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THÈSE présentée par :

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Discipline/ Spécialité : Chimie Organique

Synthèse d'hétérocycles azotés à partir d'ynamides et d'énamides

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Pr. Stèphane PERRIO	Université de Caen

AUTRES MEMBRES DU JURY :

Pr. Françoise COLOBERT	Examinateur, Université de Strasbourg

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In the first place, I would like to thank the members of the jury for kindly evaluating my PhD thesis. I want to thank Prof. Françoise Colobert from Université de Strasbourg and Dr. Stéphane Perrio from Université de Caen for their travelling to Belgium and attending my defense, as well as Prof. Cécile Moucheron from Université libre de Bruxelles to be the president of the jury.

I have been very lucky to pursue my PhD thesis in both LCO (Laboratoire de Chimie Organique, Brussels, Belgium) and LIMA-BSM (Biomoleculars, Synthesis & Methods, Mulhouse, France) over the past four years, a period which I have enjoyed my study with so many talented chemists and naturally kind people. This experience will be kept as the best part of my memory for studying in Europe.

First and foremost, I would like to thank both of my supervisors Prof. Gwilherm Evano and Nicolas Blanchard for supporting me during the past four years. I do believe that I have been much luckier than many PhD students for having these two equally talented and naturally gentle chemists as supervisors. It is a truly great honor for me to work with them and to learn chemistry from them.

I want to thank Gwilherm for kindly providing me the PhD position in his encouraging group, which offered me a valuable opportunity to carry out the research presented in this thesis. What I have learned from Gwilherm in the past four years was tremendous amount including but not limited to chemistry. I could still remember that he personally showed me how to handle key reactions in the laboratory, which showed me a standard of performing chemistry. Moreover, I would like to thank Gwilherm for giving the morning-training session to our group, which is a very valuable training process for us to practice our problem-solving ability and to improve our chemistry knowledge. For our project research, what impressed me a lot is that you are always so talented to point out the right direction of our project and bring ideas out of my imagination, which really guided my research.

I also want to thank Nicolas, who is always so kind and patient to teach me and do your best to help me both for the research and life. Your positive attitude and bright smile always brought us courage to fight with puzzle reactions. For our research, your insightful understanding about chemistry and broad thinking really gave me a deep impression, especially when I was blocked by some obstacles during my research, he could always bring some smart ideas and suggestions to move my work forward. Moreover, I really appreciate the discussion with you during which you always explained the details of our proposals and results clearly until I could understand, and the valuable training sessions, which are very useful for me to improve my basic knowledge. I am so lucky to have the chance being in your group.

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person that could work in tough environment and tolerate high pressure. I appreciated a lot for what you and Sara organized for my birthday and my departure. I really like the reindeer toy that you guys offered me, which accompanied me when I was moving.

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Sara, your outstanding ability of organizing really impressed me, as all the drinks and parties you hosted were perfect. Hope you enjoy your work as a chemist and your life with Mr. Morgan, as we know that taking care of Morgan is not an easy job.

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Clément, Jiaqi, Simone, Giles, Jérôme and Stefano, your new participation will bring more joy to the lab. Hope you will all achieve success in chemistry.

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Vincent Debrauwer, a quite gentle guy, your participation brings us a lot of joy. Sometimes you made me think about artist more than a scientist. Indeed, your kind character and clear eyes are perfect

for music, which you are also good at. After we worked together this year, your smart thinking and good understanding of chemistry really impressed me. I am sure your doctoral study will be fruitful.

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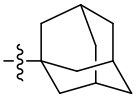
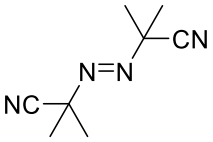
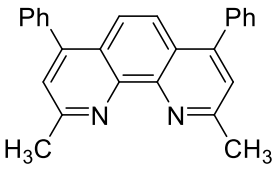
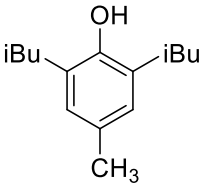
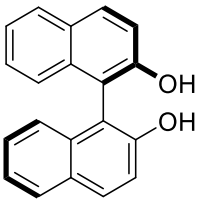
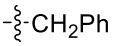
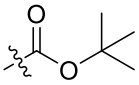
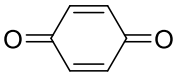
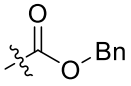
Sincerely,

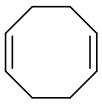
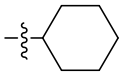
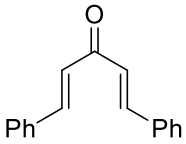
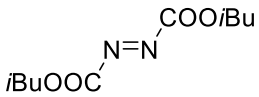
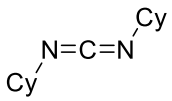
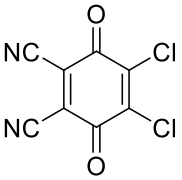
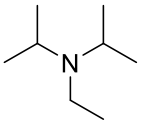
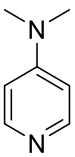
Thank you

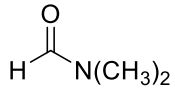
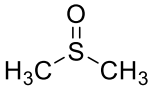
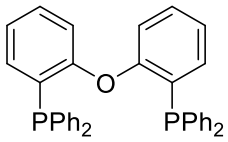
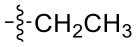
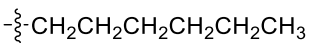
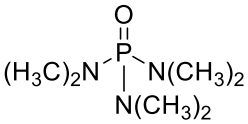
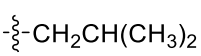
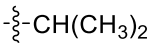
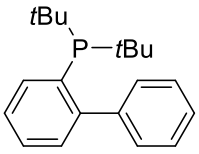
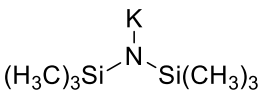
Chunyang Zhang

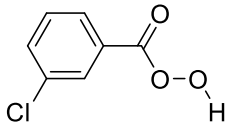
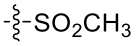
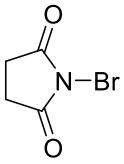
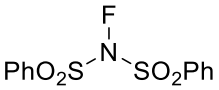
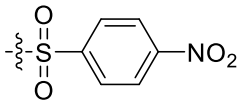
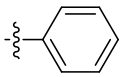
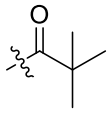
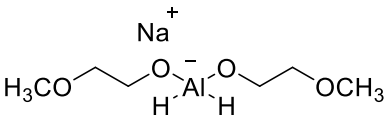
Contents

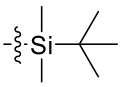
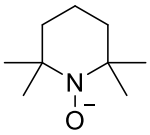
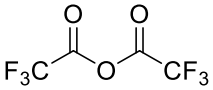
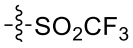
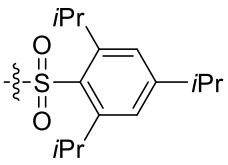
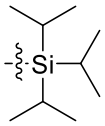
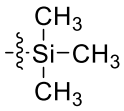
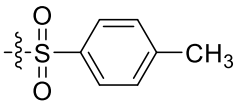
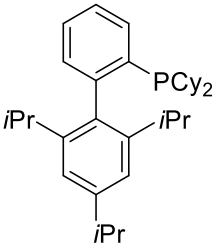
Abbreviations

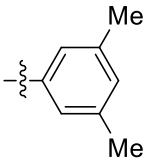
Abbreviation	Chemical Name	Chemical Structure
Ac	Acetyl	
Ad	Adamantyl	
AIBN	Azo*bis*isobutyronitrile	
Ar	Aryl	--
ATR	Attenuated total reflectance	--
bcp	Bathocuproine	
BHT	Butylated hydroxytoluene	
BINOL	1,1'-Bi-2-naphthol	
BMS	Bristol-Myers-Squibb	--
Bn	Benzyl	
Boc	*tert*-Butyloxycarbonyl	
BPMO	Biphosphine monoxide	--
BQ	1,4-Benzoquinone	
calcd	Calculated	--
Cbz	Carboxybenzyl	

Abbreviation	Chemical Name	Chemical Structure
COD	1,5-Cyclooctadiene	
CMD	Concerted metalation-deprotonation	--
CIDNP	Chemically Induced Dynamic Nuclear Polarization	--
Cp	Cyclopentadienyl	
Cy	Cyclohexyl	
dba	Dibenzylideneacetone	
D-A	Donor-acceptor	--
DBAD	Di-*tert*-butylazodicarboxylate	
DCC	*N,N'*-dicyclohexylcarbodiimide	
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	
DFT	Density Functional Theory	--
DIPEA (Hünig's base)	*N,N*-Diisopropylethylamine	
DMAP	*N*,*N*-4-Dimethylaminopyridine	
DMDO	Dimethyl dioxirane	

Abbreviation	Chemical Name	Chemical Structure
DMF	*N,N*-Dimethylformamide	
DMSO	Dimethylsulfoxide	
DPEphos	(Oxydi-2,1-phenylene)*bis*(diphenylphosphine)	
E$^+$	Electrophile	--
ee	Enantiomeric excess	--
ESI	Electrospray ionization	--
Et	Ethyl	
EPR	Electron paramagnetic resonance	--
EWG	Electron-withdrawing group	--
Hex	Hexyl	
HIV	Human immunodeficiency virus	--
HMPA	Hexamethylphosphoramide	
HRMS	High resolution mass spectrometry	--
***i*Bu**	*iso*-Butyl	
***i*Pr**	*iso*-Propyl	
IR	Infrared spectroscopy	--
Johnphos	2-(Di-*tert*-butylphosphino)biphenyl	
KHMDS	Potassium *bis*(trimethylsilyl)amide	
LED	Light-emitting diode	--

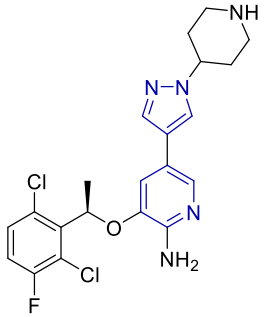
Abbreviation	Chemical Name	Chemical Structure
***m*-CPBA**	*meta*-Chloroperoxybenzoic acid	
Me	Methyl	
Mp	Melting point	--
MPAA	Mono-protected amino acid	--
MPAAM	Mono-protected aminoethyl amine	--
Ms	Mesyl (Methanesulfonyl)	
MS	Molecular sieves	--
MW	Microwave	--
NBS	*N*-Bromosuccinimide	
NFSI	*N*-Fluorobenzenesulfonimide	
NMR	Nuclear magnetic resonance	--
NOE	Nuclear Overhauser effect	--
Ns	4-Nitrobenzenesulfonyl	
PE	Petroleum ether	--
Ph	Phenyl	
piv	Pivaloyl	
Red-Al	Sodium *bis*(2-methoxyethoxy) aluminium hydride	
rt	Room temperature	--
SET	Single electron transfer	--
S_H2	Bimolecular Homolytic Substitution	--
TBAF	Tetra-*n*-butylammonium fluoride	*n*-$Bu_4N^+F^-$

Abbreviation	Chemical Name	Chemical Structure
TBS, TBDMS	*tert*-Butyldimethylsilyl	
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy	
TFAA	Trifluoroacetic anhydride	
Tf	Triflate	
THF	Tetrahydrofuran	
TIBS	2,4,6-Triisopropylbenzenesulfonyl	
TIPS	Triisopropylsilyl	
TLC	Thin-layer chromatography	--
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine	$(CH_2)_3NCH_2CH_2N(CH_3)_2$
TMS	Trimethylsilyl	
Ts	Tosyl, *p*-Toluenesulfonyl	
X-Phos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl	

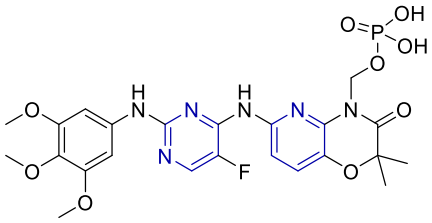
Abbreviation	Chemical Name	Chemical Structure
Xyl	*m*-Xylene	

General introduction: new approaches towards nitrogen-containing heterocycles

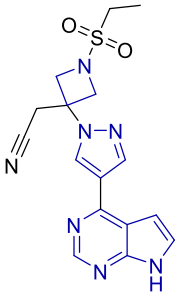
Nitrogen-containing heterocycles represent one of the most important class of structural moieties, which is widely present in metal complexes, polymeric materials as well as pharmaceuticals and agrochemical products as illustrated below. Therefore, the development of efficient and general methods to assemble and functionalize heterocyclic cores has attracted an ever-growing interest from the organic chemistry community. Consequently, it is not surprising to witness an increase in the number of synthetic methods developed towards the synthesis of *N*-containing heterocycles, especially over the past three decades, notably due to the tremendous progress in transition metal catalyzed reactions. Along these lines, intramolecular cyclization starting from ynamides has recently emerged as a powerful tool for the preparations of *N*-containing heterocycles.



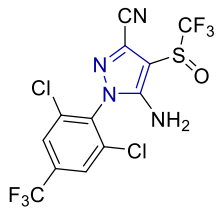
Crizotinib
(Anti-cancer drug)



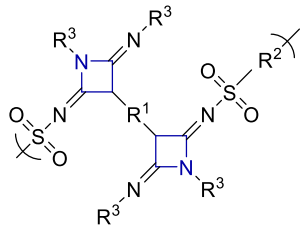
Fostanmatinib
(Spleen tyrosine kinase inhibitor)



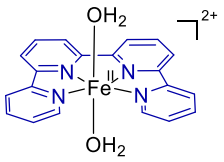
Baricitinib
(Janus kinase inhibitor)



Fipronil
(Insecticide reagent)



Luminescent polymer
(LEDs materials)



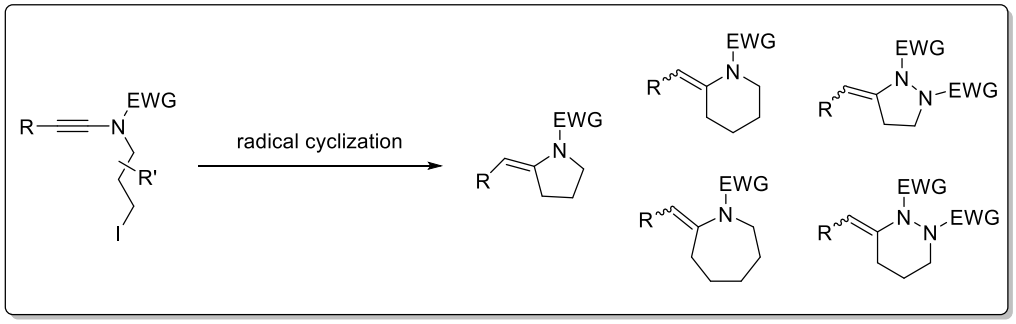
Ligands for metals
(Photocatalysis)

The high levels of reactivity and selectivity of ynamides in developing novel methods for *N*-heterocycle formations could be attributed to their unique structure, in which the triple bond is strongly polarized by the electron-donating nitrogen atom. Moreover, the reactivity and stability of ynamides is finely balanced by the introduction of a suitable electron-withdrawing group on the nitrogen atom, which not only serves to delocalize the nitrogen lone pair electron but also, in some cases, functions as an efficient directing group, chiral auxiliary, or eventually as a participating group in the reaction. With the new breakthroughs in the preparation of diversely substituted ynamides over the past ten years there have been a lot of investigations on the annulation of ynamides, which involved different reaction pathways, such as cationic-, anionic- and transition metal mediated cyclizations, ring-closing metathesis, cycloadditions and rearrangements. These successful transformations offered rapid construction of a wide range of substituted nitrogen-containing heterocyclic scaffolds from readily available ynamide structures, which further highlighted ynamides as remarkably useful and versatile synthetic intermediates in organic chemistry.

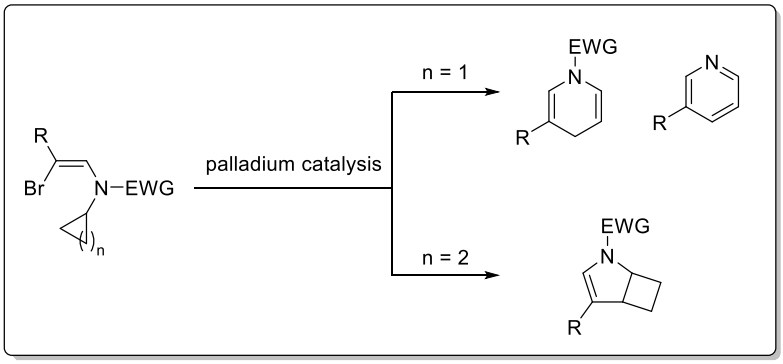
Based on the interests of our groups for the preparation and transformation of ynamides and enamides, a series of works of intramolecular cyclization of these substrates has been developed to

give nitrogen-containing heterocycles, through either cationic or anionic pathway. Indeed, previous successes encouraged us to further explore the reaction diversity of ynamides and its enamides analogue.

We first investigated the intramolecular radical cyclization of alkyl radicals onto the π-system of ynamides. Such an approach, which has no precedent in the literature, gives access to relevant *N*-containing heterocycles, such as pyrrolidine, piperidine, azepane, pyrazolidine and hexahydropyridazine derivatives. The results obtained following this strategy will be discussed in details in **Chapter 1: Radical cyclization of ynamides to 2-benzylidene-pyrrolidines** (pages 5-52).



We next turned our attention to transition metal-catalyzed cyclization reactions of β-haloenamides. Two classes of substrates were studied, differing by the nature of the nitrogen cyclic substituent: *N*-cyclopropyl and *N*-cyclobutyl. Under palladium(0)-catalysis, it was found that two types of *N*-containing heterocycles could be obtained: 3-substituted pyridines and 2-azabicyclo[3.2.0]hept-3-enes. These results are detailed in **Chapter 2: Palladium catalyzed cyclization of cyclopropyl and cyclobutyl enamides** (pages 53-98).



A **general conclusion** (pages 99-101) and a **résumé en français** (pages 103-112) followed, and the manuscript is closed by the **experimental part** (pages 113-175).

List of publications

The work of this thesis contributes the following publications:

1. "A Journey in the Chemistry of Ynamides: from Synthesis to Applications" Evano, G.; Blanchard, N.; Compain, G.; Coste, A.; Demmer, C. S.; Gati, W.; Guissart, C.; Heimburger, J.; Henry, N.; Jouvin, K.; Karthikeyan, G.; Laouiti, A.; Lecomte, M.; Martin-Mingot, A.; Métayer, B.; Michelet, B.; Nitelet, A.; Theunissen, C.; Thibaudeau, S.; Wang, J.; Zarca, M.; Zhang, C. *Chem. Lett.* **2016**, *45*, 574-585.

2. "*The anionic chemistry of ynamides: A review*" Evano, G.; Michelet, B.; Zhang C. *Comptes Rendus Chimie* **2017**, *20*, 648.

3. "Radical cyclization of ynamides to 2-benzylidene-pyrrolidines" Zhang, C.; Evano, G.; Blanchard, N.; Manuscript in preparation.

Chapter 1: Radical Cyclization of Ynamides to 2-Benzylidene-pyrrolidines

1 Introduction

Radical processes are of utmost importance, a number of biosynthetic pathways involving for example free radicals as intermediates, many of these processes being in addition directly related to our health.[1] However, and despite their importance, radical transformations have long been considered as uncontrollable by organic chemists and was much less investigated compared to ionic reactions. This preconceived idea can be attributed to the high reactivity of free radical species that is associated, for some obscure reason, to difficulties in predicting the behavior of radical intermediates. In addition, and this has actually been the main drawback of radical chemistry, the generation of radical intermediates has for long relied on the use of toxic and explosive reagents such as tin derivatives or peroxides. While radical reactions have been for a long period of time less studied and utilized both in academia and industry, they however display a number of advantages since they can be performed under mild and neutral conditions, therefore avoiding the use of acids or bases that may damage sensitive organic molecules. Moreover, many functional groups can survive under radical conditions, therefore avoiding some tedious protection/deprotection steps. With all these advantages over traditional ionic transformations and due to the development of new techniques for the generation of free radical species under mild conditions and without the need for toxic and/or hazardous reagents, radical chemistry has been widely studied recently and emerged at the forefront of many innovations in chemical synthesis.

1.1 Free radical reactions

1.1.1 General consideration on radical reactions

Free radical reactions involve, as indicated by their name, radical intermediates that are formed by homolytic bond cleavage, a process in which each fragment resulting from the bond dissociation retains one of the bonding electrons. Free radicals are highly reactive species that can react with many organic molecules and ions, including solvents. Indeed, they react so quickly, often at diffusion-controlled rates that the identification of radical species has long been a real challenge. Radical reactions can be traced back to 1900 where Gomberg[2] first reported the existence of a radical species, the triphenylmethyl radical ($Ph_3C\cdot$), which was found to be in equilibrium with a dimeric cyclohexadiene derivative. Following the pioneering study, many chemists devoted their attention to the generation of long-lived free radicals to the detection of unstable radicals by analytical techniques such as EPR (Electron Paramagnetic Resonance) spectroscopy and CIDNP (Chemically Induced Dynamic Nuclear Polarization).

The resulting deeper understanding of the structure and behavior of radical species notably enabled the development of a wide range of radical reactions which can be classified as follows.[3] Firstly,

[1] (a) Bielli, A.; Scioli, M. G.; Mazzaglia, D.; Doldo, E.; Orlandi, A. *Life Sci.* **2015**, *143*, 209-216. (b) Yokoyama, K. *Biochemistry* **2018**, *57*, 390-402.
[2] Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 757-771.
[3] (a) Rowlands, G. J. *Tetrahedron* **2009**, *65*, 8603-8655. (b) Rowlands, G. J. *Tetrahedron* **2010**, *66*, 1593-1636.

radical spieces can abstract atoms or functional groups from many types of reagents or even solvents, such processes corresponding to atom or group transfer reactions. Secondly, radicals can also undergo oxidation, notably by molecular oxygen with which they often react quickly, or reduction. Radicals can also add to π-bonds or, reversely, undergo fragmentation reactions. Based on these basic transformations, a lot of efficient tandem or cascade radical sequences have been developed: they enable the formation of several carbon-carbon or carbon-heteroatom bonds in a single operation and their efficiency has been highlighted by the total synthesis of many complicated polycyclic natural products.

From a mechanistic point of view, many free radical reactions used in synthetic chemistry consist of three phases: initiation, propagation and termination, which refer to the creation of radical species, the reaction of radical intermediates with other molecules and the reaction of two radical intermediates, respectively (Figure 1.1(a)). Each individual step in a radical chain reaction is characterized by its rate constant and the concentration of radical intermediates is typically low. In "good" chains, the rates of the transformations involved in the propagation phase are higher than the rates of termination, which ensure a reasonable chain length.[4] For example, if the rates of all the propagation steps are about 10^5 s^{-1} to 10^9 s^{-1}, then it is a "good" radical chain; if the rates are 10^3 s^{-1} to 10^4 s^{-1}, the chain would be short; if one of the propagation step is lower than 10^3 s^{-1}, the reaction would not perform well due to the competing termination steps; in this case, adding more initiator would be helpful. As depicted in Figure 1.1(b), the repeated steps of propagation phase can also be described as an innate cycle, which will be useful when drawing the mechanisms of catalytic radical cycles later on.

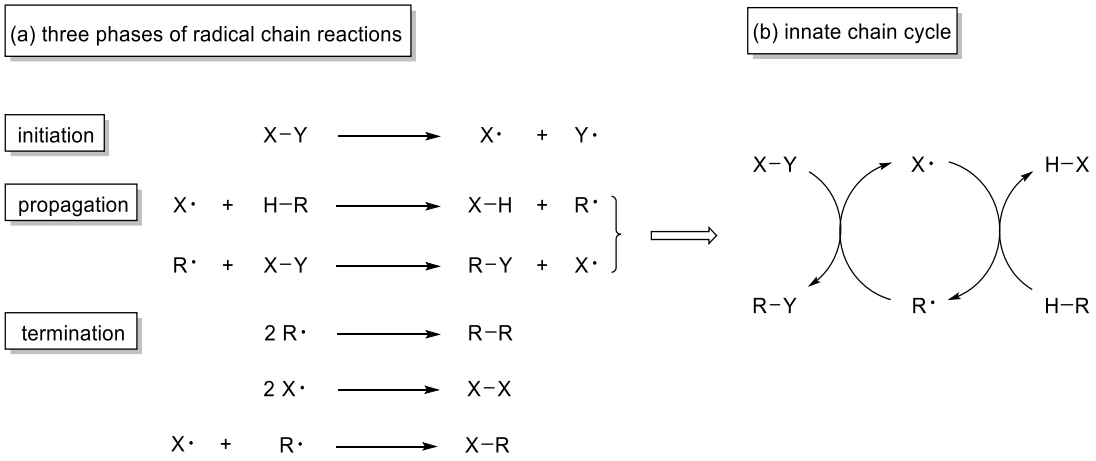


Figure 1.1: General phases of radical chain reactions and innate chain cycle.

If we now consider the reagents utilized for the generation of radical species in synthetic chemistry, the most commonly used initiators are azo compounds, peroxides and trialkylboranes. Moreover, the most widely utilized source of radical intermediates is organotin derivatives which readily generate radicals from the corresponding halides under mild conditions, their toxicity being their major drawback. Additionally, other compounds such as *N*-hydroxypyridine-2-thione esters and organic mercury derivatives are also often used as a source of radical intermediates. One example involving stannyl radicals is described in Figure 1.2: the radical resulting from the initiator abstracts a hydrogen atom of the stannane to generate the corresponding stannyl radical intermediate, which in turn

[4] Studer, A.; Curran, D. P. *Angew. Chem. Int. Ed.* **2016**, *55*, 58-102.

abstracts the halogen atom from the starting halides. The radical thus generated can for example add to a double bond and the resulting radical finally abstract a hydrogen atom from the starting stannane, therefore propagating the radical chain reactions.

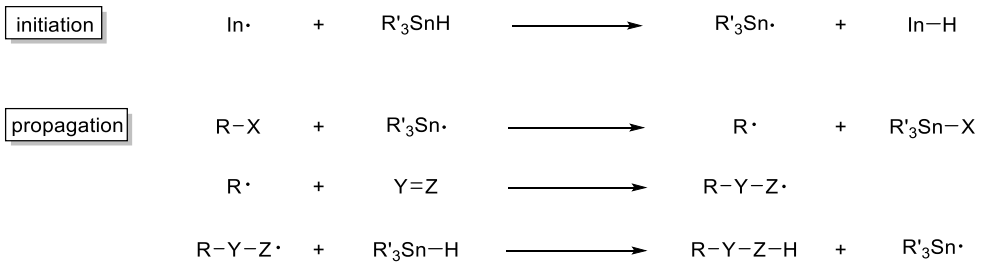


Figure 1.2: One example of radical chain reactions using tin-based reagents.

Despite the classical radical chain reaction, a catalyst can also be employed to promote radical processes: there are many possibilities for the catalysis of radical reactions which will not be overviewed here for clarity and since this is outside the scope of this manuscript. An excellent review on this topic has in addition been published by Studer and Curran.[4] One possibility for the catalysis of radical reactions that we will use to illustrate the catalysis of radical reactions relies on the catalyst promoting the regeneration of an initiator from the products of its initiation reaction. This generally requires addition of energy in the form of a co-initiator or a photon to close the catalytic cycle and is often coined as "smart initiation", a strategy that is especially valuable when short chains are involved. Figure 1.3 shows a generic depiction of smart initiation with a molecular co-initiator in a reductive mode (a converse oxidative mode is also possible). The initiator reduces the substrate Sub-X to a radical Sub· which then enters the innate chain, converting substrate molecules into product molecules until the chain terminates. In parallel, the oxidized initiator $Init^+$ is reduced by a co-initiator to close the catalytic cycle and return the original initiator, ready to start a fresh chain. This process is especially valuable for expensive initiators paired with short chains.

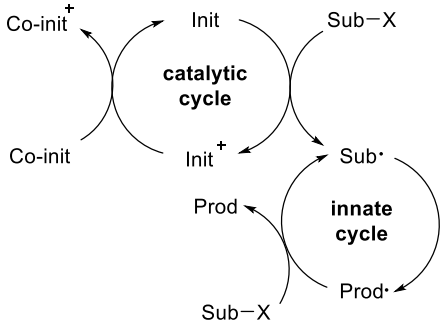


Figure 1.3: Example of catalysis of radical reactions: "smart" initiation.

A last general point that ought to be mentioned in this introductory section deals with the stereoselectivity of radical reactions which still remains a big challenge that often limits the synthetic application of radical transformations. As illustrated in Figure 1.4, one important problem is that the formed carbon-centered alkyl radical adopts a trigonal planar geometry or a pyramidal shape with a low energy barrier to invert, according to the steric effect of substituents. In very rare cases, like bridge head systems, rigid pyramidal structure of radical intermediates also exists. For the planar and

pyramidal radicals, the top and bottom faces are equal to be attacked, thus a racemic mixture of the final product will be produced. However, stereoselective versions of radical reactions have been achieved successfully in many works, by employing various strategies inspired from ionic chemistry: (a) the inherent chirality of the substrate can be transferred to the product, (b) Lewis acids (sometimes with chiral ligands) can be used to chelate the substrate to control the stereoselectivity of radical reactions, (c) chiral reagents as chiral tin hydrides have also been employed to control the stereoselectivity and, (d) some new methods have been developed for enantioselective photoredox/ photochemical processes.[5]

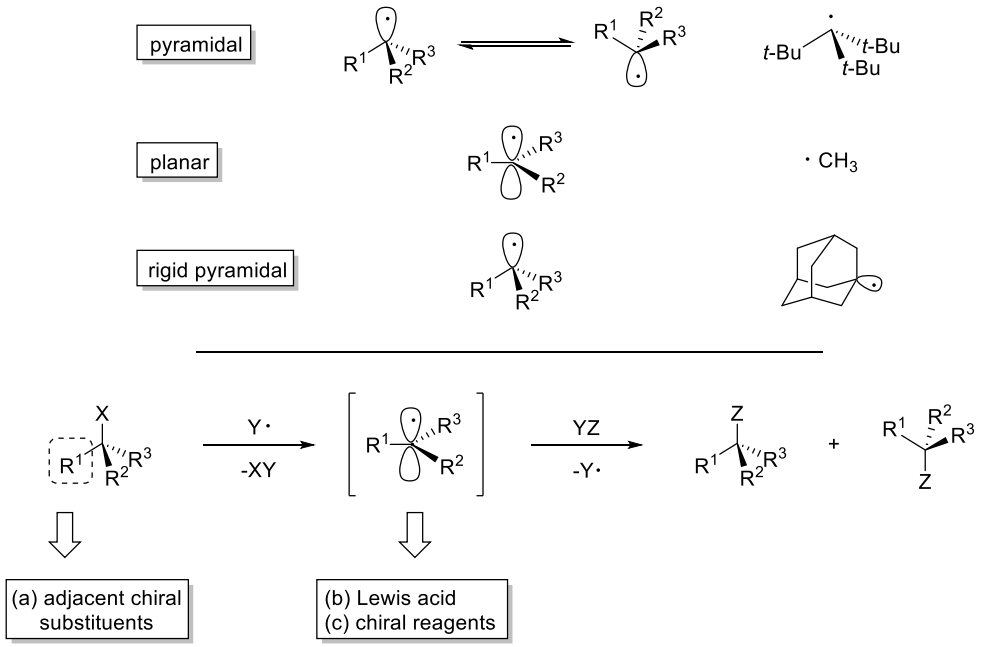


Figure 1.4: The geometry of alkyl free radicals and strategies to control the stereoselectivity of radical reactions.

After this general review of the structural features of free radicals and free radical reactions, we will next focus on one of the most useful areas of radical chemistry, radical cyclizations, and recall some general rules to predict their regioselectivity.

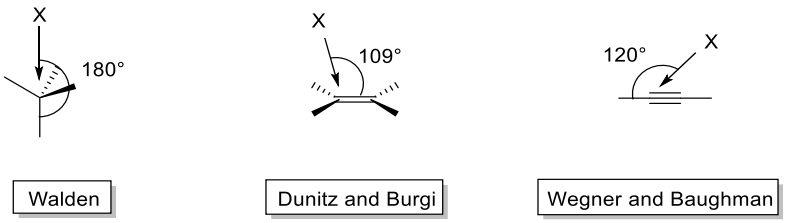
1.1.2 General rules for the regioselectivity of radical cyclizations

Radical cyclization typically involves three elementary steps: the generation of the radical species, the intramolecular addition of this radical intermediate to the unsaturated motif, and an atom or group transfer step to generate the cyclized product. To permit the generation of the desired cyclized product, the ring closure step should be faster than the atom transfer step. Two regioisomers can be formed in such process depending, with respect to the newly developing ring in the transition state, if the pair of electrons in the displaced bond is *exo* to the developing ring (*exo* attack) or part of the newly developing ring (*endo* attack). To understand, and potentially predict, the outcome of such radical cyclizations, several elements need to be taken into consideration, such as electrostatic and steric effects of

[5] For reviews, see: (a) Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251-263. (b) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263-3295. For examples of enantioselective photoredox processes, see: (a) Arceo, E.; Jurberg, I. D.; Alvarez-Fernandez, A.; Melchiorre, P. *Nat. Chem.* **2013**, *5*, 750-756. (b) Huo, H.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2016**, *138*, 6936-3939.

substituents, stereoelectronic preferences and conditions.[6] Based on literature precedents and physical calculations, several rules are available for the regioselectivity of radical reactions, the most common ones being the Baldwin and Beckwith rules.

The most important rule for ring closure is the Baldwin Rule, which was first reported in 1976 by Sir Jack E. Baldwin.[7] This rule is mostly based on the geometrical requirements of the transition states resulting from the addition to tetrahedral, trigonal (double bonds) and diagonal (triple bonds) systems to predict the favored ring sizes of the ring closure reactions. The angle of trajectory for maximum orbital overlap during the attack was mainly considered, which was supported by the data from the works of Walden, Dunitz, Burgi, Wegner and Baughmann (Figure 1.5, top). Based on these considerations and literature precedents for various ring closures, Baldwin provided a detailed table including favored and disfavored ring closure (Figure 1.5, bottom). These rules have been extensively utilized for radical cyclizations, despite many exceptions.



Nucleophilic, Electrophilic, Radical					
		3	4	5	6
-txt	*endo-*	--	--	×	×
	exo-	✓	✓	✓	✓
-trig	*endo-*	×	×	×	✓
	exo-	✓	✓	✓	✓
-dig	*endo-*	✓	✓	✓	✓
	exo-	×	×	✓	✓

Figure 1.5: Ideal angles of attack to tetrahedral, trigonal and diagonal systems for maximal orbital overlap and Baldwin's rules for ring closure.

Another set of rules, specific for radical cyclizations, the Beckwith rules,[8] are indeed more convenient, compared to the Baldwin's rules, for radical ring closures. They can be briefly summarized to three points: (a) intramolecular addition under kinetic control when $n \leq 5$ (Figure 1.6), cyclization occurs preferentially in the *exo* mode, (b) substituents disfavor cyclization at substituted position, (c) homolytic cleavage is favored when bond concerned lies close to plane of adjacent semi-occupied, filled non-bonding, or π-orbital. These guidelines allow us to better understand the regioselectivity of radical cyclizations and suffer from fewer exceptions compared to the Baldwin's rules.

[6] Alabugin, I. V.; Gilmore, K.; Manoharan, M. *J. Am. Chem. Soc.* **2011**, *133*, 12608-12623.
[7] (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736. (b) Alabugin, I. V.; Timokhin, V. I.; Abrams, J. N.; Manoharan, M.; Abrams, R.; Ghiviriga, I. *J. Am. Chem. Soc.* **2008**, *130*, 10984-10995. (c) Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513-6556.
[8] Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, *11*, 482-483.

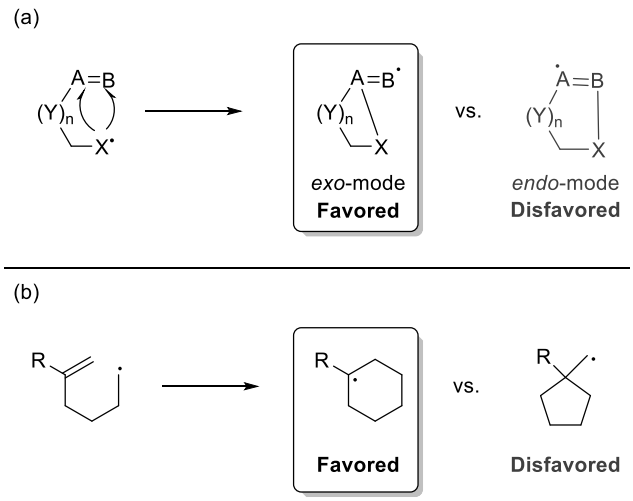


Figure 1.6: Beckwith's radical rules for ring closure.

After this overview of general features of radical reactions, we will now focus on radical reactions involving ynamides, an area still understudied that was at the core of our work.

1.1.3 The reactivity of ynamides under radical conditions

Before overviewing their radical chemistry, let's first start with a brief introduction to ynamides, nitrogen-substituted alkynes embedded with an electron-withdrawing group on the nitrogen atom.[9] As an important subgroup of heteroatom-substituted alkynes, they have evolved to be useful building blocks in organic synthesis. Since the first ynamines – less stable analogues of ynamides because of the lack of the electron-withdrawing group – was isolated by Zaugg[10] in 1958 and the first synthesis of ynamides was developed by Viehe,[11] this class of compounds have slowly envolved as remarkably useful building blocks, notably with the development of efficient synthetic routes for their preparation since the beginning of 21st century. As mentioned earlier, ynamides possess a unique structural combination of alkyne and electron-withdrawing group-substituted nitrogen atom, which provides a fine balance between stability and reactivity. As shown in Figure 1.7, the nitrogen atom polarizes the triple bond, rendering ynamides highly reactive towards nucleophiles, electrophiles, transition metals or radicals, usually with high levels of regioselectivity. Based on the nature of the electron-withdrawing group, several classes of ynamides can be defined: these include yne-amides, yne-carbamates, yne-sulfonamides, yne-hydrazides and ynimides…, whose properties and synthetic applications have been extensively investigated over the past two decades.

With these structural advantages, ynamides offer a range of opportunities in synthetic chemistry. As many practical synthetic methods of ynamides have been developed recently, a lot of transformations based on ynamides were extensively explored, including additions, reductions, cycloadditions, ring-closing metatheses, pericyclic reactions and many other processes, many of which even have been applied to natural product synthesis successfully.

[9] (a) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010,** *49*, 2840-2859. (b) Evano, G.; Jouvin, K.; Coste, A. *Synthesis* **2013**, *45*, 17-26. (c) Evano, G.; Blanchard, N.; Compain, G.; Coste, A.; Demmer, C. S.; Gati, W.; Guissart, C.; Heimburger, J.; Henry, N.; Jouvin, K.; Karthikeyan, G.; Laouiti, A.; Lecomte, M.; Martin-Mingot, A.; Métayer, B.; Michelet B.; Nitelet, A.; Theunissen, C.; Thibaudeau, S.; Wang, J.; Zarca, M.; Zhang, C. *Chem. Lett.* **2016**, *45*, 574-585. (d) Evano, G.; Michelet, B.; Zhang, C. *C. R. Chimie* **2017**, *20*, 648-664.

[10] Zaugg, H. E.; Swett, L. R.; Stone, G. R. *J. Org. Chem.* **1958**, *23*, 1389-1390.

[11] Viehe, H. G. *Angew. Chem.* **1963**, *75*, 638.

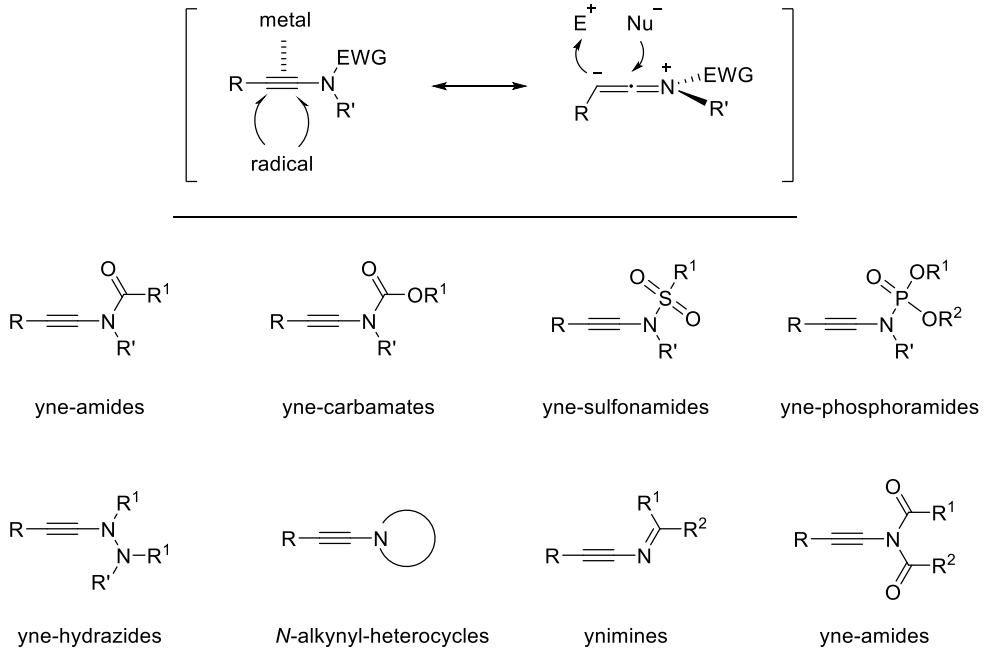


Figure 1.7: Ynamides: resonance structures and representative classes.

While a lot of facets of ynamides reactivity have been explored, their radical chemistry has been much less studied, despite the strong potential of processes that could be developed based on radical reactions involving ynamides. Advances in this area will be overviewed in the next section. We will introduce some recently developed radical reactions based on ynamides, including some pioneering works on radical cyclizations, radical addition reactions and oxidation reactions. The reactions covered will be classified primarily based on their intra-/inter-molecular nature and, secondarily, by chronological order.

1.2 The radical chemistry of ynamides

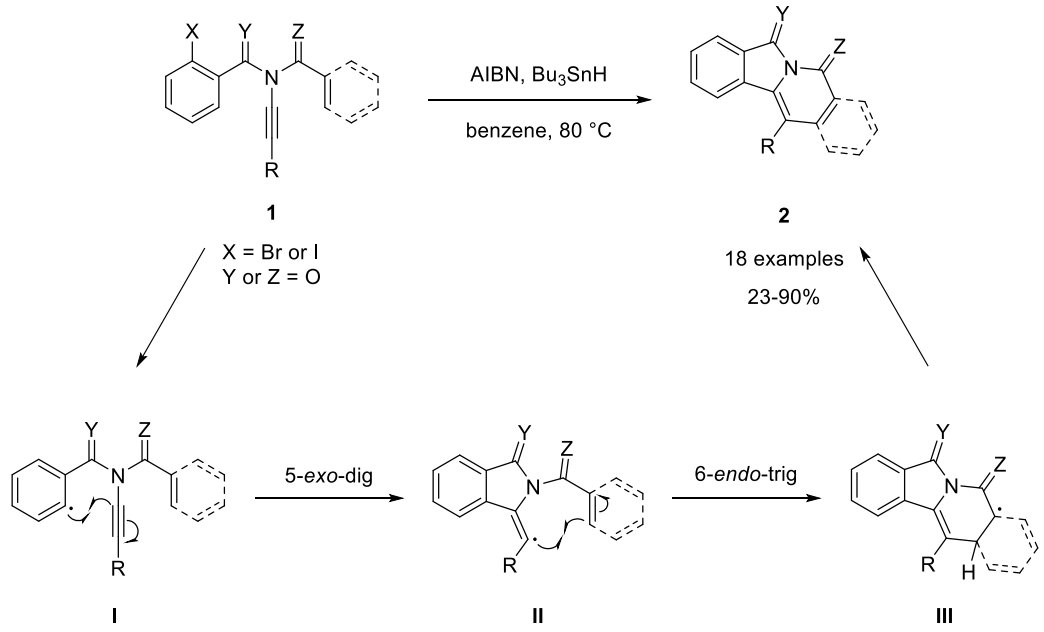
1.2.1 Intramolecular radical cyclization of ynamides

1.2.1.1 Radical cyclization of ynamides towards polycyclic compounds

The intramolecular radical cyclization of ynamides had been first reported by Malacria and co-workers in 2003 (Scheme 1.1),[12] in continuation of their interests in various radical cyclization cascade and the applications in total synthesis of natural products.[13] In searching for new partners for radical reactions, they wisely choose ynamides **1** as precursor, which could be readily prepared by Witulski's method [14] involving addition of the corresponding metallated amide to an alkynyliodonium salt followed by successive desilylation and alkylation. Using a combination of AIBN as the radical initiator and tributyltin hydride as the hydrogen source, the intramolecular transannulation of **1** was smoothly

[12] Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095-5097.
[13] (a) Dhimane, A.-L.; Aissa, C.; Malacria, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 3284-3287. (b) Fensterbank, L.; Mainetti, E.; Devin, P.; Malacria, M. *Synlett* **2000**, *9*, 1342-1344.
[14] Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 489-492.

achieved to form a variety of polycyclic products such as isoindoles, isoindolinones and pyrido-isoindolones. From a mechanistic point of view, the cascade reaction sequentially proceeds through a 5-*exo*-dig cyclization to form vinyl radical intermediate **II** followed by a 6-*endo*-trig radical addition to the conjugated arene or alkene followed by reduction and aromatization (in the case of an aromatic amide) to generate the desired polycyclic product **2**. It is worth mentioning that the carbonyl group (Z = O) turned out to have a big impact on the addition of the transient vinyl radical due to both its electronic and steric effects: without this carbonyl group, the reduction of this radical intermediate **II** occurs. In addition, this process showed excellent regioselectivity as well as high efficiency, and brought new perspectives for the application of ynamides in radical transformations.

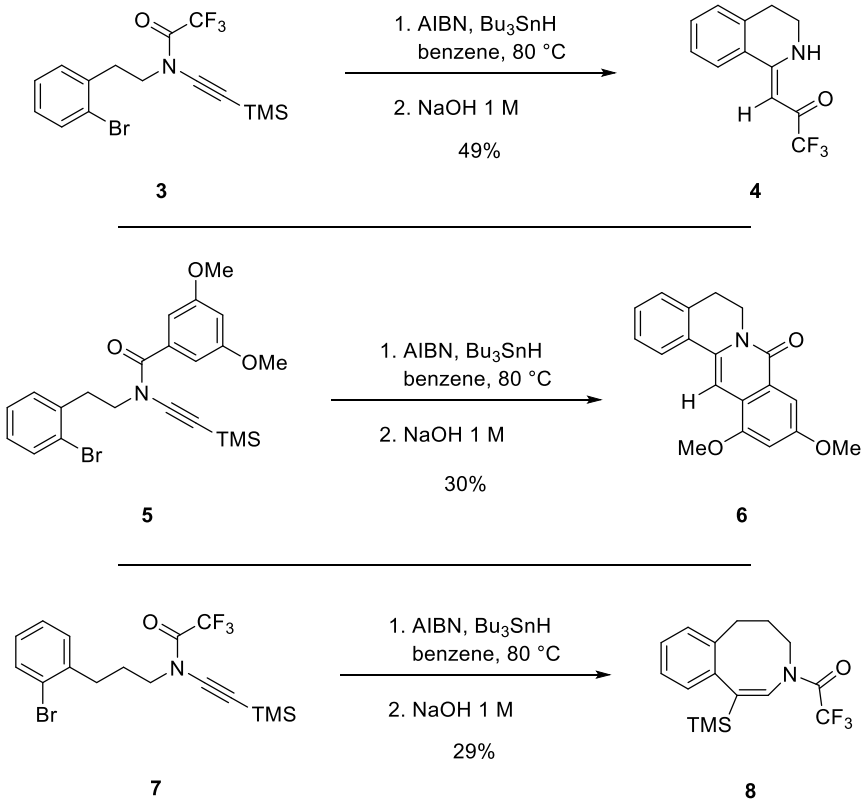


Scheme 1.1: Radical cyclization cascade of ynamides reported by Malacria and Courillon.

By using a similar strategy, in 2011[15], Courillon and co-workers reported another interesting example of radical cyclizations of ynamides providing a straightforward access to biologically valuable protoberberine analogue **6** as well as six-and eight-membered nitrogen heterocycles **4** and **8** (Scheme 1.2). In the case of protoberberine analogue **6**, the product was formed by a successive 6-*exo*-dig/6-*endo*-trig cyclization sequence, which was initiated by using a combination of AIBN and tributyltin hydride with benzene as the solvent at 80 °C. It is worth to note that for the formation of compound **4**, the *N*-trifluoroacetyl-substituted starting ynamide only underwent a 6-*exo*-dig cyclization process followed by migration of the trifluoroacetyl moiety, a process that was only known in ionic reactions before (ionic Fries rearrangement).[16] This migration was attributed to the delocalization of the enamine nitrogen atom and the hydrogen bond that was formed between the carbonyl group and the amine. Finally, employing the same protecting group, a rare 8-*endo*-dig cyclization was further realized to afford an unsaturated eight-membered ring nitrogen-heterocycle **8** whose selective formation was not rationalized by the authors. These results demonstrated the reactivity of homobenzylic ynamides

[15] Balieu, S.; Toutah, K.; Carro, L.; Chamoreau, L.; Rousseliere, H.; Courillon, C. *Tetrahedron Lett.* **2011**, *52*, 2876-2880.
[16] (a) Hallberg, A.; Svensson, A.; Martin, A. R. *Tetrohedron Lett.* **1986**, *27*, 1959-1962. (b) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112-13113.

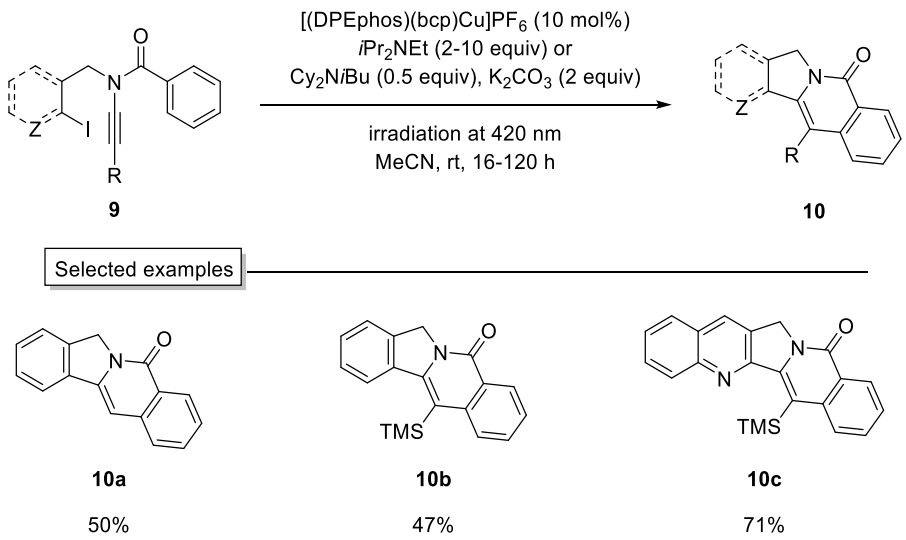
under radical conditions leading to a six-membered rings while lengthening the carbon chain between the aromatic ring and the nitrogen atom by a single methylene group selectively led to the formation of an eight-membered ring via a rarely reported 8-*endo*-dig cyclization process.



Scheme 1.2: Radical cyclization of ynamides reported by Courillon and Balieu.

More recently, the importance and efficiency of intramolecular radical polycyclization was further highlighted by our group[17] who reported, inspired by Malacria's work, an efficient copper-catalyzed photoinduced domino radical cyclization of ynamides to generate a series of bioactive and highly valuable polycyclic compounds (**10a**-**c**) (Scheme 1.3). Based on the group's interests in copper-based photocatalysts, a recently developed copper complex [(DPEphos)(bcp)Cu^{I}]PF_6 was employed as the catalyst for this transformation. The readily prepared ynamides **9** reacted with catalytic amounts of [(DPEphos)(bcp)Cu^{I}]PF_6 under light irradiation in the presence of *i*Pr_2NEt (2 equiv) or a combination of Cy_2N*i*Bu (0.5 equiv) and potassium carbonate (2 equiv) in acetonitrile at room temperature for 16-120 hours, which afforded, after desilylation, the desired heterocycles **10a-c** in moderate to good yields.

[17] Baguia, H.; Deldaele, C.; Romero, E.; Michelet, B.; Evano, G. *Synthesis* **2018**, *50*, 3022-3030.

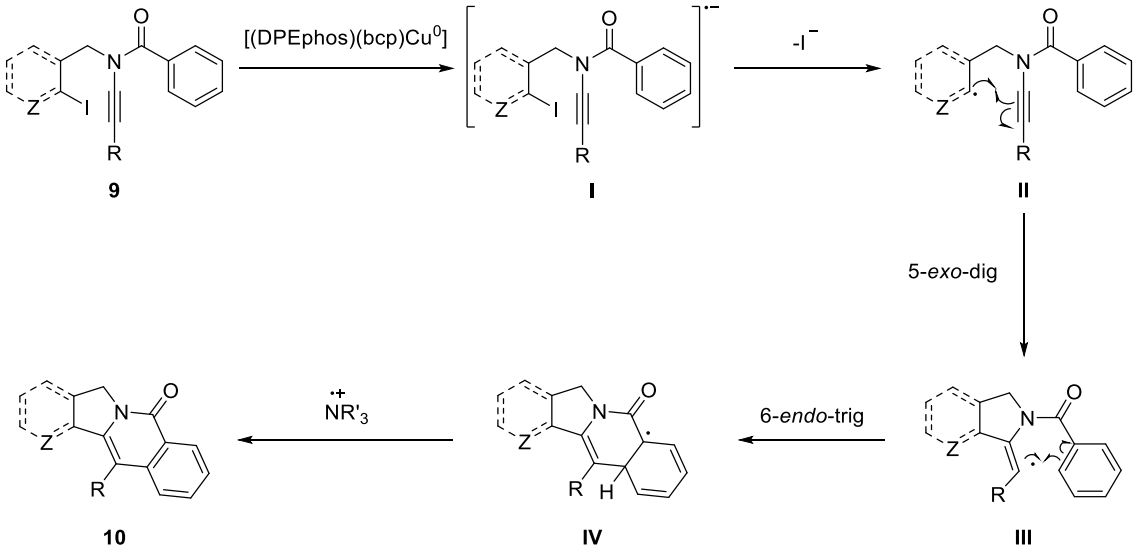


Scheme 1.3: The copper-catalyzed photoinduced radical domino cyclization reported by Evano.

Based on the mechanistic studies that had been reported for the activation of aryl halides,[18] the mechanism of this radical domino cyclization shown in Scheme 1.4 could be proposed, in which a Cu(I)/Cu(I)*/Cu(0) catalytic cycle was involved. The copper complex [(DPEphos)(bcp)Cu^{I}]PF_6 was irradiated to generate the photoexcited complex [(DPEphos)(bcp)Cu^{I}]PF_6^{*}, which was next reduced by the tertiary amine to form the active copper complex [(DPEphos)(bcp)Cu^{0}] with concomitant formation of an amine radical cation. Next, the copper(0) species reacted with the aryl halides **9** to generate radical intermediate **I**, which sequentially underwent 5-*exo*-dig and 6-*endo*-trig radical cyclizations to provide the polycyclic intermediates **IV**. Finally, the aromatization of **IV** by the amine radical cation produced the desired polycyclic product and regenerate the tertiary amine. In comparison to the traditional tin-based radical transformations,[12,15] this method is mild and more environmentally friendly, and comparing to the use of iridium and ruthenium complex catalysts,[19] much more economic.

[18] Michelet, B.; Deldaele, C.; Kajouj, S.; Moucheron, C.; Evano, G. *Org. Lett.* **2017**, *19*, 3576-3579.

[19] (a) Xie, J.; Yu, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 9416-9421. (b) Jia, W.-G.; Cheng, M.-X.; Gao, L.-L; Tan, S. M.; Wang, C.; Liu, X.; Lee, R. *Dalton Trans.* **2019**, *48*, 9949.

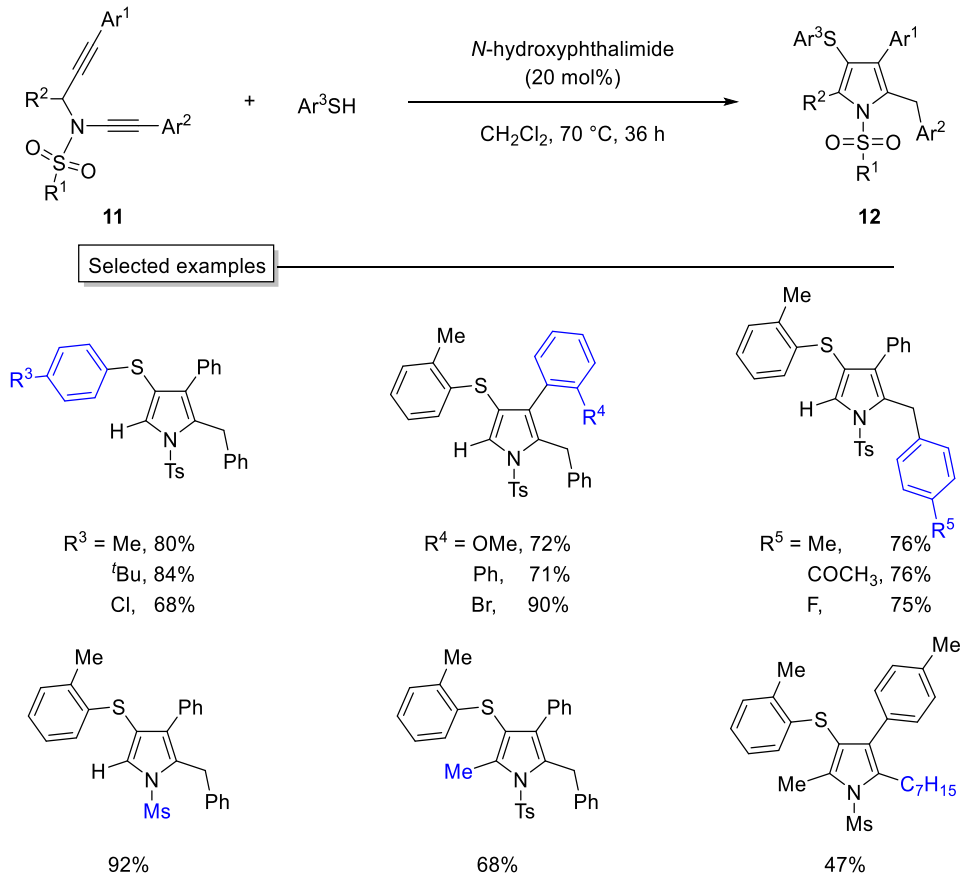


Scheme 1.4: Proposed mechanism of the copper mediated photoinduced radical domino cyclization.

1.2.1.2 Radical cyclization of ynamides towards pyrrole derivatives

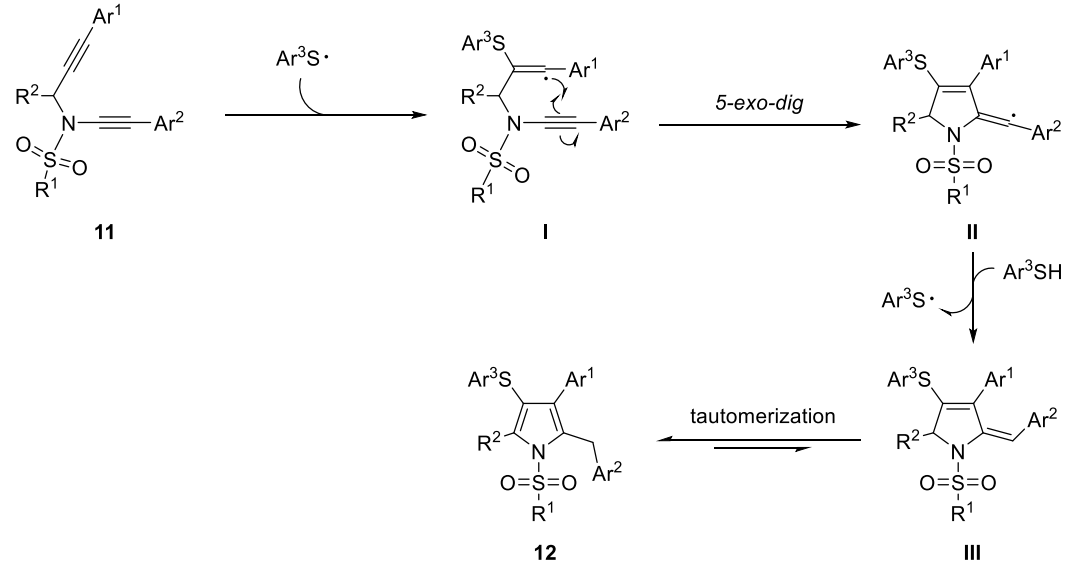
In addition to the radical (poly)cyclizations discussed above, Gandon and Sahoo[20] reported in 2019 a unique regioselective radical cyclization of yne-tethered ynamides to synthesize fully substituted pyrrole derivatives. In this process, the alkyne was found to be more reactive than the ynamide, which is in contradiction with the general impression that ynamides are more reactive than simple alkynes (Scheme 1.5). While this is actually mostly the case with cationic reactions with ynamides, the authors envisioned that the regioselectivity could be reversed by switching to a radical process, with the prediction that the alkyne motif would be firstly attacked by the radical species to generate a vinyl radical, which would next attack the ynamide moiety to form a nitrogen heterocycle. To prove the feasibility of this hypothesis, the first reaction was performed with yne-tethered ynamide **11** and benzenethiol in the presence of AIBN in acetonitrile at 70 °C for 24 hours. The desired cyclized product **12** was isolated in 40% yield, along with the formation of two main byproducts, the alkyne hydrothiolated compound (15%) and an amide resulting from the competing hydrolysis of the starting ynamide (30%). After the optimization of initiators ($K_2S_2O_8$, *N*-hydroxyphthalimide, none, air), solvents (acetonitrile, DMF, dichloromethane, 1,2-dichloroethane, acetone, toluene) and temperature (50 and 70 °C), the optimal conditions for this transformation were found to rely on the use of *N*-hydroxyphthalimide (20 mol%) in dichloromethane at 70 °C for 36 hours. A broad scope was investigated (45 examples), with respect to the substituents on the alkyne (Ar^1), the ones on the ynamide (Ar^2), aryl thiophenols (Ar^3), the nature of the electron-withdrawing group (R^1) and the substituents at the propargyl (R^2) position, which demonstrated the high efficiency and generality of this transformation.

[20] Dutta, S.; Mallick, R. K.; Prasad, R.; Gandon, V.; Sahoo, A. K. *Angew. Chem. Int. Ed.* **2019**, *58*, 2289-2294.



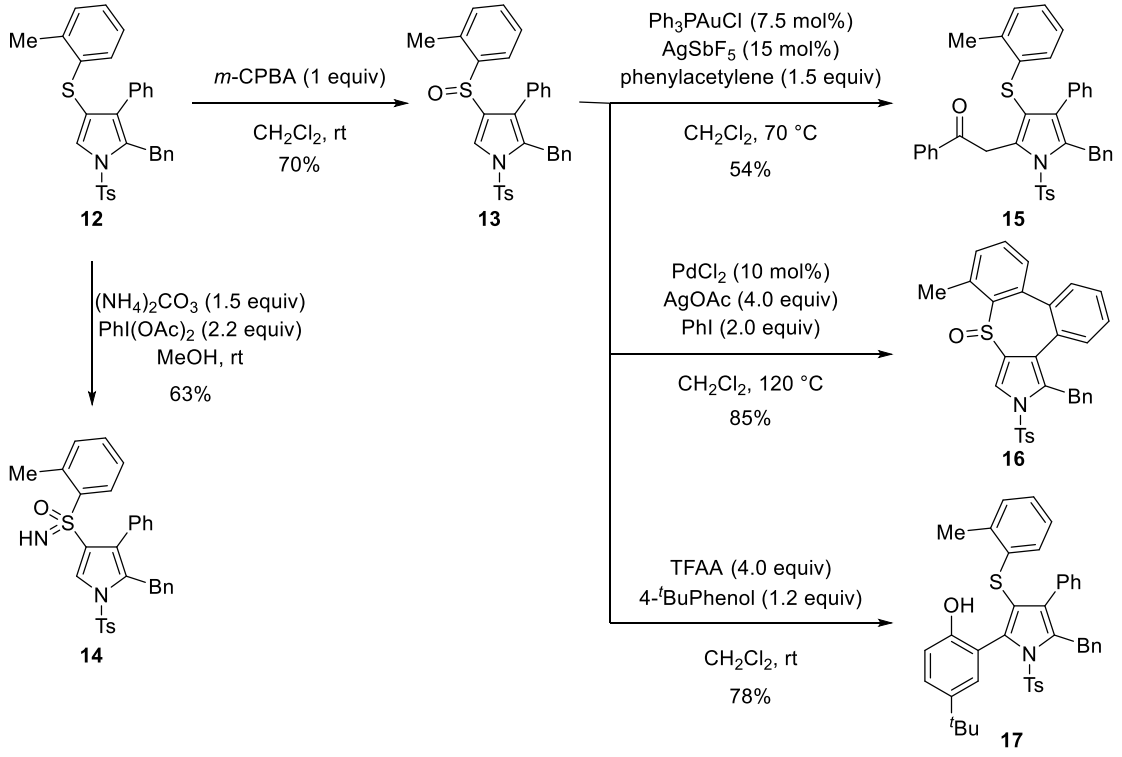
Scheme 1.5: Regioselective radical cyclization of yne-ynamides reported by Sahoo.

To gain some insights into the mechanism of the cyclization, the typical radical inhibitor TEMPO was added to the reaction, which gave the bis(4-chlorophenyl)disulfane adduct as the only product, proving that the radical intermediates are involved in this transformation. In addition, DFT computations were also carried out to support the radical mechanism. As depicted in Scheme 1.6, the generated thiyl radical would attack the triple bond of the internal propargylic alkyne to give the vinyl radical **I**, which would then react with the ynamide moiety through a 5-*exo*-dig cyclization to afford the cyclized radical intermediate **II**. After hydrogen abstraction from the thiophenol and tautomerization, the desired pyrrole compound **12** would be produced.



Scheme 1.6: Proposed mechanism for the radical cyclization of yne-ynamides.

Finally, the reactivity of the cyclized product **12** was further explored through the oxidation of the thiyl group by *m*-CPBA to give the sulfoxide **13** or transformation to the corresponding sulfoximine **14** in good yields (70% and 63%) (Scheme 1.7). The sulfoxide **13** could be further transformed to the compound **15** through a gold mediated alkylation. A dehydrogenative-coupling could be performed in the presence of $PdCl_2$, AgOAc and PhI to provide poly-cyclic compound **16**. Moreover, compound **17** could be obtained by reaction with TFAA and 4-^{t}BuPhenol through a Pummerer-type transformation.



*Scheme 1.7: Further transformations of the cyclized product **12**.*

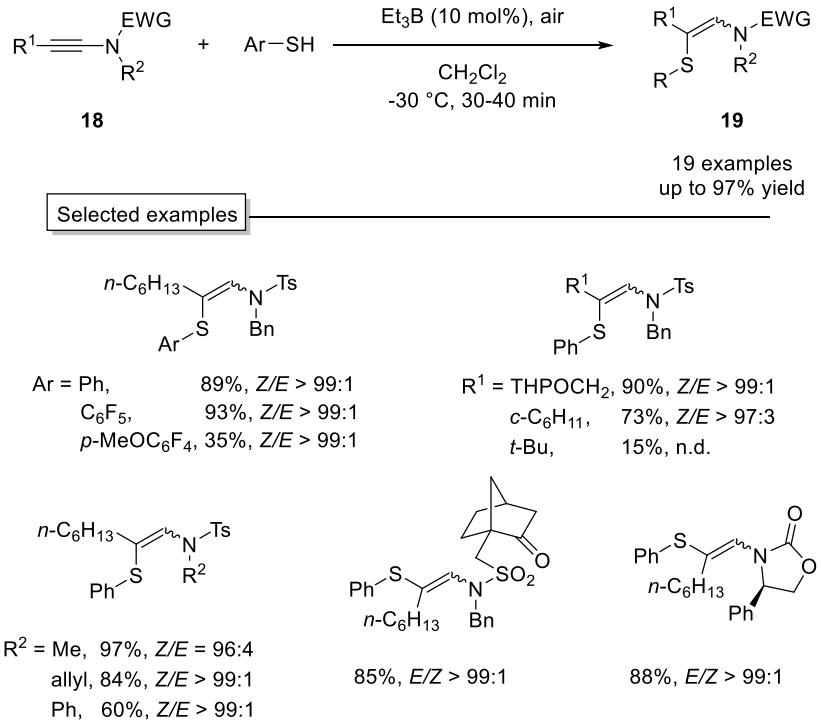
1.2.2 Radical addition of ynamides

In addition to intramolecular radical cyclization, there are many other types of free radical reactions, like radical substitution reaction, radical addition reaction, group transfer reaction, rearrangement, fragmentation and intramolecular functionalization. Surprisingly, only a few these reactions have been explored with ynamides. Recent developments for the synthesis of ynamides have however revitalized this field: these recent developments for the intermolecular radical additions to ynamides will therefore be overviewed in the next sections, starting with the radical thiylation of ynamides.

1.2.2.1 Stereoselective radical thiylation of ynamides

The first intermolecular radical addition to ynamides, their radical thiylation, was reported by the group of Yorimitsu and Oshima in 2009,[21] who developed a regio- and stereoselective radical addition of thiols to internal ynamides (Scheme 1.8). This reaction was found to be conveniently initiated by triethylborane with molecular oxygen, the combination of these reagents generating an ethyl radical which abstracts the hydrogen atom of the starting arenethiol to form an electron-deficient thiyl radical intermediate, which initiated a stereoselective addition to the ynamide **18** to generate the *Z*-1-amino-2-thio-1-alkenes **19**. During the investigation of the scope, it was found out that the use of alkyl thiols could not give a satisfactory result, which might be due to their low stability. Most of the radical hydrothiolations of *N*-*p*-toluenesulfonyl-substituted ynamides gave good levels of stereoselectivity in favor of the *Z* isomers (*Z:E* > 99:1). In comparison, the camphorsulfonamides, *N*-Boc protected ynamide and *N*-(1-alkynyl)oxazolidinones also gave excellent yields and stereoselectivities, but with the *E* isomers being formed as the major products.

