NEW METHODOLOGY FOR C-N BOND FORMATION WITHIN IODINE REDOX MANIFOLDS

Alexandra Eleni Bosnidou

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New Methodology for C-N Bond Formation within Iodine Redox Manifolds

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Alexandra Eleni Bosnidou

DOCTORAL THESIS

2019

New Methodology for C-N Bond Formation within Iodine Redox Manifolds

Alexandra Eleni Bosnidou

Doctoral Thesis

Supervised by Prof. Dr. Kilian Muñiz Klein

Institute of Chemical Research of Catalonia (ICIQ)

Tarragona
2019

Prof. Dr. Kilian Muñiz Klein, Group Leader at the Institute of Chemical Research of Catalonia (ICIQ) and Research Professor at the Catalan Institution for Research and Advanced Studies (ICREA):

I confirm that the present thesis manuscript, entitled “New Methodology for C-N Bond Formation within Iodine Redox Manifolds”, presented by Alexandra Eleni Bosnidou to receive the degree of Doctor, has been carried out under my supervision at the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, September 2nd, 2019

Doctoral Thesis Supervisor

Prof. Dr. Kilian Muñiz Klein

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List of publications resulting from this Thesis

Towards Uniform Iodine Catalysis: Intramolecular C−H Amination of Arenes under Visible Light. Claudio Martínez, Alexandra E. Bosnidou, Simon Allmendinger, Kilian Muñiz *Chem. Eur. J.* **2016**, *22*, 9929-9932.

Iodine(III)-Mediated Selective Intermolecular C-H Amination for the Chemical Diversification of Tryptamines. Alexandra E. Bosnidou, Alba Millán, Javier Ceballos, Clauddio Martínez, Kilian Muñiz *J. Org. Chem*. **2016**, *81*, 6496-6504.

Multiple Halogenation of Aliphatic C-H Bonds within the Hofmann-Löffler Manifold. Estefania Del Castillo, Mario D. Martínez, Alexandra E. Bosnidou, Thomas Duhamel, Calvin Q. O'Broin, Hongwei Zhang, Eduardo C. Escuerdo–Adán, Marta Martínez–Belmonte, Kilian Muñiz. *Chem. Eur. J*. **2018**, *24*, 17225-17229.

Intermolecular Radical C(sp^3)-H Amination under Iodine Catalysis. Alexandra E. Bosnidou, Kilian Muniz. *Angew. Chem. Int. Ed*. **2019**, *58*, 7485-7489.

Alkyliodines in High Oxidation State: Enhanced Synthetic Possibilities and Accelerated Catalyst Turn-Over. Alexandra E. Bosnidou, Kilian Muñiz, *Chem. Eur. J.* 10.1002/chem.201902687.

List of Abbreviations

Ac	Acetyl
Ar	Aryl
BDE	Bond Dissociation Energy
Bn	Benzyl
Boc	*Tert*-butyloxy carbonyl
Bz	Benzoyl
CT	Charge Transfer
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DG	Directing Group
DMAP	4-Dimethylaminopyridine
DME	Dimethoxy ethane
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl sulfoxide
EDA	Electron Donor-Acceptor-complex
EPR	Electron Paramagnetic Resonance
ESI	Electron Spray Ionization
Equiv	Equivalent
G	Gauss
HAT	Hydrogen Atom Transfer
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HRMS	High-Resolution Mass Spectrometry
Ipy$_2$BF$_4$	bis(pyridinium)iodonium (I) tetrafluoroborate
IUPAC	International Union of Pure and Applied Chemistry
KIE	Kinetic Isotope Effect
LDA	Lithium Diisopropylamide
***m*CBA**	*m*-chlorobenzoic acid
mCPBA	*meta*-Chloroperbenzoic acid

MHz	Megahertz
MO	Molecular Orbital
m.p.	Melting Point
Ms	Methanesulfonyl / Mesyl
NHPI	*N*-Hydroxyphthalimide
NIS	N-Iodosuccinimide
NMR	Nuclear magnetic resonance
Ns	4-Nitrobenzenesulfonyl / Nosyl
PhthNH	Phthalimide
PIDA	(Diacetoxyiodo)benzene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
Ph	Phenyl
PMB	*para*-Methoxy benzene
Py	Pyridine
Red-Al	Sodium bis(2-methoxyethoxy) aluminum hydride
r.t.	Room Temperature
SET	Single-Electron-Transfer
TBAF	Tetrabutylammonium Fluoride
TBAI	Tetrabutylammonium Iodide
Tf	Trifluoromethanesulfonyl / Triflyl
TFA	Trifluoroacetic Acid
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
TMSI	Trimethylsilyl Iodide
Ts	Toluenesulfonyl / Tosyl
UV	UltraViolet
°C	Celcius degrees
3c-4e	Three-center-four-electron

Table of Contents

Summary of the Thesis

This Thesis represents major advances in the field of carbon-nitrogen bond construction. Green alternatives to common synthetic methodologies have been developed with the use of hypervalent iodine reagents and molecular iodine as main promoters.

The first part deals with the use of defined hypervalent iodine reagents that promote the selective direct C-H-amination of the indole core of various tryptamines. Starting from the general amination, subsequent transformations, such as iodination, fluorination, etc. were performed to afford higher-functionalized products with a noteworthy high chemo-selectivity. As the result of this study, a higher degree of structural diversification has become available for tryptamine derivatives, providing building blocks that open chemical space for further exploration.

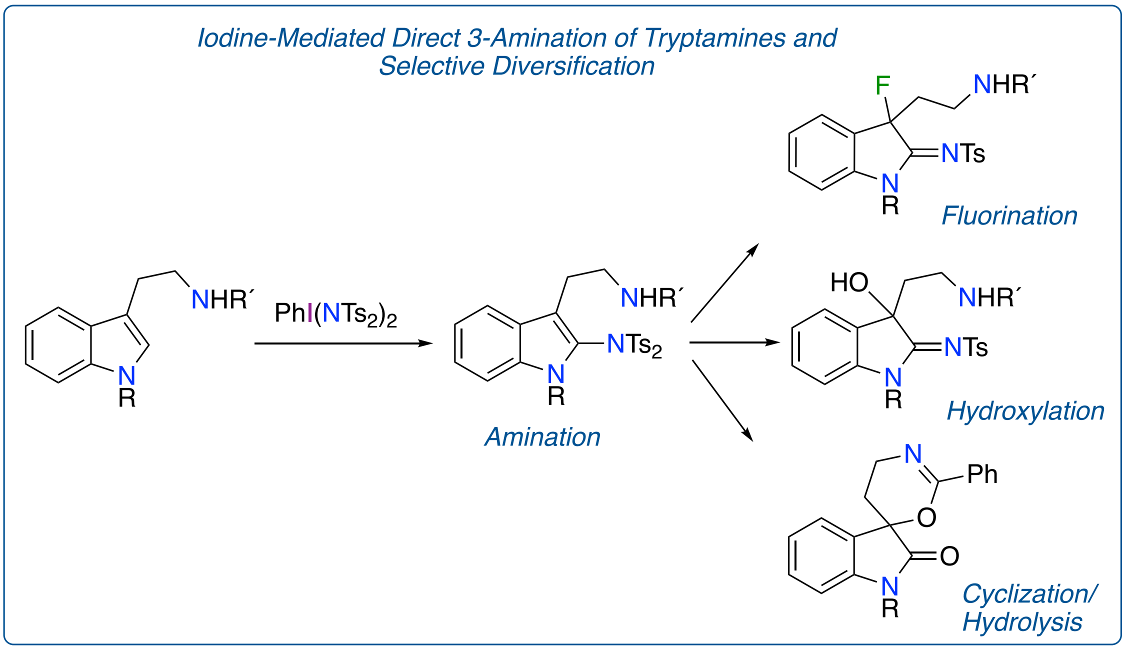

Figure I: Site-selective amination and further diversification at tryptamine cores.

The second part of this manuscript is dedicated to a photochemical catalytic amination of arenes. The reaction proceeds under benign iodine catalysis in the presence of visible light as the initiator and provides access to a range of differently substituted arylamines. A total of 29 examples demonstrate the broad applicability of this mild oxidation method. The scope of the reaction could further be expanded to silyl-tethered derivatives, which undergo intramolecular amination upon formation of seven-membered heterocycles. Cleavage of the silicon tether provides access to the corresponding 3-substitued anilines.

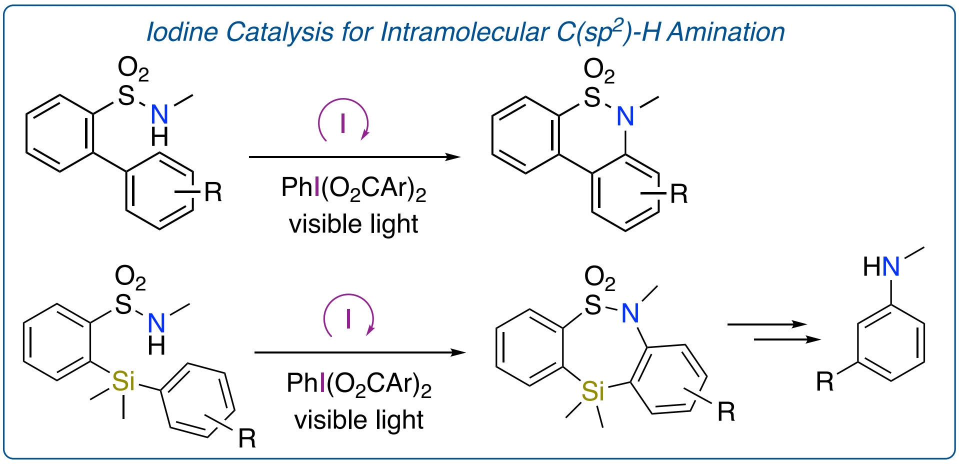

Figure II: Iodine catalyzed intramolecular C(sp^2)-H amination.

The direct amination of aliphatic C-H bonds has remained one of the most challenging transformations in organic chemistry. In the third part of this thesis, we report the elusive intermolecular C(sp^3)-H amination under a unique catalyst system, based on the recently developed intramolecular amination. This practical synthetic strategy allows the access to aminated building blocks. An extension that fosters innovative multiple C-H amination toward aminated heterocycles is also presented. The synthetic utility of the methodology is demonstrated by the synthesis of four relevant pharmaceuticals.

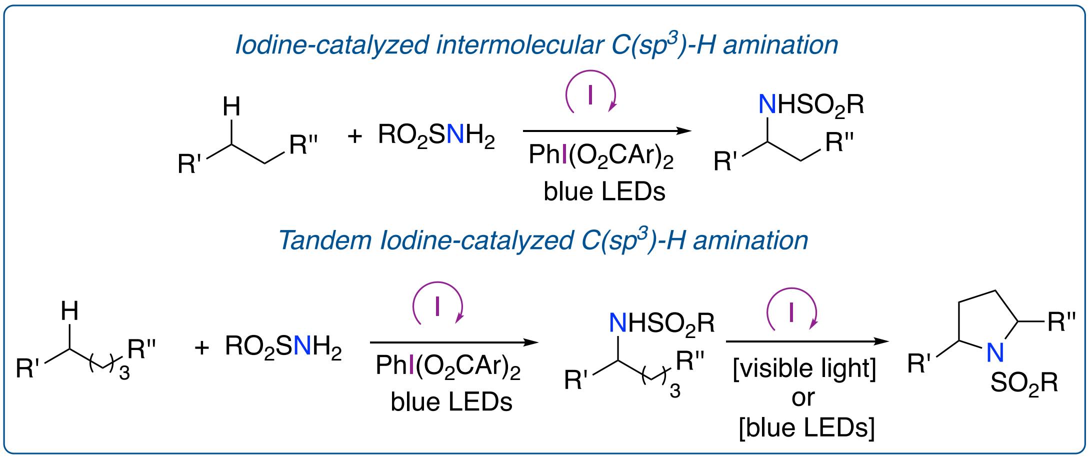

Figure III: Iodine catalysis for intermolecular C(sp^3)-H amination and tandem amination.

Chapter I. General Introduction

1.1 C-N bond presence in Nature

In Nature amines are frequently-found structural features with a broad range of applications in primary and secondary metabolism.[1] Primary metabolites, which are essential for the survival of the manufacturer, such as nucleobases or amino acids, are inconceivable without the amine functionality, that is a major structural feature in almost all biomolecules. Also secondary metabolites, which are substances that bring selection advantages in the fight for survival, commonly contain the amine functionality.[2] A very important family of the latter natural product class are the alkaloids, the structural characteristic of which is the amine functionality and that shows a broad range of bioactivity. They can thus be used as lead structures for example in drug design or crop protection.[3]

In Nature, the installation of the amino group proceeds through pre-oxidized intermediates. Among several examples, the biosynthesis of L-p-hydroxyphenylglycine, which is a crucial feature in different bioactive peptidic natural products, is relying on the formation of the corresponding ketone.[4] Oxygenated or halogenated substrates are required in these cases, that can efficiently be transformed through biocatalytic pathways to the target amine.[5] These approaches limit the functionalization of more complex structures, as they are mainly required in de novo syntheses. Thus, direct intermolecular amination, in a general concept of C-H functionalization, is considered the key to obtain nitrogenated molecules in a logical and economic fashion.[6]

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[1] A. Ricci (Ed.), *Amino Group Chemistry: From Synthesis to the Life Sciences*; Wiley−VCH, Weinheim, Germany, **2007**.

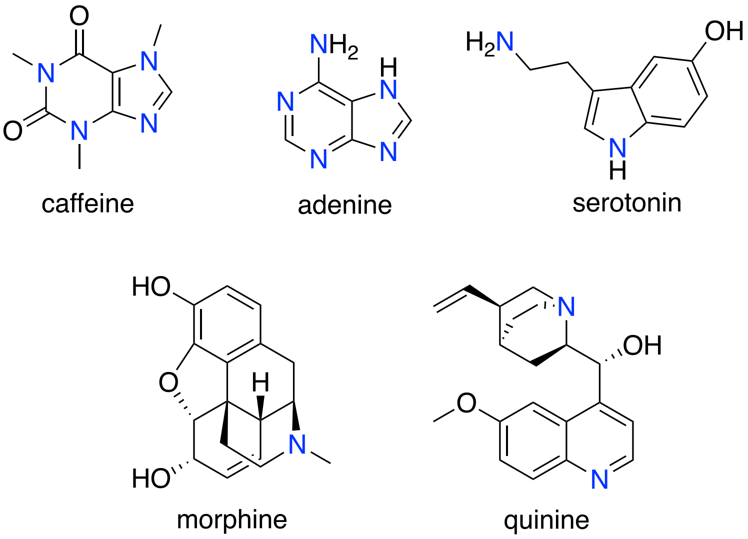
[2] R. Hili, A. K. Yudin, *Nature Chem. Biol.* **2006**, 2, 283.

[3] a) T. Eicher, S. Hauptmann, A. Speicher, *Chemistry of Heterocycles: Structure, Reactions, Synthesis and Applications*, Wiley New York **2013**; b) L. D. Quin, J. A. Tyrell, *Fundamentals of Heterocyclic Chemistry,* Wiley, **2010**.

[4] B. K. Hubbard, M. G. Thomas, C. T. Walsh, *Chem. Biol.* **2000**, *7*, 931.

[5] J. Yamaguchi, A. D. Yamaguchi, K. Itami, K. *Angew. Chem. Int. Ed*. **2012**, *51*, 8960.

[6] W. Gutenkunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976.



caffeine adenine serotonin

morphine quinine

Figure 1.1: Selected examples of nitrogenated molecules in Nature.

1.2 C-H amination in organic synthesis

The direct and selective functionalization of C-H bonds constitutes a long-standing goal for the synthetic organic community, as it leads to an increase in molecular complexity by using simpler precursors.[7] The interplay of reactivity and selectivity in the activation of C-H bonds remains a very challenging task, as the molecular properties of these structural subunits are often very similar and all present in the same molecule.[8]

In this context, oxidative amination reactions are highly important. Nature does not provide an efficient enzymatic solution for the direct amination of hydrocarbons as it was discussed in section 1.1. In order to address this problem, biochemists have developed artificially optimized enzymes. This research topic has attracted a lot of attention lately and was awarded with the Nobel Prize of Chemistry 2018, which one of the outstanding pioneers of this field, Frances Arnold, received for her work on directed evolution.[9] The activity and promiscuity of enzymes can be systematically optimized for reactions via directed evolution. By using different strategies to insert mutations into the DNA strain encoding for the target enzyme, an enormous library of genetically modified biocatalysts is produced. Via functionality screenings the most active sequence is detected and used for further optimization. Beside increasing stability, functionality and substrate tolerance

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[7] a) H. M. Davies, J. Du Bois, J.-Q. Yu, *Chem. Soc. Rev.* **2011**, *40*, 1855; b) W. Gutenkunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976.

[8] F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev.* **2011**, *40*, 1926.

[9] H. Renata, Z. J. Wang, F. H. Arnold, *Angew. Chem. Int. Ed.* **2015**, *54*, 3351.

it can also be used for the creation of new enzymatic functions.[10] As an example genetically optimized enzymes have been used for amination reactions, through nitrene transfer to furnish nitrogenated molecules.[11] On the other side, chemists have developed various transformations that employ either cross coupling reactions or direct aminations.[12] This thesis focuses on the chemical direct transformations for the generation of amines. The former are commonly dominated by transition metal catalysis. Although, this concept leads the field and displays powerful reactivity, the specific topic of regioselectivity has remained an issue in the presence of different kinds of weak C-H bonds.[13] Alternative methods include amination reactions that are promoted under metal-free conditions; therefore they constitute an attractive and environment-friendly approach towards the synthesis of biomolecules. Hypervalent iodine(III) reagents are well-known and widely established in synthetic chemistry due to their high reactivity for the general activation and functionalization of hydrocarbons.[14]

The first part of the introduction will focus on the dominant amination reactions classified according to their mechanistic pathways.

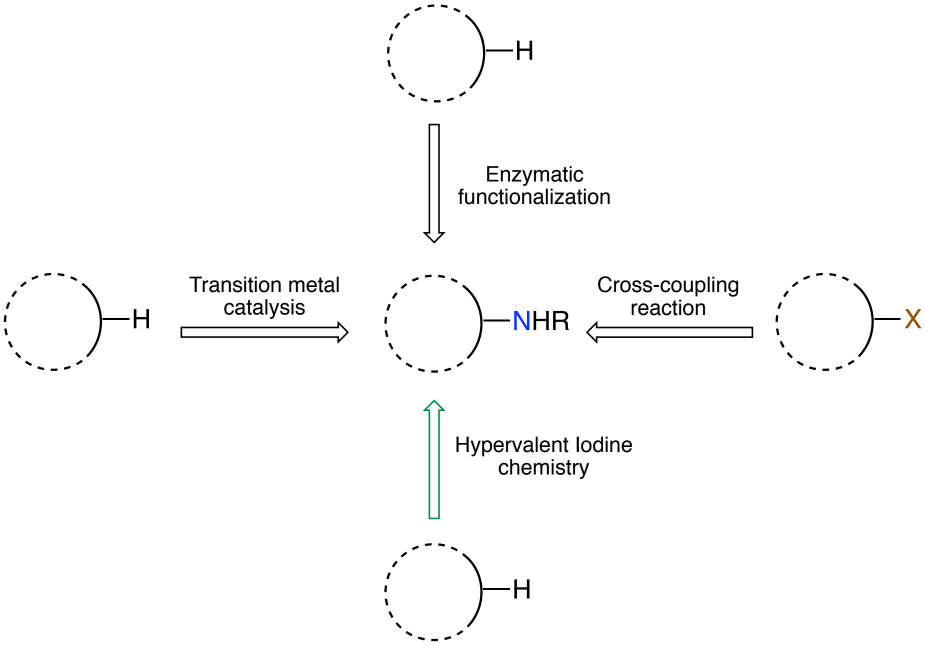

Figure 1.2: Approaches to nitrogen-functionalized molecules.

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[10] a) F. H. Arnold, *Angew. Chem. Int. Ed.* **2018**, *57*, 4143; b) F. H. Arnold, *Rev. Biophys.* **2015**, *48*, 404.

[11] a) R. K. Zhang, D. K. Romney, S. B. J. Kan, F. H. Arnold. *Directed evolution of artificial metallo-enzymes: bridging synthetic chemistry and biology*. **2017**; b) J. C. Lewis, P. S. Coelho, F. H. Arnold, *Chem. Soc. Rev.* **2011**, *40*, 2003.

[12] F. Collet, C. Lescot, P. Dauban, *Chem. Comm.* **2009**, 5061.

[13] E. N. Bess, R. J. DeLuca, D. J. Tindall, M. S. Oderinde, J. L. Roisen, J. Du Bois, M. S. Sigman, *J. Am. Chem. Soc.* **2014**, *136*, 5783.

[14] a) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328; b) T. Wirth (Ed.), *Hypervalent Iodine Chemistry*, *Top Curr Chem* **2016**.

1.3 Transition metal catalyzed C-H amination

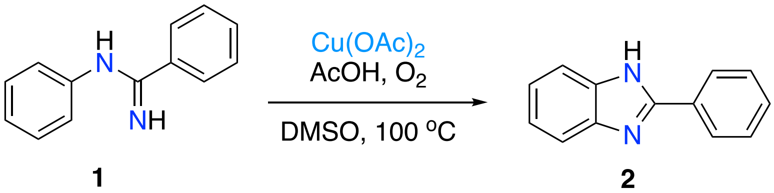
Transition metal catalyzed reactions are classified into three categories according to the mechanistic pathways that they follow:

- Catalytic C-H activation (metal coordination to the substrate)
- C-H insertion catalysis (metal coordination to the aminating agent)
- Photoredox catalysis (nitrogen-centered radicals)

1.3.1 Catalytic C-H activation

The first step of the reaction involves the metal coordination to the organic substrate. In this case the functional groups that are present in the molecule are directing the coordination of the metal to the desired C-H bond. The metalation induces polarization of the bond and increases the nucleophilicity on the carbon center. As a result, the nitrogen source can interact with the activated bond and the aminated products get accessible.

The use of functional groups, that address the metal ion complexation in a chemoselective reaction, has received a lot of attention. In the case of intramolecular amination reactions, the directing group often coincides with the nitrogen source. Several groups have reported aromatic amination reactions for the formation of heterocycles.[15] Among them is the synthesis of benzimidazoles **2**, via the Cu-catalyzed cyclization of *N*-phenylbenzamidine **1** reported by Buchwald (Scheme 1.1).[16]



Scheme 1.1: Synthesis of benzimidazoles via Cu-catalyzed intramolecular amination.

Intramolecular aminations have also been applied successfully in the synthesis of carbazoles, which are frequently found structural motives in more complex organic

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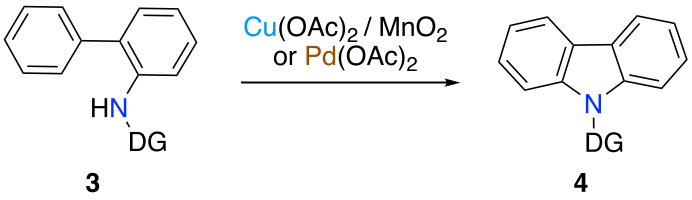
[15] Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247.

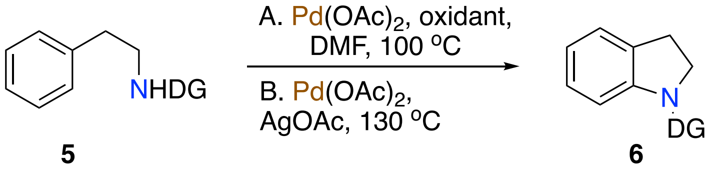
[16] G. Brasche, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2008**, *47*, 1932.

molecules. In 2014, Miura reported a synthetic route toward this compound class with copper(II) acetate as a catalyst in combination with manganese oxide.[17] Apparently, the reaction requires excessive amounts of manganese and microwave irradiation at high temperatures. In addition, Buckwald and Gaunt independently reported the use of palladium acetate for aerobic oxidation towards carbazoles **4**.[18] Also, Stahl described the aerobic palladium-catalyzed cyclization of **3** that generates carbazoles **4** in good yields (Scheme 1.2).[19]



Scheme 1.2: Metal-catalyzed synthetic routes toward carbazoles.

After Buckwald's report on the synthesis of nitrogenated rings, several groups started working on the synthesis of indazoles,[20] oxindoles[21] and indoles[22] which have been synthesized predominantly via palladium catalysis. Also indolines **6**, as important azaheterocycles, can be produced using this strategy. Hereby different oxidants or metal combinations can be used, as shown recently by Yu and Daugulis (Scheme 1.3).[23]



Scheme 1.3: Palladium catalyzed synthesis of indolines.

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[17] K. Takamatsu, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2014**, *16*, 2892.

[18] a) W. C. P. Tsang, N. Zheng, S. L. Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560; b) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M Beck, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 16184.

[19] A. B. Weinstein, S. S. Stahl, *Catal. Sci. Technol.* **2014**, *4*, 4301

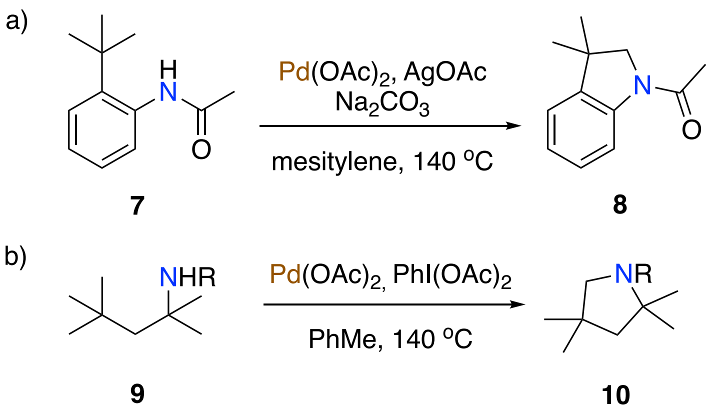
[20] K. Inamoto, T. Saito, M. Katsuno, T. Sakamoto, K. Hiroya, *Org. Lett.* **2007**, *9*, 2931.

[21] T. Miura, Y. Ito, M. Murakami, *Chem. Lett.* **2009**, *38*, 328.

[22] K. Clagg, H. Hou, A. B. Weinstein, D. Russell, S. S. Stahl, S. G. Koenig, *Org. Lett.* **2016**, *18*, 3586; b) D. J. Lee, E. J. Yoo, *Org. Lett.* **2015**, *17*, 1830.

[23] a) T. S. Mei, X. Wang, J.-Q Yu, *J. Am. Chem. Soc.* **2009**, *131*, 10806; b) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7.

An alternative synthesis of indolines **8** based on C(sp^3)-H amination via palladium catalyzed intramolecular amination was reported by Glorius (Scheme 1.4a).[24] Later on, Daugulis described a second pyrrolidine synthesis that proceeds through the chelation of palladium with picolinamide **9** (Scheme 1.4b).[25] Interestingly, other groups reported different sizes of the formed rings under similar reaction conditions.[26] The palladium in these cases seems to be the privileged metal as catalyst source. Though, intramolecular aminations towards the formation of azetidines with nickel or copper are present in the literature too.[27]



Scheme 1.4: Synthesis of indolines (a) and pyrrolidines (b) under palladium catalysis.

Along these lines, the more challenging intermolecular amination has been developed likewise. A variety of directing groups that allows the chelation of the metals with different aminating agents give rise to a great variety of aminations on arenes. For example, derivatives of morpholine **12** or morpholine **12a** have been extensively used for aminations of aromatic cores **11** (Scheme 1.5). Nakamura demonstrated the use of chloramines **12b** as aminating agents with Fe(II) based catalysts.[28] Cobalt, in combination with morpholine **12a**, was used for the formation of **13** by Niu and Song.[29] Daugulis demonstrated an aromatic amination with morpholine **12a** under Cu(II) catalysis.[30] Nickel

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[24] J. J Neumann, S. Rakshit, T. Dröge, F. Glorius, *Angew. Chem., Int. Ed.* **2009**, *48*, 6892.

[25] T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7.

[26] a) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3; b) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129.

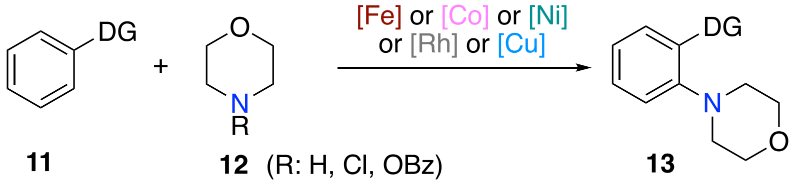
[27] a) Z. Wang, J. Ni, Y. Kuninobu, M. Kanai, *Angew. Chem. Int. Ed.* **2014**, *53*, 3496; b) X. Wu, Y. Zhao, G. Zhang, H. Ge, *Angew. Chem. Int. Ed.* **2014**, *53*, 3706; c) X. Wu, Y. Zhao, H. Ge, *Chem. Eur. J.* **2014**, *20*, 9530.

[28] T. Matsubara, S. Asako, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2014**, *136*, 646.

[29] L.-B. Zhang, S.-K. Zhang, D. Wei, X. Zhu, X.-Q. Hao, J.-H. Su, J.-L. Niu, M.-P. Song, *Org. Lett.* **2016**, *18*, 1318.

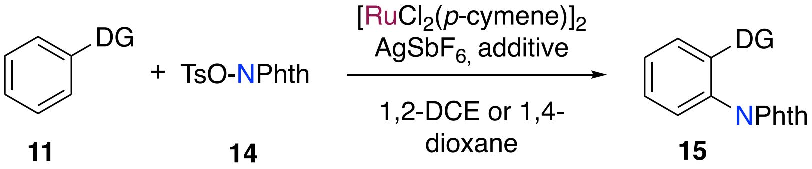
[30] L. D. Tran, J. Roane, O. Daugulis, O. *Angew. Chem. Int. Ed.* **2013**, *52*, 6043.

is the transition metal that has been used least in amination reactions. However, a Ni-based catalyst system for amination with the use of morpholine **12c** was reported by Zhang.[31] Glorius reported the use of N-chloro morpholine **12b** under rhodium catalysis for the same transformation toward **13**.[32]



Scheme 1.5: Intermolecular C(sp^2)-H amination of arenes with morpholine derivatives.

An additional class of aminating agents, containing N-O bonds was developed by Yu, who reported the amination of simple arenes **11** with O-benzoylhydroxylamines **14**, under palladium or ruthenium catalysis, for the generation of the aniline derivatives **15** (Scheme 1.6).[33] The direct C-H functionalization with ruthenium catalysts and a variety of chelating groups including O- and N- chelators was demonstrated by Sahoo and Ackermann.[34] N-substituted hydroxylamines have been also used by Chang, in an iridium-catalyzed C(sp^2)-H amidation.[35]



Scheme 1.6: Intermolecular C(sp^2)-H amination of arenes with N-O bond containing aminating agents.

2-Phenylpyridine **16** appears to be an interesting model substrate, due to its inherent binding ability with metals and general propensity for cyclometallation. Thus it has been used extensively for the selective formation of **17** with different metal catalysts (Scheme 1.7). Rhodium is the transition metal which has received certainly most attention,

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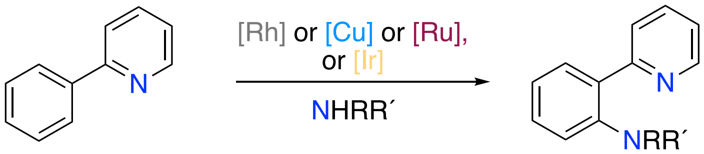
[31] Q. Yan, Z. Chen, W. Yu, H. Yin, Z. Liu, Y. Zhang, *Org. Lett.* **2015**, *17*, 2482.
[32] C. Grohmann, H. Wang, F. Glorius, *Org. Lett.* **2012**, *14*, 656.
[33] a) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan, J.-Q Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7652; b) M. Shang, S.-H. Zeng, S.-Z. Sun, H.-X. Dai, J.-Q. Yu, *Org. Lett.* **2013**, *15*, 5286.
[34] a) M. R. Yadav, M. Shankar, E. Ramesh, K. Ghosh, A. K. Sahoo, *Org. Lett.* **2015**, *17*, 1886; b) K. Raghuvanshi, D. Zell, K. Rauch, L. Ackermann, *ACS Catal.* **2016**, *6*, 3172.
[35] P. Patel, S. Chang, *Org. Lett.* **2014**, *16*, 3328.

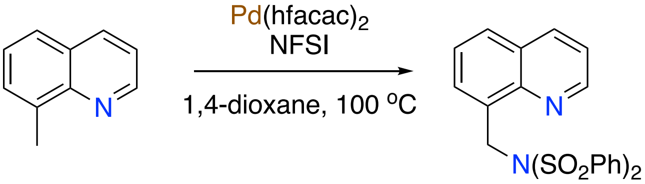
especially for aminations reactions. Amination of 2-phenylpyridines under rhodium catalysis has been reported by several groups.[36] Yu and Chatani independently reported the ortho-amination of 2-phenylpyridine **16** by copper (II) acetate.[37] Ruthenium catalysis has been implemented by Chang group for the same purpose.[38]



16 **17**

Scheme 1.7: Metal-catalyzed amination of 2-phenylpyridine.

Che reported an intermolecular C(sp^3)-H amination of unactivated bonds via palladium catalysis.[39] Quinolines **18** alkylated at the C8 position have been studied thoroughly, and had been successfully aminated under iridium,[40] rhodium[41] and cobalt[42] catalysis. Interestingly, Muñiz implemented NFSI and palladium catalysis for the generation of 8-aminated quinolines **19** (Scheme 1.8).[43]



18 **19**

Scheme 1.8: Amination of 8-methyl quinoline under palladium catalysis.

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[36] a) Y. Park, S. Jee, J. G. Kim, S. Chang, *Org. Process Res. Dev.* **2015**, *19*, 1024; b) R.-J. Tang, C.-P. Luo, L. Yang, C.-J. Li, *Adv. Synth. Catal.* **2013**, *355*, 869; c) H. Zhao, Y. Shang, W. Su, *Org. Lett.* **2013**, *15*, 5106.

[37] a) X. Chen, X. S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790; b) T. Uemura, S. Imoto, N. Chatani, *Chem. Lett.* **2006**, *35*, 842.

[38] K. Shin, J. Ryu, S. Chang, *Org. Lett.* **2014**, *16*, 2022.

[39] H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc*. **2006**, *128*, 9048.

[40] T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 4141.

[41] H. Wang, G. Tang, X. Li, *Angew. Chem. Int. Ed.* **2015**, *54*, 13049.

[42] N. Barsu, M. A. Rahman, M. Sen, B. Sundararaju. *Chem. Eur. J.* **2016**, *22*, 9135.

[43] A. Iglesias, R. Alvarez, A. R. de Lera, K. Muniz, *Angew. Chem. Int. Ed.* **2012**, *51*, 2225.

1.3.2 C-H insertion catalysis

Historically, Breslow and Gellman were the first who reported the synthetic feasibility of a catalytic nitrene transfer in the tosylamidation of cyclohexane.[44] Later on, Mansui used iminoiodanes as nitrene precursors for the catalytic aziridination of olefins.[45] The mechanism of the C-H insertion is not always clear. Two pathways might be followed. In the concerted one, the organic substrate is coordinating with the nitrenoid which upon reductive elimination is yielding the final aminated product. The term nitrene complex refers to the complex between the coordinated metal and the nitrene. The second postulated pathway involves a stepwise hydrogen atom transfer from the substrate to the nitrene complex and is followed by radical recombination (Figure 1.3).

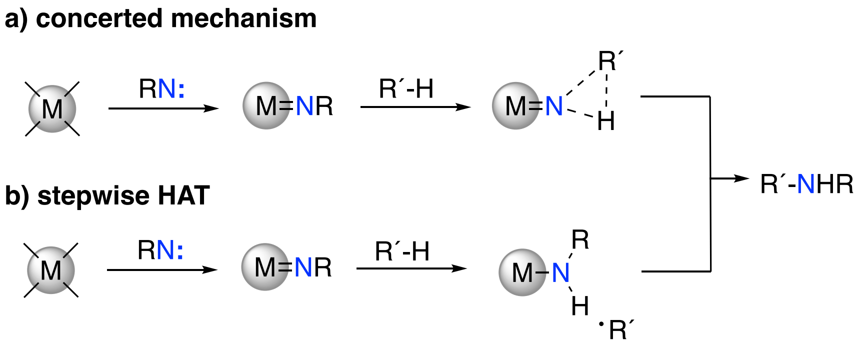

Figure 1.3: Mechanistic pathways in C-H insertion pathway.

The formation of heterocycles with transition metal catalysts relies on pre-coordination assisted C-H activation methods. Thus few nitrene insertions are known, which are dominated by rhodium- or iron-nitrenoid catalysis. The main application for these is the synthesis of substituted indoles. Interestingly, the starting materials and the mechanism of the reactions are varying. Driver reported the aromatic intramolecular amination of **20** and **22** towards indoles **21** and **23** respectively, through Rh-nitrenoid species (Scheme 1.9).[46] Mechanistic studies of the reaction revealed a cationic cyclic intermediate as the key step for the amination.[47] Other metals, such as ruthenium and iron have been used for

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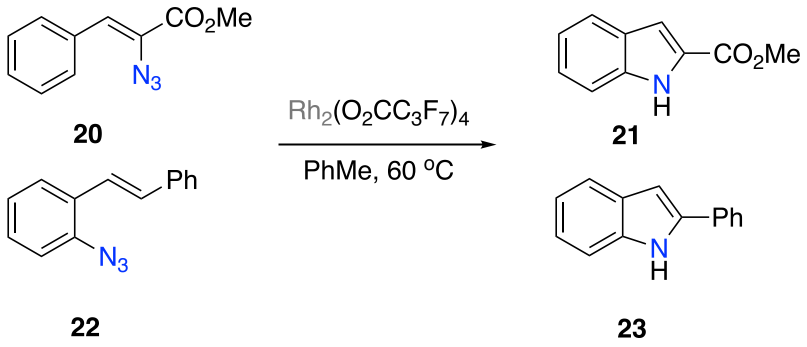
[44] a) R. Breslow, S. H. Gellman, *J. Chem. Soc., Chem. Commun*. **1982**, 1400; b) R. Breslow, S. H. Gellman, *J. Am. Chem. Soc*. **1983**, *105*, 6728.

[45] D. Mansuy, J.-P. Mahy, A. Dureault, G. Bedi, P. Battioni, *J. Chem. Soc., Chem. Commun*. **1984**, 1161.

[46] a) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey, T. G. Driver, T. G. *J. Am. Chem. Soc*. **2007**, *129*, 7500; b) M. Shen, B. E. Leslie, T. G. Driver, *Angew. Chem. Int. Ed*. **2008**, *47*, 5056; c) B. J. Stokes, B. Jovanovic, H. Dong, K. J. Richert, R. D. Riell, T. G. Driver, *J. Org. Chem*. **2009**, *74*, 3225.

[47] Q. Zhang, C. Wu, L. Zhou, J. Li, *Organometallics* **2013**, *32*, 415.

the same purpose.[48] Worthy to note is the fact that this chemistry follows the general transformation for the formation of indoles, described by Hemetsberger and Knittel, back in 1972.[49]



Scheme 1.9: Synthesis of substituted indoles through C(sp^2)-H amination.

Metalloporphyrins dominate the field on C(sp^3)-H aminations. Che as one of the main contributors to this field has developed amination reactions on unactivated C-H bonds with the use of porphyrin ligands in combination with different metals. Among them, Mn-porphyrin complexes have been described for the intramolecular amination of saturated bonds.[50] Co(II) porphyrins have been developed for the same purpose.[51] Iron and ruthenium porphyrin complexes have been also implemented independently by Che and Cenini.[52] Interestingly, in the intramolecular amination with Fe(III) porphyrins, the C-H insertion occurs in a stepwise manner (see Fig. 1.3). White has reported the intramolecular C(sp^3)-H amination of **24** with the use of Mn(III)porphyrin catalysts, to furnish 1,3-aminoalcohols **25** (Scheme 1.10).[53]

Apart from porphyrins, salen type ligands have been introduced with different metals for the successful amination of unactivated bonds. Katsuki has developed Ir(III) (salen)

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[48] a) W. G. Shou, J. Li, T. Guo, Z. Lin, G. Jia, *Organometallics* **2009**, *28*, 6847; b) J. Bonnamour, C. Bolm, *Org. Lett.* **2011**, *13*, 2012; c) Y. Liu, G.-Q. Chen, C.-W. Tse, X. Guan, Z.-J. Xu, J.-S. Huang, C.-M. Che, *Chem. Asian J.* **2015**, *10*, 100.

[49] a) H. Hemetsberger, D. Knittel, *Monatsh. Chem.* **1972**, *103*, 194; b) D. Knittel, *Synthesis***1985**,186.

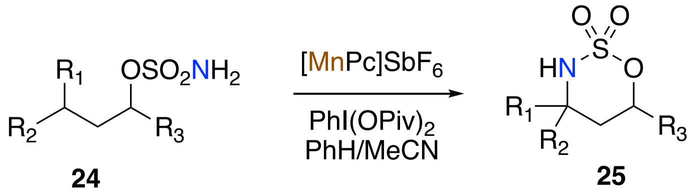
[50] X.-Q. Yu, J.-S. Huang, X.-G. Zhou, C.-M. Che, *Org. Lett.* **2000**, *2*, 2233.

[51] F. Ragaini, A. Penoni, E. Gallo, S. Tollari, C. Li Gotti, M. Lapadula, E. Mangioni, S. Cenini, *Chem. Eur. J.* **2003**, *9*, 249.

[52] a) Y. Liu, C.-M. Che, *Chem. Eur. J.* **2010**, *16*, 10494; b) S. Cenini, S. Tollari, A. Penoni, C. Cereda, *J. Mol. Catal. A: Chem.* **1999**, *137*, 135.

[53] S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller, C. M. White, *Nat. Chem.* **2015**, *7*, 987.

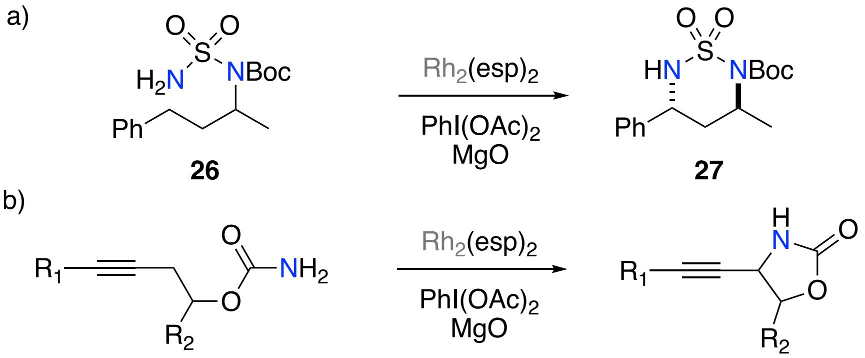
catalysts for the synthesis of indoles and carbazoles.[54] The use of other iridium catalysts was also implemented by Driver and coworkers for the same purpose.[55]



24 **25**

Scheme 1.10: Intramolecular C(sp^3)-H amination with the use of Mn(III)porphyrin catalysts.

The highlighting metal in the field of metal nitrenoids is certainly rhodium. The groups of Du Bois and Dauban independently have explored this field with several examples on amination reaction in addition to extensive mechanistic insights. The use of iminoiodanes, generated by secondary amines and (diacetoxyiodo)benzene, in combination with different rhodium dimer complexes led to the synthesis of 1,3 diamines **27** and aminations at propargylic positions, as in the examples **28** for the generation of oxazilidones **29** (Scheme 1.11).[56]



26 **27** **28** **29**

Scheme 1.11: a) Synthesis of 1,3-diamines; b) Amination at propargylic position.

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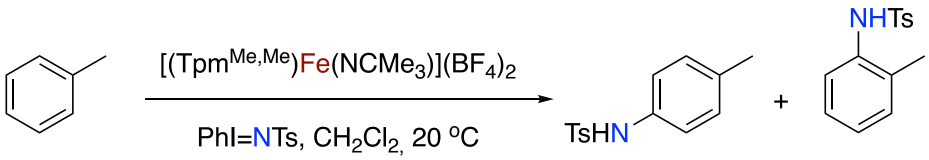
[54] M. Ichinose, H. Suematsu, Y. Yasutomi, Y. Nishioka, T. Uchida, T. Katsuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 9884.

[55] K. Sun, R. Sachwani, K. J. Richert, T. G. Driver, *Org. Lett.* **2009**, *11*, 3598.

[56] a) C. G. Espino, P. M. Wehn, J. Chow, J. Du Bois, *J. Am. Chem. Soc.* **2001**, *123*, 6935; b) T. Kurokawa, M. Kim, J. Du Bois, *Angew. Chem. Int. Ed.* **2009**, *48*, 2777; c) J. J. Fleming, K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2003**, *125*, 2028; d) R. D. Grigg, J. W. Rigoli, S. D. Pearce, J. M. Schomaker, *Org. Lett.* **2012**, *14*, 280.

Extended studies on the mechanism indicate that the reactions proceed with rhodium nitrenoids by a stepwise insertion into the C-H bond (see Fig. 1.3). Last but not least, asymmetric Rh-catalyzed C-H insertions allowed the formation of chiral amines. Davies and Du Bois are considered pioneers in this field.[57]

The intramolecular aromatic amination based on nitrene insertion is not common. This reaction requires two steps: direct C-H insertion and homolytic C-H cleavage are both energetically not favorable. Few reports on metal nitrenoid insertions are present in literature. The use of neocuproine Cu(I) for arene amination was described by Nicholas.[58] Jensen described the selective amination of toluene with a variety of metal complexes, including manganese, cobalt, nickel and iron.[59] Interestingly, the amination of toluene **30** with the iron complex does not take place at the available benzylic position but at the aromatic core affording a regioisomeric mixture of **31** (Scheme 1.12).



30

31 (1:0.7)

Scheme 1.12: Aromatic amination of toluene with the use of iron catalyst.

In contrast, nitrene insertion processes in intermolecular C(sp3)-H amination reactions are well-known. Several transition metals have been implemented for this purpose. Herein the discussion will be structured following their position in the periodic table. Starting from group VII, a manganese-catalyzed benzylic amination with the use of iminoiodane as nitrene precursor has been described by White recently.[60] Moving to group VIII, iron-based catalysis have been successfully introduced by Betley in the amination of cyclohexene **32** toward the allylic amine **33** (Scheme 1.13).[61] Gallo also described the synthesis and application of similar Ru(VI) complexes for the same transformation (Scheme 1.13).[62] Ruthenium based catalysts can be also applied in

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[57] 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.

[58] A. John, J. Byun, K. M Nicholas, *Chem. Commun.* **2013**, *49*, 10965.

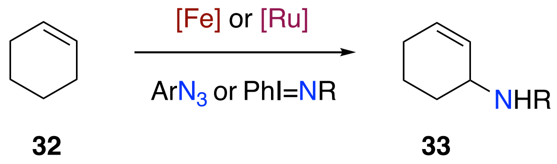
[59] S. Liang, M. P. Jensen, *Organometallics* **2012**, *31*, 8055.

[60] J. R. Clark, K. Feng, A. Sookezian, C. White, *Nat. Chem.* **2018**, *10*, 583.

[61] D. A. Iovan, T. A. Betley, *J. Am. Chem. Soc.* **2016**, *138*, 1983.

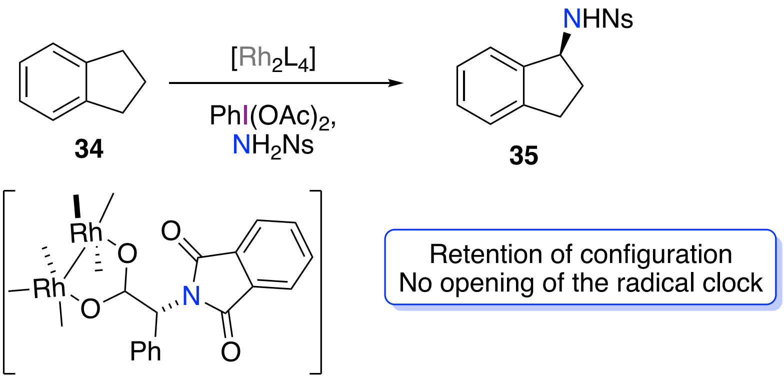
[62] D. Intrieri, A. Caselli, F. Ragaini, P. Macchi, N. Casati, E. Gallo, E. *Eur. J. Inorg. Chem.* **2012**, 569.

asymmetric intermolecular aminations, as demonstrated by Katsuki, who disclosed a chiral salen Ru(II) catalyst for the amination at benzylic and allylic positions.[63]



Scheme 1.13: Catalytic Intermolecular allylic amination of cyclohexene with iron or ruthenium complexes.

Rhodium belongs to group IX and represents one of the main elements for these aminations. An extension of the intramolecular amination developed by Du Bois was applied for the amination of tertiary carbon centers.[64] Extensive mechanistic studies were performed for this reaction.[65] A concerted pathway for the insertion of the Rh(II) dimer is postulated by Muller[66] and supported by Du Bois for the intermolecular asymmetric amination of indan **34** (Scheme 1.14). Interestingly, the reaction proceeds with retention of configuration while radical involvement is excluded as they did not observe any radical clock opening in the related control experiment.[67] This reaction constitutes a different approach than the one from Bach, who proposed a stepwise process for the hydrogen abstraction and radical recombination.[68]



Retention of configuration
No opening of the radical clock

Scheme 1.14: Concerted mechanism in Rh-catalyzed intermolecular amination of indan.

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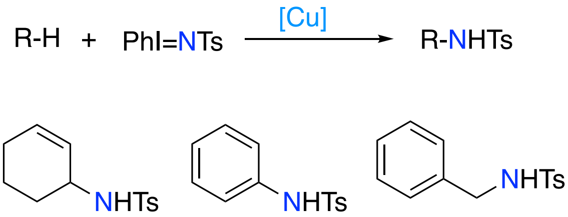
[63] Y. Nishioka, T. Uchida, T. Katsuki, *Angew. Chem. Int. Ed.* **2013**, *52*, 1739.
[64] J. L. Roizen, D. N. Zalatan, J. Du Bois, *Angew. Chem., Int. Ed.* **2013**, *52*, 11343.
[65] J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012,** *45*, 6911.
[66] I. Nağeli, C. Baud, G. Bernardinelli, Y. Jacquier, M. Moran, P. Müller, *Helv. Chim. Acta* **1997**, *80*, 1087.
[67] a) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562; b) K. W. Fiori, C. G. Espino, B. H. Brodsky, J. Du Bois, *Tetrahedron* **2009**, *65*, 3042.
[68] T. Hoke, E. Herdtweck, T. Bach, *Chem. Commun.* **2013**, *49*, 8009.

Transitions metals belonging to group X such as nickel or palladium are rather used for direct C-H activation than insertion through nitrenoids. Ending with metals of group XI, copper nitrenoids were introduced by Pérez in both cases of aliphatic and aromatic intermolecular aminations, as demonstrated in a variety of aminated products such as **36-38** (Scheme 1.15).[69] Interestingly, a tripodal copper complex was reported by Stavropoulos for the intermolecular amination of C(sp^3)-H bonds.[70]



36 **37** **38**

Scheme 1.15: Copper-catalyzed intermolecular amination over allylic, aromatic and aliphatic positions.

A silver-catalyzed amination of benzylic C-H bonds with bathophenanthroline ligands was described by He.[71] Finally, an unusual gold catalyzed intermolecular amination using pyridine or bipyridine ligands was developed by Feng[72] completing the field of transition metal catalyzed intermolecular aminations.

1.3.3 Photoredox catalysis

Next to the addition of nitrenoids, nitrogen-centered radicals can also be involved in the amination. The development and studies of nitrogen-centered radicals is a new approach in this field and still remains relatively elusive. In this context, a single electron transfer process (SET) may be involved by the use of photoredox catalysts. An example on the application of photoredox catalysis is the synthesis of azaheterocycles, that was described

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[69] a) A. Caballero, A.; M. M. Díaz-Requejo, T. R. Belderraín, M. C. Nicasio, S. Trofimenko, P. J. Peŕez, *J. Am. Chem. Soc.* **2003**, *125*, 1446; b) M. R. Fructos, S. Trofimenko, M. Diaz-Requejo, P. J. Perez, *J. Am. Chem. Soc.* **2006**, *128*, 11784.

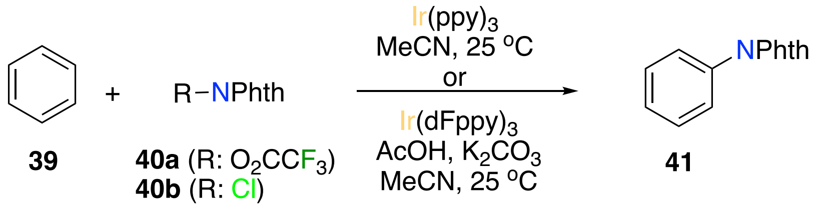
[70] V. Bagchi, P. Paraskevopoulou, P. Das, L. Chi, Q. Wang, A. Choudhury, J. S. Mathieson, L. Cronin, D. B. Pardue, T. R. Cundary, G. Mitrikas, Y. Sanakis, P. Stavropoulos, *J. Am. Chem. Soc.* **2014**, *136*, 11362.

[71] Z. Li, D. A. Capretto, R. Rahaman, C. He, *Angew. Chem. Int. Ed.* **2007**, *46*, 5184.

[72] Y. Zhang, B. Feng, C. Zhu, *Org. Biomol. Chem.* **2012**, *10*, 9137.

by Zheng for the synthesis of indoles, where he reported ruthenium based photocatalysts for the generation of nitrogen-centered radicals.[73] Some years later, Yu developed a protocol for the synthesis of phenanthridines, quinolines and pyridines based on iridium photocatalysts.[74]

Intermolecular aminations have even received more attention. Sanford reported the amination of arenes **39** with N-acyloxyphthalamides **40a**, in the presence of an Iridium photocatalyst, under mild reaction conditions.[75] Lee has improved the reaction, regarding the atom economy, by N-chlorophthalamide **40b** as radical precursor that allows the generation of the phthalimide protected anilines **41** using a lower catalyst loading and equimolar amounts of the aminating agent and the substrate (Scheme 1.16).[76] An elegant approach for a selective intermolecular amination of arenes via photoredox catalysis was reported by Nicewicz too.[77] Yu described the amination on several heteroaromatic rings, including indoles, benzofurans, pyrroles and furans.[78] Interestingly, a Minisci type-addition of radical nucleophiles to pyridines and pyrrolidines, via iridium photocatalyst, has been reported recently by Phipps.[79] This approach allows for enantioselective additions within the photoredox catalysis concept. Finally, the report from König on aromatic intermolecular amination with the use of benzoylazides as imydyl radical precursors close the strategic highlights of this section.[80]



Scheme 1.16: Use of N-protected phthalamides and iridium photoredox catalysts for intramolecular amination of arenes.

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[73] S. Maity, N. Zheng, *Angew. Chem. Int. Ed.* **2012**, *51*, 9562.
[74] Q. Qin, S. Yu, *Org. Lett.* **2014**, *16*, 3504.
[75] L. J. Allen, P. J. Cabrera, M. Lee, M. S. Sanford, *J. Am. Chem. Soc.* **2014**, *136*, 5607.
[76] H. Kim, T. Kim, D. G. Lee, S. W. Roh, C. Lee, *Chem. Commun.* **2014**, *50*, 9273.
[77] N. A. Romero, K. A. Margrey, N. E. Tay, D. A. Nicewicz, *Science* **2015**, *349*, 6254.
[78] Q. Qin, S. Yu, *Org. Lett.* **2014**, *16*, 3504.
[79] R. S. J. Proctor, H. J. Davis, R. J. Phipps, *Science* **2018**, *360*, 419.
[80] E. Brachet, T. Ghosh, I. Ghosh, B. König, *Chem. Sci.* **2015**, *6*, 987.

1.4 Hypervalent Iodine: A green alternative to transition metals

Iodine is the heaviest non-radioactive element belonging to Group XVII of the periodic table. The reactivity of iodine is quite different from the other halogens, as it is the least electronegative and most polarizable among them. Iodine may be resembled to transition metals due to its variety of oxidation states, structural features and reactivity pattern in organic transformations.[14] The first polyvalent organic iodine compound was reported by C. Willgerodt, in 1886.[81] Over the years, polyvalent iodine compounds have gained more and more popularity as they are less costly and less toxic, thus environmentally friendly, in contrast to transition metals.

1.4.1 Hypervalent iodine: Structure and bonding

Hypervalent iodine compounds can be classified by their oxidation states. In general, heavier elements such as Si, P, S and the halogens can form compounds with higher valences, that exceed the Lewis octet rule. Back in 1969, Musher introduced the term hypervalent for the description of compounds, in groups 15-18 of the periodic table, that are not following the typical 2c-2e Lewis bonding.[82]

Initially, iodine(III) reagents were called iodinanes, while periodinanes was used for the description of iodine(V) compounds. The terms λ^3-iodanes and λ^5-iodanes respectively were given by IUPAC later.

Aryl-λ^3-iodanes possess pseudotrigonal bipyramid geometry, where the free electron pairs of iodine and the aryl group are placed in equatorial positions providing a T-shaped structure of the compound (Figure 1.4a).

The aryl group is bonded to the iodine center with a σ-bond. According to molecular orbital theory, the model of three center-four electron (3c-4e) provides an understanding of the structure of the iodine-ligand bonds (Figure 1.4b). The hypervalent bonds exhibit a highly polarized nature due to the fact that the electrons of the bonding pair are delocalized to the more electronegative atoms. This polarization explains the electrophilic character at the iodine center, as well as the disposition of the most electronegative atoms,

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[81] C. Wilgerodt, *J. Prakt. Chem.* **1886**, *33*, 154.

[82] J. I. Musher, *Angew. Chem. Int. Ed.* **1969**, *8*, 54.

commonly the ligands, at the apical positions. The least electronegative carbon substituents are creating a normal covalent bond that appears in the equatorial position.

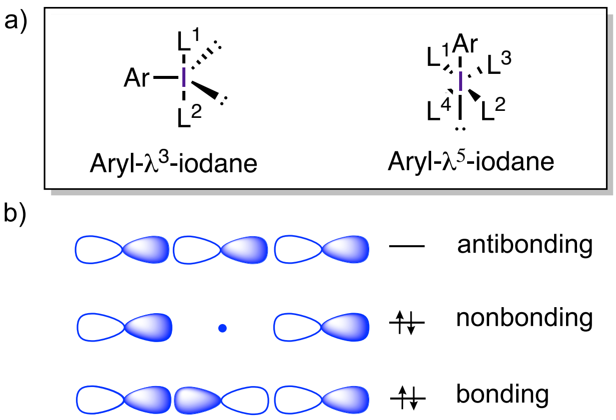
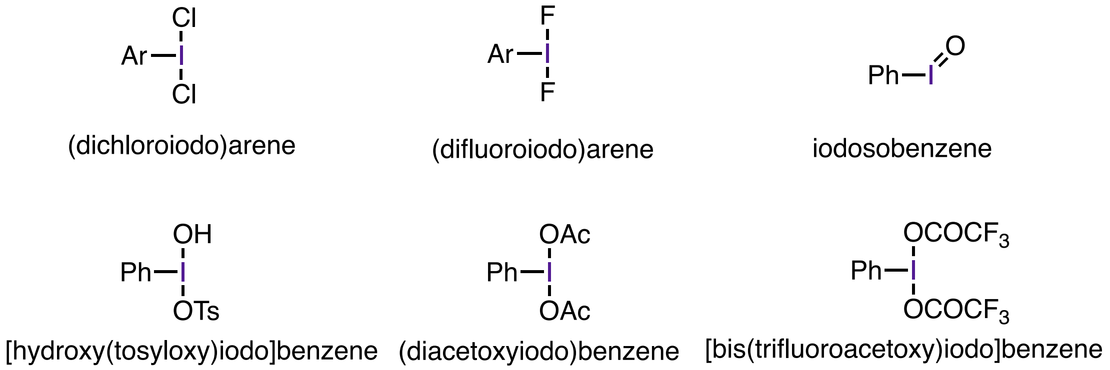


Figure 1.4: a) General structure of hypervalent iodine compounds; b) MO diagram for aryl-λ^3-iodanes.

Characteristic examples of hypervalent iodine(III) compounds are depicted in Figure 1.5.[14] Among them, (diacetoxyiodo)benzene (PIDA), [bis(trifluoroacetoxy)iodo] benzene (PIFA) and 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni´s reagent)[83] are the most widely used.



(dichloroiodo)arene (difluoroiodo)arene iodosobenzene

[hydroxy(tosyloxy)iodo]benzene (diacetoxyiodo)benzene [bis(trifluoroacetoxy)iodo]benzene

Figure 1.5: Examples of common hypervalent iodine(III) compounds.

Aryl-λ^5-iodanes possess a square pyramidal structure with an aryl bound by a two electron σ-bond to the iodine center. The two orthogonal, hypervalent 3c-4e bonds, are in the

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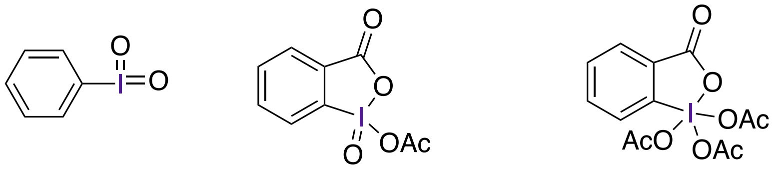
[83] J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650.

apical positions, accommodating four ligands. A variety of commonly used hypervalent iodine(V) compounds are depicted in Fig. 1.6.[84]



iodoxybenzene

o-iodobenzoic acid (IBX)

Dess-Martin periodinane (DMP)

Figure 1.6: Examples of hypervalent iodine(V) compounds.

1.4.2 Hypervalent Iodine: Reactivity

Hypervalent iodine reagents have been widely used in organic synthesis as efficient and environmentally friendly oxidizing agents. Their application though is not limited to their role as terminal oxidants in combination with transition metals. Hypervalent iodine reagents are also involved in synthetic transformations. Among them, cyclization **(i)** and **(iii)**, oxidative rearrangements **(ii)** and alpha-carbon functionalization **(iv)** that are summarized in the Scheme below (Scheme 1.17).[85]

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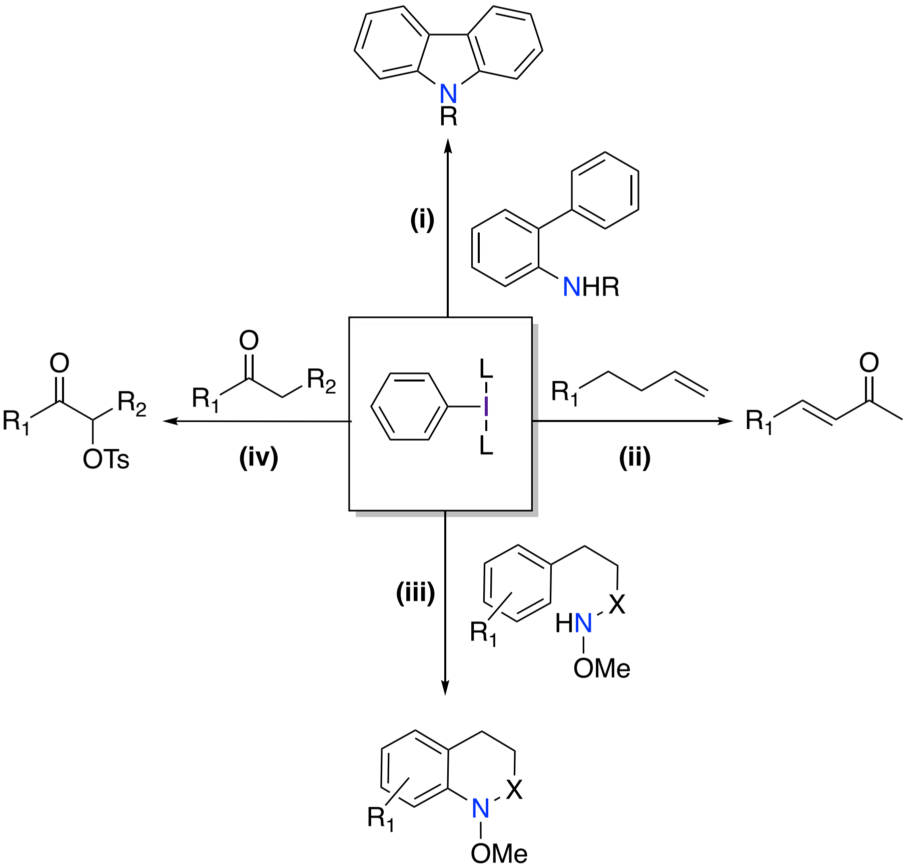
[84] a) M. Ochiai, *Top. Curr. Chem.* **2003**, *224*, 5; b) T. Kaiho, *Iodine Chemistry and Applications,* Willey, Chichester, 2014.

[85] F. V. Singh, T. Wirth, *Chem. Asian J.* **2014**, *9*, 972.



Scheme 1.17: Examples of characteristic reactions involving aryl-λ^3-iodanes.

Hypervalent iodine compounds can react through three general ways:

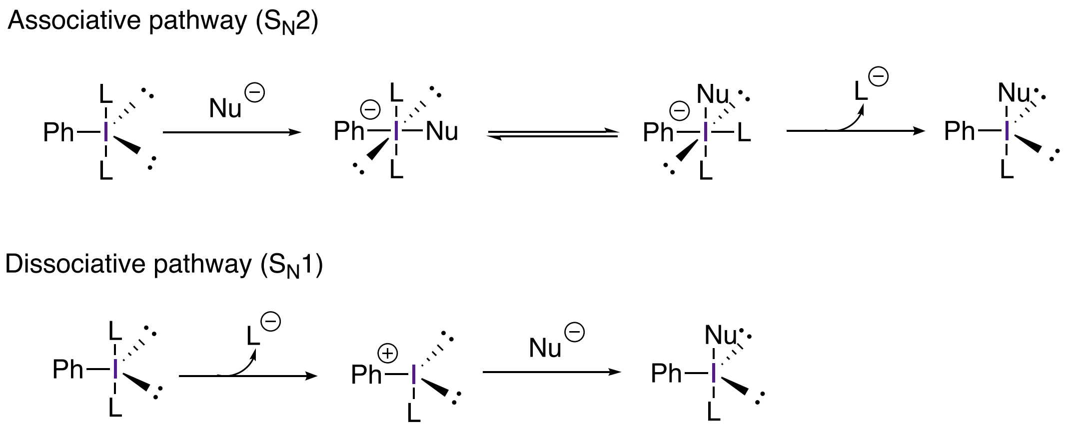
- Ligand exchange and reductive elimination
- Radical reaction
- Single electron transfer reaction (SET)

Ligand exchange

The ligand exchange at the iodine center is usually involved in the first step in the synthesis of the final product. The second step involves the reductive elimination of iodobenzene. Due to the structure of the hypervalent compounds, external nucleophiles can replace the ligands in an associative (S_N2) or dissociative (S_N1) manner. Both pathways have been validated by experimental data.

In the associative pathway, a nucleophilic attack is taking place at the electrophilic iodine center, forming an anionic *trans* hypervalent square-planar species (Scheme 1.18). After the isomerization to the *cis* species, a release of one of the ligands is occurring. X-ray diffraction analysis of the anionic stable species validate this mechanism.

In the dissociative pathway, the ligand dissociates prior to the nucleophilic attack, forming a cationic $[PhIL]^+$ species (Scheme 1.18). The dissociative path seems less probable to happen due to lower stability of the cationic intermediate $[PhIL]^+$. Nevertheless, the detection of ions in the gas phase and the presence of cations in an aqueous solution after titration of PhI(OH)(OTs) and PhI(OH)(OMs) are evidences for the existence of these intermediates.[86] Moreover, X-ray diffraction analysis revealed a T-shape of the iodonium species with one molecule of solvent in the apical position of the iodine(III) atom.



Scheme 1.18: Ligand exchange pathways in aryl-λ^3-iodanes.

After the nucleophilic attack, a reductive elimination takes place. The driving force for this step is the nuleofugacity that iodine(III) species exhibit according to Eaton.[87] The reductive elimination is leading to an Umpolung of the reactivity nucleophile. Thus this leads to the formation of different type of products, such as nucleophilic substitution, α-elimination and rearrangement products.

Radical reaction

Radical reactions in hypervalent iodine chemistry are very common, taking into account that the involved bond dissociation energies are relatively low in these cases. Thus, aryl-λ^3-iodanes can undergo homolytic cleavage of the hypervalent bond between iodine and one of the ligands under photochemical or thermal conditions. An application based on this behavior was demonstrated initially by Breslow who reported the selective

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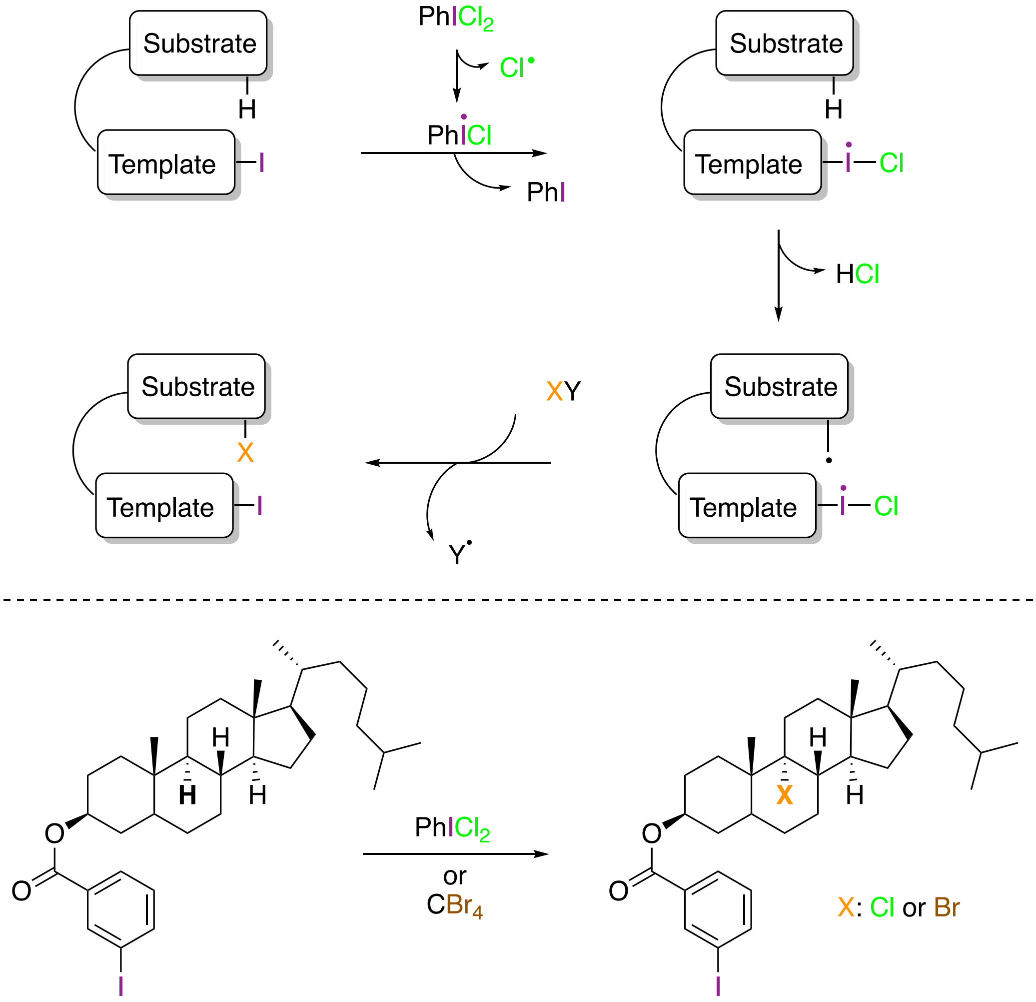
[86] H. W. Richter, B. R. Cherry, T. D. Zook, G. F. Koser, *J. Am. Chem. Soc.* **1997**, *119*, 9614.
[87] P. E. Eaton, G. T. Cunkle, *Tetrahedron Lett.* **2004**, *27*, 6055.

chlorination of steroids through an iodoaryl template group as the radical carrier (Scheme 1.19).[88] In more details, after a homolytic cleavage of the $PhICl_2$, the generated radical is transferred to the second aryiliodine **B**, in a radical chain mechanism, that finally generates selectively the carbon radical, which will then convert to the final product. Hypervalent iodine reagents that bears azides as ligands are generally unstable. Though, an azidation of unactivated hydrocarbons with the use of azidobenziodoxole was described by Zhdankin.[89] The use of benzoyl peroxide as radical initiator was crucial for the success of the reaction, due to its ability of cleaving the iodine-oxygen bond.



42 **43**

Scheme 1.19: Selective chlorination of steroids.

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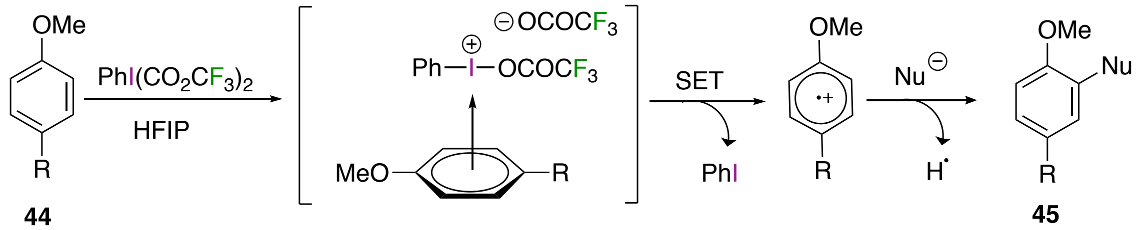
[88] a) P. White, R. Breslow, *J. Am. Chem. Soc.* **1990**, *112*, 6842; b) D. Wiendenfield, R. Breslow, *J. Am. Chem. Soc.* **1991**, *113*, 8977.

[89] V. V. Zhdankin, A. P. Krasutsky, C. J. Kuehl, A. J. Simonsen, J. K. Woodward, B. Mismash, J. T. Bolz, *J. Am. Chem. Soc.* **1996**, *118*, 5192.

Single electron transfer reaction (SET)

Reactions with hypervalent iodine reagents that involve a single-electron transfer step are the least explored. The formation of a charge-transfer complex (CT or EDA complex) between the aromatic core and the hypervalent iodine species is the initiation step, followed by the SET for the formation of the cationic radical intermediate. Such intermediates were confirmed by UV and EPR techniques by Kita, who proved the formation of an EDA complex in the reaction of *o*- and *p*-substituted phenol ethers with PIFA.[90] The final nucleophilic attack to the generated complex allows the product formation (Scheme 1.20). These reaction types require polar and non-nucleophilic solvents. For this purpose, fluoroalcohols are usually chosen.



44 **45**

Scheme 1.20: Nucleophilic aromatic substitution through SET.

1.4.3 Hypervalent Iodine: Alkyliodines in high oxidation state

Aryliodine(III) compounds have found versatile synthetic application as key tools in various areas of organic, inorganic and supramolecular chemistry. Although their chemistry dates back more than a century,[91] it has achieved particular attention over recent years and is currently experiencing a particular blooming.[14] In contrast, related alkyliodine(III) compounds have received only scant attention. This observation may be based on their notoriously lower stability in comparison to their arene counterparts. The common characteristic of the two compound families resides with the quest for reduction of the iodine(III) oxidation state to the more stable iodine(I), which is the driving force for their chemical reactivity. For $ArIX_2$ this is commonly achieved by reduction via uptake of two electrons and thus by an oxidase activity converting substrates S to oxidized products SX_2. In contrast, the alkylated iodine(III) derivatives Alk-IX_2 undergo

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[90] Y. Kita, H. Tohma, K. Hatanaka, T. Takada, S. Fujita, S. Mitoh, H. Sakurai, S. Oka, *J. Am. Chem. Soc.* **1994**, *116*, 3684.

[91] C. Willgerodt, Die Organischen Verbindungen mit mehrwertigem Jod. Verlag Enke, Stuttgart, **1914**.

nucleophilic displacement, in which the electrons for iodine reduction originate from the former C-I bond (Figure 1.7). This context had already been understood from the pioneering investigation by Thiele and Peter, who oxidized alkyl iodides with elemental chlorine and bromine to obtain short-lived species of the general structure R-IX_2.[92] Despite their correct conclusion on a significantly enhanced reactivity in comparison to the parent alkyliodides, they were able to observe and isolate compounds such as $MeICl_2$ at low temperature.

