*$_3$ (major+minor), C(O)C*H*$_2$NHCbz (minor) and C(O)NC*H*$_2$ (major+minor)), 3.54 (m, 2.3H, C(O)NC*H*$_2$ (minor) and C*H*$_2$NHAc (major+minor)), 3.17 (dd, *J* = 17.4, 5.6 Hz, 0.7H, C(O)C*H*$_2$NHCbz (major)), 2.90 (dt, *J* = 13.9, 7.0 Hz, 2H, C*H*$_2$CH$_2$NHAc (major+minor)), 2.47-1.97 (m, 4H, NCH$_2$C*H*$_2$C*H*$_2$CH (major+minor)), 1.88 (d, *J* = 14.7 Hz, 3H, NHC(O)C*H*$_3$ (major+minor)).**^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 170.7, 170.3, 168.6, 168.0, 156.5, 154.6, 154.3, 136.4, 136.2, 130.9, 129.8, 129.6, 128.8, 128.6, 128.3, 128.2, 128.1, 122.9, 122.6, 114.1, 113.0, 112.3, 112.2, 110.8, 110.2, 101.4, 101.1, 69.2, 68.5, 67.1, 56.0, 47.2, 46.1, 43.8, 43.0, 40.2, 39.5, 34.7, 32.2, 25.5, 25.0, 23.9, 23.5, 23.3, 21.8**. IR** (ν_{max}, cm^{-1}) 3330 (m), 3033 (m), 2946 (m), 2833 (m), 1715 (s), 1654 (s), 1542 (s), 1484 (s), 1453 (s), 1220 (s), 1050 (m), 909 (s), 733 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{27}H_{32}N_4NaO_5^+$ 515.2265; Found 515.2276

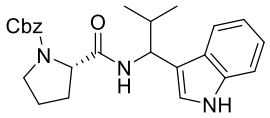
Benzyl (2-((1-(1H-indol-3-yl)-2-phenylethyl)amino)-2-oxoethyl)carbamate (5.33g)



Following General Procedure 4 and starting with Cbz-Gly-Phe (**5.17c**) (107 mg, 0.30 mmol, 1.0 equiv) and 1H-indole (36 mg, 0.31 mmol, 1.02 equiv), **5.33g** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a red amorphous solid (74 mg, 0.17 mmol, 58%).

Rf (DCM/ethyl acetate 7:3): 0.32. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.12-7.93 (m, 1H, N*H* indole), 7.64 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.34 (d, *J* = 7.9 Hz, 6H, Ar*H*), 7.24-7.06 (m, 7H, Ar*H*), 6.93-6.88 (m, 1H, Ar*H*), 6.45-6.19 (m, 1H, N*H* Phe), 5.59 (q, *J* = 7.2 Hz, 1H, NHC*H* Phe), 5.45-5.28 (m, 1H, N*H* Gly), 5.08 (s, 2H, OC*H*$_2$Ph), 3.74 (t, *J* = 6.9 Hz, 2H, NHC*H*$_2$ Gly), 3.26 (tt, *J* = 13.6, 6.7 Hz, 2H, NHCHC*H*$_2$ Phe). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 168.1, 156.7, 138.0, 136.6, 136.2, 129.4, 128.7, 128.4, 128.3, 128.2, 126.6, 125.9, 122.6, 122.1, 120.1, 119.3, 116.0, 111.6, 67.3, 48.1, 44.8, 41.1. **IR** (ν_{max}, cm^{-1}) 3344 (m), 3032 (m), 2946 (m), 1712 (s), 1661 (s), 1521 (s), 1455 (m), 1339 (m), 1259 (m), 1155 (m), 1075 (m), 910 (s), 740 (s), 699 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{26}H_{25}N_3NaO_3^+$ 450.1788; Found 450.1792

Benzyl (2S)-2-((1-(1H-indol-3-yl)-2-methylpropyl)carbamoyl)pyrrolidine-1-carboxylate (5.33h)

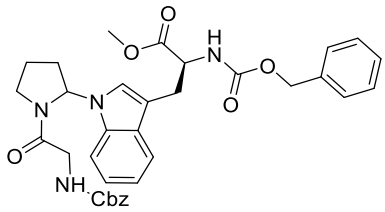


Following General Procedure 4 and starting with Cbz-Pro-Val (**5.17d**) (105 mg, 0.30 mmol, 1.0 equiv) and 1H-indole (**x**) (36 mg, 0.31 mmol, 1.02 equiv), **5.33h** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a red amorphous solid (81 mg, 0.19 mmol, 64%).

Rf (DCM/ethyl acetate 7:3): 0.29. **^{1}H NMR** (400 MHz, Chloroform-*d*, complex mixture of diastereomers and rotamers) δ 8.22-7.85 (m, 1H, N*H* indole), 7.62-7.41 (m, 1H, Ar*H*), 7.26 (m,

5H, Ar*H*), 7.14-6.74 (m, 4H, Ar*H*), 6.24 (m, 0.4H, N*H* Val not fully resolved), 5.21-4.86 (m, 3H, OCH_2Ph and NHC*H* Val), 4.47-4.19 (m, 1H, CbzNC*H* Pro), 3.56-3.18 (m, 2H, CbzNCH_2 Pro), 2.42-1.94 (m, 3H, NHCHC*H* Val and NCH$_2$CH_2CH_2CH Pro), 1.89-1.63 (m, 2H, NCH$_2$CH_2CH_2CH Pro), 0.97-0.69 (m, 6H, CH_3 Val). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 171.2, 170.7, 156.4, 155.7, 136.6, 136.5, 128.7, 128.3, 126.3, 122.1, 121.9, 119.5, 116.7, 116.2, 111.4, 67.4, 61.4, 60.8, 52.5, 47.8, 47.1, 32.8, 31.2, 28.1, 24.7, 23.6, 20.2, 19.0, 18.7. **IR** (ν_{max}, cm^{-1}) 3314 (m), 2962 (m), 2910 (m), 1690 (s), 1660 (s), 1520 (m), 1418 (s), 1356 (s), 1210 (m), 1118 (m), 909 (s), 735 (s), 698 (m). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{25}H_{29}N_3NaO_3^+$ 442.2101; Found 442.2107.

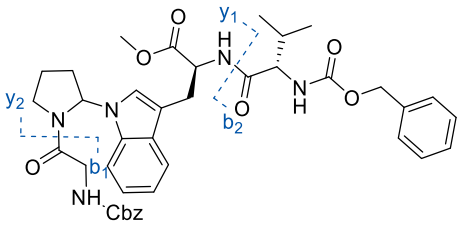
Methyl Nα-((benzyloxy)carbonyl)-1-(1-(((benzyloxy)carbonyl)glycyl)pyrrolidin-2-yl)-L-tryptophanate (5.33i)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and Z-Trp-OMe (108 mg, 0.306 mmol, 1.02 equiv), **5.33i** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a white amorphous solid (105 mg, 0.171 mmol, 57% yield).

Rf (DCM/ethyl acetate 7:3): 0.58. **^{1}H NMR** (400 MHz, Chloroform-*d*, complex mixture of diastereomers and rotamers) δ 7.57-7.39 (m, 2H, Ar*H*), 7.38-7.27 (m, 10H, Ar*H*), 7.21-7.06 (m, 2H, Ar*H*), 6.83-6.66 (m, 1H, Ar*H*), 6.45 (d, *J* = 6.2 Hz, 0.4H, C(O)NC*H* Pro), 6.17 (t, *J* = 5.5 Hz, 0.6H, C(O)NC*H* Pro), 5.66-5.22 (m, 2H, N*H* Gly+Trp), 5.05 (m, 4H, OCH_2Ph Gly+Trp), 4.76-4.64 (m, 1H, NHC*H* Trp), 4.18-3.86 (m, 2H, C(O)NCH_2 Pro and NHCH_2 Gly), 3.79-3.50 (m, 4H, OCH_3 Trp and C(O)NCH_2 Pro), 3.41-2.96 (m, 3H, NHCH_2 Gly and NHCHCH_2 Trp), 2.46-1.88 (m, 4H, NCH$_2$CH_2CH_2CH Pro). **^{13}C NMR** (101 MHz, Chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 172.5, 172.4, 172.2, 168.9, 168.8, 167.8, 156.5, 156.4, 155.9, 155.8, 136.5, 136.2, 135.5, 134.7, 129.2, 128.6, 128.5, 128.2, 128.1, 122.9, 122.8, 122.4, 122.2, 120.6, 119.9, 119.8, 119.6, 119.1, 118.8, 111.3, 110.9, 110.1, 109.8, 109.4, 68.7, 68.3, 67.0, 67.0, 55.1, 54.8, 54.6, 52.6, 52.5, 47.2, 46.1, 43.8, 43.0, 34.8, 32.2, 28.3, 28.1, 23.8, 21.5. **IR** (ν_{max}, cm^{-1}) 3411 (m), 3280 (m), 3061 (m), 2937 (m), 1716 (s), 1667 (s), 1517 (m), 1437 (m), 1344 (m), 1211 (s), 1060 (m), 911 (m), 738 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{34}H_{36}N_4NaO_7^+$ 635.2476; Found 635.2491.

Methyl Nα-(((benzyloxy)carbonyl)-L-valyl)-1-(1-(((benzyloxy)carbonyl)glycyl)pyrrolidin-2-yl)-L-tryptophanate (5.33j)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv) and Z-Val-Trp-OMe (138 mg, 0.306 mmol, 1.02 equiv), **5.33j** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a white amorphous solid (106 mg, 0.149 mmol, 50% yield).

Rf (DCM/ethyl acetate 7:3): 0.48. **^{1}H NMR** (400 MHz, Acetonitrile-d_3, complex mixture of diastereomers and rotamers) δ 7.57-7.42 (m, 2H, Ar*H*), 7.38-7.25 (m, 10H, Ar*H*), 7.18 (dt, *J* = 8.1, 4.9 Hz, 1H, Ar*H*), 7.09 (dt, *J* = 15.1, 7.5 Hz, 2H, Ar*H*), 7.04-6.98 (m, 0.5H, N*H* Trp), 6.82 (dd, *J* = 16.7, 7.4 Hz, 0.5H, N*H* Trp), 6.40-6.25 (m, 1H, C(O)NC*H* Pro), 5.91 (d, *J* = 9.0 Hz, 2H, N*H* Gly+Val), 5.12-4.95 (m, 4H, OCH_2Ph Gly+Val), 4.77-4.64 (m, 1H, NHC*H* Trp), 4.10-3.79 (m, 4H, NHCH_2 Gly, NHCH_2 Val and 1H C(O)NCH_2 Pro), 3.68-3.50 (m, 4H, OCH_3 Trp and 1H C(O)NCH_2 Pro), 3.35-2.77 (m, 2H, NHCHCH_2 Trp), 2.48-2.19 (m, 2H, NCH$_2$CH_2CH_2CH Pro), 2.13-2.01 (m, 3H, NCH$_2$CH_2CH_2CH Pro and NHCHC*H* Val), 0.94-0.72 (m, 6H, CH_3 Val). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of diastereomers and rotamers, signals not fully resolved) δ 173.1, 173.0, 172.9, 172.8, 172.3, 172.1, 169.6, 169.4, 169.2, 157.6, 157.4, 157.3, 157.0, 138.2, 138.0, 136.2, 135.8, 129.4, 129.3, 129.0, 128.8, 128.7, 128.6, 128.5, 125.1, 124.9, 124.7, 124.4, 123.2, 123.1, 122.8, 122.6, 122.5, 120.8, 120.7, 120.2, 120.1, 120.0, 119.7, 119.6, 119.1, 112.1, 111.8, 111.6, 111.1, 111.0, 110.7, 110.5, 110.0, 109.8, 106.9, 69.5, 69.3, 69.1, 67.2, 67.1, 66.9, 61.4, 61.1, 60.9, 60.3, 56.1, 54.6, 54.2, 53.9, 53.8, 53.5, 53.4, 52.7, 47.7, 47.6, 46.9, 46.8, 44.2, 43.5, 43.4, 35.4, 35.2, 33.4, 33.1, 33.0, 32.6, 32.2, 31.8, 31.7, 28.1, 28.0, 27.9, 27.8, 26.6, 25.7, 25.2, 24.3, 22.3, 22.2, 19.6, 19.5, 19.4, 19.2, 18.3, 18.1, 18.0, 17.8. **IR** (ν_{max}, cm^{-1}) 3307 (m), 2963 (m), 2892 (m), 1714 (s), 1660 (s), 1524 (s), 1438 (s), 1324 (m), 1236 (s), 1055 (m), 910 (m), 735 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{39}H_{45}N_5NaO_8^+$ 734.3160; Found 734.3167. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 734.3167. Measured b and y ions are reported in the table below

	P	**W**
N-terminal	1	2
b	-	-
C-terminal	2	1
y	521.28	479.23

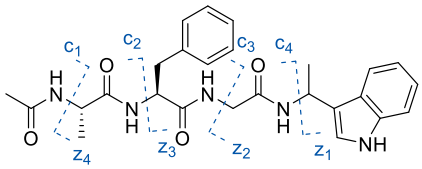
7.4.5. Scope on Tetrapeptides

General procedure 5 for the decarboxylative arylation of Tetrapeptides

A 5 mL test tube was charged under Ar with tetrapeptide (5.0 µmol, 1.0 equiv), AcO-BX (4.6 mg, 15 µmol, 3.0 equiv), Ru(bpy)$_3$Cl$_2$ (1.1 mg, 1.5 µmol, 0.30 equiv) and 1.0 mL of degassed MeCN. The solution was degassed by argon sparging for 5 mins. 0.20 mL of the solution were placed into a sealed vial under argon. The reaction mixture was irradiated using blue light LEDs at rt overnight. Then a 41 mM solution of 1H-indole in MeCN (50 µL, 2.04 µmol, 2.04 equiv) and 2,2,2-trifluoroacetic acid (1.2 µL, 15 µmol, 15 equiv) were added. The reaction was let stirring for 1h. At the end of the reaction, the crude was diluted with 3x the volume of MeCN and injected in RP-HPLC. The yields were determined as the ratio of Aprod/Atotal where Aprod = area in mAU of the product peak (blue arrow in HPLC traces) and Atotal = area in

mAU of all peptide products (product, starting material, and side-products if present (red arrow in HPLC traces)). Reported result is an average of 3 independent trials.

(2S)-N-(2-((1-(1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamide (5.36a)



Following general procedure 5, Ac-Ala-Phe-Gly-Ala-OH (**5.47a**) afforded **5.36a** in more than 95% (66% with calibration curve) yield as a mixture of diastereomers (retention time 11.299 min).

Reaction performed on 20 µmol scale afforded **5.36a** after purification by preparative RP-HPLC (gradient water-95% acetonitrile in 20 min) as a brown fluffy solid (1.7 mg, 3.6 µmol, 18%).

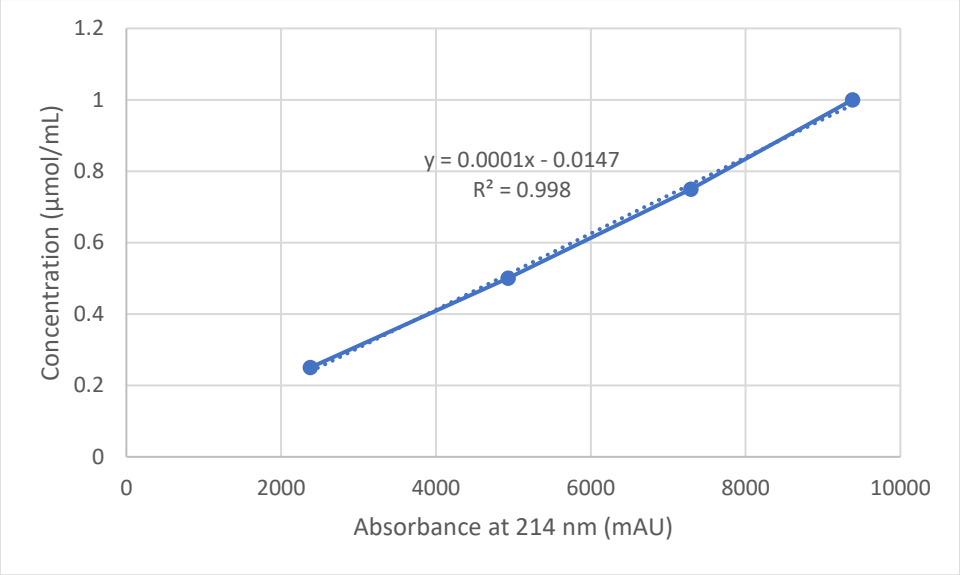
^{1}H NMR (400 MHz, Acetonitrile-d_3, complex mixture of diastereomers and rotamers) δ 9.21-9.01 (m, 1H, N*H* indole), 7.66-7.56 (m, 1H, Ar*H*), 7.42-7.35 (m, 1H, Ar*H*), 7.34-7.16 (m, 7H, Ar*H*+N*H* Gly), 7.13 (dddd, *J* = 8.2, 7.1, 4.7, 1.1 Hz, 1H, Ar*H*), 7.08-6.91 (m, 3H, Ar*H*+N*H* Ala+Phe), 6.80-6.64 (m, 1H, N*H* Ala), 5.41-5.29 (m, 1H,NHC*H*indole), 4.33 (dddt, *J* = 9.2, 7.1, 5.0, 2.2 Hz, 1H, NHC*H* Phe), 4.10-4.02 (m, 0.5H, AcNHC*H* Ala), 4.01-3.93 (m, 0.5H, AcNHC*H* Ala), 3.77-3.68 (m, 2H, NHCH_2 Gly), 3.17 (dt, *J* = 14.1, 5.0 Hz, 1H, NHCHCH_2Ph Phe), 2.94 (dt, *J* = 10.3, 5.3 Hz, 1H, NHCHCH_2Ph Phe), 1.84 (s, 1.5H C(O)CH_3 Ac-Ala), 1.77 (s, 1.5H, C(O)CH_3 Ac-Ala), 1.55 (dd, *J* = 6.9, 4.8 Hz, 3H, CH_3 Ala-indole), 1.15 (dd, *J* = 7.2, 1.5 Hz, 1.5H, CH_3 Ac-Ala), 1.08 (d, *J* = 7.2 Hz, 1.5H, CH_3 Ac-Ala). **^{13}C NMR** (101 MHz, Acetonitrile-d_3, mixture of diastereomers and rotamers, signals not fully resolved) δ 174.3, 174.2, 172.2, 172.2, 168.8, 168.7, 138.6, 138.5, 137.7, 137.6, 130.2, 129.3, 127.6, 122.7, 122.6, 122.6, 120.1, 120.1, 120.0, 120.0, 112.3, 56.2, 56.1, 50.9, 50.9, 43.7, 43.6, 42.6, 42.4, 37.2, 37.1, 22.9, 22.7, 21.6, 21.5, 17.1, 17.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{26}H_{32}N_5O_4^+$ 478.2449; Found 478.2467. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 478.2467. Measured c and z ions are reported in the table below

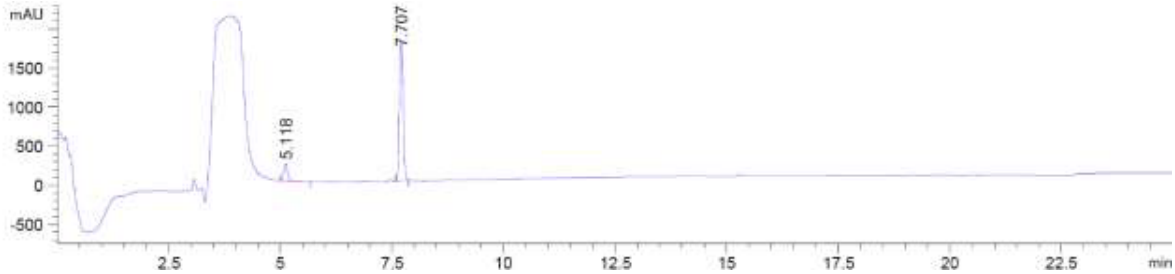
	A	**F**	**G**	**A***
N-terminal	1	2	3	4
c	-	-	-	335.17

C-terminal	4	3	2	1
z	-	-	-	144.08

Calibration with arylated **5.36a** was achieved through the preparation of several samples of different concentrations and their analysis on RP HPLC. The following linear regression was obtained y = 0,0001x - 0,0147 and R^2 = 0.998, where Y is the concentration in µmol/mL of **5.36a** and X the absorbance area of the peak at 214 nm.



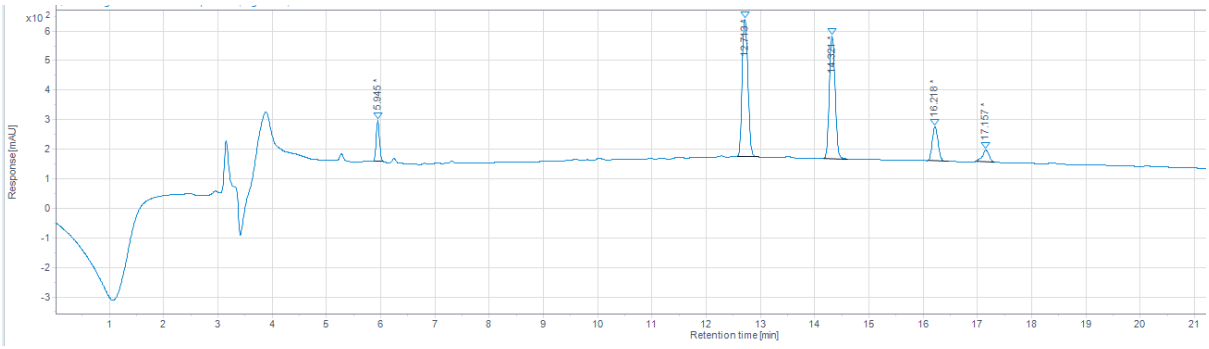
Ac-Ala-Phe-Gly-Ala-OH (**5.47a**)



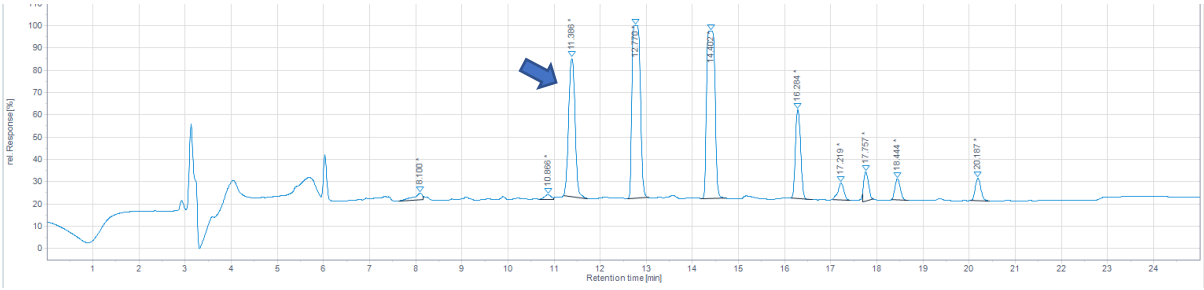
HRMS of 5.47a (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{26}N_4NaO_6^+$ 429.1745; Found 429.1736.