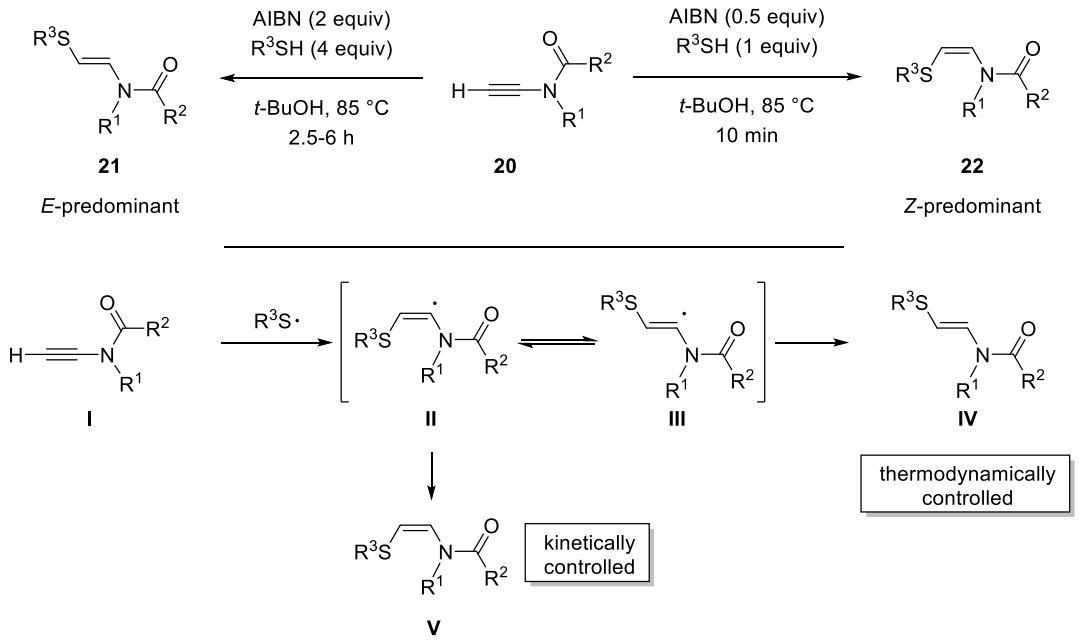
[21] (a) Sato, A.; Yorimitsu H.; Oshima, K. *Synlett* **2009**, *1*, 28-31. (b) Sato, A.; Yorimitsum H.; Oshima, K. *Bull. Korean Chem. Soc.* **2010**, *31*, 570-576.



Scheme 1.8: Regio- and stereoselective radical addition of thiols to ynamides reported by Yorimitsu and Oshima.

Based on these results, in 2010, Castle and co-workers reported two complementary protocols for the stereoselective addition of thiyl radicals to terminal ynamides, which provided efficient accesses to stereodefined β-thioenamides, a structural element found in some cyclic peptides such as lantibiotics and thioviridamide (Scheme 1.9).[22] Interestingly, the *E* isomer adduct **21** was favored under thermodynamically-controlled conditions (2 equiv of AIBN, 4 equiv of thiol, long reaction time), whereas the *Z* isomer adduct **22** predominated under kinetically-controlled conditions (0.5 equiv of AIBN, 1 equiv of thiol, short reaction time). This observation could be rationalized by the rapid equilibration of radical intermediates **II** and **III** under different conditions: when an excess amount of thiol was added to the reaction, the adduct **V** could isomerize to form adduct **IV** as a more stable product via a radical addition/thiyl radical elimination mechanism. To confirm this assumption, the *Z* enriched product was reacted under the thermodynamically-controlled radical conditions and was found to be converted to the *E* enriched adduct in good yield. This transformation was proved to be efficient for both cyclic carbamate-derived ynamides and acyclic ynamides, and Cysteine-derived thiols were also examined to construct peptide-based β-thioenamides.

[22] Banerjee, B.; Litvinov, D. N.; Kang, J.; Bettale, J. D.; Castle, S. L. *Org. Lett.* **2010**, *12*, 2650-2652.

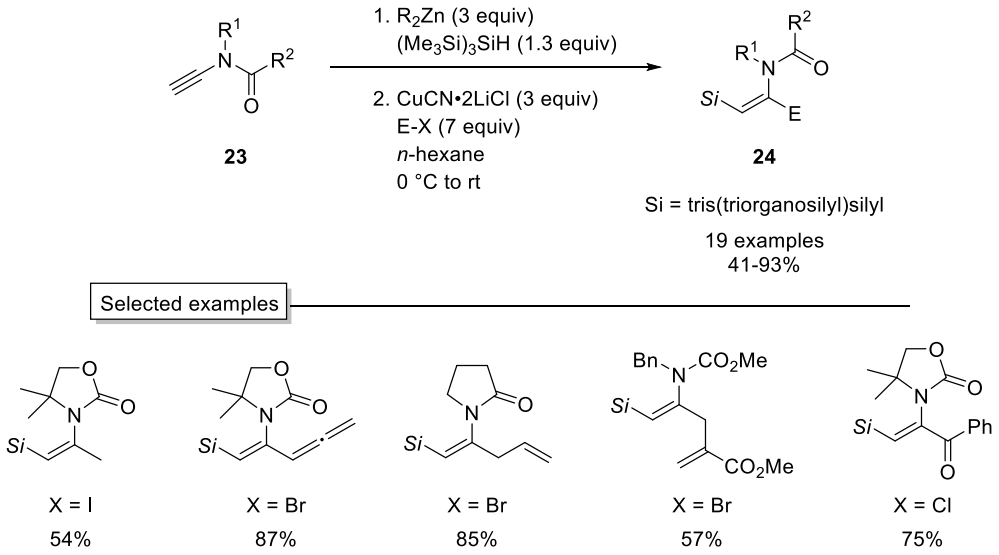


Scheme 1.9: Stereoselective radical addition of thiols to terminal ynamides reported by Castle and the proposed mechanism.

1.2.2.2 Stereoselective radical silylation of ynamides

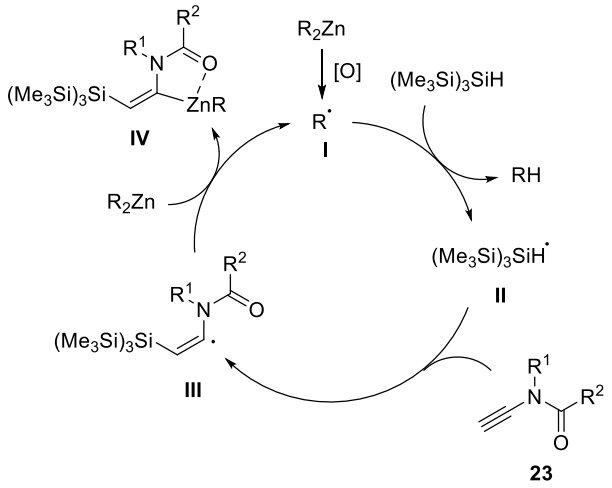
In line with these results, Perez-Luna and co-workers reported in 2014 an efficient and highly *trans*-selective radical silylzincation of terminal ynamides. [23] Combined with subsequent bromodesilylation and palladium catalyzed cross-coupling of the resulting brominated enamide, this method provides an efficient entry to a broad range of *Z*-α,β-disubstituted enamides (Scheme 1.10). Although a lot of methods have been established to synthesize 1,2-difunctionalized olefins from alkynes with concomitant introduction of a silyl group, such as silylcupration or copper catalyzed silylmagnesiation, all these methods typically yield *syn*-addition products; thus, the development of a *trans*-selective silylmetalation of alkynes has remained elusive for years. Based on previous studies on the radical *trans*-carbozincation of alkynes,[24] a radical mechanism was chosen to achieve this *trans*-stereoselective silylmetalation. Inspired by the work of Apeloig and co-workers, [25] they selected ynamides **23** as substrates: upon reaction with a combination of R_2Zn (3 equiv) and $(Me_3Si)_3SiH$ (1.3 equiv) in hexane at 0 °C, various substituted terminal ynamides could be transformed to transient α-zincated *E*-β-silylenamides which, upon transmetallation with copper cyanide complexed with lithium chloride and further trapping with an electrophile, gave α-substituted *E*-β-silylenamides **24** with high efficiency and stereoselectivity. Moreover, and as mentioned before, the silicon substituent could be further used for the introduction of a range of substituents via a bromodesilylation/Sonogashira cross-coupling sequence, which broadened the utility of this radical silylzincation method.

[23] (a) Chemla, F.; Dulong, F.; Ferreira, F.; Nullen, M. P.; Perez-Luna, A. *Synthesis* **2011**, *9*, 1347-1360. (b) Chemla, F.; Dulong, F.; Ferreira, F.; Nullen, M. P.; Perez-Luna, A. *Beilstein J. Org. Chem.* **2013**, *9*, 236-245. (c) Maury, J.; Feray, L.; Bertrand, M. P. *Org. Lett.* **2011**, *13*, 1884-1887.
[24] (a) Romain, E.; Fopp, C.; Chemla F.; Ferreira, F.; Jackowski, O.; Oestreich, M.; Perez-Luna, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 11333-11337.
[25] (a) Dobrovetsky, R.; Kratish, Y.; Tumanskii, B.; Botoshansky, M.; Bravo-Zhivotovskii, D.; Apeloig, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 4671-4675. (b) Dobrovetsky, R.; Kratish, Y.; Tumanskii, B.; Botoshansky, M.; Bravo-Zhivotovskii, D.; Apeloig, Y. *Angew. Chem.* **2012**, *124*, 4749-4753.



Scheme 1.10: Regio- and stereoselective radical silylzincation of ynamides reported by Perez-Luna.

The mechanism of this transformation is illustrated in Scheme 1.11. It starts with the generation of alkyl radical **I** from the starting dialkylzinc reagent in the presence of molecular oxygen. Then the alkyl radical would react with $(Me_3Si)_3SiH$ to generate the silyl radical **II**, which would then add to the triple bond of ynamide **23** to form the *Z*-α-amino vinylic radical **III** in a regioselective manner. After homolytic substitution (S_H2) with the dialkylzinc, α-zincated β-silylenamide intermediate **IV** was produced with the concomitant regeneration of the alkyl radical **I** to run the chain reaction cycle. According to this picture, the zincation step (**III** to **IV**) would account for the stereoselectivity of the whole process. It was estimated that the activation of dialkylzinc reagent could be facilitated through the homolytic substitution process by the formation of a chelate between the zinc and the carbonyl group on the ynamide nitrogen atom, which would also inhibit the *Z* to *E* isomerization of the vinylic radical **III**. More evidence was revealed during the optimization of the conditions, as the use of the bulky reagent $(c\text{-Hex})_2Zn$ almost gave a single *Z* isomer product (*Z:E* > 98:2) while Me_2Zn gave a mixture of two isomers (*Z:E* = 37:63), therefore highlighting the steric effect on the S_H2 process. The potential polar mechanism was excluded by control reactions in which a selected substrate reacted with a preformed $[(Me_3Si)_3Si]_2Zn$ without the participation of radical initiator and which only led to fragmentation.



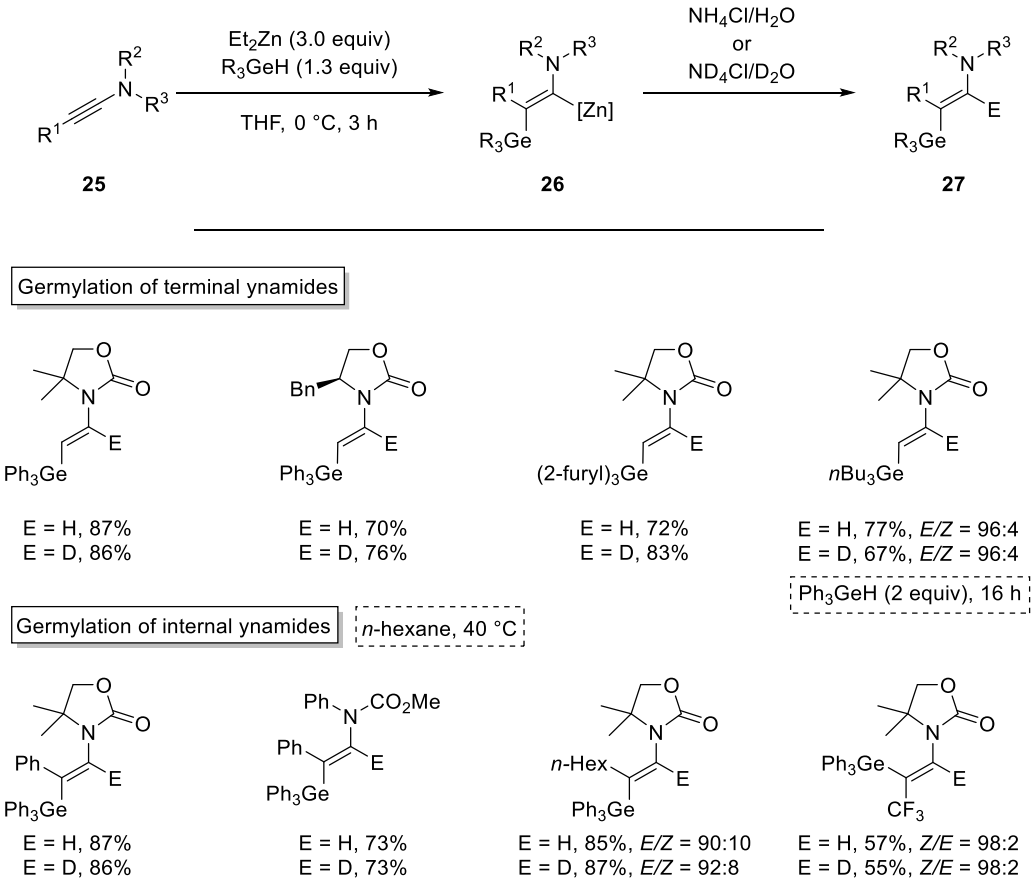
Scheme 1.11: Plausible mechanism of the radical silylzincation.

1.2.2.3 Stereoselective radical germylation of ynamides

In continuation of these studies and as a logical extension moving down the periodic table, the Perez-Luna's group next reported an efficient regio- and stereoselective radical germylzincation of ynamides, in which a C(sp^2)-Ge bond and a C(sp^2)-Zn bond are formed in a single operation.[26] As in the previous case, the newly formed carbon-metal bonds could be further utilized for the introduction of a range of functional groups, therefore providing a convenient access to various stereo-defined, poly-substituted enamides.

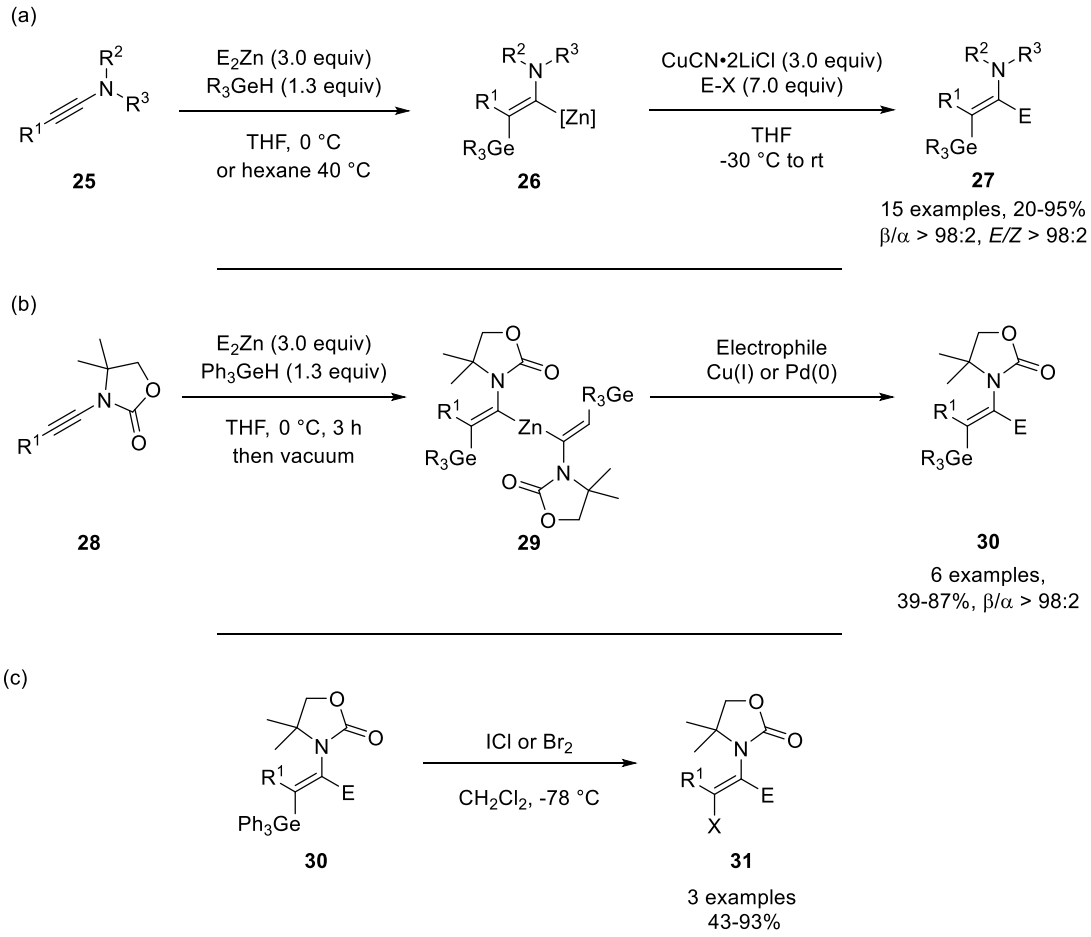
The optimization revealed that the best yields and stereoselectivities could be obtained by using a combination of Et_2Zn (3 equiv) and Ph_3GeH (1.3 equiv) in THF at 0 °C. With the optimal condition in hand, the scope of this process was extensively studied and the reaction was found to be compatible with a range of terminal and internal ynamides **25** and aryl or alkyl germanes, which gave the corresponding substituted enamides **27** with high β-regioselectivity and *cis*-stereoselectivity. It is worth to mention that, during the synthesis of cyclohexyl and trifluorocarbonyl substituted enamides, the reversed stereoselectivity was observed with the *Z* isomer being formed as the major product. In several cases and as indicated in Scheme 1.12, the standard conditions had to be slightly modified (different solvent, higher temperature or increased amount of germanes) to achieve a complete conversion. As a note, the germylzincation could even be extended to sulfur-, oxygen- and phosphorus-substituted alkynes as substrates, which gave single *E* isomers in moderate to good yields, while conventional alkynes were transformed in high *trans*-stereoselectivity.

[26] Vega-Hernandez, K.; Romain, E.; Coffinet, A.; Bijouard, K.; Gontard, G.; Chemla, F.; Ferreira, F.; Jackowski, O.; Perez-Luna, A. *J. Am. Chem. Soc.* **2018**, *140*, 17632-17642.



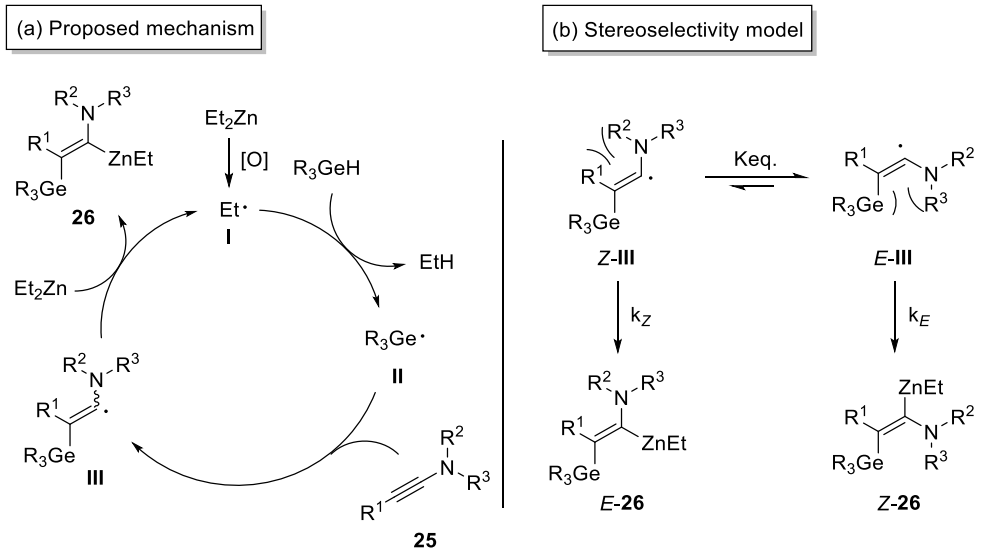
Scheme 1.12: Regio- and stereoselective radical germylzincation reported by Perez-Luna.

Having demonstrated the broad scope of germylzincation process, the authors next investigated the germylzincation/electrophilic substitution strategy to provide access to more highly substituted vinylgermanes. As indicated in Scheme 1.13(a), the germylzincation could be successfully combined with an *in situ* Cu(I) mediated trapping with a range of electrophiles, providing tri- or tetrasubstituted vinylgermanes **27** with high regio- and stereoselectivity from the corresponding terminal or internal ynamides **25**. During the development of this, they found out that the presence of excess Et_2Zn complicated in some cases this *in situ* post-functionalization: removing the volatiles under vacuum after germylzincation provided divinylzinc intermediate **29** – which has been isolated and characterized by X-ray diffraction analysis – whose copper- or palladium- mediated coupling was found to be efficient, therefore providing an alternative in cases where the direct functionalization of **25** was found to be tricky. Moreover, upon reaction with iodine monochloride or bromine, the triphenylgermylenamides **30** could be readily converted to β-halo enamides **31**, valuable intermediates for further functionalization.



Scheme 1.13: Radical germylzincation/functionalization of ynamides and halodegermylation of β-triphenylgermylenamides.

Finally, as with the silylzincation of ynamides presented in the previous section, the mechanism of this new germylzincation was proposed to involve a radical process shown in Scheme 1.14(a), a mechanism that was supported by several control experiments. It was reasoned that the ethyl radical **I** resulting from the oxidation of diethylzinc generated the germanium-centered radical **II** by hydrogen abstraction from the starting hydrogermane. This germyl radical **II** would then add to the ynamide **25** to form vinyl radical **III**, a step that would be followed by an alkylzinc group transfer with Et_2Zn through homolytic substitution (S_{H2}) producing the germylzincation product **26** with the concomitant regeneration of the ethyl radical **I** to propagate the radical chain. The stereoselectivity of the whole process was attributed to the alkylzinc group transfer (**III** to **26**) step, as illustrated in Scheme 1.14(b): the radical intermediates *Z*-**III** and *E*-**III** would be in equilibrium (characterized by the corresponding equilibrium constant K_{eq}), and the stereoselectivity of the reaction would depend on both this constant K_{eq} and the rate of the alkylzinc group transfer (k_Z and k_E). For most ynamides, the R^1 group was smaller than the germyl substituent, so that *Z*-**III** was favored over its *E*-isomer, therefore favoring the formation of the *E* isomer of **26**. In contrast, and notably when the R^1 substituent was a cyclohexyl or CF_3, the *E*-**III** intermediate was favored, resulting in a switch in the stereoselectivity yielding to the *Z* configured product *Z*-**26**.



Scheme 1.14: Proposed mechanism and stereoselectivity model of the germylzincation.

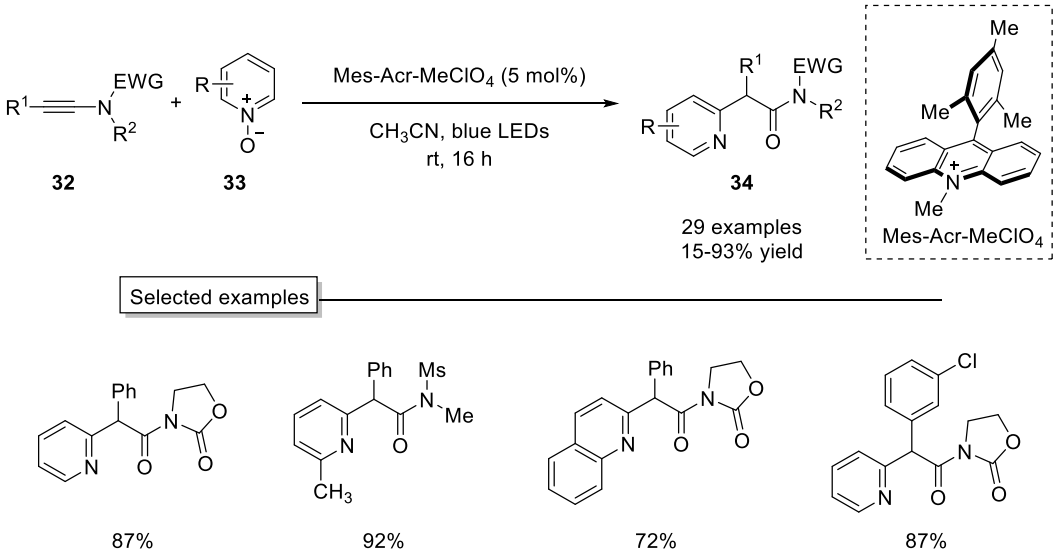
All intermolecular processes described up to now rely on well-established radical additions to the triple bond of ynamides. One last process that will be overviewed relies on a less standard single electron transfer induced by a photoredox catalyst, a strategy that could be implemented for the development of an efficient alkylation of pyridine *N*-oxides with ynamides.

1.2.3 Photocatalyzed alkylation of pyridine *N*-oxides with ynamides

Photoredox catalysis is indeed a technique that is more and more utilized for the generation of radical species under mild conditions. While, in most cases, a carbon-halogen is reduced in such processes to generate the corresponding radical species, a less explored possibility lies in single electron oxidation of alkynes resulting in the formation of transient alkyne radical cations. This strategy was elegantly implemented by the Deng's group this year who developed an elegant photocatalyzed *ortho*-alkylation of pyridine *N*-oxides **33** with ynamides **32**, providing a new route to various α–(2-pyridinyl)benzyl amides **34** (Scheme 1.15).[27]

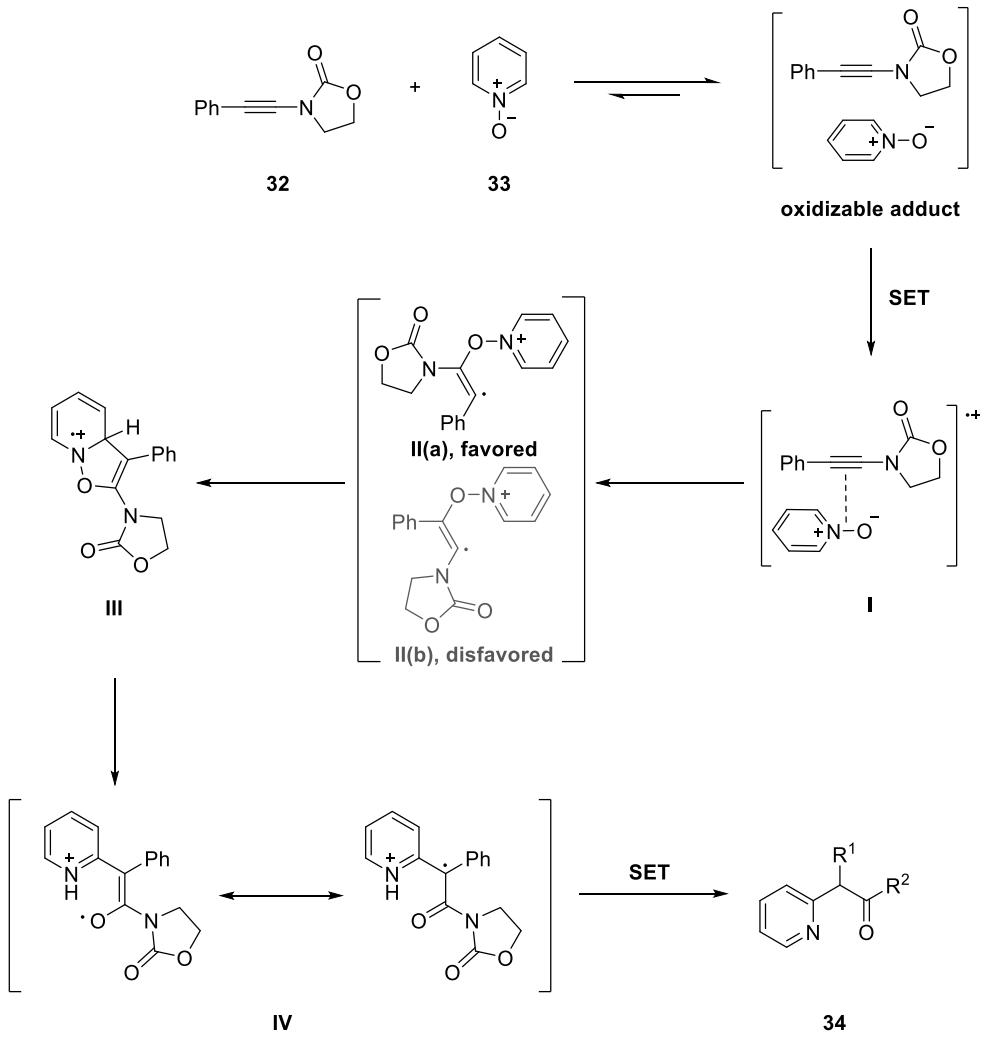
To test the feasibility of their strategy, the authors firstly carried out cyclic voltammetry measurements of mixtures of ynamides and pyridine *N*-oxides, measurements that demonstrated the π-π interactions between ynamides and pyridine *N*-oxides as well as the formation of the corresponding oxidative adducts. Based on these results, after screening a range of photocatalysts such as methylene blue, ruthenium or iridium complexes, the best result was obtained by performing the reaction with 9-mesityl-10-phenyl acridinium perchlorate (Mes-Acr-$MeClO_4$, 5 mol%) in acetonitrile under blue LED light irradiation at room temperature. In addition, the scope of this transformation was investigated by employing various substituted ynamides and heteroaromatic *N*-oxides, most of which providing efficient access to the desired oxidative adduct **34**.

[27] Markham, J. P.; Wang, B.; Stevens, E. D.; Burris, S. C.; Deng, Y. *Chem. Eur. J.* **2019,** *25*, 6638-6644.



Scheme 1.15: Photocatalyzed ortho-alkylation of pyridine N-oxides with alkynes reported by Deng.

Finally, to gain some mechanistic insights into this reaction, the authors carried out electrochemical studies, radical inhibition and trapping experiments as well as Stern-Volmer fluorescence quenching studies. It was observed that the transformation could be suppressed upon addition of 2,2,6,6,-tetramethylpiperidin-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT), and the radical intermediate could be trapped by tetrachloromethane to generate the corresponding α-chloroimide product. Furthermore, the Stern-Volmer fluorescence quenching studies proved that the presence of pyridine *N*-oxide could promote the photocatalyzed oxidation of ynamides. Based on these results, the mechanism shown in Scheme 1.16 was proposed. It was rationalized that the radical cation **I** was generated from the oxidizable adduct through a photocatalytic single electron transfer (SET) process, which would undergo nucleophilic attack by the oxygen of the pyridine *N*-oxide to yield the cationic vinyl radical **II**. The generation of resonance-stabilized cationic vinyl radical **II(a)** was favored over **II(b)**, which followed by the intramolecular Minisci-type reaction to produce the aminyl radical cation intermediate **III**. Following the sequential 1,2-electron shift, β-N-O bond scission and proton transfer the resonance-stabilized radical **IV** would be generated, which gave the desired oxidative adduct **34** through the second SET process.



Scheme 1.16: The plausible mechanism of photocatalyzed ortho-alkylation of pyridine N-oxides with ynamides.

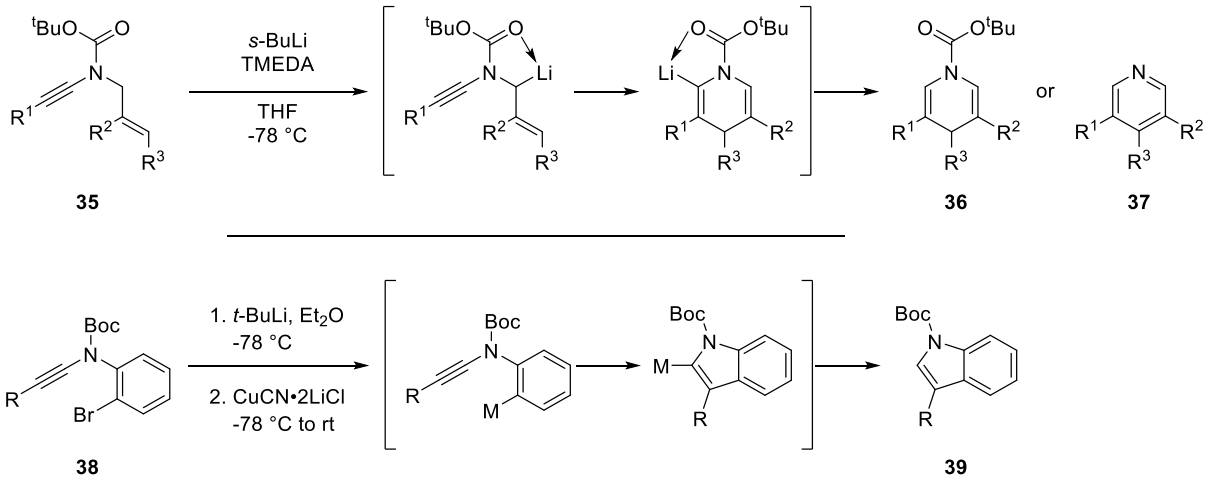
As overviewed with all examples described in the literature presentation, the radical chemistry has a strong potential to access a range of nitrogen-containing building blocks from readily available ynamides. Most processes proceed under mild conditions and tolerate a variety of functional group. Compared to ionic processes, the radical chemistry of ynamides is still underdeveloped despite its potential, notably in heterocyclic synthesis. Based on the group's interest in the chemistry of ynamides, we envisioned that properly substituted ynamides could be utilized as substrates in radical cyclizations: the objectives of this project will be presented in the next paragraphs.

2 Objectives

Nitrogen-containing heterocyclic compounds are an important family of molecules including dozens of members that can be classified according to the ring sizes, the number of nitrogen atoms, and if they are saturated or not, fused to other rings or not. These structures exist in a large number of natural products and are widely utilized for the production of pharmaceuticals, agrichemicals, functional polymeric materials or catalysts. If many nitrogen-containing heterocycles can be prepared by a range of efficient methods, some of them are still difficult to prepare, notably depending on their

substitution pattern. Thus, the development of new synthetic methods to access various substituted nitrogen heterocycles remains an important topic in organic chemistry, not only because of academic considerations, but also for industrial needs.

Encouraged by our interest in the chemistry of ynamides,[9,28] we have developed several ionic intramolecular cyclizations of ynamides, which provided efficient accesses to a variety of nitrogen heterocycles. For example, in 2012, our group reported a general and efficient anionic cyclization of ynamides **35** to synthesize 1,4-dihydropyridine **36** and pyridine **37** derivatives, this reaction proceeded through a lithiation/isomerization/intramolecular carbolithiation mechanism (Scheme 1.17).[29] Based on these results, another anionic intramolecular cyclization was explored to synthesize highly substituted indoles **39** through a lithiation/transmetallation/carbocupration sequence from *N*-bromoaryl-ynamides **38**.[30] The efficiency of this last procedure first led us to envision its extension to the synthesis of tetrahydropyridines that could potentially be obtained by an intramolecular anionic cyclization from *N*-haloalkyl-ynamides.



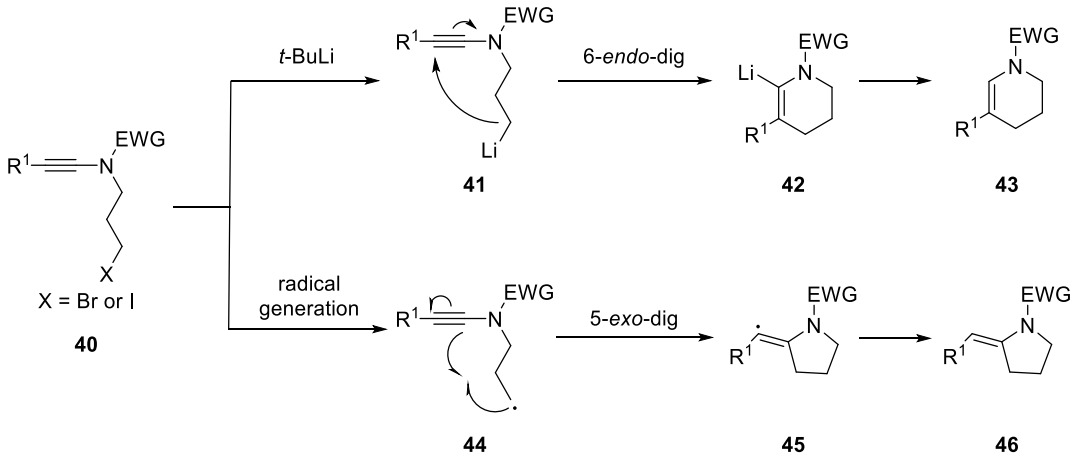
Scheme 1.17: Anionic cyclization of ynamides reported by our group.

We indeed envisioned that *N*-haloalkyl-ynamide **40** could be excellent substrates under both anionic and radical conditions as depicted below (Scheme 1.18). For the anionic strategy, the ynamide **40** was assumed to readily generate organolithium derivative **41** through a halogen-lithium exchange, upon treatment with *t*-butyllithium for example, which would be followed by a 6-*endo*-dig intramolecular carbolithiation and hydrolysis to afford tetrahydropyridines **43**. As for the radical pathway, which gave us excellent results, we envisioned that ynamide **40** could be used for the generation of alkyl radical intermediate **44**, then the alkyl radical would attack the triple bond of the ynamide which would proceed through a 5-*exo*-dig cyclization according to the Beckwith rule, and a subsequent hydrogen atom abstraction would provide the corresponding pyrrolidine derivative **46**. From the exact same substrate, we could therefore obtain either six or five membered rings in a divergent manner depending on the cyclization mode (anionic or radical).

[28] (a) Theunissen, C.; Metayer, B.; Henry, N.; Compain, G.; Marrot, J.; Martin-Mingot, A.; Thibaudeau, S.; Evano, G. *J. Am. Chem. Soc.* **2014,** *136*, 12528-12531. (b) Lecomte, M.; Evano, G. *Angew. Chem. Int. Ed.* **2016**, *55*, 4547-4551.

[29] Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc.* **2012,** *134*, 9078-9081.

[30] Gati, W.; Couty, F.; Boubaker, T.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Org. Lett.* **2013,** *15*, 3122-3125.



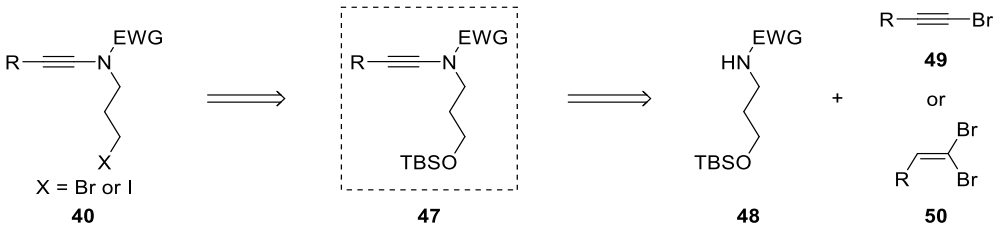
Scheme 1.18: Anionic and radical cyclization of N-haloalkyl-ynamides.

With these ideas in mind, we started with the preparation of the ynamides required and investigated their reactivity under anionic and radical conditions: results from these studies will be described in the following section, starting with the anionic conditions.

3 Attempts at anionic cyclization of ynamides to tetrahydropyridines

3.1 Synthesis of the starting ynamides

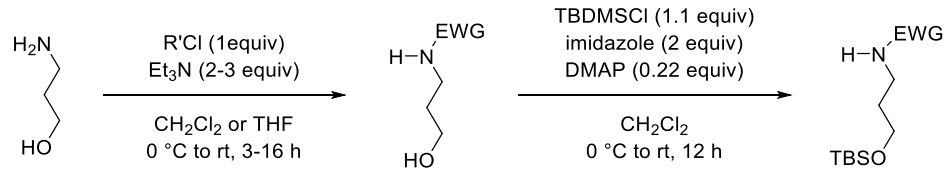
As indicated in Scheme 1.19, the desired *N*-haloalkyl-ynamide **40** could be potentially obtained from the corresponding *N*-silyloxyalkyl-ynamide **47**. This ynamide could be prepared by well-established procedures relying on copper mediated cross-coupling of amides **48** with alkynyl bromides **49** or 1,1-dibromo-1-alkenes **50**, in which the choice of copper source, ligand, base and other detailed conditions mainly depend on the substituents of the amides. Since the nature of the substituent on the ynamides as well as the nature of the electron-withdrawing group as well as the one of the halogen can be crucial for the anionic cyclization, we therefore decided to synthesize several ynamides whose reactivity under anionic conditions could then be studied.



Scheme 1.19: Retrosynthesis of the starting ynamides.

3.1.1 Synthesis of protected aminoalcohols

With this retrosynthetic analysis in mind, we started the synthesis by preparing the protected amines required for the alkynylation step. Considering the retrosynthetic analysis and the conditions typically used for the reductive lithiation step, the following deactivated protecting groups were selected: sulfonyl (tosyl and nosyl), phosphoryloxy and carbamates (methoxycarbonyl, Cbz and Boc). Commercially available 3-amino-1-propanol was used as the starting material, and was reacted with the corresponding chlorides or anhydride to generate the desired protected amines. Further silylation of the alcohol next led to the desired protected aminoalcohols **48** in moderate to good yields. All these compounds were stable and could be easily purified through flash column chromatography over silica gel (Scheme 1.20).



51

52a EWG = COOMe
52b EWG = Cbz
52c EWG = $PO(OEt)_2$
52d EWG = Ts
52e EWG = Ns
52f[a] EWG = Boc

48a EWG = COOMe, 89%
48b EWG = Cbz, 51%
48c EWG = $PO(OEt)_2$, 58%
48d EWG = Ts, 97%
48e EWG = Ns, 86%
48f EWG = Boc, 97%

[a] The conditions were $(Boc)_2O$ (1.0 equiv), THF/H_2O, rt, 3 h.

Scheme 1.20: Synthesis of protected aminoalcohols.

3.1.2 Synthesis of ynamides *via* copper mediated cross-coupling

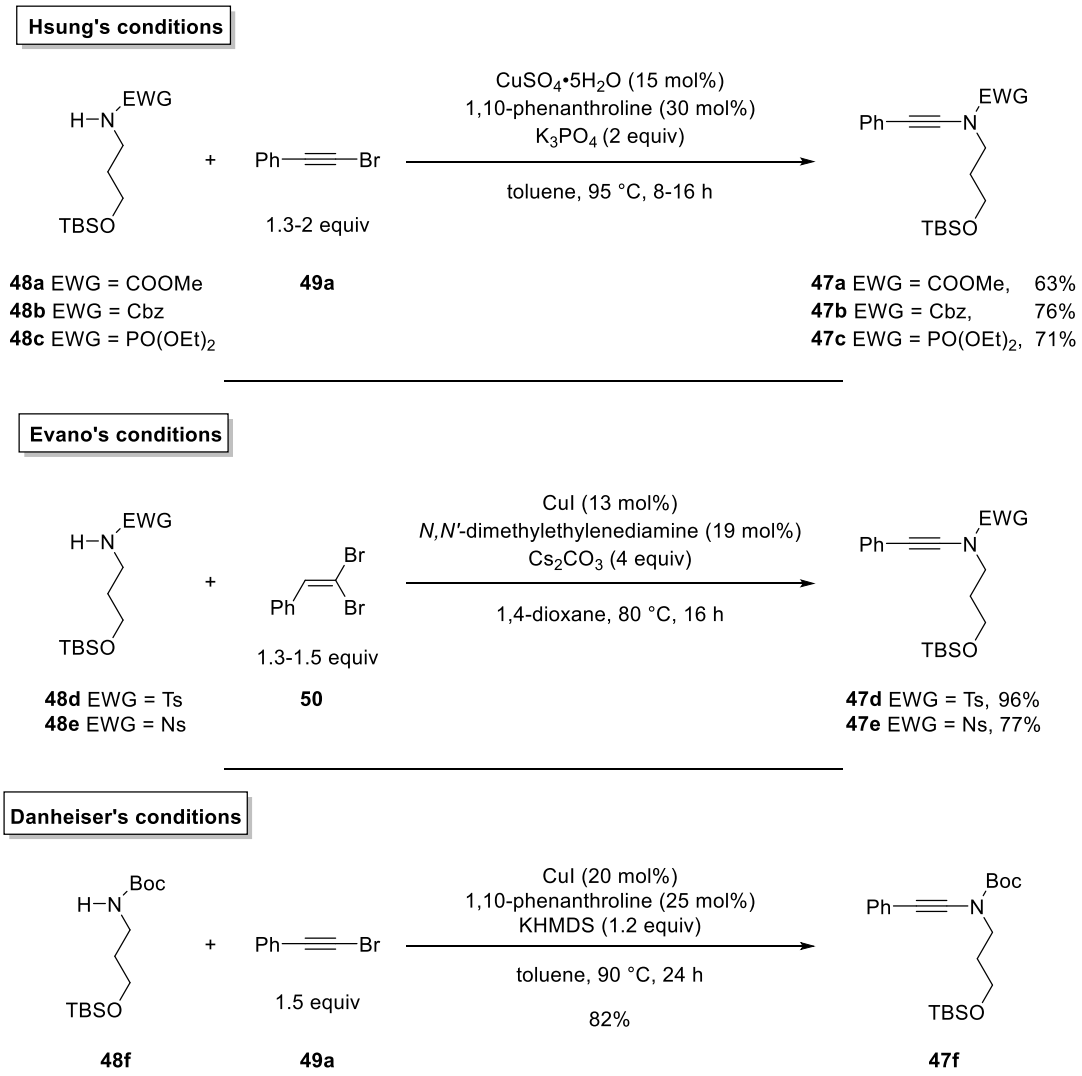
Then, we focused on the key step: the copper mediated cross-coupling to synthesize the desired ynamides. According to the literature, the most general method to date is the copper(I) catalyzed alkynylation developed by the Hsung group[31] which employs alkynyl bromides and protected amines as substrates and relies on a combination of $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline in toluene at 95 °C to generate a variety of ynamides in moderate to good yields. Using this procedure, methoxycarbonyl, Cbz and phosphoryloxy-protected ynamides **47a-c** could be obtained in good yields ranging from 63% to 76%. While this method is one of the most efficient reported to date, its main drawback lies on the use of alkynyl bromides, prepared by bromination of the corresponding terminal alkynes, which are highly lachrymatory.

Thus, for the preparation of *N*-sulfonyl-ynamines, we preferred to use the conditions developed in our group,[32] which utilize 1,1-dibromo-1-alkenes, readily prepared from the corresponding aldehydes as alkynylating agents. This procedure enables the synthesis of tosyl- and nosyl-protected ynamides **47d-e** in good to excellent yields.

The synthesis of *N*-Boc-substituted ynamide **47f** turned out to be more difficult due to the steric bulk of the Boc group: the Hsung's method gave only traces of the desired product, while the use of

[31] Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004,** *6*, 1151-1154.
[32] Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 4381-4385.

dibromoalkene gave no desired product. In both cases, increasing the temperature or adding more catalyst and ligand did not increase the yield. After screening several other synthetic methods, encouragingly, we finally found out that the conditions from Tam's work,[33] in which catalytic amounts of copper(I) iodide and 1,10-phenanthroline and slow addition of KHMDS were used, could yield the desired *N*-Boc-substituted ynamide **47f** efficiently (Scheme 1.21). As mentioned in Tam's publication, these conditions were inspired from the works of Hsung and Danheiser:[34] the rates of nitrogen deprotonation and of the alkynylation with the alkynyl bromide should match, otherwise the deprotonated amide would be able to coordinate to the copper catalyst to form an unreactive complex.[35]



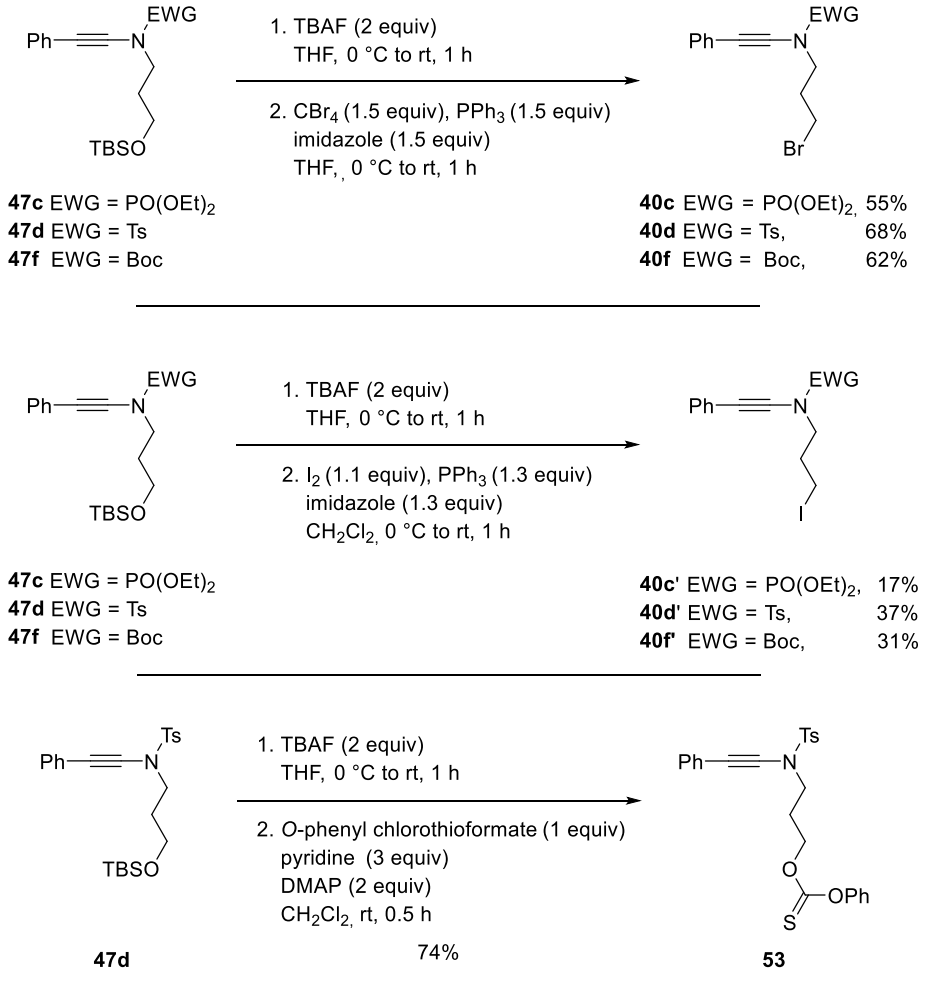
Scheme 1.21: Synthesis of the starting ynamides through copper mediated cross-coupling reactions.

[33] Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681-3684.
[34] Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011-4014.
[35] Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421-7428.

3.1.3 Synthesis of *N*-haloalkyl-ynamides

With these ynamides in hand, we next moved to the deprotection/halogenation steps as illustrated in Scheme 1.22. The TBS group was readily cleaved with excess TBAF, and the halogenation procedure we selected was the Appel reaction with tetrabromomethane or iodine. While the Appel reaction worked well for the preparation of *N*-bromoalkyl-ynamides **40c**, **40d**, **40f** that could be isolated in reasonable yields, it turned to be not so satisfactory when we moved to the iodination. However, when we modified the ratio of the reagents to make sure that no iodine would be present in the reaction mixture (from I_2 (1.3 equiv), PPh_3 (1.3 equiv), imidazole (1.3 equiv) to I_2 (1.1 equiv), PPh_3 (1.3 equiv), imidazole (1.3 equiv)), the iodination turned out to be more efficient, yielding the desired iodinated ynamides **40c'**, **40d'** and **40f'** in moderate yields however. In addition, and with the idea to evaluate the radical cyclization that we mentioned earlier on, the *O*-phenyl carbonothioate-substituted ynamide **53** could also be obtained, upon treatment of ynamide **47d** with the corresponding chlorothioformate, in 74% yield.

The *N*-methoxycarbonyl, *N*-nosyl and *N*-Cbz bromoalkyl-ynamides could not be obtained through these procedures, among which the *N*-methoxycarbonyl ynamide did not survive the desilylation step, while the bromination of *N*-nosyl and *N*-Cbz ynamides were not successful since they resulted in degradation or no conversion, respectively.



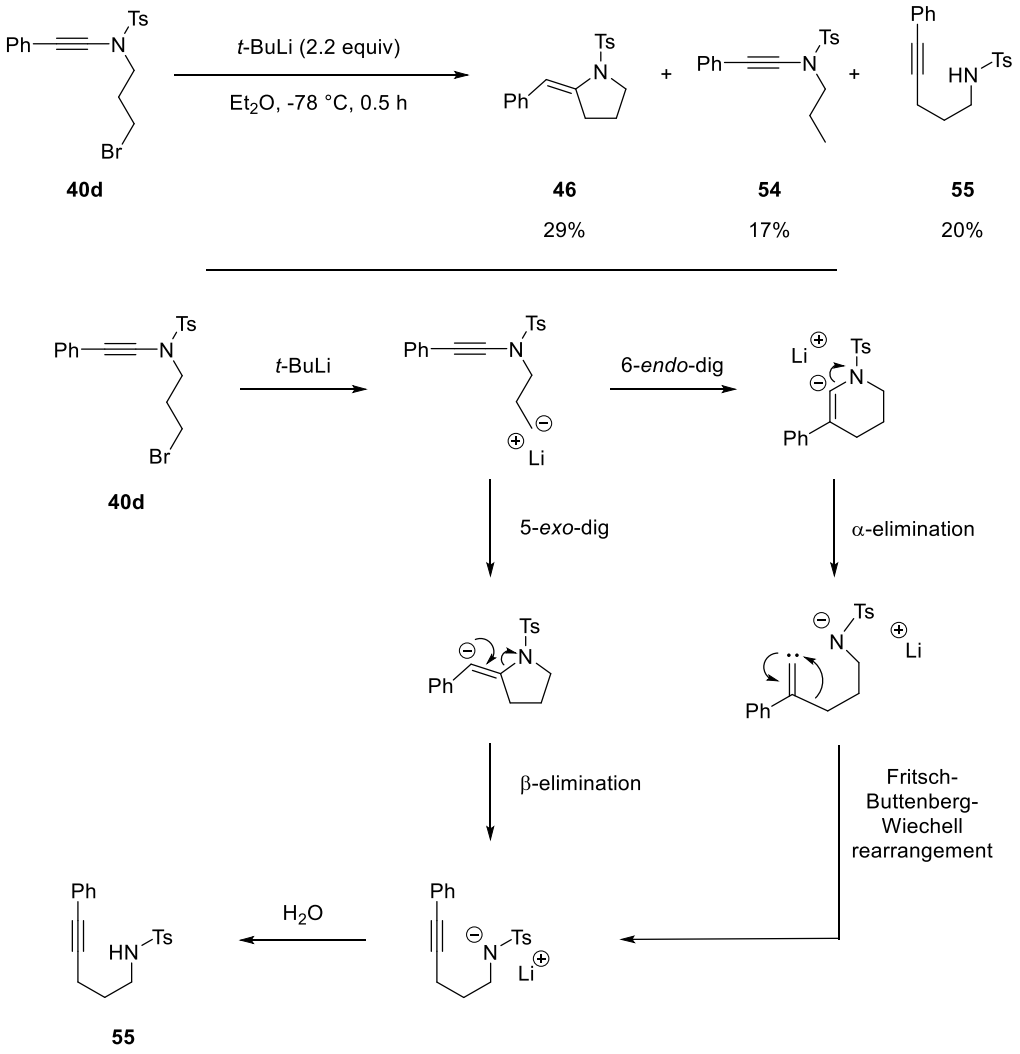
Scheme 1.22: Synthesis of the starting N-haloalkyl-ynamides and O-phenyl carbonothioate ynamide.

Having at our disposal a set of ynamides with representative electron-withdrawing groups and halogen atoms, we next moved to the study of their reactivity under anionic conditions: this will be discussed in the next section.

3.2 Attempts at anionic cyclization of ynamides to tetrahydropyridines

To test the feasibility of our hypothesis, we performed the first trial by treating the *N*-tosyl-bromoalkyl-ynamide with 2.2 equivalents of *tert*-butylithium in anhydrous and degassed diethyl ether at -78 °C for 30 minutes followed by hydrolysis of the reaction mixture (Scheme 1.23). While the starting material was almost completely consumed, several compounds were formed, separated and characterized. If the desired six-membered ring was not formed, surprisingly, a five-membered ring cyclized product (**46**) was isolated, albeit in low yield (29%), whose 1H and 13C spectra matched previously reported ones well.[36] Along with this product, two main byproducts were formed, one being the debromination product **54** (17%) resulting from the hydrolysis of the intermediate organolithium, and the other one being an acyclic amine **55** (20%). This last product could be formed through two reaction pathways involving either a 5-*exo*-dig cyclization followed by a β-elimination or a 6-*endo*-dig cyclization followed by an α-elimination and a Fritsch-Buttenberg-Wiechell rearrangement.

[36] Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328-6335.



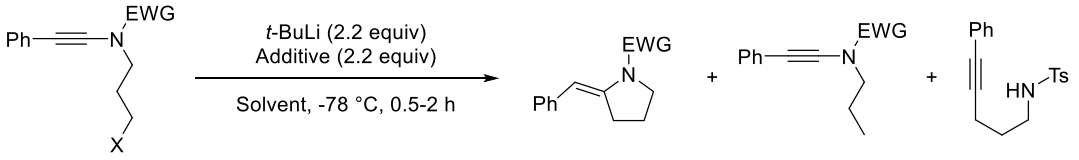
*Scheme 1.23: The reactivity of N-tosyl ynamide **40d** under anionic conditions.*

While these preliminary results clearly demonstrated the feasibility of our working hypothesis, an extensive optimization and screening of substrate was clearly needed in order to get a clean and selective reaction. We therefore evaluated a range of substrates by varying the nature of the electron-withdrawing group – which could have a strong effect on the outcome and regioselectivity of the anionic cyclization since it should stabilize the resulting vinyllithium by chelation and shouldn't be a good leaving group to avoid the formation of acyclic amine **55** – and the nature of the lithium-halogen exchange from alkyl halides with *tert*-butylithium being known to proceed through a polar mechanism in the case of alkyl iodides while alkyl bromides can involve single electron transfer that might involve a radical cyclization rather than an ionic one. The effect of the solvent (diethyl ether and THF can be used for such reactions), additives (TMEDA and HMPA) and temperature was also evaluated: some representative results are summarized below (Table 1.1). To facilitate the lithium-halogen exchange and to make sure a competing radical pathway was not operative, *N*-iodoalkyl-ynamide was used instead of *N*-bromoalkyl-ynamide (entry 2), but it gave the desired product in lower yields and acyclic amine **55** was actually formed in a higher yield. Next, ynamides with different electron-withdrawing groups were also tested under the anionic conditions, however, *N*-Boc ynamides gave a mixture of *E*

and *Z* isomers of pyrrolidine derivatives in very low yields (entries 4 and 6) and *N*-phosphoryloxy ynamides[37] led to an especially messy reaction (entry 9).

We then moved to optimize the conditions by adding additives, using different solvents and temperature. Based on previous works,[38] coordinating additives as TMEDA and HMPA were used by coordinating the lithium cation, they are known to deoligomerize organolithium reagents and to therefore increase their reactivity: they indeed worked but the yields were still far from satisfactory (entries 3, 5, 7, 8 and 10). We also studied the influence of temperature for this transformation, finding out that the results were not affected obviously at low temperature (-95, -78, -60, -40 °C) (entries 1 and 11-13), and when the temperature was above -20 °C, both the conversation and the yield of the desired product decreased dramatically, mostly because of the decomposition of *t*-butyllithium at this temperature (entry 14).

Table 1.1: Optimization of the anionic cyclization of N-haloalkyl-ynamides.



40c EWG = $PO(OEt)_2$, X = Br
40d EWG = Ts, X = Br
40f EWG = Boc, X = Br
40c' EWG = $PO(OEt)_2$, X = I
40d' EWG = Ts, X = I
40f' EWG = Boc, X = I

46a EWG = Ts
46b EWG = Boc

54 EWG = Ts
56 EWG = Boc

55

Entry	EWG	X	Solvent	Additive	Product (%)	Byproduct (%)	Conversion [a] (%)
1	Ts	Br	Et_2O	-	29	30[b]	95
2	Ts	I	Et_2O	-	10	54[b]	88
3	Ts	I	Et_2O	TMEDA	14	18[b]	57
4	Boc	Br	Et_2O	-	11	10[c]	50
5	Boc	Br	Et_2O	HMPA	25	30[c]	83
6	Boc	I	Et_2O	-	trace	23[c]	93
7	Boc	I	Et_2O	TMEDA	7	12[c]	82
8	Boc	I	THF	TMEDA	16	41[c]	91
9		Br	Et_2O	-	0	-	-
10		I	Et_2O	TMEDA	0	-	54
11	Ts	I	Et_2O	-	26	20[b]	74[d]
12	Ts	I	Et_2O	-	25	18[b]	66[e]
13	Ts	I	Et_2O	-	26	20[b]	73[f]
14	Ts	I	Et_2O	-	19	23[b]	61[g]

*[a] Measured by ^1H NMR analysis of the crude reaction mixture with 1 equiv of 1,1,2,2-tetrachloroethane as internal standard. [b]This major byproduct is acyclic amine **55**. [c]The byproduct is **56**. [d]-95 °C. [e]-60 °C. [f]-40 °C. [g] -20 °C.*

[37] DeKorver, K. A.; Walton, M. C.; North, T. D.; Hsung, R. P. *Org. Lett.* **2011**, *13*, 4862-4865.
[38] Degennaro, L.; Giovine, A.; Carroccia, L.; Luisi, R. *Practical Aspects of Organolithium Chemistry in Lithium Compounds in Organic Synthesis*. Wiley-VCH Verlag GmbH & Co. KGaA: **2014**; pp 513-538.

After all these trials, it seemed clear that the extension of previous studies from the group to the anionic cyclization of *N*-haloalkyl-ynamides was far from being trivial and we therefore decided to focus our efforts on the radical cyclization. Results from these studies will now be described.

4 Radical cyclization of ynamides to 2-benzylidene-pyrrolidines

4.1 Optimization of the reaction conditions

4.1.1 Screening of various *N*-haloalkyl-ynamides under radical conditions

To test the feasibility of the radical cyclization of ynamides, we selected classical conditions based on AIBN as the initiator and *n*-tributyltin hydride as the source of hydrogen and performed the reaction under argon at 80 °C in anhydrous and degassed toluene (Figure 1.8). We first reacted *N*-tosyl bromoalkyl- and iodoalkyl-ynamides to this condition but no desired product could be detected in crude reaction mixtures with these substrates (entries 1 and 2). In addition, a phenylthiocarbonate ester was also used to generate the radical intermediate by homolytic cleavage, however, giving no desired product under the standard conditions (entry 3). Then, we moved to the *N*-Boc-haloalkyl-ynamides: encouragingly, the *N*-Boc-bromoalkyl-ynamide gave a mixture of *E* and *Z* isomers after heating the reaction mixture for 16 hours (entry 4), while the *N*-Boc-iodoalkyl-ynamide was transformed to the desired product **46c** as a single isomer in high yield (97% crude ^{1}H NMR yield, entry 5). Finally, the *N*-phosphoryloxy ynamides were tested and only gave complex mixtures (entries 6-7). With all these results, we decided to focus on the transformation of *N*-Boc-iodoalkyl-ynamides.

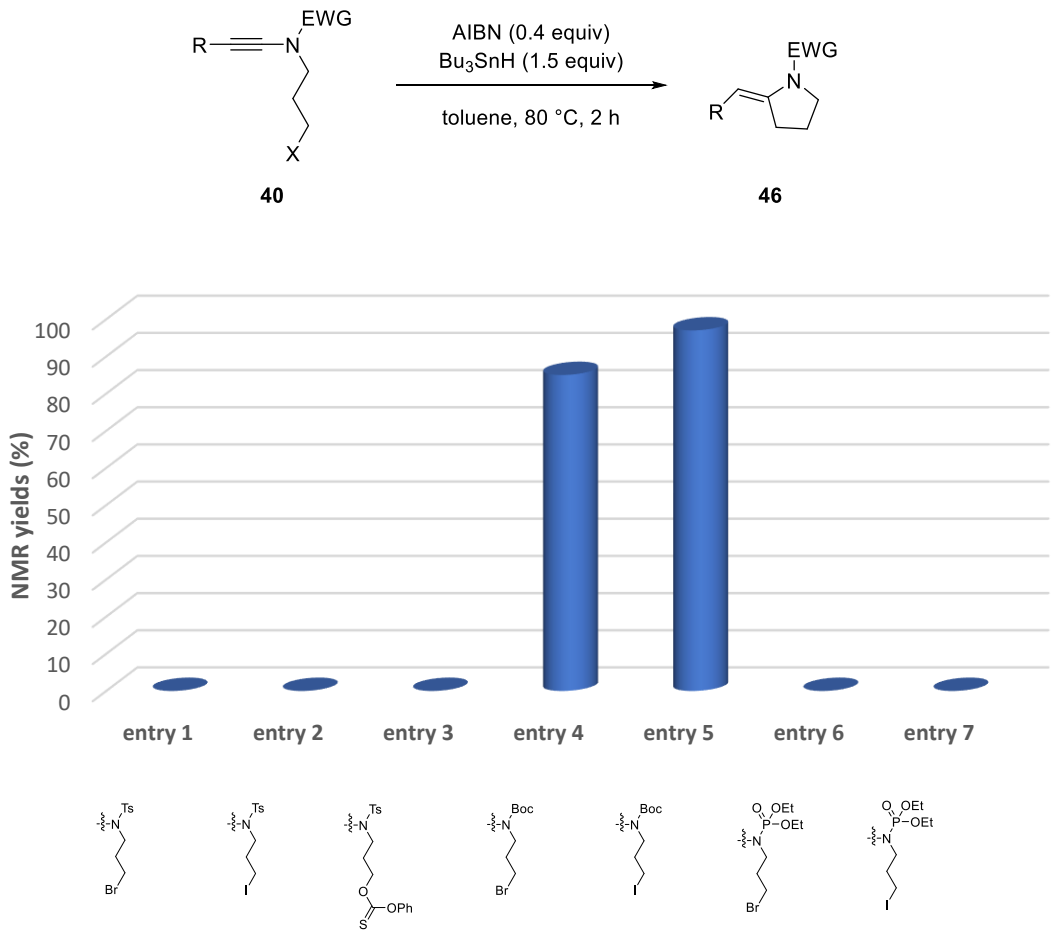
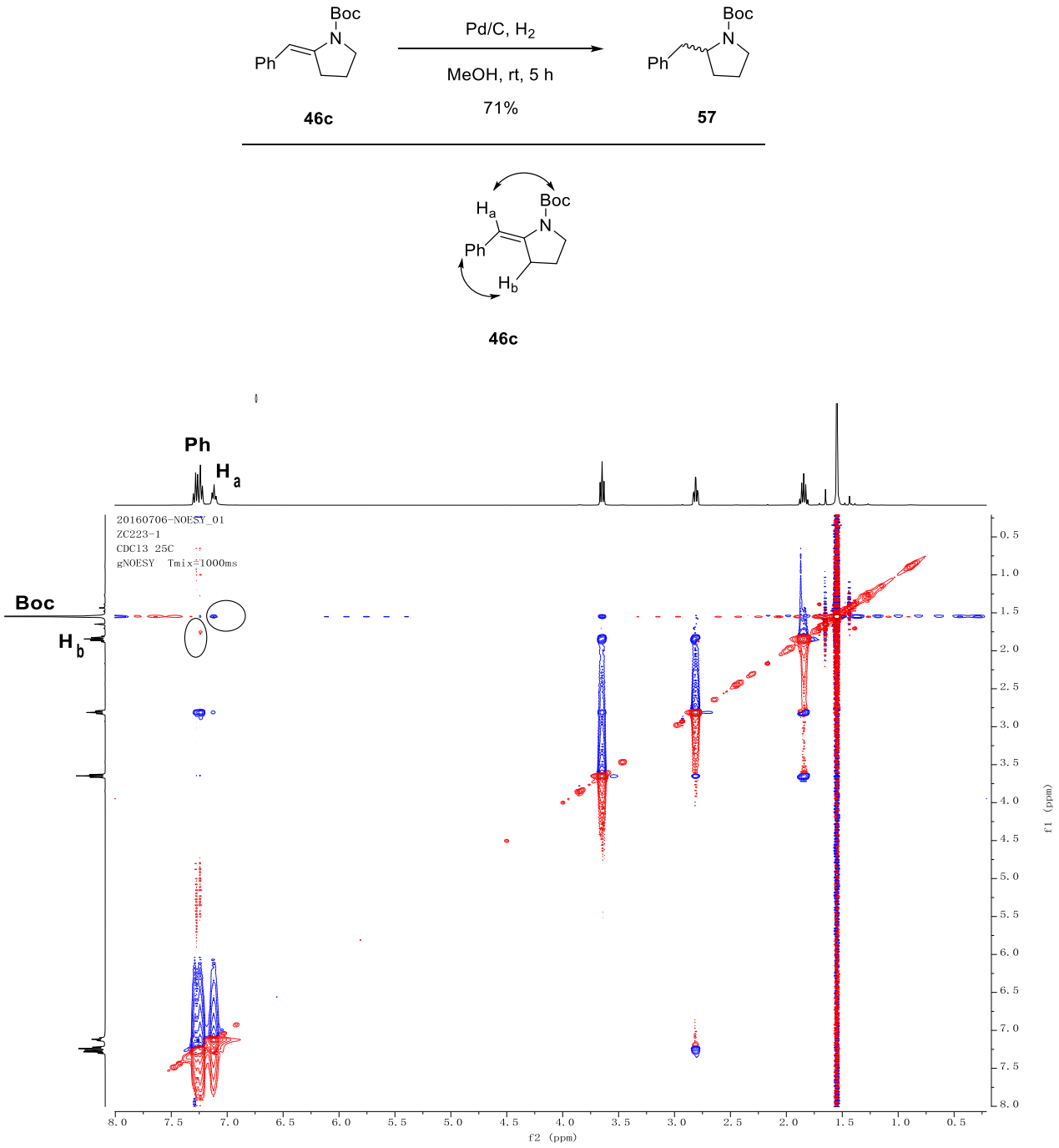


Figure 1.8: Trials of different substituted ynamides under radical conditions.

