Applications of the Hofmann-Löffler Reaction for C-H Functionalization in Total Synthesis

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UNIVERSITAT ROVIRA i VIRGILI

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ESTEFANÍA DEL CASTILLO FERNÁNDEZ

DOCTORAL THESIS
2020

Applications of the Hofmann-Löffler Reaction for C-H Functionalization in Total Synthesis

Estefanía del Castillo Fernández

Doctoral Thesis

Supervised by Prof. Kilian Muñiz Klein and Prof. Antonio M. Echavarren
Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, 2020

Prof. Antonio M. Echavarren, Group Leader of the Institute of Chemical Research of Catalonia (ICIQ):

I confirm that the present thesis manuscript, entitled "Applications of the Hofmann-Löffler Reaction for C-H Functionalization in Total Synthesis", presented by Estefanía del Castillo Fernández to receive the degree of Doctor, has been carried out under the supervision of Prof. Dr. Kilian Muñiz Klein at the Institute of Chemical Research of Catalonia (ICIQ) and that I have co-supervised this Thesis after the passing away of Prof. Muñiz.

Tarragona, October 29, 2020

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Prof. Kilian Muñiz Klein

Prof. Antonio M. Echavarren Pablos

In Memoriam

Temía fracasar, hasta que me di cuenta que únicamente fracaso cuando no lo intento

ERNEST HEMINGWAY

Acknowledgements

I want to start by expressing my utmost gratitude to my supervisor Prof. Kilian Muñiz, with great regret for his death on March, 2020. Kilian was a person with great enthusiasm for chemistry. I want to be grateful for his constant support and enthusiasm. Throughout my PhD, I still remember my first day at ICIQ, when Kilian was on holiday and everyone was speaking about how special Kilian was. Those days, I wondered if I made the correct choice for my future and this feeling was accompanying me all through that period. Now I am quite sure about it: I made the right choice. I want to remark how Kilian was "forcing us" to learn fast and improve our chemistry skills. He allowed me to attend several international and national conferences, where I could present my research in front of several people. In general, Kilian was a close person, we were speaking almost every day in his office or in the lab, and he was trying to make us laugh with his jokes. He shared with us all his special moments with famous chemists, being a really passionate person about chemistry, wines, football, and Spain's politics. I thank Kilian for all his support and all the knowledge that he transmitted to all of us.

After losing Kilian, several people took part in making our lives much easier. I would like to thank the support of Prof. Miquel Pericàs and Dr. Lluis Solà, who made it possible to continue our studies in the ICIQ and help us with all our needs. In this regard, I would like to thank Prof. Antonio M. Echavarren, who took care of my research and last months of my PhD Thesis, for all his support with the manuscritp preparation and correction, and the guidance with my last project.

During this period, I shared the lab and moments with many people, I would like to show my gratitude to all the postdocs, PhD students and visiting students in the group during these years. First, I will start expressing my gratitude to Claudio Martínez, coordinator of the group. I shared with him my first months at ICIQ, and he helped me understand how to work in this group and to have a better time here. Also, Laura F., Martín R., Nicola L., Dr. Hongwei Z., Dr. Matilde A. and Terry T., part of the members of my first year of PhD. In particular, Laura B., Belén G., and Anda B., with whom I am still in close contact, for having contributed to have nice moments in the lab. I consider them really important people in my life. Thanks for being in my life listening to my worries and my jokes every day.

Moreover, some people entered the same year as me in the PhD adventure. They were Thomas D., Daniel B., Francesca G., and Anastasia T. Thanks a lot to all of you. I considered myself lucky to have you in my life during this period. In particular, Thomas and Daniel: thanks for having a family atmosphere in lab 2.4, where we had very nice moments together. I hope this friendship will continue for years! I will miss you a lot! We will always be lab 2.4, it does not matter what. In the same year, Dr. Mario M. arrived, with whom I shared a common project. I learned so much from you and I am still continue learning from you. In addtion, Dr. Julien B. and Dr. Sebastian H. were a great source of knowledge and good frienship. Èric C. and Andrea F., the energy in person. Both of them transmit energy and positivism every day: In particular, thanks Èric for being so nice and talkative always. Without you the lab moments and party moments would have not been the same. Regarding the the german community, I would like to thank Dr. Anna S., thanks for sharing great moments there, laughing, and for bringing chocolate in all the bad moments. I appreciated it a lot.

In my last two years some extraordinary people arrived to the group: Eleni G., Dr. Kang C., Alienor J., Jiayu Z., and Jixiang N. Especially, I shared a lot of moments in the lab and outside the lab with Eleni, more known as “cara pasa” or “cara pasita”, I appreciate you a lot. Thanks for the dances in the lab together, for listening to me and making my life funnier and calmer at the same time. Ali, “hi Ali”: thanks for the moments in the lab, the gossips, the funny jokes, for being always happy and smiling, your good energy and positivism.

Finally, many people also contribute to this period. I want to thank Jorge S. with whom I shared my fume hood for some months. Thanks also to Cristian, Matthew, Ioana, and Zoritsa, kind and friendly visiting students.

In general, I considered myself a lucky person because I overcame all the difficulties that I suffered during this period. It was not a really easy PhD in general, but all of you guys make it much easier!! I thank all of you wholeheartedly!

I want to thank all the people who also make it posible: the Support Area Units, especially NMR, X-ray, ChromTae, MS Units, and logistic guys, who helped us in daily life at the ICIQ institute. I want to show special gratitude to Sorania J., Kilian’s secretary, because she was in charge of all the orders or whatever we needed during these four years. We spend a lot of time together looking for

reasonable offers and the cheap options in front of Kilian. You are a very smiling and friendly person always available for help. Thanks for being so easy-going person.

Finalmente, me gustaría agradecer a personas muy importantes en mi vida, que sin ellos esta Tesis Doctoral no hubiese sido posible: mi familia y amigos. Me gustaría empezar con mi padre, a quien quiero dedicar unas palabras por ser la persona que ha luchado siempre por mi futuro, que ha querido que siempre aspire a más, porque el conocimiento es poder. Que me ha convencido en numerosas ocasiones de que rendirse no era una opción. Él mejor que nadie sabe todo lo que ha pasado estos años en nuestras vidas y, aun así, me ha demostrado que en la vida se lucha pese a las difíciles situaciones que pueden aparecer. Gracias por ayudarme a lidiar con todo, a demostrarme que tras la tormenta siempre aparece el sol. En la misma línea su mujer Lineth, porque hemos compartido más de 14 años juntas, porque me ha visto empezar con la química y seguir adelante hacia el doctorado. Gracias por estar ahí siempre que te he necesitado y dar todo el cariño tanto a mí como a mi familia. Ambos sois auténticos pilares en mi vida. Y no por ello iba a dejar atrás a mi hermana Silvia: gracias por todo, por todo lo que hemos vivido y lo que nos queda. Por demostrarme que tengo la mejor hermana del mundo, por entenderme y ayudarme, por escucharme y aconsejarme … no sabría dónde parar. Han sido unos años muy duros para mí, pero pese a todo ninguno de vosotros dejó de ayudarme y alentarme. Con la mano en el pecho os digo, parte de todo esto os pertenece, gracias y gracias. También me gustaría agradecer a mis tíos y mis primas, por todas las reuniones familiares, por mis ganas de que llegasen las vacaciones para poder veros a todos. Porque Madrid es más bonito porque estáis vosotros y porque os quiero.

Por otra parte, mis amigos. En especial, me gustaría agradecer a Alba, Inés y Ana. Alba empiezo por ti, por todos estos años juntas, porque nos conocimos hace casi 15 años y nuestra amistad no cambia nada. Por las risas, los momentos, los recuerdos. Gracias por demostrarme que si uno lucha lo consigue. También Inés, ambas luchando por un futuro parecido, obtener el título de Doctor en Química. En eso, hemos estado codo con codo, una en Alemania y otra en Tarragona, pero hablando y ayudándonos cada día en la distancia. Gracias por estar ahí, para que pueda contarte cada cosa que pasa por mi vida. Recuerda: siempre nos quedará Madrid y así espero que sea siempre. Te veo pronto amiga. Por ultimo y no menos importante, Ana G. Nos conocimos haciendo el Máster en Madrid y ahora

estamos trabajando en el mismo sitio. Me gusta el haberte recuperado porque a veces la distancia y el tiempo hace que separe personas, pero aquí estás y espero que sea así por mucho tiempo. Gracias por tus sonrisas, tu buen humor, tu optimismo y ganas de hacer cosas. Uno se alegra de tener gente así a su alrededor.

Por último, he dejado un espacio a mi pareja José: gracias por estos años juntos, por tu constante apoyo incondicional, por tu manera de sacarme sonrisas y de quererme. Has hecho que los últimos años de mi doctorado (y de mi vida hasta ahora) sean infinitamente mucho mejor. Y quiero que sepas que me has hecho muy feliz y que espero que sea así siempre. Muchas gracias de corazón.

List of publication resulting from this Thesis:

2019

Enantioselective Synthesis of Nicotine via an Iodine-Mediated Hofmann–Löffler Reaction. E. Del Castillo and K. Muñiz, *Org. Lett.* **2019**, *21*, 705.

2018

Multiple Halogenation of Aliphatic C−H Bonds within the Hofmann–Löffler Manifold. E. Del Castillo, M. D. Martínez, A. –E. Bosnidou, T. Duhamel, C. Q. O´Broin, H. Zhang, E. C. Escudero-Adán, M. Martínez-Belmonte, K. Muñiz. Chem. Eur. J. 2018, 24, 17225.

* Some of the results presented in this Thesis have not been published

Abbreviation list

Ac- acetyl
Ar- Aryl
Bn- Benzyl
$CDCl_3$- Deuterated chloroform
DCM-Dichloromethane
DMF-Dimethylformamide
DMSO- Dimethylsulfoxide
ee- Enantiomeric excess
equiv.- Equivalent
HAT-Hydrogen Atom Transfer
HPLC- High Performance Liquid Chromatography
HRMS-High Resolution Mass Spectrometry
***i*-PrOH**- Isopropanol
Ipy_2BF_4-Bis(pyridinium)iodonium (I) tetrafluoroborateAcOH- acetic acid
IR- Infrared
LED- Light-Emitting Diode
m.p. Melting point
***m*CBA**- *m*-chlorobenzoic acid
***m*CPBA**- *m*-chloroperbenzoic acid
MHz- Megahertz
Ms- Methanesulfonyl chloride
NBS- *N*-Bromosuccinimide
NCS- *N*-Chlorosuccinimide
NFSI- *N*-fluorobenzenesulfonimide
NIS- *N*-iodosuccinimide

NMR- Nuclear Magnetic Resonance
Ns- *p*-nitrobenzenesulfonyl chloride
PA- Picolinamide
Phth- Phthalimide
PIDA - (Diacetoxyiodo)benzene
r.t-. Room temperature
SES-2-(Trimethylsilyl)ethanesulfonyl
SET- Single-Electron-Transfer
TFA-Trifluoroacetic acid
THF- Tetrahydrofuran
TMSCl- Chlorotrimethylsilane
UV-Ultraviolet

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Summary of the Thesis

The work carried out in this Doctoral Thesis represents significant advances in the application of the Hofmann-Löffler reaction in total synthesis. Moreover, this reaction was also employed as an attractive tool for the halogenation of aliphatic substrates. This reaction consists in the use of hypervalent iodine(III) reagents in combination with molecular iodine to generate the amidyl radicals for C–H functionalization of distal and nonactivated carbons.

The first part of my Thesis was focused on the multiple halogenation of aliphatic bonds through an interrupted Hofmann-Löffer reaction. We developed a selective and unprecedented method to introduce multiple halogens into an organic molecule. We started testing sulfonamides and sulfamate esters as directing groups to functionalize the δ and γ-positions of the molecule selectively. Several methods have been developed to introduce halogen atoms into organic molecules. However, direct and regioselective C–H halogenation has been recognized as one of the most efficient tools to streamline complex halogenated synthesis molecules, particularly to nonactivated aliphatic C–H bonds. We demonstrated the applicability of this method to cyclic and acyclic structures and introduced different halogens into the same molecule in a regioselective manner.

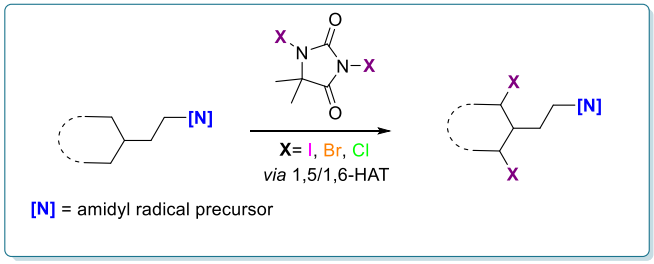


Figure 1. *General scheme for C–H halogenation over aliphatic C–H bonds.*

The second and third parts of my PhD Thesis work focused on applying the Hofmann-Löffler reaction in the synthesis of natural products. In the second chapter, we summarized our efforts at designing an enantioselective synthesis of the natural product nicotine and some important analogs such as altinicline. In these syntheses, we remarked the use of C–H functionalization through the Hofmann-Löffler manifold to generate the pyrrolidine rings in their structures. Moreover, this protocol was also applied to more complex systems as bipyridine derivatives to demonstrate the robustness and broader applicability of this strategy for total synthesis.

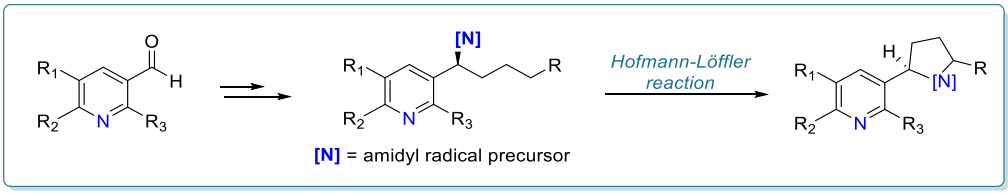


Figure 2. *Enantioselective synthesis of nicotine through Hofmann-Löffler's reaction.*

Finally, we decided to try more complex molecules and applied the Hofmann-Löffler reaction for the enantioselective synthesis of the hasubanan skeleton. Decades after their discovery, hasubanan alkaloids are still of interest to the synthetic community. While synthetically challenging, the primary reason for this interest has been due to the structural similarities to the morphinan alkaloids. The synthetic community explored the formation of the pyrrolidine ring by using different approaches, thus showing the importance of this moiety in the chemical synthesis of natural products. The Hofmann-Löffler reaction seems an ideal pathway to provide this tetracyclic core to facilitate further syntheses of this and similar features. Moreover, some studies were carried out to demonstrate the mechanism of the transformation.

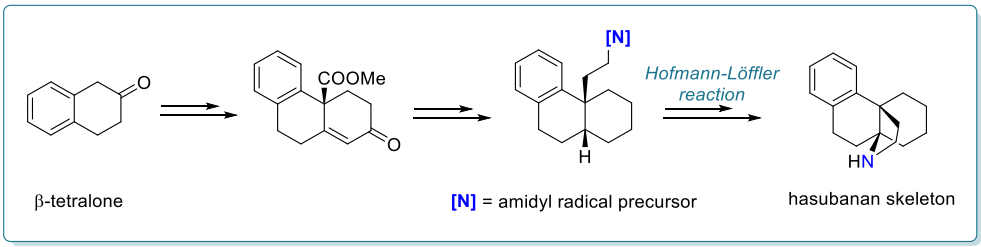


Figure 3. *Enantioselective synthesis of hasubanan skeleton through Hofmann-Löffler reaction.*

Overall objectives:

This Doctoral Thesis focuses on developing novel strategies for Csp^3-H bond functionalization, mainly related to the C–H halogenation and late-stage C–H amination in the context of the total synthesis of natural products. Hypervalent iodine (III) species are well-known to promote a selective Csp^3-H functionalization over hydrocarbons. Some years ago, our group pioneered the use of these hypervalent iodine (III) species combined with catalytic amounts of molecular iodine to promote nucleophilic aminations.

First, we decided to apply this new reactivity to introduce halogen atoms into organic molecules through an interrupted Hofmann-Löffer reaction. As it is well-known, the Hofmann-Löffler reaction provides *N*-heterocycles compounds as the final product of the transformation. The reaction starts with the formation of an amidyl radical, which generates a carbon-centered radical through 1,5-hydrogen atom transfer. Our ***first objective*** was to trap this carbon-centered radical with an appropriate moiety, such as halogen, thus developing an interesting protocol for directed-C–H halogenation over aliphatic substrates. Therefore, we envisioned the possibility to introduce halogen atoms into organic molecules using directing groups such as sulfonamides and sulfamates esters.

As a ***second objective,*** we wanted to expand the scope of the Hofmann-Löffler reaction and to apply this transformation for the synthesis of natural products. Firstly, we decided to form the pyrrolidine ring on the enantioselective nicotine alkaloid through a late-stage C–H amination promoted by the Hofmann-Löffler reaction. Then, we wanted to exploit the reactivity of the hypervalent iodine reagents in the presence of the pyridine core. Remarkably, the pyridine core combined with iodine (III) species could inhibit the reactivity of the Hofmann-Löffler reaction avoiding its use in late-stage amination steps. Finally, we wanted to investigate this reactivity on more complex molecules, such as the hasubanan skeleton. Specifically, we planned to exploit the behavior of the amidyl radical species formed into the decaline system to generate the tetracycle core of this family of natural products.

Chapter I. Introduction on Csp^3–H Functionalization

1. Carbon-nitrogen bond formation

The formation of a C–N bond in organic is one of the important transformations in the synthesis of natural products, medicinal molecules, and multifunctional materials. In fact, many of the currently used drugs have at least one C–N bond in their structure. Nitrogen is characterized for its lone pair basicity and its capacity to generate hydrogen bonds as both donor and acceptor. In nature, it is present as organic and inorganic nitrogen in a diversity of chemicals forms and oxidation states. Carbon-nitrogen bond formation reactions are vital transformations that lead to many acyclic and (hetero)cyclic compounds with biological and medicinal significance. Unlike the C–O bond, formation of C–N bonds in nature does not offer much inspiration for direct oxidative nitrogen transfer to organic molecules.[1] Despite significant improvements in this area, formation of C–N bonds is still a substantial challenge for organic chemists, owing to the need for the use of stoichiometric reagents that generate significant amounts of potentially toxic waste. Furthermore, relatively harsh reaction conditions are required. In some cases, the transformation can be performed under milder conditions with the use of precious-metal-based catalysts.[2]

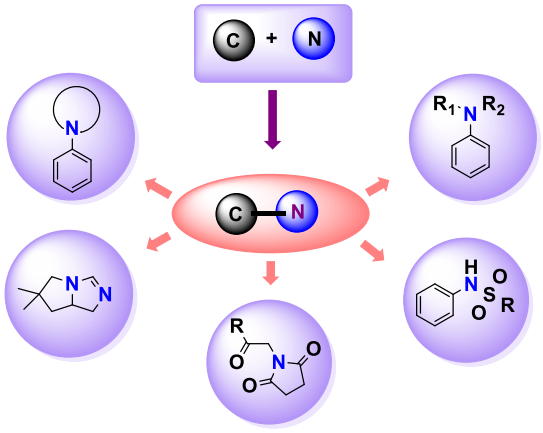


Figure 1.1. *Carbon-nitrogen bond presence in different compounds.*

[1] (a) R. Hili, A. K. Yudin, *Nat. Chem. Biol.* **2006**, *2*, 284. (b) A. Ricci, Amino Group Chemistry: From Synthesis to Life Sciences; Wiley-VCH: Weinheim, 2008. (c) M. Feher, J. M. Schmidt, *J. Chem. Inf. Comput. Sci*. **2003**, *43*, 218.

[2] (a) K. Shin, H. Kim, S. Chang, *Acc. Chem. Res*. **2015**, *48*, 1040. (b) M. Taillefer, D. Ma, Amination and formation of sp^2 C-N bonds. Springer. (c) J. Bariwal, E. V. Eycken, *Chem. Soc. Rev*. **2013**, *42*, 9283.

1.1. Introduction of nitrogen moiety in organic molecules through C–H functionalization

The transformation of an inert C–H bond into C–O or C–N bonds is considered a big challenge for synthetic chemistry. In the last decades, the introduction of nitrogen atoms to complex molecules has attracted much interest and significance in organic synthesis. The most widely employed methods for the preparation of aliphatic amines include reductive amination, imine alkylation, nucleophilic substitution, allylic amination, and alkene amination reactions (Figure 1.2).[3] Unfortunately, for these transformations, a pre-installed functionality is required.

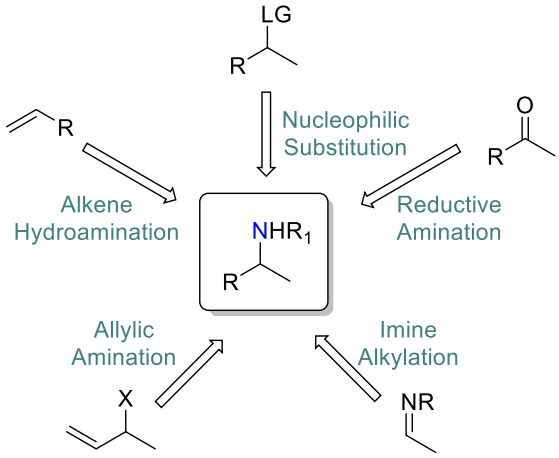
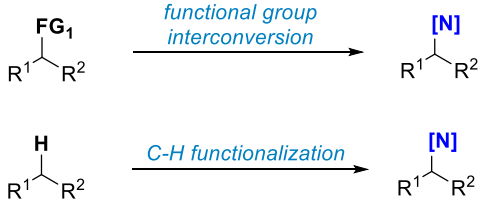


Figure 1.2. *C–N bond-forming reactions.*

Therefore, there is a general need for new methodologies and chemical methods to synthesize complex amines without the requirement of pre-functionalized molecules. Alternatively, one of the most modern strategies to install a nitrogen moiety on an organic compound is C–H functionalization, although the control of selectivity and reactivity among multiple competing C–H bonds existing in organic molecules is a significant challenge.



Scheme 1.1. *Functional group interconversion vs. C–H functionalization.*

[3] F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun*. **2009**, 5061.

To sum up, there are two main synthetic approaches for aliphatic C–H amination:

1. Transition metal-promoted C–H functionalization

- Transition metal-catalyzed C–H amination (metal coordination to the substrate).
- Catalyzed nitrene insertion (metal coordination to the aminating agent).
- Photoredox catalysis (nitrogen-centered radicals).
- Enzymatic amination

The synthetic community also relied on the use of enzymes as a suitable pathway to introduce a nitrogen moiety in organic molecules.[4]

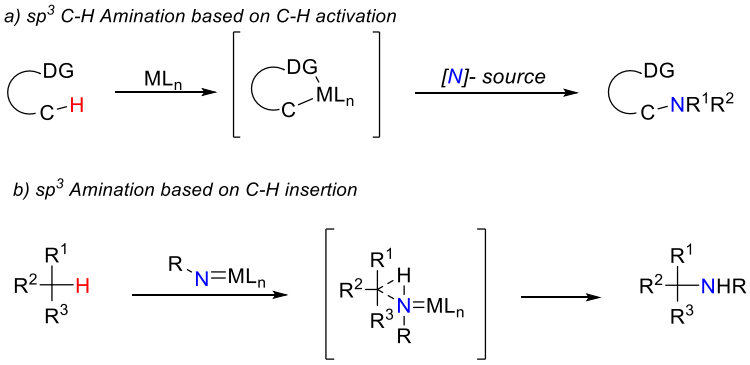
2. Metal-free amination

1.2. Csp^3–H bond amination

In the last two decades, organic synthetic chemists have focused on the Csp^2–H functionalization of arenes and heteroarenes derivatives. In contrast, fewer protocols have been explored for the amination of nonactivated Csp^3–H bonds.[5] Due to the absence of a high-filled energy level in the sp^3 orbitals for coordination with the empty orbitals of the metals, the transition metal-mediated C–H activation of these inert bonds is considered a high challenge.

In this line, the use of transition metal catalysts has been a significant step forward in the field since more sustainable and selective processes have been developed under milder reaction conditions with minor waste production.[6] Based on this, two main approaches regarding the C–H activation mechanism are described for transition metal-catalyzed C–H amination (Scheme 1.2).

[4] J. C. Lewis, P. S. Coelho, F. H. Arnold, *Chem. Soc. Rev*. **2011**, *40*, 2003.
[5] R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. - Eur. J.* **2010**, *16*, 2654.
[6] Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247.



***Scheme 1.2**. Transition metals for a) C–H activation, b) C–H functionalization via nitrene insertion.*

1.2.1. Transition metal-promoted Csp^3–H amination

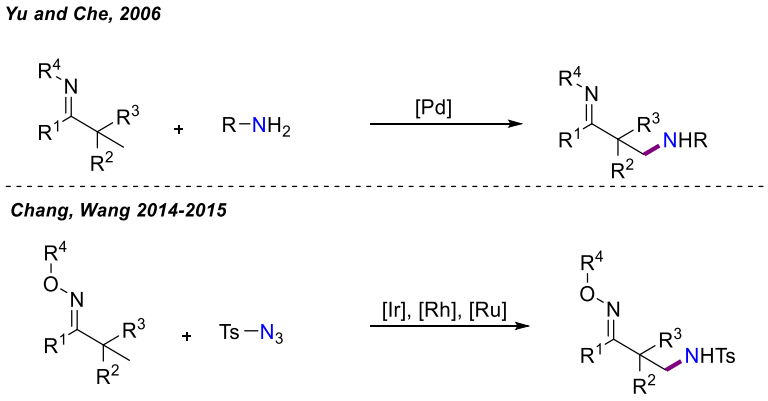
1.2.1.1 Transition metal-catalyzed C–H amination

Several procedures for metal-catalyzed amination have been developed for the remote and selective C–H activation of primary, secondary, and tertiary C–H positions in the last decades.[7] For these transformations, the strategy is based on the transition metal formal insertion into the C–H bond, generating an organometallic intermediate. Upon coordinating a suitable nitrogen source on the metal center, reductive elimination affords the aminated product. Several groups have developed different protocols for inter- and intramolecular amination. For the latter, typically, an electron-withdrawing group is used as a protecting/directing group. In this strategy, the formation of five or six-membered metallacyclic intermediates is crucial for the efficiency of the transformation. There are many intermolecular Csp^3–H amination methods using palladium, iridium, cobalt, or rhodium, among other transition metal catalysts.

Additionally, several nitrogen sources have been experimented, such as organic azides or *N*-acyloxyamide.[8] Palladium was extensively used for intermolecular amination. Thus, Yu and Che described the use of aliphatic oximes as directing groups where Pd(II) is converted into a Pd(IV) species leading to the amination of nonactivated Csp^3–H bonds (Scheme 1.3. Top).[9] Chang employed similar oximes for the amidation of aliphatic bonds by using an iridium-based catalyst and tosyl azide as a nitrogen source.[10] This methodology allowed the formation of β-amino acids by removing the *N*–*O*xime directing group after the amination.

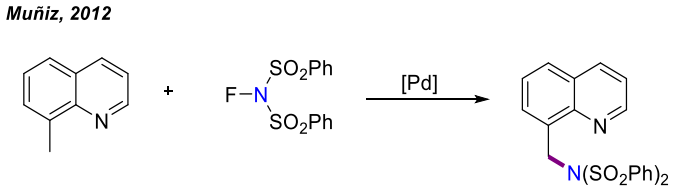
[7] M. Zhang, Q. Wang, Y. Peng, Z. Chen, C. Wan, J. Chen, Y. Zhao, R. Zhang, A. Q. Zhang, *Chem. Commun.*, **2019**, *55*, 13048.
[8] J. L. Jeffrey, R. Sarpong, *Chem. Sci*. **2013**, *4*, 4092
[9] H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048.
[10]T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, *J. Am. Chem. Soc*. **2014**, *136*, 4141.

This strategy allowed the late-stage functionalization in the context of natural product total synthesis. A similar approach was developed by Wand using rhodium and ruthenium for the amidation of Csp^3–H bonds using organic azides as nitrogen sources (Scheme 1.3. Bottom).[11]



Scheme 1.3. *Metal-catalyzed amination of aliphatic oximes substrates.*

In 2012, the group of Muñiz reported an intermolecular amidation using palladium catalysis and *N*-fluorobenzenesulfonimide (NFSI) as a nitrogen source (Scheme 1.4).[12] Theoretical studies showed that the role of the NFSI is to act as an oxidant to generate a Pd(IV) intermediate that facilitates the formation of the C–N bond.

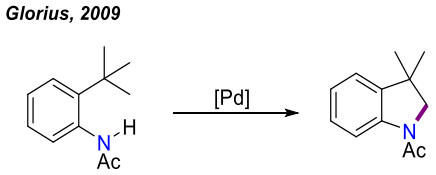


Scheme 1.4. *Pd-catalyzed C–H amidation using NFSI.*

Glorius pioneered the field of intramolecular Csp^3–H amination, publishing in 2009 a method to prepare indolines using amide-assisted palladium activation (Scheme 1.5).[13] The reaction proceeds by oxidative coupling of an amide with a Csp^3–H bond providing direct formation of a C–N bond. Two different mechanisms have been proposed for this transformation. The first one included the oxidation of Pd(II) to Pd(IV), followed by reductive elimination. On the other

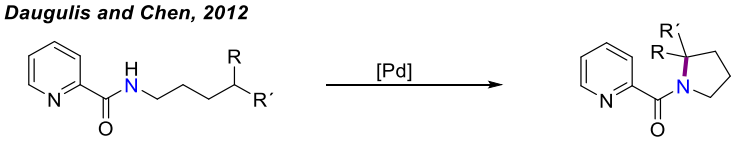
[11](a) N. Wang, R. Li, L. Li, S. Xu, H. Song, B. Wang, *J. Org. Chem*. **2014**, *79*, 5379. (b) B. Liu, B. Li, B. Wang, *Chem. Commun*. **2015**, *51*, 16334. (c) N. Wang, R. Li, L. Li, S. Xu, H. Song, B. Wang, *J. Org. Chem.* **2014**, *79*, 5379.
[12] A. Iglesias, R. Álvarez, A. R. de Lera, K. Muñiz, *Angew. Chem. Int. Ed*. **2012**, *51*, 2225.
[13] J. J Neumann, S. Rakshit, T. Dröge, F. Glorius, *Angew. Chem., Int. Ed*. **2009**, *48*, 6892.

hand, the second mechanistic proposal consisted in the Pd(II) insertion followed by direct reductive elimination.



***Scheme 1.5**. Indoline derivatives formation by Pd-catalysis.*

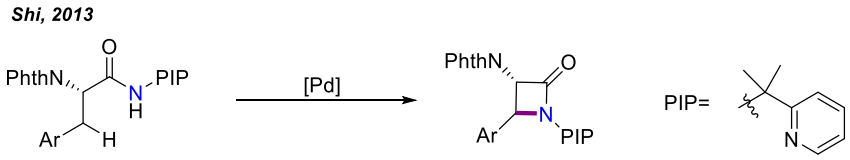
A similar approach was published in 2012 almost simultaneously by Daugulis[14] and Chen[15] to form *N*-heterocycles such as pyrrolidines, isoindolines and, indolines via C–H/C–N bond formation (Scheme 1.6). The group of Chen reported the formation of azetidines by adding acetic acid as an additive, although yields were lower when no β-substituent was presented in the molecule, pointing toward the importance of the Thorpe-Ingold effect. For this transformation, Daugulis and Chen used picolinamide (PA) as a directing group to activate the γ and δ-position. The method employs (diacetoxyiodo)benzene ($PhI(OAc)_2$) as an oxidant and $Pd(OAc)_2$ as a catalyst. Moreover, the proposed mechanism included the formation of a high oxidation state Pd(IV) intermediate, followed by reductive elimination to generate the C–N bond, recovering the catalyst.



***Scheme 1.6.** Cyclization of alkyl picolinamides.*

Since then, the PA directing group has been employed for several transformations, such as Pd-catalyzed acetoxylation of aryl C–H bonds or functionalization of nonactivated Csp^3–H bonds. One year later, Shi described a method using a bidentate directing group such as 2-(pyridine-2-yl)isopropyl for benzylic C–H amination toward the preparation of α-amino-β-lactam derivatives (Scheme 1.7).[16] A mixture of $NaIO_3$ and acetic anhydride proved useful for the oxidation of the Pd(II) species. Later, many methods for the formation of lactam derivatives were described, usually employing quinoline as a bidentate directing group. Unfortunately, the auxiliary cannot be removed from the amide derivatives limiting the application of these reactions in organic synthesis.

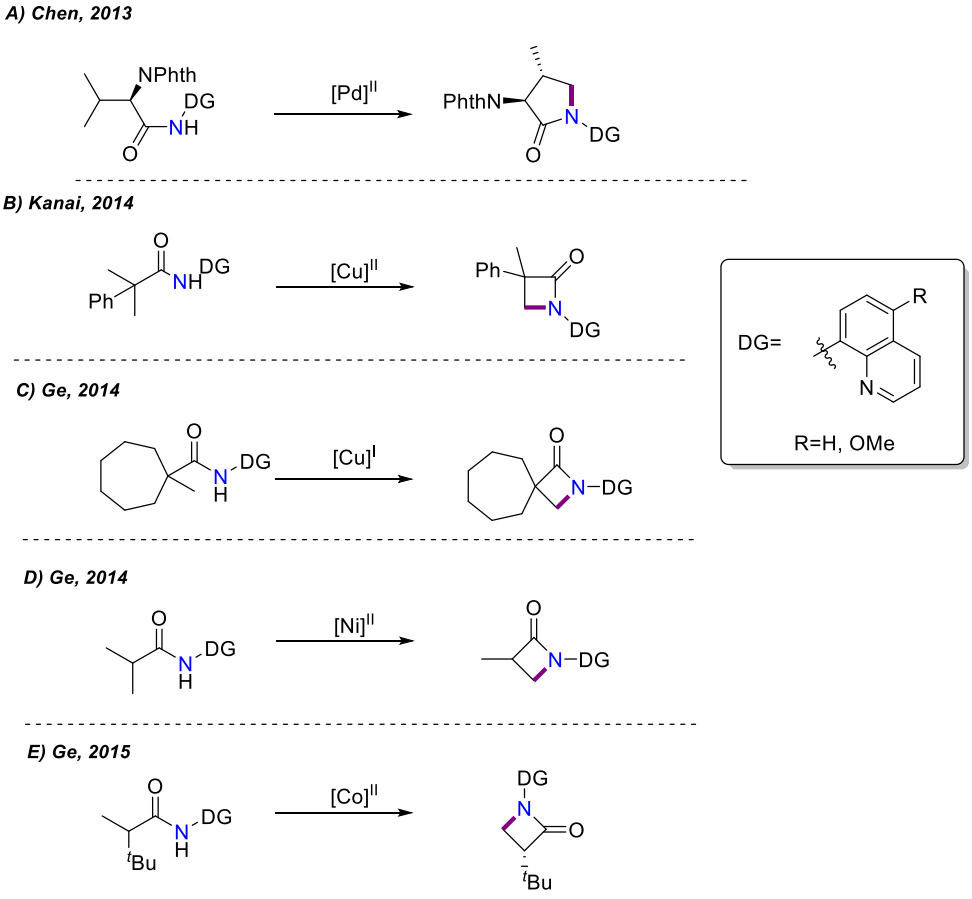
[14] E. T. Nadres, O. Daugulis *J. Am. Chem. Soc*. **2012**, *134*, 7.
[15] G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc*. **2012**, *134*, 3.
[16] Q. Zhang, K. Chen, W. Rao, Y. Zhang, F. J. Chen, B.-F. Shi, *Angew. Chem., Int. Ed*. **2013**, *52*, 13588.



Scheme 1.7. *Synthesis of α-amino-β-lactams through palladium (II) catalysis.*

Along these lines, the use of a quinoline-based directing group is not restricted to Pd-catalysis,[17] since other examples were published employing copper, nickel, and cobalt. Chen described in 2013 the use of this auxiliary for the formation of pyrrolidines. This methodology was applied for the functionalization of nonactivated primary Csp^3–H bonds. The first copper-catalyzed intramolecular Csp^3–H and Csp^2–H amidation was described by Kanai in 2014.[18] The benefit of this bidentate auxiliary is that it could be easily removed by simple oxidation, leading to a convenient and robust method for the synthesis of 2-indolinones and β-lactams derivatives. The same year, Ge and coworkers reported the formation of β-lactams analogs by copper and nickel catalysis.[19] Furthermore, just after this, the same group published a cobalt-catalyzed amidation of nonactivated Csp^3–H bonds (Scheme 1.8).[20]

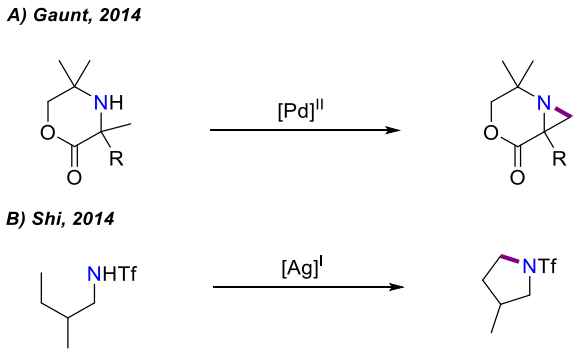
[17] G. He, S.-Y. Zhang, W. A. Nack, Q. Li, G. Chen, *Angew. Chem., Int. Ed*. **2013**, *52*, 11124.
[18] Z. Wang, J. Ni, Y. Kuninobu, M. Kanai, *Angew. Chem. Int. Ed.* **2014**, *53*, 3496.
[19] (a) X. Wu, Y. Zhao, G. Zhang, H. Ge, *Angew. Chem., Int. Ed.* **2014**, *53*, 3706. (b) X. Wu, Y. Zhao, H. Ge, *Chem. - Eur. J.* **2014**, *20*, 9530.
[20] X. Wu, K. Yang, Y. Zhao, H. Sun, G. Li, H. Ge, *Nat. Commun*. **2015**, *6*, 6462.



Scheme 1.8. *Metal-catalyzed N-heterocycle formation using a directing group.*

Gaunt reported the preparation of aziridine derivatives from unprotected amines with Pd-catalysis and $PhI(OAc)_2$ as oxidant (Scheme 1.9. Top).[21] Recently, a silver-catalyzed intramolecular amination was described by Shi in 2014 for the generation of pyrrolidine derivatives (Scheme 1.9. Bottom). For this transformation, a bidentate bipyridine auxiliary and $PhI(OTFA)_2$ were employed.[22]

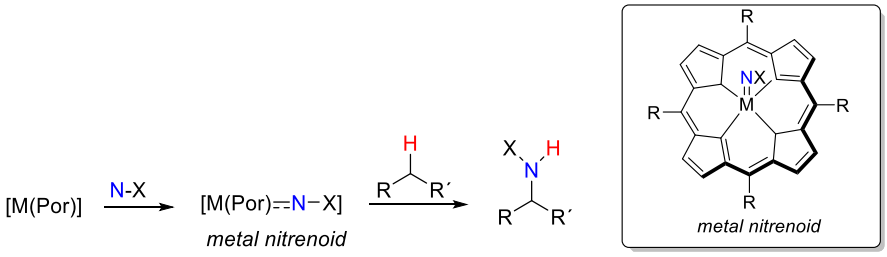
[21] (a) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129. (b) A. P. Smalley, M. J. Gaunt, *J. Am. Chem. Soc*. **2015**, *137*, 10632.
[22] M. Yang, B. Su, Y. Wang, K. Chen, X. Jiang, Y.-F. Zhang, X.-S. Zhang, G. Chen, Y. Cheng, Z. Cao, Q.-Y. Guo, L. Wang, Z.-J. Shi, *Nat. Commun*. **2014**, *5*, 4707.



Scheme 1.9. *Palladium and Silver-catalyzed intramolecular amination.*

1.2.1.2. Catalyzed nitrene insertion

Significant advances were reported on transition metal-catalyzed intramolecular Csp³–H amination proceeding via metal nitrene (nitrenoid) intermediates.[23] Usually, access to nitrene derivatives can be reached from various precursors such as azides or haloamines. Lately, the use of hypervalent iodine in combination with transition metal catalysts is a popular method for the generation of nitrenes from primary amines.[24]

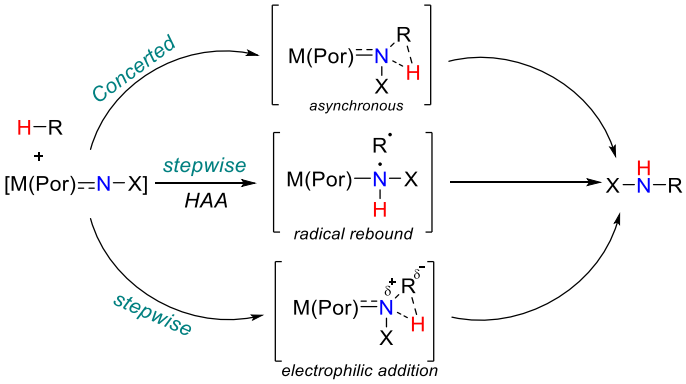


Scheme 1.10. *A simple mechanism for the metal nitrene intermediate formation.*

Three different pathways can describe the mechanism for the C–H amination event. In all cases, the first step is the generation of a nitrenoid intermediate from a nitrogen source (azide or iminoiodane) and the corresponding metal catalyst. This intermediate can then react in three different pathways. The most common mechanism is the concerted one through direct nitrene insertion into the C–H bond. A second option involves a radical recombination after the hydrogen atom abstraction process, leading to the aminated product. Finally, the third possibility involves the electrophilic addition on the nitrene complex (Scheme 1.11).

---

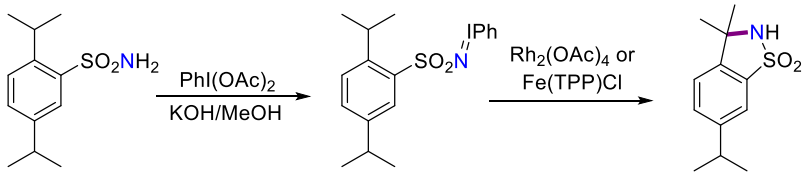
[23] (a) J. Du Bois, *Org. Process Res. Dev*. **2011**, *15*, 758. (b) J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res*. **2012**, *45*, 911. (c) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417.
[24] (a) R. Singh, A. Mukherjee, *ACS Catal*. **2019**, *9*, 3604. (b) A. Trowbridge, S. M. Walton, M. J. Gaunt, *Chem. Rev*. **2020**, *120*, 2613.



Scheme. 1.11. *Mechanistic pathways in the C–H insertion.*

The pioneering work of Breslow and Gellmann in 1982 demonstrated the use of iminoiodanes for the intermolecular amination of cyclohexane catalyzed by manganese or iron porphyrins complexes.[25] These groups also reported that cyclic sulfonamide derivatives could be synthesized employing Fe(III) and Rh(II) catalysts from the iminoiodane through an intramolecular mechanism (Scheme 1.12).[26] One year later, Mansuy reported a Fe- and Mn-porphyrin catalyzed the formation of aziridines from alkenes.[27]

Breslow, 1983

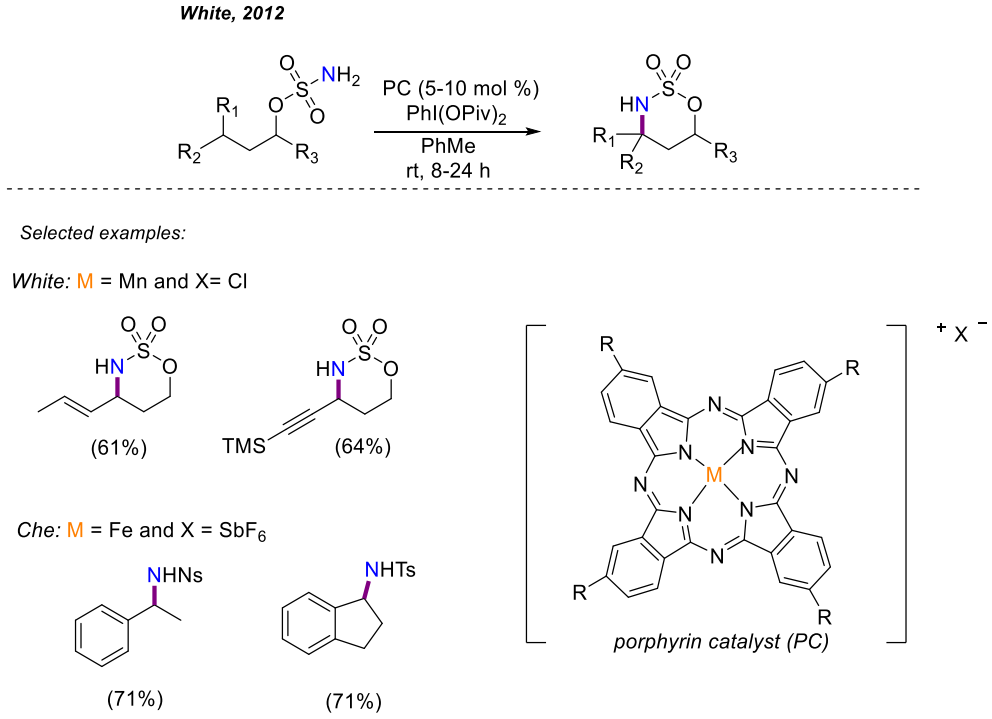


Scheme 1.12. *Intramolecular amination catalyzed by Rh(II) and Fe(III).*

Subsequently, other groups explored first-row metal catalysis to achieve environmentally benign and cheaper synthetic procedures. Also, in the context of porphyrin-metal complexes, many groups made significant contributions.[28] For example, Che, White, and Zhang described different manganese, iron, and cobalt catalysts for such purposes (Scheme 1.13). Even chiral catalysts were applied for enantioselective inter- and intramolecular amination.

[25] R. Breslow, S. H. Gellman, *J. Chem. Soc., Chem. Commun*. **1982**, 1400.
[26] R. Breslow, S. H. Gellman, *J. Am. Chem. Soc*. **1983**, *105*, 6728.
[27] D. Mansuy, J.-P. Mahy, A. Dureault, G. Bedi, P. Battioni, *J. Chem. Soc., Chem. Commun*. **1984**, 1161.
[28] P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905.

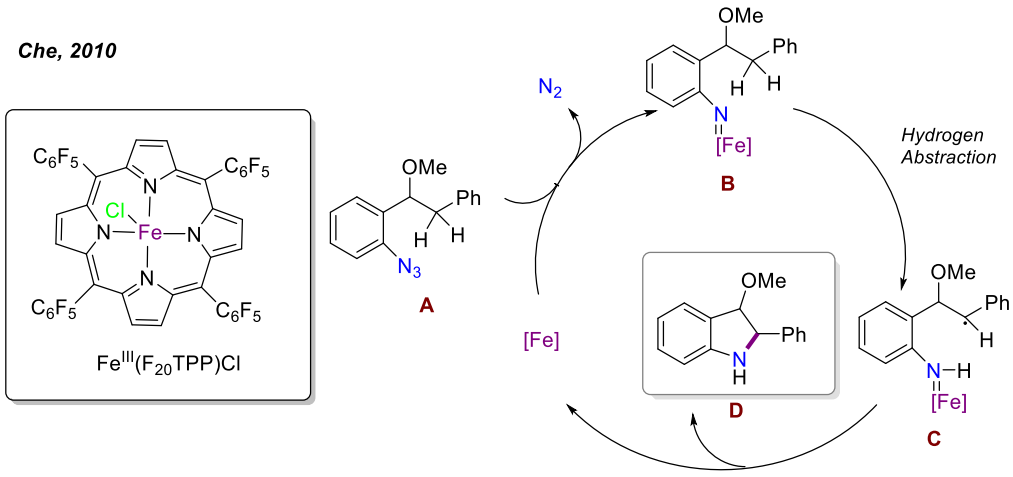
In the case of manganese and iron, the groups of White[29] and Che[30] published a similar intramolecular amidation protocol using $PhI(OPiv)_2$ as oxidant.



Scheme 1.13. *Manganese and iron catalysis for intramolecular amination.*

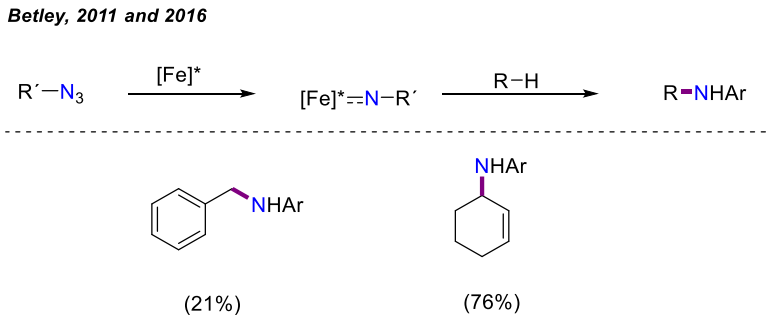
It is noteworthy that, in all these cases, the competitive aziridine formation is suppressed due to the high chemoselectivity of the porphyrin-based catalysts. Additionally, the iron catalyst achieves allylic amination. The group of Che reported in 2010 an intramolecular C–H amination employing an iron-porphyrin catalyst for the synthesis of indolines, indoles, tetrahydroquinolines, and quinalinones using aryl azides as a nitrogen source (Scheme 1.14).[31]

[29] (a) S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller, M. C. White, *Nat. Chem*. **2015**, *7*, 987. (b) J. R. Clark, K. Feng, A. Sookezian, M.C. White, *Nat. Chem*. **2018**, *10*, 583. (c) S. M. Paradine, M.C. White, *J. Am. Chem. Soc.* **2012**, *134*, 2036.
[30] (a) X-Q. Yu, J.-S. Huang, X.-G. Zhou, C.-M. Che, *Org. Lett*. **2000**, *2*, 2233. (b) Y. Liu, C.-M. Che, *Chem. - Eur. J*. **2010**, *16*, 10494.
[31] Y. Liu, J. Wei, C.-M. Che, *Chem. Commun*. **2010**, *46*, 6926.



Scheme 1.14. *Iron porphyrins for intramolecular amination.*

The development of non-heme iron catalysts for intramolecular amination of vital Csp^3–H bonds of alkanes is considered a synthetic challenge. The group of Betley studied Fe(II) and Fe(III) catalysts for the intermolecular amination using aryl azides as a nitrogen source (Scheme 1.15).[32]

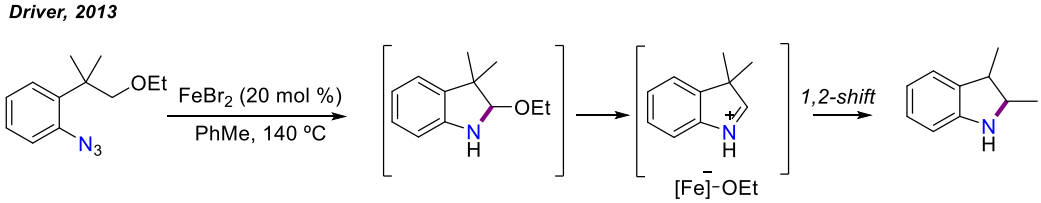


Scheme 1.15*. Iron complexes catalysis for C–H amination.*

In this manner, the group of Che reported in 2013 a non-heme iron-catalyzed amination of primary, secondary, and tertiary positions using sulfamates esters.[33] These authors suggested a mechanism that includes the formation of the iron-imido/nitrene bond between the 7-coordinated iron complex and the imido precursor. The same year, Driver and coworkers described a synthesis of 2,3-disubstituted indoles using an iron catalyst and an aryl azide as a nitrogen source

[32] (a) E. R. King, E. T. Hennessy, T. A. Betley, *J. Am. Chem. Soc.* **2011**, *133*, 4917 (b) D. A. Iovan, T. A. Betley, *J. Am. Chem. Soc.* **2016**, *138*, 1983.
[33] Y. Liu, X. Guan, E. L.-M. Wong, P. Liu, J.-S. Huang, C.-M. Che, *J. Am. Chem. Soc*. **2013**, *135*, 7194.

(Scheme 1.16).[34] In this transformation, the first step consists in the amination of the Csp^3–H position, followed by iminium ion formation and a 1,2 shift to form the final product.



***Scheme 1.16**. Synthesis of 2,3-disubstituted indoles by Fe catalysis.*

Co-porphyrin systems for intermolecular amination were pioneered by Cenini in 2003, who described a mild reaction of benzylic azides to generate imine derivatives.[35] Zhang established in 2010 the first intramolecular amination using Co(II) porphyrins.[36] The amination took place without the need for an external oxidant and under neutral conditions leading to the construction of 1,3-diamines (Scheme 1.17. A). The same group described the generation of six or seven-membered ring cyclophosphoramidates from phosphoryl azides (Scheme 1.17.B).[37] These cyclophosphoramidates were useful precursors for the synthesis of 1,3- and 1,4-amino alcohols.

Additionally, Zhang demonstrated the application of cobalt catalysts in the context of allylic amination leading to allylic 1,3-diamines (Scheme 1.17.C).[38] They also showed that this transformation involves a multi-step radical type mechanism, forming the nitrene radical after the removal of nitrogen.[39] Zhang also applied a similar Co(II) porphyrin catalyst for the amination of Csp^3–H bonds adjacent to an electron-withdrawing group.[40] In this case, for the first time, the amination occurs on an electron-deficient position through a radical mechanism that involves the Co(III)-nitrene radical intermediate undergoing a stepwise radical abstraction-substitution pathway. This strategy was also applied to the amination on propargylic positions.[41]

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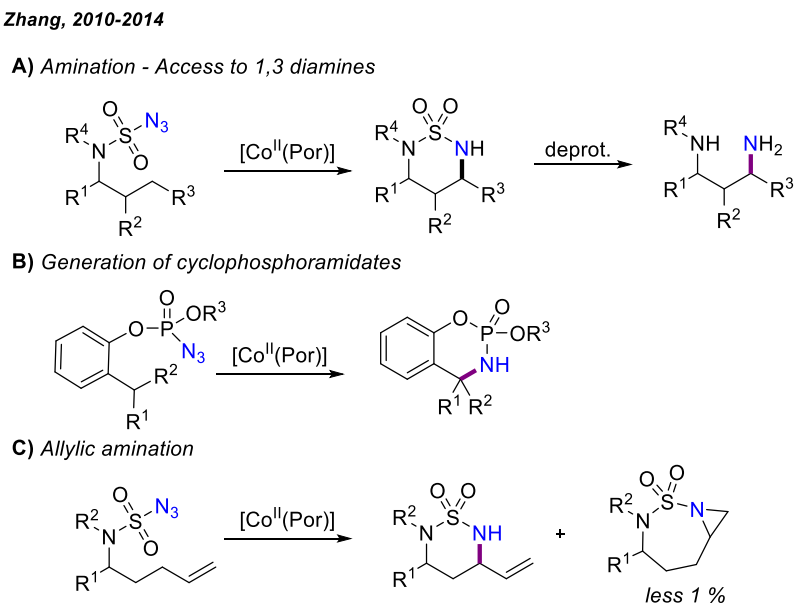
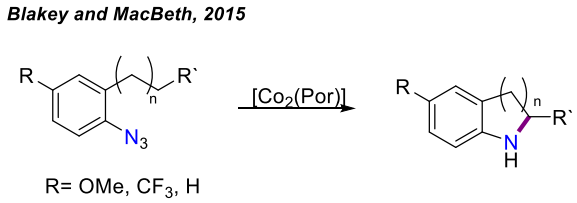
[34] Q. Nguyen, T. Nguyen, T. G. Driver, *J. Am. Chem. Soc.* **2013**, *135*, 620.
[35] F. Ragaini, A. Penoni, E. Gallo, S. Tollari, C. Li Gotti, M. Lapadula, E. Mangioni, S. Cenini, *Chem. - Eur. J.* **2003**, *9*, 249.
[36] H. Lu, H. Jiang, L. Wojtas, X. P. Zhang, *Angew. Chem., Int. Ed.* **2010**, *49*, 10192.
[37] H Lu, J. Tao, J. E. Jones, L. Wojtas, X. P. Zhang, *Org. Lett.* **2010**, *12*, 1248.
[38] H. Lu, H. Jiang, Y. Hu, L. Wojtas, X. P. Zhang, *Chem. Sci*. **2011**, *2*, 2361.
[39] V. Lyaskovskyy, A. I. O. Suarez, H. Lu, H. Jiang, X. P. Zhang, B. B. J. de Bruin, *J. Am. Chem. Soc*. **2011**, *133*, 12264.
[40] H. Lu, Y. Hu, H. Jiang, L. Wojtas, X. P. Zhang, *Org. Lett*. **2012**, *14*, 5158.
[41] H. Lu, C. Li, H. Jiang, C. L. Lizardi, X. P. Zhang, *Angew. Chem., Int. Ed*. **2014**, *53*, 7028.



Scheme 1. 17*. Co-catalysis examples from the Zhang group methodologies.*

Blakey and MacBeth synthesized a Co(II) complex supported by a redox-active ligand that could promote the catalytic dioxygen activation to form a C–O bond. Upon azide activation led to the formation of indoline products (Scheme 1.18).[42]

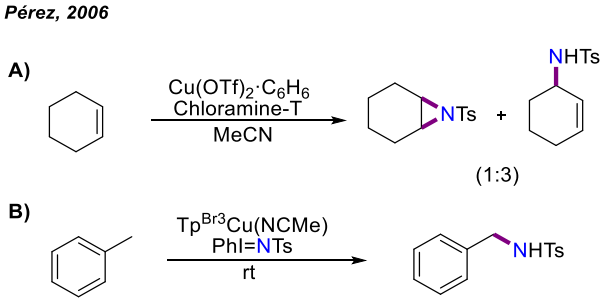


Scheme 1.18. *Indolines derivatives synthesis by Co-porphyrin.*

Among transition metals, copper leads to a broader range of *N*-containing reagents for C–H amination. In 1991, the pioneering work of Evans used a copper-catalyzed amination to generate aziridine derivatives by reaction with electron-rich and electron-deficient alkenes. In this case, (*N*-(*p*-toluensulfonyl)imido)phenyliodinane (PhI=NTs) was used as the nitrene precursor together with Cu(I) or Cu(II) catalysts.[43]

[42] O. Villanueva, N. M. Weldy, S. B. Blakey, C. E. MacBeth, *Chem. Sci.* **2015**, *6*, 6672.
[43] D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Org. Chem.* **1991**, *56*, 6744.

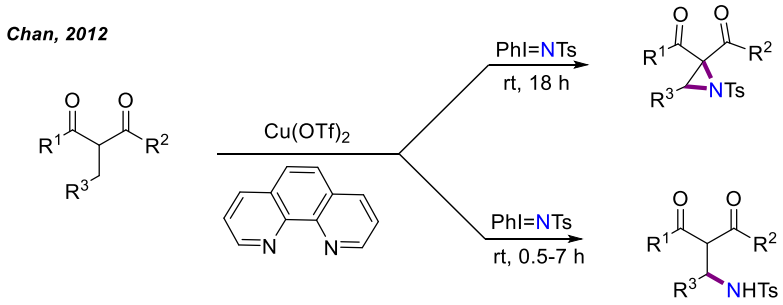
Evans and Jacobsen developed two enantioselective versions of this methodology using bis(oxazolines) ligands and chiral diamine, respectively.[44] Along these lines, the group of Taylor employed chloramine-T trihydrate as a nitrogen source for the azirination and the activation of hydrocarbons, usually at benzylic or allylic positions.[45] Another interesting example was developed by Pérez in 2006 for the intermolecular amination of Csp^2–H and Csp^3–H bonds through copper catalysis and employing PhI=NTs as nitrene precursor (Scheme 1.19).[46]



***Scheme 1.19**. Amination using PhI=NTs as a nitrogen source.*

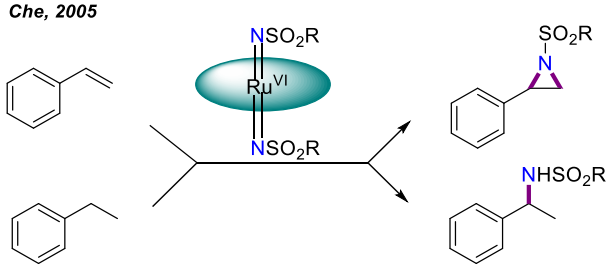
Several reports illustrate the versatility of copper as a catalyst for intermolecular amination.[47] Thus, Chan and coworkers reported the interesting Cu-catalyzed C−H amination of 1,3-dicarbonyl compounds, which proceeded with total regioselectivity (Scheme 1.20).[48]

[44] (a) D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *J. Am. Chem. Soc*. **1993**, *115*, 5328. (b) Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc*. **1993**, *115*, 5326. (c) Z. Li, R. W. Quan, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5889.
[45] D. P. Albone, P. S. Aujla, P. C. Taylor, S. Challenger, A. M. A. Derrick, *J. Org. Chem*. **1998**, *63*, 9569.
[46] M. R. Fructos, S. Trofimenko, M. M. Díaz-Requejo, P. J. Pérez, *J. Am. Chem. Soc.* **2006**, *128*, 11784.
[47] (a) K. Hou, D. A. Hrovat, X. Bao, *Chem. Commun.* **2015**, *51*, 15414. (b) Y. M. Badiei, A. Dinescu, X. Dai, R. M. Palomino, F. W. Heinemann, T. R. Cundari, T. H. Warren, *Angew. Chem., Int. Ed*. **2008**, *47*, 9961. (c) S. Wiese, Y. M. Badiei, R. T. Gephart, S. Mossin, M. S. Varonka, M. M. Melzer, K. Meyer, T. R. Cundari, T. H. Warren, *Angew. Chem., Int. Ed.* **2010**, *49*, 8850. (d) V. Bagchi, *J. Am. Chem. Soc*. **2014**, *136*, 11362.
[48] T. M. U. Ton, C. Tejo, D. L. Y. Tiong, P. W. H. Chan, *J. Am. Chem. Soc*. **2012**, *134*, 7344.



Scheme 1. 20. *Regioselective intermolecular amination using Cu-catalysis.*

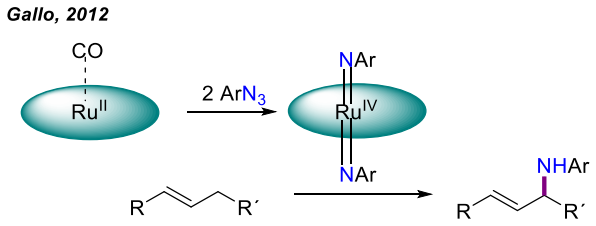
Regarding second-row transition metals, it is remarkable the extended use of rhodium and ruthenium complexes for C–H amination. Che and coworkers prepared a ruthenium porphyrin for the amino group transfer to alkenes to generate aziridine derivatives (Scheme 1.21).[49] The same group extended this methodology employing a different [Ru]-porphyrin system for the azirination and amidation of hydrocarbons.[50] An asymmetric version of this methodology was reported in 1999.[51]



Scheme 1.21. *Ru-porphyrin for aziridination and amination.*

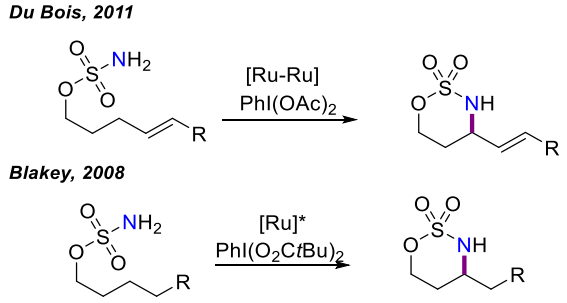
Cenini reported the first X-ray characterization of an active intermediate ruthenium bis-imido porphyrin complex in a C–H nitrene transfer reaction.[52] Ruthenium(IV) complexes are important catalysts for the C–H functionalization with aryl azides as a nitrogen source (Scheme 1.22).[53] This methodology generates molecular nitrogen as the sole stoichiometric by-product in the amination of the allylic positions.

[49] S.-M. Au, W.-H. Fung, M.-C. Cheng, C.-M. Che, S.-M Peng, *Chem. Commun*. **1997**, 1655.
[50] (a) X.-Q. Yu, J.-S. Huang, X.-G. Zhou, C.-M. Che, *Org. Lett.* **2000**, *2*, 2233. (b) S. K.-Y. Leung, W.-M. Tsui, J.-S- Huang, C.-M. Che, J.-L. Liang, N. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 16629.
[51] S.-M. Au, J.-S. Huang, W.-Y. Yu, W.-H. Fung, C.-M. Che, *J. Am. Chem. Soc*. **1999**, *121*, 9120.
[52] S. Fantauzzi, E. Gallo, A. Caselli, F. Ragaini, N. Casati, P. Macchic, S. Cenini, *Chem. Commun*. **2009**, 3952.
[53] D. Intrieri, A. Caselli, F. Ragaini, P. Macchi, N. Casati, E. Gallo, *Eur. J. Inorg. Chem.* **2012**, *2012*, 569.



***Scheme 1.22**. Ru-porphyrin catalyzed allylic amination of alkenes by aryl azides.*

A similar methodology for allylic amination was developed by Du Bois in 2011 using a mixed-valent diruthenium(II/III) catalyst with bis-(homoallylic) sulfamate esters in the presence of hypervalent iodine as oxidant. In this transformation, the allylic C–H bond was selectively activated.[54] The enantioselective version of this transformation was developed in 2008 by Blakey to prepare chiral sulfamates (Scheme 1.23).[55]

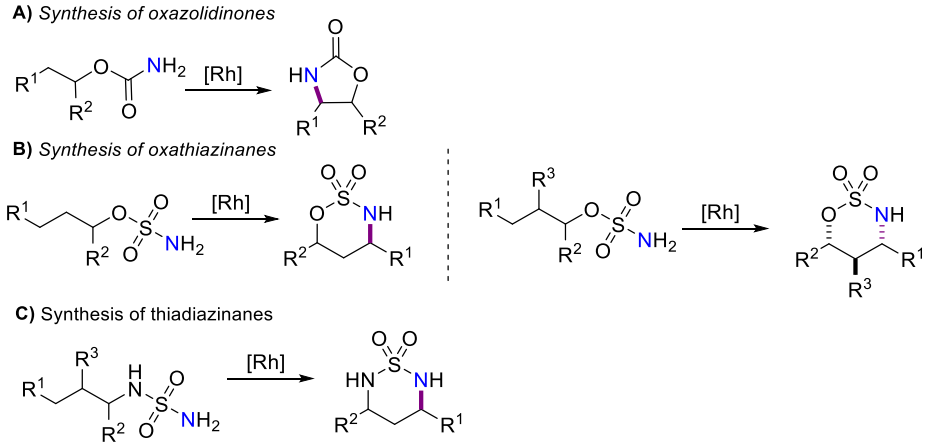


***Scheme 1.23.** Amidation of aliphatic C–H bond using Ru-catalysis.*

Along these lines, Katsuki reported an enantioselective Ru-catalyzed Csp³–H amidation protocol using (2-(trimethylsilyl)ethanesulfonyl) azide as a nitrogen source.[56] Previous reports on the catalytic activity of first-row transition metal complexes in C−H amination and their mechanistic understanding encouraged the development of rhodium complexes as catalysts. These complexes have become an important synthetic tool due to the notable reactivity for the transfer of amino groups to unreactive Csp³–H bonds. Significant efforts have been made by the groups of Du Bois and Chen to develop methods for the generation of reactive iminoiodinanes from $PhI(OAc)_2$ and primary amides.[57] Du Bois reported the first example of a catalytic method for the formation of oxazolidinones from carbamates using rhodium catalysts (Scheme 1.24. A). The same group developed a similar transformation for the generation of six-membered ring

[54] M. E. Harvey, D. G. Musaev, J. A. Du Bois, *J. Am. Chem. Soc*. **2011**, *133*, 17207.
[55] E. Milczek, N. Boudet, S. Blakey, *Angew. Chem., Int. Ed*. **2008**, *47*, 6825.
[56] Y. Nishioka, T. Uchida, T. Katsuki, *Angew. Chem., Int. Ed*. **2013**, *52*, 1739.
[57] C. G.Espino, J. Du Bois, *Angew. Chem., Int. Ed*. **2001**, *40*, 598.

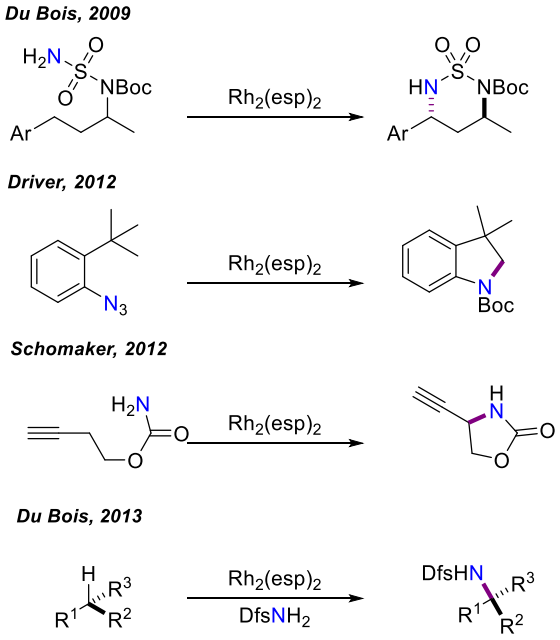
oxathiazinanes from linear sulfamates. These compounds are known as valuable precursors of 1,3-aminoalcohols.[58] The authors expanded this methodology to produce chiral sulfamates using an achiral Rh catalyst by chirality transfer from a preexisting stereogenic group (Scheme 1.24.B). Furthermore, bicycle aziridines derivatives were synthesized from homoallyl sulfamates.[59] The Rh catalysts were also applied for the preparation of other amino derivatives.[60]



Scheme 1.24. *Du Bois amidation advances for the generation of a) oxazolidinones, b) oxathiazinanes, c) thiadiazinanes through rhodium catalysis.*

In 2007, Du Bois described a catalytic intermolecular amination of benzylic and tertiary positions using dimeric Rh tetracarboxylate.[61] The use of tetramethylated *m*-benzenedipropionate as the ligand on the Rh-catalyst led to broader applicability on a variety of substrates. In this way, it is possible to achieve the diastereoselective synthesis of 1,3-diamines, the intramolecular amination of propargylic C–H bonds, and the intramolecular cyclization of azido-2-(*tert*-butyl)benzenes derivatives for the formation of indolines.[62] The same catalyst was efficient for intermolecular amination. For instance, Du Bois described a highly selective C–H amination method using 2,6-difluorophenyl sulfamate as a nitrogen source (Scheme 1.25).[63]

[58] C. G. Espino, P. M. Wehn, J. Chow, J. Du Bois, *J. Am. Chem. Soc*. **2001**, *123*, 6935.
[59] P. M. Wehn, J. Lee, J. Du Bois, *Org. Lett*. **2003**, *5*, 4823.
[60] M. Kim, J. V. Mulcahy, C. G. Espino, J. Du Bois, *Org. Lett*. **2006**, *8*, 1073.
[61] K. W. Fiori, J. Du Bois, *J. Am.Chem. Soc.* **2007**, *129*, 562.
[62] (a) T. Kurokawa, M. Kim, J. Du Bois, *Angew. Chem., Int. Ed*. **2009**, *48*, 2777. (b) R. D. Grigg, J. W. Rigoli, S. D. Pearce, J. M. Schomaker, *Org. Lett.* **2012**, *14*, 280. (c) N. Quyen, K. Sun, T. G. Driver, *J. Am. Chem. Soc*. **2012**, *134*, 7262.
[63] J. L. Roizen, D. N. Zalatan, J. Du Bois, *Angew. Chem., Int. Ed*. **2013**, *52*, 11343.



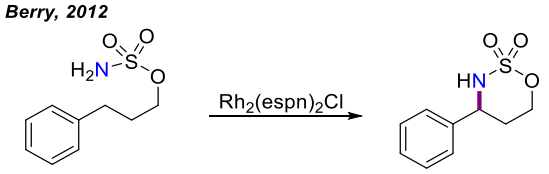
***Scheme 1.25**. Rhodium tetracarboxylate as a significant and stable catalyst.*

Zhang proposed two different mechanisms for the amination of Csp^3–H bonds with aryl azides.[64] Initially, the dirhodium complex coordinates with the substrate leading to the extrusion of nitrogen gas to produce the metal nitrene. Then, the dirhodium metal nitrene forms the C–N bond via intramolecular nitrene insertion into the C–H bond. This intermediate could evolve through two different pathways. The first one involves a concerted asynchronous insertion of singlet metal nitrene into the C–H bond. Alternatively, the nitrene triplet reacts stepwise by hydrogen atom transfer, followed by a radical combination. Mechanistic studies indicated that the energy barrier for the first pathway was lower, suggesting that the first pathway was the most viable one.

Several authors demonstrated the broad applicability of $Rh_2(esp)_2$ as a catalyst. In 2010, the group of Bach described a diastereoselective amination of aryl alkanes with a fixed stereogenic center at the β-position that does not undergo racemization during the transformation. This is a convenient approach to synthesize functionalized amines through acyclic stereocontrol. The same group carried out some mechanistic studies.[65] Some years later, Berry proposed that the oxidized species $[Rh_2(esp)_2]^+$ facilitates nitrenoid transfer, presumably via sequential proton-coupled electron transfer (PCET) processes. This last group

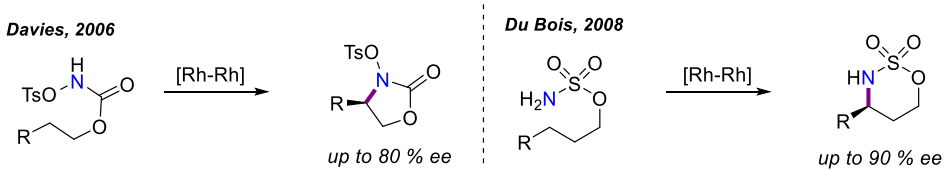
[64] H. Xu, X. Zhang, Z. Ke, C. A. Zhao, *RSC Adv.* **2016**, *6*, 29045.
[65] (a) A. Nörder, P. Herrmann, E. Herdtweck, T. Bach, *Org. Lett.* **2010**, *12*, 3690. (b) A. Nörder, S. A. Warren, E. Herdtweck, S. M. Huber, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 13524.

developed a methodology using $Ce(SO_4)_2$ as oxidant instead of $PhI(OAc)_2$.[66] Moreover, an amination using a dirhodium catalyst bearing carboxamide ligands was developed with enhanced catalyst performance (Scheme 1.26).[67] The dirhodium complex holding carboxamide ligands demonstrated significant turnover numbers (1450), higher than those obtained with $Rh_2(esp)_2$ catalyst (490) under the same oxidative conditions.



Scheme 1.26. *Selected example of Csp³–H amination using a dirhodium complex.*

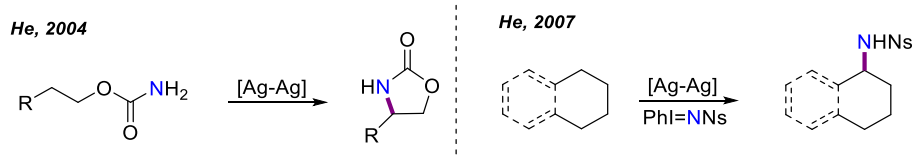
Recently, other groups have been interested in the development of asymmetric Rh-catalyzed C–H insertion. Thus, the groups of Davies and Du Bois developed methods for intramolecular and intermolecular amination with high site-selectivity (Scheme 1.27).[68]



Scheme 1.27. *Intramolecular amination using dirhodium catalysts.*

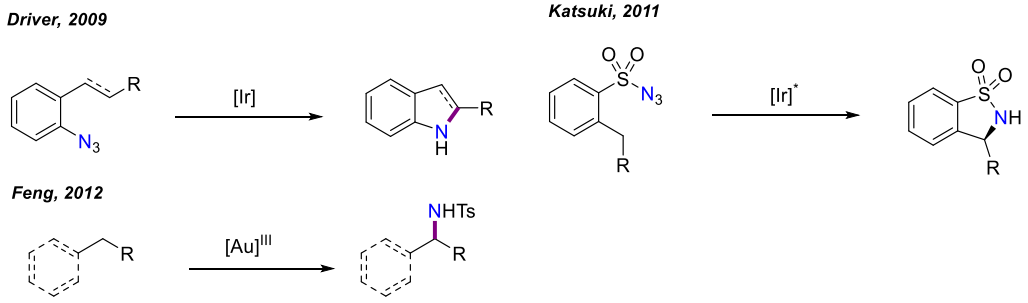
Although silver is not a frequent metal used for C–H amination, there are some interesting examples. For instance, the group of He developed an intramolecular cyclization of carbamates and an intermolecular amination on benzylic positions by *in situ* formation of a dimeric silver catalyst (Scheme 1.28).[69]

[66] (a) K. P. Kornecki, J. F. Berry, *Chem. - Eur. J.* **2011**, *17*, 5827. (b) K. P. Kornecki, J. F. Berry, *Chem. Commun*. **2012**, *48*, 12097.
[67] A. Varela-Alvarez, *et al. J. Am. Chem. Soc*. **2016**, *138*, 2327.
[68] (a) R. P. Reddy, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 5013. (b) D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 9220. (c) N. D. Chiappini, J. B. C. Mack, J. Du Bois, *Angew. Chem. Int. Ed*. **2018**, *57*, 495.
[69] (a) Y. Cui, C. He, *Angew. Chem., Int. Ed*. **2004**, *43*, 4210. (b) Z. Li, D. A. Capretto, R. Rahaman, C. He, *Angew. Chem., Int. Ed*. **2007**, *46*, 5184.



