Development of Methods and Reagents for the Trifluoromethylchalcogenation of Organic Compounds

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by

Stefan Dix, M. Sc.

from Berlin, Germany

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Authors Declaration

Hereby, I declare that the submitted thesis is my own work and was prepared autonomously without the help of other sources than the ones cited and acknowledged. The work was not submitted to any prior doctoral procedure.

Stefan Dix, July 2021

The presented research was carried out under the supervision of Prof. Dr. Matthew N. Hopkinson from March 2017 until March 2021 at the Department of Biology, Chemistry, and Pharmacy of the Freie Universität Berlin.

1. Reviewer:	Prof. Dr. Matthew Hopkinson Institute of Chemistry and Biochemistry, Freie Universität Berlin
2. Reviewer:	Prof. Dr. Beate Koksch Institute of Chemistry and Biochemistry, Freie Universität Berlin
Date of Defense:	11.10.2021

"***Yesterday is history, tomorrow is a mystery, but today is a gift.***"

Unknown author

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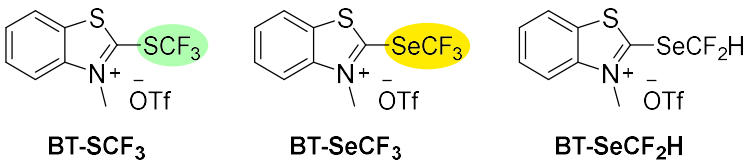
Abstract

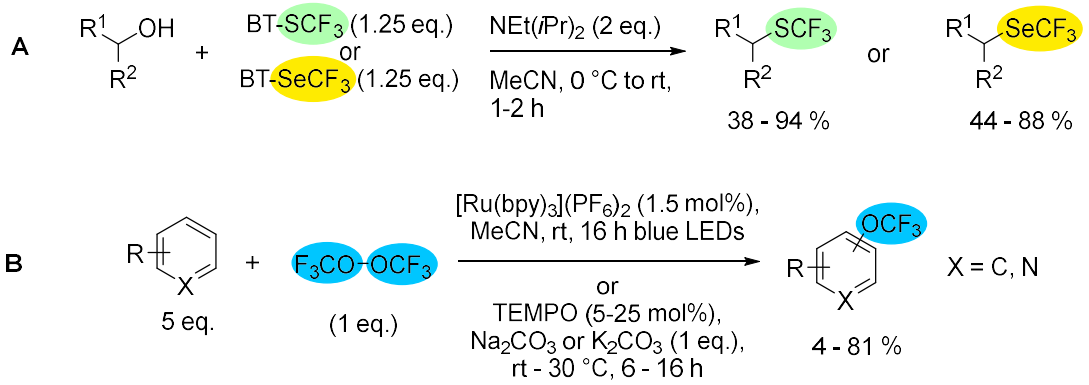
In this thesis, novel synthetic approaches towards organofluorine compounds were investigated. Overall, the reagents BT-SCF_3, BT-$SeCF_3$, BT-$SeCF_2H$ and several derivatives were introduced, and three new synthetic methods for the trifluoromethylchalcogenation of organic compounds were developed (Schemes I & II). Furthermore, C-F activation of α-fluoroketones was investigated.



BT-SCF_3 **BT-$SeCF_3$** **BT-$SeCF_2H$**

Scheme I: The newly developed reagents BT-SCF_3, BT-$SeCF_3$ and BT-$SeCF_2H$.

The reagents BT-SCF_3 and BT-$SeCF_3$ release the $^-SCF_3$ or $^-SeCF_3$ anion *in situ* upon reaction with an oxygen nucleophile. This was utilized for the development of the deoxytrifluoromethylthiolation and the deoxytrifluoromethylselenylation of alcohols. A broad range of alcohols was successfully transformed in up to excellent yields, including primary and secondary alcohols. The direct deoxytrifluoromethylselenylation of alcohols was described for the first time. Furthermore, the derivative BT-$SeCF_2H$ was used to successfully adapt a known deoxytrifluoromethylthiolation procedure for carboxylic acids to prepare a difluoromethyl selenoester.

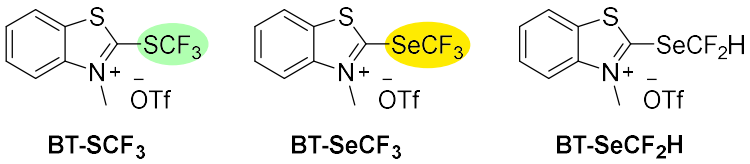


Scheme II: The developed trifluoromethylchalkogenation methods include deoxytrifluoromethylthiolation and deoxytrifluoromethylselenylation of alcohols (A) and radical trifluoromethoxylation of (hetero)arenes (B).

The reagent bis(trifluoromethyl)peroxide (BTMP) was, for the first time, used as an efficient source for the *in situ* generated ·OCF_3 radical by employing photocatalysis and TEMPO-catalysis. Earlier synthetic methods that employed BTMP delivered trifluoromethoxylated compounds only in low yields and often inseparable mixtures. In contrast, the developed trifluoromethoxylation of (hetero)arenes could provide the desired products in up to very good yields. Moreover, trifluoromethoxylated pyridines were synthesized in a single step from inexpensive substrates, while earlier methods are based on expensive reagents or cumbersome multi-step procedures.

Zusammenfassung

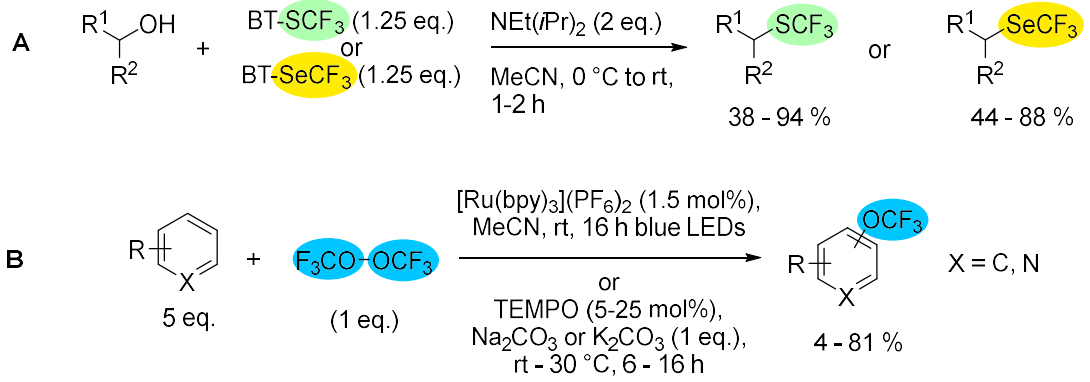
In dieser Arbeit wurden neuartige synthetische Ansätze zu Organofluorverbindungen untersucht. Insgesamt wurden die Reagenzien BT-SCF_3, BT-$SeCF_3$, BT-$SeCF_2H$ und mehrere Derivate synthetisiert und drei neue Synthesemethoden für die Trifluormethylchalkogenierung organischer Verbindungen entwickelt (Schemen I & II). Weiterhin wurde die C-F-Aktivierung von α-Fluorketonen untersucht.



BT-SCF_3 BT-$SeCF_3$ BT-$SeCF_2H$

Schema I: Die neu entwickelten Reagenzien BT-SCF_3, BT-$SeCF_3$ and BT-$SeCF_2H$.

Die Reagenzien BT-SCF_3 und BT-$SeCF_3$ setzen bei der Reaktion mit einem Sauerstoff-Nukleophil das Anion $^-SCF_3$ bzw. $^-SeCF_3$ *in situ* frei. Dies wurde für die Entwicklung von zwei Synthesemethoden, der Desoxytrifluormethylthiolierung und der Desoxytrifluormethylselenylierung von Alkoholen, genutzt. Ein breites Spektrum von Alkoholen wurde erfolgreich in bis zu exzellenten Ausbeuten transformiert, einschließlich primärer und sekundärer Alkohole. Die direkte Desoxytrifluormethylselenylierung von Alkoholen wurde zum ersten Mal beschrieben. Weiterhin wurde mit dem Derivat BT-$SeCF_2H$ ein bekanntes Desoxytrifluormethylthiolierungsverfahren für Carbonsäuren erfolgreich zur Herstellung eines Difluormethylselenoesters adaptiert.



Schema II: Die entwickelten Trifluormethylchalkogenierungsmethoden beinhalten die Deoxytrifluormethylthiolierung und Deoxytrifluormethylselenylierung von Alkoholen (A) sowie die radikalische Trifluormethoxylierung von (Hetero)arenen (B).

Das Reagenz Bis(trifluormethyl)peroxid (BTMP) wurde erstmals als effiziente Quelle für das *in situ* erzeugte ·OCF_3-Radikal unter Verwendung von Photokatalyse und TEMPO-Katalyse eingesetzt. Frühere Synthesemethoden, die BTMP einsetzten, lieferten trifluormethoxylierte Verbindungen nur in geringen Ausbeuten und in meist untrennbaren Gemischen. Im Gegensatz dazu kann die

vorgestellte radikalische Trifluormethoxylierung von (Hetero)arenen die gewünschten Produkte in bis zu sehr guten Ausbeuten liefern. Darüber hinaus konnten trifluormethoxylierte Pyridine in einem einzigen Syntheseschritt aus preiswerten Ausgangsmaterialien synthetisiert werden, während frühere Methoden entweder auf teuren Reagenzien basieren oder umständliche, mehrstufige Verfahren benötigen.

Table of Contents

Abbreviations and Acronyms

18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
4-FAc	4-fluoroacetate
4-FT	4-fluorothreonine
5'-FDA	5'-fluoro-5'-deoxyadenosine
5'-FDAS	5'-fluoro-5'-deoxyadenosine synthase
Ar	aryl
BET	back electron transfer
bmim	1-butyl-3-methylimidazolium
bpy	2,2'-bipyridine
BrettPhos	2-(Dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
BTMP	bis(trifluoromethyl)peroxide
BT-SCF_2H	2-((difluoromethyl)thio)-3-methylbenzo[*d*]thiazol-3-ium trifluoromethanesulfonate
BT-SCF_3	3-Methyl-2-((trifluoromethyl)thio)benzo[*d*]thiazol-3-ium trifluoromethanesulfonate
BT-$SeCF_2H$	2-((difluoromethyl)selanyl)-3-methylbenzo[*d*]thiazol-3-ium trifluoromethanesulfonate
BT-$SeCF_3$	3-Methyl-2-((trifluoromethyl)selanyl)benzo[*d*]thiazol-3-ium trifluoromethanesulfonate
Bu	butyl
CGRP	calcitonin gene-related peptide
COX-2	cyclooxygenase-2
DAST	diethylaminosulfur trifluoride
dF(CF_3)ppy	3,5-difluoro-2-(5-trifluoromethyl)-2-pyridine
DCE	1,2-dichloroethane
DFT	density-functional theory
DMC	dimethyl carbonate

DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPP-4	dipeptidyl peptidase-4
DSC	differential scanning calorimetry
dtbpy	4,4'-di-tert-butyl-2,2'-bipyridine
eq.	equivalents
Et	ethyl
FAld	4-fluoroacetaldehyd
HAT	H atom transfer
HDMS	hexamethyldisilazane
HFIP	hexafluoro-2-propanol
IC_{50}	half maximal inhibitory concentration
Ki	inhibitory constant
*i*Pr	*Iso*-propyl
LED	light-emitting diode
LUMO	Lowest unoccupied molecular orbital
M	molarity
Me	methyl
MeCN	acetonitrile
Ms	mesyl
MS	Mass spectrometry
MW	microwave
NFSI	*N*-fluorobenzenesulfonimide
NMR	Nuclear magnetic resonance

OAc	acetoxy
OTf	triflate
ppm	parts per million
Ph	phenyl
PhMe	toluene
pin	pinacol
pK_a	negative base-10 logarithm of the acid dissociation constant
ppy	2-phenylpyridine
PTH	10-phenylphenothiazine
R_f	perfluorinated alkyl chain
rt	room temperature
SAM	*S*-adenosyl-L-methionine
SCE	saturated calomel electrode
SET	singe electron transfer
S_N2	nucleophilic substitution
S_NAr	nucleophilic aromatic substitution
$S_{RN}1$	unimolecular radical nucleophilic substitution
$t_{1/2}$	half-life of a medicinal compound in blood plasma
TAS-OCF_3	tris(dimethylamino)sulfonium trifluoromethoxide
TBAF	tetra-*n*-butylammonium fluoride
^tBu	*tert*-butyl
TDAE	tetrakis(dimethylamino)ethylene
TEMPO	2,2,6,6-tetramethylpiperidinyloxyl
TFMS	trifluoromethyl arylsulfonate

THF	tetrahydrofuran
TMP	2,2,6,6-tetramethylpiperidine
TON	turnover number

1 Brief History of Fluorine

1.1 Natural Occurrence of Fluorine-containing Species

After the big bang, primordial nucleosynthesis led to the emergence of the first elements.[1] It is suggested that the primary source of the element fluorine in the universe are three special cosmic events.[2] For example, the rotation-vibration lines of the HF molecule can be observed in asymptotic giant branch stars, where due to the intermittent nature of the fusion reactions, convection can allow fluorine to escape the inner star before it is consumed.[3]

Fluorine's position in the periodic table of elements is in the 2nd period of the 7th main group. The naturally occurring ^{19}F consists of nine protons, ten neutrons and nine electrons (electronic configuration: [He]$2s^2 2p^5$). Therefore, the valence shell of fluorine has one filled *s*-orbital and one partly filled *p*-orbital, where only one electron is missing to fill the *p*-orbital and satisfy the octet rule. Because of this fact and the resulting radially contracted valence shell, fluorine has the highest electronegativity of all elements. This is one of the main reasons for the high reactivity of the molecule F_2. Fluorine gas is so reactive that it can be very rarely found on earth. Only with uranium-containing fluoride-rich minerals is F_2 found unambiguously in nature, as fluorine gas is produced by radiolysis inside these minerals.[4] Usually, fluorine instead appears in the form of fluoride salts on land and in the oceans. However, the concentration of fluoride salts in the oceans is relatively low, as most fluoride salts display poor solubility. On land, however, fluoride salts are common, as fluorine is the 13th most abundant element in the earth's crust. Large quantities of fluoride salts can be found in the minerals Na_3AlF_6 (cryolite), CaF_2 (fluorite), and $Ca_5(PO_4)_3F$ (fluorapatite).

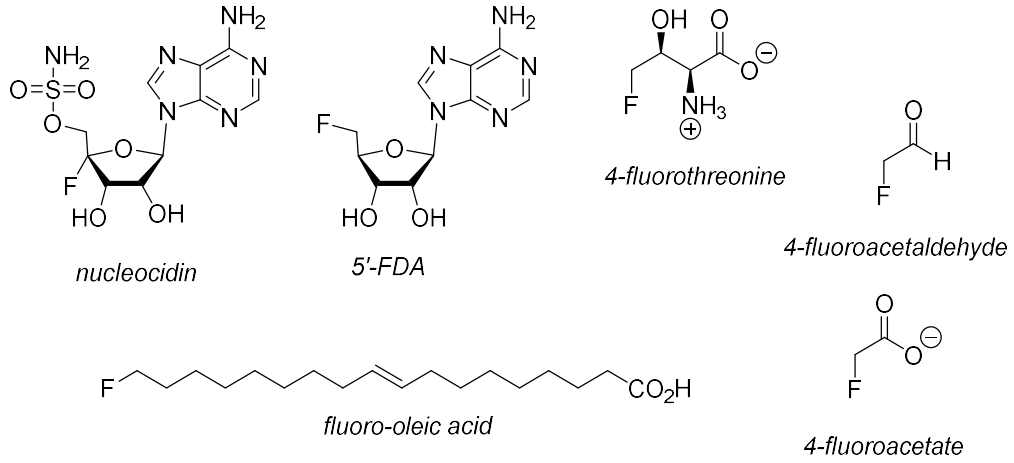


Figure 1: Naturally occurring fluorinated organic compounds.

However, in contrast to other halogens, only very few naturally occurring fluorinated organic compounds are known.[5] One example is the exceptionally toxic sodium monofluoroacetate, which

can be isolated from several Australian, Brazilian and African shrubs.[6] Sodium monofluoroacetate is the main agent responsible for the poisonous properties of these plants, which allows them to defend against predators. Another example is the fluorinated metabolite 5'-fluoro-5'-deoxyadenosine (5'-FDA), synthesized by 5'-fluoro-5'-deoxyadenosine synthase (5'-FDAS) from *S*-adenosyl-L-methionine (SAM), that can be further metabolized into the other fluorinated compounds 4-fluoroacetaldehyde (FAld), 4-fluorothreonine (4-FT), and 4-fluoroacetate (4-FAc) (Scheme 1).[7] The seeds of *Dichapetalum toxicarium* contain multiple fluorinated fatty acids, of which the toxic fluoro-oleic acid is the most common.[8]

1.2 Fluorinated products of the 20th and 21st century in medicine and agrochemistry

The first demonstrated use of fluorine by mankind was in metallurgy in the 16th century by physician Georgius Agricola.[9] He observed that using fluorspar as an additive improved the smelting of ores and slugs by lowering the required temperature and reducing viscosity. Owing to this fact, the mineral and later the element got the name fluor (latin: to flow). Finally, in 1886, the chemist Henri Moissan successfully synthesized elemental fluorine by electrolyzing a mixture of potassium fluoride and hydrogen fluoride.[10] The primary use of fluorine-containing minerals in the 21st century is still in the area of metallurgy: fluorine-containing species help to lower the melting point, reduce the viscosity of the resulting slug, and aid purification from unwanted contaminants. However, fluorine has much broader applications: as it is the most electronegative element in the periodic table, fluorine substitution can dramatically influence the physical, chemical, and biological properties of organic compounds. These features have led to numerous applications in the fields of materials, agrochemicals, and pharmaceuticals.[5, 11] Fluorinated materials such as Teflon™ or Goretex™ have found their way into households because of their water and grease repellent properties.[12] High-performance fluorine-containing refrigerants are widely used in vehicles and in industry. In 2007, 20-25 % of bioactive compounds in the pharmaceutical and agrochemical pipeline contained at least one fluorine atom, helping to improve the properties of the drug.[11a]

For the first time in 1954, it was shown that the incorporation of a fluorine atom has positive impacts on the performance of a drug compound.[13] The substitution of the 9α position of cortisol enormously improved its therapeutic index as an anti-inflammatory compound. Since then, the different impacts of substitution with fluorine or fluorinated groups on the properties of drug compounds have become better understood, and broader incorporation is in many respects limited only by synthetic accessibility.[14] Fluorine or fluorinated group substitution influences the conformation, pK_a, intrinsic potency, membrane permeability, metabolic stability, and

pharmacokinetic properties, with substitution usually taking place during lead optimization studies (Figure 2). Because of these beneficial effects, approximately 5-15 % of the drugs launched worldwide between 1957 and 2007 contained at least one fluorine atom. This percentage is expected to rise even more, as synthetic strategies to incorporate fluorine or a fluorinated group continue to improve.[15]

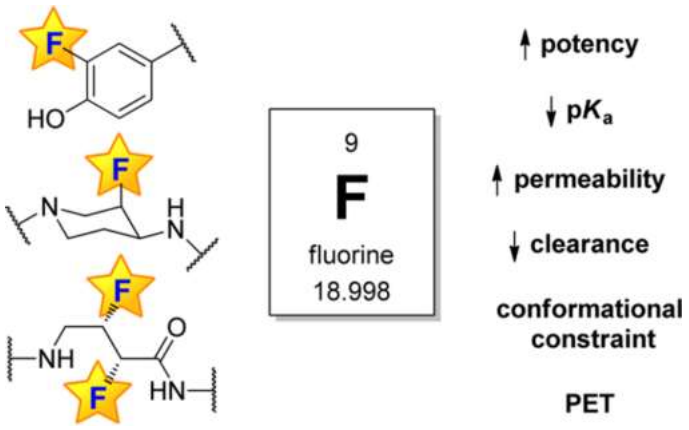


Figure 2: Impacts of fluorine substitution on the properties of drug compounds.[14] Reprinted with permission from Ref. 14. Copyright © 2015 American Chemical Society.

Another exciting example of advantageous fluorine incorporation is the drug Trelagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor used to treat type 2 diabetes (Figure 3). Here literally, one atom makes the difference. While Trelagliptin can be safely administered weekly, its non-fluorinated predecessor Alogliptin must be administered daily.[16] *In vitro* investigations revealed some of the reasons for this sustained efficacy.[17] Trelagliptin, with an IC_{50} of 1.3 nmol/L, is 4-fold more potent than Alogliptin against DDP-4. Thus, it could exhibit a similar DDP-4 inhibition at lower plasma concentrations. Furthermore, the substitution with fluorine leads to a slower dissociation rate of the inhibitor from the enzyme. Both drugs have a reversible inhibition mechanism.

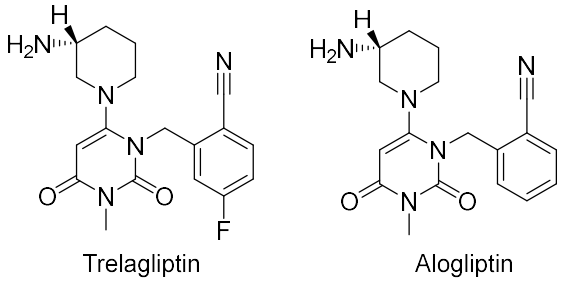
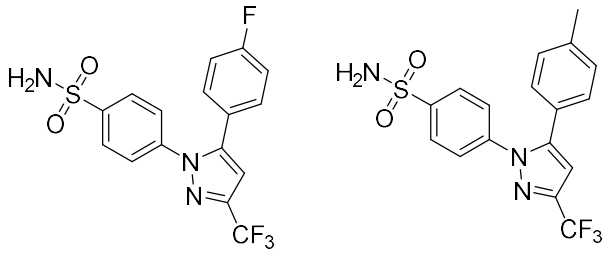


Figure 3: Trelagliptin and Alogliptin are used to treat diabetes type 2, while Alogliptin must be administered daily and Trelagliptin only weekly.

The dissociation rate is lowered by 8-fold for Trelagliptin ($t_{1/2}$~30 min) compared to Alogliptin ($t_{1/2}$~3.7 min). However, the authors clarify that these improvements alone cannot explain why

Trelagliptin has such a sustained efficacy, and the reasons are still not fully understood. It is important to note that the predecessor Alogliptin is already quite stable against metabolism. Only 10 % is metabolized, while 60-80% is excreted unchanged in the urine.[18] The improved metabolic stability imparted by fluorine atom substitution is apparent in the case of the predecessor of the drug Celecoxib (Figure 4). This compound is a selective cyclooxygenase-2 (COX-2) inhibitor that is used to treat pain and inflammation in osteoarthritis, acute pain in adults, rheumatoid arthritis, ankylosing spondylitis, painful menstruation, and juvenile rheumatoid arthritis.[15, 19]

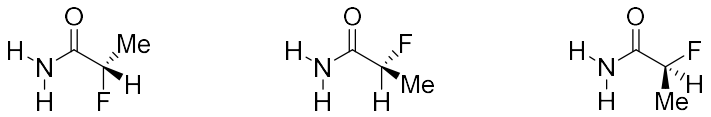


Celecoxib predecessor Celecoxib

Figure 4: Celecoxib and its fluorinated predecessor. Substitution of the fluorine atom by a methyl group lowered the unacceptable long plasma half-life in rats from 221 h to 3.5 h. [15, 19]

The predecessor of Celecoxib had many desired properties, however, it exhibited an unacceptably long plasma half-life in rats of 221 h. Therefore, attempts were made to increase the rate of metabolism, and it turned out that replacement of 4-fluorophenyl with 4-methylphenyl led to a more desirable rat plasma half-life of 3.5 h and a human plasma half-life of 11.2 h. The trifluoromethyl group itself was not replaced, as it was required for high potency and selectivity.

Fluorine substitution can also influence the conformation of a molecule. Steric effects play only a marginal role in this respect due to the small size of fluorine (van der Waals radius = 1.47 Å cf. 1.20 Å for hydrogen). Instead, electronic effects play a significant role. The high electronegativity of fluorine results in a highly polarized C-F bond which presents a strong dipole moment (μ C-F = 1.41 D) and a low lying C-F σ^* orbital available for hyperconjugative overlap.[14] When a C-F bond is adjacent to an amide functionality, the *trans* conformation has been calculated to be strongly favored over the *cis* and *gauche* conformation (Figure 5).[20] The reason for this is the stabilization of the *trans* conformer by minimization of an unfavorable dipole-dipole interaction between the C-F and C=O bonds and a favorable electrostatic interaction between the electronegative fluorine atom and the electropositive amide N-H proton.[14]



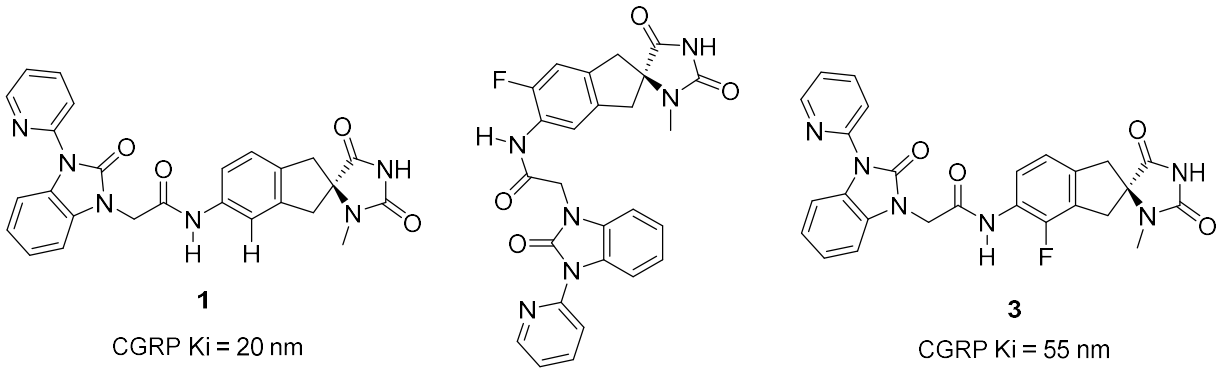
trans
0.0 kcal/mol

gauche
6 kcal/mol

cis
8 kcal/mol

Figure 5: Calculated relative energy levels of conformational isomers of α-fluoroamides.[14]

Similarly, substitution with a fluorine atom was used to investigate the optimal binding topology of antagonist **1** towards the calcitonin gene-related peptide (CGRP) receptor (Figure 6).[21] It is believed that this receptor bears potential as a therapeutic for the prevention of migraine attacks.



1
CGRP Ki = 20 nm

2
CGRP Ki = 720 nm

3
CGRP Ki = 55 nm

Figure 6: Several antagonists for the CGRP receptor, which is believed to be a potential therapeutic for migraine. Substitution with a fluorine atom toadied the understanding of the antagonist's preferred binding topology for the CGRP receptor.[21]

In this case, fluorine was used to favor one conformation of an anilide by introduction into the *ortho* position to the anilide *N*-H. The result is that complementary topologies are underpinned by a combination of repulsive steric and electrostatic interactions between the C=O and fluorine atom and an attractive electrostatic association between the *N*-H and fluorine atom. Finally, the complementary topologies are preferred by 3 kcal/mol in each case. Interestingly, the extended conformation, which is represented by structure **3**, was favored by the CGRP receptor, as the affinity of structure **3** to the CGRP receptor shows a 10-fold difference compared to structure **2**. These results prompted the scientists to synthesize antagonists with central constraints. Therefore, the anilide was exchanged for a quinoline fragment, which further increased the potency.

Table 1: The pK_a values for aliphatic, linear amines with an increasing amount of fluorine substitution.[22]

amine	**pK_a**
$CH_3CH_2NH_2$	10.7
$CH_2FCH_2NH_2$	9.0
$CHF_2CH_2NH_2$	7.3
$CF_3CH_2NH_2$	5.7

Furthermore, the strong electronegativity of fluorine will also influence other properties of a molecule, such as the basicity. In simple linear systems, the influence of every fluorine substitution is additive (Table 1). Each fluorine substitution reduces the pK_a of ethylamine by 1.6 – 1.7 units, while $CF_3CH_2NH_2$ is so weakly basic that this moiety has been exploited as an amide isostere.[22]

2 Synthetic methods to access C-F Bonds

However, all these beneficial properties are only accessible if a synthetic method is available that allows the selective incorporation of a fluorine atom. Therefore, a broad scope of synthetic methods are necessary, which are ideally safe, efficient, and high yielding. It is important to note that bulk chemicals such as F_2 are often already a suitable fluorine source, but those chemicals lack the safety and selectivity required for synthetic methods used in standard research labs. For this reason, dozens of fluorinating reagents have been developed over the last decades that offer improved reactivity, selectivity, and safety (Figure 7).

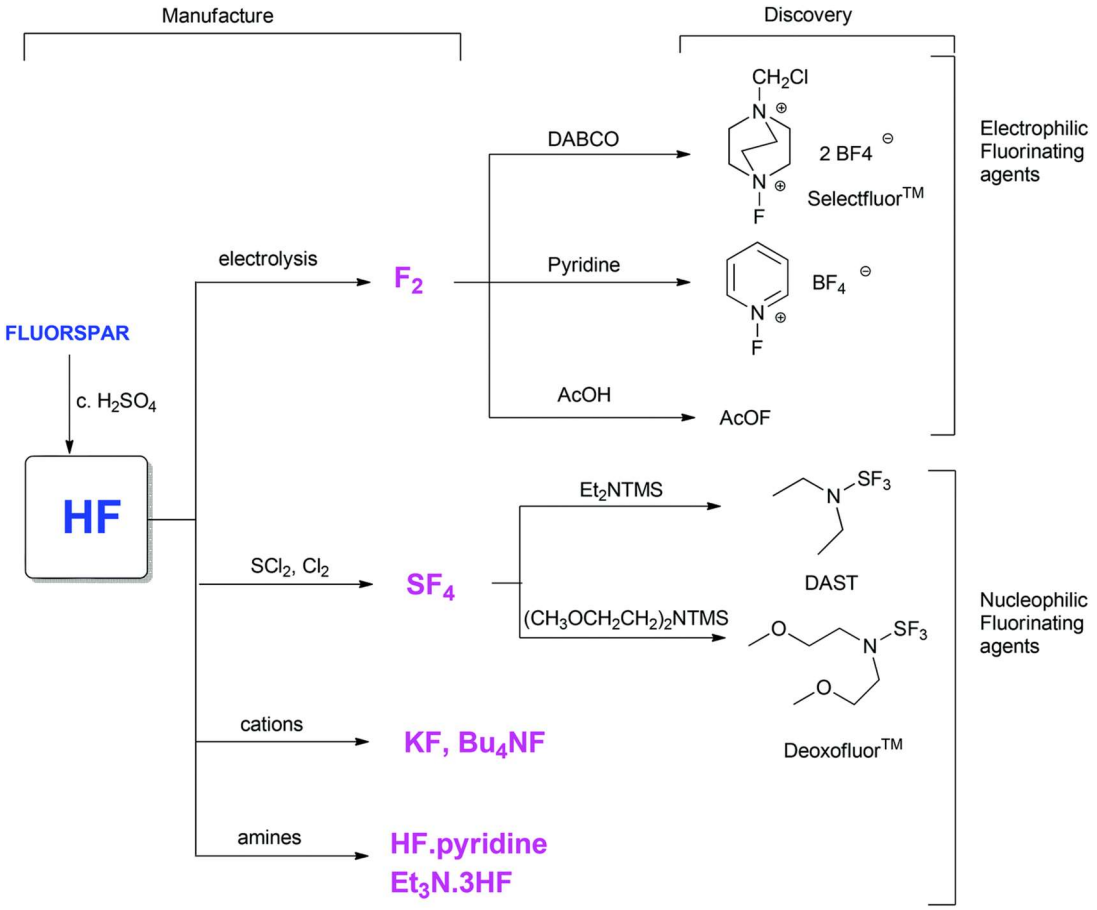
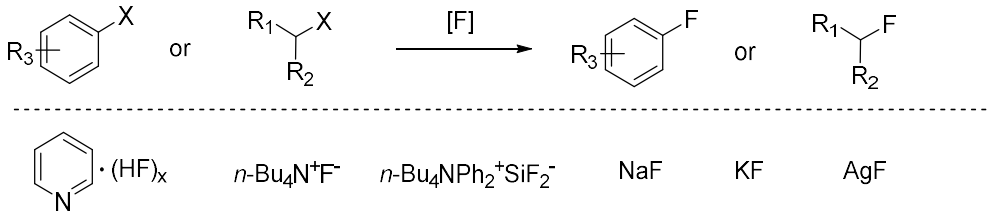


Figure 7: Basic chemicals such as HF, F_2, or KF are often suitable as reagents for fluorination but lack the needed safety, selectivity, and reactivity that reagents such as Selectfluor™ or diethylaminosulfur trifluoride (DAST) offer.[23] Reproduced from Ref. 23 with permission from the Royal Society of Chemistry.

Such fluorinating reagents furthermore enable nucleophilic, electrophilic, and radical methods to incorporate fluorine atoms into a chemical compound. Nucleophilic methods substitute leaving groups on alkyl- or aryl residues and often employ reagents such as KF, Bu_4NF, HF-Pyridine, or Et_3N-$(HF)_3$ (Scheme 1). A variant of those reactions is the deoxyfluorination reaction, which can be

conducted with various reagents (Figure 8). With aliphatic alcohols as substrates, the reagent SF_4 reacts first with HF, which is either added separately or formed by hydrolysis of SF_4, to form SF_3^+ and HF_2^-.[24]



Scheme 1: General nucleophilic fluorination reaction with a selection of commonly used reagents.

SF_3^+ serves as an electrophile for the nucleophilic alcohol, and the subsequently formed intermediate provides the product after nucleophilic substitution by a fluoride anion. In the case of ketones as substrates, first, a reaction with SF_3^+ occurs followed by elimination of SOF_2 to form a fluorinated cationic intermediate. A bifluoride anion attacks this intermediate to give the desired *gem*-difluoro product.[25] Notably, a mixture of HF and SF_4 helps to suppress the formation of often undesired *α,α'*-difluorinated ether side-products.

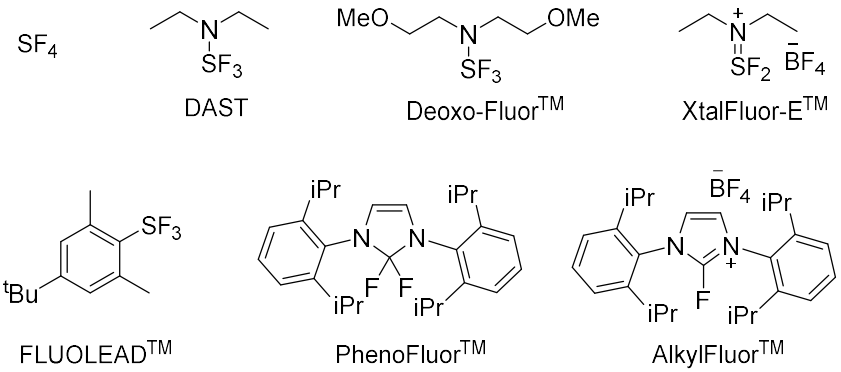
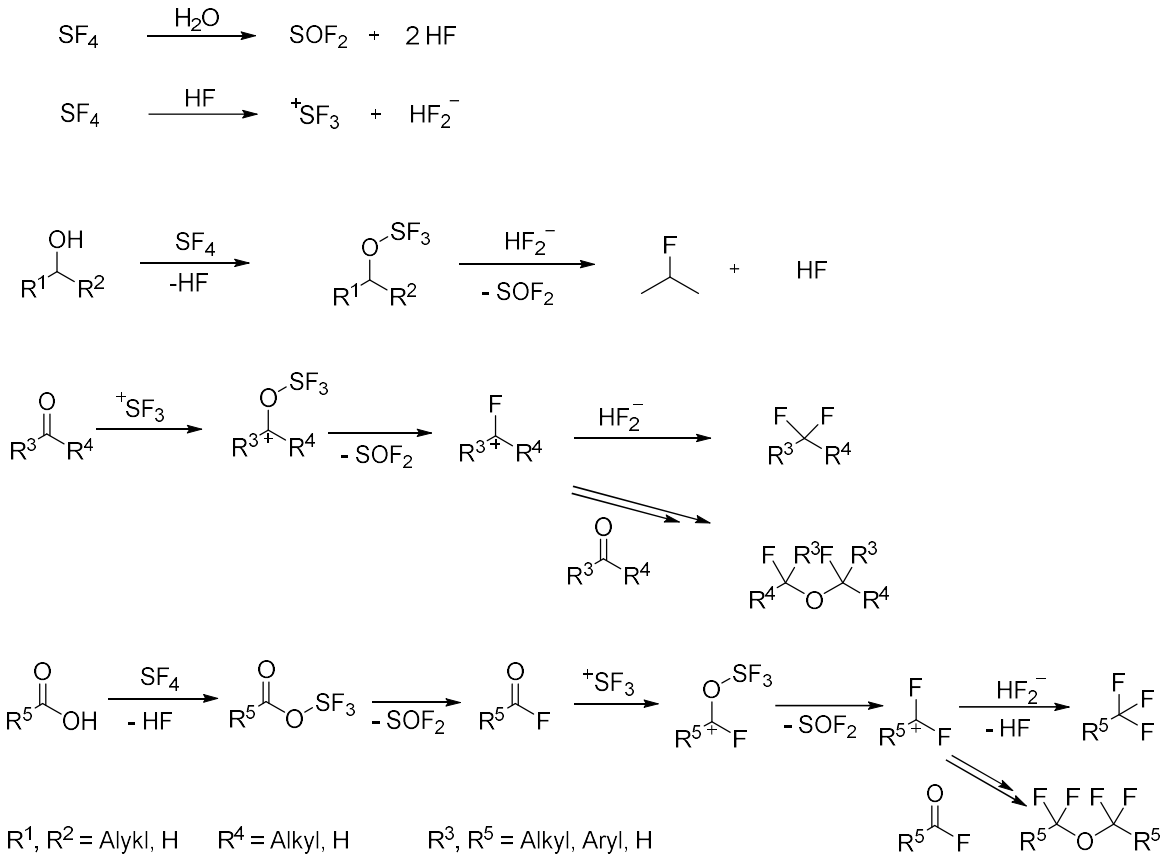


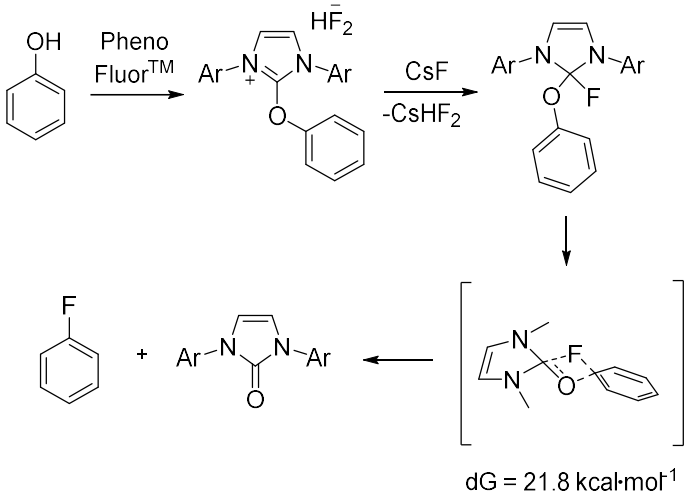
Figure 8: A selection of commonly used deoxyfluorination reagents.

With carboxylic acids as substrates, the reaction proceeds similarly to alcohols in the first step. The intermediate, which is formed upon nucleophilic attack of the carboxylic acid at the sulfur atom of the reagent in the first step, then undergoes deoxyfluorination in the second step, yielding an acid fluoride. In the case of the very reactive deoxyfluorination reagent SF_4, the acid fluoride now attacks the *in situ* formed SF_3^+ cation to generate an intermediate that subsequently undergoes deoxyfluorination.[26] With FLUOLEAD™ combined with HF-Pyridine, a similar reaction takes place.[27] The formed carbocation can now be attacked by either the *in situ* formed HF_2^- or from another acid fluoride molecule. In the former case, the desired product is formed, while in the latter case, an *α,α*-fluorinated ether by-product is obtained.



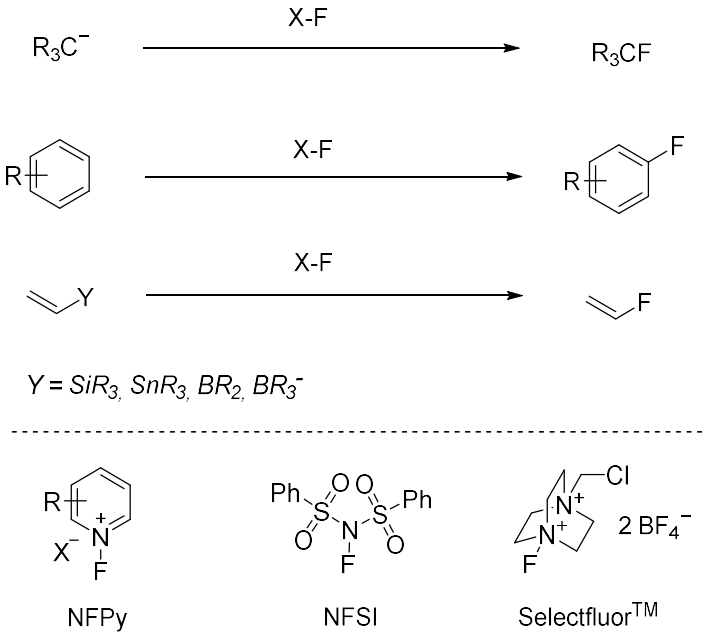
Scheme 2: General deoxyfluorination reactions of alcohols, ketones, aldehydes, or carboxylic acids using SF_4 as a reagent.

If aminosulfurane reagents such as DAST, Deoxofluor™, or Xtal-Fluor™ are used in these reactions, possible by-products are fluorinated olefins resulting from elimination. However, with those reagents, *α,α*-fluorinated ethers are not generally formed as by-products.[24] In the case of the reagent Phenofluor™, the scope for deoxyfluorination of alcohols is even extended to phenol derivatives. Mechanistic studies indicate that the reaction proceeds via a concerted nucleophilic aromatic substitution with a single four-membered transition state (Scheme 3).[28] Therefore, conventional problems of S_NAr chemistry with Meisenheimer complexes as intermediates are bypassed, as these require a two-barrier process that is higher in energy. Notably, each reagent exhibits a different scope of substrates. For example, in the case of FLUOLEAD™, other starting product classes such as thioketones or dithiocarbonates can be successfully employed when reacted with catalytic amounts of SbF_3, giving difluoromethylated or trifluoromethoxylated products.[29]



Scheme 3: Proposed mechanism for the deoxyfluorination of phenols with PhenoFluor™.[28a]

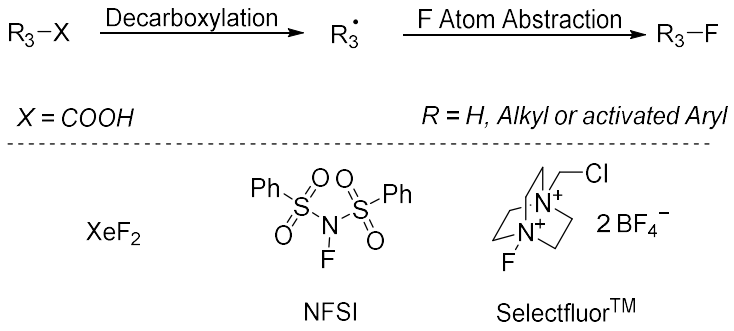
For electrophilic fluorination, the reagents are designed to deliver a fluorine atom to a nucleophilic substrate in the reaction (Scheme 4). Suitable nucleophiles are carbanions such as Grignard reagents or electron-rich aryls, alkenes, and alkynes, or substrates that bear labile and nucleophilic bonds such as silanes, organic stannanes, and boranes.[30]



Scheme 4: Electrophilic fluorination of carbanions, electron-rich arenes, alkenes, and alkynes or silanes, organic stannanes, and boranes together with a selection of suitable reagents.

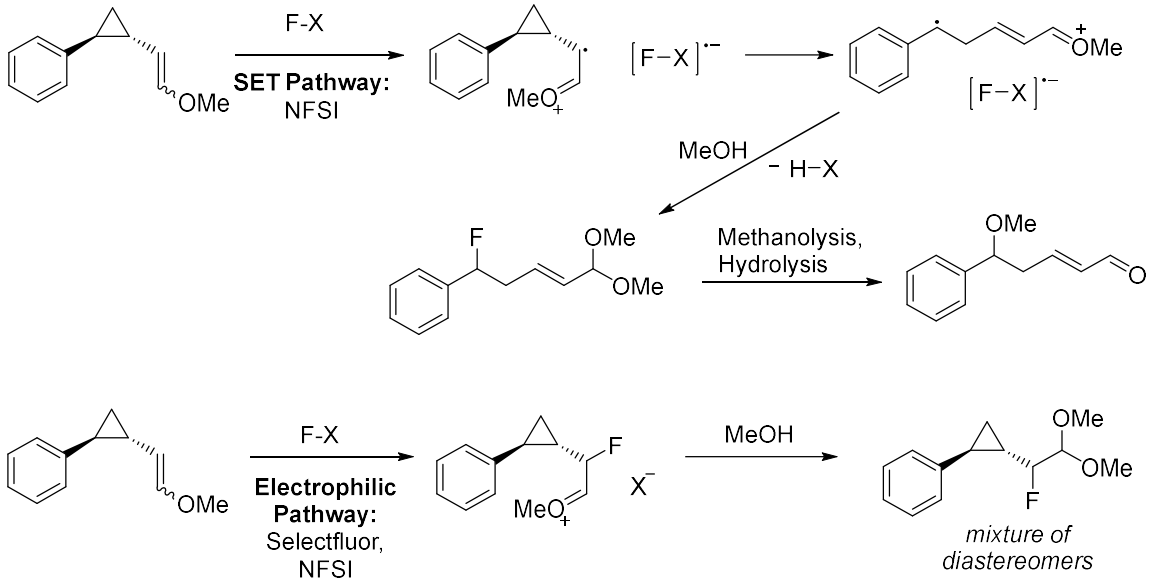
In the case of radical fluorination, it is essential to have *in situ* generated carbon-based radicals capable of reacting with a fluorine source. Reagents designed for electrophilic fluorination are most

suitable here.[30] The classical reagents such as F_2 or CF_3OF are often too reactive, and selective reactions using these fluorine atom sources are very scarce. N-F Reagents such as Selectfluor™ or *N*-fluorobenzenesulfonimide (NFSI), and in a few cases XeF_2, are most commonly used as a fluorine source (Scheme 5). XeF_2 is a special case, as it readily reacts with carboxylic acids to form a xenon ester, which collapses to yield the alkyl radical amenable to subsequent F-atom-abstraction from another XeF_2 molecule.[31] Other common methods to generate carbon-centred radicals *in situ* via decarboxylation employ metal salts in catalytic amounts or photocatalysts.[32]



Scheme 5: General radical fluorination with a selection of common fluorinating reagents.

However, while there are numerous decarboxylation methods to obtain alkyl radicals, only a few examples are reported for reliably generating aryl radicals. The *ortho*-substituents on the arene can help lower the activation energy barrier associated with the critical decarboxylation event to yield aryl radicals.[33]



Scheme 6: Reaction of an enol ether bearing a cyclopropyl group with NFSI or Selectfluor™. NFSI affords both products, while Selectfluor™ only gives the product from the electrophilic pathway.

Using Selectfluor™ as the reagent, this strategy was successfully used for decarboxylative fluorination of aryl carboxylic acids.[34] However, radical fluorination mechanisms may also operate during formal electrophilic fluorination. A few examples in the literature provide mechanistic evidence for the involvement of radical intermediates. For instance, cyclopropyl-bearing enol ethers yielded olefinic ring-opening products after reaction with NFSI or XeF_2 (Scheme 6).[35] However, when Selectfluor™ was used as a fluorinating reagent, different products were obtained. In this case, classical electrophilic fluorination took place, leaving the cyclopropyl substituents untouched. These results show that it cannot be generalized if such reactions proceed via a single-electron or two-electron process.

3 C-F Activation

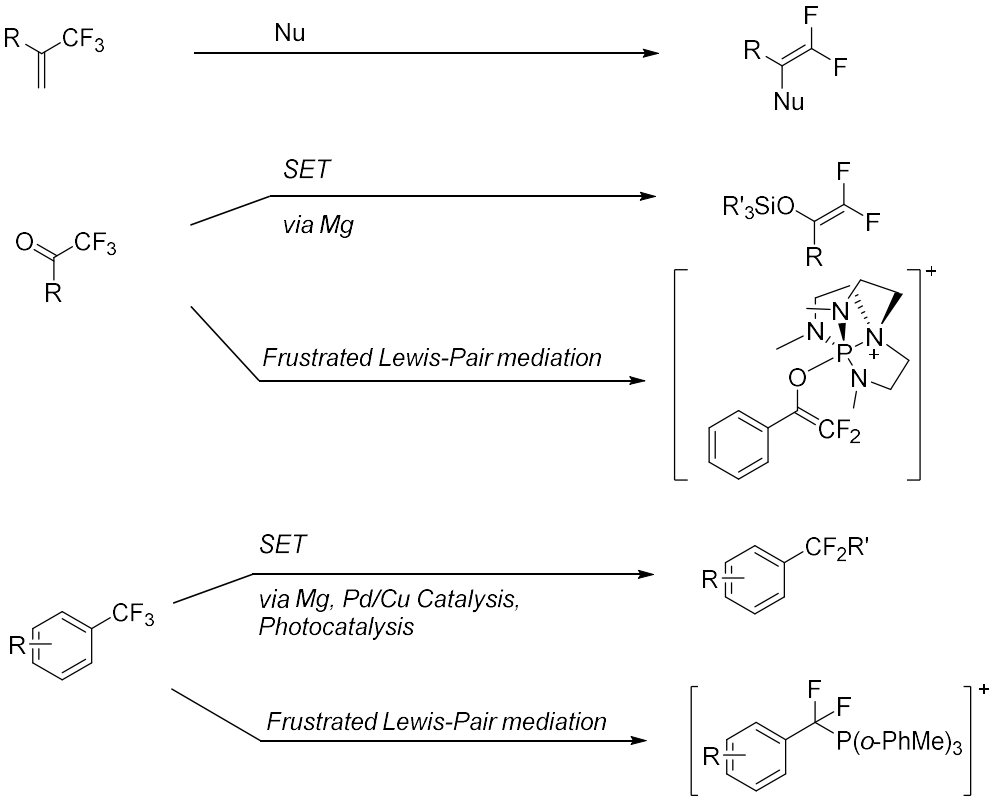
There are other partly- or perfluorinated groups that influence several physical and chemical properties if incorporated into a molecule. One of these is the CF_3 group, and its partially fluorinated versions CF_2H and CFH_2. Selective functionalization of the CF_3 group is one possibility to gain access to the latter motifs. However, such methods confront several challenges that must be overcome. First, C-F activation is an inherently challenging reaction due to the high C-F bond strength compared to the C-Cl, C-Br or C-I bond. For example, the C-X dissociation energy for halomethanes decreases in the order H_3C-F > H_3C-Cl > H_3C-Br > H_3C-I (Table 2).[36] Second, it is challenging to achieve selectivity because usually, all three C-F bonds are functionalized in such reactions. This behavior can be explained by the decreasing strength of a C-F bond when fewer fluorine atoms are bonded to the same carbon.[37]

Table 2: The C-X (X = F, Cl, Br, I) bond lengths and their dissociation energies in different halomethanes.[36-37]

Entry	Molecule	C-F Bond length [Å]	Dissociation energy [kcal/mol]
1[37]	H_3C-F	1.39	110
2[37]	H_2FC-F	1.36	120
3[37]	HF_2C-F	1.33	128
4[36]	H_3C-Cl	-	83.6 ± 0.1
5[36]	H_3C-Br	-	70.2 ± 0.3
6[36]	H_3C-I	-	57.1 ± 0.3

Especially CF_3 groups adjacent to π-systems such as arenes, alkenes, and carbonyls are of interest in this chapter (Scheme 7). Three approaches can be employed to achieve C-F activation in these systems.[37] First, nucleophilic attack on π-systems such as alkenes will generate a β-fluorinated anion which subsequently undergoes elimination to yield a difluoromethyl group – the S_N2' approach. Second, SET to a C-F bond or an adjacent π-system can lead to mesolysis, whereby fluoride is the leaving group. Third, frustrated Lewis pairs (FLPs) or Lewis acids can mediate C-F activation.

1-(Trifluoromethyl)alkenes may react with nucleophiles in an S_N2' manner to yield *gem*-difluoro alkenes.[37] In this process, C-F bond cleavage is achieved via elimination of fluoride from a β-fluoro anion intermediate. An intramolecular version of this reaction provides a wide range of difluoromethyl-bearing N, O, and S heterocycles. Several α,α,α-trifluoromethyl ketones are reported to react with Mg^0 via an SET mechanism, while the essential difluoromethylated anionic intermediate is usually trapped as a silyl enol ether with trimethylsilyl chloride to avoid further defluorination of the product. This stable intermediate can be functionalized by many different mechanisms, including addition-elimination, S_N2, and copper- or photocatalysis.[37-38]



Scheme 7: Selected C-F functionalization reactions for trifluoromethylated motifs.

Selective C-F Activation of trifluoroacetophenones is also possible by using frustrated Lewis pairs, although the obtained salts have not been widely exploited so far for further synthetic usage.[39] However, frustrated Lewis pairs were also successfully applied for C-F activation of benzotrifluorides, and in this case, the generated salts could be successfully used for further functionalization reactions with alkenes, nucleophiles, and aldehydes to give difluoromethylated products.[40] Derivatives of benzotrifluorides were also successfully functionalized by a SET mechanism, using either low-valent metals such as Mg^0, Pd/Cu-Catalysis, or photocatalysis. The selectivity of these reactions can be controlled by selecting an appropriate single electron donor.

Measurement of the reduction peak potentials from cyclic voltammetry experiments demonstrated that Ar-CF_3 are better electron acceptors than Ar-CF_2H, and that SET is therefore more favored for Ar-CF_3 (Figure 9). Careful selection of the single electron donor accordingly allows for selective mono-defluorination.[41] However, other literature reports indicate that not only the substitution pattern of the substrate itself is important for the reduction peak potential of the fluorinated substrate, but also a number of other conditions. In a case study on *α*-acetoxy acetophenone, the reduction peak potential could be lowered by modifying the solvent mixture and by employing lanthanide Lewis acids (Figure 10).[42]

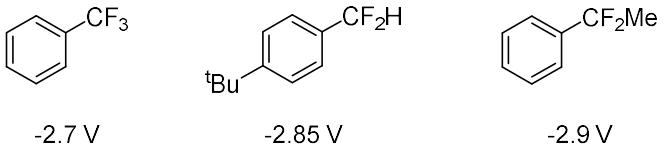


Figure 9: Reduction peak potentials of different tri- and difluoromethylated substrates, measured vs. Ag/Ag^+ in DMF containing 0.1 M Bu_4NBF_4. These values show that a SET is more straightforward with trifluorinated groups while being more difficult with difluoromethylated groups, which helps to achieve selective C-F functionalizations.

Another example for LUMO lowering is the radical amination of arenes with $[MsO\text{-}NH_3]^+[OTf]^-$ in hexafluoroisopropanol (HFIP); here DFT calculations showed that hydrogen bonding interactions with HFIP lower the LUMO of $[MsO\text{-}NH_3]^+[OTf]^-$ by 7.7 kcal mol^{-1}, thereby making single electron reduction easier.[43]

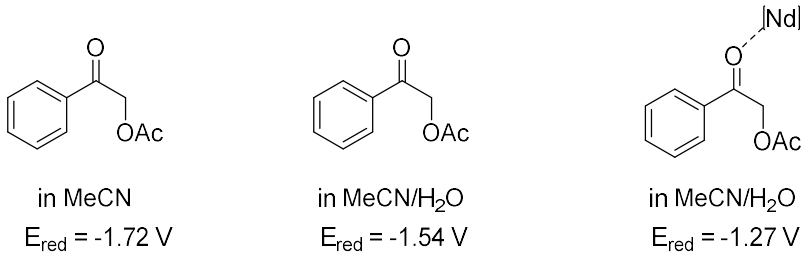
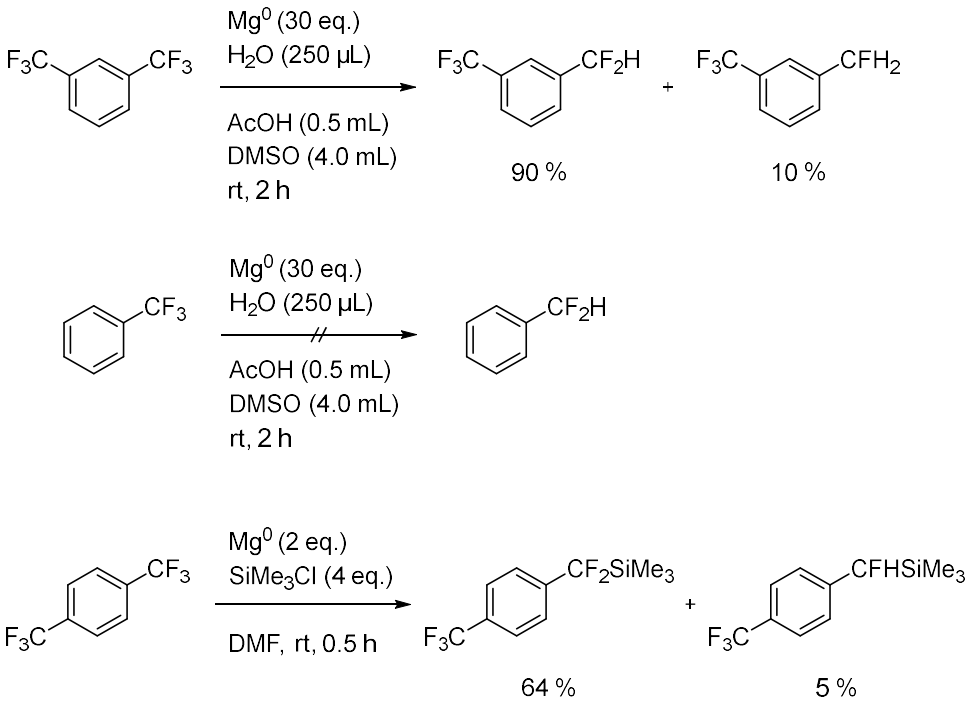


Figure 10: Reduction peak potential of α-acetoxy acetophenone under different conditions. Other solvent mixtures and lanthanide Lewis acids lowered the reduction peak potential. A carbon electrode was used for the measurements with platinum wire as the counter electrode, and an aq. 0.1 M solution of tetrabutylammonium tetrafluoroborate was applied as a supporting electrolyte.

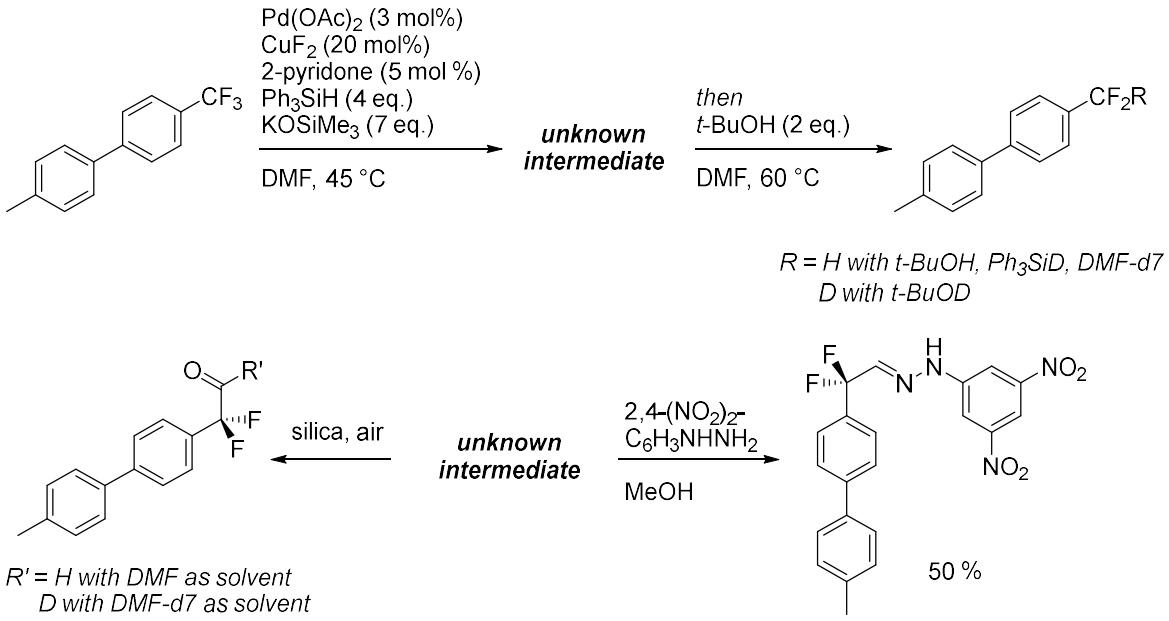
The functionalization or reduction of 1,3- or 1,4-bis(trifluoromethyl)benzene is reported employing the low-valent metal Mg^0 as a reductant (Scheme 8).[44] Under these conditions, the reaction occurs rather selectively in both cases, giving the *mono*-functionalized arene as the major product and the difunctionalized arene as a minor product. Depending on the conditions, either reduction to a C-H bond or establishment of a C-Si bond is achieved. However, only highly electron-deficient

trifluoromethylated arenes are suitable as substrates – Mg^0 cannot activate benzotrifluoride itself. This observation can be explained by the high barrier for single electron reduction in the case of simple benzotrifluorides. No attempts were made to lower this barrier by non-covalent interactions.



Scheme 8: Functionalization of 1,3- or 1,4-bis(trifluoromethyl)benzenes by employing Mg^0 as an SET reagent to activate the substrates for fluoride elimination.

Another example for selective C-F reduction used catalytic amounts of $Pd(OAc)_2$ and CuF_2, while $KOSiMe_3$ was employed as the base and DMF as the solvent.[41b] The authors suggest that SET is a critical step in their mechanism, but the exact pathway is unclear.



Scheme 9: Palladium and copper-catalyzed selective reduction of trifluoromethylated biphenyls.

Both catalysts, the base, and the use of DMF as solvent are essential for the reaction to proceed. Furthermore, it is suggested that a DMF-derived unknown intermediate is formed during the reaction, which helps in achieving selectivity (Scheme 9). The scope covers only rather electron-rich trifluoromethylated biphenyls as substrates, and reducible groups such as aryl halides, nitroarenes, or nitriles are not tolerated under these conditions. Compared to the base $KOSiMe_3$, also NaO^tBu can be used but is less selective, while KO^tBu affords the completely defluorinated product.

3.1 Photocatalysis for C-F Activation

Another strategy to functionalize trifluoromethylated arenes is photocatalysis. The photocatalyst is excited by UVA or preferably visible light, and depending on its chemical structure, becomes either a strong oxidant or reductant, or both (Figure 11).[45] This excited photocatalyst is quenched either in an oxidative or reductive pathway. In the oxidative quenching process, an electron is transferred to the desired substrate directly while, in a reductive quenching process, an external electron source reduces the excited photocatalyst, which then transfers an electron to the substrate in a subsequent step. These quenching events can be measured by using fluorescence spectroscopy, which allows for the facile screening and identification of suitable substrates for photocatalytic reactions.[46]

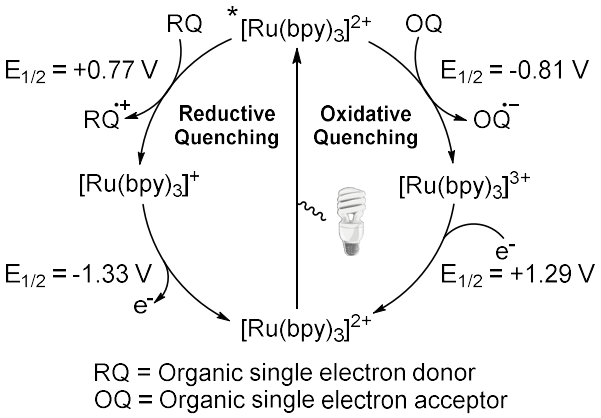
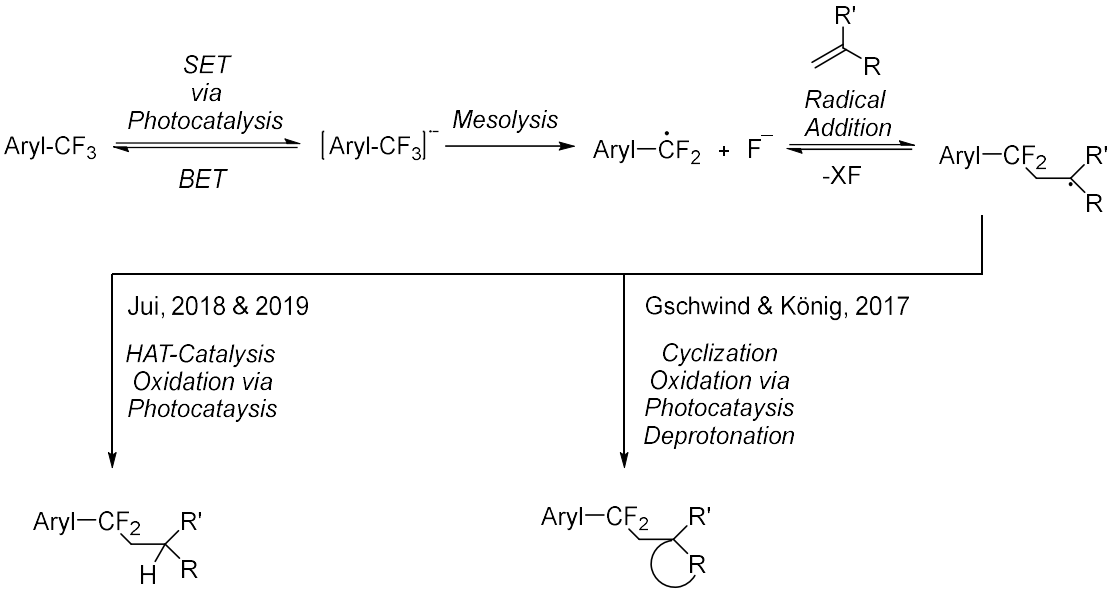


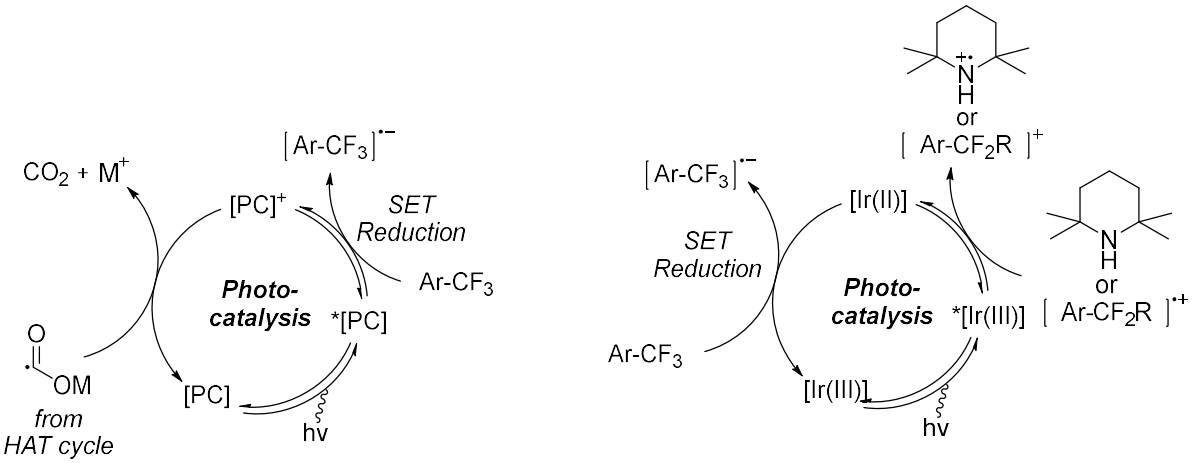
Figure 11: Reductive and oxidative quenching of a photocatalyst, in this case $[Ru(bpy)_3][(PF_6)_2]$.

In combination with a trifluoromethylated arene as the single electron transfer acceptor, the general mechanism starts with the reduction of the substrate by either the excited photocatalyst or the reduced photocatalyst, depending on the conditions (Scheme 10). This step represents the first challenge because the product radical anion can easily transfer an electron back to the photocatalyst (back electron transfer, BET). There are several possibilities to overcome this challenge: solvents or additives that stabilize the charge on the radical anion can hinder BET, as well as additives that help to abstract and stabilize the fluoride anion that emerges from the mesolysis of the radical anion. This mesolysis also yields the desired aryl-CF_2-radical. If π-systems such as alkenes are present in the reaction mixture, a radical addition reaction is likely to occur, which results in the formation of the product radical.[47] The next challenge is to obtain the final product from the product radical.



Scheme 10: Two published strategies for the photocatalytic functionalization of trifluoromethylated arenes.

Two possible strategies are reported in the literature (Scheme 10). An approach from the groups of Gschwind & König used acrylamide substrates that readily undergo a cyclization upon addition of the $ArCF_2$· radical to the alkene. The resulting radical is now more easy to oxidize and deprotonate, as these steps constitute a favorable rearomatization process.[48] A strategy for the alkylation of trifluoromethylated arenes with a broad scope was developed by the group of Jui and uses H atom transfer (HAT) catalysis as a tool to transform the product radical into the final hydrofluoroalkylated product (Scheme 11).[47] A difference can be observed when comparing both methods regarding the initial activation step. In Jui's method, an excited organocatalyst reduces the substrate (oxidative quenching) to give the radical anion and the oxidized photocatalyst. BET is expected to be a major deleterious process here, as both species formed after SET are ionic species and electron transfer is highly exergonic.[47] However, the polar solvent DMSO may help to stabilize the ionic species formed in this step, hampering BET. Potentially the polar solvent also facilitated lowering of the LUMO energy of the substrate, therefore favoring the initial electron transfer step. Interestingly, temperature also plays a significant role. By raising the reaction temperature from 23 °C to 100 °C, the scope was extended from electron-deficient, and therefore easier to reduce, arenes to electron-rich arenes. In Gschwind & König's method, the excited *fac*-$[Ir^{III}(ppy)_3]$* is first reduced by the amine TMP, which can be described as reductive quenching of the excited photocatalyst. The reduced photocatalyst now has an increased reducing power ($[Ir^{III}]/ [Ir^{II}]$), E_{red} = − 2.19 V vs. SCE), and yields the neutral *fac*-$[Ir^{III}(ppy)_3]$ catalyst after reduction of the substrate to the radical anion. BET is less likely to occur in this case as single electron transfer to the ground state $[Ir^{III}]$ species is energetically disfavored.



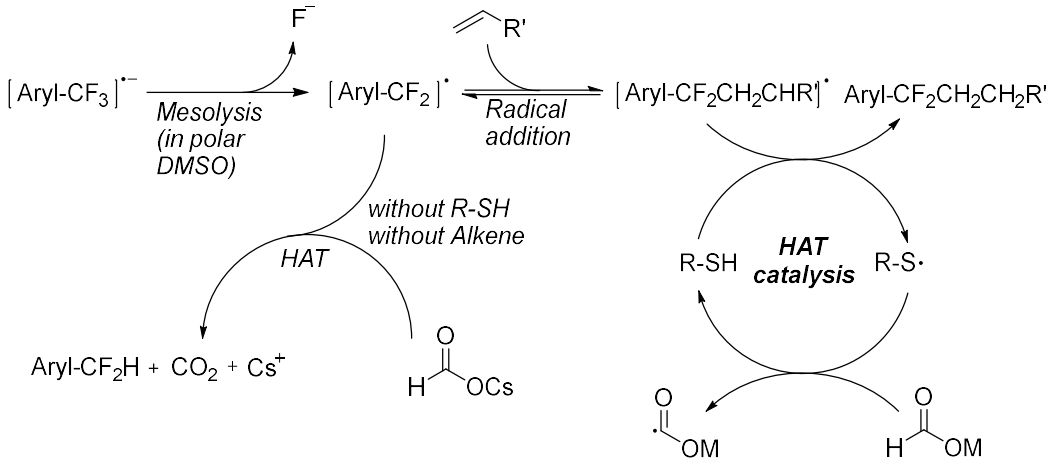
Jui 2018:
PC = PTH, in DMSO/H_2O (95:5) at 23 °C
Ar = electron deficient with -CF_3, -$C(O)NR_2$, $S(O)_2NH_2$, -$P(O)(OEt)_2$

Jui 2019:
PC = Miyake Phenoxazine, in DMSO at 100 °C
Ar = electron deficient and electron rich with -H, -Alkyl, -OR, -NHC(O)Me, NMeC(O)Me, also electron rich and deficient heterocycles like pyridine

Gschwind, König 2017:
Ir(III) = *fac*-[Ir(ppy)$_3$] in DCE at 20 °C
Ar = electron deficient with -CN, $S(O)_2N(R)_2$, -C(O)OEt, also electron deficient heterocycles like Pyridine

Scheme 11: Photocatalysis employed in different strategies to activate Ar-CF_3 via SET reduction.

Notably, the used solvent 1,2-DCE is only weakly polar. In Jui's method, the radical anion subsequently undergoes mesolysis to yield a difluorinated organic radical (Scheme 12). The polar solvent DMSO likely helps this step by stabilizing the fluoride anion. If alkenes are present in the reaction mixture, radical addition can occur leading to the product radical. Thanks to HAT catalysis, this product radical can now be easily transformed into the desired product, as the S-H bond of the HAT catalyst is weak and easy to cleave homolytically. Without a HAT catalyst, the desired product is only acquired in traces at 23 °C and in low yields at 100 °C. The HAT reaction directly between the product radical and formate seems to be more difficult. However, if no formate is present at all, product formation does not even take place in traces – even though 10 mol % of PhSH is present in the reaction mixture. The authors suggest that formate serves as a stoichiometric reductant, recovering the HAT catalyst and the photocatalyst, while the final formation of CO_2 propels the whole reaction. Another variant of this method is suitable to acquire hydrodefluorination products of Ar-CF_3 selectively. If there are no alkenes for radical addition present, the defluorinated organic radical will instead react with formate in a HAT reaction to give the hydrodefluorination product, CO_2, and formally CsF. Furthermore, no HAT catalyst is required for this reaction.

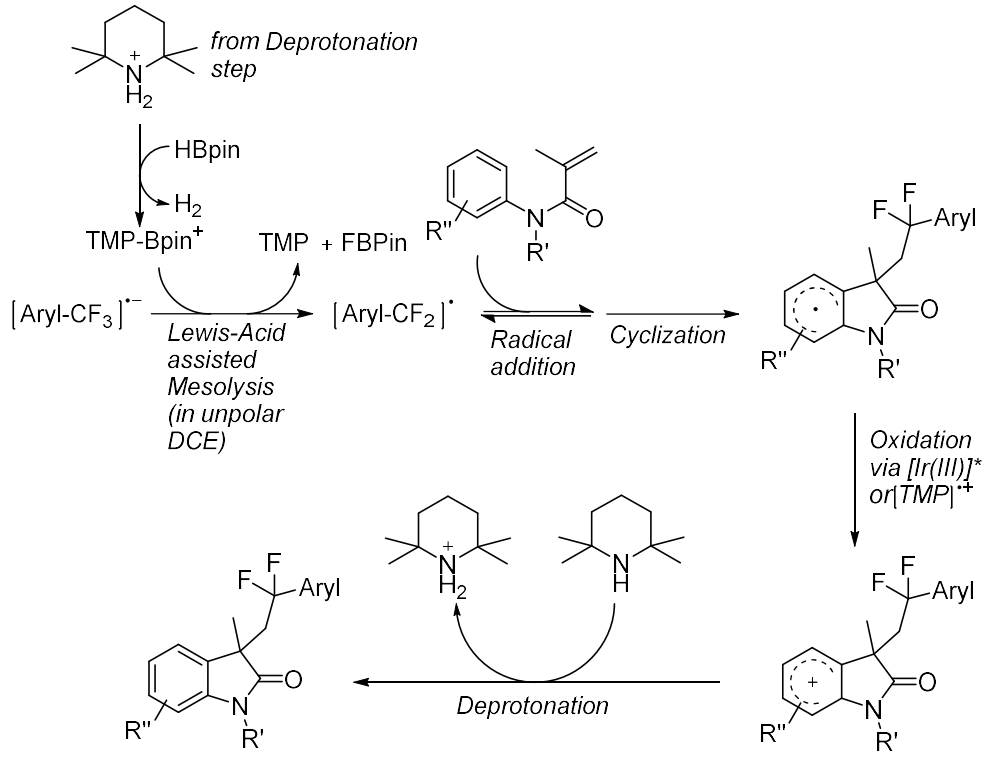


Jui 2018:
conditions = PTH (10 mol%), CySH (10 mol%), alkene (3 eq.), sodium formate (3 eq.), in DMSO/H_2O (95:5) at 23 °C, blue LED, 24 h
R' = alkyl derivatives with -OC(O)Me, -OR, -OH, -Cl, -$SiMe_3$, -NR_2, - NRC(O)R, -$C(O)NR_2$

Jui 2019:
conditions = Miyake phenoxazine (2 mol%), PhSH (10 mol%), alkene (5 eq.), potassium formate (3 eq.), in DMSO at 100 °C, blue LED, 24 h
R' = alkyl derivatives with -OC(O)Me, -OR, -OH, -$SiMe_3$, -NR_2, - NRC(O)R, -$C(O)NR_2$

Scheme 12: Mechanistic steps from the radical anion to the final product in Jui's mechanism are shown. Depending on the chosen conditions, either defluoroalkylation products or hydrodefluorination products can be obtained.

In Gschwind & Königs methods, the product radical anion undergoes Lewis acid-assisted mesolysis, meaning that the *in situ* generated Lewis acid $[TMP\text{-}Bpin]^+$ aids abstraction and stabilization of the released fluoride anion (Scheme 13).[48] The authors suggest that the Lewis acid can be seen as a fluoride scavenger, which subsequently accelerates the generation of the substrate radical so that this step can outcompete BET or other undesired pathways. The substrate radical can now react with the alkene by a radical addition mechanism, subsequently initiating a cyclization reaction which can be seen as a way of trapping the initially formed alkyl radical formed after alkene addition. Electron-rich methacrylamides generally gave higher yields than electron-deficient methacrylamides, which seems reasonable as the substrate radical is rather electron deficient. A HAT reaction between the substrate radical and the radical cation of the base TMP is not possible, as it has no H atoms in the α-position of the nitrogen atom. The yielded product radical can now be oxidized, either by the excited photocatalyst or the radical cation of TMP, and finally be deprotonated to give the desired defluoroalkylated product. The rearomatization of the product is the driving force for this last step.



Gschwind, König 2018:
conditions = *fac*-[Ir(ppy)$_3$] (1.0 mol %), alkene (2.0 eq.), TMP (2.0 eq.), HBpin (3.0 eq.) in DCE at 20 °C, blue LED, 16 - 72h
R' = -Alkyl, -Aryl
R'' = -Alkyl, -Aryl, -H, -OMe, -Cl, -F

Scheme 13: Mechanistic steps from the radical anion to the final product in Gschwind & König's mechanism are shown.

4 The Trifluoromethylthio Group

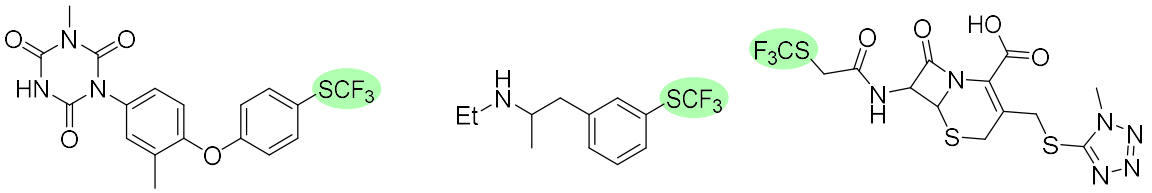
4.1 Applications of the SCF_3 group

Compared to other fluorinated groups, the trifluoromethylthio (SCF_3) group has very high lipophilicity ($\pi = 1.44$) while the electron-withdrawing power ($\sigma_m = 0.40$, $\sigma_p = 0.43$) is comparable to the trifluoromethyl (CF_3-) group (Table 3).[49] Therefore, this functional group enables the fine-tuning of the lipophilic and electronic properties of pharmaceutical- and agrochemical compounds.

Table 3: Aromatic substituents constants of selected fluorine-containing groups.[49d]

	CF_3	**OCF_3**	**SCF_3**
Π	0.88	1.04	1.44
σ_m	0.43	0.38	0.40
σ_p	0.54	0.35	0.50

Examples are the pharmaceuticals Toltrazuril, Tiflorex and Cefazaflur (Figure 12). Toltrazuril is a coccidiostatic drug that is applied against protozoan infections in mammals and birds.[50] Tiflorex is an anorectic drug.[51] Cefazaflur is a parenteral cephalosporin that has bacteriostatic properties.[52]



Toltrazuril Tiflorex Cefazaflur

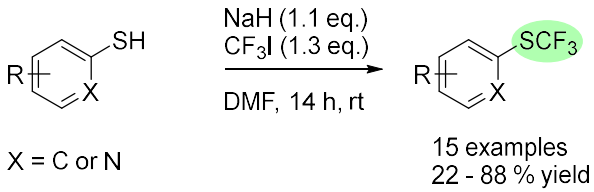
Figure 12: Pharmaceuticals that contain the SCF_3^- group: Toltrazuril, Tiflorex, and Cefazaflur.

4.2 Synthesis of Trifluoromethylthiolated Compounds

A wide range of methods are available for the direct or indirect introduction of the SCF_3-group into a compound.[49d, 53] Examples of indirect methods include the trifluoromethylation of thiols, thiocyanates, or disulfides.[54] For direct methods, a wide range of nucleophilic, electrophilic and radical trifluoromethylthiolation reagents are available.

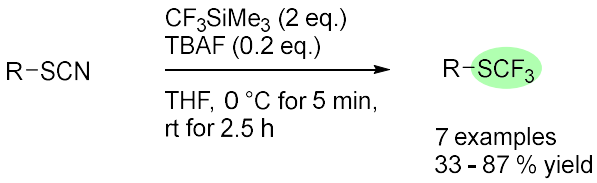
4.2.1 Trifluoromethylation of Thiols, Thiocyanates or Disulfides

The group of Rábai published a method for the trifluoromethylation of thiols using CF_3I in 2011 (Scheme 14).[55] A thiolate is produced from the reaction of the thiol and NaH, which subsequently reacts with CF_3I via an $S_{RN}1$ mechanism. This mechanism includes the usual initiation, propagation, and termination steps, with the $\cdot CF_3$ radical being formed in the initiation step via electron transfer from the thiolate. The final trifluoromethylthiolated product is formed in the final step, when the product radical anion undergoes an SET reaction to another molecule of CF_3I as part of a radical chain reaction. The method tolerates several functional groups such as -COOH, -COOMe, -Br, -I, $-NO_2$, and $-NH_2$ and gives, depending on the substrate, acceptable to very good yields.



Scheme 14: Trifluoromethylation of thiols with CF_3I by the group of Rabai in 2011.[54b]

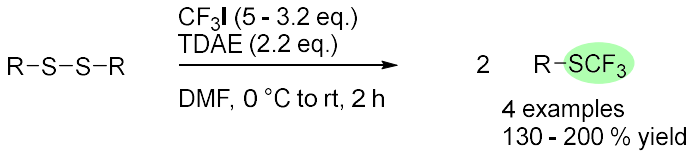
The group of Langlois published a method for the trifluoromethylation of thiocyanates in 1997 using trifluoromethyl trimethyl silane (the Ruppert-Prakash reagent, CF_3SiMe_3, Scheme 15).[54a] The fluoride anion from TBAF reacts with CF_3SiMe_3 to give the $^-CF_3$ anion, which subsequently substitutes the cyano group of the thiocyanate to yield the desired product. The released ^-CN anion reacts with another molecule of CF_3SiMe_3 to afford the $^-CF_3$ anion and Me_3SiCN. Therefore only small amounts of TBAF are needed for the initiation of the reaction. Aliphatic, benzylic, and aromatic substrates are tolerated in this method, although only Ph-SCN and 4-NO_2-C_6H_4-SCN are reported as aromatic substrates. The observed yields ranged from acceptable to very good.



Scheme 15: Trifluoromethylation of thiocyanates with CF_3SiMe_3 by the group of Langlois in 1997.[54a]

In 2003, the group of Dolbier published a method for the trifluoromethylation of disulfides using CF_3I as a reagent (Scheme 16).[54c] Interestingly, both parts of the disulfide could be converted into the products, while in earlier methods, one part of the disulfide would only act as a leaving group. They solved this problem by employing CF_3I not only as a source of the $\cdot CF_3$ radical, but also as a

source of the $^{-}CF_3$ anion using the reductant tetrakis(dimethylamino)ethylene (TDAE). After the $^{-}CF_3$ anion is generated by reduction, it reacts directly with the disulfide to give one molecules of the desired trifluoromethylthiolated product and a thiolate as the leaving group. This thiolate anion then undergoes a reaction with another molecule of CF_3I via $S_{RN}1$ to form a second trifluoromethylthiolated product. The authors showed that their method is suitable for simple disulfides featuring phenyl, pyridinyl, and alkyl groups. Based upon the number of equivalents of disulfide, the yields were in the range of 130 to 200 %. A general disadvantage is the high cost of the reductant TDAE.



Scheme 16: Trifluoromethylation of disulfides with CF_3I by the group of Dolbier in 2003.[54c]

4.2.2 Direct Trifluoromethylthiolation

Methods that enable the direct introduction of the SCF_3 group efficiently, safely and under mild conditions are of particular interest. These methods employ novel SCF_3 containing reagents that are typically bench-stable and allow for either electrophilic, nucleophilic or radical installation of the SCF_3 group (Figure 13). In contrast, older reagents such as trifluoromethylsulfenyl chloride ($Cl\text{-}SCF_3$) and bis(trifluoromethyl)disulfide ($CF_3S\text{-}SCF_3$) are highly toxic and volatile gaseous compounds.

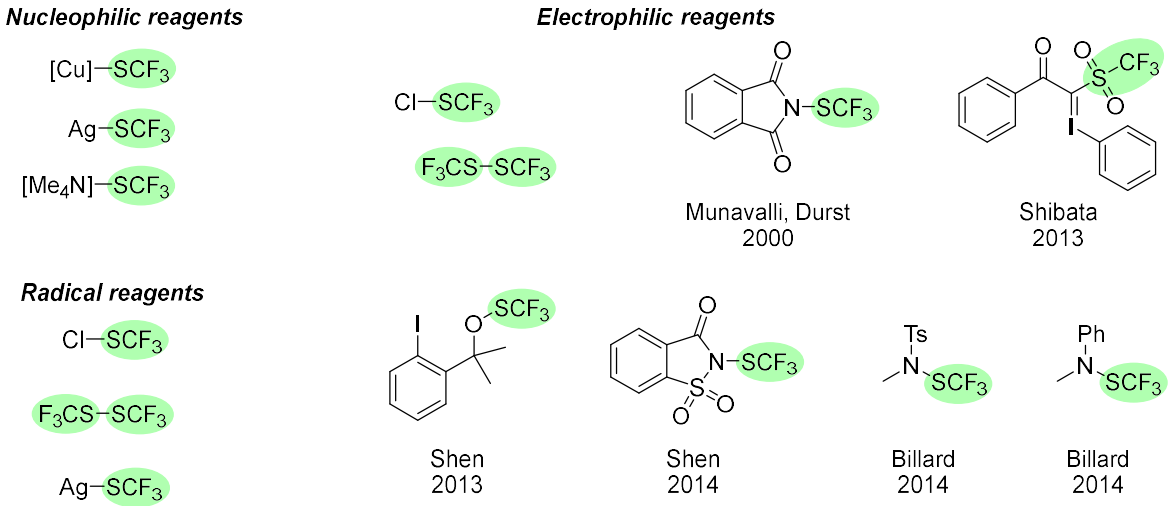
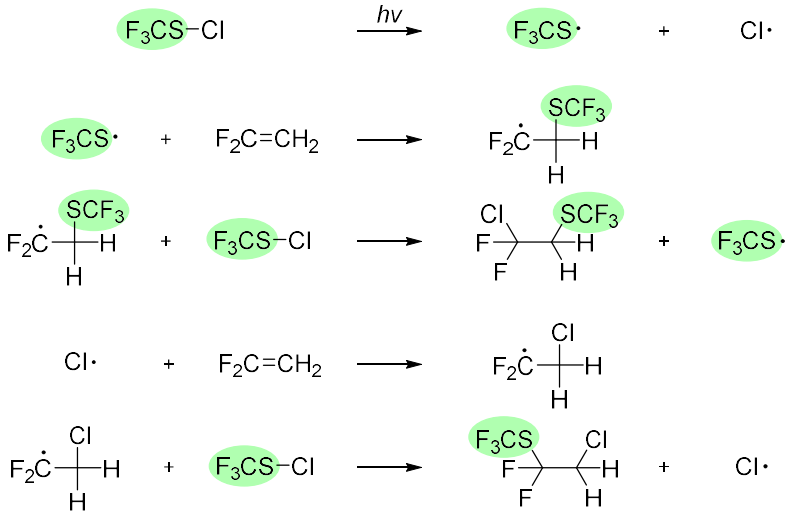


Figure 13: An overview over electrophilic, nucleophilic and radical trifluoromethylthiolation reagents.

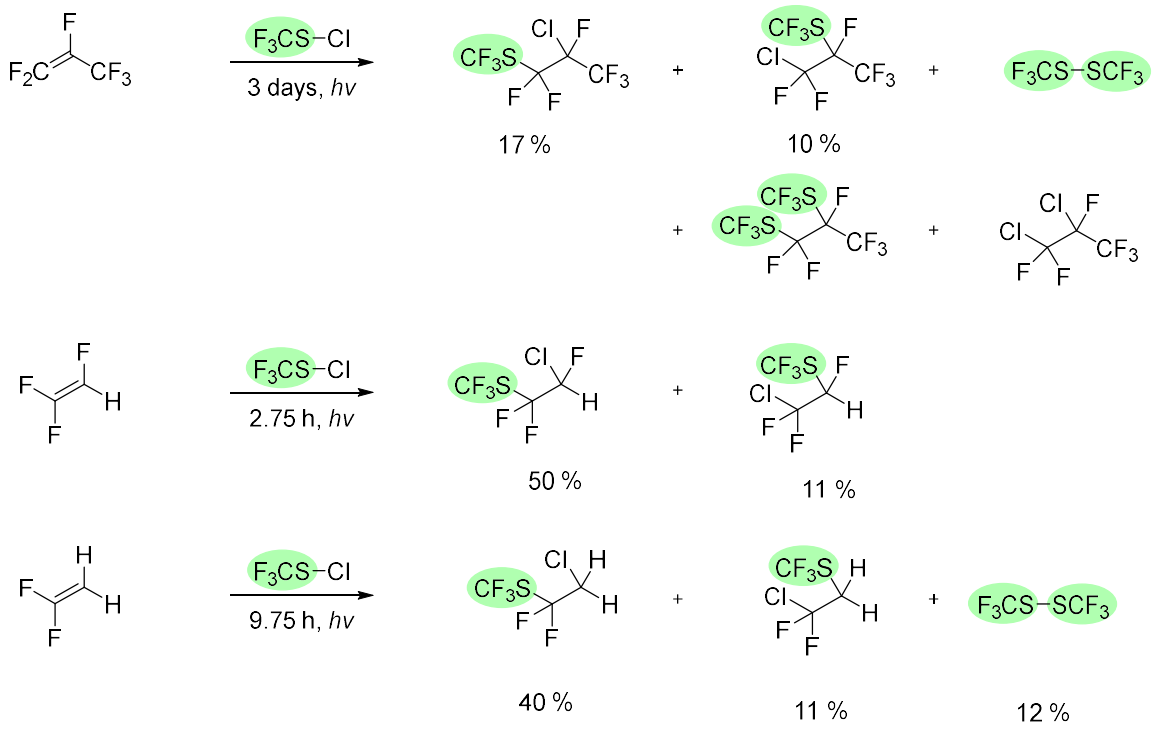
4.2.2.1 Radical Trifluoromethylthiolation

Harris published an early method for the radical trifluoromethylthiolation of alkenes in 1962.[56] To initiate the reaction and access the desired ·SCF_3 radical, either ultraviolet irradiation, X-rays or a radical initiator was suitable. This radical subsequently reacted in different propagation and termination reactions, and usually, two regioisomers were acquired as products (Scheme 17).



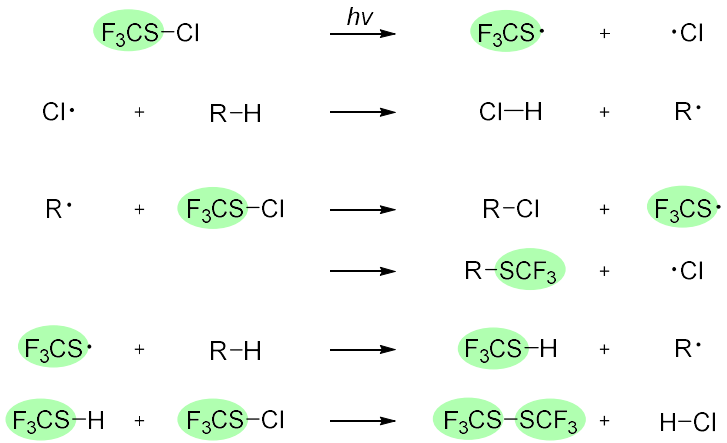
Scheme 17: The radical chain mechanism that is reported by Harris for his radical trifluoromethylthiolation reaction for alkenes.[56]

With hexafluoropropylene as substrate, the major products were the two possible radical addition products, along with three minor side products, including bis(trifluoromethyl)disulfide (Scheme 18). With trifluoroethylene and 1,1-difluoroethylene as substrates, again both radical addition products were obtained. While difunctionalized products can be obtained by this method, the isolation of the regioisomeric products is cumbersome.



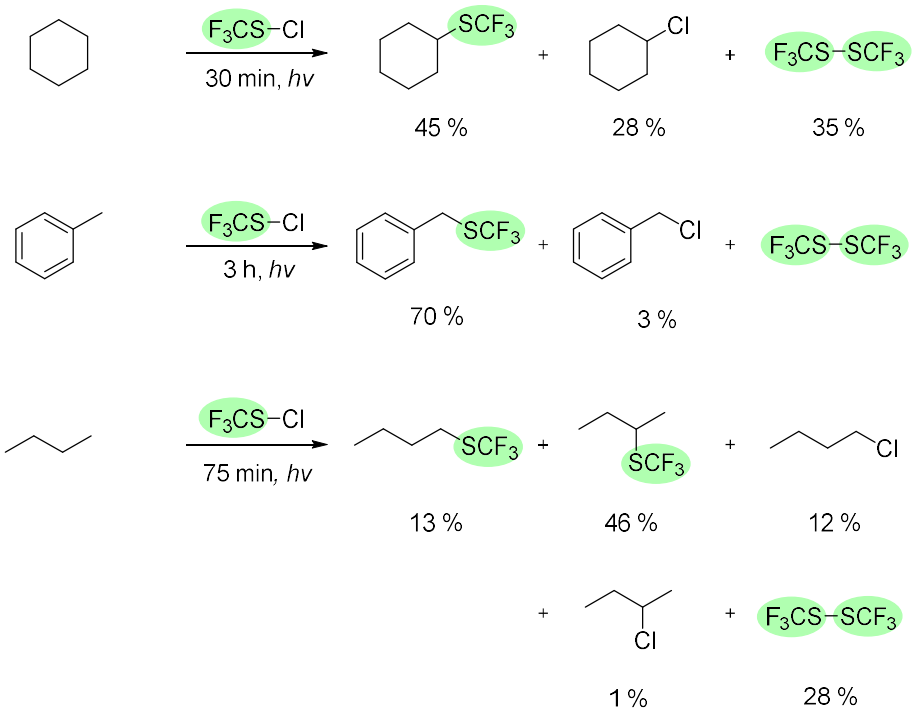
Scheme 18: The radical trifluoromethylthiolation of alkenes published by Harris in 1962.[56]

Three years later, the aforementioned trifluoromethanesulfenyl chloride was studied by Harris for the radical trifluoromethylthiolation of alkanes.[57]



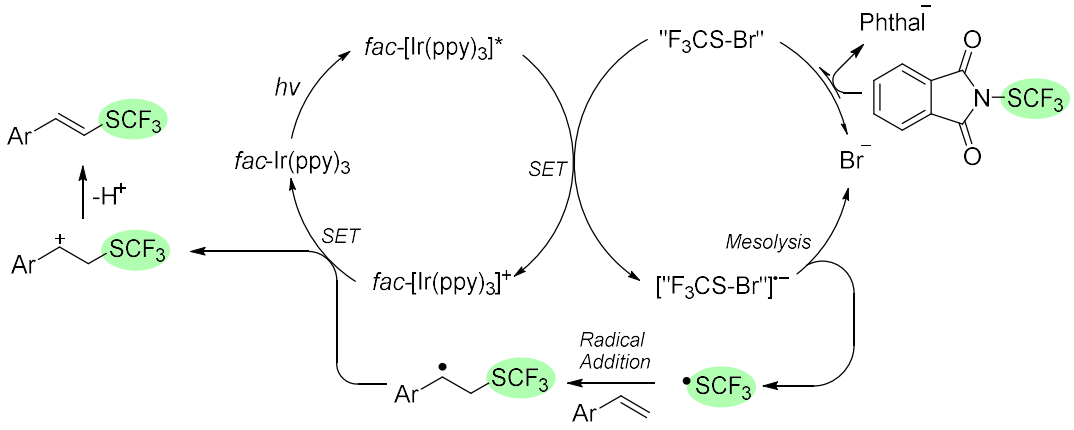
Scheme 19: The radical chain mechanism reported by Harris for his radical trifluoromethylthiolation reaction of alkanes.[57]

Under either UV irradiation or in the presence of a radical initiator such as azobis(isobutyronitrile) (AIBN), the reagent is efficiently activated and the desired ·SCF_3 radical is generated.



Scheme 20: The radical trifluoromethylthiolation of alkanes published by Harris in 1965.[57]

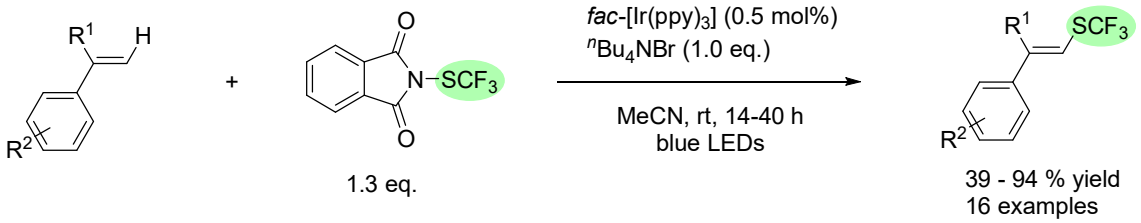
This initiation step is followed by several other propagation and termination steps which finally yield the desired trifluoromethylthiolated product along with chlorinated by-products, HCl, and bis(trifluoromethyl)disulfide (Scheme 19). In the case of cyclohexane as substrate, trifluoromethyl cyclohexyl sulfide (45 % yield) was obtained as the major product, along with cyclohexyl chloride (28 % yield) and bis(trifluoromethyl)disulfide (35 % yield) as major by-products (Scheme 20). With toluene as substrate, the desired trifluoromethyl benzyl sulfide (70 % yield) was produced as the major product, while the by-product benzyl chloride (3 % yield) was formed only in small amounts. In another experiment, *n*-butane was used as the substrate, and the products were 1-trifluoromethylthio butane (13 %) and 2-trifluoromethylthio butane (13 %) along with the by-products 1-chloro butane (12 %), 2-chloro butane (1 %), and bis(trifluoromethyl)disulfide (28 %). However, with the development of novel reagents and methods in the last decades, trifluoromethylthiolations of alkenes no longer have to be carried out with the toxic and gaseous trifluoromethylsulfenyl chloride.