HPLC-UV chromatogram at 214 nm

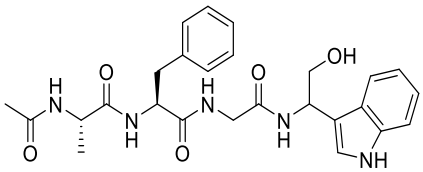
Control experiment without peptide: 2-iodobenzoic acid (12.713 min) and degradation of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (5.945, 14.321, 16.218 min) are observed.



Crude reaction mixture:



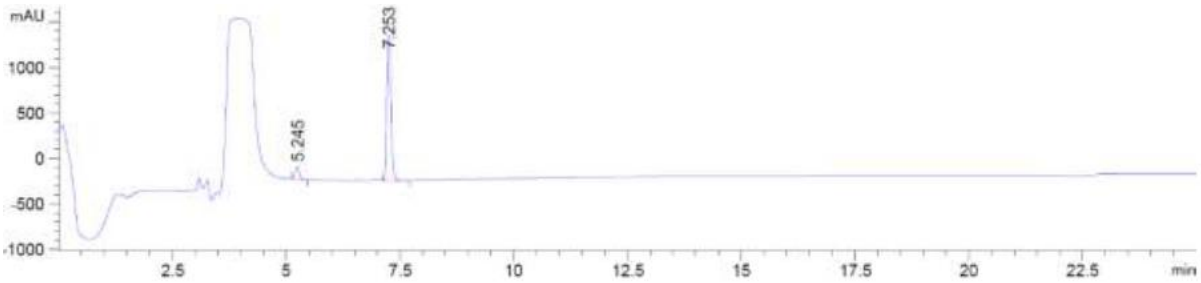
(2S)-2-((S)-2-acetamidopropanamido)-N-(2-((2-hydroxy-1-(1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-3-phenylpropanamide (5.36b)



Following general procedure 5, Ac-Ala-Phe-Gly-Ser-OH (**5.47b**) afforded **5.36b** in more than 95% yield as a mixture of diastereomers (retention time 10.186 min)

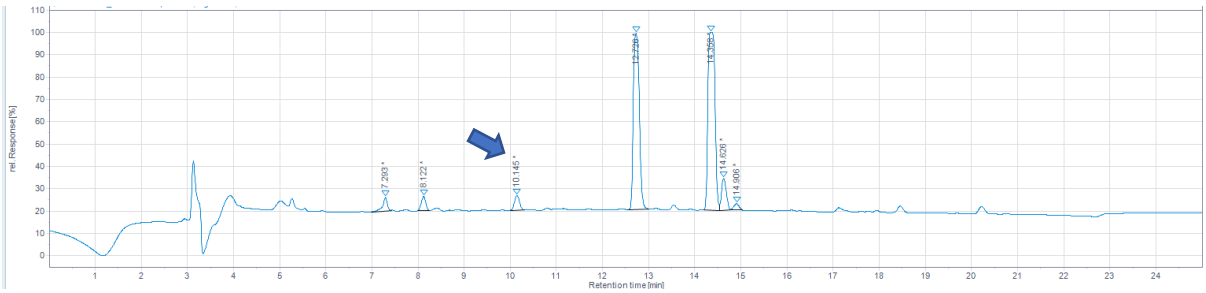
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{31}N_5NaO_5^+$ 516,2217; Found 516,2220

Ac-Ala-Phe-Gly-Ser-OH (**5.47b**)

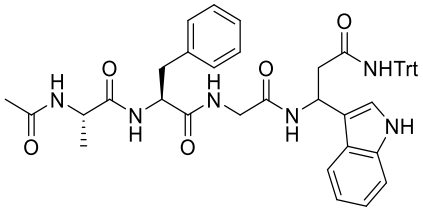


HRMS of 5.47b (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{26}N_4NaO_7^+$ 445.1694; Found 445.1688.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



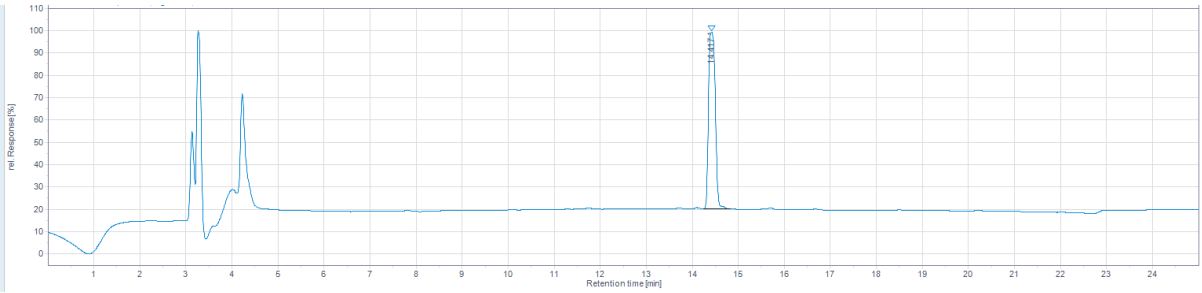
(2S)-N-(2-((1-(1H-indol-3-yl)-3-oxo-3-(tritylamino)propyl)amino)-2-oxoethyl)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamide (5.36c)



Following general procedure 5, Ac-Ala-Phe-Gly-Asn(Trt)-OH (**5.47c**) afforded **5.36c** in 43% yield as a mixture of diastereomers (retention time 16.064 min)

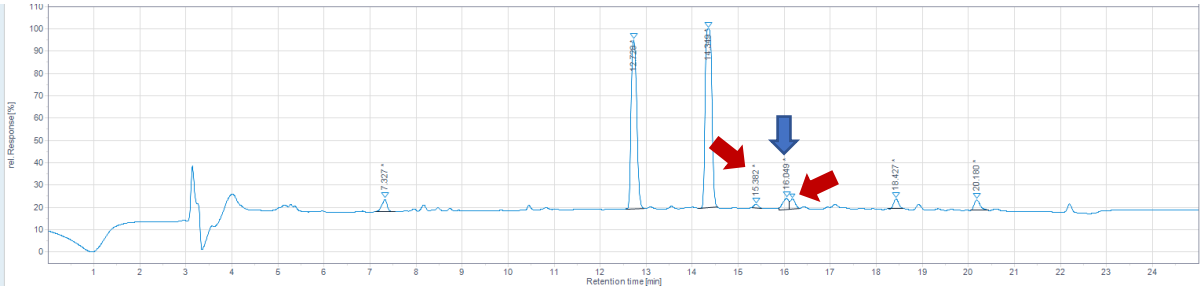
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{46}H_{47}N_6O_5^+$ 763,3602; Found 763,3605.

Ac-Ala-Phe-Gly-Asn(Trt)-OH (**5.47c**)

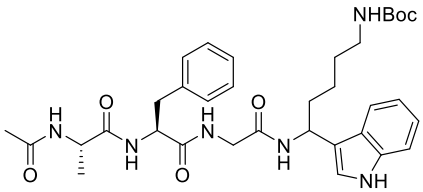


HRMS of 5.47c (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{39}H_{42}N_5O_7^+$ 692.3079; Found 692.3075.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



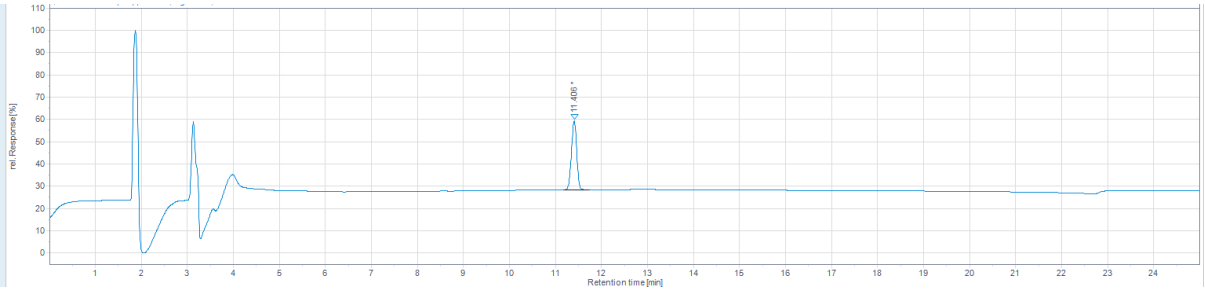
Tert-butyl ((4S,7S)-7-benzyl-13-(1H-indol-3-yl)-4-methyl-2,5,8,11-tetraoxo-3,6,9,12-tetraazaheptadecan-17-yl)carbamate (5.36d)



Following general procedure 5, Ac-Ala-Phe-Gly-Lys(Boc)-OH (**5.47d**) afforded **5.36d** in 35% yield as a mixture of diastereomers (retention time 11.683 min)

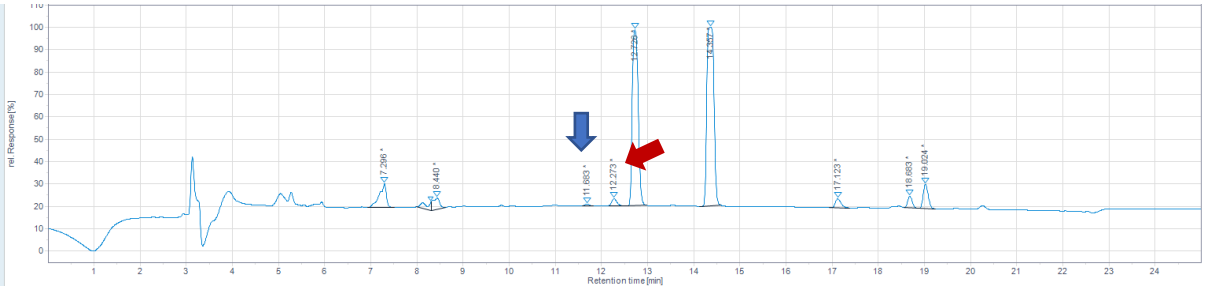
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{34}H_{47}N_6O_6^+$ 635,3552; Found 635,3564.

Ac-Ala-Phe-Gly-Lys(Boc)-OH (**5.47d**)

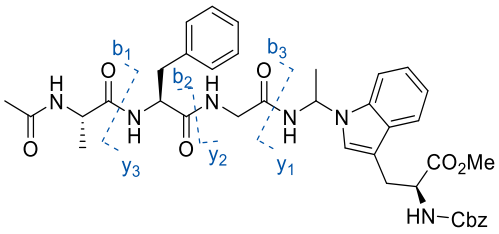


HRMS of 5.47d (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{27}H_{42}N_5O_8^+$ 564.3028; Found 564.3027.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



Methyl1-(1-(2-((S)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamido)acetamido) ethyl)-Nα-((benzyloxy)carbonyl)-L-tryptophanate (5.36e)

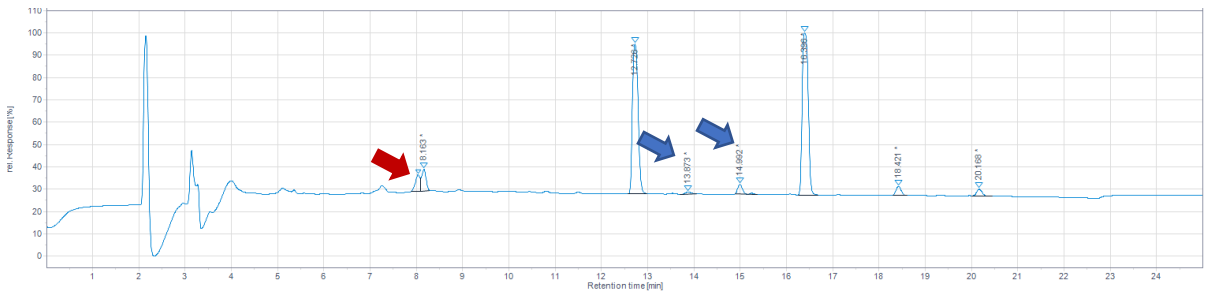


Following general procedure 5, Ac-Ala-Phe-Gly-Ala-OH (**5.47a**) afforded **5.36e** in 48% yield as a mixture of diastereomers (retention time 13.873 min + 14.992 min)

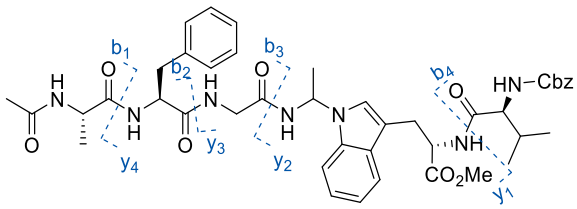
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{38}H_{45}N_6O_8^+$ 713.3293; Found 713.3287. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 713.3287. Measured b and y ions are reported in the table below

	A	F	G	A*
N-terminal	1	2	3	-
b	-	261.12	318.15	-
C-terminal	3	2	1	-
y	600.28	453.21	396.19	-

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



Methyl1-(1-(2-((S)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamido)acetamido) ethyl)-Na-(((benzyloxy)carbonyl)-L-valyl)-L-tryptophanate (5.36f)

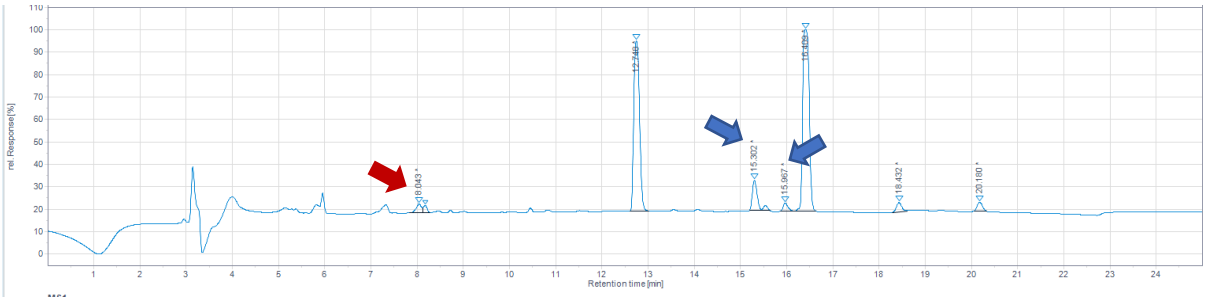


Following general procedure 5, Ac-Ala-Phe-Gly-Ala-OH (**5.47a**) afforded **5.36f** in 76% yield as a mixture of diastereomers (retention time 15.302 min + 15.965 min)

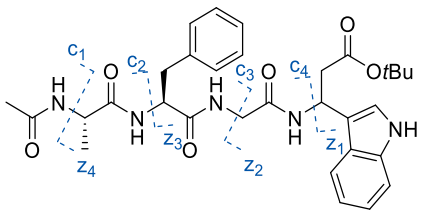
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{43}H_{54}N_7O_9^+$ 812.3978; Found 812.3973. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 812.3973. Measured b and y ions are reported in the table below

	A	F	G	A*	W*	V
N-terminal	1	2	3	-	4	-
b	-	261.12	318.15	-	-	-
C-terminal	3	2	1	-	1	-
y	-	552.28	495.26	-	579.29	-

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



Tert-butyl (4S,7S)-7-benzyl-13-(1H-indol-3-yl)-4-methyl-2,5,8,11-tetraoxo-3,6,9,12-tetraazapentadecan-15-oate (5.36g)

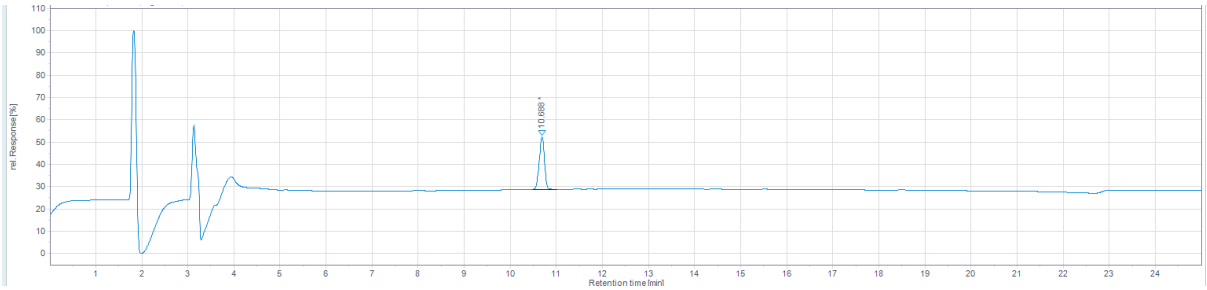


Following general procedure 5, Ac-Ala-Phe-Gly-Asp(O*t*Bu)-OH (**5.47e**) afforded **5.36g** in 26% yield as a mixture of diastereomers (retention time 13.457 min)

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{31}H_{40}N_5O_6^+$ 578.2973; Found 578.2982. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 578.2982. Measured c and z ions are reported in the table below

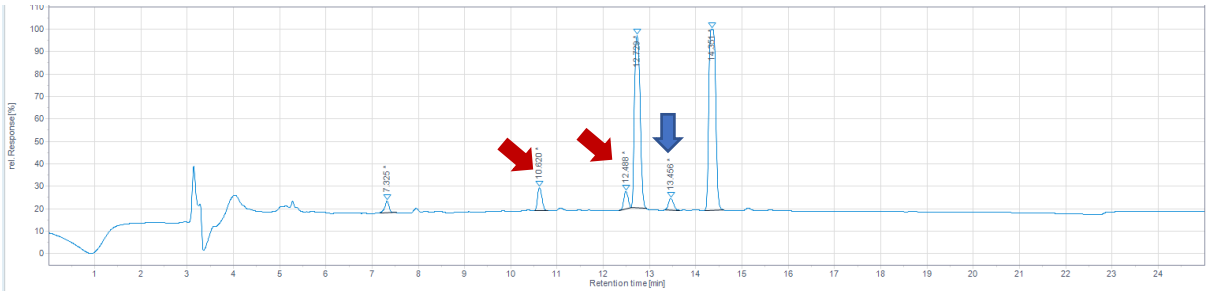
	A	F	G	A*
N-terminal	1	2	3	4
c	-	-	278.15	335.17
C-terminal	4	3	2	1
z	519.26	-	-	244.13

Ac-Ala-Phe-Gly-Asp(O*t*Bu)-OH (**5.47e**)

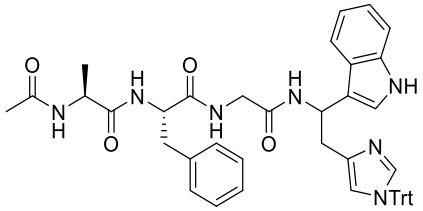


HRMS of 5.47e (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{24}H_{35}N_4O_8^+$ 507.2449; Found 507.2448.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



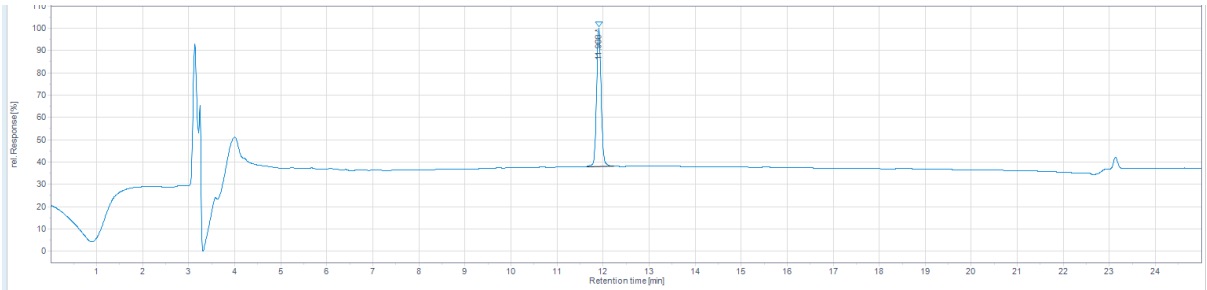
(2S)-N-(2-((1-(1H-indol-3-yl)-2-(1-trityl-1H-imidazol-4-yl)ethyl)amino)-2-oxoethyl)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamide (5.36h)



Following general procedure 5, Ac-Ala-Phe-Gly-His(Trt)-OH (**5.47f**) afforded **5.36h** in 13% yield as a mixture of diastereomers (retention time 13.098 min)

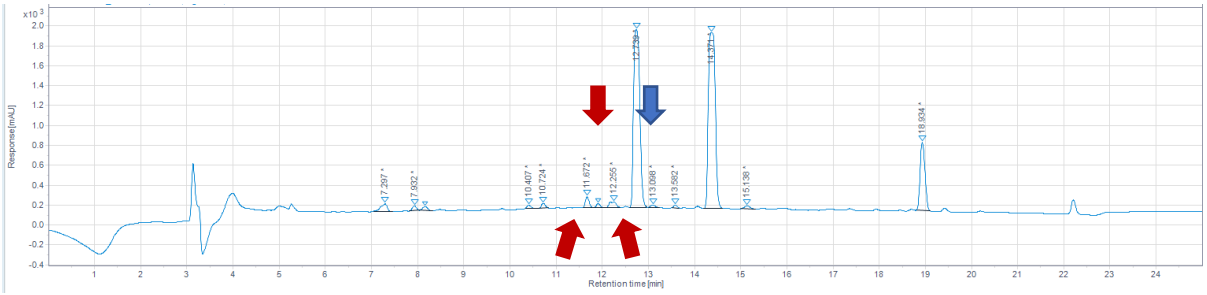
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{48}H_{48}N_7O_4^+$ 786.3762; Found 786.3744.