To confirm the structure of the cyclized product **46c**, we then reduced it with palladium on carbon (10 wt%) in methanol under an atmosphere of hydrogen (2.0 bars) at room temperature for 5 hours (Scheme 1.24, top). The desired reduced product **57** was isolated (71% yield) and its 1H and 13C NMR spectra perfectly matched previously reported ones,[39] thereby confirming the formation of a five membered ring heterocycle which is in agreement with the Beckwith rules. Moreover, the configuration of the double bond was confirmed by two-dimensional Nuclear Overhauser Effect (NOE) experiments to be *E*, which was attributed to a thermodynamically controlled pathway. As illustrated in Scheme 1.24 (bottom), the spectrum showed two strong correlation signals, one was between proton H_a and *N*-Boc group, and the other one was between proton H_b and the phenyl group, thus indicating the *E* configuration.

[S39] Massah, A. R.; Ross, A. J.; Jackson, R. F. W. *J. Org. Chem.* **2010**, *75*, 8275-8278.

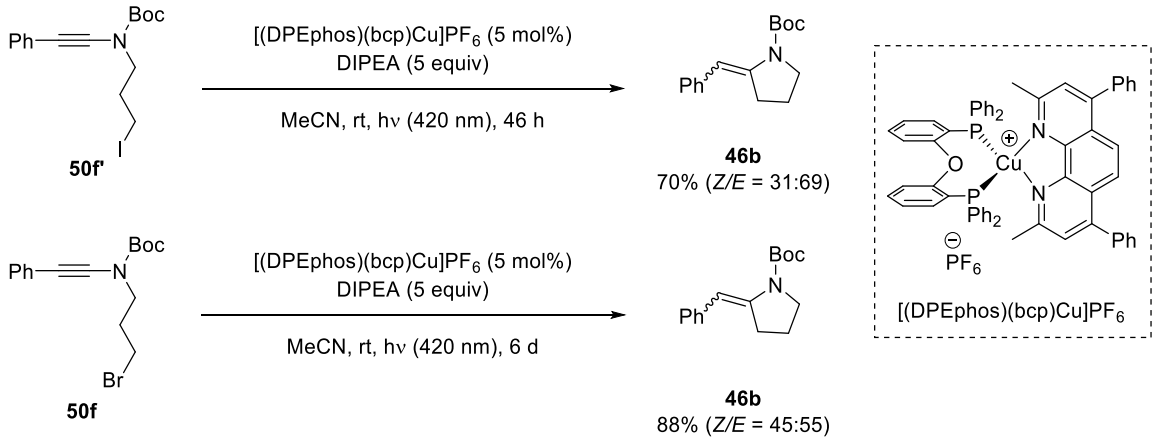


*Scheme 1.24: Reduction of the cyclized product **46c** and its NOE spectrum.*

Finally, it is worth to mention that the reaction was set at 80 °C to ensure the activation of AIBN and toluene was selected as the solvent to avoid the use of toxic benzene. Since the conversion and yield of this transformation were already excellent, no further optimization of the conditions was conducted: we therefore next focused our efforts on the study of the scope and limitations of this transformation but first quickly evaluated the possibility of replacing the classical radical reaction conditions by conditions based on the use of a photoredox catalyst.

4.1.2 Copper-catalyzed photoinduced radical cyclization of ynamides to 2-benzylidene-pyrrolidines

Having demonstrated the feasibility of the radical cyclization of ynamides to 2-benzylidene-pyrrolidines, we were curious to check if the *N*-haloalkyl-ynamide **50f** or **50f'** could be activated through photoredox catalysis, which would enable the cyclization to be performed under more environmentally friendly conditions. Based on our previously developed copper-based photoredox catalytic system, we performed the reaction in the presence of [(DPEphos)(bcp)Cu]PF_6 (5 mol%) and DIPEA (5 equiv) in acetonitrile upon LED irradiation at 420 nm at room temperature for 2-6 days, which proceeded smoothly to give the desired pyrrolidine **46b** as a mixture of *E* and *Z* isomers in good yields (70-88%) (Scheme 1.25). These results proved the feasibility of the photoinduced radical cyclization of *N*-haloalkyl-ynamides, but the photochemical conditions did not provide a good level of stereoselectivity as the classical radical conditions and required a much longer reaction time. For this reason, we decided to focus on the classical tin-based conditions.



Scheme 1.25: Copper catalyzed photoinduced cyclization of N-haloalkyl-ynamides.

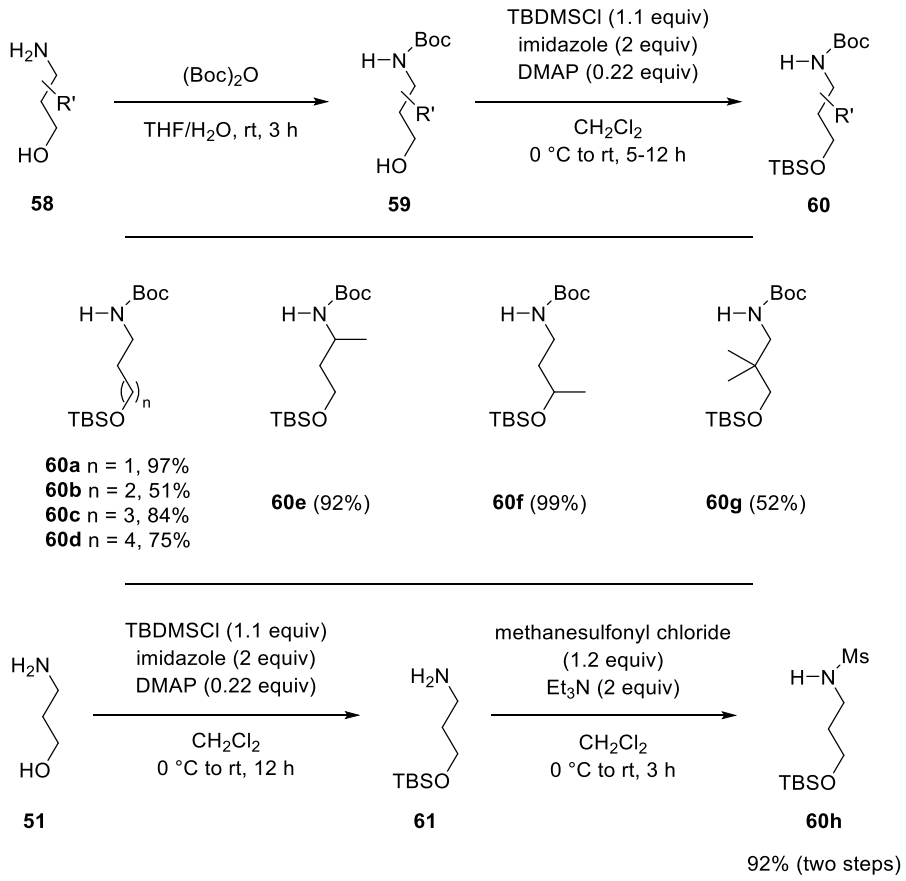
After screening the substrates and optimizing the radical conditions, we next moved to study the scope and limitations of this reaction, which started with the preparation of a collection of starting ynamides.

4.2 Synthesis of the starting ynamides

4.2.1 Synthesis of protected aminoalcohols

Following the procedure developed and described earlier, various *N*-Boc protected aminoalcohols were prepared from the corresponding commercially available aminoalcohols **58** (Scheme 1.26). Protected derivatives with 3-, 4-, 5- and 6-carbon atoms between the carbamate and the silylated alcohol could all be obtained with this simple sequence (**60a-d**), as well as α- or ϒ-methyl and β,β-dimethyl substituted branched derivatives (**60e-g**). In all cases, the bis-protected aminoalcohol derivatives were isolated in moderate to good yields. It is worth noting that for the synthesis of *N*-mesyl

derivative **60h**, the silylation should be done prior to the mesylation to avoid the mesylation of both the amine and the alcohol.

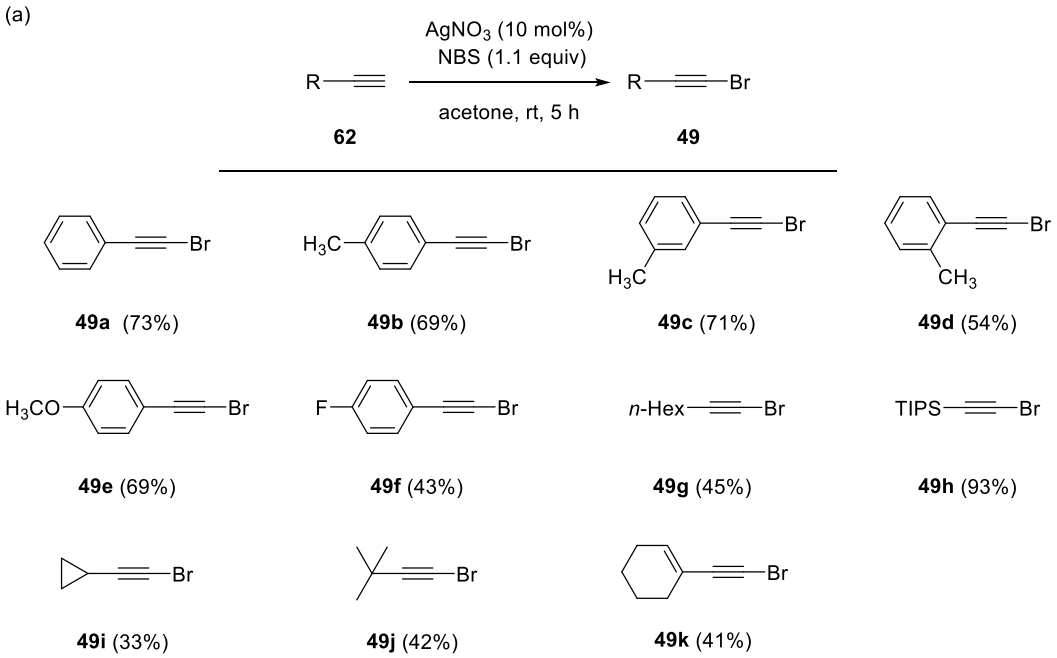


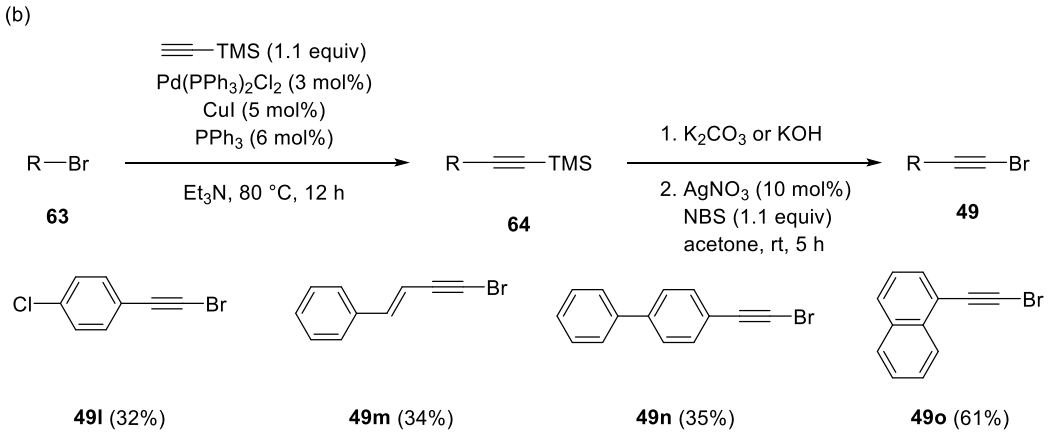
Scheme 1.26: Synthesis of protected aminoalcohols.

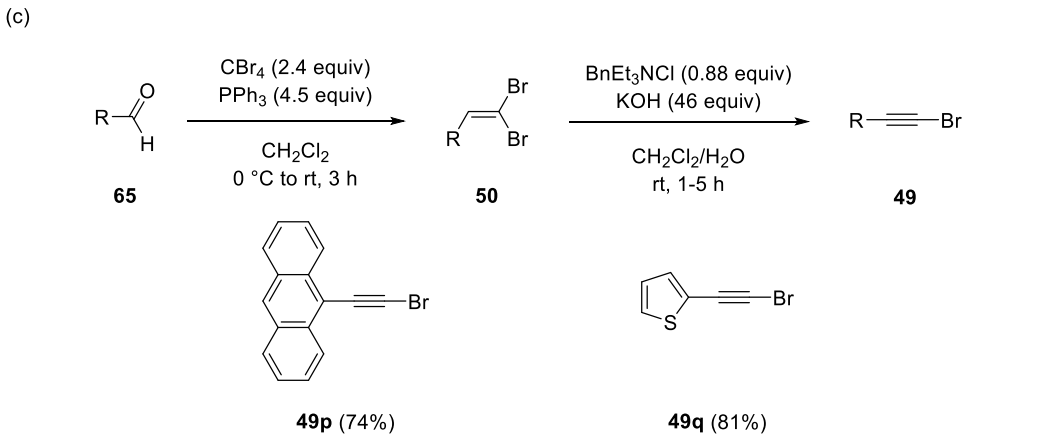
4.2.2 Synthesis of alkynyl bromides

Having in hand a library of protected aminoalcohols, we next focused on the synthesis of the alkynyl bromides required for their alkynylation. The most common and widely used process for their synthesis is based on the reaction of the corresponding terminal alkynes **62** with *N*-bromosuccinimide (NBS) and silver nitrate, which was efficient for most cases and enabled the synthesis of alkynyl bromides **49a-k** in yields ranging from 33% to 93% (Scheme 1.27(a)).

However, when we tried to synthesize alkynyl bromides **49l-q**, the corresponding terminal alkynes **62** were not commercially available or expensive. Thus, our work started from the Sonogashira coupling of the corresponding bromides **63** with trimethylsilylacetylene followed by sequential desilylation and bromination to give the desired alkynyl bromides **49l-o** (Scheme 1.27(b)). But for the preparation of **49p** and **49q**, this method led to severe decomposition for the Sonogashira coupling step. To overcome this problem, we chose to start from the corresponding aldehyde **65** proceeding through the subsequent olefination and dehydrobromination to yield the desired alkynyl bromide **49p** and **49q** in 74% and 81% yields, respectively (Scheme 1.27(c)).





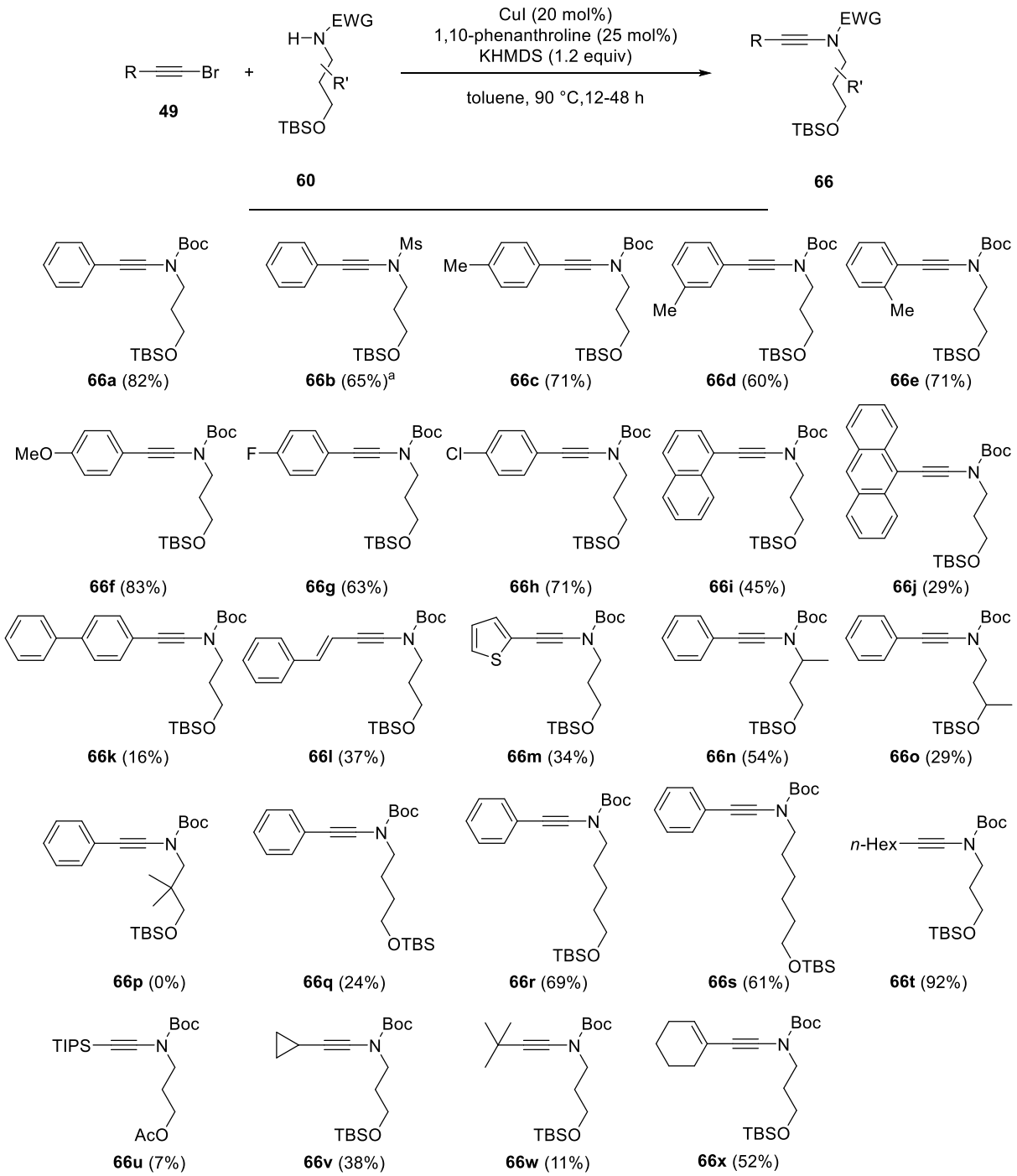


Scheme 1.27: Preparation of alkynyl bromides.

4.2.3 Synthesis of ynamides *via* copper mediated cross-coupling

Having prepared all protected aminoalcohols and alkynyl bromides, we next performed their copper-mediated cross-coupling following the Tam's procedure, which was carried out with copper(I) iodide (0.2 equiv) and 1,10-phenanthroline (0.25 equiv) in toluene at 95 °C under argon, with the slow addition of a toluene solution of potassium bis(trimethylsilyl)amide (KHMDS, 1.2 equiv) for 12-48 hours (Scheme 1.28). Additionally, for the preparation of *N*-mesyl ynamide **66b**, we followed the procedure that was developed by our group before based on the use of the corresponding dibromoalkene.

With respect to the aromatic alkynyl bromide coupling partner, the reaction turned out to be compatible with various electron-rich or electron-poor aromatic substituents (**66c** to **66h**), and naphthalene, phenanthrene, styrene and thiophene substituents were also tolerated (**66i** to **66m**). The coupling of bromophenylacetylene with various protected aminoalcohols was next investigated and worked smoothly in most cases: aminoalcohols with branched (**66n** and **66o**) or unsubstituted (**66q**-**s**) chains were excellent reaction partners; however, in the case of **66p** that was designed to take advantage of a Thorpe-Ingold effect for the cyclization, the β,β-dimethyl branched chain inhibited the cross-coupling, most certainly due to its steric bulk. It is worth to note that, for the alkynylation with aliphatic alkynyl bromides, the reaction temperature should be lower (60-80 °C) than the standard condition due to the volatility of the starting alkynyl bromides, thus most of the corresponding ynamides were isolated in lower yields (**66t** to **66x**).



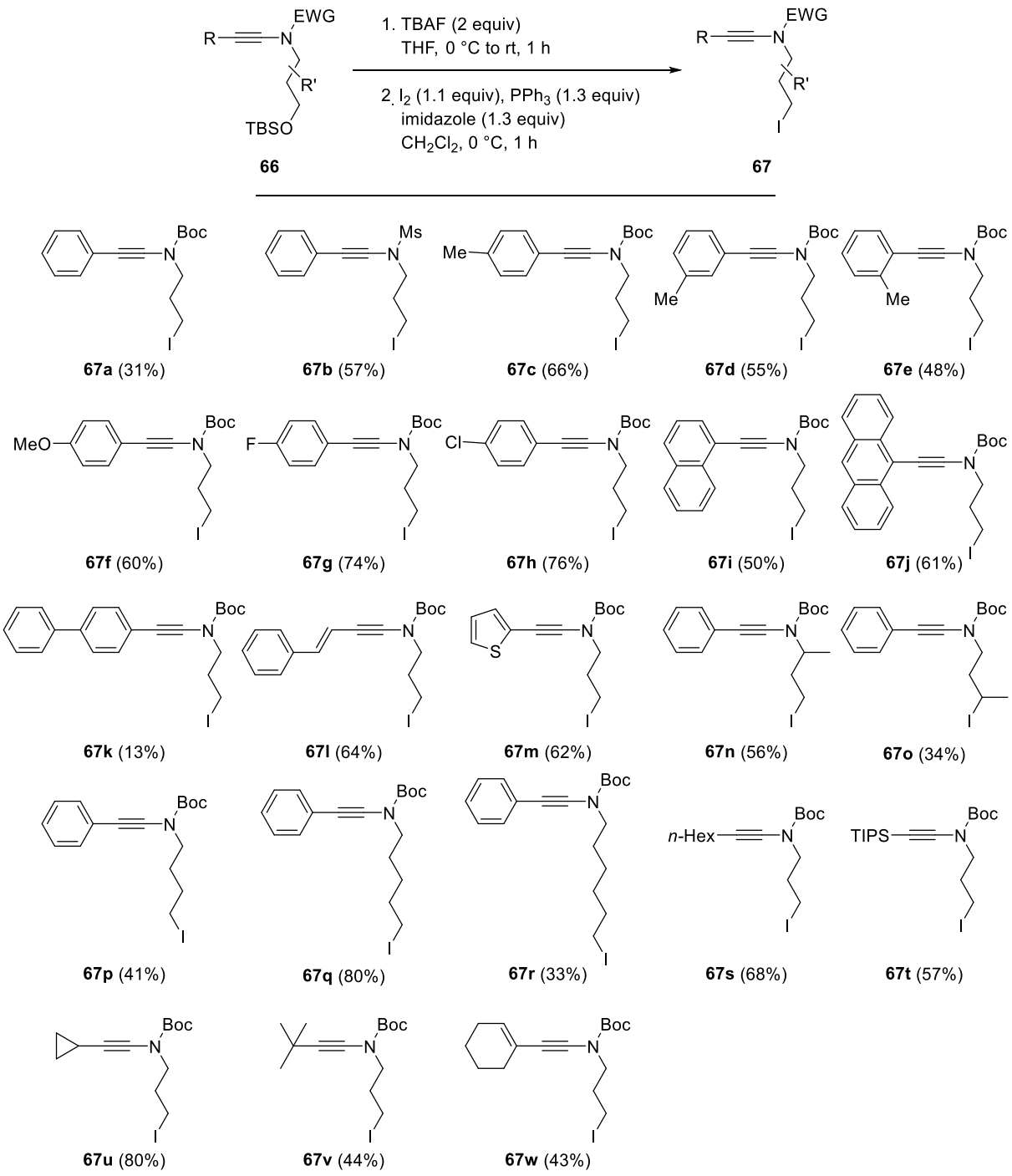
[a] The reaction conditions: 1,1-dibromo-2-phenylethene (1.3-1.5 equiv), CuI (13 mol%), *N,N'*-dimethylethylenediamine (19 mol%), Cs_2CO_3 (4 equiv), 1,4-dioxane, 80 °C, 16 h.

Scheme 1.28: Synthesis of the starting ynamides through copper mediated cross-coupling reactions.

4.2.4 Synthesis of *N*-iodoalkyl-ynamides

After the synthesis of the ynamide precursors, the desilylation and iodination reactions were next performed to produce the desired *N*-iodoalkyl-ynamides **67** (Scheme 1.29). For the desilylation step, the *N*-Boc or *N*-mesyl ynamides **66** were treated with TBAF under argon in anhydrous THF at 0 °C, then the solution was warmed to room temperature to afford a complete conversion. The reaction was

carefully monitored by TLC and quenched with water directly upon completion, since too long reaction times led to degradation. Then the iodination was performed by successively adding iodine and the *N*-hydroxylalkyl-ynamide to a mixture of triphenylphosphine and imidazole in anhydrous dichloromethane at 0 °C under argon in the dark for 1 hour. This simple sequence worked smoothly in most cases, even on a multigram scale, and provided us with a set of *N*-iodoalkyl-ynamides **67a-w** with representative substituents and substitution patterns that could next, and finally, be subjected to the radical cyclization.



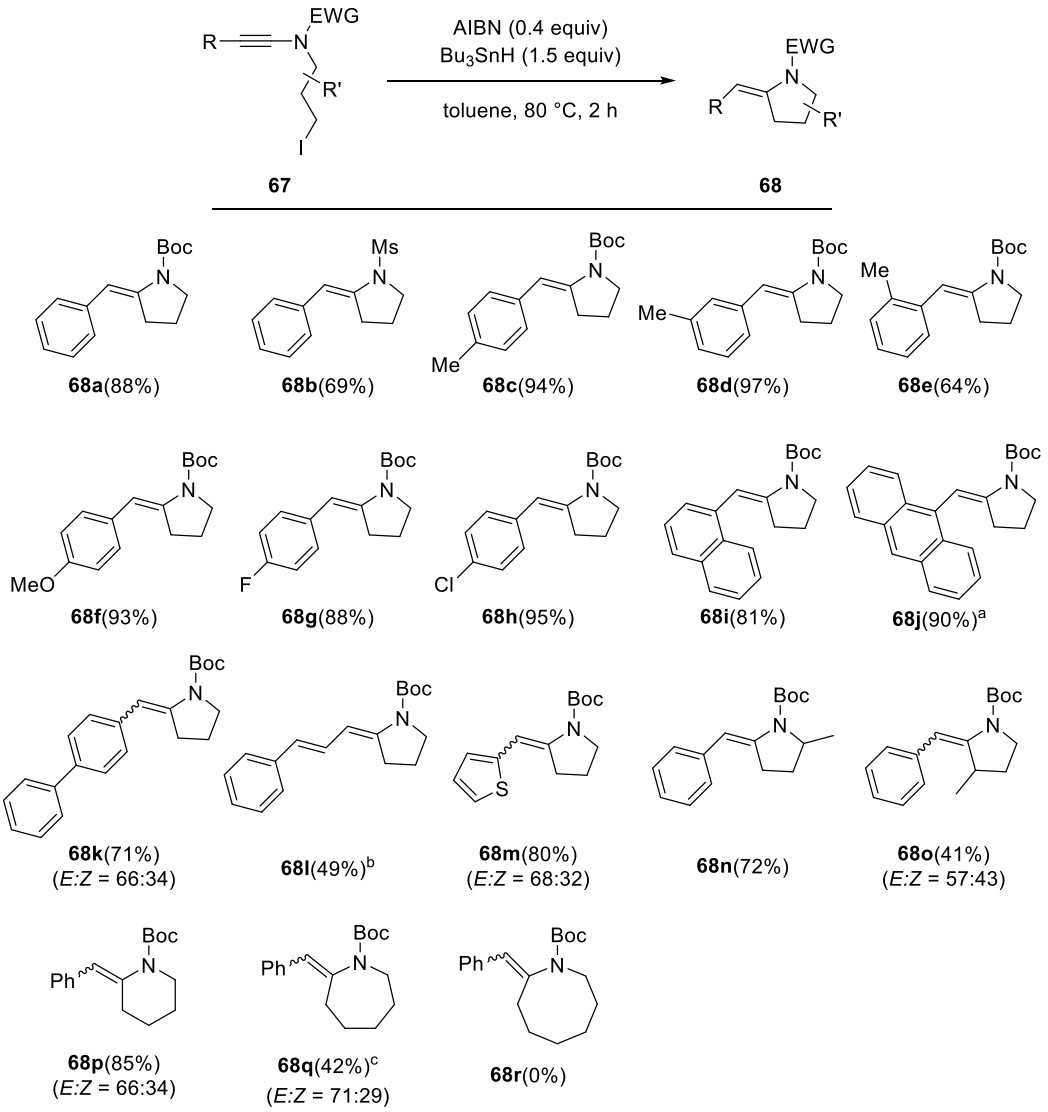
Scheme 1.29: Synthesis of the starting N-iodoalkyl-ynamides.

4.3 Scope and limitation studies

4.3.1 Scope and limitations of the radical cyclization of *N*-iodoalkyl-ynamides

With the starting *N*-iodoalkyl-ynamides in hand, we then moved to study the scope and limitation of the radical cyclization (Scheme 1.30). We initially focused on the variation of the nature of the electron-withdrawing group on the nitrogen and found out that *N*-mesyl ynamide could also cyclize to the corresponding pyrrolidine product **68b**, isolated as a single stereoisomer in 69% yield, with high efficiency under the radical condition. Various aromatic substituents on the starting ynamide were suitable for this transformation, as the cyclization proceeded equally well with electron-rich (**68c**, **68f**) and electron-poor (**68g**, **68h**) aryl groups, and the substituents at the *para* (**68c**) and *meta* (**68d**) positions of the phenyl group could be tolerated, while the presence of a substituent at the *ortho* position (**68e**) resulted in a less efficient cyclization (64%) because of the steric effect. Then more complicated aromatic ynamides were evaluated to further test the generality of the reaction, among which 1-naphtyl (**68i**), and 1,1'-biphenyl (**68k**) were well tolerated, while the cyclization of 9-anthracenyl- (**68j**) and styryl- (**68l**) substituted ynamides required slightly modified conditions (higher temperature or longer time) to achieve high efficiency. As for heteroaromatic ynamides, a 2-thiophenyl-ynamide could be converted to the corresponding cyclized product **68m,** isolated as a mixture of two isomers in good yield (80%). In addition, aliphatic substituted ynamides were found to be not suitable substrates for the radical cyclization: indeed, *n*-hexyl, triisopropylsilyl, cyclopropyl, *t*-butyl and 1-cyclohexenyl substituted ynamides were all reacted under the standard condition but they however gave no desired products, which might be attributed to a lack of stabilization of the cyclized radical intermediates.

Finally, the influence of the length of the carbon chain as well as its substitution pattern was also investigated to test the efficiency of the cyclization and potentially access either highly substituted pyrrolidine derivatives or even higher ring systems. The introduction of an additional methyl group at the α- or ϒ- position to the nitrogen atom only slightly affected the transformation (**68n** 72%, **68o** 41%), and to our delight, moving to four- or five-carbon atoms between the nitrogen and the iodine atoms provided access to synthesize piperidine **68p** and azepane **68q** derivatives in moderate to good yields (85% and 42%, respectively); however, an attempt to a cyclization to an eight membered nitrogen heterocyclic azocane **68r** only gave the debrominated product resulting from a slow cyclization and a competing reduction.



[a] The temperature was 100 °C. [b] The time was 4.5 h. [c] The temperature was 110 °C, the concentration was doubled and the *n*-Bu_3SnH was added slowly (4 h compared to the usual 1 h).

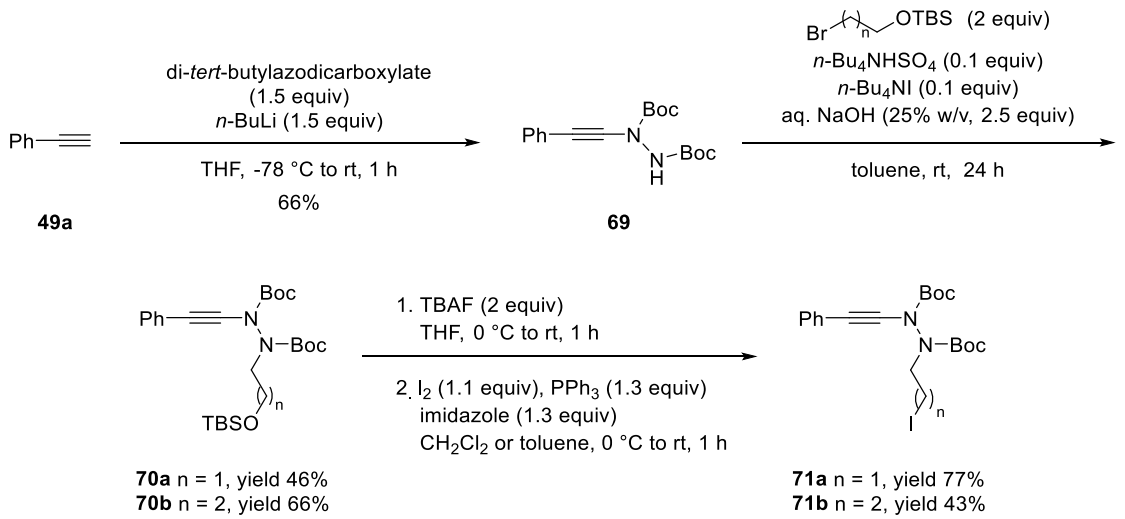
Scheme 1.30: Scope of the radical cyclizaiton of ynamides.

Importantly, scaling up the reaction did not affect its efficiency since the cyclized products **68a** and **68b** could be obtained on a 1 g scale from the corresponding ynamides in even higher yields (94% and 74%, respectively). However, as an excess amount of tributyltin hydride was used for the cyclization, particularly for the large scale reaction, the removal of the organotin impurities from the product mixture became quite challenging. Luckily, the use of a simple trick reported by the Guy's group,[40] in which during the purification of the crude reaction mixture by column chromatography, 10% w/w of finely ground potassium fluoride was mixed in the silica gel, enabled a more facile removal of the tin derivatives.

[40] Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004,** *17*, 1968-1969.

4.3.2 Radical cyclization of ynehydrazides

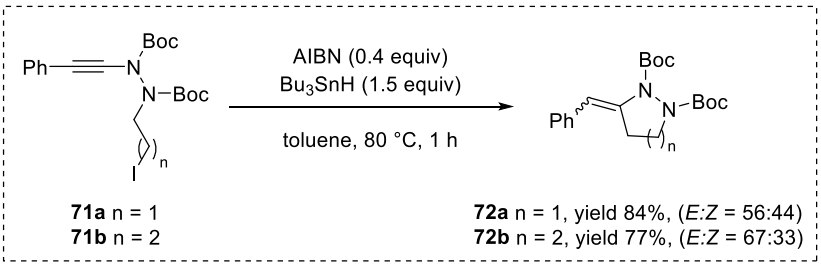
To further test the efficiency of the radical cyclization, we next investigated the possibility to synthesize other classes of nitrogen heterocycles using this method. Inspired by the work of Batey[41] who reported an efficient synthesis of ynehydrazides from commercially available precursors, we designed and synthesized two *N*-iodoalkyl-ynehydrazides **71a** and **71b** as substrates for the radical cyclization (Scheme 1.31). The synthetic sequence started by the addition of *in situ* generated lithium acetylides to commercially available di-*tert*-butylazodicarboxylate (DBAD) to generate ynehydrazide **69** which could be alkylated under phase transfer conditions to provide **70a** and **70b** in fair yields. Following by the previously developed desilylation/iodination sequence, the desired iodo-ynehydrazides **71a** and **71b** could be produced efficiently. As a note, these two steps should be performed quickly since the intermediate *N*-hydroxylalkyl-ynehydrazides resulting from the desilylation were not stable even at low temperatures. It is also worth to note that the initial synthesis of **71a** through the Appel reaction only gave trace amounts of the desired product under the standard conditions with a complete conversion of the starting material however, which might be caused by a competing attack of the Boc group to the iodinated alkyl chain to which would produce a five-membered oxazolidinone. Encouragingly, after a careful optimization of the iodination conditions, we found out that when toluene was used as solvent instead of dichloromethane, the reaction proceeded cleanly to form the desired **71a** product in high yield.



Scheme 1.31: Synthesis of the ynehydrazides.

With the ynehydrazides in hand, we next tested their reactivity under the radical conditions. To our delight, both **71a** and **71b** could be readily cyclized to the corresponding pyrazolidine and hexahydropyridazine derivatives **72a** and **72b** in 84% and 77% yields, respectively (Scheme 1.32).

[41] Beveridge, R. E.; Batey, R. A. *Org. Lett.* **2012,** *14*, 540-543.



Scheme 1.32: Radical cyclization of ynehydrazides.

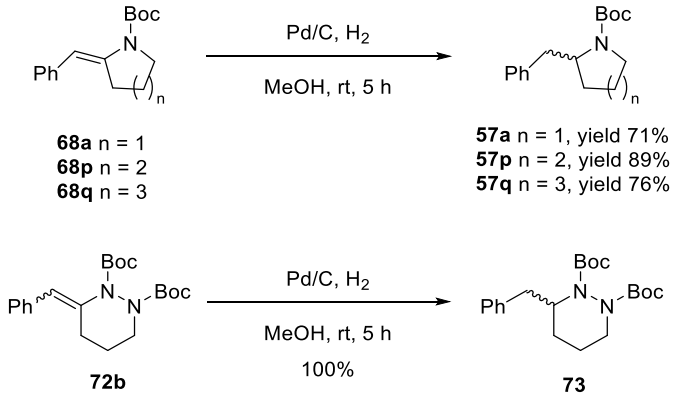
These results further proved the generality of the radical cyclization, which is not just limited to the cyclization of ynamides, but also provided a new route to synthesize diazacycles, versatile scaffolds found in many pharmaceutical and natural products and that can be rather challenging to prepare.

5 Further transformations of the cyclized products

Having demonstrated the scope and limitation of this radical cyclization method, we further explored the reactivity of the cyclized products towards hydrogenation, electrophilic addition, epoxidation as well as cyclopropanation as shown in the last part of this project.

5.1 Hydrogenation of the cyclized products

We first performed the reduction of the cyclized products **68a**, **68p**, **68q** and **72b** by using palladium on carbon (10 wt%) in methanol under an atmosphere of hydrogen (2.0 bars) at room temperature for 5 hours, which produced the desired products **57a**, **57p**, **57q** and **73** in good yields (Scheme 1.33).

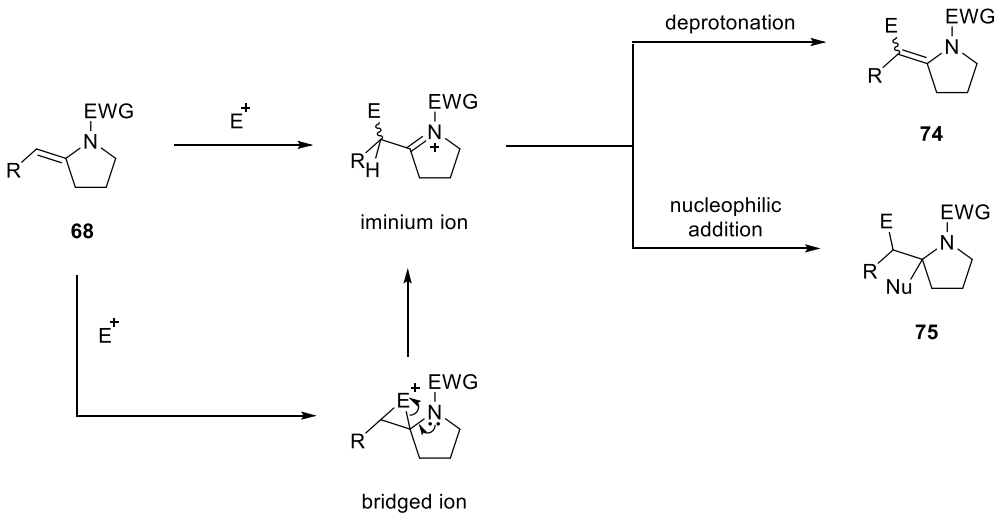


*Scheme 1.33: Hydrogenation of the cyclized products **68a**, **68p**, **68q** and **72b**.*

5.2 Electrophilic addition of the cyclized products

Next, we investigated the electrophilic functionalization of the cyclized products, whose carbon-carbon double bond possesses nucleophilic character due to the delocalization of the lone pair electron of the enamide nitrogen.

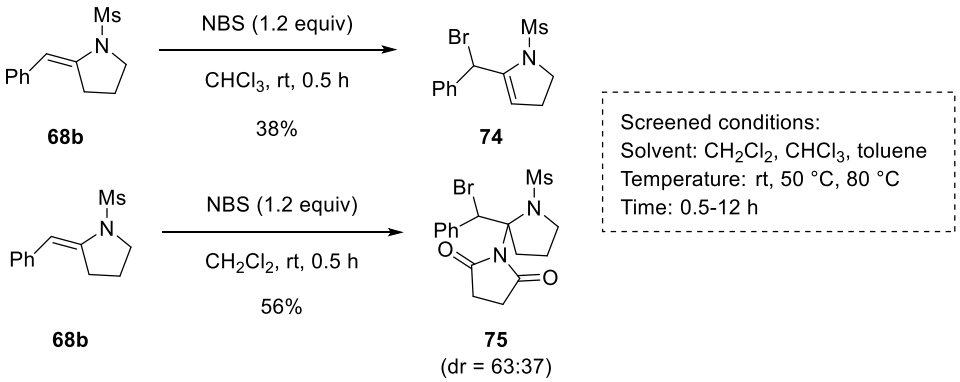
We envisioned that the addition of an electrophile onto this π-system would involve an iminium ion intermediate which could be either generated directly by the reaction of the electrophile with the enamide moiety, or possibly be generated from a bridged ion intermediate. Then, after subsequent deprotonation or nucleophilic addition, pyrrolidine derivatives **74** (as a mixture of E/Z stereoisomers) or **75** (as a mixture of diastereomers) could be produced, respectively.



Scheme 1.34: Proposed mechanism of the electrophilic addition.

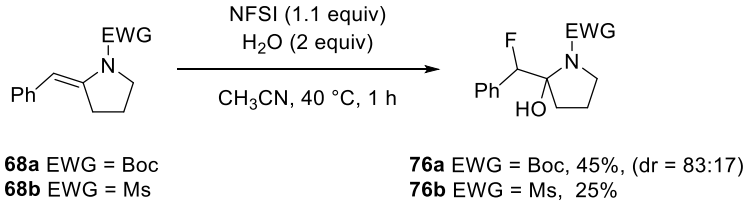
However, we found that electrophilic addition reactions based on highly substituted enamides have been rarely reported, maybe due to the poor stability of the iminium ion intermediates which would readily undergo hydrolysis upon exposure to moisture.

Thus, we started from the simplest model to evaluate our hypothesis by choosing the cyclized products **68a** and **68b** as substrates and using NBS as the source of electrophile. After screening different solvents (dichloromethane, chloroform, toluene), temperature (rt, 50 °C, 80 °C) as well as reaction time (0.5-12 h), we found that the *N*-Boc enamide **68a** gave either a complex mixture or unidentifiable products, whereas two products were generated from *N*-mesyl enesulfonamide **68b** under different conditions. As shown in Scheme 1.35, enesulfonamide **68b** was reacted with NBS in chloroform at room temperature for 30 minutes to give product **74** in moderate yield (38%), in which the proton on the pyrroline ring was eliminated. In comparison, the use of dichloromethane as solvent led to a sequential electrophilic addition of Br^+/nucleophilic addition of the succinimide which generated product **75** in 56% yield as a mixture of two diastereomers (dr = 63 : 37).



Scheme 1.35: Reactions of the cyclized products with NBS.

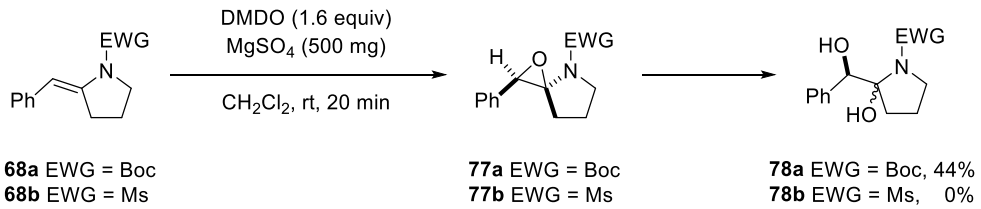
Inspired by this success, we next used the conditions of a fluorination reaction reported by the Hsung's group,[42] as shown in Scheme 1.36. Enamide **68a** and enesulfonamide **68b** were reacted with NFSI and water in acetonitrile at 40 °C for 1 hour, which led to the desired products **76a** and **76b** with complete conversion in 45% and 25% yields, respectively.



Scheme 1.36: Reactions of the cyclized products with NFSI.

5.3 Epoxidation of the cyclized products

In addition, epoxidation could also be performed following the reported procedure[43] as shown in Scheme 1.37, by treating the cyclized product **68a** with freshly prepared dimethyldioxirane (DMDO) at room temperature. Oxirane **77a** was obtained in a very rapid reaction, however, after the purification by column chromatography over silica gel only the corresponding diol **78a** was isolated which was obviously generated by hydrolysis of **77a**. In comparison, *N*-mesyl enesulfonamide **68b** gave no spiroepoxide following the same procedure.

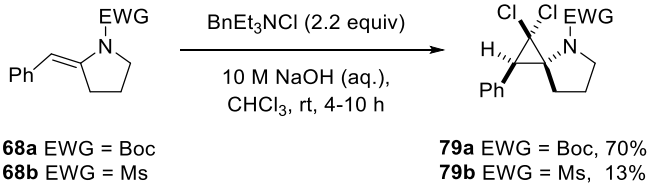


Scheme 1.37: Epoxidation of the cyclized products.

[42] Xu, Y.-S.; Tang, Y.; Feng, H.-J.; Liu, J.-T.; Hsung, R. P. *Org. Lett.* **2015,** *17*, 572-575.
[43] Bartels, A.; Jones, P. G.; Liebscher, J. *Synthesis* **2003**, *1*, 67-72.

5.4 Cyclopropanation of the cyclized products

Finally, we envisioned that a cyclopropane ring could probably be formed by cyclopropanation of enamides or enesulfonamides. Following the procedure reported by the group of Six,[44] we investigated the cyclopropanation of **68a** and **68b** as shown in Scheme 1.38. Gratifingly, relying on phase transfer conditions ($BnEt_3NCl$ as a catalyst, chloroform and aqueous sodium hydroxide at room temperature), the cyclized products **68a** and **68b** could react with *in situ* generated dichlorocarbene species smoothly to give the corresponding dichlorocyclopropyl-substituted products **79a** and **79b**, respectively. **79a** could be obtained with complete conversion in good yield (70%) after reaction for 10 hours, however, **79b** could only be generated in very low yield (13%) after reacting for 4 hours, and longer reaction time led to complete degradation.

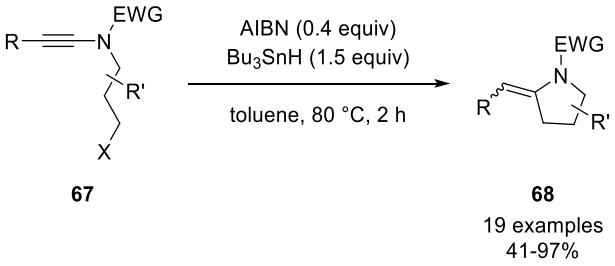


Scheme 1.38: Cyclopropanation of the cyclized products.

6 Conclusion and perspectives

In conclusion, we developed a general and efficient radical cyclization of ynamides and ynehydrazides, which provided a new route to access a variety of nitrogen heterocycles, such as pyrrolidine, piperidine, azepane and diazacycles. The radical cyclization could be performed on various aromatic substituted ynamides under the classical AIBN and tributyltin hydride conditions to give the thermodynamically-controlled products with high efficiency in most cases. In addition, copper complex catalyzed photoinduced conditions were also efficient for this radical cyclization, however, gave no stereoselectivity. Moreover, the cyclized products could be further transformed by means of hydrogenation, electrophilic addition, epoxidation and cyclopropanation. All these results highlighted the reactivity of ynamides under radical conditions and brought new perspectives for the application of ynamides and its relatives in radical chemistry.

[44] Chen, C.; Kattanguru, P.; Tomashenko, O. A.; Karpowicz, R.; Siemiaszko, G.; Bhattacharya, A.; Calasans, V.; Six, Y. *Org. Biomol. Chem.* **2017**, *15*, 5364-5372.



67 **68**

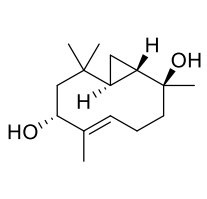
19 examples
41-97%

Scheme 1.39: Radical cyclization of ynamides.

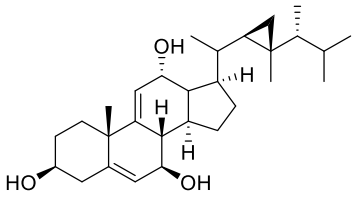
Chapter 2: Palladium Catalyzed Cyclization of Cyclopropyl and Cyclobutyl Enamides

1 Introduction

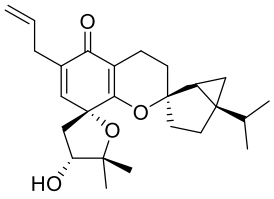
The cyclopropane and cyclobutane subunits exist in a variety of bioactive natural products, such as terpenoids, steroids and alkaloids, which exhibit unique activities towards bacteria, virus, human cancer, and some other diseases, as illustrated in Figure 2.1.[45] From a synthetic point of view, the strain energy of small rings could serve as driving force for many types of reactions, thus ring opening or expansion strategies of cyclopropane or cyclobutane rings have been applied in the natural product synthesis to achieve molecular complexity rapidly.[46] Therefore, there has been increasing interest in the synthesis and application of diversely substituted cyclopropanes and cyclobutanes, particularly for the regio- and stereoselective reactions of these small ring motifs.[47] To approach the synthesis of these target molecules, numerous advanced methodologies have been developed, among which C-H functionalization strategy emerged as a direct and important tool to introduce functional substituents to cyclopropane and cyclobutane rings, with controlled regio- and enantioselectivity.



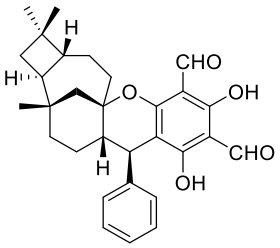
Hypocoprin A
from the horse dung
against bacteria



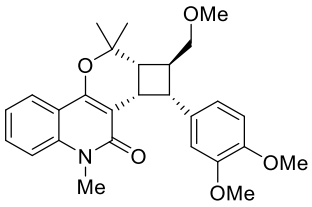
Klyflaccisteroid E
from the soft coral Klyxumflaccidum
cytoxic activity



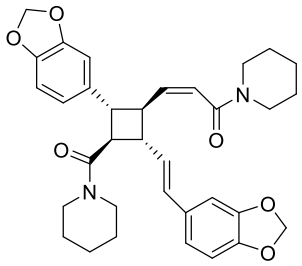
Spirooliganones A
from the roots of *Illicium oligandrum*
antiviral activity



Psiguadial B
from the leaves of *Psidium guajava*
against human hepatoma



Melicodenine D
from the leaves of *Melicope denhamii*
anti-proliferative activity



Pipercyclobutanamide A
from *Piper nigrum* leaves
human liver microsomal dextromethorphan O-demethylation activity

Figure 2.1: Bioactive compounds containing strained ring units in nature.

Herein, we mainly studied the palladium catalyzed C-H bond activation reactions of cyclopropyl and cyclobutyl substituted enamides, which provided new routes to various nitrogen heterocycles.

[45] Fan, Y.-Y.; Gao, X.-H.; Yue, J.-M. *Sci. China Chem.* **2016**, *59*, 1126-1141.
[46] Tang, P.; Qin, Y. *Synthesis* **2012**, *44*, 2969-2984.
[47] (a) Ebner, C.; Carreira, E. M. *Chem. Rev.* **2017**, *117*, 11651-11679. (b) Lebel, H.; Marcoux, J.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977-1050.

Before describing our work, a brief overview of palladium catalyzed C-H functionalization of small carbocycles is reported in the next section.

1.1 Palladium catalyzed C-H functionalization

Transition-metal catalyzed C-H activation is one of the most powerful methodologies to enable carbon-carbon bond cross-coupling or C-H bond functionalization, which avoids multistep preparative processes required for other synthetic strategies and, more importantly, provided straightforward approach to a wide range of complex structures starting from simple precursors (Figure 2.2).[48] In the special case of enantioselective C-H activation/functionalization reactions, which present a practical challenge to chemists, a variety of systems have been established by using chiral catalysts, ligands or other chiral reagents. Thus far, catalysts based on noble 4d and 5d transition metals, such as palladium, iridium, rhodium and ruthenium, are the most powerful tools and have been applied to many challenging examples. Interestingly, the recent development of catalysts based their 3d counterparts (scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper and zinc), which are more readily available and less toxic, have provided an alternative for performing C-H functionalization and have attracted more and more attention from the organic synthesis community.[49]

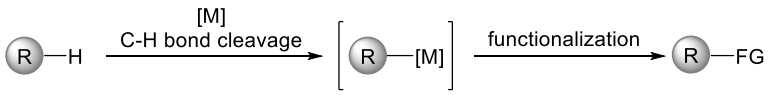


Figure 2.2: Transition-metal catalyzed C-H functionalization.

Among all these transition metals, palladium is the most employed in C-H activation processes, both for inter- and intramolecular reactions. In this field, three mechanistic scenarios have been exploited so far to explain the reaction mechanism, which include Pd(0)/Pd(II), Pd(II)/Pd(0) and Pd(II)/Pd(IV) as shown in Figures 2.3 and 2.4, respectively.[50] The Pd(0)/Pd(II) catalytic cycle starts with the oxidative addition of palladium(0) species to the C-X bond, in which the Pd(II) intermediate **I** is formed, followed by the ligand exchange with carboxylates to generate the intermediate **II**, which give the functionalized intermediate **IV** through the crucial concerted metalation-deprotonation (CMD) process. The released carboxylic acid is deprotonated by base to generate the carboxylate as cocatalyst. Finally, the desired product is provided through the subsequent reductive elimination, with the regeneration of the Pd(0) catalyst. Surprisingly, only intramolecular cyclization mode has been reported to date for this Pd(0)/Pd(II) catalytic cycle, maybe due to the difficulty of controlling stereoselectivity in the intermolecular version.

[48] Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. *Chem. Rev.* **2017**, *117*, 8908-8976.
[49] Gandeepan, P.; Muller, T.; Zell, D.; Cera, G. Warratz, S.; Ackerann, L. *Chem. Rev.* **2019**, *119*, 2192-2452.
[50] He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754-8786.

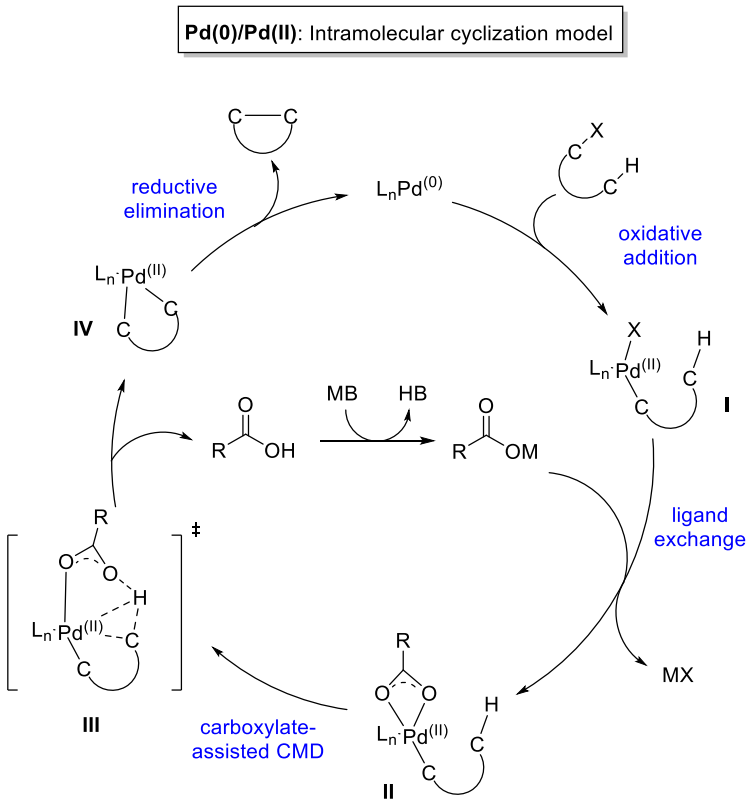


Figure 2.3: Palladium catalyzed C-H functionalization via Pd(0)/Pd(II) catalytic cycle.

The other two mechanisms, the Pd(II)/Pd(0) and the Pd(II)/Pd(IV) catalytic cycles, have been explored in both inter- and intramolecular reactions. The Pd(II)/Pd(0) catalysis proceeds through a C-H insertion/transmetalation/reductive elimination sequence to generate the coupled or functionalized product with the formation of Pd(0) species, which is oxidized to give Pd(II) by additional oxidants to complete the catalytic cycle (Figure 2.4, left). In comparison, for the Pd(II)/Pd(IV) catalytic mechanism, following the formation of intermediate **III** via C-H activation is the oxidative addition to generate an active Pd(IV) intermediate **IV**, which releases the desired product after the reductive elimination (Figure 2.4, right). It deserves to be noted that when strongly coordinating auxiliaries were employed in substrates, many examples went through the Pd(II)/Pd(IV) catalytic processes, because these strongly coordinating nitrogen or phosphine atoms in the substrates could chelate to the metal to form thermodynamically stable cyclometalated intermediates, which are not reactive enough for further functionalization. Thus, to solve this problem, the highly active Pd(IV) intermediates are generated by addition of external electrophiles and undergo the reductive elimination rapidly to produce the desired coupled or functionalized products.[50]

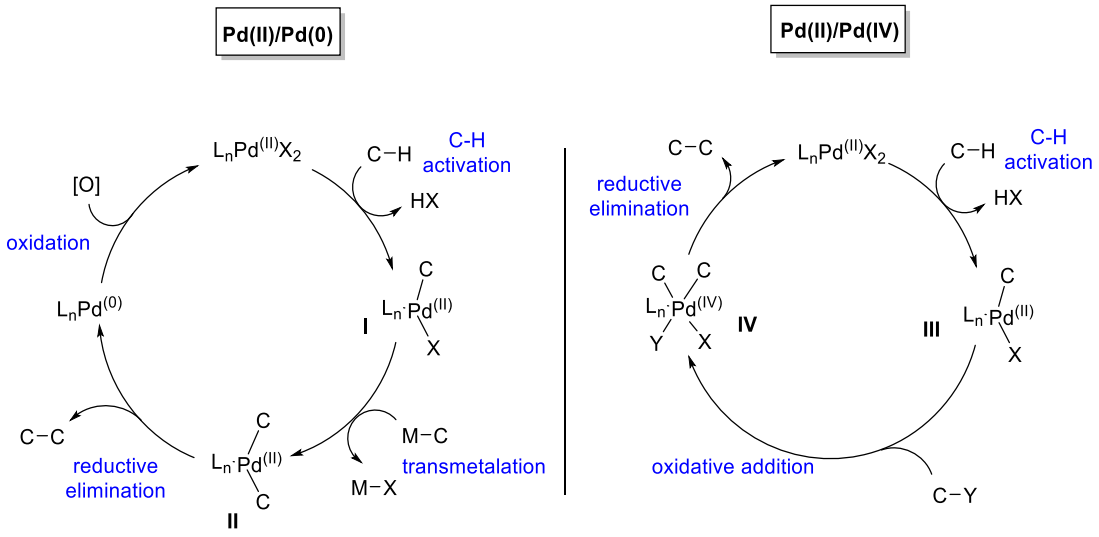


Figure 2.4: Palladium catalyzed C-H functionalization via Pd(II)/Pd(0) and Pd(II)/Pd(IV) catalytic cycles.

In addition to these three common catalytic cycles described above, some rare palladium catalyzed mechanisms have also been proposed, for example, a Pd(II) catalyzed C-H iodination reaction with molecular iodine as oxidant had been reported by Yu , Musaev and co-workers,[51] which however, will not be discussed in more details here. In the next paragraph, we will give a brief introduction of the structural features and reactivity of cyclopropanes and cyclobutanes, the functionalization of which is the core of our thesis work.

1.2 Structural features and reactivity of cyclopropanes and cyclobutanes

1.2.1 Structural features of strained ring systems

In sharp contrast to acyclic hydrocarbons, many cyclic compounds possess inherent strain energy, which influence their conformation and reactivity depending on the ring sizes (Figure 2.5). Strain energy consists of torsional strain, angle strain and strain caused by through-space interaction. In the case of strained carbocycles, the strain energy of small rings (3 and 4 membered rings) are mainly dominated by the angle and torsional strain, while common rings (5 to 7 membered rings) are usually impacted by torsional strain. In addition, for medium-size rings (more than 7 membered rings) and many other complex fused structures, cross-ring van der Waals repulsions through space might play a crucial role.

[51] Haines, B. E.; Xu, H.; Verma, P.; Wang, X.-C.; Yu, J.-Q.; Musaev, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 9022-9031.

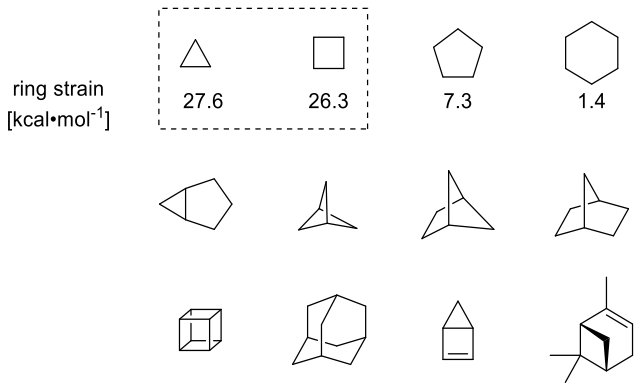


Figure 2.5: Examples of strained rings.

Among all these strained molecules, cyclopropane has caught the interest of chemists for a long time, and its properties and reactivities have been widely studied. Cyclopropane is highly strained with an energy of 27.6 kcal/mol according to the heats of combustion measurements, in comparison, the energy of a typical carbon-carbon single bond is 88 kcal/mol. This high strain energy of cyclopropane indeed enables a higher reactivity compared to acyclic alkanes in terms of carbon-carbon bond cleavage reaction. The strain energy of cyclopropane ring could be rationalized by its structure. The cyclopropane ring is planar and ideally has a geometry of an equilateral triangle, in which the C-C-C angle is 60° precisely, however, since the carbon atoms possess a sp^3 hybridization, the ideal tetrahedral angle should be 109.5° to achieve the maximum overlap of the orbitals. As a consequence, the C-C bonds of cyclopropane ring bend to form "banana bonds" with an angle of 104° as shown in Figure 2.6 (top), which is an intermediate between σ bond and π bond, and the produced angle strain energy is comparative with the bond-cleavage energy of ethylene.[52] Furthermore, from this model, we could find out that all the neighboring C-H bonds are arranged in eclipsed conformations, which is unfavorable.

Intriguingly, as a homologue of cyclopropane, cyclobutane is relatively less investigated and has just attracted the attention of chemists more recently,[53] which is surprising, as cyclobutane ring has only slightly less strain energy (26.7 kcal/mol) than cyclopropane ring. The difference could be attributed to the different contribution of angle strain and torsional strain to strain energy, as cyclobutane is flexible enough to adopt a puckered conformation (Figure 2.6, bottom), the angle strain caused by bent C-C bonds is considerably reduced, while the torsional strain energy introduced by the eclipsed hydrogens is still large enough to compensate. In addition, the strain energy of cyclobutane ring is distributed to four bonds, thus each C-C bond energy would be less important than in the cyclopropane case.

[52] Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311-365.
[53] Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 7740-7752.

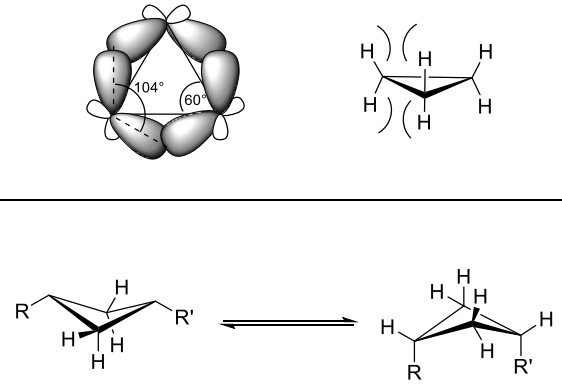


Figure 2.6: Conformational models of cyclopropane and cyclobutane rings.

As we have just seen, cyclopropanes and cyclobutanes possess considerable strain energy, which could serve as driving force for the cleavage of the C-C bond or activation of the C-H bond, thus many synthetic protocols based on cyclopropane and cyclobutane units have been investigated, which will be shown in the next sections on a selection of examples.

1.2.2 C-C bond cleavage of cyclopropanes and cyclobutanes

As previously described, strained rings including cyclopropanes and cyclobutanes are ideal candidates for C-C bond cleavage reactions and the ring-opening of cyclopropane is more readily accessible than cyclobutane. The C-C bond activation process is commonly catalyzed by transition metal complexes, which proceeds through C-C bond oxidative addition or β-carbon elimination pathways.[54] Indeed, the first oxidative addition methodology could be found as early as 1955, in which Tipper's group[55] reported the $PtCl_2$ catalyzed ring-opening of cyclopropane. So far, several classes of activated cyclopropanes have been widely investigated towards the oxidative addition process, including cyclopropenes, alkylidenecyclopropanes, vinylcyclopropenes and cyclopropyl ketones or imines (Figure 2.7, top)[54(a)] Examples involving cyclobutane derivatives are also well studied, such as in the case of cyclobutanones, benzocyclobutenones and bisphenylenes.[54(a)] The other complementary method is the β-carbon elimination, in which the transition metal was first inserted to the functional substituent of the strained ring, then a carbon connected to the β-position of the transition metal was eliminated to cleave the bond between β- and ϒ- carbons (Figure 2.7, bottom).

[54] (a) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404-9432. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117-3179.

[55] Tipper, C. F. H. *J. Chem. Soc.* **1955**, 2045-2046.

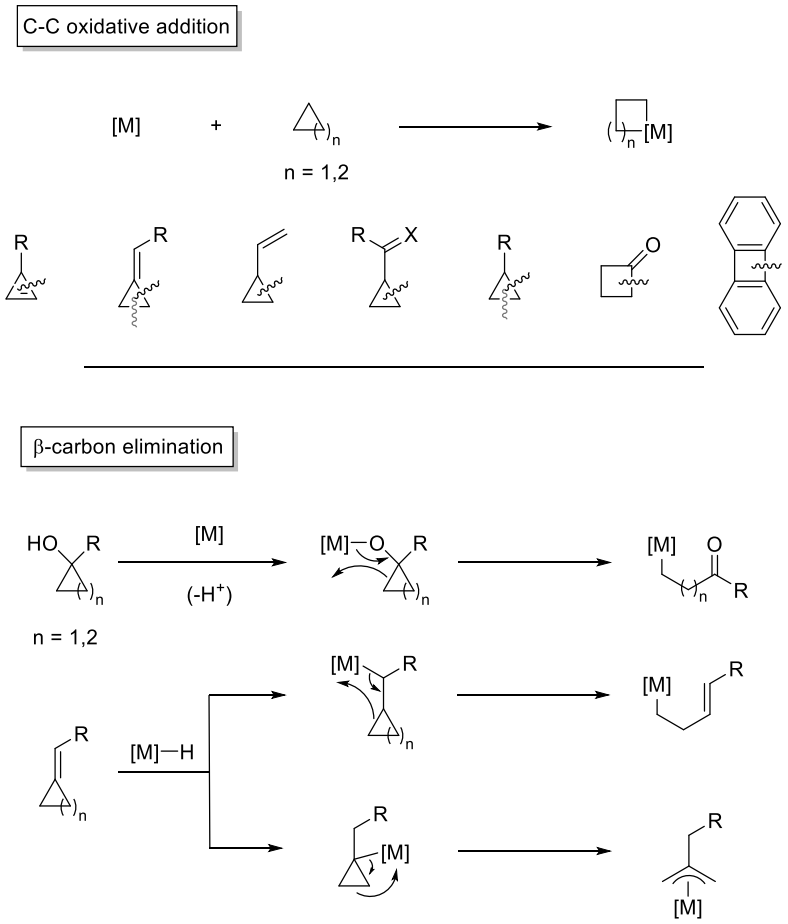


Figure 2.7: C-C bond cleavage of strained rings by transition metal catalysis.

Among these ring-strain-driven strategies based on cyclopropane and cyclobutane derivatives, it is worth to mention that donor-acceptor cyclopropanes[56] and cyclobutanes[57] are widely used as substrates, as shown in Figure 2.8. The D-A cyclopropanes and cyclobutanes are vicinally substituted with donor and acceptor groups, in which the combined effect of substituents decreases the activation barrier of the C-C bond cleavage, allowing transformations under mild conditions. This advantage can be rationalized by the resonance structures, in which the positive charge can be stabilized by the donor group and the negative charge can be stabilized by acceptor group. Therefore, the donor-acceptor small rings could readily react with electrophiles, nucleophiles, unsaturated systems and even undergo rearrangements with specific acceptors, which provides versatile access to valuable building blocks. Taking the advantages of the substituent effects on the D-A small rings, a lot of synthetic protocols based on D-A cyclopropanes has been developed, which offered versatile approaches to the total synthesis of natural products, while the study of D-A cyclobutanes has just emerged recently.