Scheme 21: The mechanism of the photocatalyzed radical trifluoromethylthiolation of styrenes published by Hopkinson and Glorius in 2016.[58]

One example is a trifluoromethylthiolation of styrenes published by Hopkinson and Glorius in 2016 using the solid reagent *N*-trifluoromethylthiophthalimide (Phthal-SCF_3).[58] Here, a formal F_3CS-Br species was generated *in situ* from Br^- and Phthal-SCF_3, which yields an $\cdot SCF_3$ radical after SET from the excited *fac*-[Ir(ppy)$_3$]* catalyst and mesolysis of the formal F_3CS-$Br^{\cdot-}$ radical anion (Scheme 21). Addition of the $\cdot SCF_3$ radical to the alkene then delivers the product radical, which can be oxidized by *fac*-[Ir(ppy)$_3$]$^+$ to give the corresponding cation, which forms the desired product after deprotonation. However, because of the low stability of the product radical, further stabilization by adjacent groups was needed, and therefore, this method is limited to styrenes and *N*-phenyl acrylamides as substrates. Other substrate classes such as simple alkenes or methylenecyclohexanes did not give any product.

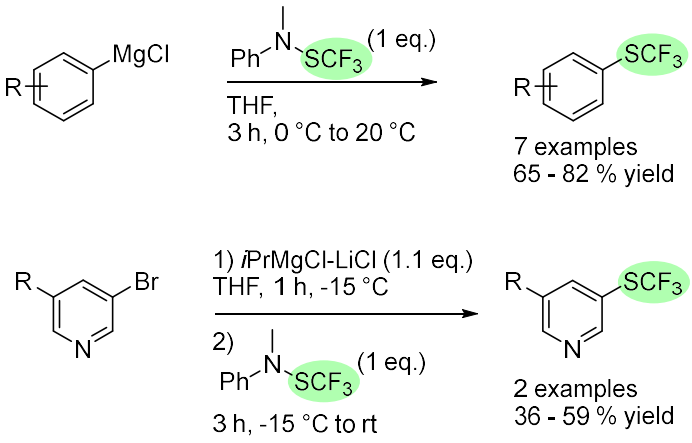
Several substrates were tested under their conditions, giving moderate to excellent yields for the desired product (Scheme 22). Various arenes and heteroarenes were employed and functional groups such as -OMe, -F, -Cl, and -Br were tolerated at the *ortho*, *meta* and *para* positions of the (hetero)arenes. Furthermore, no side reactions were observed when benzylic C-H bonds were present in the substrate. With styrenes, a moderate selectivity for the (*E*)-isomer was observed.



Scheme 22: The photocatalyzed radical trifluoromethylthiolation of styrenes published by Hopkinson and Glorius in 2016.[58]

4.2.2.2 Electrophilic Trifluoromethylthiolation

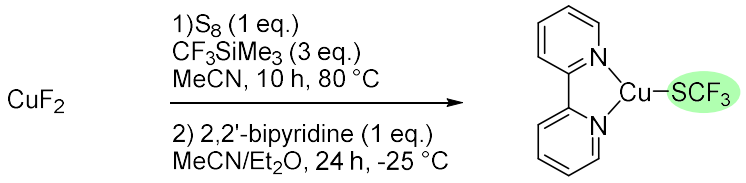
Another strategy to obtain trifluoromethylthiolated compounds is by electrophilic trifluoromethylthiolation. For example, the group of Billard published the trifluoromethylthiolation of organometallic species using trifluoromethanesulfanamides as reagents in 2012.[59] Based on their previous work, the authors hypothesized that magnesium(II) cations present in Grignard reagents would act as a Lewis acid and help to activate the reagent towards nucleophilic attack.[60] An interesting range of substrates could be efficiently trifluoromethylthiolated using the optimized method, ranging from alkyl Grignard to (hetero)aryl Grignard-reagents (Scheme 23). The main limitation is the low functional group tolerance of the Grignard reagent itself. While organozinc reagents were not suitable substrates, it was possible to extend their method to metallated terminal alkynes with the aid of *n*-BuLi or NaHMDS.



Scheme 23: The electrophilic trifluoromethylthiolation of Grignard reagents published by the group of Billard in 2012.[59]

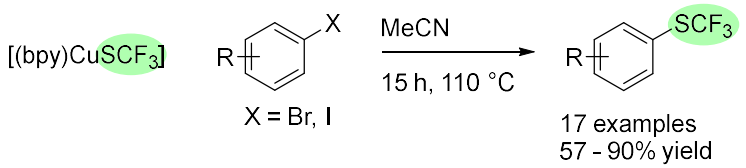
4.2.2.3 Nucleophilic Trifluoromethylthiolation

A [Cu]-SCF_3 reagent for nucleophilic trifluoromethylthiolation was developed in 2013 by the groups of Weng and Yuan.[61] With their method, aryl halides could be transformed into trifluoromethylthiolated arenes. Experimental results showed that a monomeric form of the copper complex is more reactive than the dimerized form. When 2,2'-bipyridine (bpy) or its derivatives were employed as ligands, the monomeric copper complex was generally obtained, while phenanthroline ligands typically afforded the less reactive dimeric complex. DFT calculations showed that the dimerization is exergonic for complexes with the phenanthroline ligand, while it is endergonic and not favored for 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy). This reagent can be synthesized in moderate yields from CuF_2, S_8, and CF_3SiMe_3 (Scheme 24).



Scheme 24: Synthesis of a nucleophilic SCF_3 reagent by the groups of Wenig and Yuan.[61]

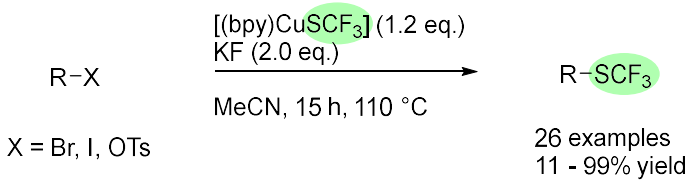
Four different mechanisms were considered for the trifluoromethylthiolation of aryl halides and DFT calculations suggested an oxidative addition and reduction elimination pathway is most favored. In this mechanism, the aryl halide would first undergo oxidative addition with the [(bpy)CuSCF$_3$] complex. In a second step, this intermediate would undergo reductive elimination, and the desired trifluoromethylthiolated arene would be obtained along with [(bpy)CuI] as a by-product. Their method was applied to 17 aryl halides in good to excellent yields and tolerates aromatic -CN, -NO_2, -CO_2Me, -C(O)Me, and -OMe groups. Furthermore, this method works with pyridines and thiophenes, while it also selectively reacts with aromatic iodide groups when aromatic chloride groups are also present (Scheme 25).



Scheme 25: The nucleophilic trifluoromethylthiolation method for aryl halides by the groups of Weng and Yuan.[61]

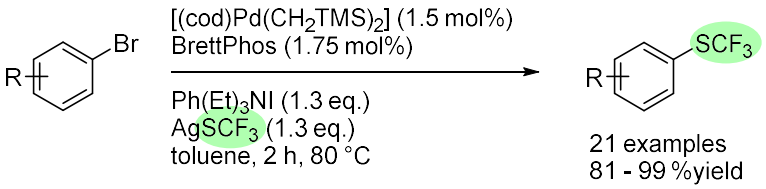
Later, in 2014, the same groups published a method for the trifluoromethylthiolation of alkyl halides using their [(bpy)CuSCF$_3$] reagent.[62] A challenge in such a reaction is to achieve high selectivity for the trifluoromethylthiolation through suppression of β-hydride elimination, which can occur from the expected alkyl metal intermediate.[63] However, when using [(bpy)CuSCF$_3$], no β-hydride elimination products were detected. In subsequent work, the same group tested alkyl tosylates as substrates, which gave very good yields. Furthermore, in this process, a different mechanism was proposed which does not involve oxidative addition and reductive elimination. Instead the trifluoromethylthiolation of alkyl halides is thought to proceed via an S_N2-type substitution.[62] Their optimized method also uses KF as an additive, although no rationalization for the role of fluoride salts in increasing the yield was provided. However, the authors were able to apply their method with moderate to very good yields to a broad range of alkyl bromides and iodides, tolerating ethers, thioethers, esters, nitriles, amides and ketals, while nitro substituents in the *para*-position diminished the yield with benzylic halides (Scheme 26). In the case of secondary

alkyl halides, the method is limited to alkyl iodides, as bromides or chlorides yielded only traces of the desired trifluoromethylthiolated product.



Scheme 26: The nucleophilic trifluoromethylthiolation method for alkyl halides by the groups of Weng and Yuan.[62]

In 2011, the group of Buchwald published a palladium-catalyzed approach for the trifluoromethylthiolation of aryl bromides (Scheme 27).[64] During the development of the catalytic method, one difficulty was the slow transmetalation step of $^{-}SCF_3$ from $AgSCF_3$ to the *in situ* formed LPdAr(Br) complex. The challenge was overcome by adding quarternary ammonium salts with $Ph(Me)_3NI$ providing the trifluoromethylthiolated products in quantitative yields. The authors hypothesized that the iodide anion binds to $AgSCF_3$, generating an anionic „ate" complex and that a large diffuse cation further aids the solubility of this complex. However, while bromide and iodide anions were suitable for the quaternary ammonium salt, chloride anions gave no product yield at all. Using this method, the authors transformed 21 (hetero)aryl bromides in very good to excellent yields into the corresponding trifluoromethylated (hetero)arene compounds.

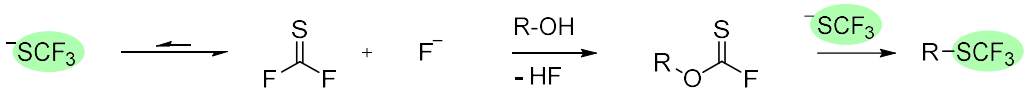


Scheme 27: The triflouromethylthiolation method for aryl bromides developed by the group of Buchwald in 2011.[64]

The method tolerated several functional groups on the arene substrate such as -CN, -OAr, -NHAr, $-N(Ar)_2$, $-CO_2R$, and -C(O)R.

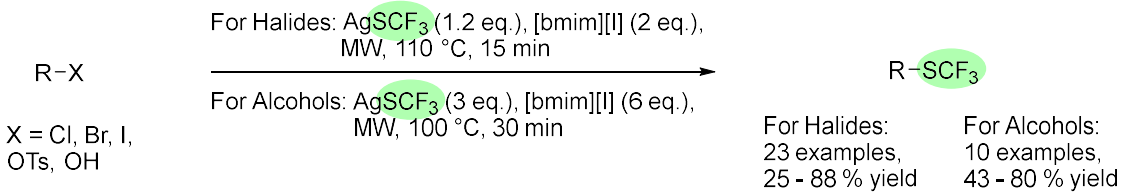
The groups of Magnier and Pégot published a selection of methods employing $AgSCF_3$ together with the ionic liquid [bmim][I].[65] Under these conditions, $[bmim][SCF_3]$ is generated, which can be applied as a reagent for nucleophilic trifluoromethylthiolation for alkyl halides or for deoxytrifluoromethylthiolation in the case of alcohols. In this deoxytrifluoromethylthiolation protocol, an excess of $AgSCF_3$ is necessary, as some of the $^{-}SCF_3$ anions undergo fluoride elimination affording difluorothiophosgene. The alcohol subsequently attacks difluorothiophosgene to form the electrophilic carbonofluoridothioate intermediate. Another $^{-}SCF_3$ anion then attacks the

generated electrophile in a nucleophilic substitution process to form the final trifluoromethylthiolated product. The group of Billiard first proposed this mechanism in 2016 for their own deoxytrifluoromethylthiolation method using an electrophilic SCF_3-source (Scheme 28).[66]



Scheme 28: Mechanism of the deoxytrifluoromethylthiolation of Magnier and Pegot.[65]

In the nucleophilic trifluoromethylthiolation of aliphatic halides, a broad scope of functionalities was tolerated including pyridine, indole, arene, ester, cyano, imide, carbamate, and lactone groups – while *N*-H moieties often led only to moderate yields (Scheme 29). Generally, the yields were very good with iodide and bromide as the leaving groups, whereas with chloride, lower yields were obtained. In the deoxytrifluoromethylthiolation method, primary benzyl, alkyl, and allylic alcohols were suitable substrates, providing the SCF_3-containing products in good yields. Long-chain aliphatic alcohols gave lower yields, likely due to the poor solubility of these substrates in the ionic liquid [bmim][I] or [bmim][SCF_3]. While secondary and tertiary alcohols were also suitable substrates, moderate yields of the desired products were typically obtained.



Scheme 29: The trifluoromethylthiolation of aliphatic halides and deoxytrifluoromethylthiolation of aliphatic alcohols published by the group of Magnier & Pégot in 2017.[65]

5 The Trifluoromethoxy Group

5.1 Applications of the OCF_3 Group

Another important trifluoromethylated chalcogen group is the trifluoromethoxy (OCF_3) group. This group has a Hansch parameter of 1.04 and Hammett constants of $\sigma_p = 0.35$ and $\sigma_m = 0.38$, and is therefore attractive for fine-tuning the lipophilic and electronic properties of a pharmaceutical or agrochemical compound.[49a-c] Furthermore, the OCF_3 group imparts unique properties when incorporated into organic molecules. For example, aryl trifluoromethyl ethers exhibit unusual conformation preferences wherein the OCF_3 group is oriented orthogonal to the plane of the aromatic ring.[67] Examples of its wide use as a substituent in arenes are the drugs Riluzole,

Celikalim, Pretomanid, and the agrochemicals Flurprimidol and Triflumuron (Figure 14). Riluzole is used to treat Lou Gehrig's disease, Celikalim is a potassium channel opener, and Pretomanid is an anti-tuberculosis agent.[49b, 68] Flurprimidol is used as a plant growth regulator and Triflumuron as an insect growth regulator.

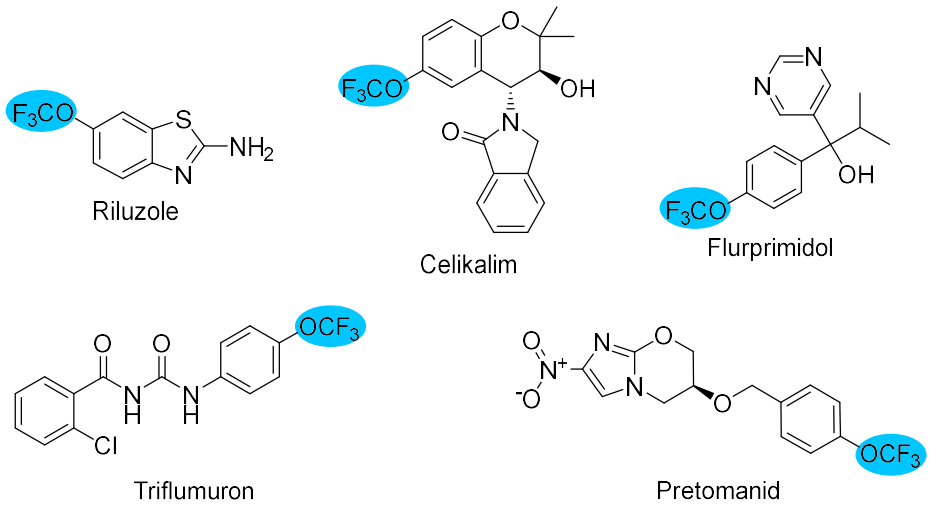
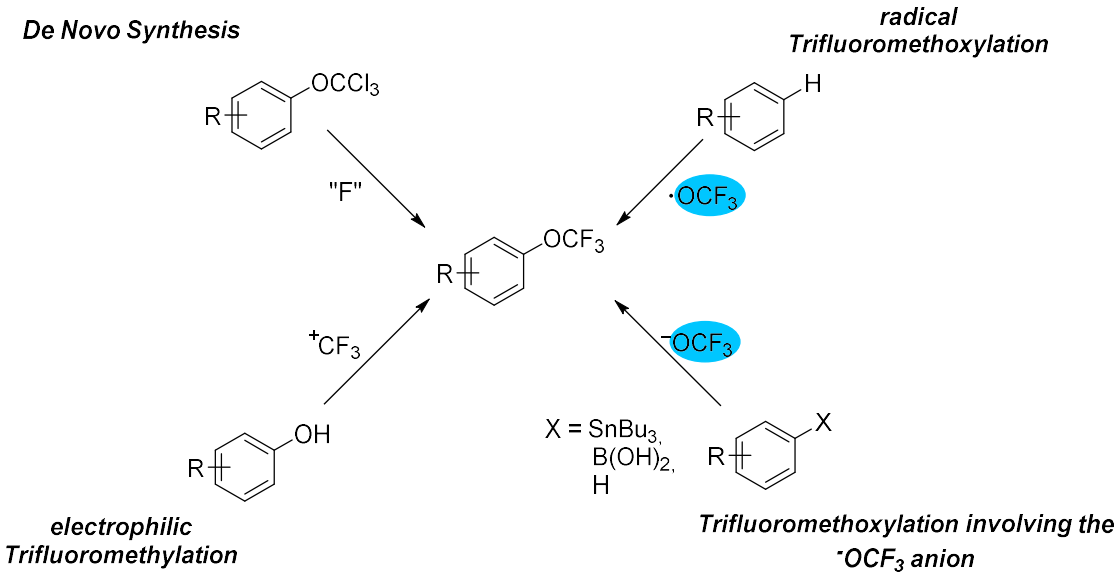


Figure 14: Drugs and agrochemicals with an aromatic OCF_3 moiety.

5.2 Synthesis of Trifluoromethoxylated (Hetero)arenes

However, compared with trifluoromethylated arenes, synthetic methods to prepare trifluoromethoxylated arenes are relatively underdeveloped and are a main area of current research interest.[68b] The available synthetic approaches are either indirect methods, such as *O*-trifluoromethylation and *De Novo* methods, or direct methods, such as radical trifluoromethoxylation or trifluoromethoxylation reactions involving the $^{-}OCF_3$ anion (Scheme 30). *O*-Trifluoromethylation, *de novo* methods and usually methods employing the $^{-}OCF_3$ anion rely on prefunctionalized substrates, while radical trifluoromethoxylation can employ simple unactivated organic starting materials.



Scheme 30: While *De novo* synthesis and electrophilic or nucleophilic methods rely on prefunctionalized substrates, radical trifluoromethoxylation does not.

5.2.1 *De Novo* Synthesis

De novo synthetic methods or processes are run on a larger scale and use bulk chemicals as substrates. These approaches can provide a wide variety of trifluoromethoxylated arenes, which are suitable as building blocks for drug compounds and agrochemicals.[49b, 68b] These synthetic *de novo* routes usually consist of three main steps: i) hydroxylation of the arene; ii) functionalization of the aromatic alcohol group; iii) halogen exchange or fluorination to obtain the aromatic OCF_3 moiety (Figure 15).[69]

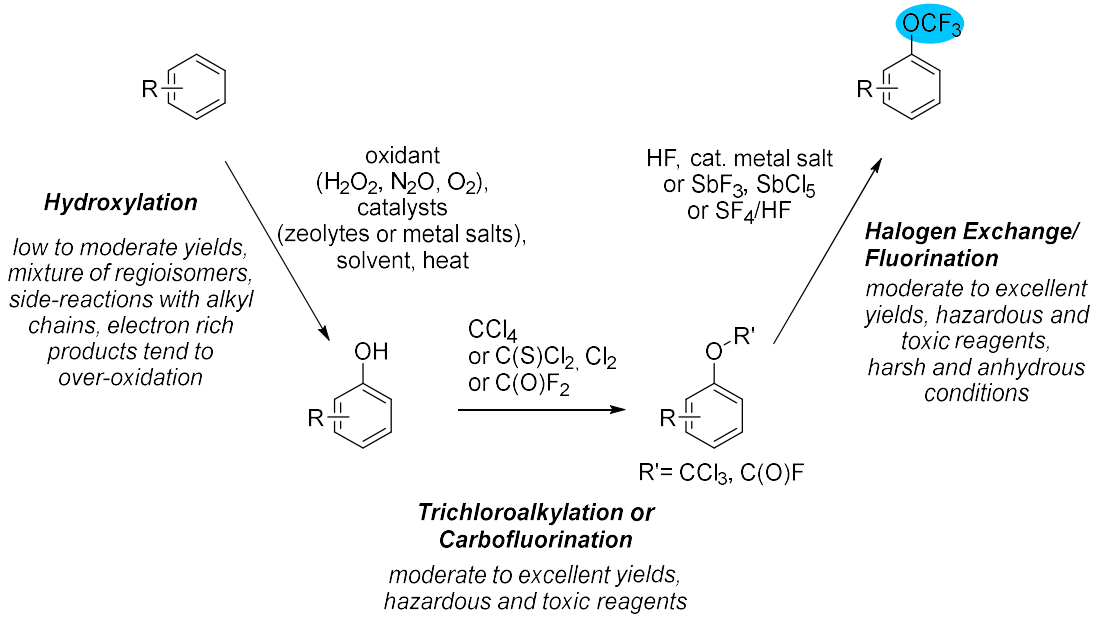
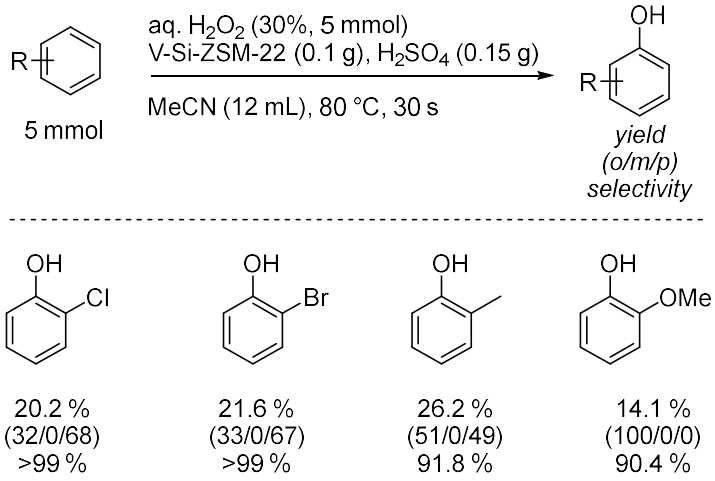


Figure 15: The three main steps for the *de novo* synthesis of trifluoromethoxylated arenes.

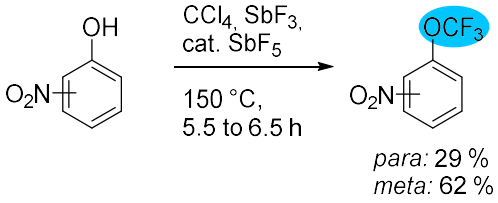
Alternatively, the first step can involve functionalization of phenol, which is abundant because of the cumene process, but this will not be discussed here.[70] In the hydroxylation of the arene, many challenges must be overcome. First, hydroxylation reactions typically afford regioisomeric product mixtures. While electron-rich substrates yield mostly *ortho* and *para* products, electron-deficient substrates typically yield *ortho*, *meta,* and *para* products. Furthermore, benzylic C_{sp3}-H bonds are not tolerated, as they are more prone to oxidation than the arene C_{sp2}-H bonds.[70] Another difficulty is the potential for over-oxidation: the product of the hydroxylation reaction is more electron-rich than the arene substrate and is thus more susceptible to oxidation. Common side-products are dihydroxylated arenes and benzoquinones. Finally, the yield for the desired mono-hydroxylated arene is usually in a low to moderate range.[71]



Scheme 31: Selective radical hydroxylation of arenes by the group of Wang in 2018.[70]

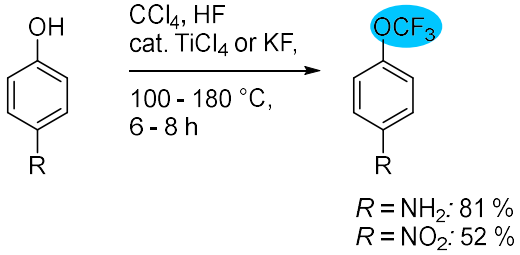
The group of Wang reported an example of radical hydroxylation of arenes in 2018.[70] While H_2O_2 was used as the oxidant, V-Si-ZSM-22 (TON type vanadium silicalite zeolites) was employed as the catalyst. Under their conditions, the hydroxylation of benzene could be achieved with a yield of 30.8 % and > 99% selectivity for mono-hydroxylation. With mono- or dialkyl benzenes and halogenated aromatic hydrocarbons, yields of up to 26.2 % were obtained with selectivity for the desired phenols of above 90% - the side reaction involving benzylic C_{sp3}-H bond is only a minor problem under these conditions (Scheme 31). Most interestingly, their reaction proceeds to completion in 30 seconds and features ultra-high turnover frequencies of up to 2315 h^{-1}. Usually, at least two steps are required to synthesize a trifluoromethoxylated arene from a phenol derivative: i) perchloroalkylation of the aromatic alcohol group and ii) halogen exchange affording the final product. It is desirable to reduce these two steps into one single step. This was shown by Dow Chemical AG in 1990 and by Bayer AG in 2001 (Scheme 32 and 33).[72] In both cases, high

temperatures, high pressure, hazardous and toxic reagents were required. While the group of Nader required stoichiometric amounts of the metal salt SbF_3, Bayer AG required only catalytic amounts of metal salts and achieved higher yields for 1-nitro-4-(trifluoromethoxy)benzene.



Scheme 32: Single-step *O*-trifluoromethylation of phenols by Dow Chemical AG in 1990.[72b]

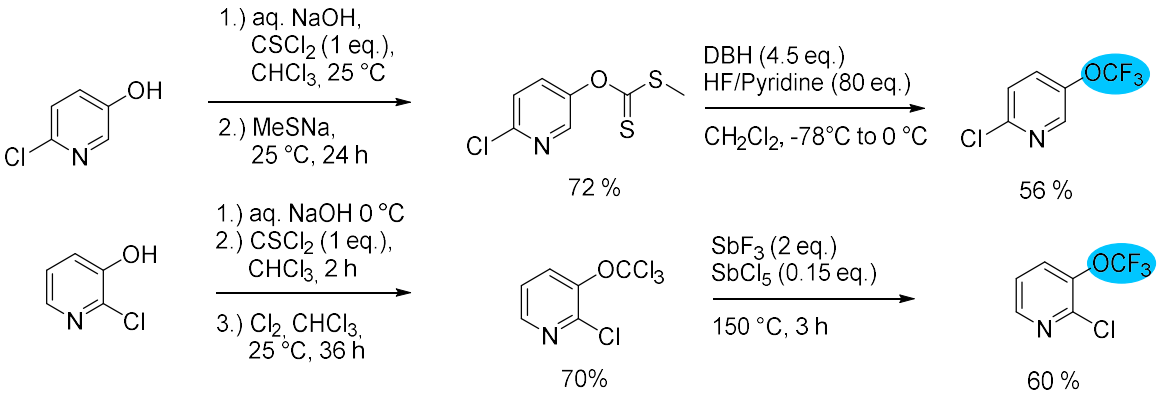
The *De novo* strategy for synthesizing trifluoromethoxy arenes can deliver affordable building blocks to prepare drugs and agrochemicals. However, the main difficulties are that in the hydroxylation step, regioisomeric product mixtures are received and that later synthetic steps are often energy-intensive and require special equipment to handle the hazardous, toxic, and gaseous reagents.



Scheme 33: Single-step O-trifluoromethylation of phenols by the Bayer AG in 2001.[72a]

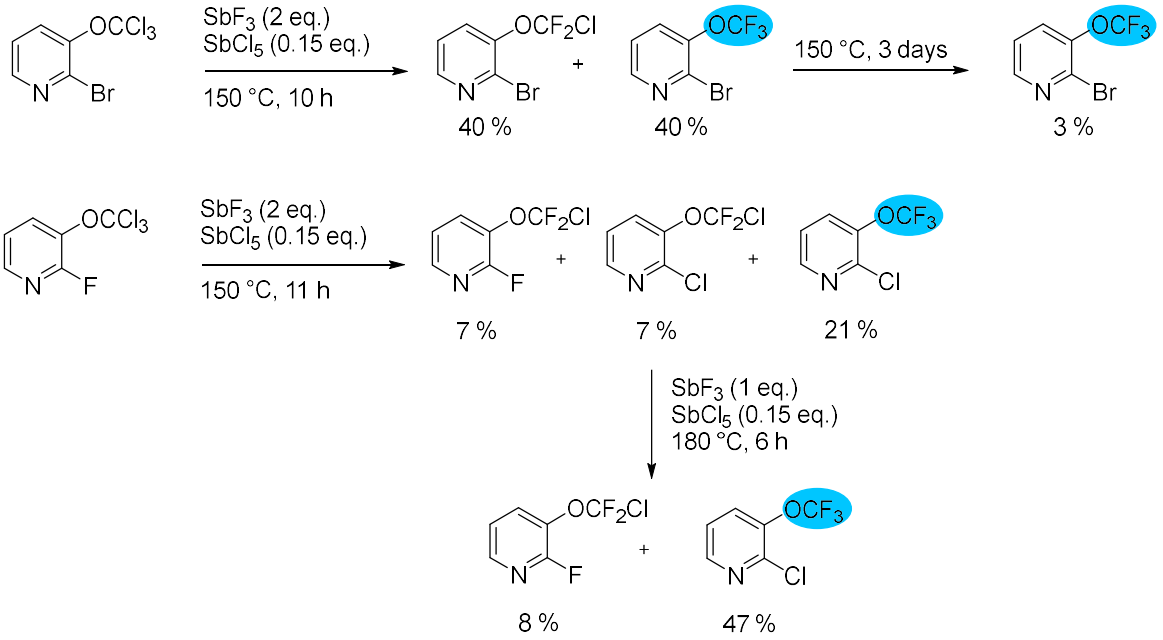
For several heterocycles, an additional challenge is to achieve complete halogen exchange from the trichloromethyl ether to the trifluoromethyl ether. For example, pyridines only undergo incomplete halogen exchange under the previously discussed conditions. The group of Leroux showed in 2010 that extremely harsh conditions and additives are required in combination with a xanthogenation strategy to obtain the trichloromethyl ether (Scheme 34).[73] As an alternative, they developed a method that relies on the fluorinating agent SbF_3 and the catalyst $SbCl_5$. However, both methods were only applicable to α-chloro(trichloromethoxy)pyridines. If the chloro substituent is exchanged with, for example, a bromo or a fluoro substituent, incomplete halogen exchange step is observed. This results in a mixture of inseparable trifluoromethyl and chlorodifluoromethyl ethers. In both cases, prolongation of the reaction times did not solve the problem (Scheme 35). Furthermore, in the case of α-fluoro(trichloromethoxy)pyridine, the fluoro substituent can also become substituted

by chloride, and adding more SbF_3 and $SbCl_5$ only increased the yield of the α-chloro(trifluoromethoxy)pyridine by-product.



Scheme 34: The group of Leroux developed methods to prepare α-chloro(trifluoromethoxy)pyridines, which are otherwise difficult to synthesize.[73]

As a consequence, all substituted (trifluoromethoxy)pyridines must be prepared in cumbersome and step-intensive procedures from α-chloro(trifluoromethoxy)pyridines.

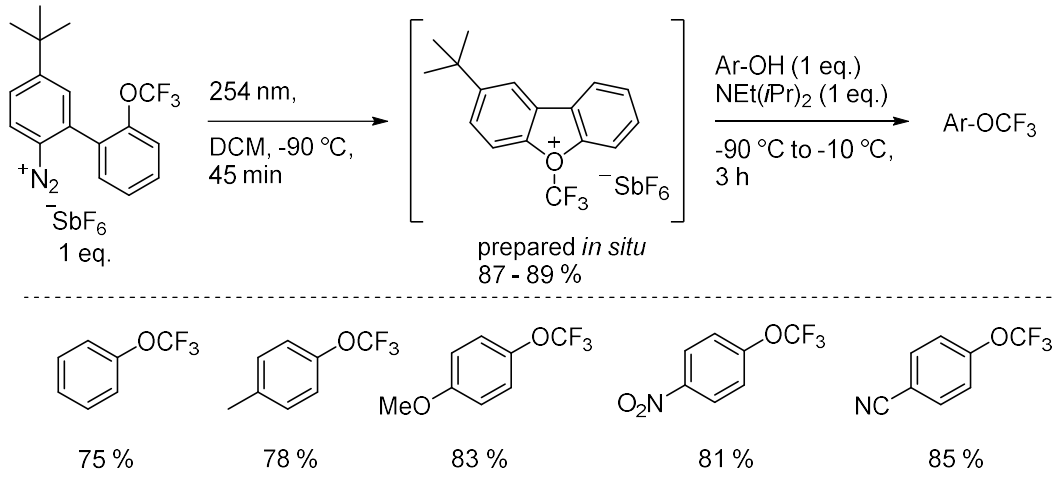


Scheme 35: Only α-chloro(trichloromethoxy)pyridines were successfully converted in the halogen exchange step. The incomplete fluorination of other (trichloromethoxy)pyridines limits the application of this method – separation of such product mixtures is very challenging. Therefore, all other (trifluoromethoxy)pyridines must be prepared from α-chloro(trifluoromethoxy)pyridines.[73]

5.2.2 Electrophilic Trifluoromethylation of Phenols

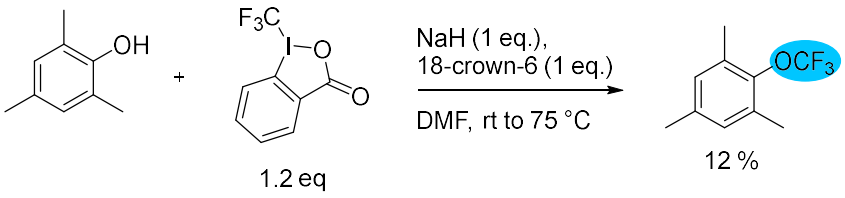
Indirect trifluoromethoxylation or electrophilic trifluoromethylation of arenes relies on phenols as substrates. These pre-functionalized substrates are cheap and widely available. While the group of

Umemoto conducted pioneering work on this conversion in 2007 followed by the group of Togni in 2008, the group of Qing developed an alternative method in 2015 that was able to deliver trifluoromethoxylated arenes from phenols using the Ruppert-Prakash reagent.[74] The group of Umemoto developed the new *O*-(trifluoromethyl)-dibenzofuranium salts, which are formed upon decomposition of 2-(trifluoromethoxy)biphenylyl-2'-diazonium salts *in situ* (Scheme 36). These act as a source for $^{+}CF_3$ when nucleophiles attack in a typical S_N2 mechanism. In the case of phenols as substrates, trifluoromethoxylated arenes were obtained in yields ranging from good to very good.



Scheme 36: Electrophilic trifluoromethylation of phenols developed by the group of Umemoto in 2007. NMR yield based on trifluorotoluene as an internal standard. The yield is calculated based upon the *in situ* formed trifluoromethylation reagent.[74]

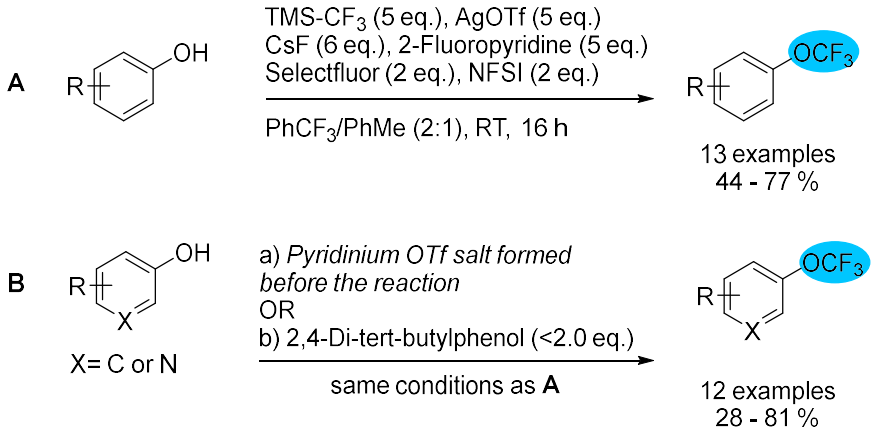
The group of Togni employed their established hypervalent iodine trifluoromethylation reagent for the conversion of the sterically hindered 2,4,6-trimethylphenol (Scheme 37) into a trifluoromethoxylated arene. However, the trifluoromethoxylated product was obtained only in low yields. Without substitution at the *ortho* and *para* positions of the phenol, *C*-trifluoromethylation becomes the dominant reaction pathway.



Scheme 37: Trifluoromethylation of phenols by the group of Togni in 2008.[74b]

The group of Qing encountered the same side reaction as well as a sulfonation side reaction in the case of electron-rich phenols but overcame this difficulty by further optimizing their conditions

(Scheme 38).[74a] Interestingly, the addition of 2,4-di-*tert*-butylphenol inhibited these side reactions and gave the desired electron-rich trifluoromethyl ethers in yields of up to 76 %, while the standard conditions for electron-poor phenols gave yields of up to 77 %.



Scheme 38: The group of Qing developed a method in 2015 to obtain (trifluoromethoxy)benzenes in high yields.[74a] For electron-rich phenols 2,4-di-*tert*-butylphenol is used as an additional additive.

$TMS\text{-}CF_3$, AgOTf, CsF, and 2-Fluoropyridine are all needed to generate the active trifluoromethylation reagent $Ag^{I}CF_3$ *in situ*. The authors concluded that Selectfluor™ and NFSI oxidize this compound to form $[Ag^{III}(CF_3)(F)]$. This complex undergoes fluoride to phenoxide exchange to afford the key intermediate $[Ag^{III}(CF_3)(OPh)]$. Reductive elimination from this complex yields the desired trifluoromethoxylated arene and regenerates Ag^{I}. A plausible mechanism for the trifluoromethylation of the arene itself was also provided. In this case, the *in situ* generated $Ag^{I}CF_3$ undergoes homolytic cleavage to afford Ag^0 and a CF_3 radical, which would react with electron-rich phenols. While the starting materials for these methods are cheap and widely available, these indirect strategies to synthesize trifluoromethoxylated (hetero)arenes generally require stoichiometric amounts of expensive reagents or additives.

5.2.3 Trifluoromethoxylation involving the $^{-}OCF_3$ anion

Nucleophilic reagents such as tris(dimethylamino)sulfonium trifluoromethoxide ($TAS\text{-}OCF_3$) or trifluoromethyl arylsulfonate (TFMS) serve as sources of the $^{-}OCF_3$ anion, which is rather unstable towards decomposition into fluoride and carbonyl difluoride. In the presence of metal salt activators featuring large, rather covalently binding cations such as silver(I) and cesium, the released $^{-}OCF_3$ anion can be sufficiently stabilized to engage in nucleophilic trifluoromethoxylation reactions (Figure 16). $TAS\text{-}OCF_3$ was used in studies by the group of Ritter for the silver-mediated trifluoromethoxylation of aryl stannanes and arylboronic acids (Scheme 39).[75] TFMS was used by the group of Tang for the C-H trifluoromethoxylation of (hetero)arenes (Scheme 40).[75a]

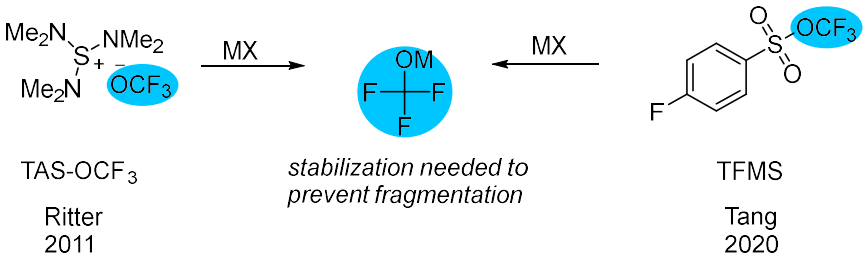
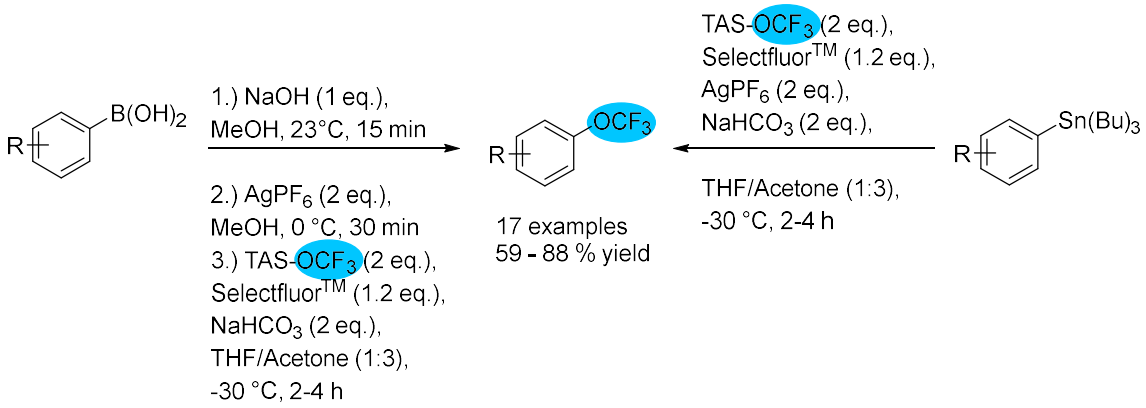


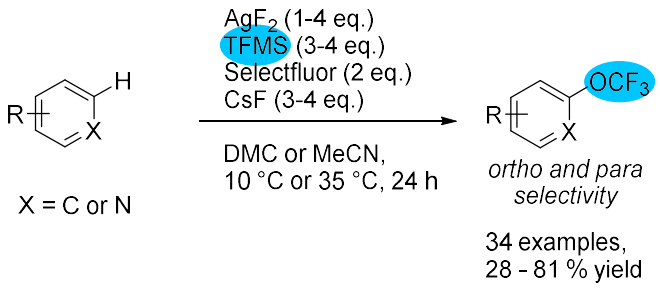
Figure 16: Both shown nucleophilic trifluoromethoxylation reagents generate a stabilized $^{-}OCF_3$ anion *in situ* to prevent fast fragmentation into fluoride and carbonyl difluoride.

The group of Ritter employed two equivalents of $AgPF_6$ with a reaction temperature of -30 °C to accomplish the trifluoromethoxylation of aryl stannanes and arylboronic acids. Higher temperatures could not be successfully used, presumably due to the thermal instability of the $^{-}OCF_3$ anion. In comparison, the group of Tang accomplished trifluoromethoxylation through C-H functionalization of (hetero)arenes by using one equivalent of AgF_2 at 35 °C.



Scheme 39: Nucleophilic trifluoromethoxylation of arylboronic acids and aryl stannans by the group of Ritter.[75b]

Furthermore, three equivalents of CsF were needed to generate the $CsOCF_3$ intermediate from the TFMS reagent. While the drawbacks are stochiometric use of expensive metal salts and, in some cases, the need for prefunctionalized substrates, the advantages of nucleophilic trifluoromethoxylation are the broad availability of nucleophilic OCF_3 reagents and the selective synthesis of trifluoromethoxylated arene products. For example, the group of Ritter were able to selectively synthesize trifluoromethoxylated arenes starting from the corresponding arylboronic acid, while the C-H functionalization approach of Tang provided only mixtures of *ortho* and *para*-substituted products. With pyridine as substrates, however, high selectivity in the C-H functionalization process for the *ortho* products was observed. While the $^{-}OCF_3$ anion is an important intermediate in these reactions, both mechanisms do not proceed via a classic S_NAr pathway.

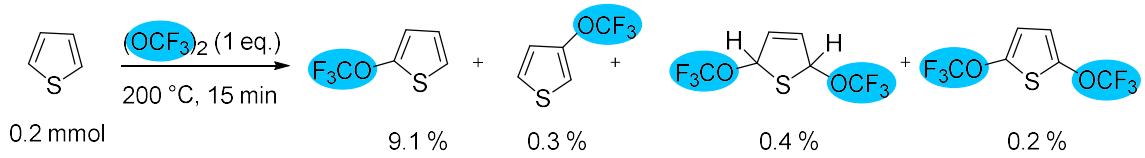


Scheme 40: C-H trifluoromethoxylation of (hetero)arenes by the group of Tang.[75a]

In the case of the method developed by the group of Tang, coordination between the nitrogen atom and the *in situ* formed $Ag^{II}OCF_3$ intermediate directs trifluoromethoxylation to the 2-position. They suggest the LAg(II)OCF_3 oxidizes the (hetero)arene and the $^{-}OCF_3$ anion is subsequently transferred, forming the (trifluoromethoxy)(hetero)arene radical. This product radical can be oxidized by Selectfluor™ and deprotonated by a fluoride anion to provide the final product. In the case of the method developed by the group of Ritter, the authors suggest that trifluoromethoxylation proceeds from discrete high-valent silver complexes, formed via oxidation of aryl silver complexes with Selectfluor™, followed by fluoride to trifluoromethoxide ligand exchange.[75b]

5.2.4 Radical Trifluoromethoxylation

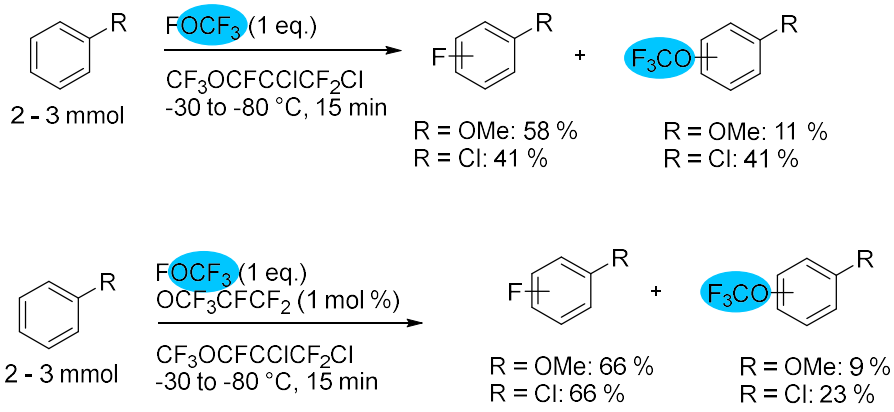
Radical trifluoromethoxylation of arenes is highly desirable, as prefunctionalization of the substrate can be avoided.[49b, 68b] The group of Argüello provided the first examples of such reactions in 2010 with further reports being disclosed by the groups of Famulari & Navarrini in 2012.[76] They applied bis(trifluoromethyl)peroxide (BTMP) in a co-thermolysis reaction with thiophene, hypothesizing that the pyrolysis of BTMP will yield ·OCF_3 radicals, which would be subsequently scavenged by thiophene to afford trifluoromethoxylated thiophene derivatives (Scheme 41).



Scheme 41: Co-thermolysis of thiophene and BTMP was done by the group of Argüello in 2010.[76a]

The co-thermolysis reaction was performed at 200 °C, and after 15 minutes, the substrate was completely consumed. The observed products were regioisomeric mixtures of trifluoromethoxylated thiophenes, along with *di*-trifluoromethoxylated thiophenes and a mixture of polymers. The authors hypothesized that the polymers arise from the decomposition of the *di*-

substituted 2,5-dihydro thiophene, which is unstable at the reaction temperatures. The groups of Navarinni and Famulari generated the ·OCF_3 radical from perfluoro-methyl-hypofluorite and incorporated it into simple arenes such as chlorobenzene and anisole (Scheme 42).



Scheme 42: Radical trifluoromethoxylation and electrophilic fluorination of arenes by $FOCF_3$ from the groups of Navarinni and Famulari in 2012.[76b, 76c]

The authors state, however, that there is always a competition between radical trifluoromethoxylation and electrophilic fluorination of the arene. While electron-rich substrates such as anisole preferably underwent electrophilic fluorination, other substrates such as chlorobenzene reacted via both pathways to a similar extent. In both cases, regioisomeric mixtures of products were obtained. By adding a perfluoro olefin during the reaction, the yield of the trifluoromethoxylated product could be increased. The authors hypothesized that the perfluoro olefin can both facilitate single electron transfer onto CF_3OF and scavenge the released fluoride. Without the perfluoro olefin, the arene itself is the only possible radical activator.

Recently, there have been breakthroughs in the area of radical trifluoromethoxylation by the groups of Ngai and Togni.[77] These new methods allow for the late-stage functionalization of drugs or agrochemicals. Essential for this breakthrough was the development of solid *N*-OCF_3 reagents that were able to selectively deliver ·OCF_3 radicals after activation by SET. These reagents are all synthesized from the corresponding *N*-oxide using the Togni Reagent I (Figure 17). Both reagent classes can be activated under mild conditions using photocatalysis, although in 2020, the group of Ngai showed that 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) can be employed as the redox catalyst.[77] While this activation method does not require the use of light, the photocatalytic method features a slightly broader substrate scope, as aromatic carboxylic acids can also be used as substrates. For both activation methods, arenes substituted with halogens, benzoic acid esters, aldehydes, nitriles, nitro groups, amides, sulfonamides, and boronic acid esters were successfully converted, while some heteroarene classes were tolerated.

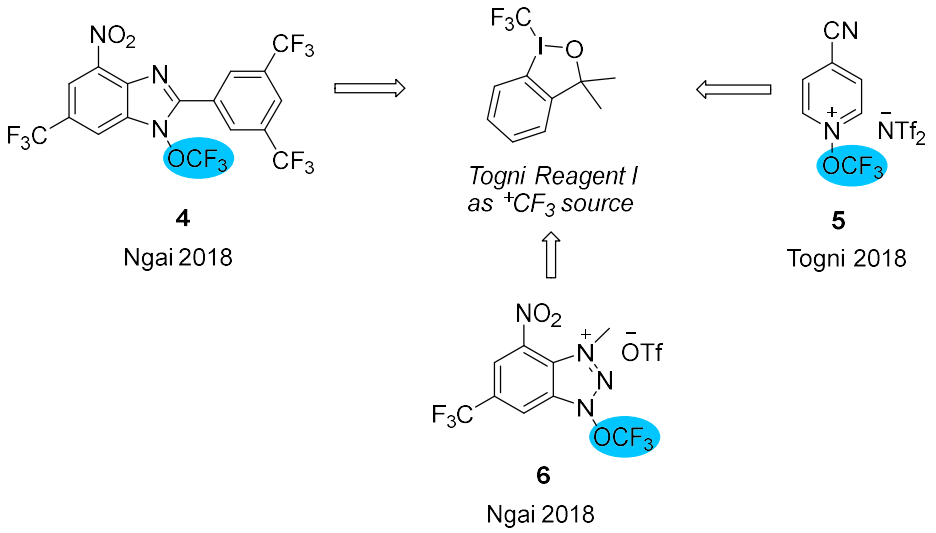
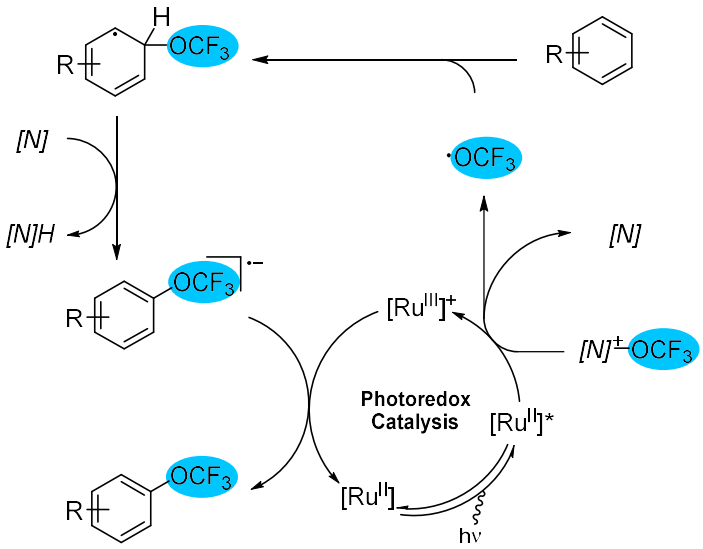


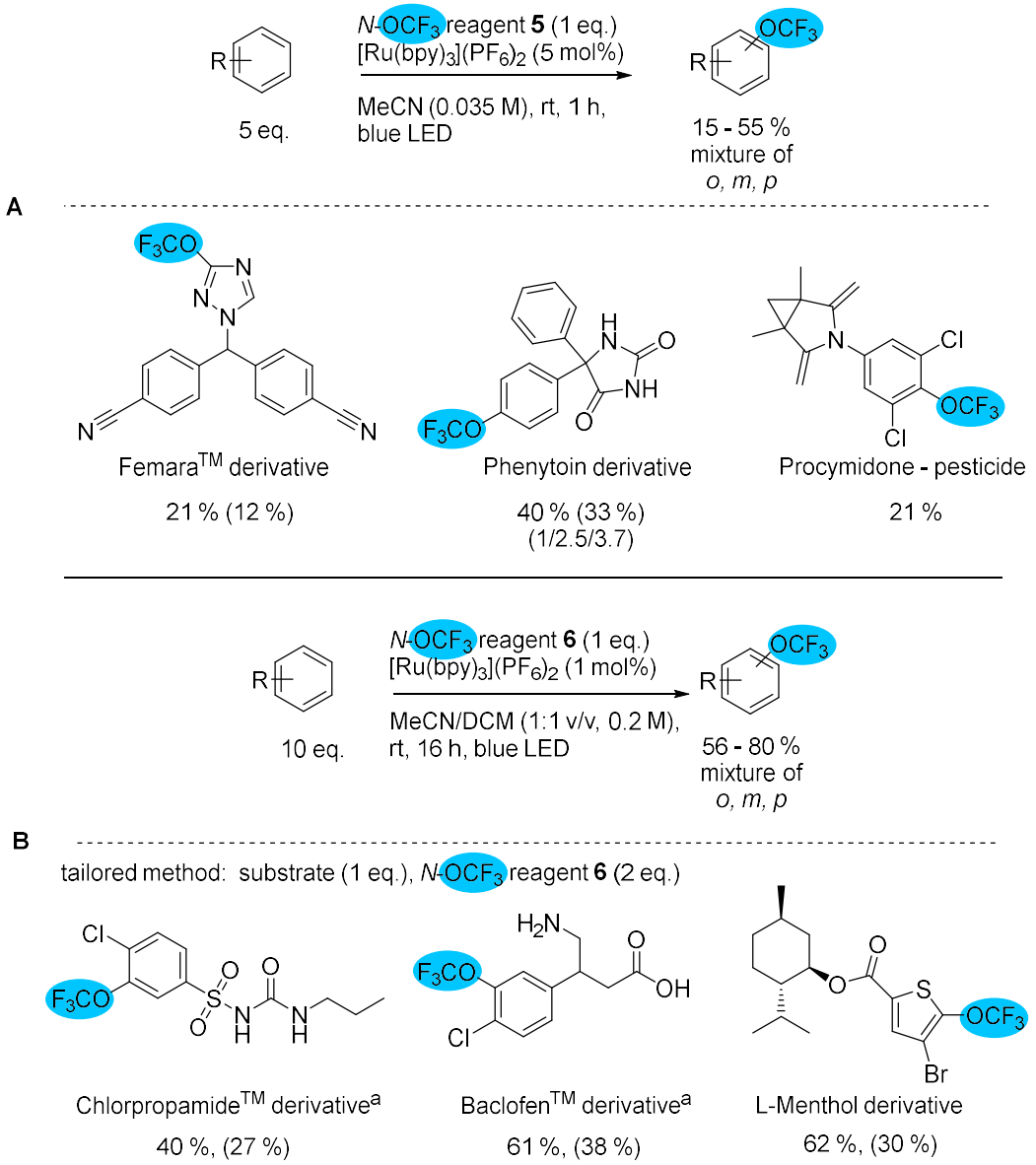
Figure 17: The novel radical trifluoromethoxylation reagents developed by the groups of Togni (reagent **5**) or Ngai (reagents **4** and **6**) are all dependent on the Togni Reagent I in their synthesis. [77a-c]

In the photocatalytic method, $[Ru^{II}(bpy)_3](PF_6)_2$ is first excited by visible light (Scheme 43). Oxidative quenching of the excited photocatalyst $[Ru^{II}]^*$ by reagent **5** or **6** affords a radical anion that can decompose through mesolysis into the $\cdot OCF_3$ radical and a neutral *N*-heteroarene. For reagent **4**, direct homolysis of the N-O bond under UVA light irradiation occurs, producing the desired $\cdot OCF_3$ radical and an *N*-heteroarene radical. The authors hypothesize that this intermediate could be further reduced under the photocatalytic conditions with the generated nitrogen anion later acting as a base. After the $\cdot OCF_3$ radical is generated *in situ,* addition to the (hetero)arene occurs in the next step. The obtained product radical is subsequently deprotonated by the previously generated *N*-heteroarene to afford the radical anion, which is then oxidized by $[Ru^{III}]^+$ to afford the product and complete the photocatalytic cycle. It is still a matter of debate in the literature regarding whether the deprotonation of a product radical occurs before the oxidation or *vice versa,* and all assumptions are based on calculations.[78] Side reactions for Togni's reagent **5** include the insertion of the $\cdot OCF_3$ radical into the neutral *N*-heteroarene which is generated during the reaction. However, this is just a minor side reaction. A side reaction for the first Ngai's reagent **4** is *N*-arylation of the substrate: after homolysis of the reagent, the formed *N*-heteroarene radical can also react with the arene substrate. For Ngai's reagent **6**, these side reactions could be successfully prevented, as it undergoes mesolysis after activation by SET and delivers a neutral *N*-heteroarene that is not susceptible to subsequent $\cdot OCF_3$ radical addition.



Scheme 43: The overall mechanism for photocatalytic methods using Ngai's reagent **6** and Togni's reagent **5**. Notably Ngai's Reagent **4** is neutral initially and becomes protonated (as [*N*]H) after the reaction.[77a, 77b]

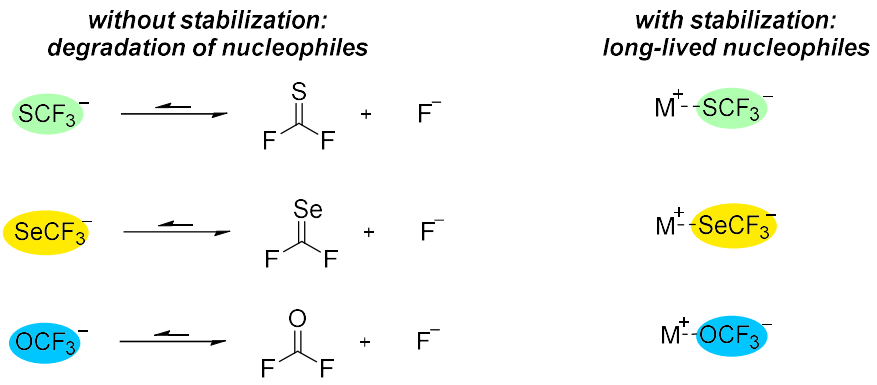
Both groups demonstrated that their reagents could be used for the late-stage functionalization of pharmaceuticals and agrochemicals by successfully employing HPLC techniques to separate the regioisomeric product mixtures (Scheme 44). The fact that regioisomers are often gained as a product mixture is beneficial, as several derivatives for biological tests can be obtained from a single reaction. However, a general drawback of these methods is that high amounts of substrates are required. Usually, 5 to 10 equivalents are needed to prevent over-oxidation. Interestingly, the group of Ngai presented an adapted method where only one equivalent of the substrate was required. Therefore, the major drawback about those new methods is the expensive trifluoromethoxylation reagents, as they are all synthesized from Togni's trifluoromethylation reagent.



Scheme 44: Trifluoromethoxylation of (hetero)arenes by the groups of Togni (A) and Ngai (B). The given yields are ^{19}F-NMR yields based on the internal standard trifluorotoluene. Isolated yields are given in brackets. [a] MeCN was used as the solvent[77a, 77b]

6 Scientific Goal

The overall goal of this project is to develop new synthetic methods that improve access to valuable organofluorine compounds. These organofluorine compounds can, for example, bear trifluoromethylchalcogen groups such as SCF_3, $SeCF_3$, or OCF_3. As part of this work, a focus is placed on the introduction and exploration of new reagents that serve as practical sources of these groups for applications in nucleophilic, electrophilic or radical reactions. For the nucleophilic approach, the corresponding nucleophiles $^-SCF_3$, $^-SeCF_3$, and $^-OCF_3$ should be stabilized by covalent or non-covalent interactions to counter the degradation to fluoride and the corresponding fluorophosgenes (Scheme 55).



Scheme 55: Stabilization of trifluoromethylchalcogenate nucleophiles counters their degradation

The developed methods should be optimized to achieve the highest possible transfer rate – in other words, a high fluorine atom economy. In addition, the mechanism of the reaction should be accordingly investigated. Furthermore, the literature should be studied to identify current synthetic challenges that can be addressed by the developed methods. For example, the number of synthetic steps to access valuable organofluorine compounds could be reduced and the cost lowered, while hitherto unsuitable yet easily accessible substrates could be employed for the first time. Finally, the synthetic procedure of newly synthesized reagents should be improved to achieve the highest possible yield and cost-efficiency.

7 Publications

7.1 Deoxytrifluoromethylthiolation and Selenylation of Alcohols by Using Benzothiazolium Reagents

Stefan Dix, Michael Jakob and Matthew N. Hopkinson

Chem. Eur. J. **2019**, *25*, 7635-7639.

https://doi.org/10.1002/chem.201901607

7.1.1 Abstract

Aliphatic compounds substituted with medicinally important trifluoromethylthio (SCF_3) and trifluoromethylselenyl ($SeCF_3$) groups were synthesized directly from alcohols by using the new benzothiazolium salts BT-SCF_3 and BT-$SeCF_3$. These bench-stable fluorine-containing reagents are facile to use and can be prepared in two steps from non-fluorinated heteroaromatic starting materials. The metal-free deoxytrifluoromethylthiolation process using BT-SCF_3 proceeds under mild conditions and the similarly efficient trifluoromethylselenylation reactions using BT-$SeCF_3$ are, to the best of our knowledge, the first reported examples of this transformation.

7.1.2 Contribution of Authors

Prof. Dr. Matthew Hopkinson developed the concept for the BT-Reagents. Michael Jakob and I optimized the synthetic method and synthesized the BT-SCF_3 reagent. I adopted a trifluoromethylation protocol designed for thiols to synthesize the BT-$SeCF_3$ reagent. The majority of the screening reactions for the scope and the optimization were conducted by me. Twenty out of forty products were isolated by me. Prof. Dr. Matthew Hopkinson supervised the project and wrote the publication.

7.2 Fluorine-containing Compounds for Use as Nucleophilic Reagents for Transferring Functional Groups onto High Value Organic Compounds

Matthew N. Hopkinson, Stefan Dix

(Freie Universität Berlin), EP3677576, **2019;** (Freie Universität Berlin), WO2020141195, **2020**

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7.2.1 Abstract

Benzothiazolium salts have been developed as new reagents for installing valuable fluorine-containing functional groups onto organic molecules. Other derivatives of BT-SCF_3 were shown to have the same reactivity.

7.2.2 Contribution of Authors

Prof. Dr. Matthew Hopkinson developed the concept for the BT-Reagents. I synthesized, purified, and characterized derivatives of BT-SCF_3 and tested them in a benchmark reaction. In addition, I synthesized BT-$SeCF_2H$ and conducted a deoxydifluoromethylselenylation of a carboxylic acid. Prof. Dr. Matthew Hopkinson synthesized and characterized BT-R_F reagents.

7.3 Trifluoromethoxylation of (Hetero)arenes with Bis(trifluoromethyl) peroxide (BTMP)

Stefan Dix, Paul Golz, Jonas R. Schmid, Sebastian Riedel, Matthew N. Hopkinson

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7.3.1 Abstract

Trifluoromethoxylated (hetero)arenes are of great interest for several disciplines, especially in agro- and medicinal chemistry. Radical C-H trifluoromethoxylation of (hetero)arenes represents an attractive approach to prepare such compounds, but the high cost and low atom economy of existing $\cdot OCF_3$ radical sources makes them unsuitable for the large-scale synthesis of trifluoromethoxylated building blocks. Herein, we introduce bis(trifluoromethyl)peroxide (BTMP, CF_3OOCF_3) as a practical and efficient trifluoromethoxylating reagent that is easily accessible from inexpensive bulk chemicals. Using either visible light photoredox or TEMPO catalysis, trifluoromethoxylated arenes could be prepared in good yields under mild conditions directly from unactivated aromatics. Moreover, TEMPO catalysis allowed for the one-step synthesis of valuable pyridine derivatives, which have been previously prepared via multi-step approaches.

7.3.2 Contribution of Authors

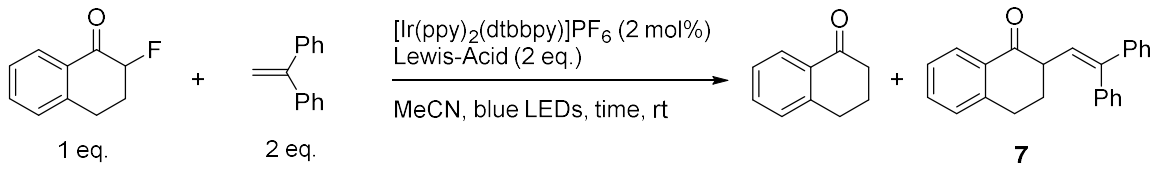
Jonas Schmid conducted early experiments and, most importantly, brought the Hopkinson and the Riedel group for this cooperation together. Paul Golz from the Riedel group supplied the BTMP reagent. I conducted literature research and developed the application strategy based on the weaknesses of the *de novo* synthetic methods in regard to (trifluoromethoxy)pyridines. Furthermore, I decided to investigate the impact of trifluoromethoxylation on the boiling point of substituted pyridines in order to verify if fractional distillation could be applied as a separation technique. All experiments for the optimization of the synthetic method and its scope, the choice of substrates, the separation of products, and their analysis were conducted by me. Prof. Dr. Matthew Hopkinson and Prof. Dr. Sebastian Hasenstab-Riedel supervised the project. The manuscript was written by me and revised by Prof. Dr. Matthew Hopkinson and Prof. Dr. Sebastian Hasenstab-Riedel.

8 Discussion of Unpublished Results

8.1 Photocatalytic C-F Activation of Organofluorine compounds

8.1.1 Photocatalytic C-F Activation of α-Fluorotetralone

The goal of this project was to explore visible light photocatalysis as an approach for achieving selective activation of C-F bond, providing organic radicals. To facilitate this step, Lewis acids were studied as additives capable of inducing LUMO lowering in the substrate through fluorine-specific interactions. Lithium tetrafluoroborate was initially used as the Lewis acid along with α-fluorotetralone as the substrate, $[Ir(ppy)_2(dtbbpy)]PF_6$ as the photocatalyst, 1,1-diphenylethylene as the coupling partner and MeCN as the solvent. After irrdiation with blue LEDs for 16 h, 17 % of the desired alkene **7** was obtained (Table 4, entry 2). This product is formed after several mechanistic steps, while the key step is the photocatalytic generation of the α-tetralone radical. To achieve this, LUMO lowering of α-fluorotetralone through fluorine-specific interactions with lithium tetrafluoroborate is required. The excited $[Ir^{II}(ppy)_2(dtbbpy)]^+$ photocatalyst can now efficiently conduct SET to α-fluorotetralone to generate the oxidized $[Ir^{III}(ppy)_2(dtbbpy)]^{2+}$ photocatalyst and the radical anion of α-fluorotetralone. After mesolysis, the α-tetralone radical is obtained and radical addition towards 1,1-diphenylethylene delivers the radical product. Oxidation of the radical product by the $[Ir^{III}(ppy)_2(dtbbpy)]^{2+}$ photocatalyst finally generates alkene **7** and completes the photocatalytic cycle by regenerating $[Ir^{II}(ppy)_2(dtbbpy)]^+$ in the ground state. Control experiments revealed that no product is obtained, if the reaction was conducted in the dark or if lithium tetrafluoroborate was absent. Lewis acids such as $La(OTf)_3$ or $AlCl_3$ were slightly less effective, while $TiCl_4$ showed the worst results with only 4 % yield of product **7** (Table 4, entry 12). The optimization study revealed that $La(NO_3)\cdot 6H_2O$ was the most effective Lewis acid for this transformation with product **7** being delivered in 50% yield (Table 4, entry 5). Other photocatalysts such as *fac*-$[Ir(ppy)_3]$ were less efficient, as they gave only 35 % yield of product **7**, compared to 50 % yield using $[Ir^{II}(ppy)_2(dtbbpy)]PF_6$ (Table 4, entry 5 and 13). Prolonging the reaction time from 16 h to 48 h increased the yield to 74 % (Table 4, entry 6).

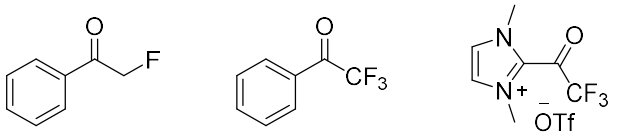


Scheme 56: Lewis acid-assisted photocatalytic C-F functionalization of α-fluorotetralone.

Table 4: The photocatalytic C-F activation of α-fluorotetralone employing Lewis acid additives. The shown yields are ^{1}H NMR yields based on the internal standard CH_2Br_2. [a] Experiment was conducted by Prof. Dr. Matthew Hopkinson. [b] Experiment was conducted by Patrick Voßnacker as part of his research internship under my supervision. [c] Reaction was conducted in the dark.

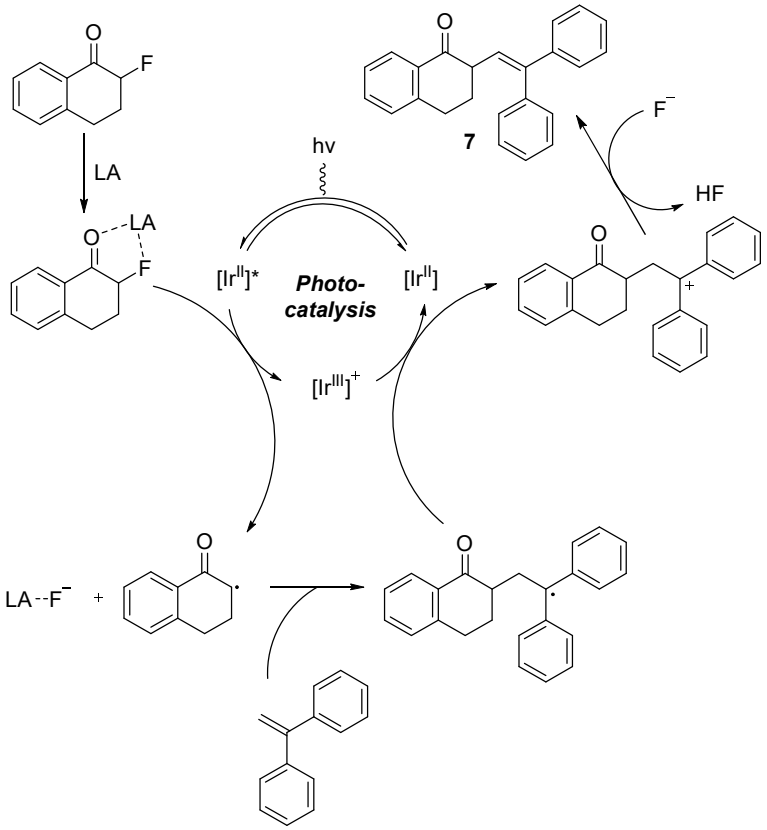
Entry	Photocatalyst (2 mol %)	Lewis Acid	Time [h]	Solvent (0.2 M)	Yield of α-Tetralone	Yield of Product
1	$[Ir(ppy)_2(dtbbpy)]PF_6$	-	16	MeCN	0 %	0 %
2	$[Ir(ppy)_2(dtbbpy)]PF_6$	$LiBF_4$ (2 eq.)	16	MeCN	traces	17 %
3[c]	$[Ir(ppy)_2(dtbbpy)]PF_6$	$LiBF_4$ (2 eq.)	16	MeCN	traces	0 %
4	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	$LiBF_4$ (2 eq.)	16	MeCN	0 %	0 %
5[c]	$[Ir(ppy)_2(dtbbpy)]PF_6$	$La(NO_3)_3{\cdot}6H_2O$ (2 eq.)	16	MeCN	0 %	50 %
6[b]	$[Ir(ppy)_2(dtbbpy)]PF_6$	$La(NO_3)_3{\cdot}6H_2O$ (2 eq.)	48	MeCN	0 %	74 %
7	$[Ir(ppy)_2(dtbbpy)]PF_6$	$La(NO_3)_3{\cdot}6H_2O$ (7 mol %)	16	MeCN	0 %	26 %
8[a]	-	$La(NO_3)_3{\cdot}6H_2O$ (2 eq.)	16	MeCN	0 %	0 %
9[a]	$[Ir(ppy)_2(dtbbpy)]PF_6$	$La(OTf)_3$ (2 eq.)	16	MeCN	2 %	19 %
10[a]	$[Ir(ppy)_2(dtbbpy)]PF_6$	$La(OTf)_3$ (2 eq.)	16	DCM	6 %	43 %
11	$[Ir(ppy)_2(dtbbpy)]PF_6$	$AlCl_3$ (2 eq.)	16	MeCN	3 %	30 %
12	$[Ir(ppy)_2(dtbbpy)]PF_6$	$TiCl_4$ (2 eq.)	16	MeCN	0 %	4 %
13[a]	*fac*-$[Ir(ppy)_3]$	$La(NO_3)_3{\cdot}6H_2O$ (2 eq.)	16	MeCN	5 %	35 %

There are three possible explanations for the role of the Lewis acid in these reactions. First, it is reported that Lewis acids can lower the reduction potential of substrates via LUMO lowering, and therefore facilitate the reduction of the substrate with the excited photocatalyst.[79]



Scheme 57: Substrates that did not generate any product in the Lewis acid assisted and photocatalytic C-F functionalisation.

Second, the Lewis Acid could possibly stabilize the reduced substrate, preventing back electron transfer, and third, it could facilitate the mesolysis step by stabilizing the eliminated fluoride anion. However, the scope for the shown method is very limited.



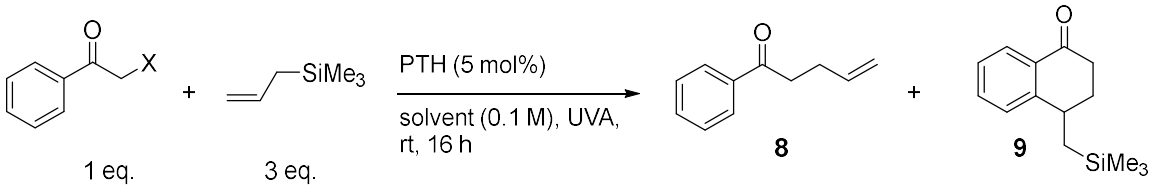
Scheme 58: Mechanistic hypothesis describing formation of alkene **7.**

With substrates such as 2-fluoroacetophenone, trifluoroacetophenone and 1,3-dimethyl-2-(2,2,2-trifluoroacetyl)-1*H*-imidazol-3-ium trifluoromethanesulfonate, no product was detected at all.

The situation is similar with the scope of coupling partners. Several styrenes and allyl silanes were tested without any product being detected. The Lewis acid additive was found to be detrimental with these substrates as undesired decomposition or polymerizationof the allyl silane or styrene often dominated. While the exact mechanism for the formation of alkene **7** is unclear, a mechanistic hypothesis is suggested (Scheme 58). First, α-fluorotetralone will get coordinated by the Lewis Acid. The coordination lowers the LUMO of α-fluorotetralone. Afterwards, a photocatalyst such as $[Ir^{II}(ppy)_2(dtbbpy)]PF_6$ will be excited by irradiation with visible light and SET occurs from the excited $[Ir^{II}]$* to the coordinated α-fluorotetralone to generate a radical anion. This radical anion undergoes mesolysis to yield fluoride and the desired substrate radical. In the next step, radical addition between 1,1-diphenylethylene and the substrate radical takes place. The recently formed product radical will now be oxidized by $[Ir^{III}]$ to yield a carbenium ion and $[Ir^{II}]$. Deprotonation of this carbenium ion by fluoride finally leads to the desired alkene **7**.

8.1.2 Photocatalytic C-F Activation of α-Fluoroacetophenone

In a further development of the aforementioned synthetic method, the more reducing photocatalyst 10-phenylphenothiazine (PTH) was employed. This photocatalyst is able to reduce the α-fluorinated carbonyl substrates more easy than the previously employed iridium(III)-based complexes such that LUMO lowering mediated by Lewis acids is no longer required. The avoidance of Lewis acids in turn allows for the use of other coupling partners such as allyl silanes. As shown in Table 5, under these conditions, a small range of α-haloacetophenone substrates were also tolerated (Scheme 59, Table 5). The desired alkene **8** was obtained in acceptable yields. Interestingly, the unexpected cyclization side-product silane **9** was also obtained. Both products were not observed in the absence of photocatalyst or light (Table 5, entry 6 and 7). The product distribution of alkene **8** and the silane **9** can be influenced by using different α-haloacetophenones. While α-bromoacetophenone only gave silane **9** in 4 % yield, it can be obtained in 14 % yield when using α-chloroacetophenone or in 28 % yield when using α-fluoroacetophenone (Table 5, entry 1, 2 and 3). Furthermore, using DMSO instead of MeCN as solvent increased the yield of silane **9** to 60 % (Table 5, entry 4). Using DCM as the solvent supressed formation of silane **9**, which was obtained in only 12 % yield (Table 5, entry 5). However, under the same conditions the yield of alkene **8** was increased to 69 %. While the exact mechanism for the formation of alkene **8** and silane **9** is unclear, a mechanistic hypothesis is suggested (Scheme 60). The photocatalyst PTH will be excited by irradiation with UVA light and SET occurs from the excited PTH* to α-fluoroacetophenone to generate a radical anion.

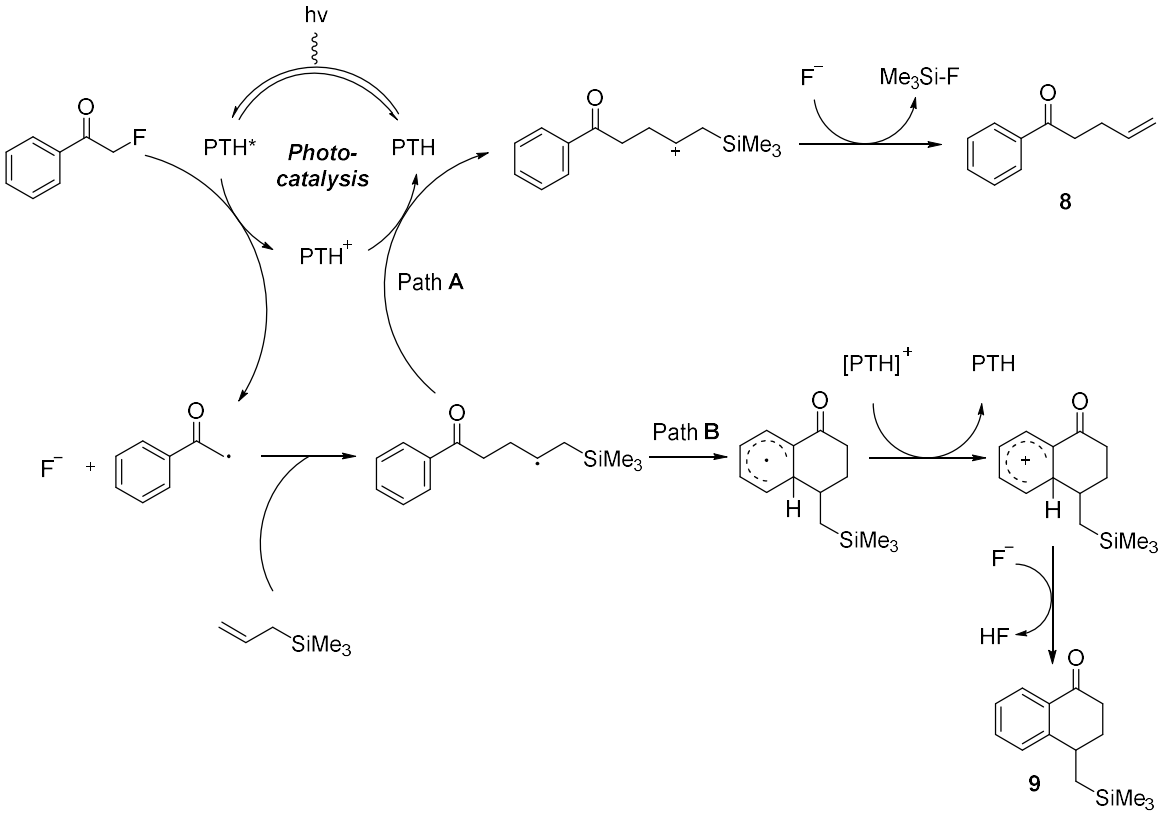


Scheme 59: C-X activation of α-haloacetophenones (X = F, Cl, Br).

Table 5: A chosen set of reaction conditions for the C-X activation of α-haloacetophenones (X = F, Cl, Br). The shown yields are ^{1}H NMR yields based on the internal standard CH_2Br_2. [a] Experiment was conducted by Prof. Dr. Matthew Hopkinson. [b] reaction was conducted in the dark. [c] Allyl silane (2 eq. instead of 3 eq.) was used. [d] No PTH was used.

Entry	Substrate	Solvent (0.1 M)	Scale	Yield of Alkene 8	Yield of Silane 9
1	α-fluoroacetophenone	MeCN	0.3 mmol	42 %	28 %
2	α-chloroacetophenone	MeCN	0.3 mmol	30 %	14 %
3	α-bromoacetophenone	MeCN	0.3 mmol	51 %	4 %
4[a]	α-fluoroacetophenone	DMSO	0.1 mmol	19 %	60 %
5[a]	α-fluoroacetophenone	DCM	0.1 mmol	69 %	12 %
6[a,b,c]	α-fluoroacetophenone	MeCN	0.1 mmol	0 %	0 %
7[a, c, d]	α-fluoroacetophenone	MeCN	0.1 mmol	0 %	0 %

This radical anion undergoes mesolysis to yield fluoride and the desired substrate radical. In the next step, radical addition between allyl silane and the substrate radical takes place. From now on two pathways are possible. The recently formed product radical can either be oxidized by PTH^+ directly to yield a carbenium ion or an intramolecular radical addition occurs to yield a bicyclic product radical. In the former case, nucleophilic attack by fluoride on the silicon atom of the carbenium ion will lead to formation of alkene **8** and trimethylsilyl fluoride. In the latter case, the bicyclic product radical will be oxidized by PTH^+ to form a bicyclic carbenium ion. Finally, the bicyclic carbenium ion will be deprotonated by fluoride and silane **9** as well as HF are obtained.



Scheme 60: Mechanistic hypothesis describing the formation of alkene **8** and silane **9**.

Both products, alkene **8** and silane **9**, were isolated and characterized. The characterization data of alkene **8** agrees with literature values.[80] In contrast, silane **9** was reported for the first time and sufficient analytical data was gathered to confirm the chemical structure. The HRMS-EI spectra shows $[M]^+$, as well as the fragment $[M\text{-}CH_3]^+$ and therefore confirms the chemical formula $C_{12}H_{20}OSi$. The ^1H NMR spectrum shows the corresponding signals to the four aromatic protons in the range of 8.0 to 7.2 ppm (Figure 18). Signals of the aromatic CH groups 8 and 5 are observed as doublets, while the signals of the aromatic CH groups 7 and 6 are observed as triplets. Notably, the doublet of group 5 and the triplet of group 6 overlap. The multiplet at 3.12 ppm corresponds to the aliphatic CH group 4, which couples with the H atoms of the aliphatic CH_2 groups 3 and 9. The protons of the aliphatic CH_2 groups 2 and 3 correspond to the detected multiplets at 2.81, 2.59, 2.28 and 1.98 ppm. These protons exhibit typical vicinal coupling as well as geminal coupling and are therefore detected as complex multiplets. The protons of the CH_2 group 9 correspond to the complex signal in the range of 1.08 to 0.99 ppm (Figure 19). Those protons undergo geminal coupling with a coupling constant of $^2J_{HH}$ = 15.01 Hz, while each proton couples to the proton of the CH group 4 with different coupling constants of $^3J_{HH}$ = 9.31 and $^3J_{HH}$ = 5.51 Hz.

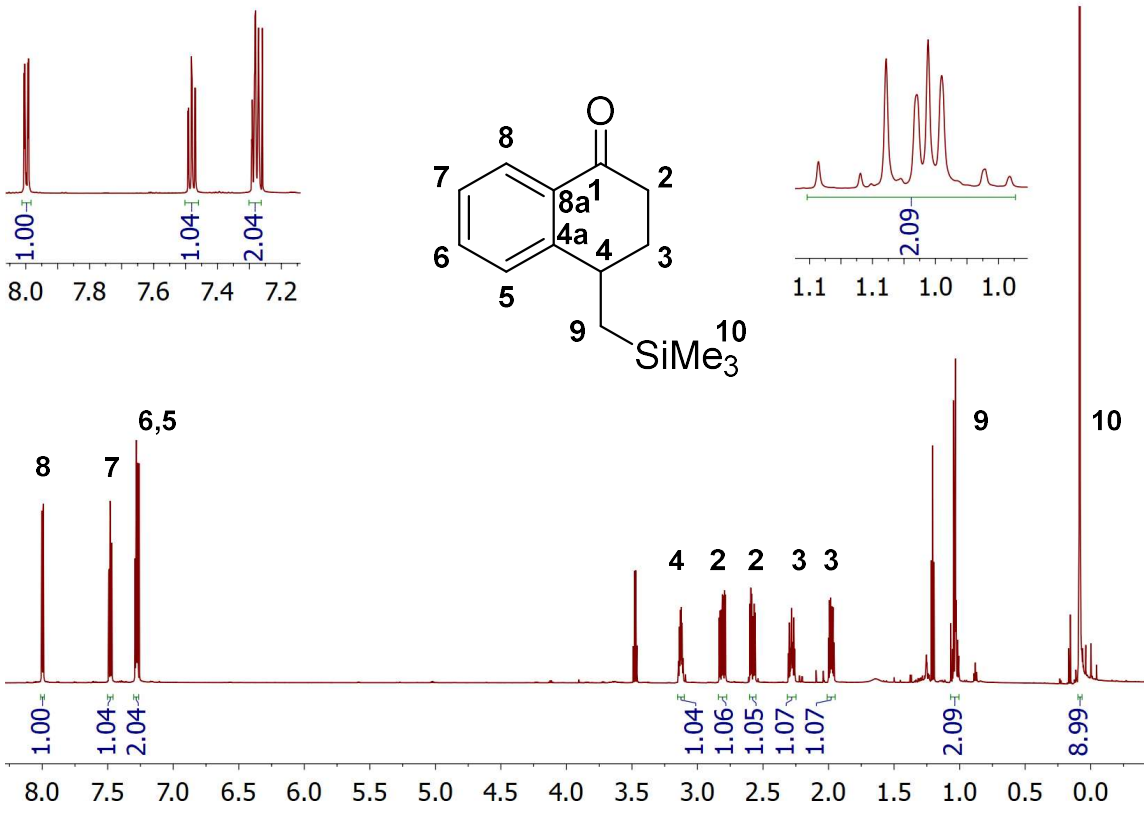


Figure 18: ^{1}H NMR spectra of 4-((trimethylsilyl)methyl)-3,4-dihydronaphthalen-1(2H)-one (**9**) in $CDCl_3$.

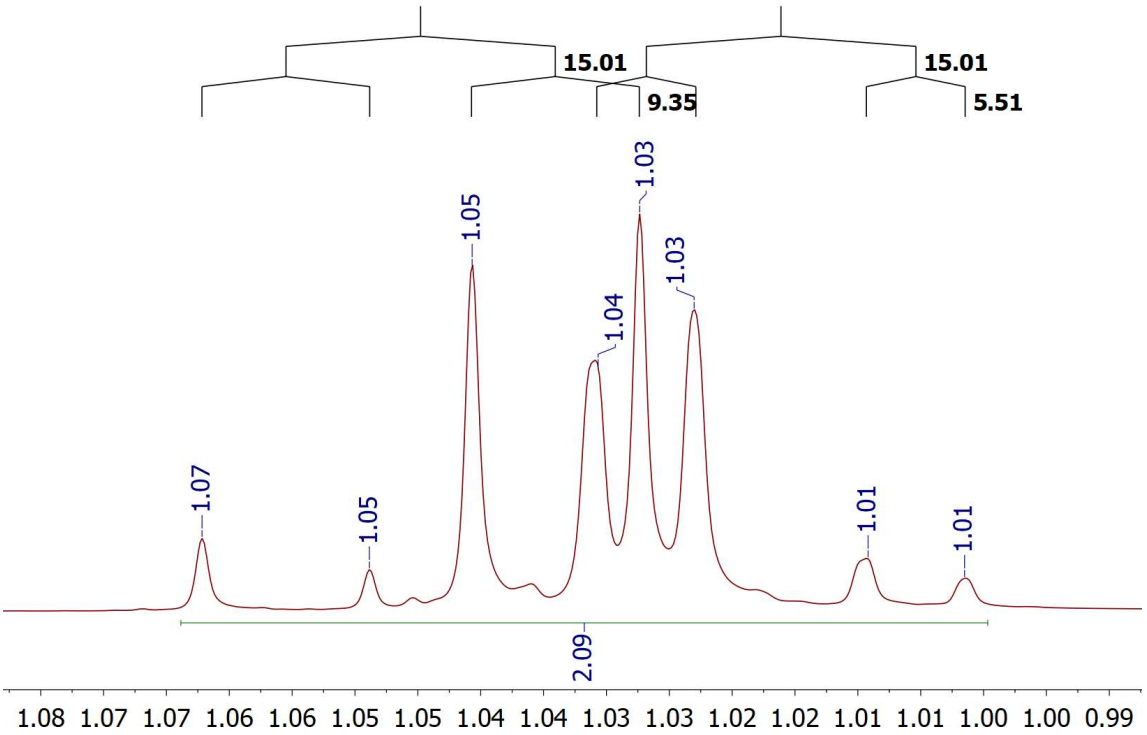


Figure 19: ^{1}H NMR spectra extract in the range of 1.08 to 0.99 ppm of 4-((trimethylsilyl)methyl)-3,4-dihydronaphthalen-1(2H)-one (**9**) in $CDCl_3$. The shown signals correspond to the CH_2 group 12.

This is a result of the chiral center at position 4 – the protons of the CH_2 group at position 9 are no longer chemically and magnetically equivalent. Therefore, the complex signal consists of two overlapping doublets of triplets that are affected by a strong roof effect. At 0.08 ppm a singlet can be observed, which corresponds to the CH_3 groups at position 10. The chemical shift value is common for methyl groups that are adjacent to silicon atoms. Overall, signals that correspond to 20 H atoms were assigned. The two signals at 3.48 and 1.21 ppm which were not discussed correspond to the CH_2 and CH_3 groups of the residual solvent diethyl ether.

The ^{13}C NMR spectra shows twelve signals of interest that correspond to the carbon atoms of 4-((trimethylsilyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (Figure 20). The methyl groups at position 10 that are adjacent to the silicon atom are chemically equivalent and therefore the signals that correspond to the carbon atoms appear together at -0.6 ppm. The carbon atoms that belong to the CH_2 groups 3, 2, 9 and the aliphatic CH group 4 correspond to the four signals at 35.1, 34.8, 29.5 and 23.6 ppm. The signals at 133.7, 127.9, 127.4 and 126.5 ppm correspond to the tertiary carbon atoms of the aromatic CH groups 5, 6, 7 and 8. The quaternary carbon atoms of the aromatic CH groups 4a and 8a correspond to the signals at 151.1 and 131.6 ppm. The signal at 198.6 ppm corresponds to the carbon atom 1 of the carbonyl group. Overall, ^{1}H and ^{13}C NMR data, as well as HRMS-EI results confirm the chemical structure of silane **9**.

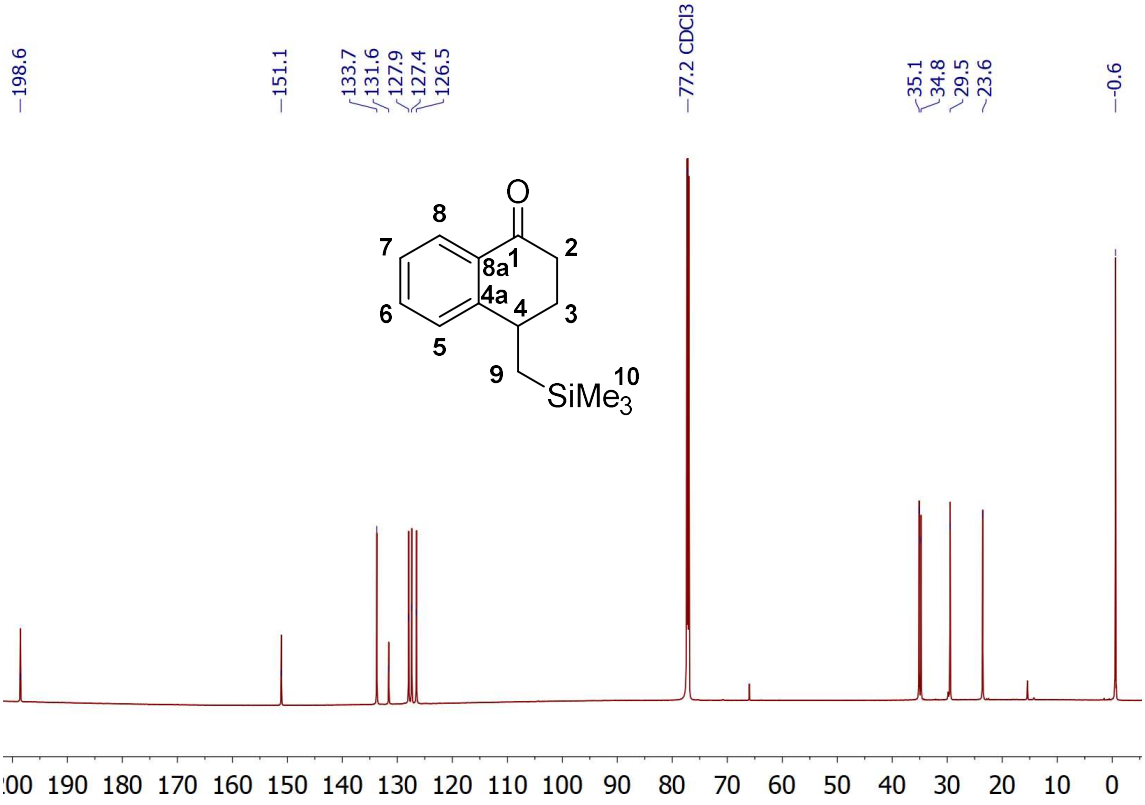
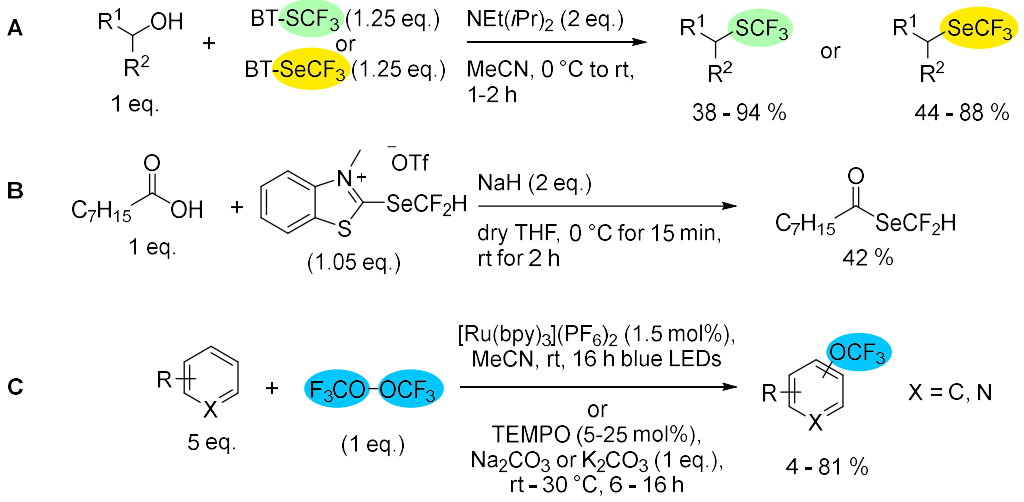


Figure 20: ^{13}C NMR spectra of 4-((trimethylsilyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (**9**) in $CDCl_3$.

9 Conclusions and Outlook

In summary, three synthetic methods have been developed that make trifluoromethylchalcogenated compounds easier to synthesize and access. These include the deoxytrifluoromethylthiolation and deoxytrifluoromethylselenylation of alcohols, the deoxydifluoromethylselenylation of carboxylic acids, and the trifluoromethoxylation of (hetero)arenes (Scheme 61). In addition, methods for the C-F activation of α-fluoroketones were investigated.



Scheme 61: The developed methods include deoxytrifluoromethylthiolation and deoxytrifluoromethylselenylation of alcohols (A), as well as deoxydifluoromethylselenylation of carboxylic acids (B) and trifluoromethoxylation of (hetero)arenes (C).

The deoxytrifluoromethylthiolation of primary and secondary alcohols proceeds without any source of metal salt as a stabilizer for the $^{-}SCF_3$ anion. As the choice of the base greatly influenced the yield of the product, the *in situ* generated protonated base possibly stabilizes the $^{-}SCF_3$ anion until the nucleophilic attack on the active electrophile is achieved. For example, using NEt(*i*Pr)$_2$ as base instead of NEt_3 or Cs_2CO_3 doubles the yield of (4-phenylbutyl)(trifluoromethyl)sulfane from 42 % to 77 %. The deoxytrifluoromethylselenylation of primary and secondary alcohols proceeds similarly to the deoxytrifluoromethylthiolation. This method represents the first published procedure for the direct deoxytrifluoromethylselenylation of alcohols. The deoxydifluoromethylselenylation of carboxylic acids was adapted from a published procedure developed in the Hopkinson group.[81]

The developed radical trifluoromethoxylation of (hetero)arenes is the first method to use the gas BTMP efficiently in a photocatalyzed or TEMPO-catalyzed protocol. Using BTMP is a great advantage, as all other methods to directly synthesize trifluoromethoxylated (hetero)arenes, rely either on the expensive Togni I or Togni II reagent. BTMP, on the other hand, can be synthesized

from the inexpensive bulk compounds COF_2 and F_2. Furthermore, *de novo* methods are cumbersome and step-intensive for many (trifluoromethoxy)pyridines, as only α-chloro(trichloromethoxy)pyridines can be completely fluorinated. This leads to long synthetic pathways, for example, 5-(trifluoromethoxy)picolinonitrile has to be synthesized in 6 to 9 steps – whereas the direct method developed in this work can access the same compound in a single step. Moreover, (hetero)aromatic amines were for the first time successfully used as starting materials in radical trifluoromethoxylation by the judicious choice of electron-deficient substrates. Before this work, unsuccessful attempts with electron-rich aromatic amines were reported in the literature by the group of Togni[77b]. Having obtained similarly unsuccessful results with anisole, the group of Ngai suggested that a side reaction occurs between electron-rich (hetero)arenes and the $\cdot OCF_3$ radical, which leads to oxidation of the (hetero)arenes and formation of the $^-OCF_3$ anion.