Ac-Ala-Phe-Gly-His(Trt)-OH (**5.47f**)

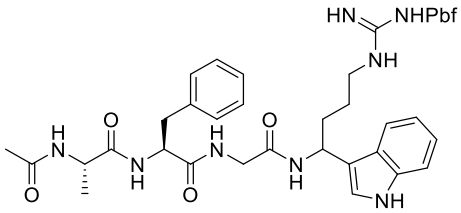


HRMS of 5.47f (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{41}H_{43}N_6O_6^+$ 715.3239; Found 715.3237.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



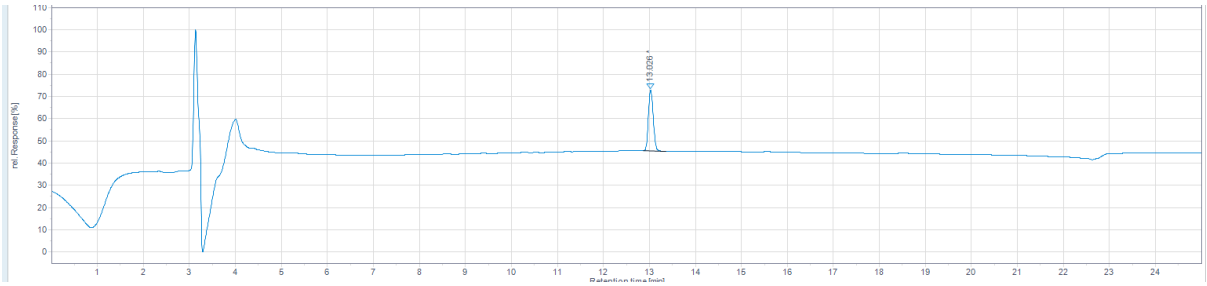
(2S)-N-(2-((1-(1H-indol-3-yl)-4-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)butyl)amino)-2-oxoethyl)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamide (5.36i)



Following general procedure 5, Ac-Ala-Phe-Gly-Arg(Pbf)-OH (**5.47g**) afforded **5.36i** in 11% yield as a mixture of diastereomers (retention time 16.150 min)

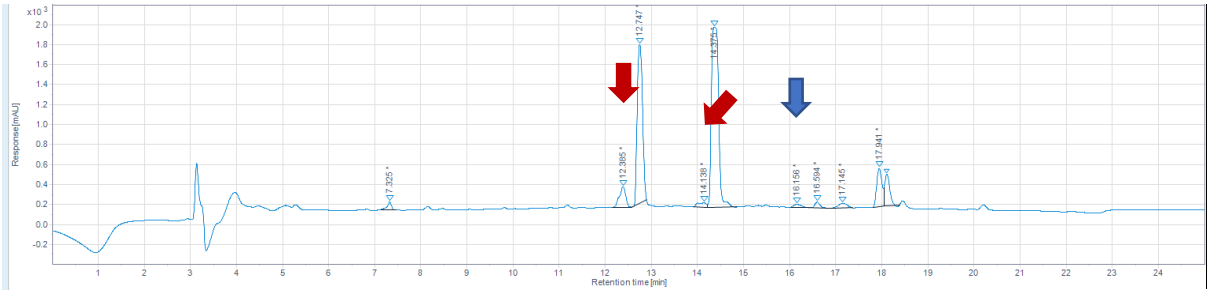
HRMS (ESI/QTOF) m/z: $[M + H_{-1}]^-$ Calcd for $C_{42}H_{53}N_8O_7S^-$ 813.3763; Found 813.3754.

Ac-Ala-Phe-Gly-Arg(Pbf)-OH (**5.47g**)



HRMS of 5.47g (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{35}H_{50}N_7O_9S^+$ 744.3385; Found 744.3383.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



7.5. Decarboxylative Cyclization of Dipeptide Derivatives

7.5.1. Synthesis of Starting Material

Dipeptides Cbz-Gly-Pro (**5.17a**), Cbz-Ala-Ala (**5.17b**), Cbz-Val-Pro (**5.17l**) and Cbz-Phe-Pro (**5.17m**) were commercially available.

General procedure A: amide bond coupling using HATU

To a solution of the appropriate carboxylic acid (1.0 equiv), with the corresponding amine (1.5 equiv), and HATU (1.1 equiv) in DMF was added DIPEA (5.0 equiv). The reaction was stirred overnight at RT. The crude mixture was diluted with 20 mL of sat. $NaHCO_3$, extracted with ethyl acetate (3 x 30 mL), washed with brine (20 mL), citric acid (10 %w, 20 mL), LiCl (5 %w, 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography.

General procedure B: amide bond coupling using EDC·HCl and DIPEA

To a solution of the appropriate carboxylic acid (1.1 equiv), with the corresponding amine (1.0 equiv), and EDC·HCl (1.1 equiv) in DCM was added DIPEA (5.0 equiv). The reaction was stirred overnight at RT. The crude mixture was washed with sat. $NaHCO_3$ (20 mL), and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography.

General procedure C: amide bond coupling using EDC·HCl and DMAP

A solution of the appropriate carboxylic acid (1.0 equiv), with the corresponding amine (4.0 equiv), and EDC·HCl (2.0 equiv) and DMAP (0.3 equiv) in DCM was stirred overnight at RT. The crude mixture was washed with water (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography.

General procedure D: saponification using LiOH in water and methanol

To a solution of the appropriate methyl ester (1.0 equiv) in water and methanol was added lithium hydroxide monohydrate (5.0 equiv). The reaction was stirred overnight at RT. The mixture was extracted with ethyl acetate (3 x 20 mL). The pH value of the aqueous layer was adjusted to 1 using HCl (1 M). The mixture was extracted with ethyl acetate (3 x 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was pure enough for the next step without further purification.

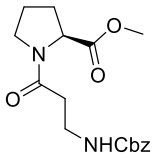
General procedure E: saponification using NaOH in water and THF

To a solution of the appropriate methyl ester (1.0 equiv) in THF and water was added sodium hydroxide (1.0 equiv). The reaction was stirred 2 h at RT. The mixture was extracted with DCM (3 x 20 mL). The pH value of the aqueous layer was adjusted to 1 using HCl (1 M). The mixture was extracted with ethyl acetate (3 x 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was pure enough for the next step without further purification.

General procedure F: saponification using LiOH in water and THF

To a solution of the appropriate methyl ester (1.0 equiv) in THF and water was added lithium hydroxide monohydrate (5.0 equiv). The reaction was stirred overnight at RT. The mixture was extracted with DCM (3 x 20 mL). The pH value of the aqueous layer was adjusted to 1 using HCl (1 M). The mixture was extracted with ethyl acetate (3 x 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was pure enough for the next step without further purification.

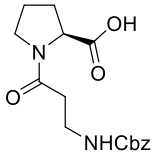
Methyl (3-(((benzyloxy)carbonyl)amino)propanoyl)-L-prolinate (5.48a)



Following the general procedure A and starting with 3-(benzyloxycarbonylamino)propionic acid (400 mg, 1.79 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (445 mg, 2.69 mmol, 1.50 equiv), HATU (749 mg, 1.97 mmol, 1.10 equiv), DIPEA (1.56 mL, 8.96 mmol, 5.00 equiv), and DMF (10.0 mL), **5.48** was obtained after column chromatography (DCM/MeOH 95:5) as a brown oil (132 mg, 0.395 mmol, 22% yield).

Rf (DCM/MeOH 95:5): 0.43. **^{1}H NMR** (400 MHz, chloroform-*d*, mixture of rotamers, unresolved mixture) δ 7.39 – 7.28 (m, 5H, Ar*H*), 5.68 (br s, 1H, N*H*Cbz), 5.08 (s, 2H, OCH_2Ph), 4.70 – 4.50 (m, 1H, NC*H*), 3.89 – 3.40 (m, 7H, COO*Me* + C(O)CH_2CH_2NHCbz + NC$H_2$$CH_2$$CH_2$CH), 2.55 – 2.49 (m, 2H, C(O)C$H_2$$CH_2$NHCbz), 2.27 – 1.86 (m, 4H, NCH_2C$H_2$$CH_2$CH + $NCH_2$$CH_2CH_2$CH). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 172.8, 172.5, 170.6, 156.6, 136.8, 128.5, 128.1, 66.6, 59.3, 58.7, 52.6, 52.4, 47.0, 46.4, 36.7, 34.5, 31.5, 29.3, 24.8, 22.6**. IR** (ν_{max}, cm^{-1}) 3564 (w), 3325 (m), 2954 (m), 2881 (w), 1712 (s), 1635 (s), 1516 (m), 1442 (s), 1250 (s), 1203 (s), 1003 (m), 733 (s), 914 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1420.

(**2S)-1-[3-(Benzyloxycarbonylamino)propanoyl]proline (5.17f)**

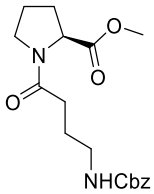


Following the general procedure D and starting with **5.48** (594 mg, 1.78 mmol, 1.00 equiv), lithium hydroxide monohydrate (373 mg, 8.89 mmol, 5.00 equiv), water (5.0 mL) and methanol (5.0 mL), **5.17f** was obtained as a brown oil (421 mg, 1.31 mmol, 74% yield).

^{1}H NMR (400 MHz, methanol-d_4, 4:1 mixture of rotamers (major/minor)) δ 7.42 – 7.23 (m, 5H, Ar*H* (major+minor)), 5.06 (s, 2H, OCH_2Ph (major+minor)), 4.55 – 4.47 (m, 0.2H, NC*H* (minor)), 4.47 – 4.34 (m, 0.8H, NC*H* (major)), 3.65 – 3.36 (m, 4H, C(O)CH_2CH_2NHCbz + NC$H_2$$CH_2$$CH_2$CH (major+minor)), 2.64 – 2.48 (m, 2H, C(O)C$H_2$$CH_2$NHCbz (major+minor)), 2.43 – 2.12 (m, 2H, NCH_2C$H_2$$CH_2$CH + $NCH_2$$CH_2CH_2$CH (major+minor)), 2.08 – 1.80 (m, 2H, NCH_2C$H_2$$CH_2$CH + $NCH_2$$CH_2CH_2$CH (major+minor)). **^{13}C NMR** (101 MHz, methanol-d_4, mixture of rotamers, signals not fully resolved) δ 175.7, 175.3, 172.7, 172.4, 158.6, 138.3, 129.4, 129.0, 128.8, 67.4, 60.8, 60.1, 47.5, 37.9, 37.7, 35.4, 35.2, 32.1, 30.3, 25.6, 23.5. **IR** (ν_{max}, cm^{-1}) 3332 (w), 2954 (w), 1716 (s), 1631 (s), 1527 (m), 1454 (m), 1257 (m), 1196 (m), 914 (w), 737 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{16}H_{20}N_2NaO_5^+$ 343.1264;

Found 343.1269. The values of the NMR spectra are in accordance with reported literature data.[1]

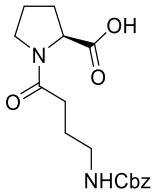
Methyl (4-(((benzyloxy)carbonyl)amino)butanoyl)-L-prolinate (5.48b)



Following the general procedure A and starting with 4-(benzyloxycarbonylamino)butyric acid (600 mg, 2.53 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (628 mg, 3.79 mmol, 1.50 equiv), HATU (1.06 g, 2.78 mmol, 1.10 equiv), DIPEA (2.20 mL, 12.6 mmol, 5.00 equiv), and DMF (15.0 mL), **5.48b** was obtained after column chromatography (DCM/MeOH 95:5) as a brown oil (446 mg, 1.28 mmol, 51% yield).

Rf (DCM/MeOH 95:5): 0.40. **^{1}H NMR** (400 MHz, chloroform-*d*, 3:1 mixture of rotamers (major/minor)) δ 7.40 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.10 (s, 2H, OC*H*$_2$Ph (major+minor)), 4.50 (dd, *J* = 8.8, 3.5 Hz, 0.75H, NC*H* (major)), 4.44 (dd, *J* = 8.5, 2.6 Hz, 0.15H, NC*H* (minor)), 3.74 (s, 0.5H, COO*Me* (minor)), 3.71 (s, 2.5H, COO*Me* (major)), 3.66 – 3.44 (m, 2H, NC*H*$_2$CH$_2$CH$_2$CH (major+minor)), 3.32 – 3.17 (m, 2H, C(O)CH$_2$CH$_2$C*H*$_2$NHCbz (major+minor)), 2.52 – 1.80 (m, 8H, C(O)C*H*$_2$CH$_2$CH$_2$NHCbz + C(O)CH$_2$C*H*$_2$CH$_2$NHCbz + NCH$_2$C*H*$_2$CH$_2$CH + NCH$_2$CH$_2$C*H*$_2$CH (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 172.9, 172.8, 171.4, 156.6, 136.8, 128.5, 128.1, 128.0, 66.5, 59.4, 58.7, 52.7, 52.3, 47.1, 46.5, 40.7, 31.7, 31.5, 29.2, 24.8, 24.5, 22.6. **IR** (ν_{max}, cm^{-1}) 3321 (m), 2954 (m), 2881 (w), 1716 (s), 1635 (s), 1527 (m), 1442 (s), 1254 (s), 1203 (s), 1018 (m), 741 (m). **HRMS** (ESI/QTOF) m/z: [M + H]$^+$ Calcd for $C_{18}H_{25}N_2O_5^+$ 349.1758; Found 349.1751.

(2S)-1-[4-(Benzyloxycarbonylamino)butanoyl]proline (5.17g)



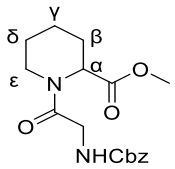
Following the general procedure D and starting with **5.48b** (431 mg, 1.24 mmol, 1.00 equiv), lithium hydroxide monohydrate (79.5 mg, 1.89 mmol, 5.0 equiv), water (3.0 mL) and methanol (3.0 mL), **5.17g** was obtained as a white sticky solid (116 mg, 0.347 mmol, 92% yield).

^{1}H NMR (400 MHz, methanol-*d*$_4$, unresolved mixture of rotamers) δ 7.35 – 7.18 (m, 5H, Ar*H*), 5.03 (s, 2H, OC*H*$_2$Ph), 4.57 – 4.33 (m, 1H, NC*H*), 3.79 – 3.42 (m, 2H, NC*H*$_2$CH$_2$CH$_2$CH), 3.18 – 3.03 (m, 2H, C(O)CH$_2$CH$_2$C*H*$_2$NHCbz), 2.39 – 1.68 (m, 8H, C(O)C*H*$_2$CH$_2$CH$_2$NHCbz + C(O)CH$_2$C*H*$_2$CH$_2$NHCbz + NCH$_2$C*H*$_2$CH$_2$CH + NCH$_2$CH$_2$C*H*$_2$CH). **^{13}C NMR** (101 MHz, methanol-*d*$_4$, unresolved mixture of rotamers) δ 174.4, 174.0, 172.8, 172.4, 157.5, 137.1, 128.1, 127.6, 127.4, 65.9, 58.8, 46.2, 39.8, 30.9, 29.0, 24.9, 24.6, 24.2, 22.1. **IR** (ν_{max}, cm^{-1})

[1] K. Ha, I. Lebedyeva, S. Hamedzadeh, Z. Li, R. Quiñones, G. G. Pillai, B. Williams, A. Nasajpour, K. Martin, A. M. Asiri and A. R. Katritzky, *Chem. Eur. J.*, 2014, **20**, 4874.

3336 (m), 2951 (w), 1716 (s), 1631 (s), 1535 (m), 1450 (s), 1254 (s), 1200 (m), 3062 (w). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1420.The values of the NMR spectra are in accordance with reported literature data.[4]

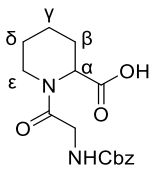
1-[2-(Benzyloxycarbonylamino)acetyl]pipecolinic acid methyl ester (5.48c)



Following the general procedure B and starting with pipecolinic acid methyl ester hydrochloride (472 mg, 2.63 mmol, 1.10 equiv), Cbz-Gly (500 mg, 2.39 mmol, 1.00 equiv), EDC·HCl (504 mg, 2.63 mmol, 1.10 equiv), DIPEA (1.67 mL, 12.0 mmol, 5.00 equiv) and DCM (8.00 mL), **5.48c** was obtained after column chromatography (DCM/MeOH 98.5:1.5) as a white sticky solid (352 mg, 1.05 mmol, 44% yield).

Rf (DCM/MeOH 98:2): 0.43. **^{1}H NMR** (400 MHz, chloroform-*d*, 4:1 mixture of rotamers (major/minor)) δ 7.41 – 7.27 (m, 5H, Ar*H* (major+minor)), 5.89 – 5.62 (m, 1H, N*H* (major+minor)), 5.30 (dd, *J* = 6.2, 2.1 Hz, 0.8H, pipHα (major)), 5.10 (s, 2H, OCH_2Ph (major+minor)), 4.54 – 4.46 (m, 0.2H, pipHε (minor)), 4.42 – 4.35 (m, 0.2H, pipHα (minor)), 4.19 – 3.95 (m, 1.8H, C(O)CH_2N (major+minor)), 3.89 – 3.81 (m, 0.2H, C(O)CH_2N (minor)), 3.80 – 3.67 (m, 3H, COO*Me* (major+minor)), 3.62 – 3.50 (m, 0.8H, pipHε (major)), 3.22 (td, *J* = 13.0, 3.1 Hz, 0.8H, pipHε (major)), 2.68 (dt, *J* = 13.5, 6.7 Hz, 0.2H, pipHε (minor)), 2.35 – 2.20 (m, 1H, pipHβ (major+minor)), 1.77 – 1.56 (m, 3H, pipHβ + pipHγ + pipHδ (major+minor)), 1.50 – 1.22 (m, 2H, pipHγ + pipHδ (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 171.4, 170.7, 168.2, 167.8, 156.3, 156.2, 136.5, 136.5, 128.5, 128.4, 128.1, 128.0, 66.9, 55.1, 52.5, 52.4, 42.9, 42.7, 42.3, 40.1, 27.1, 26.5, 25.0, 24.4, 20.8. **IR** (ν_{max}, cm^{-1}) 3406 (w), 3332 (w), 2947 (m), 2866 (w), 1732 (s), 1651 (s), 1508 (m), 1442 (s), 1219 (s), 1165 (m), 1053 (m), 1014 (m), 741 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1430.

1-[2-(Benzyloxycarbonylamino)acetyl]pipecolinic acid (5.17h)

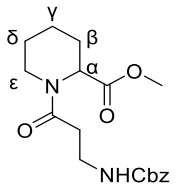


Following the general procedure E and starting with **5.48c** (244 mg, 0.730 mmol, 1.00 equiv), sodium hydroxide (0.73 mL, 0.73 mmol, 1.0M, 1.0 equiv), THF (3.7 mL) and water (3.7 mL), **5.17h** was obtained as a white sticky solid (225 mg, 0.702 mmol, 96% yield).

^{1}H NMR (400 MHz, chloroform-*d*, 4:1 mixture of rotamers (major/minor)) δ 10.03 (br s, 1H, COO*H* (major+minor)), 7.42 – 7.27 (m, 5H, Ar*H*, (major+minor)), 6.11 (br s, 0.2H, N*H* (minor)), 5.99 (t, *J* = 4.6 Hz, 0.8H, N*H* (major)), 5.31 (dd, *J* = 6.1, 2.1 Hz, 0.8H, pipHα (major)), 5.12 (s, 2H, OCH_2Ph (major+minor)), 4.53 – 4.39 (m, 0.4H, pipHα + pipHε (minor)), 4.27 – 3.90 (m, 2H, NC(O)CH_2 (major+minor)), 3.67 – 3.54 (m, 0.8H, pipHε (major)), 3.33 – 3.14 (m, 0.8H, pipHε (major)), 2.79 – 2.66 (m, 0.2H, pipHε (minor)), 2.39 – 2.19 (m, 1H, pipHβ (major+minor)), 1.83 – 1.54 (m, 3H, pipHβ + pipHγ + pipHδ (major+minor)), 1.53 – 1.30 (m, 2H, pipHγ + pipHδ

(major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 175.1, 173.7, 169.0, 168.5, 156.8, 156.6, 136.3, 128.6, 128.3, 128.2, 128.1, 67.3, 67.1, 55.1, 52.5, 42.9, 42.8, 42.5, 40.3, 27.0, 26.4, 24.9, 24.4, 20.8. **IR** (ν_{max}, cm^{-1}) 3406 (m), 2943 (m), 2866 (m), 1716 (s), 1647 (s), 1516 (m), 1450 (m), 1227 (s), 1169 (m), 1057 (m), 1014 (m), 910 (m), 733 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{16}H_{20}N_2NaO_5^+$ 343.1264; Found 343.1263.

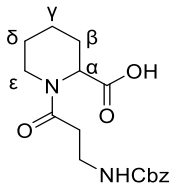
1-[3-(Benzyloxycarbonylamino)propanoyl]pipecolinic acid methyl ester (5.48d)



To a solution of pipecolinic acid methyl ester hydrochloride (241 mg, 1.34 mmol, 1.00 equiv), with Cbz-βalanine (300 mg, 1.34 mmol, 1.00 equiv), and EDC·HCl (258 mg, 1.34 mmol, 1.00 equiv), HOBt hydrate (226 mg, 1.48 mmol, 1.10 equiv) in DCM (8.00 mL) was added DIPEA (0.560 mL, 3.16 mmol, 2.35 equiv). The reaction was stirred overnight at RT. The crude mixture was washed with sat. $NaHCO_3$ (20 mL), citric acid (10 %w, 20 mL), brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography (DCM/MeOH 98:2) to afford **5.48d** (283 mg, 0.812 mmol, 60% yield).