Attempts to isolate and study such elusive alkyliodine(III) derivatives have remained challenging, even for cases of aliphatic backbones containing iodine at the bridge head.[93] The ability of iodine(III) to act as a leaving group in the solvonolysis of (4-*tert*-butyl-1-cyclohexenyl) aryliodonium tetrafluoroborates in alcohol and aqueous solutions was determined by Ochiai to be in the order of 10^6 times faster than for triflate.[94] No data is available for the corresponding aliphatic iodine(III) compounds, but the relative rates can be expected to be similarly pronounced. The development of reactivity relying on iodine in high oxidation states has largely benefited from this unparalleled leaving group ability. As a general strategy, the oxidation of alkyl iodides with a variety of oxidants is carried out in-situ and generates a transient oxidation state of iodine(III) as an exceptional nucleofuge. This intermediate can then be directed to subsequent pathways of nucleophilic substitution, elimination, α-carbon oxidation and rearrangements.[95]

Herein, general strategies on the generation of transient iodine(III) oxidation states that promote organic transformations will be discussed. The recent advance of catalytic transformations involving iodine in high oxidation state offers additional synthetic strategies and will be discussed in details in the final section of this thesis.

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[92] a) J. Thiele, W. Peter, *Chem. Ber.* **1905**, *38*, 2842; b) J. Thiele, W. Peter, *Liebigs Ann. Chem*. **1909**, *369*, 149.

[93] a) J. B. Dence, J. D. Roberts, *J. Org. Chem.* **1968**, *33*, 1251; b) D. G. Morris, A. G. Shepherd, *J. Chem. Soc., Chem. Comm.* **1981**, 1250.

[94] T. Okuyama, T. Takino, T. Sueda, M. Ochiai, *J. Am. Chem. Soc*. **1995**, *117*, 3360.

[95] P. E. Eaton, G. T. Cunkle, *Tetrahedron Lett.* **1986**, *27*, 6055.

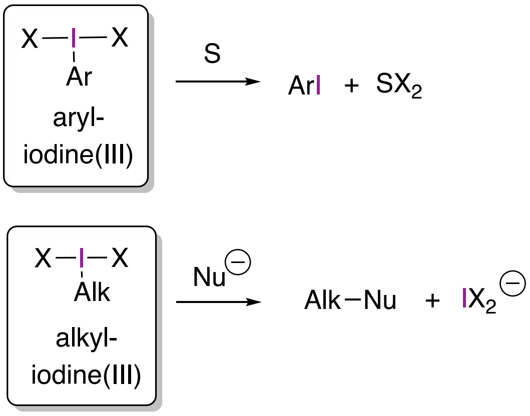

Figure 1.7: Representative classes of aryliodine(III) and alkyliodine(III) compounds and their common reaction pathways.

Substitution reactions

Owing to their reduced stability, alkyliodine(III) reagents should be considered strategic intermediates of high reactivity. In general, their in-situ formation represents the most convenient way for their synthetic application. Alkyl iodides can be oxidized to their iodine oxidation state of +III by a number of oxidizing agents introducing important synthetic flexibility.[96]

Following the pioneering work by Thiele,[92] a series of different oxidants such as molecular halogens bromine, chlorine and fluorine,[97] xenon difluoride,[98] perchlorates,[99] dichloro heptoxide,[100] and preformed polyvalent iodine reagents[101] have all found successful application in the chemoselective oxidation of defined alkyliodine(I) compounds to their corresponding high oxidation state alkyliodine(III) derivatives. The mentioned oxidants usually generate trisubstituted iodine(III) derivatives incorporating two new substituents at the iodine center (Figure 1.7 bottom).

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[96] N. S. Zefirov, V. V. Zhdankin, G. V. Makhonkova, Y. V. Dankov, A. S. Kozmin, *J. Org. Chem.* **1985**, *50*, 1872.

[97] a) E. J. Corey, W. J. Wechter, *J. Am. Chem. Soc.* **1954**, *76*, 6040; b) K. B. Wiberg, W. E. Pratt, M. G. Matturro, *J. Org. Chem.* **1982**, *47*, 2720; c) S. Rosen, M. Brand, *J. Org. Chem.* **1981**, *46*, 733.

[98] a) E. W. Della, N. J. Head, *J. Org. Chem.* **1992**, *57*, 2850; b) E. W. Della, N. J. Head, W.K. Janowski, C. H. Schiesser, *J. Org. Chem.* **1993**, *58*, 7876.

[99] a) N. S. Zefirov, V. V. Zhdankin, A. S. Kozmin. *Tetrahedron Lett.* **1986**, *27*, 1845; b) N. V. Yashin, E. B. Averina, Y. K. Grishin, V. B. Rybakov T. S. Kuznetsova, N. S. Zefirov, *Russ. Chem. Bull., Int. Ed.,* **2016**, *65*, 451.

[100] K. Baum, C. D. Beard, *J. Org. Chem.* **1975**, *40*, 2536.

[101] a) W. Willgerodt, *J. Prakt. Chem.* **1886**, *33*, 154; b) J. Gallos, A. Varvoglis, *J. Chem. Soc. Perkin Trans. 1*, **1983**, 1999.

In contrast, oxygenating peracids such as *m*-chloroperbenzoic acid (*m*CPBA) commonly lead to the formation of iodoso derivatives.[102]

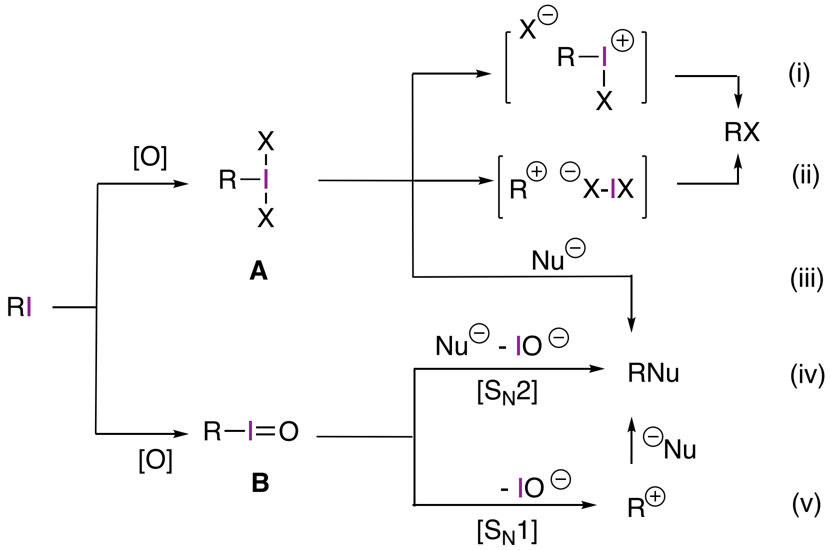

Figure 1.8: Synthetic possibilities in nucleophilic substitution arising from oxidation of alkyl iodide(I) to high oxidation state iodine(III) intermediates.

From a historic perspective, substitution reactions from the attack of a suitable nucleophile represent the most prominent transformation based on alkyliodine(III) intermediates. In the initial exploration comprising oxidation of alkyl iodidess with elementary fluorine, chlorine or bromine, or ICl, respectively, the intermediary iodine(III) initiated a useful path to halogen exchange reactions. More generally, the substitution reactions can proceed either with a suitable nucleophile arising from dissociation at the central iodine(III), which thus originated from the initial oxidant, or may proceed with a competent external nucleophile. These two approaches provide complimentary synthetic opportunities.

The underlying general mechanistic pathway for halogen interconversion was investigated for 2-iodooctane as substrate. Depending on the individual reaction conditions, inversion of configuration was deduced to constitute the major pathway,[97a,103] although certain degree of racemization could not be suppressed. The exact course of the reactions has so far not been clarified fully, but may most likely follow S_N2-characteristics.

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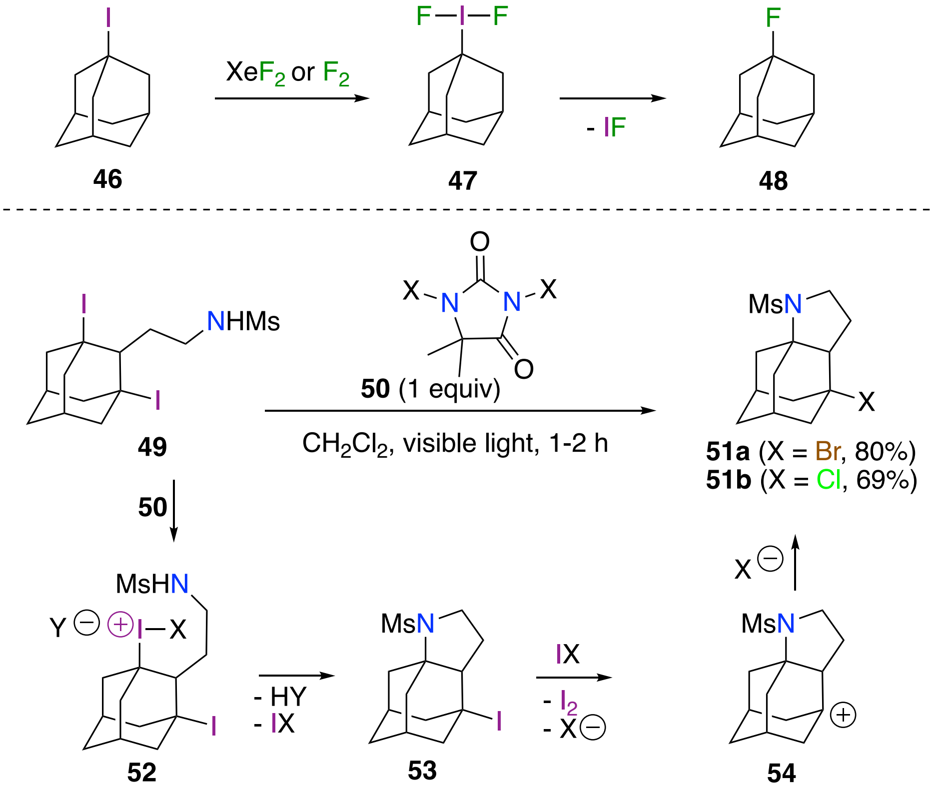
[102] a) Y. Ogata, K. Aoki, *J. Org. Chem.* **1969**, *34*, 3978; b) Y. Ogata, K. Aoki, *J. Org. Chem.* **1969**, *34*, 3974.

[103] F. M. Beringer, H. S. Schultz, *J. Am. Chem. Soc.* **1955**, *77*, 5533.



Scheme 1.21: Iodine(III)-promoted substitution processes at adamantane.

More rigid structures such as 1-iodoadamantane **46** provide the same halogen interconversions through cationic pathways as the preferential intermediates **47**.[97c] For example, for the use of XeF_2 or elemental F_2 as oxidants, clean conversion of 1-iodoadamantane into 1-fluoroadamantane proceeds readily via the corresponding hypervalent iodine(III) intermediates (Scheme 1.21 top).[97c] This exchange reaction is also feasible for other nucleophilic groups. Muñiz recently explored the oxidation of the diiodinated adamantane **49** from double Hofmann-Löffler reaction (Scheme 1.21 bottom). While the initial iodine activation promotes the formation of a pyrrolidine **53**, the second enable halogen interconversion, toward **51**.[104]

The possible involvement of cationic intermediates arising from a dissociative mechanism was also concluded from studies by Della.[98a] Additional work by Della, Schiesser and Wiberg identified the iodine(III) route as very effective for halogen exchange in bicyclic systems and for halogention at bridgeheads.[97b,98b] Wiberg also conducted an extensive research on the nucleophilic substitution of non-activated bicyclic iodides as iodonorbornane with bromine.[97b] The formation of brominated products was

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[104] E. del Castillo, M. Martínez, A. E. Bosnidou, T. Duhamel, C. O'Broin, H. Zhang, E. Escudero-Adán, M. Martínez-Belmonte, K. Muñiz, *Chem. Eur. J.* **2018**, *24*, 17225.

explained by the formation of the corresponding $RIBr_2$ complex. The observation on reaction rate acceleration in polar solvents matched similar results obtained by Corey.[97a] Evidences for cationic intermediates exclude the possibility for the S_N2 pathway. Instead, Della[98] and Rosen[97c] proposed a dissociation mechanism to a relatively stable carbocation intermediate.

A general study on the stereochemistry of the deiodination employing different nucleofuges was conducted by Zefirov and coworkers.[96] In more details, the use of different oxidants with various nucleophiles led to the substitution products in all cases of primary alkyl iodides. Diiodides usually follow the same reactivity as their monosubstituted counterparts. Alkyl iodides alpha to carbonyls, such as ketone, ester or even carboxylic acids follow the same rules.[99]

In general, peracids oxidize alkyliodides to the corresponding iodoso compounds. Peracid oxidation has largely been applied for oxygenative substitution processes. The significant increase of nucleofugacity of iodine after such an oxidation was initially demonstrated for *m*-chloroperoxybenzoic acid in alcoholic media by Kropp and Davidson. This combination affords the corresponding methyl ethers from the methanol solvent. Elimination was the predominant pathway for more complex systems.[105] It also gives the facile conversion of the very stable 1- and 7-iodobicyclo[2.2.1]heptanes to the corresponding methyl esters upon treatment with *m*-chloroperbenzoic acid in methanol. An extensive study on peracid oxidation of alkyl iodides in non-polar solvents was performed by Burka and Macdonald in 1980 preventing solvent incorporation.[102b] Evidence was encountered for intermediary iodoso compounds. The oxidation of primary alkyl iodides exclusively provided substitution products. The substitution of primary and secondary hypervalent organoiodine(III) proceeds with S_N2 characteristic inversion of configuration, although secondary alkyl iodides may afforded additional elimination and α-carbon oxidation. Finally, tertiary alkyl halides afforded a mixture of substitution and elimination products.

This strategy has been applied advantageously in various syntheses. Among them are the synthesis of phospholipids[106a] and the synthesis of ketodifluoromethylene dipeptide isostere by Hoover (Scheme 1.22, top).[106b] Another pioneering application of the

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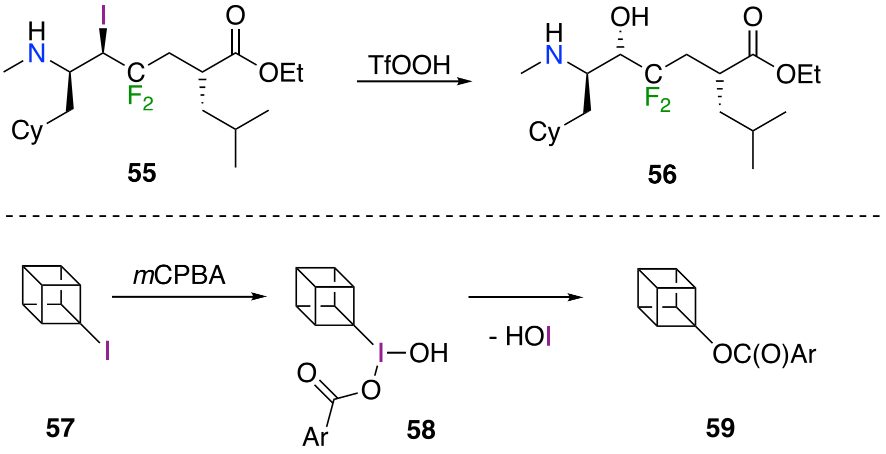
[105] a) R. I. Davidson, P. J. Kropp, *J. Org. Chem.* **1982**, *47*, 1904; b) T. L. Macdonald, N. Narasimhan, L. T. Burka, *J. Am. Chem. Soc,* **1980**, *102*, 7760.

[106] a) P. N. Guivisdalsky, R. Bittman, *J. Org. Chem.* **1989**, *54,* 4637; b) D. B. Damon, D. J. Hoover, *J. Am. Chem. Soc.* **1990**, *112*, 6439; c) R. Greenhouse, J. M. Muchowski, *Can. J. Chem.* **1981**, *59*, 1025.

nucleophilic iodine(III) displacement was applied by Greenhouse and Muchowski in the synthesis of digitoxigenin-3-alkyl ethers.[106c]



Scheme 1.22: Peracid-mediated conversion of alkyliodindes to C-O bonds. Synthesis of a ketodifluoromethylene dipeptide isostere (top) and cubane modification (bottom). Ar: 3-Cl-C_6H_4

The successful concept of iodine(III) intermediates as a precursor for cationic intermediates in strained structures was demonstrated by Eaton in his work on deiodination of strained cubyl iodides. The reaction of iodocubane **57** with *m*CBPA or XeF_2 proceeded cleanly to cubyl esters or fluorocubane, respectively (Scheme 1.22 bottom).[107] For the depicted example, the suggested mixed iodine(III) **58** is an uncommon formulation. In principle, iodoso derivatives are usually invoked to form from oxidation with peracids. Subsequent nucleophilic functionalization of the carbon skeleton then proceeds in the presence of external nucleophiles.

Within a complimentary strategy, Sicinski and Szezepek investigated the oxidation of a 19-iodo-5-androsten derivative **60**.[108] Following intermediary homoallylic iodine(III) formation, nucleophilic attack at the alkene furnishes the cyclopropyl derivatives **62** as the major product (Scheme 1.23). It is noteworthy that the oxidation at the iodine center proceeds significantly faster than the competing epoxidation of the trisubstituted alkene, which enables synthetically useful chemoselectivity.

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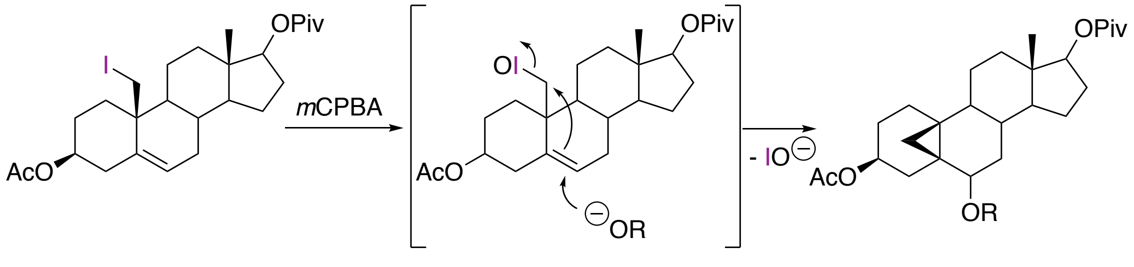
[107] P. E. Eaton, C.-X. Yang, Y. Xiong, *J. Am. Chem. Soc.* **1990**, *112*, 3225.

[108] R. R. Sicinski, W. J. Szczepek, *Tetrahedron Lett.* **1987**, *28*, 5729.



60 **61** **62** (R = H, Ac)

Scheme 1.23: Cyclopropane formation through homoallylic substitution via iodine(III) intermediates.

Oxidation with hypervalent iodine reagents

Polyvalent iodine compounds proved to be another class of effective oxidants for the oxidation of alkyl iodides. Iodine(III) trifluoroacetate as well as iodine pentafluoride was employed in the synthesis of aldehydes.[109] (Dichloroiodo)benzene has been used repeatedly for the formation of alkyl chlorides as an alternative to Cl_2.[101a] The use of PIFA and PIDA for the oxidative conversion of alkyl iodides into the corresponding esters was determined by Varvoglis as a reliable general reaction pathway under these conditions.[101b] As already revealed throughout the previous sections, the intermediacy of an alkyl iodine(III) can be crucial in order to render substitution process feasible. In some cases, preformed hypervalent reagents are promoting reactions, which otherwise would not proceed under mild conditions. One such example concerns the intramolecular amination of a terminal alkyliodide **66**, which only takes place under harsh conditions (toluene, 110^{o} C).[110] This cyclization can be significantly accelerated upon oxidation of the alkyl iodide intermediate **67**. For example, the involvement of stoichiometric amounts of preformed iodine(III) reagents can direct this reaction to completion within a room temperature process (Scheme 1.24).[111]

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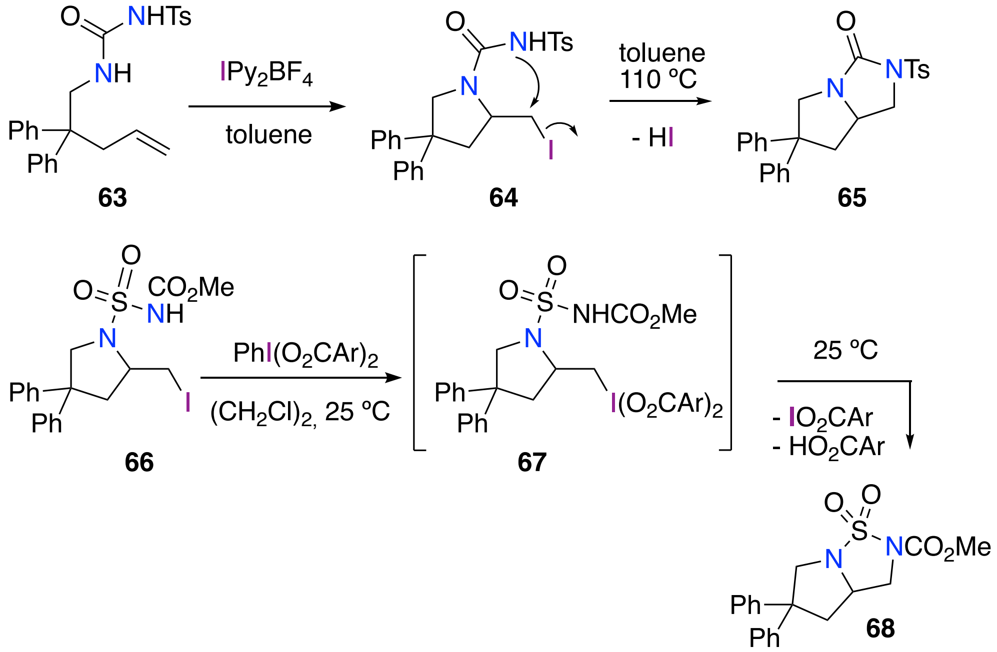
[109] a) M. Linskeseder, E. Zbiral, *Liebigs Ann. Chem.* **1977**, 1039; b) J. Buddrus, H. Plettenberg, *Chem. Ber.* **1980**, *113*,1494; c) G. A. Olah, J. Welch, *Synthesis*, **1977**, 419.

[110] K. Muñiz, C. H. Hövelmann, E. Campos-Gómez, J. Barluenga, J. M. González, J. Streuff, M. Nieger, *Chem. Asian J.* **2008**, *3*, 776.

[111] C. Martinez, K. Muñiz, *Angew. Chem. Int. Ed.* **2015***, 55,* 8287.



Scheme 1.24: Intramolecular diamination of alkenes: with IPy_2BF_4 as iodine(I) reagent vs an iodine(III) intermediate. Ar: 3-Cl-C_6H_4

Ritter reactions

In a seminal application, Olah disclosed that the activation of alkyl iodidess by nitrosonium hexafluorophosphate leads to rapid and irreversible iodine oxidation, which promotes the formation of carbocations at temperatures as low as -15 ºC.[112] In the presence of acetonitrile, high-yielding Ritter-type reactions are accomplished under mild conditions. Depending on the nature of the alkyl iodide, S_N1 or S_N2 pathways may be favored. These observations were confirmed by Bach, who employed nitrosonium tetrafluoroborate. These facts corroborate earlier investigation with nitronium tetrafluoroborate as activating agent.[113a] When the corresponding nitronium acetate or trifluoroacetate were used, the acetic or trifluoracetic esters were formed.[113b]

Minakata in 2006 reported an elegant Ritter-type amination starting directly from tertiary C–H bonds using iodic acid (HIO_3) as an oxidant and in the presence of N-hydroxyphthalimide (NHPI) as redox promoter for the selective formation of tert-alkyl radicals (Scheme 1.25). Under the redox conditions, molecular iodine is formed, which quenches the radical and installs a *tert*-alkyl iodide **71**. Oxidation to the corresponding

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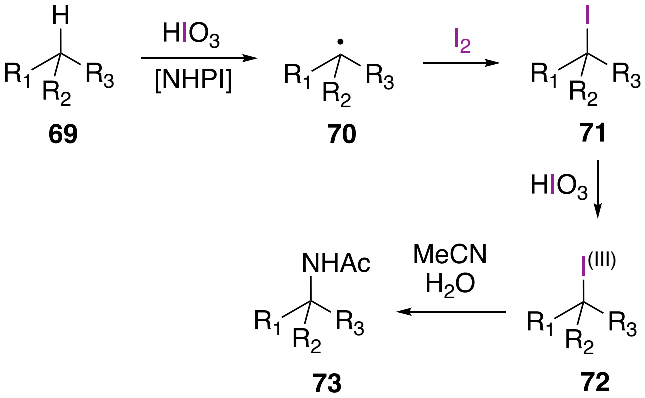
[112] G. A. Olah, J. Welch, *Synthesis* **1979**, 274.

[113] a) R. D. Bach, J. W. Holubka, T. H. Taaffee, *J. Org. Chem.* **1979**, *44*, 1739; b) R. D. Bach, T. H. Taaffee, J. W. Holubka, *J. Org. Chem.* **1980**, *45*, 3439.

alkyliodine(III) **72** takes place with iodic acid followed by Ritter-type amination at the electrophilic carbon center.[114]



Scheme 1.25: Iodine(I/III)-mediated Ritter reaction.

Rearrangements

The high propensity of alkyliodine(III) intermediates for cation formation upon reductive loss of the iodine group enables pathways other than substitution. Although usually not the main pathway, rearrangements may arise from alkyliodine(III) states, particularly those originating from primary alkyl iodidess. Where participating, migration usually follows the tendencies from classic rearrangements such as Wagner-Meerwein. In pioneering work, Beringer and Schultz had observed alkyl migration in the oxidation of terminal alkyliodides.[100] Identical conclusions were later drawn by Burka and Macdonald. In their study, oxidation of neopentyl iodide gave only the *tert*-pentyl alcohol and *m*-chlorobenzoate as a result of methyl migration and addition of the nucleophile to the tertiary carbocation. This outcome suggests an initial loss of hypoiodite thus building up significant positive charge to initiate the rearrangement.

Another noteworthy example resists with the work by Bach, who observed hydride migration in the nitrosonium oxidation of butyliodide to 2-acetamidobutane.[115] Regarding the alkene difunctionalization with the reagent combination consisting of molecular iodine and XeF_2, Patrick observed a comparably fast rearrangement and formation of carbocations **78**, which upon nucleophilic attack afforded the geminally difluorinated products **75** (Scheme 1.26).[116]

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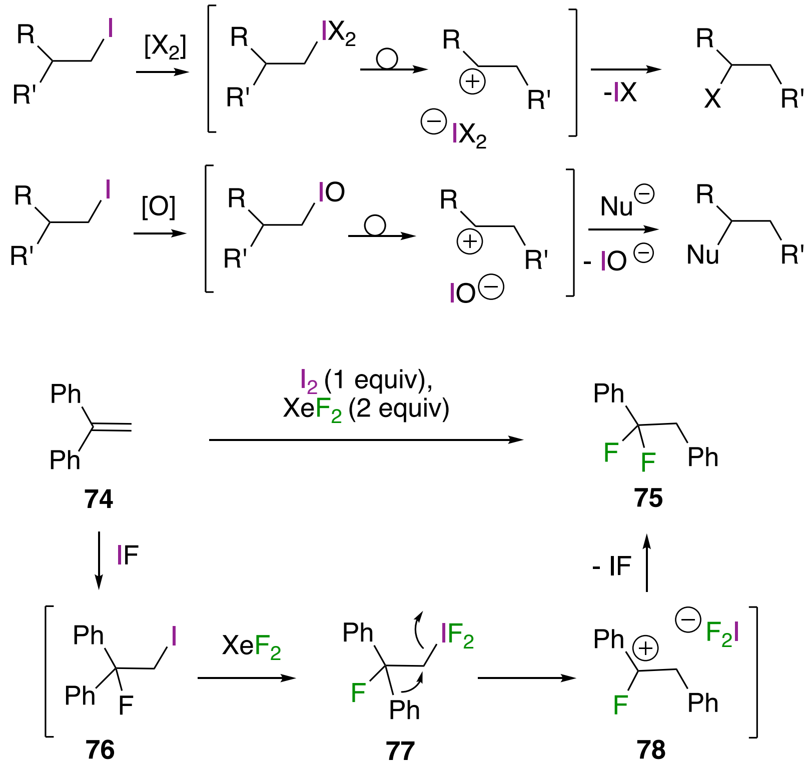
[114] K. Kiyokawa, K. Takemoto, S. Minakata, *Chem. Commun.* **2016**, *52*, 13082.

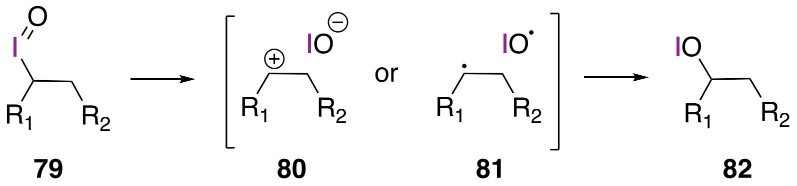
[115] R. D. Bach, T. H. Taaffee, S. J. Rajan, *J. Org. Chem.* **1980**, *45*, 165.

[116] T. Patrick, S. Qian, *Org. Lett.* **2000**, *2*, 3359.



Scheme 1.26: Iodine(III)-initiated rearrangements.

A different type of rearrangement refers to the iodine nucleofuge itself. Reich suggested that loss of hypoiodite from oxygenation alkyliodides can result in a re-addition with concomitant formation of C-O bonds and ultimately to the free alcohols (Scheme 1.27).[117]



Scheme 1.27: C-I to C-O bond rearrangement in alkyliodoso compounds.

Elimination

In 1978 Reich discussed for first time the evidence of the oxidation of alkyl iodides, in nonpolar media, to the iodoso compound **83**, which led to olefins by a *syn* elimination process upon elimination of hypoiodous acid (IOH).[117a] The reaction proceeded with *syn* elimination (in an analogous manner of amine *N*-oxide, sulfoxide, and selenoxide

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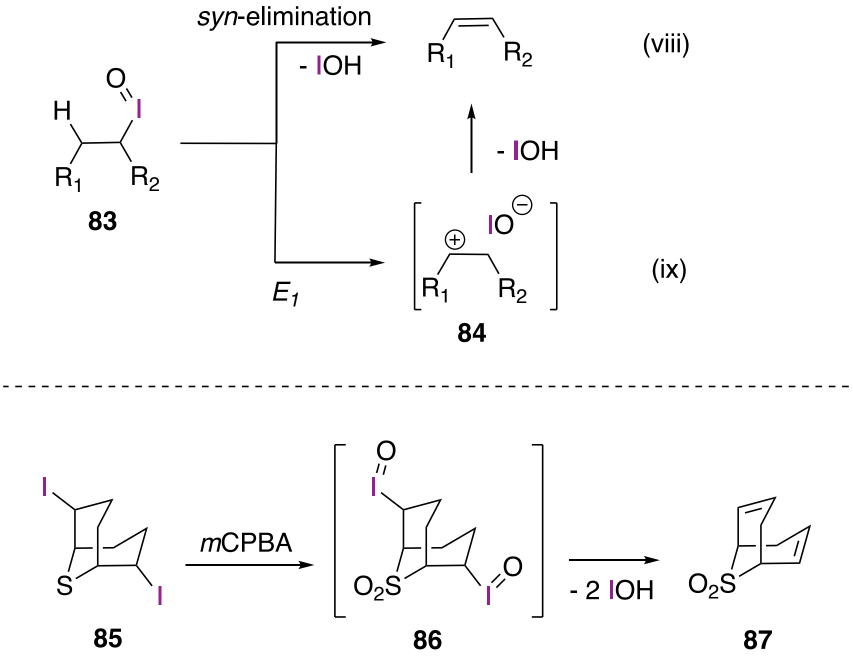
[117] a) H. J. Reich, S. L. Peake, *J. Am. Chem. Soc.* **1978**, *100,* 4888; b) J. Lee, J. Oh, S.-j. Jin, J.-R. Choi, J. L. Atwood, J. K. Cha, *J. Org. Chem.* **1994**, *59,* 6955.

eliminations). According to their studies, upon oxidation primary iodides rearranged to the corresponding secondary hypoiodite through a 1,2-alkyl shift. For oxidation of other alkyliodides, alternative dissociation of hypoiodite generates a cationic intermediate following common E1 pathways (Scheme 1.28 top). For reaction conditions with excess of oxidant, epoxidation of the alkene may become a side reaction. The reaction of hypoiodous acid with the formed olefin formed 1,2-iodohydrines.



Scheme 1.28: *Syn* elimination process of iodoso derivatives (top) and diene formation upon oxidation of diiodides (bottom).

Elimination pathways had also been identified in the pioneering study by Ogata and Aoki.[99] McCabe described the oxidative cleavage of cyclic aliphatic iodides **85** and diiodides upon treatment with *m*-chloroperbenzoic acid. The involvement of high oxidation state iodine(III) intermediates **86** lead to a *syn*-elimination process furnishing dienes. Interestingly, treatment of the diiodide with peracetic acid afforded the double substitution product **87** instead of the alkene.[118]

Along this line, Sutherland reported the synthesis of norbonene by an oxidatively induced elimination of norbornyl iodide.[119] The hindered nature of the formed double bond did not allow for further oxidation. Fuchs used the iodoso-elimination to install a double bond

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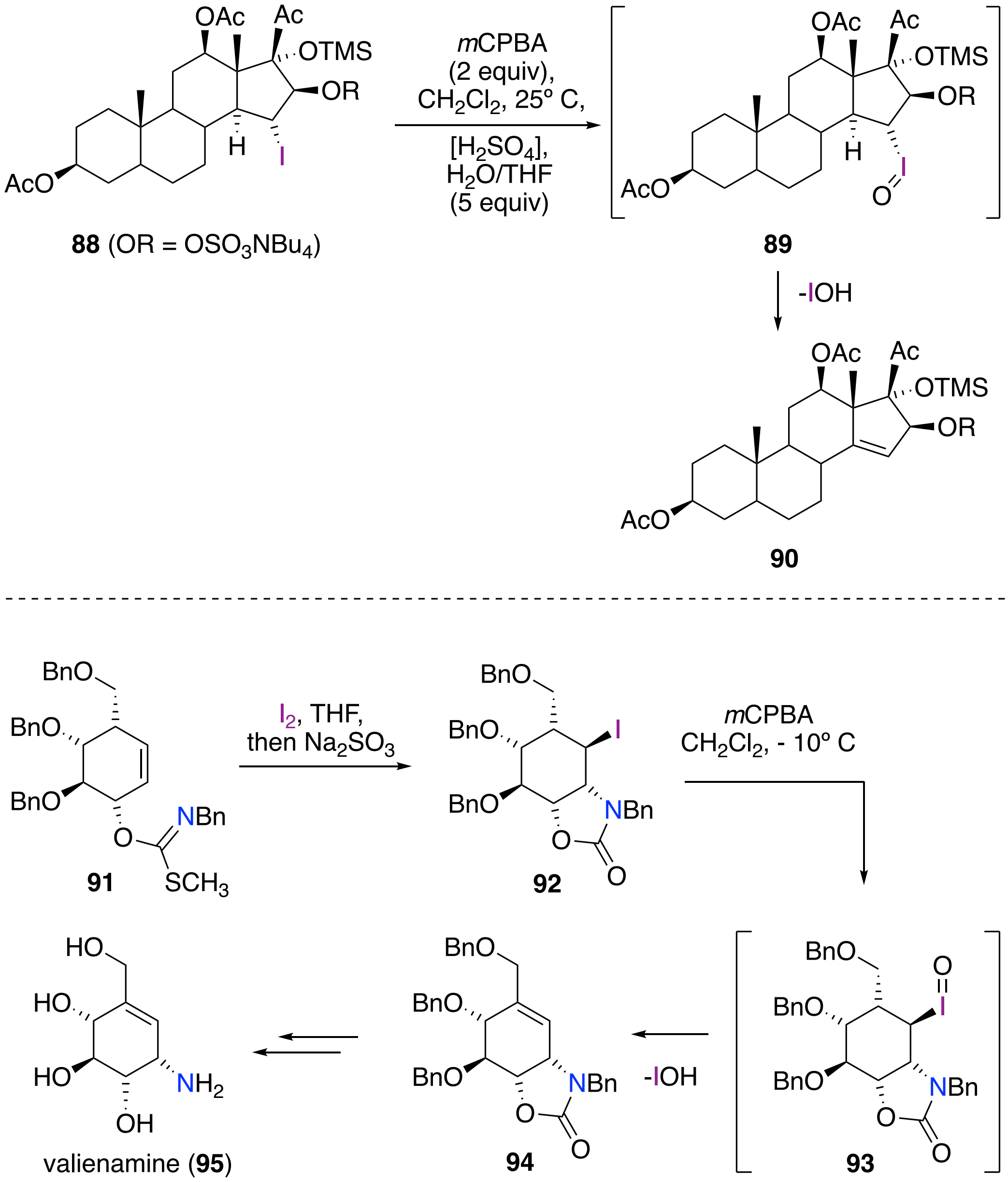
[118] P. H. McCabe, C. I. de Jenga, A. Stewart, *Tetrahedron Lett.* **1981**, *22*, 3679.

[119] N. R. A. Beeley, J. K. Sutherland, *J. C. S. Chem. Comm.* **1977**, 321.

at a late-stage in the synthesis of hexacyclic steroidal units with structural relevance to cephalostatin 7.[120]



Scheme 1.29: Cephalostatin´s (top) and valienamine´s (bottom) syntheses.

A related elimination was employed by Knapp in the synthesis of valienamine.[121] After aminoiodination of alkene **91**, oxidation of the alkyl iodide **92** to its iodoso derivative **93** provided selective elimination to the allylic amine subunit **94**, which could be converted to the target structure **95** within four standard transformations.

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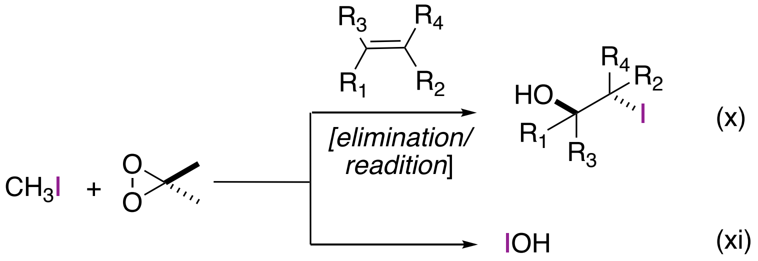
[120] S. Kim, P. L. Fuchs, *Tetrahedron Lett.* **1994**, *35*, 7163.

[121] S. Knapp, A. B. J. Naughton, T. G. M. Dhar, *Tetrahedron Lett.* **1992**, *33*, 1025.

It is of experimental significance that the manipulation of the alkyliodine(III) provides an electrophilic iodine(I) compound, which is usually considered a mere by-product of the reaction. However, in the presence of suitable reactive groups, subsequent oxidation possibilities may arise rendering the iodine(I) a useful reagent by itself. In a study along these lines, Asensio investigated the oxidation of iodomethane with dimethyldioxirane to generate hypoiodite and emphasized that in this way stable neutral hypoiodite solutions could be generated.[122]



Scheme 1.30: Iodomethane oxidation toward the formation of iodohydrines.

As to a particularly elegant application of the alkyliodine(III) reactivity, Asensio paid attention to the fate of the hypoiodite after displacement and observed clean addition to alkenes to afford iodohydrines with the expected *anti*-selectivity. This reaction sequence demonstrates that upon oxidation, iodine in alkyliodides can be extruded and subsequently used for electrophilic reactivity.[122]

All the above mentioned stoichiometric reaction follow the same concept as intermediates of the σ-alkyl iodide(III) series that are commonly formed throughout catalytic reactions, when these include the application of aryliodine(III) catalyst states. Such a concept envisions an initial functionalization of the organic substrate with an iodine(I) catalyst, which leads to the formation of an alkyliodine(I) catalyst state. In the presence of suitable oxidant, the subsequent oxidation toward a super-nucleofuge alkyliodine(III) species induces the reductive displacement of the iodine to furnish the substitution product and regenerate the iodine(I) catalyst from the outset In the present manuscript, this concept will be indeed applied into catalytic transformations.

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[122] G. Asensio, C. Andreu, C. Boix-Bernardini, R. Mello, M. E. González-Nuñez, *Org. Lett.* **1999**, *13*, 2125.

1.5 Overall aims

The direct and selective functionalization of sp^3 and sp^2-hybridized carbon centers represents an important approach in synthetic organic chemistry. In this context, oxidative amination reactions are highly important because Nature does not provide an efficient enzymatic solution for the direct amination of hydrocarbons. In particular, amination reactions that are promoted under metal-free conditions appear to be an attractive approach towards the synthesis of biomolecules with potential medical applications. Hypervalent iodine(III) reagents are well-known and widely established in organic synthetic chemistry due to their high reactivity for the general functionalization of hydrocarbons. Some years ago, our group has developed a series of new hypervalent iodine(III) reagents bearing a defined I-N single bond with a transferable nitrogen group. In contrast to the classic behavior, these reagents provide a new useful tool for nucleophilic amination.

Additionally, although more than a century old, the concept of high oxidation state alkyliodides as reagents or reactive intermediates in synthesis has been applied only scarcely and currently lies behind its transition metal counterparts. This is a surprising observation in view of the environmentally benign character of economic and easy to handle iodine.

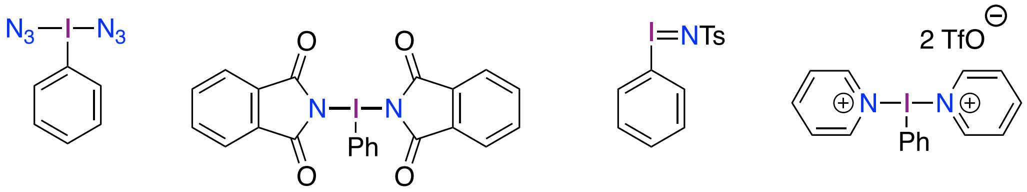
Hence, this Doctoral Thesis is aiming to the novel application of the above mentioned concepts, for the successful C-N bond construction.

Throughout this Thesis work, I have discussed amination reactions of hydrocarbons either iodine(III)-mediated, or catalyzed by molecular iodine. First, new examples for the amination of indole and tryptamine derivatives, as well as diversification of the resulting structures that opens chemical space are discussed. A novel protocol for the intramolecular C-H amination of arenes, based on molecular iodine catalysis towards the formation of anilines and a mechanistic discussion is presented. Finally, a new intermolecular $C(sp^3)$-H amination methodology and its further application toward four pharmaceutical compounds is reported.

Chapter II. Iodine(III)-mediated Intermolecular Amination for the Chemical Diversification of Tryptamines.

2.1 Introduction: Hypervalent iodine(III) reagents incorporating transferable nitrogen groups.

Hypervalent iodine(III) reagents such as (diacetoxyiodo)benzene (PIDA) or bis(trifluoroacetoxy)iodobenzene (PIFA) were dominating the chemistry field for decades as they could be used in a variety of different transformations, including aminations.[123] Hypervalent iodine compounds that contain I-N bonds are less common than the I-O bonds containing ones, probably due to their decreased stability.[14c] However, some species have been described, including azidoiodanes **96**,[124] aminoiodanes **97**,[125] iminoiodanes **98**[126] and bis(pyridinium)aryl iodine (III) salts **99**[127] (Figure 2.1).



96 **97** **98** **99**

Figure 2.1: Characteristic examples of I-N containing lamda-3-(λ^3)-iodanes.

Azidoiodane **96** has been reported by Zbiral as the reactive intermediates in azidation reaction. The class of azidoiodanes can be formed exclusively in situ by the reaction of aryliodides(III), such as iodosobenzene (PhIO), (diacetoxyiodo)benzene (PIDA), or dichloroiodobenzene with trimethylsilyl azide. Through decay at -25 °C the azido radical is formed, which promotes the azidation reaction.[124a-c]

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[123] K. Muñiz, *Acc. Chem. Res.* **2018**, *51*, 4507.

[124] a) F. Cech, E. Zbiral, *Tetrahedron* **1975**, *31*, 605; b) E. Zbiral, J. Ehrenfreud, *Tetrahedron* **1971**, *27*, 4125; c) E. Zbiral, G. Nestler, *Tetrahedron* **1970**, *26*, 2945; d) P. Magnus, J. Lacour, W. Weber, *J. Am. Chem. Soc*. **1993**, *115*, 9347; e) P. Magnus, J. Lacour, P. A. Evans, M. B. Roeand, C. Hulme, *J. Am. Chem. Soc*. **1996**, *14*, 3406.

[125] a) L. Hadjiarapoglou, S. Spyroudis, A. Varvoglis, *Synthesis* **1983**, 207; b) M. Papadopoulou, A. Varvoglis, *J. Chem. Res. Synop*. **1983**, 66; c) M. Papadopoulou, A. Varvoglis, *J. Chem. Res. Synop*. **1984**, 166.

[126] P. Dauban, R. H. Dodd, *Synleytt* **2003**, 1571.

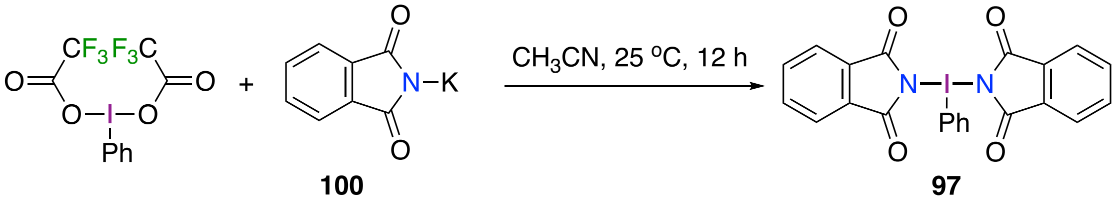
[127] R. Weiss, J. Seubert, *Angew. Chem. Int. Ed.* **1994**, *33*, 891.

The first example of a stable iodine(III) reagent, that bears amide groups in the coordination sphere of the iodine, compound **97** was synthesized by Varvoglis back in 1983, using PIFA in combination with potassium phthalimide **100** (Scheme 2.1). This reagent is insoluble in common organic solvents; thus, it had not been used in synthesis for many years.[125]

Iminoiodanes, like **98** are the I-N analogues of the iodonium ylides. They are very powerful reagents, especially as nitrene precursors.[126]

Bis(onio)-substituted aryliodine(III) salts **99** were reported by Weiss back in 1994. They can be easily isolated through precipitation from the reaction of one equivalent of iodosobenzene with trimethylsilyl triflate and 2 equivalents of pyridine.[127]

The main use of these reagents relies on their ability to perform amination reactions. In the present chapter, aminoiodanes with transferable nitrogen groups will be discussed in more details.



Scheme 2.1: Synthesis of Varvoglis reagent.

Many years after the synthesis of the stable Varvoglis reagent, in 2013, Muñiz reported on novel hypervalent iodine(III) reagents.[128] Based on the knowledge that bisulfonamides serve as excellent nitrogen sources for amination under palladium catalysis,[129] the authors considered the possibility of synthesizing hypervalent iodine(III) reagents that bear bisulfonamides as ligands on the iodine center.

The synthesis of the reagents **103** started with the synthesis of the monomeric species **101**, by treatment of (diacetoxyiodo)benzene in equimolar amounts with bistosylimide (Scheme 2.2). In presence of two equivalents of bistosylimide and water, the μ-oxo bridge **102** was obtained, which upon addition of one more equivalent of bisulfonamide led to the final reagent **3**.[129b] Alternatively, compound **103** could be directly generated in a more

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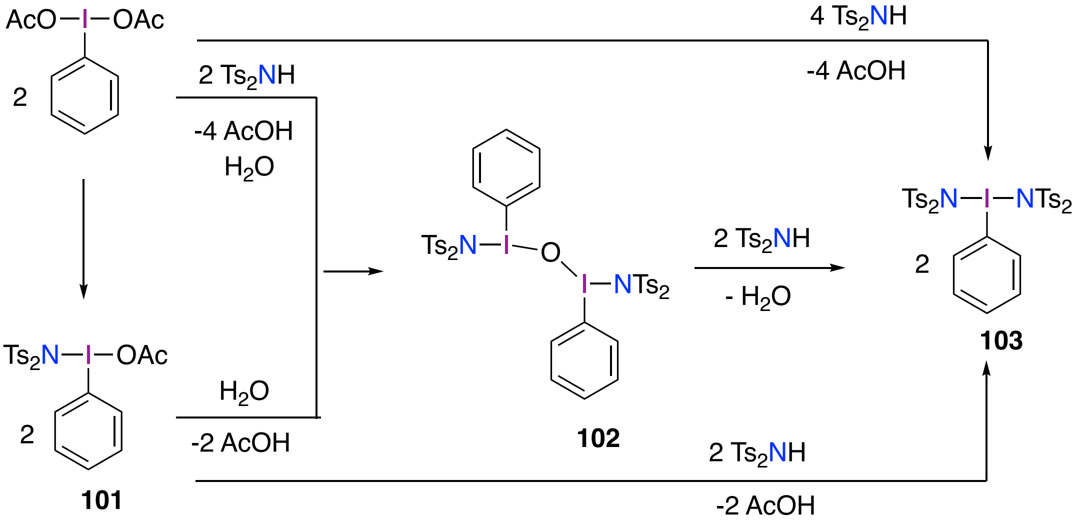
[128] a) J. A. Souto, Y. González. A. Iglesias, D. Zian, A. Lishchynskyi, K. Muñiz, *Chem. Asian J.* **2012**, *7*, 1103; b) J. A. Souto, C. Martínez, I. Velilla, K. Muñiz, *Angew. Chem. Int. Ed.* **2013**, *52*, 1324.

[129] a) C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2012**, *51*, 7031; b) Á. Iglesias, R. Álvarez, Á. R. de Lera, K. Muñiz, *Angew. Chem. Int. Ed.* **2012**, *51*, 2225.

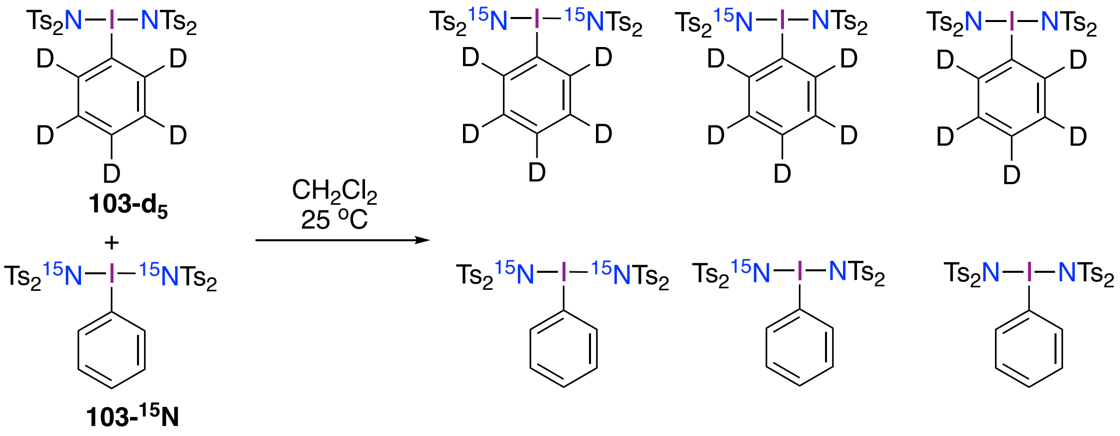
simple manner by the reaction of one equivalent of (diacetoxyiodo)benzene with two equivalents of bistosylimide in chlorobenzene at 55 °C. Upon distillation of the solvent and the generated acetic acid byproduct, the hypervalent iodine(III) reagent **103** was isolated as a white solid.



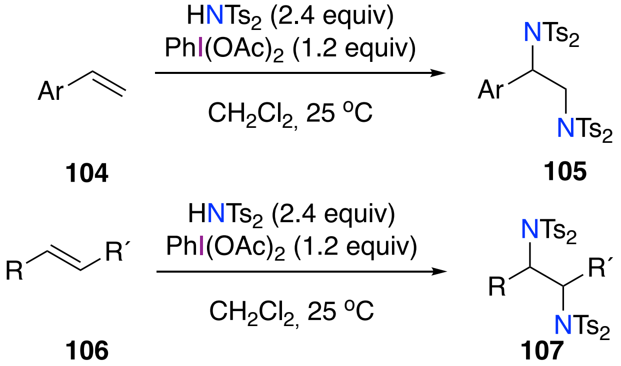
Scheme 2.2: Synthesis of $PhI(NTs_2)_2$ reagent **103**.

Muñiz has demonstrated the lability of the bisimido ligands in solution by performing isotope labelling experiments. For this purpose, derivatives with ^{15}N-labelled bistosylimides and pentadeutarated phenyl substituent of reagent **103** were synthesized and their dynamic equilibration was studied. MS experiments revealed the presence of the six possible isomeric derivatives (Scheme 2.3).

The observations led to the conclusion that these reagents react in a completely different way than other stable aminoiodanes, such as the ones bearing saccharins or phthalamides as nitrogen ligands. Thus, the electrophilicity of the iodine center is increased, allowing direct coordination to electron rich unsaturated bonds. Therefore, amination of sp^2 and sp bonds was investigated and further developed.


Scheme 2.3: Ligand dissociation evidence of bisimidoiodine(III) reagents in solution.

Initial application of these reagents included the diamination of alkenes. In situ formation from (diacetoxyiodo)benzene and bistosylimide allowed the authors to demonstrate the powerful reactivity of the reagent for more than sixty substrates, including terminal **104** and internal **106** alkenes that afford the diamines **105** and **107** respectively, in excellent yields (Scheme 2.4).[128a]


Scheme 2.4: Vicinal diamination of terminal and internal alkenes.

Further mechanistic studies, including experimental evidences and DFT calculations, revealed the mechanism of this transformation.[130] In particular, the influence of electronic parameters on the hypervalent iodine(III) reagent **103X** for the diamination reaction of *para*-fluorostyrene **104a** was investigated, indicating an acceleration of the reaction, when an electronically rich hypervalent iodine(III) reagent was involved in the reaction

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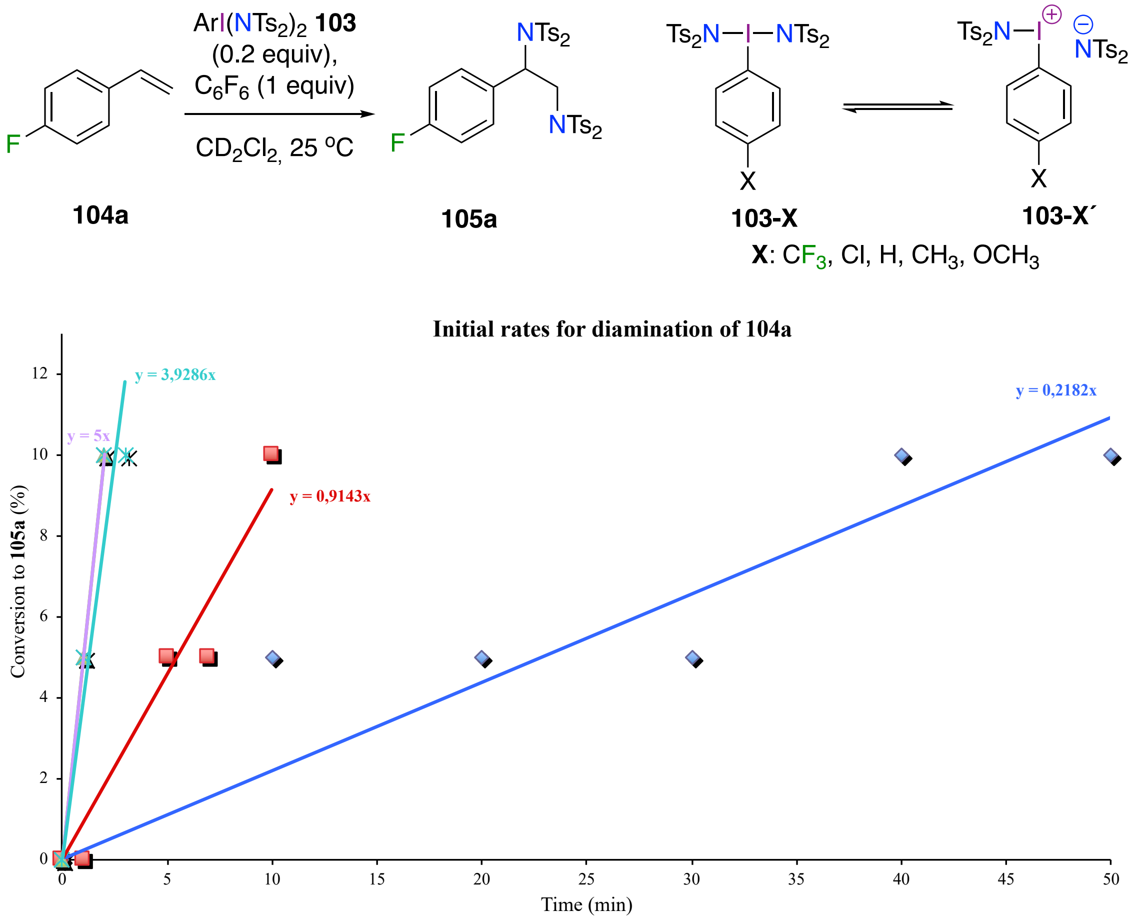
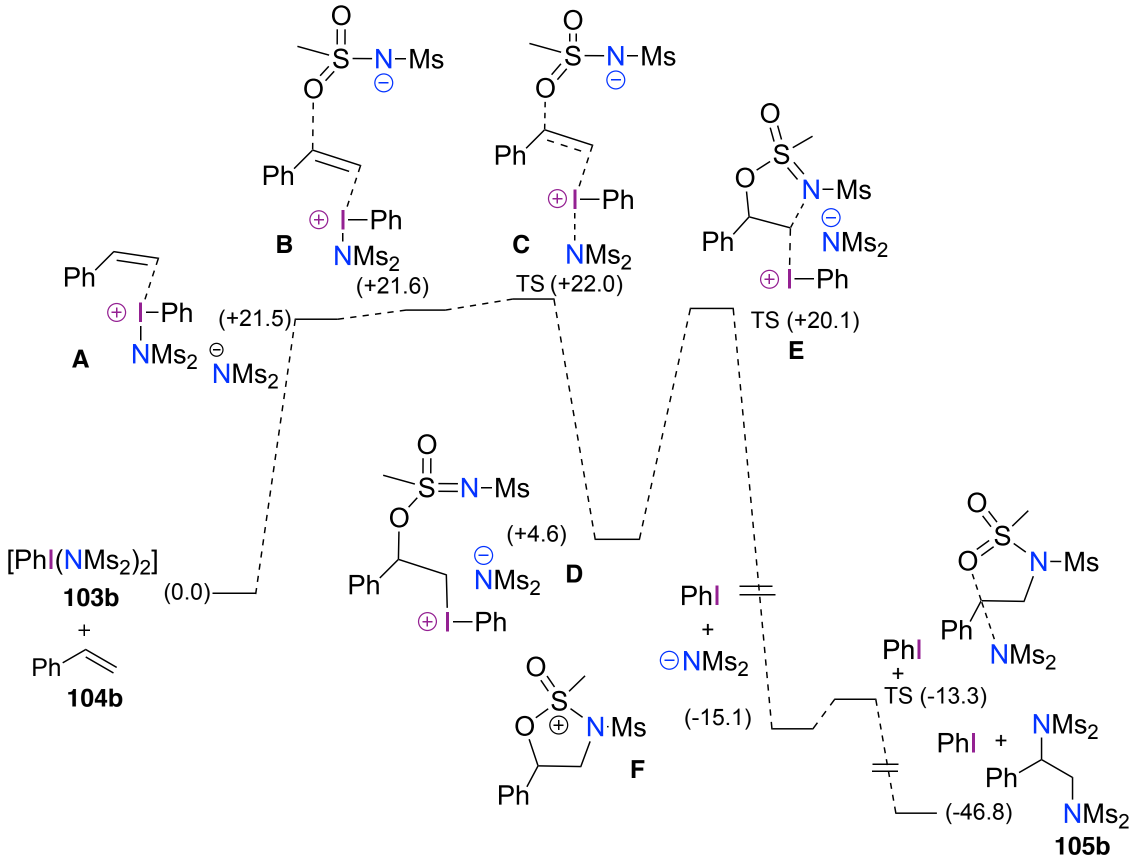
[130] a) R. M. Romero, J. A. Souto, K. Muñiz, *J. Org. Chem.* **2016**, *81,* 6118; b) I. Funes-Ardoiz, W. M. C. Sameera, R. M. Romero, C. Martínez, J. A. Souto, D. Sampedro, K. Muñiz, F. Maseras *Chem. Eur. J.* **2016**, *22*, 7545.

(Scheme 2.5). As expected, electron-donating substituents on the *para* position of the aromatic core increased the reaction rate by stabilization of cationic **103X´**.



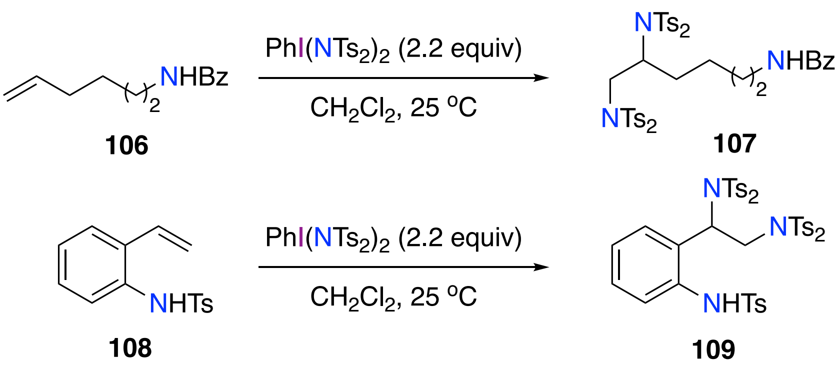
Scheme 2.5: Electronic effects on the iodine(III) reagent proven by the kinetic profiles of vicinal diamination of 4-fluorostyrene.

DFT calculations revealed a dual role of the bissulfonimide as nitrogen source, based on its O-centered nucleophilicity at the initial step of the alkene functionalization. Subsequent attack from the nitrogen formed the cyclic cationic intermediate, which upon a second nucleophilic attack of the bisimido group yields the final diamine (Scheme 2.6).[130b]



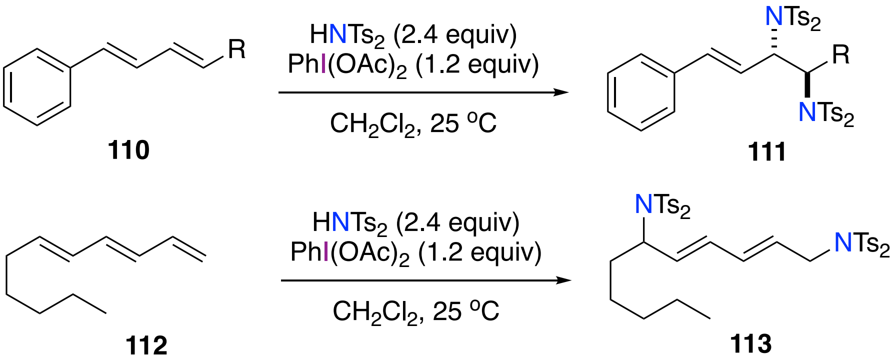
Scheme 2.6: DFT calculation for the vicinal diamination of styrene.

As previously described, in 2013 Muñiz reported the synthesis of the reagent **103** (Scheme 2.2). With the preformed reagent in hand a series of transformations were accomplished, including more challenging substrates concerning the reactivity. For instance, substrates **106** and **108**, where intramolecular amination could take place; the intermolecular one occurred affording diamines **107** and **109** respectively (Scheme 2.7).[128b]



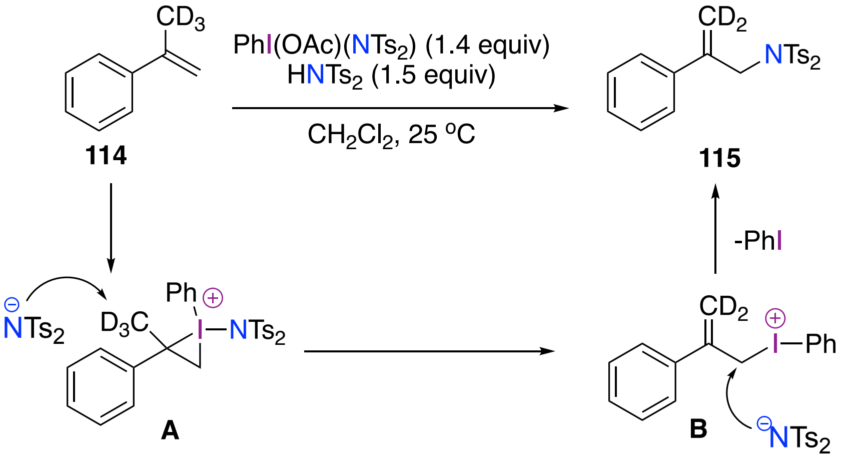
Scheme 2.7: Vicinal diamination of alkenes overriding cyclization reaction.

Further exploration on substrate range led to the development of selective diamination of various dienes **110** and trienes **112**. 1,4-disubstituted 1,3-butadienes were diaminated in a completely diastereoselective way towards **111** bearing a styrene unit as the preferential alkene (Scheme 2.8).[131]



Scheme 2.8: Vicinal diamination of conjugated alkenes.

Allylic amination was also investigated. Interestingly, in this case the mechanistic scenario differs from the vicinal diamination of alkenes (Scheme 2.9).[132] The mechanistic hypothesis was validated by control experiments. DFT calculations revealed the exact pathway of the reaction.[130b] Allylic amination with the in situ formation of the reagent **103** was also demonstrated by Minakata.[133]



Scheme 2.9: Mechanism of allylic amination of β-methyl styrene with the mixed iodine(III) reagent.

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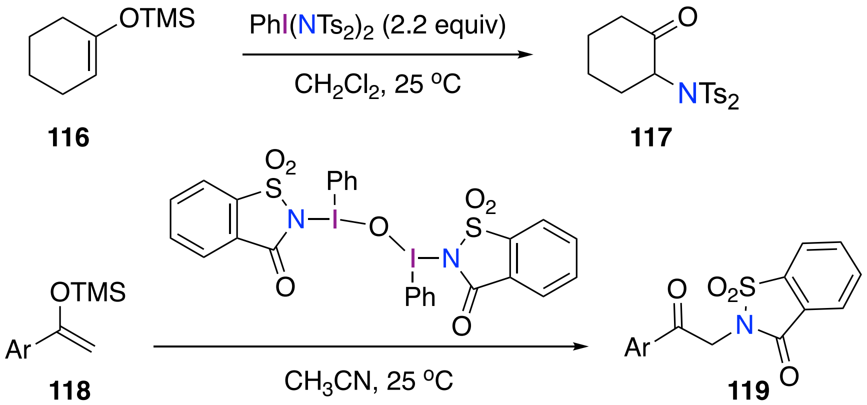
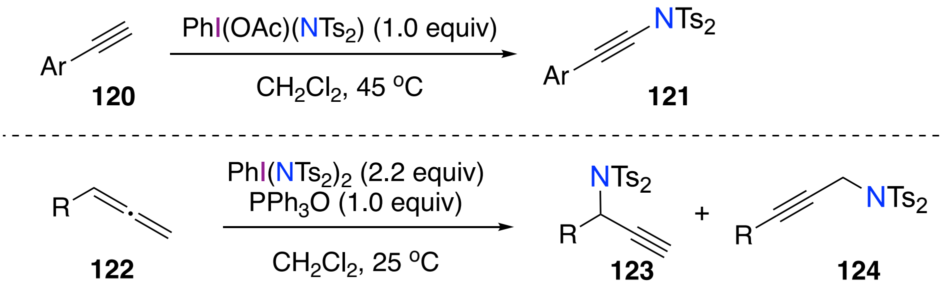
[131] A. Lishchynskyi, K. Muñiz, *Chem. Eur. J.* **2012**, *18*, 2213.
[132] J. A. Souto, D. Zian, K. Muñiz, *J. Am. Chem. Soc.* **2012**, *134*, 7242.
[133] K. Kiyokawa, S. Yahata, T. Kojima, S. Minakata, *Org. Lett.* **2014**, *16*, 4646.

These reagents provided efficient amination reactions, not only for the case of electron rich alkenes. Enol silyl ethers **116** surprisingly led to the formation of the α carbonyl-aminated products, like **117** (Scheme 2.10).[130b] The acid byproduct led to the cleavage of the silyl protecting group. Zhdankin validated the hypothesis of Muñiz by performing the same amination reaction with saccharin as aminating agent.[134]



Scheme 2.10: Iodine(III)-mediated synthesis of α amino-ketones.

Alkynes as alternative substrates were also investigated by Muñiz, leading to a successful amination of terminal acetylenes **120** (Scheme 2.11 top).[135] This example constitutes a beautiful entry into the formation of ynamides **121** as their previous synthesis was based on iodonium salts and difficult to handle lithium reagents. A logical extension towards equivalent bonds was the amination of allenes **122** that led to excellent yields of the propargylic amines **122** and **123** (Scheme 2.11 bottom).[136]



Scheme 2.11: a) Synthesis of ynamides; b) Amination of allenes.

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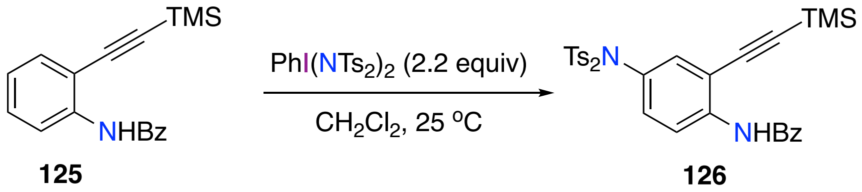
[134] A. Yoshimura, S. R. Koski, J. M. Fuchs, A. Saito, V. N. Nemykin, V. V. Zhdankin, *Chem. Eur. J.* **2015**, *21*, 5328.

[135] J. A. Souto, P. Becker, Á. Iglesias, K. Muñiz, J. Am. Chem. Soc. **2012**, *134*, 15505.

[136] N. Purkait, S. Okamura, J. A. Souto, K. Muñiz, *Org. Lett.* **2014**, *16*, 4750.

All the reactions described above demonstrate the robustness of this specific class of hypervalent iodine reagents. Extension to aromatic sp^2 bonds was also tested. In particular, a challenging substrate **125**, in which a competing intramolecular amination towards the more stable indole could occur, was submitted into reaction but once again the intermolecular aromatic amination was preferred, forming product **126** (Scheme 2.12).[126b] Noteworthy that this has remained a unique example of aromatic C-H amination with the use of these substrates, so far.



Scheme 2.12: Intermolecular aromatic amination.

Some years later, the group of Taiffeler reported a similar amide driven aromatic amination.[137] The authors proposed an ionic mechanism for the reaction. The initial interaction of the lithiated triflimide with the hypervalent iodine(III) reagent leads to an increased electrophilicity at the iodine center allowing the coordination of the acetamide. A subsequent nucleophilic attack of the triflimide anion in an associative pathway and rearomatization affords the final product **127** (Scheme 2.13). The same concept was suggested by Zhu who reported the selective amination of 8-amido quinolines in the 5-position.[138]

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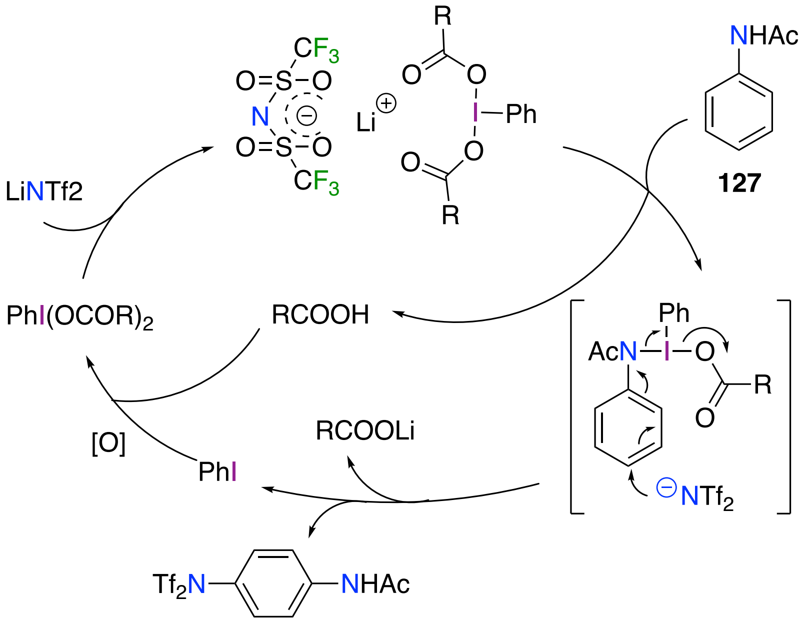
[137] A. Pialat, J. Bergés, A. Sabourin, R. Vinck, B. Liégault, M. Taillefer, *Chem. Eur. J.* **2015**, *21*, 10014.
[138] D. Ji, X. He, Y. Xu, Y. Brian, W. Liu, Q. Zhu, Y. Xu, Z. Xu, *Org. Lett.* **2016**, *18*, 4478.



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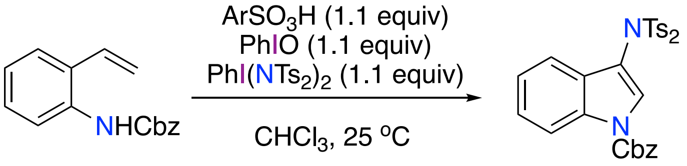
Scheme 2.13: Amide-driven aromatic intermolecular amination.

After the development of intermolecular amination reaction, Muñiz´ group was interested in the application of an iodine(III) reagent or catalyst that would suit for the synthesis of indoles by an intramolecular reaction. Indeed, they succeeded the cyclization of 2-aminostyrenes towards indoles, with the use of a sterically congested sulfonic acid and iodosobenzene for the in situ formation of a modified Koser´s type reagent. Further functionalization of the obtained indoles **130** was achieved with the use of hypervalent iodine reagent **103** that provided selective amination at the expected nucleophilic C3 position of the substrate **129** (Scheme 2.14).[139]



129 **130**

Scheme 2.14: Iodine(III) promoted sequential amination.

Within the concept of indole functionalization, C3 oxygenation by PhI(OAc)$_2$ has been reported by different groups over the recent years.[140] *Trans*-diacetoxylation of N-

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[139] L. Fra, A. Millán, J. A. Souto, K. Muñiz, *Angew. Chem. Int. Ed.* **2014**, *53*, 7349.

[140] a) K. Liu, P. Wen, J. Liu, G. Huang, *Synthesis* **2010**, 3623; b) Q. Liu, G. Li, H. Yi, P. Wu, J. Liu, A. Lei, *Chem. Eur. J.* **2011**, *17,* 2353; c) V. Soni, U. N. Patel, B. Punji, *RSC Adv.* **2015**, *5*, 57472.

protected indoles has also been accomplished.[141] Finally, the use of diaryiodonium salts for selective C3 arylation of indoles has been reported by Ackermann.[142]

With all the gained knowledge concerning this class of iodine(III) reagents and the consideration that indoles represent an interesting topic especially related to their further diversification for medicinal purposes, a plan to investigate protocols for selective C-N bond formation was set up.

In this chapter, the general results of the amination of indoles and tryptamine derivatives will be discussed. Further diversification of the new aminated products and the opening of new chemical space towards subsequent experimentation will be presented.

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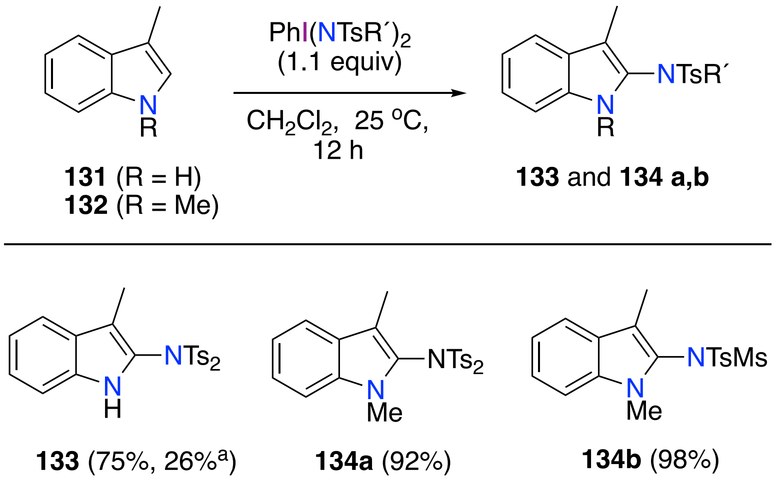
[141] Q. Liu, Q. Y. Zhao, J. Liu, P. Wu, H. Yi, A. Lei, *Chem. Commun.* **2012**, *48*, 3239.