Scheme 1.28. *Selected examples of silver-catalyzed amination from He´s group.*

Finally, regarding third-row transition metal catalysis, only gold and iridium have been explored (Scheme 1.29). Driver[70] and Katsuki[71] developed methodologies for the C–H insertion using iridium. In the first case, the authors developed a novel Ir-catalysis for intramolecular amination for Csp^2–H and Csp^3–H bonds. Regarding gold catalysis, Feng reported the use of Au III) for intermolecular benzylic Csp^3–H amination.[72]



Scheme 1.29*. Driver, Katsuki, and Feng aminations using iridium and gold catalysts.*

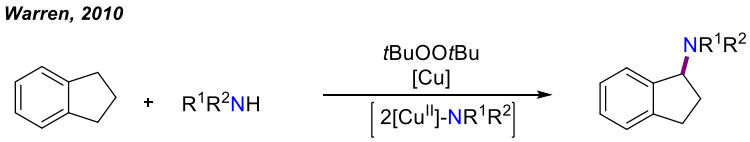
1.2.1.3. Photoredox catalysis - nitrogen-centered radicals

Aside from nitrenoids, nitrogen-centered radicals can also be employed in amination reactions. Usually, these reactive species are generated by thermolysis, photolysis, or by radical initiation. Although this field remains relatively elusive, some methodologies were reported using a single-electron-transfer process (SET) under mild conditions such as photoredox catalysis.

Many amination methods have been described using metal catalysis, while few using metals in combination with photoredox catalysts. These latest methodologies are very efficient and selective for aminations of benzylic, tertiary, secondary, and primary positions. In 2010, Warren developed a protocol for intermolecular aliphatic amination using copper catalysis (Scheme 1.30).[73]

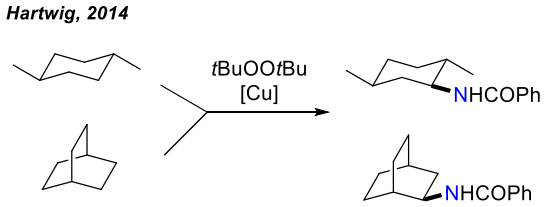
[70] K. Sun, R. Sachwani, K. J. Richert, T. G. Driver, *Org. Lett.* **2009**, *11*, 3598.
[71] M. Ichinose, H. Suematsu, Y. Yasutomi, Y. Nishioka, T. Uchida, T. Katsuki, *Angew. Chem., Int. Ed.* **2011**, *50*, 9884.
[72] Y. Zhang, B. Feng, C. Zhu, *Org. Biomol. Chem*. **2012**, *10*, 9137.
[73] S. Wiese, Y. M. Badiei, R. T. Gephart, S. Mossin, M. S. Varonka, M. M. Melzer, K. Meyer, T. R. Cundari, T. H. Warren, *Angew. Chem. Int. Ed.* **2010**, *49*, 8850.

For this transformation, the use of di-*tert*-butyl peroxide as a radical initiator was required. The intermediate Cu(II) species is responsible for the hydrogen abstraction from the substrate, generating a carbon-centered radical, which is quenched by the addition of the nitrogen source to recover the Cu(I) species that restarts the catalytic cycle.



Scheme 1. 30. *Copper-catalyzed benzylic C–H amination.*

A similar protocol was described by the group of Hartwig group in 2014 with a Cu(I)/Cu(II) catalytic system for the preferential amination of secondary and primary positions over tertiary ones (Scheme 1.31).[74]

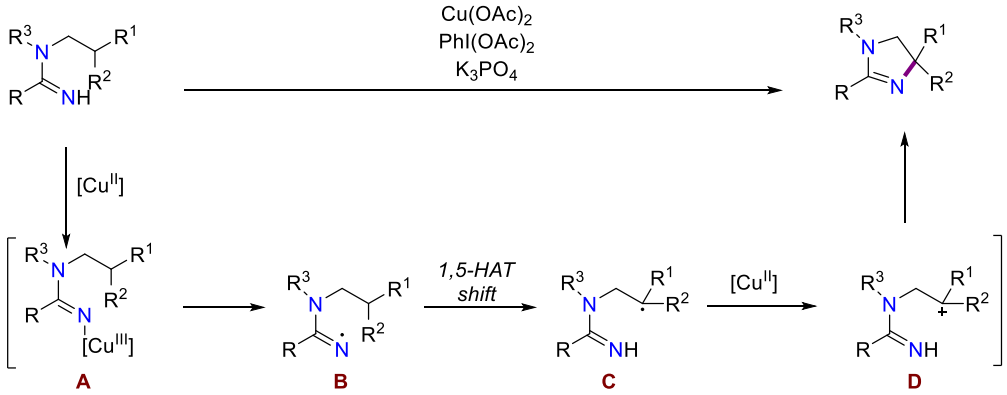


Scheme 1. 31. *Copper-catalyzed for secondary and primary positions.*

Along these lines, Baran reported an intermolecular amination through copper catalysis.[75] In this transformation, the generation of a carbon-centered radical took place, which was oxidized by Selectfluor to form a carbocation, which was trapped by acetonitrile used as a solvent. Chiba described an intramolecular amination catalyzed by copper to synthesize dihydroimidazoles and tetrahydropyrimidine.[76] These compounds could be transformed into the corresponding diamines by simple reductive transformation. While no reaction was observed using only the copper catalyst, the oxidant PIDA was crucial to initiate the reaction and formed the N–[Cu(III)] species (Scheme 1.32). Homolytic cleavage of the N–Cu bond forms intermediate **B**, which upon 1,5-hydrogen atom transfer and copper oxidation, led to the formation of the dihydroimidazole derivative. The involvement of radical/carbocation intermediates was demonstrated in an experiment where optically active molecules suffered racemization upon submission to the reaction conditions.

[74] B. L. Tran, B. Li, M. Driess, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 2555.
[75] Q. Michaudel, D. Thevenet, P. S. Baran, *J. Am. Chem. Soc*. **2012**, *134*, 2547.
[76] H. Chen, S. Sanjaya, Y.-F. Wang, S. Chiba, *Org. Lett.* **2013**, *15*, 212.

Chiba, 2013

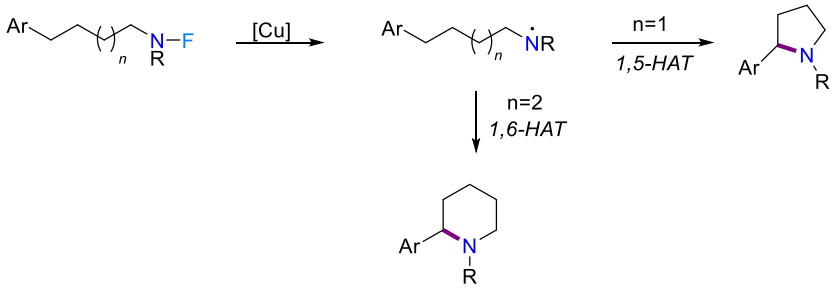


Scheme 1. 32. *Chiba´s conditions for the formation of dihydroimidazoles.*

One year later, the same group extended this methodology for the amination of amidoximes under redox neutral conditions.[77] The mechanism of these transformations follows the same previously described pathway except for the formation of the nitrogen-centered radical, which is formed by reducing the N–O bond promoted by Cu(II).

The group of Muñiz developed one of the latest examples of intramolecular C–H amination through *N*-centered radicals using metal activation to generate pyrrolidines and piperidines (Scheme 1.33).[78] The new strategy involved a dual reactivity of the *N*-fluorine bond through a Cu(I)/Cu(II) catalytic system. The mechanism of this transformation starts with the cleavage of the N–F bond by the copper catalyst through a single electron transfer process, followed by hydrogen atom transfer leading to the formation of a carbon-centered radical, which led to the formation of the C–N bond.

[77] H. Chen, S. Chiba, *Org. Biomol. Chem*. **2014**, *12*, 42.
[78] D. Bafaluy J. M. Muñoz-Molina, I. Funes-Ardoiz, S. Herold, A. J. de Aguirre, H. Zhang, F. Maseras, T. R. Belderrain, P. J. Pérez, K. Muñiz, *Angew.Chem., Int. Ed.* **2019**, *58*, 8912.



Scheme 1. 33. *Copper activation of the N-F bond for the generation of pyrrolidine and piperidine derivatives.*

1.2.2. Metal-free Csp³-H amination

Alternative pathways have been explored in the last decades from the ones described above to promote amination reactions avoiding transition metal catalysts. These strategies were devised for the directed C–H functionalization of remote and nonactivated C–H bonds under metal-free conditions. For this transformation, the process involves four steps (Figure 1.4).[79] Remarkably, the C–H functionalization at the remote C–H bond can be quite selective under milder conditions than those required by metal-catalyzed C–H functionalization.

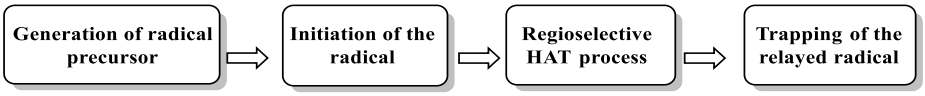
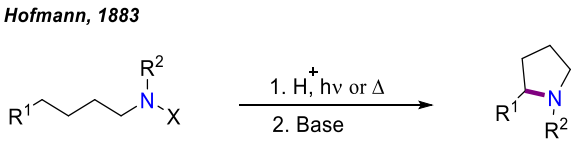


Figure 1.4. *Four steps included in the HAT process for C–H functionalization.*

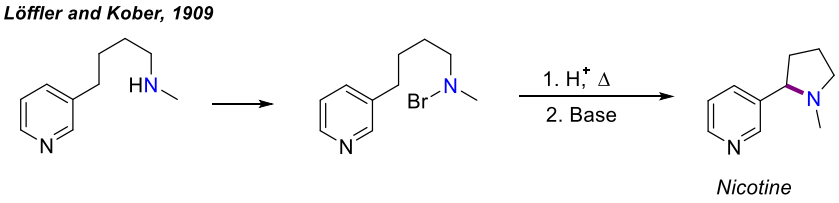
A fundamental discovery in intramolecular metal-free amination of nonactivated Csp³–H bonds was made in early 1880 with the Hofmann-Löffler reaction. This reaction is a pioneer in the generation of *N*-centered radicals to produce pyrrolidine derivatives. In 1885, Hofmann synthesized *N*-haloamine derivatives at high temperatures and in the presence of strong acids (Scheme 1.34).[80] Under these harsh conditions, the homolytic cleavage of the *N*-halogen bond takes place, allowing for the formation of the *N*-centered radical. Then, the regioselective 1,5-hydrogen atom transfer (1,5-HAT) occurs, followed by radical trapping of the halogen. Finally, nucleophilic cyclization takes place upon basic aqueous workup.

[79] G. Kumar S. Pradhan, I. Chatterjee, *Chem Asian J.* **2020**, *15*, 651.
[80] A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 5.



Scheme 1.34. *Pyrrolidines derivatives formation under Hofmann-Löffler reaction.*

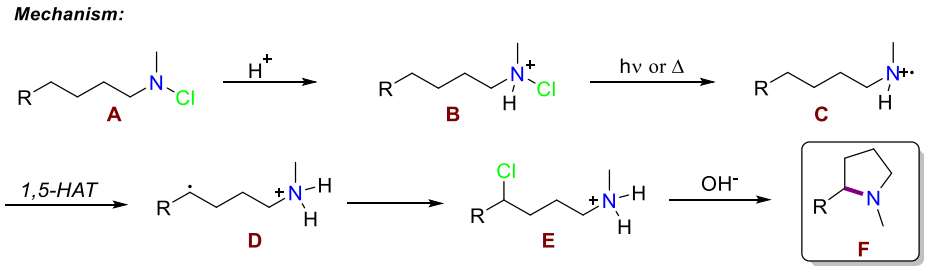
In 1909, Löffler and Kober expanded this methodology for the non-enantioselective synthesis of the natural product nicotine (Scheme 1.35). This was the first example of the application of the Hofmann-Löffler reaction for the synthesis of alkaloids starting from linear substrates.[81]



Scheme 1.35*. Classical non-enantioselective synthesis of the natural product nicotine by the Hofmann-Löffler reaction.*

In 1960, Corey developed the synthesis of cyclic amines by free-radical decomposition of *N*-haloammonium ions.[82] For such purpose, harsh conditions were required, and pre-formation of the *N*-chloro derivative followed by irradiation with ultraviolet light. This study postulated the correct mechanism of the Hofmann-Löffler reaction (Scheme 1.36). The transformation starts with the formation of the N–Cl species that is submitted to acidic conditions generating the intermediate **B**, which undergoes homolytic cleavage under thermal or photochemical activation. Intermediate **C** then generates intermediate **D** through a selective 1,5-hydrogen atom transfer process. This intermediate **D** traps a halogen from **A** to generate **E** in a radical chain propagation mechanism, followed by a basic aqueous workup leading to the pyrrolidine derivative **F**.

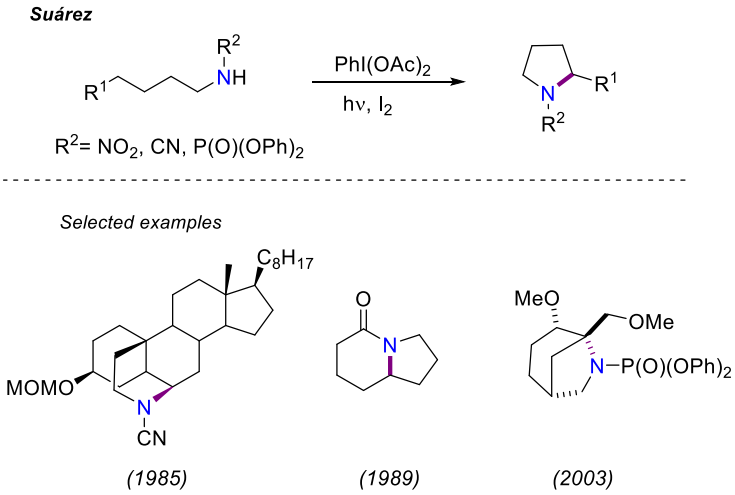
[81] (a) K. Löffler, C. Freytag, *Chem. Ber*. **1909**, *42*, 3427. (b) K. Löffler, S. Kober, *Ber. Dtsch. Chem. Ges*. **1909**, *42*, 3431.
[82] E. J. Corey, W. R. Hertler, *J. Am. Chem. Soc*. **1960**, *82*, 1657.



Scheme 1.36. *Mechanism of classical Hofmann-Löffler reaction.*

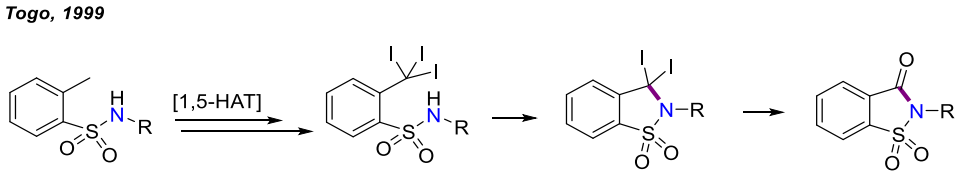
The group of Kimura presented a variant of the Hofmann-Löffler reaction under neutral conditions, applying this reaction to late-stage step functionalizations.[83] Suárez, in 1985, modified this methodology with the use of *N*-phosphoramidates, *N*-nitroamines, and *N*-cyanamides (Scheme 1.37). For this transformation, over stoichiometric amounts of hypervalent iodine species and stoichiometric amount molecular iodine were employed. In this second example, the pre-formation of the *N*-halogen bond was not necessary since the N–I bond was formed *in situ*.[84] Moreover, Suárez and coworkers used in 1989 the same methodology for transannular hydrogen abstraction to afford intramolecular functionalized derivatives such as oxoindolizidines. One decade later, the same group synthesized some carbohydrate derivatives using the same protocol.[85] While the previous Hofmann-Löffler reaction was initiated by ultraviolet light, Suárez modification proceeded under visible light. Moreover, milder conditions compared to the previous Hofmann-Löffler reaction were required, reducing the temperature from 140 ºC to 40 ºC, avoiding the use of strong acidic media such as concentrated sulfuric acid.

[83] Y. Ban, M. Kimura, T. Oishi, *Chem. Pharm. Bull*., **1976**, *24*, 1490.
[84] P. de Armas, R. Carrau, J.I. Concepción, C. G. Francisco, R. Hernández, E. Suárez, *Tetrahedron Lett*. **1985**, *26*, 2496.
[85] (a) R. L. Dorta, C.G. Francisco, E. Suárez, *J. Chem. Soc. Chem. Commun*. **1989**, 1168. (b) C.G. Francisco, A.J. Herrera, E. Suárez, *J. Org. Chem*. **2003**, *68*, 1012.



Scheme 1.37. *Cyclization of N-cyanamides, N-nitroamines, and N-phosphoramidates by HAT.*

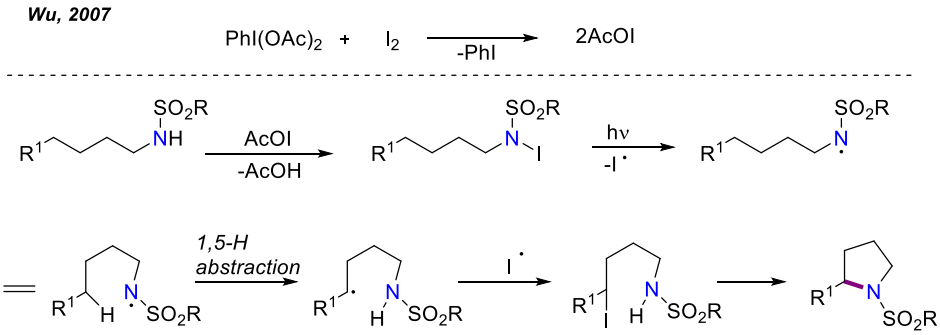
Along these lines, Togo carried out in 1999 some experiments using molecular iodine and PIDA as an oxidant for the formation of saccharine derivatives.[86] In this case, they did not observe the formation of the expected pyrrolidine derivative. Instead, they obtained saccharine derivatives (Scheme 1.38). This observation pointed toward the 1,5-HAT process occurring more than once, leading to the formation of a diiodine species, which underwent hydrolysis to form the saccharine derivatives.



Scheme 1.38. *Saccharine derivatives formation through multiple 1,5-HAT processes.*

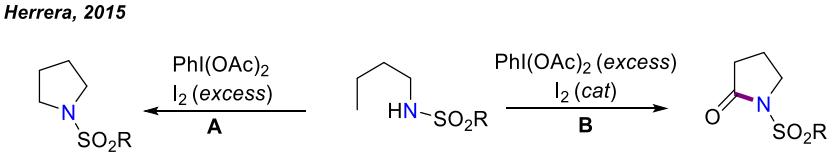
Corey reported in 2006 a similar C–H functionalization approach, which involved the use of acetyl hypobromite in the presence of CBr_4 to brominate the C5 position of isoleucine through the 1,5-HAT.[87] The C–H amination on this position requires the use of base due to the lack of nucleophilicity of the trifluoroacetamide. In 2007, Wu extended the methodology of Suárez with the use of $PhI(OAc)_2$ and molecular iodine (Scheme 1.39).[88] In this method, only the tertiary and secondary positions were accessible.

[86] M. Katohgi, H. Togo, K. Yamaguchi, Y. Masataka, *Tetrahedron* **1999**, *55*, 14885.
[87] B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 2819.
[88] R. Fan, D. Pu, F. Wen, J. Wu, *J. Org. Chem.* **2007**, *72*, 8994.



Scheme 1.39. *Mechanism of the Hofmann-Löffler reaction using $PhI(OAc)_2$ as oxidant.*

To overcome the limited scope of previously reported methodologies, Herrera developed in 2015 a protocol by controlling the amount of hypervalent iodine and molecular iodine, allowing for the functionalization of primary positions, which led to the synthesis of pyrrolidines and 2-pyrrolidones.[89] The pyrrolidine formation was controlled by a single hydrogen atom transfer process through the slow addition of the oxidant and using an excess of molecular iodine (Scheme 1.40). For the synthesis of 2-pyrrolidones, a high excess of oxidant was required where multiple hydrogen atom transfer processes took place. The triiodination over the primary position and deiodination through hydrolysis provided the 2-pyrrolidone derivative in good yield.



Scheme 1.40. *Different approaches modifying the conditions.*

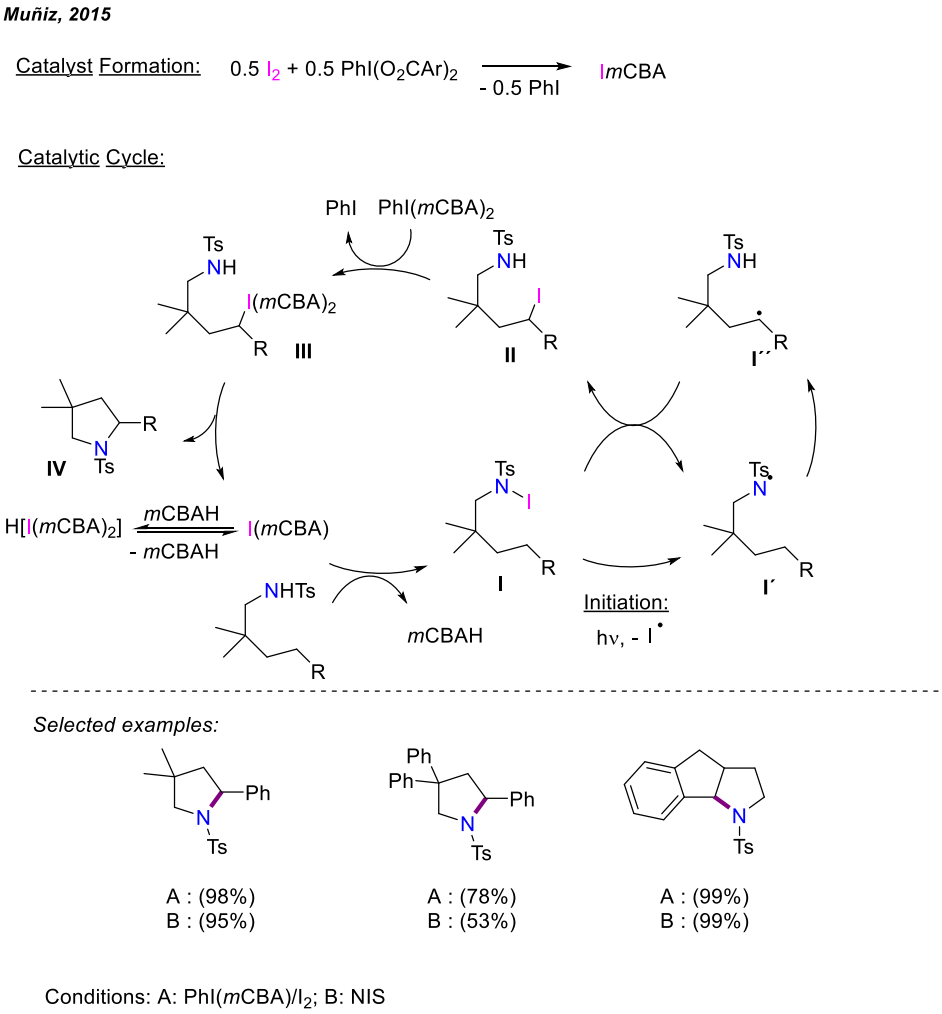
In 2015, Martínez and Muñiz implemented the use of 3-chlorobenzoate ligands on the hypervalent iodine(III) reagent, allowing the use of catalytic amounts of the halogen promoter, which is in contrast with previous works that required for high excess of terminal oxidant.[90] This was the first system that employed iodine as a catalyst and an oxidant, facilitating the efficient turnover of the active iodine species. Moreover, these conditions have no limitation in the sense of chemoselectivity and could be applied for the functionalization of tertiary, secondary, and primary positions in excellent yields.

[89] N. R. Paz, D. Rodríguez-Sosa, H. Valdés, R. Marticorena, D. Melián, M. B. Copano, C. C. González, A. J. Herrera, *Org. Lett*. **2015**, *17*, 2370.
[90] C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed*. **2015**, *54*, 8287.

The mechanism resembles what was previously described. The mixture of the hypervalent iodine oxidant and the molecular iodine forms the active I(I) catalyst that iodinates the sulfonamide (Scheme 1.41). A second catalytic cycle is linked to the previous one. This active I(I) catalyst generates the N–I bond at the sulfonamide compound. Upon light irradiation, generation of the nitrogen-centered radical occurs, followed by regioselective 1,5-HAT to form intermediate **I´´**, which abstracts a halogen from the N–I species. This process simultaneously forms the alkyl iodine and the intermediate **I´**. This mechanism was sustained by the measurement of the quantum yield with a high value of 44. Further oxidation of this alkyl iodine to the alkyl iodine(III) species increases the reactivity of this nucleofuge leading to the formation of the pyrrolidine derivatives.[91] This is a crucial process that allows the formation of the pyrrolidine derivatives on nonactivated positions such as primary Csp^3–H bonds.

One year later, the group of Muñiz demonstrated that *N*-iodosuccinimide could also be used for the formation of pyrrolidine derivatives.[92] In this case, this method was applied on activated methylene positions such as benzylic or those with an α-heteroatom since aliphatic positions led to lower conversions and yields.

[91] A. Bosnidou, K. Muñiz, *Chem. Eur. J.* **2019**, 13654.
[92] C. Q. O'Broin, P. Fernández, C. Martínez, K. Muñiz, *Org. Lett*. **2016**, *18*, 436.

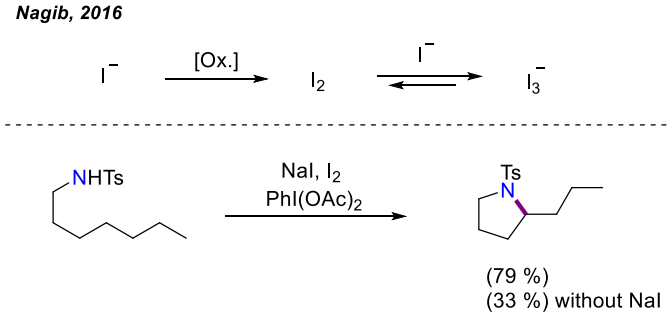


Scheme 1.41. *Mechanism and selected examples of Muñiz´s methodology.*

One year later, Nagib reported a modification of the Hofmann-Löffler reaction.[93] The mechanistic scenario described involved the formation of I_3^- generated by the mixture of NaI and $PhI(OAc)_2$ (Scheme 1.42). This approach allowed for a reduced formation of reactive AcOI, decreasing the generation of by-products by *in situ* sequestering molecular iodine as an I_3^- reservoir. The use of NaX (X = Br, Cl) allowed isolating the brominated compound on the C5 position. On the other hand, the formed N–Cl bond is less reactive towards homolytic cleavage by visible light, allowing for the isolation of this compound without further reactions. Similarly, Minakata developed a protocol for intramolecular amination

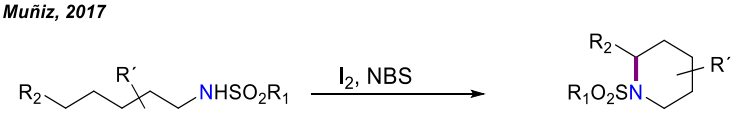
[93] E. A. Wappes, S.C. Fosu, T.C. Chopko, D.A. Nagib, *Angew. Chem. Int. Ed*. **2016**, *55*, 9974.

using sulfamates esters and NIS or *t*-butyl hypoiodite to form the N–I bond. Subsequently, a radical alkyl chain propagation process includes a 1,6-HAT process.[94]



Scheme 1.42. *Nagib´s methodology for pyrrolidine derivatives formation.*

In this way, a piperidine formation protocol was developed by the group of Muñiz using *N*-bromosuccinimide for the iodine-catalyzed C–H amination.[95] This strategy overcomes the common preference for the formation of pyrrolidines through a free-radical process involving intermolecular HAT (Scheme 1.43). In this transformation, a free radical pathway takes place different from the usual amidyl radical manifold generally engaged in the Hofmann-Löffler reaction.[96]



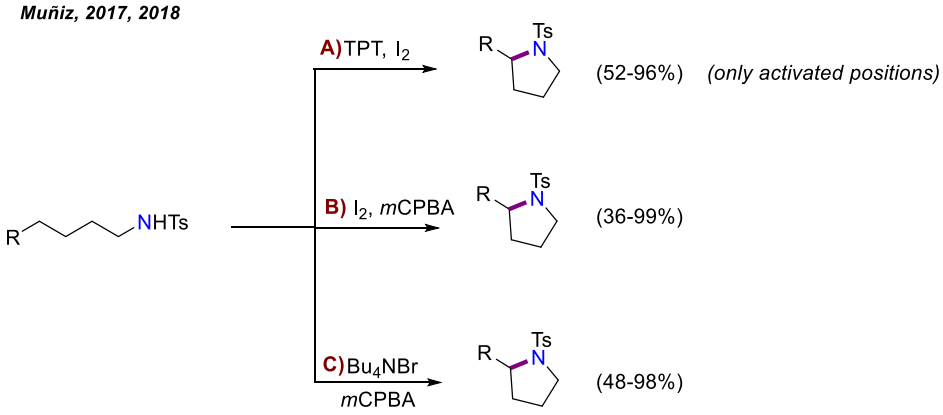
Scheme 1.43. *Iodine-catalyzed piperidine formation by using NBS.*

The group of Muñiz also developed a cooperative catalytic system that employs a photoredox catalyst and molecular iodine in catalytic amounts. This procedure consists of two independent photoinduced processes, where the iodine catalyst promotes the pyrrolidine formation.[97] The photoredox catalyst cooperates in the reoxidation of iodine to form the active hypoiodite catalyst, which initiates the transformation by *N*-iodination. Then, homolytic cleavage of the N–I bond takes place, followed by 1,5-HAT. It is noteworthy that the two processes proceed cooperatively and that the resulting methodology is environmentally benign. The main drawback of this protocol is that it is limited to benzylic C–H bond functionalization (Scheme 1.44. A). The group of Muñiz then developed in 2018

[94] K. Kiyokawa, S. Nakamura, K. Jou, K. Iwaida, S. Minakata, *Chem. Commun*. **2019**, *55*, 11782.
[95] H. Zhang, K. Muñiz, *ACS Catal*. **2017**, *7*, 4122.
[96] (a) D. Šakić, H. Zipse, *Adv.Synth. Catal*. **2016**, *358*, 3983. (b) J. M. Mayer, *Acc. Chem. Res.* **2011**, *44*, 36.
[97] P. Becker, T. Duhamel, C. J. Stein, M. Reiher, K. Muñiz, *Angew.Chem.Int. Ed*. **2017**, *56*, 8004.

an alternative methodology for the synthesis of pyrrolidines through a radical mechanism, employing molecular iodine in catalytic amounts in *tert*-butanol and *meta*-chloroperbenzoic acid as the terminal oxidant (Scheme 1.44).[98] This reaction is the most effective variant of an iodine-catalyzed Hofmann−Löffler reaction and has no limitation regarding the positions that can be functionalized. Moreover, the pre-formation of hypervalent I(III) is not required, and no chlorinated solvents are employed (Scheme 1.44. B).

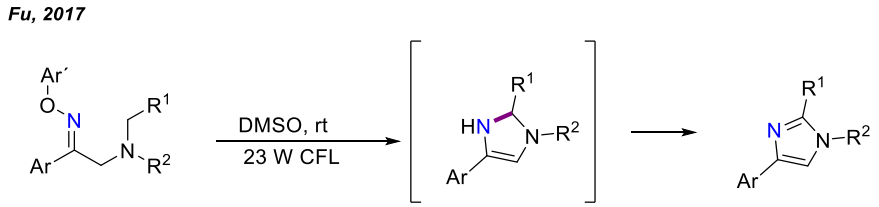
Furthermore, the methodology for the formation of pyrrolidines was extended by the design of new bromine catalysis.[99] Thus, using tetrabutylammonium bromide in catalytic amounts and 3-chloroperbenzoic acid as an oxidant, bromine(I) species were generated, allowing the construction of the N–Br bond, following the same mechanism described previously (Scheme 1.44. C).



Scheme 1.44. *Muñiz´s methodologies for pyrrolidine derivatives formation.*

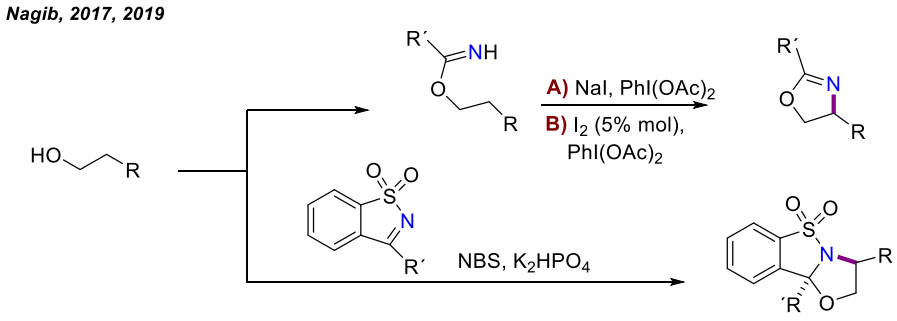
Similar to some procedures described before in Section 1.2.1.3., several authors developed methods for the formation of *N*-centered radicals using oximes. In this regard, the use of the oximes to generate amidyl radicals was described in 2017 by the group of Fu without the need for transition metals (Scheme 1.45).[100] Upon light irradiation, the N–O bond is homolytically cleaved, followed by 1,5-HAT and cyclization, generating the corresponding imidazole derivatives after aromatization.

[98] T. Duhamel, C. J. Stein, C. Martínez, M. Reihe, K. Muñiz, *ACS Catal.* **2018**, *8*, 3918.
[99] P. Becker, T. Duhamel, C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed*. **2018**, *57*, 5166.
[100] J. Li, P. Zhang, M. Jiang, H. Yang, Y. Zhao, H. Fu, *Org. Lett.* **2017**, *19*, 1994.



Scheme 1.45. *Visible-light-mediated imidazole synthesis.*

Many other contributions were made by the group of Nagib regarding the use of imidates derivatives for the generation of 1,2-aminoalcohols.[101] First, a stoichiometric protocol was described using PIDA, molecular iodine, and NaI, similar to that previously described by the same group. Intermediate imidates were easily prepared from the mixture of the alcohols and nitriles derivatives, which by nucleophilic cyclization and treatment with acidic conditions led to the final 1,2-aminoalcohols. Later, the same group described the catalytic version of this transformation.[102] These authors also implemented this methodology for the direct formation of 1,2-aminoalcohols from alcohols. In this protocol, the sulfonamide that affords the direct amination is formed *in situ* (Scheme 1.46).[103]

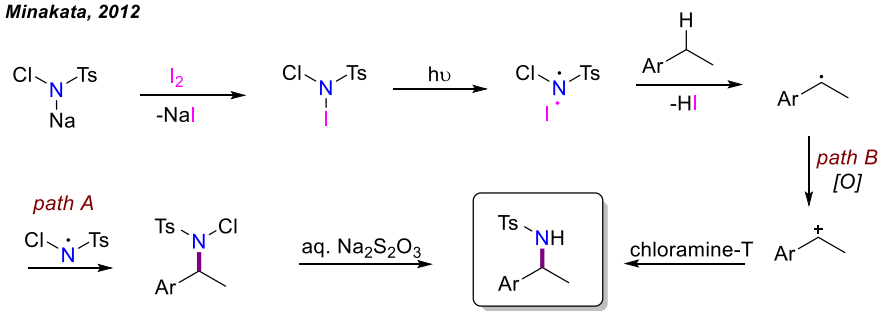


Scheme 1.46. *Nagib´s methodologies through imidyl radicals.*

In 2019, Zheng designed a visible-light-driven intramolecular protocol for the aliphatic amination under mild conditions through a long-lived photoactive photoisomer complex.[104] Some advances in intermolecular amination are based on the use of hypervalent halogen species as initiators and amines as nitrogen sources. Similar protocols for the C–H nitrene insertion were described in the

[101] E. A. Wappes, K. M. Nakafuku, D. A. Nagib, *J. Am. Chem. Soc.* **2017**, *139*, 10204.
[102] L. M. Stateman, E. A. Wappes, K. M. Nakafuku, K. M. Edwards, D. A. Nagib, *Chem. Sci.* **2019**, *10*, 2693.
[103] K. M. Nakafuku, R. K. Twumasi, A. Vanitcha, E. A. Wappes, K. Namitharan, M. Bekkaye, D. A. Nagib, *J. Org. Chem.* **2019**, *84*, 13065.
[104] D. Jing, C. Lu, Z. Chen, S. Jin, L. Xie, Z. Meng, Z. Su, K. Zheng, *Angew. Chem. Int. Ed.* **2019**, *58*, 14666.

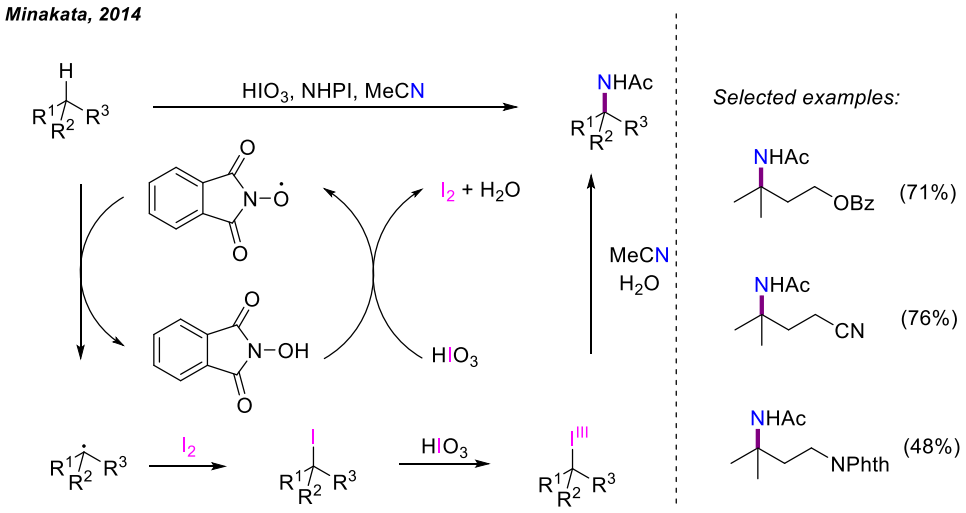
absence of metal catalysis.[105] For example, Crabtree reported in 2014 an aliphatic amination protocol using $PhI(OAc)_2$ as an oxidant in combination with sulfonamides.[106] Minakata, one year later, used Chloramine-T and -B as nitrogen sources in combination with molecular iodine toward the amination of activated positions (Scheme 1.47).[107]



Scheme 1.47. *Minakata´s methodology based on the use of Chloramine-T and -B as a nitrogen source.*

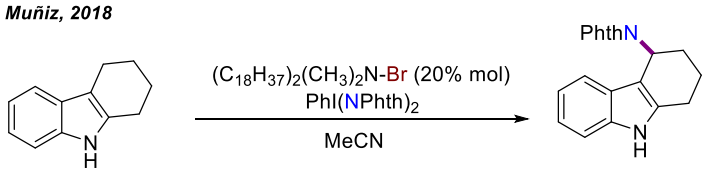
The same group developed a metal-free Ritter type amination of tertiary positions using *N*-hydroxyphthalimide (NHPI) and HIO_3 as oxidant (Scheme 1.48).[108] Some mechanistic studies were carried out to confirm alkyl iodides(I/III) were involvement as intermediates in the process.

[105] V. V: Zhdankin, M. McSherry, B. Mismash, J. T. Bolz, J. K. Woodward, R. M. Arbit, S. Erickson, *Tetrahedron Lett.* **1997**, *38*, 21.
[106] J. Campos, S. K. Goforth, R. H. Crabtree, T. B. Gunnoe, *RSC Adv*. **2014**, *4*, 47951.
[107] Y. Takeda, J. Hayakawa, K. Yano, S. Minakata, *Chem. Lett.* **2012**, *41*, 1672.
[108] K. Kiyokawa, K. Takemoto, S. Minakata, *Chem. Commu.* **2016**, *52*, 13082.



Scheme 1.48. *Metal-free Ritter-type amination over tertiary positions.*

In 2018, Muñiz designed a new strategy for the intermolecular amination of tetrahydrocarbazoles at the 4-position, instead of the most commonly activated 2-position (Scheme 1.49). For this transformation, a mixture of hypervalent iodine bearing transferable phthalimide ligands combined with an ammonium salt as a catalyst was employed.[109]

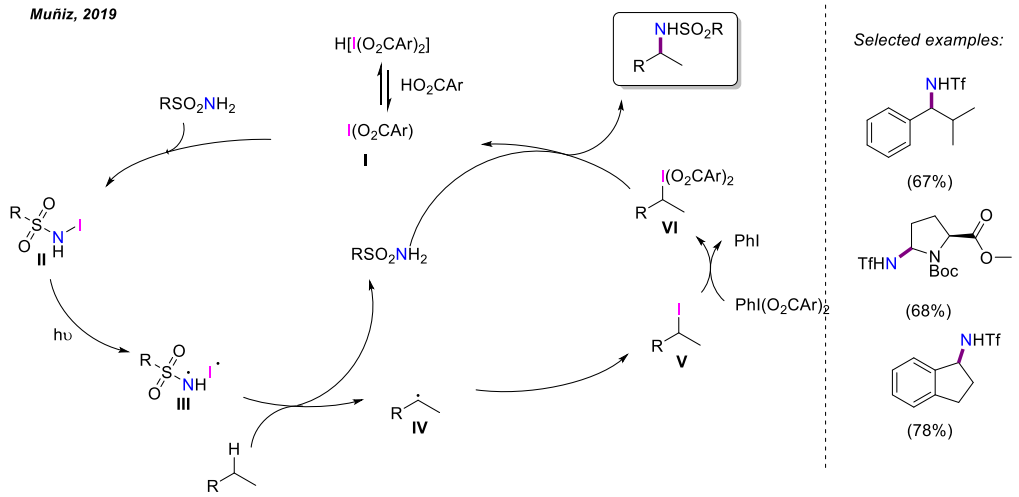


Scheme 1.49. *Bromine redox catalysis for aliphatic amination.*

One year later, this group developed the first iodine-catalyzed intermolecular aliphatic amination.[110] For this transformation, a mixture of di-(4-bromobenzyloxyiodo)benzene (PhI(*p*BBA)$_2$) as oxidant, molecular iodine in a catalytic amount, and triflamide as nitrogen source were employed. Unexpected secondary positions were functionalized preferentially over tertiary ones. A broad scope was demonstrated, including the application to the synthesis of some pharmaceutical compounds. Furthermore, the formation of pyrrolidine derivatives was carried out through a sequential inter- and intramolecular amination, combining this protocol with the described previously by the same group.[89]

[109] J. Bergès, B. García, K. Muñiz, *Angew. Chem. Int. Ed*. **2018**, *57*, 15891.
[110] A. E. Bosnidou, K. Muñiz, *Angew. Chem. Int. Ed.* **2019**, *58*, 7485.

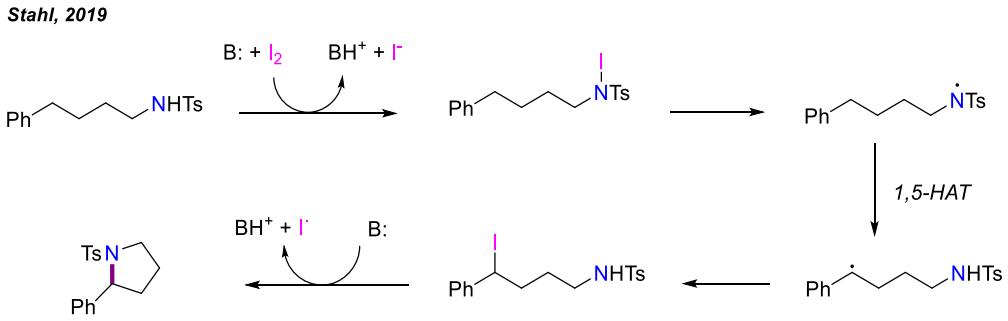
The mechanism consists in the *in situ* formation of the active catalyst iodine(I) species by comproportionation of hypervalent iodine and molecular iodine (Scheme 1.50). This active species forms the *N*-halogen bond that, by homolytic cleavage, generates the amidyl radical and the radical halogen. This amidyl radical selectively abstracts hydrogen from a hydrocarbon regenerating the amine source, leading to the formation of a radical at that position. This carbon-centered radical species evolves to the corresponding alkyl-iodine intermediate, which is oxidized to the iodine(III) species, which is an excellent leaving group for the nucleophilic attack of the nitrogen source, regenerating the active catalyst.



Scheme 1.50. *Iodine-catalyzed intermolecular C(sp^3)-H amination.*

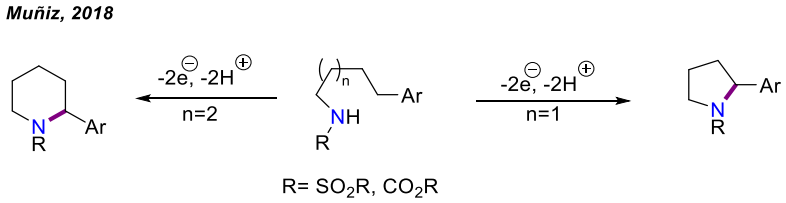
One of the latest C–H amination method via amidyl radicals was developed by Stahl using a combination of photochemical and electrochemical techniques (Scheme 1.51).[111] The use of iodine as a chemical mediator to use lower electrode potentials allows the formation of the C–N bond with broad functional group tolerance.

[111] F. Wang, S. S. Stahl, *Angew. Chem. Int. Ed*. **2019**, *58*, 6835.



Scheme 1.51. *Simplified mechanism for photo/electrochemical iodide-mediated pyrrolidine derivatives formation.*

Regarding electrochemistry, the group of Muñiz developed an electrochemical synthesis of *N*-heterocycles such as pyrrolidines and piperidines, involving an anodic C–H activation to generate the benzylic cation, which is intercepted by the nucleophilic nitrogen (Scheme 1.52).[112] This protocol represents a green alternative and shows the broad scope, although only activated positions could be activated under these conditions.



Scheme 1.52. *Uniform electrochemical anodic C–H amination.*

2. Halogen in Organic Synthesis

Alkyl halides or organic halides have a particular interest in the field of agrochemicals, material sciences, and pharmaceuticals (Figure 1.5).[113] Nearly 5000 halogenated natural products have been discovered (more than half bearing Csp^3-halogen bonds), most of which present interesting biological or pharmaceutical properties. Furthermore, alkyl halides are very useful precursors for a range of synthetic transformations, including substitution, cross-coupling, elimination, and installation of several functionalities as boron-, nitrogen-, silicon- and oxygen-based moieties.

[112] S. Herold, D. Bafaluy K. Muñiz, *Green Chem.*, **2018**, *20*, 3191.
[113] (a) Y. Lu, T. Shi, Y. Wang *et al.J Med Chem*. **2009**, *52*, 2854. (b) R. Wilcken, M. O. Zimmermann, A. Lange, A.C. Joerger, F. M. Boeckler, *J Med Chem*. **2013**, *56*, 1363.

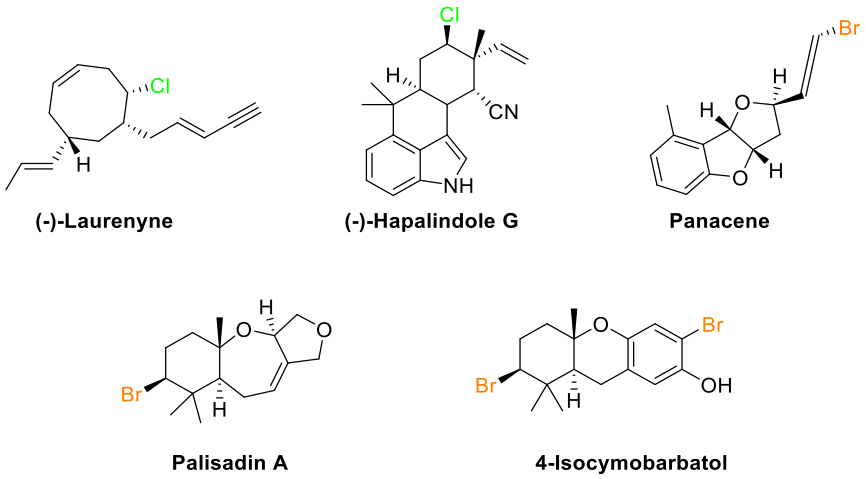
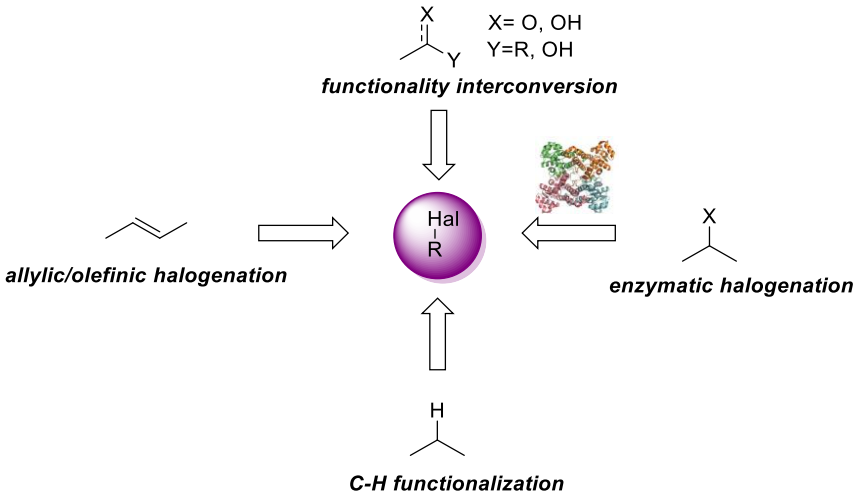


Figure 1.5. *Halogenated natural products*.

The stereochemical control in the introduction of a halogen into an organic molecule is considered a significant challenge. Several halogenation protocols have been developed to introduce halogens into organic molecules, including free radical halogenation, ketone halogenation, electrophilic halogenation, and halogen addition reaction. Nowadays, the organic synthetic community mainly relies on the use of transition metal catalysis for selective halogenation.

Halogenated organic compounds can be classified based on the nature of the hydrocarbon fragment to which the halogen (X = F, Cl, Br, I) is attached: alkane, alkene, alkyne, or aromatic. Halogenated organic molecules are used in the synthesis of many pharmaceuticals and pesticides. The conventional halogenation methods usually include toxic and corrosive elemental halogens, which produce highly poisonous and dangerous hydrohalic acid as a by-product. Many pathways are described where a functional group in the molecule is converted to a halogen. Some examples of halogen introduction are through electrophilic/nucleophilic halogenation, conversion of ketones, alcohols, carboxylic acids (Hunsdiecker reaction) into halogens, via enzymatic halogenation,[114] or C–H functionalization (Scheme 1.53). The most classical methods to introduce a halogen into an organic molecule consist in double bond functionalization, leading to an allylic/alkene halogenation.

[114] C. Schnepel, N. Sewald, *Chem. Eur. Joc*. **2017**, *7*, 12064.



Scheme 1.53. *Approaches for halogenation of organic molecules.*

2.1. Halogenation from a pre-functionalization

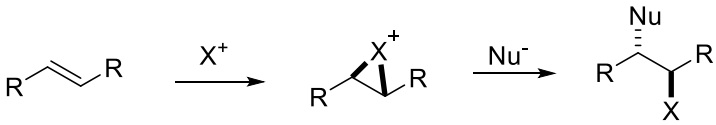
2.1.1. Allylic/ alkene halogenation

Allylic C–H bonds are particularly easy to halogenate by a free radical chain mechanism because of their relatively low C–H bond dissociation energies. Consequently, these bonds are weak and easy to break homolytically, and the resulting radicals are stabilized by resonance. The biggest problem with allylic halogenation is the competing electrophilic addition of the halogen to the C=C double bond. For bromination, this is usually overcome by using *N*-bromosuccinimide instead of molecular bromine, which is less toxic and produces molecular bromine progressively in solution (Scheme 1.54). Under these conditions with low bromine concentration, allylic bromination occurs through a free radical mechanism, and it is usually predominant over halogen electrophilic addition. In 1942, Ziegler reported the first protocol of allylic bromination using *N*-bromosuccinimide as a bromine source. Based on these ideas, several authors reported other halogenation strategies.

Scheme 1.54. *Alkeneic vs. Allylic halogenation*

This reaction is known as the Wohl-Ziegler bromination with NBS and azobisisobutyronitrile or benzoyl peroxide as radical initiators and is used for the bromination of benzylic and allylic positions.

On the other hand, the oxidative difunctionalization of alkenes with molecular bromine or electrophilic halogen sources is the most versatile and direct way to install a vicinal halogen with high and predictable diastereoselectivity. This transformation proceeds by forming halonium ions followed by ring-opening upon the attack of the suitable nucleophile (Scheme 1.55). This synthetic strategy is used for dihalogen additions, halolactonizations, haloestherifications, and halogen-induced semipinacol rearrangement.[115]



Scheme 1.55. *Electrophilic halogen addition to alkenes.*

Recent methods apply this methodology using transition metals for the stereoselective synthesis of dihaloalkenes from alkynes using palladium.[116]

2.1.2. Functionality interconversion

Halogens can be introduced in a molecule through electrophilic/nucleophilic substitutions. Within this context, the conversion of alcohols and carbonyls groups into halogens is a common strategy in synthetic chemistry. Alcohols undergo nucleophilic substitution to form haloalkanes by the use of halogen acids. This strategy is mainly applied for tertiary positions. In contrast, secondary positions often require additional activation. The carbonyl groups are mostly used for geminal α,α-dihalogenation. Furthermore, carbonyl groups are suitable precursors for electrophilic halogenation.

Unfortunately, these previously mentioned methods require pre-functionalized substrates for the synthesis of halogenated organic compounds. However, there are several protocols to introduce a halogen through C–H bond functionalization. In the next section, we will focus our attention on the Csp³–H halogenation.

2.2. Csp³–H halogenation - C–H functionalization

2.2.1. Free radical mechanism

Electrophilic and radical catalyst-free Csp³–H halogenations using *N*-halosuccinimide are common for benzylic or activated Csp³–H bonds but usually involve relatively harsh reaction conditions such as high temperature, strong acidic, basic media, or UV irradiation.

[115] U. Hennecke, *Chem. Asian J*. **2012**, *7*, 456.
[116] G. Zhu, D.Chen, Y. Wang, R. Zheng, *Chem. Commun*. **2012**, *48*, 5796.

Schreiner published in 2001 a C–H halogenation procedure for cubane using polyhalomethanes as a halogen source.[117] Iodination, bromination, and chlorination of the aliphatic carbons of the cubane were achieved by this method. Kikushima developed an example for the bromination of aliphatic carbons induced by LED irradiation using carbon tetrabromide as a bromine source.[118] The regioselectivity depends on the radical stability. In this way, tertiary and secondary radicals are much more reactive to this kind of transformation. Regarding reactivity, bromine shows to be less reactive but more selective than chlorine. Radical chlorination of alkyl Csp^3–H bonds with chlorine gas is an efficient strategy to produce alkyl chlorides. Although this transformation is effective up to 50% yield, due to the hydrochloric acid generated, the use of toxic chlorine gas as a direct halogen source is dangerous.

In general, free-radical or electrophilic halogenation are non-selective and reliable (activated positions) to introduce a halogen into an organic derivative.[119]

Conventional routes to these building blocks have commonly involved multiple steps, harsh reaction conditions, and the use of stoichiometric and/or toxic reagents. In principle, transition metal catalysis could overcome all the drawbacks of conventional halogenation.

2.2.2. Transition-metal-catalyzed direct C−H bond halogenation

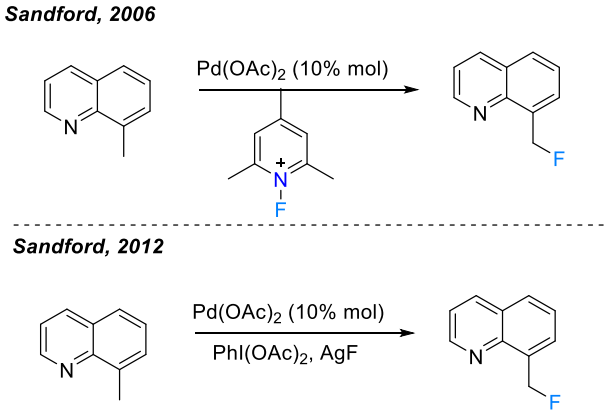
Due to the high interest in alkyl halides synthesis, the development of novel strategies that involve new, mild, regio- and chemoselective transformations are still in great demand. Several methods have been described for converting an aliphatic Csp^3–H bond into a C–N or C–O bond. However, oxidation of a specific aliphatic C–H bond in a complex molecule remains a significant challenge in reaction methods development. Nowadays, there are several methods to selectively install a halogen in an organic compound, normally consisting in the use of transition metals for a selective radical halogenation or by using amidyl radicals in an intermolecular and intramolecular manner. On the other hand, one of the most important strategies to introduce regioselectively a halogen is by using directing groups. This will be explained in detail in the next chapter.

To fill this synthetic gap, the use of transition metals to catalyze a selective Csp^3–H halogenation is an important strategy to overcome the potential downsides of conventional halogenation reactions. Compared with Csp^2–H bonds, Csp^3–H

[117] A. A. Fokin, O. Lauenstein, P. A. Gunchenko, P. R. Schreiner, *J. Am. Chem. Soc*. **2001**, *123*, 1842.
[118] Y. Nishina, B. Ohtani, K. Kikushima, *J. Org. Chem.* **2013,** *9*, 1663.
[119] (a) X. Jiang, M. Shen, Y. Tang, C. Li, *Tetrahedron Lett.* **2005**, *46*, 487. (b) T. S. Zhuk, P. A. Gunchenko, Y. Korovai, P. R. Schreiner, A. A. Fokin, *Theor. Exp. Chem*. **2008**, *44*, 48.

bonds are less acidic, and its direct halogenation is more challenging. The most often used metals for C–H halogenation are copper,[120] ruthenium, palladium, and cobalt.

Several protocols have been published for the functionalization with halogens using palladium catalysis. Sanford pioneered to use palladium catalysis for the fluorination of aliphatic bonds.[121] Her group employed quinolines and pyridines as directing/chelating groups and an electrophilic fluorine source for the transformation. Studies on chlorination were carried out by the same group.[122] Moreover, they extended this methodology using a nucleophilic fluorine source and an external oxidant to convert Pd(II) into Pd(IV), which ultimately participates in C–F bond-forming reductive elimination (Scheme 1.56).[123]

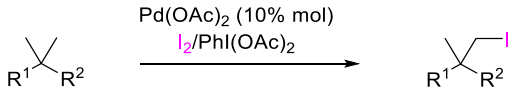


Scheme 1.56. *Fluorination methodologies using Pd-catalysis.*

Regarding Pd-catalysis, the group of Yu developed a straightforward protocol for catalytic asymmetric iodination of nonactivated C–H bonds under mild conditions (Scheme 1.57).[124] The mixture of $Pd(OAc)_2$, molecular iodine, and $PhI(OAc)_2$ led to the iodination of a variety of substrates such as cyclopropanes and aryl groups under mild conditions. Moreover, Yu extended this protocol to form cyclopropane derivatives through di-iodination leading 1,3-diiodide compounds that undergo a cyclization reaction to form the desired cyclopropane products.[125]

[120] W. Hao, Y. Liu, Beilstein, *J. Org. Chem*. **2015**, *11*, 2132.
[121] K. L. Hull, W. Q. Anani, M. S. Sandford, *J. Am. Chem. Soc*. **2006**, *128*, 7134.
[122] D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Tetrahedron* **2006**, *62*, 11483.
[123] K. B. McMurtrey, J. M. Racowski, M. S. Sanford, *Org. Lett*. **2012**, *14*, 4094.
[124] (a) R. Giri, X. Chen, J. Yu, *Angew. Chem., Int. Ed*., **2005**, *44*, 2112. (b) R. Giri, X. Chen, X. Hao, J. Li, J. Liang, Z. Fan, J. Yu, *Tetrahedron: Asymmetry*, **2005**, *16*, 3502.
[125] R. Giri, M. Wasa, S. P. Breazzano, J.-Q. Yu, *Org. Lett.* **2006**, *25*, 5685.

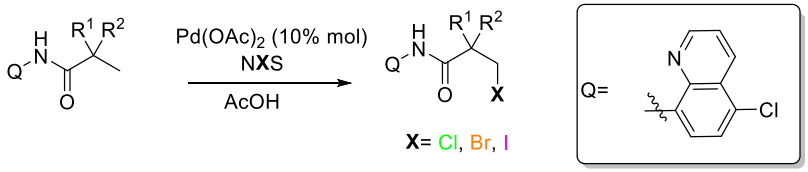
Yu, 2005



Scheme 1.57*. Iodination of C(sp³)-H bond through Pd-catalysis.*

The combination of a hindered oxazoline auxiliary, $Pd(OAc)_2$, I_2, and $PhI(OAc)_2$ was shown to be a powerful protocol for the catalytic and asymmetric iodination of inactivated C–H bonds of methyl, cyclopropyl, and aryl groups under mild conditions. Sahoo reported a directing group-assisted bromination and chlorination of Csp^3–H bonds catalyzed by palladium. The halogenation took place on the β-position providing a highly functionalized quaternary carbon.[126] Rao developed a versatile halogenation method without the requirement of a tertiary α-position (Scheme 1.58).[127] The directing group employed could be easily removed, extending the applicability of this protocol for late-stage transformations.

Rao, 2016

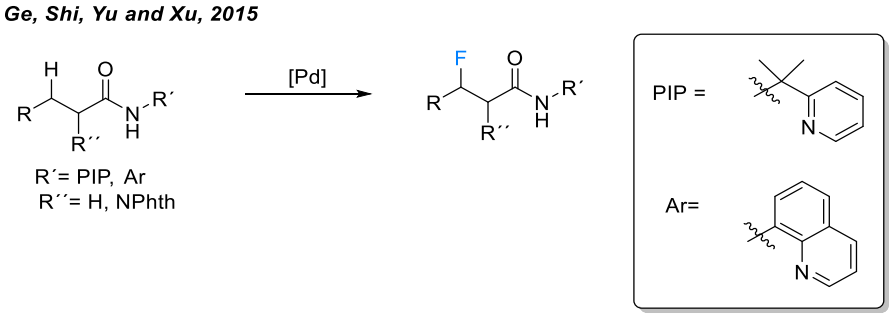


Scheme 1.58. *Pd-catalyzed iodination, bromination, and chlorination.*

Several methods were described by Ge,[128] Shi,[129] Yu,[130] and Xu,[131] allowing for the fluorination of amino acid derivatives and aliphatic amides (Scheme 1.59). Ge reported a palladium-catalyzed, ligand-directed, and site-selective fluorination of amino acid derivatives. This method showed high selectivity for nonactivated Csp^3–H bonds in β-position compared to γ-sp^2 or benzylic β-sp^3 C–H bonds. A similar strategy was developed by the group of Shi. Along these lines, Yu synthesized several non-natural enantiopure anti-β-fluoro-α-amino acids. For this transformation, the role of the ligand was crucial for the fluorination event.

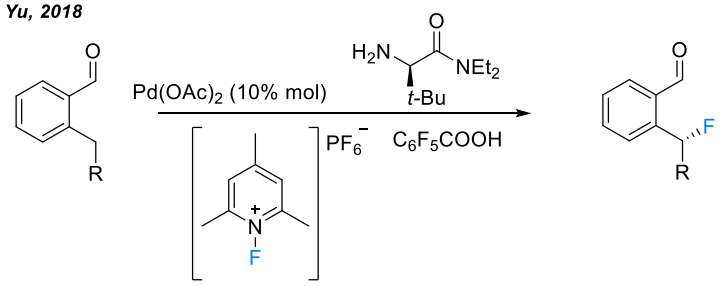
[126] R. K. Rit, M. R. Yadav, K. Ghosh, M. Shankar, A. K. Sahoo, *Org. Lett*. **2014**, *16*, 5258.
[127] X. Yang, Y. Sun, T.-Y. Sunb, Y. Rao, *Chem. Commun*., **2016**, *52*, 6423.
[128] J. Miao, K. Yang, M. Kurek, H. Ge, *Org. Lett.* **2015**, *17*, 3738.
[129] Q. Zhang, X. Yin, K. Chen, S. Zhang, B. Shi, *J. Am. Chem. Soc*. **2015**, *137*, 8219.
[130] R. Zhu, K. Tanaka, G. Li, J. He, H. Fu, S. Li, J. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 7067.
[131] Q. Zhu, D. Ji, T. Liang, X. Wang, Y. Xu, *Org. Lett*. **2015**, *17*, 3798.

Yu also extended the concept of palladium catalysis for the iodination and bromination of aliphatic carbons.[132]



Scheme 1.59. *Fluorination of amino acids at β-position.*

The latest efforts by the group of Xu applied palladium catalysis for selective Csp²–H and Csp³–H fluorination of simple alcohol derivatives bearing bidentate chelating groups in their structure and using commercially available electrophilic fluorine sources such as *N*-fluorobenzenesulphonamide (NFSI).[133] The same year, the group of Yu described the enantioselective version of the aliphatic fluorination using a chiral transient directing group (Scheme 1.60).[134]

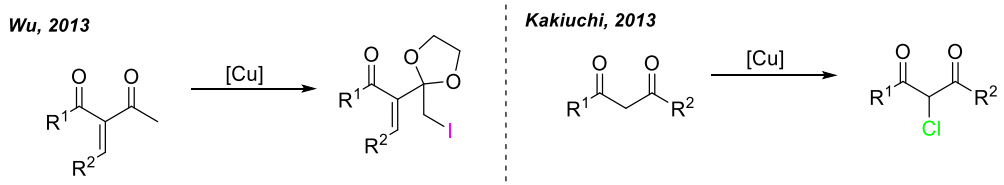


Scheme 1.60. *Enantioselective aliphatic fluorination through Pd-catalysis.*

Copper-mediated halogenation is commonly known for Csp²–H halogenation. In contrast, the Csp³–H halogenation has been barely explored. However, besides the halogenation of nonactivated C–H bonds by C–H activation, copper showed important applications for the electrophilic halogenation of esters and ketones. In this case, avoiding selectivity problems between mono and multi halogenated compound without the use of environmentally inconvenient halogenating reagents. In 2013, Wu explored the synthesis of α-iodoketals through CuO-

[132] R.-Y. Zhu, T. G. Saint-Denis, Y. Shao, J. He, J. D. Sieber, C. H. Senanayake, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 5724.
[133] Y.-J. Mao, S.-J. Lou, H.-Y. Hao, D.-Q. Xu, *Angew.Chem. Int.Ed*. **2018**, *57*,14085.
[134] H. Park, P. Verma, K. Hong, J.-Q. Yu, *Nat. Chem*. **2018**, *10*, 755.

mediated selective monohalogenation of methyl ketones and diketones using molecular iodine (Scheme 1.61). In the same year, Kakiuchi applied a similar strategy for selective chlorination of esters or amides using $Cu(OTf)_2$ as a catalyst.[135] Finally, the group of Du described the asymmetric version of this di-ketone chlorination in the presence of a chiral ligand.[136]



Scheme 1.61. *Iodination and chlorination of ketals and methyl ketones.*

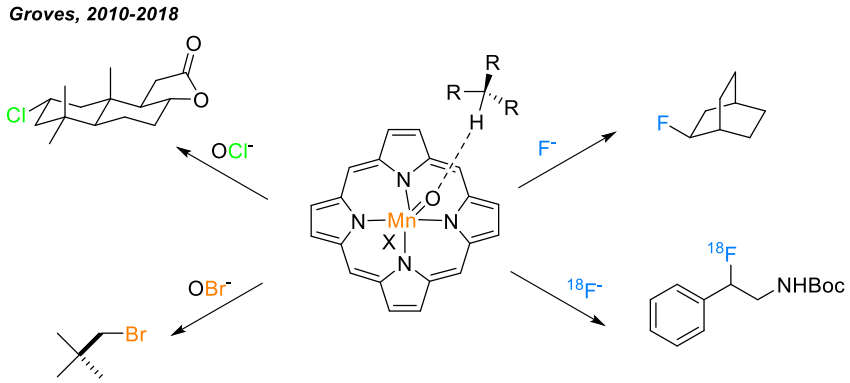
2.2.3. Radical-mediated C–H halogenation- HAA process.

Many halogenation methodologies described the formation of carbon-centered radicals that are trapped by an electrophilic halogen source generating the C–X bond at that position. The radical mechanism could provide a simple but powerful tool for selective and specific halogenation. Wirth described one of the first examples for the iodination of aliphatic carbons under metal-free conditions. For this transformation, *t*-butyl-hypohalites were used as a cheap and efficient iodine source.[137]

As described previously in Section 1.2.1.2., regarding the use of porphyrins for C–H activation, some examples appeared in the literature showing that these porphyrins could be employed for the C–X bond formation. Thus, Groves reported in 2010 a manganese porphyrin mediated C–H chlorination using sodium hypochlorite as a chlorine source, avoiding the competing oxygenation reaction.[138] This strategy was also applied for the functionalization of strong C–H bonds such as neopentane positions, obtaining the chlorinated product in good yield.

[135] (a) Yang, Y.; Gao, M.; Shu, W.-M.; Wu, L.-M.; Zhang, D.-X.; Wu, A.-X. *Org. Biomol. Chem*. **2013**, *11*, 1226. (b) Tsuchida, K.; Kochi, T.; Kakiuchi, F. *Asian J. Org. Chem*. **2013**, *2*, 935.
[136] S.-J. Jia, D.-M. Du, *Chin. Chem. Lett*. **2014**, *25*, 1479.
[137] (a) R. Montoro, T. Wirth, *Org. Lett.* **2003**, *24*, 4729. (b) R. Montoro, T. Wirth, *Synthesis* **2005**, *9*, 1473.
[138] W.Liu, J. T. Groves, *J. Am. Chem. Soc*. **2010**, *132*,12847.

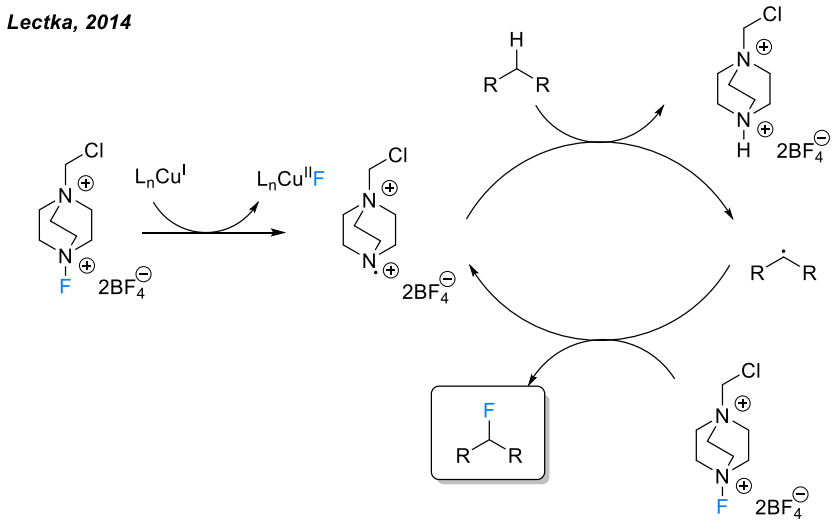
The same group extended this methodology for bromination and fluorination (Scheme 1.62).[139]



***Scheme 1.62**. Manganese porphyrin for radical halogenation.*

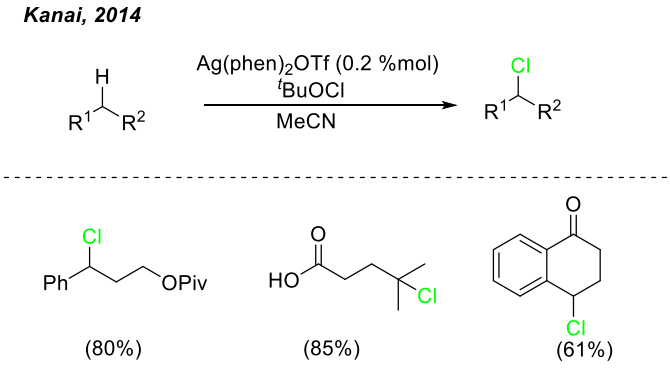
Copper was demonstrated to catalyze chlorination, bromination, and iodination. In this regard, Lectka was a pioneer using in 2012 a Cu(I)/Cu(II) catalytic system for the selective Csp³–H fluorination of alkanes.[140] This group performed extended mechanistic investigations to formulate the mechanism, starting with a single-electro-transfer (SET) process between copper and Selectfluor. Then, the copper(I) species is oxidized to Cu(II) with a loss in fluoride from Selectfluor. This species abstracts hydrogen from the hydrocarbon, generating the carbon-centered radical, which is finally trapped by fluorine (Scheme 1.63).

[139] (a) W. Liu, J. T. Groves, *Acc.Chem. Res*. **2015**, *48*, 1727. (b) G. Li, A. K. Dilger, P. T. Cheng, W. R. Ewing, J. T. Groves, *Angew. Chem. Int. Ed*. **2018**, 57, 1251. (c) W. Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard, J. T. Groves, *Science*, **2012**, *337*, 1322. (d) W. Liu, J. T Groves, *Angew. Chem. Int. Ed*. **2013**, *52*, 6024. (e) X. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker, J. T. Groves, *J. Am. Chem. Soc*. **2014**, *136*, 6842. (f) W. Liu, X. Huang, M. S. Placzek, S. W. Krska, P. McQuade, J. M. Hooker, J. T. Groves, *Chem. Sci*. **2018**, *9*, 1168.
[140] (a) S. Bloom, C. R. Pitts, D. C. Miller, N. Haselton, M. G. Holl, E. Urheim, T. Lectka, *Angew. Chem. Int. Ed.* **2012**, *51*, 10580. (b) C. R. Pitts, S. Bloom, R. Woltornist, D. J. Auvenshine, L. R. Ryzhkov, M. A. Siegler, T. Lectka, *J. Am. Chem. Soc*. **2014**, *136*, 9780.



***Scheme 1.63**. Copper catalysis of aliphatic C–H bonds.*

Other groups focused on the use of silver as a catalyst for chlorination and fluorination.[141] Li described the first catalytic Hunsdiecker reaction of aliphatic carboxylic acids.[142] Based on this precedent, Kanai developing a chlorination protocol of benzylic, tertiary, and secondary Csp³–H bonds (Scheme 1.64).[143] The mechanism starts with the formation of a Ag(II)-O*t*Bu complex, which undergoes homolytic cleavage to generate *tert*-butoxy radical that abstracts a hydrogen atom from a hydrocarbon forming the carbon-centered radical that is trapped by chlorine.

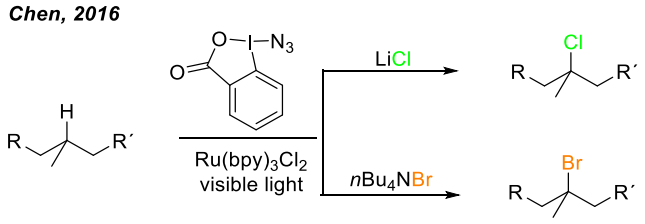


***Scheme 1.64**. Silver-catalyzed aliphatic halogenation.*

[141] D. D. Bume, S. A. Harry, T. Lectka, C. R. Pitts, *J. Org. Chem*. **2018**, *83*, 8803.
[142] Z. Wang, L. Zhu, F. Yin, Z. Su, Z. Li, C. Li, *J. Am. Chem. Soc*. **2012**, *134*, 4258.
[143] J. Ozawa, M. Kanai, *Org. Lett.* **2017**, *19*, 1430.