Rf (DCM/MeOH 98:2): 0.29. **^{1}H NMR** (400 MHz, chloroform-*d*, 4:1 mixture of rotamers (major/minor)) δ 7.39 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.57 (t, *J* = 6.4 Hz, 1H, N*H* (major+minor)), 5.39 – 5.29 (m, 0.8H, pipHα (major)), 5.07 (s, 2H, OCH_2Ph (major+minor)), 4.54 – 4.46 (m, 0.4H, pipHα + pipHε (minor)), 3.76 – 3.58 (m, 3.8H, COO*Me* (major+minor) + pipHε (major)), 3.55 – 3.41 (m, 2H, NC(O)CH_2CH_2 (major+minor)), 3.18 (td, *J* = 13.0, 3.0 Hz, 0.8H, pipHε (major)), 2.68 – 2.46 (m, 2H, NC(O)C$H_2$$CH_2$ (major+minor) + pipHβ (minor)), 2.45 – 2.32 (m, 0.2H, NC(O)C$H_2$$CH_2$ (minor)), 2.32 – 2.18 (m, 1H, pipHβ (major) + pipHε (minor)), 1.76 – 1.54 (m, 3H, pipHβ + pipHγ + pipHδ (major+minor)), 1.49 – 1.22 (m, 2H, pipHγ + pipHδ (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 171.8, 171.7, 171.2, 156.6, 136.8, 128.5, 128.1, 66.6, 55.9, 52.6, 52.3, 51.0, 43.3, 39.5, 36.9, 33.4, 33.1, 27.2, 26.6, 25.2, 24.5, 20.9. **IR** (ν_{max}, cm^{-1}) 3336 (w), 2947 (m), 2866 (w), 1720 (s), 1639 (s), 1516 (m), 1439 (s), 1242 (s), 1149 (m), 1014 (m), 3421 (w). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{18}H_{24}N_2NaO_5^+$ 371.1577; Found 371.1581.

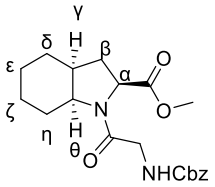
1-(3-(((Benzyloxy)carbonyl)amino)propanoyl)piperidine-2-carboxylic acid (5.17i)



Following the general procedure E and starting with **5.48d** (240 mg, 0.688 mmol, 1.00 equiv), sodium hydroxide (0.69 mL, 0.69 mmol, 1.0M, 1.0 equiv), THF (3.5 mL) and water (3.5 mL), **5.17i** was obtained as a whitish oil (215 mg, 0.643 mmol, 93% yield).

^{1}H NMR (400 MHz, chloroform-*d*, 4:1 mixture of rotamers (major/minor)) δ 8.54 (br s, 1H, COO*H* (major+minor)), 7.42 – 7.21 (m, 5H, Ar*H* (major+minor)), 6.02 (br s, 0.2H, N*H* (minor)), 5.87 – 5.66 (m, 0.8H, N*H* (major)), 5.31 (d, *J* = 5.8 Hz, 0.8H, pipHα (major)), 5.07 (s, 2H, OCH_2Ph), 4.63 – 4.36 (m, 0.4H, pipHα + pipHε (minor)), 3.75 – 3.62 (m, 0.8H, pipHε (major)), 3.59 – 3.38 (m, 2H, NC(O)CH_2CH_2NHCbz), 3.28 – 3.08 (m, 0.8H, pipHε (major)), 2.72 – 2.37 (m, 2.2H, NC(O)C$H_2$$CH_2$NHCbz (major+minor) + pipHε (minor)), 2.27 (d, *J* = 13.3 Hz, 1H, pipHβ (major+minor)), 1.77 – 1.49 (m, 3H, pipHβ + pipHγ + pipHδ (major+minor)), 1.50 – 1.27 (m, 2H, pipHγ + pipHδ (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 174.8, 173.9, 172.5, 172.0, 157.0, 156.8, 136.7, 128.5, 128.1, 66.8, 66.7, 55.9, 52.1, 43.5, 39.7, 36.9, 33.5, 33.1, 27.1, 26.5, 25.1, 24.5, 20.8. **IR** (ν_{max}, cm^{-1}) 3329 (m), 2943 (m), 1709 (s), 1624 (s), 1523 (m), 1446 (m), 1246 (s), 1142 (m), 733 (s), 1014 (m), 910 (m). **HRMS (ESI/QTOF)** m/z: [M + Na]+ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1413.

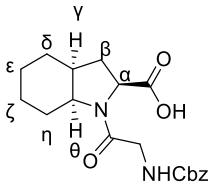
Methyl (2S,3aS,7aS)-1-(((benzyloxy)carbonyl)glycyl)octahydro-1H-indole-2-carboxylate (5.48e)



Following the general procedure B and starting with (2S,3aS,7aS)-2,3,3a,4,5,6,7,7a-octahydro-1H-indole-2-carboxylic acid methyl ester (385 mg, 2.10 mmol, 1.10 equiv), Cbz-Gly (400 mg, 1.91 mmol, 1.00 equiv), EDC·HCl (403 mg, 2.10 mmol, 1.10 equiv), DIPEA (1.67 mL, 9.56 mmol, 5.00 equiv) and DCM (15.0 mL), **5.48e** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow oil (330 mg, 0.881 mmol, 46% yield).

Rf (DCM/MeOH 98:2): 0.43. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.38 – 7.27 (m, 5H, Ar*H*), 5.70 (t, *J* = 4.6 Hz, 1H, N*H*), 5.14 – 5.04 (m, 2H, OCH_2Ph), 4.40 (dd, *J* = 10.1, 8.0 Hz, 1H, Hα), 4.12 (dd, *J* = 16.9, 4.9 Hz, 1H, C(O)CH_2N), 3.94 (dd, *J* = 16.8, 4.0 Hz, 1H, C(O)CH_2N), 3.80 – 3.68 (m, 4H, COO*Me* + Hθ), 2.47 – 2.31 (m, 1H, Hγ), 2.19 – 1.89 (m, 3H, 2Hβ + Hδ), 1.78 – 1.43 (m, 5H, Hδ + Hε + Hζ + 2Hη), 1.35 – 1.11 (m, 2H, Hε + Hζ). **^{13}C NMR** (101 MHz, chloroform-*d*) δ 172.8, 166.5, 156.3, 136.5, 128.5, 128.1, 128.0, 66.9, 59.0, 57.5, 52.4, 42.9, 37.7, 30.3, 27.7, 25.6, 23.7, 19.9. **IR** (ν_{max}, cm^{-1}) 3410 (w), 3332 (w), 2931 (m), 2858 (m), 1728 (s), 1651 (s), 1512 (m), 1439 (s), 1250 (s), 1176 (s), 1053 (m), 741 (m), 1361 (m). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{20}H_{26}N_2NaO_5^+$ 397.1734; Found 397.1737.

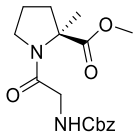
(2S,3aS,7aS)-1-(((Benzyloxy)carbonyl)glycyl)octahydro-1H-indole-2-carboxylic acid (5.17j)



Following the general procedure E and starting with **5.48e** (250 mg, 0.668 mmol, 1.00 equiv), sodium hydroxide (0.69 mL, 0.69 mmol, 1.0 M, 1.0 equiv), THF (3.8 mL) and water (3.8 mL), **5.17j** was obtained as a white sticky solid (168 mg, 0.406 mmol, 87% purity, 61% yield).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.44 – 7.28 (m, 5H, Ar*H*), 5.55 – 5.19 (m, 1H, COO*H*), 5.82 (t, *J* = 4.8 Hz, 1H, N*H*), 5.11 (s, 2H, OCH_2Ph), 4.47 (t, *J* = 9.0 Hz, 1H, Hα), 4.19 (dd, *J* = 17.0, 5.0 Hz, 1H, NC(O)CH_2), 3.95 (dd, *J* = 16.9, 3.9 Hz, 1H, NC(O)CH_2), 3.84 – 3.74 (m, 1H, Hθ), 2.37 (br s, 1H, Hγ), 2.28 – 2.14 (m, 2H, 2Hβ), 1.94 – 1.40 (m, 6H, 2Hδ + Hε + Hζ + 2Hη), 1.39 – 1.08 (m, 2H, Hε + Hζ). **^{13}C NMR** (101 MHz, chloroform-*d*) δ 174.8, 168.0, 156.5, 136.5, 128.6, 128.2, 128.1, 67.1, 59.3, 58.1, 42.9, 37.4, 29.7, 27.7, 25.6, 23.7, 19.9. **IR** (ν_{max}, cm^{-1}) 3321 (w), 3035 (w), 2931 (m), 2862 (w), 1720 (s), 1643 (s), 1523 (m), 1458 (m), 1250 (m), 1188 (m), 1057 (w), 914 (w), 737 (m). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{19}H_{24}N_2NaO_5^+$ 383.1577; Found 383.1587.

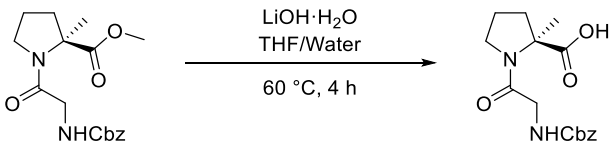
(2S)-1-[2-(Benzyloxycarbonylamino)acetyl]-2-methyl-pyrrolidine-2-carboxylic acid methyl ester (5.48f)



Following the general procedure B and starting with methyl (2S)-2-methylpyrrolidin-1-ium-2-carboxylate chloride (378 mg, 2.10 mmol, 1.10 equiv), Cbz-Gly (400 mg, 1.91 mmol, 1.00 equiv), EDC·HCl (403 mg, 2.10 mmol, 1.10 equiv), DIPEA (1.67 mL, 9.56 mmol, 5.00 equiv) and DCM (10.0 mL), **5.48f** was obtained after column chromatography (DCM/MeOH 98:2) as a brown oil (431 mg, 1.29 mmol, 67% yield).

Rf (DCM/MeOH 98:2): 0.40. **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.39 – 7.27 (m, 5H, Ar*H*), 5.70 (t, *J* = 4.3 Hz, 1H, N*H*), 5.10 (s, 2H, OCH_2Ph), 4.04 – 3.86 (m, 2H, C(O)CH_2), 3.70 (s, 3H, COO*Me*), 3.62 – 3.47 (m, 2H, NCH_2CH$_2$CH$_2$C), 2.21 – 2.12 (m, 1H, NCH$_2$CH$_2$CH_2C), 2.12 – 1.96 (m, 2H, NCH$_2$CH_2CH$_2$C), 1.96 – 1.85 (m, 1H, NCH$_2$CH$_2$CH_2C), 1.56 (s, 3H, C*Me*). **^{13}C NMR** (101 MHz, chloroform-*d*) δ 174.1, 166.3, 156.3, 136.6, 128.6, 128.1, 128.0, 66.9, 66.5, 52.6, 47.0, 43.8, 38.5, 24.0, 21.6. **IR** (ν_{max}, cm^{-1}) 3410 (w), 3336 (w), 2951 (w), 2881 (w), 1728 (s), 1655 (s), 1512 (m), 1435 (s), 1250 (m), 1219 (m), 1169 (m), 1053 (m), 741 (m**). HRMS (ESI/QTOF)** m/z: [M + Na]+ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1423.

(2S)-1-[2-(Benzyloxycarbonylamino)acetyl]-2-methyl-proline (5.17k)

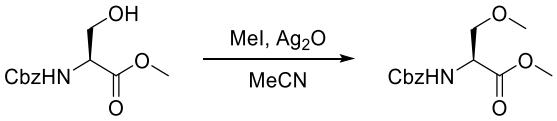


5.48f **5.17k**

To a solution of **5.48f** (371 mg, 1.11 mmol, 1.00 equiv) in THF (5.6 mL) and water (5.6 mL) was added lithium hydroxide monohydrate (46.6 mg, 1.11 mmol, 1.00 equiv). The reaction was stirred 4 h at 60 °C. The mixture was extracted with DCM (3 x 20 mL). The pH value of the aqueous layer was adjusted to 1 using HCl (1M). The mixture was extracted with ethyl acetate (3 x 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum to give **5.17k** (325 mg, 1.01 mmol, 91% yield) as a white sticky solid which was pure enough for the next step without further purification.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.38 – 7.28 (m, 5H, Ar*H*), 5.89 (t, *J* = 4.7 Hz, 1H, N*H*), 5.10 (s, 2H, OCH_2Ph), 4.04 (dd, *J* = 17.2, 5.4 Hz, 1H, NC(O)CH_2), 3.88 (dd, *J* = 17.2, 4.0 Hz, 1H, NC(O)CH_2), 3.54 (t, 2H, NCH_2CH$_2$CH$_2$), 2.36 – 2.23 (m, 1H, NCH$_2$CH$_2$CH_2), 2.11 – 1.92 (m, 2H, NCH$_2$CH_2CH$_2$), 1.92 – 1.79 (m, 1H, NCH$_2$CH$_2$CH_2), 1.57 (s, 3H, C*Me*). **^{13}C NMR** (101 MHz, chloroform-*d*) δ 176.9, 167.7, 156.6, 136.5, 128.6, 128.2, 128.1, 67.0, 66.9, 47.5, 44.0, 38.3, 24.0, 21.5. **IR** (ν_{max}, cm^{-1}) 3309 (w), 2951 (w), 1720 (s), 1651 (s), 1523 (w), 1450 (m), 1254 (m), 1176 (m), 1057 (w), 910 (w), 737 (m). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{16}H_{20}N_2NaO_5^+$ 343.1264; Found 343.1264.

Cbz-Ser(OMe)-OMe (5.50)

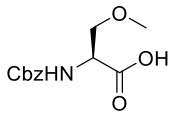


5.49 **5.50**

Following a reported procedure,[2] to a solution of MeCN (87.0 mL) and Cbz-Ser-OMe (**5.49**) (1.00 g, 3.95 mmol, 1.00 equiv) was added successively Ag_2O (4.58 g, 19.7 mmol, 5.00 equiv) and iodomethane (2.46 mL, 39.5 mmol, 10.0 equiv) and the mixture was stirred 24 h at RT. The mixture was filtered, the filtrate was concentrated under vacuum and purified by column chromatography ($CHCl_3$/MeOH 95:5) to obtain Cbz-Ser(OMe)-OMe (**5.50**) (480 mg, 1.80 mmol, 45% yield) as an oil.

[α]D^{20} = -8.9 (c = 0.66, MeOH). **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.40-7.28 (m, 5H, Ar*H*), 5.62 (d, *J* = 8.2 Hz, 1H, N*H*), 5.13 (s, 2H, OCH_2Ph), 4.49 (dt, *J* = 8.5, 3.2 Hz, 1H, NHC*H*), 3.82 (dd, *J* = 9.4, 3.1 Hz, 1H, CHCH_2), 3.77 (s, 3H, C(O)O*Me*), 3.61 (dd, *J* = 9.4, 3.3 Hz, 1H, CHCH_2), 3.33 (s, 3H, O*Me*). **^{13}C NMR** (101 MHz, chloroform-*d*) δ 170.9, 156.1, 136.4, 128.6, 128.3, 128.2, 72.5, 67.2, 59.4, 54.5, 52.8. The values of the NMR spectra and [α]D^{20} are in accordance with reported literature data.[5]

Z-Ser(OMe)-OH (5.51)



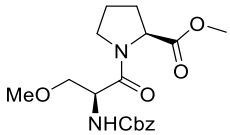
Following the general procedure D and starting with Z-Ser(OMe)-OMe (**5.50**) (430 mg, 1.61 mmol, 1.00 equiv) lithium hydroxide monohydrate (338 mg, 8.04 mmol, 5.00 equiv), water (8.6 mL) and THF (8.6 mL), Z-Ser(OMe)-OH (**5.51**) was obtained as an oil (400 mg, 1.58 mmol, 98% yield).

[α]D^{20} = +8.0 (c = 0.60, MeOH). **^{1}H NMR** (400 MHz, chloroform-*d*) δ 9.48 – 8.55 (br s, 1H, COO*H*), 7.43 – 7.29 (m, 5H, Ar*H*), 5.65 (d, *J* = 8.4 Hz, 1H, N*H*), 5.20 – 5.08 (m, 2H, OCH_2Ph), 4.53 (dt, *J* = 8.0, 3.1 Hz, 1H, NHC*H*), 3.88 (dd, *J* = 9.4, 2.9 Hz, 1H, NHCHCH_2), 3.64 (dd, *J* = 9.4, 3.5 Hz, 1H, NHCHCH_2), 3.36 (s, 3H, O*Me*). **^{13}C NMR** (101 MHz, chloroform-*d*) δ 175.2, 156.3, 136.2, 128.7, 128.4, 128.2, 72.1, 67.4, 59.5, 54.2. **IR** (ν_{max}, cm^{-1}) 2937 (m), 2812 (w), 1716 (s), 1524 (s), 1456 (m), 1414 (m), 1334 (m), 1214 (s), 1117 (s), 1059 (s), 740 (m). **HRMS**

[2] S. V. Andurkar, J. P. Stables and H. Kohn, *Tetrahedron: Asymmetry*, 1998, **9**, 3841.

(ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{12}H_{15}NNaO_5^+$ 276.0842; Found 276.0850. The values of the NMR spectra and [α]D^{20} are in accordance with reported literature data.[5]

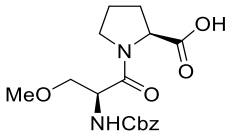
Methyl N-((benzyloxy)carbonyl)-O-methyl-L-seryl-L-prolinate (5.48g)



Following the general procedure C and starting with Cbz-Ser(OMe)-OH (400 mg, 1.58 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (1.05 g, 6.32 mmol, 4.00 equiv), EDC·HCl (606 mg, 3.16 mmol, 2.00 equiv) and DMAP (57.9 mg, 0.474 mmol, 0.300 equiv) and DCM (29 mL), **5.48g** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow oil (464 mg, 1.27 mmol, 81% yield).

Rf (DCM/MeOH 98:2): 0.32. **[α]D^{20}** = -48.4 (c = 0.81, $CHCl_3$). **^{1}H NMR** (400 MHz, chloroform-*d*, 85:15 mixture of rotamers (major+minor)) δ 7.37 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.70 – 5.54 (m, 1H, N*H* (major+minor)), 5.18 – 5.04 (m, 2H, OCH_2Ph (major+minor)), 4.83 – 4.78 (m, 0.15H, NHC*H* (minor)), 4.72 (ddt, *J* = 12.0, 8.2, 4.2 Hz, 0.85H, NHC*H* (major)), 4.59 – 4.43 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.79 – 3.68 (m, 4H, COO*Me* + $NCH_2CH_2CH_2CH$ (major+minor)), 3.67 – 3.41 (m, 3H, $NCH_2CH_2CH_2CH$ + CH_2OMe (major+minor)), 3.40 – 3.28 (m, 3H, CH_2OMe (major+minor)), 2.26 – 2.13 (m, 1H, $NCH_2CH_2CH_2CH$), 2.13 – 1.85 (m, 3H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$ (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 172.4, 172.3, 169.8, 169.1, 156.1, 155.5, 136.4, 128.6, 128.2, 128.1, 73.8, 72.8, 67.0, 59.4, 59.2, 59.0, 52.9, 52.6, 52.4, 52.0, 47.2, 46.6, 31.1, 29.1, 25.0, 22.4. **IR** (v_{max}, cm^{-1}) 3313 (w), 2953 (m), 2881 (w), 1742 (s), 1719 (s), 1647 (s), 1529 (m), 1448 (s), 1245 (s), 1198 (s), 1176 (s), 1121 (m), 1046 (m), 753 (m). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{18}H_{24}N_2NaO_6^+$ 387.1527; Found 387.1532.

N-((benzyloxy)carbonyl)-O-methyl-L-seryl-L-proline (5.17n)

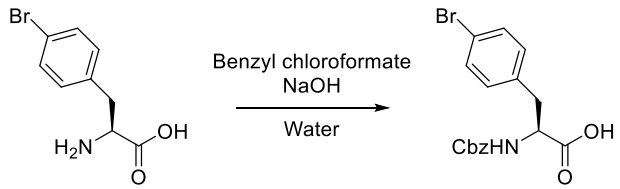


Following the general procedure F and starting with **5.48g** (430 mg, 1.18 mmol, 1.00 equiv) lithium hydroxide monohydrate (248 mg, 5.90 mmol, 5.00 equiv), water (6.3 mL) and THF (6.3 mL), **5.17n** was obtained as a white sticky solid (410 mg, 1.17 mmol, 99% yield).

[α]D^{20} = -63.4 (c = 0.66, $CHCl_3$). **^{1}H NMR** (400 MHz, chloroform-*d*, 9:1 mixture of rotamers (major/minor)) δ 9.05-8.32 (br s, 1H, COO*H* (major+minor)), 7.38 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.98 (d, *J* = 8.2 Hz, 0.1H, N*H* (minor)), 5.89-5.76 (m, 0.9H, N*H* (major)), 5.15 – 5.04 (m, 2H, OCH_2Ph (major+minor)), 4.75 (m, 1H, NHC*H* (major+minor)), 4.63 – 4.47 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.83-3.66 (m, 2H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.63 – 3.49 (m, 2H, CH_2OMe (major+minor)), 3.38-3.22 (m, 3H, O*Me* (major+minor)), 2.26 – 1.93 (m, 4H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$ (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d* mixture of rotamers, signals not fully resolved) δ 174.0, 173.7, 170.8, 170.7, 156.2, 155.9, 136.3, 136.2, 128.6, 128.3, 128.2, 72.8, 72.5, 67.3, 67.2, 59.9, 59.6, 59.4, 52.5, 52.2, 47.8, 47.6, 28.6, 28.4, 24.9, 24.7. **IR** (v_{max}, cm^{-1}) 3302 (m), 3066 (m), 2938 (w), 1718 (s),

1638 (s), 1530 (m), 1454 (s), 1192 (s), 1263 (s), 1120 (s), 979 (m), 913 (m), 737 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{17}H_{22}N_2NaO_6^+$ 373.1370; Found 373.1370.

(2S)-2-(Benzyloxycarbonylamino)-3-(4-bromophenyl)propanoic acid (5.53)

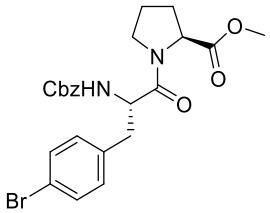


5.52 **5.53**

(2S)-2-Amino-3-(4-bromophenyl)propanoic acid (**5.52**) (1.00 g, 4.10 mmol, 1.00 equiv) and NaOH (328 mg, 8.19 mmol, 2.00 equiv) were dissolved in water (4.00 mL). Benzyl chloroformate (874 µL, 6.15 mmol, 1.50 equiv) was added dropwise at 0 °C. The reaction was stirred at 30 min at 0 °C and 1 h at RT. The reaction mixture was washed with diethyl ether (10.0 mL), acidified with 1 M HCl and extracted with ethyl acetate (3 x 10 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. (2S)-2-(Benzyloxycarbonylamino)-3-(4-bromophenyl)propanoic acid (**5.53**) (1.29 g, 3.42 mmol, 83% yield) was obtained as a white solid.