[142] L. Ackermann, M. Dell'Acqua, S. Fenner, R. Vicente, R. Sandmann, *Org. Lett.* **2011**, *13*, 2358.

2.2 Results and Discussion

We considered 3-methylindole **131** as a good starting point for our investigation, as they inhabit a special structural feature: as the commonly preferred C3-position is blocked, the amination should solely proceed to the desired C2 position. To our delight, there was no need for optimization of the reaction conditions, as the amination of the unprotected indole **131** with the preformed hypervalent iodine(III), that bears two bistolymides as ligands, provided the expected aminated product **133a** in 75% of yield (Scheme 2.15). When the nitrogen of the indole core was protected with a methyl group, the yield of **134a** was raised to 92%. A different hypervalent iodine(III) reagent bearing mixed tosyl-mesylimido ligands iodine was synthesized and tested for this transformation, allowing the formation of **134b** in 98% yield.

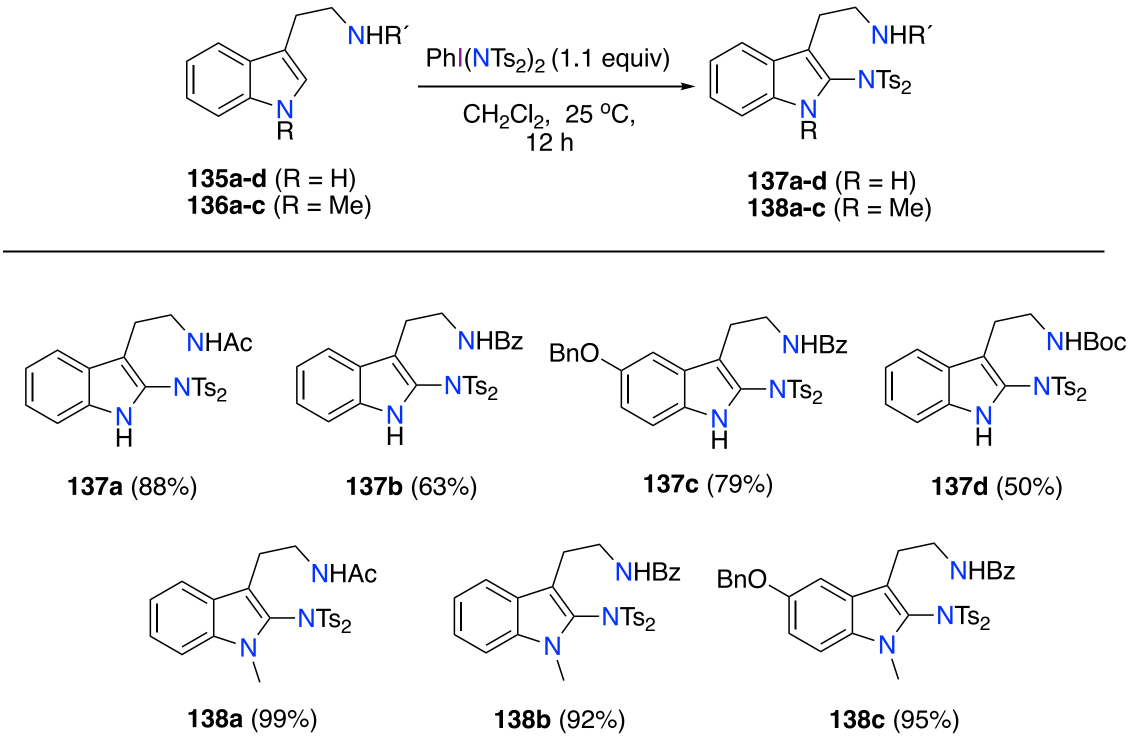


Scheme 2.15: Selective C2 amination of 3-methylindoles. ^{a}reaction performed with PhI(OAc)$_2$ (1.0 equiv)/ HNTs$_2$ (2.0 equiv).

Interestingly, the reagent combination of (diacetoxy)iodosobenzene and bistosylimide for the in situ formation of PhI(NTs$_2$)$_2$ gave inferior results, probably due to the high reactivity of the indole core. The successful formation of **133** and **134a,b** adds to recent work on iodine-mediated 2-amination of indoles.[139]

Aiming for higher functional derivatization, we turned our attention to tryptamines as suitable candidates for intermolecular amination with the present iodine(III) reagents. In the field of tryptamine alkaloids, hexahydropyrroloindole derivatives, resulting from intramolecular 2-amination, represent common entities that constitute a fascinating class of natural products.[143] Thus, we considered that tryptamine and its aminated derivatives would be interesting for further oxidative transformations. We had already experienced that the use of $PhI(NTs)_2$ with a tryptamine derivative did not give the diamination product, but the mono C2 aminated one.[128b] The logical consequence was to expand the scope of the reaction for further exploration (Scheme 2.16).

Surprisingly, the intramolecular amination did not occur in any of the cases for **135a-d** or **136a-c**. The rare observation that the intermolecular amination overperform the potentially preferred intramolecular process is a striking feature of this particular iodine(III) reagent.



Scheme 2.16: Selective C2 amination of tryptamines with $(PhINTs_2)_2$.

The scope of the reaction is sufficiently broad concerning the functional group tolerance as free tryptamines **135a-d** and N-methylated ones **136a-c** were aminated selectively at the C2 position in excellent yields.

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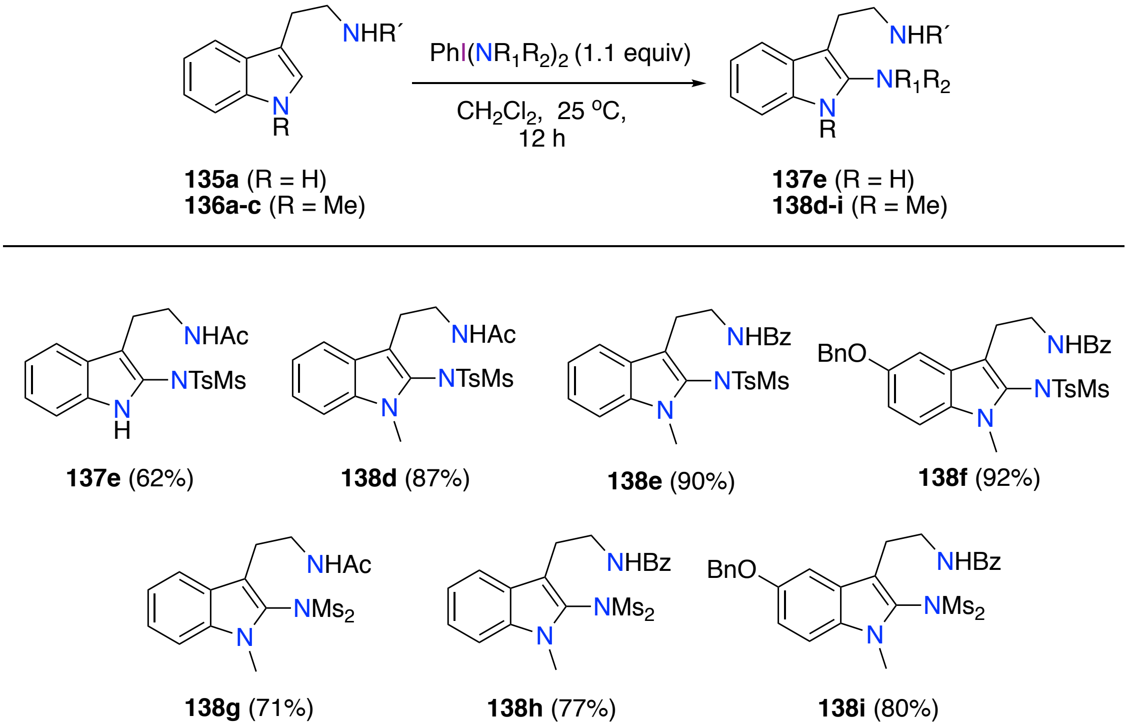
[143] a) A. Steven, L. E. Overman, L. E. *Angew. Chem. Int. Ed.* **2007**, *46*, 5488; b) D. Crich, A. Banerjee, *Acc. Chem. Res*. **2007,** *40*, 151; c) P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Álvarez, *Chem. Eur. J.* **2011**, *17*, 1388.

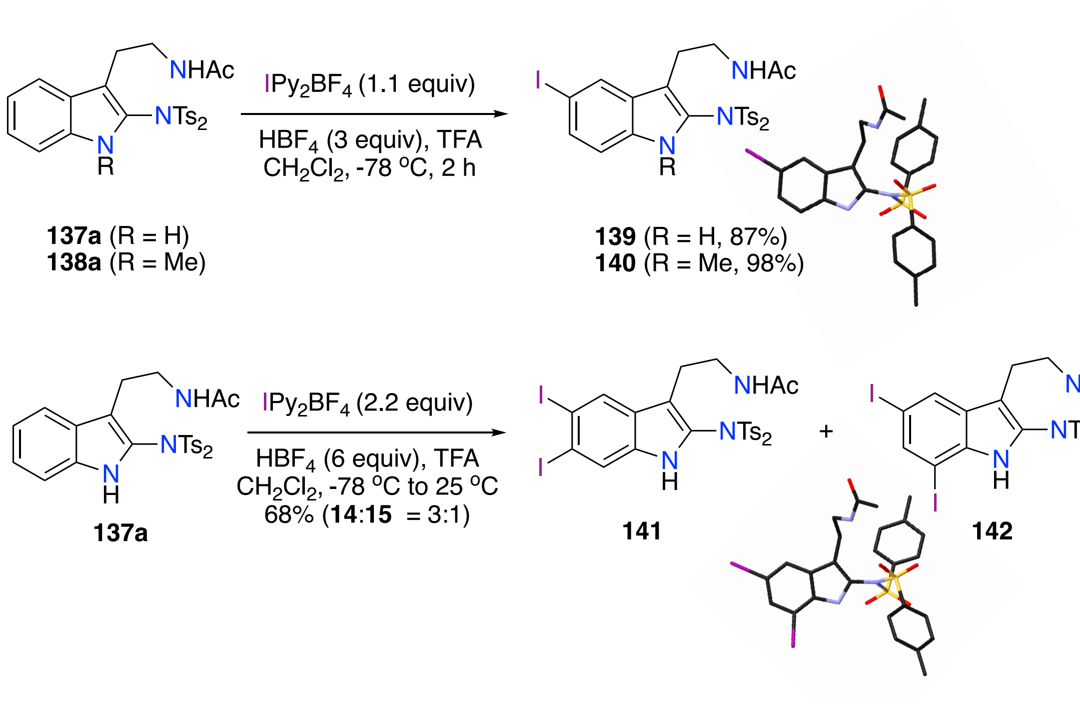
The further expansion to different transferrable sulfonamide groups including bismesylimide and mesyltosylimide was also achieved as demonstrated with the formation of **137e** and **138d-i** in good to excellent yields (Scheme 2.17).



Scheme 2.17: Selective C2 amination of tryptamines with $(PhINMs_2)_2$ and $(PhINTsMs)_2$.

We continued the investigation with additional transformations on the resulted aminated structures. Considering that iodoamination could take place in the presence of the electron-rich double bond on the tryptamine core, such a transformation would lead to the challenging installation of a carbon atom bearing three nitrogen substituents. Thus, we started the experimentation with the highly electrophilic Barluenga´s reagent. However, even after variation in conditions, only regioselective aromatic iodination was observed. Experimentation with different iodinating agents, such as N-iodosuccinimide alone or in combination with bis(trifluoroacetoxy)iodosobenzene did not yield any desired product. A possible explanation is that the steric hinderance provided by the bisulfonamide is too high leading to a blockage at the C2-C3 double bond. Interestingly, when compounds **137a** or **138a** were treated with 1.1 equivalents of the iodinating agent and in the presence of HBF_4, monoiodination was observed at the expected C5 position (Scheme 2.18a). By treating the compounds with higher amounts of the reagent, a mixture of two diiodinated regioisomers is obtained. The second iodine atom was introduced at the C6 and C7 positions of the tryptamine core affording products **141** and **142** in a 3:1

ratio respectively. Both compounds were characterized by X-Ray crystallography (Scheme 2.18b). For the latter, it is worthy to mention that the functionalization of tryptamine or indole cores at the C7 position is usually more complicated.[144] The present iodine substituent should subsequently enable further modification, under standard cross-coupling protocols.



Scheme 2.18: Selective iodination on the tryptamine core.

In order to investigate the behavior of a smaller electrophile than iodine we turned our attention to fluorine. We chose Selectfluor for the fluoroamination of tryptamines.[145] In the reported protocol, *cinchona* alkaloids were used, though for the present cases, they resulted in a complete shutdown of reactivity. However, exposing compounds **137a,b** and **138a,b**, respectively, to Selectfluor in presence of an inorganic base, resulted in a clean fluorination. First attempts for cyclization failed, thus giving the products **143a,b** and **144a,b** in high yields (Scheme 2.19). We considered that the lone pair of the nitrogen on the tryptamine core was involved in this transformation. We confirmed this hypothesis by shortening the reaction time for **137a**. This procedure resulted in the isolation and full

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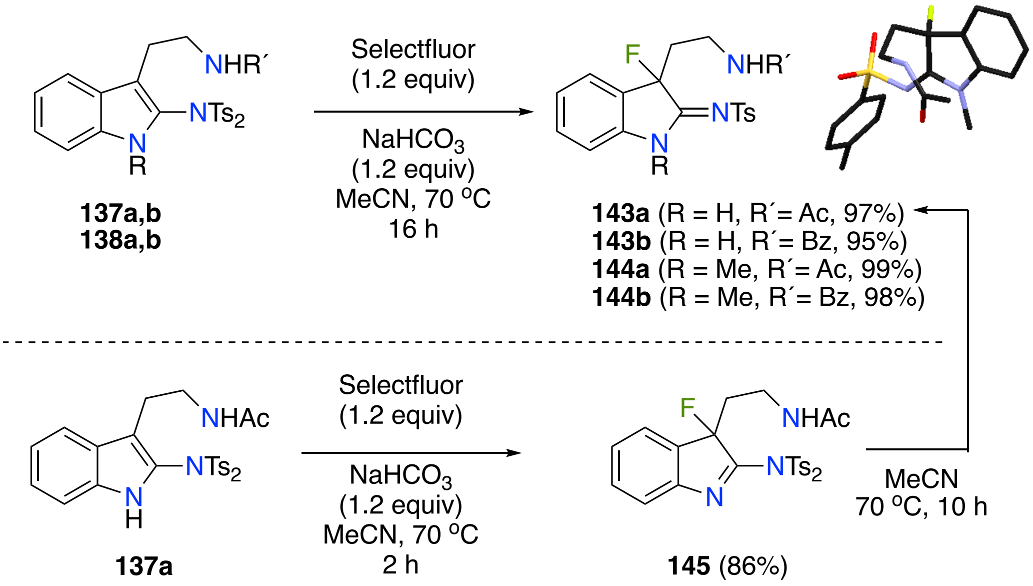
[144] R. P. Loach, O. S. Fenton, K. Amaike, D. S. Siegel, E. Ozkal, M. Movassaghi, *J. Org. Chem.* **2014**, *79*, 11254.

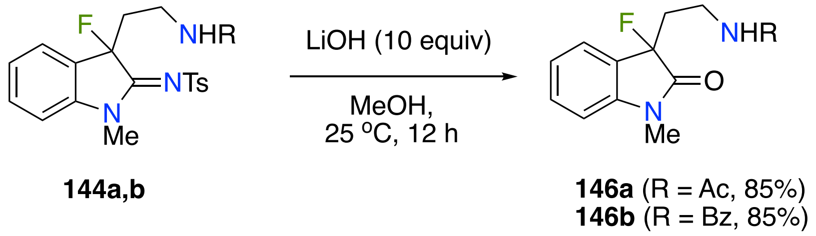
[145] O. Lozano, G. Blessley, T. Martínez del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem. Int. Ed.* **2011**, *50*, 8105.

characterization of the stable intermediate **145** in 86% yield. Additional heating in acetonitrile led to unprecedented detosylation and formation of **143a** as the only product.



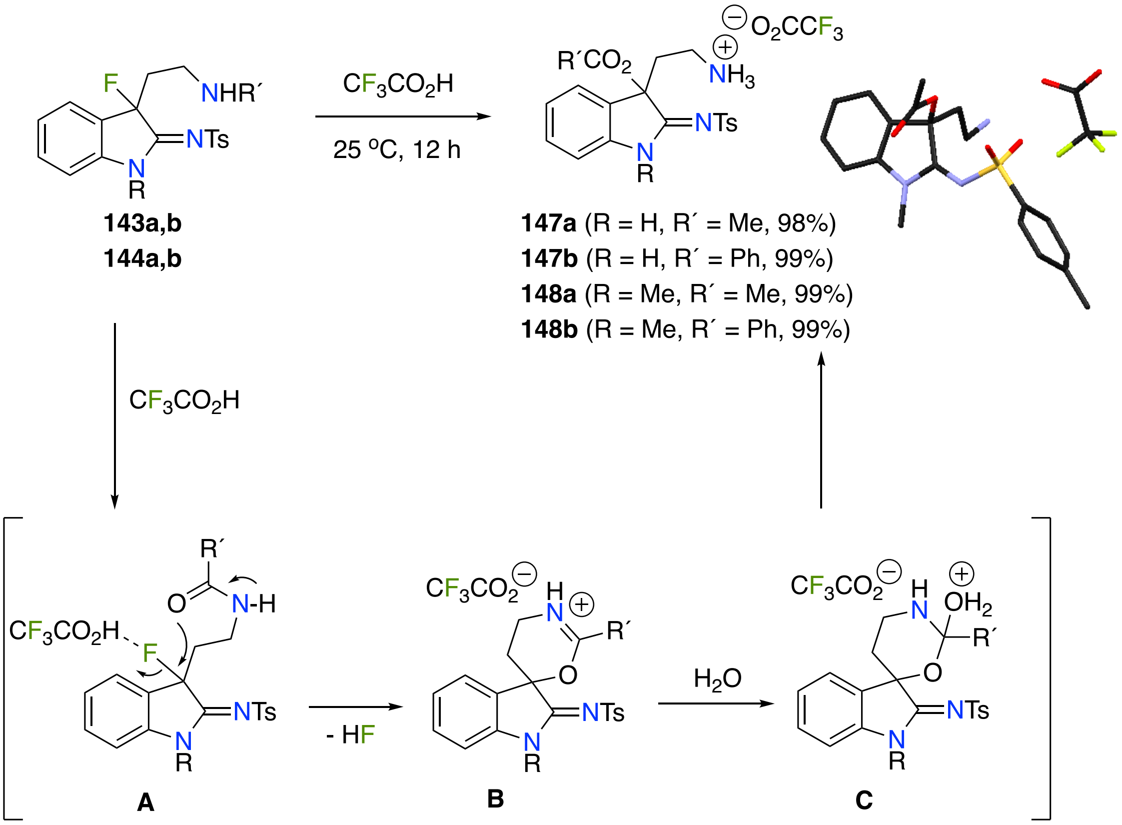
Scheme 2.19: Selective electrophilic fluorination the aminated tryptamine products.

Further treatment of **144a,b** with lithium hydroxide in methanol provided conditions for a clean hydrolysis of the tosylimido group; converting them into their corresponding new oxindole derivatives **146a,b** as the only product with complete selectivity (Scheme 2.20).



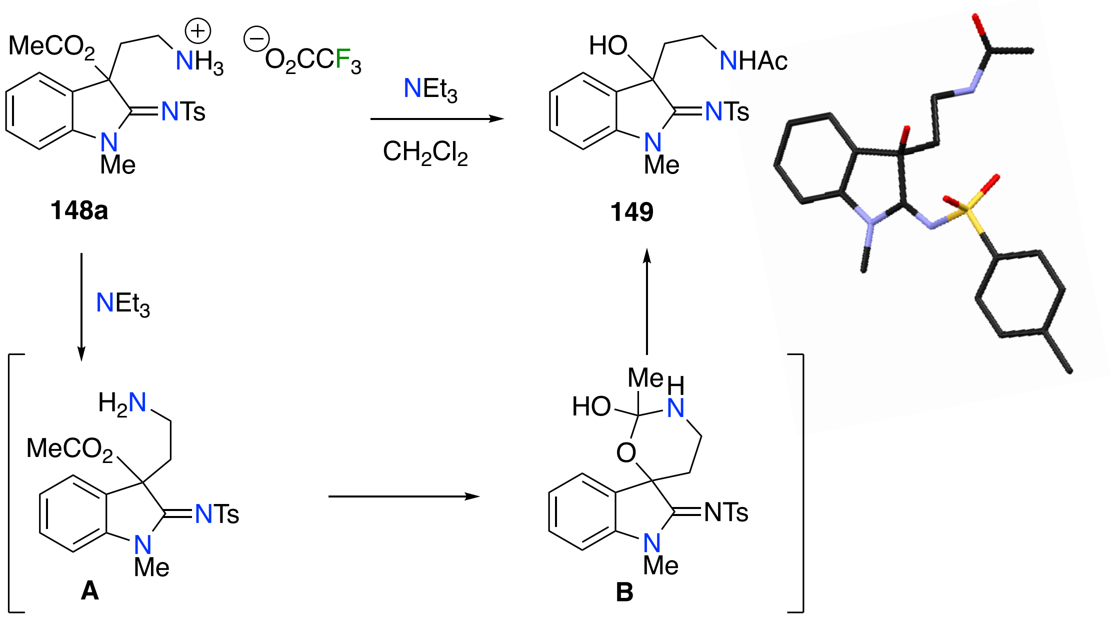
Scheme 2.20: Oxindole derivatives´ formation with the use of lithium hydroxide.

When the obtained fluorinated compounds **143a,b** and **144a,b** were treated with trifluoroacetic acid, a clean defluorination was observed (Scheme 2.21). The reaction proceeds by activation of the fluorine atom by a strong protic acid, subsequently leading to its dissociation. Mechanistically, upon oxygen attack from the amide, the spirocyclic intermediate **B** is generated. In presence of water, nucleophilic attack of the water molecule leads to the ring opening towards the esters **147a,b** and **148a,b** respectively.



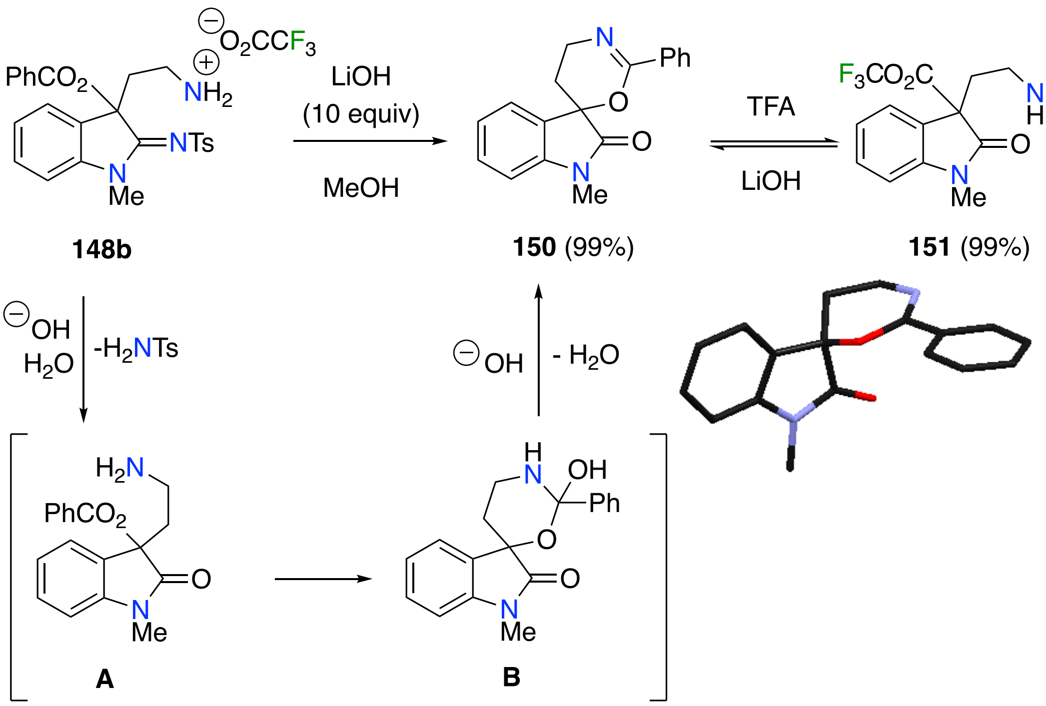
Scheme 2.21: Treatment of the fluorinated products with trifluoroacetic acid.

Subsequent exposure of the ester **148a,b** to basic conditions allowed for additional transformations. When a weak base, such as trimethylamine was used, the formation of the unexpected product **149** was observed (Scheme 2.22). Mechanistically, the formation of the primary amine **A** initiates the whole transformation. A quantitative intramolecular acetyl transfer through the cyclic tetrahedral intermediate **B** and a final ring opening reestablish the acetamide side chain providing the benzylic hydroxyl group in **149**.



Scheme 2.22: Treatment of trifluoroacetic ester products with triethylamine.

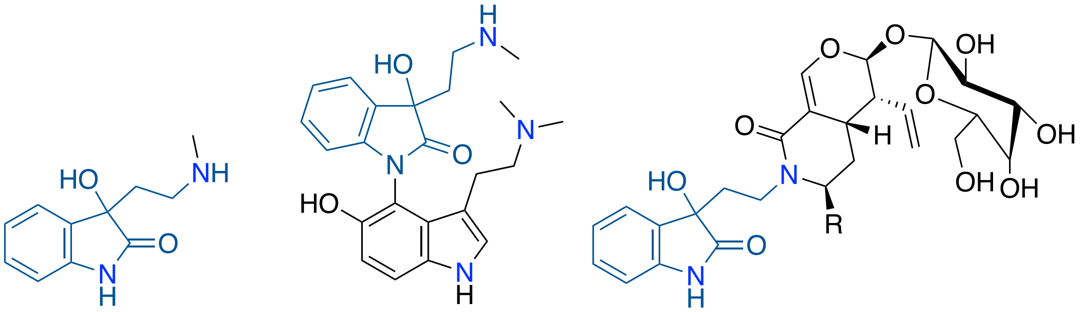
In contrast, treatment with a stronger base such as lithium hydroxide leads to detosylation toward the oxindole core as we had demonstrated with the formation of the fluorinated derivatives **146a,b** (Scheme 2.20). Under these strong basic conditions the formation of the cyclic intermediate **B** is observed. Upon final dehydratation, instead of acetyl transfer as in the case above, the *spiro*-dihydrooxazine functionality **150** was formed. Interestingly, all the mentioned transformations proceed with complete selectivity and in quantitative isolated yields. The observed rearrangement in the synthesis of **149** was also tested here. Indeed, in the presence of trifluoroacetic acid the *spiro*-dihydrooxazine **150** undergoes quantitative opening followed by a concomitant addition of one molecule of trifluoromethanesulfonic acid to furnish **151** with its benzoylamide side chain and a benzylic trifluoroacetate ester. Surprisingly, this transformation is reversible and the treatment with base led back to *spiro*-dihydrooxazine **150** (Scheme 2.23).



Scheme 2.23: Formation of *spiro*-dihydrooxazine.

2.3 Conclusions

The innovative transformations presented in this chapter provide access to a high quantity of new tryptamine derivatives. In view of the general high occurrence of the 3-(aminoethyl)-3-hydroxyoxindole motif (Figure 2.2) in nature,[146] this new methodology provides an important and unique access to this structural moiety as well as to the yet biologically unexplored classes of 2-imido and allosteric 3-fluoro derivatives.[147]



donoxaridine arundaphine paratunamides

Figure 2.2: Examples on natural products with the 3-(aminoethyl)-3-hydroxyoxindole motif.

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[146] a) S. Peddibhotla, *Curr. Bioact. Comp.* **2009**, *5*, 20; b) T. Yan, X. Wang, H. Sun, J. Liu, Y. Xie, *Molecules* **2013**, *18*, 14505.

[147] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881.

2.4 Experimental Section

2.4.1 General information

All solvents, reagents and all deuterated solvents were commercially available. Column chromatography was performed with silica gel (type 60, 0.063-0.2 mm). NMR spectra were recorded on a 400 MHz or 500 MHz spectrometer, respectively. All chemical shifts in NMR experiments were reported as ppm downfield from TMS. The following calibrations were used: $CDCl_3$ $\delta = 7.26$ and 77.0 ppm, CD_2Cl_2 $\delta = 5.32$ and 54.00 ppm, MeOD $\delta = 3.31$ and 49.0 ppm. HRMS were recorded using ESI-TOF techniques. IR spectra were taken in the solid state.

The following compounds were commercially available and used as received: tryptamine, 5-benzyloxytryptamine, tosyl chloride, mesyl chloride, triethylamine, acetyl chloride, benzoyl chloride, methyl iodide, trifluoroacetic acid, lithium hydroxide, di(acetoxy)iodobenzene, bis(pyridine)iodonium tetrafluoroborate, tetrafluoroboric acid diethyletherate, Selectfluor® and 3-methylindole.

2.4.2 General procedures

General synthetic procedure for the hypervalent reagents **103** (GP1)

To a solution of (diacetoxyiodo)benzene (0.3 mmol, 1.0 equiv) in chlorobenzene (1.5 mL) was added the corresponding bissulfonamide (0.6 mmol, 2.0 equiv), and the reaction mixture was stirred at 55 °C. The solvent was removed under reduced pressure. Chlorobenzene was added and removed three times under reduced pressure. After drying at reduced pressure, the corresponding iodine(III) compound was obtained in quantitative yield.

General synthetic procedure for the N-methylation of the indole and tryptamine core (GP2)

A mixture of the indole (0.5 mmol, 1.0 equiv), NaOH (1.5 mmol, 3.0 equiv) and Bu_4NOH (0.025 mmol, 5% mol) in CH_2Cl_2 (5 mL), was stirred at 25 °C for 10 min. MeI (0.55 mmol, 1.1 equiv) was added into the reaction mixture at 25 °C. The reaction mixture was stirred for 12 h. The reaction mixture was quenched with aqueous solution of 10% HCl and then with aqueous saturated solution of $NaHCO_3$ and was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, MeOH/CH_2Cl_2) to afford the pure product.

General synthetic procedure for the amidation of the tryptamine core (GP3)

A solution of the tryptamine (1.0 mmol, 1.0 eq) and Et_3N (3.0 mmol, 3.0 eq) in CH_2Cl_2 (5 mL) was stirred at 25 ºC for 10 min. A solution of the corresponding chloride (1.15 mmol, 1.15 eq) in CH_2Cl_2 (5 mL) was added dropwise to the above solution at 0 ºC. The reaction mixture was stirred at 25 ºC for 1h. The reaction mixture was quenched with 10% HCl and then with aqueous saturated solution of $NaHCO_3$ and was extracted with CH_2Cl_2. The combined organic layers were dried by Na_2SO_4. The solvent was removed under reduced pressure affording the pure product.

General procedure for the intermolecular C(sp_2)-H amination (GP4)

To a solution of the corresponding starting material (0.2 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added the corresponding iodine(III) reagent (0.22 mmol, 1.1 equiv) and the mixture was stirred at 25 °C for 12 h. After that time, the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 0.2/10, v/v) to obtain the pure product.

General procedure for the monoiodination reaction (GP5)

To a stirred solution of acetamide (0.091 mmol, 1.0 equiv) and TFA (2 mL) in CH_2Cl_2 (20 mL) at -78 ºC, $HBF_4{\cdot}Et_2O$ (0.3 mmol, 3.0 equiv) and bis(pyridine)iodonium tetrafluoroborate (0.091 mmol, 1 equiv) were added. The brown solution was stirred for 2 h. The reaction was quenched with cold water. The two phases were separated and the organic layer was washed with water and an aqueous saturated solution of sodium thiosulfate. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to obtain a crude product, which was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1/1, v/v) to afford the pure products.

General procedure for the fluorination reaction (GP6)

Selectfluor® (0.06 mmol, 1.2 equiv) was added to a stirred solution of the corresponding starting material (0.05 mmol, 1.0 equiv) and $NaHCO_3$ (0.06 mmol, 1.2 equiv) in acetonitrile at 70 °C. The reaction was allowed to stir at 70 °C for 16 h. The solvent was removed under reduced pressure and an aqueous saturated solution of $NaHCO_3$ was added. The residue was extracted with ethyl acetate and the combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 2/3, v/v) to afford the pure products.

<u>General procedure for the treatment with LiOH (GP7)</u>

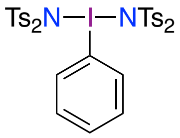
The corresponding starting material (0.11 mmol, 1.0 equiv) was dissolved in MeOH (2 mL) and LiOH (0.027, 1.1 mmol, 10.0 equiv) was added. The reaction mixture was stirred at 25 ºC for 16 h. The solvent was removed under reduced pressure. The residue was quenched with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 0.2:10, v/v) to afford the pure products.

<u>General procedure for the treatment with TFA (GP8)</u>

The corresponding starting material (0.12 mmol, 1.0 equiv) was dissolved in TFA (4 mL) and the reaction mixture was allowed to stir for 12 h under an atmosphere of argon. The solvent was removed under reduced pressure and the pure product was isolated in quantitative yield.

2.4.3 Data for the compounds

N,N'-(Phenyl-λ3-iodane)bis(4-methyl-*N*-tosylbenzenesulfonamide) 103a

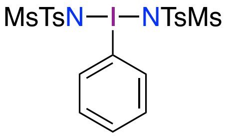


Synthesized according to GP1. 100% yield. White solid. Data in agreement with the ones reported.[128b]

^{1}H NMR (400 MHz, *d*-DMSO): δ = 2.33 (s, 12H), 7.16 (d, J = 8.0 Hz, 8H), 7.52 (d, J = 8.2 Hz, 8H), 7.60-7.62 (m, 2H), 7.63-7.72 (m, 1H), 8.22 (dd, J = 8.3,1.1 Hz, 2H).

^{13}C NMR (101 MHz, *d*-DMSO): δ = 20.9, 123.4, 126.4, 128.9, 131.2, 132.5, 134.6, 141.2, 141.3.

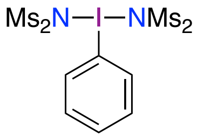
N,N'-(phenyl-λ3-iodanediyl)bis(4-methyl-*N*-(methylsulfonyl)benzenesulfonamide) 103b



Synthesized according to GP1. 100% yield. White solid. Data in agreement with the ones reported.[128b]

^{1}H NMR (500 MHz, *d*-DMSO): δ = 2.34 (s, 6H), 2.87 (s, 6H), 7.17-7.30 (m, 4H), 7.60-7.66 (m, 6H), 7.69-7.76 (m, 1H), 8.22 (dd, *J* = 8.4, 1.2 Hz, 2H).**^{13}C NMR** (126 MHz, $CDCl_3$): δ = 20.9, 43.0, 123.4, 126.5, 127.7, 128.7, 130.7, 131.2, 132.5, 134.5, 137.1, 141.1, 141.8.

N,N'-(Phenyl- λ3-iodanediyl)bis(*N*-(methylsulfonyl)methanesulfonamide) 103c

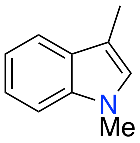


Synthesized according to GP1. 100% yield. White solid. Data in agreement with the ones reported.[128b]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 6H), 3.04 (s, 6H), 7.20 (d, J = 8.0 Hz, 4H), 7.55 (d, J = 8.3 Hz, 4H), 7.62-7.69 (m, 2H), 7.70 (d, J = 7.4 Hz, 1H), 8.12-8.23 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.9, 42.8, 126.5, 128.8, 130.7, 131.2, 134.4, 137.3, 141.0, 141.7

1,3-Dimethyl-1*H*-indole132



Synthesized according to GP2. 48% yield. Brown oil. Data in agreement with the ones reported.[148]

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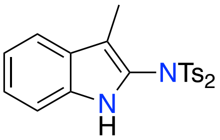
[148] D. Anumadla, C. S. Jeffrey, *J. Am. Chem. Soc.* **2015**, *137*, 14858.

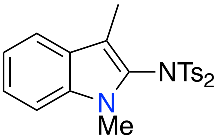
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (d, *J* = 1.1 Hz, 3H), 3.82 (s, 3H), 6.93 (s, 1H), 7.26-7.30 (m, 1H), 7.35-7.44 (m, 2H), 7.74 (d, *J* = 7.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 9.6, 32.5, 109.0, 110.1, 118.5, 119.0, 121.4, 126.6, 128.7, 137.0.

4-Ethyl-*N*-(3-methyl-1*H*-indol-2-yl)-*N*-tosylbenzenesulfonamide 133



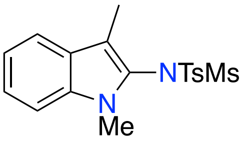
Synthesized according to GP4. 75% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.69 (s, 3H), 2.48 (s, 6H), 7.14 (m, 1H), 7.28-7.31 (m, 2H), 7.34 (d, *J* = 7.7 Hz, 4H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.82 (brs, 1H), 7.86 (d, *J* = 8.4 Hz, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 8.0, 21.8, 111.4, 115.6, 119.9, 120.0, 122.7, 124.1, 127.5, 128.6, 129.7, 135.0, 136.4, 145.3. **IR** ν(cm^{-1}): 3385, 2956, 2923, 2851, 1595, 1372, 1345, 1169, 1082, 881, 657, 549. **HRMS** (ESI-TOF): calcd. for $C_{23}H_{21}N_2O_4S_2$: 453.0943; found: 453.0927. **m.p.:** 164-165 °C.

N-(1,3-Dimethyl-1*H*-indol-2-yl)-4-methyl-*N*-tosylbenzenesulfonamide 134a



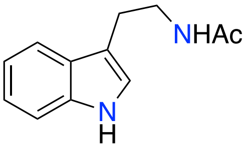
Synthesized according to GP4. 92% yield. Brown solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.66 (s, 3H), 2.40 (s, 6H), 3.19 (s, 3H), 7.03-7.08 (m, 1H), 7.15-7.23 (m, 2H), 7.26 (d, *J* = 7.7 Hz, 4H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 8.7, 21.8, 29.5, 109.8, 113.8, 119.4, 120.0, 123.7, 124.6, 126.4, 129.0, 129.7, 136.0, 136.4, 145.5. **IR** ν(cm^{-1}): 3055, 2922, 1594, 1469, 1372, 1357, 1166, 1084, 878, 738. **HRMS** (ESI-TOF): calcd. for $C_{24}H_{24}N_2NaO_4S_2$: 491.1070; found 491.1065. **m.p.:** 194-196 °C.

N-(1,3-Dimethyl-1*H*-indol-2-yl)-4-methyl-*N*-(methylsulfonyl)benzenesulfonamide 134b



Synthesized according to GP4. 98% yield. Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.01 (s, 3H), 2.49 (s, 3H), 3.44 (s, 3H), 3.61 (s, 3H), 7.14-7.19 (m, 1H), 7.24-7.32 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 8.8, 21.8, 29.4, 44.4, 109.8, 113.5, 119.5, 120.0, 123.8, 126.3, 129.2, 129.7, 135.1, 135.9, 145.9. **IR** ν(cm^{-1}): 3055, 2931, 1469, 1369, 1354, 1163, 1121, 1087, 966, 872, 737. **HRMS** (ESI-TOF): calcd. for $C_{18}H_{20}N_2NaO_4S_2$: 415.0757; found 415.0743. **m.p.:** 189-191 °C.

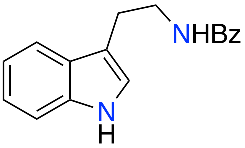
N-(2-(1*H*-Indol-3-yl)ethyl)acetamide 135a



Synthesized according to GP3. 99% yield. Colorless oil. Data in agreement with the ones reported.[149]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3H), 2.95 (td, *J* = 6.9, 0.9 Hz, 2H), 3.57 (td, *J* = 6.8, 5.7 Hz, 2H), 5.85 (d, *J* = 5.9 Hz, 1H), 6.97 (d, *J* = 2.1 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.33-7.39 (m, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 8.73 (s, 1H).

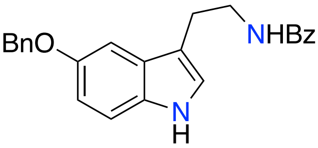
N-(2-(1*H*-Indol-3-yl)ethyl)benzamide 135b



Synthesized according to GP3. 94% yield. Yellow solid. Data in agreement with the ones reported.[128b]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10 (t, *J* = 6.6 Hz, 2H), 3.81 (q, *J* = 6.6 Hz, 2H), 6.26 (s, 1H), 7.06 (d, *J* = 2.3 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.33-7.42 (m, 3H), 7.42-7.50 (m, 1H), 7.62-7.71 (m, 3H), 8.22 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.4, 40.4, 118.9, 119.7, 122.3, 122.4, 127.0, 127.5, 128.6, 131.5, 134.8, 136.6, 167.6.

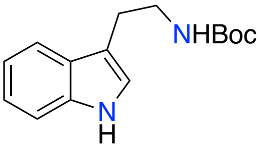
N-(2-(5-(Benzyloxy)-1*H*-indol-3-yl)ethyl)benzamide 135c



Synthesized according to GP3. 97% yield. Yellow solid. Data in agreement with the ones reported.[147]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.06 (t, *J* = 6.6 Hz, 2H), 3.79 (td, *J* = 6.4, 5.5 Hz, 2H), 5.02 (s, 2H), 6.36 (t, *J* = 5.1 Hz, 1H), 6.96 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.30-7.53 (m, 8H), 7.65-7.77 (m, 2H), 8.29 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.3, 40.4, 70.9, 102.1, 112.1, 112.8, 113.2, 123.0, 126.9, 127.6, 127.7, 127.8, 128.5, 128.5, 131.4, 131.8, 134.6, 137.5, 153.3, 167.4.

tert-Butyl (2-(1*H*-indol-3-yl)ethyl)carbamate 135d



Synthesized according to GP3. 95% yield. White solid. Data in agreement with the ones reported.[150]

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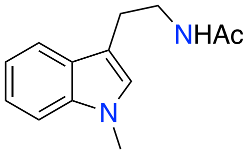
[149] H. Song, J. Yang, W. Chen, Y. Gin, *Org. Lett.* **2006**, *8*, 6011.

[150] K. C. Nicolaou, A. Krasovskiy, A. Majumder, V. E. Trepanier, D. Y.-K. Chen, *J. Am. Chem Soc.* **2009**, *131*, 3690.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.42-1.50 (m, 9H), 2.97 (t, *J* = 7.0 Hz, 2H), 3.49 (q, *J* = 6.7 Hz, 2H), 4.69 (s, 1H), 6.99 (s, 1H), 7.11-7.17 (m, 1H), 7.18-7.26 (m, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 8.31 (s, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 25.9, 28.5, 41.0, 79.3, 111.3, 113.1, 118.9, 119.4, 122.2, 127.5, 136.5, 156.2.

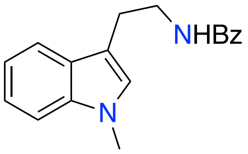
N-(2-(1-Methyl-1*H*-indol-3-yl)ethyl)acetamide 136a



Synthesized according to GP2&GP3. 50% yield. Colorless oil. Data in agreement with the ones reported.[147]

^{1}H NMR (400 MHz, CDCl$_3$): δ =1.94 (s, 3H), 2.98 (td, *J* = 6.7, 0.8 Hz, 2H), 3.60 (td, *J* = 6.7, 5.8 Hz, 2H), 3.78 (s, 3H), 5.65 (s, 1H), 6.91 (s, 1H), 7.14 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.30-7.23 (m, 1H), 7.33 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.61 (ddd, *J* = 7.9, 0.8 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 23.4, 25.2, 32.7, 40.0, 109.3, 111.5, 118.8, 119.0, 121.8, 126.8, 127.8, 137.1, 170.0.

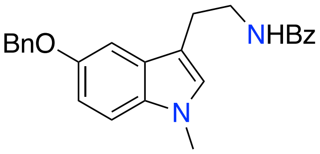
N-(2-(1-Methyl-1*H*-indol-3-yl)ethyl)benzamide 136b



Synthesized according to GP2&GP3. 53% yield. White solid. Data in agreement with the ones reported.[147]

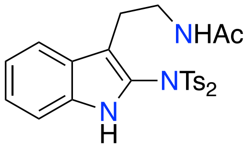
^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.97 (t, *J* = 6.7 Hz, 2H), 3.64-3.70 (m, 5H), 6.14 (s, 1H), 6.80 (s, 1H), 6.98-7.03 (m, 1H), 7.10-7.37 (m, 5H), 7.50-7.57 (m, 3H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ =25.3, 32.7, 40.6, 109.4, 111.6, 118.9, 119.0, 121.8, 126.9, 127.8, 128.5, 131.3, 134.8, 137.2, 167.5.

N-(2-(5-(Benzyloxy)-1-methyl-1H-indol-3-yl)ethyl)benzamide 136c



Synthesized according to GP2&GP3. 50% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 2.95 (t, *J* = 6.6 Hz, 2H), 3.63-3.70 (m, 5H), 4.91 (s, 2H), 6.22 (s, 1H), 6.80 (s, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.22-7.36 (m, 8H), 7.58-7.61 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 25.3, 32.8, 40.7, 71.0, 102.3, 110.2, 111.2, 112.8, 126.9, 127.5, 127.7, 127.8, 128.1, 128.5, 128.6, 131.3, 132.7, 134.7, 137.6, 153.1, 167.4. **IR** ν(cm^{-1}): 3316, 3029, 2926, 2860, 1625, 1542, 1488, 1462, 1317, 1218, 1198, 1021, 795, 695. **HRMS** (ESI-TOF): calcd. for $C_{25}H_{25}N_2O_2$: 385.1911, found: 385.1914. **m.p.:** 149-150 ºC.

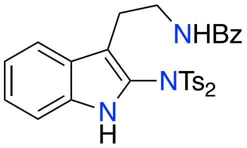
N-(2-(2-(4-Methyl-N-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)acetamide **137a**



Synthesized according to GP4. 83% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79 (s, 3H), 2.16-2.20 (t, *J* = 6.7, 2H), 2.48 (s, 6H), 3.53 (td, *J* = 6.2, 5.8 Hz, 2H), 6.24 (brs, 1H), 7.13-7.17 (m, 1H), 7.28-7.35 (m, 2H), 7.36 (d, *J* = 8.1 Hz, 4H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 4H), 8.30 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 22.9, 23.0, 38.6, 111.8, 116.2, 120.3, 120.4, 123.4, 124.5, 126.4, 128.7, 129.9, 135.2, 135.8, 145.9, 170.4. **IR** ν(cm^{-1}): 3376, 3257, 2922, 1659, 1536, 1377, 1353, 1167, 876, 773, 659, 540. **HRMS** (ESI-TOF): calcd. for $C_{26}H_{27}N_3O_5NaS_2$: 548.1290, found: 548.1277. **m.p.:** 170-171 ºC.

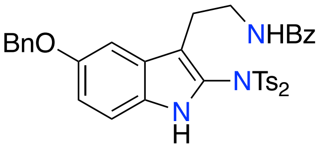
N-(2-(2-(4-Methyl-*N*-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)benzamide **137b**



Synthesized according to GP4. 63% yield. White solid. Data in agreement with the ones reported.[128b]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (t, *J* = 6.7 Hz, 2H), 2.47 (s, 6H), 3.73 (td, *J* = 6.7, 5.1 Hz, 2H), 6.67 (brs, 1H), 7.10-7.15 (m, 1H), 7.28-7.39 (m, 9H), 7.66-7.69 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 4H), 8.02 (brs, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 23.2, 39.3, 111.7, 116.3, 120.4, 120.7, 123.2, 124.5, 126.6, 127.1, 128.2, 128.7, 129.9, 131.1, 134.4, 135.1, 135.9, 145.8, 167.7.

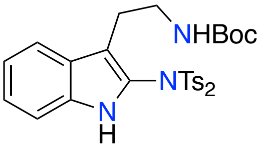
N-(2-(5-(Benzyloxy)-2-(4-methyl-*N*-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)benzamide **137c**



Synthesized according to GP4. 80% yield. Brown solid.

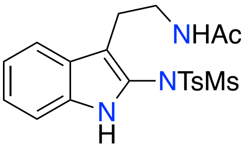
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (t, *J* = 6.6 Hz, 2H), 2.48 (s, 6H), 3.70 (td, *J* = 6.6, 5.2 Hz, 2H), 4.94 (s, 2H), 6.65 (t, *J* = 5.2 Hz, 1H), 7.00 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 8.9 Hz, 1H), 7.30-7.43 (m, 12H), 7.68-7.70 (m, 2H), 7.85-7.88 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 23.2, 39.2, 70.6, 103.0, 112.6, 116.0, 116.2, 123.6, 127.1, 127.8, 127.8, 128.3, 128.5, 128.7, 130.0, 130.2, 130.3, 131.1, 134.4, 135.9, 137.2, 137.5, 145.8, 153.6, 167.6. **IR** ν(cm^{-1}): 3384, 3191, 3059, 2922, 1640, 1579, 1485, 1376, 1187, 1165, 1083, 882. **HRMS** (ESI-TOF): calcd. for $C_{38}H_{35}N_3NaO_6S_2$: 716.1859; found: 716.1863. **m.p.:** 109-111 ºC.

tert-Butyl(2-(2-(4-methyl-*N*-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)carbamate 137d



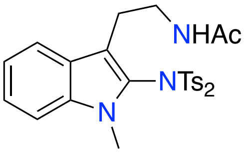
Synthesized according to GP4. 50% yield. Yellow solid. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.26 (t, *J* = 7.2 Hz, 2H), 2.48 (s, 6H), 3.24-3.29 (m, 2H), 4.73 (brs, 1H), 7.12-7.16 (m, 1H), 7.28-7.30 (m, 2H), 7.35 (d, *J* = 7.9 Hz, 4H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 4H), 7.99 (brs, 1H). ^{13}**C NMR** (101 MHz, $CDCl_3$): δ = 21.7, 24.2, 28.4, 39.8, 78.8, 111.5, 116.6, 120.1, 120.7, 122.9, 124.2, 126.7, 128.7, 129.8, 135.0, 136.0, 145.6, 155.9. **IR** ν(cm^{-1}): 3294, 2927, 1632, 1580, 1470, 1282, 1145, 1082, 770, 751, 671, 545, 461. **HRMS** (ESI-TOF): calcd. for $C_{29}H_{33}N_3O_6NaS_2$: 606.1708, found: 606.1690. **m.p.:** 102-107 ºC.

N-(2-(2-(4-Methyl-*N*-(methylsulfonyl)phenylsulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 137e



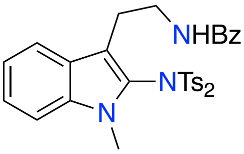
Synthesized according to GP4. 58% yield. Yellow solid. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 1.83 (s, 3H), 2.28-2.36 (m, 1H), 2.48 (s, 3H), 2.58-2.64 (m, 1H), 3.57 (td, *J* = 6.1, 5.5 Hz, 2H), 3.64 (s, 3H), 6.02 (s, 1H), 7.15-7.18 (m, 1H), 7.31-7.35 (m, 4H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 8.10 (s, 1H). ^{13}**C NMR** (101 MHz, CDCl3): δ = 21.8, 23.0, 23.3, 38.6, 44.2, 111.8, 115.3, 120.2, 120.3 122.8, 124.4, 126.2, 128.9, 129.9, 134.6, 135.1, 146.2, 170.7. IR ν(cm-1): 3358, 2928, 2880, 1646, 1550, 1369, 1347, 1165, 976, 877, 744, 664, 520. **HRMS** (ESI-TOF): calcd. for $C_{20}H_{23}N_3O_5NaS_2$: 472.0966, found: 472.0977. **m.p.:** 166-172 ºC.

N-(2-(1-Methyl-2-((4-methyl-*N*-tosylphenyl)sulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 138a



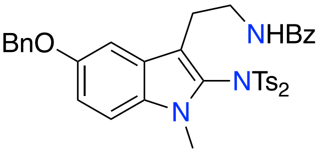
Synthesized according to GP4. 99% yield. Yellow solid. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 2.25 (t, *J* = 6.5 Hz, 2H), 2.53 (s, 6H), 3.36 (s, 3H), 3.57-3.61 (m, 2H), 6.20 (brs, 1H), 7.17-7.20 (m, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.36-7.39 (m, 1H), 7.40 (d, J = 7.8 Hz, 4H), 7.70 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.4 Hz, 4H). ^{13}**C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 23.0, 23.7, 30.0, 38.8, 110.2, 114.7, 120.0, 120.6, 124.1, 125.1, 125.5, 129.2, 129.8, 135.8, 136.3, 146.0, 170.3. **IR** ν(cm-1): 3399, 3059, 2928, 1652, 1595, 1534, 1471, 1431, 1373, 1358, 1166, 1083, 1017. **HRMS** (ESI-TOF): calcd. for C27H30N3O5S2: 540.1621; found: 540.1630. **m.p.:** 189-190 °C.

N-(2-(1-Methyl-2-(4-methyl-*N*-tosylphenyl)sulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 138b



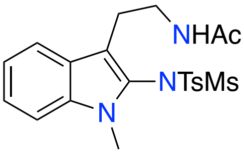
Synthesized according to GP4. 92% yield. Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.46 (t, *J* = 6.9 Hz, 2H), 2.51 (s, 6H), 3.28 (s, 3H), 3.83 (td, *J* = 6.9, 5.1 Hz, 2H), 6.70 (t, *J* = 5.0 Hz, 1H), 7.15-7.18 (m, 1H), 7.28-7.30 (m, 1H), 7.33-7.36 (m, 3H), 7.39-7.44 (m, 5H), 7.70-7.73 (m, 2H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 23.9, 29.8, 39.5, 110.1, 114.6, 120.0, 120.9, 124.0, 125.1, 125.6, 127.0, 128.2, 129.1, 129.8, 131.0, 134.5, 135.9, 136.2, 145.9, 167.6. **IR** ν(cm^{-1}): 3242, 3069, 2923, 1630, 1549, 1492, 1470, 1386, 1357, 1334, 1169, 1084, 1016. **HRMS** (ESI-TOF): calcd. for $C_{33}H_{27}N_7NaOS_2$: 624.1611; found: 624.1612. **m.p.:** 178-180 °C.

N-(2-(5-(Benzyloxy)-1-methyl-2-(4-methyl-*N*-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 138c



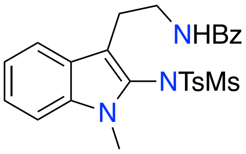
Synthesized according to GP4. 95% yield. Orange solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.41 (t, *J* = 6.7 Hz, 2H), 2.51 (s, 6H), 3.26 (s, 3H), 3.80 (td, *J* = 6.8, 5.2 Hz, 2H), 5.02 (s, 2H), 6.68 (t, *J* = 5.2 Hz, 1H), 7.08 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.20 (d, *J* = 8.9 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.33-7.42 (m, 10H), 7.46-7.48 (m, 2H), 7.71-7.73 (m, 2H), 7.91-7.93 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 23.9, 29.9, 39.4, 70.7, 103.1, 111.1, 114.2, 125.2, 125.8, 127.0, 127.1, 127.7, 127.8, 128.3, 128.4, 128.5, 129.1, 129.8, 129.9, 131.1, 131.6, 134.5, 135.9, 137.3, 145.9, 153.4, 167.6. **IR** ν(cm^{-1}): 3395, 3032, 2924, 1645, 1596, 1487, 1374, 1166, 1083, 1019, 872. **HRMS** (ESI-TOF): calcd. for $C_{39}H_{37}N_3NaO_6S_2$: 730.2016; found: 730.2048. **m.p.:** 168-170 °C.

N-(2-(1-Methyl-2-((4-methyl-*N*-(methylsulfonyl)phenyl)sulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 138d



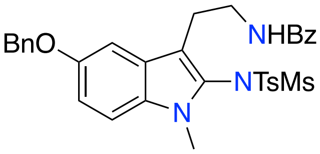
Synthesized according to GP4. 87% yield. Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.84 (s, 3H), 2.39-2.44 (m, 1H), 2.50 (s, 3H), 2.68-2.73 (m, 1H), 3.39 (s, 3H), 3.54-3.60 (m, 1H), 3.62-3.68 (m, 1H), 3.73 (s, 3H), 5.95 (s, 1H), 7.17-7.20 (m, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.35-7.37 (m, 3H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 23.0, 24.1, 29.5, 38.9, 44.6, 110.2, 114.4, 120.1, 120.4, 124.2, 124.6, 125.3, 129.2, 129.9, 134.5, 136.2, 146.3, 170.4. **IR** ν(cm^{-1}): 3316, 3017, 2982, 2936, 1642, 1549, 1448, 1368, 1355, 1345, 1295, 1167, 1087. **HRMS** (ESI-TOF): calcd. for $C_{21}H_{25}N_3NaO_5S_2$: 486.1128; found: 486.1135. **m.p.:** 119-121 °C

N-(2-(1-Methyl-2-(4-methyl-N-(methylsulfonyl)phenyl)sulfonamido)-1H-indol-3-yl)ethyl)benzamide 138e



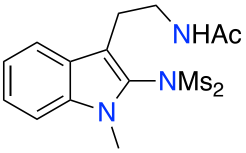
Synthesized according to GP4. 90% yield. Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.48 (s, 3H), 2.57-2.67 (m, 1H), 2.81-2.90 (m, 1H), 3.36 (s, 3H), 3.66 (s, 3H), 3.81-3.89 (m, 2H), 6.55 (s, 1H), 7.14-7.19 (m, 2H), 7.30-7.39 (m, 5H), 7.42-7.45 (m, 1H), 7.68-7.71 (m, 2H), 7.75-7.80 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 24.4, 29.4, 39.6, 44.5, 110.1, 114.4, 120.1, 120.6, 124.1, 124.5, 125.4, 127.1, 128.3, 129.2, 129.9, 131.2, 134.4, 134.6, 136.2, 146.3, 167.7. **IR** ν(cm^{-1}): 3300, 3043, 2929, 1636, 1598, 1579, 1538, 1488, 1470, 1429, 1356, 1309, 1165, 1086. **HRMS** (ESI-TOF): calcd. for $C_{26}H_{27}N_3NaO_5S_2$: 548.1284; found: 548.1291. **m.p.:** 182-184 °C.

N-(2-(5-(Benzyloxy)-1-methyl-2-(4-methyl-*N*-(methylsulfonyl)phenyl sulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 138f



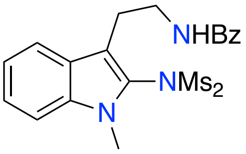
Synthesized according to GP4. 92% yield. Orange solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.49 (s, 3H), 2.52-2.62 (m, 1H), 2.77-2.87 (m, 1H), 3.34 (s, 3H), 3.66 (s, 3H), 3.83 (td, *J* = 6.6, 6.0 Hz, 2H), 5.04 (q, *J* = 11.4 Hz, 2H), 6.53 (t, *J* = 5.5 Hz, 1H), 7.07 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.20 (d, *J* = 8.9 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.34-7.47(m, 10H), 7.69-7.72 (m, 2H), 7.80 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 24.4, 29.6, 39.6, 44.5, 70.7, 103.0, 111.1, 113.9, 115.7, 124.6, 125.6, 127.1, 127.7, 128.4, 128.5, 129.2, 129.9, 131.2, 131.6, 134.4, 134.6, 136.2, 137.2, 146.3, 167.6. **IR** ν(cm^{-1}): 3410, 3033, 2928, 1648, 1486, 1370, 1353, 1163, 1086, 1025, 966, 873. **HRMS** (ESI-TOF): calcd. for $C_{33}H_{33}N_3NaO_6S_2$: 654.1703; found: 654.1709. **m.p.:** 146-148 °C.

N-(2-(1-Methyl-2-(*N*-(methylsulfonyl)methylsulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 138g



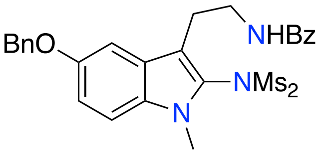
Synthesized according to GP4. 71% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.90 (s, 3H), 3.06 (t, *J* = 7.1 Hz, 2H), 3.55 (s, 6H), 3.74-3.78 (m, 5H), 5.99 (s, 1H), 7.19-7.23 (m, 1H), 7.36-7.41 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 23.1, 25.1, 29.8, 38.9, 43.3, 110.2, 114.0, 120.3, 120.4, 124.1, 124.4, 125.3, 136.3, 170.4. **IR** ν(cm^{-1}): 3425, 3023, 3002, 2942, 2923, 1663, 1531, 1469, 1361, 1347, 1290, 1225, 1158, 1101. **HRMS** (ESI-TOF): calcd. for $C_{15}H_{21}N_3NaO_5S_2$: 410.0815; found: 410.0815. **m.p.:** 209-210 °C.

N-(2-(1-Methyl-2-(*N*-(methylsulfonyl)methylsulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 138h



Synthesized according to GP4. 77% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.19 (t, *J* = 7.0 Hz, 2H), 3.53 (s, 6H), 3.76 (s, 3H), 3.99 (td, *J* = 7.0, 5.6 Hz, 2H), 6.59 (s, 1H), 7.18-7.22 (m, 1H), 7.36-7.42 (m, 4H), 7.46-7.50 (m, 1H), 7.72-7.75 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.3, 29.8, 39.6, 43.2, 110.1, 114.0, 120.4, 120.6, 124.0, 124.4, 125.4, 127.0, 128.4, 131.3, 134.3, 136.3, 167.7. **IR** ν(cm^{-1}): 3308, 2932, 1630, 1543, 1472, 1355, 1311, 1164, 962, 874, 748. **HRMS** (ESI-TOF): calcd. for $C_{20}H_{23}N_3NaO_5S_2$: 472.0971; found: 472.0979. **m.p.:** 166-168 °C.

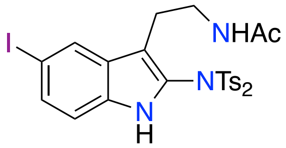
N-(2-(5-(Benzyloxy)-1-methyl-2-(*N*-(methylsulfonyl)methylsulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 138i



Synthesized according to GP4. 80% yield. Brown solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.12 (t, *J* = 6.9 Hz, 2H), 3.50 (s, 6H), 3.70 (s, 3H), 3.89-3.94 (m, 2H), 5.03 (s, 2H), 6.55 (t, *J* = 5.5 Hz, 1H), 7.08 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.23-7.27 (m, 2H), 7.31-7.45 (m, 8H), 7.70-7.72 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.1, 30.0, 39.5, 43.2, 70.8, 103.2, 111.2, 113.5, 115.9, 124.1, 125.6, 127.1, 127.7, 127.9, 128.4, 128.5, 131.4, 131.7, 134.3, 137.2, 153.6, 167.7. **IR** ν(cm^{-1}): 3341 (N-H), 3062 (Ar-H), 3033 (Ar-H), 2930 (Ar-H), 1711 (C=O), 1651, 1532, 1488, 1451, 1366, 1279, 1162, 1128, 1022, 875, 727, 694.

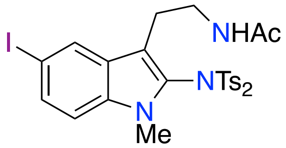
HRMS (ESI-TOF): calcd. for $C_{27}H_{29}N_3NaO_6S_2$: 578.1390; found: 578.1403. **m.p.:** 157-159 ºC.

N-(2-(5-Iodo-2-(4-methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)ethyl)acetamide 139



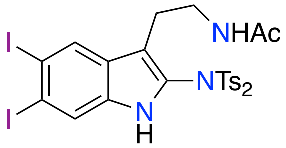
Synthesized according to GP5. 78% yield. White solid. **^{1}H NMR** (400 MHz, CD_2Cl_2): δ = 1.79 (s, 3H), 2.15 (t, *J* = 6.7 Hz, 2H), 2.48 (s, 6H), 3.35 (td, *J* = 6.2, 5.7 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 4H), 7.52 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 4H), 7.96 (s, 1H). **^{13}C NMR** (101 MHz, CD_2Cl_2): δ = 21.9, 22.9, 23.4, 39.1, 83.4, 114.3, 115.0, 124.2, 129.0, 129.1, 129.4, 130.3, 132.8, 134.6, 136.1, 146.7, 171.6. **IR** ν(cm^{-1}): 3379, 3170, 2921, 2582, 2366, 1643, 1596, 1376, 1353, 1165, 879, 660, 542. **HRMS** (ESI-TOF): calcd. for $C_{26}H_{26}IN_3O_5NaS_2$: 674.0256, found: 674.0279. **m.p.:** 187-191 ºC.

N-(2-(5-Iodo-1-methyl-2-(4-methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)ethyl)acetamide 140

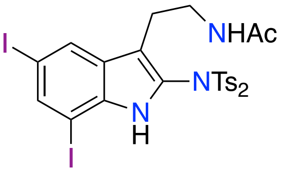


Synthesized according to GP5. 98% yield. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 2.15 (t, *J* = 6.4 Hz, 2H), 2.50 (s, 6H), 3.31 (s, 3H), 3.48-3.52 (m, 2H), 6.11 (t, *J* = 6.1 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 4H), 7.58 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 4H), 7.98 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 21.8, 23.0, 23.5, 30.0, 38.9, 83.4, 112.2, 114.1, 125.7, 127.8, 129.1, 129.3, 129.9, 132.4, 135.2, 135.5, 146.13, 170.3. **IR** ν(cm^{-1}): 3290, 2923, 2853, 1651, 1372, 1166, 873, 659, 542, 478. **HRMS** (ESI-TOF): calcd. for $C_{27}H_{28}IN_3O_5NaS_2$: 688.0413, found: 688.0437. **m.p.:** 196-197 ºC.

N-(2-(5,6-Diiodo-2-(4-methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)ethyl)acetamide and N-(2-(5,7-Diiodo-2-(4-methyl-N-tosylphenylsulfonamido) -1H-indol-3-yl)ethyl)acetamide 141 and 142



14



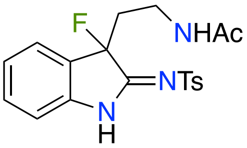
15

To a stirred solution of the acetamide **10a** (0.052 g, 0.1mmol, 1.0 equiv) and TFA (2 mL) in CH_2Cl_2 (20 mL) at -78 ºC, $HBF_4·Et_2O$ (0.086 mL, 0.6 mmol, 6.0 equiv) and bis(pyridine)iodonium tetrafluoroborate (0.082 g, 0.22 mmol, 2.2

equiv) were added. The brown solution was allowed to stir for 2 h. The reaction was quenched with cold water, after extraction the organic layer was washed with an aqueous saturated solution of $Na_2S_2O_4$. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc, 1/1, v/v) to afford a mixture of the two regioisomers in 1:3 ratio. 68% yield. White solids.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 (s, 6H), 2.12-2.15 (m, 2H), 2.19-2.22 (m, 2H), 2.52 (s, 6H), 2.53 (s, 6H), 3.43-3.48 (m, 2H), 3.64-3.68 (m, 2H), 6.12 (s, 2H), 7.39-7.44 (m, 8H), 7.84-7.89 (m, 8H), 7.93 (s, 1H), 7.95 (s, 1H), 8.17 (s, 1H), 8.18 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 22.7, 22.8, 23.0, 31.9, 38.7, 96.9, 101.7, 115.4, 122.4, 124.5, 128.5, 128.7, 128.8, 130.0, 130.1, 130.5, 135.4, 135.5, 146.1, 146.3, 170.5. **IR** ν(cm^{-1}): 3387, 2919, 2850, 1657, 1597, 1540, 1375, 1351, 1164, 1083, 876, 754, 659, 541. **HRMS** (ESI-TOF): calcd. for $C_{26}H_{26}I_2N_3O_5S_2$, 777.9398, found: 777.9418.

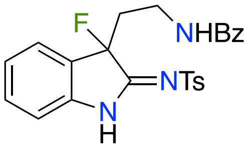
N-(2-(3-Fluoro-2-(tosylimino)indolin-3-yl)ethyl)acetamide 143a



Synthesized according to GP6. 98% yield. Yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (s, 3H), 2.27-2.50 (m, 5H), 3.33 (m, 2H), 5.93 (brs, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.31-7.37 (m, 3H), 7.42 (d, *J* = 7.5 Hz, 1H) 7.88 (d, *J* = 8.3 Hz, 2H), 9.82 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 21.6, 23.1, 33.7 (d, $J_{C\text{-}F}$ = 9.8 Hz), 35.8 (d, $J_{C\text{-}F}$ = 27.9 Hz), 97.3 (d, $J_{C\text{-}F}$ = 192.2 Hz), 111.8, 124.6 (d, $J_{C\text{-}F}$ = 2.7 Hz), 124.8, 125.6 (d, $J_{C\text{-}F}$ = 18.7 Hz), 126.8, 129.7, 131.9 (d, *J* = 3.1 Hz), 137.5, 141.0, 144.2, 165.1 (d, $J_{C\text{-}F}$ = 19.7 Hz), 170.3. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -150.3. **IR** ν(cm^{-1}): 3303, 2921, 2851, 1615, 1469, 1284, 1143, 1082, 752, 665, 546. **HRMS** (ESI-TOF): calcd. for $C_{19}H_{19}FN_3O_3S$: 388.1137, found: 388.1137. **m.p.:** 230-232 ºC.

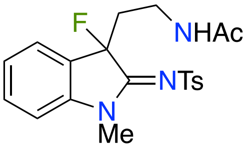
N-(2-(3-Fluoro-2-(tosylimino)indolin-3-yl)ethyl)benzamide 143b



Synthesized according to GP6. 95% yield. Yellow solid.

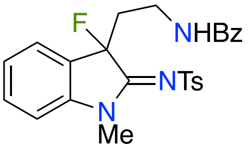
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33-2.64 (m, 5H), 3.62 (td, *J* = 6.4, 6.2 Hz, 2H), 6.52 (t, *J* = 5.8 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 7.16-7.19 (m, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.36-7.49 (m, 5H), 7.69-7.72 (m, 2H), 7.86 (d, *J* = 8.3 Hz, 2H), 9.82 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 34.2 (d, $J_{C\text{-}F}$ = 10.1 Hz), 35.6 (d, $J_{C\text{-}F}$ = 27.2 Hz), 99.2 (d, $J_{C\text{-}F}$ = 194.5 Hz) 111.8, 124.7 (d, $J_{C\text{-}F}$ = 2.7 Hz), 124.9, 126.8 (d, $J_{C\text{-}F}$ = 16.7 Hz), 129.7, 131.5, 131.9, 132.0, 134.0, 137.6, 141.0, 144.1, 164.9 (d, $J_{C\text{-}F}$ = 24.3 Hz), 167.3. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -149.8. **IR** ν(cm^{-1}): 3295, 2851, 1616, 1532, 1470, 1284, 1142, 1082, 669, 547. **HRMS** (ESI-TOF): calcd. for $C_{24}H_{22}FN_3NaO_3S$: 474.1264, found: 474.1260. **m.p.:** 202-204 ºC.

N-(2-(3-Fluoro-1-methyl-2-(tosylimino)indolin-3-yl)ethyl)acetamide 144a



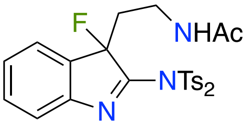
Synthesized according to GP6. 99% yield. Yellow solid. **^{1}H NMR** (500 MHz, CDCl$_3$): δ = 1.87 (s, 3H), 2.44 (s, 3H), 2.64-2.70 (m, 1H), 3.08-3.13 (m, 1H), 3.20-3.38 (m, 5H), 6.32 (s, 1H), 6.90-6.92 (m, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.41-7.44 (m, 2H), 7.92 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (125 MHz, CDCl$_3$): δ = 21.6, 23.1, 29.0, 33.9 (d, $J_{C\text{-}F}$ = 9.8 Hz), 35.6 (d, $J_{C\text{-}F}$ = 27.1 Hz), 96.9 (d, $J_{C\text{-}F}$ = 194.3 Hz), 110.0, 124.1, 124.7 (d, $J_{C\text{-}F}$ = 2.7 Hz), 126.7, 127.1 (d, $J_{C\text{-}F}$ = 19.0 Hz), 129.4, 131.8 (d, $J_{C\text{-}F}$ = 2.7 Hz), 140.0, 143.0, 143.3 (d, $J_{C\text{-}F}$ = 5.1 Hz), 164.8 (d, $J_{C\text{-}F}$ = 23.5 Hz), 170.1. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -153.0. **IR** ν(cm^{-1}): 3294, 2927, 1632, 1580, 1470, 1282, 1145, 1082, 770, 751, 671, 545, 461. **HRMS** (ESI-TOF): calcd. for $C_{20}H_{22}FN_3O_3NaS$: 426.1258; found: 426.1261. **m.p.:** 47-53 ºC.

N-(2-(3-Fluoro-1-methyl-2-(tosylimino)indolin-3-yl)ethyl)benzamide 144b



Synthesized according to GP6. 98% yield. Orange solid. **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 2.46 (s, 3H), 2.73-2.80 (m, 1H), 3.02 (s, 3H), 3.30-3.36 (m, 1H), 3.50-3.71 (m, 2H), 6.90 (d, *J* = 7.9 Hz, 1H), 7.12-7.14 (m, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.29-7.32 (m, 2H), 7.38-7.52 (m, 5H), 7.84-7.88 (m, 4H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ = 21.5, 28.7, 34.5 (d, $J_{C\text{-}F}$ = 10.1 Hz), 35.3 (d, $J_{C\text{-}F}$ = 27.4 Hz), 96.9 (d, $J_{C\text{-}F}$ = 193.6 Hz), 110.0, 124.0, 124.7 (d, *J* = 2.7 Hz), 126.6, 126.8, 127.0, 127.2, 128.4, 129.3, 131.4, 131.8 (d, $J_{C\text{-}F}$ = 2.8 Hz), 133.8, 140.0, 142.9, 143.3 (d, $J_{C\text{-}F}$ = 5.2 Hz), 165.3 (d, $J_{C\text{-}F}$ = 23.5 Hz), 166.8. **^{19}F NMR** (376 MHz, CDCl$_3$) δ = -152.8. IR ν(cm^{-1}): 3253, 3068, 2920, 1627, 1550, 1381, 1167, 876, 657, 540. **HRMS** (ESI-TOF): calcd for $C_{25}H_{24}FN_3NaO_3S$: 488.1415; found: 488.1422. **m.p.:** 128-129 ºC.

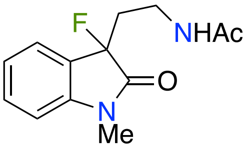
N-(2-(3-Fluoro-2-(4-methyl-*N*-tosylphenylsulfonamido)-3*H*-indol-3-yl)ethyl)acetamide 145



Synthesized according to GP6 with shorter reaction time (2 h). 86% yield. Yellow solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.90 (s, 3H), 2.13-2.25 (m, 1H), 2.26-2.40 (m, 1H), 2.51 (s, 6H), 3.15-3.23 (m, 1H), 3.34-3.43 (m, 1H), 5.51 (t, *J* = 6.0, 1H), 7.36-7.41 (m, 5H), 7.44-7.52 (m, 2H), 7.57 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 8.4, 4H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 21.8, 23.2, 33.5 (d, $J_{C\text{-}F}$ = 26.0 Hz), 34.0 (d, $J_{C\text{-}F}$ = 6.9 Hz), 100.4 (d, $J_{C\text{-}F}$ = 197.0 Hz), 101.4, 122.9, 123.9, 128.8 (d, $J_{C\text{-}F}$ = 1.6 Hz), 129.5, 129.7 (d, $J_{C\text{-}F}$ = 1.9 Hz), 131.2, 134.4 (d, $J_{C\text{-}F}$ = 18.5 Hz), 136.2, 145.8, 149.7 (d, $J_{C\text{-}F}$ = 6.3 Hz), 165.4 (d, $J_{C\text{-}F}$ = 18.8 Hz), 169.8. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -166.6. **IR** ν(cm^{-1}): 3282, 2919, 2850, 1650, 1563, 1381, 1167, 1082, 886, 659, 538. **HRMS** (ESI-TOF): calcd. for $C_{26}H_{25}FN_3O_5S_2$: 542.1225, found: 542.1221. **m.p.:** 132-134 ºC.