Silver was also employed to generate difluoromethylated arenes by activating benzylic bonds.[144] The transformation was carried out using Selectfluor as a fluorine source and $AgNO_3$ as a catalyst in aqueous media. A similar Ag(I)/Ag(II) catalytic cycle was described by Baxter for the fluorination of aliphatic carbons using glycine as a radical mediator for the hydrogen atom abstraction process.[145]

Ruthenium catalysts for C–H halogenation were barely explored. Chen described the chlorination and bromination at tertiary positions through ruthenium catalysis using azidoiodane and visible light (Scheme 1.65).[146] A radical chain propagation mechanism was proposed for this transformation. Single-electron reduction of azidoiodane by excitation of the ruthenium catalyst generates the radical species that abstracts hydrogen from the substrate. This radical abstracts a chlorine or bromine atom from the halogen sources and regenerates the iodanyl radical.



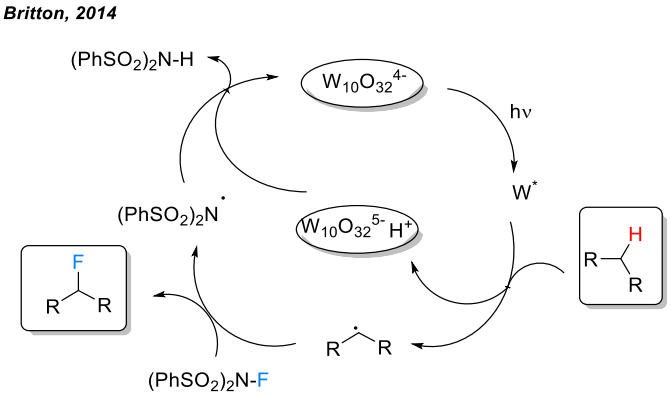
***Scheme 1.65**. Ruthenium catalysis for bromination and chlorination.*

Concerning iron, few examples were described by the groups of Lectka and Maiti. Lectka reported the formation of fluorinated compounds using commercially available iron(II) acetylacetonate and Selectfluor in a highly selective reaction.[147] Maiti described a selective strategy for bromination using a stable non-heme iron(IV)-oxo complex in combination with iron(II)-halide complex.[148]

Chen broadened the fluorination protocols of aliphatic carbons using vanadium catalysts.[149] Britton employed a decatungstate photocatalyst combined with NFSI as a fluorine source for the hydrogen atom abstraction process of nonactivated Csp^3–H bonds (Scheme 1.66).[150] With this approach, fluorinated organic

[144] P. Xu, S. Guo, L. Wang, P. Tang, *Angew. Chem. Int. Ed*. **2014**, *53*, 5955.
[145] A. M. Hua, D. N. Mai, R. Martínez, R. D. Baxter, *Org. Lett.* **2017**, *19*, 2949.
[146] Y. Wang, G.-X. Li, G. Yang, G. Hea, G. Chen, *Chem. Sci.* **2016**, *7*, 2679.
[147] S. Bloom, C. Ross Pitts, R. Woltornist, A. Griswold, M. G. Holl, T. Lectka, *Org. Lett*, **2013**, *15*, 1722.
[148] S. Rana, J. P. Biswas, A. Sen, M. Clemancey, G. Blondin, J.-M. Latour, G. Rajaraman, D. Maiti, *Chem. Sci*. **2018**, *9*, 7843.
[149] J.-B. Xia, Y. Ma, C. Chen, *Org. Chem. Front*. **2014**, *1*, 468.
[150] S. D. Halperin, H. Fan, S. Chan, R. E. Martín, R. Britton, *Angew. Chem. Int. Ed*. **2014**, *53*, 4690.

compounds were obtained. This methodology was expanded to benzylic positions one year later, showing a high selectivity over other activated positions.[151] The same group used this protocol for ^{18}F labeling peptides and amino acids for Positron Emission Tomography (PET). [152]



Scheme 1.66. *Fluorination using a tungstane-based photoredox catalyst.*

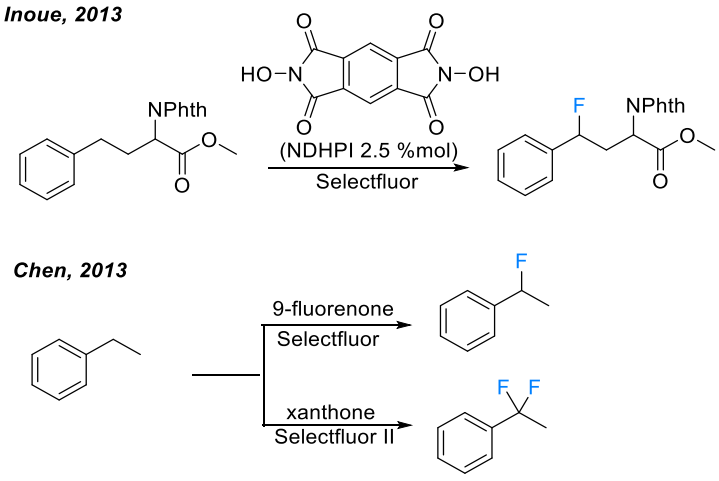
2.2.4. Metal-free radical C–H halogenation

Visible-light-driven halogenation has emerged as an important method for selective C–H halogenation, promoting C–H activation under mild conditions in an environmentally benign way.

Along these lines, several authors have developed protocols for halogenation without using transition metals to generate the carbon-centered radical at the appropriate molecule. Thus, Inoue designed in 2013 a protocol for benzylic fluorination employing a radical initiator, *N*,*N*-dihydroxypyromellitimide (NDHPI), in combination with Selectfluor as fluorine source (Scheme 1.67).[153] Other protocols were described for benzylic fluorination using photocatalyst. For example, Chen used an aryl ketone as a photocatalyst that undergoes photoexcitation generating a species capable of abstracting the hydrogen from the benzylic position leading to the carbon-centered radical.[154] The same group

[151] (a) M. B. Nodwell, A. Bagai, S. D. Halperin, R. E. Martin, H. Knustc, R. Britton, *Chem. Commun.* **2015**, *51*, 11783. (b) S. D. Halperin, D. Kwon, M. Holmes, E. L. Regalado, L.-C. Campeau, D. A. DiRocco, R. Britton, *Org. Lett.* **2015**, *17*, 5200.
[152] (a) M. B. Nodwell, H. Yang, M. Čolović, Z. Yuan, H. Merkens, R. E. Martin, F. Bénard, P. Schaffer, R. Britton, *J. Am. Chem. Soc.* **2017**, *10*, 3595. (b) Z. Yuan, M. B Nodwell, H. Yang, N. Malik, H. Merkens, F. Bénard, R. E Martin, P. Schaffer, R. Britton, *Angew. Chem. Int. Ed*, **2018**, *57*, 12733.
[153] Y. Amaoka, M. Nagatomo, M. Inoue, *Org. Lett.* **2013**, *15*, 2160.
[154] J.-B. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc*. **2013**, *135*, 1749.

expanded the protocol for difluorination using xanthone as a catalyst.[155] On the other hand, Wu designed visible-light-induced fluorination using an acridinium-based organic dye as photocatalyst. [156] Lectka studied the mechanism for C–H fluorination using photosensitizer 1,2,4,5-tetracyanobenzene (TCB).[157]



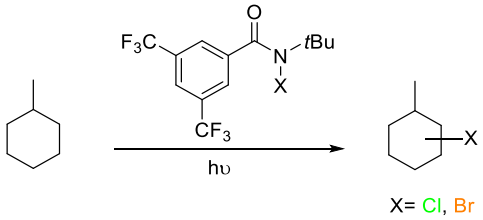
Scheme 1.67. *C–H benzylic fluorination. Top: Inoue´s methodology. Bottom: Chen´s methodology.*

Chen developed a strategy for aliphatic chlorination using benzophenone as photocatalyst and *N*-chlorosuccinimide as a chlorine source.[158] The chlorination showed lower regioselectivity than the fluorination, indicating that the HAA process is the limiting step.

The use of nitrogen-centered radicals for the functionalization of nonactivated aliphatic C–H bonds is often employed in synthesis. In the field of intermolecular selective halogenation, one of the best examples was published by Alexanian for the selective bromination and chlorination (Scheme 1.68).[159] These transformations were carried out by employing *N*-halogen amides and visible light. The group observed the selective halogenation of secondary positions even in presence of tertiary positions in the substrate, which indicates that a free-radical mechanism is not operating here. In contrast to conventional radical C–H bromination with molecular bromine, the formation of the amidyl radical and the

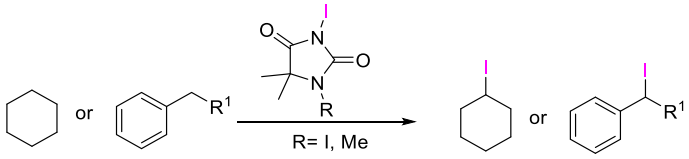
[155] J.-B. Xia, C. Zhu, C. Chen, *Chem. Commun*. **2014**, *50*, 11701.
[156] M. Xiang, Z.-K. Xin, B. Chen, C.-H. Tung, L.-Z. Wu, *Org. Lett*. **2017**, *19*, 3009.
[157] S. Bloom, J. L. Knippel, T. Lectka, *Chem. Sci.* **2014**, *5*, 1175.
[158] L. Han, J.-B. Xia, L. You, C. Chen, *Tetrahedron* **2017**, *73*, 3696.
[159] (a) V. A. Schmidt, R. K. Quinn, A. T. Brusoe, E. J. Alexanian, *J. Am. Chem. Soc.* **2014**, *136*, 14389. (b) R.K. Quinn, Z. A. Könst, S. E. Michalak, Y. Schmidt, A. R. Szklarski, A. R. Flores, S. Nam, D. A. Horne, C. D. Vanderwal, E. J. Alexanian, *J. Am. Chem. Soc.* **2016**, *138*, 696.

subsequent C–H abstraction is an irreversible step. Unfortunately, the iodination reaction could not be accessed through this protocol.



Scheme 1.68. *Aliphatic selective radical halogenation by Alexanian.*

One of the most challenging halogenations is the installation of iodine into organic compounds. This is due to the hydrogen iodide formed as a by-product, that can reduce the haloalkane to the alkane. Even in the Wohl-Ziegler reaction for benzylic halogenation, the corresponding iodination version is missing due to the endergonic nature of the process. Gandelman and Schreiner developed two protocols for metal-free iodination of aliphatic and benzylic bonds using a 1,3-diiodo-5-5-dimethylhydantoin as an iodine source that is thermally stable and soluble in nonpolar solvents (Scheme 1.69).[160]



Scheme 1.69. *Aliphatic and benzylic halogenation by Gandelman and Schreiner.*

[160] (a) A. Artaryan, A. Mardyukov, K. Kulbitski, I. Avigdori, G. A. Nisnevich, P. R. Schreiner, M. Gandelman, *J. Org. Chem.* **2017**, *82*, 7093. (b) S. H. Combe, A. Hosseini, L. Song, H. Hausmann, P. R. Schreiner, *Org. Lett.* **2017**, *19*, 6156.

Chapter II. Hofmann-Löffler Reaction for Selective Multiple Halogenation of Aliphatic Compounds.

1. Nitrogen-Centered Radicals

1.1. Nitrogen-Centered Radicals for directed δ/γ-Csp^3-H functionalization

Nitrogen centered radicals (NCRs) have been widely used as reactive intermediates in synthetic chemistry during the last decades, although they have been underexplored compared to the carbon-centered radical intermediates.[161] From this viewpoint, NCRs are considered attractive synthetic intermediates due to the reversal of polarity compared to the nucleophilic nitrogen center. The four main reactivities of these intermediates are: a) Minisci-type addition to arenes, b) cyclization onto alkenes generating *N*-heterocycles, c) radical clock transformations, and d) 1,5-hydrogen atom transfer followed by a remote functionalization.

The classic strategy for the generation of NCRs is through thermal or photochemical homolysis of labile N–X bonds under harsh conditions (e.g., strong acids). The last decades have increased the interest in using these NCRs in diverse synthetic strategies development for inter- and intramolecular transformations. Some of these strategies are mentioned in Section 2.2.4. of the previous chapter. Regarding intramolecular hydrogen atom transfer (HAT) chemistry, *N*-centered radicals have an essential role in providing regioselective functionalization of inert and distal C–H bonds.[162] For example, catching the δ-halo intermediate of the Hofmann-Löffler mechanism has been established as an important method for installing a versatile halide group at the δ position via remote C–H functionalization.

Transition metal-catalyzed reactions for the C–H functionalization usually rely on directing groups or activated C–H bonds. Amidyl or iminyl radicals trigger selective hydrogen atom transfer (HAT) processes, commonly through a 1,5-migration via a six-membered cyclic transition state. This old concept became a modern strategy for constructing a C–C bond and C–Heteroatom bonds due to new technology advances (e.g., LEDs as light source, novel photocatalysts, milder oxidants). In the last decade, the formation of the radical initiator required the use of strong acid, peroxides under refluxing conditions, or UV irradiation. Nowadays, these amidyl or iminyl radicals can be generated under milder conditions using hypervalent iodine, photoredox chemistry, or electrochemical processes.[163]

[161] M. D. Kärkäs, *ACS Catal.* **2017**, *7*, 4999.
[162] L. M. Stateman, K. M. Nakafuku, D. A. Nagib, *Synthesis* **2018**, *50*, 1569.
[163] G. Kumar, S. Pradhan, I. Chatterjee, *Chem Asian J.* **2020**, *15*, 651.

1.2. Nitrogen radical configuration

The electronic configuration of NCRs has an influence on their behavior and as a result of their reactivities. There are four types of NCR depending on the location of the electrons in the nitrogen.[164] Amidyl (comprising sulfamidyl, phosphoramidyl, and carbomyl) and aminium radicals are characterized by the electrophilic character due to the delocalization of unpaired electrons. Regarding aminium radicals, when the nitrogen is protonated, its character changes due to the removal of the lone pair repulsion. In contrast, iminyl and neutral aminyl radicals have nucleophilic character. Iminyl radicals possess σ-configuration, whereas aminyl radicals have π-configuration with the unpaired electrons occupying the higher energy level. Thus, they are the least electrophilic and present lower NCR-reactivity (Figure 2.1).[165]

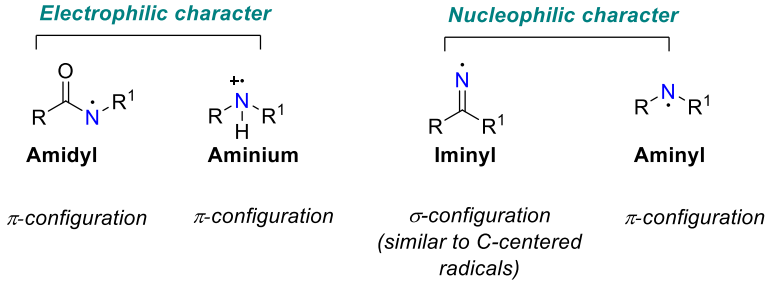


Figure 2.1. *Configuration of nitrogen centered radicals.*

Amidyl radicals are known to undergo intramolecular 1,5- and 1,6-hydrogen atom transfer processes leading to the formation of carbon-centered radicals. Several methods are described to trap the resulting radical with different groups providing the functionalization selectively over the position δ or γ from the directing group. The generation of *N*-centered radicals by photocatalysis has become an additional strategy that avoids the use of stoichiometric and toxic reagents usually required in traditional radical chemistry. The mechanism consists of 4 phases (Figure 2.2). The first one consists in forming the radical precursor **1**. As mentioned previously, the *N*-centered radical is generated by the homolysis of N–X bond, where X is halogen, oxygen, or nitrogen nucleofuge, to generate intermediate **2**. The next stage consists in the hydrogen atom transfer process for the formation of the carbon-centered radical **3**. The most typical pathway is 1,5-HAT due to a pre-organized six-membered cyclic transition state.

[164] J. C. Walton, *Acc. Chem. Res.* **2014**, *47*, 1406.
[165] (a) J. Lessard, D. Griller, K. U. Ingold, *J. Am. Chem. Soc.* **1980**, *102*, 3262. (b) W. D. Danen, R. W. Gellert, *J. Am. Chem. Soc.* **1980**, *102*, 3264.

The last step involves the radical trap affording the incorporation of a functional group with a wide reactivity scope.

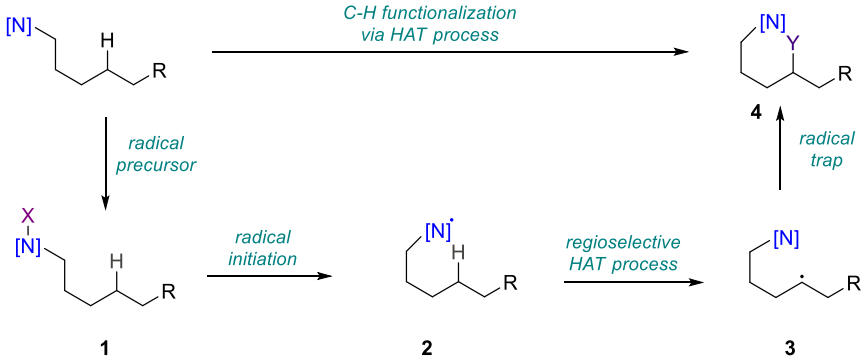


Figure 2.2. *General scheme for regioselective C–H functionalization via HAT process.*

Photochemical or photocatalyzed generation of *N*-centered radicals have benefited by the milder reaction conditions and also can avoid the use of stoichiometric and toxic reagents like tin hydrides, azobis(isobutyronitrile) (AIBN), and Et_3B used in traditional radical chemistry.

1.3. Remote C–H halogenation via selective HAT process

Several methods have been developed to introduce halogen atoms into organic molecules. In this context, direct and regioselective C–H halogenation has been recognized as one of the most efficient tools to streamline complex halogenated synthesis molecules, particularly to nonactivated aliphatic C–H bonds. In the intramolecular halogenation field, numerous methods use a directing group inside the molecule to address a selective halogenation through 1,5- or 1,6-HAT (Figure 2.3).

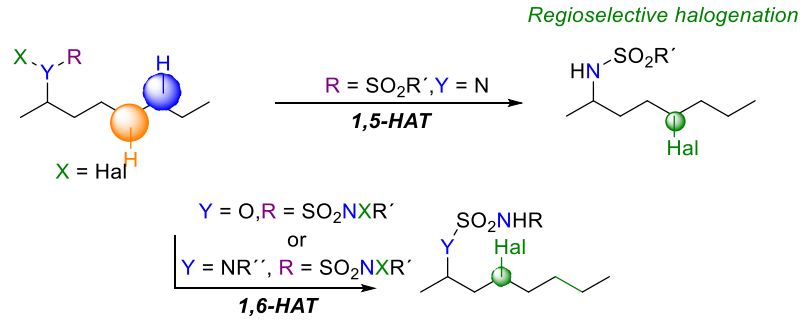
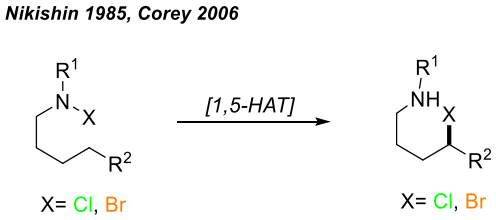


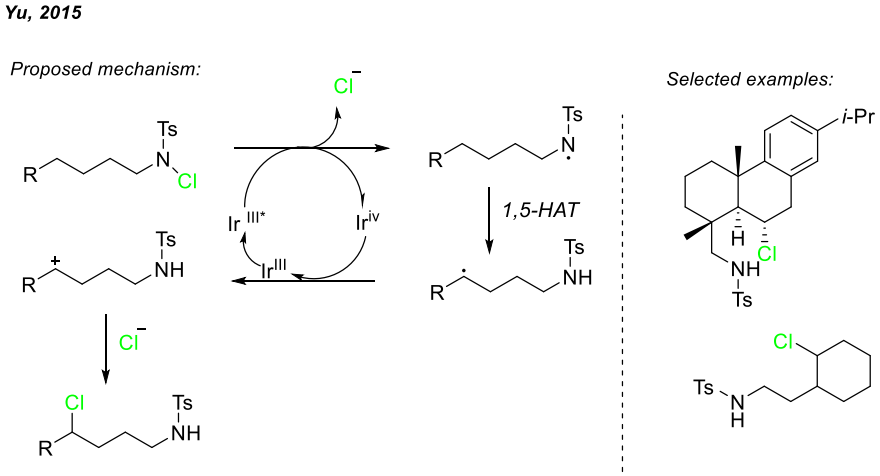
Figure 2.3. *Regioselective halogenation depending on the directing group.*

Nikishin reported the first regioselective chlorination using copper chloride and sodium persulfate (Scheme 2.1).[166] Corey discovered a similar outcome for the bromination of *N*-trifluoroacetyl-α-amino esters.[86] The mechanistic scenario is in agreement within the Hofmann-Löffler manifold, but in this case, the trifluoroacetamide is not nucleophilic enough to undergo a cyclization forming the pyrrolidine derivative, leading to the halogenation in a completely selective fashion.



Scheme 2.1. *General halogenation through 1,5-HAT.*

Yu reported a new method to access δ-chlorination using photoredox catalysis and starting from the preformed N–Cl amine (Scheme 2.2). For this variant, the N–Cl scission occurs under milder conditions than the previously described due to the use of an iridium photoredox catalyst under visible light irradiation. This transformation was applied for the late-stage Csp^3–H functionalization of complex and biologically important organic compounds.[167]

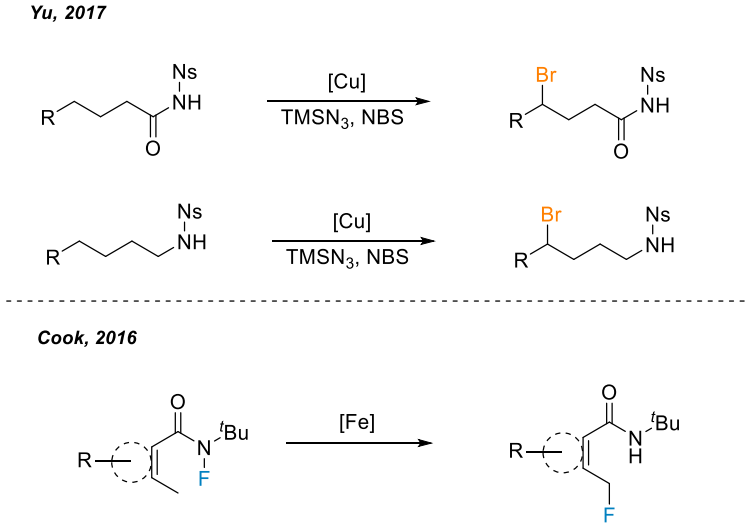


Scheme 2.2*. Visible-light promoted aliphatic chlorination.*

Some years later, Myers and Yu reported a copper-catalyzed bromination methodology to achieve a directed Csp^3–H bromination of aliphatic amines and

[166] G. I. Nikishin, E. I.Troyansky, M. I.Lazareva, *Tetrahedron Lett.* **1985**, *26*, 3743.
[167] Q. Qin, S. Yu, *Org. Lett.* **2015**, *17*, 1894.

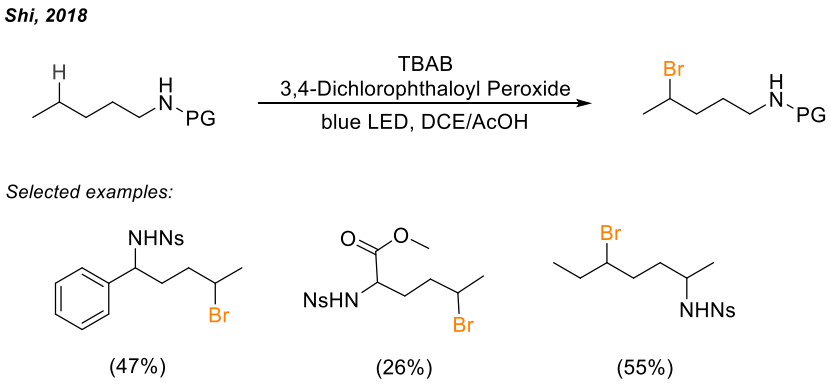
amides. The use of Me_3Si-N_3 combined with NBS allowed the amidyl radical generation that triggers the HAT event.[168] Moreover, a Fe-catalyzed δ-position selective fluorination for benzylic functionalization.[169] In this case, the preformation of the N–F bond was required (Scheme 2.3. Bottom).



Scheme 2.3. *Copper and iron remote Csp³-halogenation.*

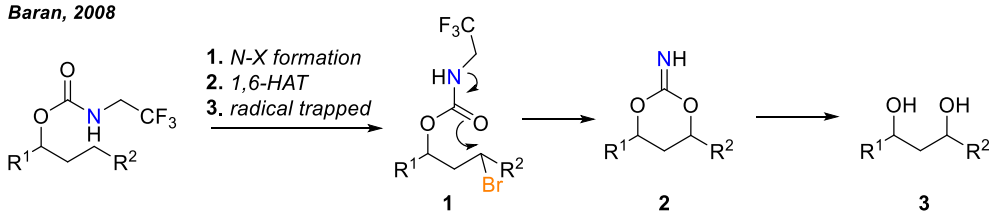
Shi and coworkers reported selective *N*-chlorination and aliphatic bromination.[170] This method uses cyclic diacyl peroxides with halide salts as halogenating sources leading to high selectivity and functional group tolerance (Scheme 2.4).

[168] T. Liu, M. C. Myers, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2017**, *56*, 306.
[169] B. J. Groendyke, D. I. Abusalim, S. P. Cook, *J. Am. Chem. Soc*. **2016**, *138*, 12771.
[170] D. Chang, R. Zhao, C. Wei, Y. Yao, Y. Liu, L. Shi, *J. Org. Chem.* **2018**, *83*, 3305.



Scheme 2.4. *Selected examples of bromination using 3,4-dichlorophthaloyl peroxide and TBAB as the halogenating source.*

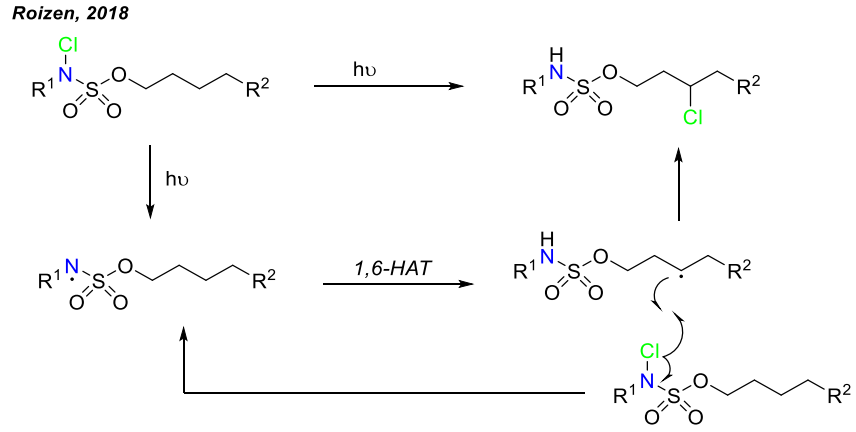
Baran was a pioneer in using the carbamates as directing groups, preferentially through a 1,6-HAT process (seven-membered transition state) to form 1,3 diols.[171] *N*-Trifluoroethyl substituted carbamates were crucial for this transformation. The first step is the bromination of this carbamate, followed by homolytic cleavage and 1,6-hydrogen atom transfer. Once the bromine is at that position, the alkyl bromide **1** is displaced, generating an amino carbamate **2**. This intermediate is hydrolyzed to unmask the 1,3-diol **3** (Scheme 2.5).



Scheme 2.5. *C–H halogenation of alcohol derivatives via N–Br homolysis.*

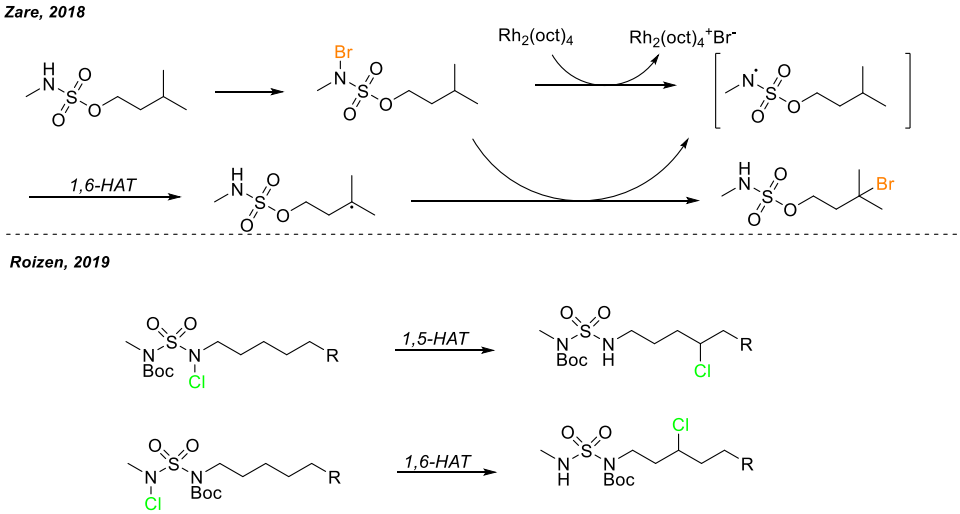
Roizen employed sulfamates esters as directing groups for selective secondary C–H chlorination.[172] Based on the behavior described by Du Bois for these sulfamates esters that prefer to evolve via 1,6-HAT, Roizen developed an aliphatic halogenation that is completely selective for secondary positions in the presence of tertiary ones (Scheme 2.6).[173] The authors reported that the seven-membered ring transition state is possible due to the elongation of the O–S and S–N bonds and compressed O–S–N bond angles, where the six-membered ring transition state is disfavored.[174]

[171] K. Chen, J. M. Richter, P. S. Baran, *J. Am. Chem. Soc*. **2008**, *130*, 7247.
[172] M. A. Short, J. M. Blackburn, J. L. Roizen, *Angew.Chem.Int. Ed.* **2018**, *57*, 296.
[173] C. G. Espino, P.M.Wehn, J. Chow, J. Du Bois, *J. Am. Chem. Soc*. **2001**, *123*, 6935.
[174] M. A. Short, J. M. Blackburn, J. L. Roizen, *Synlett* **2019**, *30*, 102.



Scheme 2.6. *Selective chlorination of aliphatic C–H bond.*

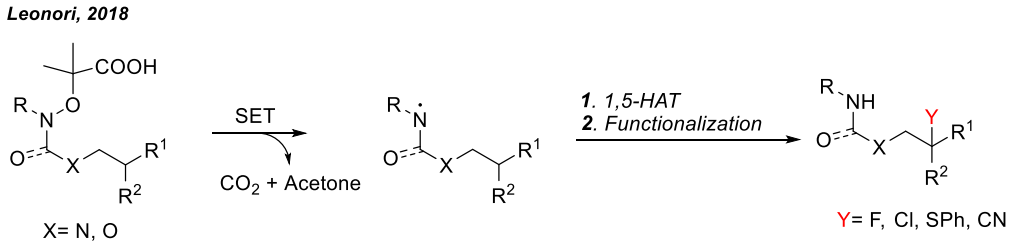
The use of sulfamates esters or sulfamides as directing groups for the C–H functionalization is currently an active growing topic. The groups of Zare[175] and Roizen[176] developed this strategy for C–H selective halogenation. In the protocol developed by Zare, rhodium metal complex as a radical initiator is required (Scheme 2.7. Top). Roizen demonstrated the dual reactivity of the sulfamides, leading to 1,5-HAT with *N*-chlorosulfamides, where the chlorine atom resides in the internal nitrogen, whereas 1,6-HAT was observed when the halogen is placed at the external nitrogen (Scheme 2.7. Bottom).



Scheme 2.7. *Top: Zare´s protocol for bromination through rhodium catalysis. Bottom: Dual reactivity of N-sulfamates esters.*

[175] S. Sathyamoorthi, S. Banerjee, J. Du Bois, N. Z. Burns, R. N. Zare, *Chem. Sci.*, **2018**, *9*, 100.
[176] M. A. Short, M. F. Shehata, M. A. Sanders, J. L. Roizen, *Chem. Sci.*, **2020**, *11*, 217.

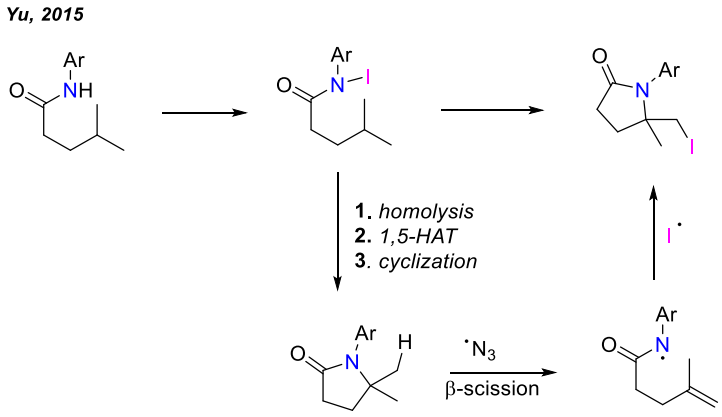
Roizen extended the use of sulfamate esters to introduce xanthate groups.[177] The same group also described the halogenation through 1,6-HAT to form *N*-substituted sulfamate esters.[178] On the other hand, the group of Leonori described and developed an interesting strategy for C–H chlorination and fluorination from amides, carbamates, and amines (Scheme 2.8).[179] This procedure involves a photocatalyzed single-electron-transfer process to generate the amidyl radical, followed by a 1,5-HAT event and further radical recombination with fluorine, chlorine, cyano, and alkyne electrophilic surrogates.



Scheme 2.8. *The mechanism for divergent functionalization of amides and amines.*

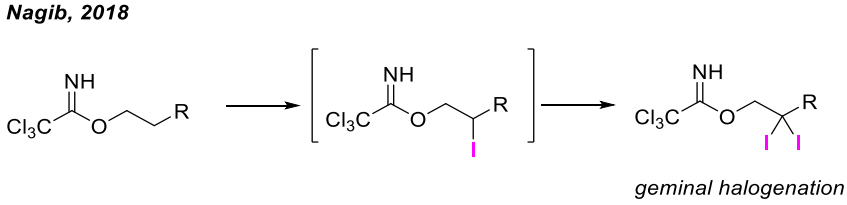
Along these lines, Yu applied a strategy to functionalize amidyl radicals by functionalization of γ and δ Csp^3–H bonds in a single cascade reaction to generate iodolactams from alkyl amides (Scheme 2.9).[180] The mechanism begins with the formation of the N–I intermediate by the use of NIS. Then, the 1,5-HAT and iodination on δ-position, followed by cyclization, leads to the lactam. The second reaction cascade consists in an azido radical-mediated β-scission of the just-formed C–N bond and the generation of the terminal alkene. Finally, a 5-*exo*-trig cyclization and trapping of the radical with iodine affords the iodo-lactams in excellent yields.

[177] S. K. Ayer, J. L. Roizen, *J. Org. Chem*. **2019**, *84*, 3508.
[178] J. M. Blackburn, M. A. Short, T. Castanheiro, S. K. Ayer, T. D. Muellers, J. L. Roizen, *Org. Lett.* **2017**, *19*, 6012.
[179] (a) E. M Dauncey, S. P Morcillo, J. J Douglas, N. S Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2018**, *57*, 744. (b) S. P. Morcillo, E. M. Dauncey, J. Kim, J. J. Douglas, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2018**, 57, 12945.
[180] T. Liu, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 5871.



Scheme 2.9. *γ and δ-functionalization*

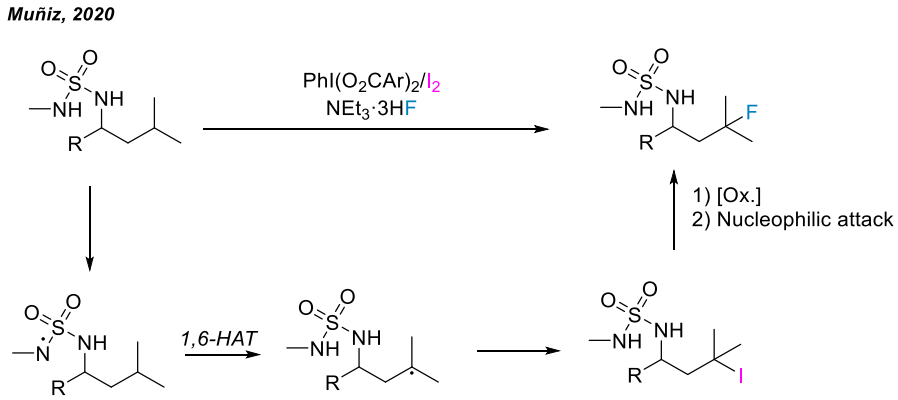
Nagib discovered a synthetic access to the formation of geminal di-halides assisted by a 1,5-HAT mechanism via an imidate radical.[181] To develop this protocol, the authors employed imidates as readily accessible radical precursors. The reaction begins with the formation of the weak Nsp^2–I bond, which undergoes rapid homolytic cleavage by visible light, followed by a 1,5-HAT process. The resulting intermediate compounds underwent a second process to generate the geminal dihalogenated compounds (Scheme 2.10).



Scheme 2.10. *Imidate radical-based 1,5-HAT event for multiple halogenation.*

An interesting result was reported by the group of Muñiz in 2020, allowing direct nucleophilic fluorination through 1,5- and 1,6-HAT processes.[182] For this protocol, the use of sulfamides and sulfonamides led to the fluorinated compounds with high regioselectivity. The transformation employs ammonium fluoride as a fluorine source facilitated by iodine-based catalysis (Scheme 2.11).

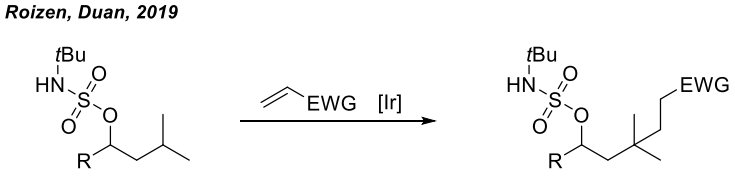
[181] E. A. Wappes, A. Vanitcha, D. A. Nagib, *Chem. Sci.*, **2018**, *9*, 4500.
[182] D. Bafaluy, Z. Georgieva, K. Muñiz, *Angew. Chem. Int. Ed.* **2020**, *59*, 14241.



Scheme 2.11. *Iodine-catalyzed nucleophilic fluorination.*

1.4. Remote C–H functionalization via Selective HAT process

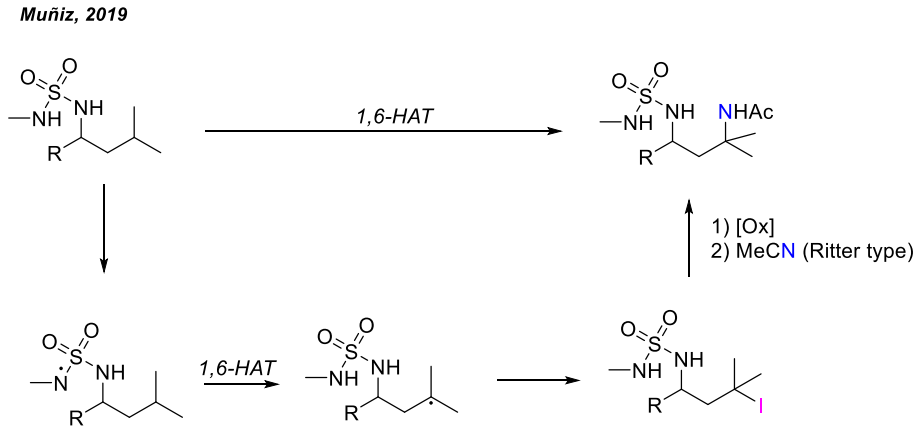
As it was previously mentioned, the regioselective functionalization through 1,5- and 1,6-HAT allowed the intramolecular amination and halogenation. Other types of functionalization are relevant because they lead to the formation of C–C, C–Ar, and C–X bonds with high regioselectivities. Roizen[183] and Duan[184] reported the C–C bond formation by visible-light-driven alkylation enabled by 1,6-HAT (Scheme 2.12). The mechanism of these transformations involves the use of an iridium complex as a photoredox catalyst for the formation of the sulfamyl radical. A similar strategy was described by Huang for a selective alkylation through a 1,6-HAT process.[185]



Scheme 2.12. *Sulfamyl radicals direct photoredox-mediated alkylation of Csp^3–H bonds.*

Regarding the use of sulfamyl radical for C–H functionalization, an important example of a Ritter-type amination was described by the group of Muñiz.[186] Notably, the intermolecular amination occurs faster than the intermolecular one, and the sulfamide behaves as a nontransferable directing group (Scheme 2.13).

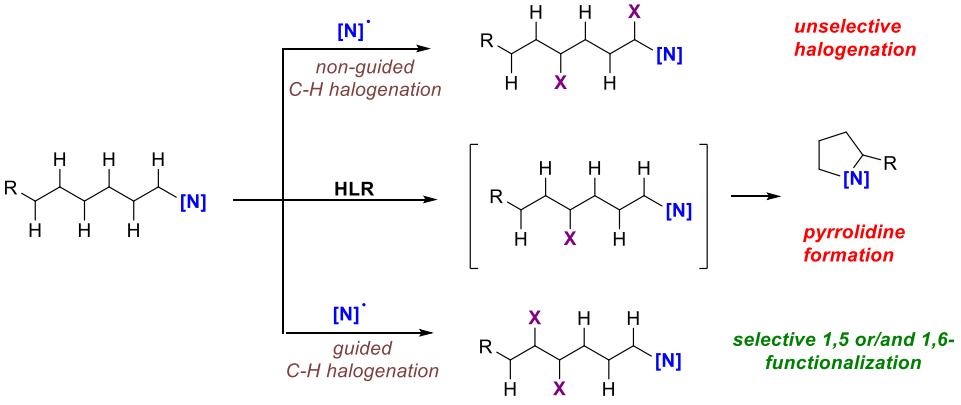
[183] A. L. G. Kanegusuku, T. Castanheiro, S. K. Ayer, J. L. Roizen, *Org. Lett.* **2019**, *21*, 6089.
[184] Z.-Y. Ma, L.-N. Guo, Y. You, F. Yang, M. Hu, X.-H Duan, *Org. Lett.* **2019**, *21*, 5500.
[185] W. Shu, H. Zhang, Y. Huang, *Org. Lett.* **2019**, *21*, 6107.
[186] T. Duhamel, M. D. Martínez, I. K. Sideri, K. Muñiz, *ACS Catal.* **2019**, *9*, 7741.



Scheme 2.13. *Guided Ritter-type amination through the 1,6-HAT process.*

2. Results and Discussion

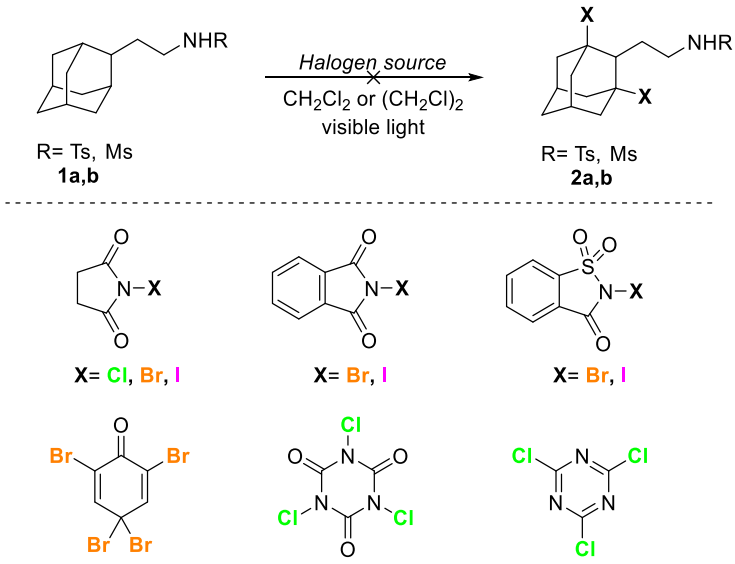
A general synthetic solution for the multiple and selective Csp^3–H halogenation is not available. Based on the previous works on selective aliphatic halogenation, a possible approach could be the use of a suitable directing group that would allow multiple and regioselective halogenation events. To address this synthetic challenge, the *in-situ* generation of amidyl radicals could be an alternative. In principle, the desired C–H halogenation will be regioselective following the 1,5- or 1,6-HAT process. The Hofmann-Löffler reaction starts with the homolytic cleavage of the N–X bond, and the transformation finishes with the nucleophilic amination affording the pyrrolidine product. In this case, we will stop the process before the last step by introducing a halogen at that position. (Scheme 2.14. Bottom)



Scheme 2.14*. Comparison between possible scenarios, a) unselective halogenation through the free-radical mechanism, b) pyrrolidine formation, c) guided halogenation by using the directing group.*

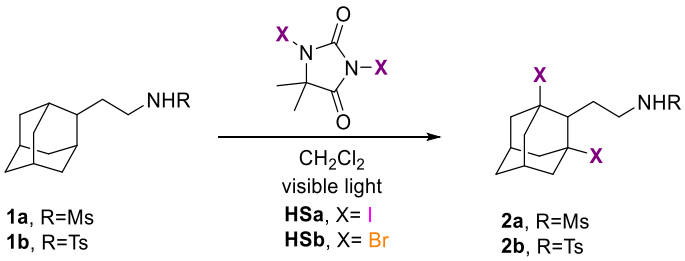
Halogen sources

Our studies started by exploring different halogen sources with the 2-adamantane derivatives **1a**,**b** as model substrates, which contain several tertiary C–H bonds in their structure. We choose this moiety as it is a rigid structure that possesses several bonds with comparable bond dissociation energies. We were looking for a guided multiple halogenation process where only the desired positions are functionalized, leaving the others untouched. Unfortunately, the employment of common halogen sources provided only complex unidentifiable product mixtures (Scheme 2.15).



Scheme 2.15. *Unsuccessful halogen sources for regioselective halogenation.*

Finally, after several optimization trials, we chose halohydantoin as the halogen source (**HS**) for selective functionalization of **1a**,**b** (Scheme 2.16). We chose dichloromethane as an appropriate solvent for the transformation and the reaction time depends on the substrate. This transformation employs halogenated hydantoins as electrophilic halogen sources that generate *in situ* the required N–X species, which are the precursors to the *N*-centered radicals by homolytic cleavage under visible light.



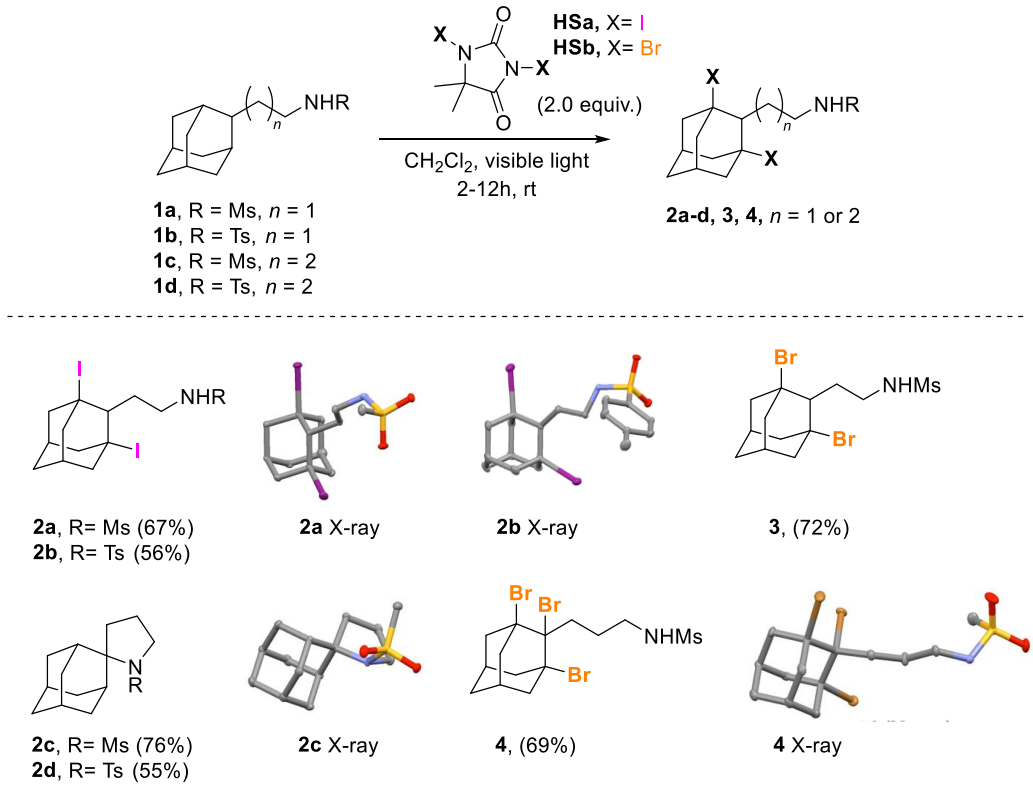
***Scheme 2.16**. A general outline of adamantane core halogenations.*

In the Hofmann-Löffler reaction, the C–H amination usually generates the heterocyclic product. In this case, the main objective was to find a protecting group for the nitrogen that remains intact during the amination step to re-engage the C–H halogenation. For this purpose, we synthesized several adamantane derivatives. To achieve this regioselectivity, we chose sulfonamides as directing groups since, as mentioned before, these groups promote the 1,5-HAT process through the six-member ring transition state installing the halogen at the δ-position.

The reaction outcome depends on the length of the alkyl chain spacer, and the optimal conditions include the use of 2.0 equiv of **HSa,b** in dichloromethane for a period of 2-12 h at room temperature under visible light (Scheme 2.17). Dihalogenated compounds **2a**,**b,** and **3** were observed, demonstrating that the transformation proceeds through the Hofmann-Löffler reaction innate pathway. The structure of **2a** was confirmed by X-ray diffraction. A lower yield was obtained for the tosyl derivative **2b**.

In contrast, the homologous propylenylamides derivatives **1c**,**d** provided a fast cyclization after the initial iodination, leading to the selective formation of the pyrrolidine products **2c**,**d**. In these cases, the selective halogenation took place in the δ-position. In these cases, nucleophilic amination occurs faster than the second halogenation. Tribrominated compound **4** was obtained from **1c** by sequential 1,5- and 1,6-HAT processes.

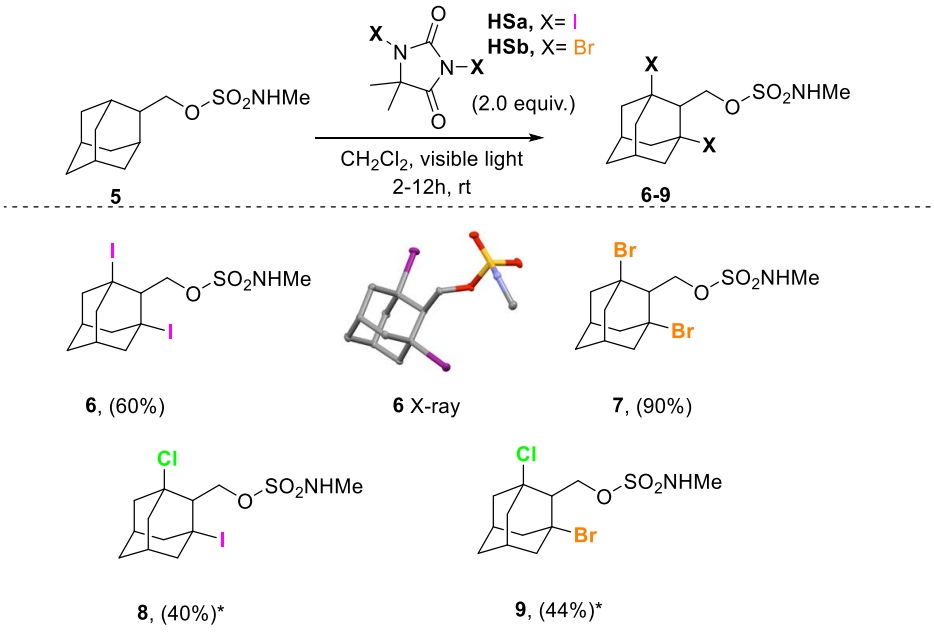
These results show that the free radical halogenation does not occur in any of these substrates, representing one of the first examples of introducing several halogens in a target molecule by a Hofmann-Löffler reaction.



Scheme 2.17. *Multiple selective halogenation on adamantane derivatives.*

We then turned our attention to sulfamates esters as directing groups. As Du Bois described in 2009, the expected reactivity of these groups is the formation of the amidyl radical, followed by the exclusive 1,6-HAT.[58] As reported in the literature, these directing groups usually need transition metals as initiators.[187] In our conditions, the reaction starts under visible light exclusively. To our delight, using the sulfamates esters as directing groups, only selective halogenation was observed, leading to the formation of the diiodinated and dibrominated compounds **6** and **7** (Scheme 2.18).

[187] M. A. Short, J. M. Blackburn, J. L. Roizen, *Synlett*, **2020**, *31*, 102.

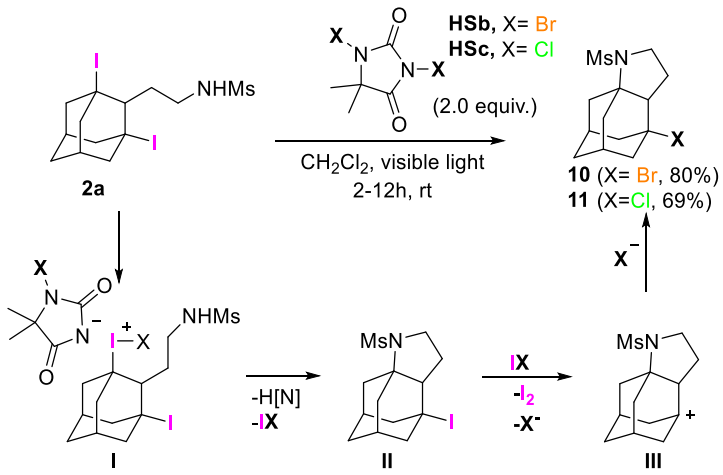


Scheme 2.18. *Sulfamates esters as directing groups for C–H halogenation.*

Based on the results reported by Roizen for the monochlorination of sulfamates esters,[172,] we decided to expand our scope using the adamantane core to introduce two different halogen atoms. Thus, first, we introduced a chlorine atom following the same procedure as Roizen. Subsequently, reaction with the halogenated hydantoins led to compounds **8** and **9** in moderate yields for the two steps.

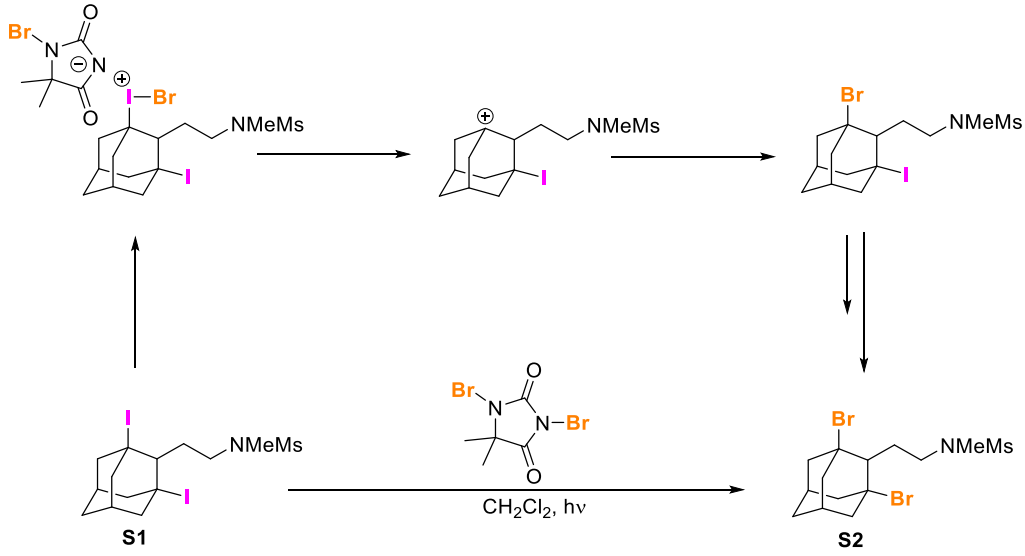
Attempts to produce such compounds through alternative halogen exchange reactions did not meet with success. For example, upon mixing the diiodinated compound **2a** with hydantoins **HSb**,**c** exchange of halogens followed by the pyrrolidine formation was observed, leading to compounds **10** and **11**, respectively (Scheme 2.19). This outcome is in agreement with halide exchange reactions promoted by alkyl iodine(III) species.[188]

[188] (a) F. M. Beringer, H. S. Schultz, *J. Am. Chem. Soc.* **1955**, *77*, 5533. (b) A. G. Yurchenko, N. I. Kulik, V. P. Kuchar, V. M. Djakovkaja, V. F. Baklan, *Tetrahedron Lett.* **1986**, *27*, 1399.



Scheme 2.19. *Halogen-exchange in the adamantane core.*

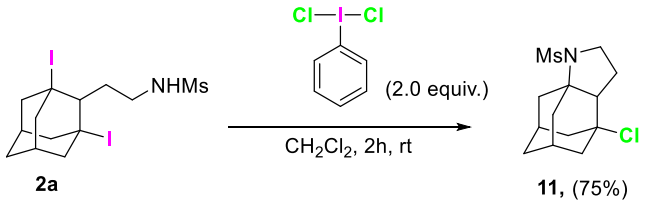
In the case of the sulfonamide, we noticed that amidyl radical was not involved in the transformation. To demonstrate this, a control experiment was carried out in the same conditions with the methylated compound of **2a** generating compound **S1,** which confirmed this hypothesis. When the formation of the amidyl radical is blocked, a double halogen exchange was achieved under standard conditions, providing the dibrominated compound **S2** (Scheme 2.20).



Scheme 2.20. *Control experiment of halogen-exchange in the adamantane core.*

A second control experiment confirmed this event by oxidation of the alkyl iodide to form the iodine(III) species **I**, generating a good leaving group for pyrrolidine formation, followed by a second halogen exchange and generation of

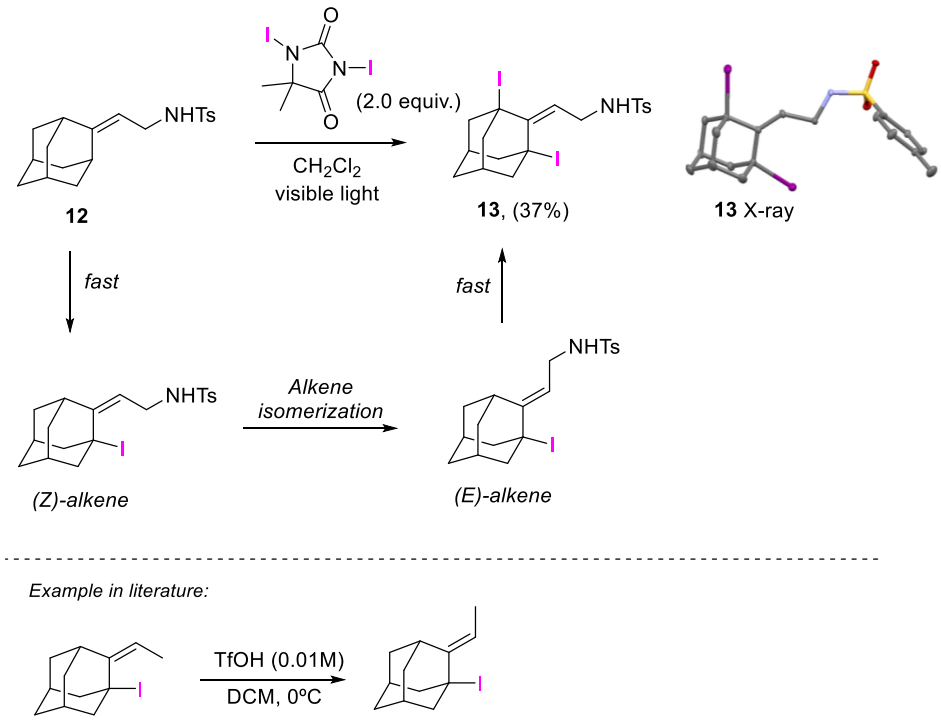
IX, which would initiate the iodine extrusion to form carbocation **III** in Scheme 2.19 and subsequent nucleophilic halogenation. To demonstrate the importance of the oxidation step in this transformation, we performed a reaction employing standard iodobenzene dichloride as oxidant generating compound **11** in good yield (Scheme 2.21). This result supports the discussed cationic exchange pathway from Scheme 2.19.



Scheme. 2.21. *Iodine (III) mediated halogen exchange.*

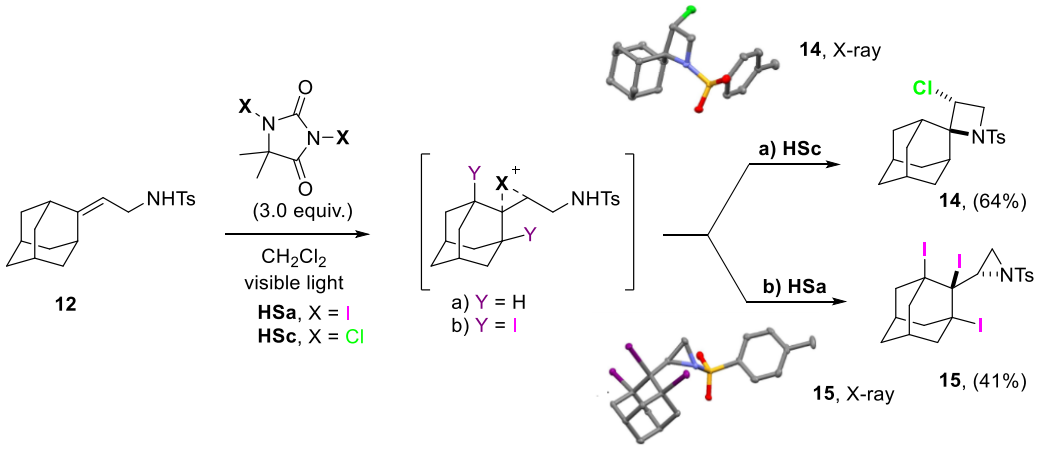
An interesting result was obtained by using these standard conditions with unsaturated substrate **12** (Scheme 2.22.). A remarkable dihalogenation was observed leading to **13**, leaving the double bond untouched. The structure of **13** was confirmed by X-ray diffraction. Mechanistically, a sequence of two Hofmann-Löffler reactions may be involved. The first iodination proceeded readily through Hofmann-Löffler-type iodination, followed by the double bond isomerization under the reaction conditions and by a second 1,5-HAT and halogenation, providing compound **13** (Scheme 2.22. Top). According to literature precedence on related adamantyl alkene derivatives (Scheme 2.22. Bottom),[189] the alkene isomerization proceeds readily in the presence of traces of acid.

[189] Y. Ohga, K. Takeuchi, *J. Phys. Org. Chem.* **1993**, *6*, 293.



Scheme 2.22. *Double 1,5-HAT via double bond isomerization.*

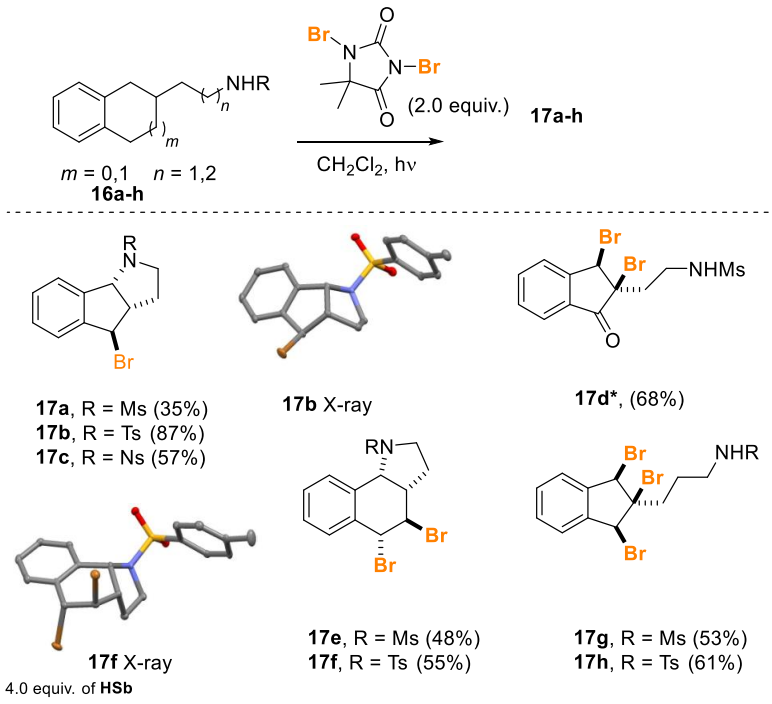
When we treated compound **12** with an excess of chloro- and iodohydantoins, we also observed the electrophilic addition to the alkene forming the corresponding chloronium or iodonium ions, which upon nucleophilic amination leads to products **14** and **15**, respectively. Clean four-membered ring formation occurred in the case of **14**, whereas the more sterically hindered diiodinated intermediate led to aziridine derivative **15** (Scheme 2.23).



***Scheme 2.23**. HAT process and electrophilic addition to the double bond.*

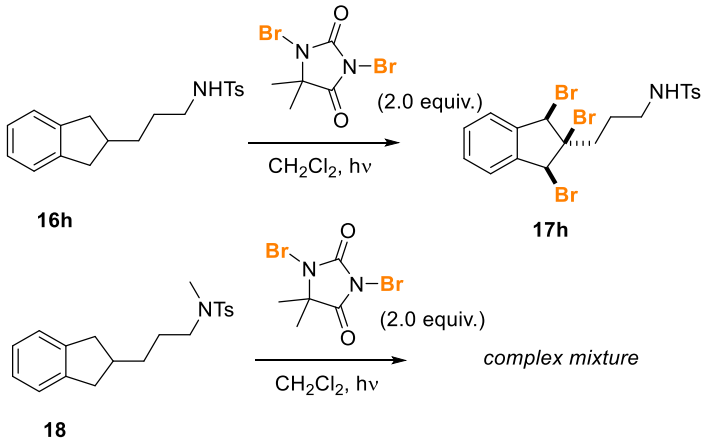
After these promising results for the adamantane core, we decided to expand the methodology for less rigid structures. Due to the noted higher stability in the brominated adamantyl derivatives and the interest in brominated organic compounds as synthons, polybromination was further explored.

We started testing the indane and tetrahydronaphtalene derivatives **16a-h**. The 2-ethylenylamides derivatives **16a-c** underwent two sequential 1,5-HAT processes followed by cyclization, leading to the pyrrolidine products **17a-c** in a totally diastereoselective fashion. Similar behavior was observed in the tetrahydronaphthalene substrates **16e,f**, which underwent selective halogenation through a 1,6-HAT process leading to compounds **17e,f**. The formation of the dibrominated ketone **17d** was observed using an excess of bromo hydantoin, giving rise to the carbonyl derivative after hydrolysis of the geminal dibromo motif. Moreover, when we increased the alkyl chain length, tribrominated compounds **17g,h** were obtained using mesyl and tosyl as directing groups (Scheme 2.24).



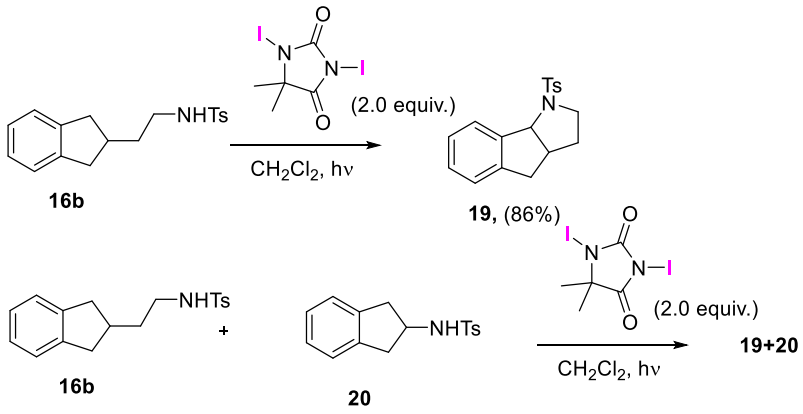
Scheme 2.24. *Multiple bromination through HAT processes in cyclic derivatives.*

To clarify the selectivity of the halogenated compounds obtained previously, we performed a control experiment using the methylated substrate **18**, synthesized from **16h**. When this substrate was submitted under the same reaction conditions for the selective bromination, a complex mixture was obtained (Scheme 2.25. Bottom). The benzylic bromination oxidation was not observed, demonstrating that the free-radical mechanism does not take place under these conditions.



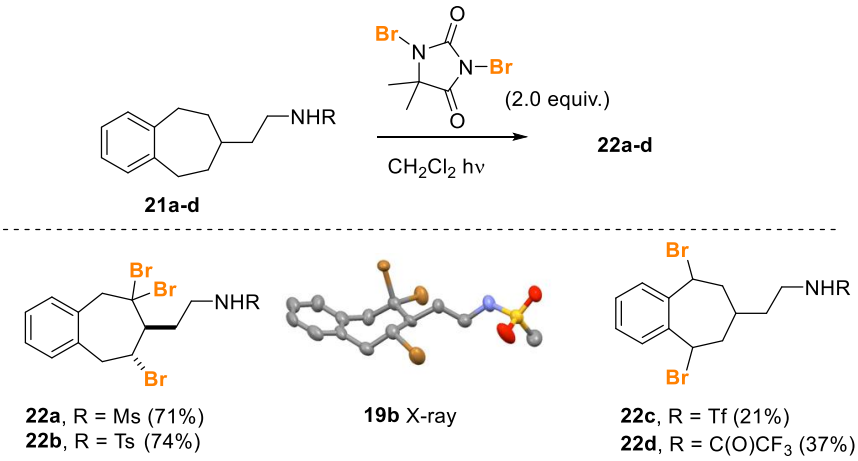
Scheme 2.25. *A control experiment with secondary vs. tertiary sulfonamide as a substrate*.

A second control experiment was also carried out. When compound **16b** was treated with iodohydantoin, only the cyclized product **19** was observed (Scheme 2.26). No benzylic iodination took place, and fast cyclization occurred before the possible second 1,5-HAT. Furthermore, the same result was observed in a competition control experiment between **16b** and **20**. When we submitted the mixture of both compounds to the reaction, we observed the formation of pyrrolidine **19,** whereas compound **20** remained untouched (Scheme 2.26. Bottom).



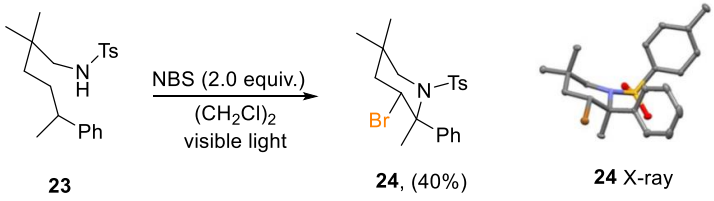
Scheme 2.26. *Control experiment 2. Possible benzylic iodination from the free-radical mechanism***.**

Further expansion of this method to other cyclic substrates was carried out. Starting from tosyl and mesyl derivatives **21a** and **21b**, the tribrominated compounds **22a** and **22b** were isolated (Scheme 2.27. Left). On the other hand, moving to trifluoroacetamide and triflamide directing groups, benzylic bromination was observed. In this case, the free-radical halogenation occurred due to the lower stabilization of the amidyl radical, which did not promote the 1,5-HAT process (Scheme 2.27. Right).



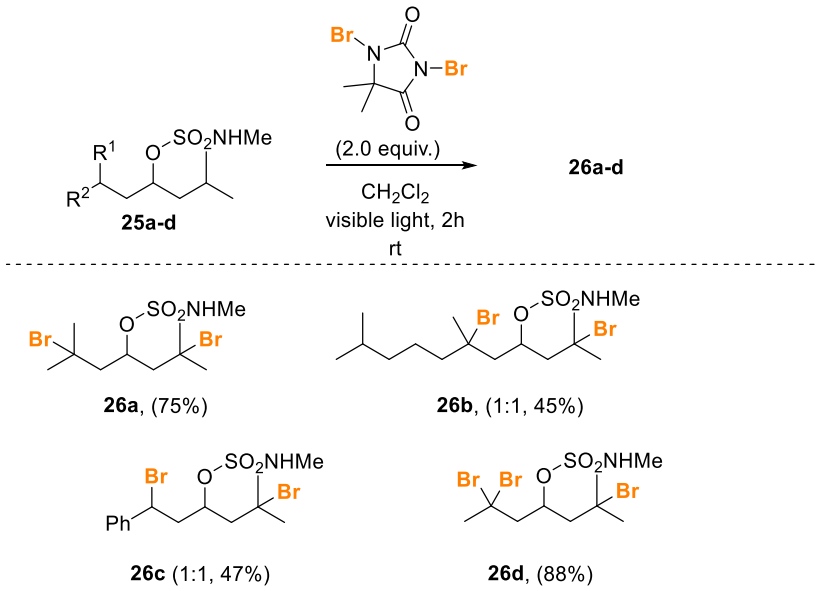
Scheme 2.27. *Comparison regioselective halogenation vs. free radical halogenation.*

Finally, we decided to apply this methodology for acyclic substrates. First, we tested several acyclic sulfonamides to investigate the reactivity under these conditions. Compound **23** gave the brominated six-membered ring derivative **24** after a sequential 1,5- and 1,6-HAT processes, followed by nucleophilic amination at the benzylic position (Scheme 2.28). We confirmed the structure of **24** by X-ray diffraction.



Scheme 2.28. *Acyclic substrates for selective bromination using sulfonamide.*

Furthermore, we investigated the use of *N*-sulfamates esters as directing groups to promote the 1,6-HAT exclusively. We were delighted to note that this protocol could be applied for bromination at benzylic, tertiary, and secondary aliphatic positions generating compounds **26a-d** in moderate to good yields (Scheme 2.29). Remarkably, we tested compound **25b**, which has several tertiary positions, and those accessible to the directing group were brominated, leaving the other positions untouched, generating **26b**.



Scheme 2.29. *Acyclic substrates for selective bromination.*

3. Conclusion

Although multiple aliphatic halogenations are almost unknown in the literature, a new protocol, which shows the broad scope, has been developed, providing access to complex polyhalogenated substrates in a selective manner.

This pioneering methodology could be applied for the synthesis of halogenated natural products.[190]

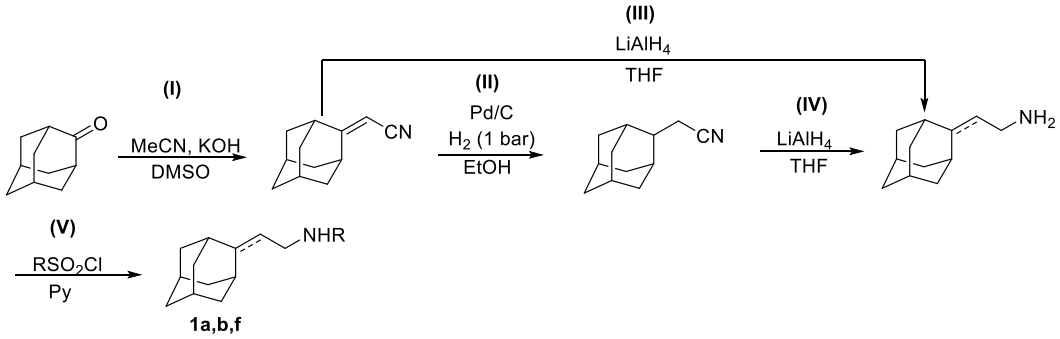
[190] W.-J. Chung, C. D. Vanderwal, *Angew. Chem. Int. Ed*. **2016**, *55*, 4396.