Several reagents were synthesized to conduct the deoxytrifluoromethylthiolation and deoxytrifluoromethylselenylation of alcohols, and the deoxydifluoromethylselenylation of carboxylic acids (Figure 21). For the synthesis of BT-SCF_3 derivatives, a two-step procedure was developed, starting with the trifluoromethylation of the substrate and methyl- or ethylation in the second step, to receive the BT-SCF_3 derivative. While the original synthetic procedure for the trifluoromethylation step used the expensive sodium trifluoromethanesulfinate as a CF_3 source for the trifluoromethylation step, the optimized synthetic procedure used the cheap CF_3I as trifluoromethylation reagent. In addition, the base NaH was exchanged with the inexpensive and less hazardous base NaOH. Furthermore, the solvent mixture MeCN/H_2O was employed to overcome the cumbersome work-up procedure when using DMF as a solvent.

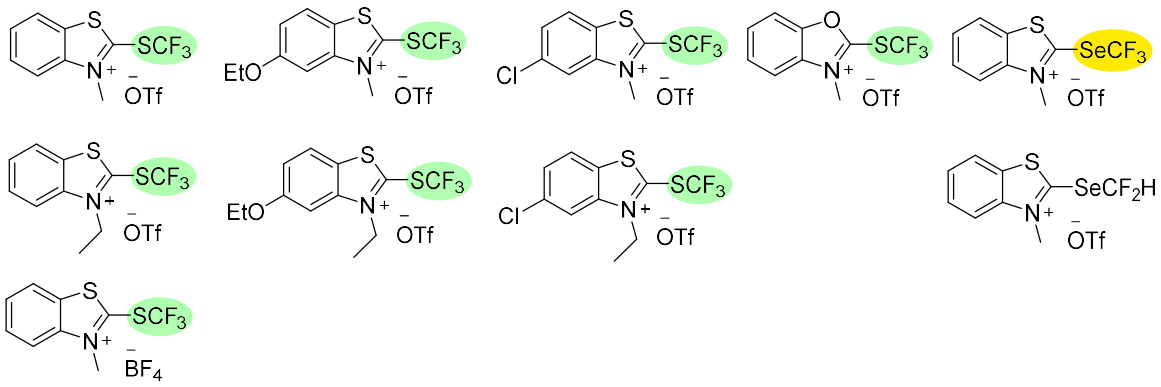


Figure 21: The synthesized reagents range from methyl- or ethylated benzothiazole to benzooxazole salts that bear the covalently bound SCF_3, $SeCF_3$, or $SeCF_2H$ group. They were prepared either as triflate or tetrafluoroborate salts.

All BT-SCF_3 triflate salt derivatives showed excellent reactivity in a deoxytrifluoromethylthiolation reaction, while the tetrafluoroborate salt gave very good yields, and the benzooxazole derivative

only fair yields. BT-$SeCF_3$ and BT-$SeCF_2H$ were both synthesized in a two-step procedure starting from *bis*(benzothiazole)diselenide. The first step included the reduction of the diselenide under oxygen-free conditions to afford the selenoate. The selenoate was either trifluoromethylated using CF_3I or difluoromethylated using difluoromethyl trifluoromethanesulfonate. In the second step, the compounds were methylated using methyl trifluoromethanesulfonate to generate the desired salt.

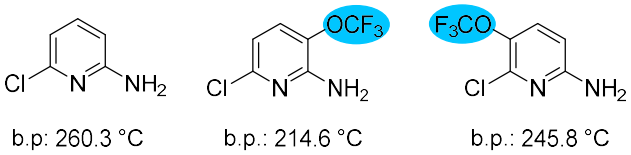
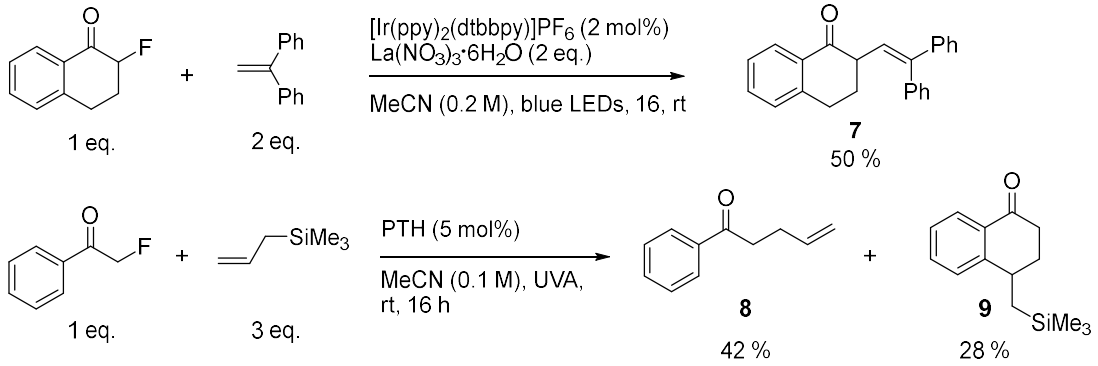


Figure 22: The observed boiling point lowering via trifluoromethoxylation is up to 46.3 °C.

Future work should focus on the application of BTMP in other synthetic methods. Most importantly, the observed boiling point lowering of up to 46.3 °C for trifluoromethoxylated 6-chloropyridine-2-amines should be further investigated (Figure 22). Knowledge about possible intramolecular fluorine-specific interactions could help in developing better boiling point prediction. In conclusion, it would be easier to identify if radical procedures can solve synthetic challenges – if the regioisomeric products can be separated via fractional distillation, this can be a promising synthetic approach.



Scheme 62: C-F activation of α-fluorotetralone and α, α, α -trifluoroacetophenone was investigated. The shown yields are ^1H NMR yields based on the internal standard CH_2Br_2.

In addition, C-F activation of α-fluorotetralone and α-fluoroacetophenone was investigated (Scheme 62). The C-F activation of α-fluoroacetophenone is a more advanced method, as no Lewis acids are required for product formation, and therefore coupling partners such as allyl silanes can be employed. Most importantly, two distinct products **8** and **9** are obtained and the product distribution can be controlled. For example, using α-fluoroacetophenone in DMSO gave the highest

yield of silane **9** (60 %), while α-bromoacetophenone in MeCN gave the lowest yield of silane **9** (4 %). However, the mechanism for the formation of silane **9** is not fully understood, and mechanistic experiments should be conducted in the future. In particular, the role of the fluorine in facilitating the cyclization process leading to **9** or alternatively disfavoring elimination leading to **8**, potentially through fluorine-specific interactions, should be determined.

10 Supporting Information

10.1 General Information

Solvents were purified either with the solvent purification system MB-SPS-800 (Braun) or by manual distillation over standard drying agents. The dried solvents were then stored over molecular sieves or transferred under argon. Blue light irradiation was provided by LED strips (λ_{max} = 440 nm, IP65) purchased from PB Versand GmbH (Type: 5630). The reaction vessel was placed at the center of a crystallization flask wrapped with the LED strips (distance from the flask to the LEDs ~ 5 cm). UVA light irradiation was provided by a LED lamp (λ_{max} = 365 nm, IP65). The photocatalysts $[Ir(ppy)_2(dtbbpy)]PF_6$,[82] *fac*-$[Ir(ppy)_3]$[83] and $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$[84] were prepared according to literature procedures. The compound α-fluorotetralone was also prepared according to literature procedures.[85] $NEt(iPr)_2$ was refluxed over KOH, distilled and stored over molecular sieves prior to use. All other employed compounds were purchased from commercial suppliers and used as received. Reactions to study C-F Activation were performed in degassed solvent under an atmosphere of argon. Flash chromatography was performed using silica gel M60 from Macherey & Nagel (particle size: 40-63 µm) or by use of the Claricep S-Series Flash columns from Bonna-Agela Technologies Inc. (spherical silica gel, 60 Å, particle size 20-35 µm). A Flash chromatography device of Büchi Labortechnik GmbH was used, consisting of Pump module C-605, UV-Photometer C-635, Control Unit C-620 and Fraction Collector C-660.

10.2 Nuclear Magnetic Resonance Spectrometry

NMR spectra were acquired on a JEOL ECX 400 (400 MHz), JEOL ECP 500/ Bruker Avance 500 (500 MHz), Varian INOVA 600 (600 MHz) or a Bruker Avance 700 (700 MHZ) in $CDCl_3$ or CD_3CN as a solvent. Chemical shifts (δ) are quoted in ppm downfield of tetramethylsilane. The residual solvent signals were used as references for ^1H and ^{13}C NMR spectra. ^{19}F NMR spectra are not calibrated by an internal reference if deuterated solvent was used. Coupling constants (*J*) are quoted in Hz. ^1H NMR yields were calculated by using CH_2Br_2 as an internal standard.

10.3 High Resolution Mass Spectrometry

Mass spectra were obtained on a ESI-FTICR-MS: Ionspec QFT-7 (Agilent/Varian) or on a HR-EI-MS: Waters Autospec Premier with Agilent 7890B GC. Infrared spectra were measured on a JASCO FT/IR-4100 Spectrometer. Characteristic absorption bands are displayed in wavenumbers $\tilde{\nu}$ in cm^{-1} and were analysed with the software Spectral Manager from JASCO.

10.4 Methods for the C-F Activation of α-Fluoroketones

10.4.1 General Method for the C-F Activation of α-Fluorotetralone

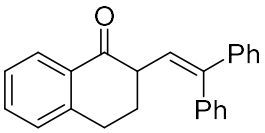
A Schlenk glass tube was charged with a stir bar, photocatalyst (2 mol %), Lewis acid (2 eq.), substrate (0.1 mmol), 1,1-diphenylethylene (2 eq.) and solvent (0.2 M). The mixture was degassed three times using the freeze-pump-thaw procedure. Afterwards the Schlenk tube was repressurized with argon. The Schlenk tube was stirred for 16 h at rt under irradiation of blue LEDs. Afterwards the mixture was concentrated *in vacuo*, internal standard dibromomethane (0.1 mmol) and $CDCl_3$ (0.6 mL) was added. The mixture was transferred into an NMR tube and the ^{1}H-NMR measurement was conducted.

10.4.2 General Method for the C-F Activation of α-Fluoroacetophenones

A Schlenk glass tube was charged with a stir bar, PTH (5 mol %), substrate (0.1 mmol), allylsilane (2 eq.) and solvent (0.1 M). The mixture was degassed three times using the freeze-pump-thaw procedure. Afterwards the Schlenk tube was repressurized with argon. The Schlenk tube was stirred for 16 h at rt under irradiation of UVA LEDs (λ_{max} = 365 nm). Afterwards the mixture was concentrated *in vacuo*, internal standard dibromomethane (0.1 mmol) and $CDCl_3$ (0.6 mL) was added. The mixture was transferred into an NMR tube and the ^{1}H-NMR measurement was conducted.

10.5 Synthesis and Characterization Data of Organic Compounds

10.5.1 2-(2,2-diphenylvinyl)-3,4-dihydronaphthalen-1(2H)-one (7)

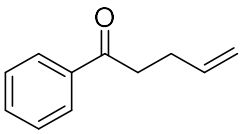


2-Fluoro-3,4-dihydronaphthalen-1(2H)-one (60.0 mg, 0.370 mmol, 1.0 eq.), ethene-1,1-diyldibenzene (128.0 µL, 0.730 mmol, 2.0 eq.), lithium tetrafluroborate (68.5 mg, 0.730 mmol, 2.0 eq.) and $Ir(ppy)_2(dtbbpy)PF_6$ (6.7 mg, 0.007 µmol, 2 mol%) were dissolved in MeCN (1 mL). The resulting solution was degassed three times using the freeze-pump-thaw procedure and stirred for 16 h under irradiation of blue LEDs. Afterwards the solvent was removed *in vacuo* and the crude product was purified by column chromatography (Pentane/EtOAc, SiO_2 with particle size 40-63 µm) to obtain alkene **7** (35.0 mg, 28%, 0.108 mmol) as a yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (d, *J*=7.8, 1H), 7.45 (dd, *J*=7.4, 1H), 7.39 – 7.18 (m, 12H), 6.18 (d, *J*=9.8, 1H), 3.43 – 3.32 (ddd, *J*=9.8, 9.9, 5.6, 1H), 3.03 – 2.89 (m, 2H), 2.23 – 2.08 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 198.9, 144.7, 144.0, 142.2, 139.8, 133.4, 132.6, 129.9, 128.8, 128.5, 128.2, 127.6, 127.6, 127.5, 127.4, 126.8, 126.5, 49.4, 30.8, 28.8.

This experiment and the purification of the product was conducted by Patrick Voßnacker. The characterization data agrees with literature values.[86]

10.5.2 1-phenylpent-4-en-1-one (8)

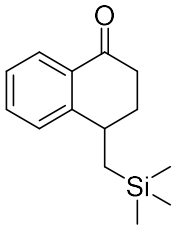


α-Fluoroacetophenone (59.9 µL, 0.5 mmol, 1.0 eq.), allyltrimethylsilane (128.0 µL, 1.5 mmol, 3.0 eq.) and PTH (6.9 mg, 25 µmol, 5 mol%) were dissolved in DCM (5 mL). The resulting solution was degassed three times using the freeze-pump-thaw procedure and stirred for 16 h under irradiation from UVA LEDs (λ_{max} = 365 nm). Afterwards the solvent was removed *in vacuo* and the crude product was purified by column chromatography (Pentane/DCM, SiO_2 spherical silica gel, 60 Å, particle size 20-35 µm) to obtain alkene **8** (26.4 mg, 33%, 0.17 mmol) as a colourless liquid.

^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 7.8, 2H), 7.55 (t, *J* = 7.4, 1H), 7.46 (dd, *J* = 7.8, 7.4, 2H), 5.94 – 5.87 (m, 1H), 5.09 (dtd (apparent dq), *J* = 17.1, 1.5, 1.5, 1.5 1H), 5.01 (dtd (apparent dq), *J* = 10.2, 1.3, 1.3, 1.3 1H), 3.07 (t, *J* = 7.3, 7.3, 2H), 2.50 (m, 2H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ = 199.5, 137.4, 137.1, 133.1, 128.7, 128.1, 115.4, 37.9, 28.3. **R_f** = 0.65 (*n*-Pentane/DCM**,** 2:15, (v/v)).

The characterization data agrees with literature values.[87]

10.5.3 4-((trimethylsilyl)methyl)-3,4-dihydronaphthalen-1(2H)-one (9)



α-Fluoroacetophenone (59.9 µL, 0.5 mmol, 1.0 eq.), allyltrimethylsilane (128.0 µL, 1.5 mmol, 3.0 eq.) and PTH (6.9 mg, 25 µmol, 5 mol%) were dissolved in DMSO (5 mL). The resulting solution was degassed (3 x freeze-pump-thaw) and stirred for 16 h under irradiation from UVA LEDs (λ_{max} = 365 nm). Afterwards Et_2O (20 mL) was added and the mixture was washed with water (5 x 10 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography in two steps (Pentane/DCM and Pentan/Et_2O, SiO_2 spherical silica gel, 60 Å, particle size 20-35 µm) to obtain silane **9** as a colourless liquid. The product yield cannot be provided due residues of diethyl ether, further concentration *in vacuo* was not possible because the overall amount of product was already strongly diminished.

^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.2 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.29 – 7.27 (m, 2H), 3.15 – 3.11 (m, 1H), 2.84 – 2.78 (m, 1H), 2.60 – 2.55 (m, 1H), 2.31 – 2.25 (m, 1H), 2.00 – 1.95 (m, 1H), 1.05 (dd, *J* = 15.0, 9.3, 1H), 1.02 (dd, *J* = 15.0, 5.5, 1H), 0.08 (s, 9H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ = 198.6, 151.1, 133.7, 131.6, 128.0, 127.4, 126.5, 35.1, 34.8, 29.5, 23.6, -0.6. **HRMS (EI)**: m/z calculated for $[C_{14}H_{20}OSi]^+$ ($[M]^+$): 232.1283, measured: 232.1292; m/z calculated for $[C_{13}H_{17}OSi]^+$ ($[M\text{-}CH_3]^+$): 217.1043, measured: 217.1054. **R_f** = 0.27 (*n*-Pentane/DCM**,** 2:15, (v/v)).

10.6 NMR Spectra of Novel Compounds

10.6.1 NMR Spectra of 4-((trimethylsilyl)methyl)-3,4-dihydronaphthalen-1(2H)-one (9)

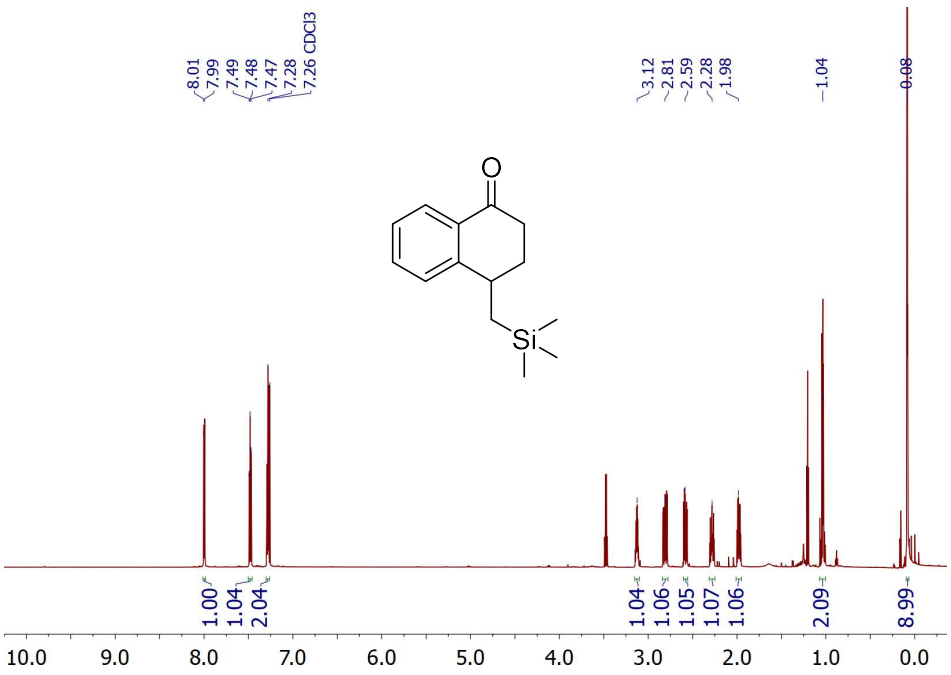


Figure S1. ^{1}H NMR spectra (700 MHz, $CDCl_3$) of **9**.

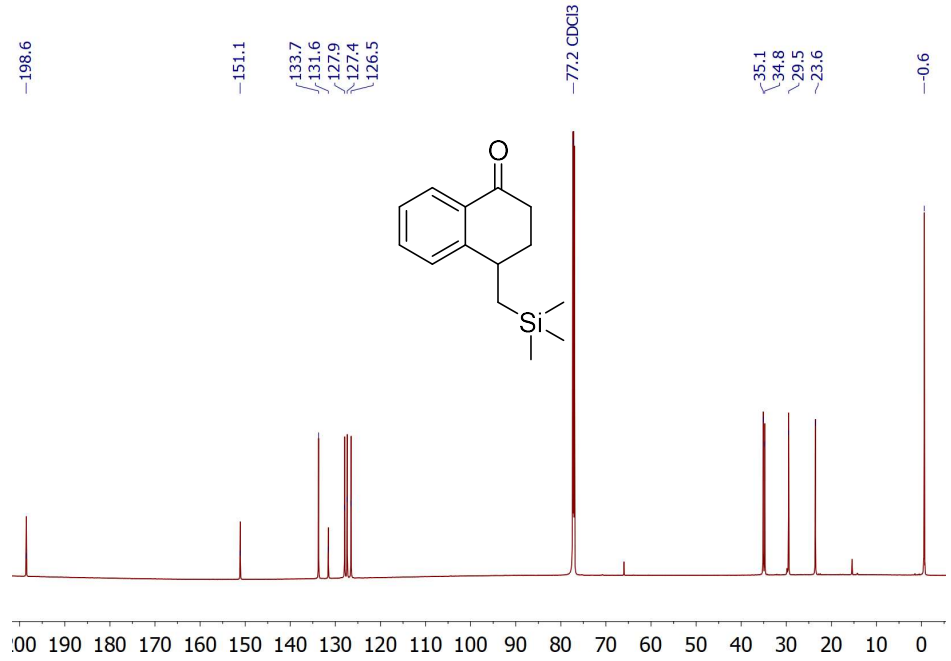


Figure S2. ^{13}C NMR spectra (176 MHz, $CDCl_3$) of **9**.

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12 Appendix

12.1 Deoxytrifluoromethylthiolation and Selenylation of Alcohols by Using Benzothiazolium Reagents

12.1.1 Abstract

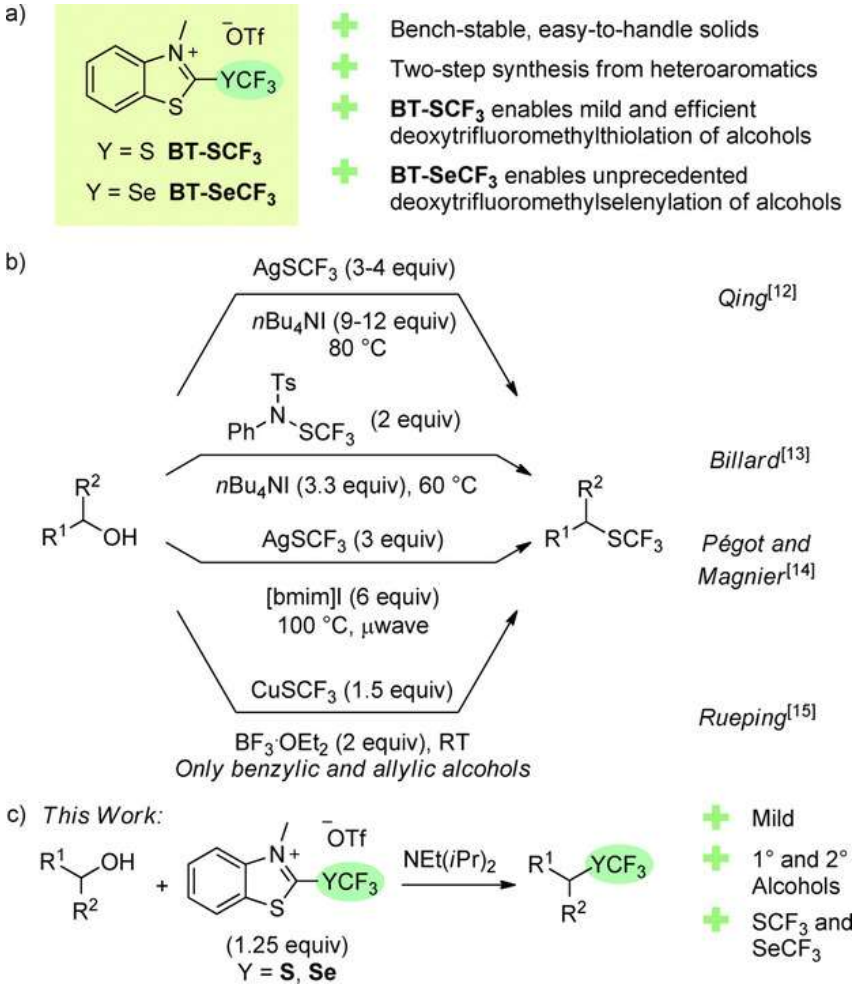
Aliphatic compounds substituted with medicinally important trifluoromethylthio (SCF_3) and trifluoromethylselenyl ($SeCF_3$) groups were synthesized directly from alcohols by using the new benzothiazolium salts **BT-SCF_3** and **BT-$SeCF_3$**. These bench-stable fluorine-containing reagents are facile to use and can be prepared in two steps from non-fluorinated heteroaromatic starting materials. The metal-free deoxytrifluoromethylthiolation process using **BT-SCF_3** proceeds under mild conditions and the similarly efficient trifluoromethylselenylation reactions using **BT-$SeCF_3$** are, to the best of our knowledge, the first reported examples of this transformation.

12.1.2 Publication

Substituting organic molecules with fluorine is a common strategy to improve their biological or physical properties.[1] In addition to single fluorine atoms and established fluorinated moieties, such as the trifluoromethyl group (CF_3), alternative fluorine-containing functional groups have been attracting increasing attention. With the highest reported Hansch parameter (π=1.44) and strong electron-withdrawing properties (Hammett parameters: σ_m=0.40, σ_p=0.50), the trifluoromethylthio (SCF_3) group in particular has emerged as a promising substituent in pharmaceuticals that counterintuitively combines significant polarity with high lipophilicity.[2]

The resurgence in interest in the SCF_3 group has been driven in large part by the introduction of new reagents for electrophilic trifluoromethylthiolation. As demonstrated in a number of impressive contributions, reagents such as *N*-(trifluoromethylthio)phthalimide, [2(2-iodophenyl)propan-2-yl)oxy](trifluoromethyl)sulfane and Billard's trifluoromethyl sulfenamides have opened up new mild synthetic routes towards SCF_3-substituted molecules that were not accessible by using the previously available toxic gases $F_3CS{-}Cl$ and $F_3CS{-}SCF_3$.[2, 3] By contrast, nucleophilic trifluoromethylthiolation reactions are typically performed by using only a handful of $^-SCF_3$ sources, such as $AgSCF_3$, $CuSCF_3$, and $[Me_4N]SCF_3$.[2] In addition to their high cost, a major challenge associated with these reagents is the relative instability of the free $^-SCF_3$ anion because β-elimination of fluoride can outcompete the desired nucleophilic trifluoromethylthiolation process.[4] An alternative strategy is to instead employ a stable organic reagent that releases $^-SCF_3$ upon in situ-activation.[5] Using this approach, free $^-SCF_3$ anions are generated in a more controlled fashion, whereas reactive electrophiles for nucleophilic substitution reactions can be generated as part of the activation process. Inspired by the success of azolium-based reagents such as 2,2-difluoro-1,3-dimethylimidazolidine (DFI) and Alkylfluor® in nucleophilic

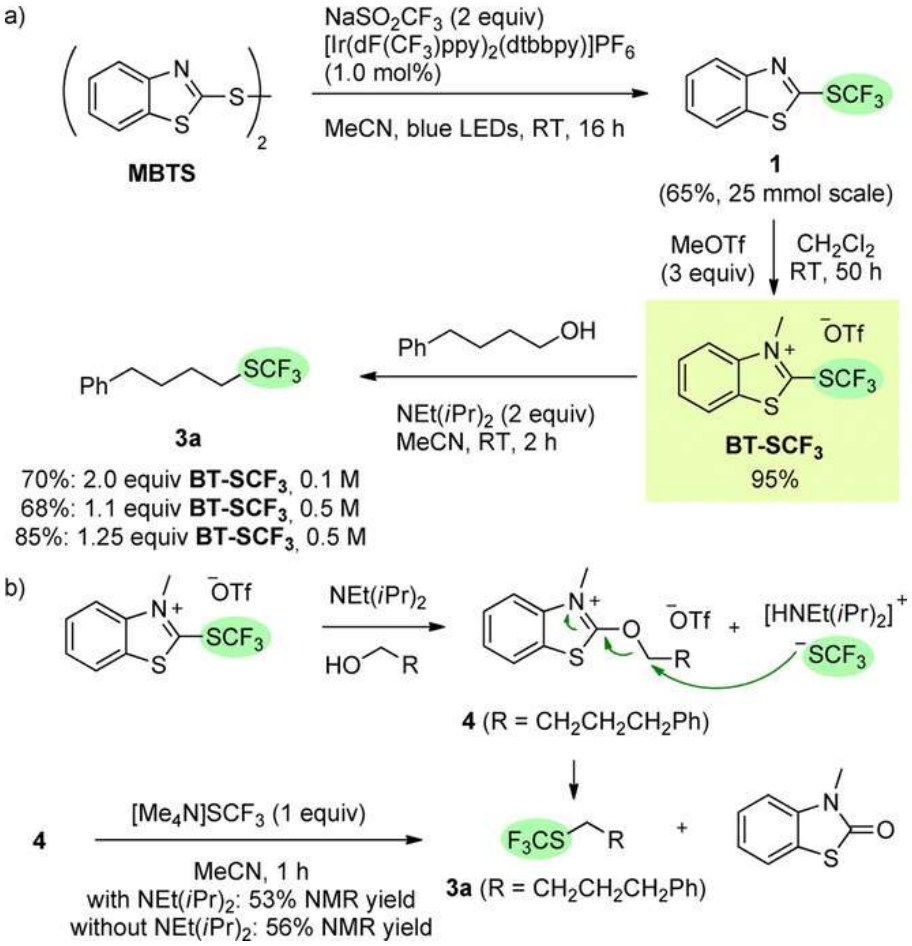
fluorination[6] and the use of benzothiazolium salts in coupling reactions,[7] we considered whether the 2-SCF_3-substituted benzothiazolium species **BT-SCF$_3$** (Scheme **1a**) could be employed as a new bench-stable metal-free reagent for nucleophilic trifluoromethylthiolation reactions. Herein, we report the synthesis of **BT-SCF$_3$** and its successful application in mild deoxytrifluoromethylthiolation reactions of aliphatic alcohols. Moreover, $SeCF_3$-substituted alkyl derivatives could be readily prepared in an unprecedented deoxytrifluoromethylselenylation process using the analogous selenium reagent **BT-SeCF$_3$**.



Scheme 1 a) Benzothiazolium Reagents **BT-SCF$_3$** and **BT-SeCF$_3$**. b) Previously reported deoxytrifluoromethylthiolation reactions of aliphatic alcohols. c) This work: Deoxytrifluoromethylthiolation and selenylation of alcohols with **BT-SCF$_3$** and **BT-SeCF$_3$**. [bmim]=1-Butyl-3-methylimidazolium.

The synthesis of **BT-SCF$_3$** is shown in Scheme **2a**. A two-step approach was investigated starting from inexpensive 2-mercaptobenzothiazole (MBT), which is an industrially produced bulk material used in the sulfur vulcanization of rubber. In the first step, trifluoromethylation of MBT affords the stable heteroaromatic species **1**, which can be readily purified by column chromatography without decomposition. A reactive reagent is only generated in the second step with simple methylation of

the benzothiazole ring nitrogen with MeOTf affording **BT-SCF$_3$**. Although there are several literature methods for conducting the *S*-trifluoromethylation of MBT,[8] we found that intermediate compound 1 could be most efficiently generated starting from the disulfide dimer MBTS through an in-house-developed photoredox catalysis method.[8a, 9] Blue-light irradiation of inexpensive MBTS with the Langlois reagent ($NaSO_2CF_3$) and the iridium photocatalyst [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ [1.0 mol %, dF(CF$_3$)ppy=3,5-difluoro-2-(5-trifluoromethyl)-2-pyridine, dtbbpy=4,4′-di-*tert*-butyl-2,2′-bipyridine] in MeCN cleanly afforded **1** in 65 % isolated yield (25 mmol scale).[10] The heteroaromatic intermediate was subsequently stirred with MeOTf (3 equiv) in CH_2Cl_2 and, after 50 h at RT, addition of Et_2O followed by filtration delivered **BT-SCF$_3$** in 95 % yield without the need for further purification.



Scheme 2 a) Two-step synthesis of **BT-SCF$_3$** and its application in the deoxytrifluoromethylthiolation of aliphatic alcohol **2a**. b) Likely reaction mechanism via 2-alkoxybenzothiazolium salt **4**.

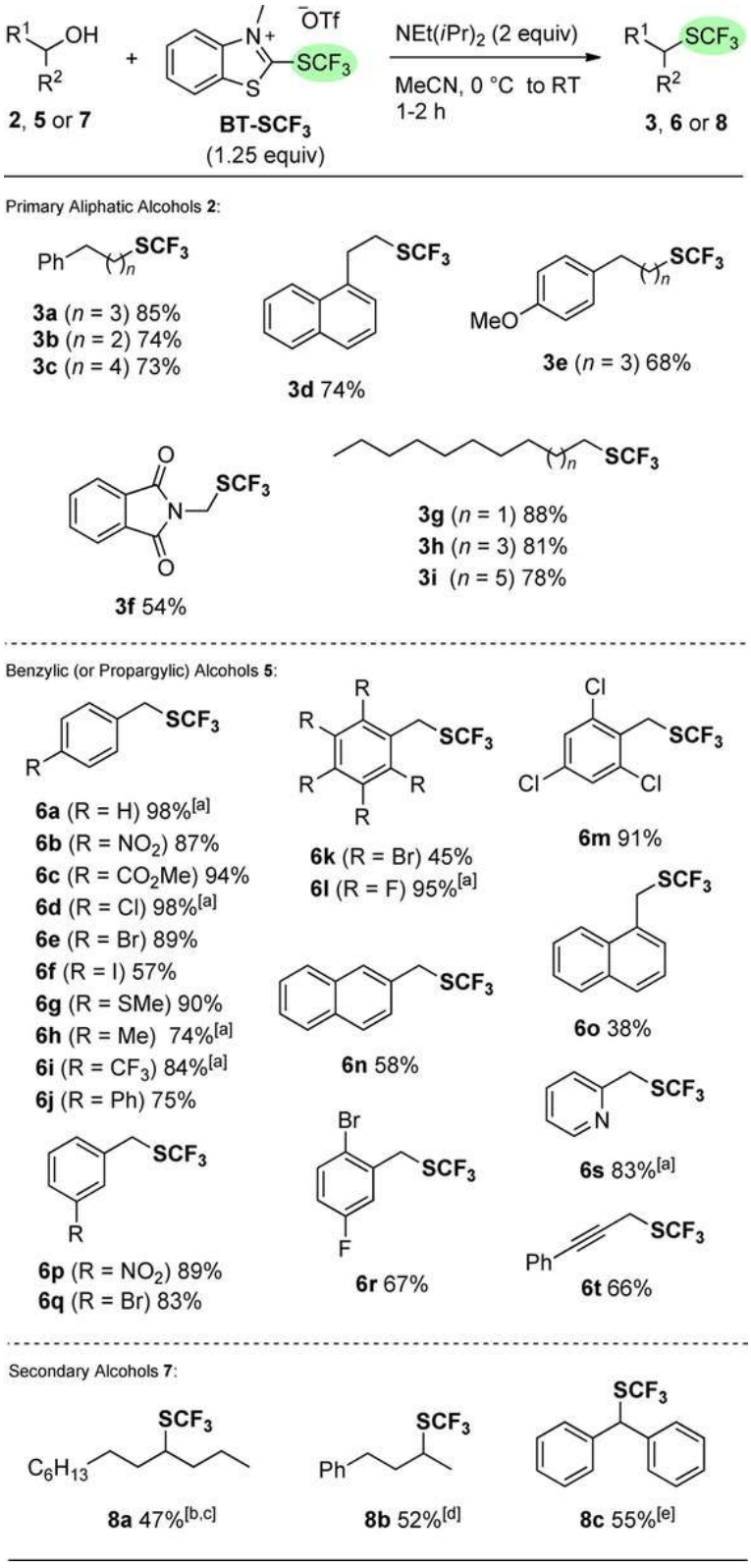
BT-SCF$_3$ is an off-white solid that is stable over at least several months under ambient conditions and hydrolyzes only slowly in neutral or acidic MeCN/H_2O solutions.[11] In the presence of Hünig's base (NEt(*i*Pr)$_2$), however, fast hydrolysis to the corresponding benzothiazolone is observed. This

result validates the proposed mode of action of **BT-SCF_3** and we accordingly turned our attention to the development of a nucleophilic trifluoromethylthiolation process. Addition of an aliphatic alcohol rather than water, for example, would deliver a 2-alkoxybenzothiazolium salt susceptible to subsequent nucleophilic substitution by the released $^-SCF_3$ anion. Deoxytrifluoromethylthiolation reactions are synthetically attractive as they avoid pre-activation steps and provide valuable alkyl-SCF_3 compounds directly from widely available alcohols. Previously reported methods by Qing,[12] Billard,[13] Pégot and Magnier[14] have exploited the aforementioned instability of $^-SCF_3$ with substitution occurring on an in situ generated carbonofluoridothioate intermediate (Scheme **1b**). This approach, however, requires excess amounts of the expensive trifluoromethylthiolating reagent and high reaction temperatures. Rueping and co-workers have reported a room temperature method using only 1.5 equivalents of $CuSCF_3$ and 2 equivalents of the Lewis acid $BF_3{\cdot}OEt_2$; however, the scope of this process was limited to activated benzylic and allylic alcohols capable of stabilizing the intermediate carbocation.[15, 16]

In an initial experiment, the primary aliphatic alcohol **2a** was reacted with 2 equivalents of both **BT-SCF_3** and $NEt(iPr)_2$ in MeCN (0.1 m). After 2 hours at rt, we were delighted to observe clean conversion to the corresponding alkyl-SCF_3 derivative **3a**, which could be isolated in 70 % yield after column chromatography. Notably, the reaction proceeded smoothly under ambient conditions and no special precautions to exclude air or moisture were required (Scheme **2a**). Optimization of the reaction conditions confirmed the requirement for a base with $NEt(iPr)_2$ (2 equiv) in MeCN providing **3a** in the highest yields.[11] Moreover, upon increasing the concentration to 0.5 m, efficient deoxytrifluoromethylthiolation could be achieved using only a slight excess of **BT-SCF_3** (68 % yield with 1.1 equiv, 85 % with 1.25 equiv). Aside from the obvious practical advantages, the low reagent loading indicates that carbonofluoridothioate intermediates generated through β-fluoride elimination of $^-SCF_3$ are not the major electrophilic species in this process and that 2-alkoxybenzothiazolium intermediates are likely involved (Scheme **2b**).[12, 13, 14] This mechanism was further validated by the successful formation of **3a** upon reacting the independently synthesized 2-(4-phenylbutoxy)benzothiazolium salt **4** with $[Me_4N]SCF_3$ [53 and 56 % ^1H NMR yield with or without $NEt(iPr)_2$, respectively].

With a set of optimized conditions in hand, the scope and limitations of the metal-free deoxytrifluoromethylthiolation process with a range of alcohols was evaluated (Scheme **3**). Primary aliphatic alcohols **2** reacted smoothly to afford the corresponding trifluoromethylthiolated products **3a**–**i** in moderate to excellent yields up to 88 %. In each case, complete conversion was observed within 2 hours under ambient conditions and the trifluoromethylthiolated products could be easily isolated by column chromatography. A wide range of diversely substituted benzylic

alcohols **5** could also be smoothly transformed into the corresponding trifluoromethyl thioethers **6a**–**t** under the same mild conditions. Benzylic alcohols bearing electron-withdrawing groups such as NO_2 and CO_2Me at the *para*-position were particularly effective substrates, delivering the corresponding SCF_3-containing products **6b** and **6c** in 87 % and 94 % yield, respectively. Comparatively electron-neutral substituents were also successfully deoxytrifluoromethylthiolated, however, strongly electron-donating *para*-substituents, such as OMe, led to complex reaction mixtures, presumably due to the instability of the 2-alkoxybenzothiazolium intermediates. The halogen substituents Cl, Br, and I were all tolerated under the reaction conditions, opening up the possibility of subsequent elaboration of the products through cross-coupling methodologies. Substitution at the *meta*-position of the aryl rings was well tolerated with the *meta*-NO_2 and *meta*-Br derivatives **6p** and **6q** being afforded in 89 and 83 % yields, respectively. Trifluoromethylthioether **6r**, which features an *ortho*-Br and *meta*-F substituent was also isolated in 67 % yield, whereas the propargyl alcohol **5t** was successfully converted to SCF_3-substituted product **6t** in 66 % yield. In addition to primary alcohols, a selection of secondary alcohols **7** could also be deoxytrifluoromethylthiolated using **BT-SCF$_3$**. Two or three equivalents of the reagent were required to effect complete conversion of these more sterically hindered substrates with the highest yields being obtained upon adding **BT-SCF$_3$** portion-wise over 2 hours.

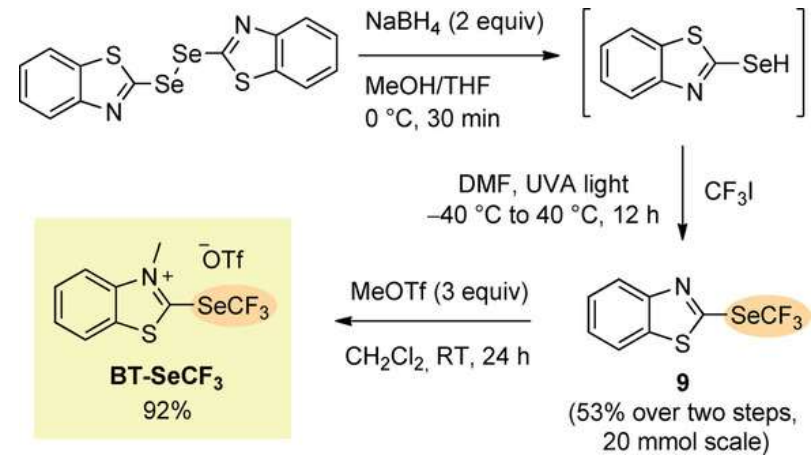


Scheme 3 Deoxytrifluoromethylthiolation of alcohols with **BT-SCF$_3$**. Reaction conditions: alcohol (**2**, **5** or **7**, 0.50 mmol), **BT-SCF$_3$** (1.25 equiv), NEt(*i*Pr)$_2$ (2 equiv), MeCN (0.50 M), 0 °C to RT, 1–2 h. Isolated yields after column chromatography unless otherwise stated. [a] ^{1}H NMR yield stated due to product volatility (internal standard: CH_2Br_2). [b]

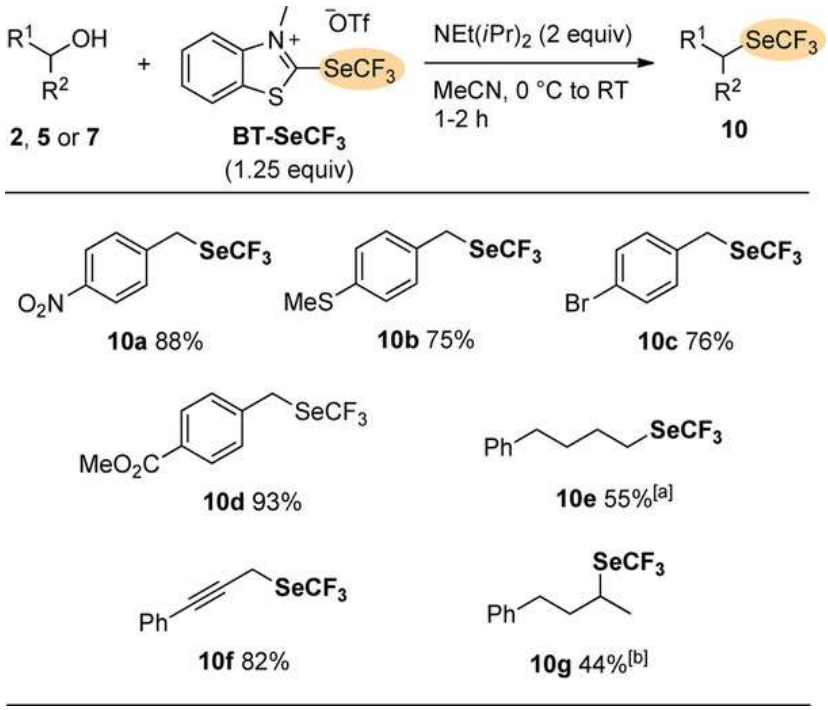
With **BT-SCF$_3$** (2 equiv), −40 °C. [c] Isolated as an inseparable mixture with alkene side products. [d] With **BT-SCF$_3$** (2 equiv) added portion-wise. [e] With **BT-SCF$_3$** (3 equiv) added portion-wise, NEt(*i*Pr)$_2$ (3 equiv).

The successful synthesis and application of **BT-SCF$_3$** as a new nucleophilic reagent for installing the trifluoromethylthio group onto organic molecules encouraged us to consider whether the same approach could be adapted to prepare $SeCF_3$-substituted compounds. Selenium derivatives are attracting increasing interest for applications in materials and medicinal chemistry.[17] With a Hansch parameter (π) of 1.29[18] and Hammett constants σ_m and σ_p of 0.44 and 0.45,[19] respectively, the $SeCF_3$ group has lipophilic and electronic properties between those of SCF_3 and OCF_3 and could thus allow for better fine tuning of a molecule's properties. Despite notable recent advances,[17, 20] the synthesis of $SeCF_3$-substituted compounds remains dominated by indirect methods and, to the best of our knowledge, there is no previous report of a direct deoxytrifluoromethylselenylation reaction of alcohols.

BT-SeCF$_3$ was synthesized through the same general strategy used to prepare **BT-SCF$_3$**. In the first stage, the known trifluoromethylselenylated benzothiazole **9**[21] was prepared in 53 % yield from bis(2-benzothiazolyl)diselenide upon sequential reduction with $NaBH_4$ and UVA light-facilitated radical trifluoromethylation with CF_3I and NaH.[9b, 22] Subsequent methylation with MeOTf (3 equiv) in CH_2Cl_2 at RT for 24 h provided pure **BT-SeCF$_3$** in 92 % yield upon precipitation with Et_2O and filtration (Scheme **4**). As for **BT-SCF$_3$**, the selenium derivative was obtained as an off-white solid that is remarkably stable towards hydrolysis in the absence of a base. With **BT-SeCF$_3$** in hand, its potential as a reagent for deoxytrifluoromethylselenylation reactions was tested with a selection of aliphatic alcohols (Scheme **5**). Upon treating the benzylic alcohol **5b** with **BT-SeCF$_3$** (1.25 equiv) under the same mild reaction conditions used with **BT-SCF$_3$**, a clean deoxytrifluoromethylselenylation process was observed leading to the $SeCF_3$-substituted product **10a** in 88 % yield. Moreover, several other benzylic and propargylic alcohols reacted with similarly high yields while, upon decreasing the reaction temperature to −40 °C, the primary aliphatic alcohol **2a** and even the secondary alcohol **7b** could be successfully transformed into the corresponding selenoethers **10e** and **10g** in 55 and 44 % yield, respectively.



Scheme 4 Synthesis of **BT-SeCF₃**.



Scheme 5 Deoxytrifluoromethylselenylation of alcohols with **BT-SeCF₃**. Reaction conditions: alcohol (**2**, **5** or **7**, 0.20 mmol), **BT-SeCF₃** (1.25 equiv), NEt(*i*Pr)₂ (2 equiv), MeCN (0.50 m), 0 °C to RT, 1–2 h. Isolated yields after column chromatography. [a] Reaction performed at −40 °C. [b] Reaction performed at −40 °C, **BT-SeCF₃** (2 equiv).

In conclusion, we have introduced two new reagents for installing valuable fluorine-containing functional groups onto organic compounds. Based on the benzothiazolium motif, **BT-SCF₃** and **BT-SeCF₃** are bench-stable and easy-to-handle solids that release $^{-}SCF_3$ or $^{-}SeCF_3$ anions in a controlled fashion upon activation in situ. Using only a slight excess of **BT-SCF₃**, a wide-range of aliphatic alcohols can be successfully converted into the corresponding trifluoromethylthioethers at room temperature, whereas **BT-SeCF₃** enables hitherto unprecedented deoxytrifluoromethyl-

selenylation reactions. We believe that benzothiazolium salts could open up new routes towards important organofluorine compounds and further studies are underway in our laboratory.

12.1.3 Acknowledgements

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12.1.5 Supporting Information

Supporting Information

for

Deoxytrifluoromethylthiolation and Selenylation of Alcohols using Benzothiazolium Reagents

Stefan Dix, Michael Jakob and Matthew N. Hopkinson

Institute for Chemistry and Biochemistry, Freie Universität Berlin

Takustrasse 3, 14195 Berlin, Germany

matthew.hopkinson@fu-berlin.de

Table of Contents

1 General Information

Solvents were purified either with the solvent purification system MB-SPS-800 (Braun) or by manual distillation over standard drying agents. The dried solvents were then stored over molecular sieves or transferred under argon. Blue light irradiation for the synthesis of compound **1** was provided by LED strips (λ_{max} = 440 nm, IP65) purchased from PB Versand GmbH (Type: 5630). UVA light irradiation for the synthesis of compound **9** was provided by LuxaLight Long Life LED strips (λ_{max} = 365 nm, IP64) purchased from LEDTuning (Type: LS24UV240X3528PLX). In each case, the reaction vessel was placed at the center of a crystallization flask wrapped with the LED strips (distance from the flask to the LEDs ~ 5 cm). $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ ($dF(CF_3)ppy$ = 3,5-difluoro-2-(5-trifluoromethyl)-2-pyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) was prepared according to literature procedures.[1] $NEt(iPr)_2$ was refluxed over KOH, distilled and stored over molecular sieves prior to use. $[Me_4N]SCF_3$[2] and bis(benzothiazole)diselenide[3] were prepared according to literature methods. Pure NaH was obtained via washing the commercially available sample (60% wt. in mineral oil) with *n*-pentane prior to use. All other compounds employed were purchased from commercial suppliers and used as received. The deoxytrifluoromethylthiolation and selenylation reactions were performed in reaction vials under an atmosphere of air. Flash chromatography was performed using silica gel M60 from Macherey & Nagel (particle size: 40-63 µm).

NMR spectra were acquired on a JEOL ECX 400 (400 MHz), JEOL ECP 500/ Bruker Avance 500 (500 MHz), Varian INOVA 600 (600 MHz) or a Bruker Avance 700 (700 MHZ) in $CDCl_3$ or CD_3CN as a solvent. Chemical shifts (δ) are quoted in ppm downfield of tetramethylsilane. The residual solvent signals were used as references for ^1H and ^{13}C NMR spectra. ^{19}F NMR spectra are not calibrated by an internal reference and coupling constants (J_{F-H}) where reported were determined from proton coupled ^{19}F NMR studies. Coupling constants (*J*) are quoted in Hz. ^1H NMR yields where reported were measured using CH_2Br_2 as an internal standard and the product peaks were correlated with literature values: **6a**,[4] **6d**,[5] **6h**,[6] **6i**,[7] **6l**,[8] **6s**.[9]

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[8] E. Anselmi, C. Simon, J. Marrot, P. Bernardelli, L. Schio, B. Pégot, E. Magnier, *Eur. J. Org. Chem.* **2017**, 6319-6326.
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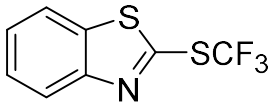
Mass spectra were obtained on a ESI-FTICR-MS: Ionspec QFT-7 (Agilent/Varian) or on a HR-EI-MS: Waters Autospec Premier with Agilent 7890B GC. Infrared spectra were measured on a JASCO FT/IR-4100 Spectrometer. Characteristic absorption bands are displayed in wavelengths $\tilde{\nu}$ in cm^{-1} and were analyzed with the software Spectral Manager from JASCO.

2 Synthesis of BT-SCF_3 and BT-$SeCF_3$

2.1 Synthesis of 2-((trifluoromethyl)thio)benzo[d]thiazole (1)[10]



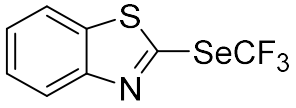
1

Bis(benzothiazole)disulfide (MBTS, 8.31 g, 25.0 mmol, 1.00 eq), sodium trifluoromethanesulfinate (Langlois' Reagent, 7.80 g, 50.0 mmol, 2.00 eq) and $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (280 mg, 0.250 mmol, 1.00 mol%) were added to a heat gun-dried Schlenk flask. MeCN (250 mL) was added and the flask was flushed with argon and sealed. The mixture was then irradiated with blue LEDs (λ_{max} = 440 nm) for 19 h at rt. The crude reaction mixture was filtered through Celite® (eluent = EtOAc, 250 mL) and then washed with water (2 × 200 mL) and brine (200 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography over silica gel (eluent = *n*-pentane:EtOAc, 20:1) afforded **1** as a colourless oil (3.83 g, 16.3 mmol, 65%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.12 (d, *J*=8.1, 1H, H_{Ar}), 7.87 (d, *J*=7.9, 1H, H_{Ar}), 7.53 (t, *J*=7.5, 1H, H_{Ar}), 7.47 (t, *J*=7.5, 1H, H_{Ar}). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -40.7. **^{13}C NMR (101 MHz, Chloroform-*d*) δ =** 153.2 (C_q), 151.9 (C_q), 138.0 (C_q), 128.3 (q, *J*=311, CF_3), 127.1 (CH), 126.8 (CH), 124.3 (CH), 121.4 (CH). **HRMS (EI):** m/z calculated for $[C_8H_4F_3NS_2]^+$ ($[M]^+$): 234.9732, measured: 234.9739. **IR (ATR):** ν (cm^{-1}): 3065, 1556, 1456, 1411, 1311, 1237, 1143, 1099, 1075, 1015, 988, 941, 852, 755, 726, 708, 676. **R_f**: (*n*-pentane/EtOAc, 20:1): 0.75.

The characterization data agree with literature values.[10]

2.2 Synthesis of 2-((trifluoromethyl)selenyl)benzo[d]thiazole (9)[11]



9

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Bis(benzothiazole)diselenide[3] (4.20 g, 9.85 mmol, 0.50 eq) was suspended in methanol (100 mL, degassed using the freeze-pump-thaw technique) and THF (25 mL, degassed using the freeze-pump-thaw technique) in a 3-necked round-bottomed flask under argon and the mixture was cooled to 0 °C. $NaBH_4$ (745 mg, 19.7 mmol, 1 equiv) was added portionwise over 5 minutes and the mixture was stirred at 0 °C for an additional 10 minutes. HCl (1 M, aq., 100 mL, degassed by argon sparging) was added via cannula resulting in the formation of a grey precipitate. The mixture was then filtered under argon and the solid was washed with water (3 × 100 mL, degassed by argon sparging) and then dried under high vacuum for 30 minutes. Separately, a solution of CF_3I in DMF was prepared by attaching a balloon of CF_3I to a flask containing freeze-pump-thaw degassed DMF under N_2. This solution (110 mL, containing 6.3 g, 32 mmol, 1.6 equiv. of CF_3I) was transferred to the round-bottomed flask via cannula and the grey solid product was re-dissolved. The mixture was cooled to -40 °C and NaH (709 mg, 29.5 mmol, 1.50 equiv.) was added portionwise over 5 minutes. A balloon containing CF_3I (14.2 g, 72.8 mmol, 3.70 equiv) was then attached and the mixture was stirred under irradiation from UVA LEDs (λ_{max} = 365 nm) for 12 h during which time the reaction temperature reached ca. 40 °C. After completion of the reaction EtOAc (250 mL) and water (300 mL) were added and the layers separated. The organic phase was then washed with water (5 × 500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography over silica gel (eluent = *n*-pentane: CH_2Cl_2, 10:1) afforded **9** as a white solid (2.95 g, 10.5 mmol, 53%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.13 (ddd, *J*=8.2, 1.3, 0.6, 1H, H_{Ar}), 7.90 (ddd, *J*=8.1, 1.3, 0.7, 1H, H_{Ar}), 7.53 (tm, *J*=7.7, 1H, H_{Ar}), 7.46 (tm, *J*=7.7, 1H, H_{Ar}). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -33.2. **^{13}C NMR (151 MHz, Chloroform-*d*) δ =** 153.8 (C_q), 147.6 (C_q), 138.5 (C_q), 126.9 (CH), 126.5 (CH), 124.0 (CH), 122.2 (q, *J*=335, CF_3), 121.2 (CH). **HRMS (EI):** m/z calculated for $[C_8H_4F_3NSSe]^+$ ($[M]^+$): 282.9176, measured: 282.9174. **IR (ATR):** ν (cm^{-1}): 3066, 2924, 1557, 1453, 1409, 1313, 1277, 1232, 1012, 858, 738, 707, 670. **R_f**: (*n*-pentane/CH_2Cl_2, 10:1): 0.20.

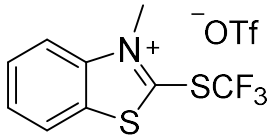
The characterization data agree with literature values.[11]

2.3 General Procedure for the *N*-Methylation of 1 and 9

2-Substituted benzothiazoles **1** or **9** (1.0 eq) were dissolved in dry CH_2Cl_2 (0.10 M) and methyl trifluoromethanesulfonate (3.0 eq) was added dropwise. The reaction mixture was stirred at rt (50 h for **BT-SCF$_3$** or 24 h for **BT-SeCF$_3$**) and the product was precipitated with diethyl ether. The suspension was then filtered, and the residue washed with diethyl ether (3 ×). After drying *in vacuo*, **BT-SCF$_3$** or **BT-SeCF$_3$** were obtained as off-white solids.

2.4 Characterization Data for BT-SCF_3 and BT-$SeCF_3$

3-Methyl-2-((trifluoromethyl)thio)benzo[*d*]thiazol-3-ium trifluoromethanesulfonate (BT-SCF_3)

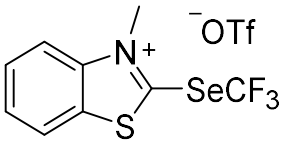


BT-SCF_3

Prepared from 2-((trifluoromethyl)thio)benzo[*d*]thiazole (**1**) on a 25.2 mmol scale. Off-white solid (9.60 g, 24.0 mmol, 95%).

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ = 8.40 (d, *J*=8.0, 1H, H_{Ar}), 8.28 (d, *J*=8.6, 1H, H_{Ar}), 8.05 (t, *J*=8.0, 1H, H_{Ar}), 7.97 (t, *J*=7.9, 1H, H_{Ar}), 4.45 (s, 3H, CH_3). **^{19}F NMR (565 MHz, Acetonitrile-d_3)** δ = -39.3 (SCF_3), -79.2 ($S(O)_2CF_3$) **^{13}C NMR (151 MHz, Acetonitrile-d_3)** δ = 160.6 (C_q), 143.8 (C_q), 134.1 (C_q), 132.4 (CH), 131.5 (CH), 127.7 (q, *J*=314, SCF_3), 125.2 (CH), 122.0 (q, *J*=321, $S(O)_2CF_3$), 119.4 (CH), 40.0 (CH_3). **HRMS (ESI):** m/z calculated for $[C_9H_7F_3NS_2]^+$ ([M−OTf]$^+$): 249.9967, measured: 249.9955. **IR (ATR):** ν (cm^{-1}): 3086, 1664, 1578, 1490, 1476, 1462, 1433, 1382, 1279, 1266, 1240, 1227, 1196, 1173, 1161, 1150, 1108, 1092, 1050, 1026, 998, 814, 760, 722, 714, 688.

3-Methyl-2-((trifluoromethyl)selanyl)benzo[d]thiazol-3-ium trifluoromethanesulfonate (BT-$SeCF_3$)



BT-$SeCF_3$

Prepared from 2-((trifluoromethyl)selanyl)benzo[d]thiazole (**9**) on a 10.5 mmol scale. White solid (4.28 g, 9.59 mmol, 92%).

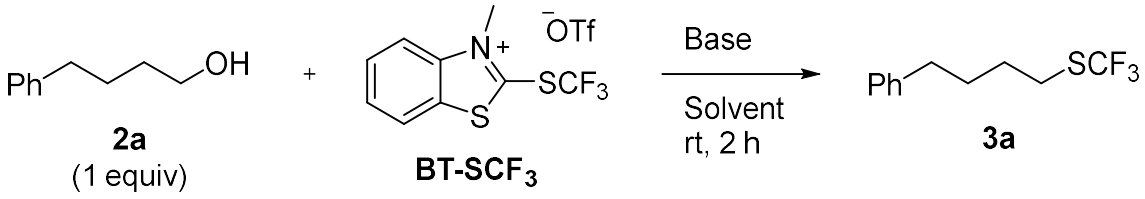
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ = 8.37 (d, *J*=7.8, 1H, H_{Ar}), 8.27 (d, *J*=8.6, 1H, H_{Ar}), 8.01 (t, *J*=8.3, 7.9, 1H, H_{Ar}), 7.93 (t, *J*=7.9, 1H, H_{Ar}), 4.47 (s, 3H, CH_3).**^{19}F NMR (376 MHz, Acetonitrile-d_3)** δ = -32.7 ($SeCF_3$), -79.3 ($S(O)_2CF_3$). **^{13}C NMR (126 MHz, Acetonitrile-d_3)** δ = 159.2 (C_q), 143.9 (C_q), 135.0 (C_q), 132.1 (CH), 131.1 (CH), 125.1 (CH), 122.7 (q, *J*=337, $SeCF_3$), 122.0 (q, *J*=321, $S(O)_2CF_3$), 119.3 (CH), 41.4 (CH_3). **CHNS Elemental Analysis:** calculated for $C_{10}H_7F_6NO_3S_2Se$: C 26.92; H 1.58; N 3.14, S 14.37; measured: C 27.00; H 1.97; N 3.14; S 14.50. **IR (ATR):** ν (cm^{-1}): 3098, 3064, 1577, 1489, 1461,

1442, 1388, 1252, 1223, 1187, 1151, 1140, 1101, 1079, 1054, 1043, 1028, 987, 962, 802, 766, 741, 729, 712.

3 Optimization and Mechanistic Studies on the Deoxytrifluoromethylthiolation of Alcohols with BT-SCF_3

3.1 Optimization Table

Table S1. Optimization of the Deoxytrifluoromethylthiolation of Alcohol **2a** with **BT-SCF_3**.



Entry[a]	Equiv. of BT-SCF_3	Solvent (M)	Base (equiv)	Yield of 3a[b]
1	2.0	MeCN (0.1 M)	NEt(*i*Pr)$_2$ (2 equiv)	80% (70%)
2	1.5	MeCN (0.1 M)	NEt(*i*Pr)$_2$ (2 equiv)	77%
3	1.5	MeCN (0.1 M)	---	---
4	1.5	MeCN (0.1 M)	NEt_3 (2 equiv)	42%
5	1.5	MeCN (0.1 M)	DBU (2 equiv)	41%
6	1.5	MeCN (0.1 M)	Cs_2CO_3 (2 equiv)	44%
7	1.5	THF (0.1 M)	NEt(*i*Pr)$_2$ (2 equiv)	62%
8	1.5	DMF (0.1 M)	NEt(*i*Pr)$_2$ (2 equiv)	11%
9	1.5	DMSO (0.1 M)	NEt(*i*Pr)$_2$ (2 equiv)	---
10	1.5	Et_2O (0.1 M)	NEt(*i*Pr)$_2$ (2 equiv)	8%
11	1.5	CH_2Cl_2 (0.1 M)	NEt(*i*Pr)$_2$ (2 equiv)	66%
12	1.5	EtOAc (0.1 M)	NEt(*i*Pr)$_2$ (2 equiv)	54%
13	1.5	Acetone (0.1 M)	NEt(*i*Pr)$_2$ (2 equiv)	58%
14	1.25	MeCN (0.1 M)	NEt(*i*Pr)$_2$ (2 equiv)	78%
15	1.1	MeCN (0.1 M)	NEt(*i*Pr)$_2$ (2 equiv)	77%

16	1.25	MeCN (0.1 M)	NEt(iPr)$_2$ (1.1 equiv)	69%
17	1.25	MeCN (0.1 M)	NEt(iPr)$_2$ (3 equiv)	81%
18	1.25	MeCN (0.2 M)	NEt(iPr)$_2$ (2 equiv)	81%
19	1.25	MeCN (0.5 M)	NEt(iPr)$_2$ (2 equiv)	88% (85%)
20	1.25	MeCN (1.0 M)	NEt(iPr)$_2$ (2 equiv)	71%
21	1.1	MeCN (0.5 M)	NEt(iPr)$_2$ (2 equiv)	79% (68%)

[a] Reaction procedure: The base was added to a solution of **BT-SCF$_3$** and **2a** (0.10 mmol) at rt. The mixture was stirred at rt for 2 h and then concentrated *in vacuo*. [b] ^{1}H NMR yields using CH_2Br_2 as an internal standard. Isolated yields in brackets. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

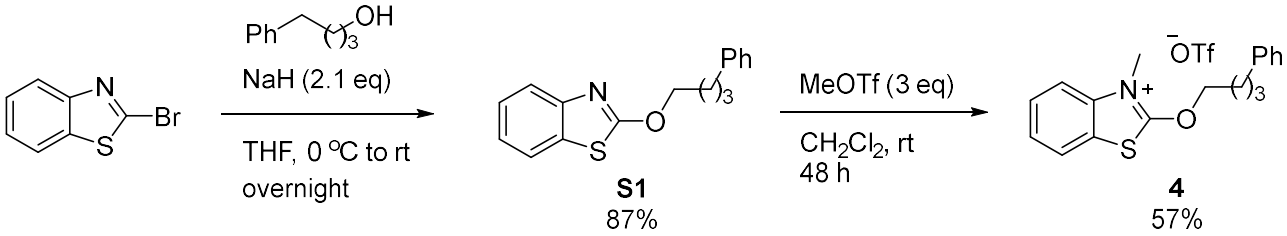
3.2 Hydrolytic Stability of BT-SCF_3

BT-SCF_3 was dissolved in MeCN, MeCN/H_2O (9:1), MeCN/HCl (1 M, aq., 9:1) or MeCN with NEt(*i*Pr)$_2$ (2 equiv) and stirred at rt for 24 h. The solvent was then evaporated *in vacuo* and the amount of remaining **BT-SCF_3** was quantified by ^{1}H NMR in CD_3CN using CH_2Br_2 as an internal reference.

Table S2. Stability of **BT-SCF_3** in various solvent mixtures.

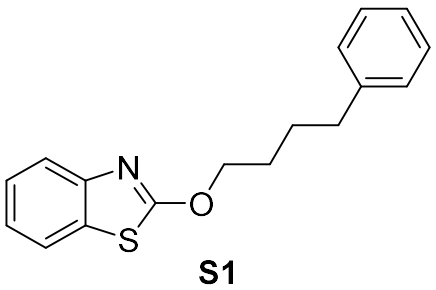
Entry	Solvent	Remaining BT-SCF_3 (%)
1	MeCN	>95%
2	MeCN / H_2O (9:1)	29%
3	MeCN / HCl (1 M, aq., 9:1)	30%
4	MeCN with with NEt(*i*Pr)$_2$ (2 equiv)	---

3.3 Synthesis of 2-Alkoxybenzothiazolium Intermediate 4



Scheme S1. Synthesis of 2-alkoxybenzothiazolium salt **4**.

2-(3-Phenylpropoxy)benzo[*d*]thiazole (S1)



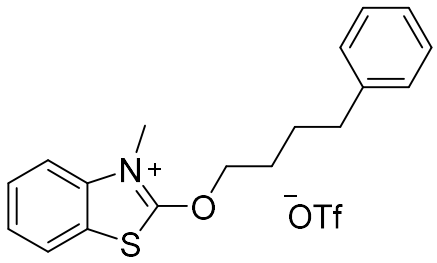
S1

NaH (60% wt. in mineral oil, 210 mg, 5.25 mmol, 2.10 eq) was added to a heat gun-dried Schlenk flask under Argon. THF (25 mL) was added via syringe and the suspension was cooled to 0 °C. 4-Phenyl-1-butanol (**2a**, 763 µL, 5.00 mmol, 2.00 eq) was added dropwise and the mixture was stirred

at 0 °C for a further 30 minutes. 2-Bromobenzothiazole (535 mg, 2.50 mmol, 1.00 eq) was then added in three portions over 1 h and the mixture was subsequently allowed to warm to rt overnight. Water (30 mL) was added and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography over silica gel (eluent: *n*-pentane/CH_2Cl_2, 1:1) afforded 2-alkoxybenzothiazole **S1** as a colourless oil (616 mg, 2.17 mmol, 87%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.72 (ddd, *J*=8.0, 1.2, 0.6, 1H, H_{Ar}), 7.65 (ddd, *J*=7.9, 1.3, 0.5, 1H, H_{Ar}), 7.39 (tm, *J*= 7.6, 1H, H_{Ar}), 7.35 – 7.29 (m, 2H, H_{Ar}), 7.27 – 7.20 (m, 4H), 4.60 (t, *J*=6.4, 2H, CH_2), 2.73 (t, *J*=7.5, 2H, CH_2), 1.96 – 1.79 (m, 4H, CH_2). **^{13}C NMR (101 MHz, Chloroform-*d*) δ =** 137.0 (C_q), 149.5 (C_q), 142.0 (C_q), 131.0 (C_q), 128.5 (CH), 128.4 (CH), 126.0 (CH), 126.0 (CH), 123.5 (CH), 121.3 (CH), 120.8 (CH), 71.9 (CH_2), 35.5 (CH_2), 28.5 (CH_2), 27.6 (CH_2). **HRMS (ESI)**: m/z calculated for $[C_{17}H_{17}NOSNa]^+$ ([M+Na]$^+$): 306.0923, measured: 306.0916. **IR (ATR):** ν (cm^{-1}): 3060, 3025, 2939, 2857, 1597, 1532, 1495, 1468, 1455, 1442, 1382, 1311, 1285, 1248, 1214, 1156, 1125, 1094, 1066, 1029, 1016, 946, 929, 908, 890, 851, 823, 751, 725, 697. **R_f**: (*n*-pentane/CH_2Cl_2, 1:1): 0.48.

3-Methyl-2-(4-phenylbutoxy)benzo[d]thiazol-3-ium (4)



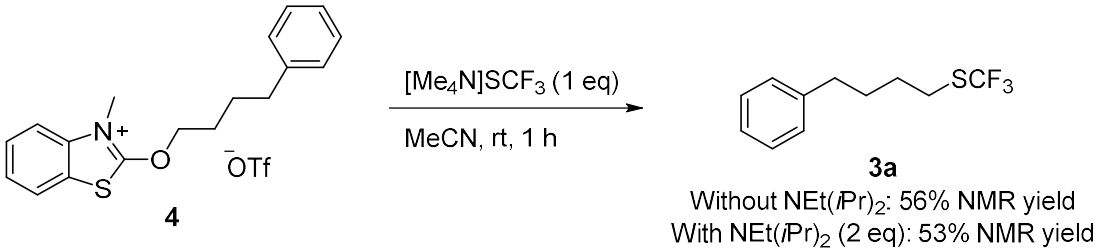
4

2-Alkoxybenzothiazole **S1** (283 mg, 1.00 mmol, 1.00 eq) was dissolved in dry CH_2Cl_2 (0.10 M) and methyl trifluoromethanesulfonate (340 µL, 3.00 mmol, 3.00 eq) was added dropwise. The reaction mixture was stirred for 48 h at rt and the product was precipitated with diethyl ether. The suspension was then filtered, and the residue washed with diethyl ether (3 × 20 mL). Any remaining solvents were removed from the residue *in vacuo* and 2-alkoxybenzothiazolium **4** was obtained as white solid that was stored under Argon (267 mg, 0.597 mmol, 60%).

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ = 8.09 (ddd, *J*=8.2, 1.1, 0.6, 1H, H_{Ar}), 7.85 – 7.77 (m, 2H, H_{Ar}), 7.66 (ddd, *J*=8.2, 7.0, 1.5, 1H, H_{Ar}), 7.33 – 7.24 (m, 4H, H_{Ar}), 7.19 (m, 1H, H_{Ar}), 4.76 (t, *J*=6.2, 2H, CH_2), 3.86 (s, CH_3), 2.73 (t, *J*=7.6, 2H, CH_2), 2.09 – 2.00 (m, 2H, CH_2), 1.91 – 1.82 (m, 2H, CH_2). **^{19}F NMR**

(376 MHz, Acetonitrile-*d*$_3$) δ = -79.2. **^{13}C NMR (101 MHz, Acetonitrile-*d*$_3$) δ =** 179.0 (C_q), 143.0 (C_q), 138.2 (C_q), 130.5 (C_q), 129.4 (CH), 129.4 (CH), 128.3 (CH), 126.9 (CH), 125.1 (CH), 123.5 (CH), 122.2 (q, *J*=321, CF_3), 116.0 (CH), 82.1 (CH_2), 35.7 (CH_2), 33.8 (CH_3), 28.8 (CH_2), 27.9 (CH_2). **HRMS (ESI)**: m/z calculated for $[C_{18}H_{20}NOS]^+$ ([M−OTf]$^+$): 298.1260, measured: 298.1271. **IR (ATR):** ν (cm^{-1}): 3087, 3031, 2935, 2862, 1591, 1565, 1496, 1471, 1455, 1419, 1383, 1359, 1333, 1310, 1259, 1223, 1165, 1147, 1064, 1030, 987, 954, 912, 854, 832, 811, 792, 764, 742, 699**.**

3.4 Trifluoromethylthiolation of 2-Alkoxybenzothiazolium Intermediate 4



Scheme S2. Trifluoromethylthiolation of 2-alkoxybenzothiazolium salt **4** with $[Me_4N]SCF_3$.

2-Alkoxybenzothiazolium salt **4** (45 mg, 0.10 mmol, 1.0 eq) and $[Me_4N]SCF_3$ (18 mg, 0.10 mmol, 1.0 eq) were stirred in MeCN at rt for 1 h either with or without NEt(*i*Pr)$_2$ (35 µL, 0.20 mmol, 2 eq). The reactions were then concentrated *in vacuo* and redissolved in $CDCl_3$. The NMR yields of **3a** were measured using CH_2Br_2 as an internal standard. In the absence of NEt(*i*Pr)$_2$, **3a** was obtained in 56% NMR yield whereas with NEt(*i*Pr)$_2$, **3a** was obtained in 53% NMR yield.

4 Scope and Limitations of the Deoxytrifluoromethylthiolation and Deoxytrifluoromethylselenylation of Alcohols

4.1 General Procedures for the Deoxytrifluoromethylthiolation reaction of Alcohols with BT-SCF_3

Method A: The alcohol (**2** or **5**, 0.50 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SCF_3** (250 mg, 0.625 mmol, 1.25 eq) was added and the reaction mixture was cooled to 0 °C. NEt(*i*Pr)$_2$ (174 µL,1.0 mmol, 2.0 eq) was then added dropwise and the reaction mixture was stirred for 1-2 h at rt. The reaction mixture was concentrated *in vacuo* and purified by column chromatography over silica gel.

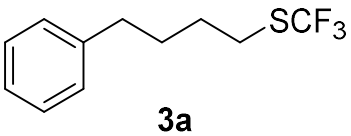
Method B: The secondary alcohol (**7**, 0.50 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SCF_3** (399 mg, 1.0 mmol, 2.0 eq) was added and the reaction mixture was cooled to −40 °C. NEt(*i*Pr)$_2$ (174 µL,1.0 mmol, 2.0 eq) was then added dropwise and the reaction mixture was stirred for 2 h at −40 °C. The reaction mixture was concentrated *in vacuo* and purified by column chromatography over silica gel.

Method C: The secondary alcohol (**7**, 0.50 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SCF_3** (133 mg, 0.33 mmol, one third of 2.0 eq) was added and the reaction mixture was cooled to 0 °C. NEt(*i*Pr)$_2$ (174 µL, 1.00 mmol, 2.00 eq) was added dropwise and the reaction mixture was stirred at rt. After 20 minutes, a second portion of **BT-SCF_3** (133 mg, 0.33 mmol) was added followed by a third portion (133 mg, 0.33 mmol) after an additional 20 minutes. The reaction was allowed to stir at rt for a further 80 minutes (total reaction time of 2 h) before being concentrated *in vacuo* and purified by column chromatography over silica gel.

Method D: The secondary alcohol (**7**, 0.50 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SCF_3** (200 mg, 0.50 mmol, one third of 3.0 eq) was added and the reaction mixture was cooled to 0 °C. NEt(*i*Pr)$_2$ (261 µL, 1.5 mmol, 3.0 eq) was added dropwise and the reaction mixture was stirred at rt. After 20 minutes, a second portion of **BT-SCF_3** (200 mg, 0.50 mmol) was added followed by a third portion (200 mg, 0.50 mmol) after an additional 20 minutes. The reaction was allowed to stir at rt for a further 80 minutes (total reaction time of 2 h) before being concentrated *in vacuo* and purified by column chromatography over silica gel.

4.2 Characterization Data for Deoxytrifluoromethylthiolation Products 3, 6 and 8

(4-Phenylbutyl)(trifluoromethyl)sulfane (3a)[7]



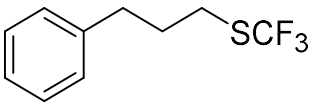
3a

Prepared from 4-phenyl-1-butanol (**2a**, 76 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (100 mg, 0.43 mmol, 85%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.31 (tm, *J*=7.7, 2H, H_{Ar}), 7.23 – 7.17 (m, 3H, H_{Ar}), 2.93 – 2.88 (m, 2H, CH_2), 2.68 – 2.63 (m, 2H, CH_2), 1.79 – 1.72 (m, 4H, CH_2) **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -41.1. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 141.8 (C_q), 131.3 (q, *J*=306, CF_3), 128.6 (CH), 128.5 (CH), 126.1 (CH), 35.3 (CH_2), 30.3 (CH_2), 29.9 (q, *J*=2, CH_2), 29.1 (CH_2). **HRMS (EI)**: m/z calculated for $[C_{11}H_{13}F_3S]^+$ ($[M]^+$): 234.0685, measured: 234.0690. **IR (ATR):** ν (cm^{-1}): 3063, 3028, 2927, 2857, 2360, 2342, 1733, 1687, 1604, 1496, 1454, 1309, 1271, 1245, 1218, 1148, 1103, 1031, 909, 806, 744, 698, 653.

The characterization data agree with literature values.[7]

(3-phenylpropyl)(trifluoromethyl)sulfane (3b)[5]



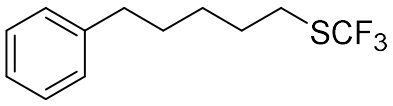
3b

Prepared from 3-phenyl-1-propanol (**2b**, 68 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (81 mg, 0.37 mmol, 74%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.31 (tm, *J*=7.5, 2H, H_{Ar}), 7.23 (tt, *J*=7.3, 2.0, 1H, H_{Ar}), 7.19 (dm, *J*=7.5, 2H, H_{Ar}), 2.89 (t, *J*=7.3, 2H, CH_2), 2.75 (t, *J*=7.5, 2H, CH_2), 2.04 (quin, *J*=7.5, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -41.8. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 140.6 (C_q), 131.3 (q, *J*=306, CF_3), 128.7 (CH), 128.6 (CH), 126.4 (CH), 34.5 (CH_2), 31.1 (CH_2), 29.3 (q, *J*=2, CH_2). **HRMS (EI)**: m/z calculated for $[C_{10}H_{11}F_3S]^+$ ($[M]^+$): 220.0528, measured: 220.0520. **IR (ATR):** ν (cm^{-1}): 3064, 3029, 2928, 1604, 1496, 1454, 1422, 1290, 1099, 1030, 970, 909, 859, 742, 698.

The characterization data agree with literature values.[5]

(5-Phenylpentyl)(trifluoromethyl)sulfane (3c)[12]



3c

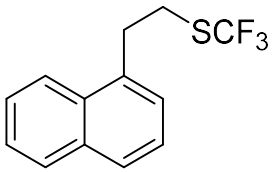
Prepared from 5-phenyl-1-pentanol (**2c**, 84 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (91 mg, 0.37 mmol, 73%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.32 – 7.27 (m, 2H, H_{Ar}), 7.22 – 7.16 (m, 3H, H_{Ar}), 2.88 (*J*=7.5, 2H, CH_2), 2.63 (dd, *J*=7.8, 7.5, 2H, CH_2), 1.78 – 1.61 (m, 4H, CH_2), 1.51 – 1.40 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -41.1. **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 142.3 (C_q), 131.3 (q, *J*=306, CF_3), 128.5 (CH), 128.5 (CH), 125.9 (CH), 35.8 (CH_2), 30.9 (CH_2), 29.9 (q, *J*=2, CH_2), 29.5 (CH_2), 28.2 (CH_2). **HRMS (EI)**: m/z calculated for $[C_{12}H_{15}F_3S]^+$ ($[M]^+$): 248.0841, measured 248.0839. **IR (ATR):** ν (cm^{-1}): 3028, 2934, 2859, 1604, 1496, 1454, 1297, 1147, 1102, 1031, 913, 797, 746, 697.

The characterization data agree with literature values.[12]

[12] J.-b. Liu, X.-h. Xu, Z.-h. Chen, F.-l. Qing, *Angew. Chem. Int. Ed.* **2015**, *54*, 897-900.

(2-(Naphthalen-1-yl)ethyl)(trifluoromethyl)sulfane (3d)[5]



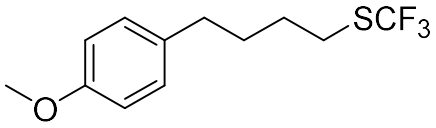
3d

Prepared from 2-(naphthalen-1-yl)ethan-1-ol (**2d**, 86 mg, 0.50 mmol) using Method A and isolated as a colourless oil (95 mg, 0.37 mmol, 74%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.00 (dm, *J*=8.2, 1H, H_{Ar}), 7.92 (dm, *J*=7.7, 1H, H_{Ar}), 7.82 (d, *J*=8.2, 1H, H_{Ar}), 7.62 – 7.52 (m, 2H, H_{Ar}), 7.46 (dd, *J*= 8.2, 7.0, 1H, H_{Ar}), 7.39 (dm, *J*=7.1, 1H, H_{Ar}), 3.50 (dd, *J*=9.5, 6.4, 2H, CH_2), 3.30 – 3.25 (m, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -41.1. **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 136.0 (C_q), 134.1 (C_q), 131.5 (C_q), 131.4 (q, *J*=306, CF_3), 129.2 (CH), 127.9 (CH), 126.9 (CH), 126.6 (CH), 125.9 (CH), 125.7 (CH), 123.1 (CH), 33.6 (CH_2), 30.6 (q, *J*=2, CH_2). **HRMS (EI)**: m/z calculated for $[C_{13}H_{11}F_3S]^+$ ($[M]^+$): 256.0528, measured 256.0536. **IR (ATR):** ν (cm^{-1}): 3061, 2941, 1598, 1510, 1458, 1395, 1233, 1217, 1097, 1044, 1018, 965, 853, 793, 774, 755, 732, 698, 660.

The characterization data agree with literature values.[5]

(4-(4-Methoxyphenyl)butyl)(trifluoromethyl)sulfane (3e)

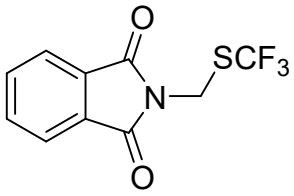


3e

Prepared from 4-(4-methoxyphenyl)-1-butanol (**2e**, 88 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (89 mg, 0.34 mmol, 68%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.10 (dm, *J*=8.2, 2H, H_{Ar}), 6.85 (dm, *J*=8.2, 2H, H_{Ar}), 3.80 (s, 3H, CH_3), 2.90 (t, *J*=6.9, 2H, CH_2), 2.60 (t, *J*=7.0, 2H, CH_2), 1.76 – 1.68 (m, 4H, CH_2). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -41.1. **^{13}C NMR (156 MHz, Chloroform-*d*) δ** = 158.0 (C_q), 133.9 (C_q), 131.3 (q, *J*=306, CF_3), 129.4 (CH), 113.9 (CH), 55.4 (CH_3), 34.4 (CH_2), 30.6 (CH_2), 29.9 (q, *J*=2, CH_2), 29.01 (CH_2). **HRMS (EI)**: m/z calculated for $[C_{12}H_{15}F_3OS]^+$ ($[M]^+$): 264.0790, measured: 264.0798. **IR (ATR):** ν (cm^{-1}): 2935, 2858, 2837, 1612, 1584, 1511, 1464, 1442, 1421, 1300, 1245, 1176, 1148, 1102, 1036, 930, 820, 809, 755, 697. **R_f**: (*n*-pentane/CH_2Cl_2, 9:1): 0.29.

2-(((Trifluoromethyl)thio)methyl)isoindoline-1,3-dione (3f)[12]



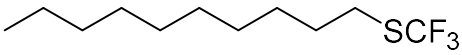
3f

Prepared from *N*-hydroxymethylphthalimide (**2f**, 72 mg, 0.50 mmol) using Method A and isolated as an orange solid (71 mg, 0.27 mmol, 54%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.94 – 7.88 (m, 2H, H_{Ar}), 7.80 – 7.75 (m, 2H, H_{Ar}), 5.09 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -40.7. **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 166.4 (C_q), 134.7 (CH), 131.9 (C_q), 130.3 (q, *J*=308, CF_3), 124.0 (CH), 36.5 (q, *J*=3, CH_2). **IR (ATR):** ν (cm^{-1}): 3002, 2928, 1780, 1713, 1627, 1610, 1466, 1412, 1380, 1308, 1294, 1154, 1102, 972, 912, 829, 795, 756, 717, 697, 680.

The characterization data agree with literature values.[12]

Decyl(trifluoromethyl)sulfane (3g)[8]



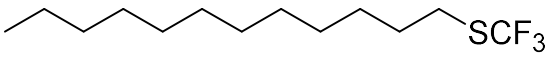
3g

Prepared from 1-decanol (**2g**, 96 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (107 mg, 0.44 mmol, 88%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 2.87 (t, *J*=7.4, 2H, CH_2SCF_3), 1.74 – 1.63 (m, 2H, CH_2), 1.45 – 1.34 (m, 2H, CH_2), 1.33 – 1.23 (m, 12H, CH_2), 0.88 (t, *J*=7.0, 3H, CH_3). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -42.0. **^{13}C NMR (101 MHz, Chloroform-*d*) δ =** 131.4 (q, *J*=306, SCF_3), 32.1 (CH_2), 30.0 (q, *J*=3, CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 22.8 (CH_2), 14.2 (CH_3). **IR (ATR):** ν (cm^{-1}): 2925, 2855, 1466, 1150, 1108, 756, 721.

The characterization data agree with literature values.[8]

Dodecyl(trifluoromethyl)sulfane (3h)[8]



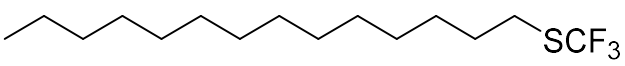
3h

Prepared from 1-dodecanol (**2h**, 112 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (110 mg, 0.41 mmol, 81%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 2.87 (t, *J*=7.4, 2H, CH_2), 1.73 – 1.64 (m, 2H, CH_2), 1.44 – 1.35 (m, 2H, CH_2), 1.34 – 1.19 (m, 16H, CH_2), 0.88 (t, *J*=6.8, 3H, CH_3). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -42.0. **^{13}C NMR (101 MHz, Chloroform-*d*) δ =** 131.3 (q, *J*=305, CF_3), 32.0 (CH_2), 30.0 (q, *J*=2, CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 22.8 (CH_2), 14.2 (CH_3) *Note: two ^{13}C peaks are not observed due to overlapping.* **HRMS (EI)**: m/z calculated for $[C_{12}H_{25}S]^+$ ($[M-CF_3]^+$): 201.1671, measured 201.1693. *Note: a molecular ion peak could not be identified by EI*. **IR (ATR):** ν (cm^{-1}): 2924, 2854, 1466, 1378, 1299, 1151, 1110, 756, 721.

The characterization data agree with literature values.[8]

Tetradecyl(trifluoromethyl)sulfane (3i)

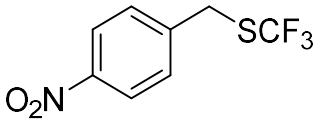


3i

Prepared from 1-tetradecanol (**2i**, 107 mg, 0.50 mmol) using Method A and isolated as a colourless liquid (116 mg, 0.39 mmol, 78%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 2.87 (t, *J*=7.5, 2H, CH_2), 1.69 (quin, *J*=7.5, 2H, CH_2), 1.42 – 1.36 (m, 2H, CH_2), 1.34 – 1.21 (m, 20H, CH_2), 0.88 (t, *J*=7.0, 3H). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -41.2 . **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 134.6 (q, *J*=306, CF_3), 32.1 (CH_2), 30.0 (q, *J*=2, CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 22.9 (CH_2), 14.3 (CH_3) *Note: one ^{13}C peak is not observed due to overlapping.* **CHNS Elemental Analysis:** calculated for $C_{15}H_{29}F_3S$: C 60.37; H 9.79; N 0.00, S 10.74; measured: C 60.39; H 9.28; N 0.00; S 10.76. **IR (ATR):** ν (cm^{-1}): 2923, 2854, 1466, 1378, 1308, 1151, 1110, 756, 721. **R_f**: (*n*-pentane): 0.93.

(4-Nitrobenzyl)(trifluoromethyl)sulfane (6b)[12]



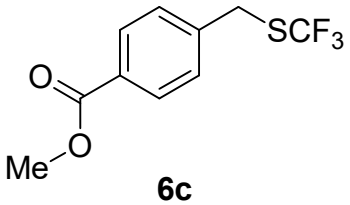
6b

Prepared from (4-nitrophenyl)methanol (**5b**, 77 mg, 0.50 mmol,) using Method A and isolated as a orange liquid (104 mg, 0.44 mmol, 88%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.20 (dm, *J*=8.8, 2H, H_{Ar}), 7.53 (dm, *J*=8.8, 2H, H_{Ar}), 4.18 (s, 2H). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -41.2. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 147.7 (C_q), 143.2 (C_q), 130.4 (q, *J*=307, CF_3), 129.9 (CH), 124.2 (CH), 33.6 (q, *J*=3, CH_2). **HRMS (EI)**: m/z calculated for $[C_8H_6F_3NO_2S]^+$ ($[M]^+$): 237.0066, measured 237.0070. **IR (ATR):** ν (cm^{-1}): 3113, 3083, 2946, 2859, 1931, 1684, 1602, 1519, 1495, 1424, 1344, 1257, 1203, 1095, 1015, 973, 890, 858, 820, 802, 755, 707.

The characterization data agree with literature values.[12]

Methyl 4-(((trifluoromethyl)thio)methyl)benzoate (6c)[7]



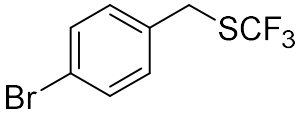
6c

Prepared from methyl 4-(hydroxymethyl)benzoate (**5c**, 83 mg, 0.50 mmol) using Method A and isolated as a colourless liquid (118 mg, 0.47 mmol, 94%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.02 (d, *J*=8.4, 2H, H_{Ar}), 7.41 (d, *J*=8.4, 2H, H_{Ar}), 4.13 (s, 2H, CH_2), 3.91 (s, 3H, CH_3). **^{19}F NMR (565 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 166.7 (C_q), 140.5 (C_q), 130.6 (q, *J*=307, CF_3), 130.2 (CH), 130.0 (C_q), 129.0 (CH), 52.3 (CH_3), 34.0 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_{10}H_9F_3O_2S]^+$ ($[M]^+$): 250.0270, measured: 250.0257. **IR (ATR):** ν (cm^{-1}): 2954, 1719, 1612, 1577, 1509, 1436, 1415, 1279, 1179, 1145, 1097, 1020, 966, 890, 860, 838, 797, 774, 756, 725, 713.

The characterization data agree with literature values.[7]

(4-Bromobenzyl)(trifluoromethyl)sulfane (6e)[7]



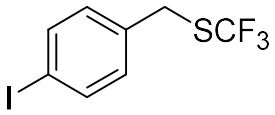
6e

Prepared from (4-bromophenyl)methanol (**5e,** 94 mg, 0.50 mmol) using Method A and isolated as a colourless liquid (121 mg, 0.45 mmol, 89%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.46 (d, *J*=8.4, 2H, H_{Ar}), 6.22 (d, *J*=8.4, 2H, H_{Ar}), 4.07 (s, 2H, CH_2). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -41.4. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 134.4 (C_q), 132.2 (CH), 130.6 (q, *J*=308, CF_3), 130.7 (CH), 122.2 (C_q), 33.8 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_6BrF_3S]^+$ ($[M]^+$): 269.9320, measured: 269.9326. **IR (ATR):** ν (cm^{-1}): 2928, 1592, 1488, 1441, 1421, 1403, 1254, 1144, 1098, 1070, 1011, 880, 828, 816, 804, 756, 741, 723, 681.

The characterization data agree with literature values.[7]

(4-Iodobenzyl)(trifluoromethyl)sulfane (6f)[7]



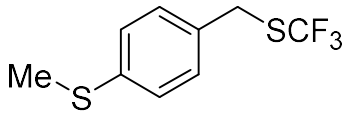
6f

Prepared from (4-iodophenyl)methanol (**5f**, 117 mg, 0.50 mmol) using Method A and isolated as a yellow liquid (91 mg, 0.29 mmol, 57%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.67 (dm, *J*=8.5, 2H, H_{Ar}), 7.09 (dm, *J*=8.3, 2H, H_{Ar}), 4.04 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 138.1 (CH), 135.0 (C_q), 130.6 (q, J=307, CF_3), 130.9 (CH), 93.7 (C_q), 33.9 (q, *J*=2, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_6F_3IS]^+$ ($[M]^+$): 317.9181, measured: 317.9165. **IR (ATR):** ν (cm^{-1}): 3031, 2924, 1901, 1588, 1484, 1420, 1398, 1253, 1201, 1096, 1060, 1008, 961, 945, 879, 824, 809, 755, 739, 721, 679.

The characterization data agree with literature values.[7]

Methyl(4-(((trifluoromethyl)thio)methyl)phenyl)sulfane (6g)

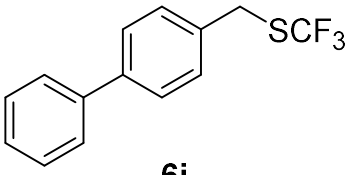


6g

Prepared from (4-(methylthio)phenyl)methanol (**5g**, 77 mg, 0.50 mmol) using Method A and isolated as an orange oil (107 mg, 0,45 mmol, 90%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.26 (dm, *J*=8.5, 2H, H_{Ar}), 7.22 (dm, *J*=8.4, 2H, H_{Ar}), 4.08 (s, 2H, CH_2), 2.47 (s, 3H, CH_3). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -41.4. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 138.7 (C_q), 131.7 (C_q), 130.7 (q, *J*=308, CF_3), 129.5 (CH), 126.8 (CH), 34.0 (q, *J*=3, CH_2), 15.7 (CH_3). **HRMS (EI):** m/z calculated for $[C_9H_9F_3S_2]^+$ ($[M]^+$): 238.0092, measured: 238.0103. **IR (ATR):** ν (cm^{-1}): 3024, 2985, 2923, 1682, 1600, 1494, 1439, 1405, 1254, 1143, 1092, 1016, 968, 957, 878, 826, 814, 755, 742, 727, 687. **R_f**: (*n*-pentane/CH_2Cl_2, 9:1): 0.55.

([1,1'-biphenyl]-4-ylmethyl)(trifluoromethyl)sulfane (6j)[7]



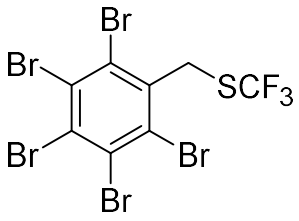
6j

Prepared from (1,1'-biphenyl-4-yl)methanol (**5j**, 92 mg, 0.50 mmol) using Method A and isolated as a white solid (89 mg, 0.33 mmol, 67%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.63 – 7.58 (m, 4H, H_{Ar}), 7.50 – 7.36 (m, 5H, H_{Ar}), 4.19 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 141.1 (C_q), 140.5 (C_q), 134.1 (C_q), 130.9 (q, *J*=307, CF_3), 129.5 (CH), 129.0 (CH), 127.7 (CH), 127.7 (CH), 127.2 (CH), 34.1 (q, *J*=2, CH_2). **HRMS (EI):** m/z calculated for $[C_{14}H_{11}F_3S]^+$ ($[M]^+$): 268.0528, measured: 268.0519. **IR (ATR):** ν (cm^{-1}): 3033, 2924, 1487, 1452, 1441, 1408, 1096, 1006, 844, 769, 755, 736, 714, 688.

The characterization data agree with literature values.[7]

((Perbromophenyl)methyl)(trifluoromethyl)sulfane (6k)

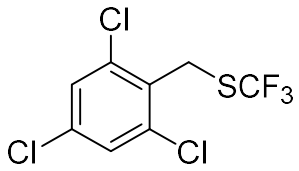


6k

Prepared from (perbromophenyl)methanol (**5k**, 251 mg, 0.50 mmol) using Method A and isolated as a white solid (132 mg, 0.22 mmol, 45%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 4.73 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -40.9. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 137.3 (C_q), 130.4 (q, *J*=307, CF_3), 130.0 (C_q), 129.8 (C_q), 127.7 (C_q), 40.6 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_2Br_5F_3S]^+$ ($[M]^+$): 581.5741, measured: 581.5741. **IR (ATR):** ν (cm^{-1}): 2923, 2853, 2223, 1514, 1460, 1416, 1405, 1337, 1322, 1307, 1271, 1256, 1229, 1213, 1189, 1164, 1148, 1098, 1061, 899, 866, 754, 702, 666. **R_f**: (*n*-pentane): 0.70.

(2,4,6-Trichlorobenzyl)(trifluoromethyl)sulfane (6m)

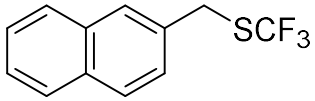


6m

Prepared from (2,4,6-trichlorophenyl)methanol (**5m**, 106 mg, 0.50 mmol) using Method A and isolated as a colourless liquid (135 mg, 0.46 mmol, 91%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.36 (s, 2H, H_{Ar}), 4.39 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 136.6 (C_q), 134.9 (C_q), 130.6 (C_q), 130.6 (q, *J*=307, CF_3), 128.6 (CH), 29.3 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_4Cl_3F_3S]^+$ ($[M]^+$): 293.9046, measured: 293.9025. **IR (ATR):** ν (cm^{-1}): 3083, 2927, 2853, 1729, 1579, 1550, 1441, 1420, 1391, 1376, 1257, 1236, 1207, 1157, 1099, 1072, 897, 874, 856, 811, 785, 755, 735, 679, 658. **R_f**: (*n*-pentane): 0.87.

(Naphthalen-2-ylmethyl)(trifluoromethyl)sulfane (6n)[7]



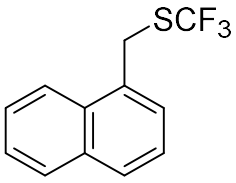
6n

Prepared from naphthalen-2-ylmethanol (**5n**, 79 mg, 0.50 mmol) using Method A and isolated as a pale yellow solid (70 mg, 0.29 mmol, 58%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.89 – 7.79 (m, 4H, H_{Ar}), 7.56 – 7.45 (m, 3H, H_{Ar}), 4.31 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 133.4 (C_q), 133.0 (C_q), 132.5 (C_q), 130.9 (q, *J*=307, CF_3), 128.9 (CH), 128.1 (CH), 127.9 (CH), 127.9 (CH), 126.7 (CH), 126.6 (CH), 126.5 (CH), 34.7 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_{12}H_9F_3S]^+$ ($[M]^+$): 242.0372, measured: 242.0368. **IR (ATR):** ν (cm^{-1}): 3049, 2927, 1598, 1578, 1512, 1453, 1398, 1353, 1250, 1236, 1219, 1138, 1097, 1017, 970, 950, 882, 867, 799, 791, 773, 756, 740, 712.

The characterization data agree with literature values.[7]

(Naphthalen-1-ylmethyl)(trifluoromethyl)sulfane (6o)[7]



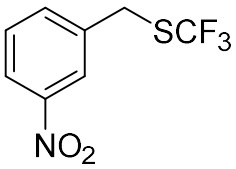
6o

Prepared from naphthalen-1-ylmethanol (**5o**, 79 mg, 0.50 mmol) using Method A and isolated as a pale yellow oil (46 mg, 0.19 mmol, 38%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.05 (d, *J*=8.4, 1H, H_{Ar}), 7.91 (dm, *J*=8.0, 1H, H_{Ar}), 7.85 (d, *J*=8.3, 1H, H_{Ar}), 7.61 (ddd, *J*=8.4, 6.9, 1.5, 1H, H_{Ar}), 7.58 – 7.50 (m, 2H, H_{Ar}), 7.44 (dd, *J*=8.2, 7.0, 1H, H_{Ar}), 4.61 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.7. **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 134.1 (C_q), 131.9 (C_q), 130.9 (q, *J*=307, CF_3), 130.2 (C_q), 129.4 (CH), 129.2 (CH), 128.2 (CH), 126.9 (CH), 126.3 (CH), 125.5 (CH), 123.3 (CH), 32.2 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_{12}H_9F_3S]^+$ ($[M]^+$): 242.0372, measured: 242.0371. **IR (ATR):** ν (cm^{-1}): 3049, 2927, 1598, 1578, 1512, 1453, 1398, 1353, 1250, 1236, 1219, 1138, 1097, 1017, 970, 950, 882, 867, 799, 791, 773, 756, 740, 712.