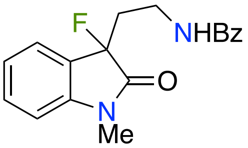
N-(2-(3-Fluoro-1-methyl-2-oxoindolin-3-yl)ethyl)acetamide 146a



Synthesized according to GP7. 85% yield. Colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.94 (s, 3H), 2.14-2.27 (m, 1H), 2.41-2.52 (m, 1H), 3.22 (s, 3H), 3.43-3.60 (m, 2H), 6.15 (brs, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.40-7.44 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 23.2, 26.3, 33.9 (d, $J_{C\text{-}F}$ = 5.9 Hz), 34.8 (d, $J_{C\text{-}F}$ = 26.8 Hz), 92.4 (d, $J_{C\text{-}F}$ = 186.9 Hz), 108.9, 123.6 (d, $J_{C\text{-}F}$ = 2.8 Hz), 124.5, 125.9 (d, $J_{C\text{-}F}$ = 18.2 Hz), 126.4, 129.7, 131.5 (d, $J_{C\text{-}F}$ = 3.0 Hz), 143.7 (d, $J_{C\text{-}F}$ = 5.4 Hz), 170.0, 172.8 (d, $J_{C\text{-}F}$ = 22.0 Hz). **^{19}F NMR** (101 MHz, CDCl$_3$): δ = -158.5. **IR** ν(cm^{-1}): 3294, 3065, 2927, 1724, 1615, 1470, 1372, 1246, 1113, 750. **HRMS** (ESI-TOF): calcd. for $C_{13}H_{15}FN_2NaO_2$: 273.1010, found: 273.1013.

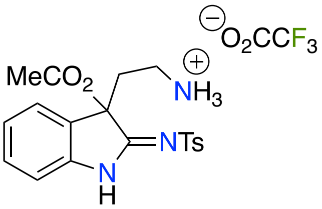
N-(2-(3-Fluoro-1-methyl-2-oxoindolin-3-yl)ethyl)benzamide 146b



Synthesized according to GP7. 85% yield. Colorless oil.

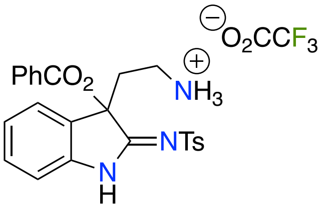
^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.23-2.36 (m, 1H), 2.57-2.67 (m, 1H), 3.18 (s, 3H), 3.63-3.71 (m, 1H), 3.78-3.87 (m, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 7.02 (brs, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.39-7.52 (m, 5H), 7.76-7.82 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 26.3, 34.3 (d, $J_{C\text{-}F}$ = 5.8 Hz), 34.8 (d, $J_{C\text{-}F}$ = 27.0 Hz), 92.5 (d, $J_{C\text{-}F}$ = 186.8 Hz), 109.0, 123.7 (d, $J_{C\text{-}F}$ = 2.7 Hz), 124.5, 125.9 (d, $J_{C\text{-}F}$ = 18.3 Hz), 126.9, 128.5, 131.4, 131.6 (d, $J_{C\text{-}F}$ = 3.2 Hz), 134.3, 143.6 (d, $J_{C\text{-}F}$ = 5.4 Hz), 167.0, 173.0 (d, $J_{C\text{-}F}$ = 22.0 Hz). **^{19}F NMR** (101 MHz, $CDCl_3$): δ = -158.3. **IR** ν(cm^{-1}): 3327, 2923, 2852, 1725, 1639, 1616, 1537, 1491, 1470, 1376, 1306, 1092, 751, 694. **HRMS** (ESI-TOF): calcd. for $C_{18}H_{17}FN_2NaO_2$: 335.1166, found: 335.1169.

2-(3-Acetoxy-2-(tosylimino)indolin-3-yl)ethanaminium trifluoroacetate 147a



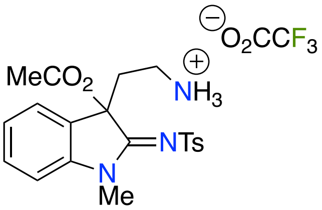
Synthesized according to GP8. 98% yield. Brown solid. **^{1}H NMR** (400 MHz, MeOD): δ = 2.43 (s, 3H), 2.51 (s, 3H), 2.55-2.56 (m, 1H), 2.73-2.81 (m, 1H), 3.77-3.83 (m, 1H), 4.09-4.18 (m, 1H), 7.29-7.35 (m, 2H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.56-7.62 (m, 2H), 7.93 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (101 MHz, MeOD): δ = 21.5, 22.5, 33.8, 37.5, 81.0, 83.5, 87.4, 113.4, 125.0, 125.4, 127.8, 130.6, 130.6, 131.7, 140.0, 142.6, 143.4, 145.2, 170.1. **^{19}F NMR** (376 MHz, MeOD): δ = -77.5. **IR** ν(cm^{-1}): 3306, 2921, 2851, 1599, 1469, 1279, 1138, 1082, 753, 666, 547. **HRMS** (ESI-TOF): calcd. for $C_{19}H_{22}N_3O_4S$: 388.1326; found: 388.1311. **m.p.:** 112-115 ºC.

2-(3-(Benzoyloxy)-2-(tosylimino)indolin-3-yl)ethanaminium 2,2,2-trifluoroacetate 147b



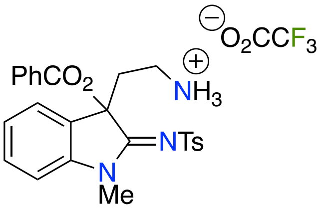
Synthesized according to GP8. 99% yield. Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.19-2.23 (m, 1H), 2.43 (s, 3H), 3.61-3.64 (m, 1H), 3.74 (td, *J* = 7.1, 6.9, 2H), 5.38 (s, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.18-7.54 (m, 8H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.6, 34.8, 37.4, 86.6, 111.7, 124.6, 126.5, 126.6, 127.0, 128.5, 128.6, 129.3, 129.7, 130.8, 131.8, 138.0, 144.0, 168.2. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -76.0. **IR** ν(cm^{-1}): 3253, 3068, 2920, 1627, 1550, 1381, 1167, 876, 657, 540. **HRMS** (ESI-TOF): calcd. for $C_{24}H_{24}N_3O_4S$: 450.1482; found: 450.1476. **m.p.:** 131-135 ºC.

2-(3-Acetoxy-1-methyl-2-(tosylimino)indolin-3-yl)ethanaminium 2,2,2-trifluoroacetate 148a



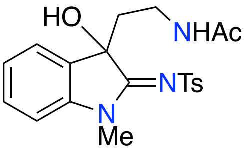
Synthesized according to GP8. 99% yield. Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.19-2.23 (m, 1H), 2.46 (s, 3H), 2.55 (s, 3H), 3.20-3.28 (m, 1H), 3.48 (s, 3H), 3.84-3.95 (m, 1H), 4.04-4.11 (m, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 7.26-7.30 (m, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.44 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.55 (td, *J* = 7.9, 1.1 Hz, 1H), 7.83-7.96 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 20.0, 21.5, 25.1, 30.4, 34.5, 84.3, 110.5, 123.7, 125.3, 126.3, 127.1, 129.6, 132.9, 138.9, 142.5, 143.8, 162.5, 172.8. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -75.9. **IR** ν(cm^{-1}): 3383, 2919, 1678, 1572, 1190, 1148, 1132, 1083, 948, 777, 760, 680. **HRMS** (ESI-TOF): calcd. for $C_{20}H_{24}N_3O_4S$: 402.1488; found: 402.1485. **m.p.:** 129-132 ºC.

2-(3-(Benzoyloxy)-1-methyl-2-(tosylimino)indolin-3-yl)ethanaminium 2,2,2-trifluoroacetate 148b



Synthesized according to GP8. 99% yield. Yellow solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 2.31-2.34 (m, 1H), 2.39 (s, 3H), 3.27-3.34 (m, 1H), 3.53 (s, 3H), 4.09-4.14 (m, 1H), 4.21-4.28 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.21-7.28 (m, 3H), 7.50-7.55 (m, 4H), 7.70-7.71 (m, 3H), 8.00-8.08 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 21.5, 25.4, 30.7, 35.1, 84.7, 110.6, 124.0, 124.9, 125.4, 126.3, 127.0, 128.9, 129.4, 129.5, 132.5, 135.9, 138.8, 142.6, 143.7, 162.2, 167.6. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -75.9. **IR** ν(cm^{-1}): 3067, 2929, 1783, 1588, 1138, 1084. **HRMS** (ESI-TOF): calcd. for $C_{25}H_{25}N_3NaO_4S$: 486.1463; found: 486.1458. **m.p.:** 56-58 ºC.

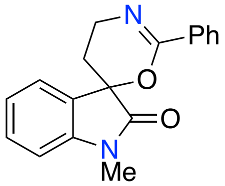
N-(3-(2-Acetamidoethyl)-3-hydroxy-1-methylindolin-2-ylidene)-4-methylbenzenesulfonamide 149



Compound **21a** (46 mg, 0.1 mmol) was dissolved in CH$_2$Cl$_2$ (0.25 mL) and Et$_3$N (0.5 mL) was added dropwise. After 16 h, additional CH$_2$Cl$_2$ (5 mL) and water were added, and the resulting mixture was extracted with diluted HCl (1M in water). The organic phase was separated and the solvent was removed under reduced pressure. The compound was isolated as a yellowish solid (40 mg, 0.1 mmol, 99% yield).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.90 (s, 3H), 2.45 (s, 3H), 3.19 (s, 3H), 2.45-2.55 (m, 1H), 2.94-3.17 (m, 3H), 3.19 (s, 3H), 6.31 (brs, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 7.19-7.23 (m, 1H), 7.32-7.34 (m, 2H), 7.35 -7.41 (m, 2H), 7.88-7.90 (m, 2H), 8.08-8.10 (m, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 21.6, 23.1, 28.4, 34.5, 38.8, 80.2, 109.8, 123.4, 125.0, 126.4, 129.4, 129.7, 130.4, 130.5, 139.1, 142.7, 143.3, 169.9, 171.2. **IR** ν(cm^{-1}): 3411, 3376, 2921, 2852, 1665, 1548, 1073, 961, 778, 752, 689, 553. **HRMS** (ESI-TOF): calcd. for $C_{20}H_{23}N_3NaO_4S$: 424.1301; found: 424.1307. **m.p.:** 135-138 ºC.

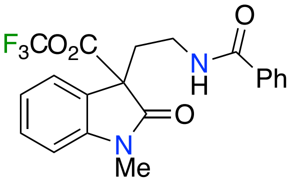
8-Methyl-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]indol-3a-yl benzoate 150



Synthesized according to GP7 from compound **21b**. 99% yield. Brownish solid.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.07 (ddd, *J* = 14.0, 7.1, 5.3 Hz, 1H), 2.23 (ddd, *J* = 14.0, 6.5, 5.3 Hz, 1H), 3.27 (s, 3H), 3.90 (ddd, *J* = 17.2, 6.5, 5.3 Hz, 1H), 4.17 (ddd, *J* = 17.2, 7.1, 5.3 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.34-7.44 (m, 5H), 7.91-7.94 (m, 2H). **^{13}C NMR** (125 MHz, CDCl$_3$): δ = 26.4, 27.5, 38.7, 76.7, 108.7, 123.4, 124.1, 127.2, 128.0, 129.1, 130.4, 130.5, 133.5, 143.2, 154.3, 174.2. **IR** ν(cm^{-1}): 3060, 2924, 1715, 1653, 1613, 1156, 1120, 1091. **HRMS** (ESI-TOF): calcd. for $C_{18}H_{17}N_2O_2$: 293.1285; found: 293.1284. **m.p.:** 45-46 ºC.

Trifluoromethyl 3-(2-benzamidoethyl)-1-methyl-2-oxoindoline-3-carboxylate 151



Synthesized according to GP8 from compound **23**. 99% yield. Yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.45-2.50 (m, 1H), 2.68-2.74 (m, 1H), 3.29 (s, 3H), 4.09-4.14 (m, 1H), 4.40-4.47 (m, 1H), 7.04 (d, *J* = 7.9, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.36-7.59 (m, 3H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.67-7.77 (m, 1H), 7.98 (d, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 25.0, 26.7, 35.8, 81.4, 109.9, 112.0, 114.3, 116.5, 118.8, 123.7, 124.0, 125.0, 128.4, 129.5, 132.8, 136.2, 143.5, 161.3 (q, *J* = 321.0 Hz), 168.4, 170.8. **^{19}F NMR** (101 MHz, CDCl$_3$): δ = -76.0. **IR** ν(cm^{-1}): 3325, 2926, 1697, 1638, 1611, 1537, 1490, 1347, 1301, 1128, 1091, 749, 695. **HRMS** (ESI-TOF): calcd. for $C_{20}H_{17}F_3N_2NaO_{24}$: 429.1038, found: 429.1026.

2.4.4. X-Ray analytical data

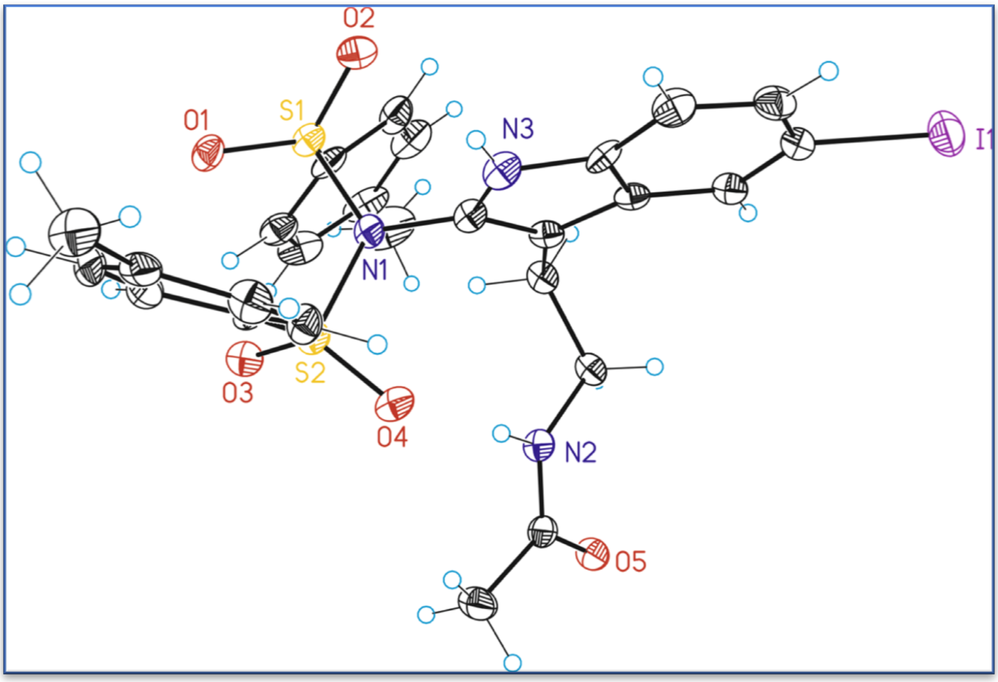
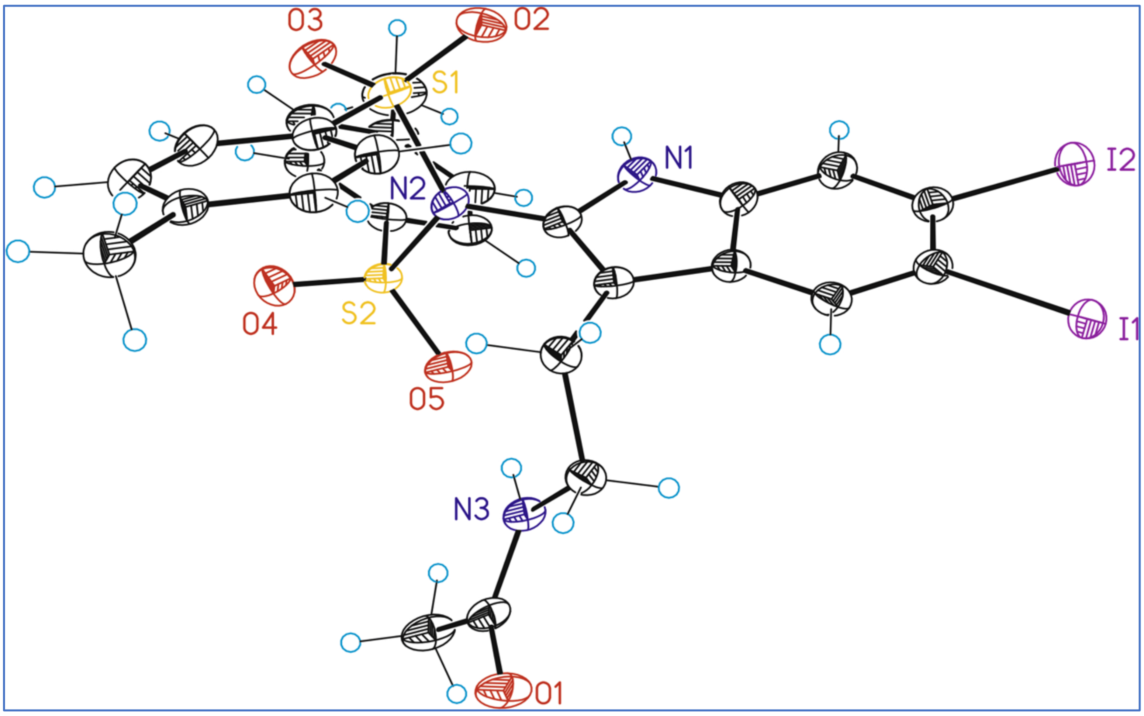


Table 2.1: Crystal data and structure refinement for **139**.

Identification code	CCDC 1465186	
Empirical formula	C28 H30 I N3 O5.50 S2	
Formula weight	687.57	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 16.845(2)Å	α= 90°.
	b = 10.5896(13)Å	β =102.939(5)°.
	c = 16.493(2)Å	γ = 90°.
Volume	2867.4(6) Å^3	
Z	4	
Density (calculated)	1.593 Mg/m^3	
Absorption coefficient	1.307 mm^{-1}	
F(000)	1392	

Crystal size	0.35 x 0.01 x 0.01 mm^3
Theta range for data collection	1.240 to 24.818°.
Index ranges	-19<=h<=19,-12<=k<=12,-15<=l<=19
Reflections collected	26667
Independent reflections	4932[R(int) = 0.0804]
Completeness to theta =24.818°	99.5%
Absorption correction	Multi-scan
Max. and min. transmission	0.987 and 0.72
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4932/ 46/ 383
Goodness-of-fit on F^2	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0462, wR2 = 0.1088
R indices (all data)	R1 = 0.0753, wR2 = 0.1229
Largest diff. peak and hole	1.118 and -0.800 e.Å^{-3}


O3
O2
S1
N1
I2
N2
O4
S2
O5
I1
N3
O1

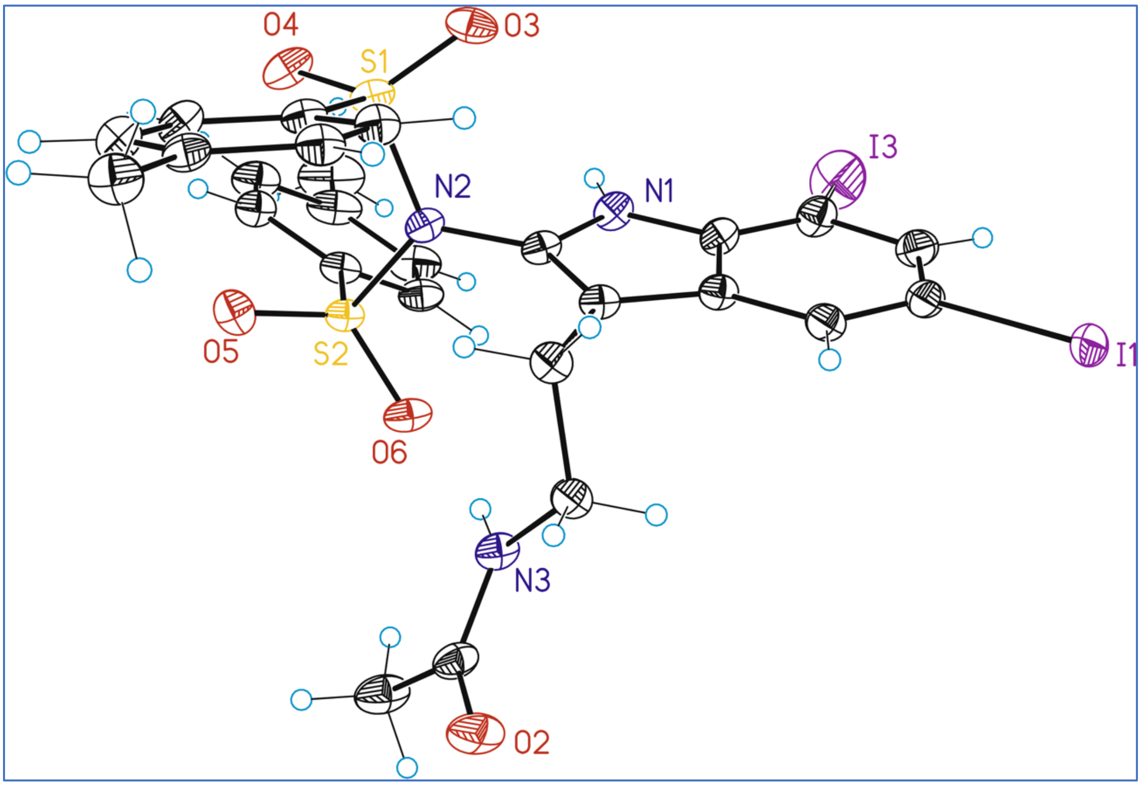

O4
O3
S1
I3
N2
N1
O5
S2
I1
O6
N3
O2

Table 2.2: Crystal data and structure refinement for **141** and **142**.

Identification code	CCDC 1465187	
Empirical formula	C27 H27 Cl2 I2 N3 O5 S2	
Formula weight	862.33	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.2918(5)Å	α = 90°.
	b = 20.7021(10)Å	β = 98.469(2)°.
	c = 16.4894(8)Å	γ = 90°.
Volume	3137.3(3) Å^3	
Z	4	
Density (calculated)	1.826 Mg/m^3	
Absorption coefficient	2.350 mm^{-1}	
F(000)	1688	
Crystal size	0.20 x 0.05 x 0.05 mm^3	
Theta range for data collection	1.589 to 33.724°.	
Index ranges	-12<=h<=14,-32<=k<=32,-18<=l<=25	
Reflections collected	24945	
Independent reflections	11725[R(int) = 0.0334]	
Completeness to theta =33.724°	93.5%	
Absorption correction	Empirical	
Max. and min. transmission	0.892 and 0.732	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11725/ 340/ 467	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0424, wR2 = 0.0929	
R indices (all data)	R1 = 0.0682, wR2 = 0.1037	
Largest diff. peak and hole	1.423 and -1.449 e.Å^{-3}	

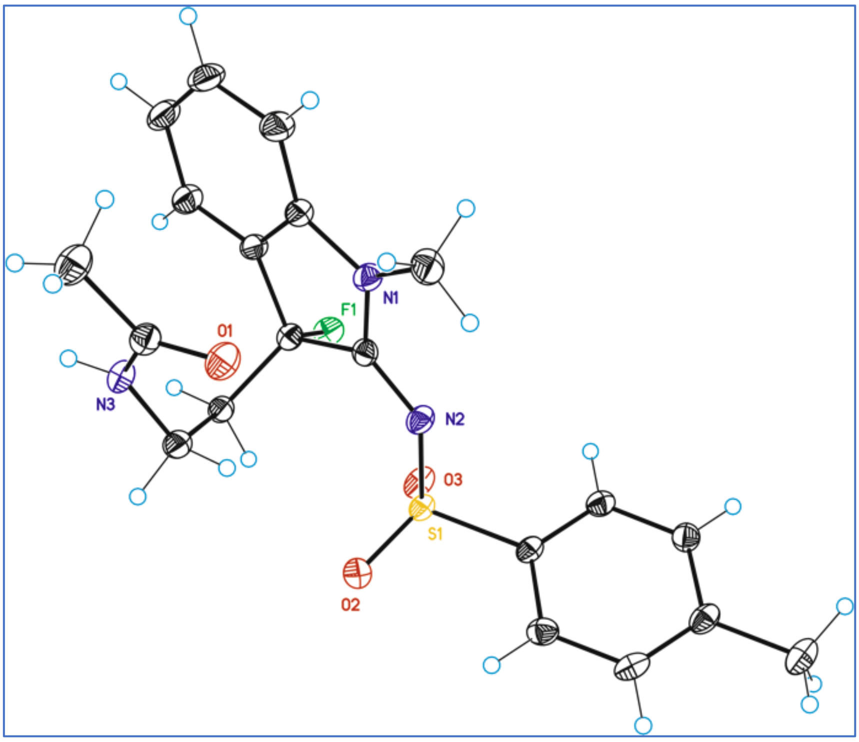


Table 2.3: Crystal data and structure refinement for **144a**.

Identification code	CCDC 1465189	
Empirical formula	C20 H22 F N3 O3 S	
Formula weight	403.47	
Temperature	100K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.4424(9) Å	α= 90.00 °.
	b = 21.6082(16) Å	β=109.547(4) °.
	c = 9.1581(9) Å	γ = 90.00 °.
Volume	1947.4(3) Å^3	
Z	4	
Density (calculated)	1.376 Mg/m^3	
Absorption coefficient	0.202 mm^{-1}	
F(000)	848	
Crystal size	0.50 x 0.50 x 0.12 mm^3	

Theta range for data collection	1.88 to 29.79 °.
Index ranges	-13 <=h<=14 ,-29 <=k<=29 ,-11 <=l<=12
Reflections collected	17463
Independent reflections	4935 [R(int) = 0.0294]
Completeness to theta =29.79 °	88.6%
Absorption correction	Empirical
Max. and min. transmission	0.9762 and 0.9057
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4935 / 1 / 259
Goodness-of-fit on F^2	1.074
Final R indices [I>2sigma(I)]	R1 = 0.0412 , wR2 = 0.1017
R indices (all data)	R1 = 0.0482 , wR2 = 0.1054
Largest diff. peak and hole	0.407 and -0.534 e.Å^{-3}

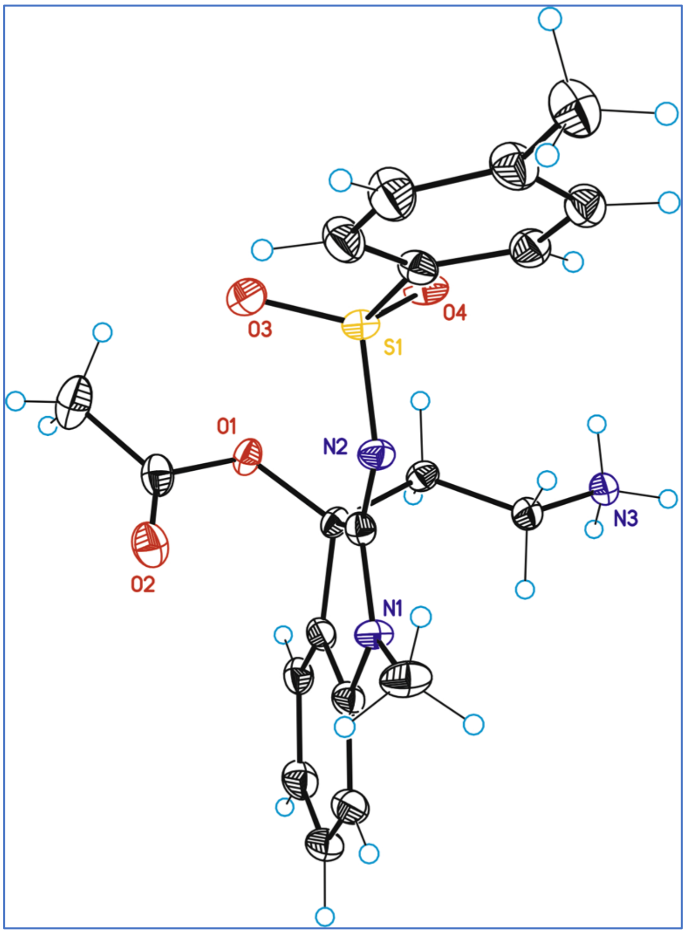


Table 2.4. Crystal data and structure refinement for **148a**.

Identification code	CCDC 1465188	
Empirical formula	C22 H26 F3 N3 O7 S	
Formula weight	533.52	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.2348(9) Å	α= 90.00 °.
	b = 16.2497(18) Å	β = 90.00 °.
	c = 18.833(2) Å	γ = 90.00 °.
Volume	2520.0(5) Å^3	
Z	4	
Density (calculated)	1.406 Mg/m^3	

Absorption coefficient	0.197 mm^{-1}
F(000)	1112
Crystal size	0.12 x 0.05 x 0.02 mm^3
Theta range for data collection	1.66 to 29.51 °.
Index ranges	-11 <=h<=10 ,-22 <=k<=22 ,-25 <=l<=24
Reflections collected	36578
Independent reflections	6775 [R(int) = 0.0606]
Completeness to theta =29.51 °	97.899994%
Absorption correction	Empirical
Max. and min. transmission	0.9961 and 0.9767
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6775 / 189 / 390
Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0437 , wR2 = 0.1001
R indices (all data)	R1 = 0.0637 , wR2 = 0.1082
Flack parameter	x =0.11(7)
Largest diff. peak and hole	0.344 and -0.296 e.Å^{-3}

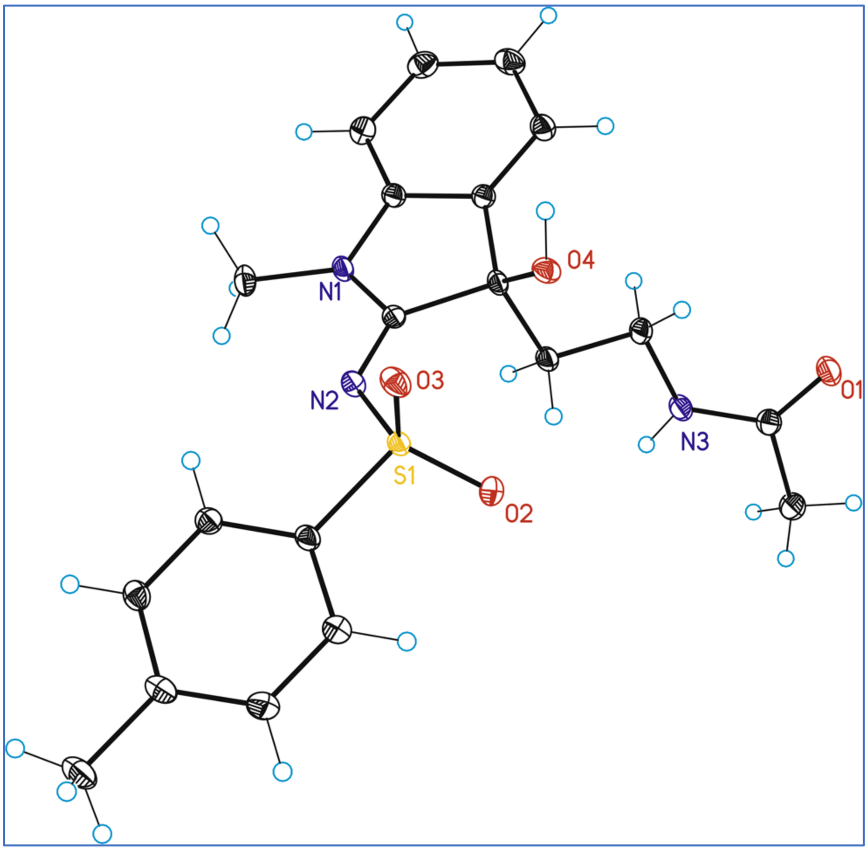


Table 2.5: Crystal data and structure refinement for **149**-CH_2Cl_2.

Identification code	CCDC 1465190	
Empirical formula	C21 H25 Cl2 N3 O4 S	
Formula weight	486.40	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.3361(4) Å	α= 104.520(2) °.
	b = 12.4151(7) Å	β = 93.010(2) °.
	c = 12.6930(7) Å	γ = 98.217(2) °.
Volume	1102.93(11) $Å^3$	
Z	2	
Density (calculated)	1.465 Mg/m^3	
Absorption coefficient	0.423 mm^{-1}	

F(000)	508
Crystal size	0.30 x 0.15 x 0.07 mm^3
Theta range for data collection	1.66 to 30.36 °.
Index ranges	-10 <=h<=9 ,-17 <=k<=16 ,-17 <=l<=16
Reflections collected	11380
Independent reflections	5714 [R(int) = 0.0209]
Completeness to theta =30.36 °	85.9%
Absorption correction	Empirical
Max. and min. transmission	0.9710 and 0.8835
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5714 / 0 / 288
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0597 , wR2 = 0.1749
R indices (all data)	R1 = 0.0693 , wR2 = 0.1842
Largest diff. peak and hole	1.207 and -1.318 e.Å^{-3}

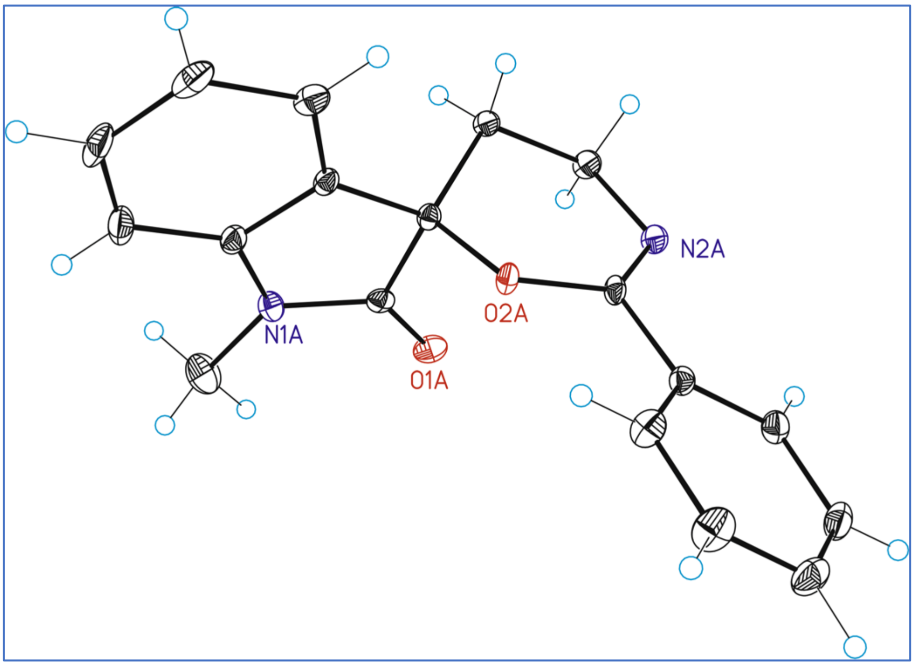


Table 2.6: Crystal data and structure refinement for **150**.

Identification code	CCDC 1465185
Empirical formula	C18 H16 N2 O2
Formula weight	292.33
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 9.5212(3)Å α= 90°.
	b = 45.9930(11)Å β = 112.281(4)°.
	c = 10.9044(4)Å γ = 90°.
Volume	4418.6(3) $Å^3$
Z	12
Density (calculated)	1.318 Mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	1848
Crystal size	0.2 x 0.1 x 0.05 mm^3
Theta range for data collection	2.066 to 32.452°.
Index ranges	-12<=h<=13,-65<=k<=65,-14<=l<=12

Reflections collected	33636
Independent reflections	12321[R(int) = 0.0246]
Completeness to theta =32.452°	87.2%
Absorption correction	Multi-scan
Max. and min. transmission	0.996 and 0.766
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12321/ 0/ 598
Goodness-of-fit on F^2	1.203
Final R indices [I>2sigma(I)]	R1 = 0.0667, wR2 = 0.1649
R indices (all data)	R1 = 0.0799, wR2 = 0.1697
Largest diff. peak and hole	0.736 and -0.337 e.Å^{-3}

Chapter III. Intramolecular Amination of Arenes under Iodine Catalysis

3.1 Introduction: Hypervalent iodine(III) reagents involved in C(sp^2)-H and C(sp^3)-H intramolecular amination

3.1.1 Hypervalent iodine(III) reagents involved in C(sp^2)-H intramolecular amination

The direct functionalization of an aromatic C-H bond either in an intramolecular or intermolecular way via direct amination strategies is of high importance for the synthetic community as discussed in the first chapter of this thesis. In particular, anilines are present in many biological structures of pharmaceutical interest.[151]

Common approaches for the C(sp^2)-H amination involve transition metals catalysis, such as palladium, iridium and rhodium.[152] These methods were summarized in the introduction chapter. However, transition metals have disadvantages as they are highly costly, provide low sustainability and raise toxicity issues in most of the cases. An interesting economically and ecologically viable alternative to these pathways includes the use of mild iodine(III) reagents.[14,153]

Some elegant approaches with the use of hypervalent iodine reagents, which give access to the cases of cyclized products onto aromatic rings have been reported.[154] In 1990, Kikugawa used (trifluoroacetoxyiodo)benzene (PIFA) for the cyclization of N-methoxy amides **152** to an aromatic core towards oxindoles **153** (Scheme 3.1 top). The reaction starts with the oxidation of the amide to the nitrenium ion that further adds to the aromatic core, yielding the final product.[155] The synthesis of cyclic ureas **156** that was developed by Romero constitutes an application of the concept shown above (Scheme 3.1 bottom).[156]

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[151] *The Chemistry of Anilines*, Z. Rappoport (Ed.), Vol. 1,2, J. Wiley Sons, New York **2007**.

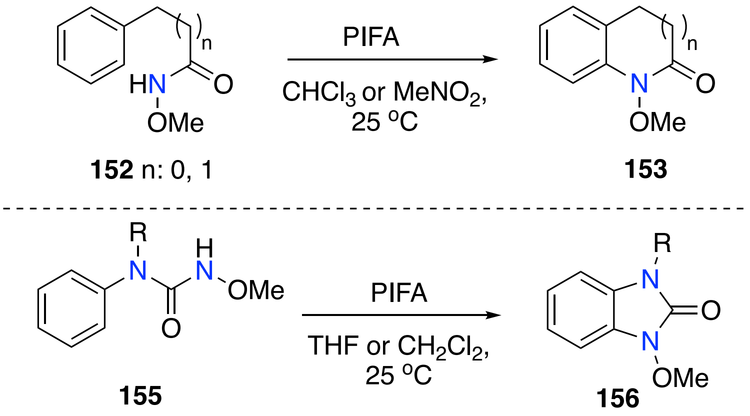
[152] Amination and Formation of sp^2 C-N Bonds, M. Taillefer, D. Ma (Eds), *Topics in Organomet. Chem.* 46, Springer, Berlin Heidelberg **2012**.

[153] a) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299; b) P. J. Stang, V V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123.

[154] R. Narayan, S. Manna, A. P. Antonchick, *Synlett* **2015**, *26*, 1785.

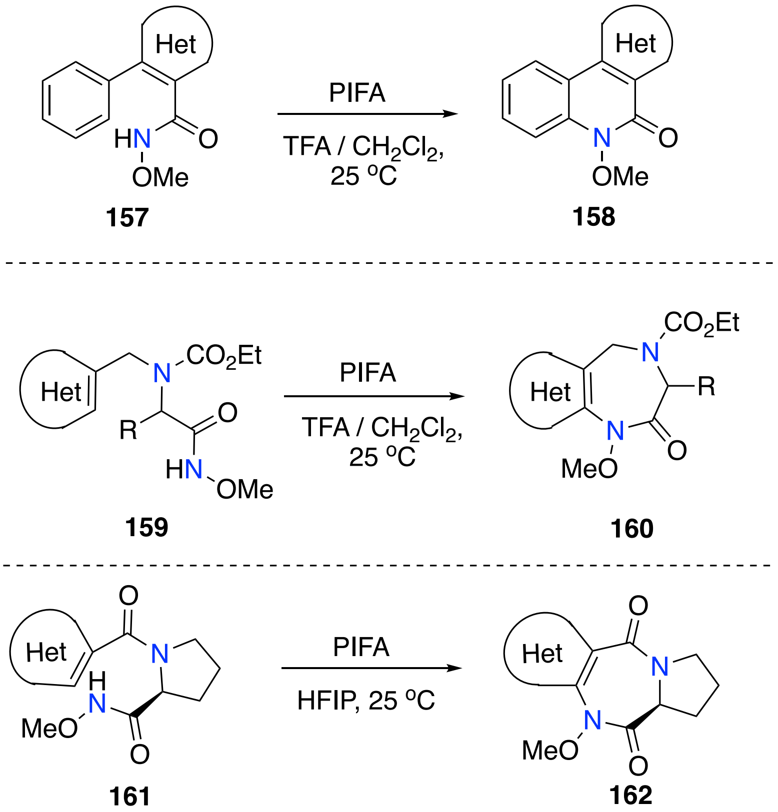
[155] Y. Kikugawa, M. Kawase, *Chem. Lett.* **1990**, 581.

[156] A. G. Romero, W. H. Darlington, E. J. Jacobsen, J. W. Michelson, *Tetrahedron* **1996**, *37*, 2361 .



Scheme 3.1: Iodine(III)-mediated electrophilic aromatic amination.

Dominguez has extended this iodine(III)-mediated approach to the synthesis of fused quinolines **158**, 1,4-diazepin-2-ones **160** and pyrrolo(benzo)diazepines **161** (Scheme 3.2), with the use of PIFA and trifluoroacetic acid.[157]



Scheme 3.2: Synthesis of fused heterocycles, by iodine(III)-mediated electrophilic amination.

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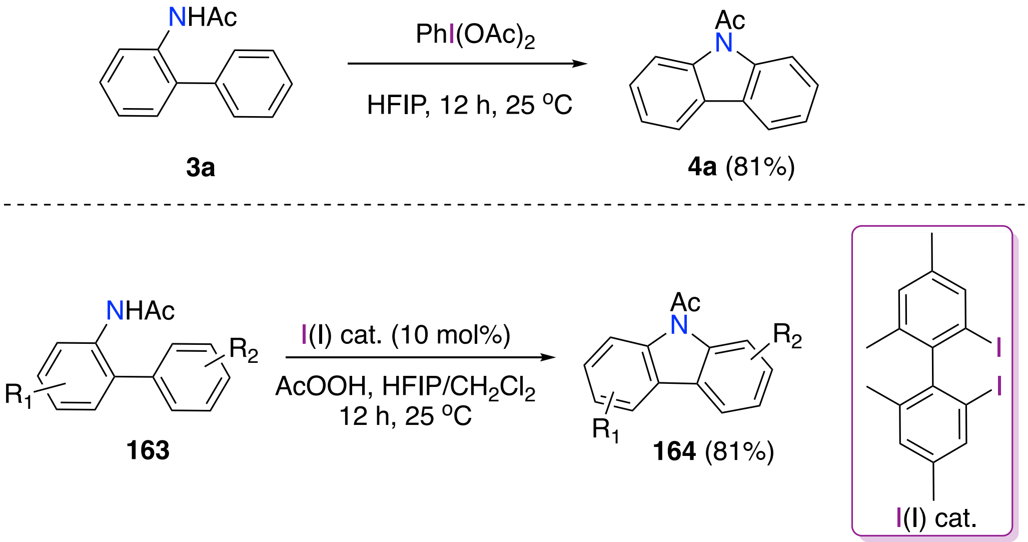
[157] a) M. T. Herrero, I. Tellitu, E. Dominguez, S. Hernandez, I. Moreno, R. SanMartin, *Tetrahedron* **2002**, *58*, 8581; b) A. Correa, M. T. Herrero, I. Tellitu, E. Dominguez, I. Moreno, R. SanMartin, *Tetrahedron* **2003**, *59*, 7103; c) A. Correa, I. Tellitu, E. Dominguez, I. Moreno, R. SanMartin, *J. Org. Chem.* **2005**, *70*, 2256.

The synthesis of carbazoles **4** through direct amination has been reported by Antonchick. In an elegant approach 2-aminobiphenyl **3a** was used in combination with (diacetoxyiodo)benzene for the formation of carbazole **4a** in good yields (Scheme 3.3 top).[158]

The catalytic version of this transformation was developed by the same authors. Based on the in situ oxidation of iodoarenes to their iodine(III) species, they reported a protocol using 10 mol% of 2,2-diiodo-4,4′,6,6′-tetramethylbiphenyl as iodine source with 2.0 equivalents of peracid for the formation of the desired carbazole **164** in excellent yields (Scheme 3.3 bottom).[159]



Scheme 3.3: Antonchick's approach for carbazole synthesis.

The synthesis of carbazoles has been reported by several groups with the use of transition metals (section 1.3) For instance, Chang reported on the synthesis of carbazoles through copper-catalyzed intramolecular C(sp^2)-H amination. Interestingly, the authors observed that the terminal oxidant can promote the amination reaction in the absence of the metal catalyst. However, the increase of the yield with the catalyst employment led the authors to complete their research with the use of the metal catalyst.[160]

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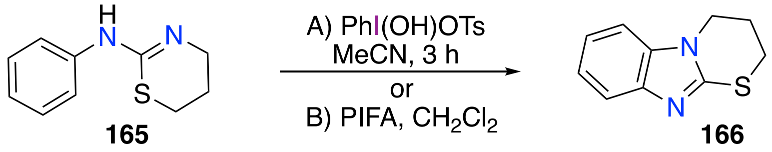
[158] A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem. Int. Ed.* **2011**, *50*, 8605.

[159] a) R. Samanta, A. P. Antonchick, *Synlett* **2012**, *23*, 809; b) R. Samanta, K. Kulikov, C. Stromann, A. P. Antonchick, *Synthesis* **2012**, *44*, 2325.

[160] S. H. Cho, J. Yoon, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 5996.

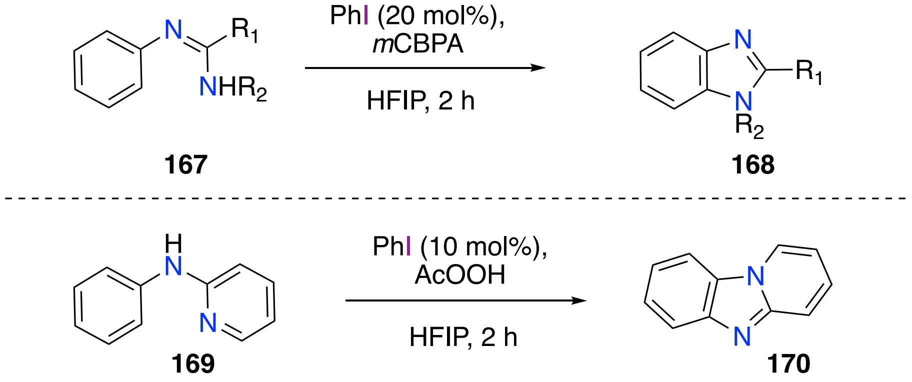
Saito has developed the hypervalent iodine(III)-mediated synthesis of N-substituted amidines **166** from N-dihydrothiazin-2-yl anilines **165** using stoichiometric amounts of Koser´s reagent or PIFA (Scheme 3.4).[161]



Scheme 3.4: Iodine(III)-mediated synthesis of benzimidazole-fused heterocycles.

The synthesis of different type of benzimidazoles **168** through an iodine(III)-catalyzed intramolecular amination of N-substituted amidines **167** was developed by Punniyamurthy.[162] The authors used catalytic amounts of iodobenzene in combination with *m*CBPA as terminal oxidant for the formation of the products in good yields (Scheme 3.5 top)

An extension toward nitrogen-containing heterocycles was developed by Zhu. In an analogous manner, the use of iodobenzene as organocatalyst and peracetic acid as terminal oxidant, yielded the fused heterocycles **170** in excellent yields (Scheme 3.5 bottom).[163]



Scheme 3.5: Benzimidazole-fused heterocycles synthesis employing iodobenzene as catalyst.

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[161] N. Kutsumura, S. Kunimatsu, K. Kagawa, T. Otani, T. Saito, *Synthesis* **2011**, 3235.

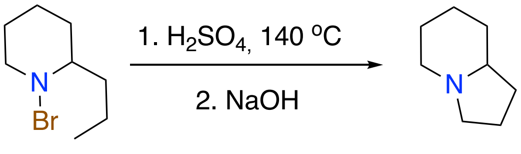
[162] S. K. Alla, R. K. Kumar, P. Sadhu, T. Punniyamurthy, *Org.Lett.* **2013**, *15*, 1334.

[163] a) D. Liang, Y. He, L. Liu, Q. Zhu, *Org. Lett.* **2013**, *15*, 3476; b) H. Wang, Y. Wang, C. Peng, J. Zhang, Q. Zhu, *J. Am. Chem. Soc.* **2010**, *132*, 13217.

3.1.2 Hypervalent iodine(III) reagents involved in C(sp^3)-H intramolecular amination

Beside anilines, saturated nitrogen containing heterocycles are also privileged motifs in bioactive compounds such as alkaloids and pharmaceutical agents.[164] Efficient ways for the formation of such cyclic structures include nucleophilic displacement (usually in presence of a good leaving group) or reductive amination. The direct installation of the amino moiety in a C(sp^3)-H bond is of great interest to the synthetic community.

Back in 1880s, the pioneering breakthrough of this chemistry came by Hofmann who reported the formation of δ-coniceine **172** from the N-brominated aliphatic amine **171** (Scheme 3.6).[165] This intramolecular amination is now known as Hofmann-Löffler reaction and it has been involved in the synthesis of 5-membered tertiary amines.[166]



171 **172**

Scheme 3.6: Original Hofmann-Löffler reaction.

In general, the formation of pyrrolidines **174** from N-halo amines **173** upon exposure to harsh acidic conditions, followed by a basification has been extensively studied over the following years. The mechanism of this transformation was studied by Corey in 1960. The reaction relies on the generation of an ammonium radical **B** by a sequence of protonation of the N-halo amine **173**, followed by cleavage of the N-chloro bond of the intermediate **A**. Subsequent intramolecular 1,5-hydrogen atom transfer (1,5-HAT) results the carbon-centered radical **C**, which abstracts a halogen from the N-halogenated ammonium intermediate **A** in a radical chain reaction. The C-chlorinated ammonium salt **D** cyclizes upon treatment with base toward pyrrolidine **174** (Scheme 3.7).

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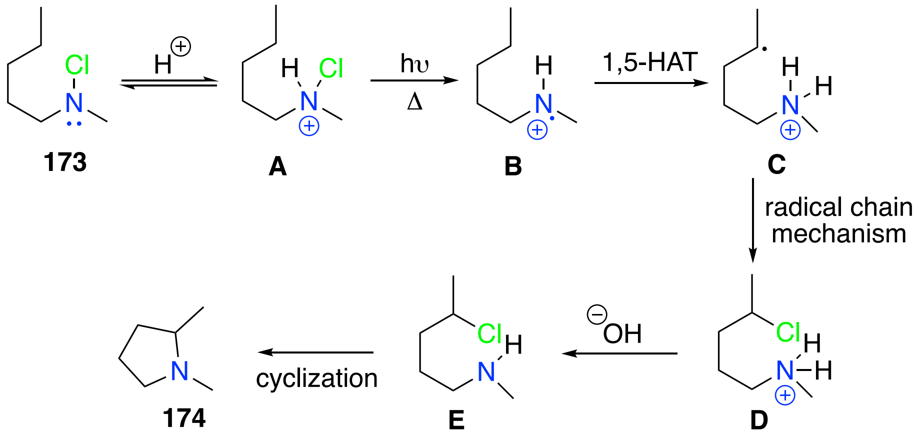
[164] a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; b) R. Hili, A. K. Yudin, *Nature Chem. Biol.* **2006**, 2, 283.

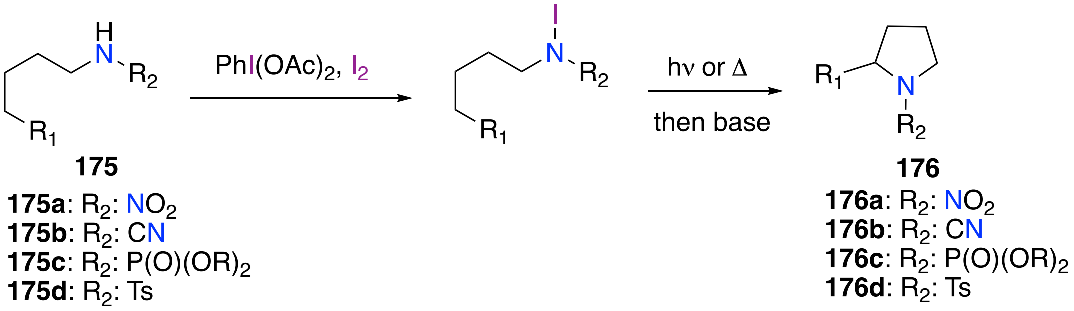
[165] a) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 558; b) K. Löffler, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3427.

[166] E. J. Corey, W. R. Hertler, *J. Am. Chem. Soc.* **1960**, *82*, 1657.



Scheme 3.7: Corey´s mechanism for the Hofmann-Löffler reaction.

Many years later, Suárez reported the same type of intramolecular amination employing an excess of iodine(III) reagent in combination with stoichiometric amounts of molecular iodine. The authors reported the cyclization of *N*-nitroamides **175a**, *N*-cyanamides **175b** and *N*-phosphoramidates **175c** with the use of 3.0 equivalents of (diacetoxyiodo)benzene and 1.0 equivalent of molecular iodine for the formation of the corresponding pyrrolidines **176** (Scheme 3.8).[167]



Scheme 3.8: Suárez modification on the Hofmann-Löffler reaction.

In 2007, Fan reported the cyclization of sulfonamides **175d** based on the Suárez modification. The authors claimed that the formation of pyrrolidines **176d** was observed only for sulfonamides. Substrates containing amides as nitrogen-substituents did not afford any product.[168] Adding to these stoichiometric reactions, Muñiz has demonstrated the use of N-iodosuccinimide alone for the formation of pyrrolidines **176d**. Worthy to

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[167] a) R. Carrau, R. Hernández, E. Suárez, C. Betancor, *J. Chem. Soc. Perkins. 1*, **1987**, 937; b) R. L. Dorta, C. G. Francisco, E. Suárez, *J. Chem. Soc. Chem. Commun.* **1989**, 1168; c) C. G. Francisco, A. J. Herrera, E. Suárez, *J. Org. Chem.* **2003**, *68*, 1012.

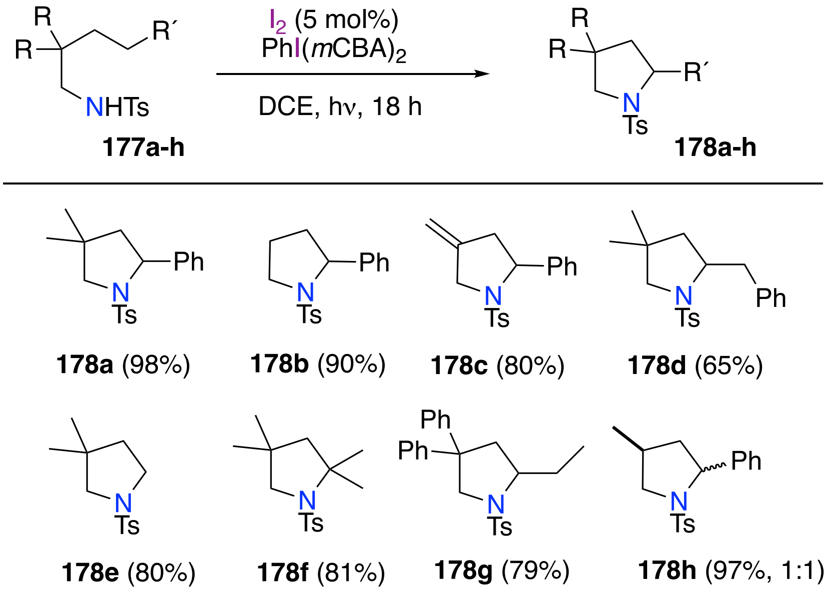
[168] R. Fan, D. Pu, F. Wen, J. Wu, *J. Org. Chem.* **2007**, *72*, 8994.

mention though is the fact that the cyclization in this case proceeds only over activated positions.[169]

Generally, the Hofmann-Löffler reaction provides 5-membered heterocycles while the 6-membered ring formation is not usually observed. This observation is probably due to the transition state of the intermediates, that affect the efficiency and the final outcome of the reaction.[170]

As indicated above, all these alternative methods for C(sp^3)-H amination reactions involve the combination of stoichiometric amounts of molecular iodine in combination with over-stoichiometric amounts of hypervalent iodine(III) reagents. The use of strong oxidants in excess amounts often leads to side-products due to over-oxidation. In addition, these procedures are not atom-economic. Thus, a well-designed catalysis would be the most elegant solution to such problems as it would allow operation under milder oxidative conditions.

The solution to this problem came from Muñiz, who recently described a well-designed iodine catalysis protocol for the Hofmann-Löffler reaction (Scheme 3.9).[171] Careful modifications on existing protocols allowed the formation of the desired pyrrolidines with the use of catalytic amounts of molecular iodine and a hypervalent iodine(III) as terminal oxidant.



Scheme 3.9: Hofmann-Löffler reaction under iodine catalysis.

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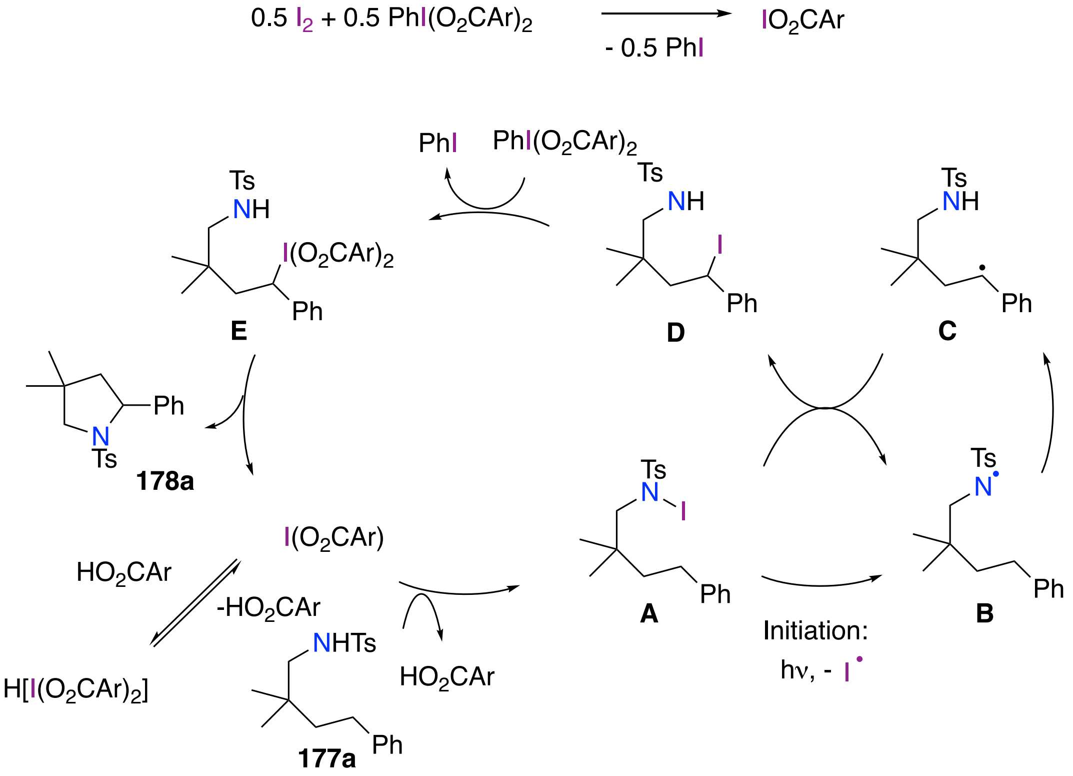
[169] C. Q. O'Broin, P. Fernández, C. Martínez, K. Muñiz, *Org. Lett.* **2016**, *183*, 436.
[170] M. W. Wolff, *Chem. Rev.* **1963**, *63*, 55.
[171] C. Martinez, K. Muñiz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8287.

The initial step of the reaction includes the comproportionation between molecular iodine and the oxidant for the formation of the iodine(I) catalyst bearing a *meta*-chlorobenzoate [I(*m*CBA)]. This newly formed electrophilic catalyst promotes the iodination of the substrate **177a**, toward **A**. Upon exposure to light, the N-I bond is cleaved affording the nitrogen-centered radical **B**, which engages the 1,5-hydrogen transfer (1,5-HAT) yielding the carbon-centered radical **C**. Iodination through iodine abstraction, from another N-iodinated intermediate in a radical chain mechanism, allows the formation of the benzylic iodide **D**. Oxidation to the alkyl iodide(III) intermediate **E** triggers the final cyclization step to the corresponding pyrrolidine product **178a**. It is known that alkyl iodine(III) species exhibit enhanced nucleofugacity, in comparison with the parent iodine(I) species, as it was thoroughly discussed in the introduction section (1.4.3). Therefore, an acceleration of the cyclization step is observed.



Scheme 3.10: Mechanistic scenario proposed by Muñiz fot the catalytic Hofmann-Löffler reaction.

Despite the general interest in the field of intramolecular aminations, a reliable iodine catalysis had remained largely unexplored.[172] With all the reported examples and the gained knowledge on iodine catalysis; we decided to study the possible extension of the previously developed conditions by our group for the intramolecular c(sp^3)-H amination to C(sp^2)-H amination. We envisioned that the use of a tether motive could finally lead to aniline derivatives.

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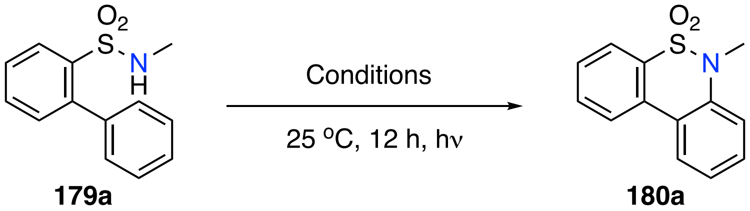
[172] a) P. Finkbeiner, B. Nachtsheim, *Synthesis* **2013**, 979; b) M. Uyanik, K. Ishihara, *ChemCatChem.* **2012**, *4*, 117.

3.2 Results and Discussion

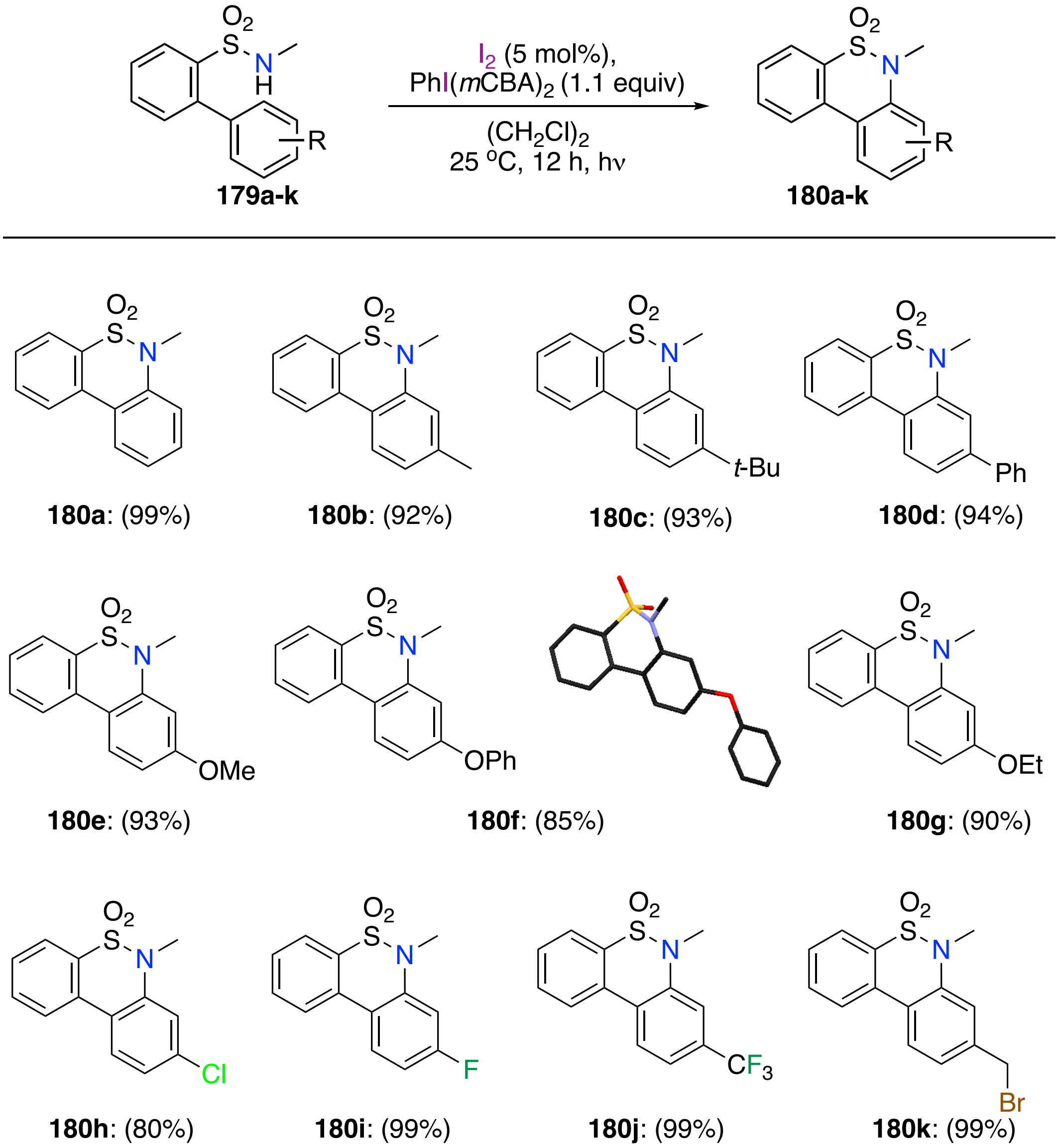
We started our exploration with biaryl derivatives, substituted at the C2 position with the N-methylsulfonamide. Initially, the undecorated biaryl substrate **179a** was submitted to the best reaction conditions that were obtained for the alkyl amination (Entry 1, Table 3.1). To our delight, the combination of 5 mol% of elemental iodine with a hypervalent iodine reagent as terminal oxidant afforded the product **180a** in quantitative yield. Apparently, the reaction proceeds only in chlorinated solvents, as toluene or acetonitrile did not lead to any conversion (Entries 2,3, Table 3.1). When the reaction was performed in the absence of the molecular iodine, no conversion to the desired product was observed. The same result was obtained by performing the reaction in the absence of light. Thus, we are introducing a clearly photochemical, iodine catalyzed intramolecular aromatic amination.



Entry	Conditions	Yield (%)
1	I_2 (5 mol%), PhI(*m*CBA)$_2$ (1.1 equiv), DCE, 400-700 nm	99
2	I_2 (5 mol%), PhI(*m*CBA)$_2$ (1.1 equiv), toluene, 400-700 nm	0
3	I_2 (5 mol%), PhI(*m*CBA)$_2$ (1.1 equiv), CH_3CN, 400-700 nm	0
4	I_2 (5 mol%), PhI(*m*CBA)$_2$ (1.1 equiv), DCE, dark lab	0
5	I_2 (0 mol%), PhI(*m*CBA)$_2$ (1.1 equiv), DCE, 400-700 nm	0

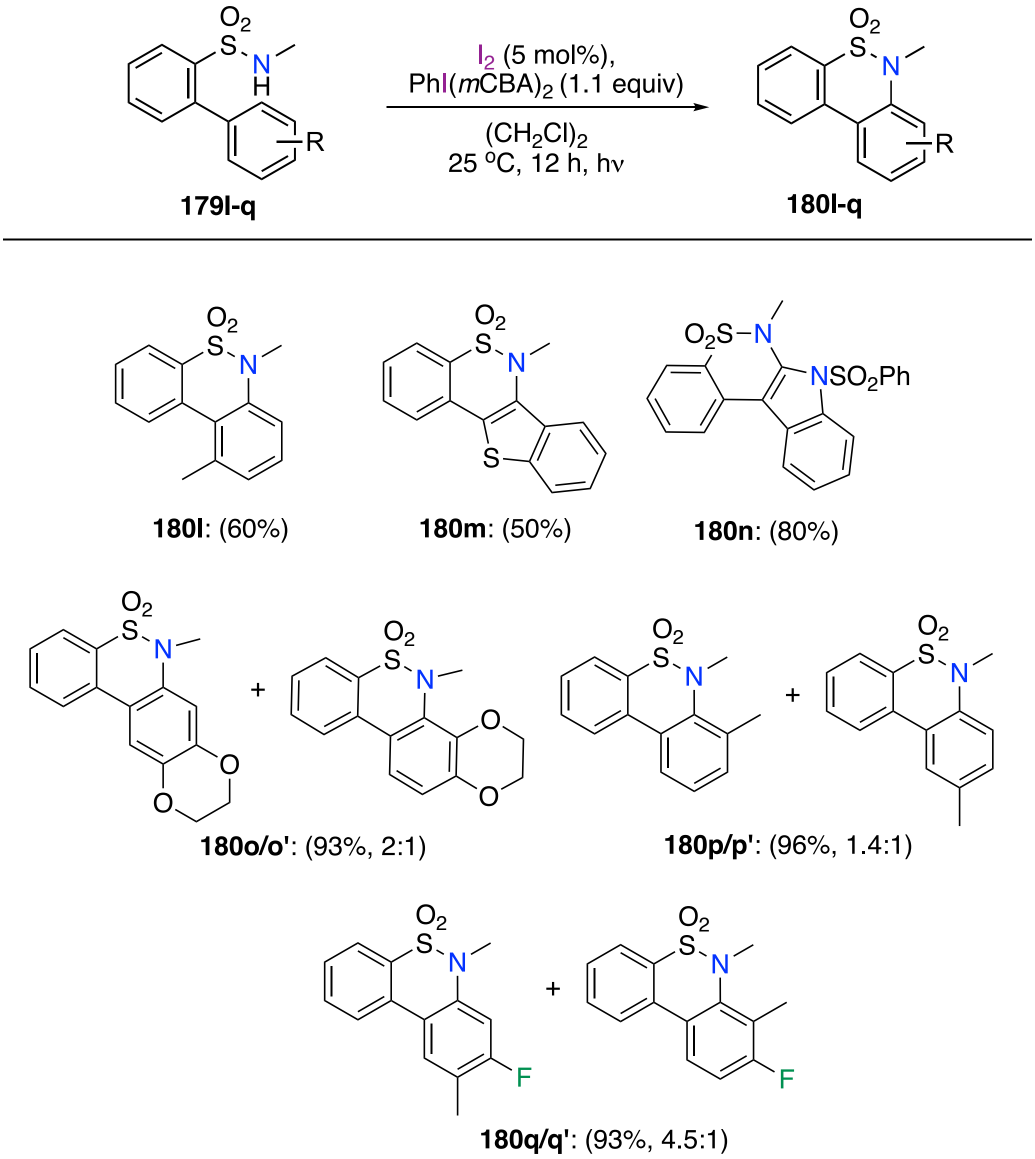
Table 3.1: Optimization conditions for the C(sp^2)-H intramolecular amination.

Interestingly, the reaction is scalable to 1.0 g (4.1 mmol) for the formation of **180a**. This fact overcomes the usual drawback of upscaling, in photochemical reactions. We decided to demonstrate the generality of the reaction by submitting different *para*-substituted arenes which gave rise to the desired products **180b-k** in excellent yields (80-99%). A worthy to mention fact is that in the present transformation, electron-rich substrates such as **179e-g** are well tolerated, in contrast to the results from the catalytic C(sp^3)-H amination. Additionally, the substrate **179k** with a benzylic bromide allowed for the amination, affording **180k** in excellent yield (Scheme 3.12). The exact structure of the products was unambiguously confirmed by X-ray analysis for the 4-phenoxy derivative **180f** (Scheme 3.12).



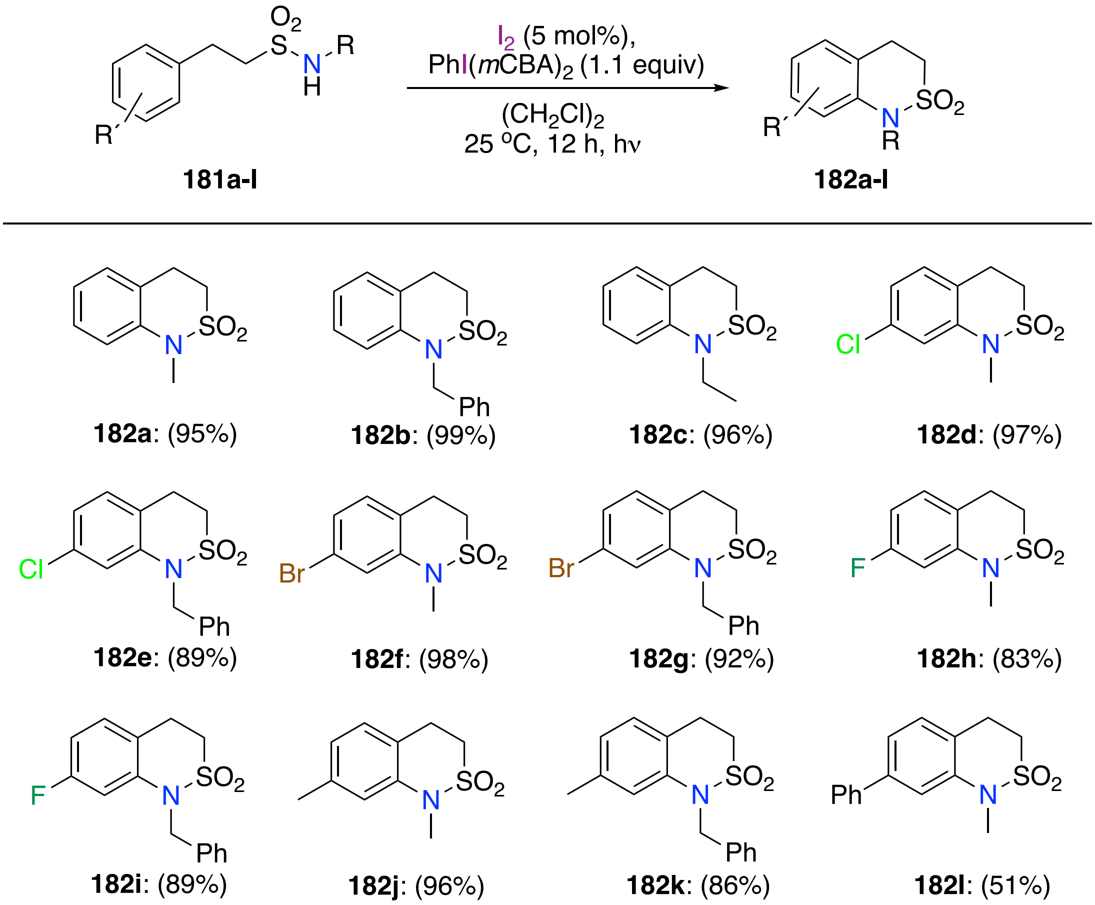
Scheme 3.12: Scope of the intramolecular C-H amination of biaryls substituted in the *para*- position.

This transformation is also feasible for the case of *ortho*-substituted arenes, as demonstrated for the case of **180l**. Different substitution patterns and heterocycles, such as benzothiophere **179m** and and indole **179n**, are tolerated and the amination products **180m** and **180n** were obtained in good yields (Scheme 3.13). Higher-substituted arenes could also undergo the intramolecular amination. However, the formation of regioisomeric mixtures in different ratios was observed for the products **180o/o´** to **180q/26q´**.



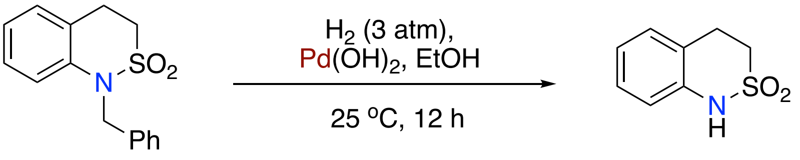
Scheme 3.13: Scope of the intramolecular C-H amination of biaryls with different substitution patterns.

Moving forward to more labile N-alkyl sulfonamides, we were able to change the biaryl scaffold and form cyclic sulfonamides as demonstrated for the substrates **181a-l**. Different alkyl groups on the nitrogen core and substitution patterns in the aromatic ring were studied, affording the products **182a-l** in good to excellent yields (Scheme 3.14).



Scheme 3.14: Scope for the intramolecular C-H amination of ethylenylarenes.

The deprotection of the nitrogen moiety on these heterocycles was easily accomplished with a simple hydrogenolysis, as demonstrated for the product **182b** (Scheme 3.15).

