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Heng-Ying Xiong

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Normandie Université

THÈSE

Pour obtenir le diplôme de doctorat

Spécialité Chimie Organique

Préparée au sein de l'INSA de Rouen

New methodologies for the introduction of the SCF₃ and Cl groups by C(sp³)-H bond functionalization and the design of original fluorinated electrophilic reagents

**Présentée et soutenue par
Heng-Ying XIONG**

Thèse soutenue publiquement le 22 mars 2017

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Abbreviations and Acronyms

AcOH	acetic acid
TFA	trifluoroacetic acid
MesCOOH	2,4,6-trimethylbenzoic acid
MsOH	methanesulfonic acid
PivOH	pivalic acid
p-TSA	p-toluenesulfonic acid
m-CPBA	3-chloroperoxybenzoic acid
NCS	N-chlorosuccinimide
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NTS	N-thiocyanatosuccinimide
NFSI	N-fluorobenzenesulfonimide
Selectfluor	N-chloromethyl-N'-fluorotriethylenediammonium bis(tetrafluoroborate)
BHT	2,6-di-tert-butyl-4-methylphenol
TEMPO	2,2,6,6-tetramethylpiperidine-N-oxyl
BQ	1,4-benzoquinone
bpy	2,2'-bipyridine
1,10-phen	1,10-phenanthroline
TCCA	trichloroisocyanuric acid
DCDMH	1,3-dichloro-5,5-dimethylhydantoin
DIEA	N,N-diisopropylethylamine
DAST	diethylaminosulfur trifluoride
CF ₃	trifluoromethyl
SCF ₃	trifluoromethylthio
Mes	mesityl

Boc	tert-butoxycarbonyl
Tc	thiophene-2-carboxylate
TPP	tetraphenylporphyrin
SIPr	1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene
TMS	trimethylsilyl
DG	directing group
TM	transition metal
DCE	1,2-dichloroethane
DMA	dimethylacetamide
DMF	N,N-dimethylformamide
DME	1,2-dimethoxyethane
DMI	1,3-dimethyl-2-imidazolidinone
THF	tetrahydrofuran
NMP	N-methyl-2-pyrrolidone
NMO	N-methylmorpholine-N-oxide
DMSO	methyl sulfoxide
HFIP	hexafluoro-2-propanol
PhCl	chlorobenzene
eq.	equivalent
h	hour
rt	room temperature
aq.	aqueous (solution)
Ar	argon
GC-MS	gas chromatography mass spectroscopy
IR	infrared
HRMS	high resolution mass spectroscopy
NMR	nuclear magnetic resonance (spectroscopy)

Abstract

The organofluorine chemistry field has witnessed a very fast expansion. In particular, the SCF₃ moiety and more recently the SCF₂R groups (R = H, SO₂Ph, SAr, COAr, R_f) have attracted a special interest from the scientific community because of their remarkable properties. In this context, the development of new methodologies and original reagents for the introduction of such fluorinated groups is particularly appealing. Therefore, the goals of this thesis were 1) to develop a new methodology for the direct introduction of the SCF₃ group by transition metal-catalyzed C(sp³)-H bond functionalization and its extension to other functional groups as well as 2) to design and study new electrophilic fluorinated reagents.

The first part of this Ph.D. thesis was dedicated to the development of an unprecedented Pd-catalyzed trifluoromethylthiolation of aliphatic amides by C-H bond functionalization (Chapter 2). Then, the Pd-catalyzed chlorination of aliphatic amides by C-H bond functionalization under mild conditions was investigated (Chapter 3).

Finally, a newly designed strategy for the synthesis of trifluoromethanesulfenamides was elaborated (Chapter 4). This approach was extended to the preparation of a new electrophilic reagent for the thiocyanation reaction. In addition, an original electrophilic SCF₂PO(OEt)₂ reagent was designed and applied to the construction of C-SCF₂PO(OEt)₂, N-SCF₂PO(OEt)₂ and S-SCF₂PO(OEt)₂ bonds as well as to the synthesis of a biorelevant compound (Chapter 4).

Résumé

Le domaine de recherche de la chimie du fluor a connu un essor considérable. En particulier, le motif SCF_3 et plus récemment les groupements SCF_2R ($\text{R} = \text{H}, \text{SO}_2\text{Ph}, \text{SAr}, \text{COAr}, \text{R}_f$) ont fait l'objet d'une attention particulière de la part de la communauté scientifique du fait de leurs propriétés remarquables. Dans ce contexte, le développement de nouvelles méthodologies et de réactifs originaux pour l'introduction de ces groupements fluorés a suscité un fort intérêt. En conséquence, les objectifs de cette thèse ont été 1) de développer de nouvelles méthodologies pour la fonctionnalisation de liaisons $\text{C}(\text{sp}^3)\text{-H}$ par l'introduction directe d'un motif SCF_3 catalysée par des métaux de transition, et son extension à d'autres groupements fonctionnels ainsi que 2) de concevoir et étudier de nouveaux réactifs fluorés électrophiles.

La première partie de cette thèse a été dédiée au développement d'une réaction de trifluorométhylthiolation d'amides aliphatiques catalysée au palladium, une transformation inédite (Chapitre 2). Puis, la chloration d'amides aliphatiques catalysée au palladium, dans des conditions douces, a été étudiée (Chapitre 3).

Enfin, une nouvelle voie de synthèse pour accéder aux sulfénamides trifluorométhylés a été développée (Chapitre 4). Cette approche a été étendue à la préparation d'un nouveau réactif électrophile pour l'introduction du groupement SCN . De plus, un réactif électrophile original, source du motif $\text{SCF}_2\text{PO}(\text{OEt})_2$, a été synthétisé et appliqué à la construction de liaisons $\text{C-SCF}_2\text{PO}(\text{OEt})_2$, $\text{N-SCF}_2\text{PO}(\text{OEt})_2$ et $\text{S-SCF}_2\text{PO}(\text{OEt})_2$ ainsi qu'à la synthèse d'un composé d'intérêt biologique (Chapitre 4).

Chapter 1

General Introduction

1 General Introduction

As a halogen element of group VII A in the second row of the periodic table, the fluorine atom is the 13th most abundant element in the earth's crust and the most abundant halogen. Its position in the periodic table determines many intrinsic properties of this atom, such as its highest electronegativity, its small atomic radius and its strong C-F bond strength. However, the natural fluorinated organic molecules are scarce, so the only way to get access to such important scaffolds is the use of organic synthesis. The first synthesis of the element fluorine (F₂) was reported by H. Moissan in 1886.^{1,2a} This discovery represents a breakthrough for the development of fluorine chemistry. Since then, more and more attention has been paid to fluorinated molecules. Indeed, the introduction of a fluorine atom and fluorinated moieties can dramatically impact a number of properties of the targeted molecules, such as the lipophilicity, the acidity or basicity of the neighboring groups, the dipole moment, the metabolic stability and the bioavailability of the molecule.² Nowadays, fluorine-containing compounds have found widespread applications in the field of pharmaceutical³ and agrochemical⁴ industries as well as material sciences.⁵ Consequently, organofluorine chemistry has experienced a resurgence of interest as witnessed by its rapid expansion.⁶

¹ Moissan, H. C. R. Acad. Sci. **1886**, 102, 1543.

² For selected reviews and books, see: (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, 37, 308; (c) O'Hagan, D.; Rzepa, H. *Chem. Commun.* **1997**, 645; (d) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *Chem. Bio. Chem.* **2004**, 5, 637; (e) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*, Blackwell, Oxford, **2009**; (f) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, **2006**; (g) Chambers, R. D. *Fluorine in Organic Chemistry*, Blackwell, Oxford, **2004**.

³ For selected reviews, see: (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, 37, 320; (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, 114, 2432; (c) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. J. *Med. Chem.* **2014**, 57, 2832; (d) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. J. *Med. Chem.* **2015**, 58, 8315; (e) Yerien, D. E.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, 14, 8398; (f) Landelle, G.; Panossian, A.; Leroux, F. R. *Curr. Top. Med. Chem.* **2014**, 14, 941; (g) Müller, K.; Faeh, C.; Diederich, F. *Science*, **2007**, 317, 1881.

⁴ For selected reviews, see: (a) Jeschke, P. *Chem. Bio. Chem.* **2004**, 5, 570; (b) Fujiwara, T.; O'Hagan, D. J. *Fluorine Chem.* **2014**, 167, 16.

⁵ For selected books, see: (a) Hougham, G.; Cassidy, P.; Johns, K.; Davidson, T. *Fluoropolymers 2: Properties*, Kluwer Academic, New York, **1999**; (b) Nakajima, T.; Groult, H. *Fluorinated Materials for Energy Conversion*, Elsevier, Oxford, **2005**.

⁶ For selected reviews, see: (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, 473, 470; (b) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, 52, 8214; (c) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *Beilstein J. Org. Chem.* **2013**, 9, 2476; (d) Egami, H.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2014**, 53, 8294; (e) Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. Eur. J.* **2014**, 20, 16830; (f) Besset, T.; Poisson, T.;

1.1 General properties of the fluorine atom and fluorinated groups

1.1.1 Lipophilic effects

The replacement of the hydrogen atom by a fluorine one often modifies the properties of the parent compounds. One of the most important features is the lipophilicity, which could affect the absorption of the pharmaceutical, the biological barrier passage, the ability to reach the targeted organs and cells.² The lipophilicity $\log P$ or Hansch-Leo π constant ($\pi = \log PC_6H_5X - \log PC_6H_5$ for substituted benzenes) can be used to describe the distribution of a compound in an n-octanol/water system.⁷ Generally, for aromatic derivatives, a compound with a higher $\log P$ or π value will be more lipophilic. To illustrate that, the lipophilicity of several selected fluorinated and non-fluorinated aromatic derivatives has been listed in Table 1. It is worth noting that the fluorobenzene is slightly more lipophilic than benzene, and the trifluorobenzene is more lipophilic than toluene.

Table 1: Hansch-Leo π values ($\pi = \log PC_6H_5X - \log PC_6H_5$ for substituted benzenes)^{7a}

Substituent X	π	Substituent X	π	Substituent X	π
F	0.14	SCF ₃	1.44	CH ₃ CH ₂	1.02
CH ₃	0.56	NSCF ₃	1.50	CF ₃ CH ₂	1.89
CF ₃	0.88	SO ₂ CH ₃	-1.63	OCH ₃	-0.02
SCH ₃	0.61	SO ₂ CF ₃	0.55	OCF ₃	1.04

Regarding the aliphatic molecules, the presence of a fluorine atom generally induces a decrease of the lipophilicity and an increase of the hydrophobicity, which is in contrast with the aromatic molecules (Table 2). As shown in the Table 2, the lipophilicity of ethane is higher than the 1,1-difluoroethane. A similar trend was observed in the case of pentane.

Pannecoucke, X. *Eur. J. Org. Chem.* **2015**, 2765; (g) Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. Eur. J.* **2015**, 21, 12836; (h) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, 115, 765; (i) Besset, T.; Jubault, P.; Pannecoucke, X.; Poisson, T. *Org. Chem. Front.* **2016**, 3, 1004; (j) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, 115, 826; (k) For a special issue on fluorine chemistry, see: *Chem. Rev.* **2015**, 115, 563; (l) Ni, C.; Hu, J. *Chem. Soc. Rev.* **2016**, 45, 5441.

⁷ (a) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, 16, 1207; (b) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, 91, 165.

Table 2: Octanol-water partition (log P) of aliphatic compounds

Compound	log P	Compound	log P
CH ₃ CH ₃	1.81	CH ₃ (CH ₂) ₃ CH ₃	3.11
CH ₃ CHF ₂	0.75	CH ₃ (CH ₂) ₃ CH ₂ F	2.33

1.1.2 Boiling point

In most cases, the introduction of a fluorine atom onto molecules makes the boiling point lower compared with their hydrogenated analogues.^{2f} For examples, the boiling point of the trifluoroacetic acid (CF₃COOH) is 40 °C, lower than its acetic acid analogue (CH₃COOH). Moreover, it is important to notice that a lot of the fluorinated compounds are volatile.

1.1.3 Steric effects

The van der Waals radius r_w of the fluorine atom (1.47 Å) is included between the ones of oxygen (1.57 Å) and hydrogen (1.20 Å) atoms. Therefore, the replacement of a hydrogen atom or a hydroxyl group by a fluorine atom barely changes the steric bulk of the molecule. Thus, as a bioisostere of the hydrogen atom or the hydroxyl group, the replacement of this atom or group by a fluorine atom was commonly applied in drug discovery.³

1.1.4. Acidity, basicity, hydrogen bond and electronic effects

Beyond the properties above-mentioned, the presence of fluorine atoms in molecules will affect the acidity or basicity in case of the organic acids^{2a,8} or the organic bases (amines),⁹ respectively. The carbon-fluorine bond is short, strong (bond energy of C-F bond: 485 kJ/mol compared to the one of a C-C bond: 346 kJ/mol), highly polarized. Moreover, due to the fact that the lone pairs of the fluorine atom are

⁸ Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, London, **1985**.

⁹ Morgenthaler, M., Schweizer, E.; Hoffmann-Roder, A. *Chem. Med. Chem.* **2007**. 2, 1100.

tightly held by the nucleus, it is a very weak hydrogen bond acceptor.¹⁰

1.2 Fluorinated compounds in industry

The incorporation of fluorine-containing moieties is a common strategy in medicinal chemistry to improve the metabolic stability and bioavailability of the pharmaceuticals.³ Thus, hundreds of fluorine-containing compounds appeared on the market including one-third of the top-performing drugs.^{3,11} Indeed, up to 30% of pharmaceuticals and 40% of agrochemicals at least contain one fluorine atom or a fluorinated group (CF₃ and more recently the emergent SCF₃, SF₅, OCF₃ or CF₂R groups).^{3a,b}

For example, one of the world's best-selling drugs is Atorvastatin (Lipitor[®], Pfizer), which contains a fluorine atom on the aromatic ring and was synthesized for the first time in 1985 (Figure 1).¹² It was used for the treatment of dyslipidemia and the prevention of cardiovascular disease.¹² Besides, Sorafenib (Nexavar[®], BAY 43-9006) is a CF₃-containing drug which was developed and launched by Bayer and Onyx in 2005 (Figure 1). It is the first oral multikinase inhibitor.¹³ Similarly, the Efavirenz (Sustiva[®], Merck & Co.) bearing a CF₃ group on a stereogenic center is a non-nucleoside reverse transcriptase inhibitor which was used in the treatment of patients with HIV infection (Figure 1).¹⁴ Moreover, the antidepressant drug Fluoxetine (Prozac[®], Eli Lilly) is one of the top-selling fluorinated pharmaceuticals, which also bears a trifluoromethyl group on one of the aryl rings (Figure 1).¹⁵ Another fluorine-containing molecule is the SF₅-analogue of the herbicide diflufenican, which shows similar level of efficiency and selectivity in the inhibition

¹⁰ Hunter, L. Beilstein J. Org. Chem. **2010**, 6, 38.

¹¹ McGrath, N. A.; Brichacek, M.; Njardarson, J. T. J. Chem. Educ. **2010**, 87, 1348.

¹² Valentovic, M. Pharm: The Comprehensive Pharmacology Reference, Elsevier, Oxford, **2007**.

¹³ Wilhelm, S.; Carter, C.; Lynch, M.; Lowinger, T.; Dumas, J.; Smith, R. A.; Schwartz, B.; Simantov, R.; Kelley, S. Nat. Rev. Drug Discov. **2006**, 5, 835.

¹⁴ (a) Plosker, G. L.; Perry, C. M.; Goa, K. L. PharmacoEconomics **2001**, 19, 421; (b) Adkins, J. C.; Noble, S. Drugs **1998**, 56, 1055.

¹⁵ (a) Wong, D. T.; Bymaster, F. P.; Engleman, E. A. Life Sci. **1995**, 57, 411; (b) Roman, D. L.; Walline, C. C.; Rodriguez, G. J.; Barker, E. L. Eur. J. Pharmacol. **2003**, 479, 53.

of the broad leaved weeds as the parent molecule diflufenican (Figure 1).¹⁶ Regarding the SCF₃-containing compounds such as Fipronil (Figure 1), a more detailed presentation will be given in chapter 2.

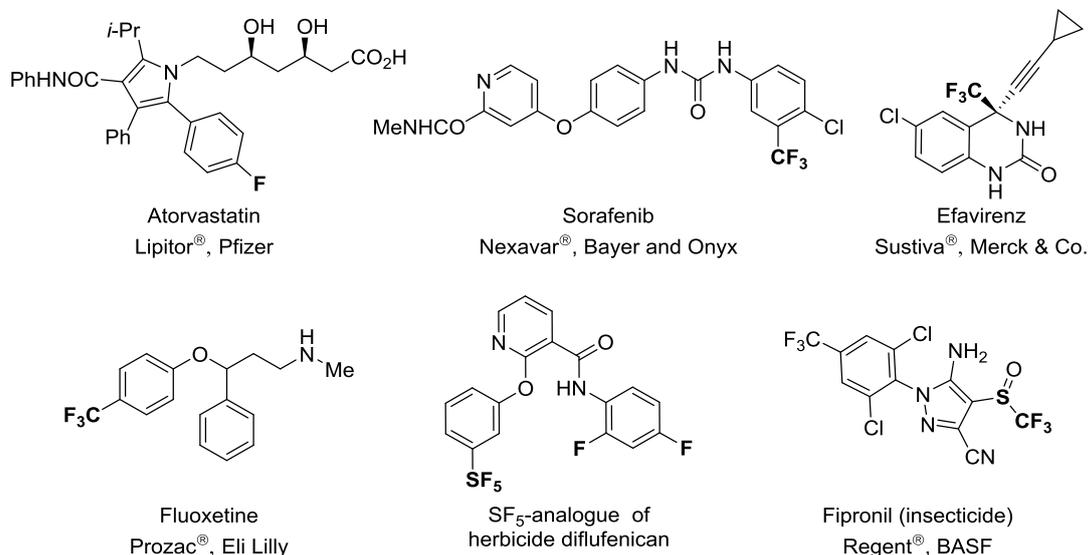


Figure 1: Examples of fluorine-containing pharmaceuticals and agrochemicals

1.3 A brief overview on the synthesis of fluorine-containing molecules

Because of the importance of fluorinated-containing molecules in pharmaceuticals³ and agrochemicals,⁴ increasing attention has been paid to the synthesis of such compounds from the organic community. In general, there are two approaches to access fluorine-containing molecules. One approach is based on the direct introduction of a fluorine atom or fluorinated groups onto a non-fluorinated precursor to access the target molecules.^{6e,17} Another methodology relies on the construction of more complex molecules using fluorinated building blocks. There are three general strategies¹⁸ concerning the construction of a C-F bond including nucleophilic,¹⁹ electrophilic²⁰ and radical pathways.²¹ Regarding the direct

¹⁶ Crowley, P. J.; Mitchell, G.; Salmon, R.; Worthington, P. A. *Chimia*. **2004**, 58, 138.

¹⁷ For selected reviews, see: (a) Campbell, M. G.; Ritter, T. *Chem. Rev.* **2014**, 115, 612; (b) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, 51, 5048.

¹⁸ Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, 115, 9073 and references cited therein.

¹⁹ For selected reviews, see: (a) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, 48, 2929; (b) Pilcher, A. S.; Ammon, H. L.; Shong, P. J. *Am. Chem. Soc.* **1995**, 117, 5166; (c) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561.

²⁰ For selected reviews, see: (a) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, 55, 12431; (b) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, 37, 31; (c) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, 96, 1737.

introduction of the CF₃ group, great progress has been achieved thanks to the development of electrophilic trifluoromethylating reagents²² and the nucleophilic trifluoromethylating reagents.²³ In addition, the radical trifluoromethylation has also made an impact on the growing of this field and great achievement has been done.²⁴

However, the development of efficient and general methodologies for the introduction of fluorine-containing moieties onto organic molecules is still highly desirable and has become one of the hottest topics in fluorine chemistry.

1.4 Transition metal-catalyzed C-H bond activation: a general introduction

The selective construction of C-C and C-X (X = N, O, S, etc.) bond is of paramount importance in organic synthesis. Over the last years, traditional approaches to synthesize molecules rely on the cross-coupling reactions (Figure 2).²⁵ In general, the following mechanism is proposed: oxidative addition of the transition metal on the C-X bond, transmetallation followed by a reductive elimination which will furnish the expected product and regenerate the catalyst. This research area has been culminated with the Nobel prize of Heck, Suzuki and Negishi in 2010 for the palladium-catalyzed cross-coupling reactions.²⁶ Despite the high interest of these transformations, several synthetic limitations remain. For example, traditional cross-coupling reactions require the need of pre-functionalized starting materials, which obviously increase the cost and the number of chemical-steps. Furthermore, the generation of waste may also be

²¹ For selected examples, see: (a) Amaoka, Y.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2013**, 15, 2160; (b) Yin, F.; Wang, Z.; Li, Z.; Li, C. J. *Am. Chem. Soc.* **2012**, 134, 10401; (c) Li, Z.; Song, L.; Li, C. J. *Am. Chem. Soc.* **2013**, 135, 4640.

²² For selected reviews, see: (a) Wang, S.-M.; Han, J.-B.; Zhang, C.-P.; Qin, H.-L.; Xiao, J.-C. *Tetrahedron* **2015**, 71, 7949; (b) Barata-Vallejo, S.; Lantaño, B.; Postigo, A. *Chem. Eur. J.* **2014**, 20, 16806; (c) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, 6, 65; (d) Yang, J.-J.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1998**, 63, 2656.

²³ For selected reviews, see: (a) Zhang, C. *Adv. Synth. Catal.* **2014**, 356, 2895; (b) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, 115, 683; For selected examples, see: (c) Inschauspe, D.; Sortais, J.-B.; Billard, T.; Langlois, B. R. *Synlett* **2003**, 2, 233; (d) Billard, T.; Bruns, S.; Langlois, B. *Org. Lett.* **2000**, 2, 2101.

²⁴ For a selected review, see: (a) Studer, A. *Angew. Chem., Int. Ed.* **2012**, 51, 8950; For a selected example, see: (b) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, 480, 224.

²⁵ For selected reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457; (b) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, 48, 5094; (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, 58, 9633.

²⁶ Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, 51, 5062.

another issue. In order to improve efficiency of multi-step synthetic pathways to access molecules, the development of more straightforward, atom- and step-economical methodologies is at the forefront of innovation. Since C-H bonds are ubiquitous in organic compounds, the direct functionalization of these bonds by transition metal (TM) catalysis would afford an eco-friendly approach and new synthetic retrosynthetic connections for the construction of complex organic frameworks (Figure 2).²⁷ As an example, a cross-dehydrogenative coupling was depicted.²⁸

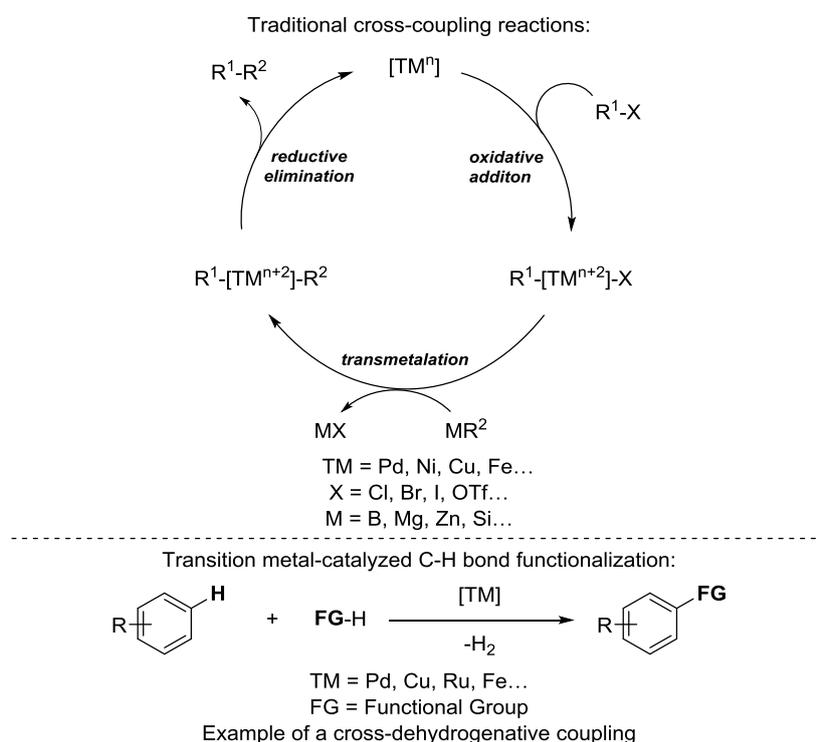


Figure 2: Cross-coupling reactions and transition metal-catalyzed C-H bond activation strategy

1.4.1 Directing group in transition metal-catalyzed C-H bond activation

Although transition metal-catalyzed C-H bond activation is attractive, reactivity and selectivity issues remain. Indeed, due to the ubiquitous and rather unactivated features of C-H bonds in organic molecules, achieving the functionalization of a specific C-H bond in a selective and efficient manner is often challenging. The most

²⁷ For selected reviews, see: (a) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, 417, 507; (b) Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *Beilstein J. Org. Chem.* **2016**, 12, 1040.

²⁸ For selected reviews, see: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, 42, 335; (b) Scheuermann, C. J. *Chem. Asian J.* **2010**, 5, 436; (c) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, 53, 74.

common strategy to overcome these challenges involves the use of substrates that contain a directing group (DG). The following mechanism might be proposed (Figure 3).²⁹

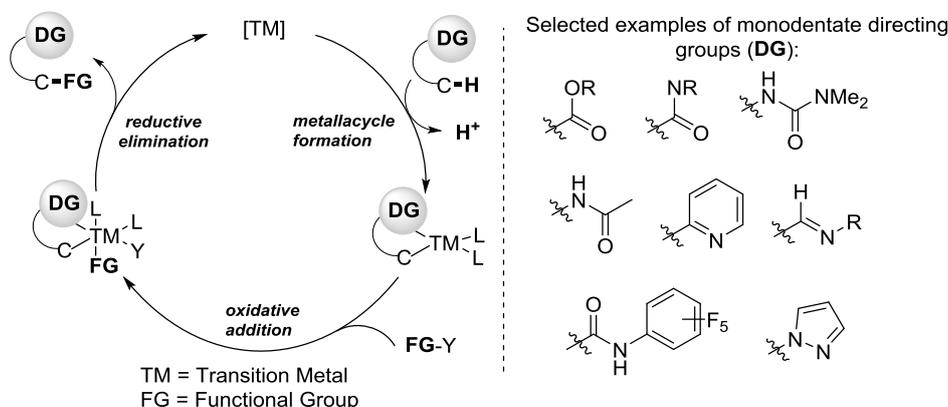


Figure 3: Directing group-assisted transition metal-catalyzed C-H bond activation

After coordination of the transition metal with a suitable DG, a thermodynamically stable five- or six-membered metallacycle intermediate will be formed. This latter will undergo an oxidative addition leading to a high valent TM,³⁰ which after reductive elimination will afford the expected product and regenerate the catalyst (Figure 3). Note that the use of high valent transition metal is known to favor the reductive elimination.³⁰ Two classes of DG are generally used: monodentate and bidentate ones. The most widely used monodentate directing groups are amides, imines, anilides, amines, heteroarenes, carboxylic acids, esters and hydroxyl groups, among others (Figure 3).^{29d,f,g} In recent years, several bidentate directing groups (N,N-bidentate,^{29b,c,31} N,O-bidentate,³² N,S-bidentate³³) which are readily available

²⁹ For selected reviews, see: (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726; (b) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053; (c) Corbet, M.; Campo, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9896; (d) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front.* **2014**, *1*, 843; (e) Rao, W.-H.; Shi, B.-F. *Org. Chem. Front.* **2016**, *3*, 1028; (f) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788; (g) Shi, G.; Zhang, Y. *Adv. Synth. Catal.* **2014**, *356*, 1419; (h) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107.

³⁰ For articles related to Pd(II)/Pd(IV), see: (a) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412; (b) Racowski, J. M.; Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18022. (c) Topczewski, J. J.; Sanford, M. S. *Chem. Sci.* **2015**, *6*, 70.

³¹ For selected examples, see: (a) Shang, R.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2015**, *137*, 7660; (b) Zhao, S.; Liu, Y.-J.; Yan, S.-Y.; Chen, F.-J.; Zhang, Z.-Z.; Shi, B.-F. *Org. Lett.* **2015**, *17*, 3338; (c) Liu, Y.-J.; Zhang, Z.-Z.; Yan, S.-Y.; Liu, Y.-H.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 7899.

³² For selected examples, see: (a) Sun, S.-Z.; Shang, M.; Wang, H.-L.; Lin, H.-X.; Dai, H.-X.; Yu, J.-Q. *J. Org. Chem.* **2015**, *80*, 8843; (b) Shang, M.; Wang, H.-L.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 11590; (c) Mei, R.; Wang, H.; Warratz, S.; Macgregor, S. A.; Ackermann, L. *Chem. Eur. J.* **2016**, *22*, 6759.

³³ For selected examples, see: (a) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *124*, 5278; (b) Parella, R.;

and easily incorporated, have been developed by several groups (Figure 4).³⁴ By coordinating the transition metal center in a bidentate fashion to form the corresponding metallacycle, the bidentate directing groups revealed to be good candidates.^{34c} Moreover, the possibility to cleave the directing group is an important asset for this approach.²⁹

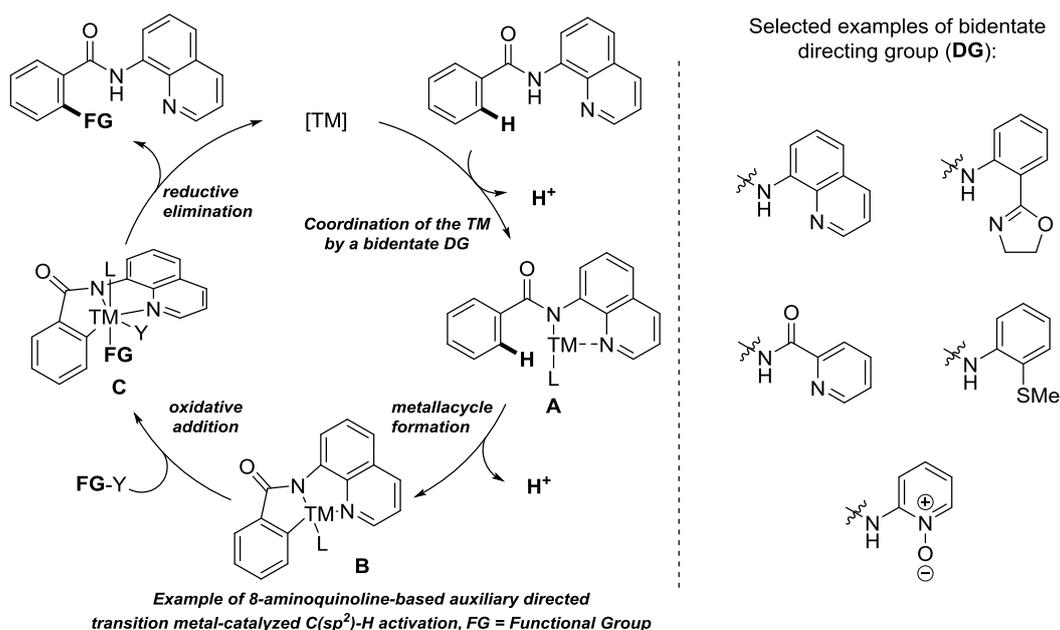


Figure 4: Bidentate directing group-assisted transition metal-catalyzed C-H bond activation

1.4.2 Transition metal-catalyzed C(sp²)-H bond activation

In the past several years, a growing interest from the scientific community has been shown in that research field and great progress has been achieved in transition metal-catalyzed C(sp²)-H bond activation allowing the functionalization of (hetero)arenes and alkenes.³⁵ Consequently, such methodologies have found impressive applications in organic synthesis such as the alkylation,³⁶ alkenylation,³⁷

Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238; (c) Ting, C. P.; Maimone, T. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3115.

³⁴ For selected reviews, see: (a) Liu, J.; Chen, G.; Tan, Z. *Adv. Synth. Catal.* **2016**, *358*, 1174; (b) Tang, H.; Huang, X.-R.; Yao, J.; Chen, H. *J. Org. Chem.* **2015**, *80*, 4672; (c) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450.

³⁵ For selected reviews and accounts, see: (a) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651; (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879; (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147; (d) Miura, M.; Satoh, T.; Hirano, K. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751; (e) Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461; (f) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236.

³⁶ For selected examples, see: (a) Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850; (b) Shabashov, D.; Daugulis, O. J.

alkoxylation,³⁸ acetoxylation,³⁹ thiolation,⁴⁰ amination,⁴¹ alkynylation^{32b,37b,42} as well as arylation⁴³ (Figure 5). Generally, Pd,⁴⁴ Ru^{35e,45} and Rh⁴⁶ complexes were used as catalysts. Recently, attention has been paid by the scientist community to the functionalization of C(sp²)-H bond using the first row transition metals such as nickel,⁴⁷ cobalt,⁴⁸ copper^{44b,49} and promising progress was obtained.

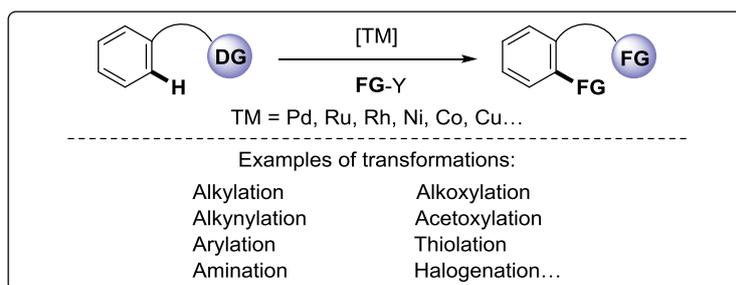


Figure 5: Transition metal-catalyzed C(sp²)-H bond functionalization

Am. Chem. Soc. **2010**, 132, 3965; (c) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. J. Org. Chem. **2013**, 78, 9689.

- ³⁷ For selected examples, see: (a) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. J. Am. Chem. Soc. **2009**, 132, 460; (b) Zhao, Y.; He, G.; Nack, W. A.; Chen, G. Org. Lett. **2012**, 14, 2948; (c) Wang, B.; Shen, C.; Yao, J.; Yin, H.; Zhang, Y. Org. Lett. **2013**, 16, 46.
- ³⁸ For selected examples, see: (a) Zhang, C.; Sun, P. J. Org. Chem. **2014**, 79, 8457; (b) Jiang, T.-S.; Wang, G.-W. J. Org. Chem. **2012**, 77, 9504.
- ³⁹ For selected examples, see: (a) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. Org. Lett. **2009**, 11, 5726; (b) Liu, P.; Han, J.; Chen, C. P.; Shi, D. Q.; Zhao, Y. S. RSC Adv. **2015**, 5, 28430.
- ⁴⁰ Zhang, X.-S.; Li, G.; Zhang, X.-G.; Zhang, X.-H. Tetrahedron **2015**, 71, 5458.
- ⁴¹ For selected examples, see: (a) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. J. Am. Chem. Soc. **2012**, 134, 3; (b) Zhu, D.; Yang, G.; He, J.; Chu, L.; Chen, G.; Gong, W.; Chen, K.; Eastgate, M. D.; Yu, J.-Q. Angew. Chem., Int. Ed. **2015**, 54, 2497; (c) Kong, W.-J.; Liu, Y.-J.; Xu, H.; Chen, Y.-Q.; Dai, H.-X.; Yu, J.-Q. J. Am. Chem. Soc. **2016**, 138, 2146.
- ⁴² Ano, Y.; Tobisu, M.; Chatani, N. Org. Lett. **2012**, 14, 354.
- ⁴³ For selected examples, see: (a) Sun, C. L.; Liu, N.; Li, B. J.; Yu, D. G.; Wang, Y.; Shi, Z. J. Org. Lett. **2010**, 12, 184; (b) Laforteza, B. N.; Chan, K. S. L.; Yu, J.-Q. Angew. Chem., Int. Ed. **2015**, 54, 11143.
- ⁴⁴ For selected accounts, see: (a) Neufeldt, S. R.; Sanford, M. S. Acc. Chem. Res. **2012**, 45, 936; (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. Acc. Chem. Res. **2009**, 42, 1074.
- ⁴⁵ For a selected example, see: (a) Hubrich, J.; Himmler, T.; Rodefeld, L.; Ackermann, L. ACS Cat. **2015**, 5, 4089; (b) Raghuvanshi, K.; Rauch, K.; Ackermann, L. Chem. Eur. J. **2015**, 21, 1790.
- ⁴⁶ For selected accounts, see: (a) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Acc. Chem. Res. **2012**, 45, 814; (b) Ye, B.; Cramer, N. Acc. Chem. Res. **2015**, 48, 1308; (c) Song, G.; Li, X. Acc. Chem. Res. **2015**, 48, 1007; For selected examples, see: (d) Lu, Y.; Wang, H.-W.; Spangler, J. E.; Chen, K.; Cui, P.-P.; Zhao, Y.; Sun, W.-Y.; Yu, J.-Q. Chem. Sci. **2015**, 6, 1923.
- ⁴⁷ For selected reviews, see: (a) amaguchi, J.; Muto, K.; Itami, K. Top. Curr. Chem. **2016**, 374, 55; (b) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Nature **2014**, 509, 299; For a selected example, see: (c) Ruan, Z.; Lackner, S.; Ackermann, L. ACS Cat. **2016**, 6, 4690.
- ⁴⁸ For selected reviews, see: (a) Moselage, M.; Li, J.; Ackermann, L. ACS Cat. **2016**, 6, 498; (b) Ackermann, L. J. Org. Chem. **2014**, 79, 8948; For selected examples, see: (c) Grigorjeva, L.; Daugulis, O. Angew. Chem., Int. Ed. **2014**, 53, 10209; (d) Yu, D.-G.; Gensch, T.; Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. J. Am. Chem. Soc. **2014**, 136, 17722.
- ⁴⁹ For a selected review, see: (a) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. Chem. Rev. **2015**, 115, 1622; For selected examples see: (b) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. Org. Lett. **2014**, 16, 5666; (c) Shang, M.; Shao, Q.; Sun, S.-Z.; Chen, Y.-Q.; Xu, H.; Dai, H.-X.; Yu, J.-Q. Chem. Sci. **2017**, DOI: 10.1039/C6SC03383K.

1.4.3 Transition metal-catalyzed C(sp³)-H bond activation

Compared with the well-developed C(sp²)-H functionalization, transition metal catalyzed C(sp³)-H bond activation is still underdeveloped. This could be explained by the inert nature and the low acidic character of the C(sp³)-H bond.⁵⁰ To overcome the tremendous challenges faced in C(sp³)-H bond activation, the use of bidentate directing groups turned out to be a very efficient tool to introduce functional groups by means of C(sp³)-H bond activation.^{29a,34a,51}

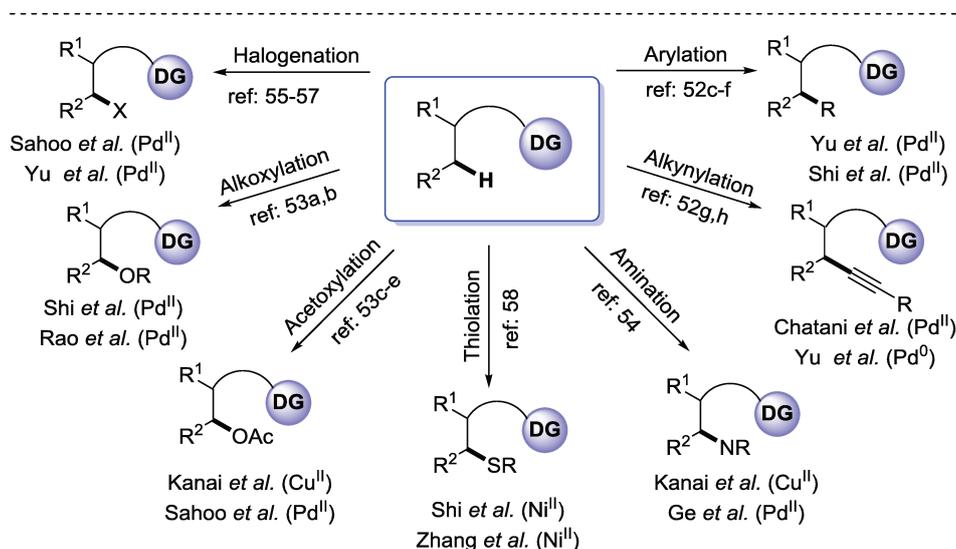


Figure 6: Directing group assisted functionalization of C(sp³)-H bonds

Indeed, a variety of transition metal-catalyzed transformations by C(sp³)-H bond activation have been developed to create C-C,⁵² C-O,⁵³ C-N,⁵⁴ and to some extent

⁵⁰ For selected reviews, see: (a) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.*, **2011**, 1, 191; (b) Baudoin, O. *Chem. Soc. Rev.* **2011**, 40, 4902; (c) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, 50, 605; (d) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, 16, 2654. (e) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, 41, 5588.

⁵¹ Yang, X.; Shan, G.; Wang, L.; Rao, Y. *Tetrahedron Lett.* **2016**, 57, 819.

⁵² For selected examples on alkylation and olefination reactions, see: (a) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, 136, 1789; (b) Wang, B.; Lu, C.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.* **2014**, 16, 6260; For selected examples on arylation reactions, see: (c) Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.* **2014**, 50, 3944; (d) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, 343, 1216; (e) Li, S.; Zhu, R.-Y.; Xiao, K.-J.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2016**, 55, 4317; (f) Pan, F.; Shen, P.-X.; Zhang, L.-S.; Wang, X.; Shi, Z.-J. *Org. Lett.* **2013**, 15, 4758; For selected examples on alkylation reactions, see: (g) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, 133, 12984; (h) He, J.; Wasa, M.; Chan, K. S.; Yu, J. Q. *J. Am. Chem. Soc.* **2013**, 135, 3387.

⁵³ For selected examples on alkoxylation reactions, see: (a) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, 4, 4187; (b) Zong, Y.; Rao, Y. *Org. Lett.* **2014**, 16, 5278; For selected examples on acetoxylation reactions, see: (c) Wang, Z.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, 16, 4790; (d) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, 14, 3724; (e) Wu, X.; Zhao, Y.; Ge, H. *Chem. Asian J.* **2014**, 9, 2736.

⁵⁴ For selected examples, see: (a) Zhu, C.; Liang, Y.; Hong, X.; Sun, H.; Sun, W.-Y.; Houk, K. N.; Shi, Z. *J. Am. Chem. Soc.* **2015**, 137, 7564; (b) Wu, X.; Yang, K.; Zhao, Y.; Sun, H.; Li, G.; Ge, H. *Nature Comm.* **2015**, 6, 6462;

C-X (X = F,⁵⁵ Cl,⁵⁶ Br,⁵⁶ I⁵⁷) bonds (Figure 6). In contrast, examples regarding the construction of C-S bonds by transition metal-catalyzed C(sp³)-H bond activation are still rare.⁵⁸

1.5 Direct introduction of fluorinated groups (F, CF₃) by transition metal-catalyzed C-H bond activation

The combination of organofluorine chemistry and C-H bond activation for the introduction of a fluorine atom or fluorine-containing moieties is particularly appealing.^{6e,59} However, note that in comparison with other C-C and C-X (X = O, N...) bond transformations, the introduction of fluorinated units by transition metal-catalyzed C-H bond functionalization is still in its infancy. In this section, a brief review on fluorination and trifluoromethylation by transition metal-catalyzed C-H bond functionalization will be depicted. The introduction of the SCF₃ group will be discussed in more details in chapter 2.

1.5.1 Transition metal-catalyzed fluorination by C-H bond activation

Generally, the introduction of a fluorine atom by C-H bond functionalization involves either a radical fluorination pathway or a transition metal-catalyzed transformation.^{17,59} Until now, there is no report regarding the transition metal-catalyzed fluorination by C(sp)-H bond activation. In this section, selected key examples of transition metal-catalyzed fluorination by C(sp²)-H and C(sp³)-H bond activation will be depicted.

(c) Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem. Int., Ed.* **2014**, 53, 3706; (d) Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2014**, 53, 3496.

⁵⁵ For selected examples, see: (a) Zhu, Q.; Ji, D.; Liang, T.; Wang, X.; Xu, Y. *Org. Lett.* **2015**, 17, 3798; (b) Zhang, Q.; Yin, X.-S.; Chen, K.; Zhang, S.-Q.; Shi, B.-F. *J. Am. Chem. Soc.* **2015**, 137, 8219.

⁵⁶ Rit, R. K.; Yadav, M. R.; Ghosh, K.; Shankar, M.; Sahoo, A. K. *Org. Lett.* **2014**, 16, 5258.

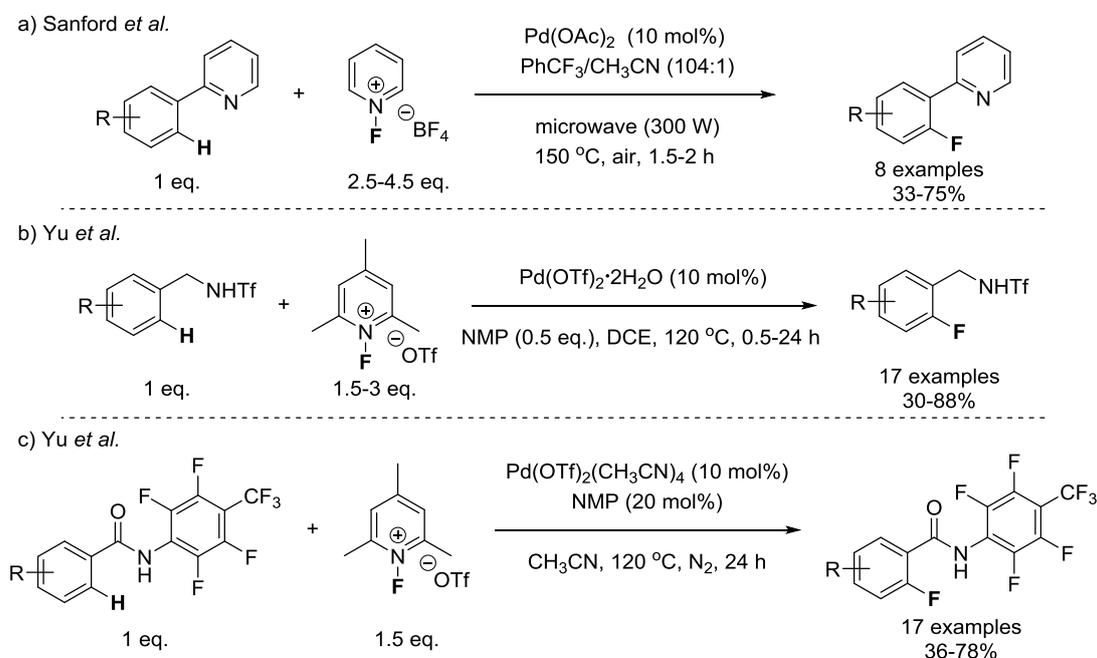
⁵⁷ Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, 44, 2112.

⁵⁸ For a selected review, see: (a) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. *Chem. Soc. Rev.* **2015**, 44, 291; For selected examples, see: (b) Lin, C.; Yu, W.; Yao, J.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, 17, 1340; (c) Yan, S.-Y.; Liu, Y.-J.; Liu, B.; Liu, Y.-H.; Zhang, Z.-Z.; Shi, B.-F. *Chem. Commun.* **2015**, 51, 7341; (d) Wang, X.; Qiu, R.; Yan, C.; Reddy, V. P.; Zhu, L.; Xu, X.; Yin, S.-F. *Org. Lett.* **2015**, 17, 1970.

⁵⁹ (a) Lin, A.; Huehls, C. B.; Yang, J. *Org. Chem. Front.* **2014**, 1, 434; (b) Ma, J.-A.; Li, S. *Org. Chem. Front.* **2014**, 1, 712.

1.5.1.1 Transition metal-catalyzed fluorination by C(sp²)-H bond activation

Since the pioneer works of Sanford and co-workers regarding the Pd-catalyzed fluorination of 2-phenylpyridine in 2006 (Scheme 1, a),⁶⁰ the construction of C(sp²)-F bonds by C-H bond activation has attracted a lot of attention. Besides, the Pd-catalyzed fluorination of aromatic C(sp²)-H bond of triflamide-protected benzylamines (Scheme 1, b)⁶¹ and N-perfluoroaryl benzamides (Scheme 1, c)⁶² was reported by Yu and co-workers. Using this strategy, a range of fluorinated benzoic acid derivatives has been prepared in good yields. Note that in these examples, pyridinium salts have been used as electrophilic fluorine sources.

Scheme 1: Pd-catalyzed fluorination of C(sp²)-H bonds

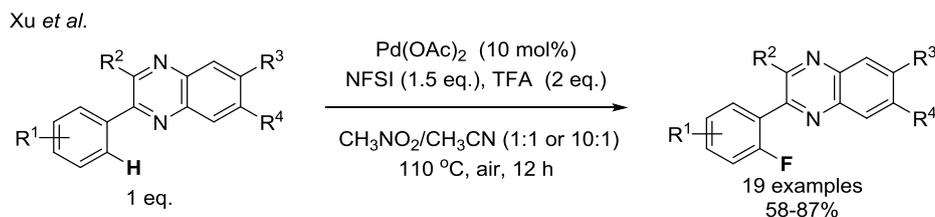
In 2013, Xu's group reported the Pd-catalyzed selective aromatic C-H bond fluorination directed by N-aryl-substituted N-heterocycles, providing a new protocol for the selective fluorination of aromatic C-H bonds (Scheme 2).⁶³

⁶⁰ Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, 128, 7134.

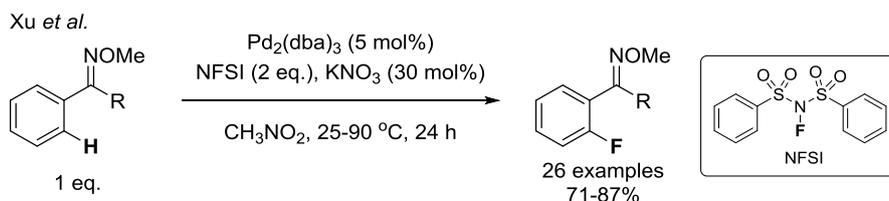
⁶¹ Wang, X.; Mei, T. S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, 131, 7520.

⁶² Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, 50, 9081.

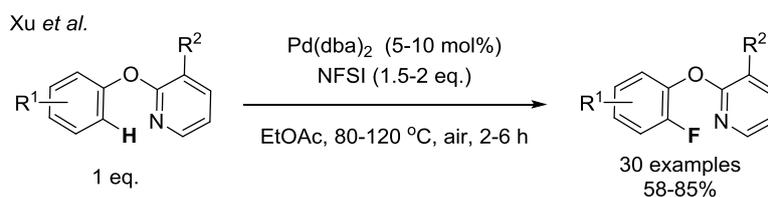
⁶³ Lou, S.-J.; Xu, D.-Q.; Xia, A.-B.; Wang, Y.-F.; Liu, Y.-K.; Du, X.-H.; Xu, Z.-Y. *Chem. Commun.* **2013**, 49, 6218.

Scheme 2: Pd-catalyzed fluorination of C(sp²)-H bonds using a quinoxaline as a directing group

Later, the same group reported the directed fluorination of both aromatic and olefinic C-H bonds under palladium catalysis using an oxime as directing group with a remarkably broad substrate scope. In this reaction, the non-toxic and inexpensive potassium nitrate was utilized as a highly efficient promoter. Indeed, in the presence of KNO₃, the initial formation of a cationic [Pd(NO₃)]⁺ species was proposed (Scheme 3).⁶⁴

Scheme 3: Pd-catalyzed fluorination of C(sp²)-H bonds using an oxime as a directing group

Most recently, they reported a Pd-catalyzed site-selective C-H bond fluorination of phenols using removable 2-pyridyloxy group as a directing group. The transformation was efficient (30 examples, 58-85%) and demonstrated a high functional group tolerance (Scheme 4).⁶⁵

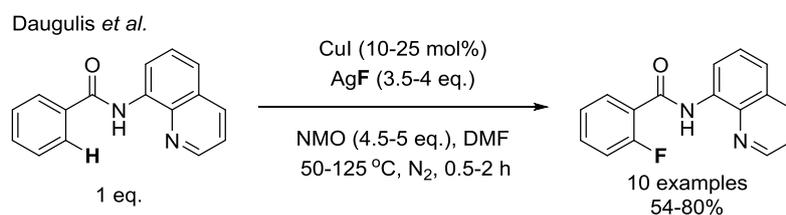
Scheme 4: Pd-catalyzed fluorination of C(sp²)-H bonds using 2-pyridyloxy group as a directing group

In 2013, Daugulis and co-workers described a Cu-catalyzed aromatic C(sp²)-H bond fluorination using an excess of N-methylmorpholine-N-oxide (NMO) as an oxidant with the assistance of the amide prepared from the 8-aminoquinoline as the

⁶⁴ Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 10330.

⁶⁵ Lou, S.-J.; Chen, Q.; Wang, Y.-F.; Xu, D.-Q.; Du, X.-H.; He, J.-Q.; Mao, Y.-J.; Xu, Z.-Y. *ACS Cat.* **2015**, *5*, 2846.

directing group (Scheme 5).⁶⁶ It is worth to mention that the selective mono or ortho, ortho' difluorination could be achieved by a simple change of the reaction conditions.



Scheme 5: Cu-catalyzed fluorination of C(sp²)-H bonds

1.5.1.2 Transition metal-catalyzed fluorination by C(sp³)-H bond activation

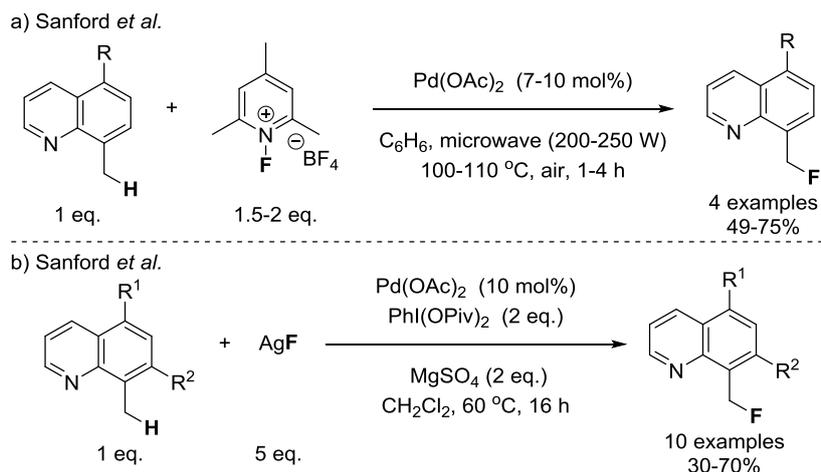
The formation of C(sp³)-F bond by the direct fluorination of aliphatic derivatives is a synthetic challenge. There are two general pathways: 1) a radical fluorination reaction or 2) a transition metal-catalyzed C(sp³)-H bond fluorination. In recent years, great progress has been achieved involving radical pathways.⁶⁷ These transformations generally used selectfluor as fluorine source and allowed the functionalization of benzylic, allylic and secondary C(sp³)-H bonds. In this part, we will only focus on the second strategy even if examples dealing with the transition metal-catalyzed C(sp³)-H bond fluorination of aliphatic derivatives are rare.

In 2006, Sanford and co-workers described the Pd-catalyzed fluorination of benzylic C(sp³)-H bonds by using N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as the fluorinating reagent (Scheme 6, a).⁶⁰ Later, the same group demonstrated that the formation of C(sp³)-F bond could also be accessed by using AgF as a fluorine source and PhI(OAc)₂ as an oxidant (Scheme 6, b).⁶⁸

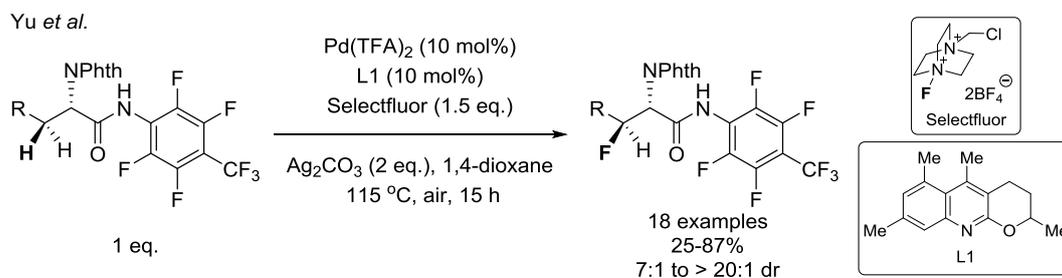
⁶⁶ Truong, T.; Klimovica, K.; Daugulis, O. J. *Am. Chem. Soc.* **2013**, 135, 9342.

⁶⁷ For selected examples, see: (a) Liu, W.; Groves, J. T. *Angew. Chem., Int. Ed.* **2013**, 52, 6024; (b) Nodwell, M. B.; Bagai, A.; Halperin, S. D.; Martin, R. E.; Knust, H.; Britton, R. *Chem. Commun.* **2015**, 51, 11783; (c) Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. *Angew. Chem., Int. Ed.* **2012**, 51, 10580; (d) Braun, M.-G.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, 135, 12990.

⁶⁸ McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, 14, 4094.

Scheme 6: Pd-catalyzed fluorination of benzylic $\text{C}(\text{sp}^3)\text{-H}$ bonds

In 2015, Yu and co-workers reported the first Pd-catalyzed $\text{C}(\text{sp}^3)\text{-H}$ bond fluorination by using selectfluor as a fluorinating reagent and the 5,7-dimethylquinoline as a ligand (Scheme 7).⁶⁹ Through this methodology, a range of unnatural fluorinated α -amino acids was synthesized in moderate to good yields and high diastereoselectivities. It was worth mentioning that the presence of the ligand could potentially promote the generation of the expected product by the reductive elimination from the Pd(IV) center.

Scheme 7: Pd-catalyzed fluorination of $\text{C}(\text{sp}^3)\text{-H}$ bonds developed by Yu

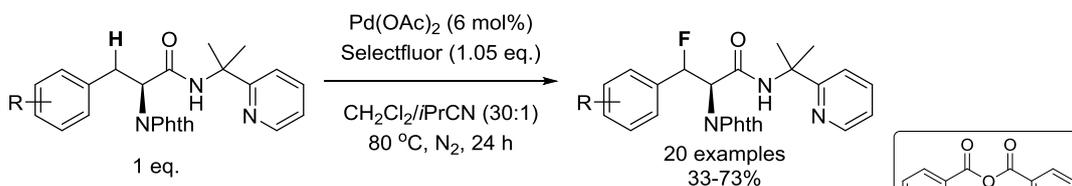
Almost at the same time, Shi and co-workers described a Pd-catalyzed fluorination of N-phthaloyl phenylalanine derivatives.^{55b} This methodology was not only compatible with benzylic $\text{C}(\text{sp}^3)\text{-H}$ bonds but also with aliphatic $\text{C}(\text{sp}^3)\text{-H}$ bonds leading to a range of β -fluorinated α -amino acids in moderate to good yields (Scheme 8). In the last case, the use of 2-methylbenzoic anhydride (2-Me-BAH) had a beneficial effect on the outcome of the transformation. However, the exact role of this

⁶⁹ Zhu, R.-Y.; Tanaka, K.; Li, G.-C.; He, J.; Fu, H.-Y.; Li, S.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, 137, 7067.

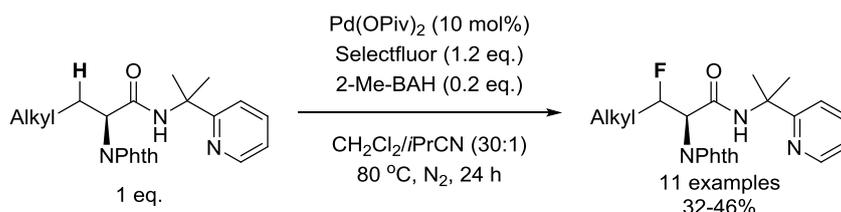
additive was not clearly identified.

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Fluorination of benzylic C(sp³)-H bond:



Fluorination of aliphatic C(sp³)-H bond:

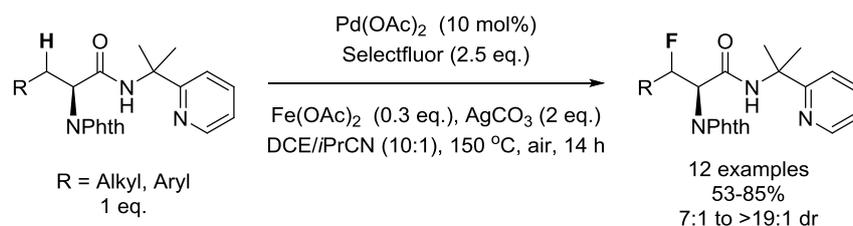


Scheme 8: Pd-catalyzed fluorination of C(sp³)-H bonds developed by Shi

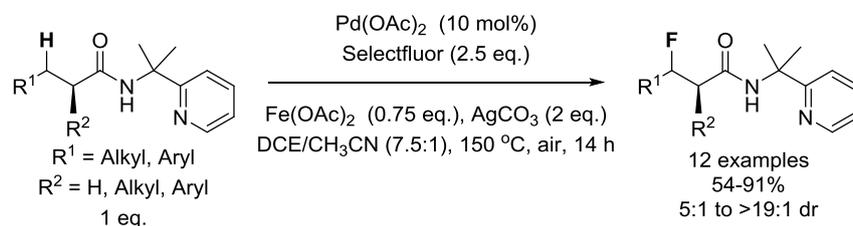
Using a similar catalytic system, Ge and co-workers developed a Pd-catalyzed fluorination of amino acid derivatives and aliphatic amides.⁷⁰ In this case, a catalytic amount of Fe(OAc)₂ was used, its role was to promote the regeneration of the Pd(II) species from the palladacycle intermediate. With this approach, a range of β -fluorinated amino acid derivatives and aliphatic amides was synthesized in moderate to good yields with high diastereoselectivities (Scheme 9).

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Fluorination of amino acid derivatives:



Fluorination of aliphatic amides:

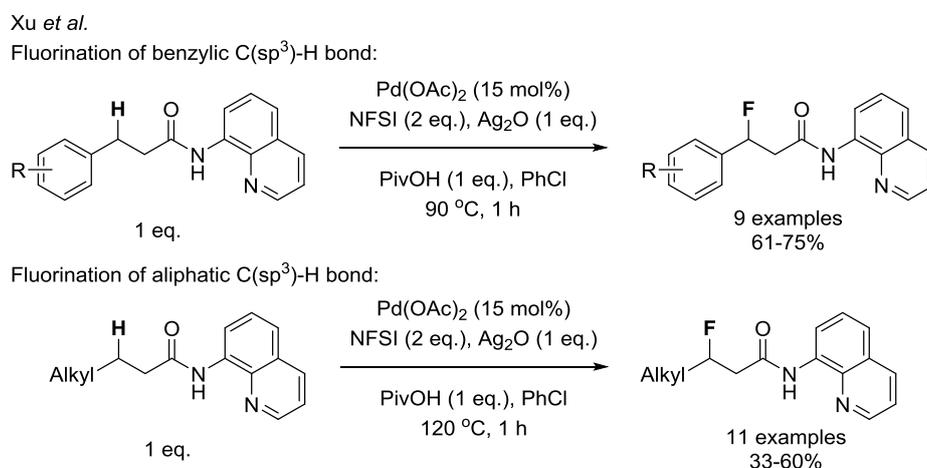


Scheme 9: Pd-catalyzed fluorination of C(sp³)-H bonds developed by Ge

By using 8-aminoquinoline derived auxiliary as directing group, NFSI as a fluorinating reagent, the Pd-catalyzed fluorination of C(sp³)-H bonds was also

⁷⁰ Miao, J.; Yang, K.; Kurek, M.; Ge, H. *Org. Lett.* **2015**, *17*, 3738.

achieved by Xu and co-workers.^{55a} Both benzylic C(sp³)-H bonds and unactivated aliphatic C(sp³)-H bonds were functionalized at 90 °C or 120 °C (Scheme 10).



Scheme 10: Pd-catalyzed fluorination of C(sp³)-H bonds developed by Xu

1.5.2 Transition metal-catalyzed trifluoromethylation by C-H bond activation

The incorporation of the trifluoromethyl moiety by transition metal-catalyzed C-H bond functionalization is a straightforward method for the synthesis of trifluoromethylated compounds. Thus, the development of efficient methodologies for the selective trifluoromethylation by C-H bond activation on C(sp), C(sp²), C(sp³) centers is of high interest.⁷¹

1.5.2.1 Transition metal-catalyzed trifluoromethylation by C(sp)-H bond activation

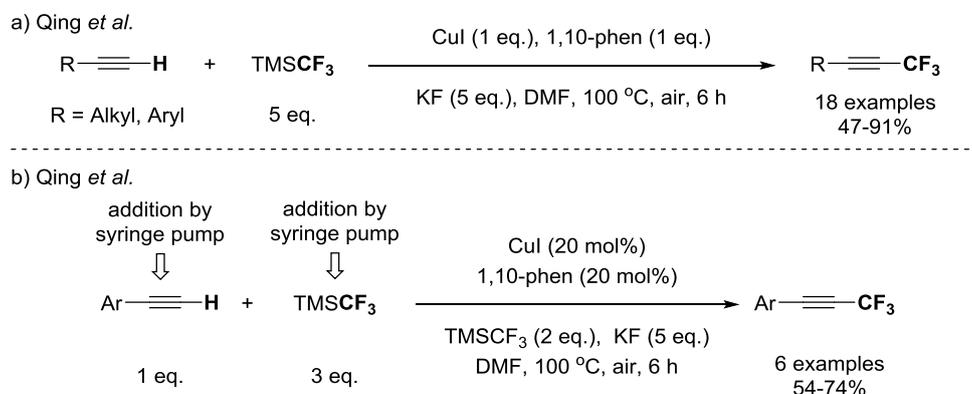
The examples regarding the transition metal-catalyzed direct trifluoromethylation of C(sp)-H bonds are rare.^{6e,72} In 2010, Qing and co-workers reported a copper-mediated oxidative trifluoromethylation of terminal alkynes using the Ruppert-Prakash reagent (TMSCF₃) as a CF₃ source (Scheme 11, a).⁷³ In order to avoid the use of a stoichiometric amount of copper catalyst to introduce the CF₃ group onto the terminal alkynes, the same group developed a more efficient method. Indeed,

⁷¹ For selected reviews, see: (a) Liu, G.; Chen, P. *Synthesis* **2013**, 45, 2919; (b) Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, 355, 617; (c) Xu, J.; Liu, X.; Fu, Y. *Tetrahedron Lett.* **2014**, 55, 585; (d) Ye, Y.; Sanford, M. S. *Synlett* **2012**, 23, 2005.

⁷² Gao, P.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *Chem. Eur. J.* **2015**, 21, 7648.

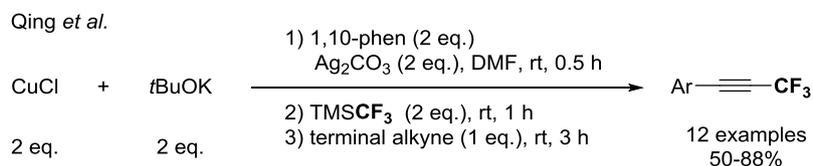
⁷³ Chu, L.; Qing, F. L. J. *Am. Chem. Soc.* **2010**, 132, 7262.

by a slow addition of the alkynes and the TMSCF_3 reagent via a syringe pump, using only 20 mol% CuI and in the presence of 1,10-phenanthroline (1,10-phen), the trifluoromethylation of aromatic alkynes occurred in good yields. (Scheme 11, b).⁷⁴



Scheme 11: Trifluoromethylation of terminal alkynes with TMSCF_3

Subsequently, Qing and co-workers further improved the procedure by using the in situ generated $(1,10\text{-phen})\text{CuCF}_3$. This process proceeded smoothly with only 2 equivalents of TMSCF_3 reagent and a lower temperature (rt vs 100°C in previous work), providing a general, straightforward method for the synthesis of trifluoromethylated acetylenes (Scheme 12).⁷⁵



Scheme 12: Trifluoromethylation of terminal alkynes by the in situ generated $(1,10\text{-phen})\text{CuCF}_3$

1.5.2.2 Transition metal-catalyzed trifluoromethylation by $\text{C}(\text{sp}^2)\text{-H}$ bond activation

Trifluoromethyl-substituted arenes and heteroarenes are widely present in pharmaceuticals and agrochemicals. Hence, the development of eco-friendly routes for the construction of $\text{C}(\text{sp}^2)\text{-CF}_3$ bonds is highly desirable and great achievements have been reached in the past few years. Among them, several approaches involving a radical pathway have been reported.^{17b,76} In this section we summarized the reports

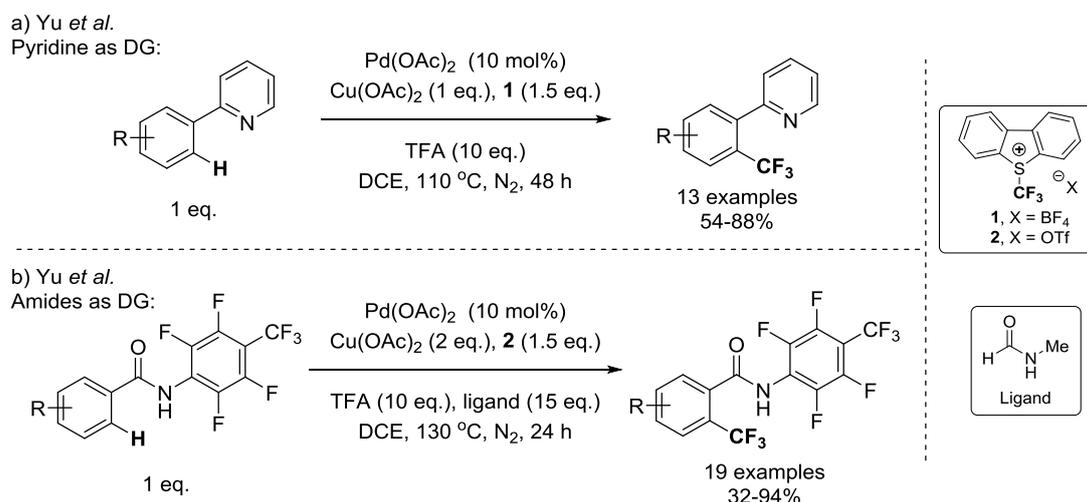
⁷⁴ Jiang, X.; Chu, L.; Qing, F.-L. *J. Org. Chem.* **2012**, *77*, 1251.

⁷⁵ Zhang, K.; Qiu, X.-L.; Huang, Y.; Qing, F.-L. *Eur. J. Org. Chem.* **2012**, 58.

⁷⁶ For a selected review, see: (a) Zhang, P.-Z.; Li, C.-K.; Zhang, G.-Y.; Zhang, L.; Jiang, Y.-J.; Zou, J.-P.

dealing with the transition metal-catalyzed trifluoromethylation processes.

In 2010, Yu and co-workers reported the Pd-catalyzed trifluoromethylation of arenes via C-H activation by using N-heterocycles as directing group. Using Umemoto's reagent **1** as a CF₃ source, a range of 2-phenylpyridine derivatives has been functionalized in moderate yields (Scheme 13, a).⁷⁷ Subsequently, a similar trifluoromethylation by using amide derived from 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline as directing group was reported by the same group. In this case, the N-methylformamide was used as a ligand and a base. The acidic amide was crucial for the transformation, providing the expected products in moderate to good yields (Scheme 13, b).⁷⁸



Scheme 13: Pd-catalyzed trifluoromethylation of C(sp²)-H bonds

Moreover, the trifluoromethylation of benzylamines has been achieved by the same group affording the expected products in good yields (Scheme 14).^{79a} The addition of the H₂O could improve the yield and the addition of Ag₂O might reoxidize

Tetrahedron **2016**, 72, 3250; For selected examples, see: (b) Mejía, E.; Togni, A. ACS Cat. **2012**, 2, 521; (c) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. Angew. Chem., Int. Ed. **2012**, 51, 536; (d) Hafner, A.; Bräse, S. Angew. Chem., Int. Ed. **2012**, 51, 3713; (e) Cheng, Y.; Yuan, X.; Ma, J.; Yu, S. Chem. Eur. J. **2015**, 21, 8355; (f) Monir, K.; Bagdi, A. K.; Ghosh, M.; Hajra, A. J. Org. Chem. **2015**, 80, 1332; (g) Shi, G.; Shao, C.; Pan, S.; Yu, J.; Zhang, Y. Org. Lett. **2015**, 17, 38; (h) Wu, M.; Ji, X.; Dai, W.; Cao, S. J. Org. Chem. **2014**, 79, 8984; (i) Cao, X.-H.; Pan, X.; Zhou, P.-J.; Zou, J.-P.; Asekun, O. T. Chem. Commun. **2014**, 50, 3359; (j) Rao, Y.; Shan, G.; Yang, X. Sci. Chin. Chem. **2014**, 57, 930; (k) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. Proc. Natl. Acad. Sci. USA **2011**, 108, 14411.

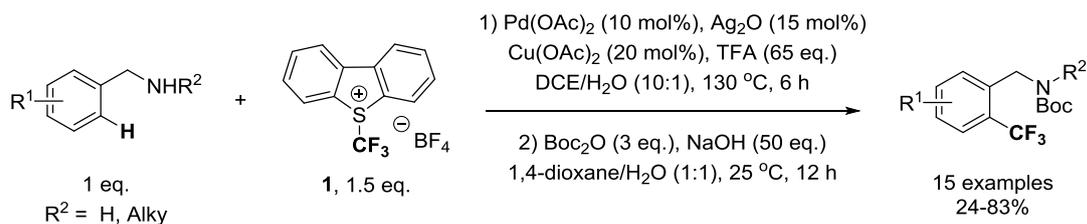
⁷⁷ Wang, X.; Truesdale, L.; Yu, J.-Q. J. Am. Chem. Soc. **2010**, 132, 3648.

⁷⁸ Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. J. Am. Chem. Soc. **2012**, 134, 11948.

⁷⁹ (a) Miura, M.; Feng, C.-G.; Ma, S.; Yu, J.-Q. Org. Lett. **2013**, 15, 5258; (b) Shang, M.; Sun, S.-Z.; Wang, H.-L.; Laforteza, B. N.; Dai, H.-X.; Yu, J.-Q. Angew. Chem., Int. Ed. **2014**, 53, 10439.

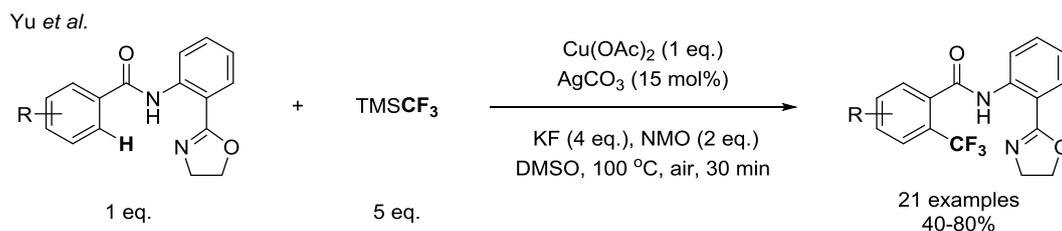
the Pd(0) generated in the course of the transformation.

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Scheme 14: Pd-catalyzed trifluoromethylation of benzylamines

It is worth to mention that the nucleophilic Ruppert-Prakash reagent (TMSCF₃) could also be used in the trifluoromethylation of C(sp²)-H bonds. Indeed, in 2014, Yu and co-workers reported the Cu-promoted trifluoromethylation of amides which were prepared from the benzoic acid and 2-(2-oxazolyl)aniline.^{79b} This reaction was efficient leading to the corresponding products in moderated yields in 30 min (Scheme 15).

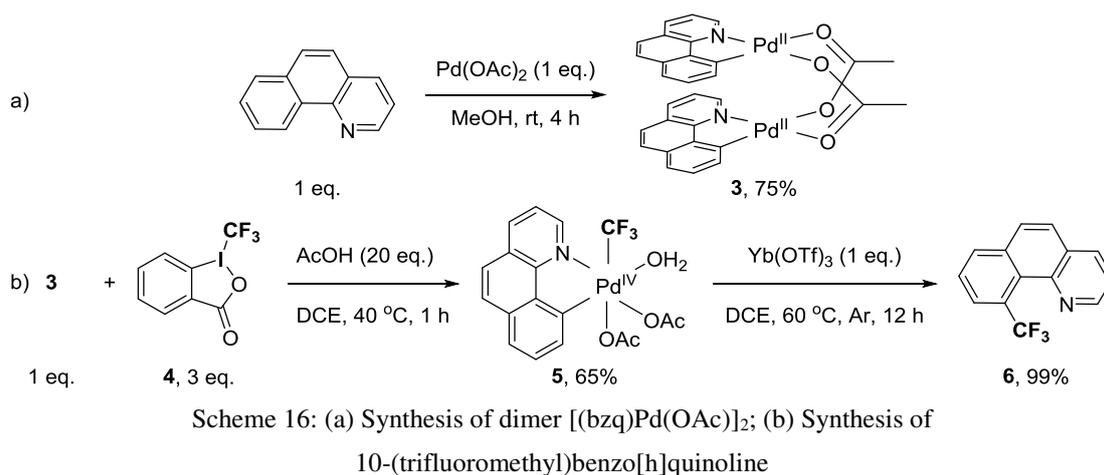


Scheme 15: Cu-promoted trifluoromethylation of C(sp²)-H bonds

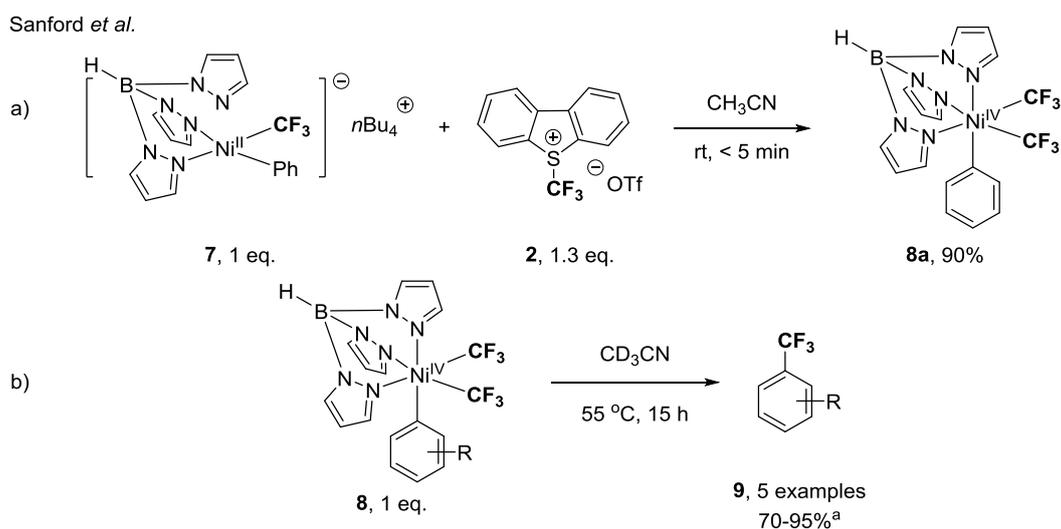
Sanford and co-workers described the formation and the reactivity of the monomeric Pd(IV) complex **3**. The treatment of the benzo[h]quinoline by Pd(OAc)₂ in methanol at room temperature for 4 h afforded the dimer [(bzq)Pd(OAc)]₂ **3** (bzq = benzo[h]quinoline) in 75% yield (Scheme 16, a). This complex further reacted with the Togni's reagent **4** to generate the stoichiometric monomeric Pd(IV) trifluoromethylated complex **5** in 65% yield. Then, a highly chemoselective C-CF₃ bond formation by the reductive elimination furnished the trifluoromethylated product **6** in 99% yield (Scheme 16, b).⁸⁰ This study provides valuable insights about a possible Pd(II)/Pd(IV) pathway for such transformation.⁸¹

⁸⁰ Ye, Y.; Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, 132, 14682.

⁸¹ (a) Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, 132, 2878; (b) Ball, N. D.; Gary, J. B.; Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, 133, 7577.



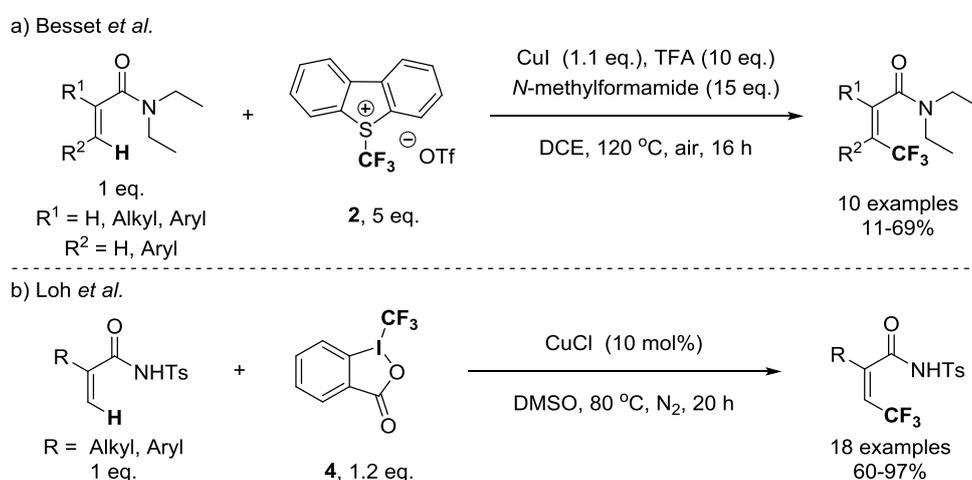
Recently, the same group described the synthesis of complex [TpNi^{IV}(Ph)(CF₃)₂] **8a** by treating the precursor [TpNi^{II}(Ph)(CF₃)]NBu₄ **7** (synthesized from [(dtbpy)Ni^{II}(CF₃)(OCOCF₃)] through several steps)⁸² with 1.3 equivalents of Umemoto's reagent **2** in acetonitrile at room temperature. The product **8a** was isolated in 90% yield. By using this methodology, a range of [TpNi^{IV}(aryl)(CF₃)₂] complexes **8** have been synthesized. Further reductive elimination of these Ni^{IV} intermediates **8** provided a range of trifluoromethylated arenes **9** in good yields (Scheme 17).⁸³ This is one of the first example of a Ni(II)/Ni(IV) catalytic process in C-H activation.



⁸² Maleckis, A.; Sanford, M. S. *Organometallics* **2014**, *33*, 3831.

⁸³ Bour, J. R.; Camasso, N. M.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 8034.

The trifluoromethylation reactions of alkenes are rare. In 2013, Besset and co-workers reported a selective Cu-mediated trifluoromethylation reaction of alkenes using the Umemoto's reagent **2** as CF₃ source, TFA and N-methylformamide as additives affording the Z-isomers in moderate yields (Scheme 18, a).⁸⁴ Meanwhile, Loh and co-workers described a similar reaction featuring an acidic N-tosylamide as directing group (DG) with Togni's reagent **4** as an electrophilic CF₃ source. This reaction was tolerated to α -aryl- as well as α -alkyl-substituted acrylate derivatives affording the expected product in moderate to high yields (Scheme 18, b).⁸⁵



Scheme 18: Cu-catalyzed trifluoromethylation of olefins

1.5.2.3 Transition metal-catalyzed trifluoromethylation by C(sp³)-H bond activation

To the best of our knowledge, only few studies dealt with the transition metal-catalyzed direct trifluoromethylation of C(sp³)-H bond by C-H bond activation limited to specific and activated substrates such as allylic derivatives. In 2011, Buchwald's (Scheme 19, a)⁸⁶ and Wang's groups (Scheme 19, b)⁸⁷ have developed a trifluoromethylation of terminal alkenes by using Togni's reagent **4**. Meanwhile, a similar reaction was reported by the group of Fu and Liu using the Umemoto's

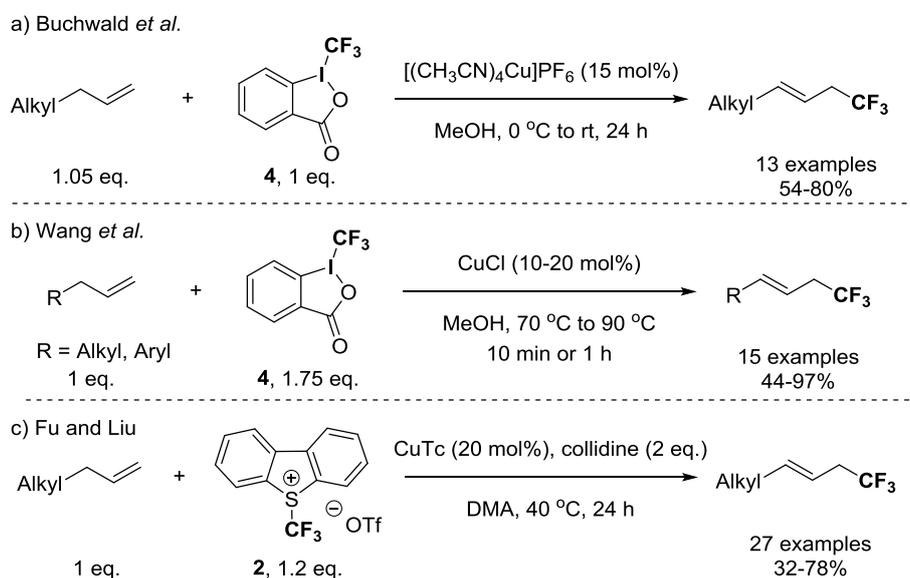
⁸⁴ Besset, T.; Cahard, D.; Pannecoucke, X. *J. Org. Chem.* **2013**, 79, 413.

⁸⁵ Feng, C.; Loh, T. P. *Angew. Chem., Int. Ed.* **2013**, 52, 12414.

⁸⁶ Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, 50, 9120.

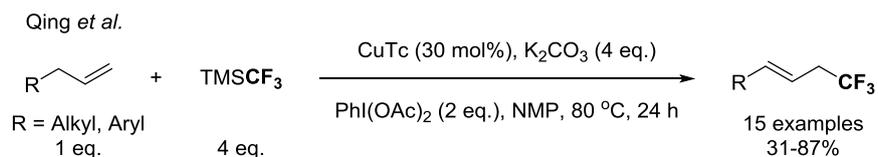
⁸⁷ Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, 133, 16410.

reagent **2** (Scheme 19, c).⁸⁸ All these methods tolerated a broad range of functional groups including sulfonate, ester, amine, nitro and ether.



Scheme 19: Trifluoromethylation of allylic C-H bond using electrophilic CF₃ reagent

In 2012, Qing and co-workers reported the Cu-catalyzed oxidative trifluoromethylation of terminal alkenes by using TMSCF₃ as nucleophilic CF₃ source (Scheme 20).⁸⁹ This strategy provided an efficient methodology for the construction of C(sp³)-CF₃ bond.



Scheme 20: Trifluoromethylation of allylic C-H bond using TMSCF₃

In conclusion, regarding the transition metal-catalyzed trifluoromethylation of unactivated C(sp³)-H bond, no report has been described to date.

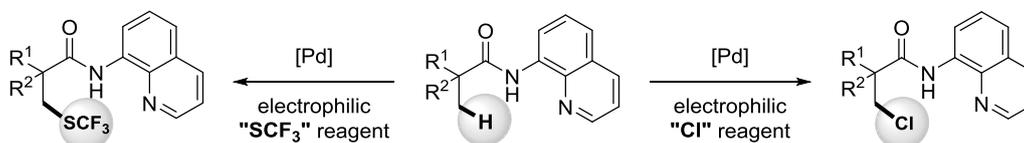
Thus, from a synthetic point of view, the direct introduction of fluorinated groups by transition metal-catalyzed C-H bond functionalization on aliphatic derivatives is highly desirable.

⁸⁸ Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300.

⁸⁹ Chu, L.; Qing, F.-L. *Org. Lett.* **2012**, *14*, 2106.

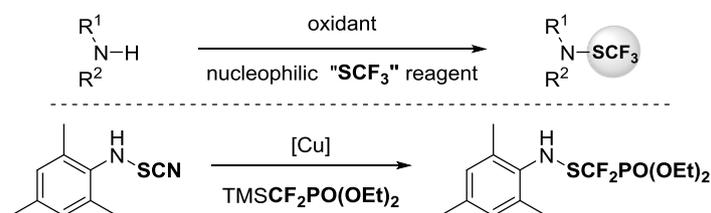
1.6 Objectives of the Ph.D. Thesis

In this thesis, we aim at tackling several synthetic challenges. As above-mentioned, any advances in transition metal-catalyzed C(sp³)-H bond functionalization will be highly valuable. Therefore, we will focus on the development of original methodologies for the introduction of functional groups by C-H bond activation: a field which is to date still underdeveloped. In this purpose, the first part of this Ph.D. thesis will be dedicated to the Pd-catalyzed trifluoromethylthiolation of aliphatic amides by C-H bond functionalization, an unprecedented transformation (Scheme 21). By serendipity, in the course of this study, we observed the product resulting from the Pd-catalyzed C(sp³)-Cl bond formation, an interesting albeit poorly developed approach to access chlorinated derivatives. Therefore, we will focus on the development of a new methodology giving an access to chlorinated aliphatic amides by a Pd-catalyzed C-H bond functionalization under mild conditions (Scheme 21).



Scheme 21: Pd-catalyzed C(sp³)-H bond functionalization

In the last part, a newly designed synthesis of electrophilic reagents especially for the emergent SCF₃ and the original SCF₂PO(OEt)₂ groups will be described (Scheme 22).



Scheme 22: Synthesis of electrophilic SCF₃ and SCF₂PO(OEt)₂ reagents

Chapter 2

Palladium(II)-Catalyzed Directed Trifluoromethylthiolation of Unactivated C(sp³)-H Bonds

Over the last years, the SCF₃ moiety became an emerging fluorinated group because of its remarkable properties. Thus, the incorporation of such group onto organic molecules by efficient and straightforward methods is highly desirable. In this context, this chapter will be dedicated to the transition metal-catalyzed trifluoromethylthiolation of unactivated C(sp³)-H bonds.

1 State of the art

Important fluorinated groups which contain a trifluoromethyl group connected with a heteroatom such as the trifluoromethoxy (OCF₃),^{6i, 90} the trifluoromethanesulfonyl (SCF₃),⁹¹ the trifluoromethanesulfonyl (SO₂CF₃),^{91e} the trifluoromethanesulfinyl (SOCF₃) units^{91e} have gained considerable attention.

1.1 Properties of the SCF₃ group

The trifluoromethylthiolated group (SCF₃) is characterized by its high electron-withdrawing property⁷ and its ability to enhance molecule lipophilicity (Hansch hydrophobic parameter: $\pi = 1.44$, see Chapter 1, Table 1).^{7a} These unique features are particularly interesting for tuning the properties of the biological molecules and in the quest of new drugs.⁹² Therefore, over the last five years, the scientific community showed an exponential interest for this emergent group.⁹¹

1.2 SCF₃-containing molecules in pharmaceuticals and agrochemicals

To date, few compounds have been already commercialized especially agrochemical derivatives or have demonstrated interesting properties as depicted in Figure 7.

For example, Fipronil (Regent[®], BASF) is a widely used phenylpyrazole insecticide.⁹³ It is highly effective against a variety of insect pests.^{93c} Toltrazuril,

⁹⁰ Tlili, A.; Toulgoat, F.; Billard, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 11726.

⁹¹ For selected reviews, see: (a) Tlili, A.; Billard, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 6818; (b) Toulgoat, F.; Alazet, S.; Billard, T. *Eur. J. Org. Chem.* **2014**, 2415; (c) Barata-Vallejo, S.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, *14*, 7150; (d) Zhang, K.; Xu, X.; Qing, F. *Chin. J. Org. Chem.* **2015**, *35*, 556. (e) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731.

⁹² Leroux, F. R. *Curr. Top. Med. Chem.* **2014**, 941.

⁹³ (a) Aajoud, A.; Raveton, M.; Azrou-Isghi, D.; Tissut, M.; Ravanel, P. J. *Agric. Food. Chem.* **2008**, *56*, 3732; (b) Islam, R.; Lynch, J. W. *Br. J. Pharmacol.* **2012**, *165*, 2707; (c) Tingle, C. C.; Rother, J. A.; Dewhurst, C. F.; Lauer,

which bears a SCF₃ group on the aromatic ring, is a very useful drug for the therapy of caecal coccidiosis.⁹⁴ Cefazaflur is the first-generation cephalosporin antibiotic containing a SCF₃ group on the aliphatic chain. It has demonstrated good in vitro antibacterial activity against gram-positive cocci for instance.⁹⁵ The Tiflorex bearing a SCF₃-substituted aromatic ring is a stimulant amphetamine, which was used as anorectic drug. Compared with its trifluoromethylated analogue (Fenfluramine), Tiflorex showed to be twice as potent as an anorectic.⁹⁶

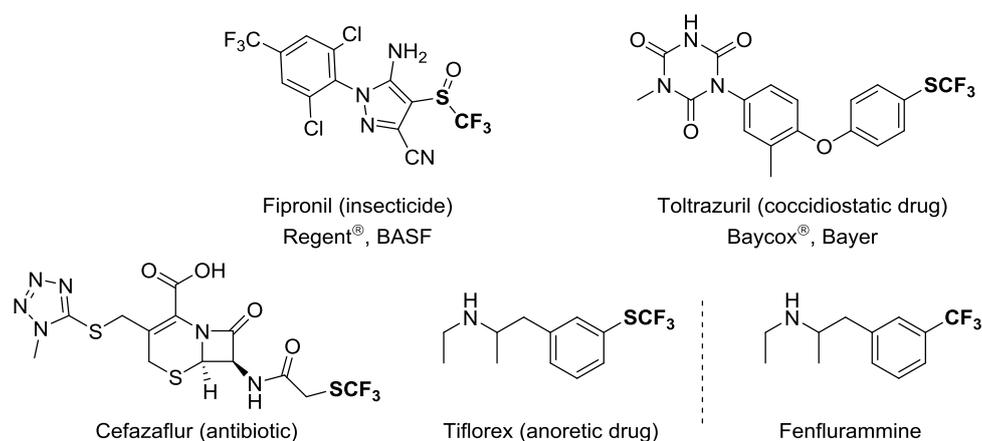


Figure 7: Selected examples of relevant compounds

1.3 Synthesis of SCF₃-containing molecules

There are two general strategies for the introduction of the SCF₃ moiety into organic molecules: indirect and direct methods (Figure 8).⁹¹ Early studies in this area focused on the indirect strategy, including nucleophilic fluorination of perchloroalkyl sulfides via a halogen-exchange process⁹⁷ and the trifluoromethylation of sulfur-containing precursors.^{91e, 98} A more efficient way is the direct trifluoromethylthiolation, which could avoid a multi-step synthesis to prepare the

S.; King, W. J. *Reviews of Environmental Contamination and Toxicology*, Springer, New York, **2003**.

⁹⁴ (a) Laczay, P.; Vörös, G.; Semjén, G. *Int. J. Parasitol.* **1995**, *25*, 753; (b) Pommier, P.; Keïta, A.; Wessel-Robert, S.; Dellac, B.; Mundt, H. C. *Rev. Med. Vet.* **2003**, *154*, 41.

⁹⁵ (a) Counts, G. W.; Gregory, D.; Zeleznik, D.; Turck, M. *Antimicrob. Agents Chemother.* **1977**, *11*, 708; (b) Aswapokee, N.; Neu, H. C. *Antimicrob. Agents Chemother.* **1979**, *15*, 444.