The characterization data agree with literature values.[7]

(3-Nitrobenzyl)(trifluoromethyl)sulfane (3p)[6]



6p

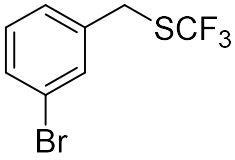
Prepared from (3-nitrophenyl)methanol (**5p**, 59 µL, 0.50 mmol) using Method A and isolated as a yellow liquid (105 mg, 0.44 mmol, 89%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.24 (s, 1H, H_{Ar}), 8.18 (dm, *J*=8.2, 1H, H_{Ar}), 7.70 (d, *J*=8.0, 1H, H_{Ar}), 7.55 (t, *J*=8.0, 1H, H_{Ar}), 4.20 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.2. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 148.5 (C_q), 137.9 (C_q), 135.0 (CH), 130.4 (q, *J*=307, CF_3), 130.0 (CH), 123.9 (CH), 123.1 (CH), 33.6 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_6F_3NO_2S]^+$ ($[M]^+$):

237.0066, measured: 237.0067. **IR (ATR):** ν (cm^{-1}): 3060, 2927, 2846, 1596, 1571, 1475, 1428, 1253, 1202, 1099, 1072, 997, 910, 888, 868, 849, 785, 756, 733, 708, 682, 667.

The characterization data agree with literature values.[6]

(3-Bromobenzyl)(trifluoromethyl)sulfane (6q)[7]



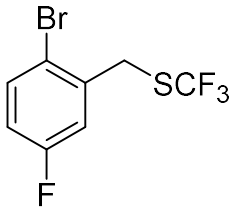
6q

Prepared from (3-bromophenyl)methanol (**5q**, 60 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (113 mg, 0.42 mmol, 83%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.51 (t, *J*=1.9, 1H, H_{Ar}), 7.44 (ddd, *J*=7.8, 2.0, 1.3, 1H, H_{Ar}), 7.28 (dt, *J*=7.7, 1.5, 1H, H_{Ar}), 7.22 (t, *J*=7.8, 1H, H_{Ar}), 4.07 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 137.6 (C_q), 132.0 (CH), 131.3 (CH), 130.6 (q, *J*=307, CF_3), 130.5 (CH), 127.6 (CH), 122.9 (C_q), 33.7 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_6BrF_3S]^+$ ($[M]^+$): 269.9320, measured: 269.9320. **IR (ATR):** ν (cm^{-1}): 3060, 2927, 2846, 1596, 1571, 1475, 1428, 1253, 1202, 1099, 1072, 997, 910, 888, 868, 849, 785, 756, 733, 708, 682, 667.

The characterization data agree with literature values.[7]

(2-Bromo-5-fluorobenzyl)(trifluoromethyl)sulfane (6r)[4]



6r

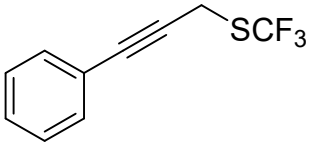
Prepared from (2-bromo-5-fluorophenyl)methanol (**5r**, 103 mg, 0.50 mmol) using Method A and isolated as a colourless liquid (96 mg, 0.33 mmol, 67%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.54 (dd, *J*=8.8, 5.3, 1H, H_{Ar}), 7.15 (dd, *J*=8.9, 3.0, 1H, H_{Ar}), 6.92 (ddd, *J*=8.7, 7.8, 3.9, 1H, H_{Ar}), 4.17 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.2 (SCF_3), -113.7 (F_{Ar}). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 162.0 (d, *J*=248, C_qF), 137.4 (d, *J*=8, C_q), 134.5 (d, *J*=8, CH), 130.7 (q, *J*=307, CF_3), 118.7 (C_q), 118.1 (d, *J*=24, CH), 117.1 (d, *J*=22, CH), 34.7 (qd,

J=3, 2, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_5BrF_4S]^+$ ($[M]^+$): 287.9231, measured: 287.9232. **IR (ATR):** ν (cm^{-1}): 3079, 2924, 1605, 1583, 1469, 1440, 1409, 1274, 1254, 1237, 1146, 1098, 1032, 958, 899, 876, 862, 812, 775, 755, 742, 731, 679.

The characterization data agree with literature values.[4]

(3-Phenylprop-2-yn-1-yl)(trifluoromethyl)sulfane (6t)[13]



6t

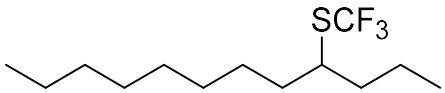
Prepared from 3-phenyl-2-propyn-1-ol (**5t**, 62 µL, 0.50 mmol) using Method A and isolated as a yellow liquid (72 mg, 0.33 mmol, 66%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.48 – 7.43 (m, 2H, H_{Ar}), 7.38 – 7.30 (m, 3H, H_{Ar}), 3.90 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -42.6. **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 131.9 (CH), 130.5 (q, *J*=308, CF_3), 128.8 (CH), 128.5 (CH), 122.4 (C_q), 84.7 (C_q), 82.34 (C_q), 19.6 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_{10}H_7F_3S]^+$ ($[M]^+$): 216.0215, measured: 216.0215. **IR (ATR):** ν (cm^{-1}): 3063, 2926, 1707, 1599, 1573, 1491, 1443, 1411, 1317, 1272, 1243, 1149, 1100, 1029, 1002, 981, 916, 885, 864, 754, 731, 714, 688.

The characterization data agree with literature values.[13]

[13] M. Rong, D. Li, R. Huang, Y. Huang, X. Han, Z. Weng, *Eur. J. Org. Chem.* **2014**, 5010-5016

Dodecan-4-yl(trifluoromethyl)sulfane (8a)[12]



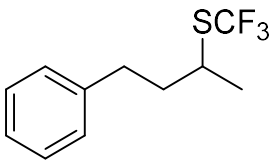
8a

Prepared from dodecan-4-ol (**7a**, 112.4 µL, 0.50 mmol) using Method B and isolated as a colourless liquid (83 mg of 1.96:1 mixture with dodecene regioisomers: calculated yield of **8a**: 47%).

*Only peaks corresponding to **8a** reported:* **^{1}H NMR (400 MHz, Chloroform-*d*) δ** = 3.16 (pent, *J*=6.5, 1H, CH), 1.73 – 1.55 (m, 4H, CH_2), 1.52 – 1.21 (m, 14 H, CH_2), 0.99 – 0.86 (m, 6H, CH_3). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -39.1. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 131.6 (q, *J*=307, CF_3), 46.6 (q, *J*=1, CH), 37.4 (CH_2), 35.2 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.5 (CH_2), 22.8 (CH_2), 19.8 (CH_2), 14.2 (CH_3), 13.9 (CH_3).

The characterization data agree with literature values.[12]

(4-Phenylbutan-2-yl)(trifluoromethyl)sulfane (8b)[12]



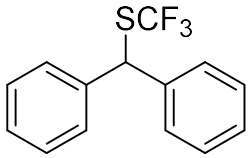
8b

Prepared from 4-phenylbutan-2-ol (**7b**, 77.4 µL, 0.50 mmol) using Method C and isolated as a colourless liquid (61 mg, 0.26 mmol, 52%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.31 (dd, *J*=7.3, 6.8, 2H, H_{Ar}), 7.24 – 7.19 (m, 3H, H_{Ar}), 3.32 (sext, *J*=6.9, 1H, CH), 2.82 – 2.73 (m, 2H, CH_2), 2.02 – 1.90 (m, 2H, CH_2), 1.48 (d, *J*=6.9, 3H, CH_3). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -38.3. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 141.0 (C_q), 131.3 (q, *J*=306, CF_3), 128.7 (CH), 128.5 (CH), 126.3 (CH), 40.6 (CH), 38.6 (CH_2), 32.9 (CH_2), 22.6 (q, *J*=1, CH_3). **HRMS (EI)**: m/z calculated for $[C_{11}H_{13}F_3S]^+$ ($[M]^+$): 234.0685, measured: 234.0685. **IR (ATR):** ν (cm^{-1}): 3029, 2931, 2863, 1604, 1496, 1455, 1383, 1297, 1247, 1145, 1100, 1031, 913, 822, 746, 698, 659.

The characterization data agree with literature values.[12]

Benzhydryl(trifluoromethyl)sulfane (8c)[12]



8c

Prepared from diphenylmethanol (**7c**, 92 mg, 0.50 mmol) using Method D and isolated as a yellow liquid (74 mg, 0.28 mmol, 55%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.43 – 7.41 (m, 4H, H_{Ar}), 7.38 – 7.34 (m, 4H, H_{Ar}), 7.31 – 7.28 (m, 2H, H_{Ar}), 5.71 (s, 1H, CH). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -40.7. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 139.3 (C_q), 130.1 (q, *J*=308, CF_3), 128.9 (CH), 128.3 (CH), 128.1 (CH), 53.6 (q, *J*=2, CH). **HRMS (EI):** m/z calculated for $[C_{14}H_{11}F_3S]^+$ ($[M]^+$): 268.0528, measured: 268.0540. **IR (ATR):** ν (cm^{-1}): 3063, 3031, 1601, 1493, 1450, 1336, 1101, 1031, 1002, 967, 918, 826, 782, 746, 714, 693.

The characterization data agree with literature values.[12]

4.3 General Procedures for the Deoxytrifluoromethylselenylation reaction of Alcohols with BT-SeCF$_3$

Method E: The benzylic or propargylic alcohol (**5**, 0.20 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SeCF$_3$** (112 mg, 0.250 mmol, 1.25 eq) was added and the reaction mixture was cooled to 0 °C. NEt(*i*Pr)$_2$ (70 µL, 0.40 mmol, 2.0 eq) was then added dropwise and the reaction mixture was stirred for 2 h at rt. The reaction mixture was concentrated *in vacuo* and purified by column chromatography over silica gel.

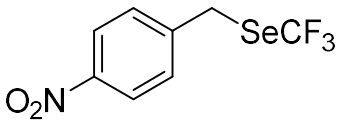
Method F: The aliphatic alcohol (**2**, 0.20 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SeCF$_3$** (112 mg, 0.250 mmol, 1.25 eq) was added and the reaction mixture was cooled to −40 °C. NEt(*i*Pr)$_2$ (70 µL, 0.40 mmol, 2.0 eq) was then added dropwise and the reaction mixture was stirred for 2 h at −40 °C. The reaction mixture was concentrated *in vacuo* and purified by column chromatography over silica gel.

Method G: The aliphatic alcohol (**7**, 0.20 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SeCF$_3$** (179 mg, 0.400 mmol, 2.00 eq) was added and the reaction mixture was cooled to −40 °C. NEt(*i*Pr)$_2$ (70 µL, 0.40 mmol, 2.0 eq) was then added dropwise and the reaction mixture was stirred for 2 h at

−40 °C. The reaction mixture was concentrated *in vacuo* and purified by column chromatography over silica gel.

4.4 Characterization Data for Deoxytrifluoromethylselenylation Products 10

(4-Nitrobenzyl)(trifluoromethyl)selane (10a)[11]



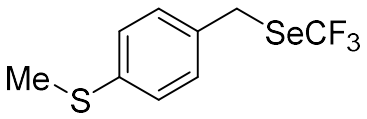
10a

Prepared from (4-nitrophenyl)methanol (**5b**, 31 mg, 0.20 mmol) using Method E and isolated as a pale yellow liquid (50 mg, 0.18 mmol, 88%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.19 (dm, *J*=8.7, 2H, H_{Ar}), 7.51 (dm, *J*=8.7, 2H, H_{Ar}), 4.28 (s, 2H). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -34.0. **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 147.5 (C_q), 144.4 (C_q), 130.1 (CH), 124.2 (CH), 122.5 (q, *J*=332, CF_3), 28.1 (q, *J*=4, CH_2). **HRMS (EI)**: m/z calculated for $[C_8H_6F_3NO_2Se]^+$ ($[M]^+$): 284.9510, measured 284.9536. **IR (ATR):** ν (cm^{-1}): 3080, 2948, 2857, 1600, 1517, 1424, 1343, 1322, 1088, 1069, 1015, 973, 858, 798, 752, 738, 695.

The characterization data agree with literature values.[11]

Methyl(4-(((trifluoromethyl)selanyl)methyl)phenyl)sulfane (10b)

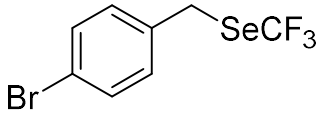


10b

Prepared from (4-(methylthio)phenyl)methanol (**5g**, 31 mg, 0.20 mmol) using Method E and isolated as a yellow liquid (43 mg, 0.15 mmol, 75%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.26 (dt, *J*=8.4, 2.1, 2H, H_{Ar}), 7.21 (dt, *J*=8.4, 2.1, 2H, H_{Ar}), 4.22 (s, 2H), 2.48 (s, 3H). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -34.2. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 138.4 (C_q), 132.8 (C_q), 129.6 (CH), 126.8 (CH), 123.0 (q, *J*=332, CF_3), 28.9 (q, *J*=2, CH_2), 15.7 (CH_3). **HRMS (EI):** m/z calculated for $[C_9H_9F_3SSe]^+$ ($[M]^+$): 285.9537, measured: 285.9545. **IR (ATR):** ν (cm^{-1}): 3022, 2984, 2922, 1599, 1493, 1438, 1404, 1325, 1275, 1222, 1198, 1087, 1069, 1015, 967, 957, 824, 811, 737, 719. **R_f**: (*n*-pentane/CH_2Cl_2, 9:1): 0.58.

(4-Bromobenzyl)(trifluoromethyl)selane (10c)

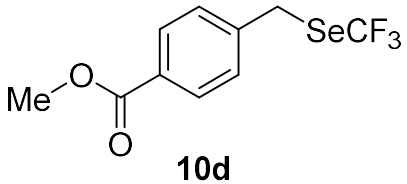


10c

Prepared from (4-bromophenyl)methanol (**5e,** 37 mg, 0.20 mmol,) using Method E and isolated as a yellow liquid (48 mg, 0.15 mmol, 76%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.46 (dm, *J*=8.5, 2H, H_{Ar}), 7.22 (dm, *J*=8.5, 2H, H_{Ar}), 4.18 (s, 2H, CH_2). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -34.2. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 135.5 (C_q), 132.2 (CH), 130.8 (CH), 122.8 (q, *J*=331, CF_3), 121.9 (C_q), 28.5 (q, *J*=2, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_6BrF_3Se]^+$ ($[M]^+$): 317.8765, measured: 317.8758. **IR (ATR):** ν (cm^{-1}): 3035, 2952, 1899, 1591, 1487, 1420, 1402, 1276, 1218, 1195, 1090, 1068, 1011, 959, 944, 826, 800, 738, 713, 663. **R_f**: (*n*-pentane): 0.70.

Methyl 4-(((trifluoromethyl)selanyl)methyl)benzoate (10d)

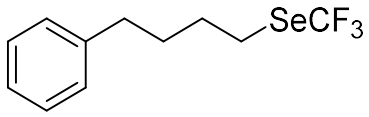


10d

Prepared from methyl 4-(hydroxymethyl)benzoate (**5c**, 33 mg, 0.20 mmol) using Method E and isolated as a colourless liquid (55 mg, 0.19 mmol, 93%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.00 (dm, *J*=8.3, 2H, H_{Ar}), 7.40 (dm, *J*=8.3, 2H, H_{Ar}), 4.25 (s, 2H, CH_2), 3.91 (s, 3H, CH_3). **^{19}F NMR (565 MHz, Chloroform-*d*)** δ = -34.2. **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 166.7 (C_q), 141.7 (C_q), 130.3 (CH), 129.7 (C_q), 129.1 (CH), 123.7 (q, *J*=331, CF_3), 52.3 (CH_3), 28.7 (q, *J*=2, CH_2). **HRMS (EI):** m/z calculated for $[C_{10}H_9F_3O_2Se]^+$ ($[M]^+$): 297.9714, measured: 297.9712. **IR (ATR):** ν (cm^{-1}): 3000, 2953, 2845, 1931, 1717, 1611, 1576, 1509, 1436, 1415, 1367, 1313, 1278, 1223, 1194, 1181, 1088, 1069, 1019, 966, 863, 838, 811, 794, 768, 738, 703, 665. **R_f**: (*n*-pentane/CH_2Cl_2, 1:1): 0.48.

(4-Phenylbutyl)(trifluoromethyl)selane (10e)

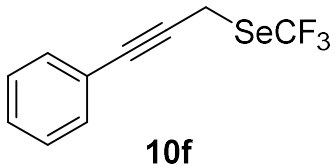


10e

Prepared from 4-phenyl-1-butanol (**2a**, 31 µL, 0.20 mmol) using Method F and isolated as a colourless liquid (31 mg, 0.11 mmol, 55%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.32 – 7.26 (m, 2H, H_{Ar}), 7.22 – 7.15 (m, 3H), 3.00 (t, *J*=7.3, 2H, CH_2), 2.65 (t, *J*=7.3, 2H, CH_2), 1.88 – 1.70 (m, 4H). **^{19}F NMR (565 MHz, Chloroform-*d*)** δ = -34.0. **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 141.9 (C_q), 128.5 (CH), 128.5 (CH), 126.1 (CH), 122.8 (q, *J*=330, CF_3), 35.3 (CH_2), 31.4 (CH_2), 29.9 (CH_2), 25.8 (q, *J*=1, CH_2). **HRMS (EI):** m/z calculated for $[C_{11}H_{13}F_3Se]^+$ ($[M]^+$): 282.0129, measured: 282.0141. **IR (ATR):** ν (cm^{-1}): 3028, 2927, 2856, 1604, 1496, 1454, 1254, 1224, 1198, 1092, 1030, 969, 908, 803, 737, 697. **R_f**: (*n*-pentane): 0.43.

(3-Phenylprop-2-yn-1-yl)(trifluoromethyl)selane (10f)[14]



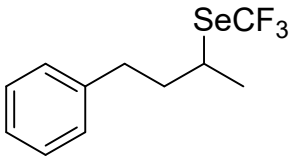
10f

Prepared from 3-phenyl-2-propyn-1-ol (**5t**, 26 mg, 0.20 mmol) using Method E and isolated as a colourless liquid (43 mg, 0.16 mmol, 82%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.42 – 7.40 (m, 2H, H_{Ar}), 7.32 – 7.28 (m, 3H, H_{Ar}), 3.90 (s, 2H, CH_2). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -34.5. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 131.8 (CH), 128.7 (CH), 128.5 (CH), 122.6 (q, *J*=332, CF_3), 122.5 (C_q), 85.0 (C_q), 83.5 (C_q), 11.7 (q, *J*=3, CH_2). **IR (ATR):** ν (cm^{-1}): 3060, 2929, 2190, 1664, 1598, 1491, 1443, 1408, 1318, 1271, 1200, 1119, 1090, 1070, 1030, 1002, 977, 916, 869, 843, 822, 755, 738, 712, 688, 669.

The characterization data agree with literature values.[14]

(4-Phenylbutan-2-yl)(trifluoromethyl)selane (10g)[15]



10g

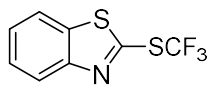
Prepared from 4-phenylbutan-2-ol (**7b**, 31 µL, 0.20 mmol, 1.0 eq) using Method G and isolated as a colourless liquid (25 mg, 0.088 mmol, 44%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.30 (tm, *J*=7.6, 2H, H_{Ar}), 7.23 – 7.18 (m, 3H, H_{Ar}), 3.53 (sext, *J*=7.0, 1H, CH), 2.82 – 2.72 (m, 2H, CH_2), 2.12 – 1.96 (m, 4H, CH_2), 1.63 (d, *J*=7.0, CH_3). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -31.9. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 140.9 (C_q), 128.6 (CH), 128.5 (CH), 126.3 (CH), 123.2 (q, *J*=331, CF_3), 39.5 (q, *J*=1), 39.3 (q, *J*=1), 33.8, 23.1 (q, *J*=1). **HRMS (EI):** m/z calculated for $[C_{11}H_{13}F_3Se]^+$ ($[M]^+$): 282.0129, measured: 282.0120. **IR (ATR):** ν (cm^{-1}): 3029, 2925, 2858, 1604, 1496, 1454, 1382, 1260, 1233, 1213, 1092, 1031, 912, 818, 738, 697.

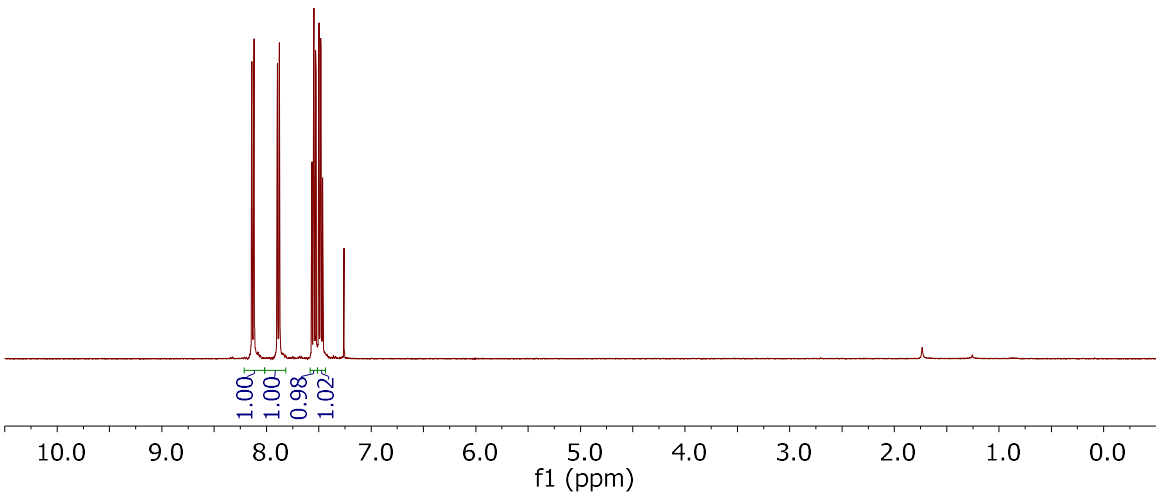
The characterization data agree with literature values.[15]

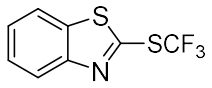
[14] M. Rong, R. Huang, Y. You, Z. Weng, *Tetrahedron* **2014**, *70*, 8872-8878.
[15] C. Chen, L. Ouyang, Q. Lin, Y. Liu, C. Hou, Y. Yuan, Z. Weng, *Chem. Eur. J.* **2014**, *20*, 657-661.

5 NMR Spectra of Novel Compounds

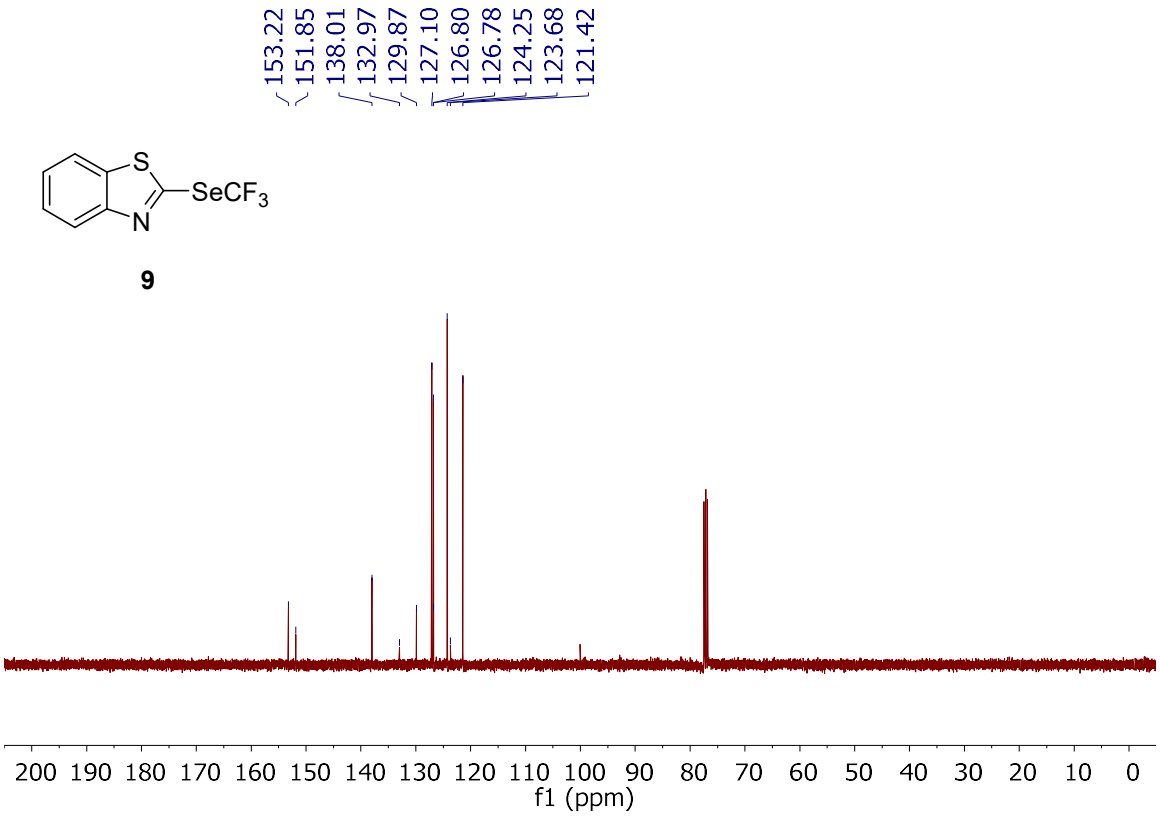


1

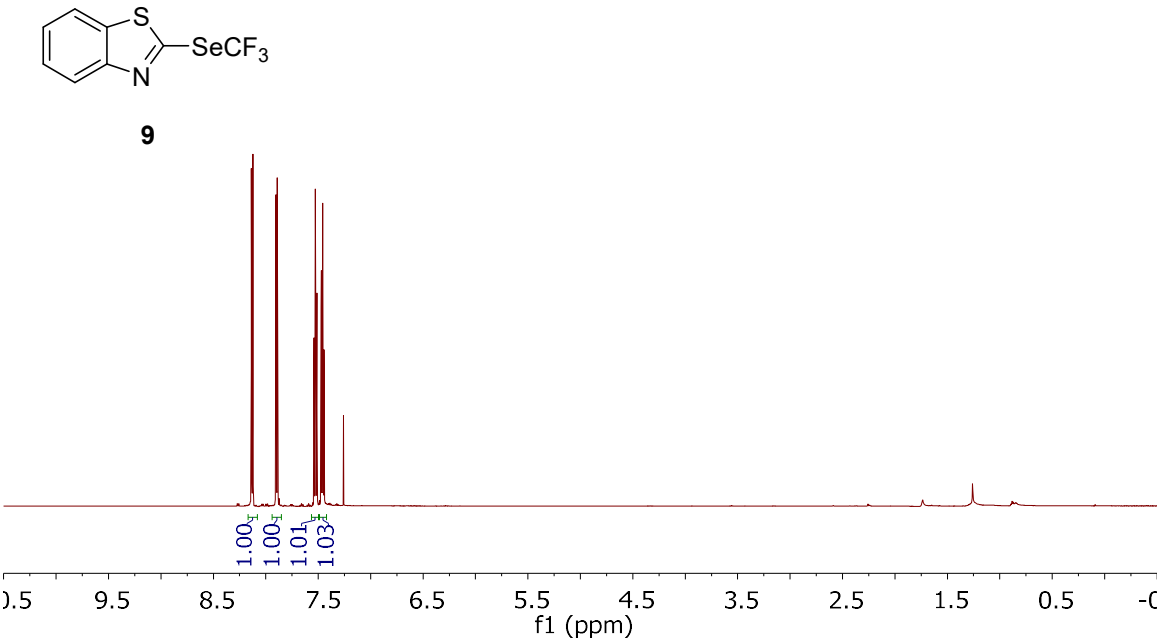




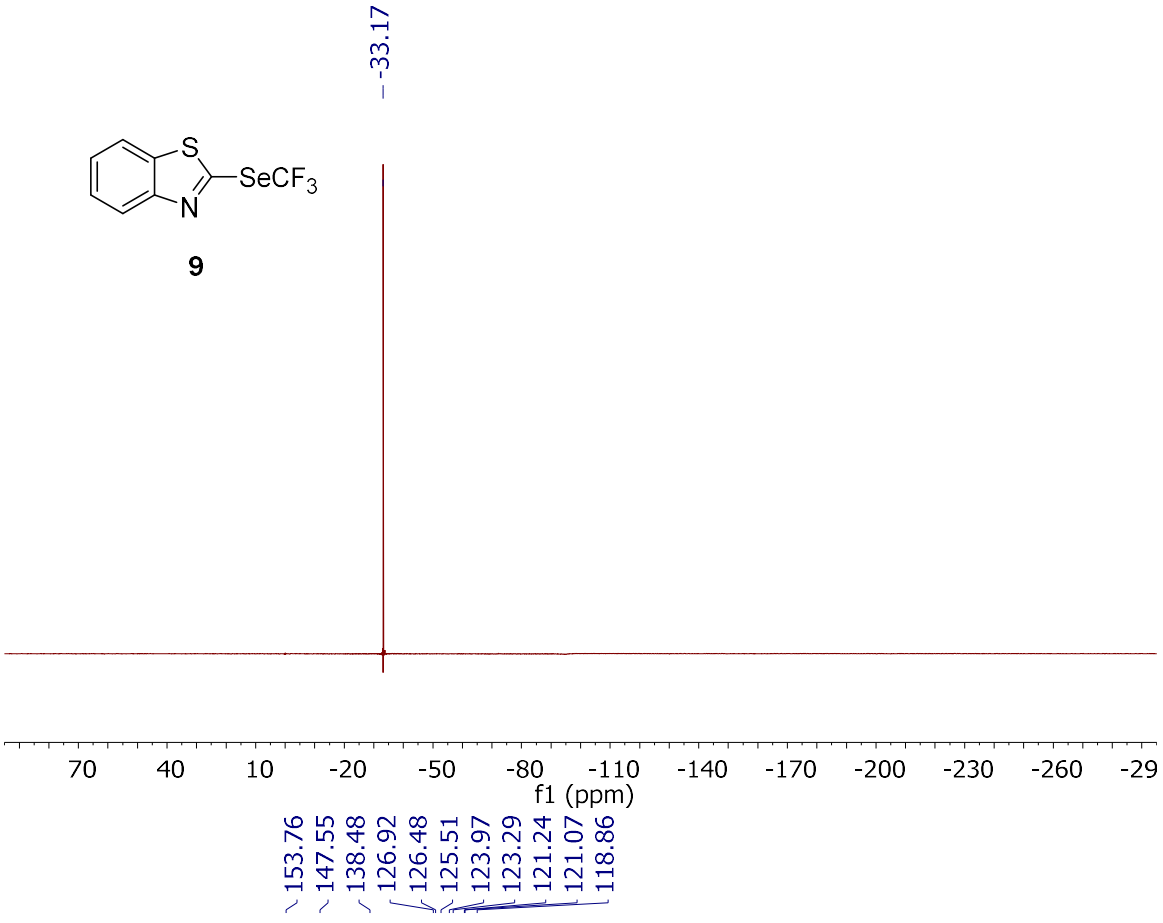
1

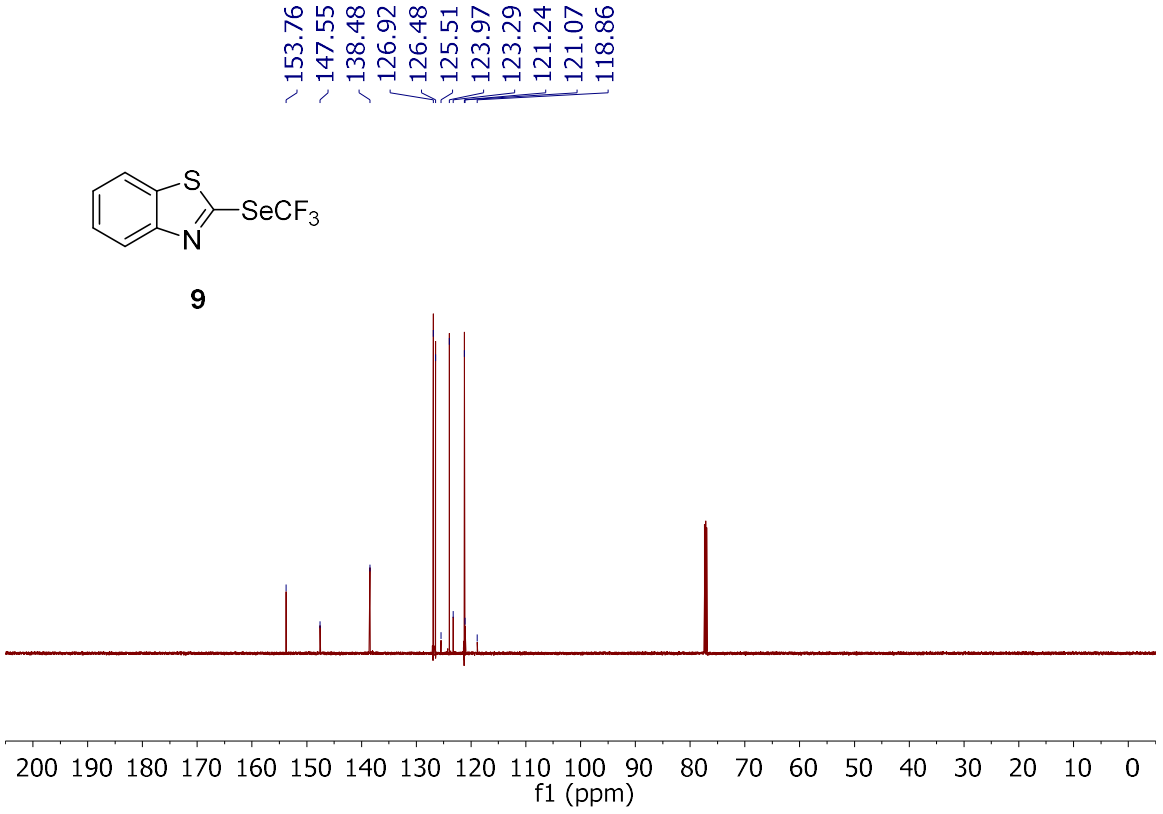

153.22
151.85
138.01
132.97
129.87
127.10
126.80
126.78
124.25
123.68
121.42
S
N
SeCF3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

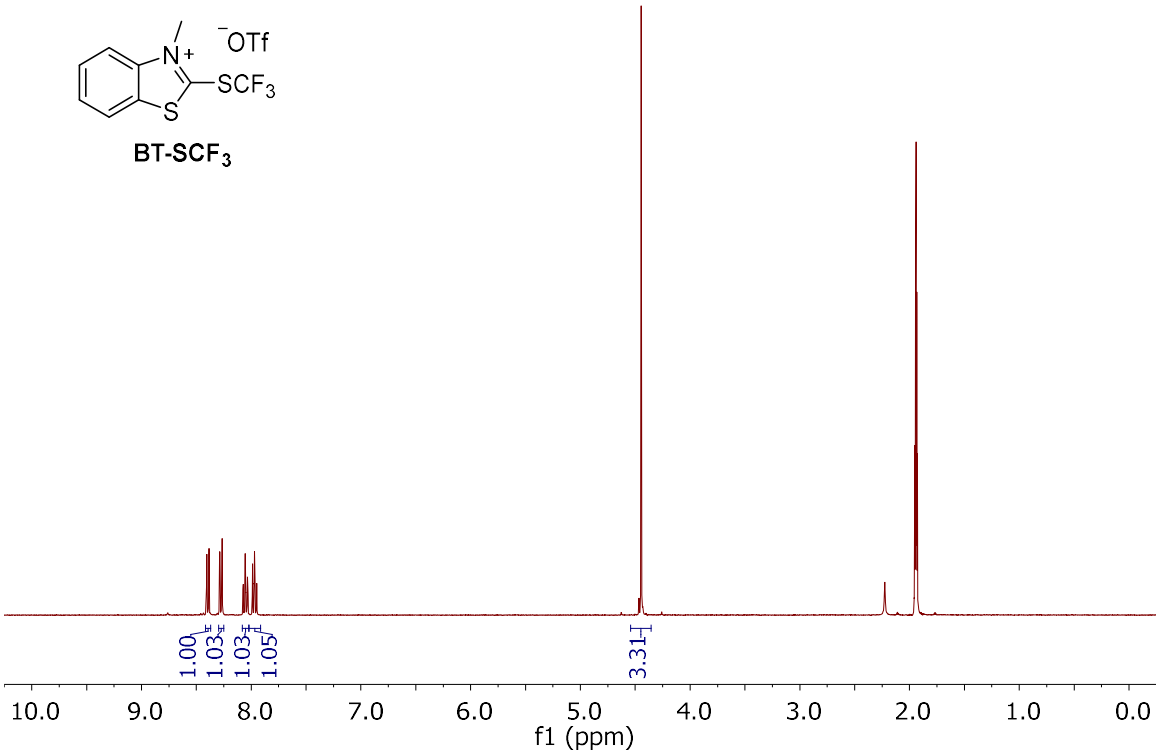
9

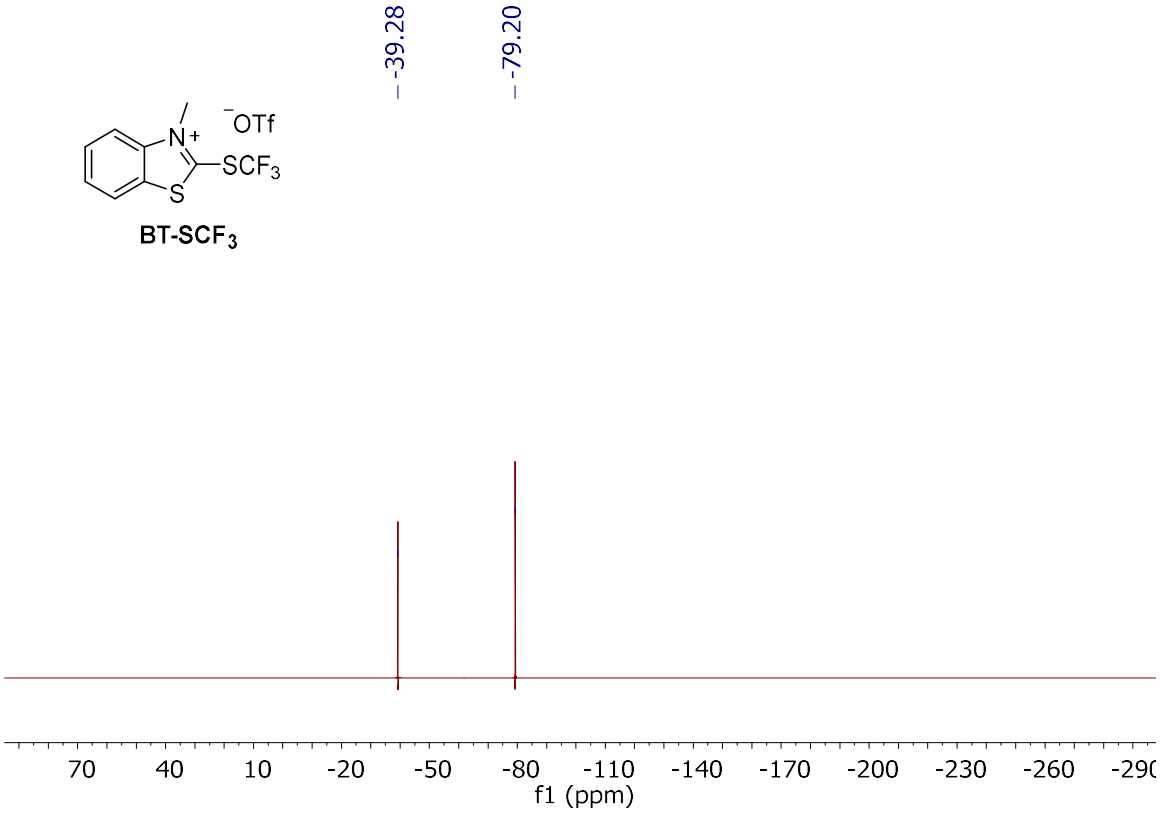

S
N
SeCF3
1.00
1.00
1.01
1.03
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
f1 (ppm)

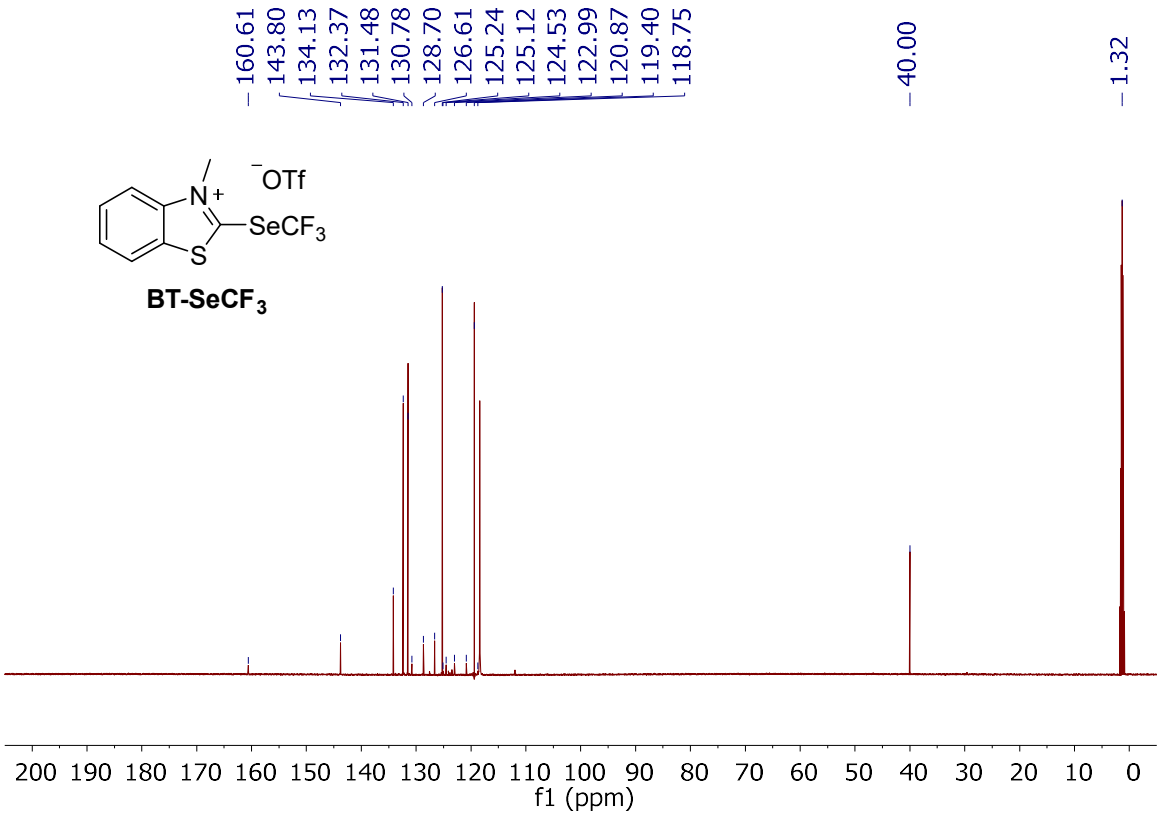
9

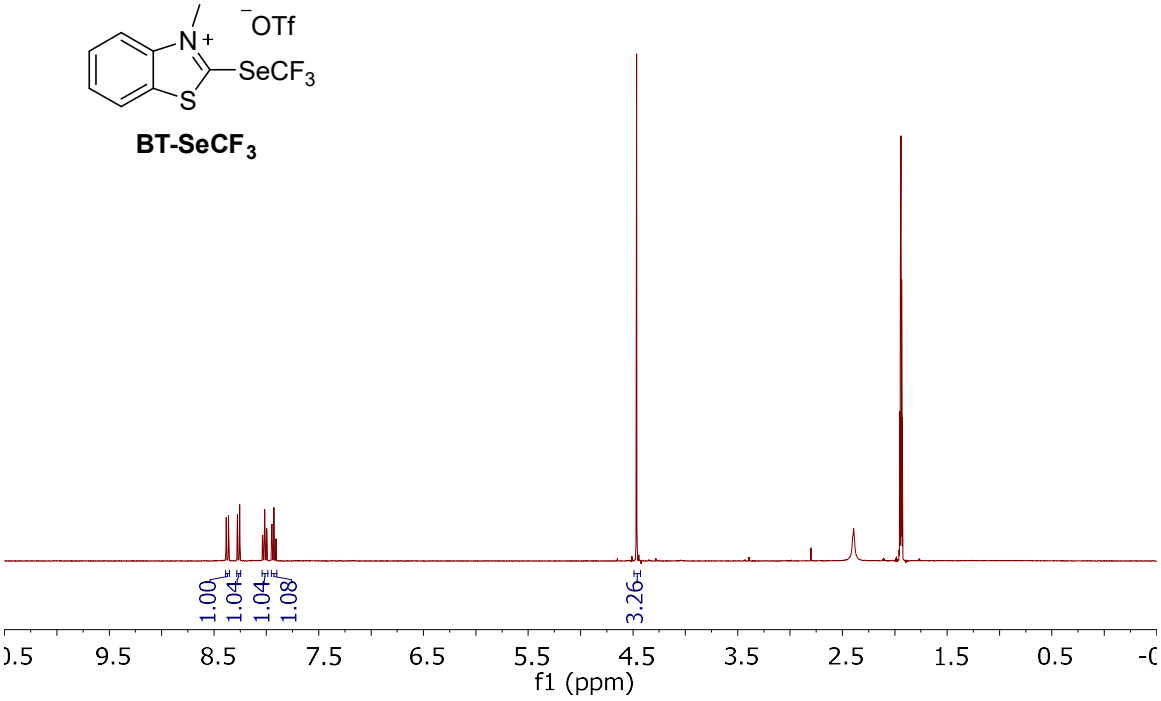

-33.17
S
N
SeCF3
9
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

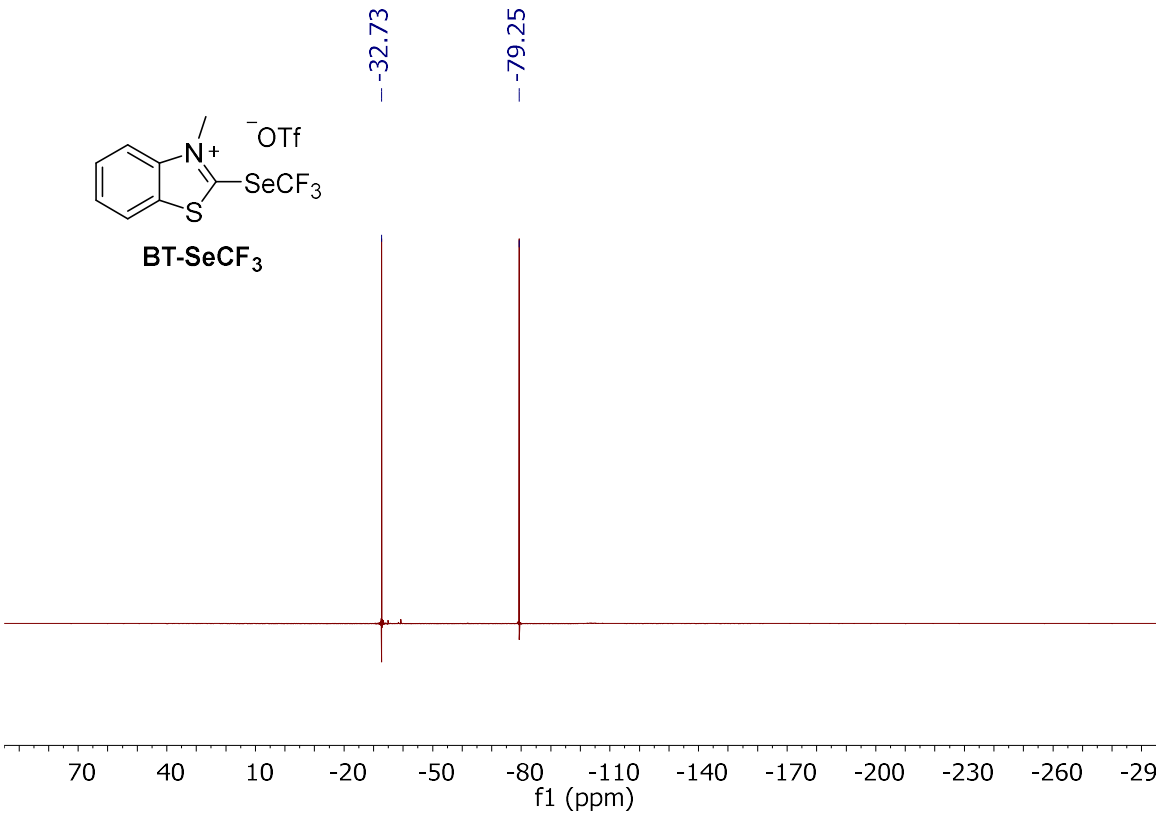

153.76
147.55
138.48
126.92
126.48
125.51
123.97
123.29
121.24
121.07
118.86
S
N
SeCF3
9
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

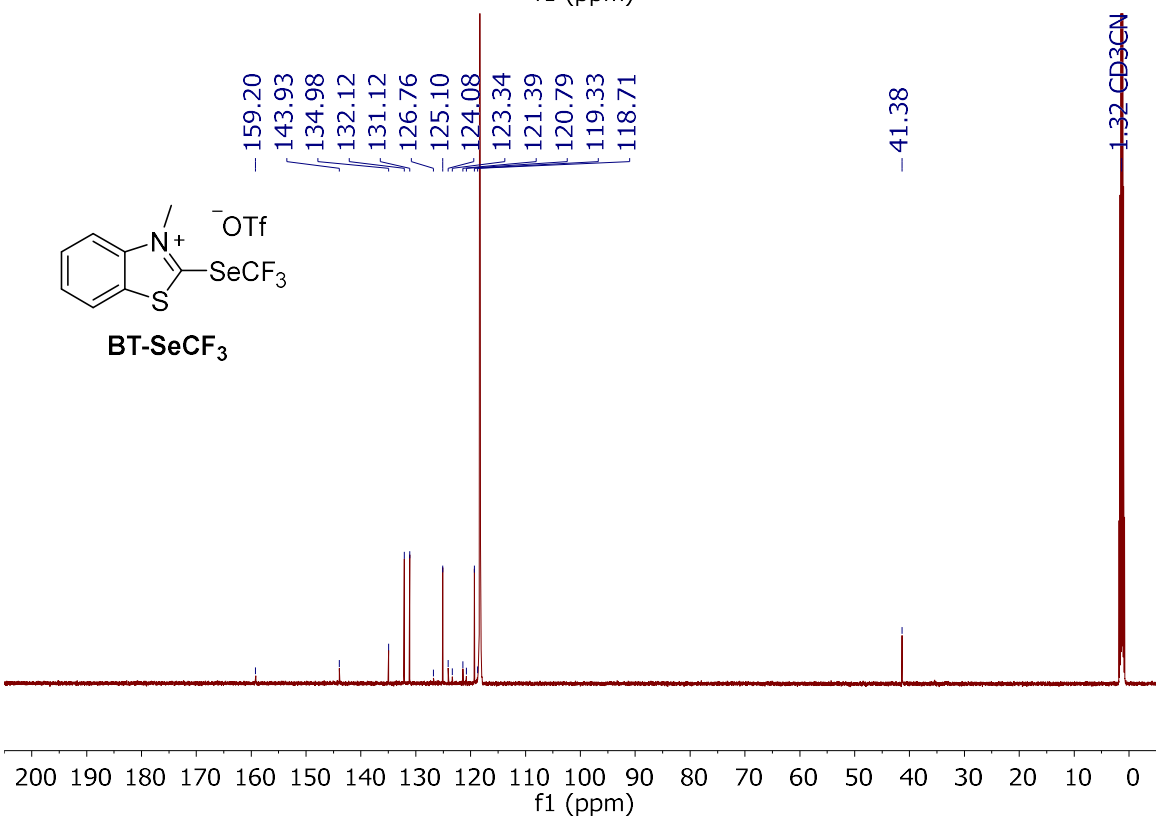

OTf
SCF3
BT-SCF3
1.00
1.03
1.03
1.05
3.31
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

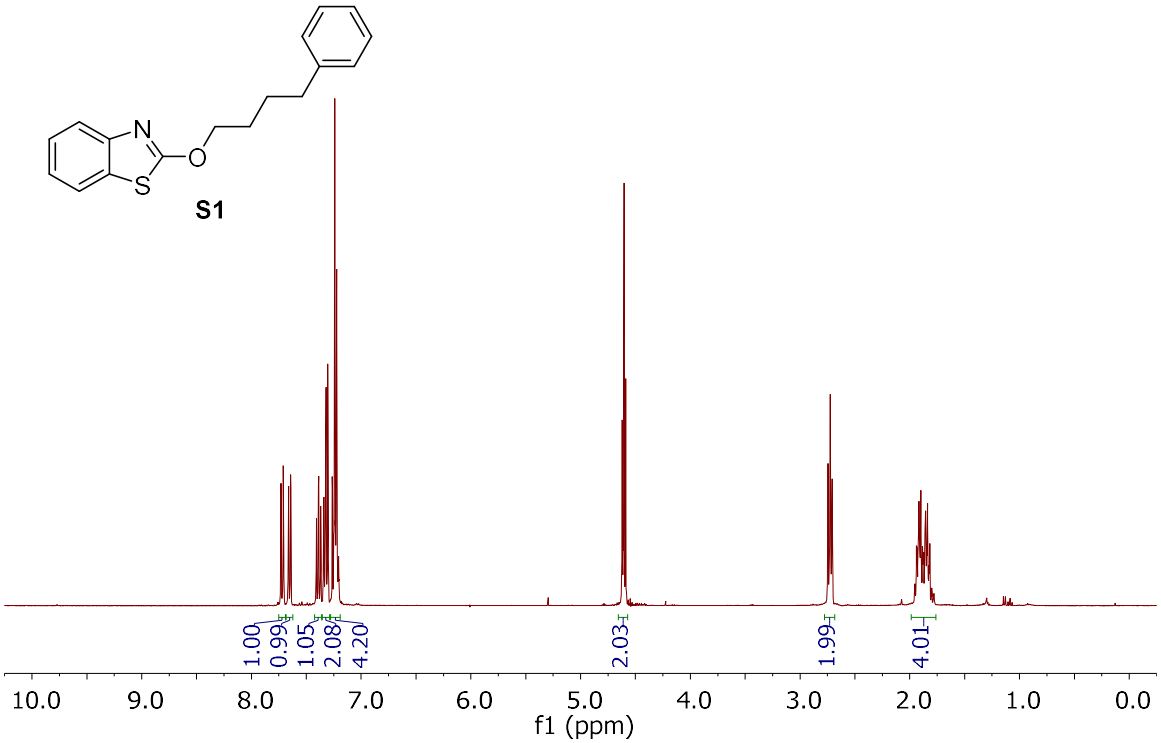

-39.28
-79.20
OTf
SCF3
BT-SCF3
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
f1 (ppm)

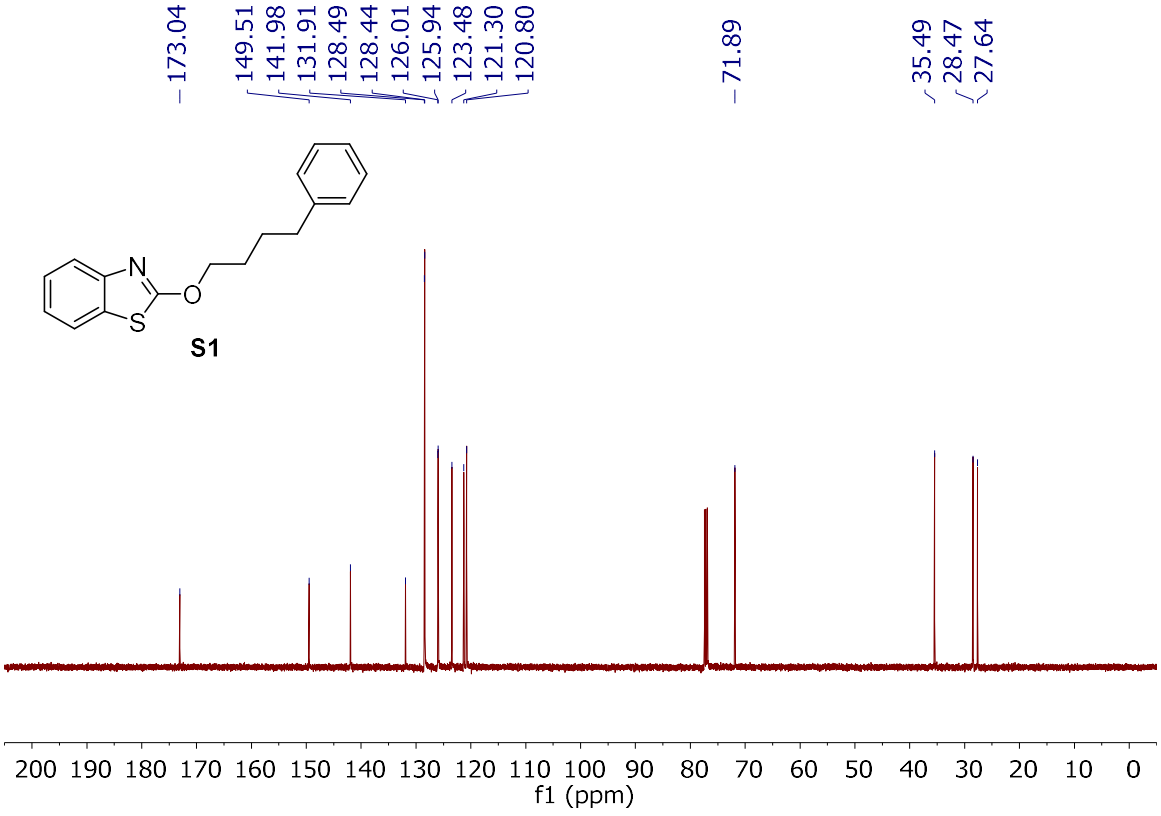

160.61
143.80
134.13
132.37
131.48
130.78
128.70
126.61
125.24
125.12
124.53
122.99
120.87
119.40
118.75
40.00
1.32
OTf
SeCF3
BT-SeCF3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

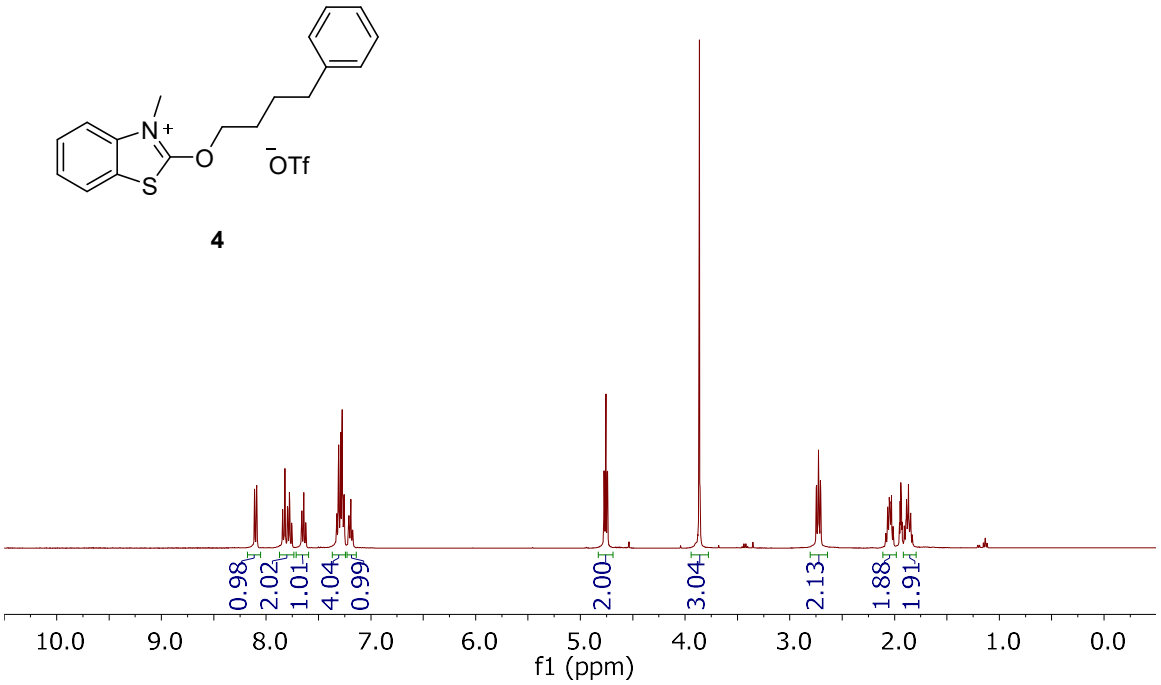

OTf
SeCF3
BT-SeCF3
1.00
1.04
1.04
1.08
3.26
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
f1 (ppm)

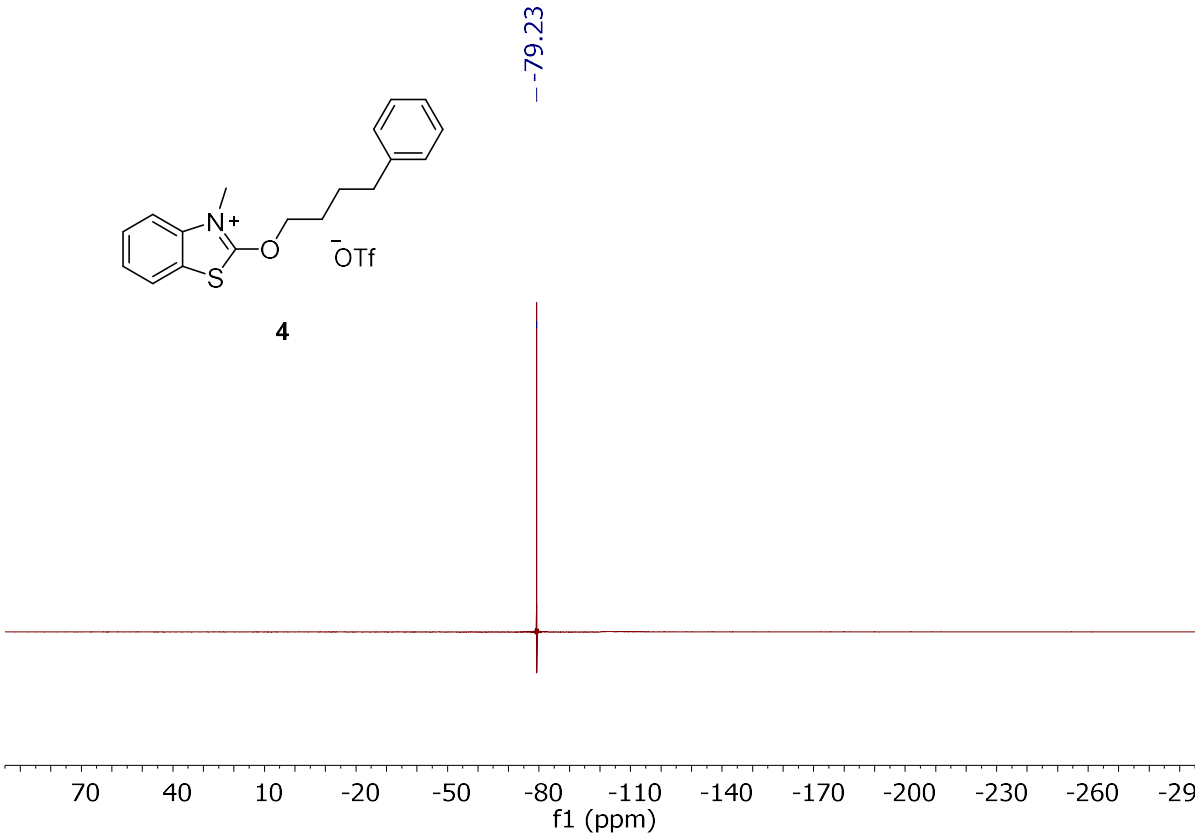

-32.73
-79.25
OTf
SeCF3
BT-SeCF3
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

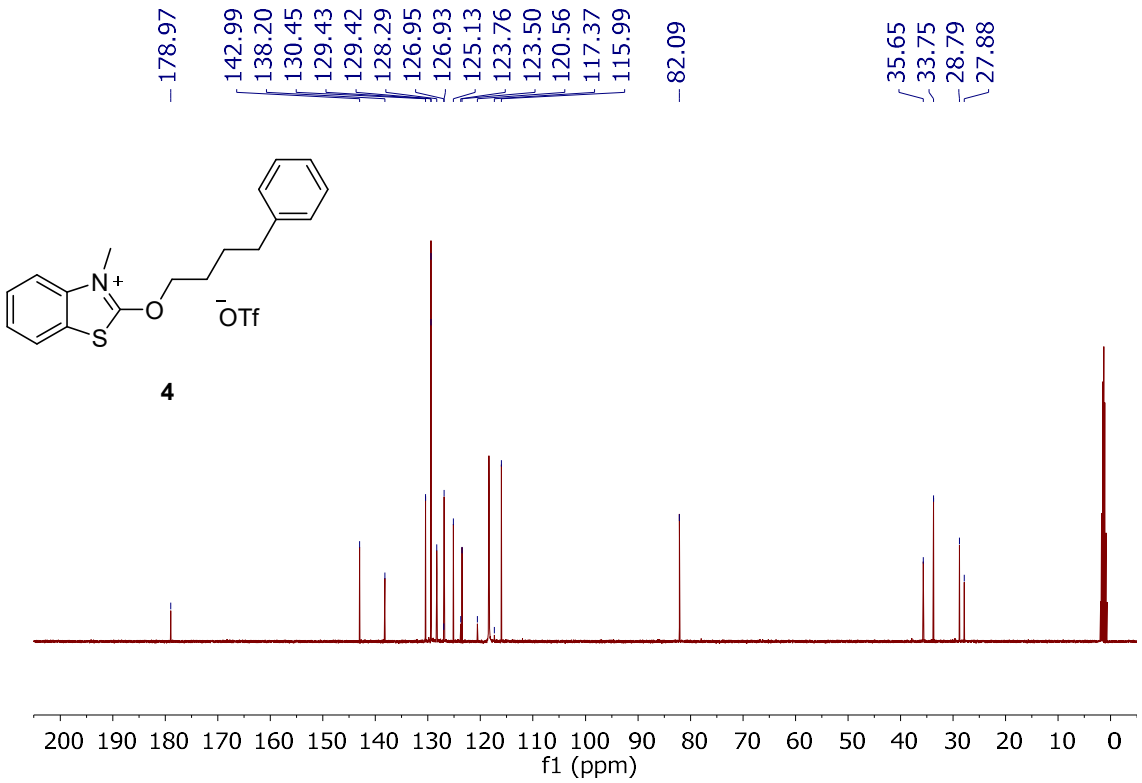

159.20
143.93
134.98
132.12
131.12
126.76
125.10
124.08
123.34
121.39
120.79
119.33
118.71
41.38
1.32 CD3CN
OTf
SeCF3
BT-SeCF3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


S1
1.00
0.99
1.05
2.08
4.20
2.03
1.99
4.01
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

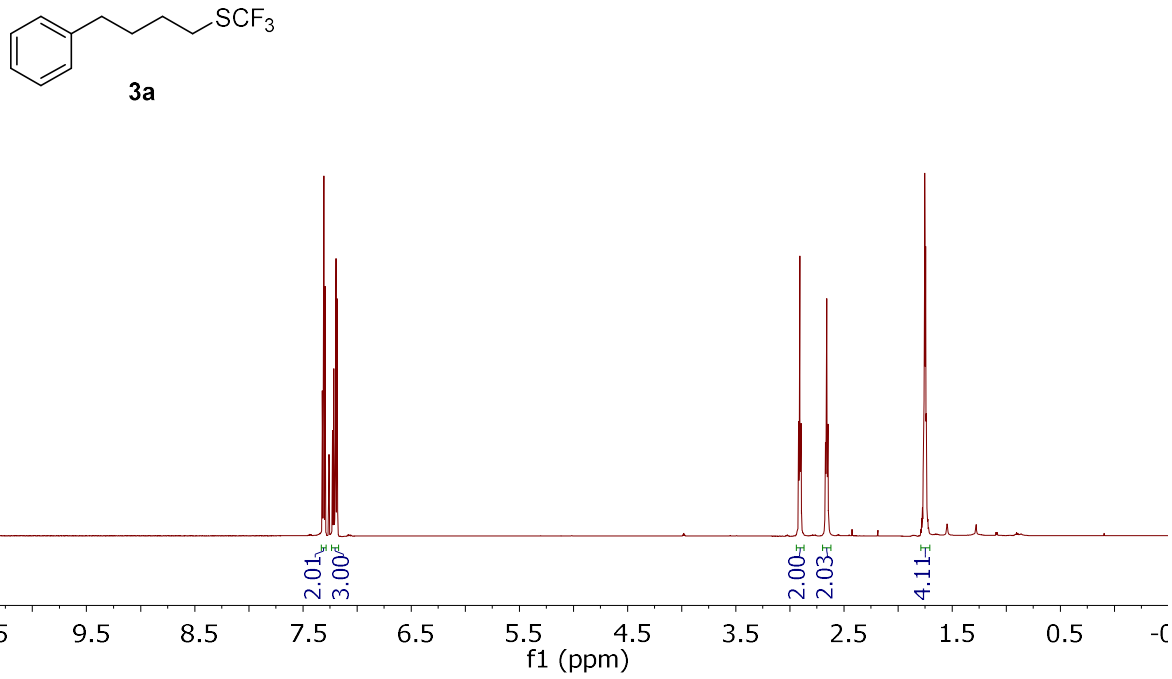

173.04
149.51
141.98
131.91
128.49
128.44
126.01
125.94
123.48
121.30
120.80
71.89
35.49
28.47
27.64
S1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


N+
O
S
OTf
4
0.98
2.02
1.01
4.04
0.99
2.00
3.04
2.13
1.88
1.91
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

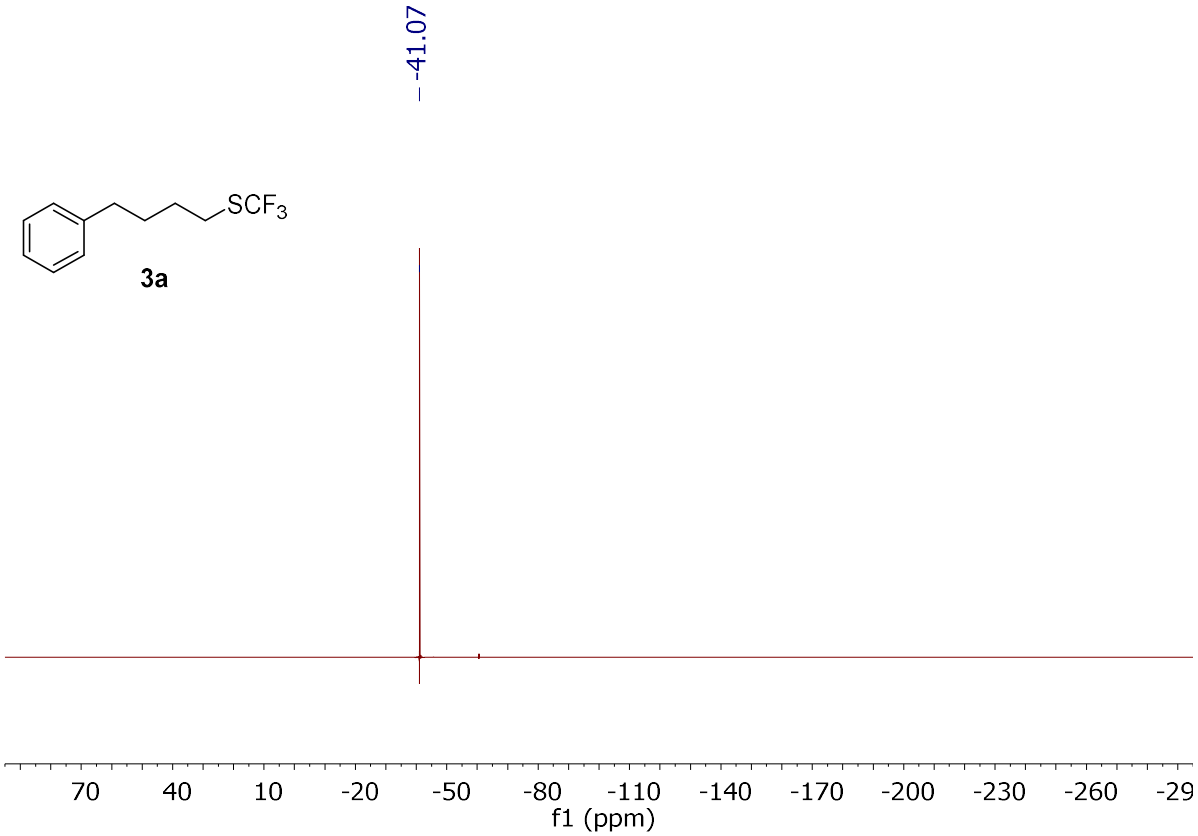

-79.23
N+
O
S
OTf
4
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
-29
f1 (ppm)

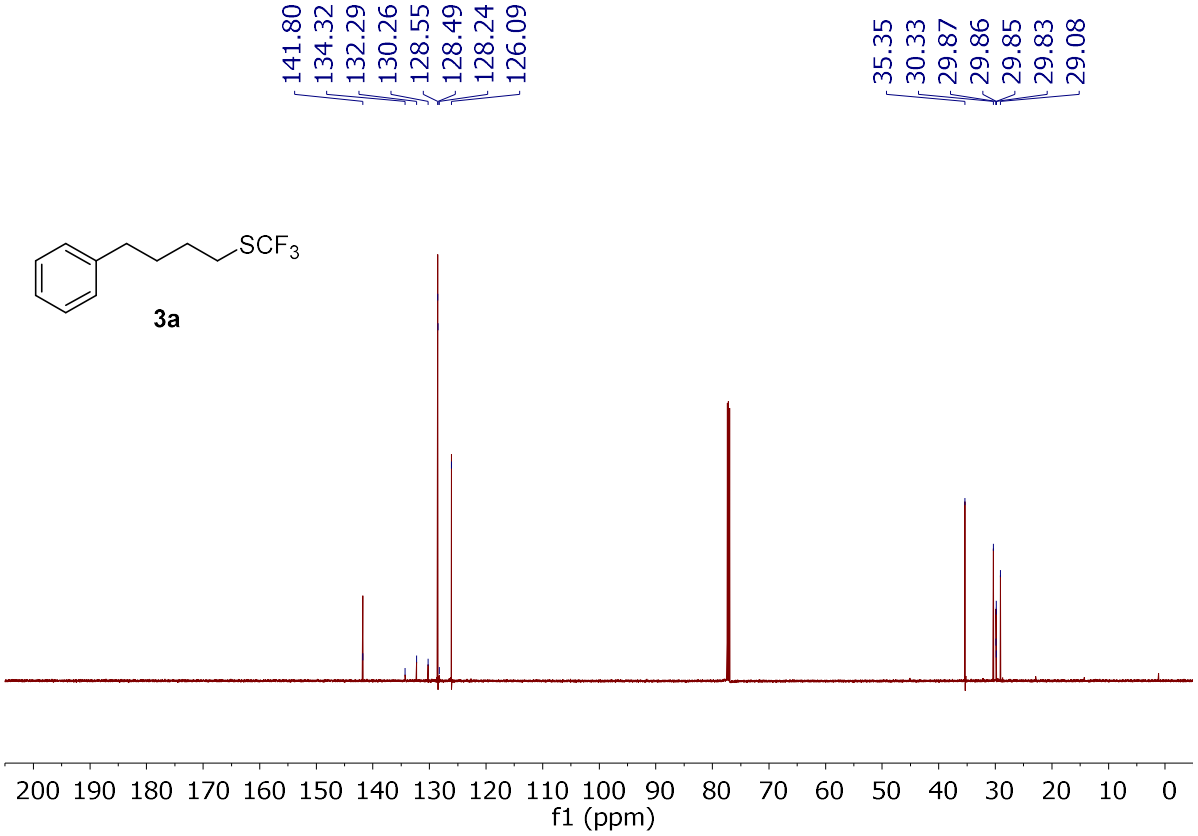

178.97
142.99
138.20
130.45
129.43
129.42
128.29
126.95
126.93
125.13
123.76
123.50
120.56
117.37
115.99
82.09
35.65
33.75
28.79
27.88
N+
O
S
OTf
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

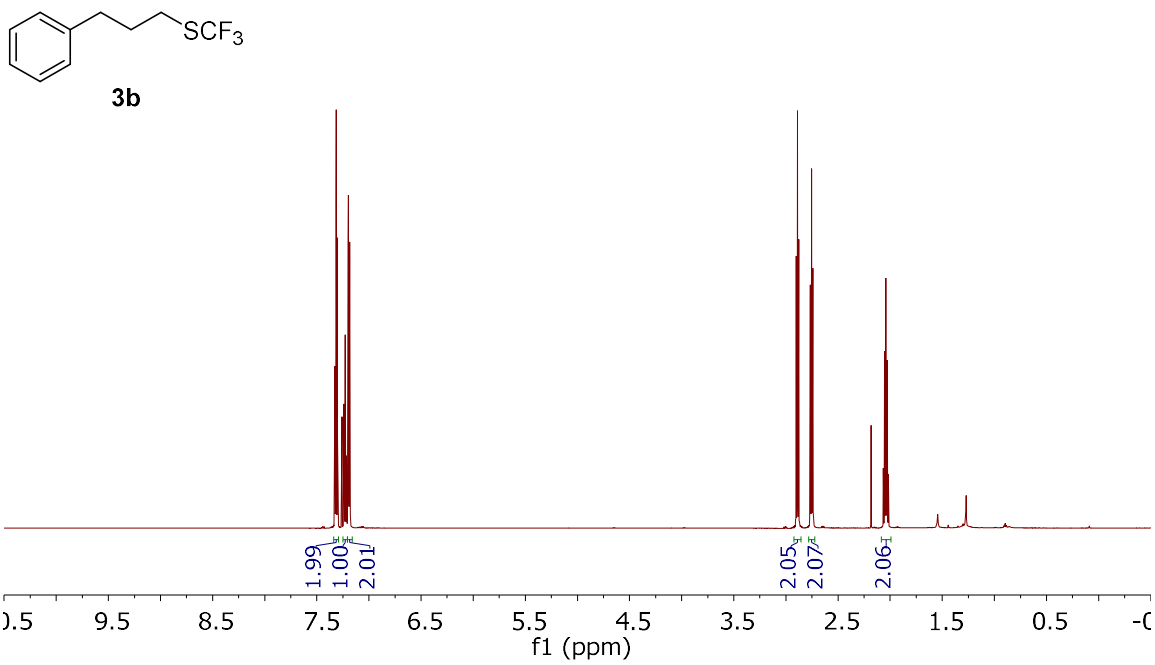
4

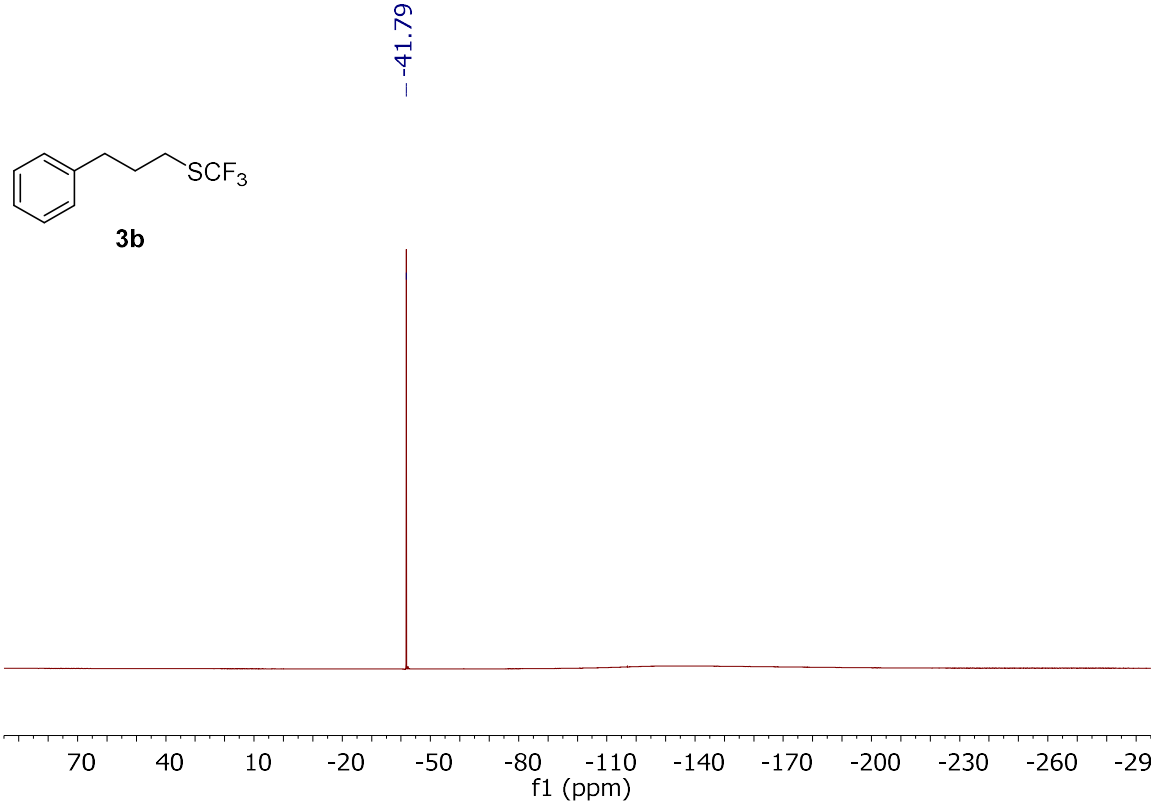

SCF3
2.01
3.00
2.00
2.03
4.11
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
f1 (ppm)

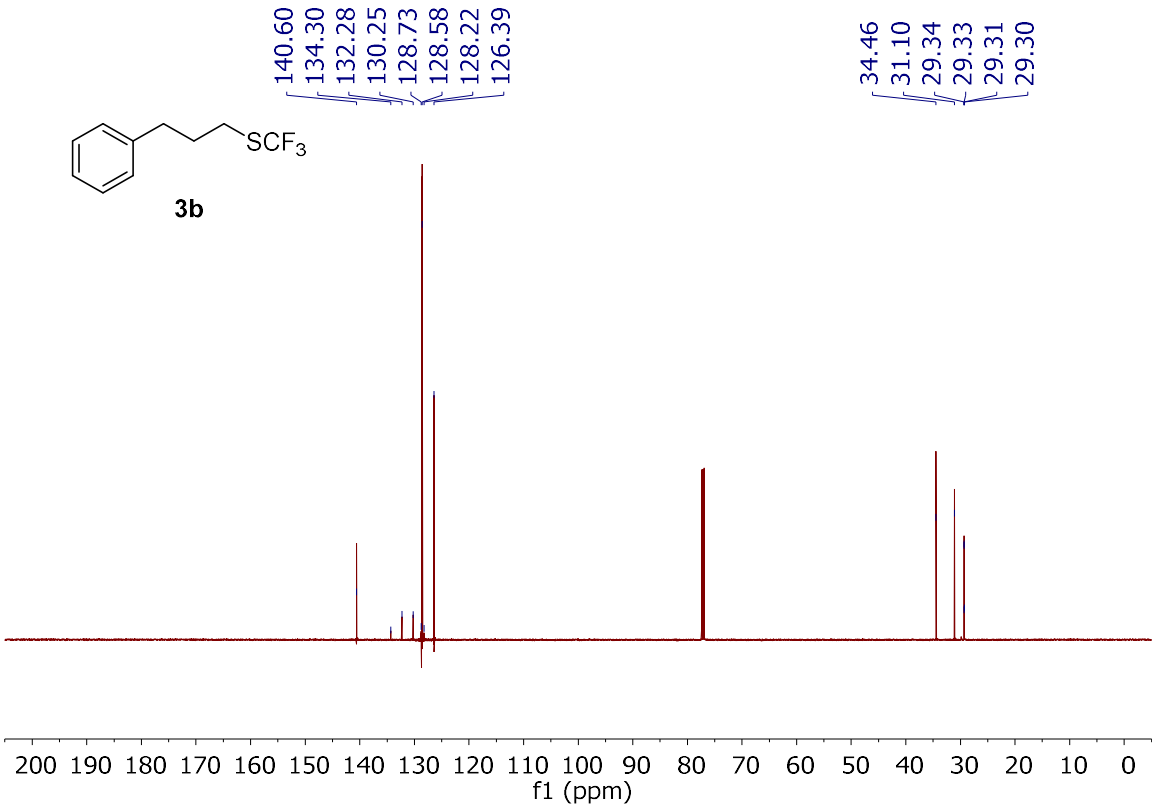
3a

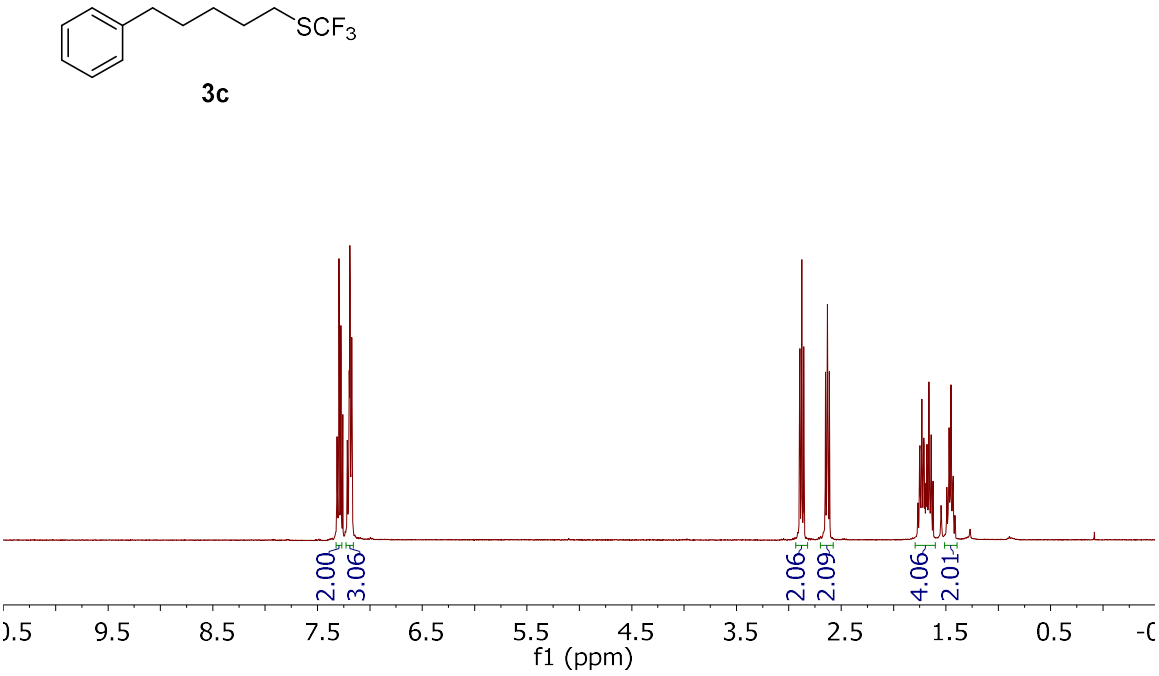

-41.07
SCF3
3a
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

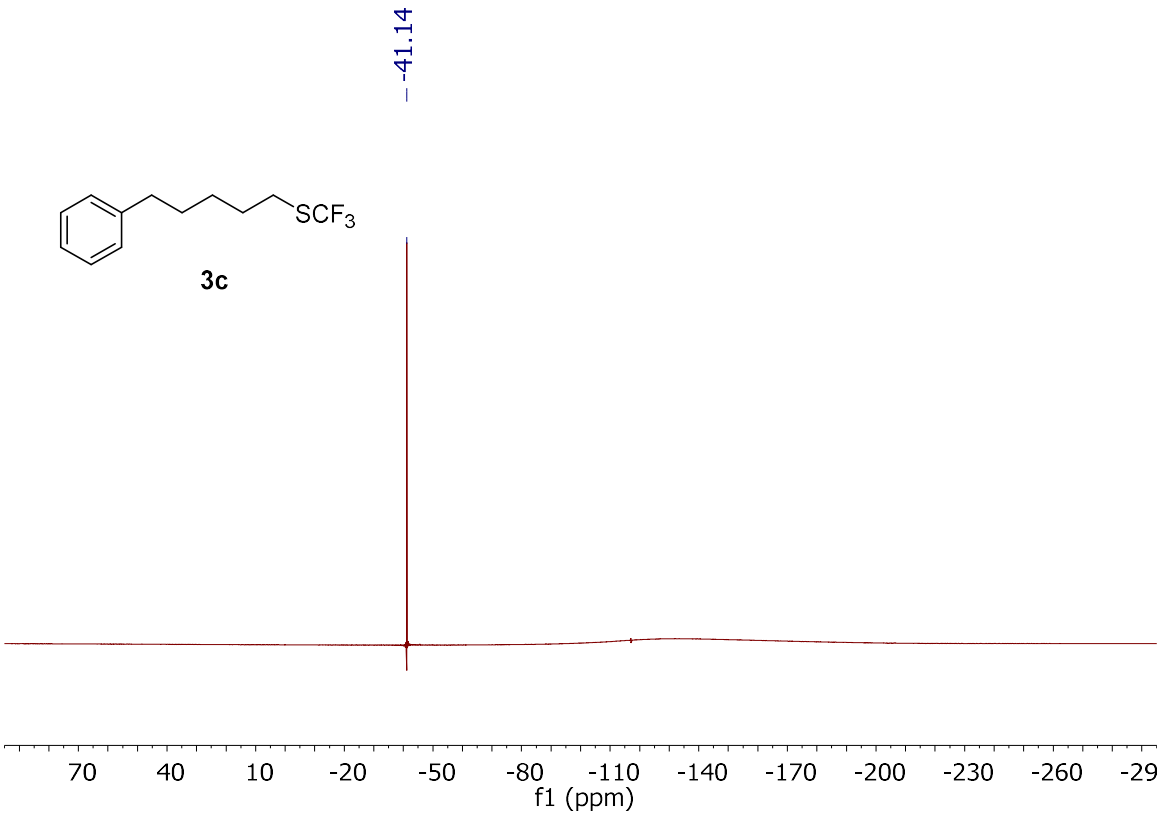

141.80
134.32
132.29
130.26
128.55
128.49
128.24
126.09
35.35
30.33
29.87
29.86
29.85
29.83
29.08
SCF3
3a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

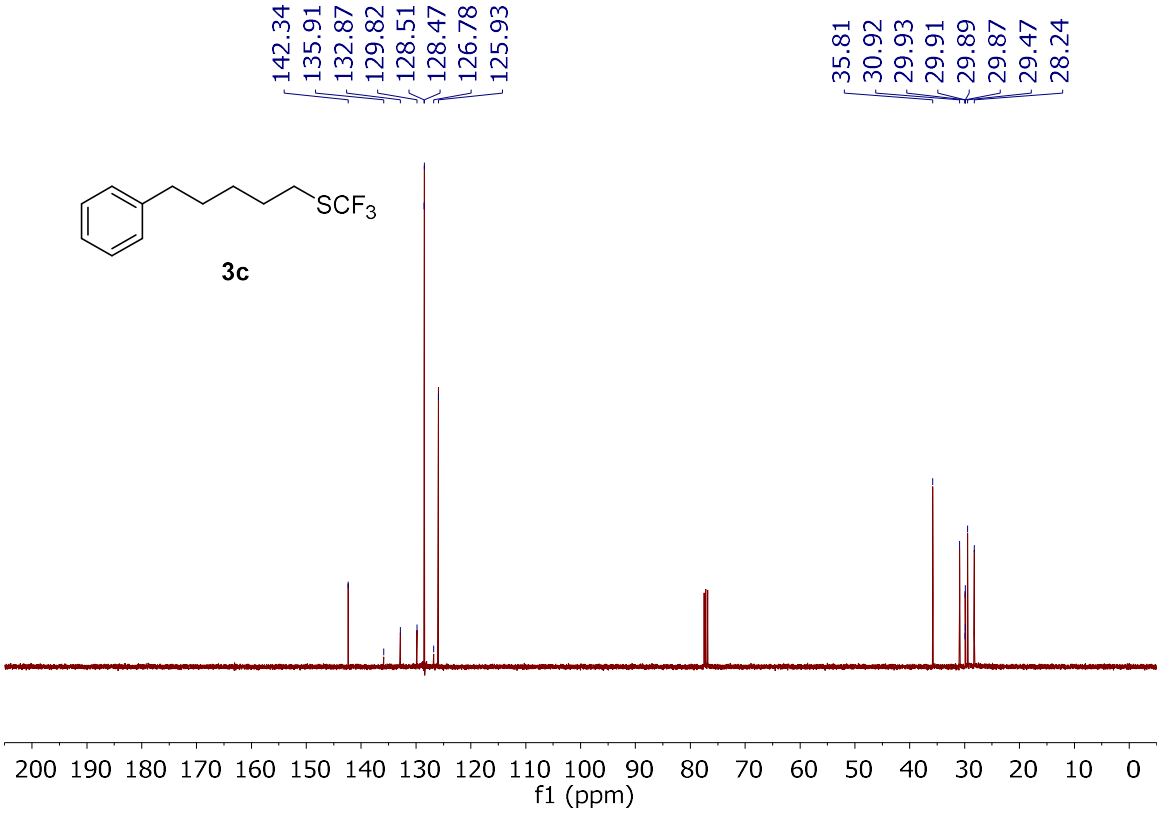

SCF3
3b
1.99
1.00
2.01
2.05
2.07
2.06
f1 (ppm)

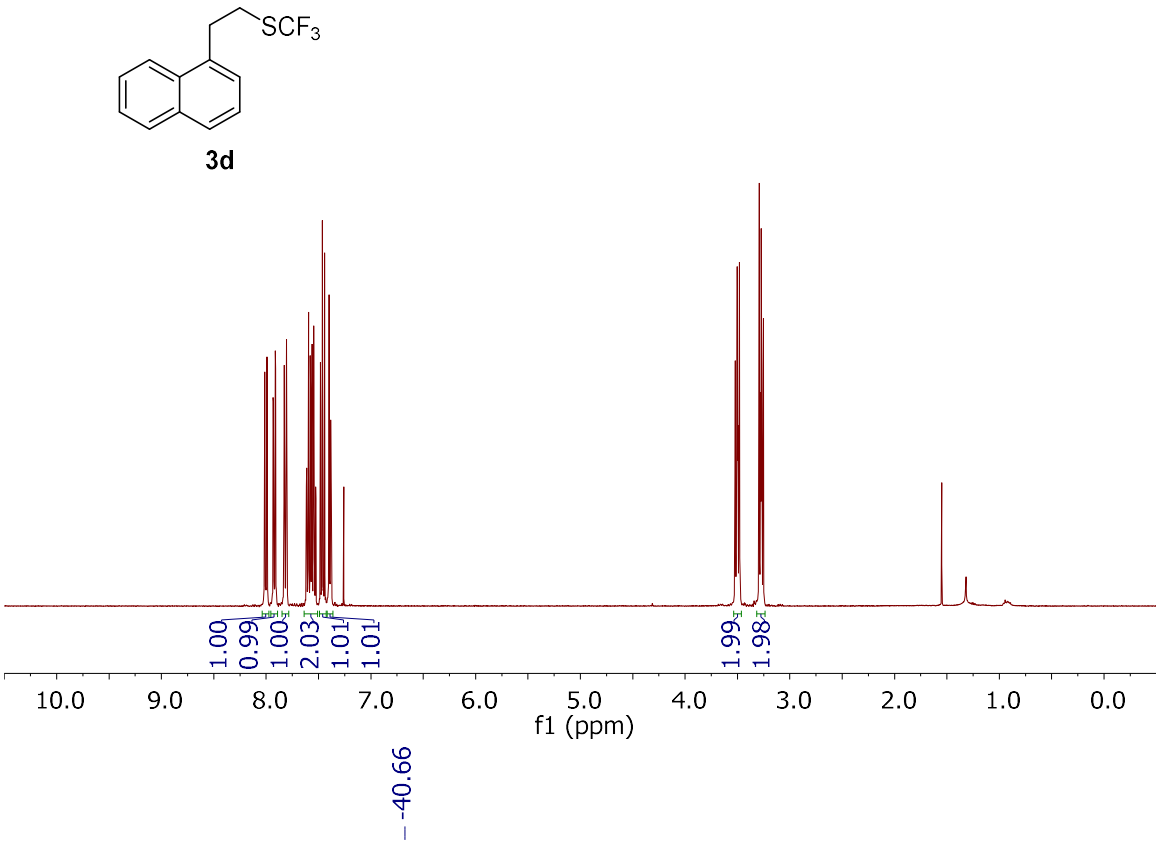

-41.79
SCF3
3b
f1 (ppm)

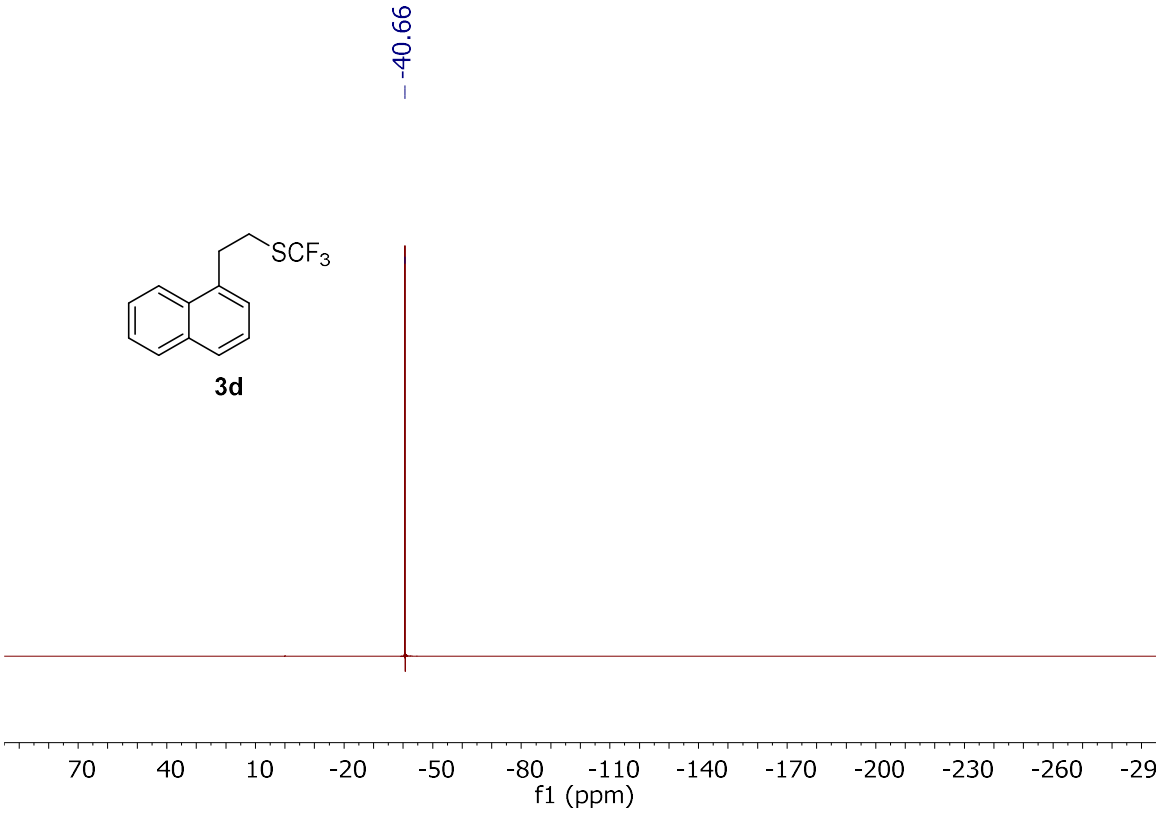

140.60
134.30
132.28
130.25
128.73
128.58
128.22
126.39
34.46
31.10
29.34
29.33
29.31
29.30
SCF3
3b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