Mp:143-145 °C. **[α]D^{20}** = +51.8 (c = 0.63, $CHCl_3$). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.04 – 12.67 (br s, 1H, COO*H*), 7.67 (d, *J* = 8.5 Hz, 1H, N*H*), 7.49 – 7.42 (m, 2H, Ar*H*), 7.37 – 7.19 (m, 7H, Ar*H*), 4.97 (s, 2H, OCH_2Ph), 4.18 (ddd, *J* = 10.7, 8.6, 4.4 Hz, 1H, NHC*H*), 3.05 (dd, *J* = 13.4, 4.4 Hz, 1H, NHCHCH_2), 2.80 (dd, *J* = 13.8, 10.7 Hz, 1H, NHCHCH_2). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 173.1, 156.0, 137.4, 137.0, 131.4, 131.0, 128.3, 127.7, 127.5, 119.6, 65.2, 55.2, 35.8. **IR** (ν_{max}, cm^{-1}) 3358 (m), 2973 (m), 1713 (s), 1531 (m), 1489 (m), 1455 (m), 1407 (m), 1342 (m), 1260 (s), 1216 (s), 1052 (s), 1012 (m), 740 (m). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{17}H_{16}{}^{79}BrNNaO_4^+$ 400.0155; Found 400.0156.

Methyl ((S)-2-(((benzyloxy)carbonyl)amino)-3-(4-bromophenyl)propanoyl)-L-prolinate (5.48h)

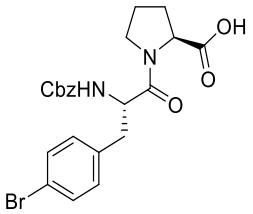


Following the general procedure C and starting with (2S)-2-(benzyloxycarbonylamino)-3-(4-bromophenyl)propanoic acid (500 mg, 1.32 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (876 mg, 5.29 mmol, 4.00 equiv), EDC·HCl (507 mg, 2.64 mmol, 2.00 equiv) and DMAP (48.5 mg, 0.397 mmol, 0.300 equiv) and DCM (24 mL), **5.48h** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow oil (515 mg, 1.05 mmol, 80% yield).

Rf (DCM/MeOH 98:2): 0.42. **[α]D^{20}** = -25.6 (c = 0.50, $CHCl_3$). **^{1}H NMR** (400 MHz, chloroform-*d*, unresolved mixture of rotamers) δ 7.45 – 7.27 (m, 7H, Ar*H*), 7.16 – 7.05 (m, 2H, Ar*H*), 5.55 (m, 1H, N*H*), 5.12 – 4.98 (m, 2H, OCH_2Ph), 4.74 – 4.65 (m, 1H, NHC*H*), 4.54 – 4.43 (m, 1H, NCH_2CH_2CH_2C*H*), 3.77 – 3.68 (m, 3H, COO*Me*), 3.68 – 3.57 (m, 1H, NCH_2CH_2CH_2CH), 3.34 – 3.23 (m, 1H, NCH_2CH_2CH_2CH), 3.14 – 3.03 (m, 1H, NHCHCH_2), 2.95 – 2.82 (m, 1H,

NHCHC*H₂*), 2.26 – 1.88 (m, 4H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$). **^{13}C NMR** (101 MHz, chloroform-*d*, unresolved mixture of rotamers) δ 172.3, 170.0, 155.8, 136.4, 135.0, 131.7, 131.6, 128.6, 128.3, 128.1, 121.1, 67.0, 59.0, 53.5, 52.4, 47.1, 38.4, 29.1, 25.0. **IR** (ν_{max}, cm^{-1}) 3281 (w), 2958 (m), 2884 (w), 1742 (s), 1718 (s), 1645 (s), 1489 (s), 1437 (s), 1250 (s), 1199 (s), 1071 (m), 1027 (m), 910 (m), 735 (s). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{23}H_{25}{}^{79}BrN_2NaO_5{}^+$ 511.0839; Found 511.0847.

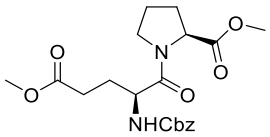
((S)-2-(((benzyloxy)carbonyl)amino)-3-(4-bromophenyl)propanoyl)-L-proline (5.17o)



Following the general procedure F and starting with **5.48h** (500 mg, 1.02 mmol, 1.00 equiv) lithium hydroxide monohydrate (214 mg, 5.11 mmol, 5.00 equiv), water (5.5 mL) and THF (5.5 mL), **5.17o** was obtained as a white sticky solid (200 mg, 0.421 mmol, 41% yield).

[α]D^{20} = -26.1 (c = 0.54, $CHCl_3$). **^{1}H NMR** (400 MHz, DMSO-d_6, unresolved mixture of rotamers) δ 13.55 – 12.78 (br s, 1H, COO*H*), 7.66 – 7.55 (m, 1H, N*H*), 7.47 – 7.39 (m, 2H, Ar*H*), 7.37 – 7.20 (m, 6H, Ar*H*), 7.19 – 7.11 (m, 1H, Ar*H*), 5.04 – 4.84 (m, 2H, OCH_2Ph), 4.46 – 4.34 (m, 1H, NHC*H*), 4.33 – 4.19 (m, 1H, $NCH_2CH_2CH_2CH$), 3.70 – 3.54 (m, 1H, $NCH_2CH_2CH_2CH$), 3.47 – 3.22 (m, 1H, $NCH_2CH_2CH_2CH$), 2.98 – 2.82 (m, 1H, NHCHC*H₂*), 2.82 – 2.65 (m, 1H, NHCHC*H₂*), 2.19 – 1.59 (m, 4H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 174.0, 169.3, 155.8, 137.3, 137.0, 131.7, 130.9, 128.3, 127.7, 127.5, 119.5, 65.3, 59.1, 53.9, 46.4, 35.8, 28.7, 24.4. **IR** (ν_{max}, cm^{-1}) 3302 (w), 3060 (w), 2878 (w), 2955 (w), 1713 (s), 1632 (s), 1489 (m), 1450 (m), 1328 (w), 1264 (m), 1041 (m), 1011 (m), 734 (s). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{22}H_{23}{}^{79}BrN_2NaO_5{}^+$ 497.0683; Found 497.0694.

Methyl ((S)-2-(((benzyloxy)carbonyl)amino)-5-methoxy-5-oxopentanoyl)-L-prolinate (5.48i)

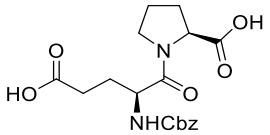


Following the general procedure C and starting with Z-Glu(OMe)-OH (500 mg, 1.69 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (1.12 g, 6.77 mmol, 4.00 equiv), EDC·HCl (649 mg, 3.39 mmol, 2.00 equiv) and DMAP (62.1 mg, 0.508 mmol, 0.300 equiv) and DCM (30 mL), **5.48i** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow oil (657 mg, 1.62 mmol, 95% yield).

Rf (DCM/MeOH 98:2): 0.31. **[α]D^{20}** = -50.5 (c = 0.57, $CHCl_3$). **^{1}H NMR** (400 MHz, chloroform-*d*, unresolved mixture of rotamers) δ 7.38 – 7.28 (m, 5H, Ar*H*), 5.59 (d, *J* = 8.4 Hz, 1H, N*H*), 5.12 – 5.03 (m, 2H, OCH_2Ph), 4.61 (tt, *J* = 8.9, 4.5 Hz, 1H, NHC*H*), 4.53 (dd, *J* = 8.7, 4.3 Hz, 1H, $NCH_2CH_2CH_2CH$), 3.83 – 3.64 (m, 8H, COO*Me* + $NCH_2CH_2CH_2CH$), 2.59 – 2.34 (m, 2H, $NHCHCH_2CH_2$), 2.32 – 2.12 (m, 2H, NHCHC*H₂* + $NCH_2CH_2CH_2CH$), 2.10 – 1.91 (m, 3H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$), 1.91 – 1.74 (m, 1H, NHCHC*H₂*). **^{13}C NMR** (101 MHz,

chloroform-*d*, unresolved mixture of rotamers) δ 173.6, 172.3, 170.4, 156.3, 136.4, 128.6, 128.3, 128.1, 67.0, 58.9, 52.4, 51.9, 51.6, 47.1, 29.2, 29.1, 27.9, 25.1. **IR** (v_{max}, cm^{-1}) 3308 (w), 2952 (w), 1737 (s), 1647 (s), 1525 (m), 1438 (s), 1247 (s), 1199 (s), 1176 (s), 1044 (m), 913 (w), 739 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{20}H_{26}N_2NaO_7^+$ 429.1632; Found 429.1629.

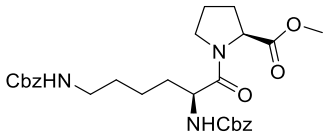
((Benzyloxy)carbonyl)-L-glutamyl-L-proline (5.17p)



Following the general procedure F and starting with **5.48i** (600 mg, 1.48 mmol, 1.00 equiv) lithium hydroxide monohydrate (310 mg, 7.38 mmol, 5.00 equiv), water (7.8 mL) and THF (7.8 mL), **5.17p** was obtained as a white sticky solid (434 mg, 1.15 mmol, 78% yield).

[α]D^{20} = -17.6 (c = 0.95, $CHCl_3$). **^{1}H NMR** (400 MHz, chloroform-*d*, unresolved mixture of rotamers) δ 9.80 – 9.41 (br s, 2H, COO*H*), 7.36 – 7.27 (m, 5H, Ar*H*), 6.36 (d, *J* = 8.5 Hz, 1H, N*H*), 5.06 (s, 2H, OCH_2Ph), 4.62 (q, *J* = 7.8 Hz, 1H, NHC*H*), 4.52 (dd, *J* = 8.4, 4.1 Hz, 1H, $NCH_2CH_2CH_2CH$), 3.80 – 3.61 (m, 2H, NCH_2CH2CH2CH), 2.55 – 2.35 (m, 2H, CH_2COOH), 2.28 – 1.81 (m, 6H, NHCHCH_2 + $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$). **^{13}C NMR** (101 MHz, chloroform-*d*, unresolved mixture of rotamers) δ 177.4, 175.5, 171.6, 156.6, 136.4, 128.6, 128.2, 128.1, 67.2, 59.2, 51.7, 47.4, 29.3, 28.8, 27.0, 24.9. **IR** (v_{max}, cm^{-1}) 3322 (m), 3092 (m), 2947 (w), 1713 (s), 1617 (s), 1532 (m), 1455 (m), 1266 (s), 1191 (s), 913 (s), 737 (s). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{18}H_{22}N_2NaO_7^+$ 401.1319; Found 401.1318.

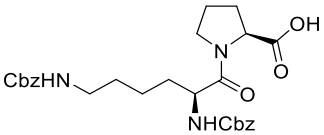
Methyl N^2,N^6-bis((benzyloxy)carbonyl)-L-lysyl-L-prolinate (5.48j)



Following the general procedure C and starting with Z-Lys(Z)-OH (800 mg, 1.93 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (1.28 g, 7.72 mmol, 4.00 equiv), EDC·HCl (740 mg, 3.86 mmol, 2.00 equiv) and DMAP (70.7 mg, 579 µmol, 0.300 equiv) and DCM (30 mL), **5.48j** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow sticky oil (881 mg, 1.68 mmol, 87% yield).

Rf (DCM/MeOH 99:1): 0.37. **[α]D^{20}** = -29.1 (c = 0.62, $CHCl_3$). **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.41 – 7.28 (m, 10H, Ar*H*), 5.66 (d, *J* = 8.4 Hz, 1H, CHN*H*), 5.27 (d, *J* = 5.5 Hz, 1H, CH_2N*H*), 5.06 (s, 4H, OCH_2Ph), 4.56 – 4.45 (m, 2H, $NCH_2CH_2CH_2CH$ + C*H*NH), 3.79 – 3.66 (m, 2H, NC$H_2CH_2CH_2CH$), 3.63 (s, 3H, COO*Me*), 3.26 – 3.08 (m, 2H, CH_2NH), 2.26 – 2.13 (m, 1H, $NCH_2CH_2CH_2CH$), 2.07 – 1.88 (m, 3H, $NCH_2CH_2CH_2CH$ + $CH_2CH_2CH_2CH_2NH$), 1.86 – 1.30 (m, 6H, $NCH_2CH_2CH_2CH$ + $CH_2CH_2CH_2CH_2NH$ + $CH_2CH_2CH_2CH_2NH$ + $CH_2CH_2CH_2CH_2NH$). **^{13}C NMR** (101 MHz, chloroform-*d*) δ 172.6, 170.8, 156.6, 156.1, 136.8, 136.4, 128.6, 128.5, 128.2, 128.1, 128.0, 128.0, 66.9, 66.6, 58.8, 52.4, 52.1, 47.0, 40.5, 32.0, 29.2, 29.0, 25.0, 21.6. **IR** (v_{max}, cm^{-1}) 3321 (m), 2951 (m), 1706 (s), 1643 (s), 1526 (s), 1438 (s), 1243 (s), 1219 (s), 1199 (s), 1027 (m), 1176 (m), 735 (s), 698 (s), 752 (s). **HRMS (nanochip-ESI/LTQ-Orbitrap)** m/z: $[M + H]^+$ Calcd for $C_{28}H_{36}N_3O_7^+$ 526.2548; Found 526.2548.

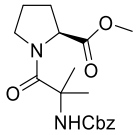
N^2,N^6-bis((benzyloxy)carbonyl)-L-lysyl-L-proline (5.17q)



Following the general procedure F and starting with **5.48j** (880 mg, 1.67 mmol, 1.00 equiv) lithium hydroxide monohydrate (351 mg, 8.37 mmol, 5.00 equiv), water (5.0 mL) and THF (5.0 mL), **5.17q** was obtained as a white sticky solid (724 mg, 1.41 mmol, 84% yield).

[α]D^{20} = -29.0 (c = 0.56, $CHCl_3$). **^{1}H NMR** (400 MHz, chloroform-*d*) δ 8.25 (s, 1H, COO*H*), 7.38 – 7.09 (m, 10H, Ar*H*), 6.54 – 6.12 (m, 1H, CHN*H*), 5.43 – 5.22 (m, 1H, CH_2N*H*), 5.20 – 4.89 (m, 4H, OCH_2Ph), 4.59 – 4.31 (m, 2H, $CH_2CH_2CH_2$C*H* + C*H*NH), 3.77 – 3.64 (m, 1H, NC$H_2CH_2CH_2$CH), 3.64 – 3.47 (m, 1H, NC$H_2CH_2CH_2$CH), 3.22 – 3.01 (m, 2H, CH_2NH), 2.18 – 1.54 (m, 6H, $NCH_2CH_2CH_2$CH + $NCH_2CH_2CH_2$CH + C$H_2CH_2CH_2CH_2$NH), 1.54 – 1.29 (m, 4H, $CH_2CH_2CH_2CH_2$NH + $CH_2CH_2CH_2CH_2$NH). **^{13}C NMR** (101 MHz, chloroform-*d*, signals not fully resolved) δ 175.0, 172.1, 156.9, 156.5, 136.8, 136.6, 128.6, 128.2, 128.2, 128.1, 66.9, 66.7, 59.6, 52.4, 47.4, 40.8, 31.7, 29.4, 28.7, 25.0, 22.1. **IR** (ν_{max}, cm^{-1}) 3327 (w), 2944 (w), 1702 (s), 1635 (s), 1529 (m), 1454 (m), 1247 (s), 736 (s), 1039 (m), 698 (m), 1028 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{27}H_{33}N_3NaO_7^+$ 534.2211; Found 534.2214.

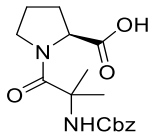
Methyl (2-(((benzyloxy)carbonyl)amino)-2-methylpropanoyl)-L-prolinate (5.48k)



Following the general procedure C and starting with 1-(phenylmethoxycarbonylamino)cyclopropane-1-carboxylic acid (500 mg, 2.13 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (1.41 g, 8.50 mmol, 4.00 equiv), EDC·HCl (815 mg, 4.25 mmol, 2.00 equiv) and DMAP (77.9 mg, 0.638 mmol, 0.300 equiv) and DCM (10 mL), **5.48k** was obtained after column chromatography (DCM/MeOH 99.5:0.5) as a yellow oil (262 mg, 0.753 mmol, 36% yield).

Rf (DCM/MeOH 99:1): 0.29. **^{1}H NMR** (400 MHz, chloroform-*d*,7:3 mixture of rotamers (major/minor)) δ 7.40 – 7.27 (m, 5H, Ar*H* (major/minor)), 5.60 (s, 0.7H, N*H* (major)), 5.39 (s, 0.3H, N*H* (minor)), 5.20 – 4.84 (m, 2H, OCH_2Ph (major+minor)), 4.53 (s, 0.7H, $NCH_2CH_2CH_2$C*H* (major)), 4.23 (s, 0.3H, $NCH_2CH_2CH_2$C*H* (minor)), 3.82 – 3.56 (m, 4H, COOMe + NC$H_2CH_2CH_2$CH (major+minor)), 3.54 – 3.26 (m, 1H, NC$H_2CH_2CH_2$CH (major+minor)), 2.14 – 1.70 (m, 4H, $NCH_2CH_2CH_2$CH + $NCH_2CH_2CH_2$CH (major+minor)), 1.70 – 1.35 (m, 6H, *Me* (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*) δ 173.1, 172.2, 154.3, 136.6, 128.6, 128.3, 128.2, 66.5, 60.9, 56.9, 52.2, 48.0, 27.8, 25.8, 24.8, 24.4. **IR** (ν_{max}, cm^{-1}) 3304 (w), 2985 (w), 2952 (m), 1717 (s), 1621 (s), 2249 (w), 1524 (m), 1410 (s), 1257 (s), 1168 (s), 1204 (s), 1073 (s), 912 (m), 732 (s), 699 (s). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2NaO_5^+$ 371.1577; Found 371.1581.

(2-(((Benzyloxy)carbonyl)amino)-2-methylpropanoyl)-L-proline (5.17r)



Following the general procedure F and starting with **5.48k** (262 mg, 0.752 mmol, 1.00 equiv) lithium hydroxide monohydrate (158 mg, 3.76 mmol, 5.00 equiv), water (1.8 mL) and THF (1.8 mL), **5.17r** was obtained as a white sticky solid (183 mg, 0.548 mmol, 73% yield).

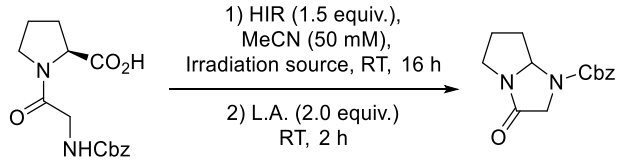
^{1}H NMR (400 MHz, chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 7.52 (br s, 1H, COO*H* (major+minor)), 7.41 – 7.29 (m, 5H, Ar*H* (major+minor)), 6.12 (s, 0.3H, N*H* (minor)), 5.54 (s, 0.7H, N*H* (major)), 5.37 (br s, 0.3H, OCH_2Ph (minor)), 5.06 (s, 1.4H, OCH_2Ph (major)), 4.97 – 4.84 (m, 0.3H, OCH_2Ph (minor)), 4.56 (t, *J* = 6.6 Hz, 0.7H, $NCH_2CH_2CH_2CH$ (major)), 4.23 (br s, 0.3H, $NCH_2CH_2CH_2CH$ (minor)), 3.67 – 3.22 (m, 2H, $NCH_2CH_2CH_2CH$ (major+minor)), 2.16 – 1.62 (m, 4H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$ (major+minor)), 1.61 – 1.36 (m, 6H, *Me* (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of diastereomers, signals not fully resolved) δ 174.6, 173.4, 154.9, 136.3, 128.6, 128.5, 67.1, 61.6, 57.1, 48.3, 27.4, 25.9, 25.2, 25.0. **IR** (v_{max}, cm^{-1}) 3298 (w), 2984 (w), 1714 (s), 1621 (m), 1527 (m), 1414 (m), 1259 (m), 1177 (m), 1075 (m), 910 (m), 731 (s), 698 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1415.

7.5.2. Optimization

Photochemistry reactions

Dry MeCN (2 mL) was added in a 5 mL test tube containing Z-Gly-Pro (**5.17a**) (31 mg, 0.10 mmol, 1.0 equiv), the HIR (0.15 mmol, 1.5 equiv), and the additional reagents under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs or 80 W CFL 16 h at RT. The reaction mixture was cooled to 0 °C and the Lewis acid (2.0 equiv) was added dropwise. The reaction was let stirring for 2 h at RT.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ (and 10 mL of $Na_2S_2O_3$ (10 %) when I_2 or NaI were used) then extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by prep-TLC (DCM/EtOAc 7:3).



5.17a 0.1 mmol → **5.32a**

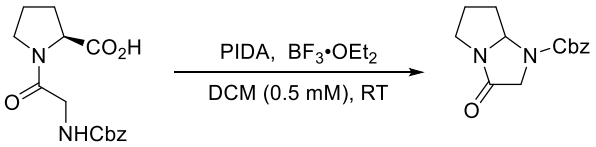
Entry	HIR source	L.A.	Additional reagent	Irradiation source	Conversion[b]	Yield[c]
1[d]	AcOBX	$BF_3{\cdot}Et_2O$	$Ru(bpy)_3Cl_2$ (3 mol%)	Blue LEDs	100%	66%
2[d]	**PIDA**	**$BF_3{\cdot}Et_2O$**	**$Ru(bpy)_3Cl_2$ (3 mol%)**	**Blue LEDs**	**6%**	**76%**
3	MeOBX	$BF_3{\cdot}Et_2O$	$Ru(bpy)_3Cl_2$ (3 mol%)	Blue LEDs	100%	54%
4	MeOBX	TFA	$Ru(bpy)_3Cl_2$ (3 mol%)	Blue LEDs	100%	54%
5	MeOBX	TFA[e]	$Ru(bpy)_3Cl_2$ (3 mol%)	Blue LEDs	100%	76%
6[f]	PIDA	$BF_3{\cdot}Et_2O$	I_2 (0.5 equiv.)	80 W CFL	100%	57%
7	PIDA[g]	$BF_3{\cdot}Et_2O$	NaI (4.0 equiv.)	80 W CFL	100%	78%
8[f]	PIDA	None	I_2 (0.5 equiv.)	None	100%	0%
9[f]	PIDA	$BF_3{\cdot}Et_2O$	None	80 W CFL	54%	92%

[a]Sequential reaction: 16 h for the first step and 2 h after the addition of the Lewis acid. [b]Measured by LCMS after the addition of the Lewis acid. [c]Isolated yield. [d]0.3 mmol scale. [e]10.0 equiv. [f]Reaction performed in DCM. [g]4.0 equiv.