⁹⁶ (a) Silverstone, T.; Fincham, J.; Plumley, J. *Br. J. Clin. Pharmacol.* **1979**, *7*, 353; (b) André, J. N.; Dring, L. G.; Gillet, G.; Mas-Chamberlin, C. *Br. J. Pharmacol.* **1979**, *66*, 506.

⁹⁷ Wakselman, C.; Tordeux, M. *J. Org. Chem.* **1985**, *50*, 4047.

⁹⁸ For selected examples, see: (a) Billard, T.; Langlois, B. R. *Tetrahedron Lett.* **1996**, *37*, 6865; (b) Billard, T.; Large, S.; Langlois, B. R. *Tetrahedron Lett.* **1997**, *38*, 65; (c) Billard, T.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **1999**, *64*, 3813; (d) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848; (e) Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 9057.

sulfur-containing precursors. In this section, we will mainly focus on the direct trifluoromethylthiolation of molecules.

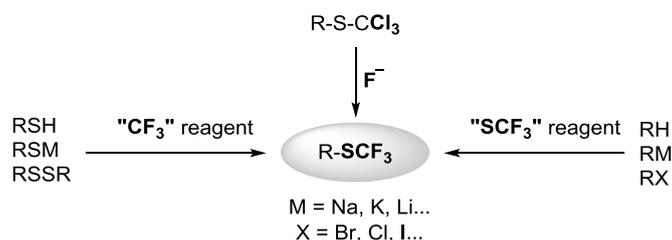


Figure 8: Synthesis of SCF₃-containing molecules

1.3.1 Direct introduction of the SCF₃ group onto molecules

The direct trifluoromethylthiolation using either a nucleophilic trifluoromethylthiolating reagent or an electrophilic trifluoromethylthiolating reagent represents one of the most straightforward and promising approaches for the synthesis of SCF₃-containing molecules. In the past several years, great efforts have been devoted in the development of new methodologies and the synthesis of new trifluoromethylthiolating reagents.⁹¹

1.3.1.1 Synthesis of SCF₃-containing molecules by nucleophilic trifluoromethylthiolation reactions

Nucleophilic trifluoromethylthiolation is one of the common strategies for the direct incorporation of the SCF₃ unit. In recent years, a variety of nucleophilic trifluoromethylthiolating reagents has been developed.⁹⁹ Among them, Hg(SCF₃)₂¹⁰⁰ and CsSCF₃¹⁰¹ are the early used nucleophilic trifluoromethylthiolating reagents. However, due to their toxicity, weak stability and difficult synthesis, these reagents are not widely used in the nucleophilic trifluoromethylthiolations. Besides, CuSCF₃ was also employed in several nucleophilic trifluoromethylthiolations.¹⁰² However,

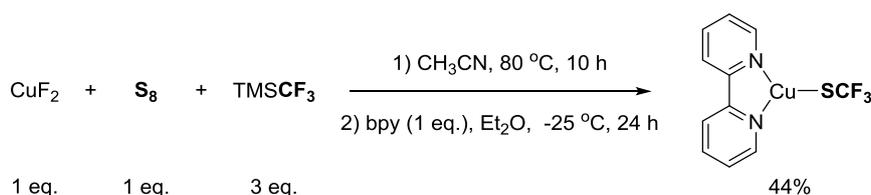
⁹⁹ Zheng, H.; Huang, Y.; Weng, Z. *Tetrahedron Lett.* **2016**, 57, 1397.

¹⁰⁰ (a) Man, E. H.; Coffman, D. D.; Muetterties, E. L. *J. Am. Chem. Soc.* **1959**, 81, 3575; (b) Harris Jr, J. F. *J. Org. Chem.* **1967**, 32, 2063.

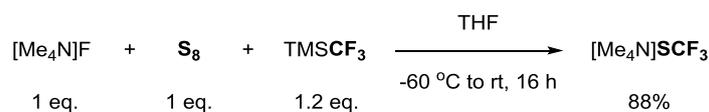
¹⁰¹ (a) Yagupolskii, W.; Naumann, D.; Hoge, B.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2003**, 119, 101; (b) Ye, K.-Y.; Zhang, X.; Dai, L.-X.; You, S.-L. *J. Org. Chem.* **2014**, 79, 12106.

¹⁰² For selected examples, see: (a) Rueping, M.; Tolstoluzhsky, N.; Nikolaienko, P. *Chem. Eur. J.* **2013**, 19, 14043; (b) Adams, D. J.; Goddard, A.; Clark, J. H.; Macquarrie, D. J. *Chem. Commun.* **2000**, 987; (c) Lefebvre, Q.; Fava, E.; Nikolaienko, P.; Rueping, M. *Chem. Commun.* **2014**, 50, 6617; (d) Nikolaienko, P.; Yildiz, T.; Rueping, M. *Eur. J. Org. Chem.* **2016**, 1091.

CuSCF₃ was sensitive to oxygen which hampered its wide application.¹⁰³ In order to solve this problem, Weng and co-workers succeeded in the synthesis of an air-stable reagent (bpy)Cu(SCF₃) (Scheme 23).¹⁰⁴ By the reaction of CuF₂, elemental sulfur and TMSCF₃, in the presence of bipyridine as ligand, the (bpy)Cu(SCF₃) was obtained in 44% yield. This reagent showed high reactivity towards various electrophiles such as aryl halides, benzyl bromides, alkyl halides, allylic bromides, acid chlorides and heteroaryl bromides.⁹⁹

Scheme 23: Synthesis of (bpy)Cu(SCF₃)

To broaden the toolbox for the introduction of the SCF₃ group onto molecules, the [Me₄N]SCF₃ reagent was synthesized by Yagupolskii and co-workers in 2003. Treating [Me₄N]F with TMSCF₃ and elemental sulfur in THF provided the [Me₄N]SCF₃ in 88% yield (Scheme 24).^{99,101a} After this pioneering work, a range of trifluoromethylthiolation reactions using [Me₄N]SCF₃ has been reported.¹⁰⁵ Moreover, its analogue [Bu₄N]SCF₃ was also found to be efficient for the trifluoromethylthiolation.^{102a}

Scheme 24: Synthesis of [Me₄N]SCF₃

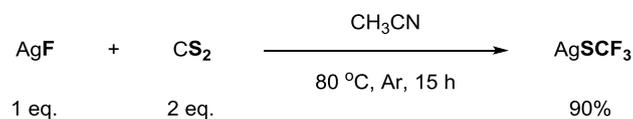
Beyond the nucleophilic trifluoromethylthiolating reagents described above, AgSCF₃ could be easily synthesized from silver fluoride and carbon disulfide in

¹⁰³ Clark, J. H.; Smith, H. J. *Fluorine Chem.* **1993**, 61, 223.

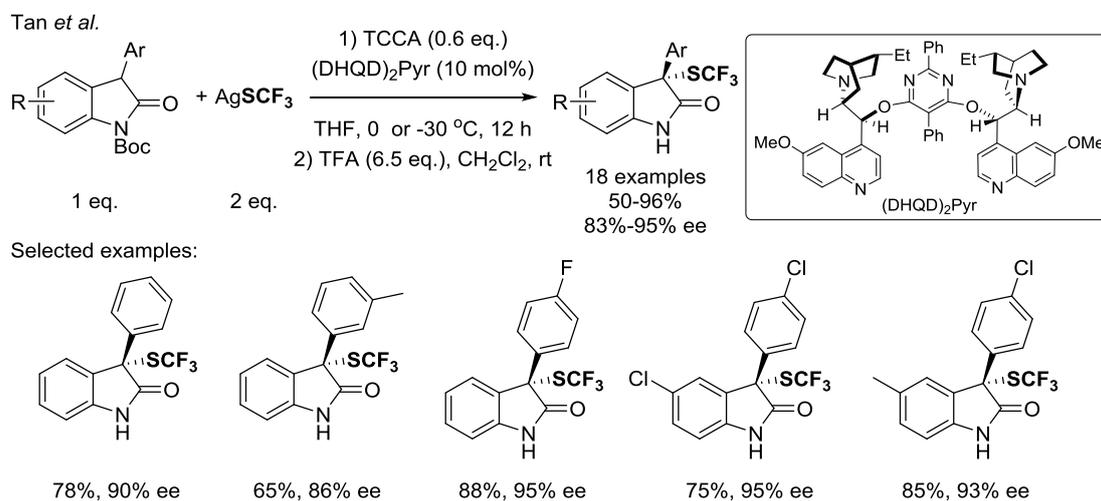
¹⁰⁴ Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K.-W. *Angew. Chem., Int. Ed.* **2013**, 52, 1548.

¹⁰⁵ For selected examples, see: (a) Kremlev, M. M.; Yagupolskii, W.; Naumann, D.; Yagupolskii, Y. L. *Tetrahedron Lett.* **2004**, 45, 6101; (b) Durr, A. B.; Yin, G.; Kalvet, I.; Napoly, F.; Schoenebeck, F. *Chem. Sci.* **2016**, 7, 1076; (c) Zhang, C.-P.; Vicic, D. A. *J. Am. Chem. Soc.* **2012**, 134, 183; (d) Zhang, C.-P.; Vicic, D. A. *Chem. Asian J.* **2012**, 7, 1756; (e) Matheis, C.; Krause, T.; Bragoni, V.; Goossen, L. J. *Chem. Eur. J.* **2016**, 22, 12270; (f) Yin, G.; Kalvet, I.; Englert, U.; Schoenebeck, F. *J. Am. Chem. Soc.* **2015**, 137, 4164; (g) Yin, G.; Kalvet, I.; Schoenebeck, F. *Angew. Chem., Int. Ed.* **2015**, 54, 6809.

CH₃CN at 80 °C for 15 h, serving as an alternative nucleophilic trifluoromethylthiolating reagent (Scheme 25).¹⁰⁶ Note that it could be also generated from [Me₄N]SCF₃ and AgNO₃.^{101a}

Scheme 25: Synthesis of AgSCF₃

This stable reagent proved to be an efficient SCF₃ source for the functionalization of various electrophiles including aryl halides, alkyl halides, propargyl bromide, alkenes, alcohols, terminal alkynes, indoles, arynes as well as methylenecyclopropanes.^{99,107} Worth mentioning that the combination of AgSCF₃ and trichloroisocyanuric acid (TCCA) could in situ generate the bis(trifluoromethyl)disulfide (CF₃SSCF₃ **10**) as the active species for the enantioselective trifluoromethylthiolation of oxindoles. Indeed, by using (DHQD)₂Pyr as catalyst, various SCF₃-containing oxindoles were synthesized in good yields and enantioselectivities (Scheme 26).¹⁰⁸



Scheme 26: Enantioselective trifluoromethylthiolation of oxindoles

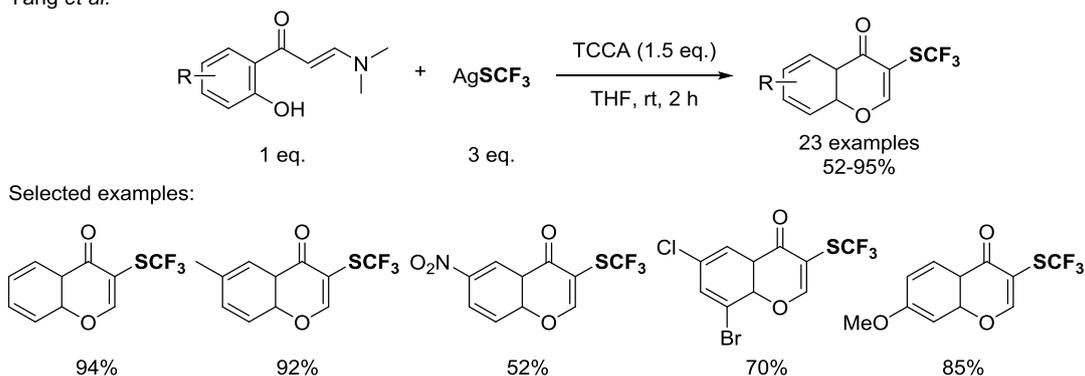
¹⁰⁶ Teverovskiy, G.; Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, 50, 7312.

¹⁰⁷ For selected examples, see: (a) Xu, C.; Chen, Q.; Shen, Q. *Chin. J. Chem.* **2016**, 34, 495; (b) Wu, W.; Dai, W.; Ji, X.; Cao, S. *Org. Lett.* **2016**, 18, 2918; (c) Ma, L.; Cheng, X.-F.; Li, Y.; Wang, X.-S. *Tetrahedron Lett.* **2016**, 57, 2972; (d) Zeng, Y.; Hu, J. *Org. Lett.* **2016**, 18, 856; (e) Shi, M.; Chen, M.-T.; Tang, X.-Y. *Org. Chem. Front.* **2016**, 4, 86.

¹⁰⁸ Zhu, X.-L.; Xu, J.-H.; Cheng, D.-J.; Zhao, L.-J.; Liu, X.-Y.; Tan, B. *Org. Lett.* **2014**, 16, 2192.

Inspired by Tan's work, Yang and co-workers then applied this strategy for the synthesis of 3-[(trifluoromethyl)thio]-chromones (Scheme 27).¹⁰⁹ This practical and easily handled reaction allowed the access to a range of 3-[(trifluoromethyl)thio]-chromones in moderate to good yields under mild conditions.

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Scheme 27: Trifluoromethylthiolation using AgSCF₃ and TCCA

Furthermore, other nucleophilic trifluoromethylthiolating reagents (TDAE)(SCF₃)₂,¹¹⁰ and O-octadecyl-S-trifluorothiolcarbonate¹¹¹ have been also used.

1.3.1.2 Synthesis of SCF₃-containing molecules by electrophilic trifluoromethylthiolation

Concerning the electrophilic trifluoromethylthiolation reagents, trifluoromethylsulfonyl chloride (CF₃SOCl) and CF₃SSCF₃ **10** were widely used in the early stage.⁹¹ However, the gaseous and toxic nature of these reagents restricted their further utilization.

To overcome these limitations, great efforts have been devoted in the design of new stable and easy-to-handle reagent.¹¹² Among them, the N-(trifluoromethylthio)phthalimide **11** was initially prepared by Munavalli and

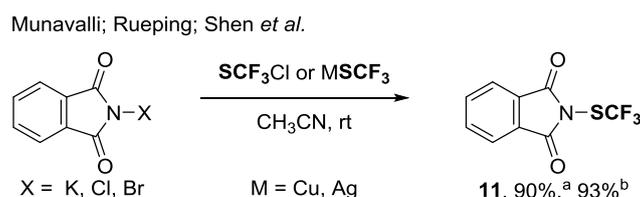
¹⁰⁹ Xiang, H.; Yang, C. *Org. Lett.* **2014**, 16, 5686.

¹¹⁰ Kolomeitsev, A.; Medebielle, M.; Kirsch, P.; Lork, E.; Roschenthaler, G.-V. *J. Chem. Soc., Perkin Trans.1* **2000**, 2183.

¹¹¹ Zard, S.Z.; Li, S.-G. *Org. Lett.* **2013**, 15, 5898.

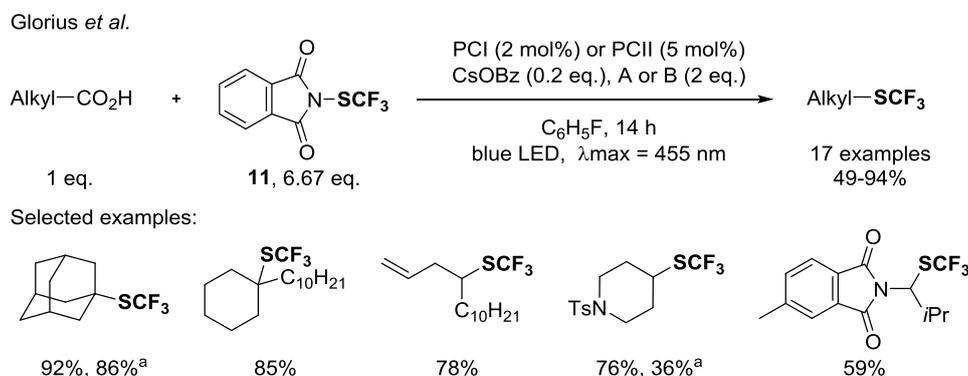
¹¹² Chachignon, H.; Cahard, D. *Chin. J. Chem.* **2016**, 34, 445.

co-workers through the reaction of potassium phthalimide with CF₃SCl in 2000 (Scheme 28).¹¹³ Later, Rueping¹¹⁴ and Shen¹¹⁵ independently reported more efficient methods toward the synthesis of **11** using CuSCF₃ or AgSCF₃ in the presence of N-chlorophthalimide or N-bromophthalimide, respectively. These extremely simple and efficient methods avoid the use of the toxic SCF₃Cl providing the **11** in high yields.



Scheme 28: Synthesis of the N-(trifluoromethylthio)phthalimide **11**. ^a Rueping's conditions: N-chlorophthalimide (1 eq.), CuSCF₃ (1.2 eq.), CH₃CN, rt, 12 h; ^b Shen's conditions: N-bromophthalimide (1 eq.), AgSCF₃ (1.3 eq.), CH₃CN, rt, 3 h.

The N-(trifluoromethylthio)phthalimide **11**^{113,114,115} was further applied by Glorius and co-workers who developed a light-promoted decarboxylative trifluoromethylthiolation of alkyl carboxylic acids in 2016 (Scheme 29).¹¹⁶



Scheme 29: Light-promoted decarboxylative trifluoromethylthiolation of alkyl carboxylic acids. ^a PCII was used instead of PCI. A = mesitylene; B = methyl 3-(methyl)benzoate.

A range of primary, secondary and tertiary alkyl carboxylic acids were efficiently converted into the trifluoromethylthiolated derivatives using PCI

¹¹³ Munavalli, S.; Rohrbaugh, D. K.; Rossmann, D. I.; Berg, F. J.; Wagner, G. W.; Durst, H. D. *Synth. Commun.* **2000**, 30, 2847.

¹¹⁴ Pluta, R.; Nikolaienko, P.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, 53, 1650.

¹¹⁵ Kang, K.; Xu, C.; Shen, Q. *Org. Chem. Front.* **2014**, 1, 294.

¹¹⁶ Candish, L.; Pitzer, L.; Gomez Suarez, A.; Glorius, F. *Chem. Eur. J.* **2016**, 22, 4753.

([Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆, dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4'-di-tert-butyl-2,2'-bipyridine) or PCII (9-mesityl-10-methylacridinium perchlorate) as catalyst under mild reaction conditions.

Moreover, N-(trifluoromethylthio)succinimide **12** (Figure 9)¹¹⁵ which was initially synthesized by Haas using CF₃SCl in 1996¹¹⁷ and the N-(trifluoromethylthio)saccharin **13** (Figure 9)¹¹⁸ were synthesized by Shen and co-workers in the similar manner as for **11**. These newly developed electrophilic trifluoromethylthiolating reagents showed high reactivity towards the trifluoromethylthiolation of various nucleophiles.^{112,119}

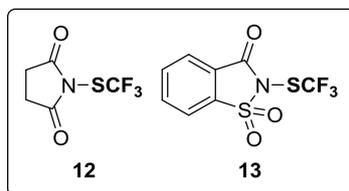


Figure 9: N-(trifluoromethylthio)succinimide **12** and N-(trifluoromethylthio)saccharin **13**

Early in 2008, the trifluoromethanesulfenamide **14a** was synthesized by Billard-Langlois and co-workers after addition of the aniline derivatives to the mixture of Ruppert-Prakash reagent (TMSCF₃), diethylaminosulfur trifluoride (DAST) and N,N-diisopropylethylamine (DIEA) in dichloromethane (Scheme 30).¹²⁰ The analogue of **14a**, N-methyl-N-[(trifluoromethyl)thio]aniline **14b**¹²¹ and the N-methyl-N-tosyl-trifluoromethanesulfenamides **14c**^{121,122} were prepared from the methylation of the corresponding amide in the presence of MeI and nBuLi by the same group. These reagents have been used with various nucleophiles such as

¹¹⁷ Haas, A.; Möller, G. *Chem. Ber.* **1996**, 129, 1383.

¹¹⁸ Xu, C.; Ma, B.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, 53, 9316.

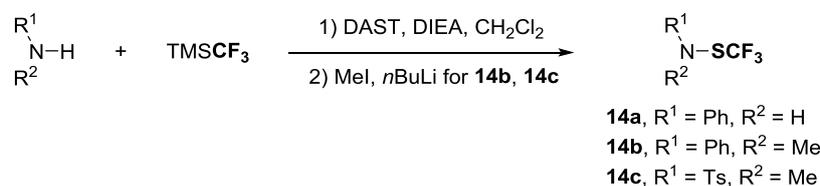
¹¹⁹ For selected examples using **12** as the SCF₃ source, see: (a) Xu, C.; Shen, Q. *Org. Lett.* **2014**, 16, 2046; (b) Liao, K.; Zhou, F.; Yu, J.-S.; Gao, W.-M.; Zhou, J. *Chem. Commun.* **2015**, 51, 16255; For selected examples using **13** as the SCF₃ source, see: (c) Maeno, M.; Shibata, N.; Cahard, D. *Org. Lett.* **2015**, 17, 1990; (d) Wang, Q.; Qi, Z.; Xie, F.; Li, X. *Adv. Synth. Catal.* **2015**, 357, 355; (e) Luo, J.; Zhu, Z.; Liu, Y.; Zhao, X. *Org. Lett.* **2015**, 17, 3620; (f) Xu, C.; Shen, Q. *Org. Lett.* **2015**, 17, 4561; (g) Wu, J.-J.; Xu, J.; Zhao, X. *Chem. Eur. J.* **2016**, 22, 15265; For an account regarding the application of **13** and **16**, see: (h) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *Acc. Chem. Res.* **2015**, 48, 1227.

¹²⁰ Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. J. *Org. Chem.* **2008**, 73, 9362.

¹²¹ Glenadel, Q.; Alazet, S.; Baert, F.; Billard, T. *Org. Process Res. Dev.* **2016**, 20, 960.

¹²² Alazet, S.; Zimmer, L.; Billard, T. *Chem. Eur. J.* **2014**, 20, 8589.

electron-rich arenes, heteroarenes, allylsilanes, amines, thiols, phenols, among others.¹²³



Scheme 30: Synthesis of the Billard-Langlois reagent **14a** and Billard reagents **14b**, **14c**

Very recently, the development of another shelf-stable, easily prepared trifluoromethylthiolating reagent, the N-trifluoromethylthiodibenzene-sulfonimide **15** (Figure 10) was described by the group of Shen¹²⁴ and Zhao¹²⁵ almost at the same time. It was demonstrated that this new reagent could be applied in the trifluoromethylthiolation of a variety of nucleophiles such as electron-rich arenes, activated heteroarenes, styrenes and thiols,¹²⁴ as well as the enantioselective trifluoromethylthiolating lactonization of 4-aryl-substituted but-3-enoic acids.¹²⁵ Moreover, the reagent **16a** (Figure 10), introduced by Lu and Shen,¹²⁶ was synthesized by the reaction of 1-chloro-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole with AgSCF₃. It has shown interesting reactivity towards the trifluoromethylthiolation of β -ketoesters, terminal alkynes, aryl or vinyl boronic acids.^{119g} Interestingly, the structure of **16a** was established by Buchwald and co-workers, and the X-ray analysis showed that the SCF₃ group was connected to the oxygen atom instead of the iodine

¹²³ For selected examples using **14a** as the SCF₃ source, see: (a) Ferry, A.; Billard, T.; Bacqué, E.; Langlois, B. R. J. Fluorine Chem. **2012**, 134, 160; (b) Yang, Y.; Jiang, X.; Qing, F.-L. J. Org. Chem. **2012**, 77, 7538; (c) Liu J.; Chu L.; Qing, F.-L. Org. Lett. **2013**, 15, 894; (d) Sheng, J.; Wu, J. Org. Biomol. Chem. **2014**, 12, 7629; (e) Jereb, M.; Dolenc, D. RSC Adv. **2015**, 5, 58292; (f) Jereb, M.; Gosak, K. Org. Biomol. Chem. **2015**, 13, 3103; (g) Wu, W.; Zhang, X.; Liang, F.; Cao, S. Org. Biomol. Chem. **2015**, 13, 6992; (h) Xiao, Q.; Sheng, J.; Chen, Z.; Wu, J. Chem. Commun. **2013**, 49, 8647; (i) Li, Y.; Li, G.; Ding, Q. Eur. J. Org. Chem. **2014**, 2014, 5017; (j) Sheng, J.; Fan, C.; Wu, J. Chem. Commun. **2014**, 50, 5494; (k) Sheng, J.; Li, S.; Wu, J. Chem. Commun. **2014**, 50, 578; (l) Xiao, Q.; Zhu, H.; Li, G.; Chen, Z. Adv. Synth. Catal. **2014**, 356, 3809; For selected examples using **14b** as the SCF₃ source, see: (m) Glenadel, Q.; Alazet, S.; Billard, T. J. Fluorine Chem. **2015**, 179, 89; (n) Baert, F.; Colomb, J.; Billard, T. Angew. Chem., Int. Ed. **2012**, 51, 10382; (o) Alazet, S.; Zimmer, L.; Billard, T. Angew. Chem., Int. Ed. **2013**, 52, 10814; (p) Alazet, S.; Ollivier, K.; Billard, T. Beilstein J. Org. Chem. **2013**, 9, 2354; For selected examples using **14c** as the SCF₃ source, see: (q) Glenadel, Q.; Tlili, A.; Billard, T. Eur. J. Org. Chem. **2016**, 1955; (r) Alazet, S.; Zimmer, L.; Billard, T. J. Fluorine Chem. **2015**, 171, 78; (s) Glenadel, Q.; Alazet, S.; Tlili, A.; Billard, T. Chem. Eur. J. **2015**, 14694; (t) Alazet, S.; Billard, T. Synlett **2015**, 26, 76; (u) Glenadel, Q.; Bordy, M.; Alazet, S.; Tlili, A.; Billard, T. Asian J. Org. Chem. **2016**, 5, 428; (v) Glenadel, Q.; Billard, T. Chin. J. Chem. **2016**, 34, 455.

¹²⁴ Zhang, P.; Li, M.; Xue, X.-S.; Xu, C.; Zhao, Q.; Liu, Y.; Wang, H.; Guo, Y.; Lu, L.; Shen, Q. J. Org. Chem. **2016**, 81, 7486.

¹²⁵ Liu, X.; An, R.; Zhang, X.; Luo, J.; Zhao, X. Angew. Chem., Int. Ed. **2016**, 55, 5846.

¹²⁶ Shao, X.; Wang, X.; Yang, T.; Lu, L.; Shen, Q. Angew. Chem., Int. Ed. **2013**, 52, 3457.

one.¹²⁷ Later, a simplified electrophilic trifluoromethylthiolating reagent **16b** (Figure 10) was also prepared by Lu and Shen, which showed similar reactivity as **16a**.^{119h} Finally, a hypervalent iodonium ylide reagent **17a** (Figure 10)¹²⁸ and its analogue **17b** (Figure 10)¹²⁹ were developed by Shibata and co-workers, and were employed in the trifluoromethylthiolation of several nucleophiles such as enamines, indoles, β -ketoesters, pyrroles as well as anilines.¹³⁰

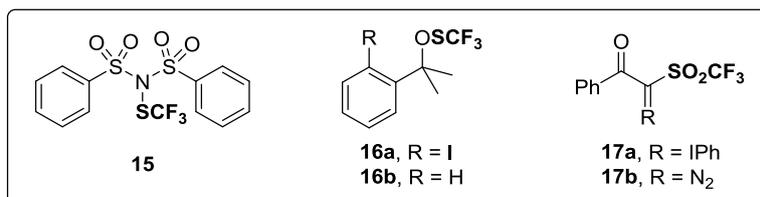


Figure 10: Electrophilic trifluoromethylthiolating reagents **15**, **16**, **17**

1.3.1.3 Oxidative trifluoromethylthiolation

The use of a nucleophilic trifluoromethylating reagent and a sulfur source under oxidative conditions is an alternative strategy to introduce the SCF₃ group. For example, the combination of TMSCF₃ and S₈ was successfully employed in the oxidative trifluoromethylthiolation of aryl boronic acids using Ag₂CO₃ as oxidant (Scheme 31, a).¹³¹ A range of boronic acids was converted into the trifluoromethylthiolated derivatives in good yields at room temperature. Similarly, sodium trifluoroacetate could also be applied in such transformation affording the desired products albeit in moderate yields (Scheme 31, b).¹³²

¹²⁷ Vinogradova, E. V.; Müller, P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2014**, 53, 3125.

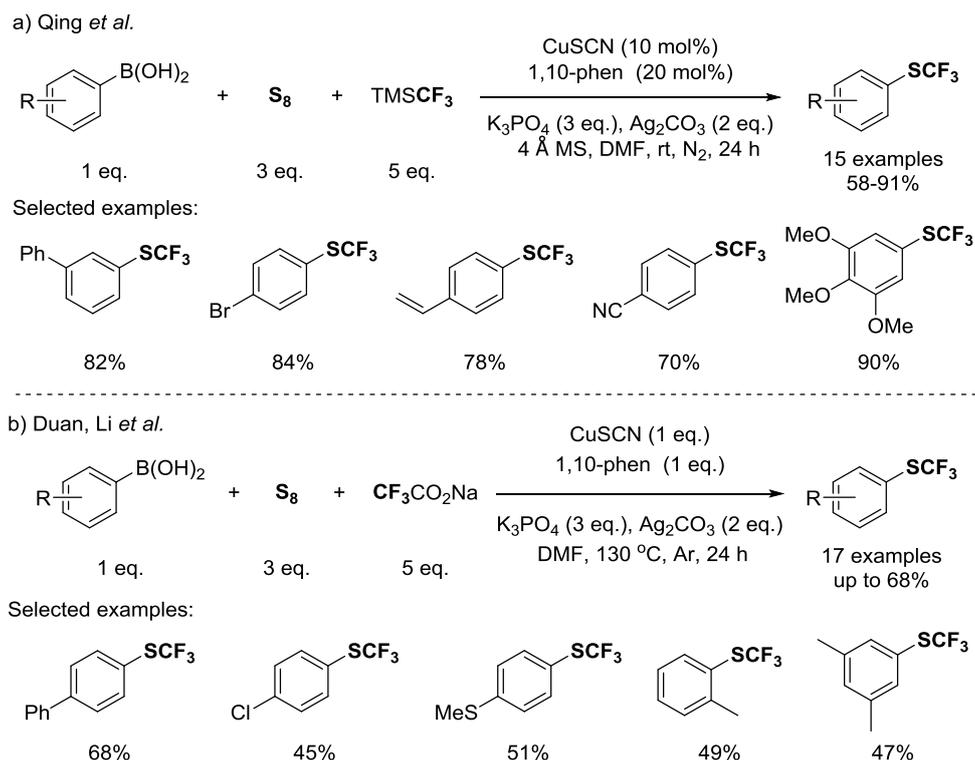
¹²⁸ Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, 135, 8782.

¹²⁹ Huang, Z.; Okuyama, K.; Wang, C.; Tokunaga, E.; Li, X.; Shibata, N. *Chem. Open* **2016**, 5, 188.

¹³⁰ For selected examples, see: (a) Huang, Z.; Yang, Y.-D.; Tokunaga, E.; Shibata, N. *Asian J. Org. Chem.* **2015**, 4, 525; (b) Huang, Z.; Yang, Y.-D.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2015**, 1094; (c) Arimori, S.; Takada, M.; Shibata, N. *Org. Lett.* **2015**, 17, 1063; (d) Arimori, S.; Takada, M.; Shibata, N. *Dalton trans.* **2015**, 44, 19456.

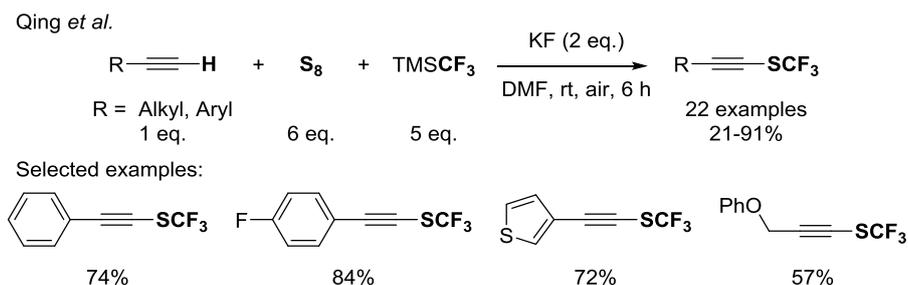
¹³¹ Chen, C.; Xie, Y.; Chu, L.; Wang, R.-W.; Zhang, X.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2012**, 51, 2492.

¹³² Zhai, L.; Li, Y.; Yin, J.; Jin, K.; Zhang, R.; Fu, X.; Duan, C. *Tetrahedron* **2013**, 69, 10262.



Scheme 31: Oxidative trifluoromethylthiolation of boronic acids

Moreover, this strategy could also be applied in the synthesis of trifluoromethylthiolated alkynes, affording the corresponding products in good yields (Scheme 32).¹³³ Inspired by these reports, the trifluoromethylthiolation of Morita-Baylis-Hillman carbonates,¹³⁴ aryl and alkyl halides¹³⁵ were also developed.

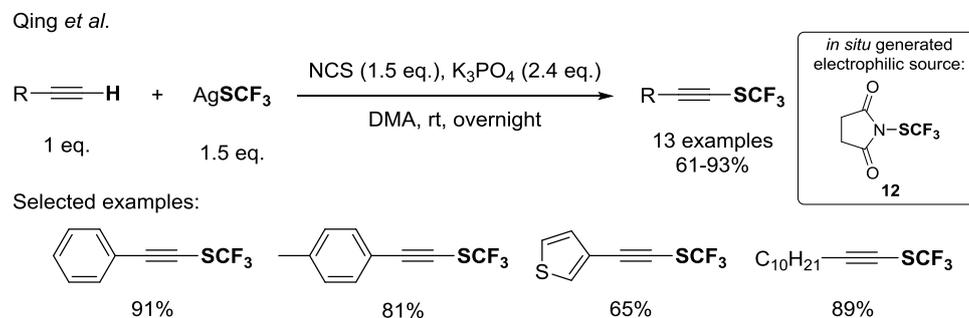


Scheme 32: Oxidative trifluoromethylthiolation of alkynes

Subsequently, Qing and co-workers reported the oxidative trifluoromethylthiolation of terminal alkynes using AgSCF₃ as the nucleophilic SCF₃ source and NCS as an oxidant (Scheme 33).¹³⁶ A range of (hetero)aryl and alkyl

¹³³ Chen, C.; Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, 134, 12454.¹³⁴ Dai, X.; Cahard, D. *Synlett* **2014**, 26, 40.¹³⁵ Zhong, W.; Liu, X. *Tetrahedron Lett.* **2014**, 55, 4909.¹³⁶ Zhu, S.-Q.; Xu, X.-H.; Qing, F.-L. *Eur. J. Org. Chem.* **2014**, 4453.

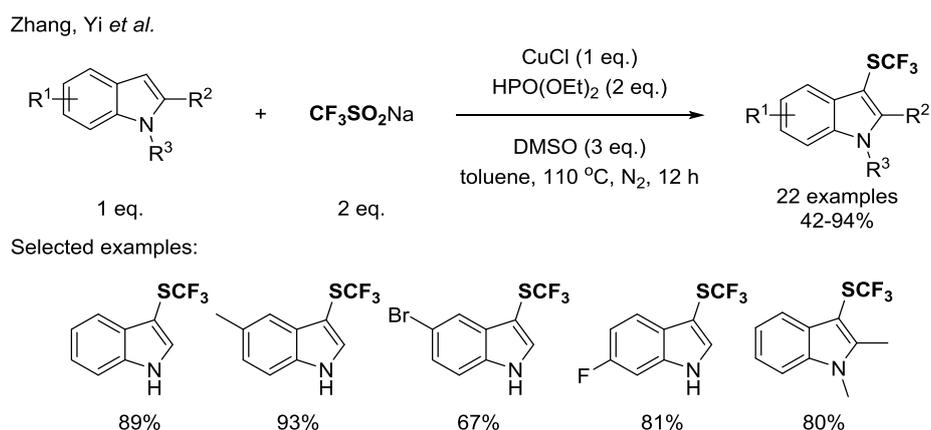
derived alkynes were functionalized in good yields. Control experiments showed that the in situ generated electrophilic source **12** might be the active species in the reaction system.



Scheme 33: Trifluoromethylthiolation of terminal alkynes using AgSCF₃

1.3.1.4 Synthesis of SCF₃-containing molecules by the reduction of CF₃SO₂Na and CF₃SO₂Cl reagents

Recently, Zhang and Yi developed the trifluoromethylthiolation of indole derivatives using the Langlois' reagent CF₃SO₂Na as SCF₃ source (Scheme 34).¹³⁷ In this reaction system, the reduction of CF₃SO₂Na with HPO(OEt)₂ led to the in situ formation of a plausible CF₃S(O)H intermediate. CuCl could serve as both a reducing reagent for the conversion of CF₃S(O)H intermediate into CF₃SSCF₃ **10** as the reactive species for the trifluoromethylthiolation reaction.

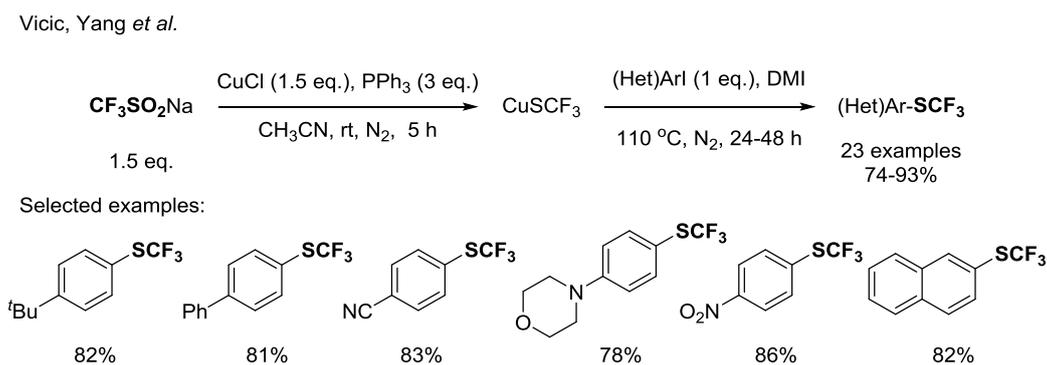


Scheme 34: Trifluoromethylthiolation of indole derivatives using CF₃SO₂Na

Meanwhile, Vicic and Yang developed a practical method for the in situ

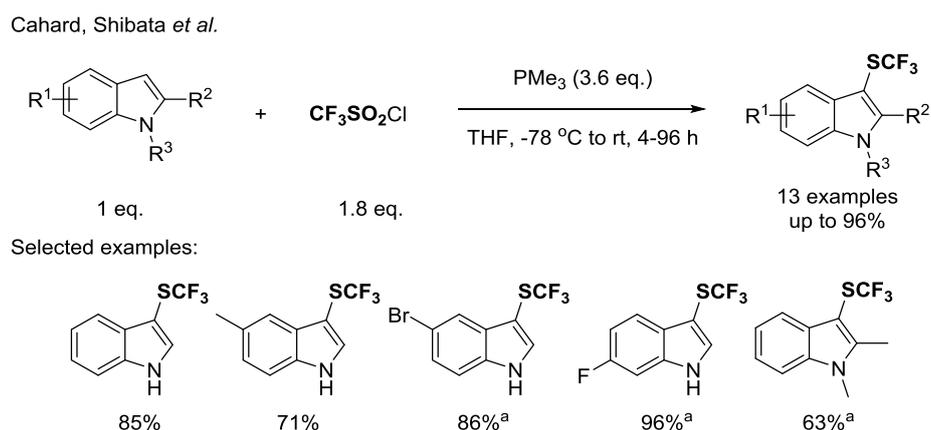
¹³⁷ Jiang, L.; Qian, J.; Yi, W.; Lu, G.; Cai, C.; Zhang, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 14965.

generation of CuSCF_3 from $\text{CF}_3\text{SO}_2\text{Na}$ through a triphenylphosphine-mediated deoxygenative reduction process.¹³⁸ This CuSCF_3 intermediate could be subsequently applied in the trifluoromethylthiolation of various of (hetero)aryl iodides giving access to the trifluoromethylthiolated (hetero)arenes in good yields (Scheme 35). Chai and co-workers further applied the $\text{CF}_3\text{SO}_2\text{Na}$ for the trifluoromethylthiolation of indole, pyrrole and enamine derivatives under mild conditions.¹³⁹



Scheme 35: Trifluoromethylthiolation of (hetero)arenes using $\text{CF}_3\text{SO}_2\text{Na}$

The use of $\text{CF}_3\text{SO}_2\text{Cl}$ for the metal-free electrophilic trifluoromethylthiolation of indole derivatives under reductive conditions was achieved by Cahard and Shibata (Scheme 36).¹⁴⁰ In the presence of PMe_3 , a range of trifluoromethylthiolated indole derivatives was synthesized in good yields.



Scheme 36: Trifluoromethylthiolation of indole derivatives using $\text{CF}_3\text{SO}_2\text{Cl}$. ^a 2.2 eq. of $\text{CF}_3\text{SO}_2\text{Cl}$, 4.4 eq. of PMe_3 were used.

¹³⁸ Yang, Y.; Xu, L.; Yu, S.; Liu, X.; Zhang, Y.; Vicic, D. A. *Chem. Eur. J.* **2016**, *22*, 858.

¹³⁹ Bu, M.-J.; Lu, G.-P.; Cai, C. *Org. Chem. Front.* **2017**, *4*, 266.

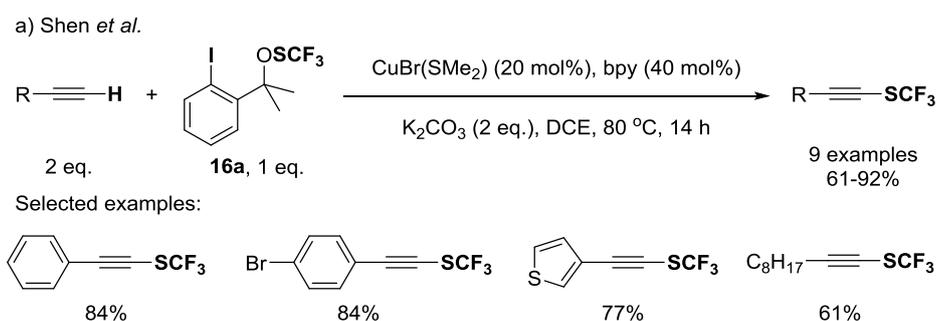
¹⁴⁰ Chachignon, H.; Maeno, M.; Kondo, H.; Shibata, N.; Cahard, D. *Org. Lett.* **2016**, *18*, 2467.

1.3.2 Transition metal-catalyzed trifluoromethylthiolation by C-H bond activation

Over the last years, a strong interest has been shown for the introduction of the SCF₃ group by the transition metal-catalyzed C-H bond activation.^{6c,91c,141} A few works have been reported, which were limited to C(sp)-H bonds and aromatic C(sp²)-H bonds.

1.3.2.1 Transition metal-catalyzed trifluoromethylthiolation of C(sp) centers

In 2013, Shen and co-workers showed the Cu-catalyzed trifluoromethylthiolation of terminal alkynes with the electrophilic reagent **16a** in good to high yields (Scheme 37).¹²⁶



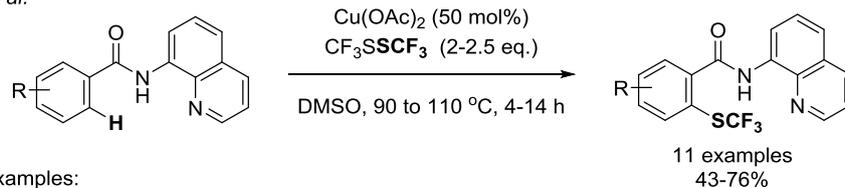
Scheme 37: Trifluoromethylthiolation of terminal alkynes using **16a**

1.3.2.2 Transition metal-catalyzed trifluoromethylthiolation of C(sp²) centers

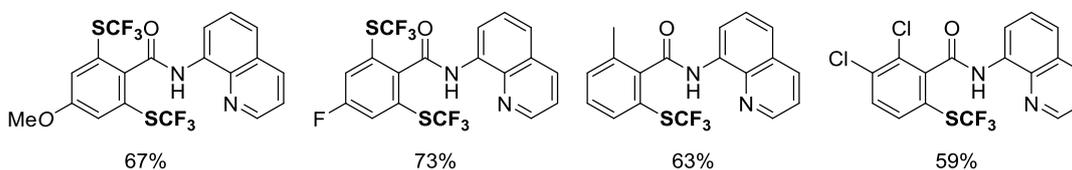
In 2012, with respect to C(sp²)-SCF₃ bond formation, Daugulis and co-workers reported the Cu-promoted mono and ditrifluoromethylthiolation of amides prepared from 8-aminoquinoline. This reaction constituted the first example of the introduction of the SCF₃ unit by transition metal-mediated C-H bond functionalization. Nevertheless, this reaction employed the volatile and toxic CF₃SSCF₃ **10** and required high catalyst loading, which limited the wide applications of such approach (Scheme 38).¹⁴²

¹⁴¹ Lin, J.-H.; Ji, Y.-L.; Xiao, J.-C. *Curr. Org. Chem.* **2015**, 19, 1541

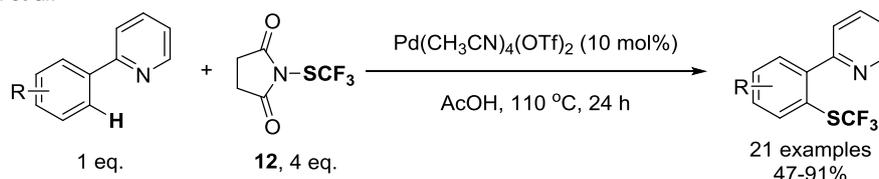
¹⁴² Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, 134, 18237.

Daugulis *et al.*

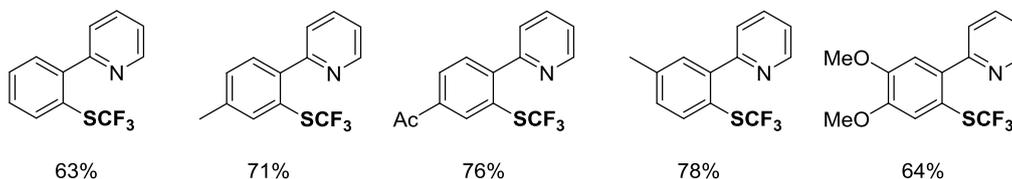
Selected examples:

Scheme 38: Cu-promoted trifluoromethylthiolation of C(sp²)-H bonds using CF₃SSCF₃ **10**

Later, Shen and co-workers reported an elegant Pd-catalyzed trifluoromethylthiolation of aromatic C-H bond by using the electrophilic reagent **12**. The reaction was compatible with a variety of functional groups with moderate yields, but a large excess of **12** was required (Scheme 39).^{119a}

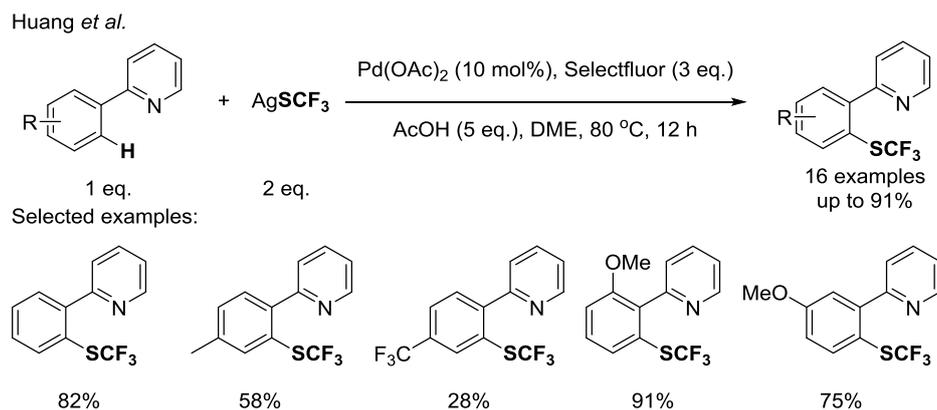
Shen *et al.*

Selected examples:

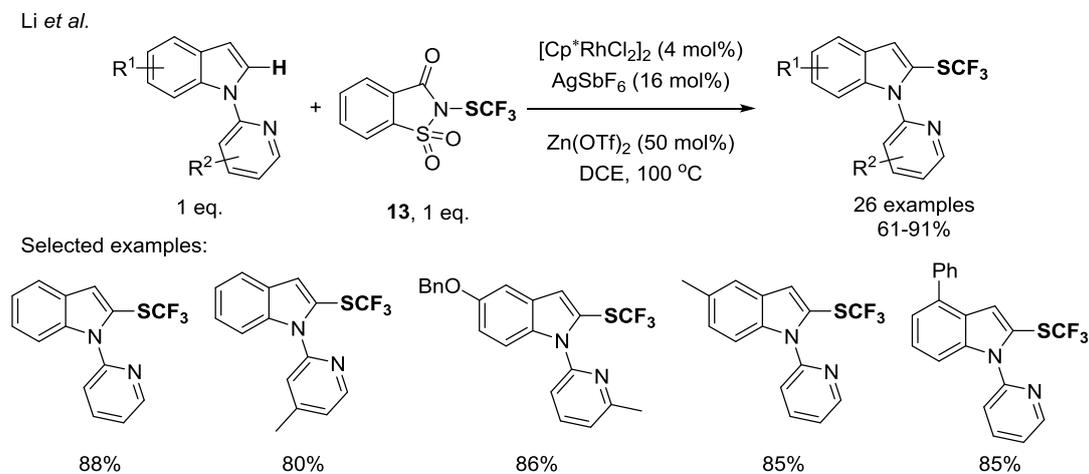
Scheme 39: Pd-catalyzed trifluoromethylthiolation of C(sp²)-H bonds using **12**

As a complementary approach, Huang and co-workers succeeded in the Pd-catalyzed ortho-trifluoromethylthiolation of 2-phenylpyridine derivatives using AgSCF₃ as the nucleophilic reagent and selectfluor as the oxidant (Scheme 40).¹⁴³ In this case, a ligand exchange pathway was considered for the transformation.

¹⁴³ Yin, W.; Wang, Z.; Huang, Y. *Adv. Synth. Catal.* **2014**, 356, 2998.

Scheme 40: Pd-catalyzed trifluoromethylthiolation of C(sp²)-H bonds using AgSCF₃

More recently, Li and co-workers developed the Rh(III)-catalyzed trifluoromethylthiolation of indoles by using the reagent **13** (Scheme 41).¹⁴⁴ This method selectively functionalized the 2-position of indoles with good substituent tolerance. The role of Zn(OTf)₂ was probably used as a Lewis acid to activate the reagent **13**.



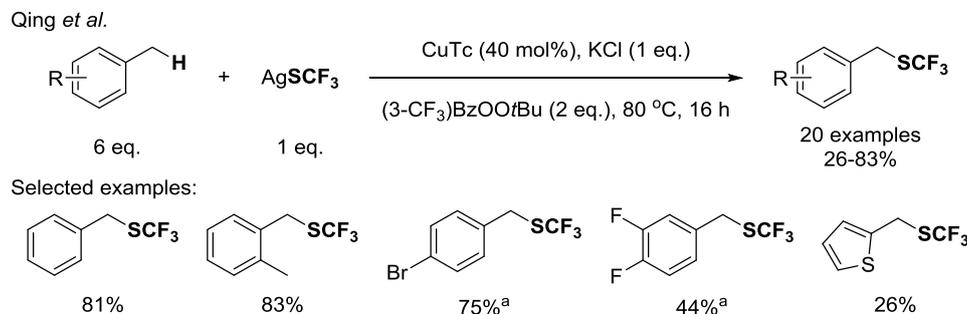
Scheme 41: Rh(III)-catalyzed trifluoromethylthiolation of indole derivatives

1.3.2.3 Transition metal-catalyzed trifluoromethylthiolation of C(sp³) centers

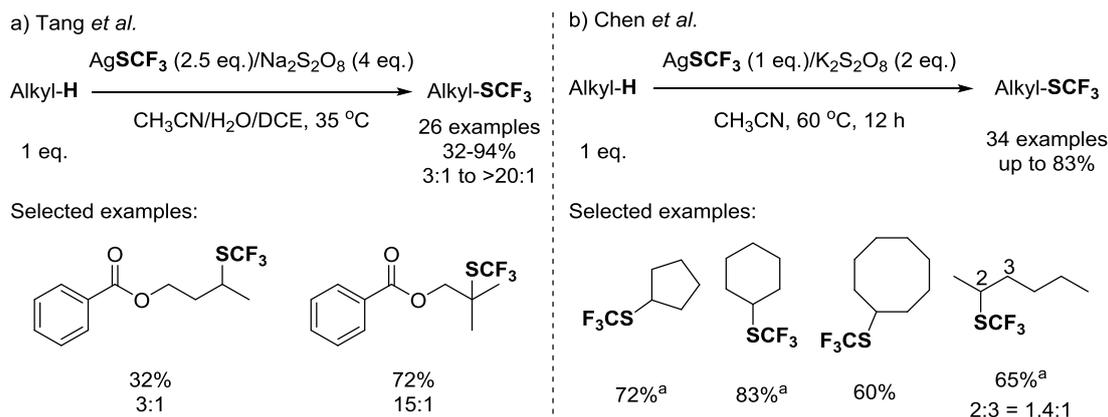
Examples involving the trifluoromethylthiolation of alkyl chains by C(sp³)-H bond functionalization are rare. Recently, Qing and co-workers disclosed the first example of Cu-catalyzed trifluoromethylthiolation of benzylic C(sp³)-H bonds

¹⁴⁴ Wang, Q.; Xie, F.; Li, X. *J. Org. Chem.* **2015**, *80*, 8361.

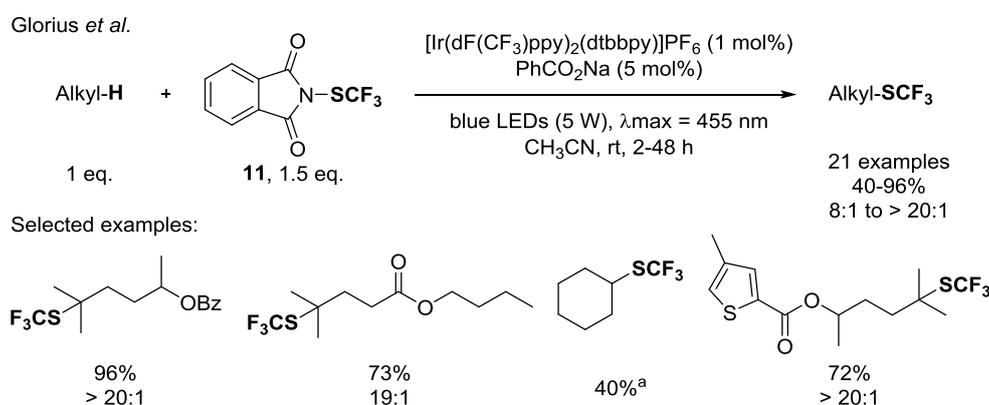
through a radical pathway under mild conditions. Although the reaction provided a straightforward method for the formation of benzyl trifluoromethyl sulfides, a large excess of the substrate was required (Scheme 42).¹⁴⁵

Scheme 42: Trifluoromethylthiolation of benzylic C(sp³)-H bonds

More recently (March, 2015), a trifluoromethylthiolation of aliphatic C(sp³)-H bonds via a radical pathway using AgSCF₃/K₂S₂O₈ was reported by Tang and co-workers (Scheme 43, a).¹⁴⁶ Meanwhile, Chen and Liu described a similar aliphatic C(sp³)-H bond trifluoromethylthiolation in the presence of AgSCF₃/Na₂S₂O₈ (Scheme 43, b).¹⁴⁷ Despite of the good functional group tolerance of these reactions, a mixture of regioisomers were obtained in most cases and the substrates were limited to secondary and tertiary C(sp³)-H bonds.

Scheme 43: Trifluoromethylthiolation of C(sp³)-H bonds by a radical pathway. ^a NMR yield were determined by ¹⁹F NMR using α,α,α -trifluorotoluene as an internal standard.¹⁴⁵ Chen, C.; Xu, X.-H.; Yang, B.; Qing, F.-L. *Org. Lett.* **2014**, *16*, 3372.¹⁴⁶ Guo, S.; Zhang, X.; Tang, P. *Angew. Chem., Int. Ed.* **2015**, *54*, 4065.¹⁴⁷ Wu, H.; Xiao, Z.; Wu, J.; Guo, Y.; Xiao, J.-C.; Liu, C.; Chen, Q.-Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 4070.

Glorius and co-workers described a photoredox-mediated trifluoromethylthiolation reaction of unactivated C(sp³)-H bonds using [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ as a photocatalyst (dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4'-di-tert-butyl-2,2'-bipyridine) (Scheme 44).¹⁴⁸ A range of secondary and tertiary unactivated C(sp³)-H bonds were functionalized in good yields and high selectivities under the standard reaction conditions.



Scheme 44: Photoredox-mediated trifluoromethylthiolation reaction of C(sp³)-H bonds. ^a NMR yields were determined by ¹⁹F NMR using trifluoromethoxybenzene as an internal standard.

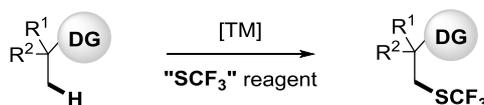
In conclusion, although great progress has been made in the introduction of the SCF₃ group onto molecules by C-H bond activation, the existing examples are mainly based on the C(sp)-H and C(sp²)-H bond functionalization. In terms of the transition metal-catalyzed trifluoromethylthiolation of unactivated C(sp³)-H bonds, the relevant reports are rare. Thus, the development of transition metal-catalyzed trifluoromethylthiolation of unactivated C(sp³)-H bonds especially on primary position is highly desirable.

1.4 Objectives

At the outset of this study (2014), there was no report dealing with the transition metal-catalyzed trifluoromethylthiolation of unactivated C(sp³)-H bonds. In the first

¹⁴⁸ Mukherjee, S.; Maji, B.; Tlahuext-Aca, A.; Glorius, F. J. Am. Chem. Soc. **2016**, 138, 16200.

project of this Ph.D. thesis, we would like to realize the first trifluoromethylthiolation of unactivated aliphatic amides bearing a suitable directing group (Scheme 45).



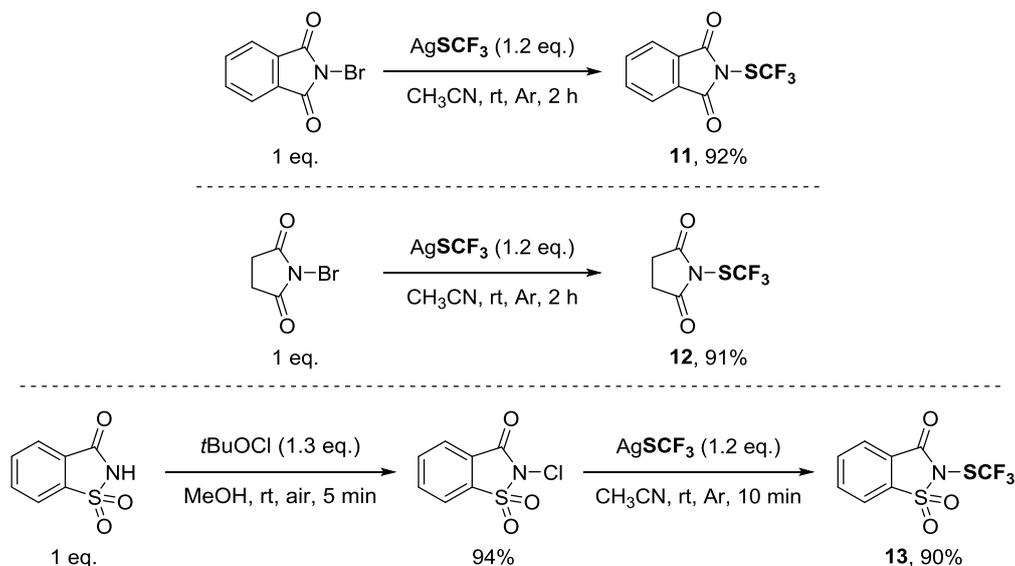
Scheme 45: Our objective

2 Optimization of the reaction conditions

2.1 Synthesis of the electrophilic trifluoromethylthiolating reagents

At the beginning of our study, we anticipated that one of the main synthetic issues to tackle would be the competing reductive elimination pathways over the desired C(sp³)-SCF₃ bond formation.^{30b,68,119a} We hypothesized that the astute use of a readily available electrophilic SCF₃ reagent, which might act as both oxidant and SCF₃ source, would allow the selective trifluoromethylthiolation event. Followed the reported literature,¹⁰⁶ the nucleophilic trifluoromethylthiolating reagent AgSCF₃, an important precursor for the synthesis of several electrophilic trifluoromethylthiolating reagents, was synthesized in 87% yield on a 0.12 mol scale.

Having the AgSCF₃ in hand, we next synthesized several different electrophilic trifluoromethylthiolating reagents **11**,¹¹⁵ **12**,¹¹⁵ **13**¹¹⁸ according to the reported procedures. After the reaction of N-bromophthalimide or N-bromosuccinimide with AgSCF₃ in CH₃CN at room temperature for 2 h, **11** and **12** were obtained in 92% and 91% yields, respectively (Scheme 46). Similarly, the N-(trifluoromethylthio)saccharin **13** was synthesized in 85% yield starting from the saccharin in two steps (Scheme 46).

Scheme 46: Synthesis of electrophilic trifluoromethylthiolating reagents **11-13**

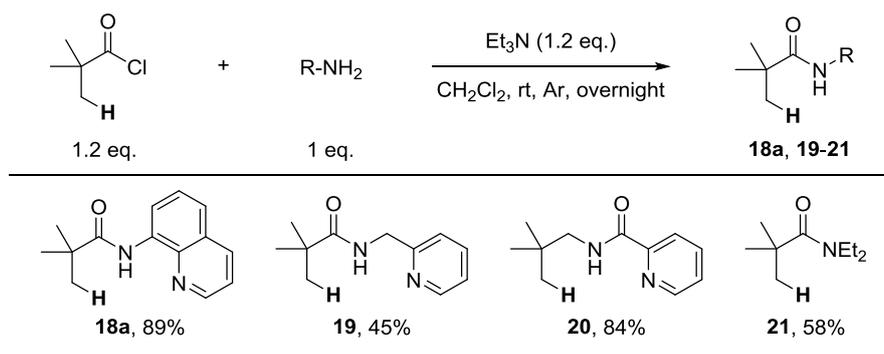
Furthermore, the electrophilic trifluoromethylthiolating reagent **14b** was synthesized according to Shen's procedure.¹¹⁸ Indeed, by the reaction of the N-methylaniline and the electrophilic trifluoromethylthiolating reagent **13**, the corresponding product **14b** was synthesized in 83% yield (Scheme 47).

Scheme 47: Synthesis of **14b**

2.2 Synthesis of the substrates bearing different directing groups (DG)

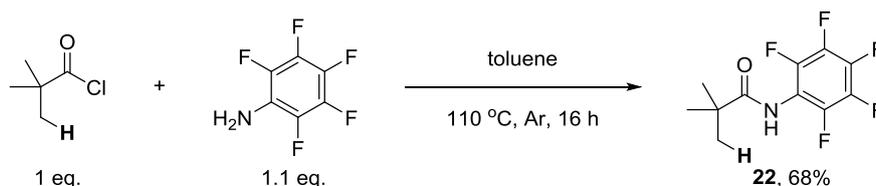
The nature of the directing group is crucial in transition metal-catalyzed C(sp³)-H activation.^{29a,51} At the beginning of our study, various substrates containing different mono or bidentate directing groups were synthesized in moderate to good yields starting from the commercially available corresponding amines and pivaloyl chloride according to the reported procedures (Scheme 48, **18a**, **19-21**).¹⁴⁹

¹⁴⁹ Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. J. Am. Chem. Soc. **2013**, 135, 6030.



Scheme 48: Synthesis of substrates containing different directing groups

Moreover, since N-(perfluorophenyl)pivalamide **22** showed high reactivity in the transition metal-catalyzed functionalization of unactivated C-H bonds,¹⁵⁰ it was synthesized from the 2,3,4,5,6-pentafluoroaniline and the pivaloyl chloride in 68% yield (Scheme 49).

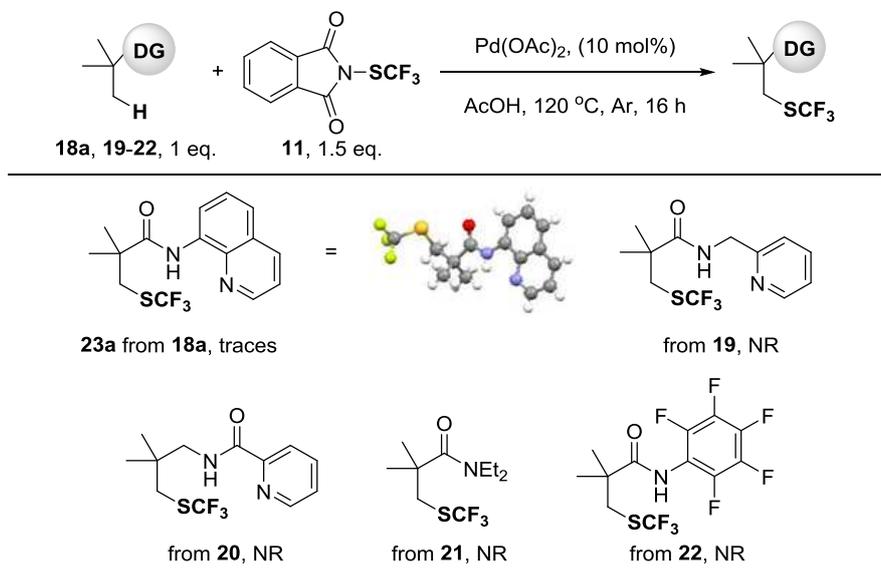
Scheme 49: Synthesis of N-(perfluorophenyl)pivalamide **22**

2.3 Screening of the directing groups

With different electrophilic trifluoromethylthiolating reagents and substrates in hand, we investigated the influence of the nature of the directing group on the synthesis of the trifluoromethylthiolated product using **11** as the SCF₃ source, Pd(OAc)₂ as the catalyst and AcOH as the solvent (Table 3). Pleasingly, when the bidentate amide derived from the 8-aminoquinoline (substrate **18a**) was used, traces of the expected product **23a** were observed by GC-MS while no product was detected with other bidentate and monodentate directing groups. This result indicated that the 8-aminoquinoline based auxiliary is a suitable directing group in our study. Moreover, the structure of **23a** was confirmed by NMR experiments and X-Ray crystallographic analysis, which allowed us to ensure the regioselectivity for the

¹⁵⁰ Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680.

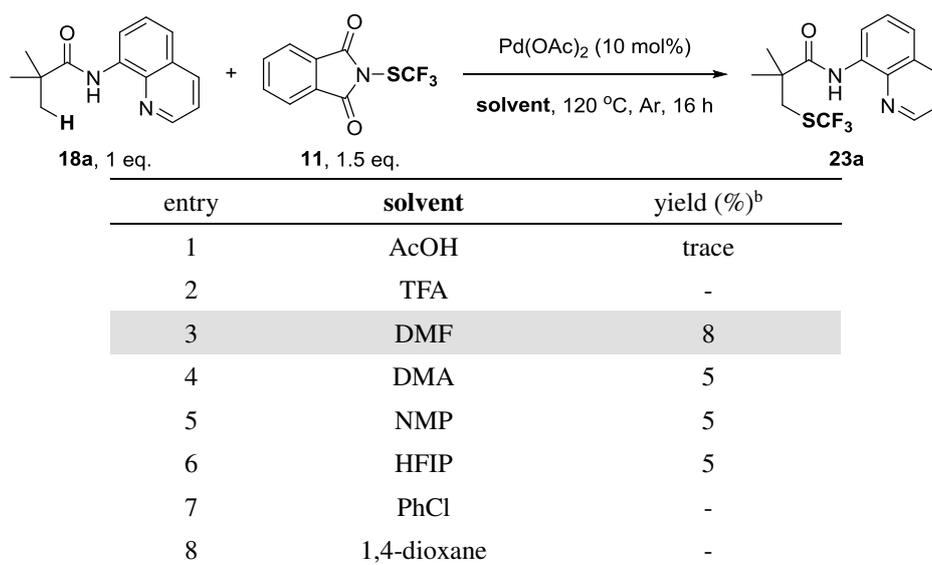
trifluoromethylthiolation on the C(sp³) center rather than C(sp²) center on the aromatic ring.

Table 3: Screening of directing groups^a

^a Reaction conditions: **18a**, **19-22** (0.1 mmol, 1 eq.), **11** (0.15 mmol, 1.5 eq.), Pd(OAc)₂ (0.01 mmol, 10 mol%), AcOH (1 mL), 120 °C, Ar, 16 h, NR = no reaction.

2.4 Screening of the solvents

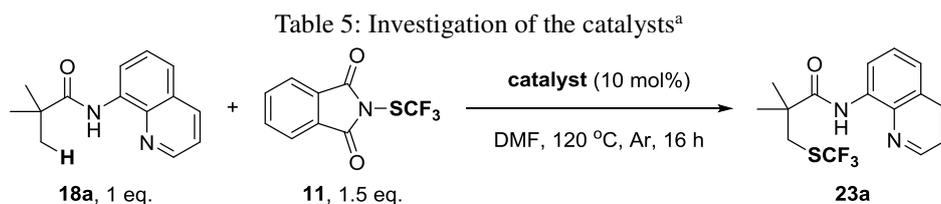
Encouraged by this promising result, we pursued our investigation by screening the reaction conditions, since we anticipated that parameters such as solvents, catalysts, temperatures and additives would be crucial for this transformation. First, several solvents were tested. When the reaction was carried out in strong acidic conditions (Table 4, entry 2), no product was detected. In polar solvents such as DMF, DMA, NMP and HFIP (Table 4, entries 3-6), the desired product **23a** was detected in low NMR yields, while other solvents did not provide the expected trifluoromethylthiolated product **23a** (Table 4, entries 7 and 8). Thus, DMF was proved to be the best solvent in such Pd-catalyzed C-H bond functionalization reaction (Table 4, entry 3), as it might limit the degradation of the catalyst into palladium black.

Table 4: Investigation of solvents^a

^a Reaction conditions: **18a** (0.1 mmol, 1 eq.), **11** (0.15 mmol, 1.5 eq.), Pd(OAc)₂ (0.01 mmol, 10 mol%), solvent (1 mL), 120 °C, Ar, 16 h; ^b NMR yields determined by ¹⁹F NMR using α,α,α-trifluoroacetophenone as an internal standard.

2.5 Screening of the catalysts

Next, several catalysts were evaluated such as Pd(OAc)₂, Pd(TFA)₂, Pd(OPiv)₂, Pd₂(dba)₃, Pd(CH₃CN)₄(BF₄)₂ and Pd(CH₃CN)₂Cl₂ (Table 5, entries 1-6). In all cases, traces or no product were obtained, except in the case of Pd(CH₃CN)₂Cl₂ for which the product **23a** was obtained in a slightly better yield (16%, Table 5, entry 6). These results might be explained by the degradation of the electrophilic trifluoromethylthiolating reagent **11** in such reaction conditions. To circumvent this problem, the amount of **11** was increased. However, no beneficial effect on the yield was observed (Table 5, entry 7 vs 6). In contrast, when **11** was used as the limiting reagent, the yield was slightly improved (Table 5, entry 8). Note that a control experiment was performed and no product **23a** was obtained in the absence of catalyst, demonstrating the crucial role of the palladium catalyst in such transformation (Table 5, entry 9).

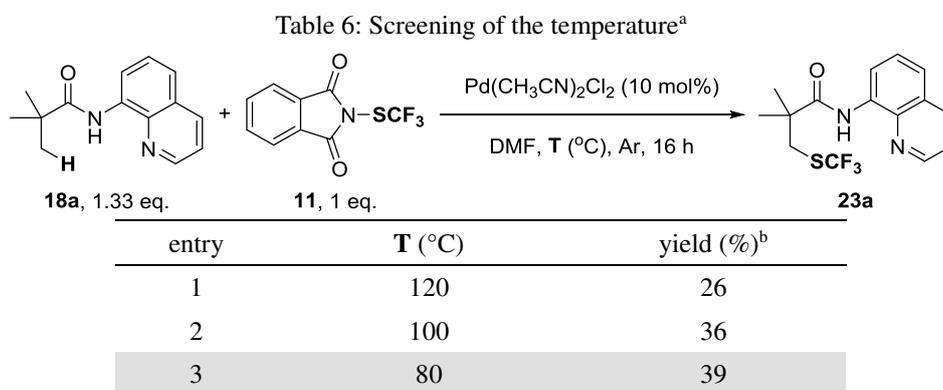


entry	catalyst	yield (%) ^b
1	Pd(OAc) ₂	8
2	Pd(TFA) ₂	4
3	Pd(OPiv) ₂	1
4	Pd ₂ (dba) ₃	-
5	Pd(CH ₃ CN) ₄ (BF ₄) ₂	1
6	Pd(CH ₃ CN) ₂ Cl ₂	16
7 ^c	Pd(CH ₃ CN) ₂ Cl ₂	14
8 ^d	Pd(CH ₃ CN) ₂ Cl ₂	26
9	-	-

^a Reaction conditions: **18a** (0.1 mmol, 1 eq.), **11** (0.15 mmol, 1.5 eq.), catalyst (0.01 mmol, 10 mol%), DMF (1 mL), 120 °C, Ar, 16 h; ^b NMR yields determined by ¹⁹F NMR using α,α,α-trifluoroacetophenone as an internal standard; ^c **18a** (0.1 mmol, 1 eq.), **11** (0.3 mmol, 3 eq.); ^d **18a** (0.133 mmol), **11** (0.1 mmol, 1 eq.).

2.6 Screening of the temperature

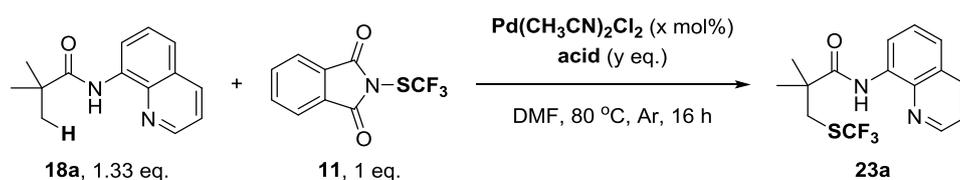
During the course of our investigation, we noticed that when the reaction was performed at 120 °C, no electrophilic trifluoromethylthiolating reagent **11** was left at the end of the reaction in most cases. We hypothesized that this observation could be explained by the decomposition of the trifluoromethylthiolating reagent **11** at such high temperature. Thus, we tried to decrease the reaction temperature to 100 °C and 80 °C (Table 6, entries 2 and 3). Pleasingly, it was found that a reaction performed at 80 °C was beneficial to promote the transformation affording the expected product **23a** in 39% NMR yield (Table 6, entries 1-3).



^a Reaction conditions: **18a** (0.133 mmol, 1.33 eq.), **11** (0.1 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.01 mmol, 10 mol%), DMF (1 mL), T (°C), Ar, 16 h; ^b NMR yields determined by ¹⁹F NMR using α,α,α-trifluoroacetophenone as an internal standard.

2.7 Screening of other parameters (acids, catalyst loading)

It is known that acids might play an important role on the regeneration of the active catalyst and the protonation of the product, or facilitate the C-H activation process by coordinating with the metal.⁵⁶ Inspired by these studies, we envisioned to investigate acids as additives to promote the reaction. When TFA was used as additive, the expected product **23a** was obtained in a slightly lower yield (Table 7, entry 2). The addition of 2 equivalents of PivOH affording the desired product **23a** in NMR 43% yield (Table 7, entry 3). Increasing the catalyst loading to 20 mol% was also beneficial providing **23a** in 53% NMR yield which was isolated in 31% yield (Table 7, entry 4). In order to further improve the yield, 1 equivalent of other acids was used as additive such as AcOH, PhCOOH, MesCOOH (Table 7, entries 5-7). However, the reaction outcome did not improve significantly. Note that a slightly lower yield (31% NMR yield) was obtained in the case of 2 equivalents of p-TSA at 85 °C (Table 7, entry 8). Finally, the PivOH was identified as a pivotal additive for this transformation (Table 7, entry 4). As some degradation of **11** was still observed at 80 °C, we imagined that decreasing the reaction temperature to 70 °C might minimize its decomposition. To find the right balance between decomposition and conversion, we performed a reaction at 70 °C for 60 h. Gratifyingly, the expected product **23a** was obtained in 41% isolated yield (Table 7, entry 9). Further increasing the amount of PivOH to 5 equivalents afforded the expected product **23a** in 48% isolated yield after 70 h (Table 7, entry 10). However, traces of the SCF₃ reagent **11** still recovered according to the ¹⁹F NMR analysis in this case. To ensure the full conversion of **11**, we then further increased the amount of PivOH to 10 equivalents. Finally, the trifluoromethylthiolated product **23a** was obtained in 53% isolated yield after stirring the reaction mixture at 70 °C for 70 h (Table 7, entry 11).

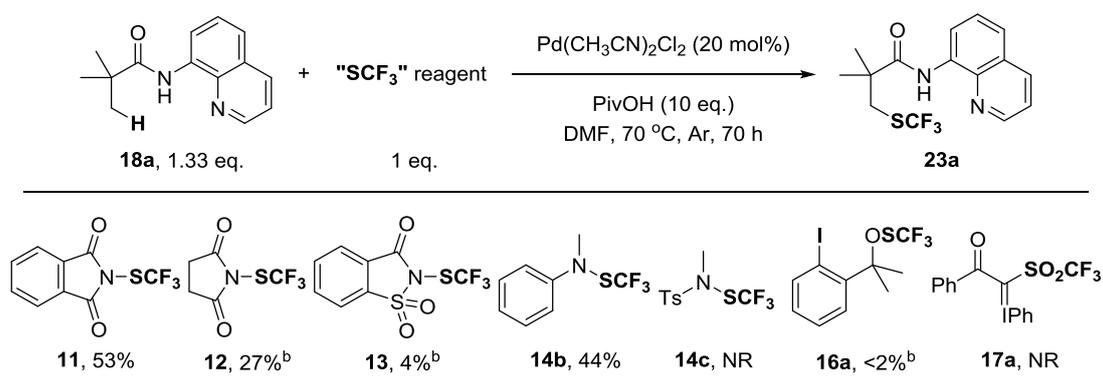
Table 7: Investigation of the acids and the catalyst loading^a

entry	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (x mol%)	acid (y eq.)	yield (%)
1	10	-	39 ^b
2	10	TFA (1)	36 ^b
3 ^c	10	PivOH (2)	43 ^b
4 ^c	20	PivOH (2)	53 ^b (31)
5	20	AcOH (1)	40 ^b
6	20	PhCOOH (1)	44 ^b
7	20	MesCOOH (1)	41 ^b
8 ^c	20	p-TSA (2)	31 ^b
9 ^{d,e}	20	PivOH (2)	(41)
10 ^{e,f}	20	PivOH (5)	(48)
11 ^{e,f}	20	PivOH (10)	(53)

^a Reaction conditions: **18a** (0.133 mmol, 1.33 eq.), **11** (0.1 mmol, 1 eq.), $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (x mmol, x mol%), DMF (1 mL), 80 °C, Ar, 16 h, isolated yield are given in parentheses; ^b NMR yields determined by ¹⁹F NMR using α,α,α -trifluoroacetophenone as an internal standard; ^c 85 °C, 16 h; ^d 70 °C, 60 h; ^e Reaction performed on a 0.2 mmol scale; ^f 70 °C, 70 h.

2.8 Screening of the electrophilic trifluoromethylthiolating reagents

We next examined the efficiency of other electrophilic trifluoromethylthiolating reagents (Table 8). The electrophilic trifluoromethylthiolating reagent **12** or Shen's reagent **13** led to the desired product **23a** in only 27% and 4% NMR yields, respectively. Gratifyingly, when the reaction was carried out with the reagent **14b**, a comparable yield (44%) of **23a** was obtained. However, when the more electron-withdrawing reagent **14c** was used, no desired product was detected. Note that other electrophilic trifluoromethylthiolating reagents (**16a**, **17a**) were not efficient in this transformation (Table 8).

Table 8: Screening of the electrophilic trifluoromethylthiolating reagents^a

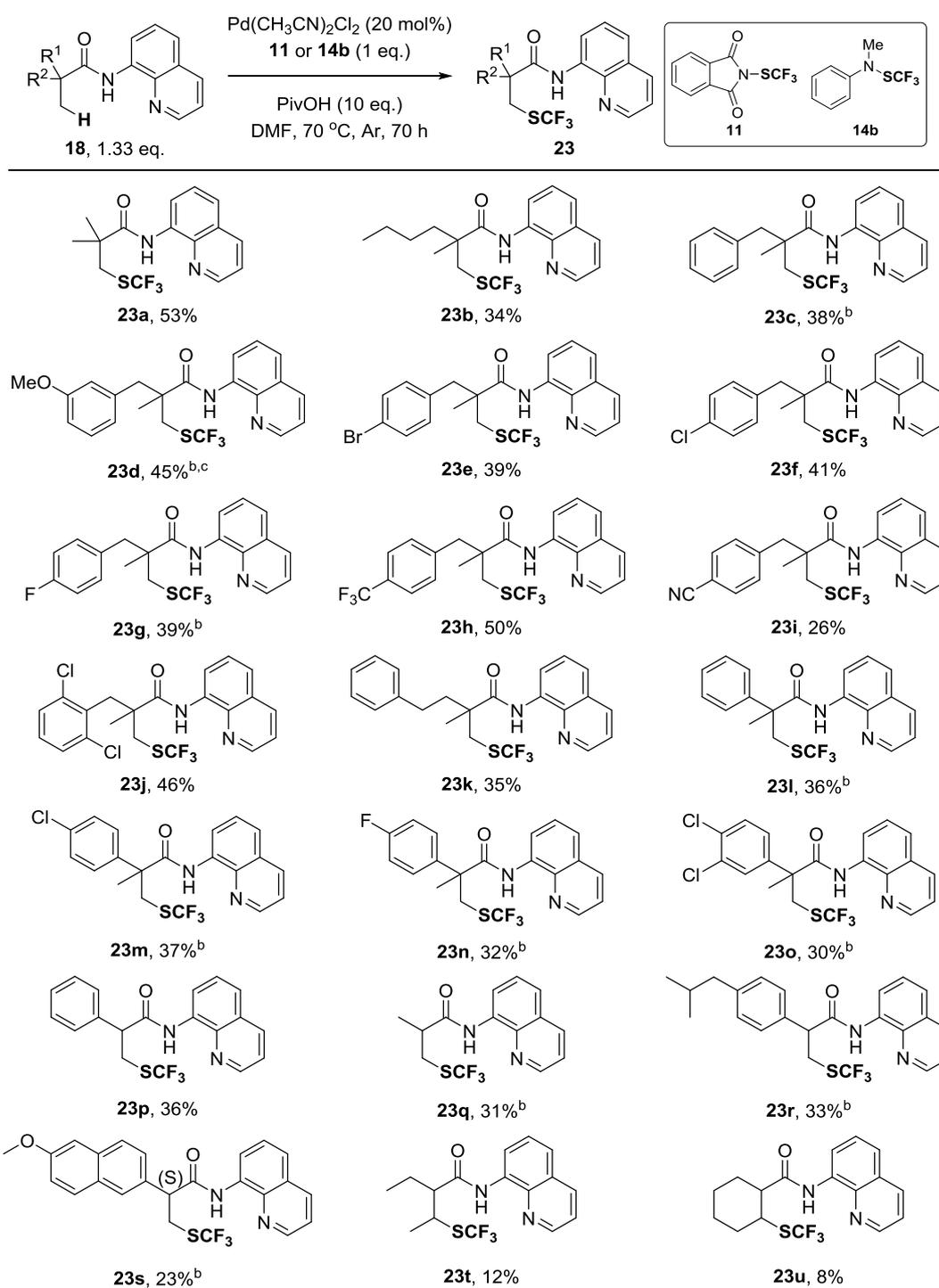
^a Reaction conditions: **18a** (0.266 mmol, 1.33 eq.), "SCF₃" reagent (0.2 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.04 mmol, 20 mol%), DMF (2 mL), 70 °C, Ar, 70 h, isolated yield, NR = no reaction; ^b NMR yields determined by ¹⁹F NMR using α,α,α-trifluoroacetophenone as an internal standard.

Thus, **11** and **14b** turned out to be the most efficient electrophilic trifluoromethylthiolating reagents for the introduction of SCF₃ group in the C(sp³)-H bonds.

3 Scope of the Pd-catalyzed trifluoromethylthiolation reaction

With the optimized reaction conditions in hand, we then evaluated the substrate scope of this reaction. Various aliphatic amides bearing primary β-C(sp³)-H bond with different patterns were examined (Table 9). The reaction of α,α-dialkyl substituted amides **18a** and **18b** furnished the corresponding trifluoromethylthiolated products **23a** and **23b** in 53% and 34% yields, respectively. Then, amides (**18c-o**) having an α-quaternary center were evaluated. The α,α-dimethylated hydrocinnamic acid derivatives (**18c-j**) delivered the corresponding products (**23c-j**) in moderate to good yields. Substrates with aromatic rings having either an electron-donating (OMe, **18d**) or an electron-withdrawing group (halogens, CF₃ or CN; **18e-j**) were functionalized, demonstrating the functional group tolerance of the process. Interestingly, in the case of **18c-j** and **18k**, which bear a benzylic or a homobenzylic substituent, the introduction of the SCF₃ group on the highly activated benzylic position or on the aromatic ring of the directing group was not observed. Next, we turned our attention to evaluate the amides which were prepared from phenylacetic acid derivatives (**18l-o**). Gratefully, no

trifluoromethylthiolation reaction has been observed on the aromatic ring and the expected products (**23l-o**) were produced in 30-37% yields. Moreover, more challenging amides bearing an α -C-H bond (**18p** and **q**) were well tolerated under the standard reaction conditions producing regioselectively **23p** and **23q** in 36% and 31% yields, respectively. It is worth mentioning that the electrophilic trifluoromethylthiolating reagent **14b** was proved to be more efficient in some cases. Furthermore, the utility of the current methodology was extended to the synthesis of the SCF₃-containing analogues of bioactive molecules such as Ibuprofen **18r** and Naproxen **18s**. Albeit the desired products **23r** and **23s** were delivered in moderate-to-low yields (33% and 23%, respectively), these results showcased the utility of such approach for the late-stage functionalization of complex molecules. At last, when the reaction was carried out using highly challenging substrates bearing secondary C(sp³)-H bonds, the corresponding products (**23t** and **23u**) were obtained albeit in low yields.

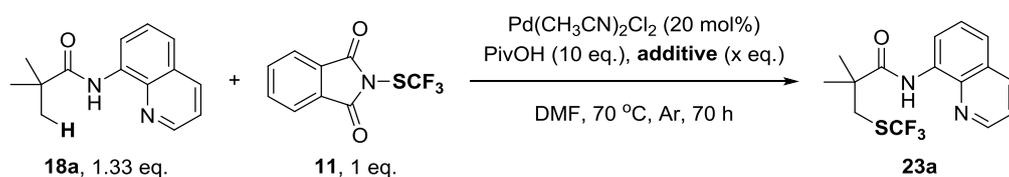
Table 9: Substrate scope^a

^a Reaction conditions: **18** (0.266 mmol, 1.33 eq.), **11** (0.2 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.04 mmol, 20 mol%), PivOH (2 mmol, 10 eq.), DMF (2 mL), 70 °C, Ar, isolated yield; ^b **14b** was used instead of **11** as electrophilic SCF₃ reagent; ^c **23d** was contaminated with 10% of an inseparable impurity.

4 Rudimental mechanism studies

4.1 Radical trapping experiments

In order to have a better understanding of the reaction mechanism, radical trapping experiments were performed. Firstly, we conducted the reaction in the presence of the commonly used radical quenchers 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO, 40 mol% and 1 eq.) and 2,6-di-tert-butyl-4-methylphenol (BHT, 1 eq.). It was found that the addition of TEMPO led to lower yields (Table 10, entries 2 and 3). In the presence of BHT, the reaction was slightly slower but no deleterious effect on the reaction yield was observed (Table 10, entry 4). Taking into consideration these observations, a plausible radical pathway might be thereby ruled out.

Table 10: Radical trapping experiments^a

entry	additive (x eq.)	yield (%) ^b
1	-	53
2	TEMPO (1.1 eq.)	36 ^b
3	TEMPO (40 mol %)	39
4	BHT (1.1 eq.)	42 ^b

^a Reaction conditions: **18a** (0.266 mmol, 1.33 eq.), **11** (0.2 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.04 mmol, 20 mol%), PivOH (2 mmol, 10 eq.), additive (x eq.), DMF (2 mL), 70 °C, Ar, 70 h, isolated yield; ^b Average yields based on two reactions.

To explain the lower yields obtained when the reaction was performed in the presence of TEMPO, a control experiment was realized. When the electrophilic trifluoromethylthiolating reagent **11** and TEMPO were mixed in the absence of amide **18a**, two new signals (-48.51 ppm and -78.56 ppm, Figure 11) were detected by ¹⁹F NMR analysis. Even though their structures were not elucidated, the degradation of the limiting reagent **11** in the presence of TEMPO might easily explain the difference

of yields.

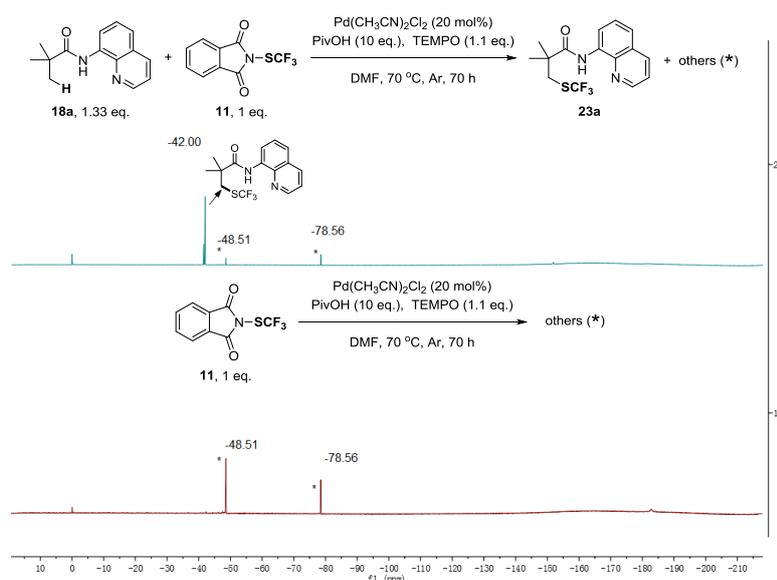


Figure 11: ¹⁹F NMR spectra of the control experiments

4.2 Proposed mechanism

A plausible mechanism has been proposed based on the above observations and previous studies reported in the literature.^{53c,d,56} First, the chelation of the Pd(II)-catalyst with the bidentate directing group (intermediate **A**) is followed by the formation of the key palladacycle (intermediate **B**) after the activation of the

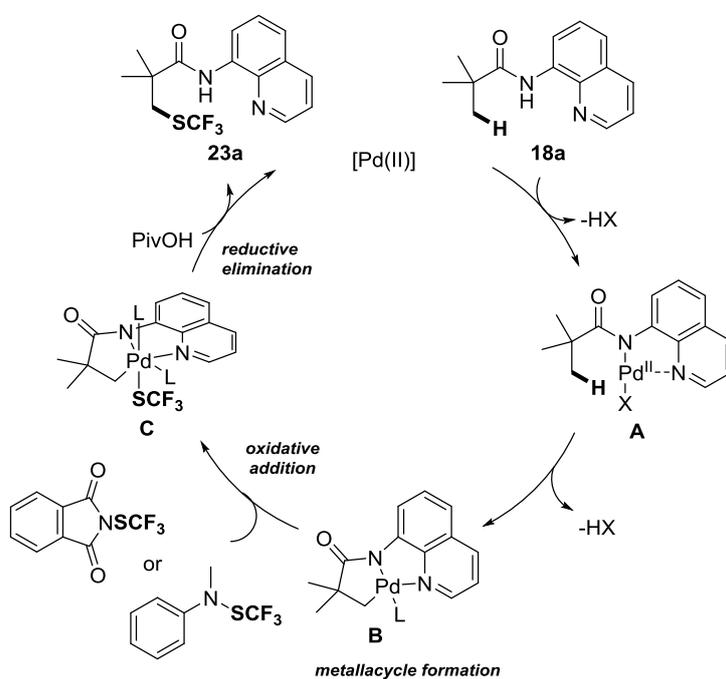


Figure 12: Proposed mechanism

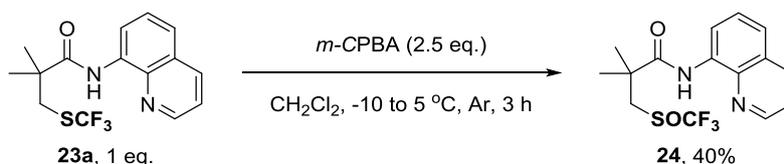
β -C(sp³)-H bond according to a plausible concerted metalation-deprotonation pathway. This latter undergoes an oxidative addition in the N-SCF₃ bond of the electrophilic reagent, leading to a putative Pd(IV) species **C**. Finally, a selective reductive

elimination and a final protonation of the amide intermediate then affords the desired trifluoromethylthiolated derivative **23a** and regenerates the catalyst (Figure 12). Despite the fact that the role of PivOH has not been elucidated and in accordance with what has been mentioned before,^{53c,d,56} it is reasonable to propose that the acid might be involved in the C-H activation event as ligand on the Pd catalyst or might assist the regeneration of the active catalyst.^{53c} Note that in the case of the electrophilic trifluoromethylthiolating reagent **14b**, acidic conditions are often necessary to promote the reaction by activating the SCF₃ reagent.¹⁵¹

5 Post-functionalizations of products

5.1 Oxidation

Trifluoromethanesulfoxide is an important class of compounds as illustrated by Fipronil (Figure 7), a widely used phenylpyrazole insecticide.⁹³ Thanks to our study, we have an access to a panel of derivatives that might lead in a one-step process to the corresponding SOCF₃-containing products. In the presence of *m*-CPBA, **23a** could be easily oxidized to the corresponding sulfoxide **24** in 40% yield (Scheme 50).

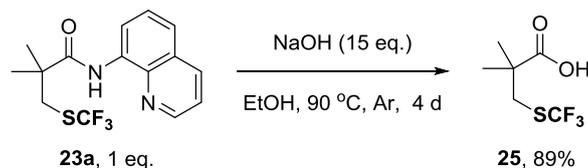


Scheme 50: Oxidation of **23a**

5.2 Cleavage of the directing group

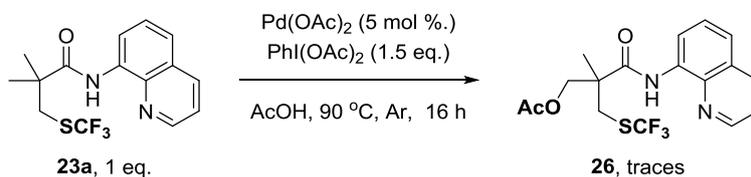
In addition, the amide **23a** can be cleaved efficiently under basic conditions, which highlights the synthetic value of our approach and the traceless character of the directing group. Indeed, the treatment of the product **23a** with NaOH, in the presence of EtOH at 90 °C for 4 days afforded the expected acid **25** in 89% yield (Scheme 51).

¹⁵¹ Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8551.