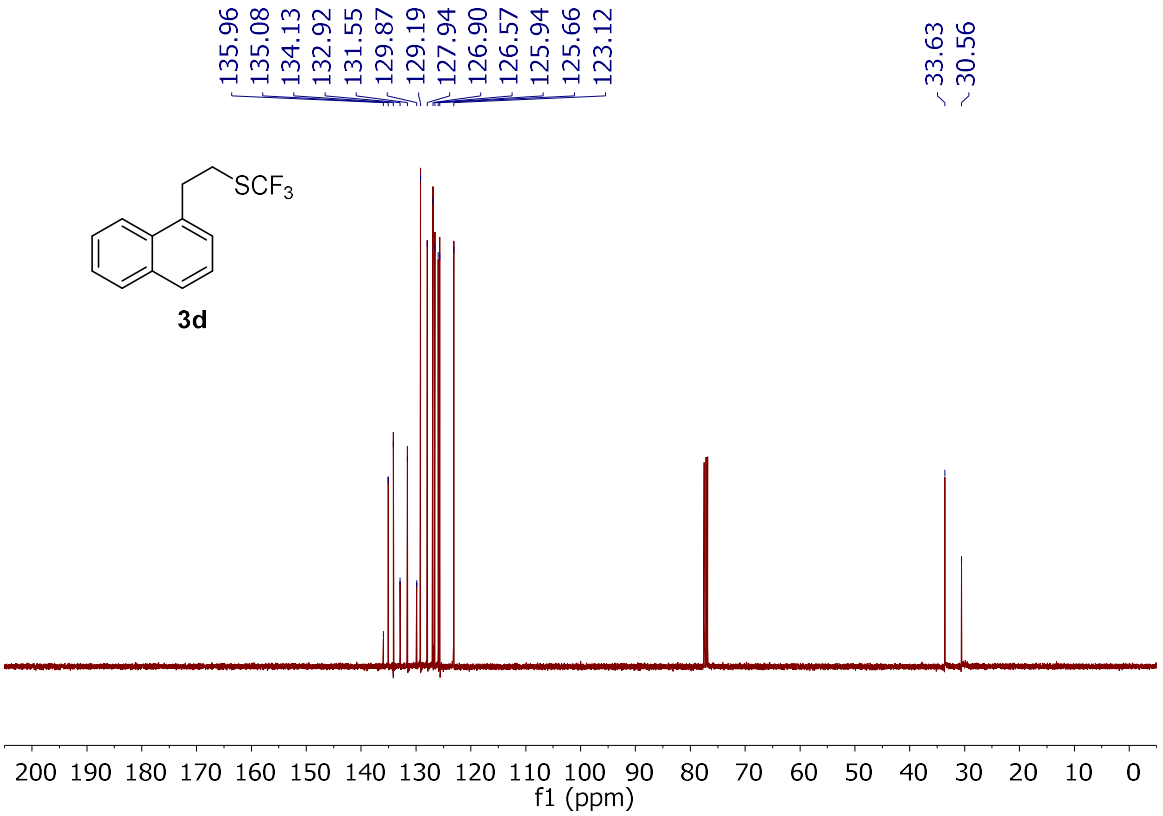

SCF3
3c
2.00
3.06
2.06
2.09
4.06
2.01
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
f1 (ppm)

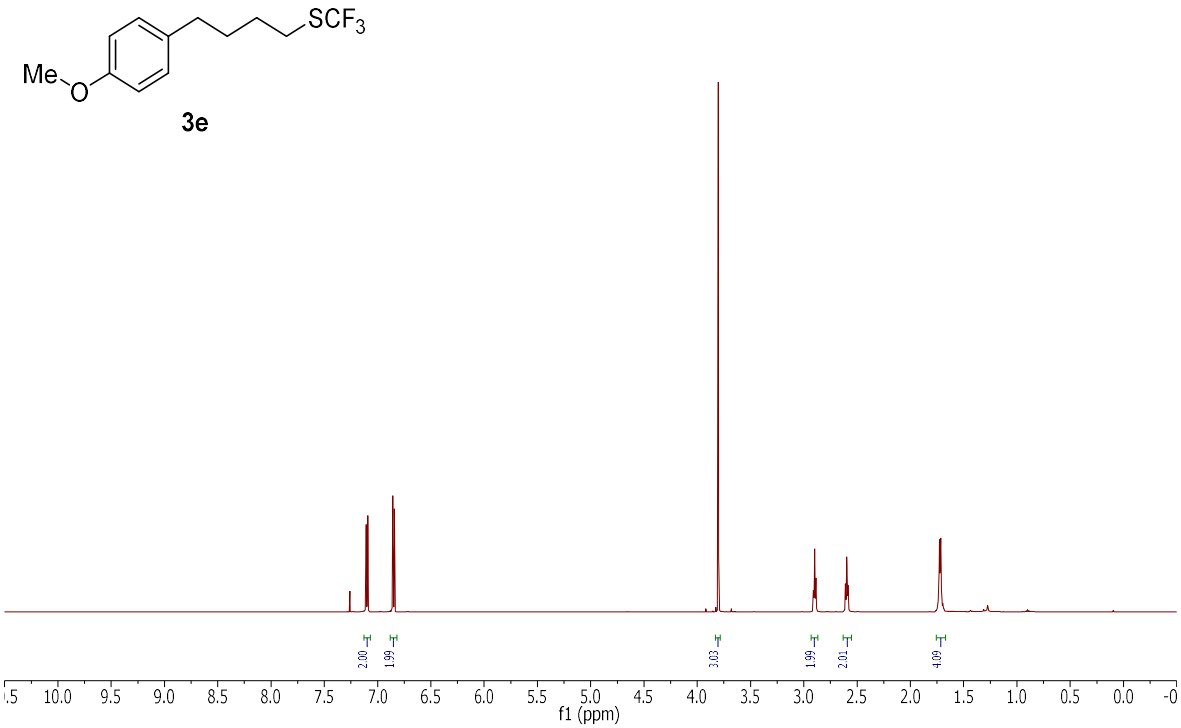

-41.14
SCF3
3c
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

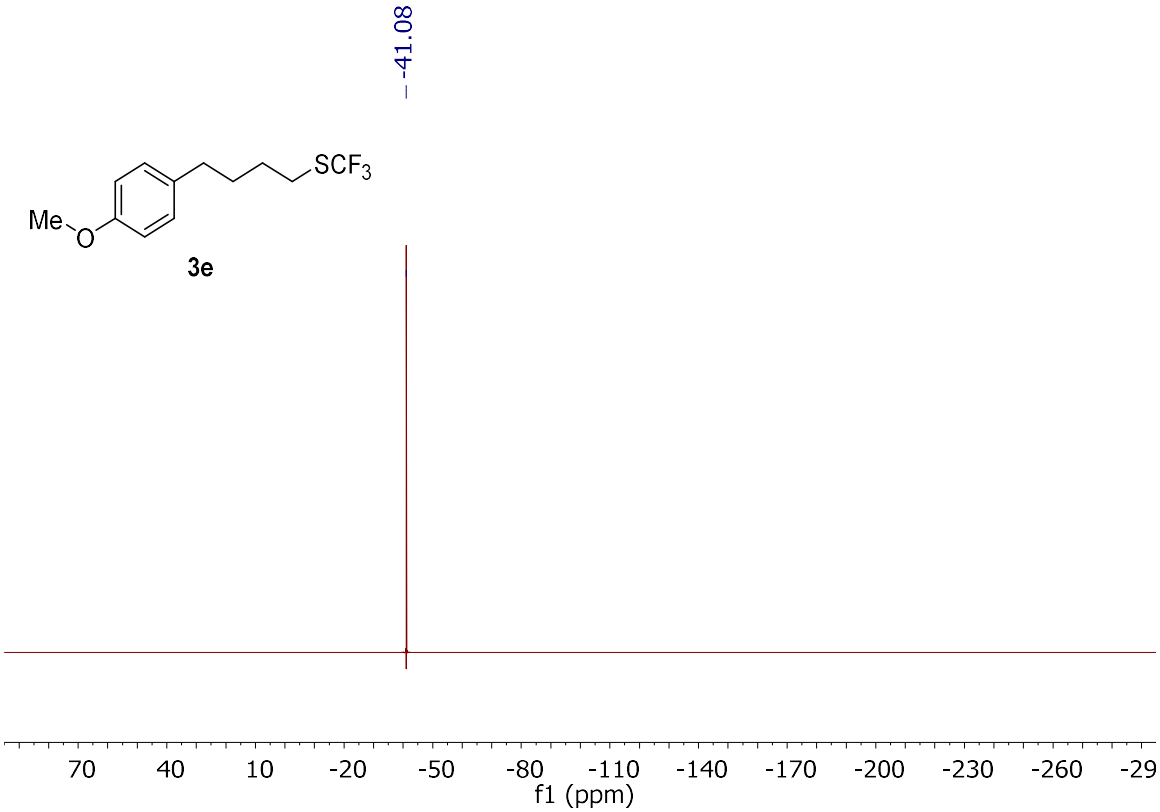

142.34
135.91
132.87
129.82
128.51
128.47
126.78
125.93
35.81
30.92
29.93
29.91
29.89
29.87
29.47
28.24
SCF3
3c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

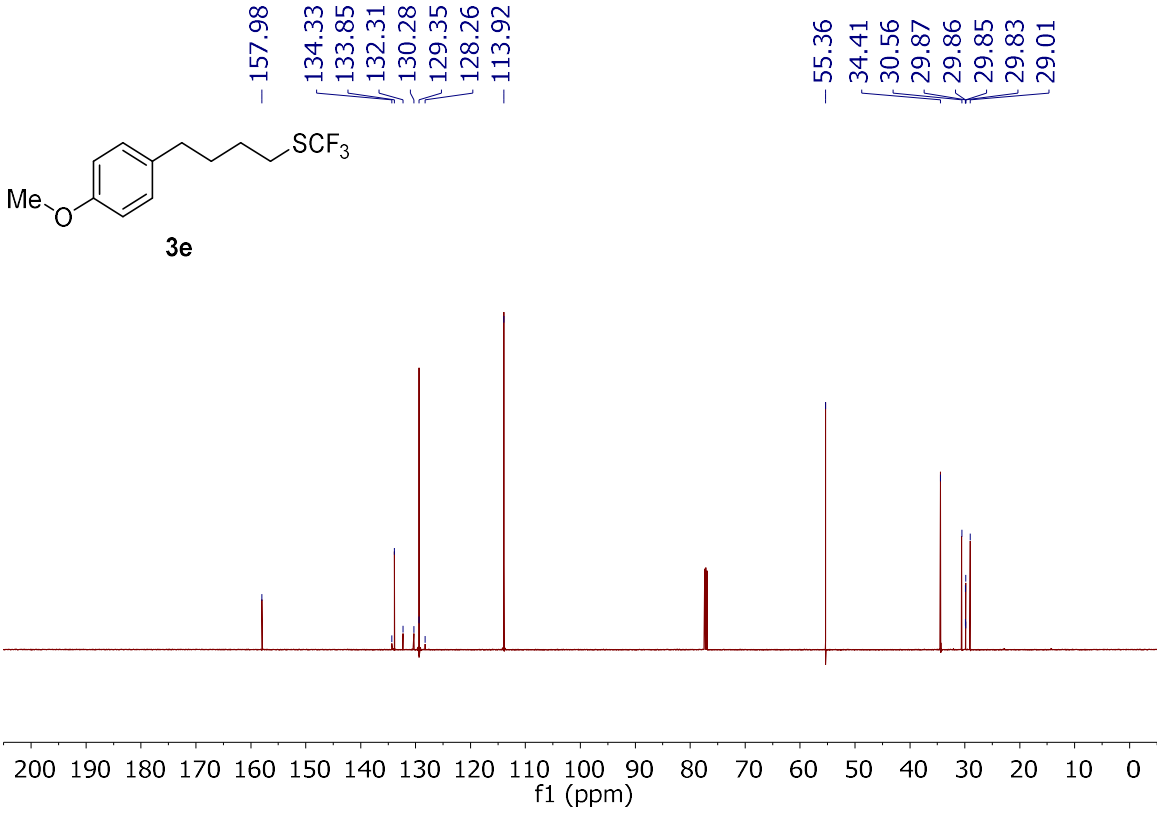

SCF3
3d
1.00
0.99
1.00
2.03
1.01
1.01
1.99
1.98
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

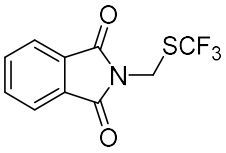

-40.66
SCF3
3d
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
-29
f1 (ppm)


135.96
135.08
134.13
132.92
131.55
129.87
129.19
127.94
126.90
126.57
125.94
125.66
123.12
33.63
30.56
SCF3
3d
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

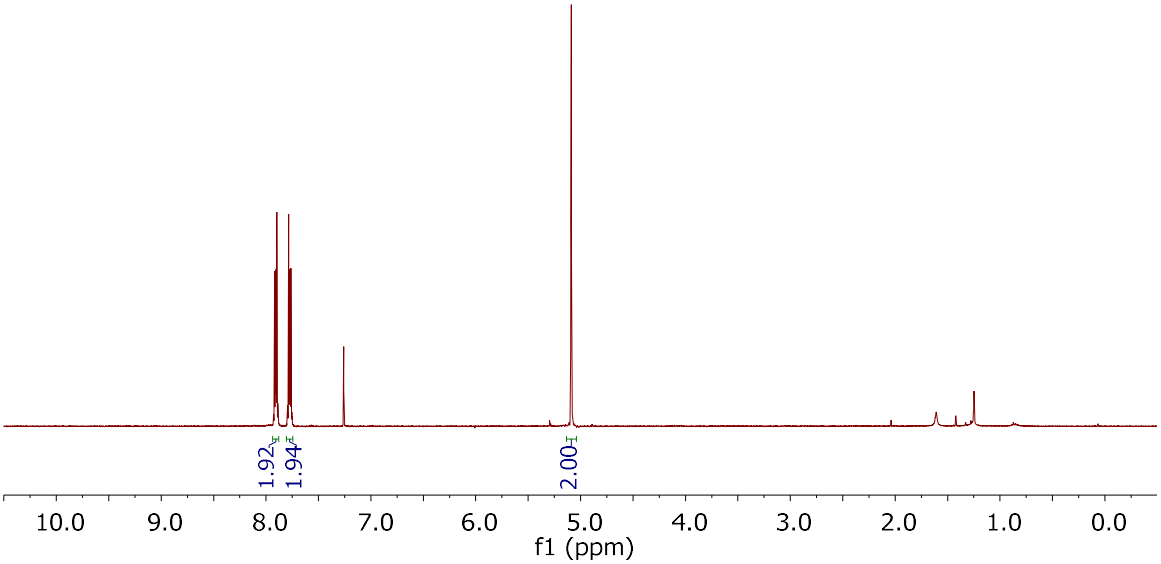

SCF3
Me
O
3e
2.00
1.99
3.03
1.99
2.01
4.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

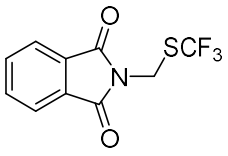

-41.08
SCF3
Me
O
3e
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
-29
f1 (ppm)


157.98
134.33
133.85
132.31
130.28
129.35
128.26
113.92
55.36
34.41
30.56
29.87
29.86
29.85
29.83
29.01
SCF3
Me
O
3e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
SCF3
N
O

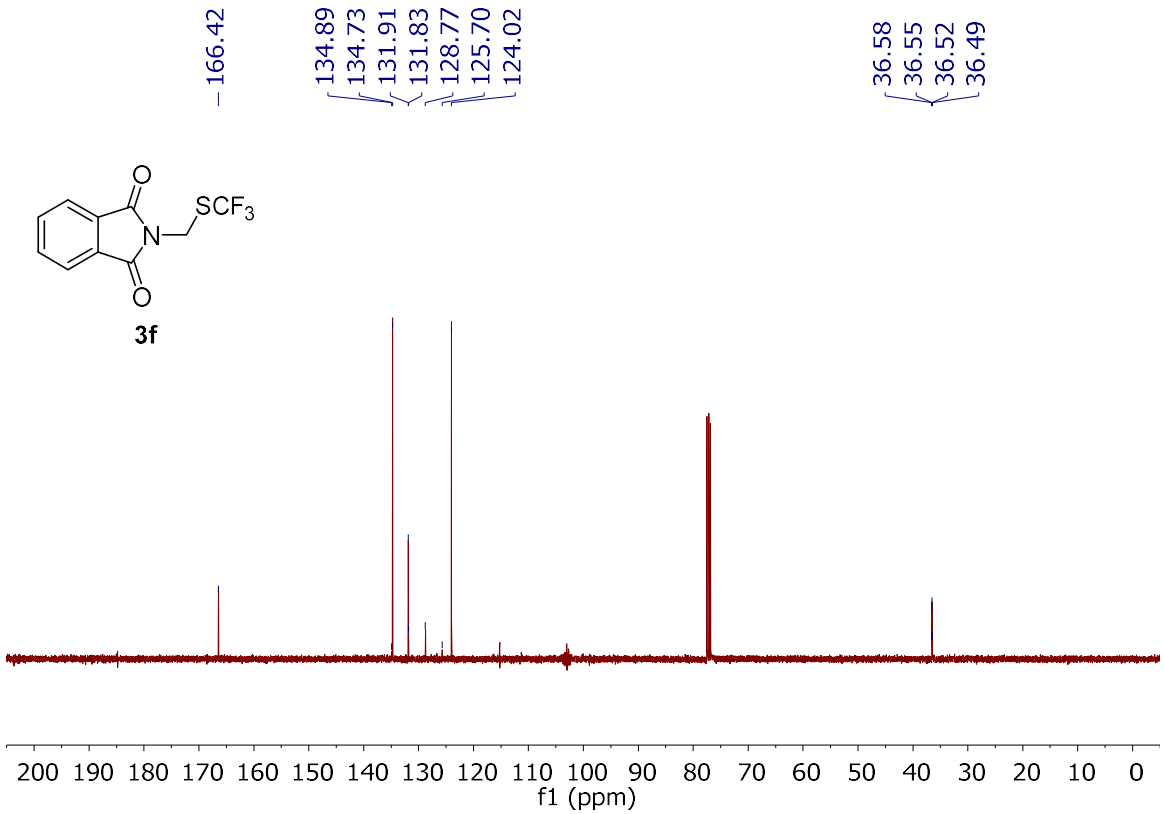
3f

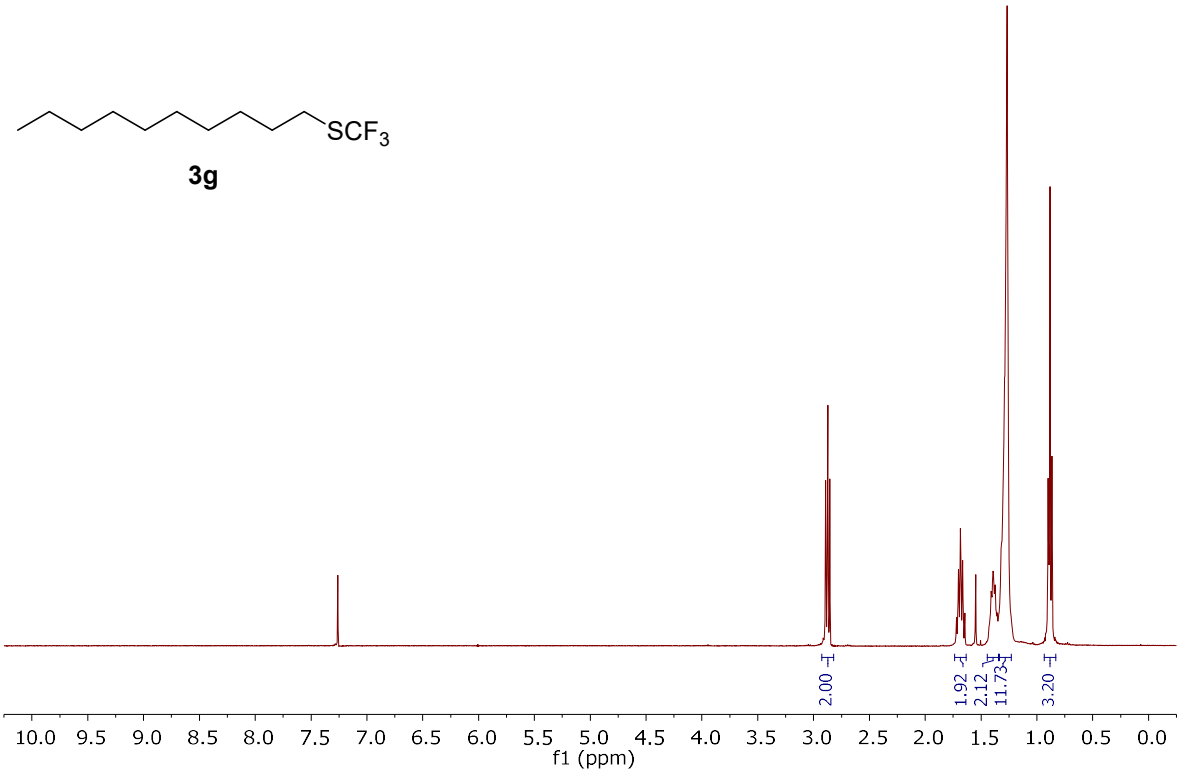

1.92
1.94
2.00
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

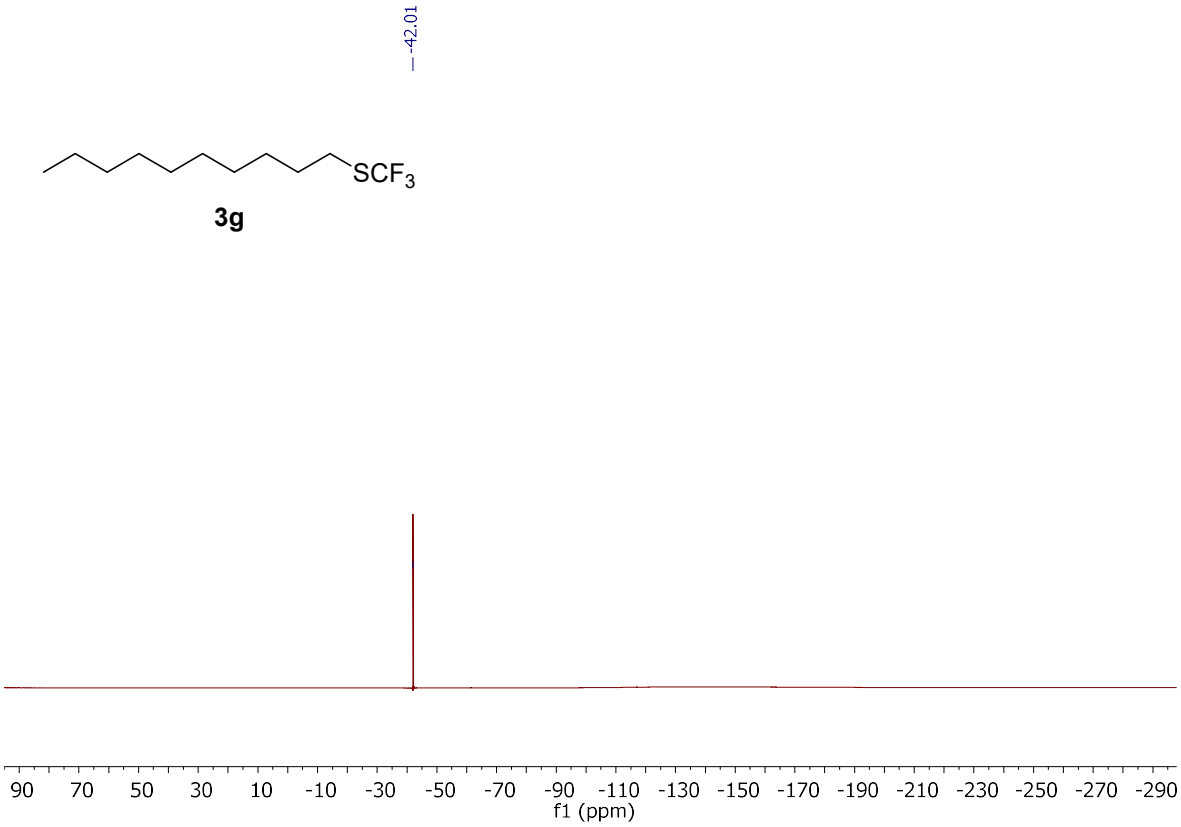

O
SCF3
N
O

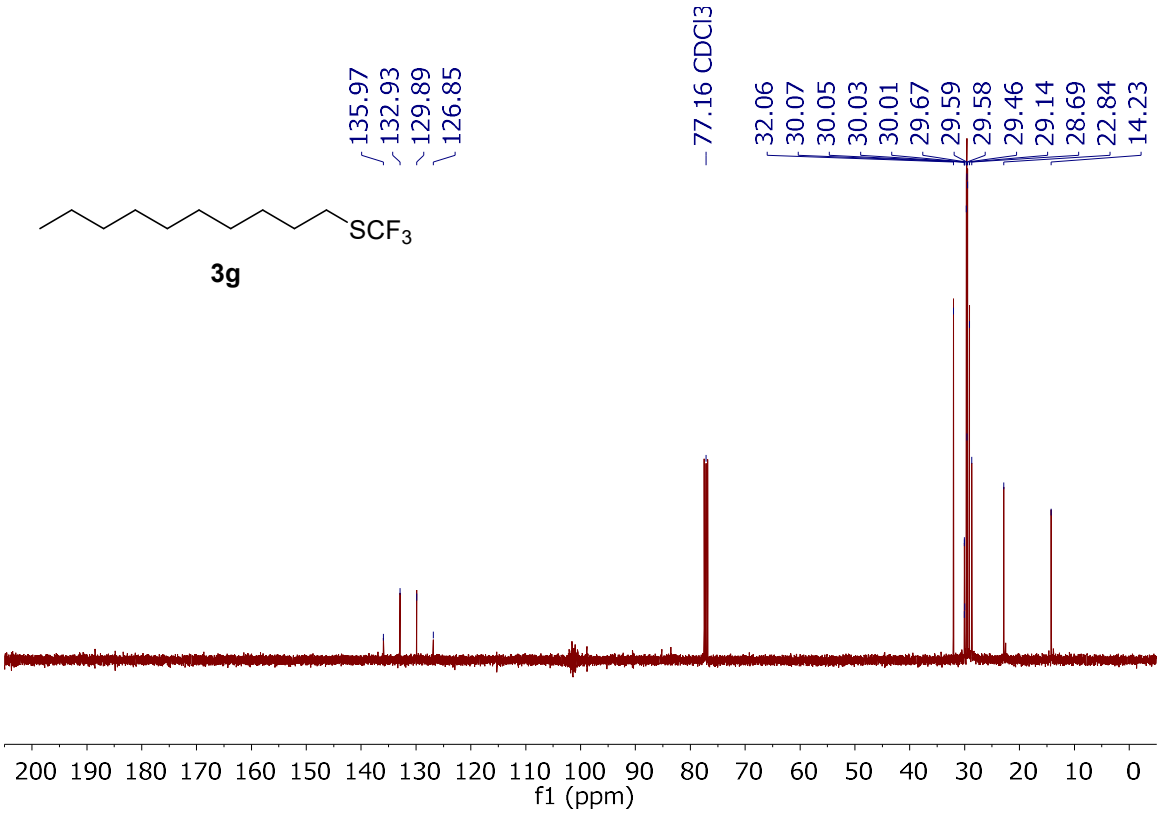
3f

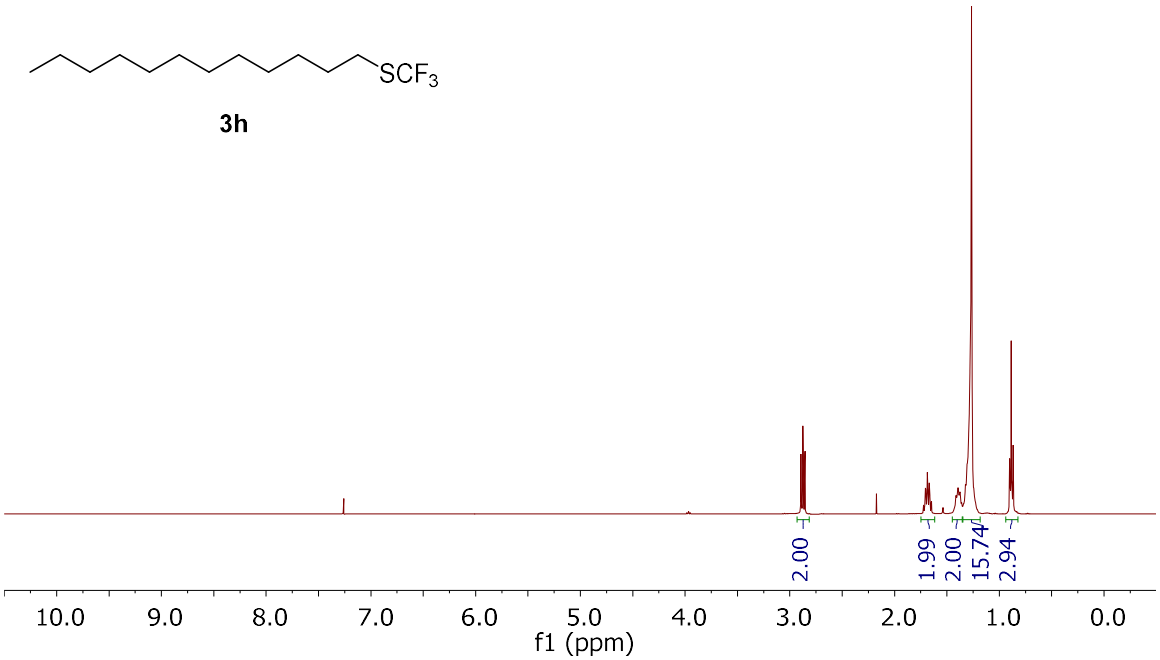
-40.74
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
-29
f1 (ppm)

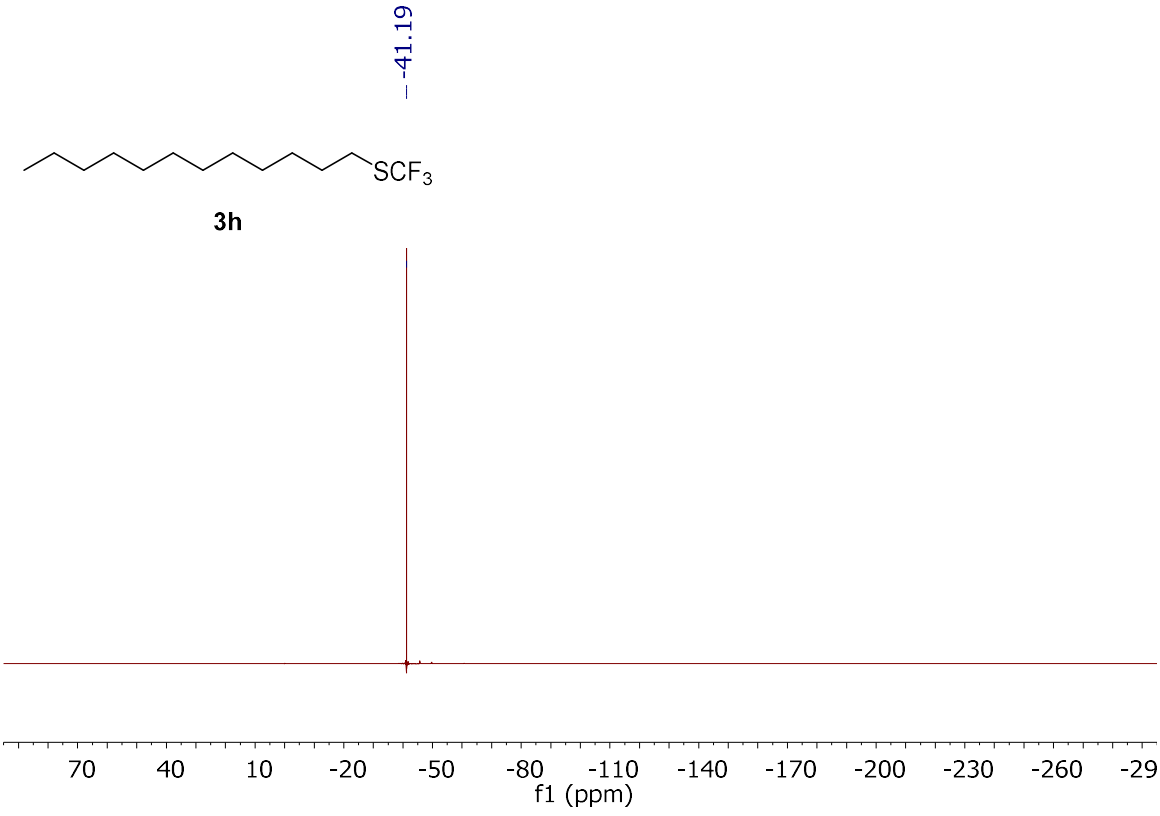

166.42
134.89
134.73
131.91
131.83
128.77
125.70
124.02
36.58
36.55
36.52
36.49
O
N
O
SCF3
3f
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

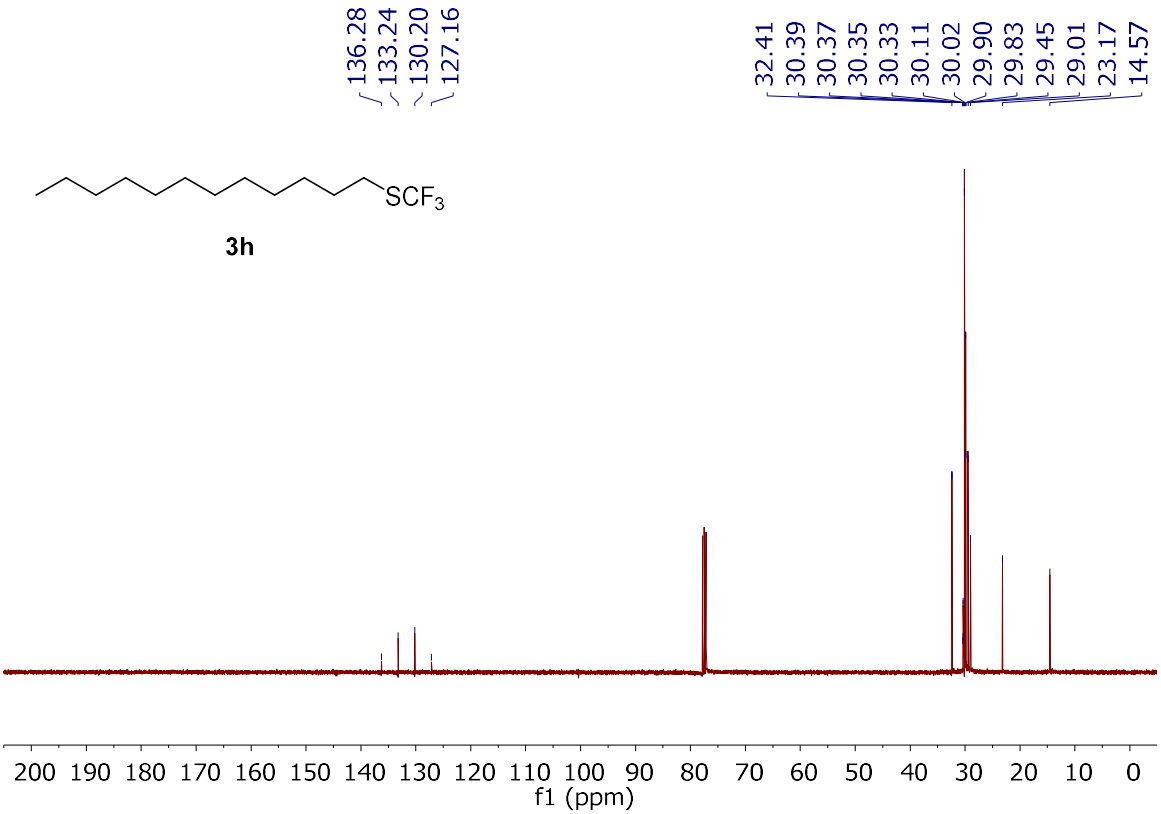

SCF3
3g
2.00
1.92
2.12
11.73
3.20
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

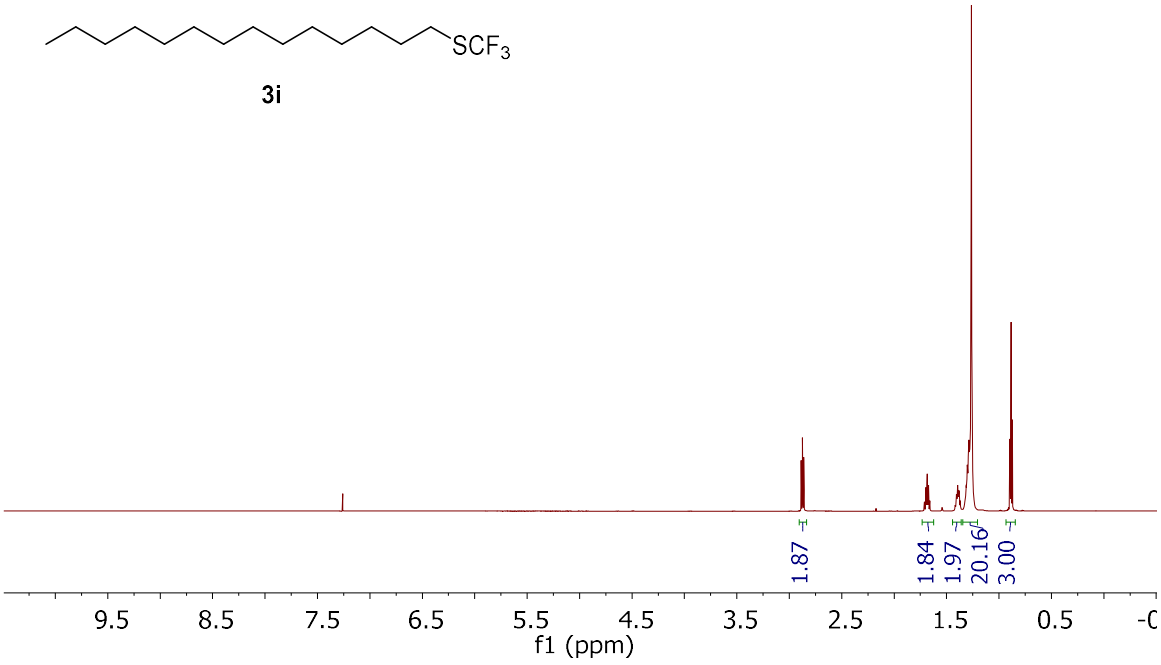

-42.01
SCF3
3g
90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290
f1 (ppm)

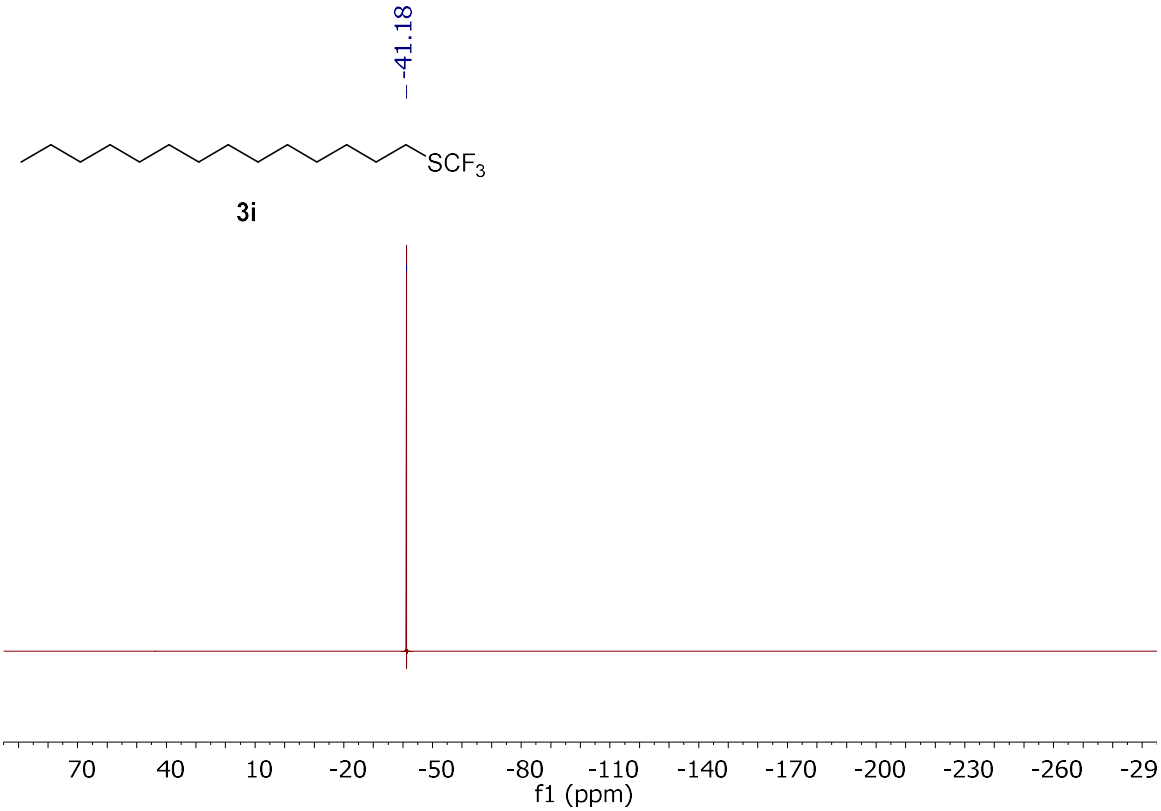

135.97
132.93
129.89
126.85
77.16 CDCl3
32.06
30.07
30.05
30.03
30.01
29.67
29.59
29.58
29.46
29.14
28.69
22.84
14.23
SCF3
3g
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

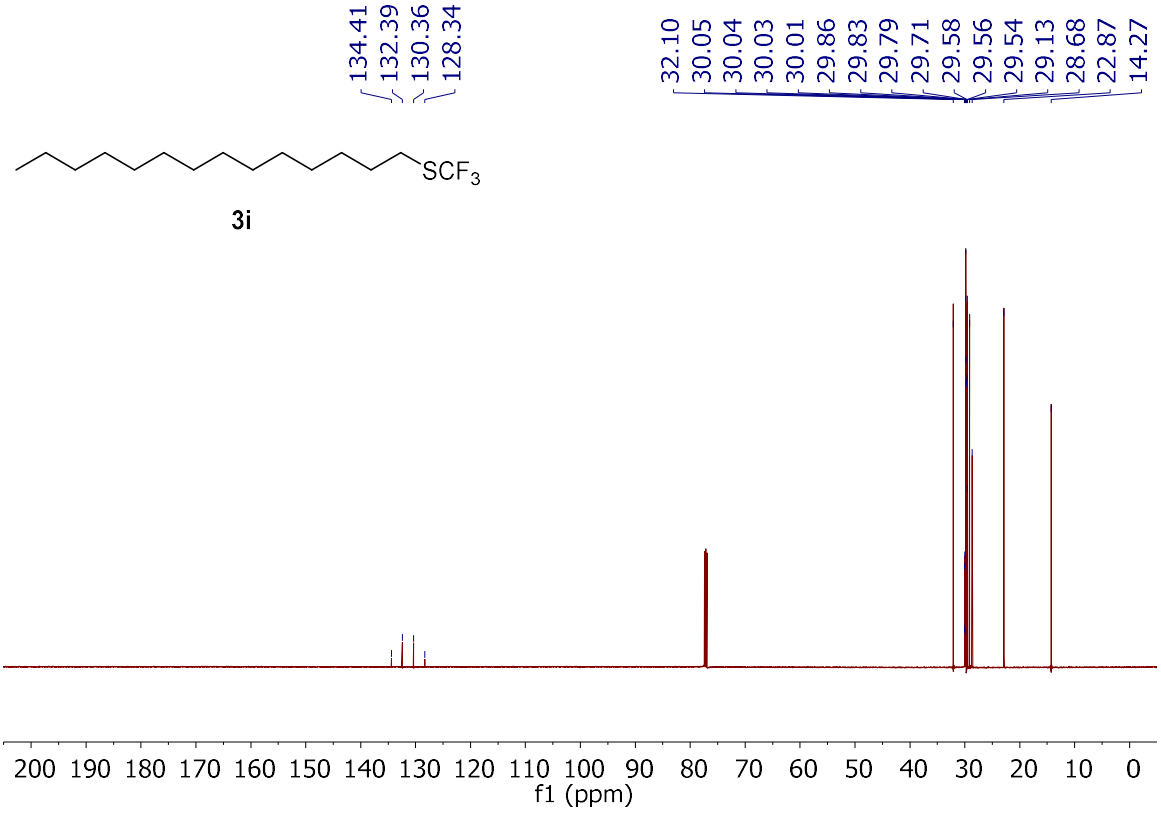

SCF3
3h
2.00
1.99
2.00
15.74
2.94
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

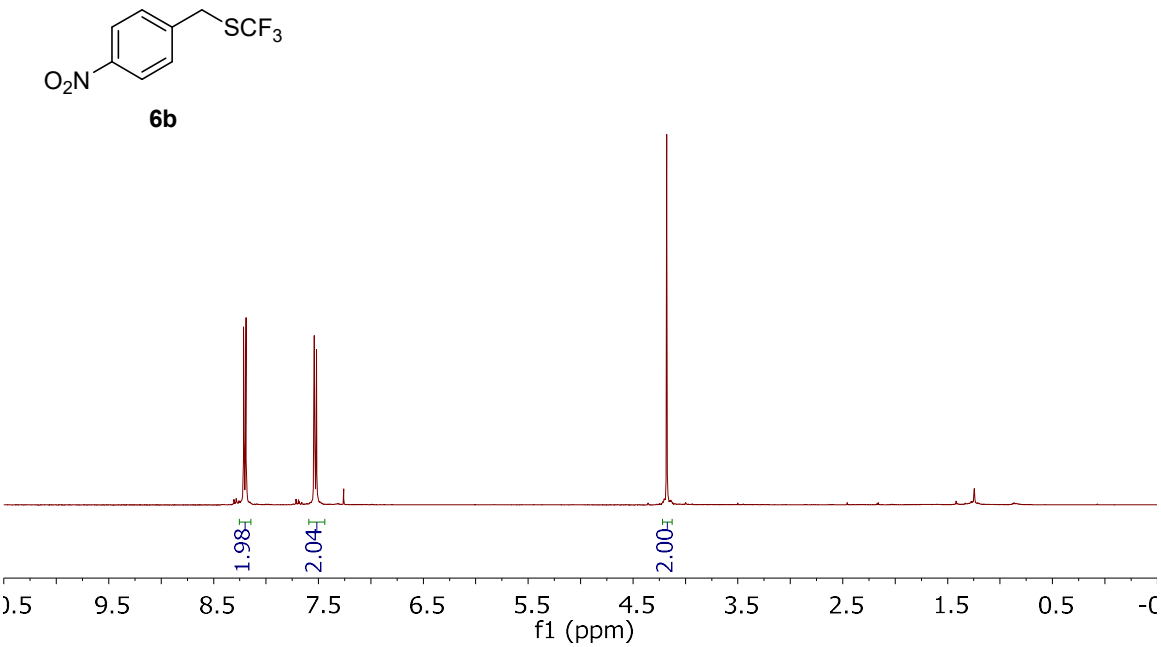

-41.19
SCF3
3h
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
-29
f1 (ppm)

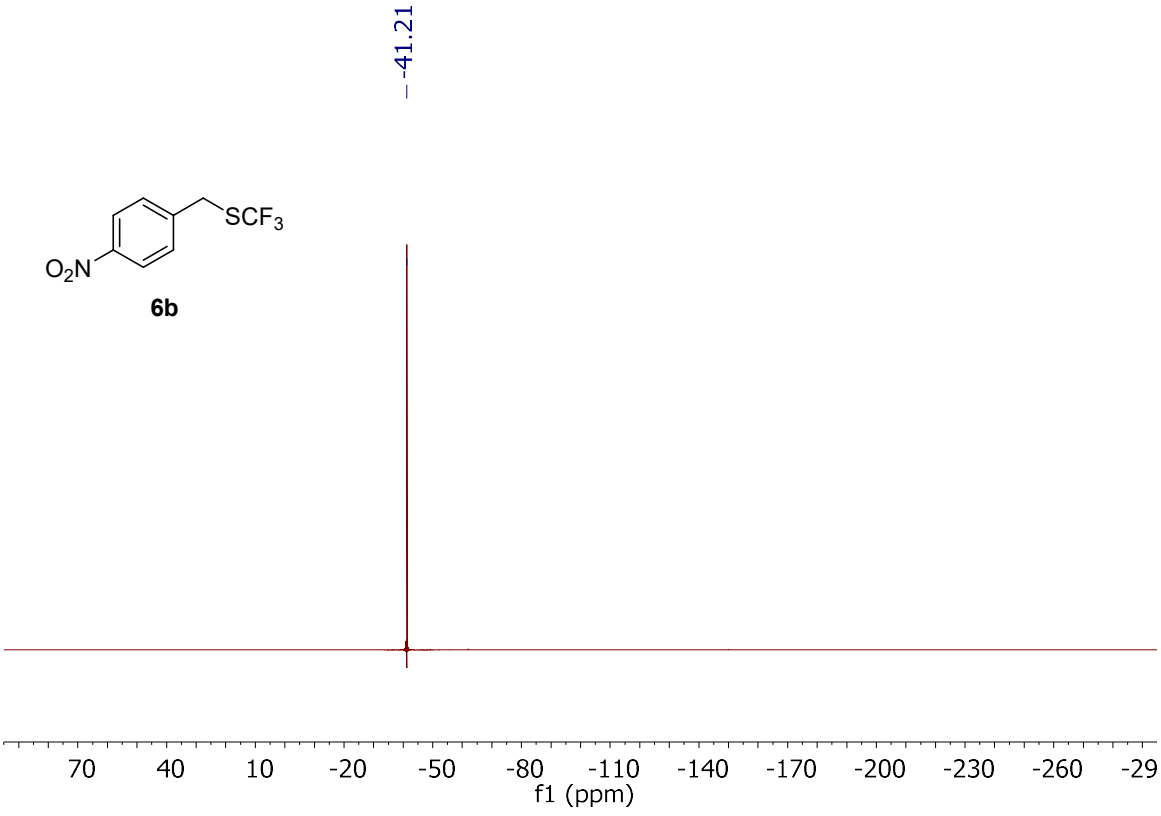

136.28
133.24
130.20
127.16
32.41
30.39
30.37
30.35
30.33
30.11
30.02
29.90
29.83
29.45
29.01
23.17
14.57
SCF3
3h
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

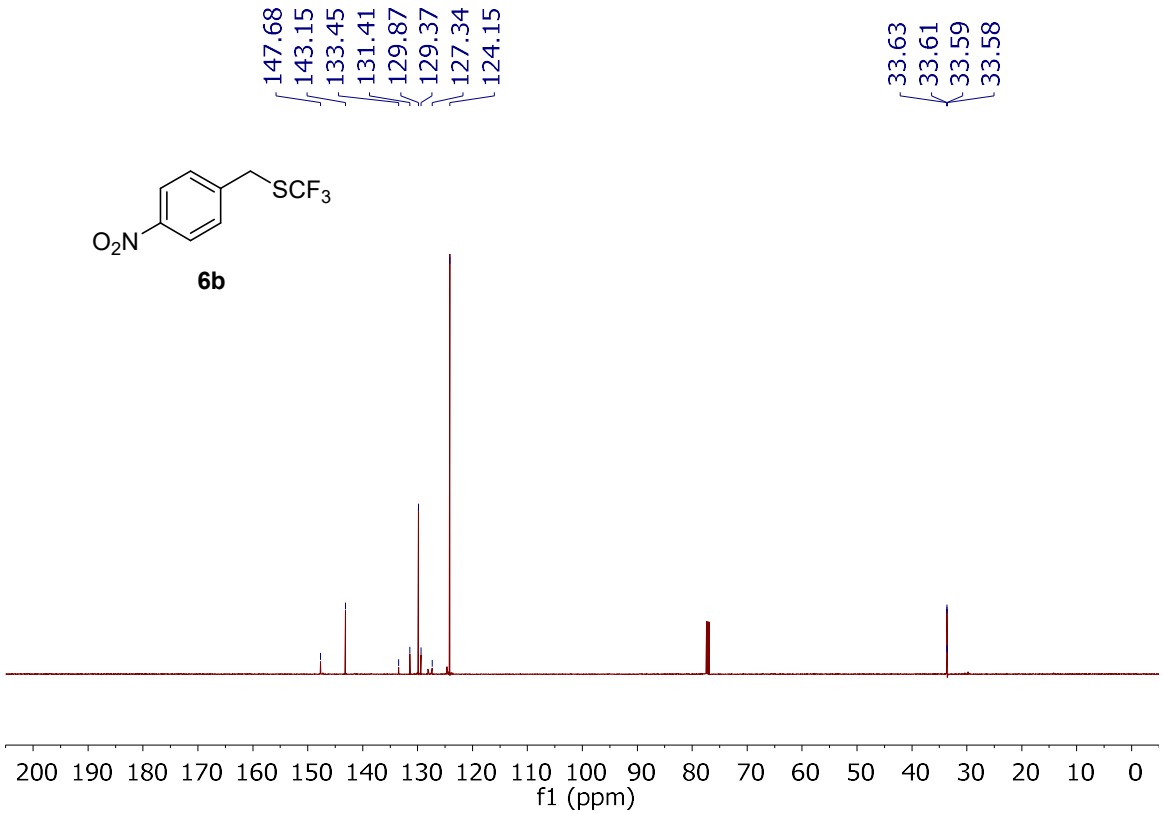

SCF3
3i
1.87
1.84
1.97
20.16
3.00
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
f1 (ppm)

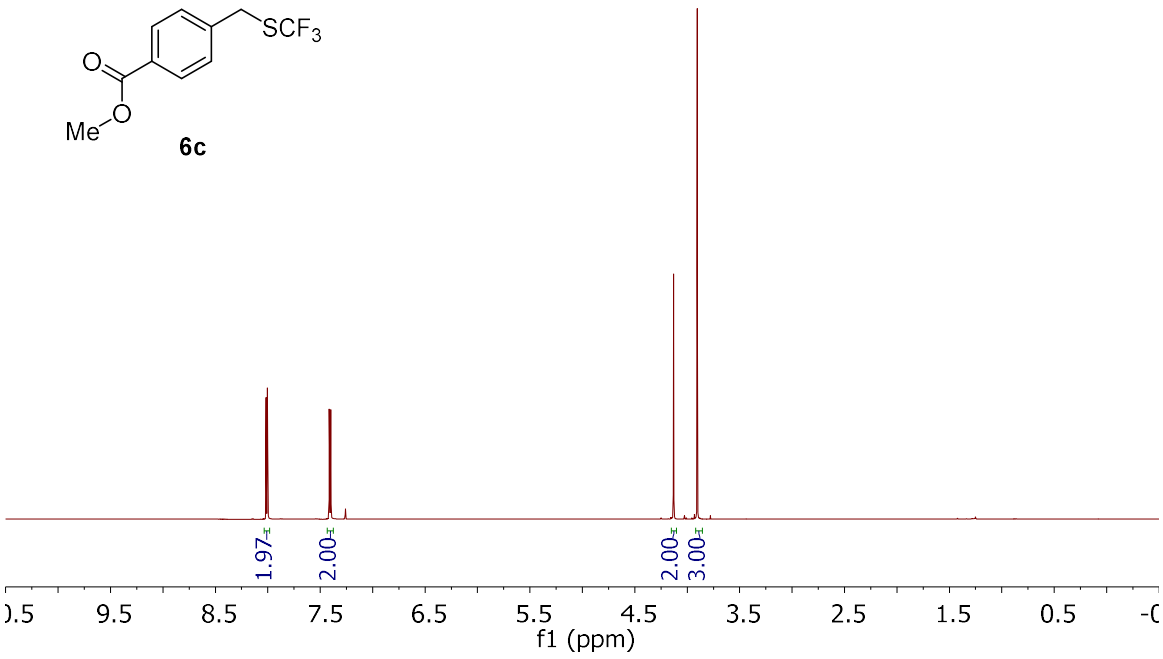

-41.18
SCF3
3i
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

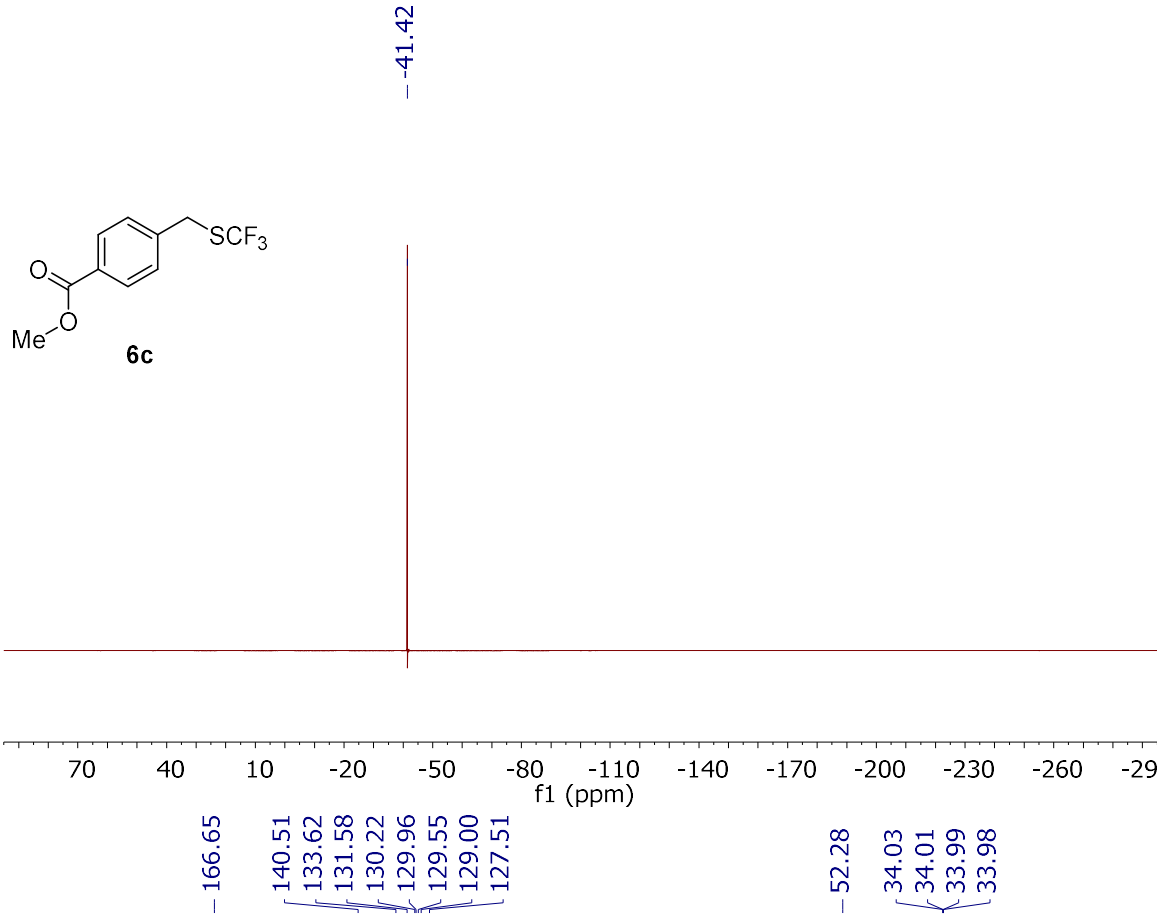

134.41
132.39
130.36
128.34
32.10
30.05
30.04
30.03
30.01
29.86
29.83
29.79
29.71
29.58
29.56
29.54
29.13
28.68
22.87
14.27
SCF3
3i
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

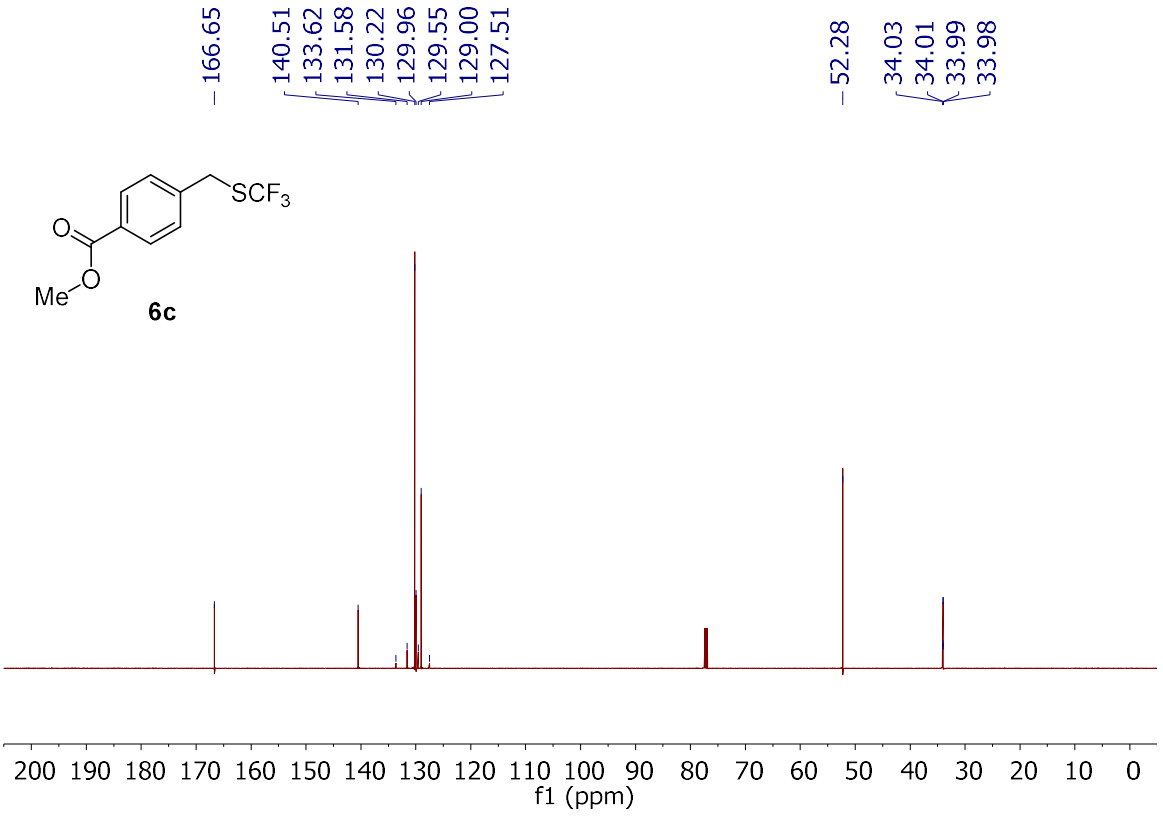

SCF3
O2N
6b
1.98
2.04
2.00
f1 (ppm)

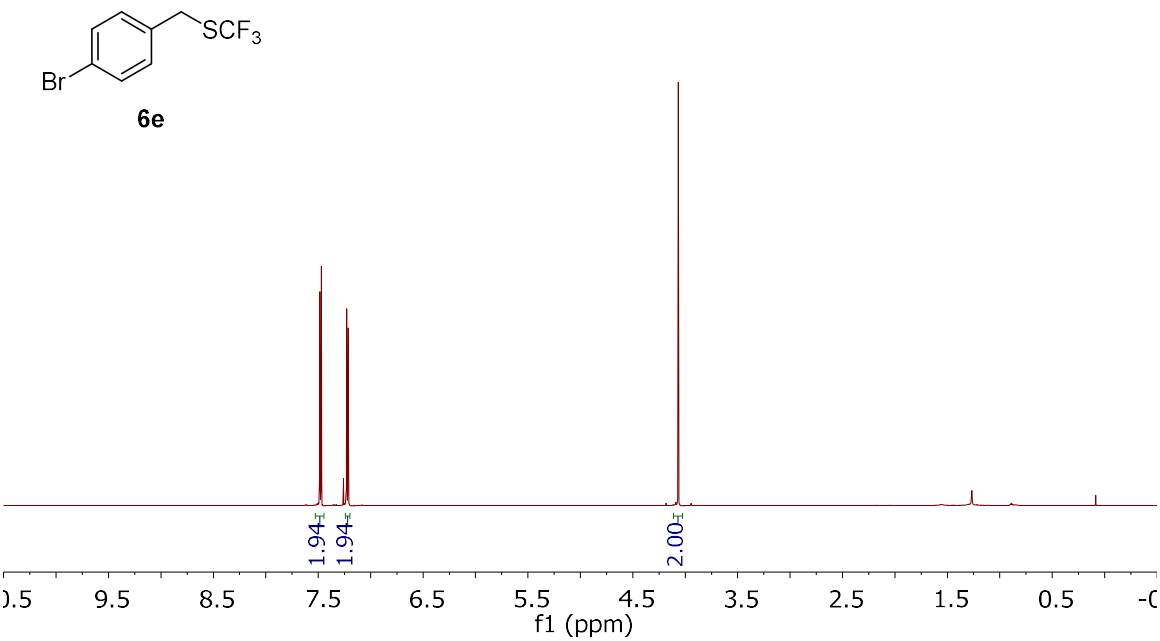

-41.21
SCF3
O2N
6b
f1 (ppm)

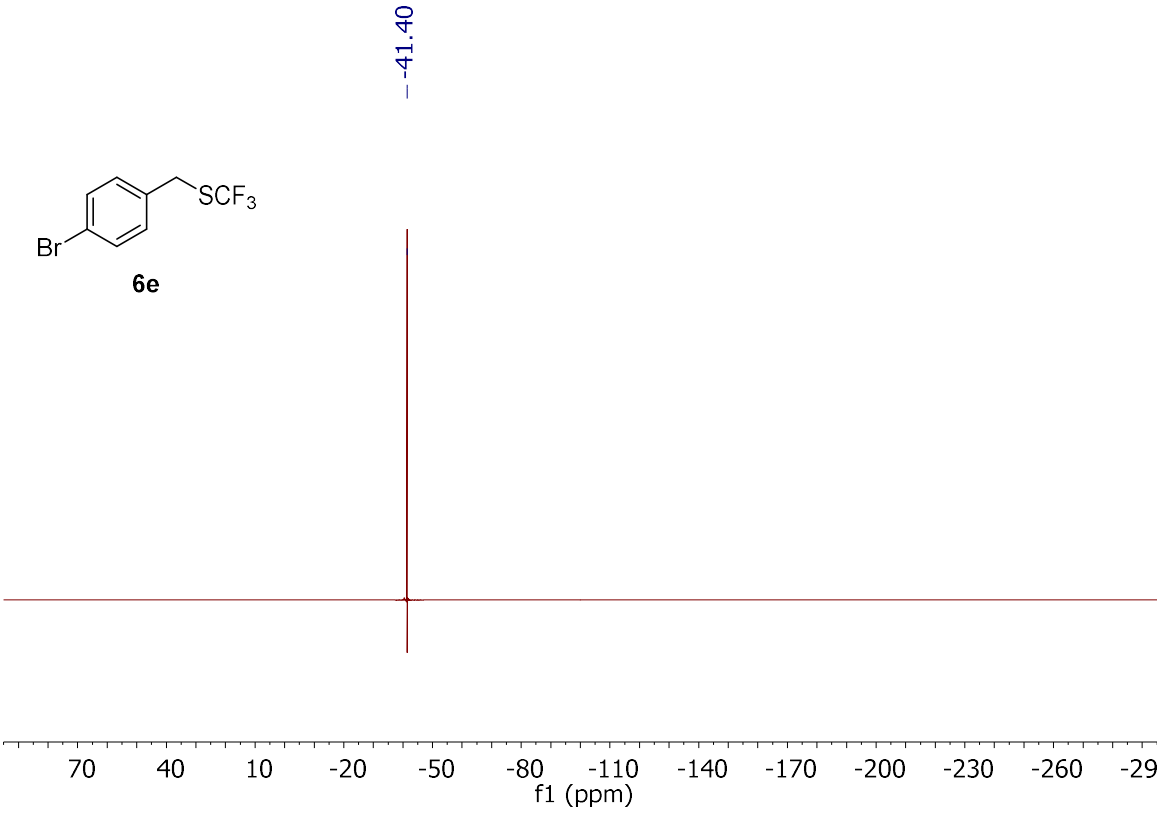

147.68
143.15
133.45
131.41
129.87
129.37
127.34
124.15
33.63
33.61
33.59
33.58
SCF3
O2N
6b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

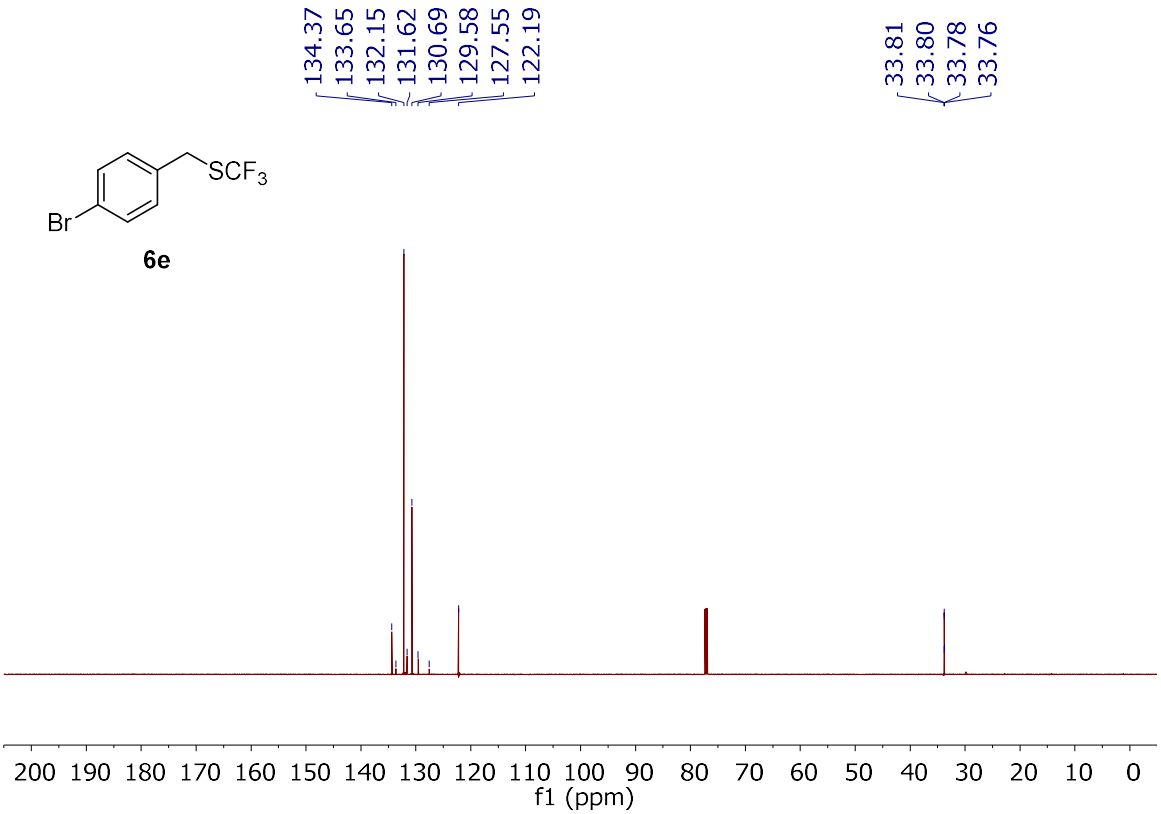

SCF3
O
O
Me
6c
1.97
2.00
2.00
3.00
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
f1 (ppm)

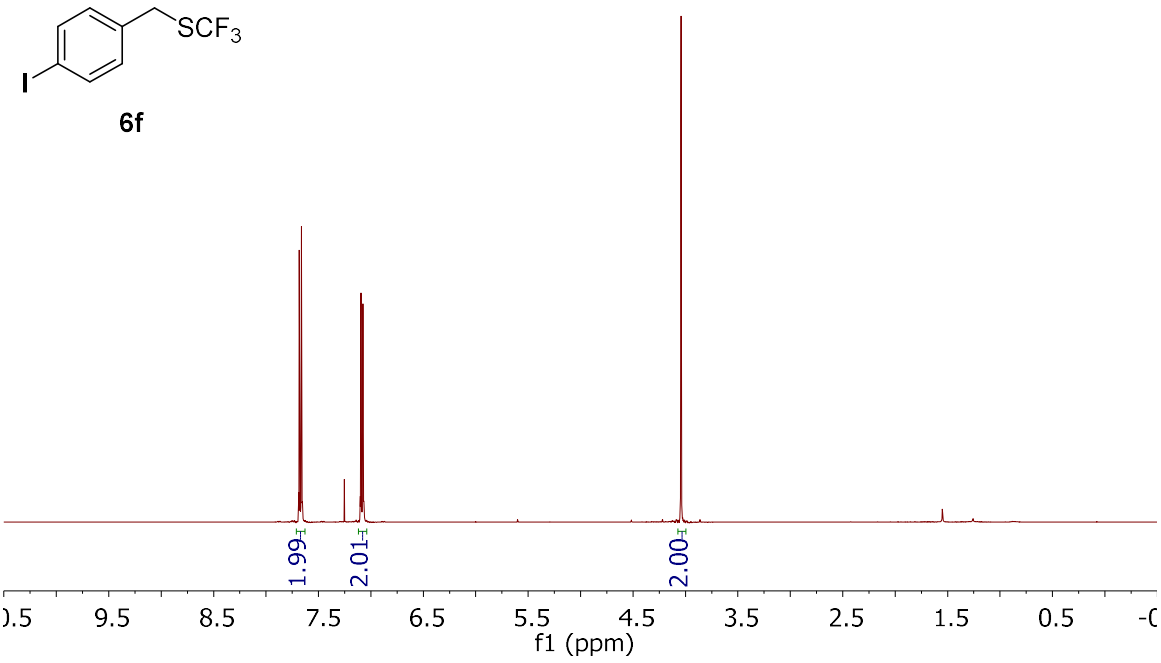

-41.42
SCF3
O
O
Me
6c
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

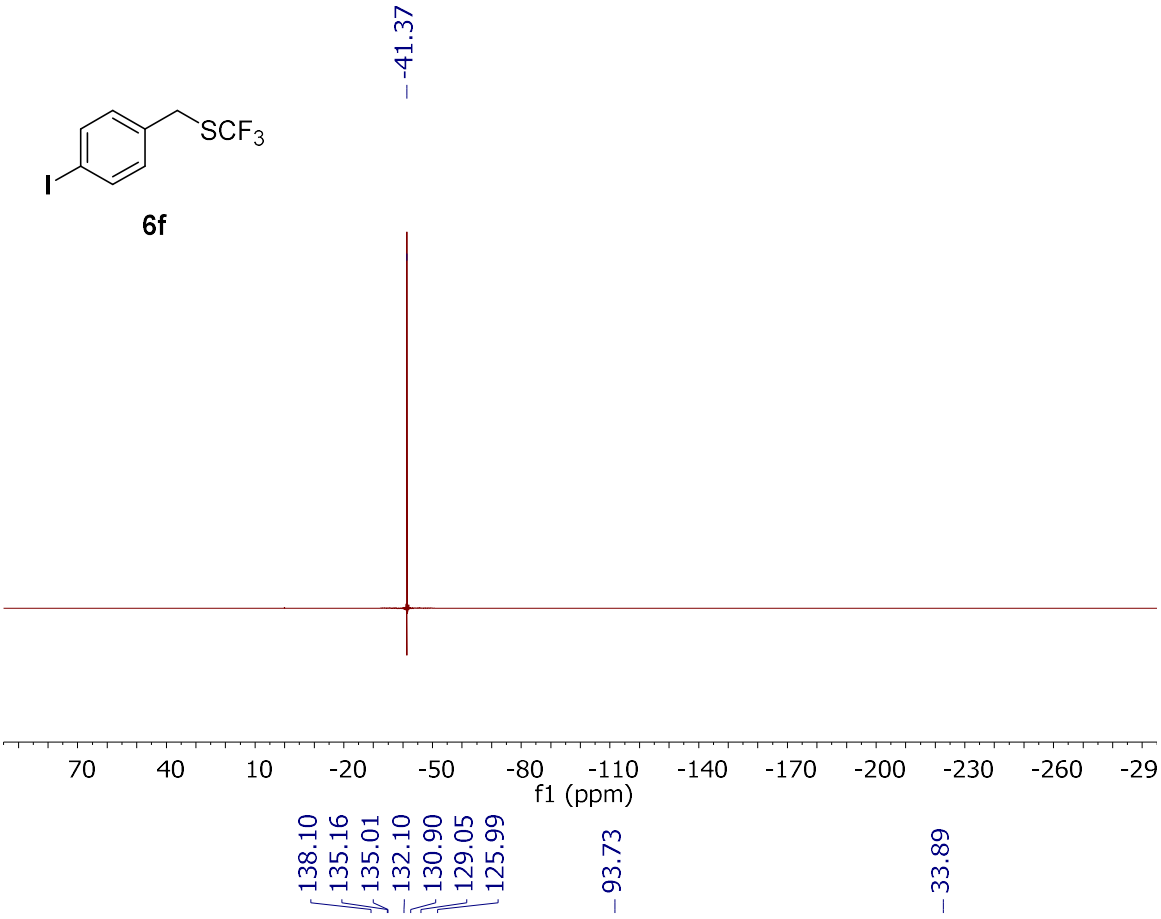

166.65
140.51
133.62
131.58
130.22
129.96
129.55
129.00
127.51
52.28
34.03
34.01
33.99
33.98
SCF3
O
O
Me
6c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

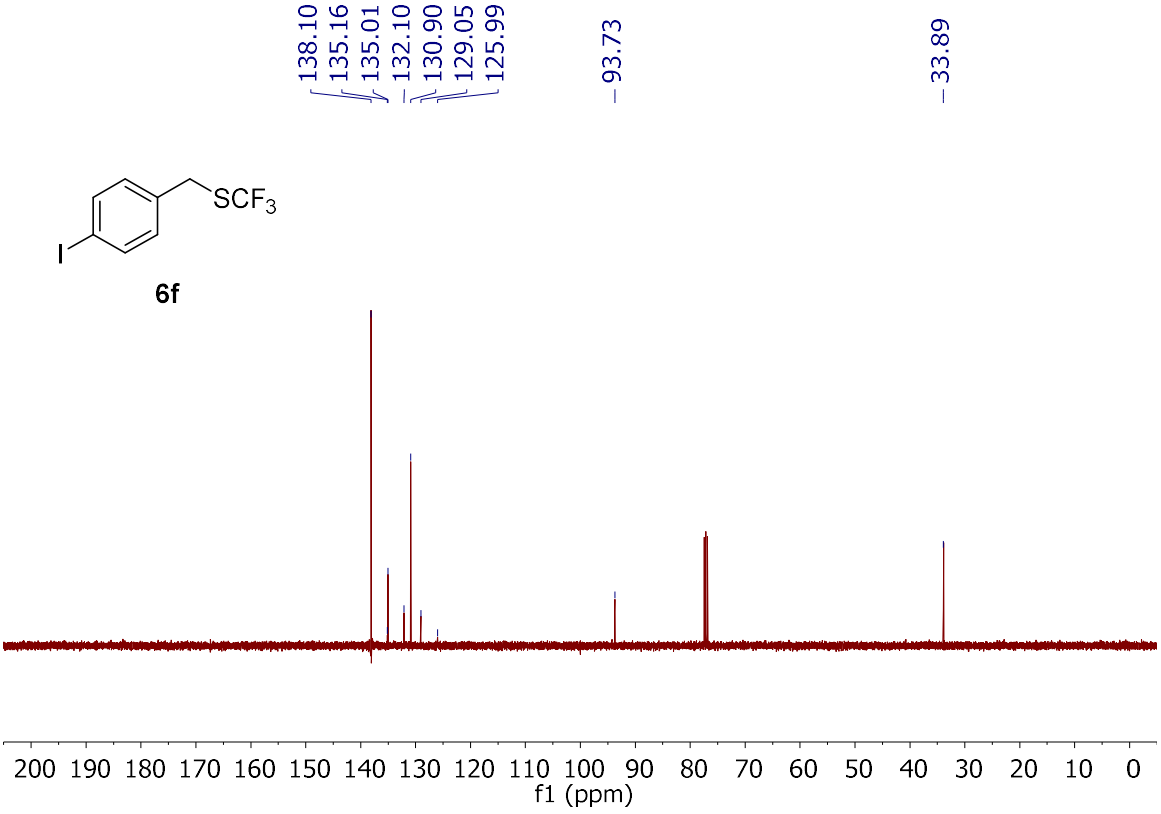

SCF3
Br
6e
1.94
1.94
2.00
f1 (ppm)

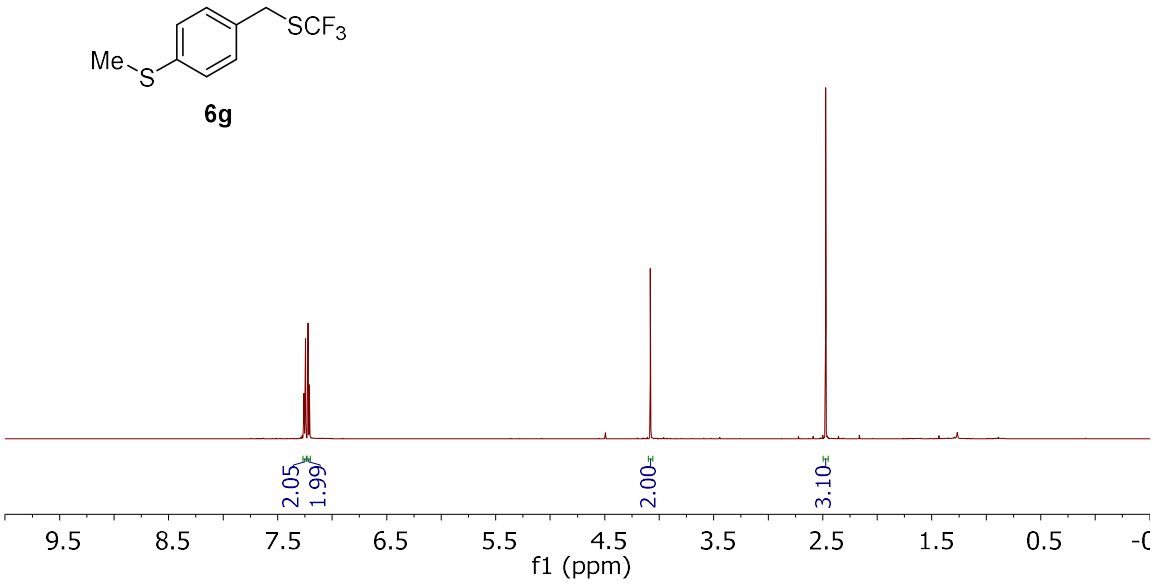

-41.40
SCF3
Br
6e
f1 (ppm)

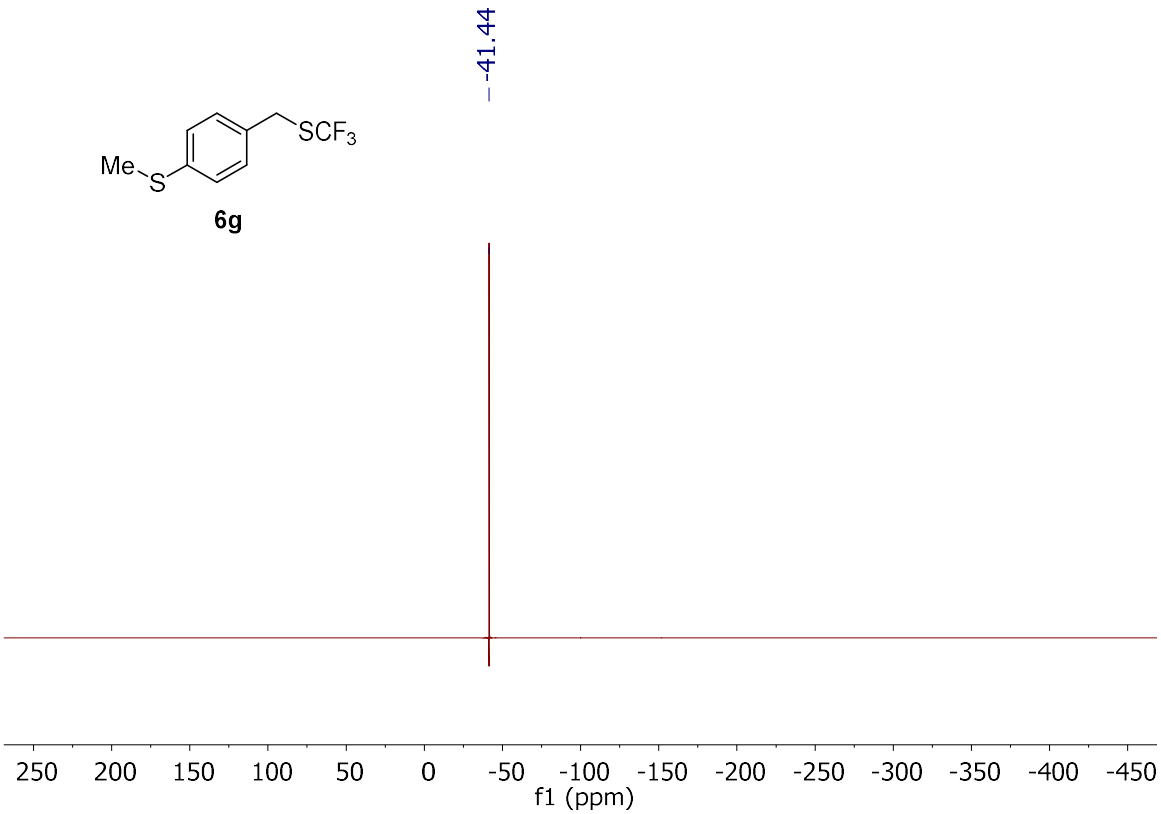

134.37
133.65
132.15
131.62
130.69
129.58
127.55
122.19
33.81
33.80
33.78
33.76
SCF3
Br
6e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

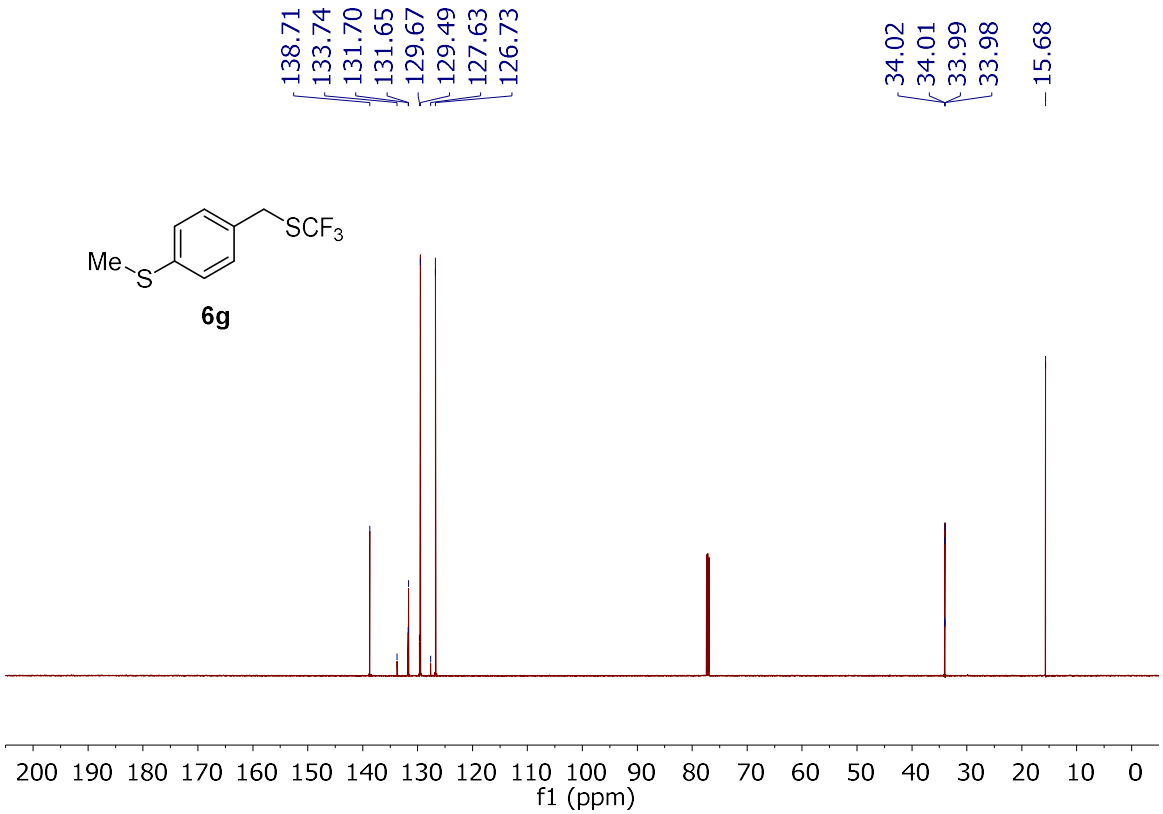

SCF3
I
6f
1.99
2.01
2.00
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
f1 (ppm)

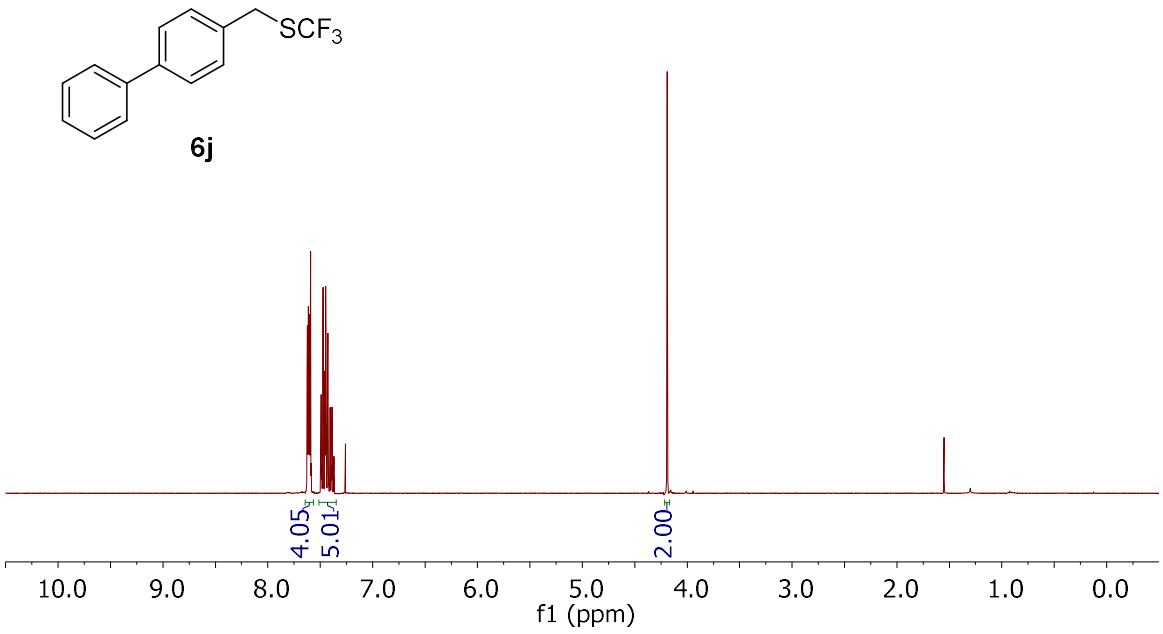

-41.37
SCF3
I
6f
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

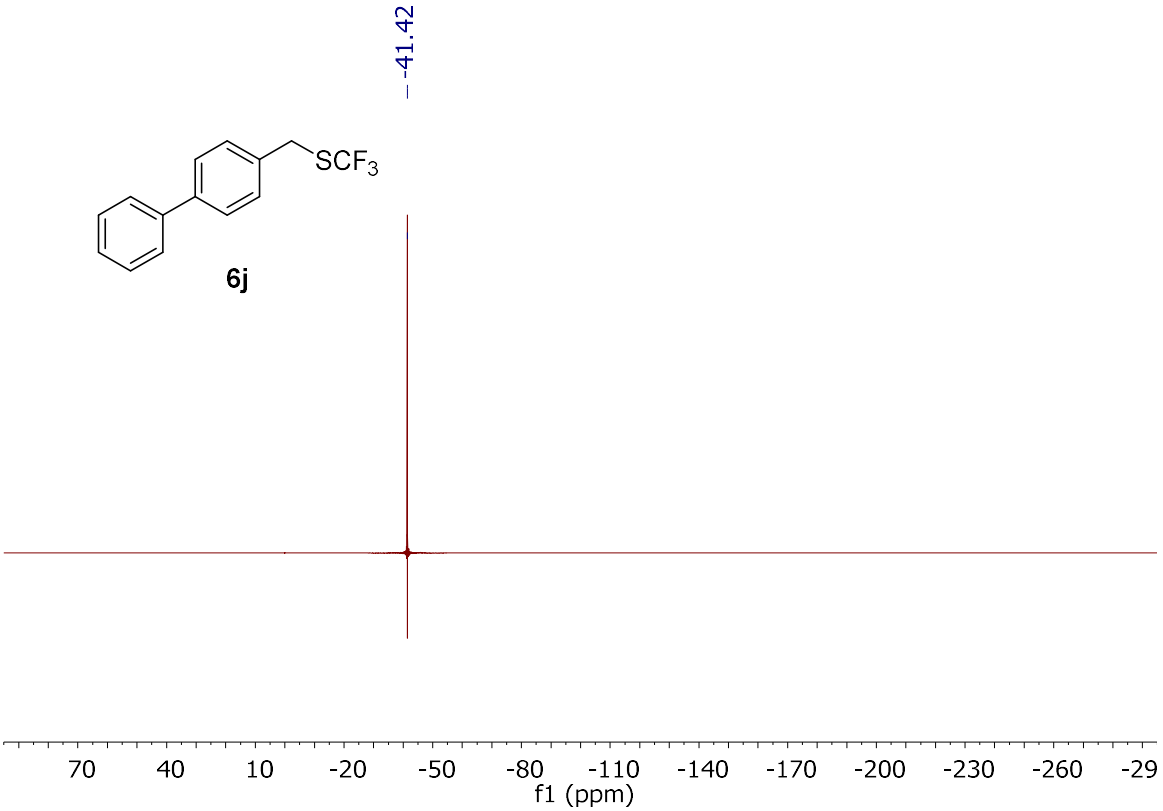

138.10
135.16
135.01
132.10
130.90
129.05
125.99
93.73
33.89
SCF3
I
6f
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

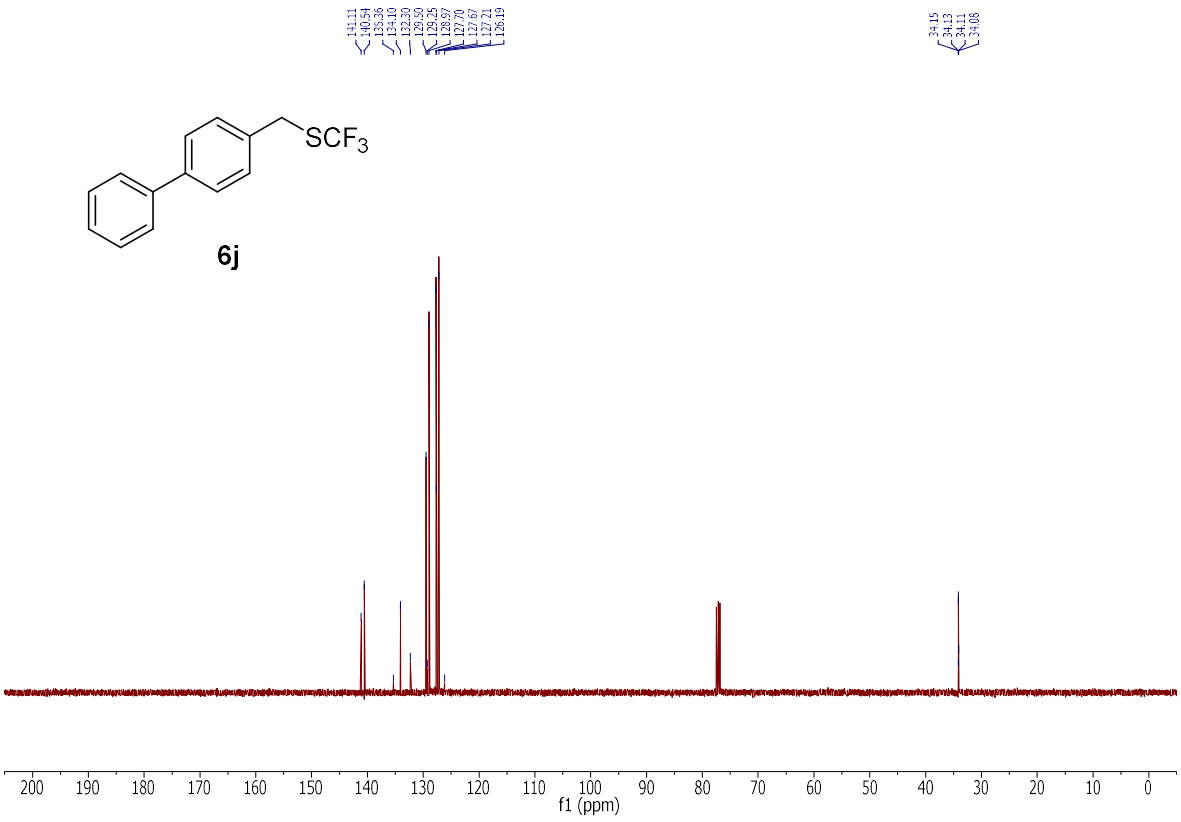

SCF3
Me
S
6g
2.05
1.99
2.00
3.10
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