Oxidative reactions

Dry DCM (2 mL) was added in a 5 mL test tube containing Z-Gly-Pro (**5.17a**) (31 mg, 0.10 mmol, 1.0 equiv) and PIDA under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and $BF_3 \cdot OEt_2$ was added dropwise. The reaction was let stirring at RT.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ then extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting mixture was analyzed by ^{1}H NMR (400 MHz, $CDCl_3$) using CH_2Br_2 as an internal standard.



5.17a 0.1 mmol — **5.32a**

Entry	Solvent	PIDA	$BF_3 \cdot Et_2O$	Time (h)	NMR Yield[a]
1	MeCN	1.5 equiv.	2.0 equiv.	2	88%[b]
2	**DCM**	**1.5 equiv.**	**2.0 equiv.**	**2**	**quant. (97)[b]**
4	DCM	1.5 equiv.	1.0 equiv.	2	quant%
5	DCM	1.0 equiv.	1.0 equiv.	2	88%
6	DCM	None	1.0 equiv.	1	0%
7	DCM	1.0 equiv.	None	1	0%
8[c]	DCM	2.0 equiv.	2.0 equiv.	4[d]	96%[b]

[a]^{1}H NMR of the crude mixture with CH_2Br_2 as an internal standard. [b]Isolated yield. [c]0.3 mmol scale. [d]Sequential reaction: the reaction started with PIDA (1.0 equiv) and $BF_3 \cdot Et_2O$ (1.0 equiv), after 2 h a second equivalent of each is added and the reaction stirred for 2 more h.

Additionally, other protecting groups than Cbz (Boc or Ac) were not compatible with the decarboxylative cyclisation reaction.

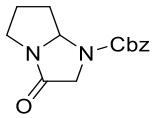
7.5.3. Synthesis of Aminal Heterocycles

General procedure G for the decarboxylative cyclisation of dipeptides derivatives

Dry DCM (6 mL) was added in a 10 mL test tube containing the corresponding dipeptide or small molecule (0.30 mmol, 1.0 equiv) and PIDA (97 mg, 0.30 mmol, 1.0 equiv) under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (79 µL, 0.30 mmol, 1.0 equiv) was added dropwise. The reaction was let stirring for 2 h at RT. Then, PIDA (97 mg, 0.30 mmol, 1.0 equiv) was added. The mixture was degassed by Ar bubbling, cooled to 0 °C and $BF_3{\cdot}OEt_2$ (79 µL, 0.30 mmol, 1.0 equiv) was added dropwise. The reaction was let stirring for 2 h at RT.

The crude mixture was diluted with 15 mL of sat. $NaHCO_3$ then extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel. Compounds **5.32a** to **5.32e, 5.32g** and **5.32n** are obtained as a racemic mixture.

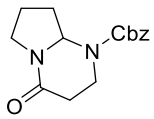
3-Keto-5,6,7,7a-tetrahydro-2H-pyrrol[1,2-a]imidazole-1-carboxylic acid benzyl ester (5.32a)



Following the general procedure G and starting with Cbz-Gly-Pro (**5.17a**) (92 mg, 0.30 mmol, 1.0 equiv), **5.32a** was obtained after column chromatography (DCM/EtOAc 4:1) as a white oil (75 mg, 0.29 mmol, 96% yield).

Rf (DCM/EtOAc 7:3): 0.57. **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.41 – 7.29 (m, 5H, Ar*H*), 5.26 – 5.09 (m, 3H, OCH_2Ph + NC*H*), 4.28 – 4.17 (m, 1H, NC(O)CH_2NCbz), 4.07 – 3.95 (m, 1H, NC(O)CH_2NCbz), 3.77 – 3.65 (m, 1H, NCH_2CH$_2$CH$_2$CHN), 3.19 – 3.04 (m, 1H, NCH_2CH$_2$CH$_2$CHN), 2.46 – 1.86 (m, 3H, NCH$_2$CH_2CH$_2$CHN+ NCH$_2$CH$_2$CH_2CHN), 1.52 – 1.38 (m, 1H, NCH_2CH$_2$CH_2CHN). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 170.4, 170.1, 153.9, 153.5, 136.0, 128.7, 128.4, 128.1, 77.0, 76.6, 67.7, 67.5, 51.3, 51.2, 41.6, 32.2, 31.6, 24.5, 24.4. **IR** (ν_{max}, cm^{-1}) 2951 (w), 2897 (w), 1712 (s), 1408 (m), 1358 (m), 1300 (m), 1122 (m), 1014 (w), 748 (w). **HRMS (nanochip-ESI/LTQ-Orbitrap)** m/z: $[M + H]^+$ Calcd for $C_{14}H_{17}N_2O_3^+$ 261.1234; Found 261.1231.

Benzyl 4-oxohexahydropyrrolo[1,2-a]pyrimidine-1(2H)-carboxylate (5.32b)

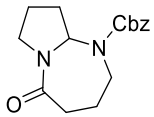


Following the general procedure G and starting with **5.17f** (96 mg, 0.30 mmol, 1.0 equiv), **5.32b** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow oil (56 mg, 0.21 mmol, 68% yield).

Rf (DCM/MeOH 98:2): 0.34. **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.38 – 7.28 (m, 5H, Ar*H*), 5.22 – 5.03 (m, 3H,OCH_2Ph + NC*H*), 4.21 – 4.11 (m, 1H, NC(O)CH$_2$CH_2N), 3.76 – 3.64 (m, 1H, NCH_2CH$_2$CH$_2$CHN), 3.38 (ddd, *J* = 12.3, 9.4, 3.0 Hz, 1H, NCH_2CH$_2$CH$_2$CHN), 3.17 (ddd,

J = 13.1, 10.9, 4.3 Hz, 1H, NC(O)CH_2CH_2N), 2.54 – 2.41 (m, 1H, $NCH_2CH_2CH_2$CHN), 2.41 – 2.30 (m, 2H, NC(O)CH_2CH_2N), 2.00 – 1.58 (m, 3H, $NCH_2CH_2CH_2$CHN + $NCH_2CH_2CH_2$CHN). **^{13}C NMR** (101 MHz, chloroform-*d*) δ 168.3, 154.4, 136.0, 128.6, 128.4, 128.2, 70.0, 67.7, 43.3, 39.0, 32.9, 32.3, 19.8. **IR** (v_{max}, cm^{-1}) 3533 (w), 2951 (w), 2889 (w), 1705 (s), 1655 (s), 1450 (s), 1415 (s), 1358 (m), 1200 (s), 1107 (m), 737 (m), 698 (m). **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O_3^+$ 275.1390; Found 275.1394.

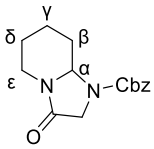
Benzyl 5-oxooctahydro-1H-pyrrolo[1,2-a][1,3]diazepine-1-carboxylate (5.32c)



Following the general procedure G and starting with **5.17g** (100 mg, 0.300 mmol, 1.00 equiv), **5.32c** was obtained after column chromatography (DCM/MeOH 99:1) as a yellow oil (78 mg, 0.27 mmol, 91% yield).

Rf (DCM/MeOH 98:2): 0.37. **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.43 – 7.27 (m, 5H, Ar*H*), 5.41 (t, *J* = 6.0 Hz, 1H, NC*H*), 5.22 – 5.09 (m, 2H, OCH_2Ph), 3.84 – 3.70 (m, 1H, $NCH_2CH_2CH_2$CHN), 3.61 – 3.50 (m, 2H, NC(O)$CH_2CH_2CH_2$N), 3.23 – 3.07 (m, 1H, $NCH_2CH_2CH_2$CHN), 2.52 – 2.28 (m, 3H, NC(O)$CH_2CH_2CH_2$N + $NCH_2CH_2CH_2$CHN), 2.11 – 1.65 (m, 5H, $NCH_2CH_2CH_2$CHN + $NCH_2CH_2CH_2$CHN + NC(O)$CH_2CH_2CH_2$N). **^{13}C NMR** (101 MHz, chloroform-*d*, one aliphatic signal not resolved) δ 171.7, 154.9, 136.3, 128.7, 128.3, 128.0, 72.2, 67.4, 46.2, 42.3, 33.5, 23.3, 21.9. **IR** (v_{max}, cm^{-1}) 3537 (w), 2951 (m), 2885 (w), 1701 (s), 1647 (s), 1450 (m), 1412 (s), 1647 (s), 1257 (m), 1180 (m), 1018 (m), 741 (m). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{16}H_{20}N_2NaO_3^+$ 311.1366; Found 311.1373.

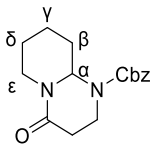
Benzyl 3-oxohexahydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (5.32d)



Following the general procedure G and starting with **5.17h** (96 mg, 0.30 mmol, 1.0 equiv), **5.32d** was obtained after column chromatography (DCM/EtOAc 9:1) as a yellow oil (74 mg, 0.27 mmol, 90% yield).

Rf (DCM/EtOAc 9:1): 0.35. **^{1}H NMR** (400 MHz, chloroform-*d*, 3:2 mixture of rotamers (major/minor)) δ 7.42 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.24 – 5.09 (m, 2H, OCH_2Ph (major+minor)), 4.91 (t, *J* = 12.9 Hz, 1H, pipHα (major+minor)), 4.26 (ddt, *J* = 13.4, 5.2, 1.7 Hz, 1H, pipHε (major+minor)), 4.18 – 4.00 (m, 1H, NC(O)CH_2N (major+minor)), 3.97 – 3.84 (m, 1H, NC(O)CH_2N (major+minor)), 2.81 – 2.66 (m, 1H, pipHε (major+minor)), 2.57 – 2.46 (m, 0.6H, pipHβ (major)), 2.38 – 2.24 (m, 0.4H, pipHβ (minor)), 1.97 – 1.84 (m, 1H, pipHγ (major+minor)), 1.74 – 1.60 (m, 1H, pipHδ (major+minor)), 1.60 – 1.43 (m, 1H, pipHγ (major+minor)), 1.43 – 1.28 (m, 1H, pipHδ (major+minor)), 1.28 – 1.13 (m, 1H, pipHβ (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 165.6, 153.7, 136.1, 128.7, 128.4, 128.3, 128.1, 72.3, 72.0, 67.7, 67.4, 48.2, 39.9, 32.9, 32.2, 24.4, 22.2, 22.1. **IR** (v_{max}, cm^{-1}) 3564 (w), 2943 (w), 2866 (w), 1705 (s), 1450 (m), 1412 (s), 1361 (m), 1304 (m), 1281 (m), 1119 (m), 984 (w), 752 (w). **HRMS (ESI/QTOF)** m/z: [M + H]+ Calcd for $C_{15}H_{19}N_2O_3^+$ 275.1390; Found 275.1397.

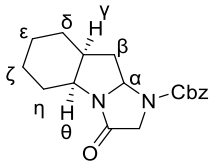
Benzyl 4-oxohexahydro-2H-pyrido[1,2-a]pyrimidine-1(6H)-carboxylate (5.32e)



Following the general procedure G and starting with **5.17i** (0.10 g, 0.30 mmol, 1.0 equiv), **5.32e** was obtained after column chromatography (DCM/EtOAc 9:1) as a white sticky solid (68 mg, 0.24 mmol, 79% yield).

Rf (DCM/EtOAc 9:1): 0.27. **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.43 – 7.30 (m, 5H, Ar*H*), 5.37 – 5.23 (m, 1H, pipHα), 5.17 (s, 2H, OCH_2Ph), 4.79 (dd, *J* = 13.3, 1.9 Hz, 1H, pipHε), 4.18 (br s, 1H, NC(O)CH_2CH_2N), 3.27 (s, 1H, NC(O)CH_2CH_2N), 2.61 – 2.44 (m, 2H, pipHε + NC(O)C$H_2$$CH_2$N), 2.42 – 2.32 (m, 1H, NC(O)C$H_2$$CH_2$N), 2.01 – 1.76 (m, 2H, pipHβ + pipHγ), 1.75 – 1.57 (m, 3H, pipHβ + pipHγ + pipHδ), 1.45 – 1.28 (m, 1H, pipHδ). **^{13}C NMR** (101 MHz, chloroform-*d*) δ 166.1, 154.0, 136.1, 128.7, 128.5, 128.1, 68.7, 67.9, 43.5, 37.0, 32.6, 31.2, 24.9, 24.2. **IR** (ν_{max}, cm^{-1}) 2939 (m), 3510 (w), 2862 (w), 1705 (s), 1427 (s), 1200 (s), 1122 (m), 1011 (m), 744 (m), 1315 (m), 1269 (m). **HRMS (ESI/QTOF)** m/z: [M + H]$^+$ Calcd for $C_{16}H_{21}N_2O_3^+$ 289.1547; Found 289.1547.

Benzyl (4aS,8aS)-3-oxodecahydro-1H-imidazo[1,2-a]indole-1-carboxylate (5.32f)

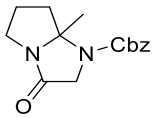


Following the general procedure G and starting with **5.17j** (108 mg, 0.300 mmol, 1.00 equiv), **5.32f** was obtained after column chromatography (DCM/EtOAc 97:3) as a yellow oil (29.0 mg, 92.0 µmol, 31% yield, dr 3:2).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereomers by integrating the NC(O)CH_2N proton of each diastereomer. Attributions of protons for each diastereomers was supported by 2D experiments.

Rf (DCM/EtOAc 97:3): 0.20. **^{1}H NMR** (400 MHz, chloroform-*d*, 3:2 mixture of diastereomers (major/minor)) δ 7.46 – 7.29 (m, 5H, Ar*H* (major+minor)), 5.42 (br s, 1H, Hα (major+minor)), 5.25 – 5.09 (m, 2H, OCH_2Ph (major+minor)), 4.21 – 4.10 (m, 1H, NC(O)CH_2N (major+minor)), 4.10 – 4.02 (m, 1H, Hθ (major+minor)), 4.00 – 3.96 (m, 0.6H, NC(O)CH_2N (major)), 3.96 – 3.91 (m, 0.4H, NC(O)CH_2N (minor), 2.39 – 2.03 (m, 2H, Hβ + Hη (major+minor)), 1.95 – 1.60 (m, 3H, Hβ + Hγ + Hη (major+minor)), 1.60 – 1.19 (m, 6H, 2Hδ + 2Hε +2Hζ (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of diastereomers, signals not fully resolved) δ 172.1, 154.0, 153.7, 136.1, 128.7, 128.4, 128.2, 75.8, 75.3, 67.5, 56.3, 51.1, 37.7, 36.5, 35.8, 27.5, 26.8, 22.4, 21.2. **IR** (ν_{max}, cm^{-1}) 2931 (m), 2862 (w), 1709 (s), 1419 (m), 1396 (m), 1354 (m), 1304 (m), 1119 (m), 1007 (w), 741 (m). **HRMS (ESI/QTOF)** m/z: [M + H]$^+$ Calcd for $C_{18}H_{23}N_2O_3^+$ 315.1703; Found 315.1706.

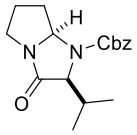
7a-Methyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (5.32g)



Following the general procedure G and starting with **5.17k** (96 mg, 0.30 mmol, 1.0 equiv), **5.32g** was obtained after column chromatography (DCM/EtOAc 4:1) as a yellow oil (38 mg, 0.14 mmol, 47% yield).

Rf (DCM/EtOAc 4:1): 0.27. **^{1}H NMR** (400 MHz, chloroform-*d*, 3:2 mixture of rotamers (major/minor)) δ 7.41 – 7.30 (m, 5H, Ar*H* (major+minor)), 5.19 – 5.09 (m, 2H, OC*H*$_2$Ph (major+minor)), 4.25 – 4.03 (m, 2H, NC(O)C*H*$_2$N (major+minor)), 3.80 – 3.68 (m, 1H, NC*H*$_2$CH$_2$CH$_2$C (major+minor)), 3.19 – 3.03 (m, 1H, NC*H*$_2$CH$_2$CH$_2$C (major+minor)), 2.41 – 2.28 (m, 0.6H, NCH$_2$CH$_2$C*H*$_2$C (major)), 2.24 – 1.97 (m, 2.4H, NCH$_2$C*H*$_2$CH$_2$C + NCH$_2$CH$_2$C*H*$_2$C (minor)), 1.92 – 1.73 (m, 1H, NCH$_2$CH$_2$C*H*$_2$C (major+minor)), 1.59 (s, 1.8H, C*Me* (major)), 1.51 (s, 1.2H, C*Me* (minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of rotamers) δ 168.6, 168.2, 152.8, 152.5, 136.2, 136.0, 128.7, 128.6, 128.4, 128.3, 128.2, 127.9, 84.7, 84.2, 67.7, 67.1, 51.8, 51.3, 40.5, 40.4, 37.4, 36.5, 24.8, 24.7, 24.1, 23.1. **IR** (ν_{max}, cm^{-1}) 3552 (w), 2970 (w), 1705 (s), 1423 (m), 1392 (m), 1354 (m), 1304 (w), 1215 (w), 1103 (m), 1068 (m), 756 (m). **HRMS (ESI/QTOF)** m/z: [M + H]$^+$ Calcd for $C_{15}H_{19}N_2O_3^+$ 275.1390; Found 275.1397.

Benzyl 2-isopropyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (5.32h)

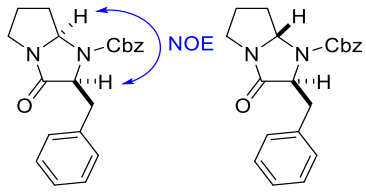


Following the general procedure G and starting with Cbz-Val-Pro (**5.17l**) (105 mg, 0.300 mmol, 1.00 equiv), **5.32h** was obtained after column chromatography (DCM/ EtOAc 95:5) as a colorless oil (90 mg, 0.30 mmol, 99% yield, dr 70:30).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereomers by integrating the NC(O)C*H*N proton of each diastereomer. Attributions of protons for each diastereomers was supported by 2D experiments.

Rf (DCM/ EtOAc 95:5): 0.28. **[α]D^{20}** = +55.8 (c = 0.79, CHCl$_3$, diastereomeric mixture). **^{1}H NMR** (400 MHz, acetonitrile-*d*$_3$, 7:3 mixture of diastereomers (major/minor), complex mixture of rotamers) δ 7.43 – 7.29 (m, 5H, Ar*H* (major+minor)), 5.21 – 5.06 (m, 3H, OC*H*$_2$Ph + NC*H* (major+minor)), 4.29 – 4.23 (m, 0.3H, NC(O)C*H*N (minor)), 4.12 – 4.06 (m, 0.7H, NC(O)C*H*N (major)), 3.64 – 3.50 (m, 1H, NC*H*$_2$CH$_2$CH$_2$CHN (major+minor)), 3.10 – 2.96 (m, 1H, NC*H*$_2$CH$_2$CH$_2$CHN (major+minor)), 2.54 – 1.97 (m, 4H, C*H*iPr + NCH$_2$C*H*$_2$CH$_2$CHN + NCH$_2$CH$_2$C*H*$_2$CHN (major+minor)), 1.55 – 1.37 (m, 1H, NCH$_2$CH$_2$C*H*$_2$CHN (major+minor)), 1.12 – 0.83 (m, 6H, *Me* (major+minor)). **^{13}C NMR** (101 MHz, acetonitrile-*d*$_3$, mixture of diastereomers and rotamers, signals not fully resolved) δ 172.0, 171.8, 154.0, 153.6, 137.9, 137.8, 129.5, 129.0, 128.9, 128.8, 128.7, 128.6, 77.4, 77.1, 67.9, 67.8, 67.7, 67.6, 67.5, 42.2, 42.1, 42.0, 33.2, 32.3, 31.1, 29.8, 24.9, 24.8, 24.8, 18.6, 18.5, 18.3, 17.8, 16.9. **IR** (ν_{max}, cm^{-1}) 2962 (m), 2893 (w), 1705 (s), 1396 (s), 1119 (m), 1427 (m), 1358 (m), 1331 (m), 1018 (m), 918 (w), 744 (m). **HRMS (ESI/QTOF)** m/z: [M + H]+ Calcd for $C_{17}H_{23}N_2O_3^+$ 303.1703; Found 303.1707.

Benzyl 2-benzyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (5.32i)



77 : 23

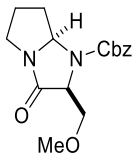
Following the general procedure G and starting with Cbz-Phe-Pro (**5.17m**) (119 mg, 0.300 mmol, 1.00 equiv), **5.32i** was obtained after column chromatography (DCM/EtOAc 9:1) as a pale-white oil (99 mg, 0.28 mmol, 94% yield, dr 77:23).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereomers by integrating the NC*H*N proton of each diastereomer. Attributions of protons for each diastereomers was supported by 2D experiments.