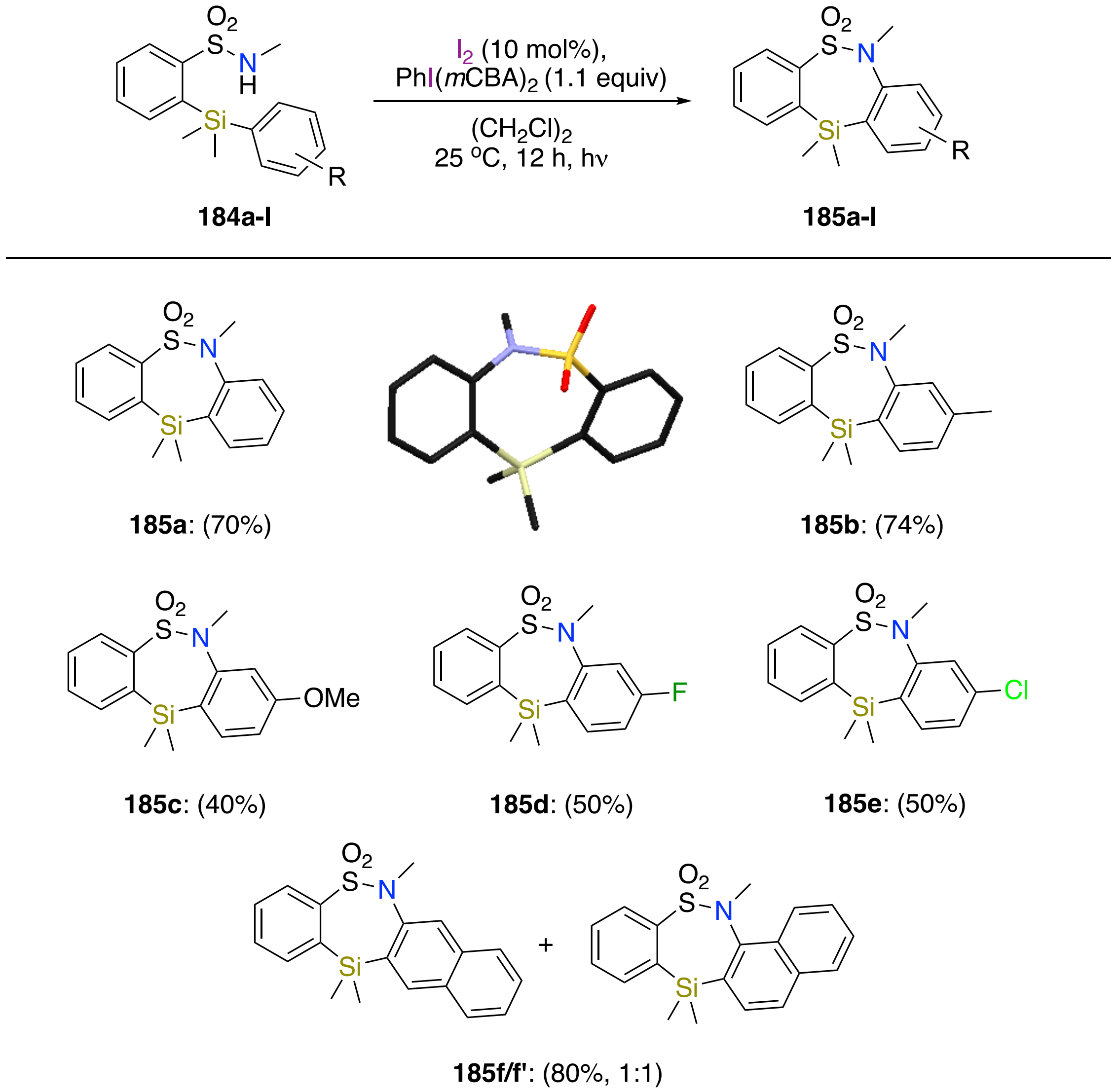


182b **183b** (91%)

Scheme 3.15: Hydrogenolysis of the benzyl protection.

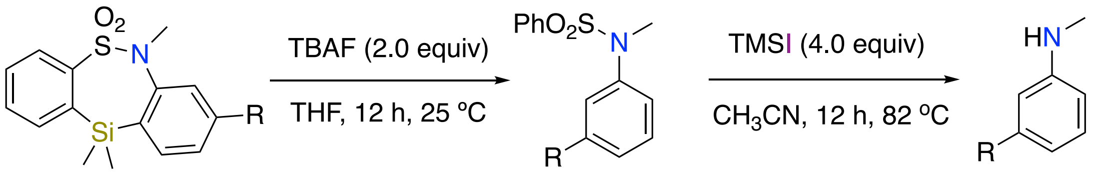
As the reaction seemed of general interest, we reflected on the possibility of creating substrates that could facilitate the access toward the final anilines. Thus, we synthesized the silicon-tethered arenes **184**. For these particular substrates, containing seven-membered rings with long carbon-silicon bonds, a higher amount of molecular iodine (10 mol%) in order to arrive at a viable catalysis is needed for an efficient catalyst turnover. Under these conditions the expected heterocycles **185a-l** were obtained (Scheme 3.16).

The observed selectivity was confirmed by X-ray analysis for the **185a** derivative. Arenes **184b-e** with different substituents in the *para* position underwent the intramolecular C-H amination to afford the products in good yields as well (40-78%). For the 2-naphthalene derivative **184f**, a regioisomeric mixture of the two amination products **31f/f'** was observed in 80% yield.



Scheme 3.16: Scope for the intramolecular C-H amination using silyl-tether.

Likewise, products **185a** and **185d** were submitted to conditions for the silyl tether removal and subsequent sulfonamide deprotection, yielding the final methylanilines **187a** and **187d** in 95% overall yield under moderately mild conditions with absolute selectivity (Scheme 3.17). This type of substitution pattern would be synthetically difficult via a direct aromatic amination or not accessible from standard electrophilic aromatic substitution.



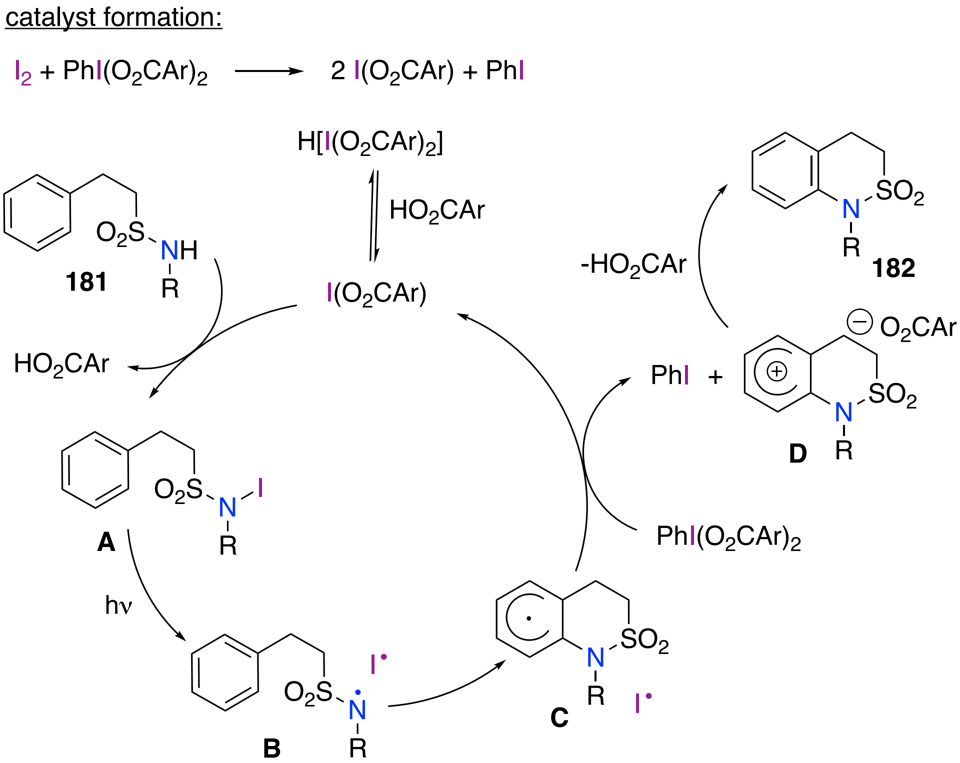
185a: (R = H)
185d: (R = F)

186a: (R = H)
186d: (R = F)

187a: (R = H)
187d: (R = F)

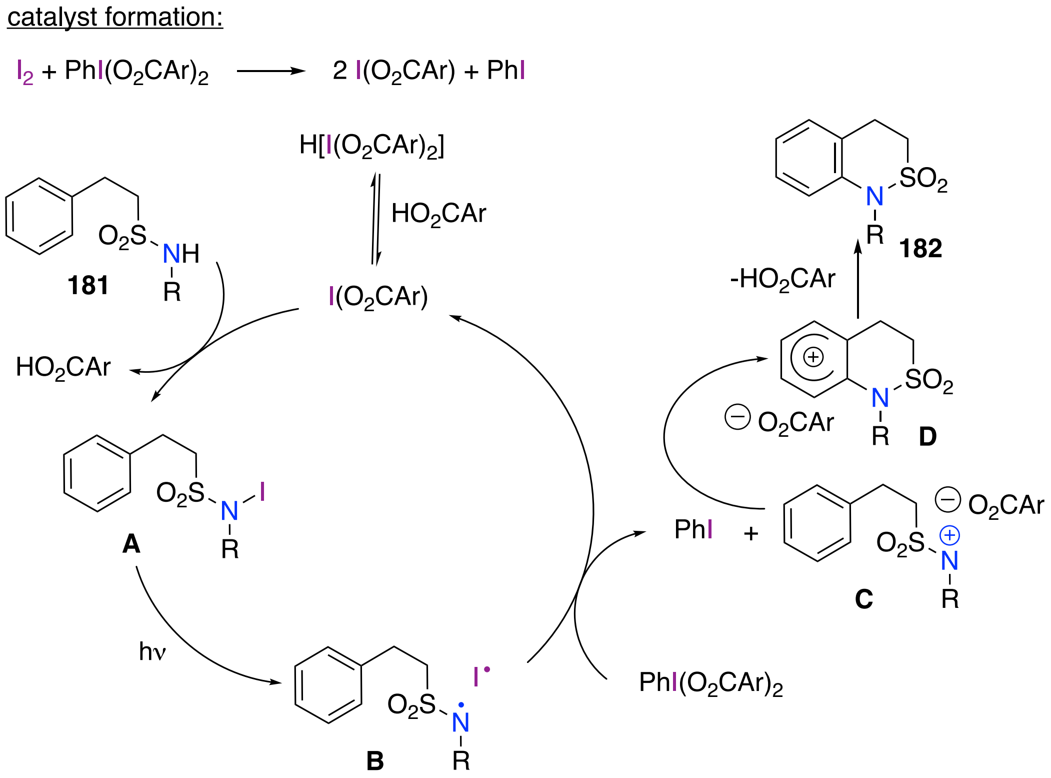
Scheme 3.17: Representative cleavage of the tether and deprotection.

From the mechanistic point of view, we were considering that the initial step in the mechanism is the electrophilic iodine(I) catalyst formation; as previously proved in the established C(sp^3)-H amination. The comproportionation reaction between molecular iodine and the iodine(III) is forming the electrophilic iodine(I) catalyst, which is promoting the iodination of the nitrogen core of the substrate, leading to intermediate **A** (Scheme 3.18). Upon exposure to light, the N-I bond is cleaved homolytically, yielding the nitrogen-centered radical **B**. An aromatic addition via oxidative dearomatization is taking place to generate intermediate **C** which is further oxidized via single electron transfer (SET) to the cationic intermediate **D**. Another SET allows the regeneration of the catalyst. Final rearomatization by proton loss, provides the final product **182** formation.



Scheme 3.18: Mechanistic concept with a radical carbon-nitrogen bond formation. Ar: 3-ClC$_6$H$_4$.

An alternative mechanistic pathway starts with the same initial steps (Scheme 3.17). Nevertheless, after the nitrogen radical formation (intermediate **B**), a subsequent radical oxidation could take place at this stage. The generated electrophilic nitrogen (intermediate **C**) could induce aromatic electrophilic substitution, obtaining the cyclic intermediate **D**. This species are the same as in the first proposed catalytic cycle. The final product formation is taking place by re-aromatization.



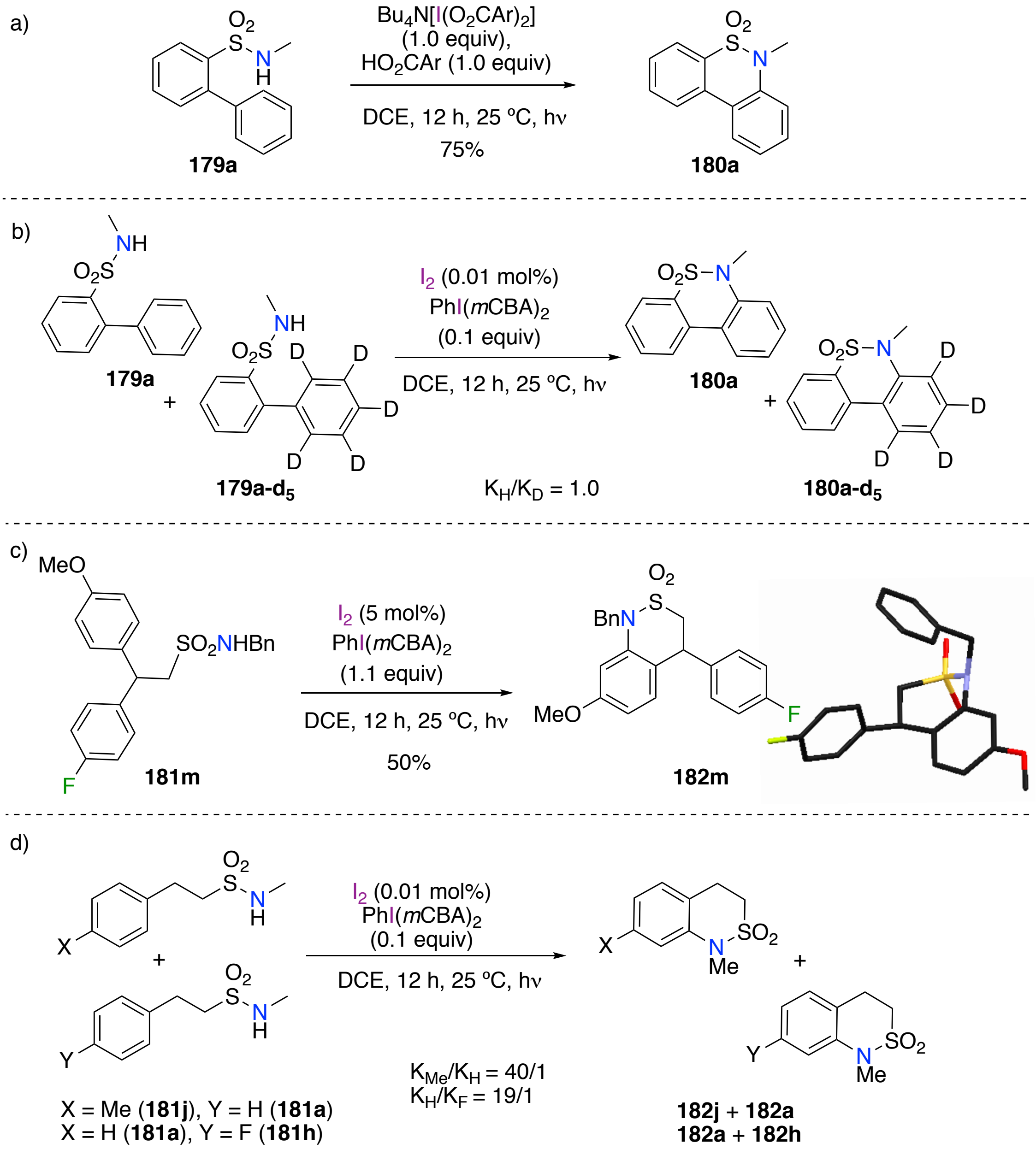
Scheme 3.19: Alternative route for the mechanism with electrophilic carbon-nitrogen bond formation. Ar: 3-ClC_6H_4.

In order to clarify which of both mechanisms is operative, we conducted several control experiments.

For the proofs on the formation of the electrophilic iodine (I) catalyst, we synthesized and isolated the related tertrabutylammonium derivative $Bu_4N[I(m\text{CBA})_2]$ as a remisent to the active catalyst of the reaction. Satisfyingly, the stoichiometric reaction with the synthesized salt proceeded equally (Scheme 3.20a); excluding any alternative pathway of aryl radical cations generated from the hypervalent iodine reagent itself.

An intermolecular kinetic isotope effect (KIE) was studied from competition between **179a** and its pentadeuterated analogue [D_5]-**179a**. The individual rates do not present any difference as the KIE is equal to 1 (Scheme 3.20b). This outcome points out that, as expected the dearomatization is a fast step in the reaction.

Finally, an internal electronic competition was conducted by submitting to reaction the precursor **181m**. This experiment was designed in order to study the electronic differentiation between different aryl groups. Interestingly, exclusive amination took place on the electron-rich anisole ring, as it was confirmed by X-ray analysis (Scheme 3.20c). A similar outcome was observed in the initial rates of the intermolecular competition experiment between **181a** with **181j** and **181a** with **181h** respectively. A significant preference for the electron-rich arene was observed in these cases (Scheme 3.20d).



Scheme 3.20: Control experiments.

As pointed out previously the whole mechanistic scenario is based on the generation of the nitrogen-centered radical and subsequent radical addition (Scheme 3.16) or oxidation to an electrophilic nitrogen and Friedel-Crafts aromatic addition. Apparently, the mechanistic investigation by performing the above mentioned control experiments did not lead to any conclusion for that particular steps of the reaction. Probably, the electrophilic aromatic addition is more prompted to happen, though there is no definite proof for excluding the radical addition to the aromatic core.

2.3 Conclusions

In summary, we have developed an iodine catalysis protocol that provides conditions for a mild and selective intramolecular aryl amination reaction. This chemistry demonstrates that photochemical iodine catalysis can provide general oxidative amination conditions for the cases of aliphatic and aromatic hydrocarbons alike. This broad scope is unprecedented in the area and should stimulate the development of additional reactivity. The elegant approach for the formation of anilines, through a removable silicon tether has direct consequences on the formation of this class of compounds. Finally, a detailed mechanistic discussion with different alternatives and discussion has also been disclosed.

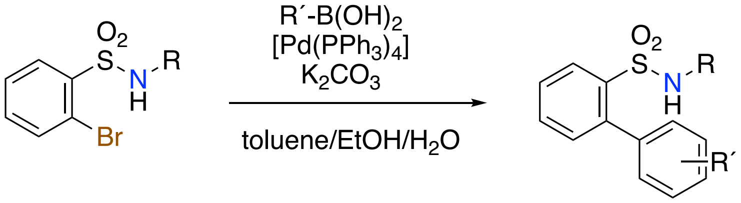
3.4 Experimental section

3.4.1 General information

All solvents, reagents and all deuterated solvents were commercially available. Column chromatography was performed with silica gel (type 60, 0.063-0.2 mm). NMR spectra were recorded on a 400 MHz or 500 MHz spectrometer, respectively. All chemical shifts in NMR experiments were reported as ppm downfield from TMS. The following calibrations were used: $CDCl_3$ $\delta = 7.26$ and 77.0 ppm, CD_2Cl_2 $\delta = 5.32$ and 54.00 ppm, MeOD $\delta = 3.31$ and 49.0 ppm. HRMS were recorded using ESI-TOF techniques. IR spectra were taken in the solid state. The following compounds were commercially available and used as received: methylamine, ethylamine, benzylamine, 2-bromobenzen-1-sulfonyl chloride, phenylboronic acid, *p*-tolylboronic acid, (4-(*tert*-butyl)phenyl)boronic acid, [1,1'-biphenyl]-4-ylboronic acid, (4-methoxyphenyl)boronic acid, (4-phenoxyphenyl)boronic acid, (4-ethoxyphenyl)boronic acid, (4-fluorophenyl)boronic acid, (4-chlorophenyl)boronic acid, (4-(trifluoromethyl)phenyl)boronic acid, *o*-tolylboronic acid, *m*-tolylboronic acid, (4-fluoro-3-methylphenyl)boronic acid, (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid, benzo[*b*]thiophen-2-ylboronic acid, (1-(phenylsulfonyl)-1*H*-indol-3-yl)boronic acid, (2-bromoethyl)benzene, 1-(2-bromoethyl)-4-fluorobenzene, 1-(2-bromoethyl)-4-chlorobenzene, 1-bromo-4-(2-bromoethyl)benzene, 1-(2-bromoethyl)-4-methylbenzene, tetrakis(triphenylphosphine)palladium, *N*-chlorosuccinimide, dichlorodimethylsilane, phenylmagnesium bromide, (4-fluorophenyl)magnesium bromide, (4-methoxyphenyl)magnesium bromide, iodotrimethylsilane and iodine.

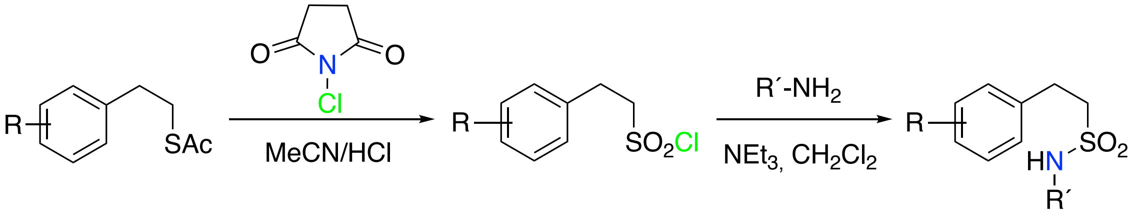
3.4.2 General procedures

General procedure for the synthesis of the biaryls 25a-25l (GP1)



The bromide (1.0 equiv), the corresponding boronic acid (1.5 equiv) and K_2CO_3 (4.0 equiv) were suspended in a mixture of toluene, EtOH and H_2O (0.1 M, 5/2/1, v/v/v) and heated to reflux under argon for 30 min. [Pd(PPh_3)$_4$] (2.5 mol%) was added and the resulting dark suspension was heated to reflux until complete conversion (monitored by TLC, reaction time variation: 3-24 h). The mixture was cooled, H_2O and EtOAc (1/1 v/v) were added and the two phases were separated. The aqueous phases were extracted with EtOAc (3x). Next, the organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *n*-hexane/EtOAc) and (if necessary) by a subsequent crystallization from *n*-hexane/EtOAc.

General procedure for the synthesis of the sulfonamides 26a-26l (GP2)



Step 1: Potassium thioacetate (1.1 equiv) was dissolved in DMF (0.3 M) and cooled to 0 °C. The corresponding bromide (1.0 equiv) was added drop-wise and the resulting suspension was stirred for 2 h at 25 ºC. After that time, brine was added, and the mixture was extracted with Et_2O (4x). The combined organic phases were washed with brine (4x), dried over Na_2SO_4 and evaporated under reduced pressure to afford the pure product, which was directly used without further purification in the next step.

Step 2: *N*-Chlorosuccinimide (4.0 equiv) was added to a mixture of CH_3CN / 2M HCl (5/1, v/v) and cooled to 0 °C. The corresponding thioacetate, obtained from step 1, (1.0 equiv) was added drop-wise. The mixture was stirred until completion of the reaction (monitored by TLC, usual reaction time: 1 h) and Et_2O was added. The aqueous phase was extracted with Et_2O. The organic phases were washed with brine (2x) and dried over Na_2SO_4. The solvent was remover under reduced pressure to afford the pure product, which was directly used without further purification.

Step 3: A solution of the corresponding amine (1.0 equiv) and NEt_3 (1.5 equiv) in DCM (0.2 M) was cooled to 0 °C and the corresponding sulfonyl chloride, obtained from step 2, (1.1 equiv) was added portion-wise. The resulting cloudy solution was stirred for 12 h at 25 ºC, washed successively with an aqueous solution of HCl (2 M), a saturated aqueous solution of $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude material was purified by column chromatography (SiO_2, *n*-hexane/EtOAc) to give the pure product.

General procedure for the intramolecular C(sp_2)-H amination (GP3)

A dried Schlenk tube equipped with a stirrer bar was charged with the sulfonamide substrate (0.45 mmol, 1.0 equiv), I_2 (5 mol%) and $PhI(mcba)_2$ (0.49 mmol, 1.1 equiv), evacuated and backfilled with argon, before 2 mL of absolute dichloroethane were added. The solution was stirred at 25 °C for 12 h under visible light. DCM was added and the mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$. The aqueous phase was extracted with DCM (2x). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (SiO_2, *n*-hexane/EtOAc) to give the pure product.

General procedure for hydrogenolysis of benzyl group (GP4)

Palladium hydroxide (125 mg) was added to a solution of **29a** (0.62 mmol, 1 equiv) in EtOAc (3 mL) and EtOH (3 mL). The mixture was stirred at 25 ºC for 12h under H_2 atmosphere. After this time, the mixture was poured into CH_2Cl_2 and washed with water (3x). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *n*-hexane/EtOAc).

General procedure for silicon tether cleavage (GP5)

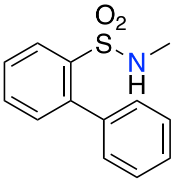
A Schlenk tube equipped with a stirrer bar was charged with **185a** or **185d** (0.11 mmol, 1.0 equiv), THF (10 mL) and TBAF (0.22 mmol, 2 equiv). The mixture was stirred at 25 ºC for 12 h. CH_2Cl_2 was added and the resulting solution was washed with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated under reduced pressure. The crude material was purified by chromatography (silica gel, *n*-hexane/ethyl acetate, 4/1, v/v) to give the pure products.

General procedure for sulphonamide deprotection (GP6)

To a solution of the corresponding sulfonamide **186a** and **186d** (0.4 mmol, 1.0 equiv) in CH_3CN (10 mL) was added TMSI (0.22 mL, 4.0 equiv) and the reaction mixture was heated for 12 h at 82 ºC. CH_2Cl_2 was added and the mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$. The combined organic layers were dried over Na_2SO_4 and solvents were evaporated under reduced pressure. The crude material was purified by chromatography (silica gel, *n*-hexane/ethyl acetate, 4/1, v/v) to afford the pure product.

3.4.3 Data for compounds

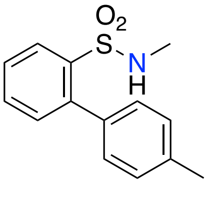
N-Methyl-[1,1'-biphenyl]2-sulfonamide 179a



Synthesized according to GP1. 89% yield. White solid. Data in agreement with the ones reported. [173]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (d, J = 5.4 Hz, 3H), 3.34 (q, J = 5.6 Hz, 1H), 7.37 (dd, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.46-7.53 (m, 5H), 7.55 (td, J = 7.7, 1.5 Hz, 1H), 7.63 (td, J = 7.5, 1.5 Hz, 1H), 8.18 (dd, J = 7.9, 1.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 29.0, 128.0, 128.3, 128.6, 129.0, 129.8, 132.1, 132.3, 137.0, 138.9, 140.1.

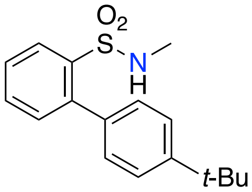
N,4'-Dimethyl-[1,1'-biphenyl]-2-sulfonamide179b



Synthesized according to GP1. 92% yield. White solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (d, J = 5.4 Hz, 3H), 2.45 (s, 3H), 3.39 (q, J = 5.7 Hz, 1H), 7.27-7.30 (m, 2H), 7.35 (dd, J = 7.5, 1.0 Hz, 1H), 7.38-7.42 (m, 2H), 7.54 (td, J = 7.7, 1.4 Hz, 1H), 7.62 (td, J = 7.5, 1.4 Hz, 1H), 8.17 (dd, J = 8.0, 1.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 21.3, 29.1, 127.9, 128.9, 129.0, 129.8, 132.1, 132.3, 135.8, 136.9, 128.6, 140.2. **IR** ν(cm^{-1}): 3344, 1464, 14078, 1316, 1154, 1130, 1086, 822, 763, 668, 586, 550, 536, 476. **HRMS** (m/z): calcd. for $C_{14}H_{15}NNaO_2S$, 284.0716; found: 284.0711. **m.p.**: 96-97 °C.

4'-(*tert*-Butyl)-N-methyl-[1,1'-biphenyl]-2-sulfonamide 179c



Synthesized according to GP1. 96% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9H), 2.35 (d, J = 5.4 Hz, 3H), 3.38 (q, J = 4.8 Hz, 1H), 7.26 (dd, J = 7.5, 1.4 Hz, 1H), 7.42-7.46 (m, 2H), 7.48-7.51 (m, 2H), 7.53 (td, J = 7.7, 1.5 Hz, 1H), 7.61 (td, J = 7.5, 1.4 Hz, 1H), 8.17 (dd, J = 7.9, 1.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 29.1, 31.3, 34.7, 125.2, 127.8, 128.7, 129.8, 132.2, 132.3, 135.7, 136.9, 140.2, 151.8. **IR** ν(cm^{-1}): 3277, 2957, 1465, 1433, 1398, 1313, 1153, 1095, 1003, 841, 761, 575, 543, 496. **HRMS** (m/z): calcd. for $C_{17}H_{21}NNaO_2S$, 326.1185; found: 326.1181. **m.p.**: 101-102 °C.

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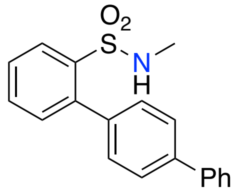
[173] S. A. Glover, A. Goosen, C. W. McCleland, J. L. Schoonraad, *J. Chem. Soc. Perkin Trans. 2* **1986**, 645.

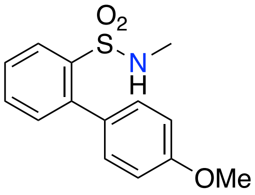
N-Methyl-[1,1':4',1''-terphenyl]-2-sulfonamide 179d



Synthesized according to GP1. 87% yield. White solid.

^{1}H NMR (400 MHz, CDCl$_3$):δ = 2.40 (d, *J* = 5.4 Hz, 3H), 3.49 (q, *J* = 5.9 Hz, 1H), 7.38-7.46 (m, 2H), 7.48-7.54 (m, 2H), 7.55-7.62 (m, 3H), 7.63-7.75 (m, 5H), 8.21 (dd, *J* = 7.9, 1.4 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 29.0, 126.9, 127.1, 127.8, 128.1, 129.0, 129.5, 129.9, 132.2, 132.4, 137.0, 137.8, 139.9, 140.0, 140.4. **IR** ν(cm^{-1}): 3281, 1469, 1328, 1151, 1071, 1005, 838, 763, 702, 670, 569, 520, 454. **HRMS** (m/z): calcd. for $C_{19}H_{17}NNaO_2S$, 346.0872; found: 346.0858. **m.p.**: 134-135 °C.

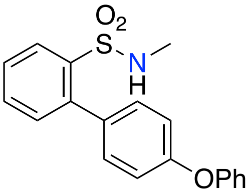
4'-Methoxy-*N*-methyl-[1,1'-biphenyl]-2-sulfonamide 179e



Synthesized according to GP1. 70% yield. White solid.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.35 (d, *J* = 5.4 Hz, 3H), 3.41 (q, *J* = 4.7 Hz, 1H), 3.90 (s, 3H), 6.99-7.03 (m, 2H), 7.35 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.43-7.47 (m, 2H), 7.53 (td, *J* = 7.7, 1.4 Hz, 1H), 7.61 (td, *J* = 7.5, 1.4 Hz, 1H), 8.17 (dd, *J* = 8.0, 1.0 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 29.0, 55.3, 113.7, 127.8, 129.9, 130.3, 130.8, 132.3, 137.0, 139.9, 159.8. **IR** ν(cm^{-1}): 3273, 1606, 1510, 1461, 1431, 1314, 1247, 1153, 1108, 1087, 1035, 836, 766, 665, 584, 555, 538, 468. **HRMS** (m/z): calcd. for $C_{14}H_{15}NNaO_3S$, 300.0665; found: 300.0669. Synthesized according to GP1. 89% yield. White solid. Data in agreement with the ones reported. **m.p.**: 104-105 °C.

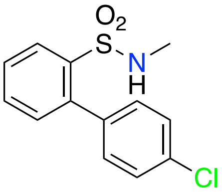
N-Methyl-4'-phenoxy-[1,1'-biphenyl]-2-sulfonamide 179f



Synthesized according to GP1. 99% yield. White solid.

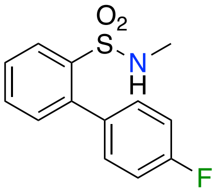
^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.37 (d, *J* = 5.4 Hz, 3H), 3.48 (q, *J* = 5.4 Hz, 1H, NH), 7.04-7.11 (m, 4H), 7.13-7.22 (m, 1H), 7.35 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.37-7.46 (m, 4H), 7.52 (td, *J* = 7.7, 1.4 Hz, 1H), 7.60 (td, *J* = 7.5, 1.5 Hz, 1H), 8.15 (dd, *J* = 8.0, 1.3 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 29.2, 117.9, 119.9, 124.3, 128.1, 130.0, 130.1, 120.7, 132.6, 132.5, 133.3, 137.2, 139.8, 156.3, 158.2. **IR** ν(cm^{-1}): 3366, 3059, 3028, 3011, 2973, 2935, 2929, 2918, 2856, 1586, 1464, 1302, 1234, 1154, 1069, 832, 765, 571. **HRMS** (m/z): calcd. for $C_{19}H_{17}NNaO_3S$, 362.0821; found: 362.0827. **m.p.**: 145-146 ºC.

4’-Chloro-*N*-methyl-[1,1’-biphenyl]-2-sulfonamide 179h



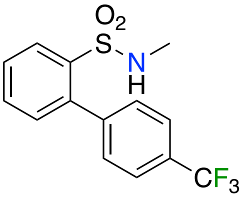
Synthesized according to GP1. 82% yield. White solid. ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 2.41 (d, *J* = 5.4 Hz, 3H), 3.47 (q, *J* = 5.7 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.43-7.47 (m, 4H), 7.56 (td, *J* = 7.7, 1.5 Hz, 1H), 7.63 (td, *J* = 7.5, 1.5 Hz, 1H), 8.17 (dd, *J* = 7.9, 1.4 Hz, 1H). ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 28.9, 128.3, 128.5, 130.0, 130.5, 132.1, 132.5, 134.8, 137.1, 137.3, 139.1. **IR** ν(cm^{-1}): 3279, 1596, 1463, 1313, 1294, 1154, 1088, 1002, 836, 764, 580, 538, 493, 463**.** **HRMS** (m/z): calcd. for $C_{13}H_{12}ClNNaO_2S$, 304.0169 found: 304.0165. **m.p.**: 102-103 °C.

4'-Fluoro-*N*-methyl-[1,1'-biphenyl]-2-sulfonamide 179i



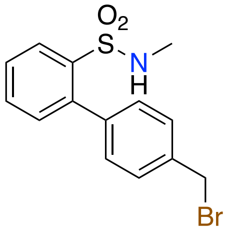
Synthesized according to GP1. 81% yield. Yellow solid. ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 2.37 (d, *J* = 5.4 Hz, 3H), 3.43 (q, *J* = 5.5 Hz, 1H, NH), 7.10-7.19 (m, 2H), 7.32 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.43-7.48 (m, 2H), 7.53 (td, *J* = 7.7, 1.5 Hz, 1H), 7.60 (td, *J* = 7.5, 1.5 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.7 Hz, 1H). ^{13}**C NMR** (126 MHz, CDCl$_3$): δ = 28.9, 115.4 (d, *J* = 21.5 Hz), 128.3, 130.1, 131.0, 131.1, 132.5 (d, *J* = 11.5 Hz), 134.9 (d, *J* = 3.5 Hz), 137.3, 139.3, 162.9 (d, *J* = 248.9 Hz). ^{19}**F NMR** (376 MHz, CDCl$_3$): δ = -112.8. **IR** ν(cm^{-1}): 3325, 3051, 2979, 2920, 2896, 1512, 1464, 1304, 1226, 1157, 1121, 1086, 1075, 840, 760. **HRMS** (m/z): calcd. for $C_{13}H_{11}FNO_2S$, 264.0500; found: 264.0490. **m.p.**: 116-117 ºC.

N-Methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-sulfonamide 179j



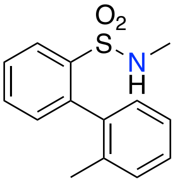
Synthesized according to GP1. 99% yield. White solid. ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 2.42 (d, *J* = 5.4 Hz, 3H), 3.51 (q, *J* = 5.4 Hz, 1H, NH), 7.31 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.53-7.61 (m, 3H), 7.64 (td, *J* = 7.5, 1.5 Hz, 1H), 7.69-7.73 (m, 2H), 8.16 (dd, *J* = 7.7, 1.6 Hz, 1H). ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 28.9, 125.2 (q, *J* = 3.8 Hz), 125.8 (q, *J* = 272.3 Hz), 128.1, 128.7, 129.7, 130.1, 130.7 (q, *J* = 32.8 Hz), 132.2, 132.6, 132.8, 137.2, 139.2, 142.9. ^{19}**F NMR** (376 MHz, CDCl$_3$): δ = -62.7. **IR** ν(cm^{-1}): 3281, 3065, 2999, 2984, 2953, 2814, 1405, 1321, 1161, 1106, 1062, 1004, 838, 766, 582. **HRMS** (m/z): calcd. for $C_{14}H_{11}F_3NO_2S$, 314.0468; found: 314.0455. **m.p.**: 103-104 ºC.

4'-(Bromomethyl)-*N*-methyl-[1,1'-biphenyl]-2-sulfonamide 179k



Synthesized according to GP1. 78% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 2.36 (d, *J* = 5.4 Hz, 3H), 3.43 (q, *J* = 5.4 Hz, 1H, NH), 4.54 (s, 2H), 7.32 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.43-7.50 (m, 4H), 7.53 (td, *J* = 7.7, 1.5 Hz, 1H), 7.61 (td, *J* = 7.5, 1.4 Hz, 1H), 8.14 (dd, *J* = 7.8, 1.4 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 29.1, 32.8, 128.3, 128.9, 129.6, 129.9, 132.2, 132.5, 137.1, 138.3, 139.1, 139.7. **IR** ν(cm^{-1}): 3342, 3062, 3027, 2981, 2954, 2920, 2893, 2851, 1740, 1383, 1308, 1154, 1122, 1081, 758, 574. **HRMS** (m/z): calcd. for $C_{14}H_{14}BrNNaO_2S$, 361.9821; found: 361.9827. **m.p.**: 86-87 ºC.

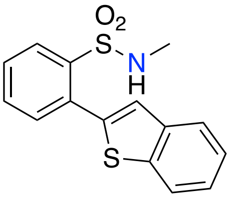
N,2'-Dimethyl-[1,1'-biphenyl]-2-sulfonamide 179l



Synthesized according to GP1. 59% yield. White solid. **^{1}H NMR** (500 MHz, CDCl$_3$): δ = 2.13 (s, 3H), 2.52 (d, *J* = 5.3 Hz, 3H), 3.52 (q, *J* = 5.2 Hz, 1H), 7.21 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.24-7.31 (m, 2H), 7.32-7.40 (m, 2H), 7.55 (td, *J* = 7.7, 1.4 Hz, 1H), 7.64 (td, *J* = 7.5, 1.4 Hz, 1H), 8.19 (dd, *J* = 7.9, 1.4 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 20.3, 29.1, 125.1, 127.8, 128.3, 128.8, 129.9, 130.5, 131.8, 132.4, 137.2, 138.2, 140.0.

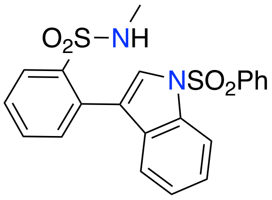
IR ν(cm^{-1}): 3299, 1463, 1431, 1308, 1158, 1117, 1084, 1042, 851, 759, 681, 584, 558, 453. **HRMS** (m/z): calcd. for $C_{14}H_{15}NNaO_2S$, 284.0716; found: 284.0714. **m.p.**: 62-63 °C.

2-(Benzo[b]thiophen-2-yl)-*N*-methyl-benzenesulfonamide 179m



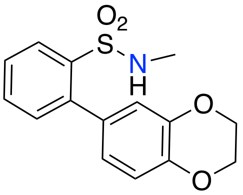
Synthesized according to GP1. 46% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 2.47 (d, *J* = 5.4 Hz, 3H), 3.92 (q, *J* = 5.0 Hz, 1H), 7.41-7.49 (m, 2H), 7.57-7.68 (m, 3H), 7.70 (d, *J* = 0.7 Hz, 1H), 7.86-7.91 (m, 2H), 8.22-8.28 (m, 1H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 29.5, 122.0, 124.5, 125.0, 125.2, 126.6, 129.0, 130.4, 132.2, 132.4, 133.4, 137.8, 138.2, 139.7, 140.1. **IR** ν(cm^{-1}): 3310, 1565, 1467, 1428, 1308, 1156, 1122, 1086, 837, 770, 752, 725, 575, 543, 473. **HRMS** (m/z): calcd. for $C_{15}H_{12}NO_2S_2$, 302.0315; found: 302.0310.n **m.p.**: 103-104 °C.

N-Methyl-2-(1-(phenylsulfonyl)-1*H*-indol-3-yl)benzenesulfonamide 179n



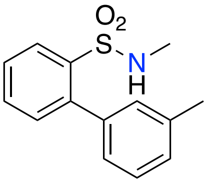
Synthesized according to GP1. 61% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.13 (d, *J* = 5.4 Hz, 3H), 3.12 (q, *J* = 5.4 Hz, 1H, NH), 7.22-7.29 (m, 2H), 7.40 (ddd, *J* = 8.4, 6.5, 2.0 Hz, 1H), 7.44-7.49 (m, 1H), 7.50-7.53 (m, 2H), 7.54-7.61 (m, 2H), 7.64 (td, *J* = 7.5, 1.5 Hz, 1H), 7.94 (s, 1H), 8.00-8.03 (m, 2H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.21 (dd, *J* = 7.9, 1.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 29.4, 114.3, 119.0, 119.6, 124.2, 125.6, 127.2, 127.3, 128.5, 129.7, 130.4, 130.7, 130.8, 132.6, 133.1, 134.3, 134.6, 138.1, 138.2. **IR** ν(cm^{-1}): 3360, 3114, 3095, 3067, 2980, 2924, 1447, 1349, 1328, 1160, 1127, 1080, 748, 568. **HRMS** (m/z): calcd for $C_{21}H_{17}N_2O_4S_2$, 425.0635; found: 425.0637. **m.p.**: 163-164 ºC.

2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-methylbenzenesulfonamide 179o



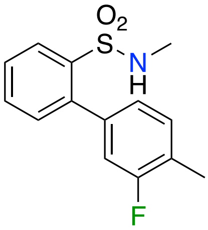
Synthesized according to GP1. 74% yield. Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.39 (d, *J* = 5.4 Hz, 3H), 3.58 (q, *J* = 5.4 Hz, 1H, NH), 4.21-4.41 (m, 4H), 6.93-7.0 (m, 2H), 7.02 (d, *J* = 2.0 Hz, 1H), 7.34 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.52 (td, *J* = 7.7, 1.5 Hz, 1H), 7.59 (td, *J* = 7.5, 1.5 Hz, 1H), 8.15 (dd, *J* = 8.0, 1.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 29.3, 64.5, 64.6, 117.3, 118.2, 122.3, 127.9, 129.9, 131.9, 132.4, 137.0, 139.8, 143.3, 144.1. **IR** ν(cm^{-1}): 3345, 2995, 2944, 2888, 1468, 1396, 1309, 1277, 1220, 1158, 1061, 820, 775, 575. **HRMS** (m/z): calcd. for $C_{15}H_{15}NNaO_4S$, 328.0614; found: 328.0621. **m.p.**: 134-135 ºC.

N,3'-Dimethyl-[1,1'-biphenyl]-2-sulfonamide 179p



Synthesized according to GP1. 69% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.36 (d, *J* = 5.4 Hz, 3H), 2.44 (s, 3H), 3.37 (q, *J* = 5.6 Hz, 1H), 7.27-7.40 (m, 5H), 7.54 (td, *J* = 7.1, 1.5 Hz, 1H), 7.62 (td, *J* = 7.5, 1.4 Hz, 1H), 8.17 (dd, *J* = 7.9, 1.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 21.4, 29.1, 125.9, 127.9, 128.2, 129.4, 129.7, 129.8, 132.0, 132.3, 136.9, 138.1, 138.8, 140.2. **IR** ν (cm^{-1}): 3359, 1464, 1379, 1319, 1160, 1119, 1074, 836, 797, 764, 735, 708, 685, 575, 545, 472, 449. **HRMS** (m/z): calcd. for $C_{14}H_{15}NNaO_2S$, 284.0716; found: 284.0708. **m.p.**: 153-154 °C.

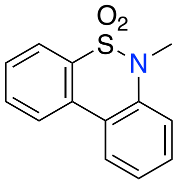
3'-Fluoro-*N*,4'-dimethyl-[1,1'-biphenyl]-2-sulfonamide 179q



Synthesized according to GP1. 95% yield. Yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (d, *J* = 2.0 Hz, 3H), 2.41 (d, *J* = 5.6 Hz, 3H), 3.54 (q, *J* = 5.6 Hz, 1H, NH), 7.14-7.20 (m, 2H), 7.26-7.30 (m, 1H), 7.33 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.55 (td, *J* = 7.7, 1.5 Hz, 1H), 7.62 (td, *J* = 7.5, 1.5 Hz, 1H), 8.16 (dd, *J* = 8.0, 1.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 14.6, 29.1, 116.0 (d, *J* = 23.3 Hz), 124.6, 124.7, 125.5 (d, *J* = 17.2 Hz), 128.3, 130.0, 131.4 (d, *J* = 5.6 Hz), 132.3, 132.5, 138.3 (d, *J* = 7.8 Hz), 139.1, 160.7 (d, *J* = 246.9 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -116.4. **IR** ν(cm^{-1}): 3353, 3067, 2976, 2930, 2926, 2894, 1468, 1396, 1320, 1157, 1123, 755, 581. **HRMS** (m/z): calcd. for $C_{14}H_{14}FNNaO_2S$, 302.0621; found: 302.0623. **m.p.**: 108-109 ºC.

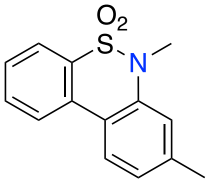
6-Methyl-6*H*-dibenzo[c,e][1,2]thiazine 5,5-dioxide 180a



Synthesized according to GP3. 99% yield. White solid. Data in agreement with the ones reported.[174]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.48 (s, 3H), 7.32-7.40 (m, 2H), 7.54 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1H), 7.60 (td, *J* = 7.7, 1.1 Hz, 1H), 7.74 (ddd, *J* = 8.0, 7.4, 1.4 Hz, 1H), 8.00 (ddt, *J* = 8.1, 1.1, 0.5 Hz, 1H), 8.03-8.06 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 32.8, 119.4, 122.5, 124.0, 124.7, 125.4, 125.5, 128.2, 130.4, 132.4, 134.2, 139.5.

6,8-Dimethyl-6*H*-dibenzo[c,e][1,2]thiazine 5,5-dioxide 180b



Synthesized according to GP3. 92% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3H), 3.46 (s, 3H), 7.14 (s, 1H), 7.18 (ddd, *J* = 8.0, 1.7, 0.8 Hz, 1H), 7.56 (td, *J* = 7.7, 1.1 Hz, 1H), 7.71 (ddd, *J* = 8.0, 7.4, 1.4 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.01 (dd, *J* = 7.8, 1.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.7, 32.8, 119.9, 121.4, 122.5, 125.1, 125.4, 125.7, 127.8, 132.4, 132.5, 133.8, 139.4, 141.0. **IR** ν(cm^{-1}): 1611, 1578, 1470, 1318, 1268, 1201, 1175, 1164, 1132, 1060, 937, 877, 806, 767, 745, 720, 697, 609, 569, 556, 455. **HRMS** (m/z): calcd. for $C_{14}H_{14}NO_2S$, 260.0704; found: 260.0738. **m.p.**: 134-135 °C.

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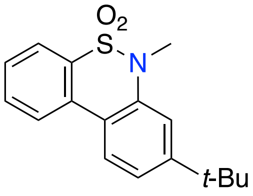
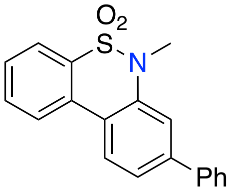
[174] N. Conde, F. Churruca, R. Sanmartin, M. T. Herrero, E. Dominguez, *Adv. Synth. Catal.* **2015**, *357*, 1525.

8-(*tert*-Butyl)-6-methyl-6*H*-dibenzo[c,e][1,2]thiazine 5,5-dioxide 180c



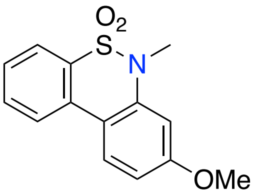
Synthesized according to GP3. 93% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 1.41 (s, 9H), 3.47 (s, 3H), 7.32 (d, *J* = 1.9 Hz, 1H), 7.40 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.56 (td, *J* = 7.6, 1.1 Hz, 1H), 7.72 (ddd, *J* = 8.1, 7.4, 1.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.95-7.98 (m, 1H), 8.02 (ddd, *J* = 7.8, 1.4, 0.5 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 31.2, 33.4, 35.1, 116.7, 121.4, 122.3, 122.6, 125.1, 125.2, 127.8, 132.4, 133.8, 139.3, 154.2. **IR** ν(cm^{-1}): 2957, 2927, 2688, 1610, 1576, 1470, 1321, 1171, 1129, 1062, 927, 846, 778, 748, 721, 577, 560, 508. **HRMS** (m/z): calcd. for $C_{17}H_{19}NNaO_2S$, 324.1029; found: 324.1031. **m.p.**: 167-169 °C.

6-Methyl-8-phenyl-6*H*-dibenzo[c,e][1,2]thiazine 5,5-dioxide 180d



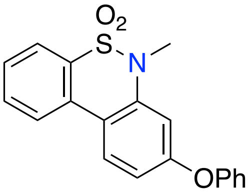
Synthesized according to GP3. 94% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 3.54 (s, 3H), 7.42-7.47 (m, 1H), 7.49-7.55 (m, 3H), 7.57-7.64 (m, 2H), 7.65-7.70 (m, 2H), 7.76 (ddd, *J* = 8.0, 7.4, 1.4 Hz, 1H), 8.01-8.04 (m, 1H), 8.06 (ddd, *J* = 7.9, 1.4, 0.5 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 32.9, 118.0, 122.6, 122.8, 123.6, 125.3, 125.9, 127.2, 128.2, 129.0, 132.2, 132.5, 134.1, 139.9, 143.6. **IR** ν(cm^{-1}): 1688, 1608, 1594, 1572, 1468, 1402, 1320, 1238, 1167, 1127, 1061, 902, 781, 759, 697, 683, 557, 509. **HRMS** (m/z): calcd. for $C_{19}H_{16}NO_2S$, 322.0896; found: 322.0897. **m.p.**: 210-211 °C.

8-Methoxy-6-methyl-6*H*-dibenzo[c,e][1,2]thiazine 5,5-dioxide 180e



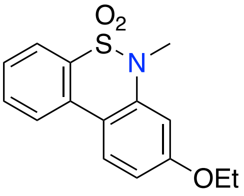
Synthesized according to GP3. 93% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 3.46 (s, 3H), 3.93 (s, 3H), 6.82 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.52 (td, *J* = 7.8, 1.1 Hz, 1H), 7.70 (ddd, *J* = 8.1, 7.4, 1.4 Hz, 1H), 7.88-7.91 (m, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 8.00 (ddd, *J* = 7.9, 1.4, 0.5 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 32.4, 55.6, 104.8, 110.6, 116.9, 122.5, 124.7, 126.8, 127.2, 132.4, 132.5, 133.0, 140.9, 161.3. **IR** ν(cm^{-1}): 1614, 1581, 1557, 1471, 1315, 1282, 1220, 1167, 1123, 1046, 851, 775, 698, 591, 567, 552, 461. **HRMS** (m/z): calcd. for $C_{14}H_{13}NaO_3S$, 298.0508; found: 298.0518. **m.p.**: 138-139 °C.

6-Methyl-8-phenoxy-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide 180f



Synthesized according to GP3. 85% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.39 (s, 3H), 6.89-6.93 (m, 2H), 7.09-7.13 (m, 2H), 7.18-7.23 (m, 1H), 7.38-7.44 (m, 2H), 7.53 (td, *J* = 7.6, 1.1 Hz, 1H), 7.69 (ddd, *J* = 8.1, 7.4, 1.1 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 9.4 Hz, 1H), 7.99 (dd, *J* = 7.9, 1.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 32.3, 108.5, 114.2, 118.7, 120.0, 122.6, 124.6, 125.1, 127.1, 127.8, 130.2, 132.3, 132.6, 133.5, 141.0, 155.9, 159.7. **IR** ν(cm^{-1}): 3070, 3051, 2979, 2958, 2921, 2851, 1614, 1588, 1488, 1471, 1319, 1218, 1163, 1126, 756, 693, 556. **HRMS** (m/z): calcd. for $C_{19}H_{15}NNaO_3S$, 360.0665; found: 360.0668. **m.p.**: 174-175 ºC.

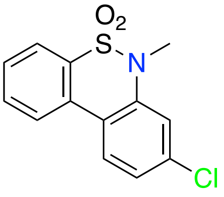
8-Ethoxy-6-methyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide 180g



Synthesized according to GP3. 90% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.0 Hz, 3H), 3.41 (s, 3H), 4.11 (q, *J* = 7.0 Hz, 2H), 6.78 (d, *J* = 2.5 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.47 (td, *J* = 7.6, 1.1 Hz, 1H), 7.65 (td, *J* = 7.8, 1.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.96 (dd, *J* = 8.1, 1.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 14.8, 32.5, 64.0, 105.4, 110.9, 116.8, 122.5, 124.8, 126.9, 127.2, 132.5, 132.6, 133.1, 140.9, 160.8.

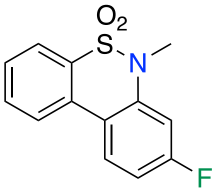
IR ν(cm^{-1}): 3065, 2971, 2929, 2892, 2861, 1614, 1557, 1470, 1313, 1277, 1160, 1114, 1053, 777, 558. **HRMS** (m/z): calcd. for $C_{15}H_{15}NNaO_3S$, 312.0665; found: 312.0664. **m.p.**: 140-141 ºC.

8-Chloro-6-methyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide 180h



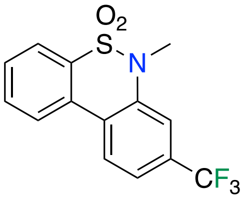
Synthesized according to GP3. 80% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.47 (s, 3H), 7.30 (dq, *J* = 3.4, 1.9 Hz, 2H), 7.55-7.65 (m, 1H), 7.72 (ddd, *J* = 9.3, 6.2, 1.4 Hz, 1H), 7.93 (td, *J* = 7.4, 2.3 Hz, 2H), 7.99-8.08 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 32.2, 119.1, 122.3, 122.5, 124.7, 125.3, 126.6, 128.5, 131.5, 132.6, 134.0, 136.1, 140.3. **IR** ν(cm^{-1}): 3093, 3062, 2945, 2918, 1886, 1859, 1597, 1323, 1168, 1125, 898, 775, 556. **HRMS** (m/z): calcd. for $C_{13}H_{10}ClNNaO_2S$, 302.0013; found: 302.0012. **m.p.**: 138-139 ºC.

8-Fluoro-6-methyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide 180i



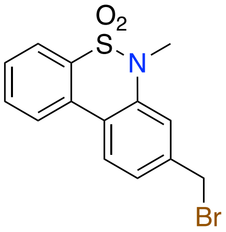
Synthesized according to GP3. 99% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 3.45 (s, 3H), 6.98-7.06 (m, 2H), 7.56 (td, *J* = 7.6, 1.1 Hz, 1H), 7.70 (td, *J* = 7.8, 1.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.95-8.02 (m, 2H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 32.0, 106.2 (d, *J* = 25.6 Hz), 111.9 (d, *J* = 22.0 Hz), 120.1 (d, *J* = 3.3 Hz), 122.5, 125.3, 127.5 (d, *J* = 9.8 Hz), 128.2, 131.8, 132.7, 133.6, 141.0 (d, *J* = 10.2 Hz), 163.7 (d, *J* = 250.9 Hz). **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -118.3. **IR** ν(cm^{-1}): 3087, 3063, 2950, 2920, 2851, 1612, 1590, 1473, 1321, 1293, 1202, 1161, 1123, 1054, 959, 854, 774, 553. **HRMS** (m/z): calcd. for $C_{13}H_{10}FNNaO_2S$, 286.0308; found: 286.0305. **m.p.**: 105-106 ºC.

6-Methyl-8-(trifluoromethyl)-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide 180j



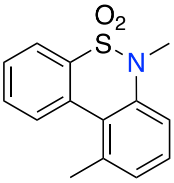
Synthesized according to GP3. 99% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 3.52 (s, 3H), 7.53 (s, 1H), 7.56-7.60 (m, 1H), 7.66 (td, *J* = 7.6, 1.1 Hz, 1H), 7.77 (td, *J* = 7.8, 1.4 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 8.05 (dd, *J* = 7.9, 1.3 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 32.6, 116.2 (q, *J* = 3.9 Hz), 121.2 (q, *J* = 3.7 Hz), 122.7, 124.7 (q, *J* = 202.5 Hz), 126.0, 126.3, 129.5, 131.3, 132.1, 132.5, 132.8, 134.9, 139.8. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -62.8. **IR** ν(cm^{-1}): 2956, 2918, 2850, 1325, 1258, 1163, 1123, 1085, 1054, 908, 780, 718, 564. **HRMS** (m/z): calcd. for $C_{16}H_{10}ClN_2NaO_3$, 336.0272; found: 336.0269. **m.p.**: 197-198 ºC.

8-(Bromomethyl)-6-methyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide 180k



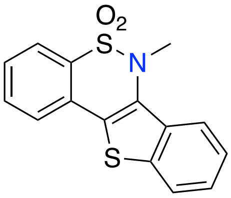
Synthesized according to GP3. 99% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 3.47 (s, 3H), 4.55 (s, 2H), 7.32 (d, *J* = 1.7 Hz, 1H), 7.35 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.58 (td, *J* = 7.7, 1.1 Hz, 1H), 7.71 (ddd, *J* = 8.0, 7.4, 1.4 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 8.01 (dd, *J* = 7.9, 1.3 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 32.5, 32.7, 119.8, 122.6, 123.9, 125.3, 125.6, 126.1, 128.6, 131.9, 132.6, 134.3, 139.8, 140.3. **IR** ν(cm^{-1}): 3073, 2986, 2921, 2851, 1579, 1470, 1320, 1295, 1277, 1171, 1156, 1100, 1058, 746, 555. **HRMS** (m/z): calcd. for $C_{14}H_{12}BrNNaO_2S$, 359.9665; found: 359.9664. **m.p.**: 194-195 ºC.

6,10-Dimethyl-6*H*-dibenzo[c,e][1,2]thiazine 5,5-dioxide 180l



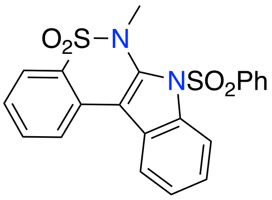
Synthesized according to GP3. 60% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.76 (s, 3H), 3.36 (s, 3H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.26 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.58 (td, *J* = 7.6, 1.2 Hz, 1H), 7.68 (ddd, *J* = 8.0, 7.4, 1.5 Hz, 1H), 7.89 (ddd, *J* = 8.1, 1.1, 0.5 Hz, 1H), 8.03 (ddd, *J* = 7.8, 1.5, 0.5 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ = 23.3, 33.8, 117.8, 122.7, 124.9, 127.6, 128.9, 129.3, 129.4, 131.1, 132.4, 135.9, 136.4, 140.1. **IR** ν(cm^{-1}): 2922, 2854, 1591, 1576, 1467, 1450, 1434, 1336, 1184, 1162, 1132, 1095, 1069, 1008, 932, 823, 797, 755, 737, 717, 652, 596, 584, 561, 551, 504, 451. **HRMS** (m/z): calcd. for $C_{14}H_{14}NO_2S$, 260.0740; found: 260.0743. **m.p.**: 145-146 °C.

6-Methyl-6*H*-benzo[e]benzo[4,5]thieno[3,2-c][1,2]thiazine 5,5-dioxide 180m



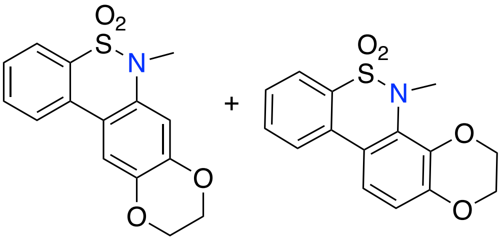
Synthesized according to GP3. 50% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.33 (s, 3H), 7.46-7.55 (m, 2H), 7.62 (ddd, *J* = 7.8, 6.7, 2.0 Hz, 1H), 7.69-7.76 (m, 2H), 7.88-7.94 (m, 2H), 8.00-8.04 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 38.2, 121.9, 123.3, 124.5, 125.4, 125.9, 126.1, 126.6, 129.2, 129.6, 130.9, 132.9, 134.1, 134.8, 137.2. **IR** ν(cm^{-1}): 1588, 1571, 1525, 1441, 1369, 1331, 1245, 1201, 1168, 1165, 1123, 1074, 1061, 1013, 968, 948, 847, 790, 763, 746, 710, 662, 650, 595, 556, 513, 500, 442. **HRMS** (m/z): calcd. for $C_{15}H_{11}NNaO_2S_2$, 324.0123; found: 324.0128. **m.p.**: 198-199 °C.

6-Methyl-7-(phenylsulfonyl)-6,7-dihydrobenzo[5,6][1,2]thiazino[3,4-*b*]indole 5,5-dioxide 180n



Synthesized according to GP3. 80% yield. Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.38 (s, 3H), 7.34-7.41 (m, 3H), 7.42-7.50 (m, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.91-8.02 (m, 4H), 8.10 (d, *J* = 7.9 Hz, 1H), 8.33 (d, *J* = 8.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 40.7, 109.3, 116.0, 120.3, 125.1, 125.2, 125.3, 125.6, 125.9, 127.8, 128.2, 129.2, 129.4, 130.8, 133.1, 143.6, 134.9, 136.8, 138.4. **IR** ν(cm^{-1}): 3078, 3022, 3009, 2953, 2926, 2853, 1430, 1345, 1178, 1126, 1090, 744, 577. **HRMS** (m/z): calcd. for $C_{21}H_{17}N_2O_4S_2$, 425.0624; found: 425.0619. **m.p.**: 224-225 ºC.

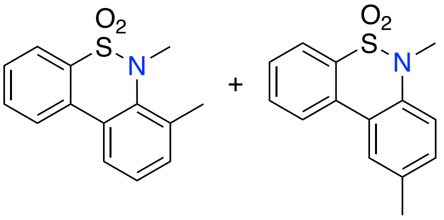
6-Methyl-9,10-dihydro-6*H*-[1,4]dioxino[2',3':4,5]benzo[1,2-*c*]benzo[*e*][1,2]thiazine 5,5-dioxide and 5-Methyl-3,5-dihydro-2*H*-[1,4]dioxino[2',3':5,6]benzo[1,2-*c*]benzo [*e*][1,2] thiazine 6,6-dioxide 180o and 180o´



Synthesized according to GP3. 93% Yield (2:1 regioisomers). White solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.09 (s, 3H), 3.31 (s, 3H), 4.29-4.35 (m 4H), 4.41 (ddd, *J* = 6.0, 2.9, 1.4 Hz, 4H), 6.83 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.46 (s, 1H), 7.47-7.54 (m, 2H), 7.65 (td, *J* = 7.8, 1.4 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.80-7.86 (m, 1H), 7.89-7.98 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 34.1, 37.8, 64.3, 64.4, 64.6, 64.9, 109.4, 114.0, 116.4, 117.7, 118.3, 120.8, 122.9, 124.2, 125.1, 125.6, 127.7, 127.9, 130.0, 132.4, 132.6, 132.7, 132.8, 133.1, 133.5, 134.3, 138.7, 141.4, 145.2, 145.5. **IR** ν(cm^{-1}): 2977, 2930, 2917, 2878, 2849, 1561, 1465, 1307, 1218, 1155, 1056, 893, 751, 712, 552. **HRMS** (m/z): calcd. for $C_{15}H_{13}NNaO_4S$, 326.0457; found: 326.0463.

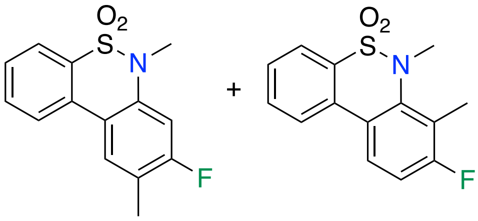
6,9-Dimethyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide and 6,7-Dimethyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide 180p and 180p´



Synthesized according to GP3. 96% Yield (1.4:1 regiosomers). White solid.

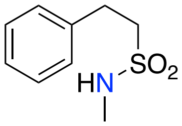
^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.46 (s, 3H), 2.52 (s, 3H), 2.95 (s, 3H), 3.42 (s, 3H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.29-7.39 (m, 3H), 7.55-7.60 (m, 2H), 7.68-7.83 (m, 4H), 7.91-8.03 (m, 4H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 17.6, 21.1, 33.4, 38.5, 119.9, 122.6, 123.7, 123.9, 124.9, 125.5, 125.9, 126.0, 127.5, 127.8, 128.2, 128.8, 131.3, 132.3, 132.4, 132.5, 132.8, 132.9, 133.3, 134.2, 134.6, 135.9, 137.3, 140.1. **IR** ν(cm^{-1}): 2959, 2922, 2851, 1439, 1336, 1176, 1127, 1097, 768, 725, 565. **HRMS** (m/z): calcd. for $C_{14}H_{13}NNaO_2S$, 282.0559; found: 282.0562.

8-Fluoro-6,9-dimethyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide and 8-Fluoro-6,7-dimethyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide 180q and180q´



Synthesized according to GP3. 93% Yield (4.5:1 regioisomers). White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.19 (s, 3H), 3.37 (s, 3H), 7.15 (d, *J* = 6.7 Hz, 1H), 7.23 (tt, *J* = 8.0, 0.8 Hz, 1H), 7.55-7.65 (m, 4H), 7.67-7.73 (m, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.98 (tdd, *J* = 7.7, 1.4, 0.5 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 14.9 (d, *J* = 4.0 Hz), 15.0 (d, *J* = 3.0 Hz), 34.3, 38.4, 111.7 (d, *J* = 25.3 Hz), 120.3 (d, *J* = 4.1 Hz), 123.0, 123.5 (d, *J* = 5.5 Hz), 123.7 (d, *J* = 8.1 Hz), 124.1, 125.4, 125.9, 126.3, 127.5 (d, *J* = 16.1 Hz), 127.9 (d, *J* = 19.0 Hz), 128.7, 128.9, 129.4, 129.5, 131.8 (d, *J* = 2.3 Hz), 132.4 (d, *J* = 2.7 Hz), 132.7, 132.8, 133.7, 134.1, 135.7 (d, *J* = 2.3 Hz), 155.4 (d, *J* = 249.5 Hz), 158.7 (d, *J* = 243.3 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -120.9, -124.9. **IR** ν(cm^{-1}): 2990, 2923, 2852, 1460, 1333, 1183, 1159, 1057, 776, 554. **HRMS** (m/z): calcd. for $C_{14}H_{12}FNNaO_2S$, 300.0465; found: 300.0458.

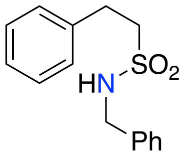
N-Methyl-2-phenylethanesulfonamide 181a



Synthesized according to GP2. 89% yield. White solid. Data in agreement with the ones reported.[175]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.74 (d, *J* = 5.3 Hz, 3H), 3.11-3.21 (m, 2H), 3.28-3.37 (m, 2H), 4.04 (q, *J* = 5.5 Hz, 1H), 7.24-7.32 (m, 3H), 7.33-7.39 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 29.3, 30.0, 52.3, 127.0, 128.4, 128.9, 137.9.

N-Benzyl-2-phenylethanesulfonamide 181b



Synthesized according to GP2. 80% yield. White solid. Data in agreement with the ones reported.[176]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.06-3.12 (m, 2H), 3.20-3.29 (m, 2H), 4.25 (d, *J* = 6.1 Hz, 2H), 4.37 (t, *J* = 6.1 Hz, 1H), 7.12-7.18 (m, 2H), 7.23-7.43 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.0, 47.3, 54.3, 127.0, 128.0, 128.2, 128.4, 128.9, 128.9, 136.7.

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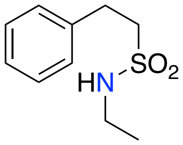
[175] H. Togo, N. Takahiro, K. Yamaguchi *J. Org. Chem.* **2000**, *65*, 8391.

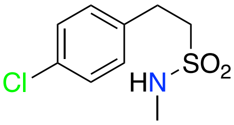
[176] J. Zinczuk, I. H. Sorokin, O. O. Orazi, R. A. Corral, *J. Heterocyclic Chem.* **1992**, *29*, 859.

_N_-Ethyl-2-phenylethanesulfonamide 181c



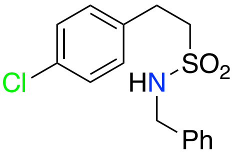
Synthesized according to GP2. 88% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 1.15 (t, *J* = 7.2 Hz, 3H), 3.03-3.20 (m, 4H), 3.28-3.36 (m, 2H), 3.93 (brs, 1H, NH), 7.23-7.32 (m, 3H), 7.32-7.40 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 15.7, 30.1, 38.3, 53.5, 127.0, 128.4, 128.9, 138.0. **IR** ν(cm^{-1}): 3264, 3061, 3027, 2975, 2928, 1603, 1497, 1449, 1432, 1308, 1264, 1131, 1105, 1057, 944, 871, 774, 740, 694, 600, 518, 485, 451. **HRMS** (m/z): calcd. for $C_{10}H_{15}NNaO_2S$, 236.0716; found: 236.0707. **m.p.**: 53-54 °C.

2-(4-Chlorophenyl)-_N_-methyletahnesulfonamide 181d



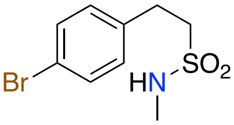
Synthesized according to GP2. 97% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 2.78 (d, *J* = 5.3 Hz, 3H), 3.08-3.16 (m, 2H), 3.25-3.32 (m, 2H), 4.14 (q, *J* = 5.6 Hz, 1H), 7.17-7.21 (m, 2H), 7.30-7.34 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 29.3, 29.3, 52.4, 129.0, 129.7, 132.9, 136.3. **IR** ν(cm^{-1}): 3280, 1492, 1450, 1411, 1298, 1238, 1150, 1116, 1093, 1068, 1016, 978, 867, 834, 810, 744, 710, 665, 621, 552, 515, 458, 409. **HRMS** (m/z): calcd. for $C_9H_{11}ClNO_2S$, 232.0205; found: 232.0204. **m.p.**: 104-105 °C.

_N_-Benzyl-2-(4-chlorophenyl)ethanesulfonamide 181e



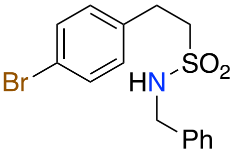
Synthesized according to GP2. 86% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 3.01-3.05 (m, 2H), 3.15-3.19 (m, 2H), 4.28 (d, *J* = 6.0 Hz, 2H), 4.54 (t, *J* = 6.0 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.27-7.32 (m, 2H), 7.33-7.41 (m, 5H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 29.4, 47.2, 54.3, 128.0, 128.2, 129.0, 129.7, 132.8, 136.6. **IR** ν(cm^{-1}): 3280, 3064, 3027, 2989, 1491, 1453, 1297, 1126, 1083, 1064, 1015. **HRMS** (m/z): calcd. for $C_{15}H_{15}ClNO_2S$, 308.0518; found: 308.0516. **m.p.**: 142-143 °C.

2-(4-Bromophenyl)-_N_-methyletahnesulfonamide 181f



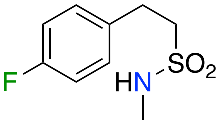
Synthesized according to GP2. 89% yield. White solid. **^{1}H NMR** (500 MHz, CDCl$_3$): δ = 2.78 (d, *J* = 4.9 Hz, 3H), 3.07-3.14 (m, 2H), 3.25-3.33 (m, 2H), 4.08 (brs, 1H, NH), 7.11-7.16 (m, 2H), 7.44-7.51 (m, 2H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 29.4, 29.4, 52.3, 120.9, 130.1, 132.0, 136.9. **IR** ν(cm^{-1}): 3297, 3264, 1489, 1406, 1313, 1231, 1149, 1115, 1062, 1010, 863, 833, 800, 745, 704, 642, 544, 504, 457. **HRMS** (m/z): calcd. for $C_9H_{12}BrNNaO_2S$, 299.9664; found: 299.9663. **m.p.**: 103-104 °C.

N-Benzyl-2-(4-bromophenyl)ethanesulfonamide 181g



Synthesized according to GP2. 96% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.93-3.07 (m, 2H), 3.08-3.32 (m, 2H), 4.28 (d, *J* = 6.0 Hz, 2H), 4.56 (t, *J* = 6.0 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.30-7.50 (m, 7H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 29.4, 47.2, 54.2, 120.8, 128.0, 128.2, 129.0, 130.1, 136.7, 136.8. **IR** ν(cm^{-1}): 3279, 3025, 2952, 2925, 2851, 1487, 1453, 1434, 1310, 1296, 1262, 1125, 1063, 1011. **HRMS** (m/z): calcd. for $C_{15}H_{15}BrNO_2S$, 352.0012; found: 352.0005.**m.p.**:143-144 °C.

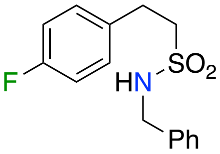
2-(4-Fluorophenyl)-*N*-methylethanesulfonamide 181h



Synthesized according to GP2. 78% yield. White solid. Data in agreement with the ones reported.[177]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.77 (d, *J* = 5.3 Hz, 3H), 3.04-3.17 (m, 2H), 3.21-3.48 (m, 2H), 4.11 (d, *J* = 5.5 Hz, 1H), 7.01-7.09 (m, 2H), 7.19-7.24 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 29.1, 29.3, 52.4, 115.6 (d, *J* = 21.4 Hz), 129.9 (d, *J* = 8.0 Hz), 133.6 (d, *J* = 3.3 Hz), 161.8 (d, *J* = 245.6 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -115.8.

N-Benzyl-2-(4-fluorophenyl)ethanesulfonamide 181i



Synthesized according to GP2. 83% yield. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 3.01-3.08 (m, 2H), 3.13-3.25 (m, 2H), 4.29 (d, *J* = 6.0 Hz, 2H), 4.51 (d, *J* = 6.0 Hz, 1H), 6.97-7.03 (m, 2H), 7.05-7.11 (m, 2H), 7.30-7.44 (m, 5H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 29.2, 47.2, 54.5, 115.7 (d, *J* = 21.3 Hz), 128.0, 128.2, 129.0, 129.8 (d, *J* = 8.1 Hz), 133.4 (d, *J* = 3.3 Hz), 136.7, 161.8 (d, *J* = 245.5 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -115.8. **IR** ν(cm^{-1}): 3264, 3236, 3066, 3037, 2950, 1602, 1509, 1494, 1454, 1435, 1297, 1221, 1141, 1124, 1055, 836, 697. **HRMS** (m/z): calcd. for $C_{15}H_{16}FNNaO_2S$, 316.0778; found: 316.0773. **m.p.**: 136-137 °C.

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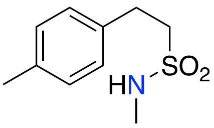
[177] A. Moroda, S. Furuyama, H. Togo, *Synlett* **2009**, *8*, 1336.

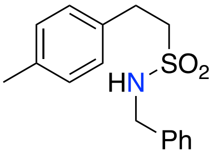
N-Methyl-2-(*p*-tolyl)ethanesulfonamide 181j



Synthesized according to GP2. 99% yield. White solid. Data in agreement with the ones reported.[175]

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.36 (s, 3H), 2.73 (d, *J* = 5.3 Hz, 3H), 3.09-3.12 (m, 2H), 3.28-3.32 (m, 2H), 3.90 (s, 3H), 7.13-7.18 (m, 4H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 21.0, 29.3, 29.5, 52.4, 128.2, 129.6, 134.7, 136.7.