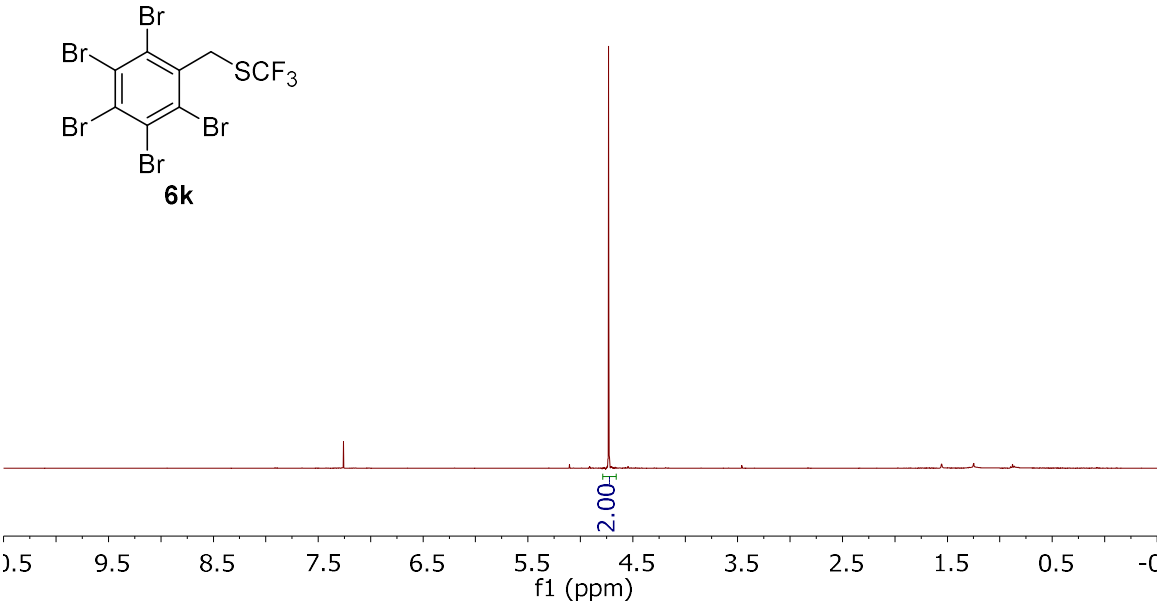

-41.44
SCF3
Me
S
6g
250
200
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
-400
-450
f1 (ppm)

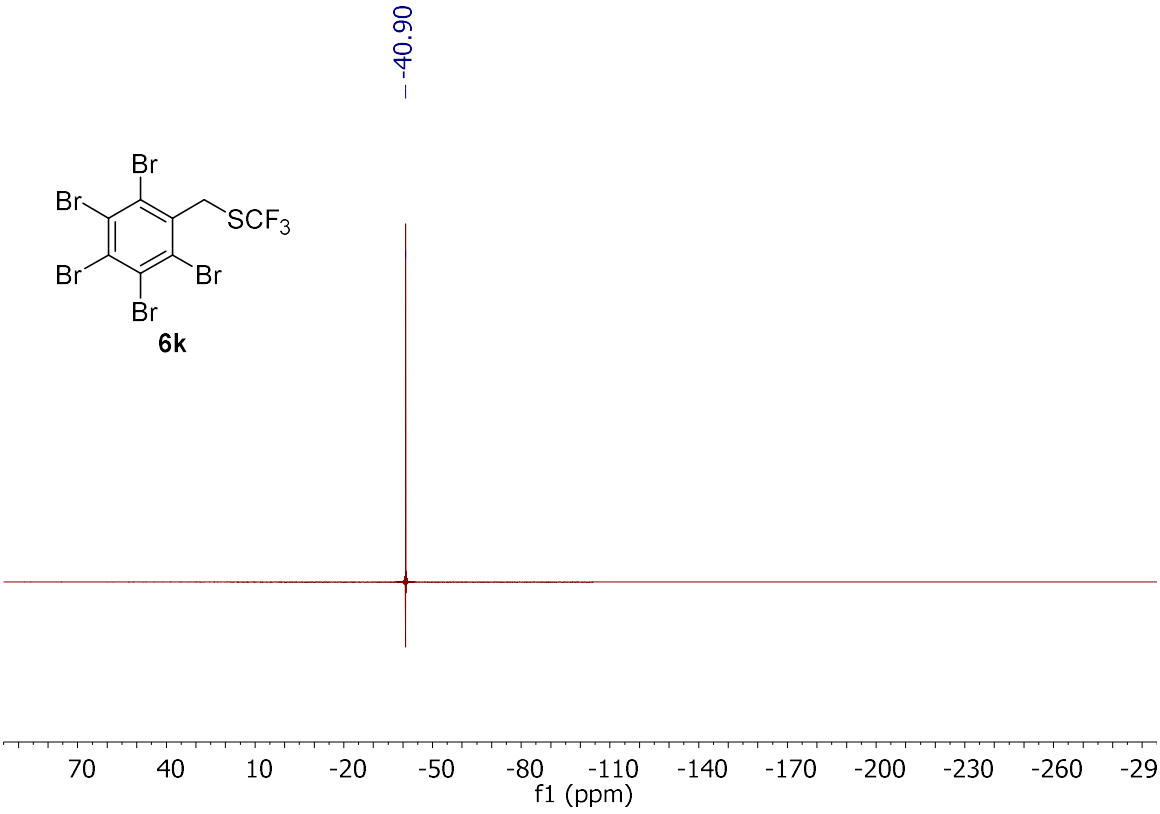

138.71
133.74
131.70
131.65
129.67
129.49
127.63
126.73
34.02
34.01
33.99
33.98
15.68
SCF3
Me
S
6g
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

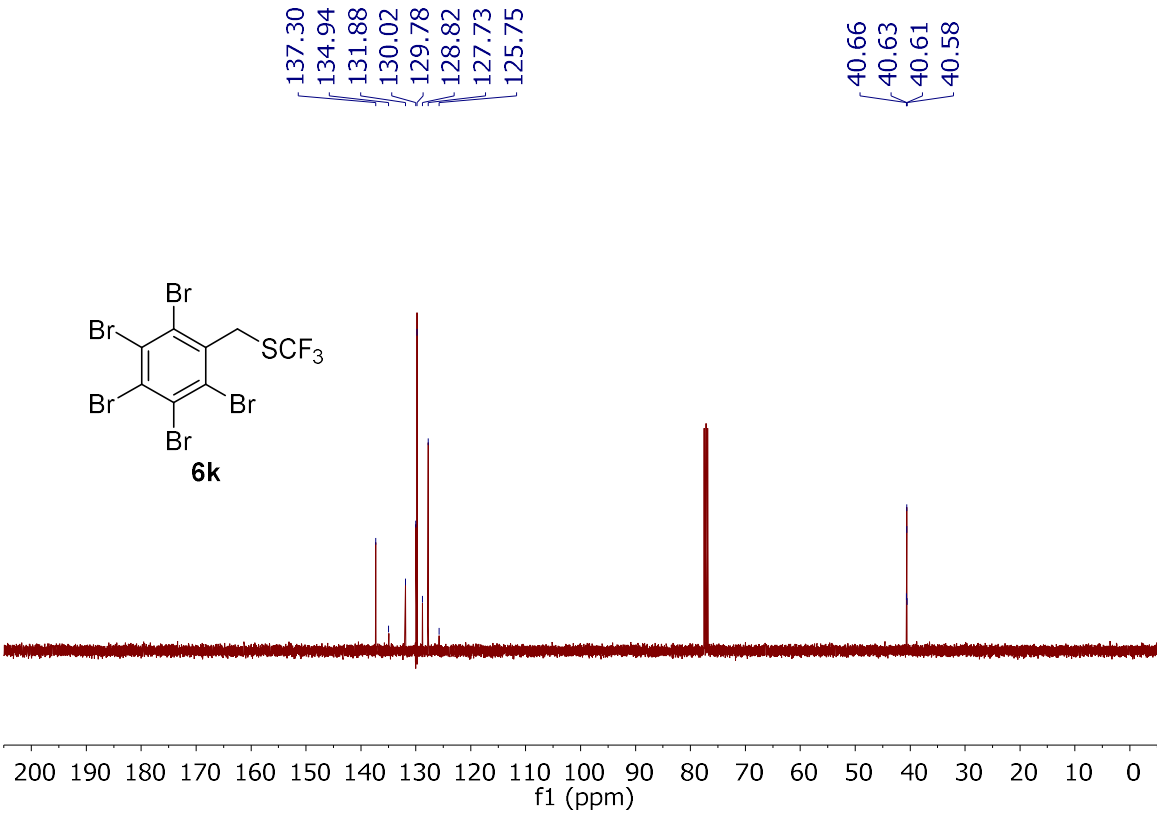

SCF3
6j
4.05
5.01
2.00
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

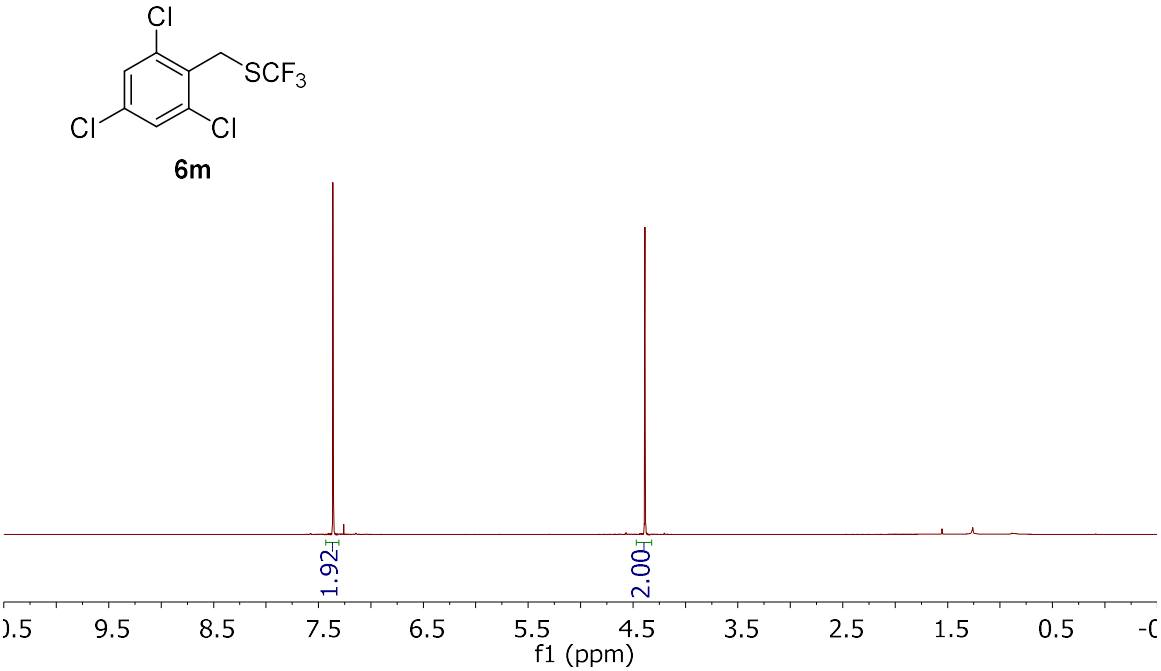

-41.42
SCF3
6j
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
-29
f1 (ppm)

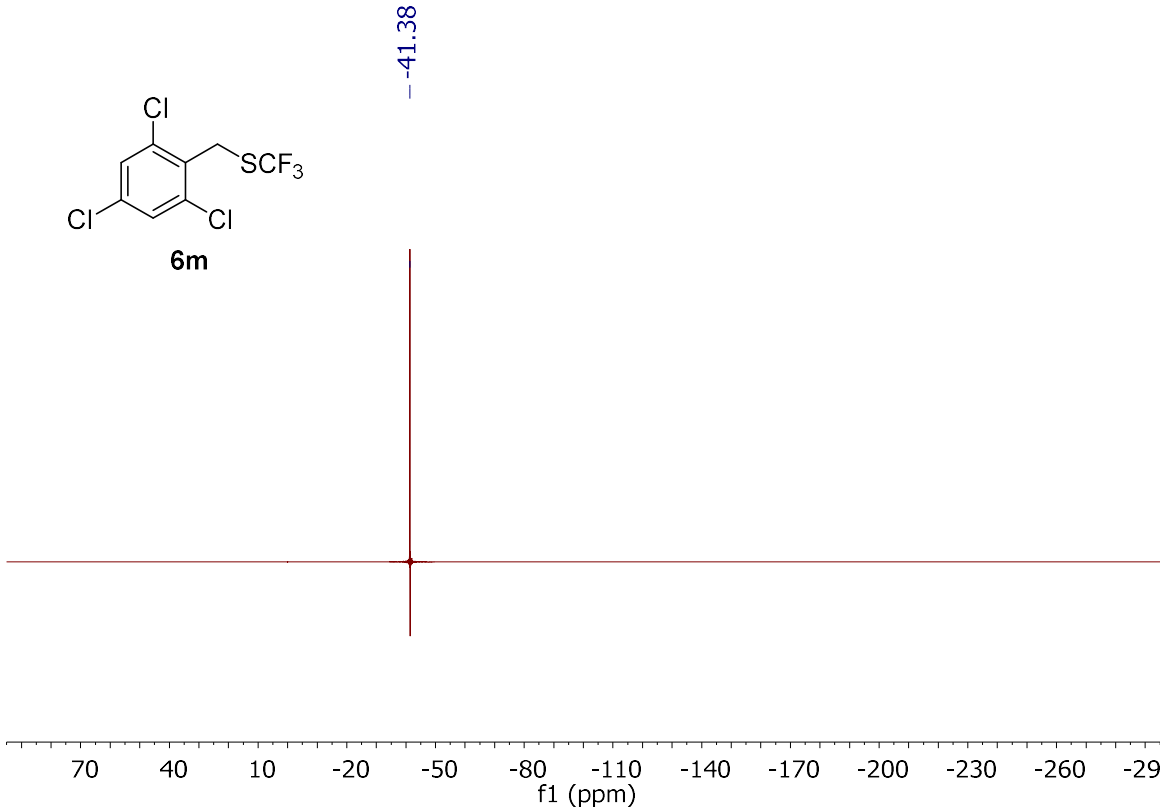

141.11
140.54
135.36
134.10
132.30
129.50
129.25
128.97
127.70
127.67
127.21
126.19
34.15
34.13
34.11
34.08
SCF3
6j
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

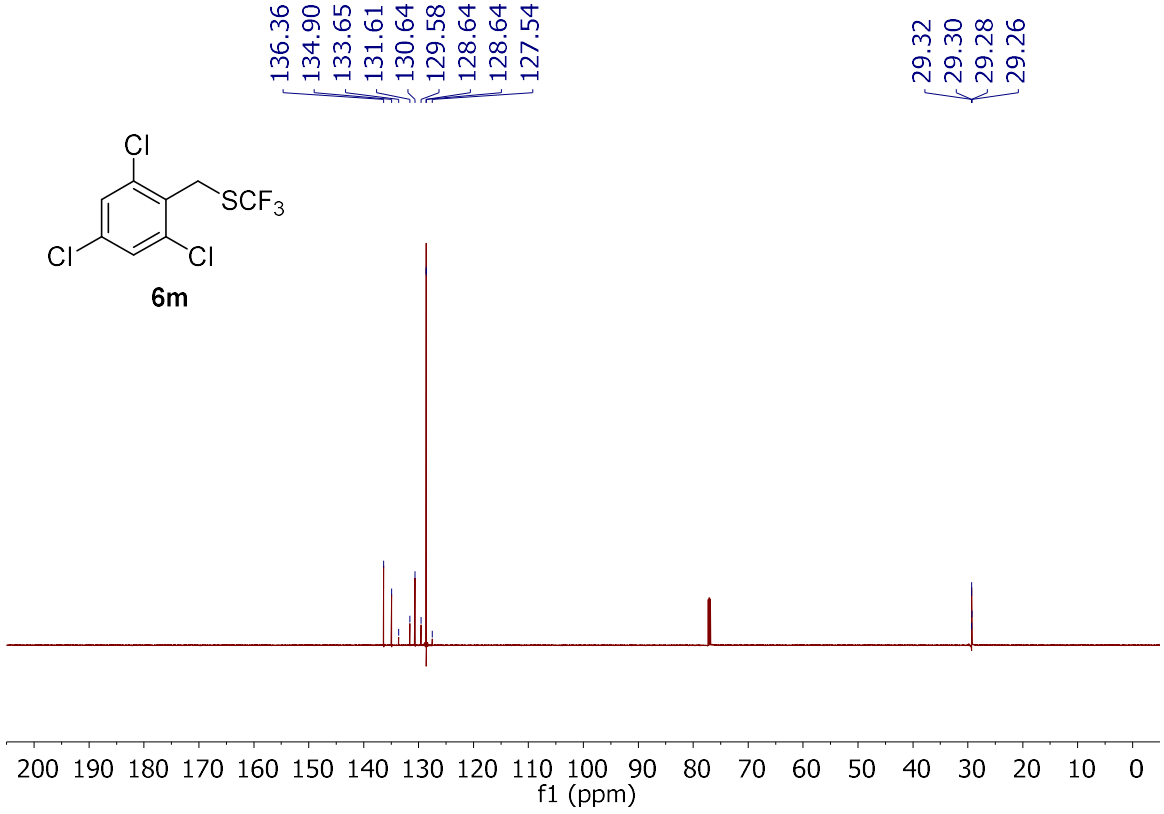

Br
Br
SCF3
Br
Br
Br
6k
2.00
f1 (ppm)

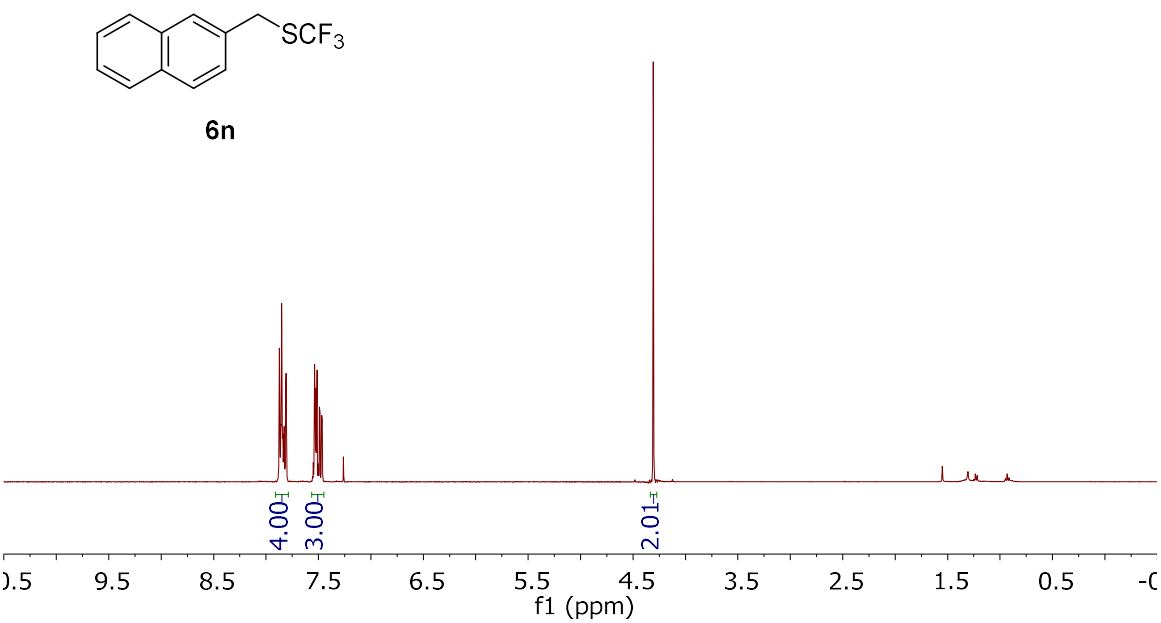

-40.90
Br
Br
SCF3
Br
Br
Br
6k
f1 (ppm)

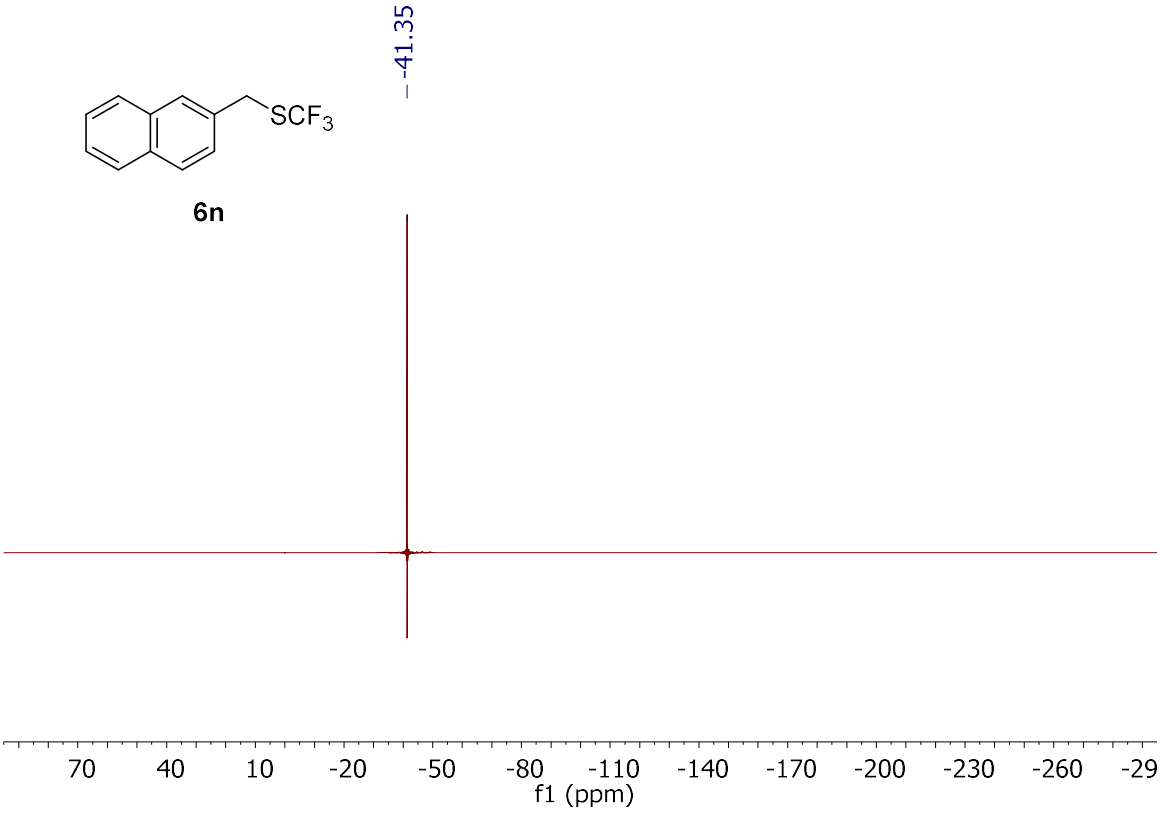

137.30
134.94
131.88
130.02
129.78
128.82
127.73
125.75
40.66
40.63
40.61
40.58
Br
Br
SCF3
Br
Br
Br
6k
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

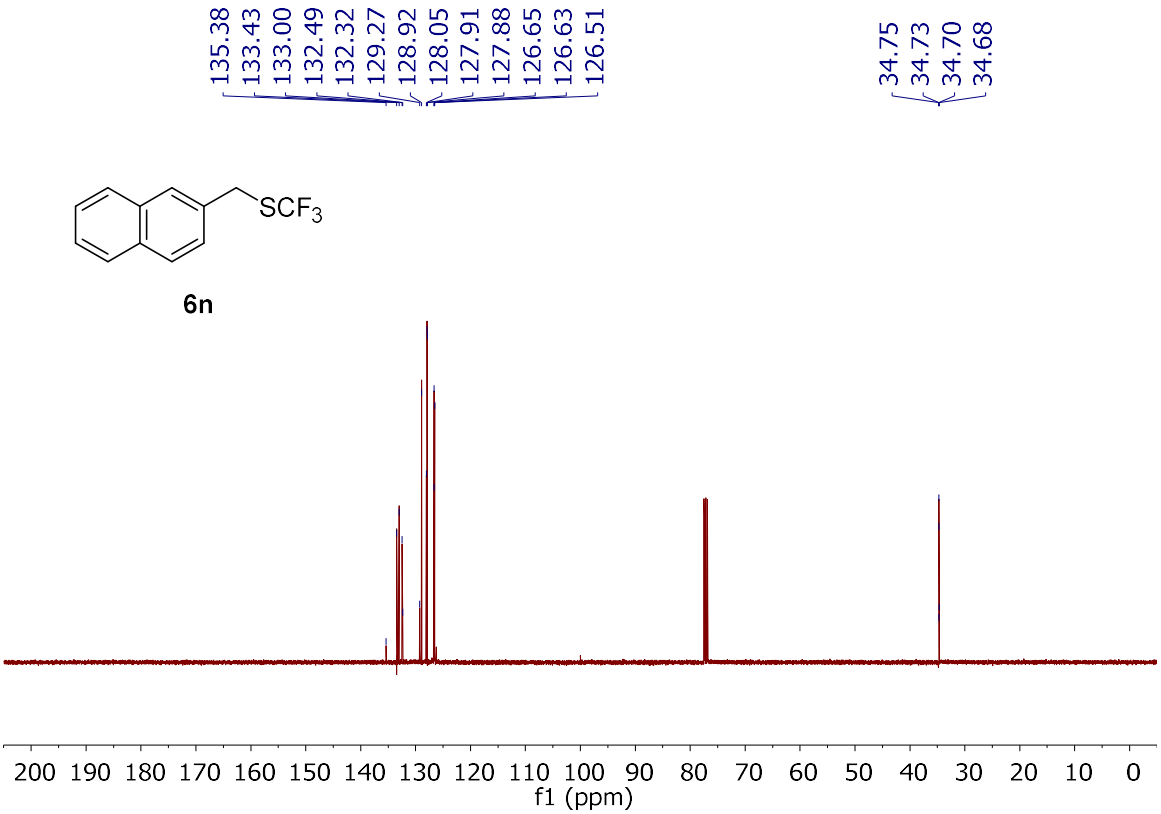

Cl
SCF3
Cl
Cl
6m
1.92
2.00
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
f1 (ppm)


-41.38
Cl
SCF3
Cl
Cl
6m
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

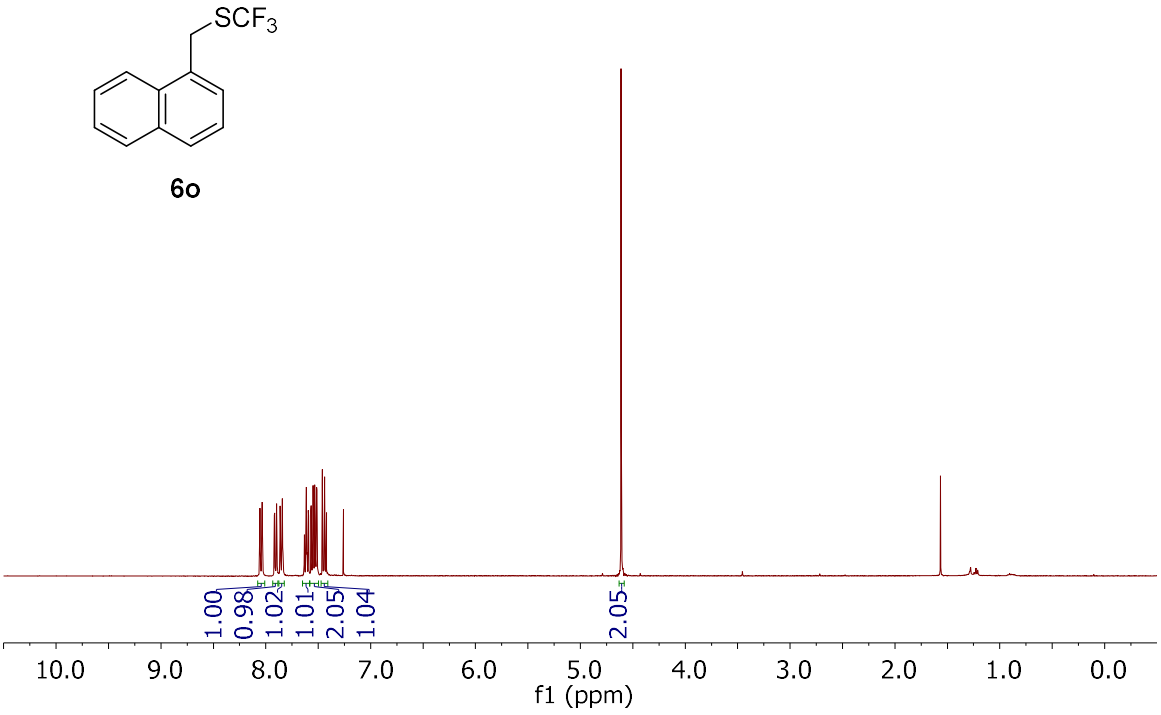

136.36
134.90
133.65
131.61
130.64
129.58
128.64
128.64
127.54
29.32
29.30
29.28
29.26
Cl
SCF3
Cl
Cl
6m
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


SCF3
6n
4.00
3.00
2.01
f1 (ppm)

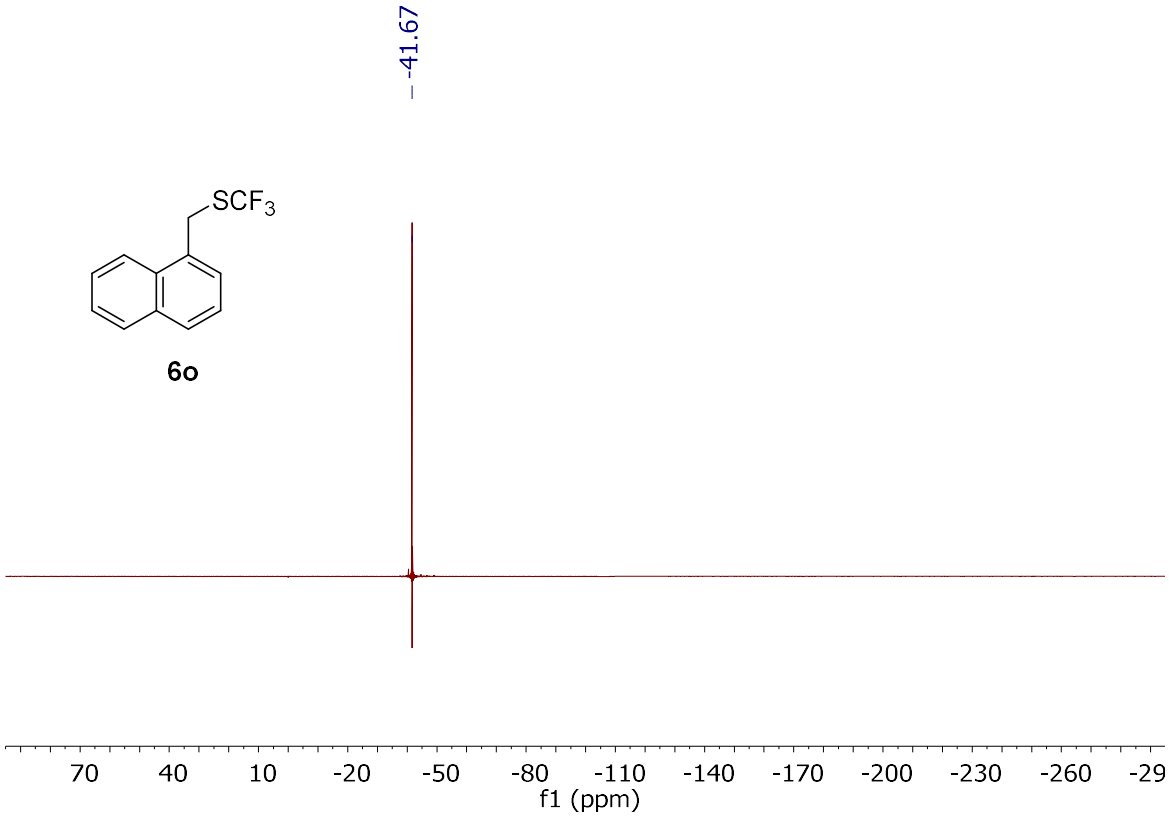

-41.35
SCF3
6n
f1 (ppm)

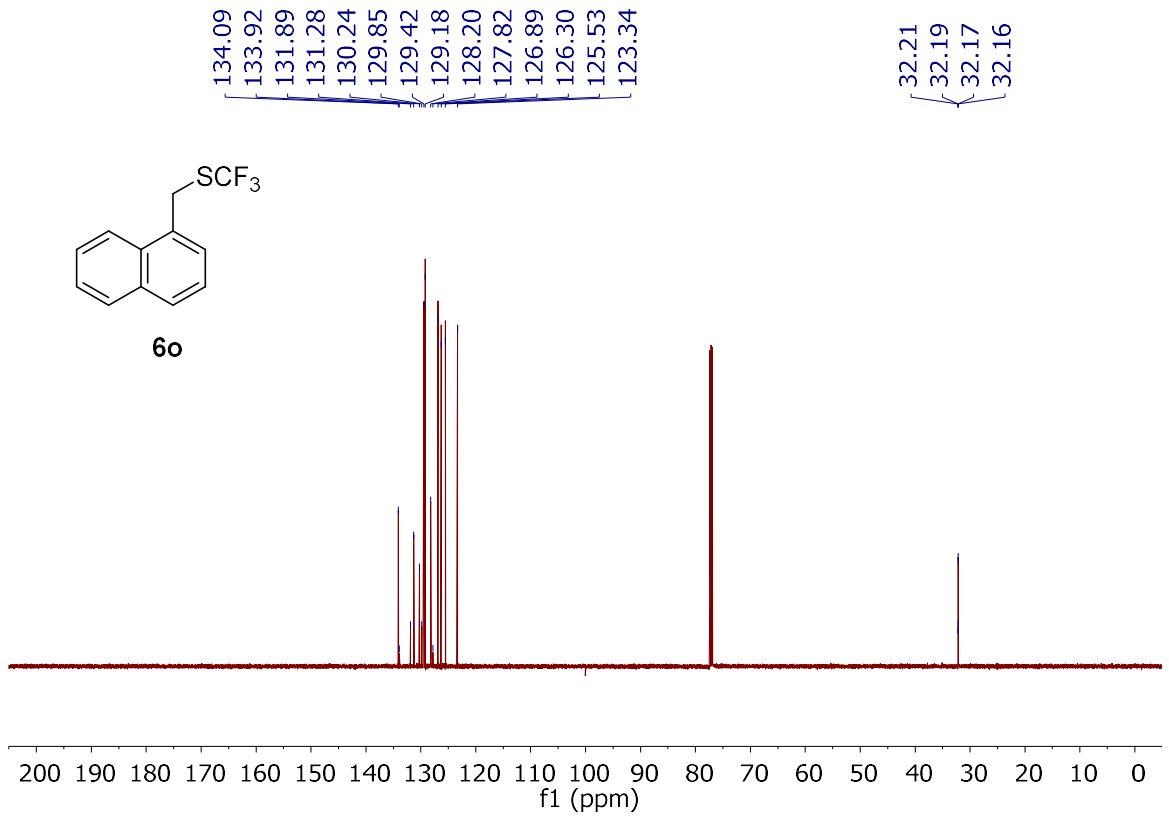

135.38
133.43
133.00
132.49
132.32
129.27
128.92
128.05
127.91
127.88
126.65
126.63
126.51
34.75
34.73
34.70
34.68
SCF3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

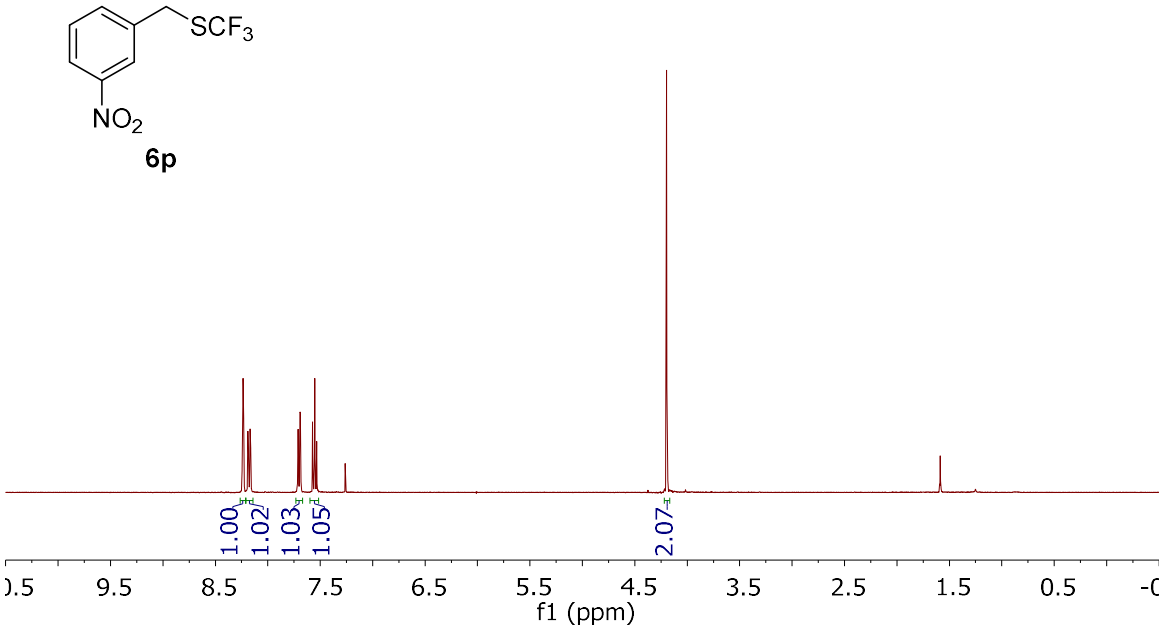
6n

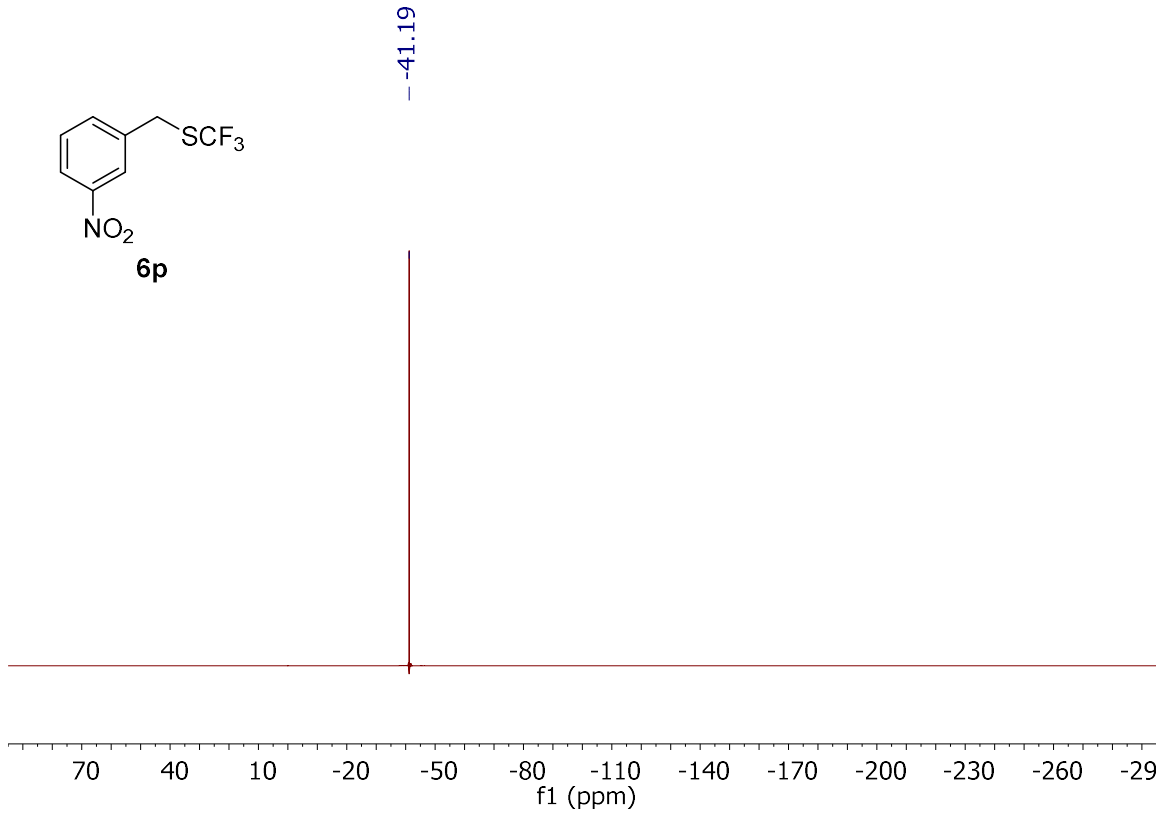

SCF3
1.00
0.98
1.02
1.01
2.05
1.04
2.05
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

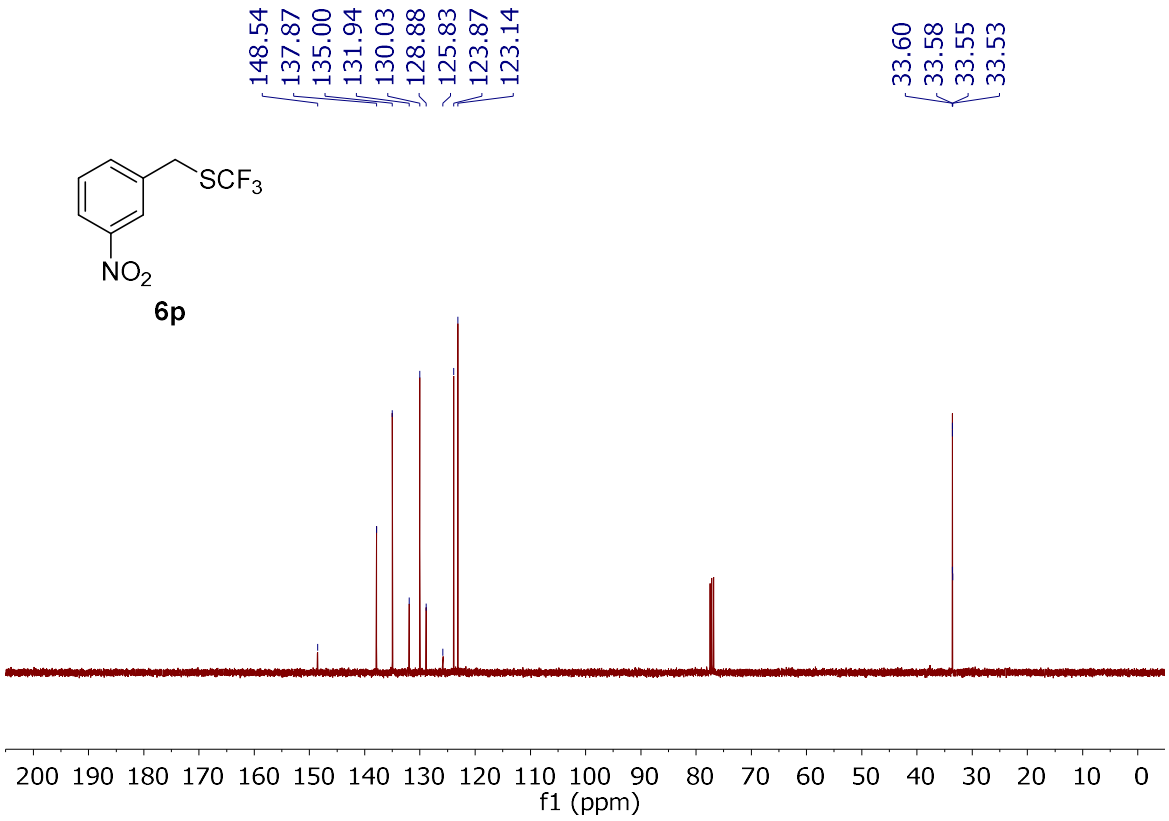
6o


-41.67
SCF3
6o
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

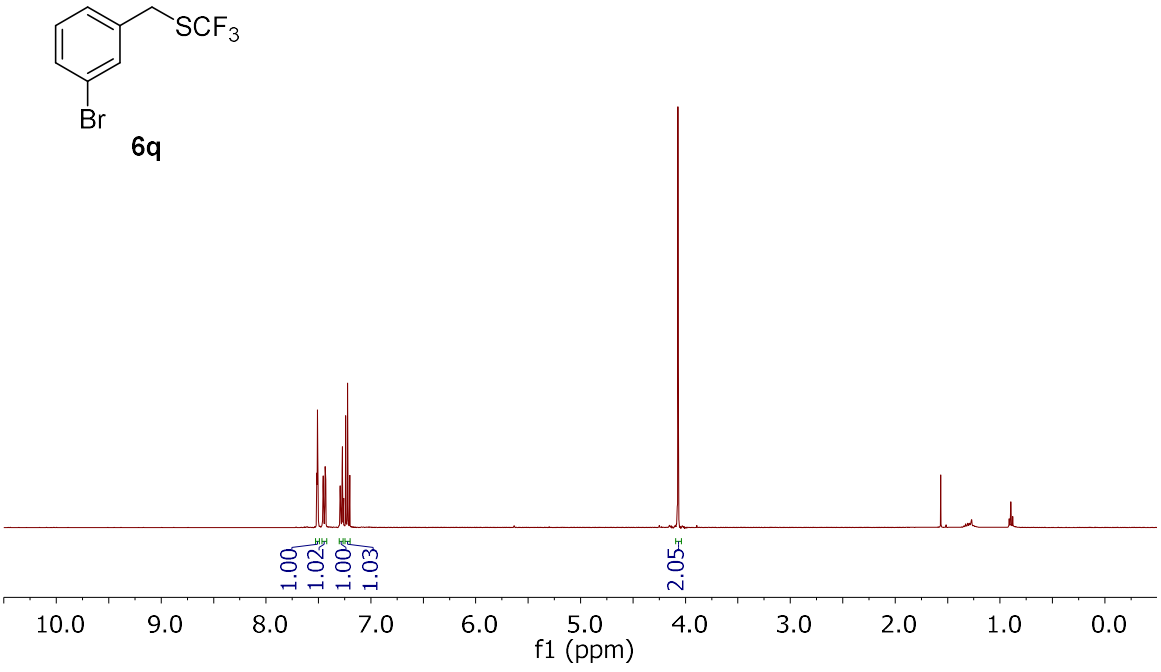

134.09
133.92
131.89
131.28
130.24
129.85
129.42
129.18
128.20
127.82
126.89
126.30
125.53
123.34
32.21
32.19
32.17
32.16
SCF3
6o
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


SCF3
NO2
6p
1.00
1.02
1.03
1.05
2.07
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

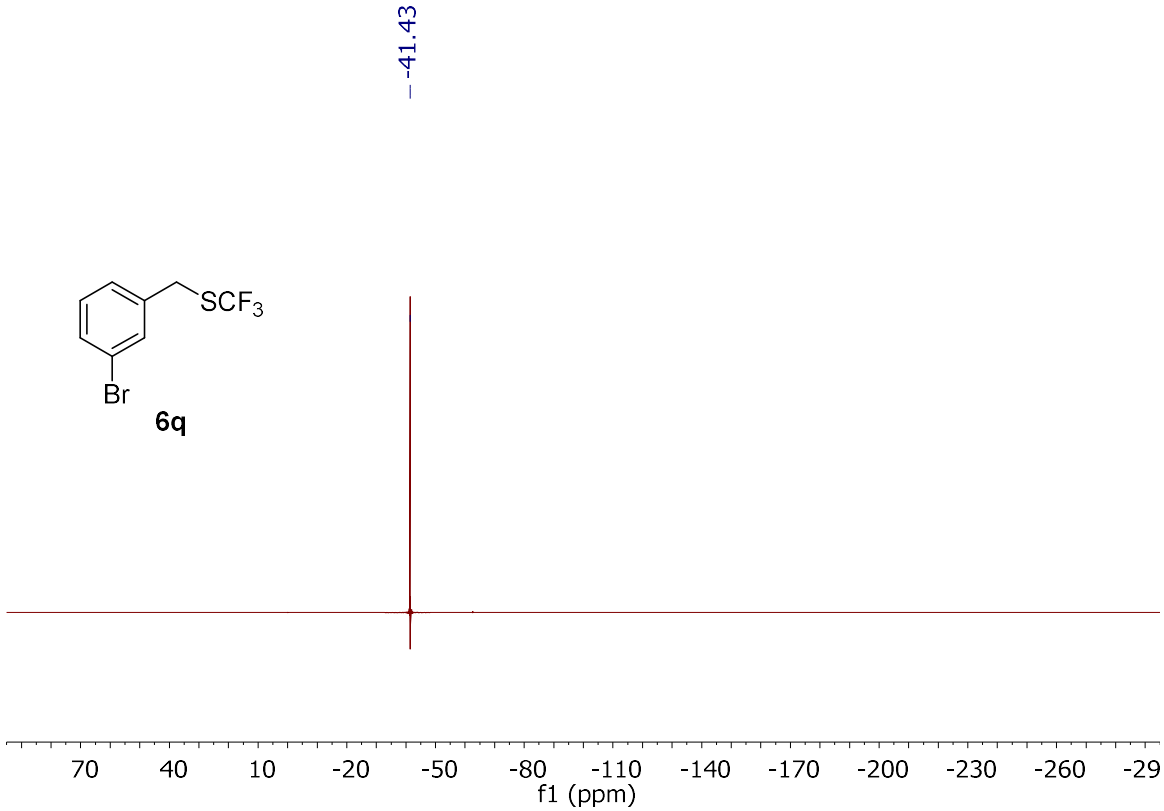

-41.19
SCF3
NO2
6p
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
f1 (ppm)

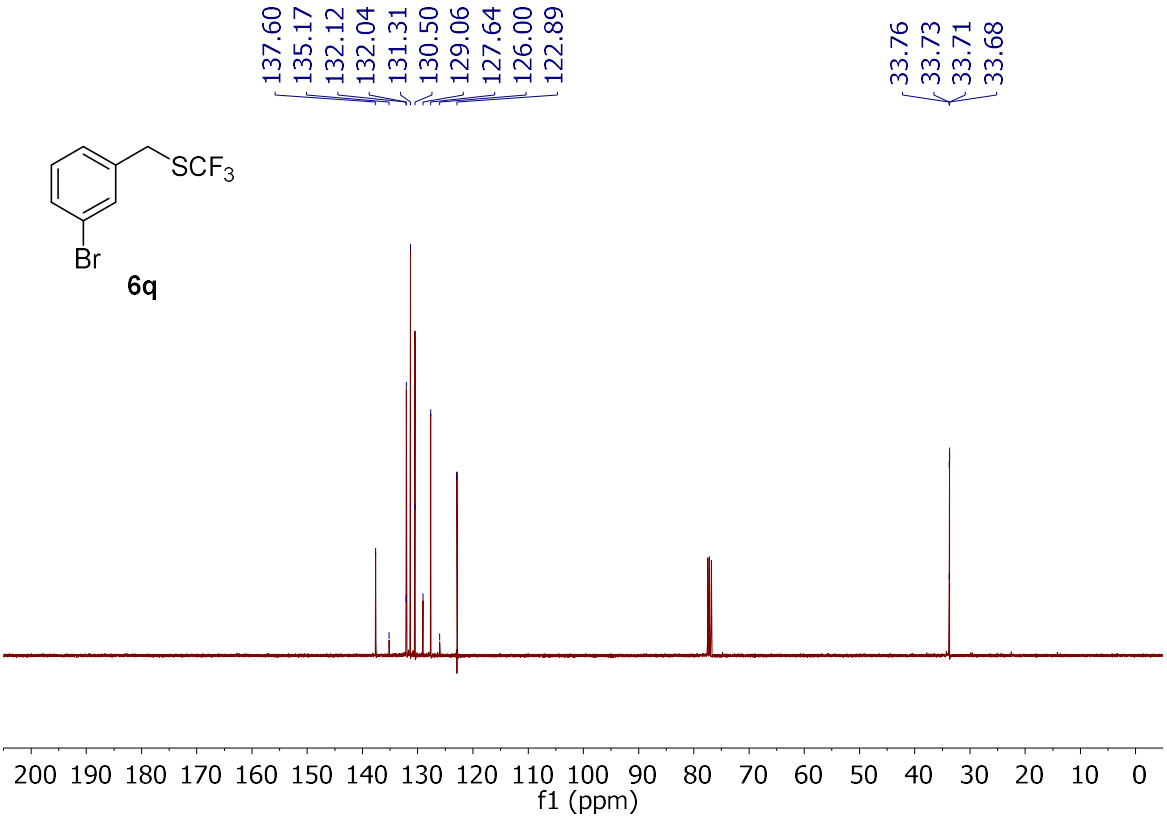

148.54
137.87
135.00
131.94
130.03
128.88
125.83
123.87
123.14
33.60
33.58
33.55
33.53
SCF3
NO2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

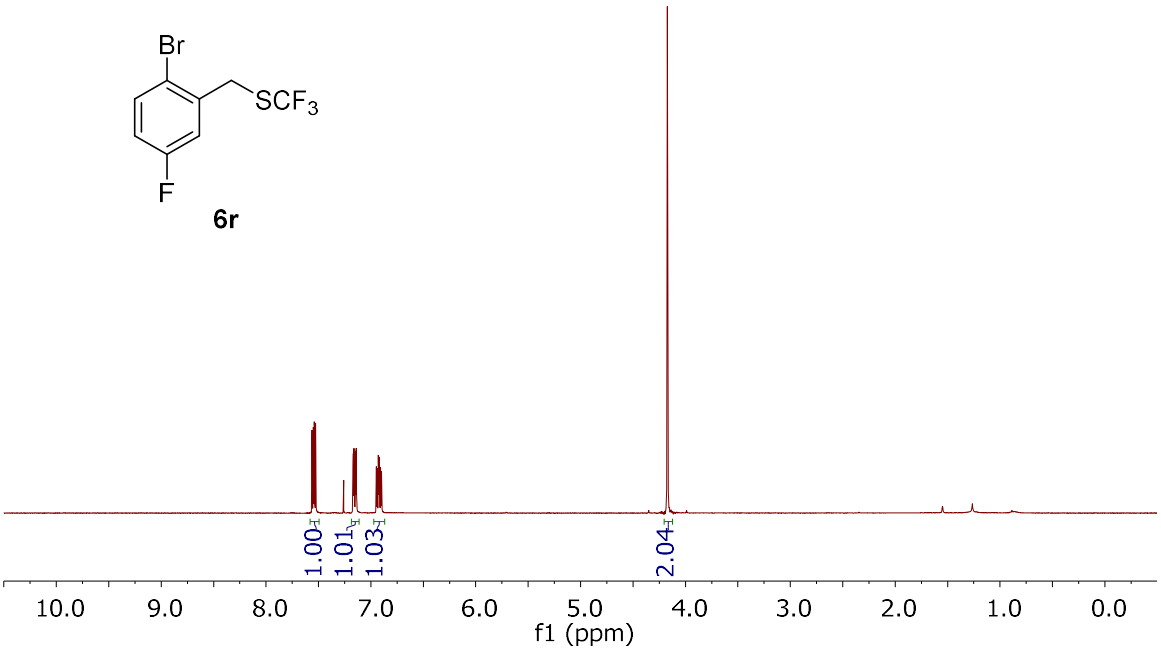
6p

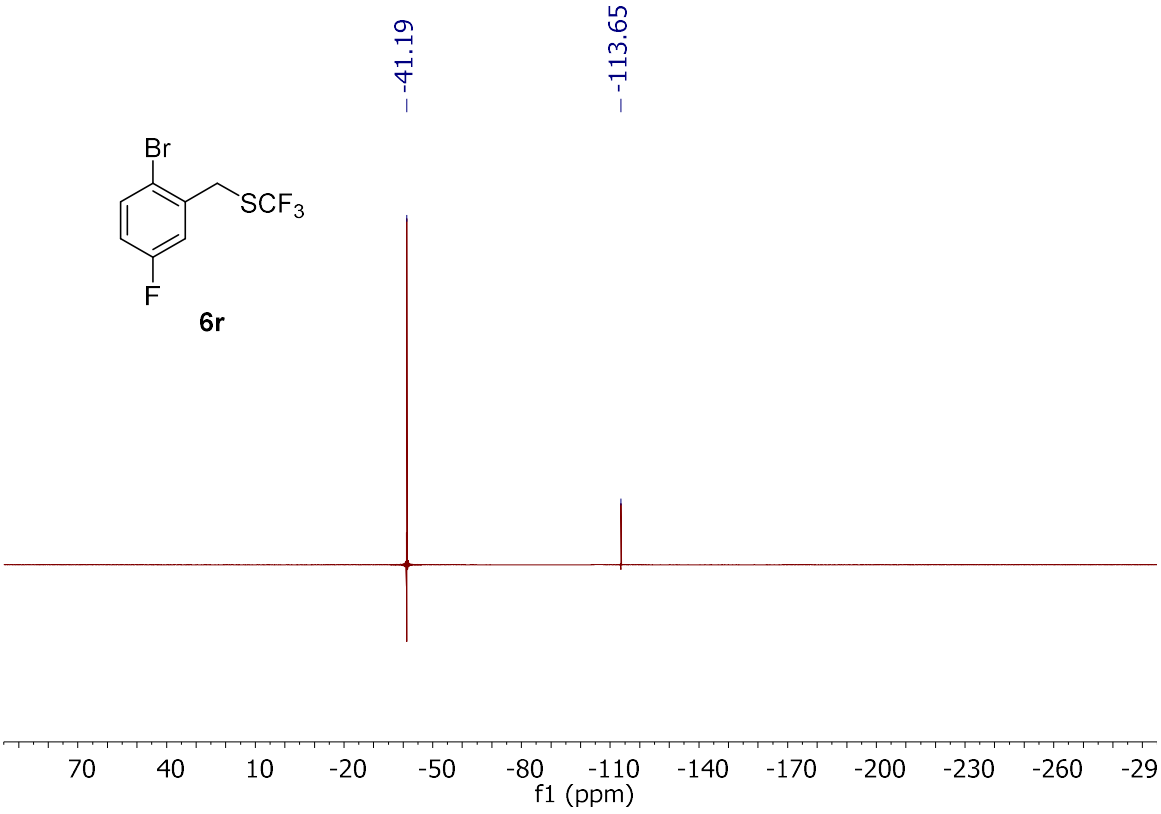

SCF3
Br
1.00
1.02
1.00
1.03
2.05
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

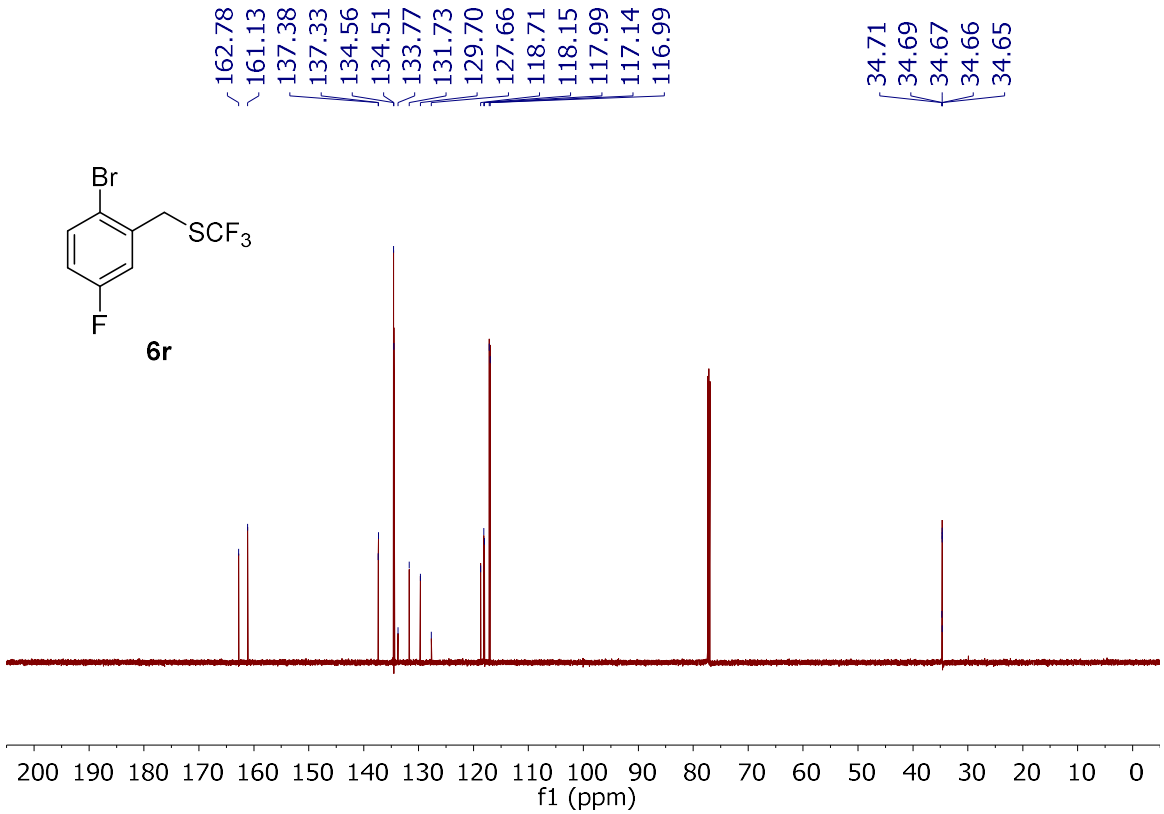
6q

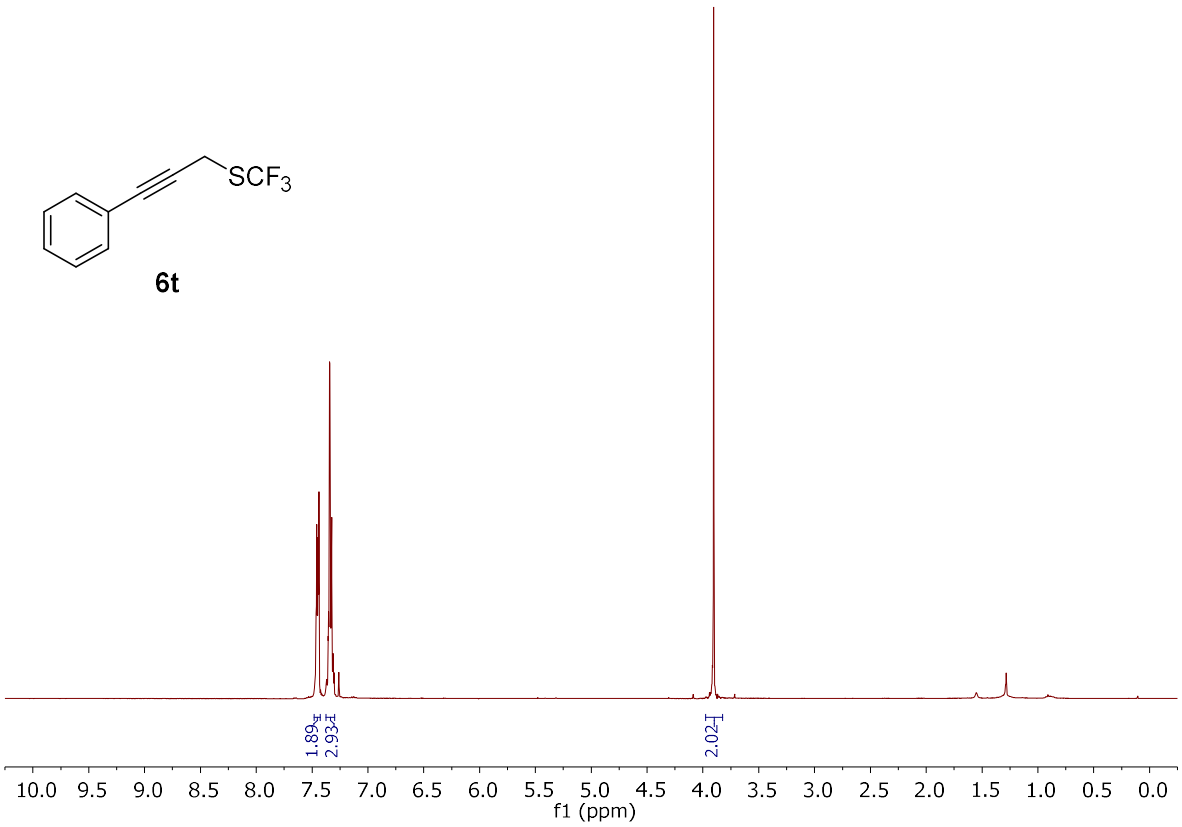

-41.43
SCF3
Br
6q
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
-29
f1 (ppm)

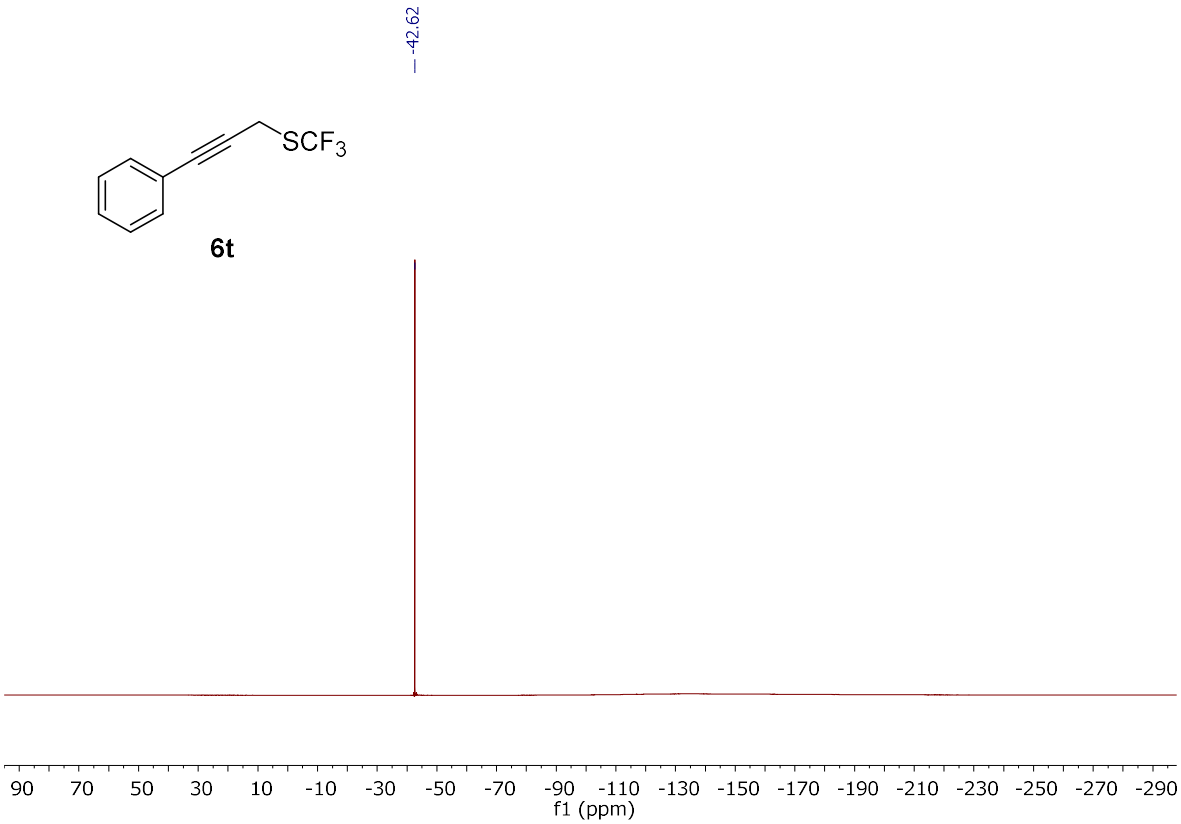

137.60
135.17
132.12
132.04
131.31
130.50
129.06
127.64
126.00
122.89
33.76
33.73
33.71
33.68
SCF3
Br
6q
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

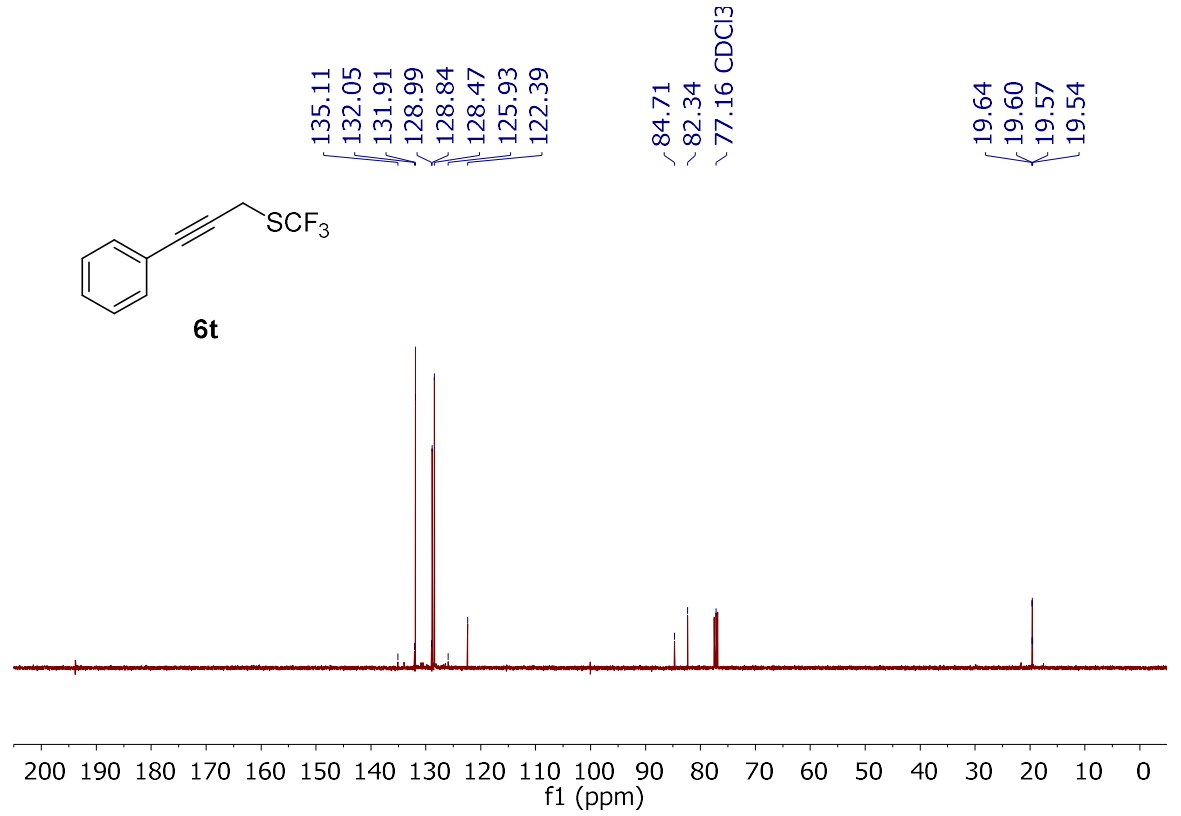

Br
SCF3
F
6r
1.00
1.01
1.03
2.04
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

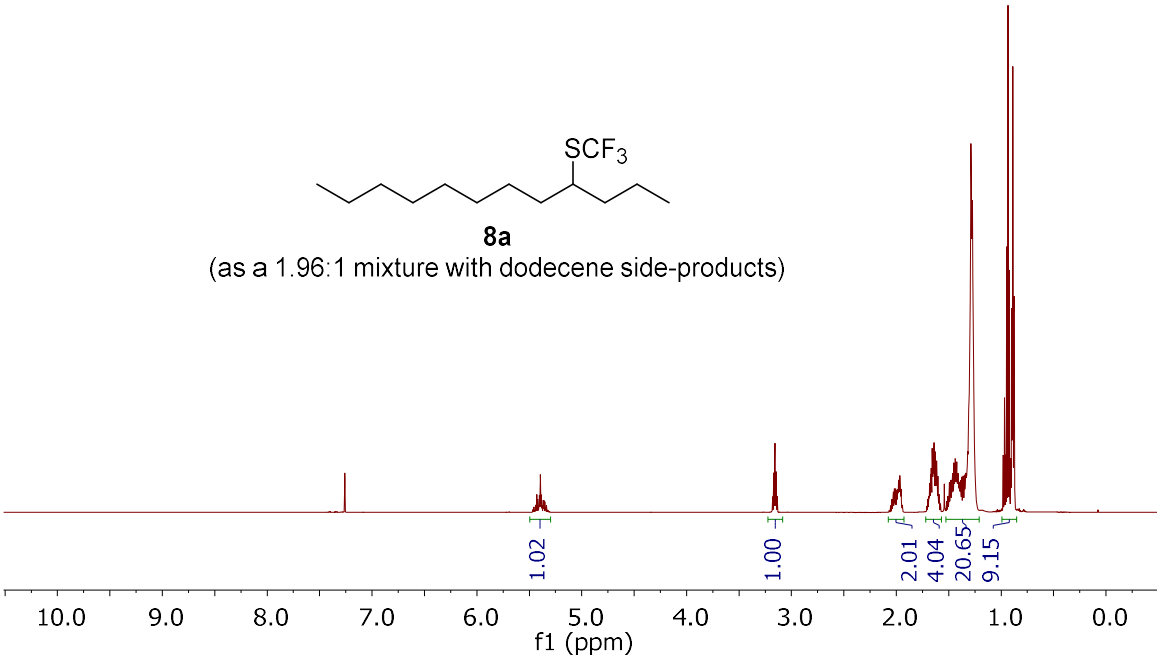

-41.19
-113.65
Br
SCF3
F
6r
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
-29
f1 (ppm)

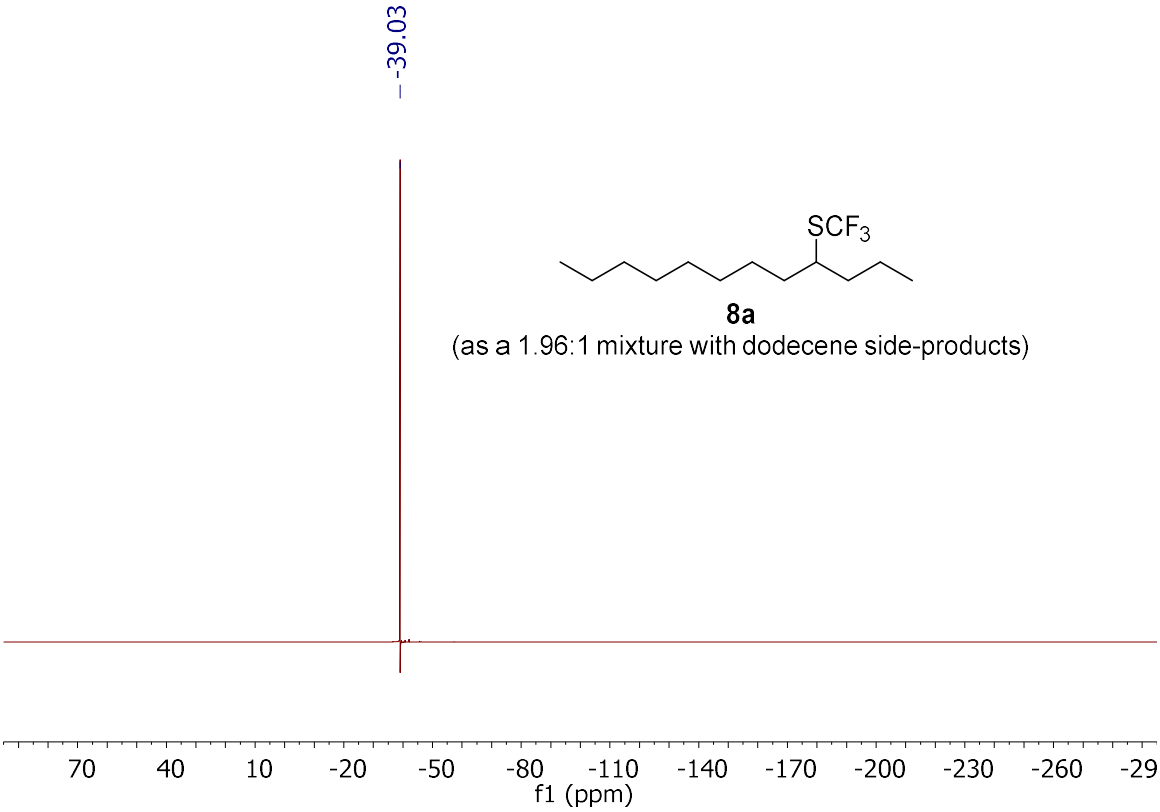

162.78
161.13
137.38
137.33
134.56
134.51
133.77
131.73
129.70
127.66
118.71
118.15
117.99
117.14
116.99
34.71
34.69
34.67
34.66
34.65
Br
SCF3
F
6r
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

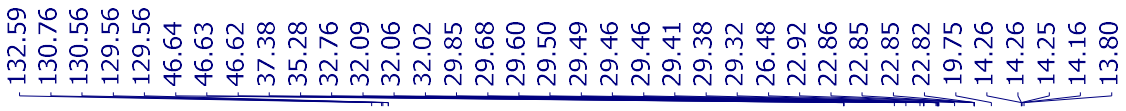

SCF3
6t
1.89
2.93
2.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

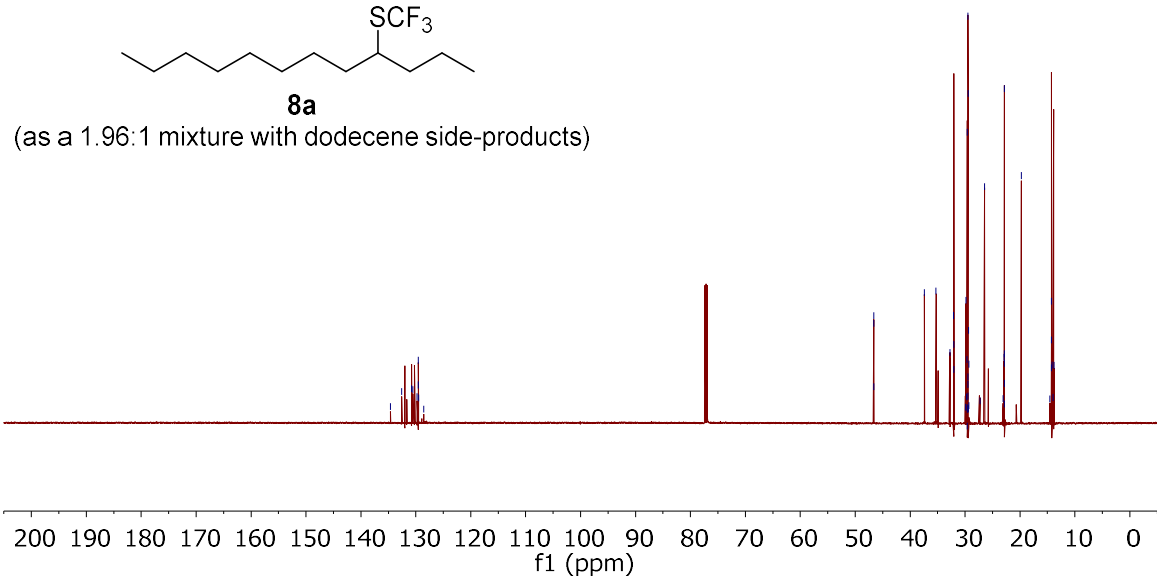

-42.62
SCF3
6t
90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290
f1 (ppm)


135.11
132.05
131.91
128.99
128.84
128.47
125.93
122.39
84.71
82.34
77.16 CDCl3
19.64
19.60
19.57
19.54
SCF3
6t
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


SCF3
8a
(as a 1.96:1 mixture with dodecene side-products)
1.02
1.00
2.01
4.04
20.65
9.15
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

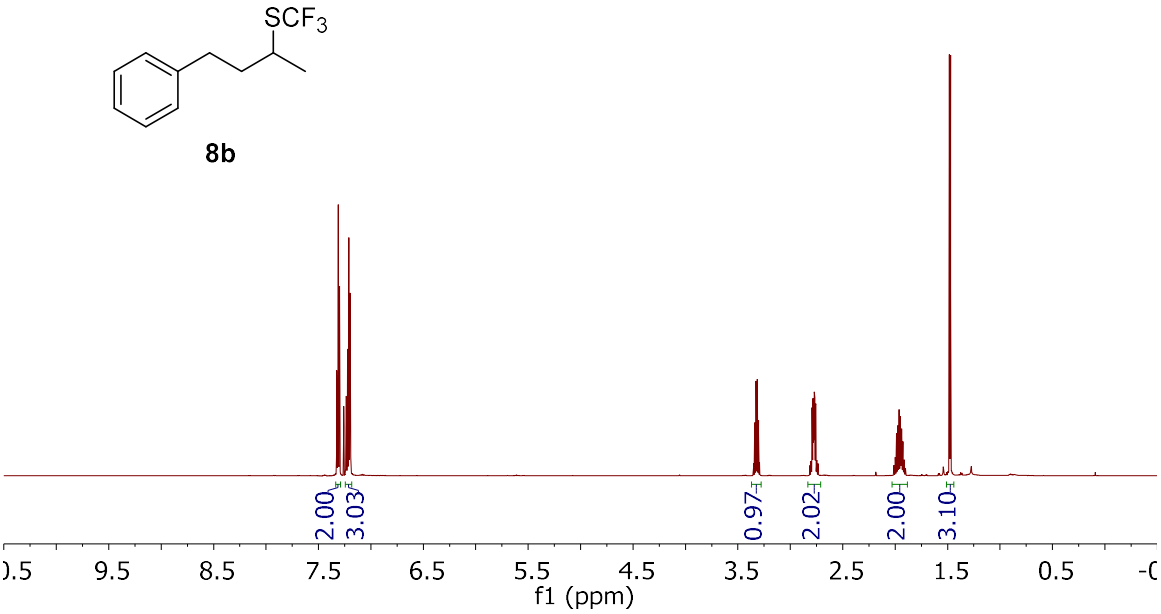

-39.03
SCF3
8a
(as a 1.96:1 mixture with dodecene side-products)
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
-29
f1 (ppm)



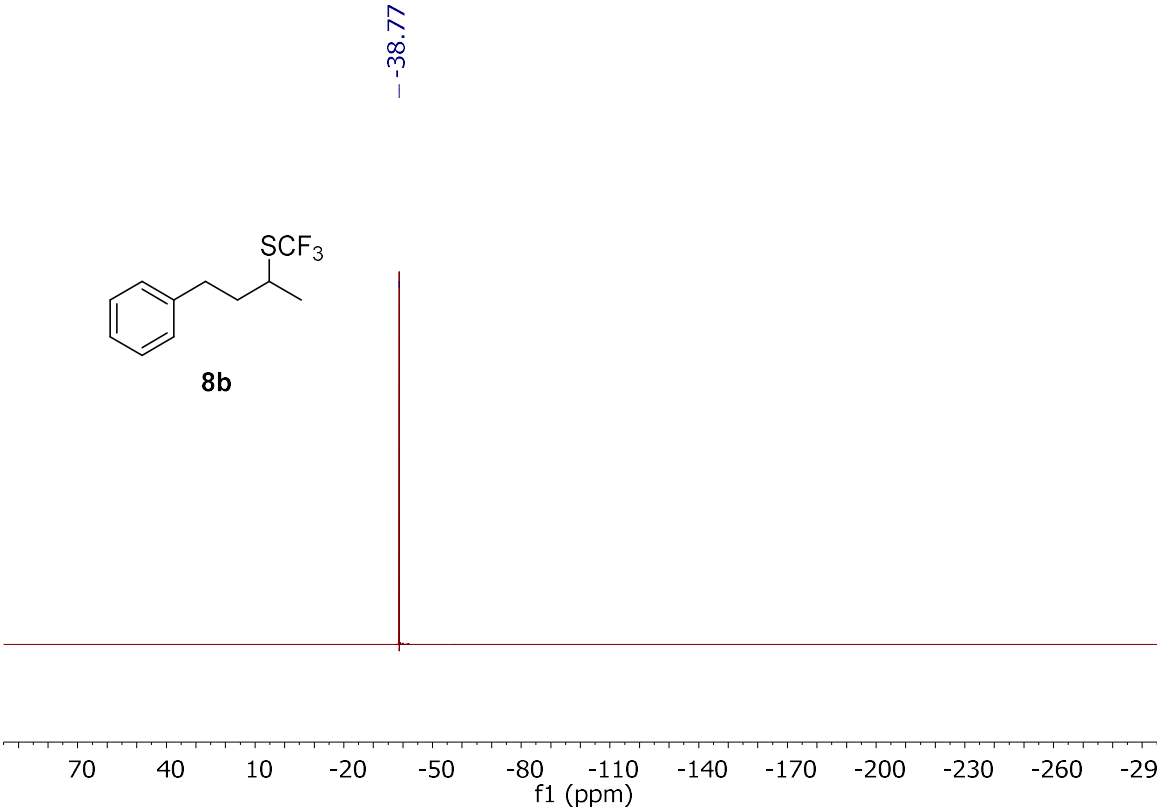


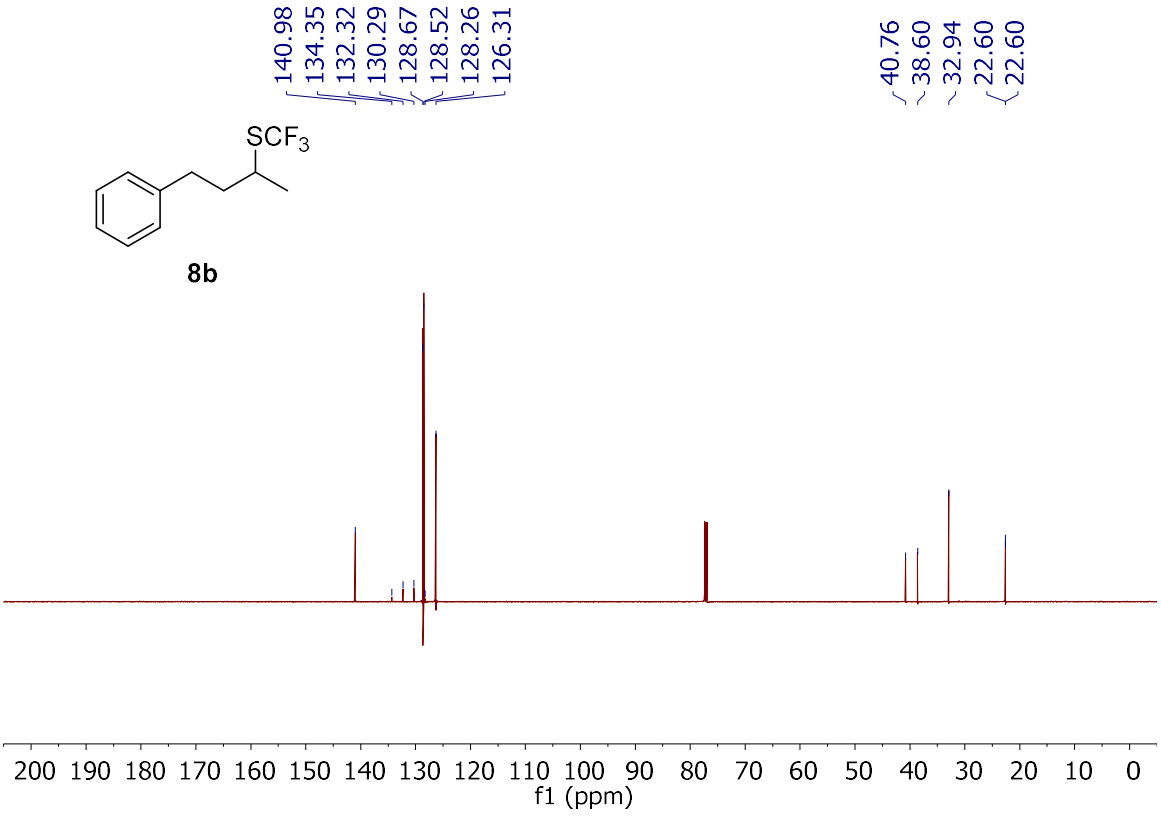
8a

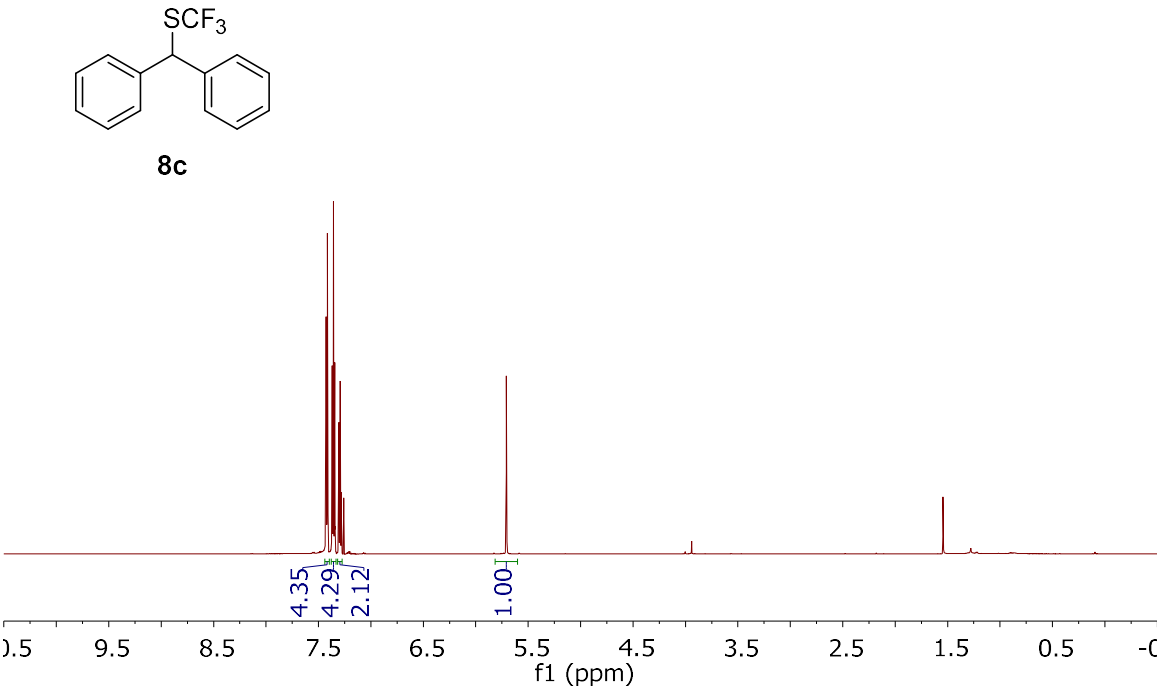
(as a 1.96:1 mixture with dodecene side-products)

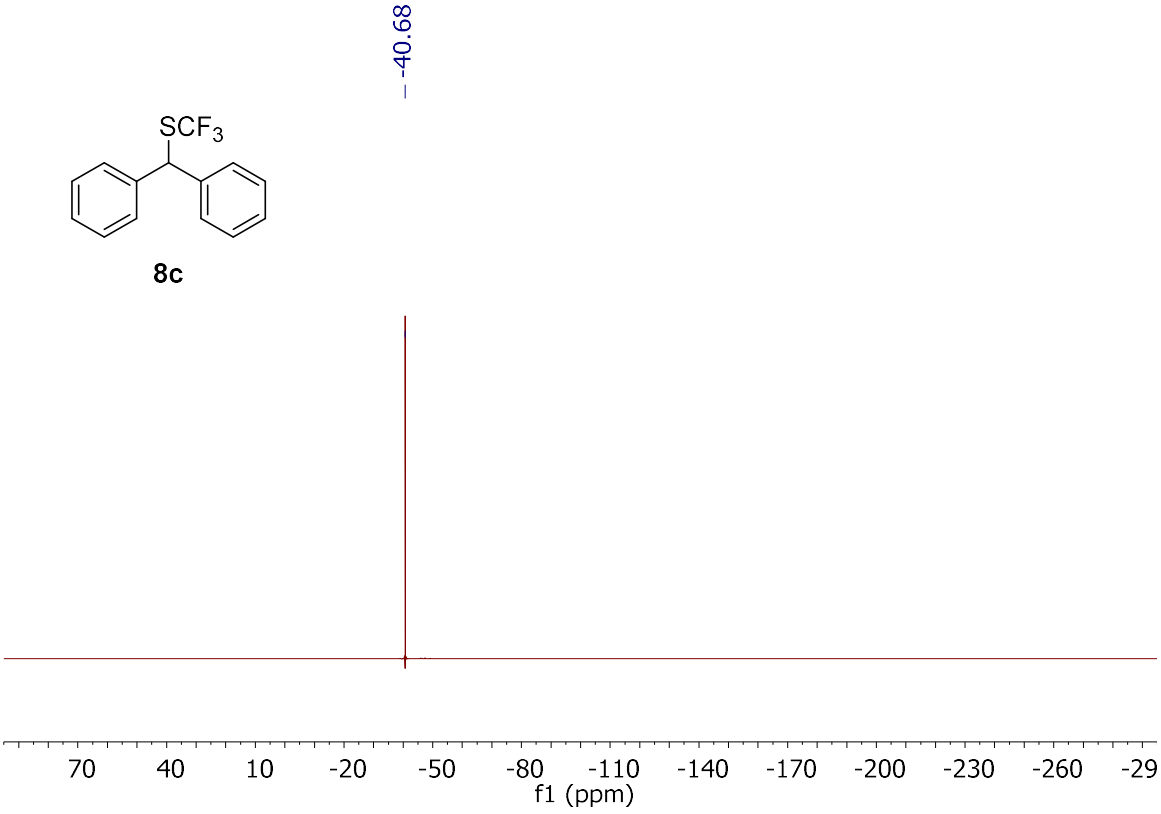


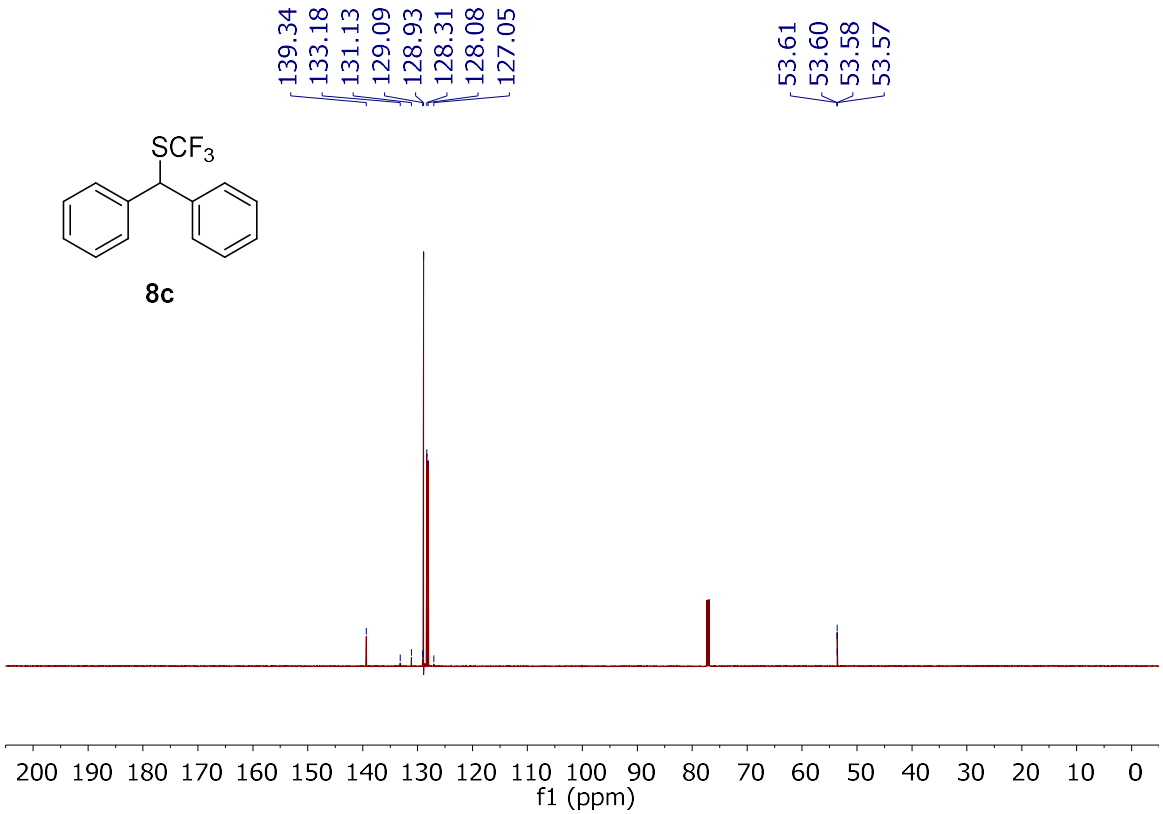
8b


-38.77
SCF3
8b
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

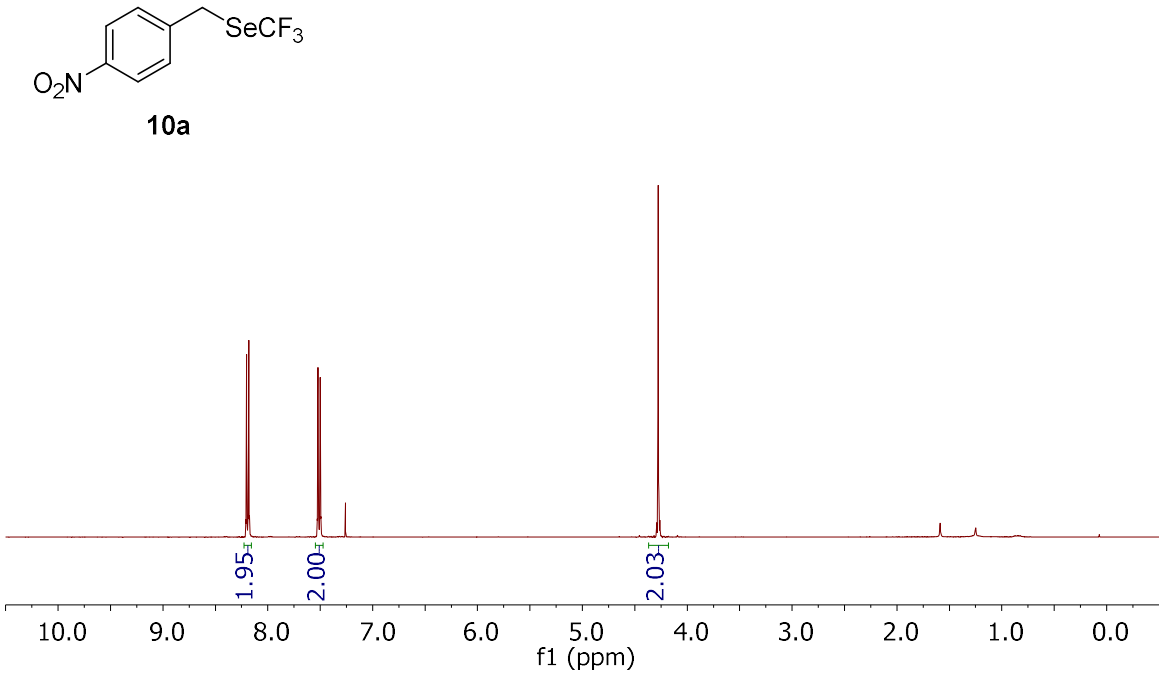

140.98
134.35
132.32
130.29
128.67
128.52
128.26
126.31
40.76
38.60
32.94
22.60
22.60
SCF3
8b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


SCF3
8c
4.35
4.29
2.12
1.00
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