Rf (DCM/ethyl acetate 9:1): 0.26. **[α]D^{20}** = +115.6 (c = 0.64, $CHCl_3$, diastereomeric mixture). **^{1}H NMR** (400 MHz, chloroform-*d*, 77:23 mixture of diastereomers (major/minor), complex mixture of rotamers) δ 7.53 – 7.31 (m, 5H, Ar*H* (major+minor)), 7.23 – 7.11 (m, 3H, Ar*H* (major+minor)), 7.09 – 6.91 (m, 2H, Ar*H* (major+minor)), 5.42 – 5.08 (m, 2H, OC*H*$_2$Ph (major+minor)), 4.99 (ddd, *J* = 14.1, 8.5, 4.7 Hz, 0.77H, NC*H*N (major)), 4.73 – 4.58 (m, 0.77H, NC(O)C*H*$_2$N (major)), 4.58 – 4.46 (m, 0.23H, NC(O)C*H*$_2$N (minor)), 4.30 – 4.16 (m, 0.23H, NC*H*N (minor)), 3.63 – 3.52 (m, 0.46H, CHC*H*$_2$Ph (minor) + NC*H*$_2$CH$_2$CH$_2$CH (minor)), 3.48 – 3.33 (m, 1.54H, CHC*H*$_2$Ph (major) + NC*H*$_2$CH$_2$CH$_2$CH (major)), 3.32 – 3.23 (m, 0.77H, CHC*H*$_2$Ph (major)), 3.18 (dd, *J* = 13.8, 5.7 Hz, 0.12H, CHC*H*$_2$Ph (minor)), 3.07 (dd, *J* = 9.4, 2.4 Hz, 0.12H, CHC*H*$_2$Ph (minor)), 2.99 – 2.84 (m, 1H, NC*H*$_2$CH$_2$CH$_2$CH (major+minor)), 2.34 (dddd, *J* = 12.5, 7.4, 5.0, 2.2 Hz, 0.12H, NCH$_2$CH$_2$C*H*$_2$CH (minor)), 2.13 (dddd, *J* = 12.2, 7.1, 4.9, 2.1 Hz, 0.12H, NCH$_2$CH$_2$C*H*$_2$CH (minor)), 2.09 – 1.94 (m, 0.23H, NCH$_2$C*H*$_2$CH$_2$CH (minor)), 1.94 – 1.56 (m, 1.77H, NCH$_2$C*H*$_2$CH$_2$CH (major+minor) + NCH$_2$CH$_2$C*H*$_2$CH (major)), 1.56 – 1.43 (m, 0.77H, NCH$_2$C*H*$_2$CH$_2$CH (major), 1.43 – 1.27 (m, 0.23H, NCH$_2$CH$_2$C*H*$_2$CH (minor)), -0.22 – -0.40 (m, 0.77H, NCH$_2$CH$_2$C*H*$_2$CH (major)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 171.7, 171.6, 171.1, 170.9, 154.3, 153.5, 153.2, 152.8, 136.7, 136.4, 136.7, 136.0, 135.7, 135.3, 130.5, 129.9, 129.8, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.0, 126.9, 76.3, 76.0, 75.9, 75.5, 67.8, 67.6, 67.3, 67.4, 64.3, 64.1, 63.8, 63.6, 41.3, 41.1, 40.9, 36.3, 35.8, 34.6, 32.3, 31.5, 30.4, 29.8, 24.3, 24.2, 23.8, 23.7. **IR** (ν_{max}, cm^{-1}) 3032 (w), 2951 (w), 2897 (w), 1709 (s), 1427 (m), 1404 (m), 1361 (m), 1300 (w), 1126 (m), 1026 (w), 760 (m), 702 (m). **HRMS (ESI/QTOF)** m/z: [M + Na]$^{+}$ Calcd for $C_{21}H_{22}N_2NaO_3^{+}$ 373.1523; Found 373.1530.

A gram scale experiment with Cbz-Phe-Pro (**5.17m**) (1.00 g, 2.52 mmol, 1.00 equiv) was also accomplished using the same procedure and led to **5.32i** (846 mg, 2.41 mmol, 96%, dr 77:23) with a similar yield and identical dr ratio.

Benzyl 2-(methoxymethyl)-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (5.32j)

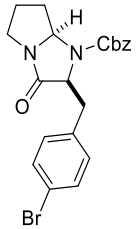


Following the general procedure G and starting with **5.17n** (105 mg, 0.300 mmol, 1.00 equiv), **5.32j** was obtained after column chromatography (DCM/EtOAc 9:1) as a yellow oil (79.0 mg, 0.260 mmol, 87% yield, dr 55:45).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereomers by integrating the $NCH_2CH_2CH_2CH$ proton of each diastereomer. Attributions of protons for each diastereomers was supported by 2D experiments.

Rf (DCM/EtOAc 9:1): 0.38. **[α]D^{20}** = +63.2 (c = 0.63, $CHCl_3$, diastereomeric mixture). **^{1}H NMR** (400 MHz, chloroform-*d*, 55:45 mixture of diastereomers (major/minor)) δ 7.41 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.30 – 5.05 (m, 3H, OCH_2Ph + NC*H*N (major+minor)), 4.28 (dt, *J* = 2.8, 1.7 Hz, 0.45H, NC(O)C*H*N (minor)), 4.23 – 4.18 (m, 0.55H, NC(O)C*H*N (major)), 4.10 (dd, *J* = 10.0, 2.7 Hz, 0.55H, CHCH_2OMe (major)), 3.80 (dd, *J* = 10.0, 2.9 Hz, 0.45H, CHCH_2OMe (minor)), 3.72 – 3.61 (m, 2H, CHCH_2OMe + NC$H_2CH_2CH_2$CH (major+minor)), 3.33 (s, 1.65H, OMe (major)), 3.23 (s, 1.35H, OMe (minor)), 3.21 – 3.12 (m, 1H, NC$H_2CH_2CH_2$CH (major+minor)), 2.52 (dddd, *J* = 12.3, 7.2, 5.0, 2.2 Hz, 0.45H, $NCH_2CH_2CH_2$CH (minor)), 2.31 (dddd, *J* = 12.2, 7.1, 4.9, 2.0 Hz, 0.55H, $NCH_2CH_2CH_2$CH (major)), 2.20 – 1.91 (m, 2H, $NCH_2CH_2CH_2$CH (major+minor)), 1.54 – 1.37 (m, 1H, $NCH_2CH_2CH_2$CH (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of diastereomers) δ 170.4, 170.2, 153.3, 152.9, 136.2, 136.1, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 77.1, 76.6, 70.3, 68.9, 67.4, 67.4, 64.0, 63.8, 59.6, 59.5, 41.6, 41.5, 32.6, 31.8, 24.7, 24.5. **IR** (ν_{max}, cm^{-1}) 3553 (w), 2925 (w), 1706 (s), 1434 (m), 1402 (s), 1361 (m), 1121 (s), 1037 (m), 767 (m), 699 (m). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{16}H_{20}N_2NaO_4^+$ 327.1315; Found 327.1309.

Benzyl 2-(4-bromobenzyl)-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (5.32k)



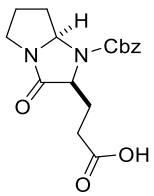
Following the general procedure G and starting with **5.17o** (0.14 g, 0.30 mmol, 1.0 equiv), **5.32k** was obtained after column chromatography (DCM/EtOAc 9:1) as a yellow oil (99 mg, 0.23 mmol, 77% yield, dr 75:25).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereomers by integrating the NC*H*N proton of each diastereomer. Attributions of protons for each diastereomers was supported by 2D experiments.

Rf (DCM/EtOAc 9:1): 0.39. **[α]D^{20}** = +123.9 (c = 0.69, $CHCl_3$, diastereomeric mixture). **^{1}H NMR** (400 MHz, chloroform-*d*, 3:1 mixture of diastereomers (major/minor), complex mixture of rotamers) δ 7.65 – 7.45 (m, 5H, Ar*H* (major+minor)), 7.45 – 7.36 (m, 2H, Ar*H* (major+minor)), 7.09 – 6.85 (m, 2H, Ar*H* (major+minor)), 5.56 – 5.22 (m, 2H, OCH_2Ph (major+minor)), 5.21 – 5.10 (m, 0.75H, NC*H*N (major)), 4.84 – 4.72 (m, 0.75H, NC(O)C*H*N (major)), 4.69 – 4.59 (m, 0.25H, NC(O)C*H*N (minor)), 4.44 (tdd, *J* = 8.9, 5.0, 1.8 Hz, 0.25H, NC*H*N (minor)), 3.74 (dtd, *J* = 11.7, 8.4, 5.2 Hz, 0.25H, NC$H_2CH_2CH_2$CH (minor)), 3.65 (dd, *J* = 13.8, 5.5 Hz, 0.25H, $CHCH_2$Ar (minor)), 3.59 – 3.46 (m, 1.5H, $CHCH_2$Ar (major) + NC$H_2CH_2CH_2$CH (major)), 3.40 – 3.31 (m, 0.75H, $CHCH_2$Ar (major)), 3.31 – 3.22 (m, 0.25H, $CHCH_2$Ar (minor)), 3.16 – 3.06

(m, 1H, NC*H*$_2$CH$_2$CH$_2$CH (major+minor)), 2.51 (dddd, *J* = 12.3, 7.1, 4.9, 2.1 Hz, 0.13H, NCH$_2$CH$_2$C*H*$_2$CH (minor)), 2.31 (dddd, *J* = 12.3, 7.2, 5.0, 2.0 Hz, 0.13H, NCH$_2$CH$_2$C*H*$_2$CH (minor)), 2.23 – 2.12 (m, 0.25H, NCH$_2$C*H*$_2$CH$_2$CH (minor)), 2.04 – 1.66 (m, 2.25H, NCH$_2$C*H*$_2$CH$_2$CH (major+minor) + NCH$_2$CH$_2$C*H*$_2$CH (major)), 1.54 – 1.43 (m, 0.25H, NCH$_2$CH$_2$C*H*$_2$CH (minor)), 0.00 (br p, *J* = 9.6 Hz, 0.75H, NCH$_2$CH$_2$C*H*$_2$CH (major)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 171.7, 171.6, 171.1, 171.0, 154.3, 153.5, 153.2, 152.8, 136.7, 136.4, 136.3, 136.0, 135.7, 135.3, 130.5, 129.9, 129.8, 128.8, 128.8, 128.7, 128.4, 128.3, 128.2, 128.0, 127.0, 126.9, 76.3, 76.0, 75.9, 75.5, 67.8, 67.6, 67.3, 67.2, 64.3, 64.1, 63.8, 63.6, 41.3, 41.1, 41.0, 36.3, 35.8, 34.6, 32.3, 31.5, 30.4, 29.8, 24.3, 24.2, 23.8, 23.8. **IR** (ν_{max}, cm^{-1}) 2958 (w), 1709 (s), 1429 (m), 1401 (s), 1123 (m), 755 (m), 1026 (m), 1357 (m), 699 (m), 1487 (m), 1012 (m). **HRMS (ESI/QTOF)** m/z: [M + H]$^+$ Calcd for $C_{21}H_{22}{}^{79}BrN_2O_3^+$ 429.0808; Found 429.0796.

3-(1-((Benzyloxy)carbonyl)-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazol-2-yl)propanoic acid (5.32l)



Dry DCM (6 mL) was added in a 10 mL test tube containing **5.17p** (114 mg, 0.300 mmol, 1.00 equiv) and PIDA (97 mg, 0.30 mmol, 1.0 equiv) under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (79 µL, 0.30 mmol, 1.0 equiv) was added dropwise. The reaction was let stirring for 2 h at RT. Then, PIDA (97 mg, 0.30 mmol, 1.0 equiv) was added. The mixture was degassed by Ar bubbling, cooled to 0 °C and $BF_3{\cdot}OEt_2$ (79 µL, 0.30 mmol, 1.0 equiv) was added dropwise. The reaction was let stirring for 2 h at RT.

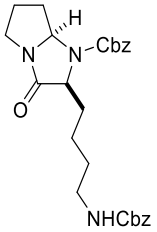
The crude mixture was diluted with 15 mL of sat. $NaHCO_3$ then extracted with diethyl ether (3 x 30 mL), washed with brine (30 mL). The combined aqueous layers were acidified with HCl (1 M) to pH=1 and then extracted with EtOAc (3 x 50 mL). All the organic layers were reunited, dried over $MgSO_4$, filtered, and concentrated under vacuum. **5.32l** was obtained after prep-TLC (DCM/MeOH 97:3) as a yellow sticky oil (54 mg, 0.16 mmol, 54% yield, dr 67:33).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereomers by integrating the NC(O)CHN proton of each diastereomer. Attributions of protons for each diastereomers was supported by 2D experiments.

Rf (DCM/MeOH 97:3): 0.30. **[α]D^{20}** = +31.4 (c = 0.40, $CHCl_3$, diastereomeric mixture). **^{1}H NMR** (400 MHz, chloroform-*d*, 67:33 mixture of diastereomers (major/minor)) δ 7.45 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.27 – 5.05 (m, 3H, OC*H*$_2$Ph + NC*H*N (major+minor)), 4.48 (s, 0.67H, NC(O)C*H*N (major)), 4.41 – 4.30 (m, 0.33H, NC(O)C*H*N (minor)), 3.77 – 3.59 (m, 1H, NC*H*$_2$CH$_2$CH$_2$CH (major+minor)), 3.20 – 3.06 (m, 1H, NC*H*$_2$CH$_2$CH$_2$CH (major+minor)), 2.60 – 1.95 (m, 7H, NCH$_2$C*H*$_2$CH$_2$CH + NCH$_2$CH$_2$C*H*$_2$CH + NCHC*H*$_2$CH$_2$COOH + NCHCH$_2$C*H*$_2$COOH (major+minor)), 1.56 – 1.33 (m, 1H, NCH$_2$CH$_2$C*H*$_2$CH (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of diastereomers, signals not fully resolved) δ 177.8, 171.8, 171.6, 155.0, 154.5, 153.3, 152.8, 135.9, 135.8, 128.7, 128.5, 128.8, 128.3, 76.5, 76.1, 67.9, 67.8, 67.7, 61.6, 61.5, 41.5, 41.4, 32.5, 32.0, 31.7, 29.8, 29.4, 26.2, 25.3, 24.4, 24.3. **IR** (ν_{max}, cm^{-1}) 2952 (w), 1704 (s), 1445 (m), 1401 (s), 1355 (s), 1130 (m), 1029 (w), 911 (m), 729

(s), 698 (m), 3214 (w), 2581 (w). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}N_2NaO_5^+$ 355.1264; Found 355.1262.

Benzyl 2-(4-(((benzyloxy)carbonyl)amino)butyl)-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (5.32m)

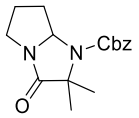


Following the general procedure G and starting with **5.17q** (153 mg, 0.300 mmol, 1.00 equiv), **5.32m** was obtained after column chromatography (DCM/MeOH 99:1) as a yellow oil (131 mg, 0.280 mmol, 93% yield, dr 80:20).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereomers by integrating the $NCH_2CH_2CH_2CH$ proton of each diastereomer. Attributions of protons for each diastereomers was supported by 2D experiments.

Rf (DCM/MeOH 99:1):.0.23. **[α]D^{20}** = +44.8 (c = 0.53, $CHCl_3$, diastereomeric mixture). **^{1}H NMR** (400 MHz, chloroform-*d*, 4:1 mixture of diastereomers (major+minor)) δ 7.45 – 7.27 (m, 10H, Ar*H* (major+minor)), 5.31 – 5.00 (m, 5.2H, OCH_2Ph (major+minor) + NC*H*N (major+minor) + N*H* (minor)), 4.98 – 4.58 (m, 0.8H, N*H* (major)), 4.51 – 4.21 (m, 1H, $NC(O)CH_2N$ (major+minor)), 3.74 – 3.54 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.26 – 2.97 (m, 3H, $NCH_2CH_2CH_2CH$ + CH_2NH (major+minor)), 2.59 – 2.45 (m, 0.2H, $NCH_2CH_2CH_2CH$ (minor)), 2.39 – 2.20 (m, 0.8H, $NCH_2CH_2CH_2CH$ (major)), 2.20 – 1.78 (m, 4H, $NCH_2CH_2CH_2CH$ + $CHCH_2CH_2CH_2CH_2NH$ (major+minor)), 1.60 – 1.06 (m, 5H, $NCH_2CH_2CH_2CH$ + $CHCH_2CH_2CH_2CH_2NH$ + $CHCH_2CH_2CH_2CH_2NH$ (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of diastereomers, signals not fully resolved) δ 172.4, 172.3, 156.5, 153.4, 152.8, 136.8, 136.1, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 76.5, 76.2, 67.6, 67.5, 67.4, 66.6, 62.4, 62.3, 41.5, 41.4, 40.9, 40.8, 32.6, 31.8, 30.6, 29.6, 29.5, 24.5, 24.3, 21.6, 21.1, 21.0. **IR** (ν_{max}, cm^{-1}) 3345 (w), 2936 (w), 1699 (s), 1400 (s), 1245 (m), 1530 (m), 1130 (m), 734 (s), 697 (m), 912 (m), 1356 (m). **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{26}H_{32}N_3O_5^+$ 466.2336; Found 466.2325.

Benzyl 2,2-dimethyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (5.32n)

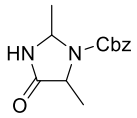


Following the general procedure G and starting with **5.17r** (0.10 g, 0.30 mmol, 1.0 equiv), **5.32n** was obtained after column chromatography (DCM/EtOAc 9:1) as a yellow oil (85 mg, 0.29 mmol, 98% yield).

Rf (DCM/EtOAc 8:2): 0.35. **^{1}H NMR** (400 MHz, chloroform-*d*, 56:44 mixture of rotamers (major/minor)) δ 7.46 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.25 – 5.03 (m, 3H, $NC(O)CH_2$ + NC*H*N(major+minor)), 3.76 – 3.65 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.19 – 3.03 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 2.54 – 2.44 (m, 0.44H, $NCH_2CH_2CH_2CH$

(major+minor)), 2.37 – 2.24 (m, 0.56H, $NCH_2CH_2CH_2CH$ (major+minor)), 2.18 – 1.90 (m, 2H, $NCH_2CH_2CH_2CH$ (major+minor)), 1.57 (s, 3.36H, Me (major)), 1.48 (d, *J* = 4.9 Hz, 2.64H, Me (minor)), 1.43 – 1.29 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of diastereomers, signals not fully resolved) δ 175.8, 154.4, 152.6, 136.3, 136.0, 128.7, 128.4, 128.3, 128.2, 128.0, 74.7, 74.5, 67.5, 67.0, 64.9, 64.6, 41.6, 41.4, 33.3, 32.6, 25.1, 24.1, 24.0, 22.9. **IR** (ν_{max}, cm^{-1}) 2979 (w), 1706 (s), 1422 (s), 1397 (s), 1354 (s), 1285 (m), 1091 (s), 999 (m), 769 (m), 753 (m), 698 (m). **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_3^+$ 289.1547; Found 289.1553.

Benzyl 2,5-dimethyl-4-oxoimidazolidine-1-carboxylate (5.32o)



Following the general procedure G and starting with Cbz-Ala-Ala (**5.17b**) (88 mg, 0.30 mmol, 1.0 equiv), **5.32o** was obtained after column chromatography (DCM/MeOH 97:3) as a white sticky solid (65 mg, 0.26 mmol, 87% yield)**.**

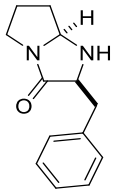
Rf (DCM/MeOH 97:3): 0.47. **[α]D^{20}** = +24.4 (c = 0.46, $CHCl_3$, diastereomeric mixture). **^{1}H NMR** (400 MHz, chloroform-*d*, unresolved mixture of diastereomers and rotamers) δ 8.07 – 7.84 (m, 1H, N*H*), 7.41 – 7.28 (m, 5H, Ar*H*), 5.29 – 5.02 (m, 3H, OCH_2Ph + NC*H*), 4.41 – 4.03 (m, 1H, NC(O)C*H*NCbz), 1.61 – 1.32 (m, 6H, *Me*). **^{13}C NMR** (101 MHz, chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 174.1, 173.9, 153.9, 153.3, 136.1, 136.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 67.4, 66.4, 66.2, 65.9, 54.6, 54.3, 54.1, 24.5, 23.8, 23.0, 21.7, 19.3, 18.6, 17.9, 16.4. **IR** (ν_{max}, cm^{-1}) 3275 (w), 2935 (w), 1705 (s), 1450 (m), 1408 (m), 1358 (m), 1300 (m), 1107 (m), 1061 (m), 1045 (m), 737 (m), 698 (m). **HRMS (nanochip-ESI/LTQ-Orbitrap)** m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}N_2O_3^+$ 249.1234; Found 249.1230.

7.5.4. Product Modifications

General procedure H for Cbz deprotection

The corresponding carbamate (1.0 equiv) was dissolved in ethanol (30 mM), and $Pd(OH)_2$ (10 mol %) was added. The mixture was stirred overnight at RT under H_2. The catalyst was removed by filtration, the filtrate was concentrated under reduced pressure and purified by prep-TLC.

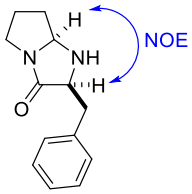
2-Benzylhexahydro-3H-pyrrolo[1,2-a]imidazol-3-one (5.54)



Following the general procedure H and starting with **5.32i** (35 mg, 0.10 mmol, 1.0 equiv), $Pd(OH)_2$/C (7.0 mg, 10 µmol, 0.10 equiv), and ethanol (3.3 mL), **5.54** was obtained as an oil (21 mg, 0.10 mmol, 97%, dr 77:23) after prep-TLC (DCM/EtOAc 7:3) allowing the isolation

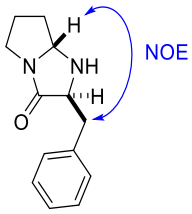
and clean NMR characterization of the major diastereomer. The minor isomer was not obtained as a pure fraction but a ^{1}H and ^{13}C NMR are still provided.

Data for the major cis- diastereomer:



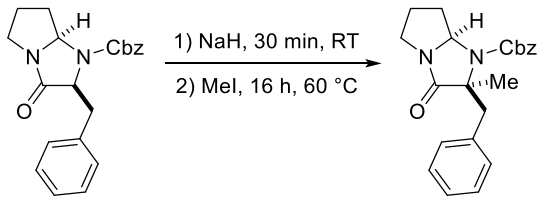
Rf (DCM/EtOAc 7:3): 0.25. **^{1}H NMR** (400 MHz, acetonitrile-d_3) δ 7.33 – 7.15 (m, 5H, Ar*H*), 4.76 – 4.67 (m, 1H, NC*H*NH), 4.05 (dd, *J* = 8.6, 3.6 Hz, 1H, NC(O)C*H*NH), 3.45 (dt, *J* = 11.4, 7.3 Hz, 1H, NCH_2CH$_2$CH$_2$CH), 3.06 (dd, *J* = 13.9, 3.9 Hz, 1H, CH_2Ph), 3.00 – 2.90 (m, 1H, NCH_2CH$_2$CH$_2$CH), 2.71 – 2.47 (m, 2H, CH_2Ph + N*H*), 1.92 – 1.81 (m, 3H, NCH$_2$CH_2CH$_2$CH + NCH$_2$CH$_2$CH_2CH), 1.13 – 1.01 (m, 1H, NCH$_2$CH$_2$CH_2CH). **^{13}C NMR** (101 MHz, acetonitrile-d_3) δ 176.0, 140.3, 130.4, 129.1, 127.1, 76.7, 64.9, 42.3, 39.9, 33.9, 25.4. **IR** (ν_{max}, cm^{-1}) 3349 (w), 3524 (w), 2949 (w), 1691 (s), 1496 (m), 1402 (m), 1336 (m), 1132 (w), 1031 (w), 907 (w), 749 (m), 700 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{13}H_{16}N_2NaO^+$ 239.1155; Found 239.1148.