[56] (a) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504-5523. (b) Budynina, E. M.; Ivanov, K. L.; Sorokin, I. D.; Melnikov, M. Y. *Synthesis* **2017**, *49*, 3035-3068.

[57] Reissig, H.; Zimmer, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 5009-5011.

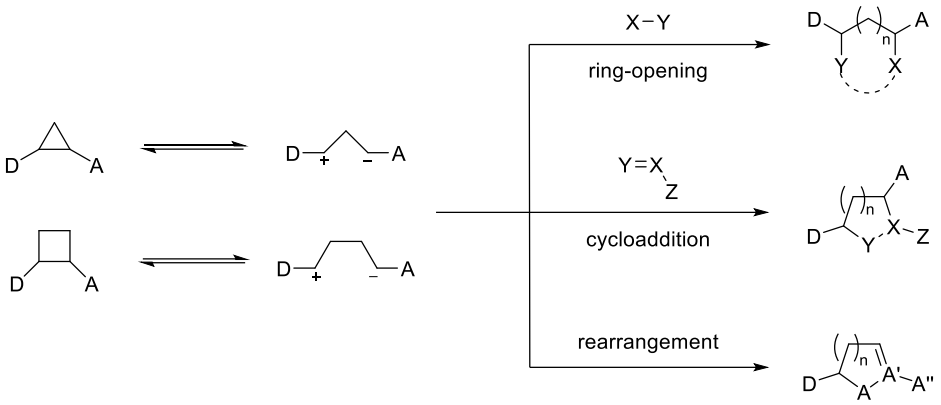


Figure 2.8: Different types of reactions of donor-acceptor cyclopropane and cyclobutane rings.

After this brief introduction of C-C bond cleavage of cyclopropane and cyclobutane rings, in the next section, we will focus on the methods studying C-H bond activation of small rings by transition-metal catalysis.

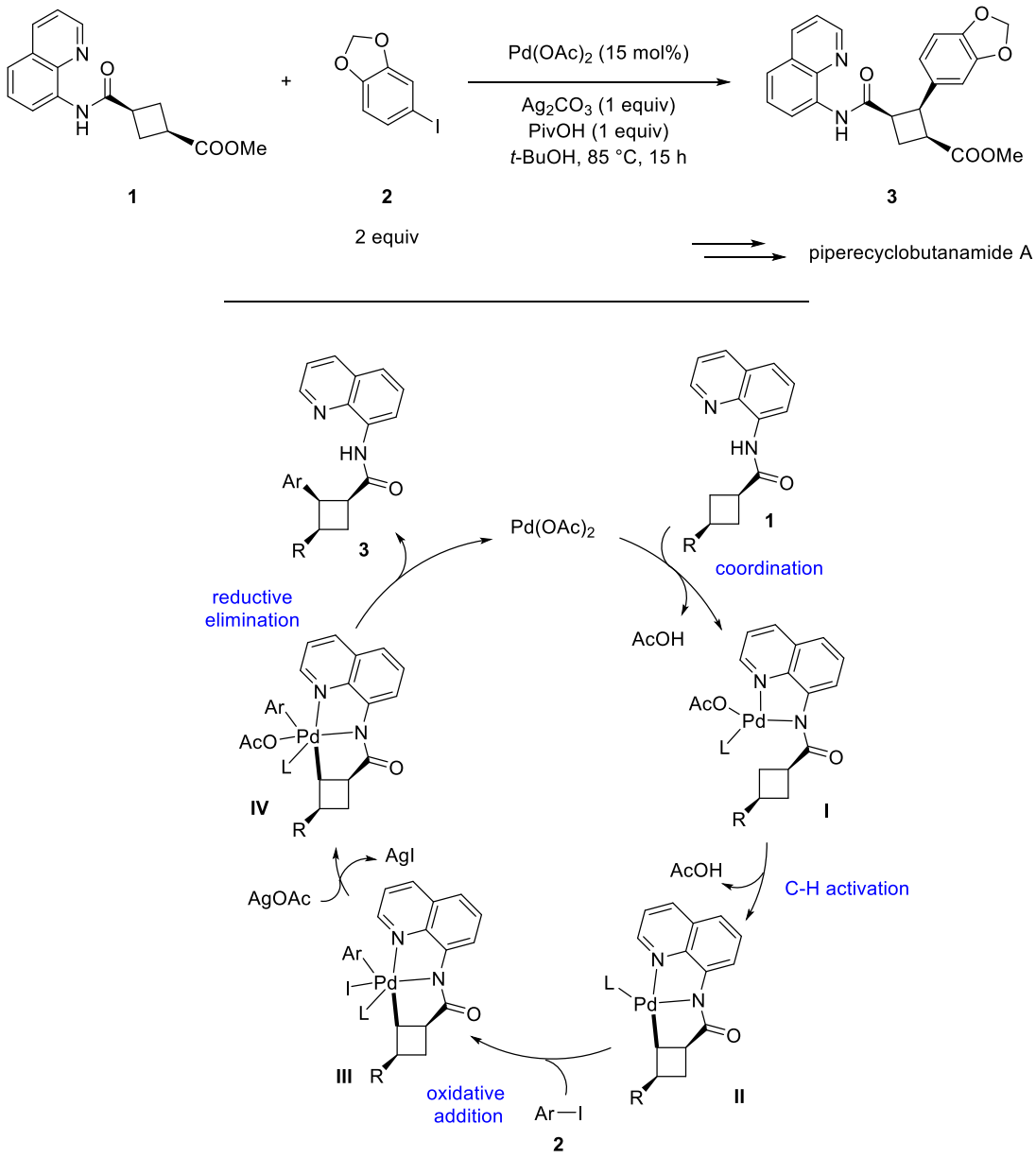
1.2.3 C-H activation of cyclopropanes and cyclobutanes via palladium catalysis

Although the study of palladium catalyzed C-H activation has a long history, the protocols based on strained ring systems have only been realized quite recently, which indeed proved to be a powerful tool for constructing complexity in synthetic chemistry. [58] In comparison to the developed prefunctionalization strategies, C-H activation provides an alternative approach to access substituted cyclopropane and cyclobutane rings, in which a high level of regio- and stereoselectivity could be achieved by employing chiral auxiliaries, catalysts, ligands and other reagents. For examples, In 2011 and 2012, Baran's group reported the C-H arylation of cyclobutane rings during their synthesis of natural products, such as pipearborenies and pipercyclobutanamide A, in which chiral auxiliaries were installed in the substrates to enable the palladium catalyzed C-H activation.[59] In line with the research reported by Daugulis, Chen and Charette,[60] the auxiliary-assisted Pd(II)/Pd(IV) catalytic cycle was proposed as depicted in Scheme 2.1, in which the auxiliary could chelate to palladium to facilitate the C-H activation step and stabilize the highly reactive Pd(IV) intermediate **III**. The presence of silver salt was supposed to promote the catalytic cycle by abstracting the halogen atom.

[58] (a) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *J. Org. Chem.* **2013**, *78*, 11911-11934. (b) Gutekunst, W. R.; Baran, P. S. *J. Org. Chem.* **2014**, *79*, 2430-2452.

[59] (a) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076-19079. (b) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 7507-7510.

[60] (a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *132*, 3965-3972. (b) He, G.; Chen, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 5192-5196. (c) Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 4394-4397.

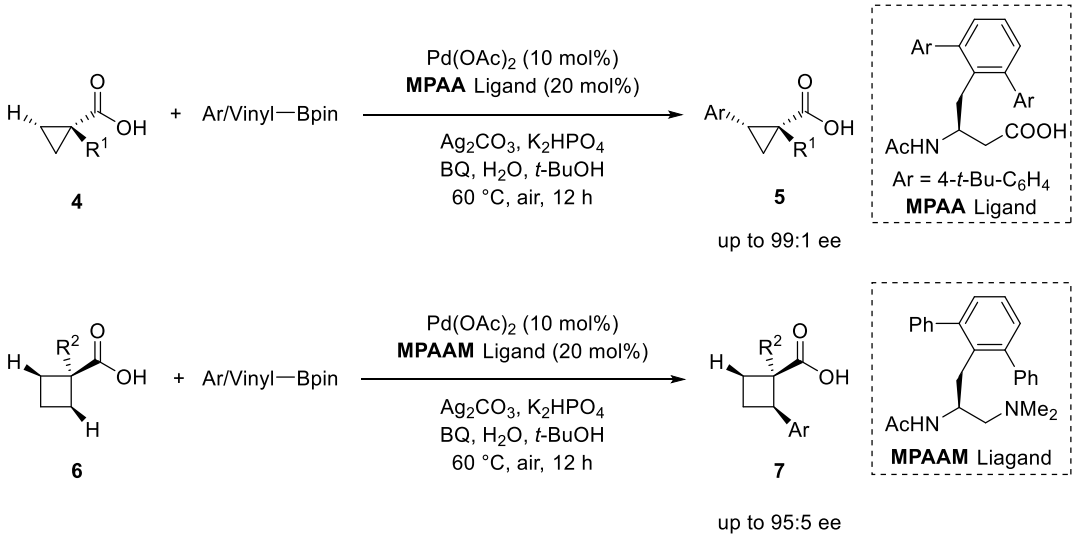


Scheme 2.1: Plausible mechanism for the auxiliary-aided C-H arylation of cyclobutane ring reported by Baran.

It is worth to mention that Yu's group has disclosed many elegant palladium catalyzed asymmetric C-H activation of cyclopropanes and cyclobutanes, which could achieve high levels of enantioselectivity by systematic tuning of chiral ligands and reaction conditions.[61] All these transformations proved to be efficient and general, with the substrates ranging from amides to carboxylic acid derivatives, and various aryl- and vinyl-boron reagents or iodide compounds have been employed as coupling partners. Nowadays, this field has become a hot topic in synthetic chemistry along with brilliant developments presented frequently. For example, a recent work from Yu's group features an enantioselective C-H

[61] (a) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598-19601. (b) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138-8142. (c) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 2042-2046. (d) He, J.; Jiang, H.; Takise, R.; Zhu, R.-Y.; Chen, G.; Dai, H.-X.; Dhar, T. G. M.; Shi, J.; Zhang, H.; Cheng, P. T. W.; Yu J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 785-789. (e) He, J.; Shao, Q.; Wu, Q.; Yu, J.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 3344-3347. (f) Shao, Q.; Wu, Q.-F.; He, J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 5322-5325. (g) Hu, L.; Shen, P.-X.; Shao, Q.; Hong, K.; Qiao, J. X.; Yu J.-Q. *Angew. Chem. Int. Ed.* **2019**, *58*, 2134-2138.

activation of both cyclopropane and cyclobutane derived carboxylic acids, which was compatible with both aryl and vinyl boron coupling partners (Scheme 2.2). The use of chiral bidentate **MPAA** and **MPAAM** ligands were crucial to achieve high efficiency and enantioselectivity.[62, 61(f)]



Scheme 2.2: Palladium catalyzed C-H functionalization of cyclopropyl and cyclobutyl carboxylic acids.

Inspired by the success of intermolecular C-H functionalization of cyclopropanes and cyclobutanes, intramolecular C-H activations of cyclopropanes have also been investigated recently, which does not just represent a theoretical interest, but also provides new routes to synthesize heterocycles, fused or spiro compounds and other complex molecules. In the next section, we will mainly focus on a brief introduction of palladium-catalyzed intramolecular C-H activation of cyclopropanes.

1.3 Palladium catalyzed intramolecular C-H activation of cyclopropanes

1.3.1 C-H arylation of cyclopropanes

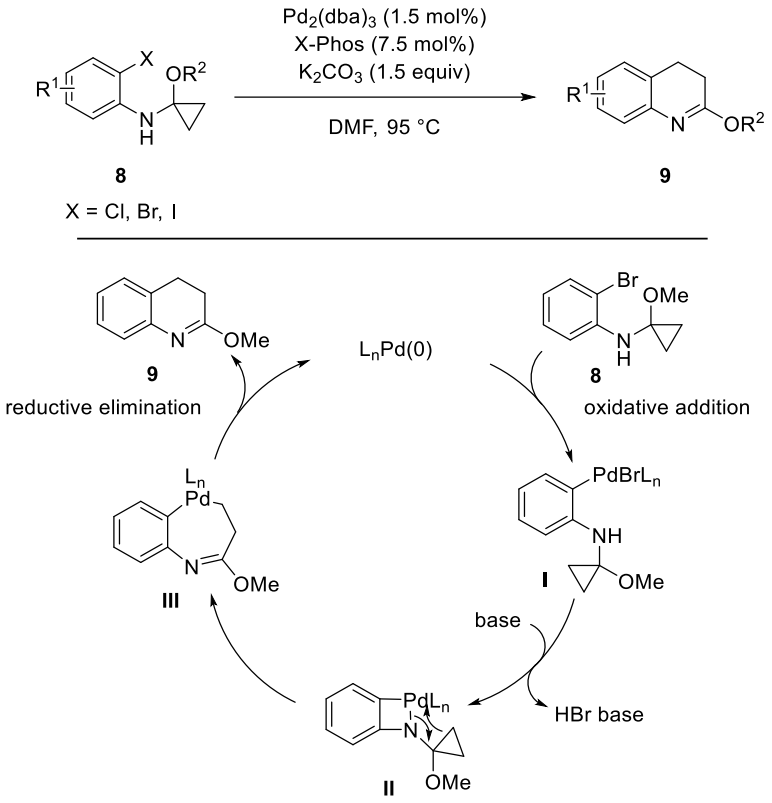
1.3.1.1 Methylene C-H arylation followed by ring-opening of cyclopropanes

The intramolecular C-H activation of cyclopropane was firstly explored by Tsuritani's group,[63] which found an unexpected side reaction during their study of Larock indole synthesis starting from *N*-(1'-methoxy)cyclopropyl-2-iodoaniline **8** (Scheme 2.3, top). After the structural identification of the byproduct, they realized that an interesting 3,4-dihydroquinoline compound **9** was formed through an intramolecular C-H arylation process of cyclopropyl motif followed by the ring opening of the cyclopropane. With the optimized condition, the Pd(0) catalyzed cyclopropane ring expansion proved to be efficient and general (10 examples, up to 90% yield) and gave access to various 3,4-dihydro-2(^{1}H)-quinolinones, which belong to the class of benzo-fused lactams that are pharmacologically and biologically active. The mechanism was also proposed and is depicted in Scheme 2.3 (bottom). The

[62] Wu, Q.-F.; Shen, P.-X.; He, J.; Wang, X.-B.; Zhang, F.; Shao, Q.; Zhu, R.-Y.; Mapelli, C.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. *Science* **2017**, *355*, 499-503.

[63] Tsuritani, T.; Yamamoto, Y.; Kawasaki, M.; Mase, T. *Org. Lett.* **2009**, *11*, 1043-1045.

Pd(0) inserts into the C-X bond by an oxidative addition process to form the intermediate **I**, which is next transformed to the four-membered azapalladacycle **II** upon treatment with base followed by an intramolecular ligand exchange. Then, palladium rearrangement followed by cyclopropane ring opening afforded the energetically favored intermediate palladacycle **III**, which finally generates the desired 3,4-dihydro-2(^{1}H)-quinolinone product **9** through a reductive elimination process.

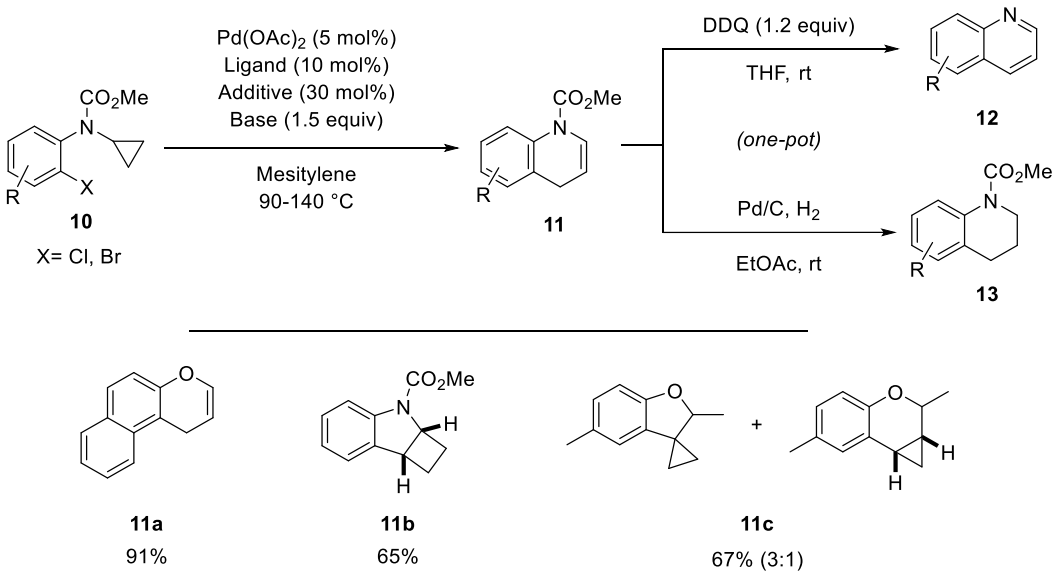


Scheme 2.3: Intramolecular C-H functionalization reported by Tsuritani and the plausible mechanism.

Another interesting example was reported in 2012 by the group of Rousseaux, in which an intramolecular C-H arylation of unactivated cyclopropane **10** was investigated to generate the derivatives of quinoline **12** and tetrahydroquinoline **13** via a C-H activation/ring expansion and sequential oxidation or reduction processes as shown in Scheme 2.4.[64] Optimal conditions for the C-H activation of the bromophenyl cyclopropyl carbamate was achieved by using a combination of palladium acetate (5 mol%) as catalyst, P(^{t}Bu)$_2$Me (10 mol%) as *in situ* generated ligand (from the corresponding HBF_4 salt), cesium pivalate (30 mol%) as additive and potassium phosphate (1.5 equiv) as base in anhydrous mesitylene at 90-110 °C. Switching to the more difficult to activate aryl chlorides required slightly modified conditions: PCy_3 as *in situ* generated ligand, pivalic acid as additive and cesium carbonate as base at higher temperature (100-140 °C). The desired 1,4-dihydroquinoline derivative **11** could not be isolated due to its poor stability, thus one-pot oxidation or hydrogenation was conducted to afford the aromatic quinoline **12** or saturated tetrahydroquinoline compound **13**,

[64] Rousseaux, S.; Liégault, B.; Fagnou, K. *Chem. Sci.* **2012**, *3*, 244-248.

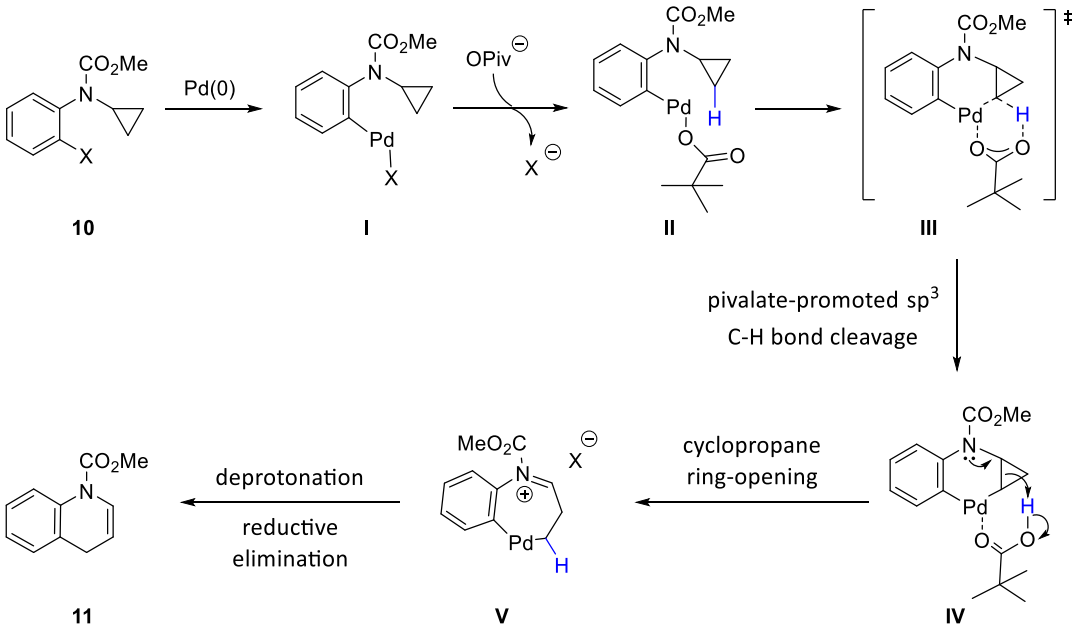
respectively. Moreover, this transformation turned out to be quite efficient also for oxygen-containing **11a** and **11c** and for the arylation of cyclobutyl derivatives such as **11b**.



Scheme 2.4: Synthesis of quinoline and tetrahydroquinoline derivatives reported by Rousseaux.

The mechanism of Pd(0)-catalyzed intramolecular C(sp^3)-H activation of cyclopropane has been extensively studied in previous works,[65] in which mechanistic studies (kinetic isotope effects, intermediate isolation), DFT calculations and kinetic studies (reagent order) were all well investigated. Based on these results, a plausible mechanism was disclosed, as shown in Scheme 2.5. Oxidative addition of aryl halides **10** to palladium(0) afforded Pd(II) intermediate **I**, which undergoes ligand exchange with pivalate to give intermediate **II**. Then, pivalate assisted the C(sp^3)-H bond cleavage via CMD transition-state **III** followed by the ring-opening of cyclopropane ring of **IV** to form the palladacycle intermediate **V**, which next went through a deprotonation and reductive elimination sequence to generate the desired 1,4-dihydroquinoline compound **11**.

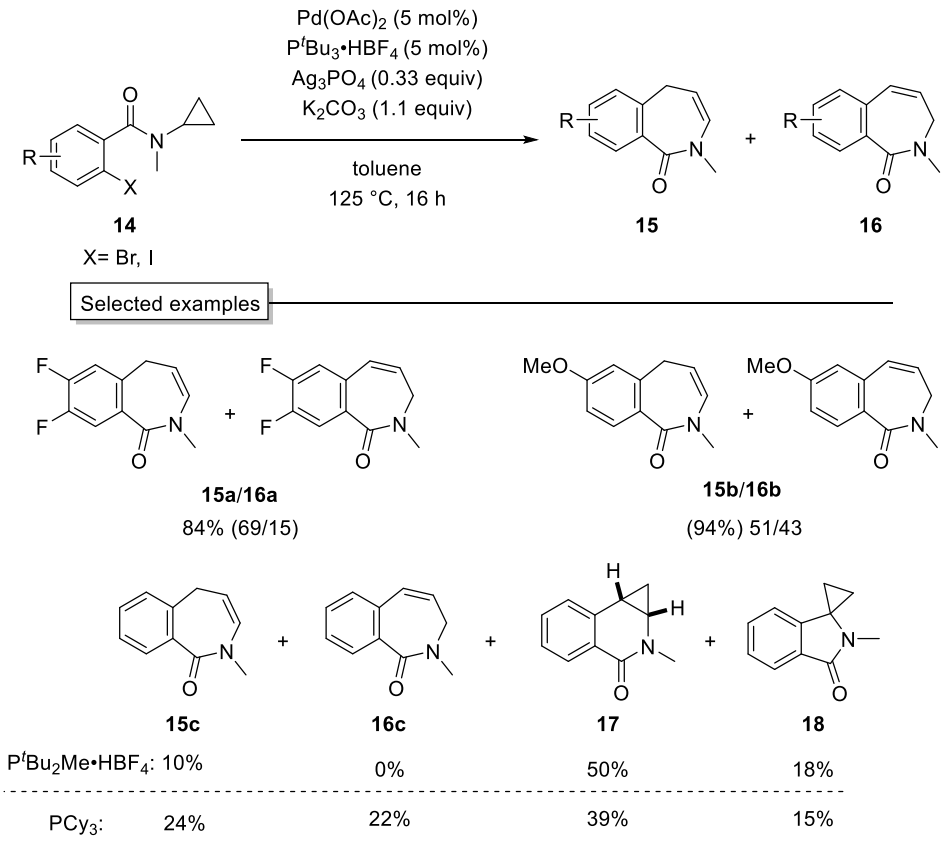
[65] (a) Lafrance, M.; Gorelsky, S. I. Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570-14571. (b) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 10692-10705. (c) Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706-10716.



Scheme 2.5: Proposed mechanism for the Pd(0) catalyzed cyclopropane C-H bond functionalization.

Interestingly, inspired by previous work from Rousseaux,[64] Charette's group later disclosed a palladium catalyzed C-H arylation/ring expansion reaction to synthesize seven-membered benzo[c]azepine-1-ones, which were obtained as a mixture of two isomers (**15** and **16**) as depicted in Scheme 2.6.[66] In comparison to the work of Rousseaux, the C-H activation step was promoted by silver instead of pivalate, and steric and electronic effects of the phosphine ligand were crucial for the efficiency and regioselectivity of this C-H functionalization. For example, it was realized that the replacement of $P^tBu_3{\cdot}HBF_4$ with PPh_3 resulted in low conversion and the use of $P^tBu_2Me{\cdot}HBF_4$ or PCy_3 led to the formation of cyclopropyl fused or spiro compounds **17** and **18**. The proposed mechanism was consistent with the work of Rousseaux, except that the CMD step was facilitated by silver salt instead of pivalate.

[66] Ladd, C. L.; Roman, D. S.; Charette, A. B. *Tetrahedron* **2013**, *69*, 4479-4487.



Scheme 2.6: Synthesis of benzo[c]azepine-1-ones reported by Charette.

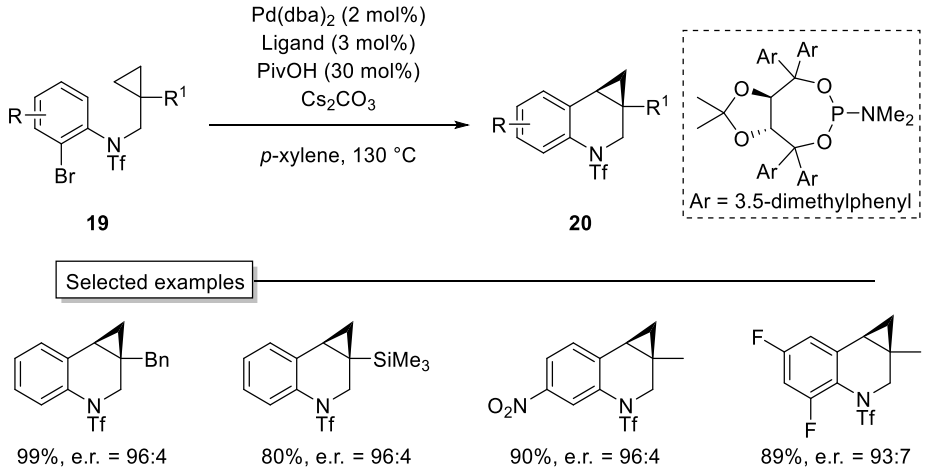
Palladium-catalyzed C-H activation of cyclopropanes was not only involved in ring-opening process but also in intramolecular C-H activation reactions without ring-expansion, which will be discussed in the following paragraph.

1.3.1.2 Methylene C-H arylation without ring-opening

In 2012, Cramer's group reported an interesting example of enantioselective intramolecular methylene C-H arylation of cyclopropylmethyl anilines **19** as shown in Scheme 2.7, which provided a convenient approach to access tetrahydroquinoline scaffolds **20** with high efficiency and excellent enantioselectivity.[67] This C-H functionalization proceeded through the CMD process by forming a seven-membered palladacycle, which was quite rare for the C(sp^3)-H activation. After the optimization of ligands and aliphatic acids, the best reaction outcome was achieved by using a catalytic system consisting of $Pd(dba)_2$, a TADDOL-derived phosphoramidite as ligand and pivalic acid as additive in the presence of cesium carbonate as base in *p*-xylene at 130 °C. In addition, this transformation turned out to proceed efficiently even with quite low catalyst loading (2 mol%). The scope and limitation of this reaction was evaluated by using various substitution patterns on the aromatic group and the cyclopropane ring of **19**; the reaction proceeded smoothly to give the desired products with several functional substituents. It was worth noting that the presence of R^1 substitution was crucial for this transformation, otherwise the methine C-H activation would occur to generate a spirocompound as the major product. Finally, the triflyl group on the nitrogen of the cyclized product **20** could be removed

[67] Saget, T.; Cramer, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 12842-12845.

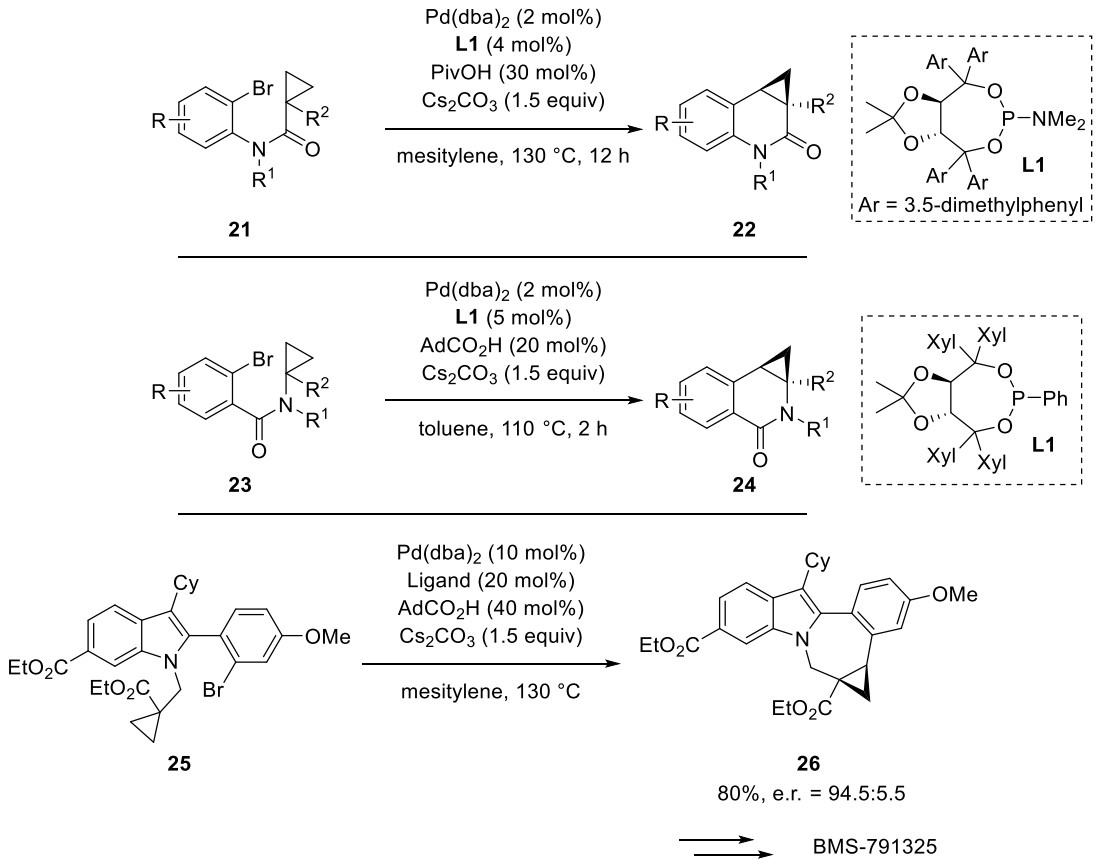
under mild conditions (Red-Al, toluene, 50 °C) and the cyclopropane motif could be expanded to form a seven-membered ring via an enantiospecific cyclopropane hydrogenation, which further proved the utility of this methodology.



Scheme 2.7: Synthesis of functionalized tetrahydroquinolines via enantioselective C-H arylation reported by Cramer.

In continuation of their previous work, the group of Cramer reported another interesting example of enantioselective palladium-catalyzed intramolecular C-H arylation of cyclopropanes (Scheme 2.8), in which both cyclopropanecarboxamides **21** and aminocyclopropanes **23** were used as substrates to generate valuable nitrogen heterocycles by using a Taddol-derived phosphoramidite ligand.[68] The scope proved to be large with respect to the substituent on the amide nitrogen, the aniline moiety and the cyclopropane ring, which smoothly provided access to diversely substituted dihydroquinolones **22** and dihydroisoquinolones **24** with high efficiency and enantioselectivity. In addition, the efficiency of this method was further proved by the synthesis of BMS-791325 ring system, a Bristol-Myers-Squibb small molecule which showed attractive pharmacological properties and served as a virus replicase inhibitor. By employing the optimized palladium catalytic condition, the seven-membered ring core of the cyclopropyl indolobenzazepine compound **26** could be established via a convenient and direct way.

[68] Pedroni, J.; Saget, T.; Donets, P. A.; Cramer, N. *Chem. Sci.* **2015**, *6*, 5164-5171.

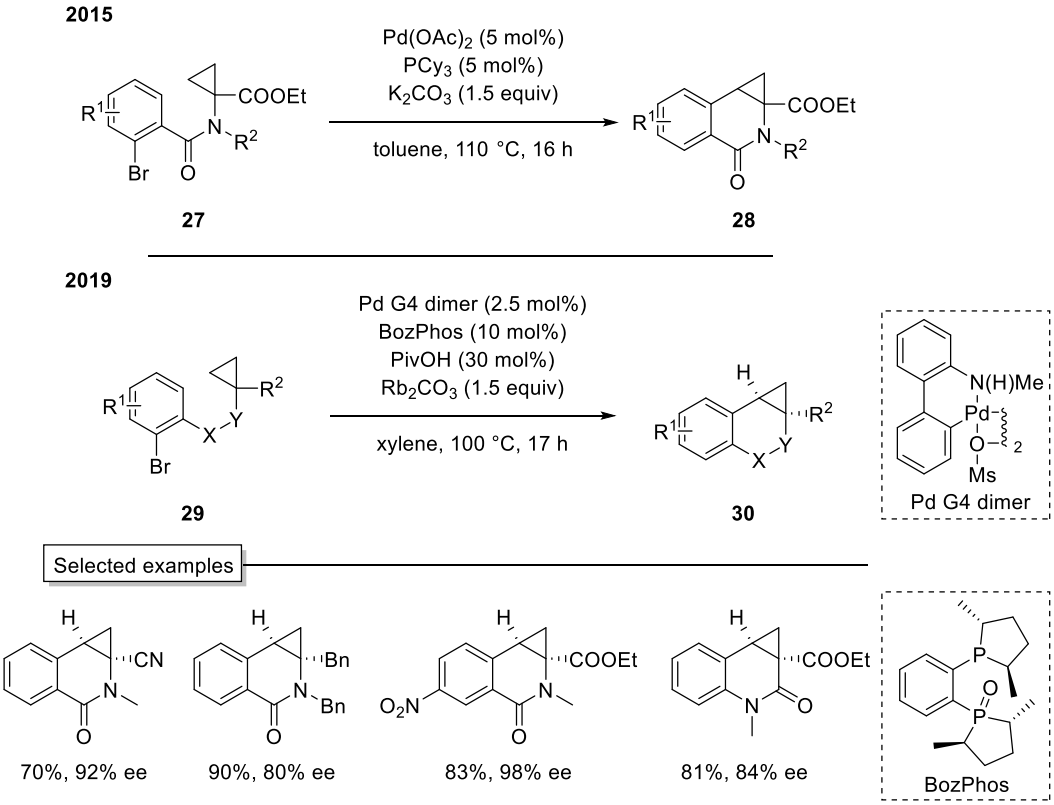


Scheme 2.8: Synthesis of dihydroquinolones, dihydroisoquinolones and BMS-791325 via intramolecular C-H activation reported by Cramer.

Furthermore, the group of Charette also contributed to some impressive examples in this field based on their interest in the construction and synthetic applications of cyclopropane rings.[47b] A racemic version of intramolecular C-H arylation of methylene was first disclosed in 2015, in which the starting α-amino acid-derived benzamide **27** was smoothly transformed into the desired ethyl 1,2,3,4-tetrahydroisoquinolone-3-carboxylates **28** without using silver ion or pivalate as additive (Scheme 2.9).[69] Interestingly, an asymmetric version of this transformation was reported by the same group in 2019 to synthesize functionalized dihydroisoquinolones and dihydroquinolones **30**,[70] in which a hemilabile ligand BozPhos was used to achieve high efficiency and enantioselectivity. The wise selection of biphosphine monoxide (BPMO) as ligand was based on the previous reports,[71] which described that the BPMO ligands (containing both phosphine and oxygen as soft and hard coordinating centers, respectively) were able to weakly chelate transition metal to form highly reactive complexes. In addition, to avoid the unexpected oxidation of BPMO to inert dioxide species,[72] the Buchwald's fourth generation dimer (Pd G4 dimer) was selected as source of palladium(0).[73] The BozPhos-Pd(II) complex intermediate was successfully isolated and proved to be effective catalytic species for this transformation, which provided further insights into the properties of the catalytic intermediates.

[69] Ladd, C. L.; Belouin, A. V.; Charette, A. B. *J. Org. Chem.* **2016**, *81*, 256-264.
[70] Mayer, C.; Ladd, C. L.; Charette, A. B. *Org. Lett.* **2019**, *21*, 2639-2644.
[71] Grushin, V. V. *Chem. Rev.* **2004**, *104*, 1629-1662.
[72] Li, H.; Belyk, K. M.; Yin, J.; Chen, Q.; Hyde, A.; Ji, Y.; Oliver, S.; Tudge, M. T.; Campeau, L.; Campos, K. R. *J. Am. Chem. Soc.* **2015**, *137*, 13728-13731.
[73] Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 4161-4166.

Under the optimized conditions, a broad spectrum of desired cyclized products with variation on the nitrogen, cyclopropane and aryl groups were obtained in good yields and enantioselective values.



Scheme 2.9: Enantioselective C-H arylation to functionalized tetrahydroquinolines reported by Cramer.

Besides the activation of methylene C-H bond by palladium catalysis, methine C-H activation was also reported in some interesting works, leading to the formation of spirocyclopropyl products. This research is discussed in the following paragraph.

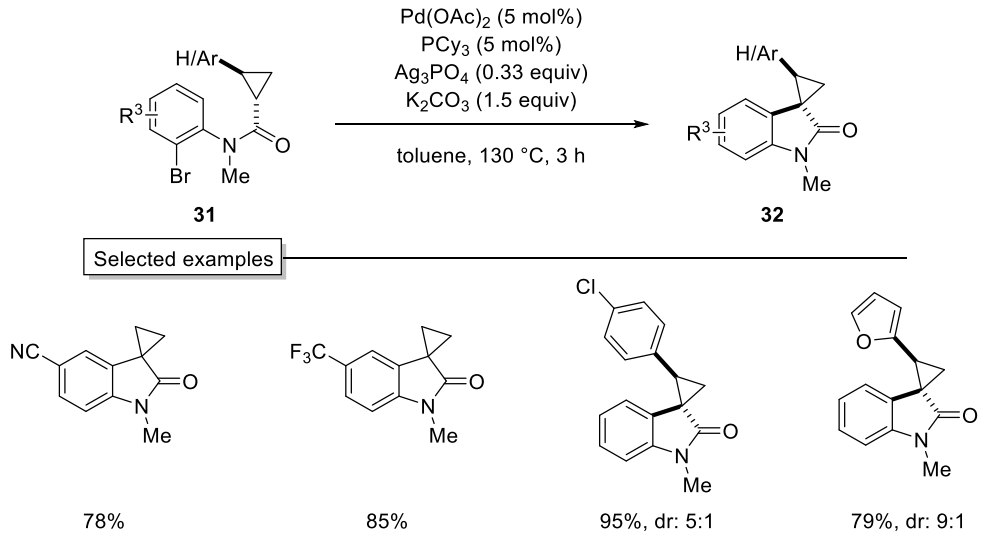
1.3.1.3 Methine C-H arylation

The spirocyclopropyl oxindole scaffolds are quite unique structural moieties, which could be found in many bioactive compounds, including agrochemicals and pharmaceuticals (such as inhibitors of HIV).[74] Moreover, from a synthetic point of view, these motifs could serve as intermediates to access oxindole alkaloids with medium-sized rings via ring-expansion process.[75] Common routes to synthesize spirocyclopropyl oxindoles mainly involve the construction of cyclopropane ring based on oxindole precursors. Alternatively, intramolecular C-H arylation of a cyclopropyl unit provides a more straightforward synthetic pathway starting from the corresponding cyclopropyl anilides. However, due to the increased steric effect and the decreased acidity of tertiary C(sp^3)-H bond, functionalization of methine C-H bond remained largely elusive. Based on this strategy, Charette's group in 2013 reported

[74] (a) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Tuntland, T.; Zhang, K.; Karanewsky, D.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2109-2112. (b) Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem. Eur. J.* **2011**, *17*, 2842-2845. (c) Cao, Z.-Y.; Zhou, F.; Yu, Y.-H.; Zhou, J. *Org. Lett.* **2013**, *15*, 42-45.

[75] Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505-11515.

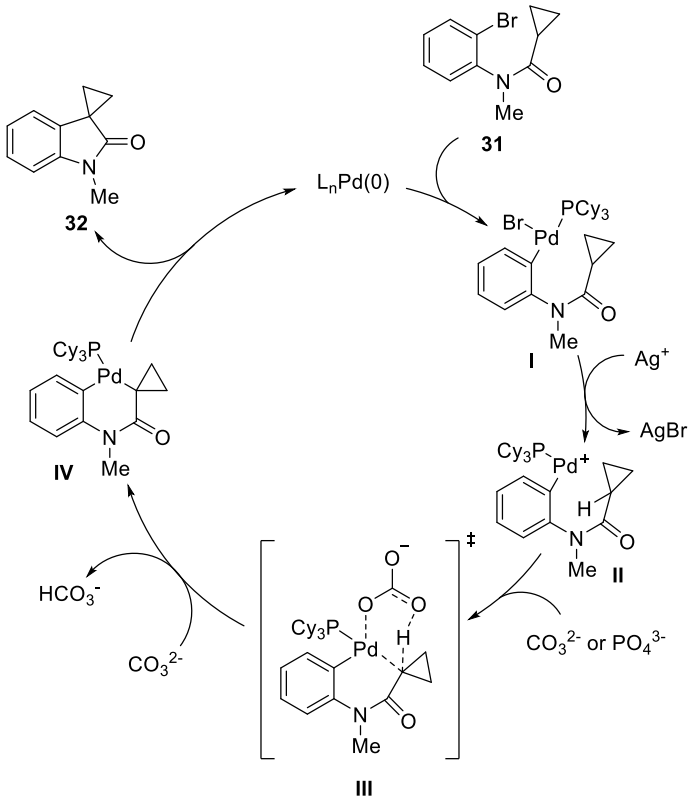
a palladium(0) catalyzed arylation of 2-bromoanilides **31** to access spiro 3,3'-cyclopropyl oxindoles **32**, which was promoted by silver(I) instead of pivalate (Scheme 2.10).[76] Under the optimized conditions, various substrates bearing different substituents on the aromatic ring turned out to be smoothly transformed into their corresponding products and moreover, it showed a good tolerance to a series of functional groups, such as cyano-, trifluoromethyl- and carboxyl- groups. In addition, the effect of cyclopropane substitution was also investigated, a range of aromatic substituents on cyclopropane could be tolerated and gave the desired products in good yields.



Scheme 2.10: Synthesis of spiro 3,3'-cyclopropyl oxindoles reported by Charette.

Based on control experiments, a plausible mechanism was proposed as shown in Scheme 2.11. Oxidative addition of Pd(0) to carbon-halogen bond generated the intermediate **I**, which was converted to cationic palladium species **II** via a silver(I) mediated halogen abstraction. Then the counterions (CO_3^{2-} and PO_4^{3-}) facilitated the CMD process (transition state **III**) leading to palladacycle **IV**. Eventually, reductive elimination gave the desired spirocompound **32**. It deserves to be mentioned that the presence of silver(I) was crucial for this transformation, by promoting the formation of reactive cationic intermediate **II** via halide abstraction.

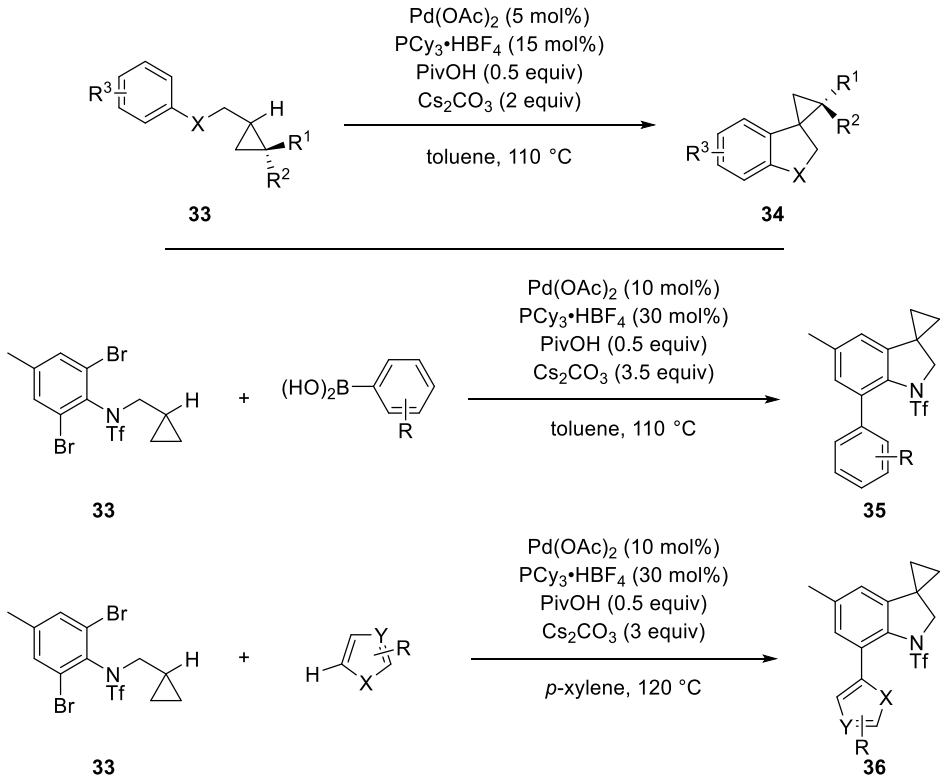
[76] Ladd, C. L.; Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 1350-1353.



Scheme 2.11: Plausible mechanism of palladium catalyzed C-H arylation assisted by silver.

Another interesting example was reported by the group of Cramer at the same year, in which a palladium catalyzed methine C-H arylation was explored to synthesize functionalized cyclopropyl spiroindolines **34** (Scheme 2.12).[77] The cyclopropyl spiroindoline scaffolds were potentially applicable in medicinal chemistry but far less explored than cyclopropyl spirooxindoles, maybe due to the limitations of existing synthetic methods.[78] Moreover, it was surprising to find out that the tertiary C-H activation dominated over the secondary C-H activation completely, which could be attributed to the favored formation of a six-membered palladacycle intermediate rather than the seven-membered one. The scope of this transformation proved to be quite large, leading to a collection of functionalized cyclopropyl spiroindolines. As the reaction is stereospecific, the stereochemistry of the cyclopropanes could be transferred with great fidelity into the cyclized products. Moreover, the intramolecular C-H arylation could be further combined with intermolecular reactions (such as Suzuki cross-coupling or C-H cross-coupling with heteroaromatics), thereby increasing molecular complexity via tandem processes (**35** and **36**).

[77] Saget, T.; Perez, D.; Cramer, N. *Org. Lett.* **2013**, *15*, 1354-1357.
[78] Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, *18*, 3003-3025.



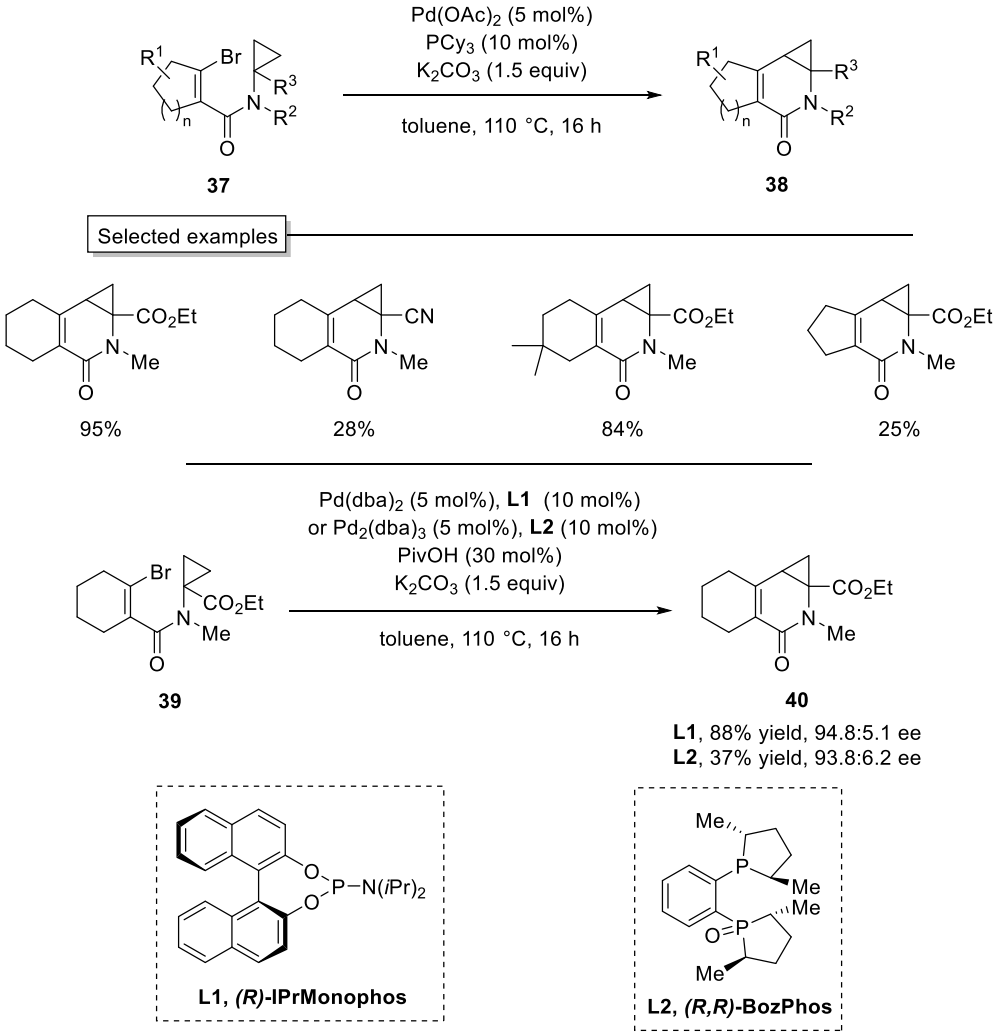
Scheme 2.12: Synthesis of spiroindolines reported by Cramer.

So far, all the examples we described above used aryl halides as the starting material for the oxidative addition step. However, it is also possible to use vinyl halides to initiate the reaction sequence, as discussed in the next section.

1.3.2 C-H alkenylation of cyclopropanes

A rare alkenylation strategy was reported by the group of Charette in 2016, which investigated a palladium catalyzed methylene C-H alkenylation to give cyclopropyl-fused azacycles shown in Scheme 2.13.[79] The 2-bromocycloalkenyl amide **37** could be transformed to the desired cyclized product **38** by using a simple combination of palladium acetate, tricyclohexylphosphine and potassium carbonate in toluene at 110 °C without the addition of pivalic acid or silver salt as additives, whose presence actually did not improve the outcome of this transformation. To test the feasibility of the enantioselective version, a BINOL-derived phosphoramidite ligand was evaluated in combination with $Pd(dba)_2$ as the catalyst. The desired product was obtained in 88% yield and 94.8:5.1 ee value, while the combination of $Pd_2(dba)_3$ and BozPhos gave a lower yield (37%) while maintaining a very good enantioselectivity.

[79] Ladd, C. L.; Charette, A. B. *Org. Lett.* **2016**, *18*, 6046-6049.

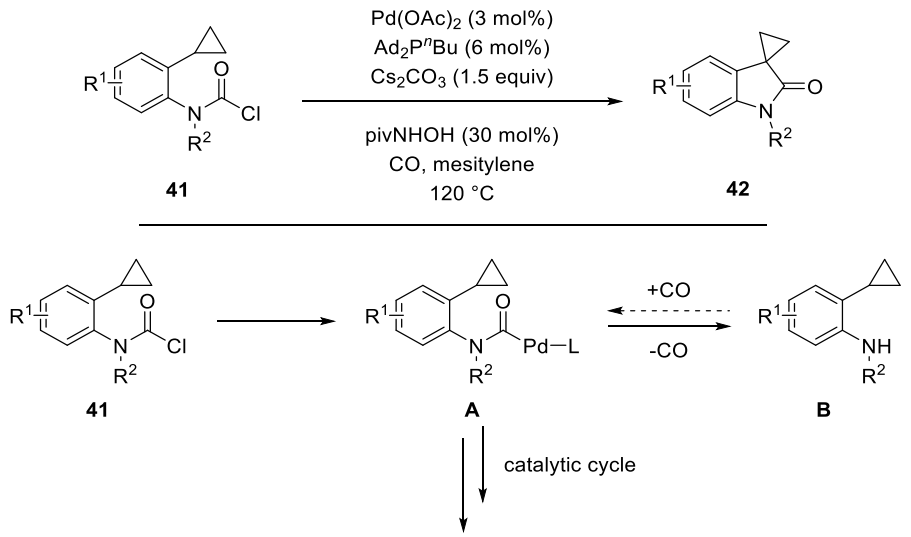


Scheme 2.13: Palladium catalyzed intramolecular C-H alkenylation reported by Charette.

1.3.3 C-H functionalization of cyclopropanes with other electrophilic partners

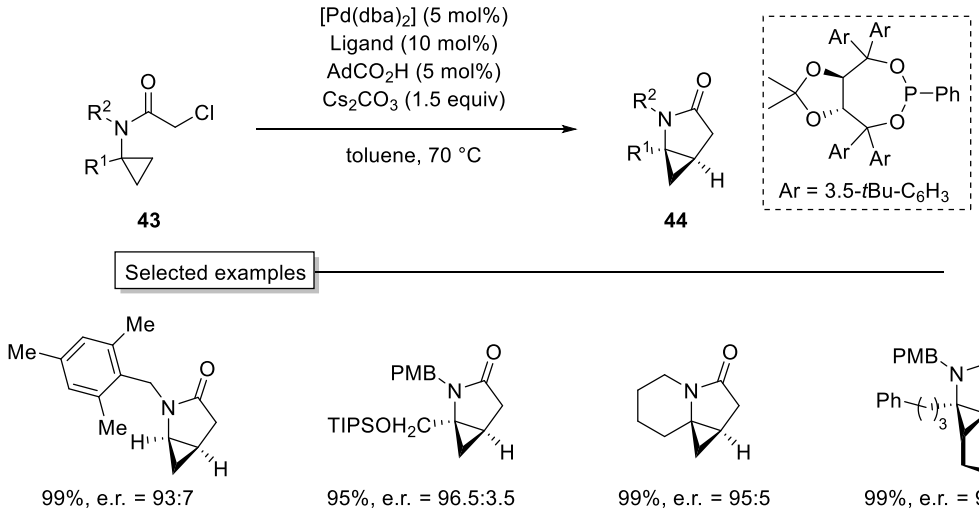
Except for the intramolecular C-H arylation and alkenylation reactions listed above, a few examples of intramolecular C-H functionalization of cyclopropanes with other electrophilic components have also been developed recently, as complementary protocols to synthesize spiro or fused ring systems. As early as 2013, Takemoto's group had reported a methine C-H activation of carbamoyl chlorides **41**, which provided an alternative way to synthesize cyclopropyl spirooxindoles **42** as shown in Scheme 2.14.[80] The employed catalytic condition had been previously published for C(sp^3)-H functionalization,[81] in which the addition of CO gas proved to be crucial to achieve efficient transformation by suppressing the side reactions. The role of CO was rationalized from a mechanistic point of view: oxidative addition of palladium to the substrate led to the intermediate **A**, which could readily eliminate CO to give the byproduct **B**, while the presence of CO gas retarded the process and promoted the desired cyclization and reductive elimination sequence.

[80] Tsukano, C.; Okuno, M.; Takemoto, Y. *Chem. Lett.* **2013**, *42*, 753-755.
[81] Tsukano, C.; Okuno, M.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 2763-2766.



Scheme 2.14: Methine C-H activation of carbamoyl chlorides reported by Takemoto.

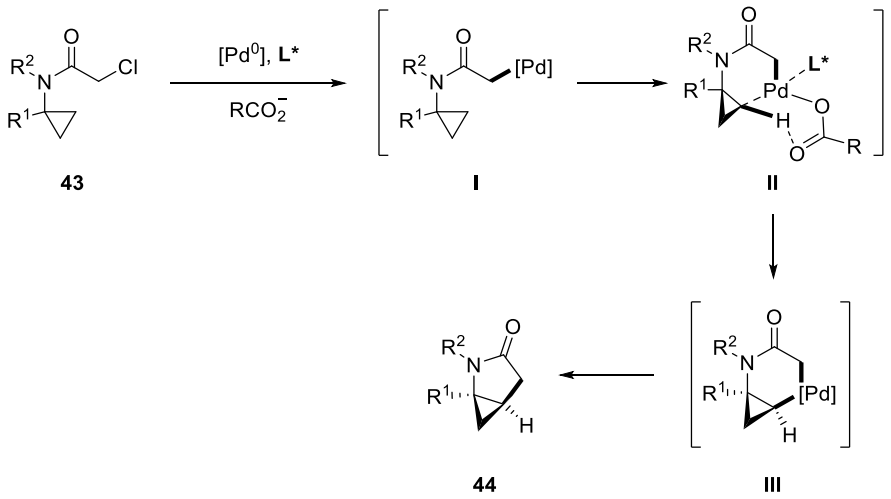
A more challenging work was reported by Cramer's group in 2015 as shown in Scheme 2.15,[82] which described an enantioselective C-H functionalization of chloroacetamides to generate cyclopropyl-fused pyrrolidine units via the formation of a C(sp^3)-C(sp^3) bond that was rarely explored comparing to aryl-aryl coupling. The readily prepared chloroacetamide substrates **43** could be transformed to azabicyclo[3.1.0]hexane derivatives **44** with high efficiency and enantioselectivity, by employing $Pd(dba)_2$ as palladium(0) source, a suitable substituted Taddol-derived phosphoramidite ligand and 1-adamantanecarboxylic acid as additive. The scope of the reaction was broad with respect to the protecting group on the nitrogen and the cyclopropyl moiety. As indicated below, various alkyl and aryl groups could be well tolerated and the presence of versatile functional groups had no negative impact on the reaction outcome. Remarkably, polycyclic scaffolds could be prepared by this method in high yields and enantioselectivities.



Scheme 2.15: Enantioselective methylene C-H activation of chloroacetamides to access chiral γ-lactams reported by Cramer.

[82] Pedroni, J.; Cramer, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 11826-11829.

The plausible mechanism was also proposed as depicted in Scheme 2.16, the chloroacetamide motif of **43** served as an electrophile to react with the palladium catalyst to give the intermediate **I**, which then was converted to the intermediate **II** through a ligand exchange process. The key C-H activation proceeded via a CMD transition-state to generate the palladacycle intermediate **III**, which was next processed through reductive elimination to provide the desired ϒ-lactam product **44**. It is noteworthy to mention that chloroacetamide has been rarely used as electrophilic partner for C-H activation process.[83]

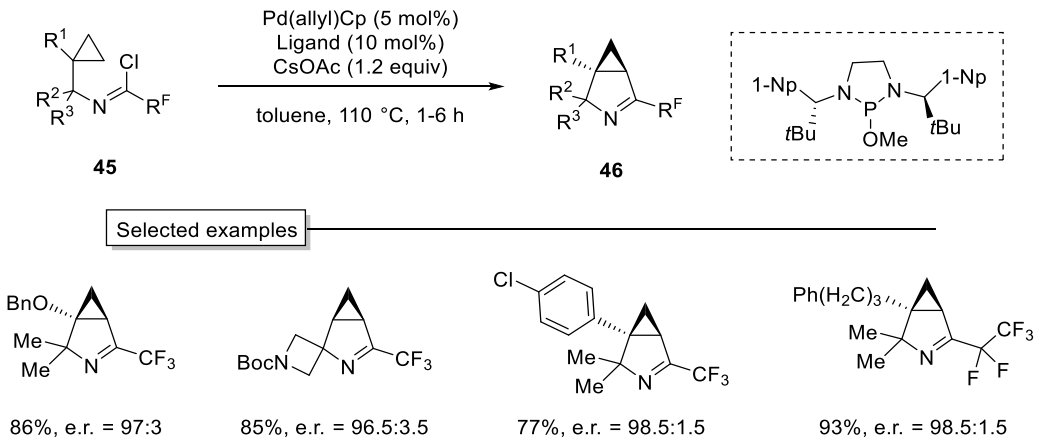


Scheme 2.16: Proposed mechanism of methylene C-H activation of chloroacetamides.

Two years later, the same group reported another interesting example as shown in Scheme 2.17, in which an enantioselective intramolecular C-H activation of trifluoroacetimidoyl chloride **45** was disclosed to provide perfluoroalkylated 3-azabicyclo[3.1.0]hexane scaffolds **46.** The latter present biological activities and have potential use in pharmaceutical studies due to the unique combination of nitrogen heterocycle, rigid cyclopropane ring and fluorine-containing substituents.[84] In the optimal condition, a chiral alkoxy diazaphospholidine ligand was shown to be suitable for this C-H functionalization, which was different from the previously used TADDOL-derived phosphoramidite ligands.[82] Interestingly, during the optimization process, they found out that the chemoselectivity of this reaction could be controlled by tuning the ligands, as the use of the standard chiral ligand could afford the desired cyclopropyl C(sp^3)-H activation product, while triphenylphosphine led to the C(sp^2)-H activation of the α-position on aromatic R^1 group. This trend was investigated by evaluating several aromatic substituted substrates under parallel conditions, and the selectivity proved to be reliable. To demonstrate the generality of this transformation, the scope was investigated with substrates **45** bearing various R^1, R^2, R^3 and R^F substituents, giving valuable fluoro-substituted spirocompounds **46**.

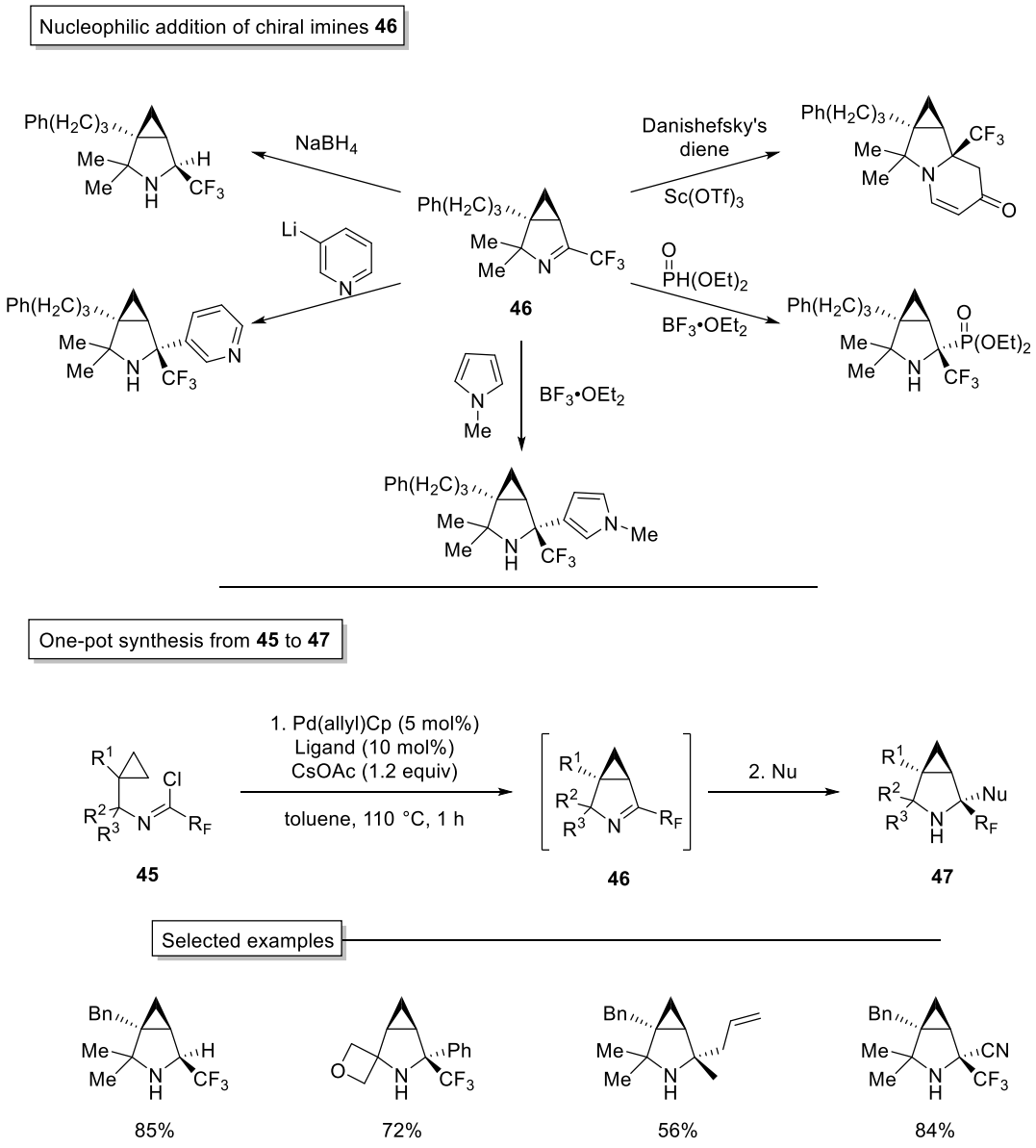
[83] (a) Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 9064-9067. (b) Shi, S.-L.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1646-1650.

[84] Pedroni, J.; Cramer, N. *J. Am. Chem. Soc.* **2017**, *139*, 12398-12401.



Scheme 2.17: Methylene C-H activation of trifluoroacetimidoyl chlorides reported by Cramer.

Moreover, considering that the chiral ketimine **46** could serve as electrophilic intermediate towards nucleophiles, a broad range of highly substituted pyrrolidines **47** with a quaternary chiral center was next generated by subsequent nucleophilic addition reactions of **46**, in which the fused cyclopropane ring effectively guided the direction of the addition of the nucleophile. As illustrated in Scheme 2.18 (top), many nucleophilic addition reactions were investigated, including reduction, Friedel-Crafts reaction, Pudovic reaction and some other transformations. One step further, one-pot synthesis from **45** to **47** could also be performed (Scheme 2.18, bottom), which involved the C-H functionalization and sequential reduction, addition of Grignard reagents, lithium organometallics or Lewis acid mediated reactions, enabling rapid construction of highly substituted and stereodefined pyrrolidine derivatives. Both of these two strategies could deliver the multi-substituted spirocompounds without loss of enantioselectivity.



*Scheme 2.18: Reaction of **46** with nucleophiles and one-pot synthesis towards highly substituted pyrrolidines.*

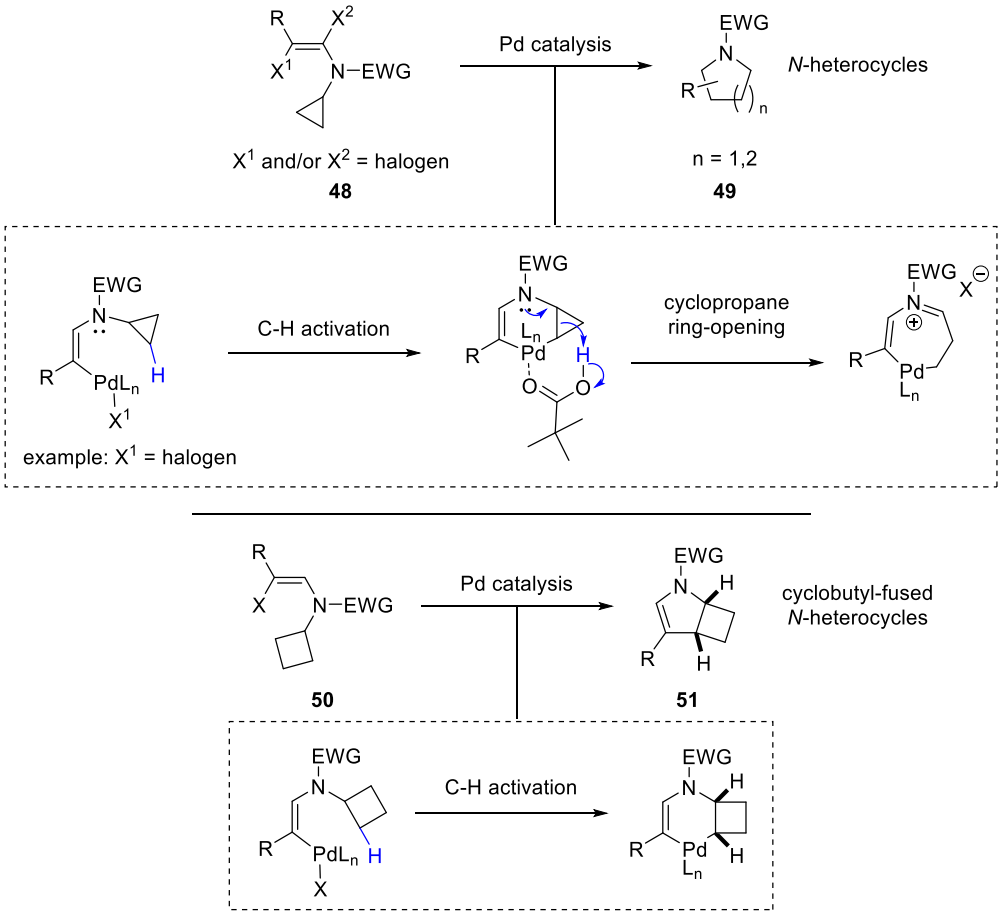
All the intramolecular C-H functionalization of cyclopropane derivatives presented here showed the powerful ability of this strategy for the synthesis of various nitrogen heterocyclic scaffolds, and some of these protocols have already been applied to the synthesis of pharmaceuticals or natural products. Considering this body of literature, it could be concluded that most of the works have been focusing on the arylation of C-H bond, while alkenylation and reactions with several other electrophilic motifs have only been rarely investigated. On the other hand, based on the advantages of high strain energy, cyclopropanes have been widely explored in the palladium-catalyzed C-H activation reaction. However, surprisingly, the intramolecular C-H activation of its cyclobutane homologue has rarely been studied except for only two isolated examples, which only show no enantioselectivity or low efficiency,[63,85] and will not be discussed in detail here.