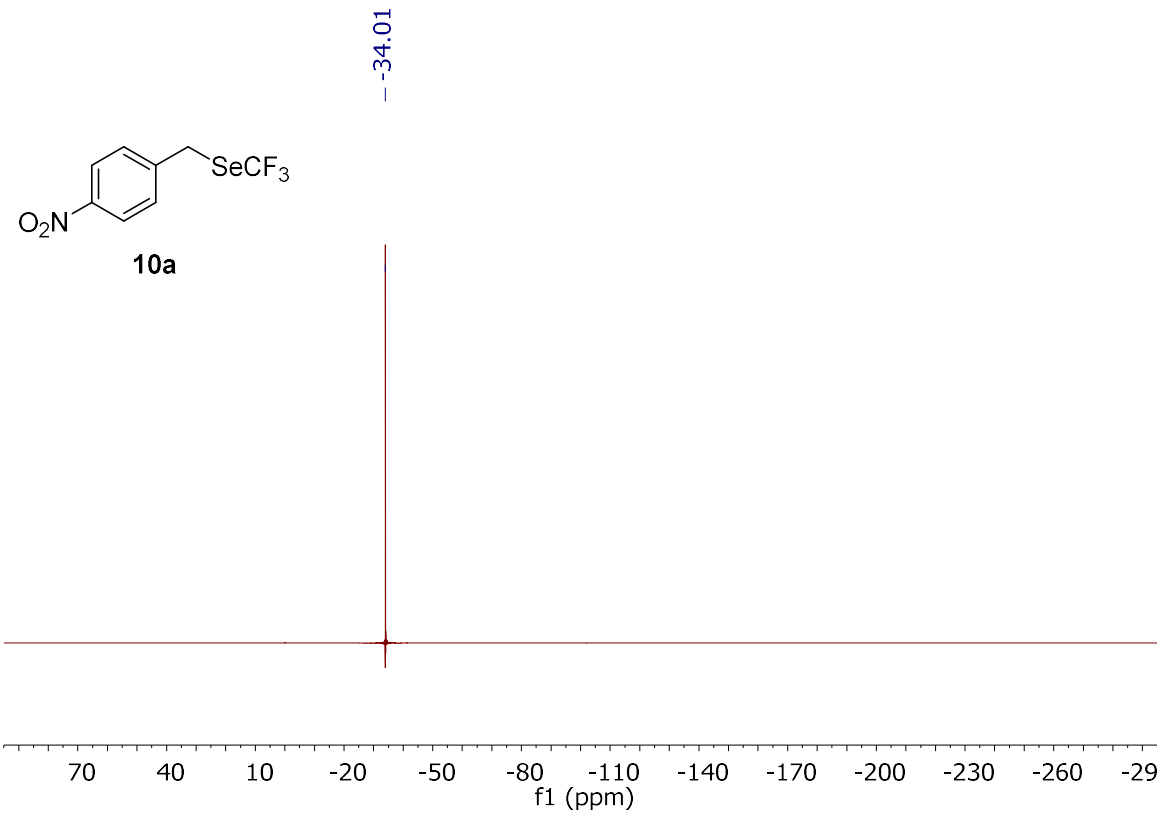

-40.68
SCF3
8c
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
f1 (ppm)

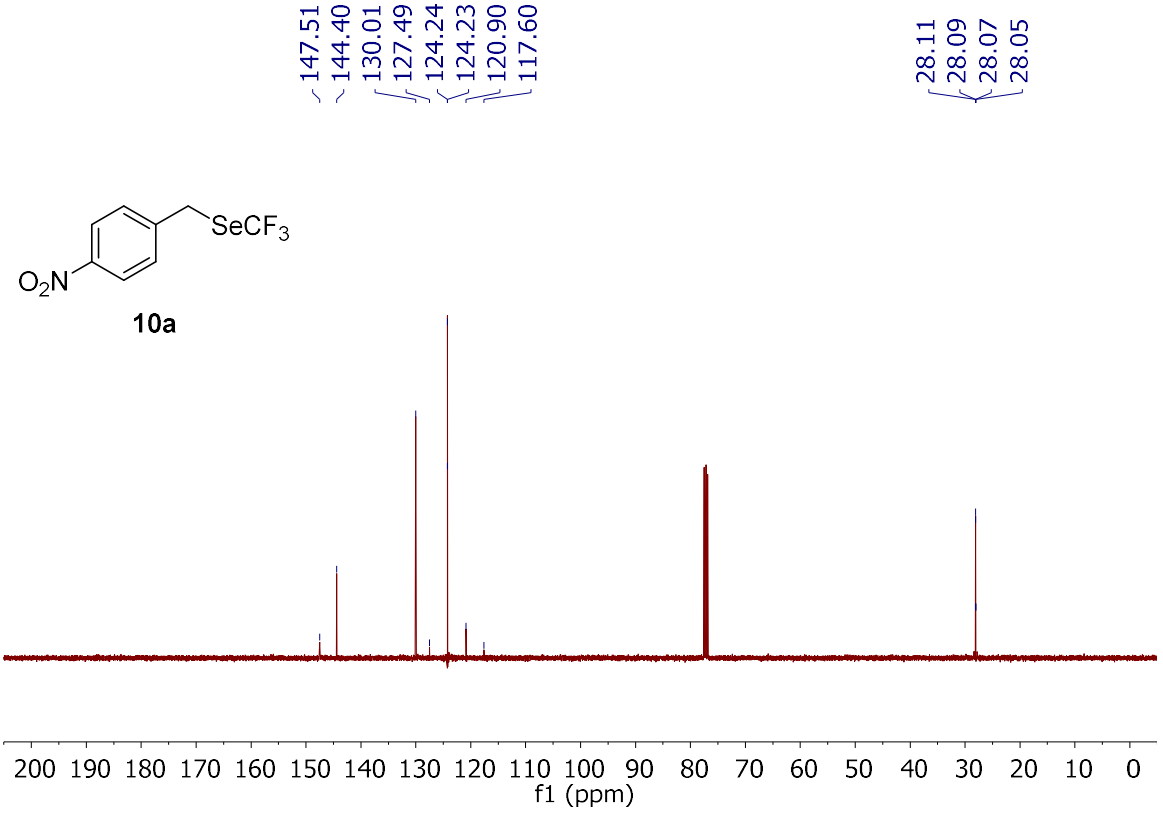

139.34
133.18
131.13
129.09
128.93
128.31
128.08
127.05
53.61
53.60
53.58
53.57
SCF3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

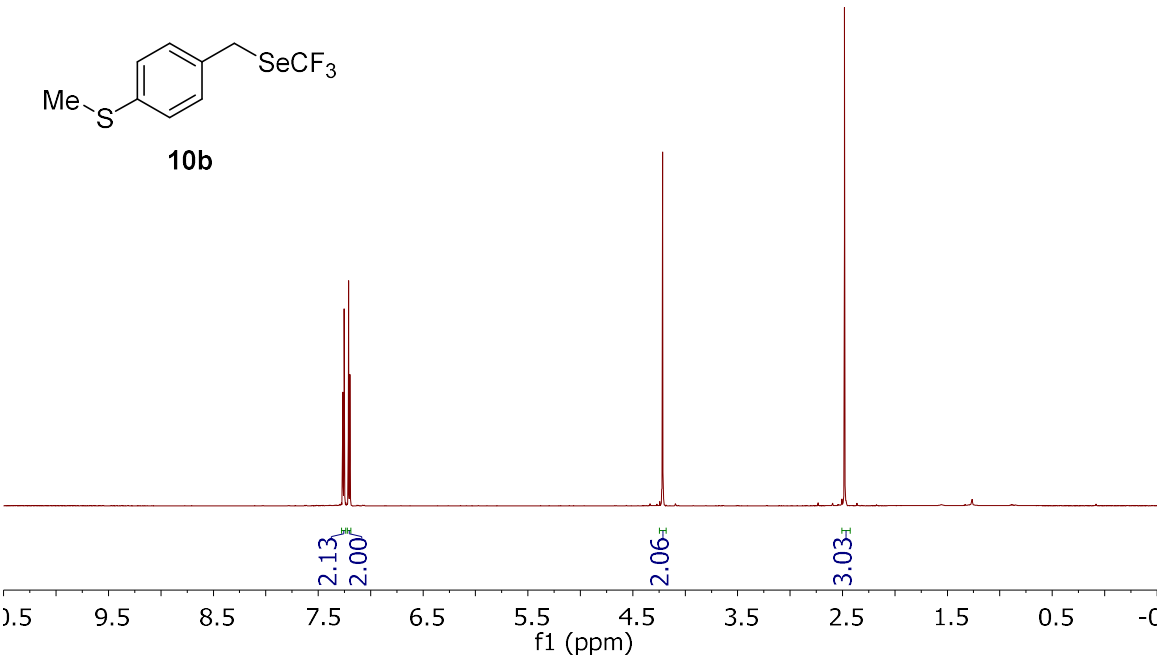
8c

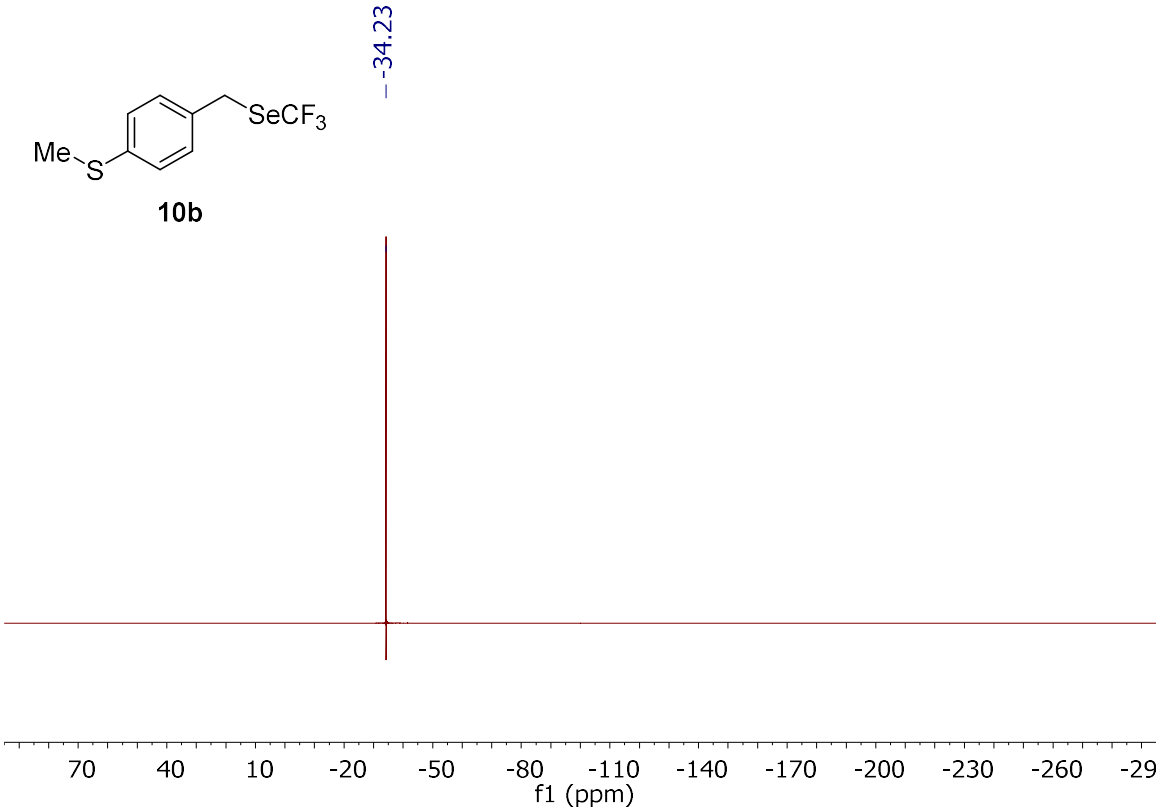

SeCF3
O2N
1.95
2.00
2.03
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

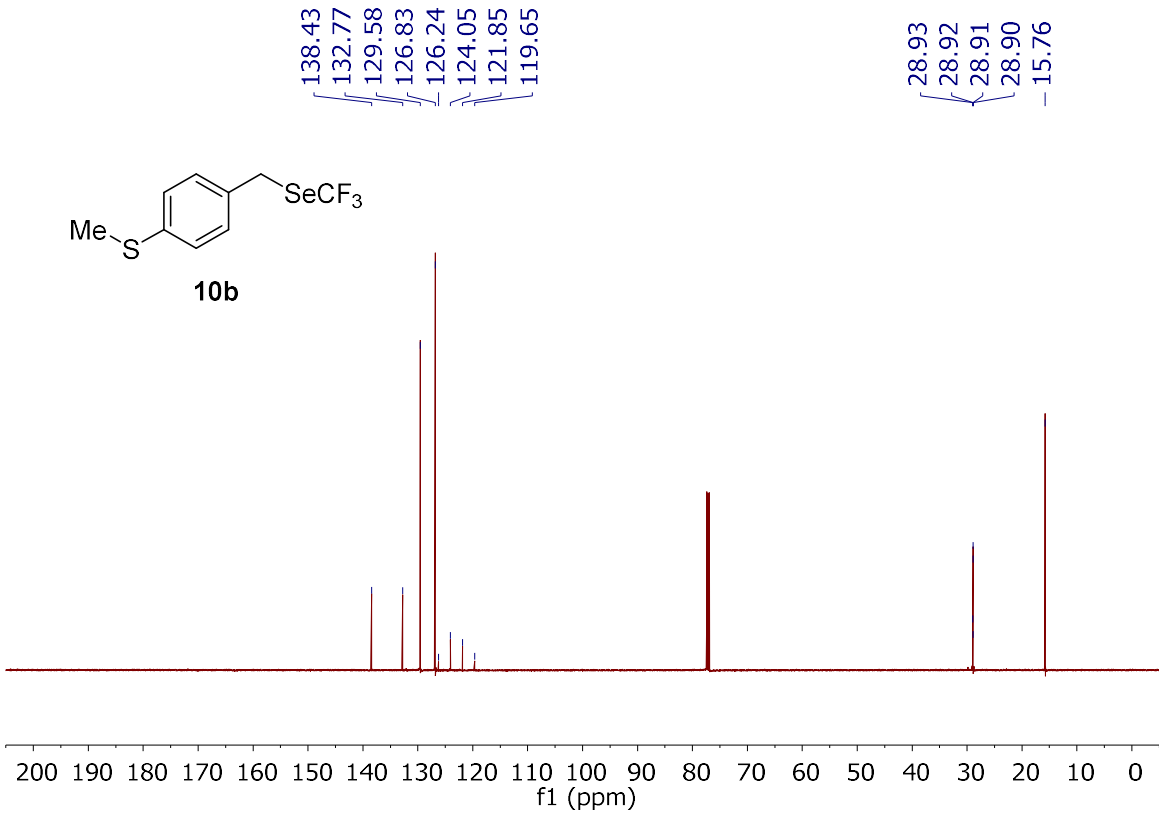
10a

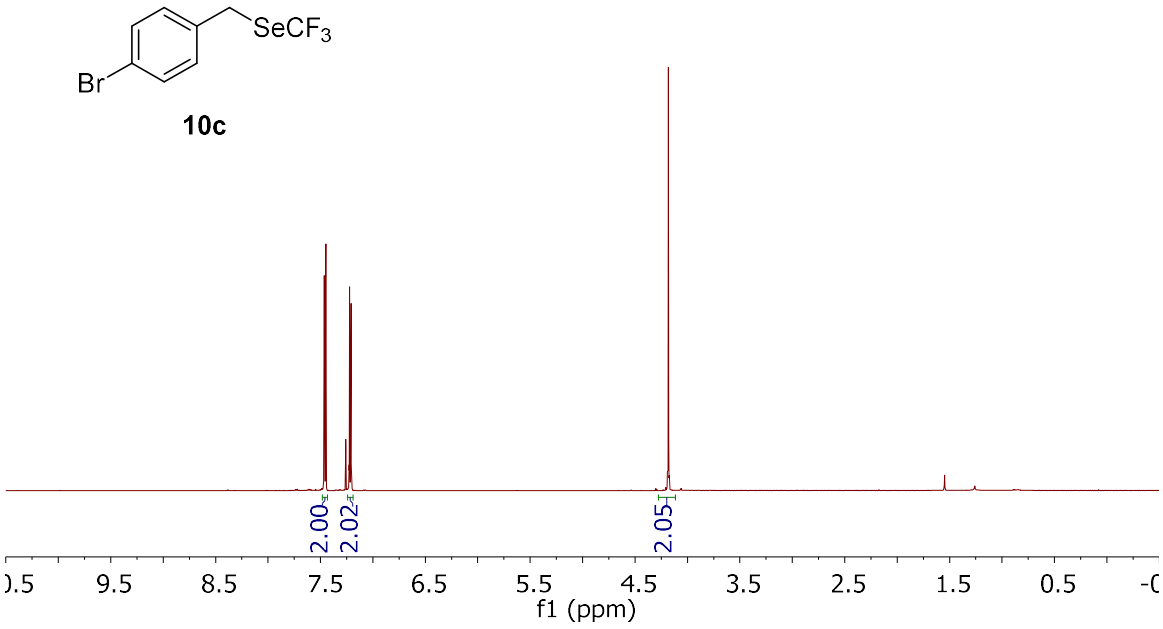

-34.01
SeCF3
O2N
10a
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

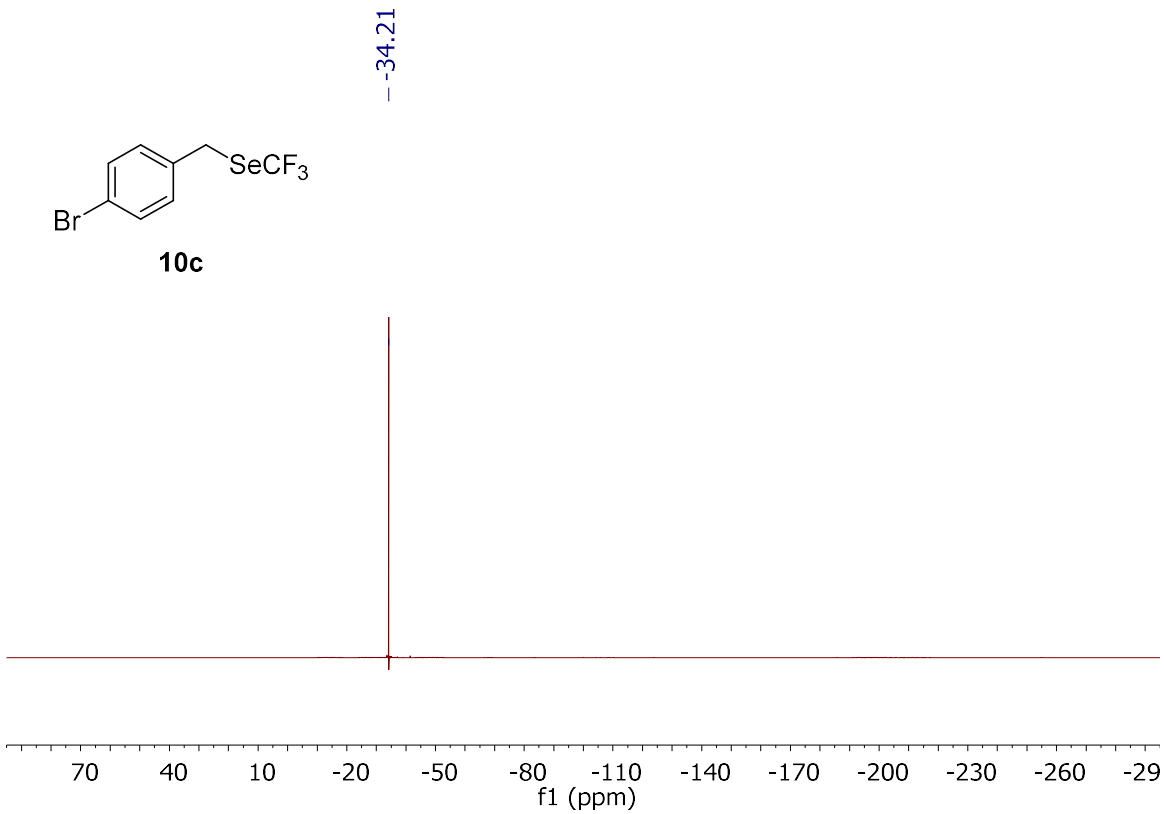

147.51
144.40
130.01
127.49
124.24
124.23
120.90
117.60
28.11
28.09
28.07
28.05
SeCF3
O2N
10a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

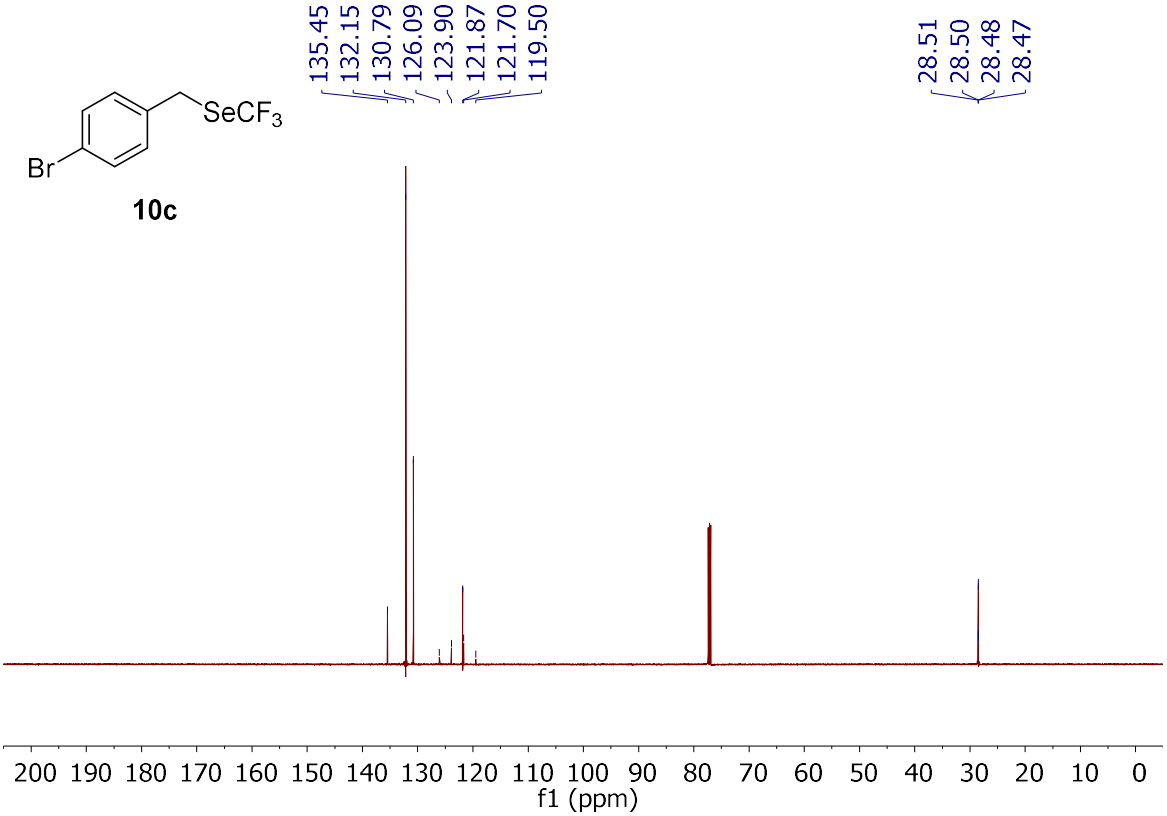

SeCF3
Me
S
10b
2.13
2.00
2.06
3.03
f1 (ppm)

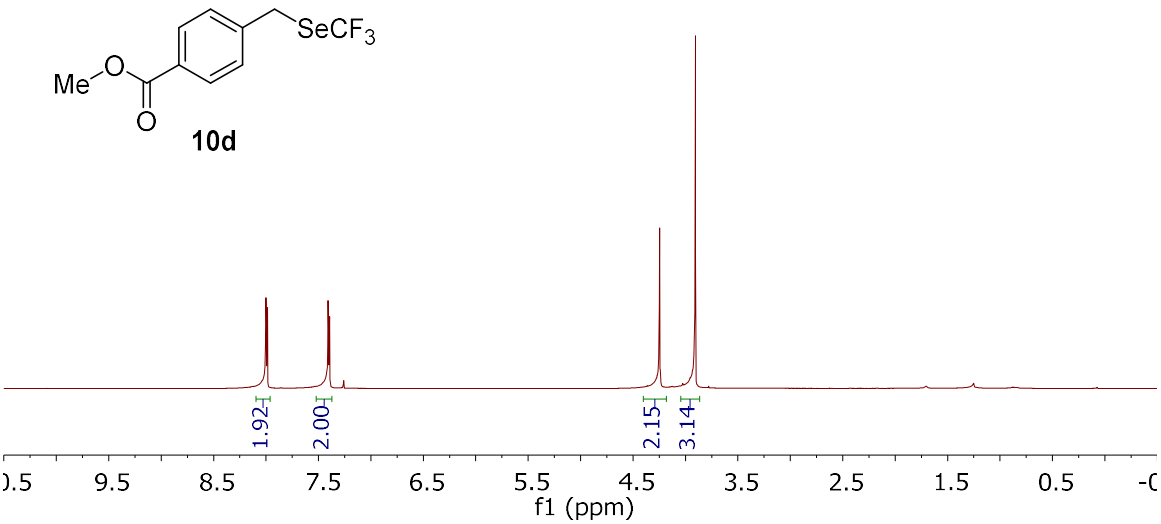

-34.23
SeCF3
Me
S
10b
f1 (ppm)

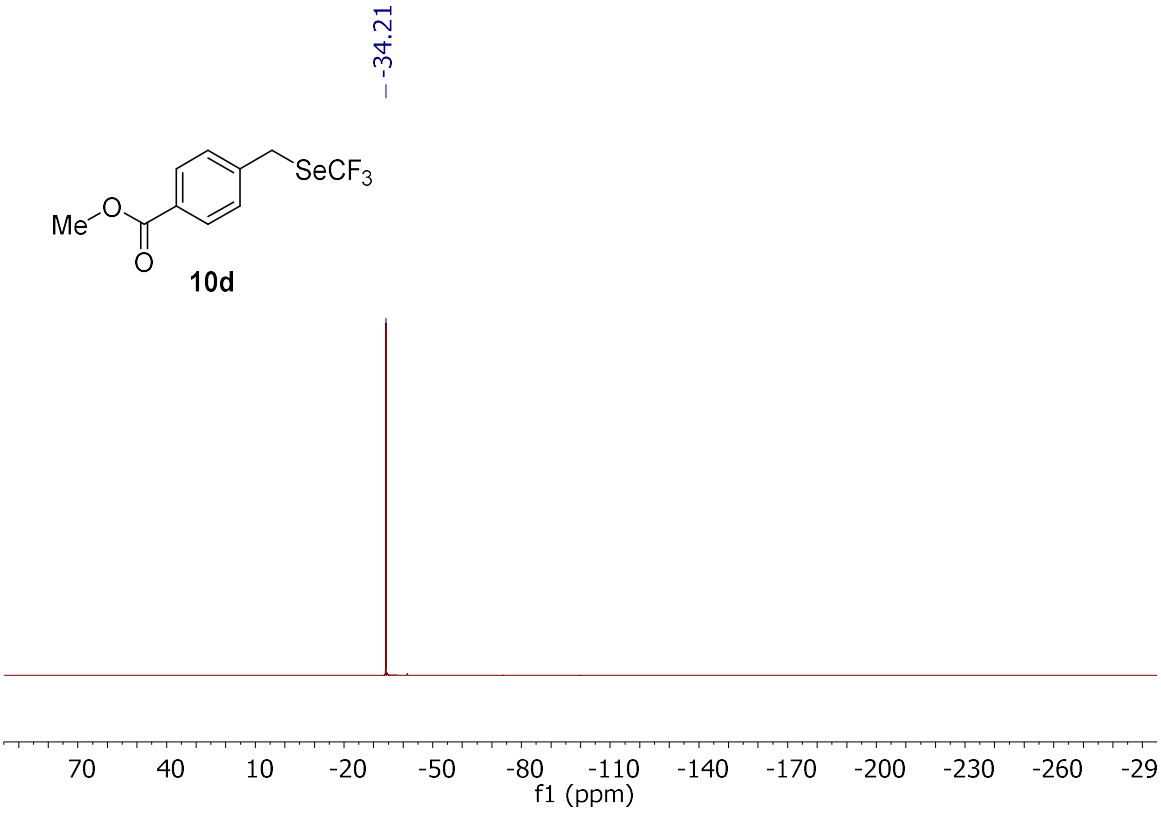

138.43
132.77
129.58
126.83
126.24
124.05
121.85
119.65
28.93
28.92
28.91
28.90
15.76
SeCF3
Me
S
10b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

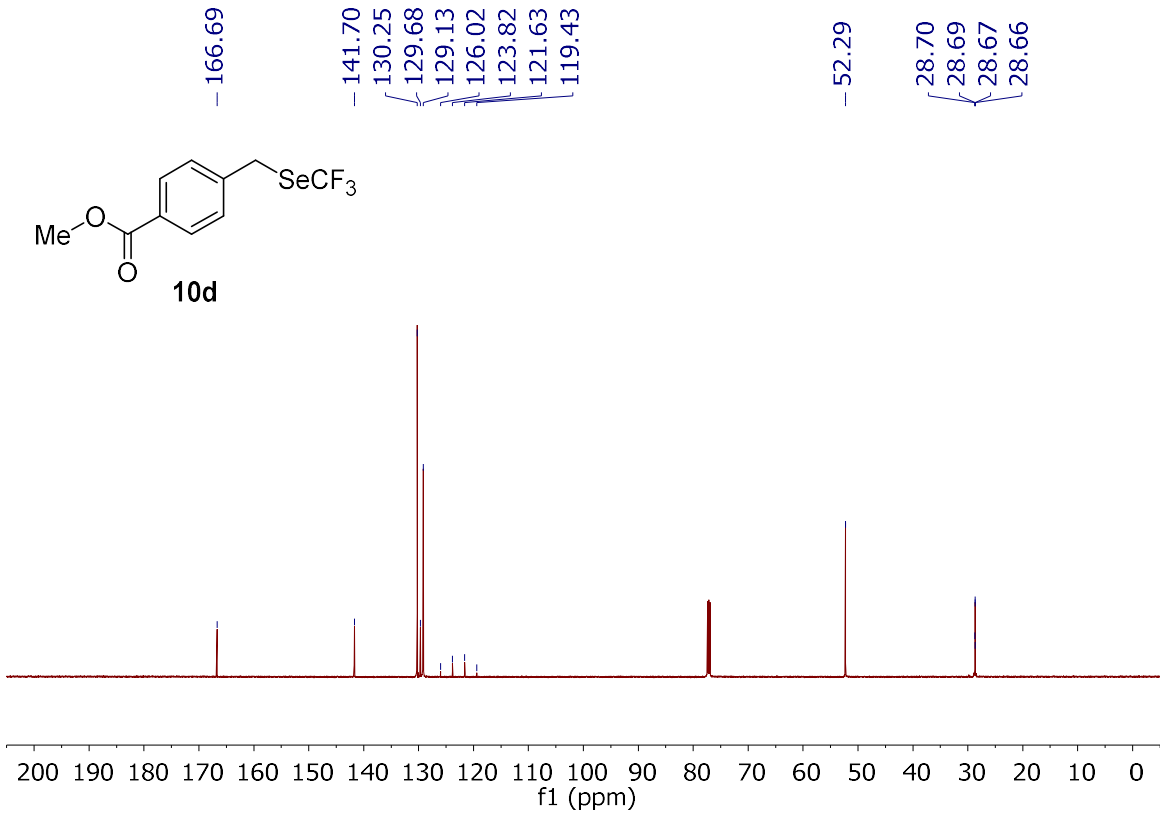

SeCF3
Br
10c
2.00
2.02
2.05
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
f1 (ppm)


-34.21
SeCF3
Br
10c
70
40
10
-20
-50
-80
-110
-140
-170
-200
-230
-260
-29
f1 (ppm)

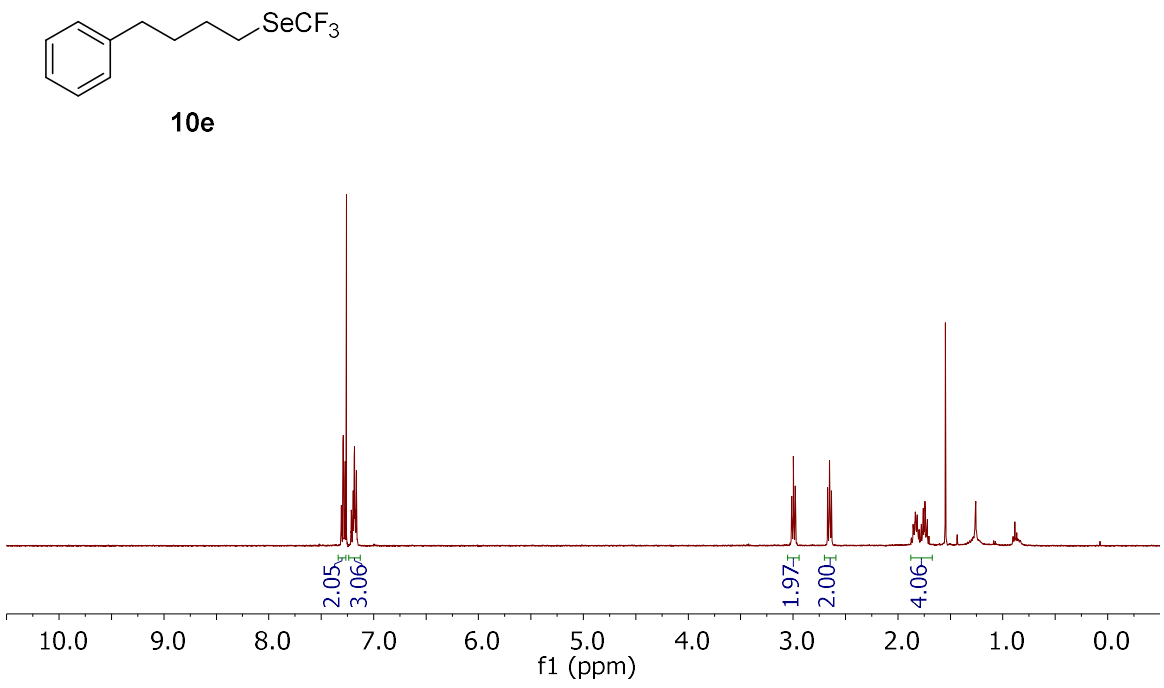

135.45
132.15
130.79
126.09
123.90
121.87
121.70
119.50
28.51
28.50
28.48
28.47
SeCF3
Br
10c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


SeCF3
Me
O
O
10d
1.92
2.00
2.15
3.14
f1 (ppm)

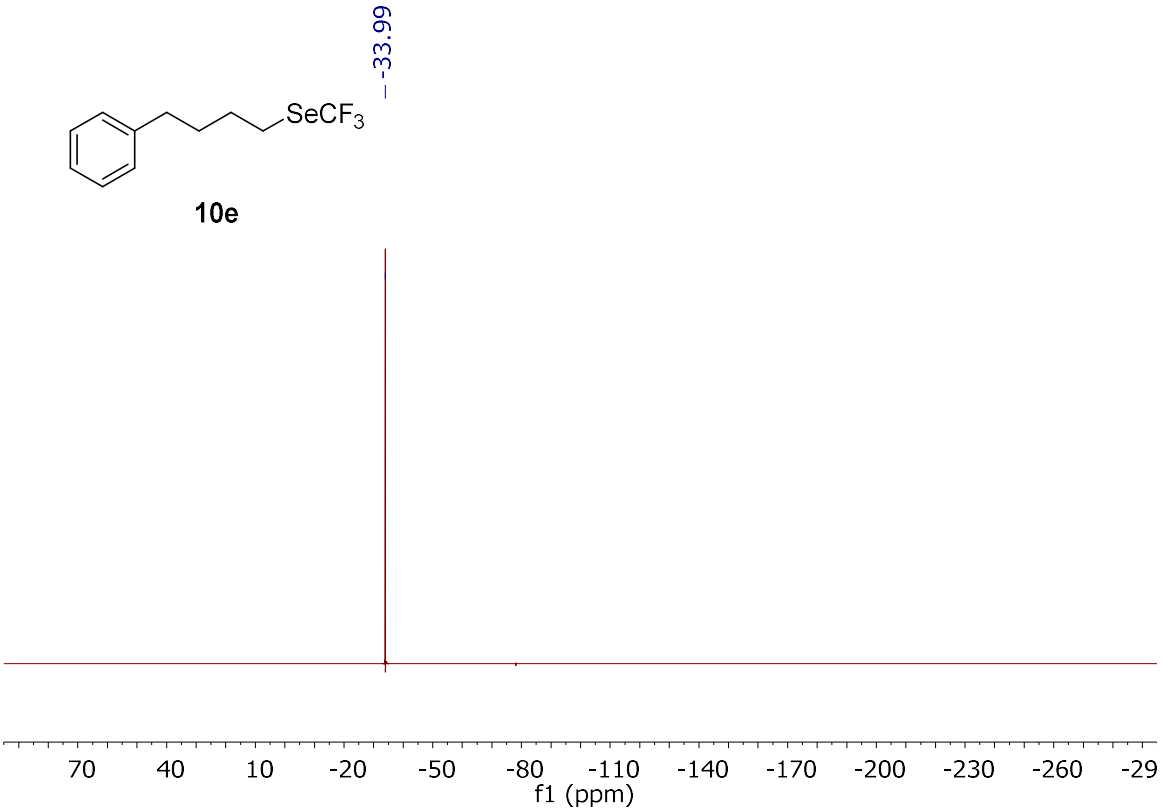

-34.21
SeCF3
Me
O
O
10d
f1 (ppm)

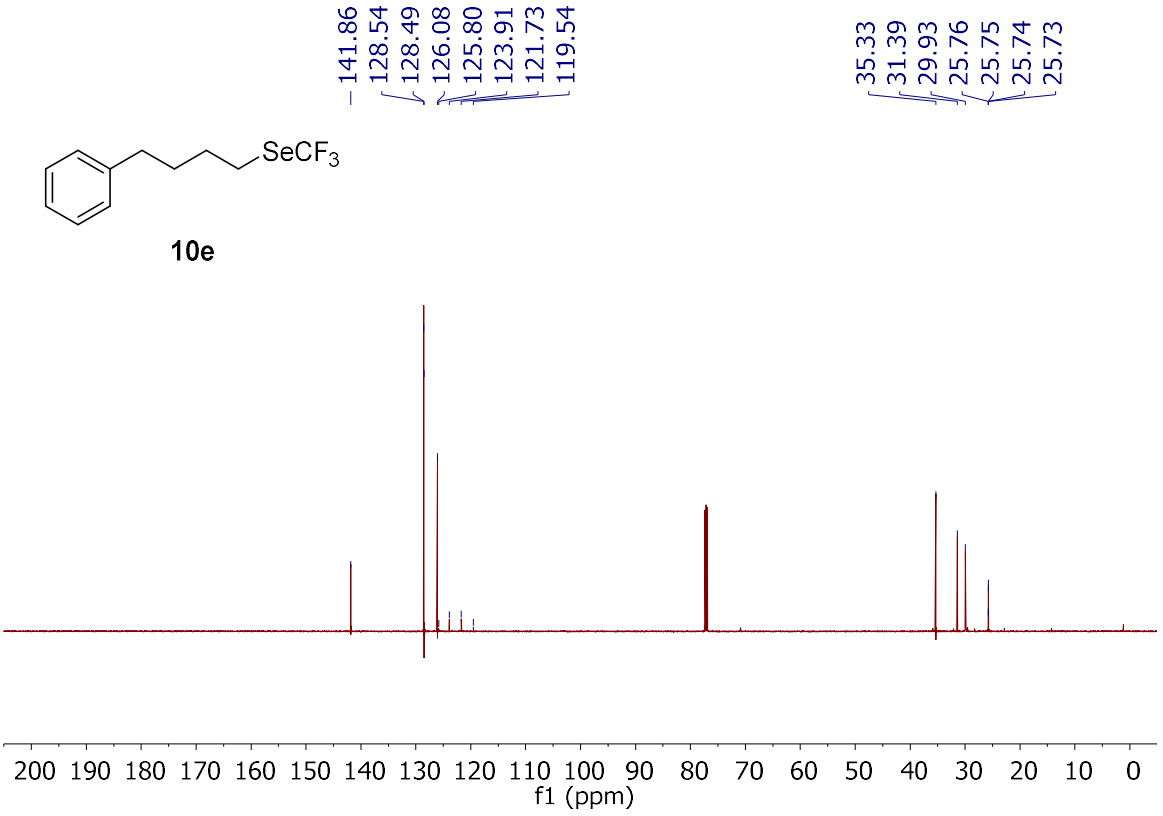

166.69
141.70
130.25
129.68
129.13
126.02
123.82
121.63
119.43
52.29
28.70
28.69
28.67
28.66
SeCF3
Me
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

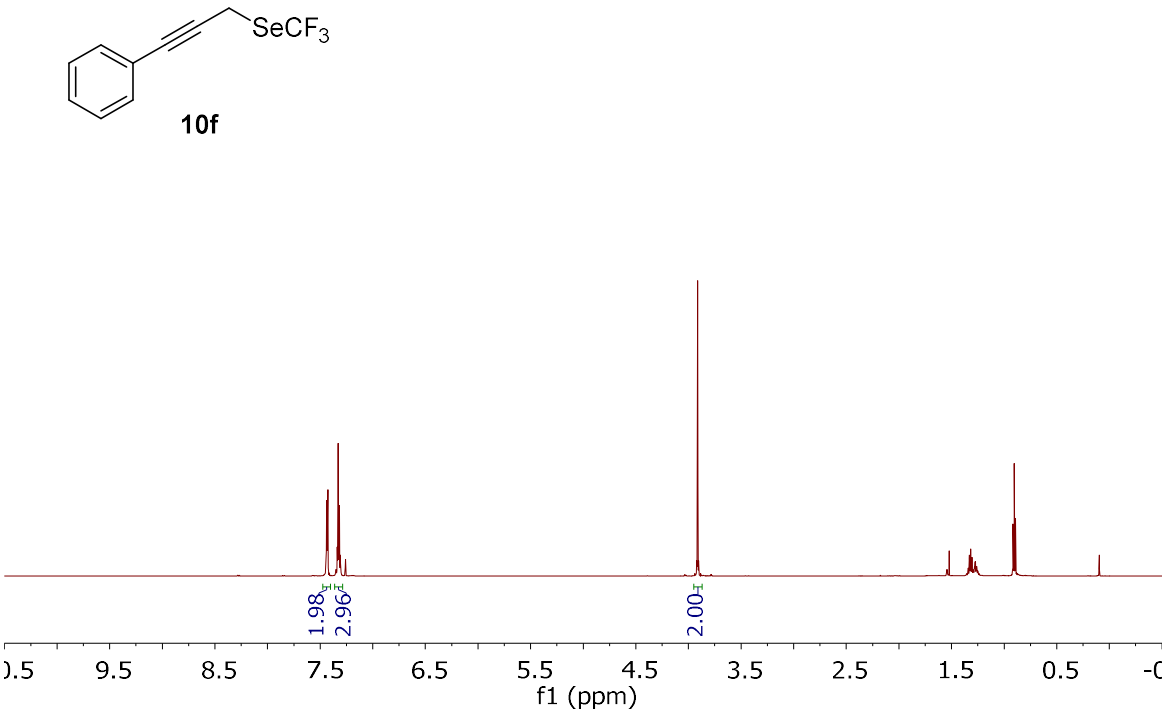
10d

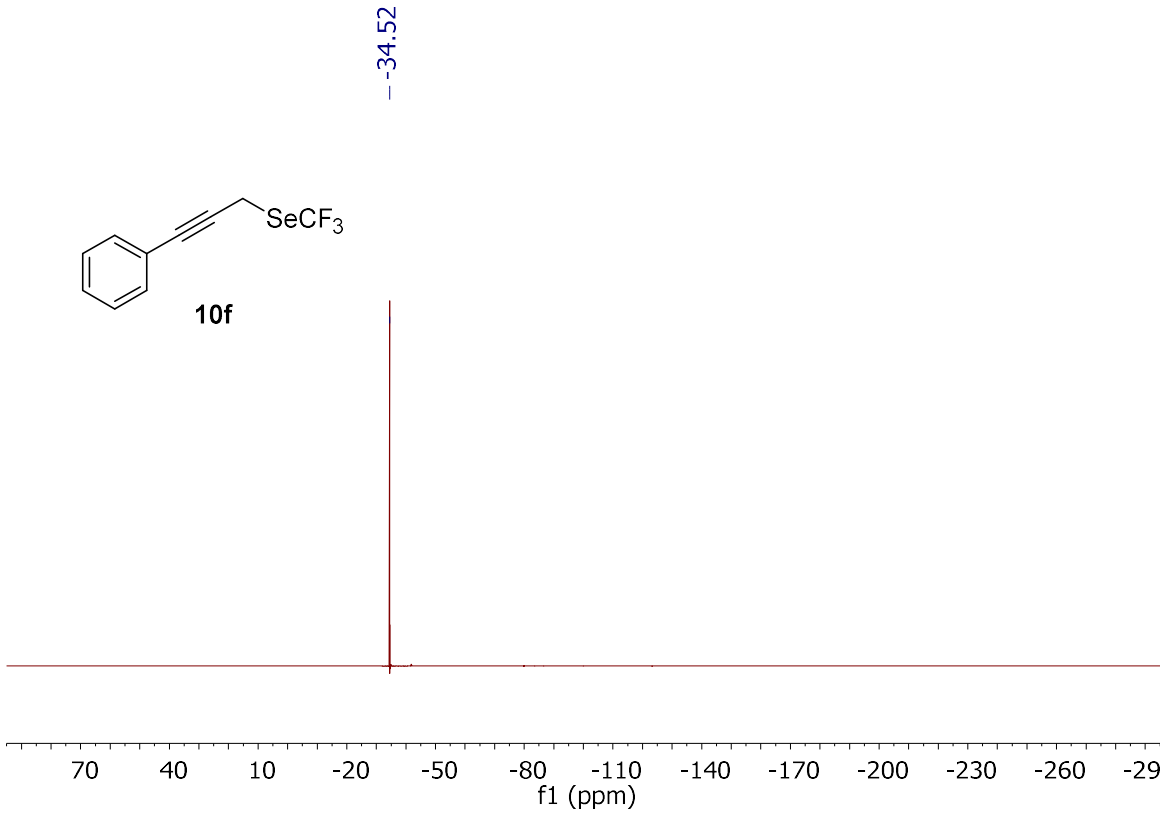

SeCF3
2.05
3.06
1.97
2.00
4.06
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

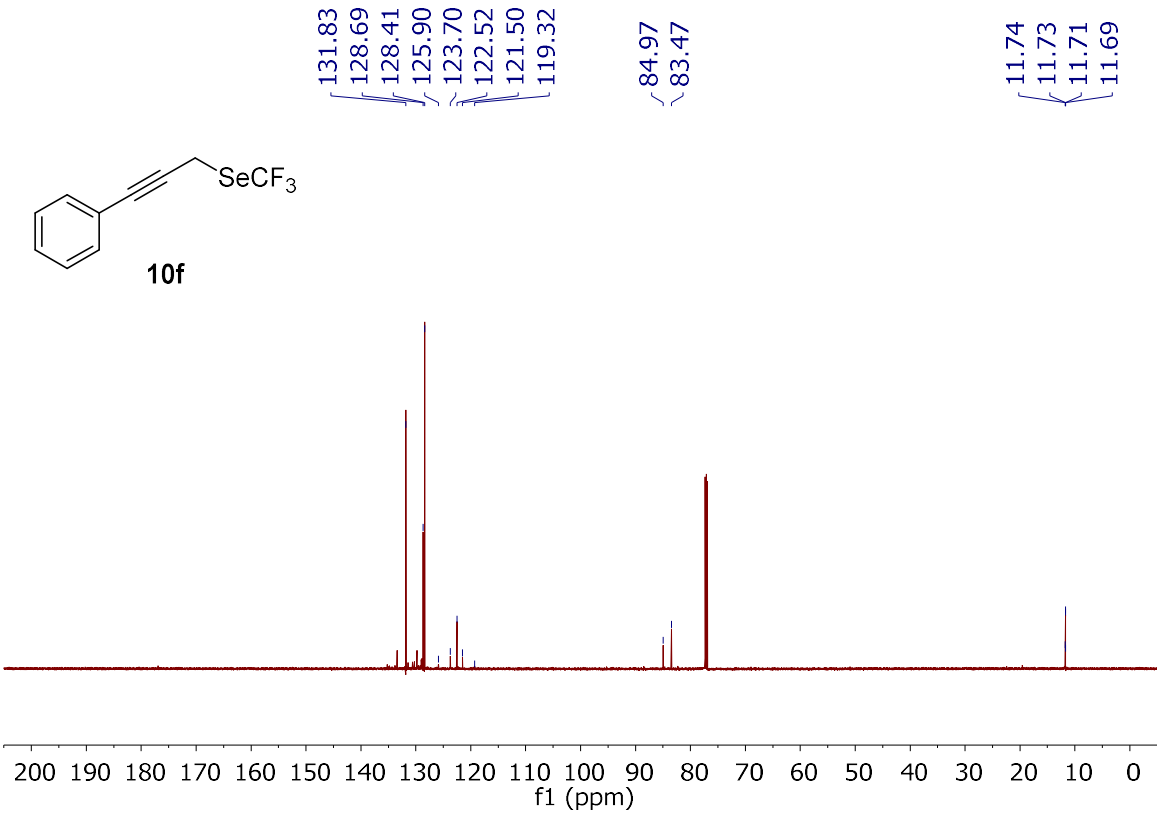
10e

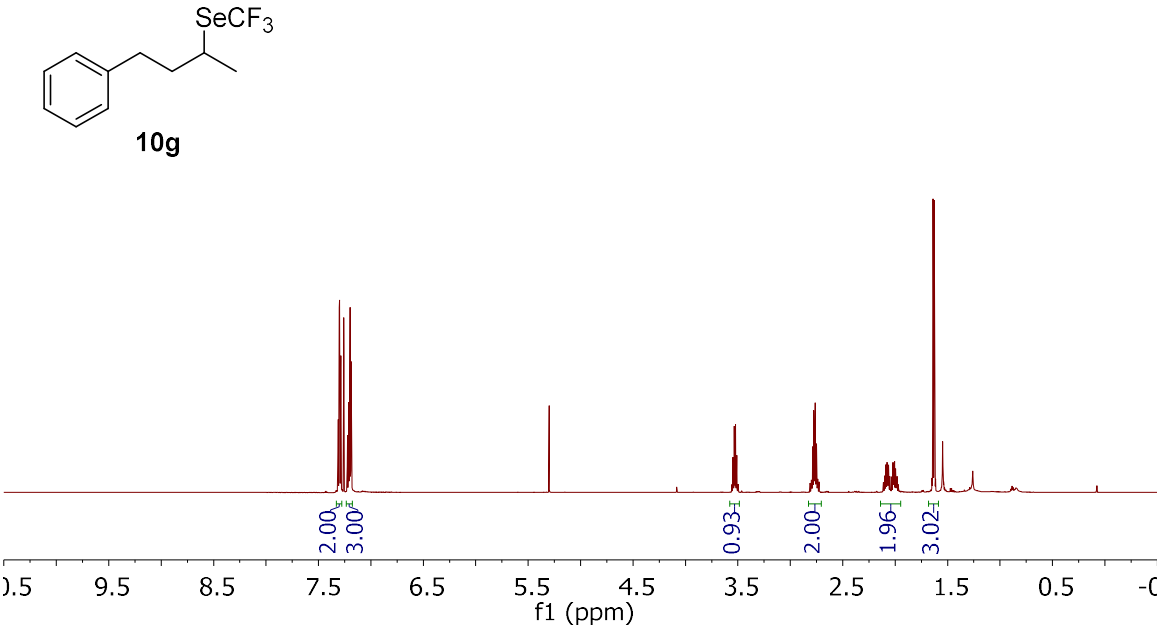

-33.99
SeCF3
10e
70 40 10 -20 -50 -80 -110 -140 -170 -200 -230 -260 -29
f1 (ppm)

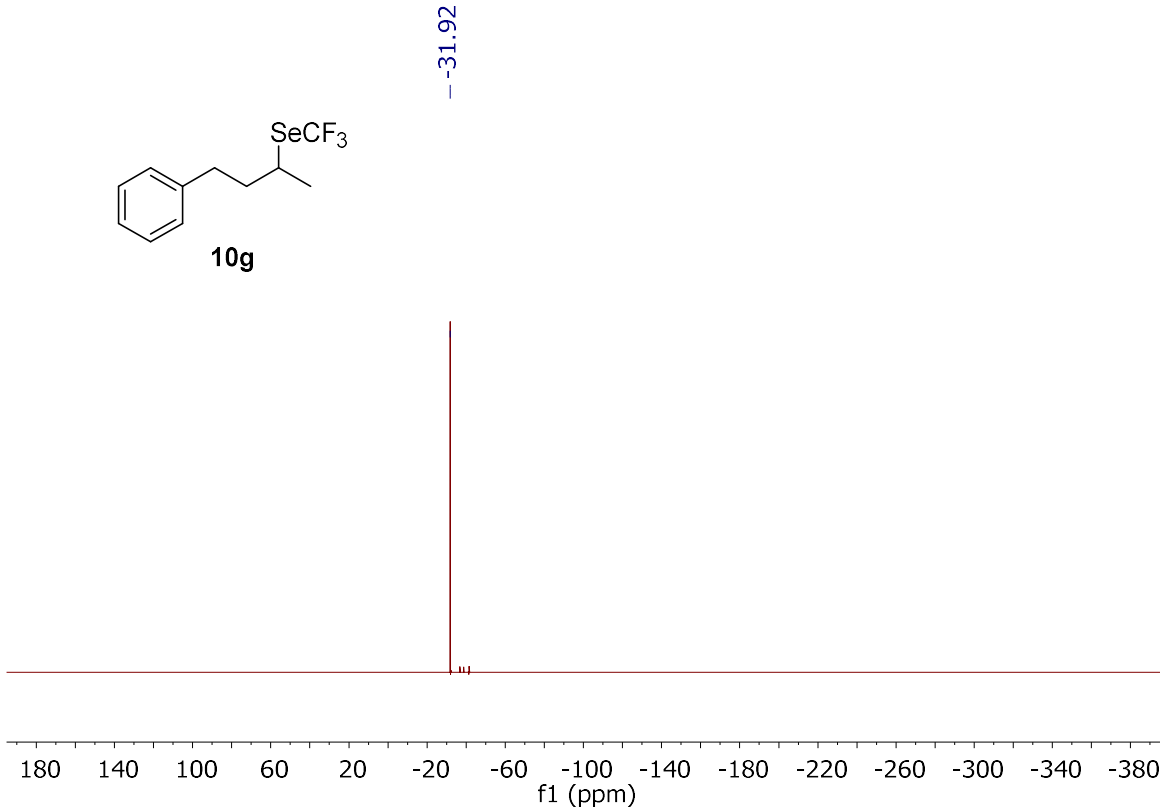

141.86
128.54
128.49
126.08
125.80
123.91
121.73
119.54
35.33
31.39
29.93
25.76
25.75
25.74
25.73
SeCF3
10e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

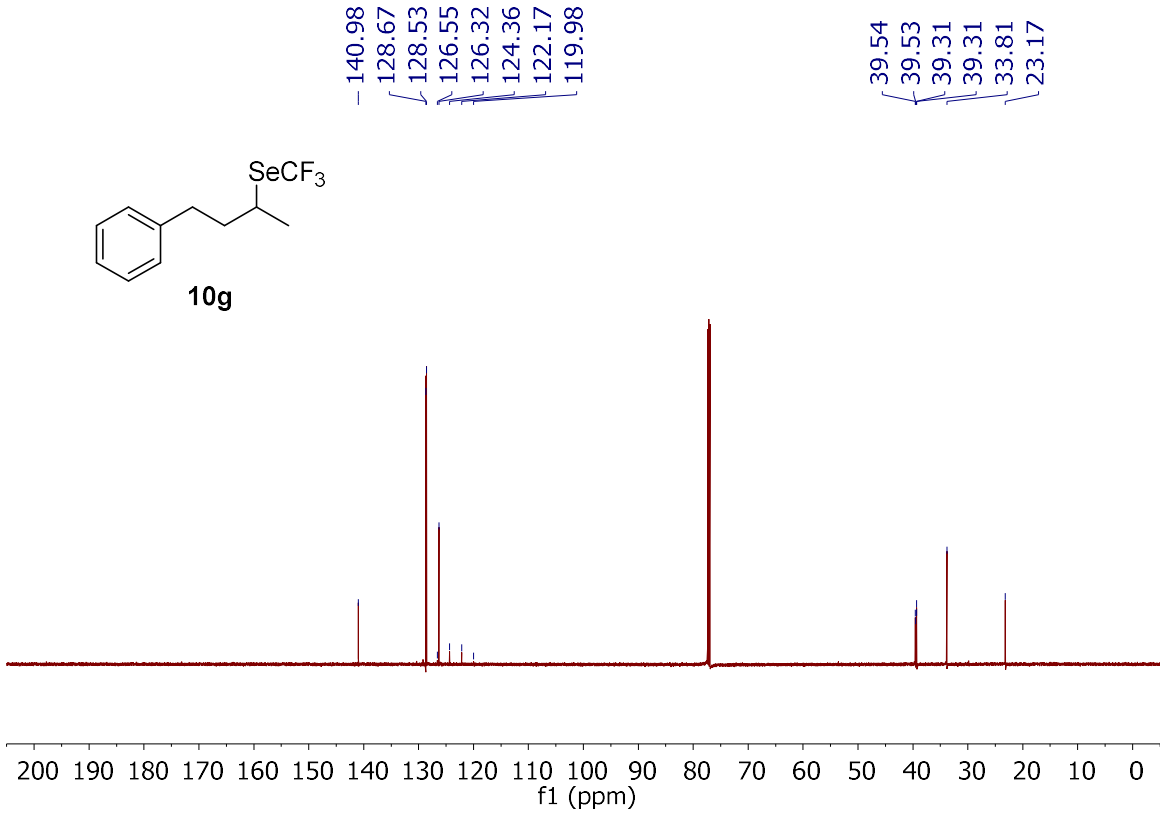

SeCF3
10f
1.98
2.96
2.00
f1 (ppm)


-34.52
SeCF3
10f
f1 (ppm)


131.83
128.69
128.41
125.90
123.70
122.52
121.50
119.32
84.97
83.47
11.74
11.73
11.71
11.69
SeCF3
10f
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


SeCF3
10g
2.00
3.00
0.93
2.00
1.96
3.02
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
f1 (ppm)


-31.92
SeCF3
10g
180 140 100 60 20 -20 -60 -100 -140 -180 -220 -260 -300 -340 -380
f1 (ppm)


140.98
128.67
128.53
126.55
126.32
124.36
122.17
119.98
39.54
39.53
39.31
39.31
33.81
23.17
SeCF3
10g
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

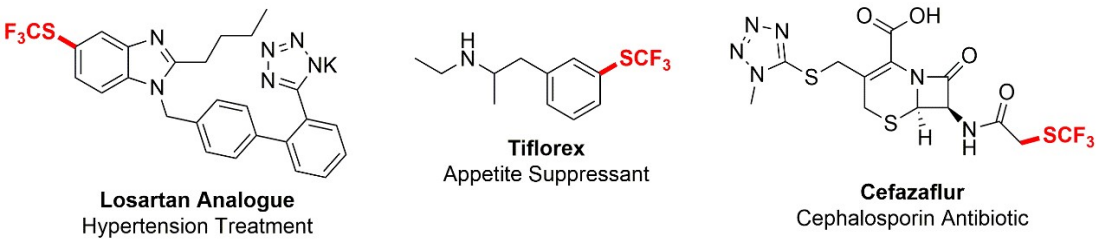
12.2 Fluorine-containing Compounds for Use as Nucleophilic Reagents for Transferring Functional Groups onto High Value Organic Compounds

The present invention relates to fluorine-containing compounds for use as nucleophilic reagents for transferring functional groups onto high value organic compounds and methods for synthesizing them.

Description

Fluoroalkyl groups, in particular fluoroalkyl-containing thiol-groups, such as SCF_3, are attracting increasing attention in medicinal chemistry as a substituent that when incorporated into pharmaceuticals and other biologically-active compounds, can improve their potency and bioavailability.

In particular, the SCF_3 group is one of the most lipophilic moieties available and can allow for an increase in the membrane permeability of drug targets. To date, several SCF_3-containing pharmaceuticals have been introduced and medicinal chemistry programs now routinely investigate SCF_3-substituted derivatives of potential drug candidates alongside those labelled with more traditional fluorinated (eg. trifluoromethyl, CF_3) or non-fluorinated groups (scheme 1).

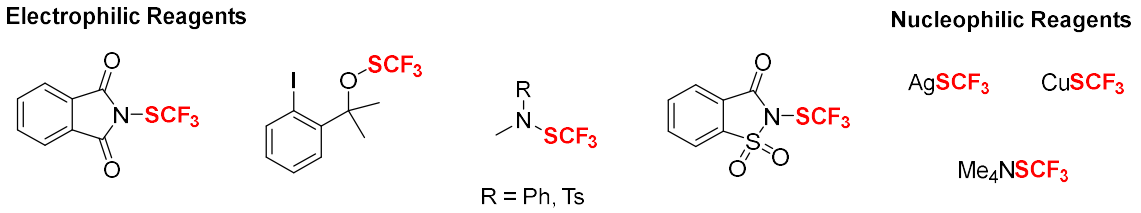


Scheme 1: Selected examples of drug candidates containing SCF_3 groups.

The synthesis of SCF_3-containing molecules can be achieved using a number of different strategies. A useful approach in the context of medicinal chemistry is direct trifluoromethylthiolation wherein the SCF_3 moiety is attached directly as a whole intact group onto a target substrate. These reactions can potentially be conducted on the same substrates used when installing other related groups (eg. CF_3) and thus are simple to incorporate into screening studies.

Until the last few years, there existed only a few known reagents such as the highly toxic and difficult to handle gaseous species SCF_3X (X = Cl, Br) and F_3CSSCF_3 for electrophilic trifluoromethylthiolation reactions.

In recent years, however, a number of bench-stable and easy-to-use electrophilic trifluoromethylthiolating reagents have been developed and, as a result, the use of the SCF_3 group in research laboratories and in pharmaceutical development has increased dramatically (Scheme 2).



Scheme 2: Examples of trifluoromethylthiolating reagents.

However, nucleophilic sources of SCF_3 are limited to a relatively small number of stable metal or ammonium salts [M][SCF_3] (M = eg. Ag, Cu, Me_4N) which, in most cases, contain rather expensive metal cations.

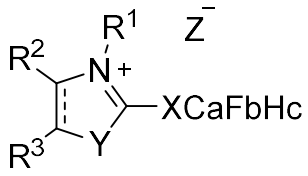
It is thus desirable to provide alternative nucleophilic sources for fluoroalkyl-containing thiol-groups, which do not require metal cations and are purely organic.

Furthermore, nucleophilic sources of related fluoroalkyl-containing groups such as SC_nF_{2n+1} (n > 1) or SCF_2H are even more scarce due to the instability of simple metal salts with these anions.

The incorporation of fluoroalkyl selenyl (eg. $SeCF_3$) or fluoroalkoxy (eg. OCF_3) groups into organic molecules would also benefit from the availability of new practical nucleophilic reagents.

These objectives are solved by compounds as described in claim 1.

Accordingly, a fluorine containing compound of the general formulae (I)



(I)

is provided, wherein

- R^1 is C1-C20 alkyl;
- R^2, R^3 are in each case an alkyl, a cycloalkyl, an aryl, a heteroaryl, a halogen, a halogen substituted alkyl or both R^2 and R^3 are part of a cyclic system;
- X is S, O, Se, Te; preferably S, O, Se;
- Y is S, O;
- Z^- is $R^4SO_3^-$ with R^4 being H, C1-C10 alkyl, aryl, CaFbHc, in particular ^-OTf ($CF_3SO_3^-$), $PhSO_3$- or p-Tos-; I^-, Cl^-, ClO_4^-, BF_4^-;
- a is 1-20, preferably 1-12, more preferably 1-8;
- b is (2a+1) - c,
- c is 0-10, preferably 0-5, more preferably 0, 1, 2.

Rather than acting as an electrophilic trifluoromethylthiolating reagent, the compound of formulae (I) acts a source of nucleophilic $^-XC_aF_bH_c$, such as $^-SCF_3$. Unlike most existing species, this compound does not contain expensive metal cations and is purely organic in nature. The compound of general formulae (I) is a solid that is easy to handle under ambient conditions and is bench-stable over extended periods.

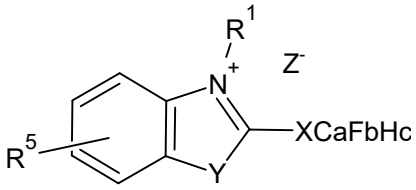
In an embodiment of the present compound moiety R^1 is C1-C10 alkyl, preferably C1-C5 alkyl, more preferably C1-C3 alkyl. In a particular preferred embodiment moiety R^1 is a methyl group (-CH_3) or an ethyl group (-C_2H_5).

In a further embodiment of the present compound the moieties R^2 and R^3 are part of an aromatic system, preferably of a C6-C10 aryl ring, more preferably of a C6 aryl ring, which may be further substituted. This may comprise a non-substituted or substituted C6 aryl ring or non-substituted or substituted naphthyl ring.

In another embodiment of the present compound the moieties have the following meaning:

- R^1 is C1-C3 alkyl;
- R^2, R^3 are part of an unsubstituted or substituted C6 aryl ring or naphthyl ring,
- X is S, O, Se;
- Y is S, O;
- Z^- being R^4 being aryl or $C_aF_bH_c$, in particular – OTf ($CF_3SO_3^-$), p-Tos; Ph-SO_3-; or BF_4^-;
- a is 1-8;
- b is (2a+1) - c;
- c is 0, 1, 2.

In a further embodiment the present compound is of the general formulae (II)

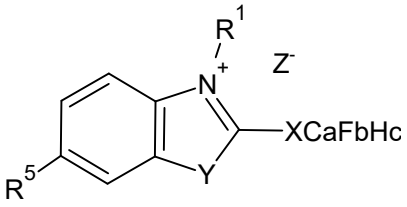


(II)

wherein R^1, X, Y, Z, a, b, c have one of the above meanings, and

wherein R^5 is absent or a C1-C10 alkyl, a C1-C10 alkoxy, in particular C1-C5 alkoxy, or a halogen, in particular Cl or Br.

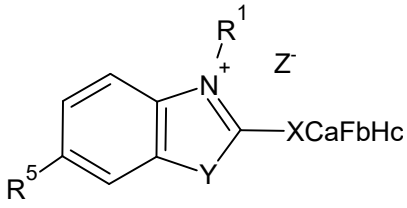
In yet a further embodiment the present compound is of the general formulae (IIa)



(IIa)

wherein R^1, R^5, X, Z, a, b, c have the above meanings.

In still a further embodiment the present compound is of the general formulae (IIb)

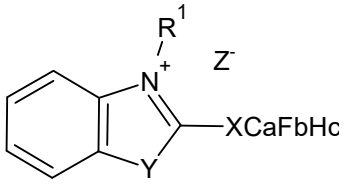


(IIb)

wherein

- R^1 is C1-C3 alkyl;
- R^5 is absent or C1-C5 alkoxy, or Cl.
- X is S, O, Se;
- Y is S, O;
- Z^- being – OTf ($CF_3SO_3^-$), p-Tos; Ph-SO_3-; BF_4^-;
- a is 1-8;
- b is (2a+1) - c;
- c is 0, 1, 2.

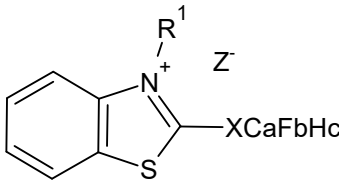
In another embodiment the present compound is of the general formulae (III)



(III)

wherein R^1, X, Y, Z, a, b, c have the above meanings.

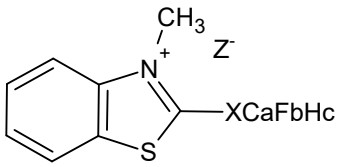
In yet a further embodiment the present compound is of the general formulae (IV)



(IV)

wherein R^1, X, Z, a, b, c have the above meanings.

In still another embodiment the present compound is of the general formulae (IVa)



(IVa)

wherein X, Z, a, b, c have the above meanings.

In a variant wherein c = 0 the moiety $-XC_aF_bH_c$ does not contain any hydrogen. In such a case the moiety is $-XC_aF_b$, as for example $-XCF_3$, $-XCF(CF_3)_2$ or $-XC_8F_{17}$, in particular $-SCF_3$, $-SeCF_3$, $-OCF_3$ or $-SC_8F_{17}$. However, any perfluoralkyl moiety is suitable.

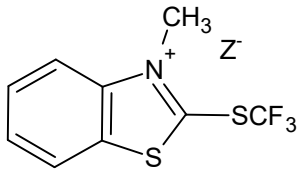
In variants wherein c = 1 or 2 the moiety $-XC_aF_bH_c$ may be $-XCF_2H$ or $-XCFH_2$, in particular $-SCF_2H$ or $-SCFH_2$.

It is to be understood that the moieties R^1, R^2, R^3 and R^5 can be non-substituted or further substituted.

Here the term “substituted”, in particular in connection to alkyl, cycloalkyl, aryl or heteroaryl relates to the substitution of one or more atoms, usually H-atoms, by one or more of the following substituents: halogen, hydroxy, protected hydroxy, oxo, C_3-C_{10}-cycloalkyl, aryl, heteroaryl, naphthyl, imino, imido, isocyano, amino, protected amino, primary or secondary amino, heterocyclic ring, carbonate, imidazolyl, indolyl, pyrrolidinyl, C_1-C_{12}-alkoxy, C_1-C_{12}-acyl, C_1-C_{12}-acyloxy, nitro, nitroso, carboxy, ester, aldehyde, ketone, sulfonic acid, sulfinic acid, thiocarbonyl, phosphate, phosphonate, boronate, carbamoyl, carboxamide, N-(C_1-C_{12}-alkyl)carboxamide, N,N-

Di(C_1-C_{12}-alkyl)carboxamide, cyano, alkylsulfonylamino, arylsulfonylamino, arylsulfonyl, alkylsulfinyl, arylsulfinyl, thiol, C_1-C_{10}-alkylthio, arylthiol, C_1-C_{12}-(per)fluoroalkyl and C_1-C_{10}-alkylsulfonyl. The substituted groups can be once or twice substituted with same or different substituents. The alkyl moieties may also comprise one or multiple double bonds.

Preferred embodiments of the present compound include:



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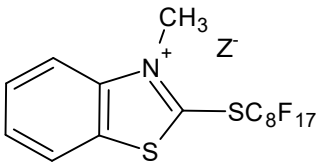

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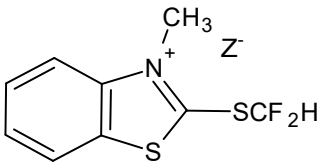

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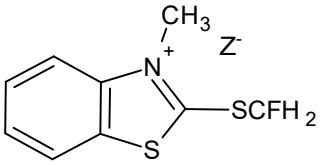

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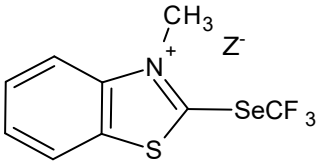

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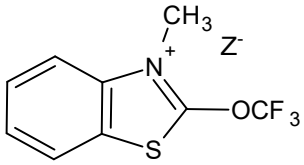

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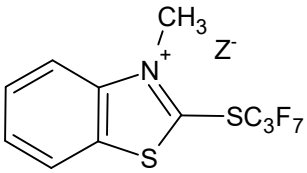

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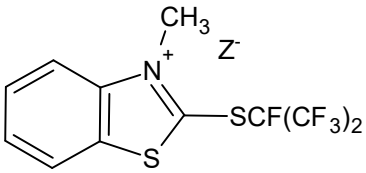

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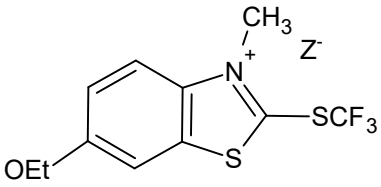

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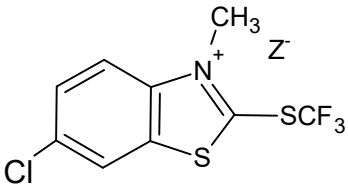
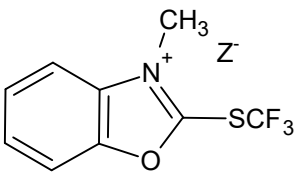
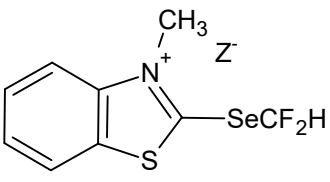
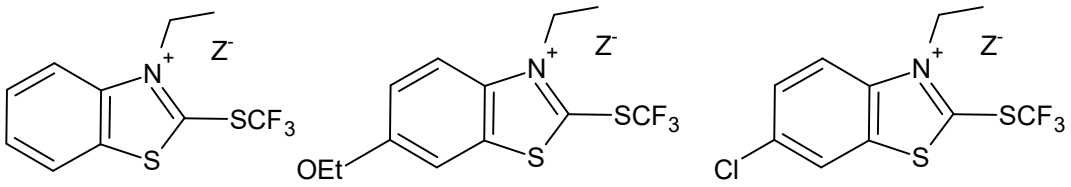






10 11 12



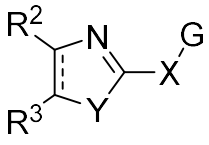
13 14 15

wherein Z^- is any of the above, preferably ^-OTf or BF_4^-

It is to be understood that a methylsulfate salt of compound 3 is disclaimed.

The present compound is obtained in a process comprising the following steps:

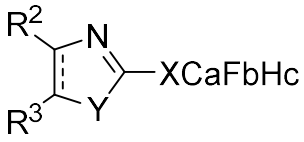
- providing a compound of general formulae (V)



(V)

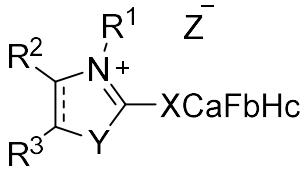
wherein G is H or a suitable leaving group as starting material;

- reacting the compound of general formulae (V) with at least one fluoroalkylating agent thereby providing an intermediate compound of general formulae (VI)



(VI)

- alkylating the ring nitrogen of general formulae (VI) thereby providing the compound of general formulae (I)



(I)

wherein R^1, R^2, R^3, X, Y, Z, a, b, c have the above meanings.

A major advantage of the present compounds is their simple synthesis from relatively inexpensive precursor substrates.

As mentioned G may be H, in particular in case of electrophilic or oxidative fluoroalkylation, or a leaving group such as a halogen, -XR (such as -SR, -SeR), -CN or others, in particular in case for nucleophilic fluoroalkylation.

For example a suitable starting material would be R-SH, R-S-S-R or R-Se-Se-R wherein R may be a benzothiazole or a benzoxazole.

In an embodiment of the present process the fluoroalkylating agent is selected from a group containing a compound of general formulae (VII) $NaSO_2C_aF_bH_c$ wherein a, b and c have the above meanings. A preferred variant of a fluoroalkylating agent is $NaSO_2CF_3$ (Langlois reagent). The reaction may be carried out under photoredox catalysis conditions.

The reaction of compound (V) with at least one fluoroalkylating agent of general formulae (VII) may be carried in the presence of an oxidizing agent such as $K_2S_2O_8$ or a photocatalyst, such as 9-mesityl-10-methylacridinium perchlorate or $[Ir(dF(CF_3)ppy)(dtbbpy]PF_6$ ($dF(CF_3)ppy$ = 2-(2,4-

difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4’-di-tert-butyl-2,2’-biyridine). In the latter case R-S-S-R or R-Se-Se-R may be used as starting materials and photoredox conditions such as blue light irradiation may be applied.

In another embodiment of the present process at least one fluoroalkylating agent is selected from a group containing a compound of general formulae (VIII) Hal $C_aF_bH_c$ wherein Hal is I, Br, or Cl and wherein a, b, c have the above meanings. A preferred variant of a fluoroalkylating agent of formulae (VIII) is $IC_aF_bH_c$, such as ICF_3 or IC_8F_{17}. The fluoroalkylating agent of formulae (VIII) is employed together with a suitable base (such as NaH or NaOH) under heating or irradiation with UVA light. In these cases, R-SH or R-SeH may be used as starting materials.

In another embodiment of the present process at least one alkylating agent selected from a group containing alkyl trifluoromethanesulfonate, alkyl iodide, trialkyl oxonium tetrafluoroborate, alkyl sulfate is employed for alkylating the intermediate compound of general formulae (VI).

As pointed out above, the present compound can be used as a nucleophilic reagent for transferring a fluorine-containing functional group onto high value organic compounds, in particular pharmaceutical or agrochemical targets.

For example, the present compound can be used as a nucleophilic reagent for transferring a fluorine-containing functional group onto alcohols, carboxylic acids or even alkyl halogenides, such as alkyl bromides. In one variant alkyl bromides may react with the present compound in a silver-mediated reaction.

The invention is explained in more detail by means of the following examples.

Example 1: Synthesis of 3-methyl-2-((trifluoromethyl)thio)benzo[d]thiazol-3-ium trifluoromethanesulfonate) (BT-SCF_3, Compound 1)

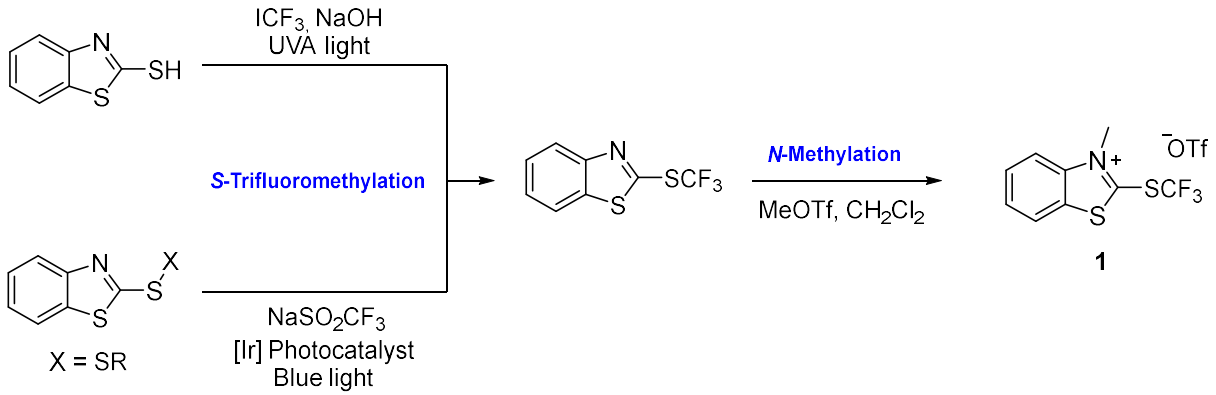
Compound **1** can bes prepared in two steps from the cheap starting material 2,2’-dithiobis(benzothiazole) (MBTS) which is a bulk chemical used in the industrial vulcanisation of rubber.

The trifluoromethyl group can be installed using the relatively inexpensive reagent $NaSO_2CF_3$ (Langlois’ reagent) using published procedures leading to the intermediate compound. This species is a stable, non-reactive heteroaromatic compound that can be readily purified without decomposition.

In a second step, methylation of the ring nitrogen using methyl trifluoromethanesulfonate cleanly affords the reagent **1** which is obtained as a pure compound upon simple filtration. Although the Langlois reagent is used as the CF_3 source, the two-step synthetic strategy towards compound **1** can be modified to enable even less expensive trifluoromethylthiolating reagents to be employed.

For example, compound **1** can be prepared in two steps from the inexpensive industrial compound 2-mercaptobenzothiazole (MBT) using CF_3I as a trifluoromethylating reagent in the presence a base and UV light irradiation. The procedure for this first step is described in Example 5 and the general procedure for the methylation in described in Example 8. The same general approach for the first fluoroalkylation step can be used to prepare related compounds featuring longer perfluoroalkyl chains as described in Examples 3 and 11.

Furthermore alternative strategies for the first step could be potentially realised. In particular, nucleophilic trifluoromethylation of disulfides or other sulfur compounds has been reported using the least expensive and therefore most industrially-attractive CF_3 source fluoroform (HCF_3).



Scheme 3: Two-step synthesis of compound **1**

Analytical data: ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ = 8.40 (d, *J*=8.0, 1H, H_{Ar}), 8.28 (d, *J*=8.6, 1H, H_{Ar}), 8.05 (t, *J*=8.0, 1H, H_{Ar}), 7.97 (t, *J*=7.9, 1H, H_{Ar}), 4.45 (s, 3H, CH_3). ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ = -39.3 (SCF_3), -79.3 ($S(O)_2CF_3$). ^{13}C NMR (151 MHz, Acetonitrile-d_3) δ = 160.6 (C_q), 143.8 (C_q), 134.1 (C_q), 132.4 (CH), 131.5 (CH), 127.7 (q, *J*=314, SCF_3), 125.2 (CH), 122.0 (q, *J*=321, $S(O)_2CF_3$), 119.4 (CH), 40.0 (CH_3).HRMS (ESI): m/z calculated for $[C_9H_7F_3NS_2]^+$ ($[M-(SO_3CF_3)]^+$): 249.9967, measured: 249.9955. IR (ATR): ν (cm^{-1}): 3086, 1664, 1578, 1490, 1476, 1462, 1433, 1382, 1279, 1266, 1240, 1227, 1196, 1173, 1161, 1150, 1108, 1092, 1050, 1026, 998, 814, 760, 722, 714, 688.

Example 2

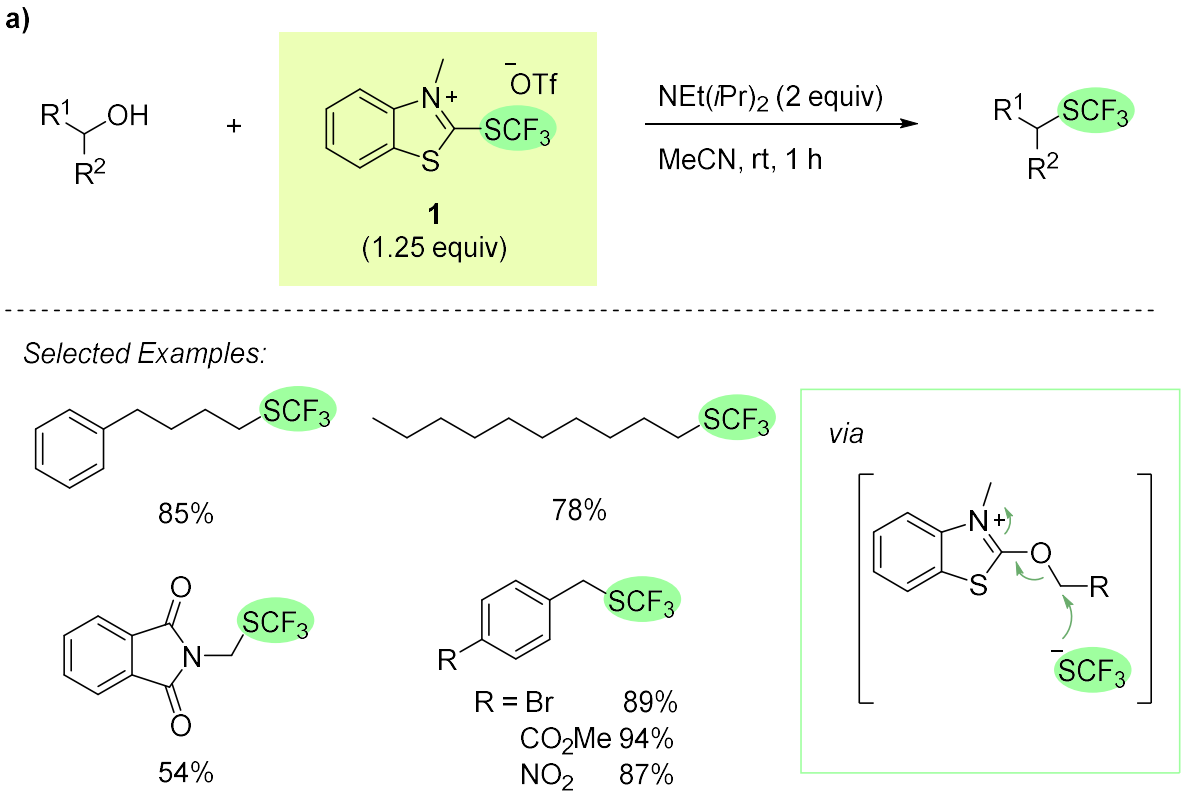
Compound **1** (BT-SCF_3) was employed in deoxytrifluoromethylthiolation reactions of aliphatic alcohols (Hopkinson*, Chem. Eur. J.* **2019**, *25*, 7635, see scheme 4a). This reaction is very useful as hydroxy groups are widespread in organic molecules and the ability to directly convert them into SCF_3 groups avoids the preparation of alkyl halide or pseudohalide precursors, reducing the overall number of synthetic steps required to prepare SCF_3-containing molecules.

Existing published methods for conducting this reaction use super-stoichiometric amounts of expensive $AgSCF_3$, $CuSCF_3$ or electrophilic trifluoromethylthiolating reagents in combination with excess Lewis acid or tetrabutylammonium iodide activators (Qing, *Angew. Chem. Int. Ed.* **2015**; Rueping, *Chem. Eur. J.* **2014**; Billard, *Eur. J. Org. Chem*. **2016**; Magnier, *Eur. J. Org. Chem*. **2017**). Most methods also require high reaction temperatures.

By contrast, the same process can be achieved using only a slight excess of metal-free compound **1** (1.25 equivalents) in acetonitrile (0.5 M) at room temperature with just 2 equivalents of an organic amine base (such as di(isopropyl)ethyl amine). The procedure for the deoxytrifluoromethylthiolation of alcohols using compound **1** is described in Example 12. Related reactions using derivatives of compound **1** is described in Example 13.

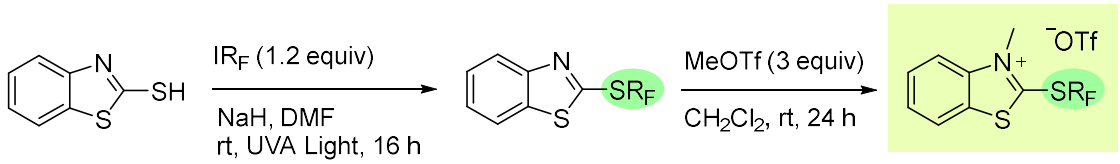
Compound **1** can also be employed in deoxytrifluoromethylthiolation reactions of carboxylic acids affording trifluoromethylthioesters. The synthesis of these products is typically achieved using acid chloride substrates and there exists to the best of our knowledge only one recent report for the direct conversion of readily available carboxylic acids (Hu, *Chem. Sci.* **2019**). The procedure for this reaction is described in Example 14.

In addition to acting as a reagent for deoxytrifluoromethylthiolation, compound **1** can also serve as a more general source of $^-SCF_3$ upon addition of a suitable metal or ammonium salt activator. This could potentially be achieved catalytically; $AgSCF_3$, for example, could be generated *in situ* upon activation of **1** with small amounts a soluble, inexpensive silver(I) salt such as Ag_2O or $AgNO_3$ (see Scheme 4b).



Scheme 4: a) Deoxytrifluoromethylthiolation of aliphatic alcohols using reagent **1**: b) Catalytic generation of metal SCF_3 salts from reagent **1**.

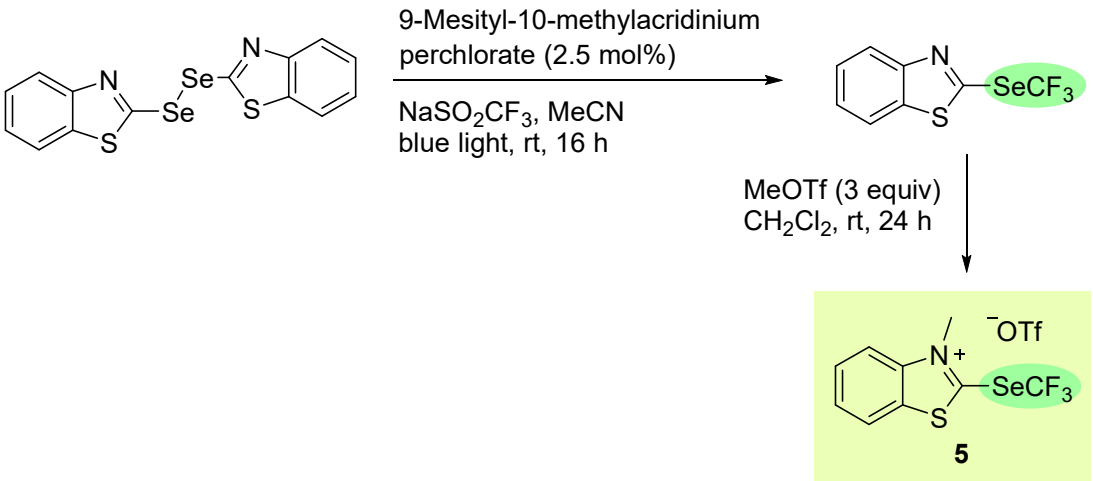
Example 3: Synthesis of 3-methyl-2-((perfluorooctyl)thio)benzo[d]thiazol-3-ium trifluoromethanesulfonate (BT-SC_8F_{17}, Compound 2)



3-Methyl-2-((perfluorooctyl)thio)benzo[d]thiazol-3-ium trifluoromethanesulfonate was synthesized in two steps from 1-mercaptobenzothiazole. In the first step the C_8F_{17} group was installed using a modified literature procedure employing the commercially-available perfluoroalkyl iodide IC_8F_{17} and sodium hydride under irradiation with UVA light. N-Methylation using methyl trifluoromethanesulfonate was then conducted in analogy to the method used in Example 1.

Analytical data: ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ = 8.40 (d, *J*=8.4, 1H, H_{Ar}), 8.29 (d, *J*=8.7, 1H, H_{Ar}), 8.07 (t, *J*=7.6, 1H, H_{Ar}), 7.99 (t, *J*=7.8, 1H, H_{Ar}), 4.47 (s, 3H, CH_3). ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ = -79.3 ($S(O)_2CF_3$), -81.4 (t, *J*=10, CF_3), -82.5 (t, *J*=14, SCF_2), -118.4 – -118.6 (m, CF_2), -121.2 – -121.5 (m, CF_2), -121.8 – -122.1 (m, CF_2), -122.1 – -122.3 (m, CF_2), -122.9 – -123.1 (m, CF_2), -126.4 – -126.6 (m, CF_2). HR-MS (ESI): m/z calculated for $[C_{16}H_7F_{17}NS_2]^+$ ($[M]^+$-SO_3CF_3): 599.9743, measured: 599.9730. IR (ATR): ν (cm^{-1}): 3101, 2361, 1576, 1490, 1461, 1435, 1370, 1328, 1281, 1251, 1200, 1149, 1134, 1097, 1054, 1031, 958, 930, 849, 816, 798, 768, 756, 741, 723, 714, 707, 655.

Example 4: Synthesis of 3-methyl-2-((trifluoromethyl)selanyl)benzo[d]thiazol-3-ium trifluoromethanesulfonate (BT-$SeCF_3$, Compound 5)



3-Methyl-2-((trifluoromethyl)selanyl)benzo[d]thiazol-3-ium trifluoromethanesulfonate was synthesized in two steps from 1,2-bis(benzo[d]thiazol-2-yl)diselane. In the first step the CF_3 group

was installed under photoredox catalysis conditions using $NaSO_2CF_3$. N-Methylation using methyl trifluoromethanesulfonate was then conducted in analogy to the method used in Example 1.

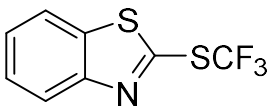
The reactivity exhibited by the selenium derivative (compound **5**) is similar to the reactivity of compound **1** (Hopkinson*, Chem. Eur. J.* **2019**, *25*, 7635). The general procedure for deoxytrifluoromethylselenylation of alcohols is described in Example 19. An alternative method for the synthesis of Compound **5** uses ICF_3 as a trifluoromethylating reagent. This method is described in Example 20.

Analytical data: ^{1}H NMR (400 MHz, Acetonitrile-*d*$_3$) δ = 8.37 (d, *J*=7.8, 1H, H_{Ar}), 8.27 (d, *J*=8.6, 1H, H_{Ar}), 8.01 (t, *J*=8.3, 7.9, 1H, H_{Ar}), 7.93 (t, *J*=7.9, 1H, H_{Ar}), 4.47 (s, 3H, CH_3). ^{19}F NMR (376 MHz, Acetonitrile-*d*$_3$) δ = -32.7 ($SeCF_3$), -79.3 ($S(O)_2CF_3$). ^{13}C NMR (126 MHz, Acetonitrile-*d*$_3$) δ = 159.2 (C_q), 143.9 (C_q), 135.0 (C_q), 132.1 (CH), 131.1 (CH), 125.1 (CH), 122.7 (q, *J*=337, $SeCF_3$), 122.0 (q, *J*=321, $S(O)_2CF_3$), 119.3 (CH), 41.4 (CH_3). CHNS Elemental Analysis: calculated for $C_{10}H_7F_6NO_3S_2Se$: C 26.92; H 1.58; N 3.14, S 14.37; measured: C 27.00, H 1.97, N 3.14, S 14.50. IR (ATR): ν (cm-1): 3098, 3064, 1577, 1489, 1461, 1442, 1388, 1252, 1223, 1187, 1151, 1140, 1101, 1079, 1054, 1043, 1028, 987, 962, 802, 766, 741, 729, 712.

Example 5: General Procedure for the Trifluoromethylation of Mercaptobenzothiazoles

Mercaptobenzothiazole (1.0 eq) and NaOH (1.1 eq) were dissolved in MeCN/H_2O (9:1, 0.5 M), the Schlenk flask was closed and the mixture frozen by using a liquid nitrogen bath. High vacuum was applied to the Schlenk flask and afterwards CF_3I (2.0 eq) was condensed into the frozen mixture. The nitrogen bath was removed, Argon was added until standard pressure was achieved and an empty balloon was attached to the Schlenk flask. The frozen mixture was allowed to thaw by using a water bath and the mixture was stirred under irradiation from UVA LEDs (λ_{max} = 365 nm) for 6 h. DCM and H_2O were added to the mixture, the organic phase was separated, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, Pentane/DCM).

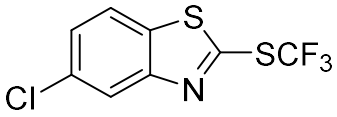
2-((trifluoromethyl)thio)benzo[d]thiazole



Prepared using 5-chloro-2-mercapto-benzothiazole on a 5.00 mmol scale. White solid (0.94 g, 4.0 mmol, 80 %).**^{1}H NMR (400 MHz, Chloroform-d) δ** = 8.12 (d, *J*=8.1, 1H, H_{Ar}), 7.87 (d, *J*=7.9, 1H, H_{Ar}),

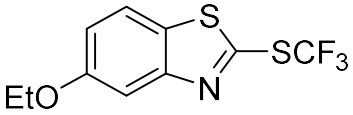
7.53 (t, *J*=7.5, 1H, H_{Ar}), 7.47 (t, *J*=7.5, 1H, H_{Ar}). **^{19}F NMR (376 MHz, Chloroform-d) δ** = -40.7. **^{13}C NMR (101 MHz, Chloroform-d) δ** = 153.2, 151.9, 138.0, 128.3 (q, J=311), 127.1, 126.8, 124.3, 121.4. **HRMS (EI):** m/z calculated for $[C_8H_4F_3NS_2]^+$ ($[M]^+$): 234.9732, measured: 234.9739. **IR (ATR):** ν (cm-^{1}): 3065, 1556, 1456, 1411, 1311, 1237, 1143, 1099, 1075, 1015, 988, 941, 852, 755, 726, 708, 676. **R_f**: (*n*-pentane/EtOAc, 20:1): 0.75.

5-chloro-2-((trifluoromethyl)thio)benzo[d]thiazole



Prepared using 5-chloro-2-mercapto-benzothiazole on a 5.00 mmol scale. White solid (0.90 g, 3.34 mmol, 67 %).**^{1}H NMR (400 MHz, Chloroform-d) δ** = 8.06 (d, *J*=2.0, 1H, H_{Ar}), 7.80 (d, *J*=8.6, 1H, H_{Ar}), 7.42 (dd, *J*=8.6, 2.0, H_{Ar}), **^{19}F NMR (376 MHz, Chloroform-d) δ** = -39.9. **^{13}C NMR (101 MHz, Chloroform-d) δ** = 154.1 (q, *J*=3), 153.8, 135.9, 133.3, 128.2 (q, *J*=311), 127.3, 123.9, 122.1. **HRMS (EI)**: m/z calculated for $[C_8H_3ClF_3NS_2]^+$ ($[M]^+$): 268.9348, measured: 268.9348.

5-ethoxy-2-((trifluoromethyl)thio)benzo[d]thiazole



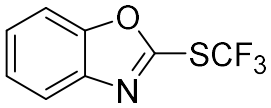
Prepared using 5-ethoxy-2-mercapto-benzothiazole on a 5.00 mmol scale. White solid (0.63 g, 2.25 mmol, 45 %). **^{1}H NMR (400 MHz, Chloroform-d) δ** = 7.94 (d, *J*=9.0, 1H, H_{Ar}), 7.21 (d, *J*=2.5, 1H, H_{Ar}), 7.08 (dd, *J*=9.0, 2.5, 1H, H_{Ar}), 4.03 (q, *J*=7.0, 2H, CH_2), 1.42 (t, *J*=7.0, 3H, CH_3). **^{19}F NMR (376 MHz, Chloroform-d) δ** = -40.7. **^{13}C NMR (101 MHz, Chloroform-d) δ** = 158.3, 147.8, 147.4 (q, *J*=3.0), 140.0, 128.3 (q, *J*=311.1), 124.8, 117.4 , 103.7, 64.2, 14.7. **HRMS (EI)**: m/z calculated for $[C_{10}H_8F_3NOS_2]^+$ ($[M]^+$): 278.9999, measured: 278.9983.

Example 6: General Procedure for the Trifluoromethylation of Mercaptobenzoxazoles

Mercaptobenzoxazole (1.0 eq) and NaH (3 eq, as 60% wt in mineral oil) were dissolved in dry MeCN (0.2 M), the Schlenk flask was closed and the mixture frozen using a liquid nitrogen bath. High vacuum was applied to the Schlenk flask and afterwards CF_3I (2.0 eq) was condensed into the frozen mixture. The nitrogen bath was removed, Argon was added until standard pressure was achieved

and an empty balloon was attached to the Schlenk flask. The frozen mixture was allowed to thaw by using an water bath and the mixture was stirred under irradiation from UVA LEDs (λ_{max} = 365 nm) for 6 h. Remaining NaH was filtered off from the reaction and quenched. DCM and H_2O were added to the mixture, the organic phase was separated, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, Pentane/DCM).

2-((trifluoromethyl)thio)benzo[d]oxazole

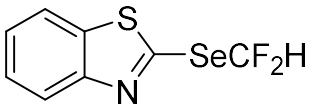


Prepared using 2-mercapto-benzooxazole on a 5.00 mmol scale. Colourless liquid (0.30 g, 1.36 mmol, 27 %). **^{1}H NMR (400 MHz, Chloroform-d) δ** = 7.79 – 7.75 (m, 1H, H_{Ar}), 7.60 – 7.55 (m, 1H, H_{Ar}), 7.45 – 7.34 (m, 2H, H_{Ar}). **^{19}F NMR (376 MHz, Chloroform-d) δ** = -38.6. **^{13}C NMR (101 MHz, Chloroform-d) δ** = 152.89 (q, *J*=3), 152.51, 141.50, 127.81 (q, *J*=312), 126.60, 125.41, 120.61, 110.97. **HRMS (EI)**: m/z calculated for $[C_8H_4F_3NOS]^+$ ($[M]^+$): 218.9966, measured: 218.9978.

Example 7: Synthesis of Difluoromethylated Benzothiazole derivatives

Compounds featuring a CF_2H group can be prepared using the same general sequence with installation of the CF_2H moiety being achieved using HCF_2OTf as a source of difluorocarbene. This approach has been previously reported using aromatic thiols as substrates (Hartwig, *Angew. Chem. Int. Ed*. **2013**, *52*, 2092 –2095)..