4. Experimental section

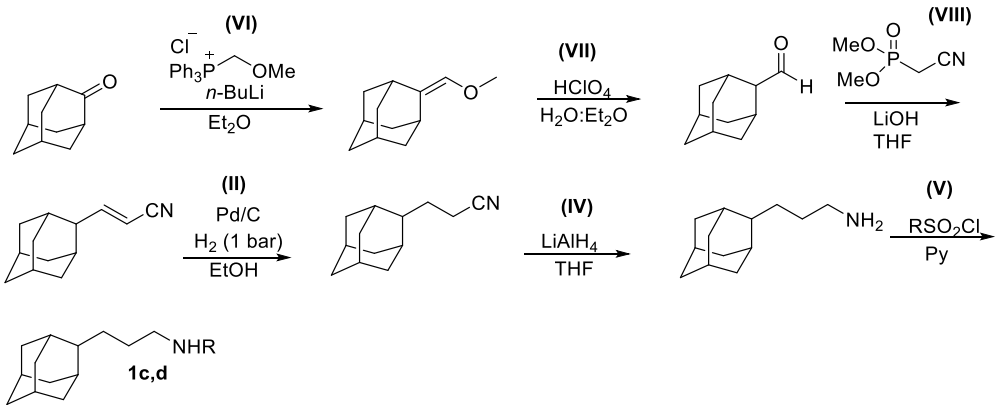
All solvents (including deuterated ones) were commercially available and were used as received. Column chromatography was performed with silica gel (type 60, 0.063-0.2 mm). NMR spectra were recorded on a 300, 400 MHz, or 500 MHz spectrometer, with reference to ^{1}H. All chemical shifts in NMR experiments were reported as ppm downfield from TMS. The following calibrations were used: $CDCl_3$ $\delta = 7.26$ and 77.16 ppm. HRMS were recorded using ESI-TOF techniques. IR spectra were taken in the solid-state. The following compounds are commercially available and were used as received: tosyl chloride, mesyl chloride, triethylamine, lithium hydroxide, sodium azide, *n*-butyl lithium solution (2 M in cyclohexane), palladium on charcoal (10% w/w), potassium cyanate, triflic anhydride, trifluoroacetic anhydride, potassium hydroxide, trimethyl phosphonoacetate, dimethylcyanomethylphosphonate, 1,3-diiodo-5,5-dimethylhydantoin, 1,3-dibromo-5,5-dimethylhydantoin and 1,3-dichloro-5,5-dimethylhydantoin.

The following starting materials were synthesized according to literature procedures: **17b**[90], **17f**[90], **17h**[90,] and **25**[95].

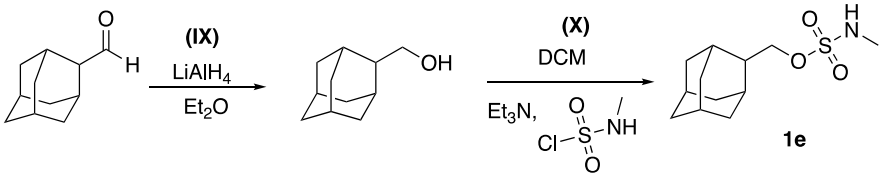
Procedures for starting materials:



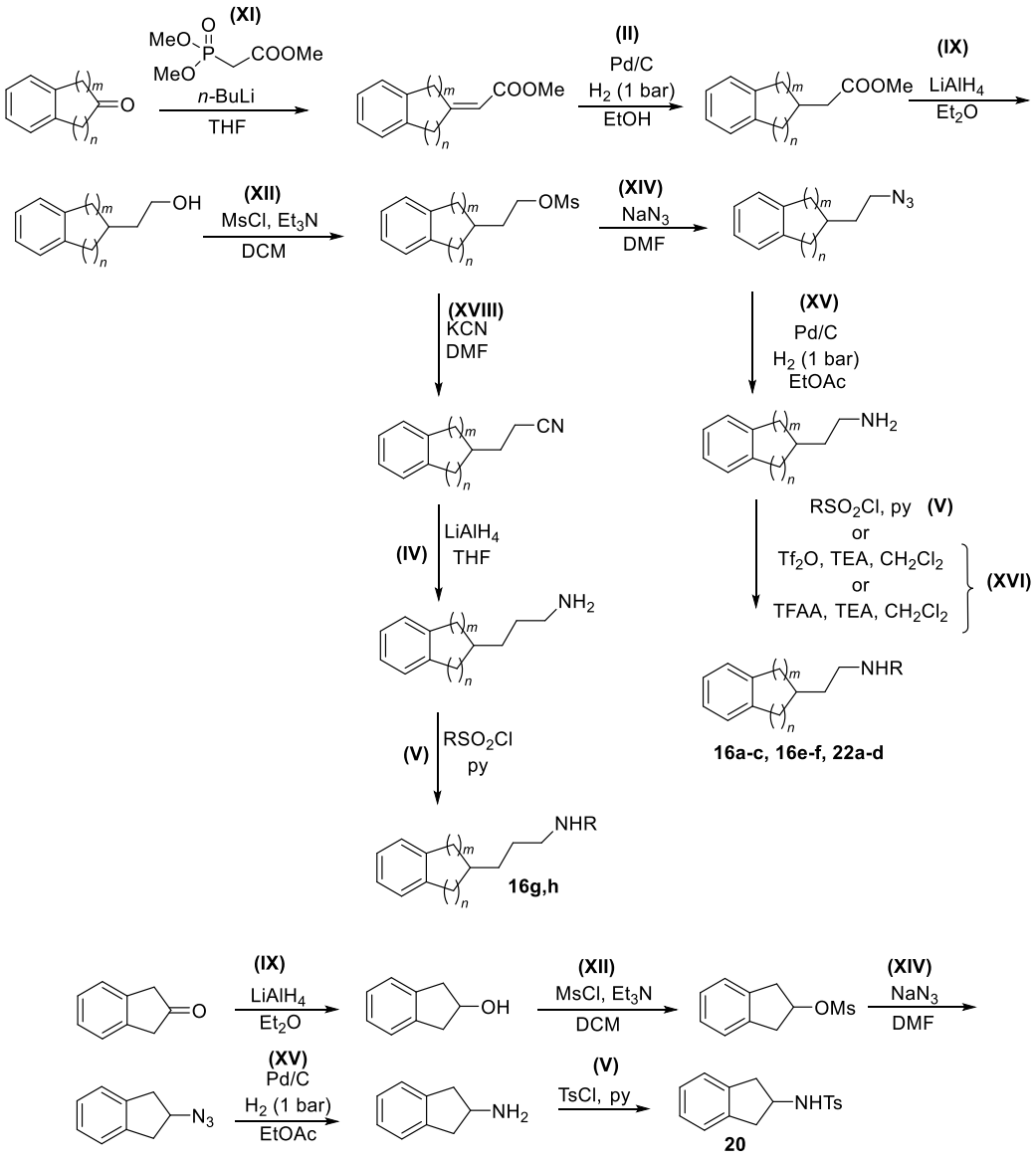
Scheme 2.30. *Synthetic route for compounds* ***1a-b*** *and* ***1f****.*



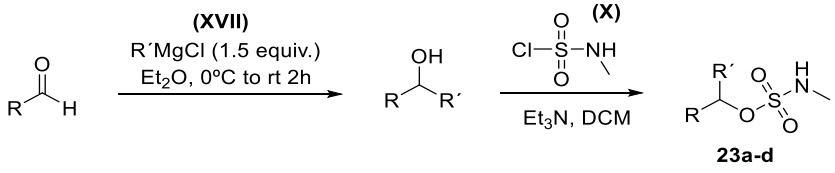
Scheme 2.31. *Synthetic route for compounds* ***1c-d****.*



Scheme 2.32. *Synthetic route for compound* ***5****.*



Scheme 2.33. *Synthetic route for compounds* ***16a-c***, ***16e-h, 22a-d***, *and* ***20***.



Scheme 2.34. *Synthetic route for compounds* ***23a-d***.

Step I. A round-bottomed flask equipped with a magnetic stirrer was charged with the ketone (1.0 equiv) and acetonitrile (1.5 equiv), then granulated KOH (3.0 equiv) in DMSO (0.3 mL/mmol) was added. The mixture was refluxed under stirring for 10 h. After the reaction was completed, water was added, and the mixture was cooled. The solid phase was filtered off and used directly in the following step.

Step II. A Schlenk flask equipped with a stirrer bar was charged with the corresponding α,β-unsaturated compound, Pd/C (20 % w/w) and EtOH or EtOAc (5 mL/mmol). The reaction was stirred under an atmosphere of dihydrogen for 12 h using a gas balloon. The mixture was filtered through a pad of Celite and concentrated under reduced pressure to yield the crude ester, which was used in the further step.

Step III. A flame-dried Schlenk equipped with a stirrer bar was charged with $LiAlH_4$ (2 equiv), anhydrous THF was added carefully, and the mixture was cooled to 0 ºC. The corresponding nitrile (1 equiv) was added drop-wise to the $LiAlH_4$/THF suspension under argon atmosphere. The mixture was stirred at room temperature for 2 h and then cooled to 0 ºC. A solution of NaOH (1 M) was added. After filtration over Na_2SO_4 and evaporation of the solvent under reduced pressure, the crude amine was obtained in quantitative yield and was directly used in the following step.

Step IV. A flame-dried Schlenk equipped with a stirrer bar and a reflux condenser was charged with $LiAlH_4$ (2 equiv), anhydrous THF was added carefully, and the mixture was cooled to 0 ºC. The corresponding nitrile (1 equiv) was added drop-wise to the $LiAlH_4$/THF suspension under an argon atmosphere. The mixture was then heated to reflux for 2 h and cooled to 0 ºC. A solution of NaOH (1 M) was added. After filtration over Na_2SO_4 and evaporation of the solvent under reduced pressure, the crude amine was obtained in quantitative yield and was directly used in the following step.

Step V. To a solution of the corresponding crude amine in pyridine (5 mL/mmol) the respective sulfonyl chloride was added (1.6 equiv), and the mixture was stirred at room temperature for 18 h. After that, the reaction mixture was quenched with HCl (1 M) and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using a gradient of ethyl acetate and hexane.

Step VI. A round-bottomed flask equipped with a magnetic stirrer was charged with methoxymethyltriphenylphosphonium chloride (1.0 equiv). After purging with nitrogen, dry Et_2O was added (5 mL/mmol). The flask was cooled to 0 °C,

and *n*-BuLi (2.0 M solution in cyclohexane, 1.3 equiv) was slowly injected by syringe over 5 min. The scarlet-red suspension was stirred for 1 h under a nitrogen atmosphere. In another round-bottom flask, the corresponding ketone was dissolved in dry Et_2O (2 mL/mmol) and added drop-wise to the separately prepared mixture via a double-ended needle. The mixture was stirred at room temperature for 15 h. After that, the obtained solution was vigorously stirred, while anhydrous zinc chloride (1.5 equiv) was added to precipitate the triphenylphosphine oxide. The ether layer was decanted, recovered, and evaporated under reduced pressure to yield the enol ether that was used in the following step without further purification.

Step VII. The enol ether was dissolved in Et_2O (1 mL/mmol). Perchloric acid (70 %v/v, 1.0 equiv) and water (0.1 mL/mmol) were added, and the mixture was refluxed for 1 h. After that, the mixture was poured into water; the organic layer was separated, washed with water, and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield the aldehyde, which was used without purification in the following step.

Step VIII. A round-bottomed flask equipped with a magnetic stirrer was charged with dry THF, and LiOH (1.1 equiv) and dimethyl cyanomethylphosphonate (1.2 equiv) were added successively. The reaction was stirred for 30 min at 70 ºC, after which the aldehyde (1.0 equiv) was added, and the mixture was stirred for 18 h at room temperature. After that, a solution of HCl (1 M in water) was added, and the resulting mixture was extracted with Et_2O (3x). The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was filtered through a silica pad and was used without further purification.

Step IX. A flame-dried Schlenk equipped with a stirrer bar and a reflux condenser was charged with $LiAlH_4$ (2 equiv), Et_2O is added carefully, and the mixture was cooled to 0 ºC. The aldehyde (1 equiv) was added to the $LiAlH_4/Et_2O$ suspension under argon atmosphere. The mixture was heated to reflux for 2 h and cooled to 0 ºC afterward. A solution of NaOH (1 M in water) was added. After filtration over Na_2SO_4 and evaporation of the solvent under reduced pressure, the crude alcohol was obtained in quantitative yield and was used in the following step.

Step X. Compound **5** and **23a-e** were synthesized following a previously described procedure.[175]

Step XI. A flame-dried Schlenk tube equipped with a stirrer bar was charged with the trimethylphosphonium acetate (1.0 equiv) and THF (5 mL/mmol). The mixture was cooled to 0 ºC, and *n*-BuLi (2.0 M solution in cyclohexane, 1.0

equiv) was added drop-wise under an argon atmosphere. The reaction mixture was stirred for 1 h, and then the ketone (1.0 equiv) was added, and the mixture was finally stirred for 18 h at room temperature. A saturated aqueous solution of NH_4Cl was added, and the resulting mixture was extracted with Et_2O (3x). The organic layer was dried over Na_2SO_4, and the solvents were evaporated under reduced pressure. The crude product was filtered through a silica pad and was used without further purification.

Step XII. A flame-dried Schlenk tube equipped with a stirrer bar was charged with crude alcohol (1.0 equiv) and dichloromethane (5 mL/mmol), and the vessel was cooled to 0 ºC. Triethylamine (2.0 equiv) and mesyl chloride (2.0 equiv) were added, and the reaction was stirred overnight at room temperature under argon atmosphere. The reaction mixture was quenched with HCl (1 M in water) and extracted with dichloromethane (3x). The combined organic layers were washed with water, a saturated aqueous solution of $NaHCO_3$ and brine sequentially, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to yield the crude mesylate.

Step XIII. A Schlenk flask equipped with a stirrer bar was charged with the corresponding mesylate (1.0 equiv) in DMF (5 mL/mmol), then was added potassium cyanide (3.0 equiv). The mixture was stirred at 70 ºC for 18 h. The reaction mixture was quenched with NaOH (2 M) and extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was obtained in quantitative yield and was directly used in the following step.

Step XIV. A flamed-dried Schlenk flask equipped with a stirrer bar was charged with the crude mesylate (1.0 equiv), dimethylformamide (5 mL/mmol), and sodium azide (1.5 equiv) under argon atmosphere. The reaction mixture was stirred overnight at 90 ºC. Water was added, and the resulting mixture was extracted with Et_2O (3x). The combined organic layers were washed with a saturated aqueous solution of sodium acetate and with water. They were dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to yield the crude azide.

Step XV. A Schlenk flask equipped with a stirrer bar was charged with the corresponding crude azide, Pd/C (20 %w/w), and ethyl acetate (5 mL/mmol). The reaction was stirred under a dihydrogen atmosphere for 12 h using a gas balloon. The mixture was filtered through a pad of Celite and concentrated under reduced pressure to yield the crude amine.

Step XVI. To a solution of the corresponding crude amine in DCM (5 mL/mmol), triethylamine (3.0 equiv) and triflic anhydride (3.0 equiv) or trifluoroacetic

anhydride (3.0 equiv) was added, and the mixture was stirred at room temperature. After 18 h, the reaction mixture was quenched with HCl (1 M in water) and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography using a gradient of ethyl acetate and hexane.

Step XVII. To a solution of the aldehyde in Et_2O (5 mL/mmol) at 0ºC was added Grignard reagent (2-3 M in Et_2O or THF, 1.1 equiv) dropwise over 15 min. Then, the mixture was allowed to reach room temperature for 2h. The reaction mixture was quenched by the slow addition of NH_4Cl and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was obtained in quantitative yield and was directly used in the following step.

General procedure for polyhalogenation reactions (GPP)

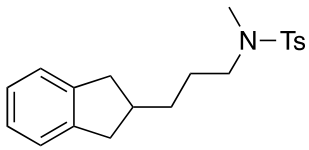
A flame-dried and argon backfilled Schlenk tube equipped with a stirrer bar was charged with the corresponding starting material (0.20 mmol, 1.0 equiv). Anhydrous dichloromethane (4 mL) and the corresponding 1,3-dihalo-5,5-dimethylhydantoins (**HSa-c,** a=iodo, b=bromo, c=chloro) (0.4 mmol, 2.0 equiv) were added. The reaction mixture was stirred at room temperature under light exposure until the complete conversion of the starting material was observed (followed by TLC). The reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$ and extracted with dichloromethane (2x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane or dichloromethane and hexane.

Procedure for sequential halogenation reactions (PSH)

The initial monochlorination reaction was performed following the previously described procedure [172], employing **HSc** as a halogenating source. After standard work-up, the crude monochlorinated compound was used in the subsequent halogenation step using GPP with **HSa,b**, respectively.

Data for compounds from control experiments

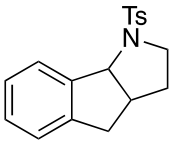
***N*-(3-(2,3-Dihydro-1*H*-inden-2-yl)propyl)-*N*-methyl-4-methylbenzenesulfonamide (18)**



White solid. **m.p.** 70-71 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.52-1.65 (m, 4H), 2.38-2. 48 (m, 4H), 2.57 (dd, *J* = 15.4, 8.1 Hz, 2H), 2.73 (s, 3H), 2.97-3.10 (m, 4H), 7.10- 7.19 (m, 4H), 7.29-7.35 (m, 2H), 7.65-

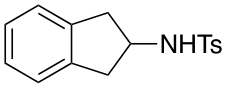
7.70 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 26.6, 32.6, 34.8, 39.3, 39.9, 50.3, 124.5, 126.2, 127.5, 129.8, 134.7, 143.3, 143.4. **IR** ν(cm^{-1}): 2823, 1417, 1181, 703, 545. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{20}H_{25}NNaO_2S$, 366.1498; found, 366.1500.

1-Tosyl-1,2,3,3a,4,8b-hexahydroindeno[1,2-b]pyrrole (17f)



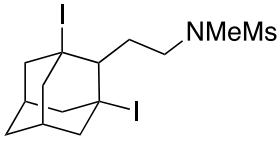
Spectroscopic data were in agreement with the ones previously described. [90] Yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.46-1.60 (m, 1H), 1.84 (dtd, *J* = 14.3, 7.1, 4.4 Hz, 1H), 2.45 (s, 3H), 2.64- 2.77 (m, 2H), 3.03 (dd, *J* = 16.3, 7.8 Hz, 1H), 3.24 (ddd, *J* = 10.3, 8.7, 6.7 Hz, 1H), 3.37 (ddd, *J* = 10.3, 7.2, 4.4 Hz, 1H), 5.15 (d, *J* = 7.8 Hz, 1H), 7.13- 7.20 (m, 1H), 7.22- 7.30 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.76- 7.83 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ= 21.6, 31.5, 35.9, 41.9, 49.3, 68.8, 125.0, 126.9, 127.4, 127.8, 128.3, 129.8, 135.0, 141.0, 142.0, 143.6.

***N*-(2,3-dihydro-1H-inden-2-yl)-4-methylbenzenesulfonamide (20)**



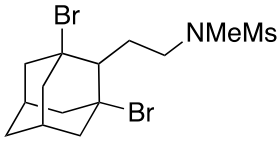
Brownish solid. **m.p**. 132-133 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 2.66- 2.77 (m, 2H), 3.06-3.13 (m, 2H), 4.02-4.14 (m, 1H), 5.09 (d, *J* = 8.0 Hz, 1H), 7.13 (s, 4H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.72- 7.89 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ= 21.7, 40.3, 54.8, 124.7, 127.0, 127.2, 129.8, 137.8, 140.2, 143.6. **IR** ν(cm^{-1}): 3221, 1221, 1213, 1207, 1170. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{16}H_{16}NO_2S$, 286.0907; found, 286.0919.

***N*-(2-(-1,3-Diiodoadamantan-2-yl)ethyl)-*N*-methylmethanesulfonamide (S1)**



Quantitative yield. Yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.71-1.75 (m, 1H), 1.83-1.91 (m, 3H), 2.16-2.24 (m, 2H), 2.44-2.48 (m, 3H), 2.62 (dd, *J* = 12.9, 3.3 Hz, 2H), 2.73-2.86 (m, 4H), 2.88 (s, 3H), 2.99 (s, 3H), 3.45-3.58 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ= 34.3, 34.9, 36.6, 36.6, 37.1, 37.4, 44.7, 50.3, 52.8, 53.8, 60.0. **IR** ν (cm^{-1})**:** 2907, 2852, 1443, 1312, 1138. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{14}H_{23}I_2NNaO_2S$, 545.9431; found, 545.9427

***N*-(2-(1,3-Dibromoadamantan-2-yl)ethyl)-*N*-methylmethanesulfonamide (S2)**

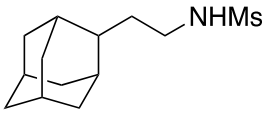


40% overall (3 steps from **3a**), white solid. **m.p.:** 182-183 ºC. **^{1}H NMR** (300Hz, $CDCl_3$): δ = 1.55 (s, 1H), 1.71 (t, *J* = 2.8 Hz, 2H), 2.05-2.22 (m, 5H), 2.26-2.31 (m, 1H), 2.34-2.41 (m, 2H), 2.44 (d, *J* = 2.9 Hz, 4H), 2.84 (s, 3H),

2.94 (s, 3H), 3.28-3.51 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 31.6, 34.1, 34.9, 34.9, 35.1, 36.3, 42.0, 50.0, 51.4, 58.0, 69.1. **IR** ν (cm^{-1}): 3288, 2821, 2853, 1720, 1452, 1317, 1142. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{14}H_{23}Br_2NNaO_2S$, 449.9708; found, 449.9697.

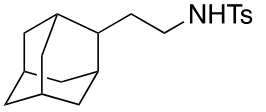
Data for starting materials

***N*-(2-(Adamantan-2-yl)ethyl)methanesulfonamide (1a)**



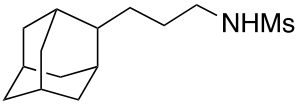
Yellow solid. **m.p.:** 114-115 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.53-1.50 (m, 1H), 1.56-1.54 (m, 1H), 1.76-1.64 (m, 9H), 1.91-1.78 (m, 6H), 2.95 (s, 3H), 3.10-3.16 (m, 2H), 4.40 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ= 28.0, 28.2, 31.7, 31.8, 33.2, 38.3, 39.1, 40.3, 41.7, 42.0. **IR** ν (cm^{-1})**:** 3272, 2903, 2849, 2808, 1329, 1137. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{23}NNaO_2S$, 280.1342; found, 280.1343.

***N*-(2-(Adamantan-2-yl)ethyl)-4-methylbenzenesulfonamide (1b)**



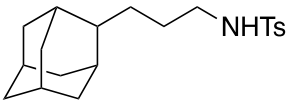
White solid. **m.p.:** 111-112 ºC **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.44-1.49 (m, 2H), 1.91-1.53 (m, 15H), 2.43 (s, 3H), 2.91-2.96 (m, 2H), 4.36 (t, *J* = 6.2 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.7, 28.0, 28.2, 31.7, 31.8, 32.7, 38.3, 39.1, 41.5, 41.8, 127.3, 129.8, 137.2, 143.5. **IR** ν (cm^{-1}): 3259, 2902, 2851, 1435, 1326, 1157, 1062, 814. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{27}NNaO_2S$, 356.1655; found, 356.1647.

***N*-(3-(Adamantan-2-yl)propyl)methanesulfonamide (1c)**



White solid. **m.p.:** 87-88 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.40-1.62 (m, 7H), 1.65-1.77 (m, 6H), 1.77-1.99 (m, 6H), 2.96 (s, 3H), 3.08-3.28 (m, 2H), 4.27 (d, *J* = 8.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 28.2, 28.4, 28.5, 29.7, 31.7, 32.0, 38.5, 39.3, 40.5, 43.9, 44.2. **IR** ν (cm^{-1}): 3206, 28221, 2848, 1303, 1157, 1143, 1065, 789, 522. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{14}H_{25}NNaO_2S$, 294.1498; found, 294.1498.

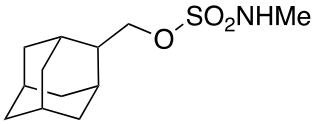
***N*-(Adamantan-2-yl)propyl)-4-methylbenzenesulfonamide (1d)**



White solid **m.p.:** 91-92 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.51-1.30 (m, 5H), 1.86-1.53 (m, 14H), 2.42 (s, 3H), 2.93 (q, *J* = 6.4 Hz, 2H), 4.57 (t, *J* = 6.3 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ= 21.6, 27.8, 28.1, 28.4, 29.6, 31.6, 31.8, 38.5, 39.3, 43.7, 44.0, 127.3,

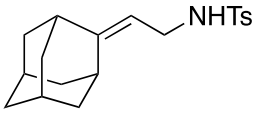
129.8, 137.2, 143.5. **IR** ν (cm^{-1}): 3259, 2900, 2850, 1426, 1322, 1157, 1093. **HRMS** (m/z): $[M+Na]^+$ for $C_{20}H_{29}NNaO_2S$, 370.1811; found, 370.1815.

(Adamantan-2-yl)methyl methylsulfamate (5)



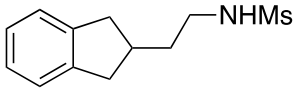
White solid. **m.p.**: 88-89 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.60 (d, *J* = 12.6 Hz, 2H), 1.70-2.00 (m, 12H), 2.05-2.26 (m, 1H), 2.81 (d, *J* = 4.0 Hz, 3H), 4.23 (d, *J* = 7.7 Hz, 2H), 4.37 (brs, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 27.8, 28.1, 29.1, 30.0, 31.9, 38.1, 38.6, 43.4, 73.0. **IR** ν (cm^{-1}): 3312, 2896, 2850, 1425, 1351, 1173, 868, 796, 545, 527. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{12}H_{20}NO_3S$, 258.1169; found, 258.1159.

***N*-(2)-Adamantan-2-ylidene)ethyl)-4-methylbenzenesulfonamide (12)**



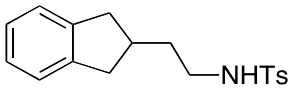
Yellowish solid. **m.p.:** 103-104 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 1.57-1.62 (m, 2H), 1.65-1.70 (m, 2H), 1.77-1.86 (m, 6H), 1.89-1.94 (m, 2H), 2.27 (s, 1H), 2.43 (s, 3H), 2.62 (s, 1H), 3.54 (dd, *J* = 7.3, 5.7 Hz, 2H), 4.12-4.19 (m, 1H), 4.99 (t, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ= 21.7, 28.4, 32.4, 37.1, 39.1, 39.7, 39.9, 40.4, 110.7, 127.4, 129.8, 137.2, 143.5, 154.1. **IR** ν (cm^{-1}): 3262, 2903, 2848, 1428, 1322, 1154, 1091. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{25}NNaO_2S$, 354.1498; found, 354.1500.

***N*-(2-(2,3-Dihydro-1*H*-inden-2-yl)ethyl)methanesulfonamide (16a)**



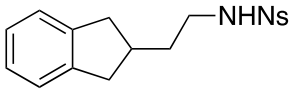
Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.80 (q, *J* = 7.2 Hz, 2H), 2.51 (dt, *J* = 14.7, 7.3 Hz, 1H), 2.58-2.68 (m, 2H), 2.97 (s, 3H), 3.09 (dd, *J* = 14.9, 7.4 Hz, 2H), 3.18-3.28 (m, 2H), 7.08-7.16 (m, 2H), 7.17-7.23 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 36.2, 37.4, 39.1, 40.5, 42.5, 124.6, 126.5, 142.9. **IR** ν (cm^{-1}): 3329, 2932, 2833, 1140, 1050, 742, 521. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{12}H_{17}NNaO_2S$, 262.0872; found, 262.0878

***N*-(2-(2,3-Dihydro-1*H*-inden-2-yl)ethyl)-4-methylbenzenesulfonamide (16b)**



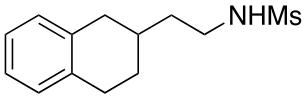
Spectroscopic data were in agreement with the ones previously described. [90] White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.67 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 2.41-2.56 (m, 3H), 2.94-3.06 (m, 4H), 4.41 (t, 1H, NH), 7.09-7.17 (m, 4H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 21.6, 29.7, 49.5, 52.7, 53.9, 66.9, 125.8, 127.0, 127.7, 129.3, 129.9, 130.2, 134.4, 141.1, 142.4, 143.9.

_N_-(2-(2,3-Dihydro-1_H_-inden-2-yl)ethyl)-4-nitrobenzenesulfonamide (16c)



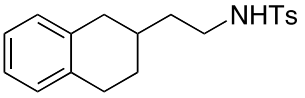
Brownish solid. **m.p.:** 97-99 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.71 (q, *J* = 7.2 Hz, 2H), 2.38 -2.60 (m, 3H), 2.94-3.05 (m, 2H), 3.05-3.15 (m, 2H), 4.94 (t, *J* = 5.9 Hz, 1H), 7.10-7.16 (m, 4H), 8.00-8.10 (m, 2H), 8.27-8.45 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 35.7, 37.3, 39.0, 42.5, 124.5, 124.6, 126.5, 128.4, 142.7, 146.1, 150.2. **IR** ν (cm^{-1}): 3271, 2922, 2885, 1530, 1438, 1156, 1069, 734, 570. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{17}H_{18}N_2NaO_4S$, 369.0879; found, 369.0872.

_N_-(2-(1,2,3,4-Tetrahydronaphthalen-2-yl)ethyl)methanesulfonamide (16e)



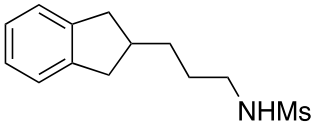
Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.39-1.49 (m, 1H), 1.60-1.73 (m, 2H), 1.80-1.89 (m, 1H), 1.87-2.05 (m, 1H), 2.46 (dd, *J* = 16.3, 10.4 Hz, 1H), 2.73-2.91 (m, 3H), 2.97 (s, 3H), 3.25 (dt, *J* = 7.2, 4.0 Hz, 2H), 4.51 (s, 1H), 6.96-7.18 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 28.9, 29.3, 31.7, 35.9, 36.7, 40.4, 41.3, 125.7, 125.8, 129.0, 129.2, 135.9, 136.5. **IR** ν (cm^{-1}): 3285, 2918, 1434, 1312, 1144, 1079, 743, 520. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{19}NNaO_2S$, 276.1029; found, 276.1030.

4-Methyl-_N_-(2-(1,2,3,4-tetrahydronaphthalen-2-yl)ethyl) benzenesulfonamide (16f)



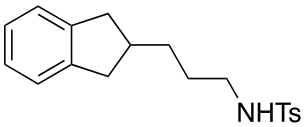
Spectroscopic data were in agreement with the ones previously described.[90] White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.34 (dtd, *J* = 12.8, 10.5, 6.4 Hz, 1H), 1.52 (qd, *J* = 7.0, 1.6 Hz, 2H), 1.69-1.78 (m, 1H), 1.80-1.86 (m, 1H), 2.35 (dd, *J* = 16.7, 10.1 Hz, 1H), 2.42 (s, 3H), 2.71-2.76 (m, 3H), 3.07 (q, *J* = 6.9 Hz, 2H), 4.56 (t, *J* = 6.9 Hz, 1H, NH), 6.98-7.00 (m, 1H), 7.03-7.09 (m, 3H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 21.6, 29.7, 49.5, 52.7, 53.9, 66.9, 125.8, 127.0, 127.7, 129.3, 129.9, 130.2, 134.4, 141.1, 142.4, 143.9.

_N_-(3-(2,3-Dihydro-1_H_-inden-2-yl)propyl)methanesulfonamide (16g)



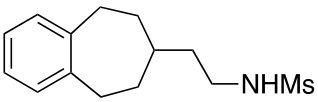
Yellowish solid. **m.p.:** 73-75 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.54-1.59 (m, 2H), 1.61-1.69 (m, 2H), 2.38-2.50 (m, 1H), 2.59 (dd, *J* = 15.3, 8.0 Hz, 2H), 2.96 (s, 3H), 3.06 (dd, *J* = 15.2, 7.7 Hz, 2H), 3.15 (q, *J* = 6.8 Hz, 2H), 4.64 (t, *J* = 6.2 Hz, 1H), 6.99-7.26 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 29.1, 32.6, 39.3, 39.8, 40.3, 43.5, 124.5, 126.3, 143.2. **IR** ν (cm^{-1}): 3239, 2923, 2858, 1303, 1135, 1067, 969, 746, 521. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{19}NNaO_2S$, 276.1029; found, 276.1030.

_N_-(3-(2,3-Dihydro-1_H_-inden-2-yl)propyl)-4-methylbenzenesulfonamide (16h)



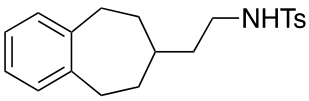
Spectroscopic data were in agreement with the ones previously described. [95] White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ =1.42-1.48 (m, 2H) 1.50-1.56 (m, 2H), 2.34 (ddd, *J* = 15.1, 8.2, 7.1 Hz, 1H), 2.43 (s, 3H), 2.50 (dd, *J* = 15.4, 8.1 Hz, 2H), 2.97 (ddt, *J* = 9.2, 6.4, 3.5 Hz, 4H), 7.13-7.09 (m, 2H), 4.65 (s, 1H), 7.18-7.13 (m, 2H), 7.31 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.76 (dd, *J* = 8.3, 1.1 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ =21.5, 28.4, 32.5, 39.1, 39.6, 43.4, 124.4, 126.1, 127.1, 129.7, 137.0, 143.2, 143.4.

_N_-(2-(6,7,8,9-Tetrahydro-5_H_-benzo[7]annulen-7-yl)ethyl) methanesulfonamide (21a)



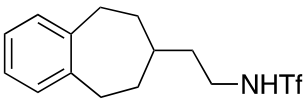
Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.15-1.21 (m, 2H), 1.55 (q, *J* = 7.0 Hz, 2H), 1.75-1.85 (m, 1H), 1.93-2.02 (m, 2H), 2.74-2.90 (m, 4H), 2.99 (s, 3H), 3.22 (t, *J* = 7.5 Hz, 2H), 4.17-4.38 (m, 1H), 7.12 (s, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 34.2, 34.8, 38.1, 40.4, 40.5, 41.3, 126.3, 129.0, 142.8. **IR** ν (cm^{-1}): 3280, 2921, 2841, 1141, 1320, 1152. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{14}H_{21}NNaO_2S$, 290.1185; found, 290.1195.

4-Methyl-_N_-(2-(6,7,8,9tetrahydro5_H_benzo[7]annulen7yl)ethyl)benzenesulfonamide (22b)



Yellow solid. **m.p.:** 84-85 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.00-1.08 (m, 2H), 1.35-1.43 (m, 2H), 1.63-1.64 (m, 1H), 1.79-1.87 (m, 2H), 2.44 (s, 3H), 2.64-2.80 (m, 4H), 2.99 (q, *J* = 6.9 Hz, 2H), 4.58 (t, *J* = 6.2 Hz, 1H), 7.06 - 7.10 (m, 4H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ= 21.7, 34.0, 34.8, 37.5, 40.4, 41.1, 126.3, 127.3, 128.9, 129.9, 137.1, 142.9, 143.6. **IR** ν (cm^{-1}): 3284, 2918, 2844, 1449, 1320, 1155, 1072. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{20}H_{25}NNaO_2S$, 366.1498; found, 366.1491.

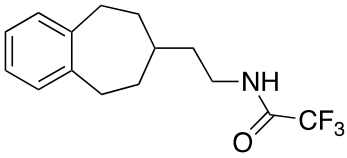
1,1,1-Trifluoro-_N_-(2-(6,7,8,9-tetrahydro-5H-benzo[7]annulen-7-yl)ethyl)methanesulfonamide (22c)



Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.10-1.20 (m, 2H), 1.56 (dt, *J* = 8.3, 6.6 Hz, 2H), 1.71-1.79 (m, 1H), 1.90-1.97 (m, 2H), 2.59-2.93 (m, 5H), 3.22-3.50 (m, 2H), 4.79 (s, 1H), 7.04-7.20 (m, 4H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ = 34.0, 34.8, 38.2, 40.3, 42.5, 119.8 (q, *J* = 321.3 Hz), 126.4, 129.0, 142.7.**^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.3. **IR** ν(cm^{-1}): 3311, 2920, 2849, 1370, 1188,

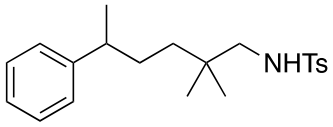
1145, 909, 733, 608. **HRMS** (m/z): $[M-H]^-$ for $C_{14}H_{17}F_3NO_2S$, 320.0938; found, 320.0940.

2,2,2-Trifluoro-*N*-(2-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)ethyl)acetamide (22d)



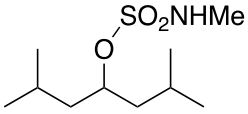
White solid. **m.p.:** 108-111 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.01-1.33 (m, 2H), 1.44-1.63 (m, 2H), 1.62-1.82 (m, 1H), 1.88-2.12 (m, 2H), 2.64-2.99 (m, 4H), 3.43 (q, *J* = 6.9 Hz, 2H), 6.22 (brs, 1H), 7.10 (brs, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 34.2, 34.8, 37.0, 38.0, 40.9, 116.0 (q, *J* = 287.9 Hz), 126.4, 129.0, 142.8, 157.3 (q, *J* = 36.1 Hz). **^{19}F NMR** (376 MHz, CDCl3): δ = -76.0. **IR** ν (cm^{-1}): 3229, 2321, 2853, 1693, 1168, 742, 705. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{15}H_{18}F_3NNaO$, 308.1233; found, 308.1235.

***N*-(2,2-Dimethyl-5-phenylhexyl)-4-methylbenzenesulfonamide (23)**



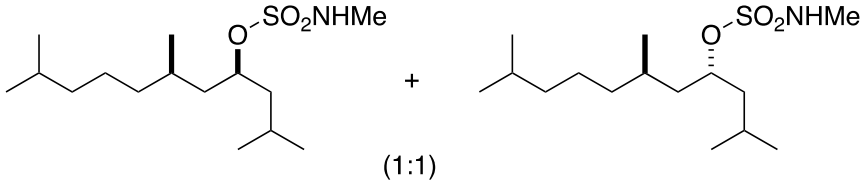
White solid. **mp**: 115-116 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 4.2 Hz, 6H), 0.92-1.02 (m, 1H), 1.18–1.11 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.48-1.38 (m, 2H), 2.43 (s, 3H), 2.54 (q, *J* = 7.0 Hz, 1H), 2.63 (dd, *J* = 6.9, 3.4 Hz, 2H), 4.15 (t, *J* = 6.8 Hz, 1H), 7.15-7.11 (m, 2H), 7.22-7.16 (m, 1H), 7.33-7.26 (m, 4H), 7.71 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.5, 22.5, 24.9, 32.1, 33.6, 37.3, 40.5, 52.8, 126.0, 126.9, 127.1, 128.4, 129.7, 137.0, 143.3, 147.4. **IR** ν (cm^{-1}): 3259, 3064, 3030, 2956, 2924, 2866, 2847. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{29}NNaO_2S$, 382.1811; found, 382.1810.

2,6-Dimethylheptan-4-yl methylsulfamate (25a)



Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.89-0.99 (m, 12H), 1.41-1.49 (m, 2H), 1.63-1.83 (m, 4H), 2.81 (d, *J* = 5.3 Hz, 3H), 4.32 (bs, 1H), 4.62-4.70 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.6, 22.9, 24.6, 30.1, 43.9, 81.9. **IR** ν(cm^{-1}): 3200, 2871, 1313, 1190, 900. **HRMS** (m/z): $[M+H]^-$ calcd. for $C_{10}H_{22}NO_3S$, 236.1326; found, 236.1329.

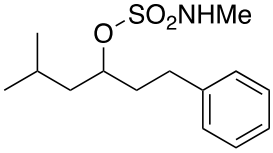
2,6,10-Trimethylundecan-4-yl methylsulfamate (25b)



Colorless oil. **^{1}H NMR** (400

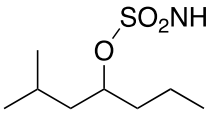
MHz, $CDCl_3$): δ = 0.94-0.98 (m, 30H, C-C**H₃**), 1.05-1.89 (m, 26H, C-C**H₂**+C-C**H**), 2.70-2.90 (brd, *J* = 5.2 Hz, 6H, N-C**H₃**), 4.14-4.30 (m, 2H, N-**H**), 4.62-4.74 (m, 2H, O-C-**H**). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 19.7, 19.8, 22.3, 22.7, 22.7, 22.8, 22.8, 23.2, 24.5, 24.6, 24.7, 24.7, 28.1, 28.1, 29.2, 29.6, 30.1, 37.4, 37.6, 39.3, 42.3, 42.3, 43.7, 44.2, 81.9, 82.0. **IR** ν(cm^{-1}): 3219, 2813, 1301, 1170, 899. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{15}H_{32}NO_3S$, 306.2108; found, 306.2113.

5-Methyl-1-phenylhexan-3-yl methylsulfamate (25c)



Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.88-0.96 (m, 6H), 1.43- 1.51 (m, 1H), 1.68-1.79 (m, 2H), 1.97-2.06 (m, 2H), 2.67- 2.75 (m, 2H), 2.78 (s, 3H), 4.30 (bs, 1H), 4.61-4.68 (m, 1H), 7.16-7.20 (m, 3H), 7.25 – 7.30 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.5, 22.9, 24.6, 30.1, 31.1, 36.3, 43.3, 82.4, 126.2, 128.5, 128.6, 141.4. **IR** ν(cm^{-1}): 3215, 2821, 1291, 1173, 891. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{14}H_{22}NO_3S$, 284.1326; found, 284.1327.

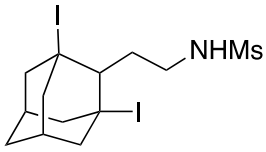
2-Methylheptan-4-yl methylsulfamate (25d)



Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.87-0.98 (m, 9H), 1.30- 1.49 (m, 3H), 1.59-1.79 (m, 4H), 2.79 (d, *J* = 5.3 Hz, 3H), 4.51 (bs, 1H), 4.55-4.68 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 14.1, 18.0, 22.5, 22.9, 24.5, 30.0, 36.7, 43.3, 82.9. **IR** ν(cm^{-1}): 3270, 2901, 1321, 1182, 853. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_9H_{20}NO_3S$, 222.1169; found, 222.1180.

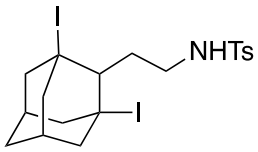
<u>Data for products from halogenation</u>

***N*-((1,3-Diiodoadamantan-2-yl)ethyl)methanesulfonamide (2a)**



Synthesized according to GPP using **HSa**. 67%, white solid. **m.p.:** 157-158 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.70-1.77 (m, 1H), 1.84-1.92 (m, 3H), 2.25-2.12 (m, 2H), 2.42-2.48 (m, 2H), 2.55-2.61 (m, 3H), 2.92-2.72 (m, 4H), 3.04 (s, 3H), 3.62-3.42 (m, 2H), 4.57 (t, *J* = 5.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ= 34.3, 36.6, 37.1, 39.4, 40.7, 43.9, 44.7, 53.1, 53.8, 60.1. **IR** ν (cm^{-1}): 3259, 2904, 2852, 1444, 1310, 1138. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{21}I_2NNaO_2S$, 531.9275; found, 531.9270.

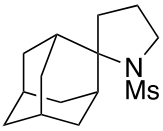
***N*-(1,3-diiodoadamantan-2-yl)ethyl)-4-methylbenzenesulfonamide (2b)**



Synthesized according to GPP using **HSa**.56%, white solid. **m.p.:** 162-163 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.68-1.72 (m, 1H), 1.81-1.90 (m, 3H), 2.02-2.11 (m, 2H), 2.34-2.38 (m, 1H), 2.39-2.41 (m, 1H), 2.42-2.44 (m, 1H),

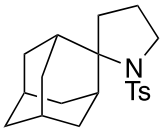
2.44 (s, 3H), 2.51 (dt, *J* = 13.4, 3.1 Hz, 2H), 2.64 (dt, *J* = 12.2, 3.1 Hz, 2H), 2.79 (m, 2H), 3.28-3.41 (m, 2H), 4.78 (t, *J* = 6.0 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.86 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ= δ 21.7, 34.2, 36.6, 37.1, 38.5, 43.8, 44.6, 53.1, 53.7, 59.7, 127.7, 129.8, 137.3, 143.4. **IR** ν (cm^{-1}): 3228, 2926, 2886, 2869, 1329, 1079. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{25}I_2NNaO_2S$, 607.9588; found, 607.9568.

1'-(Methylsulfonyl)spiro[adamantane-2,2'-pyrrolidine] (2c)



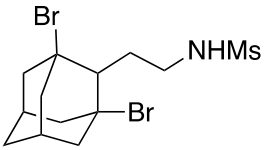
Synthesized according to GPP using **HSa**.76%, yellowish solid. **m.p.:** 136-137 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.58-1.67 (m, 2H), 1.70-1.80 (m, 4H), 1.83-1.94 (m, 6H), 1.99-2.07 (m, 2H), 2.11 (s, 2H), 2.43-2.53 (m, 2H), 2.91 (s, 3H), 3.55-3.64 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ= 21.0, 27.3, 27.5, 34.1, 34.2, 34.4, 35.6, 38.3, 41.1, 47.6, 78.1. **IR** ν (cm^{-1}): 2933, 2903, 2859, 2847, 1450, 1330, 1146, 961. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{27}NNaO_2S$, 292.1342; found, 292.1341.

1'-(4-Methylbezenesulfonyl)spiro[adamantane-2,2'-pyrrolidine] (2d)



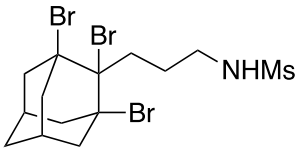
Synthesized according to GPP using **HSa**. 55%, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.60-1.68 (m, 4H), 1.70-1.75 (m, 3H), 1.75-1.85 (m, 5H), 1.87-1.94 (m, 2H), 2.17 (s, 2H), 2.41 (s, 3H), 2.53-2.60 (m, 2H), 3.45-3.50 (m, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ= 20.9, 21.6, 27.3, 27.7, 34.0, 34.3, 34.3, 35.5, 38.3, 47.7, 78.4, 127.8, 129.6, 139.2, 143.1. **IR** ν (cm^{-1}): 2901, 2878, 2844, 1336, 1154. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{20}H_{27}NNaO_2S$, 368.1655; found, 368.1652.

***N*-((-1,3-Dibromoadamantan-2-yl)ethyl)methanesulfonamide (3)**



Synthesized according to GPP using **HSb**. 72%, yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.71 (t, *J* = 3.1 Hz, 2H), 2.05-2.20 (m, 6H), 2.34 (dd, *J* = 12.9, 3.5 Hz, 2H), 2.39-2.42 (m, 1H), 2.45 (d, *J* = 3.2 Hz, 4H), 3.00 (s, 3H), 3.42 (td, *J* = 7.8, 6.0 Hz, 2H), 4.51 (bs, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ= 33.3, 34.1, 34.9, 35.1, 40.4, 41.9, 44.4, 50.0, 57.9, 69.2. **IR** ν (cm^{-1})**:** 3290, 2823, 2852, 1721, 1450, 1317, 1144. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{21}Br_2NNaO_2S$, 435.9552; found, 435.9569.

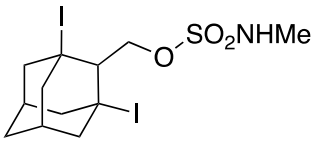
***N*-(3-(1,2,3-Tribromoadamantan-2-yl)propyl)methanesulfonamide (4)**



Synthesized according to GPP using **HSb**. 69%, white solid. **m.p.:** 154-156 ºC **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.54-1.57 (m, 1H), 1.72-1.75 (m, 2H), 2.00-2.11 (m, 1H), 2.13-2.34 (m, 4H), 2.37-2.43 (m, 2H), 2.44-

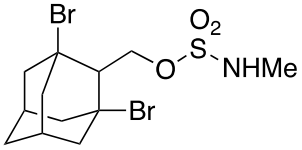
2.56 (m, 2H), 2.74 (d, *J* = 13.3 Hz, 2H), 3.00 (s, 3H), 3.13-3.38 (m, 4H), 4.34 (bs, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 32.3, 34.6, 34.7, 35.7, 36.0, 40.7, 43.6, 44.4, 47.1, 72.4, 87.6. **IR** ν (cm^{-1}): 3269, 2925, 2859, 1448, 1312, 1141, 1071, 959, 765, 580. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{14}H_{22}Br_3NNaO_2S$, 527.8814; found, 527.8831.

(1,3-Diiodooadamantan-2-yl)methyl methylsulfamate (6)



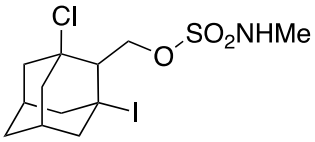
Synthesized according to GPP using **HSa**. 60%, white solid. **m.p.:** 124-125 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.74-1.81 (m, 1H), 1.86-1.95 (m, 3H), 2.53 (m, 4H), 2.78-2.86 (m, 4H), 2.93 (d, *J* = 5.2 Hz, 4H), 4.59 (q, *J* = 5.2 Hz, 1H), 4.78 (d, *J* = 2.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.5, 34.0, 36.2, 36.9, 45.8, 48.8, 53.9, 61.6, 78.4. **IR** ν (cm^{-1}): 3278, 2917, 2891, 2853, 1346, 1173, 1011. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{12}H_{18}I_2NO_3S$, 509.9102; found, 509.9086.

(1,3-Dibromoadamantan-2-yl)methyl methylsulfamate (7)



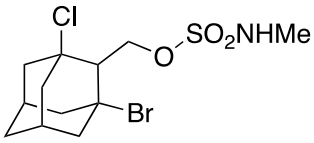
Synthesized according to GPP using **HSb**. 90%, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.72 (brs, 2H), 2.07-2.25 (m, 4H), 2.32 (brd, *J* = 11.7 Hz, 2H), 2.40-2.52 (m, 1H), 2.45 (d, *J* = 3.0 Hz, 3H), 2.73 (brs, 1H), 2.86 (d, *J* = 5.1 Hz, 3H), 4.62-4.68 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 30.1, 33.8, 34.5, 34.9, 43.1, 50.2, 59.6, 65.9, 72.5. **IR** ν (cm^{-1}): 3315, 2936, 2863, 1345, 1173, 973, 865, 815, 685, 551. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{12}H_{19}Br_2NNaO_3S$, 437.9345 found 437.9351

(1-Iodo-3-chloroadamantan-2-yl)methyl methylsulfamate (8)



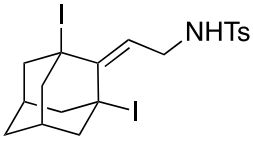
Synthesized according to PSH using **HSa**. 40% (3 steps), colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.73-1.79 (m, 2H), 2.03-2.12 (m, 3H), 2.21 (ddq, *J* = 10.3, 3.1, 1.6 Hz, 1H), 2.29 (d, *J* = 3.2 Hz, 2H), 2.38 (ddt, *J* = 13.1, 3.1, 1.6 Hz, 1H), 2.46 (ddq, *J* = 13.1, 2.8, 1.4 Hz, 1H), 2.71 (t, *J* = 3.1 Hz, 3H), 2.89 (d, *J* = 5.4 Hz, 3H), 4.42 (m, 1H), 4.63 (dd, *J* = 10.1, 2.7 Hz, 1H), 4.72 (dd, *J* = 10.1, 2.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.3, 33.9, 34.4, 35.0, 42.0, 45.7, 48.8, 49.9, 53.6, 60.3, 68.1, 73.8. **IR** ν (cm^{-1}): 3315, 2933, 2861, 1453, 1412, 1341, 1172. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{12}H_{18}ClINO_3S$, 417.9746; found, 417.9732.

(1-Bromo-3-chloroadamantan-2-yl)methyl methylsulfamate (9)



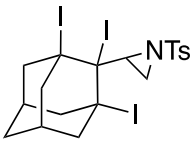
Synthesized according to PSH using **HSb**. 44% (3 steps), colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.66-1.74 (m, 2H), 1.96-2.05 (m, 1H), 2.13-2.31 (m, 7H), 2.40-2.49 (m, 2H), 2.62 (tt, *J* = 2.9, 1.6 Hz, 1H), 2.86 (d, *J* = 5.3, 3H), 4.42 (m, 1H), 4.59-4.70 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.1, 33.5, 33.8, 33.9, 41.8, 43.1, 48.6, 50.1, 59.1, 66.1, 69.3, 70.9. **IR** ν (cm^{-1}): 3316, 2937, 2864, 1454, 1341, 1172. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{12}H_{18}BrClNO_3S$, 369.9885; found, 369.9870.

***N*-(2-(1,3-Diiodoadamantan-2-ylidene)ethyl)-4-methylbenzenesulfonamide (13)**



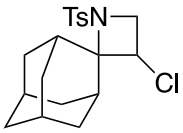
Synthesized according to GPP using **HSa**, reaction time 30 min. 37%, white solid. **m.p.:** 144-145 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.77 (s, 2H), 1.90 (s, 2H), 2.42 (s, 3H), 2.58 (d, *J* = 12.2 Hz, 2H), 2.66 (d, *J* = 12.4 Hz, 2H), 2.84 (d, *J* = 12.7 Hz, 2H), 2.94 (d, *J* = 12.4 Hz, 2H), 4.35 (t, *J* = 6.4 Hz, 2H), 4.61 (t, *J* = 6.6 Hz, 1H), 6.09 (t, *J* = 6.4 Hz, 1H), 7.30-7.33 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ= 21.7, 31.1, 33.5, 36.8, 42.8, 54.4, 56.1, 60.3, 127.5, 129.8, 130.0, 137.4, 143.6, 145.2. **IR** ν (cm^{-1}): 3258, 2907, 2850, 1439, 1309, 1151, 1090. **HRMS** (m/z): $[M+Na]^+$ for $C_{19}H_{23}I_2NNaO_2S$, 605.9431; found, 605.9434.

1-(4-Methylbezenesulfonyl)-2-(1,2,3-triiodoadamantan-2-yl)aziridine (15)



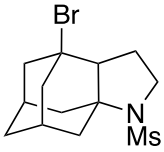
Synthesized according to GPP, using 3 equivalents of **HSa**. 41%, yellowish solid. **m.p.:** 175-176 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.48 (brs, 1H), 1.91 (s, 2H), 2.01 (brs, 1H), 2.45 (s, 3H), 2.70 (d, *J* = 7.6 Hz, 1H), 2.83 (dt, *J* = 13.5, 2.5 Hz, 1H), 2.90-2.98 (m, 3H), 3.02 (ddd, *J* = 13.2, 2.8, 2.1 Hz, 1H), 3.35-3.43 (m, 2H), 3.47-3.51 (m, 1H), 3.54 (dt, *J* = 13.3, 3.4 Hz, 1H), 3.65 (dt, *J* = 13.5, 3.6 Hz, 1H), 7.36 (d, *J* = 8.6, 2H), 7.92 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ= 21.9, 36.6, 36.7, 37.2, 39.9, 44.5, 45.2, 48.5, 49.7, 53.4, 55.0, 58.8, 78.3, 128.7, 129.9, 134.4, 145.0. **IR** ν (cm^{-1}): 2924, 2854, 1329, 1151, 1100, 1080. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{22}I_3NNaO_2S$, 731.8398; found, 731.8425.

3'-Chloro-1'-(4-methylbezenesulfonyl)spiro[adamantane-2,2'-azetidine] (14)



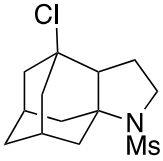
Synthesized according to GPP using **HSc**. 64%, white solid. **m.p.:** 172-173 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.55-1.62 (m, 3H), 1.69-1.78 (m, 4H), 1.86-1.90 (m, 1H), 1.90-1.96 (m, 2H), 2.17-2.23 (m, 2H), 2.43 (s, 3H), 2.55-2.62 (m, 1H), 2.68-2.73 (m, 1H), 3.70 (dd, *J* = 10.2, 2.4 Hz, 1H), 4.23 (dd, *J* = 6.3, 2.4 Hz, 1H), 4.39 (dd, *J* = 10.2, 6.3 Hz, 1H), 7.27-7.32 (m, 2H), 7.76-7.83 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ= 21.7, 26.6, 26.6, 32.5, 32.6, 33.0, 34.5, 35.0, 37.5, 37.6, 57.6, 58.2, 87.0, 127.8, 129.6, 138.0, 143.6. **IR ν** (cm^{-1}): 3258, 2907, 2860, 1452, 1321, 1150, 1115, 1091. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{24}ClNNaO_2S$, 388.1108; found: 388.1107.

4-Bromo-1-(methylsulfonyl)decahydro-4,8:6,9a-dimethanocycloocta[*b*]pyrrole (10)



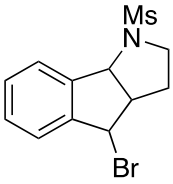
Synthesized according to GPP twice using first **HSa** and after **HSb**. 42% (2 steps from **2a**), white solid. **m.p.:** 179-180 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.59-1.69 (m, 2H), 1.78-1.85 (m, 2H), 1.96-2.21 (m, 5H), 2.26-2.40 (m, 4H), 2.42 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.61-2.66 (m, 1H), 2.88 (s, 3H), 3.41 (td, *J* = 9.7, 7.9 Hz, 1H), 3.59 (td, *J* = 9.7, 1.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.4, 33.0, 34.0, 34.9, 36.2, 40.7, 41.6, 41.6, 46.1, 50.5, 59.5, 64.1, 65.2. **IR** ν (cm^{-1}): 2911, 2851, 1357, 1145, 961. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{20}BrNNaO_2S$, 356.0290; found, 356.0282.

4-Chloro-1-(methylsulfonyl)decahydro-4,8:6,9a-dimethanocycloocta[*b*]pyrrole (11)



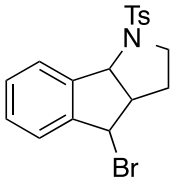
Synthesized according to GPP twice using first **HSa** and after **HSc**. 36% (2 steps from **2a**), white solid. **m.p.:** 92-93 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.57-1.60 (m, 2H), 1.73-1.80 (m, 2H), 1.90-2.22 (m, 8H), 2.25-2.32 (m, 1H), 2.36-2.44 (m, 1H), 2.56-2.62 (m, 1H), 2.88 (s, 3H), 3.41 (td, *J* = 9.7, 7.9 Hz, 1H), 3.58 (td, *J* = 9.7, 1.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ= 23.9, 32.4, 33.4, 34.9, 36.3, 40.2, 40.7, 41.5, 46.5, 49.1, 58.5, 65.4, 67.9. **IR ν** (cm^{-1}): 2907, 2853, 1352, 1144, 961. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{20}ClNNaO_2S$, 312.0795; found, 312.0789.

4-Bromo-1-(methylsulfonyl)-1,2,3,3a,4,8b-hexahydroindeno[1,2-*b*]pyrrole (17a)



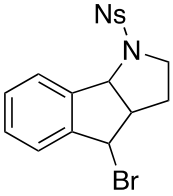
Synthesized according to GPP using **HSb**. 35%, yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.65-1.75 (m, 1H), 2.25-2.35 (m, 1H), 2.92 (s, 3H), 3.38-3.53 (m, 3H), 5.30 (d, *J* = 1.5 Hz, 1H), 5.42 (d, *J* = 7.1 Hz, 1H), 7.33-7.41 (m, 3H), 7.70-7.74 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 30.0, 36.1, 49.3, 52.6, 54.6, 66.9, 126.1, 126.9, 129.6, 130.2, 141.4, 142.2. **IR** ν (cm^{-1}): 2929, 1330, 1148, 1011, 753, 547, 516. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{12}H_{14}BrNNaO_2S$, 337.9821; found, 337.9812.

4-Bromo-1-(4-methylbezenesulfonyl)-1,2,3,3a,4,8b-hexahydroindeno[1,2-*b*]pyrrole (17b)



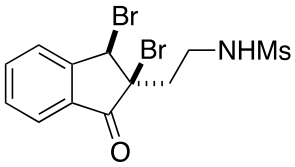
Synthesized according to GPP using **HSb**. 87%, pale yellow crystals. **m.p.:** 122-124º C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 1.48-1.58 (m, 1H), 1.92-2.01 (m, 1H), 2.46 (s, 3H), 3.03-3.09 (m, 1H), 3.24-3.28 (m, 1H), 3.39-3.44 (m, 1H), 5.22 (d, *J* = 1.1 Hz, 1H), 5.36 (d, *J* = 7.2 Hz, 1H), 7.32-7.43 (m, 5H), 7.78-7.86 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 21.7, 29.8, 49.6, 52.8, 54.0, 67.0, 125.9, 127.1, 127.8, 129.4, 130.1, 130.3, 134.5, 141.2, 142.6, 144.0. **IR** ν (cm^{-1}): 2990, 2959, 2885, 1596, 1492, 1450, 1338, 1295, 1092, 1010, 663, 585. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{18}H_{18}BrNNaO_2S$, 414.0134; found, 414.0133

4-Bromo-1-(4-nitrobenzenesulfonyl)-1,2,3,3a,4,8b-hexahydroindeno[1,2-*b*]pyrrole (17c)



Synthesized according to GPP using **HSb**. 57%, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 1.58-1.73 (m, 1H), 1.99-2.11 (m, 1H), 3.03-3.20 (m, 1H), 3.25-3.31 (m, 1H), 3.47-3.53 (m, 1H), 5.22 (d, *J* = 1.3 Hz, 1H), 5.39 (d, *J* = 7.1 Hz, 1H), 7.37-7.43 (m, 3H), 7.82 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.08-8.12 (m, 2H), 8.40-8.45 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 29.7, 49.6, 52.1, 54.3, 67.3, 124.7, 126.2, 127.0, 129.0, 129.8, 130.4, 141.4, 141.6, 143.6, 150.5. **IR** ν (cm^{-1}): 2922, 1526, 1345, 1162, 1104, 1005, 734, 607. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{17}H_{15}BrN_2NaO_4S$, 444.9828; found, 444.9825.

_N_-(2-(1,2-Dibromo-3-oxo-2,3-dihydroinden-2-yl)ethyl)methanesulfonamide (17d)



Synthesized according to GPP using **HSb**. 37% (68% yield employing 5 equiv of **HSb**), yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.47-2.56 (m, 1H), 2.61-2.77 (m, 1H), 3.03 (s, 3H), 3.63-3.79 (m, 2H), 4.81 (s, 1H), 5.90 (s, 1H), 7.56 (td, *J* = 7.5, 1.1 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.75 (td, *J* = 7.5, 1.2 Hz, 1H), 7.82-7.90 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 36.9, 40.8, 41.1, 53.7, 64.5, 126.0, 127.2, 130.9, 131.4, 136.7, 149.9, 195.5. **IR** ν (cm^{-1}): 3227, 2919, 1722, 1314, 1143, 756, 518. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{12}H_{13}Br_2NNaO_2S$, 431.8875; found, 431.8864.

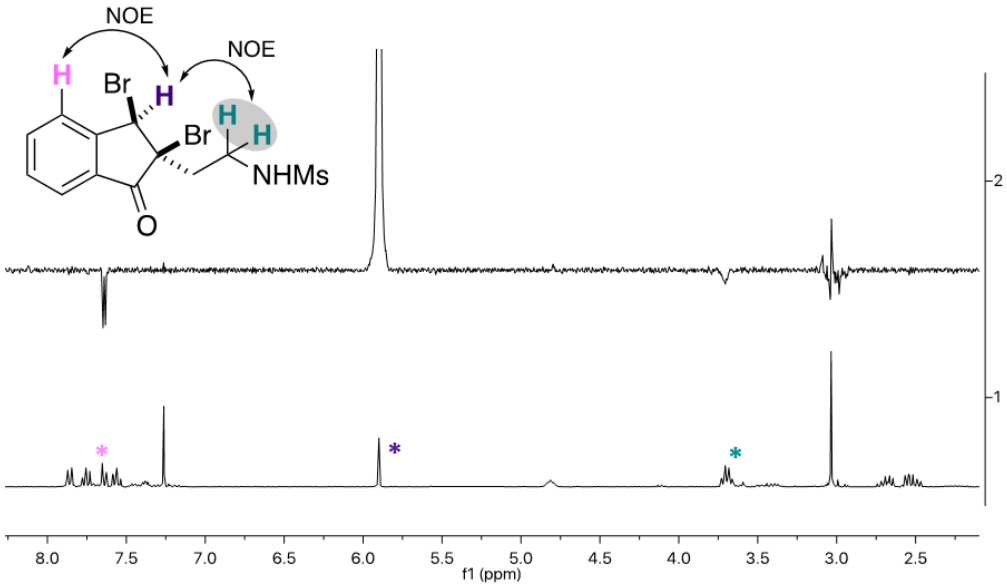
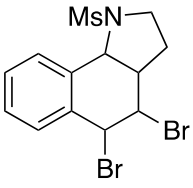


Figure 2.4**. NOE experiment for substrate **17d.

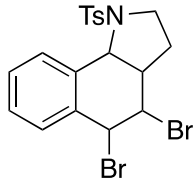
4,5-Dibromo-1-(methylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*g*]índole (17e)



Synthesized according to GPP using **HSb**. 48%, yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.22-2.31 (m, 1H), 2.74-2.80 (m, 1H), 2.95 (s, 3H), 2.98-3.06 (m, 1H), 3.42-3.61 (m, 2H), 5.09 (dd, *J* = 3.2, 2.0 Hz, 1H), 5.19 (d, *J* = 6.9 Hz, 1H), 5.79 (s, 1H), 7.33-7.44 (m, 3H), 7.89 (d, *J* = 7.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 29.8, 35.9, 45.6, 47.4, 48.7, 50.0, 58.6, 128.7, 130.0, 130.3,

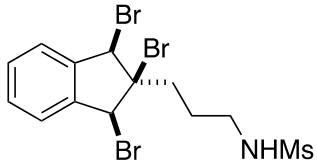
131.0, 131.5, 133.9. **IR** ν (cm^{-1}): 2839, 1324, 1147, 1015, 962, 751, 513. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{15}NNaO_2S^{79}Br^{81}Br$, 431.9062; found, 431.9059.

4,5-Dibromo-1-(4-methylbezenesulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*g*]índole (17f)



Synthesized according to GPP using **HSb**. 55%, brown crystals. **m.p.:** 145-146º C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 1.88-1.97 (m, 1H), 2.16-2.24 (m, 1H), 2.47 (s, 3H), 2.54-2.65 (m, 1H), 3.26 (td, *J* = 10.3, 7.2 Hz, 1H), 3.55 (ddd, *J* = 10.6, 8.6, 2.0 Hz, 1H), 4.89 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.21 (d, *J* = 6.9 Hz, 1H), 5.73 (s, 1H), 7.31-7.47 (m, 5H), 7.79-7.83 (m, 2H), 8.03-8.06 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 21.7, 29.4, 44.3, 47.2, 48.8, 50.1, 59.1, 127.8, 128.5, 130.0, 130.2, 130.4, 130.7, 131.4, 134.0, 134.3, 144.2. **IR** ν (cm^{-1}): 3068, 2951, 1595, 1472, 1460, 1348, 1156, 1088, 1010, 757, 657, 541. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{12}H_{13}Br_2N$, 505.9395; found, 505.9387.

***N*-(3-(1,2,3-Tribromo-2,3-dihydroinden-2-yl)propyl)methanesulfonamide (17g)**



Synthesized according to GPP using **HSb**. 53%, white solid. **m.p.**: 113-114 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 2.06-2.23 (m, 2H), 2.51-2.70 (m, 2H), 3.03 (s, 3H), 3.34-3.39 (m, 2H), 4.48 (t, *J* = 6.3 Hz, 1H), 5.80 (s, 2H), 7.3-7.56 (m, 4H). **^{13}C NMR** = (125 MHz, $CDCl_3$): δ = 28.0, 37.9, 40.8, 43.1, 57.6, 75.8, 126.2, 130.5, 141.6. **IR** ν (cm^{-1}): 3208, 2932, 1142, 1069, 982, 720, 525. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{16}Br_3NNaO_2S$, 509.8344; found, 509.8358.

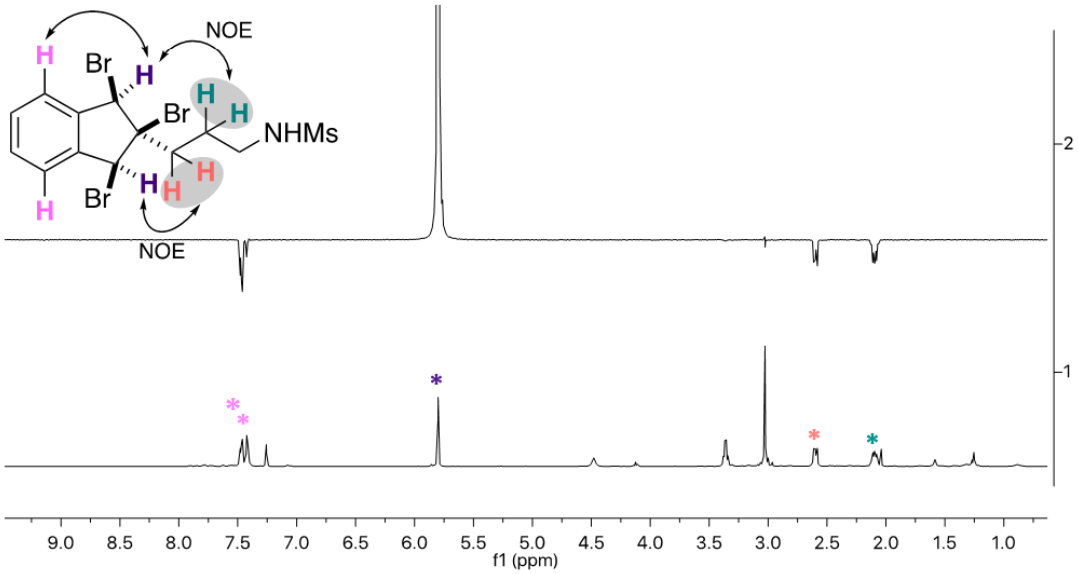
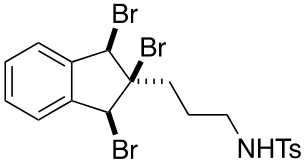


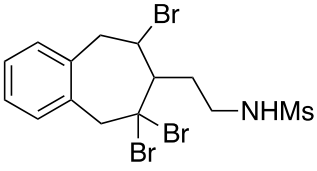
***Figure 2.5**. NOE experiment for substrate **17g**.*

4-Methyl-*N*-(3-(1,2,3-tribromo-2,3-dihydro-1*H*-inden-2-yl)propyl) benzenesulfonamide (17h)



Synthesized according to GPP using **HSb**. 61%, white solid. **m.p.:** 144-146 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.92-2.04 (m, 2H), 2.43 (s, 3H), 2.44-2.53 (m, 2H), 3.11-3.20 (m, 2H), 4.58 (s, 1H), 5.73 (s, 2H), 7.30-7.35 (m, 2H), 7.38-7.50 (m, 4H), 7.80 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 21.7, 27.5, 37.8, 43.0, 57.5, 75.9, 126.1, 127.4, 130.0, 130.4, 137.0, 141.6, 143.7. **IR** ν (cm^{-1}): 3207, 2922, 1324, 1153, 1088, 816, 664, 530. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{19}H_{19}NO_2S^{79}Br_2{}^{81}Br$, 563.8672; found, 563.8692.

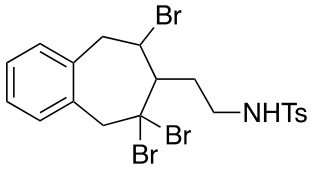
***N*-(2-(6,6,8-Tribromo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)ethyl)methanesulfonamide (22a)**



Synthesized according to GPP, using 3 equivalents of **HSb**. 71%, white solid. **m.p.:** 168-169 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.01-2.10 (m, 1H), 2.36-2.60 (m, 2H), 3.00 (s, 3H), 3.42-3.69 (m, 4H), 3.82-4.24 (m, 3H), 4.50 (bs, 1H), 7.05-7.52 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 40.9, 43.9, 44.9, 55.5, 56.9, 57.0, 68.3, 73.2, 128.0, 128.6, 128.8, 129.9, 131.7, 136.5. **IR** ν (cm^{-1}): 3257, 2959, 1454, 1317, 1157, 1143.

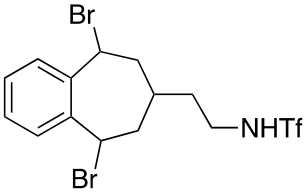
HRMS (m/z): $[M+Na]^+$ calcd. for $C_{14}H_{18}Br_3NNaO_2S$, 523.8501; found, 523. 8483.

4-Methyl-*N*-(2-(6,6,8-tribromo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)ethyl)benzenesulfonamide (22b)



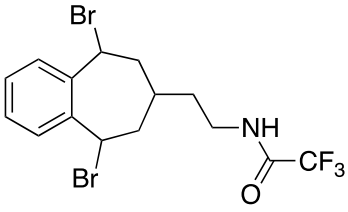
Synthesized according to GPP, using 3 equivalents of **HSb**. 74%, white solid. **m.p.:** 167-168 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 1.83-1.91 (m, 1H), 2.24-2.36 (m, 2H), 2.40-2.42 (m, 1H), 2.42 (s, 3H), 3.35-3.60 (m, 4H), 3.98 (s, 2H), 4.63 (t, *J* = 6.1 Hz, 1H), 7.10-7.27 (m, 4H), 7.29-7.33 (m, 2H), 7.78-7.82 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 21.7, 43.7, 44.8, 55.3, 56.8, 56.9, 68.1, 73.0, 127.5, 127.9, 128.5, 128.7, 129.8, 129.8, 131.6, 136.5, 137.3, 143.5. **IR** ν (cm^{-1}): 3288, 2962, 2922, 1421, 1316, 1154. **HRMS** (m/z): $[M+Na]^+$ calcd for $C_{20}H_{22}Br_3NNaO_2S$, 599.8814; found, 599.8799.

***N*-(2-(5,9-Dibromo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)ethyl)-1,1,1-trifluoromethanesulfonamide (22c)**



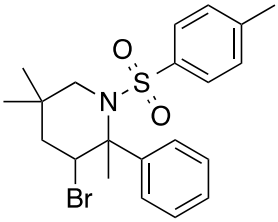
Synthesized according to GPP, using 3 equivalents of **HSb**. 21%, yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.71-1.78 (m, 2H), 1.94-2.05 (m, 2H), 2.42 (dd, *J* = 14.7, 5.3 Hz, 2H), 3.07 (d, *J* = 6.2 Hz, 1H), 3.44-3.51 (m, 2H), 4.87 (t, *J* = 5.5 Hz 1H), 5.61 (dd, *J* = 5.2, 2.4 Hz, 2H), 7.27-7.37 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.6, 37.4, 42.3, 43.2, 55.4, 119.8 (q, *J* = 322.5 Hz), 129.5, 132.2, 140.1. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.3. **IR** ν (cm^{-1}): 3309, 2927, 1370, 1187, 1144, 760, 606. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{14}H_{15}Br_2F_3NO_2S$, 475.9148; found, 475.9149.

***N*-(2-(5,9-Dibromo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)ethyl)-2,2,2-trifluoroacetamide (22d)**



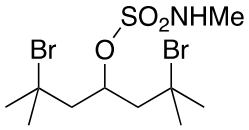
Synthesized according to GPP, using 3 equivalents of **HSb**. 37%, brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.72 (dt, *J* = 8.8, 7.1 Hz, 2H), 1.99 (ddd, *J* = 14.8, 11.1, 2,4 Hz, 2H), 2.41-2.48 (m, 2H), 3.03-3.12 (m, 1H), 3.51-3.57 (m, 2H), 5.62 (dd, *J* = 5.2, 2.4 Hz, 2H), 6.42 (bs, 1H), 7.26-7.34 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.8, 35.7, 37.7, 43.1, 55.6, 115.9 (q, *J* = 288.1 Hz), 129.4, 132.2, 140.1, 157.4 (q, *J* = 37.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -75.6. **IR** ν (cm^{-1}): 3308, 2922, 2852, 1704, 1154, 762, 581. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{15}H_{15}Br_2F_3NO$, 439.9478, found 439.9457.

2,5,5-Trimethyl-2-phenyl-1-(4-methylbezenesulfonyl)piperidine (24)



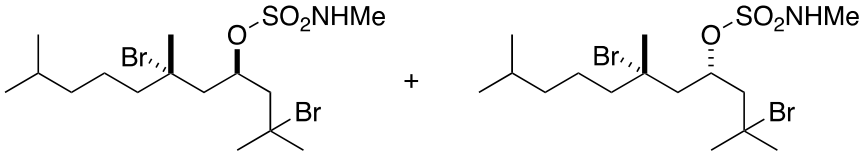
Synthesized according to the literature procedure.[95] 40%, white solid. **m.p.**: 160-161 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.05 (s, 3H), 1.12 (s, 3H), 2.09-1.96 (m, 5H), 2.40 (s, 3H), 3.14 (d, *J* = 12.8 Hz, 1H), 3.44 (dd, *J* = 13.0, 1.7 Hz, 1H), 4.54 (dd, *J* = 12.0, 5.4 Hz, 1H), 7.12-7.16 (m, 2H), 7.17-7.24 (m, 3H), 7.29-7.33 (m, 2H), 7.34-7.38 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 24.1, 29.0, 33.7, 45.2, 54.5, 59.8, 66.1, 127.3, 127.4, 127.5, 127.7, 129.2, 138.7, 143.0, 143.1. **IR** ν (cm^{-1}): 3050, 3015, 2958, 2936, 2872. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{27}NNaBrO_2S$, 458.0760; found, 458.0754.