[85] Yang, L.; Melot, R.; Neuburger, M.; Baudoin, O. *Chem. Sci.* **2017**, *8*, 1344-1349.

In the continuation of our research interest of nitrogen-containing heterocyclic compounds, our project aims at studying a novel method to generate various nitrogen heterocycles via intramolecular C-H activation of cyclopropanes and cyclobutanes, which will be presented in more detail in the following sections.

2 Objectives

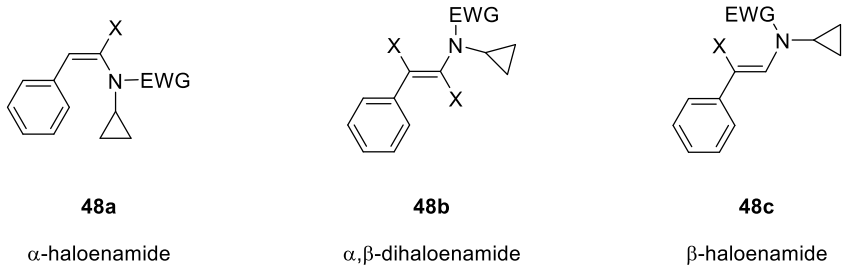
Inspired by the palladium mediated C-H activation methodologies reported in the previous section, we envisioned that a palladium-catalyzed intramolecular cyclization of cyclopropyl or cyclobutyl enamides may be feasible as shown in Scheme 2.19. Starting from the appropriate halo-enamides **48** or **50** possessing either a *N*-cyclopropyl or a *N*-cyclobutyl motif, a Pd(0)/Pd(II) cyclization could lead to relevant nitrogen-containing heterocycles **49** or **51**. In the first case, by analogy with the results from the Rousseaux's group,[64] the C-H activation process could lead to the cyclopropane opening, thereby delivering compounds **49**. On the other hand, starting from a *N*-cyclobutylenamide **50** should not trigger a cyclobutane opening and pyrrolidines fused to a cyclobutyl ring **51** should be obtained. The latter is an interesting scaffold for further functionalization reactions.



Scheme 2.19: Palladium catalyzed intramolecular C-H alkenylation of cyclopropyl and cyclobutyl enamides.

3 Palladium catalyzed cyclization of cyclopropyl enamides

As we discussed in the objective section, we supposed that a suitable halo-enamide would readily react with palladium(0) via oxidative addition, then the weak C-H bond of the strained ring could be activated to form a palladacycle intermediate. After a final reductive elimination step, the desired nitrogen heterocyclic scaffolds would be generated. Since both α- and β- positions (relative to the nitrogen atom) of the enamide were potential oxidative addition sites for the palladium(0), we designed three classes of enamides, including α-haloenamide **48a**, α,β-dihaloenamide **48b** and β-haloenamide **48c** as shown in Scheme 2.20, and evaluated their reactivity towards palladium catalysis.



48a α-haloenamide

48b α,β-dihaloenamide

48c β-haloenamide

Scheme 2.20: Three classes of halo-enamides.

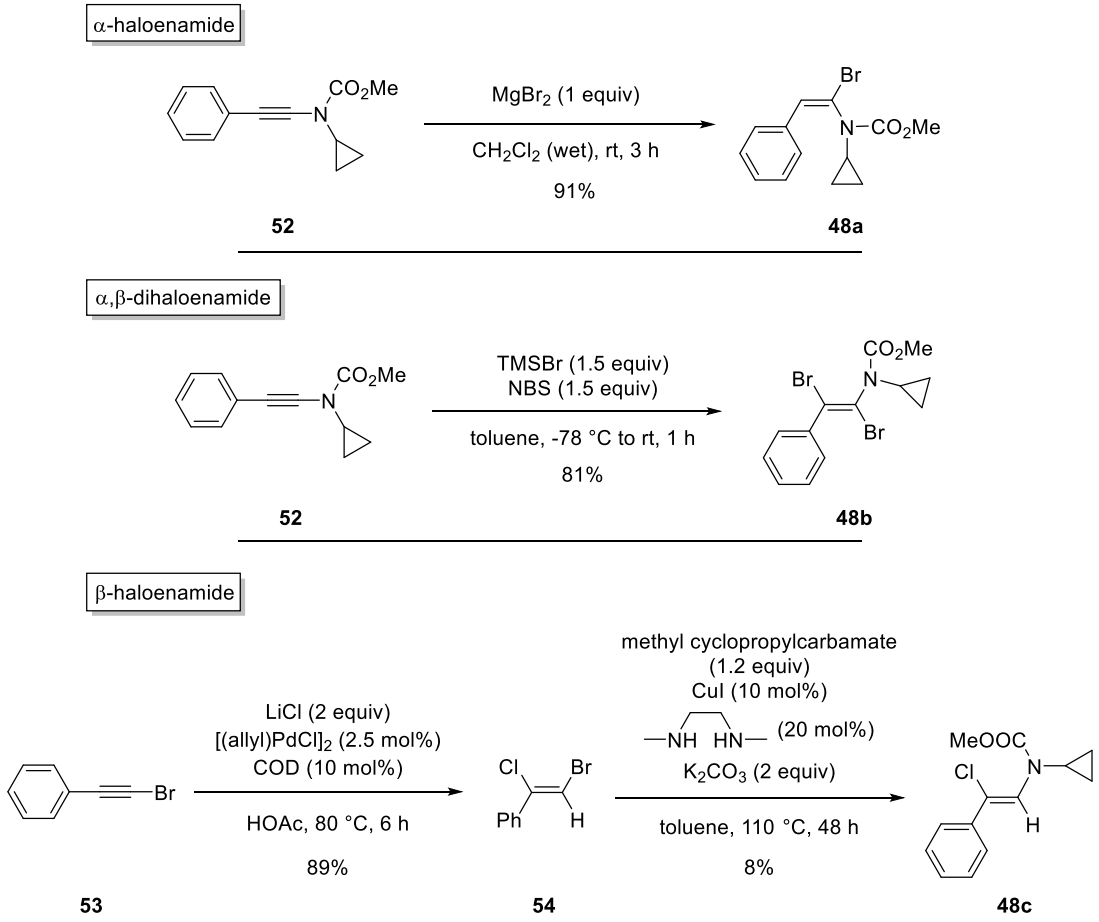
3.1 Palladium catalyzed cyclization of cyclopropyl enamides

3.1.1 Synthesis of the starting enamides

To prepare the desired halo-enamides, we first considered to use the corresponding ynamides as starting materials, which would be readily prepared from the copper catalyzed cross-coupling methods in high yield.[9, 86] Based on previous reports of Hsung's group,[87] ynamide **52** could react with magnesium bromide in wet dichloromethane at room temperature for 3 hours to give the desired α-bromoenamide **48a** in 91% yield (Scheme 2.21, top). Next, we successfully synthesized 1,2-dibromoenamide by employing the condition developed by Iwasawa's group,[88] in which ynamide **52** reacted with a combination of bromotrimethylsilane and *N*-bromosuccinimide in toluene at -78 °C to room temperature to afford the dibromoenamide **48b** in 81% yield (Scheme 2.21, middle). Finally, the synthesis of β-haloenamide was complicated, since all the reported examples of hydrohalogenation of ynamides only provided α-haloenamides to date. Thus, we proposed to prepare 1-chloro-2-bromoalkene **54** first, which could react with the corresponding amide to generate enamide **48c** via transition metal catalyzed coupling. Based on this strategy, we conducted the hydrochlorination of phenylethynyl bromide **53** by using lithium chloride, $[(allyl)PdCl]_2$ and *cis,cis*-1,5-cyclooctadiene,[89] which generated compound **54** with high regio- and stereoselectivity. Based on the higher reactivity of C-Br bond towards copper insertion compared to the C-Cl bond, the copper mediated coupling between **54** and methyl cyclopropylcarbamate was performed under the conditions developed by

[86] DeKorver K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110,* 5064-5106.
[87] Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547-1550.
[88] Ide, M.; Yauchi, Y.; Iwasawa, T. *Eur. J. Org. Chem.* **2014**, *15*, 3262-3267.
[89] Zhu, G.; Chen, D.; Wang, Y.; Zheng, R. *Chem. Commun.* **2012**, *48*, 5796-5798.

Buchwald,[90] which gave the desired enamide **48c** in low yield (8%) with recovery of the starting materials (Scheme 2.21, bottom). Although the yield of **48c** was not satisfactory, we still isolated enough of the desired β-bromoenamide to test our hypothesis.

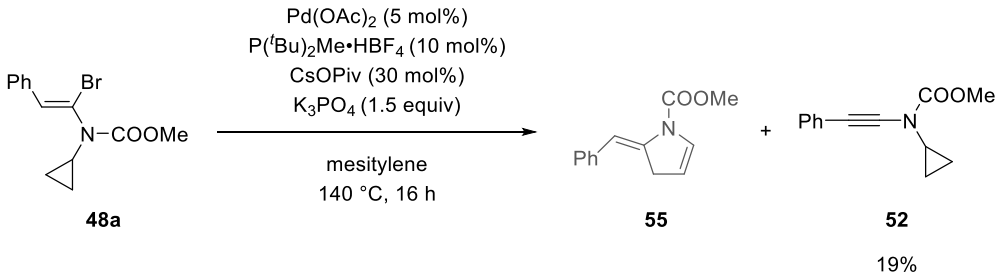


Scheme 2.21: Synthesis of three classes of halo-enamides.

3.1.2 The reactivity of various halo-enamides via palladium catalysis

With all these starting halo-enamides in hand, we next evaluated their reactivity under palladium catalysis. The reactivity of α-bromoenamide **48a** was studied using the Rousseaux's conditions as shown in Scheme 2.22.[64] Complete conversion of **48a** was observed but the only product that could be isolated and characterized was ynamide **52** arising from a base-mediated elimination of the bromine atom. The use of potassium carbonate as the base did not improve the result.

[90] Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667-3669.



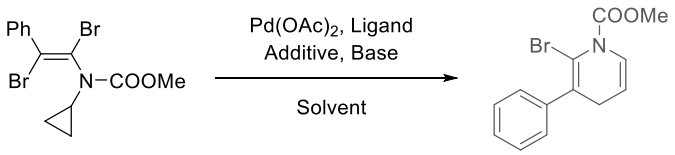
48a **55** **52**

19%

Scheme 2.22: The reactivity of α-bromoenamide via palladium catalysis.

Then the reactivity of α,β-dibromoenamide **48b** was evaluated, with the aim of preparing dihydropyridine **56** (Table 2.1). The standard Rousseaux condition was employed for the first trial, which gave a complex mixture with a complete consumption of the starting enamide **48b** (entry 1). Switching to cesium pivalate as additive and potassium phosphate as base did not affect the reaction outcome (entry 2), while the use of steric bulky ligand $P^tBu_2Me{\cdot}HBF_4$ at 110 °C and 140 °C also led to complex mixture (entries 3-4). Employing stronger bases or polar solvents gave no better results (entries 5-6). Despite all these efforts, no desired cyclized product was generated.

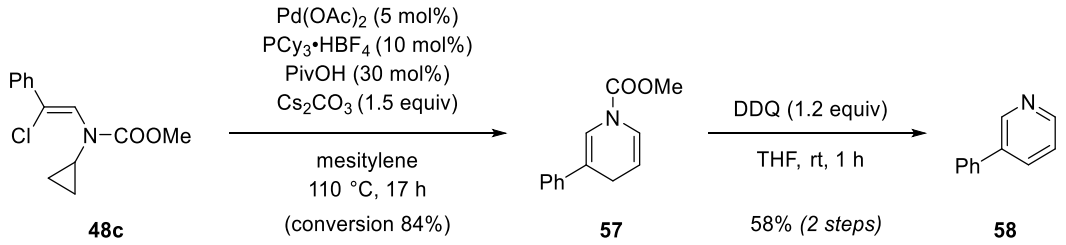
Table 2.1: The reactivity of α,β-dibromoenamide via palladium catalysis.



48b **56**

Entry	Ligand	Additive	Base	Solvent	Temperature	Results
1	$PCy_3{\cdot}HBF_4$	PivOH	Cs_2CO_3	mesitylene	110-140 °C	mixture
2	$PCy_3{\cdot}HBF_4$	CsOPiv	K_3PO_4	mesitylene	110-140 °C	mixture
3	$P^tBu_2Me{\cdot}HBF_4$	CsOPiv	K_3PO_4	mesitylene	110 °C	mixture
4	$P^tBu_2Me{\cdot}HBF_4$	CsOPiv	K_3PO_4	mesitylene	140 °C	mixture
5	$P^tBu_2Me{\cdot}HBF_4$	CsOPiv	Cs_2CO_3	mesitylene	110-140 °C	mixture
6	$P^tBu_2Me{\cdot}HBF_4$	CsOPiv	Cs_2CO_3	DMF	110-140 °C	mixture

Finally, and much to our delight, when we evaluated the reactivity of β-chloroenamide **48c** with a combination of palladium acetate, $PCy_3{\cdot}HBF_4$, pivalic acid and cesium carbonate in mesitylene at 110 °C for 17 hours, the desired 1,4-dihydropyridine **57** could be detected. After subsequent oxidation with DDQ at room temperature, the desired pyridine product **58** could be isolated in 58% yield together with 16% of starting enamide **48c** (Scheme 2.23). The partial conversion was due to the low reactivity of **48c**, in which the carbon-chloride bond was not as reactive as carbon-bromide bond towards oxidative addition.



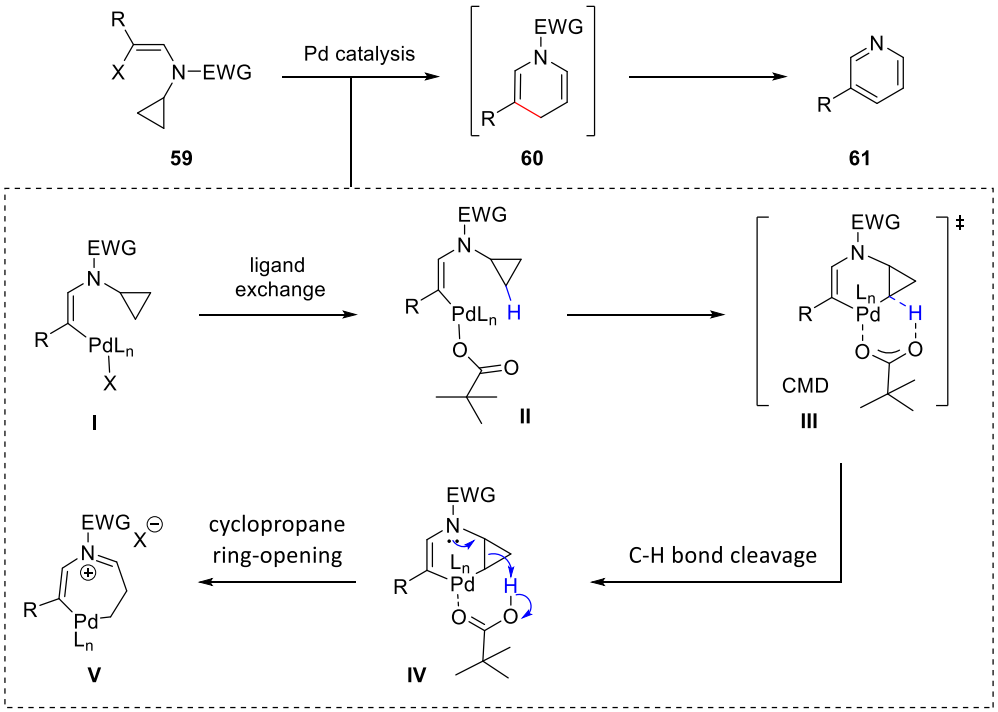
Scheme 2.23: Palladium catalyzed cyclization of β-chloroenamide.

After screening the three classes of starting halo-enamides, we realized that β-haloenamide was the most promising substrate for the palladium catalyzed intramolecular cyclization. Thus, we next focus on the synthesis and palladium catalyzed transformation of β-haloenamides, which is described in the next section.

3.2 Palladium catalyzed cyclization of β-bromoenamides

Depending on the mechanisms proposed in the previous publications, as shown in Scheme 2.24 we envisioned that the cyclopropyl enamide **59** would readily undergo oxidative addition with *in situ* generated palladium(0) species to provide intermediate **I**, which would undergo ligand exchange to generate intermediate **II**. The secondary C(sp^3)-H bond of cyclopropane ring would then be activated via CMD transition-state **III**, which would be promoted by the additive to form intermediate **IV**, then the cyclopropane would ring open to generate palladacycle **V**. After deprotonation and reductive elimination, the desired 1,4-dihydropyridine compound **60** would be obtained. According to the previous publication,[91] the product **60** has a limited stability towards oxidative conditions (even exposure to air) and is therefore difficult to isolate. So we opted for an *in situ* oxidation that would give the final pyridine derivative **61**.

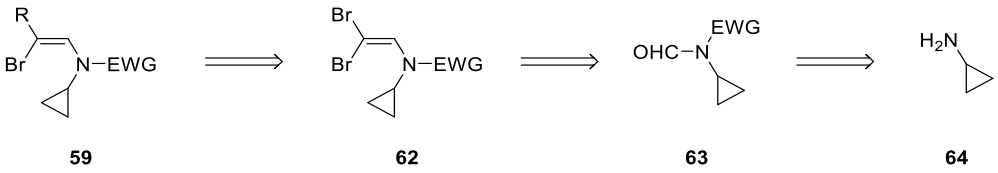
[91] Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc.* **2012**, *134*, 9078-9081.



Scheme 2.24: Palladium catalyzed intramolecular C-H alkenylation of cyclopropyl enamides.

3.2.1 Second synthetic strategy for the preparation of β-bromoenamides

Considering that the current synthetic method generated the starting enamide in low yield, we next focused on developing a more efficient synthetic sequence to access β-bromoenamides. As illustrated in Scheme 2.25, the desired β-bromoenamide **59** could be synthesized from dibromoalkene **62** via transition metal catalyzed cross-coupling with corresponding organoboronic acid, in which product distribution (mono- *vs* bis- Suzuki cross-coupling) could be controlled by the ratio of the reactants. Dibromoalkene **62** could be obtained from formamide **63** by olefination, while commercially available amine **64** could be protected and formylated to give **63**.

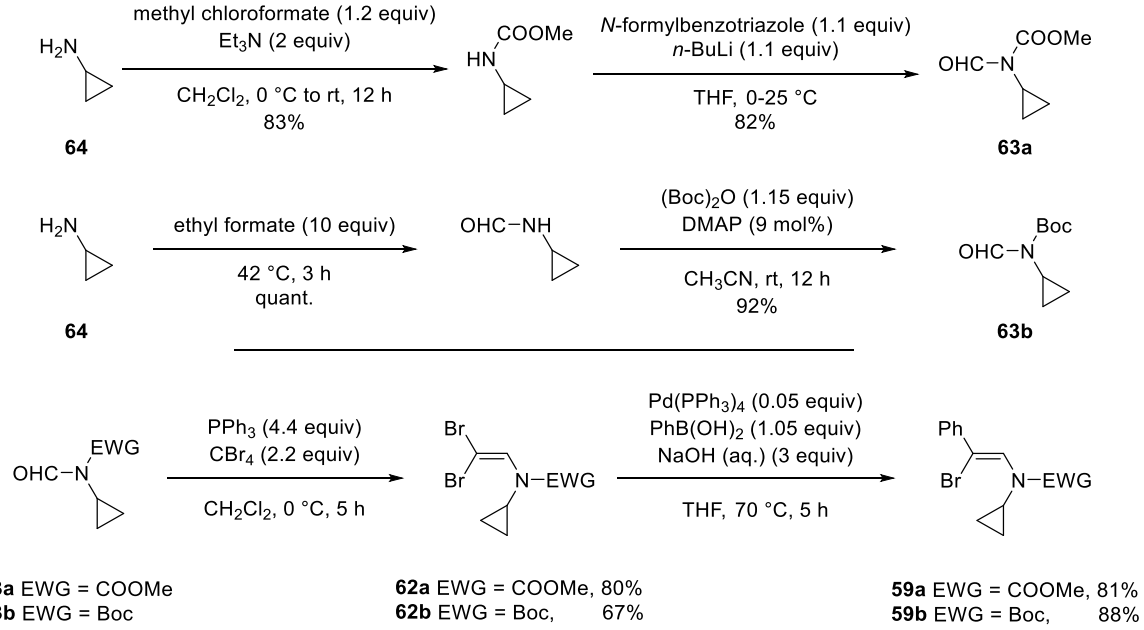


Scheme 2.25: Retrosynthesis of β-bromoenamides.

According to this synthetic plan, we performed the protection and formylation of the nitrogen atom of cyclopropylamine which gave the protected formamide **63a** and **63b** in good yields (Scheme 2.26, top). During the optimization of the formylation process, we noticed that *N*-formylbenzotriazole outperformed other reagents as an efficient and mild formylating reagent.[92] In the case of the synthesis of *N*-Boc substituted formamide **63b**, the order of the formylation step and protection step is reversed as we experimentally found difficult to formylate the *N*-Boc-cyclopropylamine.

[92] Matheson, M.; Pasqua, A. E.; Sewell, A. L.; Marquez, R. *Org. Synth.* **2013**, *90*, 358-366.

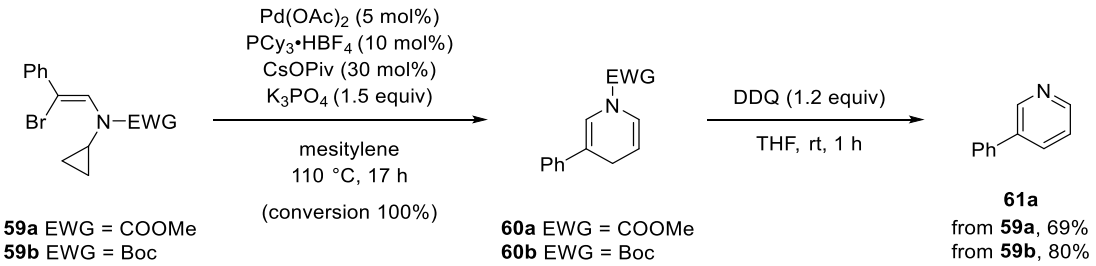
Ramirez olefination of **63a** and **63b** smoothly generated β,β-dibromoenamides **62a** and **62b** in good yields (80% and 67%, respectively) (Scheme 2.26, bottom). **62a** and **62b** were next transformed into the desired β-bromoenamides **59a** and **59b** via Suzuki cross-coupling with phenylboronic acid, the amount of which needs to be strictly controlled, since excess organoboronic acid could react with the *Z*-bromide to form the β,β-disubstituted enamide which is difficult to eliminate by flash chromatography on silica gel.



Scheme 2.26: Second synthetic strategy towards β-bromoenamides.

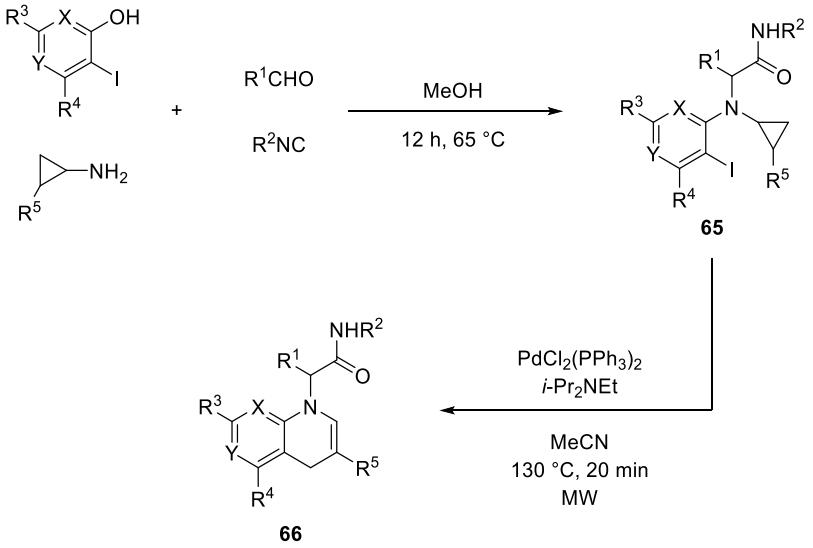
3.2.2 The reactivity of *N*-cyclopropyl-β-bromoenamides via palladium catalysis

With the readily prepared starting enamides in hand, we tested the reactivity of both **59a** and **59b** under the standard Rousseaux conditions, which gave the desired pyridine derivative **61a** after oxidation in 69% and 80% yields respectively with a complete conversion (Scheme 2.27). These results demonstrated the high reactivity of *N*-cyclopropyl-β-bromoenamides towards palladium catalysis and prompted us to further optimize the reaction conditions.



Scheme 2.27: Palladium catalyzed cyclization of β-bromoenamide under the Rousseaux's conditions.

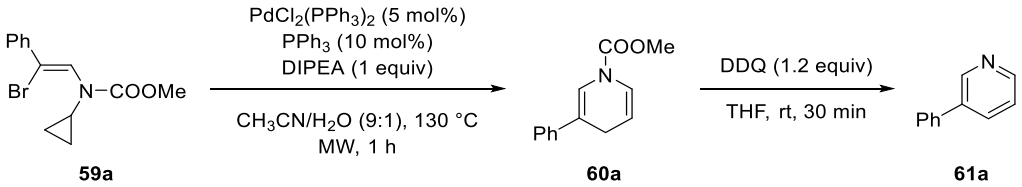
In parallel to this work, we were inspired by the work of El Kaïm and Grimaud,[93] who disclosed a palladium-catalyzed cyclopropane ring-opening/cyclization sequence of **65** itself obtained via a four-component Ugi-Smiles reaction, as shown in Scheme 2.28.



Scheme 2.28: Palladium catalyzed ring opening/cyclization of aminocyclopropyl Ugi adducts reported by El Kaïm and Grimaud.

Interestingly, we noticed that the palladium-catalyzed conditions applied to this cyclization were different from most of the previously reported catalytic systems, as they employed a combination of palladium(II) and tertiary amine in acetonitrile at 130 °C under microwave oven irradiation for only 20 minutes. Obviously, this catalytic system was much more convenient and efficient. Thus, we evaluated the cyclization of *N*-cyclopropyl-β-bromoenamides under these modified conditions; results are listed in Table 2.2.

Table 2.2: Optimization of the conditions.



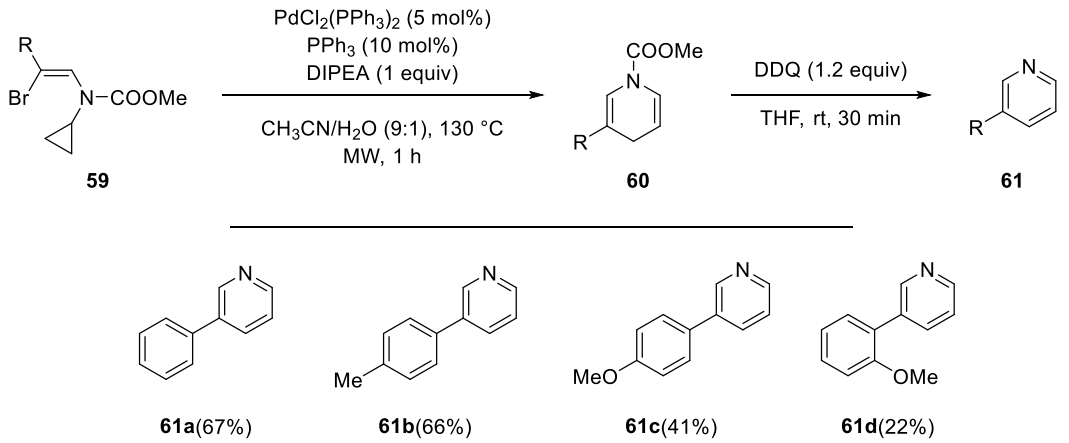
Entry	Modification of the conditions	Yield (%)
1	-	67
2	without PPh_3	14
3	without water	32
4	without microwave, 16 h	55

[93] Dos Santos, A.; El Kaïm, L.; Grimaud, L.; Ramozzi, R. *Synlett* **2012**, *23*, 438-442.

The preliminary optimization showed that the presence of phosphine ligand and water were crucial for this transformation, as they reduce palladium(II) to active palladium(0) species (entries 2-3). This process was supported by kinetic studies,[94] which demonstrated that EtN(*i*Pr)$_2$, water and PPh_3 were reducing agents of the palladium(II). Moreover, the use of microwave oven facilitates this transformation obviously, since the reaction time is reduced under microwave conditions (1 vs 16 h, entry 4).

3.2.3 Preliminary study of the scope

Next, we investigated the scope of the cyclization of *N*-cyclopropyl-β-bromoenamides under the microwave irradiation condition (Scheme 2.29). It could be indicated that electron-donating groups on the aryl motif slightly affected the transformation (**61a**-**c**), as the electron rich substituents would make the oxidative insertion of palladium(0) to C-Br bond more difficult. It was also observed that the enamides substituted with *ortho*-methoxyphenyl group gave lower yield (**61d**), which could be attributed to an increased steric effect.



Scheme 2.29: Preliminary study of the scope.

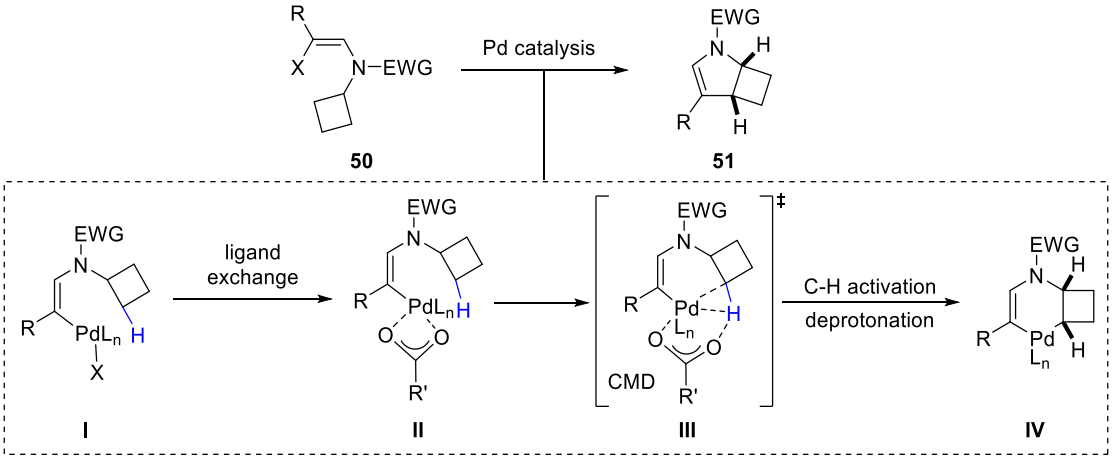
Having demonstrated the cyclization/oxidation of *N*-cyclopropyl-β-bromoenamides into 3-arylated pyridines, we next turned our attention to the corresponding *N*-cyclobutyl series. These results are described in detail in the following section.

4 Palladium catalyzed cyclization of *N*-cyclobutyl-β-bromoenamides and enesulfonamides

We envisioned that *N*-cyclobutyl-β-bromoenamides **50** would react readily with palladium(0) to form intermediate **I**, which would lead to intermediate **II** after ligand exchange. Then the subsequent C-H activation would proceed via an additive assisted CMD transition state **III** to form intermediate **IV**, in which the ring-opening of the cyclobutane ring would not occur because of its low angle strain. After

[94] Amatore, C.; El Kaïm, L.; Grimaud, L.; Jutand, A.; Meignie, A.; Romanov, G. *Eur. J. Org. Chem.* **2014**, *22*, 4709-4713.

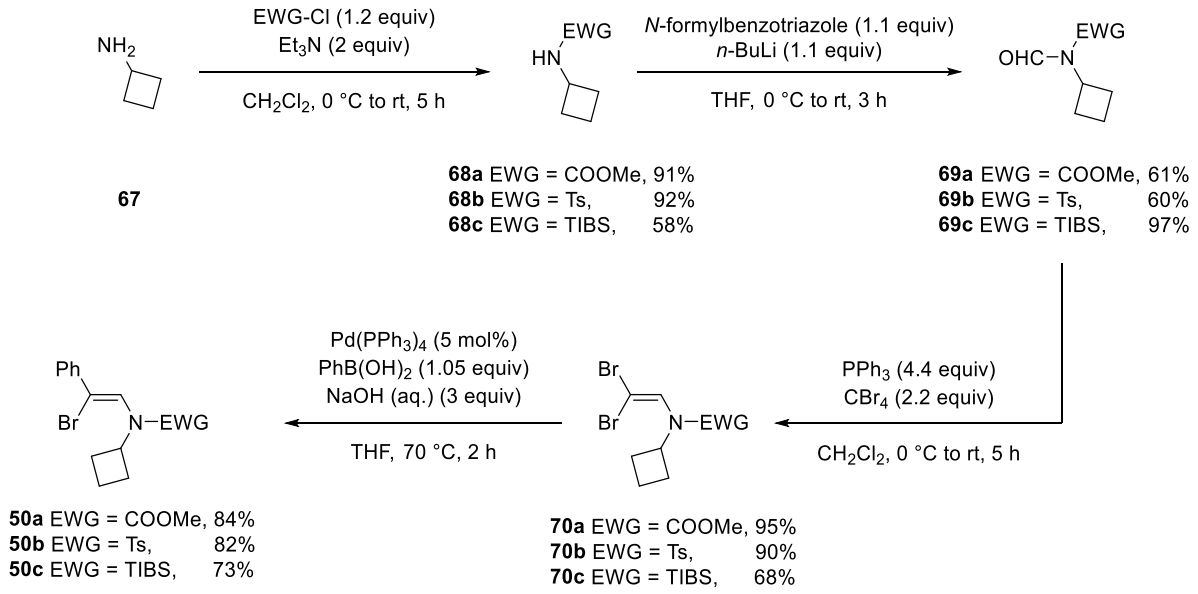
the reductive elimination, a rarely reported cyclobutyl-fused pyrrolidine compound **51** would be generated (Scheme 2.30). To achieve this reaction sequence, the installation of a suitable protecting group of the nitrogen atom is crucial; indeed this protecting group has to fulfill multiple roles such as enhancing the acidity of the secondary hydrogen on the cyclobutyl motif and also facilitates the cyclization reaction by restricting the number of conformations of the *N*-cyclobutyl-β-bromoenamide. A bulky and electron-withdrawing protecting group is therefore a logical choice.



Scheme 2.30: Palladium catalyzed C-H alkenylation of N-cyclobutyl-β-bromoenamides.

4.1 Synthesis of *N*-cyclobutyl-β-bromoenamides and enesulfonamides

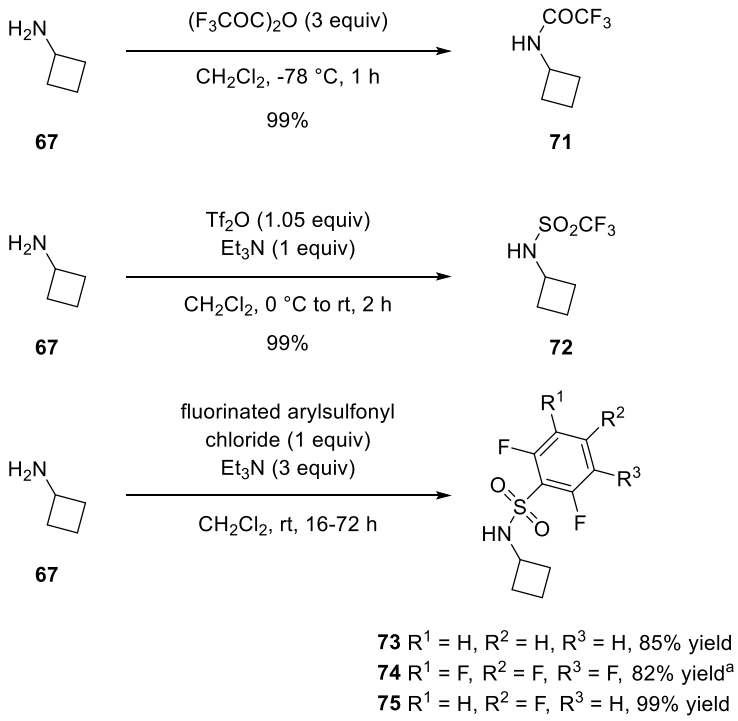
To test the feasibility of our proposal, we first prepared several enamides and enesulfonamides **50a-c**, which were decorated with various nitrogen substituents, including methoxycarbonyl, tosyl and 2,4,6-triisopropylbenzenesulfonyl (TIBS) groups, as shown in Scheme 2.31. Among them, methoxycarbonyl substituent proved to be suitable in previous examples (the cyclization of N-cyclopropyl-β-bromoenamides in last section), which gave the desired cyclized products in good yields with complete conversion. On the other hand, the tosyl group possesses an enhanced electron withdrawing ability (**50b**) and the TIBS group provides additional steric shielding (**50c**), both of which being able to facilitate the C-H activation process. Following the procedure developed in the last section, the synthetic sequence started from cyclobutyl amine **67**, and proceeded through nitrogen protection, formylation, olefination and Suzuki cross-coupling to generate the desired enamide **50a** and enesulfonamides **50b** and **50c** in good yields.



*Scheme 2.31: Synthesis of N-cyclobutyl-β-bromoenamides **50a** and enesulfonamides **50b** and **50c**.*

Keeping in mind that lowering the pKa of the hydrogen atoms of the cyclobutyl unit should favor the palladium-catalyzed C-H activation/cyclization reaction, we next turned our attention to the synthesis of *N*-cyclobutyl-β-bromoenamides and enesulfonamides possessing a strongly electron-withdrawing protecting group on the nitrogen atom, such as trifluoroacetyl, trifluoromethanesulfonyl and polyfluorinated benzenesulfonyl groups.

Trifluoroacetylation of cyclobutylamine **67** under classical conditions led to quantitative yield of the desired amide **71** (Scheme 2.32, top). Triflation of **67** using triethylamine in dichloromethane led to **72** also in quantitative yield. Finally, three different fluorinated arylsulfonyl groups were introduced on cyclobutylamine **67**: the 2,6-difluoro, the 2,3,4,5,6-pentafluoro and the 2,4,6-trifluoro. The corresponding sulfonamides **73**, **74** and **75** were obtained in good to excellent yields (85, 82 and 99% respectively).



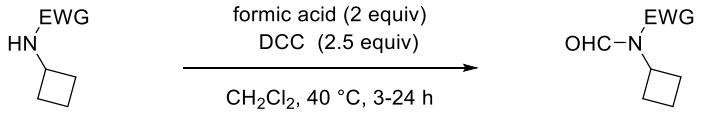
73 R^1 = H, R^2 = H, R^3 = H, 85% yield
74 R^1 = F, R^2 = F, R^3 = F, 82% yield[a]
75 R^1 = H, R^2 = F, R^3 = H, 99% yield

[a] 4 equiv. of DIPEA was used as base.

*Scheme 2.32: Synthesis of N-cyclobutyl amide **71** and sulfonamides **72-75**.*

Having in hand these five protected cyclobutylamines, we performed the formylation with *N*-formylbenzotriazole and *n*-butyllithium by analogy with the previous substrates (Scheme 2.31). Quite surprisingly, the reactions were inefficient, forcing us to switch to a second set of conditions. After a screening of the formylation conditions, we found that **72-75** could react with formic acid and DCC to generate the desired formamides **76-79** in low to excellent yields (Scheme 2.33).[95] It is worth to mention that for the formation of **75**, the addition of a catalytic amount of DMAP could increase the yield from 45% to 61% with a complete consumption of the starting sulfonamide **75**. However, this enhancement of yield using nucleophilic catalysis does not hold true for all the substrates (e.g. **73** to **77**, 26% yield). Finally, the formylation of trifluoroacetyl amide **71** failed under these two sets of conditions; we also evaluated the reverse sequence of reactions (formylation then trifluoroacetylation) but the trifluoroacetylation proved to be very difficult, leading us to discard this type of protecting group.

[95] (a) Bruckner, D. *Synlett* **2000**, *10*, 1402-1404. (b) Couty, S.; Barbazanges, M.; Meyer, C.; Cossy, J. *Synlett* **2005**, *6*, 905-910. (c) Bruckner, D. *Tetrahedron* **2006**, *62*, 3809-3814.



72 EWG = trifluoromethanesulfonyl
73 EWG = 2,6-difluorobenzenesulfonyl
74 EWG = pentafluorobenzenesulfonyl
75 EWG = 2,4,6-trifluorobenzenesulfonyl

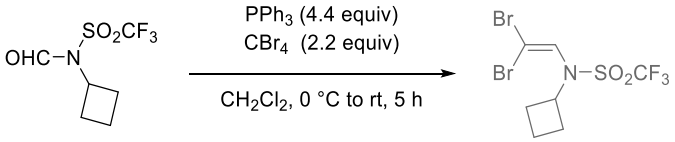
76 EWG = trifluoromethanesulfonyl, 82% yield
77 EWG = 2,6-difluorobenzenesulfonyl, 26% yield[a]
78 EWG = pentafluorobenzenesulfonyl, 82% yield
79 EWG = 2,4,6-trifluorobenzenesulfonyl, 61% yield[a]

[a] 0.36 equiv of DMAP was added.

*Scheme 2.33: Formylation reactions of sulfonamides **72-75**.*

With formamides **76-79** in hand, we then investigated the Ramirez olefination. As illustrated in Table 2.3, the transformation of formamide **76** under the most commonly employed conditions gave no conversion (entries 1-2), while increasing the reaction temperature (entry 3) or moving to electron-rich phosphite reagent (entry 4) had no positive impact on the reaction outcome. Then we tried to use a modified version that employed zinc as a reducing agent and a reduced stoichiometry of triphenylphosphine,[96] however these trials also failed to give the desired product (entries 5-6). Based on the work of Marquez's group,[97] we prepared (bromomethyl)-triphenylphosphonium bromide which is an alternative reagent to smoothly generate the desired dibromophosphonium ylide. The latter was reported to react with *N*-formylimides, thus leading to various β,β-dibromo-enamides. However, these conditions were once again unsuccessful (entry 7). Unluckily, all these trials provided no positive results. These Ramirez olefination studies were also conducted on formamide **78** without success.

Table 2.3: Optimization of the olefination conditions.

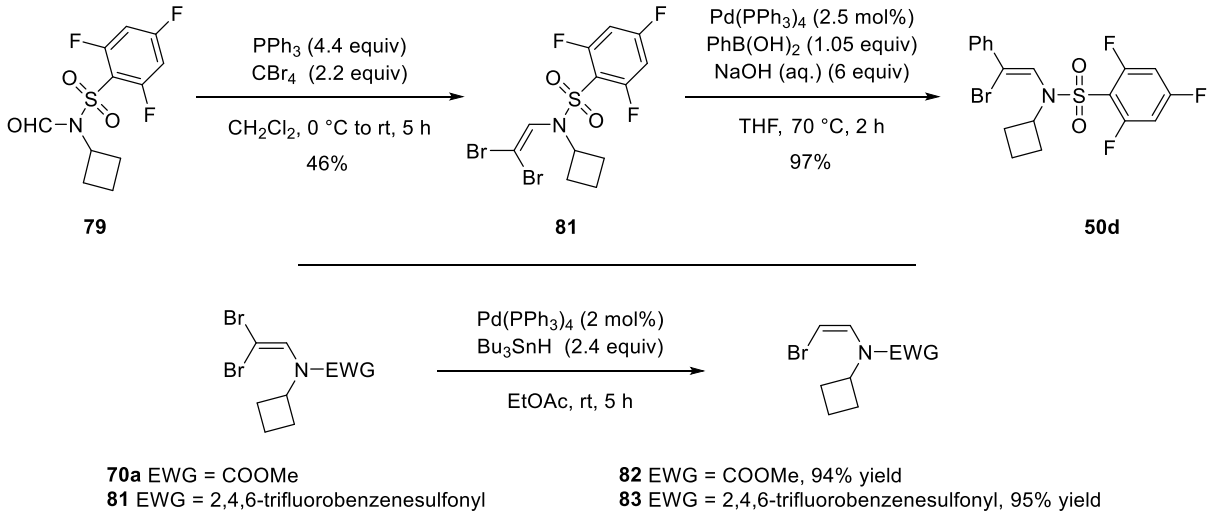


76 **80**

Entry	Conditions	Yield (%)
1	PPh_3 (4.4 equiv), CBr_4 (2.2 equiv), CH_2Cl_2, rt, 0.5 h	0
2	PPh_3 (4.4 equiv), CCl_4 (2.2 equiv), THF, rt to 60 °C, 0.5 h	0
3	PPh_3 (4.4 equiv), CBr_4 (2.2 equiv), THF, 40-60 °C, 0.5 h	0
4	$P(OiPr)_3$ (2 equiv), CBr_4 (1.5 equiv), CH_2Cl_2, rt, 12 h	0
5	PPh_3 (2 equiv), CBr_4 (2 equiv), Zn (2 equiv), CH_2Cl_2, 0 °C to rt, 3 h	0
6	PPh_3 (3 equiv), CBr_4 (3 equiv), Zn (3 equiv), CH_2Cl_2, 0 °C to rt, 3 h	0
7	$Ph_3P^+CH_2BrBr^-$ (10 equiv), *t*-BuOK (10 equiv), THF, 40 °C, 16 h	0

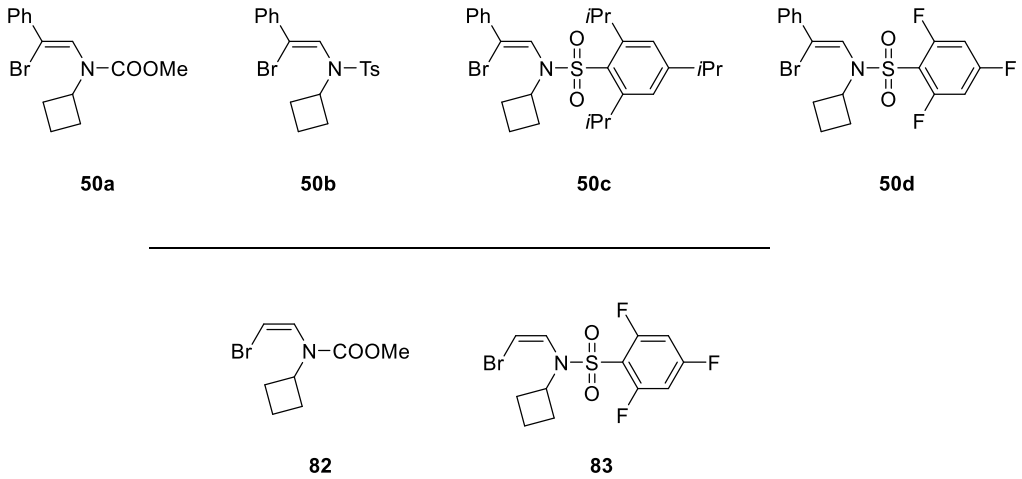
[96] Heravi, M. M.; Asadi, S.; Nazari, N.; Lashkariani, B. M. *Curr. Org. Chem.* **2015**, *19*, 2196-2219.
[97] Pasqua, A. E.; Crawford, J. J.; Long, D.-L.; Marquez, R. *J. Org. Chem.* **2012**, *77*, 2149-2158.

Finally, to our delight, the olefination of 2,4,6-trifluorobenzenesulfonyl formamide **79** proceeded well. Indeed, the reaction of **79** with the Marquez phosphonium salt ($Ph_3P^+CH_2Br$, Br^-, 5 equiv) and *t*-BuOK (5 equiv) did afford the desired dibromoenesulfonamide **81** in moderate yield (50%) with complete conversion. It was also found that the classical Ramirez conditions could give similar yield (46%) with a more practical protocol as shown in Scheme 2.34 (top). Next, compound **81** was successfully converted to β-bromoenesulfonamide **50d** via Suzuki cross-coupling. It should be mentioned here that slightly revised reaction conditions were required to avoid the formation of β,β-disubstituted enesulfonamide as byproduct. It was found that using a smaller amount of the palladium catalyst (from 5 mol% to 2.5 mol%) and a two-fold increase in the amount of the base (from 3 equiv to 6 equiv) led to excellent yield (97% vs 56%). In addition, we also performed mono-debromination reactions of β,β-dibromoenamide **70a** and enesulfonamide **81** using tributyltin hydride and Pd(0),[95] which generated β-bromoenamides **82** and enesulfonamide **83** in good yields (Scheme 2.34, bottom).



*Scheme 2.34: Synthesis of N-cyclobutyl-β-bromoenecarbamate **82** and N-cyclobutyl-β-bromoenesulfonamides **50d** and **83**.*

Overall, we obtained a collection of *N*-cyclobutyl-β-bromoenamides and enesulfonamides **50a-d** and β-bromoenamides and enesulfonamides **82** and **83**, ready to be evaluated in the palladium-catalyzed C-H activation/cyclization (Scheme 2.35). The results of these studies are discussed in the next section.



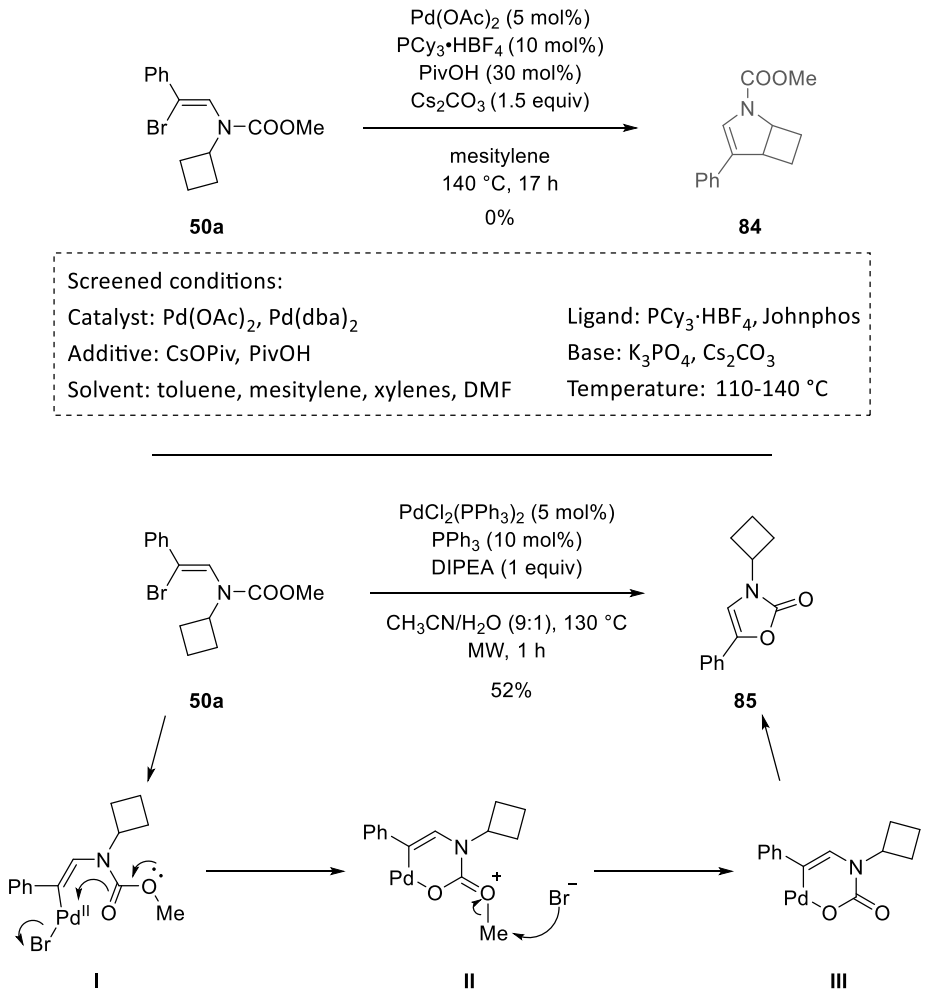
*Scheme 2.35: N-cyclobutyl-β-bromoenamides **50a** and **82** and N-cyclobutyl- β-bromoenesulfonamides **50b-d** and **83**.*

4.2 Studies of the palladium-catalyzed C-H activation/cyclization reactions of *N*-cyclobutyl-β-bromoenamides and sulfonamides

To evaluate our research hypothesis, we performed the palladium-catalyzed C-H activation/cyclization of enamide (**50a** and **82)** and enesulfonamides (**50b-d** and **83**) under both the Rousseaux's conditions (Conditions **A**) and the El Kaïm/Grimaud conditions (Conditions **B**), the results are reported in Schemes 2.36-2.40.

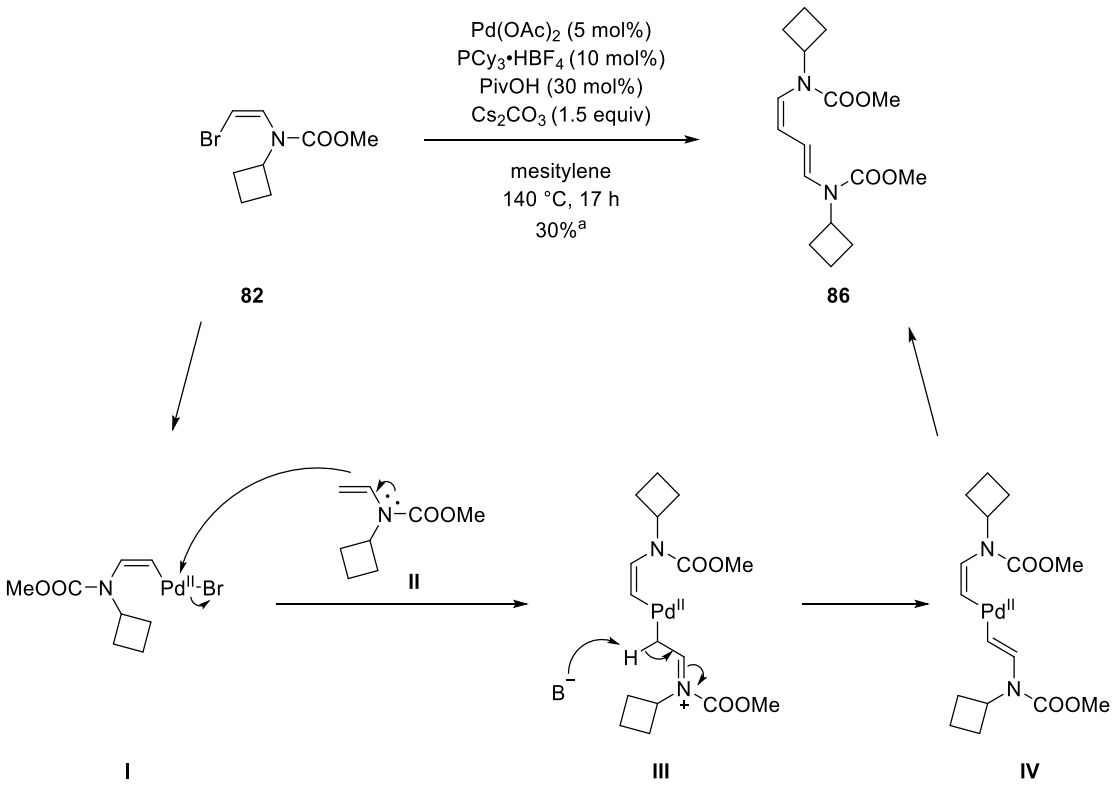
We first focused on *N*-cyclobutyl-β-bromoenamide **50a**, whose nitrogen atom is protected by methoxycarbonyl group. Under Rousseaux conditions ($Pd(OAc)_2$ (5 mol%), $PCy_3{\cdot}HBF_4$ (10 mol%), PivOH (30 mol%), Cs_2CO_3 (1.5 equiv), mesitylene, 110 °C, 17 h), only a complex mixture was obtained (Scheme 2.36, top). While switching to $Pd(dba)_2$ as catalyst, CsOPiv or silver salt as additive, or Johnphos as ligand led to no conversion or a complex mixture, and the use of several other solvents such as toluene, mesitylene, xylenes and DMF at higher temperature (130-160 °C) also had no positive impact on the reaction outcome.

In comparison, the reaction of **50a** under conditions **B** ($PdCl_2(PPh_3)_2$ (5 mol%), PPh_3 (10 mol%), DIPEA (1.5 equiv), CH_3CN/H_2O, 130 °C, microwave oven, 1 h) proceeded smoothly to generate 3-cyclobutyl-5-phenyloxazol-2(3*H*)-one **85** as the only isolated product in 52% yield (Scheme 2.36, bottom). The latter is formed by the oxidative insertion of Pd(0) to the carbon-bromide bond, nucleophilic attack of the carbamate onto the Pd(II) intermediate **I** followed by reductive elimination.



*Scheme 2.36: Palladium catalyzed cyclization of N-cyclobutyl-β-bromoenamide **50a**.*

In the same series, the reactivity of **82** was studied. The absence of the *E*-phenyl group in the β position of this enamide should lead to a more flexible substrate which could potentially lead to a more efficient CMD step. However, this did not turn out to be the case since only the protected butan-1,3-diene-1,4-diamine **86** was obtained in low to moderate yields under conditions **A** (30%) or **B** (5%) (Scheme 2.37). Compound **86** might arise from the nucleophilic attack of the Pd(II) intermediate **I** by the protodebrominated enamide **II**, followed by reductive elimination and prototropy.

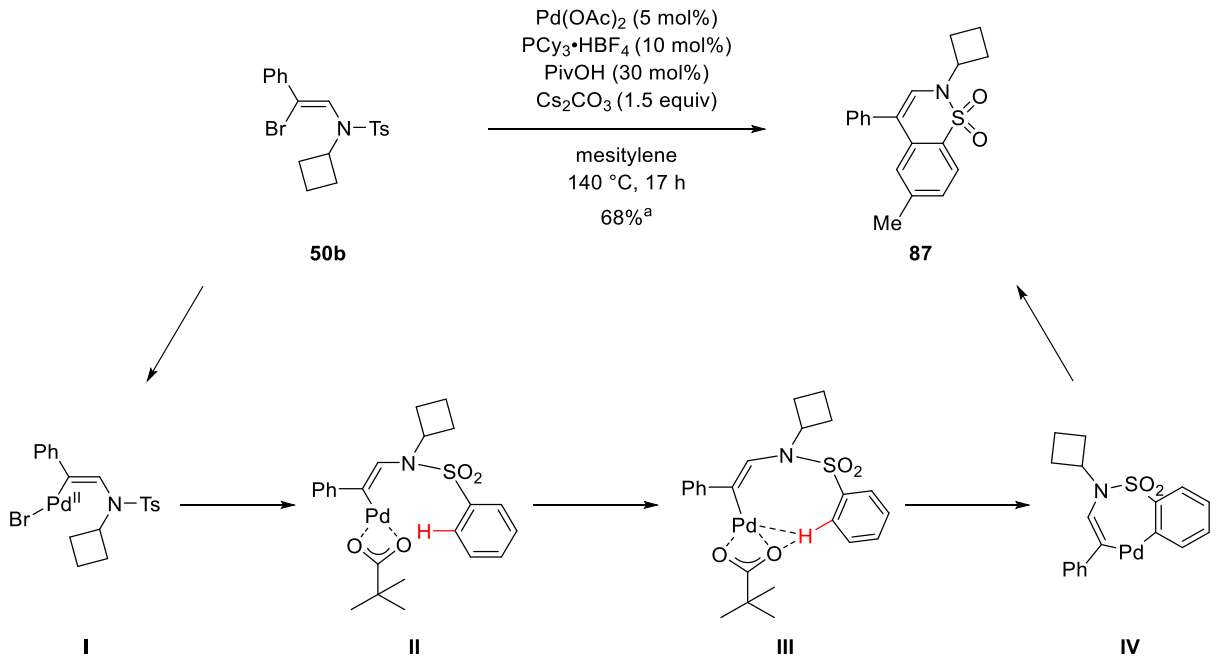


[a] Conditions **B** gave 5% yield of compound **86**.

*Scheme 2.37: Palladium catalyzed cyclization of N-cyclobutyl-β-bromoenamide **82**.*

The screening of substrates continued with the reaction of **50b** whose nitrogen atom is protected as a tosyl group (Scheme 2.38). 2*H*-Benzo[*e*][1,2]thiazine 1,1-dioxide **87** was cleanly obtained in 68% yield under conditions **A**. This compound arises from the oxidative insertion of Pd(0) to the carbon-bromide bond, ligand exchange with the pivalate and CMD of the aromatic hydrogen atom in red. A last step of reductive elimination of the palladacycle **IV** led to the observed compound. This type of reactivity under palladium catalysis has already been reported in the literature.[98] Under conditions **B**, only a complex mixture was obtained. From these experiments, it appears that the aromatic sulfonamide must be substituted in the 2,6-positions to prevent the CMD step. We thus chose to study the reactivity of **50c**, whose nitrogen atom is substituted by a 2,4,6-triisopropylphenylsulfonyl group.

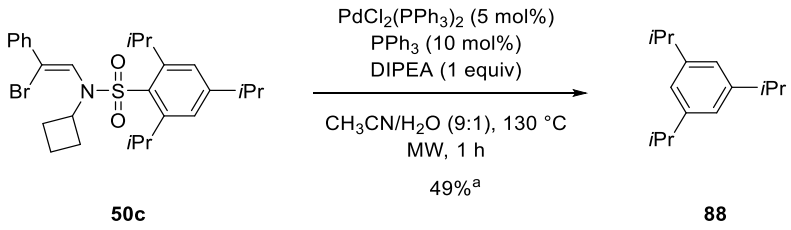
[98] (a) Huang, R. Y. ; Franke, P. T. ; Nicolaus, N. ; Lautens, M. *Tetrahedron* **2013**, *69*, 4395-4402. (b) Rocaboy, R.; Dailler, D.; Baudoin O. *Org. Lett.* **2018**, *20*, 772-775.



[a] Conditions **B** gave a complex mixture

*Scheme 2.38: Palladium catalyzed cyclization of N-cyclobutyl-β-bromoenesulfonamide **50b**.*

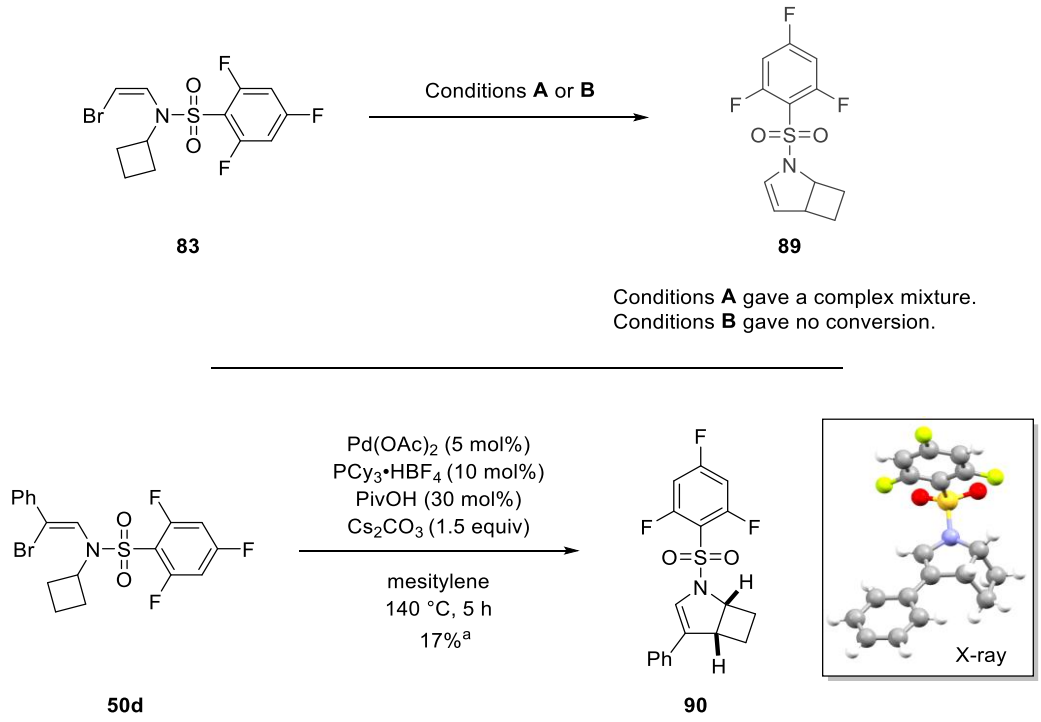
As depicted in Scheme 2.39, the reaction of **50c** under conditions **A** did not lead to any identifiable products. Under conditions **B**, only 1,3,5-triisopropylbenzene **88** could be detected in the crude reaction mixture, accompanied with strong sulfur dioxide vapors indicating decomposition of enesulfonamide **50c**.



[a] Conditions **A** gave a complex mixture.

*Scheme 2.39: Palladium catalyzed cyclization of N-cyclobutyl-β-bromoenesulfonamide **50c**.*

Finally, the reactivity of the *N*-cyclobutyl-β-bromoenesulfonamides **83** and **50d** whose nitrogen atoms are protected with a 2,4,6-trifluorobenzenesulfonyl substituent was studied (Scheme 2.40). Compound **83** did not lead to any productive results since a complex mixture was obtained under conditions **A** and no reaction occurred under conditions **B**. Finally, compound **50d** was studied and led also to a complex mixture under conditions **B**. Quite gratifyingly, under Rousseaux conditions we were able to isolate 17% of the desired C-H activation/cyclization product **90**, with complete conversion of the starting material. The structure of this protected 4-phenyl-2-azabicyclo[3.2.0]hept-3-ene was determined by extensive NMR experiments (1D and 2D) as well as X-ray crystallography studies.

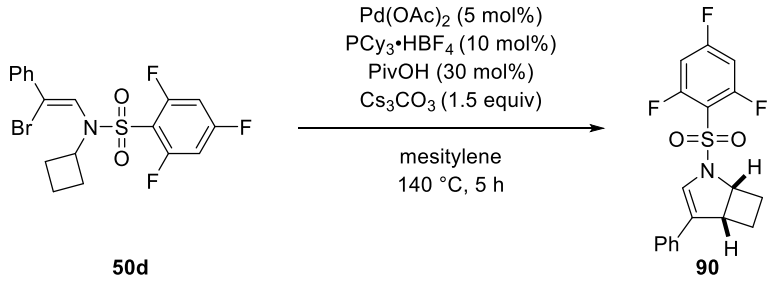


*Scheme 2.40: Palladium catalyzed cyclization of N-cyclobutyl-β-bromoenesulfonamide **83** and **50d**.*

Based on this exciting result, we briefly screened some variations of the reaction conditions that are summarized in Table 2.4. Switching from palladium acetate to $Pd(dba)_2$ shut down the conversion, quite surprisingly (entry 1). A more bulky ligand, such as $P(^tBu)_2Me$ instead of PCy_3 led to a slight increase in yield (19% vs 17%, entry 3). The nature of the carboxylic acid was also evaluated and it was found that 1-adamantanecarboxylic acid offered a decreased yield (10%, entry 4). Finally, silver carbonate was used as a halide abstractor (Ag^+) and a base (CO_3^{2-}), delivering a similar yield of 16% (entry 5).

Overall, these results demonstrate that it is indeed possible to perform a C-H activation/cyclization in the challenging context of a β-haloenesulfonamide possessing a *N*-cyclobutyl motif. This reaction is currently under optimization as many parameters need to be evaluated, such as different catalytic systems (especially the nature of the ligand), bases, solvents,… Control experiments are also underway, in order to shed light on the mechanism of this transformation. Preliminary studies indicate that both starting material **50d** and product **90** are stable in mesitylene at 140 °C for 17 h.

*Table 2.4: Optimization of the palladium catalyzed cyclization of N-cyclobutyl-β-bromoenesulfonamide **50d**.*



50d **90**

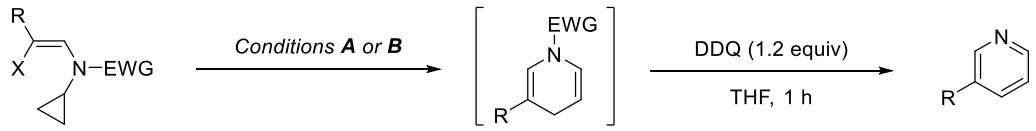
Entry	Modification of the conditions	Result
1	-	17[a]
2	$Pd(dba)_2$ instead of $Pd(OAc)_2$	0
3	$P(^tBu)_2Me{\cdot}HBF_4$ instead of $PCy_3{\cdot}HBF_4$	19[b]
4	$AdCO_2H$ instead of PivOH	10[b]
5	Ag_2CO_3 instead of PivOH	16[b]

[a] Isolated yield. [b] NMR yield.

5 Conclusion and perspectives

Herein, we disclosed a palladium catalyzed cyclization of cyclopropyl β-haloenamides **59**, which proceeded through an intramolecular C-H alkenylation/cyclopropane ring-opening sequence, allowing the synthesis of 1,4-dihydropyridine and pyridine derivatives **60** and **61** (Scheme 2.41, top). This protocol employed enamides as substrates, which was rarely reported before, and a unique microwave irradiation condition had also proved to be efficient for this transformation, which was more economic and convenient in comparison to the commonly employed catalytic systems.