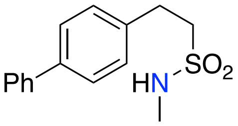
N-Benzyl-2-(*p*-tolyl)ethanesulfonamide 181k



Synthesized according to GP2. 99% yield. White solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.33 (s, 3H), 3.02-3.06 (m, 2H), 3.20-3.24 (m, 2H), 4.22 (d, *J* = 6.1 Hz, 2H), 4.38 (t, *J* = 6.0 Hz, 1H), 7.02-7.04 (m, 2H), 7.11-7.14 (m, 2H), 7.30-7.39 (m, 5H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 21.0, 29.6, 47.3, 54.3, 128.0, 128.1, 128.2, 128.9, 129.5, 134.7, 136.6, 136.7. **IR** ν(cm^{-1}): 3273, 3063, 3030, 2963, 2919, 2857, 1515, 1433, 1307, 1261, 1150, 1130, 1084, 1052, 1025. **HRMS** (m/z): calcd. for $C_{16}H_{19}NNaO_2S$, 312.1029; found: 312.1026. **m.p.**: 134-135 ºC.

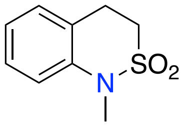
2-([1,1'-Biphenyl]-4-yl)-*N*-methylethanesulfonamide 181l



Synthesized according to GP2. 51% yield. White solid. Data in agreement with the ones reported.[178]

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.77 (t, *J* = 5.3 Hz, 3H), 3.16-3.23 (m, 2H), 3.32-3.43 (m, 2H), 3.94-3.96 (m, 1H), 7.33-7.35 (m, 2H), 7.38-7.40 (m, 1H), 7.45-7.49 (m, 2H), 7.58-7.61 (m, 3H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 29.4, 29.6, 52.4, 127.0, 127.4, 127.6, 128.8, 128.9, 136.9, 140.0, 140.5.

1-Methyl-3,4-dihydro-1*H*-benzo[c][1,2]thiazine 2,2-dioxide 182a



Synthesized according to GP3. 95% yield. White solid. Data in agreement with the ones reported.[173]

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.33 (s, 3H), 3.32-3.41 (m, 2H), 3.44-3.52 (m, 2H), 6.99 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.07 (td, *J* = 7.5, 1.2 Hz, 1H), 7.19 (dq, *J* = 7.7, 1.4 Hz, 1H), 7.26-7.34 (m, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 28.0, 32.0, 45.6, 117.5, 122.8, 123.2, 127.9, 129.3, 141.1.

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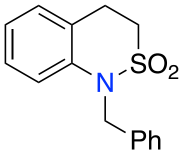
[178] H. Zilaout, A. van den Hoogenband, L. Jelle, T. Jos, W. Jan, *Tetrahedron Lett.* **2011**, *52*, 5934.

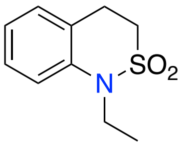
1-Benzyl-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 182b



Synthesized according to GP3. 99% yield. Colorless oil. Data in agreement with the ones reported.[175]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.26 (t, J = 7.0 Hz, 2H), 3.45 (t, J = 7.0 Hz, 2H), 5.02 (s, 2H), 6.90 (d, J = 8.6 Hz, 2H), 7.02 (t, J = 7.4 Hz, 1H), 7.12-7.17 (m, 2H), 7.27-7.37 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 28.2, 45.9, 51.2, 119.1, 123.1, 123.5, 127.2, 127.7, 127.9, 128.8, 129.6, 136.7, 140.3.

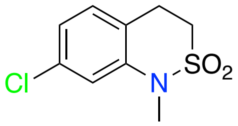
1-Ethyl-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 182c



Synthesized according to GP3. 96% yield. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3H), 3.28 (t, J = 7.0 Hz, 2H), 3.43 (t, J = 7.0 Hz, 2H), 3.91 (q, J = 7.1 Hz, 2H), 6.98-7.07 (m, 2H), 7.16 (d, J = 7.7 Hz, 1H), 7.22-7.29 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 14.4, 28.2, 41.9, 46.3, 118.4, 123.3, 123.4, 127.9, 129.8, 139.8. **IR** ν(cm^{-1}): 2975, 2935, 2914, 2875, 1490, 1325, 1292, 1162, 1149, 1121, 1048, 913, 757. **HRMS** (m/z): calcd. for $C_{10}H_{13}NNaO_2S$, 324.0559; found: 234.0568.

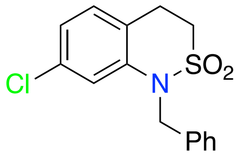
7-Chloro-1-methyl-3,4-dihydro-1*H*-benzo[c][1,2]thiazine 2,2-dioxide 182d



Synthesized according to GP3. 97% yield. White solid. Data in agreement with the ones reported.[173]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32 (s, 3H), 3.32-3.41 (m, 2H), 3.42-3.48 (m, 2H), 6.96 (d, J = 8.2 Hz, 1H), 7.04 (dd, J = 8.2, 2.0 Hz, 1H), 7.11 (dt, J = 8.1, 0.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 27.5, 31.4, 45.5, 117.1, 120.9, 123.0, 130.4, 133.7, 142.1.

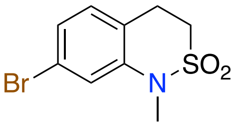
1-Benzyl-7-chloro-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 182e



Synthesized according to GP3. 89% yield. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.28 (t, J = 7.0 Hz, 2H), 3.44 (t, J = 7.0 Hz, 2H), 5.02 (s, 2H), 6.92 (d, J = 2.0 Hz, 1H), 7.01-7.03 (m, 1H), 7.08-7.10 (m, 1H), 7.31-7.38 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 27.8, 45.7, 50.9, 118.9, 121.4, 123.5, 127.1, 127.9, 128.9, 130.6, 133.4, 135.9, 141.3. **IR** ν(cm^{-1}): 3064, 3030, 2933, 2914, 1597, 1569, 1488, 1453, 1329, 1293, 1270, 1232, 1203, 1157, 1127, 1061, 1026, 888. **HRMS** (m/z): calcd. for $C_{15}H_{14}ClNNaO_2S$, 330.0326; found: 330.0321.

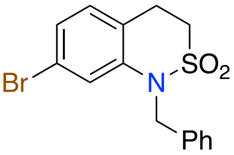
7-Bromo-1-methyl-3,4-dihydro-1*H*-benzo[c][1,2]thiazine 2,2-dioxide 182f



Synthesized according to GP3. 98% yield. White solid. Data in agreement with the ones reported.[175]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (s, 3H), 3.34-3.39 (m, 2H), 3.40-3.46 (m, 2H), 7.05 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.10 (d, *J* = 1.9 Hz, 1H), 7.19 (dd, *J* = 8.1, 1.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 27.6, 31.5, 45.5, 120.0, 121.4, 121.4, 125.9, 130.7, 142.3.

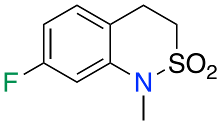
1-Benzyl-7-bromo-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 182g



Synthesized according to GP3. 92% yield. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.25-3.29 (m, 2H), 3.40-3.43 (m, 2H), 5.01 (s, 2H), 7.01 (s, 1H), 7.08 (d, *J* = 1.9 Hz, 1H), 7.16 (d, *J* = 8.2Hz, 1H), 7.35-7.38 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 27.8, 45.7, 51.0, 121.0, 121.9, 126.5, 127.2, 127.9, 128.9, 130.9, 135.8, 141.4. **IR** ν(cm^{-1}): 3063, 3031, 2933, 1591, 1566, 1485, 1454, 1407, 1334, 1293, 1157, 1129, 1028. **HRMS** (m/z): calcd. for $C_{15}H_{14}BrNNaO_2S$, 373.9821; found 373.9823.

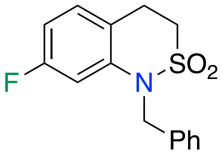
7-Fluoro-1-methyl-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 182h



Synthesized according to GP3. 83% yield. Colorless oil. Data in agreement with the ones reported.[175]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (s, 3H), 3.23 (t, *J* = 7.0 Hz, 2H), 5.01 (s, 2H), 6.76 (s 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.35-7.36 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 27.3, 31.2, 45.6, 104.3 (d, *J* = 2.3 Hz), 109.6 (d, *J* = 21.4 Hz), 118.1 (d, *J* = 3.4 Hz), 130.7 (d, *J* = 9.5 Hz), 142.4 (d, *J* = 9.9 Hz), 162.2 (d, *J* = 245.3 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -113.3.

1-Benzyl-7-fluoro-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 182i

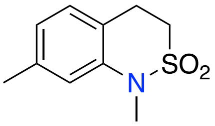


Synthesized according to GP3. 89% yield. Colorless oil. Data in agreement with the ones reported.[175]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.29 (t, *J* = 6.7 Hz, 2H), 3.43 (t, *J* = 7.2 Hz, 2H), 4.99 (s, 2H), 6.60 (dd, *J* = 10.7, 2.5 Hz, 1H), 6.72 (td, *J* = 8.2, 2.5 Hz, 1H), 7.09 (dd, *J* = 8.6, 6.2 Hz, 1H), 7.27-7.37 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 27.7, 45.9, 50.6, 105.9 (d, *J* = 26.2 Hz), 110.4 (d, *J* = 21.6 Hz), 118.5

(d, J = 3.4 Hz), 127.0, 127.9, 129.0, 130.9 (d, J = 9.4 Hz), 136.1, 141.6 (d, J = 10.1 Hz), 162.1 (d, J = 245.5 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -113.3.

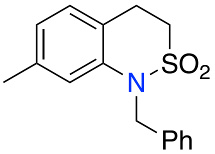
1,7-Dimethyl-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 182j



Synthesized according to GP3. 96% yield. White solid. Data in agreement with the ones reported.[175]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3H), 3.28-3.32 (m, 5H), 3.40 (t, J = 7.0 Hz, 2H), 6.77 (s, 1H), 6.86 (d, J = 6.9 Hz, 1H), 7.04 (d, J = 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.4, 27.7, 32.3, 45.7, 118.3, 119.9, 124.1, 129.3, 137.9, 141.1.

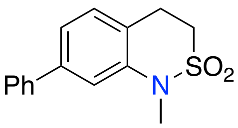
1-Benzyl-7-methyl-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 182k



Synthesized according to GP3. 86% yield. Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (s, 3H), 3.23 (t, J = 7.0 Hz, 3H), 3.42 (t, J = 7.0 Hz, 2H), 5.01 (s, 2H), 6.76 (s 1H), 6.87 (d, J = 7.8 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 7.35-7.36 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.2, 27.7, 45.9, 51.4, 119.8, 120.2, 124.5, 127.5, 127.6, 128.7, 129.3, 136.6, 137.7, 140.1. **IR** ν(cm^{-1}): 3063, 3030, 2921, 2856, 1615, 1573, 1506, 1454, 1365, 1333, 1317, 1293, 1156, 1128, 10666, 1028. **HRMS** (m/z): calcd. for $C_{16}H_{17}NNaO_2S$, 310.0872; found 310.0870.

1-Methyl-7-phenyl-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 182l

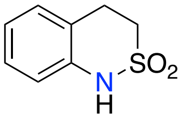


Synthesized according to GP3. 51% yield. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37-3.44 (m, 5H), 3.48-3.57 (m, 2H), 7.17 (d, J = 1.6 Hz, 1H), 7.25-7.29 (m, 2H), 7.38-7.42 (m, 2H), 7.56-7.59 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 27.7, 32.2, 45.5, 116.4, 121.7, 122.1, 127.1, 128.6, 129.8, 129.9. **IR** ν(cm^{-1}): 3063, 3031, 2933, 1591, 1566, 1485, 1454, 1407, 1334, 1293, 1157, 1129, 1028. **HRMS** (m/z): calcd. for $C_{15}H_{15}NNaO_2S$, 296.0716; found: 296.0708.

m.p.: 112-113 °C.

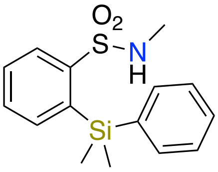
3,4-Dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 183b



Synthesized according to GP4. 91% yield. White solid. Data in agreement with the ones reported.[175]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.24-3.36 (m, 2H), 3.48 (t, *J* = 6.7 Hz, 2H), 6.62 (brs, 1H, NH), 6.75 (d, *J* = 8.6 Hz, 1H), 7.04 (td, *J* = 7.5, 1.2 Hz, 1H), 7.15-7.23 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 28.4, 45.9, 118.8, 120.9, 123.8, 128.1, 129.7, 137.1.

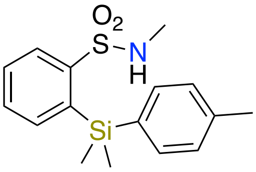
2-(Dimethyl(phenyl)silyl)-*N*-methylbenzenesulfonamide 184a



Synthesized according to GP1. 50% yield. White solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.69 (s, 6H), 2.15 (d, *J* = 5.4 Hz, 3H), 2.52 (q, *J* = 5.4 Hz, 1H, NH), 7.36-7.42 (m, 3H), 7.49-7.64 (m, 4H), 7.91 (dd, *J* = 7.1, 1.7 Hz, 1H), 7.96 (dd, *J* = 7.6, 1.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = -0.34, 29.2, 128.1, 129.6, 129.8, 130.2, 131.6, 134.6, 137.4, 137.7, 138.5, 143.7. **IR** ν(cm^{-1}): 3347, 3089, 3069, 3045, 3025, 2996, 2951, 2898, 1426, 1308, 1154, 1106, 822, 702. **HRMS** (m/z): calcd. for $C_{15}H_{18}NO_2SSi$, 304.0833; found: 304.0837. **m.p.:** 117-118 ºC.

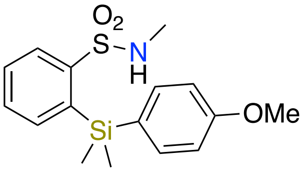
2-(Dimethyl(*p*-tolyl)silyl)-*N*-methylbenzenesulfonamide 184b



Synthesized according to GP1. 50% yield. Yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.70 (s, 6H), 2.17 (d, *J* = 5.4 Hz, 3H), 2.39 (s, 3H), 2.64 (q, *J* = 5.6 Hz, 1H, NH), 7.24 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.55 (td, *J* = 7.6, 1.5 Hz, 1H), 7.61 (td, *J* = 7.4, 1.4 Hz, 1H), 7.93 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.99 (7.8, 1.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = -0.28, 21.6, 29.2, 128.9, 129.5, 130.2, 131.6, 134.7, 137.6, 137.7, 139.9, 143.6. **IR** ν(cm^{-1}): 3320, 3065, 3011, 2956, 2921, 1435, 1420, 1392, 1324, 1251, 1162, 1106, 798, 758, 585. **HRMS** (m/z): calcd. for $C_{16}H_{20}NO_2SSi$, 318.0989; found: 318.0994.

2-((4-Methoxyphenyl)dimethylsilyl)-*N*-methylbenzenesulfonamide 184c

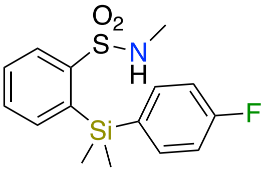


Synthesized according to GP1. 60% yield. Yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.67 (s, 6H), 2.17 (d, *J* = 5.4 Hz, 3H), 2.68 (q, *J* = 5.4 Hz, 1H, NH), 3.82 (s, 3H), 6.94 (d, *J*

= 8.6 Hz, 2H), 7.50-7.54 (m, 3H), 7.58 (td, *J* = 7.4, 1.4 Hz, 1H), 7.90 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.97 (dd, *J* = 7.8, 1.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = -0.17, 29.3, 55.3, 113.9, 128.9, 129.5, 130.2, 131.6, 136.2, 137.7, 137.8, 143.6, 160.9. **IR** ν(cm^{-1}): 3316, 3013, 2952, 2902, 2837, 1592, 1502, 1325, 1277, 1247, 1162, 1109, 1028, 817, 761. **HRMS** (m/z): calcd. for $C_{16}H_{21}NNaO_3SSi$, 358.0904; found: 358.0908.

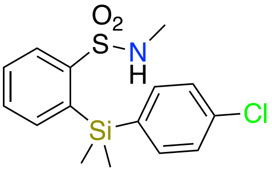
2-((4-Fluorophenyl)dimethylsilyl)-*N*-methylbenzenesulfonamide 184d



Synthesized according to GP1. 40% yield. Yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.68 (s, 6H), 2.25 (d, *J* = 5.3 Hz, 3H), 2.78 (q, *J* = 5.6 Hz, 1H, NH), 7.0-7.17 (m, 2H), 7.46-7.64 (m, 4H), 7.83-7.88 (m, 1H), 7.92-7.99 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = -0.11, 29.2, 115.3 (*J* = 19.6 Hz), 129.9 (d, *J* = 17.1 Hz, 131.7, 134.2 (d, *J* = 4.0 Hz), 136.6 (d, *J* = 7.3 Hz), 137.1, 137.8, 143.8, 163.9 (d, *J* = 250.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -110.5. **IR** ν(cm^{-1}): 3301, 3060, 2952, 2899, 1728, 1697, 1587, 1498, 1386, 1324, 1229, 1161, 1104, 821, 587. **HRMS** (m/z): calcd. for $C_{15}H_{18}FNNaO_2SSi$, 346.0704; found: 346.0694.

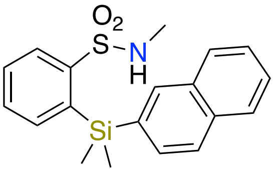
2-((4-Chlorophenyl)dimethylsilyl)-*N*-methylbenzenesulfonamide 184e



Synthesized according to GP1. 45% yield. Yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.68 (s, 6H), 2.28 (d, *J* = 5.3 Hz, 3H), 3.08 (q, *J* = 5.6 Hz, 1H, NH), 7.35-7.37 (m, 2H), 7.49-7.51 (m, 2H), 7.52-7.59 (m, 2H), 7.81-7.84 (m, 1H), 7.91-7.98 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = -0.25, 29.1, 128.2, 129.7, 129.9, 131.7, 135.9, 136.8, 137.2, 137.8, 143.7. **IR** ν(cm^{-1}): 3334, 3059, 3018, 2953, 2900, 1320, 1160, 1108, 1082, 807, 737, 587. **HRMS** (m/z): calcd. for $C_{15}H_{17}ClNO_2SSi$, 338.0439; found: 338.0443.

2-(Dimethyl(naphthalen-2-yl)silyl)-*N*-methylbenzenesulfonamide 184f

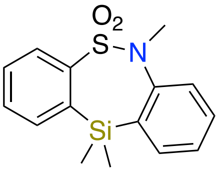


Synthesized according to GP1. 50% yield. Yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (s, 6H), 2.11 (d, *J* = 5.4 Hz, 2H), 2.92 (q, *J* = 5.4 Hz, 1H, NH), 7.50-7.54 (m, 2H), 7.58 (ddd, *J* = 17.1, 7.5, 1.5 Hz, 2H), 7.61-7.64 (m, 1H), 7.84-7.88 (m, 3H), 7.94 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.99 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.15 (s, 1H). **^{13}C NMR**

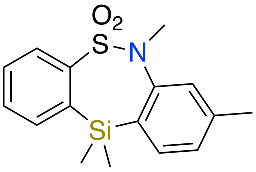
(126 MHz, $CDCl_3$): δ = -0.20, 28.9, 126.5, 126.9, 127.3, 127.8, 128.2, 129.7, 129.9, 130.4, 131.6, 132.8, 133.7, 135.2, 135.9, 137.3, 137.9, 143.7. **IR** ν(cm^{-1}): 3319, 3052, 2952, 2900, 1323, 1250, 1162, 1081, 812, 758. **HRMS** (m/z): calcd. for $C_{19}H_{21}NNaO_2SSi$, 378.0954; found: 378.0957.

6,11,11-Trimethyl-6,11-dihydrodibenzo[*c*,*f*][1,2,5]thiazasilepine 5,5-dioxide 185a



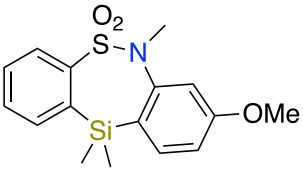
Synthesized according to GP3. 70% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.58 (s, 6H), 3.12 (s, 3H), 7.31 (dtd, *J* = 7.3, 3.5, 1.2 Hz, 2H), 7.39-7.48 (m, 1H), 7.55 (td, *J* = 7.5, 1.6 Hz, 1H), 7.59 (td, *J* = 7.4, 1.7 Hz, 2H), 7.83 (dd, *J* = 7.0, 1.8 Hz, 1H), 8.10 (dd, *J* = 7.3, 1.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 0.7, 38.6, 126.3, 126.4, 128.0, 129.6, 130.9, 131.8, 134.7, 135.2, 135.9, 136.1, 145.3, 147.2. **IR** ν(cm^{-1}): 2959, 2923, 2851, 1476, 1419, 1330, 1260, 1154, 1109, 1051, 899, 813, 751, 559. **HRMS** (m/z): calcd. for $C_{15}H_{18}NO_2SSi$, 304.0822; found: 304.0818. **m.p.**: 136-137 ºC.

6,8,11,11-Tetramethyl-6,11-dihydrodibenzo[*c*,*f*][1,2,5]thiazasilepine 5,5-dioxide 185b



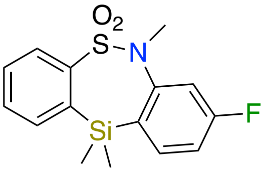
Synthesized according to GP3. 74% yield. Yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.56 (s, 6H), 2.38 (s, 3H), 3.11 (s, 3H), 7.12-7.16 (m, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.54 (td, *J* = 7.5, 1.6 Hz, 1H), 7.59 (td, *J* = 7.4, 1.6 Hz, 1H), 7.82 (dd, *J* = 6.9, 1.8 Hz, 1H), 8.10 (dd, *J* = 7.4, 1.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 0.72, 21.4, 38.6, 127.1, 127.5, 128.1, 129.6, 131.0, 131.7, 135.2, 135.9, 136.3, 141.2, 145.3, 147.2. **IR** ν(cm^{-1}): 3054, 3015, 2957, 2923, 2855, 1337, 1259, 1160, 1125, 1110, 1049, 950, 810, 758, 572. **HRMS** (m/z): calcd. for $C_{16}H_{20}NO_2SSi$, 318.0979; found: 318.0980.

8-Methoxy-6,11,11-trimethyl-6,11-dihydrodibenzo[*c*,*f*][1,2,5]thiazasilepine 5,5-dioxide 185c



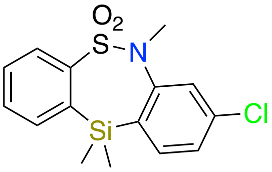
Synthesized according to GP3. 40% yield. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.55 (s, 6H), 3.11 (s, 3H), 3.84 (s, 3H), 6.82-6.91 (m, 2H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.54 (td, *J* = 7.5, 1.6 Hz, 1H), 7.59 (td, *J* = 7.4, 1.6 Hz, 1H), 7.77-7.85 (m, 1H), 8.06-8.12 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 0.84, 38.7, 55.5, 112.1, 112.9, 125.4, 128.1, 129.6, 131.8, 135.9, 136.3, 136.4, 145.2, 148.6, 161.8. **IR** ν(cm^{-1}): 3059, 2960, 2938, 1594, 1458, 1332, 1224, 1157, 1108, 1043, 960, 814, 686, 574. **HRMS** (m/z): calcd. for $C_{16}H_{20}NO_3SSi$, 334.0924; found: 3340928.

8-Fluoro-6,11,11-trimethyl-6,11-dihydrodibenzo[*c,f*][1,2,5]thiazasilepine 5,5-dioxide 185d



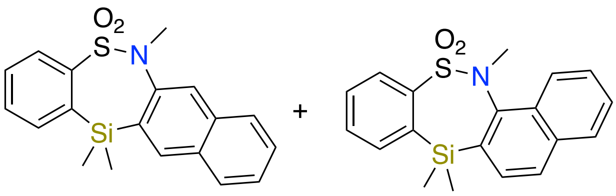
Synthesized according to GP3. 50% yield. Yellow oil. ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 0.57 (s, 6H), 3.12 (s, 3H), 6.99-7.06 (m, 2H), 7.53-7.63 (m, 3H), 7.80-7.83 (m, 1H), 8.03-8.12 (m, 1H). ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 0.78, 38.4, 113.3 (d, *J* = 21.7 Hz), 113.8 (d, *J* = 19.9 Hz), 127.9, 129.8, 129.9 (d, *J* = 3.6 Hz), 131.9, 135.8, 135.9, 136.7 (d, *J* = 8.9 Hz), 145.1, 148.9 (d, *J* = 9.4 Hz), 164.2 (d, *J* = 250.4 Hz). ^{19}**F NMR** (376 MHz, CDCl$_3$): δ = -110.0. **IR** ν(cm^{-1}): 2956, 2923, 2852, 1591, 1482, 1392, 1342, 1207, 1170, 1112, 1045, 971, 813, 746, 690, 590. **HRMS** (m/z): calcd. for $C_{15}H_{16}FNNaO_2SSi$, 344.0541; found: 344.0564.

8-Chloro-6,11,11-trimethyl-6,11-dihydrodibenzo[*c,f*][1,2,5]thiazasilepine 5,5-dioxide 184e



Synthesized according to GP3. 50% yield. Yellow oil. ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 0.57 (s, 6H), 3.12 (s, 3H), 7.24-7.31 (m, 2H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.56 (td, *J* = 7.6, 1.5 Hz, 1H), 7.61 (td, *J* = 7.4, 1.4 Hz, 1H), 7.82 (dd, *J* = 7.1, 1.5 Hz, 1H), 8.09 (dd, *J* = 7.8, 1.2 Hz, 1H). ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 0.67, 38.4, 126.1, 126.6, 128.0, 129.8, 132.0, 132.9, 135.7, 135.9, 136.2, 136.4, 145.0, 148.3. **IR** ν(cm^{-1}): 3057, 2956, 2925, 2853, 1576, 1469, 1341, 1162, 1111, 927, 811, 759, 591. **HRMS** (m/z): calcd. for $C_{15}H_{17}ClNO_2SSi$, 338.0432; found: 338.0433.

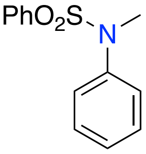
6,13,13-Trimethyl-6,13-dihydrobenzo[*f*]naphtho[2,3-*c*][1,2,5]thiazasilepine 5,5-dioxide and 7,7,13-Trimethyl-7,13-dihydrobenzo[*f*]naphtho[1,2-*c*][1,2,5] thiazasilepine 12,12-dioxide 185f and 185f′



Synthesized according to GP3. 80% Yield (1:1 regioisomers). Yellow oil. ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 0.61 (s, 6H), 0.67 (s, 6H), 3.11 (s, 6H), 7.55-7.69 (m, 10H), 7.88-7.90 (m, 6H), 8.23 (d, *J* = 7.5, 1.6 Hz, 2H), 8.29 (d, *J* =

8.1 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 0.31, 0.80, 39.1, 123.8, 127.3, 127.6, 127.9, 128.4, 129.1, 129.9, 130.1, 131.1, 131.8, 133.7, 135.6, 135.9, 136.2, 143.8, 144.7. **IR** ν(cm^{-1}): 3064, 3048, 2961, 2926, 2904, 1328, 1247, 1164, 1109, 1022, 811, 761, 574. **HRMS** (m/z): calcd. for $C_{19}H_{19}NNaO_2SSi$, 376.0798; found: 376.0801.

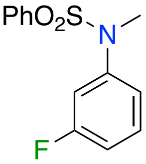
N-Methyl-*N*-phenylbenzenesulfonamide 186a



Synthesized according to GP5. 70% yield. White solid. Data in agreement with the ones reported.[179]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.20 (s, 3H), 7.07-7.13 (m, 2H), 7.26-7.36 (m, 3H), 7.44-7.51 (m, 2H), 7.52-7.65 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 38.3, 126.8, 127.5, 127.9, 128.8, 129.0, 132,9, 136.6, 141.6.

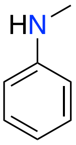
N-(3-Fluorophenyl)-*N*-methylbenzenesulfonamide 186d



Synthesized according to GP5. 82% yield. Yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.19 (s, 3H), 6.87 (dt, *J* = 10.1, 2.3 Hz, 1H), 6.93 (ddd, *J* = 8.1, 2.1, 0.9 Hz, 1H), 6.99 (tdd, *J* = 8.3, 2.5, 1.0 Hz, 1H), 7.28 (td, *J* = 8.2, 6.4 Hz, 1H), 7.49 (td, *J* = 7.8, 6.9, 1.2 Hz, 2H), 7.54-7.65 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 38.1, 113.9 (d, *J* = 23.2 Hz), 114.4 (d, *J* = 21.0 Hz), 122.1 (d, *J* = 3.1 Hz), 127.9, 128.9, 129.9 (d, *J* = 9.1 Hz), 133.1, 136.4, 143.2 (d, *J* = 9.6 Hz), 162.6 (d, *J* = 247.3 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -111.1. **IR** ν(cm^{-1}): 3071, 2979, 2945, 2915, 2884, 1608, 1592, 1480, 1446, 1350, 1168, 1089, 955, 724, 689, 588. **HRMS** (m/z): calcd. for $C_{13}H_{12}FNNaO_2S$, 288.0465; found: 288.0459.

N-Methylaniline 187a



Synthesized according to GP6. 91% yield. Yellow oil. Data in agreement with the ones reported.[180]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.90 (s, 3H), 3.71 (brs, 1H, NH), 6.70 (dq, *J* = 7.7, 1.2 Hz, 2H), 6.81 (tdt, *J* = 7.3, 2.1, 1.1 Hz, 1H), 7.25-7.33 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.8, 112.5, 117.3, 129.3, 149.4.

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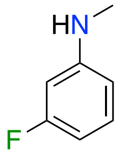
[179] W. Wei, L. Chunli, Y. Daoshan, W. Jiangwei, Y, Jinmao, W. Hau, *Adv. Synth Catal.* **2015**, *357*, 987.

[180] A. A. Trabanco, J. A. Vega, M. Fernandez, M. Alejandro, *J. Org. Chem.* **2007**, *72*, 8146.

3-Fluoro-*N*-methylaniline 187d

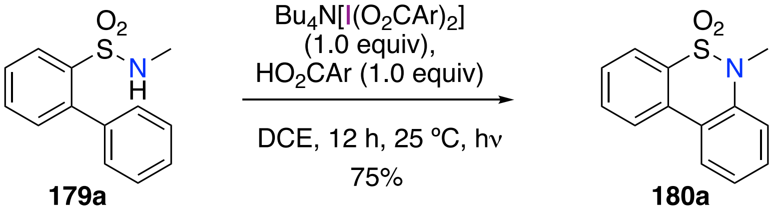


Synthesized according to GP6. 85% yield. Yellow oil. Data in agreement with the ones reported.[178]

^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.82 (s, 3H), 3.88 (brs, 1H, NH), 6.29 (dt, *J* = 11.7, 2.3 Hz, 1H), 6.38 (dddt, *J* = 11.3, 6.9, 2.3, 0.9 Hz, 2H), 7.10 (td, *J* = 8.1, 6.7 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 30.7, 99.0 (d, *J* = 25.3 Hz), 103.7 (d, *J* = 21.6 Hz), 108.5, 130.3 (d, *J* = 10.3 Hz), 151.3 (d, *J* = 10.8 Hz), 164.3 (d, *J* = 242.5 Hz). **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -113.2.

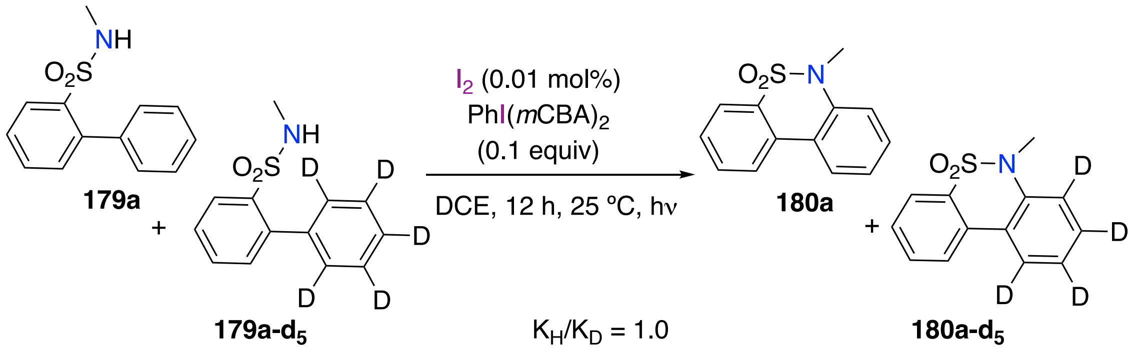
3.4.4 Control experiments

Control experiment with preformed Bu$_4$[I(*m*CBA)$_2$] in stoichiometric amount



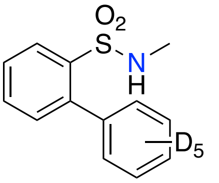
A dried Schlenk tube equipped with a stirrer bar was charged with **25a** (111 mg, 0.45 mmol, 1.0 equiv), Bu$_4$[I(*m*CBA)$_2$] (306 mg, 0.45 mmol, 1.0 equiv) and *m*CBA (70 mg, 0.45 mmol, 1.0 equiv), evacuated and backfilled with argon. Afterwards, 2 mL of absolute dichloroethane were added. The solution was stirred at 25 °C for 12 h under visible light. DCM was added and the mixture was washed with a saturated aqueous solution of Na$_2$S$_2$O$_3$ and NaHCO$_3$. The aqueous phase was extracted with DCM (2x). The combined organic phases were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (SiO$_2$, *n*-hexane/EtOAc) to yield the pure product **26a** in 75% yield.(83 mg).

Control experiment for the determination of the Kinetic Isotope Effect



The reaction was carried out according to GP3, with 5.0 equivalents of substrate **25a** and 5.0 equivalents of substrate **25a-d$_5$** in presence of 5 mol% of molecular iodine and 1.0 equivalent of the hypervalent iodine(III) reagent. The reaction was complete with a total of 10% of conversion. The KIE was determined by integrating the ^{1}H NMR spectrum of the crude reaction mixture and revealed the isotope effect equal to 1.0 ($K_H/K_D = 1.0$).

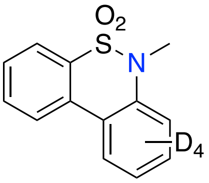
N-Methyl-2',3',4',5',6'-pentadeutero-[1,1'-biphenyl]2-sulfonamide 179a-d$_5$



Synthesized according to GP1. 89%. White solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.36 (d, *J* = 5.4 Hz, 3H), 3.32 (q, *J* = 5.3 Hz, 1H), 7.37 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.55 (td, *J* = 7.7, 1.5 Hz, 1H), 7.63 (td, *J* = 7.5, 1.5 Hz, 1H), 8.19 (dd, *J* = 7.9, 1.3 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ= 29.0, 127.8 (t, *J* = 24.5 Hz), 128.0, 128.1 (t, *J* = 24.4 Hz), 128.6 (t, *J* = 24.4 Hz), 129.8, 132.1, 132.3, 137.0, 138.7, 140.1. **IR** ν(cm^{-1}): 3340, 1467, 1380, 1307, 1157, 1121, 1084, 848, 761, 678, 575, 555, 501, 459. **HRMS** (m/z): calcd. for $C_{13}H_8D_5NNaO_2S$, 275.0873; found: 275.0869. **m.p.**: 122-123 °C.

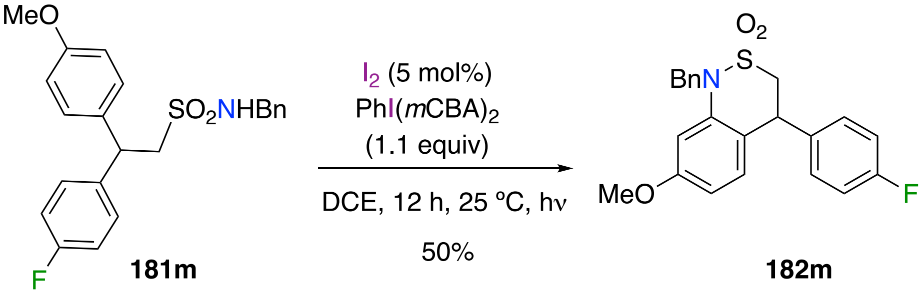
6-Methyl-7,8,9,10,tetradeutero-6*H*-dibenzo[c,e][1,2]thiazine 5,5-dioxide 180a-d$_5$



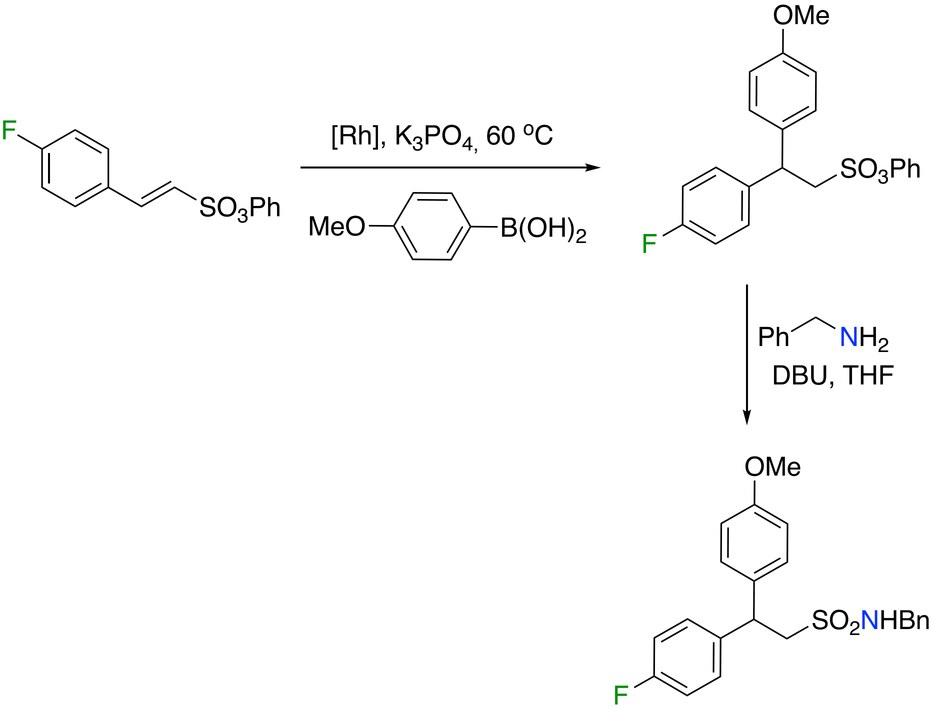
Synthesized according to GP3. White solid.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.48 (s, 3H), 7.60 (td, *J* = 7.7, 1.1 Hz, 1H), 7.74 (ddd, *J* = 8.1, 7.4, 1.4 Hz, 1H), 8.00 (ddd, *J* = 8.1, 1.2, 0.6 Hz, 1H), 8.04 (ddd, *J* = 7.8, 1.4, 0.6 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 32.7, 119.0 (t, *J* = 24.6 Hz), 122.5, 123.9, 124.1 (t, *J* = 24.8 Hz), 125.1 (t, *J* = 24.3 Hz), 125.4, 128.2, 129.9 (t, *J* = 24.8 Hz), 132.4, 134.2, 139.4. **IR** ν(cm^{-1}): 1576, 1482, 1396, 1361, 1319, 1228, 1164, 1133, 1073, 1056, 1006, 823, 784, 768, 755, 717, 660, 592, 562, 537, 493, 473, 440. **HRMS** (m/z): calcd. for $C_{13}H_7D_4NNaO_2S$, 272.0654; found: 272.0654. **m.p.**: 112-113 °C.

Internal electronic competition experiment



For the synthesis of the starting material, the following sequence was carried out.



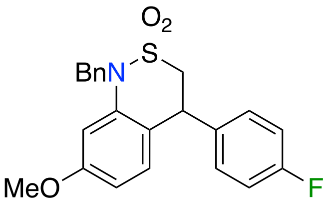
Step 1: To a Schlenk tube, evacuated and backfilled with argon, [RhCl(CO)$_2$]$_2$ (11 mg, 0.03 mmol, 3 mol%) and 1,5-cyclooctadiene (6 mg, 0.06 mmol, 6 mol%) were added. CH$_2$Cl$_2$ (0.14 mL) was added and the reaction mixture was stirred at 25 °C for 2 h. After the solvent was removed under reduced pressure, the sulfonate (270 mg, 0.97 mmol, 1 equiv), 4-methoxyphenyl boronic acid (220 mg, 1.5 mmol, 1.5 equiv) and K$_3$PO$_4$ (200 mg, 0.97 mmol, 1 equiv) were added to the Schlenk tube. 1,4-Dioxane (3.5 mL) and H$_2$O (0.5 mL) were added successively and the reaction mixture was stirred at 60 °C for 12 h. The solvent was removed under reduced pressure and the residue is purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 4/1, v/v) to afford the compound as colourless oil (280 mg, 0.72 mmol, 85%).

^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.81 (s, 3H), 3.99 (d, *J* = 7.2 Hz, 1H), 4.74 (t, *J* = 7.1 Hz, 1H), 6.79-6.81 (m, 1H), 6.88-6.91 (m, 2H), 7.02-7.06 (m, 3H), 7.19-7.22 (m, 2H), 7.27-7.31 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 45.0, 55.3, 56.3, 114.4, 115.8 (d, *J* = 21.6 Hz), 116.0, 121.8, 127.1, 128.6, 129.2 (d, *J* = 8.0 Hz), 129.9, 133.2, 137.3 (d, *J* = 3.4 Hz), 148.9, 158.8, 161.8 (d, *J* = 254.0 Hz). **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -115.35. **IR** ν(cm^{-1}): 3005, 2960, 2838, 1605, 1508, 1487, 1548, 1440, 1354, 1249, 1228, 1193, 1180, 1141, 1030. **HRMS** (m/z): calcd. for $C_{21}H_{20}NaFO_4S$, 410.0964; found: 410.0950.

Step 2: To a Schlenk tube, evacuated and backfilled with argon, the sulfonate (250 mg, 0.65 mmol, 1 equiv), benzylamine (210 mg, 1.95 mmol, 3 equiv) and DBU (120 mg, 0.78 mmol, 1.2 equiv) were added. THF (15 mL) was added and the reaction mixture was heated to reflux for 12 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 4/1, v/v) to afford **181m** as colorless oil (160 mg, 0.40 mmol, 60%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.72 (dd, *J* = 7.3, 5.0 Hz, 2H), 3.77 (s, 3H), 3.89 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.99 (dd, *J* = 13.6, 5.6 Hz, 1H), 4.57 (t, *J* = 7.3 Hz, 1H), 6.85-6.87 (m, 2H), 6.99-7.03 (m, 2H), 7.11-7.13 (m, 2H), 7.16-7.18 (m, 2H), 7.19-7.23 (m, 2H), 7.30-7.32 (m, 3H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 45.2, 47.2, 55.3, 57.6, 114.5, 114.8, 115.7, 115.9, 116.0, 128.0, 128.1, 128.7 (d, *J* = 12.0 Hz), 129.0 (d, *J* = 8.0 Hz), 133.6, 136.2, 138.0 (d, *J* = 3.4 Hz), 158.8, 161.7 (d, *J* = 246.3 Hz). **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -115.43. **IR** ν(cm^{-1}): 3036, 2935, 2837, 1586, 1508, 1441, 1369, 1249, 1227, 1180, 1160, 1141, 1070, 1029. **HRMS** (m/z): calcd. for $C_{22}H_{22}FNNaO_3S$, 422.1197; found: 422.1189.

1-Benzyl-4-(4-fluorophenyl)-7-methoxy-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 182m



Synthesized according to GP3. 50% yield. White solid. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 2.99 (t, *J* = 13.4 Hz, 1H), 3.47-3.52 (m, 1H), 3.72 (s, 3H), 4.62 (dd, *J* = 12.6, 6.5 Hz, 1H), 5.08 (s, 2H), 6.55 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 6.67 (dd, *J* = 8.8, 1.0 Hz, 1H), 6.91-6.95 (m, 2H), 6.97-7.02 (m, 2H), 7.34-7.39 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 43.9, 52.9, 53.0, 55.3, 106.4, 115.9 (d, *J* = 21.5 Hz), 120.7, 128.2, 128.9, 130.1 (d, *J* = 8.4 Hz), 131.3, 135.7, 137.5 (d, *J* = 3.4 Hz), 140.8, 159.4, 162.1 (d, *J* = 247.0 Hz). **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -115.47. **IR** ν(cm^{-1}): 2966, 2903, 2840, 1611, 1510, 1492, 1457, 1439, 1342, 1253, 1228, 1162, 1140, 1047, 1039. **HRMS** (m/z): calcd. for $C_{22}H_{21}FNO_2S$, 398.1221; found: 398.1237.**m.p.**: 146-148 °C.

3.4.5 X-Ray analytical data

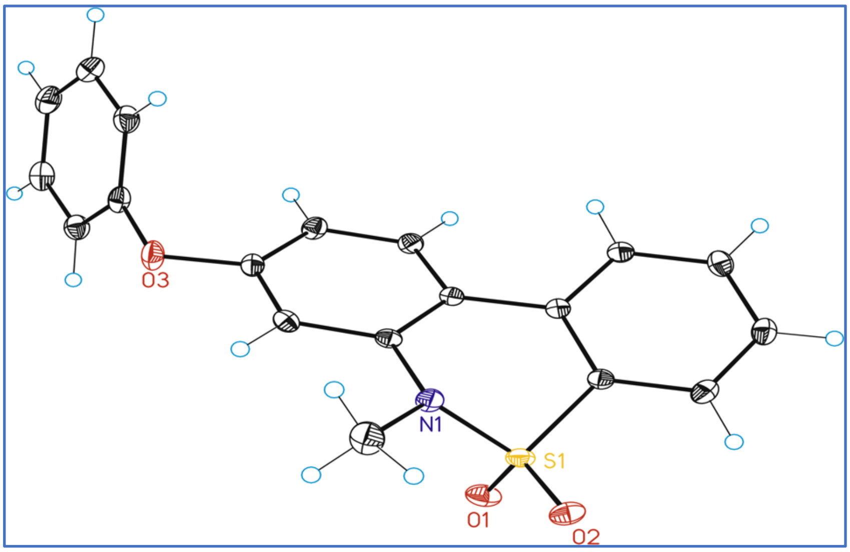


Table 3.2: Crystal data and structure refinement for **180f**.

Identification code	CCDC1449544	
Empirical formula	C19 H15 N O3 S	
Formula weight	337.38	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.4906(16)Å	α= 90°.
	b = 8.9225(18)Å	β = 90°.
	c = 23.355(5)Å	γ = 90°.
Volume	1560.9(6) $Å^3$	
Z	4	
Density (calculated)	1.436 Mg/m^3	
Absorption coefficient	0.225 mm^{-1}	
F(000)	704	
Crystal size	0.40 x 0.30 x 0.05 mm^3	
Theta range for data collection	2.444 to 30.091°.	
Index ranges	-10<=h<=10,-12<=k<=11,-32<=l<=25	
Reflections collected	10661	
Independent reflections	4376[R(int) = 0.0316]	

Completeness to theta =30.091°	97.899994%
Absorption correction	Multi-scan
Max. and min. transmission	0.989 and 0.761
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4376/ 0/ 218
Goodness-of-fit on F^2	1.075
Final R indices [I>2sigma(I)]	R1 = 0.0267, wR2 = 0.0725
R indices (all data)	R1 = 0.0277, wR2 = 0.0728
Flack parameter	x =0.02(2)
Largest diff. peak and hole	0.314 and -0.354 e.Å^{-3}

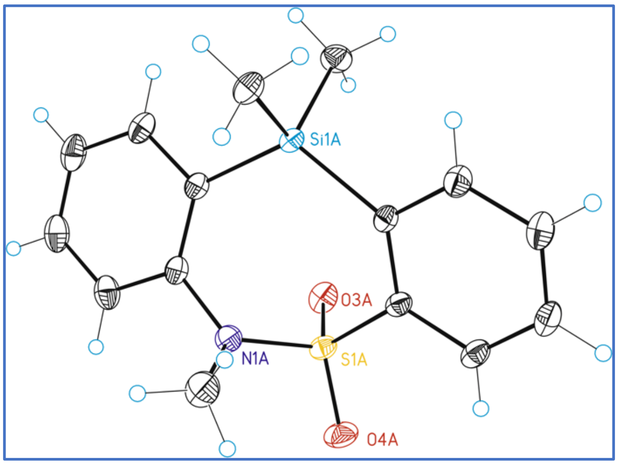


Table 3.3: Crystal data and structure refinement for **185a**.

Identification code	CCDC1449543	
Empirical formula	C15 H17 N O2 S Si	
Formula weight	303.44	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 26.3120(12)Å	α= 90°.
	b = 8.4836(3)Å	β = 90°.
	c = 13.1455(7)Å	γ = 90°.
Volume	2934.4(2) Å^3	
Z	8	
Density (calculated)	1.374 Mg/m^3	
Absorption coefficient	0.303 mm^{-1}	
F(000)	1280	
Crystal size	0.3 x 0.3 x 0.2 mm^3	
Theta range for data collection	2.190 to 36.965°.	
Index ranges	-44<=h<=44,-14<=k<=13,-21<=l<=21	
Reflections collected	33171	
Independent reflections	13852[R(int) = 0.0997]	
Completeness to theta =36.965°	96.4%	
Absorption correction	Multi-scan	

Max. and min. transmission 0.928 and 0.714

Refinement method Full-matrix least-squares on F^2

Data / restraints / parameters 13852/ 1/ 367

Goodness-of-fit on F^2 1.031

Final R indices [I>2sigma(I)] R1 = 0.0629, wR2 = 0.1590

R indices (all data) R1 = 0.0665, wR2 = 0.1661

Flack parameter x =0.09(7)

Largest diff. peak and hole 1.504 and -0.575 e.Å^{-3}

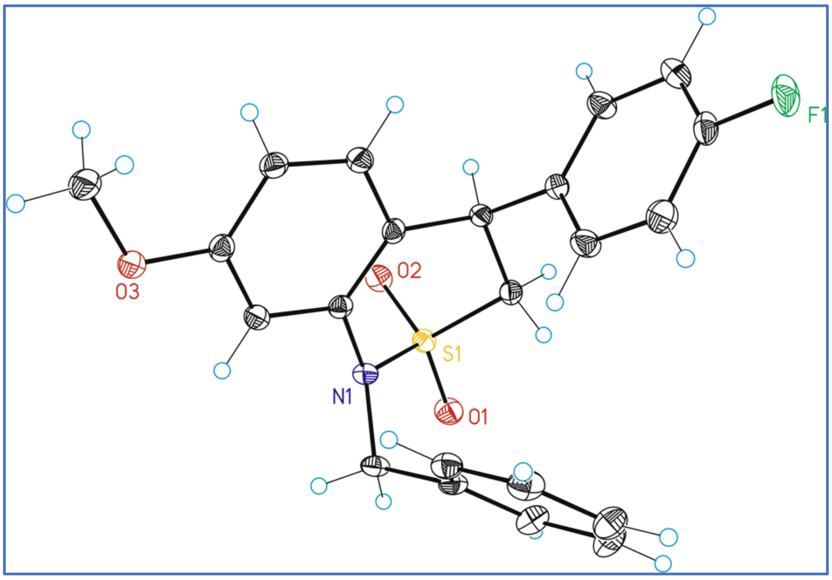


Table 3.4: Crystal data and structure refinement for **182m**.

Identification code	CCDC1449545	
Empirical formula	C22 H20 F N O3 S	
Formula weight	397.45	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.5549(6)Å	α= 90°.
	b = 10.7424(8)Å	β = 92.097(2)°.
	c = 18.1864(12)Å	γ = 90°.
Volume	1865.4(2) Å^3	
Z	4	
Density (calculated)	1.415 Mg/m^3	
Absorption coefficient	0.207 mm^{-1}	
F(000)	832	
Crystal size	0.40 x 0.20 x 0.10 mm^3	
Theta range for data collection	2.133 to 30.568°.	
Index ranges	-13<=h<=13,-14<=k<=15,-25<=l<=18	
Reflections collected	17619	

Independent reflections	5547[R(int) = 0.0447]
Completeness to theta =30.568°	96.8%
Absorption correction	Multi-scan
Max. and min. transmission	0.980 and 0.812
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5547/ 0/ 254
Goodness-of-fit on F^2	1.045
Final R indices [I>2sigma(I)]	R1 = 0.0491, wR2 = 0.1264
R indices (all data)	R1 = 0.0609, wR2 = 0.1353
Largest diff. peak and hole	0.935 and -0.525 e.Å^{-3}

Chapter IV. Intermolecular Radical C(sp^3)-H Amination under Iodine Catalysis

4.1 Introduction: Metal-free C(sp^3)-H Amination

Nitrogen can be installed at C(sp^3) cores through metal-mediated or metal-free processes. While the former was introduced in the first chapter of this thesis, in this section, transformations that do not involve transition metals will be highlighted.

Outstanding advances in the field of C-H functionalization have been achieved via nitrene insertion reactions. Nitrenes have been widely recognized as useful two electron oxidants that allow for C-N bond formation.[181] In particular, the use of hypervalent iodine reagents in reactions involving nitrene transfer has being widely studied.[182] Several examples have been reported over the last decade, including iminoiodanes as nitrene precursors for the amination of aliphatic C-H bonds.[183] Some characteristic model reactions have been discussed in the introduction of this thesis (Section 1.3).

Besides transition metal catalyzed aminations, alternatives including hypervalent iodine reagents or employment of halogen allow the generation of amines as well. A protocol including halogen in combination with iminoiodanes as nitrene precursors have been reported for C(sp^3)-H amination reaction. Lamar has described the successful amination of tertiary alkyl halides **188** by reaction with iminoiodane in the presence of stoichiometric amounts of molecular iodine (Scheme 4.1 top).[184]

The authors suggest that this reaction is initiated by the diiodination of nitrene **A**. Subsequent homolytic cleavage of the N-I bond leads to the generation of the nitrogen-centered radical **B**. Halogen abstraction, either from the nitrogen source or the halogen radical, is supposed to be facilitated and the final radical recombination allows the formation of the mixed halogenated species **C**, which upon second N-X dissociation and

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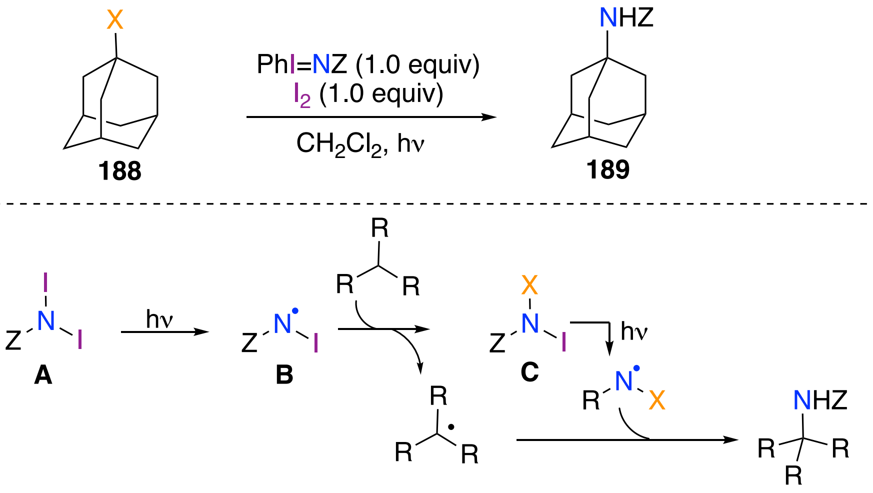
[181] a) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061; b) J. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911.

[182] B. Darses, R. Rodriguez, L. Neuville, M. Mazurais, P. Dauban, *Chem. Comm.* **2017**, *53*, 493.

[183] a) G. Desquirez, V. Pons, P. Dauban, *Angew. Chem. Int. Ed.* **2012**, *51*, 7384; b) J. R. Clarke, K. Feng, A. Sookezian, C. M. White, *Nature Chem.* **2018**, *10*, 583; c) C. K. Prier, R. K. Zhang, A. R. Buller, S. Brinkmann-Chen, F. H. Arnold, *Nature Chem.* **2017**, *9*, 629; d) D. Chiappini, J. B. C. Mack, J. Du Bois, *Angew. Chem. Int. Ed.* **2018**, *57*, 4956.

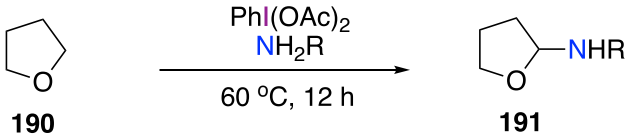
[184] A. C. Brueckner, E. N. Hancock, E. J. Anders, M. M. Tierney, H. R. Morgan, K. A. Scottb A. A. Lamar, *Org. Biomol. Chem.* **2016**, *14*, 4387.

recombination with the carbon radical, yields the final aminated product (Scheme 4.1 bottom).



Scheme 4.1: Visible light mediated amination of halogenated hydrocarbons.

Different approaches include the use of an amine source and a hypervalent iodine reagent for the in situ generation of the nitrene species. Crabtree and Gunnoe have described the α-amination of tetrahydrofuran **190** with a variety of sulfonamides in presence of (diacetoxyiodo)benzene (Scheme 4.2).[185] According to the authors, the reaction proceeds only in the absence of the halogen catalyst while they did not provide any mechanistic discussion on the transformation.



Scheme 4.2: Iodine(III)-mediated amination of tetrahydrofuran.

Kawasaki has reported the amination of carbazoles **192** by a combination of iodosobenzene and trimethylsilyl azide ($TMSN_3$). Interestingly, the amination is taking place on the C2 position, as depicted in the scheme 4.3 (top).[186] Liu has also described a general method for an iodine-catalyzed amination of tetrahydrocarbazole derivatives **192** with chloramine salts towards the regioselective formation of **193** (Scheme 4.3 bottom).[187]

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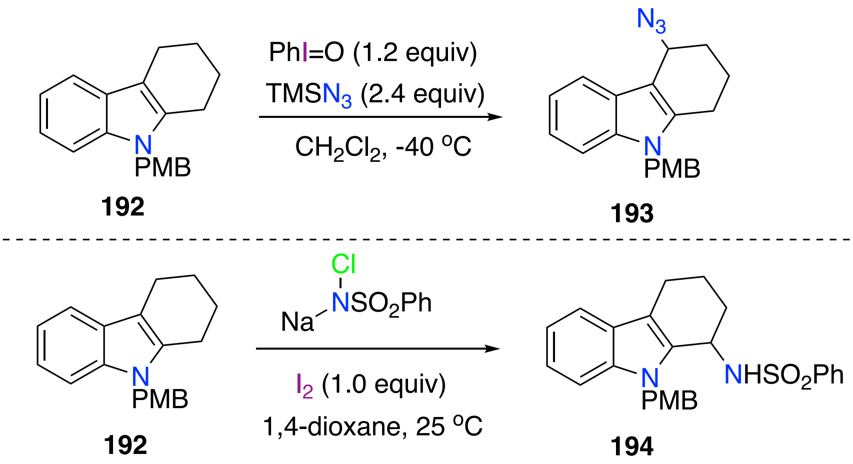
[185] J. Campos, S. K. Goforth, R. H. Crabtree, T. B. Gunnoe, *RSC Adv.* **2014**, *4*, 47951.
[186] K. Higuchi, M. Inaba, A. Nagamura, T. Ishizaki, M. Tayu, T. Kawasaki, *Heterocycles* **2014**, *89*, 2105.
[187] X. Liu, Y. Zhou, Z. Yang, Q. Li, L. Zhao, P. Liu, *J. Org. Chem.* **2018**, *83*, 4665.



Scheme 4.3: Regioselective amination on tertahydrocarbazole derivatives, depending on the reagent combination.

Extending the application of hypervalent iodine reagents toward C-N bond formation; Zhdankin has described stable aminoiodanes, that are able to perform the amination of organic substrates such as adamantane. Alpha-nitrogen amination were also possible under these conditions.[188] Minakata further developed on this idea, by synthesizing a cyclic iodine(III) reagent **196** that bears one phthalimide as ligand. This particular iodine(III) reagent **196** was used for the development of the oxidative C(sp^3)-H amination on *N,N*-dimethylanilines yielding satisfactory yields of products **197** and **199** (Scheme 4.4).[189] Remarkably, the same reagent was reported in the same study for performing diamination reaction through rearrangement pathways.

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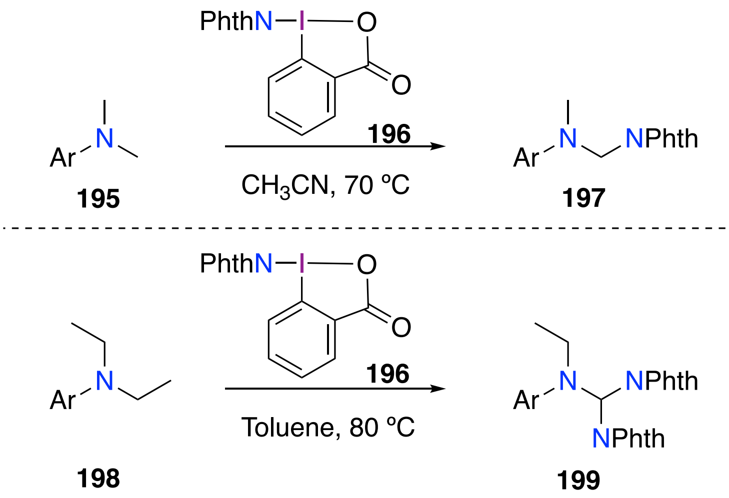
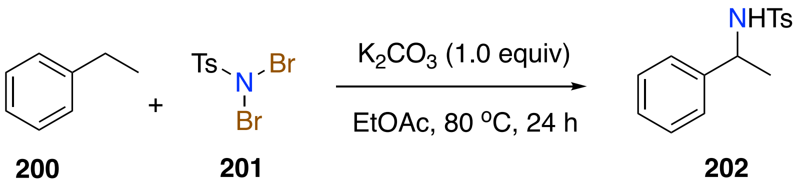
[188] V. V: Zhdankin, M. McSherry, B. Mismash, J. T. Bolz, J. K. Woodward, R. M. Arbit, S. Erickson, *Tetrahedron Lett.* **1997**, *38*, 21.

[189] K. Kiyokawa, T. Kosaka, T. Kojima, S. Minakata, *Angew. Chem. Int. Ed.* **2015**, *54*, 13719.



Scheme 4.4: Oxidative C(sp^3)-H amination on *N,N*-dialkylanilines.

Along the same lines, Minakata has described the use of chloramine-T in combination with molecular iodine in stoichiometric amounts for the successful amination of hydrocarbons, such as indan.[190] In the field of haloamines, another efficient protocol for the amination of alkylarenes, such as ethylbenzene **200** was demonstrated by Phukan, with the use of N-dibromotosylamide **201** in the presence of an inorganic base (Scheme 4.5). The aminated products, such as **202**, were obtained in good yields.



Scheme 4.5: $TsNBr_2$ as an alternative aminating agent.

The use of hypervalent bromine reagents was pioneered by Ochiai, who described the synthesis and isolation of a hypervalent bromine reagent.[191] Interestingly, hypervalent aryl-λ^3-bromanes are more reactive than their iodine analogues. This fact is probably due to their increased electronegativity. Ochiai has demonstrated their potential as aminating agents over a series of aliphatic substrates under mild conditions (Scheme 4.6).[192]

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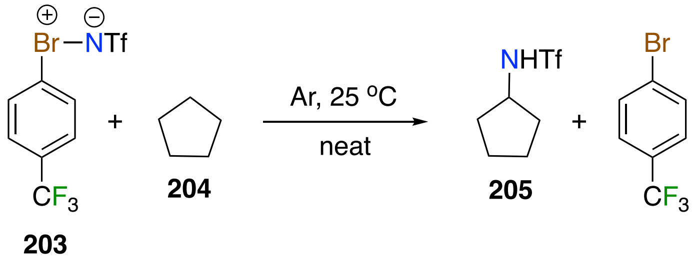
[190] Y. Takeda, J. Hayakawa, K. Yano, S. Minakata, *Chem. Lett.* **2012**, *41*, 1672.

[191] M. Ochiai, T. Kaneaki, N. Tada, K. Miyamoto, H. Chuman, M. Shiro, S. Hayashi, W. Nakanishi, *J. Am. Chem. Soc.* **2007**, *129*, 12938.

[192] M. Ochiai, K. Miyamoto, T. Kaneaki, S. Hayashi, W. Nakanishi, *Science* **2011**, *332*, 448.



Scheme 4.6: Intermolecular amination by hypervalent aryl-λ^3-bromanes.

Recently, we became interested in the employment of halogen catalysis in combination with hypervalent iodine reagents for C-H amination reactions as outlined in the previous chapter.[193] Three conceptually new protocols for the catalytic Hofmann-Löffler reactions have been designed based on molecular iodine[189a,b] or an ammonium bromide salt[189c] as the respective pre-catalysts in the presence of matching terminal oxidants. The conceptual outlook is the following: under the optimized catalysis conditions, hypoiodite(I) (ROX) and a related iodine(I) derivative or hypobromite(I), respectively, are formed in situ, and, these active reagents convert the sulfonamide substrate **177a** into the corresponding N-halogenated species **A** (Scheme 4.7). The innate reactivity of such key N-X intermediates **A** under visible light enables the formation of the crucial amidyl radical **B**, that promotes the selective remote C-H functionalization through a 1,5-hydrogen atom transfer (1,5-HAT). The intermediate C-centered radical **C** then undergoes halogenation. Depending on the chosen terminal oxidant and the degree of reactivity at the respective halogenated carbon of **C**, immediate cyclization to the pyrrolidine **178a** can occur directly at this stage through the nitrogen nucleophile (orange pathway). Alternatively, suitably engineered oxidation to an intermediary alkyl iodide(III) state **E** may be pursued (dark green pathway). It is well established that iodine(III) acts as an excellent nucleofuge, as discussed in the introduction (1.4.3) and this capacity accelerates the cyclization step to the corresponding pyrrolidine product **187a**.

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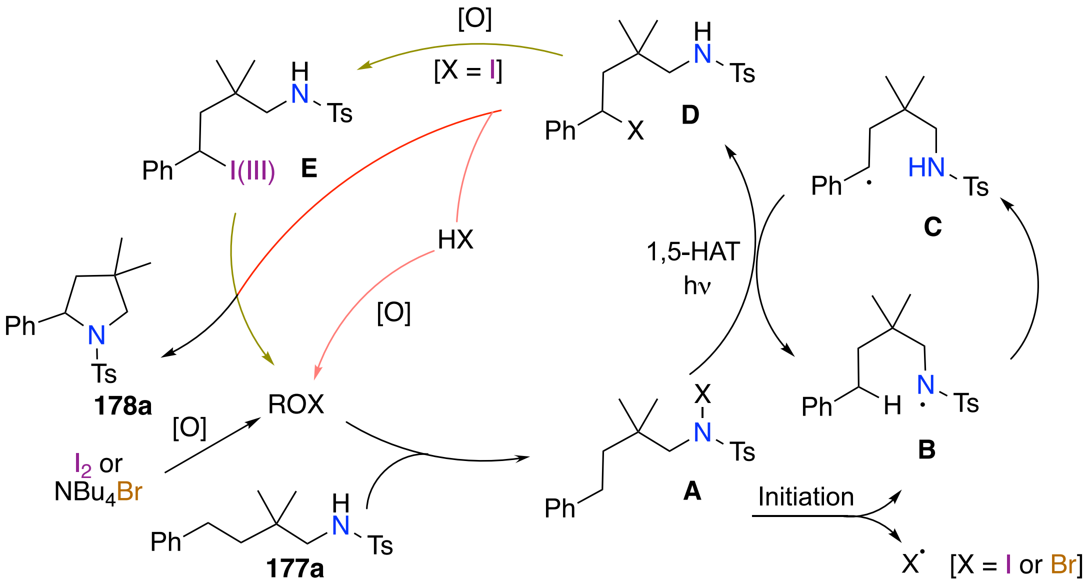
[193] a) C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8287; b) T. Duhamel, C. J. Stein, C. Martínez, M. Reiher, K. Muñiz, *ACS Catal.* **2018**, *8*, 3918; c) P. Becker, T. Duhamel, C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2018**, *57*, 5166.



Scheme 4.7: Mechanistic context for the formation of pyrrolidines via catalytic Hofmann-Löffler reactions.

4.2 Results and Discussion

Transition metal catalysis displays powerful reactivity and dominates the field of amination reaction. Nevertheless, regioselectivity has remained an issue in the presence of multiple C-H bonds.[194] Moreover, the high binding affinity between amines and transition metals can pose problems for the catalyst turnover and the product purity in particular cases. As explained in this chapter, methods have been developed to employ non-contaminative iodine catalysis for related intramolecular radical C-H amination reactions as summarized in the previous section. We strongly believed that the elaboration of such a process for the realization of the more challenging intermolecular reaction scenario would be extremely important. We envisioned a powerful transformation for C-N bond formation that would allow for several applications.

For the elaboration of this transformation, we based our hypothesis on the generation and further elaboration of nitrogen-centered radicals. We were confident that *N*-haloamines could be involved in the generation of this type of radicals, as *N*-halogenated amines constitute a versatile tool for the direct C-H halogenation through amidyl radicals intermediates, which has led to an extensive development in C-H functionalization.[195] With this knowledge, a three-phase catalysis manifold toward intermolecular amination was designed. Its conceptual background is depicted in figure 4.1.

The reaction should start with the formation of an electrophilic iodine(I) catalyst **A** that would halogenate the N-H bond of the sulfonamide, affording the N-iodinated sulfonamide **B**. A light-induced homolysis of the N-I bond should generate the nitrogen-centered radical, that would promote a hydrogen atom abstraction from an unactivated C-H bond, generating a C-centered radical. Direct quench with iodine radical would lead to the formation of the alkyliodide(I) **C**. Within this step, regeneration of the initial nitrogen compound occurs. We could also assign a catalytic role to the aminating agent throughout this C-H iodination phase. For the final substitution process, an alkyliodine(I) oxidation to its iodine(III) counterpart **D** should be implemented. This oxidation process has to occur in order to enhance the leaving group capacity of the polyvalent iodine,[196] thus electronic effects from substituents at the nitrogen source could be suspended. Hence, this

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[194] C. Lescot, B. Darses, F. Collet, P. Retailleau, P. Dauban, *J. Org. Chem.* **2012**, *77*, 7232.
[195] M. D. Kärkäs, *ACS Catal.* **2017**, *7* ,4999.
[196] A. E. Bosnidou, K. Muñiz, *submitted.*

conceptual set-up would enable an amination event, completely independent of the amide nucleophilicity.

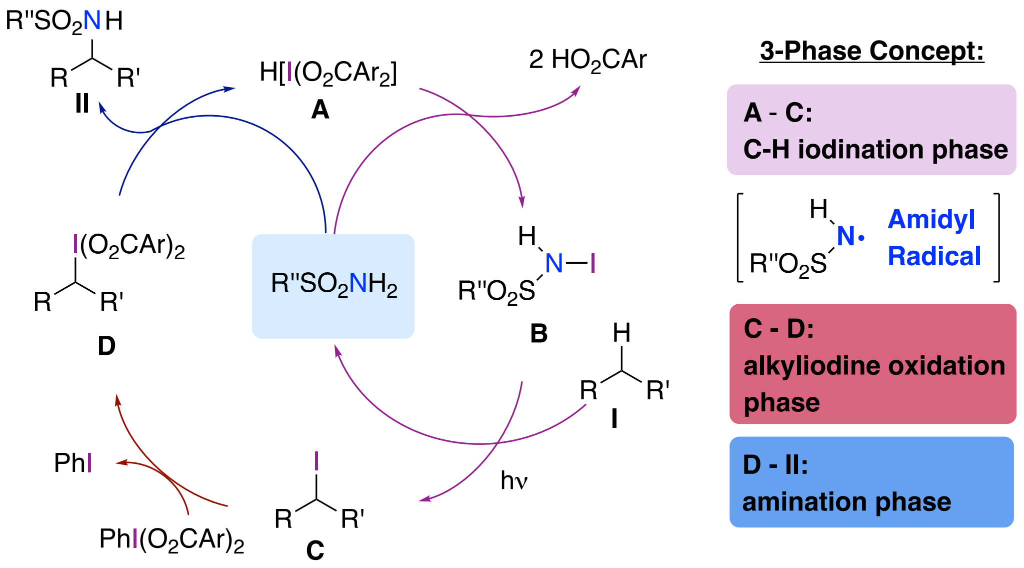
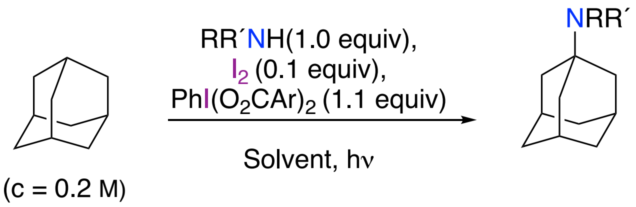


Figure 4.1: Three-phase iodine(I/III) catalysis manifold as a strategic approach to C(sp^3)-H amination.

With this concept in mind, we started our initial experimentation with the tuned conditions used for the intramolecular amination.[189a] We considered using molecular iodine as catalyst source and different hypervalent iodine(III) reagents PhI(O$_2$CR)$_2$. Variation of solvents, light sources as well as aminating agents were investigated.

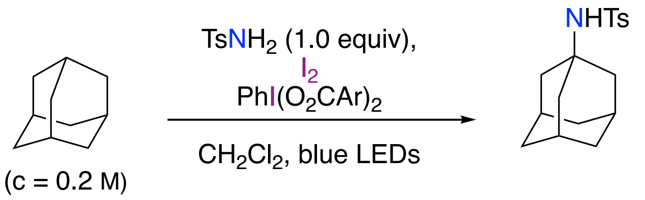
We decided to start the optimization of the reaction conditions, by using a rigid structure such as adamantane. Initial attempts for amination with Ts$_2$NH or Ms$_2$NH as nitrogen sources under the standard conditions used in the related intramolecular amination, led to no conversion (Entry 1,2 Table 4.1). Switching to TsNH$_2$ as nitrogen source afforded the desired product in 38% isolated yield (Entries 5-7, Table 4.1). Different solvents and wavelengths were subsequently tested. Non-chlorinated solvents led to no conversion, while the use of hexafluoro-2-propanol (HFIP) did not further improve the yield (Entries 6-8, Table 4.1). Among different light sources, the use of blue LEDs proved to be optimum (Entry 11 , Table 4.1), while a reaction in the dark lab did not proceed (Entry 13, Table 4.1).



Entry	Amine Source	Solvent	Wavelength (nm)	Yield (%)
1	Ts_2NH	CH_2Cl_2	400-700 (vis)	0
2	Ms_2NH	CH_2Cl_2	400-700 (vis)	0
3	$TsNH_2$	CH_2Cl_2	400-700	38
4	$TsNH_2$	$CHCl_3$	400-700	30
5	$TsNH_2$	CH_3CN	400-700	15
6	$TsNH_2$	EtOAc	400-700	0
7	$TsNH_2$	TBME	400-700	0
8	$TsNH_2$	CH_2Cl_2:HFIP (1:1)	400-700	34
9	$TsNH_2$	C_6H_5Cl	400-700	32
10	$TsNH_2$	CH_2Cl_2	400 (purple LED)	30
11	$TsNH_2$	CH_2Cl_2	475 (blue LED)	35
12	$TsNH_2$	CH_2Cl_2	510 (green LED)	20
13	$TsNH_2$	CH_2Cl_2	Dark lab	10

Table 4.1: Optimization of solvents and wavelength for adamantane as substrate. Ar:3-ClC_6H_4 (*m*CBA).

With the optimum solvent and wavelength in hand for this transformation, we continued the optimization by testing different catalyst loading, followed by different oxidants.

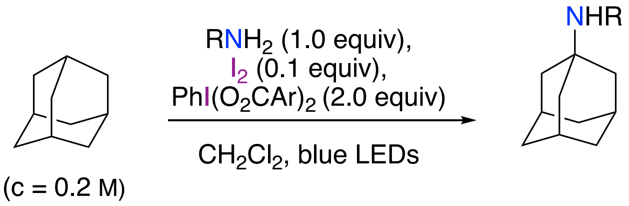


Entry	Catalyst (equiv)	Oxidant	Yield (%)
1	I_2 (0.5 equiv)	$PhI(O_2CAr)_2$ (2.0 equiv)	40
2	I_2 (0.2 equiv)	$PhI(O_2CAr)_2$ (2.0 equiv)	50
3	I_2 (0.05 equiv)	$PhI(O_2CAr)_2$ (2.0 equiv)	32
4	I_2 (0 equiv)	$PhI(O_2CAr)_2$ (2.0 equiv)	0
5	I_2 (0.1 equiv)	$PhI(O_2CAr)_2$ (1.0 equiv)	31
6	I_2 (0.1 equiv)	$PhI(O_2CAr)_2$ (2.0 equiv)	38
6	I_2 (0.1 equiv)	$PhI(O_2CAr)_2$ (3.0 equiv)	34

7	I_2 (0.1 equiv)	$PhI(OAc)_2$ (2.0 equiv)	34
8	I_2 (0.1 equiv)	$PhI(O_2CCF_3)_2$ (2.0 equiv)	56
9	I_2 (0.1 equiv)	PhI(OH)(OTs) (2.0 equiv)	23
10	I_2 (0.1 equiv)	$PhICl_2$ (2.0 equiv)	0
11	I_2 (0.1 equiv)	*m*CPBA (2.0 equiv)	0

Table 4.2: Catalyst and oxidant optimization with adamantane as substrate. Ar: 3-ClC_6H_4 (*m*CBA).