Scheme 51: Cleavage of the directing group on compound **23a**

5.3 Sequential C-H functionalization reactions

The introduction of an acetoxy group onto molecules is important since a range of natural products, drugs, and agricultural chemicals contains acetoxy groups.¹⁵² In this context, the subsequent introduction of an acetoxy group on **23** would lead to a highly functionalized quaternary carbon center. Thus, the acetoxylation of **23a** was carried out under Sahoo's reaction conditions.^{53d} However, only traces of the acetoxyated product **26** were detected by GC-MS after treating **23a** with PhI(OAc)₂ and Pd(OAc)₂ in AcOH at 90 °C for 16 h (Scheme 52). This poor yield might be explained by the steric hindrance of the SCF₃ group, which affected the sequential introduction of the acetoxy group.

Scheme 52: Attempt of the acetoxylation of **23a**

6 Conclusion

In conclusion, the first part of this Ph.D. thesis was dedicated to the development of a new methodology for the trifluoromethylthiolation of primary and secondary C(sp³)-H bond on aliphatic acid derivatives.¹⁵³ Using a bidentate directing group, the combination of an electrophilic trifluoromethylthiolating reagent with Brønsted acid (PivOH) allowed the first Pd-catalyzed direct introduction of a SCF₃ moiety on a C(sp³)-H bond under mild conditions. Various amides were compatible and a series of

¹⁵² Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, 8, 3391 and references cited therein

¹⁵³ Xiong, H.-Y.; Besset, T.; Cahard, D.; Pannecoucke, X. *J. Org. Chem.* **2015**, 80, 4204.

alkyl trifluoromethylated sulfides have been prepared. This novel approach offers a new disconnection for the preparation of tertiary and quaternary β -SCF₃-containing aliphatic acids.

Chapter 3

Palladium(II)-Catalyzed Directed Chlorination of Unactivated C(sp³)-H Bonds at Room Temperature

During our investigations on the trifluoromethylthiolation reaction (Chapter 2), we observed, at an early stage, the formation of a chlorinated by-product. The formation of a C-Cl bond could be explained by the reductive elimination from the Pd(IV) intermediate generated from the Pd(CH₃CN)₂Cl₂ catalyst which contained a chlorine atom in its coordination sphere. Thus, in this chapter, the development of a new methodology for the chlorination of unactivated C(sp³)-H bond will be presented.

1 The importance of the halogenated compounds

Organohalides are a class of important and valuable compounds due to their versatile applications.¹⁵⁴ In consequence, organohalides occupy a crucial position in organic chemistry community. First, organohalides could be used as electrophiles and converted into various valuable synthons by nucleophilic substitution.^{154c,d} Second, their use as precursors for the preparation of organometallic reagents made organohalides highly valuable.^{154e,f} Moreover, alkyl or aryl halides are important structural motifs in natural products,^{154a} biologically active compounds and drugs.¹⁵⁵ Among them, the alkyl or aryl chlorides are widely presented. For instance, the isoquinoline carboxamide compound PK11195 which possesses a phenyl ring substituted by a chlorine atom (Figure 13) is widely considered as a prototypical translocator protein (TSPO) ligand, used as a reference compound for the imaging studies.¹⁵⁶ Besides, Vismodegib (Erivedge[®], Roche, Figure 13) contains two chlorine atoms on the aromatic ring. It is used to treat adults for skin cancer.¹⁵⁷ Another chlorine-containing biological active compound is the Lonafarnib (Figure 13)¹⁵⁸

¹⁵⁴ For selected reviews and books, see: (a) Gribble, G. W. Naturally Occurring Organohalogen Compounds-A Comprehensive Update, Springer Science, New York, **2009**; (b) Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, 106, 3364; (c) Crampton, M. R. *Organic Reaction Mechanism*, Wiley, New York, **2007**; (d) Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagents*, Marcel Dekker, New York, **1996**; (e) Sotomayor, N.; Lete, E. *Curr. Org. Chem.* **2003**, 7, 275; (f) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, 42, 4302.

¹⁵⁵ Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. *J. Med. Chem.* **2013**, 56, 1363.

¹⁵⁶ (a) Trapani, A.; Palazzo, C.; Candia, M.; Lasorsa, F. M.; Trapani, G. *Bioconjugate Chem.* **2013**, 24, 1415; (b) Manning, H. C.; Goebel, T.; Marx, J. N.; Bornhop, D. J. *Org. Lett.* **2002**, 4, 1075.

¹⁵⁷ (a) Dlugosz, A.; Agrawal, S.; Kirkpatrick, P. *Nat Rev Drug Discov* **2012**, 11, 437; (b) Xin, M.; Wen, J.; Tang, F.; Tu, C.; Shen, H.; Zhao, X. *Bioorg. Med. Chem. Lett.* **2013**, 23, 6777.

¹⁵⁸ Basso, A. D.; Mirza, A.; Liu, G.; Long, B. J.; Bishop, W. R.; Kirschmeier, P. *J. Biol. Chem.* **2005**, 280, 31101.

which is a farnesyl transferase inhibitor (FTI). It was found that its ability to bind with the farnesyl protein transferase (FTase) was greatly enhanced by the presence of halogens on the tricyclic ring system.¹⁵⁹ The anti-tumor agent dichlorolissoclimide bearing two chlorine atoms on the aliphatic ring (Figure 13) was isolated from the *Lissoclinum voeltzkowi* Michaelson (Urochordata).¹⁶⁰ It has demonstrated a strong cytotoxic activity.¹⁶¹

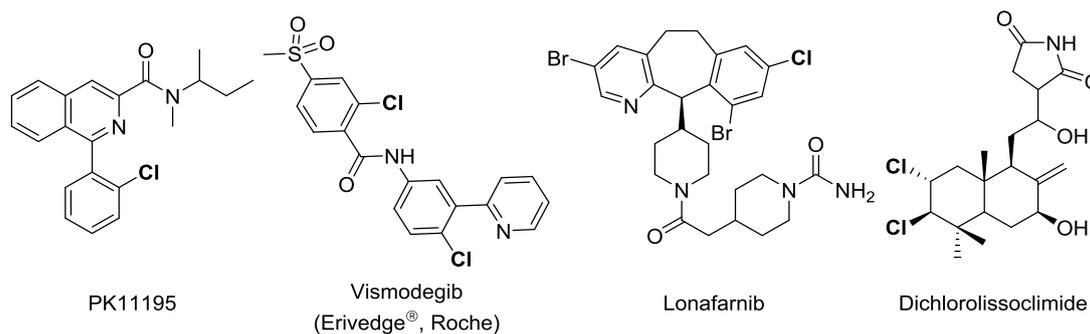


Figure 13: Examples of relevant chlorine-containing compounds

2 Synthesis of chlorinated molecules

Because of the high importance of chlorine-containing molecules, considerable efforts have been devoted in the development of synthetic methods for the introduction of a chlorine atom onto molecules and great advances have been observed over the last decades.¹⁶² Consequently, several synthetic pathways might be used for the synthesis of chlorine-containing molecules, and an overview will be depicted on this section with a special focus on the aliphatic chlorinated molecules.

2.1 Synthesis of chloroalkanes from functionalized precursors

A number of approaches towards the practical synthesis of chloroalkanes have

¹⁵⁹ Njoroge, F. G.; Vibulbhan, B.; Pinto, P.; Strickland, C.; Bishop, W. R.; Nomeir, A.; Girijavallabhan, V. *Bioorg. Med. Chem. Lett.* **2006**, 16, 984.

¹⁶⁰ Toupet, L.; Biard, J.-F.; Verbist, J.-F. *J. Nat. Prod.* **1996**, 59, 1203.

¹⁶¹ (a) Malochet-Grivois, C.; Cotelte, P.; Biard, J. F.; Hénichart, J. P.; Debitus, C.; Roussakis, C.; Verbist, J. F. *Tetrahedron Lett.* **1991**, 32, 6701; (b) Malochet-Grivois, C.; Roussakis, C.; Robillard, N.; Biard, J. F.; Riou, D.; Débitus, C.; Verbist, J. F. *AntiCancer Drug Des.* **1992**, 7, 493.

¹⁶² For selected reviews, see: (a) Janin, Y. L. *Chem. Rev.* **2012**, 112, 3924; (b) Hao, W.; Liu, Y. *Beilstein J. Org. Chem.* **2015**, 11, 2132; (c) Petrone, D. A.; Ye, J.; Lautens, M. *Chem. Rev.* **2016**, 116, 8003.

been reported.¹⁶² As a representative example, the conversion of alcohols into the corresponding chloroalkanes using various chlorinating reagents through a nucleophilic substitution has been reported by several groups (eg. Scheme 53, a).¹⁶³ Among others, the transformations of carboxylic acids (eg. Scheme 53, b)¹⁶⁴ and diazo compounds (eg. Scheme 53, c)¹⁶⁵ to the corresponding products were also described. Molander and co-workers have reported a metal-free chlorination of alkyl trifluoroborates using trichloroisocyanuric acid (TCCA) as the chlorine source (eg. Scheme 53, d).¹⁶⁶ Moreover, carbonyl compounds (eg. Scheme 53, e).¹⁶⁷ were also suitable precursors for the construction of chloroalkanes. Other alternatives and complementary approaches to access such compounds rely on the chlorination of olefins (eg. Scheme 53, f)¹⁶⁸ and alkynes (eg. Scheme 53, g).¹⁶⁹

¹⁶³ For selected examples, see: (a) Vanos, C. M.; Lambert, T. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 12222; (b) Pouliot, M.-F.; Mahé, O.; Hamel, J.-D.; Desroches, J.; Paquin, J.-F. *Org. Lett.* **2012**, *14*, 5428; (c) Villalpando, A.; Ayala, C. E.; Watson, C. B.; Kartika, R. *J. Org. Chem.* **2013**, *78*, 3989; (d) Nguyen, T. V.; Bekensir, A. *Org. Lett.* **2014**, *16*, 1720; (e) Moerdyk, J. P.; Bielawski, C. W. *Chem. Eur. J.* **2014**, *20*, 13487.

¹⁶⁴ For selected examples, see: (a) Johnson, R. G.; Ingham, R. K. *Chem. Rev.* **1956**, *56*, 219; (b) Wang, Z.; Zhu, L.; Yin, F.; Su, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 4258; (c) Sakai, N.; Nakajima, T.; Yoneda, S.; Konakahara, T.; Ogiwara, Y. *J. Org. Chem.* **2014**, *79*, 10619; (d) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979; (e) Kochi, J. K. *J. Am. Chem. Soc.* **1965**, *87*, 2500.

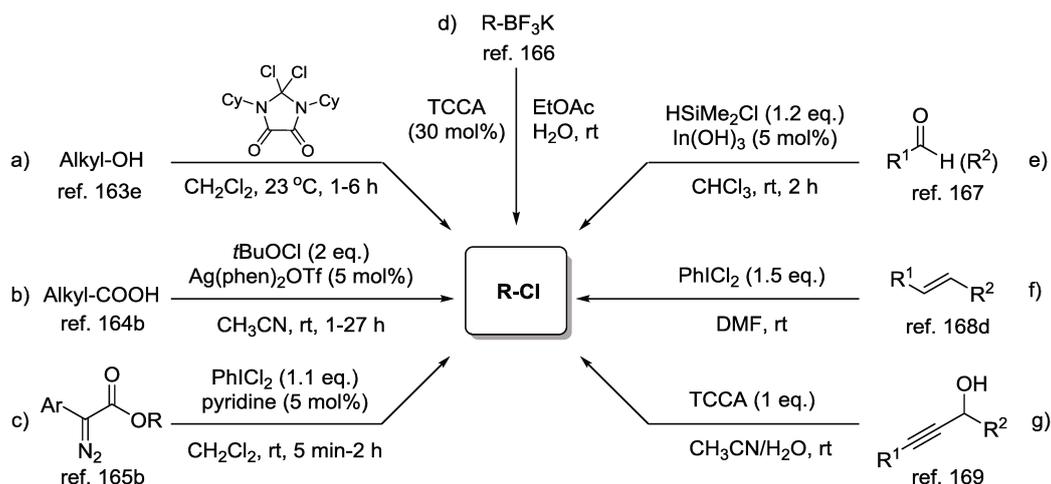
¹⁶⁵ For selected examples, see: (a) Somai Magar, K. B.; Lee, Y. R. *Adv. Synth. Catal.* **2014**, *356*, 3422; (b) Tao, J.; Tran, R.; Murphy, G. K. *J. Am. Chem. Soc.* **2013**, *135*, 16312; (c) Murphy, G. K.; Abbas, F. Z.; Poulton, A. V. *Adv. Synth. Catal.* **2014**, *356*, 2919; (d) Coffey, K. E.; Moreira, R.; Abbas, F. Z.; Murphy, G. K. *Org. Biomol. Chem.* **2015**, *13*, 682.

¹⁶⁶ For a selected example, see: Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem.* **2011**, *76*, 7195.

¹⁶⁷ For a selected example, see: Onishi, Y.; Ogawa, D.; Yasuda, M.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13690.

¹⁶⁸ For selected examples, see: (a) Cresswell, A. J.; Eey, S. T. C.; Denmark, S. E. *Nat. Chem.* **2014**, *7*, 146; (b) Soltanzadeh, B.; Jaganathan, A.; Staples, R. J.; Borhan, B. *Angew. Chem., Int. Ed.* **2015**, *127*, 9653; (c) Du, W.; Tian, L.; Lai, J.; Huo, X.; Xie, X.; She, X.; Tang, S. *Org. Lett.* **2014**, *16*, 2470; (d) Liu, L.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2014**, *16*, 436; (e) Tay, D. W.; Tsoi, I. T.; Er, J. C.; Leung, G. Y. C.; Yeung, Y.-Y. *Org. Lett.* **2013**, *15*, 1310; (f) Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 8134; (g) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5758.

¹⁶⁹ D'Oyley, J. M.; Aliev, A. E.; Sheppard, T. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 10747.



Scheme 53: Selected examples for the synthesis of chloroalkanes starting from various precursors

Although great achievements have been made in traditional transformations, the relevant precursors are not always easy to obtain. Therefore, the development of atom- and step-economical direct chlorination of inert C-H bonds is highly valuable from a synthetic point of view.

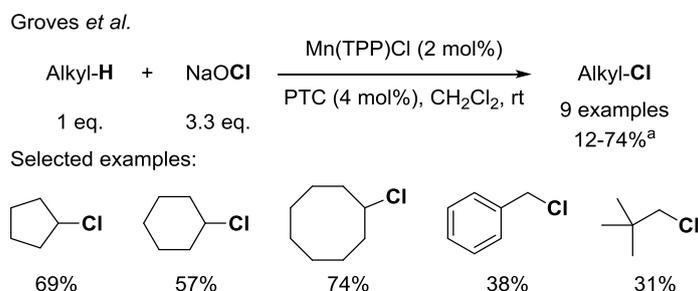
2.2 Synthesis of chloroalkanes through a radical pathway

Since C-H bonds are ubiquitous in the organic molecules, the direct functionalization of C-H bonds has appeared as a promising and pivotal strategy for the introduction of a diversity of functional groups onto molecules.²⁷ Especially, the direct chlorination of unactivated C-H bonds represents an efficient approach for the synthesis of chlorinated compounds. Thus, the chlorination of unactivated alkanes through a radical pathway provides a simple and powerful synthetic pathway to access chloroalkanes.^{162,170} Indeed, several works dealing with the radical chlorination of alkanes have been described in recent years.¹⁷¹ Among them, the selective chlorination of unactivated hydrocarbons catalyzed by the meso-tetraphenylporphyrin

¹⁷⁰ For selected reviews, see: (a) McBee, E. T.; Hass, H. B.; Neher, C. M.; Strickland, H. *Ind. Eng. Chem.* **1942**, 34, 296; (b) McBee, E. T.; Hass, H. B. *Ind. Eng. Chem.* **1941**, 33, 137.

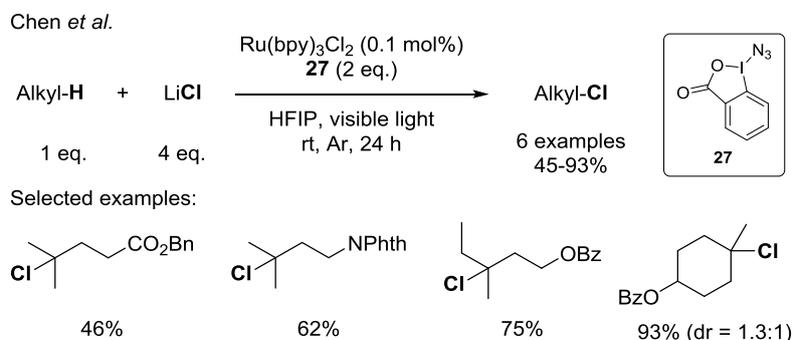
¹⁷¹ For selected examples, see: (a) Kundu, R.; Ball, Z. T. *Org. Lett.* **2010**, 12, 2460; (b) Quinn, R. K.; Könst, Z. A.; Michalak, S. E.; Schmidt, Y.; Szklarski, A. R.; Flores, A. R.; Nam, S.; Horne, D. A.; Vanderwal, C. D.; Alexanian, E. J. *J. Am. Chem. Soc.* **2016**, 138, 696; (c) Huang, F.-Q.; Xie, J.; Sun, J.-G.; Wang, Y.-W.; Dong, X.; Qi, L.-W.; Zhang, B. *Org. Lett.* **2016**, 18, 684; (d) Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, 132, 12847; (e) Wang, Y.; Li, G.-X.; Yang, G.; He, G.; Chen, G. *Chem. Sci.* **2016**, 7, 2679.

manganese (III) chloride complex (Mn(TPP)Cl) was described by Groves and co-workers (Scheme 54).^{171d} In the presence of a catalytic amount of [Mn(TPP)Cl], tetrabutylammonium chloride as a phase transfer catalyst (PTC) and NaOCl as the chlorine source, benzylic, secondary and tertiary C(sp³)-H bonds were functionalized.



Scheme 54: Chlorination of unactivated alkenes with NaOCl. ^a Yields were determined by GC.

Recently, Chen and co-workers disclosed a visible-light-promoted radical chlorination of aliphatic C-H bonds using LiCl as the chlorine source (Scheme 55).^{171e} Under the visible light irradiation and in the presence of 2 equivalents of **27**, the chlorination of tertiary aliphatic C-H bonds of various substrates proceeded smoothly at room temperature affording the desired products in moderate yields.



Scheme 55: Visible-light-promoted radical chlorination of aliphatic C-H bonds

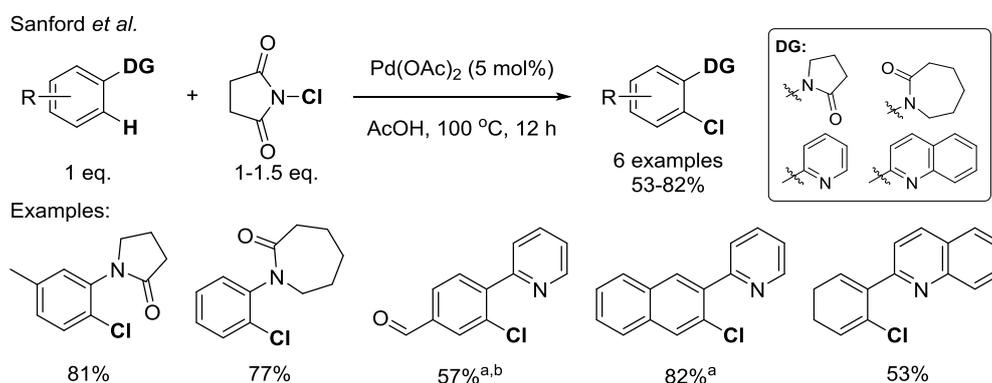
However, despite the fact that the radical chlorination offers a straightforward approach for the formation of chloroalkanes, the transformations were mainly limited to the functionalization of secondary and tertiary C(sp³)-H bonds and the relatively poor selectivity observed in some cases hampered their applications.

2.3 Synthesis of chlorinated molecules through transition metal-catalyzed C-H bond activation

In sharp contrast with the radical chlorination, the transition metal-catalyzed chlorination was studied. Taking benefit from the assistance of a directing group, high control of regioselectivity was achieved. In recent years, great progresses have been achieved in the transition metal-catalyzed chlorination by C-H bond functionalization.^{162b,c}

2.3.1 Transition metal-catalyzed chlorination by C(sp²)-H bond activation

In 2004, Sanford reported the Pd-catalyzed ortho C-H bond chlorination and bromination of benzoquinolines using N-halosuccinimides as halogen sources.¹⁷² In 2006, the same group described a Pd-catalyzed directed ortho C-H bond chlorination of arenes using the N-chlorosuccinimide (NCS) as the chlorinating reagent under mild reaction conditions, which offered a complementary pathway to access chlorinated products compared to traditional synthetic methods (Scheme 56).¹⁷³ Since only 6 examples were reported, the same group further extended the reaction scope under similar reaction conditions.¹⁷⁴ Mechanistic studies were also carried out suggesting a plausible Pd(II)/Pd(IV) pathway.¹⁷⁵



Scheme 56: Pd-catalyzed chlorination of arenes bearing various directing groups. ^a CH₃CN was used as solvent instead of AcOH; ^b 120 °C.

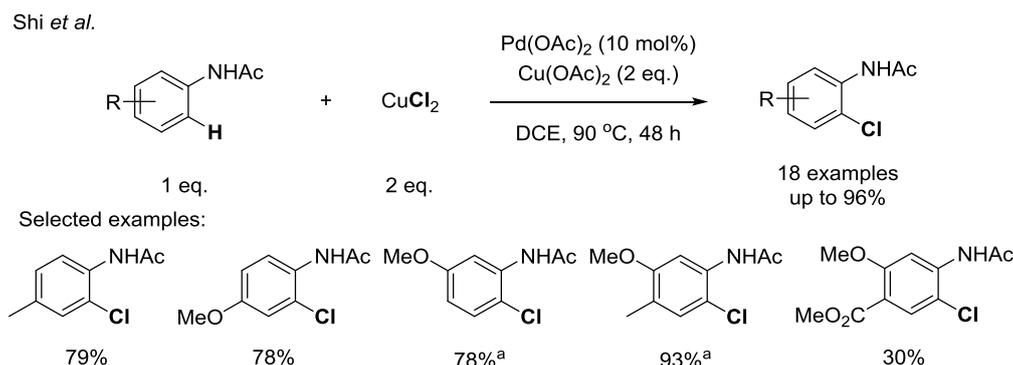
¹⁷² Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, 126, 2300.

¹⁷³ Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, 8, 2523.

¹⁷⁴ Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, 62, 11483.

¹⁷⁵ Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, 129, 15142.

Meanwhile, Shi and co-workers reported the Pd-catalyzed ortho C-H bond chlorination of acetanilide derivatives using CuCl₂ as the chlorinating source.¹⁷⁶ Interestingly, in addition to CuCl₂, they found that Cu(OAc)₂ was also required for this transformation (Scheme 57). Note that electron-rich acetanilides usually gave better results.



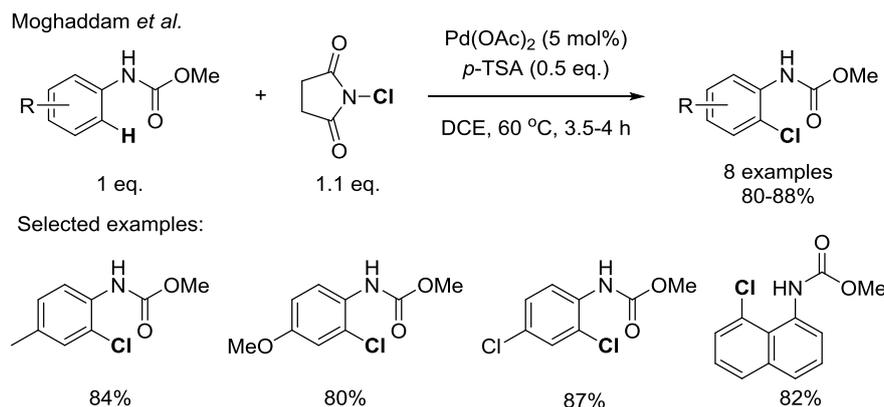
Scheme 57: Pd-catalyzed chlorination of acetanilide derivatives. ^a 5 mol% of Pd(OAc)₂ was used.

Since these pioneering works, a lot of progress has been made in the Pd-catalyzed chlorination reactions.¹⁷⁷ More recently, Moghaddam and co-workers reported the ortho-selective chlorination using NCS as both oxidant and halogen source under mild conditions. Using a weak and removable directing group, this reaction showed a broad functional group tolerance and the products were formed in good yields with high selectivity in general (Scheme 58).¹⁷⁸

¹⁷⁶ Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, 128, 7416.

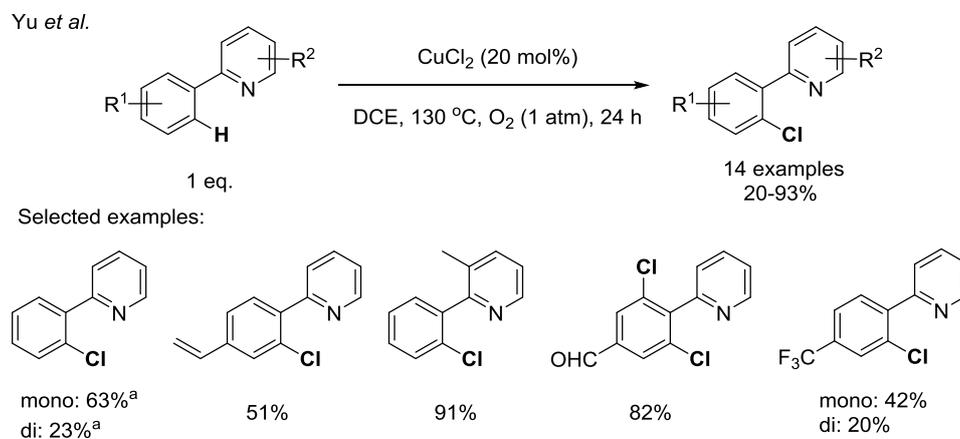
¹⁷⁷ For selected examples, see: (a) Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. *J. Am. Chem. Soc.* **2009**, 131, 11310; (b) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, 131, 3466; (c) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, 1, 302; (d) Song, B.; Zheng, X.; Mo, J.; Xu, B. *Adv. Synth. Catal.* **2010**, 352, 329; (e) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem., Int. Ed.* **2011**, 50, 5524; (f) Du, B.; Jiang, X.; Sun, P. *J. Org. Chem.* **2013**, 78, 2786; (g) Sarkar, D.; Melkonyan, F. S.; Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, 52, 10800; (h) Lu, C.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Tetrahedron* **2014**, 70, 4197; (i) Péron, F.; Fossey, C.; Sopkova-Oliveira Santos, J.; Cailly, T.; Fabis, F. *Chem. Eur. J.* **2014**, 20, 7507; (j) Zhang, Q.; Yang, F.; Wu, Y. *Org. Chem. Front.* **2014**, 1, 694; (k) Purohit, V. B.; Karad, S. C.; Patel, K. H.; Raval, D. K. *Catal. Sci. Technol.* **2015**, 5, 3113; (l) Santra, S. K.; Banerjee, A.; Khatun, N.; Samanta, A.; Patel, B. K. *RSC Adv.* **2015**, 5, 11960.

¹⁷⁸ Moghaddam, F. M.; Tavakoli, G.; Saeednia, B.; Langer, P.; Jafari, B. *J. Org. Chem.* **2016**, 81, 3868.



Scheme 58: Pd-catalyzed chlorination of N-arylcarbamate derivatives

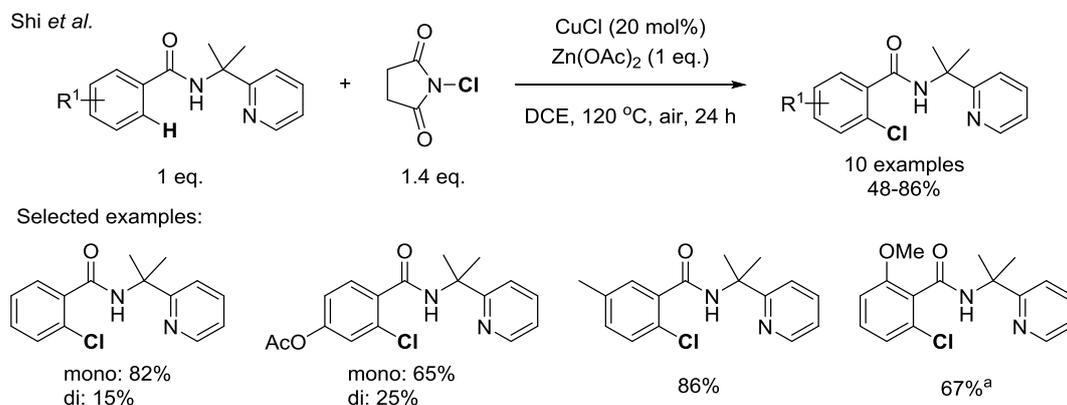
In addition, copper catalysts also proved to be efficient for the chlorination of unactivated C(sp²)-H bonds.¹⁷⁹ Indeed, Yu and co-workers disclosed the Cu-catalyzed chlorination of 2-arylpyridine derivatives in 2006.^{179a} In the presence of a catalytic amount of CuCl₂, the corresponding chlorinated products were synthesized in moderate to good yields (Scheme 59). However, the dichlorinated products were obtained as by-products and in some cases were selectively synthesized.

Scheme 59: Cu-catalyzed chlorination of 2-arylpyridine derivatives. ^a 100 °C

Recently, Shi and co-workers developed a Cu-catalyzed chlorination of benzamides using the readily available and removable amide derived from the 2-(pyridin-2-yl)isopropylamine as the directing group. This transformation was

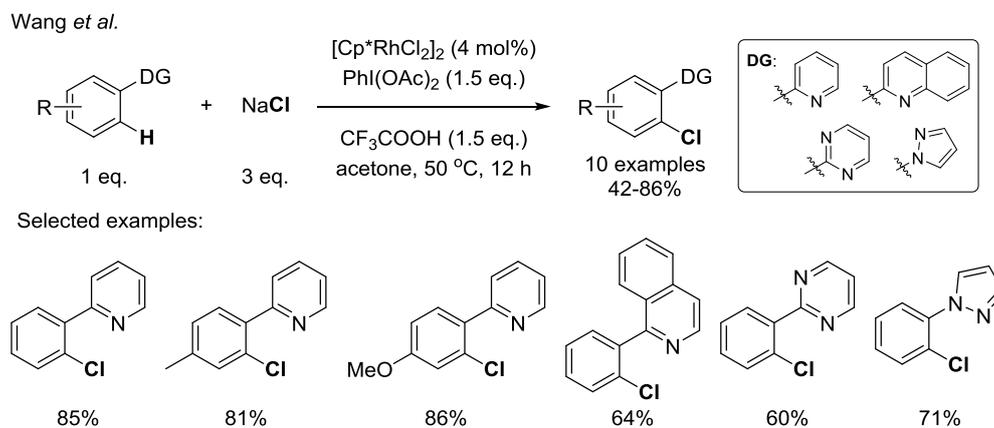
¹⁷⁹ For selected examples, see: (a) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790; (b) Wang, W.; Pan, C.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 3978; (c) Lu, Y.; Wang, R.; Qiao, X.; Shen, Z. *Synlett* **2011**, 1038; (d) Mo, S.; Zhu, Y.; Shen, Z. *Org. Biomol. Chem.* **2013**, *11*, 2756; (e) Du, Z.-J.; Gao, L.-X.; Lin, Y.-J.; Han, F.-S. *ChemCatChem* **2014**, *6*, 123; (f) Urones, B.; Martínez, Á. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun.* **2013**, *49*, 11044; (g) Du, Z.; Gao, L.; Lin, Y. *Chem. Res. Chin. Univ.* **2015**, *31*, 167.

compatible with a wide range of functional groups affording the expected monochlorinated products in moderate to good yields. The role of Zn(OAc)₂ might be to activate the chlorinating reagent as a Lewis acid. It is worth to mention that the dichlorinated products were isolated as by-products in some cases (Scheme 60).¹⁸⁰



Scheme 60: Cu-catalyzed chlorination of benzamide derivatives. ^a 48 h.

Moreover, rhodium catalysts were applied in the chlorination of C(sp²)-H bonds. In 2015, Wang and co-workers described a Cp^{*}Rh(III)-catalyzed chlorination of arylpyridines, arylisoquinolines, arylpyrazoles and arylpyrimidines using PhI(OAc)₂ as the oxidant and NaCl as the chlorinating reagent. The [Cp^{*}RhCl₂]₂ and PhI(OAc)₂ system allowed the selective ortho-chlorination under quite mild conditions with a large substrate scope (Scheme 61).¹⁸¹ The role of CF₃COOH was to generate an activated catalyst [Cp^{*}Rh(OCOCF₃)₂] through an anion exchange.

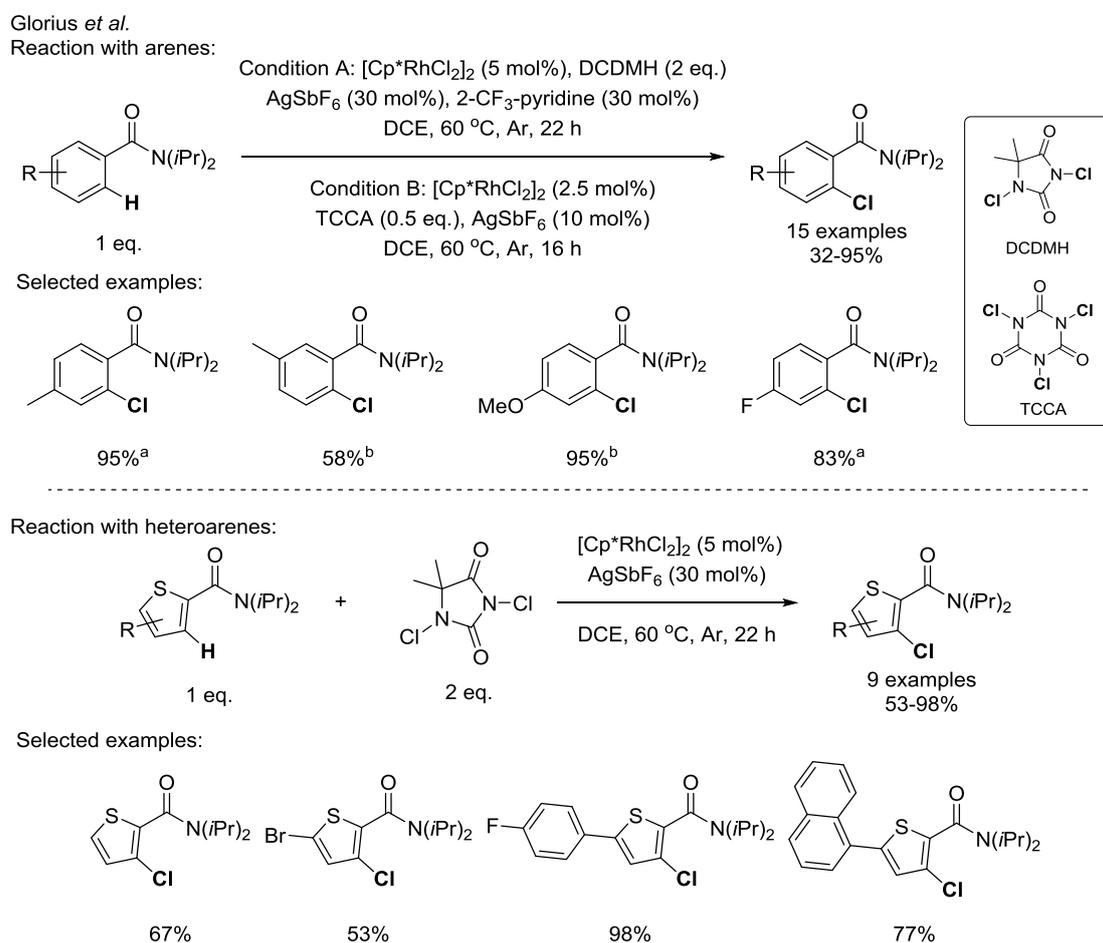


Scheme 61: Rh(III)-catalyzed chlorination of aryl derivatives bearing an heterocycle as a directing group

¹⁸⁰ Li, B.; Liu, B.; Shi, B.-F. *Chem. Commun.* **2015**, 51, 5093.

¹⁸¹ Zhang, P.; Hong, L.; Li, G.; Wang, R. *Adv. Synth. Catal.* **2015**, 357, 345.

Very recently, Glorius and co-workers reported the Cp^{*}Rh(III)-catalyzed chlorination of aryl derivatives and electron-rich heterocycles under mild reaction conditions using the cheap and commercially available 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) or trichloroisocyanuric acid (TCCA) as the chlorinating reagent. Under the assistance of N,N-diisopropylcarboxamide as directing group, a range of aryl derivatives with different substitution patterns and various substituted thiophenes were smoothly converted into the corresponding monochlorinated products in moderate to high yields (Scheme 62).¹⁸²



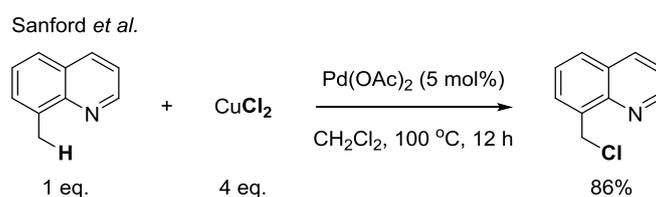
Scheme 62: Rh(III)-catalyzed chlorination of aryl derivatives and thiophenes. ^a Condition A; ^b Condition B.

2.3.2 Transition metal-catalyzed chlorination by C(sp³)-H bond activation

Despite great advances have been made in the chlorination of C(sp²)-H bonds,

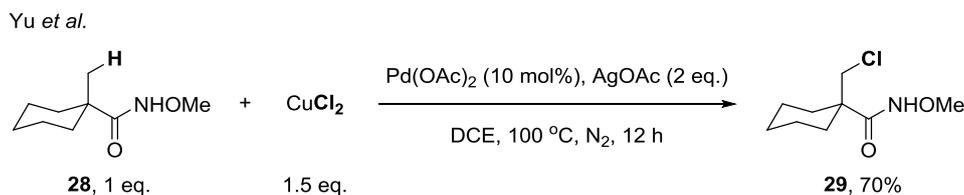
¹⁸² Lied, F.; Lerchen, A.; Knecht, T.; Mück-Lichtenfeld, C.; Glorius, F. *ACS Cat.* **2016**, *6*, 7839.

only few examples dealt with the formation of C(sp³)-Cl bonds by transition metal-catalyzed C-H bond activation. Using a directing group, chloroalkanes were synthesized with good selectivity. Note that such approach is complementary to the radical pathways. In 2006, Sanford and co-workers reported the Pd-catalyzed direct chlorination of 8-methylquinoline using CuCl₂ as both the chlorine source and the oxidant affording the corresponding product in 86% yield (Scheme 63).¹⁷⁴ Although one example was depicted, this pioneering result represented a proof-of-concept of such approach.



Scheme 63: Pd-catalyzed chlorination of 8-methylquinoline

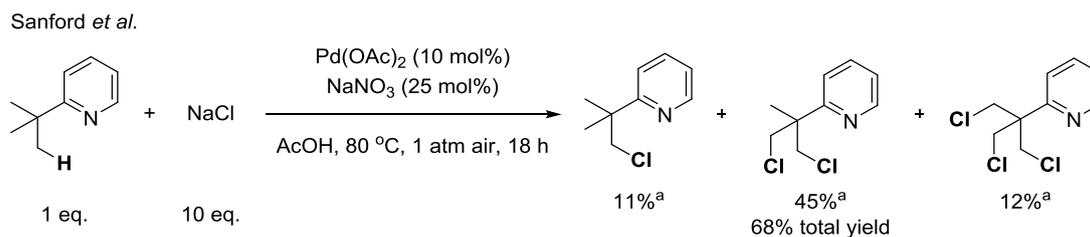
In 2008, during their investigation on the synthesis of β -, δ - and γ -lactams via Pd-catalyzed C-H bond activation, Yu and co-workers obtained the β -chlorinated product **29** in 70% yield as by-product when they treated the N-methoxy-1-methyl-cyclohexanecarboxamide **28** with CuCl₂, AgOAc in the presence of a catalytic amount of Pd(OAc)₂ in DCE at 100 °C for 12 h (Scheme 64).¹⁸³

Scheme 64: Pd-catalyzed chlorination of **28**

Additionally, in the course of their studies on the Pd(OAc)₂/NaNO₃-catalyzed acetoxylation of unactivated C(sp³)-H bonds, Sanford and co-workers reported the chlorination of the 2-(tertbutyl)pyridine with a catalytic amount of Pd(OAc)₂, NaNO₃ and an excess of NaCl. An inseparable mixture of mono, di and trichlorinated

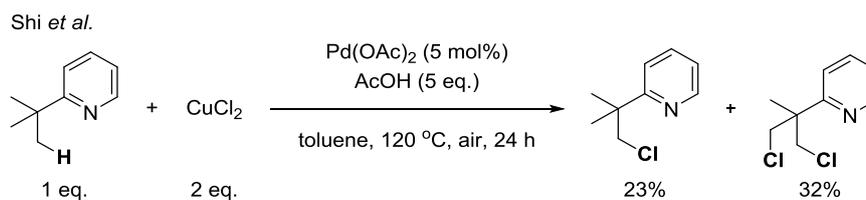
¹⁸³ Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, 130, 14058.

products were obtained in 68% total yield (Scheme 65).¹⁸⁴



Scheme 65: Pd-catalyzed chlorination of 2-(tertbutyl)pyridine with NaCl. ^a Yields was reported based on the proportion of each product in the material isolated by column chromatography.

Similarly, the reaction of 2-(tertbutyl)pyridine in the presence of a catalytic amount of Pd(OAc)₂ with an excess of CuCl₂ and acetic acid was carried out by Shi and co-workers. Under these reaction conditions, the corresponding mono and dichlorinated 2-(tertbutyl)pyridine were obtained in 23% and 32% yield, respectively (Scheme 66).¹⁸⁵



Scheme 66: Pd-catalyzed chlorination of 2-(tertbutyl)pyridine with CuCl₂

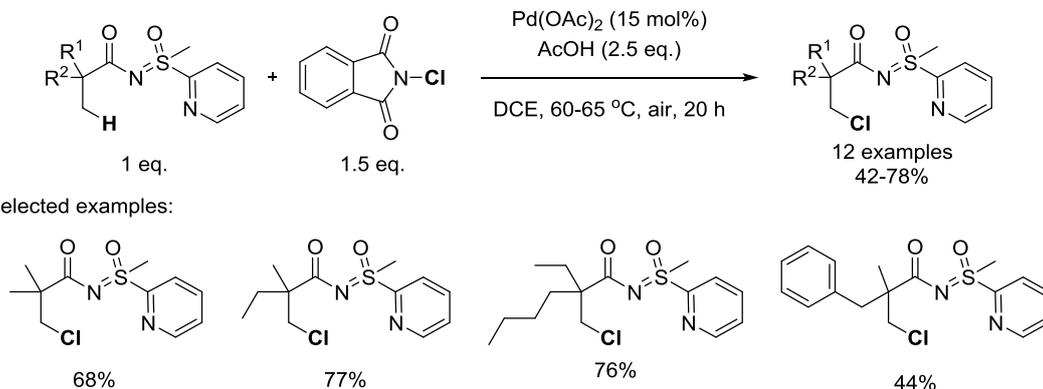
In all cases, the poor selectivity is the main synthetic issue for this transformation. In 2014, Sahoo and co-workers described an efficient synthetic pathway for the direct introduction of the chlorine atom by Pd-catalyzed C(sp³)-H bond activation. Indeed, using amide derived from methyl-2-pyridylsulfoximine as the directing group, in the presence of a catalytic amount of Pd(OAc)₂ and an excess of N-chlorophthalimide or N-bromophthalimide, the chlorination and bromination reactions proceeded smoothly.⁵⁶ In the case of the chlorination, a variety of monochlorinated products with different functional groups was obtained in moderate to good yields at 60-65 °C (Scheme 67). Although this elegant report constituted a considerable advance, the multi-step synthesis of the directing group (4 steps) might

¹⁸⁴ Stowers, K. J.; Kubota, A.; Sanford, M. S. *Chem. Sci.* **2012**, 3, 3192.

¹⁸⁵ Li, B.; Wang, S.-Q.; Liu, B.; Shi, B.-F. *Org. Lett.* **2015**, 17, 1200.

be considered as a limitation of this method.

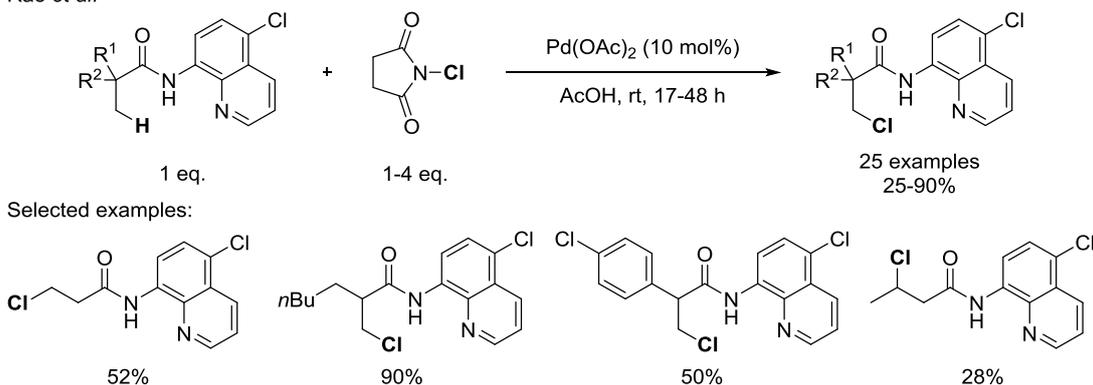
Sahoo *et al.*



Scheme 67: Pd-catalyzed monochlorination of methyl-2-pyridylsulfoximine-N-amides

In 2016, Rao and co-workers reported the Pd-catalyzed halogenation of unactivated C(sp³)-H bond at room temperature using the 5-chloro-8-aminoquinoline derived auxiliary as the directing group.¹⁸⁶ Under the optimized reaction conditions, a range of aliphatic carboxylic acid derivatives was converted into the corresponding chlorinated products in moderate to good yields with a wide functional group tolerance (Scheme 68). In this case, the use of 5-chloro-8-aminoquinoline derived auxiliary as fancy directing group was beneficial to avoid any side reactions (eg. electrophilic aromatic chlorination) at the C-5 position.

Rao *et al.*



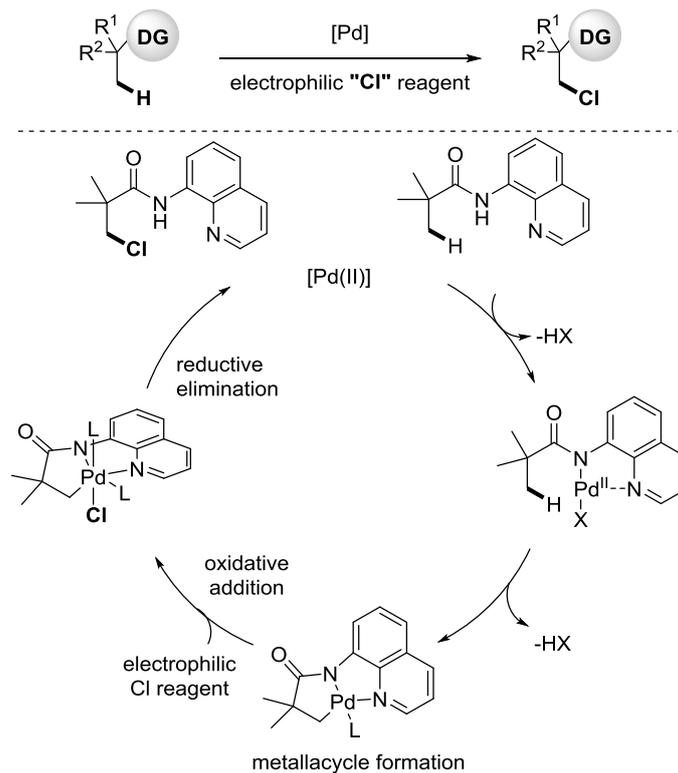
Scheme 68: Pd-catalyzed chlorination of unactivated amides using the 5-chloro-8-aminoquinoline derived auxiliary as the directing group

¹⁸⁶ Yang, X.; Sun, Y.; Sun, T.; Rao, Y. *Chem. Commun.* **2016**, 52, 6423.

Since only few examples dealt with the transition metal-catalyzed halogenations of unactivated C(sp³)-H bonds, the development of new methodologies allowing the selective preparation of such highly valuable compounds will be highly desirable. Note that Rao and co-workers reported their Pd-catalyzed halogenation of unactivated aliphatic amides at room temperature at the end of our investigations on the Pd-catalyzed chlorination of aliphatic amides. Thus, no report regarding the introduction of a chlorine atom on unactivated aliphatic amides under mild conditions has been reported at the outset of our study.

3 Our objectives

We would like to develop a new methodology for the chlorination of unactivated aliphatic amides (Scheme 69). Taking benefit from our studies on the Pd-catalyzed trifluoromethylthiolation by C(sp³)-H bond activation using an electrophilic SCF₃ reagent, we hypothesized that a similar approach using an electrophilic chlorinating reagent, which might play the role of both oxidant and chlorinating source, will be suitable. We envisioned that the chelation of the Pd(II) catalyst with the bidentate chelating group followed by the formation of the palladacycle would occur. This intermediate might undergo an oxidative addition in the presence of a suitable electrophilic chlorinating reagent leading to a plausible Pd(IV) species. Then, a reductive elimination and a final protonation of the amide would afford the chlorinated product (Scheme 69).



4 Optimization of the monochlorination reaction conditions

With these considerations in mind, we decided to start our investigation with the same model substrate (N-(quinolin-8-yl)pivalamide **18a**) as we used in the Pd-catalyzed directed trifluoromethylthiolation of unactivated C(sp³)-H bonds (Chapter 2). Several reaction parameters were investigated.

4.1 Screening of the solvents

We first screened various solvents using Pd(CH₃CN)₂Cl₂ as the catalyst and N-chlorosuccinimide (NCS) as the readily available chlorinating reagent. It was found that except the case of 1,4-dioxane as solvent, in which traces of the product were detected by GC-MS (Table 11, entry 1), other solvents such as DMSO, CH₃CN, toluene, DMF, HFIP were not efficient at all in this transformation (Table 11, entries 2-6).

Table 11: Screening of the solvents^a

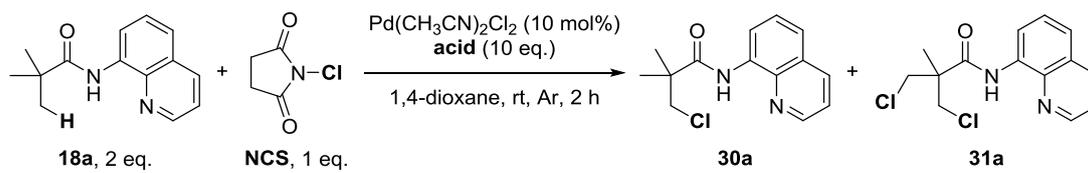
The reaction scheme shows the chlorination of 18a (2 equivalents) with NCS (1 equivalent) using Pd(CH₃CN)₂Cl₂ (10 mol%) as a catalyst in various solvents at room temperature under an argon atmosphere for 2 hours. The products are 30a (mono-chlorinated) and 31a (di-chlorinated).

entry	solvent	yield 30a (%) ^b	yield 31a (%) ^b
1	1,4-dioxane	traces	-
2	DMSO	-	-
3	CH ₃ CN	-	-
4	toluene	-	-
5	DMF	-	-
6	HFIP	-	-

^a Reaction conditions: **18a** (0.2 mmol, 2 eq.), NCS (0.1 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.01 mmol, 10 mol%), solvent (1 mL), rt, Ar, 2 h; ^b NMR yields determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

4.2 Screening of the additives

Based on our previous observations on the direct introduction of the SCF₃ group onto aliphatic amides, acids used to play a key role during the C-H functionalization process. Thus, several acids were evaluated (Table 12). To our delight, in the case of acetic acid (AcOH, Table 12, entry 1), camphor-10-sulfonic acid (Table 12, entry 2), 2,4,6-trimethylbenzoic acid (MesCOOH, Table 12, entry 3), adamantyl acid (Table 12, entry 4), or benzoic acid (PhCOOH, Table 12, entry 4) as additive, **30a** was obtained in 12-18% NMR yields. Trifluoroacetic acid (TFA) and 2-NO₂-C₆H₄COOH showed good efficiency, giving the products in good yields and the mono and dichlorinated products were obtained, **30a** being the major product (Table 12, entries 6 and 7). Thus, TFA was selected.

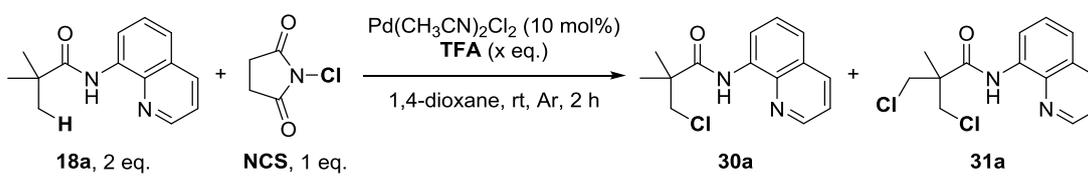
Table 12: Screening of the acids^a


entry	acid (10 eq.)	yield 30a (%) ^b	yield 31a (%) ^b
1	AcOH	14	3
2	camphor-10-sulfonic acid	14	0
3	MesCOOH	18	0
4	adamantyl acid	12	0
5	PhCOOH	13	2
6	TFA	52	16
7	2-NO ₂ -C ₆ H ₄ COOH	45	12

^a Reaction conditions: **18a** (0.2 mmol, 2 eq.), NCS (0.1 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.01 mmol, 10 mol%), acid (1 mmol, 10 eq.), 1,4-dioxane (1 mL), rt, Ar, 2 h; ^b NMR yields determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

4.3 Screening of the stoichiometry of the TFA

With these encouraging results, we next studied the stoichiometry of the TFA. When the amount of TFA was decreased to 5 equivalents, a significant drop of the yield was noticed (Table 13, entry 2). On the other hand, when the amount of TFA was increased to 20 equivalents or 50 equivalents, no improvement was observed (Table 13, entries 3 and 4).

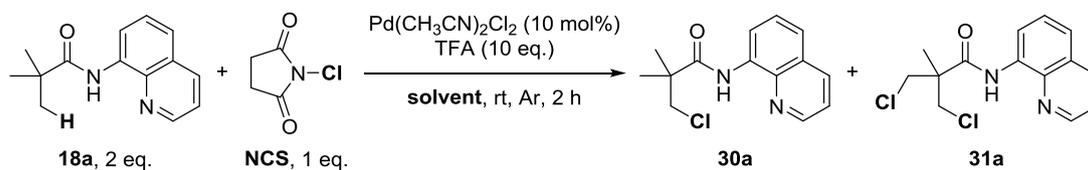
Table 13: Screening of the stoichiometry of TFA^a


entry	TFA (x eq.)	yield 30a (%) ^b	yield 31a (%) ^b
1	10	52	16
2	5	30	6
3	20	49	12
4	50	36	14

^a Reaction conditions: **18a** (0.2 mmol, 2 eq.), NCS (0.1 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.01 mmol, 10 mol%), TFA (x eq.), 1,4-dioxane (1 mL), rt, Ar, 2 h; ^b NMR yields determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

4.4 Screening of the solvents using TFA as additive

Next, we went back to the solvent investigations, hoping to find more selective reaction conditions for the monochlorination reaction. Reactions performed in DMSO, DCE, CH₃CN or toluene led to no conversion at all (Table 14, entries 2-5). When methanol was used, the expected monochlorinated product **30a** was obtained in only 23% NMR yield while the dichlorinated one **31a** was obtained in 7% NMR yield (Table 14, entry 6). Finally, 1,4-dioxane was proved to be the optimal solvent for this transformation (Table 14, entry 1).

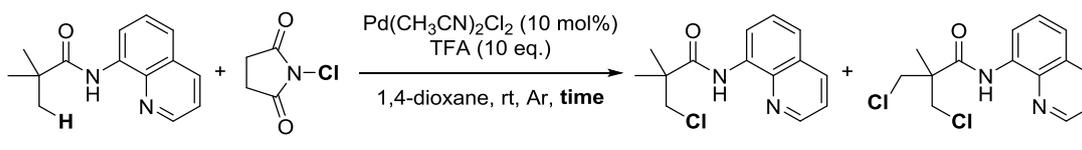
Table 14: Screening of the solvents using TFA as additive^a

entry	solvent	yield 30a (%) ^b	yield 31a (%) ^b
1	1,4-dioxane	52	16
2	DMSO	-	-
3	DCE	-	-
4	CH ₃ CN	-	-
5	toluene	-	-
6	methanol	23	7

^a Reaction conditions: **18a** (0.2 mmol, 2 eq.), NCS (0.1 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.01 mmol, 10 mol%), TFA (1 mmol, 10 eq.) solvent (1 mL), rt, Ar, 2 h; ^b NMR yields determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

4.5 Investigation on the ratio of **18a**/NCS and the reaction time

The study on the ratio of the starting materials and the reaction time was carried out. When the amount of the amide **18a** was decreased to 1.5 or 1 equivalents, a lower yield was observed (Table 15, entries 2 and 3). A shorter reaction time (1 h) afforded the monochlorinated product **30a** in 42% NMR yield and the dichlorinated one **31a** in 7% NMR yield (Table 15, entry 4). After prolonging the reaction time to 4 or 16 h, a lower yield was obtained in both cases indicating that 2 h was the optimal reaction time (Table 15, entries 5 and 6).

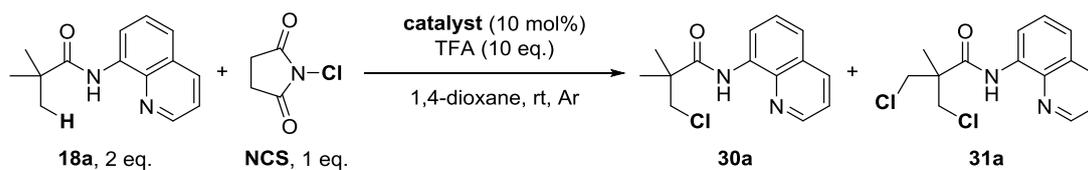
Table 15: Investigation on the ratio of **18a**/NCS and the reaction time^a


entry	18a /NCS	time (h)	yield 30a (%) ^b	yield 31a (%) ^b
1	2/1	2	52	16
2	1.5/1	2	41	13
3	1/1	2	32	9
4	2/1	1	42	7
5	2/1	4	46	11
6	2/1	16	36	9

^a Reaction conditions: **18a** (x eq.), NCS (0.1 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.01 mmol, 10 mol%), TFA (1 mmol, 10 eq.) solvent (1 mL), rt, Ar, 2 h; ^b NMR yields determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

4.6 Screening of the catalysts

After then, other Pd(II) and Pd(0) catalysts were investigated. However, when Pd(OAc)₂, Pd(TFA)₂ and Pd(OPiv)₂ were used as the catalyst, no improvement was observed (Table 16, entries 2-4). It was found that PdCl₂ and Pd(PhCN)₂Cl₂ showed comparable catalytic activity, affording the expected products in slightly lower yields (Table 16, entries 5 and 6). Worth mentioning that Pd₂(dba)₃ showed the worst performance, precluding the involvement of a Pd(0)/Pd(II) catalytic cycle (Table 16, entry 7). At last, Pd(CH₃CN)₂Cl₂ was proved to be the optimal catalyst for this transformation (Table 16, entry 1). Notably, a control experiment was performed and in the absence of a Pd catalyst, no reaction occurred (Table 16, entry 8).

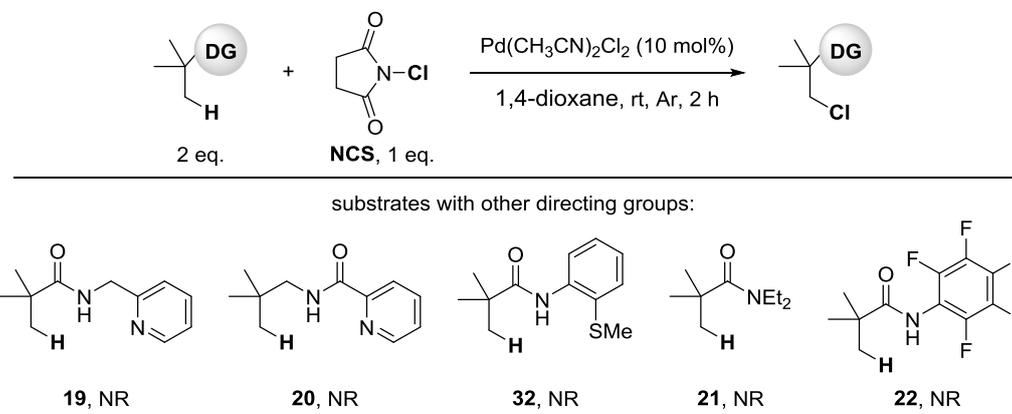
Table 16: Screening of the catalysts^a

entry	catalyst	yield 30a (%) ^b	yield 31a (%) ^b
1	Pd(CH ₃ CN) ₂ Cl ₂	52	16
2	Pd(OAc) ₂	10	6
3	Pd(TFA) ₂	7	4
4	Pd(OPiv) ₂	36	9
5	PdCl ₂	43	14
6	Pd(PhCN) ₂ Cl ₂	50	15
7	Pd ₂ (dba) ₃	2	4
8	-	-	-

^a Reaction conditions: **18a** (0.2 mmol, 2 eq.), **NCS** (0.1 mmol, 1 eq.), catalyst (0.01 mmol, 10 mol%), TFA (1 mmol, 10 eq.), 1,4-dioxane (1 mL), rt, Ar, 2 h; ^b NMR yields determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

4.7 Screening of the directing groups

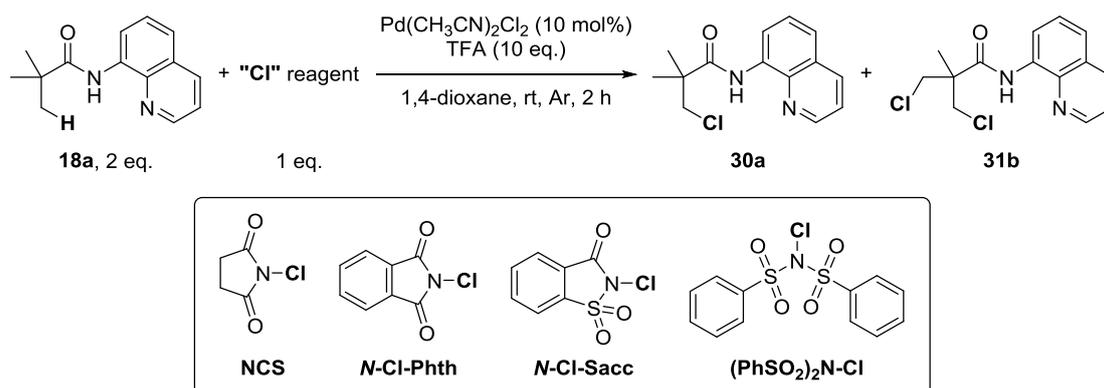
We next surveyed the efficiency of a range of other directing groups, which were frequently employed in the C-H bond functionalization reactions in recent years. As shown in Table 17, no product was detected with other directing groups (substrates: **19-22**, **32**) and the starting materials were recovered. These results showcased that the 8-aminoquinoline based auxiliary proved to be the most suitable directing group.

Table 17: Screening of the directing group^a

^a Reaction conditions: **19-22**, **32** (0.2 mmol, 2 eq.), **NCS** (0.1 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.01 mmol, 10 mol%), TFA (1 mmol, 10 eq.), 1,4-dioxane (1 mL), rt, Ar, 2 h, NR = no reaction; ^b NMR yields determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

4.8 Screening of the electrophilic chlorinating reagents

At last, we tried to examine various electrophilic chlorinating reagents. It was found that the N-chlorophthalimide (N-Cl-Phth) could also furnish the expected product albeit in a lower yield (Table 18, entry 2), while other chlorinating reagents such as N-Chloro-saccharin (N-Cl-Sacc) and (PhSO₂)₂N-Cl showed no reactivity (Table 18, entries 3 and 4). Thus, NCS was chosen as the chlorinating reagent for our next investigations. Finally, we decided to use Pd(CH₃CN)₂Cl₂ (10 mol%) as the catalyst, NCS as the chlorine source, 1,4-dioxane as the solvent and TFA as the additive for this transformation.

Table 18: Screening of the chlorinating reagents^a

entry	"Cl" reagent	yield 30a (%) ^b	yield 31a (%) ^b
1	NCS	52	16
2	N-Cl-Phth	40	9
3	N-Cl-Sacc	-	-
4	(PhSO ₂) ₂ N-Cl	-	-

^a Reaction conditions: **18a** (0.2 mmol, 2 eq.), "Cl" reagent (0.1 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.01 mmol, 10 mol%), TFA (1 mmol, 10 eq.), 1,4-dioxane (1 mL), rt, Ar, 2 h; ^b NMR yields determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

5 Substrate scope of the chlorination reaction of aliphatic amides

Under our optimal reaction conditions, we examined the substrate scope for the chlorination of amides. A range of aliphatic amides having primary C(sp³)-H bonds with different patterns was examined (Table 19).

Table 19: Scope of the Pd-catalyzed chlorination reaction of amides^a

substrate 18			
yield 30 (%)	40	54	44
yield 31 (%)	8	20	20
substrate 18			
yield 30 (%)	42	43	49
yield 31 (%)	17	15	20
substrate 18			
yield 30 (%)	51	41	48
yield 31 (%)	17	28	21
substrate 18			
yield 30 (%)	46	31	48
yield 31 (%)	20	-	9 ^f

^a Reaction conditions: **18** (0.4 mmol, 2 eq.), NCS (0.2 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.02 mmol, 10 mol%), TFA (2 mmol, 10 eq.), 1,4-dioxane (2 mL), rt, Ar, 2 h; ^b 8 h; ^c 5 h; ^d 4 h; ^e 16 h; ^f The compound **31w** contains traces of an inseparable impurity.

This transformation turned out to be not only tolerant to α,α -dialkyl-substituted amides but also to amides derived from α,α -dimethylated hydrocinnamic acid derivatives. Various monochlorinated products **30** and the dichlorinated one **31** were

synthesized at room temperature in good overall yields (48-74%), taking into consideration that the NCS was used as a limiting reagent in this transformation. Notably, the mono and dichlorinated products **30** and **31** were obtained with a **30/31** ratio ranging from 59:41 to 83:17 and could be easily separated by flash column chromatography.

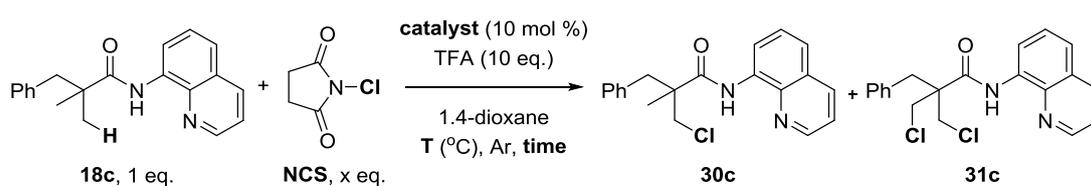
The amide bearing equally nine protons (**18a**) could be converted into the corresponding monochlorinated products **30a** as the major species in 40 % yield. The transformation of α,α -dimethylated hydrocinnamic acid derivatives was then evaluated. The results proved that the nature of the substituent on the aromatic ring of compounds (**18c-h**, **18j**) have no considerable influence on the reactivity. Indeed, substrates with a phenyl ring bearing either a halogen (Br, Cl, F; **18e-g**, **18j**), an electron-withdrawing group (CF₃; **18h**) or an electron-donating one (OMe; **18d**) were smoothly functionalized. Moreover, a substrate bearing a homobenzylic substituent (**18k**) was also compatible leading to the corresponding monochlorinated product **30k** in 48% yield and dichlorinated product **31k** in 21% yield. It was worth mentioning that the reaction was chemo-selective towards the unactivated C(sp³)-H bond since no chlorination of the aromatic ring or the reactive benzylic position was detected. The functionalization of substrate **18b** with an alkyl chain was also achieved affording the expected monochlorinated product **30b** in 46% yield and the dichlorinated one **31b** in 20% yield. Furthermore, α -cyclic amide **18v** was a suitable substrate for this reaction affording the chlorinated product **30v** in 31% yield. At last, we found that using a directing group substituted by a methoxy group at the C-5 position furnished the corresponding monochlorinated product **30w** in a slightly higher yield.

6 Optimization of the Pd-catalyzed dichlorination reaction of amide **18c**

Since suitable reaction conditions were found leading to the monochlorinated chlorinated products **31** in 31-54% yields, we were wondering if the dichlorination

reaction could be selectively achieved by tuning the reaction conditions. Thus, amide **18c** was chosen to be the model substrate, and several reaction parameters were investigated (Table 20). When 5 equivalents of NCS was used, the monochlorinated amide **30c** was obtained as the major product in 28% NMR yield with the dichlorinated one **31c** in 11% NMR yield after 24 h (Table 20, entry 1). Increasing the temperature to 100 °C did not afford the expected product probably due to the instability of the starting material or the product under harsher reaction conditions (Table 20, entry 2). Interestingly, switching the catalyst to Pd(TFA)₂ provided the monochlorinated product **30c** in 17% NMR yield and the dichlorinated one **31c** in 40% NMR yield at 25 °C after 16 h (Table 20, entry 3). It was found that increasing the amount of the NCS was beneficial since the product **31c** was obtained in 60% NMR yield (isolated in 49% yield), along with the monochlorinated product **30c** in 20% NMR yield (isolated in 7% yield) (Table 20, entry 4). We then tried to increase the reaction temperature to 50 °C in order to get a better conversion, but no improvement was observed (Table 20, entry 5). Finally, it was found that a higher reaction concentration (0.2 M) could afford the dichlorinated product **31c** in 51% isolated yield without any traces of **30c** (Table 20, entry 6).

Table 20: Optimization of the dichlorination reaction

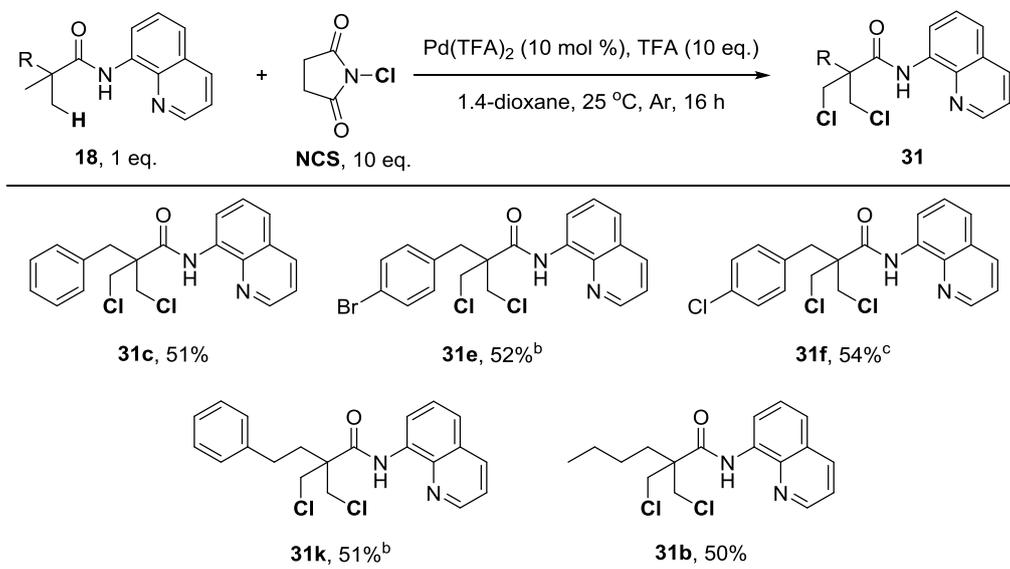


entry	catalyst	NCS (x eq.)	T (°C)	time (h)	yield 30c (%) ^b	yield 31c (%) ^b
1	Pd(CH ₃ CN) ₂ Cl ₂	5	25	24	28	11
2	Pd(CH ₃ CN) ₂ Cl ₂	5	100	6	-	-
3	Pd(TFA) ₂	5	25	16	17	40
4	Pd(TFA) ₂	10	25	16	20 (7) ^c	60 (49) ^c
5	Pd(TFA) ₂	10	50	5	5	50
6 ^d	Pd(TFA) ₂	10	25	16	-	51 ^c

^a Reaction conditions: **18c** (0.1 mmol, 1 eq.), NCS (x eq.), catalyst (0.01 mmol, 10 mol%), TFA (1 mmol, 10 eq.), 1,4-dioxane (1 mL), T (°C), Ar, time (h); ^b NMR yields determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard; ^c Isolated yield; ^d Reaction run at a concentration of 0.2 M.

7 Substrate scope for the Pd-catalyzed dichlorination reaction of aliphatic amides

Having obtained the optimal reaction conditions, we next investigated the scope of this dichlorination reaction (Table 21). First, amides derived from α,α -dimethylated hydrocinnamic acid derivatives were evaluated and the expected dichlorinated products **31** were obtained in good yields under the standard reaction conditions. Substrates with a halogen substituent (Br, Cl; **18e**, **18f**) on the aromatic ring were converted into the corresponding dichlorinated products (**31e** and **31f**) in 52% and 54% yield, respectively. These results showed the potential for post-functionalization of these products. Moreover, substrates with a homobenzylic substituent (**18k**) or a nbutyl chain (**18b**) were compatible in this transformation offering the expected products in 51% and 50% yields, respectively.

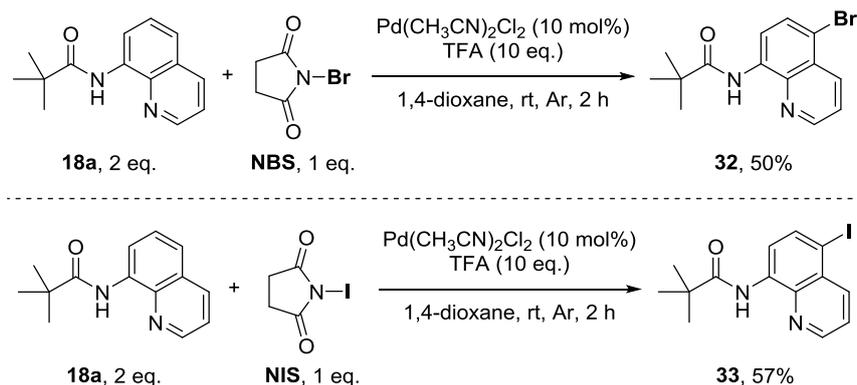
Table 21: Pd-catalyzed dichlorination of amides^a

^a Reaction conditions: **18** (0.2 mmol, 1 eq.), NCS (2 mmol, 10 eq.), Pd(TFA)₂ (0.02 mmol, 10 mol%), TFA (2 mmol, 10 eq.), 1,4-dioxane (2 mL), 25 °C, Ar, 16 h; ^b 17 h; ^c 18 h.

8 Extension to the iodination and bromination of aliphatic amides

With these promising results in hand, we then turned our attention to the bromination and iodination of the C(sp³)-H bond. Under the optimal reaction

conditions, the reaction of N-(quinolin-8-yl)pivalamide **18a** with the NBS or the NIS were carried out. Instead of the expected products, the bromination or iodination at the C-5 position of the quinoline moiety occurred affording the brominated product **32** in 50% yield and the iodinated product **33** in 57% yield (Scheme 70). However, several reports already dealt with such transformations¹⁸⁷ and we did not investigate further these promising results.

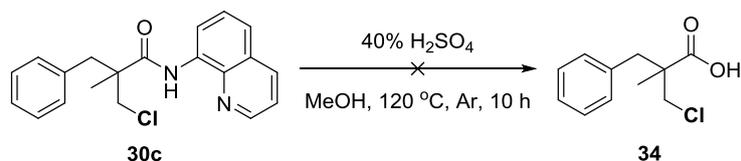


Scheme 70: Halogenation at the C-5 position of the quinoline part

9 Post-functionalizations

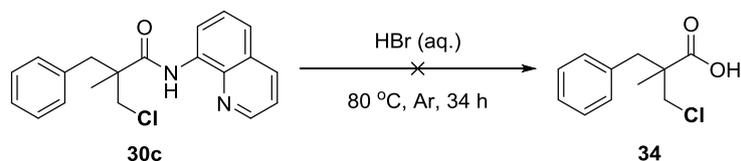
9.1 Cleavage of the directing group: from the amide **30c** to the corresponding carboxylic acid

To further broaden the synthetic application of this methodology, the removal of the 8-aminoquinoline group was carried out based on the reported procedure.^{36b} First, the chlorinated compound **30c** was treated with 40% H₂SO₄ in methanol at 120 °C for 10 h. However, no reaction occurred and the starting material **30c** was recovered (Scheme 71).

Scheme 71: Cleavage of the directing group with H₂SO₄

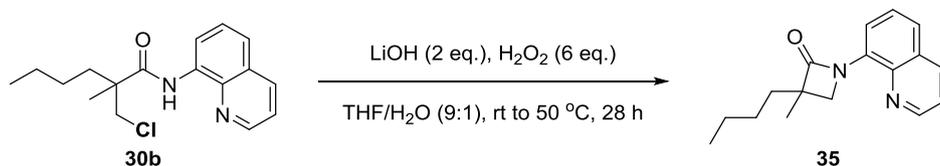
¹⁸⁷ (a) Xu, J.; Shen, C.; Zhu, X.; Zhang, P.; Ajitha, M. J.; Huang, K.-W.; An, Z.; Liu, X. *Chem. Asian J.* **2016**, 11, 882; (b) Xu, J.; Zhu, X.; Zhou, G.; Ying, B.; Ye, P.; Su, L.; Shen, C.; Zhang, P. *Org. Biomol. Chem.* **2016**, 14, 3016; (c) Guo, H.; Chen, M.; Jiang, P.; Chen, J.; Pan, L.; Wang, M.; Xie, C.; Zhang, Y. *Tetrahedron* **2015**, 71, 70; (d) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, 135, 9797.

It was reported by Xu and co-workers that the 8-aminoquinoline derived auxiliary could be removed with aqueous HBr.^{55a} Thus, we tried to cleave the directing group using aqueous HBr (Scheme 72). Unfortunately, no expected product was detected after heating the reaction mixture at 80 °C for 34 h and the starting material was recovered.



Scheme 72: Cleavage of the directing group with HBr

Since we did not succeed in the cleavage of the directing group under acidic conditions, we decided to perform the reaction under basic conditions according to the reported procedure.¹⁸⁸ Upon treatment of the chlorinated product **30b** with 2 equivalents of LiOH and 6 equivalents of H₂O₂ in the solution of THF and H₂O, no expected product was detected. In contrast, the β -lactam **35** was detected by GC-MS (Scheme 73). Finally, we did not succeed to cleave the directing group into the corresponding acid derivative.

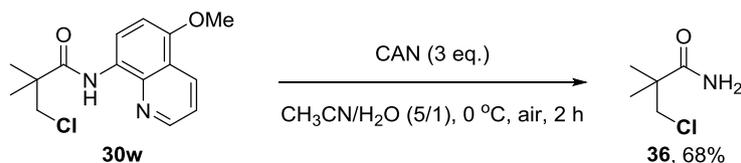


Scheme 73: Cleavage of the directing group under basic conditions

9.2 Cleavage of the directing group: from the amide **30w** to the corresponding primary amide

We then turned our attention to the cleavage of 5-methoxyquinolyl group of **30w** according to the reported procedure.^{54c} Gratifyingly, subjecting the chlorinated compound **30w** with 3 equivalents of ceric ammonium nitrate (CAN) in the mixture of CH₃CN/H₂O at 0 °C for 2 h led to the corresponding amide **36** in 68% yield (Scheme 74).

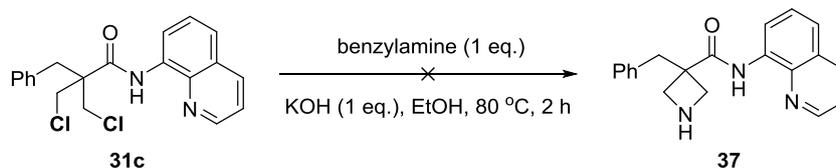
¹⁸⁸ Shinohara, N.; Haga, J.; Yamazaki, T.; Kitazume, T.; Nakamura, S. *J. Org. Chem.* **1995**, 60, 4363.



Scheme 74: Cleavage of the directing group

9.3 Synthesis of azetidines

Azetidines are a class of important compounds which have been found in diverse of nature products and served as valuable synthetic intermediates.¹⁸⁹ With the dichlorinated products in hand, we were wondering whether these compounds could be converted into the corresponding azetidines. However, when the chlorinated product **31c** was reacted with benzylamine under the reported reaction conditions,¹⁹⁰ the expected azetidine was not found (Scheme 75). Instead, the corresponding β -lactam **37** was detected by GC-MS probably owing to the presence of the base.

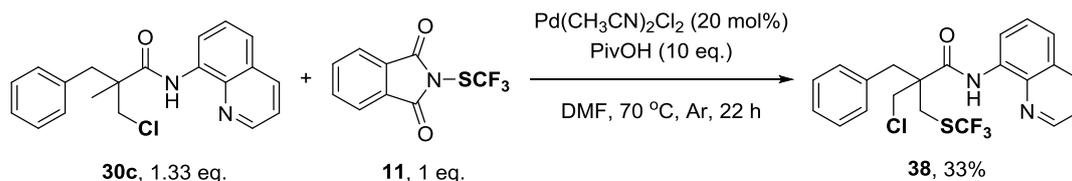
Scheme 75: Attempt to synthesize the azetidine **37**

9.4 Sequential C-H bond functionalization reaction

Inspired by the trifluoromethylthiolation of C(sp³)-H bond we developed in the Chapter 2,¹⁵³ we assumed that a trifluoromethylthiolation of the monochlorinated product via a sequential C-H bond functionalization reaction would lead to a highly functionalized quaternary carbon center. Thus, following the standard reaction conditions we developed,¹⁵³ the monochlorinated product **30c** was converted into the expected product **38** in 33% yield (Scheme 76).

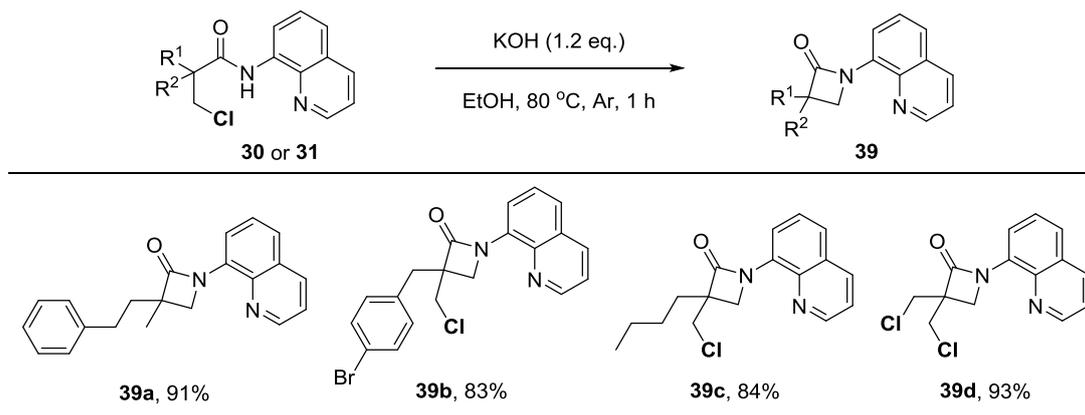
¹⁸⁹ For selected examples, see: (a) Couty, F.; Prim, D. *Tetrahedron: Asymmetry* **2002**, 13, 2619; (b) Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, 7, 5861; (c) Van Brabandt, W.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, 8, 1101; (d) Ghorai, M. K.; Kumar, A.; Das, K. *Org. Lett.* **2007**, 9, 5441; (e) Burkhard, J. A.; Guérot, C.; Knust, H.; Carreira, E. M. *Org. Lett.* **2012**, 14, 66.

¹⁹⁰ Stocks, M. J.; Hamza, D.; Pairedeau, G.; Stonehouse, J. P.; Thorne, P. V. *Synlett* **2007**, 2587.

Scheme 76: Trifluoromethylthiolation of **30c**

9.5 Synthesis of lactams

As an application of these chlorinated products, we successfully synthesized the β -lactams.¹⁹¹ In the presence of an excess of KOH, several β -lactams bearing a quaternary center at the α -position of the amide substituted with a methyl group **39a** or a chloromethylene motif (**39b-d**) were prepared in high yields (83-93%), demonstrating the synthetic utility of these products (Table 22).

Table 22: Synthesis of β -lactams^a

^a Reaction conditions: **30** or **31** (0.1 mmol, 1 eq.), KOH (0.12 mmol, 1.2 eq.), EtOH (1 mL), 80 °C, Ar, 1 h.

10 Mechanistic studies

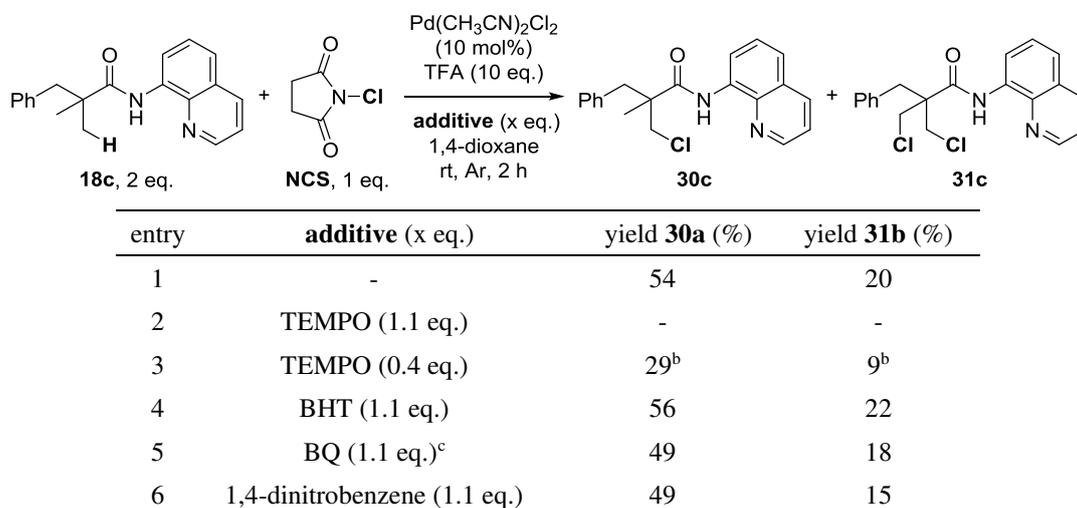
10.1 Radical trapping experiments

In order to gain insights into the reaction mechanism, we performed the reaction of **18c** and NCS in the presence of radical inhibitors or scavengers (Table 23). When

¹⁹¹ For selected reviews, see: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, 107, 4437; (b) Aranda, M. T.; Perez-Faginas, P.; González-Muñiz, R. *Cur. Org. Synth.* **2009**, 6, 325; For selected examples, see: (c) Gembus, V.; Poisson, T.; Oudeyer, S.; Marsais, F.; Levacher, V. *Synlett* **2009**, 2437; (d) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, 52, 13588; (e) Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, 53, 9064; (f) Sun, W.-W.; Cao, P.; Mei, R.-Q.; Li, Y.; Ma, Y.-L.; Wu, B. *Org. Lett.* **2014**, 16, 480; (g) Wang, C.; Yang, Y.; Qin, D.; He, Z.; You, J. *J. Org. Chem.* **2015**, 80, 8424.

the reaction was carried out with 1.1 equivalents of 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) under the standard reaction conditions, no product was detected (Table 23, entry 2). Indeed, a plausible reaction between the TEMPO reagent and the NCS might explain the absence of product when a stoichiometric amount of TEMPO was employed (note that when TEMPO was engaged in our standard reaction conditions in the absence of starting material **18c**, a chlorinated product generated from the reaction of TEMPO and NCS was detected by GC-MS). The addition of 0.4 equivalents of TEMPO afforded the expected products **30c** and **31c** in slightly lower yields (Table 23, entry 3). Other additives such as 2,6-di-tert-butyl-4-methylphenol (BHT), 1,1-benzoquinone (BQ) or 1,4-dinitrobenzene showed no deleterious effect on the outcome of the reaction (Table 23, entries 4-6). Thus, taking into account these observations, a plausible radical pathway might be thereby ruled out.

Table 23: Radical trapping experiments



^a Reaction conditions: **18c** (0.4 mmol, 2 eq.), NCS (0.2 mmol, 1 eq.), Pd(CH₃CN)₂Cl₂ (0.02 mmol, 10 mol %), TFA (2 mmol, 10 eq.), additive (x eq.), 1,4-dioxane (2 mL), rt, Ar, 2 h.; ^b NMR yields determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^c BQ = 1,4-benzoquinone.

10.2 Proposed mechanism

Based on the aforementioned observations and the literature data,^{53c,d,56} we envisaged the following reaction pathway: first, the chelation of the Pd(II) catalyst to

the bidentate directing group would lead to the intermediate **A**. Then, the concerted metalation-deprotonation would furnish the corresponding palladacycle (intermediate **B**). This intermediate then would undergo a subsequent oxidative addition in the presence of the electrophilic NCS reagent leading to a plausible Pd(IV) species (intermediate **C**). Finally, a reductive elimination and a final protonation of the amide would furnish the expected product and regenerate the catalyst (Figure 14)

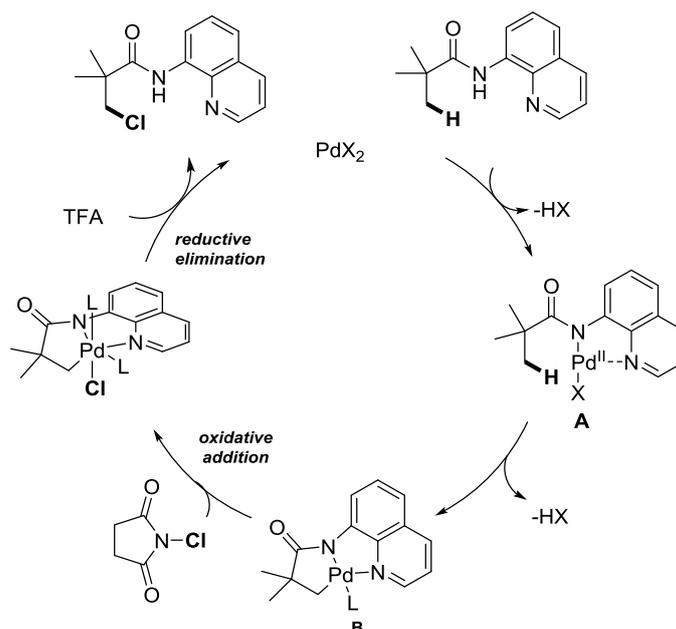


Figure 14: Proposed mechanism

11 Conclusion

In conclusion, by using the 8-aminoquinolinyl derived amide as directing group, we have developed the selective chlorination of aliphatic amides.¹⁹² In the presence of N-chlorosuccinimide (NCS), the valuable chlorinated products have been obtained in moderate to good yields at room temperature. Besides, the dichlorination reaction could also be achieved under modified reaction conditions. These key scaffolds were further applied in the synthesis of valuable building blocks, the β -lactams for instance. This approach represents a rare example for the transition metal-catalyzed directed chlorination by C(sp³)-H bond activation, providing an mild and efficient pathway.

¹⁹² Xiong, H.-Y.; Cahard, D.; Pannecoucke, X.; Besset, T. *Eur. J. Org. Chem.* **2016**, 3625.

Chapter 4
Design and Synthesis of Original
Electrophilic Reagents

This chapter is dedicated to the design and the synthesis of original electrophilic reagents and will be organized in two main parts:

1) Oxidative trifluoromethylthiolation and thiocyanation of amines: a general approach to N-S bond formation.

2) An electrophilic reagent for the direct introduction of the $\text{SCF}_2\text{PO}(\text{OEt})_2$ group onto molecules

1 Oxidative trifluoromethylthiolation and thiocyanation of amines: a general approach to N-S bond formation

Sulfenamides are a class of interesting compounds.¹⁹³ Thus, in this section, we will focus on the development of a general and efficient approach for the construction of N-S bonds mainly based on a newly designed synthetic pathway. It will be organized in two parts: the construction of the N- SCF_3 bond and the N-SCN bond.

1.1 The properties of sulfenamides

The sulfenamides have found to be important because of their wide utilization in different fields^{194a} such as organic synthesis,^{194b-d} pharmaceuticals^{194a,195} and material sciences.^{194a} For instance, the fungicide captan (Figure 15) is used on a variety of fruits and vegetables.¹⁹⁶ Another fungicide is the dichlofluanid which was widely used for the protection of fruits and vegetables from scab, black spot, gray mold, among others.¹⁹⁷ In addition, the postulated active forms of proton pump inhibitors

¹⁹³ For selected reviews, see: (a) Davis, F. A. *J. Org. Chem.* **2006**, 71, 8993; (b) Craine, L.; Raban, M. *Chem. Rev.* **1989**, 89, 689; (c) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, 38, 1162; (d) Petrov, K. A.; Rudnev, G. V.; Sorokin, V. D. *Russ. Chem. Rev.* **1990**, 59, 832; For a selected example, see: (e) Lee, C.; Lim, Y. N.; Jang, H.-Y. *Eur. J. Org. Chem.* **2015**, 5934.

¹⁹⁴ For a selected review, see: (a) Koval, I. V. *Russ. Chem. Rev.* **1996**, 65, 421; For selected examples, see: (b) Knapton, D. J.; Meyer, T. Y. *J. Org. Chem.* **2005**, 70, 785; (c) Spitz, C.; Lohier, J.-F.; Reboul, V.; Metzner, P. *Org. Lett.* **2009**, 11, 2776; (d) Kuniyasu, H.; Kato, T.; Asano, S.; Ye, J.-H.; Ohmori, T.; Morita, M.; Hiraike, H.; Fujiwara, S.; Terao, J.; Kurosawa, H. *Tetrahedron Lett.* **2006**, 47, 1141.

¹⁹⁵ For selected reviews, see: (a) Guarino, V. R.; Karunaratne, V.; Stella, V. J. *Bioorg. Med. Chem. Lett.* **2007**, 17, 4910; (b) Lindberg, P.; Nordberg, P.; Alminger, T.; Braendstroem, A.; Wallmark, B. *J. Med. Chem.* **1986**, 29, 1327; (c) Shin, J. M.; Munson, K.; Vagin, O.; Sachs, G. *Pflugers Arch-Eur J Physiol* **2009**, 457, 609.

¹⁹⁶ (a) Chen, S.-K.; Edwards, C. A.; Subler, S. *Soil Biol. Biochem.* **2001**, 33, 1971; (b) Cengiz, M. F.; Certel, M.; Karakaş, B.; Göçmen, H. *Food Chem.* **2007**, 100, 1611.