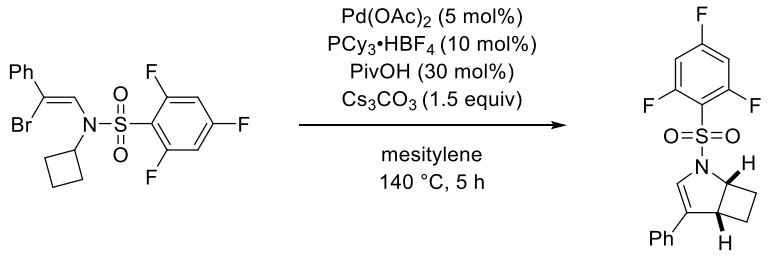
More interestingly, a palladium catalyzed cyclization of cyclobutyl β-haloenesulfonamides **50d** proved to be feasible, after screening a variety of enamides and enesulfonamides (Scheme 2.41, bottom). Further optimization of the conditions will be performed in our group and we also plan to achieve an enantioselective version of this cyclization, which would focus on the employment of suitable chiral phosphine ligands. This protocol will provide direct and versatile access to chiral cyclobutyl-fused nitrogen heterocyclic scaffolds, which is a challenging target in synthetic chemistry and has never been achieved using this strategy.



59 **60** **61**

Conditions ***A***: $Pd(OAc)_2$ (5 mol%), $PCy_3 \cdot HBF_4$ (10 mol%), K_3PO_4 (1.5 equiv.), CsOPiv (10 mol%), mesitylene, 110 °C, 17 h;

Conditions ***B***: $PdCl_2(PPh_3)_2$ (5 mol%), PPh_3 (10 mol%), DIPEA (1.5 equiv.), CH_3CN/H_2O, 130 °C, microwave oven, 1 h.



50d **90**

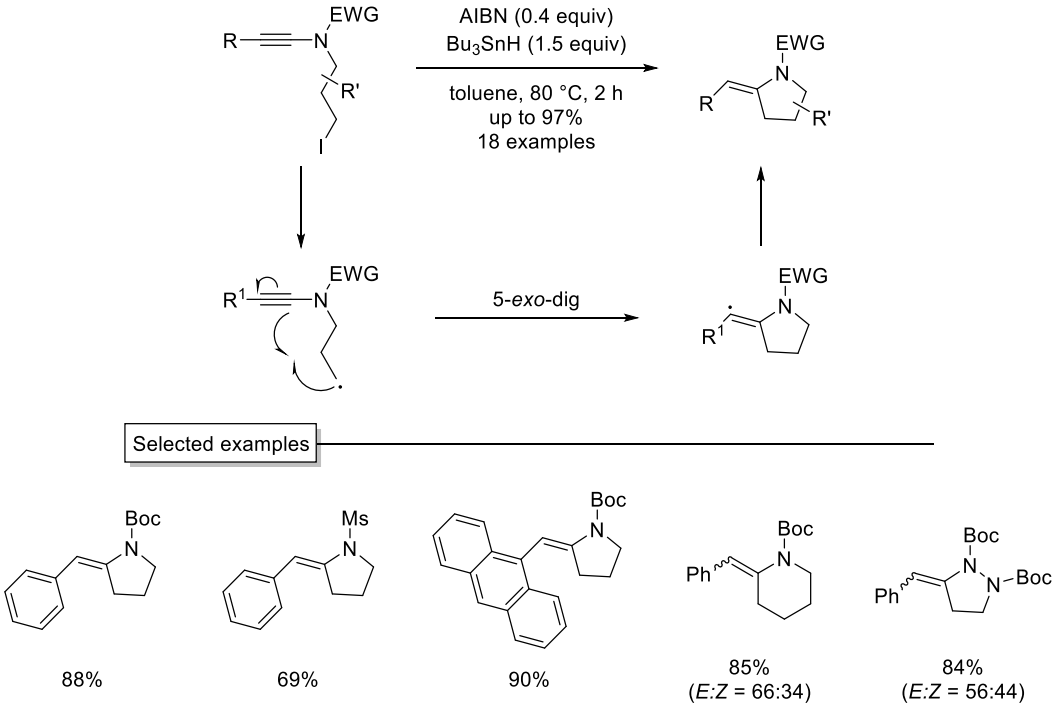
Scheme 2.41: Palladium catalyzed cyclization of cyclopropyl enamides and cyclobutyl enesulfonamides.

General conclusion

This thesis has mainly focused on the development of new methods towards the synthesis of highly valuable *N*-containing heterocycles starting from either ynamides or their enamides analogue, in which a radical-mediated intramolecular cyclization of ynamides was eventually developed for the synthesis of a series of nitrogen-containing heterocycles. Moreover, by using both *N*-cyclopropyl and *N*-cyclobutyl enamides as substrates, two palladium catalyzed intramolecular cyclizations were accomplished to give the corresponding 1,4-dihydropyridines and cyclobutyl-fused pyrrolidines, respectively. The latter not only possesses theoretical significance, but also provides new routes to a variety of nitrogen heterocyclic compounds that are valuable building blocks in medicinal chemistry.

- ***Radical cyclization of ynamides***

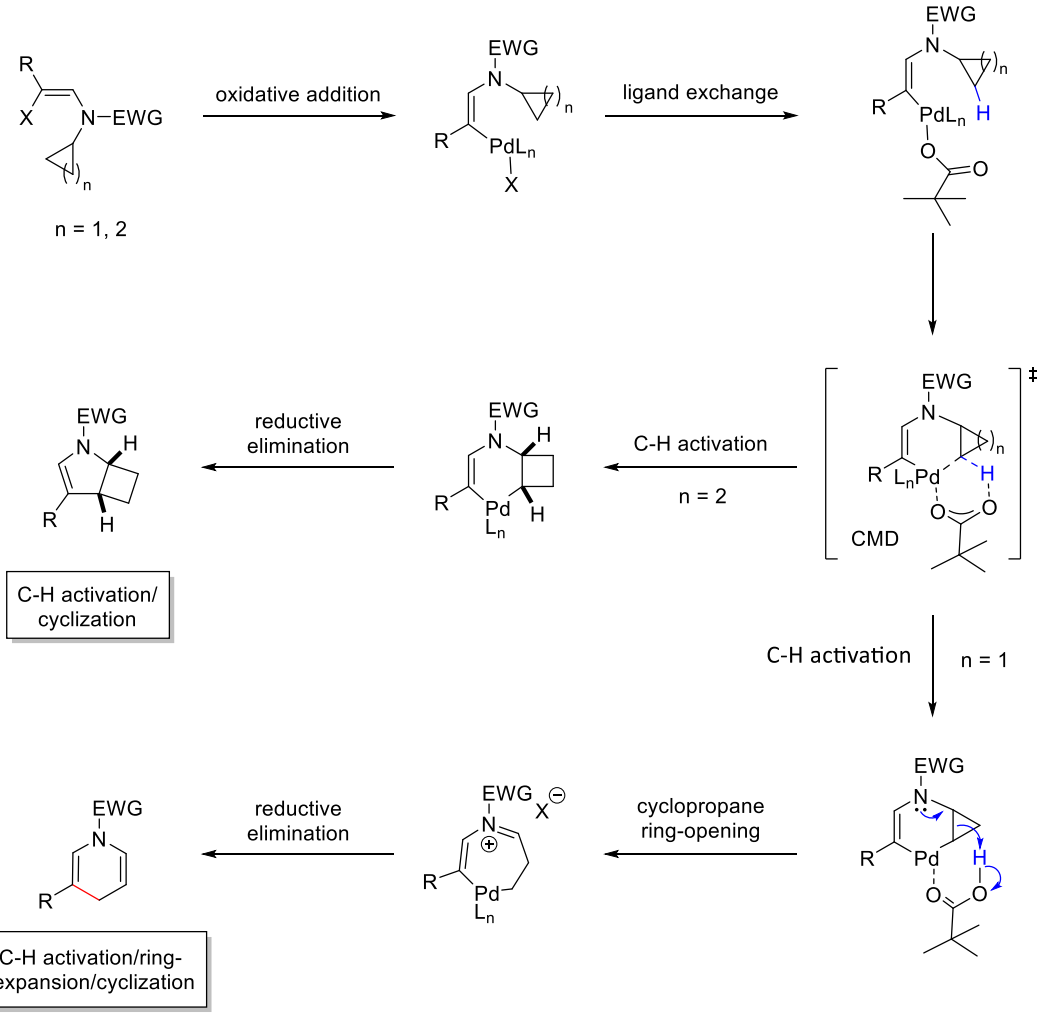
We have successfully developed an efficient and general radical cyclization of ynamides, which provides an access to a variety of nitrogen heterocycles, such as pyrrolidine, piperidine, azepane, pyrazolidine and hexahydropyridazine derivatives in good to excellent yields with high stereoselectivity. This method not only further highlighted the efficiency of ynamide derivatives as versatile building blocks in radical transformations, but also provided a rapid pathway for the construction of nitrogen heterocyclic scaffolds. Moreover, the cyclized products also proved to be versatile and highly valuable synthetic intermediates as shown in downstream reactions, such as hydrogenation, electrophilic addition, epoxidation and cyclopropanation. Further developments could focus on the application of this method to the total synthesis of natural products and/or the integration of the process into new radical cascades.



- ***Palladium catalyzed cyclization of N-cyclopropyl and N-cyclobutyl enamides***

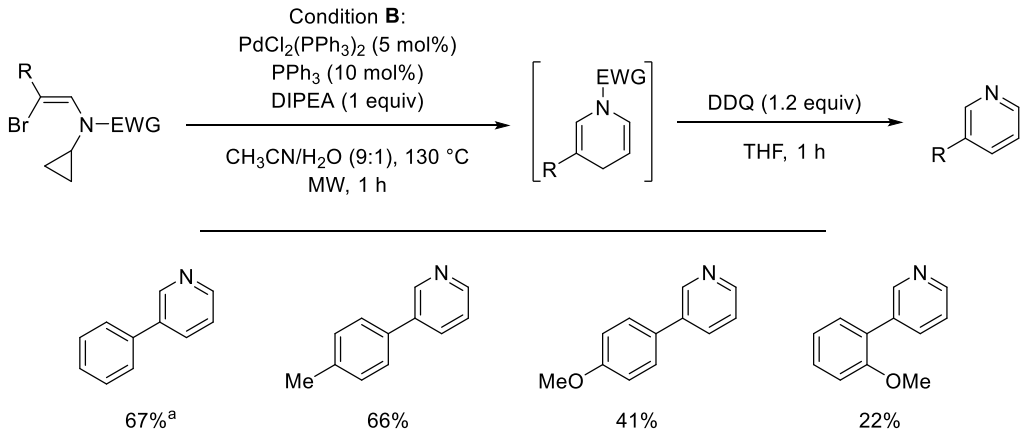
Encouraged by the success of the radical-mediated intramolecular cyclization of ynamides, we next switched our attention to the exploration of the palladium catalyzed intramolecular cyclization of cyclopropyl and cyclobutyl enamides, which was expected to proceed through a rarely reported intramolecular secondary C(sp^3)-H alkenylation of cyclopropane or cyclobutane ring. From a mechanistic point of view, the vinyl bromide motif first undergoes an oxidative addition by Pd(0), which is followed by a rapid ligand exchange and a concerted-metallation deprotonation (CMD) C-H activation sequence to give a common intermediate for both cyclopropyl-substituted and cyclobutyl-substituted enamides. In the case of cyclopropyl-substituted enamide, the intermediate undergoes ring-opening driven by its strong angle strain followed by a reductive elimination step to give the corresponding 1,4-dihydropyridine products. In comparison, the *N*-cyclobutyl enamide leads to a palladacycle that delivers 2-azabicyclo[3.2.0]hept-3-enes after reductive elimination.

After screening various substituted halo-enamides, we found that β-bromoenamides were suitable substrates for this transformation, and a reliable synthetic sequence had been developed to access the starting β-bromoenamides. This sequence involved protection of the amine, formylation, olefination and Suzuki cross-coupling.



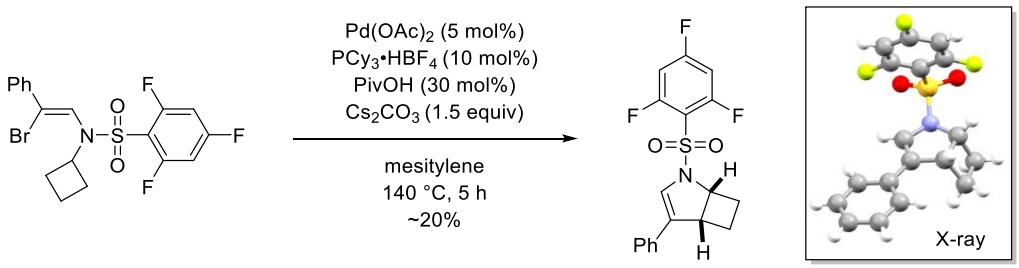
The intramolecular cyclization of cyclopropyl enamides was first developed, in which the cyclopropane was expanded to form a more stable six-membered nitrogen heterocycle involving a Pd-

catalyzed C-H activation/cyclopropane ring-opening sequence as key steps. To our delight, this transformation could be equally well realized by using two conditions, among which conditions **A** (Rousseaux's conditions) had been better explored employing the inorganic base and additive, while conditions **B** (El Kaïm and Grimaud's conditions) were promoted by microwave irradiation conditions employing less expensive ligand and organic base. These two catalytic systems were equally efficient, even though conditions **B** were more economic.



[a] Conditions **A** ($Pd(OAc)_2$ (5 mol%), PCy_3•BF_4 (10 mol%), CsOPiv (10 mol%), K_3PO_4 (1.5 equiv), mesitylene, 110 °C, 17 h) gave 69% yield.

Finally, in continuation of our study on the intramolecular cyclization of enamides, we further studied the possibility of using less-strained cyclobutyl ring-substituted enamides and enesulfonamides as substrates in palladium catalyzed intramolecular C-H activation reaction. Preliminary studies demonstrated that, indeed, 2-azabicyclo[3.2.0]hept-3-enes could be obtained in low yield (~20%) from β-bromoenesulfonamide. The former are interesting *N*-containing heterocycles that could find applications in medicinal chemistry. It is worthy to mention that the choice of the electron-withdrawing group on the nitrogen was crucial for the success as highly electron-withdrawing nitrogen substituents would facilitate the key C-H activation of the cyclobutyl ring. Further work is currently ongoing in our group towards the optimization of the conditions as well as development of an enantioselective version of this transformation.



Résumé en Français

Résumé en français

1. Introduction

Les hétérocycles azotés constituent une classe de composés organiques structurellement importants, largement présents en tant que ligands de métaux précieux et non précieux, dans de nombreux composés bioactifs en pharmacie ou en agrochimie, mais également en tant que briques élémentaires dans des matériaux ou des polymères (Schéma 1). Ces hétérocycles sont donc centraux pour de nombreux domaines de notre société et le besoin de nouvelles architectures moléculaires et de nouvelles méthodes de préparation est constant. Il est en effet important de pouvoir accéder à de nouveaux espaces chimiques qui sont sous-peuplés à l'heure actuelle, ainsi que de développer des méthodes de synthèse organique se démarquant de l'état de l'art par leur efficacité accrue, leur impact sur l'environnement le plus minime possible et leur aspect pratique amélioré. La chimie hétérocyclique est par conséquent un domaine très actif, conduisant à des avancées notables reposant sur la chimie organométallique, ionique, radicalaire ou péricyclique.

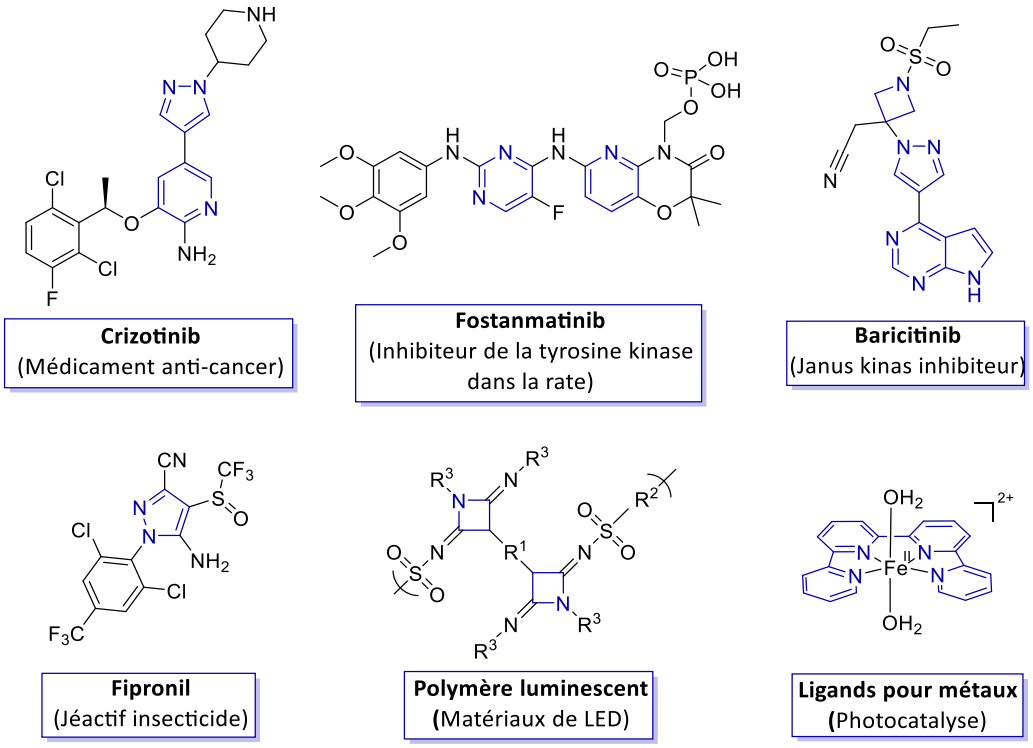


Schéma 1.

Dans le cadre de ce travail de doctorat conduit en co-tutelle entre les équipes du Professeur Gwilherm Evano (Université Libre de Bruxelles, Belgique) et du Docteur Nicolas Blanchard (UHA-Unistra-CNRS, Mulhouse), nous nous sommes intéressés à la synthèse de plusieurs classes d'hétérocycles azotés à partir de précurseurs simples tels que les ynamides et les énamides. Ces briques élémentaires ont suscité de nombreuses études depuis les années 2000 en raison de leur équilibre entre réactivité et stabilité. En effet, le doublet non-liant de l'atome d'azote peut se délocaliser dans le groupement éléctro-attracteur, lui conférant une relative stabilité par rapport aux analogues ynamines et énamines, mais également dans le système pi lié à l'atome d'azote (Schéma 2). Ce dernier phénomène confère aux ynamides et énamides une nucléophilie en béta de l'atome d'azote, tout en révélant une forme iminium conférant une forte électrophilie au carbone alpha.

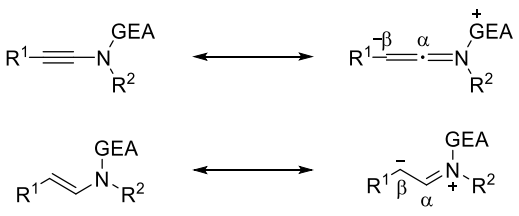


Schéma 2.

De très nombreux travaux ont démontré le potentiel de ces briques élémentaires à trois atomes dans les réactions métallo-catalysées, ioniques et péricycliques. Toutefois, la réactivité des ynamides et énamides reste un domaine fertile dont le potentiel en chimie hétérocyclique n'est pas complètement exploré.

Ce travail est divisé en deux chapitres distincts, chacun organisé en plusieurs sous-sections : état de l'art, résultats et discussions, conclusion, partie expérimentale. Ce résumé décrit uniquement les résultats obtenus, le lecteur intéressé par l'état de l'art et la partie expérimentale de chaque chapitre est redirigé vers la sous-section appropriée, en anglais.

2. Résultats et discussions

2.1 Réactivité des ynamides en cyclisations radicalaires intramoléculaires

Dans le premier chapitre, nous nous sommes proposés d'étudier la réactivité des ynamides en cyclisations radicalaires intramoléculaires afin d'accéder à des structures hétérocycliques de type pyrrolidine, pipéridine, azépane, pyrazolidine et hexahydropyridazine (Schéma 3).

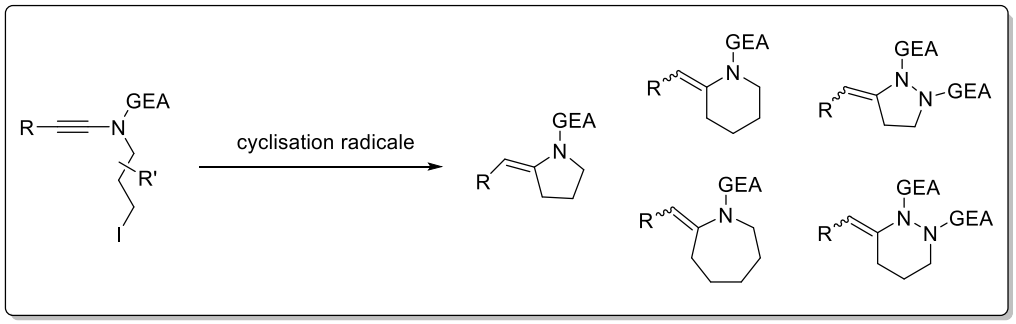


Schéma 3.

La chimie radicalaire des ynamides est relativement peu développée et seuls quelques travaux ont été rapportés concernant l'addition de radicaux thiyls, silyls ou germyls. Nous avons souhaité étudier la version intramoléculaire d'addition de radicaux carbonés sur le système pi de l'ynamide, afin de former des cycles à 5 ou 6 chaînons. De manière surprenante, cette transformation conceptuellement simple n'a jamais été rapportée dans la littérature.

Dans un premier temps, nous avons préparé les substrats de départ de type ynamides par réaction de couplage croisé entre un carbamate et un bromo-alcyne (Schéma 4). Les dérivés de type carbamate sont aisément préparés en deux étapes à partir d'amino-alcool commercialement disponibles. Le groupement protecteur de l'atome d'azote de type Boc a été sélectionné par un criblage (non détaillé dans ce résumé). Après protection sous forme de carbamate de *tert*-butyl, le groupement hydroxyl est transformé en éther silylé. En parallèle, les bromo-alcynes sont synthétisés à partir d'aldéhydes en 2 étapes : une première réaction de dibromooléfination de Ramirez permet d'accéder aux dibromo-oléfines dans des conditions simples, suivie d'une réaction d'élimination de bromure en conditions basiques de transfert de phase. Les ynamides sont préparées par couplage de l'amidure de potassium avec le bromo-alcyne souhaité, en présence de CuI (20 mol%) et de 1,10-phénanthroline (25 mol%). Enfin, une dernière étape de déprotection

de l'éther silylé par le TBAF dans le THF, suivie d'une transformation de l'alcool primaire en dérivé iodé correspondant permet de préparer les précurseurs de réaction de cyclisation intramoléculaire radicalaire.

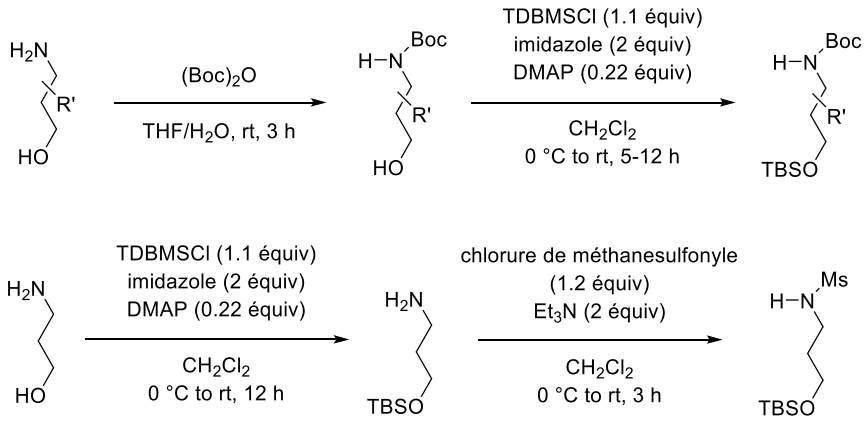
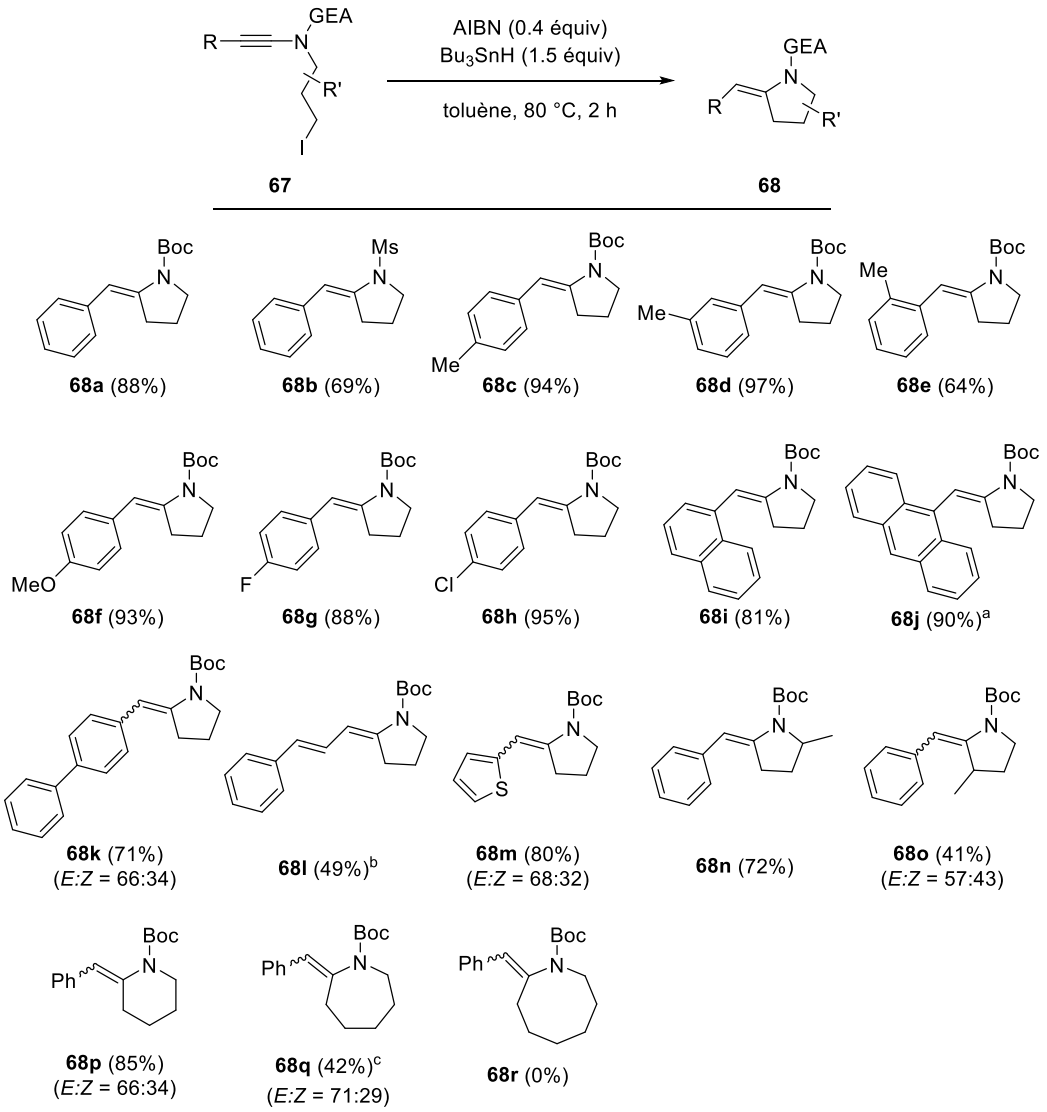


Schéma 4.

En présence d'AIBN (40 mol%) et d'hydrure de tri-n-butylétain dans le toluène à 80 °C pendant 2 h, la liaison carbone-iode se rompt de manière homolytique (par attaque du radical tri-n-butylstannyl) et conduit au radical primaire correspondant. Après réaction de cyclisation de type *endo*-dig, un radical vinylique est obtenu, qui arrache un atome d'hydrogène à une seconde molécule d'hydrure de tri-n-butylétain, permettant ainsi la propagation de la réaction radicalaire. Cette transformation permet de préparer des cycles à 5 et 6 chaînons avec une très bonne efficacité, ce qui n'est pas le cas pour des cycles de taille supérieure. La double liaison *exo* ainsi préparée est présente dans certains cas sous la forme de deux isomères, *Z* et *E*. Il est à noter également que les ynamides possédant un groupement alkyl sur la triple liaison ne sont pas réactifs dans ces conditions.



[a] La température était de 100 °C. [b] Le temps était 4.5 h. [c] La température était 110 °C, a concentration a été doublée et le *n*-Bu_3SnH a été ajouté lentement (4 h contre 1 h habituel).

Schéma 5.

Nous avons également étudié la réactivité d'ynhydrazines en réactions de cyclisation radicalaire. Ces précurseurs sont relativement simples à préparer par condensation d'un alcynure de lithium sur un azodicarboxylate dans le THF à froid. L'yne-hydrazine protégée par deux groupements Boc est ainsi obtenu avec un rendement de 66%. L'alkylation de l'atome d'azote par un bromure d'alkyle en conditions de transfert de phase, suivie de la déprotection de l'éther silylé puis de la transformation de l'alcool primaire en dérivé iodé conduit aux précurseurs souhaités avec de bons rendements. La cyclisation de ces composés a ensuite été évaluée. Pour notre plus grand plaisir, les conditions précédemment établies se sont révélées efficaces et ont conduit aux hétérocycles attendus avec de bons à très bons rendements.

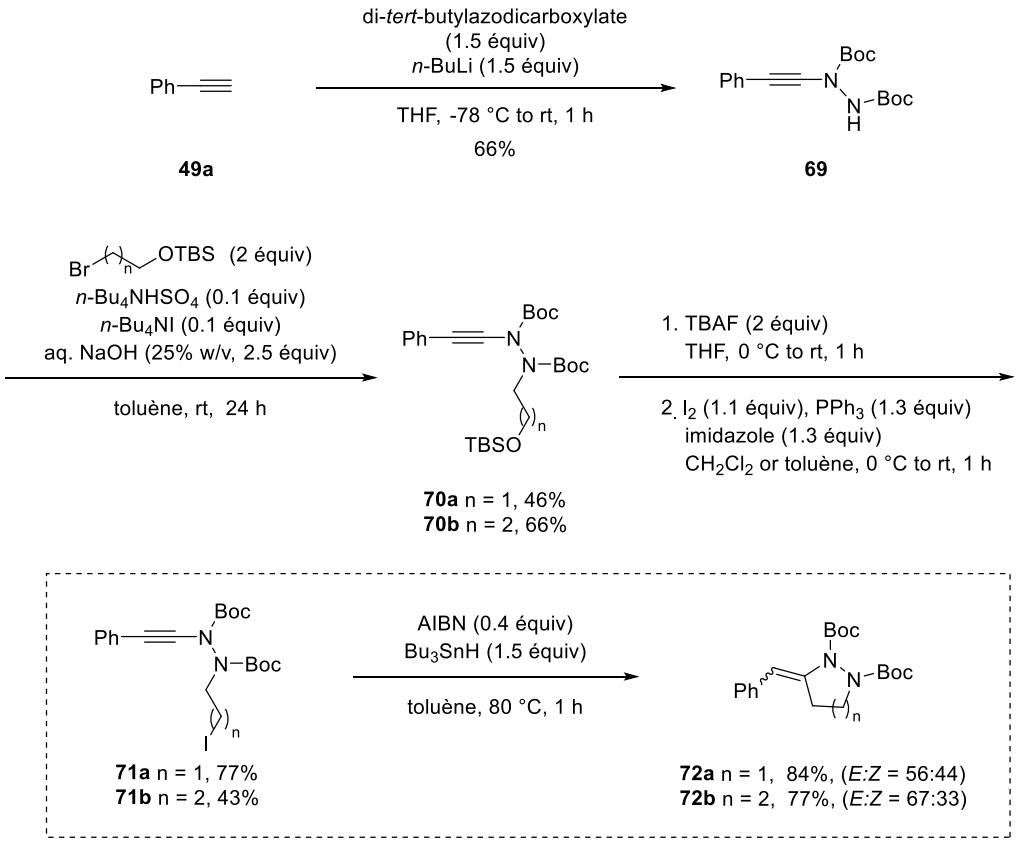


Schéma 6.

Dans un dernier temps, nous nous sommes penchés sur les réactions de fonctionnalisation des hétérocycles ainsi préparés. En effet, la double liaison exocyclique des composés **68** peut être hydrogénée (Schéma 7, éq. 1), ou traitée par le *N*-bromosuccinimide (éq 2). Dans ce cas, l'atome de brome est incorporé en position béta de l'énamide et l'iminium intermédiaire est piégé par le succinimide. Nous avons également montré que ce système pi peut être époxydé par le DMDO dans le dichlorométhane (éq. 3). Le spiro-époxyde ainsi formé n'est pas stable et conduit à **79a** avec un rendement modeste. Enfin, nous avons pu obtenir le spiro-cyclopropane **80a** par réaction de **68** avec le chloroforme en conditions de transfert de phase fortement basiques (éq. 4).

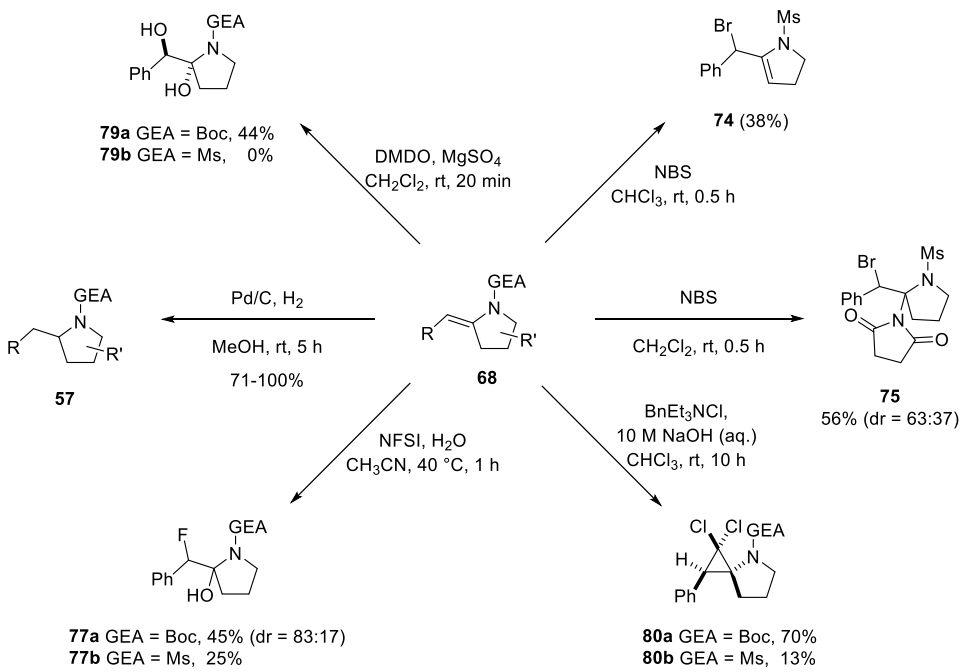


Schéma 7.

En conclusion de ce premier chapitre, nous avons montré que les ynamides étaient des partenaires efficaces en réactions de cyclisation radicalaire, conduisant à divers hétérocycles azotés avec de bons rendements. Ces composés peuvent par la suite être fonctionnalisés par réduction, époxydation ou cyclopropanation.

2.2 Réactivité des *N*-cycloalkyl-β-bromoénamides en cyclisations pallado-catalysées intramoléculaires

Encouragés par le succès de la cyclisation intramoléculaire radicalaire des ynamides, nous nous sommes ensuite tournés vers l'exploration de la cyclisation intramoléculaire catalysée par le palladium des *N*-cycloalkyl énamides. L'hypothèse de travail est qu'il devrait être possible d'activer une liaison C-H d'un *N*-cyclopropyl ou d'un *N*-cyclobutyl énamide (Schéma 8). D'un point de vue mécanistique, le bromure de vinyle subirait d'abord une addition oxydante par un complexe du Pd(0), suivie d'un échange rapide de ligand et d'une séquence d'activation CH par métallation-déprotonation concertée (CMD) pour donner un intermédiaire commun. Dans le cas de l'énamide dont l'atome d'azote est substitué par un cyclopropyl, l'intermédiaire devrait subir une réaction d'ouverture de cycle dont la force motrice est le relâchement de la tension de cycle inhérente aux cyclopropanes suivie par une étape d'élimination réductrice pour donner

les 1,4-dihydropyridines correspondantes. En revanche, la situation devrait être différente dans le cas des *N*-cyclobutyl énamides : l'étape CMD conduirait à un palladacycle qui pourrait délivrer les 2-azabicyclo [3.2.0] hept-3-ènes après une étape d'élimination réductrice ; le cyclobutane étant bien moins contraint que le cyclopropane, la réaction d'ouverture de cycle n'est pas attendue dans ce cas.

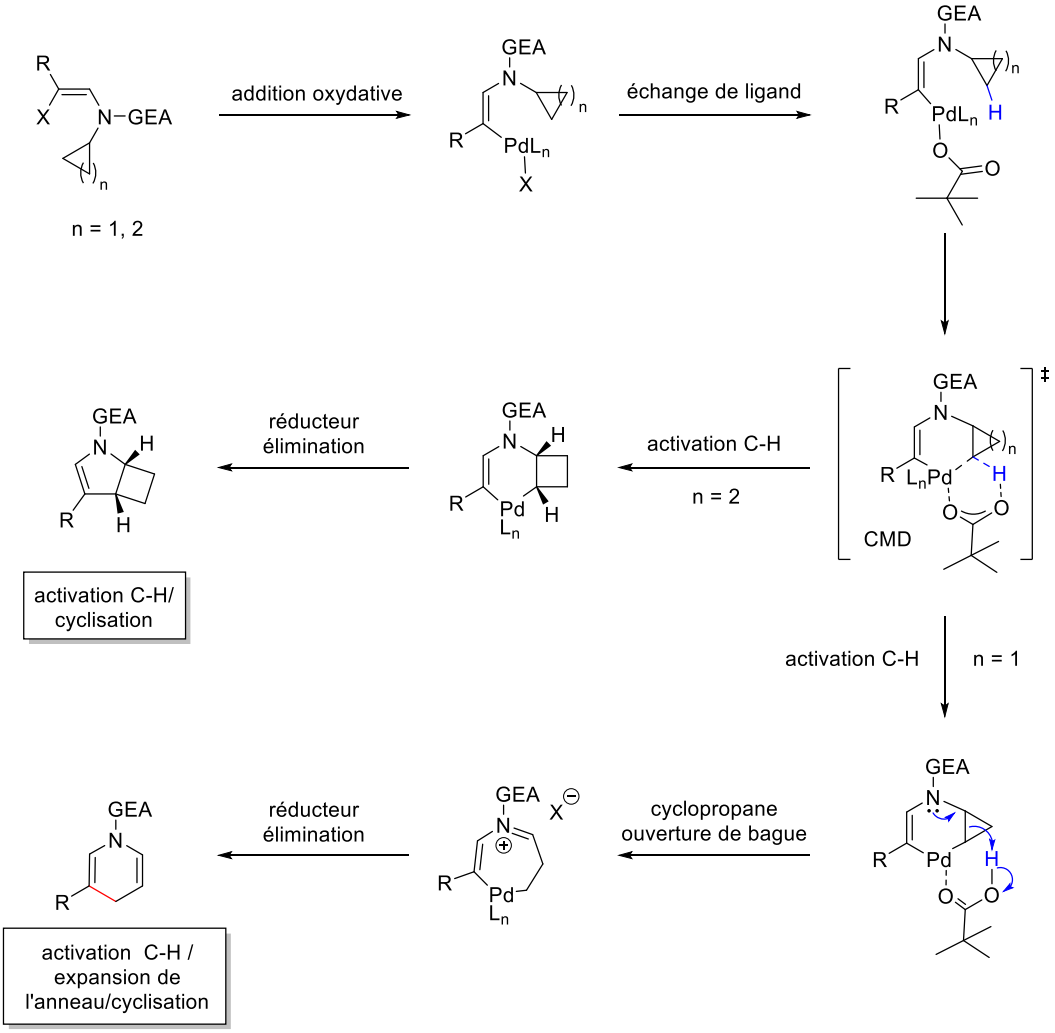
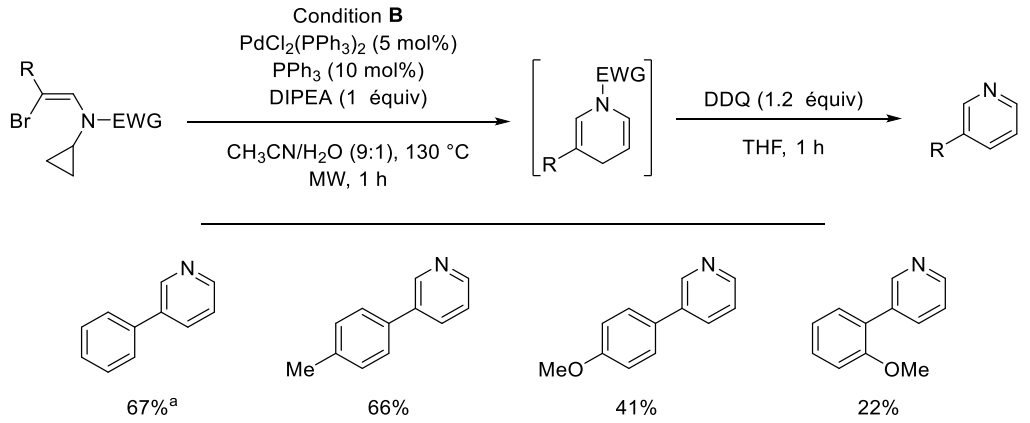


Schéma 8.

Après avoir examiné divers halo-énamides substitués, nous avons constaté que les β-bromoenamides étaient des substrats appropriés pour cette transformation, et une séquence synthétique fiable a été mise au point pour accéder aux β-bromoenamides de départ. Cette séquence implique la protection de la *N*-cyclopropyl ou *N*-cyclobutylamine puis sa formylation. Le formamide ainsi obtenu est ensuite soumis à une

réaction de Ramirez permettant de préparer la dibromo-oléfine correspondante. Un dernier couplage croisé de type Suzuki permettant de créer une liaison carbone-carbone en béta de l'atome d'azote.

La cyclisation intramoléculaire des *N*-cyclopropyl énamides a d'abord été développée, dans laquelle le cyclopropane a subi une réaction d'ouverture conduisant à un hétérocycle azoté à six chaînons (Schéma 9). Pour notre plus grand plaisir, cette transformation peut être réalisée en utilisant deux jeux de conditions, les conditions **A** (rapportées par Rousseaux en 2012) et les conditions **B** (proposées par El Kaïm et Grimaud). Ces deux systèmes catalytiques sont aussi efficaces l'un que l'autre, même si les conditions **B** sont plus économiques.



[a] Conditions **A** ($Pd(OAc)_2$ (5 mol%), PCy_3•BF_4 (10 mol%), CsOPiv (10 mol%), K_3PO_4 (1.5 équiv), mésitylène, 110 °C, 17 h): 69% rendement.

Schéma 9.

Enfin, dans le prolongement de notre étude sur la cyclisation intramoléculaire des énamides, nous avons étudié plus avant la possibilité d'utiliser des énamides substitués par un *N*-cyclobutyl comme substrats dans la réaction d'activation de C-H intramoléculaire catalysée au palladium. Des études préliminaires ont démontré que les 2-azabicyclo[3.2.0]hept-3-ènes pouvaient en effet être obtenus avec un faible rendement (~ 20%) à partir de β-bromoénamides (Schéma 10). Ces 2-azabicyclo[3.2.0]hept-3-ènes sont des hétérocycles intéressants qui pourraient trouver des applications en chimie médicale. Il est important de mentionner que le choix du groupe attracteur d'électrons sur l'atome d'azote s'est révélé crucial pour le

succès de cette transformation. En effet, celui-ci doit être fortement attracteurs d'électrons afin de faciliter l'activation C-H du cycle cyclobutyle, non activé.

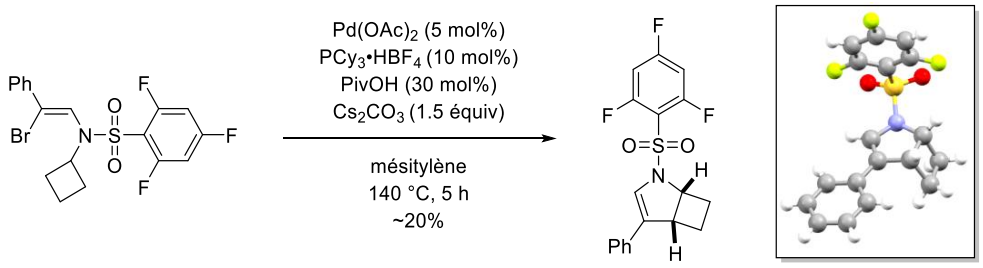


Schéma 10.

En conclusion, nous avons pu valider l'hypothèse de travail et démontrer qu'une réaction d'activation C-H de *N*-cyclobutylénamide était possible (Schéma 11). Notre groupe poursuit actuellement ces travaux en vue d'optimiser les conditions et de mettre au point une version énantiosélective de cette transformation.

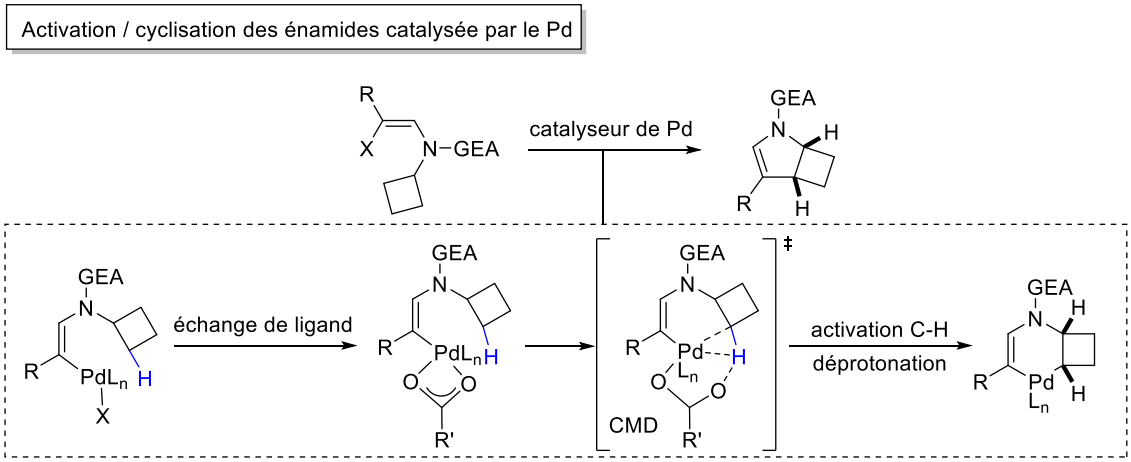


Schéma 11.

Experimental part

General Information

All reactions were carried out in oven-dried glassware under an argon or nitrogen atmosphere employing standard techniques in handling air-sensitive materials.

All solvents were reagent grade. Dichloromethane, acetonitrile and *N*,*N*-dimethylformamide were freshly distilled from calcium hydride under argon or nitrogen. Tetrahydrofuran was freshly distilled from sodium/benzophenone under argon or nitrogen. Toluene (99.85%, Extra Dry over Molecular Sieve, Acroseal®) and 1,4-dioxane (99.5%, Extra Dry over Molecular Sieve, AcroSeal®) were purchased from ACROS Organics and used as supplied.

Copper(I) iodide (99.999% purity) and copper sulfate pentahydrate (98+%) were purchased from Sigma-Aldrich and were used as supplied. 1,10-Phenanthroline (98+%) was purchased from Alfa Aesar and was used as supplied. Bis(trimethylsilyl)amide (KHMDS, 0.5 M solution in toluene) was purchased from Aldrich. 2,2'-Azobis(2-methylpropionitrile) (98%) was purchased from ACROS Organics and recrystallized with 95% ethanol twice. Tributyltin hydride (97%) was purchase from ACROS Organics. All other reagents were used as supplied. Palladium acetate (98%), tricyclohexylphosphine tetrafluoroborate (97%), pivalic acid (99%) and cesium pivalate (98%) were purchased from Aldrich and were used as supplied. Cesium carbonate was purchased from Fluorochem and was used as purchased.

Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kiesegel $60F_{254}$ plates. Flash chromatography was performed with silica gel 60 (particle size 35-70 µm) supplied by Merck. Yield refer to chromatographically and spectroscopically pure compounds unless otherwise stated.

Proton NMR spectra were recorded using an internal deuterium lock at ambient temperature on Bruker 300, 400, 500 and 600 MHz spectrometers. Internal reference of δ_H 7.26 was used for $CDCl_3$. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, sext. = sextuplet, m = multiplet, br. = broad, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, td = triplet of doublets), coupling constant (*J*/Hz) and integration. Carbon-13 NMR spectra were recorded at 75, 100, 125 and 150 MHz using $CDCl_3$ (δ_C 77.16) as internal reference. Fluorine-19 NMR spectra were recorded at 471 MHz.

Melting points were recorded on a Stuart Scientific Analogue SMP11. Infrared spectra were recorded on a Bruker Alpha (ATR) or Perkin Elmer UATR Two. High-resolution mass-spectra were obtained on Agilent QTOF 6520.

Experimental part of chapter 1

Experimental Procedures and Characterization Data: Synthesis of Amides from Aminoalcohols

General procedure I:

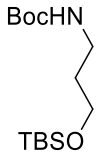
To a solution of aminoalcohol (20 mmol) in a mixture of THF/H_2O (v/v = 1:1, 20 mL) was added a solution of di-*tert*-butyl dicarbonate (4.37 g, 20 mmol) in a mixture of THF/H_2O (v/v = 1:1, 20 mL) dropwise over 30 minutes. The reaction mixture was stirred at room temperature for 3 hours and then quenched by addition of a 5% aqueous solution of citric acid (50 mL), the aqueous layer was extracted with EtOAc and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the desired *N*-Boc-aminoalcohol which could be used in the next step without further purification.

To a solution of *tert*-butyldimethylsilyl chloride (3.32 g, 22 mmol), imidazole (2.04 g, 30 mmol), and 4-dimethylaminopyridine (367 mg, 3 mmol) in dichloromethane (30 mL) was added a solution of *N*-Boc-aminoalcohol in dichloromethane (20 mL) at 0 °C. The resulting reaction mixture was warmed to room temperature, stirred for 12 hours and quenched by addition of water (50 mL). The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatograph over silica gel to give the desired product.

General procedure II:

To a solution of *tert*-butyldimethylsilyl chloride (1.66 g, 11 mmol), imidazole (1.02 g, 15 mmol), and 4-dimethylaminopyridine (183 mg, 1.5 mmol) in dichloromethane (10 mL) at 0 °C was added a solution of 3-aminopropanol (751 mg, 10 mmol) in dichloromethane (10 mL). The resulting mixture was warmed to room temperature, stirred for 12 hours and quenched by addition of water (50 mL). The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the desired *tert*-butyldimethylsilylhydroxylamine which was used in the next step without further purification.

To the solution of *tert*-butyldimethylsilylhydroxylamine and triethylamine (2.8 mL, 20 mmol) in dichloromethane (20 mL) was added a solution of methanesulfonyl chloride (1.37 g, 12 mol) in dichloromethane (20 mL) at 0 °C, and the resulting reaction mixture was allowed to warm to room temperature, stirred for 3 hours and quenched by addition of water (50 mL). The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatograph over silica gel to give the desired product.

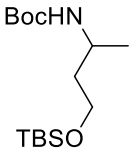


60a

***tert*-Butyl [3-(*tert*-butyldimethylsilyloxy)propyl]carbamate 60a.** Prepared according to the general procedure I. Yield: 97% (5.6 g, 19.4 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Colorless oil; This compound has been previously reported. [S1]

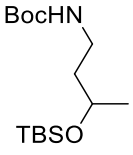
60h

***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]methanesulfonamide 60h.** Prepared according to the general procedure II. Yield: 92% (2.46 g, 9.2 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 1/1; Colorless oil; This compound has been previously reported. [S2]



60e

***tert*-Butyl [4-(*tert*-butyldimethylsilyloxy)butan-2-yl]carbamate 60e.** Prepared according to the general procedure I. Yield: 92% (5.6 g, 18.5 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Colorless oil; This compound has been previously reported. [S3]

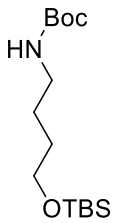


60f

***tert*-Butyl [3-(*tert*-butyldimethylsilyloxy)butyl]carbamate 60f.** Prepared according to the general procedure I. Yield: 99% (6.0 g, 19.7 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 (br., 1H), 3.96-3.89 (m, 1H), 3.27-3.14 (m, 2H), 1.69-1.52 (m, 2H), 1.42 (s, 9H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H);

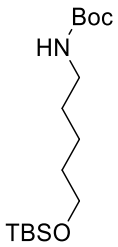
[S1] Molander, G. A.; Cormier, E. P. *J. Org. Chem.* **2005**, *70*, 2622-2626.
[S2] Lee, G. G. M. *U.S.* **1992**, US5081261 A 19920114.
[S3] Ahn, J. M.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2017**, *139*, 18101-18106.

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 78.9, 68.0, 38.5, 37.9, 28.6, 26.0, 23.6, 18.1, -4.2, -4.8; IR (ATR): ν_{max} 2930, 2247, 1722, 1457, 1389, 1369, 1291, 1257, 1163, 1102, 836, 765, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{15}H_{33}NNaO_3Si$ $[M+Na]^+$ 326.2122, found 326.2124.



60b

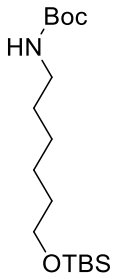
***tert*-Butyl [4-(*tert*-butyldimethylsilyloxy)butyl]carbamate 60b.** Prepared according to the general procedure I. Yield: 51% (3.1 g, 10.2 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Colorless oil; This compound has been previously reported. [S4]



60c

***tert*-Butyl [5-(*tert*-butyldimethylsilyloxy)pentyl]carbamate 60c.** Prepared according to the general procedure I. Yield: 84% (5.3 g, 16.7 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Colorless oil; This compound has been previously reported. [S5]

[S4] McLaughlin, N. P.; Evans, P. *J. Org. Chem.* **2010**, *75*, 518-521.
[S5] Hernandez, J. N.; Ramirez, M. A.; Martin, V. S. *J. Org. Chem.* **2003**, *68*, 743-746.



60d

***tert*-Butyl [6-(*tert*-butyldimethylsilyloxy)hexyl]carbamate 60.** Prepared according to the general procedure I. Yield: 75% (5.0 g, 15.1 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Colorless oil; This compound has been previously reported. [S6]

[S6] Yoritate, M.; Meguro, T.; Matsuo, N.; Shirokane, K.; Sato, T.; Chida, N. *Chem. Eur. J.* **2014**, *20*, 8210-8216.

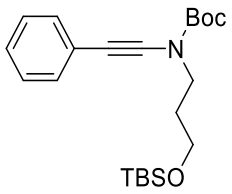
Experimental Procedure and Characterization Data: Synthesis of Ynamides

General procedure I: synthesis of ynamides from alkynyl bromides[S7]

A 15 mL pressure tube was charged with the amide (5 mmol), alkynyl bromide (10 mmol), copper(I) iodide (190 mg, 1 mmol) and 1,10-phenanthroline (225 mg, 1.25 mmol). The tube was fitted with a rubber septum, evacuated under vacuum and backfilled with argon for three times. Then dry toluene (10 mL) was next added, and the yellow or brown suspension was heated to 90 °C before the addition of bis(trimethylsilyl)amide (KHMDS, 0.5 M solution in toluene, 12 mL, 6 mmol) via a syringe pump over 2 hours. After the addition, the rubber septum was replaced by a Teflon-coated screw cap, and the brown or black reaction mixture was stirred at 90 °C for 12-48 hours. The resulting suspension was filtered through a plug of silica gel (washed with EtOAc) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product.

General procedure II: synthesis of ynamides from dibromoalkenes[S8]

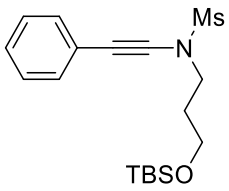
A 15 mL pressure tube was charged with the sulfonamide (5 mmol), the 1,1-dibromo-1-alkene (7.5 mmol), cesium carbonate (6.5 g, 20 mmol) and copper(I) iodide (119 mg, 0.63 mmol). The tube was fitted with a rubber septum, evacuated under high vacuum and backfilled with argon for three times. Dry 1,4-dioxane (10 mL) and *N*,*N*'-dimethylethylenediamine (100 µL, 0.94 mmol) were next added, the rubber septum was replaced by a Teflon-coated screw cap and the light blue-green suspension was heated at 80 °C for 24 hours. The blue suspension was cooled to room temperature, filtered through a plug of silica gel (washed with EtOAc) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product.



66a

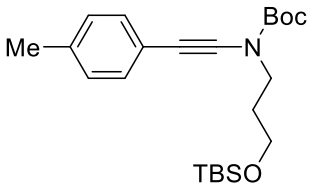
***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-phenylethynylamine 66a.** Prepared according to the general procedure I. Yield: 82% (1.59 g, 4.08 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.2 Hz, 2H), 7.31-7.20 (m, 3H), 3.71 (t, *J* = 6.1 Hz, 2H), 3.60 (t, *J* = 7.2 Hz, 2H), 1.94 (quint., *J* = 6.7 Hz, 2H), 1.52 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 130.7 (br.), 128.3, 127.1, 124.0, 84.2, 82.4, 70.5 (br.), 60.4, 46.5 (br.), 31.4, 28.2, 26.2, 18.4, -5.2; IR (ATR): ν_{max} 2956, 2244, 1722, 1393, 1369, 1291, 1257, 1158, 1102, 836, 752, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{22}H_{35}NNaO_3Si$ $[M+Na]^+$ 412.2278, found 412.2278.

[S7] Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681-3684.
[S8] Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 4381-4385.



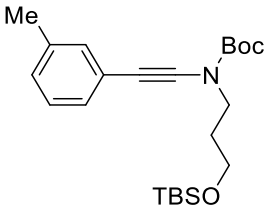
66b

***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-(methylsulfonyl)phenylethynylamine 66b.** Prepared according to the general procedure II. Yield: 65% (1.19 g, 3.24 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.38 (m, 2H), 7.33-7.28 (m, 3H), 3.75 (t, *J* = 5.9 Hz, 2H), 3.67 (t, *J* = 7.0 Hz, 2H), 3.14 (s, 3H), 2.01 (quint., *J* = 6.5 Hz, 2H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.6, 128.4, 128.1, 122.7, 81.7, 71.2, 59.6, 48.8, 38.2, 31.6, 26.0, 18.4, -5.2; IR (ATR): ν_{max} 2930, 2237, 1472, 1361, 1257, 1166, 1098, 959, 836, 776, 755, 692 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{30}INO_3SSi$ $[M+H]^+$ 368.1710, found 368.1710.



66c

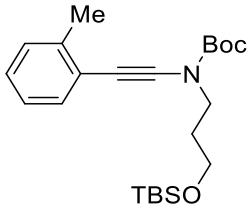
***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-4-tolylethynylamine 66c.** Prepared according to the general procedure I. Yield: 71% (1.43 g, 3.54 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 3.71 (t, *J* = 6.2 Hz, 2H), 3.59 (t, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 1.94 (quint., *J* = 6.7 Hz, 2H), 1.52 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 137.2, 130.8 (br.), 129.1, 120.8, 83.4, 82.3, 60.4, 31.4 (br.), 28.2, 26.1, 21.5, 18.4, -5.2; IR (ATR): ν_{max} 2954, 2245, 1722, 1393, 1369, 1307, 1255, 1160, 1103, 837, 815, 775 cm^{-1}; ESIHRMS *m/z* calcd for $C_{23}H_{37}NNaO_3Si$ $[M+Na]^+$ 426.2435, found 426.2431.



66d

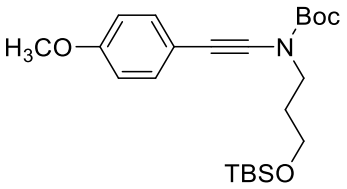
***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-3-tolylethynylamine 66d.** Prepared according to the general procedure I. Yield: 60% (1.22 g, 3.02 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.16 (m, 3H), 7.06-7.04 (m, 1H), 3.71 (t, *J* = 6.2 Hz, 2H), 3.60 (t, *J* = 7.2 Hz, 2H), 2.31 (s, 3H), 1.94 (quint., *J* = 6.7 Hz, 2H), 1.53 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 137.9, 131.4 (br.),

128.2, 128.1, 127.9 (br.), 123.8 (br.), 114.4, 83.8, 82.4, 60.4 (br.), 46.6 (br.), 31.5, 28.2, 26.1, 21.4, 18.4, -5.2; IR (ATR): ν_{max} 2930, 2247, 1722, 1457, 1389, 1369, 1291, 1257, 1163, 1102, 836, 765, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{23}H_{37}NNaO_3Si$ $[M+Na]^+$ 426.2435, found 426.2435.



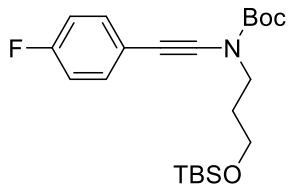
66e

***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-2-tolylethynylamine 66e.** Prepared according to the general procedure I. Yield: 71% (1.44 g, 3.57 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (d, *J* = 6.2 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.14 (td, *J* = 7.3 Hz and 1.6 Hz, 1H), 7.10 (td, *J* = 7.7 Hz and 1.4 Hz, 1H), 3.72 (t, *J* = 6.2 Hz, 2H), 3.63 (t, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.97 (quint., *J* = 6.7 Hz, 2H), 1.53 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.1, 138.7 (br.), 130.6 (br.), 129.4, 127.0, 125.6, 123.8, 88.0, 82.5, 60.4, 46.8 (br.), 31.4, 29.8, 28.3, 26.1, 21.0, 18.4, -5.2; IR (ATR): ν_{max} 2930, 2242, 1721, 1457, 1391, 1369, 1291, 1256, 1157, 1103, 969, 836, 753 cm^{-1}; ESIHRMS *m/z* calcd for $C_{23}H_{37}NNaO_3Si$ $[M+Na]^+$ 426.2435, found 426.2437.



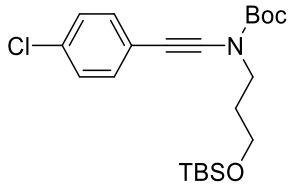
66f

***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-(4-methoxyphenyl)ethynyl-amine 66f.** Prepared according to the general procedure I. Yield: 83% (1.74 g, 4.15 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.71 (t, *J* = 6.2 Hz, 2H), 3.58 (t, *J* = 7.2 Hz, 2H), 1.94 (quint., *J* = 6.7 Hz, 2H), 1.52 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 154.3, 132.6 (br.), 116.0, 114.0, 82.6, 82.3, 60.5, 55.4, 46.6 (br.), 31.4, 28.2, 26.1, 18.4, -5.2; IR (ATR): ν_{max} 2955, 2246, 1720, 1514, 1393, 1286, 1247, 1170, 1104, 832, 776 cm^{-1}; ESIHRMS *m/z* calcd for $C_{23}H_{37}NNaO_4Si$ $[M+Na]^+$ 442.2384, found 442.2387.



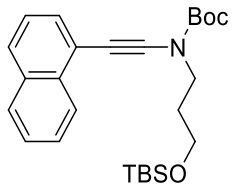
66g

***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-(4-fluorophenyl)ethynylamine 66g.** Prepared according to the general procedure I. Yield: 63% (1.28 g, 3.14 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.32 (t, *J* = 6.7 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 3.71 (t, *J* = 6.1 Hz, 2H), 3.59 (t, *J* = 7.2 Hz, 2H), 1.93 (quint., *J* = 6.7 Hz, 2H), 1.52 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ^{13}C dec ^{19}F): δ161.0, 153.1, 131.6 (br.), 119.0, 114.5, 82.8, 81.5, 68.4 (br.), 59.4, 45.7 (br.), 30.4, 27.2, 26.1, 17.4, -6.2; IR (ATR): ν_{max} 2955, 2247, 1723, 1511, 1394, 1369, 1291, 1255, 1230, 1154, 1102, 834, 776 cm^{-1}; ESIHRMS *m/z* calcd for $C_{22}H_{34}FNNaO_3Si$ $[M+Na]^+$ 430.2184, found 430.2191.



66h

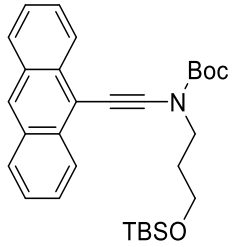
***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-(4-chlorophenyl)ethynyl-amine 66h.** Prepared according to the general procedure I. Yield: 71% (1.51 g, 3.56 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.28-7.23 (m, 4H), 3.71 (t, *J* = 6.1 Hz, 2H), 3.60 (t, *J* = 7.2 Hz, 2H), 1.93 (quint., *J* = 6.6 Hz, 2H), 1.52 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ154.0, 133.0, 131.9 (br.), 128.6, 122.5, 85.2, 82.6, 69.6 (br.), 60.3, 46.6 (br.), 31.4, 28.2, 26.0, 18.4, -5.2; IR (ATR): ν_{max} 2955, 2243, 1724, 1494, 1395, 1369, 1289, 1255, 1158, 1091, 1014, 835, 776 cm^{-1}; ESIHRMS *m/z* calcd for $C_{22}H_{38}ClN_2O_3Si$ $[M+NH_4]^+$ 441.2335, found 441.2339.



66i

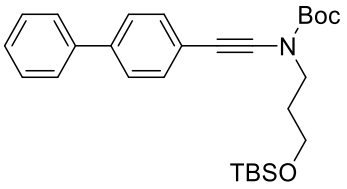
***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-(naphthalene-1-yl)ethynyl-amine 66i.** Prepared according to the general procedure I. Yield: 45% (990 mg, 2.25 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (d, *J* = 9.3 Hz, 1H), 7.83 (d, *J* = 9.3 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.55-7.49 (m, 3H), 7.40 (dd, *J* =

8.2 and 7.2 Hz, 1H), 3.77 (t, *J* = 6.1 Hz, 2H), 3.72 (t, *J* = 7.2 Hz, 2H), 2.05 (quint., *J* = 6.7 Hz, 2H), 1.61 (s, 9H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ154.1, 133.4, 132.9, 128.3, 128.2 (br.), 127.2, 126.6, 126.3, 125.4, 121.8, 89.0, 82.8, 69.3 (br.), 60.4, 46.8 (br.), 31.5, 28.3, 26.1, 18.4, -5.2; IR (ATR): ν_{max} 2955, 2241, 1721, 1370, 1290, 1256, 1161, 1105, 967, 837, 798, 773 cm^{-1}; ESIHRMS *m/z* calcd for $C_{26}H_{38}NO_3Si$ $[M+H]^+$ 440.2615, found 440.2618.



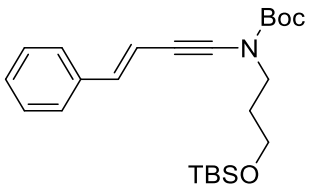
66j

***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-(anthracen-9-yl)ethynylamine 66j.** Prepared according to the general procedure I. Yield: 29% (710 mg, 1.45 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Red oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ8.53 (d, *J* = 8.8 Hz, 2H), 8.32 (s, 1H), 8.00-7.98 (m, 2H), 7.53-7.46 (m, 4H), 3.87 (t, *J* = 7.3 Hz, 2H), 3.84 (t, *J* = 6.1 Hz, 2H), 2.17 (quint., *J* = 6.7 Hz, 2H), 1.68 (s, 9H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ154.0, 131.4, 128.7, 127.0, 126.0, 125.72, 125.66, 118.6, 95.4, 83.1, 68.7 (br.), 60.5, 47.3 (br.), 31.6, 28.4, 26.1, 18.5, -5.2; IR (ATR): ν_{max} 2957, 2232, 1723, 1457, 1392, 1369, 1292, 1255, 1150, 1099, 968, 837, 776, 734 cm^{-1}; ESIHRMS *m/z* calcd for $C_{30}H_{40}NO_3Si$ $[M+H]^+$ 490.2772, found 490.2765.



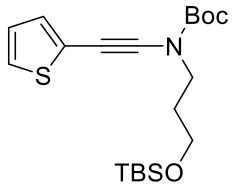
66k

***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-[(1,1'-biphenyl)-4-yl]ethynyl-amine 66k.** Prepared according to the general procedure I. Yield: 16% (361 mg, 775 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.59 (d, *J* = 7.1 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 4H), 7.34 (t, *J* = 7.4 Hz, 1H), 3.73 (t, *J* = 6.1 Hz, 2H), 3.62 (t, *J* = 7.2 Hz, 2H), 1.96 (quint., *J* = 6.7 Hz, 2H), 1.54 (s, 9H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ154.2, 140.7, 139.9, 131.2 (br.), 129.0, 127.5, 127.1, 127.0, 84.9, 82.6, 60.4, 31.4, 29.9, 28.2, 26.1, 25.9, 18.4, -2.8, -5.2; IR (ATR): ν_{max} 2930, 2241, 1720, 1472, 1394, 1369, 1290, 1257, 1157, 1103, 836, 763, 697 cm^{-1}; ESIHRMS *m/z* calcd for $C_{28}H_{39}NNaO_3Si$ $[M+Na]^+$ 488.2591, found 488.2598.



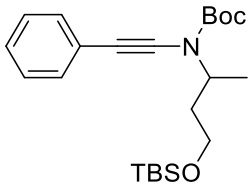
66l

***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-(4-phenylbut-3-en-1-yn-1-yl) amine 66l.** Prepared according to the general procedure I. Yield: 37% (769 mg, 1.85 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.1 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 16.1 Hz, 1H), 6.28 (d, *J* = 16.2 Hz, 1H), 3.71 (t, *J* = 6.1 Hz, 2H), 3.58 (t, *J* = 7.1 Hz, 2H), 1.92 (quint., *J* = 6.6 Hz, 2H), 1.53 (s, 9H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 137.8, 137.0, 128.8, 128.1, 126.0, 108.5, 86.5, 82.6, 70.1 (br.), 60.3, 46.7 (br.), 31.4, 28.2, 26.1, 18.4, -5.2; IR (ATR): ν_{max} 2930, 2229, 1721, 1472, 1392, 1369, 1294, 1255, 1217, 1161, 1098, 949, 836, 776, 747, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{24}H_{41}N_2O_3Si$ $[M+NH_4]^+$ 433.2881, found 433.2880.