Data for the minor trans- diastereomer:



Rf (DCM/EtOAc 7:3): 0.10. **^{1}H NMR** (400 MHz, acetonitrile-d_3, 85:15 mixture of diastereomers (trans:cis), only peaks for minor are given) δ 7.35 – 7.16 (m, 5H, Ar*H*), 4.67 – 4.57 (m, 1H, NC*H*NH), 3.70 (ddd, *J* = 8.3, 4.4, 1.2 Hz, 1H, NC(O)C*H*NH), 3.53 – 3.42 (m, 1H, NCH_2CH$_2$CH$_2$CH), 3.02 (dd, *J* = 14.1, 4.4 Hz, 1H, NCH_2CH$_2$CH$_2$CH), 2.99 – 2.91 (m, 1H, CH_2Ph), 2.86 (dd, *J* = 14.0, 8.3 Hz, 1H, CH_2Ph), 2.54 – 2.36 (m, 1H, N*H*), 2.00 – 1.80 (m, 3H, NCH$_2$CH_2CH$_2$CH + NCH$_2$CH$_2$CH_2CH), 1.33 – 1.19 (m, 1H, NCH$_2$CH$_2$CH_2CH). **^{13}C NMR** (101 MHz, acetonitrile-d_3, 85:15 mixture of diastereomers (trans:cis), only peaks for trans- are given) δ 178.0, 139.2, 130.2, 129.3, 127.4, 78.0, 64.9, 42.4, 38.8, 32.6, 25.1. **IR** (ν_{max}, cm^{-1}) 3470 (w), 3332 (w), 2942 (m), 2892 (w), 1692 (s), 1496 (m), 1454 (m), 1397 (m), 1335 (m), 1080 (w), 911 (w), 751 (m), 701 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{13}H_{16}N_2NaO^+$ 239.1155; Found 239.1148.

Benzyl 2-benzyl-2-methyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (5.55)

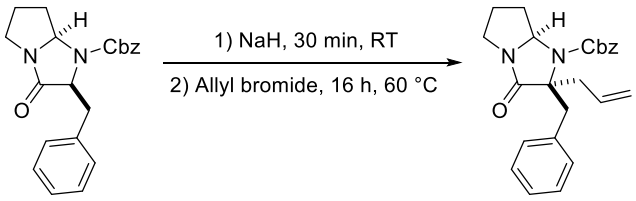


5.32i **5.55**

An oven-dried microwave vial was charged with sodium hydride (60% in mineral oil) (40 mg, 1.0 mmol, 10 equiv). After 3 vacuum/N_2 cycles, 1 mL of dry THF was added and the reaction was cooled to 0 °C. A solution of **5.32i** (35 mg, 0.10 mmol, 1.0 equiv) in 1 mL of dry THF was added dropwise and the reaction mixture was stirred for 30 minutes at RT. Iodomethane (19 µL, 0.30 mmol, 3.0 equiv) was added dropwise and the reaction was stirred overnight at 60 °C. The mixture was then allowed to cool to RT, quenched by addition of saturated aqueous NH_4Cl solution, and extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by prep-TLC (DCM/EtOAc 9:1) afforded **5.55** (19 mg, 52 µmol, 52% yield) as an oil.

Rf (DCM/EtOAc 9:1): 0.5. **^{1}H NMR** (400 MHz, chloroform-*d*, unresolved mixture of diastereomers and rotamers) δ 7.53 – 7.31 (m, 5H, Ar*H*), 7.19 – 6.93 (m, 5H, Ar*H*), 5.39 – 5.33 (m, 1H, OC*H*$_2$Ph), 5.32 – 5.26 (m, 0.4H, OC*H*$_2$Ph), 5.04 – 4.99 (m, 0.6H, OC*H*$_2$Ph), 4.99 – 4.89 (m, 1H, NC*H*N), 3.47 – 3.35 (m, 1.6H, NC*H*$_2$CH$_2$CH$_2$CH + CC*H*$_2$Ph), 3.20 – 3.09 (m, 1.4H, CC*H*$_2$Ph), 3.00 – 2.89 (m, 1H, NC*H*$_2$CH$_2$CH$_2$CH), 1.88 – 1.78 (m, 0.5H, NCH$_2$C*H*$_2$CH$_2$CH), 1.71 (s, 2H, Me), 1.69 – 1.64 (m, 1H, NCH$_2$CH$_2$C*H*$_2$CH), 1.63 – 1.59 (m, 1.5H, Me + NCH$_2$C*H*$_2$CH$_2$CH), 1.50 – 1.39 (m, 1H, NCH$_2$C*H*$_2$CH$_2$CH), -0.28 – -0.51 (m, 1H, NCH$_2$CH$_2$C*H*$_2$CH). **^{13}C NMR** (101 MHz, chloroform-*d*, unresolved mixture of diastereomers and rotamers) δ 174.3, 174.2, 153.9, 152.5, 137.8, 137.4, 136.6, 135.9, 130.3, 128.9, 128.7, 128.7, 128.3, 128.2, 127.0, 126.9, 75.0, 74.7, 70.6, 70.2, 67.8, 66.9, 41.7, 41.3, 41.1, 40.6, 31.6, 30.5, 29.7, 24.1, 23.6, 23.5, 22.8. **IR** (ν_{max}, cm^{-1}) 2972 (w), 1707 (s), 1454 (m), 1425 (s), 1398 (s), 1357 (m), 1283 (m), 1116 (m), 1075 (m), 1056 (s), 911 (w), 767 (m), 743 (m), 702 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{22}H_{24}N_2NaO_3^+$ 387.1679; Found 387.1682.

Benzyl 2-allyl-2-benzyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (5.56)



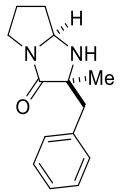
5.32i **5.56**

An oven-dried microwave vial was charged with sodium hydride (60% in mineral oil) (40 mg, 1.0 mmol, 10 equiv). After 3 vacuum/N_2 cycles, 1 mL of dry THF was added and the reaction was cooled to 0 °C. A solution of **5.32i** (35 mg, 0.10 mmol, 1.0 equiv) in 1 mL of dry THF was added dropwise and the reaction mixture was stirred for 30 minutes at RT. Allyl bromide (26 µL, 0.30 mmol, 3.0 equiv) was added dropwise and the reaction was stirred overnight at 60 °C. The mixture was then allowed to cool to RT, quenched by addition of saturated aqueous NH_4Cl solution, and extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by prep-TLC (DCM/EtOAc 9:1) afforded **5.56** (39 mg, 0.10 mmol, 100% yield) as an oil.

Rf (DCM/EtOAc 9:1): 0.53. **^{1}H NMR** (400 MHz, acetonitrile-*d*$_3$, unresolved mixture of diastereomers and rotamers) δ 7.58 – 7.53 (m, 0.6H, Ar*H*), 7.49 – 7.33 (m, 4.4H, Ar*H*), 7.22 – 7.12 (m, 3H, Ar*H*), 7.04 – 6.92 (m, 2H, Ar*H*), 5.75 – 5.54 (m, 1H, CH$_2$C*H*=CH$_2$), 5.35 – 5.24 (m, 1.4H, OC*H*$_2$Ph), 5.11 – 4.90 (m, 2.6H, CH$_2$CH=C*H*$_2$ + OC*H*$_2$Ph), 4.87 – 4.74 (m, 1H, NC*H*N), 3.35 – 3.25 (m, 1.6H, CC*H*$_2$Ph + NC*H*$_2$CH$_2$CH$_2$CH), 3.13 – 3.04 (m, 2H, CC*H*$_2$Ph +

C*H*$_2$CH=CH$_2$), 2.96 – 2.80 (m, 1.4H, C*H*$_2$CH=CH$_2$ + NC*H*$_2$CH$_2$CH$_2$CH), 2.52 – 2.42 (m, 1H, C*H*$_2$CH=CH$_2$), 1.77 – 1.55 (m, 2H, NCH$_2$C*H*$_2$CH$_2$CH + NCH$_2$CH$_2$C*H*$_2$CH), 1.44 – 1.29 (m, 1H, NCH$_2$C*H*$_2$CH$_2$CH), -0.35 – -0.53 (m, 1H, NCH$_2$CH$_2$C*H*$_2$CH). **^{13}C NMR** (101 MHz, acetonitrile-*d*$_3$, unresolved mixture of diastereomers and rotamers) δ 173.4, 173.2, 154.3, 153.3, 138.2, 138.1, 138.0, 137.4, 133.2, 133.0, 131.1, 130.1, 129.6, 129.5, 129.4, 129.1, 129.0, 128.9, 128.8, 127.8, 127.7, 119.8, 76.4, 76.3, 74.7, 74.3, 68.1, 67.3, 42.0, 41.9, 41.2, 40.9, 39.7, 31.3, 30.6, 24.1, 24.0. **IR** (v_{max}, cm^{-1}) 3068 (m), 2938 (w), 1706 (s), 1604 (w), 1496 (m), 1441 (s), 1397 (s), 1357 (s), 1288 (m), 1072 (m), 996 (m), 923 (m), 767 (m), 701 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{24}H_{26}N_2NaO_3^+$ 413.1836; Found 413.1837.

2-Benzyl-2-methylhexahydro-3H-pyrrolo[1,2-a]imidazol-3-one (5.57)

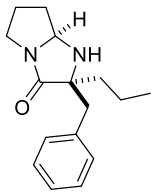


Following the general procedure H and starting with **5.55** (36 mg, 0.10 mmol, 1.0 equiv), Pd(OH)$_2$/C (7.0 mg, 10 µmol, 0.10 equiv), and ethanol (3.3 mL), **5.57** was obtained after prep-TLC (DCM/EtOAc 7:3) as an oil (18 mg, 78 µmol, 78%, dr 93:7).

The dr ratio was measured from the ^{1}H NMR spectrum of the mixture of diastereomers by integrating the NC*H*NH proton of each diastereomer. Attributions of protons for each diastereomers was supported by 2D experiments. The dr of the crude mixture was 88:12 whereas the dr of the isolated product was 93:7.

Rf (DCM/EtOAc 9:1): 0.21. **^{1}H NMR** (400 MHz, acetonitrile-*d*$_3$, 93:7 mixture of diastereomers (major/minor)) δ 7.30 – 7.15 (m, 5H, Ar*H* (major+minor)), 4.70 (dd, *J* = 8.0, 5.2 Hz, 0.93H, NC*H*NH (major)), 4.37 – 4.30 (m, 0.07H, NC*H*NH (minor)), 3.48 – 3.38 (m, 0.07H, NC*H*$_2$CH$_2$CH$_2$CH (minor)), 3.32 (dt, *J* = 11.1, 7.7 Hz, 0.93H, NC*H*$_2$CH$_2$CH$_2$CH (major)), 2.98 – 2.86 (m, 2H, NC*H*$_2$CH$_2$CH$_2$CH + CC*H*$_2$Ph (major+minor)), 2.71 (d, *J* = 13.4 Hz, 0.07H, CC*H*$_2$Ph (minor)), 2.62 (d, *J* = 13.2 Hz, 0.93H, CC*H*$_2$Ph (major)), 2.23 (br s, 1H, N*H* (major+minor)), 1.83 – 1.59 (m, 3H, NCH$_2$C*H*$_2$CH$_2$CH + NCH$_2$CH$_2$C*H*$_2$CH (major+minor)), 1.27 (br s, 3H, Me (major+minor)), 0.61 – 0.46 (m, 1H, NCH$_2$CH$_2$C*H*$_2$CH (major+minor)). **^{13}C NMR** (101 MHz, acetonitrile-*d*$_3$, mixture of diastereomers) δ 178.7, 178.3, 139.0, 138.2, 131.8, 131.2, 128.9, 128.6, 127.5, 127.2, 75.5, 75.3, 68.7, 68.5, 45.7, 44.4, 42.2, 42.0, 33.9, 33.4, 26.0, 25.5, 25.1, 25.0. **IR** (v_{max}, cm^{-1}) 2929 (m), 1694 (s), 1604 (m), 1482 (m), 1453 (m), 1408 (s), 1304 (m), 1088 (m), 1197 (w), 977 (w), 765 (m), 701 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{14}H_{18}N_2NaO^+$ 253.1311; Found 253.1311.

2-Benzyl-2-propylhexahydro-3H-pyrrolo[1,2-a]imidazol-3-one (5.58)



Following the general procedure H and starting with **5.56** (30 mg, 77 µmol, 1.0 equiv), $Pd(OH)_2/C$ (5.4 mg, 7.7 µmol, 0.10 equiv), and ethanol (2.5 mL), **5.58** was obtained after prep-TLC (DCM/EtOAc 7:3) as an oil (12 mg, 46 µmol, 60%, dr 15:85).

The dr ratio was measured from the ^{1}H NMR spectrum of the mixture of diastereomers by integrating the NC*H*NH proton of each diastereomer. Attributions of protons for each diastereomers was supported by 2D experiments. The dr of the crude mixture was 67:33 whereas the dr of the isolated product was 15:85.

Rf (DCM/EtOAc 7:3): 0.45. **^{1}H NMR** (400 MHz, chloroform-*d*, 15:85 mixture of diastereomers (major/minor)) δ 7.29 – 7.17 (m, 5H, Ar*H* (major+minor)), 4.89 (dd, *J* = 8.5, 5.2 Hz, 0.15H, NC*H*NH (major)), 4.65 (dd, *J* = 8.1, 4.9 Hz, 0.85H, NC*H*NH (minor)), 3.40 (dt, *J* = 11.6, 7.6 Hz, 1H, CCH_2CH$_2$CH$_3$ (major+minor)), 3.33 (d, *J* = 13.3 Hz, 0.15H, CCH_2Ph (major)), 3.19 (d, *J* = 13.3 Hz, 1H, CCH_2Ph (major+minor)), 2.98 (ddt, *J* = 11.5, 8.7, 3.8 Hz, 1H, CCH_2CH$_2$CH$_3$ (major+minor)), 2.60 (d, *J* = 13.3 Hz, 0.85H, CCH_2Ph (minor)), 2.42 – 2.32 (m, 0.15H, CCH_2CH$_2$CH$_3$ (major)), 1.90 – 1.27 (m, 7.85H, N*H* + CCH_2CH$_2$CH$_3$+ CCH$_2$CH_2CH$_3$ + NCH$_2$CH_2CH$_2$CH + NCH$_2$CH$_2$CH_2CH (major+minor)), 0.94 (t, *J* = 7.2 Hz, 3H, CH_3 (major+minor)), 0.25 (qdd, *J* = 12.1, 7.3, 4.5 Hz, 0.85H, NCH$_2$CH$_2$CH_2CH (minor)), -0.27 – -0.39 (m, 0.15H, NCH$_2$CH$_2$CH_2CH (major)). **^{13}C NMR** (101 MHz, chloroform-*d,* mixture of diastereomers) δ 176.8, 173.4, 137.6, 137.5, 130.4, 130.2, 128.4, 128.2, 127.0, 126.8, 75.8, 75.7, 74.8, 72.4, 44.4, 44.0, 41.6, 41.3, 40.8, 37.7, 32.8, 30.0, 29.8, 24.5, 23.6, 17.7, 14.5, 14.0. **IR** (ν_{max}, cm^{-1}) 3343 (w), 2957 (m), 2872 (m), 1687 (s), 1454 (m), 1405 (m), 1284 (w), 1176 (w), 1031 (w), 908 (w), 733 (m), 701 (s). **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{16}H_{22}N_2NaO^+$ 281.1624; Found 281.1625.

Chapter 8:

Annexes

8. Annexes

8.1. NMR spectra of new compounds

See USB stick for spectra.

8.2. Curriculum Vitae

ELIOTT LE DU

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Contact Information:
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1023, Crissier (VD), Switzerland
+33667547987
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Education

Ph.D. in Organic Chemistry Sep. 2018 – Nov. 2022
École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
"Hypervalent Iodine: New Reagents and Functionalization of Peptides"
Supervisor: Prof. Jérôme Waser

Master of Science in Molecular and Biological Chemistry Sep. 2016 – Jul. 2018
École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland

Master of Science in Chemistry Sep. 2015 – Jul. 2018
École Normale Supérieure de Lyon (ENS Lyon), Lyon, France

Bachelor of Science in Chemistry Sep. 2014 – Jul. 2015
École Normale Supérieure de Lyon (ENS Lyon), Lyon, France

Research Experience

Master Thesis Feb. 2018 – Jun. 2018
École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
"Synthesis and Reactivity of Triazene-Substituted Donor-Acceptor Cyclopropanes"
Supervisors: Prof. Kay Severin and Prof. Jérôme Waser

Master Internship Aug. 2017 – Dec. 2017
École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
"Synthesis and Reactivity of Triazene-Substituted Donor-Acceptor Cyclopropanes"
Supervisors: Prof. Kay Severin and Prof. Jérôme Waser

Master Internship May 2016 – Jul. 2016
Queen Mary University of London, London, United Kingdom
"Construction of Quaternary Centers Through a One-Pot Double Tsuji-Trost Alkylation"
Supervisor: Dr. Stellios Arseniyadis

Bachelor Internship Jun. 2015 – Jul. 2015
École Normale Supérieure de Lyon (ENS Lyon), Lyon, France
"Synthesis of Water Soluble Two-Photon Probes"
Supervisor: Dr. Yann Bretonnière

Scientific Contributions

17th Belgian Organic Synthesis Symposium, Namur, Belgium Jul. 2022
Poster presentation: Decarboxylative Functionalization of Small Peptides using Hypervalent Iodine Reagents

Swiss Chemical Society Fall Meeting, Switzerland (online) Sep. 2021
Poster presentation: Structure and Reactivity of New cyclic Alkynyl Hypervalent Iodine Reagents

American Chemical Society Spring Meeting, San Francisco, USA (online) Apr. 2021
Lightning talk and poster presentation: C-Terminal Oxidative Decarboxylative Functionalization of Small Peptides: a Toolbox Towards Structural Diversity

3rd Swiss Industrial Chemistry Symposium, Switzerland (online) Oct. 2020
Poster presentation: C-Terminal Oxidative Decarboxylative Functionalization of Small Peptides: a Toolbox Towards Structural Diversity

Swiss Chemical Society Fall Meeting, Switzerland (online) Aug. 2020
Poster presentation: C-Terminal Oxidative Decarboxylative Functionalization of Small Peptides: a Toolbox Towards Structural Diversity

Teaching Experience

Teaching Assistant at EPFL Sep. 2018 – Nov. 2022
Organic chemistry lectures and experimental chemistry courses (597 hours)

Supervision of a MSc Student Feb. 2021 – Jul. 2021
Master Thesis: "Synthesis of Aminal Heterocycles via Decarboxylative Cyclization of Dipeptide Derivatives"

Personal Skills

Linguistics: French (native speaker), English (fluent), German (basic knowledge)

Technical skills: multistep synthesis, reaction development, retrosynthetic analysis, handling of air- and moisture-sensitive compounds (glovebox and Schlenk techniques), common analytical techniques (NMR, HRMS, HPLC, LC/GC-MS), digital competences (ChemDraw, MestReNova, Scifinder, Reaxys).

Laboratory: Safety delegate assistant and in charge of the maintenance and troubleshooting of the glovebox in the group of Prof. Jérôme Waser. Efforts recognized with an award.

Scholarships

Élève normalien scholarship 2014 – 2018
obtained upon selection after the national competitive entrance examinations to ENS Lyon

Referees

Prof. Jérôme Waser, EPFL, jerome.waser@epfl.ch

Prof. Kay Severin, EPFL, kay.severin@epfl.ch

Dr. Stellios Arseniyadis, QMUL, s.arseniyadis@qmul.ac.uk

8.3. List of Publications

Copper-Catalyzed Alkynylation of Hydrazides: An Easy Access to Functionalized Azadipeptides, E. Le Du,‡ J. Borrel,‡ J. Waser, *Org. Lett.* **2022**, *24*, 6614-6618.

Synthesis of Aminal Heterocycles via Decarboxylative Cyclisation of Dipeptide Derivatives, E. G. L. Robert,‡ E. Le Du,‡ J. Waser, *Chem. Commun.* **2022**, *58*, 3473-3476.

Inhibition of Thiol-Mediated Uptake with Irreversible Covalent Inhibitors, B. Lim, Y. Cheng, T. Kato, A.-T Pham, E. Le Du, A. K. Mishra, E. Grinhagena, D. Moreau, N. Sakai, J. Waser, S. Matile, *Helv. Chim. Acta* **2021**, *104*, e2100085.

Structure and Reactivity of N-Heterocyclic Alkynyl Hypervalent Iodine Reagents, E. Le Du, T. Duhail, M. D. Wodrich, R. Scopelliti, F. Fadaei-Tirani, E. Anselmi, E. Magnier, J. Waser, *Chem. Eur. J.* **2021**, *27*, 10979-10986.

Small Peptide Diversification Through Photoredox-Catalyzed Oxidative C-Terminal Modification, E. Le Du,‡ M. Garreau,‡ J. Waser, *Chem. Sci.* **2021**, *12*, 2467-2473.

Triazene-Activated Donor-Acceptor Cyclopropanes: Ring-Opening and (3+2) Annulation Reactions, A. A. Suleymanov, E. Le Du, Z. Dong, B. Muriel, R. Scopelliti, F. Fadaei-Tirani, J. Waser, K. Severin, *Org. Lett.* **2020**, *22*, 4517–4522.

‡ Denotes equal contributions.