¹⁹⁷ (a) Rial-Otero, R.; Arias-Estévez, M.; López-Periágo, E.; Cancho-Grande, B.; Simal-Gándara, J. J. *Agric. Food*

are of high interest mainly used for the reduction of gastric acid production.^{195c}

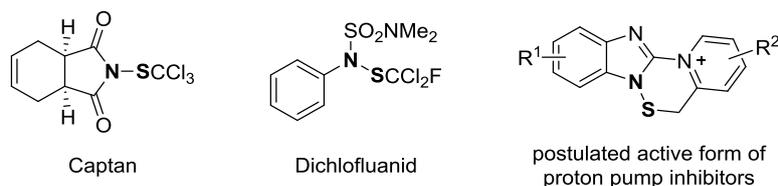


Figure 15: Examples of bioactive compounds bearing a sulfenamide moiety

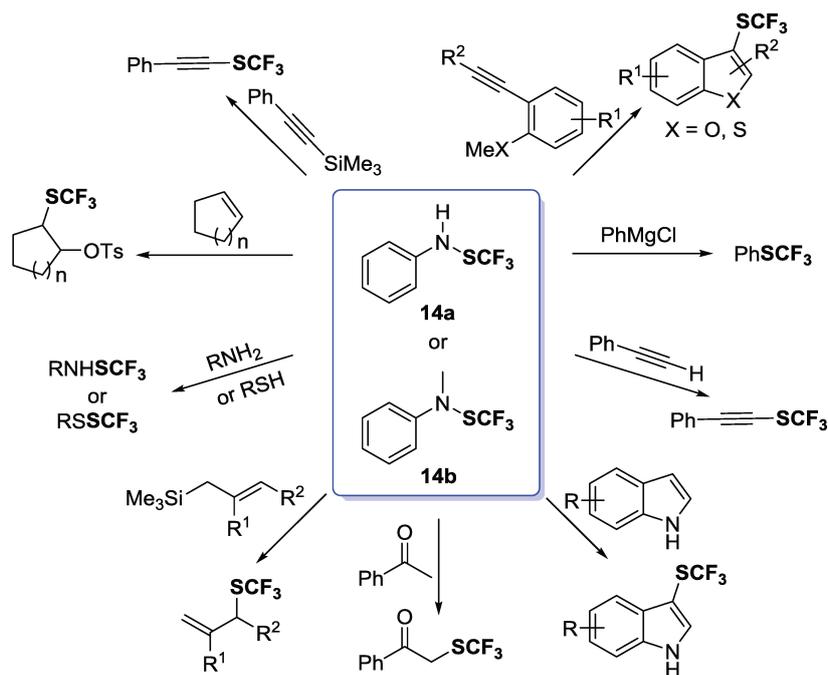
1.2 The importance of NSCF₃-containing molecules

As introduced in chapter 1, the incorporation of fluorinated groups would modify the biological and physical properties of the molecules due to their special properties. It is worth to note that, the Hansch hydrophobic parameter of the NSCF₃ group is 1.50 (Chapter 1, Table 1), which is significantly higher than the value for the CF₃ moiety ($\pi = 0.88$) and slightly higher than the one of the SCF₃ group ($\pi = 1.44$).⁷ Thus, NSCF₃-containing molecules are of great interest in the development of new drugs and agrochemicals.¹⁹⁸

Besides, trifluoromethanesulfenamides, which contain a NSCF₃ group, have been reported to be versatile electrophilic trifluoromethylthiolating reagents (Chapter 2, compounds **11-15**).¹¹² The efficiency of these reagents has been demonstrated by their ability to transfer the SCF₃ group in the construction of C(sp³)-SCF₃, C(sp²)-SCF₃, C(sp)-SCF₃, S-SCF₃, N-SCF₃ as well as O-SCF₃ bonds. Among them, Billard-(Langlois) reagents **14a**, **14b** have showed wide utility for the trifluoromethylthiolation reactions (Figure 16).^{123a-p} Thus, the development of efficient methodologies for the synthesis of such important compounds is highly valuable.

Chem. **2005**, 53, 4471; (b) Vaquero-Fernández, L.; Sanz-Asensio, J.; López-Alonso, M.; Martínez-Soria, M.-T. Food Addit. Contam. **2009**, 26, 164.

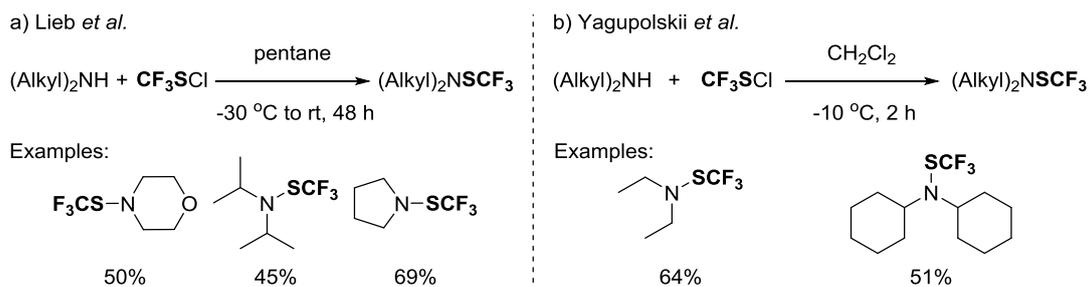
¹⁹⁸ Sahu, K. K.; Ravichandran, V.; Mourya, V. K.; Agrawal, R. K. Med. Chem. Res. **2007**, 15, 418.

Figure 16: Trifluoromethylthiolation reactions with **14a** and **14b**

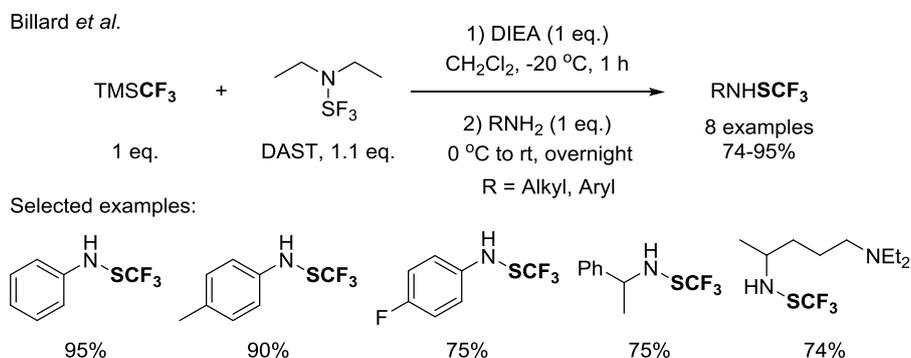
1.3 Usual pathways for the construction of the N-SCF₃ bond

The trifluoromethylthiolation of amines is the most straightforward pathway for the construction of N-SCF₃ bonds. Early approaches relied on the use of ClSCF₃ or CF₃SSCF₃ **10**, which were toxic and volatile.¹⁹⁹ For instance, in 1995, Lieb and co-workers synthesized the trifluoromethanesulfenamides by the trifluoromethylthiolation of amines using SCF₃Cl (Scheme 77, a).^{199g} Only secondary amines were functionalized. A similar approach was also reported by Yagupolskii and co-workers in 2006 (Scheme 77, b).^{199h}

¹⁹⁹ For selected examples, see: (a) Peach, M. *Can. J. Chem.* **1967**, 45, 429; (b) Gupta, O.; Kamil, W. A.; Shreeve, J. M. *Inorg. Chem.* **1985**, 24, 2126; (c) Geisel, M.; Mews, R. *Chem. Ber.* **1987**, 120, 1675; (d) Haas, A.; Lorenz, R. Z. *Anorg. Allg. Chem.* **1971**, 385, 33; (e) Haas, A.; Kortmann, D.; Hoffman, R.; Vömel, W. *J. Fluorine Chem.* **1978**, 11, 337; (f) Kost, D.; Egozy, H. *J. Org. Chem.* **1989**, 54, 4909; (g) Kolasa, A.; Lieb, M. *J. Fluorine Chem.* **1995**, 70, 45; (h) Yagupol'skii, L. M.; Bezdudnyi, A. V.; Yagupol'skii, Y. L. *Russ. J. Org. Chem.* **2006**, 42, 1275.

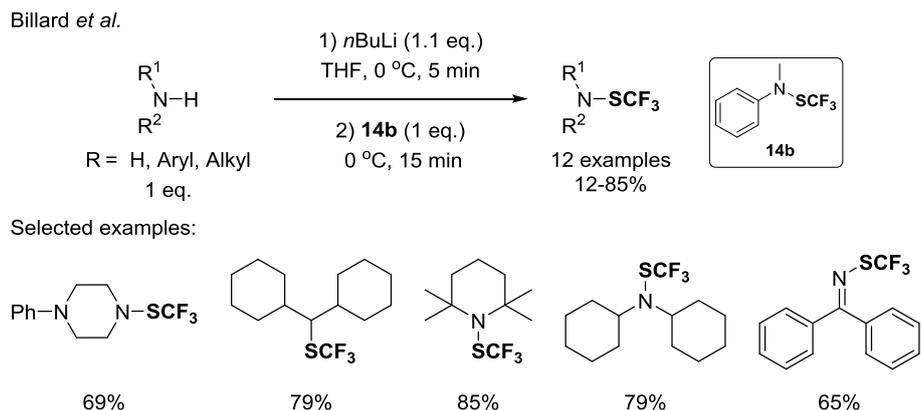
Scheme 77: Trifluoromethylthiolation of amines with SCF_3Cl

In order to avoid the use of toxic and volatile reagent, Billard and co-workers described an original synthesis of N-[(trifluoromethyl)thio]anilines.¹²⁰ By mixing the Ruppert-Prakash reagent (TMSCF_3) and diethylaminosulfur trifluoride (DAST) in the presence of N,N-diisopropylethylamine (DIEA) in dichloromethane at $-20\text{ }^\circ\text{C}$ for 1 h, followed by the addition of the suitable amine, a range of trifluoromethanesulfenamides was obtained in moderate to high yields (Scheme 78). However, this method was only compatible with primary anilines as no reaction occurred with the secondary anilines under standard reaction conditions. Note that aliphatic primary amines were also suitable substrates for this transformation.

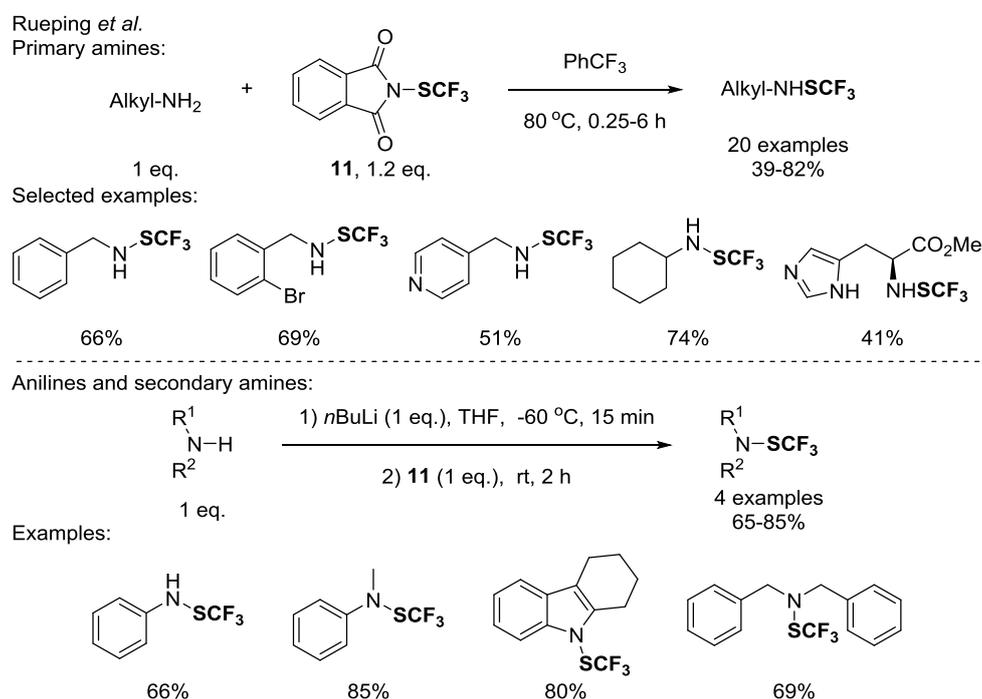


Scheme 78: Trifluoromethylthiolation of amines with the Ruppert-Prakash reagent

In order to overcome the limitations and access to secondary amines, the same group developed an alternative methodology. Indeed, after the deprotonation of the secondary amines with $n\text{BuLi}$ at $0\text{ }^\circ\text{C}$, the electrophilic trifluoromethylthiolating reagent was added.^{123p} Hence, a range of secondary amines was converted into the corresponding products with good yields (Scheme 79). This methodology provides an access to a large panel of trifluoromethanesulfenamides.

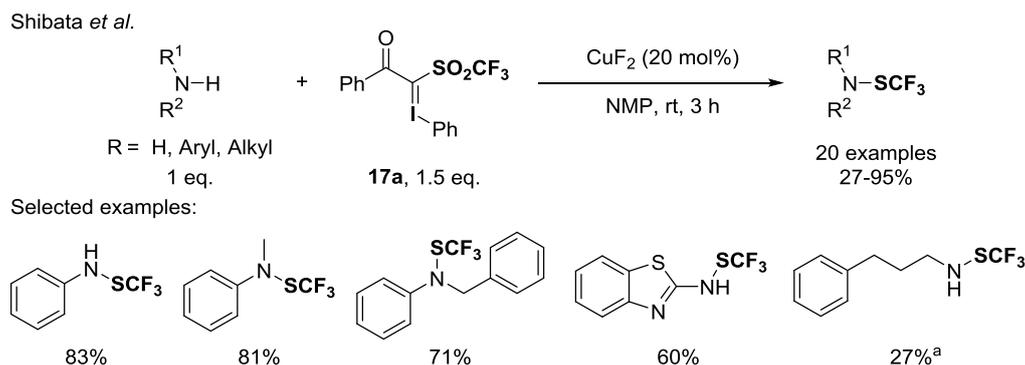
Scheme 79: Trifluoromethylthiolation of amines with the electrophilic reagent **14b**

In 2014, to develop an efficient procedure for the synthesis of trifluoromethylsulfenamides without the use of a strong base (*n*BuLi), Rueping and co-workers reported the direct synthesis of such compounds using the *N*-(trifluoromethylthio)phthalimide **11** as the SCF₃ source in PhCF₃ under mild reaction conditions (Scheme 80).²⁰⁰

Scheme 80: Trifluoromethylthiolation of amines with the electrophilic reagent **11**

Despite various primary amines were converted into the corresponding products

²⁰⁰ Pluta, R.; Rueping, M. *Chem. Eur. J.* **2014**, *20*, 17315.



Scheme 82: Trifluoromethylthiolation of amines with reagent **17a**. ^a DMF was used instead of NMP, 2 equivalents of MgO were used as an additive, yield determined by ¹⁹F NMR using α,α,α -trifluorotoluene as an internal standard.

Despite the great advance made in the synthesis of trifluoromethanesulfenamides, the main strategies relied on the use of either toxic, volatile reagents or the electrophilic trifluoromethylthiolating reagents (most of them being synthesized from the nucleophilic trifluoromethylthiolating reagents: AgSCF₃, CuSCF₃). Thus, the development of efficient and straightforward methodologies for the synthesis of trifluoromethanesulfenamides is still needed.

1.4 The importance of SCN-containing molecules

Organic thiocyanates are molecules of interest as they play an important role in organic synthesis due to their potential to access a range of valuable sulfur-containing molecules.²⁰¹ As a class of important synthetic precursor, thiocyanates could be easily converted into thiols,²⁰² thioethers,²⁰³ disulfides,²⁰⁴ thiocarbamates,²⁰⁵ sulfur containing-heterocycles,²⁰⁶ trifluoromethylsulfides^{98b} as well as

²⁰¹ (a) Erian, A. W.; Sherif, S. M. *Tetrahedron* **1999**, 55, 7957; (b) Castanheiro, T.; Suffert, J.; Donnard, M.; Gulea, M. *Chem. Soc. Rev.* **2016**, 45, 494 and references cited therein; (c) Nikoofar, K. *Chem Sci Trans* **2013**, 2, 691.

²⁰² (a) Linderoth, L.; Fristrup, P.; Hansen, M.; Melander, F.; Madsen, R.; Andresen, T. L.; Peters, G. H. *J. Am. Chem. Soc.* **2009**, 131, 12193; (b) Brown, S. P.; Smith, A. B. *J. Am. Chem. Soc.* **2015**, 137, 4034.

²⁰³ (a) Ke, F.; Qu, Y.; Jiang, Z.; Li, Z.; Wu, D.; Zhou, X. *Org. Lett.* **2011**, 13, 454; (b) Still, I. W. J.; Toste, F. D. *J. Org. Chem.* **1996**, 61, 7677; (c) Pakulski, Z.; Pierożyński, D.; Zamojski, A. *Tetrahedron* **1994**, 50, 2975.

²⁰⁴ (a) Sengupta, D.; Basu, B. *Tetrahedron Lett.* **2013**, 54, 2277; (b) Prabhu, K. R.; Ramesha, A. R.; Chandrasekaran, S. *J. Org. Chem.* **1995**, 60, 7142.

²⁰⁵ (a) Riemschneider, R.; Wojahn, F.; Orlick, G. *J. Am. Chem. Soc.* **1951**, 73, 5905; (b) Riemschneider, R. *J. Am. Chem. Soc.* **1956**, 78, 844.

²⁰⁶ D'Hooghe, M.; Waterinckx, A.; De Kimpe, N. *J. Org. Chem.* **2005**, 70, 227.

difluoromethylsulfides.²⁰⁷ Moreover, thiocyanates could also serve as cyanating reagents in organic synthesis.²⁰⁸

Additionally, organic thiocyanates are also building blocks in some bioactive natural molecules and pesticides. For examples, the natural compound Fascicularin is a thiocyanate-containing tricyclic alkaloid which was isolated from the ascidian *nephteis fascicularis* (Figure 17).²⁰⁹ Fascicularin showed modest cytotoxicity of the cellular DNA.²¹⁰ 9-thiocyanato pupukeanane was isolated from nudibranch phyllidia *varicose*, which has been reported to be a potent antimalarial and antifouling (Figure 17).²¹¹ The Psammaplin B is a thiocyanate bromotyrosine derivative which was isolated from *psammaplysilla purpurea* (Figure 17).²¹²

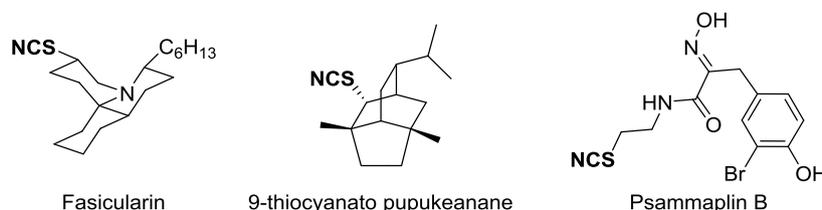


Figure 17: Selected examples of interesting thiocyanate derivatives

1.5 Synthesis of thiocyanate derivatives

Since the thiocyanates are highly useful intermediates in organic synthesis, the introduction of a SCN group has attracted a lot of attention. Generally, the thiocyanate derivatives could be synthesized by the cyanation of sulfur-containing molecules with cyanating reagents or by the thiocyanation of non sulfur-containing molecules with the thiocyanating reagents (Scheme 83).^{201b,c}

²⁰⁷ Bayarmagnai, B.; Matheis, C.; Jouvin, K.; Goossen, L. J. *Angew. Chem., Int. Ed.* **2015**, 54, 5753.

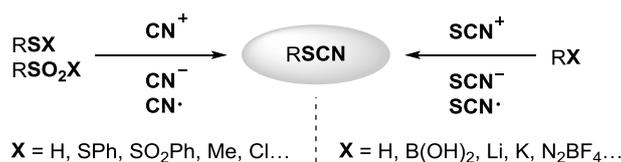
²⁰⁸ Zhang, Z.; Liebeskind, L. S. *Org. Lett.* **2006**, 8, 4331.

²⁰⁹ Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett.* **1997**, 38, 363.

²¹⁰ Dutta, S.; Abe, H.; Aoyagi, S.; Kibayashi, C.; Gates, K. S. *J. Am. Chem. Soc.* **2005**, 127, 15004.

²¹¹ (a) Pham, A. T.; Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Uchida, T.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1991**, 32, 4843; (b) Yasman; Edrada, R. A.; Wray, V.; Proksch, P. J. *Nat. Prod.* **2003**, 66, 1512.

²¹² (a) Piña, I. C.; Gautschi, J. T.; Wang, G.-Y.-S.; Sanders, M. L.; Schmitz, F. J.; France, D.; Cornell-Kennon, S.; Sambucetti, L. C.; Remiszewski, S. W.; Perez, L. B.; Bair, K. W.; Crews, P. *J. Org. Chem.* **2003**, 68, 3866; (b) Jiménez, C.; Crews, P. *Tetrahedron* **1991**, 47, 2097.



Scheme 83: Classical synthetic pathways to synthesize thiocyanate derivatives

1.5.1 Cyanation of sulfur-containing molecules

The introduction of a CN group onto sulfur-containing derivatives by using a nucleophilic or an electrophilic cyanating reagent is the common strategy. Moreover, a radical cyanation pathway was also an efficient approach for the construction of thiocyanates.²⁰¹

Generally, the nucleophilic cyanation involved a nucleophilic attack of the nucleophilic cyanating reagent (eg: KCN,²⁰¹ NaCN,²⁰¹ TMS-CN,^{201,213} CuCN^{201,214}) on the electrophilic substrates such as disulfides or sulfenyl halides affording the corresponding thiocyanates.^{201b} In terms of the electrophilic cyanations, several reagents (Figure 18) could be used such as cyanogen chloride,²¹⁵ the cyanobenziodoxolones (**CDBX**, **CBX**),²¹⁶ the 2-cyanopyridazin-3(2H)-ones (**40a**, **40b**),²¹⁷ the di(trifluoromethyl)phenyl(cyano)iodonium triflate (**41**),²¹⁸ the imidazolium thiocyanate (**42**),²¹⁹ the 1-cyanoimidazole (**43**),²²⁰ the 1-cyano-4-dimethylaminopyridium tetrafluoroborate (**44**),²²¹ as well as the p-toluenesulfonyl cyanides (**45**)²²² In addition, the azobisisobutyronitrile (**AIBN**) was also an efficient cyanide source for the synthesis of thiocyanates. In this case, a cyano radical intermediate was involved in the transformation.²²³

²¹³ For selected examples, see: (a) Kagabu, S.; Sawahara, K.; Maehara, M.; Ichihashi, S.; Saito, K. *Chem. Pharm. Bull.* **1991**, 39, 784; (b) Kagabu, S.; Maehara, M.; Sawahara, K.; Saito, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1485; (c) Yamaguchi, K.; Sakagami, K.; Miyamoto, Y.; Jin, X.; Mizuno, N. *Org. Biomol. Chem.* **2014**, 12, 9200.

²¹⁴ Castanheiro, T.; Gulea, M.; Donnard, M.; Suffert, J. *Eur. J. Org. Chem.* **2014**, 7814.

²¹⁵ Wheland, R. C.; Martin, E. L. *J. Org. Chem.* **1975**, 40, 3101.

²¹⁶ Frei, R.; Courant, T.; Wodrich, M. D.; Waser, J. *Chem. Eur. J.* **2015**, 21, 2662.

²¹⁷ Kim, J.-J.; Kweon, D.-H.; Cho, S.-D.; Kim, H.-K.; Jung, E.-Y.; Lee, S.-G.; Falck, J. R.; Yoon, Y.-J. *Tetrahedron* **2005**, 61, 5889.

²¹⁸ Zhu, D.; Chang, D.; Shi, L. *Chem. Commun.* **2015**, 51, 7180.

²¹⁹ Talavera, G.; Peña, J.; Alcarazo, M. J. *Am. Chem. Soc.* **2015**, 137, 8704.

²²⁰ Wu, Y.; Limburg, D. C.; Wilkinson, D. E.; Hamilton, G. S. *Org. Lett.* **2000**, 2, 795.

²²¹ D Miao, Z.; Tam, J. P. *Org. Lett.* **2000**, 2, 3711.

²²² Miyashita, A.; Nagasaki, I.; Kawano, A.; Suzuki, Y.; Iwamoto, K.; Higashino, T. *Heterocycles* **1997**, 4, 745.

²²³ Teng, F.; Yu, J.-T.; Yang, H.; Jiang, Y.; Cheng, J. *Chem. Commun.* **2014**, 50, 12139.

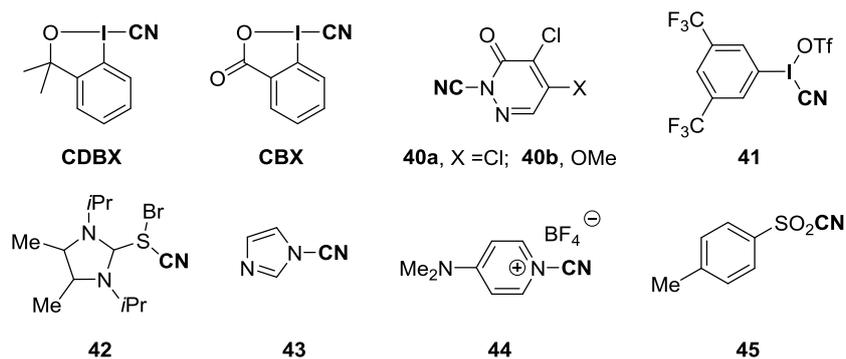


Figure 18: General electrophilic cyanating reagents used in the synthesis of thiocyanates

The limitation of this strategy was the requirement of the synthesis of pre-functionalized sulfur-containing substrates. As an alternative approach for the formation of thiocyanates, the direct introduction of a SCN group turned out to be an efficient solution.

1.5.2 Direct thiocyanation reactions

1.5.2.1 Thiocyanation with nucleophilic thiocyanating reagents

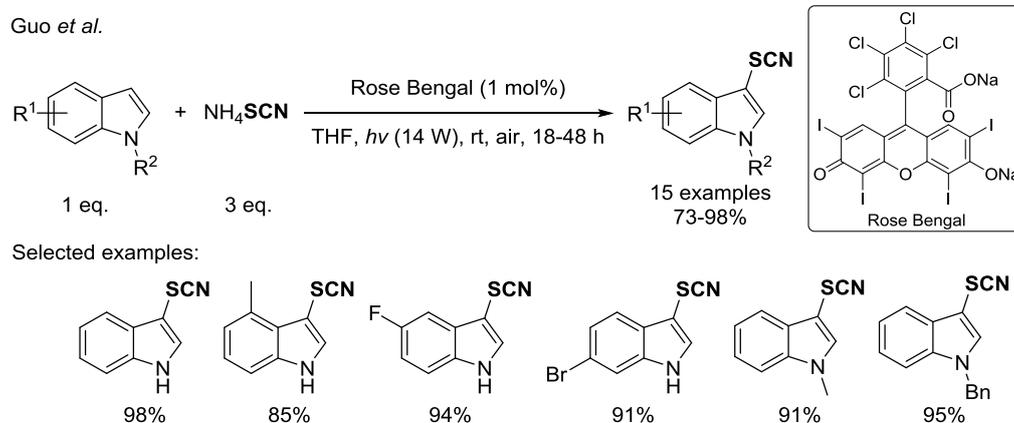
The nucleophilic thiocyanation is the main strategy for the introduction of SCN group. In general, thiocyanate salts are the most commonly used SCN sources. Among them, potassium thiocyanate (KSCN) has been widely applied in the nucleophilic thiocyanations.²²⁴

Ammonium thiocyanate (NH₄SCN) was also widely used as the thiocyanate source.²²⁵ In 2014, Li and co-workers described a simple and efficient visible-light-promoted thiocyanation of indoles. Using the readily available Rose Bengal as the photocatalyst and air as the terminal oxidant, several indole derivatives could be selectively converted into the 3-thiocyanatoindoles in high yields (Scheme

²²⁴ For selected examples, see: (a) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, 71, 6697; (b) Wang, Y.-F.; Zhou, Y.; Wang, J.-R.; Liu, L.; Guo, Q.-X. *Chin. Chem. Lett.* **2006**, 17, 1283; (c) Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. *Mendeleev Commun.* **2006**, 16, 250; (d) Sun, N.; Zhang, H.; Mo, W.; Hu, B.; Shen, Z.; Hu, X. *Synlett* **2013**, 24, 1443; (e) Grant, M. S.; Snyder, H. R. *J. Am. Chem. Soc.* **1960**, 82, 2742; (f) Yang, D.; Yan, K.; Wei, W.; Li, G.; Lu, S.; Zhao, C.; Tian, L.; Wang, H. *J. Org. Chem.* **2015**, 80, 11073; (g) Yadav, J. S.; Reddy, B. V. S.; Gupta, M. K. *Synthesis* **2004**, 1983.

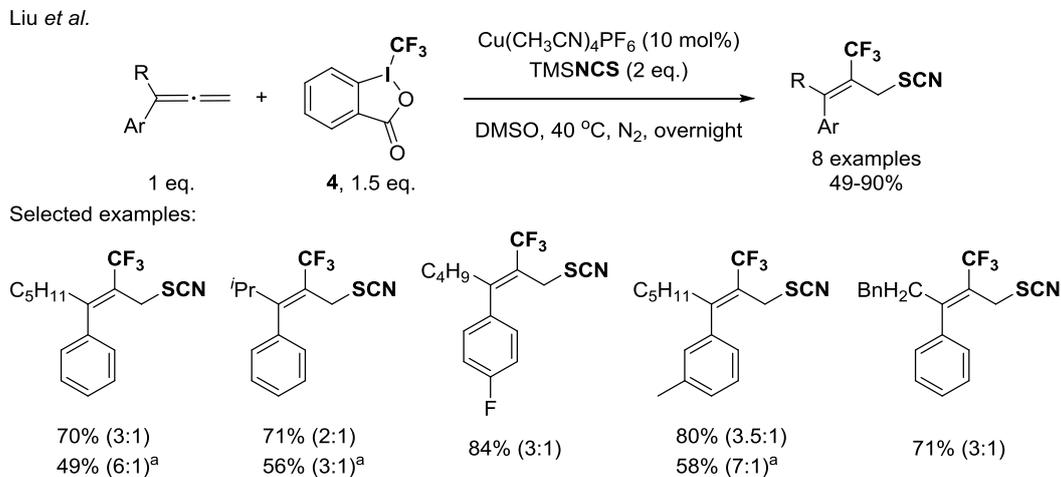
²²⁵ For selected examples, see: (a) Sayyahi, S.; Menati, S.; Karamipour, M. *J. Chem.* **2012**, 2013, 1; (b) Jiao, J.; Nguyen, L. X.; Patterson, D. R.; Flowers, R. A. *Org. Lett.* **2007**, 9, 1323; (c) Jadhav, V. K.; Pal, R. R.; Wadgaonkar, P. P.; Salunkhe, M. M. *Synth. Commun.* **2001**, 31, 3041; (d) Iranpoor, N.; Firouzabadi, H.; Shaterian, H. R. *Tetrahedron Lett.* **2002**, 43, 3439.

84).²²⁶ This transformation showed high efficiency with low catalyst loading and mild reaction conditions.



Scheme 84: Visible-light-promoted thiocyanation of indole derivatives

Recently, Liu and co-workers reported a Cu-catalyzed concomitant intermolecular introduction of CF_3 and SCN groups on allenes. In that purpose, the Togni's reagent **4** was used as a CF_3 source with the trimethylsilylisothiocyanate (TMSNCS) as a nucleophilic thiocyanate reagent (Scheme 85).²²⁷



Scheme 85: Cu-catalyzed intermolecular trifluoromethyl-thiocyanation of allenes, E/Z ratio was determined by ^{19}F NMR for the crude product. ^a Methanol was used as solvent, rt.

A variety of functional groups were compatible under the standard reaction conditions, furnishing the expected products in good yields and slightly low regioselectivities (Z/E ratio from 3:1 to 7:1). When methanol was used as the solvent,

²²⁶ Fan, W.; Yang, Q.; Xu, F.; Li, P. J. *Org. Chem.* **2014**, 79, 10588.

²²⁷ Zhu, N.; Wang, F.; Chen, P.; Ye, J.; Liu, G. *Org. Lett.* **2015**, 17, 3580.

the desired products were obtained in slightly lower yields at room temperature.

In addition, tetrabutylammonium thiocyanate (NBu₄SCN)²²⁸ and [bmim][SCN] (bmim = 1-nbutyl-3-methylimidazolium)²²⁹ were also reported as nucleophilic thiocyanating reagents for the construction of thiocyanates. However, despite numbers of nucleophilic thiocyanating reagents are available now, the development of new thiocyanating reagents is still desirable.

1.5.2.2 Thiocyanation with electrophilic thiocyanating reagents

Compared with the nucleophilic thiocyanation reactions, the reports regarding the electrophilic thiocyanation reactions are rare. The most widely used electrophilic thiocyanating reagent is the thiocyanogen (SCN)₂²³⁰ and various nucleophiles such as aromatic amines,²³¹ alcohols,²³² organometallic compounds,²³³ nitrogen heterocycles,²³⁴ reactive carcinogenic hydrocarbons,²³⁵ olefins,²³⁶ and acetylenes²³⁷ could be converted into the corresponding thiocyanates. However, the rather unstable character of (SCN)₂ was the main drawback.²³⁸ Thus, attention has been paid to the development of more convenient strategies for the introduction of the SCN group.

In 1995, Toste and co-workers proposed the N-thiocyanatosuccinimide (NTS) which was generated from NaSCN and N-bromosuccinimide (NBS) as an intermediate during the preparation of the aryl thiocyanates.²³⁸ Using this strategy, Firouzabadi and Iranpoor described the ring-expansion thiocyanation of 1,3-dithiolanes and 1,3-dithianes with the in situ generated NTS by mixing the NH₄SCN and NBS in dry CH₃CN at 0 °C.²³⁹ However, this intermediate has not been isolated till the study

²²⁸ Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N. *Tetrahedron* **2006**, 62, 5498.

²²⁹ Liu, Y.; Xu, Y.; Jung, S. H.; Chae, J. *Synlett* **2012**, 23, 2692.

²³⁰ Schwan, A. L. *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, **2001**.

²³¹ Slabko, O. Y.; Kachanov, A. V.; Kaminskii, V. A. *Synth. Commun.* **2012**, 42, 2464.

²³² Larsen, L.; Rowe, D. J.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans.1* **1989**, 2317.

²³³ (a) Chauhan, A. K. S.; Anamika; Kumar, A.; Srivastava, R. C.; Butcher, R. J. *J. Organomet. Chem.* **2005**, 690, 313; (b) Shukla, S. K.; Ranjan, A.; Saxena, A. K. *J. Fluorine Chem.* **2003**, 122, 165.

²³⁴ Maggiolo, A. J. *Am. Chem. Soc.* **1951**, 73, 5815.

²³⁵ Wood, J. L.; Fieser, L. F. *J. Am. Chem. Soc.* **1941**, 63, 2323.

²³⁶ Weigl, H.; Gleiter, R. *Tetrahedron Lett.* **1997**, 38, 1541.

²³⁷ Giffard, M.; Cousseau, J.; Gouin, L. *Tetrahedron* **1986**, 42, 2243.

²³⁸ Toste, F. D.; Stefano, V. D.; Still, I. W. *J. Synth. Commun.* **1995**, 25, 1277.

²³⁹ Firouzabadi, H.; Iranpoor, N.; Garzan, A.; Shaterian, H. R.; Ebrahimzadeh, F. *Eur. J. Org. Chem.* **2005**, 416.

of Ashby and co-workers. They first developed the synthesis of NTS and characterized its structure by X-ray crystallography in 2004.²⁴⁰ Indeed, mixing NaSCN and NBS in dry dichloromethane at room temperature for 2 h would afford the expected product NTS easily (Scheme 86). Note that the crude was used without further purification and contained traces of succinimide.



Scheme 86: Synthesis of N-thiocyanatosuccinimide from NaSCN and NBS

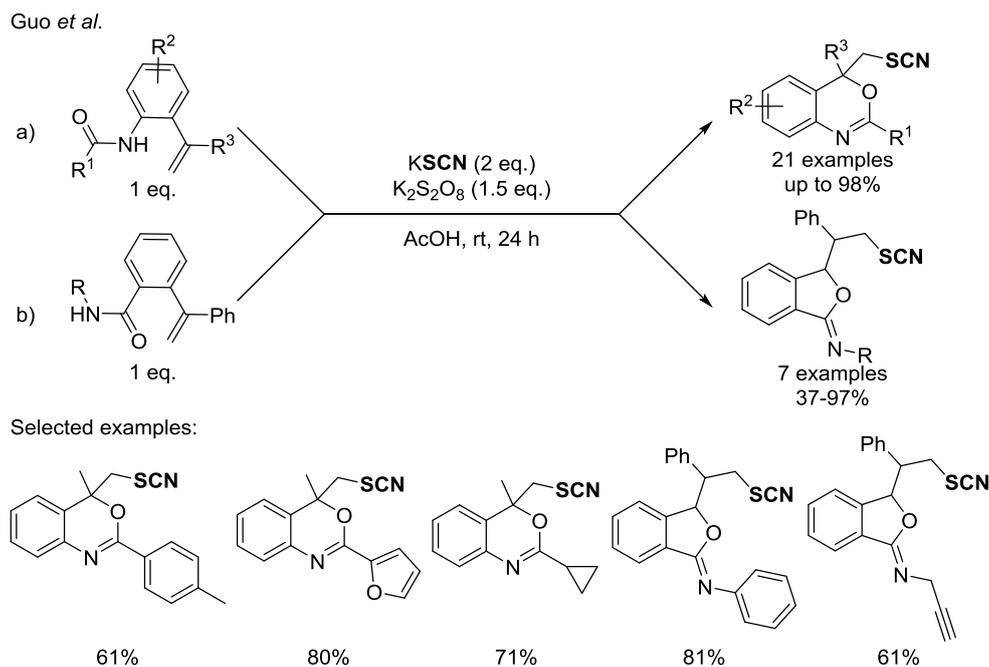
1.5.2.3 Thiocyanation through a radical pathway

The combination of KSCN and an oxidant could generate a thiocyanate radical, which could further act as key intermediate in the thiocyanation of indoles,^{224e} imidazopyridines,^{224f} as well as the dithiocyanation of olefins.^{224g}

Such strategy was applied by Guo and co-workers who successfully reported the thiocyanooxygenation of olefinic amides in the presence of KSCN and $\text{K}_2\text{S}_2\text{O}_8$ ²⁴¹ Hence, a range of 4-thiocyanatomethylbenzoxazines was synthesized in moderate to high yields (Scheme 87, a). Under the same reaction conditions, the cyclization reaction of the 2-vinylbenzamide olefinic amides proceeded smoothly affording the corresponding imino-isobenzofurans in moderate to good yields (Scheme 87, b).

²⁴⁰ Ashby, M. T.; Aneetha, H. J. *Am. Chem. Soc.* **2004**, 126, 10216.

²⁴¹ Yang, H.; Duan, X.-H.; Zhao, J.-F.; Guo, L.-N. *Org. Lett.* **2015**, 17, 1998.



Scheme 87: Thiocyanooxygenation of olefinic amides

In conclusion, the existing electrophilic thiocyanating reagents which could be directly applied in the thiocyanation reactions are rare. Thus, the design and synthesis new electrophilic thiocyanating reagents will enlarge the synthetic toolbox for the direct introduction of SCN group.

1.6 Our objectives

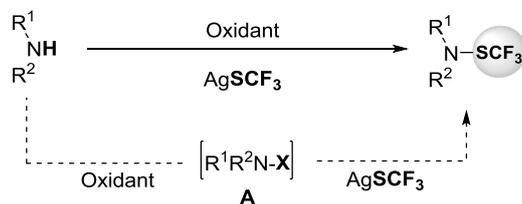
Taking these considerations in mind, we would like to focus on the development of efficient and straightforward methodologies for the synthesis of trifluoromethanesulfenamides, the synthesis of the N-(cyanosulfanyl)anilines and their further applications as new electrophilic thiocyanating reagents.

1.7 Optimization of the trifluoromethylthiolation of amines

1.7.1 Concept

In order to achieve our goal, an oxidative trifluoromethylthiolation of amines as feedstock with AgSCF_3 was envisioned. We hypothesized that the in situ generation of

an N-haloamine, derived from the reaction of an amine and a suitable oxidant, followed by an anionic metathesis with AgSCF_3 would afford the expected product (Scheme 88).



Scheme 88: The concept of the oxidative trifluoromethylthiolation of amines

However, to get the expected compound, several synthetic issues were anticipated and will need to be tackled. First, once the N-haloamine **A** formed, its possible decomposition into the corresponding halogenated compound via an irreversible intramolecular halogenation reaction might be a competitive pathway as reported by Haberfield and Paul.²⁴² Second, the selective generation of the required N-halo (aryl)amine should occur prior the formation of the unreactive electrophilic SCF_3 source (N-(trifluoromethylthio)succinimide, **12**),^{136,243} resulting from the in situ reaction of the AgSCF_3 and the oxidant. With all the considerations in mind, we then focused on the exploration of the oxidative trifluoromethylthiolation reaction.

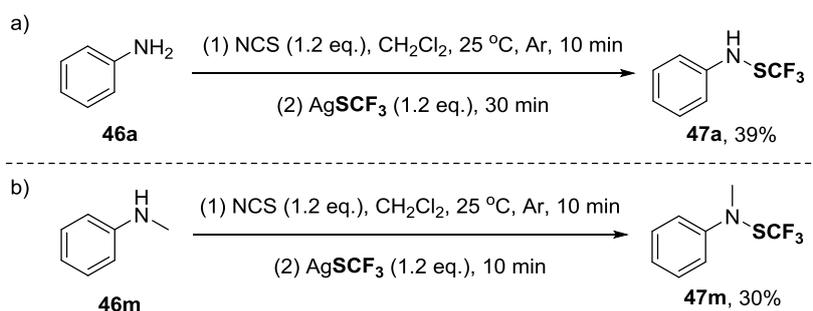
1.7.2 A one-pot sequential reaction

At the outset of our study, in order to validate our hypothesis, we carried out a reaction using the commercially available aniline **46a** and the N-chlorosuccinimide (NCS) in dichloromethane at 25 °C for 10 min. As we expected, a N-chloro-substituted aniline was detected by the GC-MS analysis. Consequently, 1.2 equivalents of AgSCF_3 were added in the reaction mixture assuming that an anionic metathesis might occur to provide the expected compound. Indeed, after 30 min of the reaction, a new singlet at $\delta = -53.4$ ppm was detected by ^{19}F NMR, a typical shift for

²⁴² Haberfield, P.; Paul, D. J. Am. Chem. Soc. **1965**, 87, 5502.

²⁴³ Note that Rueping and co-workers demonstrated that the Munavalli reagent was not suitable to perform the direct trifluoromethylthiolation of aniline derivatives without the addition of *n*BuLi, see ref. 200. Moreover, anilines **46d** and **46m** were unreactive with N-(trifluoromethylthio)succinimide **12**, see Scheme 98.

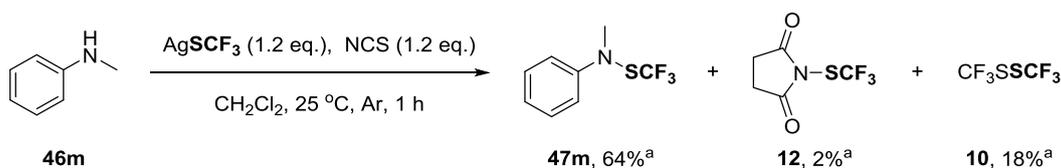
NSCF₃-containing compound.¹²⁰ This data fits well with the N-[(trifluoromethyl)thio]aniline as described in the literature^{118,120} and the expected product was isolated in 39% yield (Scheme 89, a). Note that, if the reaction occurred on the aromatic ring of the aniline, a signal at $\delta = -44.4$ ppm by ¹⁹F NMR should be observed.²⁴⁴ Under the same reaction conditions, the N-methyl-N-[(trifluoromethyl)thio]aniline **47m** was obtained in 30% yield (Scheme 89, b).



Scheme 89: A one-pot sequential reaction

1.7.3 One-pot reaction

Having this pioneering result in hand, we were wondering if it was possible to carry out a one-pot reaction. Thus, the reaction of N-methylaniline **46m** with AgSCF₃ in the presence of NCS in dichloromethane was performed (Scheme 90). Indeed, the N-methylaniline **46m** was converted to **47m** in 64% NMR yield, the N-(trifluoromethylthio)succinimide **12** and **10** were obtained as by-products in 2% and 18% ¹⁹F NMR yields, respectively. This promising result encouraged us to investigate other reaction conditions to avoid the generation of the by-products.

Scheme 90: One-pot reaction. ^a NMR yield determined by ¹⁹F NMR using α,α,α -trifluoroacetophenone as an internal standard.²⁴⁴ Tang, R.-Y.; Zhong, P.; Lin, Q.-L. J. Fluorine Chem. **2007**, 128, 636.

1.7.4 Screening of the oxidants

In order to monitor the conversion of the amine into the expected product by ^{19}F NMR, we choose the 4-fluoroaniline **46d** as standard substrate to investigate the reaction conditions. We began our exploration by reacting the **46d** with AgSCF_3 in the presence of various oxidants in dichloromethane (Table 24).

Table 24: Investigation of oxidants^a

Nc1ccc(F)cc1 (**46d**) $\xrightarrow[\text{CH}_2\text{Cl}_2, 25\text{ }^\circ\text{C, Ar, 2 h}]{\text{AgSCF}_3 (1.2 \text{ eq.}), \text{oxidant} (1.2 \text{ eq.})}$ N(C(F)(F)F)c1ccc(F)cc1 (**47d**)

NCS N-Cl-Phth N-Cl-Sacc I NBS N-Br-Phth

entry	oxidant	yield (%) ^b
1	NCS	86
2	N-Cl-Phth	79
3	N-Cl-Sacc	11
4	I	-
5	NBS	4
6	N-Br-Phth	7
7	NaOCl	trace
8	SO ₂ Cl ₂	-
9	CuCl ₂	-
10	tBuOCl	37

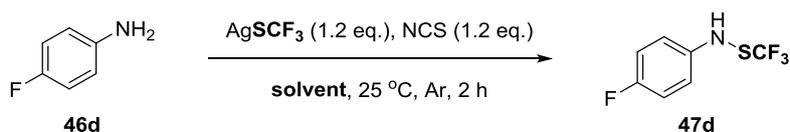
^a Reaction conditions: **46d** (0.2 mmol, 1 eq.), AgSCF_3 (0.24 mmol, 1.2 eq.), oxidant (0.24 mmol, 1.2 eq.), CH_2Cl_2 (2 mL), 25 °C, Ar, 2 h; ^b NMR yield determined by ^{19}F NMR using α,α,α -trifluoroacetophenone as an internal standard.

As shown in Table 24, it was found that the nature of the oxidant was essential for the outcome of the reaction. When NCS was used as oxidant for the transformation, the trifluoromethylthiolated aniline **47d** was obtained in 86% NMR yield (Table 24, entry 1). The replacement of the NCS by N-chlorophthalimide (N-Cl-Phth) resulted in a slight decrease of the yield affording the expected product in 79% NMR yield (Table 24, entry 2). Note that the N-chlorosaccharin (N-Cl-Sacc) was not efficient and a significant decrease of the yield was observed (Table 24, entry 3).

When **I** was used as oxidant, only traces of CF_3SSCF_3 **10** were detected instead of the desired product and the starting material **46d** was recovered (Table 24, entry 4). N-bromosuccinimide (NBS) and N-bromophthalimide (N-Br-Phth) gave traces of the product (Table 24, entries 5 and 6). Other sources were also tested for the chlorination step such as NaOCl, SO_2Cl_2 or CuCl_2 . In all cases, traces or no expected product were observed (Table 24, entries 7-9) and a large amount of CF_3SSCF_3 **10** was detected by ^{19}F NMR. When tBuOCl was engaged as an oxidant to the reaction mixture, the expected products were obtained in only but promising 37% NMR yield (Table 24, entry 10). Finally, NCS was found the best oxidant in this process.

1.7.5 Screening of the solvents

Then, we decided to investigate other solvents. Switching the dichloromethane to acetonitrile, CCl_4 or NMP, the trifluoromethylthiolated product **47d** was obtained with lower yields (Table 25, entries 2-4). Gratifyingly, this transformation showed high efficiency when THF was employed as the solvent, affording the expected product in quantitative yield (Table 25, entry 5). Notably, in the case of THF, only traces of CF_3SSCF_3 **10** was detected and the generation of N-(trifluoromethylthio)succinimide **12** as by-product was not observed, which indicated that the solvent played an important role in the reaction. Further investigations showed that the reaction also proceeded well in toluene or Et_2O affording the product **47d** in good yields (Table 25, entries 6 and 7). Therefore, THF was chosen as the optimal solvent for this transformation.

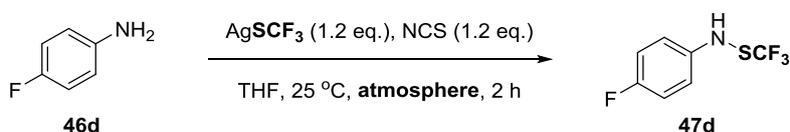
Table 25: Investigation of solvents^a

entry	solvent	yield (%) ^b
1	CH ₂ Cl ₂	86
2	CH ₃ CN	41
3	CCl ₄	44
4	NMP	51
5	THF	100
6	toluene	83
7	Et ₂ O	88

^a Reaction conditions: **46d** (0.1 mmol, 1 eq.), AgSCF₃ (0.12 mmol, 1.2 eq.), NCS (0.12 mmol, 1.2 eq.), solvent (1 mL), 25 °C, Ar, 2 h; ^b NMR yield determined by ¹⁹F NMR using α,α,α -trifluoroacetophenone as an internal standard.

1.7.6 Effects of the atmosphere

Exploring the effect of the atmosphere (Table 26, entries 1-3) on the oxidative trifluoromethylthiolation reaction showed that the transformation proceeded well under inert atmosphere (Ar, N₂) and even under air. Indeed, the product **47d** was obtained in a similar NMR yield (98%) and was isolated in 92% yield (Table 26, entry 3), showcasing hence the robustness of the transformation.

Table 26: Investigation of the atmosphere^a

entry	atmosphere	yield (%) ^b
1	Ar	100
2	N ₂	99
3	air	98 (92) ^c

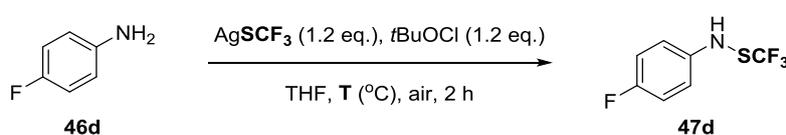
^a Reaction conditions: **46d** (0.1 mmol, 1 eq.), AgSCF₃ (0.12 mmol, 1.2 eq.), NCS (0.12 mmol, 1.2 eq.), THF (1 mL), 25 °C, 2 h; ^b NMR yield determined by ¹⁹F NMR using α,α,α -trifluoroacetophenone as an internal standard; ^c Isolated yield.

1.7.7 Optimization of the reaction conditions by using tBuOCl as an oxidant

1.7.7.1 Investigation of the temperature

As shown in Table 24 (entry 10), the trifluoromethylthiolated product could also be synthesized in the presence of tBuOCl with 37% NMR yield. This result is promising since such oxidant will generate less waste in comparison with NCS. Thus, a further optimization by using tBuOCl as the oxidant was conducted.

Table 27: Investigation of the temperature by using tBuOCl as oxidant^a



entry	T (°C)	yield (%) ^b
1	25	37
2	5	40
3	0	40
4	-10	39
5	-20	24

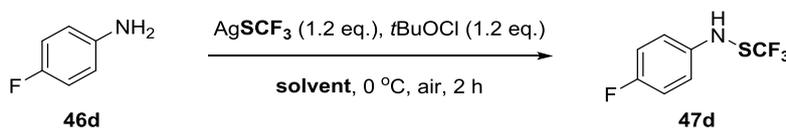
^a Reaction conditions: **46d** (0.1 mmol, 1 eq.), AgSCF₃ (0.12 mmol, 1.2 eq.), tBuOCl (0.12 mmol, 1.2 eq.), THF (1 mL), air, 2 h; ^b NMR yield determined by ¹⁹F NMR using α,α,α -trifluoroacetophenone as an internal standard.

When tBuOCl was used as oxidant (Table 24, entry 10), the main reaction was the generation of the CF₃SSCF₃ **10**. Apparently, the CF₃SSCF₃ species was not the active species to lead to the expected product. To prevent the formation of this by-product, the temperature was decreased. Indeed, a slightly higher yield was obtained when the reaction was performed at lower temperature (Table 27, entries 2 and 3). However, when the temperature was decreased further, no improvement was noticed (Table 27, entries 4 and 5). In all cases, a degradation of the AgSCF₃ into the CF₃SSCF₃ species was observed and the optimization was conducted at 0 °C.

1.7.7.2 Investigation of the solvents

Taking benefit from our knowledge, the solvent used to play a key role in the oxidative trifluoromethylthiolation reaction. Thus, its effect was then examined again

with the new oxidant. Since AgSCF_3 was soluble in acetonitrile, we assumed that it might be beneficial for increasing the efficiency of the transformation. However, against all expectations, a similar result was obtained when the reaction was conducted in acetonitrile affording the product **47d** in 37% NMR yield (Table 28, entry 2). Other solvents such as dichloromethane, toluene, 1,2-dichloroethane (DCE) or chlorobenzene (PhCl) resulted in a lower yield (Table 28, entries 3-6). Pleasingly, a slight improvement was observed by switching the solvent to DMF providing the trifluoromethylthiolated product in 44% NMR yield (Table 28, entry 7). Thus, DMF was proved to be the optimal solvent for this reaction.

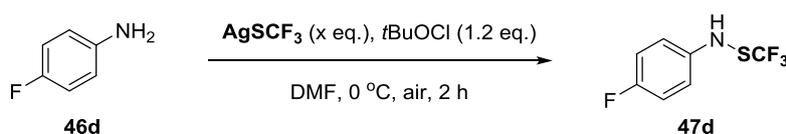
Table 28: Investigation of the solvents by using tBuOCl as oxidant^a

entry	solvent	yield (%) ^b
1	THF	33
2	CH_3CN	37
3	CH_2Cl_2	18
4	toluene	22
5	DCE	22
6	PhCl	10
7	DMF	44

^a Reaction conditions: **46d** (0.1 mmol, 1 eq.), AgSCF_3 (0.12 mmol, 1.2 eq.), tBuOCl (0.12 mmol, 1.2 eq.), solvent (1 mL), 0 °C, air, 2 h; ^b NMR yield determined by ^{19}F NMR using α,α,α -trifluoroacetophenone as an internal standard.

1.7.7.3 Screening of the stoichiometry of AgSCF_3

As the AgSCF_3 was partially converted into the CF_3SSCF_3 **10**, we anticipated that using an excess of AgSCF_3 might be suitable to form the expected transformation. It was shown that increasing the amount of AgSCF_3 from 1.2 to 1.5 equivalents resulted in a similar yield (Table 29, entry 2). In contrast, when 2 equivalents of AgSCF_3 were used, the desired product was obtained in 70% NMR yield (Table 29, entry 3).

Table 29: Screening the equivalent of AgSCF₃^a

entry	AgSCF ₃ (x eq.)	yield (%) ^b
1	1.2	50
2	1.5	51
3	2	70

^a Reaction conditions: **46d** (0.1 mmol, 1 eq.), AgSCF₃ (x eq.), tBuOCl (0.12 mmol, 1.2 eq.), DMF (1 mL), 0 °C, air, 2 h; ^b NMR yield determined by ¹⁹F NMR using α,α,α -trifluoroacetophenone as an internal standard.

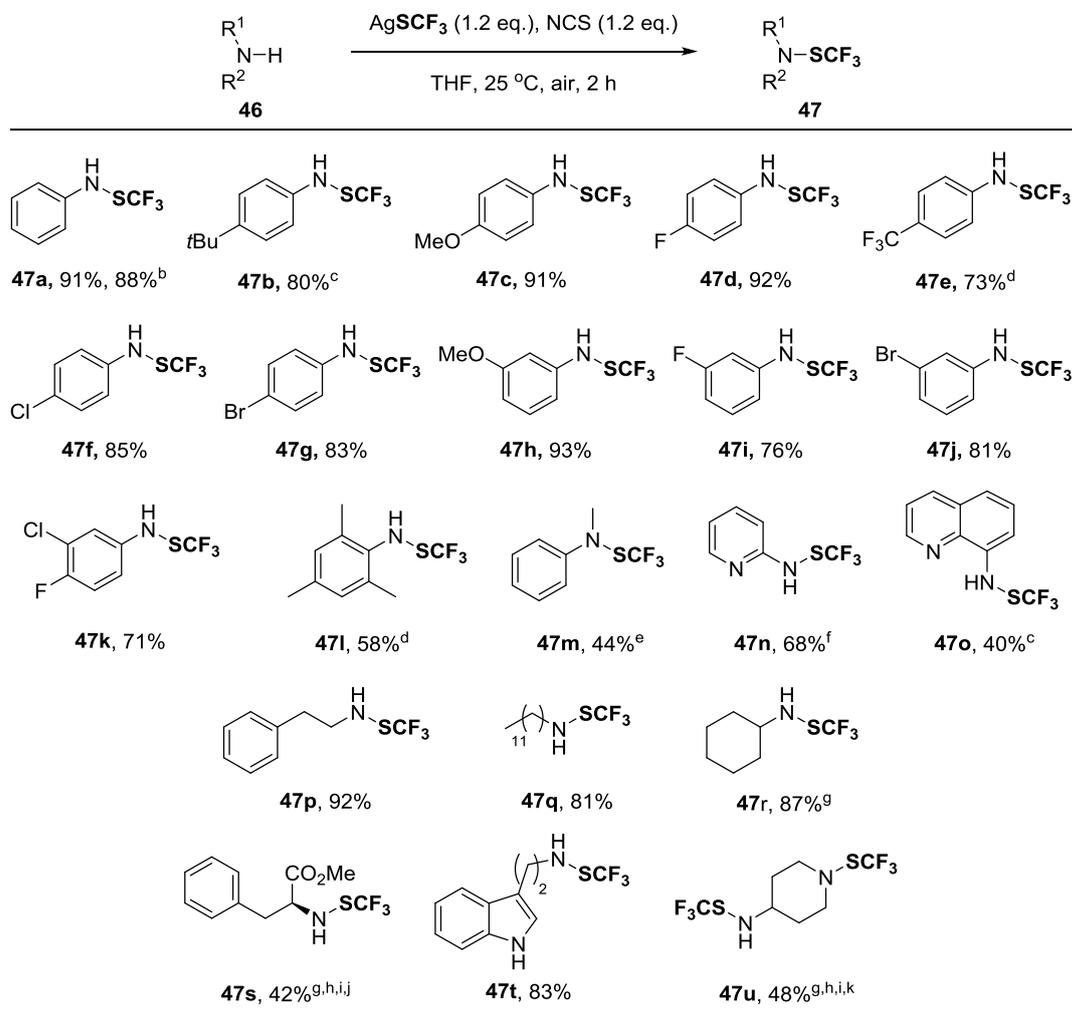
Taking into account the high loading of the AgSCF₃ salts by using tBuOCl as an oxidant for this transformation, we finally decided to choose NCS as the oxidant and THF as solvent for the exploration of the reaction scope.

1.8 Substrate scope for the trifluoromethylthiolation of amines

Under the optimized reaction conditions, we next investigated the scope of the oxidative trifluoromethylthiolation reaction. The results were summarized in Table 30.

Various primary aniline derivatives with different substitution patterns were converted into the corresponding trifluoromethanesulfenamides in moderate to good yields. Indeed, when the effect of the presence of electron-donating (**46b**, **46c**, **46h**) and electron-withdrawing (**46d-g**, **46i**, **46j**, **46k**) groups on the aromatic ring was evaluated, no considerable influence on the reaction yields was observed and the corresponding products were obtained in good yields. Note that the presence of halogens (**46d**, **46f**, **46g**, **46i-k**) was well tolerated. Moreover, these results showed that the para- and meta-substituted pattern on the aromatic ring did not have influence on the outcome of the reaction since the meta-substituted anilines with various substituents (**46h-k**) were also converted to the trifluoromethylthiolated products in good yields. We also tested the reactivity of the di- and tri-substituted anilines. The 2-chloro-4-fluoroaniline (**46k**) afforded the trifluoromethylthiolated products (**47k**) in 71% yield while 2,4,6-trimethylaniline (**46l**) providing compound **47l** in 58% yield,

which might be probably explained by the effect of the steric hindrance of the starting materials.

Table 30: Scope of the trifluoromethylthiolation reaction of amine derivatives^a

^a Reaction conditions: **46** (0.2 mmol, 1 eq.), AgSCF₃ (0.24 mmol, 1.2 eq.), NCS (0.24 mmol, 1.2 eq.), THF (2 mL), 25 °C, air, 2 h;

^b The reaction was carried out on a 3 mmol scale; ^c 20 h; ^d 24 h; ^e 12 h; ^f 8 h; ^g The reaction was carried out on a 0.5 mmol scale; ^h 4 h; ⁱ 2.4 eq. of AgSCF₃ were used; ^j 1 eq. of Et₃N was used; ^k 2.4 eq. of NCS were used.

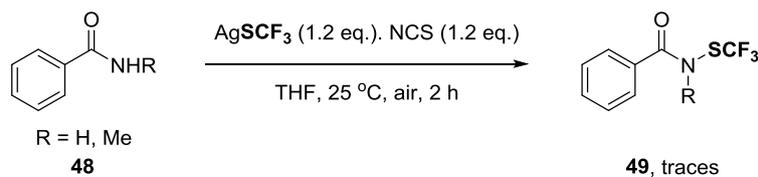
Notably, **47a** and **47m** are electrophilic trifluoromethylthiolating reagents for the synthesis of SCF₃-containing molecules.^{123a-p} With this approach, the N-[(trifluoromethyl)thio]aniline **47a** could be obtained in 91% yield and N-methyl-N-[(trifluoromethyl)thio]aniline **47m** was produced albeit in a lower yield (44%). Moreover, a reaction has been performed on a 3 mmol scale, affording the corresponding product **47a** in 88% yield. It is important to highlight that, in contrast

with other approaches,^{123p,130a,118,200} the synthesis of **47a** and **47m** does not require another electrophilic SCF₃ reagent generally itself prepared in a multi-step synthesis. Therefore, this strategy using a nucleophilic SCF₃ source by an oxidative trifluoromethylthiolation process constitutes an alternative and straightforward access to the electrophilic Billard-Langlois reagents.

Next, we turned our attention to the functionalization of primary heteroaryl amines. Thus, 2-aminopyridine **46n** and 8-aminoquinoline **46o** were engaged under the best reaction conditions leading to the expected products (**47n** and **47o**) in decent yields. The results showed that our reaction system was also tolerant with primary heteroaryl amines.

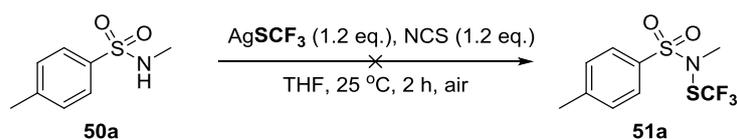
At last, a range of aliphatic primary and secondary amines were investigated. The desired products were obtained in moderate to high yields (**47p-u**, 42%-92%). It is worth noting that starting from L-phenylalanine methyl ester hydrochloride in combination with 1 equivalent of Et₃N, the SCF₃-containing analogues of biorelevant L-phenylalanine derivative **47s** could be obtained in 42% yield. Moreover, the trifluoromethylthiolated tryptamine derivative **47t** was obtained in 83% yield through the selective functionalization of the primary amine over the indole part, demonstrating the versatility of our methodology. Interestingly, the diamine **46u** could be functionalized using an excess of AgSCF₃, offering the bis-trifluoromethylthiolated compound **47u** in 48% yield.

Having successfully developed the synthesis of trifluoromethylthiolated amines, we then turned our attention to extend the methodology to other classes of compounds. Thus, we performed the reaction with benzamide or N-methylbenzamide in the presence of AgSCF₃ under the same reaction conditions. Unfortunately, only traces of products were detected by the ¹⁹F NMR and a large amount of the by-product (CF₃SSCF₃, **10**) was observed (Scheme 91).



Scheme 91: Oxidative trifluoromethylthiolation of amides

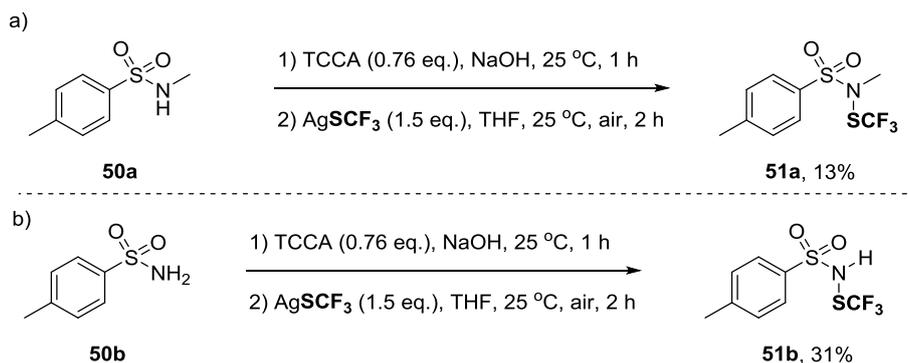
Since N-methyl-N-tosyl-trifluoromethanesulfenamide has showed high reactivity as an electrophilic SCF_3 source,^{123q-v} we were wondering if it was possible to access to the compound by the developed strategy. This would be particularly interesting as it would avoid the multi-step synthesis using the toxic reagent DAST, which was generally employed to get this important compound. However, when the N-methyl-4-methylbenzenesulfonamide **50a** was used as starting material, no expected product was detected and starting material **50a** was recovered (Scheme 92).



Scheme 92: Oxidative trifluoromethylthiolation of N-methyl-4-methylbenzenesulfonamide

Since a one-step procedure was not suitable, we envisioned to get the expected product via a two-step sequence. It was reported that N-methyl-4-methylbenzenesulfonamide **50a** could be converted into its chlorinated salt in the presence of TCCA under basic reaction conditions.²⁴⁵ Inspired by this work, we generated the corresponding chlorinated salt, which was then directly engaged in the reaction with AgSCF_3 . However, product **51a** was obtained in only 13% yield (Scheme 93, a). Note that the synthesis of N-tosyl-trifluoromethanesulfenamide **50b** through this approach provided the expected product **51b** in 31% yield (Scheme 93, b).

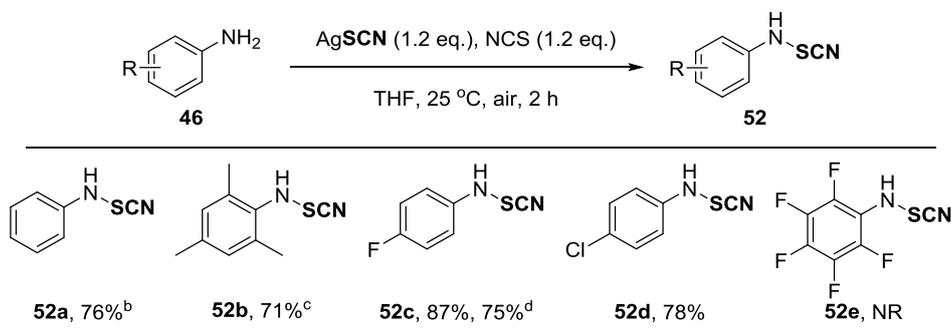
²⁴⁵ Shiri, A.; Khoramabadizad, A. *Synthesis* **2009**, 2797.



Scheme 93: Synthesis of N-tosyl-trifluoromethanesulfenamides

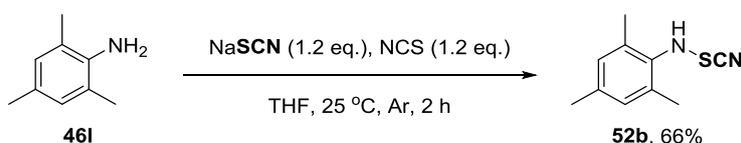
1.9 Substrate scope for the thiocyanation of amines

Inspired by the synthesis of trifluoromethanesulfenamides, we desired to extend our strategy to the preparation of thiocyanate derivatives, a class of important and versatile compounds.²⁰¹ Indeed, several anilines bearing different substitution patterns were functionalized in good yields (Table 31). The sterically hindered substrate **46l** was converted into the corresponding product **52b** in 71% yield, while the para-fluorinated or para-chlorinated anilines offered the desired products (**52c**, **52d**) in 87% and 78% yields, respectively. In the case of 2,3,4,5,6-pentafluoroaniline **46v**, no product was detected and the starting material was recovered. It is worth to mention that the inexpensive NaSCN can be used as a nucleophilic SCN source converting the 4-fluoroaniline into the corresponding product **52c** in 75% yield.

Table 31: Scope of the thiocyanation of aniline derivatives^a

^a Reaction conditions: amines **46** (2 mmol, 1 eq.), AgSCN (2.4 mmol, 1.2 eq.), NCS (2.4 mmol, 1.2 eq.), THF (20 mL), 25 °C, air, 2 h; ^b The reaction was carried out on a 3 mmol scale; ^c 18 h; ^d The reaction was carried out on a 0.2 mmol scale and NaSCN was used instead of AgSCN.

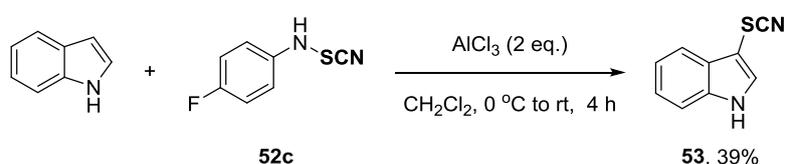
To further demonstrate the synthetic utility of our approach, a reaction of 2,4,6-trimethylaniline **46l** on a 10 mmol scale using NaSCN as the nucleophilic SCN source was carried out. Gratefully, the expected product **52b** was obtained in 66% yield (Scheme 94). Note that in the course of the purification, we found that the thiocyanate derivatives are somehow sensitive to water. Thus, we carried out the reaction under Ar to prevent the degradation of the product and proceeded with a quick purification (on a Biotage Isolera One flash purification system).



Scheme 94: Synthesis of **52b** using NaSCN on a 10 mmol scale

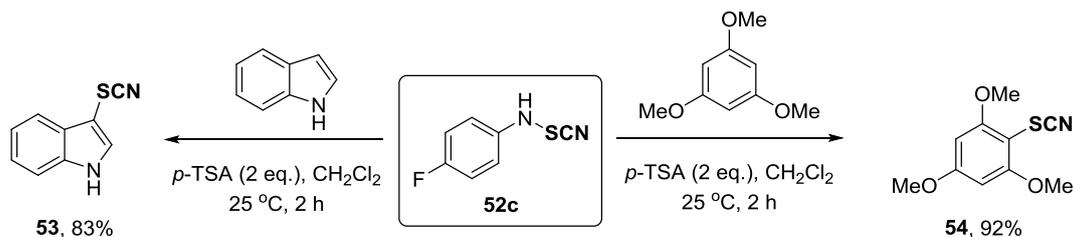
1.10 Application of the N-(cyanosulfanyl)aniline **52c** as an electrophilic SCN source

Having the N-(cyanosulfanyl)anilines in hand, we assumed that these derivatives might be also considered as electrophilic thiocyanating sources. Thus, the reaction of the non-protected indole and N-(cyanosulfanyl)-4-fluoroaniline **52c** in the presence of AlCl₃ was conducted. However, the desired product **53** was isolated in only 39% yield (Scheme 95).

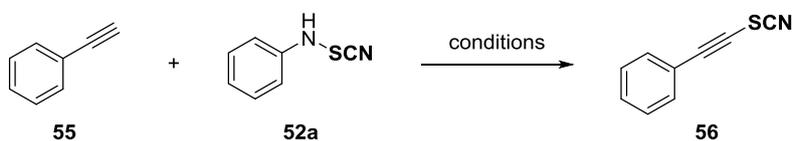


Scheme 95: Thiocyanation of indole using AlCl₃ as additive

Gratifyingly, the replacement of AlCl₃ with p-TSA led to the expected product **53** in 83% yield at 25 °C. In addition, 1,3,5-trimethoxybenzene, an electron rich aromatic derivative was also functionalized into the corresponding thiocyanate derivative **54** in 92% yield (Scheme 96). This represents a straightforward method for the introduction of a thiocyanate group onto aromatic and heteroaromatic compounds.

Scheme 96: Application of **52c** as an electrophilic thiocyanating reagent

Then, we tried to extend the scope of the thiocyanation reaction to alkynes. We first conducted the reaction of phenylacetylene **55** with N-(cyanosulfanyl)aniline **52a** using the reaction conditions reported by Shen and co-workers.¹²⁶ Under a copper catalysis, the degradation of **52a** was observed and no expected product was detected (Table 32, entry 1). Next, we used nBuLi to deprotonate the phenylacetylene followed by the addition of the **52a** according to Billard's procedure regarding the trifluoromethylthiolation of alkynes.¹²³ⁿ However, the degradation of **52a** was observed and 1,4-diphenylbuta-1,3-diyne was detected by GC-MS as by-product (Table 32, entry 2)

Table 32: thiocyanation of phenylacetylene^a

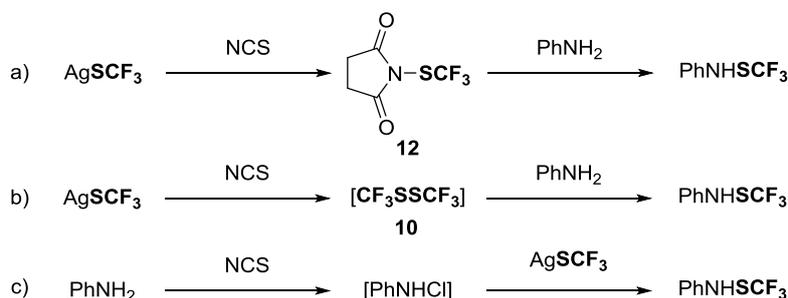
entry	conditions	results
1	CuTc (0.1 eq.), bpy (0.2 eq.), diglyme, 50 °C, 6 h	degradation of 52a
2	BuLi (1 eq.), THF, -78 °C, 1 h	degradation of 52a 1,4-diphenylbuta-1,3-diyne was detected

^a Reaction conditions: phenylacetylene **55** (0.1 mmol, 1 eq.), **52a** 0.12 mmol, 1.2 eq.), solvent (0.1 mL), Ar.

1.11 Mechanistic studies

From a mechanistic point of view, several possible pathways might be envisioned for the trifluoromethylthiolation transformation: 1) the in situ formation of the electrophilic trifluoromethylthiolating reagent **12** followed by the nucleophilic attack of the amine (Scheme 97, a); 2) the electrophilic trifluoromethylthiolation of the amine with the in situ generated CF_3SSCF_3 **10** from the reaction of AgSCF_3 and

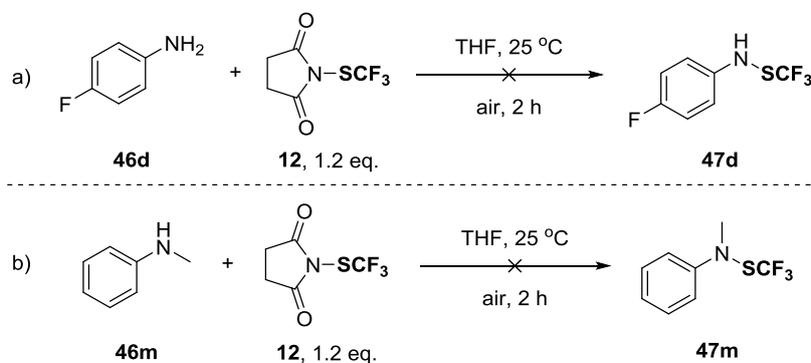
NCS (Scheme 97, b) and 3) the synthesis of the N-chloroamine followed by an anionic metathesis with AgSCF_3 (Scheme 97, c)



Scheme 97: Possible reaction pathways

1.11.1 Reaction of anilines with the electrophilic SCF_3 source **12**

To understand the reaction mechanism, we first performed the reaction of **46d** or **46m** in the presence of the electrophilic trifluoromethylthiolating reagent **12** in THF at 25 °C. The reactions did not provide any expected products as in both cases, only the starting materials were recovered after 2 h according to the ^{19}F NMR (Scheme 98).

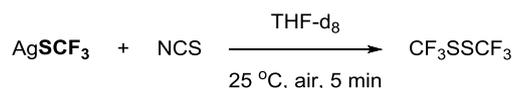


Scheme 98: Control experiments

Based on these results, a pathway involved the initial formation of N-(trifluoromethylthio)succinimide **12** from the reaction of NCS and AgSCF_3 , followed by nucleophilic trifluoromethylthiolation was convincingly excluded (Scheme 97, a).

1.11.2 Studies on the role of CF₃SSCF₃ **10**

It was known that the AgSCF₃ might undergo an oxidative reaction affording the CF₃SSCF₃ **10** in the presence of NCS.¹³⁶ Thus, in order to study the role of the CF₃SSCF₃ **10** in the reaction, several experiments were performed. We carried out the reaction of AgSCF₃ with NCS in THF-d₈ (Scheme 99).



Scheme 99: The reaction of AgSCF₃ and NCS in THF-d₈

Interestingly, a large amount of CF₃SSCF₃ **10** ($\delta = -46.2$ ppm) was observed in 5 min by ¹⁹F NMR and no residual AgSCF₃ ($\delta = -22.2$ ppm) was detected in the reaction mixture (Figure 19). This observation indicated that the generation of CF₃SSCF₃ **10** might be involved in our reaction system.

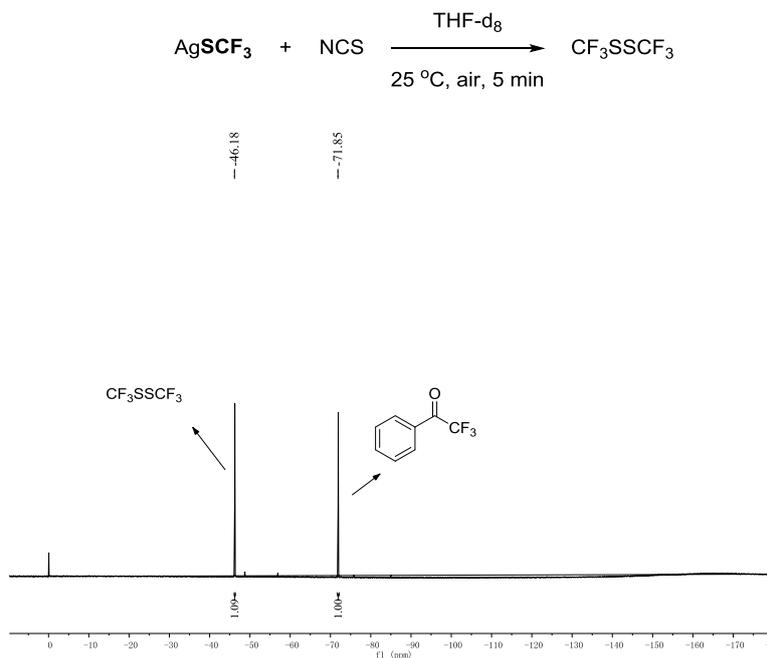
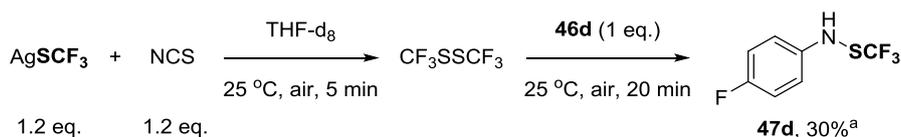


Figure 19: ¹⁹F NMR spectra of the reaction of AgSCF₃ and NCS in THF-d₈. Note: α,α,α -trifluoroacetophenone was used as an internal standard.

Then, we were wondering whether the in situ generated CF₃SSCF₃ **10** was the active species in the reaction. Thus, 4-fluoroaniline **46d** was engaged in the above reaction mixture (Scheme 100)



Scheme 100: The reaction of the in situ generated CF_3SSCF_3 with **46d**. ^a NMR yields determined by ^{19}F NMR using α,α,α -trifluoroacetophenone as an internal standard.

Interestingly, once the 4-fluoroaniline **46d** was added, the expected product **47d** was detected in 30% NMR yield after 20 min (Figure 20), indicating that the in situ generated CF_3SSCF_3 **10** could be involved in the trifluoromethylthiolation reaction (Table 33, entry 1).

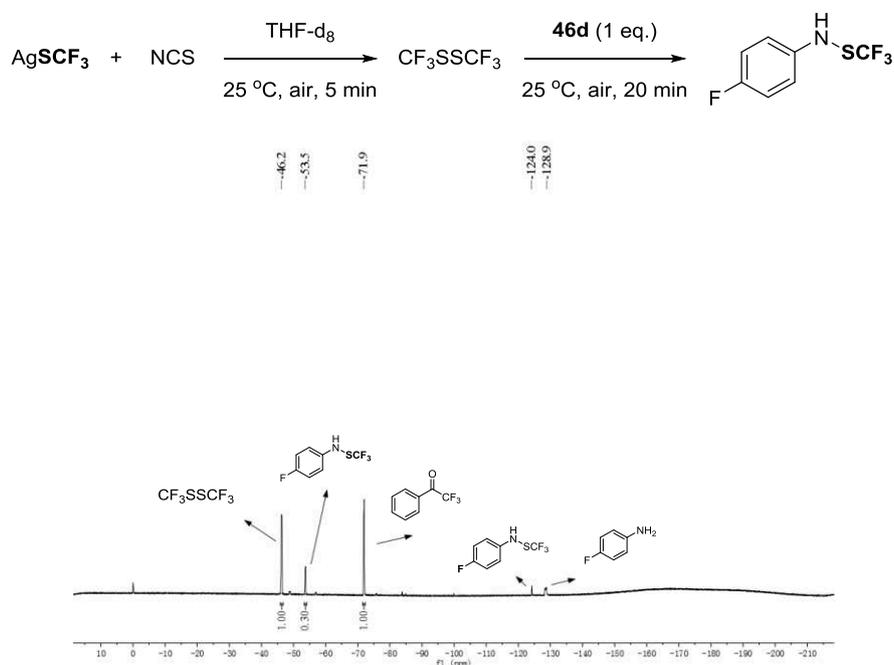


Figure 20: ^{19}F NMR spectra of the reaction of the in situ generated CF_3SSCF_3 and **46d** after 20 min

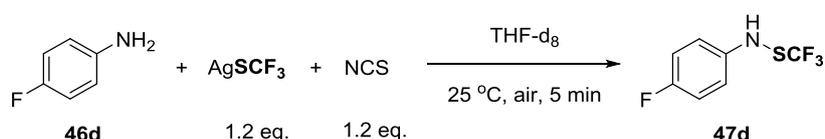
Then, the reaction mixture was monitored by the ^{19}F NMR spectroscopy. We observed a slight decrease of the amount of CF_3SSCF_3 along with a slow increase of the expected product **47d** (Table 33, entries 1-3). After 2 h, the desired product **47d** was detected in only 59% NMR yield with a large amount of CF_3SSCF_3 **10** recovered (Table 33, entry 3). However, in our standard reaction conditions, the product **47d** was obtained in 92% yield.

Table 33: Monitoring the reaction process by ^{19}F NMR

entry	time (min)	yield (%) ^b
1	20	30
2	50	40
3	120	59

^a Reaction conditions: amines **46d** (0.05 mmol, 1 eq.), NCS (0.06 mmol, 1.2 eq.), AgSCF_3 (0.06 mmol, 1.2 eq.), THF- d_8 (0.5 mL), Ar; ^b NMR yield determined by ^{19}F NMR using α,α,α -trifluoroacetophenone as an internal standard.

Based on these observations, a one pot reaction was performed. We carried out the reaction of 4-fluoroaniline **46d** and AgSCF_3 in the presence of NCS in THF- d_8 (Scheme 101).

Scheme 101: The reaction of 4-fluoroaniline **46d**, NCS and AgSCF_3 in THF- d_8

After only 5 min, a large amount of product **47d** was observed and traces of CF_3SSCF_3 **10** were detected by ^{19}NMR spectroscopy. It is important to mention that we did not observe the generation of the N-(trifluoromethylthio)succinimide **12** in this case.

Despite all our efforts, we could not conclude about the possible role of the CF_3SSCF_3 species as the active electrophilic reagent in our transformation. It might be a competitive pathway but not the main one as demonstrated by the difference of the yield after 2 h reaction (59% vs 92%). Moreover, the stoichiometry of the oxidant (1.2 eq.) and AgSCF_3 (1.2 eq.) made this pathway rather unlikely. Indeed, to reach the observed yields (up to 92%) at least 2 equivalents of oxidant and AgSCF_3 are necessary. Therefore, the third proposed mechanism (Scheme 97, c) seems more likely as the main pathway.

1.11.3 Identification of a new intermediate

In order to observe the formation of the N-chloro-4-fluoroaniline intermediate, we decided to monitor the reaction of 4-fluoroaniline **46d** and NCS in THF- d_8 by ^1H

NMR and ^{19}F NMR spectroscopy. It was shown from the ^1H NMR spectra that the NH_2 signal ($\delta = 4.33$ ppm) of **46d** was disappeared after the addition of NCS (Figure 21). This observation indicated the formation of a new intermediate **57** during this process.

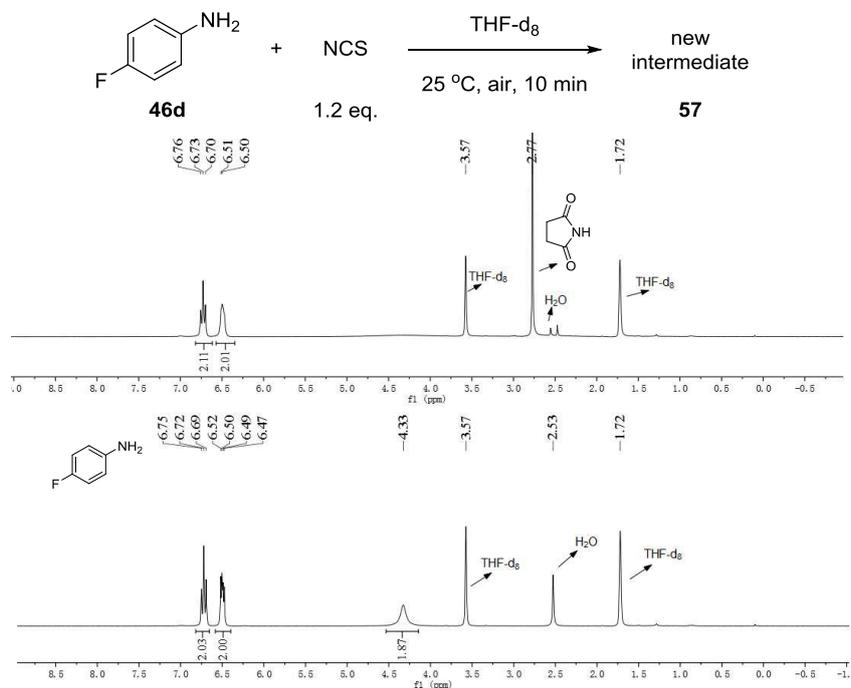


Figure 21: ^1H NMR spectra of the reaction 4-fluoroaniline **46d** with NCS in THF- d_8

Moreover, a new singlet ($\delta = -129.8$ ppm) along with the fluorine signal of **46d** ($\delta = -129.9$ ppm) were detected by ^{19}F NMR (Figure 22). This result represented a complementary indication of the formation of a new intermediate.

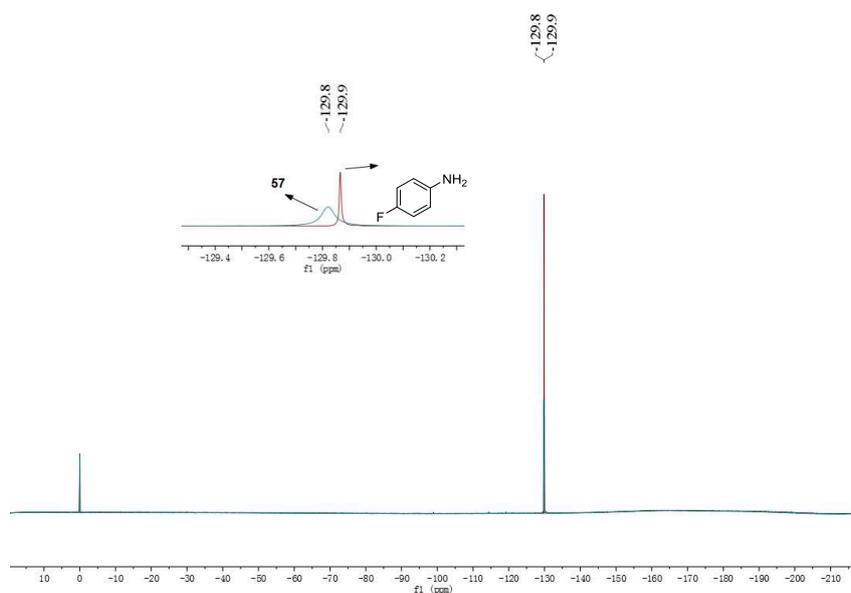
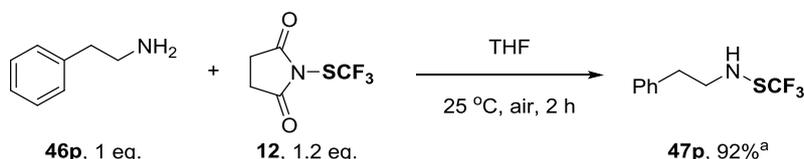


Figure 22: ^{19}F NMR spectra of the reaction of 4-fluoroaniline and NCS in THF- d_8

It was worthy to mention that the formation of N-chloro-2,4,6-trimethyl aniline as an intermediate has been identified by Yamamoto and Samanta during their studies on the selective halogenation of heteroaromatic derivatives.²⁴⁶ However, the intermediate R^1R^2NCl derived from amine derivatives was impossible to isolate. So we could not confirm its structure and conduct a stoichiometric reaction of the $RNHCl$ and $AgSCF_3$ to probe that this is the intermediate of the reaction.

1.11.4 Reaction of aliphatic amines with the electrophilic SCF_3 source **12**

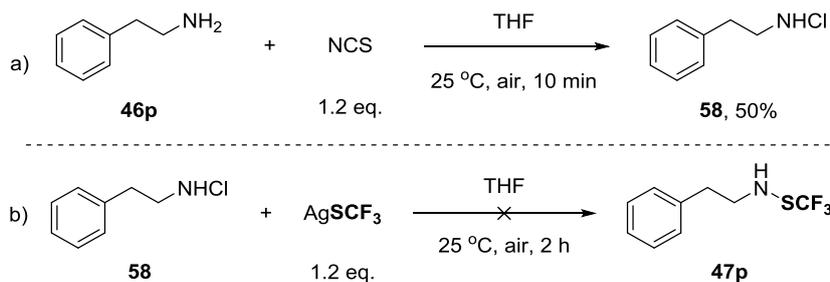
Interestingly, the reaction pathway was more complicated in the case of aliphatic amine and might be different from the one observed for aromatic amines. We carried out the reaction of **46p** in the presence of N-(trifluoromethylthio)succinimide **12** in THF, the trifluoromethylthiolated product **47p** was obtained in 92% NMR yield after 2 h (Scheme 102). This observation might be explained by the high nucleophilic character of the aliphatic amine, indicating that N-(trifluoromethylthio)succinimide **12** might act as an active species in our reaction system in the case of aliphatic amines.



Scheme 102: Reaction of phenethylamine and SCF_3 reagent **12**. ^a NMR yield determined by ^{19}F NMR using α,α,α -trifluoroacetophenone as an internal standard.

In order to obtain more details of the reaction process, we carried out the reaction of **46p** in the presence of NCS in THF for 10 min and the chlorinated aniline **58** was isolated in 50% yield which has been proved by the HRMS analysis (Scheme 103, a). Then, we tried to conduct a stoichiometric reaction of **58** and $AgSCF_3$ in THF, but unfortunately we did not detect the trifluoromethylthiolated product **47p** by ^{19}F NMR in 2 h (Scheme 103, b). According to this result, we assumed that other intermediates might be involved in the reaction in the case of aliphatic amine derivatives.

²⁴⁶ Samanta, R. C.; Yamamoto, H. Chem. Eur. J. **2015**, 21, 11976.



Scheme 103: Mechanism studies of the reaction of aliphatic amines

1.11.5 Reaction mechanism

Based on these observations, we proposed the following plausible pathway: first, the chlorination of the aniline derivatives **46** by NCS would afford a plausible N-chloroamine as an intermediate. Then, this N-chloroamine compound might undergo an anionic metathesis in the presence of AgSCF₃ to afford the expected product (Scheme 104).



Scheme 104: Proposed mechanism

1.12 Conclusion

In conclusion, we have successfully developed an oxidative trifluoromethylthiolation of amines for the construction of N-SCF₃ bond.²⁴⁷ By using AgSCF₃ and a suitable oxidant, a panel of primary and secondary amines was functionalized in good yields at room temperature. Moreover, this general approach was further applied to the thiocyanation of anilines and the corresponding products can be readily used as SCN electrophilic sources. This practical method would enlarge the toolbox for the synthesis of trifluoromethanesulfenamides and organic thiocyanate derivatives.

²⁴⁷ Xiong, H.-Y.; Pannecoucke, X.; Besset, T. *Org. Chem. Front.* **2016**, 3, 620.

2 An electrophilic reagent for the direct introduction of the SCF₂PO(OEt)₂ group to molecules

As we discussed in chapter 2, an exponential interest has been noticed for the SCF₃ group⁹¹ and more recently to the SCF₂H unit.²⁴⁸ In this context, a shift of interest might be expected to their analogues such as the SCF₂FG residues (FG = SO₂Ph, SAr, COAr, R_f) due to their possibility in modulating their intrinsic properties thanks to the presence of an additional FG group.²⁴⁸ As a consequence, it would be highly desirable to design and develop original SCF₂R residues for the bioactive molecules discovery. In this section, we will focus on the construction of SCF₂H- and SCF₂FG-containing molecules.

2.1 The properties of SCF₂H-containing molecules

The SCF₂H group is generally considered as a highly lipophilic hydrogen-bonding donor.²⁴⁹ It has demonstrated interesting features and several drugs and agrochemicals bear a difluoromethylthio unit, such as the pesticide Pyriprole, the β -lactamase-resistant oxcephalosporin antibiotic flomoxef sodium and the broad-spectrum paddy herbicide Pyrimisulfan (Figure 23).