66m

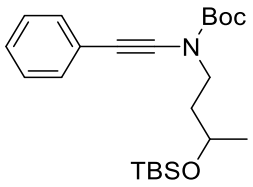
***N*-[3-(*tert*-Butyldimethylsilyloxy)propyl]-*N*-*tert*-butoxycarbonyl-(thiophen-2-yl)ethynylamine 66m.** Prepared according to the general procedure I. Yield: 34% (669 mg, 1.69 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (dd, *J* = 5.2 and 1.1 Hz, 1H), 7.12 (d, *J* = 3.4 Hz, 1H), 6.95 (dd, *J* = 5.2 and 3.6 Hz, 1H), 3.70 (t, *J* = 6.2 Hz, 2H), 3.59 (t, *J* = 7.1 Hz, 2H), 1.92 (quint., *J* =. 6.7 Hz, 2H), 1.51 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 131.3 (br.), 127.0, 126.5, 124.0, 87.4, 82.7, 63.6 (br.), 60.4, 47.0 (br.), 31.4, 28.2, 26.1, 18.4, -5.2; IR (ATR): ν_{max} 2954, 2241, 1723, 1472, 1385, 1369, 1342, 1295, 1256, 1161, 1101, 968, 835, 765, 697 cm^{-1}; ESIHRMS *m/z* calcd for $C_{20}H_{33}NNaO_3SSi$ $[M+Na]^+$ 418.1843, found 418.1846.



66n

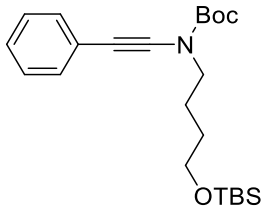
***N*-[4-(*tert*-Butyldimethylsilyloxy)butan-2-yl]-*N*-*tert*-butoxycarbonyl-phenylethynylamine 66n.** Prepared according to the general procedure I. Yield: 54% (1.08 g, 2.68 mmol). Solvent system for flash

column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.1 Hz, 2H), 7.31-7.22 (m, 3H), 4.42-4.34 (m, 1H), 3.67 (dd, *J* = 6.9 and 5.8 Hz, 2H), 2.05-1.96 (m, 1H), 1.78-1.70 (m, 1H), 1.55 (s, 9H), 1.29 (d, *J* = 6.7 Hz, 3H), 0.91 (s, 9H), 0.05 (d, *J* = 1.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 130.7 (br.), 128.3, 127.0, 124.1, 82.3, 81.2, 72.8 (br.), 60.0, 49.8 (br.), 37.6, 28.2, 26.1, 19.1, 18.4, -5.3; IR (ATR): ν_{max} 2931, 2242, 1719, 1473, 1402, 1369, 1297, 1256, 1159, 1100, 903, 835, 776, 753, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{23}H_{37}NNaO_3Si$ $[M+Na]^+$ 426.2435, found 426.2439.



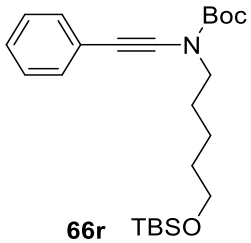
66o

***N*-[3-Methyl-3-(*tert*-butyldimethylsilyloxy)butyl]-*N*-*tert*-butoxycarbonyl-phenylethynylamine 66o.** Prepared according to the general procedure I. Yield: 29% (582 mg, 1.44 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.1 Hz, 2H), 7.30-7.21 (m, 3H), 3.94 (sext., *J* = 6.0 Hz, 1H), 3.65-3.50 (m, 2H), 1.93-1.79 (m, 2H), 1.65-1.58 (m, 2H), 1.53 (s, 9H), 1.20 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.07 (d, *J* = 1.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 130.8 (br.), 128.3, 127.1, 124.0, 84.2, 82.4, 66.4, 46.8 (br.), 37.8, 28.2, 26.0, 24.0, 18.2, -4.2, -4.7; IR (ATR): ν_{max} 2930, 2245, 1722, 1459, 1393, 1369, 1300, 1256, 1147, 1043, 996, 836, 753, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{23}H_{37}NNaO_3Si$ $[M+Na]^+$ 426.2435, found 426.2438.



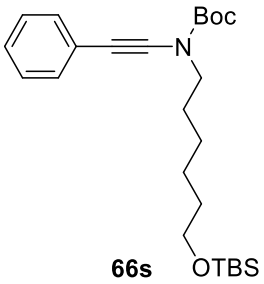
3q

***N*-[4-(*tert*-Butyldimethylsilyloxy)butyl]-*N*-*tert*-butoxycarbonyl-phenylethynylamine 66q.** Prepared according to the general procedure I. Yield: 24% (482 mg, 1.19 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.2 Hz, 2H), 7.30-7.21 (m, 3H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.53 (t, *J* = 7.2 Hz, 2H), 1.80 (quint., *J* = 7.4 Hz, 2H), 1.64-1.57 (m, 2H), 1.53 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 130.7, 128.3, 127.1, 124.0, 84.1, 82.4, 70.5 (br.), 62.7, 49.0 (br.), 29.8, 28.2, 26.1, 24.7, 18.4, -5.2; IR (ATR): ν_{max} 2931, 2244, 1721, 1462, 1394, 1369, 1303, 1256, 1147, 1101, 836, 775, 753, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{23}H_{41}N_2O_3Si$ $[M+NH_4]^+$ 421.2881, found 421.2884.



66r

***N*-[5-(*tert*-Butyldimethylsilyloxy)pentyl]-*N*-*tert*-butoxycarbonyl-phenylethynylamine 66r.** Prepared according to the general procedure I. Yield: 69% (1.45 g, 3.47 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.1 Hz, 2H), 7.30-7.21 (m, 3H), 3.62 (t, *J* = 6.4 Hz, 2H), 3.51 (t, *J* = 7.2 Hz, 2H), 1.74 (quint., *J* = 7.5 Hz, 2H), 1.61-1.53 (m, 2H), 1.53 (s, 9H), 1.46-1.38 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 130.8 (br.), 128.3, 127.1, 124.0, 84.2, 82.4, 63.1, 49.4 (br.), 32.6, 28.2, 28.0, 26.1, 22.9, 18.5, 1.2, -5.1; IR (ATR): ν_{max} 2932, 2243, 1721, 1472, 1394, 1369, 1300, 1255, 1159, 1100, 1098, 835, 753, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{24}H_{43}N_2O_3Si$ $[M+NH_4]^+$ 435.3037, found 435.3038.



66s

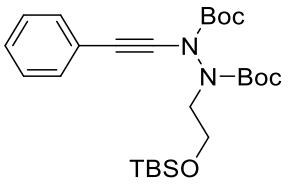
***N*-[6-(*tert*-Butyldimethylsilyloxy)hexyl]-*N*-*tert*-butoxycarbonyl-phenylethynylamine 66s.** Prepared according to the general procedure I. Yield: 61% (1.32 g, 3.05 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.2 Hz, 2H), 7.30-7.21 (m, 3H), 3.60 (t, *J* = 6.5 Hz, 2H), 3.50 (t, *J* = 7.2 Hz, 2H), 1.77-1.68 (m, 2H), 1.57-1.50 (m, 11H), 1.40-1.37 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 130.7 (br.), 128.3, 127.1, 124.0, 84.2, 82.4, 70.5 (br.), 63.3, 49.4 (br.), 32.9, 28.2, 28.1, 26.4, 26.1, 25.7, 18.5, -5.1; IR (ATR): ν_{max} 2934, 2243, 1721, 1462, 1394, 1369, 1300, 1253, 1160, 1099, 835, 775, 753, 690 cm^{-1}; ESIHRMS *m/z* calcd for $C_{25}H_{45}N_2O_3Si$ $[M+NH_4]^+$ 449.3194, found 449.3196.

Experimental Procedure and Characterization Data: Synthesis of Ynehydrazides

General procedure:[S9]

To a stirring solution of phenylacetylene (0.55 mL, 5.0 mmol) in THF (40 mL) was added *n*-BuLi (2.4 M solution in THF, 3.1 mL, 7.5 mmol) dropwise under argon at −78 °C. The resulting mixture was stirred for 15 minutes at −78 °C before the addition of a solution of di-*tert*-butylazodicarboxylate (1.73 g, 7.5 mmol) in THF (40 mL). The reaction mixture was slowly warmed to room temperature over 30 minutes and stirred for a further 30 minutes. Then the reaction was quenched with saturated aqueous ammonium chloride (50 mL) and the aqueous layer was extracted with EtOAc, washed with water and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was finally purified by flash column chromatography over silica gel to give the desired ynehydrazide as a colorless oil (1.10 g, 3.31 mmol, 66%).

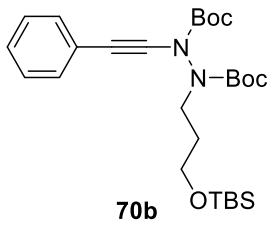
To a solution of ynehydrazide (1.33 g, 4 mmol), (2-bromoethoxy)-*tert*-butyldimethylsilane or (3-bromopropoxy)-*tert*-butyldimethylsilane (8 mmol), tetrabutylammonium hydrogen sulfate (136 mg, 0.4 mmol) and tetrabutylammonium iodide (148 mg, 0.4 mmol) in toluene (40 mL) was added aqueous sodium hydroxide solution (40 mL, 25% w/v) and the biphasic mixture was stirred vigorously for 24 hours at room temperature. The reaction was quenched with saturated aqueous ammonium chloride solution (60 mL), extracted with EtOAc, washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel to give the desired product.



70a

Di-*tert*-butyl 1-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2-(phenylethynyl)hydrazine-1,2-dicarboxylate 70a. Yield: 46% (903 mg, 1.84 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6, 353 K): δ7.40-7.32 (m, 5H), 3.82 (t, J = 6.0 Hz, 2H), 3.78-3.70 (m, 1H), 3.44 (dt, J = 11.2 and 5.5 Hz, 1H), 1.50 (s, 9H), 1.45 (s, 9H), 0.87 (s, 9H), 0.05 (d, J = 2.3 Hz, 6H); ^{13}C NMR (400 MHz, DMSO-d_6, 353 K): δ152.7, 151.1, 130.3, 128.1, 127.6, 122.0, 83.4, 82.3, 81.1, 59.6, 27.4, 27.2, 25.3, 17.4, -5.8 (d, J = 3.5 Hz); IR (ATR): ν_{max} 2931, 2252, 1749, 1723, 1473, 1369, 1294, 1256, 1148, 1108, 837, 753, 601 cm^{-1}; ESIHRMS *m/z* calcd for $C_{26}H_{42}N_2NaO_5Si$ $[M+Na]^+$ 513.2755, found 513.2753.

[S9] C. D. Campbell, R. L. Greenaway, O. T. Holton, P. R. Walker, H. A. Chapman, C. A. Russell, G. Carr, A. L. Thomson and E. A. Anderson, *Chem. Eur. J.* **2015**, *21*, 12627.



70b

Di-*tert*-butyl 1-[3-(*tert*-butyldimethylsilyloxy)propyl]-2-(phenylethynyl)hydrazine-1,2-dicarboxylate 70b. Yield: 66% (1.33 g, 2.64 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6, 353 K): δ7.40-7.33 (m, 5H), 3.71 (t, *J* = 6.2 Hz, 2H), 3.67 (t, *J* = 6.2 Hz, 1H), 3.48 (quint., *J* = 7.0 Hz, 1H), 1.81 (quint., *J* = 6.6 Hz, 2H), 1.50 (s, 9H), 1.45 (s, 9H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, 353 K): δ152.8, 151.1, 130.3, 128.2, 127.6, 121.8, 83.4, 82.2, 81.0, 59.6, 30.0, 27.4, 27.2, 25.3, 17.4, -5.8; IR (ATR): ν_{max} 2931, 2252, 1750, 1723, 1473, 1369, 1295, 1255, 1152, 1106, 1007, 836, 753, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{27}H_{44}N_2NaO_5Si$ $[M+Na]^+$ 527.2912, found 527.2911.

Experimental Procedure and Characterization Data: Synthesis of the Starting Ynamides and Ynehydrazides

General procedure I: synthesis of *N*-iodoalkyl-ynamides and *N*-iodoalkyl-yne-hydrazides

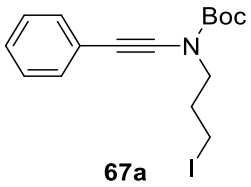
To a solution of the ynamide or ynehydrazide (2 mmol) in dry THF (20 mL) was added tetrabutylammonium floride (TBAF, 1M solution in THF, 4 mmol, 4 mL) under argon at 0 °C dropwise. The resulting mixture was stirred for 30 minutes at 0 °C, warmed to room temperature and stirred for another 30 minutes. The reaction was quenched by addition of water (20 mL) and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the desired hydroxyl ynamide or ynehydrazide which was used in the next step without further purification.

To a solution of triphenylphosphine (682 mg, 2.6 mmol) and imidazole (177 mg, 2.6 mmol) in dichloromethane (10 mL) was added iodine (558 mg, 2.2 mmol) in one portion at 0 °C under argon in dark. The resulting mixture was stirred for 5 minutes before adding a solution of hydroxyl ynamide or ynehydrazide (2 mmol) in dichloromethane (10 mL) via syringe. The light yellow solution was stirred for 1 hour at 0 °C, warmed to room temperature, filtered through a plug of silica gel (washed with EtOAc) and concentrated under reduced pressure. The crude residue was finally purified by flash column chromatography over silica gel to give the desired *N*-iodoalkyl-ynamide or *N*-iodoalkyl-ynehydrazide.

General procedure II: synthesis of *N*-bromoalkyl-ynamides

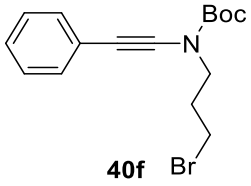
To a solution of the ynamide (2 mmol) in dry THF (20 mL) was added tetrabutylammonium fluoride (TBAF, 1M solution in THF, 4 mmol, 4 mL) dropwise under argon at 0 °C. The resulting mixture was stirred for 30 minutes at 0 °C, warmed to room temperature and stirred for another 30 minutes. The reaction was quenched by addition of water (20 mL) and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the desired hydroxyl ynamide which was used in the next step without further purification.

To a solution of triphenylphosphine (1.05 g, 4 mmol), imidazole (272 mg, 4 mmol) and tetrabromomethane (862 mg, 2.6 mmol) in THF (10 mL) at 0 °C under argon was added a solution of hydroxyl ynamide (2 mmol) in THF (10 mL) via syringe. The resulting solution was stirred for 1 hour at 0 °C, warmed to room temperature, filtered through a plug of silica gel (washed with EtOAc) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired *N*-bromoalkyl-ynamide.



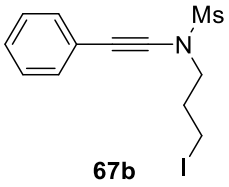
67a

***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-phenylethynylamine 67a.** Prepared according to general procedure I starting from 2.0 mmol of ynamide. Yield 31% (240 mg, 623 µmol). Solvent system for flash column chromatography: PE/EtOAc: 15/1; Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.8 Hz, 2H), 7.32-7.22 (m, 3H), 3.63 (t, *J* = 6.6 Hz, 2H), 3.27 (t, *J* = 6.9 Hz, 2H), 2.25 (quint., *J* = 6.7 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 130.8, 128.4, 127.4, 123.6, 109.7, 83.8, 82.9, 49.9 (br.), 32.3, 28.2, 2.1; IR (ATR): ν_{max} 2979, 2244, 1720, 1394, 1369, 1307, 1242, 1150, 857, 754, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{16}H_{20}INNaO_2$ $[M+Na]^+$ 408.0431, found 408.0410.



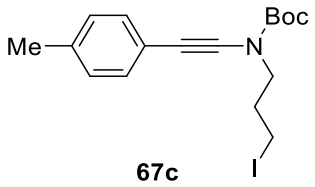
40f

***N*-(3-Bromopropyl)-*N*-*tert*-butoxycarbonyl-phenylethynylamine 40f.** Prepared according to general procedure II starting from 1.60 mmol of ynamide. Yield: 62% (333 mg, 984 µmol). Solvent system for flash column chromatography: PE/EtOAc: 5/1; Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.35 (m, 2H), 7.31-7.21 (m, 3H), 3.68 (t, *J* = 6.6 Hz, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 2.28 (quint., *J* = 6.6 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9, 130.8, 128.3, 127.3, 123.6, 83.7, 82.9, 48.0, 31.5, 30.1, 21.8; IR (ATR): ν_{max} 2978, 2244, 1720, 1394 1369, 1308, 1254, 1151, 857, 754, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{16}H_{20}BrNNaO_2$ $[M+Na]^+$ 360.0570, found 360.0575.



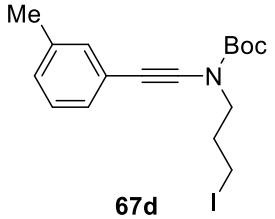
67b

***N*-(3-Iodopropyl)-*N*-(methylsulfonyl)phenylethynylamine 67b.** Prepared according to general procedure I starting from 3.23 mmol of ynamide. Yield: 57% (677 mg, 1.86 mmol). Solvent system for flash column chromatography: PE/EtOAc: 15/1; White solid; Mp: 43-45 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44-7.41 (m, 2H), 7.33-7.30 (m, 3H), 3.66 (t, *J* = 6.6 Hz, 2H), 3.30 (t, *J* = 6.8 Hz, 2H), 3.16 (s, 3H), 2.31 (quint., *J* = 6.7 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 131.6, 128.5, 128.3, 122.3, 81.3, 71.5, 52.1, 38.4, 32.5, 1.3; IR (ATR): ν_{max} 1351, 1150, 962, 781, 758, 692, 631 cm^{-1}; ESIHRMS *m/z* calcd for $C_{12}H_{15}INO_2S$ $[M+H]^+$ 363.9863, found 363.9863.



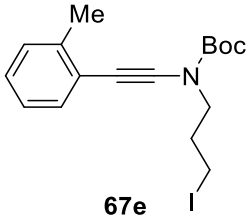
67c

***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-(4-tolylethynyl)amine 67c.** Prepared according to general procedure I starting from 3.54 mmol of ynamide. Yield: 66% (926 mg, 2.32 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Pale yellow solid; Mp: 36-38 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.9 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.26 (t, *J* = 6.9 Hz, 2H), 2.34 (s, 3H), 2.25 (quint., *J* = 6.7 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 137.4, 130.8, 129.1, 120.4, 82.9, 82.8, 70.6 (br.), 49.8 (br.), 32.3, 28.2, 21.5, 2.1; IR (ATR): ν_{max} 2980, 2244, 1716, 1440, 1392, 1368, 1305, 1242, 1146, 855, 815, 764 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{22}INNaO_2$ $[M+Na]^+$ 422.0587, found 422.0567.



67d

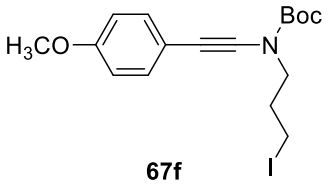
***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-(3-tolylethynyl)amine 67d.** Prepared according to general procedure I starting from 3.0 mmol of ynamide. Yield: 55% (654 mg, 1.64 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20-7.16 (m, 3H), 7.08-7.06 (m, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.26 (t, *J* = 6.9 Hz, 2H), 2.32 (s, 3H), 2.25 (quint., *J* = 6.8 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.0, 138.0, 131.4 (br.), 128.3, 127.9, 126.9, 123.4, 83.3, 82.8 (br.), 70.8 (br.), 49.9 (br.), 32.3, 28.2, 21.4, 2.0; IR (ATR): ν_{max} 2975, 2246, 1720, 1390, 1369, 1308, 1248, 1154, 852, 782, 763, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{22}INNaO_2$ $[M+Na]^+$ 422.0587, found 422.0586.



67e

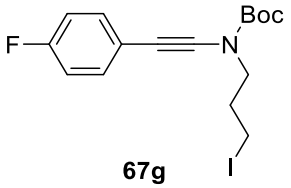
***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-(2-tolylethynyl)amine 67e.** Prepared according to general procedure I starting from 3.57 mmol of ynamide. Yield: 48% (678 mg, 1.70 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.2 Hz, 1H), 7.19-7.10 (m, 3H), 3.65 (t, *J* = 6.6 Hz, 2H), 3.27 (t, *J* = 6.9 Hz, 2H), 2.42 (s, 3H), 2.28 (quint., *J* = 6.8 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.0, 138.8, 130.7 (br.), 129.4,

127.2, 125.6, 123.4, 87.6, 82.9, 70.0 (br.), 49.9 (br.), 32.3, 28.3, 21.0, 2.0; IR (ATR): ν_{max} 2980, 2242, 1718, 1456, 1391, 1369, 1307, 1242, 1150, 856, 754 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{22}INNaO_2$ $[M+Na]^+$ 422.0587, found 422.0593.



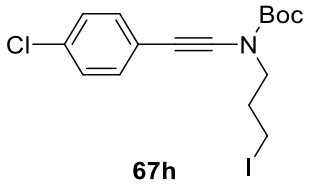
67f

***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-(4-methoxyphenyl)ethynylamine 67f.** Prepared according to general procedure I starting from 4.15 mmol of ynamide. Yield: 60% (1.03 g, 2.48 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.26 (t, *J* = 6.9 Hz, 2H), 2.24 (quint., *J* = 6.8 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 154.1, 134.2, 132.6 (br.), 115.6, 114.0, 82.8, 82.2, 55.4, 50.1 (br.), 32.3, 28.2, 2.1; IR (ATR): ν_{max} 2976, 1710, 1604, 1510, 1456, 1367, 1298, 1253, 1176, 1148, 1033, 829, 784 cm^{-1}; ESIHRMS m/z calcd for $C_{17}H_{22}INNaO_3$ $[M+Na]^+$ 438.0537, found 438.0523.



67g

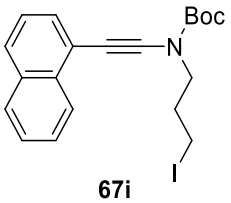
***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-(4-fluorophenyl)ethynylamine 67g.** Prepared according to general procedure I starting from 1.58 mmol of ynamide. Yield: 74% (473 mg, 1.17 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 28-30 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (t, *J* = 6.8 Hz, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.26 (t, *J* = 6.9 Hz, 2H), 2.24 (quint., *J* = 6.7 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ^{13}C dec ^{19}F): δ 162.1, 153.9, 132.7, 119.6, 115.6, 83.3, 83.0, 69.6 (br.), 50.0 (br.), 32.3, 28.2, 2.0; IR (ATR): ν_{max} 2979, 2247, 1721, 1601, 1511, 1394, 1369, 1308, 1233, 1151, 834, 763 cm^{-1}; ESIHRMS m/z calcd for $C_{16}H_{19}FINNaO_2$ $[M+Na]^+$ 426.0377, found 426.0348.



67h

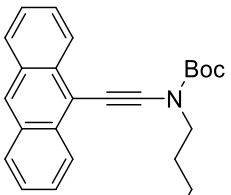
***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-(4-chlorophenyl)ethynylamine 67h.** Prepared according to general procedure I starting from 3.56 mmol of ynamide. Yield: 76% (1.14 g, 2.71 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Pale yellow solid; Mp: 45-47 °C; ^{1}H

NMR (300 MHz, $CDCl_3$): δ 7.31-7.24 (m, 4H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.25 (t, *J* = 6.9 Hz, 2H), 2.23 (quint., *J* = 6.7 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8, 133.2, 132.0, 128.7, 122.1, 84.7, 83.1, 69.8 (br.), 50.0 (br.), 32.3, 28.2, 2.0; IR (ATR): ν_{max} 3005, 2363, 1714, 1390, 1369, 1308, 1260, 1159, 823, 750 cm^{-1}; ESIHRMS m/z calcd for $C_{16}H_{19}ClINNaO_2$ $[M+Na]^+$ 442.0041, found 442.0062.



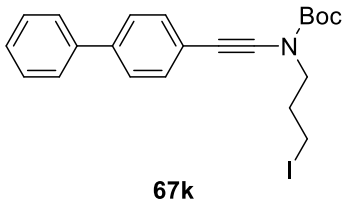
67i

***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-(naphthalen-1-yl)ethynylamine 67i.** Prepared according to general procedure I starting from 2.03 mmol of ynamide. Yield: 50% (434 mg, 1.01 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 9.1 Hz, 1H), 7.86-7.83 (m, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.56-7.49 (m, 2H), 7.42 (t, *J* = 7.7 Hz, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.32 (t, *J* = 6.9 Hz, 2H), 2.35 (quint., *J* = 6.8 Hz, 2H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 133.3, 132.8, 128.3, 127.4, 126.5, 126.42, 126.37, 125.4, 121.4, 88.6, 83.2, 69.5 (br.), 50.0 (br.), 32.3, 28.3, 2.1; IR (ATR): ν_{max} 2978, 2241, 1719, 1370, 1305, 1241, 1147, 847, 798, 772 cm^{-1}; ESIHRMS m/z calcd for $C_{20}H_{23}INO_2$ $[M+H]^+$ 436.0768, found 436.0769.



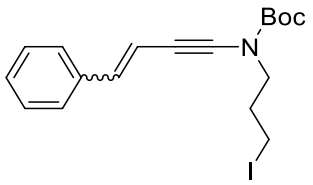
67j

***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-(anthracen-9-yl)ethynylamine 67j.** Prepared according to general procedure I starting from 1.39 mmol of ynamide. Yield: 61% (410 mg, 845 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Red solid; Mp: 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 8.4 Hz, 2H), 8.34 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 2H), 7.54-7.47 (m, 4H), 3.88 (t, *J* = 6.8 Hz, 2H), 3.37 (t, *J* = 6.8 Hz, 2H), 2.46 (quint., *J* = 6.8 Hz, 2H), 1.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 131.43, 131.40, 128.8, 127.0, 126.2, 126.0, 125.7, 118.2, 94.8, 83.6, 68.9 (br.), 50.5 (br.), 32.4, 28.4, 2.0; IR (ATR): ν_{max} 3411, 3343, 3093, 2958, 2236, 1710, 1299, 1148, 735, 667 cm-1; ESIHRMS m/z calcd for $C_{24}H_{25}INO_2$ $[M+H]^+$ 486.0930, found 486.0910.



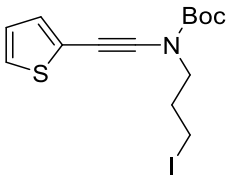
67k

***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-[(1,1'-biphenyl)-4-yl]ethynylamine 67k.** Prepared according to general procedure I starting from 770 µmol of ynamide. Yield: 13% (46 mg, 100 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.53 (m, 4H), 7.46-7.42 (m, 4H), 7.37-7.33 (m, 1H), 3.65 (t, *J* = 6.6 Hz, 2H), 3.29 (t, *J* = 6.9 Hz, 2H), 2.28 (quint., *J* = 6.7 Hz, 2H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 140.6, 140.1, 131.2, 128.9, 127.6, 127.1, 122.6, 84.4, 83.0, 70.6 (br.), 50.0 (br.), 32.3, 28.3, 28.2, 2.1; IR (ATR): ν_{max} 2975, 2241, 1717, 1394, 1369, 1308, 1243, 1150, 840, 763, 697 cm-1; ESIHRMS m/z calcd for $C_{22}H_{24}INNaO_2$ $[M+Na]^+$ 484.0744, found 484.0748.



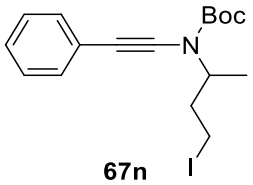
67l

***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-(4-phenylbut-3-en-1-yn-1-yl)amine 67l.** Prepared according to general procedure I starting from 1.72 mmol of ynamide. Yield: 64% (454 mg, 1.10 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.5 Hz, 0.36H), 7.38-7.23 (m, 4.64H), 6.82 and 6.50 (d, *J* = 16.2 Hz, 0.82H, d, *J* = 11.9 Hz, 0.18H), 6.28 and 5.83 (d, J = 16.2 Hz, 0.82 H, d, J = 11.9 Hz, 0.18 H), 3.64-3.57 (m, 2H), 3.26-3.20 (m, 2H), 2.27-2.19 (m, 2H), 1.54 and 1.53 (s, 1.62H, s, 7.38H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9 (major isomer), 153.8 (minor isomer), 138.4 (major isomer), 136.9 (minor isomer), 136.8 (major isomer), 134.9 (minor isomer), 128.8 (major isomer), 128.4 (minor isomer), 128.3 (minor isomer), 128.2 (major isomer), 128.1 (minor isomer), 126.1 (major isomer), 108.2 (major isomer), 107.3 (minor isomer), 85.9 (major isomer), 83.3 (minor isomer), 83.1 (major isomer), 70.4 (br., major isomer), 70.3 (minor isomer), 50.4 (br., major isomer), 50.1 (minor isomer), 32.3 (major isomer), 32.2 (minor iomer), 28.3 (minor isomer), 28.2 (major isomer), 2.0 (major isomer), 1.7 (minor isomer); IR (ATR): ν_{max} 2980, 2228, 1719, 1392, 1369, 1297, 1234, 1151, 949, 854, 748, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{22}INNaO_2$ $[M+Na]^+$ 434.0587, found 434.0593.



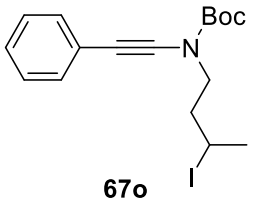
67m

***N*-(3-Iodopropyl)-*N*-*tert*-butoxycarbonyl-(thiophen-2-yl)ethynylamine 67m.** Prepared according to general procedure I starting from 1.43 mmol of the corresponding ynamide. Yield: 62% (348 mg, 889 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 5.2 Hz, 1H), 7.15 (d, *J* = 3.4 Hz, 1H), 6.96 (t, *J* = 4.4 Hz, 1H), 3.61 (t, *J* = 6.7 Hz, 2H), 3.24 (t, *J* = 6.9 Hz, 2H), 2.23 (quint., *J* = 6.8 Hz, 2H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 131.6 (br.), 127.0, 126.8, 123.6, 86.9, 83.2, 50.2 (br.), 32.2, 28.2, 25.8, 1.8; IR (ATR): ν_{max} 2979, 2241, 1720, 1441, 1385, 1369, 1297, 1240, 1152, 909, 847, 763, 733, 700 cm^{-1}; ESIHRMS *m/z* calcd for $C_{14}H_{18}INNaO_2S$ $[M+Na]^+$ 413.9995, found 413.9996.



67n

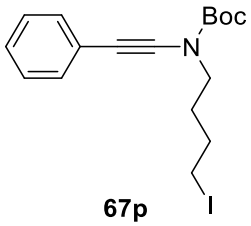
***N*-(4-Iodobutan-2-yl)-*N*-*tert*-butoxycarbonyl-phenylethynylamine 67n.** Prepared according to general procedure I starting from 2.7 mmol of ynamide. Yield: 56% (599 mg, 1.50 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 32-34 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.23 (m, 3H), 7.14-7.10 (m, 2H), 4.28-4.20 (m, 1H), 2.93-2.76 (m, 2H), 2.02-1.92 (m, 1H), 1.61-1.52 (m, 1H), 1.55 (s, 9H), 1.27 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 140.9, 139.1, 128.3, 128.1, 125.1, 108.5, 80.6, 55.9, 29.3, 28.7, 28.6, 20.0; IR (ATR): ν_{max} 2979, 2242, 1717, 1399, 1369, 1297, 1252, 1155, 861, 754, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{22}INNaO_2$ $[M+Na]^+$ 422.0587, found 422.0595.



67o

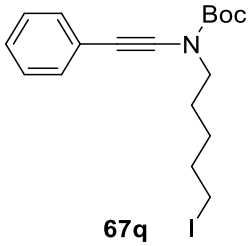
***N*-(3-Iodobutyl)-*N*-*tert*-butoxycarbonyl-phenylethynylamine 67o.** Prepared according to general procedure I starting from 1.26 mmol of ynamide. Yield: 34% (171 mg, 428 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.0 Hz, 2H), 7.31-7.22 (m, 3H), 4.31-4.22 (m, 1H), 3.75-3.68 (m, 1H), 3.66-3.57 (m, 1H), 2.27-2.18 (m, 1H), 2.13-2.04 (m, 1H), 1.99 (d, *J* = 6.9 Hz, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 130.8, 128.4, 127.3, 123.6, 83.8, 82.9, 49.7 (br.), 41.2, 29.1, 28.2, 24.8; IR (ATR): ν_{max} 2979, 2245, 1721, 1443,

1394, 1369, 1296, 1236, 1150, 908, 857, 754, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{22}INNaO_2$ $[M+Na]^+$ 422.0587, found 422.0591.



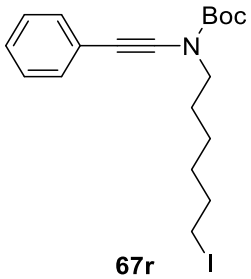
67p

***N*-(4-Iodobutyl)-*N*-*tert*-butoxycarbonyl-phenylethynylamine 67p.** Prepared according to general procedure I starting from 890 µmol of ynamide. Yield: 41% (145 mg, 363 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.0 Hz, 2H), 7.31-7.23 (m, 3H), 3.55 (t, *J* = 6.6 Hz, 2H), 3.24 (t, *J* = 6.7 Hz, 2H), 1.96-1.81 (m, 2H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 130.8, 128.4, 127.3, 123.8, 83.8, 82.7, 48.0 (br.), 30.3, 29.0, 28.3, 28.2, 6.0; IR (ATR): ν_{max} 2979, 2243, 1717, 1394, 1369, 1292, 1253, 1151, 851, 754, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{22}INNaO_2$ $[M+Na]^+$ 422.0587, found 422.0593.



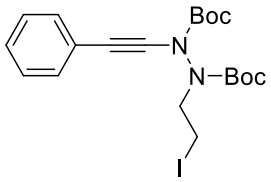
67q

***N*-(5-Iodopentyl)-*N*-*tert*-butoxycarbonyl-phenylethynylamine 67q.** Prepared according to general procedure I starting from 3.47 mmol of ynamide. Yield: 80% (1.15 g, 2.78 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.1 Hz, 2H), 7.31-7.22 (m, 3H), 3.52 (t, *J* = 7.1 Hz, 2H), 3.19 (t, *J* = 7.0 Hz, 2H), 1.89 (quint., *J* = 7.3 Hz, 2H), 1.75 (quint., *J* = 7.4 Hz, 2H), 1.54 (s, 9H), 1.54-1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 130.8, 128.4, 127.2, 123.8, 84.0, 82.6, 48.9 (br.), 33.2, 28.2, 27.5, 27.1, 6.6; IR (ATR): ν_{max} 2935, 2244, 1718, 1394, 1360, 1303, 1150, 856, 754, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{24}INNaO_2$ $[M+Na]^+$ 436.0744, found 436.0549.



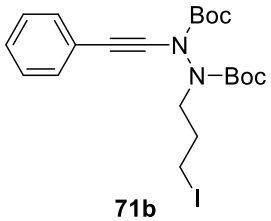
67r

***N*-(6-Iodohexyl)-*N*-*tert*-butoxycarbonyl-phenylethynylamine 67r.** Prepared according to general procedure I starting from 3.0 mmol of ynamide. Yield: 33% (422 mg, 988 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.1 Hz, 2H), 7.31-7.21 (m, 3H), 3.51 (t, *J* = 7.2 Hz, 2H), 3.18 (t, *J* = 7.0 Hz, 2H), 1.84 (quint., *J* = 7.1 Hz, 2H), 1.74 (quint., *J* = 7.2 Hz, 2H), 1.53 (s, 9H), 1.48-1.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 130.7, 128.3, 127.2, 123.9, 84.1, 82.5, 49.1 (br.), 33.5, 30.2, 28.3, 28.2, 27.9, 25.5, 6.9; IR (ATR): ν_{max} 2933, 2243, 1717, 1394, 1368, 1303, 1256, 1149, 855, 753, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{19}H_{26}INNaO_2$ $[M+Na]^+$ 450.0900, found 450.0908.



71a

Di-*tert*-butyl 1-(2-iodoethyl)-2-(phenylethynyl)hydrazine-1,2-dicarboxylate 71a. Prepared according to the general procedure using toluene as the solvent instead of dichloromethane, starting from 450 µmol of the corresponding hydrazide. Yield: 77% (168 mg, 345 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6, 353 K): δ 7.41-7.33 (m, 5H), 4.01 (quint., *J* = 7.4 Hz, 1H), 3.78-3.72 (m, 1H), 3.42 (t, *J* = 6.9 Hz, 2H), 1.51 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, 353 K): δ 152.2, 150.9, 130.3, 128.2, 127.6, 121.8, 110.2, 84.7, 82.2, 81.6, 61.9, 43.7, 27.4, 27.2, 23.3, 1.2; IR (ATR): ν_{max} 2980, 1728, 1541, 1457, 1385, 1369, 1280, 1258, 1150, 755, 693 cm^{-1}; ESIHRMS *m/z* calcd for $C_{20}H_{27}IN_2NaO_4$ $[M+Na]^+$ 509.0908, found 509.0915.



71b

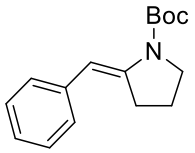
Di-*tert*-butyl 1-(3-iodopropyl)-2-(phenylethynyl)hydrazine-1,2-dicarboxylate 71b. Prepared according to general procedure I starting from 2.75 mmol of the corresponding hydrazide. Yield: 43% (588 mg, 1.18 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H

NMR (400 MHz, DMSO-d_6, 353 K): δ 7.39-7.35 (m, 5H), 3.68 (quint., *J* = 6.9 Hz, 1H), 3.51 (quint., *J* = 6.9 Hz, 1H), 3.34 (t, *J* = 7.0 Hz, 2H), 2.13 (quint., *J* = 6.8 Hz, 2H), 1.51 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, 353 K): δ 152.7, 151.0, 130.3, 128.2, 127.7, 121.7, 83.6, 81.8, 81.3, 73.7, 58.0, 49.0, 31.0, 27.4, 27.2, 23.3, 3.3; IR (ATR): ν_{max} 2979, 1748, 1722, 1456, 1369, 1295, 1256, 1148, 858, 753, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{21}H_{29}IN_2NaO_4$ $[M+Na]^+$ 523.1064, found 523.1067.

Experimental Procedure and Characterization Data: Radical Cyclization to Azacycles and Diazacycles

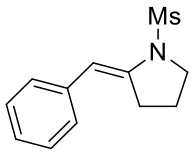
General procedure:

An oven-dried 50 mL two-necked round bottom flask was charged with the *N*-haloalkyl-ynamide (0.25 mmol) and 2,2'-Azobis(2-methylpropionitrile) (16.4 mg, 0.1 mmol). The flask was fitted with a condenser and rubber septa, evacuated under high vacuum and backfilled with argon for 3 times before the addition of degassed toluene (6.5 mL). The resulting mixture was heated to 80 °C for 10 minutes in dark. After that, a solution of *n*-Bu_3SnH (101 µL, 0.375 mmol) in degassed toluene (6.5 mL) was added dropwise via a syringe pump over 1 hour. After the addition, the reaction was stirred at 80 °C for 1 hour before cooling down to room temperature. The reaction was quenched by addition of saturated aqueous solution of potassium fluoride (10 mL) and the mixture was stirred for another 1 hour at room temperature. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired cyclized product.



68a

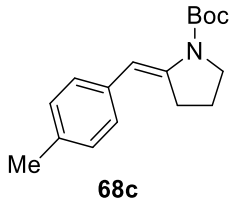
***(E)-N-tert*-Butoxycarbonyl-2-benzylidenepyrrolidine 68a.** Yield: 88% (57 mg, 220 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 72-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.22 (m, 4H), 7.14-7.09 (m, 2H), 3.65 (t, *J* = 7.0 Hz, 2H), 2.81 (td, *J* = 7.4 and 2.0 Hz, 2H), 1.85 (quint., *J* = 7.2 Hz, 2H), 1.55 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.0, 141.0, 139.1, 128.3, 128.1, 125.1, 108.5, 80.8, 49.0, 30.7, 28.6, 22.2; IR (ATR): ν_{max} 3064, 2925, 1699, 1391, 1331, 1161, 1140, 855, 749, 697 cm^{-1}; ESIHRMS *m/z* calcd for $C_{16}H_{21}NNaO_2$ $[M+Na]^+$ 282.1465, found 282.1500.



68b

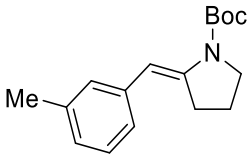
***(E)-N*-Methylsulfonyl-2-benzylidenepyrrolidine 68b.** Yield: 69% (41 mg, 173 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow solid; Mp: 105-107 °C; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 7.31 (t, *J* = 5.1 Hz, 2H), 7.23 (d, *J* = 5.2 Hz, 2H), 7.17 (t, *J* = 4.9 Hz, 1H), 6.62 (s, 1H), 3.70 (dt, *J* = 4.5 and 0.5 Hz, 2H), 2.97 (d, *J* = 0.5 Hz, 3H), 2.86 (dt, *J* = 4.8 and 1.1 Hz, 2H), 1.96 (quint., *J* = 4.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 137.5, 128.4, 128.2, 126.0, 108.2, 50.9, 34.5, 30.8, 22.5; IR (ATR): ν_{max} 2930, 1647, 1448, 1332, 1202, 1148 1087, 1015, 973, 760, 700, 688, 649, 638 cm^{-1}; ESIHRMS *m/z* calcd for $C_{12}H_{16}NO_2S$ $[M+Na]^+$ 238.0896, found 238.0894.



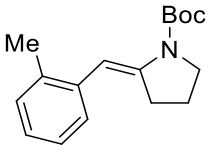
68c

***(E)-N-tert*-Butoxycarbonyl-2-(4-methylbenzylidene)pyrrolidine 68c.** Yield: 94% (64 mg, 234 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 56-58 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15-7.08 (m, 5H), 3.64 (t, *J* = 7.0 Hz, 2H), 2.80 (td, *J* = 7.4 and 1.9 Hz, 2H), 2.32 (s, 3H), 1.84 (quint., *J* = 7.2 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.0, 140.4, 136.1, 134.7, 128.9, 128.2, 108.4, 80.7, 49.0, 30.7, 28.6, 22.2, 21.2; IR (ATR): ν_{max} 3365, 2978, 2363, 1703, 1686, 1390, 1366, 1329, 1252, 1161, 1142, 860, 764, 637 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{23}NNaO_2$ $[M+Na]^+$ 282.1465, found 282.1500.



68d

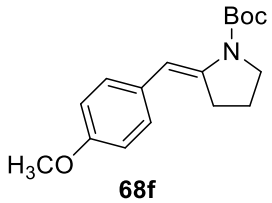
***(E)-N-tert*-Butoxycarbonyl-2-(3-methylbenzylidene)pyrrolidine 68d.** Yield: 97% (66 mg, 241 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (t, *J* = 7.8 Hz, 1H), 7.12-6.99 (m, 3H), 6.94 (d, *J* = 7.5 Hz, 1H), 3.65 (t, *J* = 7.0 Hz, 2H), 2.81 (td, *J* = 7.4 and 1.9 Hz, 2H), 2.33 (s, 3H), 1.84 (quint., *J* = 7.2 Hz, 2H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 140.8, 139.0, 137.6, 129.1, 128.0, 125.9, 125.3, 108.5, 80.7, 48.9, 30.7, 28.6, 22.2, 21.6; IR (ATR): ν_{max} 3373, 2975, 1712, 1516, 1455, 1392, 1366, 1251, 1169, 1042, 750, 701 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{24}NO_2$ $[M+H]^+$ 274.1802, found 274.2796.



68e

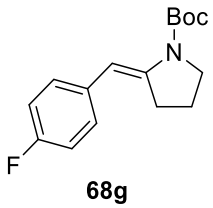
***(E)-N-tert*-Butoxycarbonyl-2-(2-methylbenzylidene)pyrrolidine 68e.** Yield: 64% (44 mg, 161 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.02 (m, 5H), 3.66 (t, *J* = 6.9 Hz, 2H), 2.68 (td, *J* = 7.4 and 2.0 Hz, 2H), 2.30 (s,

3H), 1.81 (quint., *J* = 7.2 Hz, 2H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 140.6, 138.0, 136.4, 129.7, 128.4, 125.7, 125.4, 106.8, 80.7, 49.2, 30.6, 28.6, 22.2, 20.4; IR (ATR): ν_{max} 2274, 1706, 1387, 1330, 1249, 1161, 1142, 1001, 748 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{23}NNaO_2$ $[M+Na]^+$ 296.1621, found 296.1626.



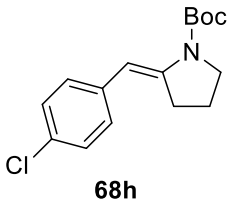
68f

***(E)-N-tert*-Butoxycarbonyl-2-(4-methoxybenzylidene)pyrrolidine 68f.** Yield: 93% (67 mg, 232 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Pale yellow solid; Mp: 37-39 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.7 Hz, 2H), 7.06 (br., 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H), 3.63 (t, *J* = 7.0 Hz, 2H), 2.77 (td, *J* = 7.4 and 2.0 Hz, 2H), 1.83 (quint., *J* = 7.2 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 153.0, 139.6, 131.6, 129.3, 113.6, 108.0, 80.6, 55.3, 48.9, 30.5, 28.5, 22.2; IR (ATR): ν_{max} 2979, 2363, 1694, 1511, 1389, 1367, 1330, 1248, 1164, 1143, 1039, 1003, 861, 826, 764, 750 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{23}NNaO_3$ $[M+Na]^+$ 312.1570, found 312.1574.



68g

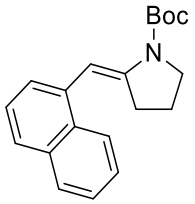
***(E)-N-tert*-Butoxycarbonyl-2-(4-fluorobenzylidene)pyrrolidine 68g.** Yield: 88% (61 mg, 220 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 78-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 8.7 and 5.6 Hz, 2H), 7.07 (br., 1H), 6.96 (t, *J* = 8.8 Hz, 2H), 3.64 (t, *J* = 7.0 Hz, 2H), 2.75 (td, *J* = 7.4 and 1.9 Hz, 2H), 1.84 (quint., *J* = 7.2 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ^{13}C dec ^{19}F): δ 160.7, 153.0, 140.8, 135.1, 129.6, 115.0, 107.4, 80.8, 49.0, 30.5, 28.5, 22.2; IR (ATR): ν_{max} 2933, 2334, 1704, 1508, 1387, 1331, 1226, 1144, 1003, 858, 824, 769, 667 cm^{-1}; ESIHRMS *m/z* calcd for $C_{16}H_{20}FNNaO_2$ $[M+Na]^+$ 300.1370, found 300.1376.



68h

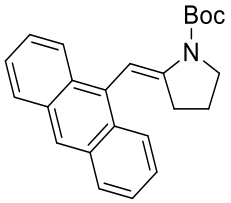
***(E)-N-tert*-Butoxycarbonyl-2-(4-chlorobenzylidene)pyrrolidine 68h.** Yield: 95% (70 mg, 238 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 95-97 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.07 (br., 1H), 3.64 (t, *J* = 7.0 Hz, 2H), 2.75 (td, *J* = 7.4 and 2.0 Hz, 2H), 1.84 (quint., *J* = 7.2 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (75

MHz, $CDCl_3$): δ152.9, 141.6, 137.6, 130.5, 129.4, 128.2, 107.2, 80.9, 49.0, 30.7, 28.5, 22.1; IR (ATR): ν_{max} 3360, 2978, 1708, 1639, 1490, 1387, 1367, 1328, 1244, 1162, 1143, 1091, 1003, 859, 742 cm^{-1}; ESIHRMS *m/z* calcd for $C_{16}H_{20}ClNNaO_2$ $[M+Na]^+$ 316.1075, found 316.1080.



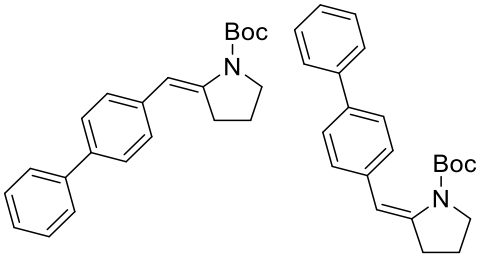
68i

***(E)-N-tert*-Butoxycarbonyl-2-(naphthalen-1-ylmethylene)pyrrolidine 68i.** Yield: 81% (63 mg, 204 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 93-95 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ8.17-8.14 (m, 1H), 7.86-7.82 (m, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.55-7.35 (m, 5H), 3.72 (t, *J* = 6.9 Hz, 2H), 2.69 (td, *J* = 7.4 and 2.0 Hz, 2H), 1.80 (quint., *J* = 7.1 Hz, 2H), 1.60 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ153.1, 141.8, 136.3, 133.7, 132.3, 128.3, 126.2, 125.9, 125.7, 125.6, 125.39, 125.36, 105.3, 80.8, 49.4, 30.8, 28.6, 22.2; IR (ATR): ν_{max} 2924, 2363, 1697, 1388, 1366, 1331, 1259, 1166, 1144, 856, 800, 780, 765, 752, 646 cm^{-1}; ESIHRMS *m/z* calcd for $C_{20}H_{23}NNaO_2$ $[M+Na]^+$ 332.1621, found 332.1626.



68j

***(E)-N-tert*-Butoxycarbonyl-2-(anthracen-9-ylmethylene)pyrrolidine 68j.** Yield: 90% (81 mg, 225 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Red oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ8.36 (s, 1H), 8.30-8.28 (m, 2H), 8.02-7.98 (m, 2H), 7.51-7.41 (m, 5H), 3.77 (t, *J* = 6.9 Hz, 2H), 2.09 (td, *J* = 7.5 and 1.9 Hz, 2H), 1.71 (quint., *J* = 7.2 Hz, 2H), 1.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ153.2, 142.6, 133.9, 131.7, 130.0, 128.7, 127.0, 125.5, 125.14, 125.08, 103.0, 80.9, 49.8, 30.6, 28.7, 21.7; IR (ATR): ν_{max} 2975, 1705, 1383, 1326, 1259, 1161, 1143, 909, 845, 735 cm^{-1}; ESIHRMS *m/z* calcd for $C_{24}H_{26}NO_2$ $[M+H]^+$ 360.1958, found 360.1945.

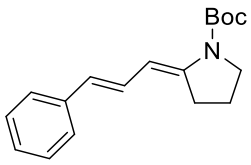


68k **68k'**

***(E)-N-tert*-Butoxycarbonyl-2-[(1,1'-biphenyl)-4-ylmethylene]pyrrolidine 68k and *(Z)-N-tert*-Butoxycarbonyl-2-[(1,1'-biphenyl)-4-ylmethylene]pyrrolidine 68k'.** Starting from 76 µmol of the corresponding *N*-iodoalkyl-ynamide. Two separable isomers were obtained with a ratio of 66:34.

- ***(E)-N-tert*-Butoxycarbonyl-2-[(1,1'-biphenyl)-4-ylmethylene]pyrrolidine 68k** *(faster eluting isomer).* Yield: 47% (12 mg, 36 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 63-65 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.2 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 3H), 7.16 (br., 1H), 3.67 (t, *J* = 7.0 Hz, 2H), 2.87 (td, *J* = 7.4 and 1.9 Hz, 2H), 1.88 (quint., *J* = 7.2 Hz, 2H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 141.3, 141.1, 138.2, 137.8, 128.9, 128.6, 127.1, 127.0, 126.9, 108.1, 80.9, 49.0, 30.9, 29.8, 28.6, 27.6, 22.3; IR (ATR): ν_{max} 3468, 3342, 2364, 1698, 1398, 1335, 1276, 1142, 750 cm^{-1}; ESIHRMS *m/z* calcd for $C_{22}H_{25}NNaO_2$ $[M+Na]^+$ 358.1778, found 358.1783.

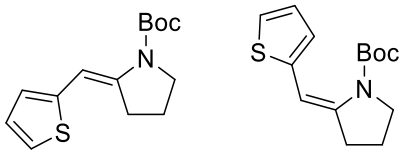
- ***(Z)-N-tert*-Butoxycarbonyl-2-[(1,1'-biphenyl)-4-ylmethylene]pyrrolidine 68k'** *(slower eluting isomer).* Yield: 24% (6 mg, 18 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 64-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.1 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.34-7.29 (m, 3H), 5.84 (s, 1H), 3.75 (t, *J* = 7.1 Hz, 2H), 2.57 (td, *J* = 7.4 and 1.2 Hz, 2H), 1.94 (quint., *J* = 7.3 Hz, 2H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 138.4, 138.3, 137.5, 128.9, 128.4, 127.1, 127.0, 126.5, 110.2, 80.9, 49.6, 33.8, 28.0, 21.4; IR (ATR): ν_{max} 2968, 2362, 1691, 1486, 1389, 1330, 1276, 1159, 860, 751, 697 cm^{-1}; ESIHRMS *m/z* calcd for $C_{22}H_{25}NNaO_2$ $[M+Na]^+$ 358.1778, found 358.1781.



68l

***(E)-N-tert*-Butoxycarbonyl-2-[3-phenylallylidene]pyrrolidine 68l.** Yield: 49% (35 mg, 123 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.87 (br., 1H), 6.81 (d, *J* = 11.1 Hz, 1H), 6.42 (d, *J* = 14.6 Hz, 1H), 3.67 (t, *J* = 7.0 Hz, 2H), 2.82 (t, *J* = 7.6 Hz, 2H), 1.89 (quint., *J* = 7.3 Hz, 2H), 1.55 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 141.8, 138.7, 128.6, 127.8, 127.3, 126.4, 125.9, 108.1, 81.0, 49.7, 29.5, 28.5, 21.5; IR (ATR): ν_{max} 3433, 2979, 1779, 1711, 1453, 1368, 1310,

1253, 1156, 847, 750, 701 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{23}NNaO_2$ $[M+Na]^+$ 308.1621, found 308.1630.

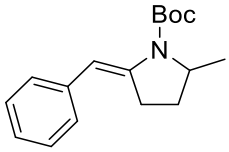


68m **68m'**

***(E)-N-tert*-Butoxycarbonyl-2-(thiophen-2-ylmethylene)pyrrolidine 68m and *(Z)-N-tert*-Butoxycarbonyl-2-(thiophen-2-ylmethylene)pyrrolidine 68m'.** Two separable isomers were obtained with a ratio of 68:32.

- ***(E)-N-tert*-Butoxycarbonyl-2-(thiophen-2-ylmethylene)pyrrolidine 68m** *(faster eluting isomer).* Yield: 54% (36 mg, 136 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; white solid; Mp: 37-39 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (br., 1H), 7.12 (d, *J* = 5.0 Hz, 1H), 6.98 (d, *J* = 3.6 Hz, 0.5H), 6.96 (d, *J* = 3.6 Hz, 0.5H), 6.85 (d, *J* = 3.5 Hz, 1H), 3.67 (t, *J* = 7.1 Hz, 2H), 2.87 (td, *J* = 7.6 and 2.0 Hz, 2H), 1.92 (quint., *J* = 7.3 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 142.5, 140.0, 127.1, 124.5, 122.7, 102.3, 81.0, 49.4, 31.0, 28.5, 21.7; IR (ATR): ν_{max} 2979, 2247, 1721, 1601, 1511, 1394, 1369, 1308, 1233, 1151, 834, 763 cm^{-1}; ESIHRMS *m/z* calcd for $C_{14}H_{19}NNaO_2S$ $[M+Na]^+$ 288.1029, found 288.1030.

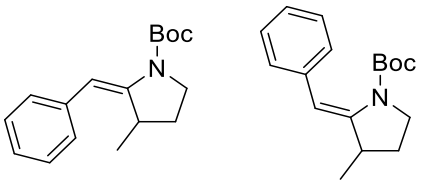
- ***(Z)-N-tert*-Butoxycarbonyl-2-(thiophen-2-ylmethylene)pyrrolidine 68m'** *(slower eluting isomer).* Yield: 26% (17 mg, 64 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 5.1 Hz, 1H), 6.91 (dd, *J* = 4.7 and 3.6 Hz, 1H), 6.85 (d, *J* = 3.1 Hz, 1H), 6.04 (s, 1H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 1.90 (quint., *J* = 7.3 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 137.8, 126.3, 125.4, 123.2, 105.6, 80.9, 49.5, 33.0, 28.5, 28.2, 21.5; IR (ATR): ν_{max} 2923, 1698, 1456, 1366, 1330, 1245, 1163, 853, 766, 688 cm^{-1}; ESIHRMS *m/z* calcd for $C_{14}H_{19}NNaO_2S$ $[M+Na]^+$ 288.1029, found 288.1025.



68n

***(E)-N-tert*-Butoxycarbonyl-2-benzylidene-5-methylpyrrolidine 68n.** Yield: 72% (49 mg, 179 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.23 (m, 4H), 7.14 (br., 1H), 7.13-7.09 (m, 1H), 4.27-4.20 (m, 1H), 2.93-2.76 (m, 2H), 2.04-1.92 (m, 1H), 1.61-1.54 (m, 1H), 1.55 (s, 9H), 1.27 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 140.9, 139.1, 128.3, 128.1, 125.1, 108.5, 80.6, 55.9, 29.4, 28.7, 28.6, 20.0; IR (ATR): ν_{max}

2975, 1704, 1384, 1347, 1319, 1296, 1257, 1170, 1141, 1025, 858, 765, 749, 697 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{24}NO_2$ $[M+H]^+$ 274.1802, found 294.1796.

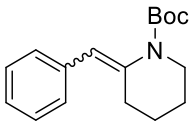


68o **68o'**

***(E)-N-tert*-Butoxycarbonyl-2-benzylidene-3-methylpyrrolidine 68o and *(Z)-N-tert*-Butoxycarbonyl-2-benzylidene-3-methylpyrrolidine 68o'.** Two separable isomers were obtained with a ratio of 57:43.

- ***(E)-N-tert*-Butoxycarbonyl-2-benzylidene-3-methylpyrrolidine 68o** *(faster eluting isomer).* Yield: 23% (16 mg, 59 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 4.5 Hz, 4H), 7.16-7.11 (m, 1H), 7.07 (br., 1H), 3.76-3.59 (m, 2H), 3.32 (quint., *J* = 7.1 Hz, 1H), 2.01-1.91 (m, 1H), 1.58 (d, *J* = 6.4 Hz, 1H), 1.54 (s, 9H), 1.16 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 146.0, 138.6, 128.3, 128.1, 125.3, 108.7, 80.7, 46.5, 35.0, 29.5, 28.6, 19.0; IR (ATR): ν_{max} 2974, 1706, 1519, 1455, 1366, 1253, 1170, 1042, 858, 750, 699 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{23}NNaO_2$ $[M+Na]^+$ 296.1621, found 296.1622.

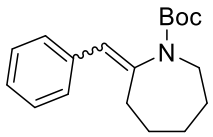
- ***(Z)-N-tert*-Butoxycarbonyl-2-benzylidene-3-methylpyrrolidine 68o'** *(slower eluting isomer).* Yield: 18% (12 mg, 44 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.21 (m, 4H), 7.12-7.08 (m, 1H), 5.69 (d, *J* = 1.7 Hz, 1H), 3.70-3.60 (m, 2H), 2.69-2.60 (m, 1H), 2.15-2.07 (m, 1H), 1.54 (s, 1H), 1.52-1.43 (m, 1H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.14 (br., 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 138.5, 128.0, 127.8, 125.7, 109.2, 80.6, 47.2, 38.1, 29.9, 28.6, 27.9, 17.2; IR (ATR): ν_{max} 3391, 2975, 1706, 1516, 1455, 1366, 1251, 1170, 1042, 731, 699 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{24}NO_2$ $[M+H]^+$ 274.1802, found 274.1792.



68p

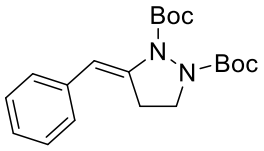
***N-tert*-Butoxycarbonyl-2-benzylidenepiperidine 68p.** Two inseparable isomers were obtained with a ratio of 66:34. Yield: 85% (58 mg, 212 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1. White solid; This compound has been previously reported.[S10]

[S10] Z. Szakonyi; M. D'hooghe; I. Kanizsai; F. Fueloep; N, De Kimpe, *Tetrahedron* **2005**, *61*, 1595.

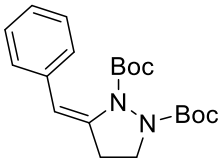


68q

***N-tert*-Butoxycarbonyl-2-benzylideneazepane 68q.** Starting from 500 µmol of the corresponding *N*-iodoalkyl-ynamide and double the concentration. Two inseparable isomers were obtained with a ratio of 71:29. Yield: 42% (61 mg, 212 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.36-7.18 (m, 5H), 6.43 and 6.11 (s, 0.71H, s, 0.29H), 3.92-3.87 (m, 0.29H), 3.52 (t, *J* = 5.8 Hz, 1.43H), 2.96-2.90 (m, 0.29H), 2.63 (t, *J* = 5.1 Hz, 1.43H), 2.57-2.45 (m, 0.58H), 1.72-1.54 (m, 6H), 1.48 and 1.29 (s, 6.39H, s, 2.61H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8 (major isomer), 154.4 (minor isomer), 142.3 (major isomer), 140.4 (minor isomer), 136.7 (major isomer), 136.3 (minor isomer), 128.9 (major isomer), 128.6 (minor isomer), 128.3 (major isomer), 128.0 (minor isomer), 127.4 (major isomer), 127.0 (minor isomer), 126.8 (major isomer), 124.4 (minor isomer), 79.6 (minor isomer), 79.5 (major isomer), 49.6 (major isomer), 47.0 (minor isomer), 36.6 (minor isomer), 31.6 (major isomer), 28.6 (major isomer), 28.3 (major isomer), 28.1 (minor isomer), 27.8 (minor isomer), 27.7 (major isomer), 27.5 (minor isomer), 27.4 (minor isomer), 26.3 (major isomer); IR (ATR): ν_{max} 2929, 1695, 1448, 1390, 1365, 1255, 1160, 1003, 861, 755, 697 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{25}NNaO_2$ $[M+Na]^+$ 310.1778, found 310.1779.



72a



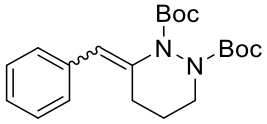
72a'

***(E)*-Di-*tert*-butyl 3-benzylidenepyrazolidine-1,2-dicarboxylate 72a and *(Z)*-Di-*tert*-butyl 3-benzylidenepyrazolidine-1,2-dicarboxylate 72a'.** Starting from 83 µmol of the corresponding iodo-hydrazine. Two separable isomers were obtained with a ratio of 56:44.

- ***(E)*-Di-*tert*-butyl 3-benzylidenepyrazolidine-1,2-dicarboxylate 72a.** *(faster eluting isomer).* Yield: 47% (14 mg, 39 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 61-64 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.33-7.26 (m, 4H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.04 (s, 1H), 4.26-4.13 (m, 1H), 3.32-3.24 (m, 1H), 3.00-2.93 (m, 2H), 1.55 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ156.5, 152.6, 137.4, 136.3, 128.5, 128.2, 126.1, 111.5, 82.1, 46.4, 31.3, 29.8, 28.4, 28.3. IR (ATR): ν_{max} 2930, 2856, 1712, 1456, 1367, 1341, 1258, 1147, 855, 754, 693 cm^{-1}; ESIHRMS *m/z* calcd for $C_{20}H_{28}NNaO_4$ $[M+Na]^+$ 383.1941, found 383.1943.

- ***(Z)*-Di-*tert*-butyl 3-benzylidenepyrazolidine-1,2-dicarboxylate 72a'** *(slower eluting isomer).* Yield: 37% (11 mg, 31 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 111-113 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ7.55 (d, *J* = 7.6 Hz, 2H), 7.26 (t, *J* =

7.7 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.00 (s, 1H), 4.03-3.99 (m, 1H), 3.34 (q, *J* = 9.2 Hz, 1H), 2.95-2.90 (m, 1H), 2.86-2.80 (m, 1H), 1.54 (s, 9H), 1.18 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 156.8, 152.5, 136.7, 134.3, 128.3, 128.0, 126.8, 114.8, 82.3, 81.7, 43.9, 32.4, 28.4, 27.8. IR (ATR): ν_{max} 2960, 1724, 1366, 1300, 1147, 846, 751, 699, 668, 629, 610 cm^{-1}; ESIHRMS *m/z* calcd for $C_{20}H_{28}NNaO_4$ $[M+Na]^+$ 383.1941, found 383.1943.



72b

***Di-tert*-butyl 3-benzyltetrahydropyridazine-1,2-dicarboxylate 72b.** Two inseparable isomers were obtained with a ratio of 67:33. Yield: 77% (72 mg, 192 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.61 (m, 1.34H), 7.38-7.10 (m, 3.99H), 6.05 (s, 0.67H), 4.19-3.92 (m, 1H), 3.22-3.00 (m, 1H), 2.74-2.65 (m, 0.33H), 2.43-2.30 (m, 1.67H), 1.97-1.83 (m, 1H), 1.77-1.74 (m, 1H), 1.72 (s, 2.97H), 1.51 (s, 6.03H), 1.49 (d, *J* = 3.8 Hz, 6.03H), 1.23 (br., 2.97H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9 (major isomer), 135.7 (major isomer), 135.6 (minor isomer), 135.0 (minor isomer), 129.0 (major isomer), 128.9 (minor isomer), 128.3 (minor, isomer), 128.0 (major isomer), 127.2 (major isomer), 126.9 (minor isomer), 122.9 (major isomer), 119.2 (minor isomer), 81.9 (major isomer), 81.34 (major isomer), 81.26 (minor isomer), 80.0 (minor isomer), 68.3 (major isomer), 44.2 (minor isomer), 43.0 (major isomer), 31.0 (minor isomer), 28.5 (major isomer), 28.4 (minor isomer), 28.3 (minor isomer), 27.9 (major isomer), 25.3 (minor isomer), 25.2 (major isomer), 24.2 (major isomer), 23.9 (minor isomer). IR (ATR): ν_{max} 2977, 1724, 1392, 1367, 1301, 1254, 1152, 1077, 853, 755, 697 cm^{-1}; ESIHRMS *m/z* calcd for $C_{21}H_{30}N_2NaO_4$ $[M+Na]^+$ 397.2098, found 397.2100.

Experimental Procedure and Characterization Data: Gram Scale Synthesis of 68a and 68b

General procedure:

An oven-dried 250 mL two-necked round bottom flask was charged with the *N*-haloalkyl-ynamide **67a** (1.16 g, 3 mmol) or **67b** (1.09 g, 3 mmol) and 2,2'-Azobis(2-methylpropionitrile) (197.1 mg, 1.2 mmol). The flask was fitted with a condenser and rubber septa, evacuated under high vacuum and backfilled with argon for 3 times before the addition of degassed toluene (78 mL). The resulting mixture was heated to 80 °C for 20 minutes in dark. After that, a solution of *n*-Bu_3SnH (1.21 mL, 4.5 mmol) in degassed toluene (78 mL) was added dropwise via a syringe pump over 9 hours. After the addition, the reaction was stirred at 80 °C for 9 hours before cooling down to room temperature. The reaction was quenched by addition of saturated aqueous solution of potassium fluoride (70 mL) and the mixture was stirred for another 1 hour at room temperature. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel (with 10% w/w of finely ground potassium fluoride)[S11] to give the desired cyclized product **68a** (731.5 mg, 2.82 mmol, 94%) or **68b** (529.3 mg, 2.23 mmol, 74%).

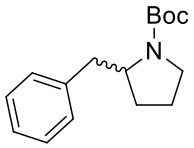
Characterization data for this tetrahydropyridine can be found on page 140.

[S11] Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004**, *17*, 1968-1969.

Experimental Procedure and Characterization Data: Hydrogenation of the Cyclized Products

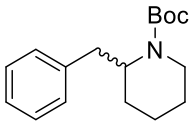
General procedure:

To a solution of the cyclized product (0.15 mmol) in methanol (20 mL) was added palladium on carbon (10% wt., 60 mg, 0.15 mmol). The reaction mixture was stirred under a hydrogen atmosphere (2.0 bars) at room temperature for 5 hours. The resulting reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product.



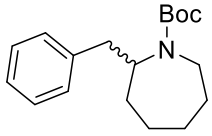
57a

***N*-*tert*-Butoxycarbonyl-2-benzylpyrrolidine 57a.** Two inseparable enantiomers were obtained. Yield: 71% (28 mg, 107 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; This compound has been previously reported. [S12]



57p

***N*-*tert*-Butoxycarbonyl-2-benzylpiperidine 57p.** Two inseparable enantiomers were obtained. Yield: 89% (37 mg, 134 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1. White solid; This compound has been previously reported. [S13]

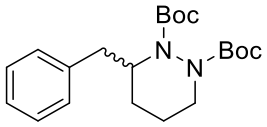


57q

***N*-*tert*-Butoxycarbonyl-2-benzylazepane 57q.** Two inseparable enantiomers were obtained with a ratio of 57:43. Yield: 76% (33 mg, 114 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow solid; Mp: 34-36 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.12 (m, 5H), 4.29-

[S12] Massah, A. R.; Ross, A. J.; Jackson, R. F. W. *J. Org. Chem.* **2010**, *75*, 8275-8278.
[S13] Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216-12217.