2,6-Dibromo-2,6-dimethylheptan-4-yl methylsulfamate (26a)



Synthesized according to GPP using **HSb**. 75%, brownish oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.87 (s, 6H), 1.90 (s, 6H), 2.44 (dd, *J* = 5.3, 1.7 Hz, 4H), 2.86 (d, *J* = 5.0 Hz, 3H), 4.49- 4.55 (m, 1H), 5.10 (p, *J* = 5.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ =30.2, 34.3, 35.7, 52.4, 64.1, 79.9. **IR** ν(cm^{-1}): 3225, 1311, 1190, 869. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{10}H_{20}Br_2NO_3S$, 391.9536; found, 391.9524.

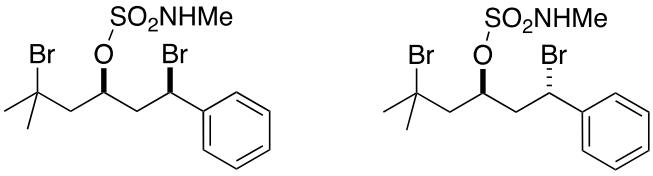
2,6-Dibromo-2,6,10-trimethylundecan-4-yl methylsulfamate (26b+26b')



(1:1)

Synthesized according to GPP using **HSb**. 45% combined yield, yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.84-0.94 (m, 12H, CH-(C**H**$_3$)$_2$), 1.16-1.26 (m, 4H), 1.42-1.64 (m, 6H), 1.69-1.97 (m, 22H), 2.30-2.56 (m, 6H), 2.78-2.98 (m, 8H), 4.40-4.56 (m, 2H), 5.08-5.20 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.7, 23.7, 23.8, 28.0, 28.0, 29.8, 30.2, 30.2, 31.5, 32.4, 34.2, 34.5, 35.7, 35.9, 38.9, 38.9, 46.0, 47.3, 50.4, 50.8, 52.4, 52.6, 64.0, 64.3, 70.2, 70.2, 79.8, 80.0. **IR** ν(cm^{-1}): 3231, 2890, 1368, 1191, 853. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{15}H_{30}NO_3S^{79}Br_2$, 462.0319; found, 462.0296.

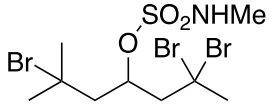
1,5-Dibromo-5-methyl-1-phenylhexan-3-yl methylsulfamate (26c+26c')



(58:42)

Synthesized according to GPP using **HSb**. A *dr* of 1:1 was determined from the crude ^{1}H NMR. The products after the purification by column chromatography were slightly enriched in favor of the *syn* isomer. The major diasteromer was assigned using 2D-NMR spectra analysis. 47% combined yield, yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.81 (d, *J* = 10.6 Hz, 6H *major*), 1.89 (d, *J* = 4.2 Hz, 6H *minor*), 2.27- 2.62 (m, 3H *major* + 3H *minor*), 2.85 (d, *J* = 5.3 Hz, 3H *major*), 2.91 (d, *J* = 5.2 Hz, 3H *minor*), 2.74-3.02 (m, 1H *major* + 1H *minor*), 4.35 (d, *J* = 5.3 Hz, 1H *major*), 4.45 (d, *J* = 5.4 Hz, 1H *minor*), 4.77 (dq, *J* = 6.5, 5.4 Hz, 1H *major*), 5.03- 5.10 (m, 1H *minor*), 5.13 (t, *J* = 7.5 Hz, 1H *major*), 5.18-5.25 (m, 1H *minor*), 7.13- 7.66 (m, 5H *major* + 5H *minor*). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.3, 30.4, 33.8, 34.2, 35.7, 35.9, 45.9, 46.0, 49.3, 51.1, 51.3, 51.4, 63.4, 63.5, 79.6, 79.9, 128.9, 129.0, 129.0, 129.1, 140.8, 141.3. **IR** ν(cm^{-1}): 3220, 1303, 1195, 891. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{14}H_{20}Br_2NO_3S$, 439.9536; found, 439.9548

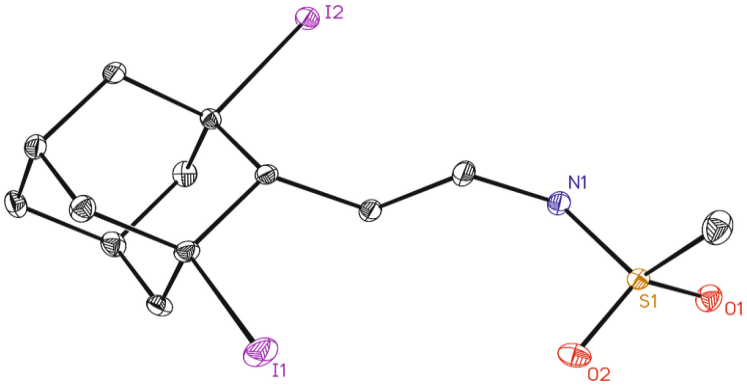
4,4-Dibromo-2-(2-bromo-2-methylpropyl)-*N*-methylpentane-1-sulfonamide (26d)



Synthesized according to GPP, using 4 equivalents of **HSb** 88%, brownish oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.89 (s, 3H), 1.92 (s, 3H), 2.45 – 2.57 (m, 2H), 2.66 (s, 3H), 2.88 (d, *J* = 5.2 Hz, 3H), 3.01 – 3.14 (m, 2H), 4.47 (d, *J* = 5.1 Hz, 1H), 5.15 (p, *J* = 5.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ =30.3, 34.4, 35.7, 41.7, 51.8, 57.1, 62.3, 63.5, 79.8. **IR** ν(cm^{-1}): 3227, 1307, 1190, 897. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_9H_{17}Br_3NO_3S$, 455.8485; found, 455. 8478.

X-ray analytical data

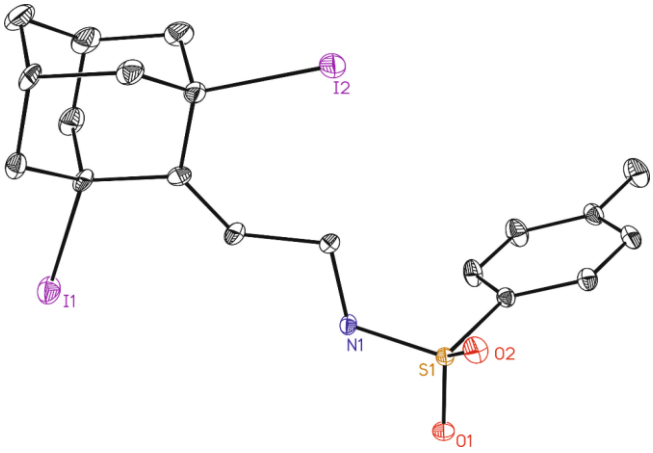
*X-Ray data of compound **2a***



Identification code	CCDC 1838889
Empirical formula	C13 H21 I2 N O2 S
Formula weight	509.17
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 11.58400(10)Å α= 90°.
	b = 10.37410(10)Å β = 103.0020(10)°.
	c = 13.69220(10)Å γ = 90°.
Volume	1603.25(2) $Å^3$
Z	4
Density (calculated)	2.109 Mg/m^3
Absorption coefficient	4.052 mm^{-1}
F(000)	976
Crystal size	0.25 x 0.25 x 0.2 mm^3
Theta range for data collection	1.804 to 32.249°.
Index ranges	-17<=h<=16,-15<=k<=15,-20<=l<=20
Reflections collected	53430
Independent reflections	5498[R(int) = 0.0245]
Completeness to theta =32.249°	96.6%

Absorption correction	Multi-scan
Max. and min. transmission	0.498 and 0.383
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5498/ 510/ 348
Goodness-of-fit on F^2	1.280
Final R indices [I>2sigma(I)]	R1 = 0.0171, wR2 = 0.0435
R indices (all data)	R1 = 0.0177, wR2 = 0.0437
Largest diff. peak and hole	0.700 and -0.540 e.Å^{-3}

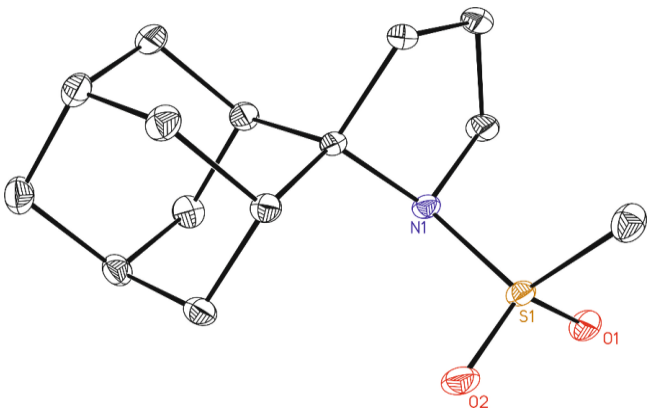
*X-Ray data of compound **2b***



Identification code	CCDC 1838890
Empirical formula	C19 H23 I2 N O2 S
Formula weight	583.24
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 11.0053(2)Å α= 90°.
	b = 6.18540(10)Å β = 95.4070(10)°.
	c = 29.1965(4)Å γ = 90°.
Volume	1978.63(6) Å^3

Z	4
Density (calculated)	1.958 Mg/m^3
Absorption coefficient	3.297 mm^{-1}
F(000)	1128
Crystal size	? x ? x ? mm^3
Theta range for data collection	1.924 to 32.067°.
Index ranges	-16<=h<=16,-9<=k<=9,-43<=l<=43
Reflections collected	11776
Independent reflections	11776[R(int) =?]
Completeness to theta =32.067°	97.0%
Absorption correction	Multi-scan
Max. and min. transmission	0.908 and 0.698
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11776/ 0/ 229
Goodness-of-fit on F^2	1.204
Final R indices [I>2sigma(I)]	R1 = 0.0355, wR2 = 0.1072
R indices (all data)	R1 = 0.0362, wR2 = 0.1076
Largest diff. peak and hole	1.687 and -0.962 $e.Å^{-3}$

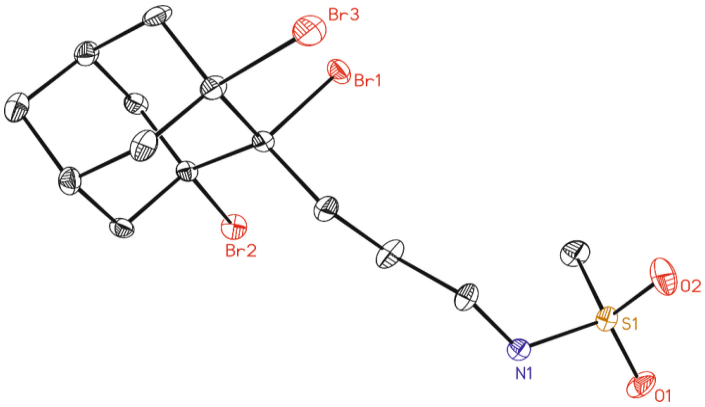
*X-Ray data of compound **2c***



Identification code	CCDC 1838891
Empirical formula	C14 H23 N O2 S

Formula weight	269.39
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 16.7403(2)Å α= 90°.
	b = 7.45020(8)Å β = 107.3720(14)°.
	c = 10.88900(14)Å γ = 90°.
Volume	1296.12(3) $Å^3$
Z	4
Density (calculated)	1.381 Mg/m^3
Absorption coefficient	0.244 mm^{-1}
F(000)	584
Crystal size	? x ? x ? mm^3
Theta range for data collection	2.550 to 32.107°.
Index ranges	-25<=h<=24,-11<=k<=11,-15<=l<=16
Reflections collected	41491
Independent reflections	4403[R(int) = 0.0234]
Completeness to theta =32.107°	96.7%
Absorption correction	Multi-scan
Max. and min. transmission	0.964 and 0.742
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4403/ 0/ 164
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0293, wR2 = 0.0780
R indices (all data)	R1 = 0.0340, wR2 = 0.0800
Largest diff. peak and hole	0.489 and -0.277 e.$Å^{-3}$

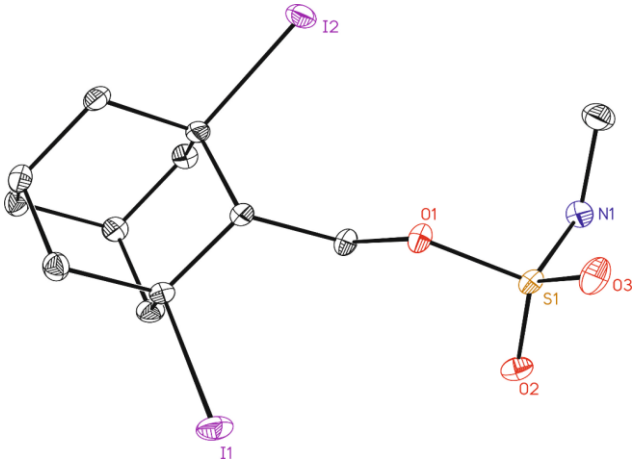
X-Ray data of compound ***4***



Identification code	CCDC 1838892
Empirical formula	C14 H22 Br3 N O2 S
Formula weight	508.11
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 15.0290(7)Å α= 90°.
	b = 9.0726(4)Å β = 94.6124(13)°.
	c = 12.5886(5)Å γ = 90°.
Volume	1710.92(13) $Å^3$
Z	4
Density (calculated)	1.973 Mg/m^3
Absorption coefficient	7.199 mm^{-1}
F(000)	1000
Crystal size	0.30 x 0.20 x 0.01 mm^3
Theta range for data collection	2.625 to 30.682°.
Index ranges	-19<=h<=21,-12<=k<=12,-13<=l<=17
Reflections collected	19727
Independent reflections	5053[R(int) = 0.0395]
Completeness to theta =30.682°	95.5%

Absorption correction	Multi-scan
Max. and min. transmission	0.931 and 0.716
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5053/ 0/ 196
Goodness-of-fit on F^2	1.001
Final R indices [I>2sigma(I)]	R1 = 0.0280, wR2 = 0.0595
R indices (all data)	R1 = 0.0425, wR2 = 0.0641
Largest diff. peak and hole	0.743 and -0.484 e.$Å^{-3}$

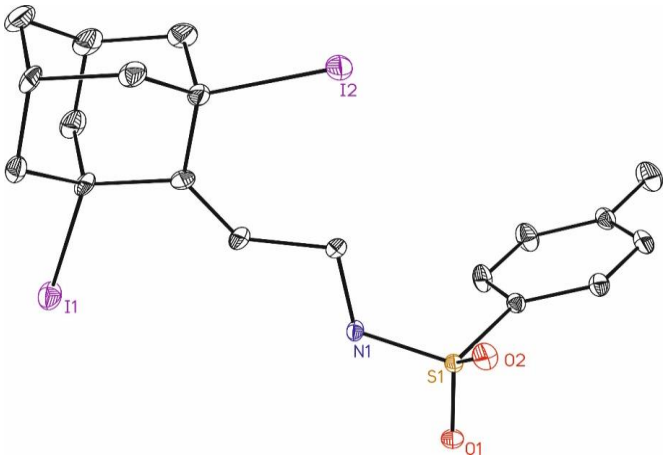
X-Ray data of compound ***6***



Identification code	CCDC 1838893
Empirical formula	C12 H19 I2 N O3 S1
Formula weight	511.14
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 10.3858(2)Å α= 90°.
	b = 8.60040(10)Å β = 106.354(2)°.
	c = 18.4118(3)Å γ = 90°.
Volume	1578.04(5) $Å^3$

Z	4
Density (calculated)	2.151 Mg/m^3
Absorption coefficient	4.121 mm^{-1}
F(000)	976
Crystal size	0.3 x 0.15 x 0.15 mm^3
Theta range for data collection	2.044 to 39.883°.
Index ranges	-18<=h<=18,-15<=k<=15,-32<=l<=33
Reflections collected	63411
Independent reflections	9570[R(int) = 0.0225]
Completeness to theta =39.883°	98.299995%
Absorption correction	Multi-scan
Max. and min. transmission	0.577 and 0.444
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9570/ 0/ 173
Goodness-of-fit on F^2	1.197
Final R indices [I>2sigma(I)]	R1 = 0.0217, wR2 = 0.0531
R indices (all data)	R1 = 0.0240, wR2 = 0.0538
Largest diff. peak and hole	1.624 and -1.082 $e.Å^{-3}$

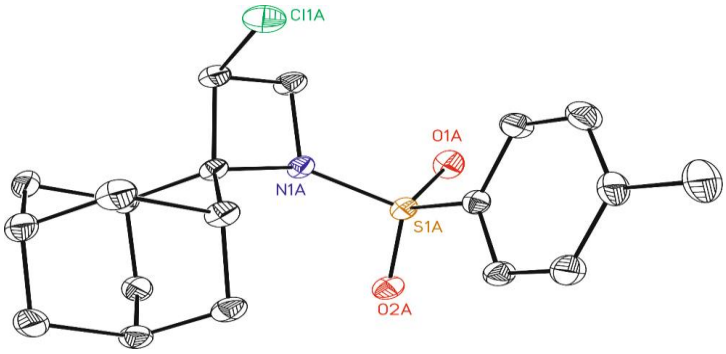
*X-Ray data of compound **13***



Identification code	CCDC 1838898

Empirical formula	C19 H23 I2 N O2 S
Formula weight	583.24
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 11.0053(2)Å α= 90°.
	b = 6.18540(10)Å β = 95.4070(10)°.
	c = 29.1965(4)Å γ = 90°.
Volume	1978.63(6) $Å^3$
Z	4
Density (calculated)	1.958 Mg/m^3
Absorption coefficient	3.297 mm^{-1}
F(000)	1128
Crystal size	? x ? x ? mm^3
Theta range for data collection	1.924 to 32.067°.
Index ranges	-16<=h<=16,-9<=k<=9,-43<=l<=43
Reflections collected	11776
Independent reflections	11776[R(int) =?]
Completeness to theta =32.067°	97.0%
Absorption correction	Multi-scan
Max. and min. transmission	0.908 and 0.698
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11776/ 0/ 229
Goodness-of-fit on F^2	1.204
Final R indices [I>2sigma(I)]	R1 = 0.0355, wR2 = 0.1072
R indices (all data)	R1 = 0.0362, wR2 = 0.1076
Largest diff. peak and hole	1.687 and -0.962 $e.Å^{-3}$

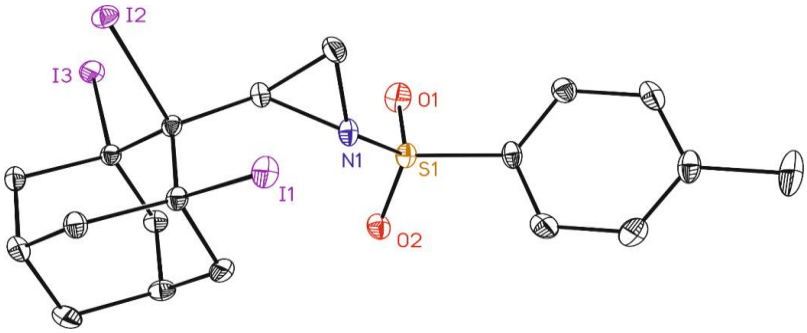
X-Ray data of compound ***14***



Identification code	CCDC 1838895
Empirical formula	C19 H24 Cl N O2 S
Formula weight	365.90
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 12.24825(13)Å α= 89.3167(8)°.
	b = 16.86662(18)Å β = 87.5127(8)°.
	c = 17.04271(17)Å γ = 87.9184(9)°.
Volume	3514.97(6) $Å^3$
Z	8
Density (calculated)	1.383 Mg/m^3
Absorption coefficient	0.348 mm^{-1}
F(000)	1552
Crystal size	? x ? x ? mm^3
Theta range for data collection	1.665 to 40.097°.
Index ranges	-22<=h<=22,-30<=k<=30,-30<=l<=30
Reflections collected	204940
Independent reflections	42752[R(int) = 0.0382]
Completeness to theta =40.097°	97.5%
Absorption correction	Multi-scan
Max. and min. transmission	0.950 and 0.731

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	42752/ 0/ 869
Goodness-of-fit on F^2	1.082
Final R indices [I>2sigma(I)]	R1 = 0.0461, wR2 = 0.1212
R indices (all data)	R1 = 0.0653, wR2 = 0.1288
Largest diff. peak and hole	0.819 and -0.513 e.Å^{-3}

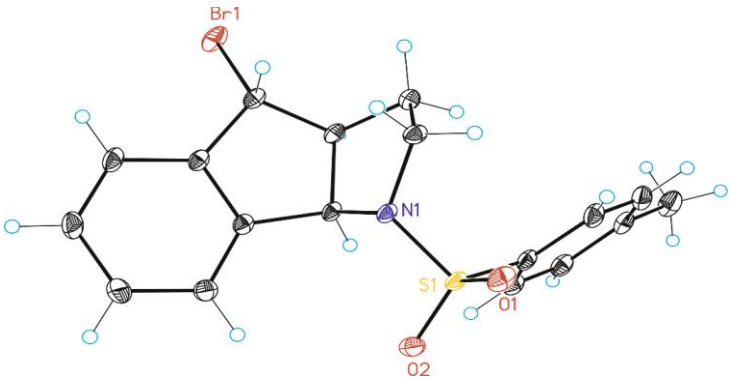
*X-Ray data of compound **15***



Identification code	CCDC 1838894
Empirical formula	C19 H22 I3 N O2 S
Formula weight	709.13
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 16.74294(13)Å α= 90°.
	b = 7.69626(5)Å β = 107.5359(8)°.
	c = 17.13630(13)Å γ = 90°.
Volume	2105.53(3) Å^3
Z	4
Density (calculated)	2.237 Mg/m^3
Absorption coefficient	4.567 mm^{-1}
F(000)	1336
Crystal size	? x ? x ? mm^3

Theta range for data collection	2.434 to 28.279°.
Index ranges	-22<=h<=22,-10<=k<=10,-22<=l<=22
Reflections collected	71100
Independent reflections	5227[R(int) = 0.0261]
Completeness to theta =28.279°	100.0%
Absorption correction	Multi-scan
Max. and min. transmission	0.658 and 0.506
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5227/ 57/ 263
Goodness-of-fit on F^2	1.216
Final R indices [I>2sigma(I)]	R1 = 0.0209, wR2 = 0.0509
R indices (all data)	R1 = 0.0210, wR2 = 0.0510
Largest diff. peak and hole	2.302 and -1.214 e.$Å^{-3}$

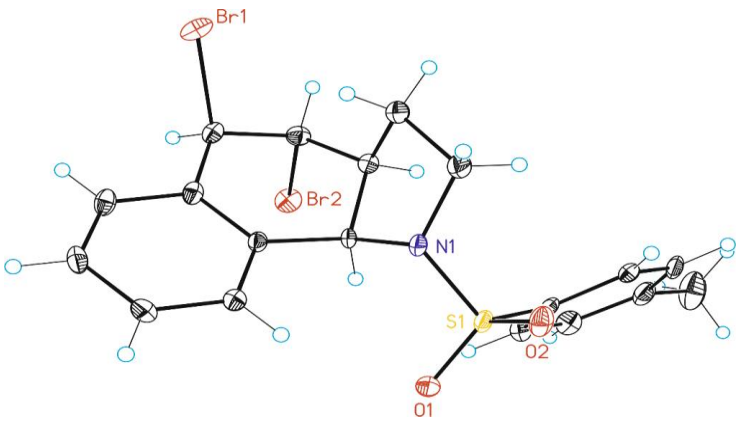
*X-Ray data of compound **17b***



Identification code	CCDC 1838896
Empirical formula	C18 H18 Br N O2 S
Formula weight	392.30
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.5287(4)Å α= 80.7457(12)°.

	b = 10.6006(5)Å β = 77.8958(12)°.
	c = 10.8502(6)Å γ = 77.6530(13)°
Volume	820.99(7) $Å^3$
Z	2
Density (calculated)	1.587 Mg/m^3
Absorption coefficient	2.639 mm^{-1}
F(000)	400
Crystal size	0.50 x 0.40 x 0.10 mm^3
Theta range for data collection	1.934 to 34.348°.
Index ranges	-11<=h<=9,-14<=k<=16,-16<=l<=16
Reflections collected	12130
Independent reflections	6377[R(int) = 0.0305]
Completeness to theta =34.348°	92.9%
Absorption correction	Multi-scan
Max. and min. transmission	0.778 and 0.397
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6377/ 0/ 209
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0338, wR2 = 0.0898
R indices (all data)	R1 = 0.0391, wR2 = 0.0923
Largest diff. peak and hole	0.812 and -1.519 $e.Å^{-3}$

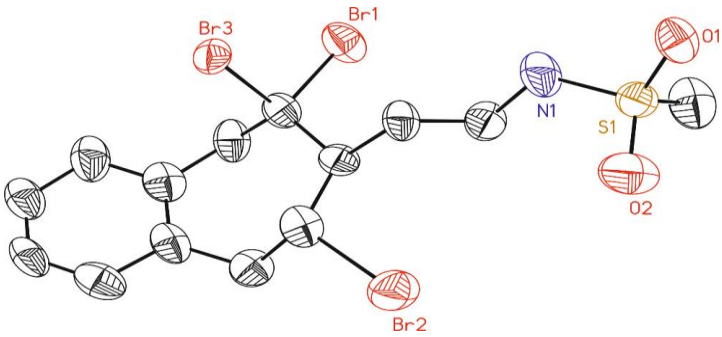
*X-Ray data of compound **17f***



Identification code	CCDC 1838897	
Empirical formula	C19 H19 Br2 N O2 S	
Formula weight	485.23	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.4674(4)Å	α= 90°.
	b = 10.0979(4)Å	β = 90°.
	c = 19.6421(8)Å	γ = 90°.
Volume	1877.80(13) $Å^3$	
Z	4	
Density (calculated)	1.716 Mg/m^3	
Absorption coefficient	4.441 mm^{-1}	
F(000)	968	
Crystal size	0.30 x 0.20 x 0.20 mm^3	
Theta range for data collection	2.074 to 30.581°.	
Index ranges	-13<=h<=11,-12<=k<=14,-20<=l<=28	
Reflections collected	16820	
Independent reflections	5698[R(int) = 0.0290]	
Completeness to theta =30.581°	99.4%	

Absorption correction	Multi-scan
Max. and min. transmission	0.470 and 0.239
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5698/ 0/ 228
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R1 = 0.0273, wR2 = 0.0649
R indices (all data)	R1 = 0.0307, wR2 = 0.0664
Flack parameter	x =0.504(8)
Largest diff. peak and hole	0.949 and -0.557 e.$Å^{-3}$

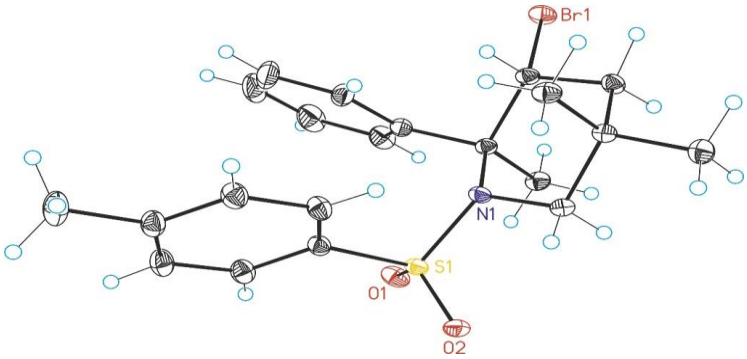
*X-Ray data of compound **22a***



Identification code	CCDC 1838890	
Empirical formula	C16 H21 Br3 N2 O2 S	
Formula weight	545.14	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.84205(16)Å	α= 90°.
	b = 9.9441(3)Å	β = 90°.
	c = 30.5368(8)Å	γ = 90°.
Volume	2077.67(9) $Å^3$	
Z	4	
Density (calculated)	1.743 Mg/m^3	

Absorption coefficient	5.936 mm^{-1}
F(000)	1072
Crystal size	? x ? x ? mm^3
Theta range for data collection	2.154 to 26.418°.
Index ranges	-8<=h<=8,-12<=k<=12,-38<=l<=38
Reflections collected	38698
Independent reflections	4263[R(int) = 0.1086]
Completeness to theta =26.418°	99.5%
Absorption correction	Multi-scan
Max. and min. transmission	0.756 and 0.582
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4263/ 99/ 225
Goodness-of-fit on F^2	1.128
Final R indices [I>2sigma(I)]	R1 = 0.0761, wR2 = 0.2144
R indices (all data)	R1 = 0.0863, wR2 = 0.2210
Flack parameter	x =0.47(4)
Largest diff. peak and hole	1.362 and -1.293 e.$Å^{-3}$

*X-Ray data of compound **24***



Identification code	CCDC 1838899
Empirical formula	C21 H25.97 Br Cl0.04 N O2 S
Formula weight	437.60
Temperature	100(2) K
Wavelength	0.71073 Å

Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 12.6378(3)Å α= 90°.
	b = 6.40927(15)Å β = 98.827(2)°.
	c = 24.6143(6)Å γ = 90°.
Volume	1970.13(8) $Å^3$
Z	4
Density (calculated)	1.475 Mg/m^3
Absorption coefficient	2.213 mm^{-1}
F(000)	906
Crystal size	0.25 x 0.20 x 0.20 mm^3
Theta range for data collection	2.511 to 35.630°.
Index ranges	-20<=h<=20,-10<=k<=10,-40<=l<=39
Reflections collected	42341
Independent reflections	8763[R(int) = 0.0306]
Completeness to theta =35.630°	96.3%
Absorption correction	Multi-scan
Max. and min. transmission	0.666 and 0.512
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8763/ 0/ 247
Goodness-of-fit on F^2	1.036
Final R indices [I>2sigma(I)]	R1 = 0.0222, wR2 = 0.0605
R indices (all data)	R1 = 0.0277, wR2 = 0.0624
Largest diff. peak and hole	0.527 and -0.333 e.$Å^{-3}$

Chapter III. Enantioselective Synthesis of Nicotine via an Iodine-Mediated Hofmann–Löffler reaction

1. *N*-Heterocycles in organic synthesis

N-Heterocyclic compounds are of great importance in synthetic organic chemistry, as well as in the pharmaceutical and agrochemical industry and material science (Figure 3.1). In particular, pyrrolidine, piperidine, and morpholine derivatives are present in many natural and non-natural compounds with interesting biological properties. Nitrogen-containing alkaloids bearing five-membered *N*-heterocycles represent some of the most used organocatalysts and are essential building blocks in organic synthesis.

Pyrrolidine derivatives are common among natural alkaloids, such as nicotine, or amino acids, such as proline. As mentioned in Section 1.2.1.3., intramolecular Csp^3–H direct amination represents an effective method for constructing nitrogen heterocyclic scaffolds. In particular, many efforts have been made in radical chemistry using *N*-centered radicals to form pyrrolidine and piperidine rings for the total synthesis of alkaloids.

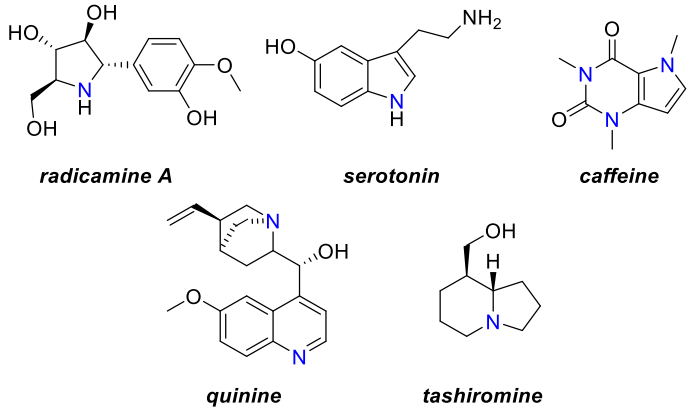
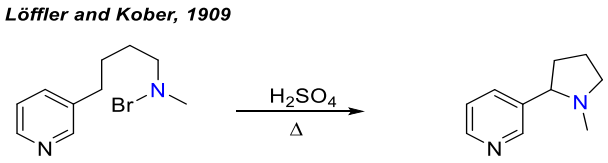


Figure 3.1. *Examples of natural products containing N-heterocycles derivatives.*

2. Hofmann-Löffler reaction in total synthesis

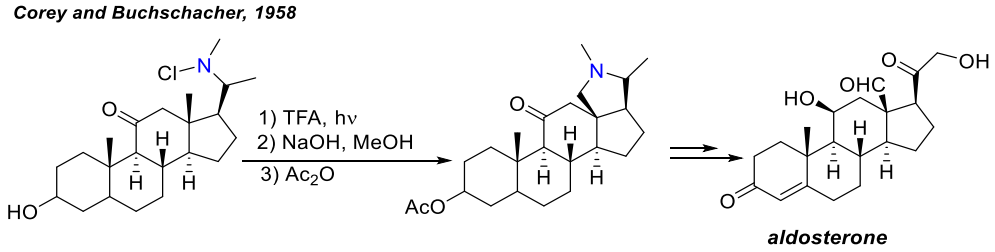
The Hofmann-Löffler reaction offers an efficient method to increase the molecular complexity from unexpensive and simpler precursors.

The Hofmann-Löffler-Freytag reaction represents the earliest example of producing nitrogen centered radicals to generate pyrrolidine heterocycles from simple linear substrates. The first example applied in natural product synthesis was the formation of the racemic natural product nicotine in 1909 by Löffler and Kober,[81] by a clean late-stage C–H amination at the benzylic secondary position (Scheme 3.1). Due to the absence of enantiocontrol, the racemic compound was obtained. For this transformation, harsh conditions, such as concentrated sulfuric acid and high temperature, were necessary.



Scheme 3.1. *Non-enantioselective synthesis of nicotine through Hofmann-Löffler late-stage amination.*

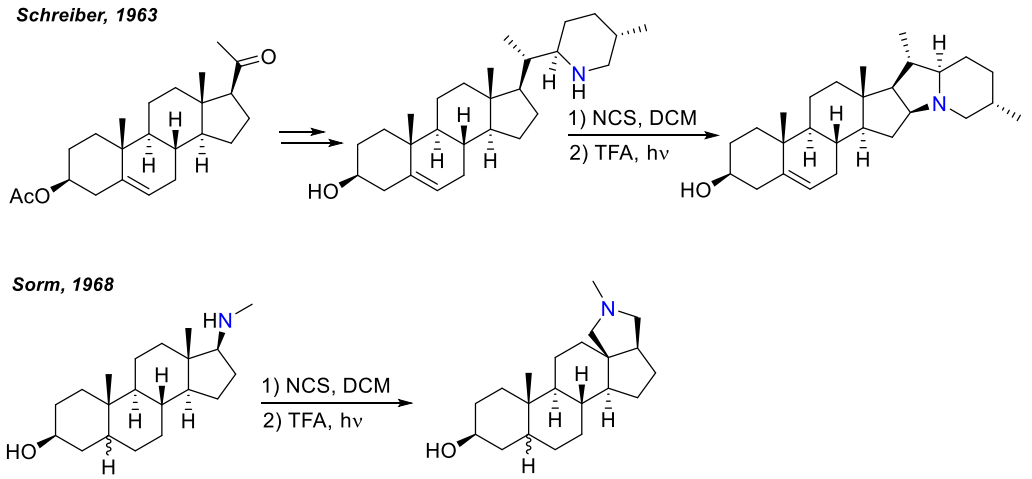
In 1958, the groups of Corey and Arigoni independently published a method for C-18 steroid functionalization that provided the skeleton of the *Holarrhena* alkaloids (Scheme 3.2).[191] Thus, a directed-radical chain decomposition of *N*-chloro-20-aminosteroid upon irradiation with ultraviolet light under acidic conditions and subsequent cyclization with the use of base led to the formation of the pyrrolidine ring. Later, Wolff described a partial synthesis of aldosterone via the Hofmann-Löffler reaction.[192]



Scheme 3.2. *Hofmann-Löffler reaction for functionalization of C18 in steroid.*

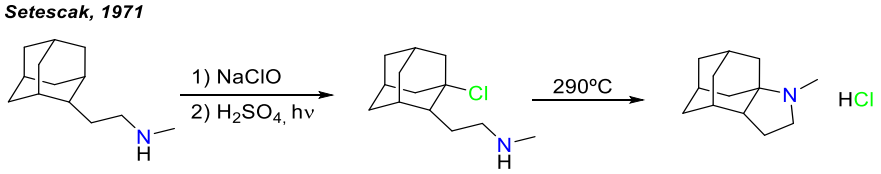
During this decade, several synthetic chemists were interested in applying this reaction to synthesize several steroids and other intermediates.[193] Adam and Schreiber reported in 1963 the synthesis of steroids starting from commercially available pregnenolone acetate as the precursor (Scheme 3.3. Top).[194] Furthermore, Sorm synthesized 18-dimethylamino-3-β-hydroxyandrostan-17-one via a Hofmann-Löffler reaction (Scheme 3.3. Bottom).[195]

[191] (a) E. J. Corey, W. R. Hertler, *J. Am. Chem. Soc.* **1958**, *80*, 2903. (b) P. Buchschacher, J. Kalvoda, D. Arigoni, O. Jeger, *J. Am. Chem. Soc.* **1958**, *80*, 2905.
[192] M. E. Wolff, J. F. Kerwin, F. F. Owings, B. B. Lewis, B. Blank A. Magnani, V. Georgian, *J. Am. Chem. Soc.* **1960**, *82*, 4117.
[193] (a) J. F. Kerwin, M. E. Wolff, F. F. Owings, B. B. Lewis, B. Blank A. Magnani, V. Georgian, *J. Org. Chem.* **1962**, *27*, 3628. (b) M. E. Wolff, *Chem. Rev*. **1963**, *63*, 55.
[194] G. Adam, K. Schreiber, *Tetrahedron Lett.* **1963**, *4*, 943.
[195] J. Hora, F. Šorm, *Chem. Commun*. **1968**, *33*, 2059.



Scheme 3.3. *1,5-HAT process for functionalization of steroids.*

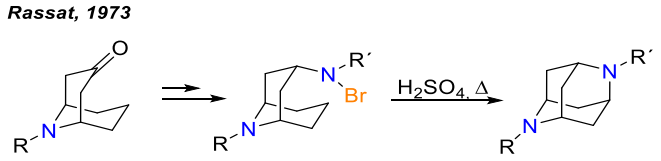
Setescak and Narayanan reported in 1971 the synthesis of aminoadamantane and some derivatives, which showed interesting biological activity.[196] Here, a Hofmann-Löffler reaction via a six-atom cyclic transition state led to chlorination at the tertiary position and, finally, to the formation of 1-methyladamantano[1,2-*b*]pyrrolidine (Scheme 3.4).



Scheme 3.4. *Synthesis of 1-methyladamantano[1,2-b] pyrrolidine.*

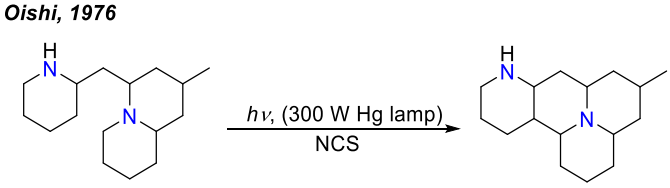
Uskokovic applied this methodology for the generation of intermediates of the *Cinchona* alkaloids.[197] The same research group reported the synthesis of the key intermediate meroquinene.[198] Dupeyre and Rassat published the synthesis of 2,6-diazaadamantane derivatives (Scheme 3.5).[199]

[196] V. L. Narayanan, L. Setescak, *J. Org. Chem.* **1971**, *36*, 4127.
[197] G. Grethe, H. L. Lee, T. Mitt, M. R. Uskokovic, *Helv. Chim. Acta* **1973**, *56*, 1485.
[198] M. R. Uskokovic, T. Henderson, C. Reese, H. L. Lee, G. Grethe, J. Gutzwiller, *J. Am. Chem. Soc.* **1978**, *100*, 571.
[199] R.-M. Dupeyre, A. Rassat, *Tetrahedron Lett.* **1973**, *29*, 2699.



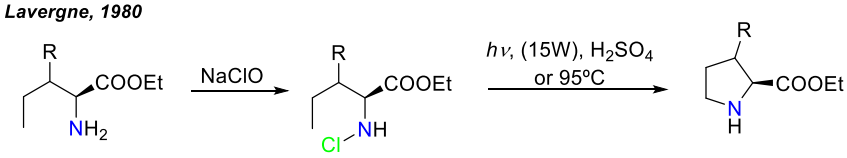
Scheme 3.5. *Application of the Hofmann-Löffler reaction for the synthesis of diazadamantane derivatives.*

Oliver and Sonnet applied a similar strategy for the synthesis of 3-butyl-5-methyloctahydroindolizine.[200] Oishi described a Hofmann-Löffler type reaction for the non-enantioselective synthesis of dihydrodeoxyepiallocernuine (Scheme 3.6). In this case, the hydrogen atom transfer took place differently in which the abstraction was α to heteroatom nitrogen. The cyclization did not involve the 1,5-HAT process. For this transformation, any strong acid was required; that means any aminium radical was present in this reaction.[201]



Scheme 3.6. *Hofmann-Löffler type reaction applied for the formation of piperidine derivative.*

Baldwin described a 1,5-process for the ring-closing step of the synthesis of *Gelsemium* alkaloids tricyclic core.[202] Lavergne carried out the stereospecific synthesis of L-proline and some derivatives (Scheme 3.7).[203] These reaction conditions did not affect the already existent stereocenters, providing the same enantioselectivity after the N–Cl decomposition.

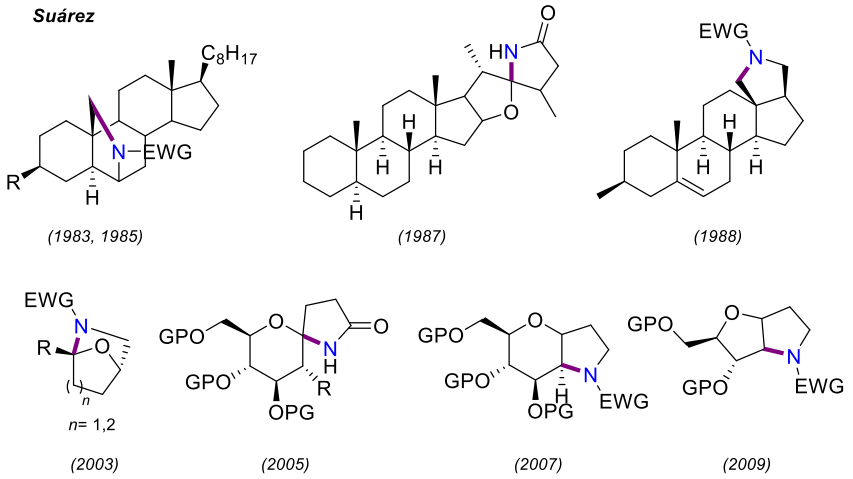


Scheme 3.7. *Hofmann-Löffler reaction for aminoacid modification.*

Suárez developed one of the most significant changes in this methodology using molecular iodine and $Pb(OAc)_4$ as oxidant.[84,204] The advantages of these

[200] P. E. Sonnet, J. E. Oliver, *J. Heterocycl. Chem*. **1965**, *12*, 289.
[201] Y. Ban, M. Kimura, T. Oishi, *Chem. Pharm. Bull.* **1976**, *24*, 1490.
[202] S. M. Baldwin, R. J. Doll, *Tetrahedron* **1979**, *35*, 3275.
[203] S. L. Titouani, J.-P. Lavergne, P. Viallefont, R. Jacquier, *Tetrahedron Lett.* **1980**, *36*, 2961.
[204] C. Betancor, J. I. Concepción, R. Hernández, J. A. Salazar, E. Suárez, *J. Org. Chem*. **1983**, *48*, 4430.

modifications consist in that the preformation of the N–X bond was not required, and milder conditions could be used, opening the possibility of applying this methodology to more sensitive molecules. The synthesis of 1,4-epidemine compounds was the first example of the contribution of Suárez using diethyl phosphoramidates. Several compounds were synthesized by the same group demonstrating the broader applicability and robustness of this protocol. Later, they reported the use of iodosobenzene diacetate ($PhI(OAc)_2$) and molecular iodine for the photolysis of several nitrosamines, cyanamides, and phosphoroamidates.[205] Moreover, they proved the application of this methodology for the synthesis of 2-hemiaminals related to 2-amino-C-glycosides (Scheme 3.8).[85,206]



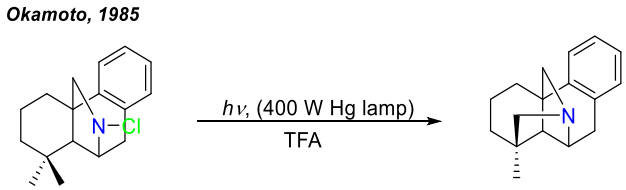
Scheme 3.8. *Hofmann-Löffler's reaction applied by Suárez to complex molecules.*

Okamoto and coworkers synthesized kobusine and nominine, characterized by having a bridged azabicyclic structure, using a variant of the Hofmann-Löffler reaction (Scheme 3.9).[207] For the C–N bond formation, the preformation of the N–X bond and irradiation with a 400W mercury lamp were required.

[205] (a) C. Betancor, J. I. Concepcion, R. Hernandez, J. A. Salazar, E. Suárez, *J. Org. Chem*. **1983**, *48*, 4430. (b) R. Hernández, M. Medina, J. Salazar, E. Suárez, T. Prangé, *Tetrahedron Letters* **1987**, *28*, 2533. (c) R. Carrau, R. Hernández, E. Suárez, C. Betancor, *J. Chem. Soc., Perkin Trans.* **1987**, *1*, 937. (d) P. de Armas, C. G. Francisco, R. Hernández, J. A. Salazar, E. Suárez, *J. Chem. Soc., Perkin Trans.* **1988**, *1*, 3255. (e) A. Martín, I. Pérez-Martín, E. Suárez, *Org. Lett.* **2005**, *7*, 2027.

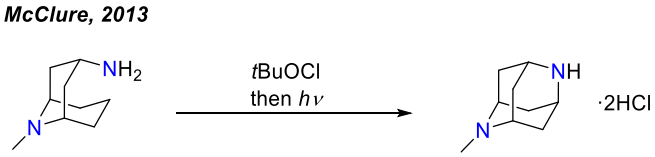
[206] (a) C. G. Francisco, A. J. Herrera, A. Martín, I. Pérez-Martín, E. Suárez *Tetrahedron Letters* **2007**, *48*, 6384. (b) A. Martín, I. Pérez-Martín, E. Suárez, *Tetrahedron Letters*, **2009**, *65*, 6147.

[207] Y. Shibanuma, T. Okamoto, *Chem. Pharm. Bull.* **1985**, *33*, 3187.



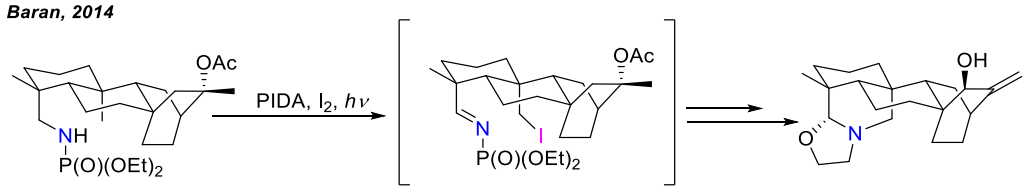
Scheme 3.9. *Synthesis of kobusine through late-stage amination using the Hofmann-Löffler reaction.*

The company Pfizer published a synthesis of diazatricyclodecane agonists using a Hofmann-Löffler reaction as the key step (Scheme 3.10).[208]



Scheme 3.10. *Synthesis of diazatricyclodecane through Hofmann-Löffler reaction.*

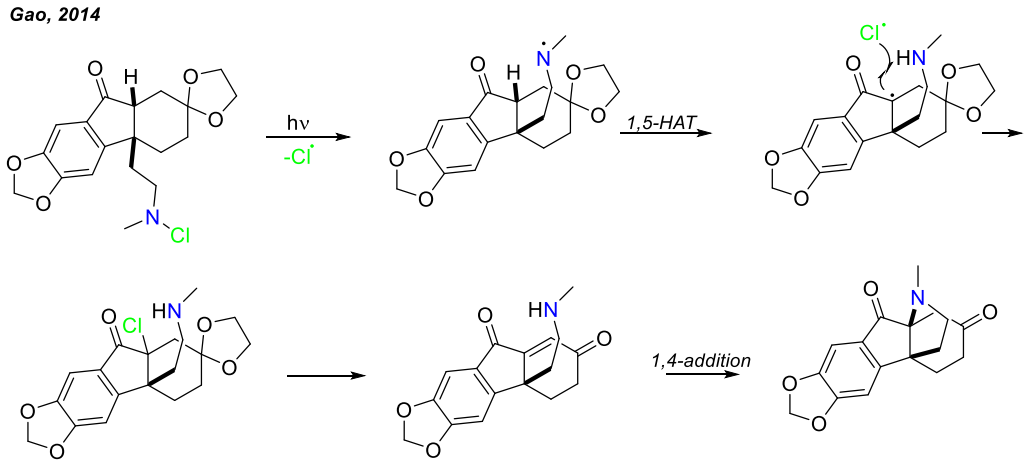
Along these lines, the group of Baran applied the Suárez modification of the Hofmann-Löffler reaction for a C–H activation through 1,6-HAT providing the iodo-imine at the neopentyl position, leading to the natural products *ent*-atisane, atisine, and hetidine (Scheme 3.11).[209]



Scheme 3.11. *C-20 selective activation using Suárez modification of the Hofmann-Löffler reaction for the synthesis of (-)-isoatisine.*

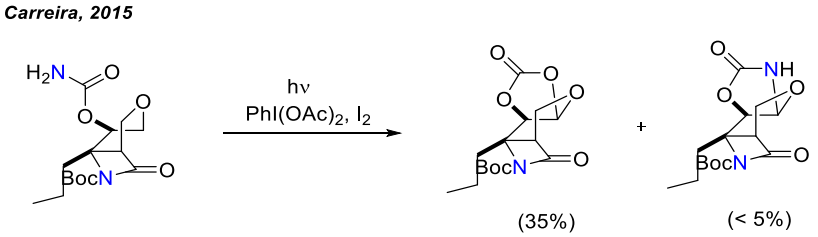
Another noteworthy example was reported by Gao and Cai in the total synthesis of gracilamine (Scheme 3.12). A classical C–H functionalization was carried out using sodium hypochlorite as a chlorinating agent.[210] After some optimizations with different strong acids, the pyrrolidine derivative was formed.

[208] E. Darout, *et al. J. Med. Chem.* **2013**, *56*, 301.
[209] E. C. Cherney, J. M. Lopchuk, J. C. Green, P. S. Baran, *J. Am. Chem. Soc*. **2014**, *136*, 12592.
[210] Y. Shi, B. Yang, S. Cai, S. Gao, *Angew. Chem. Int. Ed*. **2014**, *53*, 9539.



Scheme 3.12. *Synthesis of gracilamine via Hofmann-Löffler manifold and 1,4 addition.*

Carreira reported an interesting synthesis of gelsemoxonine, in which a C–H functionalization directed by primary carbamate was considered one of the strategies (Scheme 3.13).[211] Unfortunately, the desired oxazolidinone was obtained in low yield compared to the formation of the cyclic carbonate.



Scheme 3.13. *Formation of cyclic carbonate and oxazolidinone in a minor amount.*

3. Nicotine properties and syntheses

The nicotine alkaloid is one of the most abundant alkaloids isolated from plants of the genus *Nicotiniana.* Another important alkaloid in this plant is nornicotine, the demethylated derivative of nicotine (Figure 3.2).[212] Nicotine was isolated in 1828 by Posselt and Reimann, although its empirical formula was only correctly proposed in 1843 by Melsens. More than four decades later, Pinner determined

[211] S. Diethelm, E. M. Carreira, *J. Am. Chem. Soc.* **2015**, *137*, 6084.
[212] J. W. Gorrod, P. Jacob III, Analytical Determination of Nicotine and Related Compounds and their Metabolites, *Elsevier*, **1999**, Chapter1, 1-9

the correct structure of the molecule[213] and, finally, Pictet and Rostchy completed the first synthesis.[214]

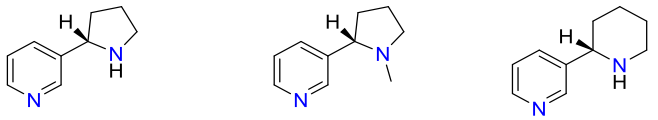


Figure 3.2. *Structures of natural nornicotine, nicotine, and anabasine.*

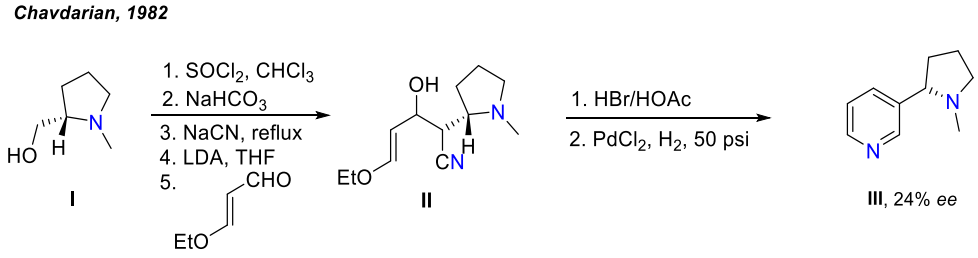
3.1. Biological properties

Nicotine represents one of the best-known alkaloids, which displays a variety of biological and medicinal properties.[215] Having a substantial effect on the central nervous system enhances memory and attention, decreases anxiety, and has a relaxing effect. Additionally, nicotine has been widely used in the past years as an insecticide.

3.2. Previous works on the synthesis of nicotine derivatives

From 1969 to 1996, several groups described a variety of methods to synthesize nicotine and its analogs, most of them starting from a pyridine derivative as starting material onto which the pyrrolidine ring was constructed.

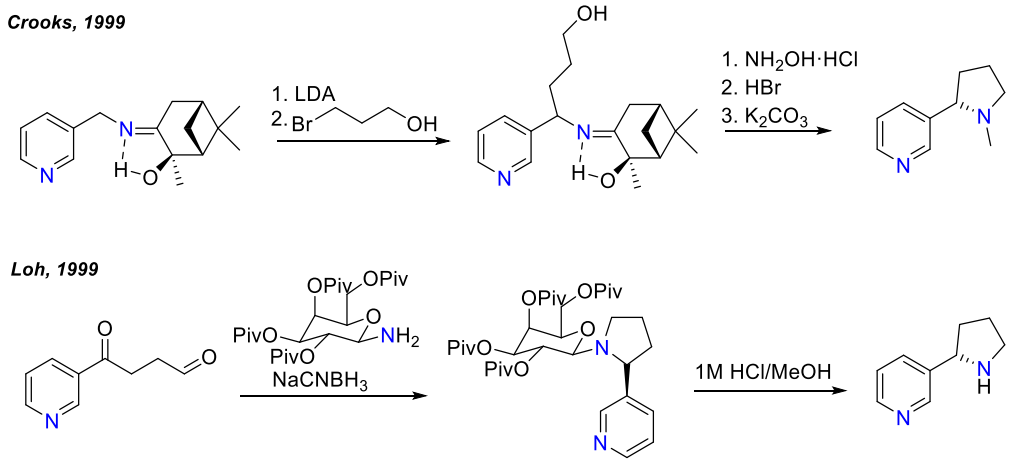
The first synthesis of optically active nicotine was reported in 1982 by Chavdarian.[216] The synthesis started from L-proline, which was converted to amino alcohol **I**. Sequential treatment with thionyl chloride, sodium cyanide, deprotonation using LDA, followed by 1,2 addition generated **II**. This intermediate was submitted to hydrobromic acid to form an intermediate bromopyridine, whose debromination led to nicotine with 24% *ee* (Scheme 3.14).



Scheme 3.14. *Synthesis of optically active nicotine by Chavdarian.*

[213] A. Pinner, *Ber. Dtsch. Chem. Ges*. **1893**, *26*, 292.
[214] A. Pictet, A. Rotschy, *Ber. Dtsch. Chem. Ges.* **1904.** *37*, 1225.
[215] (a) M. W. Decker, J. D. Brioni, *Life. Sci*. **1995**, *56*, 545. (b) S. Dehaene, J. P. Changeux, *Ann. NY Acad. Sci.* **1995**, *769*,305.
[216] C. G. Chavdarian, J. I. Seeman, *Tetrahedron Letters*, **1982**, *23*, 2519.

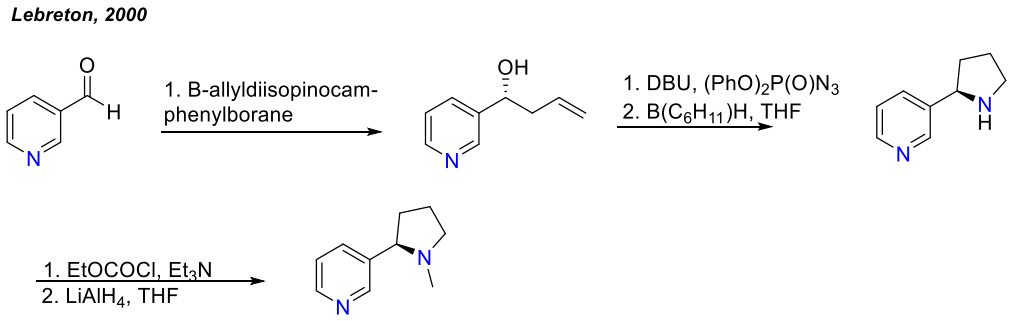
The group of Crooks and Loh simultaneously described an enantioselective synthesis of nornicotine.[217] Crooks employed an alkylation of a chiral 2-hydroxy-3-pinanone ketimine as a key step in the synthesis (Scheme 3.15. Top). In the synthesis reported by Loh, a chiral auxiliary was used, which was easily cleaved under acidic conditions (Scheme 3.15. Bottom).



Scheme 3.15. *Synthesis of Crooks and Loh nicotine and nornicotine alkaloids in 1999.*

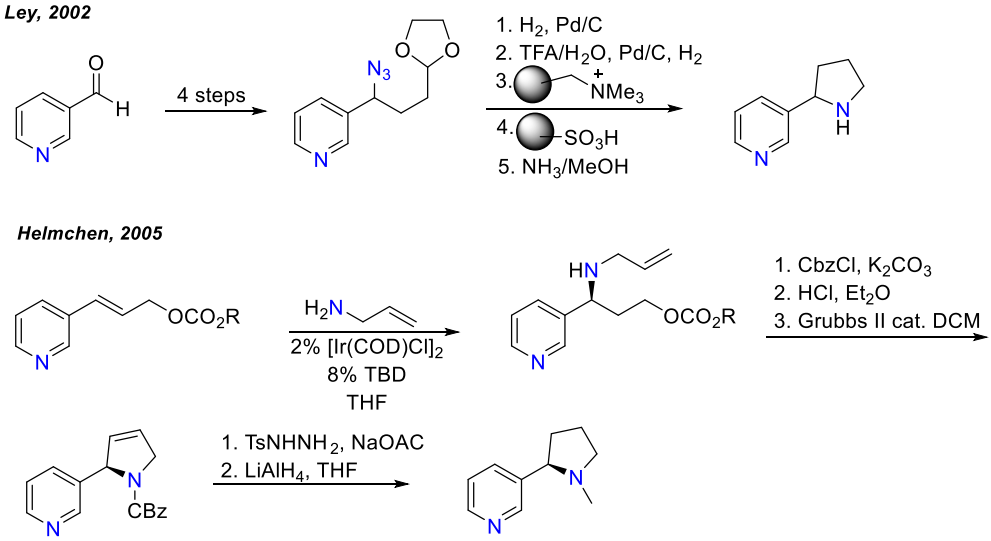
Another remarkable example on the enantioselective synthesis of nicotine was reported by the groups of Lebreton (Scheme 3.16), Ley, and Helmchen.[218] Lebreton described a short synthesis for the nonnatural (*R*)-nicotine. Starting from 3-pyridine carboxaldehyde, the homoallylic alcohol was obtained with B-allyldiisopinocamphenylborane in high enantioselectivity, which was followed by inversion of the configuration in the formation of the azide. The synthesis was completed with the formation of the pyrrolidine ring through intramolecular hydroboration, cyclization, and methylation.

[217] (a) J. H. Swango, B. S. Bhatti, M. M. Qureshi, P. A. Crooks, *Chirality* **1999**, *11*, 316. (b) T.-P. Loh, J. R. Zhou, X.-R. Li, K.-Y. Sim, *Tetrahedron Lett.* **1999**, *40*, 7847.
[218] (a) S. Girard, R. J. Robins, J. Villieras, J. Lebreton, *Tetrahedron Lett.* **2000**, *41*, 9245. (b) F.-X. Felpin, S. Girard, G. Vo-Thanh, R. J. Robins, J. Villieras, J. Lebreton, *J. Org. Chem*. **2001**, *66*, 6305. (c) C. Welter, R. M. Moreno, S. Streiff, G. Helmchen, *Org. Biomol. Chem*. **2005**, *3*, 3266. (d) I. R. Baxendale, G. Brusotti, M. Matsuoka, S. V. Ley, *J. Chem. Soc., Perkin Trans*. **2002**, *1*, 143.



Scheme 3.16. *(R)-nicotine synthesis using B-allyldiisopinocamphenylborane as a reductant agent.*

Ley carried out a nine-step synthesis of racemic nicotine through a five-step sequence employing solid-supported reagents to provide nornicotine in 90 % purity (Scheme 3.17. Top). Helmchen reported an enantioselective nicotine synthesis with 99 % *ee* by an asymmetric Ir-catalyzed allylic amination, followed by ring-closing metathesis (Scheme 3.17. Bottom).



Scheme 3.17. *Ley and Helmchem syntheses of nicotine and nornicotine.*

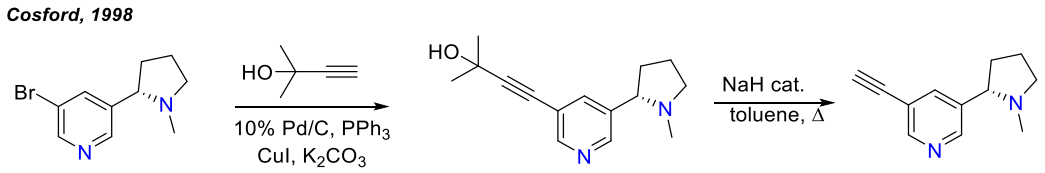
3.3. Synthesis of derivatives of nicotine

During the last decades, many derivatives of nicotine have been synthesized because of their biological and medicinal properties.[219] Usually, the modifications consist in the incorporation of a halogen into the pyridine core.

[219] F. F. Wagner, D. L. Comins, *Tetrahedron* **2007**, *63*, 8065.

These modifications in the structure allow further diversification by the formation of C–C, and C–N bonds.

One of the prominent examples came out from the transformation of 5-bromonicotine into (*S*)-(-)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine maleate (SIB-1508Y), which is known by the commercial name of Altinicline. This compound was developed by SIBIA Neurosciendes Inc. and is an antagonist of human neuronal nAChRs for Parkinson's disease. However, studies in the clinical phase were stopped but still is the subject of ongoing research. The first synthesis of Altinicline was described by Cosford, starting from commercially available ethyl 5-bromonicotinate (Scheme 3.18).[220] Once the 5-bromonicotine was obtained after 5-steps synthesis, it was converted to the final product through a Sonogashira cross-coupling.



Scheme 3.18. *The first synthesis of Altinicline by Cosford.*

In general, functionalized nicotine derivatives have been considered a synthetic challenge. Some notable examples were reported by Seeman, who studied the methylation of nicotine with MeLi.[221] Similarly, Comins established a method for the synthesis of 4,5-disubstituted nicotines.[222]

This chapter focuses on the synthesis of nicotine and some analogs using the Hofmann-Löffler methodology for the late-stage C–H amination.

4. Results and Discussion

More than a century after the pioneering original Löffler and Kober non-enantioselective synthesis of the natural product nicotine, we decided to go one step further and applied the catalytic conditions of our group in the enantioselective synthesis of nicotine.

First, we were focused on the retrosynthetic analysis. In the case of Löffler and Kober, the disconnection occurred at the benzylic C–N bond. Consequently, the

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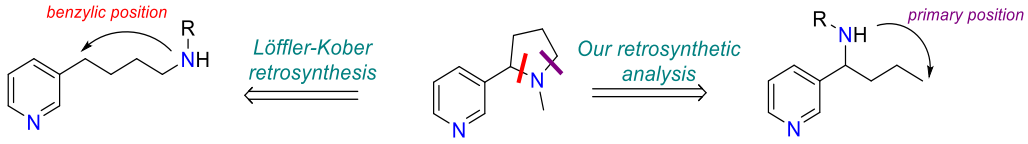
[220] L. S. Bleicher, N. D. P. Cosford, A. Herbaut, J. S. McCallum, I. A. McDonald, *J. Org. Chem.* **1998**, *63*, 1109.
[221] (a) J. I. Seeman, H. V. Secor, C. R. Howe, C. G. Chavdarian, L. W. Morgan, *J. Org. Chem.* **1983**, *48*, 4899. (b) J. I. Seeman, C. G. Chavdarian, R. A. Kornfeld, J. D. Naworal, *Tetrahedron* **1985**, *41*, 595.
[222] F. F. Wagner, D. L. Comins, *Eur. J. Org. Chem.* **2006**, 3562.

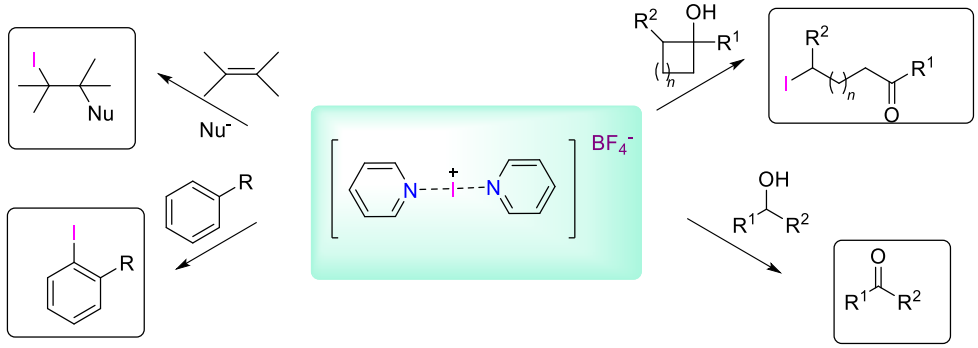
nucleophilic cyclization generated a chiral C–N bond in a nonselective manner, providing the formation of the racemic product. Furthermore, relatively harsh conditions, such as high temperature and strong acidic media, were required.

To overcome all these synthetic drawbacks, we designed a synthesis where the disconnection is at the alternative primary position (Scheme 3.19). Thus, enabling a synthesis where the chiral benzylic C–N bond is formed in an enantiopure manner. For this transformation, we envisioned moderated reaction conditions that tolerate the free pyridine core in the presence of electrophilic iodine reagents.



Scheme 3.19. *Retrosynthetic analysis of the Löffler-Kober synthesis vs Muñiz group synthesis.*

The use of electrophilic iodine reagents in the presence of the pyridine core of nicotine faces some challenges since pyridines are known to coordinate to electrophilic iodine centers. In the present case, such coordination could slow down or even completely inhibit the desired iodine-based C–H amination chemistry. In fact, Barluenga described bis(pyridine)iodonium(I) tetrafluoroborate $(IPy)_2BF_4$ as a stable reagent for a significant number of transformations (Scheme 3.20).[223]



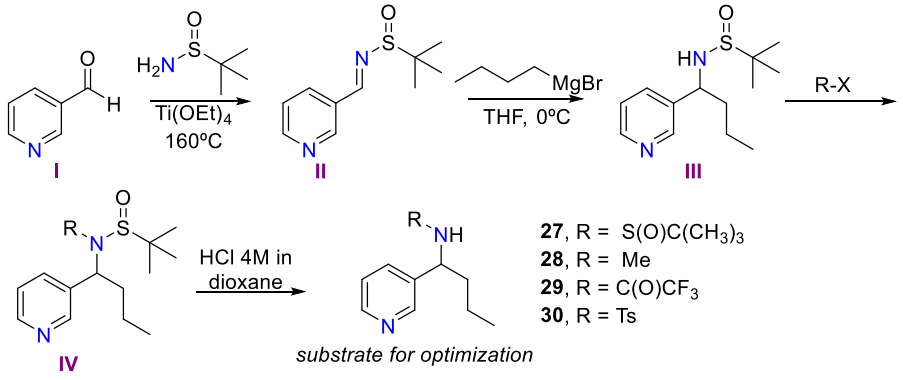
Scheme 3.20*. Barluenga's reagent and typical reactivity.*

[223] J. Barluenga, J. M. González, P. J. Campos, G. Asensio, *Angew. Chem. Int. Ed*. **1985**, *24*, 319.

4.1. Optimization studies

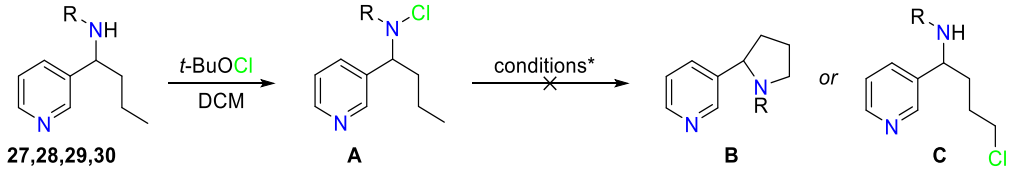
We first explored the classical Hofmann-Löffler reaction in which the aminium radical would be generated by homolytic cleavage of the *N*-halogen bond under acidic media or visible light irradiation. A variety of solvents, light sources as well as additives were investigated.

We synthesized compounds **27-30** starting from the commercially available pyridine 3-carboxaldehyde, followed by the formation of imine **II** (Scheme 3.21). Upon addition of the Grignard reagent, intermediate **III** was derivatized with different protecting/directing groups as sulfonamides, acetamide, or methyl groups. Finally, the sulfinyl group was removed under acidic conditions to afford compounds **27-30**.



Scheme 3.21. *Formation of optimization substrate employed for studies of reactivity under Hofmann-Löffler reaction conditions.*

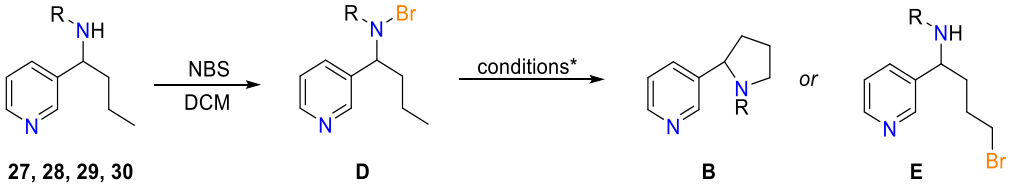
With substrates **27-30** in hand, we performed several experiments irradiating with visible, purple, and blue LEDs to promote the N–X bond homolytic cleavage. For this transformation, the preformed the *N*-chlorinated and *N*-brominated derivatives. We synthesized the N–Cl derivative using *tert*-butyl hypochlorite in dichloromethane. This compound was directly submitted to the Hofmann-Löffler reaction conditions (Table 3.1). Unfortunately, under all the conditions examined, neither **B** nor **C** were formed. In most cases, the free amine was obtained, showing that the cleavage of the N–Cl bond was possible, but the regioselective 1,5-HAT process did not occur, generating the free amine.



Entry	R	Wavelength (nm)	Acid	Solvent
1	Me	400-700 (visible)	-	DCM
2	Me	400-700 (visible)	TFA	DCM
3	Me	400 (purple)	TFA	DCM
4	Me	400-700 (visible)	AcOH	DCM
5	Me	475 (blue)	-	DCE
6	Me	475 (blue)	-	HFIP
7	Me	475 (blue)	-	$CHCl_3$
8	Me	400-700 (visible)	$MeSO_3H$	DCM
9	Me	400-700 (visible)	H_2SO_4	DCM
10	$COCF_3$	400-700 (visible)	-	DCM
11	$COCF_3$	400-700 (visible)	TFA	DCM
12	$COCF_3$	400-700 (visible)	HCl	DCM
13	$COCF_3$	400-700 (visible)	AcOH	DCM
14	*t*-BuSO	400-700 (visible)	-	DCM
15	*t*-BuSO	400-700 (visible)	TFA	DCM
16	SO_2PhMe	400-700 (visible)	TFA	DCM
17	SO_2PhMe	400-700 (visible)	-	DCM

Table 3.1. *Attempts to C–H amination under Hofmann-Löffler reaction from N–Cl substrate.*

In the same way, we investigated the *N*-brominated derivative **D**, which was formed by reaction with *N*-bromosuccinimide in dichloromethane. This compound should be freshly prepared because its half-life is 30 minutes approximately. Subsequently, we submitted *N*-brominated compound **D** to classical and non-classical Hofmann-Löffler conditions using visible and blue LEDs (Table 3.2). Once again, compounds **B** or **E** were not obtained. In most cases, the free amine was obtained.



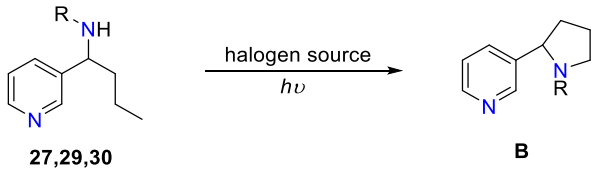
27, 28, 29, 30 **D** **B** **E**

Entry	R	Wavelength (nm)	Acid	Solvent
1	Me	400-700 (visible)	TFA	DCM
2	Me	475 (blue)	TFA	DCM
3	Me	400-700 (visible)	-	DCM
4	Me	475 (blue)	-	DCM

5	$COCF_3$	400-700 (visible)	-	DCM
6	$COCF_3$	475 (blue)	-	DCM
7	t-BuSO	400-700 (visible)	-	DCM
8	SO_2PhMe	400-700 (visible)	-	DCM
9	SO_2PhMe	475 (blue)	-	DCM

Table 3.2. *Attempts to C–H amination under Hofmann-Löffler reaction from N–Br substrate.*

After all these non-satisfactory results, we decided to try the effect of hypervalent iodine reagents based on the Suárez modification of the Hofmann-Löffler reaction in combination with the methodology described by the group of Muñiz using compounds **27**, **29**, and **30** (Table 3.3). In this transformation, the preformation of the N–I bond is not necessary. We tested *N*-iodosuccinimide and the catalytic version using molecular iodine and hypervalent iodine(III) species with *m*-chlorobenzoic acetate as ligands. Unfortunately, the desired product was not obtained in any of these cases.

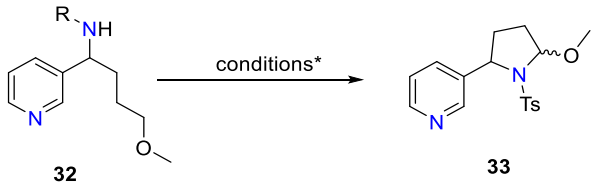


27,29,30 **B**

Entry	R	Wavelength (nm)	Halogen source	Solvent
1	$COCF_3$	400-700 (visible)	NIS	DCM
2	$COCF_3$	400-700 (visible)	PhI(*m*CBA)$_2$/ I_2	DCM
3	t-BuSO	400-700 (visible)	NIS	DCM
4	t-BuSO	400-700 (visible)	PhI(*m*CBA)$_2$/ I_2	DCM
5	SO_2PhMe	400-700 (visible)	NIS	DCM
6	SO_2PhMe	400-700 (visible)	PhI(*m*CBA)$_2$/ I_2	DCM

Table 3.3. *Attempts to C–H amination under Hofmann-Löffler reaction from N-H substrate.*

Then we decided to facilitate the reaction using a methoxy group at the end of the alkyl chain, which should stabilize the resulting carbon-centered radical. To our delight, the combination of 40% of molecular iodine with the hypervalent iodine reagent afforded the product **33** in moderate yield (Table 3.4, Entry 7.).