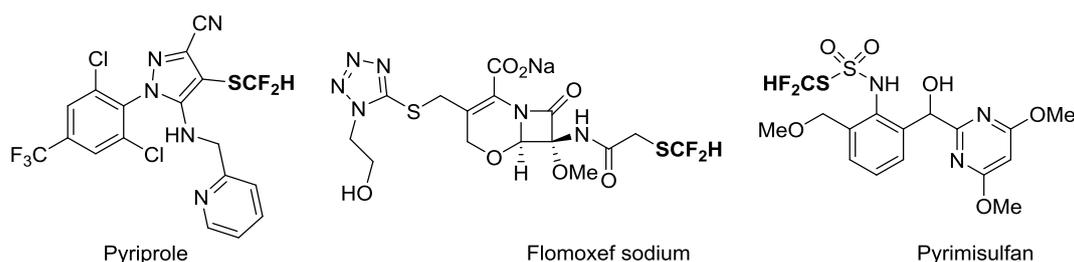


Figure 23: Selected examples of relevant compounds

2.2 Synthesis of SCF₂R-containing molecules

There are two general pathways for the synthesis of difluoromethylthiolated

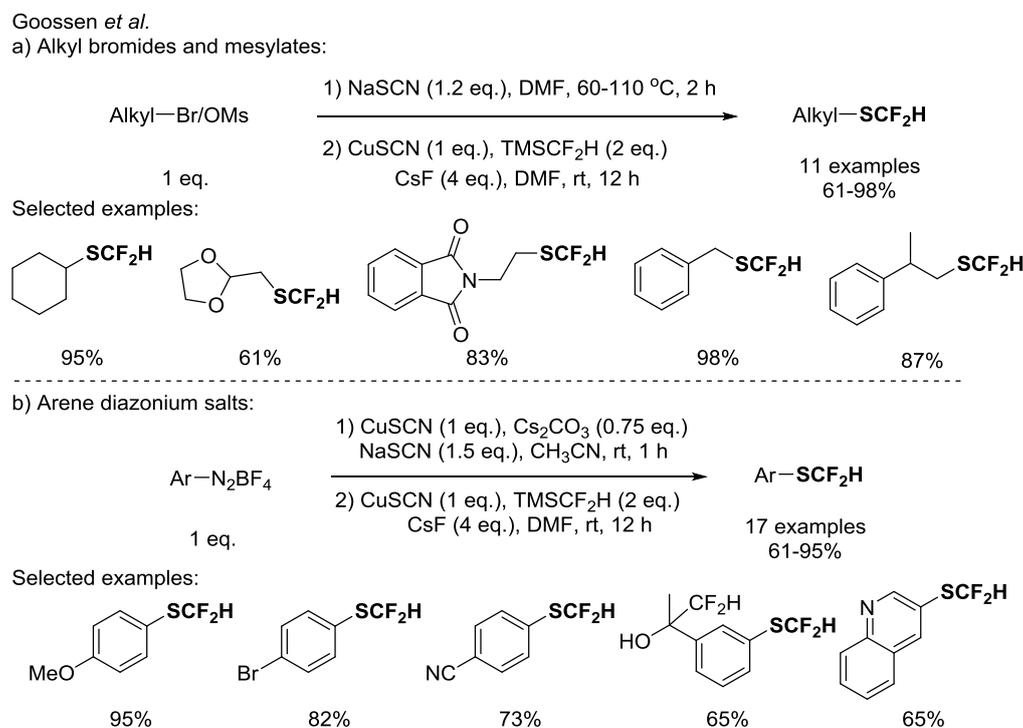
²⁴⁸ Xiong, H.-Y.; Pannecoucke, X.; Besset, T. *Chem. Eur. J.* **2016**, *22*, 16734.

²⁴⁹ Han, J.-B.; Qin, H.-L.; Ye, S.-H.; Zhu, L.; Zhang, C.-P. *J. Org. Chem.* **2016**, *81*, 2506 and reference cited therein.

direct way to access difluoromethylthioethers since the preparation of sulfur-containing molecules could be avoided. Key examples will be presented below.

2.2.2.1 Nucleophilic difluoromethylthiolation reactions²⁴⁸

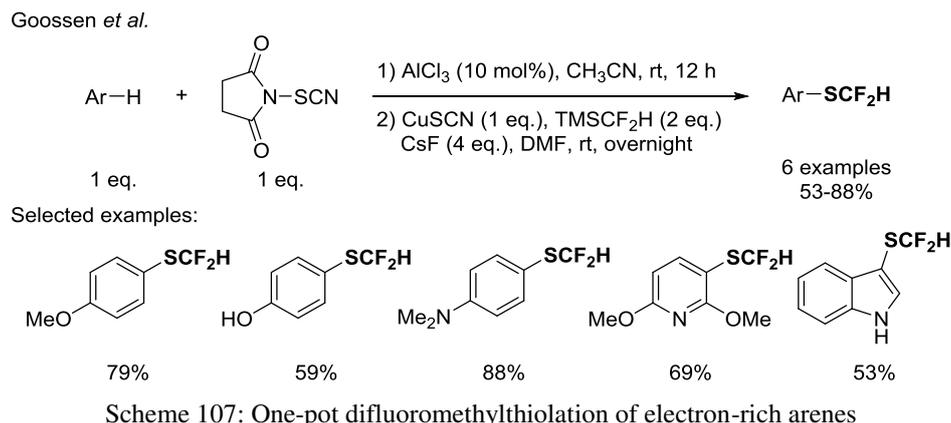
In 2015, Goossen and co-workers introduced the SCF₂H group by difluoromethylation of organothiocyanates (in situ generated from the substrates bearing a leaving group and CuSCN) with TMSCF₂H. Using this strategy, various alkyl bromides and mesylates were functionalized in high yields (Scheme 106, a), and this approach was extended to the arene diazonium salts (Scheme 106, b).²⁰⁷



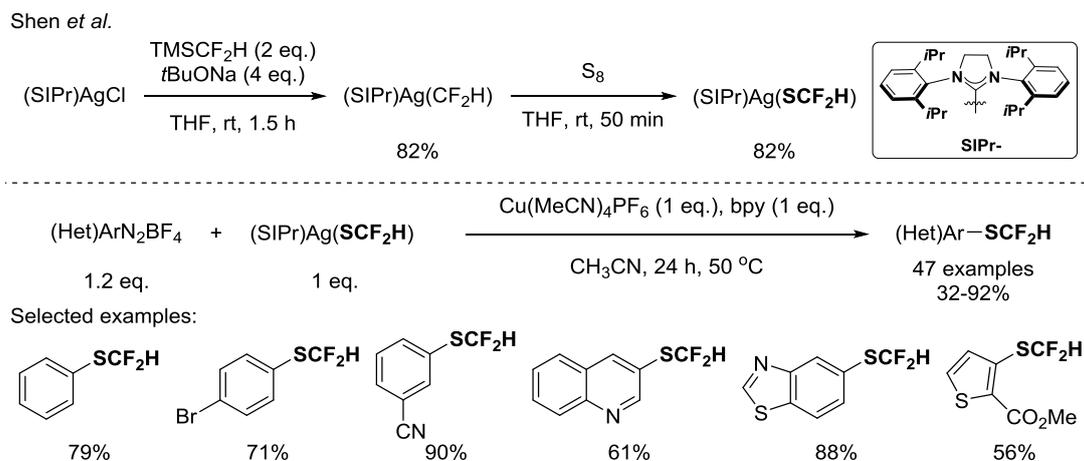
Scheme 106: Difluoromethylation of the in situ generated organothiocyanates

Later, this methodology was then applied for the difluoromethylthiolation of electron-rich arenes by C-H bond functionalization via a one-pot C-H thiocyanation/difluoromethylation process (Scheme 107).²⁵⁴

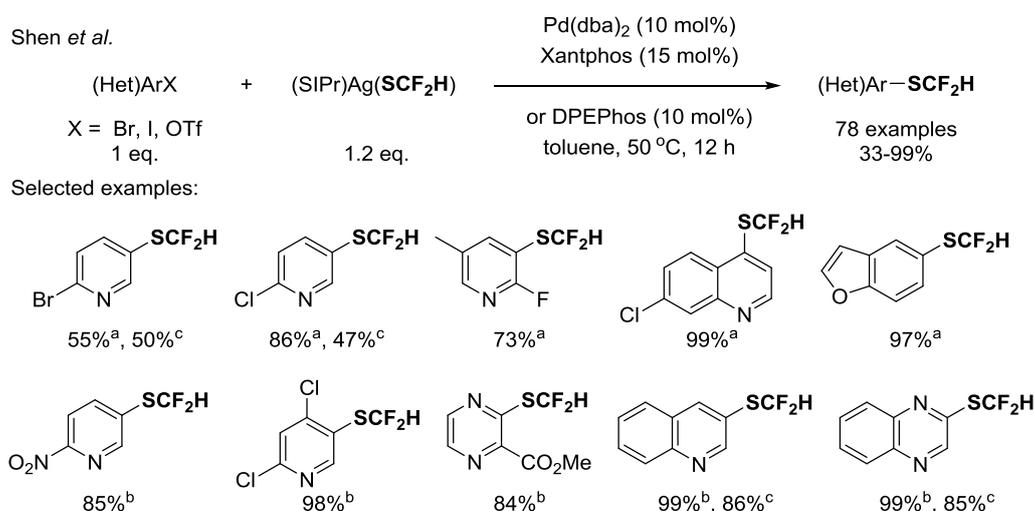
²⁵⁴ Jouvin, K.; Matheis, C.; Goossen, L. J. *Chem. Eur. J.* **2015**, *21*, 14324.



Then, Shen and co-workers disclosed for the first time an elegant solution for the direct introduction of the SCF₂H unit onto molecules using a newly designed difluoromethylthiolating reagents. By employing a bulky N-heterocyclic carbene (SIPr) to stabilize the AgSCF₂H, which is less stable compared to its analogue AgSCF₃, the first nucleophilic difluoromethylthiolating reagent (SIPr)Ag(SCF₂H) has been synthesized (Scheme 108).²⁵⁵ Indeed, when [(SIPr)Ag(CF₂H)] was reacted with elementary sulfur in THF at room temperature, the (SIPr)Ag(SCF₂H) complex could be obtained in 82% yield. Under the mediation of a copper salt (Cu(MeCN)₄PF₆ in the presence of bipyridine), a Sandmeyer reaction with various aryl and heteroaryl diazonium salts furnished the corresponding difluoromethylthiolated products in moderate to excellent yields (Scheme 108).

Scheme 108: Synthesis and application of the (SIPr)Ag(SCF₂H) reagent²⁵⁵ Wu, J.; Gu, Y.; Leng, X.; Shen, Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 7648.

In addition, Shen and co-workers further developed a general approach in the application of (SIPr)Ag(SCF₂H) by a Pd-catalyzed difluoromethylthiolation of (hetero)aryl halides and triflates, which includes a large panel of electron-rich and electron poor (hetero)aromatic derivatives. Indeed, hetero(aryl) iodides, bromides or triflates were efficiently difluoromethylthiolated under mild reaction conditions, furnishing the corresponding difluoromethylthiolated products in moderate to excellent yields (Scheme 109).²⁵⁶



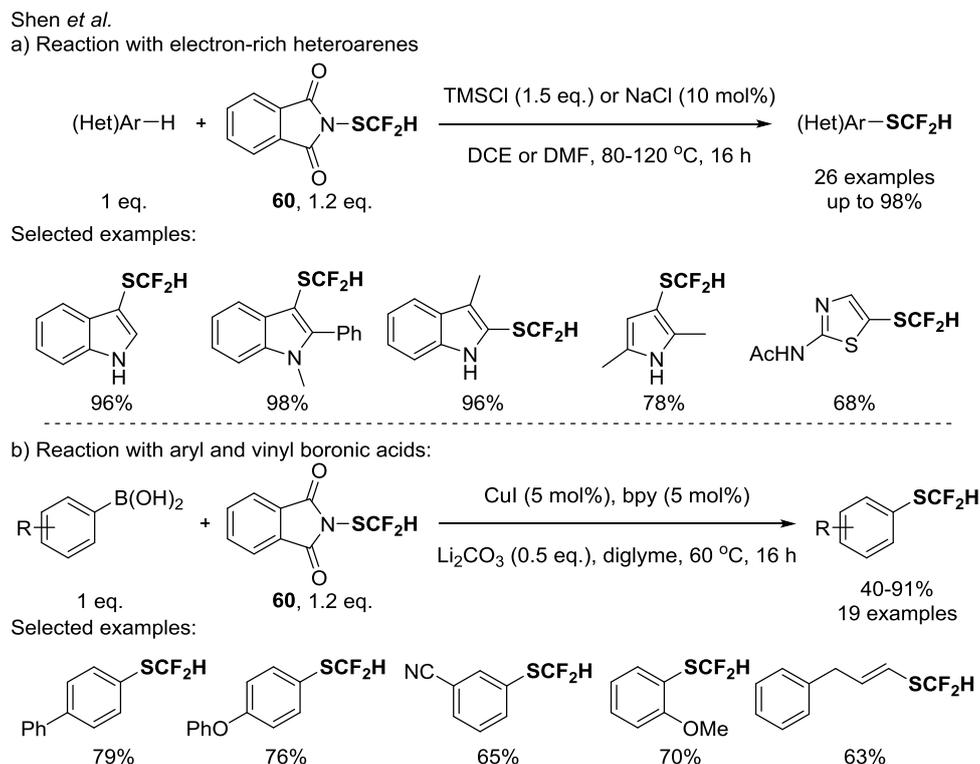
Scheme 109: Pd-catalyzed difluoromethylthiolation of (hetero)aryl halides and triflates. ^a From heteroaryl iodides; ^b From heteroaryl bromides; ^c From heteroaryl triflates

Recently, Goossen and co-workers reported the sandmeyer-type pentafluoroethylthiolation of arene diazonium tetrafluoroborates using the pentafluoroethylthiolating reagent TMSC₂F₅^{101a} as SC₂F₅ source. In the presence of catalytic amount of elemental copper, a wide range of aromatic and heteroaromatic diazonium salts were smoothly converted into the corresponding pentafluoroethyl thioethers at room temperature (Scheme 110).²⁵⁷

²⁵⁶ Wu, J.; Liu, Y.; Lu, C.; Shen, Q. *Chem. Sci.* **2016**, *7*, 3757.

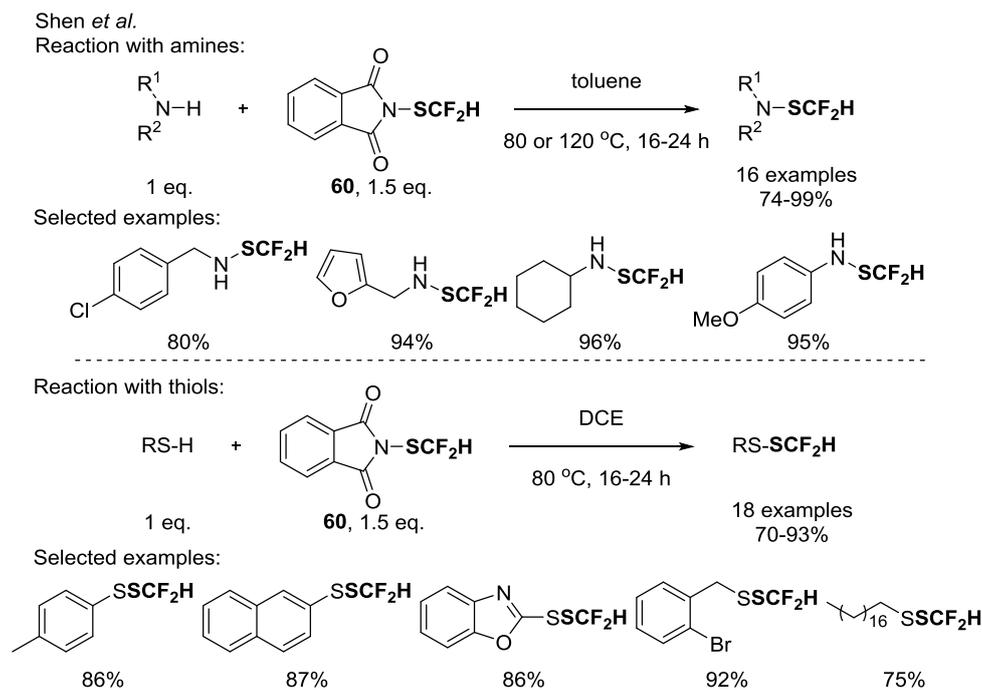
²⁵⁷ Matheis, C.; Bayarmagnai, B.; Jouvin, K.; Goossen, L. *J. Org. Chem. Front.* **2016**, *3*, 949.

TMSCl or catalytic amount of NaCl (Scheme 112, a). Moreover, aryl and vinyl boronic acids were converted into the corresponding products in moderate to good yields by means of a Cu-catalyzed difluoromethylthiolation, offering an access to a large variety of difluoromethylthiolated arenes and alkenes (Scheme 112, b).²⁵⁸



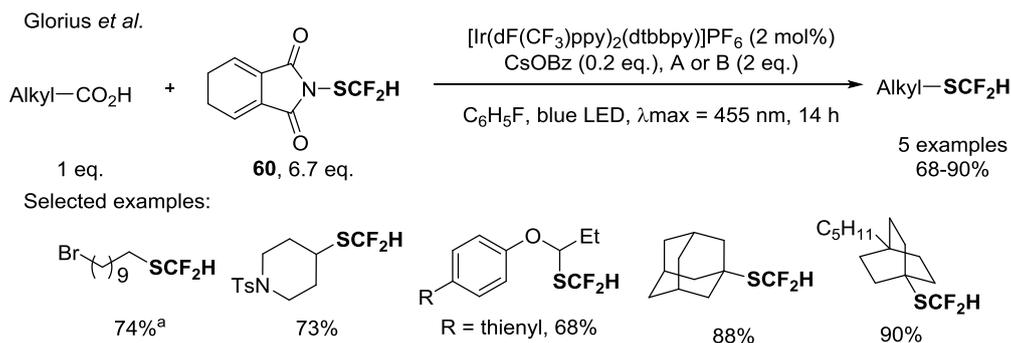
Scheme 112: Difluoromethylthiolation of electron-rich heteroarenes, aryl and vinyl boronic acids

A Cu-catalyzed direct introduction of the SCF_2H moiety onto a variety of alkynes allowed the formation of the $\text{C}(\text{sp})-\text{SCF}_2\text{H}$ bond in good to excellent yields (Scheme 113, a). The transformation was tolerant to various functional groups like nitrile, nitro, ester and halogens, and was also compatible to heteroaryl alkynes. Furthermore, under basic conditions, the difluoromethylthiolation of β -ketoesters and 2-oxindoles were also succeeded at room temperature, affording the corresponding products in good yields (Scheme 113, b).²⁵⁸



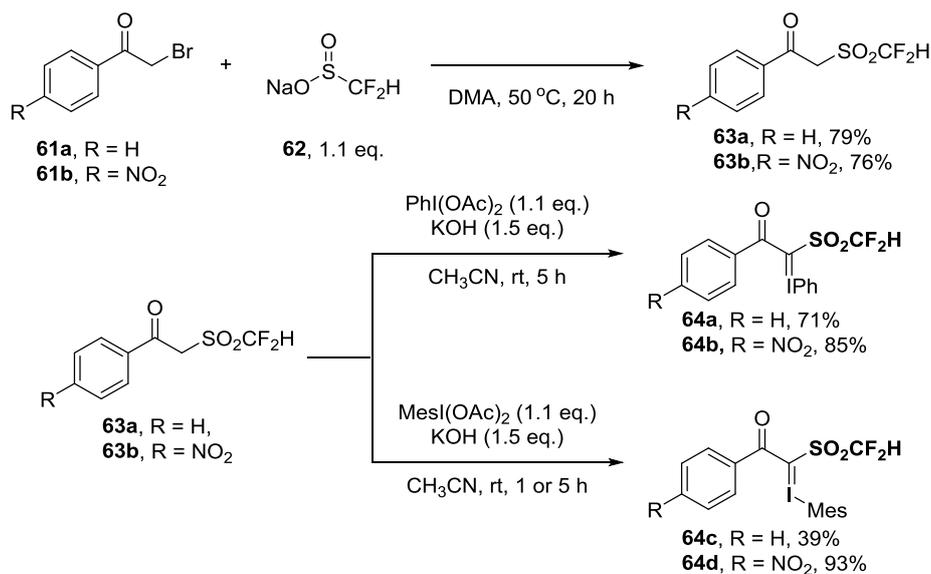
Scheme 114: Difluoromethylthiolation of amines and thiols

In 2016, Glorius and co-workers applied **60** in a light-promoted decarboxylative difluoromethylthiolation reaction of alkyl carboxylic acids using $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ as a photocatalyst ($\text{dF}(\text{CF}_3)\text{ppy}$ = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine).¹¹⁶ Under the irradiation with blue LEDs at room temperature, a range of carboxylic acids such as primary, secondary and tertiary alkyl carboxylic acids were converted into the expected SCF_2H -containing products (Scheme 115). In this case, the additive mesitylene or methyl-3-(methyl)benzoate were used to suppress the degradation of **60**. Starting from readily available starting materials, this approach constitutes an efficient synthetic tool for the $\text{C}(\text{sp}^3)\text{-SCF}_2\text{H}$ bond formation.



Scheme 115: A light-promoted decarboxylative difluoromethylthiolation reaction of alkyl carboxylic acids. A = mesitylene. B = methyl-3-(methyl)benzoate.

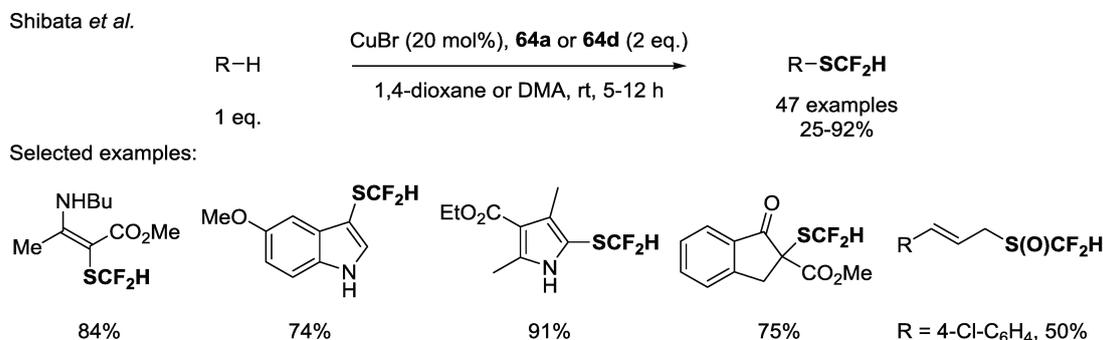
In order to broaden the toolbox of the electrophilic SCF₂H reagents, Shibata and co-workers developed a series of difluoromethanesulfonyl hypervalent iodonium ylides **64** as electrophilic difluoromethylthiolation reagents for the introduction of the SCF₂H residue (Scheme 116).²⁵⁹ Treating 2-bromoacetophenone **61a** with sodium difluoromethanesulfinate **62** in dimethylacetamide (DMA) at 50 °C for 20 h would afford the 2-difluoromethanesulfonyl acetophenone (**63a**) in 79% yield. The reaction of **63a** with phenyliodonium diacetate (PhI(OAc)₂) in the presence of potassium hydroxide provided **64a** in 71% yield. In a similar manner, **64b**, **64c**, **64d** were synthesized in moderate to high yields (Scheme 116).



Scheme 116: Synthesis of difluoromethanesulfonyl hypervalent iodonium ylides **64**

²⁵⁹ Arimori, S.; Matsubara, O.; Takada, M.; Shiro, M.; Shibata, N. *R. Soc. Open Sci.* **2016**, *3*, 160102.

These reagents were successfully applied for the Cu-catalyzed difluoromethylthiolation of various nucleophiles such as enamines, indoles, pyrroles, β -keto esters and silyl enol ethers (Scheme 117).²⁵⁹



Scheme 117: Application of difluoromethanesulfonyl hypervalent iodonium ylides **64**

Additionally, Billard and co-workers developed a range of pentafluoroethylthiolating reagents (**65**, **66**, **67**, Figure 24) for the introduction of SCF_2R_f group onto various substrates including Grignard reagent,¹²³ⁿ thiols,^{123v} amines^{123p} and terminal alkynes.^{123o} More recently, the group of Billard described the synthesis of the (benzenesulfonyl)difluoromethanesulfenamide **68** (Figure 24) and their application in the (benzenesulfonyl)difluoromethylthiolation of alkenes, alkynes, indoles, pyrroles as well as the electron-rich arenes.²⁶⁰

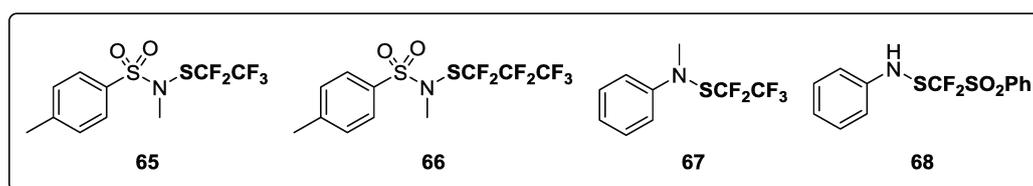


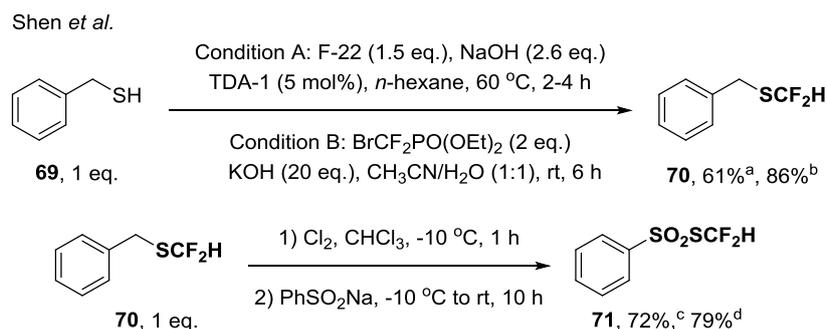
Figure 24: Billard's pentafluoroethylthiolating reagents **65-67** and (benzenesulfonyl)difluoromethanesulfenamide **68**

By using the corresponding perfluoroalkanesulfenamides (**65** or **66**) and Bu_4NI , Billard and co-workers reported the perfluoroalkylthiolation of various electrophiles with different leaving groups.^{123u} In this case, a plausible in situ generated ISCF_2R_f ($\text{R}_f = \text{CF}_2, \text{CF}_2\text{CF}_3$) intermediate was proposed as the reactive species.

²⁶⁰ Ismalaj, E.; LeBars, D.; Billard, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 4790.

2.2.2.3 Radical difluoromethylthiolation reactions

More recently, Shen and co-workers described the synthesis of S-(difluoromethyl)benzenesulfonothioate (PhSO₂SCF₂H, **71**), a new, easily scalable, shelf-stable reagent and its application for the direct radical difluoromethylthiolation.²⁶¹ The treatment of the commercially available benzyl mercaptan **69** with the ozone depleting chlorodifluoromethane (F-22) or BrCF₂PO(OEt)₂ under basic conditions afforded the benzyl(difluoromethyl)thioether **70** in a good yield. The addition of the obtained benzyl(difluoromethyl)thioether **70** into a saturated solution of chlorine in CHCl₃ at -10 °C for 1 h would in situ generate HCF₂SOCl, followed by the subsequent nucleophilic substitution of the intermediate with PhSO₂Na to provide the PhSO₂SCF₂H **71** in 72% yield (Scheme 118).

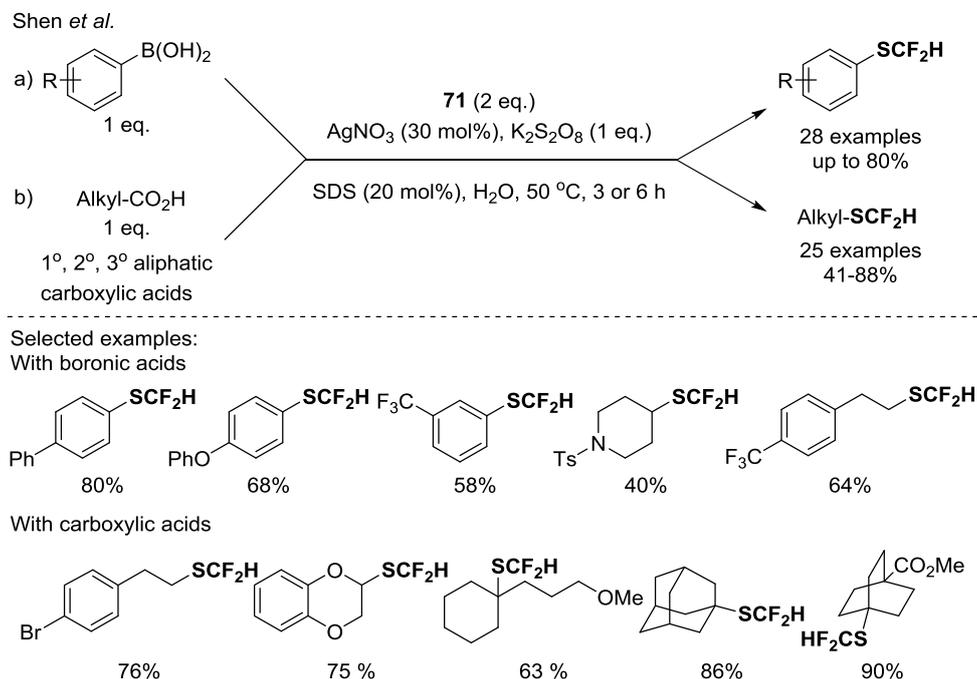


Scheme 118: Synthesis of PhSO₂SCF₂H **71**. ^a Condition A; ^b Condition B; ^c on a 120 mmol scale; ^d on a 20 mmol scale. TDA-1 = tris(2-(2-methoxyethoxy)ethyl)amine, F-22 = chlorodifluoromethane.

This reagent has proved to be an efficient radical difluoromethylthiolating reagent for the introduction of the SCF₂H group onto boronic acids and carboxylic acids. In the presence of AgNO₃ and sodium dodecyl sulfate (SDS), a variety of aryl boronic acids with either electron-donating or electron-withdrawing groups was difluoromethylthiolated in moderate to high yields. It is worth mentioning that alkyl boronic acids including primary and secondary ones were also favorable to afford the alkyl difluoromethylsulfides in moderate yields (Scheme 119, a).²⁶¹ In addition, the difluoromethylthiolation of primary, secondary and tertiary alkyl carboxylic acids

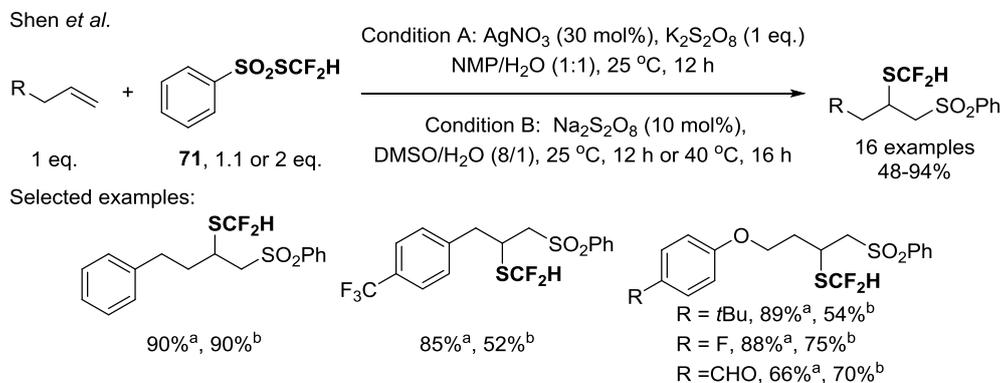
²⁶¹ Zhu, D.; Shao, X.; Hong, X.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 15807.

proceeded smoothly under the optimized reaction conditions, affording the corresponding products in high yields (Scheme 119, b).²⁶¹



Scheme 119: Radical difluoromethylthiolation reactions of boronic acid and carboxylic acids. SDS = sodium dodecyl sulfate.

Furthermore, $\text{PhSO}_2\text{SCF}_2\text{H}$ **71** turned out to be highly reactive towards the difunctionalization of alkenes. In the presence of 30 mol% AgNO_3 and 1 equivalent of $\text{K}_2\text{S}_2\text{O}_8$, a variety of alkenes was converted into the corresponding products in high yields (Scheme 120, Condition A). It is worthy to mention that under the metal-free conditions (Scheme 120, Condition B), the desired products could also be obtained in moderate to good yields.²⁶¹

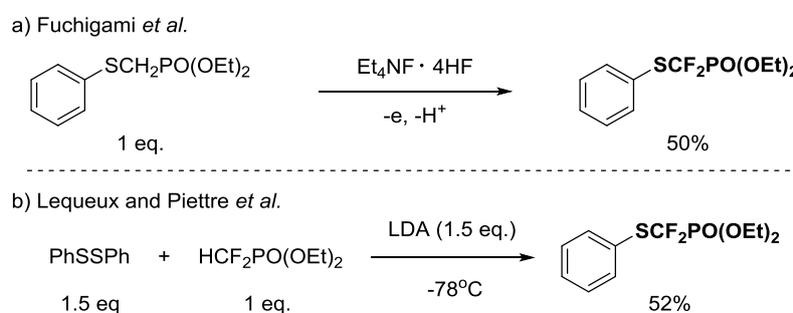


Scheme 120: Phenylsulfonyl-difluoromethylthio difunctionalization of alkenes. ^a Condition A; ^b Condition B.

This newly developed difluoromethylthiolating reagent showed high reactivity for the direct radical difluoromethylthiolation of boronic acids, alky carboxylic acids as well as alkenes with good functional-group tolerance, providing a complementary methodology for the direct difluoromethylthiolation using either electrophilic or nucleophilic difluoromethylthiolating reagents.

2.2.3 Synthesis of SCF₂PO(OR)₂-containing molecules

In terms of the synthesis of SCF₂PO(OR)₂ (R = Et, iPr)-containing molecules, the relevant reports are rare. In 1997, Fuchigami and co-workers reported the difluorination of PhSCH₂PO(OEt)₂ by an electrochemical pathway using Et₄NF·4HF as a fluorine source. The PhSCF₂PO(OEt)₂ was obtained in 50% yield (Scheme 121, a).²⁶² Alternatively, PhSCF₂PO(OEt)₂ could also be synthesized by the nucleophilic addition of the in situ generated LiCF₂PO(OEt)₂ to diphenyl disulfide as reported by Lequeux and Piettre (Scheme 121, b).²⁶³



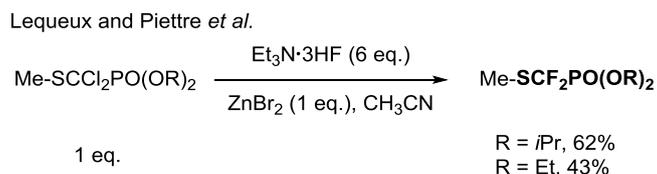
Scheme 121: Synthesis of the PhSCF₂PO(OEt)₂

Moreover, the same group described the synthesis of methylsulfanyldifluoromethylphosphonates by means of a halogen-exchange pathway.²⁶³ Indeed, the treatment of the methylsulfanyldichloromethylphosphonates with Et₃N·3HF and zinc bromide in acetonitrile afforded the corresponding difluorophosphonates in moderate yields (Scheme 122). This strategy was also

²⁶² Konno, A.; Fuchigami, T. *J. Org. Chem.* **1997**, 62, 8579.

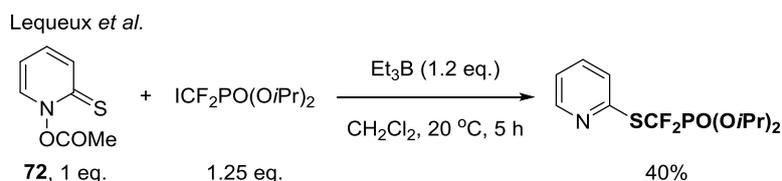
²⁶³ Lequeux, T.; Lebouc, F.; Lopin, C.; Yang, H.; Gouhier, G.; Piettre, S. R. *Org. Lett.* **2001**, 3, 185.

applied to the synthesis of biologic active compounds.²⁶⁴



Scheme 122: Synthesis of MeSCF₂PO(OR)₂, R = *i*Pr or Et

In 2013, during their investigation of the radical conjugate addition of the alkenes, Lequeux and co-workers isolated the PySCF₂PO(O*i*Pr)₂ in 40 % yield when 2-thioxopyridin-1(2H)-yl acetate **72** was used as a radical scavenger (Scheme 123).²⁶⁵ This product was generated through the free radical addition of the fluorinated radical onto the 2-thioxopyridin-1(2H)-yl acetate **72**.



Scheme 123: Synthesis of PySCF₂PO(O*i*Pr)₂ with ICF₂PO(O*i*Pr)₂

The construction of SCF₂H- or SCF₂PO(OEt)₂-containing molecules by using the corresponding reagent represents a conceptually straightforward approach and there is no general and efficient access to such compounds. In this context, the design of bench-stable reagents to directly introduce a SCF₂H or a SCF₂FG will enlarge the toolbox of fluorinated groups.

2.3 Our objectives

In this part of this Ph.D. thesis, we would like to design and synthesize new SCF₂H- or SCF₂FG-containing reagents and study their applications. Note that, no difluoromethylthiolating reagent was reported at the outset of our studies in March 2015.

²⁶⁴ (a) Henry-dit-Quesnel, A.; Toupet, L.; Pommelet, J.-C.; Lequeux, T. *Org. Biomol. Chem.* **2003**, 1, 2486; (b) Aliouane, L.; Chao, S.; Brizuela, L.; Pfund, E.; Cuvillier, O.; Jean, L.; Renard, P.-Y.; Lequeux, T. *Biol. Med. Chem.* **2014**, 22, 4955.

²⁶⁵ Schutter, C.; Pfund, E.; Lequeux, T. *Tetrahedron* **2013**, 69, 5920.

2.4 Investigation for the synthesis of a new SCF₂H reagent

Due to the special features of the difluoromethylthio group (SCF₂H), the development of new methodologies for the introduction of such group is of high interest.²⁴⁸ Thus, we first would like to focus on the design of new SCF₂H reagents for the construction of difluoromethylthiolated molecules. The synthesis of three newly designed difluoromethylthiolating reagents (**60**, **73**, **74**) was envisioned and investigated (Figure 25).

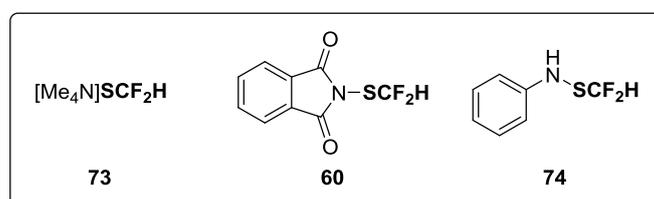


Figure 25: Towards newly designed difluoromethylthiolating reagents

2.4.1 Synthesis of a $[\text{Me}_4\text{N}]\text{SCF}_2\text{H}$ reagent

Inspired by the pioneering work of Yagupolskii and co-workers regarding the synthesis of $[\text{Me}_4\text{N}]\text{SCF}_3$ from the commercially available Ruppert-Prakash reagent (TMSCF_3), $[\text{Me}_4\text{N}]\text{F}$ in the presence of elemental sulfur in THF (Chapter 2, Scheme 24),^{101a} we assumed that its analogue $[\text{Me}_4\text{N}]\text{SCF}_2\text{H}$ could be synthesized in a similar way and be used as a nucleophilic SCF₂H reagent. Thus, we prepared the TMSCF_2H from TMSCF_3 and NaBH_4 according to the reported procedure.^{207,266} Starting from the reaction conditions reported by Yagupolskii and co-workers,^{101a} several reaction parameters were examined (Table 34).

²⁶⁶ Tyutyunov, A.; Boyko, V.; Igoumnov, S. *Fluorine notes* **2011**, 1, 74.

Table 34: Investigation of the reaction conditions

$$\text{TMSCF}_2\text{H} + \text{S}_8 + [\text{Me}_4\text{N}]\text{F} \xrightarrow[\text{T } (^\circ\text{C}), \text{Ar, time}]{\text{solvent}} [\text{Me}_4\text{N}]\text{SCF}_2\text{H} + \text{TMSF}$$

1.2 eq. 1 eq. 1 eq.

entry	solvent	T (°C)	time (h)	results
1	THF	-60 to 70	72	degradation of TMSCF ₂ H
2	1,4-dioxane	50 to 70	44	CH ₂ F ₂
3	diglyme	50 to 70	44	CH ₂ F ₂
4	CH ₃ CN	70	18	CH ₂ F ₂
5	Et ₂ O	50	44	TMSCF ₂ H recovered

^a Reaction conditions: TMSCF₂H (0.4 mmol, 1.2 eq.), S₈ (0.33 mmol, 1 eq.), [Me₄N]F (0.33 mmol, 1 eq.), solvent (2.7 mL), Ar.

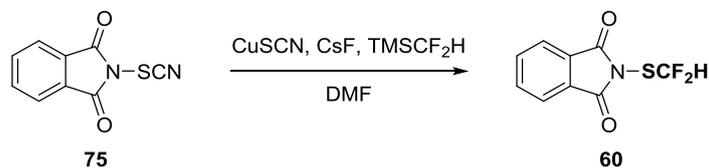
First, we carried out the reaction of TMSCF₂H, S₈ and [Me₄N]F in THF at -60 °C for 0.5 h. No new signal was detected by ¹⁹F NMR. We then slowly increased the temperature to 70 °C and monitored the reaction by ¹⁹F NMR. However, no new signal was detected by ¹⁹F NMR either (Table 34, entry 1). When the reaction was performed at 50 °C using 1,4-dioxane or diglyme as solvent, the starting materials were recovered (Table 34, entries 2 and 3). Further increasing the reaction temperature to 70 °C led to the degradation of the TMSCF₂H into CH₂F₂ (δ = -144.3 ppm).²⁶⁷ When CH₃CN was used as solvent, the same degradation of TMSCF₂H was observed after heating the reaction mixture at 70 °C for 18 h. When the reaction was performed in Et₂O, a starting material was recovered (Table 34, entry 5) Since only degradation of the TMSCF₂H was observed in the investigation, we thought that this strategy might be not suitable for the preparation of [Me₄N]SCF₂H. Thus, we decided to turn our attention to other classes of SCF₂H reagent.

2.4.2 Synthesis of the N-(difluoromethylthio)phthalimide

Goossen and co-workers described the nucleophilic cyanide-CF₂H substitution of the in situ generated thiocyanate through the CuCF₂H intermediate (Scheme 106).²⁰⁷ Through a similar strategy, we envisioned the difluoromethylation of the corresponding thiocyanate might afford the N-(difluoromethylthio)phthalimide **60**

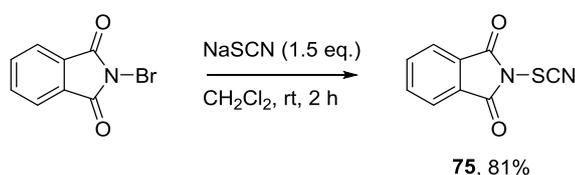
²⁶⁷ Bhadury, P. S.; Palit, M.; Sharma, M.; Raza, S. K.; Jaiswal, D. K. J. Fluorine Chem. **2002**, 116, 75.

which might be an electrophilic difluoromethylthiolating reagent (Scheme 124). Note that when these studies were conducted in spring 2015, Shen and co-workers did not reported yet the synthesis of this reagent from the (SIPr)Ag(CF₂H).²⁵⁸



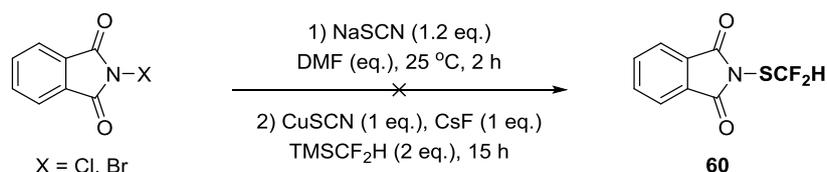
Scheme 124: Strategy for the synthesis of N-(difluoromethylthio)phthalimide **60**

Keeping this idea in mind, we first tried to synthesize the N-(thiocyano)phthalimide **75** from the commercially available N-bromophthalimide and NaSCN using the modified reaction conditions according to the reported procedure.²⁴⁰ The expected product was obtained in 81% yield with 10% of phthalimide which might be due to the degradation of N-(thiocyano)phthalimide **75** (Scheme 125).



Scheme 125: Synthesis of N-(thiocyano)phthalimide **75**

We then decided to perform our reaction in a one-pot/two steps process since the N-(thiocyano)phthalimide **75** was not stable. N-bromo- and N-chloro-phthalimide were tested (Scheme 126). However, no new signals were detected by ¹⁹F NMR in 15 h. When the reaction mixture was heated to 70 °C for 16 h, only the degradation of the TMSCF₂H was observed. It turned out that the TMSCF₂H reagent was quite easy to decompose. Thus, the search for other approaches was highly desirable.



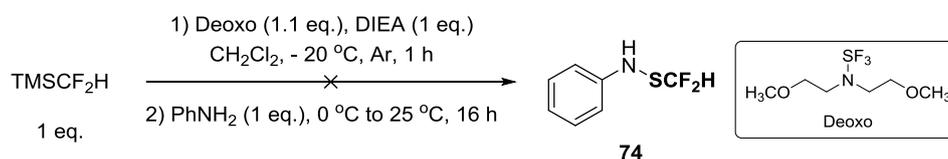
Scheme 126: Attempts to synthesize N-(difluoromethylthio)phthalimide **60** in a one-pot process

2.4.3 Synthesis of difluoromethylthiolated anilines

2.4.3.1 Difluoromethylthiolation of the aniline using TMSCF_2H

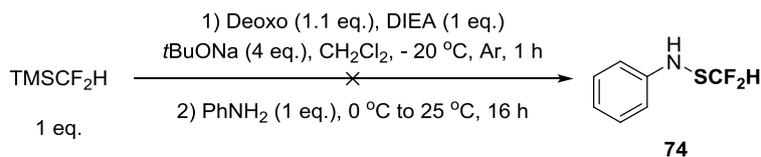
Trifluoromethanesulfenamides **14a** were prepared by Billard and co-workers from TMSCF_3 and diethylaminosulfur trifluoride (DAST) in the presence of *N,N*-diisopropylethylamine (DIEA).¹²⁰ Inspired by this pioneering work, we wondered if switching TMSCF_3 to TMSCF_2H would offer a difluoromethanesulfenamide reagent which will be further applied for the introduction of the SCF_2H group as a new electrophilic source.

We first treated TMSCF_2H with Deoxo and DIPEA in CH_2Cl_2 at $-20\text{ }^\circ\text{C}$ for 1 h, followed by the addition of aniline at $0\text{ }^\circ\text{C}$. After stirring the reaction mixture at room temperature for 16 h, TMSCF_2H was recovered and no new fluorine signal was observed (Scheme 127). We then heated the reaction mixture at $50\text{ }^\circ\text{C}$ for 24 h, but no reaction occurred either. When the reaction temperature was further heated to $100\text{ }^\circ\text{C}$, the degradation of the TMSCF_2H occurred.



Scheme 127: Attempt to synthesize **74**

It was reported that a $\text{Si-CF}_2\text{H}$ bond is more inert compared to a Si-CF_3 bond.²⁶⁸ On the other hand, strong bases such as *t*BuONa, *t*BuOK were believed to be beneficial for the activation of TMSCF_2H .²⁶⁹ Thus, *t*BuONa was engaged in this reaction for the activation of TMSCF_2H . However, no product was detected after stirring at room temperature for 16 h (Scheme 128).

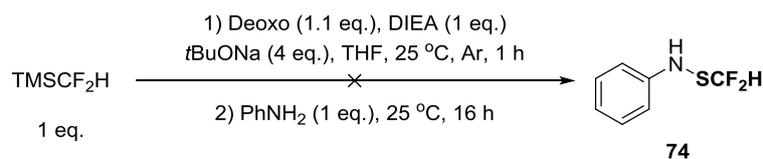


Scheme 128: Attempt to synthesize **74** by using *t*BuONa as additive in CH_2Cl_2

²⁶⁸ Hagiwara, T.; Fuchikami, T. *Synlett* **1995**, 717.

²⁶⁹ (a) Jiang, X.-L.; Chen, Z.-H.; Xu, X.-H.; Qing, F.-L. *Org. Chem. Front.* **2014**, 1, 774. (b) Gu, Y.; Leng, X.; Shen, Q. *Nat. Comm.* **2014**, 5, 5405.

Since the reaction did not work as we expected, we decided to increase the reaction temperature to 25 °C and switch the solvent to THF because it is known to increase the solubility of the tBuONa salt (Scheme 129).²⁷⁰ However, no new signal was detected by ¹⁹F NMR after 16 h. A subsequent increase of the reaction temperature to 50 °C led to a partial degradation of TMSCF₂H.

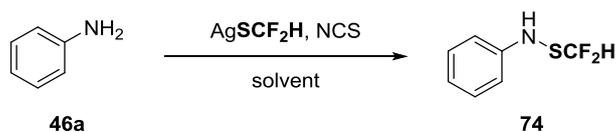


Scheme 129: Attempt to synthesize **74** by using tBuONa as additive in THF

Finally, we did not succeed in the synthesis of N-(difluoromethylthio)aniline **74** through the reaction of aniline and TMSCF₂H probably due to the unstable feature of the TMSCF₂H reagent in these reaction conditions.

2.4.3.2 Oxidative difluoromethylthiolation of the aniline

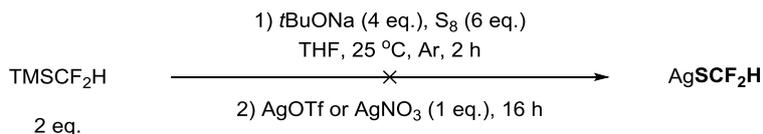
Inspired by the methodology of the oxidative trifluoromethylthiolation reaction of amines,²⁴⁷ we envisioned that a similar oxidative difluoromethylthiolation reaction of aniline would afford the N-(difluoromethylthio)aniline **74** (Scheme 130).



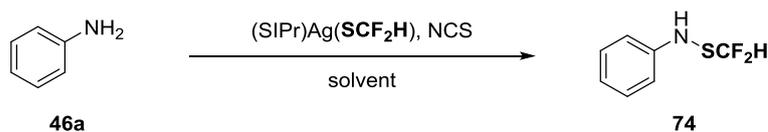
Scheme 130: Strategy for the synthesis of N-(difluoromethylthio)aniline **74** from AgSCF₂H

To verify our hypothesis, we started our studies by the synthesis of AgSCF₂H. Following the reaction condition for the synthesis of AgSCF₃ reported by Yagupolskii and co-workers,^{101a} we treated TMSCF₂H with tBuONa and elemental sulfur in THF, followed by the addition of AgOTf or AgNO₃. However, only the degradation of TMSCF₂H (CF₂H₂) was observed (Scheme 131).

²⁷⁰ Zhao, Y.; Huang, W.; Zheng, J.; Hu, J. *Org. Lett.* **2011**, 13, 5342.

Scheme 131: Attempt to synthesize AgSCF₂H

In the meantime, Shen and co-workers reported the synthesis of the first nucleophilic difluoromethylthiolating reagent (SIPr)Ag(SCF₂H) by using a bulky N-heterocyclic carbene (SIPr) as the ligand to stabilize the AgSCF₂H species (Scheme 108).²⁵⁵ According to Shen's description, AgSCF₂H was not stable enough to be isolated. Thus, we decided to take benefit from the methodology developed by Shen regarding the synthesis of (SIPr)Ag(SCF₂H), and to apply it in our oxidative difluoromethylthiolation reaction of the aniline (Scheme 132).

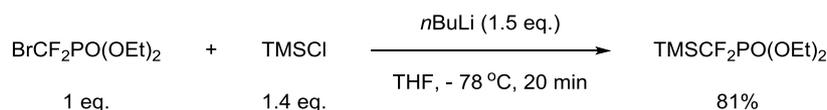
Scheme 132: Strategy for the synthesis of N-(difluoromethylthio)aniline **74** from (SIPr)Ag(SCF₂H)

Firstly, we synthesized (SIPr)AgCl from the commercially available (SIPr)·HCl and Ag₂O in CH₂Cl₂ in 76% yield according to the reported procedure.²⁷¹ With the (SIPr)AgCl in hand, we then turned our attention to the synthesis of the (SIPr)Ag(SCF₂H) complex according to Shen's procedure.²⁷² When we treated the (SIPr)AgCl with TMSCF₂H and tBuONa, only traces of (SIPr)Ag(CF₂H) was detected by ¹⁹F NMR. The further addition of elemental sulfur provided a small amount of the (SIPr)Ag(SCF₂H) (Scheme 133). Due to the difficulties we met, all the reaction parameters including the temperature, the time and the quality of our reagents were checked. Unfortunately, all the attempts we made failed and the (SIPr)Ag(SCF₂H) complex was not obtained in sufficient quantity. Note that, according to procedure of Shen and co-workers, the reaction needs to be performed in

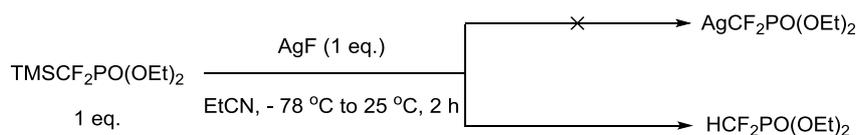
²⁷¹ Frémont, P.; Scott, N. M.; Stevens, E. D.; Ramnial, T.; Lightbody, O. C.; Macdonald, C. L. B.; Clyburne, J. A. C.; Abernethy, C. D.; Nolan, S. P. *Organometallics* **2005**, 24, 6301.

²⁷² Gu, Y.; Chang, D.; Leng, X.; Gu, Y.; Shen, Q. *Organometallics* **2015**, 34, 3065.

Since the $\text{TMSCF}_2\text{PO}(\text{OEt})_2$ reagent has been widely applied for the introduction of $\text{CF}_2\text{PO}(\text{OEt})_2$ group, our first attempt was to use it to prepare the $\text{AgCF}_2\text{PO}(\text{OEt})_2$ reagent. Thus, we synthesized the $\text{TMSCF}_2\text{PO}(\text{OEt})_2$ starting from the commercially available $\text{BrCF}_2\text{PO}(\text{OEt})_2$ and TMSCl , in the presence of $n\text{BuLi}$ according to the reported literature (Scheme 135).²⁷⁶

Scheme 135: Synthesis of the $\text{TMSCF}_2\text{PO}(\text{OEt})_2$ reagent

Then, the reaction of the obtained $\text{TMSCF}_2\text{PO}(\text{OEt})_2$ and AgF in propionitrile was carried out.^{101a} However, only the decomposition of $\text{TMSCF}_2\text{PO}(\text{OEt})_2$ into the $\text{HCF}_2\text{PO}(\text{OEt})_2$ was observed in these reaction conditions (Scheme 136).

Scheme 136: Attempts to synthesize $\text{AgCF}_2\text{PO}(\text{OEt})_2$

The formation of the $\text{HCF}_2\text{PO}(\text{OEt})_2$ species might be either explained by the direct degradation of $\text{TMSCF}_2\text{PO}(\text{OEt})_2$,²⁷⁷ or by the degradation of the in situ generated $\text{AgCF}_2\text{PO}(\text{OEt})_2$. Since the synthesis of such compound has never been reported so far and its stability is unknown, it is difficult to understand the mechanism. Therefore, switching our strategy to other well developed $\text{CF}_2\text{PO}(\text{OEt})_2$ salt might be beneficial for our investigation.

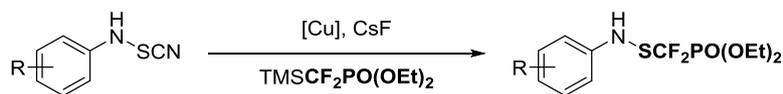
We then turned our attention to the $\text{CuCF}_2\text{PO}(\text{OEt})_2$ species, since impressive progress has been achieved in the construction of $\text{CF}_2\text{PO}(\text{OEt})_2$ -containing molecules through the in situ generated $\text{CuCF}_2\text{PO}(\text{OEt})_2$ in our group.²⁷⁸ Inspired by the recent studies of Goossen and co-workers,^{207,254} and taking the advantage of our expertise for

²⁷⁶ Nieschalk, J.; Batsanov, A. S.; O'Hagan, D.; Howard, J. *Tetrahedron* **1996**, 52, 165.

²⁷⁷ Feng, Z.; Min, Q.-Q.; Xiao, Y.-L.; Zhang, B.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, 53, 1669.

²⁷⁸ (a) Ivanova, M. V.; Bayle, A.; Besset, T.; Poisson, T.; Pannecoucke, X. *Angew. Chem. Int. Ed.* **2015**, 54, 13406; (b) Bayle, A.; Cocaud, C.; Nicolas, C.; Martin, O. R.; Poisson, T.; Pannecoucke, X. *Eur. J. Org. Chem.* **2015**, 3787.

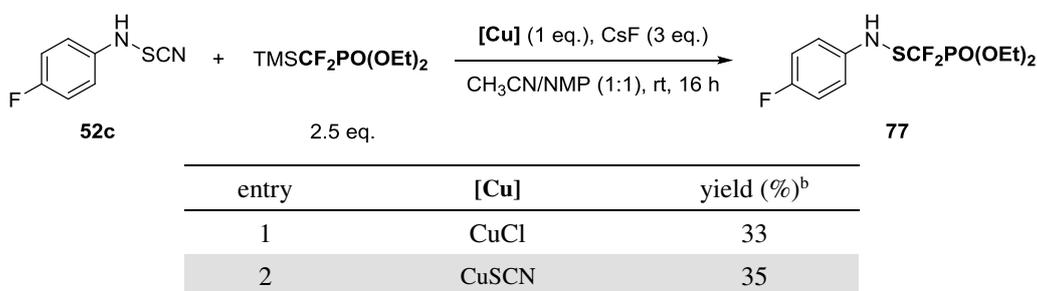
the preparation of N-(cyanosulfanyl)aniline derivatives,²⁴⁷ we hypothesized that a similar cyanide-CF₂PO(OEt)₂ substitution reaction from the readily N-(cyanosulfanyl)aniline derivative **52** and TMSCF₂PO(OEt)₂ might be applicable (Scheme 137).



Scheme 137: Strategy for the synthesis of (diethyl phosphono)difluoromethylthiolated anilines

We chose the 4-F-N-(cyanosulfanyl)aniline **52c** for our initial investigations. By treating **52c** with the in situ prepared CuCF₂PO(OEt)₂ species from CuCl and TMSCF₂PO(OEt)₂,²⁷⁸ the (diethyl phosphono)difluoromethylthiolated aniline **77** was obtained in 33% NMR yield (Table 35, entry 1). Switching the copper salt to CuSCN provided a similar result and the product was obtained in 35% NMR yield (Table 35, entry 2).

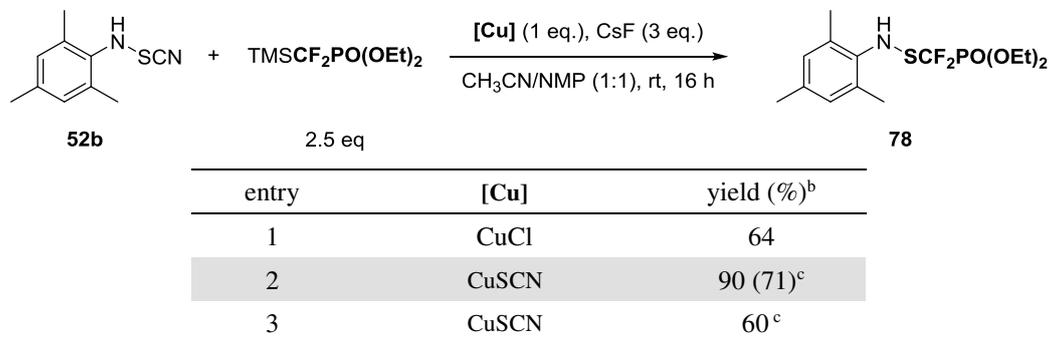
Table 35: Synthesis of the electrophilic SCF₂PO(OEt)₂ reagent **77**^a



^a Reaction conditions: **52c** (0.6 mmol, 1 eq.), TMSCF₂PO(OEt)₂ (1.5 mmol, 2.5 eq.), [Cu] (0.6 mmol, 1 eq.), CsF (1.8 mmol, 3 eq.), CH₃CN (1.2 mL), NMP (1.2 mL), rt, Ar, 16 h; ^b NMR yield was determined by ¹⁹F NMR using α,α,α -trifluorotoluene as internal standard.

Then, we turned our attention to the functionalization of **52b**. Pleasingly, the desired product **78** was obtained in 64% NMR yield (Table 36, entry 1). When CuSCN was employed, the expected product was obtained in 90% NMR yield (71% isolated yield) (Table 36, entry 2). The nature of the copper salt has a strong effect on the efficiency of the transformation. To showcase the synthetic potential of the procedure, this transformation was investigated in 4.4 mmol scale (Table 36, entry 3),

indicating that the proposed procedure can be employed for the synthesis of **78** in a large scale.

Table 36: Synthesis of the electrophilic $\text{SCF}_2\text{PO}(\text{OEt})_2$ reagent **78**^a

^a Reaction conditions: **52b** (0.25 mmol, 1 eq.), $\text{TMSCF}_2\text{PO}(\text{OEt})_2$ (0.625 mmol, 2.5 eq.), [Cu] (0.25 mmol, 1 eq.), CsF (0.75 mmol, 3 eq.), CH_3CN (0.5 mL), NMP (0.5 mL), rt, Ar, 16 h; ^b NMR yield was determined by ¹⁹F NMR using α,α,α -trifluorotoluene as an internal standard; ^c Isolated yield.

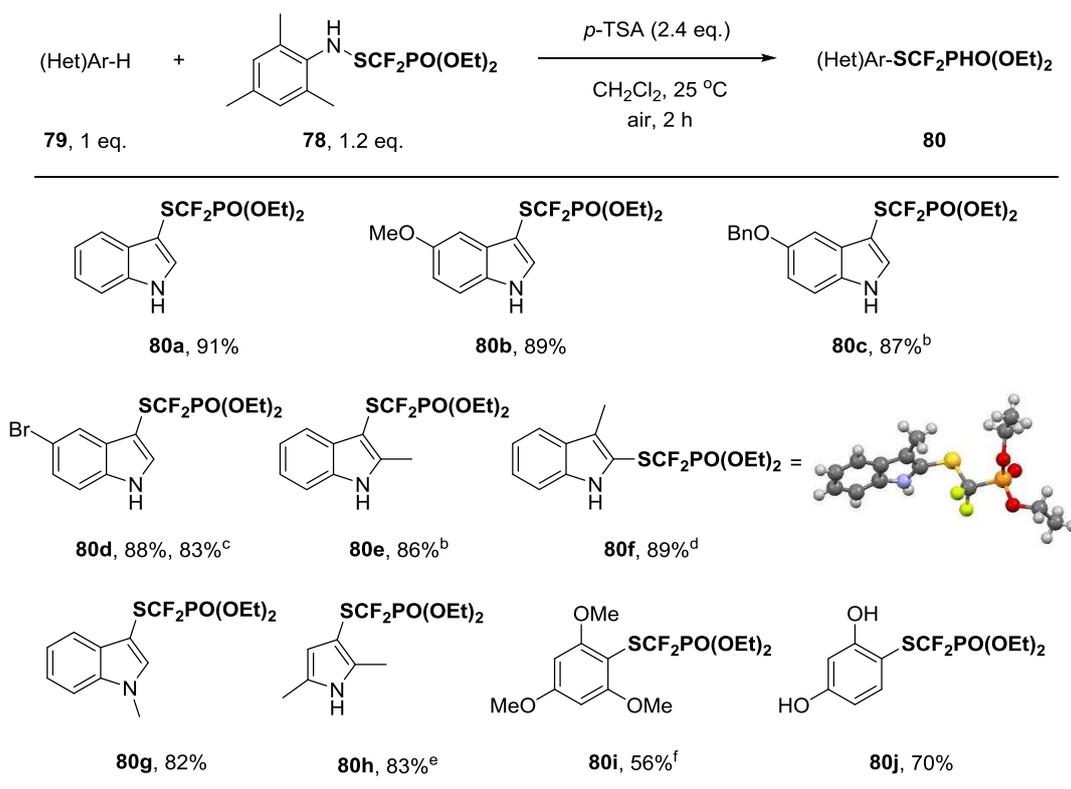
2.6 Applications of the $\text{SCF}_2\text{PO}(\text{OEt})_2$ reagent **78**

Having this new electrophilic reagent **78** in hand, we then turned our attention to the investigation of its reactivity.

2.6.1 Electrophilic substitution of electron-rich arenes and heteroarenes with reagent **78**

First, the electrophilic (diethyl phosphono)difluoromethylthiolation reaction of a range of electron-rich (hetero)arenes with **78** was evaluated (Table 37). According to a Friedel-Crafts type reaction conditions, we engaged the reagent **78** with the indole **79a** in the presence of p-TSA as additive in dichloromethane at room temperature. It was found that the reaction occurred smoothly affording the product **80a** in 91% yield at the C-3 position (Table 37). Further investigations showed that the reaction was tolerant to not only electron-donating (**79b**, **79c**) but also the halogen substituted indoles (Table 37, **79d**). In addition, the reaction of 2- or 3-methyl-substituted indoles led to the corresponding products (**80e**, **80f**) in 86% and 89% yields, respectively. Note that the structure of the compound **80f** was confirmed by X-ray analysis. N-methylindole **79g** was also converted into the desired product in 82% yield.

Similarly, pyrrole **79h** was efficiently converted into the (diethyl phosphono)difluoromethylthiolated product **80h** in 83% yield. We then extended our scope to anisole and phenol derivatives. Pleasingly, the expected product **80i** and **80j** were obtained in 56% and 70% yields, respectively, and no O-SCF₂PO(OEt)₂ bond formation was observed.

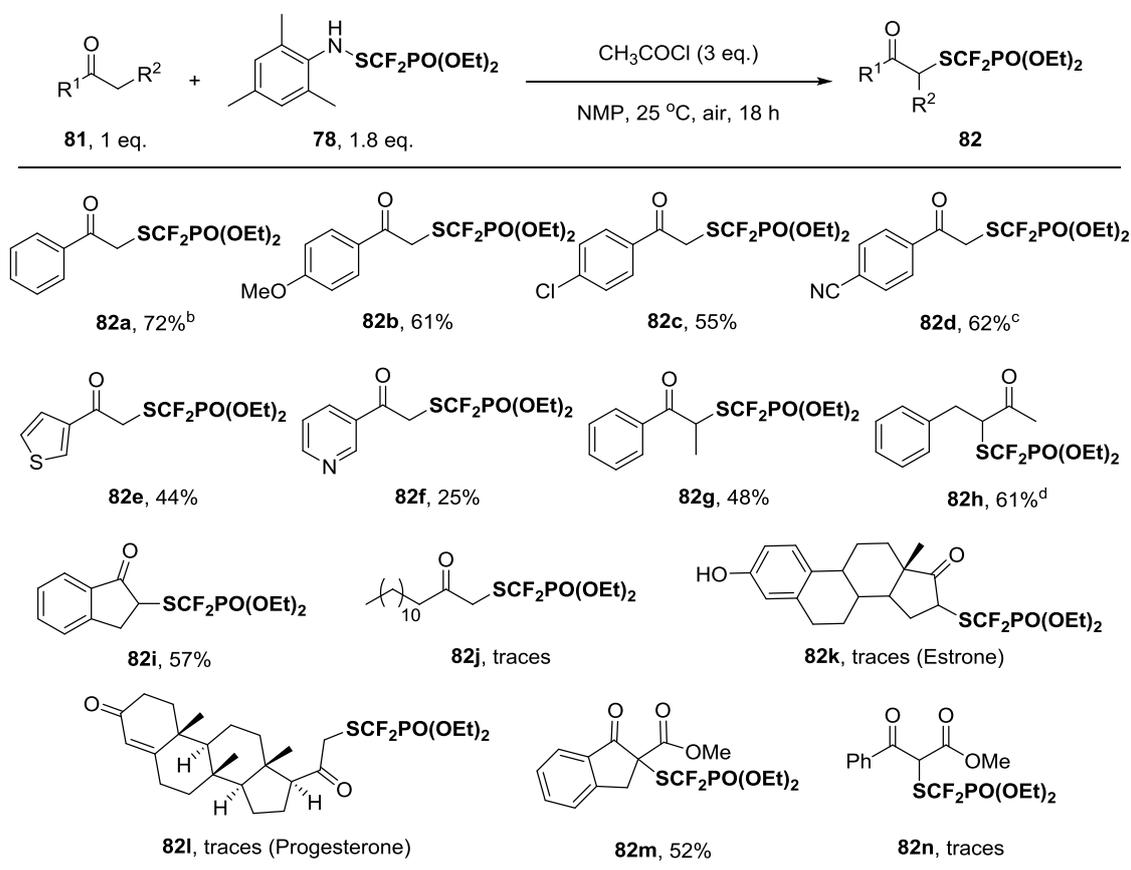
Table 37: Electrophilic substitution of electro-rich arenes and heteroarenes^a

^a Reaction conditions: **79** (0.15 mmol, 1 eq.), **78** (0.18 mmol, 1.2 eq.), p-TSA (0.36 mmol, 2.4 eq.), CH₂Cl₂ (1.5 mL), 25 °C, air, 2 h;

^b 4 h; ^c reaction performed on 2 mmol scale; ^e 1 h; ^f 12 h.

With the developed methodology, we then tried to extend the reaction scope to other electron-rich arenes and heteroarenes (Table 38) such as benzothiophene **79k**, benzofuran **79l**, 7-azaindole **79m**, 1H-imidazoles (**79n** and **79o**), as well as N-(phenyl)pivalamides (**79p** and **79q**). However, no expected product was obtained probably because such substrates are not electron-rich enough.

However, note that only traces of the product were obtained when the 2-tetradecanone **81j** was used as substrate.

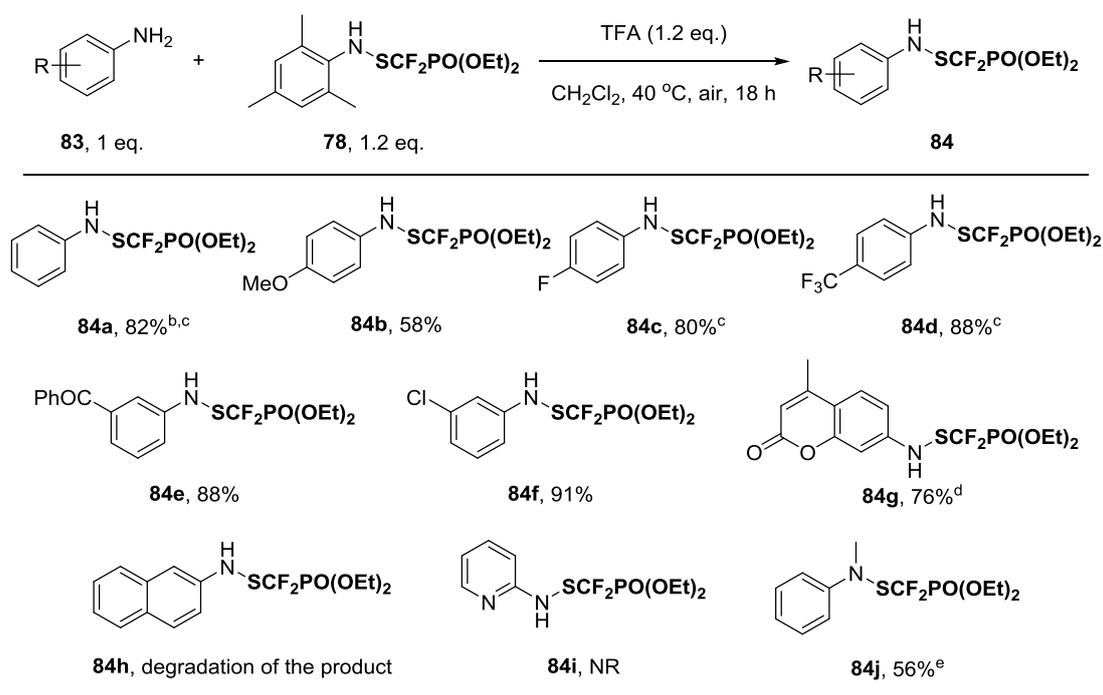
Table 39: (Diethyl phosphono)difluoromethylthiolation of ketones and β -ketoester^a

^a Reaction conditions: **81** (0.2 mmol, 1 eq.), **78** (0.36 mmol, 1.8 eq.), CH_3COCl (0.6 mmol, 3 eq.), NMP (2 mL), 25 °C, air, 18 h; ^b 1.5 eq. of **78** was used; ^c 3 eq. of **78** were used, 20 h; ^d 16 h. NMP = N-methylmorpholine-N-oxide.

With the above results, we next turned our attention to the application of this methodology for the functionalization of natural products (Estrone **81k** and Progesterone **81l**). Unfortunately, only traces of the expected products were detected in both cases. Apart from ketones, β -ketoesters were also tested in the electrophilic (diethyl phosphono)difluoromethylthiolation. Interestingly, conducting the reaction on the cyclic β -ketoester **81m** with the reagent **78** under the standard reaction conditions, the expected product was obtained in 59% yield. However, the β -ketoester **81n** was less reactive as only traces of the expected product were detected by ^{19}F NMR.

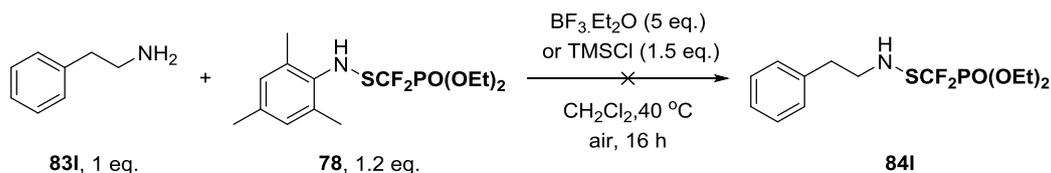
2.6.3 Reaction of aniline derivatives with the reagent **78**

With the successful introduction of the $\text{SCF}_2\text{PO}(\text{OEt})_2$ group into arenes, heteroarenes and ketones, we next sought to investigate the electrophilic (diethyl phosphono)difluoromethylthiolation of amines. As depicted in Table 40, the reaction of aromatic amines **83** with the reagent **78** in the presence of TFA occurred smoothly at 40 °C in 18 h to generate the corresponding products **84** in good to high yields.

Table 40: Reaction of aniline derivatives with reagent **78**^a

^a Reaction conditions: **83** (0.2 mmol, 1 eq.), **78** (0.24 mmol, 1.2 eq.), TFA (0.24 mmol, 1.2 eq.), CH_2Cl_2 (2 mL), 40 °C, air, 18 h; ^b 25 °C, 0.15 mmol scale; ^c 18 h; ^d 42 h; ^e 72 h, 50 °C. NR = no reaction, TFA = trifluoroacetic acid.

Anilines substituted by electron-donating (MeO, **83b**) or electron-withdrawing groups (halogens, CF_3 , ketones, **83c-f**) were well tolerated, offering the functionalized products in good yields (58%-91%). Furthermore, the synthesis of $\text{SCF}_2\text{PO}(\text{OEt})_2$ -containing analogues of biorelevant molecules such as triflumidate, diflumidone (**84e**) as well as coumarin 120 (**84g**) were successfully achieved, demonstrating the versatility of the method. It was worth mentioning that in the case of **83h**, a full conversion of the starting material was detected by TLC. However,

Scheme 138: Reaction of phenethylamine with reagent **78**

2.6.4 Reactions of thiol derivatives with the reagent **78**

We also turned our attention to the synthesis of unsymmetrical disulfide derivatives. First, the reaction of the thiophenol **85a** with an excess of reagent **78** in the presence of TFA was performed (Table 42, entry 1). However, only traces of the expected product was detected by ^{19}F NMR and a large amount of diphenyldisulfide was observed by GC-MS. Since the degradation of the thiophenols is the main reaction pathway in this system, we decided to increase the amount of thiophenol. Indeed, when we switched the ratio of **85a** and **78** from 1:1.2 to 2:1, the yield of the product **86a** increased to 13% (Table 42, entry 2). We then replaced TFA with methanesulfonic acid (MsOH) as the additive for the transformation. Gratifyingly, the product **86a** was isolated in 71% yield when the reaction was performed with 1.2 equivalents of MsOH as additive and 1.5 equivalents of thiophenol under Ar for 14 h (Table 42, entry 3).

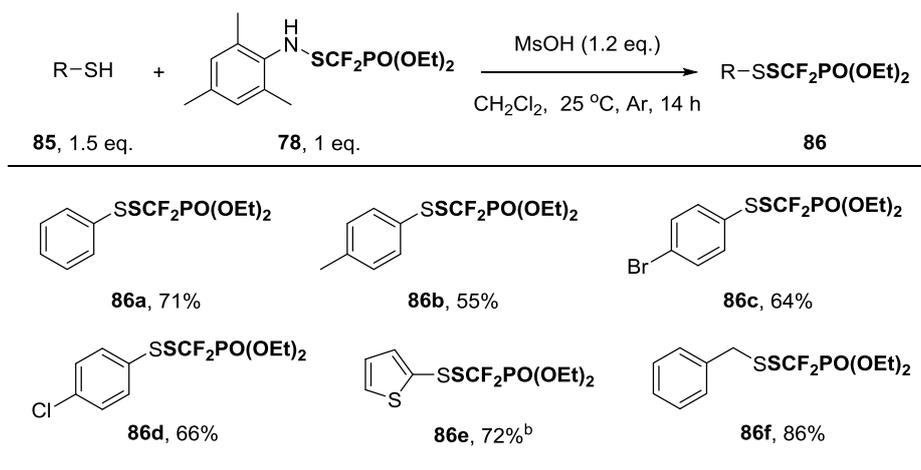
Table 42: Investigation of the reaction of thiols and reagent **78**^a

entry	85a/78 (eq.)	additive	time (h)	yield (%)
1	1/1.2	TFA	20	traces
2	2/1	TFA	18	13%
3 ^b	1.5/1	MsOH	14	71%

^a Reaction conditions: **85a** (0.2 mmol, 1 eq.), **78** (0.24 mmol, 1.2 eq.), additive (0.24 mmol, 1.2 eq.), CH_2Cl_2 (2 mL), 25°C , air, isolated yield; ^b Ar.

Under the optimized reaction conditions, we next investigated the scope of this transformation. As summarized in Table 43, thiophenol derivatives bearing an electron-donating substituent (Me; **85b**) was transformed to the expected product **86b**

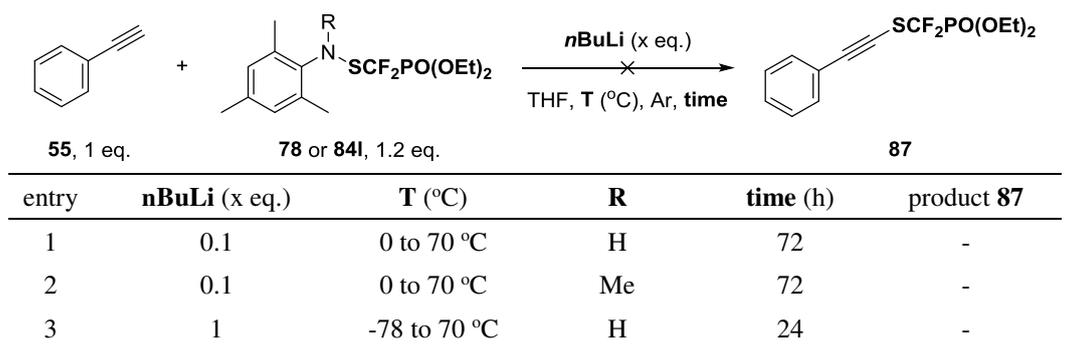
in 55% yield, while those substituted with halogens (Br, Cl; **85c**, **85d**) providing the desired products (**86c** and **86d**) in 64% and 66% yields, respectively. Importantly, the presence of a halogen on the aryl group might allow further functionalization. Moreover, heteroaromatic and benzyl thiols (**85e** and **85f**) were also efficiently functionalized affording the corresponding products in good yields.

Table 43: Synthesis of unsymmetrical disulfides^a

^a Reaction conditions: **85** (0.3 mmol, 1.5 eq.), **78** (0.2 mmol, 1 eq.), MsOH (0.24 mmol, 1.2 eq.), CH₂Cl₂ (2 mL), 25 °C, Ar, 14 h; ^b 1.7 eq. of **78** was used, 18 h. MsOH = methanesulfonic acid.

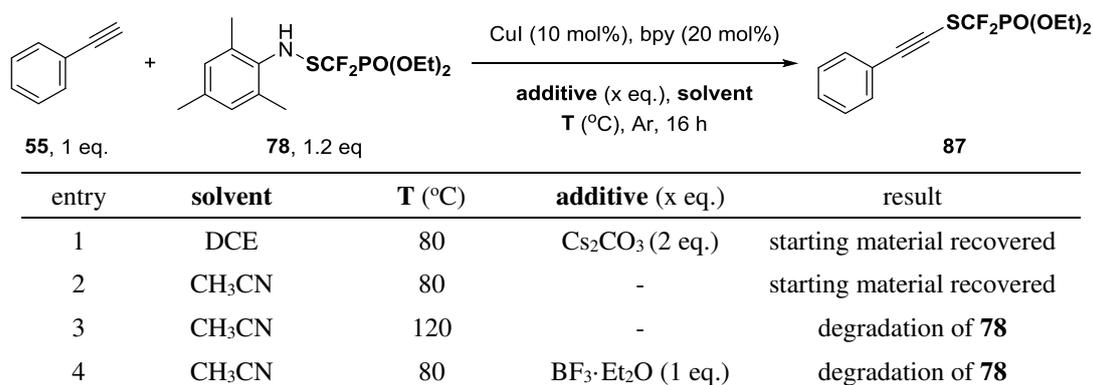
2.6.5 Reaction of alkynes with reagent **78**

To further examine the reactivity of the reagent **78**, we next studied the (diethyl phosphono)difluoromethylthiolation of alkynes. When phenylacetylene **55** was reacted with reagent **78** in the presence of a catalytic amount of nBuLi in THF at 70 °C,^{123n,o} no conversion of the starting material was observed (Table 44, entry 1). We speculated that the presence of the NH group in the reagent **78** might affect the transformation. However, the replacement of reagent **78** by **84I** did not afford the expected product either (Table 44, entry 2). We next tried to increase the amount of nBuLi to deprotonate the phenylacetylene **55**, followed by the addition of reagent **78**. Unfortunately, no conversion of the starting material was observed (Table 44, entry 3).

Table 44: Investigation of the reaction of alkynes with reagent **78**^a

^a Reaction conditions: **55** (0.1 mmol, 1 eq.), **78** or **84I** (0.12 mmol, 1.2 eq.), nBuLi (x eq.), THF (1 mL), Ar.

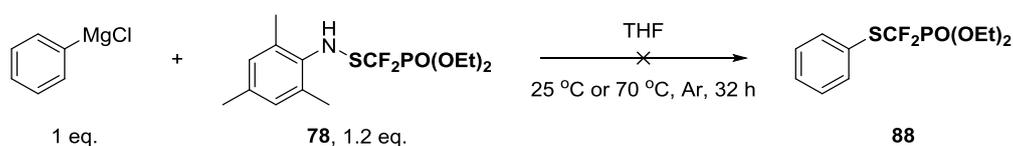
Since the expected product was not obtained, we decided to investigate the copper mediated (diethyl phosphono)difluoromethylthiolation of alkynes by using the reported reaction conditions.¹³⁶ When the reaction was performed at 80 °C using DCE as solvent, CuI as catalyst and Cs₂CO₃ as base (Table 45, entry 1), no expected product was detected and all the starting materials were recovered. Replacing the solvent with CH₃CN, no reaction occurred after heating the reaction at 80 °C for 16 h (Table 45, entry 2). Increasing the temperature to 120 °C led to the degradation of the reagent **78** (Table 45, entry 3). We considered that the addition of Lewis acid might be beneficial for the activation of the reagent. Thus, BF₃·Et₂O was used as additive for the reaction leading to the degradation of the reagent **78** (Table 45, entry 4).

Table 45: Cu-catalyzed (diethyl phosphono)difluoromethylthiolation of alkynes^a

^a Reaction conditions: **55** (0.1 mmol, 1 eq.), **78** (0.12 mmol, 1.2 eq.), solvent (1 mL), Ar, 16 h.

2.6.6 Reaction with phenylmagnesium chloride

In addition, the (diethyl phosphono)difluoromethylthiolation of phenylmagnesium chloride was tested to generate the corresponding product. We first carried out the reaction of phenylmagnesium chloride with reagent **78** at room temperature for 16 h. However, no expected product was observed. Heating the reaction mixture at 70 °C for 32 h did not afford the desired product either (Scheme 139).

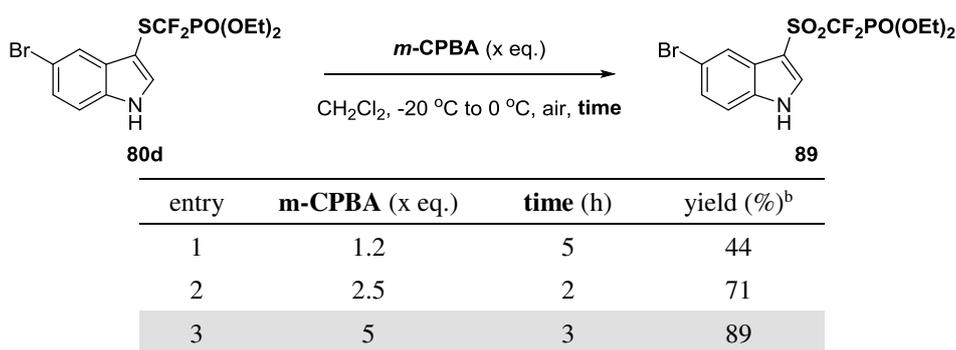


Scheme 139: Reaction with phenylmagnesium chloride with reagent **78**

2.6.7 Post-functionalization reactions

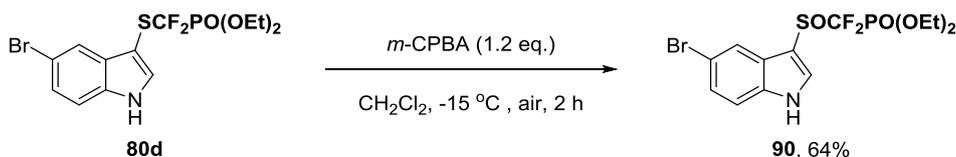
2.6.7.1 Oxidation

From the $\text{SCF}_2\text{PO}(\text{OEt})_2$ moiety, new functionalized fluorinated groups might be synthesized. The oxidation of the product **80** with a suitable oxidant might lead to the corresponding sulfone and sulfoxide. First, we treated the obtained product **80d** with *m*-CPBA in CH_2Cl_2 at -20 °C, which was then slowly warmed up to 0 °C and kept at that temperature for 5 h. In these reaction conditions, the starting material was partially converted into the corresponding sulfone **89** and was isolated in 44% yield (Table 46, entry 1). We then tried to investigate the amount of *m*-CPBA to improve the yield. When 2.5 equivalents of *m*-CPBA were used, the corresponding product **89** was obtained in 71% yield (Table 46, entry 2). Then, 5 equivalents of *m*-CPBA were used. The full conversion of **80d** was observed and the desired product **89** was obtained in 89% yield (Table 46, entry 3).

Table 46: Synthesis of sulfone **89**^a

^a Reaction conditions: **80d** (0.1 mmol, 1 eq.), m-CPBA (x eq.), CH₂Cl₂ (1 mL), -20 °C to 0 °C, air.

Aiming at selectively converting **80d** into the corresponding sulfoxide **90**, we then decreased the amount of m-CPBA to 1.2 equivalents and performed the reaction at a lower temperature. Pleasingly, the expected product was obtained in 64% yield after 2 h at -15 °C (Scheme 140).

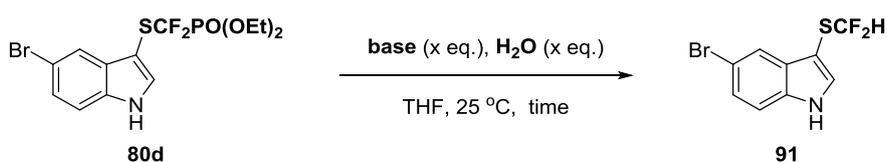
Scheme 140: Synthesis of sulfoxide **90**

2.6.7.2 Cleavage of the C-P bond

Since the SCF₂H group is considered as an emergent fluorinated moiety,²⁴⁸ we were wondering whether the SCF₂PO(OEt)₂ group could be converted into the SCF₂H unit. It was reported that the cleavage of the C-P bond would occur under basic conditions.²⁷⁹ Thus, we treated **80d** with LiOH and H₂O (5 eq.) in THF at 25 °C. However, no reaction occurred after stirring the reaction mixture for 24 h (Table 47, entry 1). We hypothesized that LiOH might not be basic enough to cleave the S-P bond, and more basic base should be investigated. Indeed, the replacement of LiOH by NaOH afforded the expected product **91** in 22% yield in 1 h (Table 47, entry 2). Pleasingly, the desired product **91** was obtained in 32% yield when only 1.2 equivalents of H₂O were employed (Table 47, entry 3).

²⁷⁹ Beier, P.; Alexandrova, A. V.; Zibinsky, M.; Surya Prakash, G. K. *Tetrahedron* **2008**, 64, 10977.

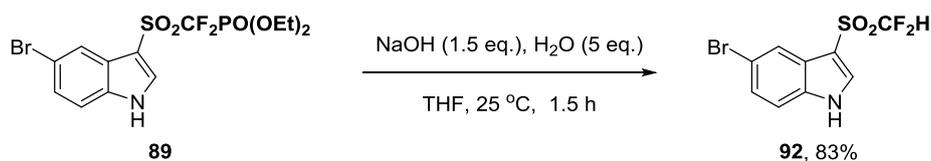
Table 47: Cleavage of the C-P bond



entry	base (x eq.)	H ₂ O (x eq.)	time (h)	yield (%)
1	LiOH (1.5 eq.)	5	24	-
2	NaOH (1.5 eq.)	5	1	22
3 ^b	NaOH (1.5 eq.)	1.2	4	32

^a Reaction conditions: **80d** (0.1 mmol, 1 eq.), base (x mmol, x eq.), H₂O (x mmol, x eq.), THF (1 mL), 25 °C. ^b Reaction performed on a 0.2 mmol scale.

In a similar manner, the SO₂CF₂PO(OEt)₂ group was converted into the corresponding SO₂CF₂H moiety providing the compound **92** in 89% yield (Scheme 141).

Scheme 141: Synthesis of compound **92**

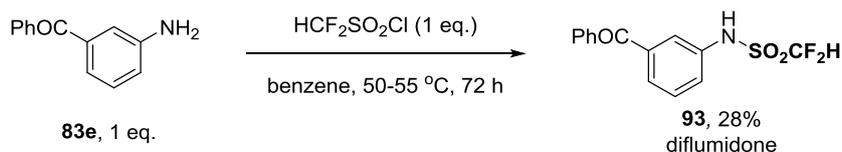
2.6.7.3 Synthesis of diflumidone

Diflumidone **93** is a non-steroidal anti-inflammatory drug,²⁸⁰ which is generally synthesized by using the rather expensive difluoromethanesulfonyl chloride²⁸¹ in a low yield (28%, Scheme 142).^{280b} Note that the HCF₂SO₂Cl is generally prepared in two-steps from the phenylmethanethiol and the ozone-depleting HCF₂Cl. In this context, we would like to apply the established methodology for the synthesis of diflumidone. Indeed, we anticipated that its preparation could be achieved in a three-steps sequence: 1) the (diethyl phosphono)difluoromethylthiolation of the 3-aminobenzophenone **83e**, 2) the oxidation of the **84e** and 3) the cleavage of the S-P bond (Scheme 142).

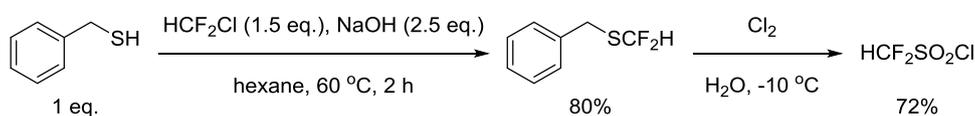
²⁸⁰ (a) Vigdahl, R. L.; Tukey, R. H. *Biochem. Pharmacol.* **1977**, 26, 307; (b) Harrington, J. K.; Robertson, J. E.; Kvam, D. C.; Hamilton, R. R.; McGurran, K. T.; Trancik, R. J.; Swingle, K. F.; Moore, G. G. I.; Gerster, J. F. J. *Med. Chem.* **1970**, 13, 137.

²⁸¹ difluoromethanesulfonyl chloride (CAS: 1512-30-7): 25 mg/48.6€, Sigma-Aldrich Ltd, 2017.

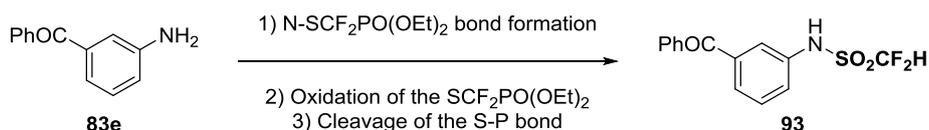
Traditional approach for the synthesis of diflumidone:



Synthesis of the $\text{HCF}_2\text{SO}_2\text{Cl}$:

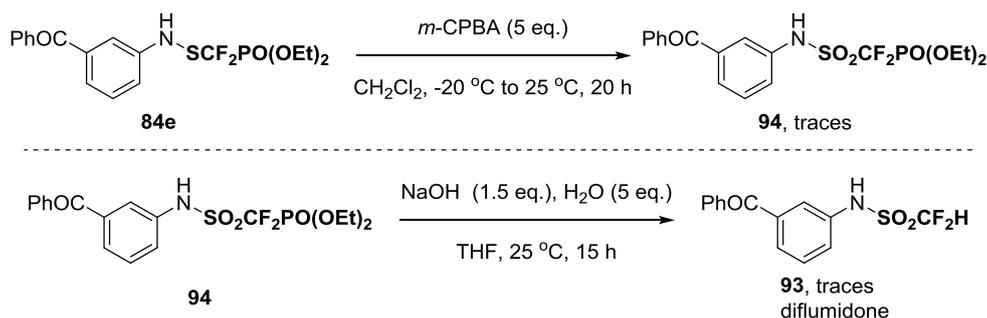


Our approach for the synthesis of diflumidone:



Scheme 142: The synthesis of diflumidone: traditional synthetic pathway and our approach

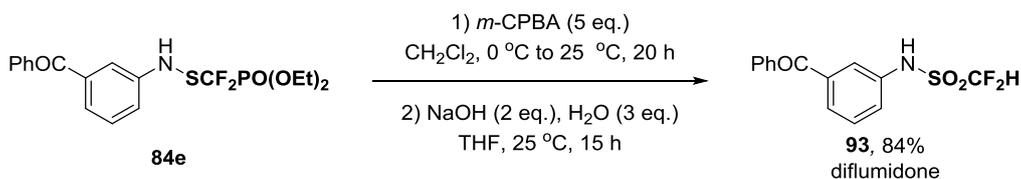
Since we have obtained the product **84e** from the (diethyl phosphono)difluoromethylthiolation of 3-aminobenzophenone **83e**, we then tried to oxidize it with *m*-CPBA. However, we found that **84e** was less reactive and only traces of the product were obtained in 20 h. Further attempts to convert sulfone **94** into the diflumidone **93** afforded traces of the product (Scheme 143). In the course of our investigations, we met some issues during the extraction as the product was not well soluble in dichloromethane or diethyl ether, which might explain the low yield.



Scheme 143: Synthesis of diflumidone in two steps from **84e**

In order to improve the yield, we decided to use ethyl acetate for the extraction and engaged the obtained sulfone **94** directly into the next step (cleavage of the S-P bond) without purification. Finally, the diflumidone **93** was furnished in 84% yield starting from **84e** (Scheme 144). This approach offered a new synthetic pathway to

access such important compound efficiently.²⁸²



Scheme 144: Synthesis of diflumidone in a two steps/one-purification sequence from **84e**

2.7 Conclusion

In this section of this thesis, a newly designed electrophilic $\text{SCF}_2\text{PO(OEt)}_2$ reagent was successfully synthesized in two steps from the corresponding and readily available 2,4,6-trimethylaniline and $\text{TMSCF}_2\text{PO(OEt)}_2$.²⁸³ This new reagent was efficiently applied to the functionalization of $\text{C(sp}^2\text{)}$ and $\text{C(sp}^3\text{)}$ centers. In addition, nucleophiles such as primary and secondary amines as well as aromatic and aliphatic thiols were efficiently functionalized. The potential of the $\text{SCF}_2\text{PO(OEt)}_2$ group was further investigated by its conversion into the corresponding SCF_2H and $\text{SO}_2\text{CF}_2\text{H}$ groups. Furthermore, thanks to the new electrophilic $\text{SCF}_2\text{PO(OEt)}_2$ reagent, the synthesis of diflumidone, a biorelevant molecule, was accomplished in high yield (84% over two steps).