Scanning among different molecular iodine loadings, we cobserved that the reaction with higher amounts of I_2 increased the yield only slightly (Entries 1,2, Table 4.2) compared with 10 mol% catalyst loading (Entry 3, Table 4.1). The reaction proved to give the same conversion with lower molecular iodine loading, (Entry 3, Table 4.2), but in order to be more accurate while in its amount, we continued using 10 mol%. Different oxidants did not further improve the yield of this reaction (Entries 1, 9, 10, Table 4.2), except when PIFA was tested, that afford a 56% yield (Entry 8, Table 4.2). Interestingly, only iodine(III) reagents [$PhI(OR)_2$] with oxygen ligands afforded the desired product as $PhICl_2$ or *m*CPBA as terminal oxidants did not afford any product (Entries 10-11, Table 4.2).

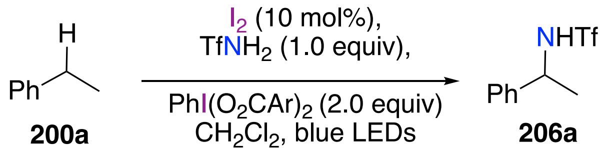


Entry	Amine Source	Oxidant	Yield (%)
1	$NsNH_2$ (1.0 equiv)	$PhI(CO_2CF_3)_2$ (2.0 equiv)	30
2	$MsNH_2$ (1.0 equiv)	$PhI(CO_2CF_3)_2$ (2.0 equiv)	60
3	$MeONH_2$ (1.0 equiv)	$PhI(CO_2CF_3)_2$ (2.0 equiv)	0
4	$PhthNH_2$ (1.0 equiv)	$PhI(CO_2CF_3)_2$ (2.0 equiv)	0
5	$TfNH_2$ (1.0 equiv)	$PhI(CO_2CF_3)_2$ (2.0 equiv)	70
6	$TfNH_2$ (1.0 equiv)	PhI(O2CAr)2 (2.0 equiv)	95

Table 4.3: Amine sources optimization with adamantane as substrate. Ar: Ar:3-ClC_6H_4 (*m*CBA).

Turning our attention to different nitrogen sources such as $NsNH_2$ led to a significant drop in yield (Entry 1, Table 4.3), while it rose to 60% with the less bulky $MsNH_2$ (Entry 15, Table 4.3). Nitrogen sources based on amines and amides, instead of sulfonamides did not lead to any desired product (Entries 3-4, Table 4.3). Finally, the electron deficient triflamide (NH_2Tf) proved to be the best aminating agent we had tried so far as it led to 100% of conversion with 85% of isolated yield (Entry 6, Table 4.3).

With the optimized conditions in hand, we decided to explore different hydrocarbon substrates. As benzyl amines constitute a privileged structural motif in pharmacologically relevant molecules, we considered ethylbenzene **200a** as an interesting model to continue the exploration. Besides, this material contains only a secondary benzylic and a methyl position. Surprisingly, the anticipated reagent combination led only to 52% yield (Entry 1, Table 4.4). This drop in product formation is due to the oxygen insertion from the ligand of the iodine(III) oxidant, that becomes a competitive pathway for this class of substrates. In order to overcome this problem, hypervalent iodine(III) reagents bearing different benzoate groups in the coordination sphere of the iodine were tested. The bis(4-bromobenzoate)iodobenzene proved to be the best oxidant in this transformation, leading to exclusive formation of the amination product (Entry 10, Table 4.4). As expected, selective amination took place at one of the internal C-H bonds to generate the benzyl triflamide **206a**.

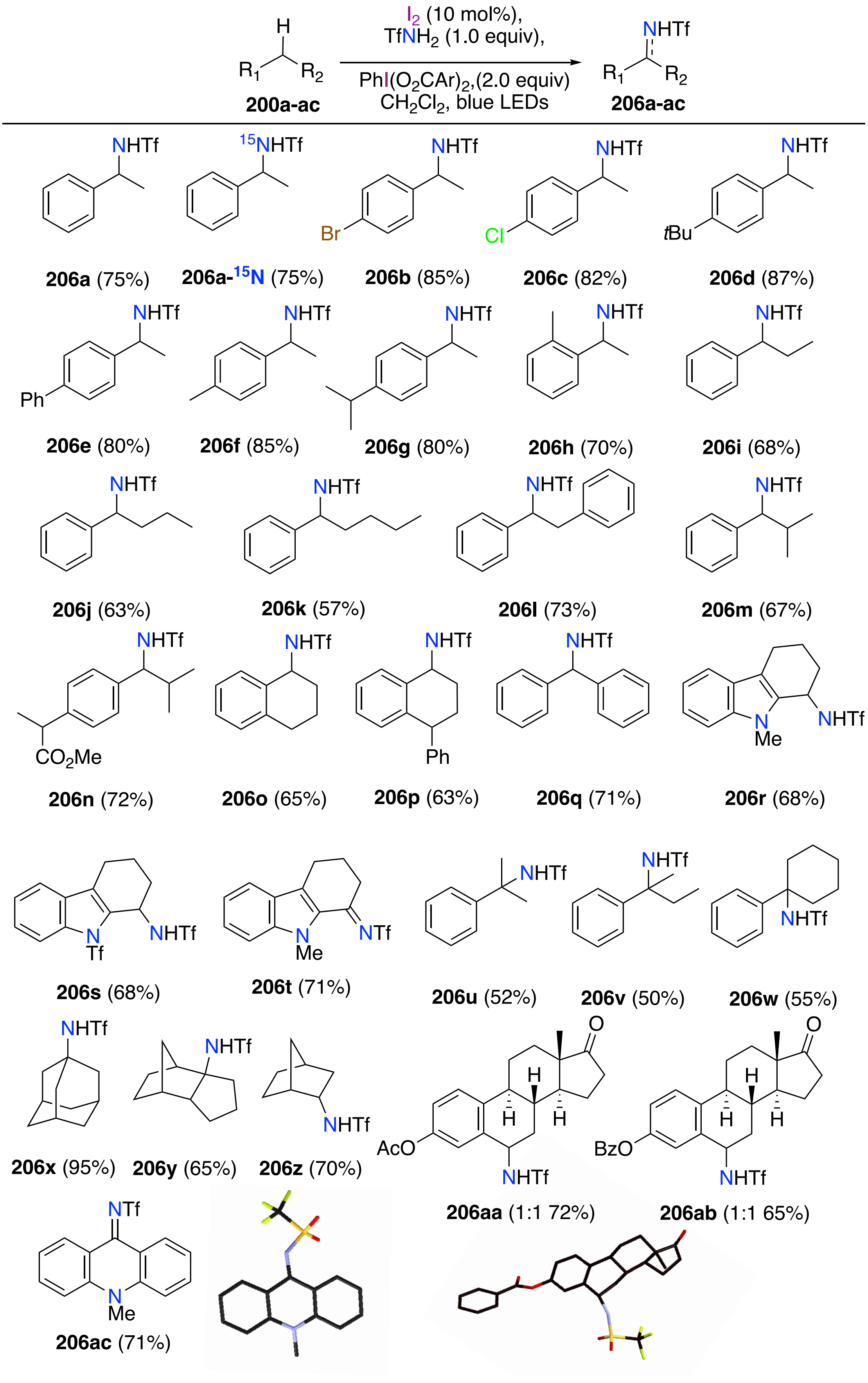


Entry	Oxidant	Temperature	Yield (%)
1	PhI(*m*CBA)$_2$	25 °C	52
2	PhI(*p*CBA)$_2$	25 °C	55
3	PhI(*m*FBA)$_2$	25 °C	45
4	PhI(*m*MeBA)$_2$	25 °C	24
5	PhI(*m*OMeBA)$_2$	25 °C	0
6	PhI(O_2CCF_3)$_2$	25 °C	55
7	PhI(O_2CPh)$_2$	25 °C	72
8	PhI(*p*MeBA)$_2$	25 °C	38
9	PhI(*p*BBA)$_2$	25 °C	80
10	PhI(*p*BBA)$_2$	50 °C	92

Table 4.4: Optimization of the oxidant for ethylbenzene as substrate. *m*CBA: 3-chlorobenzoate, *p*CBA: 4-chlorobenzoate, *m*FBA: 3-fluorobenzoate, *m*MeBA: 3-methyl benzoate, *m*OMeBA: 3-methoxy benzoate, *p*MeBA: 4-methyl benzoate, *p*BBA: 4-bromobenzoate.

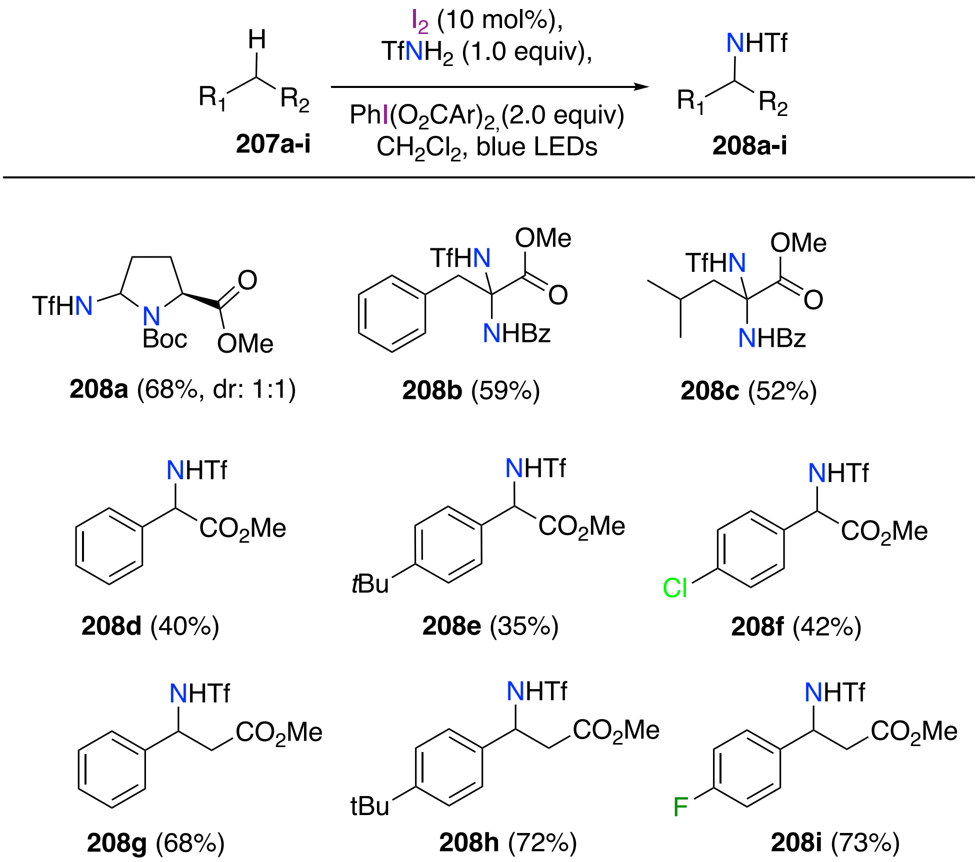
With the fully optimized conditions in hand we started exploring the general reactivity of the reaction. Following the C-H amination of **200a**, the same outcome was obtained for a ^{15}N-labeled nitrogen source. It enables application of the new technology to nitrogen isotope-labelling (**206a-^{15}N**, Scheme 4.8). Identical C-H amination was further observed for various derivatives **200b-xg** containing electron withdrawing and donating aromatic substituents at different positions. A variety of alkyl substituents including branched and linear hydrocarbon chains is well tolerated as demonstrated with the products **200i-xq** (Scheme 4.8). The obtained high regioselectivity deserves to be mentioned. For instance, an interesting intramolecular competition experiment between a tertiary and a secondary benzylic position was performed. For compound **200g**, the amination proceeds selectively at the secondary position overriding the commonly more reactive tertiary alkyl one. Additionally, when **200n** was submitted to reaction, the alpha-carboxylate position remains unfunctionalized, indicating that the electrophilic C-H oxidation is not the case under the present radical conditions. Interestingly, the diastereoselective amination at the benzylic methylene position over a dibenzylic methine position was observed for product **206p**, while the feasibility of amination at a dibenzylic position was demonstrated for

206q. Hexahydrocarbazole derivative **220r** was regioselectively aminated at the C1 position. Interestingly, the oxidation toward the tetrahydrocarbazole core was observed. In contrast, the tetrahydrocarbazole **200s**, that bears an electron withdrawing group as a protecting group on the nitrogen, provided the aminated product without further oxidation. An interesting outcome was observed for the case of **200t**, in which the imine formation takes place due to overoxidation, in the presence of the iodine(III) oxidant. Although the overall transformation is powerful for secondary positions, overriding the tertiary ones in the substrates containing both, tertiary C-H bonds can also undergo amination as demonstrated for products **200u-w** under slightly forced conditions. The same results were obtained for aliphatic derivatives **200x,y**, while norbornane **200z** yielded the expected methylene amination product **206z**. Additional scope includes position-selective C-H functionalization of steroid derivatives **200aa** and **200ab**, which provide the corresponding methylene amination products as separable mixture of diastereoisomers. Finally, overoxidation toward the imine was observed in the case of **200ac**, where the imine imposes to the formation of a fully conjugated system.



Scheme 4.8: Iodine-catalyzed C(sp^3)-H amination: Scope. Ar: 4-BrC$_6$H$_4$.

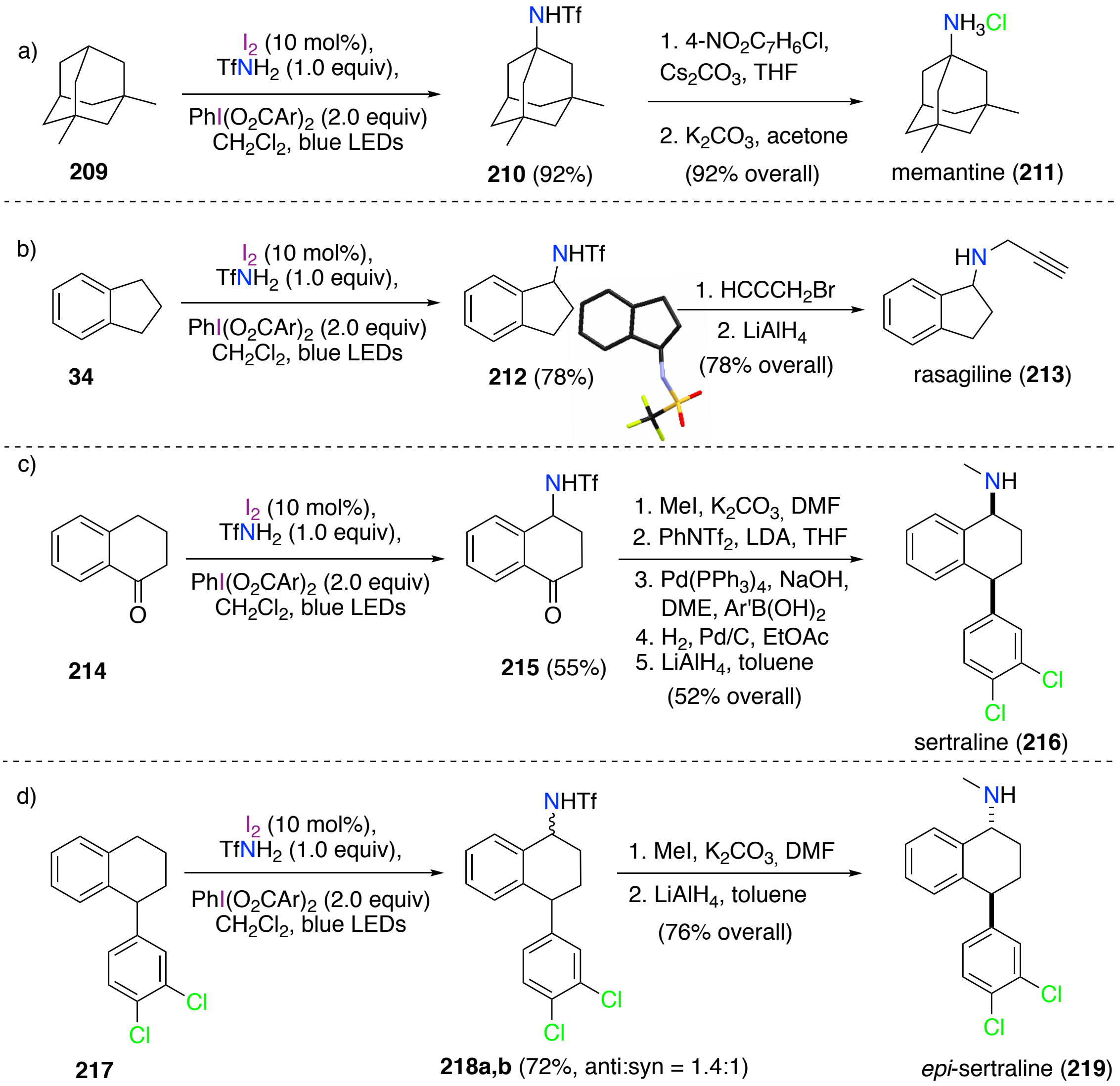
Further exploration revealed an unprecedented reactivity in amino acid derivatization and formation, respectively (Scheme 4.9). Upon exposure to the amination conditions, amino ester derivatives undergo clean aminal formation. In the case of proline derivative **207a**, the amination proceeds at the secondary methylene group instead of the alternative tertiary C-H bond, while for alicyclic amino acids, the reaction forms the aminal products **208b,c** as quaternary stereocenters. Aryl acetates offer an entry to the important class of α-aryl glycines **207d-f**. The homologated 3-aryl propionates produce selectively the β-glycene derivatives **208g-i** confirming the preference of a benzylic C-H amination over the alpha-carboxylate functionalization.



Scheme 4.9: Modification of amino acid derivatives and synthesis of α- and β-aryl glycines. Ar: 4-BrC$_6$H$_4$.

An advanced application of this methodology was demonstrated by the synthesis of three different pharmaceutical compounds. The first one includes the selective C-H amination at dimethyl adamantane **209**. The formation of the precursor **210** was obtained in 92% yield and a following two-step deprotection of the secondary triflamide allowed the generation of the commercial anti-Alzheimer drug memantine **211** in 92% overall yield

(Scheme 4.10a). The synthesis of rasagiline, a common drug against Parkinson´s disease, can be carried out within a three-step procedure. C-H amination of indan **34** generates the benzylic triflamide **212**, which in two steps, including allylation and subsequent deprotection can be converted to rasagiline **213** (Scheme 4.10b). For the synthesis of sertraline, a usual antidepressant, two different synthetic pathways were designed. One comprises to a complete stereospecific synthesis, while the other proceeds through a late stage amination. Iodine-catalyzed amination of tetralone **214** preferentially oxidizes the benzylic methylene over the highly reactive, neighboring methylene of the carbonyl, as expected. Conversion of the amination product **215** into sertraline **126** proceeds readily within four conventional steps, including methylation of the sulfonamide moiety, enol triflate formation followed by a Suzuki cross coupling reaction with the corresponding boronic acid. Stereospecific hydrogenation with a subsequent cleavage of the triflamide protecting group afforded sertraline **216** in 52% overall yield (Scheme 4.10c). Alternatively, direct amination of substrate **217** occurs in a completely selective manner, favoring the benzylic methylene over the tertiary diarylmethine position to provide a diastereomeric mixture **218a** and **218b**, which can be readily separated and used as direct precursors to sertraline **216** and to the corresponding *epi*-sertraline **219** (Scheme 4.10d).



Scheme 4.10: Iodine-catalyzed C-H amination for the synthesis of pharmaceuticals. Ar: 4-BrC$_6$H$_4$, Ar´: 3,4-Cl$_2$C$_6$H$_3$.

As noted before, we had designed the above catalytic transformation very carefully and we demonstrated its synthetic potential. At this point, experimental evidences for the full mechanistic picture will be provided. This mechanism is based on two hypotheses. The first one is the independence on the nucleophilicity degree of the nitrogen source, because this amination process is based on the iodine leaving group capacity, which empowers irreversible C-N bond construction. The second one is the formation of the nitrogen-centered radical, which enables the proton abstraction toward the carbon core functionalization. Control experiments confirmed these hypotheses, revealing a clear image on the reaction mechanism, which is in consistence with our initial proposal.

In order to confirm the presence of the nitrogen-centered radical and its involvement in the reaction, we conducted EPR (electron paramagnetic resonance) measurements. Investigation of a representative reaction mixture allowed the detection (by EPR) of the expected nitrogen-centered radical signals that arise from the homolytic N-I bond cleavage of **B** (Figure 4.2).

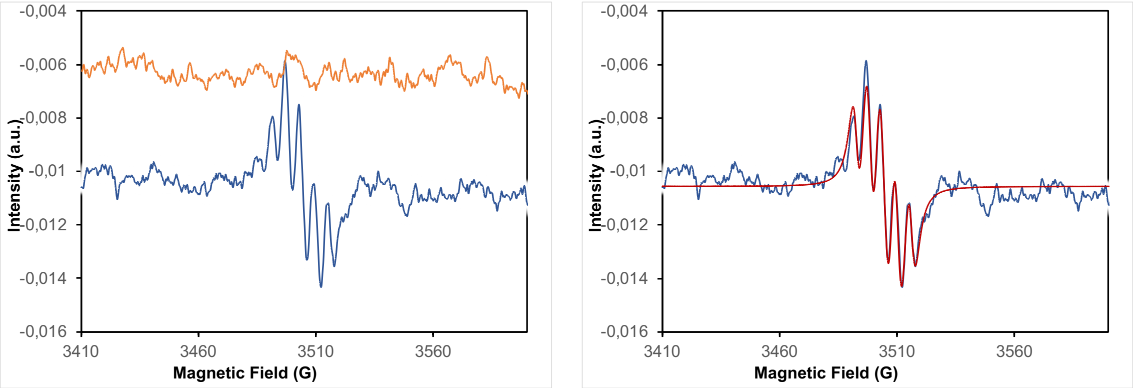
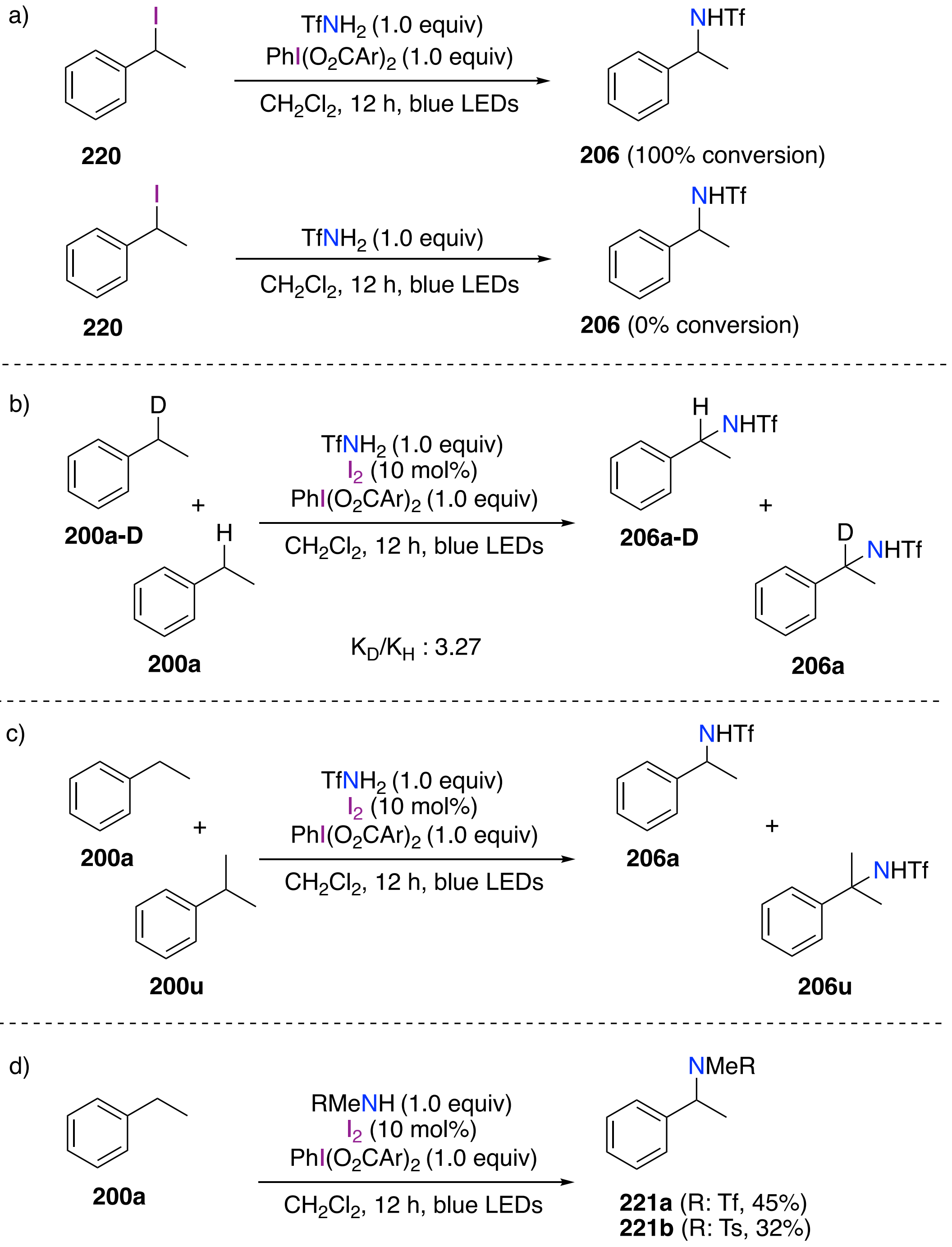


Figure 4.2: EPR Detection of N-centered radical intermediate. Left: EPR silent experimental spectrum (orange) and EPR spectrum for the reaction mixture of molecular iodine, $TfNH_2$ and $PhI(O_2CAr)_2$ [Ar = 4-Br-C_6H_4] after irradiation (blue). Right: Overlay between the experimental (blue) and the simulated (red) spectrum.

In order to confirm the oxidation of the putative intermediate alkyliodide(I) towards the alkyliodide(III), 1-phenylethyliodide **220** was chosen as model. This substrate was submitted to two different conditions, with and without terminal oxidant, to observe if the enhanced nucleofugacity of the I(III) is required. As expected, only in the presence of the iodine(III) reagent, the present substrate undergoes clean reaction to product **206a** (Scheme 4.11a). The determination of the kinetic isotope effect, equal to 3.3, indicates that the hydrogen atom abstraction is the slowest step of the catalytic cycle (Scheme 4.11b).

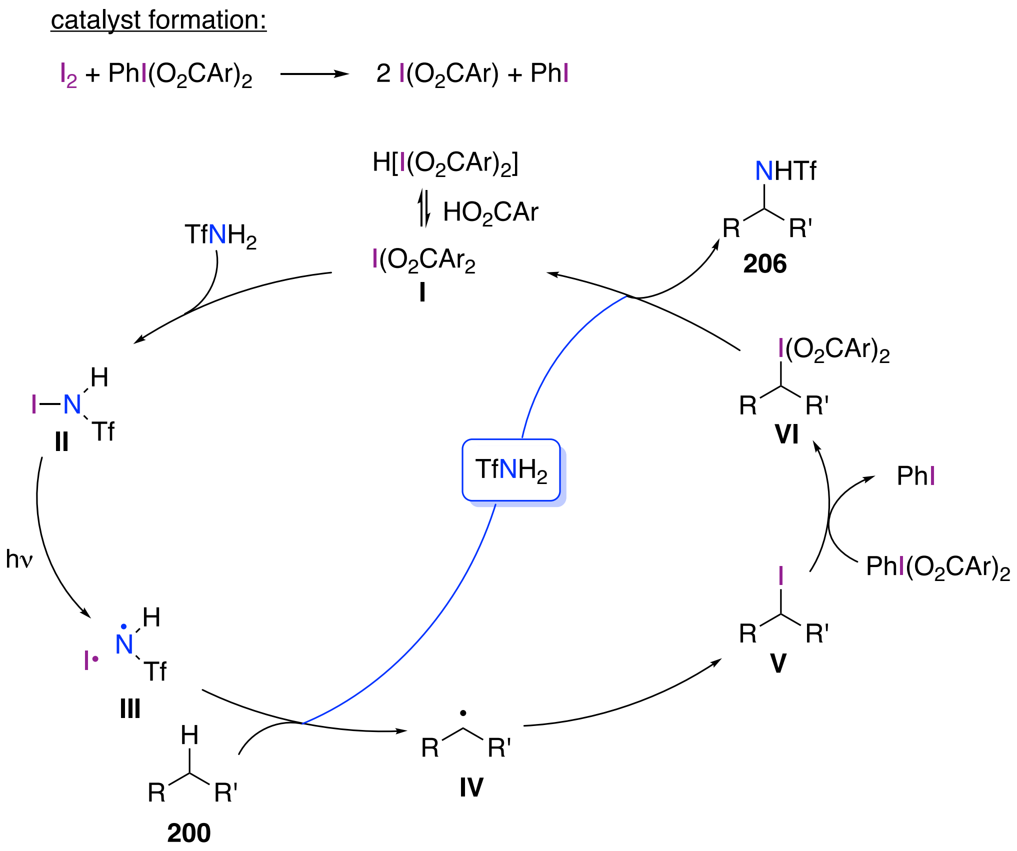
The noted uncommon predominance of secondary over tertiary C-H bonds is attributed to a kinetic preference for the more accessible secondary center exercised by the highly reactive amidyl radical. This is observed in the cases of intra- or intermolecular competition. As an example of the former, compound **206g** was exclusively formed (see Scheme 4.8). For the latter, an intermolecular competition experiment between **200a** and **200u** demonstrates the complete preference for the secondary position over the tertiary one (Scheme 4.11c).

The reaction on substrate **200a** proceeds equally using N-methyl sulfonamides as nitrogen sources (Scheme 4.11d). Formation of the corresponding amides **221a** and **221b** corroborates with the mechanistic outset from figure 4.1 and precludes the assumption of nitrene pathways.



Scheme 4.11: Control experiments for the determination of the mechanism. Ar:4-BrC_6H_4.

All these information led us to conclude the mechanistic scenario, which is in full consistence with the initial idea and is depicted in details below (Scheme 4.12).



Scheme 4.12: Mechanism of the iodine(III)-catalyzed intermolecular amination.

The above discussed C-H amination methodology has direct consequences for C-H functionalization logic.[197] The traditional nitrene-based chemistry can only be employed to arise single C-H amination events, while the herein described iodine catalysis offers a conceptual catalysis plan for two sequential C-H amination events. Our idea was to drive a pyrrolidine retrosynthetically back to a simple linear hydrocarbon chain, by two C-N bond disconnections. The correctness of this analysis was proven for the conversion of four alkylbenzenes **222a-d** (Scheme 4.13) to the corresponding pyrrolidines **224** within two amination events. Interestingly, the intramolecular amination proved to be feasible for primary **222a**, secondary **222b,d** and tertiary positions **222c**, uniformly. For these

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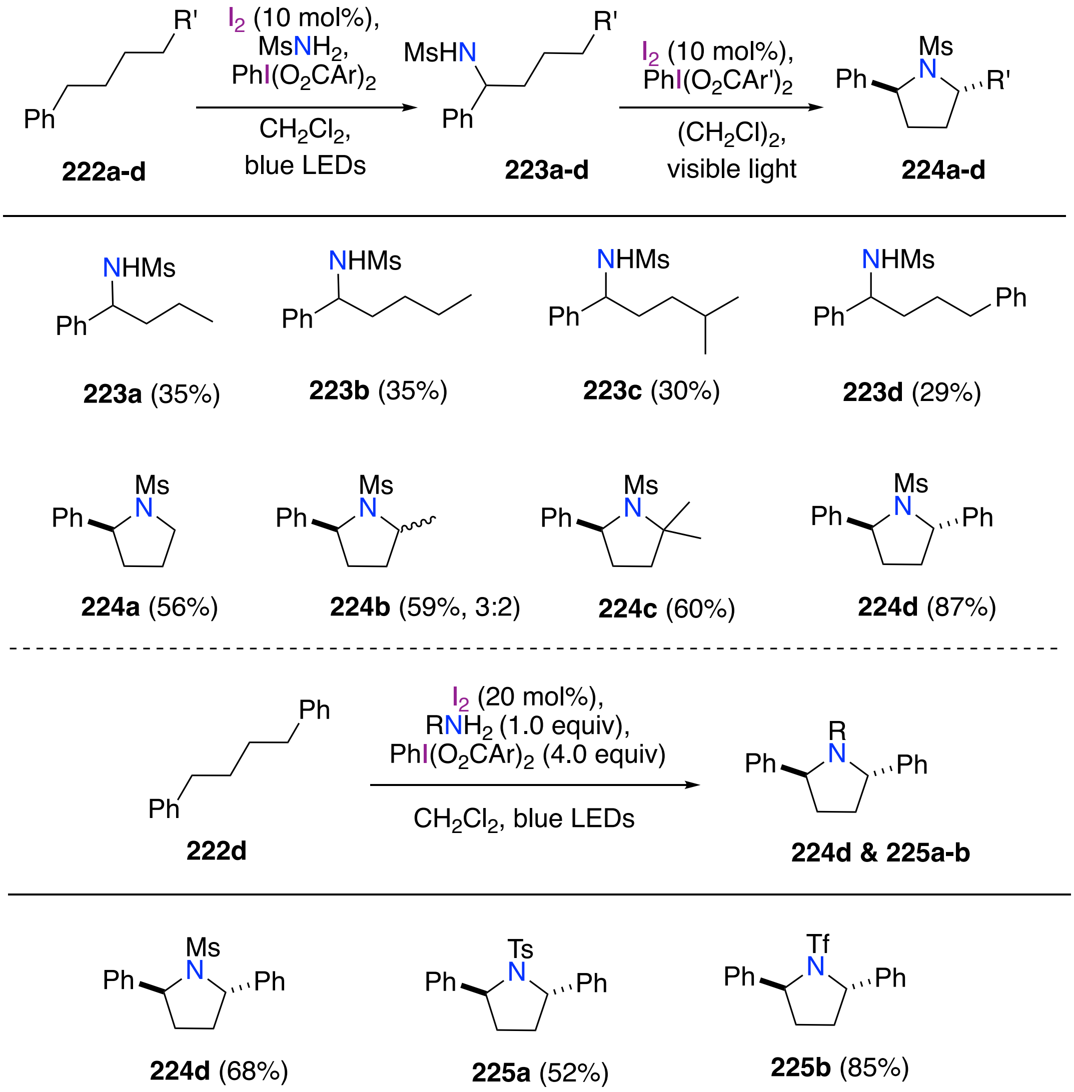
[197] a) H. M. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; b) T. Brückl, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* **2012**, *45*, 826; c) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976.

exploratory transformations, mesylamide was employed due to its prominent performance in the intramolecular C-H amination.

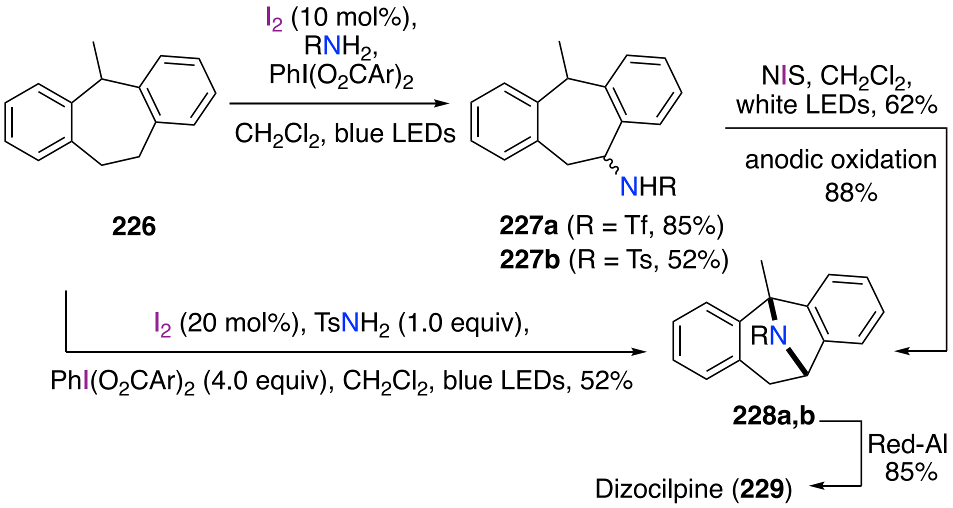
It is important to note that the reaction can be conducted in a single batch operation when the second amination event is taking place on a relatively activated benzylic position. Such an one-pot tandem amination was demonstrated for **222d** using three different nitrogen sources, which all involve in the corresponding diastereoselective production of pyrrolidines **225a,b** (Scheme 4.13).



Scheme 4.13: Tandem iodine-catalyzed two-fold C-H amination approach to pyrrolidine synthesis. Ar: 4-BrC$_6$H$_4$, Ar′: 3-ClC$_6$H$_4$.

The feasibility of this tandem C-H amination concept was further explored in the synthesis of the anticonvulsant and anaesthetic agent dizocilpine (MK-801) (Scheme 4.14). Starting from undecorated hydrocarbon **226**, intermolecular iodine-catalyzed amination with triflamide is directed to one of the methylene positions providing a 3:1 diastereomeric mixture of **227a**. Apparently, the subsequent cyclization toward the precursor of dizocipline **228** could only be carried out for the minor *anti*-isomer of **227a**, recovering the *syn*-isomer.

Thus, an alternative route for the intramolecular cyclisation was designed, involving the recently developed methodology for electrochemical cyclization.[198] The feasibility of this option is based on the carbocation formation during the course of the electrocyclization. In this manner, both diastereoisomers could react, affording the desired product. For this purpose, the triflamide as an amine source is not a suitable choice, as its nucleophilicity is not high enough to promote the electrocyclization. Thus, the intermolecular amination was performed with tosylamide affording a 3:1 diastereomeric mixture of **227b**, which was subsequently submitted to the electrochemical conditions providing **228** in an excellent 88% isolated yield (Scheme 4.14). For the case of tosylamide as nitrogen source, the immediate conversion of **226** to **228** was realized as an one-pot operation, demonstrating the advanced possibilities of the radical-based C-H amination platform under molecular iodine catalysis. Final deprotection, under strong reductive conditions afforded the pharmaceutical dizocilpine **229** in 52% overall yield.



Scheme 4.14: Synthesis of dizocilpine via tandem C-H amination strategy. Ar: 4-BrC_6H_4.

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[198] S. Herold, D. Bafaluy, K. Muñiz, *Green Chem.* **2018**, *20*, 3191.

4.3 Conclusions

In conclusion, we have developed a unique iodine catalysis that enables the selective intermolecular C-H amination of aliphatic C-H bonds. The highlight of this transformation is the unexpected preference for secondary methylene positions over tertiary ones and for more hydridic C-H bonds over acidic ones. This transformation allows for a conceptually new C-N bond formation. It streamlines the synthesis of amines from both conventional feedstock and more elaborated molecules.

This practical synthetic strategy empowers the access to aminated building blocks and promotes innovative multiple C-H amination within a conceptually novel logic toward aminated heterocycles. The synthetic potential is demonstrated by the synthesis of four relevant pharmaceuticals.

4.4 Experimental Section

4.4.1 General information

All solvents, reagents and all deuterated solvents were commercially available. Column chromatography was performed with silica gel (type 60, 0.063-0.2 mm). NMR spectra were recorded on a 400 MHz or a 500 MHz spectrometer, respectively. All chemical shifts in NMR experiments are reported as ppm downfield from TMS. The following calibrations, for ^{1}H and ^{13}C NMR, respectively, were used: $CDCl_3$ $\delta = 7.26$ and 77.16 ppm, CD_2Cl_2 $\delta = 5.32$ and 54.00 ppm, CD_3OD $\delta = 3.31$ and 49.00, $(CD_3)_2SO$ $\delta = 2.50$ and 39.52 ppm and CD_3CN $\delta = 1.94$ and 1.32 ppm (^{1}H NMR). The multiplicities are stated as follows: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HRMS were recorded using ESI-TOF techniques. IR spectra were taken in the solid state. Continuous wave (CW) EPR spectra were obtained at room temperature on a Bruker EMX Micro X-band spectrometer operating at $9.826e^9$ using a Bruker ER 1164 HS resonator.

The following compounds were commercially available and used as received: ethylbenzene, 1-bromo-4-ethylbenzene, 1-chloro-4-ethylbenzene, 1-*tert*-butyl-4-ethylbenzene, 4-ethylbiphenyl, 4-ethyltoluene, 2-ethyltoluene, 4-isopropyl benzaldehyde, *n*-butyl lithium solution, methyltriphenylphosphonium bromide, propylbenzene, butylbenzene, pentylbenzene, bibenzyl, isobutylbenzene, ibuprofen, 1,2,3,4-tetrahydronaphtalene, indan, estrone, benzoyl chloride, acetyl chloride, triethylamine, diphenylmethane, xanthene, 9,10-dihydroacridine, iodomethane, 1,2,3,4-tetrahydrocarbazole, palladium on charcoal, triflic anhydride, cumene, *sec*-butylbenzene, phenylcyclohexane, adamantane, 1,3-dimethyladamantane, norbornane, tetrahydrodicyclopentadiene, alpha-tetralone, phenyl boronic acid, tetrakis (triphenylphosphine)palladium(0), 3,4-dichlorobenzene boronic acid, cyclohexane carboxaldehyde, benzyltriphenylphosphonium bromide, benzaldehyde, Boc- L-proline methyl ester, L-phenylalanine, L-leucine, di-*tert*-butyl dibarbonate, *para*-bromobenzoic acid, diacetoxy iodobenzene, methyl phenylacetate, methyl 4-*tert*-butyl phenylacetate, methyl 4-chloro phenylacetate, methyl-3-phenylpropionate, 3-[(4-*tert*-butyl)phenyl] propanoic acid, methyl 3-(4-fluorophenyl)propanoate, 3-(chlorophenyl) propanoic acid, methyl 2-(4-isobutylphenyl)propanoate, dibenzosuberone.

4.4.2 General procedures

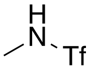
A. Synthesis of ^{15}N-trifluoromethanesulfonamide

$^{15}NH_2Tf$

To a solution of nitrogen-15 labeled ammonium chloride (214 mg, 4.00 mmol, 1.0 equiv) and THF (2 mL) at 0 °C was slowly added a solution of trifluoromethanesulfonyl chloride (842 mg, 5.00 mmol, 1.25 equiv) in THF (2 mL). A solution of aqueous NaOH (10M, 0.4 mL) was added and the mixture was stirred for 2 h. The solid was filtered through a short pad of silica and washed with acetonitrile. The filtrate was evaporated under reduced pressure to yield the product as a brownish solid, which was recrystallized from MeOH to yield the pure product as colorless crystals. Spectroscopic data were in accordance with the literature for $^{14}NH_2Tf$ isotope (*3*).

^{19}F NMR (376 MHz, $CDCl_3$): δ = -79.2.

B. Synthesis of Trifluoro-*N*-methylmethanesulfonamide



A solution of trifluoromethanesulfonyl chloride (842 mg, 5.00 mmol, 1.25 equiv) in THF (2.5 mL), was added to as solution of methylamine hydrochloride (270 mg, 4.00 mmol, 1.0 equiv) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 5 min, and an aqueous solution of NaOH (10M, 0.4 mL) was added. The reaction was stirred for 2 h at 0 °C. The reaction mixture was warmed to r.t. and 1N HCl aqueous solution was added. The organic phase was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure, to yield the product as brownish oil in 72% yield. Spectroscopic data were in accordance with the literature (*4*).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.90 (dd, *J* = 4.8, 1.4 Hz, 3H), 5.70 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.2, 119.9 (q, *J* = 321.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = -77.4.

C. General synthetic procedure for Wittig reactions

A flame-dried Schlenk tube equipped with a magnetic stir bar was charged with the corresponding triphenylphosphonium bromide (1.1 equiv) and THF (5 mL/mmol). The mixture was cooled to 0 ºC and *n*-BuLi (2.0 M solution in cyclohexane, 1.1 equiv) was added drop-wise under argon atmosphere. The reaction mixture was stirred for 1 h and then, the corresponding ketone (1.0 equiv) was added. The final mixture was allowed to stir for 18 h at room temperature. A saturated aqueous solution of NH_4Cl was added and the resulting mixture was extracted with Et_2O (3 times). The organic layer was dried over Na_2SO_4 and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, *n*-hexane) to afford the pure products.

D. General synthetic procedure for catalytic hydrogenations

A Schlenk flask equipped with a magnetic stir bar was charged with the corresponding alkene substrate, Pd/C (20 % w/w) and EtOAc (5 mL/mmol). The reaction was stirred under an atmosphere of dihydrogen for 12 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure to yield the pure product.

E. General synthetic procedure for esterification reactions

A Schlenk flask equipped with a magnetic stir bar was charged with the corresponding carboxylic acid, MeOH (5 mL/mmol) and H_2SO_4 in catalytic amounts. The reaction mixture was stirred for 12 h. The mixture was partially concentrated under reduced pressure and subsequently washed with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to yield the pure corresponding methyl ester.

F. General procedure for the intermolecular C-H amination (GP1)

The corresponding starting material (0.2 mmol, 1.0 equiv), trifluoromethanesulfonamide (30 mg, 0.2 mmol, 1.0 equiv), I_2 (5 mg, 0.02 mmol, 10 mol%) and PhI(*p*BBA)$_2$ (241 mg, 0.40 mmol, 2.0 equiv) were charged into a dried Schlenk tube (evacuated and backfilled with argon), equipped with a magnetic stir bar. 2 mL of absolute dichloromethane were added and the reaction mixture was irradiated under blue LEDs at r.t.. After 14h, dichloromethane was added and the mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ and then with a saturated aqueous solution of $NaHCO_3$. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (SiO_2, *n*-hexane/EtOAc) to give the pure product.

G. General procedure for the intramolecular C-H amination (GP2)

The corresponding starting material (0.2 mmol, 1.0 equiv), I_2 (5 mg, 0.02 mmol, 10 mol%) and PhI(*m*CBA)$_2$ (113 mg, 0.22 mmol, 1.1 equiv) were charged into a dried Schlenk tube (evacuated and backfilled with argon), equipped with a magnetic stir bar. 2 mL of absolute dichloroethane were added and the reaction mixture was irradiated under white LEDs at r.t.. After 14 h, dichloromethane was added and the mixture was washed with an aqueous solution of $Na_2S_2O_3$ and then with a saturated aqueous solution of $NaHCO_3$. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (SiO_2, *n*-hexane/EtOAc) to give the pure product.

H. General deprotection procedures for the tertiary sulfonamides

Red-Al protocol

A flame-dried Schlenk tube (evacuated and backfilled with argon), equipped with a magnetic stir bar was charged with the corresponding aminated product (1.0 equiv) dissolved in dry toluene (1 mL/ 0.1 mmol) and cooled to 0 ºC. A solution of Red-Al (60% in toluene, 10 equiv) was added drop-wise. The mixture was then heated at 50 ºC for 14h. A solution of NH_4Cl (5% aq) was added and the organic phase was separated. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (SiO_2, *n*-hexane/EtOAc) to give the pure product.

$LiAlH_4$ protocol

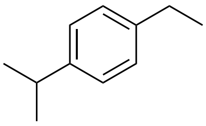
A flame-dried Schlenk equipped with a magnetic stir bar and a reflux condenser was charged with $LiAlH_4$ (5.0 equiv), anhydrous toluene was added carefully and the mixture was cooled to 0 ºC. The corresponding aminated product (1.0 equiv) was dissolved in dry toluene (5 mL/mmol) and was added dropwise to the $LiAlH_4$/toluene suspension under an argon atmosphere. The mixture was then heated to reflux for 5 h and cooled to 0 ºC. An aqueous solution of NaOH (1 M) was added. After filtration over Na_2SO_4 and evaporation of the solvent under reduced pressure, the amine was obtained in quantitative yield.

I. General deprotection procedure for the secondary sulfonamides

The corresponding aminated substrate (1.0 equiv), K_2CO_3 (1.2 equiv), 4-nitrobenzyl bromide (1.2 equiv) were added in a round bottom flask equipped with a magnetic stir bar. Acetone (1 mL/ 0.1 mmol) was added and the suspension was stirred at room temperature overnight. After evaporation of the solvent H_2O was added and the mixture was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was dissolved in THF (1 mL/0.1 mmol) and Cs_2CO_3 (2.0 equiv) was added. The suspension was stirred at 50 °C for 14h. . The reaction mixture was then acidified with aqueous HCl (1 M), and the THF was evaporated under reduced pressure. The aqueous phase was washed with Et_2O. The aqueous phase was evaporated under reduced pressure to yield the pure product.

4.3.3 Data for compounds

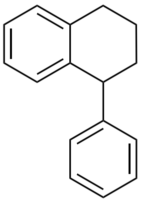
1-Ethyl-4-isopropylbenzene 200g



Synthesized from 4-isopropyl benzaldehyde and methyltriphenyl phosphonium bromide with a Wittig reaction followed by application of the catalytic hydrogenation protocol. Spectroscopic data were in accordance with the literature.[199] 98% yield. Colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.26-1.32 (m, 9H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.85-2.91 (m, 1H), 7.07-7.18 (m, 4H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 15.7, 24.2, 28.5, 33.8, 126.5, 128.0, 141.7, 146.2.

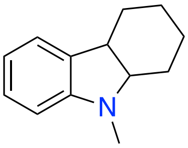
1-Phenyl-1,2,3,4-tetrahydronaphthalene 200p



Synthesized from 3,4-dihydronaphthalen-1-trifluoromethanesulfonate and phenyl boronic acid according to a literature procedure[200] followed by application of the catalytic hydrogenation protocol. Spectroscopic data in full agreement with the ones reported previously.[201] 68% yield (over two steps). Yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.74-1.89 (m, 1H), 1.89-2.03 (m, 2H), 2.14-2.29 (m, 1H), 2.81-3.03 (m, 2H), 4.18 (t, *J* = 6.7 Hz, 1H), 6.83-6.94 (m, 1H), 7.08 (ddd, *J* = 7.7, 6.3, 2.4 Hz, 1H), 7.14-7.19 (m, 4H), 7.21-7.31 (m, 1H), 7.31-7.37 (m, 2H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ = 21.1, 29.9, 33.4, 45.7, 125.7, 126.0, 126.0, 128.3, 128.9, 129.1, 130.3, 137.7, 139.5, 147.6

c 200r



Synthesized according to a literature procedure. Spectroscopic data were in accordance with the literature.[202] 99% yield. Brown solid.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.32-1.75 (6H, m), 1.78-1.98 (2H, m), 2.76 (3H, s), 3.05 (1H, dt, *J* = 9.2, 6.5 Hz), 3.29 (1H, dt, *J* = 6.8, 4.4 Hz), 6.61 (1H, d, *J* = 7.8 Hz), 6.78 (1H, td, *J* = 7.3, 1.0 Hz), 7.09-7.24 (2H, m). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 21.2, 22.2, 23.3, 23.4, 29.1, 40.8, 58.7, 108.6, 117.8, 118.7, 120.6, 135.8, 148.6.

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[199] R. K. Zhang, K. Chen, X. Huang, L. Wohlsclager, H. Renata, F. H. Arnold, *Nature* **2019**, *565*, 67.

[200] T. Watanabe, N. Miyaura, A. Suzuki, *Synlett*, **1992**, 207.

[201] S. T. Bright, J. M. Coxon, P. J. Steel, *J. Org. Chem.* **1990**, 55, 1338.

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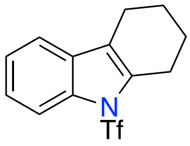
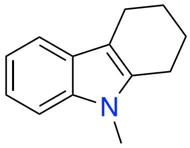
9-(Trifluoromethyl)sulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole 200s



Synthesized according to a literature procedure. Spectroscopic data were in accordance with the literature.[203] 50% yield. Yellow solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.69-1.99 (m, 4H), 2.61-2.69 (m, 2H), 2.76-3.07 (m, 2H), 7.30-7.36 (m, 2H), 7.39-7.47 (m, 1H), 7.90-7.96 (m, 1H). **^{13}C NMR** (125 MHz, CDCl$_3$): δ = 21.2, 21.9, 23.2, 24.0, 114.4, 118.6, 119.9 (q, *J* = 324.54 Hz), 120.9, 124.9, 125.0, 130.7, 135.9, 136.3. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -75.3.

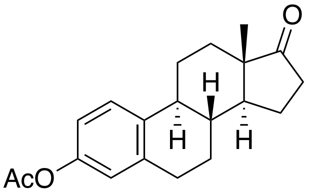
9-Methyl-2,3,4,9-tetrahydro-1*H*-carbazole 200t



Synthesized according to a literature procedure. Spectroscopic data were in accordance with the literature.[204] 99% yield. Yellow solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.99-2.08 (m, 2H), 2.08-2.16 (m, 2H), 2.85 (ddd, *J* = 7.9, 4.0, 1.7 Hz, 2H), 2.91 (ddd, *J* = 6.1, 4.4, 1.7 Hz, 2H), 3.72 (s, 3H), 7.26 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 7.30-7.37 (m, 1H), 7.40 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.59-7.70 (m, 1H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ = 21.2, 22.1, 23.3, 28.8, 108.5, 109.2, 117.7, 118.6, 120.5, 127.2, 135.7, 136.8.

(8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl acetate 200aa



Synthesized according to a literature procedure. Spectroscopic data were in accordance with the literature.[205] 98% yield. White solid.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.91 (s, 3H), 1.37-1.69 (m, 6H), 1.88-2.22 (m, 4H), 2.25-2.37 (m, 1H), 2.28 (s, 3H), 2.36-2.43 (m, 1H), 2.46-2.59 (m, 1H), 2.83-2.98 (m, 2H), 6.79-6.82 (m, 1H), 6.85 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.28 (dt, *J* = 8.5, 0.8 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.8, 21.1, 21.6, 25.7, 26.3, 29.4, 31.5, 35.9, 37.9, 44.1, 47.9, 50.4, 118.7, 121.6, 126.4, 137.4, 138.0, 148.5, 169.9, 221.3.

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[203] P. I. Jolly, N. Fleary-Roberts, S. O´Sullivan, E. Doni, S. Zhou, J. Murphy, *Org. Biomol. Chem.*, **2012**, *10*, 5807.

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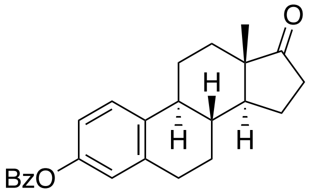
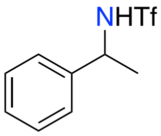
(8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl benzoate 200ab



Synthesized according to a literature procedure. Spectroscopic data were in accordance with the literature.[206] 96% yield. Yellowish solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H), 1.38-1.71 (m, 5H), 1.95-2.45 (m, 7H), 2.51 (dd, *J* = 18.4, 8.5 Hz, 1H), 2.85-3.09 (m, 2H), 6.89-7.13 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.44-7.54 (m, 2H), 7.57-7.65 (m, 1H), 8.02-8.25 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 13.8, 21.6, 25.8, 26.4, 29.4, 31.6, 35.9, 38.0, 44.2, 47.9, 50.4, 119.0, 121.7, 126.5, 128.6, 129.7, 130.1, 133.5, 137.4, 138.1, 148.9, 165.4, 220.8.

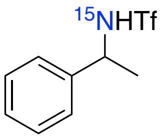
1,1,1-Trifluoro-*N*-(1-phenylethyl)methanesulfonamide 206a



Synthesized from ethylbenzene according to GP1. Data in agreement with the ones reported.[207] 75% yield. Yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (d, *J* = 6.9 Hz, 3H), 4.80 (q, *J* = 7.3 Hz, 1H), 5.10 (d, *J* = 6.6 Hz, 1H), 7.28-7.53 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 23.5, 55.4, 119.7 (q, *J* = 321.2 Hz), 128.5, 129.2, 141.1. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.6.

1,1,1-Trifluoro-N-(1-phenylethyl)methanesulfonamide-15N 206a-^{15}N



Synthesized from ethylbenzene according to GP1. 62% yield. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (dd, *J* = 3.5, 6.9 Hz, 3H), 4.77-4.84 (m, 1H), 5.09 (dd, *J* = 8.4, 89.9 Hz, 1H), 7.29-7.47 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 23.5, 55.4 (d, *J* = 5.9 Hz), 120.0 (dq, *J* = 9.29, 330.06 Hz), 126.0, 128.6, 129.2, 141.0. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.7 (d, *J* = 1.7 Hz). **^{15}N NMR** (41 MHz, $CDCl_3$): δ = -279.5.

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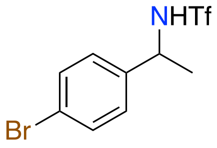
[207] K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562.

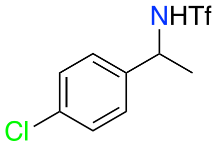
N-(1-(4-Bromophenyl) ethyl)-1,1,1-trifluoromethanesulfonamide 206b



Synthesized from 1-bromo-4-ethylbenzene according to GP. 85% yield. Yellow solid.

^{1}H NMR (400 MHz, CD_3CN): δ = 1.53 (d, *J* = 7.0 Hz, 3H), 4.75-4.82 (m, 1H), 7.23 (s, 1H), 7.18-7.40 (m, 2H), 7.55 (d, *J* = 8.5 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 23.4, 54.8, 119.6 (q, *J* = 320.9 Hz), 122.5, 127.8, 132.3, 140.2. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.6. **IR** ν (cm^{-1}): 3312, 2993, 1435, 1367, 1226, 1182, 1145, 1019, 984, 821, 510. **HRMS**: Anal. Calcd. for $C_9H_9BrF_3NO_2S$: 329.9417, found: 329.9408. **m.p.**: 84-86 °C

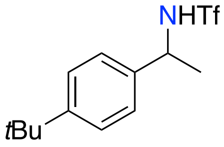
N-(1-(4-Chlorophenyl) ethyl)-1,1,1-trifluoromethanesulfonamide 206c



Synthesized from 1-chloro-4-ethylbenzene according to GP. 82% yield. Yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62 (d, *J* = 6.9 Hz, 3H), 4.76-4.80 (m, 1H), 5.31 (s, 1H), 7.23-7.32 (m, 2H), 7.33-7.41 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 23.5, 54.7, 119.6 (q, *J* = 320.9 Hz), 127.5, 129.4, 134.4, 139.7. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.7. **IR** ν (cm^{-1}): 3298, 2930, 1371, 1229, 1189, 1145, 1093, 978, 826, 606. **HRMS**: Anal. Calcd. for $C_9H_8ClF_3NO_2S$: 285.9922, found: 285.9911. **m.p.**: 90-92 °C

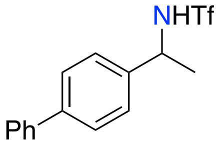
N-(1-(4-(*tert*-Butyl) phenyl) ethyl)-1,1,1-trifluoromethanesulfonamide 206d



Synthesized from 1-*tert*-butyl-4-ethylbenzene according to GP. 87% yield. Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 9H), 1.64 (d, *J* = 6.9 Hz, 3H), 4.75-4.82 (m, 1H), 5.20 (d, *J* = 8.3 Hz, 1H), 7.24-7.31 (m, 2H), 7.37-7.44 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 23.3, 31.4, 34.7, 55.1, 119.7 (q, *J* = 321.0 Hz), 125.8, 126.1, 137.9, 151.6. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.6. **IR** ν (cm^{-1}): 3298, 2964, 1369, 1189, 1146, 1072, 980, 756, 610. **HRMS**: Anal. Calcd. for $C_{13}H_{18}F_3NaNO_2S$: 332.0903, found: 332.0900.

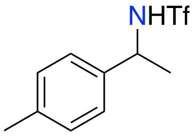
N-(1-([1,1'-Biphenyl]-4-yl) ethyl)-1,1,1-trifluoromethanesulfonamide 206e



Synthesized from 4-ethylbiphenyl according to GP. 67% yield. Yellow solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.69 (d, J = 6.9 Hz, 3H), 4.82-4.90 (m, 1H), 5.13 (d, J = 8.4 Hz, 1H), 7.33-7.42 (m, 3H), 7.42-7.48 (m, 2H), 7.55-7.65 (m, 4H). **^{13}C NMR** (125 MHz, CDCl$_3$): δ = 23.5, 55.2, 119.7 (q, J = 320.9 Hz), 126.5, 127.2, 127.8, 127.9, 129.0, 139.9, 140.4, 141.6. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.6. **IR** ν (cm^{-1}): 3283, 1441, 1370, 1184, 1147, 1080, 982, 764. **HRMS**: Anal. Calcd. for $C_{15}H_{14}F_3NaNO_2S$: 352.0590, found: 352.0589. **m.p.**: 99-101 °C

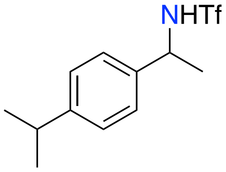
1,1,1-Trifluoro-*N*-(1-(*p*-tolyl)ethyl) methanesulfonamide 206f



Synthesized from 4-ethyltoluene according to GP. Data in agreement with the ones reported.[208] 85% yield. Yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.62 (d, J = 6.9 Hz, 3H), 2.36 (s, 3H), 4.73-4.80 (m, 1H), 5.17 (d, J = 8.4 Hz, 1H), 7.13-7.25 (m, 4H). **^{13}C NMR** (125 MHz, CDCl$_3$): δ = 21.2, 23.5, 55.3, 119.7 (q, J = 321.0 Hz), 125.8, 138.1, 138.4. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.6.

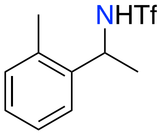
1,1,1-Trifluoro-*N*-(1-(4-isopropylphenyl)ethyl) methanesulfonamide 206g



Synthesized from 1-isopropyl-4-ethylbenzene according to GP. 60% yield. Yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.27 (d, J = 6.9 Hz, 6H), 1.65 (d, J = 6.9 Hz, 3H), 2.90-2.97 (m, 1H), 4.73-4.88 (m, 1H), 5.29 (d, J = 8.2 Hz, 1H), 7.21-7.43 (m, 4H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 24.0, 29.7, 33.9, 55.2, 119.7 (q, J = 320.9 Hz), 126.1, 127.2, 138.3, 149.3. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.3. **IR** ν (cm^{-1}): 3322, 2964, 1367, 1189, 1145, 983, 614. **HRMS**: Anal. Calcd. for $C_{12}H_{15}F_3NO_2S$: 294.0781, found:.294.0780.

1,1,1-Trifluoro-*N*-(1-(*o*-tolyl) ethyl) methanesulfonamide 206h



Synthesized from 2-ethyltoluene according to GP. Data in agreement with the ones reported.[207] 70% yield. Yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.61 (d, J = 6.6 Hz, 3H), 2.41 (s, 3H), 5.08-5.11 (m, 1H), 5.15 (d, J = 6.6 Hz, 1H), 7.14-7.31 (m, 4H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 19.1, 23.6, 51.7, 119.6 (q, J = 321.1 Hz), 124.7, 127.0, 128.3, 131.2, 134.7, 139.6. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.6.

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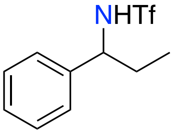
[208] L. Chu, K. -J. Xiao, J. –Q. Yu, *Science* **2014**, *346*, 451.

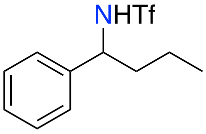
1,1,1-Trifluoro-*N*-(1-phenylpropyl) methanesulfonamide 206i



Synthesized from propylbenzene according to GP. Data in agreement with the ones reported.[209] 68% yield. Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3H), 1.85-1.98 (m, 2H), 4.46-4.52 (m, 1H), 5.27 (d, *J* = 8.7 Hz, 1H), 7.23-7.25 (m, 2H), 7.30-7.40 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 10.5, 30.8, 61.4, 119.7 (q, *J* = 321.0 Hz), 126.2, 128.3, 129.0, 140.0. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.2.

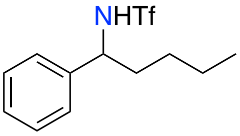
1,1,1-Trifluoro-*N*-(1-phenylbutyl)methanesulfonamide 206j



Synthesized from butylbenzene according to GP. Data in agreement with the ones reported.[210] 63% yield. Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3H), 1.17-1.45 (m, 2H), 1.86 (ddt, *J* = 6.1, 7.5, 9.0 Hz, 2H), 4.53-4.60 (m, 1H), 5.25 (d, *J* = 8.7 Hz, 1H), 7.19-7.26 (m, 1H), 7.28-7.53 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 13.6, 19.3, 40.0, 59.9, 119.6 (q, *J* = 321.2 Hz), 126.3, 128.4, 129.1, 140.4. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.3.

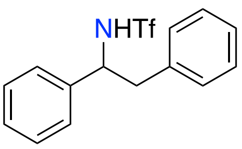
1,1,1-Trifluoro-*N*-(1-phenylpentyl)methanesulfonamide 206k



Synthesized from pentylbenzene according to GP. Data in agreement with the ones reported.[208] 57% yield. Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1 Hz, 3H), 1.16-1.41 (m, 4H), 1.80 -1.97 (m, 2H), 4.52-4.58 (m, 1H), 5.25 (d, *J* = 8.7 Hz, 1H), 7.22-7.26 (m, 2H), 7.30-7.40 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 13.9, 22.3, 28.1, 37.6, 60.2, 119.56 (q, *J* = 321.0 Hz), 126.3, 128.4, 129.1, 140.4. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.6.

N-(1,2-Diphenylethyl)-1,1,1-trifluoromethanesulfonamide 206l



Synthesized from bibenzyl according to GP. Data in agreement with the ones reported.[208] 73% yield. Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10-3.13 (m, 2H), 4.79-4.85 (m, 1H), 5.15 (d, *J* = 8.6 Hz, 1H), 6.87-6.96 (m, 2H), 7.09 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.15-

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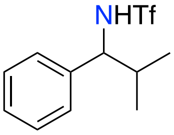
[209] K. Miyamoto, Md. M. Hoque, S. Ogasa, *J. Org. Chem.* **2012**, *77*, 8317.

[210] M. Yang, B. Su, Y. Wang, K. Chen, X. Jiang, Y. –F. Zhang, X. –S. Zhang, G. Chen, Y. Cheng, Z. Cao, *Nat. Commun.* **2014**, 5:4707.

7.21 (m, 3H), 7.24-7.30 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 44.3, 60.6, 119.5 (q, *J* = 321.2 Hz), 126.4, 127.4, 128.4, 128.8, 129.0, 129.7, 135.4, 139.6. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.6.

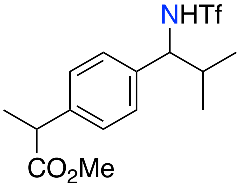
1,1,1-Trifluoro-*N*-(2-methyl-1-phenylpropyl) methanesulfonamide 206m



Synthesized from isobutylbenzene according to GP. Data in agreement with the ones reported.[211] 67% yield. Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.7 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 2.01-2.05 (m, 1H), 4.30 (d, *J* = 5.1 Hz, 1H), 5.28 (brs, 1H), 7.14 -7.22 (m, 2H), 7.27-7.41 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 18.7, 19.6, 34.8, 65.9, 119.5 (q, *J* = 321.0 Hz), 126.5, 128.2, 128.9, 139.7. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.4.

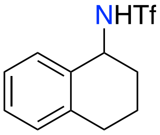
Methyl-2-(4-(2-methyl-1-((trifluoromethyl)sulfonamido)propyl)phenyl)propanoate 206n



Synthesized from ibuprofen methyl ester according to GP. 72% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.7 Hz, 3H), 1.01 (dd, *J* = 6.7, 0.9 Hz, 3H), 1.50 (d, *J* = 7.2 Hz, 3H), 2.00-2.07 (m, 1H), 3.68 (s, 3H), 3.73 (q, *J* = 7.2 Hz, 1H), 4.24-4.33 (m, 1H), 5.40 (d, *J* = 9.4 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 18.6, 18.7 (d, *J* = 2.8 Hz), 19.7, 34.7, 45.2, 52.3, 65.5 (d, *J* = 1.3 Hz), 119.5 (q, *J* = 321.0 Hz), 126.8, 128.0, 138.7, 140.3, 175.1. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.4. **IR** ν (cm^{-1}): 3240, 2969, 1715, 1448, 1374, 1189, 1148, 1040, 611. **HRMS**: Anal. Calcd. for $C_{15}H_{20}F_3NNaO_4S$: 390.0957, found: 390.0963. **m.p.**: 115-117 °C

1,1,1-Trifluoro-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl) methanesulfonamide 206o



Synthesized from 1,2,3,4-tetrahydronaphthalene according to GP. 65% yield. White solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79-1.96 (m, 2H), 1.94-2.25 (m, 2H), 2.60-3.08 (m, 2H), 4.70-4.86 (m, 1H), 4.97 (d, *J* = 8.7 Hz, 1H), 7.10 (dd, *J* = 5.5, 3.6 Hz, 1H), 7.16-7.26 (m, 2H), 7.36 (dd, *J* = 5.6, 3.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.2, 28.9, 31.6, 54.3, 119.8 (q, *J* = 321.0 Hz), 126.9, 128.5, 128.9, 129.6, 134.1, 137.8.

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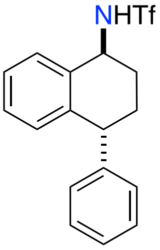
[211] L. Chu, X. C. Wang, C. E. Moore, A. Rheingold, J. -Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 16344.

^{19}F NMR (376 MHz, CDCl$_3$): δ = -77.4. **IR** ν (cm^{-1}): 3286, 2945, 1433, 1370, 1228, 1180, 1141, 1003, 745, 595. **HRMS**: Anal. Calcd. for $C_{11}H_{11}F_3NO_2S$: 278.0468, found: 278.0474. **m.p.**: 89-91 °C.

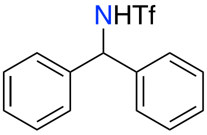
1,1,1-Trifluoro-*N*-4-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl-methanesulfonamide 206p



Synthesized from 1-phenyl-1,2,3,4-tetrahydronaphthalene according to GP (1:0.6 d.r.). 63 % yield. Colorless oil. Data for the major diastereoisomer.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.85-2.00 (m, 2H), 2.21-2.33 (m, 2H), 4.06-4.26 (m, 1H), 4.81-5.06 (m, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 7.00-7.11 (m, 2H), 7.17-7.24 (m, 2H), 7.26-7.34 (m, 3H), 7.48 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 29.4, 31.9, 44.8, 54.6, 119.7 (q, *J* = 320.9 Hz), 126.5, 127.3, 128.1, 128.5, 128.5, 128.6, 130.8, 134.7, 140.0, 145.8. **^{19}F NMR (376 MHz, CDCl$_3$)**: δ = -77.4. **IR** ν (cm^{-1}): 3303, 2922, 2852, 1450, 1373, 1228, 1190, 1145, 756, 701. **HRMS:** Anal. Calcd. for $C_{17}H_{15}F_3NO_2S$: 354.0781, found: 354.0784.

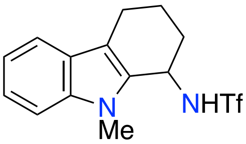
N-Benzhydryl-1,1,1-trifluoromethanesulfonamide 206q



Synthesized from diphenylmethane according to GP. Data in agreement with the ones reported.[211] 71% yield. White solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.53 (d, *J* = 8.8 Hz, 1H), 5.88 (d, *J* = 8.7 Hz, 1H), 7.23-7.28 (m, 5H), 7.33-7.42 (m, 5H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ = 62.6, 119.6 (q, *J* = 321.1 Hz), 127.3, 128.5, 129.1, 139.7. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.3.

1,1,1-Trifluoro-*N*-(9-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl) methanesulfonamide 206r

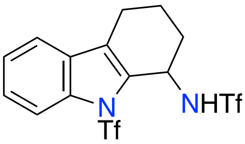


Synthesized from 9-Methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole according to GP. 60% yield. Yellow solid.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.74-1.94 (m, 1H), 1.98-2.16 (m, 2H), 2.24-2.36 (m, 1H), 2.65 (ddd, *J* = 16.4, 11.4, 5.5 Hz, 1H), 2.81-2.96 (m, 1H), 3.75 (s, 3H), 5.02 (brs, 2H), 7.06-7.18 (m, 1H), 7.21-7.37 (m, 2H), 7.51-7.54 (m, 1H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 18.0, 20.7, 29.5, 31.5, 48.3, 109.4, 114.0, 117.1 (q, *J* = 320.9 Hz), 119.1, 119.6, 123.2, 126.0, 130.3, 137.7. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -

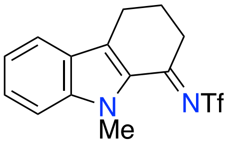
77.7. **IR** ν (cm^{-1}): 3318, 2930, 2852, 1471, 1422, 1371, 1225, 1184, 1139, 1004, 734, 619. **HRMS**: Anal. Calcd. for $C_{14}H_{14}F_3N_2O_2S$: 331.0734, found: 331.0731. **m.p.**: 148-150 °C

1,1,1-Trifluoro-*N*-(9-((trifluoromethyl)sulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl)methanesulfonamide 206s



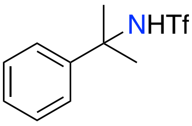
Synthesized from 9-(trifluoromethylsulfonyl)-2,3,4,9-tetrahydro carbazole according to GP. 62% yield. Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.85-1.99 (m, 2H), 2.03-2.12 (m, 1H), 2.48 (d, *J* = 12.0 Hz, 1H), 2.69 (ddd, *J* = 17.4, 11.1, 6.6 Hz, 1H), 2.91 (dd, *J* = 17.5, 4.9 Hz, 1H), 4.95 (brs, 1H), 5.28 (brs, 1H), 7.37-7.49 (m, 2H), 7.51-7.55 (m, 1H), 7.99 (brs, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 15.8, 21.0, 30.2, 48.6, 115.2, 119.3 (q, *J* = 320.8 Hz), 119.8 (q, *J* = 325.4 Hz), 119.9, 125.7, 127.5, 129.3, 130.7, 136.8. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -74.4, -77.9. **IR** ν (cm^{-1}): 3252, 2924, 1415, 1195, 1194, 979, 755, 608. **HRMS:** Anal. Calcd. for: $C_{14}H_{12}F_6NaNO_4S$ 473.0035, found: 473.0042. **m.p.**: 163-165 °C

1,1,1-Trifluoro-*N*-(9-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-ylidene) methanesulfonamide 206t



Synthesized from 9-methyl-2,3,4,4a,9,9a-hexahydrocarbazole according to GP. 71% yield. Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.15-2.21 (2H, m), 3.04 (2H, t, *J* = 6.2 Hz), 3.24-3.31 (2H, m), 3.99 (3H, s), 7.13-7.21 (1H, m), 7.35 (1H, d, *J* = 8.7 Hz), 7.49 (1H, ddd, *J* = 1.2, 6.9, 8.6 Hz), 7.60-7.68 (1H, m). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 21.8, 23.9, 32.8, 35.2, 110.8, 119.2 (q, *J* = 319.0 Hz), 121.1, 121.9, 124.8, 129.6, 134.8, 135.3, 142.5, 175.5. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -79.7. **IR** ν (cm^{-1}): 3318, 2930, 2852, 1471, 1422, 1371, 1225, 1184, 1139, 1004, 734, 619. **HRMS**: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{14}F_3N_2O_2S$: 331.0734, found: 331.0731. **m.p.**: 105-107 °C.

1,1,1-Trifluoro-*N*-(2-phenylpropan-2-yl) methanesulfonamide 206u



Synthesized from cumene according to GP at 50 °C. Data in agreement with the ones reported.[212] 52% yield. Yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ =1.81 (s, 6H), 5.14 (s, 1H), 7.30-7.35 (m, 1H), 7.38-7.42 (m, 2H), 7.44-7.51 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 29.7,

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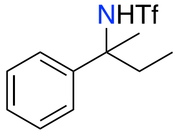
[212] N. K. Mishra, J. Park, S. Sharma, S. Han, M. Kim, Y. Shin, J. Jang, J. H. Kwak, Y. H. Jung, I. S. Kim, *Chem. Comm.* **2014**, *50*, 2350.