32 **33**

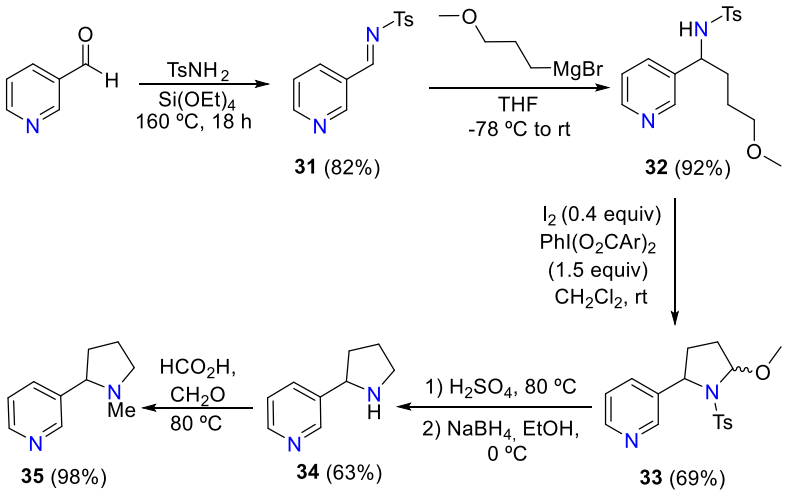
Entry	Iodine source	Equiv	Solvent	Conversion (%) (Isolated yield(%))
1	NIS	5.0	DCM	100 (43)
2	NIS	2.0	DCM	100 (54)
3	PhI(*m*CBA)$_2$ / I_2	1.5 / 0.1	DCE	22
4	PhI(*m*CBA)$_2$ / I_2	1.5 / 0.2	DCE	54
5	PhI(*m*CBA)$_2$ / I_2	1.5 / 0.3	DCE	80
6	PhI(*m*CBA)$_2$ / I_2	1.5 / 0.4	DCE	100 (65)
7	PhI(*m*CBA)$_2$ / I_2	1.5 / 0.4	DCM	100 (69)
8	PhI(*m*CBA)$_2$ / I_2	1.5 / 0.6	DCM	100 (66)
9	PhI(*m*CBA)$_2$ / I_2	1.5 / 1	DCM	100 (58)

Table 3.4. *Optimization table condition of the Hofmann-Löffler reaction conditions.*

With these promising results in hand, we decided to perform the synthesis of racemic nicotine.

4.2. Non-enantioselective synthesis

The first step consisted in the formation of the 3-pyridinyl *N*-tosylamine **31** from commercial pyridine 3-carboxaldehyde, followed by alkylation with the corresponding Grignard reagent to give rise to **32** (Scheme 3.22). A clean C–H amination took place with the combination of hypervalent iodine(III) oxidant and molecular iodine to from **33**. For this step, only 40 mol% of iodine was necessary to achieve full conversion and good isolated yield.

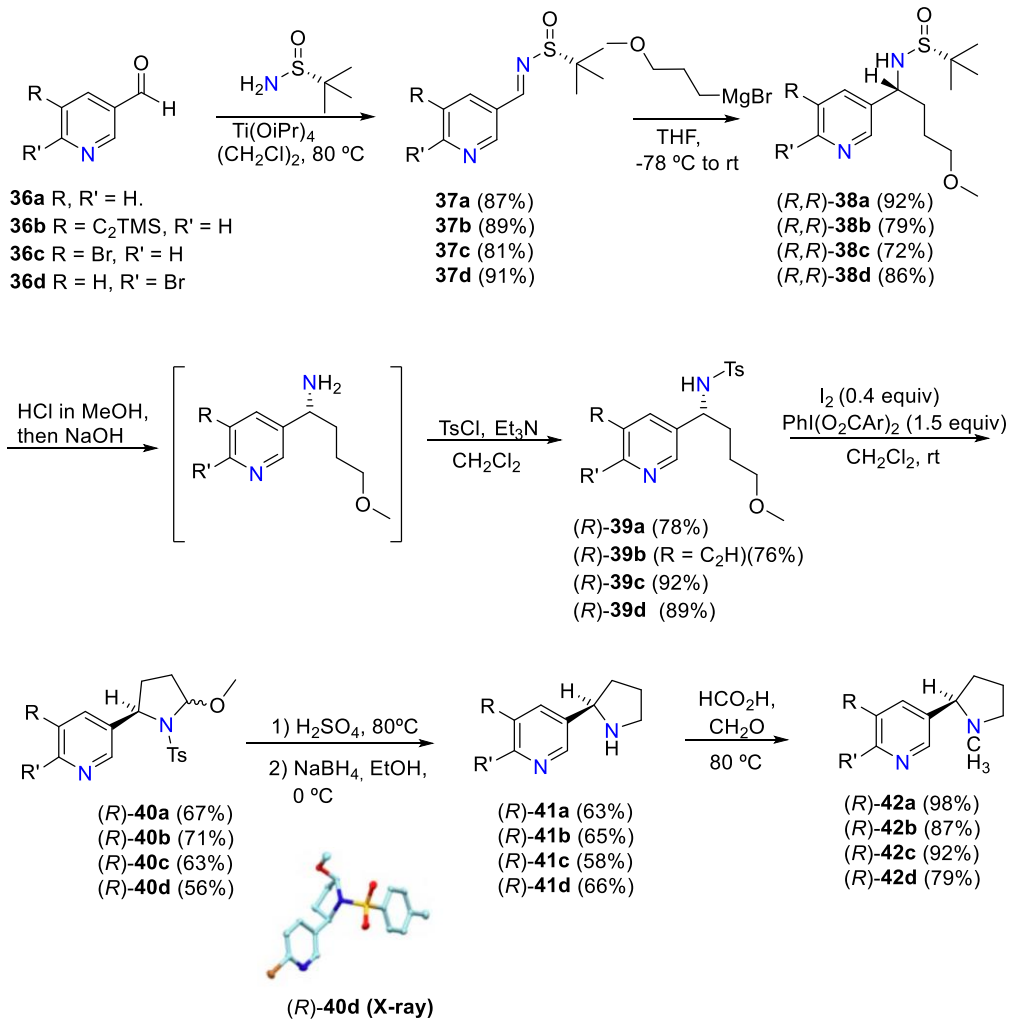


Scheme 3.22. *Non-enantioselective synthesis pathway for nicotine alkaloid formation.*

The hemiaminal **33** was submitted to an acid-promoted detosylation, followed by imine reduction to give **34**, which led to racemic nicotine **35** by *N*-methylation using the Eschweiler-Clarke reaction.

4.3. Enantioselective synthesis

Based on the developed successful sequence for the synthesis of racemic nicotine, an enantioselective route was developed (Scheme 3.23). This approach was based on the use of Ellman's *tert*-butanesulfinylamide as a chiral, non-racemic auxiliary. Starting from pyridine 3-carboxaldehyde, the corresponding chiral sulfimine **37a** was generated. Then, the addition of the same Grignard reagent as before provided **38a** in excellent diastereoselectivity. Products **38b-d** were prepared similarly from **36b-d**. Amine deprotection and tosylation led to **39a-d** in good to excellent yields. The Hofmann-Löffler reaction gave the hemiaminal derivatives, and following the same reaction sequence for the non-enantioselective synthesis, (*R*)-nicotine **42a** and its analogs **42b-c** were obtained in enantiopure form.



36a R, R' = H.
36b R = C_2TMS, R' = H
36c R = Br, R' = H
36d R = H, R' = Br

37a (87%)
37b (89%)
37c (81%)
37d (91%)

(*R,R*)-**38a** (92%)
(*R,R*)-**38b** (79%)
(*R,R*)-**38c** (72%)
(*R,R*)-**38d** (86%)

(*R*)-**39a** (78%)
(*R*)-**39b** (R = C_2H)(76%)
(*R*)-**39c** (92%)
(*R*)-**39d** (89%)

(*R*)-**40a** (67%)
(*R*)-**40b** (71%)
(*R*)-**40c** (63%)
(*R*)-**40d** (56%)

(*R*)-**40d (X-ray)**

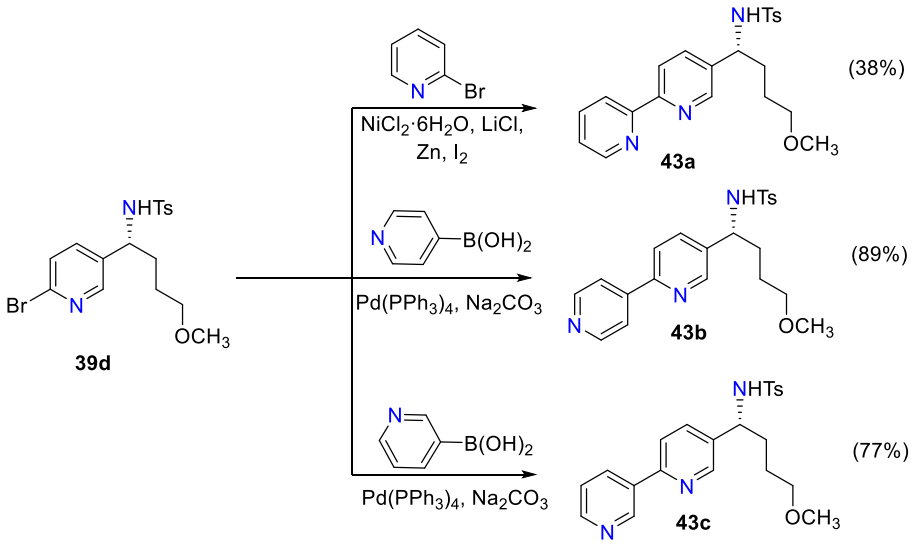
(*R*)-**41a** (63%)
(*R*)-**41b** (65%)
(*R*)-**41c** (58%)
(*R*)-**41d** (66%)

(*R*)-**42a** (98%)
(*R*)-**42b** (87%)
(*R*)-**42c** (92%)
(*R*)-**42d** (79%)

Scheme 3.23. *Enantioselective synthesis of nicotine and analogs.*

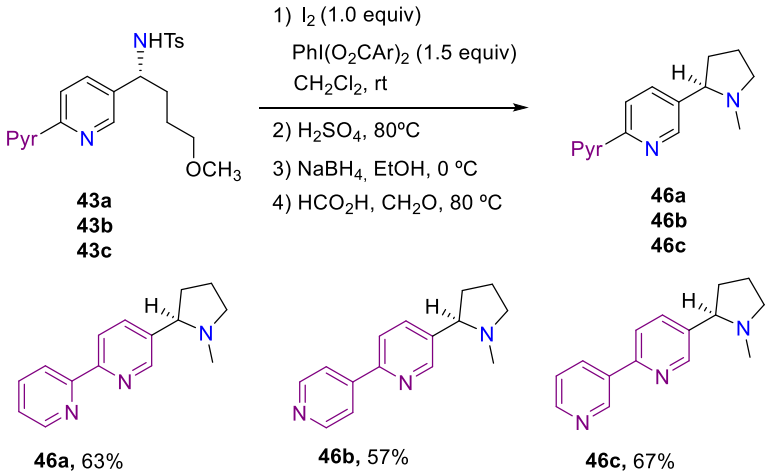
The derivative with the acetylene substituent **42b** is the pharmaceutical product Altinicline, which was obtained in an enantioselective fashion. Remarkably, the alkyne group of **39b** was tolerated by the electrophilic iodine reagent under the conditions of the Hofmann-Löffler reaction.

To extend these successful results further, we decided to apply the Hofmann-Löffler reaction on more challenging bipyridine derivatives. First, we carried out the coupling reactions between previously prepared compound **39d** and different pyridine reagents to form **43a-c** (Scheme 3.24). For the synthesis of the 2,2'-bipyridine **43a**, a reductive nickel coupling was carried out, whereas, for the preparation of 2,4'- and 2,3'-bipyridines **43b,c,** a conventional Suzuki coupling was used.



***Scheme 3.24**. Couplings of the bipyridine derivatives **43a-c**.*

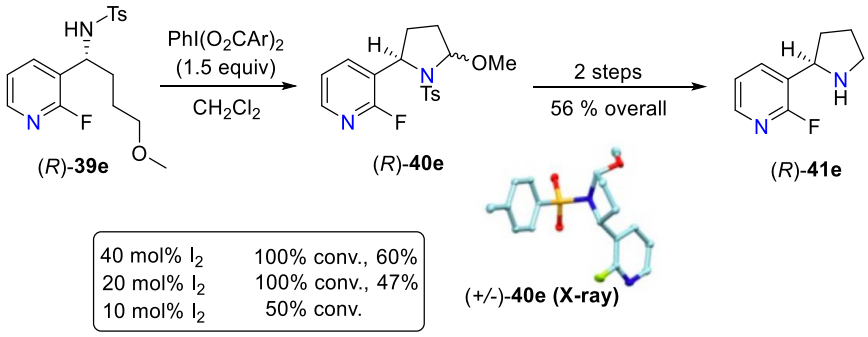
We then submitted substrates **43a-c** to the Hofmann-Löffler reaction (Scheme 3.25). We observed that more molecular iodine was required for these transformations due to the higher coordination of the bipyridine derivatives. Once the pyrrolidine derivatives were formed, we completed the enantioselective synthesis of **46a-c** in the same way as described above.



***Scheme 3.25**. Final steps of the synthesis of pyridylnicotine derivatives.*

Finally, we addressed the synthesis of 2-fluoronornicotine (**41e**), which allowed us to study the fluorine substituent effect on iodine loading. The group of Frontera had studied the halogen bonding interactions between the pyridine nitrogen a hydrogen or halogen when the fluorine was placed in the *meta*- and *para*-

position, finding lower coordination when the fluorine was in one of the pyridine positions.[224] As expected, the required amount of molecular iodine in the Hofmann-Löffler reaction of **39e** could be reduced to 20 mol% (Scheme 3.26).



***Scheme 3.26**. Synthesis of fluorononicotine and the effect of fluorine on iodine loading.*

5. Conclusions

The Hofmann-Löffler reaction has been widely investigated to generate a C–N bond. In particular, this reaction has been applied for the synthesis of both racemic and enantiomerical enriched nicotine, as well as several analogs, including the pharmaceutical compound Altinicline.

[224] A. Bauzá, A. Frontera, *Phys. Chem. Chem. Phys*. **2016**, *18*, 20381.

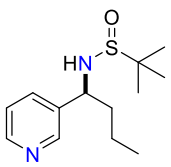
6. Experimental section

All solvents (including deuterated ones) were commercially available and were used as received. Column chromatography was performed with silica gel (type 60, 0.063-0.2 mm). NMR spectra were recorded on a 300, 400 MHz, or 500 MHz spectrometer, with reference to ^{1}H. All chemical shifts in NMR experiments were reported as ppm downfield from TMS. The following calibrations were used: $CDCl_3$ δ = 7.26 and 77.16 ppm. Supelco C8 (5 cm × 4.6 mm, 5μm particles) column was used with a linear elution gradient from 100% H_2O (0.5%HCO_2H) to 100% MeCN in 13 min at a flow rate of 0.5 mL/min. MS (EI)and HRMS experiments were performed on a Kratos MS 50 within the service departments at ICIQ. Melting points were determined with a Buchi Melting Point B-540 apparatus. IR spectra were taken with a Bruker Alpha instrument in the solid-state. Specific optical rotation values were measured with a Polarimeter JascoP1030 equipped with a 100 mm cell. HPLC measurements were carried out on an Acquity UPLC® system (Waters) UltraPerformance Convergence Chromatography™ (UPC2™) equipped with a detector Acquity UPLC PDA (Photodiode Array detector). The respective chiral stationary phase (Chiralpak IA, IC, IG, ID, or IE) and exact conditions are specified for each individual compound within the compound characterization section.

The following compounds are commercially available and were used as received: tosyl chloride, triethylamine, 2-bromopyridine 2-fluoro-3-formylpyridine, 3-pyridinecarboxaldehyde, 98% pyridine-3-boronic acid, pyridine-4-boronic acid, titanium isopropoxide, (*R*)-(+)-2-methyl-2-propanesulfinamide, 3-methoxypropyl bromide, sodium borohydride, formaldehyde, formic acid, sulfuric acid, tetrakis(triphenylphosphine)palladium(0), nickel(II) chloride hexahydrate, lithium chloride, zinc dust

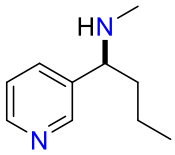
Data for the compounds of the optimization table

2-Methyl-*N*-(1-(pyridin-3-yl)butyl)propane-2-sulfinamide (27)



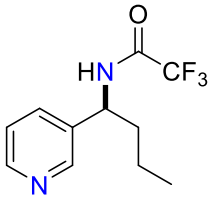
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3H), 1.12 - 1.34(m, 11H), 1.68 – 1.76 (m, 1H), 2.01 (ddd, *J* = 10.4, 5.2, 3.4 Hz, 1H), 3.43 (d, *J* = 4.4 Hz, 1H), 4.37 (ddd, *J* = 8.4, 5.8, 4.4 Hz, 1H), 7.26 – 7.31 (m, 1H), 7.65 (dt, *J* = 7.8, 2.0 Hz, 1H), 8.53 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.56 (d, *J* = 0.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 13.9, 19.0, 22.7, 38.7, 56.0, 57.1, 123.7, 134.9, 138.2, 145.0, 149.4. **IR ν** (cm^{-1}): 3202, 2967, 2870, 1047, 747. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{13}H_{23}N_2OS$, 253.1380; found, 253.1378.

***N*-methyl-1-(pyridin-3-yl)butan-1-amine (28)**



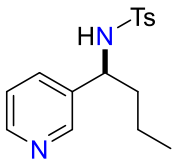
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.3 Hz, 3H), 1.11 – 1.29 (m, 2H), 1.54 – 1.77 (m, 2H), 2.25 (s, 3H), 3.50 (dd, *J* = 8.0, 6.0 Hz, 1H), 7.24 – 7.29 (m, 1H), 7.64 (dt, *J* = 7.8, 1.9 Hz, 1H), 8.49 (d, *J* = 4.9 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 14.1, 19.4, 34.4, 39.7, 62.9, 123.8, 134.9, 138.9, 148.7, 149.6. **IR ν** (cm^{-1}): 3297, 2957, 2872, 2792, 1426, 715. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{10}H_{17}N_2$, 165.1386; found, 165.1387.

2,2,2-Trifluoro-*N*-(1-(pyridin-3-yl)butyl)acetamide (29)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3H), 1.24 – 1.43 (m, 2H), 1.79 – 1.96 (m, 2H), 4.99 (q, *J* = 7.8 Hz, 1H), 7.30 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 7.62 (dt, *J* = 7.9, 2.0 Hz, 1H), 8.54 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.56 (d, *J* = 2.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 13.5, 19.3, 37.1 (d, *J* = 3.7 Hz), 45.7, 52.2, 124.1, 135.6 (d, *J* = 11.6 Hz), 136.9, 147.3, 148.2. **IR ν** (cm^{-1}): 3283, 2948, 2875, 2790, 1428, 711. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{11}H_{14}F_3N_2O$, 247.1050; found, 247.1049. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -75.7.

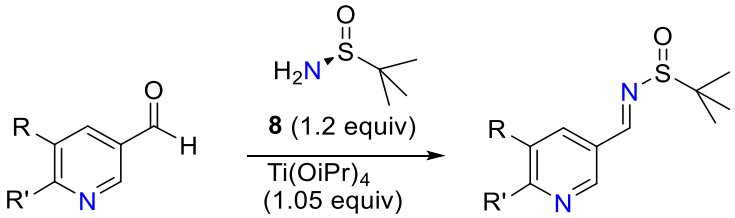
4-methyl-*N*-(1-(pyridin-3-yl)butyl)benzenesulfonamide (30)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (td, *J* = 7.4, 1.2 Hz, 3H), 1.15 – 1.34 (m, 2H), 1.57 – 1.79 (m, 2H), 2.35 (s, 3H), 4.31 (q, *J* = 7.2 Hz, 1H), 5.35 (dd, *J* = 7.1, 3.1 Hz, 1H), 7.07 (ddt, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.11 – 7.16 (m, 2H), 7.36 – 7.44 (m, 1H), 7.47 – 7.55 (m, 2H), 8.29 (d, *J* = 2.3 Hz, 1H), 8.38 (dd, *J* = 4.8, 1.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 13.4, 19.1, 21.6, 39.6, 55.8, 123.4, 127.1, 129.6, 134.1, 136.9,137.5, 143.4, 148.5, 148.6. **IR ν** (cm^{-1}): 3252, 2879, 2759, 2722, 1412, 552. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{16}H_{19}N_2O_2S$, 303.1173; found, 303.1165.

Enantioselective synthesis of Nicotine and Nicotine analogs

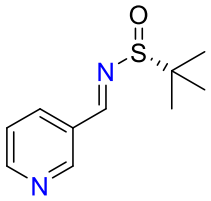
Step I: Imine Formation



General procedure: (GP1)

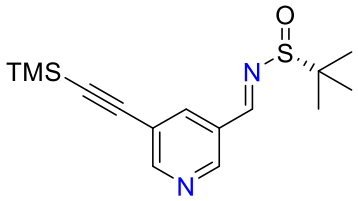
A mixture of the corresponding 3-pyridine carboxaldehyde, (*R*)-(+)-2-Methyl-2-propanesulfinamide (1.2 equiv) and titanium isopropoxide (1.05 equiv) in dichloroethane (1.2 mL/mmol) were added to a Schlenk tube that has been previously evacuated and filled with Argon. The mixture was stirred at 80ºC for 18h. Then, to the mixture was added water, and the solution was filtered through celite, and extracted with DCM (3x), washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane or ethyl acetate methanol.

(*R, E*)-2-Methyl-*N*-(pyridin-3-ylmethylene) propane-2-sulfinamide (37a)



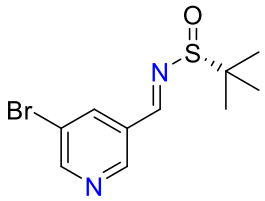
On a 6.0 mmol scale, **37a** was isolated as a yellow oil with 87% yield (1.10 g). Spectroscopic data in agreement with the one previously described.[225] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.22 (s, 9H), 7.38 (dd, *J* = 8.0, 4.8 Hz, 1H), 8.12 (dt, *J* = 7.9, 2.0 Hz, 1H), 8.59 (s, 1H), 8.68 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.98 (d, *J* = 2.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.6, 58.1, 123.9, 129.6, 135.6, 151.0, 152.9, 160.4.

(*R,E*)-2-Methyl-*N*-((5-((trimethylsilyl)ethynyl)pyridin-3-yl)methylene)propane-2-sulfinamide (37b)



On a 5.2 mmol scale, **37b** was isolated as a yellow solid with 89% yield (1.42 g). **m.p.:** 107-108ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ =0.29 (s, 9H), 1.29 (d, *J* = 1.4 Hz, 9H), 8.21 (t, *J* = 2.1 Hz, 1H), 8.62 (d, *J* = 4.0 Hz, 1H), 8.78 (d, *J* = 2.0 Hz, 1H), 8.91 (d, *J* = 2.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = -0.1, 22.8, 58.4, 100.1, 100.5, 121.0, 129.2, 138.2, 149.8, 155.5, 159.9. **IR** ν(cm^{-1}): 1604, 1411, 1250, 1082, 942. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{15}H_{23}N_2OSSi$, 307.1293; found, 307.1295. **$[\alpha]_D^{28}$=** -5.4 (c = 0.11, $CHCl_3$).

***(R, E)*-*N*-((5-bromopyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide (37c)**

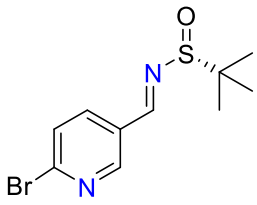


On a 5.0 mmol scale, **37c** was isolated as a yellow solid with 81% yield (1.17 g). **m.p.:** 102-103 ºC **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.23 (s, 9H), 8.28 (t, *J* = 2.1 Hz, 1H), 8.56 (s, 1H), 8.74 (d, *J* = 2.3 Hz, 1H), 8.86 (d, *J* = 1.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.7, 58.4, 121.4, 131.0, 137.6, 149.1, 153.9, 159.1. **IR** ν (cm^{-1}): 1633,

[225] T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 12.

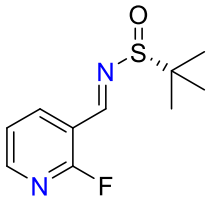
1407, 1119, 1103, 804. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{10}H_{13}BrN_2NaOS$, 310.9284; found, 310.9834. **$[\alpha]_D^{28}$=** -26.9 (c = 0.08, $CHCl_3$).

(*R,E*)-*N*-((6-bromopyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide (37d)



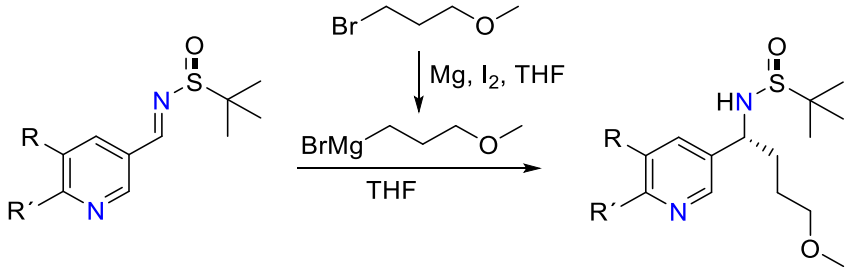
On a 5.0 mmol scale, **37d** was isolated as a yellow solid with 91% yield (1.32 g). 91%, yellow solid. **m.p.:** 96-97ºC **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.24 (s, 9H), 7.59 (d, *J* = 8.3 Hz, 1H), 8.01 (dd, *J* = 8.3, 2.4 Hz, 1H), 8.58 (s, 1H), 8.73 (d, *J* = 2.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.7, 58.4, 128.9, 129.0, 137.6, 146.0, 151.4, 159.4. **IR** ν(cm^{-1}): 1601, 1423, 1132, 1129, 849. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{10}H_{14}BrN_2OS$, 289.0005; found, 289.0006. **$[\alpha]_D^{28}$=** -112.3(c = 0.13, $CHCl_3$).

***(R, E)*-*N*-((2-fluoropyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide (37e)**



On a 6.0 mmol scale, **37e** was isolated as a yellow solid with 92% yield (1.26 g). **m.p.:** 65-66ºC **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.24 (s, 9H), 7.28 – 7.32 (m, 1H), 8.34 (ddd, *J* = 4.8, 2.1, 1.0 Hz, 1H), 8.38 (ddd, *J* = 9.3, 7.5, 2.0 Hz, 1H), 8.78 (t, *J* = 0.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.7, 58.4, 117.0 (d, J_{CF} = 24.1 Hz), 122.2 (d, J_{CF} = 4.4 Hz), 139.4 (d, J_{CF} = 3.0 Hz), 151.4 (d, J_{CF}= 15.4 Hz), 155.8 (d, J_{CF} = 2.1 Hz), 162.3 (d, J_{CF} = 247.0 Hz). **IR** ν(cm^{-1}): 2967, 1599, 1566, 1422, 1004, 807. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{10}H_{13}FN_2NaOS$, 251.0625; found, 251.0619. **^{19}F** NMR (376 MHz, $CDCl_3$): δ = -71.8. **$[\alpha]_D^{28}$=** +164.4 (c = 0.11, $CHCl_3$).

Step II: Grignard Addition

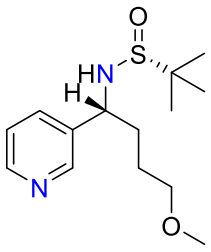


General Procedure (GP2) employing *in situ* Formation of the Grignard reagent: To a suspension of magnesium (2.0 equiv) containing I_2 (small crystal) was added a few drops of 3-methoxy propyl bromide in dry THF (0.5 mL/mmol). Then, the rest of the brominated compound was dissolved in dry THF (1.5mL/mmol) and

added drop by drop over 15 min. After the complete addition of methoxy propyl bromide, the mixture was refluxed for 1h and used as it is for the next step.

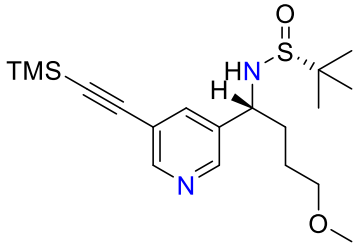
To a solution of the corresponding imine in dry THF (10 mL/mmol) at -78ºC was added (3-methoxy propyl) magnesium bromide (0,5M in THF, 1.2equiv) dropwise over 15 min. After stirring 3h at -78 ºC, the reaction was allowed to warm gradually to room temperature overnight. The reaction was quenched by the slow addition of NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane or ethyl acetate methanol.

***(R)-N*-((R)4-methoxy-1-(pyridin-3-yl) butyl)-2-methylpropane-2-sulfinamide (38a)**



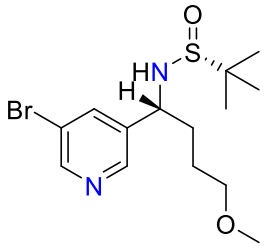
On a 5.2 mmol scale, **38a** was isolated as a yellow oil with 92% yield (1.36 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.22 (s, 9H), 1.38 – 1.45 (m, 1H), 1.51 – 1.60 (m, 1H), 1.81 – 1.88 (m, 1H), 2.07 - 2.17 (dd, *J* = 8.4, 5.2 Hz, 1H), 3.28 (s, 3H), 3.31 – 3.38 (m, 2H), 3.49 – 3.57 (m, 1H), 4.27 – 4.53 (m, 1H), 7.28 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 7.67 (ddt, *J* = 7.9, 2.2, 1.0 Hz, 1H), 8.54 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.58 (d, *J* = 2.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.7, 26.0, 33.5, 56.1, 57.2, 58.7, 72.3, 123.8, 135.1, 138.0, 149.1, 149.5. **IR ν** (cm^{-1}): 3215, 2926, 2867, 1116,1046, 714. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{14}H_{25}N_2O_2S$, 285,1631; found: 285,1633. **$[\alpha]_D^{28}$=** +71.7 (c = 0.10, $CHCl_3$).

***(R)-N*-((*R*)-4-methoxy-1-(5-((trimethylsilyl)ethynyl)pyridin-3-yl)butyl)-2-methylpropane-2-sulfinamide (38b)**



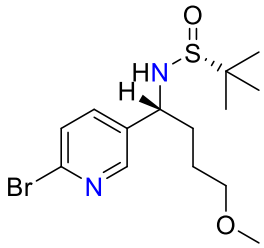
On a 4.6 mmol scale, **38b** was isolated as a yellow solid with 79% yield (1.38 g). **m.p.:** 123-124ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.25 (s, 9H), 1.20 (s, 9H), 1.37 – 1.49 (m, 1H), 1.54 - 1.58 (m, 1H), 1.73-1.90 (m, 1H), 2.00-2.15 (m, 1H), 3.26 (s, 3H), 3.29 – 3.36 (m, 2H), 3.55 (d, *J* = 4.6 Hz, 1H), 4.35 (ddd, *J* = 7.9, 6.0, 4.6 Hz, 1H), 7.69 (t, *J* = 2.1 Hz, 1H), 8.47 (t, *J* = 2.0 Hz, 1H), 8.58 (d, *J* = 1.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = -0.1, 22.7, 25.9, 33.4, 56.2, 56.8, 58.7, 72.2, 98.9, 101.3, 120.4, 137.4, 137.5, 148.1, 152.2. **IR** ν(cm^{-1}): 2955, 1148, 1249, 1118, 1045, 941. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{32}N_2NaO_2SSi$, 403.1846; found, 403.1859. **$[\alpha]_D^{28}$=** -8.5 (c = 0.08, $CHCl_3$).

(*R*)-*N*-((*R*)-1-(5-bromopyridin-3-yl)-4-methoxybutyl)-2-methylpropane-2-sulfinamide (38c)



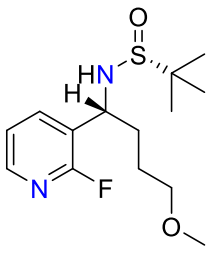
On a 4.0 mmol scale, **38c** was isolated as a yellow solid with 72% yield (1.05 g). **m.p.:** 92-93ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.20 (s, 9H), 1.42 (ddt, *J* = 16.0, 13.5, 5.6 Hz, 1H), 1.53 – 1.61 (m, 1H), 1.79 – 1.87 (m, 1H), 2.03 – 2.11 (m, 1H), 3.27 (s, 3H), 3.33 (td, *J* = 6.1, 1.1 Hz, 2H), 3.69 (d, *J* = 5.2 Hz, 1H), 4.35 (ddd, *J* = 7.8, 6.7, 5.1 Hz, 1H), 7.80 (t, *J* = 2.1 Hz, 1H), 8.47 (d, *J* = 2.0 Hz, 1H), 8.56 (d, *J* = 2.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.7, 26.0, 33.6, 56.3, 56.9, 58.7, 72.1, 121.0, 137.5, 140.0, 147.2, 150.4. **IR** ν(cm^{-1}): 3113, 2870, 1423, 1117, 1041. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{14}H_{23}BrN_2NaO_2S$, 385.0556; found, 385.0546. **$[\alpha]_D^{28}$=** +90.0 (c = 0.08, $CHCl_3$).

(*R*)-*N*-((*R*)-1-(6-bromopyridin-3-yl)-4-methoxybutyl)-2-methylpropane-2-sulfinamide (38d)



On a 4.3 mmol scale, **38d** was isolated as a yellow solid with 86% yield (1.34 g). **m.p.:** 101-102ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.20 (s, 9H), 1.38 – 1.47 (m, 1H), 1.49 – 1.62 (m, 1H), 1.77 – 1.87(m, 1H), 2.03 – 2.12 (m, 1H), 3.28 (s, 3H), 3.31 – 3.40 (m, 2H), 3.58 (d, *J* = 5.1 Hz, 1H), 4.29 – 4.42 (m, 1H), 7.45 – 7.49 (m, 1H), 7.55 (dd, *J* = 8.3, 2.6 Hz, 1H), 8.32 (d, *J* = 2.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.7, 26.0, 33.5, 56.3, 56.7, 58.8, 72.2, 128.3, 137.5, 137.7, 141.6, 149.3. **IR** ν(cm^{-1}): 2821, 1421, 1113, 1090, 1049. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{14}H_{23}$ BrN_2NaO_2S, 385.0556; found, 385.0565. **$[\alpha]_D^{28}$=** +33.2 (c = 0.1, $CHCl_3$).

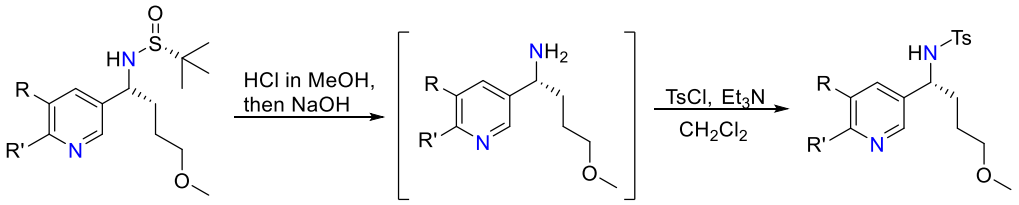
***(R)*-*N*-((*R*)-1-(2-fluoropyridin-3-yl)-4-methoxybutyl)-2-methylpropane-2-sulfinamide (38e)**



On a 4.0 mmol scale, **38e** was isolated as a yellow oil with 84% yield (1.02 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.21 (s, 9H), 1.47 – 1.57 (m, 1H), 1.66 – 1.71 (m, 1H), 1.81 – 1.93 (m, 1H), 1.95 – 2.06 (m, 1H), 3.30 (s, 3H), 3.37 (ddd, *J* = 6.7, 6.1, 1.0 Hz, 2H), 3.83 (d, *J* = 8.0 Hz, 1H), 4.50 (q, *J* = 7.4 Hz, 1H), 7.18 (ddd, *J* = 7.4, 4.9, 1.8 Hz, 1H), 7.78 (ddd, *J* = 9.5, 7.4, 2.0 Hz, 1H), 8.12 (ddd, *J* = 4.9, 1.9, 1.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.7, 26.3, 33.3 (d, J_{CF}= 1.6 Hz), 55.6 (d, J_{CF}= 3.2 Hz), 56.4, 58.8, 72.3, 121.8 (d, J_{CF}= 4.3 Hz), 125.1 (d, J_{CF}= 27.8 Hz), 139.5 (d, J_{CF}= 5.4 Hz), 146.7 (d, J_{CF}= 15.3 Hz), 161.1 (d, J_{CF}= 238.3 Hz). **IR** ν(cm^{-1}): 3021, 1603,

1571, 1420. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{14}H_{23}FN_2NaO_2S$, 325.1356; found, 325.1347. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -70.9 **$[\alpha]_D^{28}$=** +46.8 (c = 0.08, $CHCl_3$).

Step III and IV. Deprotection and tosylation

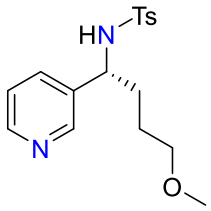


General Procedure (GP3):

Step III. To the sulfonamide compound in MeOH (8mL/mmol) was added HCl (2.4 equiv, 4M in dioxane) or HCl (2.4 equiv, 37% in water), the mixture was stirred overnight at rt. The solvent was removed under reduced pressure, then water was added, and NaOH (2M in water) to basify, extracted with DCM (3x), dried over Na_2SO_4, and concentrated under reduced pressure. The product was used as it is to the next step without further purification.

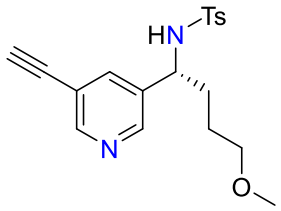
Step IV. To the free amine dissolved in dry DCM (15 mL/mmol) were added Et_3N (3 equiv) and tosyl chloride (1.5 equiv) at 0ºC. Then, the mixture reaction was allowed to warm to rt overnight. To the mixture was added NH_4Cl and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane or ethyl acetate methanol.

(*R*)-*N*-(4-methoxy-1-(pyridin-3-yl)butyl)-4-methylbenzenesulfonamide (39a)



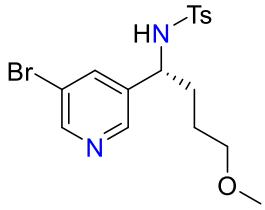
On a 3.6 mmol scale, **39a** was isolated as a yellow solid with 78% yield (0.94 g, over two steps). **m.p.** 124-125ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.34-1.63 (m, 2H), 1.66-1.96 (m, 2H), 2.35 (s, 3H), 3.22-3.36 (m, 5H), 4.28-4.32 (m, 1H), 6.40 (d, *J* = 6.7 Hz, 1H), 7.08 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 7.11- 7.18 (m, 2H), 7.45 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.52-7.59 (m, 2H), 8.33 (d, *J* = 2.3 Hz, 1H), 8.38 (dd, *J* = 4.8, 1.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.5, 25.8, 34.7, 55.7, 58.7, 71.9, 123.3, 127.1, 129.5, 134.1, 136.8, 137.4, 143.3, 148.4, 148.6. **IR ν** (cm^{-1}): 3023, 2827, 1321, 1151, 1091, 667, 543. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{23}N_2O_3S$, 335,1424; found: 335,1428. **$[\alpha]_D^{28}$=** +77.5 (c = 0.08, $CHCl_3$).

(*R*)-*N*-(1-(5-ethynylpyridin-3-yl)-4-methoxybutyl)-4-methylbenzenesulfonamide (39b)



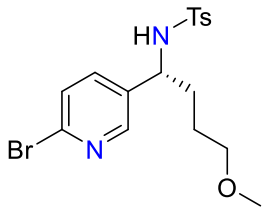
On a 3.5 mmol scale, **39b** was isolated as a yellow solid with 76% yield (0.95 g, over two steps). **m.p.:** 84-85ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.40 – 1.56 (m, 2H), 1.71 – 1.86 (m, 2H), 2.34 (s, 3H), 3.16 (s, 1H), 3.26 – 3.38 (m, 5H), 4.29 (dt, *J* = 7.9, 6.3 Hz, 1H), 6.37 (d, *J* = 6.5 Hz, 1H), 7.08 – 7.17 (m, 2H), 7.41 (t, *J* = 2.1 Hz, 1H), 7.47 – 7.54 (m, 2H), 8.30 (d, *J* = 2.2 Hz, 1H), 8.44 (d, *J* = 2.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.5, 25.9, 34.5, 55.5, 58.7, 71.9, 80.1, 80.8, 119.0, 127.1, 129.6, 136.4, 137.3, 137.3, 143.5, 147.9, 151.3. **IR** ν(cm^{-1}): 2871, 1468, 1328, 1159, 664. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{22}N_2NaO_3S$, 381.1243; found, 381.1238. **$[\alpha]_D^{28}$=** +90.0 (c = 0.08, $CHCl_3$).

***(R)*-*N*-(1-(5-bromopyridin-3-yl)-4-methoxybutyl)-4-methylbenzenesulfonamide (39c)**



On a 4.0 mmol scale, **39c** was isolated as a yellow solid with 92% yield (1.52 g, over two steps. **m.p.** 97-98ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.41 – 1.59 (m, 2H), 1.79 (td, *J* = 6.9, 6.4, 1.7 Hz, 2H), 2.37 (s, 3H), 3.24 – 3.52 (m, 5H), 4.30 (q, *J* = 6.6 Hz, 1H), 6.11 (d, *J* = 5.9 Hz, 1H), 7.12 – 7.17 (m, 2H), 7.44 – 7.47 (m, 1H), 7.48 – 7.55 (m, 2H), 8.28 (d, *J* = 1.8 Hz, 1H), 8.42 (d, *J* = 2.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 25.9, 34.8, 55.3, 58.9, 72.0, 120.8, 127.2, 129.6, 136.9, 137.3, 138.6, 143.7, 146.7, 149.7. **IR** ν(cm^{-1}): 3051, 2870, 1452, 1328, 1157,662. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{22}BrN_2O_3S$, 413.0529; found, 413.0528. **$[\alpha]_D^{28}$=** +69.7 (c = 0.13, $CHCl_3$).

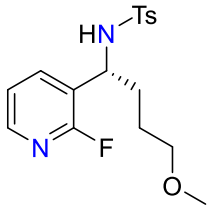
***(R)*-*N*-(1-(6-bromopyridin-3-yl)-4-methoxybutyl)-4-methylbenzenesulfonamide (39d)**



On a 3.2 mmol scale, **39d** was isolated as a yellow solid with 89% yield (1.18 g, over two steps). **m.p.:** 125-126ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.40 – 1.49 (m, 2H), 1.67 – 1.80 (m, 2H), 2.37 (s, 3H), 3.20 – 3.35 (m, 5H), 4.23 (dt, *J* = 7.9, 6.5 Hz, 1H), 6.33 (d, *J* = 6.7 Hz, 1H), 7.10 – 7.16 (m, 2H), 7.17 – 7.22 (m, 1H), 7.28 – 7.33 (m, 1H), 7.46 – 7.54 (m, 2H), 8.04 (d, *J* = 2.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 25.8, 34.3, 55.23, 58.7, 71.9, 127.1, 127.8, 129.6, 136.3, 136.9, 137.2, 140.8, 143.6, 148.9. **IR** ν(cm^{-1}): 1450, 1328, 1154, 1113, 1069, 810. **HRMS**

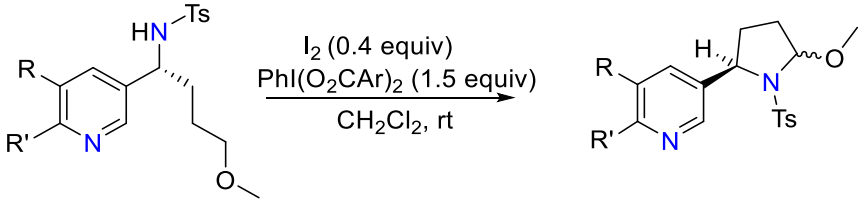
(m/z): $[M+H]^+$ calcd. for $C_{17}H_{22}BrN_2O_3S$, 413.0529; found, 413.0533. **$[\alpha]_D^{28}$=** +83.0 (c = 0.1, $CHCl_3$).

(*R*)-*N*-(1-(2-fluoropyridin-3-yl)-4-methoxybutyl)-4-methylbenzene-sulfonamide (39e)



On a 3.8 mmol scale, **39e** was isolated as a white solid with 78% yield (1.04 g, over two steps). **m.p.:** 142-143ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.40 – 1.52 (m, 2H), 1.79 (q, *J* = 8.4, 7.1 Hz, 2H), 2.34 (s, 3H), 3.28 – 3.37 (m, 5H), 4.43 (q, *J* = 7.2 Hz, 1H), 6.03 (d, *J* = 7.4 Hz, 1H), 6.98 – 7.04 (m, 1H), 7.11 – 7.17 (m, 2H), 7.55 – 7.59 (m, 2H), 7.60 – 7.65 (m, 1H), 7.98 (ddd, *J* = 4.9, 2.0, 1.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.5, 25.9, 33.1 (d, J_{CF}= 1.6 Hz), 52.8 (d, J_{CF}= 3.2 Hz), 58.8, 72.0, 121.5 (d, J_{CF}= 4.3 Hz), 123.7 (d, J_{CF}= 27.7 Hz), 127.1, 129.58, 137.1, 139.5 (d, J_{CF}= 5.2 Hz), 143.5, 146.3 (d, J_{CF}= 15.1 Hz), 160.5 (d, J_{CF}= 237.9 Hz). **IR** ν(cm^{-1}): 2870, 1605, 1428, 1323, 1150. **HRMS** (m/z): $[M-H]^-$ calcd. for $C_{17}H_{20}FN_2O_3S$, 351.1184; found, 351.1189. **^{19}F NMR (376 MHz, $CDCl_3$)**: δ = -72.2 **$[\alpha]_D^{28}$=** +84.7 (c = 0.13, $CHCl_3$).

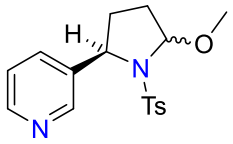
Step V: Hofmann-Löffler reaction



General procedure (GP4):

The tosyl amine was dissolved in dry DCM (15 mL/mmol) then, PhI(*m*cba)$_2$ (1.5 equiv) and I_2 (0.4 equiv) were added. The reaction was stirred at rt overnight under visible light. To the mixture were added $Na_2S_2O_3$ and $NaHCO_3$ and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane or ethyl acetate methanol.

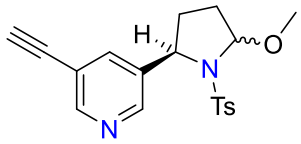
3-((2*R*)-5-methoxy-1-tosylpyrrolidin-2-yl) pyridine (40a)



On a 1.0 mmol scale, **40a** was isolated as a colorless oil with 67% yield (0.22 g). Mixture of diastereomers (1:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.42 (ddd, *J* = 12.8, 7.5, 5.0 Hz, 1H), 1.71 – 1.79 (m, 1H), 1.95 (ddd, *J* = 17.8, 8.7, 3.9 Hz, 2H),

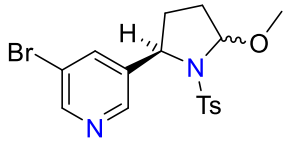
2.06 (ddd, *J* = 13.0, 9.7, 6.4 Hz, 1H), 2.29 (dt, *J* = 12.5, 7.3 Hz, 1H), 2.40 (d, *J* = 6.2 Hz, 6H), 2.53 – 2.60 (m, 1H), 3.38 (s, 3H), 3.56 (s, 3H), 4.54 (dd, *J* = 9.5, 7.5 Hz, 1H), 4.75 (d, *J* = 9.0 Hz, 1H), 5.27 – 5.29 (m, 1H), 5.40 (d, *J* = 3.6 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.31 (m, 3H).7.40 (t, *J* = 7.9 Hz, 1H), 7.53 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.60 – 7.64 (m, 2H), 7.65 – 7.71 (m, 2H), 8.00 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.10 (t, *J* = 1.8 Hz, 1H), 8.48 – 8.57 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 28.6, 32.9, 33.1, 34.7, 55.4, 55.7, 59.8, 62.5, 92.8, 93.1, 123.3, 123.6, 127.5, 128.0, 129.2, 129.8, 129.8, 133.9, 134.7, 135.4, 137.2, 138.4, 143.4, 144.0, 147.7, 148.3, 148.5, 148.5. **IR ν** (cm-1): 1580, 1452, 1162, 990, 661. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{21}N_2O_3S^+$: 333,1267; found: 333, 1265.

3-ethynyl-5-((2*R*)-5-methoxy-1-tosylpyrrolidin-2-yl)pyridine (40b)



On a 1.0 mmol scale, **40b** was isolated as a yellow oil with 71% yield (0.25 g). Mixture of diastereomers (1:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.44 – 1.56 (m, 1H), 1.80 (dd, *J* = 12.4, 6.5 Hz, 1H), 1.91 – 2.16 (m, 4H), 2.32 – 2.40 (m, 1H), 2.43 (d, *J* = 2.0 Hz, 8H), 2.54 – 2.65 (m, 1H), 3.42 (s, 3H), 3.58 (s, 3H), 4.59 – 4.69 (m, 1H), 4.79 (d, *J* = 9.1 Hz, 1H), 5.35 (d, *J* = 4.8 Hz, 1H), 5.42 (d, *J* = 3.7 Hz, 1H), 7.20 – 7.31 (m, 4H), 7.45 (d, *J* = 1.7 Hz, 1H), 7.56 – 7.76 (m, 6H), 8.40 (d, *J* = 14.0 Hz, 1H), 8.54 (d, *J* = 5.9 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.7, 28.8, 33.3, 34.9, 55.7, 56.0, 59.6, 62.0, 83.1, 83.3, 83.4, 85.6, 91.6, 91.7, 92.8, 93.2, 124.6, 126.6, 127.4, 127.7, 128.1, 129.5, 130.0, 130.1, 134.4, 135.5, 137.3, 143.7, 144.2, 144.2, 147.7, 148.2, 148.3, 148.4. **IR** ν(cm^{-1}): 1502, 1370, 11551, 1089, 703. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{19}H_{21}N_2O_3S$, 357.1267; found, 357.1261.

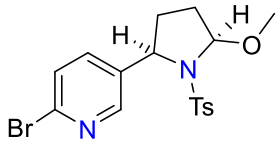
3-Bromo-5-((2*R*)-5-methoxy-1-tosylpyrrolidin-2-yl)pyridine (40c)



On a 1.0 mmol scale, **40c** was isolated as a yellow oil with 63% yield (0.26 g). Mixture of diastereoisomers (d.r. = 1:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.37 – 1.50 (m, 1H), 1.68 – 1.84 (m, 1H), 1.91 – 2.06 (m, 4H), 2.19 – 2.34 (m, 1H), 2.39 – 2.42 (m, 6H), 2.53 – 2.62 (m, 1H), 3.39 (s, 3H), 3.55 (s, 3H), 4.46 – 4.60 (m, 1H), 4.71 (dd, *J* = 9.2, 1.4 Hz, 1H), 5.30 (d, *J* = 4.8 Hz, 1H), 5.34 – 5.45 (m, 1H), 7.20 – 7.25 (m, 4H), 7.58 (tdd, *J* = 4.7, 3.5, 1.9 Hz, 3H), 7.64 (d, *J* = 6.6 Hz, 2H), 7.68 (t, *J* = 2.1 Hz, 1H), 8.41 (d, *J* = 1.9 Hz, 1H), 8.45 (dd, *J* = 4.5, 2.1 Hz, 1H), 8.50 (dd, *J* = 3.8, 2.2 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.7, 28.9, 32.8, 33.1, 34.5, 34.8, 55.6, 55.9, 61.5, 61.8, 92.7, 93.3, 120.8, 120.9, 127.6, 128.0, 129.4, 129.9, 135.5, 135.6, 136.4, 137.5, 140.1, 140.2, 143.8, 144.2, 146.5, 146.7, 149.6, 149.7. **IR** ν(cm^{-1}): 1423, 1342, 1155, 1093,

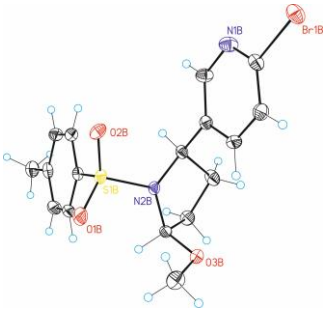
669. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{20}BrN_2O_3S$, 411.0373; found, 411.0366.

2-Bromo-5-((2*R*, 5*R*)-5-methoxy-1-tosylpyrrolidin-2-yl)pyridine (40d)



On a 1.0 mmol scale, **40d** was isolated as a white solid with 56% yield (0.23 g). **m.p.:** 129-130ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.36 – 1.46 (m, 1H), 1.94 – 2.04 (m, 2H), 2.21 – 2.31 (m, 1H), 2.41 (s, 3H), 3.52 (s, 3H), 4.47 (dd, *J* = 9.3, 7.5 Hz, 1H), 5.26 (d, *J* = 4.8 Hz, 1H), 7.22 – 7.28 (m, 2H), 7.32 – 7.39 (m, 1H), 7.48 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.57 – 7.62 (m, 2H), 8.20 – 8.27 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 32.9, 34.6, 55.5, 61.7, 92.8, 127.6, 128.1, 129.9, 135.4, 137.5, 137.9, 140.9, 144.3, 145.0. **IR** ν(cm^{-1}): 1581, 1453, 1392, 1160, 993. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{20}BrN_2O_3S$, 411.0373; found, 411.0364. **[α]$_D^{28}$=** 186.6 (c = 0.17, $CHCl_3$).

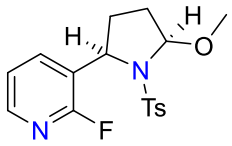
*X-Ray data of compound **40d***



Identification code	CCDC 1883568
Empirical formula	C17 H19 Br N2 O3 S
Formula weight	411.31
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 7.4842(12)Å α= 90°.
	b = 11.1401(18)Å β= 95.438(4)°.
	c = 21.301(3)Å γ = 90°.

Volume	1768.0(5) $Å^3$
Z	4
Density (calculated)	1.545 Mg/m^3
Absorption coefficient	2.461 mm^{-1}
F(000)	840
Crystal size	0.20 x 0.08 x 0.03 mm^3
Theta range for data collection	2.065 to 33.861°.
Index ranges	-11<=h<=11,-15<=k<=17,-33<=l<=33
Reflections collected	31633
Independent reflections	12663[R(int) = 0.0356]
Completeness to theta =33.861°	99.0%
Absorption correction	Multi-scan
Max. and min. transmission	0.930 and 0.8
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12663/ 214/ 496
Goodness-of-fit on F^2	1.120
Final R indices [I>2sigma(I)]	R1 = 0.0394, wR2 = 0.0760
R indices (all data)	R1 = 0.0571, wR2 = 0.0803
Flack parameter	x =-0.004(4)
Largest diff. peak and hole	1.714 and -0.924 $e.Å^{-3}$

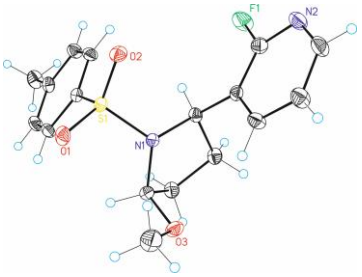
2-fluoro-3-((2*R*,5*R*)-5-methoxy-1-tosylpyrrolidin-2-yl)pyridine (40e)



On a 1.0 mmol scale, **40e** was isolated as a white solid with 60% yield (0.21 g). Mixture of diastereoisomers (d.r. = 1:4), given data corresponds to the major one. **m.p.:** 131-132ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.23 – 1.37 (m, 1H), 1.84 – 2.00 (m, 2H), 2.25 – 2.38 (m, 1H), 2.43 (s, 3H), 3.60 (s, 3H), 4.72 (dd, *J* = 9.0, 7.5 Hz, 1H), 5.22 (d, *J* = 5.0 Hz, 1H), 7.19 (ddd, *J* = 7.2, 4.9, 1.8 Hz, 1H), 7.29 – 7.37 (m, 2H), 7.65 – 7.73 (m, 2H), 7.94 (ddd, *J* = 9.6,

7.5, 2.0 Hz, 1H), 8.07 – 8.12 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.7, 32.9, 33.3, 55.6, 57.8 , 93.1, 122.1 (d, *J* = 4.1 Hz), 125.4 (d, J_{C-F} = 27.8 Hz), 127.7, 130.1, 134.8, 139.2 (d, J_{C-F} = 4.8 Hz), 144.3, 146.2 (d, J_{C-F} = 14.9 Hz), 160.6 (d, J_{C-F} = 237.2 Hz). **IR** ν(cm^{-1}): 1560, 1437, 1346, 1158, 670. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{19}FN_2NaO_3S$, 373.0993; found, 373.0969. **^{19}F NMR (376 MHz, $CDCl_3$)**: δ = -74.7

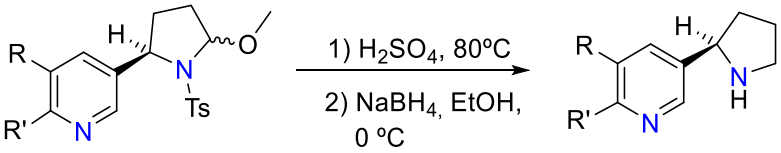
*X-Ray data of compound **40e***



Identification code	CCDC 1883567
Empirical formula	C17 H19 F N2 O3 S
Formula weight	350.40
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 13.8691(9)Å α= 90°. b = 7.4650(5)Å β = 96.293(2)°. c = 16.0743(10)Å γ = 90°.
Volume	1654.19(19) $Å^3$
Z	4
Density (calculated)	1.407 Mg/m^3
Absorption coefficient	0.224 mm^{-1}
F(000)	736

Crystal size	0.25 x 0.15 x 0.05 mm^3
Theta range for data collection	2.054 to 30.605°.
Index ranges	-19<=h<=16,-10<=k<=10,-22<=l<=22
Reflections collected	27953
Independent reflections	5067[R(int) = 0.0523]
Completeness to theta =30.605°	99.4%
Absorption correction	Multi-scan
Max. and min. transmission	0.989 and 0.887
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5067/ 0/ 219
Goodness-of-fit on F^2	1.020
Final R indices [I>2sigma(I)]	R1 = 0.0429, wR2 = 0.0975
R indices (all data)	R1 = 0.0711, wR2 = 0.1080
Largest diff. peak and hole	0.438 and -0.508 e.$Å^{-3}$

Step VI and VII: Detosylation and Reduction of Imines



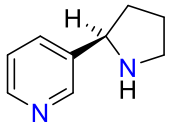
General procedure (GP5):

Step VI: To the corresponding pyrrolidine compound was added concentrated H_2SO_4, and the mixture was heated at 85 ºC for 4 hours. Then, the flask was introduced in an ice bath, and it was added NaOH (2M in water) to basify pH = 11-12. The aqueous layer was extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The product was used as it is for the next step.

Step VII: To the imine compound dissolved in ethanol (7.5 mL/mmol) was added $NaBH_4$ (2.0 equiv) at 0ºC. The reaction was stirred at this temperature for 2 hours. Then, it was added a solution of 1M of HCl and extracted with DCM. The

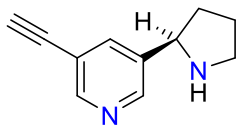
aqueous layer was basified to pH 11 and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. In this step, usually after acid-basic extraction, the compound is clean; no purification step was required.

(*R*)-3-(Pyrrolidin-2-yl)pyridine (41a)



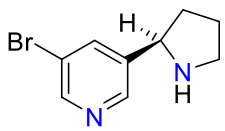
On a 0.6 mmol scale, **41a** was isolated as a brownish oil with 63% yield (56 mg, over two steps). Spectroscopic data in agreement with the one previously described.[226] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.80 – 1.55 (m, 1H), 2.04 – 1.80 (m, 2H), 2.33 – 2.14 (m, 1H), 3.28 – 2.97 (m, 2H), 4.15 (t, *J* = 7.7 Hz, 1H), 7.24 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H), 7.71 (dt, *J* = 7.8, 2.0 Hz, 1H), 8.47 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.58 (d, *J* = 2.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.6, 34.4, 47.1, 60.2, 123.5, 134.3, 140.2, 148.4, 148.6.

(*R*)-3-Ethynyl-5-(pyrrolidin-2-yl)pyridine (41b)



On a 0.8 mmol scale, **41b** was isolated as a colorless oil with 65% yield (89 mg, over two steps). Spectroscopic data in agreement with the one previously described.[226] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.62 – 1.72 (m, 1H), 1.84 – 2.01 (m, 2H), 2.19 – 2.29 (m, 1H), 3.07 (ddd, *J* = 10.1, 8.2, 6.7 Hz, 1H), 3.21 (s, 1H), 3.16 – 3.25 (m, 1H), 4.18 (t, *J* = 7.6 Hz, 1H), 7.84 (td, *J* = 2.1, 0.7 Hz, 1H), 8.55 (d, *J* = 2.2 Hz, 1H), 8.58 (d, *J* = 2.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.6, 34.6, 47.1, 59.6, 80.4, 80.7, 119.0, 137.3, 140.3, 148.2, 151.2.

***(R)*-3-bromo-5-(pyrrolidin-2-yl)pyridine (41c)**

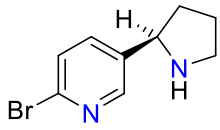


On a 0.5 mmol scale, **41c** was isolated as a colorless oil with 58% yield (66 mg, over two steps). Spectroscopic data in agreement with the one previously described.[227] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.59 – 1.71 (m, 1H), 1.81 – 1.98 (m, 2H), 2.18 – 2.30 (m, 1H), 3.03 – 3.10 (m, 1H), 3.14 – 3.20 (m, 1H), 4.18 (t, *J* = 7.6 Hz, 1H), 7.91 (t, *J* = 2.1 Hz, 1H), 8.49 (d, *J* = 1.9 Hz, 1H), 8.53 (d, *J* = 2.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.6, 34.7, 47.1, 59.4, 120.9, 136.9, 142.8, 146.8, 149.2.

[226] S. Girard, G. Vo-Thanh, R. J. Robins, J. Villiéras, J. Lebreton J. *J. Org. Chem.* **2001**, *66*, 6305.

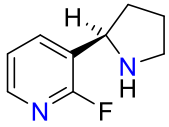
[227] F.-X. Felpin, M.-J. Bertrand, J. Lebreton, *Tetrahedron* **2002**, *58*, 7381.

(R)-2-bromo-5-(pyrrolidin-2-yl)pyridine (41d)

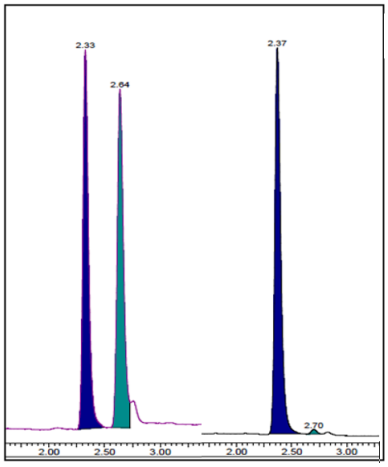


On a 0.5 mmol scale, **41d** was isolated as a colorless oil with 66% yield (75 mg, over two steps). Spectroscopic data in agreement with the one previously described.[228] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.56 – 1.64 (m, 1H), 1.80 – 1.95 (m, 2H), 2.17-2.22 (m, 1H), 3.03 (ddd, *J* = 10.1, 8.2, 6.7 Hz, 1H), 3.15 (ddd, *J* = 10.1, 7.6, 5.4 Hz, 1H), 4.12 (t, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.58 (ddd, *J* = 8.2, 2.5, 0.6 Hz, 1H), 8.32 (d, *J* = 2.6 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 25.5, 34.6, 47.0, 59.4, 127.9, 137.1, 140.0, 140.3, 148.9.

(*R*)-2-fluoro-3-(pyrrolidin-2-yl)pyridine (41e)



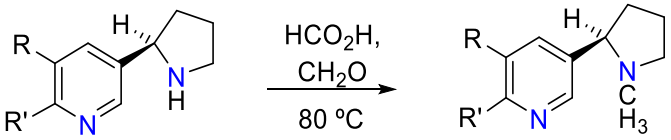
On a 0.6 mmol scale, **41e** was isolated as a colorless oil with 56% yield (56 mg, over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.54 – 1.63 (m, 1H), 1.83 (dtq, *J* = 15.0, 7.6, 5.1 Hz, 2H), 2.20 – 2.30 (m, 1H), 2.72 (bs, 1H), 2.97-3.17 (m, 2H), 4.33 (t, *J* = 7.5 Hz, 1H), 7.11 (ddt, *J* = 7.1, 4.8, 2.3 Hz, 1H), 7.92 (ddd, *J* = 9.6, 7.3, 2.0 Hz, 1H), 8.02 (dt, *J* = 4.9, 1.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.5, 33.0, 46.8, 55.5 (d, J_{CF}= 2.9 Hz), 121.5 (d, J_{CF}= 4.1 Hz), 127.1 (d, J_{CF}= 28.1 Hz), 138.3 (d, J_{CF}= 5.9 Hz), 145.3 (d, J_{CF}= 14.9 Hz), 161.2 (d, J_{CF}= 238.5 Hz). **IR** ν(cm^{-1}): 1513, 1129, 1046, 977, 670. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_9H_{12}FN_2$, 167.0979; found, 167.0974. **^{19}F NMR (376 MHz, $CDCl_3$)**: δ = -72.0. **$[\alpha]_D^{28}$=** 90.9 (c = 0.11, $CHCl_3$). **HPLC: UPC** Chiralpack IG (100x4.6mm, 3 μm), Isocratic CO_2/MeOH/DEA 80:20:0.1, v/v, 2 mL/min, 2000 psi. *ee* (%) = 97%.



[228] C. Guo, D.-W. Sun, S. Yang, S.-J. Mao, X.-H. Xu, S.-F. Zhu, Q.-L. Zhou, *J. Am. Chem. Soc.* **2015**, *137*, 90.

Figure 3.4. *Racemic vs. Enantioselective HPLC-chromatogram of compound* ***41h****.*

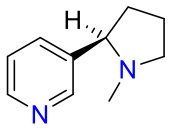
Step VIII. Eschweiler-Clarke reaction



General procedure (GP6):

Step VIII: To the amine was added formic acid (1.8 equiv) and 37% aqueous solution of formaldehyde (1.1 equiv). The mixture was heated at 80ºC for 18h. It was then cooled at 25 ºC and water, and HCl (1M) were added before it was extracted with DCM. The aqueous phase was basified to pH 11 and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane or ethyl acetate methanol.

(*R*)-3-(1-methylpyrrolidin-2-yl)pyridine (42)



On a 0.2 mmol scale, **42** was isolated as a brown oil with 98% yield (32 mg). Spectroscopic data in agreement with the one previously described.[227] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.66 – 1.87 (m, 2H), 1.91 – 2.03 (m, 1H), 2.16 (s, 3H), 2.18 – 2.24 (m, 1H), 2.31 (tdd, *J* = 9.5, 8.3, 1.3 Hz, 1H), 3.08 (t, *J* = 8.3 Hz, 1H), 3.24 (ddt, *J* = 9.5, 8.0, 1.9 Hz, 1H), 7.23 – 7.26 (m, 1H), 7.69 (dq, *J* = 7.8, 1.8 Hz, 1H), 8.49 (dt, *J* = 4.8, 1.4 Hz, 1H), 8.53 (dt, *J* = 2.2, 1.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.8, 35.4, 40.5, 57.2, 69.1, 123.7, 135.0, 138.9, 148.8, 149.8. **$[\alpha]_D^{28}$=** +136.7 (c = 0.1, $CHCl_3$). **HPLC: UPC** Chiralpack IC (100x4.6mm, 3 µm), Isocratic CO_2/EtOH/DEA 90:10:0.1, v/v, 3 mL/min, 1500 psi. *ee* (%) = 96%.

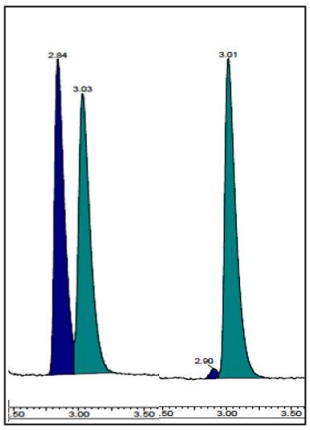
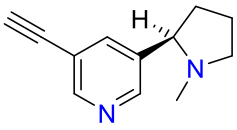


Figure 3.5. *Racemic vs. Enantioselective HPLC-chromatogram of compound* ***42****.*

(*R*)-3-Ethynyl-5-(1-methylpyrrolidin-2-yl)pyridine (42b)



On a 0.2 mmol scale, **42b** was isolated as a brown oil with 87% yield (32 mg). Spectroscopic data in agreement with the one previously described.[227] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.65 – 1.77 (m, 1H), 1.78 – 1.90 (m, 1H), 1.92 – 2.03 (m, 1H), 2.18 (s, 3H), 2.16 – 2.27 (m, 1H), 2.33 (q, *J* = 9.1 Hz, 1H), 3.10 (t, *J* = 8.3 Hz, 1H), 3.19 (s, 1H), 3.19 – 3.29 (m, 1H), 7.81 (t, *J* = 2.1 Hz, 1H), 8.49 (d, *J* = 2.1 Hz, 1H), 8.60 (d, *J* = 2.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.8, 35.4, 40.5, 57.1, 68.6, 80.3, 80.7, 119.3, 137.9, 149.2, 151.7. **HPLC: UPC** Chiralpack ID (100x4.6mm, 3 µm), Isocratic CO_2/EtOH/DEA 80:20:0.1, v/v, 3 mL/min, 1500 psi. *ee* (%) = 99%.

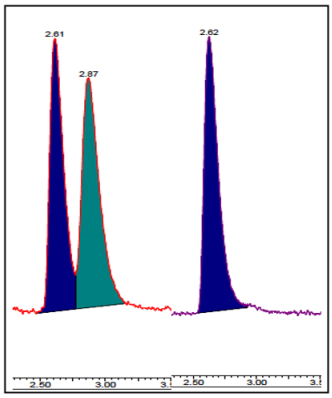
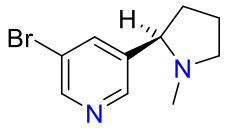


Figure 3.6. *Racemic vs. Enantioselective HPLC-chromatogram of compound* ***42b****.*

(*R*)-3-bromo-5-(1-methylpyrrolidin-2-yl)pyridine (42c)



On a 0.3 mmol scale, **42c** was isolated as a brown oil with 92% yield (66 mg).Spectroscopic data in agreement with the one previously described.[227] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.65 – 1.72 (m, 1H), 1.78 – 1.88 (m, 1H), 1.90 – 2.01 (m, 1H), 2.19 (s, 3H), 2.20 – 2.26 (m, 1H), 2.33 (td, *J* = 9.3, 8.2 Hz, 1H), 3.11 (t, *J* = 8.3 Hz, 1H), 3.24 (ddd, *J* = 9.7, 7.9, 2.2 Hz, 1H), 7.88 (t, *J* = 2.1 Hz, 1H), 8.44 (d, *J* = 1.8 Hz, 1H), 8.55 (d, *J* = 2.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.9, 35.5, 40.6, 57.1, 68.3, 121.2, 137.6, 147.7, 149.8. **HPLC: UPC** Chiralpack IG (100x4.6mm, 3 µm), Isocratic CO_2/EtOH/DEA 95:5:0.1, v/v, 2 mL/min, 2000 psi. *ee* (%) = 95%.

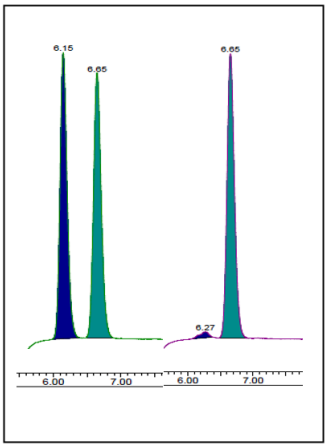
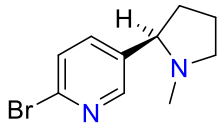


Figure 3.7. *Racemic vs. Enantioselective HPLC-chromatogram of compound* ***42c****.*

(*R*)-2-bromo-5-(1-methylpyrrolidin-2-yl)pyridine (42d)



On a 0.2 mmol scale, **42d** was isolated as a brown oil with 79% yield (38 mg). Spectroscopic data in agreement with the one previously described.[228] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.60 – 1.70 (m, 1H), 1.75 – 1.85 (m, 1H), 1.89 – 2.00 (m, 1H), 2.14 (s, 3H), 2.17 – 2.23 (m, 1H), 2.30 (q, *J* = 9.2 Hz, 1H), 3.06 (t, *J* = 8.3 Hz, 1H), 3.22 (ddd, *J* = 9.7, 7.9, 2.2 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.57 (dd, *J* = 8.2, 2.5 Hz, 1H), 8.27 (d, *J* = 2.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.8, 35.4, 40.5, 57.1, 68.2, 128.2, 137.8, 138.6, 140.7, 149.9. **HPLC: UPC** Chiralpack IA (100x4.6mm, 3 µm), Isocratic CO_2/AcN/DEA 95:5:0.1, v/v, 3 mL/min, 1500 psi. *ee* (%) = 99%.

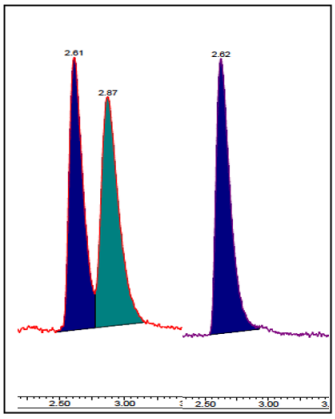
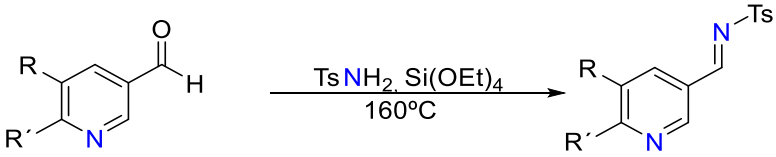


Figure 3.8. *Racemic vs. Enantioselective HPLC-chromatogram of compound* ***42d****.*

Non-enantioselective synthesis

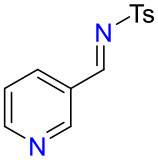
Step I: Racemic imine formation



General Procedure (GP7):

A mixture of the corresponding 3-pyridine carboxaldehyde, p-toluensulfonamide, and tetraethyl orthosilicate was warmed at 160 ºC for 18 h. Then, to the mixture was added a mixture of solvents (ethyl acetate- diethyl ether (1/1- 8/2, v/v)), and the solid was filtered and dried under reduced pressure.

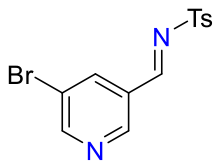
(*E*)-4-methyl-*N*-(pyridin-3-ylmethylene)benzenesulfonamide (31a)



On a 6.0 mmol scale, **31a** was isolated as a white solid with 82% yield (1.28 g).Spectroscopic data in agreement with the one previously described.[229] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 7.33 – 7.38 (m, 2H), 7.44 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.86 – 7.94 (m, 2H), 8.27 (dt, *J* = 8.0, 2.0 Hz, 1H), 8.81 (dd, *J* = 4.8, 1.8 Hz, 1H), 9.05 (d, *J* = 2.2 Hz, 1H), 9.08 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 124.3, 126.6, 128.4, 130.1, 134.6, 137.0, 145.2, 153.1, 155.2, 167.7.

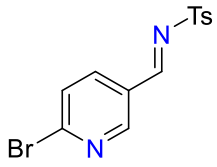
***(E)*-*N*-((5-bromopyridin-3-yl)methylene)-4-methylbenzenesulfonamide (31c)**

[229] B. M. Trost, C. Marrs, *J. Org. Chem*. **1991**, *56*, 6468.



On a 5.5 mmol scale, **31c** was isolated as a brown solid with 80% yield (1.49 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 7.34 – 7.46 (m, 2H), 7.86 – 7.93 (m, 2H), 8.42 (d, *J* = 2.1 Hz, 1H), 8.86 (d, *J* = 2.3 Hz, 1H), 8.93 (d, *J* = 1.8 Hz, 1H), 9.04 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.9, 121.7, 128.5, 129.8, 130.2, 134.3, 138.8, 145.5, 151.0, 156.2, 166.1. **IR** ν(cm^{-1}): 1654, 1230, 1132, 1088, 921, 542. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{11}BrN_2NaO_2S$, 360.9617; found, 360.9611

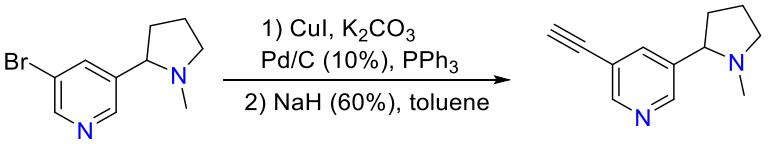
(*E*)-*N*-((6-bromopyridin-3-yl)methylene)-4-methylbenzenesulfonamide (31d)



On a 5.0 mmol scale, **31d** was isolated as a brownish solid with 88% yield (1.49 g). **m.p.:** 194-195ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 8.10 (dd, *J* = 8.3, 2.3 Hz, 1H), 8.77 (d, *J* = 2.2 Hz, 1H), 9.04 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 127.7, 128.5, 129.2, 130.1, 134.3, 138.6, 145.4, 148.8, 153.3, 166.4. **IR** ν(cm^{-1}): 1651, 1232, 1129, 1088, 540. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{11}BrN_2NaO_2S$, 360.9617; found, 360.9609.