²⁸² Note that since the reaction for the cleavage of S-P bond was performed in basic conditions, it is necessary to neutralize the reaction mixture with 2M HCl till the pH = 2 before the extraction to ensure a good yield.

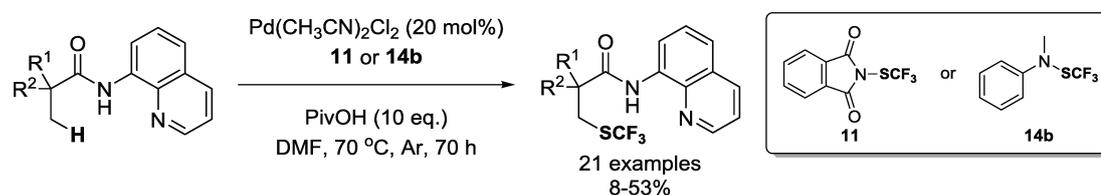
²⁸³ Xiong, H.-Y.; Bayle, A.; Pannecoucke, X.; Besset, T. *Angew. Chem., Int. Ed.* **2016**, 55, 13490.

**General Conclusion
and
Perspectives**

1 Conclusion

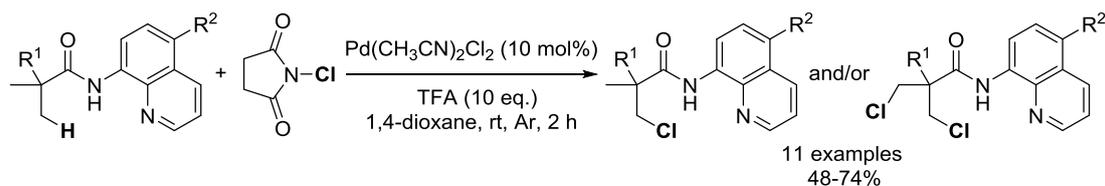
In this Ph.D. thesis, we have focused on the development of new methodologies for the direct introduction of fluorinated groups or a chlorine atom onto aliphatic molecules by C-H bond functionalization as well as on the design of new electrophilic fluorinated reagents and the study of their applications.

First, an unprecedented methodology for the Pd-catalyzed trifluoromethylthiolation of primary and secondary C(sp³)-H bonds on aliphatic acid derivatives was developed. The combination of an electrophilic SCF₃ reagent with a Brønsted acid (PivOH) using a bidentate directing group allowed the Pd-catalyzed direct introduction of a SCF₃ moiety on a C(sp³) center under mild conditions. Various amides were compatible and a panel of alkyl trifluoromethylated sulfides has been prepared in a regio-selective manner (Scheme).



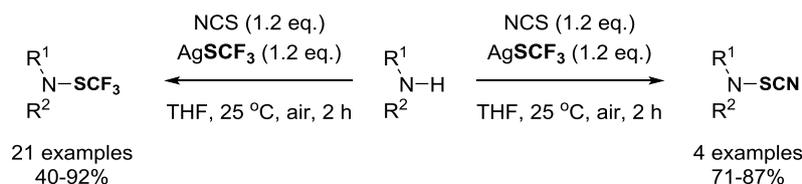
Scheme 145: Pd-catalyzed directed trifluoromethylthiolation of unactivated aliphatic amides

Taking benefit from this first experience in transition metal-catalyzed C(sp³)-H bond activation, we then have developed a Pd-catalyzed directed chlorination of unactivated C(sp³)-H bond at room temperature (Scheme 146). By the use of the amide derived from 8-aminoquinoline as a directing group, the selective chlorination of aliphatic amides was achieved in moderate to good yields at room temperature in the presence of N-chlorosuccinimide. Valuable chlorinated molecules were constructed by this approach and the dichlorination reaction could also be achieved by using slightly modified reaction conditions.



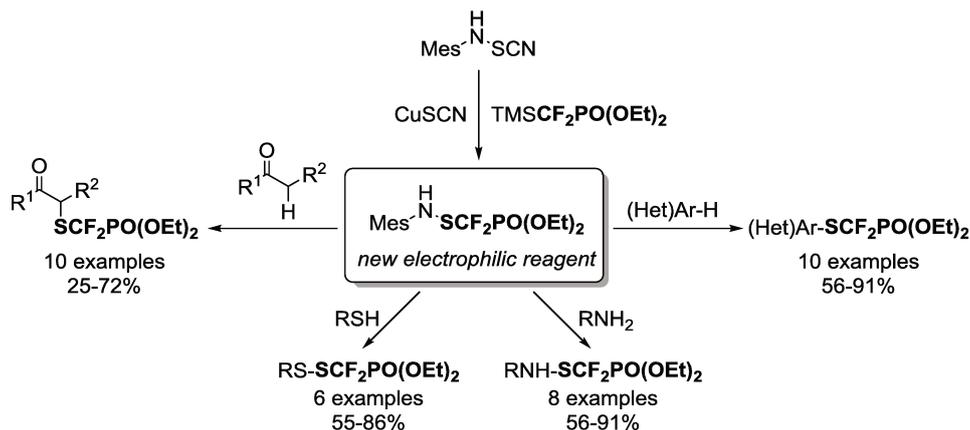
Scheme 146: Pd-catalyzed directed chlorination of unactivated C(sp³)-H bonds at room temperature

Moreover, an oxidative trifluoromethylthiolation of amines for the construction of a N-SCF₃ bond was developed. By using AgSCF₃ and a suitable oxidant, a panel of primary and secondary amines was functionalized in good yields at room temperature. This general approach was further applied to the thiocyanation of anilines and the corresponding products can be readily used as an electrophilic thiocyanating reagent (Scheme 147).



Scheme 147: Synthesis of N-(trifluoromethylthio)aniline and N-(cyanosulfanyl)aniline derivatives

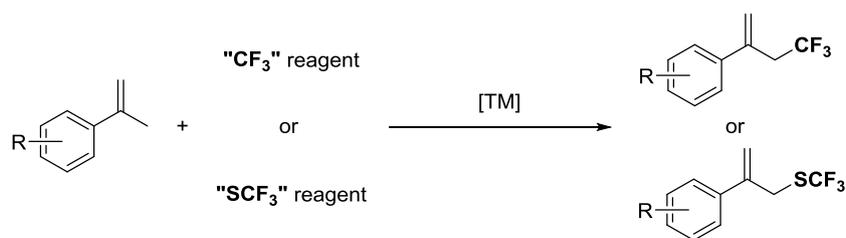
At last, a new, bench-stable and easy-to-handle electrophilic SCF₂PO(OEt)₂ reagent **78** was synthesized from the readily available N-(cyanosulfanyl)aniline derivative and TMSCF₂PO(OEt)₂ reagent. This new reagent was efficiently applied to the functionalization of C(sp²) and C(sp³) centers. In addition, nucleophiles such as primary or secondary amines and aromatic or aliphatic thiols were efficiently functionalized (Scheme 148).

Scheme 148: Synthesis of the $\text{SCF}_2\text{PO(OEt)}_2$ reagent **78** and its applications

2 Perspectives

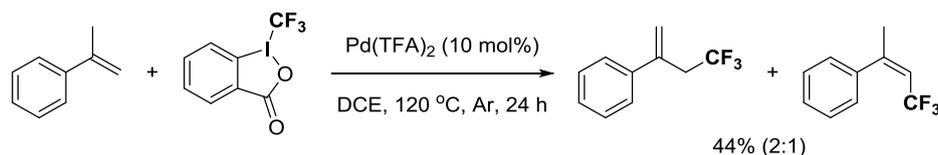
2.1 Transition metal-catalyzed trifluoromethylation and trifluoromethylthiolation of branched terminal alkenes

The trifluoromethylated or trifluoromethylthiolated alkenes are important building blocks for various synthetic purposes. However, the direct selective installation of a CF_3 or a SCF_3 group onto an allylic position remains a challenging task. To date, only few examples dealt with the allylic trifluoromethylation or trifluoromethylthiolation affording the linear functionalized alkenes. Moreover, methodologies for the synthesis of branched trifluoromethylated or trifluoromethylthiolated alkenes are limited to the use of pre-functionalized alkenes as substrates. In contrast, to the best of our knowledge, transition metal-catalyzed trifluoromethylation or trifluoromethylthiolation of $\text{C}(\text{sp}^3)\text{-H}$ bond of branched terminal alkenes remained unprecedented. In this context, we would like to develop an efficient pathway for the synthesis of branched trifluoromethylated and trifluoromethylthiolated alkenes (Scheme 149).



Scheme 149: Transition metal-catalyzed trifluoromethylation and trifluoromethylation of branched terminal alkenes

Preliminary tests on trifluoromethylation of the α -methylstyrene showed that the combination of a palladium catalyst and the Togni reagent would afford the expected product in an encouraging yield (44%) as a mixture of two isomers (ratio 2:1) (Scheme 150).

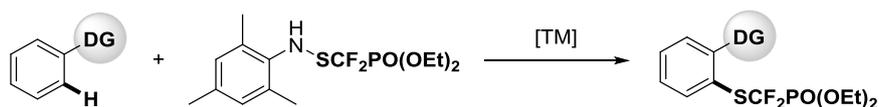


Scheme 150: Pd-catalyzed trifluoromethylation branched terminal alkene

Next, we will pursue our investigations to selectively form a $C(sp^3)$ - CF_3 bond. In that purpose, several parameters such as catalysts, temperatures, solvents, additives, ligands and trifluoromethylation reagents will be screened. Moreover, the study of the trifluoromethylthiolation of the branched terminal alkenes will be carried out.

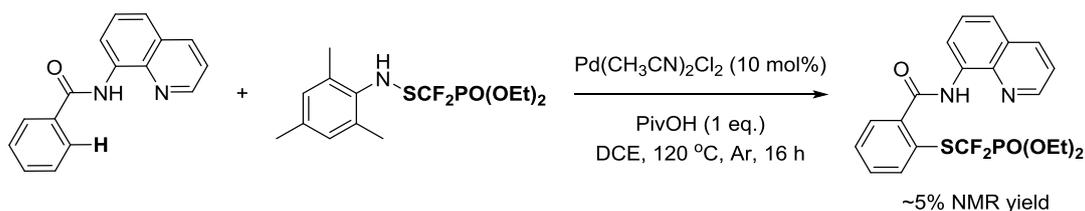
2.2 Introduction of $SCF_2PO(OEt)_2$ group onto molecules by C-H bond functionalization

With the new $SCF_2PO(OEt)_2$ reagent **78** in hand, two main objectives for the future work are envisioned to extend its application. First, we will focus on the introduction of the $SCF_2PO(OEt)_2$ group by transition metal-catalyzed C-H bond functionalization on aromatic derivatives bearing a suitable directing group (Scheme 151).



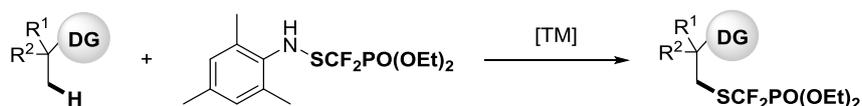
Scheme 151: Transition metal-catalyzed (diethyl phosphono)difluoromethylthiolation of aromatic derivatives

Indeed, several attempts have already been performed for such approach. Preliminary result showed that when amide derived from 8-aminoquinoline was used as the directing group, $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (10 mol%) as catalyst and 1 equivalent of PivOH as additive, the expected product was obtained in a low yield (about 5%) after heating the reaction mixture at 120 °C for 16 h (Scheme 152). Note that the product was isolated and its structure was confirmed by NMR analysis. Despite the low yield, this important result represents a proof-of-concept of such transformation. In order to improve the yield, an optimization study will be conducted.



Scheme 152: Pd-catalyzed (diethyl phosphono)difluoromethylthiolation of amide derivative

Taking benefit from our experience in the transition metal-catalyzed $\text{C}(\text{sp}^3)\text{-H}$ bond functionalization, we will then turn our attention to the more challenge (diethyl phosphono)difluoromethylthiolation of aliphatic chains by C-H bond functionalization (Scheme 153). Various transition metals, such as palladium, copper, cobalt and nickel, which are frequently used in the functionalization of unactivated $\text{C}(\text{sp}^3)\text{-H}$ bonds will be investigated.



Scheme 153: Transition metal-catalyzed (diethyl phosphono)difluoromethylthiolation of alkyl chains

Experimental Section

General information

All reactions were carried out using oven-dried glassware and magnetic stirring. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Analytical thin layer chromatography was performed on silica gel aluminum plates with F-254 indicator and visualized by UV light (254 nm) and/or chemical staining with a KMnO_4 solution or a phosphomolybdic acid solution. Flash column chromatography was performed using 0.040 – 0.063 mm silica gel or a Biotage Isolera One flash purification system. ^1H NMR spectra were recorded on a Bruker DXP 300 MHz spectrometer at 300.13 MHz, ^{13}C NMR spectra at 75.5 MHz, ^{19}F NMR spectra at 282.4 MHz and ^{31}P NMR at 121.5 MHz. Chemical shifts (δ) are quoted in ppm relative to CDCl_3 (^1H) and CFCl_3 (^{19}F). Coupling constants (J) are quoted in Hz. The following abbreviations were used to show the multiplicities: s: singlet, d: doublet, t: triplet, q: quadruplet, dd: doublet of doublet, m: multiplet. The residual solvent signals were used as references (THF- d_8 : δ H = 1.72 ppm, δ H = 3.58 ppm, δ C = 67.21 ppm, δ C = 25.31 ppm. CDCl_3 : δ H = 7.26 ppm, δ C = 77.00 ppm or relative to external CFCl_3 , δ F = 0 ppm). High-resolution mass spectrometry (HRMS) was carried out on an electrospray ionization mass spectrometer with a micro-TOF analyzer. IR spectra were recorded on a PerkinElmer Spectrum 100, the wave numbers (ν) of recorded IR-signals (ATR) are quoted in cm^{-1} . Melting points were reported for new compounds, recorded on a Heizbank system kofler WME and were uncorrected.

Materials

Anhydrous acetonitrile, DMF and 1,4-dioxane were purchased from Acros Organics (Solvents Extra Dry over Molecular Sieve, AcroSeal[®]). Dichloromethane and NMP were purified by distillation over CaH_2 . Tetrahydrofuran (THF) was distilled over sodium/benzophenone prior to use. CsF was purchased from Apollo Scientific Ltd and Sigma-Aldrich Ltd, $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ was purchased from

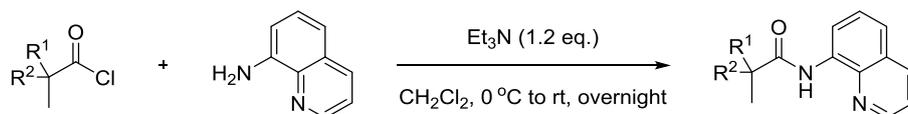
Sigma-Aldrich Ltd or TCI Ltd. PivOH and CuSCN was purchased from Sigma-Aldrich Ltd. Chlorotrimethylsilane was purchased from Sigma-Aldrich Ltd and freshly distilled over CaH₂. All the amine substrates and N-chlorosuccinimide (NCS) were commercially available and were used as received unless otherwise stated.

1 Palladium(II)-Catalyzed Directed Trifluoromethylthiolation of Unactivated C(sp³)-H Bonds

1.1 General Procedure for the Synthesis of 18

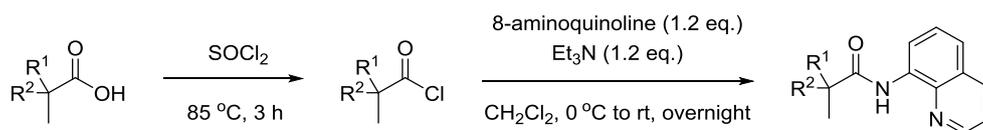
The known trifluoromethylated reagents and amides the were prepared according to the literature procedures: **11**,¹¹⁵ **12**,¹¹⁵ **13**,¹¹⁸ **14b**,¹¹⁸ **18a**,¹⁴⁹ **18c**,¹⁴⁹ **18d**,¹⁴⁹ **18e**,¹⁴⁹ **18f**,^{54d,149} **18g**,^{54d,149} **18h**,^{54d,149} **18k**,^{54d,149} **18u**.¹⁴⁹

General procedure A:



To a solution of 8-aminoquinoline (1 eq.) and Et₃N (1.2 eq.) in CH₂Cl₂ (C = 0.25 mol/L) was slowly added, at 0 °C, the acid chloride (1.2 eq.), and the reaction mixture was allowed to warm to room temperature and stirred overnight. Then, the reaction mixture was diluted with CH₂Cl₂ and washed with water and saturated aqueous NaHCO₃. The aqueous layers were extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, filtered and evaporated under vacuum. The residue was purified by flash column chromatography to afford the corresponding amide.

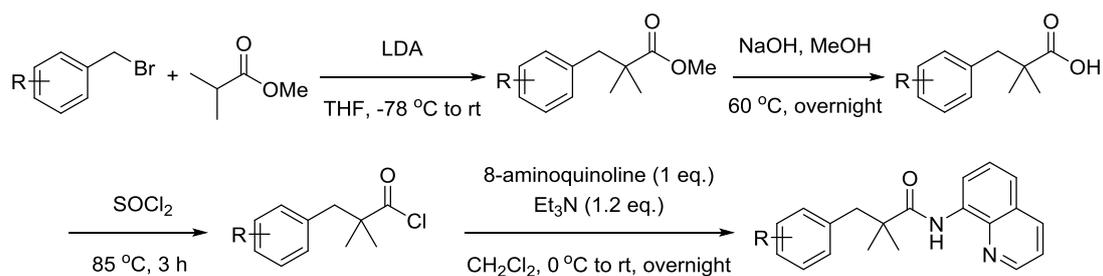
General procedure B:



To an oven-dried flask containing a carboxylic acid (1.2 eq.) was slowly added SOCl₂ (1.2 M). The reaction mixture was heated at 85 °C for 3 h and then evaporated under

vacuum to provide the crude acid chloride, which was used immediately without further purification. CH_2Cl_2 was added to the acid chloride (0.4 M). Then, a solution of 8-aminoquinoline (1 eq.) and Et_3N (1.2 eq.) in CH_2Cl_2 (0.1 M) was added dropwise at $0\text{ }^\circ\text{C}$ to the solution of acid chloride in CH_2Cl_2 . The reaction mixture was allowed to warm up to room temperature and stirred overnight. Then, the reaction mixture was diluted with CH_2Cl_2 and washed with water and saturated aqueous NaHCO_3 . The aqueous layers were extracted with CH_2Cl_2 ($3 \times 50\text{ mL}$). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel to afford the corresponding amide.

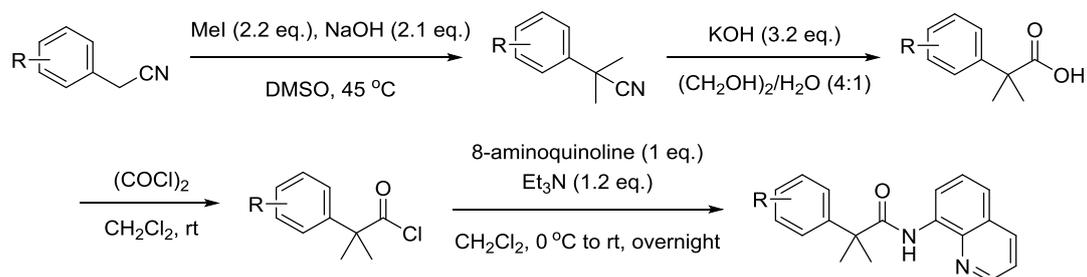
General procedure C:



To a solution of diisopropylamine (DIPA) (1.25 eq.) in THF (0.4 M) at $-78\text{ }^\circ\text{C}$ was slowly added $n\text{BuLi}$ (1.6 M in hexane, 1.17 eq.), and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was then cooled down to $-78\text{ }^\circ\text{C}$, and methyl isobutyrate (1 eq.) was added dropwise at the same temperature. The reaction mixture was stirred for 1 h at $-78\text{ }^\circ\text{C}$. Then, a solution of the corresponding benzyl bromide (1.1 eq.) in THF (4.5 M) was added dropwise. After the addition, the mixture was slowly warmed up to room temperature and stirred overnight. Then, the reaction mixture was quenched with water at $0\text{ }^\circ\text{C}$ and extracted with EtOAc (50 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and then evaporated under vacuum to give the corresponding ester. To the obtained ester was added an aqueous solution of NaOH (2 M) and methanol, and the reaction mixture was stirred at $60\text{ }^\circ\text{C}$ overnight. Once the reaction mixture was cooled to room

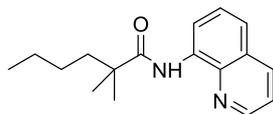
temperature, methanol was removed under vacuum and the mixture was diluted with water and extracted with CH_2Cl_2 (3×50 mL). Then, the aqueous layer was acidified with 2 M HCl until $\text{pH} = 2$ and extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and evaporated under vacuum to afford the crude carboxylic acid, which was used directly for the next step without further purification. To an oven-dried round-bottom flask containing a carboxylic acid (1.2 eq.) was slowly added SOCl_2 (1.2 M). The reaction mixture was refluxed at 85 °C for 3 h and then evaporated under vacuum to provide the crude acid chloride, which was used immediately without further purification. Then, a solution of 8-aminoquinoline (1 eq.) and Et_3N (1.2 eq.) in CH_2Cl_2 (1.0 M) was added dropwise at 0 °C to a solution of acid chloride (1 eq.) in CH_2Cl_2 (0.3 M). After addition, the reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with water and saturated aqueous NaHCO_3 . The aqueous layers were extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel to afford the corresponding amide.

General procedure D:



To a solution of benzyl cyanide (1 eq.), MeI (2.2 eq.) in DMSO (2 M) was added a 50 wt % aqueous solution of NaOH (2.1 eq.) via a syringe pump over 1 h at 45 °C. After the addition, the reaction mixture was stirred for 1 h. Once cooled down to room temperature, water was added to the solution and the aqueous layer was extracted with hexane/ Et_2O (1:1, 3×50 mL). The combined organic layers were dried over MgSO_4 ,

filtered and evaporated under vacuum to afford the corresponding dialkylated product, which was used directly for the next step without further purification. To a 100 mL three-necked round-bottom flask with a reflux condenser were added dialkylated benzyl cyanide (1 eq.) and ethylene glycol/H₂O (4:1, 1 M). Solid KOH (3.2 eq.) was added portionwise to the mixture. The reaction mixture was stirred at 100 °C for 48 h. Once cooled to room temperature, the mixture was washed with CHCl₃ (3 × 50 mL). Then, the aqueous layer was acidified with 2 M HCl until pH = 2 and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and evaporated under vacuum to afford the corresponding carboxylic acid, which was used directly for the next step without further purification. The acyl chloride was prepared according to the literature procedure²⁸⁴ with oxalyl chloride and then engaged with 8-aminoquinoline according to procedure A.



Chemical Formula: C₁₇H₂₂N₂O
Molecular Weight: 270.38 g/mol

2,2-Dimethyl-N-(quinolin-8-yl)hexanamide 18b. Following the general procedure B, **18b** was obtained as a colorless oil (78% overall yield) starting from 2,2-dimethylhexanoic acid. R_f(pentane/EtOAc = 90:10): 0.42.

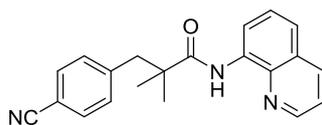
¹H NMR (300.13 MHz, CDCl₃) δ 10.16 (broad s, 1H), 8.75 – 8.67 (m, 2H), 8.02 (dd, J = 8.1, 1.5 Hz, 1H), 7.47 – 7.27 (m, 3H), 1.66 – 1.55 (m, 2H), 1.30 (s, 6H), 1.27 – 1.18 (m, 4H), 0.78 (t, J = 6.9 Hz, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 176.6, 148.1, 138.7, 136.2, 134.6, 127.9, 127.4, 121.4, 121.1, 116.1, 43.7, 41.3, 27.1, 25.6, 23.2, 13.9.

IR (neat, cm⁻¹) ν: 3367, 2960, 1680, 1523, 1484, 1387, 1325, 1253, 1147, 1009, 790, 680.

HRMS (ESI⁺) calcd for C₁₇H₂₃N₂O m/z 271.1810 [M+H]⁺, Found 271.1802.

²⁸⁴ Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. Chem. Eur. J. **2011**, 17, 7167.



Chemical Formula: C₂₁H₁₉N₃O
Molecular Weight: 329.40 g/mol

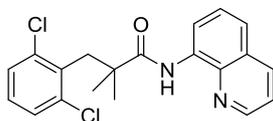
3-(4-Cyanophenyl)-2,2-dimethyl-N-(quinolin-8-yl)propanamide 18i. Following the general procedure C, **18i** was obtained as a pale yellow vitreous solid (13% overall yield) starting from 4-(bromomethyl)benzonitrile. R_f (pentane/EtOAc = 90:10): 0.21.

¹H NMR (300.13 MHz, CDCl₃) δ 10.11 (broad s, 1H), 8.79 (dd, J = 6.9, 2.1 Hz, 1H), 8.73 (dd, J = 4.2, 1.5 Hz, 1H), 8.16 (dd, J = 8.4, 1.5 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.49 – 7.41 (m, 3H), 7.30 (d, J = 8.1 Hz, 2H), 3.08 (s, 2H), 1.44 (s, 6H).

¹³C NMR (75.5 MHz, CDCl₃) δ 175.0, 148.2, 143.7, 138.6, 136.3, 134.1, 131.8, 130.9, 127.9, 127.3, 121.7, 121.6, 118.9, 116.3, 110.3, 46.9, 45.1, 25.4.

IR (neat, cm⁻¹) v: 3360, 2225, 1672, 1470, 1418, 1379, 1311, 917, 858, 798, 690.

HRMS (ESI⁺) calcd for C₂₁H₂₀N₃O m/z 330.1606 [M+H]⁺, Found 330.1597.



Chemical Formula: C₂₀H₁₈Cl₂N₂O
Molecular Weight: 373.28 g/mol

3-(2,6-Dichlorophenyl)-2,2-dimethyl-N-(quinolin-8-yl)propanamide 18j.

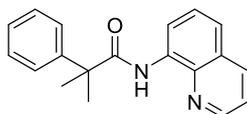
Following the general procedure C, **18j** was obtained as a white solid (74% overall yield) starting from 2-(bromomethyl)-1,3-dichlorobenzene. R_f (pentane/EtOAc = 90:10): 0.40.

¹H NMR (300.13 MHz, CDCl₃) δ 10.22 (s, 1H), 8.82 (dd, J = 7.5, 1.5 Hz, 1H), 8.72 (dd, J = 4.2, 1.5 Hz, 1H), 8.15 (dd, J = 8.4, 1.5 Hz, 1H), 7.59 – 7.47 (m, 2H), 7.42 (dd, J = 8.4, 4.2 Hz, 1H), 7.26 (d, J = 3.0 Hz, 1H), 7.23 (s, 1H), 7.05 (dd, J = 8.4, 7.5 Hz, 1H), 3.50 (s, 2H), 1.53 (s, 6H).

¹³C NMR (75.5 MHz, CDCl₃) δ 175.7, 148.0, 138.8, 137.1, 136.2, 134.8, 134.7, 128.4, 128.0, 127.8, 127.5, 121.4, 121.2, 116.3, 45.6, 40.0, 25.7.

IR (neat, cm⁻¹) v: 3360, 2947, 1671, 1528, 1485, 1142, 1053, 917, 825, 791, 678.

HRMS (ESI⁺) calcd for C₂₀H₁₉Cl₂N₂O m/z 373.0874 [M+H]⁺, Found 373.0867.



Chemical Formula: C₁₉H₁₈N₂O
Molecular Weight: 290.37 g/mol

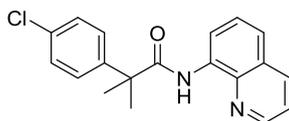
2-Methyl-2-phenyl-N-(quinolin-8-yl)propanamide 18l. Following the general procedure D, **18l** was obtained as a white vitrous solid (24% overall yield) starting from 2-phenylpropanenitrile. R_f (pentane/EtOAc = 90:10): 0.33.

¹H NMR (300.13 MHz, CDCl₃) δ 9.89 (broad s, 1H), 8.74 (dd, J = 7.2, 1.5 Hz, 1H), 8.64 (dd, J = 4.2, 1.5 Hz, 1H), 8.10 (dd, J = 8.4, 1.5 Hz, 1H), 7.63 – 7.42 (m, 5H), 7.41 – 7.32 (m, 3H), 1.76 (s, 6H).

¹³C NMR (75.5 MHz, CDCl₃) δ 175.1, 148.2, 143.5, 138.6, 136.1, 134.5, 132.9, 128.8, 127.8, 127.3, 121.5, 121.4, 116.0, 48.0, 26.9. one carbon is overlapped.

IR (neat, cm⁻¹) v: 3340, 2973, 1676, 1524, 1488, 1388, 1324, 1104, 826, 681.

HRMS (ESI⁺) calcd for C₁₉H₁₉N₂O m/z 291.1497 [M+H]⁺, Found 291.1487.



Chemical Formula: C₁₉H₁₇ClN₂O
Molecular Weight: 324.81 g/mol

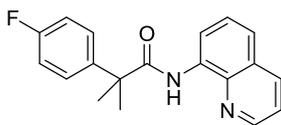
2-(4-Chlorophenyl)-2-methyl-N-(quinolin-8-yl)propanamide 18m. Following the general procedure D, **18m** was obtained as a pale yellow vitrous solid (23% overall yield) starting from (4-chlorophenyl)acetonitrile. R_f (pentane/EtOAc = 90:10): 0.46.

¹H NMR (300.13 MHz, CDCl₃) δ 9.87 (broad s, 1H), 8.77 (d, J = 7.5 Hz, 1H), 8.60 (dd, J = 4.2, 1.5 Hz, 1H), 8.09 (dd, J = 8.1, 1.5 Hz, 1H), 7.57 – 7.32 (m, 7H), 1.79 (s, 6H).

¹³C NMR (75.5 MHz, CDCl₃) δ 175.8, 148.1, 144.8, 138.6, 136.1, 134.7, 128.7, 127.8, 127.3, 127.0, 126.3, 121.4, 121.2, 115.9, 48.4, 27.0.

IR (neat, cm⁻¹) v: 2929, 1666, 1520, 1387, 1090, 829, 656.

HRMS (ESI⁺) calcd for C₁₉H₁₈ClN₂O m/z 324.1029 [M+H]⁺, Found 324.1035.



Chemical Formula: $C_{19}H_{17}FN_2O$
Molecular Weight: 308.36 g/mol

2-(4-Fluorophenyl)-2-methyl-N-(quinolin-8-yl)propanamide 18n. Following the general procedure D, **18n** was obtained as a pale yellow vitrous solid (15% overall yield) starting from 4-fluorophenylacetonitrile. R_f (pentane/EtOAc = 90:10): 0.55.

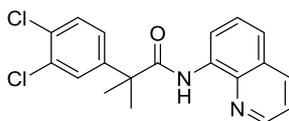
1H NMR (300.13 MHz, $CDCl_3$) δ 9.88 (broad s, 1H), 8.76 (dd, $J = 7.5, 1.5$ Hz, 1H), 8.62 (dd, $J = 4.2, 1.5$ Hz, 1H), 8.09 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.55 – 7.43 (m, 4H), 7.37 (dd, $J = 8.1, 4.2$ Hz, 1H), 7.14 – 7.04 (m, 2H), 1.77 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.5, 161.8 (d, $J = 246.1$ Hz), 148.2, 140.7 (d, $J = 3.0$ Hz), 138.6, 136.1, 134.5, 128.1 (d, $J = 7.6$ Hz), 127.8, 127.2, 121.5, 121.3, 115.9, 115.5 (d, $J = 21.1$ Hz), 47.9, 27.1.

^{19}F NMR (282.4 MHz, $CDCl_3$) δ – 116.5.

IR (neat, cm^{-1}) ν : 3320, 2980, 1669, 1511, 1484, 1384, 1324, 1232, 1151, 1097, 821, 785.

HRMS (ESI⁺) calcd for $C_{19}H_{18}FN_2O$ m/z 309.1403 [M+H]⁺, Found 309.1412.



Chemical Formula: $C_{19}H_{16}Cl_2N_2O$
Molecular Weight: 359.25 g/mol

2-(3,4-Dichlorophenyl)-2-methyl-N-(quinolin-8-yl)propanamide 18o. Following the general procedure D, **18o** was obtained as a pale yellow oil (7% overall yield) starting from 3,4-dichlorophenylacetonitrile. R_f (pentane/EtOAc = 82:8): 0.61.

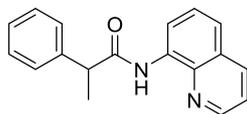
1H NMR (300.13 MHz, $CDCl_3$) δ 9.95 (broad s, 1H), 8.72 (d, $J = 6.9$ Hz, 1H), 8.68 (d, $J = 4.2$ Hz, 1H), 8.12 (d, $J = 8.1$ Hz, 1H), 7.63 (d, $J = 1.8$ Hz, 1H), 7.46 – 7.45 (m, 3H), 7.44 – 7.33 (m, 2H), 1.76 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.3, 148.3, 145.3, 138.6, 136.2, 134.3, 132.8, 131.1,

130.6, 128.5, 127.8, 127.3, 126.0, 121.6, 121.6, 116.1, 48.0, 26.8.

IR (neat, cm^{-1}) ν : 2927, 1664, 1526, 1384, 1090, 829, 658.

HRMS (ESI⁺) calcd for $\text{C}_{19}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}$ m/z 359.0718 [M+H]⁺, Found 359.0713.



Chemical Formula: $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$
Molecular Weight: 276.34 g/mol

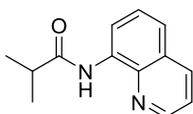
2-Phenyl-N-(quinolin-8-yl)propanamide 18p. Following the general procedure B, **18p** was obtained as a white vitreous solid (72% overall yield) starting from 2-phenylpropionic acid. R_f (petroleum ether/EtOAc = 90:10): 0.36.

¹H NMR (300.13 MHz, CDCl_3) δ 9.90 (broad s, 1H), 8.77 (dd, $J = 7.2, 1.8$ Hz, 1H), 8.71 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.11 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.55 – 7.44 (m, 4H), 7.43 – 7.35 (m, 3H), 7.33 – 7.27 (m, 1H), 3.94 (q, $J = 7.2$ Hz, 1H), 1.70 (d, $J = 7.2$ Hz, 3H).

¹³C NMR (75.5 MHz, CDCl_3) δ 172.5, 148.0, 141.0, 138.3, 136.0, 134.4, 128.8, 127.7, 127.6, 127.2, 121.3, 116.1, 65.7, 48.5, 18.5, 15.2.

IR (neat, cm^{-1}) ν : 3340, 2803, 1741, 1688, 1523, 1482, 1228, 823.

HRMS (ESI⁺) calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}$ m/z 277.1341 [M+H]⁺, Found 277.1334.



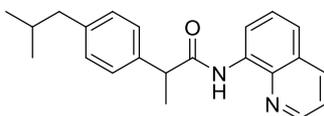
Chemical Formula: $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$
Molecular Weight: 214.27 g/mol

N-(quinolin-8-yl)isobutyramide 18q. Following the general procedure A, **18q** was obtained as a yellow oil (93% overall yield) starting from isobutyryl chloride. R_f (petroleum ether/EtOAc = 91:9): 0.47.

¹H NMR (300.13 MHz, CDCl_3) δ 9.90 (broad s, 1H), 8.84 – 8.76 (m, 2H), 8.15 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.59 – 7.40 (m, 3H), 2.85 – 2.70 (m, 1H), 1.36 (d, $J = 6.9$ Hz, 6H). **¹³C NMR** (75.5 MHz, CDCl_3) δ 175.7, 148.1, 138.5, 136.3, 134.6, 127.9, 127.4, 121.5, 121.3, 116.4, 37.1, 19.7.

IR (neat, cm^{-1}) ν : 3353, 2968, 1684, 1520, 1483, 1422, 1383, 1322, 1155, 936, 825, 790, 673.

HRMS (ESI^+) calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}$ m/z 215.1184 $[\text{M}+\text{H}]^+$, Found 215.1181.



Chemical Formula: $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}$
Molecular Weight: 332.45 g/mol

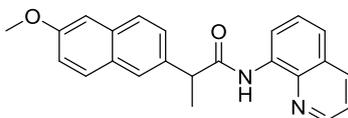
2-(4-Isobutylphenyl)-N-(quinolin-8-yl)propanamide 18r. Following the general procedure B, **18r** was obtained as a white vitrous solid (63% overall yield) starting from 2-(4-isobutylphenyl)propanoic acid. R_f (pentane/EtOAc = 90:10): 0.36.

^1H NMR (300.13 MHz, CDCl_3) δ 9.88 (broad s, 1H), 8.78 (dd, $J = 7.2, 1.8$ Hz, 1H), 8.66 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.10 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.54 – 7.43 (m, 2H), 7.41 – 7.35 (m, 3H), 7.17 (d, $J = 8.1$ Hz, 2H), 3.91 (q, $J = 7.2$ Hz, 1H), 2.48 (d, $J = 7.2$ Hz, 2H), 1.78 – 1.95 (m, 1H), 1.69 (d, $J = 7.2$ Hz, 3H), 0.91 (d, $J = 6.6$ Hz, 6H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 173.1, 148.0, 140.8, 138.5, 138.2, 136.2, 134.6, 129.7, 127.8, 127.5, 127.3, 121.4, 121.3, 116.2, 48.3, 45.0, 30.2, 22.4, 18.5.

IR (neat, cm^{-1}) ν : 3347, 2953, 1683, 1521, 1484, 1423, 1323, 1161, 922, 825, 790, 755.

HRMS (ESI^+) calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}$ m/z 333.1967 $[\text{M}+\text{H}]^+$, Found 333.1980.



Chemical Formula: $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2$
Molecular Weight: 356.43 g/mol

(S)-2-(6-methoxynaphthalen-2-yl)-N-(quinolin-8-yl)propanamide 18s. Following the general procedure B, **18s** was obtained as a white solid (73% overall yield) starting from (S)-2-(6-methoxynaphthalen-2-yl)propanoic acid. R_f (petroleum ether/EtOAc = 86:14): 0.27.

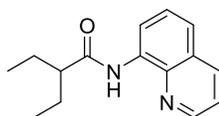
^1H NMR (300.13 MHz, CDCl_3) δ 9.96 (broad s, 1H), 8.79 (dd, $J = 7.5, 1.5$ Hz, 1H), 8.61 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.09 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.87 (s, 1H), 7.76 (dd, $J =$

8.4, 3.0 Hz, 2H), 7.57 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.54 – 7.42 (m, 2H), 7.36 (dd, $J = 8.4, 4.2$ Hz, 1H), 7.18 – 7.10 (m, 2H), 4.07 (q, $J = 6.9$ Hz, 1H), 3.91 (s, 3H), 1.77 (d, $J = 6.9$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3): δ 172.8, 157.6, 148.1, 138.4, 136.3, 136.1, 134.5, 133.8, 129.3, 129.1, 127.8, 127.5, 127.3, 126.3, 126.2, 121.4, 121.4, 119.0, 116.2 (s, CH), 105.6 (s, CH), 55.3 (s, CH_3), 48.6 (s, CH), 18.7 (s, CH_3).

IR (neat, cm^{-1}) v: 3351, 2980, 1687, 1524, 1483, 1384, 1229, 1172, 1026, 855, 791, 649.

HRMS (ESI⁺) calcd for $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_2$ m/z 357.1603 $[\text{M}+\text{H}]^+$, Found 357.1607.



Chemical Formula: $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}$
Molecular Weight: 242.32 g/mol

2-Ethyl-N-(quinolin-8-yl)butanamide 18t. Following the general procedure A, **18t** was obtained as a colorless oil (87% overall yield) starting from 2-ethylbutyryl chloride. R_f (petroleum ether/EtOAc = 90:10): 0.47.

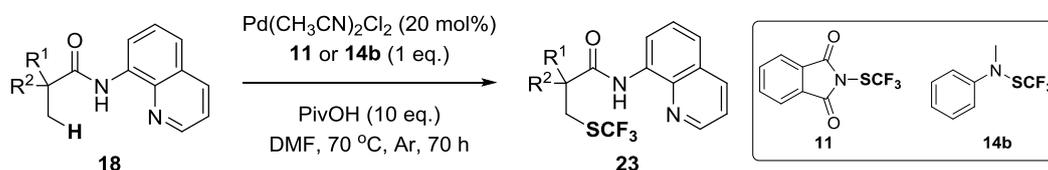
^1H NMR (300.13 MHz, CDCl_3) δ 9.75 (broad s, 1H), 8.81 – 8.64 (m, 2H), 7.99 (d, $J = 8.1$ Hz, 1H), 7.46 – 7.24 (m, 3H), 2.27 – 2.13 (m, 1H), 1.80 – 1.63 (m, 2H), 1.62 – 1.45 (m, 2H), 0.89 (t, $J = 7.2$ Hz, 6H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 174.6, 148.0, 138.3, 136.1, 134.4, 127.8, 127.2, 121.4, 121.2, 116.3, 52.5, 25.7, 12.0.

IR (neat, cm^{-1}) v: 3359, 2958, 1677, 1593, 1523, 1484, 1324, 1191, 1175, 827, 794, 682.

HRMS (ESI⁺) calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}$ m/z 243.1497 $[\text{M}+\text{H}]^+$, Found 243.1504.

1.2 General procedure for the Palladium(II)-catalyzed trifluoromethylthiolation of **18**.



General procedure E: An oven-dried 10 mL glassware equipped with a stir bar was charged with Pd(CH₃CN)₂Cl₂ (10.4 mg, 0.04 mmol, 20 mol%), **11** (49.6 mg, 0.2 mmol, 1 eq.) or **14b** (41.4 mg, 0.2 mmol, 1 eq.), PivOH (204.2 mg, 2 mmol, 10 eq.), and 2 mL of DMF under argon. Then, amide derivative **18** (0.266 mmol, 1.33 eq.) was added. The tube was flushed with argon, sealed, and then placed in an oil bath preheated to 70 °C and stirred rigorously (see time for each compound). The reaction mixture was cooled to room temperature and diluted with diethyl ether (20 mL) and water. The organic layer was washed with saturated aqueous NaHCO₃ (3 × 20 mL) and brine (20 mL), dried over MgSO₄, filtered, and evaporated under vacuum. The crude was purified by flash chromatography on silica gel to give the desired product. Note that, in the case of solid amides, these are added in the tube before the solvent.



Chemical Formula: C₁₅H₁₅F₃N₂OS
Molecular Weight: 328.35 g/mol

2,2-Dimethyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide **23a**.

Following the procedure E, from **18a** and **11** (70 h). Product purified by flash chromatography on silica gel (height 30 cm, width 2 cm, pentane/dichloromethane = 60:40) as a pale yellow solid (34.6 mg, 53%). R_f (pentane/dichloromethane = 60:40): 0.35.

¹H NMR (300.13 MHz, CDCl₃) δ 10.30 (broad s, 1H), 8.83 (dd, J = 4.2, 1.5 Hz, 1H), 8.79 – 8.69 (m, 1H), 8.17 (dd, J = 8.4, 1.5 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.47 (dd, J =

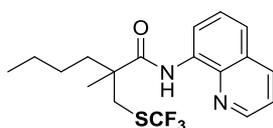
8.4, 4.2 Hz, 1H), 3.22 (s, 2H), 1.58 (s, 6H).

^{19}F NMR (282.4 MHz, CDCl_3) δ - 42.3 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 174.0, 148.4, 138.7, 136.4, 134.0, 131.1 (q, $J = 306.5$ Hz), 127.9, 127.4, 121.8, 121.7, 116.6, 44.4, 39.2 (q, $J = 2.3$ Hz), 25.2, 25.2.

IR (neat, cm^{-1}) ν : 3327, 2927, 1667, 1535, 1464, 1423, 1386, 1328, 1293, 1136, 1096, 926, 822, 784, 693, 623.

HRMS (ESI $^+$) calcd for $\text{C}_{15}\text{H}_{16}\text{F}_3\text{N}_2\text{OS}$ m/z 329.0930 $[\text{M}+\text{H}]^+$, Found 329.0948.



Chemical Formula: $\text{C}_{18}\text{H}_{21}\text{F}_3\text{N}_2\text{OS}$
Molecular Weight: 370.43 g/mol

2-Methyl-N-(quinolin-8-yl)-2-[(trifluoromethylthio)methyl]hexanamide **23b.**

Following the procedure E, from **18b** and **11** (60 h). Product purified by flash chromatography on silica gel (height 32 cm, width 2 cm, pentane/dichloromethane = 60:40) as a colorless oil (25.3 mg, 34%). R_f (pentane/dichloromethane = 60:40): 0.55.

^1H NMR (300.13 MHz, CDCl_3) δ 10.28 (broad s, 1H), 8.83 (dd, $J = 4.2, 1.5$ Hz, 1H), 8.79 – 8.71 (m, 1H), 8.18 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.58 – 7.50 (m, 2H), 7.47 (dd, $J = 8.4, 4.2$ Hz, 1H), 3.46 (d, $J = 12.9$ Hz, 1H), 3.04 (d, $J = 12.9$ Hz, 1H), 1.95 – 1.82 (m, 1H), 1.81 – 1.68 (m, 1H), 1.45 – 1.17 (m, 6H), 0.97 – 0.76 (m, 4H).

^{19}F NMR (282.4 MHz, CDCl_3) δ - 42.1 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 173.5, 148.4, 138.7, 136.4, 134.0, 131.1 (q, $J = 306.5$ Hz), 127.9, 127.4, 121.8, 121.7, 116.5, 47.7, 39.3, 37.8 (q, $J = 2.3$ Hz), 26.6, 23.0, 21.8, 13.8.

IR (neat, cm^{-1}) ν : 3353, 2960, 2932, 1674, 1527, 1487, 1424, 1326, 1146, 1103, 825, 790.

HRMS (ESI $^+$) calcd for $\text{C}_{18}\text{H}_{22}\text{F}_3\text{N}_2\text{OS}$ m/z 371.1405 $[\text{M}+\text{H}]^+$, Found 371.1416.



Chemical Formula: $C_{21}H_{19}F_3N_2OS$
Molecular Weight: 404.45 g/mol

2-Benzyl-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23c.

Following the procedure E, from **18c** and **14b** (70 h). Product purified by flash chromatography on silica gel (height 32 cm, width 2 cm, pentane/dichloromethane = 60:40) as a white vitreous solid (30.8 mg, 38%). R_f (pentane/dichloromethane = 60:40): 0.43.

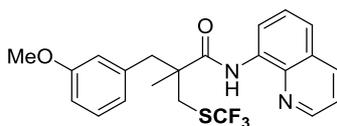
1H NMR (300.13 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.80 – 8.70 (m, 2H), 8.16 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.59 – 7.50 (m, 2H), 7.44 (dd, $J = 8.1, 4.2$ Hz, 1H), 7.21-7.14 (m, 5H), 3.53 (d, $J = 12.9$ Hz, 1H), 3.26 (d, $J = 13.5$ Hz, 1H), 3.00 (d, $J = 13.2$ Hz, 2H), 1.59 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$) δ – 42.0 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.7, 148.3, 138.6, 136.2, 135.9, 133.7, 131.0 (q, $J = 306.5$ Hz), 130.1, 128.3, 127.8, 127.3, 127.0, 121.9, 121.6, 116.5, 48.8, 45.5, 38.0 (q, $J = 1.5$ Hz), 21.0.

IR (neat, cm^{-1}) ν : 3353, 2927, 2853, 1671, 1531, 1485, 1422, 1144, 788, 687.

HRMS (ESI⁺) calcd for $C_{21}H_{20}F_3N_2OS$ m/z 405.1248 $[M+H]^+$, Found 405.1257.



Chemical Formula: $C_{22}H_{21}F_3N_2O_2S$
Molecular Weight: 434.48 g/mol

2-(3-Methoxybenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23d.

Following the procedure E, from **18d** and **14b** (61 h). Product purified by flash chromatography on silica gel (height 31 cm, width 2 cm, pentane/dichloromethane = 30:70) as a pale yellow oil (38.7 mg, 45%). R_f (pentane/dichloromethane = 30:70): 0.38.

1H NMR (300.13 MHz, $CDCl_3$) δ 10.14 (broad s, 1H), 8.77 (dd, $J = 6.0, 3.0$ Hz, 1H), 8.73 (dd, $J = 4.2, 1.5$ Hz, 1H), 8.15 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.58 – 7.49 (m, 2H), 7.43

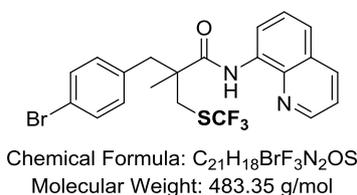
(dd, $J = 8.4, 4.2$ Hz, 1H), 7.16 – 7.06 (m, 1H), 6.80 – 6.63 (m, 3H), 3.54 (d, $J = 12.6$ Hz, 1H), 3.53 (s, 3H), 3.23 (d, $J = 13.5$ Hz, 1H), 3.03 (d, $J = 12.6$ Hz, 1H), 2.96 (d, $J = 13.5$ Hz, 1H), 1.60 (s, 3H).

^{19}F NMR (282.4 MHz, CDCl_3) δ – 42.0 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 172.7, 159.4, 148.3, 138.6, 137.4, 136.2, 133.7, 131.0 (q, $J = 306.5$ Hz), 129.1, 127.8, 127.3, 122.5, 121.9, 121.6, 116.5, 115.2, 112.9, 54.9, 48.9, 45.6, 38.1 (q, $J = 1.5$ Hz), 21.0.

IR (neat, cm^{-1}) ν : 3350, 2934, 1671, 1527, 1487, 1262, 1106, 1043, 825, 789, 755, 695.

HRMS (ESI⁺) calcd for $\text{C}_{22}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_2\text{S}$ m/z 435.1349 $[\text{M}+\text{H}]^+$, Found 435.1352.



2-(4-Bromobenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23e. Following the procedure E, from **18e** and **11** (40 h). Product purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 80:20 + 1% Et_3N) as a white vitreous solid (37.8 mg, 39%). R_f (pentane/dichloromethane = 60:40): 0.40.

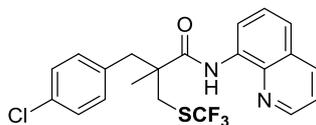
^1H NMR (300.13 MHz, CDCl_3) δ 9.97 (broad s, 1H), 8.70 – 8.57 (m, 2H), 8.06 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.47 – 7.40 (m, 2H), 7.35 (dd, $J = 8.4, 4.2$ Hz, 1H), 7.21 – 7.15 (m, 2H), 6.93 (d, $J = 8.4$ Hz, 2H), 3.40 (d, $J = 12.9$ Hz, 1H), 3.12 (d, $J = 13.2$ Hz, 1H), 2.92 (d, $J = 12.6$ Hz, 1H), 2.80 (d, $J = 13.5$ Hz, 1H), 1.47 (s, 3H).

^{19}F NMR (282.4 MHz, CDCl_3) δ – 42.0 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 172.3, 148.4, 138.6, 136.3, 135.0, 133.6, 131.8, 131.4, 130.9 (q, $J = 305.8$ Hz), 127.9, 127.3, 122.1, 121.7, 121.1, 116.0, 48.1, 44.8, 38.2 (q, $J = 2.3$ Hz), 20.8.

IR (neat, cm^{-1}) ν : 3348, 2924, 1671, 1528, 1487, 1425, 1385, 1326, 1261, 1103, 1012, 824, 790, 686.

HRMS (ESI⁺) calcd for C₂₁H₁₉BrF₃N₂OS m/z 483.0348 [M+H]⁺, Found 483.0353.



Chemical Formula: C₂₁H₁₈ClF₃N₂OS
Molecular Weight: 438.89 g/mol

2-(4-Chlorobenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23f. Following the procedure E, from **18f** and **11** (40 h). Product purified by flash chromatography on silica gel (height 35 cm, width 2 cm, pentane/dichloromethane = 60:40) as a pale yellow oil (36.1 mg, 41%). R_f (pentane/dichloromethane = 60:40): 0.50.

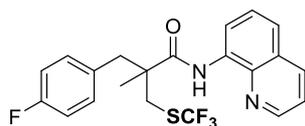
¹H NMR (300.13 MHz, CDCl₃) δ 10.08 (broad s, 1H), 7.79 – 7.68 (m, 2H), 8.16 (dd, J = 8.1, 1.2 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.45 (dd, J = 8.1, 4.2 Hz, 1H), 7.19 – 7.05 (m, 4H), 3.50 (d, J = 12.6 Hz, 1H), 3.24 (d, J = 13.5 Hz, 1H), 3.03 (d, J = 12.6 Hz, 1H), 2.92 (d, J = 13.5 Hz, 1H), 1.57 (s, 3H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 42.0 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 172.3, 148.4, 138.5, 136.3, 134.5, 133.6, 133.0, 131.4, 130.9 (q, J = 306.5 Hz), 128.5, 127.8, 127.3, 122.0, 121.7, 116.7, 48.8, 44.7, 38.2 (q, J = 1.5 Hz), 20.8.

IR (neat, cm⁻¹) v: 3347, 1670, 1527, 1487, 1425, 1384, 1325, 1260, 1103, 1016, 825, 790, 684.

HRMS (ESI⁺) calcd for C₂₁H₁₉ClF₃N₂OS m/z 439.0853 [M+H]⁺, Found 439.0847.



Chemical Formula: C₂₁H₁₈F₄N₂OS
Molecular Weight: 422.44 g/mol

2-(4-Fluorobenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23g. Following the procedure E, from **18g** and **14b** (86 h). Product purified by flash chromatography on silica gel (height 34 cm, width 2 cm, toluene/pentane = 60:40 + 1%

Et₃N) as a colorless oil (33.1 mg, 39%). R_f (pentane/dichloromethane = 60:40): 0.44.

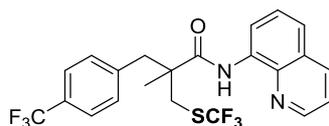
¹H NMR (300.13 MHz, CDCl₃) δ 10.09 (broad s, 1H), 8.77 – 8.70 (m, 2H), 8.16 (dd, J = 8.4, 1.5 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.44 (dd, J = 8.4, 4.2 Hz, 1H), 7.17 – 7.08 (m, 2H), 6.90 – 6.80 (m, 2H), 3.51 (d, J = 12.6 Hz, 1H), 3.24 (d, J = 13.5 Hz, 1H), 3.02 (d, J = 12.6 Hz, 1H), 2.93 (d, J = 13.5 Hz, 1H), 1.58 (s, 3H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 42.0 (s), – 116.3 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 172.4, 162.0 (d, J = 246.1 Hz), 148.3, 138.6, 136.3, 133.6, 131.7 (d, J = 3.0 Hz), 131.6 (d, J = 7.6 Hz), 130.9 (q, J = 305.8 Hz), 127.8, 127.3, 122.0, 121.7, 116.5, 115.2 (d, J = 21.9 Hz), 48.9, 44.6, 38.1 (q, J = 1.5 Hz), 20.8.

IR (neat, cm⁻¹) ν: 3348, 2927, 1673, 1528, 1510, 1487, 1224, 1102, 826, 790.

HRMS (ESI⁺) calcd for C₂₁H₁₉F₄N₂OS m/z 423.1154 [M+H]⁺, Found 423.1147.



Chemical Formula: C₂₂H₁₈F₆N₂OS
Molecular Weight: 472.45 g/mol

2-Methyl-N-(quinolin-8-yl)-2-(4-(trifluoromethyl)benzyl)-3-(trifluoromethylthio)

propanamide 23h. Following the procedure E, from **18h** and **11** (60 h). Product purified by flash chromatography on silica gel (height 35 cm, width 2 cm, pentane/dichloromethane = 60:40) as a pale yellow oil (46.8 mg, 50%). R_f (pentane/dichloromethane = 60:40): 0.49.

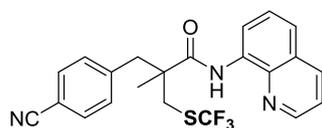
¹H NMR (300.13 MHz, CDCl₃) δ 9.98 (broad s, 1H), 8.69 - 8.64 (m, 1H), 8.61 (dd, J = 4.2, 1.5 Hz, 1H), 8.09 (dd, J = 8.4, 1.5 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.39 – 7.30 (m, 3H), 7.21 (d, J = 8.4 Hz, 2H), 3.45 (d, J = 12.9 Hz, 1H), 3.27 (d, J = 13.2 Hz, 1H), 2.99 (d, J = 12.9 Hz, 1H), 2.92 (d, J = 13.2 Hz, 1H), 1.51 (s, 3H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 42.0 (s), – 63.1 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 172.0, 148.4, 140.2, 138.5, 136.3, 133.5, 130.9 (q, J = 306.5 Hz), 130.4, 129.3 (q, J = 33.2 Hz), 127.8, 127.3, 125.2 (q, J = 3.8 Hz), 124.0 (q, J = 271.8 Hz), 122.1, 121.7, 116.6, 48.9, 45.1, 38.3 (q, J = 2.3 Hz), 20.8.

IR (neat, cm^{-1}) ν : 3347, 2927, 2853, 1673, 1529, 1487, 1424, 1385, 1323, 1258, 1105, 1067, 906, 791, 687.

HRMS (ESI^+) calcd for $\text{C}_{22}\text{H}_{19}\text{F}_6\text{N}_2\text{OS}$ m/z 473.1117 $[\text{M}+\text{H}]^+$, Found 473.1119.



Chemical Formula: $\text{C}_{22}\text{H}_{18}\text{F}_3\text{N}_3\text{OS}$
Molecular Weight: 429.46 g/mol

2-(4-Cyanobenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23i. Following the procedure E, from **18i** and **11** (39 h). Product purified by flash chromatography on silica gel (height 35 cm, width 2 cm, dichloromethane) as a pale yellow oil (22.3 mg, 26%). R_f (dichloromethane): 0.48.

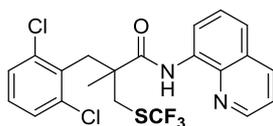
^1H NMR (300.13 MHz, CDCl_3) δ 9.96 (broad s, 1H), 8.68 – 8.59 (m, 2H), 8.09 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.47 (d, $J = 4.5$ Hz, 2H), 7.41 – 7.33 (m, 3H), 7.20 (d, $J = 7.2$ Hz, 2H), 3.44 (d, $J = 12.9$ Hz, 1H), 3.28 (d, $J = 13.2$ Hz, 1H), 3.00 (d, $J = 12.9$ Hz, 1H), 2.88 (d, $J = 13.2$ Hz, 1H), 1.50 (s, 3H).

^{19}F NMR (282.4 MHz, CDCl_3) δ – 41.9 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 171.7, 148.4, 141.7, 138.5, 136.4, 133.3, 132.0, 130.8, 130.8 (q, $J = 306.5$ Hz), 127.8, 127.2, 122.3, 121.8, 118.6, 116.6, 111.0, 48.9, 45.3, 38.4 (q, $J = 1.5$ Hz), 20.6.

IR (neat, cm^{-1}) ν : 3347, 2228, 1670, 1525, 1487, 1425, 1385, 1103, 826, 790.

HRMS (ESI^+) calcd for $\text{C}_{22}\text{H}_{19}\text{F}_3\text{N}_3\text{OS}$ m/z 430.1195 $[\text{M}+\text{H}]^+$, Found 430.1195.



Chemical Formula: $\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{F}_3\text{N}_2\text{OS}$
Molecular Weight: 473.34 g/mol

2-(2,6-Dichlorobenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23j. Following the procedure E, from **18j** and **11** (45 h). Product purified by flash chromatography on silica gel (height 31 cm, width 2 cm,

pentane/dichloromethane = 60:40) as a vitrous white solid (43.1 mg, 46%). R_f (pentane/dichloromethane = 60:40): 0.45.

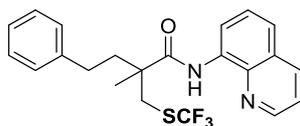
$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 10.08 (broad s, 1H), 8.73 (dd, $J = 6.6, 2.1$ Hz, 1H), 8.65 (d, $J = 4.2$ Hz, 1H), 8.14 (d, $J = 8.1$ Hz, 1H), 7.58 – 7.48 (m, 2H), 7.41 (dd, $J = 8.1, 4.2$ Hz, 1H), 7.21 (d, $J = 7.8$ Hz, 2H), 7.04 (t, $J = 7.8$ Hz, 1H), 3.66 (t, $J = 14.4$ Hz, 2H), 3.46 (d, $J = 14.1$ Hz, 1H), 3.14 (d, $J = 12.9$ Hz, 1H), 1.71 (s, 3H).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ – 42.3 (s).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 172.3, 148.1, 138.5, 137.1, 136.2, 134.0, 133.0, 131.1 (q, $J = 306.5$ Hz), 128.6, 128.6, 127.7, 127.4, 121.7, 121.5, 116.6, 49.6, 39.5, 38.8 (q, $J = 1.5$ Hz), 21.3.

IR (neat, cm^{-1}) ν : 3340, 1666, 1532, 1437, 1324, 1112, 781, 760.

HRMS (ESI^+) calcd for $\text{C}_{21}\text{H}_{18}\text{Cl}_2\text{F}_3\text{N}_2\text{OS}$ m/z 473.0464 $[\text{M}+\text{H}]^+$, Found 473.0447.



Chemical Formula: $\text{C}_{22}\text{H}_{21}\text{F}_3\text{N}_2\text{OS}$
Molecular Weight: 418.48 g/mol

2-Methyl-4-phenyl-N-(quinolin-8-yl)-2-((trifluoromethylthio)methyl)butanamide

23k. Following the procedure E, from **18k** and **11** (40 h). Product purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 70:30 + 1% Et_3N) as a white vitrous solid (29.1 mg, 35%). R_f (pentane/dichloromethane = 60:40): 0.33.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 10.29 (broad s, 1H), 8.76 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.73 – 8.65 (m, 1H), 8.12 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.50 – 7.45 (m, 2H), 7.41 (dd, $J = 8.4, 4.2$ Hz, 1H), 7.23 – 7.04 (m, 5H), 3.45 (d, $J = 12.9$ Hz, 1H), 3.05 (d, $J = 12.9$ Hz, 1H), 2.63 (dd, $J = 9.6, 7.8$ Hz, 2H), 2.22 – 2.06 (m, 1H), 2.05 – 1.91 (m, 1H), 1.59 (s, 3H).

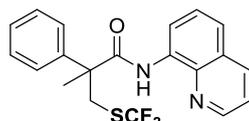
$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ – 42.0 (s).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 173.0, 148.4, 141.1, 138.7, 136.4, 133.9, 131.0 (q, $J =$

306.5 Hz), 128.5, 128.3, 127.9, 127.4, 126.1, 121.9, 121.7, 116.6, 47.7, 41.5, 37.8 (q, J = 2.3 Hz), 31.0, 21.9.

IR (neat, cm^{-1}) v: 3353, 2933, 1673, 1527, 1486, 1469, 1424, 1384, 1326, 1253, 1105, 893, 825, 790, 697.

HRMS (ESI⁺) calcd for $\text{C}_{22}\text{H}_{22}\text{F}_3\text{N}_2\text{OS}$ m/z 419.1399 [M+H]⁺, Found 419.1390.



Chemical Formula: $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_2\text{OS}$
Molecular Weight: 390.42 g/mol

2-Methyl-2-phenyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23l.

Following the procedure E, from **18l** and **14b** (143 h). Product purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 60:40 + 1% Et₃N) as a white vitreous solid (28.4 mg, 36%). R_f (pentane/dichloromethane = 60:40): 0.37.

¹H NMR (300.13 MHz, CDCl₃) δ 9.83 (broad s, 1H), 8.70 (dd, J = 6.6, 2.1 Hz, 1H), 8.63 (dd, J = 4.2, 1.5 Hz, 1H), 8.11 (dd, J = 8.4, 1.5 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.47 – 7.36 (m, 6H), 3.66 (d, J = 13.2 Hz, 1H), 3.34 (d, J = 13.2 Hz, 1H), 2.00 (s, 3H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 42.5 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 172.8, 148.4, 139.4, 138.4, 136.2, 134.2, 133.9, 131.0 (q, J = 306.5 Hz), 129.3, 128.1, 127.8, 127.2, 122.0, 121.7, 116.3, 51.7, 39.5 (q, J = 1.5 Hz), 22.2.

IR (neat, cm^{-1}) v: 3327, 1664, 1522, 1486, 1327, 1141, 1106, 825, 760.

HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{18}\text{F}_3\text{N}_2\text{OS}$ m/z 391.1086 [M+H]⁺, Found 391.1082.



Chemical Formula: $\text{C}_{20}\text{H}_{16}\text{ClF}_3\text{N}_2\text{OS}$
Molecular Weight: 424.87 g/mol

2-(4-Chlorophenyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanam

ide 23m. Following the procedure E, from **18m** and **14b** (143 h). Product purified by flash chromatography on silica gel (height 31 cm, width 2 cm, toluene/pentane = 50:50 + 1% Et₃N) as a white amorphous solid (31.2 mg, 37%). R_f (toluene/pentane = 50:50 + 1% Et₃N): 0.30.

¹H NMR (300.13 MHz, CDCl₃) δ 9.83 (broad s, 1H), 8.73 (d, J = 7.2 Hz, 1H), 8.59 (d, J = 4.2 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.54–7.33 (m, 7H), 3.72 (d, J = 12.9 Hz, 1H), 3.38 (d, J = 12.9 Hz, 1H), 2.03 (s, 3H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 42.6 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 173.5, 148.2, 140.8, 138.5, 136.1, 134.1, 131.1 (q, J = 305.8 Hz), 129.1, 128.1, 127.8, 127.2, 126.6, 121.8, 121.6, 116.2, 52.1, 39.6 (q, J = 2.3 Hz), 22.2.

IR (neat, cm⁻¹) v: 3333, 1672, 1527, 1489, 1135, 1099, 1054, 824, 792.

HRMS (ESI⁺) calcd for C₂₀H₁₇ClF₃N₂OS m/z 425.0697 [M+H]⁺, Found 425.0705.



Chemical Formula: C₂₀H₁₆F₄N₂OS
Molecular Weight: 408.41 g/mol

2-(4-Fluorophenyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide

de 23n. Following the procedure E, from **18n** and **14b** (143 h). Product purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 50:50 + 1% Et₃N) as a white amorphous solid (26.2 mg, 32%). R_f (toluene/pentane = 50:50 + 1% Et₃N): 0.44.

¹H NMR (300.13 MHz, CDCl₃) δ 9.82 (broad s, 1H), 8.71 (dd, J = 6.9, 1.8 Hz, 1H), 8.62 (dd, J = 4.2, 1.2 Hz, 1H), 8.11 (dd, J = 8.1, 1.2 Hz, 1H), 7.55 – 7.45 (m, 4H), 7.39 (dd, J = 8.1, 4.2 Hz, 1H), 7.12 (t, J = 8.7 Hz, 2H), 3.67 (d, J = 13.2 Hz, 1H), 3.36 (d, J = 13.2 Hz, 1H), 2.01 (s, 3H).

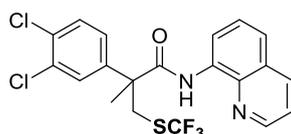
¹⁹F NMR (282.4 MHz, CDCl₃) δ – 42.5 (s), – 114.3 (m).

¹³C NMR (75.5 MHz, CDCl₃) δ 173.2, 162.4 (d, J = 248.4 Hz), 148.3, 138.4, 136.6 (d,

$J = 3.8$ Hz), 136.2, 133.9, 131.0 (q, $J = 305.8$ Hz), 128.6 (d, $J = 27.9$ Hz), 127.8, 127.2, 121.9, 121.6, 116.3 (d, $J = 8.3$ Hz), 115.9, 51.6, 39.7 (q, $J = 1.5$ Hz), 22.4.

IR (neat, cm^{-1}) ν : 3327, 1668, 1527, 1488, 1141, 1100, 826, 790, 691.

HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{17}\text{F}_4\text{N}_2\text{OS}$ m/z 409.0992 $[\text{M}+\text{H}]^+$, Found 409.1012.



Chemical Formula: $\text{C}_{20}\text{H}_{15}\text{Cl}_2\text{F}_3\text{N}_2\text{OS}$
Molecular Weight: 459.31 g/mol

2-(3,4-Dichlorophenyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23o. Following the procedure E, from **18o** and **14b** (86 h). Product purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 60:40 + 1% Et_3N) as a colorless oil (27.3 mg, 30%). R_f (pentane/dichloromethane = 50:50): 0.68.

^1H NMR (300.13 MHz, CDCl_3) δ 9.88 (s, 1H), 8.69 (dd, $J = 6.3, 2.7$ Hz, 1H), 8.67 (dd, $J = 4.8, 1.8$ Hz, 1H), 8.13 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.62 (d, $J = 2.1$ Hz, 1H), 7.55 – 7.45 (m, 3H), 7.41 (dd, $J = 8.4, 4.2$ Hz, 1H), 7.34 (dd, $J = 8.4, 2.1$ Hz, 1H), 3.65 (d, $J = 13.2$ Hz, 1H), 3.33 (d, $J = 13.2$ Hz, 1H), 2.00 (s, 3H).

^{19}F NMR (282.4 MHz, CDCl_3) δ – 42.5 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 172.0, 148.5, 141.2, 138.4, 136.3, 133.7, 133.3, 132.5, 131.0, 130.8 (q, $J = 306.5$ Hz), 128.7, 127.8, 127.2, 126.2, 122.1, 121.7, 116.2, 51.7, 39.4 (q, $J = 2.3$ Hz), 22.1.

IR (neat, cm^{-1}) ν : 3327, 1668, 1527, 1488, 1141, 1100, 825, 790, 691.

HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{16}\text{Cl}_2\text{F}_3\text{N}_2\text{OS}$ m/z 459.0312 $[\text{M}+\text{H}]^+$, Found 459.0305.



Chemical Formula: $\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_2\text{OS}$
Molecular Weight: 376.40 g/mol

2-Phenyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23p. Following

the procedure E, from **18p** and **11** (60 h). Product purified by flash chromatography on silica gel (height 32 cm, width 2 cm, pentane/dichloromethane = 60:40) as a pale yellow oil (27 mg, 36%). R_f (pentane/dichloromethane = 60:40): 0.51.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 9.93 (broad s, 1H), 8.79 – 8.70 (m, 2H), 8.12 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.54 – 7.45 (m, 4H), 7.44 – 7.32 (m, 4H), 4.13 (dd, $J = 9.0, 6.0$ Hz, 1H), 3.76 (dd, $J = 14.1, 9.0$ Hz, 1H), 3.30 (dd, $J = 14.1, 6.0$ Hz, 1H).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) $\delta - 41.8$.

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 169.4, 148.3, 138.2, 137.4, 136.2, 134.0, 131.2 (q, $J = 306.5$ Hz), 129.3, 128.3, 127.9, 127.8, 127.2, 121.9, 121.6, 116.5, 54.7, 32.6 (q, $J = 2.3$ Hz).

IR (neat, cm^{-1}) ν : 3340, 2925, 2855, 1688, 1527, 1486, 1462, 1385, 1324, 1276, 1111, 825, 791, 698.

HRMS (ESI $^+$) calcd for $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_2\text{OS}$ m/z 377.0930 $[\text{M}+\text{H}]^+$, Found 377.0935.



Chemical Formula: $\text{C}_{14}\text{H}_{13}\text{F}_3\text{N}_2\text{OS}$
Molecular Weight: 314.33 g/mol

2-Methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23q. Following the procedure E, from **18q** and **14b** (143 h). Product purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene + Et_3N 1%) as pale yellow oil (19.6 mg, 31%). R_f (toluene + Et_3N 1%): 0.28.

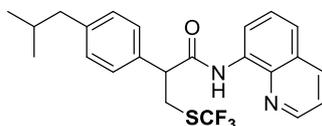
$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 9.97 (broad s, 1H), 8.83 (dd, $J = 4.2, 1.5$ Hz, 1H), 8.80 – 8.73 (m, 1H), 8.17 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.58 – 7.51 (m, 2H), 7.47 (dd, $J = 8.1, 4.2$ Hz, 1H), 3.39 – 3.26 (m, 1H), 3.11 – 2.95 (m, 2H), 1.47 (d, $J = 6.6$ Hz, 3H). $^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) $\delta - 41.7$ (s).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 172.3, 148.3, 138.3, 136.4, 134.0, 131.1 (q, $J = 305.8$ Hz), 127.9, 127.3, 121.9, 121.7, 116.7, 43.0, 32.8 (q, $J = 2.3$ Hz), 18.0.

IR (neat, cm^{-1}) ν : 3347, 2927, 1688, 1526, 1486, 1457, 1426, 1379, 1323, 1258, 1105,

942, 826, 791, 671.

HRMS (ESI⁺) calcd for C₁₄H₁₄F₃N₂OS m/z 315.0773 [M+H]⁺, Found 315.0784.



Chemical Formula: C₂₃H₂₃F₃N₂OS
Molecular Weight: 432.51 g/mol

2-(4-Isobutylphenyl)-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23r.

Following the procedure E, from **18r** and **14b** (143 h). Product purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 80:20 + 1% Et₃N) as a pale yellow oil (28.2mg, 33%). R_f (toluene/pentane = 80:20 + 1% Et₃N): 0.48.

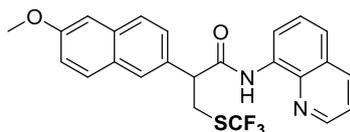
¹H NMR (300.13 MHz, CDCl₃) δ 9.91 (broad s, 1H), 8.76 (dd, J = 6.9, 2.1 Hz, 1H), 8.70 (dd, J = 4.2, 1.5 Hz, 1H), 8.11 (dd, J = 8.1, 1.5 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.41 (dd, J = 8.4, 4.5 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 4.10 (dd, J = 9.0, 6.0 Hz, 1H), 3.76 (dd, J = 13.8, 9.0 Hz, 1H), 3.29 (dd, J = 13.8, 6.0 Hz, 1H), 2.47 (d, J = 7.2 Hz, 2H), 1.91 – 1.78 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 41.8 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 169.7, 148.2, 141.9, 138.3, 136.2, 134.6, 134.1, 131.3 (q, J = 306.5 Hz), 130.0, 127.8, 127.6, 127.2, 121.9, 121.6, 54.3, 45.1, 32.6 (q, J = 2.3 Hz), 30.2, 22.3, 22.3.

IR (neat, cm⁻¹) v: 3340, 2953, 2920, 1683, 1525, 1486, 1148, 1104, 825, 790.

HRMS (ESI⁺) calcd for C₂₃H₂₄F₃N₂OS m/z 433.1556 [M+H]⁺, Found 433.1548.



Chemical Formula: C₂₄H₁₉F₃N₂O₂S
Molecular Weight: 456.48 g/mol

(S)-2-(6-methoxynaphthalen-2-yl)-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide 23s. Following the procedure E, from **18s** and **14b** (143 h). Product purified by

flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 90:10 + 1% Et₃N) as a yellow oil (21.2 mg, 23%). R_f (toluene/pentane = 80:20 + 1% Et₃N): 0.26.

¹H NMR (300.13 MHz, CDCl₃) δ 9.98 (broad s, 1H), 8.78 (dd, J = 7.2, 1.8 Hz, 1H), 8.67 (dd, J = 4.2, 1.8 Hz, 1H), 8.10 (d, dd, J = 8.4, 1.8 Hz, 1H), 7.87 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.58 – 7.46 (m, 3H), 7.38 (dd, J = 8.4, 4.2 Hz, 1H), 7.17 (dd, J = 9.0, 2.4 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 4.26 (dd, J = 9.0, 6.0 Hz, 1H), 3.91 (s, 3H), 3.83 (dd, J = 13.8, 9.0 Hz, 1H), 3.37 (dd, J = 13.8, 6.0 Hz, 1H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 41.7 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 169.6, 158.0, 148.2, 138.2, 136.2, 134.3, 134.0, 132.4, 131.3 (q, J = 306.5 Hz), 129.4, 129.0, 128.0, 127.8, 127.2, 127.0, 125.7, 121.9, 121.6, 119.4, 116.5, 105.6, 55.3, 54.6, 32.6 (q, J = 2.3 Hz).

IR (neat, cm⁻¹) ν: 3333, 2923, 1680, 1633, 1525, 1484, 1262, 1099, 1028, 789.

HRMS (ESI⁺) calcd for C₂₄H₂₀F₃N₂O₂S m/z 457.1192 [M+H]⁺, Found 457.1208.



Chemical Formula: C₁₆H₁₇F₃N₂OS
Molecular Weight: 342.38 g/mol

2-Ethyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)butanamide 23t. Following the procedure E, from **18t** and **11** (60 h). Product purified by flash chromatography on silica gel (height 31 cm, width 1.5 cm, pentane/dichloromethane = 40:60) as a colorless oil (8.3 mg, 12%). R_f (pentane/dichloromethane = 40:60): 0.42.

¹H NMR (300.13 MHz, CDCl₃) δ 9.92 (broad s, 1H), 8.86 – 8.74 (m, 2H), 8.18 (dd, J = 8.4, 1.8 Hz, 1H), 7.54 (d, J = 4.5 Hz, 2H), 7.48 (dd, J = 8.4, 4.2 Hz, 1H), 3.63 – 3.49 (m, 1H), 2.74 – 2.62 (m, 1H), 2.07 – 1.94 (m, 1H), 1.92 – 1.79 (m, 1H), 1.57 (d, J = 6.3 Hz, 3H), 1.08 (t, J = 7.5 Hz, 3H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 41.3 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 171.5, 148.3, 138.4, 136.4, 133.9, 127.9, 127.4, 121.9,

121.7, 116.8, 55.4, 42.3 (q, $J = 306.5$ Hz), 23.9, 21.6, 12.0. The CF_3 -carbon was not detectable.

IR (neat, cm^{-1}) ν : 3347, 2966, 1682, 1524, 1487, 1425, 1324, 1110, 826, 791, 679.

HRMS (ESI^+) calcd for $\text{C}_{16}\text{H}_{18}\text{F}_3\text{N}_2\text{OS}$ m/z 343.1086 $[\text{M}+\text{H}]^+$, Found 343.1086.



Chemical Formula: $\text{C}_{17}\text{H}_{17}\text{F}_3\text{N}_2\text{OS}$
Molecular Weight: 354.39 g/mol

N-(quinolin-8-yl)-2-(trifluoromethylthio)cyclohexane-1-carboxamide **23u.**

Following the procedure E, from **18u** and **11** (60 h). Product purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 94:6 + Et_3N 1%) as a colorless oil (5.6 mg, 8%). R_f (pentane/dichloromethane = 40:60): 0.26.

^1H NMR (300.13 MHz, CDCl_3) δ 9.87 (broad s, 1H), 8.84 – 8.76 (m, 2H), 8.17 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.59 – 7.50 (m, 2H), 7.47 (dd, $J = 8.4, 4.2$ Hz, 1H), 3.66 – 3.47 (m, 1H), 2.69 – 2.53 (m, 1H), 2.46 – 2.32 (m, 1H), 2.25 – 2.11 (m, 1H), 1.93 – 1.69 (m, 4H), 1.55 – 1.34 (m, 2H).

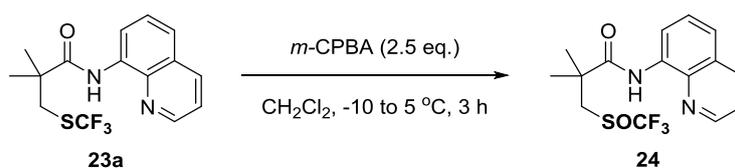
^{19}F NMR (282.4 MHz, CDCl_3) δ – 38.1 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 171.5, 148.2, 138.4, 136.4, 134.2, 127.9, 127.4, 121.8, 121.6, 116.8, 52.1, 45.5, 34.5, 31.3, 26.0, 24.5, the CF_3 -carbon was not detectable.

IR (neat, cm^{-1}) ν : 3347, 2933, 2860, 1683, 1524, 1486, 1325, 1099, 790.

HRMS (ESI^+) calcd for $\text{C}_{17}\text{H}_{18}\text{F}_3\text{N}_2\text{OS}$ m/z 355.1086 $[\text{M}+\text{H}]^+$, Found 355.1091.

1.3 Procedure for the oxidation of compound 23a



An oven-dried 10 mL flask equipped with a stir bar was charged with **23a** (32.8 mg, 0.1 mmol, 1 eq.), distilled CH_2Cl_2 (1.5 mL) and the reaction mixture was cooled down to

-10 °C. Then, m-CPBA (61.6 mg, 0.25 mmol, 2.5 eq., assay ca.70%) was added portionwise while keeping the temperature at -10 °C. The reaction mixture was allowed to warm up to 5 °C and was stirred for 3 h until complete disappearance of the starting material. Then, the reaction mixture was diluted with CH₂Cl₂ (5 mL) and water (5 mL). The organic layer was washed with sodium sulfite solution (5 mL), aqueous NaHCO₃ solution (5 mL), brine (5 mL), dried over MgSO₄ and concentrated. The product was purified by flash chromatography on silica gel (petroleum ether/dichloromethane = 40:60) to afford the desired product **24** as pale yellow vitreous solid (13.9 mg, 40%). R_f (pentane/dichloromethane = 30:70): 0.15.



Chemical Formula: C₁₅H₁₅F₃N₂O₂S
Molecular Weight: 344.35 g/mol

2,2-Dimethyl-N-(quinolin-8-yl)-3-(trifluoromethylsulfinyl)propanamide **24**.

¹H NMR (300.13 MHz, CDCl₃) δ 10.41 (broad s, 1H), 8.83 (dd, J = 4.2, 1.5 Hz, 1H), 8.77 – 8.69 (m, 1H), 8.19 (dd, J = 8.1, 1.5 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.49 (dd, J = 8.1, 4.2 Hz, 1H), 3.58 (d, J = 13.5 Hz, 1H), 3.09 (d, J = 13.5 Hz, 1H), 1.78 (s, 3H), 1.67 (s, 3H).

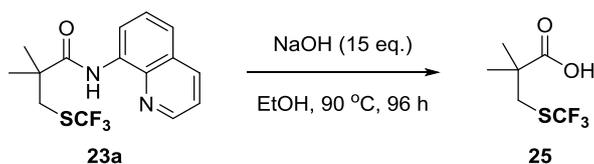
¹⁹F NMR (282.4 MHz, CDCl₃) δ – 74.5 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 173.4, 148.5, 138.6, 136.4, 133.7, 127.9, 127.3, 125.6 (q, J = 334.5 Hz), 122.2, 121.8, 116.7, 59.6 (q, J = 3.0 Hz), 42.9, 27.5, 25.2.

IR (neat, cm⁻¹) ν: 3333, 2958, 1670, 1531, 1489, 1328, 1173, 1137, 1064, 791, 695.

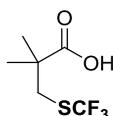
HRMS (ESI⁺) calcd for C₁₅H₁₆F₃N₂O₂S m/z 345.0885 [M+H]⁺, Found 345.0887.

1.4 Procedure for the cleavage of the directing group on compound **23a**



An oven-dried 10 mL flask equipped with a stir bar was charged with **23a** (65.6 mg, 0.2

mmol, 1 eq.), NaOH (120 mg, 3 mmol, 15 eq.) and EtOH (1 mL). The resulting mixture was stirred at 90 °C for 4 days. After completion, the reaction mixture was cooled to room temperature, water (20 mL) was added, and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The pH of the aqueous layer was adjusted to 2 with HCl (1M) and the resulting aqueous layer was extracted with CH₂Cl₂ (4 × 20 mL), dried over MgSO₄, filtered and the solvent was evaporated under vacuum to afford pure product **25** (34.6 mg, 86%) as yellow oil.



Chemical Formula: C₆H₉F₃O₂S
Molecular Weight: 202.19 g/mol

2,2-Dimethyl-3-(trifluoromethylthio)propanoic acid **25**.

¹H NMR (300.13 MHz, CDCl₃) δ 10.21 (broad s, 1H), 3.08 (s, 2H), 1.35 (s, 6H).

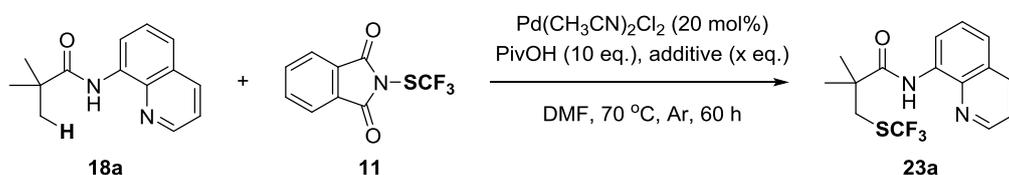
¹⁹F NMR (282.4 MHz, CDCl₃) δ - 42.2 (s).

¹³C NMR (75.5 MHz, CDCl₃): δ 182.4, 130.8 (q, J = 305.8 Hz), 42.9, 38.2 (q, J = 2.3 Hz), 24.3.

IR (neat, cm⁻¹) v: 2983, 2940, 1702, 1477, 1151, 1099.

HRMS (ESI⁻) calcd for C₆H₈F₃O₂S m/z 201.0197 [M-H]⁻, Found 201.0193.

1.5 Radical trapping experiments



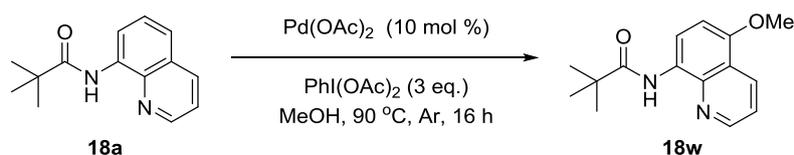
entry	additive	isolated yield (%)
1	TEMPO (1.1 eq.)	37
2	TEMPO (1.1 eq.)	35
3	TEMPO (40 mol %)	39
4	BHT (1.1 eq.)	44
5	BHT (1.1 eq.)	39

An oven-dried 10 mL glassware equipped with a stir bar was charged with Pd(CH₃CN)₂Cl₂ (10.4 mg, 0.04 mmol, 0.2 eq.), **11** (49.6 mg, 0.2 mmol, 1 eq.), PivOH (204.2 mg, 2 mmol, 10 eq.), TEMPO (34.4 mg, 0.22 mmol, 1.1 eq.) or TEMPO (12.5 mg, 0.08 mmol, 0.4 eq.) or BHT (48.5 mg, 0.22 mmol, 1.1 eq.) and 2 mL of DMF under argon. Then, amide derivative **18a** (60.8 mg, 0.266 mmol, 1.33 eq.) was added. The tube was flushed with argon, sealed and then placed in an oil bath preheated to 70 °C and stirred rigorously (see time for each compound). The reaction mixture was cooled to room temperature and diluted with diethyl ether (20 mL) and water. The organic layer was washed with saturated aqueous NaHCO₃ (3 × 20 mL) and brine (20 mL), dried over MgSO₄, filtered and evaporated under vacuum. The crude was purified by flash chromatography on silica gel to give the desired product **23a**.

2 Palladium(II)-Catalyzed Directed Chlorination of Unactivated C(sp³)-H Bonds at Room Temperature

2.1 Synthesis of N-(5-methoxyquinolin-8-yl)pivalamide **18w**

The N-(5-methoxyquinolin-8-yl)pivalamide **18w** was prepared via the methoxylation of N-(quinolin-8-yl)pivalamide using a reported procedure.^{53a}



An oven-dried 20 mL glassware equipped with a stirring bar was charged with Pd(OAc)₂ (11.2 mg, 0.05 mmol, 0.1 eq.), PhI(OAc)₂ (483.2 mg, 1.5 mmol, 3 eq.) and 5 mL of MeOH under argon. Then, N-(quinolin-8-yl)pivalamide (114.1 mg, 0.5 mmol, 1 eq.) was added. The tube was flushed with argon, sealed and stirred vigorously at 90 °C for 16 h. The solvent was evaporated under vacuum. The product was purified by flash chromatography on silica gel (height 19 cm, width 2 cm, toluene/diethyl ether = 90/10) as a yellow vitrous solid (40.2 mg, 31%). R_f (toluene/diethyl ether = 90/10): 0.38.



Chemical Formula: C₁₅H₁₈N₂O₂
Exact Mass: 258.1368

N-(5-methoxyquinolin-8-yl)pivalamide **18w**.

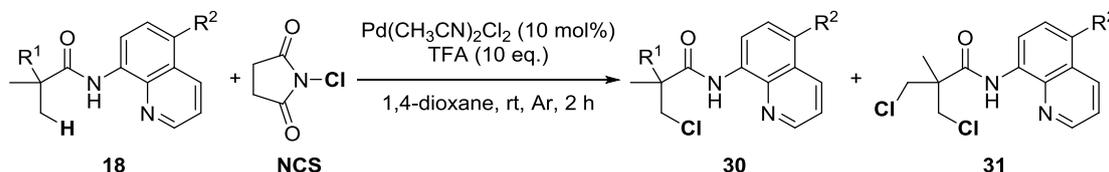
¹H NMR (300.13 MHz, CDCl₃) δ 10.03 (s, 1H), 8.81 (dd, J = 4.2, 1.5 Hz, 1H), 8.72 (d, J = 8.7 Hz, 1H), 8.55 (dd, J = 8.4, 1.5 Hz, 1H), 7.42 (dd, J = 8.4, 4.2 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 3.97 (s, 3H), 1.42 (s, 9H).

¹³C NMR (75.5 MHz, CDCl₃) δ 176.8, 150.0, 148.6, 139.4, 131.1, 128.1, 120.6, 120.4, 116.2, 104.3, 55.7, 40.1, 27.7.

IR (neat, cm⁻¹) v: 3367, 2959, 1661, 1531, 1495, 1400, 1271, 1158, 1090, 833, 794, 677.

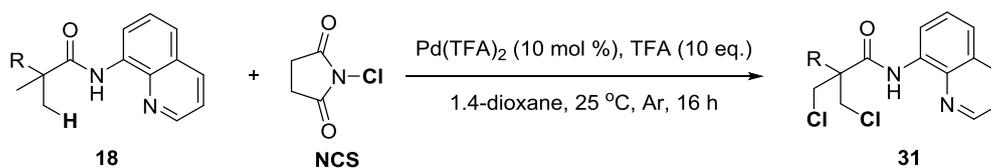
HRMS (ESI⁺) calcd for C₁₅H₁₉N₂O₂ m/z 259.1441 [M+H]⁺, Found 259.1444.

2.2 General procedure for the chlorination reaction

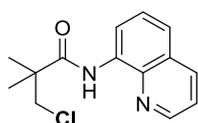


Procedure F: An oven-dried 10 mL glassware equipped with a stirring bar was charged with Pd(CH₃CN)₂Cl₂ (5.2 mg, 0.02 mmol, 0.1 eq.), N-chlorosuccinimide (NCS) (26.6 mg, 0.2 mmol, 1 eq.) and 2 mL of 1,4-dioxane under argon. Then, amide derivatives **18** (0.4 mmol, 2 eq.) and TFA (228.9 mg, 2.0 mmol, 10 eq.) were added. The tube was flushed with argon, sealed, and stirred vigorously at room temperature until NCS was fully consumed. Then, the reaction mixture was diluted with diethyl ether (20 mL) and water. The organic layer was washed with saturated aqueous NaHCO₃ (3 × 20 mL), dried over MgSO₄, filtered and evaporated under vacuum. The crude reaction mixture was purified by flash chromatography on silica gel to afford the desired product. Note that, in the case of solid amides, these are added in the tube before the solvent.

2.3 General procedure for the dichlorination reaction



Procedure G: An oven-dried 10 mL glassware equipped with a stirring bar was charged with Pd(TFA)₂ (6.6 mg, 0.02 mmol, 0.1 eq.), N-chlorosuccinimide (NCS, 133.5 mg, 2.0 mmol, 10 eq.) and 2 mL of 1,4-dioxane under argon. Then, amide derivatives **18** (0.2 mmol, 1 eq.) and TFA (228.9 mg, 2.0 mmol, 10 eq.) were added. The tube was flushed with argon, sealed and stirred vigorously at room temperature until **18** was fully consumed. Then, the reaction mixture was diluted with diethyl ether (20 mL) and water. The organic layer was washed with saturated aqueous NaHCO₃ (3 × 20 mL), dried over MgSO₄, filtered and evaporated under vacuum. The crude reaction mixture was purified by flash chromatography on silica gel to afford the desired product. Note that, in the case of solid amides, these are added in the tube before the solvent.



Chemical Formula: C₁₄H₁₅ClN₂O
Molecular Weight: 262.74 g/mol

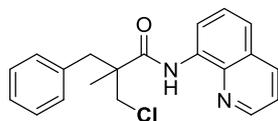
3-Chloro-2,2-dimethyl-N-(quinolin-8-yl)propanamide 30a. The product was purified by flash chromatography on silica gel (height 23 cm, width 1.5 cm, toluene + 1% Et₃N) as a colorless oil (21.2 mg, 40%). R_f (toluene + 1% Et₃N): 0.34.

¹H NMR (300.13 MHz, CDCl₃) δ 10.37 (s, 1H), 8.86 – 8.78 (m, 2H), 8.17 (dd, J = 8.4, 1.5 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.47 (dd, J = 8.4, 4.2 Hz, 1H), 3.80 (s, 2H), 1.55 (s, 6H).

¹³C NMR (75.5 MHz, CDCl₃) δ 173.4, 148.3, 138.8, 136.3, 134.2, 127.9, 127.4, 121.7, 121.6, 116.5, 52.8, 45.8, 23.7.

IR (neat, cm⁻¹) ν: 3350, 2975, 1669, 1531, 1488, 1424, 1383, 1327, 1284, 1133, 1061, 922, 824, 788, 682, 617.

HRMS (ESI⁺) calcd for C₁₄H₁₆ClN₂O m/z 263.0946 [M+H]⁺, Found 263.0950.



Chemical Formula: C₂₀H₁₉ClN₂O
Molecular Weight: 338.84 g/mol

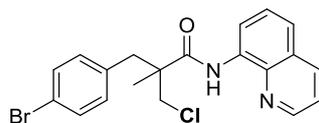
2-Benzyl-3-chloro-2-methyl-N-(quinolin-8-yl)propanamide 30c. The product was purified by flash chromatography on silica gel (height 23 cm, width 1.5 cm, toluene + 1% Et₃N) as a colorless oil (36.6 mg, 54%). R_f (toluene + 1% Et₃N): 0.38.

¹H NMR (300.13 MHz, CDCl₃) δ 10.15 (s, 1H), 8.74 (dd, J = 7.3, 1.5 Hz, 1H), 8.64 (dd, J = 4.2, 1.5 Hz, 1H), 8.03 (dd, J = 8.1, 1.5 Hz, 1H), 7.50 – 7.27 (m, 3H), 7.18 – 7.02 (m, 5H), 3.88 (d, J = 10.8 Hz, 1H), 3.58 (d, J = 10.8 Hz, 1H), 3.18 (d, J = 13.2 Hz, 1H), 2.94 (d, J = 13.2 Hz, 1H), 1.44 (s, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 172.4, 148.2, 138.7, 136.2, 136.1, 134.0, 130.2, 128.2, 127.8, 127.3, 126.8, 121.7, 121.5, 116.5, 51.1, 50.2, 42.9, 20.1.

IR (neat, cm⁻¹) v: 3354, 2964, 1674, 1527, 1509, 1487, 1424, 1383, 1325, 1261, 1104, 909, 825, 791, 701.

HRMS (ESI⁺) calcd for C₂₀H₂₀ClN₂O m/z 339.1259 [M+H]⁺, Found 339.1257.