62.3, 119.4 (q, J = 321.1 Hz), 125.1, 128.2, 129.0, 145.3. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.7.

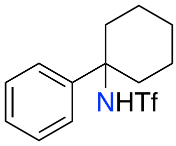
1,1,1-Trifluoro-*N*-(2-phenylbutan-2-yl) methanesulfonamide 206v



Synthesized from *sec*-butylbenzene according to GP at 50 °C. 42% yield. Yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (t, J = 7.4 Hz, 3H), 1.82 (s, 3H), 1.98-2.14 (m, 2H), 5.07 (s, 1H), 7.28-7.34 (m, 1H), 7.37-7.44 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 8.7, 24.9, 36.2, 65.7, 119.3 (q, J = 321.2 Hz), 125.6, 127.9, 128.9, 143.7. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.6. **IR** ν (cm^{-1}): 3298, 2925, 2854, 1367, 1189, 1143, 1012, 699. **HRMS**: Anal. Calcd. for $C_{11}H_{13}F_3NO_2S$: 280.0625, found: 280.0626.

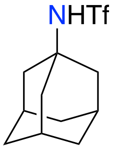
1,1,1-Trifluoro-*N*-(1-phenylcyclohexyl) methanesulfonamide 206w



Synthesized from phenylcyclohexane according to GP at 50 °C. 62% yield. Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17-1.29 (m, 2H), 1.40-1.46 (m, 2H), 1.60-1.80 (m, 2H), 2.22-2.32 (m, 4H), 4.97 (brs, 1H), 7.29-7.44 (m, 3H), 7.46-7.54 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 22.6, 25.3, 37.0, 63.8, 119.1 (d, J = 321.5 Hz), 126.4, 128.1, 128.8, 142.5. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.7. **IR** ν (cm^{-1}): 3290, 2929, 2855, 1600, 1492, 1267, 1188, 1107, 1068, 710, 698. **HRMS**: Anal. Calcd. for $C_{13}H_{15}F_3NO_2S$: 306.0781, found: 306.0778.

***N*-(Adamantan-1-yl)-1,1,1-trifluoromethanesulfonamide 206x**



Synthesized from adamantane according to Table S1. Data in agreement with the ones reported.[213] 95% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56-1.71 (m, 6H), 1.98 (d, J = 2.9 Hz, 6H), 2.12-2.14 (m, 3H), 4.91 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 29.8, 35.8, 43.3, 58.7, 119.36 (q, J = 321.0 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.7.

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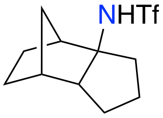
[213] M. Ochiai, K. Miyamoto, S. Hayashi, W. Nakanishi, *Science,* **2011**, *332*, 448.

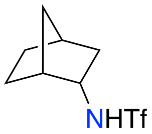
1,1,1-Trifluoro-*N*-(Octahydro-1*H*-4,7-methanoinden-3a-yl)methanesulfonamide 2y



Synthesized from tetrahydrodicyclopentadiene according to GP. 65% yield. Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35-1.57 (m, 6H), 1.64-1.74 (m, 1H), 1.81-1.96 (m, 4H), 2.18 (dd, *J* = 9.4, 4.7 Hz, 2H), 2.26 (d, *J* = 4.3 Hz, 1H), 2.51 (d, *J* = 4.3 Hz, 1H) 4.96 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 22.1, 23.8, 25.9, 28.8, 36.3, 40.9, 41.9, 47.9, 56.1, 77.8, 119.3 (q, *J* = 321.2 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -78.2. **IR** ν (cm^{-1}): 3291, 2959, 2882, 1421, 1360, 1187, 1139, 994, 606. **HRMS**: Anal. Calcd. for $C_{11}H_{15}F_3NO_2S$: 282.0781, found: 282.0786.

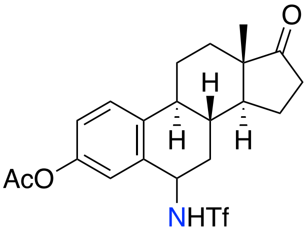
N-(Bicyclo[2.2.1] heptan-2-yl)-1,1,1-trifluoromethanesulfonamide 206z



Synthesized from norbornane according to GP. Data in agreement with the ones reported.[213] 70% yield. Brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09-1.39 (m, 5H), 1.54-1.60 (m, 2H), 1.90 (ddd, *J* = 2.3, 8.1, 13.7 Hz, 1H), 2.34 (brs, 2H), 3.52 (dt, *J* = 5.0, 10.1 Hz, 1H), 4.67 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 26.4, 27.8, 35.4, 35.8, 41.4, 43.6, 58.5, 119.8 (q, *J* = 321.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.3.

(8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-6-((trifluoromethyl)sulfonamido)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl acetate 206aa/206aa′



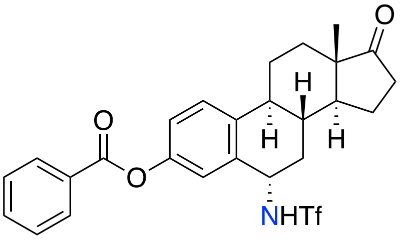
Synthesized from estrone acetate according to GP. (1:1 d.r.) 72% yield. White foam. After column chromatography the clean fraction was diastereomerically enriched.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85-0.93 (m, 3H *major* + 3H *minor*), 1.37-1.82 (m, 5H *major* + 5H *minor*), 1.90-2.21 (m, 3H *major* + 3H *minor*), 2.34 (s, 3H *major* + 3H *minor*), 2.42–2.57 (m, 2H *major* + 2H *minor*), 4.77–4.95 (m, 1H *major* + 1H *minor*), 5.51–5.99 (m, 1H *major* + 1H *minor*), 6.95–7.18 (m, 2H *major* + 2H *minor*), 7.28–7.37 (m, 1H *major* + 1H *minor*). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 13.7, 13.8, 21.0, 21.1, 21.3, 21.4, 25.4, 25.7, 31.3, 31.4, 32.7, 34.2, 35.7, 36.1, 37.8, 39.2, 43.9, 44.1, 49.5, 49.6, 53.2, 55.3, 119.6 (q, *J* = 321.0 Hz), 119.7 (q, *J* = 320.9 Hz), 120.3, 121.7, 122.3, 125.3, 127.0, 127.1, 128.2, 129.0, 137.9, 138.0, 149.3, 149.4, 169.7, 169.8, 218.9, 219.2. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.2,

-77.4. **IR** ν (cm^{-1}): 3182, 2927, 1731, 1371, 1187, 1146, 752, 605. **HRMS:** Anal. Calcd. for $C_{21}H_{24}F_3NNaO_5S$: 482.1219, found: 482.1221.

(6*S*,8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-6-((trifluoromethyl)sulfonamido)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl benzoate

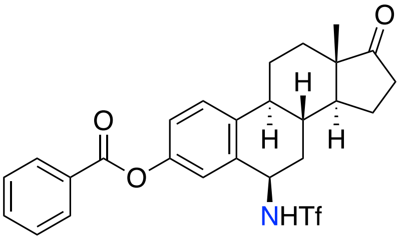
206ab



Synthesized from estrone benzoate according to GP. 65% yield (1:1 d.r.). White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.92 (s, 3H), 1.47-1.84 (m, 6H), 1.99 (dd, *J* = 9.1, 2.2 Hz, 1H), 2.04-2.21 (m, 2H), 2.32-2.45 (m, 2H), 2.47-2.59 (m, 2H), 4.95 (dd, *J* = 11.3, 6.5 Hz, 1H), 5.35 (s, 1H), 7.15 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.30 (dd, *J* = 2.5, 0.9 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.49-7.58 (m, 2H), 7.6-7.70 (m, 1H), 8.14-8.30 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 13.9, 21.5, 25.9, 31.5, 35.8, 36.5, 37.9, 44.3, 47.9, 49.7, 55.5, 116.59 (q, *J* = 327.0 Hz), 120.9, 122.0, 127.3, 128.8, 129.3, 130.4, 134.0, 135.9, 138.2, 149.8, 165.6, 220.0. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.3. **IR** ν (cm^{-1}): 3210, 2923, 1735, 1373, 1223, 1146, 1060, 1023, 707, 609. **HRMS:** Anal. Calcd. for $C_{26}H_{26}F_3NNaO_5S$: 544.1376, found: 544.1379.

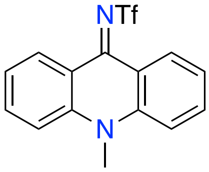
(6*R*,8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-6-((trifluoromethyl)sulfonamido)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl benzoate

206aa′



Synthesized from estrone benzoate according to GP. 65% yield (1:1 d.r.). White solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.96 (s, 3H), 1.48-1.70 (m, 4H), 1.74-1.82 (m, 2H), 1.96-2.35 (m, 5H), 2.42-2.51 (m, 1H), 2.54 (dd, *J* = 18.9, 8.2 Hz, 1H), 4.92 (s, 1H), 7.15-7.24 (m, 2H), 7.42 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.48-7.58 (m, 2H), 7.61-7.71 (m, 1H), 8.17-8.27 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 14.0, 21.4, 25.6, 31.5, 32.9, 34.4, 35.8, 44.1, 48.1, 49.7, 53.4, 119.9 (d, *J* = 321.2 Hz), 122.7, 122.9, 127.3, 128.8, 129.2, 130.4, 134.0, 134.6, 138.2, 149.8, 165.5, 220.3. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.1. **IR** ν (cm^{-1}): 3210, 2923, 1735, 1373, 1223, 1146, 1060, 1023, 707, 609. **HRMS:** Anal. Calcd. for $C_{26}H_{26}F_3NNaO_5S$: 544.1376, found: 544.1405. **m.p.**: 146-148°C.

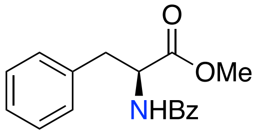
1,1,1-Trifluoro-*N*-(10-methylacridin-9(10*H*)-ylidene)methanesulfonamide 206ac



Synthesized from 10-methyl-9,10-Dihydroacridine according to GP. 76% yield. Yellow solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 3.46 (3H, s), 7.68 (2H, ddd, *J* = 0.9, 6.8, 8.6 Hz), 8.11 (2H, ddd, *J* = 1.6, 6.8, 9.1 Hz), 8.27 (2H, d, *J* = 9.0 Hz), 8.55 (2H, dd, *J* = 1.5, 8.5 Hz). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$): δ = 36.2, 117.6, 120.3, 120.6 (q, *J* = 320.8 Hz), 124.1, 128.1, 136.5, 141.5, 162.1. **^{19}F NMR** (376 MHz, $(CD_3)_2SO$): δ = -77.9. **IR** ν (cm^{-1}): 2921, 2851, 1611, 1582, 1478, 1450, 1302, 1281, 1157, 1101, 741,595, 503. **HRMS**: Anal. Calcd. for $[M+Na]^+$ $C_{15}H_{11}F_3N_2NaO_2S$: 363.0386, found: 363.0392. **m.p.**: 230-232 °C.

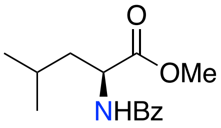
N-Benzoyl-*L*-phenylalanine methyl ester 207b



Synthesized from *L*-phenylalanine methyl ester according to a literature procedure.[204] Data in agreement with the ones reported.[214] 80% yield. White solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.15-3.40 (m, 2H), 3.78 (s, 3H), 5.11 (dt, *J* = 7.6, 5.6 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 7.15 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.29 (ddd, *J* = 6.6, 4.9, 2.1 Hz, 3H), 7.44 (dd, *J* = 8.2, 6.5 Hz, 2H), 7.48-7.56 (m, 1H), 7.67-7.82 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 38.0, 52.6, 53.6, 127.1, 127.3, 128.5, 129.5, 131.9, 134.0 136.0, 166.9, 172.2.

N-Benzoyl-*L*-leucine methyl ester 207c



Synthesized from *L*-leucine methyl ester according to literature procedure.[204] Data in agreement with the ones reported.[215] 83% yield. White solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 5.9 Hz, 6H), 1.50-1.87 (m, 3H), 3.75 (s, 3H), 4.68-4.96 (m, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 7.35-7.57 (m, 3H), 7.69-7.87 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 22.1, 22.9, 25.1, 41.9, 51.2, 52.5, 127.2, 128.7, 131.8, 134.0, 167.2, 173.9.

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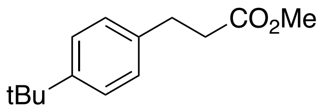
[214] A. J. Metrano, S. J. Miller, *J. Org. Chem.* **2014**, *79*, 1542.

[215] A. Alanthanka, C. U. Maheswari, *Adv. Synth. Catal.* **2015**, *357*, 1199.

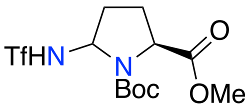
Methyl 3-(4-(*tert*-butyl)phenyl)propanoate xi



Synthesized from 3-[(4-*tert*-butyl)phenyl] propanoic acid by application of the esterification protocol. Data in agreement with the ones reported.[216] 99% yield. Colorless oil.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.34 (d, *J* = 0.8 Hz, 9H), 2.66 (dd, *J* = 8.8, 7.1 Hz, 2H), 2.95 (dd, *J* = 8.9, 6.9 Hz, 2H), 3.71 (s, 3H), 6.88-7.22 (m, 2H), 7.28-7.56 (m, 2H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ = 30.5, 31.5, 34.5, 35.8, 51.7, 125.5, 128.0, 137.6, 149.2, 173.6.

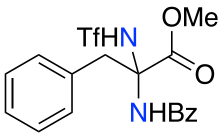
1-(*tert*-Butyl) 2-methyl (2*S*)-5-((trifluoromethyl)sulfonamido)pyrrolidine-1,2-dicarboxylate 208a



Synthesized from N-Boc-proline methyl ester according to GP. (1:1 d.r.) 68% yield. Yellow oil. After column chromatography the fraction was diastereomerically enriched.

^{1}H NMR (500 MHz, CDCl$_3$, 313K): δ= 1.44 (s, 9H) *minor*, 1.49 (s, 9H) *major*, 2.01 (brs, 2H) *major*, 2.15 (brs, 2H) *minor*, 2.25-2.36 (m, 2H) *major*, 2.57-2.68 (m, 2H) *minor*, 3.79 (s, 3H) *major,* 3.81 (s, 3H) *minor*, 4.19-4.33 (m, 1H) *minor*, 4.38-4.49 (m, 1H) *major*, 5.47-5.56 (m, 1H) *major*, 5.63 (brs, 1H) *minor*, 6.17 (brs, 1H) *minor*, 6.46 (brs, 1H) *major*. **^{13}C NMR** (126 MHz, CDCl$_3$, 313K): δ = 28.1 *minor* , 28.3 *major*, 33.7 *minor*, 34.4 *major*, 38.1 *major*, 38.9 *minor*, 53.0 major/minor, 53.4 *major*, 58.6 *minor*, 59.1 *major*, 69.8 *major*, 83.0 *major*, 83.7 *minor*, 119.7 (q, *J* = 320.6 Hz) *major*, 119.5 (d, *J* = 320.9 Hz) *minor*, 151.9 *minor*, 152.5 *major*, 174.7 *minor*, 175.7 *major*. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -78.4, -77.4. **IR** ν (cm^{-1}): 3201, 2980, 1682, 1685, 1368, 1180, 1158, 1012, 755, 604. **HRMS:** Anal. Calcd. for $C_{12}H_{18}F_3NO_6S$: 375.0843, found: 375.0850.

Methyl 2-benzamido-3-phenyl-2-((trifluoromethyl)sulfonamido)propanoate 208b



Synthesized from N-benzoyl phenylalanine methyl ester according to GP. 54% yield. Yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ= 3.59 (d, *J* = 13.2 Hz, 1H), 3.89 (s, 3H), 3.91 (d, *J* = 13.3 Hz, 1H), 7.07-7.12 (m, 2H), 7.27-7.29 (m, 3H), 7.38 (brs, 1H), 7.44-7.51 (m, 4H), 7.73-7.84 (m, 2H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ= 42.8, 54.1, 74.1, 119.1 (q, *J* = 321.5 Hz), 125.8, 127.3, 128.3, 128.9, 129.0, 130.2, 132.3, 132.7, 167.5,

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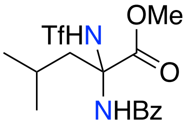
[216] T. O. Vieira, M. J. Green, *Org. Lett.* **2006**, *8*, 6143.

168.0. **^{19}F NMR** (376 MHz, CDCl$_3$): δ= -77.4. **IR** ν (cm^{-1}): 3402, 3334, 1744, 1655, 1486, 1376, 1198, 1139, 712, 608. **HRMS:** Anal. Calcd. for $C_{18}H_{17}F_3N_2NaO_5S$: 453.0702, found: 453.0668.

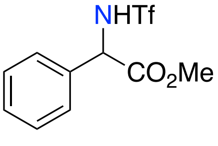
Methyl 2-benzamido-4-methyl-2-((trifluoromethyl)sulfonamido)pentanoate 208c



Synthesized from N-benzoyl leucine methyl ester according to GP. 65% yield. Yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ= 0.90 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 1.73-1.79 (m, 1H), 2.26-2.40 (m, 2H), 3.88 (s, 3H), 6.99 (s, 1H), 7.27 (s, 1H), 7.42-7.57 (m, 4H), 7.73-7.78 (m, 1H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ= 23.0, 23.7, 24.1, 45.8, 54.2, 72.9, 119.1 (q, *J* = 321.2 Hz), 127.3, 129.0, 132.7, 135.3, 167.0, 169.3. **^{19}F NMR** (376 MHz, CDCl$_3$): δ= -77.6. **IR** ν (cm^{-1}): 3334, 2956, 1736, 1648, 1523, 1298, 1197, 711, 692, 612. **HRMS:** Anal. Calcd. for $C_{15}H_{19}F_3N_2NaO_5S$: 419.0859, found: 419.0862.

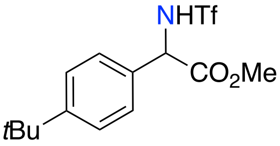
Methyl 2-phenyl-2-((trifluoromethyl)sulfonamido) acetate 208d



Synthesized from methyl phenylacetate according to GP. Data in agreement with the ones reported.[211] 40 % yield. Yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.78 (s, 3H), 5.30 (d, *J* = 8.5 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 7.32-7.36 (m, 2H), 7.37-7.42 (m, 3H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 53.7, 60.3, 119.5 (q, *J* = 320.9 Hz), 127.1, 129.4, 129.5, 134.9, 170.2. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.7.

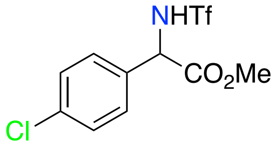
Methyl 2-(4-(*tert*-butyl)phenyl)-2-((trifluoromethyl)sulfonamido)acetate 208e



Synthesized from methyl 4- *tert*-butyl-phenylacetate according to GP. 35% yield. Yellow oil.

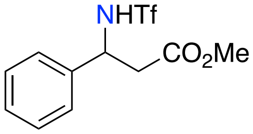
^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.31 (s, 9H), 3.77 (s, 1H), 3.79 (s, 3H), 5.24 (s, 1H), 7.24-7.25 (m, 2H), 7.37-7.44 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 31.2, 34.8, 53.4, 59.9, 119.4 (q, *J* = 320.5 Hz), 126.6,126.8, 131.6, 152.6, 170.1. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.6. **IR** ν (cm^{-1}): 3238, 2928, 1730, 1378, 1192, 1142, 756, 606. **HRMS:** Anal. Calcd. for $C_{14}H_{18}F_3NNaO_4S$: 376.0801, found: 376.0797.

Methyl 2-(4-chlorophenyl)-2-((trifluoromethyl)sulfonamido)acetate 208f



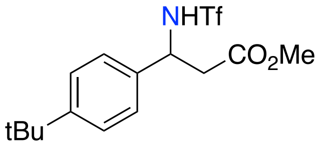
Synthesized from methyl 4-chloro phenylacetate according to GP. 42% yield. Yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 3.75 (s, 3H), 5.27 (d, *J* = 7.3 Hz, 1H), 6.20 (d, *J* = 7.3 Hz, 1H), 7.29-7.33 (m, 2H), 7.43 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 53.6, 60.2, 119.3 (q, *J* = 320.8 Hz), 127.0, 129.3, 134.8, 137.1, 171.4. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.5. **IR** ν (cm^{-1}): 3204, 2926, 1744, 1492, 1378, 1229, 1193, 1092, 772, 603. **HRMS:** Anal. Calcd. for $C_{10}H_8ClF_3NO_4S$: 329.9820, found: 329.9818.

Methyl 3-phenyl-3-((trifluoromethyl)sulfonamido) propanoate 208g



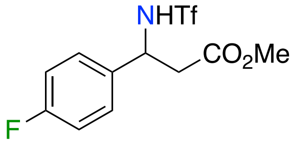
Synthesized from methyl 3-phenylpropionate according to GP. Data in agreement with the ones reported.[208] 68% yield. Yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 2.89-3.08 (m, 2H), 3.65 (s, 3H), 5.01 (dt, *J* = 9.7, 5.2 Hz, 1H), 6.60 (d, *J* = 9.0 Hz, 1H), 7.28-7.43 (m, 5H). **^{13}C NMR** (126 MHz, CDCl$_3$): δ = 40.9, 52.4, 55.4, 119.6 (q, *J* = 320.8 Hz), 126.0, 128.6, 129.1, 138.7, 171.3. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.7.

Methyl 3-(4-(*tert*-butyl)phenyl)-3-((trifluoromethyl)sulfonamido)propanoate 208h



Synthesized from 3-(4-*tert*-butyl)-phenylpropanoate according to GP. 72% yield. Yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 1.31 (s, 9H), 2.98 (dd, *J* = 1.6, 5.4 Hz, 2H), 3.66 (s, 3H), 4.99 (dt, *J* = 5.3, 9.8 Hz, 1H), 6.51 (d, *J* = 9.1 Hz, 1H), 7.20-7.25 (m, 2H), 7.35-7.44 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 31.4, 34.7, 40.7, 52.4, 55.2, 119.6 (q, *J* = 320.8 Hz), 125.7, 126.0, 135.7, 151.6, 171.4. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.7. **IR** ν (cm^{-1}): 3148, 2961, 1721, 1377, 1196, 1145, 1055, 600, 585. **HRMS:** Anal. Calcd. for $C_{15}H_{20}F_3NNaO_4S$: 390.0957, found: 390.0964.

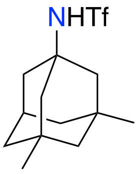
Methyl 3-(4-fluorophenyl)-3-((trifluoromethyl)sulfonamido) propanoate 208f



Synthesized from methyl 3-(4-fluorophenyl)propanoate according to GP. Data in agreement with the ones reported.[206] 73% yield. Yellow oil.

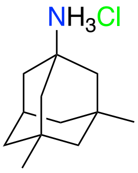
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.83-3.11 (m, 2H), 3.66 (s, 3H), 5.00 (dt, *J* = 5.2, 9.7 Hz, 1H), 6.66 (d, *J* = 9.1 Hz, 1H), 7.01-7.11 (m, 2H), 7.27-7.33 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 40.9, 52.5, 54.8, 116.1 (d, $^2J_{CF}$ = 21.8 Hz), 119.6 (q, *J* = 320.6 Hz), 127.9 (d, $^3J_{CF}$ = 8.4 Hz), 134.7 (d, $^4J_{CF}$ = 3.3 Hz), 162.6 (d, $^1J_{CF}$ = 247.8 Hz), 171.2. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -113.0, -77.4.

_N_-((1,3,5,7)-3,5-Dimethyladamantan-1-yl)-1,1,1-trifluoromethanesulfonamide 210



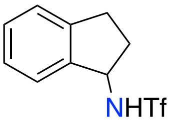
Synthesized from 1,3-dimethyl adamantane according to GP. Data in agreement with the ones reported.[211] 92% yield. Colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 6H), 1.12-1.18 (m, 2H), 1.25-1.42 (m, 4H), 1.54-1.72 (m, 4H), 1.82 (dd, *J* = 1.5, 3.2 Hz, 2H), 2.20 (p, *J* = 3.2 Hz, 1H), 4.85 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 29.9, 30.4, 33.1, 41.7, 42.1, 49.2, 50.1, 60.1, 119.3 (q, *J* = 320.9 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -78.1.

1,3-Dimethyladamantanamine hydrochloride 211



Synthesized from **6** according to the deprotection procedure for secondary amines. Data in agreement with the ones reported.[217] 92% yield. White solid.
^{1}H NMR (500 MHz, CDC13): δ = 0.85 (s, 6H), 1.08-1.20 (m, 2H), 1.24-1.45 (m, 4H), 1.58-1.80 (m, 4H), 1.88 (brs, 2H), 2.19 (brs, 1H), 8.32 (brs, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 29.7, 29.9, 32.7, 39.3, 41.9, 46.5, 49.9, 54.5.

_N_-(2,3-dihydro-1_H_-inden-1-yl)-1,1,1-trifluoromethanesulfonamide 212



Synthesized from indan according to GP. 78% yield. White solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91-2.08 (m, 1H), 2.59-2.67 (m, 1H), 2.81-2.89 (m, 1H), 2.96-3.04 (m, 1H), 5.07 (d, *J* = 5.4 Hz, 1H), 7.18-7.30 (m, 3H), 7.33-7.39 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 30.0, 35.0, 60.8, 119.9 (q, *J* = 320.8 Hz), 124.3, 125.3, 127.5, 129.2, 140.5, 143.1. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.6. **IR** ν (cm^{-1}): 3318, 2960, 1439, 1376, 1228, 1178, 1144, 1071, 751, 591. **HRMS**: Anal. Calcd. for $C_{10}H_9F_3NO_2S$: 264.0312, found: 264.0313. **m.p.**: 98-100 °C.

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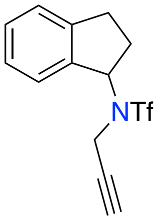
[217] N. Basílio, U. Pischel, *Chem. Eur. J.* **2016**, *22*, 15208.

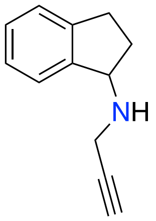
N-(2,3-Dihydro-1*H*-inden-1-yl)-1,1,1-trifluoro-*N*-(prop-2-yn-1-yl)methanesulfonamide S212a



The compound was synthesized from **212** according to literature procedure.[218] 99% yield. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (t, *J* = 2.5 Hz, 1H), 2.52-2.57 (m, 2H), 2.91 (dt, *J* = 16.1, 7.8 Hz, 1H), 3.17 (dt, *J* = 16.3, 7.0 Hz, 1H), 3.55-3.69 (m, 1H), 4.17 (d, *J* = 18.8 Hz, 1H), 5.61 (t, *J* = 7.5 Hz, 1H), 7.27-7.37 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.4, 33.9, 65.7, 73.0, 120.0 (q, *J* = 322.6 Hz), 124.8, 125.5, 127.5, 129.4, 131.4, 131. 8, 138.0, 144.4. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -76.0. **HRMS:** Anal. Calcd. for $C_{13}H_{12}F_3NNaO_2S$ 326.0433; found 326.0430. **IR** ν (cm^{-1}): 2926, 1396, 1227, 1191, 1142, 760, 622.

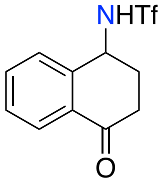
N-(Prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine 213



The compound was synthesized from **S9a** according to the deprotection protocol for tertiary sulfonamides. Data in agreement with the ones reported.[219] 78% yield. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62 (brs, 1H), 1.84-1.90 (m, 1H), 2.26 (t, *J* = 2.4 Hz, 1H), 2.37-2.44 (m, 1H), 2.80-2.86 (m, 1H), 3.01-3.07 (m, 1H), 3.53 (dd, *J* = 3.9, 2.4 Hz, 2H), 4.42 (dd, *J* = 6.8, 5.2 Hz, 1H), 7.17-7.25 (m, 3H), 7.33 7.38 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.6, 33.5, 36.3, 62.0, 71.5, 82.6, 124.3, 125.0, 126.4, 127.8, 144.0, 144.6.

1,1,1-Trifluoro-*N*-(4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)methanesulfonamide 215



Synthesized from α-tetralone according to GP. 55% yield. Red oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28-2.36 (m, 1H), 2.48-2.56 (m, 1H), 2.66-2.74 (m, 1H), 2.82-2.90 (m, 1H), 4.99 (td, *J* = 4.2, 8.6 Hz, 1H), 5.67 (d, *J* = 9.0 Hz, 1H), 7.45-7.47 (m, 1H), 7.53-7.56 (m, 1H), 7.64-7.68 (m, 1H), 8.01 (dd, *J* = 1.5, 7.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 30.9, 35.1, 53.7, 119.8 (q, *J* = 320.7 Hz), 127.7, 127.8, 129.4, 131.8, 134.9, 140.9, 196.8. **^{19}F NMR** (376

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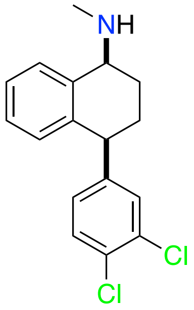
[218] Y. Liu, A. De Nisi, A. Cerveri, M. Monari, M. Bandini, *Org. Lett.* **2017**, *19*, 5034.

[219] G.A. Aleku, S. P. France, H. Man, J. Mangas-Sanchez, S. L. Montgomery, M. Sharma, F. Leipold, S. Hussain, G. Grogan, N. J. Turner, *Nat. Chem.* **2017**, *9*, 961.

MHz, $CDCl_3$): δ = -77.4. **IR** ν (cm^{-1}): 3186, 2923, 1735, 1376, 1185, 1029, 766, 596. **HRMS**: Anal. Calcd. for: $C_{11}H_9F_3NO_3S$ 292.0261, found: 292.0251.

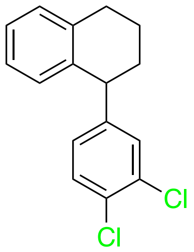
(1*S*,4*S*)-4-(3,4-Dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine 216



Synthesized from **12** after the following sequence: A) methylation of the sulfonamide,[205] B) formation of the enol-triflate,[220] C) Suzuki coupling,[200] D) Catalytic hydrogenation, E) Deprotection for tertiary sulfonamides. Data in agreement with the ones reported.[205] 52% yield (over 5 steps). Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.84-1.95 (m, 1H), 1.96-2.17 (m, 3H), 2.53 (s, 3H), 3.33 (brs, 1H), 3.81 (t, J = 4.3 Hz, 1H), 3.97 (dd, J= 9.3, 5.5 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 7.00 (dd, J = 8.3, 2.1 Hz, 1H), 7.13 (td, J = 7.5, 1.4 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 2.1 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.43-7.40 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 25.4, 28.4, 33.7, 45.4, 57.3, 126.9, 127.8, 128.4, 129.5, 130.1, 130.3, 130.9, 131.2, 132.7, 137.9, 139.0, 147.2.

1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalene 217



Synthesized from 3,4-dihydronaphthalen-1-trifluoromethanesulfonate and 3,4-Dichlorobenzene boronic acid according to literature procedure; followed by catalytic hydrogenation. Data in agreement with the ones reported.[200] 65% yield (over two steps). Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67-1.96 (m, 3H), 2.06-2.24 (m, 1H), 2.77-3.02 (m, 2H), 4.11 (t, *J* = 6.4 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.94 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.01-7.13 (m, 1H), 7.13-7.24 (m, 3H), 7.35 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 20.8, 29.7, 33.2, 45.0, 126.0, 126.5, 128.4, 129.3, 130.0, 130.1, 130.3, 130.8, 132.3, 137.7, 138.1, 148.0.

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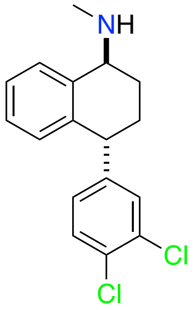
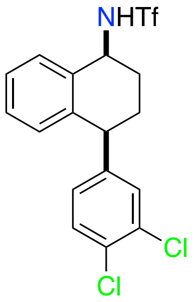
[220] Y. S. Hon, T. W. Tseng, C. -Y. Cheng, *Chem. Comm.* **2009**, *53*, 5618.

N-((1*S*,4*R*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-1,1,1-trifluoro-methanesulfonamide 218a



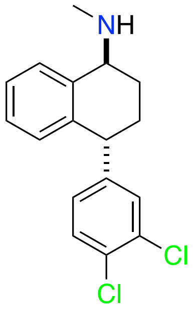
Synthesized from **217** according to GP (1:0.6 dr). 72% yield. Yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 1.86-2.00 (m, 2H), 2.24-2.37 (m, 2H), 4.16 (t, *J* = 6.2 Hz, 1H), 4.88-4.99 (m, 1H), 5.14 (d, *J* = 8.8 Hz, 1H), 6.78-6.94 (m, 2H), 7.11-7.15 (m, 1H), 7.20-7.24 (m, 1H), 7.30-7.32 (m, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ = 29.5, 44.2, 54.4, 119.8 (q, *J* = 326.8 Hz), 127.9, 128.1, 128.5, 128.9, 130.6, 130.7, 130.8, 132.7, 134.9, 138.8, 146.2. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.4. **IR** ν (cm^{-1}): 3311, 2929, 1373, 1186, 1143, 1029, 821, 755, 601. **HRMS:** Anal. Calcd. for $C_{17}H_{13}Cl_2F_3NO_2S$ 422.0002; found 422.0002.

N-((1*S*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-1,1,1-trifluoro-methanesulfonamide 218b



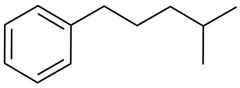
Synthesized from **14** according to GP. 52% yield. Yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 1.92-2.00 (m, 1H), 2.10-2.18 (m, 3H), 4.06 (dd, *J* = 8.5, 5.5 Hz, 1H), 4.89 (dt, *J* = 9.5, 5.3 Hz, 1H), 5.32 (d, *J* = 8.4 Hz, 1H), 6.89 (dt, *J* = 7.8, 1.2 Hz, 1H), 6.95 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.26 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.31-7.36 (m, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.47-7.52 (m, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 28.7, 29.2, 44.5, 54.2, 119.9 (q, *J* = 321.0 Hz), 127.9, 128.2, 129.1, 129.3, 130.5, 130.8, 131.0, 132.8, 134.5, 138.9, 146.1. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -77.3. **IR** ν (cm^{-1}): 3311, 2929, 1373, 1186, 1143, 1029, 821, 755, 601. **HRMS:** Anal. Calcd. for $C_{17}H_{13}Cl_2F_3NO_2S$ 422.0002; found 422.0004.

(1*S*,4*R*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine 219



Synthesized from **218a** after methylation of the sulfonamide;[205] followed by the deprotection procedure for tertiary sulfonamides. Data in agreement with the ones reported.[221] 80% yield (over 2 steps). Colorless oil. **^{1}H NMR** (500 MHz, CDCl$_3$): δ = 1.63-1.87 (m, 2H), 1.96-2.16 (m, 4H), 2.52 (s, 3H), 3.91 (t, *J* = 5.0 Hz, 1H), 4.14 (t, *J* = 5.8 Hz, 1H), 6.80-6.89 (m, 2H), 7.10 (d, *J* = 2.1 Hz, 1H), 7.10 - 7.19 (m, 1H), 7.23 (d, *J* = 6.7 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 24.2, 28.7, 33.0, 44.2, 56.9, 126.9, 127.6, 128.1, 128.7, 130.1, 130.22, 130.2, 130.6, 132.3, 138.4, 147.3.

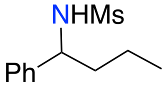
(4-Methylpentyl)benzene 222c



Synthesized from benzaldehyde and isopentyltriphenyl phosphonium bromide with a Wittig reaction followed by application of the catalytic hydrogenation protocol. Data in agreement with the ones reported.[222] 95% yield. Colorless oil.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.79 (dd, *J* = 6.6, 0.7 Hz, 6H), 1.04-1.22 (m, 2H), 1.41-1.64 (m, 3H), 2.35-2.65 (m, 2H), 7.04-7.10 (m, 2H), 7.12-7.25 (m, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ = 22.7, 28.1, 29.5, 36.4, 38.8, 125.7, 128.4, 128.5, 143.1.

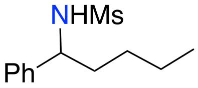
***N*-(1-Phenylbutyl)methanesulfonamide 223a**



Synthesized from butylbenzene according to GP with NH$_2$Ms (1.0 equiv). 35% yield. Colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.92 (t, *J* = 7.4 Hz, 3H), 1.20-1.44 (m, 2H), 1.67-1.86 (m, 2H), 2.54 (s, 3H), 4.42-4.47 (m, 1H), 4.76 (d, *J* = 7.3 Hz, 1H), 7.30 (td, *J* = 6.8, 1.6 Hz, 3H), 7.37 (ddd, *J* = 7.7, 6.1, 1.1 Hz, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 13.7, 19.4, 39.9, 42.0, 58.2, 126.8, 128.1, 129.1, 141.7. **IR** ν (cm^{-1}): 3321, 2924, 1425, 1367, 1188, 1143, 1028, 999, 698, 623, 514. **HRMS:** Anal. Calcd. for $C_{11}H_{17}NNaO_2S$: 250.0872; found: 250.0868.

***N*-(1-Phenylpentyl)methanesulfonamide 223b**



Synthesized from pentylbenzene according to GP with NH$_2$Ms (1.0 equiv). 30% yield. Colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.87 (t, *J* = 7.1 Hz, 3H), 1.18-1.37 (m, 4H), 1.72-1.86 (m, 2H), 2.54 (s, 3H), 4.40-4.45 (m, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 7.27-7.33 (m, 2H), 7.33-7.42 (m, 3H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 14.0, 22.4, 28.3, 37.6, 42.1, 58.5,

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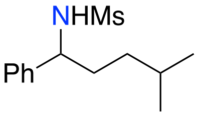
[221] J. Liu, C. -G. Cao, H. -B. Sun, X. Zhang, D. Niu, *J. Am. Chem. Soc.* **2016**, *138*, 13103.
[222] U. P. N. Tran, K. J. Hock, C. P. Gordon, R. M. Koenigs, T. V. Nguyen, *Chem. Commun.* **2017**, *53*, 4950.

126.8, 128.1, 129.1, 141.7. **HRMS:** Anal. Calcd. for $C_{12}H_{19}NNaO_2S$: 264.1029; found: 264.1039. **IR** ν (cm^{-1}): 3329, 2927, 1611, 1304, 1145, 897, 747.

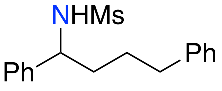
N-(4-Methyl-1-phenylpentyl)methanesulfonamide 223c



Synthesized from (4-methylpentyl)benzene according to GP with NH_2Ms (1.0 equiv). 30% yield. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 1.6 Hz, 3H), 0.86 (d, *J* = 1.6 Hz, 3H), 1.03-1.15 (m, 1H), 1.49-1.59 (m, 2H), 1.74-1.86 (m, 2H), 2.53 (s, 3H), 4.39-4.42 (m, 1H), 4.72 (s, 1H), 7.27-7.43 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.5, 22.6, 27.8, 35.2, 35.8, 42.0, 58.8, 126.8, 128.1, 129.1, 141.7. **HRMS:** Anal. Calcd. for $C_{13}H_{21}NNaO_2S$: 278.1185; found: 278.1180. **IR** ν (cm^{-1}): 3279, 2955, 1317, 1150, 980, 759, 702, 517.

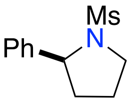
N-(1,4-Diphenylbutyl)methanesulfonamide 223d



Synthesized from 1,4-diphenylbutane according to GP with NH_2Ms (1.0 equiv). 29% yield. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59-1.86 (m, 4H), 2.46 (s, 3H), 2.55 (t, *J* = 7.4 Hz, 2H), 4.45-4.50 (m, 1H), 4.53 (d, *J* = 7.2 Hz, 1H), 6.96-7.34 (m, 10H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 27.9, 35.4, 37.2, 42.0, 58.4, 126.1, 126.7, 128.2, 128.5, 128.8, 129.2, 141.4, 141.7. **IR** ν (cm^{-1}): 3280, 2930, 1313, 1146, 976, 751, 700, 515. **HRMS:** Anal. Calcd. for $C_{17}H_{20}NO_2S$: 302.1220; found: 302.1223.

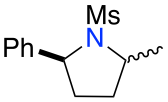
1-(Methylsulfonyl)-2-phenylpyrrolidine 224a



Synthesized from **223a** according to GP2. Data in agreement with the ones reported.[223] 56% yield. White solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90-2.07 (m, 3H), 2.35-2.44 (m, 1H), 2.68 (s, 3H), 3.55-3.72 (m, 2H), 4.90 (dd, *J* = 8.1, 4.1 Hz, 1H), 7.28-7.38 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 24.7, 36.4, 38.4, 49.2, 63.2, 126.5, 127.6, 128.7, 142.9.

2-Methyl-1-(methylsulfonyl)-5-phenylpyrrolidine 224b



Synthesized from **223b** according to GP2. 59% yield (3:2 d.r.). Colorless oil.

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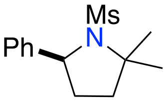
[223] E. A. Wappes, S. C. Fosu, T. C. Chopko, D. A. Nagib, *Angew. Chem. Int. Ed.* **2016**, *55*, 9974.

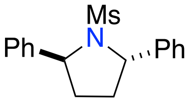
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.3 Hz, 3H, *major*), 1.47 (d, *J* = 6.3 Hz, 3H, *minor*), 1.64-1.71 (m, 2H *major*), 1.83-1.90 (m, 2H, *minor*), 2.00-2.16 (m, 2H, *major*), 2.30-2.36 (m, 2H, *minor*), 2.54 (s, 3H, *major*), 2.67 (s, 3H, *minor*), 4.13-4.19 (m, 1H, *minor*), 4.26-4.36 (m, 1H, *major*), 4.86 (d, *J* = 6.6 Hz, 1H, *minor*), 4.89 (d, *J* = 9.4 Hz, 1H, *major*), 7.28-7.43 (m, 10H, *major*+*minor*). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 21.4 (*major*), 22.4 (*minor*), 29.7 (*major*), 31.5 (*minor*), 32.5 (*minor*), 33.2 (*major*), 39.2 (*minor*), 41.4 (*major*), 57.4 (*minor*), 57.5 (*major*), 62.7 (*major*), 64.7 (*minor*), 126.5 (*minor*), 126.7 (*major*), 127.4 (*minor*), 127.5 (*major*), 128.6 (*major*), 128.8 (minor), 142.4 (*minor*), 142.9 (*major*). **HRMS:** Anal. Calcd. for $C_{12}H_{17}NNaO_2S$: 262.0872; found: 262.0879.

2,2-Dimethyl-1-(methylsulfonyl)-5-phenylpyrrolidine 224c



Synthesized from **223c** according to GP2. 60% yield. Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.57 (s, 3H), 1.72 (s, 3H), 1.74-1.84 (m, 2H), 2.08-2.20 (m, 1H), 2.49 (ddd, *J* = 12.9, 6.5, 2.6 Hz, 1H), 2.56 (s, 3H), 4.88-5.15 (m, 1H), 7.31-7.38 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 27.2, 28.5, 32.1, 40.6, 42.7, 64.7, 66.6, 126.6, 127.4, 128.6, 143.3. **IR** ν (cm^{-1}): 2928, 1322, 1144, 758, 701, 518. **HRMS:** Anal. Calcd. for $C_{13}H_{19}NNaO_2S$: 276.1029; found: 276.1029.

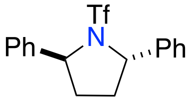
1-(Methylsulfonyl)-2,5-diphenylpyrrolidine 224d



Synthesized from **223d** according to GP2. 87% yield. Colorless oil. Alternatively synthesized from **222d** according to GP with NH_2Ms (1.0 equiv), PhI(*m*CBA)$_2$ (4.0 equiv) and 20% mol of I_2. 68% yield. Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.84-2.00 (m, 2H), 2.34 (s, 3H), 2.72 (td, *J* = 7.9, 2.5 Hz, 2H), 5.23 (d, *J* = 7.7 Hz, 2H), 7.28-7.45 (m, 10H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 33.6, 41.8, 64.5, 126.5, 127.7, 128.8, 143.3. **IR** ν (cm^{-1}): 2929, 1322, 1141, 1076, 963, 754, 699, 513. **HRMS:** Anal. Calcd. for $C_{17}H_{19}NNaO_2S$: 324.1029; found: 324.1039.

2,5-Diphenyl-1-((trifluoromethyl)sulfonyl)pyrrolidine 225b

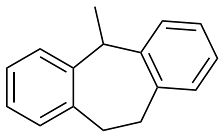


Synthesized from **222d** according to GP with NH_2Tf (1.0 equiv), PhI(*m*CBA)$_2$ (4.0 equiv) and 20% mol of I_2. 85% yield. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93-2.05 (m, 2H), 2.79-2.83 (m, 2H), 5.34 (d, *J* = 7.8 Hz, 2H), 7.29-7.46 (m, 10H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 33.5, 66.4, 119.5 (q, *J* = 328.8 Hz), 126.4, 128.1, 128.8, 137.9. **^{19}F NMR** (376 MHz, $CDCl_3$): δ =-75.3. **IR** ν (cm^{-}

^{1}): 2924, 1470, 1365, 1228, 755, 698. **HRMS:** Anal. Calcd. for $C_{17}H_{16}F_3NNaO_2S$: 378.0746; found: 378.0744.

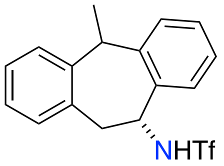
5-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene 226



Synthesized from dibenzosuberone and methyltriphenyl phosphonium bromide with a Wittig reaction followed by application of the catalytic hydrogenation protocol. Data in agreement with the ones reported.[224] 98% yield. Colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (d, *J* = 7.4 Hz, 2H), 3.18-3.27 (m, 2H), 4.44 (q, *J* = 7.4 Hz, 1H), 7.08-7.17 (m, 6H), 7.22-7.25 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 22.1, 33.3, 43.8, 126.3, 126.4, 127.5, 130.1, 139.3, 143.3.

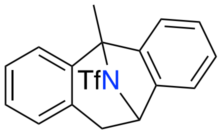
1,1,1-Trifluoro-*N*-(5-methyl-10,11-dihydro-5*H*-dibenzo[7]annulen-10-yl)methane sulfonamide 227a



Synthesized from **226** according to GP. 85% yield. Orange solid. Isolated and characterized only the major diasteroisomer.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67 (d, *J* = 7.5 Hz, 3H), 3.24 (dd, *J* = 14.5, 6.6 Hz, 1H), 3.90 (dd, *J* = 14.5, 2.5 Hz, 1H), 4.30 (q, *J* = 7.6 Hz, 1H), 4.59 (d, *J* = 9.6 Hz, 1H), 5.20 (ddd, *J* = 9.3, 6.5, 2.4 Hz, 1H), 7.20-7.33 (m, 7H), 7.38-7.53 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 24.6, 38.8, 48.0, 57.6, 119.8 (q, *J* = 320.9 Hz), 127.5, 127.5, 128.1, 129.0, 129.4, 131.2, 131.8, 132.7, 133.8, 136.2, 142.5, 143.9. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -77.6. **IR** ν (cm^{-1}): 3282, 2923, 1326, 1154, 1090, 813, 751, 662, 541. **HRMS:** Anal. Calcd. for $C_{17}H_{16}F_3NNaO_2S$: 378.0746; found: 378.0739.

5-Methyl-12-((trifluoromethyl)sulfonyl)-10,11-dihydro-5*H*-5,10-epiminodibenzo [7]annulene 228a



Synthesized from **227a** according to GP2. 62% yield. Orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.31 (s, 3H), 2.86 (d, *J* = 17.2 Hz, 1H), 3.84 (dd, *J* = 17.2, 5.8 Hz, 1H), 5.47 (d, *J* = 5.8 Hz, 1H), 6.77-7.45 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 17.2, 35.3, 63.8, 70.6, 118.7, 119.5 (d, *J* = 321.6 Hz), 121.2, 121.3, 126.7, 128.1, 128.2, 128.5, 130.8, 131.3, 134.3, 138.5, 148.7.

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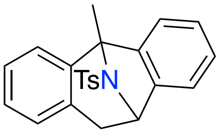
[224] R. Schwesinger, R. Link, P. Wenzl, S. Kossek, *Chem. Eur. J.* **2006**, *12*, 438.

^{19}F NMR (376 MHz, $CDCl_3$) δ = -78.0. **IR** ν (cm^{-1}): 1375, 1187, 1025, 758, 743, 652, 591, 579. **HRMS:** Anal. Calcd. for $C_{17}H_{14}F_3NNaO_2S$: 376.0590; found: 376.0584.

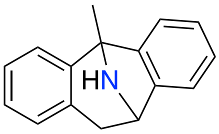
5-Methyl-12-tosyl-10,11-dihydro-5*H*-5,10-epiminodibenzo[7]annulene 228b



Synthesized from **226** according to GP with NH_2Ts (1.0 equiv), PhI(*m*CBA)$_2$ (4.0 equiv) and 20% mol of I_2. 52% yield. Yellow solid. Alternatively, synthesized from **227b** by anodic oxidation.[225] 88% yield. Yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 3H), 2.30 (s, 3H), 2.64 (d, *J* = 17.3 Hz, 1H), 3.57 (dd, *J* = 17.3, 5.8 Hz, 1H), 5.50 (d, *J* = 5.6 Hz, 1H), 6.69 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.94-7.07 (m, 5H), 7.14 (ddd, *J* = 8.6, 7.0, 1.3 Hz, 2H), 7.17-7.24 (m, 1H), 7.27-7.36 (m, 1H), 7.58 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 18.2, 21.5, 33.4, 62.2, 67.6, 121.1, 121.6, 126.2, 127.3, 127.4, 127.5, 127.6, 129.0, 130.3, 131.8, 138.8, 140.2, 141.9, 142.9, 149.9. **IR** ν (cm^{-1}): 2921, 1330, 155, 1090, 748, 679, 567, 542. **HRMS:** Anal. Calcd. for $C_{23}H_{21}NNaO_2S$: 398.1185; found: 398.1182.

5-Methyl-10,11-dihydro-5*H*-5,10-epiminodibenzo[7]annulene 229



Synthesized from **228a** according to the deprotection procedure for secondary sulfonamides. Data in agreement with the ones reported.[226] 83% yield. White solid.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.77 (d, *J* = 7.1 Hz, 3H), 4.54 (q, *J* = 7.1 Hz, 1H), 4.69 (d, *J* = 8.7 Hz, 1H), 5.38 (d, *J* = 8.7 Hz, 1H), 7.10-7.24 (m, 5H), 7.25-7.31 (m, 1H), 7.32-7.37 (m, 1H), 7.62 (dd, *J* = 7.5, 1.5 Hz, 1H). **^{13}C NMR** (101 MHz, CD_3OD): δ = 16.9, 30.7, 75.6, 79.6, 124.5, 125.2, 126.7, 127.0, 127.5, 127.9, 128.5, 132.5, 139.6, 140.3, 143.7, 145.7.

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[225] S. Herold, D. Bafaluy, K. Muñiz, *Green Chem.* **2018**, *20*, 3191.
[226] G. A. Molander, E. D. Dowdy, *J. Org. Chem.* **1999**, *64*, 6515.

3.4.4 Control Experiments

EPR measurments for the detection of the nitrogen-centered radical

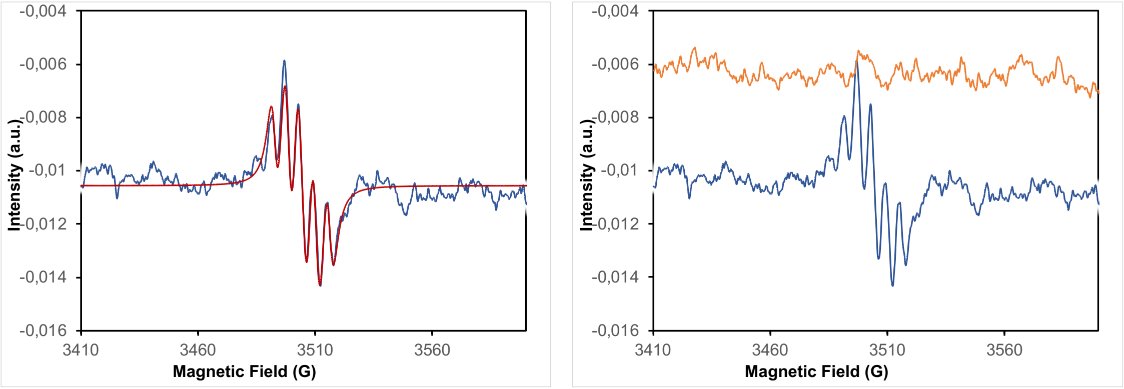


Figure 4.2: EPR Detection of N-centered radical intermediate. Left: EPR silent experimental spectrum (orange) and EPR spectrum for the reaction mixture of molecular iodine, $TfNH_2$ and $PhI(O_2CAr)_2$ [Ar = 4-Br-C_6H_4] after irradiation (blue). Right: Overlay between the experimental (blue) and the simulated (red) spectrum.

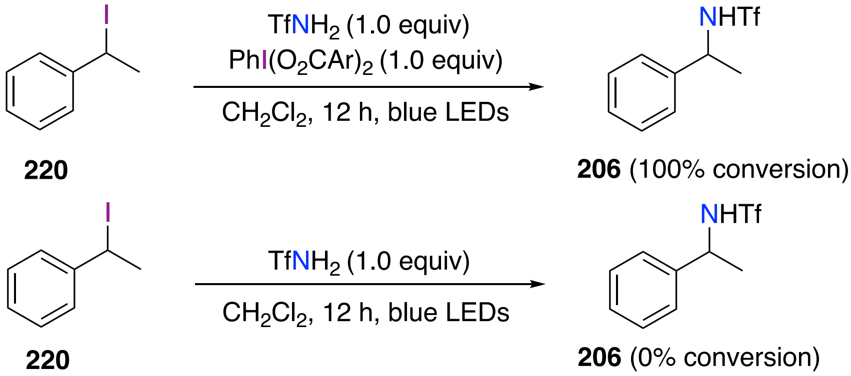
Three different stock solutions were prepared: In three Schlenk tubes (evacuated and backfilled with argon) were added respectively molecular iodine (51 mg, 0.2 mmol) in toluene (2 mL) in the first, trifluoromethanesulfonamide (30 mg, 0.2 mmol) in toluene (2 mL) in the second and the PhI(*p*BBA)$_2$ (120 mg, 0.2 mmol) in toluene (2 mL) in the third. Four different measurements were performed. Into the first EPR tube (evacuated and backfilled with argon) were added 0.4 mL of the stock solution of PhI(*p*BBA)$_2$ and 0.4 mL of the stock solution of molecular iodine. Into the second EPR tube (evacuated and backfilled with argon) stock solutions of PhI(*p*BBA)$_2$ (0.4 mL) and trifluoromethanesulfonamide (0.4 mL) were introduced successively. The third EPR tube (evacuated and backfilled with argon) was charged successively with trifluoromethanesulfonamide (0.4 mL) and molecular iodine (0.4 mL) stock solutions. Finally, into the fourth EPR tube (evacuated and backfilled with argon) were added stock solutions of all three components (I_2, NH_2Tf, PhI(*p*BBA)$_2$). The first three samples were found to be EPR silent, while only the fourth one reveled a clear image of the nitrogen-centered radical (Fig. 4.2 left).

The spectral data was collected at 298 K with the following spectrometer settings: g-factor = 2.00322, microwave power = 2.02 mW; center field = 3510.25 G, sweep width

= 200 G, sweep time = 30 s, modulation frequency = 100 KHz, modulation amplitude = 1 G, power attenuation = 20 dB, time constant = 0.01 ms, conversion time = 15 ms, gain = 30 dB.

The simulated spectrum was generated applying the Spinfit module of the Xenon software. Lineshape was evaluated from curve fit to a Lorentzian function.

Control experiment for the confirmation of intermediate **VI**



220 → **206** (100% conversion)

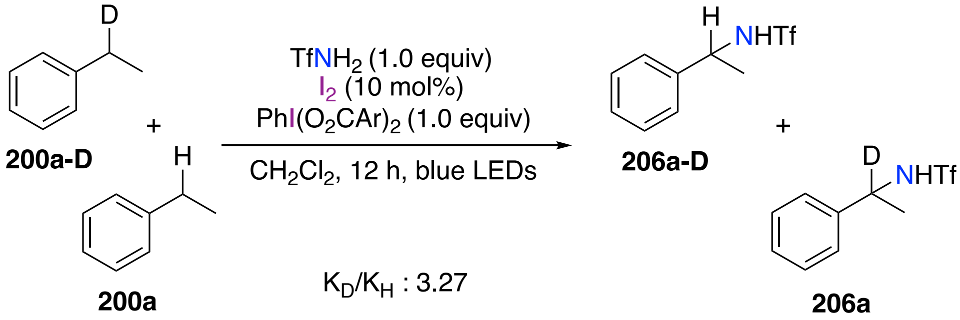
220 → **206** (0% conversion)

1-Iodoethyl benzene **220** (46 mg, 0.2 mmol, 1.0 equiv), triflamide (30 mg, 0.2 mmol, 1 equiv) and PhI(*p*BBA)$_2$ (121 mg, 0.20 mmol, 1.0 equiv) were added into a dried Schlenk tube (evacuated and backfilled with argon), equipped with a magnetic stir bar. 2 mL of absolute dichloromethane were added and the reaction mixture was irradiated under blue LED light for 12 h.

1-Iodoethyl benzene **220** (46 mg, 0.2 mmol, 1.0 equiv) and triflamide (30 mg, 0.2 mmol, 1 equiv) were added into another dried Schlenk tube (evacuated and backfilled with argon), equipped with a magnetic stir bar. 2 mL of absolute dichloromethane were added and the reaction mixture was irradiated under blue LED light for 12 h.

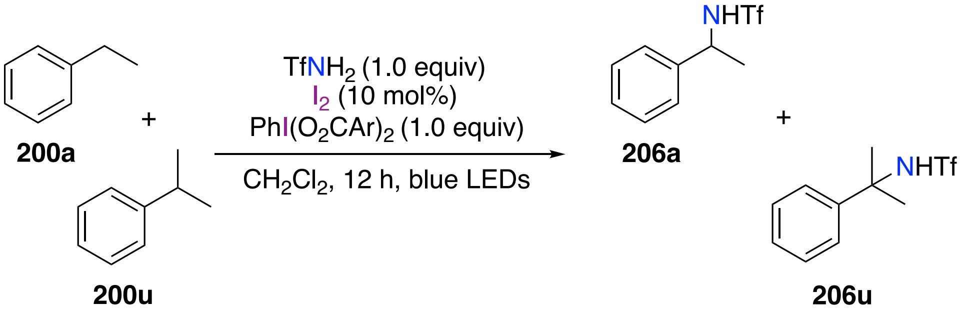
After that time, dichloromethane was added to both reactions and both mixtures were washed with an aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was analyzed by ^1H NMR indicating full conversion of the starting material to the product **206** only for the reaction from top equation where the iodine(III) oxidant was present. In contrast, the second reaction from bottom equation led to no conversion.

Determination of the Kinetic Isotope Effect



The kinetic isotope effect for the hydrogen atom abstraction was determined by an intramolecular control experiment with isotopic labeled starting material **200a-d$_1$**, which was synthesized according to a literature procedure and submitted to the optimized reaction conditions. After 12 h with blue light irradiation, the solvent was removed and the crude was dissolved in $CDCl_3$ and analyzed by ^1H NMR. Analysis of the NMR spectrum revealed a KIE of 3.27 indicating that the hydrogen atom abstraction is the rate limiting step of the catalytic cycle.

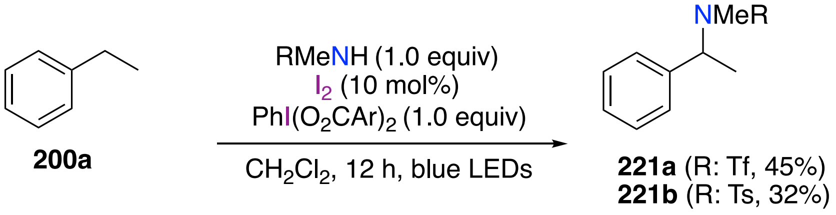
Intermolecular competition experiment for determining the site-selectivity regarding C-H bond selection.



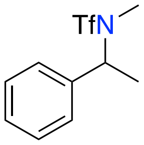
An intermolecular control experiment was conducted by submitting to reaction an equimolar mixture of ethylbenzene **200a** and cumene **200u**, in order to study the site-selectivity regarding C-H bond selection.

Ethylbenzene (25 µL, 0.2 mmol, 1.0 equiv), cumene (28 µL, 0.2 mmol, 1.0 equiv), triflamide (30 mg, 0.2 mmol, 1 equiv), I_2 (5 mg, 0.02 mmol, 10 mol%) and PhI(*p*BBA)$_2$ (241 mg, 0.40 mmol, 2.0 equiv) were charged into a dried Schlenk tube (evacuated and backfilled with argon), equipped with a magnetic stir bar. 2 mL of absolute dichloromethane were added and the reaction mixture was irradiated under blue LEDs for 12 h. Dichloromethane was added and the mixture was washed with an aqueous solution of $Na_2S_2O_3$ and then with an aqueous saturated solution of $NaHCO_3$. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was analyzed by ^{1}H NMR revealing clean conversion (65%) of ethylbenzene to the corresponding aminated derivative **206a**, together with unreacted cumene.

Control experiment in order to exclude nitrene pathways.

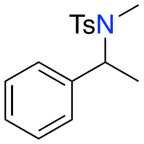


1,1,1-Trifluoro-*N*-methyl-*N*-(1-phenylethyl)methanesulfonamide 3a



Synthesized from ethylbenzene according to GP. 44% yield. Colorless oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 1.66 (d, *J* = 7.1 Hz, 3H), 2.76 (d, *J* = 1.1 Hz, 3H), 5.32 (q, *J* = 7.1 Hz, 1H), 7.36-7.47 (m, 5H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 29.4, 29.7, 57.0, 120.2 (q, *J* = 323.0 Hz), 127.3, 128.4, 128.8, 137.9. **^{19}F NMR** (376 MHz, CDCl$_3$): δ = -76.0. **IR** ν (cm^{-1}): 2918, 2950, 1462, 1389, 1260, 801, 594. **HRMS:** Anal. Calcd. for $C_{10}H_{12}NNaO_2S$: 290.0433; found: 290.0435.

N,4-Dimethyl-*N*-(1-phenylethyl)benzenesulfonamide 3b



Synthesized from ethylbenzene according to GP. Data in agreement with the ones reported.[227] 32% yield. White solid.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.29 (d, *J* = 7.1 Hz, 3H), 2.44 (s, 3H), 2.57 (s, 3H), 5.26-5.33 (m, 1H), 7.27-7.38 (m, 7H), 7.69-7.77 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 15.4, 21.7, 28.5, 54.9, 127.3, 127.4, 127.7, 128.5, 129.8, 137.4, 140.1, 143.2.

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[227] D. A. Powell, H. Fan, *J. Org. Chem.* **2010**, *75*, 2726.

4.3.5 X-ray analytical data

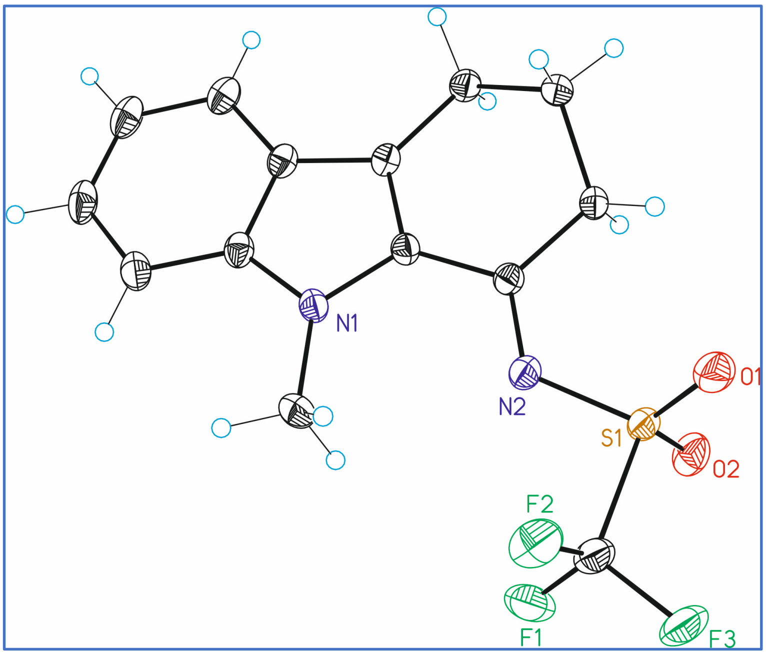

Table 4.5: Crystal data and structure refinement for **206t**.

Identification code	mo_4APB56_0m	
Empirical formula	C14 H13 F3 N2 O2 S	
Formula weight	330.32	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.5365(6)Å	α= 67.801(2)°.
	b = 9.1582(7)Å	β= 83.780(2)°.
	c = 11.1039(8)Å	γ = 80.623(2)°.
Volume	699.19(9) Å^3	
Z	2	
Density (calculated)	1.569 Mg/m^3	
Absorption coefficient	0.275 mm^{-1}	
F(000)	340	
Crystal size	0.12 x 0.04 x 0.04 mm^3	
Theta range for data collection	1.983 to 30.149°.	
Index ranges	-10<=h<=10,-12<=k<=12,-15<=l<=11	
Reflections collected	8721	
Independent reflections	3499[R(int) = 0.0345]	
Completeness to theta =30.149°	84.799995%	

Absorption correction	Multi-scan
Max. and min. transmission	0.989 and 0.723
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3499/ 0/ 200
Goodness-of-fit on F^2	1.032
Final R indices [I>2sigma(I)]	R1 = 0.0356, wR2 = 0.0949
R indices (all data)	R1 = 0.0381, wR2 = 0.0969
Largest diff. peak and hole	0.369 and -0.498 e.Å^{-3}

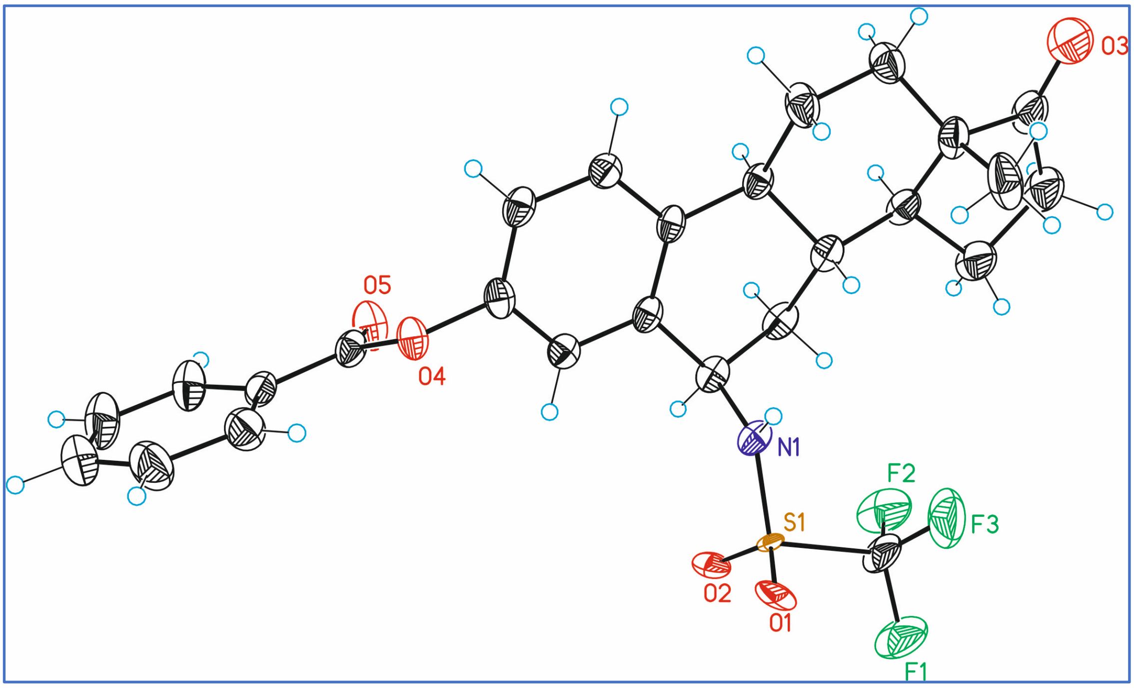

Table 4.6: Crystal data and structure refinement for compound **206ab**.

Identification code	CCDC-1869454	
Empirical formula	C26 H26 F3 N O5 S	
Formula weight	521.54	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 11.4619(9)Å	α = 90°.
	b = 7.4835(7)Å	β = 107.621(2)°.
	c = 15.2816(12)Å	γ = 90°.
Volume	1249.28(18) $Å^3$	
Z	2	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.190 mm^{-1}	
F(000)	544	
Crystal size	0.75 x 0.15 x 0.05 mm^3	
Theta range for data collection	1.864 to 25.705°.	
Index ranges	-13<=h<=13,-9<=k<=8,-18<=l<=18	

Reflections collected	4515
Independent reflections	4515[R(int) = ?]
Completeness to theta =25.705°	99.6%
Absorption correction	Multi-scan
Max. and min. transmission	0.991 and 0.762
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4515/ 118/ 389
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0416, wR2 = 0.0996
R indices (all data)	R1 = 0.0525, wR2 = 0.1038
Flack parameter	x =0.05(6)
Largest diff. peak and hole	0.186 and -0.243 e.Å^{-3}

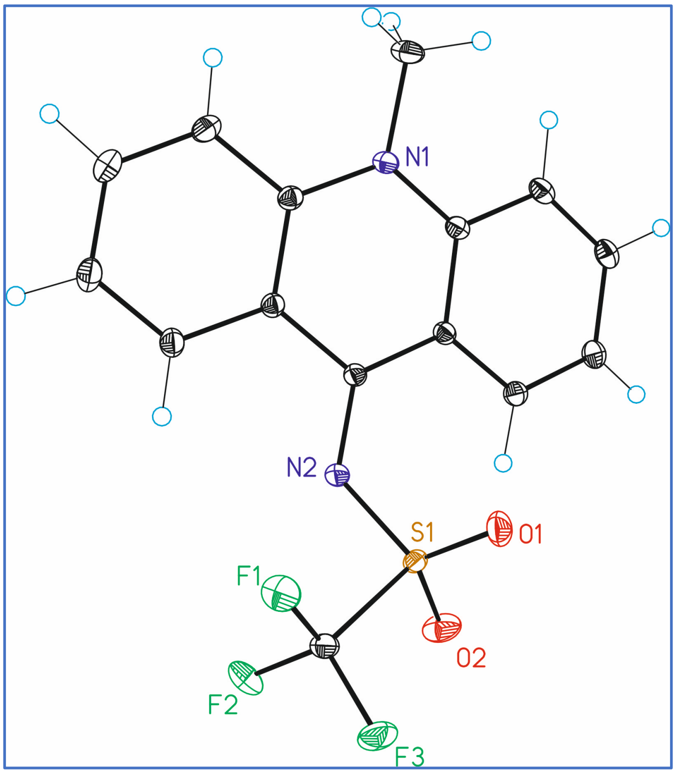

Table 4.7: Crystal data and structure refinement for **206ac**.

Identification code	3APB52	
Empirical formula	C16 H12 Cl3 F3 N2 O2 S1	
Formula weight	459.68	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.2645(2)Å	α= 91.1076(19)°.
	b = 10.0028(2)Å	β = 113.531(2)°.
	c = 10.5068(2)Å	γ = 91.7078(19)°.
Volume	891.79(4) Å^3	
Z	2	
Density (calculated)	1.712 Mg/m^3	
Absorption coefficient	0.676 mm^{-1}	
F(000)	464	
Crystal size	0.20 x 0.10 x 0.01 mm^3	
Theta range for data collection	2.888 to 40.808°.	
Index ranges	-16<=h<=17,-14<=k<=18,-18<=l<=19	
Reflections collected	20327	
Independent reflections	10394[R(int) = 0.0138]	

Completeness to theta =40.808°	89.5%
Absorption correction	Multi-scan
Max. and min. transmission	0.823 and 0.633
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10394/ 0/ 292
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0226, wR2 = 0.0690
R indices (all data)	R1 = 0.0247, wR2 = 0.0699
Largest diff. peak and hole	0.690 and -0.531 e.Å^{-3}

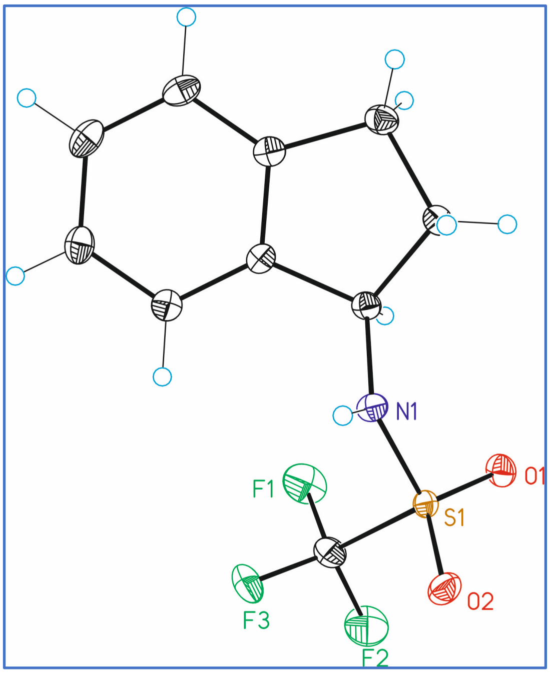

Table 4.8: Crystal data and structure refinement for compound **212**.

Identification code	CCDC-1869455	
Empirical formula	C10 H10 F3 N O2 S	
Formula weight	265.25	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.8155(4)Å	α= 90°.
	b = 5.0729(2)Å	β = 90.8009(11)°.
	c= 21.8825(8)Å	γ = 90°.
Volume	1089.49(7) Å^3	
Z	4	
Density (calculated)	1.617 Mg/m^3	
Absorption coefficient	0.328 mm^{-1}	
F(000)	544	
Crystal size	0.20 x 0.10 x 0.01 mm^3	
Theta range for data collection	1.861 to 31.062°.	
Index ranges	-14<=h<=13,-7<=k<=6,-31<=l<=19	
Reflections collected	11307	

Independent reflections	3356[R(int) = 0.0246]
Completeness to theta =31.062°	96.0%
Absorption correction	Multi-scan
Max. and min. transmission	0.997 and 0.933
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3356/ 0/ 154
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0361, wR2 = 0.0883
R indices (all data)	R1 = 0.0472, wR2 = 0.0941
Largest diff. peak and hole	0.482 and -0.397 e.Å^{-3}

Overall Conclusions

This Doctoral Thesis aimed to develop novel applications for the successful C-N bond construction at ubiquitous hydrocarbon positions. It devised either iodine(III)-mediated or molecular iodine-catalyzed processes to enable these transformations. The most important conclusions from this scientific enterprise are summarized below:

A. An iodine(III)-mediated approach for the amination of indole and tryptamine derivatives gives rise to new selectively aminated products. Further diversification of the resulting structures opened chemical space toward a high quantity of new tryptamine derivatives. In addition, this new aromatic functionalization methodology provides an important and unique access to the as yet biologically unexplored classes of 2-imido and their allosteric 3-fluoro derivatives.

B. A novel protocol based on iodine catalysis that provides conditions for a mild and selective intramolecular aryl amination reaction has been elaborated. This intramolecular C-H amination process allows for the formation of anilines in good yields with a broad scope as demonstrated for a total of 29 examples. This photochemical iodine catalysis can provide general oxidative amination conditions for the cases of aliphatic and aromatic hydrocarbons alike. The elegant approach for the formation of unprotected anilines, through a removable silicon tether has direct consequences on the strategic formation of this class of compounds.

C. A conceptually innovative intermolecular C(sp^3)-H amination methodology based on a unique iodine catalysis was devised and applied to a number of different substrates. The highlight of this transformation is the unexpected preference for secondary methylene positions over tertiary ones and for more hydridic C-H bonds over acidic ones. It streamlines the synthesis of amines from both conventional feedstock and more elaborated molecules. Overall, this novel synthetic strategy empowers access to aminated building blocks. Furthermore, an innovative multiple C-H amination give rise to nitrogenated heterocycles from simple hydrocarbons. The synthetic potential was demonstrated by the synthesis of four relevant pharmaceuticals.

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