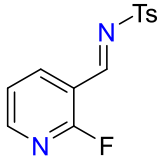
Sonogashira coupling to the racemic product of **42b**

The formation of the imine with the compound **36b** was not possible; the synthesis of racemic **42b** was carried out through the racemic **42c**, described below:



Compound **42b** was synthesized following a previously described procedure.[230]

***N*-((2-fluoropyridin-3-yl)methylene)-4-methylbenzenesulfonamide. (31h)**



On a 5.0 mmol scale, **3h** was isolated as a brownish solid with 85% yield (1.18 g). **m.p.:** 108-109ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 7.33 (td, *J* = 6.2, 5.5, 2.7 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.86 – 7.93 (m, 2H), 8.43 – 8.47 (m, 1H), 8.50 (ddd, *J* = 9.3, 7.6, 2.1 Hz, 1H), 9.25 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 115.7 (d, J_{CF}= 23.6 Hz), 122.5 (d, J_{CF}= 4.5 Hz), 128.6, 130.1, 134.3, 140.3 (d, J_{CF}= 2.1 Hz), 145.4, 154.0 (d, J_{CF}= 16.1 Hz), 162.6, 163.8 (d,

[230] L. S. Bleicher, N. D. P. Cosford, A. Herbaut, J. S. McCallum, I. A. McDonald, *J. Org. Chem.* **1998**, *63* ,1109.

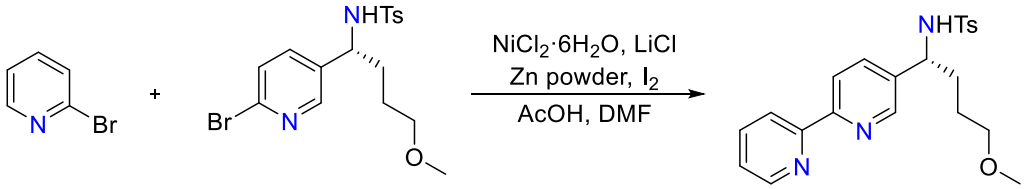
J_{CF}= 248.5 Hz). **IR** ν(cm^{-1}): 2522, 1604, 1433, 1332, 1157, 1067. **HRMS** (m/z): [M+H]$^+$ calcd. for $C_{13}H_{12}FN_2O_2S$, 279.0598; found, 279.0598. **^{19}F NMR (376 MHz, $CDCl_3$)**: δ = -70.7

Enantioselective synthesis of the bipyridyl derivatives

Specific procedures for bipyridine couplings

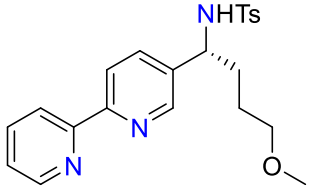
(*R*)-*N*-(1-([2,2'-bipyridin]-5-yl)-4-methoxybutyl)-4-methylbenzenesulfonamide (43a)

Compound **5e** was synthesized following a previously described procedure.[231]



Procedure:

A round-bottom flask was charged with $NiCl_2 \cdot 6H_2O$ (0.025 equiv) and DMF (3.5 mL/mmol). The resulting solution was stirred and heated to 40°C, and then 2-halopyridine or 2- halopicoline (one-third of the 2.5 equiv), functionalized 2-halopyridine (one-third of 1 equiv), anhydrous LiCl (3.5 equiv), and zinc dust (4.2 equiv) were added. When the temperature rose to 50 °C, a grain of iodine crystal and two drops of acetic acid were added to initiate the reaction. The solution of the remaining 2-halopyridine (2-halopicoline) (two thirds) and functionalized 2-halopyridine (two thirds) in DMF (3.5 mL/mmol) was added dropwise into the mixture at 60 – 70 ° C throughout 3 h. The resulting mixture was then stirred at 60 −70°C for an additional 3 h until complete conversion of 2-halopyridine (monitored by TLC). To the cooled reaction was added HCl (1M in water) to consume the remaining zinc dust. The resulting mixture was made alkaline with NH_4OH (30% in water), extracted with DCM and dried over Na_2SO_4, and concentrated under reduced pressure.

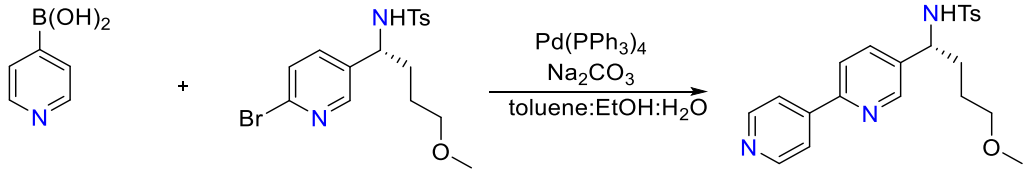


On a 2.5 mmol scale, **43a** was isolated as colorless oil with 38% yield (0.39g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.48 – 1.58 (m, 2H), 1.80 – 1.92 (m, 2H), 2.26 (s, 3H), 3.30 – 3.37 (m, 5H), 4.38 (q, *J* = 6.7 Hz, 1H), 5.84 (d, *J* = 6.4 Hz, 1H), 7.06 – 7.12 (m, 2H), 7.30 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.51 – 7.54 (m, 1H), 7.54 – 7.56 (m, 2H), 7.80 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.2, 0.8 Hz, 1H), 8.30 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.34 – 8.39 (m, 1H), 8.65 (ddd, *J* = 4.8, 1.8, 0.9

[231] L.-Y. Liao, X.-R. Kong, X.-F. Duan, *J. Org. Chem.*, **2014**, *79*, 777.

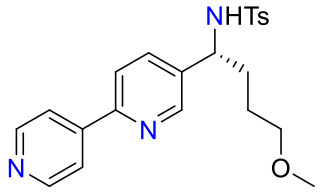
Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.5, 25.9, 34.7, 55.8, 58.8, 72.1, 120.8, 121.1, 123.8, 127.2, 129.6, 135.1, 136.7, 137.0, 137.5, 143.4, 148.0, 149.3, 155.4, 155.9. **IR ν** (cm^{-1}): 2892, 1890, 1459, 1155, 1090, 799. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{22}H_{26}N_3O_3S$, 412.1689; found, 412.1685. **$[\alpha]_D^{28}$=** +114.6 (c = 0.1, $CHCl_3$).

(R)-N-(1-([2,4'-bipyridin]-5-yl)-4-methoxybutyl)-4-methylbenzenesulfonamide (43b)



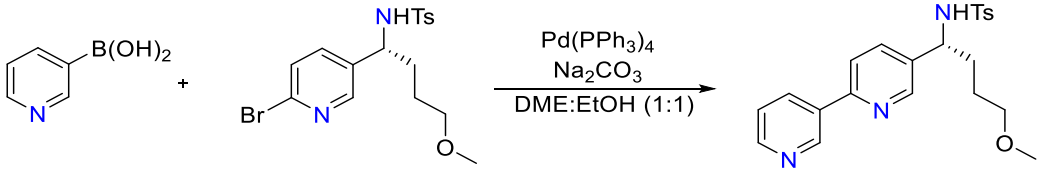
Procedure:

To a Schlenk tube were added the bromo compound, 4-pyridylboronic acid (1 equiv), $Pd(PPh_3)_4$ (0.015 equiv) and Na_2CO_3 (3.2 equiv) in a mixture of solvents (toluene: ethanol: water (3:1:1)), the mixture was refluxed for 18 h, then it was cooled down the layers were separated and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography ethyl acetate.



On a 3.2 mmol scale, **43b** was isolated as a pink oil with 89% yield. (1.17g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.46 – 1.55 (m, 2H), 1.81 – 1.88 (m, 2H), 2.31 (s, 3H), 3.28 – 3.35 (m, 2H), 3.36 (s, 3H), 4.35 (q, *J* = 6.4 Hz, 1H), 6.14 (d, *J* = 5.9 Hz, 1H), 7.13 – 7.17 (m, 2H), 7.56 – 7.60 (m, 2H), 7.64 (t, *J* = 1.5 Hz, 2H), 7.88 – 7.92 (m, 2H), 8.48 (t, *J* = 1.6 Hz, 1H), 8.72 – 8.76 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 25.9, 34.8, 55.7, 58.9, 72.1, 120.8, 121.4, 127.3, 129.6, 135.6, 137.4, 137.9, 143.5, 147.4, 149.1, 149.4, 153.0. **IR ν** (cm^{-1}): 2872, 1893, 1506, 1091, 785. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{22}H_{26}N_3O_3S$, 412.1689; found, 412.1692. **$[\alpha]_D^{28}$=** +2.25 (c = 0.08, $CHCl_3$).

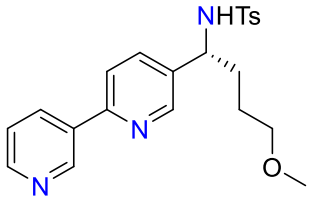
(*R*)-*N*-(1-([2,3'-bipyridin]-5-yl)-4-methoxybutyl)-4-methylbenzenesulfonamide (43c)



Compound **43c** was synthesized following a previously described procedure.[232]

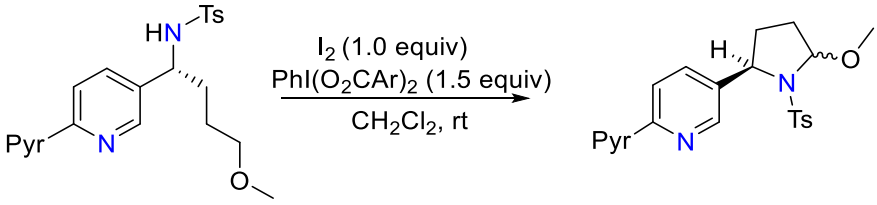
Procedure:

To a Schlenk tube was added the bromocompound followed by a solution of $Pd(PPh_3)_4$ (0.015 equiv) and Na_2CO_3 (2M in water, 2 equiv) in DME, the mixture was stirred for 10 minutes, and then, 3-pyridylboronic acid (1.25 equiv) in ethanol was added. The reaction mixture was stirred at 90ºC for 18h. It was then cooled down to rt, filtrated through a celite pad and washed with DCM, dried with Na_2SO_4, concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.



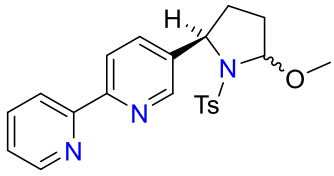
On a 3.0 mmol scale, **43c** was isolated as a yellow oil with 77% yield (0.95g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.46-1.60 (m, 2H), 1.73 – 1.92 (m, 2H), 2.30 (s, 3H), 3.27 – 3.39 (m, 5H), 4.31-4.39 (m, 1H), 6.06 (d, *J* = 6.1 Hz, 1H), 7.08 – 7.18 (m, 2H), 7.40 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 7.49 – 7.62 (m, 4H), 8.24 (ddd, *J* = 8.0, 2.3, 1.7 Hz, 1H), 8.40-8.44 (m, 1H), 8.64 (dd, *J* = 4.8, 1.7 Hz, 1H), 9.10 (dd, *J* = 2.4, 0.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.5, 26.0, 34.5, 55.7, 58.7, 72.0, 120.2, 123.73, 127.2, 129.5, 134.4, 134.7, 135.3, 136.2, 137.6, 143.3, 148.1, 148.9, 149.9, 153.8. **IR** ν(cm^{-1}): 2830, 1450, 1329, 1140, 1127, 1090. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{22}H_{26}N_3O_3S$, 412.1689; found, 412.1695. **$[\alpha]_D^{28}$=** +74.2 (c = 0.1, $CHCl_3$).

Step V: Hofmann-Löffler reaction for compounds **44a-c**



They were synthesized using GP4 (with 1.0 equiv of iodine).

5-((2*R*)-5-Methoxy-1-tosylpyrrolidin-2-yl)-2,2'-bipyridine (44a)

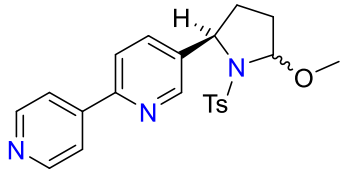


On a 1.0 mmol scale, **44a** was isolated as a yellow oil with 63% yield (0.26g). Mixture of diastereomers (d.r. = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.47 (tdd, *J* = 12.8, 7.5, 5.0 Hz, 1H), 1.75 – 1.80 (m, 2H), 1.93 – 2.04 (m, 3H), 2.12 (tdd, *J* = 13.1, 10.7, 6.6 Hz, 1H), 2.35 (d, *J* = 4.0 Hz, 6H), 2.58 (tdd, *J* = 12.9, 9.2, 7.1 Hz, 1H), 3.40 (s, 3H),

[232] T. T. Denton, X. Zhang, J. R. J. Cashman, *Med. Chem*. **2005**, *48*, 224.

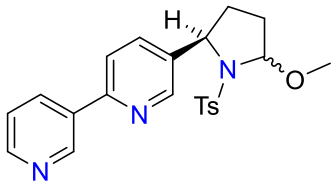
3.56 (s, 3H), 4.53 – 4.65 (m, 1H), 4.79 (d, *J* = 9.0 Hz, 1H), 5.32 (d, *J* = 4.9 Hz, 1H), 5.42 (d, *J* = 3.9 Hz, 1H), 7.17 – 7.21 (m, 2H), 7.21 – 7.24 (m, 1H), 7.30 (ddt, *J* = 7.5, 4.8, 1.3 Hz, 2H), 7.60 – 7.63 (m, 1H), 7.65 (ddd, *J* = 8.2, 2.3, 0.5 Hz, 1H), 7.67 – 7.70 (m, 2H), 7.72 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.78 – 7.84 (m, 3H), 8.27 (ddd, *J* = 9.9, 8.2, 0.8 Hz, 2H), 8.35 (ddt, *J* = 8.0, 4.8, 1.1 Hz, 2H), 8.48 – 8.51 (m, 2H), 8.54 – 8.57 (m, 1H), 8.67 (dddd, *J* = 4.7, 2.8, 1.8, 0.9 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 29.0, 33.0, 33.3, 34.7, 55.5, 55.9, 59.9, 62.5, 92.8, 93.3, 120.8, 121.1, 121.2, 121.2, 123.8, 127.1, 127.4, 127.7, 128.1, 129.3, 129.7, 129.8, 129.9, 134.9, 135.7, 137.0, 137.5, 138.3, 143.5, 144.0, 147.4, 148.2, 149.3, 155.3, 155.4, 156.1, 156.1. **IR ν** (cm^{-1}): 1583, 1458, 1341, 1157, 992,670. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{22}H_{24}N_3O_3S$, 410.1533; found, 410.1527.

5-((2*R*)- (5-methoxy-1-tosylpyrrolidin-2-yl)-2,4'-bipyridine (44b)



On a 1.0 mmol scale, **44b** was isolated as a colorless oil with 57% yield (0.23g). Mixture of diastereomers (d.r. = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.38 – 1.49 (m, 1H), 1.77 – 1.84 (m, 2H), 1.97 (tdd, *J* = 12.2, 8.5, 5.0 Hz, 2H), 2.06 – 2.15 (m, 1H), 2.27 – 2.34 (m, 1H), 2.39 (d, *J* = 3.4 Hz, 6H), 2.58 (tt, *J* = 12.6, 8.6 Hz, 1H), 3.39 (s, 3H), 3.58 (s, 3H), 4.47 – 4.60 (m, 1H), 4.78 (dd, *J* = 9.1, 1.3 Hz, 1H), 5.29 (d, *J* = 4.9 Hz, 1H), 5.38 – 5.46 (m, 1H), 7.20 – 7.28 (m, 5H), 7.43 – 7.48 (m, 2H), 7.52 – 7.56 (m, 1H), 7.62 – 7.65 (m, 2H), 7.65 – 7.67 (m, 1H), 7.69 – 7.74 (m, 4H), 7.77 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.86 (dt, *J* = 4.5, 1.8 Hz, 4H), 8.55 – 8.68 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.7, 28.9, 29.8, 33.0, 33.3, 34.8, 55.6, 56.0, 59.8, 62.3, 92.9, 93.2, 120.6, 120.9, 121.1, 121.2, 127.7, 128.2, 128.6, 128.7, 129.4, 129.9, 132.1, 132.1, 132.2, 132.3, 135.1, 135.8, 138.8, 144.1, 146.4, 148.4, 149.1, 150.5, 153.6, 153.8. **IR ν** (cm^{-1}): 2730, 1792, 1841, 1503, 1072, 689. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{22}H_{24}N_3O_3S$, 410.1533; found, 410.1520.

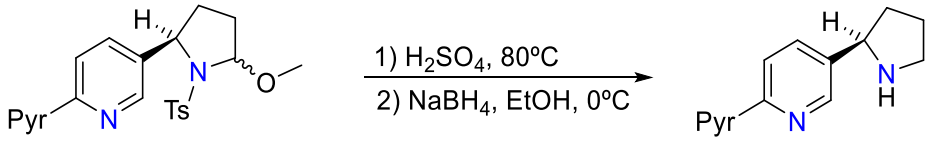
5-((2*R*)-5-Methoxy-1-tosylpyrrolidin-2-yl)-2,3'-bipyridine (44c)



On a 1.0 mmol scale, **44c** was isolated as a colorless oil with 67% yield (0.27g). Mixture of diastereomers. (d.r. = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.37 – 1.52 (m, 1H), 1.81 (dt, *J* = 12.6, 6.2 Hz, 2H), 1.99 (ddd, *J* = 13.8, 6.8, 4.1 Hz, 2H), 2.08 – 2.12 (m, 1H), 2.27 – 2.35 (m, 1H), 2.39 (d, *J* = 3.5 Hz, 6H), 2.53 – 2.65 (m, 1H), 3.40 (s, 3H), 3.58 (s, 3H), 4.57 (dd, *J* = 9.6, 7.5 Hz, 1H), 4.78 (d, *J* = 8.8 Hz, 1H), 5.31 (d, *J* = 4.9 Hz, 1H), 5.42 (d, *J* = 3.6 Hz, 1H), 7.21 – 7.27 (m, 4H), 7.39 – 7.48 (m, 3H), 7.51 – 7.59 (m, 1H), 7.62 – 7.77 (m, 6H), 8.26 – 8.34 (m, 2H), 8.54 (q, *J* = 0.9 Hz, 1H), 8.60 (d, *J* = 2.1 Hz,

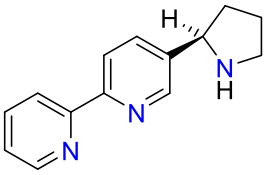
1H), 8.65 (s, 2H), 9.16 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.7, 28.9, 33.0, 33.3, 34.8, 34.9, 55.6, 56.0, 59.8, 62.3, 92.9, 93.2, 120.3, 120.6, 123.8, 127.4, 127.7, 128.2, 128.6, 128.7, 129.4, 129.9, 130.0, 132.3, 134.6, 134.6, 135.0, 135.6, 135.8, 137.4, 137.7, 137.8, 143.6, 144.1, 148.2, 148.3, 149.1, 149.8, 153.8, 153.9. **IR** ν(cm^{-1}): 2748, 1776, 1840, 1516, 1070, 671. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{22}H_{24}N_3O_3S$, 410.1533; found, 410.1539.

Step VI and VII: Detosylation and reduction of the imines



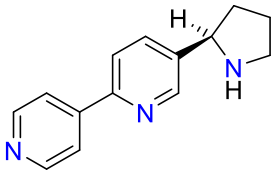
Synthesized using GP5.

(*R*)-5-(Pyrrolidin-2-yl)-2,2'-bipyridine (45a)



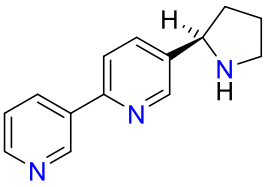
On a 0.5 mmol scale, **45a** was isolated as a brown oil with 97% yield (0.11g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.63 – 1.76 (m, 1H), 1.82 – 1.99 (m, 2H), 2.15 – 2.30 (m, 2H), 3.00 – 3.08 (m, 1H), 3.17 – 3.24 (m, 1H), 4.13 – 4.25 (m, 1H), 7.27 – 7.31 (m, 1H), 7.77 – 7.86 (m, 2H), 8.34 (dd, *J* = 12.7, 8.0 Hz, 2H), 8.65 (dt, *J* = 9.3, 3.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.7, 34.5, 47.1, 60.1, 120.9, 121.1, 123.6, 135.1, 137.0, 140.6, 148.1, 149.3, 154.9, 156.3. **IR ν** (cm^{-1}): 1579, 1451, 1313, 1152, 992, 671. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{14}H_{16}N_3$, 226.1339; found, 226.1335. **$[\alpha]_D^{28}$=** 85.3 (c = 0.18, $CHCl_3$).

(*R*)-5-(pyrrolidin-2-yl)-2,4'-bipyridine (45b)



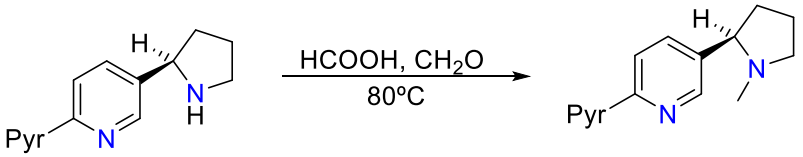
On a 0.5 mmol scale, **45b** was isolated as a yellow oil with 82% yield (92 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.61 – 1.72 (m, 1H), 1.85 – 1.96 (m, 2H), 2.20 – 2.29 (m, 1H), 2.32 (bs, 1H), 3.00 – 3.09 (m, 1H), 3.15 – 3.23 (m, 1H), 4.19 (dt, *J* = 12.0, 7.7 Hz, 1H), 7.60 – 7.66 (m, 1H), 7.72 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.80 – 7.84 (m, 1H), 7.84 – 7.86 (m, 2H), 8.65 – 8.68 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.5, 34.3, 46.9, 59.7, 120.6, 121.0, 135.2, 140.7, 146.4, 148.9, 150.2, 152.9. **IR ν** (cm^{-1}): 3329, 2966, 1489, 1465, 1398, 1296. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{14}H_{16}N_3$, 226.1339; found, 226.1342. **$[\alpha]_D^{28}$=** 112.1 (c = 0.10, $CHCl_3$).

***(R)*-5-(pyrrolidin-2-yl)-2,3'-bipyridine (45c)**



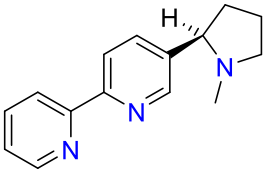
On a 0.5 mmol scale, **45c** was isolated as a brown oil with 68% yield (77 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.61 – 1.71 (m, 1H), 1.83 – 1.97 (m, 2H), 2.16 – 2.33 (m, 2H), 3.02 – 3.08 (m, 1H), 3.17 – 3.23 (m, 1H), 4.19 (d, *J* = 7.7 Hz, 1H), 7.34 – 7.41 (m, 1H), 7.66 – 7.70 (m, 1H), 7.77 – 7.82 (m, 1H), 8.28 (ddd, *J* = 6.6, 2.4, 1.2 Hz, 1H), 8.61 (td, *J* = 4.5, 1.8 Hz, 1H), 8.66 – 8.70 (m, 1H), 9.15 (td, *J* = 2.4, 1.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.7, 34.5, 47.1, 59.9, 120.4, 123.7, 134.3, 135.0, 135.2, 139.7, 148.2, 148.9, 149.8, 153.4. **IR** ν(cm^{-1}): 3340, 2960, 1592, 1466, 1418, 1332. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{14}H_{16}N_3$, 226.1339; found, 226.1333. **$[\alpha]_D^{28}$=** +105.1 (c = 0.1, $CHCl_3$).

Step VIII: Eschweiler-Clarke reaction



Synthesized using GP6.

(*R*)-5-(1-methylpyrrolidin-2-yl)-2,2'-bipyridine (46a)



On a 0.2 mmol scale, **46a** was isolated as a brown oil with 98% yield (47 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.70 – 1.89 (m, 2H), 1.93 – 2.04 (m, 1H), 2.19 (s, 3H), 2.21 – 2.27 (m, 1H), 2.32 (td, *J* = 9.3, 8.2 Hz, 1H), 3.14 (t, *J* = 8.3 Hz, 1H), 3.22 – 3.30 (m, 1H), 7.27 – 7.31 (m, 1H), 7.77 – 7.87 (m, 2H), 8.31 – 8.39 (m, 2H), 8.58 – 8.60 (m, 1H), 8.64 – 8.68 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.8, 35.3, 40.5, 57.2, 68.9, 121.1, 121.2, 123.6, 136.0, 137.0, 139.1, 149.1, 149.3, 155.4, 156.4. **HPLC: UPC** Chiralpack IC (100x4.6mm, 3 μm), Isocratic CO_2/EtOH/DEA 75:25:0.1, v/v, 3 mL/min, 1500 psi. *ee* (%) = 97%.

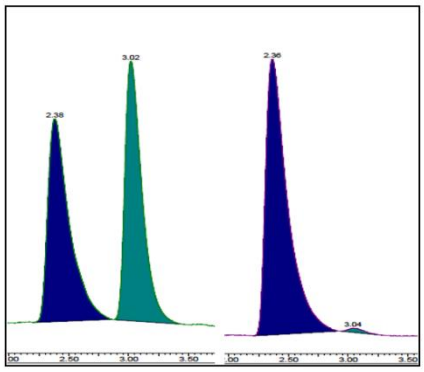
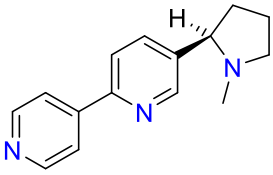


Figure 3.9. *Racemic vs. Enantioselective HPLC-chromatogram of compound* ***46a****.*

(*R*)-5-(1-methylpyrrolidin-2-yl)-2,4'-bipyridine (46b)



On a 0.2 mmol scale, **46b** was isolated as a yellow oil with 95% yield (45 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.75- 1.79 (m, 1H), 1.83 – 1.89 (m, 1H), 1.95 – 2.04 (m, 1H), 2.20 (s, 3H), 2.22 – 2.28 (m, 1H), 2.34 (td, *J* = 9.3, 8.3 Hz, 1H), 3.13 – 3.20 (m, 1H), 3.23 – 3.30 (m, 1H), 7.77 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.83 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.86 – 7.91 (m, 2H), 8.65 (d, *J* = 2.2 Hz, 1H), 8.69 – 8.72 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.8, 35.5, 40.6, 57.2, 68.7, 121.0, 121.1, 136.1, 139.5, 146.5, 150.0, 150.5, 153.7. **IR ν** (cm^{-1}): 2958, 1589, 1460, 1412, 1331. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{15}H_{18}N_3$, 240.1495; found, 240.1503. **$[\alpha]_D^{28}$=** 131.3 (c = 0.12, $CHCl_3$). **HPLC: UPC** Chiralpack IC (100x4.6mm, 3 μm), Isocratic CO_2/AcN/DEA 70:30:0.1, v/v, 3 mL/min, 1500 psi. *ee* (%) = 97%.

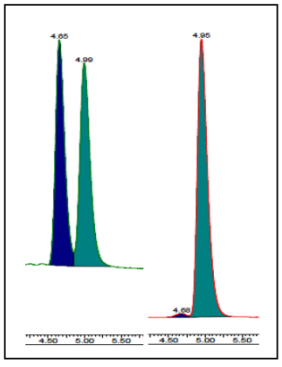
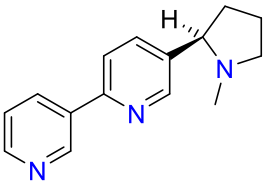


Figure 3.10. *Racemic vs. Enantioselective HPLC-chromatogram of compound* ***46b****.*

3-Pyridylnicotine (46c)



On a 0.2 mmol scale, **46c** was isolated as a yellow oil with 92% yield (44 mg). Spectroscopic data in agreement with the one previously described.[233] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.69 – 1.90 (m, 2H), 1.91 – 2.03 (m, 1H), 2.19 (s, 3H), 2.20 – 2.26 (m, 1H). 2.33 (td, *J* = 9.3, 8.3 Hz, 1H), 3.15 (t, *J* = 8.3 Hz, 1H), 3.23 – 3.29 (m, 1H), 7.38 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 7.70 – 7.83 (m, 2H), 8.30 (dt, *J* = 7.9, 2.0 Hz, 1H), 8.60 – 8.65 (m, 2H), 9.17 (dd, *J* = 2.3, 0.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.8, 35.4, 40.5, 57.1, 68.7, 120.7, 123.7, 134.3, 135.0, 136.0, 138.3, 148.3, 149.8, 149.9, 153.9. **HPLC: UPC** Chiralpack ID (100x4.6mm, 3 μm), Isocratic CO_2/EtOH/DEA 80:20:0.1, v/v, 3 mL/min, 1500 psi. *ee* (%) = 91%.

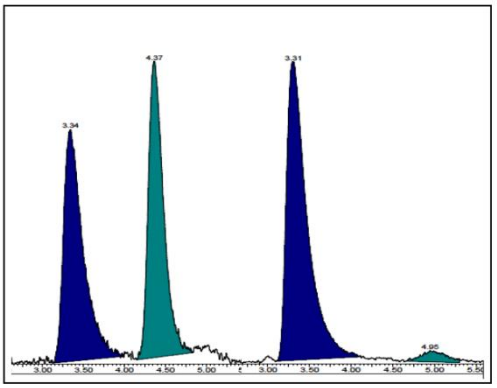


Figure 3.11. *Racemic vs. Enantioselective HPLC-chromatogram of compound* ***46c****.*

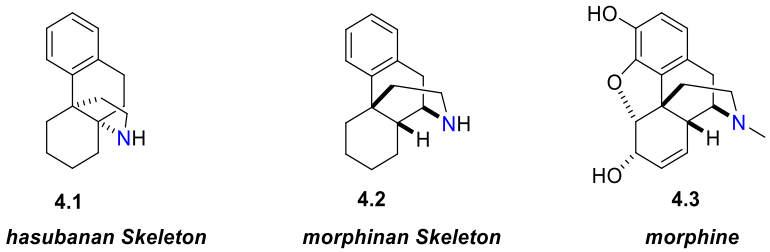
[233] L. Miao, S. C. Di Maggio, M. L. Trudell, *Synthesis* **2010**, *1*, 91.

Chapter IV. Catalytic Enantioselective Synthesis of the Hasubanan Skeleton - Exploiting Iodine-Catalyzed C–N Bond Formation

1. Hasubanan derivatives

The hasubanan alkaloids comprise a large class of natural products isolated from the *Menispermaceae* family of plants, which have long been used in traditional Chinese medicine for the treatment of pain, arthritis, fever, and many other illnesses. These alkaloids are a family of secondary metabolites that share a tetracyclic propellane core, including more than 40 examples.

The main synthetic challenge presented by these alkaloids is the construction of the tetracyclic framework with an α-tertiary amine moiety. The hasubanan alkaloids display promising biological properties and received particular attention due to their close similarity to the morphine alkaloids.[234] However, the structure of the hasubanan natural products is different from the morphinan alkaloids: while the hasubanan alkaloids possess an α-oriented five-membered pyrrolidine ring, the natural enantiomers of the morphinan alkaloids contain a β-oriented six-membered piperidine ring, corresponding to the antipodal absolute configuration of the hasubanan natural products (Figure 4.1).



4.1 ***hasubanan Skeleton*** **4.2** ***morphinan Skeleton*** **4.3** ***morphine***

Figure 4.1. *Structures of hasubanan and morphinan skeletons and morphine*

The hasubanan core is present in several alkaloids of this family, such as hasubanonine, runanine, delavayine, cepharamine, and longanine, which are classified into three classes depending on the oxidation pattern of the C-ring (Figure 4.2). Hasubanonine, runanine, aknadinine, and delavayine are closely related, showing minor variations in the substitution pattern of the aromatic system. In contrast, cepharamine and 8-demetroxyrunanine constitute the least oxidized hasubanan alkaloids with variations in the oxidation at C-8. Additional derivatization is presented in the oxo-bridged-propellane alkaloids at C-10 (Figure 4.2c).

[234] H. Zhang, J.-M. Yue, *J. Nat. Prod.* **2005**, *68*, 1201.

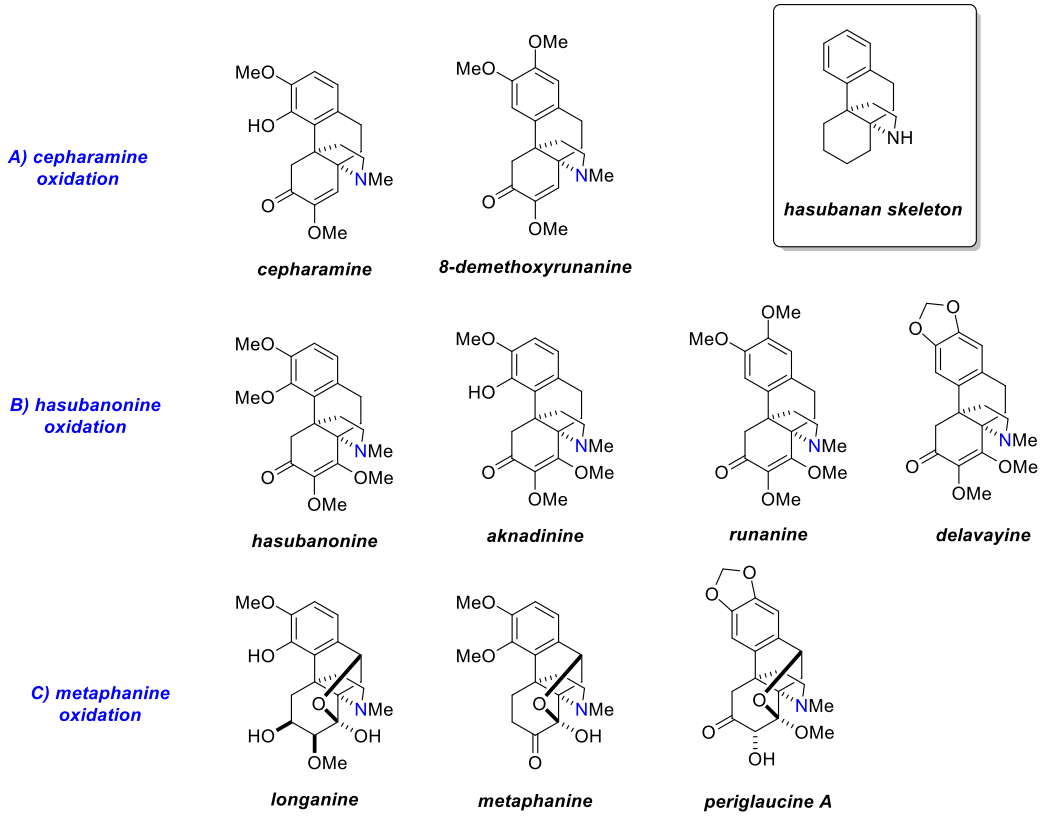
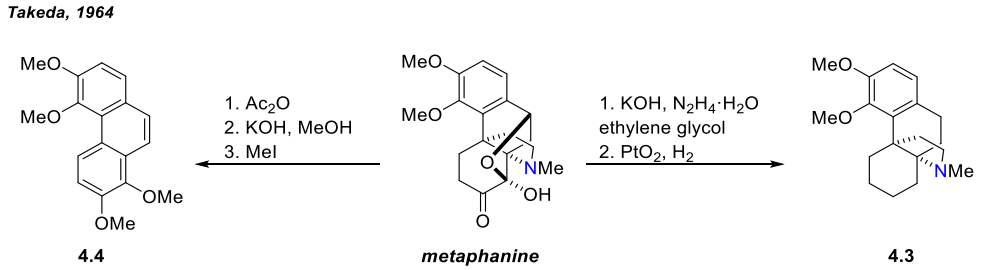


Figure 4.2. *Alkaloids that contain the characteristic hasubanan core.*

1.1. Isolation of hasubanan derivatives

Due to the similarity with the morphine core, the hasubanan alkaloids have attracted considerable attention from the synthetic community since their first description and structure elucidation in the 1960s. Kondo was the first to isolate metaphanine in 1924, although the correct structure was elucidated 40 years by Takeda and coworkers.[235] This was performed through complex degradation studies of metaphanine under reductive conditions, leading to the anthracene derivative **4.4** (Scheme 4.1). In contrast, a sequential reduction of the alkaloid produces the hasubanan derivative **4.3**, a known compound from the codeinone alkaloid biosynthetic pathway.

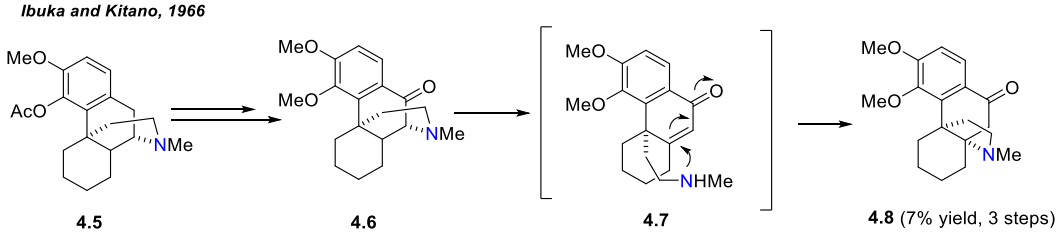
[235] (a) H. Kondo, T. Sanada, *Yakuga. Zasshi* **1924**, *44*, 1034. (b) M. Tomita, T. Ibuka, Y. Inubuahi, K. Takeda, *Tetrahedron Lett*. **1964**, *5*, 3605. (c) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, M. Matsui, *Tetrahedron Lett* **1964**, *5*, 2937. (d) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, M. Matsui, *Chem. Pharm. Bull* **1965**, *13*, 538.



***Scheme 4.1**. Structural elucidation of metaphanine*

1.2. Synthetic Studies

Many syntheses of racemic hasubanan derivatives have been described, whereas few reports of the enantioselective version have appeared in the literature. The most important challenge in the synthesis of these tetracyclic derivatives has been the formation of the pyrrolidine ring in a late-stage intramolecular amino cyclization. Ibuka and Kitano carried out the earliest synthetic studies in 1966.[236] The propellane derivative was made by benzylic oxidation to generate compound **4.6**, followed by reductive cleavage of the C-9-nitrogen bond using zinc, with the direct formation of the enone **4.7**, which undergoes spontaneously amino cyclization to form **4.8** (Scheme 4.2).

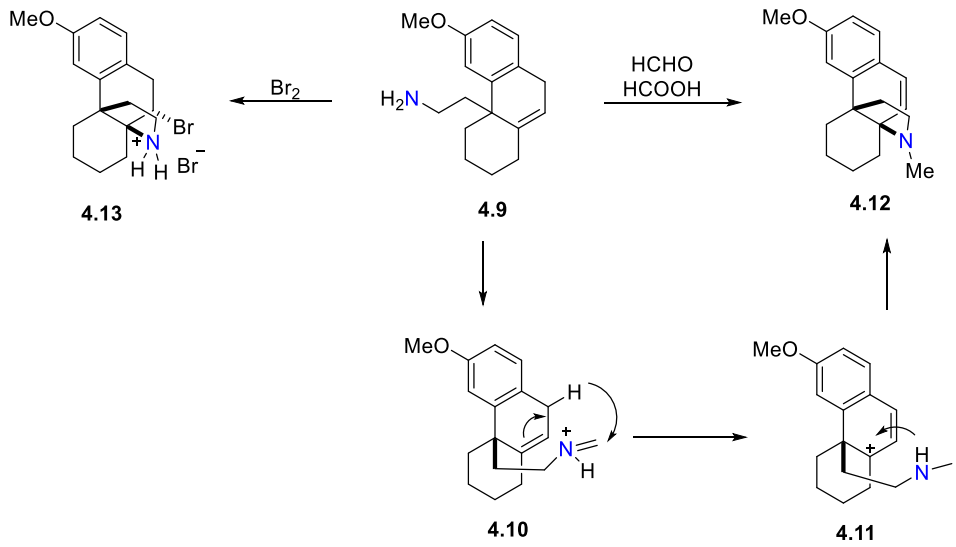


***Scheme 4.2**. Conversion of morphinans to propellane derivatives*

Belleau and coworkers developed a different strategy by cyclizing intermediate **4.9** with bromine to form the hydrobromide salt of propellane **4.13** (Scheme 4.3).[237] Kometani reported the formation of a similar tetracycle **4.12** through the use of paraformaldehyde and formic acid. The described mechanism proceeded through carbocation formation under the conditions of the Eschweiler-Clark methylation.[238]

[236] (a) M. Tomita, M. Kozuka, *Tetrahedron Lett.* **1966**, *7*, 6229. (b) M. Tomita, T. Ibuka, M. Kitano, *Tetrahedron Lett*. **1966**, *7*, 6233.
[237] I. Monković, T. T. Conway, H. Wong, Y. G. Perron, I. J. Pachter, B. J. Belleau, *J. Am. Chem. Soc.* **1973**, *95*, 7910.
[238] S. Shiotani, T. Kometani, *Tetrahedron Lett.* **1976**, *17*, 767.

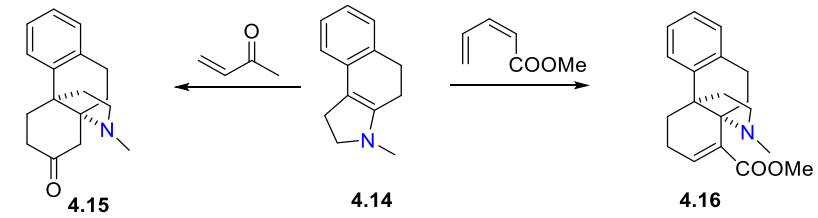
Belleau 1973 and Kometani 1976



***Scheme 4.3**. Belleau and Kometani amino cyclizations.*

In 1969, another approach for the amino cyclization was independently reported by Tahk and Evans via a Robinson annulation of **4.15** with methyl vinyl ketone (Scheme 4.4).[239] Evans with Sims improved the formation of the tetracyclic core by using methyl pentadienoate as an electrophile for the annulation to generate **4.16** product.[240]

Evans 1969 and Tahk 1970

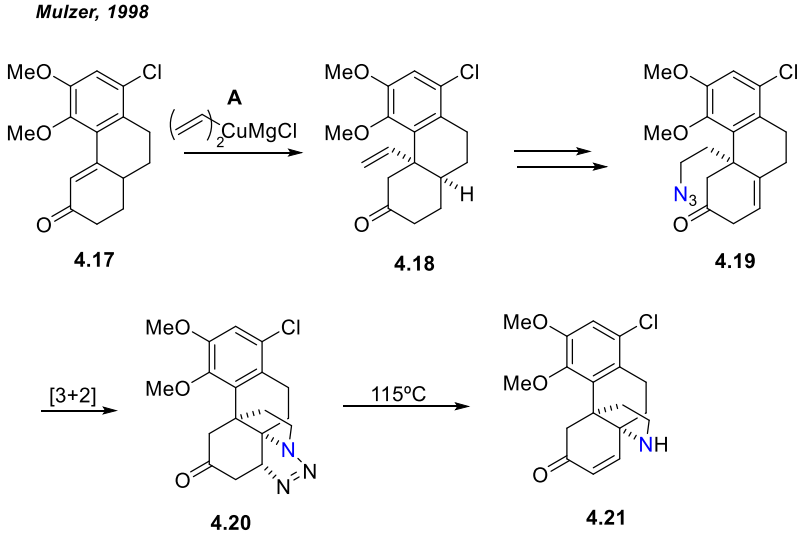


***Scheme 4.4**. Evans and Tahk aminocyclizations*

Mulzer used the tricyclic enone **4.17** as a starting point, which is accessible from the commercially available 4-(3,4-dimethoxyphenyl)butyric acid (Scheme 4.5).[241] The reaction of **4.17** with divinyl cuprate **A** led to **4.18**, which was

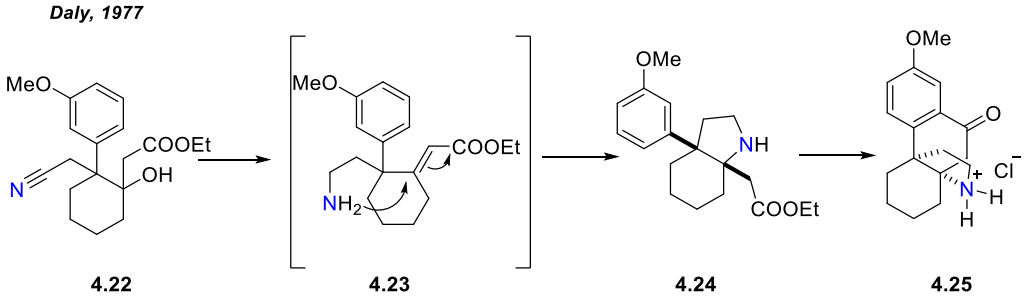
[239] (a) D. A. Evans, *Tetrahedron Lett.* **1969**, *10*, 1573. (b) S. L. Keely, A. J. Martinez, F. C. Tahk, *Tetrahedron* **1970**, *26*, 4729. (c) D. Evans, C. A. Bryan, G. M. Wahl, *J. Org. Chem.* **1970**, *35*, 4122.
[240] D. A. Evans, C. A. Bryan, C. L. Sims, *J. Am. Chem. Soc*. **1972**, *94*, 2891.
[241] D. Trauner, S. Porth, T. Opatz, J. W. Bats, G. Giester, J. Mulzer, *Synthesis* **1998,** *1998*, 653.

converted into azide **4.19**. Azide **4.19** underwent a thermal 1,3-dipolar cycloaddition to form triazene **4.20**, which was finally converted into **4.21** by thermal extrusion of N_2.



Scheme 4.5. *Mulzer synthesis of hasubanan skeleton derivatives.*

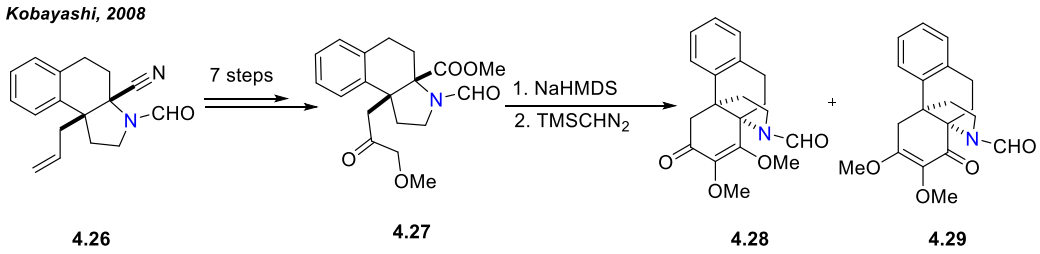
Daly and a group of Hofmann-La Roche developed a new strategy for the synthesis of the tetracycle **4.25** (Scheme 4.6).[242] The starting point was the addition of the enolate of ethyl acetate to the appropriate ketone with LiHMDS, leading to compound **4.22**. In the next stage of the synthesis, ester **4.24** was obtained via **4.23** by dehydration of the alcohol, nitrile reduction, and spontaneous cyclization. An acid-mediated Friedel-Crafts reaction of compound **4.24** afforded the hasubanan skeleton **4.25**.



Scheme 4.6. *Synthesis of **4.25** derivative.*

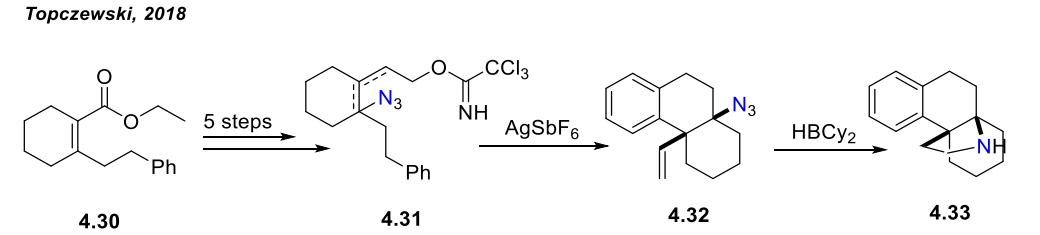
[242] H. Bruderer, K. Dietmar, J. J. Daly, *Helv. Chim. Act.* **1977**, *60*, 1935.

Kobayashi developed one of the most recent syntheses of the hasubanan skeleton (Scheme 4.7).[243] Starting from commercially available β-tetralone, intermediate **4.27** was prepared in several steps. A Dieckmann condensation and methylation with $TMSCHN_2$ afforded a 1:1mixture of isomers **4.28** and **4.29**.



Scheme 4.7. *Kobayashi´s synthesis of hasubanan derivatives II and III.*

The most recent synthesis of the hasubanan core was described by Topczewski in 2018 via a tandem allylic azide rearrangement-Friedel-Crafts alkylation to generate compound **4.32**, leading to **4.33** (Scheme 4.8).[244]



Scheme 4.8. *Synthesis of hasubanan skeleton by the Tandem process.*

2. Results and Discussion

Our goal was to synthesize the hasubanan skeleton employing the Hofmann-Löffler reaction for the formation of the pyrrolidine ring.

We initiated the project with the synthesis of the racemic hasubanan skeleton. We hypothesized that the D-ring could be readily accessed through C–H functionalization by the Hofmann-Löffler reaction in the late-stage of the synthesis (Figure 4.3).

[243] T. X. Nguyen, Y. Kobayashi, *J. Org. Chem.* **2008**, *73*, 5536.
[244] M. R. Porter, R. M. Shaker, C. Calcanas, J. J. Topczewski, *J. Am. Chem. Soc*. **2018**, *140*, 1211.

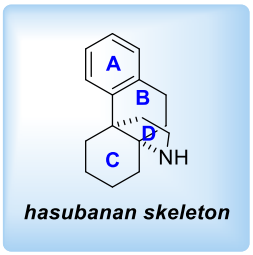
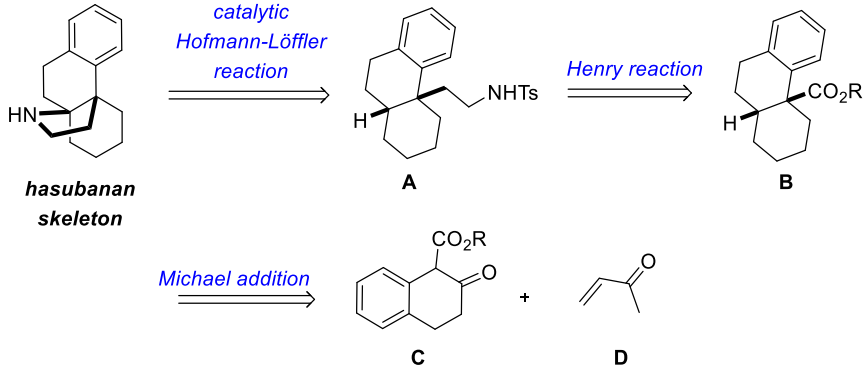


Figure 4.3. *Structure of tetracycle hasubanan skeleton.*

2.1. Retrosynthetic Analysis

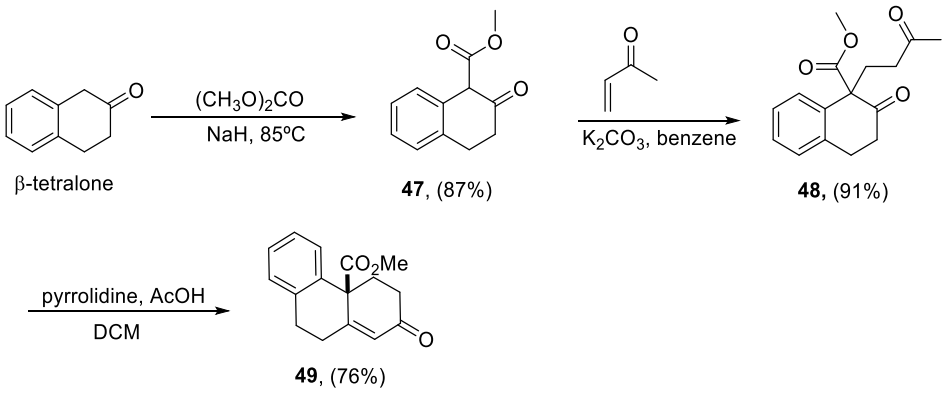
We expected that starting a catalytic Hofmann-Löffler reaction would allow the formation of the pyrrolidine ring from a compound of type **A** with *cis*-decaline configuration (Scheme 4.9). Intermediate **A** could be accessed by the Henry reaction to introduce the nitrogen in the molecule coming from the ester function of **B**. This intermediate **B** could be prepared by the Michael addition of the enolate of tetralone **C** to methyl vinyl ketone **D**, followed by intramolecular aldol reaction (Robinson annulation).



Scheme 4.9. *Retrosynthetic analysis of hasubanan skeleton.*

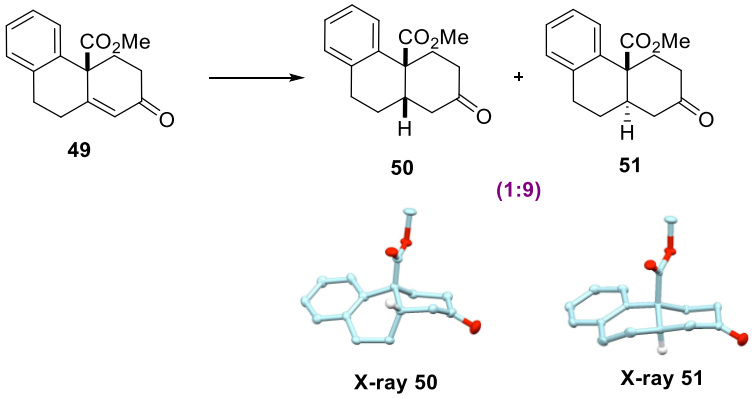
2.2. Synthesis of the Racemic Hasubanan Skeleton

We started using β-tetralone as a commercially available starting material, and we performed a carboxylation at C-1 leading to **47** (Scheme 4.10). The Michael reaction between **47** and methyl vinyl ketone led to **48**, which was submitted to Robinson annulation to generate the third ring in the structure **49**.



Scheme 4.10. *First steps of the synthesis of racemic of hasubanan skeleton.*

The reduction of the double bond of **49** was not straightforward since a mixture of the two diastereoisomers **50,** and **51** in a 9:1 ratio was obtained, favoring the formation of undesired **51**. The structures of **50** and **51** were confirmed by X-ray diffraction (Scheme 4.11)



Scheme 4.11. *Hydrogenation of the alkene **49**.*

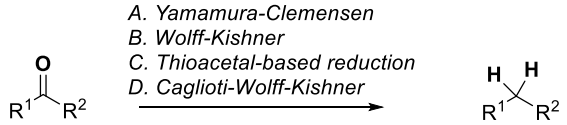
After some optimization, we obtained a 4:1 ratio of **50** and **51** using palladium 10% on carbon as the catalyst, pyridine as a solvent, and *ca*. 4 bars of H_2 (Table 4.1, Entry 7). A similar result had been obtained by the group of Chakravarty in.[245] Moreover, after several recrystallizations, this ratio was improved up to 95:5.

[245] G. Sinha, S. K. Maji, U. R. Ghatak, M. Mukherjee, A. K. Mukherjee, A. K. Chakravarty *J. Chem. Soc., Perkin Trans.* **1983,** *1***,** 2519**.**

Conditions	Solvent	Product	ratio (*cis: trans*)
Pd/C (15 mol%), 1 bar H_2	EtOAc	*trans*	(1:9)
Pd/C (15 mol%), 1 bar H_2	MeOH	*trans*	(1:9)
Pd/C (15 mol%), 1 bar H_2	pyridine	SM	-
(+)-limonene, Pd/C (15 mol%)	-	*trans*	(1:9)
(-)-limonene, Pd/C (15 mol%)	-	*trans*	(1:9)
Et_3SiH (2.0 equiv), CuCl (1.0 equiv)	DMI	SM	-
Pd/C (15 mol%), 4 bar H_2	pyridine	*cis*	(4:1)

Table 4.1. *Optimization conditions for hydrogenation of the double bond*

Next, we focused on the reductive elimination of the carbonyl moiety of **50**. For this transformation, the most common methodologies are summarized in Scheme 4.12 and were applied to our substrate, as shown in Table 4.2.



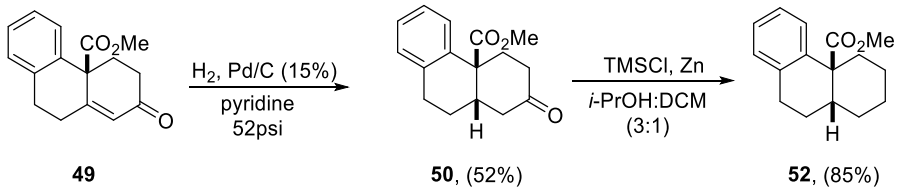
Scheme 4.12. *Classical approaches to remove a carbonyl group*

Conditions	Product
Tosyl hydrazide (1.1 equiv), then $NaBH_4$ (3.0 equiv)	45%
1,2-Ethaneditiol (5.0 equiv), BF_3OEt_2 (1.0 equiv), then Bu_3SnH (2.0 equiv), AIBN (0.15 equiv)	22%
$NaBH_4$ (3.0 equiv), TFA, MeCN, AcOH	31%
Tosyl hydrazide (1.0 equiv), $NaBH_3CN$ (1.0 equiv), $ZnCl_2$ (0.5 equiv)	-
Zn (45.0 equiv), AcOH	-
Zn (10.0 equiv), TMSCl (10.0 equiv)	85%

Table 4.2. *Optimization conditions of the removal of the carbonyl group*

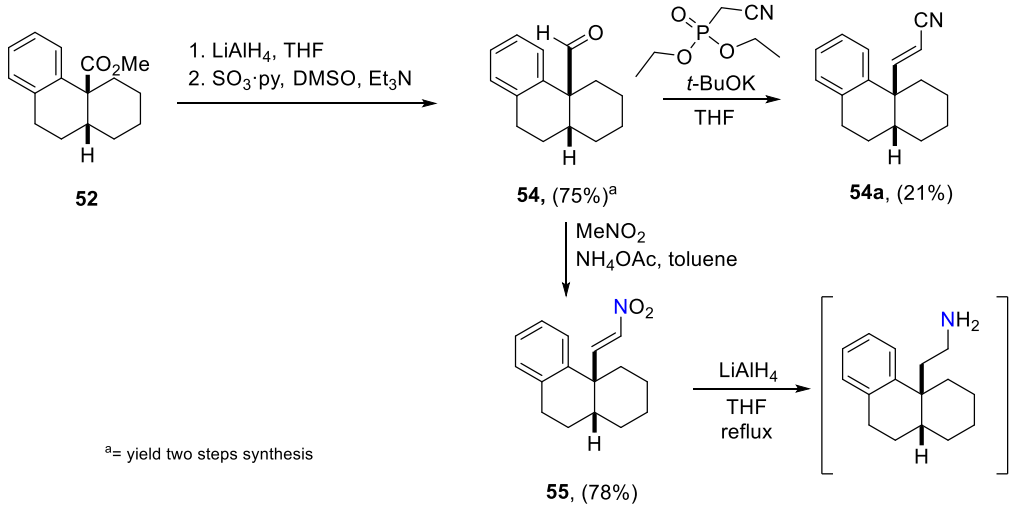
The best yield was obtained using a modification of the Clemmensen-reduction with Zn and TMSCl (Table 4.2, Entry 7.). Thus compound **52** was obtained in reasonable yield and diastereoselectivity from **49** in two steps (Scheme 4.13). A similar approach had been reported by the group of Arimoto with a different substrate.[246]

[246] S. Xu, T. Toyama, J. Nakamura, H. Arimoto, *Tetrahedron Letters*, **2010**, *51*, 4534.



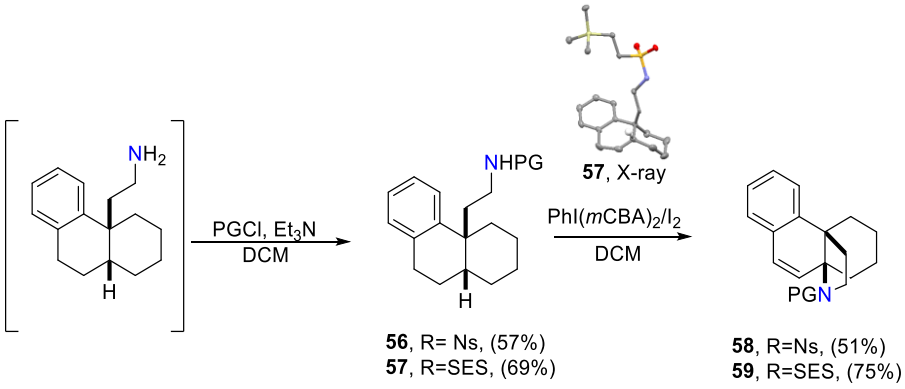
***Scheme 4.13**. Hydrogenation and Clemmensen modification´s reaction.*

To replace the ester function of compound **52** with an alkylamine, first, we tried the reduction of the ester **54** to the alcohol **53** and then the oxidation to the aldehyde using Parikh-Doering oxidation to provide aldehyde **54** in good yield. After Wittig reaction with diethyl cyano-methyl phosphonate and potassium *tert*-butoxide in THF, **54** was converted into **54a** although in only low yield (Scheme 4.14).



***Scheme 4.14**. Moieties modification to lead the alkylamine chain.*

On the other hand, the Henry reaction of **54** with nitromethane and ammonium acetate in toluene gave **55** in good yield. Reduction of **55** to the primary amine, using lithium aluminum hydride, and reaction with sulfonamides gave **56** and **57** in good overall yields (Scheme 4.15). The Hofmann-Löffler reaction was performed under the previously described conditions using hypervalent iodine mixed with molecular iodine.[90] After some optimization (Table 4.3), the best result was obtained by mixing 3.0 equiv of hypervalent iodine(III) species with 0.2 equiv of molecular iodine.

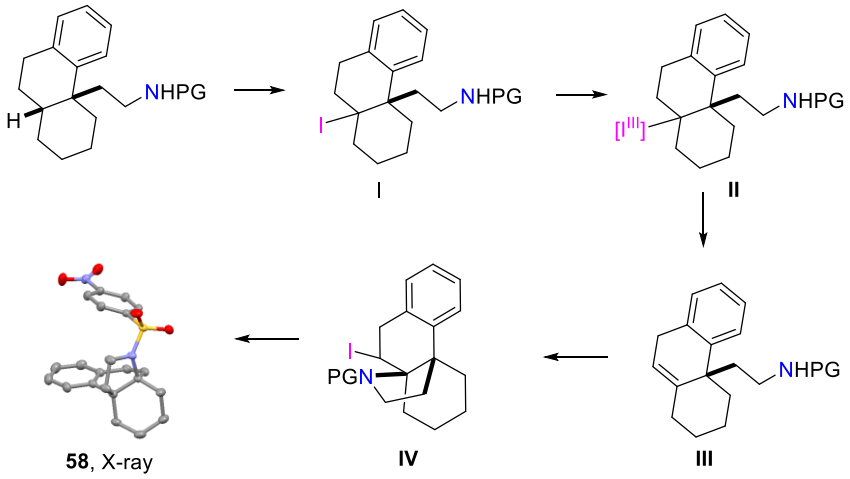


Scheme 4.15. *Protection and Hofmann-Löffler reaction to produce propellane core.*

PhI(*m*cba)$_2$ (equiv)	I_2 (equiv)	solvent	time	LEDs	Product (%)
1.5	0.1	DCM	12 h	visible light	33
1.2	1.0	DCM	12 h	visible light	-
1.0	0.1	DCM	3 h	white LEDs	28
1.5	0.5	DCM	4 h	white LEDs	42
2.0	0.1	DCM	6 h	white LEDs	47
3.0	0.1	DCM	3 h	white LEDs	56
3.0	0.2	DCM	3 h	white LEDs	75

Table 4.3. *Optimization conditions of the Hofmann-Löffler reaction.*

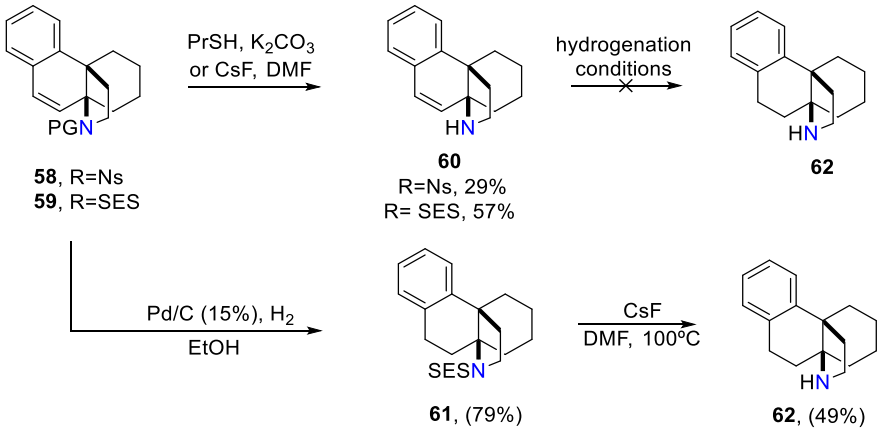
To our surprise, the obtained pyrrolidine products **58** and **59** have an alkene conjugated with the aryl ring as confirmed by X-ray diffraction for product **58**. The proposed mechanism of the reaction is shown in Scheme 4.16 and involves a sequence of oxidation/elimination steps starting with an amidyl radical promoted C–H iodination, followed by oxidation of the iodide **I** to an I(III) species **II**, elimination to form **III**, amino-iodination of the alkene to generate **IV**, and elimination of HI to give **58**.



Scheme 4.16. *The sequence of the intermediates formed in the Hofmann-Löffler reaction.*

To obtain the hasubanan skeleton, we needed to remove the protecting group and reduce the double bond.

First, we tried the deprotection of the sulfonamides, followed by hydrogenation. However, the secondary amine **60** was not stable enough and decomposed under the conditions of the hydrogenation. Then, we tried to hydrogenate first the alkene of **58** or **59** (Scheme 4.17). In the hydrogenation experiments, we noticed that residual molecular iodine present in compound **59** interfered with the reduction. The problem was solved by quenching the Hofmann-Loffler reaction with an excess of sodium thiosulfate for 12 h to remove the I_2. Thus, hydrogenation of **59** led to **61**, which was deprotected using CsF at 100 ºC in DMF, leading to the racemic hasubanan core **62**.

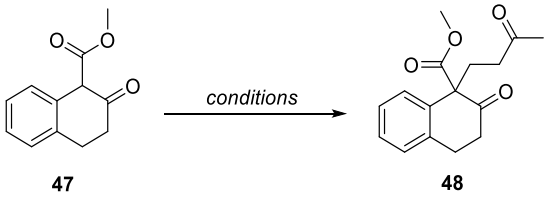


Scheme 4.17. *Last steps in the synthesis of racemic hasubanan skeleton **62**.*

2.3. Enantioselective synthesis

After accomplishing the synthesis of the racemic hasubanan skeleton, we devised the developed the enantioselective synthesis of this compound.

We started our study using the cinchona alkaloids as catalysts to generate the quaternary center in **48** in an enantioselective manner by the Michael addition of **47** to methyl vinyl ketone (Scheme 4.18).



Scheme 4.18 *Enantioselective Michael addition.*

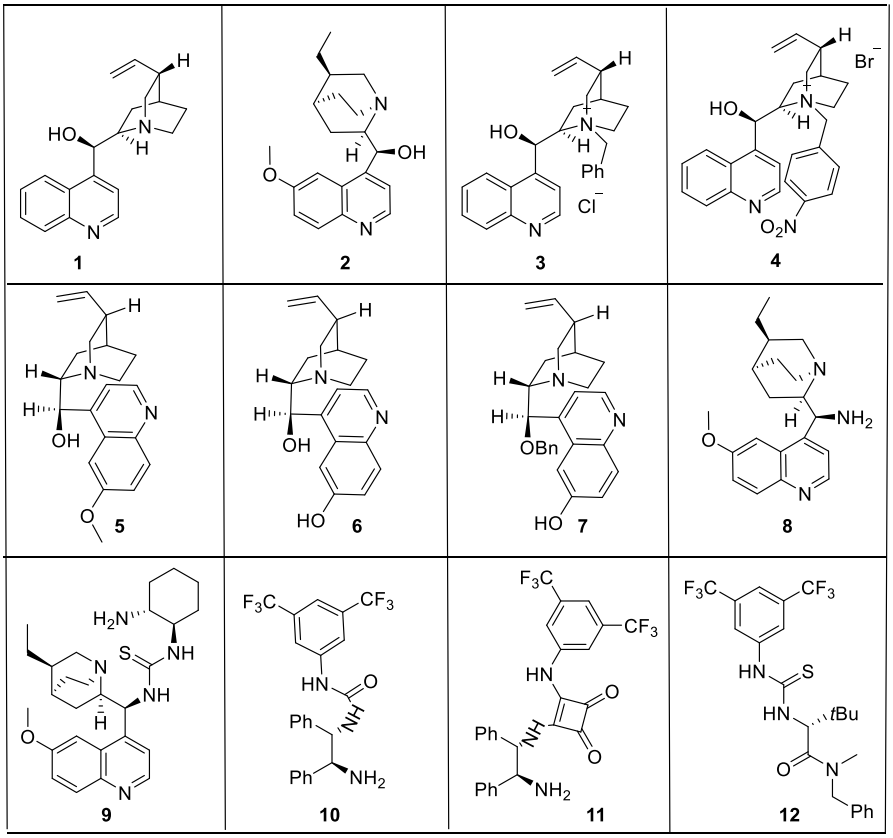


Figure 4.4. *Structures of the catalysts* [247]

Catalyst	Base (20 mol%)	Solvent	Time (h)	T[a]	Product	*ee (%)*
1	-	toluene	12	rt	-	-
1	K_2CO_3	toluene	12	rt	50%	0
2	-	toluene	12	rt	25%	20
2	K_2CO_3	toluene	12	rt	60%	0
2	-	toluene	12	rt	20%	20
2	-	toluene	>48	rt	-	-
4	-	toluene	>48	rt	-	-

[247] (a) F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem. Int. Ed.* **2006**, *45*, 4301. (b) M.-X. Zhao, H.-K. Zhu, T.-L. Dai, M. Shi, *J. Org. Chem.* **2019**, *22*, 14487. (c) X.-H. Ding, X. Li, D. Liu, W.-C. Cui, X. Ju, S. Wang, Z.-J. Yao, *Tetrahedron* **2012**, *68*, 6240. (d) F. Wu, H. Li, R. Hong, L. Deng, *Angew. Chem. Int. Ed*. **2006**, *45*, 947. (e) S. Tarí, R. Chinchilla, C. Nájera, *Tetrahedron: Asymmetry* **2010**, *21*, 2872. (f) A. Sera, K. Takagi, H. Katayama, H. Yamada, *J. Org. Chem*. **1988**, *53*, 1157. (g) J. Yang, W. Li, Z. Jin, X. Liang, J. Ye, *Org. Lett*. **2010**, *12*, 5128.

4	K_2CO_3	toluene	12	rt	25%	25
5	-	toluene	>48	rt	-	-
5	K_2CO_3	toluene	>48	rt	20%	12
6	-	toluene	>48	rt	-	-
6	K_2CO_3	toluene	12	rt	52%	0
7	-	toluene	>72	rt	-	-
7	K_2CO_3	toluene	12	rt	26%	0
8	-	toluene	>72	rt	-	-
8	K_2CO_3	toluene	12	rt	30%	0
9	-	toluene	>48	rt	-	-
10	-	toluene*	>48	rt	-	-
11	-	toluene*	>48	rt	-	-
12	-	toluene*	>48	rt	-	-

*Additive $PhCO_2H$ (0.2% mmol).

Table 4.4. *Conditions of the enantioselective Michael reaction.*

Although several conditions on enantioselective transformations with β-keto esters using Cinchona alkaloids derivatives as catalysts were investigated, only low yield and enantioselectivity could be achieved (Table 4.4).

As a second approach, we tried forming chiral enamines to install the quaternary center. For this transformation, different amines **1**-**4** were tested (Figure 4.5)

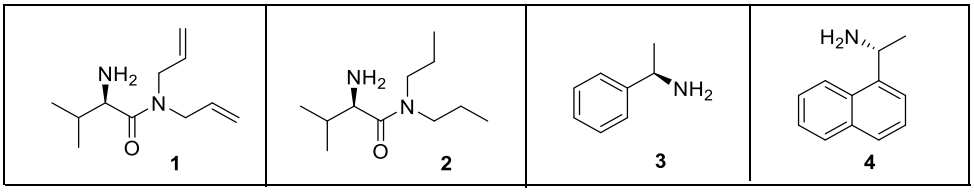
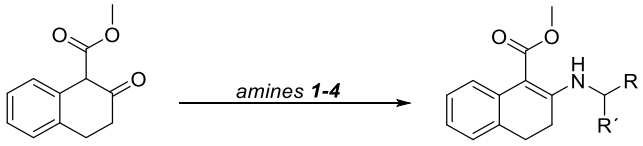


Figure 4.5. *Structures of the chiral primary amines employed.*

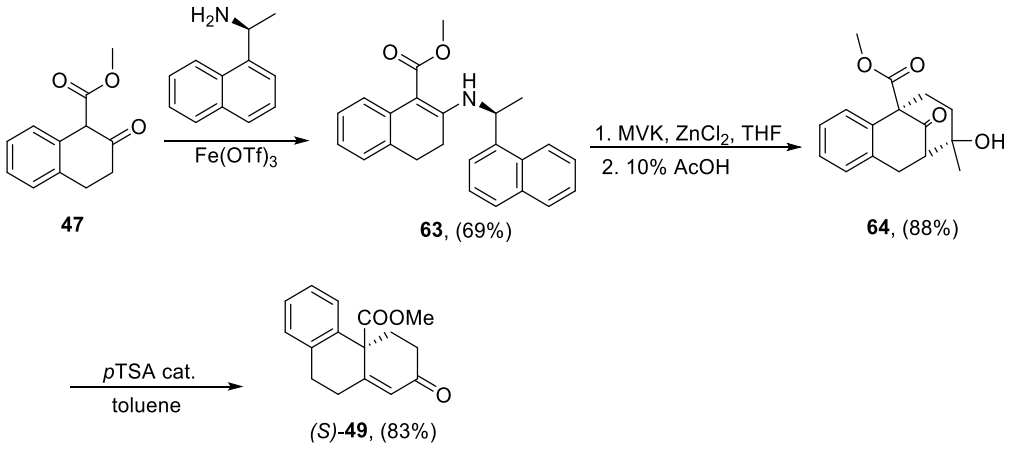


Scheme 4.19. *General reaction for the enamine derivatives.*

The enamines formed with the primary amines **1** and **2** showed no reactivity with the methyl vinyl ketone (Figure 4.5).[248] In contrast, the enamines prepared from **3** and **4** provide the target product. Best results were observed by addition **4** to tetralone **47** in the presence of $FeCl_3$ or $Fe(OTf)_3$ as catalysts forming the

[248] T. Volpe, G. Revial, M. Pfau, J. d'Angelo, *Tetrahedron Lett.***1987**, *28*, 2367.

enamine **63** with 69% yield. The subsequent Michael addition with methyl vinyl ketone gave tricycle **64** with good *ee* values (up to 95%) in the presence of 0.2 equiv of $ZnCl_2$ at 0 ºC. After the enantioselective addition was established, compound **64** was rearranged with *p*-toluene sulfonic acid (*p*TSA) as a catalyst in toluene to generate the (*S*)-**49** (Scheme 4.20).



Scheme 4.20. *The sequence of steps of the Michael addition and the rearrangement.*

MVK (Equiv)	$ZnCl_2$	solvent	T[a] (ºC)	time	Yield* (%)	*ee***
1.5	10% sol. Et_2O	THF	-20	24 h	45	82
1.5	20% sol. Et_2O	THF	-20	24 h	54	80
1.5	20% solid	THF	-20	24 h	37	76
1.5	20% solid	THF	-10	12 h	45	75
1.5	20% solid	toluene	-10	12 h	65	78
3.0	20% solid	THF	0	3 h	62	88
4.5	20% solid	THF	0	3 h	88	**95**

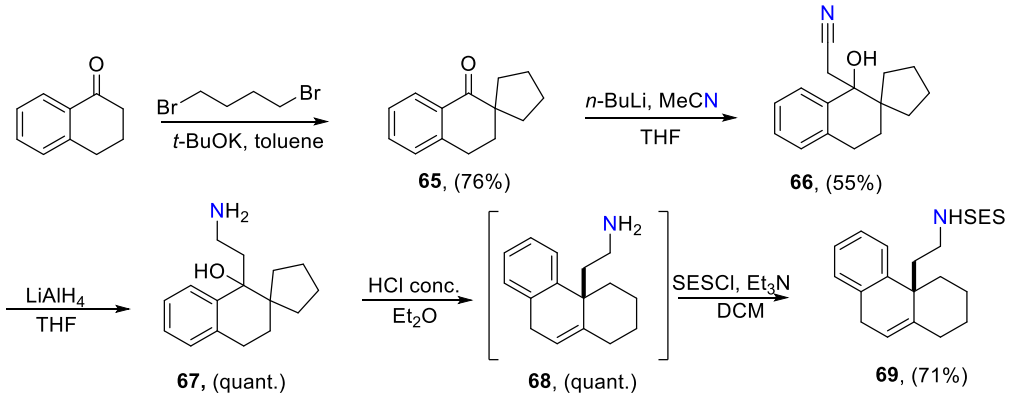
Table 4.5. *Optimization conditions for enamine 4. *yield of the Michael addition, **ee of the compound **49**.*

We measured the enantiomeric excess by chiral HPLC, comparing the racemic compound **49** with its enantiomeric version.