Chemical Formula: C₂₀H₁₈BrClN₂O
Molecular Weight: 417.73 g/mol

2-(4-Bromobenzyl)-3-chloro-2-methyl-N-(quinolin-8-yl)propanamide 30e. The product was purified by flash chromatography on silica gel (height 24 cm, width 1.5 cm, toluene + 1% Et₃N) as a white vitrous solid (36.8 mg, 44%). R_f (toluene + 1% Et₃N): 0.43.

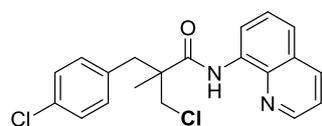
¹H NMR (300.13 MHz, CDCl₃) δ 10.18 (s, 1H), 8.81 – 8.72 (m, 2H), 8.16 (dd, J = 8.4, 1.5 Hz, 1H), 7.57 – 7.41 (m, 3H), 7.30 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 3.95 (d, J = 10.8 Hz, 1H), 3.68 (d, J = 10.8 Hz, 1H), 3.23 (d, J = 13.5 Hz, 1H), 2.94 (d, J =

13.5 Hz, 1H), 1.53 (s, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 172.0, 148.3, 138.6, 136.3, 135.2, 133.8, 131.8, 131.4, 127.9, 127.3, 121.9, 121.7, 120.9, 116.6, 51.1, 50.2, 42.3, 20.0.

IR (neat, cm^{-1}) v: 3335, 2958, 1677, 1526, 1486, 1424, 1383, 1326, 1220, 1073, 1012, 907, 824, 790, 729, 623.

HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{19}\text{BrClN}_2\text{O}$ m/z 417.0364 [M+H]⁺, Found 417.0356.



Chemical Formula: $\text{C}_{20}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}$
Molecular Weight: 373.28 g/mol

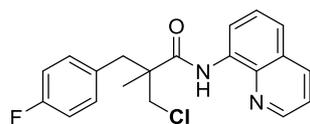
3-Chloro-2-(4-chlorobenzyl)-2-methyl-N-(quinolin-8-yl)propanamide 30f. The product was purified by flash chromatography on silica gel (height 22 cm, width 1.5 cm, toluene + 1% Et_3N) as a white vitrous solid (31.5 mg, 42%). R_f (toluene + 1% Et_3N): 0.43.

^1H NMR (300.13 MHz, CDCl_3) δ 10.19 (s, 1H), 8.86 – 8.68 (m, 2H), 8.15 (dd, $J = 8.4$, 1.5 Hz, 1H), 7.58 – 7.36 (m, 3H), 7.19 – 7.09 (m, 4H), 3.95 (d, $J = 10.8$ Hz, 1H), 3.68 (d, $J = 10.8$ Hz, 1H), 3.25 (d, $J = 13.5$ Hz, 1H), 2.96 (d, $J = 13.5$ Hz, 1H), 1.53 (s, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 172.0, 148.3, 138.6, 136.2, 134.7, 133.8, 132.8, 131.4, 128.4, 127.9, 127.3, 121.9, 121.6, 116.5, 51.1, 50.2, 42.2, 20.0.

IR (neat, cm^{-1}) v: 3352, 2927, 1674, 1526, 1486, 1424, 1383, 1324, 1284, 1092, 909, 827, 790, 683.

HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{19}\text{Cl}_2\text{N}_2\text{O}$ m/z 373.0869 [M+H]⁺, Found 373.0876.



Chemical Formula: $\text{C}_{20}\text{H}_{18}\text{ClFN}_2\text{O}$
Molecular Weight: 356.83 g/mol

3-Chloro-2-(4-fluorobenzyl)-2-methyl-N-(quinolin-8-yl)propanamide 30g. The product was purified by flash chromatography on silica gel (height 25 cm, width 1.5 cm,

toluene/petroleum ether = 90/10 + 1% Et₃N) as a colorless oil (30.8 mg, 43%). R_f (toluene + 1% Et₃N): 0.36.

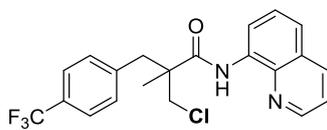
¹H NMR (300.13 MHz, CDCl₃) δ 10.19 (s, 1H), 8.88 – 8.65 (m, 2H), 8.15 (dd, J = 8.1, 1.5 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.44 (dd, J = 8.1, 4.2 Hz, 1H), 7.22 – 7.12 (m, 2H), 6.93 – 6.82 (m, 2H), 3.95 (d, J = 10.8 Hz, 1H), 3.68 (d, J = 10.8 Hz, 1H), 3.25 (d, J = 13.5 Hz, 1H), 2.98 (d, J = 13.5 Hz, 1H), 1.54 (s, 3H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 116.6 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 172.2, 161.9 (d, J = 245.4 Hz), 148.3, 138.7, 136.3, 133.9, 131.9 (d, J = 3.0 Hz), 131.6 (d, J = 8.3 Hz), 127.9, 127.3, 121.9, 121.6, 116.5, 115.1 (d, J = 21.1 Hz), 51.1, 50.3, 42.1, 20.0.

IR (neat, cm⁻¹) v: 3354, 2965, 1674, 1526, 1509, 1486, 1424, 1383, 1324, 1221, 1159, 1076, 909, 824, 789, 675.

HRMS (ESI⁺) calcd for C₂₀H₁₉ClFN₂O m/z 357.1164 [M+H]⁺, Found 357.1160.



Chemical Formula: C₂₁H₁₈ClF₃N₂O
Molecular Weight: 406.83 g/mol

3-Chloro-2-methyl-N-(quinolin-8-yl)-2-(4-(trifluoromethyl)benzyl)propanamide

30h. The product was purified by flash chromatography on silica gel (height 23 cm, width 1.5 cm, toluene/petroleum ether = 90:10 + 1% Et₃N) as a colorless oil (39.8 mg, 49%). R_f (toluene + 1% Et₃N): 0.31.

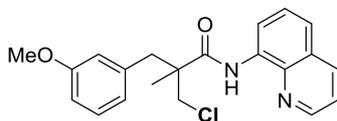
¹H NMR (300.13 MHz, CDCl₃) δ 10.18 (s, 1H), 8.85 – 8.67 (m, 2H), 8.14 (dd, J = 8.4, 1.5 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.47 – 7.28 (m, 5H), 3.97 (d, J = 11.1 Hz, 1H), 3.71 (d, J = 11.1 Hz, 1H), 3.34 (d, J = 13.2 Hz, 1H), 3.04 (d, J = 13.2 Hz, 1H), 1.56 (s, 3H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 63.0 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 171.8, 148.3, 140.5 (q, J = 1.5 Hz), 138.6, 136.2, 133.7, 130.5, 129.2 (q, J = 32.5 Hz), 127.9, 127.3, 125.1 (q, J = 3.8 Hz), 124.1 (q, J = 271.8 Hz), 122.0, 121.6, 116.6, 51.1, 50.2, 42.6, 20.0.

IR (neat, cm^{-1}) ν : 3353, 2962, 1675, 1527, 1487, 1424, 1384, 1322, 1162, 1114, 1066, 910, 824, 790, 678.

HRMS (ESI^+) calcd for $\text{C}_{21}\text{H}_{19}\text{ClF}_3\text{N}_2\text{O}$ m/z 407.1133 $[\text{M}+\text{H}]^+$, Found 407.1152.



Chemical Formula: $\text{C}_{21}\text{H}_{21}\text{ClN}_2\text{O}_2$
Molecular Weight: 368.86 g/mol

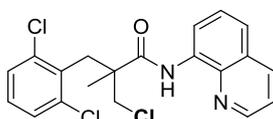
3-Chloro-2-(3-methoxybenzyl)-2-methyl-N-(quinolin-8-yl)propanamide 30d. The product was purified by flash chromatography on silica gel (height 28 cm, width 1.5 cm, toluene/diethyl ether = 98/2 + 1% Et_3N) as a colorless oil (37.4 mg, 51%). R_f (toluene/diethyl ether = 98/2 + 1% Et_3N): 0.37.

^1H NMR (300.13 MHz, CDCl_3) δ 10.23 (s, 1H), 8.89 – 8.66 (m, 2H), 8.15 (d, $J = 8.1$ Hz, 1H), 7.61 – 7.37 (m, 3H), 7.12 (t, $J = 7.8$ Hz, 1H), 6.85 – 6.62 (m, 3H), 3.99 (d, $J = 10.8$ Hz, 1H), 3.68 (d, $J = 10.8$ Hz, 1H), 3.58 (s, 3H), 3.25 (d, $J = 13.2$ Hz, 1H), 2.99 (d, $J = 13.2$ Hz, 1H), 1.55 (s, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 172.5, 159.4, 148.3, 138.7, 137.7, 136.2, 134.0, 129.2, 127.9, 127.3, 122.6, 121.8, 121.6, 116.5, 115.3, 112.7, 54.9, 51.2, 50.3, 43.1, 20.1.

IR (neat, cm^{-1}) ν : 3360, 2942, 1675, 1523, 1486, 1385, 1324, 1192, 1057, 903, 659.

HRMS (ESI^+) calcd for $\text{C}_{21}\text{H}_{22}\text{ClN}_2\text{O}_2$ m/z 369.1364 $[\text{M}+\text{H}]^+$, Found 369.1357.



Chemical Formula: $\text{C}_{20}\text{H}_{17}\text{Cl}_3\text{N}_2\text{O}$
Molecular Weight: 407.72 g/mol

3-Chloro-2-(2,6-dichlorobenzyl)-2-methyl-N-(quinolin-8-yl)propanamide 30j. The product was purified by flash chromatography on silica gel (height 23 cm, width 1.5 cm, toluene + 1% Et_3N) as a white vitreous solid (33.6 mg, 41%). R_f (toluene + 1% Et_3N): 0.43.

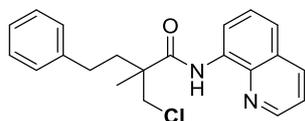
^1H NMR (300.13 MHz, CDCl_3): δ 10.27 (s, 1H), 8.89 – 8.63 (m, 2H), 8.14 (dd, $J = 8.4$,

1.5 Hz, 1H), 7.61 – 7.36 (m, 3H), 7.24 (d, $J = 8.1$ Hz, 2H), 7.06 (dd, $J = 8.4, 7.5$ Hz, 1H), 4.32 (d, $J = 10.5$ Hz, 1H), 3.76 (d, $J = 10.8$ Hz, 1H), 3.57 (d, $J = 14.4$ Hz, 1H), 3.49 (d, $J = 14.4$ Hz, 1H), 1.67 (s, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 171.9, 148.1, 138.7, 136.9, 136.2, 134.2, 133.5, 128.5, 128.5, 127.8, 127.4, 121.6, 121.5, 116.6, 52.3, 50.7, 38.1, 19.2.

IR (neat, cm^{-1}) ν : 3305, 2961, 1670, 1531, 1487, 1429, 1391, 1330, 1261, 1087, 1020, 907, 822, 790, 774, 571.

HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{18}\text{Cl}_3\text{N}_2\text{O}$ m/z 407.0479 $[\text{M}+\text{H}]^+$, Found 407.0493.



Chemical Formula: $\text{C}_{21}\text{H}_{21}\text{ClN}_2\text{O}$
Molecular Weight: 352.86 g/mol

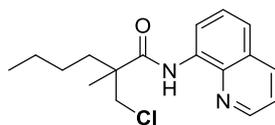
2-(Chloromethyl)-2-methyl-4-phenyl-N-(quinolin-8-yl)butanamide 30k. The product was purified by flash chromatography on silica gel (height 20 cm, width 1.5 cm, toluene/petroleum ether = 90:10 + 1% Et_3N) as a white vitreous solid (33.9 mg, 48%). R_f (toluene + 1% Et_3N): 0.40.

^1H NMR (300.13 MHz, CDCl_3) δ 10.33 (s, 1H), 8.80 – 8.69 (m, 2H), 8.10 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.53 – 7.35 (m, 3H), 7.21 – 7.05 (m, 5H), 3.92 (d, $J = 11.1$ Hz, 1H), 3.68 (d, $J = 11.1$ Hz, 1H), 2.73 – 2.50 (m, 2H), 2.28 – 2.10 (m, 1H), 1.94 – 1.79 (m, 1H), 1.58 (s, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 172.6, 148.4, 141.4, 138.8, 136.3, 134.1, 128.4, 128.4, 127.9, 127.4, 126.0, 121.8, 121.7, 116.5, 51.5, 49.2, 39.7, 31.0, 20.6.

IR (neat, cm^{-1}) ν : 3339, 2956, 1680, 1528, 1486, 1424, 1327, 1262, 1078, 908, 825, 791, 751, 699.

HRMS (ESI⁺) calcd for $\text{C}_{21}\text{H}_{22}\text{ClN}_2\text{O}$ m/z 353.1415 $[\text{M}+\text{H}]^+$, Found 353.1412.



Chemical Formula: C₁₇H₂₁ClN₂O
Molecular Weight: 304.82 g/mol

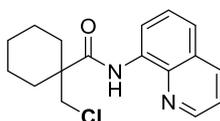
2-(Chloromethyl)-2-methyl-N-(quinolin-8-yl)hexanamide 30b. The product was purified by flash chromatography on silica gel (height 23 cm, width 1.5 cm, toluene + 1% Et₃N) as a colorless oil (28.1 mg, 46%). R_f (toluene + 1% Et₃N): 0.50.

¹H NMR (300.13 MHz, CDCl₃) δ 10.33 (s, 1H), 8.87 – 8.75 (m, 2H), 8.15 (dd, J = 8.4, 1.5 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.45 (dd, J = 8.1, 4.2 Hz, 1H), 3.96 (d, J = 10.8 Hz, 1H), 3.68 (d, J = 10.8 Hz, 1H), 1.61 – 1.24 (m, 9H), 0.89 (t, J = 6.6 Hz, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 173.0, 148.3, 138.8, 136.2, 134.2, 127.9, 127.3, 121.6, 121.6, 116.4, 51.8, 49.1, 37.4, 26.6, 23.1, 20.4, 13.8.

IR (neat, cm⁻¹) v: 3358, 2956, 1674, 1525, 1486, 1424, 1382, 1324, 1240, 1132, 1079, 916, 825, 790, 676.

HRMS (ESI⁺) calcd for C₁₇H₂₂ClN₂O m/z 305.1415 [M+H]⁺, Found 305.1429.



Chemical Formula: C₁₇H₁₉ClN₂O
Molecular Weight: 302.80 g/mol

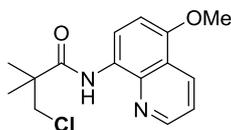
1-(Chloromethyl)-N-(quinolin-8-yl)cyclohexane-1-carboxamide 30v. The product was purified by flash chromatography on silica gel (height 23 cm, width 1.5 cm, petroleum ether/diethyl ether 94:6) as a colorless oil (18.8 mg, 31%), R_f (petroleum ether/diethyl ether 80:20): 0.42.

¹H NMR (300.13 MHz, CDCl₃): δ 10.42 (s, 1H), 8.82 (s, 2H), 8.16 (d, J = 8.4 Hz, 1H), 7.61 – 7.40 (m, 3H), 3.78 (s, 2H), 2.42 – 2.19 (m, 2H), 1.79 – 1.52 (m, 8H).

¹³C NMR (75.5 MHz, CDCl₃): δ 172.5, 148.4, 138.8, 136.3, 134.2, 127.9, 127.4, 121.6, 121.6, 116.5, 51.9, 49.6, 32.2, 25.7, 22.6.

IR (neat, cm⁻¹) v: 3353, 2930, 1674, 1525, 1509, 1486, 1423, 1385, 1325, 1260, 1166, 904, 825, 789, 670.

HRMS (ESI⁺) calcd for C₁₇H₂₀ClN₂O m/z 303.1264 [M+H]⁺, Found 303.1266.



Chemical Formula: C₁₅H₁₇ClN₂O₂
Molecular Weight: 292.76 g/mol

3-Chloro-N-(5-methoxyquinolin-8-yl)-2,2-dimethylpropanamide 30w. The product was purified by flash chromatography on silica gel (height 28 cm, width 1.5 cm, toluene/diethyl ether = 90/10) as a yellow vitrous solid (28.1 mg, 48%). R_f (toluene/diethyl ether = 90/10): 0.42.

¹H NMR (300.13 MHz, CDCl₃) δ 10.12 (s, 1H), 8.83 (dd, J = 4.2, 1.5 Hz, 1H), 8.72 (d, J = 8.7 Hz, 1H), 8.57 (dd, J = 8.4, 1.5 Hz, 1H), 7.44 (dd, J = 8.4, 4.5 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 3.98 (s, 3H), 3.79 (s, 2H), 1.53 (s, 6H).

¹³C NMR (75.5 MHz, CDCl₃) δ 172.9, 150.4, 148.8, 139.4, 131.2, 127.6, 120.7, 120.4, 116.6, 104.2, 55.7, 52.9, 45.6, 23.6.

IR (neat, cm⁻¹) v:3330, 2922, 2852, 1673, 1538, 1498, 1439, 1274, 1091, 836, 783, 703.

HRMS (ESI⁺) calcd for C₁₅H₁₈ClN₂O₂ m/z 293.1051 [M+H]⁺, Found 293.1046.



Chemical Formula: C₁₄H₁₄Cl₂N₂O
Molecular Weight: 297.18 g/mol

3-Chloro-2-(chloromethyl)-2-methyl-N-(quinolin-8-yl)propanamide 31a. The product was purified by flash chromatography on silica gel (height 23 cm, width 1.5 cm, toluene + 1% Et₃N) as a white vitrous solid (4.8 mg, 8%). R_f (toluene + 1% Et₃N): 0.48.

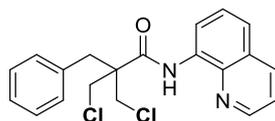
¹H NMR (300.13 MHz, CDCl₃) δ 10.42 (s, 1H), 8.84 (dd, J = 4.2, 1.5 Hz, 1H), 8.81 – 8.73 (m, 1H), 8.18 (dd, J = 8.4, 1.5 Hz, 1H), 7.58 – 7.44 (m, 2H), 3.95 (q, J = 12.3, 4H), 1.69 (s, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 170.1, 148.5, 138.7, 136.4, 133.8, 127.9, 127.3, 122.1,

121.7, 116.7, 50.7, 48.7, 19.4.

IR (neat, cm^{-1}) ν : 3332, 2962, 1688, 1532, 1489, 1426, 1391, 1332, 1063, 908, 823, 789, 695, 651.

HRMS (ESI^+) calcd for $\text{C}_{14}\text{H}_{15}\text{Cl}_2\text{N}_2\text{O}$ m/z 297.0381 $[\text{M}+\text{H}]^+$, Found 297.0556.



Chemical Formula: $\text{C}_{20}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}$
Molecular Weight: 373.28 g/mol

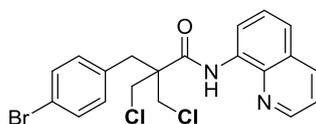
2-Benzyl-3-chloro-2-(chloromethyl)-N-(quinolin-8-yl)propanamide 31c. The product was purified by flash chromatography on silica gel (height 23 cm, width 1.5 cm, toluene + 1% Et_3N) as a white vitreous solid (14.8 mg, 20%, procedure F; 38.2 mg, 51%, procedure G). R_f (toluene + 1% Et_3N): 0.53.

^1H NMR (300.13 MHz, CDCl_3) δ 10.21 (s, 1H), 8.84 – 8.69 (m, 2H), 8.17 (d, $J = 8.4$ Hz, 1H), 7.60 – 7.38 (m, 3H), 7.35 – 7.10 (m, 5H), 4.07 – 3.85 (m, 4H), 3.29 (s, 2H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 168.9, 148.4, 138.6, 136.3, 134.7, 133.5, 129.9, 128.6, 127.8, 127.3, 127.3, 122.1, 121.7, 116.8, 55.3, 45.6, 37.9.

IR (neat, cm^{-1}) ν : 3341, 2959, 1678, 1526, 1509, 1486, 1424, 1386, 1325, 1260, 1167, 1089, 907, 825, 790, 700.

HRMS (ESI^+) calcd for $\text{C}_{20}\text{H}_{19}\text{Cl}_2\text{N}_2\text{O}$ m/z 373.0869 $[\text{M}+\text{H}]^+$, Found 373.0871.



Chemical Formula: $\text{C}_{20}\text{H}_{17}\text{BrCl}_2\text{N}_2\text{O}$
Molecular Weight: 452.17 g/mol

2-(4-Bromobenzyl)-3-chloro-2-(chloromethyl)-N-(quinolin-8-yl)propanamide 31e.

The product was purified by flash chromatography on silica gel (height 24 cm, width 1.5 cm, toluene + 1% Et_3N) as a white vitreous solid (18.3 mg, 20%, procedure F; 47.1 mg, 52%, procedure G). R_f (toluene + 1% Et_3N): 0.59.

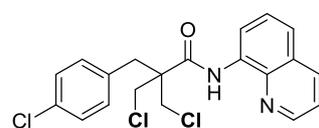
^1H NMR (300.13 MHz, CDCl_3) δ 10.13 (s, 1H), 8.81 – 8.67 (m, 2H), 8.18 (dd, $J = 8.4$,

1.5 Hz, 1H), 7.62 – 7.42 (m, 3H), 7.35 – 7.27 (m, 2H), 7.20 – 7.13 (m, 2H), 4.06 – 3.88 (m, 4H), 3.22 (s, 2H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 168.5, 148.5, 138.5, 136.4, 133.7, 133.3, 131.7, 131.6, 127.9, 127.3, 122.3, 121.8, 121.5, 116.9, 55.3, 45.4, 37.5.

IR (neat, cm^{-1}) v: 3350, 2927, 1673, 1525, 1486, 1423, 1383, 1324, 1260, 1112, 1072, 909, 824, 789, 677.

HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{18}\text{BrCl}_2\text{N}_2\text{O}$ m/z 450.9974 [M+H]⁺, Found 450.9970.



Chemical Formula: $\text{C}_{20}\text{H}_{17}\text{Cl}_3\text{N}_2\text{O}$
Molecular Weight: 407.72 g/mol

3-Chloro-2-(4-chlorobenzyl)-2-(chloromethyl)-N-(quinolin-8-yl)propanamide 31f.

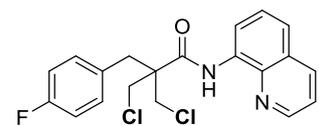
The product was purified by flash chromatography on silica gel (height 22 cm, width 1.5 cm, toluene + 1% Et_3N) as a white vitreous solid (13.9 mg, 17%, procedure F; 43.7 mg, 54%, procedure G). R_f (toluene + 1% Et_3N): 0.63.

^1H NMR (300.13 MHz, CDCl_3) δ 10.13 (s, 1H), 8.81 – 8.67 (m, 2H), 8.18 (dd, $J = 8.4$, 1.5 Hz, 1H), 7.61 – 7.42 (m, 3H), 7.23 – 7.13 (m, 4H), 4.06 – 3.88 (m, 4H), 3.23 (s, 2H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 168.6, 148.5, 138.5, 136.4, 133.3, 131.2, 128.8, 127.9, 127.3, 122.3, 121.8, 119.5, 116.9, 115.1, 55.4, 45.4, 37.5.

IR (neat, cm^{-1}) v: 3420, 2917, 1699, 1580, 1485, 1399, 1327, 1261, 1087, 1019, 796, 749, 596.

HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{18}\text{Cl}_3\text{N}_2\text{O}$ m/z 407.0479 [M+H]⁺, Found 407.0492.



Chemical Formula: $\text{C}_{20}\text{H}_{17}\text{Cl}_2\text{FN}_2\text{O}$
Molecular Weight: 391.27 g/mol

3-Chloro-2-(chloromethyl)-2-(4-fluorobenzyl)-N-(quinolin-8-yl)propanamide 31g.

The product was purified by flash chromatography on silica gel (height 25 cm, width

1.5 cm, toluene/petroleum ether = 90/10 + 1% Et₃N) as a colorless oil (11.8 mg, 15%).

R_f (toluene + 1% Et₃N): 0.56.

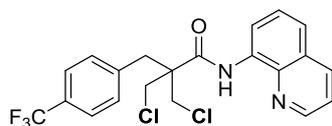
¹H NMR (300.13 MHz, CDCl₃) δ 10.07 (s, 1H), 8.74 – 8.60 (m, 2H), 8.10 (dd, J = 8.4, 1.5 Hz, 1H), 7.56 – 7.33 (m, 3H), 7.23 – 7.14 (m, 2H), 6.88 – 6.71 (m, 2H), 3.98 – 3.78 (m, 4H), 3.16 (s, 2H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 115.6 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 168.6, 162.2 (d, J = 246.1 Hz), 148.5, 138.6, 136.4, 133.4, 131.5 (d, J = 8.3 Hz), 130.5 (d, J = 3.8 Hz), 127.9, 127.3, 122.2, 121.8, 116.8, 115.5 (d, J = 21.1 Hz), 55.4, 45.4, 37.3.

IR (neat, cm⁻¹) v: 3339, 2959, 1677, 1509, 1486, 1424, 1387, 1325, 1222, 1133, 1100, 908, 824, 731, 668.

HRMS (ESI⁺) calcd for C₂₀H₁₈Cl₂FN₂O m/z 391.0775 [M+H]⁺, Found 391.0786.



Chemical Formula: C₂₁H₁₇Cl₂F₃N₂O
Molecular Weight: 441.28 g/mol

3-Chloro-2-(chloromethyl)-N-(quinolin-8-yl)-2-(4-(trifluoromethyl)benzyl)propanamide 31h. The product was purified by flash chromatography on silica gel (height 23 cm, width 1.5 cm, toluene/petroleum ether = 90:10 + 1% Et₃N) as a colorless oil (17.4 mg, 20%). R_f (toluene + 1% Et₃N): 0.51.

¹H NMR (300.13 MHz, CDCl₃): δ 10.12 (s, 1H), 8.78 – 8.67 (m, 2H), 8.17 (dd, J = 8.1, 1.5 Hz, 1H), 7.56 (d, J = 4.5 Hz, 2H), 7.49 – 7.37 (m, 5H), 4.11 – 3.88 (m, 4H), 3.31 (s, 2H).

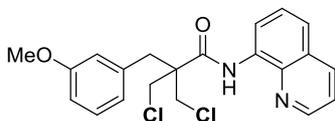
¹⁹F NMR (282.4 MHz, CDCl₃) δ – 63.2 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 168.3, 148.5, 139.0, 138.5, 136.4, 133.3, 130.3, 129.7 (q, J = 32.5 Hz), 127.9, 127.3, 125.5 (q, J = 3.8 Hz), 124.0 (q, J = 272.6 Hz), 122.4, 121.8, 116.9, 55.4, 45.3, 38.0.

IR (neat, cm⁻¹) v: 3353, 2965, 1676, 1527, 1487, 1424, 1322, 1162, 1115, 1067, 910,

825, 791, 628.

HRMS (ESI⁺) calcd for C₂₁H₁₈Cl₂F₃N₂O m/z 441.0743 [M+H]⁺, Found 441.0750.



Chemical Formula: C₂₁H₂₀Cl₂N₂O₂
Molecular Weight: 403.30 g/mol

3-Chloro-2-(chloromethyl)-2-(3-methoxybenzyl)-N-(quinolin-8-yl)propanamide

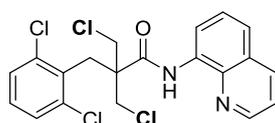
31d. The product was purified by flash chromatography on silica gel (height 28 cm, width 1.5 cm, toluene/diethyl ether = 98:2 + 1% Et₃N) as a white vitreous solid (13.3 mg, 17%). R_f (toluene/diethyl ether = 98/2 + 1% Et₃N): 0.50.

¹H NMR (300.13 MHz, CDCl₃) δ 10.18 (s, 1H), 8.81 – 8.70 (m, 2H), 8.17 (dd, J = 8.1, 1.5 Hz, 1H), 7.58 – 7.42 (m, 3H), 7.12 (t, J = 8.1 Hz, 1H), 6.93 – 6.66 (m, 3H), 4.08 – 3.90 (m, 4H), 3.53 (s, 3H), 3.26 (s, 2H).

¹³C NMR (75.5 MHz, CDCl₃) δ 168.9, 159.6, 148.4, 138.6, 136.3, 136.2, 133.5, 129.5, 127.8, 127.3, 122.2, 122.1, 121.7, 116.8, 114.9, 113.4, 55.4, 54.9, 45.6, 38.1.

IR (neat, cm⁻¹) v: 3339, 2961, 1677, 1527, 1509, 1486, 1424, 1386, 1324, 1261, 1169, 1076, 908, 825, 789, 697.

HRMS (ESI⁺) calcd for C₂₁H₂₁Cl₂N₂O₂ m/z 403.0975 [M+H]⁺, Found 403.0995.



Chemical Formula: C₂₀H₁₆Cl₄N₂O
Molecular Weight: 442.16 g/mol

3-Chloro-2-(chloromethyl)-2-(2,6-dichlorobenzyl)-N-(quinolin-8-yl)propanamide

31j. The product was purified by flash chromatography on silica gel (height 23 cm, width 1.5 cm, toluene + 1% Et₃N) as a white vitreous solid (25.1 mg, 28%). R_f (toluene + 1% Et₃N): 0.60.

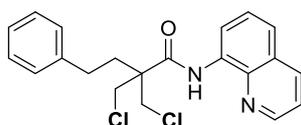
¹H NMR (300.13 MHz, CDCl₃) δ 9.90 (s, 1H), 8.71 – 8.50 (m, 2H), 8.12 (dd, J = 8.4, 1.5 Hz, 1H), 7.57 – 7.34 (m, 3H), 7.14 (d, J = 7.8 Hz, 2H), 6.99 (dd, J = 8.4, 7.5 Hz, 1H),

4.40 (d, $J = 11.7$ Hz, 2H), 4.24 (d, $J = 11.7$ Hz, 2H), 3.65 (s, 2H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 167.9, 147.9, 138.3, 137.3, 136.1, 133.8, 132.0, 128.9, 128.5, 127.7, 127.4, 121.7, 121.5, 116.6, 54.9, 46.8, 35.7.

IR (neat, cm^{-1}) ν : 3355, 2970, 1678, 1527, 1487, 1424, 1383, 1324, 1263, 1086, 908, 825, 790, 759, 676.

HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{17}\text{Cl}_4\text{N}_2\text{O}$ m/z 441.0090 $[\text{M}+\text{H}]^+$, Found 441.0099.



Chemical Formula: $\text{C}_{21}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}$
Molecular Weight: 387.30 g/mol

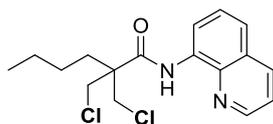
2,2-Bis(chloromethyl)-4-phenyl-N-(quinolin-8-yl)butanamide 31k. The product was purified by flash chromatography on silica gel (height 20 cm, width 1.5 cm, toluene/petroleum ether = 90/10 + 1% Et_3N) as a white vitreous solid (16.3 mg, 21%, procedure F; 39.3 mg, 51%, procedure G). R_f (toluene + 1% Et_3N): 0.58.

^1H NMR (300.13 MHz, CDCl_3) δ 10.32 (s, 1H), 8.81 – 8.63 (m, 2H), 8.12 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.53 – 7.36 (m, 3H), 7.21 – 7.06 (m, 5H), 4.09 – 3.94 (m, 4H), 2.69 – 2.56 (m, 2H), 2.21 – 2.08 (m, 2H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 169.3, 148.5, 140.6, 138.6, 136.4, 133.6, 128.5, 128.4, 127.9, 127.3, 126.2, 122.1, 121.8, 116.8, 53.7, 45.8, 35.4, 30.5.

IR (neat, cm^{-1}) ν : 3355, 2952, 1674, 1525, 1486, 1423, 1383, 1325, 1261, 1156, 1077, 906, 825, 790, 732, 697.

HRMS (ESI⁺) calcd for $\text{C}_{21}\text{H}_{21}\text{Cl}_2\text{N}_2\text{O}$ m/z 387.1025 $[\text{M}+\text{H}]^+$, Found 387.1017.



Chemical Formula: $\text{C}_{17}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}$
Molecular Weight: 339.26 g/mol

2,2-Bis(chloromethyl)-N-(quinolin-8-yl)hexanamide 31b. The product was purified by flash chromatography on silica gel (height 23 cm, width 1.5 cm, toluene + 1% Et_3N)

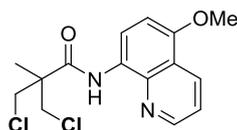
as a colorless oil (13.4 mg, 20%, procedure F; 34.2 mg, 50%, procedure G). R_f (toluene + 1% Et₃N): 0.53.

¹H NMR (300.13 MHz, CDCl₃) δ 10.31 (s, 1H), 8.83 (dd, $J = 4.2, 1.5$ Hz, 1H), 8.78 – 8.70 (m, 1H), 8.18 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.57 – 7.44 (m, 3H), 4.12 – 3.97 (m, 4H), 1.98 – 1.84 (m, 2H), 1.44 – 1.32 (m, 4H), 0.94 – 0.83 (m, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 169.7, 148.4, 138.7, 136.4, 133.8, 127.9, 127.3, 122.0, 121.7, 116.7, 53.7, 46.0, 32.9, 26.1, 22.9, 13.7.

IR (neat, cm⁻¹) ν : 3340, 2958, 1680, 1526, 1486, 1424, 1386, 1326, 1288, 1102, 909, 825, 790, 749, 670, 575.

HRMS (ESI⁺) calcd for C₁₇H₂₁Cl₂N₂O m/z 339.1025 [M+H]⁺, Found 339.1021.



Chemical Formula: C₁₅H₁₆Cl₂N₂O₂
Molecular Weight: 327.21 g/mol

3-Chloro-2-(chloromethyl)-N-(5-methoxyquinolin-8-yl)-2-methylpropanamide

31w. The product was purified by flash chromatography on silica gel (height 28 cm, width 1.5 cm, toluene/diethyl ether = 90/10) as a yellow vitrous solid (6.1 mg, 9%). The product contains an inseparable impurity. R_f (toluene/diethyl ether = 90/10): 0.53.

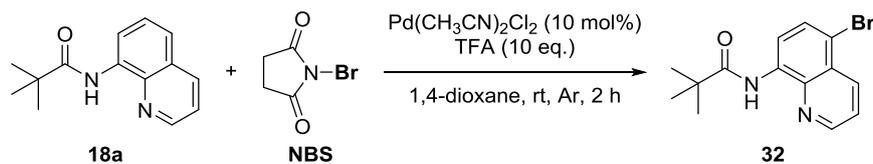
¹H NMR (300.13 MHz, CDCl₃) δ 10.16 (s, 1H), 8.84 (d, $J = 3.0$ Hz, 1H), 8.69 (d, $J = 8.4$ Hz, 1H), 8.58 (d, $J = 7.8$ Hz, 1H), 7.45 (dd, $J = 8.4, 4.2$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 4.03 – 3.85 (m, 7H), 1.67 (s, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 169.5, 150.7, 148.9, 139.4, 131.3, 127.2, 120.8, 120.4, 116.9, 104.1, 55.8, 50.5, 48.8, 19.3.

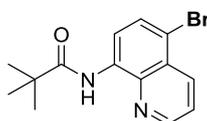
IR (neat, cm⁻¹) ν : 3351, 2958, 1670, 1529, 1495, 1399, 1269, 1089, 907, 816, 786, 730, 605.

HRMS (ESI⁺) calcd for C₁₅H₁₉N₂O₂ m/z 327.0662 [M+H]⁺, Found 327.0673.

2.4 Procedure for the remote bromination with N-bromosuccinimide (NBS)



An oven-dried 10 mL glassware equipped with a stirring bar was charged with Pd(CH₃CN)₂Cl₂ (2.6 mg, 0.01 mmol, 0.1 eq.), N-Bromosuccinimide (NBS, 17.8 mg, 0.1 mmol, 1 eq.) and 2 mL of 1,4-dioxane under argon. Then, N-(quinolin-8-yl)pivalamide **18a** (45.6 mg, 0.2 mmol, 2 eq.) and TFA (1 mmol, 10 eq.) was added. The tube was flushed with argon, sealed, and stirred vigorously at room temperature until NBS was fully consumed. Then, the reaction mixture was diluted with diethyl ether (20 mL) and water. The organic layer was washed with saturated aqueous NaHCO₃ (3 × 20 mL), dried over MgSO₄, filtered and evaporated under vacuum. The product was purified by flash chromatography on silica gel (height 12 cm, width 1.5 cm, petroleum ether/diethyl ether = 90/10) as a white vitreous solid (15.2 mg, 50%).



Chemical Formula: C₁₄H₁₅BrN₂O
 Molecular Weight: 307.19 g/mol

N-(5-bromoquinolin-8-yl)pivalamide **32**.

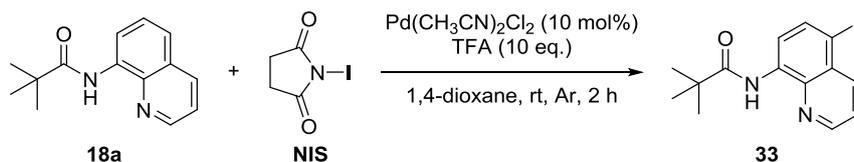
¹H NMR (300.13 MHz, CDCl₃) δ 10.23 (s, 1H), 8.83 (dd, J = 4.2, 1.5 Hz, 1H), 8.69 (d, J = 8.4 Hz, 1H), 8.51 (dd, J = 8.4, 1.5 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.55 (dd, J = 8.4, 4.2 Hz, 1H), 1.42 (s, 9H).

¹³C NMR (75.5 MHz, CDCl₃) δ 176.4, 150.6, 144.0, 135.8, 134.2, 134.2, 126.8, 122.7, 120.1, 118.5, 43.0, 31.8.

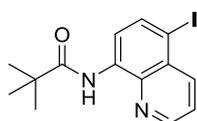
IR (neat, cm⁻¹) ν: 3371, 2969, 1676, 1516, 1482, 1366, 1318, 1178, 1145, 930, 834, 781, 679, 547.

HRMS (ESI⁺) calcd for C₁₄H₁₆BrN₂O m/z 307.0441 [M+H]⁺, Found 307.0433.

2.5 Procedure for the remote iodination with N-iodosuccinimide (NIS)



An oven-dried 10 mL glassware equipped with a stirring bar was charged with Pd(CH₃CN)₂Cl₂ (5.2 mg, 0.02 mmol, 0.1 eq.), N-iodosuccinimide (NIS, 22.7 mg, 0.2 mmol, 1 eq.) and 2 mL of 1,4-dioxane under argon. Then, N-(quinolin-8-yl)pivalamide **18a** (45.6 mg, 0.2 mmol, 2 eq.) and TFA (1 mmol, 10 eq.) was added. The tube was flushed with argon, sealed and stirred vigorously at room temperature until NIS was fully consumed. Then, the reaction mixture was diluted with diethyl ether (20 mL) and water. The organic layer was washed with saturated aqueous NaHCO₃ (3 × 20 mL), dried over MgSO₄, filtered and evaporated under vacuum. The product was purified by flash chromatography on silica gel (height 14 cm, width 1.5 cm, petroleum ether/diethyl ether = 85/15) as a white vitreous solid (20.2 mg, 57%). R_f (petroleum ether/diethyl ether = 80/20): 0.26.



Chemical Formula: C₁₄H₁₅IN₂O
Molecular Weight: 354.19 g/mol

N-(5-iodoquinolin-8-yl)pivalamide **33**.

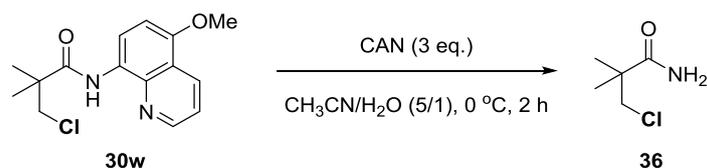
¹H NMR (300.13 MHz, CDCl₃) δ 10.26 (s, 1H), 8.78 (dd, J = 4.2, 1.5 Hz, 1H), 8.57 (d, J = 8.4 Hz, 1H), 8.36 (dd, J = 8.4, 1.5 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.53 (dd, J = 8.4, 4.2 Hz, 1H), 1.42 (s, 9H).

¹³C NMR (75.5 MHz, CDCl₃) δ 177.3, 148.7, 140.7, 139.4, 138.3, 135.6, 129.5, 123.0, 117.6, 88.9, 40.4, 27.6.

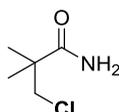
IR (neat, cm⁻¹) ν: 3370, 2962, 1675, 1515, 1479, 1358, 1315, 1175, 1145, 926, 834, 780, 676.

HRMS (ESI⁺) calcd for C₁₄H₁₆IN₂O m/z 355.0302 [M+H]⁺, Found 355.0313.

2.6 Procedure for the cleavage of the directing group on compound **30w**



An oven-dried 10 ml glassware equipped with a stirring bar was charged with **30w** (29.2 mg, 0.11 mmol, 1 eq.), dissolved in a mixture of CH₃CN and H₂O (5/1, 1.8 mL). The reaction mixture was cooled to 0 °C and ceric ammonium nitrate (CAN) (164.5 mg, 0.33 mmol, 3 eq.) was added. The obtained reaction mixture was stirred at 0 °C for 2 h. Then, water (20 mL) was added and the aqueous layer was extracted with EtOAc (20 mL). The organic layer was washed with saturated NaHCO₃ (2 × 20 mL), and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered and the solvent was evaporated under vacuum. The reaction mixture was purified by flash chromatography on silica gel (height 18 cm, width 1.5 cm, petroleum ether/ethyl acetate = 50/50) and the product **36** was obtained after precipitation of a residual impurity in hot ethanol as a pale brown vitrous solid (10.1 mg, 68%). R_f (petroleum ether/ethyl acetate = 50/50): 0.32.



Chemical Formula: C₅H₁₀ClNO
Molecular Weight: 135.59 g/mol

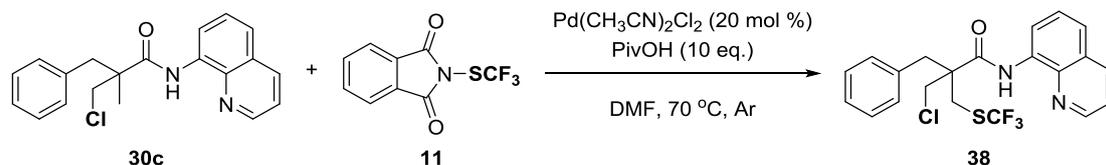
3-Chloro-2,2-dimethylpropanamide **36**.

¹H NMR (300.13 MHz, CDCl₃) δ 5.77 (s, 2H), 3.62 (s, 2H), 1.32 (s, 6H).

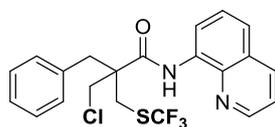
¹³C NMR (75.5 MHz, CDCl₃) δ 177.4, 52.4, 44.1, 23.7.

IR (neat, cm⁻¹) ν: 3400, 3210, 2926, 1651, 1478, 1366, 1256, 1161, 1109, 912, 708, 604.

2.7 Procedure for the trifluoromethylthiolation of **38**



An oven-dried 10 mL glassware equipped with a stirring bar was charged with $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (2.6 mg, 0.01 mmol, 0.2 eq.), **11** (12.4 mg, 0.05 mmol, 1 eq.), PivOH (51.1 mg, 0.5 mmol, 10 eq.), and 0.5 mL of DMF under argon. Then, **30c** (23.7 mg, 0.07 mmol, 1.3 eq.) was added. The tube was flushed with argon, sealed and then placed in an oil bath preheated to 70 °C and stirred vigorously for 22 h. The reaction mixture was cooled to room temperature and diluted with diethyl ether (20 mL). The organic layer was washed with saturated aqueous NaHCO_3 (3 × 20 mL) and brine (20 mL), dried over MgSO_4 , filtered and evaporated under vacuum. The crude was purified by flash chromatography on silica gel (height 18 cm, width 1.5 cm, pentane/dichloromethane = 70/30) to give the product **38** as a yellow oil (7.3 mg, 33%). R_f (pentane/dichloromethane = 70/30): 0.50.



Chemical Formula: $\text{C}_{21}\text{H}_{18}\text{ClF}_3\text{N}_2\text{OS}$
 Molecular Weight: 438.89 g/mol

2-Benzyl-3-chloro-N-(quinolin-8-yl)-2-(((trifluoromethyl)thio)methyl)propanamide **38**

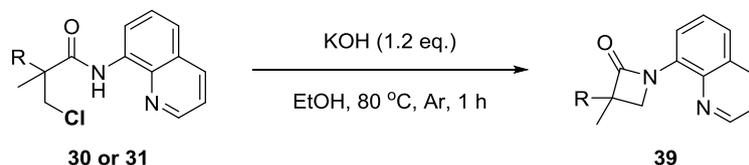
$^1\text{H NMR}$ (300.13 MHz, CDCl_3): δ 10.14 (s, 1H), 8.75 – 7.56 (m, 2H), 8.10 (d, $J = 8.1$ Hz, 1H), 7.52 – 7.34 (m, 3H), 7.21 – 7.09 (m, 5H), 3.89 (s, 2H), 3.46 – 3.26 (m, 2H), 3.22 (d, $J = 2.5$ Hz, 2H).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3): δ – 41.6 (s).

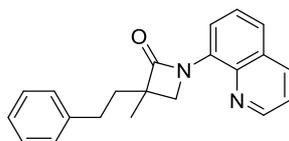
$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3): δ 169.0, 148.4, 138.6, 136.1, 134.5, 133.3, 130.5 (q, $J = 306.5$ Hz), 129.9, 128.7, 127.8, 127.5, 127.3, 122.2, 121.8, 116.8, 53.7, 46.1, 39.7, 33.5.

IR (neat, cm^{-1}) ν : 3336, 3031, 2927, 1676, 1527, 1487, 1425, 1326, 1104, 906, 825, 790,

755, 701.

2.8 Procedure for the synthesis of lactames

An oven-dried 10 ml glassware equipped with a stirring bar was charged with amide **30** or **31** (0.1 mmol, 1 eq.) and 2 mL of EtOH under argon. The reaction mixture was stirred at 80 °C for 1 h. After completion, the reaction mixture was cooled down to room temperature and water (10 mL) was added. Then, the aqueous layer was extracted with ether (3 × 10 mL), dried over MgSO₄, filtered and the solvent was evaporated under vacuum. The reaction mixture was purified by flash chromatography on silica gel to afford the desired product **39**.



Chemical Formula: C₂₁H₂₀N₂O
Molecular Weight: 316.40 g/mol

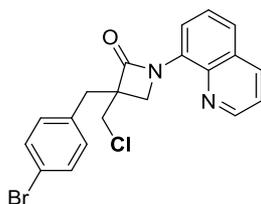
3-Methyl-3-phenethyl-1-(quinolin-8-yl)azetidin-2-one 39a. The product was purified by flash chromatography on silica gel (height 12 cm, width 1.5 cm, petroleum ether/diethyl ether = 60/40) as a yellow oil (20.1 mg, 91%, on 0.07 mmol scale). R_f (petroleum ether/diethyl ether = 50/50): 0.58.

¹H NMR (300.13 MHz, CDCl₃) δ 8.73 (dd, J = 4.2, 1.5 Hz, 1H), 8.48 – 8.36 (m, 1H), 8.02 (dd, J = 8.4, 1.5 Hz, 1H), 7.48 – 7.25 (m, 3H), 7.23 – 7.05 (m, 5H), 4.39 (d, J = 7.5 Hz, 1H), 4.22 (d, J = 7.2 Hz, 1H), 2.90 – 2.54 (m, 2H), 2.08 – 1.91 (m, 2H), 1.44 (s, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 172.8, 148.5, 141.8, 140.4, 135.9, 135.0, 128.9, 128.4, 128.3, 126.7, 125.9, 122.8, 121.2, 119.5, 58.5, 55.2, 37.0, 31.2, 19.6.

IR (neat, cm⁻¹) ν: 2961, 1733, 1569, 1504, 1473, 1399, 1345, 1197, 1150, 824, 788, 824, 697.

HRMS (ESI⁺) calcd for C₂₁H₂₁N₂O m/z 317.1648 [M+H]⁺, Found 317.1647.



Chemical Formula: $C_{20}H_{16}BrClN_2O$
Molecular Weight: 415.72 g/mol

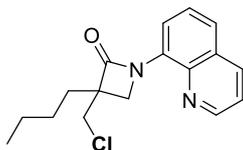
3-(4-Bromobenzyl)-3-(chloromethyl)-1-(quinolin-8-yl)azetidin-2-one 39b. The product was purified by flash chromatography on silica gel (height 15 cm, width 1.5 cm, petroleum ether/diethyl ether = 50/50) as a colorless oil (34.4 mg, 83%). R_f (petroleum ether/diethyl ether = 50/50): 0.25.

1H NMR (300.13 MHz, $CDCl_3$) δ 8.71 (dd, $J = 3.9, 1.5$ Hz, 1H), 8.28 (dd, $J = 7.2, 1.2$ Hz, 1H), 8.02 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.49 – 7.24 (m, 5H), 7.21 – 7.10 (m, 2H), 4.51 (d, $J = 8.1$ Hz, 1H), 4.28 (d, $J = 7.8$ Hz, 1H), 3.85 (d, $J = 11.4$ Hz, 1H), 3.68 (d, $J = 11.4$ Hz, 1H), 3.24 – 3.03 (m, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.0, 148.7, 140.4, 135.9, 134.7, 134.0, 131.8, 131.6, 128.9, 126.6, 123.6, 121.3, 121.1, 119.8, 60.7, 54.3, 46.0, 36.7.

IR (neat, cm^{-1}) ν : 2918, 1737, 1505, 1474, 1402, 1354, 1154, 1012, 906, 824, 788, 659.

HRMS (ESI⁺) calcd for $C_{20}H_{17}BrClN_2O$ m/z 415.0207 $[M+H]^+$, Found 415.0214.



Chemical Formula: $C_{17}H_{19}ClN_2O$
Molecular Weight: 302.80 g/mol

3-Butyl-3-(chloromethyl)-1-(quinolin-8-yl)azetidin-2-one 39c. The product was purified by flash chromatography on silica gel (height 15 cm, width 1.5 cm, petroleum ether/diethyl ether = 70/30) as a colorless oil (25.6 mg, 84%). R_f (petroleum ether/diethyl ether = 60/40): 0.47.

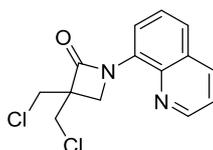
1H NMR (300.13 MHz, $CDCl_3$) δ 8.82 (dd, $J = 3.9, 1.5$ Hz, 1H), 8.47 (dd, $J = 6.9, 1.8$ Hz, 1H), 8.11 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.57 – 7.44 (m, 2H), 7.39 (dd, $J = 8.4, 4.2$ Hz,

1H), 4.55 (d, J = 7.8 Hz, 1H), 4.45 (d, J = 7.8 Hz, 1H), 3.93 (d, J = 11.4 Hz, 1H), 3.82 (d, J = 11.4 Hz, 1H), 2.01 – 1.81 (m, 2H), 1.63 – 1.31 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 169.0, 148.6, 140.3, 135.9, 134.3, 128.9, 126.6, 123.2, 121.2, 119.6, 60.4, 54.9, 46.2, 31.3, 26.5, 23.0, 13.9.

IR (neat, cm⁻¹) v: 2931, 1736, 1504, 1474, 1399, 1351, 1152, 825, 788, 756.

HRMS (ESI⁺) calcd for C₁₇H₂₀ClN₂O m/z 303.1259 [M+H]⁺, Found 303.1260.



Chemical Formula: C₁₄H₁₂Cl₂N₂O
Molecular Weight: 295.16 g/mol

3,3-bis(chloromethyl)-1-(quinolin-8-yl)azetidin-2-one 39d. The product was purified by flash chromatography on silica gel (height 12 cm, width 1.5 cm, petroleum ether/ethyl acetate = 90/10) as a white solid (15.7 mg, 99%). R_f (petroleum ether/ethyl acetate = 90/10): 0.42.

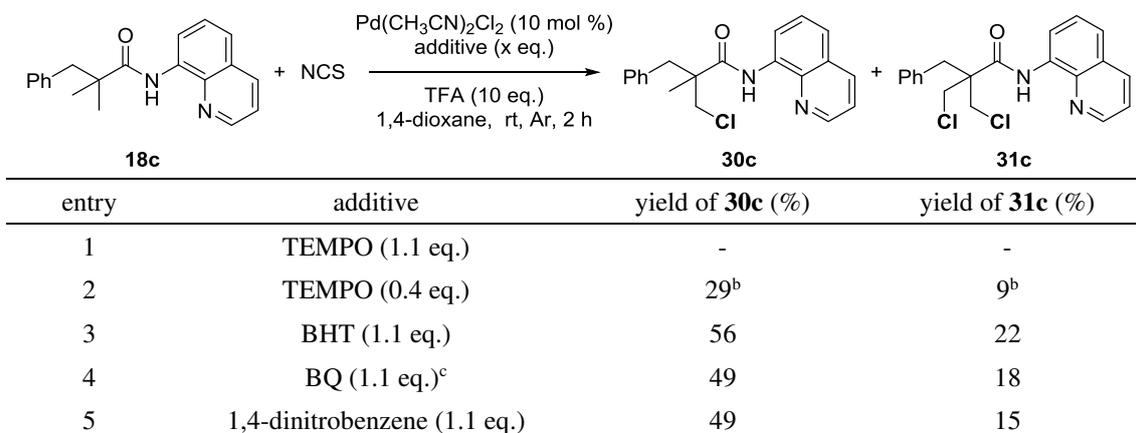
¹H NMR (300.13 MHz, CDCl₃): δ 8.83 (dd, J = 4.2, 1.5 Hz, 1H), 8.44 (dd, J = 7.5, 1.2 Hz, 1H), 8.13 (dd, J = 8.1, 1.5 Hz, 1H), 7.62 – 7.47 (m, 2H), 7.41 (dd, J = 8.1, 4.2 Hz, 1H), 4.65 (s, 2H), 4.03 (s, 4H).

¹³C NMR (75.5 MHz, CDCl₃): δ 165.4, 148.8, 140.4, 136.0, 133.8, 128.9, 126.6, 121.4, 119.9, 61.3, 54.0, 43.9.

IR (neat, cm⁻¹) v: 2961, 1731, 1505, 1357, 1156, 1113, 902, 822, 787, 755, 610.

HRMS (ESI⁺) calcd for C₁₄H₁₃Cl₂N₂O m/z 295.0399 [M+H]⁺, Found 295.0408.

2.9 Radical trapping experiments^a



^a Reaction conditions: **18c** (0.4 mmol), NCS (0.2 mmol), Pd[CH₃CN]₂Cl₂ (10 mol %), TFA (10 equiv.), additive (x mmol), 1,4-dioxane (2 mL), rt, Ar, 2 h. Isolated yields. ^b NMR yields were determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^c BQ = 1,4-benzoquinone.

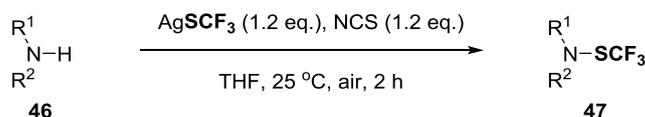
An oven-dried 10 ml glassware equipped with a stirring bar was charged with Pd(CH₃CN)₂Cl₂ (5.2 mg, 0.02 mmol, 0.1 eq.), NCS (26.6 mg, 0.2 mmol, 1 eq.), **18c** (121.6 mg, 0.4 mmol, 2 eq.), additive (0.4 eq. or 1.1 eq.) and 2 mL of 1,4-dioxane under argon. Then, TFA (228.9 mg, 2 mmol, 10 eq.) was added and the tube was flushed with argon, sealed and stirred at room temperature for 2 h. The reaction mixture was diluted with diethyl ether (20 mL) and water. The organic layer was washed with saturated aqueous NaHCO₃ (3 × 20 mL), dried over MgSO₄, filtered and evaporated under vacuum. The reaction mixture was purified by flash chromatography on silica gel to give the desired product **30c** and **31c**.

3. Design and synthesis of original electrophilic reagent

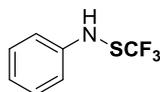
3.1 Oxidative trifluoromethylthiolation and thiocyanation of amines: a general approach to N-S bond formation

The AgSCF₃,¹⁰⁶ and N-chlorosaccharin¹¹⁸ were prepared according to previously reported procedures.

3.1.1 General procedure for the trifluoromethylthiolation reaction of amine derivatives



An oven-dried 10 mL glassware equipped with a stirring bar was charged with AgSCF₃ (50.2 mg, 0.24 mmol, 1.2 eq.) and THF (2 mL). Amine derivatives **46** (0.2 mmol, 1 eq.) and N-chlorosuccinimide (NCS, 32.1 mg, 0.24 mmol, 1.2 eq.) were added to the reaction mixture. The resulted reaction mixture was stirred at 25 °C until the TLC control showed complete conversion. The solvent was evaporated under reduce pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product **47**. Note that, in the case of solid amines, these are added in the tube before the solvent. Caution: the products are volatile.



Chemical Formula: C₇H₆F₃NS
Molecular Weight: 193.19 g/mol

N-[(Trifluoromethyl)thio]aniline 47a. The product was purified by flash column chromatography on silica gel (height 19 cm, width 1.5 cm, pentane/diethyl ether = 91:9) as a pale yellow oil (35.2 mg, 91%, 2 h; 509.6 mg, 88% on a 3 mmol scale, 2 h). R_f (petroleum ether/diethyl ether = 90:10): 0.50.

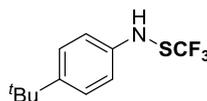
¹H NMR (300.13 MHz, CDCl₃) δ 7.20 (d, J = 7.5 Hz, 2H), 7.00 (d, J = 7.8 Hz, 2H), 6.89 (t, J = 7.5 Hz, 1H), 5.01 (s, 1H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ - 53.4 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 145.0, 129.4 (q, J = 317.1 Hz), 129.3, 121.9, 115.1.

IR (neat, cm⁻¹) ν: 2923, 2853, 1601, 1496, 1466, 1260, 1118, 1029, 800, 741.

HRMS (CI) calcd for C₇H₇F₃NS m/z 194.0246 [M+H]⁺, Found 194.0260.



Chemical Formula: C₁₁H₁₄F₃NS
Molecular Weight: 249.30 g/mol

4-Tert-butyl-N-[(trifluoromethyl)thio]aniline 47b. The product was purified by flash column chromatography on silica gel (height 18 cm, width 1.5 cm, pentane/diethyl ether = 90:10) as an orange oil (39.7 mg, 80%, 20 h), R_f (petroleum ether/diethyl ether = 90:10): 0.62.

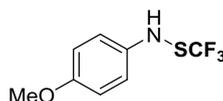
¹H NMR (300.13 MHz, CDCl₃) δ 7.34 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 5.05 (s, 1H), 1.34 (s, 9H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ - 53.5 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 144.8, 142.5, 129.4 (q, J = 317.9 Hz), 126.1, 114.8, 34.1, 31.4.

IR (neat, cm⁻¹) v: 3347, 2966, 1611, 1512, 1239, 1105, 923, 830, 748, 553.

HRMS (CI) calcd for C₁₁H₁₅F₃NS m/z 250.0872 [M+H]⁺, Found 250.0871.



Chemical Formula: C₈H₈F₃NOS
Molecular Weight: 223.21 g/mol

4-Methoxy-N-[(trifluoromethyl)thio]aniline 47c. The product was purified by flash column chromatography on silica gel (height 19 cm, width 1.5 cm, pentane/diethyl ether = 83:17) as an orange oil (40.4 mg, 91%, 2 h). R_f (petroleum ether/diethyl ether = 80:20): 0.47.

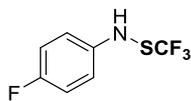
¹H NMR (300.13 MHz, CDCl₃) δ 7.02 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 4.95 (s, 1H), 3.78 (s, 3H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ - 53.5 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 155.0, 138.6, 129.5 (q, J = 317.9 Hz), 116.5, 114.6, 55.6.

IR (neat, cm⁻¹) v: 3327, 2841, 1506, 1444, 1285, 1225, 1109, 1028, 927, 816, 513.

HRMS (CI) calcd for C₈H₉F₃NOS m/z 224.0351 [M+H]⁺, Found 224.0354.



Chemical Formula: C₇H₅F₄NS
Molecular Weight: 211.18 g/mol

4-Fluoro-N-[(trifluoromethyl)thio]aniline 47d. The product was purified by flash column chromatography on silica gel (height 14 cm, width 1.5 cm, pentane/diethyl ether = 90:10) as a yellow oil (38.9 mg, 92%, 2 h). R_f (petroleum ether/diethyl ether = 90:10): 0.50.

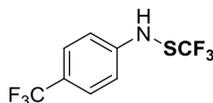
¹H NMR (300.13 MHz, CDCl₃) δ 7.12 – 6.87 (m, 4H), 5.04 (s, 1H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 53.4 (s), – 123.0 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 158.2 (d, J = 240.8 Hz), 141.1 (d, J = 2.3 Hz), 129.4 (q, J = 317.9 Hz), 116.4 (d, J = 8.3 Hz), 115.9 (d, J = 22.7 Hz).

IR (neat, cm⁻¹) ν: 3415, 1863, 1505, 1453, 1376, 1281, 1210, 1109, 926, 824, 750, 509.

HRMS (CI) calcd for C₇H₆F₄NS m/z 212.0157 [M+H]⁺, Found 212.0157.



Chemical Formula: C₈H₅F₆NS
Molecular Weight: 261.19 g/mol

4-Trifluoromethyl-N-[(trifluoromethyl)thio]aniline 47e. The product was purified by flash column chromatography on silica gel (height 18 cm, width 1.5 cm, pentane/diethyl ether = 90:10) as a yellow liquid (38.1 mg, 73%, 24 h). R_f (petroleum ether/diethyl ether = 90:10): 0.43.

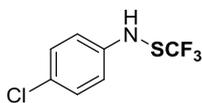
¹H NMR (300.13 MHz, CDCl₃) δ 7.54 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 5.33 (s, 1H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 53.1 (s), – 62.2 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 148.0, 129.1 (q, J = 317.1 Hz), 126.7 (q, J = 3.8 Hz), 124.2 (q, J = 271.8 Hz), 124.1 (q, J = 32.5 Hz), 114.9.

IR (neat, cm^{-1}) ν : 3425, 1617, 1520, 1324, 1296, 1242, 1107, 1067, 1011, 832, 638, 592.

HRMS (CI) calcd for $\text{C}_8\text{H}_6\text{F}_6\text{NS}$ m/z 262.0125 $[\text{M}+\text{H}]^+$, Found 262.0128.



Chemical Formula: $\text{C}_7\text{H}_5\text{ClF}_3\text{NS}$
Molecular Weight: 227.63 g/mol

4-Chloro-N-[(trifluoromethyl)thio]aniline 47f. The product was purified by flash column chromatography on silica gel (height 19 cm, width 1.5 cm, pentane/diethyl ether = 91:9) as a pale yellow oil (38.7 mg, 85%, 2 h). R_f (petroleum ether/diethyl ether = 90:10): 0.39.

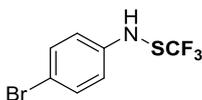
^1H NMR (300.13 MHz, CDCl_3) δ 7.24 (d, $J = 9.0$ Hz, 2H), 7.02 (d, $J = 9.0$ Hz, 2H), 5.10 (s, 1H).

^{19}F NMR (282.4 MHz, CDCl_3) δ - 53.3 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 143.7, 129.2, 129.2 (q, $J = 317.1$ Hz), 126.8, 116.3.

IR (neat, cm^{-1}) ν : 3387, 1596, 1490, 1443, 1375, 1277, 1232, 1107, 927, 820, 658.

HRMS (CI) calcd for $\text{C}_7\text{H}_6\text{ClF}_3\text{NS}$ m/z 227.9856 $[\text{M}+\text{H}]^+$, Found 227.9873.



Chemical Formula: $\text{C}_7\text{H}_5\text{BrF}_3\text{NS}$
Molecular Weight: 272.08 g/mol

4-Bromo-N-[(trifluoromethyl)thio]aniline 47g. The product was purified by flash column chromatography on silica gel (height 19 cm, width 1.5 cm, pentane/diethyl ether = 91:9) as an orange liquid (45.3 mg, 83%, 2 h). R_f (petroleum ether/diethyl ether = 90:10): 0.41.

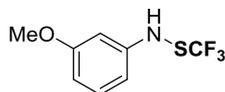
^1H NMR (300.13 MHz, CDCl_3) δ 7.37 (d, $J = 8.7$ Hz, 2H), 6.97 (d, $J = 8.7$ Hz, 2H), 5.11 (s, 1H).

^{19}F NMR (282.4 MHz, CDCl_3) δ - 53.3 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 144.2, 132.1, 129.2 (q, $J = 317.9$ Hz), 116.8, 114.1.

IR (neat, cm^{-1}) ν : 3380, 1591, 1485, 1440, 1232, 1107, 1005, 926, 816, 750, 635, 501.

HRMS (CI) calcd for $\text{C}_7\text{H}_6\text{BrF}_3\text{NS}$ m/z 271.9351 $[\text{M}+\text{H}]^+$, Found 271.9362.



Chemical Formula: $\text{C}_8\text{H}_8\text{F}_3\text{NOS}$
Molecular Weight: 223.21 g/mol

3-Methoxy-N-[(trifluoromethyl)thio]aniline 47h. The product was purified by flash column chromatography on silica gel (height 19 cm, width 1.5 cm, pentane/diethyl ether = 85:15) as a white solid (41.3 mg, 93%, 2 h). R_f (petroleum ether/diethyl ether = 80:20): 0.54.

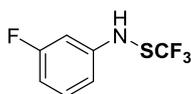
^1H NMR (300.13 MHz, CDCl_3) δ 7.18 (t, $J = 8.1$ Hz, 1H), 6.73 – 6.62 (m, 2H), 6.53 (dd, $J = 8.1, 1.8$ Hz, 1H), 5.13 (s, 1H), 3.81 (s, 3H).

^{19}F NMR (282.4 MHz, CDCl_3) δ – 53.4 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 160.7, 146.5, 130.1, 129.3 (q, $J = 317.1$ Hz), 107.8, 107.2, 101.2, 55.2.

IR (neat, cm^{-1}) ν : 3321, 2937, 1598, 1507, 1480, 1277, 1107, 1051, 966, 836, 761, 685.

HRMS (CI) calcd for $\text{C}_8\text{H}_9\text{F}_3\text{NOS}$ m/z 224.0351 $[\text{M}+\text{H}]^+$, Found 224.0356.



Chemical Formula: $\text{C}_7\text{H}_5\text{F}_4\text{NS}$
Molecular Weight: 211.18 g/mol

3-Fluoro-N-[(trifluoromethyl)thio]aniline 47i. The product was purified by flash column chromatography on silica gel (height 18 cm, width 1.5 cm, pentane/diethyl ether = 90:10) as a yellow liquid (32.2 mg, 76%, 2 h). R_f (petroleum ether/diethyl ether = 94:6): 0.36.

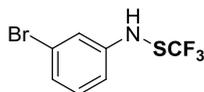
^1H NMR (300.13 MHz, CDCl_3) δ 7.19 – 7.06 (m, 1H), 6.82 – 6.68 (m, 2H), 6.58 (td, $J = 8.4, 2.1$ Hz, 1H), 5.09 (s, 1H).

^{19}F NMR (282.4 MHz, CDCl_3) δ – 53.3 (s), – 112.2 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 163.7 (d, $J = 245.4$ Hz), 147.0 (d, $J = 9.8$ Hz), 130.5 (d, $J = 9.8$ Hz), 129.2 (q, $J = 317.1$ Hz), 110.9 (d, $J = 2.3$ Hz), 108.7 (d, $J = 21.1$ Hz), 102.5 (d, $J = 26.4$ Hz).

IR (neat, cm^{-1}) ν : 3416, 2962, 1615, 1490, 1277, 1110, 972, 847, 768, 680.

HRMS (CI) calcd for $\text{C}_7\text{H}_6\text{F}_4\text{NS}$ m/z 212.0152 $[\text{M}+\text{H}]^+$, Found 212.0160.



Chemical Formula: $\text{C}_7\text{H}_5\text{BrF}_3\text{NS}$
Molecular Weight: 272.08 g/mol

3-Bromo-N-[(trifluoromethyl)thio]aniline 47j. The product was purified by flash column chromatography on silica gel (height 19 cm, width 1.5 cm, pentane/diethyl ether = 90:10) as an orange oil (43.8 mg, 81%, 2 h). R_f (petroleum ether/diethyl ether = 90:10): 0.35.

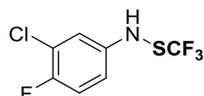
^1H NMR (300.13 MHz, CDCl_3) δ 7.17 (s, 1H), 7.12 – 6.98 (m, 2H), 6.97 – 6.86 (m, 1H), 5.05 (s, 1H).

^{19}F NMR (282.4 MHz, CDCl_3) δ – 53.2 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 146.4, 130.6, 129.2 (q, $J = 317.9$ Hz), 125.0, 123.1, 118.2, 113.8.

IR (neat, cm^{-1}) ν : 3379, 1594, 1474, 1457, 1281, 1108, 933, 850, 768, 679.

HRMS (CI) calcd for $\text{C}_7\text{H}_6\text{BrF}_3\text{NS}$ m/z 271.9351 $[\text{M}+\text{H}]^+$, Found 271.9361.



Chemical Formula: $\text{C}_7\text{H}_4\text{ClF}_4\text{NS}$
Molecular Weight: 245.62 g/mol

3-Chloro-4-fluoro-N-[(trifluoromethyl)thio]aniline 47k. The product was purified by flash column chromatography on silica gel (height 20 cm, width 1.5 cm, pentane/diethyl ether = 90:10) as a yellow oil (35.1 mg, 71%, 2 h). R_f (petroleum ether/diethyl ether = 90:10): 0.40.

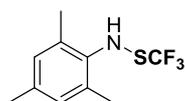
^1H NMR (300.13 MHz, CDCl_3) δ 7.18 – 6.87 (m, 3H), 5.10 (s, 1H).

^{19}F NMR (282.4 MHz, CDCl_3) δ – 53.3 (s), – 125.4 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 153.6 (d, $J = 242.4$ Hz), 141.8 (d, $J = 2.3$ Hz), 129.2 (q, $J = 317.9$ Hz), 121.5 (d, $J = 18.9$ Hz), 117.0 (d, $J = 9.8$ Hz), 116.9 (d, $J = 12.8$ Hz), 114.5 (d, $J = 6.8$ Hz).

IR (neat, cm^{-1}) ν : 3405, 1708, 1497, 1363, 1209, 1108, 943, 808, 751, 542.

HRMS (CI) calcd for $\text{C}_7\text{H}_5\text{ClF}_4\text{NS}$ m/z 245.9762 $[\text{M}+\text{H}]^+$, Found 245.9772.



Chemical Formula: $\text{C}_{10}\text{H}_{12}\text{F}_3\text{NS}$
Molecular Weight: 235.27 g/mol

2,4,6-Trimethyl-N-[(trifluoromethyl)thio]aniline 47l. The product was purified by flash column chromatography on silica gel (height 12 cm, width 1.5 cm, pentane/diethyl ether = 95:5) as an orange oil (27.3 mg, 58%, 24 h). R_f (petroleum ether/diethyl ether = 90:10): 0.68.

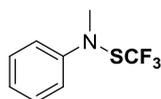
^1H NMR (300.13 MHz, CDCl_3) δ 6.86 (s, 2H), 4.59 (s, 1H), 2.32 (s, 6H), 2.26 (s, 3H).

^{19}F NMR (282.4 MHz, CDCl_3) δ – 52.6 (s).

^{13}C NMR (75.5 MHz, CDCl_3) δ 139.4, 134.5, 131.5, 130.3 (q, $J = 318.6$ Hz), 129.6, 20.6, 18.1.

IR (neat, cm^{-1}) ν : 3394, 2971, 1480, 1216, 1117, 849, 747, 581.

HRMS (CI) calcd for $\text{C}_{10}\text{H}_{13}\text{F}_3\text{NS}$ m/z 236.0715 $[\text{M}+\text{H}]^+$, Found 236.0723.



Chemical Formula: $\text{C}_8\text{H}_8\text{F}_3\text{NS}$
Molecular Weight: 207.21 g/mol

N-Methyl-N-[(trifluoromethyl)thio]aniline 47m. The product was purified by flash column chromatography on silica gel (height 14 cm, width 1.5 cm, pentane/diethyl ether = 85:15) as a colorless liquid (18.3 mg, 44%, 12 h), R_f (petroleum ether/diethyl ether = 96:4): 0.67.

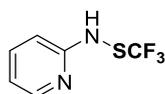
¹H NMR (300.13 MHz, CDCl₃) δ 7.26 – 7.10 (m, 4H), 6.89 (d, J = 7.2 Hz, 1H), 3.39 (s, 3H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 50.9 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 148.6, 130.3 (q, J = 320.9 Hz), 129.0, 121.2, 115.9, 46.1.

IR (neat, cm⁻¹) v: 2955, 1599, 1495, 1266, 1107, 1032, 873, 748, 689.

HRMS (CI) calcd for C₈H₉F₃NS m/z 208.0402 [M+H]⁺, Found 208.0405.



Chemical Formula: C₆H₅F₃N₂S
Molecular Weight: 194.18 g/mol

N-[(Trifluoromethyl)thio]pyridin-2-amine 47n. The product was purified by flash column chromatography on silica gel (height 18 cm, width 1.5 cm, pentane/diethyl ether = 60:40) as a yellow solid (26.3 mg, 68%, 8 h). R_f (petroleum ether/diethyl ether = 70:30): 0.34.

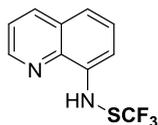
¹H NMR (300.13 MHz, CDCl₃) δ 8.35 (s, 1H), 8.13 (d, J = 5.1 Hz, 1H), 7.65 – 7.54 (m, 1H), 7.27 – 7.17 (m, 1H), 6.82 (dd, J = 6.9, 5.1 Hz, 1H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ – 53.4 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 158.5, 147.8, 138.7, 129.4 (q, J = 316.3 Hz), 117.1, 107.7.

IR (neat, cm⁻¹) v: 3134, 2848, 1604, 1584, 1500, 1448, 1299, 1112, 996, 945, 771, 591.

HRMS (CI) calcd for C₆H₆F₃N₂S m/z 195.0198 [M+H]⁺, Found 195.0212.



Chemical Formula: C₁₀H₇F₃N₂S
Molecular Weight: 244.24 g/mol

N-[(Trifluoromethyl)thio]quinolin-8-amine 47o. The product was purified by flash column chromatography on silica gel (height 12 cm, width 1.5 cm, pentane/diethyl

ether = 60:40) as a colorless oil (19.6 mg, 40%, 20 h). R_f (petroleum ether/diethyl ether = 70:30): 0.73.

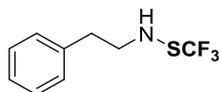
$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 8.79 (dd, $J = 4.2, 1.5$ Hz, 1H), 8.14 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.65 – 7.32 (m, 5H).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) $\delta - 52.9$ (s).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 148.2, 141.8, 138.9, 136.1, 129.4 (q, $J = 317.1$ Hz), 128.3, 127.1, 121.8, 119.3, 110.0.

IR (neat, cm^{-1}) ν : 3341, 2917, 2160, 1418, 1324, 1235, 1099, 1008, 733, 669, 592.

HRMS (CI) calcd for $\text{C}_{10}\text{H}_8\text{F}_3\text{N}_2\text{S}$ m/z 245.0355 $[\text{M}+\text{H}]^+$, Found 245.0353.



Chemical Formula: $\text{C}_9\text{H}_{10}\text{F}_3\text{NS}$
Molecular Weight: 221.24 g/mol

N-[(Trifluoromethyl)thio]-2-phenylethan-1-amine 47p. The product was purified by flash column chromatography on silica gel (height 14 cm, width 1.5 cm, pentane/diethyl ether = 90:10) as a colorless oil (40.8 mg, 92%, 2 h). R_f (petroleum ether/diethyl ether = 80:20): 0.80.

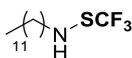
$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.28 – 7.20 (m, 2H), 7.19 – 7.05 (m, 3H), 3.26 (dd, $J = 12.8, 6.6$ Hz, 2H), 2.76 (t, $J = 7.0$ Hz, 2H).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) $\delta - 53.0$ (s).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 138.4, 130.4 (q, $J = 317.1$ Hz), 128.8, 128.6, 126.5, 54.6, 36.6.

IR (neat, cm^{-1}) ν : 3367, 2933, 1604, 1455, 1112, 746, 699, 560.

HRMS (CI) calcd for $\text{C}_9\text{H}_{11}\text{F}_3\text{NS}$ m/z 222.0559 $[\text{M}+\text{H}]^+$, Found 222.0560.



Chemical Formula: $\text{C}_{23}\text{H}_{47}\text{F}_3\text{NS}$
Molecular Weight: 445.64 g/mol

N-[(Trifluoromethyl)thio]dodecan-1-amine 47q. The product was purified by flash column chromatography on silica gel (height 18 cm, width 1.5 cm, pentane/diethyl

ether = 85:15) as a colorless oil (46.2 mg, 81%, 2 h). R_f (petroleum ether/diethyl ether = 90:10): 0.83.

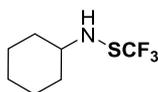
$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 3.15 – 2.97 (m, 2H), 2.82 (s, 1H), 1.58 – 1.44 (m, 2H), 1.26 (m, 18H), 0.88 (t, $J = 6.9$ Hz, 3H).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ – 52.9 (s).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 130.5 (q, $J = 317.9$ Hz), 53.7, 31.9, 30.2, 29.6, 29.6, 29.6, 29.5, 29.4, 29.3, 26.5, 22.7, 14.1.

IR (neat, cm^{-1}) ν : 2925, 2855, 1467, 1154, 1120, 722.

HRMS (CI) calcd for $\text{C}_{13}\text{H}_{27}\text{F}_3\text{NS}$ m/z 286.1811 $[\text{M}+\text{H}]^+$, Found 286.1829.



Chemical Formula: $\text{C}_7\text{H}_{12}\text{F}_3\text{NS}$
Molecular Weight: 199.24 g/mol

N-[(Trifluoromethyl)thio]cyclohexanamine 47r. The product was purified by flash column chromatography on silica gel (height 15 cm, width 2.0 cm, pentane) as a colorless oil (86.2 mg, 87%, on a 0.5 mmol scale, 2 h). R_f (petroleum ether): 0.49.

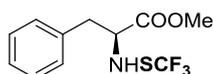
$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 2.98 – 2.64 (m, 2H), 2.10 – 1.87 (m, 2H), 1.81 – 1.50 (m, 3H), 1.40 – 0.98 (m, 5H).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ – 53.4 (s).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 130.3 (q, $J = 317.1$ Hz), 59.5, 33.2, 25.6, 24.5.

IR (neat, cm^{-1}) ν : 1264, 896, 731, 703.

HRMS (CI) calcd for $\text{C}_7\text{H}_{13}\text{F}_3\text{NS}$ m/z 200.0715 $[\text{M}+\text{H}]^+$, Found 200.0715.



Chemical Formula: $\text{C}_{11}\text{H}_{12}\text{F}_3\text{NO}_2\text{S}$
Molecular Weight: 279.28 g/mol

Methyl [(trifluoromethyl)thio]-L-phenylalaninate 47s. The product was purified by flash column chromatography on silica gel (height 25 cm, width 2.0 cm, petroleum ether/acetone = 94:6) as a colorless oil (58.3 mg, 42%, on a 0.5 mmol scale, 4 h). R_f

(petroleum ether/acetone = 95:5): 0.47.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.38 – 7.22 (m, 3H), 7.20 – 7.08 (m, 2H), 3.97 (dt, $J = 8.4, 6.3$ Hz, 1H), 3.73 (s, 3H), 3.34 (d, $J = 8.1$ Hz, 1H), 3.07 (qd, $J = 13.8, 6.6$ Hz, 2H).

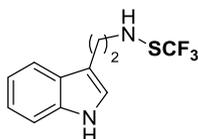
$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) $\delta - 54.0$ (s).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 172.9, 135.6, 129.8 (q, $J = 314.8$ Hz), 129.2, 128.6, 127.1, 66.6, 52.2, 39.3.

IR (neat, cm^{-1}) ν : 3347, 2964, 1738, 1497, 1439, 1214, 1155, 1116, 743, 699.

HRMS (CI) calcd for $\text{C}_{11}\text{H}_{13}\text{F}_3\text{NO}_2\text{S}$ m/z 280.0619 $[\text{M}+\text{H}]^+$, Found 280.0632

Note that, Et_3N (50.6 mg, 0.2 mmol, 1 eq.), was added in the reaction mixture 2 h before adding the NCS and AgSCF_3 .



Chemical Formula: $\text{C}_{10}\text{H}_9\text{F}_3\text{N}_2\text{S}$
Molecular Weight: 246.25 g/mol

N-[(Trifluoromethyl)thio]-2-(1H-indol-3-yl)ethan-1-amine 47t. The product was purified by flash column chromatography on silica gel (height 15 cm, width 1.5 cm, pentane/diethyl ether = 67:33) as a colorless oil (43.3 mg, 83%, 2 h). R_f (petroleum ether/diethyl ether = 67:33): 0.35.

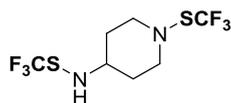
$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.85 (s, 1H), 7.51 (d, $J = 7.8$ Hz, 1H), 7.27 (d, $J = 8.1$ Hz, 1H), 7.18 – 7.00 (m, 2H), 6.91 (d, $J = 1.8$ Hz, 1H), 3.31 (dd, $J = 12.6, 6.3$ Hz, 2H), 2.90 (t, $J = 6.6$ Hz, 2H), 2.82 (s, 1H).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) $\delta - 53.0$ (s).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 136.7, 130.4 (q, $J = 317.9$ Hz), 127.2, 122.2, 122.0, 119.5, 118.6, 112.5, 111.2, 53.6, 26.2.

IR (neat, cm^{-1}) ν : 3398, 3326, 2929, 1458, 1338, 1108, 809, 749, 581.

HRMS (CI) calcd for $\text{C}_{11}\text{H}_{12}\text{F}_3\text{N}_2\text{S}$ m/z 261.0668 $[\text{M}+\text{H}]^+$, Found 261.0684.



Chemical Formula: C₇H₁₀F₆N₂S₂
Molecular Weight: 300.28 g/mol

S-(Trifluoromethyl)-N-(1-((trifluoromethyl)thio)piperidin-4-yl)thiohydroxylamine 47u. The product was purified by flash column chromatography on silica gel (height 14 cm, width 2.0 cm, pentane/diethyl ether = 95:5) as a colorless oil (72.1 mg, 48%, on a 0.5 mmol scale, 2.4 eq. of NCS and AgSCF₃ were used, 4 h), R_f (petroleum ether/diethyl ether = 90:10): 0.62.

¹H NMR (300.13 MHz, CDCl₃) δ 3.44 – 3.28 (m, 2H), 3.26 – 3.07 (m, 2H), 3.04 – 2.77 (m, 2H), 2.08 – 1.86 (m, 2H), 1.61 – 1.42 (m, 2H).

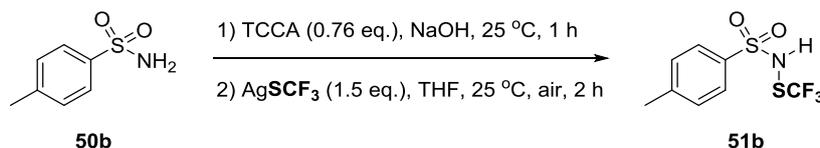
¹⁹F NMR (282.4 MHz, CDCl₃) δ – 47.0 (s), – 53.1 (s).

¹³C NMR (75.5 MHz, CDCl₃) δ 131.4 (q, J = 323.1 Hz), 130.1 (q, J = 316.3 Hz), 55.9, 55.7, 33.3.

IR (neat, cm⁻¹) v: 3373, 2932, 2854, 1375, 1101, 949, 744.

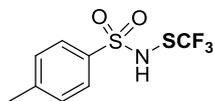
HRMS (CI) calcd for C₇H₁₁F₆N₂S₂ m/z 301.0262 [M+H]⁺, Found 301.0260.

3.1.2 Preparation of the N-[(Trifluoromethyl)thio]-4-methylbenzenesulfonamide 51b



An oven-dried 10 mL glassware equipped with a stirring bar was charged with TCCA (34.9, 0.15 mmol, 0.76 eq.), **50b** (45.5 mg, 0.2 mmol, 1 eq.) and 2 M NaOH (1 mL). The reaction mixture was stirred at 25 °C for 1 h. Then, the reaction mixture was filtered and dried under reduce pressure. The obtained residue was dissolved in THF and AgSCF₃ (62.7 mg, 0.3 mmol, 1.5 eq.) was added. The resulted reaction mixture was stirred at 25 °C for 2 h. The solvent was evaporated under reduce pressure. The residue was purified by flash column chromatography on silica gel (height 18 cm, width 1.5 cm,

pentane/diethyl ether = 50:50) to afford the desired product **51b** as a vitreous solid (16.6 mg, 31%), R_f (petroleum ether/diethyl ether = 50:50): 0.38.



Chemical Formula: $C_8H_8F_3NO_2S_2$
Molecular Weight: 271.27 g/mol

N-[(Trifluoromethyl)thio]-4-methylbenzenesulfonamide **51b**.

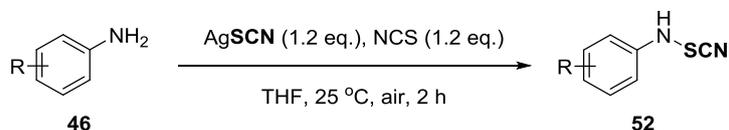
1H NMR (300.13 MHz, $CDCl_3$) δ 7.81 (d, $J = 8.1$ Hz, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 6.32 (s, 1H), 2.45 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$) $\delta -51.9$ (s).

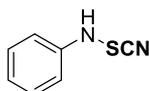
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.1, 135.0, 129.9, 128.0 (q, $J = 314.8$ Hz), 127.9, 21.7.

HRMS (ESI⁺) calcd for $C_8H_9F_3NO_2S_2$ m/z 272.0021 $[M+H]^+$, Found 272.0014.

3.1.3 General procedure for the thiocyanation reaction of aniline derivatives



An oven-dried 50 mL flask equipped with a stirring bar was charged with AgSCN (398.3 mg, 2.4 mmol, 1.2 eq.) and THF (20 mL). Amine derivatives **46** (2 mmol, 1 eq.) and N-chlorosuccinimide (NCS, 320.5 mg, 2.4 mmol, 1.2 eq.) were added to the reaction mixture. The obtained reaction mixture was stirred at 25 °C until the TLC control showed complete conversion. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product **52**.



Chemical Formula: $C_7H_6N_2S$
Molecular Weight: 150.20 g/mol

N-(Cyanosulfanyl)aniline **52a**. The product was purified by flash column

chromatography on silica gel (height 18 cm, width 2.0 cm, pentane/diethyl ether = 50:50) as a white solid (334.8 mg, 76%, on a 3 mmol scale, 2 h). R_f (petroleum ether/diethyl ether = 50:50): 0.39.

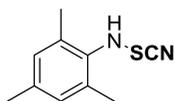
Mp: 75 – 76 °C.

^1H NMR (300.13 MHz, CDCl_3) δ 7.42 – 7.29 (m, 2H), 7.16 – 7.07 (m, 2H), 5.10 (s, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 143.3, 129.6, 123.2, 116.5, 113.3.

IR (neat, cm^{-1}) ν : 3259, 2849, 2152, 1501, 1469, 1209, 1101, 912, 826, 762, 611.

HRMS (CI) calcd for $\text{C}_7\text{H}_7\text{N}_2\text{S}$ m/z 151.0324 $[\text{M}+\text{H}]^+$, Found 151.0335.



Chemical Formula: $\text{C}_{10}\text{H}_{12}\text{N}_2\text{S}$
Molecular Weight: 192.28 g/mol

N-(Cyanosulfanyl)-3,4,6-trimethylaniline 52b. The product was purified by flash column chromatography on silica gel (height 15 cm, width 2.0 cm, pentane/diethyl ether = 50:50) as a yellow solid (271.2 mg, 71%, 18 h). R_f (petroleum ether/diethyl ether = 50:50): 0.75.

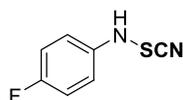
Mp: 79 – 80 °C.

^1H NMR (300.13 MHz, CDCl_3) δ 6.89 (s, 2H), 4.93 (s, 1H), 2.34 (s, 6H), 2.27 (s, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 138.2, 135.8, 132.0, 129.9, 114.4, 20.7, 17.9.

IR (neat, cm^{-1}) ν : 3318, 2964, 2915, 2140, 1481, 1209, 883, 723, 603, 568.

HRMS (CI) calcd for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{S}$ m/z 193.0794 $[\text{M}+\text{H}]^+$, Found 193.0786.



Chemical Formula: $\text{C}_7\text{H}_5\text{FN}_2\text{S}$
Molecular Weight: 168.19 g/mol

N-(Cyanosulfanyl)-4-fluoroaniline 52c. The product was purified by flash column chromatography on silica gel (height 18 cm, width 2.0 cm, pentane/diethyl ether =

50:50) as a yellow solid (293.8 mg, 87%, 2 h). R_f (petroleum ether/diethyl ether = 50:50): 0.50.

Mp: 77 – 78 °C.

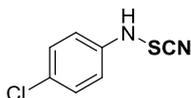
$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.12 – 6.96 (m, 4H), 5.15 (s, 1H).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ – 120.6 (s).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 159.1 (d, $J = 242.4$ Hz), 139.5 (d, $J = 2.3$ Hz), 118.3 (d, $J = 8.3$ Hz), 116.3 (d, $J = 22.7$ Hz), 113.3.

IR (neat, cm^{-1}) ν : 3260, 2151, 1502, 1209, 1100, 911, 827, 763, 610, 505.

HRMS (CI) calcd for $\text{C}_7\text{H}_6\text{FN}_2\text{S}$ m/z 169.0230 $[\text{M}+\text{H}]^+$, Found 169.0229.



Chemical Formula: $\text{C}_7\text{H}_5\text{ClN}_2\text{S}$
Molecular Weight: 184.64 g/mol

N-(Cyanosulfonyl)-4-chloroaniline 52d. The product was purified by flash column chromatography on silica gel (height 18 cm, width 1.5 cm, pentane/diethyl ether = 50:50) as a pale yellow solid (288.4 mg, 78%, 2 h). R_f (petroleum ether/diethyl ether = 50:50): 0.37.

Mp: 81 – 82 °C.

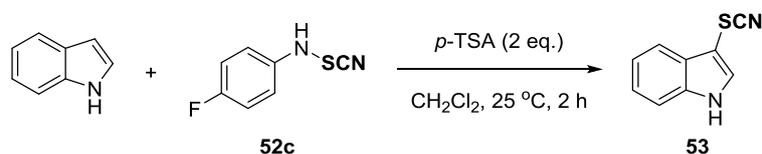
$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.30 (d, $J = 8.7$ Hz, 2H), 7.04 (d, $J = 8.7$ Hz, 2H), 5.24 (s, 1H).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 142.0, 129.6, 128.4, 117.8, 113.0.

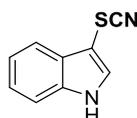
IR (neat, cm^{-1}) ν : 3288, 2153, 1595, 1488, 1283, 1231, 1092, 916, 815, 563.

HRMS (CI) calcd for $\text{C}_7\text{H}_6\text{ClN}_2\text{S}$ m/z 184.9935 $[\text{M}+\text{H}]^+$, Found 184.9947.

3. 1.4 Procedure for the thiocyanation of indole



An oven-dried 10 mL glassware equipped with a stirring bar was charged with indole (23.4 mg, 0.2 mmol, 1 eq.), CH₂Cl₂ (2 mL), N-(cyanosulfanyl)-4-fluoroaniline **52c** (67.3 mg, 0.4 mmol, 2 eq.) and p-TSA (68.9 mg, 0.4 mmol, 2 eq.). The resulted reaction mixture was stirred at 25 °C for 2 h. The solvent was evaporated under reduced pressure. The product **53** was purified by flash column chromatography on silica gel (height 13 cm, width 1.5 cm, petroleum ether/diethyl ether = 80:20) as a vitrious white solid (28.9 mg, 83%). R_f (petroleum ether/diethyl ether = 65:35): 0.21.



Chemical Formula: C₉H₆N₂S
Molecular Weight: 174.22 g/mol

3-Thiocyanato-1H-indole **53**.

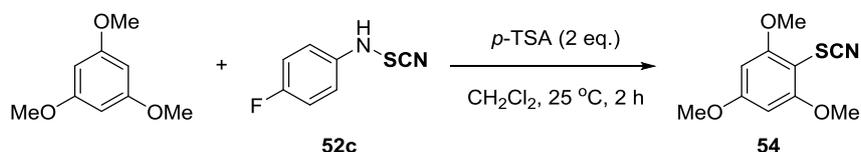
¹H NMR (300.13 MHz, CDCl₃) δ 8.80 (s, 1H), 7.86 – 7.74 (m, 1H), 7.50 – 7.27 (m, 4H).

¹³C NMR (75.5 MHz, CDCl₃) δ 136.0, 131.0, 127.6, 123.8, 121.8, 118.6, 112.1, 91.8. one carbon is overlapped.

IR (neat, cm⁻¹) v: 3370, 3047, 1577, 1503, 1467, 1380, 1317, 1112, 822, 793, 757, 459.

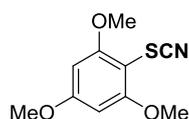
HRMS (CI) calcd for C₉H₇N₂S m/z 175.0324 [M+H]⁺, Found 175.0324.

3.1.5 Procedure for the thiocyanation of 1,3,5-trimethoxybenzene



An oven-dried 10 mL glassware equipped with a stirring bar was charged with 1,3,5-trimethoxybenzene (33.6 mg, 0.2 mmol, 1 eq.), CH₂Cl₂ (2 mL), N-(cyanosulfanyl)-4-fluoroaniline **52c** (67.3 mg, 0.4 mmol, 2 eq.) and p-TSA (68.9 mg, 0.4 mmol, 2 eq.). The resulted reaction mixture was stirred at 25 °C for 2 h. The solvent was evaporated under reduced pressure. The product **54** was purified by flash column chromatography on silica gel (height 15 cm, width 1.5 cm, petroleum ether/diethyl

ether = 50:50) as a vitrious yellow solid (41.4 mg, 92%). R_f (petroleum ether/diethyl ether = 67:33): 0.18.



Chemical Formula: $C_{10}H_{11}NO_3S$
Molecular Weight: 225.26 g/mol

2,4,6-Trimethoxy-phenylthiocyanate **54**.

1H NMR (300.13 MHz, $CDCl_3$) δ 6.15 (s, 2H), 3.91 (s, 6H), 3.84 (s, 3H).

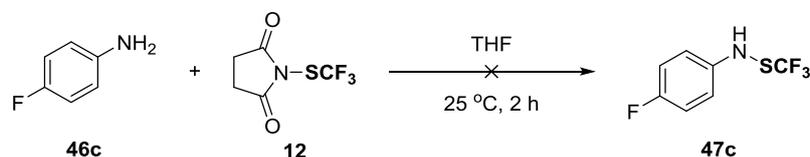
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.2, 161.3, 111.8, 91.2, 89.5, 56.3, 55.5.

IR (neat, cm^{-1}) ν : 2924, 2149, 1583, 1456, 1415, 1344, 1205, 1127, 1085, 914, 821, 804.

HRMS (CI) calcd for $C_{10}H_{12}NO_3S$ m/z 226.0538 $[M+H]^+$, Found 226.0532.