4.22 and 4.12-4.02 (m, 0.43H, m, 0.57H), 3.81 and 3.61 (d, *J* = 14.2 Hz, 0.57H, d, *J* = 14.6 Hz, 0.43H), 2.85-2.72 (m, 1H), 2.67-2.56 (m, 2H), 1.96-1.50 (m, 5H), 1.44 and 1.35 (s, 3.87H, s, 5.13H), 1.29-1.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ155.8 (minor isomer), 155.6 (major isomer), 139.3 (major isomer), 139.1 (minor isomer), 129.6 (minor isomer), 129.5 (major isomer), 128.4 (major isomer), 128.2 (minor isomer), 126.2 (major isomer), 126.1 (minor isomer), 79.1 (major isomer), 79.0 (minor isomer), 57.5 (major isomer), 56.5 (minor isomer), 42.3 (minor isomer), 41.6 (major isomer), 41.5 (major isomer), 41.1 (minor isomer), 34.2 (major isomer), 33.3 (minor isomer), 30.0 (major isomer), 29.8 (minor isomer), 29.6 (minor isomer), 29.0 (major isomer), 28.7 (minor isomer), 28.5 (major isomer), 25.4 (major isomer), 25.3 (minor isomer). IR (ATR): ν_{max} 2928, 1688, 1454, 1411, 1364, 1278, 1171, 1101, 988, 749, 700 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{27}NNaO_2$ $[M+Na]^+$ 312.1934, found 312.1934.



73

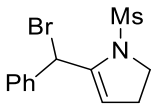
Di-*tert*-butyl 3-benzyltetrahydropyridazine-1,2-dicarboxylate 73. Two inseparable isomers were obtained with a ratio of 87:13. Starting from 134 µmol of the cyclized product **72b**. Yield: 99% (50 mg, 133 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; This compound has been previously reported. [S14]

[S14] Hu, A.; Guo, J.-J.; Pan, H.; Tang, H.; Gao Z.; Zuo, Z. *J. Am. Chem. Soc.* **2018**, *140*, 1612-1616.

Experimental Procedure and Characterization Data: Synthesis of Compound 74, 75, 77, 78 and 79

I. Bromination to compound 74

Argon was bubbled to a solution of the cyclic enamide **68b** (59.3 mg, 0.25 mmol) and *N*-bromosuccinimide (53.4 mg, 0.3 mmol) in chloroform (5 mL) for 5 minutes. The reaction solution was stirred at room temperature for 30 minutes before concentrating under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product **74**.

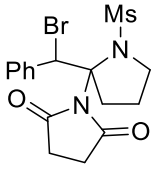


74

***N*-(Methylsulfonyl)-2-[bromo(phenyl)methyl]-4,5-dihydro-pyrrole 74.** Yield: 38% (30 mg, 95 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; White solid; Mp: 105-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 6.77 (s, 1H), 5.20 (d, *J* = 4.3 Hz, 1H), 3.95-3.85 (m, 2H), 3.05 (s, 3H), 2.42-2.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.0, 135.8, 128.9, 128.7, 127.3, 114.0, 49.7, 48.0, 34.5, 34.0; IR (ATR): ν_{max} 2922, 1638, 1342, 1226, 1201, 1153, 1079, 1048, 1008, 976, 881, 757, 704, 637 cm^{-1}; ESIHRMS *m/z* calcd for $C_{12}H_{15}BrNO_2S$ $[M+H]^+$ 316.0008, found 316.0001.

II. Synthesis of compound 75

A solution of the cyclic enamide **68b** (59.3 mg, 0.25 mmol) and *N*-bromosuccinimide (53.4 mg, 0.3 mmol) in degassed dichloromethane (5 mL) was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product **75**.



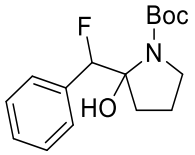
75

***tert*-Butyl 2'-[bromo(phenyl)methyl]-2,5-dioxo-[1,2'-bipyrrolidine]-1'-carboxylate 75.** Two inseparable diastereoisomers were obtained with a ratio of 63:37. Yield: 56% (58 mg, 140 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 1/1; Colorless oil; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 7.72-7.70 (m, 0.74H, minor diastereoisomer), 7.45-7.29 (m, 4.26H), 7.20 and 5.45 (s, 0.37H, s, 0.63H, diastereoisomer), 4.42 (t, *J* = 5.9 Hz, 0.63H, major diastereoisomer), 3.57-3.51 (m, 0.37H, minor diastereoisomer), 3.30-3.21 (m, 0.37H, minor diastereoisomer), 3.09 (q, *J* = 6.6 Hz, 1.26H, major diastereoisomer), 2.90 and 2.65 (s, 1.89H, s, 1.11H, diastereoisomers), 2.69-2.67 (m, 4.26H), 2.55-2.49 (m, 0.37H, minor diastereoisomer), 2.17-2.06 (m, 0.37H, minor diastereoisomer), 1.90-1.79 (m, 1.26H, major diastereoisomer), 1.37-1.27 (m, 0.74H, minor diastereoisomer), 0.93-0.81 (m, 0.37H, minor diastereoisomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.2 (major diastereoisomer), 177.1 (minor diastereoisomer), 136.0 (minor), 135.0 (major diastereoisomer), 131.3 (minor diastereoisomer), 129.4 (major diastereoisomer), 129.2 (major diastereoisomer), 129.0 (major diastereoisomer), 128.9 (minor diastereoisomer), 128.2 (minor diastereoisomer), 88.4 (major diastereoisomer), 56.8 (minor diastereoisomer), 55.6 (major diastereoisomer), 51.5 (minor diastereoisomer), 42.3 (major diastereoisomer), 40.3 (major diastereoisomer), 39.2 (minor diastereoisomer), 35.8 (minor diastereoisomer), 35.6 (major diastereoisomer), 29.8 (minor diastereoisomer), 29.7 (major diastereoisomer), 28.6 (minor diastereoisomer), 24.4 (major diastereoisomer), 22.1 (minor diastereoisomer); IR (ATR): ν_{max} 3275, 2935, 1713, 1454, 1320, 1150, 1089, 1030, 973, 759, 702, 666 cm^{-1}; ESIHRMS *m/z* calcd for $C_{16}H_{19}BrNNaO_4S$ $[M+Na]^+$ 437.0141, found 437.0136.

III. Synthesis of compound 76a

To a solution of the cyclic enamide **68a** (64.8 mg, 0.25 mmol) and *N*-Fluorobenzenesulfonimide (71 mg, 0.23 mmol) in chloroform (2 mL) was added distilled water (9 µL, 0.5 mmol). The reaction mixture was stirred at 40 °C for 1 h and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product **76a**.



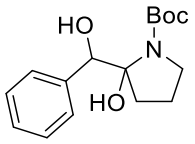
76a

***tert*-Butyl 2-[fluoro(phenyl)methyl]-2-hydroxypyrrolidine-1-carboxylate 76a.** Two inseparable diastereoisomers were obtained with a ratio of 83:17. Yield: 45% (33 mg, 112 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45-7.36 (m, 5H), 6.02 and 5.71 (d, *J* = 45.1 Hz, 0.17H, d, *J* = 48.5 Hz, 0.83H, diastereoisomers), 5.10 and 4.51 (s, 0.17H, s, 0.83H, diastereoisomers), 3.69-3.37 (m, 0.34H), 3.06 (q, *J* = 4.5 Hz, 1.66H), 2.71-2.16 (m, 2H), 1.77-1.70 (m, 2H), 1.51 and 1.42 (s, 1.53H, s, 7.47H, diastereoisomers); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 156.1 (major diastereoisomer), 134.2 (d, *J* = 17 Hz) (major diastereoisomer), 130.0 (minor diastereoisomer), 129.6 (minor diastereoisomer), 129.5 (major diastereoisomer), 129.1 (major diastereoisomer), 128.4 (minor diastereoisomer), 128.2 (d, *J* = 6 Hz) (minor diastereoisomer), 128.0 (minor diastereoisomer), 126.5 (d, *J* = 8 Hz) (minor diastereoisomer), 126.1 (d, *J* = 7 Hz) (major diastereoisomer), 95.9 (d, *J* = 187 Hz) (major diastereoisomer), 81.0 (minor diastereoisomer), 79.4 (major diastereoisomer), 48.3 (major diastereoisomer), 41.0 (minor diastereoisomer), 39.8 (major

diastereoisomer), 34.7 (major diastereoisomer), 33.0 (minor diastereoisomer), 28.6 (minor diastereoisomer), 28.5 (major diastereoisomer), 24.0 (minor diastereoisomer), 23.5 (major diastereoisomer), 21.6 (minor diastereoisomer); IR (ATR): ν_{max} 3373, 2977, 1695, 1516, 1454, 1393, 1366, 1251, 1168, 1002, 750, 699, 613 cm^{-1}; ESIHRMS *m/z* calcd for $C_{16}H_{19}BrNNaO_4S$ $[M+Na]^+$ 437.0141, found 437.0136.

IV. Epoxidation and hydrolysis to compound 78

To a solution of the cyclic enamide **68a** (64.8 mg, 0.25 mmol) in dichloromethane (4 mL) was added anhydrous magnesium sulfate (500 mg) and a freshly prepared 0.03 M solution of dimethyldioxirane in acetone (12 mL). The reaction mixture was stirred at room temperature for 20 minutes. The solution was concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the diol **78**.

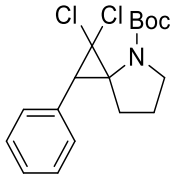


78

***tert*-Butyl 2-hydroxy-2-[hydroxy(phenyl)methyl]pyrrolidine-1-carboxylate 78.** Yield: 44% (32 mg, 109 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 5.09 (d, *J* = 4.2 Hz, 1H), 4.46 (br., 1H), 4.33 (d, *J* = 4.3 Hz, 1H), 3.06-2.90 (m, 2H), 2.45-2.29 (m, 2H), 1.76-1.59 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.3, 156.1, 138.1, 129.1, 128.9, 127.4, 79.9, 79.4, 39.6, 34.9, 28.5, 24.2; IR (ATR): ν_{max} 3366, 2978, 1693, 1519, 1454, 1392, 1366, 1252, 1168, 1023, 857, 750, 701 cm^{-1}; ESIHRMS *m/z* calcd for $C_{16}H_{23}NNaO_4$ $[M+Na]^+$ 316.1519, found 316.1517.

V. Cyclopropanation with dichlorocarbene to compound 79

To a solution of the cyclic enamide **68a** (64.8 mg, 0.25 mmol) and benzyltriethylammonium chloride (125.3 mg, 0.55 mmol) in chloroform (2 mL) was added 10 M aqueous solution of sodium hydroxide (2 mL). The reaction mixture was stirred at room temperature for 10 hours to give a light yellow solution. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product **79**.

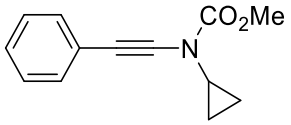


79

***tert*-Butyl 1,1-dichloro-2-phenyl-4-azaspiro[2.4]heptane-4-carboxylate 79.** Yield: 70% (60 mg, 175 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 60-61 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 4H), 7.29-7.25 (m, 1H), 4.66 (br., 1H), 3.75-3.69 (m, 1H), 3.57-3.51 (m, 1H), 2.13-1.80 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 133.9, 129.4, 128.4, 127.3, 80.5, 67.8, 56.9, 47.4, 38.9, 30.1, 28.6, 21.4; IR (ATR): ν_{max} 2976, 1699, 1447, 1378, 1334, 1171, 1143, 1094, 961, 885, 740, 699, 624 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{21}Cl_2NNaO_2S$ $[M+Na]^+$ 364.0842, found 364.0836.

Experimental part of chapter 2

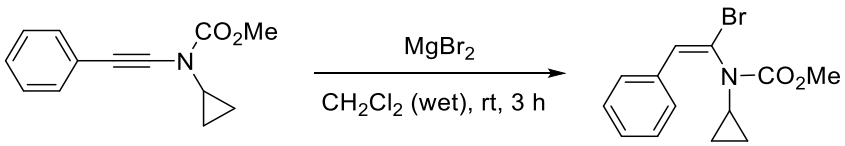
Experimental Procedure and Characterization Data: Synthesis of the starting enamides



52

Methylcyclopropyl-phenylethynyl-carbamate 52. A 15 mL Schlenk tube was charged with the amide (5 mmol), (2-bromoethenyl)benzene (6 mmol), potassium phosphate (2.12 g, 10 mmol) and copper sulfate pentahydrate (187 mg, 0.75 mmol). The tube was evacuated under high vacuum and backfilled with nitrogen for three times. Dry toluene (10 mL) was added and the reaction was heated at 95 °C for 48 hours. The dark brown suspension was cooled to room temperature, filtered through a plug of silica gel (washed with EtOAc) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product. Yield: 44% (476 mg, 2.2 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.39 (m, 2H), 7.32-7.26 (m, 3H), 3.85 (s, 3H), 3.13-3.08 (m, 1H), 0.96-0.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 131.3, 128.4, 127.7, 123.3, 81.8, 71.0, 54.2, 31.8, 7.1; IR (ATR): ν_{max} 2960, 2249, 1731, 1438, 1373, 1300, 1215, 1066, 753, 691, 571 cm^{-1}; ESIHRMS *m/z* calcd for $C_{13}H_{14}NO_2$ $[M+H]^+$ 216.1019, found 216.1022.

General procedure I: synthesis of α-bromo enamide 48a

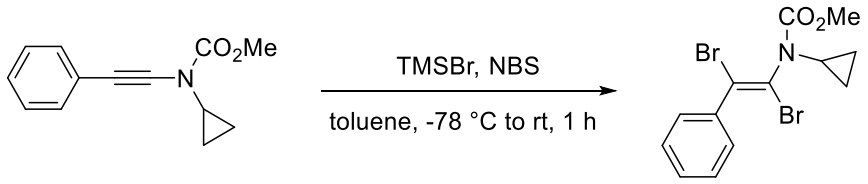


52 **48a**

Methyl *(E)*-(1-bromo-2-phenylvinyl)(cyclopropyl)carbamate 48a. To a solution of the ynamide (335 mg, 1.6 mmol) in dichloromethane (10 mL) was added $MgBr_2$ (287 mg, 1.6 mmol) at room temperature. After stirring for 3 h, the reaction was quenched at 0 °C with saturated aqueous sodium thiosulfate and stirred for 10 min. The solution was warmed to room temperature, extracted with dichloromethane, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatograph over silica gel to give the desired product. Yield 91% (419 mg, 1.41 mmol). Solvent system for flash column chromatography: PE/EtOAc: 15/1; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.26 (m, 3H), 7.21-7.19 (m, 2H), 6.78 (s, 1H), 3.81 (s, 3H), 2.82-2.78 (m, 1H), 0.85-0.80 (m, 2H), 0.74-0.68 (m, 1H), 0.57-0.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1, 134.3, 133.1,

128.8, 128.6, 127.9, 53.9, 31.1, 7.9, 5.7; IR (ATR): ν_{max} 2957, 1722, 1438, 1299, 1135, 1065, 774, 740, 691, 560 cm^{-1}; ESIHRMS *m/z* calcd for $C_{13}H_{15}BrNO_2$ $[M+H]^+$ 296.0281, found 296.0281.

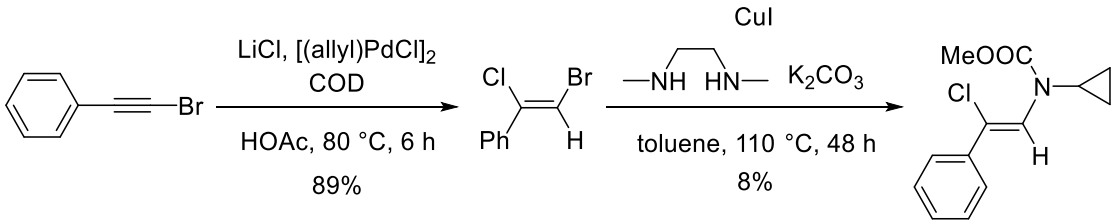
General procedure II: synthesis of α, β-bromo enamide 48b



52 **48b**

Methyl *(E)*-cyclopropyl(1,2-dibromo-2-phenylvinyl)carbamate 48b. To a solution of NBS (186 mg, 1.05 mmol) in dry toluene (10 mL) at -78 °C was added bromotrimethylsilane (1 M solution in dichloromethane, 1 mL) dropwise over 2 min under nitrogen. After stirring for 1 min the ynamide (150 mg, 0.7 mmol) in toluene (5 mL) was slowly added over 2 min, and the reaction was warmed to room temperature. After stirring for 1 h, the reaction was quenched at 0 °C with saturated aqueous sodium thiosulfate and stirred for 10 min. The solution was warmed to room temperature, extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatograph over silica gel to give the desired product. Yield 81% (212 mg, 566 µmol). Solvent system for flash column chromatography: PE/EtOAc: 5/1; Yellow solid; Mp: 75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.33-7.27 (m, 5H), 3.80 (s, 3H), 2.49-2.44 (m, 1H), 0.71-0.61 (m, 2H), 0.58-0.52 (m, 1H), 0.48-0.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ155.8, 138.0, 129.2, 128.5, 127.9, 123.6, 53.8, 31.4, 6.7, 6.4; IR (ATR): ν_{max} 2957, 1716, 1439, 1315, 1073, 741, 699, 680, 586 cm^{-1}; ESIHRMS *m/z* calcd for $C_{13}H_{14}Br_2NO_2$ $[M+H]^+$ 375.9365, found 375.9360.

General procedure III: synthesis of β-chloro enamide

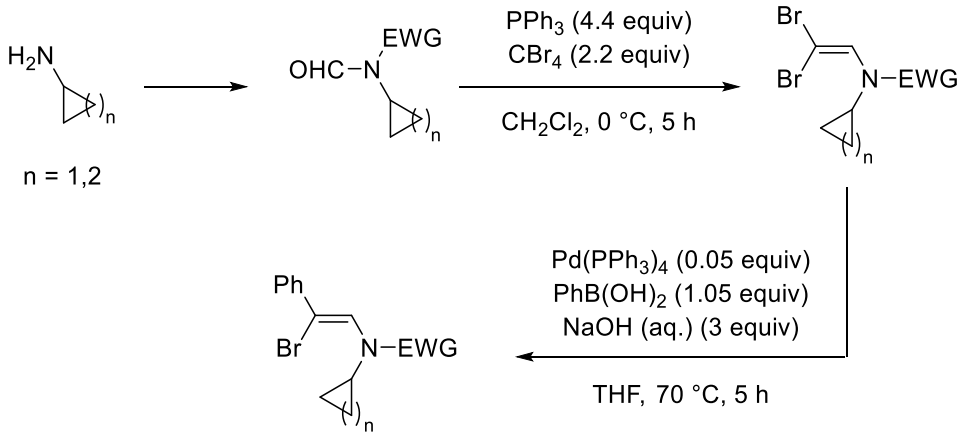


53 **54** **48c**

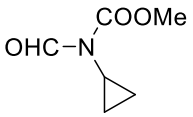
Methyl *(Z)*-(2-chloro-2-phenylvinyl)(cyclopropyl)carbamate 48c. To a solution of LiCl (170 mg, 4 mmol) and $[(allyl)PdCl]_2$ (18 mg, 0.05 mmol) in acetic acid (5 mL) was added *cis,cis*-1,5-cyclooctadiene (25 µL, 0.2 mmol) and phenylethynyl chloride (362 mg, 2 mmol). After stirring for 6 h at 80 °C, the reaction mixture was quenched with water (5 mL), extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel (PE) to give the desired product. Yield 89% (387 mg, 1.78 mmol).

A Schlenk tube was charged with the amide (445 mg, 3.9 mmol), copper(I) iodide (61 mg, 0.32 mmol) and potassium carbonate (890 mg, 6.4 mmol), evacuated and backfilled with nitrogen. Then *N*,*N*'-dimethylethylenediamine (69 µL, 0.64 mmol), vinyl bromide (700 mg, 3.2 mmol) and toluene (37 mL) were added and the reaction was stirred at 110 °C for 48 h. The dark brown suspension was cooled to room temperature, filtered through a plug of silica gel (washed with EtOAc) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product. Yield 8% (68 mg, 0.27 mmol). Solvent system for flash column chromatography: PE/EtOAc = 15/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.55 (m, 2H), 7.38-7.33 (m, 3H), 6.83 (s, 1H), 3.78 (s, 3H), 3.12-3.07 (m, 1H), 0.95-0.90 (m, 2H), 0.73-0.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 136.7, 128.8, 128.5, 127.9, 126.7, 125.1, 53.4, 30.5, 9.3.

Experimental Procedure and Characterization Data: Synthesis of the β-bromo Enamides



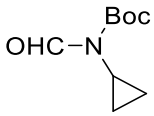
Procedure I: protection and formylation



63a

Methyl cyclopropyl(formyl)carbamate 63a. To a solution of cyclopropylamine (2.28 g, 40 mmol) and triethylamine (11.1 mL, 80 mmol) in dichloromethane (20 mL) was added a solution of methyl chloroformate (3.7 mL, 48 mmol) in dichloromethane (10 mL) at 0 °C. After stirring for 1 hour, the reaction was quenched with 1 M HCl, extracted with dichloromethane, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired amide. Solvent system for flash column chromatography: petroleum ether/EtOAc: 3/1; Yield: 83% (3.80 g, 33.0 mmol).

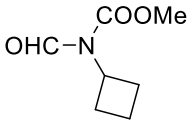
To a solution of the amide (1.15 g, 10 mmol) in THF (40 mL) was added *n*-BuLi (2.06 M solution in THF, 5.3 mL) at 0 °C under nitrogen. After 30 min, a solution of *N*-formylbenzotriazole in THF (10 mL) was added and the mixture was stirred at room temperature for 2 h. Then the reaction was quenched with aqueous saturated NH_4Cl solution, extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Yield: 82% (1.17 g, 8.17 mmol). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.18 (s, 1H), 3.89 (s, 3H), 2.53-2.49 (m, 1H), 1.03-0.99 (m, 2H), 0.73-0.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.0, 155.7, 54.1, 23.9, 7.9; IR (ATR): ν_{max} 2960, 1740, 1697, 1440, 1353, 1278, 1236, 1081, 946, 771, 729 cm^{-1}.



63b

***tert*-Butyl cyclopropyl(formyl)carbamate 63b.** A mixture of cyclopropylamine (0.35 mL, 5 mmol) in ethyl formate (4 mL, 50 mmol) was stirred at 40 °C for 3 hours and cooled to room temperature. The resulting light yellow solution was evaporated under reduced pressure to give the desired *N*-cyclopropylformamide. Light yellow oil; Yield: 100% (426 mg, 5 mmol).

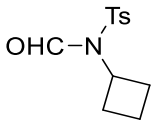
To a solution of *N*-cyclopropylformamide (426 mg, 5 mmol) in anhydrous acetonitrile (20 mL) was added 4-dimethylaminopyridine (55 mg, 0.45 mmol) and di-*tert*-butyl dicarbonate (1.23 mL, 5.75 mmol). After stirring at room temperature overnight, the reaction was quenched with water, extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired amide. Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1; Yield: 92% (856 mg, 4.6 mmol). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 2.49-2.43 (m, 1H), 1.54 (s, 9H), 1.01-0.96 (m, 2H), 0.70-0.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 153.6, 83.9, 28.2, 23.8, 8.0; IR (ATR): ν_{max} 3263, 3018, 2861, 1651, 1528, 1385, 1261, 1024, 943, 730, 461 cm^{-1}.



69a

Methyl cyclobutyl(formyl)carbamate 69a. To a solution of cyclobutylamine (710 mg, 10 mmol) and triethylamine (2.78 mL, 20 mmol) in dichloromethane (20 mL) was added a solution of methyl chloroformate (0.93 mL, 12 mmol) in dichloromethane (10 mL) at 0 °C. After stirring for 5 h, the reaction was quenched with water, extracted with dichloromethane, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired amide. Solvent system for flash column chromatography: petroleum ether/EtOAc: 3/1; Yield: 91% (1.18 g, 9.1 mmol).

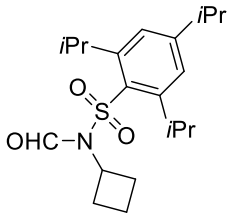
To a solution of the amide (1.17 g, 9.06 mmol) in THF (40 mL) was added *n*-BuLi (2.3 M solution in THF, 4.3 mL) at 0 °C under nitrogen. After 30 min, a solution of *N*-formylbenzotriazole in THF (15 mL) was added and the mixture was stirred at room temperature for 2 h. Then the reaction was quenched with aqueous saturated NH_4Cl solution, extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Yield: 61% (874 mg, 5.56 mmol). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.16 (s, 1H), 4.76 (quint., J = 8.9 Hz, 1H), 3.89 (s, 3H), 2.69-2.60 (m, 2H), 2.24-2.18 (m, 2H), 1.85-1.79 (m, 1H), 1.73-1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5, 154.8, 53.8, 47.1, 28.3, 15.2; IR (ATR): ν_{max} 2956, 1741, 1690, 1440, 1327, 1299, 1289, 1191, 1090, 775, 628 cm^{-1}.



69b

***N*-Cyclobutyl-*N*-tosylformamide 69b**. To a solution of cyclobutylamine (500 mg, 4.7 mmol) and triethylamine (1.94 mL, 13.9 mmol) in dichloromethane (15 mL) was added a solution of tosyl chloride (1.63 g, 5.6 mmol) in dichloromethane (10 mL) at 0 °C. After stirring for 12 hours at room temperature, the reaction was quenched with water, extracted with dichloromethane, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired amide. Solvent system for flash column chromatography: petroleum ether/EtOAc: 3/1; Yield: 92% (0.96 g, 4.3 mmol).

To a solution of the amide (1.0 g, 4.4 mmol) in THF (20 mL) was added *n*-BuLi (2.5 M solution in THF, 2.0 mL) at 0 °C under nitrogen. After 30 minutes, a solution of *N*-formylbenzotriazole in THF (5 mL) was added and the mixture was stirred at room temperature for 2 h. Then the reaction was quenched with aqueous saturated NH_4Cl solution, extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Yield: 60% (0.67 g, 2.7 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 4.31 (quint., *J* = 8.8 Hz, 1H), 2.71-2.60 (m, 2H), 2.46 (s, 3H), 2.03-1.97 (m, 2H), 1.82-1.74 (m, 1H), 1.66-1.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 130.2, 129.7, 127.1, 127.0, 50.0, 31.8, 28.1, 15.6; IR (ATR): ν_{max} 2972, 1700, 1354, 1163, 1091, 1033, 969, 814, 670, 592, 550 cm^{-1}.

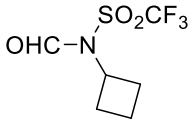


69c

***N*-Cyclobutyl-*N*-[(2,4,6-triisopropylphenyl)sulfonyl]formamide 69c**. To a solution of cyclobutylamine (356 mg, 5 mmol) and triethylamine (1.39 mL, 10 mmol) in dichloromethane (10 mL) was added a solution of 2,4,6-triisopropylbenzenesulfonyl chloride (1.82 g, 6 mmol) in dichloromethane (5 mL) at 0 °C. After stirring for 12 hours at room temperature, the reaction was quenched with water, extracted with dichloromethane, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired amide. Solvent system for flash column chromatography: petroleum ether/EtOAc: 3/1; Yield: 58% (976 mg, 2.9 mmol).

To a solution of the amide (1.0 g, 4.4 mmol) in THF (10 mL) was added *n*-BuLi (2.3 M solution in THF, 1.37 mL) at 0 °C under nitrogen. After 30 minutes, a solution of *N*-formylbenzotriazole in THF (7 mL) was added and the mixture was stirred at room temperature for 2 h. Then the reaction was quenched with aqueous saturated NH_4Cl solution, extracted with ethyl acetate, dried over magnesium sulfate,

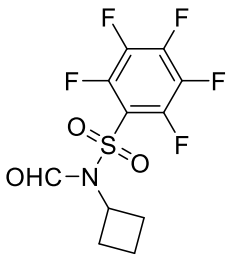
filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product. Yield: 97% (1.02 g, 2.80 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; White solid; Mp: 84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (s, 1H), 7.20 (s, 2H), 4.19-4.13 (m, 1H), 4.04-3.99 (m, 2H), 2.80-2.72 (m, 2H), 1.99-1.94 (m, 2H), 1.27-1.25 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 154.9, 151.3, 124.5, 123.9, 50.0, 34.4, 29.4, 25.0, 24.8, 23.6, 15.6; IR (ATR): ν_{max} 2960, 1695, 1342, 1266, 1236, 1216, 1030, 968, 888, 666, 591, 553 cm^{-1}.



76

***N*-Cyclobutyl-trifluoromethanesulfonamide 72.** To a solution of cyclobutylamine (711 mg, 10 mmol) and triethylamine (1.39 mL, 10 mmol) in dichloromethane (20 mL) was added trifluoromethanesulfonic anhydride (1.74 mL, 10.5 mmol) at -78 °C. After stirring for 1 hour, the reaction was quenched with ice, extracted with dichloromethane, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was used for the next step without further purification. Yield: 99% (2.01 g, 9.9 mmol). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.73 (d, *J* = 8.5 Hz, 1H), 4.09-4.00 (m, 1H), 2.39-2.33 (m, 2H), 2.09-2.01 (m, 2H), 1.75-1.60 (m, 2H); IR (ATR): ν_{max} 3273, 2980, 1449, 1310, 1138, 979, 766, 519 cm^{-1}.

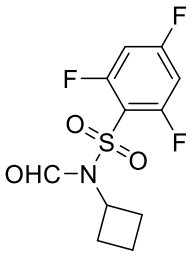
***N*-Cyclobutyl-*N*-[(trifluoromethyl)sulfonyl]formamide 76.** To a solution of amide (2.0 g, 9.8 mmol) in dichloromethane (10 mL) at 0 °C was successively added formic acid (0.74 mL, 19.7 mmol) and *N,N'*-dicyclohexylcarbodiimide (4.06 g, 19.7 mmol).Then the white suspension was stirred at 40 °C for 3 hours, cooled to room temperature, filtered through a plug of silica gel (ethyl acetate) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product. Yield: 82% (1.86 g, 8.0 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86 (s, 1H), 4.61 (quint., *J* = 8.8 Hz, 1H), 2.88-2.79 (m, 2H), 2.32-2.26 (m, 2H), 1.96-1.89 (m, 1H), 1.77-1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.3, 119.1 (q, J_{CF} = 320.0 Hz), 52.2, 28.6, 15.1; IR (ATR): ν_{max} 2968, 1730, 1416, 1198, 1119, 970, 624, 582, 534 cm^{-1}.



78

***N*-Cyclobutyl-pentafluorobenzenesulfonamide 74.** To a solution of cyclobutylamine (1.28 mL, 15 mmol) and *N*,*N*-diisopropylethylamine (9.92 mL, 60 mmol) in dichloromethane (9 mL) was added pentafluorobenzenesulfonyl chloride (2.23 mL, 15 mmol) at 0 °C. After stirring for 16 hours at room temperature, the reaction was quenched with water, extracted with dichloromethane, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product. Yield: 82% (1.86 g, 8.0 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 4/1; Yellow solid; Mp: 88 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ5.37 (d, *J* = 8.5 Hz, 1H), 4.00 (sixt., *J* = 8.3 Hz, 1H), 2.28-2.22 (m, 2H), 1.98-1.90 (m, 2H), 1.75-1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ144.5, 144.0, 138.1, 117.2, 48.5, 31.7, 15.1 (the aromatic carbons are not visible due to the multiplicity); ^{19}F NMR (471 MHz, $CDCl_3$): δ-136.9 , -146.0 (tt, *J* = 42.6 and 4.9 Hz), -158.6 (the couplings are not visible due to the multiplicity); IR (ATR): ν_{max} 3283, 3005, 1518, 1502, 1353, 1298, 1164, 1098, 992, 646, 605, 580, 534 cm^{-1}.

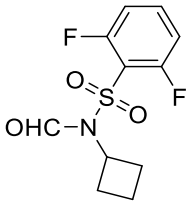
***N*-Cyclobutyl-*N*-[(perfluorophenyl)sulfonyl]formamide 78.** To a solution of amide (3.5 g, 11.6 mmol) in dichloromethane (10 mL) at 0 °C was successively added formic acid (0.88 mL, 23.2 mmol) and *N*,*N*'-dicyclohexylcarbodiimide (5.99 g, 29.0 mmol).Then the white suspension was stirred at 40 °C for 16 hours, cooled to room temperature, filtered through a plug of silica gel (ethyl acetate) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product. Yield: 82% (3.1 g, 9.5 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1; White solid; Mp: 34 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.06 (s, 1H), 4.49 (quint., *J* = 8.9 Hz, 1H), 2.70-2.61 (m, 2H), 2.18-2.12 (m, 2H), 1.90-1.83 (m, 1H), 1.76-1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ161.7 (t, *J* = 2.5 Hz), 145.2, 144.9, 138.2, 115.4, 50.2, 28.6, 15.8 (the aromatic carbons are not visible due to the multiplicity); ^{19}F NMR (471 MHz, $CDCl_3$): δ-136.1, -141.9, -156.8 (the couplings are not visible due to the multiplicity); IR (ATR): ν_{max} 2960, 1716, 1522, 1499, 1376, 1204, 1176, 1101, 992, 648, 610, 564 cm^{-1}.



79

***N*-Cyclobutyl-2,4,6-trifluorobenzenesulfonamide 75.** To a solution of cyclobutylamine (1.79 g, 25.1 mmol) and triethylamine (10.5 mL, 75.5 mmol) in dichloromethane (126 mL) was added 2,4,6-trifluorobenzenesulfonyl chloride (5.8 g, 25.2 mmol) at 0 °C. After stirring for 16 hours at room temperature, the reaction was quenched with water, extracted with dichloromethane, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product. Yield: 99% (6.58 g, 24.8 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 4/1; Yellow solid; Mp: 76 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ6.81-6.76 (m, 2H), 5.13 (d, *J* = 8.8 Hz, 1H), 3.96 (sixt., *J* = 8.4 Hz, 1H), 2.22-2.17 (m, 2H), 1.93-1.84 (m, 2H), 1.71-1.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ165.0 (dt, J_{CF} = 256.3 and 16.3 Hz), 160.5 (ddd, J_{CF} = 257.5, 15.0 and 6.3 Hz), 116.1 (td, J_{CF} = 31.3 and 5.0 Hz), 102.1 (ddd, J_{CF} = 28.8, 25.0 and 3.8 Hz), 48.4, 31.7, 15.1; ^{19}F NMR (471 MHz, $CDCl_3$): δ-99.1 (t, *J* = 11.0 Hz), -103.8 (d, *J* = 10.8 Hz); IR (ATR): ν_{max} 3286, 1607, 1595, 1351, 1168, 1090, 1036, 1005, 847, 665, 535, 512 cm^{-1}.

***N*-Cyclobutyl-*N*-[(2,4,6-trifluorophenyl)sulfonyl]formamide 79.** To a solution of amide (7.9 g, 29.8 mmol) and 4-dimethylaminopyridine (1.31 g, 10.7 mmol) in dichloromethane (60 mL) at 0 °C was successively added formic acid (2.25 mL, 59.6 mmol) and *N*,*N*'-dicyclohexylcarbodiimide (15.36 g, 74.5 mmol). Then the white suspension was stirred at 40 °C for 24 hours, cooled to room temperature, filtered through a plug of silica gel (ethyl acetate) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product. Yield: 61% (5.32 g, 18.1 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 4/1; White solid; Mp: 43 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ9.07 (s, 1H), 6.87-6.82 (m, 2H), 4.44 (quint., *J* = 8.9 Hz, 1H), 2.69-2.61 (m, 2H), 2.11-2.05 (m, 2H), 1.85-1.79 (m, 1H), 1.71-1.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2 (dt, J_{CF} = 260.0 and 15.0 Hz), 162.3 (t, J_{CF} = 6.3 Hz), 160.7 (ddd, J_{CF} = 260.0, 16.3 and 6.3 Hz), 160.2 (td, J_{CF} = 10.0 and 5.0 Hz), 102.7 (ddd, J_{CF} = 26.9, 25.0 and 3.8 Hz), 49.9, 28.3, 15.8; ^{19}F NMR (471 MHz, $CDCl_3$): δ-94.9 (t, *J* = 12.2 Hz), -102.9 (d, *J* = 12.2 Hz); IR (ATR): ν_{max} 2960, 1708, 1611, 1595, 1372, 1177, 1136, 1092, 845, 670, 620, 571, 533, 512 cm^{-1}.



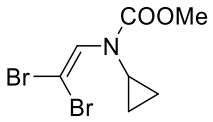
77

***N*-Cyclobutyl-2,6-difluorobenzenesulfonamide 73.** To a solution of cyclobutylamine (356 mg, 5 mmol) and triethylamine (2.09 mL, 15 mmol) in dichloromethane (10 mL) was added 2,6-difluorobenzenesulfonyl chloride (678 µL, 5 mmol) at 0 °C. After stirring for 16 hours at room temperature, the reaction was quenched with water, extracted with dichloromethane, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product. Yield: 85% (1.05 g, 4.25 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 4/1; White solid; Mp: 131 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.47 (m, 1H), 7.02 (t, *J* = 8.9 Hz, 2H), 5.11 (d, *J* = 8.5 Hz, 1H), 3.97 (sixt., *J* = 8.4 Hz, 1H), 2.21-2.14 (m, 2H), 1.92-1.84 (m, 2H), 1.70-1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6 (dd, J_{CF} = 256.3 and 5.0 Hz), 134.4 (t, J_{CF} = 11.3 Hz), 119.1 (t, J_{CF} = 15.6 Hz), 113.2 (dd, J_{CF} = 23.8 and 3.8 Hz), 48.4, 31.6, 15.1; ^{19}F NMR (471 MHz, $CDCl_3$): δ -107.8; IR (ATR): ν_{max} 3283, 2952, 1613, 1467, 1355, 1171, 1000, 917, 787, 646, 565, 539 cm^{-1}.

***N*-Cyclobutyl-*N*-[(2,6-difluorophenyl)sulfonyl]formamide 77.** To a solution of amide (1.05 g, 4.2 mmol) and 4-dimethylaminopyridine (187 mg, 1.5 mmol) in dichloromethane (20 mL) at 0 °C was successively added formic acid (320 µL, 8.5 mmol) and *N*,*N*'-dicyclohexylcarbodiimide (2.19 g, 10.6 mmol). Then the white suspension was stirred at 40 °C for 24 hours, cooled to room temperature, filtered through a plug of silica gel (ethyl acetate) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired product. Yield: 26% (309 mg, 1.12 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; White solid; Mp: 110 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.11 (s, 1H), 7.66-7.60 (m, 2H), 7.09 (t, *J* = 8.7 Hz, 2H), 4.46 (quint., *J* = 8.9 Hz, 1H), 2.71-2.62 (m, 2H), 2.10-2.04 (m, 2H), 1.84-1.78 (m, 1H), 1.70-1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6 (t, J_{CF} = 2.5 Hz), 159.6 (dd, J_{CF} = 258.8 and 2.5 Hz), 136.4 (t, J_{CF} = 22.5 Hz), 117.3 (t, J_{CF} = 14.4 Hz), 113.7 (dd, J_{CF} = 22.5 and 3.8 Hz), 49.9, 28.3, 15.8; ^{19}F NMR (471 MHz, $CDCl_3$): δ -106.9; IR (ATR): ν_{max} 3286, 1698, 1610, 1467, 1368, 1171, 1033, 1004, 974, 797, 647, 622, 593, 534 cm^{-1}.

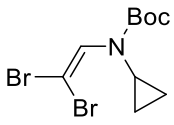
General procedure II: Ramirez olefination reaction

To a solution of triphenylphosphine (1.05 g, 4 mmol) in dichloromethane was added a solution of tetrabromomethane (862 mg, 2.6 mmol) in dichloromethane (10 mL) at 0 °C under nitrogen. After stirring for 30 minutes, a solution of formamide (2 mmol) in dichloromethane (10 mL) was added. The resulting solution was stirred for 1 hour at 0 °C, warmed to room temperature, filtered through a plug of silica gel (washed with EtOAc) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired 1,1-dibromo-1-alkene.



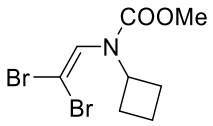
62a

Methyl 2,2-dibromovinyl-cyclopropyl-carbamate 62a. Starting from 2.8 mmol of the corresponding formamide. Yield: 80% (667 mg, 2.2 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (s, 1H), 3.76 (s, 3H), 2.98-2.92 (m, 1H), 0.92-0.87 (m, 2H), 0.70-0.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 133.3, 100.1, 87.1, 53.5, 29.9, 9.3; IR (ATR): ν_{max} 3016, 2952, 1714, 1439, 1301, 1268, 1194, 1146, 1077, 825, 769 cm^{-1}.



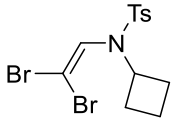
62b

***tert*-Butyl 2,2-dibromovinyl-cyclopropyl-carbamate 62b.** Starting from 4.0 mmol of the corresponding formamide. Yield: 67% (909 mg, 2.7 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1; White solid; Mp: 71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (s, 1H), 2.91-2.86 (m, 1H), 1.48 (s, 9H), 0.90-0.85 (m, 2H), 0.68-0.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 133.8, 132.1, 85.4, 81.8, 29.6, 28.4, 9.5; IR (ATR): ν_{max} 2981, 1710, 1366, 1306, 1147, 827, 843, 742, 695, 541 cm^{-1}.



70a

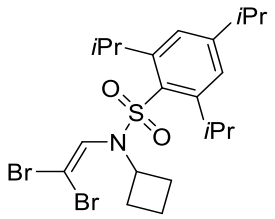
Methyl 2,2-dibromovinyl-cyclobutyl-carbamate 70a. Starting from 5.6 mmol of the corresponding formamide. Yield: 95% (1.65 g, 5.3 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (s, 1H), 4.49 (quint., J = 8.6 Hz, 1H), 3.72 (s, 3H), 2.22-2.17 (m, 2H), 2.14-2.07 (m, 2H), 1.71-1.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 131.6, 96.6, 53.2, 52.3, 28.6, 15.1; IR (ATR): ν_{max} 2952, 1706, 1440, 1328, 1255, 1142, 846, 829, 768, 648, 555 cm^{-1}.



70b

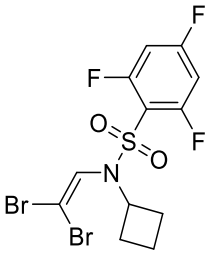
***N*-Cyclobutyl-*N*-(2,2-dibromovinyl)-4-methylbenzenesulfonamide 70b.** Starting from 7.5 mmol of the corresponding formamide. Yield: 90% (2.76 g, 6.7 mmol). Solvent system for flash column

chromatography: petroleum ether/EtOAc: 5/1; White solid; Mp: 100 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.42 (s, 1H), 4.23 (quint., *J* = 8.5 Hz, 1H), 2.43 (s, 3H), 2.03-1.96 (m, 4H), 1.66-1.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2, 135.7, 129.9, 129.4, 127.7, 103.9, 53.8, 28.7, 21.8, 15.4; IR (ATR): ν_{max} 2963, 1698, 1351, 1163, 1030, 964, 813, 667, 588, 548 cm^{-1}.



70c

***N*-Cyclobutyl-*N*-(2,2-dibromovinyl)-2,4,6-triisopropylbenzenesulfonamide 70c.** Starting from 2.8 mmol of the corresponding formamide. Yield: 68% (997 mg, 1.9 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 84 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (s, 2H), 6.82 (s, 1H), 4.54 (quint., *J* = 7.5 Hz, 1H), 2.17-2.12 (m, 4H), 1.70-1.64 (m, 2H), 1.29-1.24 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.6, 151.6, 132.3, 130.2, 124.1, 121.9, 102.8, 53.6, 34.3, 30.2, 29.0, 25.2, 23.7, 15.6; IR (ATR): ν_{max} 2958, 1702, 1604, 1327, 1154, 1037, 881, 843, 795, 666, 586, 555 cm^{-1}.



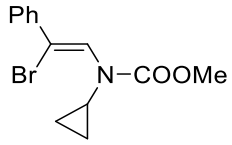
81

***N*-Cyclobutyl-*N*-(2,2-dibromovinyl)-2,4,6-trifluorobenzenesulfonamide 81.** Starting from 18.0 mmol of the corresponding formamide. Yield: 46% (3.7 g, 8.24 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1; White solid; Mp: 43 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78 (t, *J* = 18.5 Hz, 2H), 6.73 (s, 1H), 4.51 (quint., *J* = 8.6 Hz, 1H), 2.17-2.05 (m, 4H), 1.72-1.61 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5 (dt, J_{CF} = 257.5 and 15.0 Hz), 161.0 (ddd, J_{CF} = 260.0, 15.0 and 6.3 Hz), 128.5, 114.9 (ddd, J_{CF} = 21.3, 16.3 and 5.0 Hz), 104.6, 102.3 (ddd, J_{CF} = 30.0, 26.3 and 3.8 Hz), 54.1, 29.1, 15.3; ^{19}F NMR (471 MHz, $CDCl_3$): δ -97.8 (t, *J* = 11.8 Hz), -101.2 (d, *J* = 14.1 Hz); IR (ATR): ν_{max} 2933, 1703, 1595, 1609, 1443, 1171, 1039, 843, 664, 530 cm^{-1}.

General procedure III: Suzuki cross-coupling

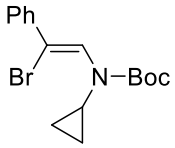
To a solution of dibromoenamide (1 mmol), tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol), benzeneboronic acid (116 mg, 0.95 mmol) in THF (20 mL) was added aqueous sodium

hydroxide (1 M solution, 3 mL), then nitrogen was bubbled to the solution for 15 minutes and the mixture was heated to 70 °C for 3 hours. The resulting solution was cooled to room temperature, filtered through a plug of celite (washed with EtOAc), washed with water, extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired enamide.



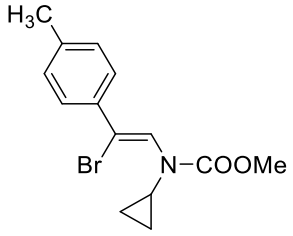
59a

***Z*-(2-Bromo-2-phenylvinyl)-cyclopropylmethylcarbamate 59a.** Starting from 4.1 mmol of the corresponding dibromoenamide. Yield: 81% (1.0 g, 3.4 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.53 (m, 2H), 7.37-7.32 (m, 3H), 6.90 (s, 1H), 3.11 (s, 3H), 3.15-3.09 (m, 1H), 0.95-0.90 (m, 2H), 0.75-0.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 138.1, 128.9, 128.5, 128.2, 128.0, 119.0, 53.4, 30.5, 9.4; IR (ATR): ν_{max} 2952, 1710, 1439, 1309, 1216, 1190, 1075, 1028, 908, 830, 751, 692, 534 cm^{-1}; ESIHRMS *m/z* calcd for $C_{13}H_{15}BrNO_2$ $[M+H]^+$ 296.0281, found 296.0278.



59b

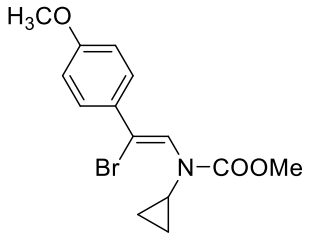
***Z*-(2-Bromo-2-phenylvinyl)-*tert*-butyl-cyclopropylcarbamate 59b.** Starting from 7.3 mmol of the corresponding dibromoenamide. Yield: 88% (2.18 g, 6.4 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 55 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.52 (m, 2H), 7.35-7.30 (m, 3H), 6.90 (s, 1H), 3.07-3.03 (m, 1H), 1.50 (s, 9H), 0.92-0.88 (m, 2H), 0.72-0.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.8, 138.5, 128.7, 128.4, 127.9, 81.3, 30.2, 28.4, 9.5; IR (ATR): ν_{max} 2979, 1719, 1628, 1366, 1352, 1304, 1151, 1069, 762, 722, 694 cm^{-1}.



59c

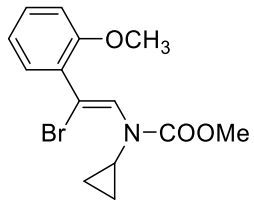
***Z*-[2-Bromo-2-(*p*-tolyl)vinyl]-cyclopropyl-methylcarbamate 59c.** Starting from 2.0 mmol of the corresponding dibromoenamide. Yield: 30% (189 mg, 0.61 mmol). Solvent system for flash column

chromatography: petroleum ether/EtOAc: 5/1; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 2H), 6.84 (s, 1H), 3.77 (s, 3H), 3.14-3.08 (m, 1H), 2.36 (s, 3H), 0.92-0.88 (m, 2H), 0.74-0.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 139.0, 135.3, 129.1, 127.8, 127.4, 119.4, 53.3, 30.5, 21.3, 9.2; IR (ATR): ν_{max} 2960, 1710, 1605, 1508, 1439, 1303, 1247, 1177, 1076, 1028, 828, 771, 543 cm^{-1}; ESIHRMS *m/z* calcd for $C_{14}H_{17}BrNO_2$ $[M+H]^+$ 310.0437, found 310.0436.



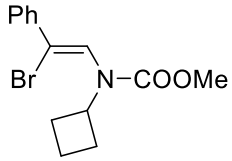
59d

***Z*-[2-Bromo-2-(4-methoxyphenyl)vinyl]-cyclobutyl-methylcarbamate 59d.** Yield: 50% (323 mg, 0.99 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; White solid; Mp: 42 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.45 (m, 2H), 6.88-6.76 (m, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.13-3.07 (m, 1H), 0.93-0.88 (m, 2H), 0.74-0.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 156.5, 130.6, 129.3, 126.7, 113.8, 55.5, 53.3, 30.5, 9.1; IR (ATR): ν_{max} 2963, 1700, 1437, 1338, 1322, 1134, 1075, 818, 772, 471 cm^{-1}; ESIHRMS *m/z* calcd for $C_{14}H_{17}BrNO_3$ $[M+H]^+$ 326.0386, found 326.0385.



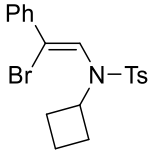
59e

***Z*-[2-Bromo-2-(2-methoxyphenyl)vinyl]-cyclopropyl-methylcarbamate 59e.** Yield: 94% (64 mg, 234 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; White solid; Mp: 57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 7.6 and 1.7 Hz, 1H), 7.30 (ddd, *J* = 8.2, 7.5 and 1.8 Hz, 1H), 6.94 (td, *J* = 7.5 and 1.0 Hz, 1H), 6.90 (dd, *J* = 8.3 and 0.7 Hz, 1H), 6.70 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.15-3.10 (m, 1H), 0.96-0.91 (m, 2H), 0.82-0.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 156.4, 131.6, 130.4, 130.3, 127.7, 120.5, 111.4, 55.9, 53.2, 30.4, 9.3; IR (ATR): ν_{max} 3365, 2978, 2363, 1703, 1686, 1390, 1366, 1329, 1252, 1161, 1142, 860, 764, 637 cm^{-1}; ESIHRMS *m/z* calcd for $C_{14}H_{17}BrNO_3$ $[M+H]^+$ 326.0386, found 326.0392.



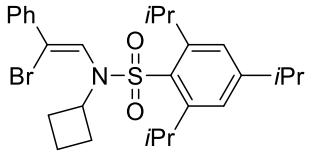
50a

***Z*-(2-Bromo-2-phenylvinyl)-cyclobutyl-methylcarbamate 50a.** Starting from 5.3 mmol of the corresponding dibromoenamide. Yield: 84% (1.37 g, 4.4 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 38 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60-7.58 (m, 2H), 7.40-7.35 (m, 3H), 6.73 (s, 1H), 4.60 (quint., *J* = 5.6 Hz, 1H), 3.73 (s, 3H), 2.29-2.16 (m, 4H), 1.71-1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ154.9, 137.5, 129.4, 128.6, 128.4, 128.1, 126.1, 53.0, 52.8, 28.8, 15.2; IR (ATR): ν_{max} 2952, 2239, 1709, 1440, 1354, 1160, 958, 751, 692, 545, 515 cm^{-1}; ESIHRMS *m/z* calcd for $C_{14}H_{17}BrNO_2$ $[M+H]^+$ 310.0437, found 310.0441.



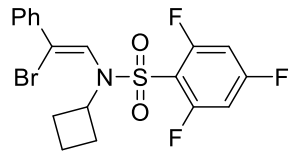
50b

***Z*-*N*-(2-Bromo-2-phenylvinyl)-*N*-cyclobutyl-4-methylbenzenesulfonamide 50b.** Starting from 2.4 mmol of the corresponding dibromoenamide. Yield: 82% (814 mg, 2.0 mmol). Solvent system for flash column chrocmatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 77 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.74 (d, *J* = 8.3 Hz, 2H), 7.56-7.54 (m, 2H), 7.38-7.37 (m, 3H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.32 (s, 1H); 4.36 (quint., *J* = 4.3 Hz, 1H), 2.43 (s, 3H), 2.12-2.07 (m, 4H), 1.65-1.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ143.9, 137.4, 136.2, 134.1, 129.9, 129.8, 128.6, 128.3, 127.8, 123.7, 54.2, 28.9, 21.7, 15.5; IR (ATR): ν_{max} 3676, 2988, 1347, 1164, 1066, 813, 703, 663, 575 cm^{-1}; ESIHRMS *m/z* calcd for $C_{19}H_{21}BrNO_2S$ $[M+H]^+$ 406.0471, found 406.0475.



50c

***Z*-*N*-(2-Bromo-2-phenylvinyl)-*N*-cyclobutyl-2,4,6-triisopropylbenzenesulfonamide 50c.** Starting from 1.7 mmol of the corresponding dibromoenamide. Yield: 73% (637 mg, 1.2 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 77 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.57-7.55 (m, 2H), 7.37-7.35 (m, 3H), 7.13 (s, 2H), 6.75 (s, 1H), 4.63 (quint., *J* = 8.6 Hz, 1H), 4.16-4.08 (m, 2H), 2.89 (quint., *J* = 6.9 Hz, 1H), 2.28-2.17 (m, 4H), 1.69-1.62 (m, 2H), 1.24 (d, *J* = 6.8 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): δ153.2, 151.4, 137.1, 133.2, 132.8, 129.7, 128.4, 128.1, 124.2, 123.8, 53.9, 34.1, 30.0, 29.0, 25.1, 23.6, 15.6; IR (ATR): ν_{max} 3347, 2976, 1309, 1150, 1043, 878, 805, 760, 678, 649, 595, 551 cm^{-1}; ESIHRMS *m/z* calcd for $C_{27}H_{37}BrNO_2S$ $[M+H]^+$ 518.1723, found 518.1726.



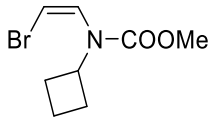
50d

***Z*-*N*-(2-Bromo-2-phenylvinyl)-*N*-cyclobutyl-2,4,6-trifluorobenzenesulfonamide 50d.** Starting from 1.2 mmol of the corresponding dibromoenamide. Yield: 97% (502 mg, 1.13 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 65 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.55 (m, 2H), 7.40-7.36 (m, 3H), 6.77 (t, *J* = 8.4 Hz, 2H), 6.60 (s, 1H), 4.66 (quint., *J* = 8.6 Hz, 1H), 2.22-2.17 (m, 4H), 1.70-1.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3 (dt, *J* = 256.3 and 15.0 Hz), 161.1 (ddd, *J* = 259.4, 15.0 and 6.3 Hz), 137.0, 134.9, 130.2, 128.7, 128.3, 122.8, 102.1 (ddd, *J* = 27.5, 25.0 and 3.8 Hz), 54.5, 29.3, 15.4; ^{19}F NMR (471 MHz, $CDCl_3$): δ -98.6 (t, *J* = 23.6 Hz), -101.2 (d, *J* = 14.1 Hz); IR (ATR): ν_{max} 3360, 2978, 1708, 1639, 1490, 1387, 1367, 1328, 1244, 1162, 1143, 1091, 1003, 859, 742 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{18}BrF_3NO_2S$ $[M+H]^+$ 446.0032, found 446.0032.

Experimental Procedure and Characterization Data: Synthesis of enamides through tin-mediated reduction

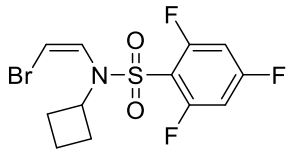
General procedure:

To a solution of dibromoenamide (3.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (74 mg, 0.06 mmol) in anhydrous ethyl acetate was added tributyltin hydride (2.1 mL, 7.7 mmol). The resulting solution was stirred at room temperature for 5 hours. The mixture was filtered through a plug of celite (washed with ethyl acetate) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel (mixed with 5% w/w dry potassium fluoride powder) to give the desired product.



82

***Z*-(2-Bromovinyl)-cyclobutyl-methylcarbamate 82.** Yield: 94% (64 mg, 234 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ6.67 (d, *J* = 5.4 Hz, 1H), 6.21 (d, *J* = 5.4 Hz, 1H), 4.49 (quint., *J* = 8.6 Hz, 1H), 3.72 (s, 3H), 2.24-2.12 (m, 4H), 1.70-1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ154.5, 130.1, 106.9, 53.0, 52.5, 28.7, 15.0; IR (ATR): ν_{max} 2957, 1703, 1614, 1441, 1344, 1299, 1256, 1174, 1132, 754, 723, 664, 531 cm^{-1}; ESIHRMS *m/z* calcd for $C_8H_{13}BrNO_2$ $[M+H]^+$ 234.0124, found 234.0125.



83

***Z*-*N*-(2-Bromovinyl)-*N*-cyclobutyl-2,4,6-trifluorobenzenesulfonamide 83.** Yield: 95% (70 mg, 238 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 84 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ6.76 (t, *J* = 8.6 Hz, 2H), 6.58 (s, 2H), 4.58 (quint., *J* = 8.5 Hz, 1H), 2.17-2.09 (m, 4H), 1.67-1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ165.3 (dt, *J* = 256.3 and 15.0 Hz), 161.1 (ddd, *J* = 258.8, 15.0 and 6.3 Hz), 127.4, 115.5, 115.3 (td, *J* = 16.3 and 3.8 Hz), 102.1 (ddd, *J* = 27.5, 25.0 and 3.8 Hz), 54.0, 29.2, 15.2; ^{19}F NMR (471 MHz, $CDCl_3$): δ-98.5 (t, *J* = 23.6 Hz), -101.3 (d, *J* = 3.8 Hz); IR (ATR): ν_{max} 2989, 1611, 1592, 1440, 1368, 1172, 1038, 862, 847, 747, 657, 532, 513 cm^{-1}; ESIHRMS *m/z* calcd for $C_{12}H_{12}BrF_3NO_2S$ $[M+H]^+$ 369.9719, found 369.9717.

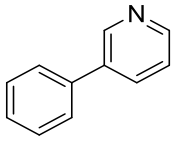
Experimental Procedure and Characterization Data: palladium catalyzed ring-opening/cyclization of cyclopropyl enamides

General procedure I:

A Schlenk tube was charged with the enamide (0.3 mmol), palladium acetate (3 mg, 0.015 mmol), $P^tBu_2Me{\cdot}HBF_4$ (7 mg, 0.03 mmol), K_3PO_4 (96 mg, 0.45 mmol) and CsOPiv (21 mg, 0.09 mmol). Then the tube was evacuated under high vacuum and backfilled with nitrogen three times. Anhydrous mesitylene (1.5 mL) was added and the mixture was stirred at 110 °C for 16 h. The reaction was then cooled to room temperature and diluted with THF (2 mL). DDQ (82 mg, 0.36 mmol) was added and the mixture was stirred for 1 hour. The suspension was filter through a plug of silica gel (washed with ethyl acetate) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired cyclized product.

General procedure II:

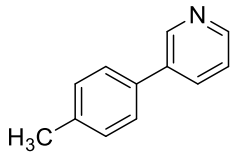
To a solution of enamide (0.3 mmol), bis(triphenylphosphine)palladium(II) chloride (11 mg, 0.05 mmol) and triphenylphosphine (8 mg, 0.03 mmol) in a mixed solvent of acetonitrile (2.7 mL) and water (0.3 mL) was added *N*,*N*-diisopropylethylamine (50 µL, 0.3 mmol). The resulting mixture was stirred at 130 °C under microwave irradiation (100 W, 13 bars) for 1 hour. The reaction was then cooled to room temperature and diluted with THF (2 mL). DDQ (82 mg, 0.36 mmol) was added and the mixture was stirred for 1 hour. The suspension was filter through a plug of silica gel (washed with ethyl acetate) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired cyclized product.



61a

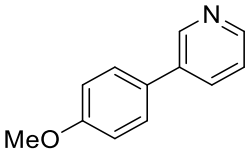
3-Phenylpyridine 61a. Prepared according to the general procedure I. Yield: 69% (31 mg, 0.2 mmol). Prepared according to the general procedure II. Yield: 67% (30 mg, 0.19 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; This compound has been previously reported. [S15]

[S15] Alacid, E.; Najera, C. *Org. Lett.* **2008**, *10*, 5011-5014.



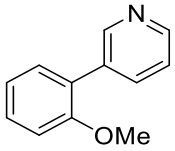
61b

3-(4-Tolyl)pyridine 61b. Prepared according to the general procedure II. Yield: 66% (33 mg, 197 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 2/1; This compound has been previously reported.[S16]



61c

3-(4-Methoxyphenyl)pyridine 61c. Prepared according to the general procedure II. Yield: 41% (23 mg, 122 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 2/1; This compound has been previously reported.[S17]



61d

3-(2-Methoxyphenyl)pyridine 61d. Yield: 22% (12 mg, 65 µmol). Prepared according to the general procedure II. Solvent system for flash column chromatography: petroleum ether/EtOAc: 5/1; This compound has been previously reported.[S18]

[S16] Wang, L.; Wei, Y.-M.; Zhao, Y.; Duan, X.-F. *J. Org. Chem.* **2019**, *84*, 5176-5186.
[S17] Louaisil, N.; Pham, P. D.; Boeda, F.; Faye, D.; Castanet, A.; Legoupy, S. *Eur. J. Org. Chem.* **2011**, *1*, 143-149.
[S18] Li, Y.; Liu, W.; Kuang, C. *Chem. Commun.* **2014**, *50*, 7124-7127.

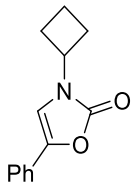
Experimental Procedure and Characterization Data: palladium catalyzed C-H activation/cyclization of the cyclobutyl enamides

General procedure I:

A Schlenk tube was charged with the enamide (0.2 mmol), palladium acetate (2 mg, 0.05 mmol), $PCy_3 \cdot HBF_4$ (7 mg, 0.02 mmol), cesium carbonate (98 mg, 0.3 mmol) and pivalic acid (6 mg, 0.06 mmol), then the tube was evacuated under high vacuum and backfilled with nitrogen for three times. Anhydrous mesitylene (1 mL) was added and the mixture was stirred at 140 °C for 17 h. The reaction was then cooled to room temperature, the suspension was filtered through a plug of silica gel (washed with ethyl acetate) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the product.

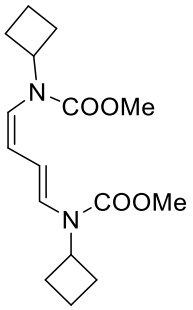
General procedure II:

To a solution of enamide (0.3 mmol), bis(triphenylphosphine)palladium(II) chloride (11 mg, 0.05 mmol) and triphenylphosphine (8 mg, 0.03 mmol) in a mixed solvent of acetonitrile (2.7 mL) and water (0.3 mL) was added *N*,*N*-diisopropylethylamine (50 µL, 0.3 mmol). The resulting mixture was stirred at 140 °C under microwave irradiation (100 W, 13 bars) for 1 hour. The suspension was filtered through a plug of silica gel (washed with ethyl acetate) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to give the desired cyclized product.



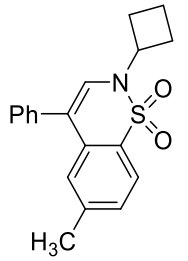
85

3-Cyclobutyl-5-phenyloxazol-2(3H)-one 85. Prepared according to the general procedure II. Yield: 52% (22 mg, 104 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; Red oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.48 (m, 2H), 7.39-7.36 (m, 2H), 7.30-7.27 (m, 1H), 6.90 (s, 1H), 4.61-4.54 (m, 1H), 2.46-2.40 (m, 2H), 2.33-2.24 (m, 2H), 1.89-1.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2, 139.3, 129.0, 128.2, 127.6, 123.0, 106.9, 48.2, 29.9, 24.0, 14.9 cm^{-1}; IR (ATR): ν_{max} 3320, 3107, 2976, 1733, 1644, 1450, 1393, 1268, 1095, 1047, 739, 691, 670 cm^{-1}; ESIHRMS *m/z* calcd for $C_{13}H_{14}NO_2$ $[M+H]^+$ 216.1019, found 216.1033.



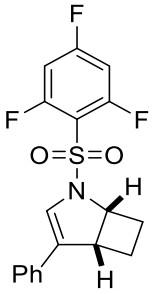
86

Dimethyl [(1*Z*,3*E*)-buta-1,3-diene-1,4-diyl]bis(cyclobutylcarbamate) 86. Prepared according to the general procedure I, starting from 0.3 mmol of the corresponding enamide. Yield: 30% (23 mg, 91 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1; Light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ6.87 (d, *J* = 14.4 Hz, 1H), 5.97 (dd, *J* = 11.0 and 7.7 Hz, 1H), 5.70 (d, *J* = 7.7 Hz, 1H), 5.64 (dd, *J* = 15.0 and 11.1 Hz, 1H), 4.53 (t, *J* = 7.6 Hz, 1H), 4.20 (quint., *J* = 8.5 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.32-2.27 (m, 4H), 2.13-2.08 (m, 4H), 1.74-1.67 (m, 2H), 1.63-1.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ155.7, 154.6, 131.7, 128.1, 121.4, 107.8, 53.0, 52.8, 52.6, 51.4, 29.5, 28.4, 14.9; IR (ATR): ν_{max} 2951, 1699, 1608, 1441, 1311, 1249, 1189, 1137, 1030, 964, 768 cm^{-1}.



87

2-Cyclobutyl-6-methyl-4-phenyl-2H-benzo[e][1,2]thiazine 1,1-dioxide 87. Prepared according to the general procedure I, starting from 0.3 mmol of the corresponding enamide. Yield: 68% (64 mg, 0.2 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 105 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.87 (d, *J* = 8.1 Hz, 1H), 7.49-7.45 (m, 2H), 7.43-7.41 (m, 3H), 7.30-7.29 (m, 1H), 7.05 (s, 1H), 6.77 (s, 1H), 4.87 (quint., *J* = 8.7 Hz, 1H), 2.43-2.36 (m, 4H), 2.34 (s, 3H), 1.85-1.76 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ142.6, 137.1, 133.5, 129.8, 129.0, 128.8, 128.0, 127.4, 126.3, 126.2, 122.2, 50.0, 30.2, 21.9, 15.1; IR (ATR): ν_{max} 2957, 1600, 1322, 1252, 1233, 1168, 1140, 737, 701, 658, 541 cm^{-1}; MS *m/z* calcd for $C_{19}H_{20}NO_2S$ $[M+H]^+$ 326.1, found 326.1.



90

4-Phenyl-2-[(2,4,6-trifluorophenyl)sulfonyl]-2-azabicyclo[3.2.0]hept-3-ene 90. Prepared according to the general procedure I (the reaction time is 5 hours). Yield: 17% (12 mg, 34 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1; White solid; Mp: 92 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.30 (m, 2H), 7.26-7.21(m, 3H), 6.97 (s, 1H), 6.76 (t, *J* = 8.4 Hz, 2H), 4.80 (q, *J* = 6.8 Hz, 1H), 3.96 (t, *J* = 8.2 Hz, 1H), 2.67-2.59 (m, 1H), 2.54-2.45 (m, 2H), 2.17-2.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2 (dt, *J* = 256.3 and 16.3 Hz), 160.8 (ddd, *J* = 258.8, 15.0 and 6.3 Hz), 132.6, 130.1, 128.9, 127.5, 125.1, 124.8, 113.9 (td, *J* = 16.3 and 5.0 Hz), 102.3 (ddd, *J* = 28.8, 25.0 and 3.8 Hz), 59.2, 45.3, 29.6, 26.5; ^{19}F NMR (471 MHz, $CDCl_3$): δ -98.5 (t, *J* = 11.8 Hz), -101.0 (d, *J* = 9.4 Hz); IR (ATR): ν_{max} 2949, 1611, 1596, 1370, 1178, 1133, 1086, 1039, 878, 847, 759, 666, 580, 536 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{15}F_3NO_2S$ $[M+H]^+$ 366.0770, found 366.0768.

Chunyang ZHANG

Synthèse d'hétérocycles azotés à partir d'ynamides et d'énamides

Résumé

Cette thèse a principalement porté sur le développement de nouvelles méthodes pour la synthèse d'hétérocycles azotés, à partir d'ynamides ou énamides. Dans un premier temps, nous nous sommes intéressés à une réaction de cyclisation intramoléculaire radicalaire permettant la synthèse d'une série d'hétérocycles azotés tels que des pyrrolidines, pipéridines, azépanes, pyrazolidines et hexahydropyridazines. Dans un second temps, nous avons étudié deux cyclisations catalysées au palladium faisant appel à un processus intramoléculaire d'alcénylation de C(sp3)-H de *N*-cyclopropyl énamides et de *N*-cyclobutyl énesulfonamides. Cette transformation conduit à des 1,4-dihydropyridines et des pyrrolines fusionnées à un cyclobutane.

Mots-clés : radicaux, ynamide, catalyse au palladium, cyclopropyle, cyclobutyle, énamide, cyclisation

Résumé en anglais

This thesis has mainly focused on the development of new methods towards the synthesis of highly valuable nitrogen-containing heterocycles starting from either ynamides or their relatives, in which a radical-mediated intramolecular cyclization of ynamides was eventually developed for the synthesis of a series of *N*-heterocycles, such as pyrrolidine, piperidine, azepane, pyrazolidine and hexahydropyridazine derivatives. Moreover, by using both *N*-cyclopropyl enamides and *N*-cyclobutyl enesulfonamides as substrates, two palladium catalyzed cyclizations involving a rarely reported intramolecular secondary C(sp^3)-H alkenylation process were accomplished to give the corresponding 1,4-dihydropyridines and cyclobutyl-fused pyrrolidines, respectively.

Key-words : radical, ynamide, palladium catalysis, cyclopropyl, cyclobutyl, enamide, cyclization