Having these promising results in hand, we carried out the synthesis in an enantioselective way, following the same sequence described for the racemic one. The synthesis finished with the formation of the (*R*, *S*)-hasubanan enantiomer in moderate good yields and 97% *ee*.

2.4. Synthesis of the intermediate III

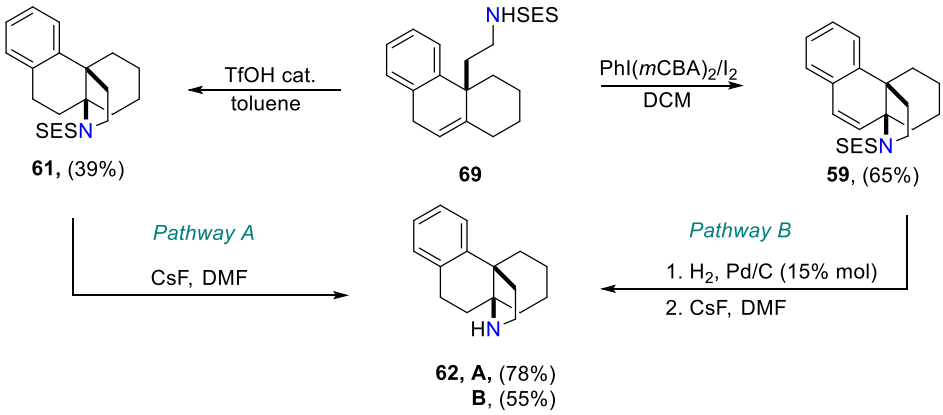
To prove the formation of **III** in Scheme 4.16 in the Hofmann-Löffler reaction for the synthesis of the hasubanan skeleton, we decided to synthesize this intermediate (Scheme 4.21). Thus, a five-step synthesis was carried out starting from commercially available α-tetralone. Formation of compound **65** was carried out through double α-alkylation using 1,4-dibromobutane, followed by the addition of the lithium anion of acetonitrile to the ketone to give alcohol **66**. Reduction of the nitrile to the primary amine using lithium aluminum hydride, followed by acid-promoted rearrangement, and sulfonamide formation provided compound **69**.



Scheme 4.21. *Synthesis of intermediate **III**, compound **69**.*

Then we submitted **69** to the catalytic Hofmann-Löffler conditions (Scheme 4.22). In this case, we reduced the amount of oxidant and molecular iodine to obtain a better yield. As proposed, **69** provided the targeted product **59** under the conditions of the Hofmann-Löffler reaction conditions, which demonstrates that this product is an intermediate in the transformation. Moreover, when **69** was submitted to triflic acid, pyrrolidine **61** was formed. This acid-catalyzed formation of a pyrrolidine ring by protonation of the alkene with a very strong Brønsted acid is reminiscent of the work recently developed by Widenhoefer on the intramolecular hydrofunctionalization of nonactivated cyclic alkenes.[249]

[249] R. E. M. Brooner, R. A. Widenhoefer, *Chem. Eur. J.* **2011**, *17*, 6170.



Scheme 4.22. *Final steps of the hasubanan* ***62*** *from intermediate* ***69****.*

2.5. Decaline system

The established iodine-catalyzed elimination/functionalization/elimination sequence for the formation of a pyrrolidine unit from the allylic amine could also be used in a decaline core. Therefore, to investigate the iodine tandem sequence, we synthesized a different substrate, compound **75** (Figure 4.6).

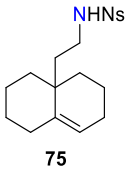
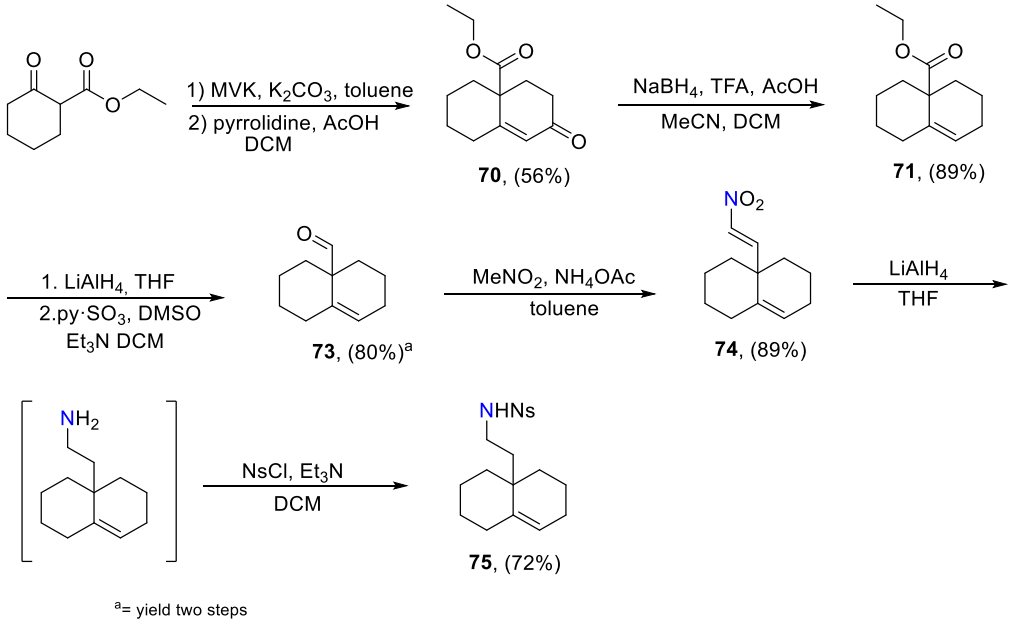


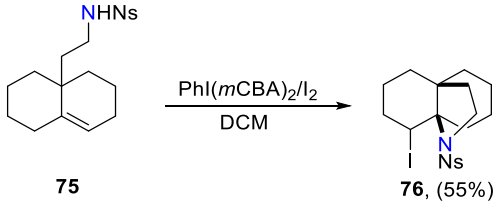
Figure 4.6. *Substrate for the mechanism control experiment.*

For the synthesis of **75**, we started by Robinson annulation of ethyl 2-oxocyclohexane-1-carboxylate with methyl vinyl ketone to form compound **70** (Scheme 4.23). Reduction of the carbonyl moiety using sodium borohydride in a mixture of acetic acid and trifluoroacetic acid led to **71**. Next, reduction of the ester to the alcohol, followed by oxidation, gave aldehyde **73,** which was submitted to the Henry reaction. The resulting vinyl nitro derivative **74** was reduced using lithium aluminum hydride, and the resulting primary amine, without isolation, was treated with nosyl chloride to give **75**.



Scheme 4.23. *Synthesis of substrate **75**.*

When **75** was submitted to the Hofmann-Löffler reaction conditions, iodinated pyrrolidine **76** was isolated (Scheme 4.24). After some optimization, **76** was obtained in 55% yield (Table 4.6).

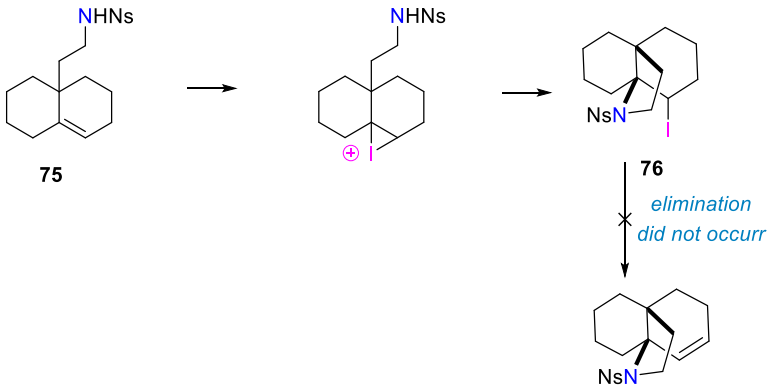


Scheme 4.24. *Hofmann-Löffler reaction for compound **75**.*

PhI(*m*cba)$_2$ (equiv)	I_2 (equiv)	solvent	time	Product (%)
1.5	0.2	DCM	3 h	37
2.0	0.2	DCM	3 h	39
2.0	0.5	DCM	3 h	55

Table 4.6. *Hofmann-Löffler conditions. The reaction was under white LEDs.*

This result indicates that **75** reacts under these conditions by electrophilic addition to give the product of iodo amination (Scheme 4.25). The elimination of the iodine did not occur in this case because, unlike in the tetralone core structure **59**, the resulting alkene would not be conjugated with an aryl ring.



Scheme 4.25. *The sequence of the reaction of 75 under the Hofmann-Löffler reaction conditions.*

3. Conclusions

A synthetic approach to the hasubanan scaffold has been developed, which generates its central *tert*-alkyl amine unit by an amidyl radical-promoted C–H functionalization. Contrarily to the expected Hofmann-Löffler pathway, the C–H amination takes place through an unprecedented iodine-catalyzed elimination/difunctionalization/ elimination sequence that forms the pyrrolidine unit as well as an additional alkene.

Furthermore, we have synthesized a proposed intermediate in the transformation and have studied the reaction on a non-aromatic cyclic derivative.

We have also developed an enantioselective synthesis leading to the (*S*)-hasubanan skeleton based on an enantioselective Michael reaction of a chiral enamine. This approach could open access to complex alkaloids of this family of natural products.

4. Experimental Section

All solvents (including deuterated ones) were commercially available and were used as received. Column chromatography was performed with silica gel (type 60, 0.063-0.2 mm). NMR spectra were recorded on a 300, 400 MHz, or 500 MHz spectrometer, with reference to ^{1}H. All chemical shifts in NMR experiments were reported as ppm downfield from TMS. The following calibrations were used: $CDCl_3$ δ = 7.26 and 77.16 ppm. Supelco C8 (5 cm × 4.6 mm, 5μm particles) column was used with a linear elution gradient from 100% H_2O (0.5%HCO_2H) to 100% MeCN 13 min at a flow rate of 0.5 mL/min. MS (EI)and HRMS experiments were performed on a Kratos MS 50 within the service departments at ICIQ. Melting points were determined with a Buchi Melting Point B-540

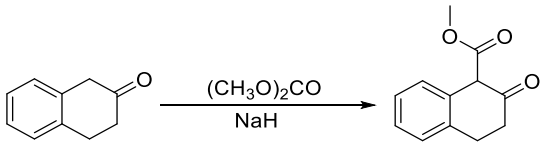
apparatus. IR spectra were taken with a Bruker Alpha instrument in the solid-state. Specific optical rotation values were measured with a Polarimeter JascoP1030 equipped with a 100 mm cell. HPLC measurements were carried out on an Acquity UPLC® system (Waters) UltraPerformance Convergence Chromatography™ (UPC2™) equipped with a detector Acquity UPLC PDA (Photodiode Array detector). The respective chiral stationary phase (Chiralpak IA, IC, IG, ID, or IE) and exact conditions are specified for each individual compound within the compound characterization section.

The following compounds are commercially available and were used as received:

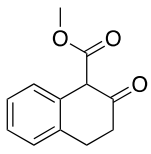
Dimethyl carbonate, sodium hydride (60% dispersion in oil), iron (III) chloride, iron (III) trifluoromethane sulfonate, methyl vinyl ketone, zinc dust, acetic acid, *p*-toluensulfonic acid, palladium on carbon (10%), trimethylsilyl chloride, lithium aluminum hydride, pyridine sulfur trioxide, nitromethane, ammonium acetate, triethylamine, molecular iodine, cesium fluoride, pyrrolidine, sodium borohydride, nosyl chloride, 1,4-dibromobutane, *n*-butyl lithium (2.5M in hexanes) and (-)-a-(1-naphtyl)-ethylamine.

Enantioselective synthesis of hasubanan skeleton

Methyl 2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate. (47)



A mixture of ß-tetralone with dimethyl carbonate (1.5 equiv) was cooled at 0 ºC, then NaH (60% dispersion in oil, 1.5 equiv) was added. The mixture was stirred to 85ºC for 30 min. Then, HCl 1M was added at 0 ºC to the mixture and extracted with Et_2O (3x), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.

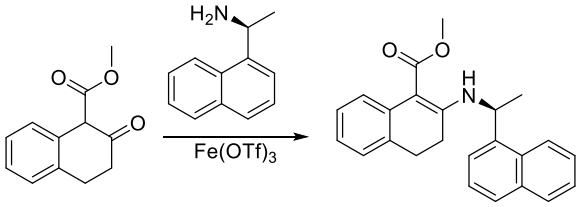


On a 60 mmol scale, **47** was isolated as a colorless oil with 87% yield (10.54 g). Spectroscopic data in agreement with the one previously described.[250] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.47 – 2.62 (m, 2H), 2.76 – 2.88 (m, 2H), 3.92 (d, *J* = 0.5 Hz, 3H), 7.07 (tt, *J* = 7.3, 0.9 Hz, 1H), 7.13 (ddt, *J* = 7.5, 1.6, 0.7 Hz, 1H), 7.18 – 7.22 (m, 1H), 7.69 (ddt, *J* = 7.9, 1.2, 0.6 Hz, 1H), 7.9, 1.2, 0.6 Hz, 1H).. **^{13}C NMR**

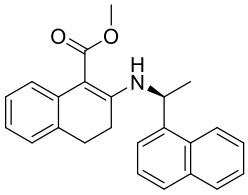
[250] S. G. Hammer, S. Goblederb, F. Naporrab, H.-J. Wittmannc, S. Elzb, M. R. Heinricha, A. Strasse, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 292.

(101 MHz, $CDCl_3$): δ =27.9, 29.7, 51.9, 100.0, 125.1, 126.0, 126.5, 127.3, 131.5, 133.3, 172.6, 178.5.

Methyl (*S*)-2-((1-(naphthalen-1-yl)ethyl)amino)-3,4-dihydronaphthalene-1-carboxylate. (63)

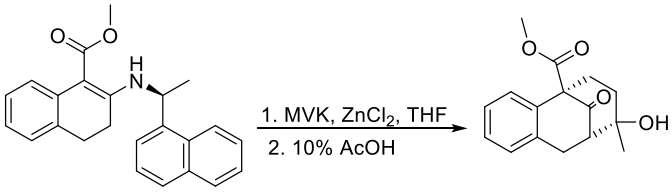


To methyl 2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate was added $FeCl_3$ or $Fe(OTf)_3$ (0.1 equiv) and (R)-1-(naphthalen-1-yl)ethan-1-amine (1.2 equiv), the mixture was stirred at rt overnight. The crude was purified directly by column chromatography using a gradient of ethyl acetate and hexane.



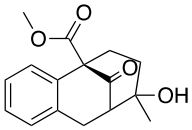
On a 10 mmol scale, **63** was isolated as a yellow solid with 69% yield (2.46 g). **Mp**: 102-103 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.74 (d, *J* = 6.7 Hz, 3H), 1.96 – 2.05 (m, 1H), 2.31 – 2.40 (m, 2H), 2.47 (dd, *J* = 10.5, 9.1 Hz, 1H), 3.87 (s, 3H), 5.56 (p, *J* = 6.6 Hz, 1H), 6.88 – 6.98 (m, 2H), 7.12 – 7.17 (m, 1H), 7.40 – 7.48 (m, 2H), 7.50 – 7.55 (m, 1H), 7.59 (ddd, *J* = 8.5, 6.8, 1.6 Hz, 1H), 7.65 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.72 – 7.78 (m, 1H), 7.91 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 10.27 (d, *J* = 6.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 23.9, 26.6, 27.9, 49.8, 50.7, 93.8, 122.1, 122.7, 123.30, 125.9, 126.1, 126.3, 126.5, 126.5, 126.6, 127.9, 129.4, 129.9, 133.0, 134.1, 134.5, 140.4, 164.3, 170.7. **IR** ν(cm^{-1}): 2941, 1638, 1562, 1224, 1024, 775. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{24}H_{24}NO_2$, 358.1802; found, 358.1800.

Methyl (5*R*,8*S*,9*R*)-8-hydroxy-8-methyl-11-oxo-7,8,9,10-tetrahydro-5,9-methanobenzo[8]annulene-5(6*H*)-carboxylate. (64)



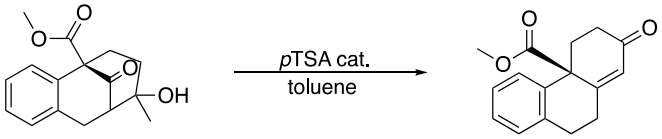
The enamine derivative **63** was added to a solution of zinc chloride (0.2 equiv) in THF (2 mL/mmol) at 0 °C; the mixture reaction was stirred for 45 min at 0 ºC. Then, methyl vinyl ketone (3.0 equiv) was added at 0 ºC, and the reaction was stirred at 0 ºC for 3 hours. To this mixture was added 10% acetic acid (2

mL/mmol) in water and stirred at room temperature for 12h. After the addition of ethyl acetate, the mixture was washed with water, followed by brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.

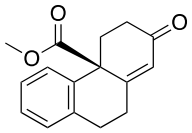


On a 5 mmol scale, **64** was isolated as a colorless oil with 88% yield (1.21 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.34 - 1.42 (m, 4H), 1.56 – 1.62 (m, 2H), 1.93 (ddd, *J* = 13.5, 4.7, 2.1 Hz, 1H), 2.63 (dt, *J* = 6.8, 1.5 Hz, 1H), 2.79 (td, *J* = 13.6, 4.2 Hz, 1H), 3.18 (dd, *J* = 18.0, 1.2 Hz, 1H), 3.44 (ddd, *J* = 18.0, 6.9, 1.1 Hz, 1H), 3.81 (s, 3H), 6.83 – 6.87 (m, 1H), 7.10 – 7.17 (m, 1H), 7.20 – 7.25 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 28.1, 29.8, 32.1, 34.1, 35.6, 52.6, 58.1, 63.1, 78.8, 127.4, 127.5, 127.7, 133.5, 137.4, 172.3, 208.0. **IR** ν(cm^{-1}): 3435, 2923, 1735, 1700, 1243, 755. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{18}NaO_4$, 297.1097; found, 297.1101.

Methyl (*S*)-2-oxo-3,4,9,10-tetrahydrophenanthrene-4a(2*H*)-carboxylate. (49)



To a solution of **64** in toluene (1 mL/mmol) was added *p*TSA (0.1 equiv). The reaction mixture was refluxed for 4h. The residue was dissolved in EtOAc and washed with $NaHCO_3$. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.



On a 15 mmol scale, **49** was isolated as a yellow oil with 83% yield (3.19 g). Spectroscopic data in agreement with the one previously described.[251] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.00 – 2.10 (m, 1H), 2.54 (dddd, *J* = 17.9, 4.6, 2.4, 1.0 Hz, 1H), 2.61 – 2.79 (m, 2H), 2.85 – 2.93 (m, 1H), 2.96 – 3.14 (m, 3H), 3.68 (s, 3H), 6.03 (t, *J* = 1.2 Hz, 1H), 7.13 – 7.16 (m, 1H), 7.20 – 7.26 (m, 2H), 7.47 (dd, *J* = 7.4, 1.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.4, 32.8, 36.1, 50.4, 53.1, 126.6, 126.9, 127.3,

[251]K. Takatori, S. Ota, K. Tendo, K. Matsunaga, K. Nagasawa, S. Watanabe, A. Kishida, H.Kogen, H.Nagaoka, *Org. Lett.* **2017**, *19*, 3763.

127.6, 129.2, 136.2, 136.8, 162.5, 172.0, 198.7. **$[\alpha]_D^{28}$= -153.9** (c = 0.14, $CHCl_3$). **HPLC:** Chiralpack IB (250x4.6mm, 5 μm), Isocratic IPA:Hex 10:90, v/v, 0.8mL/min,. *ee* (%) = 95%.

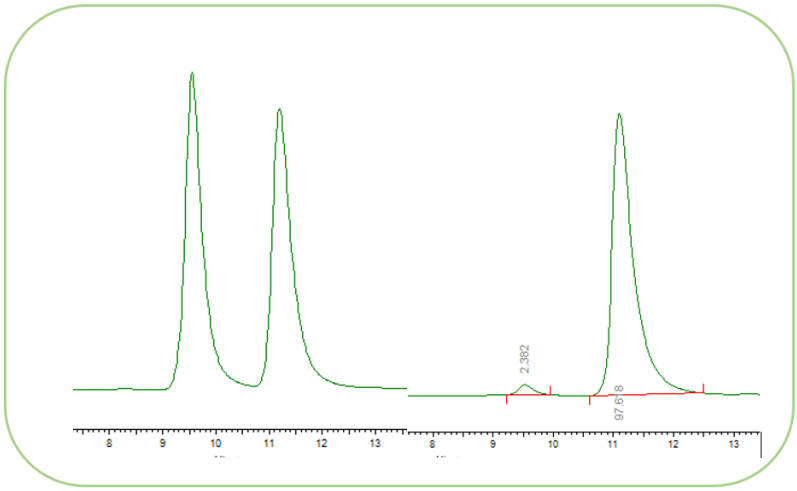
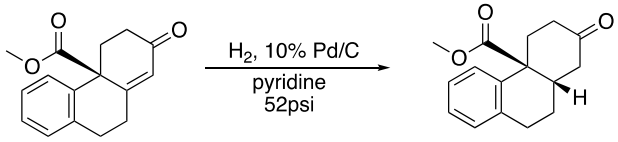
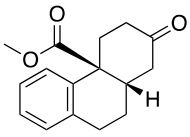


Figure 4.7. *Racemic vs. Enantioselective HPLC-chromatogram of compound* ***49.***

Methyl *(S)*- 2-oxo-1,3,4,9,10,10a-hexahydrophenanthrene-4a(2*H*)-carboxylate. (50)



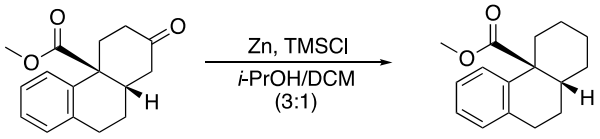
The unsaturated keto-ester **49** was dissolved in dry pyridine, Pd/C (10% on charcoal) was added, and the reaction mixture was stirred for 16h at rt under 52 psi of hydrogen pressure. Then, the catalyst was filtered through a celite pad, and the organic phase was washed using 1M HCl and extracted with DCM (3x). The solvent was removed under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane. A mixture of diastereoisomers (3:1) was obtained. After crystallization (mixture DCM: Hexane), a mixture of diastereoisomers 95:5 was obtained.



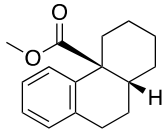
On a 8 mmol scale, **50** was isolated as a yellow solid with 52% yield (1.07 g) of the *cis*-derivative. **Mp**: 104-105 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.66 – 1.76 (m, 1H), 1.89 (ddt, *J* = 13.3, 6.2, 3.5 Hz, 1H), 2.14 (ddd, *J* = 14.3, 11.8, 5.0 Hz, 1H), 2.27 (dddd, *J* = 14.7, 6.0, 3.9, 2.1 Hz, 2H), 2.51 – 2.66 (m, 2H), 2.67 – 2.77 (m, 1H), 2.83 – 2.96 (m, 2H), 2.95 – 3.06 (m, 1H), 3.76 (s, 3H), 7.08 – 7.23 (m, 4H). **^{13}C**

NMR (101 MHz, $CDCl_3$): δ = 25.4, 28.9, 34.5, 38.9, 39.3, 45.0, 50.6, 52.7, 126.6, 126.8, 127.3, 129.8, 134.8, 137.3, 175.7, 210.6. **IR** ν(cm^{-1}): 2951, 1712, 1433, 1239, 1213, 747. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{18}NaO_3$, 281.1148; found, 281.1144. **$[\alpha]_D^{28}$=** -114.4 (c = 0.19, $CHCl_3$).

Methyl (4a*S*,10a*R*)-1,3,4,9,10,10a-hexahydrophenanthrene-4a(2*H*)-carboxylate. (52)

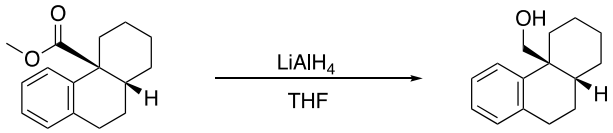


Methyl 2-oxo-1,3,4,9,10,10a-hexahydrophenanthrene-4a(2H)-carboxylate was dissolved in a mixture of *i*-PrOH:DCM (3:1). Then, activated Zn (10.00 equiv) and TMSCl (10.00 equiv) stepwise were added at 0 ºC. After completing the reaction, $NaHCO_3$ (24.00 equiv) was added, the mixture was stirred for 5 min and filtered through celite, and concentrated under pressure. The residue was purified by column chromatography using a gradient of ethyl acetate and hexane.



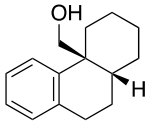
On a 4.6 mmol scale, **52** was isolated as a white solid with 85% yield (955 mg). **Mp:** 51-52 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.45 – 1.70 (m, 6H), 1.75 – 1.82 (m, 1H), 1.87 – 2.02 (m, 2H), 2.22 (ddd, *J* = 13.9, 5.7, 3.4 Hz, 1H), 2.61 – 2.69 (m, 1H), 2.91 – 2.97 (m, 2H), 3.71 (s, 3H), 7.12 – 7.20 (m, 3H), 7.25 – 7.30 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 23.4, 24.7, 29.1, 29.2, 34.1, 36.5, 51.3, 52.2, 126.1, 126.5, 127.1, 129.5, 135.9, 138.9, 176.7. **IR** ν(cm^{-1}): 2940, 2846, 1720, 1430, 1202, 759. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{20}NaO_3$, 267.1356; found, 267.1348. **$[\alpha]_D^{28}$=** -65.9 (c = 0.18, $CHCl_3$).

((4a*S*,10a*R*)-1,3,4,9,10,10a-hexahydrophenanthren-4a(2*H*)-yl)methanol. (53)



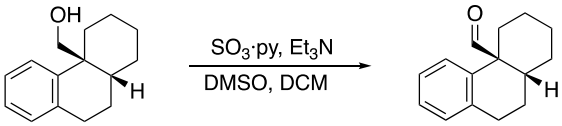
A flame-dried Schlenk equipped with a stirrer bar was charged with $LiAlH_4$ (2.0 equiv), anhydrous, then THF (5mL/mmol) was added carefully, and the mixture was cooled to 0 ºC. The corresponding ester **52** (1 equiv) was added dropwise to the $LiAlH_4$/THF suspension under an argon atmosphere. The mixture was stirred for 2h and then cooled to 0 ºC. A solution of NaOH (1 M) was added. After filtration over Na_2SO_4 and evaporation of the solvent under reduced pressure, the

crude amine was obtained in quantitative yield and was directly used in the following step.

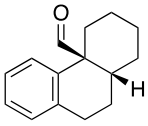


On a 3.6 mmol scale, **53** was isolated as a colourless oil with 92% yield (636 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.24 (ddd, *J* = 12.7, 6.6, 2.7 Hz, 1H), 1,36 – 1.61 (m, 7H), 1.63 – 1.74 (m, 1H), 1.97 (dd, *J* = 9.2, 3.8 Hz, 1H), 2.07 (ddt, *J* = 13.4, 6.4, 3.3 Hz, 1H), 2.15 – 2.26 (m, 1H), 2.68 – 2.98 (m, 2H), 3.53 – 3.71 (m, 2H), 7.09 – 7.19 (m, 3H), 7.28 – 7.32 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.47, 24.28, 25.19, 26.87, 28.10, 32.92, 35.57, 43.36, 71.34, 126.09, 126.47, 129.89, 137.80, 139.54. **IR** ν(cm^{-1}): 3384, 2923, 2855, 1448, 1025, 755. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{15}H_{20}NaO$, 239.1406; found, 239.1407. **$[\alpha]_D^{28}$=** -81.0 (c = 0.25, $CHCl_3$).

(4a*S*,10a*R*)-1,3,4,9,10,10a-hexahydrophenanthrene-4a(2H)-carbaldehyde. (54)

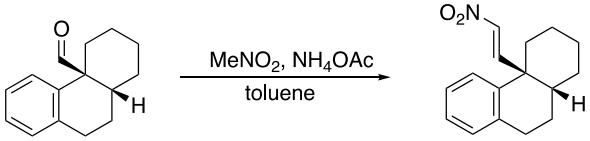


The corresponding alcohol **53** was dissolved in DCM (5 mL/mmol), then pyridine sulfur trioxide (4.0 equiv), triethylamine (10.0 equiv), and DMSO (2.8 mL/mmol) were added at 0 ºC. After 1 h at this temperature, to this mixture, 1 M HCl was added and extracted with DCM (3x), the organic layer was washed with $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.

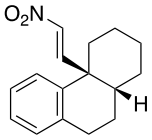


On a 3.2 mmol scale, **54** was isolated as a colourless oil with 82% yield (562 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.40 – 1.63 (m, 6H), 1.80 (dtd, *J* = 13.3, 5.9, 3.2 Hz, 1H), 1.88 – 2.04 (m, 2H), 2.27 (ddq, *J* = 11.4, 8.0, 4.4, 3.9 Hz, 1H), 2.81 – 3.05 (m, 3H), 7.03 – 7.09 (m, 1H), 7.13 – 7.21 (m, 3H), 9.35 – 9.50 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.1, 22.6, 24.4, 28.7, 28.9, 31.1, 34.4, 54.8, 126.4, 127.1, 128.2, 130.1, 135.1, 137.5, 203.5. **IR** ν(cm^{-1}): 2972, 2841, 1713, 1423, 755. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{15}H_{18}NaO$, 237.1250; found, 237.1255. **$[\alpha]_D^{28}$=** -10.7 (c = 0.07, $CHCl_3$).

(4a*R*,10a*R*)-4a-((E)-2-nitrovinyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (55)

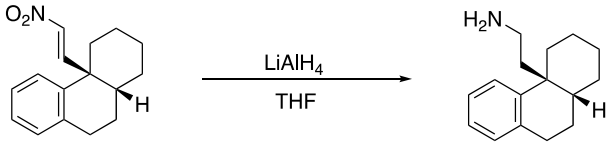


To a solution of the aldehyde **54** and ammonium acetate (5.7 equiv) in CH_3NO_2 (2 mL/mmol), toluene (0.6 mL/mmol) was added. The mixture was stirred at 100 ºC overnight. The mixture was concentrated under vacuum, and the residue was dissolved in DCM, washed with $NaHCO_3$, dried over Na_2SO4, and concentrated in vacuo. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.



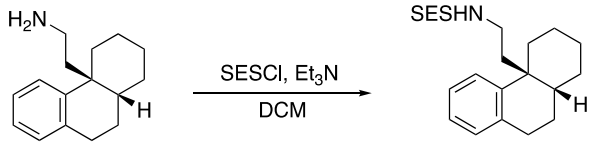
On a 2.5 mmol scale, **55** was isolated as a yellowish solid with 78% yield (501 mg). **Mp:** 131-132 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 12.1 Hz, 1H), 1.37 – 1.46 (m, 2H), 1.52 – 1.76 (m,5H), 1.89 (dtt, *J* = 17.2, 6.9, 3.6 Hz, 2H), 2.32 (d, *J* = 13.8 Hz, 1H), 2.77 (ddd, *J* = 17.7, 6.8, 3.5 Hz, 1H), 2.90 (ddd, *J* = 17.4, 10.4, 6.9 Hz, 1H), 6.31 (d, *J* = 13.4 Hz, 1H), 7.11 – 7.17 (m, 1H), 7.17 – 7.22 (m, 3H), 7.33 (d, *J* = 13.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 25.0, 26.2, 26.8, 29.9, 35.2, 39.9, 44.0, 126.5, 127.1, 127.2, 130.2, 136.9, 140.9, 153.1. **IR** ν(cm^{-1}): 2930, 2859, 1722, 1512, 1344, 727. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{16}H_{20}NO_2$, 258.1489, found, 258.1490. **$[\alpha]_D^{28}$=** -17.0 (c = 0.16, $CHCl_3$).

2-((4aS,10aR)-1,3,4,9,10,10a-hexahydrophenanthren-4a(2H)-yl)ethan-1-amine.



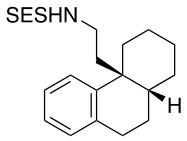
A flame-dried Schlenk equipped with a stirrer bar was charged with $LiAlH_4$ (2 equiv), anhydrous THF was added carefully, and the mixture was cooled to 0 ºC. The corresponding nitro compound (1 equiv) was added dropwise to the $LiAlH_4$/THF suspension under argon atmosphere. The mixture was warmed up to reflux and stirred for 3 h; then, it was cooled to 0 ºC. A solution of NaOH (1M) was added. After filtration over Na_2SO_4 and evaporation of the solvent under reduced pressure, the crude amine was obtained in quantitative yield and was directly used in the following step.

***N*-(2-((4a*S*,10a*R*)-1,3,4,9,10,10a-hexahydrophenanthren-4a(2H)-yl)ethyl)-2-(trimethylsilyl)ethane-1-sulfonamide. (57)**



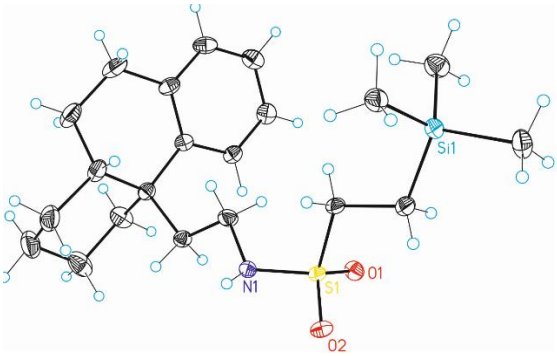
The 2-((4aR)-1,3,4,9,10,10a-hexahydrophenanthren-4a(2H)-yl)ethan-1-amine was dissolved in anhydrous DCM (5 mL/mmol) and then triethylamine and

SESCl were added carefully at ºC. Then, the mixture reaction was allowed to warm to rt overnight. To the mixture was added NH_4Cl and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.



On a 1.8 mmol scale, **57** was isolated as a yellow solid with 69% yield (488 mg). **Mp:** 117-118 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.01 (s, 9H), 0.86 – 0.92 (m, 2H), 1.21 – 1.64 (m, 7H), 1.68 – 1.86 (m, 3H), 1.94 (d, *J* = 9.7 Hz, 1H), 2.02 – 2.16 (m, 2H), 2.72 – 2.88 (m, 3H), 2.97 (dt, *J* = 10.4, 6.3 Hz, 2H), 3.77 (t, *J* = 6.0 Hz, 1H), 7.04 – 7.10 (m, 2H), 7.12 (td, *J* = 7.3, 2.1 Hz, 1H), 7.19 (dd, *J* = 7.6, 1.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = -1.85, 10.73, 22.47, 24.32, 27.56 (d, *J* = 6.9 Hz), 28.18, 35.14 – 36.90 (m), 37.58 – 38.59 (m), 39.65, 40.08, 41.99, 48.74, 125.87, 126.03, 126.17, 129.91, 136.67, 141.92. **IR** ν(cm^{-1}): 3220, 2922, 2859, 1131, 759. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{35}NNaO_2SSi$, 416.2050; found, 416.2051. **[α]$_D^{28}$=** -45.5 (c = 0.10, $CHCl_3$).

*X-ray data compound **57***



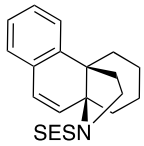
Identification code	mo_KMEC1446_0m
Empirical formula	C21 H35 N O2 S Si
Formula weight	393.65
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P 21
Unit cell dimensions	a = 10.7183(10)Å α= 90°.

	b = 7.3056(7)Å β = 109.387(2)°.
	c = 14.6030(14)Å γ = 90°.
Volume	1078.63(18) $Å^3$
Z	2
Density (calculated)	1.212 Mg/m^3
Absorption coefficient	0.221 mm^{-1}
F(000)	428
Crystal size	0.200 x 0.050 x 0.050 mm^3
Theta range for data collection	2.014 to 30.499°.
Index ranges	-15<=h<=15,-10<=k<=10,-20<=l<=20
Reflections collected	24747
Independent reflections	6593[R(int) = 0.0224]
Completeness to theta =30.499°	99.9%
Absorption correction	Multi-scan
Max. and min. transmission	0.74 and 0.71
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6593/ 87/ 304
Goodness-of-fit on F^2	1.224
Final R indices [I>2sigma(I)]	R1 = 0.0279, wR2 = 0.0785
R indices (all data)	R1 = 0.0295, wR2 = 0.0795
Flack parameter	x =-0.007(14)
Largest diff. peak and hole	0.434 and -0.191 $e.Å^{-3}$

(4b*S*,8a*S*)-11-((2-(trimethylsilyl)ethyl)sulfonyl)-5,6,7,8-tetrahydro-8a,4b-(epiminoethano)phenanthrene. (59)

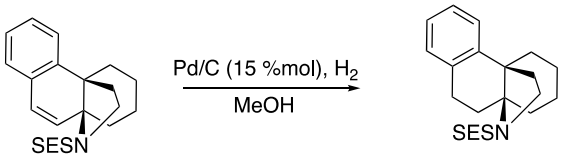
The corresponding sulfonamide **58** was dissolved in dry DCM (15 mL/mmol) then, PhI(*m*cba)$_2$ (3.0 equiv) and I_2 (0.2 equiv) were added. The reaction was stirred at rt for 3 h under white LEDs. Then, to the mixture were added $Na_2S_2O_3$

and $NaHCO_3$ and stirred for 24 h; DCM (3x) was added and separated. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.

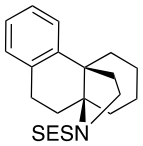


On a 0.3 mmol scale, **59** was isolated as a yellow oil with 75% yield (88 mg).**^{1}H NMR** (400 MHz, $CDCl_3$): δ = -0.15 (s, 9H), 0.21 – 0.36 (m, 1H), 0.69 (ddd, *J* = 13.8, 11.2, 6.2 Hz, 1H), 1.23 – 1.31 (m, 3H), 1.35 – 1.46 (m, 2H), 1.69 (dd, *J* = 11.6, 6.7 Hz, 2H), 1.88 (td, *J* = 13.5, 3.5 Hz, 1H), 2.27 (d, *J* = 13.8 Hz, 1H), 2.41 (dd, *J* = 12.7, 7.2 Hz, 1H), 2.55 – 2.69 (m, 2H), 2.97 – 3.13 (m, 1H), 3.71 (td, *J* = 9.0, 1.6 Hz, 1H), 6.03 (d, *J* = 9.6 Hz, 1H), 6.68 (d, *J* = 9.6 Hz, 1H), 7.14 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.22 (td, *J* = 7.4, 1.3 Hz, 1H), 7.27 – 7.31 (m, 1H), 7.38 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = -2.0, 10.1, 20.5, 22.9, 29.5, 34.6, 36.8, 46.8, 49.5, 49.8, 65.3, 124.5, 126.9, 127.9, 129.0, 129.9, 130.8, 131.5, 140.8. **IR** ν(cm^{-1}): 2812, 1343, 1113, 1079, 804. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{31}NNaO_2SSi$, 412.1737; found, 412.1730. **[α]$_D^{28}$=** +96.0 (c = 0.11, $CHCl_3$).

(4b*S*,8a*S*)-11-((2-(trimethylsilyl)ethyl)sulfonyl)-5,6,7,8,9,10-hexahydro-8a,4b-(epiminoethano)phenanthrene. (61)



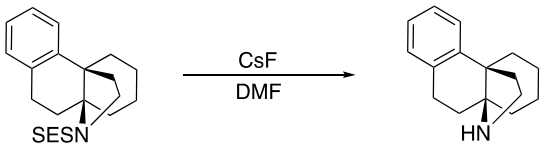
A Schlenk flask equipped with a stirrer bar was charged with the compound **59**, Pd/C (15 % mmol), and MeOH (5 mL/mmol). The reaction was stirred under an atmosphere of dihydrogen for 12 h using a gas balloon. The mixture was filtered through a pad of Celite and concentrated under reduced pressure to yield compound **61**. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.



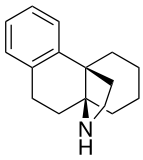
On a 0.2 mmol scale, **61** was isolated as a yellowish oil with 79% yield (62 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.02 (s, 9H), 0.93 – 1.14 (m, 2H), 1.35 – 1.46 (m, 1H), 1.47 – 1.56 (m, 3H), 1.61 – 1.76 (m, 2H), 2.00 – 2.06 (m, 2H), 2.15 (ddd, *J* = 13.3, 10.9, 5.3 Hz, 2H), 2.34 (ddd, *J* = 13.7, 5.6, 3.8 Hz, 1H), 2.41 – 2.51 (m, 1H), 2.70 – 2.78 (m, 1H), 2.83 (td, *J* = 13.5, 4.5 Hz, 1H), 2.89 – 3.01 (m, 2H), 3.13 (ddd, *J* = 17.0, 11.2, 5.6 Hz, 1H), 3.46 (td, *J* = 10.0, 9.1, 3.4 Hz, 1H), 7.06 – 7.09 (m, 1H), 7.11 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.16 (td, *J* = 7.3, 1.9 Hz, 1H), 7.24 (dd, *J* = 7.6, 1.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = -1.80 10.2, 22.3, 22.8, 26.6, 27.6, 33.2, 34.9, 35.6, 46.0, 49.0, 49.3, 68.7, 126.1, 126.3, 126.6, 129.1, 136.0, 142.3. **IR**

ν(cm^{-1}): 2841, 1775, 1142, 775, 513. **HRMS** (m/z): [M+Na]$^+$ calcd. for $C_{21}H_{33}NNaO_2SSi$, 414.1893; found, 414.1910. **[α]$_D^{28}$=** +25.8 (c = 0.12, $CHCl_3$).

(4b*S*,8a*S*)-5,6,7,8,9,10-hexahydro-8a,4b-(epiminoethano)phenanthrene. (62)



The compound **61** was dissolved in anhydrous DMF (1.0 mL/mmol), then CsF (2.0 equiv) was added, and the mixture was stirred at 100 ºC for 12 h. H_2O was added and extracted with Et_2O (3x), washed with brine. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure.



On a 0.1mmol scale, **62** was isolated as a brown oil with 78% yield (18 mg).Spectroscopic data in agreement with the one previously described.[244] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.21- 1.30 (m, 1H), 1.41 – 1.58 (m, 2H), 1.63 – 1.80 (m, 3H), 1.88 (dt, *J* = 13.2, 7.0 Hz, 3H), 1.99 (dt, *J* = 13.6, 6.6 Hz, 1H), 2.09 – 2.21 (m, 3H), 2.85 – 2.99 (m, 2H), 3.06 (q, *J* = 10.0 Hz, 1H), 3.25 – 3.33 (m, 1H), 7.06 – 7.09 (m, 1H), 7.10 – 7.13 (m, 1H), 7.18 (td, *J* = 7.4, 1.7 Hz, 1H), 7.29 – 7.32 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.9, 22.3, 26.1, 28.5, 31.9, 34.4, 38.8, 41.7, 47.6, 126.0, 126.6, 127.2, 129.3, 134.3, 142.2. . **[α]$_D^{28}$=** +61.9 (c = 0.06, $CHCl_3$). **HPLC:** Chiralpack IB (250x4.6mm, 5 μm), Isocratic IPA:Hex 20:80, v/v, 0.7mL/min,. *ee* (%) = 97%.

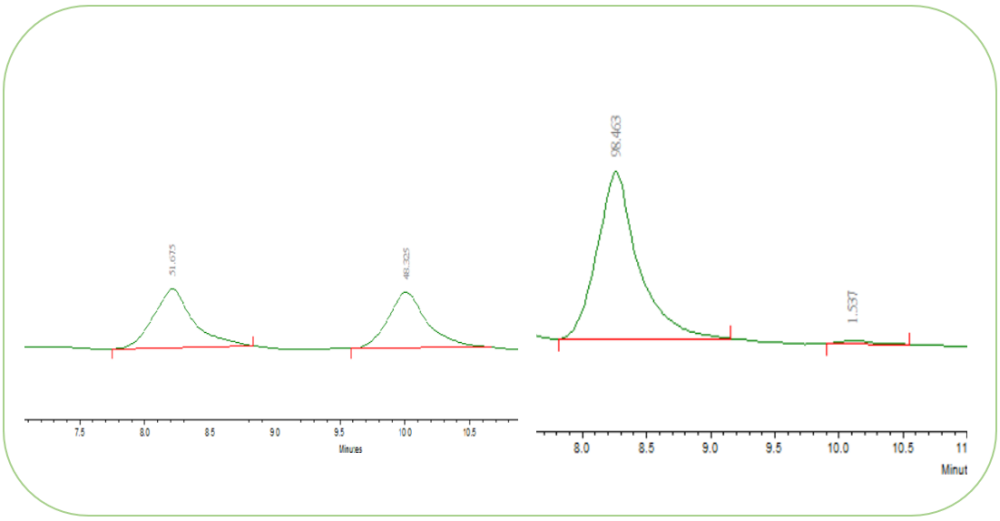
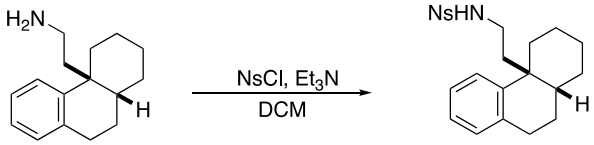


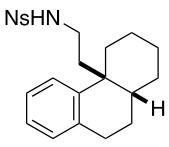
Figure 4.8. *Racemic vs. Enantioselective HPLC-chromatogram of compound* ***62.***

Racemic Hofmann-Löffler reaction with 4-nitrobenzenesulfonamide as directing group.

***N*-(2-(1,3,4,9,10,10a-hexahydrophenanthren-4a(2*H*)-yl)ethyl)-4-nitrobenzenesulfonamide. (56)**

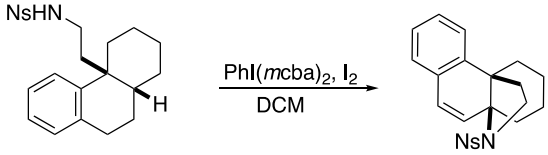


The 2-((4aR)-1,3,4,9,10,10a-hexahydrophenanthren-4a(2H)-yl)ethan-1-amine was dissolved in anhydrous DCM (5 mL/mmol) and then triethylamine (1.5 equiv) and NsCl (1.2 equiv) were added carefully at 0 ºC. Then, the mixture reaction was allowed to warm to rt overnight. To the mixture was added NH_4Cl and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.



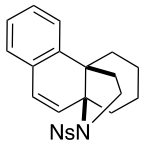
On a 1.0 mmol scale, **56** was isolated as a yellow oil with 57% yield. (236 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.15 – 1.41 (m, 3H), 1.44 – 1.57 (m, 3H), 1.60 – 1.74 (m, 3H), 1.78 – 1.88 (m, 1H), 1.95 (dt, *J* = 14.9, 7.7 Hz, 1H), 2.02 – 2.13 (m, 1H), 2.62 – 2.71 (m, 1H), 2.75 – 2.85 (m, 1H), 2.88 – 2.99 (m, 2H), 4.31 (t, *J* = 6.0 Hz, 1H), 7.01 – 7.17 (m, 4H), 7.84 – 7.90 (m, 2H), 8.22 – 8.31 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.4, 24.2, 24.4, 27.3, 28.1, 35.7, 38.6, 39.7, 40.0, 41.4, 124.4, 126.0, 126.1, 128.3, 130.0, 136.7, 141.29, 146.1, 150.1. **IR** ν(cm^{-1}): 3225, 2925, 2859, 1132, 755. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{22}H_{26}N_2NaO_4S$, 437.1505; found, 437.1499.

(4b*S*,8a*S*)-11-((4-nitrophenyl)sulfonyl)-5,6,7,8-tetrahydro-8a,4b-(epiminoethano)phenanthrene. (58)



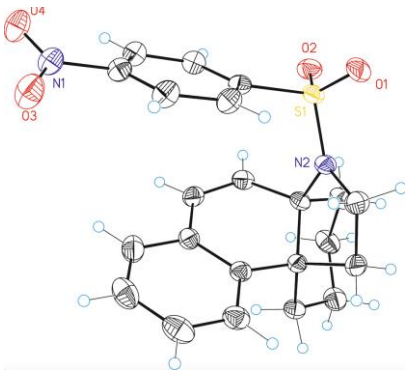
The corresponding sulfonamide **56** was dissolved in dry DCM (15 mL/mmol) then, PhI(*m*cba)$_2$ (3.0 equiv) and I_2 (0.2 equiv) were added. The reaction was stirred at rt for 3 h under white LEDs. Then, to the mixture were added $Na_2S_2O_3$ and $NaHCO_3$ and stirred for 24h. DCM (3x) was added and separated. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced

pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.



On a 0.2 mmol scale, **58** was isolated as a yellow solid with 51% yield (42 mg). **Mp**: 147-148 ºC **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.19 – 1.32 (m, 2H), 1.40 (tt, *J* = 8.2, 3.6 Hz, 2H), 1.65 (dddd, *J* = 11.4, 4.8, 3.3, 1.5 Hz, 2H), 1.95 (td, *J* = 13.4, 3.6 Hz, 1H), 2.26 (dt, *J* = 13.7, 3.7 Hz, 1H), 2.40 (ddd, *J* = 13.0, 7.4, 1.6 Hz, 1H), 2.57 – 2.67 (m, 1H), 3.03 (ddd, *J* = 10.3, 9.0, 7.4 Hz, 1H), 3.80 (td, *J* = 8.9, 1.6 Hz, 1H), 5.88 (d, *J* = 9.6 Hz, 1H), 6.33 (d, *J* = 9.5 Hz, 1H), 6.64 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.01 (td, *J* = 7.4, 1.3 Hz, 1H), 7.17 (td, *J* = 7.6, 1.5 Hz, 1H), 7.21 – 7.26 (m, 1H), 7.56 – 7.62 (m, 2H), 7.98 – 8.03 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 20.3, 22.6, 29.4, 34.1, 37.2, 46.9, 49.2, 66.4, 123.3, 124.0, 126.7, 127.4, 127.8, 128.1, 129.0, 130.8, 130.9, 139.5, 146.8, 149.3. **IR** ν(cm^{-1}): 2928, 1522, 1341, 1153, 735. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{22}H_{22}N_2NaO_4S$, 433.1192; found, 433.1187.

*X-ray data compound **58***

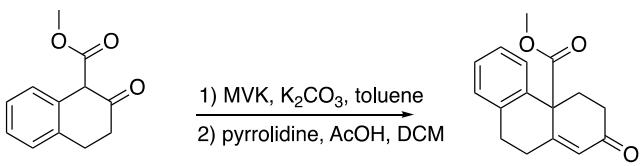


Identification code	EC1190
Empirical formula	C22 H22 N2 O4 S
Formula weight	410.47
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P 21/c
Unit cell dimensions	a = 9.69640(10)Å α= 90°.

	b = 10.65470(10)Å β = 97.8270(10)°.
	c = 18.7895(2)Å γ = 90°.
Volume	1923.10(3) $Å^3$
Z	4
Density (calculated)	1.418 Mg/m^3
Absorption coefficient	0.201 mm^{-1}
F(000)	864
Crystal size	0.200 x 0.150 x 0.050 mm^3
Theta range for data collection	2.120 to 32.310°.
Index ranges	-14<=h<=14,-15<=k<=15,-28<=l<=28
Reflections collected	67722
Independent reflections	6615[R(int) = 0.0304]
Completeness to theta =32.310°	96.5%
Absorption correction	Multi-scan
Max. and min. transmission	1.00 and 0.90
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6615/ 0/ 262
Goodness-of-fit on F^2	1.066
Final R indices [I>2sigma(I)]	R1 = 0.0475, wR2 = 0.1322
R indices (all data)	R1 = 0.0543, wR2 = 0.1357
Largest diff. peak and hole	0.501 and -0.292 $e.Å^{-3}$

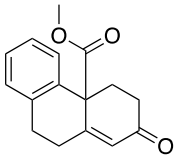
Racemic Michael addition and Robinson annulation

Methyl 2-oxo-3,4,9,10-tetrahydrophenanthrene-4a(2*H*)-carboxylate. (49)



Ethyl 2-oxocyclohexane-1-carboxylate was dissolved in toluene (4 mL/mmol) then, methyl vinyl ketone (1.1 equiv), and potassium carbonate (0.6 equiv) were added at room temperature. The mixture was stirred for 12h. Then, the reaction mixture was filtered through celite and washed with DCM. The filtrate was concentrated under reduced pressure. The product was submitted to the following

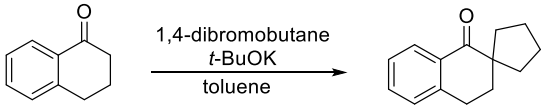
step directly. It was dissolved in DCM, and pyrrolidine (1.0 equiv) and acetic acid (1.0 equiv) were added at 0 ºC, and the reaction mixture was stirred 17h at room temperature. To the mixture was added water and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.



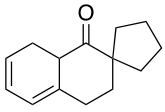
On a 10 mmol scale, **49** was isolated as a yellow oil with 69% yield (1.62 g). Spectroscopic data in agreement with the one previously described.[251] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.00 – 2.10 (m, 1H), 2.54 (dddd, *J* = 17.9, 4.6, 2.4, 1.0 Hz, 1H), 2.61 – 2.79 (m, 2H), 2.85 – 2.93 (m, 1H), 2.96 – 3.14 (m, 3H), 3.68 (s, 3H), 6.03 (t, *J* = 1.2 Hz, 1H), 7.13 – 7.16 (m, 1H), 7.20 – 7.26 (m, 2H), 7.47 (dd, *J* = 7.4, 1.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.4, 32.8, 36.1, 50.4, 53.1, 126.6, 126.9, 127.3, 127.6, 129.2, 136.2, 136.8, 162.5, 172.0, 198.7.

Synthesis of Intermediate III of the Hofmann-Löffler reaction

3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-1'-one. (65)



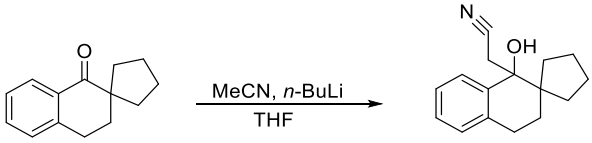
The commercially available α-tetralone was dissolved in toluene, and *t*-BuOK (2.0 equiv) is added at room temperature. The mixture is stirred for 30 min at this temperature, then 1,4-dibromobutane (1.0 equiv) is added, the reaction is warmed to reflux for 5 h. The mixture was cooled down to rt and quenched by the addition of 1M HCl, extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.



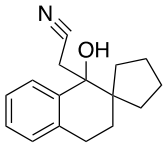
On a 10 mmol scale, **65** was isolated as a yellow oil with 76% yield (1.53 g). Spectroscopic data in agreement with the one previously described.[252] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.49 – 1.58 (m, 2H), 1.66 – 1.74 (m, 2H), 1.74 – 1.83 (m, 2H), 2.03 – 2.06 (m, 2H), 2.09 – 2.16 (m, 2H), 2.99 (t, *J* = 6.2 Hz, 2H), 7.21 (dp, *J* = 7.8, 0.9 Hz, 1H), 7.29 (tdd, *J* = 8.0, 2.0, 0.8 Hz, 1H), 7.44 (td, *J* = 7.4, 1.5 Hz, 1H), 8.04 (dd, *J* = 7.8, 1.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.5, 26.6, 35.3, 53.2, 126.5, 127.9, 128.5, 131.8, 132.9, 143.6, 202.5.

[252] B. C. Ranu, U. Jana *J. Org. Chem.* **1999**, *64*, 6380.

2-(1'-hydroxy-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-1'-yl)acetonitrile. (66)

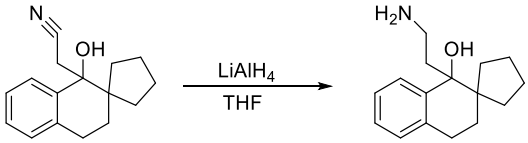


n-BuLi (3.0 equiv, 2.5M in cyclohexanes) was added to anhydrous THF (2 mL/mmol) at -78ºC, then MeCN (3.6 equiv) was added. The mixture was stirred for 1 hour, then 3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-1'-one was added; the reaction mixture was stirred at -78ºC for 3 h. The reaction could warm to room temperature and quench by the addition of NH_4Cl, extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.

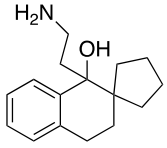


On a 4 mmol scale, **66** was isolated as a colorless oil with 55% yield (0.53 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.34 – 1.59 (m, 4H), 1.60 – 1.72 (m, 1H), 1.74 – 1.90 (m, 3H), 1.97 – 2.16 (m, 1H), 2.71 (d, *J* = 16.4 Hz, 1H), 2.81 – 2.91 (m, 2H), 2.93 – 3.02 (m, 1H), 7.06 – 7.15 (m, 1H), 7.19 – 7.30 (m, 2H), 7.75 – 7.81 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.2, 25.5, 26.3, 30.4, 31.3, 34.1, 49.6, 75.0, 117.8, 125.9, 126.4, 128.1, 129.0, 135.5, 140.2. **IR** ν(cm^{-1}): 3467, 2946, 2869, 1055, 769, 726. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{19}NNaO$, 264.1359; found, 264.1353.

1'-(2-aminoethyl)-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-1'-ol. (67)

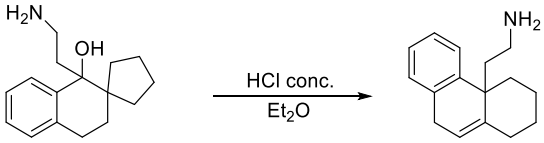


A flame-dried Schlenk equipped with a stirrer bar was charged with $LiAlH_4$ (3.0 equiv), anhydrous THF was added carefully, and the mixture was cooled to 0 ºC. The corresponding cyano compound (1.0 equiv) was added dropwise to the $LiAlH_4$/THF suspension under argon atmosphere. The mixture was warmed up to room temperature and stirred for 3 h; then, it was cooled to 0 ºC. A solution of NaOH (1M) was added. After filtration over Na_2SO_4 and evaporation of the solvent under reduced pressure, the crude amine was obtained in quantitative yield and was directly used in the following step.



On a 2 mmol scale, **67** was isolated as a colorless oil with quant. yield (0.49 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.10 – 1.19 (m, 1H), 1.25 – 1.34 (m, 2H), 1.49 – 1.76 (m, 10H), 1.86 – 1.95 (m, 2H), 2.14 – 2.24 (m, 1H), 2.72 – 2.85 (m, 2H), 2.87 – 2.97 (m, 2H), 7.05 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.15 (dddd, *J* = 16.2, 8.8, 4.9, 2.3 Hz, 3H), 7.62 (dd, *J* = 7.6, 1.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.3, 26.0, 26.2, 31.3, 34.7, 37.7, 50.1, 75.6, 78.2, 124.9, 126.2, 126.6, 128.7, 135.8, 144.0. **IR** ν(cm^{-1}): 3361, 2941, 2865, 1469, 1036, 754. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{16}H_{24}NO$, 246.1852; found, 246.1851.

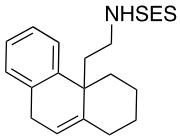
2-(1,3,4,9-tetrahydrophenanthren-4a(2*H*)-yl)ethan-1-amine



1'-(2-aminoethyl)-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-1'-ol was dissolved in Et_2O (2 mL/mmol), then HCl conc. (12M in H_2O) was added. The mixture was stirred at reflux for 12h. To this mixture, water and DCM were added, the organic layer was discarded. The aqueous layer was basified to pH 12 and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude amine was submitted to the following step without purification.

***N*-(2-(1,3,4,9-tetrahydrophenanthren-4a(2H)-yl)ethyl)-2-(trimethylsilyl)ethane-1-sulfonamide. (69)**

The 2-(1,3,4,9-tetrahydrophenanthren-4a(2H)-yl)ethan-1-amine was dissolved in anhydrous DCM (5 mL/mmol), and then triethylamine (2.0 equiv) and SESCl (1.5 equiv) were added carefully at ºC. Then, the mixture reaction was allowed to warm to rt overnight. To the mixture was added NH_4Cl and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.

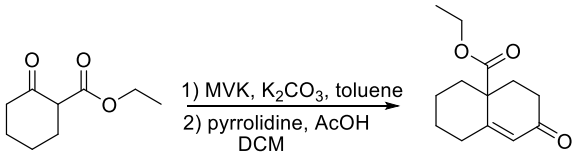


On a 2 mmol scale of compound 67, **69** was isolated as a yellowish oil with 71% yield (0,55 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.01 (s, 9H), 0.82 – 0.94 (m, 3H), 1.26 – 1.35 (m, 1H), 1.54 – 1.60 (m, 2H), 1.71 – 1.83 (m, 2H), 2.16 – 2.24 (m,

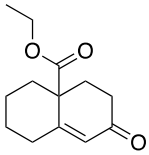
1H), 2.27 – 2.37 (m, 1H), 2.56 – 2.66 (m, 2H), 2.69 – 2.77 (m, 2H), 2.79 – 2.92 (m, 1H), 3.40 (t, *J* = 3.2 Hz, 2H), 3.85 (s, 1H), 5.70 – 5.76 (m, 1H), 7.08 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.15 (td, *J* = 7.4, 1.4 Hz, 1H), 7.21 (ddd, *J* = 7.9, 7.1, 1.6 Hz, 1H), 7.27 – 7.30 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = -1.9, 10.7, 22.9, 27.7, 29.9, 33.1, 38.8, 40.3, 41.1, 41.4, 48.4, 119.4, 125.7, 126.3, 126.9, 128.5, 133.6, 138.1, 141.5. **IR** ν(cm^{-1}): 3221, 2927, 2857, 1342, 975.

Decaline system

Ethyl 7-oxo-1,3,4,5,6,7-hexahydronaphthalene-4a(2H)-carboxylate. (70)



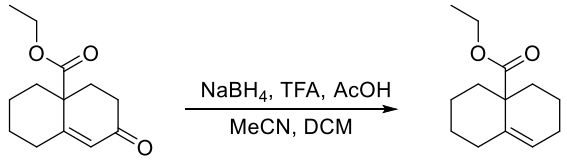
Ethyl 2-oxocyclohexane-1-carboxylate was dissolved in toluene (4 mL/mmol) then, methyl vinyl ketone (1.1 equiv), and potassium carbonate (0.6 equiv) were added at room temperature. The mixture was stirred for 12 h. Then, the reaction mixture was filtered through celite and washed with DCM. The filtrate was concentrated under reduced pressure. The product was submitted to the following step directly. It was dissolved in DCM, and pyrrolidine (1.0 equiv) and acetic acid (1.0 equiv) were added at 0 ºC, and the reaction mixture was stirred 17 h at room temperature. To the mixture was added water and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane



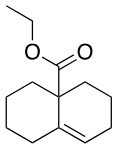
On a 10 mmol scale, **70** was isolated as a yellow oil with 56% yield (1.24 g).Spectroscopic data in agreement with the one previously described.[253] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.24 – 1.29 (m, 4H), 1.30 – 1.35 (m, 1H), 1.39 – 1.50 (m, 2H), 1.71 – 1.76 (m, 1H), 1.89 (ddt, *J* = 9.9, 7.5, 2.1 Hz, 2H), 2.28 – 2.37 (m, 3H), 2.39 – 2.47 (m, 3H), 4.02 – 4.30 (m, 2H), 5.92 (q, *J* = 1.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 14.4, 23.3, 26.7, 34.4, 34.9, 35.0, 38.6, 49.1, 61.6, 126.7, 163.3, 173.5, 199.0.

Ethyl 1,3,4,5,6,7-hexahydronaphthalene-4a(2H)-carboxylate. (71)

[253] C. L. Diedrich, W. Frey, J. Christoffers, *Eur. J. Org. Chem.* **2007**, 4731.

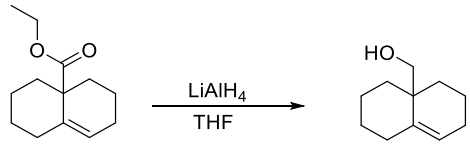


To a cooled solution of MeCN (0,5 mL/mmol), TFA (2.5 mL/mmol) and glacial acetic acid (2.5 mL/mmol), $NaBH_4$ (12.0 equiv) was added. The mixture was stirred for 5 min at 0 ºC, starting material dissolved in DCM (1 mL/mmol) was added dropwise for 5 min. The reaction mixture was stirred for 2 h at 0 ºC. To the mixture was added water and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.

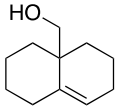


On a 6.5 mmol scale, **71** was isolated as a yellow oil with 89% yield (1.2 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = δ 1.08 – 1.31 (m, 5H), 1.35 – 1.76 (m, 6H), 1.93 – 2.09 (m, 3H), 2.17 (dq, *J* = 7.6, 2.2 Hz, 2H), 2.28 (dq, *J* = 12.5, 2.2 Hz, 1H), 4.17 (qt, *J* = 7.1, 0.7 Hz, 2H), 5.49 – 5.58 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 14.5, 19.5, 24.1, 25.6, 27.8, 34.3, 36.5, 38.6, 48.5, 60.6, 122.7, 138.3, 176.6. **IR** ν(cm^{-1}): 3429, 2933, 2861, 1719, 1190, 1012. **HRMS** (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{20}NaO_2$, 231.1356; found, 234.1353.

(1,3,4,5,6,7-hexahydronaphthalen-4a(2H)-yl)metanol. (72)



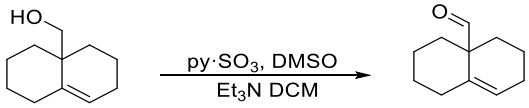
A flame-dried Schlenk equipped with a stirrer bar was charged with $LiAlH_4$ (2 equiv), anhydrous THF was added carefully, and the mixture was cooled to 0 ºC. The ester **71** was added dropwise to the $LiAlH_4$/THF suspension under an argon atmosphere. The mixture was stirred for 2 h at rt and then cooled to 0 ºC. A solution of NaOH (1 M) was added. After filtration over Na_2SO_4 and evaporation of the solvent under reduced pressure, the crude amine was obtained in quantitative yield and was directly used in the following step.



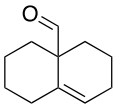
On a 5.7 mmol scale, **72** was isolated as a yellow oil with 98% yield (0.92 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.12 – 1.20 (m, 3H), 1.24 – 1.34 (m, 1H), 1.50 – 1.58 (m, 3H), 1.59 – 1.69 (m, 1H), 1.70 – 1.80 (m, 2H), 1.86 (ddd, *J* = 13.4, 6.4, 3.2 Hz, 1H), 1.96 (tt, *J* = 5.9, 3.0 Hz, 2H), 2.00 – 2.05 (m, 1H), 2.10 (dddd, *J* = 11.3, 8.7, 5.7, 3.0 Hz, 1H), 3.63 (dd, *J* = 75.8, 11.0 Hz, 2H), 5.57 (td, *J* = 3.9, 1.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$):

δ = 19.2, 22.4, 25.8, 28.3, 32.9, 34.3, 35.9, 40.2, 65.1, 124.1, 139.9. **IR** ν(cm^{-1}): 3297, 2923, 2853, 1044, 1029. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{11}H_{17}$, 149.1325; found, 149.1325.

1,3,4,5,6,7-hexahydronaphthalene-4a(2H)-carbaldehyde. (73)

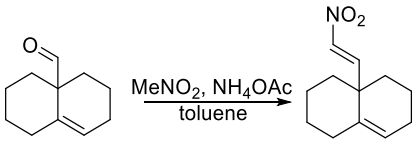


The corresponding alcohol **72** was dissolved in DCM (5 mL/mmol), then pyridine sulfur trioxide (4.0 equiv), triethylamine (10.0 equiv), and DMSO (2.8 mL/mmol) were added at 0 ºC. After 1 h at this temperature, to this mixture 1 M HCl was added and extracted with DCM (3x), the organic layer was washed with $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.

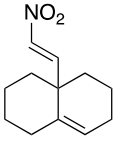


On a 5.0 mmol scale, **73** was isolated as a yellow oil with 82% yield (0,67 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.20 – 1.43 (m, 5H), 1.51 – 1.62 (m, 1H), 1.64 – 1.69 (m, 1H), 1.70 – 1.78 (m, 1H), 1.84 – 1.93 (m, 1H), 1.99 – 2.22 (m, 5H), 5.71 (td, *J* = 3.7, 1.8 Hz, 1H), 9.44 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 19.0, 23.7, 25.5, 27.5, 32.2, 34.0, 35.4, 52.2, 124.4, 136.3, 205.3. **IR** ν(cm^{-1}): 3420, 2928, 1702, 1439, 1173, 948.

(E)-4a-(2-nitrovinyl)-1,2,3,4,4a,5,6,7-octahydronaphthalene. (74)



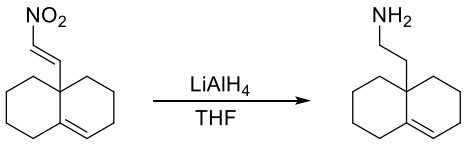
To a solution of the corresponding aldehyde and ammonium acetate (5.7 equiv) in CH_3NO_2 (2 mL/mmol), toluene (0.6 mL/mmol) was added. The mixture was stirred at 100 ºC overnight. The mixture was concentrated under vacuum, and the residue was dissolved in DCM, washed with $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.



On a 4,7 mmol scale, **74** was isolated as a yellow oil with 89% yield (0,87 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.25 – 1.30 (m, 1H), 1.32 – 1.35 (m, 1H), 1.38 (ddt, *J* = 7.3, 3.4, 1.7 Hz, 1H), 1.44 (dd, *J* = 13.4, 3.3 Hz, 1H), 1.55 – 1.61 (m, 2H), 1.64 – 1.73 (m, 2H), 1.75 (dtd, *J* = 10.4, 2.7, 1.4 Hz, 1H), 1.92 (dq, *J* = 12.9, 2.7 Hz, 1H), 1.99 – 2.04 (m, 2H), 2.05 – 2.13 (m, 2H), 5.58 – 5.64 (m, 1H), 6.82 (d, *J* = 13.5 Hz, 1H), 7.11 (d, *J* = 13.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 17.89, 23.7, 25.5, 27.8, 32.9, 36.6,

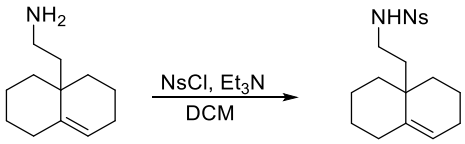
41.4, 41.4, 124.7, 136.9, 141.9, 149.9. **IR** ν(cm^{-1}): 2927, 2854, 1520, 1347, 995. **HRMS** (m/z): [M+Na]$^+$ calcd. for $C_{12}H_{17}NNaO_2$, 230.1151; found, 230.1152.

2-(1,3,4,5,6,7-Hexahydronaphthalen-4a(2H)-yl)ethan-1-amine.

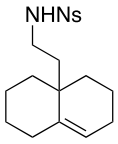


A flame-dried Schlenk equipped with a stirrer bar was charged with $LiAlH_4$ (2.0 equiv), anhydrous THF was added carefully, and the mixture was cooled to 0 ºC. The corresponding nitro compound (1.0 equiv) was added dropwise to the $LiAlH_4$/THF suspension under argon atmosphere. The mixture was warmed up to reflux and stirred for 3 h; then, it was cooled to 0 ºC. A solution of NaOH (1M) was added. After filtration over Na_2SO_4 and evaporation of the solvent under reduced pressure, the crude amine was obtained in quantitative yield and was directly used in the following step.

***N*-(2-(1,3,4,5,6,7-hexahydronaphthalen-4a(2H)-yl)ethyl)-4-nitrobenzenesulfonamide. (75)**

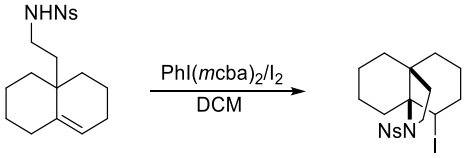


2-(1,3,4,5,6,7-Hexahydronaphthalen-4a(2H)-yl)ethan-1-amine was dissolved in anhydrous DCM (5 mL/mmol) and then triethylamine (2.0 equiv) and NsCl (1.5 equiv) were added carefully at ºC. Then, the mixture reaction was allowed to warm to rt overnight. To the mixture was added NH_4Cl and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.

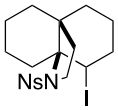


On a 1.2 mmol scale, **75** was isolated as a yellow oil with 72% yield (0.31 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.12 – 1.28 (m, 3H), 1.37 – 1.61 (m, 7H), 1.70 – 1.77 (m, 1H), 1.79 – 1.87 (m, 2H), 1.88 – 1.97 (m, 2H), 1.99 – 2.05 (m, 1H), 2.87 – 3.09 (m, 2H), 4.56 (t, *J* = 6.0 Hz, 1H), 5.40 (td, *J* = 4.0, 1.6 Hz, 1H), 7.99 – 8.09 (m, 2H), 8.37 (dq, *J* = 9.2, 2.2 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 19.4, 22.2, 25.7, 28.4, 32.6, 35.3, 35.8, 37.2, 38.9, 39.8, 121.9, 124.5, 128.4, 142.3, 146.3, 150.2. **IR** ν(cm^{-1}): 3252, 2925, 2854, 1529, 1430, 1155. 735. **HRMS** (m/z): [M-H]$^-$calcd. for $C_{18}H_{23}N_2O_4S$, 363.1384; found, 363.1381.

(4aS,8aR)-4-iodo-11-((4-nitrophenyl)sulfonyl)octahydro-4a,8a-(epiminoethano)naphthalene. (76)



The corresponding sulfonamide **75** was dissolved in dry DCM (15 mL/mmol) then, PhI(*m*cba)$_2$ (2.0 equiv) and I_2 (0.5 equiv) were added. The reaction was stirred at rt 2 h under white LEDs. To the mixture were added $Na_2S_2O_3$ and $NaHCO_3$ and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using a gradient of ethyl acetate and hexane.



On a 0.2 mmol scale, **76** was isolated as a yellow oil with 55% yield (53 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.21 – 1.26 (m, 1H), 1.28 – 1.34 (m, 1H), 1.39 – 1.66 (m, 7H), 1.69 – 1.78 (m, 1H), 1.80 – 1.91 (m, 1H), 1.97 (td, *J* = 14.0, 4.9 Hz, 1H), 2.09 – 2.21 (m, 1H), 2.21 – 2.31 (m, 1H), 2.33 – 2.43 (m, 1H), 2.99 – 3.10 (m, 2H), 3.59 (d, *J* = 9.3 Hz, 1H), 4.41 (dd, *J* = 13.3, 4.3 Hz, 1H), 8.26 – 8.38 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.1, 22.6, 24.1, 28.4, 28.7, 31.5, 36.1, 39.0, 43.8, 45.2, 47.8, 76.6, 123.9, 129.8, 146.6, 149.9. **IR** ν(cm^{-1}): 2922,01691, 1527, 1302, 688. **HRMS** (m/z): $[M-H]^-$calcd. for $C_{18}H_{23}IN_2O_4S$, 513.0315; found, 513.0309.

5. Overall conclusions

This Doctoral Thesis aimed at extending the Csp^3-H bond functionalization by applying the Hofmann-Löffler reaction for the synthesis of complex molecules. The most important conclusions are summarized below:

1. We investigated the interrupted Hofmann-Löffler reaction for the generation of multiple halogenated compounds. Our unprecedented strategy allows for selective halogenation via 1,5/1,6-HAT processes. Acyclic and acyclic compounds were selectively halogenated, where multiple and mixed halogenation was also achieved. Moreover, several control experiments were carried out to test the mechanism of the transformation.

2. We develop an efficient method to generate the pyrrolidine ring employing the Hofmann-Löffler reaction. Specifically, we have demonstrated that the Hofmann-Löffler reaction can be applied for the late-stage amination in the presence of a pyridine core, which allowed developing efficient syntheses of nicotine, the pharmaceutical compound Altinicline, and other nicotine analogs, including bipyridine derivatives.

3. Finally, we investigated the application of the Hofmann-Löffler reaction to synthesize the tetracyclic core of the hasubanan family of alkaloids. We observed an unprecedented iodine-catalyzed elimination/difunctionalization/elimination sequence that forms the pyrrolidine unit along with an additional carbon-carbon double bond. This cascade process opens access to more complex alkaloid structures due to the possibility of further diversification of the new double bond formed. Furthermore, we investigated the behavior of the intermediate of the transformation under the same conditions. Finally, we tested the same reaction conditions to an unsaturated decaline system.

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