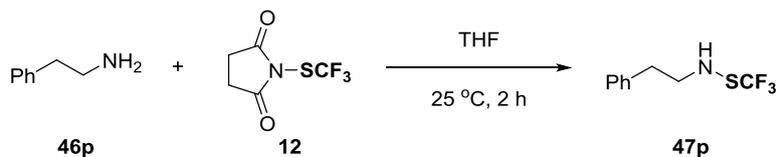
3.1.6 Control experiments

3.1.6.1 Reaction of anilines with the electrophilic SCF_3 source **12**



An oven-dried 10 mL glassware equipped with a stirring bar was charged with **12** (23.9 mg, 0.12 mmol, 1.2 eq.) and THF (1 mL). 4-fluoroaniline **46c** (11.1 mg, 0.1 mmol, 1 eq.) was added to the reaction mixture. The resulted reaction mixture was stirred at 25 °C for 2 h. The desired product **47c** was not observed.

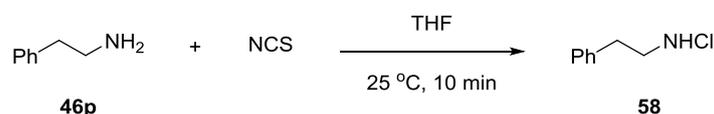
3.1.6.2 Reaction of the aliphatic amine **46p** with the electrophilic SCF_3 source **12**



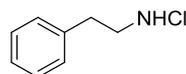
An oven-dried 10 mL glassware equipped with a stirring bar was charged with **12** (23.9 mg, 0.12 mmol, 1.2 eq.) and THF (1 mL). 2-phenylethan-1-amine **46p** (12.1 mg, 0.1 mmol, 1 eq.) was added to the reaction mixture. The resulted reaction mixture was

stirred at 25 °C for 2 h affording **47p** in 92%. The yield was determined by ^{19}F NMR on the crude reaction mixture using α,α,α -trifluoroacetophenone as an internal standard.

3.1.6.3 Reaction of aliphatic amine **46p** with NCS



An oven-dried 10 mL glassware equipped with a stirring bar was charged with NCS (32.1 mg, 0.24 mmol, 1.2 eq.) and THF (2 mL). 2-phenylethan-1-amine **46p** (24.2 mg, 0.2 mmol, 1 eq.) was added to the reaction mixture. The resulted reaction mixture was stirred at 25 °C for 10 min. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (height 14 cm, width 1.5 cm, petroleum ether/diethyl ether = 80:20) as a colorless oil (15.4 mg, 50%). R_f (petroleum ether/diethyl ether = 80:20): 0.53.



Chemical Formula: $\text{C}_8\text{H}_{10}\text{ClN}$
Molecular Weight: 155.63 g/mol

N-chloro-2-phenylethan-1-amine **58**.

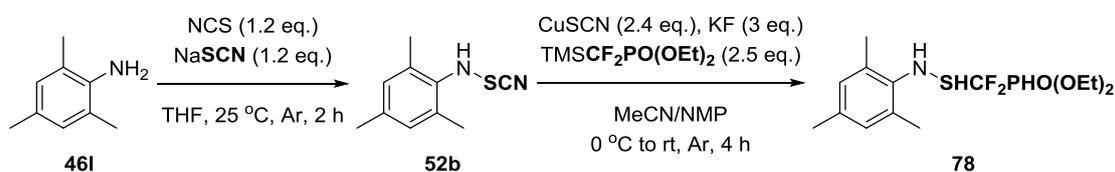
^1H NMR (300.13 MHz, CDCl_3) δ 7.37 – 7.14 (m, 5H), 3.95 – 3.75 (m, 2H), 3.16 – 2.93 (m, 2H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 137.0, 128.8, 128.7, 126.8, 76.6, 34.8.

HRMS (CI) calcd for $\text{C}_8\text{H}_{11}\text{ClN}$ m/z 156.0580 $[\text{M}+\text{H}]^+$, Found 156.0578.

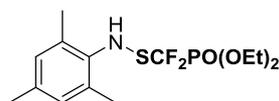
3.2 A New Electrophilic Reagent for the Direct Introduction of the $\text{SCF}_2\text{PO}(\text{OEt})_2$ Group onto Molecules

3.2.1 Procedure for the synthesis of **78**



An oven-dried 250 mL flask equipped with a stirring bar was charged with NaSCN (972.8 mg, 12 mmol, 1.2 eq.), THF (100 mL) and 2,4,6-trimethylaniline **46l** (1.35 g, 10 mmol, 1 eq.). Then, N-chlorosuccinimide (NCS, 1.6 g, 12 mmol, 1.2 eq.) was added to the reaction mixture. The obtained reaction mixture was stirred at 25 °C for 2 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (Biotage system 50 g, height 90 mm, width 40 mm, pentane/diethyl ether, gradient: 88:12 to 0:100, rate: 50 mL/min) to afford N-(cyanosulfanyl)-2,4,6-trimethylaniline **52b** as a pale yellow solid (1.26 g, 66%).

In a glove box, an oven-dried 100 mL sealed tube equipped with a stirring bar was loaded with CuSCN (535.2 mg, 4.4 mmol, 1 eq.) and CsF (2.0 g, 13.2 mmol, 3 eq.), then sealed with a rubber septum. After being moved out from the glove box, the tube was placed at 0 °C and dry acetonitrile was added (8.8 mL). Diethyl [(trimethylsilyl)difluoromethyl]phosphonate (2.86 g, 11 mmol, 2.5 eq.) was added dropwise and the reaction mixture was heated at 40 °C for 1 h, cooled to 0 °C and allowed to stir at this temperature for 1 h. Subsequently, a solution of N-(cyanosulfanyl)-2,4,6-trimethylaniline **52b** (846.0 mg, 4.4 mmol, 1 eq.) in freshly distilled NMP (8.8 mL) was added dropwise to the reaction mixture, and the tube was sealed with a Teflon-lined screw cap. The resulting suspension was stirred at 0 °C for 3 h, warmed to room temperature and stirred at this temperature for 16 h. The reaction mixture was then diluted with ethyl acetate (180 mL) and filtered through a plug of silica. The organic layer was washed with water (3 × 180 mL), brine (180 mL), dried over Na₂SO₄ and the solvents were carefully removed under reduced pressure to afford a brown oil, which was purified by flash column chromatography on silica gel. The product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 70:30) to afford the desired product **78** as a pale yellow oil (936 mg, 60%). **78** was obtained in 71% yield starting on 0.25 mmol scale. R_f (petroleum ether/ethyl acetate = 60:40): 0.50.



Chemical Formula: C₁₄H₂₂F₂NO₃PS
Molecular Weight: 353.36 g/mol

N-[(diethyl phosphonodifluoromethyl)sulfanyl]-2,4,6-trimethylaniline **78**.

¹H NMR (300.13 MHz, CDCl₃) δ 6.81 (s, 2H), 4.64 (s, 1H), 4.34 – 4.19 (m, 4H), 2.34 (s, 6H), 2.23 (s, 3H), 1.36 (t, J = 7.2 Hz, 6H).

¹⁹F{¹H} NMR (282.4 MHz, CDCl₃) δ – 93.4 (d, J = 96.0 Hz).

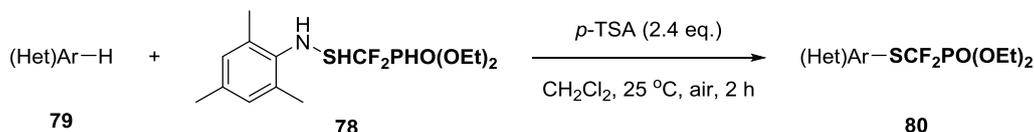
³¹P{¹H} NMR (121.5 MHz, CDCl₃) δ 4.2 (t, J = 103.3 Hz).

¹³C NMR (75.5 MHz, CDCl₃) δ 140.7, 133.5, 130.6, 129.5, 126.8 (td, J = 300.5 Hz, J = 202.3 Hz), 65.2 (d, J = 6.8 Hz), 20.5, 18.3, 16.2 (d, J = 5.3 Hz).

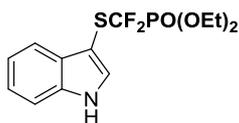
IR (neat, cm⁻¹) ν: 3301, 2984, 1481, 1265, 1115, 1012, 853, 745, 643, 535.

HRMS (ESI) calcd for C₁₄H₂₃F₂NO₃PS m/z 354.1099 [M+H]⁺, Found 354.1112.

3.2.2 General procedure for the synthesis of derivatives **80**



An oven-dried 10 mL tube equipped with a stirring bar was charged with the derivatives **79** (0.15 mmol, 1 eq.), CH₂Cl₂ (1.5 mL), **78** (63.6 mg, 0.18 mmol, 1.2 eq.) and p-TSA (62.0 mg, 0.36 mmol, 2.4 eq.) under air. The resulting reaction mixture was stirred at 25 °C for 2 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product **80**.



Chemical Formula: C₁₃H₁₆F₂NO₃PS
Molecular Weight: 335.31 g/mol

3-[(Diethyl phosphonodifluoromethyl)sulfanyl]indole **80a**. Reaction time: 2 h. The product was purified by flash column chromatography on silica gel (height 15 cm,

width 1.5 cm, petroleum ether/ethyl acetate = 20:80) as a pale yellow oil (45.8 mg, 91%). R_f (petroleum ether/ethyl acetate = 20:80): 0.56.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 9.16 (s, 1H), 7.79 – 7.64 (m, 1H), 7.44 – 7.36 (m, 1H), 7.35 – 7.25 (m, 1H), 7.20 – 7.10 (m, 2H), 4.31 – 4.14 (m, 4H), 1.28 (t, $J = 7.2$ Hz, 6H).

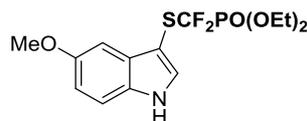
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 85.3 (d, $J = 104.5$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 4.2 (t, $J = 104.5$ Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 136.2, 133.4, 130.1, 124.6 (td, $J = 298.2$ Hz, $J = 214.4$ Hz), 122.8, 121.0, 119.4, 111.7, 94.0 (td, $J = 4.5$ Hz, $J = 3.8$ Hz), 65.4 (d, $J = 6.8$ Hz), 16.2 (d, $J = 5.3$ Hz).

IR (neat, cm^{-1}) ν : 3249, 2986, 1456, 1256, 1114, 1008, 911, 741, 644, 536.

HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{F}_2\text{NO}_3\text{PS}$ m/z 336.0629 $[\text{M}+\text{H}]^+$, Found 336.0627.



Chemical Formula: $\text{C}_{14}\text{H}_{18}\text{F}_2\text{NO}_4\text{PS}$
Molecular Weight: 365.33 g/mol

3-[(Diethyl phosphonodifluoromethyl)sulfanyl]-5-methoxyindole 80b. Reaction time: 2 h. The product was purified by flash column chromatography on silica gel (height 15 cm, width 1.5 cm, petroleum ether/ethyl acetate = 35:65) as a pale yellow oil (48.8 mg, 89%). R_f (petroleum ether/ethyl acetate = 35:65): 0.44.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 9.04 (s, 1H), 7.36 (d, $J = 2.7$ Hz, 1H), 7.24 – 7.11 (m, 2H), 6.80 (dd, $J = 8.7$, $J = 2.4$ Hz, 1H), 4.33 – 4.13 (m, 4H), 3.79 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 6H).

$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 85.3 (d, $J = 101.7$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 4.2 (t, $J = 103.3$ Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 155.2, 133.7, 131.1, 130.9, 124.7 (td, $J = 298.2$ Hz, $J = 214.4$ Hz), 113.4, 112.5, 100.7, 93.6 (m), 65.3 (d, $J = 6.8$ Hz), 55.7, 16.3 (d, $J = 5.3$ Hz).

IR (neat, cm^{-1}) ν : 3254, 2988, 1488, 1258, 1169, 1025, 919, 797, 629, 549.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{19}\text{F}_2\text{NO}_4\text{PS}$ m/z 366.0735 $[\text{M}+\text{H}]^+$, Found 366.0726.



Chemical Formula: $C_{20}H_{22}F_2NO_4PS$
Molecular Weight: 441.43 g/mol

3-[(Diethyl phosphonodifluoromethyl)sulfanyl]-5-benzyloxyindole 80c. Reaction time: 4 h. The product was purified by flash column chromatography on silica gel (height 16 cm, width 1.5 cm, pentane/ethyl acetate = 50:50) as a pale yellow oil (57.3 mg, 87%). R_f (petroleum ether/ethyl acetate = 50:50): 0.26.

1H NMR (300.13 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.52 – 7.04 (m, 8H), 6.84 (dd, $J = 8.7$, $J = 2.1$ Hz, 1H), 5.00 (s, 2H), 4.31 – 4.06 (m, 4H), 1.25 (t, $J = 7.2$ Hz, 6H).

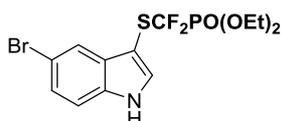
$^{19}F\{^1H\}$ NMR (282.4 MHz, $CDCl_3$) δ – 85.2 (d, $J = 104.5$ Hz).

$^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$) δ 4.2 (t, $J = 104.5$ Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.3, 137.3, 133.9, 131.3, 130.9, 128.4, 127.8, 127.6, 124.7 (td, $J = 298.2$ Hz, $J = 214.4$ Hz), 113.8, 112.6, 102.2, 93.3 (td, $J = 4.5$ Hz, $J = 3.8$ Hz), 70.6, 65.3 (d, $J = 6.8$ Hz), 16.2 (d, $J = 5.3$ Hz).

IR (neat, cm^{-1}) ν : 3248, 2985, 1484, 1258, 1177, 1014, 911, 735, 697, 528.

HRMS (ESI) calcd for $C_{20}H_{23}F_2NO_4PS$ m/z 442.1048 $[M+H]^+$, Found 442.1043.



Chemical Formula: $C_{13}H_{15}BrF_2NO_3PS$
Molecular Weight: 414.20 g/mol

3-[(Diethyl phosphonodifluoromethyl)sulfanyl]-5-bromoindole 80d. Reaction time: 2 h. The product was purified by flash column chromatography on silica gel (height 15 cm, width 1.5 cm, petroleum ether/ethyl acetate = 40:60) as a pale yellow oil (54.5 mg, 88%; 689.6 mg, 83%, on a 2 mmol scale). R_f (petroleum ether/ethyl acetate = 35:65): 0.42.

1H NMR (300.13 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.90 (s, 1H), 7.44 (d, $J = 2.7$ Hz, 1H), 7.28 (dd, $J = 8.7$ Hz, $J = 1.5$ Hz, 1H), 7.17 (d, $J = 8.7$ Hz, 1H), 4.41 – 4.21 (m, 4H), 1.39 (t, $J = 7.2$ Hz, 6H).

$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ - 85.6 (d, $J = 107.3$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.1 (t, $J = 104.5$ Hz).

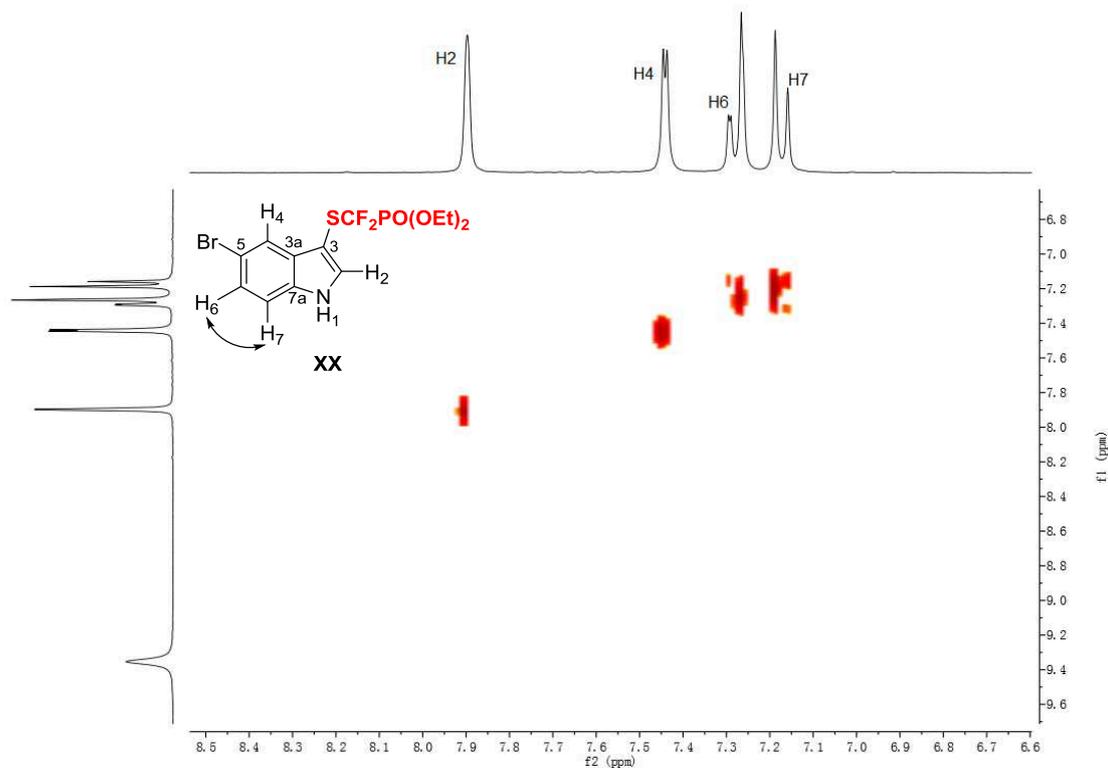
^{13}C NMR (75.5 MHz, CDCl_3) δ 134.9, 134.5, 131.8, 125.7, 124.3 (td, $J = 299.0$ Hz, $J = 215.9$ Hz), 121.9, 114.5, 113.3, 93.5 (td, $J = 4.5$ Hz, $J = 3.8$ Hz), 65.5 (d, $J = 6.8$ Hz), 16.3 (d, $J = 5.3$ Hz).

IR (neat, cm^{-1}) ν : 3238, 2985, 1454, 1254, 1107, 1019, 912, 796, 610, 549.

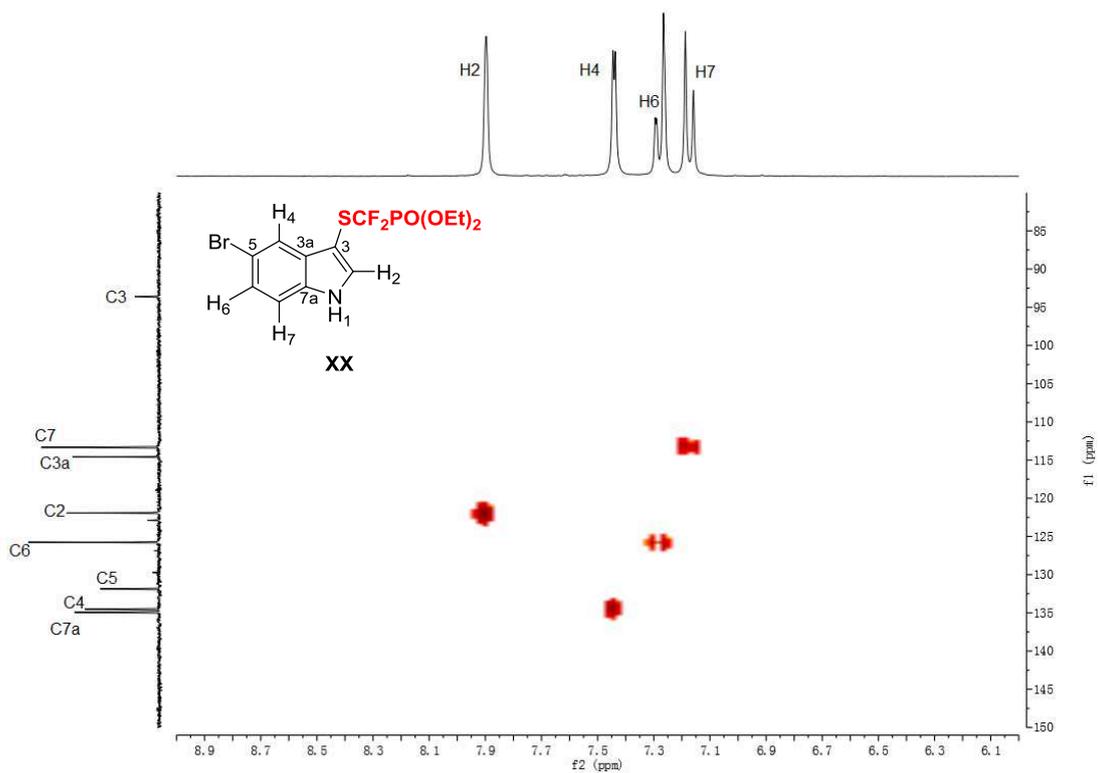
HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{16}\text{BrF}_2\text{NO}_3\text{PS}$ m/z 413.9734 $[\text{M}+\text{H}]^+$, Found 413.9744.

The structure of **80d** was confirmed by NMR experiment.

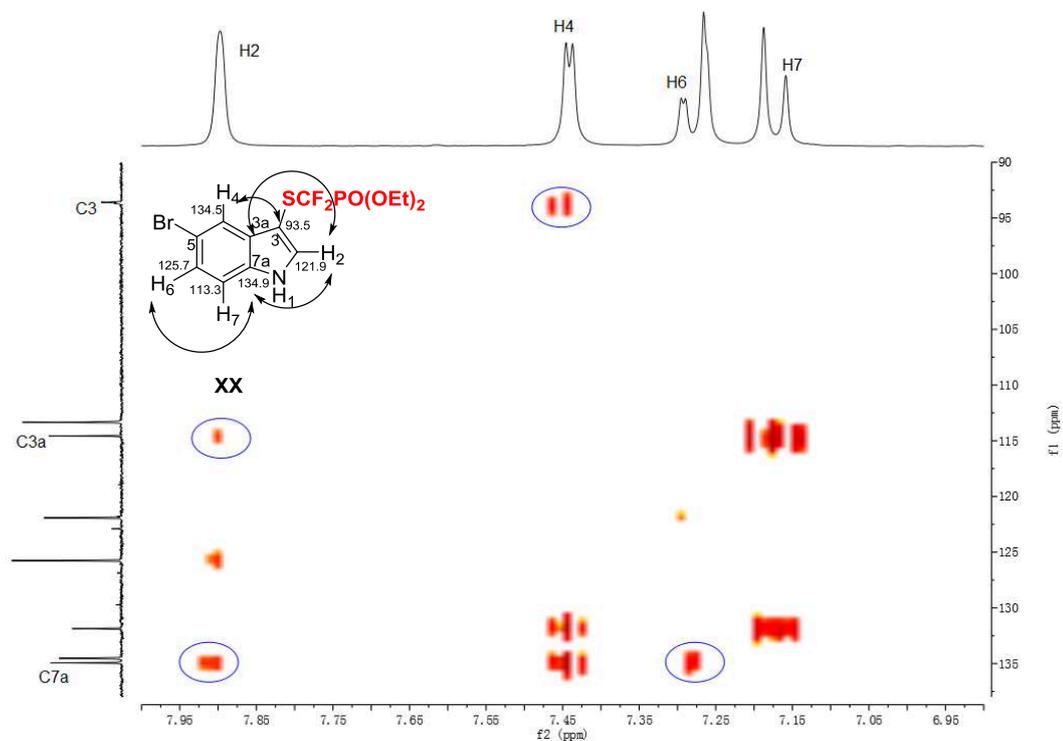
The ^1H - ^1H COSY 2D NMR of **80d**:

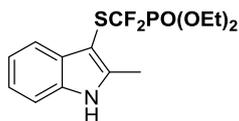


The HMQC 2D NMR of **80d**:



The HMBC 2D NMR of **80d**:





Chemical Formula: C₁₄H₁₈F₂NO₃PS
Molecular Weight: 349.33 g/mol

2-Methyl-3-[(diethyl phosphonodifluoromethyl)sulfonyl]indole 80e. Reaction time: 4 h. The product was purified by flash column chromatography on silica gel (height 16 cm, width 1.5 cm, pentane/ethyl acetate = 50:50) as a colorless oil (45.3 mg, 86%). R_f (petroleum ether/ethyl acetate = 60:40): 0.26.

¹H NMR (300.13 MHz, CDCl₃) δ 8.84 (s, 1H), 7.69 – 7.55 (m, 1H), 7.25 – 7.17 (m, 1H), 7.15 – 7.01 (m, 2H), 4.32 – 4.13 (m, 4H), 2.44 (s, 3H), 1.29 (t, J = 7.2 Hz, 6H).

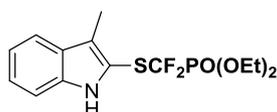
¹⁹F{¹H} NMR (282.4 MHz, CDCl₃) δ – 84.8 (d, J = 104.5 Hz).

³¹P{¹H} NMR (121.5 MHz, CDCl₃) δ 4.3 (t, J = 103.3 Hz).

¹³C NMR (75.5 MHz, CDCl₃) δ 143.9, 135.2, 131.3, 125.3 (td, J = 298.2 Hz, J = 213.7 Hz), 122.0, 120.8, 118.8, 110.8, 91.3 (m), 65.2 (d, J = 6.8 Hz), 16.3 (d, J = 6.0 Hz), 12.2.

IR (neat, cm⁻¹) ν: 3254, 2986, 1455, 1257, 1112, 1024, 910, 742, 630, 550.

HRMS (ESI) calcd for C₁₄H₁₉F₂NO₃PS m/z 350.0786 [M+H]⁺, Found 350.0793.



Chemical Formula: C₁₄H₁₈F₂NO₃PS
Molecular Weight: 349.33 g/mol

2-[(Diethyl phosphonodifluoromethyl)sulfonyl]-3-methylindole 80f. Reaction time: 8 h. The product was purified by flash column chromatography on silica gel (height 16 cm, width 1.5 cm, pentane/diethyl ether = 35:65) as a white solid (46.5 mg, 89%). R_f (petroleum ether/diethyl ether = 35:65): 0.29.

Mp: 66 – 68 °C.

¹H NMR (300.13 MHz, CDCl₃) δ 8.88 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 8.1 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 4.33 – 4.11 (m, 4H), 2.35 (s, 3H), 1.27 (t, J = 7.2 Hz, 6H).

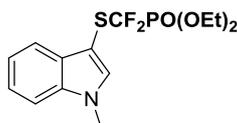
¹⁹F{¹H} NMR (282.4 MHz, CDCl₃) δ – 86.8 (d, J = 104.5 Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.9 (t, $J = 104.5$ Hz).

^{13}C NMR (75.5 MHz, CDCl_3) δ 137.5, 128.0, 124.0, 123.5 (td, $J = 303.5$ Hz, $J = 220.5$ Hz), 123.0, 119.5, 119.5, 114.0 (td, $J = 3.8$ Hz, $J = 3.0$ Hz), 111.1, 65.6 (d, $J = 6.8$ Hz), 16.2 (d, $J = 5.3$ Hz), 9.5.

IR (neat, cm^{-1}) ν : 3276, 2991, 1443, 1255, 1123, 1015, 911, 751, 634, 545.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{19}\text{F}_2\text{NO}_3\text{PS}$ m/z 350.0786 $[\text{M}+\text{H}]^+$, Found 350.0783.



Chemical Formula: $\text{C}_{14}\text{H}_{18}\text{F}_2\text{NO}_3\text{PS}$
Molecular Weight: 349.33 g/mol

N-Methyl-3-[(diethyl phosphonodifluoromethyl)sulfanyl]indole 80g. Reaction time: 2 h. The product was purified by flash column chromatography on silica gel (height 21 cm, width 1.5 cm, petroleum ether/ethyl acetate = 60:40) as a colorless oil (43.2 mg, 82%). R_f (petroleum ether/ethyl acetate = 60:40): 0.18.

^1H NMR (300.13 MHz, CDCl_3) δ 7.71 (d, $J = 7.5$ Hz, 1H), 7.34 – 7.08 (m, 4H), 4.35 – 4.09 (m, 4H), 3.72 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 6H).

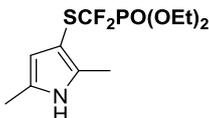
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 85.4 (d, $J = 101.7$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 4.5 (t, $J = 102.1$ Hz).

^{13}C NMR (75.5 MHz, CDCl_3) δ 137.1, 137.1, 130.9, 124.5 (td, $J = 298.2$ Hz, $J = 212.9$ Hz), 122.6, 120.9, 119.6, 109.6, 92.2 (td, $J = 4.5$ Hz, $J = 3.8$ Hz), 65.1 (d, $J = 6.0$ Hz), 33.2, 16.2 (d, $J = 5.3$ Hz).

IR (neat, cm^{-1}) ν : 2985, 2916, 1512, 1483, 1270, 1108, 1009, 909, 740, 647, 539, 425.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_3\text{PS}$ m/z 367.1051 $[\text{M}+\text{NH}_4]^+$, Found 367.1052.



Chemical Formula: $\text{C}_{11}\text{H}_{18}\text{F}_2\text{NO}_3\text{PS}$
Molecular Weight: 313.30 g/mol

2,5-Dimethyl-3-[(diethyl phosphonodifluoromethyl)sulfanyl]pyrrole 80h. Reaction

time: 1 h. The product was purified by flash column chromatography on silica gel (height 14 cm, width 1.5 cm, pentane/diethyl ether = 20:80) as a yellow oil (38.8 mg, 83%). R_f (petroleum ether/diethyl ether = 20:80): 0.62.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 8.30 (s, 1H), 5.93 (s, 1H), 4.38 – 4.21 (m, 4H), 2.29 (s, 3H), 2.19 (s, 3H), 1.38 (t, $J = 7.2$ Hz, 6H).

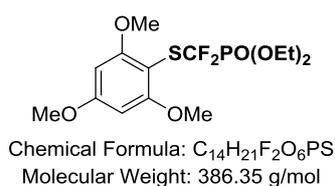
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 85.9 (d, $J = 101.7$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 4.6 (t, $J = 103.3$ Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 134.6, 126.4, 124.8 (td, $J = 296.7$ Hz, $J = 212.9$ Hz), 112.9, 96.3 (m), 65.1 (d, $J = 6.0$ Hz), 16.3 (d, $J = 5.3$ Hz), 12.8, 11.3.

IR (neat, cm^{-1}) ν : 3280, 2987, 1594, 1393, 1258, 1111, 1020, 792, 634, 540.

HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{19}\text{F}_2\text{NO}_3\text{PS}$ m/z 314.0786 $[\text{M}+\text{H}]^+$, Found 314.0790.



S-[Diethyl phosphonodifluoromethyl]-2,4,6-trimethoxythiophenol 80i. Reaction time: 12 h. The product was purified by flash column chromatography on silica gel (height 15 cm, width 1.5 cm, petroleum ether/ethyl acetate = 70:30) as a yellow solid (28.7 mg, 56%). R_f (petroleum ether/ethyl acetate = 70:30): 0.38.

Mp: 57 – 59 °C.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 6.15 (s, 2H), 4.42 – 4.27 (m, 4H), 3.84 (s, 9H), 1.39 (t, $J = 7.2$ Hz, 6H).

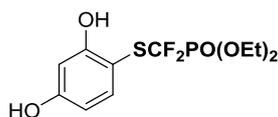
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 84.5 (d, $J = 104.5$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 4.2 (t, $J = 103.3$ Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 164.0, 163.7, 124.5 (td, $J = 300.5$ Hz, $J = 213.7$ Hz), 91.6 (m), 91.0, 65.1 (d, $J = 6.0$ Hz), 56.2, 55.4, 16.3 (d, $J = 6.0$ Hz).

IR (neat, cm^{-1}) ν : 2984, 1578, 1416, 1276, 1233, 1125, 1019, 911, 813, 747, 531.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{22}\text{F}_2\text{O}_6\text{PS}$ m/z 387.0837 $[\text{M}+\text{H}]^+$, Found 387.0846.



Chemical Formula: C₁₁H₁₅F₂O₅PS
Molecular Weight: 328.27 g/mol

S-[Diethyl phosphonodifluoromethyl]-2,4-dihydroxythiophenol 80j. Reaction time: 2 h. The product was purified by flash column chromatography on silica gel (height 14 cm, width 1.5 cm, pentane/diethyl ether = 20:80) as a pale yellow oil (34.3 mg, 70%). R_f (petroleum ether/diethyl ether = 20:80): 0.19.

¹H NMR (300.13 MHz, CDCl₃) δ 7.53 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 6.57 (s, 1H), 6.46 (d, J = 8.7 Hz, 1H), 4.39 – 4.18 (m, 4H), 1.36 (t, J = 7.2 Hz, 6H).

¹⁹F{¹H} NMR (282.4 MHz, CDCl₃) δ – 86.9 (d, J = 104.5 Hz).

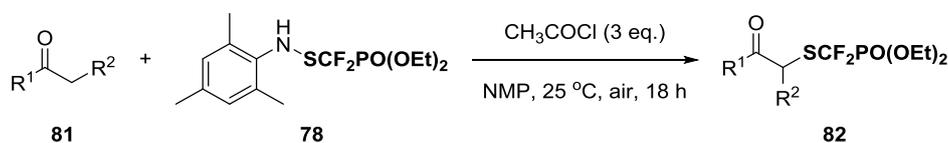
³¹P{¹H} NMR (121.5 MHz, CDCl₃) δ 4.0 (t, J = 104.5 Hz).

¹³C NMR (75.5 MHz, CDCl₃) δ 161.3, 160.0, 140.0, 123.7 (td, J = 300.5 Hz, J = 220.5 Hz), 109.5, 103.3, 98.9 (m), 66.0 (d, J = 7.6 Hz), 16.2 (d, J = 6.0 Hz).

IR (neat, cm⁻¹) v: 3253, 1708, 1590, 1463, 1240, 1161, 1019, 973, 910, 850, 796, 643, 552.

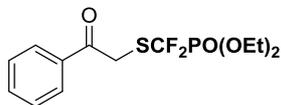
HRMS (ESI) calcd for C₁₁H₁₆F₂O₅PS m/z 329.0419 [M+NH₄]⁺, Found 329.0429.

3.2.3 General procedure for the synthesis of derivatives 82



An oven-dried 10 mL tube equipped with a stirring bar was charged with the derivative **81** (0.2 mmol, 1 eq.), NMP (2 mL) and **78** (127.2 mg, 0.36 mmol, 1.8 eq.). CH₃COCl (47.1 mg, 0.6 mmol, 3 eq.) was added dropwise to the reaction mixture and stirred at 25 °C for 18 h. The mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with a saturated NH₄Cl aqueous solution (10 mL), water (10 mL) and dried over Na₂SO₄. The solvent

was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (or with a Biotage Isolera One flash purification system) to afford the desired product **82**.



Chemical Formula: C₁₃H₁₇F₂O₄PS
Molecular Weight: 338.31 g/mol

2-[(Diethyl phosphonodifluoromethyl)sulfanyl]-1-phenylethan-1-one **82a**.

Reaction time: 18 h, 1.5 eq. of **78** was added. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, pentane/diethyl ether, gradient: 88:12 to 0:100, rate: 20 mL/min) as a pale yellow oil (48.6 mg, 72%). R_f (petroleum ether/diethyl ether = 50:50): 0.22.

¹H NMR (300.13 MHz, CDCl₃) δ 7.96 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 4.60 (s, 2H), 4.40 – 4.26 (m, 4H), 1.39 (t, J = 7.2 Hz, 6H).

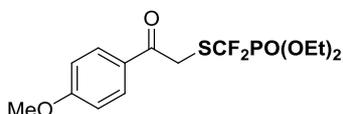
¹⁹F{¹H} NMR (282.4 MHz, CDCl₃) δ – 86.8 (d, J = 104.5 Hz).

³¹P{¹H} NMR (121.5 MHz, CDCl₃) δ 3.0 (t, J = 103.3 Hz).

¹³C NMR (75.5 MHz, CDCl₃) δ 193.0, 135.0, 133.9, 128.8, 128.4, 125.0 (td, J = 299.0 Hz, J = 222.0 Hz), 65.6 (d, J = 6.8 Hz), 37.1 (m), 16.3 (d, J = 5.3 Hz).

IR (neat, cm⁻¹) ν: 2985, 1685, 1598, 1449, 1269, 1114, 1014, 750, 645, 534.

HRMS (ESI) calcd for C₁₃H₂₁F₂NO₄PS m/z 356.0891 [M+NH₄]⁺, Found 356.0895.



Chemical Formula: C₁₄H₁₉F₂O₅PS
Molecular Weight: 368.33 g/mol

2-[(Diethyl phosphonodifluoromethyl)sulfanyl]-1-(4-methoxyphenyl)ethan-1-one **82b**.

Reaction time: 18 h. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, pentane/diethyl ether, gradient: 88:12 to 0:100, rate: 20 mL/min) as a pale yellow oil (45.1 mg, 61%). R_f (petroleum ether/diethyl ether = 50:50): 0.14.

¹H NMR (300.13 MHz, CDCl₃) δ 7.94 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 4.55 (s, 2H), 4.42 – 4.20 (m, 4H), 3.86 (s, 3H), 1.38 (t, J = 7.2 Hz, 6H).

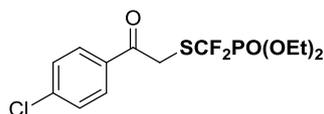
¹⁹F{¹H} NMR (282.4 MHz, CDCl₃) δ – 86.8 (d, J = 101.7 Hz).

³¹P{¹H} NMR (121.5 MHz, CDCl₃) δ 3.1 (t, J = 103.3 Hz).

¹³C NMR (75.5 MHz, CDCl₃) δ 191.4, 164.1, 130.8, 128.0, 125.1 (td, J = 298.2 Hz, J = 222.0 Hz), 113.9, 65.5 (d, J = 6.8 Hz), 55.5, 36.8 (m), 16.3 (d, J = 5.3 Hz).

IR (neat, cm⁻¹) ν: 2918, 1674, 1599, 1512, 1261, 1208, 1171, 1112, 1016, 831, 739, 632, 554.

HRMS (ESI) calcd for C₁₄H₂₃F₂NO₅PS m/z 386.0997 [M+NH₄]⁺, Found 386.1021.



Chemical Formula: C₁₃H₁₆ClF₂O₄PS
Molecular Weight: 372.75 g/mol

2-[(Diethyl phosphonodifluoromethyl)sulfanyl]-1-(4-chlorophenyl)ethan-1-one

82c. Reaction time: 18 h. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, pentane/diethyl ether, gradient: 88:12 to 0:100, rate: 20 mL/min) as a pale yellow oil (40.8 mg, 55%).

R_f (petroleum ether/diethyl ether = 50:50): 0.37.

¹H NMR (300.13 MHz, CDCl₃) δ 7.92 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 4.55 (s, 2H), 4.47 – 4.20 (m, 4H), 1.39 (t, J = 7.2 Hz, 6H).

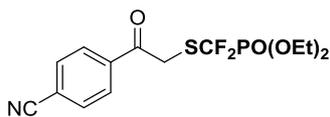
¹⁹F{¹H} NMR (282.4 MHz, CDCl₃) δ – 87.1 (d, J = 101.7 Hz).

³¹P{¹H} NMR (121.5 MHz, CDCl₃) δ 2.9 (t, J = 103.3 Hz).

¹³C NMR (75.5 MHz, CDCl₃) δ 192.0, 140.5, 133.4, 129.9, 129.2, 124.9 (td, J = 299.0 Hz, J = 222.0 Hz), 65.7 (d, J = 6.8 Hz), 36.9 (m), 16.3 (d, J = 6.0 Hz).

IR (neat, cm⁻¹) ν: 2987, 1685, 1589, 1402, 1269, 1115, 1092, 1012, 927, 817, 766, 636, 526.

HRMS (ESI) calcd for C₁₃H₂₀ClF₂NO₄PS m/z 390.0502 [M+NH₄]⁺, Found 390.0511.



Chemical Formula: C₁₄H₁₆F₂NO₄PS
Molecular Weight: 363.32 g/mol

2-[(Diethyl phosphonodifluoromethyl)sulfanyl]-1-(4-cyanophenyl)ethan-1-one

82d. Reaction time: 20 h (after 12 h an additional 1.2 eq. of **78** was added and stirred for additional 8 h). The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, petroleum ether/ethyl acetate, gradient: 93:7 to 40:60, rate: 20 mL/min) as a pale yellow oil (45.3 mg, 62%). R_f (petroleum ether/ethyl acetate = 70:30): 0.13.

¹H NMR (300.13 MHz, CDCl₃) δ 8.06 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 4.57 (s, 2H), 4.42 – 4.20 (m, 4H), 1.39 (t, J = 7.2 Hz, 6H).

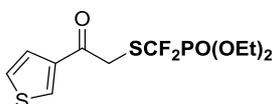
¹⁹F{¹H} NMR (282.4 MHz, CDCl₃) δ – 87.3 (d, J = 101.7 Hz).

³¹P{¹H} NMR (121.5 MHz, CDCl₃) δ 2.7 (t, J = 103.3 Hz).

¹³C NMR (75.5 MHz, CDCl₃) δ 192.1, 138.0, 132.7, 128.9, 124.7 (td, J = 299.7 Hz, J = 222.7 Hz), 117.6, 117.1, 65.7 (d, J = 6.8 Hz), 37.0 (m), 16.3 (d, J = 6.0 Hz).

IR (neat, cm⁻¹) v: 2989, 2228, 1702, 1267, 1209, 1105, 1008, 928, 826, 764, 645, 574, 544.

HRMS (EI) calcd for C₁₄H₁₆F₂NO₄PS m/z 363.0506 [M], Found 363.0505.



Chemical Formula: C₁₁H₁₅F₂O₄PS₂
Molecular Weight: 344.33 g/mol

2-[(Diethyl phosphonodifluoromethyl)sulfanyl]-1-(thiophen-3-yl)ethan-1-one **82e.**

Reaction time: 18 h. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, pentane/diethyl ether, gradient: 88:12 to 0:100, rate: 25 mL/min) as a pale yellow oil (30.6 mg, 44%). R_f (petroleum ether/diethyl ether = 50:50): 0.16.

¹H NMR (300.13 MHz, CDCl₃) δ 8.25 – 8.10 (m, 1H), 7.55 (d, J = 5.1 Hz, 1H), 7.40 –

7.28 (m, 1H), 4.44 (s, 2H), 4.39 – 4.24 (m, 4H), 1.38 (t, J = 7.2 Hz, 6H).

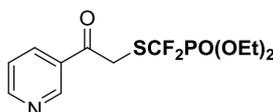
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 86.8 (d, J = 101.7 Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 2.9 (t, J = 103.3 Hz).

^{13}C NMR (75.5 MHz, CDCl_3) δ 187.2, 140.0, 133.4, 126.9, 126.8, 124.9 (td, J = 299.0 Hz, J = 222.0 Hz), 65.6 (d, J = 6.8 Hz), 37.2 (m), 16.3 (d, J = 5.3 Hz).

IR (neat, cm^{-1}) ν : 3094, 2986, 1674, 1511, 1394, 1267, 1114, 1015, 927, 869, 794, 633, 536.

HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{19}\text{F}_2\text{NO}_4\text{PS}_2$ m/z 362.0456 $[\text{M}+\text{NH}_4]^+$, Found 362.0460.



Chemical Formula: $\text{C}_{12}\text{H}_{16}\text{F}_2\text{NO}_4\text{PS}$
Molecular Weight: 339.29 g/mol

2-[(Diethyl phosphonodifluoromethyl)sulfanyl]-3-pyridinyl-ethanone 82f.

Reaction time: 18 h. The product was purified by flash column chromatography on silica gel (height 22 cm, width 1.5 cm, petroleum ether/ethyl acetate = 50:50 to pure ethyl acetate) as a colorless oil (16.8 mg, 25%). R_f (pure ethyl acetate): 0.26.

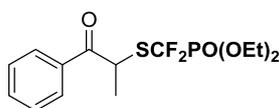
^1H NMR (300.13 MHz, CDCl_3) δ 9.20 (s, 1H), 8.84 (s, 1H), 8.27 (d, J = 8.1 Hz, 1H), 7.52 – 7.40 (m, 1H), 4.56 (s, 2H), 4.36 – 4.28 (m, 4H), 1.40 (d, J = 7.2 Hz, 6H). $^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 87.1 (d, J = 101.7 Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 2.8 (t, J = 102.1 Hz).

^{13}C NMR (75.5 MHz, CDCl_3) δ 192.2, 154.1, 149.8, 135.8, 130.6, 124.8 (td, J = 297.7 Hz, J = 222.0 Hz), 123.8, 65.7 (d, J = 6.8 Hz), 36.8, 16.3 (d, J = 6.0 Hz).

IR (neat, cm^{-1}) ν : 2963, 1689, 1586, 1260, 1013, 795, 702, 535.

HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{17}\text{F}_2\text{NO}_4\text{PS}$ m/z 340.0578 $[\text{M}+\text{H}]^+$, Found 340.0572.



Chemical Formula: $\text{C}_{14}\text{H}_{19}\text{F}_2\text{O}_4\text{PS}$
Molecular Weight: 352.33 g/mol

2-[(Diethyl phosphonodifluoromethyl)sulfanyl]-1-phenylprop-1-one 82g. Reaction time: 18 h. The product was purified by flash column chromatography on silica gel (Biotage system 50 g, height 90 mm, width 40 mm, petroleum ether/ethyl acetate, gradient: 93:7 to 40:60, rate: 50 mL/min) as a colorless oil (33.7 mg, 48%). R_f (petroleum ether/ethyl acetate = 70:30): 0.28.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 8.02 (d, $J = 7.2$ Hz, 2H), 7.60 (t, $J = 7.2$ Hz, 1H), 7.48 (t, $J = 7.5$ Hz, 2H), 5.27 (q, $J = 7.2$ Hz, 1H), 4.39 – 4.18 (m, 4H), 1.68 (d, $J = 7.2$ Hz, 3H), 1.41 – 1.29 (m, 6H).

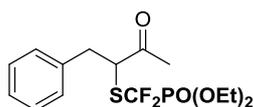
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 84.2 (dd, $J = 257.0$ Hz, $J = 101.7$ Hz), – 85.2 (dd, $J = 257.0$ Hz, $J = 101.7$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 2.9 (t, $J = 102.1$ Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 197.4, 134.4, 133.7, 128.8, 128.8, 125.6 (td, $J = 299.0$ Hz, $J = 222.5$ Hz), 65.6 (d, $J = 6.8$ Hz), 65.5 (d, $J = 6.8$ Hz), 42.5 (m), 20.2, 16.3 (d, $J = 5.3$ Hz), 16.3 (d, $J = 5.3$ Hz).

IR (neat, cm^{-1}) ν : 2985, 1683, 1449, 1273, 1116, 1016, 794, 701, 639, 535.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{23}\text{F}_2\text{NO}_4\text{PS}$ m/z 370.1048 $[\text{M}+\text{NH}_4]^+$, Found 370.1055.



Chemical Formula: $\text{C}_{15}\text{H}_{21}\text{F}_2\text{O}_4\text{PS}$
Molecular Weight: 366.36 g/mol

3-[(Diethyl phosphonodifluoromethyl)sulfanyl]-4-phenylbutan-2-one 82h.

Reaction time: 16 h. The product was purified by flash column chromatography on silica gel (height 16 cm, width 1.5 cm, pentane/diethyl ether = 50:50) as a pale yellow oil (44.5 mg, 61%). R_f (petroleum ether/diethyl ether = 50:50): 0.29.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.31 – 7.05 (m, 5H), 4.41 – 4.02 (m, 5H), 3.18 (dd, $J = 13.8, 9.3$ Hz, 1H), 3.00 (dd, $J = 13.8, 6.3$ Hz, 1H), 2.09 (s, 3H), 1.30 (t, $J = 6.9$ Hz, 6H).

$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 83.7 (dd, $J = 257.0$ Hz, $J = 98.8$ Hz), – 85.5 (dd,

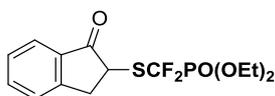
$J = 257.0 \text{ Hz}$, $J = 101.7 \text{ Hz}$).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 2.7 (t, $J = 100.8 \text{ Hz}$).

^{13}C NMR (75.5 MHz, CDCl_3) δ 204.7, 137.1, 129.2, 128.6, 127.0, 125.2 (td, $J = 299.0 \text{ Hz}$, $J = 219.7 \text{ Hz}$), 65.6 (d, $J = 6.8 \text{ Hz}$), 65.6 (d, $J = 6.8 \text{ Hz}$), 51.7 (m), 38.2, 28.6, 16.3, 16.2.

IR (neat, cm^{-1}) ν : 2986, 1717, 1272, 1115, 1015, 919, 750, 699, 640, 534.

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{25}\text{F}_2\text{NO}_4\text{PS}$ m/z 384.1204 $[\text{M}+\text{NH}_4]^+$, Found 384.1210.



Chemical Formula: $\text{C}_{14}\text{H}_{17}\text{F}_2\text{O}_4\text{PS}$
Molecular Weight: 350.32 g/mol

2-[(Diethyl phosphonodifluoromethyl)sulfonyl]-1-indanone 82i. Reaction time: 18 h. The product was purified by flash column chromatography on silica gel (height 15 cm, width 1.5 cm, petroleum ether/diethyl ether = 50:50) as a colorless oil (40.2 mg, 57%). R_f (petroleum ether/diethyl ether = 50:50): 0.22.

^1H NMR (300.13 MHz, CDCl_3) δ 7.79 (d, $J = 7.5 \text{ Hz}$, 1H), 7.64 (t, $J = 7.5 \text{ Hz}$, 1H), 7.53 – 7.35 (m 2H), 4.57 – 4.23 (m, 5H), 3.81 (dd, $J = 17.7, 7.8 \text{ Hz}$, 1H), 3.37 (dd, $J = 17.7, 4.2 \text{ Hz}$, 1H), 1.47 – 1.37 (m, 6H).

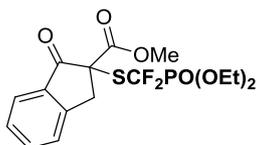
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 83.5 (dd, $J = 254.2 \text{ Hz}$, $J = 101.7 \text{ Hz}$), – 84.4 (dd, $J = 254.2 \text{ Hz}$, $J = 101.7 \text{ Hz}$).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 2.8 (t, $J = 100.8 \text{ Hz}$).

^{13}C NMR (75.5 MHz, CDCl_3) δ 200.2, 152.1, 135.7, 134.8, 128.0, 126.3, 125.6 (td, $J = 299.7 \text{ Hz}$, $J = 219.7 \text{ Hz}$), 124.5, 65.9 (d, $J = 6.8 \text{ Hz}$), 65.5 (d, $J = 6.8 \text{ Hz}$), 46.6 (m), 37.2, 16.4 (d, $J = 6.0 \text{ Hz}$), 16.3 (d, $J = 5.3 \text{ Hz}$).

IR (neat, cm^{-1}) ν : 2986, 1721, 1608, 1272, 1115, 1008, 920, 794, 747, 642, 539.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{21}\text{F}_2\text{NO}_4\text{PS}$ m/z 368.0891 $[\text{M}+\text{NH}_4]^+$, Found 368.0894.



Chemical Formula: C₁₆H₁₉F₂O₆PS
Molecular Weight: 408.35 g/mol

Methyl 2-[(diethyl phosphonodifluoromethyl)sulfanyl]-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **82m.** Reaction time: 18 h. The product was purified by flash column chromatography on silica gel (height 18 cm, width 1.5 cm, petroleum ether/diethyl ether = 30:70) as a colorless oil (42.4 mg, 52%). R_f (petroleum ether/diethyl ether = 30:70): 0.20.

¹H NMR (300.13 MHz, CDCl₃) δ 7.79 (d, J = 7.8 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 4.43 – 4.27 (m, 4H), 4.23 (d, J = 18.0 Hz, 1H), 3.78 (d, J = 18.0 Hz, 1H), 3.75 (s, 3H), 1.46 – 1.30 (m, 6H).

¹⁹F{¹H} NMR (282.4 MHz, CDCl₃) δ –80.2 (dd, J = 251.3 Hz, J = 96.0 Hz), –82.8 (dd, J = 251.3 Hz, J = 96.0 Hz).

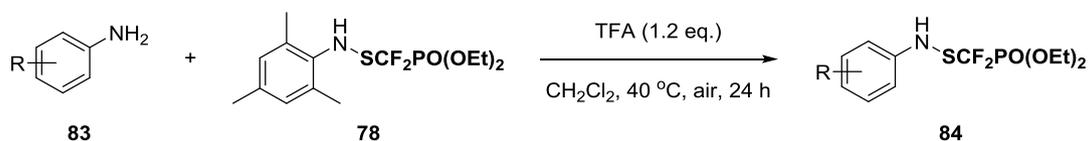
³¹P{¹H} NMR (121.5 MHz, CDCl₃) δ 2.2 (t, J = 96.0 Hz).

¹³C NMR (75.5 MHz, CDCl₃) δ 195.5, 167.7, 152.1, 136.3, 132.8, 128.2, 126.2, 126.1 (td, J = 302.0 Hz, J = 215.9 Hz), 125.5, 65.8 (d, J = 6.8 Hz), 65.8 (d, J = 6.8 Hz), 63.3 (m), 54.0, 40.8, 16.3, 16.2.

IR (neat, cm⁻¹) ν: 2987, 1722, 1606, 1271, 1120, 1020, 916, 757, 644, 554.

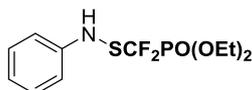
HRMS (ESI) calcd for C₁₆H₂₃F₂NO₆PS m/z 426.0946 [M+NH₄]⁺, Found 426.0955.

3.2.4 General procedure for the synthesis of derivatives **84**



An oven-dried 10 mL tube equipped with a stirring bar was charged with the derivative **83** (0.2 mmol, 1 eq.), CH₂Cl₂ (2 mL) and **78** (84.8 mg, 0.24 mmol, 1.2 eq.) under air. Then, TFA (36.0 mg, 0.24 mmol, 1.2 eq.) was added dropwise to the reaction mixture and stirred at 40 °C for 24 h. After cooling down to room

temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL). The organic layers were washed with a saturated NaHCO_3 aqueous solution (10 mL), water (10 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (or with a Biotage Isolera One flash purification system) to afford the desired product **84**.



Chemical Formula: $\text{C}_{11}\text{H}_{16}\text{F}_2\text{NO}_3\text{PS}$
Molecular Weight: 311.28 g/mol

N-[(Diethyl phosphonodifluoromethyl)sulfanyl]aniline 84a. Reaction time: 18 h, the reaction was performed at 25 °C on a 0.15 mmol scale. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, pentane/diethyl ether, gradient: 88:12 to 0:100, rate: 20 mL/min) as a pale yellow oil (38.5 mg, 82%). R_f (petroleum ether/diethyl ether = 50:50): 0.17.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.30 – 6.69 (m, 5H), 5.18 (s, 1H), 4.34 – 4.09 (m, 4H), 1.30 (t, $J = 6.9$ Hz, 6H).

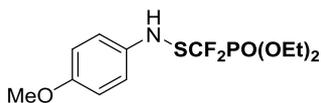
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 94.9 (d, $J = 98.8$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.6 (t, $J = 100.8$ Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 146.2, 129.0, 125.4 (td, $J = 302.8$ Hz, $J = 208.4$ Hz), 121.2, 115.3, 65.3 (d, $J = 6.8$ Hz), 16.3 (d, $J = 5.3$ Hz).

IR (neat, cm^{-1}) ν : 3271, 1600, 1496, 1260, 1123, 1010, 915, 749, 692, 536.

HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{17}\text{F}_2\text{NO}_3\text{PS}$ m/z 312.0629 $[\text{M}+\text{H}]^+$, Found 312.0649.



Chemical Formula: $\text{C}_{12}\text{H}_{18}\text{F}_2\text{NO}_4\text{PS}$
Molecular Weight: 341.31 g/mol

N-[(Diethyl phosphonodifluoromethyl)sulfanyl]-4-methoxyaniline 84b. Reaction time: 24 h. The product was purified by flash column chromatography on silica gel

(Biotage system 25 g, height 80 mm, width 30 mm, pentane/diethyl ether, gradient: 90:10 to 0:100, rate: 25 mL/min) as a pale yellow oil (39.7 mg, 58%). R_f (petroleum ether/diethyl ether = 40:60): 0.27.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.03 (d, $J = 8.7$ Hz, 2H), 6.79 (d, $J = 8.7$ Hz, 2H), 5.09 (s, 1H), 4.46 – 4.09 (m, 4H), 3.75 (s, 3H), 1.37 (t, $J = 7.2$ Hz, 6H).

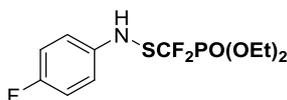
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 94.9 (d, $J = 101.7$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.7 (t, $J = 100.8$ Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 154.5, 139.9, 125.5 (td, $J = 302.8$ Hz, $J = 208.4$ Hz), 116.7, 114.4, 65.3 (d, $J = 6.0$ Hz), 55.6, 16.3 (d, $J = 6.0$ Hz).

IR (neat, cm^{-1}) ν : 3274, 2933, 1671, 1507, 1263, 1227, 1120, 1013, 921, 825, 736, 643, 541.

HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{19}\text{F}_2\text{NO}_4\text{PS}$ m/z 342.0735 $[\text{M}+\text{H}]^+$, Found 342.0750.



Chemical Formula: $\text{C}_{11}\text{H}_{15}\text{F}_3\text{NO}_3\text{PS}$
Molecular Weight: 329.27 g/mol

N-[(Diethyl phosphonodifluoromethyl)sulfanyl]-4-fluoroaniline 84c. Reaction time: 18 h. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, pentane/diethyl ether, gradient: 88:12 to 0:100, rate: 25 mL/min) as a pale yellow oil (52.6 mg, 80%). R_f (petroleum ether/diethyl ether = 50:50): 0.18.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.13 – 6.82 (m, 4H), 5.29 (s, 1H), 4.40 – 4.16 (m, 4H), 1.36 (t, $J = 7.2$ Hz, 6H).

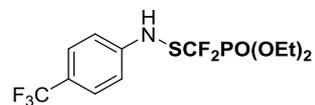
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 95.0 (d, $J = 101.7$ Hz), – 124.0 (s).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.5 (t, $J = 100.8$ Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 157.8 (d, $J = 239.3$ Hz), 142.5 (d, $J = 2.3$ Hz), 125.4 (td, $J = 302.8$ Hz, $J = 209.1$ Hz), 116.5 (d, $J = 7.6$ Hz), 115.5 (d, $J = 22.7$ Hz), 65.3 (d, $J = 6.8$ Hz), 16.3 (d, $J = 5.3$ Hz).

IR (neat, cm^{-1}) ν : 3271, 2987, 1505, 1261, 1211, 1121, 1011, 826, 736, 543.

HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_3\text{PS}$ m/z 347.0801 $[\text{M}+\text{NH}_4]^+$, Found 347.0797.



Chemical Formula: $\text{C}_{12}\text{H}_{15}\text{F}_5\text{NO}_3\text{PS}$
Molecular Weight: 379.28 g/mol

N-[(Diethyl phosphonodifluoromethyl)sulfanyl]-4-trifluoromethylaniline 84d.

Reaction time: 18 h. The product was purified by flash column chromatography on silica gel (height 15 cm, width 1.5 cm, pentane/diethyl ether = 50:50) as a pale yellow oil (66.8 mg, 88%). R_f (petroleum ether/diethyl ether = 50:50): 0.12.

^1H NMR (300.13 MHz, CDCl_3) δ 7.47 (d, $J = 8.4$ Hz, 2H), 7.17 (d, $J = 8.4$ Hz, 2H), 5.76 (s, 1H), 4.39 – 4.20 (m, 4H), 1.37 (t, $J = 7.2$ Hz, 6H).

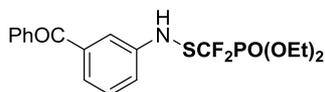
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 62.1 (s), – 94.8 (d, $J = 101.7$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.2 (t, $J = 100.8$ Hz).

^{13}C NMR (75.5 MHz, CDCl_3) δ 149.5, 126.3 (q, $J = 3.8$ Hz), 125.2 (td, $J = 303.5$ Hz, $J = 209.9$ Hz), 124.4 (q, $J = 271.0$ Hz), 123.1 (q, $J = 33.2$ Hz), 115.0, 65.5 (d, $J = 6.8$ Hz), 16.2 (d, $J = 5.3$ Hz).

IR (neat, cm^{-1}) ν : 3258, 2988, 1615, 1523, 1323, 1249, 1110, 1010, 918, 835, 638, 543.

Elemental Anal. calculated for $\text{C}_{12}\text{H}_{15}\text{F}_5\text{NO}_3\text{PS}$: C, 38.00; H, 3.99; S, 8.45; N, 3.69, found: C, 37.94; H, 4.16; S, 8.93; N, 3.58.



Chemical Formula: $\text{C}_{18}\text{H}_{20}\text{F}_2\text{NO}_4\text{PS}$
Molecular Weight: 415.39 g/mol

N-[(Diethyl phosphonodifluoromethyl)sulfanyl]-3-benzoylaniline 84e. Reaction time: 24 h. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, pentane/diethyl ether, gradient: 83:17 to 0:100, rate: 25 mL/min) as a pale yellow oil (72.9 mg, 88%). R_f (petroleum

ether/diethyl ether = 30:70): 0.20.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.71 (d, $J = 7.2$ Hz, 2H), 7.53 – 7.15 (m, 7H), 5.69 (s, 1H), 4.38 – 4.04 (m, 4H), 1.27 (t, $J = 7.2$ Hz, 6H).

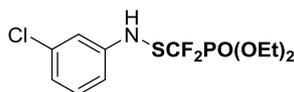
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 94.4 (d, $J = 98.8$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.4 (t, $J = 100.8$ Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 196.4, 146.6, 138.3, 137.4, 132.4, 130.0, 128.9, 128.2, 125.4 (td, $J = 302.8$ Hz, $J = 209.1$ Hz), 123.0, 119.1, 116.5, 65.4 (d, $J = 6.8$ Hz), 16.3 (d, $J = 6.0$ Hz).

IR (neat, cm^{-1}) ν : 3266, 2986, 1656, 1585, 1468, 1260, 1122, 1013, 908, 723, 642, 538.

HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{F}_2\text{N}_2\text{O}_4\text{PS}$ m/z 433.1157 $[\text{M}+\text{NH}_4]^+$, Found 433.1169.



Chemical Formula: $\text{C}_{11}\text{H}_{15}\text{ClF}_2\text{NO}_3\text{PS}$
Molecular Weight: 345.73 g/mol

N-[(Diethyl phosphonodifluoromethyl)sulfanyl]-3-chloroaniline 84f. Reaction time: 24 h. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, pentane/diethyl ether, gradient: 83:17 to 0:100, rate: 25 mL/min) as a pale yellow oil (63.3 mg, 91%). R_f (petroleum ether/diethyl ether = 30:70): 0.25.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.18 – 7.07 (m, 2H), 6.96 (dd, $J = 8.1, 1.8$ Hz, 1H), 6.86 (d, $J = 8.1$ Hz, 1H), 5.55 (s, 1H), 4.38 – 4.20 (m, 4H), 1.37 (t, $J = 7.2$ Hz, 6H).

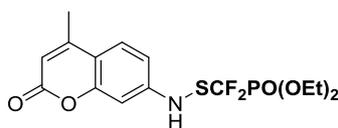
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 94.8 (d, $J = 101.7$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.4 (t, $J = 100.8$ Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 147.8, 134.8, 130.0, 125.2 (td, $J = 302.8$ Hz, $J = 208.4$ Hz), 121.1, 115.4, 113.6, 65.4 (d, $J = 6.8$ Hz), 16.3 (d, $J = 6.0$ Hz).

IR (neat, cm^{-1}) ν : 3260, 2986, 1595, 1474, 1258, 1012, 930, 770, 683, 537.

HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{19}\text{ClF}_2\text{N}_2\text{O}_3\text{PS}$ m/z 363.0505 $[\text{M}+\text{NH}_4]^+$, Found 363.0497.



Chemical Formula: C₁₅H₁₈F₂NO₅PS
Molecular Weight: 393.34 g/mol

N-[(Diethylphosphonodifluoromethyl)sulfonyl]-7-amino-4-methylcoumarin 84g.

Reaction time: 42 h. The product was purified by flash column chromatography on silica gel (Biotage system 50 g, height 90 mm, width 40 mm, petroleum ether/ethyl acetate, gradient: 88:12 to 0:100, rate: 50 mL/min) as a yellow solid (60.1 mg, 76%). R_f (petroleum ether/ethyl acetate = 50:50): 0.24.

Mp: 148 – 150 °C.

¹H NMR (300.13 MHz, CDCl₃) δ 7.41 (d, J = 8.7 Hz, 1H), 7.17 – 6.96 (m, 2H), 6.24 (s, 1H), 6.06 (s, 1H), 4.44 – 4.16 (m, 4H), 2.34 (s, 3H), 1.37 (t, J = 7.2 Hz, 6H).

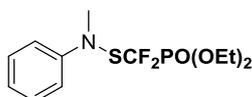
¹⁹F{¹H} NMR (282.4 MHz, CDCl₃) δ – 94.1 (d, J = 98.8 Hz).

³¹P{¹H} NMR (121.5 MHz, CDCl₃) δ 3.1 (t, J = 98.4 Hz).

¹³C NMR (75.5 MHz, CDCl₃) δ 161.4, 154.8, 152.7, 150.6, 125.3, 125.2 (td, J = 302.8 Hz, J = 209.1 Hz), 113.7, 112.0, 111.5, 102.6, 65.5 (d, J = 6.8 Hz), 18.5, 16.3 (d, J = 5.3 Hz).

IR (neat, cm⁻¹) v: 3261, 2988, 1698, 1612, 1389, 1266, 1121, 1012, 814, 746, 639, 550.

HRMS (ESI) calcd for C₁₅H₂₂F₂N₂O₅PS m/z 411.0950 [M+NH₄]⁺, Found 411.0950.



Chemical Formula: C₁₂H₁₈F₂NO₃PS
Molecular Weight: 325.31 g/mol

N-Methyl-N-[(diethyl phosphonodifluoromethyl)sulfonyl]aniline 84j. Reaction time: 72 h, the reaction was performed at 50 °C. The product was purified by flash column chromatography on silica gel (height 15 cm, width 1.5 cm, pentane/diethyl ether = 50:50) as a pale yellow oil (36.3 mg, 56%, 72 h). R_f (petroleum ether/diethyl ether = 50:50): 0.26.

¹H NMR (300.13 MHz, CDCl₃) δ 7.28 – 7.10 (m, 4H), 6.92 – 6.78 (m, 1H), 4.31 – 4.13

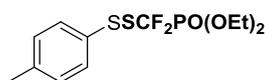
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ - 87.6 (d, J = 98.8 Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.2 (t, J = 98.4 Hz).

^{13}C NMR (75.5 MHz, CDCl_3) δ 135.4, 129.8, 129.1, 128.3, 123.8 (td, J = 303.5 Hz, J = 210.6 Hz), 65.5 (d, J = 6.0 Hz), 16.2 (d, J = 6.0 Hz).

IR (neat, cm^{-1}) ν : 2986, 1441, 1274, 1123, 1009, 891, 794, 740, 687, 641, 554.

Elemental Anal. calculated for $\text{C}_{11}\text{H}_{15}\text{F}_2\text{O}_3\text{PS}_2$: C, 40.24; H, 4.61; S, 19.53, found: C, 39.99; H, 4.61; S, 19.31.



Chemical Formula: $\text{C}_{12}\text{H}_{17}\text{F}_2\text{O}_3\text{PS}_2$
Molecular Weight: 342.36 g/mol

S-[(Diethyl phosphonodifluoromethyl)sulfonyl]-4-methylthiophenol 86b. Reaction time: 14 h. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, petroleum ether/ethyl acetate, gradient: 93:7 to 20:80, rate: 25 mL/min) as a pale yellow oil (37.6 mg, 55%). R_f (petroleum ether/ diethyl ether = 50:50): 0.33.

^1H NMR (300.13 MHz, CDCl_3) δ 7.49 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 4.39 – 4.17 (m, 4H), 2.33 (s, 3H), 1.36 (t, J = 7.2 Hz, 6H).

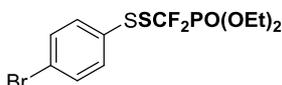
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ - 87.5 (d, J = 98.8 Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.3 (t, J = 98.4 Hz).

^{13}C NMR (75.5 MHz, CDCl_3) δ 138.9, 132.0, 130.9, 129.8, 123.9 (td, J = 303.5 Hz, J = 210.6 Hz), 65.4 (d, J = 6.8 Hz), 21.1, 16.2 (d, J = 6.0 Hz).

IR (neat, cm^{-1}) ν : 2985, 1491, 1274, 1120, 1009, 892, 805, 739, 641, 554.

Elemental Anal. calculated for $\text{C}_{12}\text{H}_{17}\text{F}_2\text{O}_3\text{PS}_2$: C, 42.10; H, 5.01; S, 18.73, found: C, 41.87; H, 5.20; S, 19.07.



Chemical Formula: $\text{C}_{11}\text{H}_{14}\text{BrF}_2\text{O}_3\text{PS}_2$
Molecular Weight: 407.22 g/mol

S-[(Diethyl phosphonodifluoromethyl)sulfanyl]-4-bromothiophenol 86c. Reaction time: 14 h. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, petroleum ether/ethyl acetate, gradient: 93:7 to 20:80, rate: 25 mL/min) as a colorless oil (51.9 mg, 64%). R_f (petroleum ether/ethyl acetate = 60:40): 0.57.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.53 – 7.37 (m, 4H), 4.43 – 4.15 (m, 4H), 1.38 (t, J = 7.2 Hz, 6H).

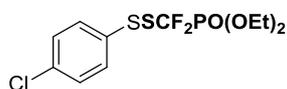
$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 87.5 (d, J = 98.8 Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.1 (t, J = 97.2 Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 134.8, 132.2, 131.4, 123.9 (td, J = 303.5 Hz, J = 210.6 Hz), 122.6, 65.6 (d, J = 6.8 Hz), 16.3 (d, J = 5.3 Hz).

IR (neat, cm^{-1}) ν : 2985, 1473, 1388, 1274, 1124, 1005, 891, 811, 794, 641, 554.

Elemental Anal. calculated for $\text{C}_{11}\text{H}_{14}\text{BrF}_2\text{O}_3\text{PS}_2$: C, 32.44; H, 3.47; S, 15.75, found: C, 32.75; H, 3.54; S, 15.47.



Chemical Formula: $\text{C}_{11}\text{H}_{14}\text{ClF}_2\text{O}_3\text{PS}_2$
Molecular Weight: 362.77 g/mol

S-[(Diethyl phosphonodifluoromethyl)sulfanyl]-4-chlorothiophenol 86d. Reaction time: 14 h. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, petroleum ether/ethyl acetate, gradient: 93:7 to 40:60, rate: 25 mL/min) as a pale yellow oil (47.6 mg, 66%). R_f (petroleum ether/ethyl acetate = 70:30): 0.38.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.52 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 4.44 – 4.16 (m, 4H), 1.37 (t, J = 7.2 Hz, 6H).

$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 87.5 (d, J = 96.0 Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.1 (t, J = 98.4 Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 134.6, 134.1, 131.4, 129.3, 123.9 (td, J = 303.5 Hz, J = 211.4 Hz), 65.6 (d, J = 6.8 Hz), 16.3 (d, J = 5.3 Hz).

IR (neat, cm^{-1}) ν : 2975, 1647, 1476, 1382, 1272, 1045, 879, 640, 558.

HRMS (EI) calcd for $\text{C}_{11}\text{H}_{14}\text{ClF}_2\text{O}_3\text{PS}_2$ m/z 361.9779 [M], Found 361.9785.



Chemical Formula: $\text{C}_9\text{H}_{13}\text{F}_2\text{O}_3\text{PS}_3$
Molecular Weight: 334.35 g/mol

S-[(Diethyl phosphonodifluoromethyl)sulfanyl]-2-thienylthiol 86e. Reaction time: 18 h, 1.7 eq. of **78** was used. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, petroleum ether/ethyl acetate, gradient: 93:7 to 40:60, rate: 25 mL/min) as a colorless oil (48.3 mg, 72%). R_f (petroleum ether/ethyl acetate = 70:30): 0.38.

^1H NMR (300.13 MHz, CDCl_3) δ 7.53 – 7.32 (m, 2H), 6.97 (dd, $J = 5.1, 3.9$ Hz, 1H), 4.41 – 4.14 (m, 4H), 1.35 (t, $J = 7.2$ Hz, 6H).

$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 87.5 (d, $J = 98.8$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.2 (t, $J = 98.4$ Hz).

^{13}C NMR (75.5 MHz, CDCl_3) δ 137.1, 133.7, 132.6, 127.7, 124.1 (td, $J = 302.8$ Hz, $J = 211.4$ Hz), 65.5 (d, $J = 6.8$ Hz), 16.2 (d, $J = 6.0$ Hz).

IR (neat, cm^{-1}) ν : 2985, 1396, 1272, 1120, 1008, 893, 708, 641, 553.

Elemental Anal. calculated for $\text{C}_9\text{H}_{13}\text{F}_2\text{O}_3\text{PS}_3$: C, 32.33; H, 3.92; S, 28.77, found: C, 32.19; H, 4.02; S, 28.70.



Chemical Formula: $\text{C}_{12}\text{H}_{17}\text{F}_2\text{O}_3\text{PS}_2$
Molecular Weight: 342.36 g/mol

S-[(Diethyl phosphonodifluoromethyl)sulfanyl]phenylmethanethiol 86f. Reaction time: 14 h. The product was purified by flash column chromatography on silica gel (Biotage system 25 g, height 80 mm, width 30 mm, petroleum ether/ethyl acetate, gradient: 93:7 to 40:60, rate: 25 mL/min) as a colorless oil (58.6 mg, 86%). R_f (petroleum ether/ethyl acetate = 70:30): 0.36.

$^1\text{H NMR}$ (300.13 MHz, CDCl_3) δ 7.53 – 7.15 (m, 5H), 4.45 – 4.21 (m, 4H), 4.11 (s, 2H), 1.41 (t, $J = 7.2$ Hz, 6H).

$^{19}\text{F}\{^1\text{H}\}$ NMR (282.4 MHz, CDCl_3) δ – 88.0 (d, $J = 98.8$ Hz).

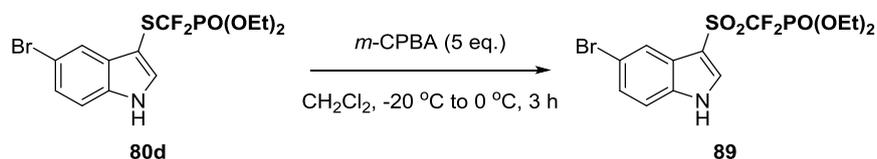
$^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3) δ 3.3 (t, $J = 98.4$ Hz).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 135.7, 129.4, 128.6, 127.8, 124.5 (td, $J = 302.0$ Hz, $J = 210.6$ Hz), 65.4 (d, $J = 6.0$ Hz), 44.7, 16.3 (d, $J = 5.3$ Hz).

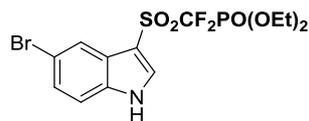
IR (neat, cm^{-1}) ν : 2985, 1455, 1273, 1120, 1009, 895, 763, 698, 641, 552.

HRMS (EI) calcd for $\text{C}_{12}\text{H}_{17}\text{F}_2\text{O}_3\text{PS}_2$ m/z 342.0325 [M], Found 342.0336.

3.2.6 Procedure for the synthesis of **89**



An oven-dried 10 mL tube equipped with a stirring bar was charged with **80d** (41.4 mg, 0.1 mmol, 1 eq.), CH_2Cl_2 (1 mL) and the reaction mixture was cooled down to $-20\text{ }^\circ\text{C}$. Then, *m*-CPBA (246.5 mg, 0.5 mmol, 5 eq., assay ca. 35%) was added portionwise while keeping the temperature at $-20\text{ }^\circ\text{C}$. The reaction mixture was allowed to warm up to $0\text{ }^\circ\text{C}$ and was stirred for 3 h until complete conversion. Then, the reaction mixture was diluted with CH_2Cl_2 (10 mL). Then organic layer was washed with a saturated Na_2SO_3 aqueous solution (10 mL), a saturated NaHCO_3 aqueous solution (10 mL), brine (10 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, petroleum ether/ethyl acetate, gradient: 88:20 to 0:100, rate: 25 mL/min) to afford the desired product **89** as a white solid in 89% yield (39.5 mg). R_f (petroleum ether/ethyl acetate = 30:70): 0.29.



Chemical Formula: C₁₃H₁₅BrF₂NO₅PS
Molecular Weight: 446.20 g/mol

3-[(Diethyl phosphonodifluoromethyl)sulfonyl]-5-bromo-indole **89**.

Mp: 146 – 148 °C.

¹H NMR (300.13 MHz, CDCl₃) δ 11.05 (s, 1H), 8.02 – 7.85 (m, 2H), 7.36 – 7.23 (m, 2H), 4.49 – 4.18 (m, 4H), 1.33 (t, J = 7.2 Hz, 6H).

¹⁹F{¹H} NMR (282.4 MHz, CDCl₃) δ – 110.3 (d, J = 84.7 Hz).

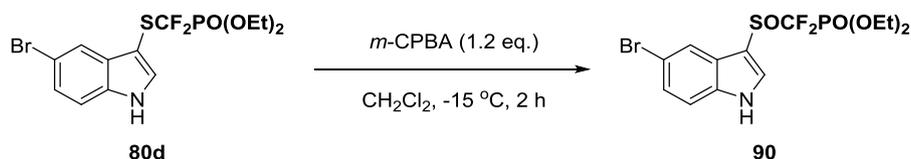
³¹P{¹H} NMR (121.5 MHz, CDCl₃) δ – 0.2 (t, J = 86.3 Hz).

¹³C NMR (75.5 MHz, CDCl₃) δ 136.9, 135.3, 127.3, 126.4, 122.1, 118.1 (td, J = 307.3 Hz, J = 193.3 Hz), 116.7, 114.4, 105.0 (d, J = 3.8 Hz), 66.7 (d, J = 6.8 Hz), 16.2 (d, J = 5.3 Hz).

IR (neat, cm⁻¹) v: 3180, 2922, 1422, 1339, 1260, 1172, 1022, 888, 792, 708, 660, 603.

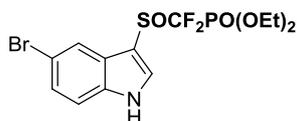
HRMS (ESI) calcd for C₁₃H₁₆BrF₂NO₅PS m/z 445. 9633 [M+H]⁺, Found 445.9638.

3.2.7 Procedure for the synthesis of **90**



An oven-dried 10 mL tube equipped with a stirring bar was charged with **80d** (41.4 mg, 0.1 mmol, 1 eq.), CH₂Cl₂ (1 mL) and the reaction mixture was cooled down to –15 °C. Then, m-CPBA (59.2 mg, 0.12 mmol, 1.2 eq., assay ca. 35%) was added portionwise while keeping the temperature at –15 °C. The reaction mixture was stirred at –15 °C for 2 h. Then, the reaction mixture was diluted with CH₂Cl₂ (10 mL), washed with a saturated Na₂SO₃ aqueous solution (10 mL), a saturated NaHCO₃ aqueous solution (10 mL) and brine (10 mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (height 12 cm, width 1.5 cm, pentane/ethyl acetate = 30:70) to afford

the desired product **90** as a white solid in 64% yield (27.4 mg). R_f (petroleum ether/ethyl acetate = 30:70): 0.19.



Chemical Formula: $C_{13}H_{15}BrF_2NO_4PS$
Molecular Weight: 430.20 g/mol

3-[(Diethyl phosphonodifluoromethyl)sulfinyl]-5-bromo-indole **90**.

Mp: 132 – 134 °C.

1H NMR (300.13 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.05 (s, 1H), 7.67 (d, $J = 3.0$ Hz, 1H), 7.37 – 7.22 (m, 2H), 4.39 – 4.25 (m, 2H), 4.22 – 4.09 (m, 2H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.21 (t, $J = 7.2$ Hz, 3H).

$^{19}F\{^1H\}$ NMR (282.4 MHz, $CDCl_3$) δ – 109.6 (dd, $J = 273.9$ Hz, $J = 90.4$ Hz), – 113.3 (dd, $J = 273.9$ Hz, $J = 90.4$ Hz).

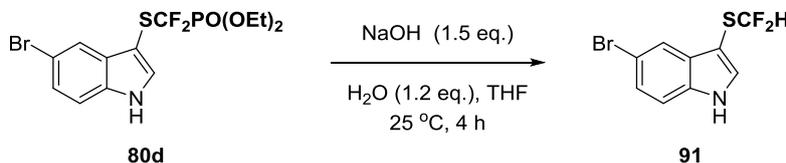
$^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$) δ 1.7 (t, $J = 88.7$ Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.5, 132.0, 126.9, 126.5, 123.0 (td, $J = 315.6$ Hz, $J = 196.3$ Hz), 122.8, 115.5, 114.0, 107.4, 66.0 (d, $J = 6.8$ Hz), 65.9 (d, $J = 6.8$ Hz), 16.2 (d, $J = 5.3$ Hz), 16.0 (d, $J = 5.3$ Hz).

IR (neat, cm^{-1}) ν : 3164, 1454, 1404, 1272, 1158, 1017, 866, 800, 603, 537.

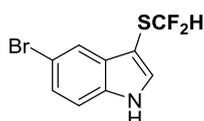
HRMS (ESI) calcd for $C_{13}H_{16}BrF_2NO_4PS$ m/z 429.9684 $[M+H]^+$, Found 429.9674.

3.2.8 Procedure for the cleavage of S-P bond on compound **80d**



An oven-dried 10 mL tube equipped with a stirring bar was charged with **80d** (82.8 mg, 0.2 mmol, 1 eq.) and THF (4 mL). Then, NaOH (12.0 mg, 0.3 mmol, 1.5 eq.) and H₂O (4.3 mg, 0.24 mmol, 1.2 eq.) were added. The reaction mixture was stirred at 25 °C for 4 h, then diluted with diethyl ether (10 mL). The organic layer was washed with water (2 × 10 mL), the combined aqueous layers were extracted with diethyl

ether (3 × 10 mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, pentane/diethyl ether, gradient: 80:20 to 0:100, rate: 25 mL/min) to afford the desired product **91** as a colorless oil in 32% yield (17.6 mg). R_f (petroleum ether/diethyl ether = 20:80): 0.52.



Chemical Formula: C₉H₆BrF₂NS
Molecular Weight: 278.11 g/mol

3-[(Difluoromethyl)thio]- 5-bromoindole **91**.

¹H NMR (300.13 MHz, CDCl₃) δ 8.42 (s, 1H), 7.83 (s, 1H), 7.38 (d, J = 2.7 Hz, 1H), 7.28 (dd, J = 8.7, 1.5 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 6.59 (t, J = 57.3 Hz, 1H).

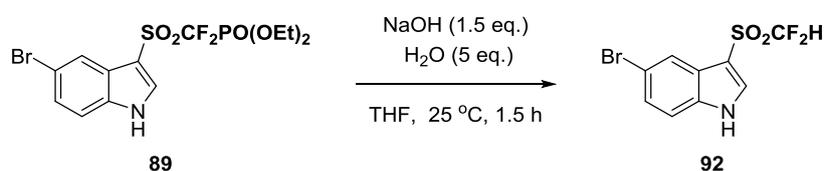
¹⁹F NMR (282.4 MHz, CDCl₃) δ - 92.6 (d, J = 59.3 Hz).

¹³C NMR (75.5 MHz, CDCl₃) δ 134.7, 132.9, 131.5, 126.3, 122.0, 120.5 (t, J = 276.3 Hz), 114.8, 113.1, 96.2 (t, J = 3.8 Hz).

IR (neat, cm⁻¹) v: 3460, 1676, 1446, 1306, 1238, 1093, 1050, 1012, 874, 792, 748, 691, 581.

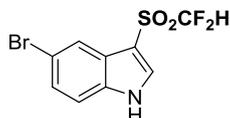
HRMS (ESI) calcd for C₉H₅BrF₂NS m/z 275.9294 [M-H]⁻, Found 275.9282.

3.2.9 Procedure for the cleavage of S-P bond on compound **89**



An oven-dried 10 mL tube equipped with a stirring bar was charged with **89** (22.3 mg, 0.05 mmol, 1 eq.) and THF (1 mL). Then, NaOH (3.0 mg, 0.075 mmol, 1.5 eq.) and H₂O (4.5 mg, 0.25 mmol, 5 eq.) were added. The reaction mixture was stirred at 25 °C for 1.5 h. The reaction mixture was diluted with diethyl ether (10 mL), washed with water (2 × 10 mL). The combined aqueous layers were extracted with diethyl ether (3 × 10 mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure.

The residue was purified by flash column chromatography (height 12 cm, width 1.5 cm, petroleum ether/ethyl acetate, 30:70) to afford the desired product **92** as a white solid in 83% yield (12.9 mg). R_f (petroleum ether/ethyl acetate = 30:70): 0.46.



Chemical Formula: $C_9H_6BrF_2NO_2S$
Molecular Weight: 310.11 g/mol

3-((Difluoromethyl)sulfonyl)-5-bromoindole **92**.

Mp: 195 – 197 °C.

1H NMR (300.13 MHz, THF- d_8) δ 8.11 (s, 1H), 8.03 (s, 1H), 7.50 – 7.34 (m, 2H), 6.62 (t, $J = 53.7$ Hz, 1H).

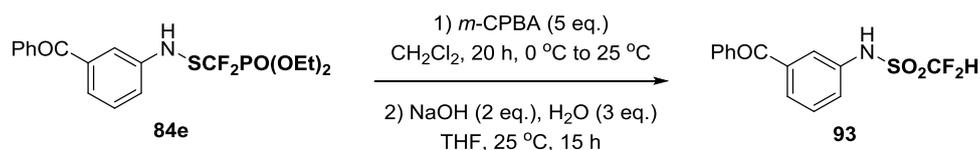
^{19}F NMR (282.4 MHz, THF- d_8) δ – 124.1 (d, $J = 53.7$ Hz).

^{13}C NMR (75.5 MHz, THF- d_8) δ 137.1, 136.5, 127.6, 127.5, 122.8, 116.6, 116.1 (t, $J = 281.6$ Hz), 114.9, 106.8.

IR (neat, cm^{-1}) ν : 3346, 1416, 1332, 1294, 1236, 1090, 1024, 887, 804, 671, 621, 519.

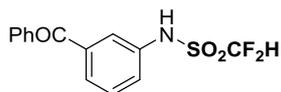
HRMS (ESI) calcd for $C_9H_5BrF_2NO_2S$ m/z 307.9192 $[M-H]^-$, Found 307.9185.

3.2.10 Procedure for the synthesis of **93**



An oven-dried 10 mL tube equipped with a stirring bar was charged with **84e** (62.3 mg, 0.15 mmol, 1 eq.) and CH_2Cl_2 (1.5 mL), the reaction mixture was cooled down to 0 °C. Then, *m*-CPBA (369.8 mg, 0.5 mmol, 5 eq., assay ca. 35%) was added portionwise while keeping the temperature at 0 °C. The reaction mixture was allowed to warm up to 25 °C and was stirred for 20 h until the complete disappearance of the starting material. Then, the reaction mixture was diluted with ethyl acetate (10 mL). The organic layer was washed with a saturated $NaHCO_3$ aqueous solution (2×10 mL), the combined aqueous layers were extracted with ethyl acetate (3×10 mL).

Then the combined organic layers were dried over MgSO_4 and the solvent was removed under reduced pressure. The crude was directly engaged in the next step without any purification. The obtained residue was dissolved in THF (1.5 mL), NaOH (12 mg, 0.3 mmol, 2 eq.) and H_2O (8.1 mg, 0.45 mmol, 3 eq.) were added. The reaction mixture was stirred at 25 °C for 15 h. Then, water (10 mL) was added to the reaction mixture, extracted with ethyl acetate (10 mL). The aqueous layer was neutralized with 2M HCl till pH = 5 and extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over MgSO_4 , and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (height 15 cm, width 1.5 cm, pentane/ethyl acetate = 80:20) to afford the desired product **93** as a white solid in 84% yield over two steps (39.3 mg). R_f (petroleum ether/ethyl acetate = 80:20): 0.28.



Chemical Formula: $\text{C}_{14}\text{H}_{11}\text{F}_2\text{NO}_3\text{S}$
Molecular Weight: 311.30 g/mol

N-(3-benzoylphenyl)-1,1-difluoromethanesulfonamide 93.

Mp: 90 – 92 °C.

^1H NMR (300.13 MHz, CDCl_3) δ 7.91 – 7.74 (m, 3H), 7.72 – 7.57 (m, 3H), 7.56 – 7.38 (m, 3H), 6.31 (t, $J = 53.7$ Hz, 1H).

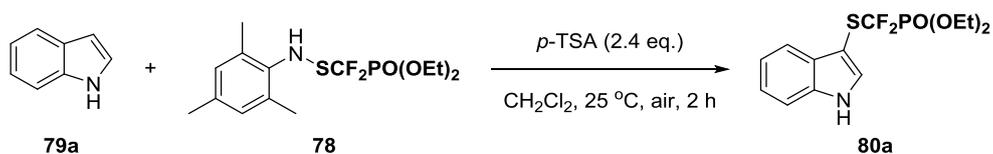
^{19}F NMR (282.4 MHz, CDCl_3) δ – 121.1 (d, $J = 53.7$ Hz).

^{13}C NMR (75.5 MHz, CDCl_3) δ 196.4, 138.5, 136.6, 135.7, 133.2, 130.3, 129.5, 128.5, 128.2, 126.2, 123.8, 113.8 (t, $J = 282.4$ Hz).

IR (neat, cm^{-1}) ν : 3174, 2922, 1652, 1599, 1464, 1362, 1286, 1169, 1103, 923, 781, 720, 684, 542.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{10}\text{F}_2\text{NO}_3\text{S}$ m/z 310.0349 $[\text{M}-\text{H}]^-$, Found 310.0345.

3.2.11 Test on the stability of reagent **78**



While stored for three months at room temperature under aerobic conditions, no degradation of **78** was observed as its reactivity remained unchanged as demonstrated by the following experiment.

An oven-dried 10 mL tube equipped with a stirring bar was charged with **79a** (0.03 mmol, 1 eq.), CH₂Cl₂ (0.3 mL), **78** (12.7 mg, 0.36 mmol, 1.2 eq.) and p-TSA (12.4 mg, 0.07 mmol, 2.4 eq.) under air. The resulting reaction mixture was stirred at 25 °C for 2 h affording **80a** in 98% NMR yield. The NMR yield was determined by ¹⁹F NMR using α,α,α -trifluoroacetophenone as an internal standard.

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Annex

From my master thesis:

7. **H.-Y. Xiong**, Z.-Y. Yang, Z. Chen, J.-L. Zeng, J. Nie, J.-A. Ma. "Copper-Catalyzed One-Pot Denitrogenative-Dehydrogenative-Decarboxylative Coupling of β -Ketoacids with Trifluorodiazethane: Facile Access to Trifluoromethylated Aldol Products" *Chem. Eur. J.* **2014**, 20, 8325.
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11. J. Nie, M.-Q. Hua, **H.-Y. Xiong**, Y. Zheng, J.-A. Ma. "Asymmetric phase-transfer-catalyzed conjugate addition of glycine imine to exocyclic α,β -unsaturated ketones construction of polycyclic imines containing three stereocenters". *J. Org. Chem.* **2012**, 77, 4209.

Scientific records

- Poster presentation in **14th national meeting on fluorine chemistry**, FuZhou, China, November, 2016.
- Poster presentation in **Bermen Fluorine Days**, Bremen, Germany, July, 2016.
- Oral communication in **Journées Nord-Ouest Européennes des Jeunes Chercheurs (JNOEJC)**, Rouen, France, May, 2015.
- Poster presentation in **JNOEJC**, Lille, France, June, 2014.

Honors & Awards

- Doctoral Scholarship, CSC, China, 2013-2017.
- National Scholarship for Master Student, Tianjin University, 2012.
- Distinguished Student, School of Science, Tianjin University, 2011-2012.
- Distinguished Student, School of Science, Neijiang Normal University, 2007-2008.
- National Encouragement Scholarship, Neijiang Normal University, 2008.

Technical skills & Language level

- Scientific: NMR (^1H , ^{13}C , ^{19}F , 2D NMR), IR, GC-MS, HPLC, Glove box, Schlenk technique.
- Computer: MS Office, ChemDraw, SciFinder, MestReNova.
- Advanced English (Conversation, Reading, Writing), Chinese (Native), French (Basic).

Interests

- Traveling, Cooking, Swimming

The organofluorine chemistry field has witnessed a very fast expansion. In particular, the SCF₃ moiety and more recently the SCF₂R groups (R = H, SO₂Ph, SAr, COAr, R_f) have attracted a special interest from the scientific community because of their remarkable properties. In this context, the development of new methodologies and original reagents for the introduction of such fluorinated groups is particularly appealing. Therefore, the goals of this thesis were 1) to develop a new methodology for the direct introduction of the SCF₃ group by transition metal-catalyzed C(sp³)-H bond functionalization and its extension to other functional groups as well as 2) to design and study new electrophilic fluorinated reagents.

The first part of this Ph.D. thesis was dedicated to the development of an unprecedented Pd-catalyzed trifluoromethylthiolation of aliphatic amides by C-H bond functionalization (Chapter 2). Then, the Pd-catalyzed chlorination of aliphatic amides by C-H bond functionalization under mild conditions was investigated (Chapter 3).

Finally, a newly designed strategy for the synthesis of trifluoromethanesulfenamides was elaborated (Chapter 4). This approach was extended to the preparation of a new electrophilic reagent for the thiocyanation reaction. In addition, an original electrophilic SCF₂PO(OEt)₂ reagent was designed and applied to the construction of C-SCF₂PO(OEt)₂, N-SCF₂PO(OEt)₂ and S-SCF₂PO(OEt)₂ bonds as well as to the synthesis of a biorelevant compound (Chapter 4).

Le domaine de recherche de la chimie du fluor a connu un essor considérable. En particulier, le motif SCF₃ et plus récemment les groupements SCF₂R (R = H, SO₂Ph, SAr, COAr, R_f) ont fait l'objet d'une attention particulière de la part de la communauté scientifique du fait de leurs propriétés remarquables. Dans ce contexte, le développement de nouvelles méthodologies et de réactifs originaux pour l'introduction de ces groupements fluorés a suscité un fort intérêt. En conséquence, les objectifs de cette thèse ont été 1) de développer de nouvelles méthodologies pour la fonctionnalisation de liaisons C(sp³)-H par l'introduction directe d'un motif SCF₃ catalysée par des métaux de transition, et son extension à d'autres groupements fonctionnels ainsi que 2) de concevoir et étudier de nouveaux réactifs fluorés électrophiles.

La première partie de cette thèse a été dédiée au développement d'une réaction de trifluorométhylthiolation d'amides aliphatiques catalysée au palladium, une transformation inédite (Chapitre 2). Puis, la chloration d'amides aliphatiques catalysée au palladium, dans des conditions douces, a été étudiée (Chapitre 3).

Enfin, une nouvelle voie de synthèse pour accéder aux sulfénamides trifluorométhylés a été développée (Chapitre 4). Cette approche a été étendue à la préparation d'un nouveau réactif électrophile pour l'introduction du groupement SCN. De plus, un réactif électrophile original, source du motif SCF₂PO(OEt)₂, a été synthétisé et appliqué à la construction de liaisons C-SCF₂PO(OEt)₂, N-SCF₂PO(OEt)₂ et S-SCF₂PO(OEt)₂ ainsi qu'à la synthèse d'un composé d'intérêt biologique (Chapitre 4).