Procedure for the Synthesis of 2-((difluoromethyl)selanyl)benzo[d]thiazole

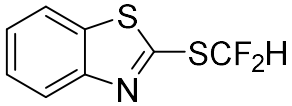


1,2-Bis(benzo[d]thiazol-2-yl)diselane (0.8 eq, 3.2 mmol, 1.36 g) was suspended in degassed MeOH/THF (4:1, 40 mL) and $NaBH_4$ (1.6 eq, 6.4 mmol, 0.24 g) was added portionwise under

vigorous stirring at 0 °C. After 10 min degassed 1M HCl (80 mL) was added and the precipitate was washed with degassed H_2O (3 x 50 mL). The solid was added to a degassed solution of 6M KOH (6 mL) and MeCN (6 mL), afterwards difluoromethyl trifluoromethanesulfonate (1 eq, 4.0 mmol, 0.8 g) was added to the mixture at 0 °C. The mixture was stirred for 15 min at 0 °C and was diluted with H_2O (25 mL) and extracted with diethyl ether (100 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo.* The crude product is purified by column chromatography (SiO_2, Pentane/DCM). Colourless solid (0.56 g, 2.12 mmol, 53 %).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.04 (d, *J*=8.8, 1H, H_{Ar}), 7.86 (d, *J*=6.4, 1H, H_{Ar}), 7.84 (t, *J*=54.5, 2H, CF_2H), 7.49 (t, *J*=7.4, 1H, H_{Ar}), 7.40 (t, *J*=7.6, 1H, H_{Ar}). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -90.11 (d, *J*=54). **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 153.68 , 151.55 (t, *J*=4), 137.06 , 126.61 , 125.61 , 122.93 , 121.20 , 117.83 (t, *J*=291). **HRMS (EI)**: m/z calculated for $[C_8H_5F_2NSSe]^+$ ($[M]^+$): 264.9276, measured: 264.9296.

Procedure for the Synthesis of 2-((difluoromethyl)thio)benzo[d]thiazole



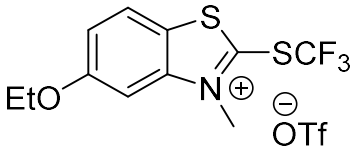
2-Mercaptobenzothiazole (1.0 eq, 3.0 mmol, 0.5 g) was added to a solution of 6M KOH (6 mL) and MeCN (6 mL), afterwards difluoromethyl trifluoromethanesulfonate (3 eq, 9.0 mmol, 1.2 mL) was added to the mixture. The mixture was stirred for 2 min and was diluted with H_2O (25 mL) and extracted with diethyl ether (3 x 10 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Colourless solid (0.57 g, 2.6 mmol, 87 %).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.01 (d, *J* = 8.2, 1H, H_{Ar}), 7.84 (d, *J* = 8.0, 1H, H_{Ar}), 7.65 (t, *J* = 56.3, 1H, CF_2H), 7.49 (t, *J* = 8.0, 1H, H_{Ar}), 7.41 (t, *J* = 7.6, 1H). **^{19}F NMR (376 MHz, Chloroform-*d*)**: δ -93.08 (d, *J* = 56). The Analytical data is in agreement to literature (Hu, *Org. Lett*. **2010**, *12*, 1444−1447).

Example 8: General Procedure for the Methylation of Tri- or Difluoromethylated Chalcogenated Heterocycles using Methyl trifluoromethanesulfonate

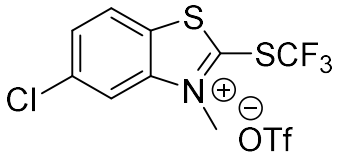
The (fluoroalkyl)chalcogen-substituted benzothiazole or benzoxazole (1.0 eq) was dissolved in dry CH_2Cl_2 (1.0 M) at rt. Methyl trifluoromethanesulfonate (3.0 eq) was added and the mixture was stirred overnight at rt. Et_2O was added and the precipitated product was collected by filtration.

5-ethoxy-3-methyl-2-((trifluoromethyl)thio)benzo[d]thiazol-3-ium trifluoromethanesulfonate



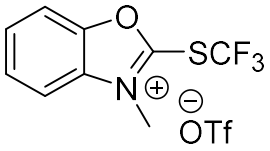
Prepared using 5-ethoxy-2-((trifluoromethyl)thio)benzo[d]thiazole on a 0.61 mmol scale. White solid (245 mg, 0.55 mmol, 90 %).**^{1}H NMR (400 MHz, Acetonitrile-d_3) δ** = 8.17 (d, *J*=9.5, 1H, H_{Ar}), 7.82 (d, *J*=2.5, 1H, H_{Ar}), 7.57 (dd, *J*=9.6, 2.5, 1H, H_{Ar}), 4.22 (q, *J*=7.0, 2H, CH_2), 1.45 (t, *J*=7.0, 3H, CH_3). **^{19}F NMR (376 MHz, Acetonitrile-d_3) δ** = -39.8, -79.2. **^{13}C NMR (101 MHz, Acetonitrile-d_3) δ** = 161.7, 138.3, 136.9, 127.7 (q, *J*=314.9), 123.4, 122.0 (q, *J*=321.0), 120.5, 120.5, 118.4, 106.6, 66.3, 40.0, 14.7. **HRMS (ESI)**: m/z calculated for $[C_{11}H_{14}NO_2S]^+$ ($[M\text{-}SO_3CF_3\text{-}SCF_3 + OCH_3]^+$): 224.0740, measured: 224.0743.

5-chloro-3-methyl-2-((trifluoromethyl)thio)benzo[d]thiazol-3-ium trifluoromethanesulfonate



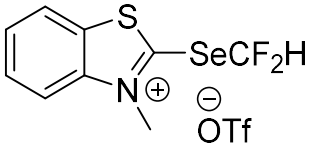
Prepared using 5-chloro-2-((trifluoromethyl)thio)benzo[d]thiazole on a 0.85 mmol scale. White solid (325 mg, 0.75 mmol, 88 %). **^{1}H NMR (400 MHz, Acetonitrile-d_3) δ** = 8.40 – 8.36 (m, 2H, H_{Ar}), 7.95 – 7.92 (m, 1H, H_{Ar}), 4.41 (s, 3H, CH_3). **^{19}F NMR (376 MHz, Acetonitrile-d_3) δ** = -39.1, -79.2. **^{13}C NMR (126 MHz, Acetonitrile-d_3) δ** = 162.8, 144.6, 138.5, 132.7, 132.0, 127.6 (q, *J*=314), 126.6, 122.0 (q, *J*=321), 119.4, 40.3. **HRMS (ESI)**: m/z calculated for $[C_9H_9ClNOS]^+$ ($[M\text{-}SO_3CF_3\text{-}SCF_3 + OCH_3]^+$): 214.0088, measured: 214.0084.

3-methyl-2-((trifluoromethyl)thio)benzo[d]oxazol-3-ium trifluoromethanesulfonate (BO-SCF_3)



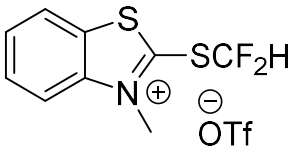
Prepared using 2-((trifluoromethyl)thio)benzo[d]oxazole on a 0.91 mmol scale. White solid (70 mg, 0.18 mmol, 20 %). **^{1}H NMR (400 MHz, Acetonitrile-d_3) δ** = 8.11 – 7.99 (m, 2H, H_{Ar}), 7.96 – 7.83 (m, 2H, H_{Ar}), 7.27 – 7.18 (m, 1H, H_{Ar}), 7.17 – 7.03 (m, 1H, H_{Ar}), 4.19 (s, 3H, CH_3). **^{19}F NMR (376 MHz, Acetonitrile-d_3) δ** = -35.1, -79.3. **HRMS (ESI)**: m/z calculated for $[C_8H_8NO_2]^+$ ($[M\text{-}SO_3CF_3\text{-}SCF_3 +OH]^+$): 150.0550, measured: 150.0555.

2-((difluoromethyl)selanyl)-3-methylbenzo[d]thiazol-3-ium trifluoromethanesulfonate (BT-$SeCF_2H$)



Prepared using 2-((difluoromethyl)selanyl)benzo[d]thiazole on a 0.91 mmol scale. White solid (362 mg, 0.85 mmol, 93%).**^{1}H NMR (400 MHz, Acetonitrile-d_3) δ** = 8.31 (d, *J*=8.5, 1H, H_{Ar}), 8.19 (d, *J*=8.6, 1H, H_{Ar}), 7.94 (t, *J*=8.1, 1H, H_{Ar}), 7.85 (t, *J*=7.2, 1H, H_{Ar}), 7.79 (t, *J*=52.4, 2H, CF_2H), 4.34 (s, 3H, CH_3). **^{19}F NMR (376 MHz, Acetonitrile-d_3) δ** = -79.2 , -87.9 (d, *J*=52). **^{13}C NMR (101 MHz, Acetonitrile-d_3) δ** = 164.1, 143.8, 133.9, 131.4 , 130.2, 124.8, 122.0 (q, *J*=321), 118.6 (t, *J*=296), 118.5, 40.9. **HRMS (ESI)**: m/z calculated for $[C_9H_{10}NOS]^+$ ($[M\text{-}SO_3CF_3\text{-}SeCF_3 +OCH_3]^+$): 180.0478, measured: 180.0495.

2-((difluoromethyl)thio)-3-methylbenzo[d]thiazol-3-ium trifluoromethanesulfonate (BT-SCF_2H)



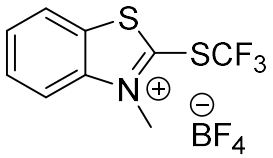
Prepared using 2-((difluoromethyl)thio)benzo[d]thiazole on a 2.4 mmol scale. White solid (0.79 g, 2.0 mmol, 84%). **^{1}H NMR (400 MHz, Acetonitrile-d_3) δ** = 8.28 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 8.13 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 7.95 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 7.86 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 7.52 (t, *J* = 53.4 Hz, 1H, CF_2H), 4.26 (s, 3H, CH_3).**^{19}F NMR (376 MHz, Acetonitrile-d_3) δ** = -79.28, -91.53 (d, *J* = 53 Hz).**CHNS Analysis:**

Calculated for $C_{10}H_8F_5NO_3S_3$ C: 31.50%; H: 2.11%; N: 3.67%; S: 25.22% , found to be C: 31.53% ; H: 2.12% ; N: 3.72% ; S: 25.12%

Example 9: General Procedure for the Methylation of Trifluoromethylated Chalkogen Derivatives using Trimethyloxonium Tetrafluoroborate

The Chalkogen derivative (1.0 eq) was dissolved in dry CH_2Cl_2 (1.0 M) at rt. Trimethyloxonium Tetrafluoroborate (3.0 eq) was added and the mixture was stirred overnight at rt. The crude mixture was filtered and extracted with DCM. Et_2O was added to the filtrate and the precipitated product was collected by filtration.

3-methyl-2-((trifluoromethyl)thio)benzo[d]thiazol-3-ium tetrafluoroborate

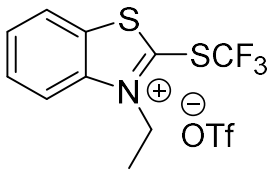


Prepared using 2-((trifluoromethyl)thio)benzo[d]thiazole on a 1.15 mmol scale. White solid (40 mg, 0.12 mmol, 10 %). **^{1}H NMR (400 MHz, Acetonitrile-d_3) δ** = 8.39 (d, *J*=8.3, 1H, H_{Ar}), 8.28 (d, *J*=8.6, 1H, H_{Ar}), 8.05 (t, *J*=8.3, 1H, H_{Ar}), 7.97 (t, *J*=8.1, 1H, H_{Ar}), 4.45 (s, 3H, CH_3). **^{19}F NMR (376 MHz, Acetonitrile-d_3) δ** = -39.1, -151.5. **HRMS (ESI)**: m/z calculated for $[C_9H_{10}NOS+]^+$ ($[M\text{-}BF_4\text{-}SCF_3 + OCH_3]^+$): 180.0478, measured: 180.0478.

Example 10: General Procedure for the Ethylation of Trifluoromethylated Chalkogen Derivatives

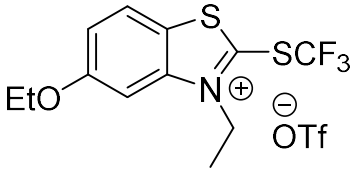
The Chalkogen derivative (1.0 eq) was dissolved in dry CH_2Cl_2 (1.0 M) at rt. Ethyl trifluoromethanesulfonate (3.0 eq) was added and the mixture was stirred overnight at rt. Et_2O was added and the precipitated product was collected by filtration.

3-ethyl-2-((trifluoromethyl)thio)benzo[d]thiazol-3-ium trifluoromethanesulfonate



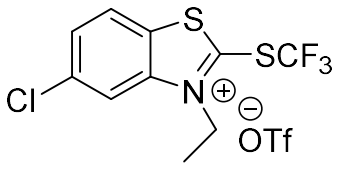
Prepared using 2-((trifluoromethyl)thio)benzo[d]thiazole on a 1.15 mmol scale. White solid (230 mg, 0.56 mmol, 48 %).**^{1}H NMR (400 MHz, Acetonitrile-d_3) δ** = 8.48 – 8.28 (m, 2H, H_{Ar}), 8.14 – 7.85 (m, 2H, H_{Ar}), 5.03 (q, *J*=7.5, 2H, CH_2), 1.61 (t, *J*=7.5, 3H, CH_3). **^{19}F NMR (376 MHz, Acetonitrile-d_3) δ** = -39.2, -79.2. **^{13}C NMR (126 MHz, Acetonitrile-d_3) δ** = 160.3, 142.8, 134.8, 132.5, 131.4, 127.6 (*J*=314), 125.5, 122.1 (q, *J*=321), 119.2, 49.6, 14.5. **HRMS (ESI)**: m/z calculated for $[C_{10}H_{12}NOS]^+$ ([M-SO_3CF_3 -SCF_3 +OCH_3]$^+$): 194.0634, measured: 194.0643.

5-ethoxy-3-ethyl-2-((trifluoromethyl)thio)benzo[d]thiazol-3-ium trifluoromethanesulfonate



Prepared using 5-ethoxy-2-((trifluoromethyl)thio)benzo[d]thiazole on a 0.61 mmol scale. White solid (214 mg, 0.47 mmol, 77 %).**^{1}H NMR (400 MHz, Acetonitrile-d_3) δ** = 8.22 (d, *J*=9.5, 1H, H_{Ar}), 7.84 (d, *J*=2.5, 1H, H_{Ar}), 7.56 (dd, *J*=9.5, 2.5, 1H, H_{Ar}), 4.98 (q, *J*=7.4, 2H, CH_2), 4.23 (q, *J*=7.0, 2H, CH_2), 1.58 (t, *J*=7.4, 3H, CH_3), 1.45 (t, *J*=7.0, 3H, CH_3).**^{19}F NMR (376 MHz, Acetonitrile-d_3) δ** = -39.7, -79.2. **^{13}C NMR (126 MHz, Acetonitrile-d_3) δ** = 161.6, 154.6, 137.6, 137.2, 127.7 (q, *J*=314), 123.5, 122.1 (q, *J*=321), 120.3, 106.9, 66.3, 49.5, 14.7, 14.6. **HRMS (ESI)**: m/z calculated for $[C_{12}H_{16}NO_2S]^+$ ([M-SO_3CF_3 -SCF_3 +OCH_3]$^+$): 238.0896, measured: 238.0902.

5-chloro-3-ethyl-2-((trifluoromethyl)thio)benzo[d]thiazol-3-ium trifluoromethanesulfonate



Prepared using 5-chloro-2-((trifluoromethyl)thio)benzo[d]thiazole on a 0.85 mmol scale. White solid (63 mg, 0.14 mmol, 16 %). **^{1}H NMR (400 MHz, Acetonitrile-d_3) δ** = 8.44 – 8.34 (m, 2H, H_{Ar}), 7.93 (dd, *J*=8.9, 1.8, 1H, H_{Ar}), 4.96 (q, *J*=7.4, 2H, CH_2), 1.58 (t, *J*=7.4, 3H, CH_3). **^{19}F NMR (376 MHz,**

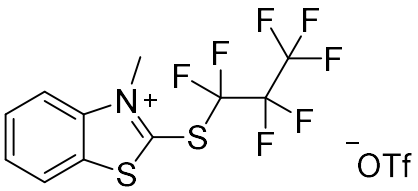
Acetonitrile-d_3) δ = -39.0, -79.2. **HRMS (ESI)**: m/z calculated for $[C_{10}H_{11}ClNOS]^+$ ($[M\text{-}SO_3CF_3\text{-}SCF_3+OCH_3]^+$): 228.0244, measured: 228.0247.

Example 11: General Procedure for the Synthesis of BT-SR_F Reagents (R_F = perfluoroalkyl)

1st Step: Mercaptobenzothiazole (1.0 eq) was dissolved in DMF under argon. Sodium hydride (60% wt in mineral oil, 1.1 eq) was added and the mixture was stirred at rt for 30 min. The perfluoroalkyl iodide (1.2 eq) was then added and the mixture was stirred under irradiation from UVA LEDS (λ_{max} = 365 nm) overnight. Water was added and the crude product was extracted with EtOAc (3×). The combined organic fractions were washed with water (3x), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography over silica gel afforded the 2-((perfluoroalkyl)thio)benzo[d]thiazole intermediate.

2nd Step: The 2-((perfluoroalkyl)thio)benzo[d]thiazole intermediate (1.0 eq) was dissolved in CH_2Cl_2 at rt. Methyl trifluoromethanesulfonate (3.0 eq) was added and the mixture was stirred overnight at rt. Et_2O was added and the precipitated 3-methyl-2-((perfluoroalkyl)thio)benzo[d]thiazol-3-ium trifluoromethanesulfonate (**BT-SR_F**) salt was collected by filtration.

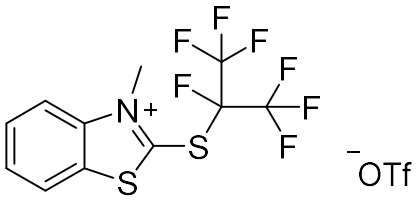
3-Methyl-2-((perfluoropropyl)thio)benzo[d]thiazol-3-ium Trifluoromethanesulfonate (BT-SC_3F_7)



Prepared using perfluoro-*n*-propyl iodide on an 8.40 mmol scale. Yield of first step = 70%, yield of 2nd step = 94%). Off-white solid (1.94 g, 5.53 mmol).

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ = 8.44 (d, *J*=8.3, 1H, H_{Ar}), 8.33 (d, *J*=8.7, 1H, H_{Ar}), 8.05 (ddd, *J*=8.6, 7.2, 1.2, 1H, H_{Ar}), 7.97 (ddd, *J*=8.3, 7.2, 1.1, 1H, H_{Ar}), 4.51 (s, 3H, CH_3). **^{19}F NMR (376 MHz, Acetonitrile-d_3) δ** = -79.2, -80.5 (t, *J*=9), -83.8 (q, *J*=10), -123.2. **^{13}C NMR (151 MHz, Acetonitrile-d_3) δ** = 158.7, 144.1, 134.7, 132.6, 131.8, 125.3, 122.0 (q, *J*=320), 119.7, 39.7 (CH_2). *Note: Three perfluoroalkyl ^{13}C peaks are not observed*. **HRMS (ESI)**: m/z calculated for $[C_{11}H_7F_7NS_2]^+$ ($[M\text{-}SO_3CF_3]^+$): 349.9903, measured: 349.9922.

3-Methyl-2-((perfluoropropan-2-yl)thio)benzo[d]thiazol-3-ium Trifluoromethanesulfonate (BT-SCF(CF_3)$_2$)



Prepared using perfluoropropan-2-yl iodide on a 14.1 mmol scale. Yield of first step = 91%, yield of 2nd step = 83%). Off-white solid (3.73 g, 10.65 mmol).

^{1}H NMR (400 MHz, Acetone-*d*$_6$) δ = 8.63 (dm, *J*=7.9, 1H, H_{Ar}), 8.57 (dm, *J*=8.6, 1H, H_{Ar}), 8.11 (m, 1H, H_{Ar}), 8.03 (m, 1H, H_{Ar}), 4.75 (s, 3H, CH_3). **^{19}F NMR (376 MHz, Acetone-*d*$_6$) δ** = -74.7 (d, *J*=11), -78.9, -154.7 (sept, *J*=11). **^{13}C NMR (151 MHz, Acetonitrile-*d*$_3$) δ** = 158.5, 143.2, 134.8, 132.7, 131.9, 125.4, 122.0 (q, *J*=320), 119.7, 40.0 (CH_2). *Note: Two perfluoroalkyl ^{13}C peaks are not observed*. **HRMS (ESI)**: m/z calculated for $[C_{11}H_7F_7NS_2]^+$ ($[M\text{-}SO_3CF_3]^+$): 349.9903, measured: 349.9923.

Example 12: General Procedures for the Deoxytrifluoromethylthiolation reaction of Alcohols with BT-SCF_3

Method A: The primary alcohol (0.50 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SCF_3** (250 mg, 0.625 mmol, 1.25 eq) was added and the reaction mixture was cooled to 0 °C. NEt(*i*Pr)$_2$ (174 µL,1.0 mmol, 2.0 eq) was then added dropwise and the reaction mixture was stirred for 1-2 h at rt. The reaction mixture was concentrated *in vacuo* and purified by column chromatography over silica gel.

Method B: The secondary alcohol (0.50 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SCF_3** (399 mg, 1.0 mmol, 2.0 eq) was added and the reaction mixture was cooled to −40 °C. NEt(*i*Pr)$_2$ (174 µL,1.0 mmol, 2.0 eq) was then added dropwise and the reaction mixture was stirred for 2 h at −40 °C. The reaction mixture was concentrated *in vacuo* and purified by column chromatography over silica gel.

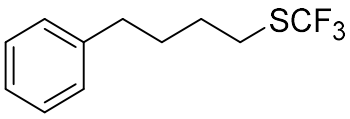
Method C: The secondary alcohol (0.50 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SCF_3** (133 mg, 0.33 mmol, one third of 2.0 eq) was added and the reaction mixture was cooled to 0 °C. NEt(*i*Pr)$_2$ (174 µL, 1.00 mmol, 2.00 eq) was added dropwise and the reaction mixture was stirred at rt. After 20 minutes, a second portion of **BT-SCF_3** (133 mg, 0.33 mmol) was added followed by a third portion (133 mg, 0.33 mmol) after an additional 20 minutes. The reaction was allowed to stir

at rt for a further 80 minutes (total reaction time of 2 h) before being concentrated *in vacuo* and purified by column chromatography over silica gel.

Method D: The secondary alcohol (0.50 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SCF_3** (200 mg, 0.50 mmol, one third of 3.0 eq) was added and the reaction mixture was cooled to 0 °C. $NEt(iPr)_2$ (261 µL, 1.5 mmol, 3.0 eq) was added dropwise and the reaction mixture was stirred at rt. After 20 minutes, a second portion of **BT-SCF_3** (200 mg, 0.50 mmol) was added followed by a third portion (200 mg, 0.50 mmol) after an additional 20 minutes. The reaction was allowed to stir at rt for a further 80 minutes (total reaction time of 2 h) before being concentrated *in vacuo* and purified by column chromatography over silica gel.

Characterization Data for Deoxytrifluoromethylthiolation Products:

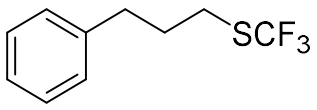
(4-Phenylbutyl)(trifluoromethyl)sulfane



Prepared from 4-phenyl-1-butanol (76 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (100 mg, 0.43 mmol, 85%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.31 (tm, *J*=7.7, 2H, H_{Ar}), 7.23 – 7.17 (m, 3H, H_{Ar}), 2.93 – 2.88 (m, 2H, CH_2), 2.68 – 2.63 (m, 2H, CH_2), 1.79 – 1.72 (m, 4H, CH_2) **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -41.1. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 141.8 (C_q), 131.3 (q, *J*=306, CF_3), 128.6 (CH), 128.5 (CH), 126.1 (CH), 35.3 (CH_2), 30.3 (CH_2), 29.9 (q, *J*=2, CH_2), 29.1 (CH_2). **HRMS (EI)**: m/z calculated for $[C_{11}H_{13}F_3S]^+$ ($[M]^+$): 234.0685, measured: 234.0690. **IR (ATR):** ν (cm^{-1}): 3063, 3028, 2927, 2857, 2360, 2342, 1733, 1687, 1604, 1496, 1454, 1309, 1271, 1245, 1218, 1148, 1103, 1031, 909, 806, 744, 698, 653.

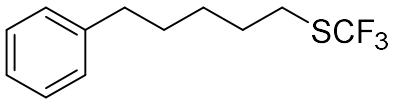
(3-phenylpropyl)(trifluoromethyl)sulfane



Prepared from 3-phenyl-1-propanol (68 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (81 mg, 0.37 mmol, 74%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.31 (tm, *J*=7.5, 2H, H_{Ar}), 7.23 (tt, *J*=7.3, 2.0, 1H, H_{Ar}), 7.19 (dm, *J*=7.5, 2H, H_{Ar}), 2.89 (t, *J*=7.3, 2H, CH_2), 2.75 (t, *J*=7.5, 2H, CH_2), 2.04 (quin, *J*=7.5, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -41.8. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 140.6 (C_q), 131.3 (q, *J*=306, CF_3), 128.7 (CH), 128.6 (CH), 126.4 (CH), 34.5 (CH_2), 31.1 (CH_2), 29.3 (q, *J*=2, CH_2). **HRMS (EI)**: m/z calculated for $[C_{10}H_{11}F_3S]^+$ ([M]$^+$): 220.0528, measured: 220.0520. **IR (ATR):** ν (cm^{-1}): 3064, 3029, 2928, 1604, 1496, 1454, 1422, 1290, 1099, 1030, 970, 909, 859, 742, 698.

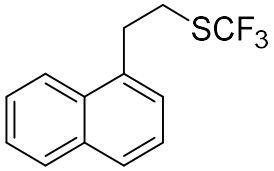
(5-Phenylpentyl)(trifluoromethyl)sulfane



Prepared from 5-phenyl-1-pentanol (84 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (91 mg, 0.37 mmol, 73%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.32 – 7.27 (m, 2H, H_{Ar}), 7.22 – 7.16 (m, 3H, H_{Ar}), 2.88 (*J*=7.5, 2H, CH_2), 2.63 (dd, *J*=7.8, 7.5, 2H, CH_2), 1.78 – 1.61 (m, 4H, CH_2), 1.51 – 1.40 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -41.1. **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 142.3 (C_q), 131.3 (q, *J*=306, CF_3), 128.5 (CH), 128.5 (CH), 125.9 (CH), 35.8 (CH_2), 30.9 (CH_2), 29.9 (q, *J*=2, CH_2), 29.5 (CH_2), 28.2 (CH_2). **HRMS (EI)**: m/z calculated for $[C_{12}H_{15}F_3S]^+$ ([M]$^+$): 248.0841, measured 248.0839. **IR (ATR):** ν (cm^{-1}): 3028, 2934, 2859, 1604, 1496, 1454, 1297, 1147, 1102, 1031, 913, 797, 746, 697.

(2-(Naphthalen-1-yl)ethyl)(trifluoromethyl)sulfane

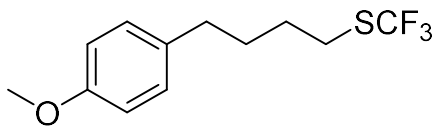


Prepared from 2-(naphthalen-1-yl)ethan-1-ol (86 mg, 0.50 mmol) using Method A and isolated as a colourless oil (95 mg, 0.37 mmol, 74%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.00 (dm, *J*=8.2, 1H, H_{Ar}), 7.92 (dm, *J*=7.7, 1H, H_{Ar}), 7.82 (d, *J*=8.2, 1H, H_{Ar}), 7.62 – 7.52 (m, 2H, H_{Ar}), 7.46 (dd, *J*= 8.2, 7.0, 1H, H_{Ar}), 7.39 (dm, *J*=7.1, 1H, H_{Ar}), 3.50 (dd, *J*=9.5, 6.4, 2H, CH_2), 3.30 – 3.25 (m, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -41.1. **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 136.0 (C_q), 134.1 (C_q), 131.5 (C_q), 131.4 (q, *J*=306, CF_3), 129.2 (CH), 127.9 (CH), 126.9 (CH), 126.6 (CH), 125.9 (CH), 125.7 (CH), 123.1 (CH), 33.6 (CH_2), 30.6 (q, *J*=2, CH_2). **HRMS (EI)**: m/z calculated for $[C_{13}H_{11}F_3S]^+$ ([M]$^+$): 256.0528, measured 256.0536. **IR (ATR):** ν

(cm^{-1}): 3061, 2941, 1598, 1510, 1458, 1395, 1233, 1217, 1097, 1044, 1018, 965, 853, 793, 774, 755, 732, 698, 660.

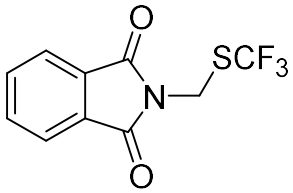
(4-(4-Methoxyphenyl)butyl)(trifluoromethyl)sulfane



Prepared from 4-(4-methoxyphenyl)-1-butanol (88 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (89 mg, 0.34 mmol, 68%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.10 (dm, *J*=8.2, 2H, H_{Ar}), 6.85 (dm, *J*=8.2, 2H, H_{Ar}), 3.80 (s, 3H, CH_3), 2.90 (t, *J*=6.9, 2H, CH_2), 2.60 (t, *J*=7.0, 2H, CH_2), 1.76 – 1.68 (m, 4H, CH_2). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -41.1. **^{13}C NMR (156 MHz, Chloroform-*d*) δ** = 158.0 (C_q), 133.9 (C_q), 131.3 (q, *J*=306, CF_3), 129.4 (CH), 113.9 (CH), 55.4 (CH_3), 34.4 (CH_2), 30.6 (CH_2), 29.9 (q, *J*=2, CH_2), 29.01 (CH_2). **HRMS (EI)**: m/z calculated for $[C_{12}H_{15}F_3OS]^+$ ($[M]^+$): 264.0790, measured: 264.0798. **IR (ATR):** ν (cm^{-1}): 2935, 2858, 2837, 1612, 1584, 1511, 1464, 1442, 1421, 1300, 1245, 1176, 1148, 1102, 1036, 930, 820, 809, 755, 697. **R_f**: (*n*-pentane/CH_2Cl_2, 9:1): 0.29.

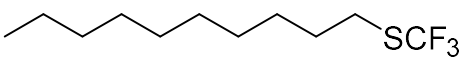
2-(((Trifluoromethyl)thio)methyl)isoindoline-1,3-dione



Prepared from *N*-hydroxymethylphthalimide (72 mg, 0.50 mmol) using Method A and isolated as an orange solid (71 mg, 0.27 mmol, 54%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.94 – 7.88 (m, 2H, H_{Ar}), 7.80 – 7.75 (m, 2H, H_{Ar}), 5.09 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -40.7. **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 166.4 (C_q), 134.7 (CH), 131.9 (C_q), 130.3 (q, *J*=308, CF_3), 124.0 (CH), 36.5 (q, *J*=3, CH_2). **IR (ATR):** ν (cm^{-1}): 3002, 2928, 1780, 1713, 1627, 1610, 1466, 1412, 1380, 1308, 1294, 1154, 1102, 972, 912, 829, 795, 756, 717, 697, 680.

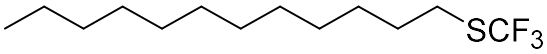
Decyl(trifluoromethyl)sulfane



Prepared from 1-decanol (96 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (107 mg, 0.44 mmol, 88%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 2.87 (t, *J*=7.4, 2H, CH_2SCF_3), 1.74 – 1.63 (m, 2H, CH_2), 1.45 – 1.34 (m, 2H, CH_2), 1.33 – 1.23 (m, 12H, CH_2), 0.88 (t, *J*=7.0, 3H, CH_3). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -42.0. **^{13}C NMR (101 MHz, Chloroform-*d*) δ =** 131.4 (q, *J*=306, SCF_3), 32.1 (CH_2), 30.0 (q, *J*=3, CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 22.8 (CH_2), 14.2 (CH_3). **IR (ATR):** ν (cm^{-1}): 2925, 2855, 1466, 1150, 1108, 756, 721.

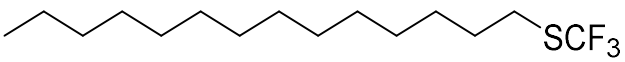
Dodecyl(trifluoromethyl)sulfane



Prepared from 1-dodecanol (112 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (110 mg, 0.41 mmol, 81%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 2.87 (t, *J*=7.4, 2H, CH_2), 1.73 – 1.64 (m, 2H, CH_2), 1.44 – 1.35 (m, 2H, CH_2), 1.34 – 1.19 (m, 16H, CH_2), 0.88 (t, *J*=6.8, 3H, CH_3). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -42.0. **^{13}C NMR (101 MHz, Chloroform-*d*) δ =** 131.3 (q, *J*=305, CF_3), 32.0 (CH_2), 30.0 (q, *J*=2, CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 22.8 (CH_2), 14.2 (CH_3) *Note: two ^{13}C peaks are not observed due to overlapping.* **HRMS (EI)**: m/z calculated for $[C_{12}H_{25}S]^+$ ($[M-CF_3]^+$): 201.1671, measured 201.1693. *Note: a molecular ion peak could not be identified by EI*. **IR (ATR):** ν (cm^{-1}): 2924, 2854, 1466, 1378, 1299, 1151, 1110, 756, 721.

Tetradecyl(trifluoromethyl)sulfane

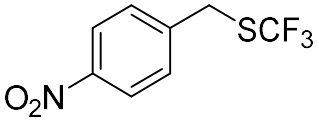


Prepared from 1-tetradecanol (**1**07 mg, 0.50 mmol) using Method A and isolated as a colourless liquid (116 mg, 0.39 mmol, 78%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 2.87 (t, *J*=7.5, 2H, CH_2), 1.69 (quin, *J*=7.5, 2H, CH_2), 1.42 – 1.36 (m, 2H, CH_2), 1.34 – 1.21 (m, 20H, CH_2), 0.88 (t, *J*=7.0, 3H). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -41.2 . **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 134.6 (q, *J*=306, CF_3), 32.1 (CH_2), 30.0 (q, *J*=2, CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 28.7 (CH_2),

22.9 (CH_2), 14.3 (CH_3) *Note: one ^{13}C peak is not observed due to overlapping.* **CHNS Elemental Analysis:** calculated for $C_{15}H_{29}F_3S$: C 60.37; H 9.79; N 0.00, S 10.74; measured: C 60.39; H 9.28; N 0.00; S 10.76. **IR (ATR):** ν (cm^{-1}): 2923, 2854, 1466, 1378, 1308, 1151, 1110, 756, 721. **R_f**: (*n*-pentane): 0.93.

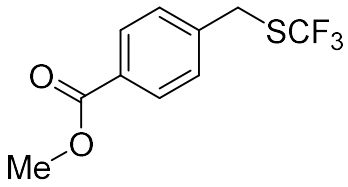
(4-Nitrobenzyl)(trifluoromethyl)sulfane



Prepared from (4-nitrophenyl)methanol (77 mg, 0.50 mmol,) using Method A and isolated as a orange liquid (104 mg, 0.44 mmol, 88%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.20 (dm, *J*=8.8, 2H, H_{Ar}), 7.53 (dm, *J*=8.8, 2H, H_{Ar}), 4.18 (s, 2H). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -41.2. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 147.7 (C_q), 143.2 (C_q), 130.4 (q, *J*=307, CF_3), 129.9 (CH), 124.2 (CH), 33.6 (q, *J*=3, CH_2). **HRMS (EI)**: m/z calculated for $[C_8H_6F_3NO_2S]^+$ ($[M]^+$): 237.0066, measured 237.0070. **IR (ATR):** ν (cm^{-1}): 3113, 3083, 2946, 2859, 1931, 1684, 1602, 1519, 1495, 1424, 1344, 1257, 1203, 1095, 1015, 973, 890, 858, 820, 802, 755, 707.

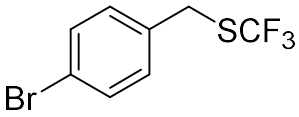
Methyl 4-(((trifluoromethyl)thio)methyl)benzoate



Prepared from methyl 4-(hydroxymethyl)benzoate (83 mg, 0.50 mmol) using Method A and isolated as a colourless liquid (118 mg, 0.47 mmol, 94%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.02 (d, *J*=8.4, 2H, H_{Ar}), 7.41 (d, *J*=8.4, 2H, H_{Ar}), 4.13 (s, 2H, CH_2), 3.91 (s, 3H, CH_3). **^{19}F NMR (565 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 166.7 (C_q), 140.5 (C_q), 130.6 (q, *J*=307, CF_3), 130.2 (CH), 130.0 (C_q), 129.0 (CH), 52.3 (CH_3), 34.0 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_{10}H_9F_3O_2S]^+$ ($[M]^+$): 250.0270, measured: 250.0257. **IR (ATR):** ν (cm^{-1}): 2954, 1719, 1612, 1577, 1509, 1436, 1415, 1279, 1179, 1145, 1097, 1020, 966, 890, 860, 838, 797, 774, 756, 725, 713.

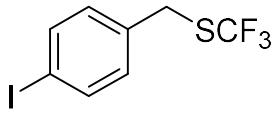
(4-Bromobenzyl)(trifluoromethyl)sulfane



Prepared from (4-bromophenyl)methanol (94 mg, 0.50 mmol) using Method A and isolated as a colourless liquid (121 mg, 0.45 mmol, 89%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.46 (d, *J*=8.4, 2H, H_{Ar}), 7.22 (d, *J*=8.4, 2H, H_{Ar}), 4.07 (s, 2H, CH_2). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -41.4. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 134.4 (C_q), 132.2 (CH), 130.6 (q, *J*=308, CF_3), 130.7 (CH), 122.2 (C_q), 33.8 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_6BrF_3S]^+$ ($[M]^+$): 269.9320, measured: 269.9326. **IR (ATR):** ν (cm^{-1}): 2928, 1592, 1488, 1441, 1421, 1403, 1254, 1144, 1098, 1070, 1011, 880, 828, 816, 804, 756, 741, 723, 681.

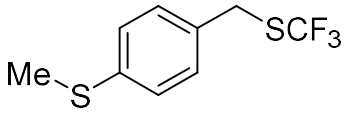
(4-Iodobenzyl)(trifluoromethyl)sulfane



Prepared from (4-iodophenyl)methanol (117 mg, 0.50 mmol) using Method A and isolated as a yellow liquid (91 mg, 0.29 mmol, 57%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.67 (dm, *J*=8.5, 2H, H_{Ar}), 7.09 (dm, *J*=8.3, 2H, H_{Ar}), 4.04 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 138.1 (CH), 135.0 (C_q), 130.6 (q, J=307, CF_3), 130.9 (CH), 93.7 (C_q), 33.9 (q, *J*=2, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_6F_3IS]^+$ ($[M]^+$): 317.9181, measured: 317.9165. **IR (ATR):** ν (cm^{-1}): 3031, 2924, 1901, 1588, 1484, 1420, 1398, 1253, 1201, 1096, 1060, 1008, 961, 945, 879, 824, 809, 755, 739, 721, 679.

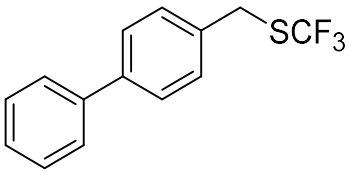
Methyl(4-(((trifluoromethyl)thio)methyl)phenyl)sulfane



Prepared from (4-(methylthio)phenyl)methanol (77 mg, 0.50 mmol) using Method A and isolated as an orange oil (107 mg, 0,45 mmol, 90%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.26 (dm, *J*=8.5, 2H, H_{Ar}), 7.22 (dm, *J*=8.4, 2H, H_{Ar}), 4.08 (s, 2H, CH_2), 2.47 (s, 3H, CH_3). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -41.4. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 138.7 (C_q), 131.7 (C_q), 130.7 (q, *J*=308, CF_3), 129.5 (CH), 126.8 (CH), 34.0 (q, *J*=3, CH_2), 15.7 (CH_3). **HRMS (EI):** m/z calculated for $[C_9H_9F_3S_2]^+$ ($[M]^+$): 238.0092, measured: 238.0103. **IR (ATR):** ν (cm^{-1}): 3024, 2985, 2923, 1682, 1600, 1494, 1439, 1405, 1254, 1143, 1092, 1016, 968, 957, 878, 826, 814, 755, 742, 727, 687. **R_f**: (*n*-pentane/CH_2Cl_2, 9:1): 0.55.

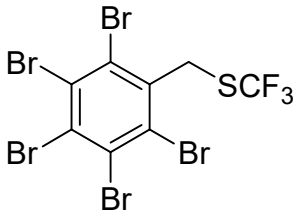
([1,1'-biphenyl]-4-ylmethyl)(trifluoromethyl)sulfane



Prepared from (1,1'-biphenyl-4-yl)methanol (92 mg, 0.50 mmol) using Method A and isolated as a white solid (89 mg, 0.33 mmol, 67%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.63 – 7.58 (m, 4H, H_{Ar}), 7.50 – 7.36 (m, 5H, H_{Ar}), 4.19 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 141.1 (C_q), 140.5 (C_q), 134.1 (C_q), 130.9 (q, *J*=307, CF_3), 129.5 (CH), 129.0 (CH), 127.7 (CH), 127.7 (CH), 127.2 (CH), 34.1 (q, *J*=2, CH_2). **HRMS (EI):** m/z calculated for $[C_{14}H_{11}F_3S]^+$ ($[M]^+$): 268.0528, measured: 268.0519. **IR (ATR):** ν (cm^{-1}): 3033, 2924, 1487, 1452, 1441, 1408, 1096, 1006, 844, 769, 755, 736, 714, 688.

((Perbromophenyl)methyl)(trifluoromethyl)sulfane

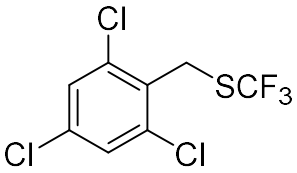


Prepared from (perbromophenyl)methanol (251 mg, 0.50 mmol) using Method A and isolated as a white solid (132 mg, 0.22 mmol, 45%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 4.73 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -40.9. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 137.3 (C_q), 130.4 (q, *J*=307, CF_3), 130.0 (C_q), 129.8 (C_q), 127.7 (C_q), 40.6 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_2Br_5F_3S]^+$ ($[M]^+$): 581.5741, measured: 581.5741. **IR (ATR):** ν (cm^{-1}): 2923, 2853, 2223, 1514, 1460, 1416, 1405, 1337, 1322,

1307, 1271, 1256, 1229, 1213, 1189, 1164, 1148, 1098, 1061, 899, 866, 754, 702, 666. **R_f**: (*n*-pentane): 0.70.

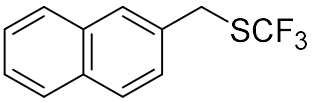
(2,4,6-Trichlorobenzyl)(trifluoromethyl)sulfane



Prepared from (2,4,6-trichlorophenyl)methanol (106 mg, 0.50 mmol) using Method A and isolated as a colourless liquid (135 mg, 0.46 mmol, 91%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.36 (s, 2H, H_{Ar}), 4.39 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 136.6 (C_q), 134.9 (C_q), 130.6 (C_q), 130.6 (q, *J*=307, CF_3), 128.6 (CH), 29.3 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_4Cl_3F_3S]^+$ ($[M]^+$): 293.9046, measured: 293.9025. **IR (ATR):** ν (cm^{-1}): 3083, 2927, 2853, 1729, 1579, 1550, 1441, 1420, 1391, 1376, 1257, 1236, 1207, 1157, 1099, 1072, 897, 874, 856, 811, 785, 755, 735, 679, 658. **R_f**: (*n*-pentane): 0.87.

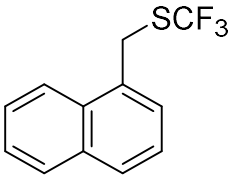
(Naphthalen-2-ylmethyl)(trifluoromethyl)sulfane



Prepared from naphthalen-2-ylmethanol (79 mg, 0.50 mmol) using Method A and isolated as a pale yellow solid (70 mg, 0.29 mmol, 58%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.89 – 7.79 (m, 4H, H_{Ar}), 7.56 – 7.45 (m, 3H, H_{Ar}), 4.31 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 133.4 (C_q), 133.0 (C_q), 132.5 (C_q), 130.9 (q, *J*=307, CF_3), 128.9 (CH), 128.1 (CH), 127.9 (CH), 127.9 (CH), 126.7 (CH), 126.6 (CH), 126.5 (CH), 34.7 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_{12}H_9F_3S]^+$ ($[M]^+$): 242.0372, measured: 242.0368. **IR (ATR):** ν (cm^{-1}): 3049, 2927, 1598, 1578, 1512, 1453, 1398, 1353, 1250, 1236, 1219, 1138, 1097, 1017, 970, 950, 882, 867, 799, 791, 773, 756, 740, 712.

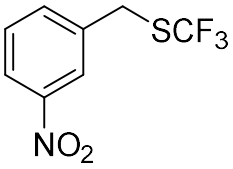
(Naphthalen-1-ylmethyl)(trifluoromethyl)sulfane



Prepared from naphthalen-1-ylmethanol (79 mg, 0.50 mmol) using Method A and isolated as a pale yellow oil (46 mg, 0.19 mmol, 38%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.05 (d, *J*=8.4, 1H, H_{Ar}), 7.91 (dm, *J*=8.0, 1H, H_{Ar}), 7.85 (d, *J*=8.3, 1H, H_{Ar}), 7.61 (ddd, *J*=8.4, 6.9, 1.5, 1H, H_{Ar}), 7.58 – 7.50 (m, 2H, H_{Ar}), 7.44 (dd, *J*=8.2, 7.0, 1H, H_{Ar}), 4.61 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.7. **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 134.1 (C_q), 131.9 (C_q), 130.9 (q, *J*=307, CF_3), 130.2 (C_q), 129.4 (CH), 129.2 (CH), 128.2 (CH), 126.9 (CH), 126.3 (CH), 125.5 (CH), 123.3 (CH), 32.2 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_{12}H_9F_3S]^+$ ($[M]^+$): 242.0372, measured: 242.0371. **IR (ATR):** ν (cm^{-1}): 3049, 2927, 1598, 1578, 1512, 1453, 1398, 1353, 1250, 1236, 1219, 1138, 1097, 1017, 970, 950, 882, 867, 799, 791, 773, 756, 740, 712.

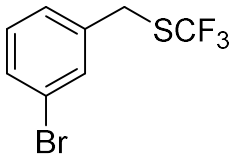
(3-Nitrobenzyl)(trifluoromethyl)sulfane



Prepared from (3-nitrophenyl)methanol (59 µL, 0.50 mmol) using Method A and isolated as a yellow liquid (105 mg, 0.44 mmol, 89%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.24 (s, 1H, H_{Ar}), 8.18 (dm, *J*=8.2, 1H, H_{Ar}), 7.70 (d, *J*=8.0, 1H, H_{Ar}), 7.55 (t, *J*=8.0, 1H, H_{Ar}), 4.20 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.2. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 148.5 (C_q), 137.9 (C_q), 135.0 (CH), 130.4 (q, *J*=307, CF_3), 130.0 (CH), 123.9 (CH), 123.1 (CH), 33.6 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_6F_3NO_2S]^+$ ($[M]^+$): 237.0066, measured: 237.0067. **IR (ATR):** ν (cm^{-1}): 3060, 2927, 2846, 1596, 1571, 1475, 1428, 1253, 1202, 1099, 1072, 997, 910, 888, 868, 849, 785, 756, 733, 708, 682, 667.

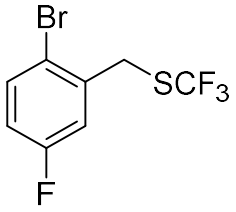
(3-Bromobenzyl)(trifluoromethyl)sulfane



Prepared from (3-bromophenyl)methanol (60 µL, 0.50 mmol) using Method A and isolated as a colourless liquid (113 mg, 0.42 mmol, 83%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.51 (t, *J*=1.9, 1H, H_{Ar}), 7.44 (ddd, *J*=7.8, 2.0, 1.3, 1H, H_{Ar}), 7.28 (dt, *J*=7.7, 1.5, 1H, H_{Ar}), 7.22 (t, *J*=7.8, 1H, H_{Ar}), 4.07 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.4. **^{13}C NMR (101 MHz, Chloroform-*d*)** δ = 137.6 (C_q), 132.0 (CH), 131.3 (CH), 130.6 (q, *J*=307, CF_3), 130.5 (CH), 127.6 (CH), 122.9 (C_q), 33.7 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_6BrF_3S]^+$ ($[M]^+$): 269.9320, measured: 269.9320. **IR (ATR):** ν (cm^{-1}): 3060, 2927, 2846, 1596, 1571, 1475, 1428, 1253, 1202, 1099, 1072, 997, 910, 888, 868, 849, 785, 756, 733, 708, 682, 667.

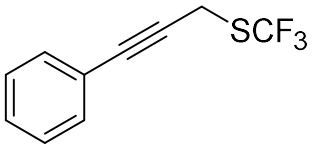
(2-Bromo-5-fluorobenzyl)(trifluoromethyl)sulfane



Prepared from (2-bromo-5-fluorophenyl)methanol (103 mg, 0.50 mmol) using Method A and isolated as a colourless liquid (96 mg, 0.33 mmol, 67%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.54 (dd, *J*=8.8, 5.3, 1H, H_{Ar}), 7.15 (dd, *J*=8.9, 3.0, 1H, H_{Ar}), 6.92 (ddd, *J*=8.7, 7.8, 3.9, 1H, H_{Ar}), 4.17 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*)** δ = -41.2 (SCF_3), -113.7 (F_{Ar}). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 162.0 (d, *J*=248, C_qF), 137.4 (d, *J*=8, C_q), 134.5 (d, *J*=8, CH), 130.7 (q, *J*=307, CF_3), 118.7 (C_q), 118.1 (d, *J*=24, CH), 117.1 (d, *J*=22, CH), 34.7 (qd, *J*=3, 2, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_5BrF_4S]^+$ ($[M]^+$): 287.9231, measured: 287.9232. **IR (ATR):** ν (cm^{-1}): 3079, 2924, 1605, 1583, 1469, 1440, 1409, 1274, 1254, 1237, 1146, 1098, 1032, 958, 899, 876, 862, 812, 775, 755, 742, 731, 679.

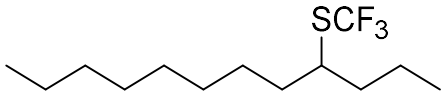
(3-Phenylprop-2-yn-1-yl)(trifluoromethyl)sulfane



Prepared from 3-phenyl-2-propyn-1-ol (62 µL, 0.50 mmol) using Method A and isolated as a yellow liquid (72 mg, 0.33 mmol, 66%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.48 – 7.43 (m, 2H, H_{Ar}), 7.38 – 7.30 (m, 3H, H_{Ar}), 3.90 (s, 2H, CH_2). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -42.6. **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 131.9 (CH), 130.5 (q, *J*=308, CF_3), 128.8 (CH), 128.5 (CH), 122.4 (C_q), 84.7 (C_q), 82.34 (C_q), 19.6 (q, *J*=3, CH_2). **HRMS (EI):** m/z calculated for $[C_{10}H_7F_3S]^+$ ([M]$^+$): 216.0215, measured: 216.0215. **IR (ATR):** ν (cm^{-1}): 3063, 2926, 1707, 1599, 1573, 1491, 1443, 1411, 1317, 1272, 1243, 1149, 1100, 1029, 1002, 981, 916, 885, 864, 754, 731, 714, 688.

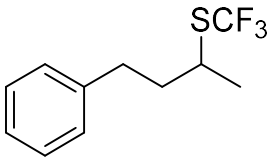
Dodecan-4-yl(trifluoromethyl)sulfane



Prepared from dodecan-4-ol (112.4 µL, 0.50 mmol) using Method B and isolated as a colourless liquid (83 mg of 1.96:1 mixture with dodecene regioisomers: calculated yield of dodecan-4-yl(trifluoromethyl)sulfane: 47%).

Only peaks corresponding to dodecan-4-yl(trifluoromethyl)sulfane reported: **^{1}H NMR (400 MHz, Chloroform-*d*) δ** = 3.16 (pent, *J*=6.5, 1H, CH), 1.73 – 1.55 (m, 4H, CH_2), 1.52 – 1.21 (m, 14 H, CH_2), 0.99 – 0.86 (m, 6H, CH_3). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -39.1. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 131.6 (q, *J*=307, CF_3), 46.6 (q, *J*=1, CH), 37.4 (CH_2), 35.2 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.5 (CH_2), 22.8 (CH_2), 19.8 (CH_2), 14.2 (CH_3), 13.9 (CH_3).

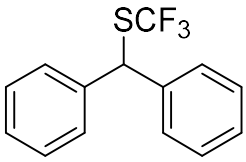
(4-Phenylbutan-2-yl)(trifluoromethyl)sulfane



Prepared from 4-phenylbutan-2-ol (**7b**, 77.4 µL, 0.50 mmol) using Method C and isolated as a colourless liquid (61 mg, 0.26 mmol, 52%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.31 (dd, *J*=7.3, 6.8, 2H, H_{Ar}), 7.24 – 7.19 (m, 3H, H_{Ar}), 3.32 (sext, *J*=6.9, 1H, CH), 2.82 – 2.73 (m, 2H, CH_2), 2.02 – 1.90 (m, 2H, CH_2), 1.48 (d, *J*=6.9, 3H, CH_3). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -38.3. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 141.0 (C_q), 131.3 (q, *J*=306, CF_3), 128.7 (CH), 128.5 (CH), 126.3 (CH), 40.6 (CH), 38.6 (CH_2), 32.9 (CH_2), 22.6 (q, *J*=1, CH_3). **HRMS (EI)**: m/z calculated for $[C_{11}H_{13}F_3S]^+$ ($[M]^+$): 234.0685, measured: 234.0685. **IR (ATR):** ν (cm^{-1}): 3029, 2931, 2863, 1604, 1496, 1455, 1383, 1297, 1247, 1145, 1100, 1031, 913, 822, 746, 698, 659.

Benzhydryl(trifluoromethyl)sulfane



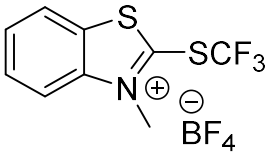
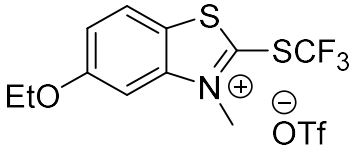
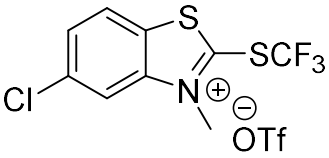
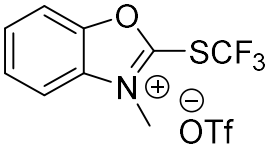
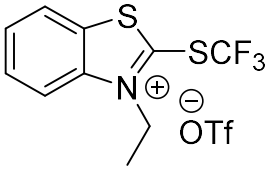
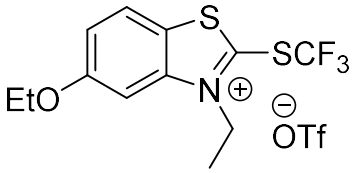
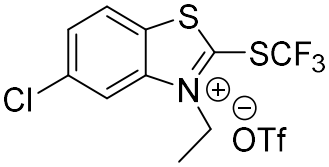
Prepared from diphenylmethanol (92 mg, 0.50 mmol) using Method D and isolated as a yellow liquid (74 mg, 0.28 mmol, 55%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.43 – 7.41 (m, 4H, H_{Ar}), 7.38 – 7.34 (m, 4H, H_{Ar}), 7.31 – 7.28 (m, 2H, H_{Ar}), 5.71 (s, 1H, CH). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -40.7. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 139.3 (C_q), 130.1 (q, *J*=308, CF_3), 128.9 (CH), 128.3 (CH), 128.1 (CH), 53.6 (q, *J*=2, CH). **HRMS (EI):** m/z calculated for $[C_{14}H_{11}F_3S]^+$ ($[M]^+$): 268.0528, measured: 268.0540. **IR (ATR):** ν (cm^{-1}): 3063, 3031, 1601, 1493, 1450, 1336, 1101, 1031, 1002, 967, 918, 826, 782, 746, 714, 693.

Example 13: Deoxytrilfuoromethylthiolation of Alcohols with BT-SCF_3 and BO-SCF_3 derivatives.

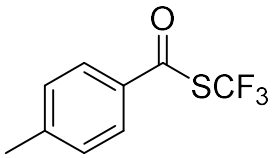
4-Bromobenzyl alcohol (1.0 eq, 0.1 mmol, 18.7 mg) was dissolved together with BT-SCF_3 or BO-SCF_3 derivative (1.25 eq) in MeCN (0.5 mL) and DIPEA (2.0 eq, 0.2 mmol, 35 mmL) was added dropwise at 0 °C. After the mixture was stirred for 2 h at rt, the mixture was concentrated *in vacuo.* The crude product was redissolved in $CDCl_3$ (0.75 mL) and Dibromomethane (7 mmL) was added as an internal standard.

Table 1: Deoxytrifluoromethylthiolation of Alcohols with different BT-SCF_3 or BO-SCF_3 derivatives. Given yields are ^{1}H-NMR-Yields, calculated using Dibromomethane as an internal standard.

BT-SCF_3 or BO-SCF_3 Derivative	**Yield of (4-bromobenzyl)(trifluoromethyl)sulfane**
	87 %
	98 %
	95 %
	65 %
	96 %
	97 %
	97 %

Example 14: Deoxytrifluoromethylthiolation of Carboxylic Acids with BT-SCF_3

S-(trifluoromethyl) 4-methylbenzothioate

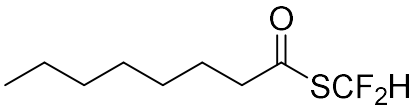


BT-SCF_3 (1.25 eq, 0.63 mmol, 250 mg) and NaH (60% in mineral oil, 3 eq, 1.5 mmol, 60 mg) were suspended in dry THF (7.5 mL) at -78 °C and 4-Methylbenzoic acid (1.0 eq, 0.5 mmol, 68.1 mg) was added dropwise to the mixture. The mixture was stirred for 30 min at -78 °C and was afterwards quenched with sat. NH_4Cl solution. The organic phase was washed with H_2O (3 x 20 mL), the aqueous phases were extracted with DCM (2 x 10 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, Pentane/Ethyl acetate). The product was obtained as a colourless oil (82 mg, 0.37 mmol, 74 %).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.75 (d, *J*=8.3, 2H, H_{Ar}), 7.31 (d, *J*=7.9, 2H, H_{Ar}), 2.44 (s, 3H, CH_3). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -39.6. The analytical data is in agreement to the literature (Glorius *ACS Catal.* **2018**, *8, 7*, 5842-5846).

Example 15: Deoxydifluoromethylthiolation of Carboxylic Acids with BT-SCF_2H

S-(difluoromethyl) octanethioate



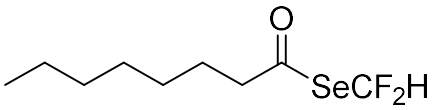
n-Octanoic Acid (1.0 eq, 0.5 mmol, 68.1 mg) and NaH (60% in mineral oil, 2 eq, 1.0 mmol, 60 mg) were suspended in dry THF (5.0 mL) and stirred for 1 h at rt. BT-SCF_2H (2.0 eq, 1.0 mmol, 381 mg) was added and the mixture was allowed to stir for another 2 h at rt. Afterwards, the mixture was

quenched with sat. NH_4Cl solution. The organic phase was washed with H_2O (3 x 20 mL), the aqueous phases were extracted with DCM (2 x 10 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, Pentane). The product was obtained as a colourless oil (92 mg, 0.44 mmol, 87 %).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.30 (t, *J*=55.1, 1H, CF_2H), 2.61 (t, *J*=7.5, 2H, CH_2), 1.78 – 1.60 (m, 2H, CH_2), 1.38 – 1.19 (m, 8H, CH_2), 0.89 (t, *J*=7.0, 3H, CH_3). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -100.1 (d, *J*=55). The analytical data is in agreement to the literature (Wang, *Angew. Chem. Int. Ed*. **2018**, *57*, 1663-1667).

Example 16: Deoxydifluoroselenylation of Carboxylic Acids with BT-$SeCF_2H$

Se-(difluoromethyl) octaneselenoate

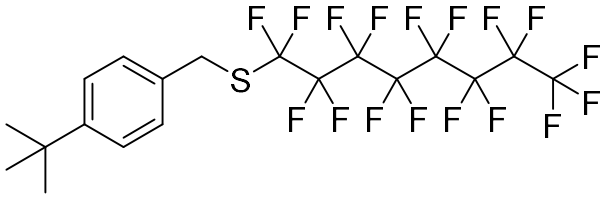


n-Octanoic acid (1.0 eq, 0.5 mmol, 72.1 mg) and NaH (2 eq, 1.0 mmol, 24 mg) were suspended in dry THF (5.0 mL) and stirred for 15 min at 0 °C. BT-$SeCF_2H$ (1.05 eq, 0.525 mmol, 225 mg) was added and the mixture was allowed to stir for another 2 h at rt. Afterwards, the mixture was quenched with sat. NH_4Cl solution. The organic phase was washed with H_2O (1 x 5 mL), the aqueous phases were extracted with DCM (2 x 10 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, Pentane). The product was obtained as a colourless oil (53 mg, 0.21 mmol, 42 %).

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.43 (t, *J*=53.5, 1H, CF_2H), 2.68 (t, *J*=7.5, 2H, CH_2,), 1.71 – 1.63 (m, 2H, CH_2), 1.37 – 1.22 (m, 8H, CH_2), 0.90 – 0.85 (m, 3H, CH_3). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -96.18 (d, *J*=54). **^{13}C NMR (126 MHz, Chloroform-*d*) δ** = 198.2 (t, *J*=3), 120.2 (t, *J*=283) 49.2 (t, *J*=3), 31.7, 29.0, 28.8, 25.0, 22.7, 14.2.

Example 17: Silver-Mediated Perfluoromethylthiolation of Alkyl Bromides with BT-SR$_F$ Reagents

(4-(*tert*-Butyl)benzyl)(perfluorooctoyl)sulfane

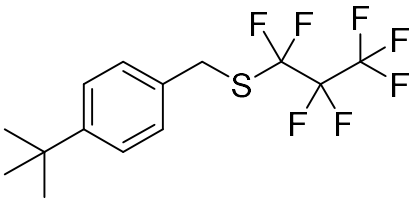


4-(*tert*)-Butyl benzyl bromide (46 µL, 0.25 mmol, 1.0 eq), **BT-SC$_8$F$_{17}$** (234 mg, 0.313 mmol, 1.25 eq) and silver oxide (116 mg, 0.500 mmol, 2.00 eq) were stirred in MeCN overnight. The mixture was then filtered through Celite (eluent: CH_2Cl_2) and concentrated *in vacuo*. Purification by column chromatography over silica gel afforded the product as a white solid (120 mg, 0.20 mmol, 80%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.38 (dm, *J*=8.4, 2H, H_{Ar}), 7.29 (dm, *J*=8.5, 2H, H_{Ar}), 4.17 (s, 2H, CH_2), 1.32 (s, 9H, *t*Bu). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -80.7 (d, *J*=3), -87.5 (d, *J*=4), -119.6, -121.1, -121.7, -121.8, -122.6, -126.1. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 152.3, 131.4, 129.0, 126.1, 34.7, 32.8 (t, *J*=9), 31.4. *Note: Eight fluoroalkyl ^{13}C peaks were not observed.* **HRMS (EI)**: m/z calculated for $[C_{19}H_{15}F_{17}S]^+$ ($[M]^+$): 598.0618, measured: 598.0648.

Example 18: Deoxyperfluoroalkylthiolation of Alcohols with BT-SR$_F$ Reagents

(4-(*tert*-Butyl)benzyl)(perfluoropropyl)sulfane



4-(*tert*)-Butyl benzyl alcohol (44 µL, 0.25 mmol, 1.0 eq) was dissolved in MeCN (1 mL), **BT-SC$_3$F$_7$** (156 mg, 0.31 mmol, 1.25 eq) was added and the reaction mixture was cooled to 0 °C. NEt(*i*Pr)$_2$ (87 µL, 0.50 mmol, 2.0 eq) was then added dropwise and the reaction mixture was stirred for 2 h at rt. Purification by column chromatography over silica gel afforded the product as a colourless oil (60 mg, 0.17 mmol, 69%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.39 (dm, *J*=8.4, 2H, H_{Ar}), 7.29 (dm, *J*=8.4, 2H, H_{Ar}), 4.17 (s, 2H, CH_2), 1.33 (s, 9H, *t*Bu). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -80.0 (t, *J*=9), -88.3 (tq, *J*=9, 5), -

124.0 (t, *J*=5). **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 151.4, 131.4, 129.0, 126.1, 34.8, 32.6 (m), 31.4. *Note: Two fluoroalkyl ^{13}C peaks were not observed.* **HRMS (EI)**: m/z calculated for $[C_{14}H_{15}F_7S]^+$ ($[M]^+$): 348.0777, measured: 348.0780.

Example 19: General Procedures for the Deoxytrifluoromethylselenylation reaction of Alcohols with BT-SeCF$_3$

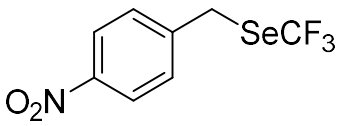
Method E: The benzylic or propargylic alcohol (0.20 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SeCF$_3$** (112 mg, 0.250 mmol, 1.25 eq) was added and the reaction mixture was cooled to 0 °C. NEt(*i*Pr)$_2$ (70 µL, 0.40 mmol, 2.0 eq) was then added dropwise and the reaction mixture was stirred for 2 h at rt. The reaction mixture was concentrated *in vacuo* and purified by column chromatography over silica gel.

Method F: The aliphatic alcohol (0.20 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SeCF$_3$** (112 mg, 0.250 mmol, 1.25 eq) was added and the reaction mixture was cooled to −40 °C. NEt(*i*Pr)$_2$ (70 µL, 0.40 mmol, 2.0 eq) was then added dropwise and the reaction mixture was stirred for 2 h at −40 °C. The reaction mixture was concentrated *in vacuo* and purified by column chromatography over silica gel.

Method G: The aliphatic alcohol (0.20 mmol, 1.0 eq) was dissolved in MeCN (0.50 M), **BT-SeCF$_3$** (179 mg, 0.400 mmol, 2.00 eq) was added and the reaction mixture was cooled to −40 °C. NEt(*i*Pr)$_2$ (70 µL, 0.40 mmol, 2.0 eq) was then added dropwise and the reaction mixture was stirred for 2 h at −40 °C. The reaction mixture was concentrated *in vacuo* and purified by column chromatography over silica gel.

Characterization Data for Deoxytrifluoromethylselenylation Products

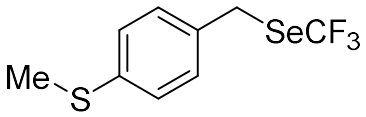
(4-Nitrobenzyl)(trifluoromethyl)selane



Prepared from (4-nitrophenyl)methanol (31 mg, 0.20 mmol) using Method E and isolated as a pale yellow liquid (50 mg, 0.18 mmol, 88%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.19 (dm, *J*=8.7, 2H, H_{Ar}), 7.51 (dm, *J*=8.7, 2H, H_{Ar}), 4.28 (s, 2H). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -34.0. **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 147.5 (C_q), 144.4 (C_q), 130.1 (CH), 124.2 (CH), 122.5 (q, *J*=332, CF_3), 28.1 (q, *J*=4, CH_2). **HRMS (EI)**: m/z calculated for $[C_8H_6F_3NO_2Se]^+$ ($[M]^+$): 284.9510, measured 284.9536. **IR (ATR):** ν (cm^{-1}): 3080, 2948, 2857, 1600, 1517, 1424, 1343, 1322, 1088, 1069, 1015, 973, 858, 798, 752, 738, 695.

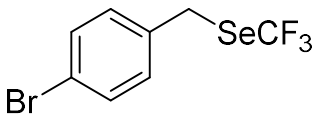
Methyl(4-(((trifluoromethyl)selanyl)methyl)phenyl)sulfane



Prepared from (4-(methylthio)phenyl)methanol (31 mg, 0.20 mmol) using Method E and isolated as a yellow liquid (43 mg, 0.15 mmol, 75%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.26 (dt, *J*=8.4, 2.1, 2H, H_{Ar}), 7.21 (dt, *J*=8.4, 2.1, 2H, H_{Ar}), 4.22 (s, 2H), 2.48 (s, 3H). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -34.2. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 138.4 (C_q), 132.8 (C_q), 129.6 (CH), 126.8 (CH), 123.0 (q, *J*=332, CF_3), 28.9 (q, *J*=2, CH_2), 15.7 (CH_3). **HRMS (EI):** m/z calculated for $[C_9H_9F_3SSe]^+$ ($[M]^+$): 285.9537, measured: 285.9545. **IR (ATR):** ν (cm^{-1}): 3022, 2984, 2922, 1599, 1493, 1438, 1404, 1325, 1275, 1222, 1198, 1087, 1069, 1015, 967, 957, 824, 811, 737, 719. **R_f**: (*n*-pentane/CH_2Cl_2, 9:1): 0.58.

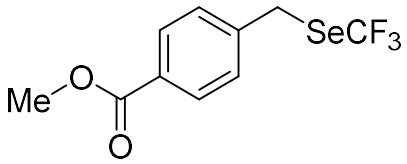
(4-Bromobenzyl)(trifluoromethyl)selane



Prepared from (4-bromophenyl)methanol (37 mg, 0.20 mmol,) using Method E and isolated as a yellow liquid (48 mg, 0.15 mmol, 76%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.46 (dm, *J*=8.5, 2H, H_{Ar}), 7.22 (dm, *J*=8.5, 2H, H_{Ar}), 4.18 (s, 2H, CH_2). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -34.2. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 135.5 (C_q), 132.2 (CH), 130.8 (CH), 122.8 (q, *J*=331, CF_3), 121.9 (C_q), 28.5 (q, *J*=2, CH_2). **HRMS (EI):** m/z calculated for $[C_8H_6BrF_3Se]^+$ ($[M]^+$): 317.8765, measured: 317.8758. **IR (ATR):** ν (cm^{-1}): 3035, 2952, 1899, 1591, 1487, 1420, 1402, 1276, 1218, 1195, 1090, 1068, 1011, 959, 944, 826, 800, 738, 713, 663. **R_f**: (*n*-pentane): 0.70.

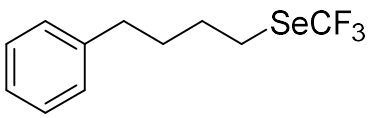
Methyl 4-(((trifluoromethyl)selanyl)methyl)benzoate



Prepared from methyl 4-(hydroxymethyl)benzoate (33 mg, 0.20 mmol) using Method E and isolated as a colourless liquid (55 mg, 0.19 mmol, 93%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.00 (dm, *J*=8.3, 2H, H_{Ar}), 7.40 (dm, *J*=8.3, 2H, H_{Ar}), 4.25 (s, 2H, CH_2), 3.91 (s, 3H, CH_3). **^{19}F NMR (565 MHz, Chloroform-*d*)** δ = -34.2. **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 166.7 (C_q), 141.7 (C_q), 130.3 (CH), 129.7 (C_q), 129.1 (CH), 123.7 (q, *J*=331, CF_3), 52.3 (CH_3), 28.7 (q, *J*=2, CH_2). **HRMS (EI):** m/z calculated for $[C_{10}H_9F_3O_2Se]^+$ ($[M]^+$): 297.9714, measured: 297.9712. **IR (ATR):** ν (cm^{-1}): 3000, 2953, 2845, 1931, 1717, 1611, 1576, 1509, 1436, 1415, 1367, 1313, 1278, 1223, 1194, 1181, 1088, 1069, 1019, 966, 863, 838, 811, 794, 768, 738, 703, 665. **R_f**: (*n*-pentane/CH_2Cl_2, 1:1): 0.48.

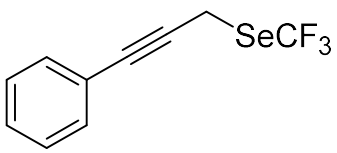
(4-Phenylbutyl)(trifluoromethyl)selane



Prepared from 4-phenyl-1-butanol (31 µL, 0.20 mmol) using Method F and isolated as a colourless liquid (31 mg, 0.11 mmol, 55%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.32 – 7.26 (m, 2H, H_{Ar}), 7.22 – 7.15 (m, 3H), 3.00 (t, *J*=7.3, 2H, CH_2), 2.65 (t, *J*=7.3, 2H, CH_2), 1.88 – 1.70 (m, 4H). **^{19}F NMR (565 MHz, Chloroform-*d*)** δ = -34.0. **^{13}C NMR (151 MHz, Chloroform-*d*)** δ = 141.9 (C_q), 128.5 (CH), 128.5 (CH), 126.1 (CH), 122.8 (q, *J*=330, CF_3), 35.3 (CH_2), 31.4 (CH_2), 29.9 (CH_2), 25.8 (q, *J*=1, CH_2). **HRMS (EI):** m/z calculated for $[C_{11}H_{13}F_3Se]^+$ ($[M]^+$): 282.0129, measured: 282.0141. **IR (ATR):** ν (cm^{-1}): 3028, 2927, 2856, 1604, 1496, 1454, 1254, 1224, 1198, 1092, 1030, 969, 908, 803, 737, 697. **R_f**: (*n*-pentane): 0.43.

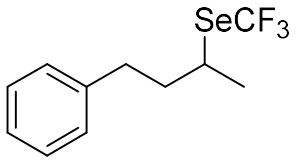
(3-Phenylprop-2-yn-1-yl)(trifluoromethyl)selane



Prepared from 3-phenyl-2-propyn-1-ol (26 mg, 0.20 mmol) using Method E and isolated as a colourless liquid (43 mg, 0.16 mmol, 82%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.42 – 7.40 (m, 2H, H_{Ar}), 7.32 – 7.28 (m, 3H, H_{Ar}), 3.90 (s, 2H, CH_2). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -34.5. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 131.8 (CH), 128.7 (CH), 128.5 (CH), 122.6 (q, *J*=332, CF_3), 122.5 (C_q), 85.0 (C_q), 83.5 (C_q), 11.7 (q, *J*=3, CH_2). **IR (ATR):** ν (cm^{-1}): 3060, 2929, 2190, 1664, 1598, 1491, 1443, 1408, 1318, 1271, 1200, 1119, 1090, 1070, 1030, 1002, 977, 916, 869, 843, 822, 755, 738, 712, 688, 669.

(4-Phenylbutan-2-yl)(trifluoromethyl)selane

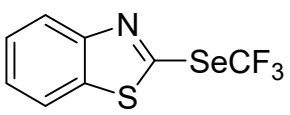


Prepared from 4-phenylbutan-2-ol (31 µL, 0.20 mmol, 1.0 eq) using Method G and isolated as a colourless liquid (25 mg, 0.088 mmol, 44%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.30 (tm, *J*=7.6, 2H, H_{Ar}), 7.23 – 7.18 (m, 3H, H_{Ar}), 3.53 (sext, *J*=7.0, 1H, CH), 2.82 – 2.72 (m, 2H, CH_2), 2.12 – 1.96 (m, 4H, CH_2), 1.63 (d, *J*=7.0, CH_3). **^{19}F NMR (565 MHz, Chloroform-*d*) δ** = -31.9. **^{13}C NMR (151 MHz, Chloroform-*d*) δ** = 140.9 (C_q), 128.6 (CH), 128.5 (CH), 126.3 (CH), 123.2 (q, *J*=331, CF_3), 39.5 (q, *J*=1), 39.3 (q, *J*=1), 33.8, 23.1 (q, *J*=1). **HRMS (EI):** m/z calculated for $[C_{11}H_{13}F_3Se]^+$ ($[M]^+$): 282.0129, measured: 282.0120. **IR (ATR):** ν (cm^{-1}): 3029, 2925, 2858, 1604, 1496, 1454, 1382, 1260, 1233, 1213, 1092, 1031, 912, 818, 738, 697.

Example 20: Alternative Method for the 3-Methyl-2-((trifluoromethyl)selanyl) benzo[d]thiazol-3-ium trifluoromethanesulfonate (BT-SeCF$_3$, Compound 5)

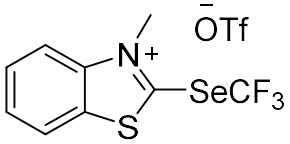
Synthesis of 2-(trifluoromethyl)selenyl)benzo[d]thiazole



Bis(benzothiazole)diselenide (4.20 g, 9.85 mmol, 0.50 eq) was suspended in methanol (100 mL, degassed using the freeze-pump-thaw technique) and THF (25 mL, degassed using the freeze-pump-thaw technique) in a 3-necked round-bottomed flask under argon and the mixture was cooled to 0 °C. $NaBH_4$ (745 mg, 19.7 mmol, 1 equiv) was added portionwise over 5 minutes and the mixture was stirred at 0 °C for an additional 10 minutes. HCl (1 M, aq., 100 mL, degassed by argon sparging) was added via cannula resulting in the formation of a grey precipitate. The mixture was then filtered under argon and the solid was washed with water (3 × 100 mL, degassed by argon sparging) and then dried under high vacuum for 30 minutes. Separately, a solution of CF_3I in DMF was prepared by attaching a balloon of CF_3I to a flask containing freeze-pump-thaw degassed DMF under N_2. This solution (110 mL, containing 6.3 g, 32 mmol, 1.6 equiv. of CF_3I) was transferred to the round-bottomed flask via cannula and the grey solid product was re-dissolved. The mixture was cooled to -40 °C and NaH (709 mg, 29.5 mmol, 1.50 equiv.) was added portionwise over 5 minutes. A balloon containing CF_3I (14.2 g, 72.8 mmol, 3.70 equiv) was then attached and the mixture was stirred under irradiation from UVA LEDs (λ_{max} = 365 nm) for 12 h during which time the reaction temperature reached ca. 40 °C. After completion of the reaction EtOAc (250 mL) and water (300 mL) were added and the layers separated. The organic phase was then washed with water (5 × 500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography over silica gel (eluent = *n*-pentane:DCM, 10:1) afforded 2-(trifluoromethyl)selenyl)benzo[d]thiazole as a white solid (2.95 g, 10.5 mmol, 53%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.13 (ddd, *J*=8.2, 1.3, 0.6, 1H, H_{Ar}), 7.90 (ddd, *J*=8.1, 1.3, 0.7, 1H, H_{Ar}), 7.53 (tm, *J*=7.7, 1H, H_{Ar}), 7.46 (tm, *J*=7.7, 1H, H_{Ar}). **^{19}F NMR (376 MHz, Chloroform-*d*) δ** = -33.2. **^{13}C NMR (151 MHz, Chloroform-*d*) δ =** 153.8 (C_q), 147.6 (C_q), 138.5 (C_q), 126.9 (CH), 126.5 (CH), 124.0 (CH), 122.2 (q, *J*=335, CF_3), 121.2 (CH). **HRMS (EI):** m/z calculated for $[C_8H_4F_3NSSe]^+$ ($[M]^+$): 282.9176, measured: 282.9174. **IR (ATR):** ν (cm^{-1}): 3066, 2924, 1557, 1453, 1409, 1313, 1277, 1232, 1012, 858, 738, 707, 670. **R_f**: (*n*-pentane/CH_2Cl_2, 10:1): 0.20.

Synthesis of 3-Methyl-2-((trifluoromethyl)selanyl)benzo[d]thiazol-3-ium trifluoromethanesulfonate

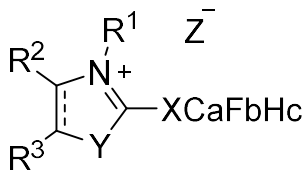


2-(trifluoromethyl)selenyl)benzo[d]thiazole (1.0 eq, 10.5 mmol, 2.96 g) was dissolved in dry CH_2Cl_2 (0.10 M) and methyl trifluoromethanesulfonate (3.0 eq, 31.5 mmol , 3.45 mL) was added dropwise. The reaction mixture was stirred at rt for 24 h and the product was precipitated with diethyl ether. The suspension was then filtered, and the residue washed with diethyl ether (3 × 100 mL). After drying in vacuo, BT-$SeCF_3$ was obtained as off-white solid (4.28 g, 9.59 mmol, 92%).

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ = 8.37 (d, *J*=7.8, 1H, H_{Ar}), 8.27 (d, *J*=8.6, 1H, H_{Ar}), 8.01 (t, *J*=8.3, 7.9, 1H, H_{Ar}), 7.93 (t, *J*=7.9, 1H, H_{Ar}), 4.47 (s, 3H, CH_3). **^{19}F NMR (376 MHz, Acetonitrile-d_3) δ** = -32.7 ($SeCF_3$), -79.3 ($S(O)_2CF_3$). **^{13}C NMR (126 MHz, Acetonitrile-d_3) δ** = 159.2 (C_q), 143.9 (C_q), 135.0 (C_q), 132.1 (CH), 131.1 (CH), 125.1 (CH), 122.7 (q, *J*=337, $SeCF_3$), 122.0 (q, *J*=321, $S(O)_2CF_3$), 119.3 (CH), 41.4 (CH_3). **CHNS Elemental Analysis**: calculated for $C_{10}H_7F_6NO_3S_2Se$: C 26.92; H 1.58; N 3.14, S 14.37; measured: C 27.00, H 1.97, N 3.14, S 14.50. **IR (ATR): ν (cm-1)**: 3098, 3064, 1577, 1489, 1461, 1442, 1388, 1252, 1223, 1187, 1151, 1140, 1101, 1079, 1054, 1043, 1028, 987, 962, 802, 766, 741, 729, 712.

Claims

1. A fluorine containing compound according to the general formulae (I)



(I)

wherein

- R^1 is C1-C20 alkyl;
- R^2, R^3 are in each case an alkyl, a cycloalkyl, an aryl, a heteroaryl, halogen, fluoroalkyl or both R^2 and R^3 are part of a cyclic system;
- X is S, O, Se, Te; preferably S, O, Se;
- Y is S, O;
- Z^- is $R^4SO_3^-$ with R^4 being H, C1-C10 alkyl, aryl, $C_aF_bH_c$, in particular – OTf ($CF_3SO_3^-$), p-Tos; Ph-SO_3-; or I^-, Cl^-, ClO_4^-, BF_4^-;
- a is 1-20, preferably 1-12, more preferably 1-8;
- b is (2a+1) - c;
- c is 0-10, preferably 0-5, more preferably 0, 1, 2.

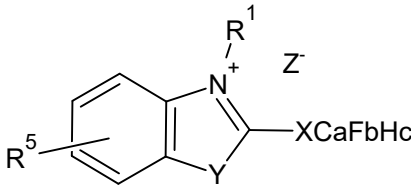
2. Compound according to claim 1, characterized in that R^1 is C1-C10 alkyl, preferably C1-C5 alkyl, more preferably C1-C3 alkyl.

3. Compound according to claim 1 or 2, characterized in that R^2 and R^3 are part of an aromatic system, preferably of a C6 aryl ring.

4. Compound according to one of the preceding claims, characterized in that

- R^1 is C1-C3 alkyl;
- R^2, R^3 are part of a unsubstituted or substituted C6 aryl ring or naphthyl ring,
- X is S, O, Se;
- Y is S, O;
- Z^- is $R^4SO_3^-$ with being R^4 being aryl, $C_aF_bH_c$, in particular – OTf ($CF_3SO_3^-$), p-Tos; Ph-SO_3-; or BF_4^-;
- a is 1-8;
- b is (2a+1) - c;
- c is 0, 1, 2.

5. Compound according to one of the preceding claims, characterized by the general formulae (II)

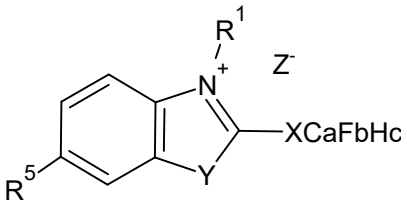


(II)

wherein R^1, X, Y, Z, a, b, c have the above meanings, and

wherein R^5 is absent or a C1-C10 alkyl, a C1-C10 alkoxy, in particular C1-C5 alkoxy, or a halogen, in particular Cl, Br.

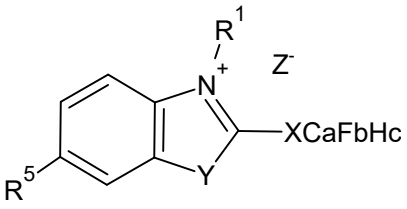
6. Compound according to one of the preceding claims, characterized by the general formulae (IIa)



(IIa)

wherein R^1, R^5, X, Z, a, b, c have the above meanings.

7. Compound according to claim 6, characterized by the general formulae (IIb)



(IIb)

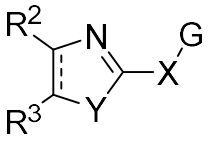
wherein

- R^1 is C1-C3 alkyl;
- R^5 is absent or C1-C5 alkoxy, or Cl, Br.

- X is S, O, Se;
- Y is S, O;
- Z^- being – OTf ($CF_3SO_3^-$), p-Tos; Ph-SO_3-; BF_4^-;
- a is 1-8;
- b is (2a+1) - c;
- c is 0, 1, 2.

8. Process for obtaining a compound according to one of the preceding claims, comprising the following steps:

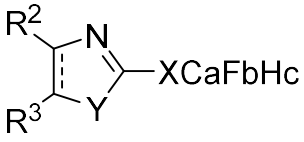
- providing a compound of general formulae (V)



(V)

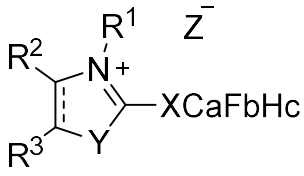
wherein G is H or a leaving group as starting material;

- reacting the compound of general formulae (V) with at least one fluoroalkylating agent thereby providing an intermediate compound of general formulae (VI)



(VI)

- alkylation of the ring nitrogen of general formulae (VI) thereby providing the compound of general formulae (I)



(I)

wherein R^1, R^2, R^3, X, Y, Z, a, b, c have the above meanings.

9. Process according to claim 8, characterized in that at least one fluoroalkylating agent is selected from a group containing a compound of general formulae (VII) $NaSO_2C_aF_bH_c$ wherein a, b, c have the above meanings.

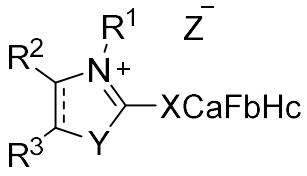
10. Process according to claim 8, characterized in that at least one fluoroalkylating agent is selected from a group containing a compound of general formulae (VIII) Hal $C_aF_bH_c$ wherein Hal is I, Br, or Cl and wherein a, b, c have the above meanings.

11. Process according to claim 8-10, characterized in that at least one alkylating agent selected from a group containing alkyl trifluoromethanesulfonate, alkyl iodide, alkyl sulfate is employed.

12. Use of a compound according to one of claims 1 - 7 as a nucleophilic reagent for transferring a fluorine-containing functional group onto high value organic compounds, in particular pharmaceutical and agrochemical targets.

Abstract

The present invention relates to a compound of general formulae (I)



(I).

12.3 Trifluoromethoxylation of (Hetero)arenes with Bis(trifluoromethyl) peroxide (BTMP)

12.3.1 Abstract

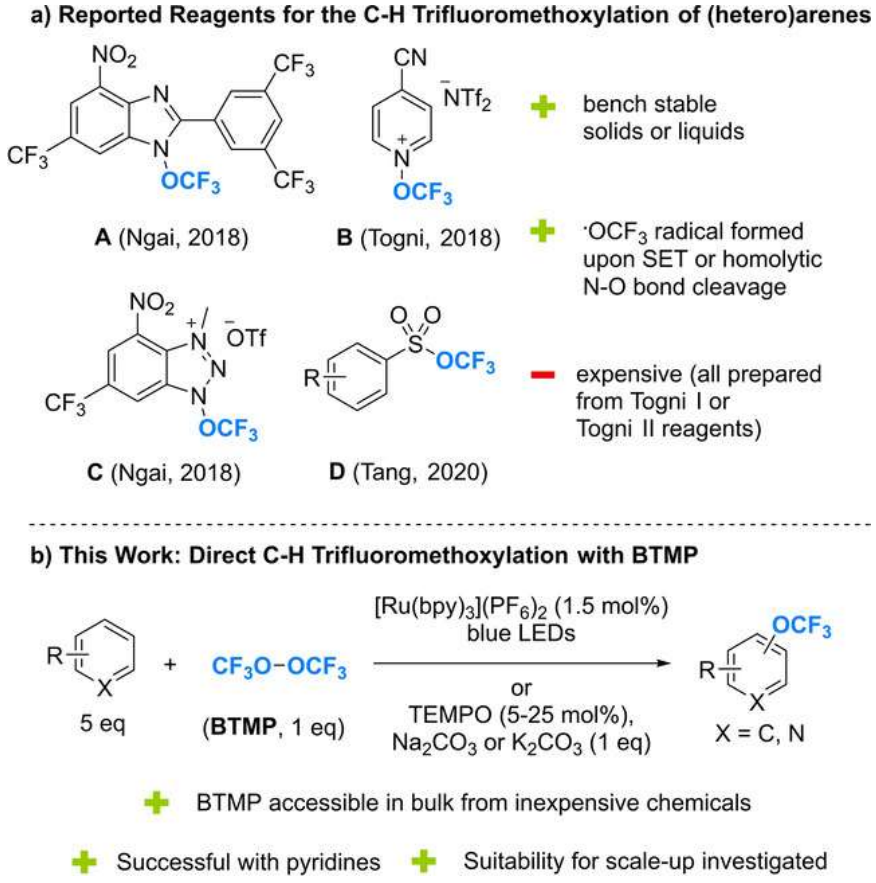
Trifluoromethoxylated (hetero)arenes are of great interest for several disciplines, especially in agro- and medicinal chemistry. Radical C−H trifluoromethoxylation of (hetero)arenes represents an attractive approach to prepare such compounds, but the high cost and low atom economy of existing $^{\cdot}OCF_3$ radical sources make them unsuitable for the large-scale synthesis of trifluoromethoxylated building blocks. Herein, we introduce bis(trifluoromethyl)peroxide (BTMP, CF_3OOCF_3) as a practical and efficient trifluoromethoxylating reagent that is easily accessible from inexpensive bulk chemicals. Using either visible light photoredox or TEMPO catalysis, trifluoromethoxylated arenes could be prepared in good yields under mild conditions directly from unactivated aromatics. Moreover, TEMPO catalysis allowed for the one-step synthesis of valuable pyridine derivatives, which have been previously prepared via multi-step approaches.

12.3.2 Publication

Fluorinated agrochemicals and pharmaceuticals are of great importance due to the beneficial effects fluorine and fluorinated groups can have on a molecule's potency, metabolic stability, selectivity and toxicity.[1] In the last three decades, compounds containing one or more fluorine atoms made up 22 % of all globally registered small-molecule drugs[1k] while, in the time period 1998–2020, 53 % of all new agrochemicals were organofluorine compounds.[1l] Trifluoromethoxylated arenes and heteroarenes are attracting increasing attention as up-and-coming fluorine-containing moieties. With a Hansch parameter (Π=1.04) in between that of SCF_3 (1.44) and CF_3 (0.88) and a notably lower electron-withdrawing influence than many other commonly employed fluorinated groups (σ_p=0.54 (CF_3), 0.50 (SCF_3), 0.35 (OCF_3)),[2] the OCF_3 moiety allows for a fine-tuning of a molecule's biological activity and bioavailability. Furthermore, fluorine-specific stereoelectronic effects result in unconventional conformational preferences not encountered with other substituents.[3] To date, several drugs (e. g. Pretomanid, Delamanid, Sonidegib, Riluzol, Celikalim) and agrochemicals (e. g. Indoxacarb, Thifluzamide, Flurprimidol) featuring an Ar-OCF_3 moiety, have been developed.[4]

Despite this great potential, the study of OCF_3-substituted (hetero)arenes has been hindered by the lack of practical methods to synthesize them.[4] Direct trifluoromethoxylation reactions, wherein the OCF_3 moiety is installed as an intact functional group onto an arene or heteroarene are especially scarce. With no electrophilic sources of the OCF_3 group available and cross-coupling methodologies hampered by the inherent instability of the $^{-}OCF_3$ anion towards β-fluoride elimination, radical

trifluoromethoxylation arguably represents the most attractive approach. In 2018, Ngai and co-workers reported a breakthrough in this area by introducing a bench stable reagent **A** (Scheme **1a**) that provides the ·OCF_3 radical upon photochemical activation.[5] Subsequent reports by the groups of Ngai, Togni and Tang disclosed additional ·OCF_3 sources (**B**-**D**), which could be employed in radical C−H trifluoromethoxylation reactions with unactivated arenes.[6] While these reagents are bench stable and convenient on a laboratory scale, each is prepared from either the Togni I or Togni II electrophilic trifluoromethylating reagents. The high cost of these precursors makes large-scale applications unpractical while stoichiometric amounts of organic by-products are produced, which must be separated from the reaction mixture.



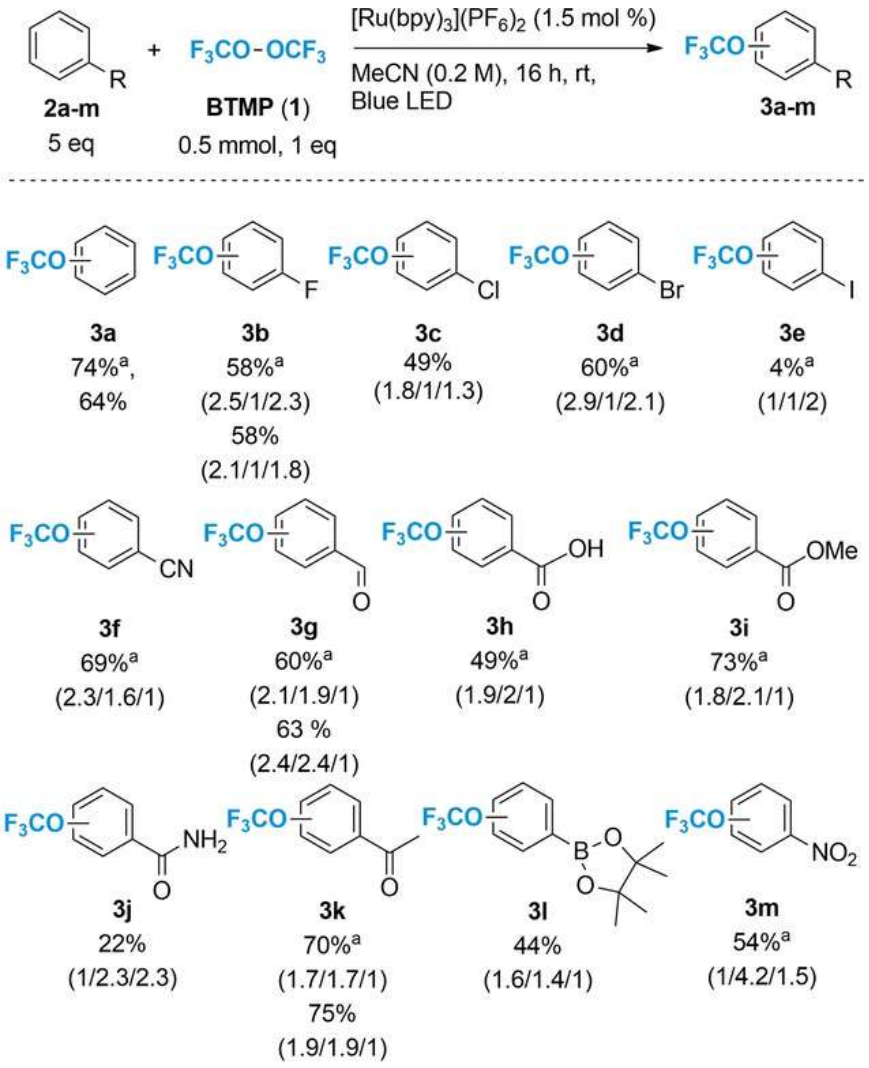
Scheme 1 Radical C−H trifluoromethoxylation of (hetero)arenes. a) Previously reported reagents. b) This work: BTMP as a practical ·OCF_3 source.

With the aim of developing a practical method suitable for larger scale production of trifluoromethoxylated arene and heteroarene building blocks, our attention was drawn to bis(trifluoromethyl)peroxide (BTMP, **1**) as a potential source of ·OCF_3. This compound can be prepared on a large scale from the inexpensive bulk chemicals CO and F_2, and is remarkably stable towards both thermal and photochemical decomposition.[7] A small number of studies demonstrate, however, that BTMP can transfer an OCF_3 group onto organic substrates, although the forcing

conditions (high temperature,[8] UVA light[9]) employed to activate the peroxide drastically limited the substrate scope and resulted in only low yields and selectivities. Here we report the successful application of BTMP as a practical trifluoromethoxylating reagent under mild conditions employing either visible light photoredox or TEMPO catalysis (Scheme **1b**). Using both activation modes, trifluoromethoxylated arenes could be prepared in a single step from simple aromatic feedstocks. The potential of these methods for the production of valuable OCF_3-containing building blocks is further demonstrated by the one-step preparation of (trifluoromethoxy)pyridines, which till now have been prepared via multi-step syntheses.

In an initial experiment, BTMP (**1**, 1 eq.) was condensed into an acetonitrile solution containing the photocatalyst $[Ru(bpy)_3][PF_6]_2$ (bpy=2,2'-bipyridine, 1 mol%) and benzene (**2a**, 10 eq.).[10] After 16 h irradiation with visible light from blue LEDs, we were delighted to observe efficient formation of (trifluoromethoxy)benzene **3a** in 48 % ^{19}F NMR yield (internal standard=$PhCF_3$). Working on the hypothesis that single electron transfer from the excited photocatalyst to BTMP followed by mesolysis results in $^{\cdot}OCF_3$ formation, alternative single electron reductants were tested.[11] In addition to light-mediated activation of BTMP by various photocatalysts, the simple metal salt CuCl (1 eq.) also led to the formation **3a** in 50 % NMR yield without light irradiation. Photocatalysis with $[Ru(bpy)_3][PF_6]_2$, however, remained the most efficient approach and optimization of the other reaction parameters led to a set of standard conditions that provided **3a** in 74 % NMR yield (1.5 mol% $[Ru(bpy)_3][PF_6]_2$, 5 eq. **2a**, 0.1 eq. KF, 0.2 M MeCN, blue LEDs, rt, 16 h).

The scope of the photocatalytic C–H trifluoromethoxylation with a selection of aromatic feedstocks is shown in Scheme **2**. A range of diverse substituents on the arene was tolerated, with electron-withdrawing groups generally leading to the highest yields. In most cases, BTMP provided similar yields of products **3** to those previously reported using reagents **A**-**D**. Deviations were observed, however, for benzonitrile **2f** and methyl benzoate **2i** with the corresponding trifluoromethoxylated arenes being delivered in significantly higher yields (**3f** = 69 %, **3i** = 73 %), while iodobenzene **2e** was much less efficiently converted (4 %). The successful synthesis of the halogenated arenes **3c** and **3d** as well as the boronic ester species **3l** is particularly noteworthy as these products can serve as OCF_3-containing building blocks for cross-coupling methodologies. The regioselectivity of the photocatalytic trifluoromethoxylation with BTMP also mirrored that obtained using the previously reported reagents **A**-**D** and reflects the inherent electronic properties of the aromatic substrates. In each case, only trace amounts of bis(trifluoromethoxy)arene side-products were observed in the crude reaction mixtures, while waste species derived from the $^{-}OCF_3$ by-product could be readily removed upon aqueous work-up.

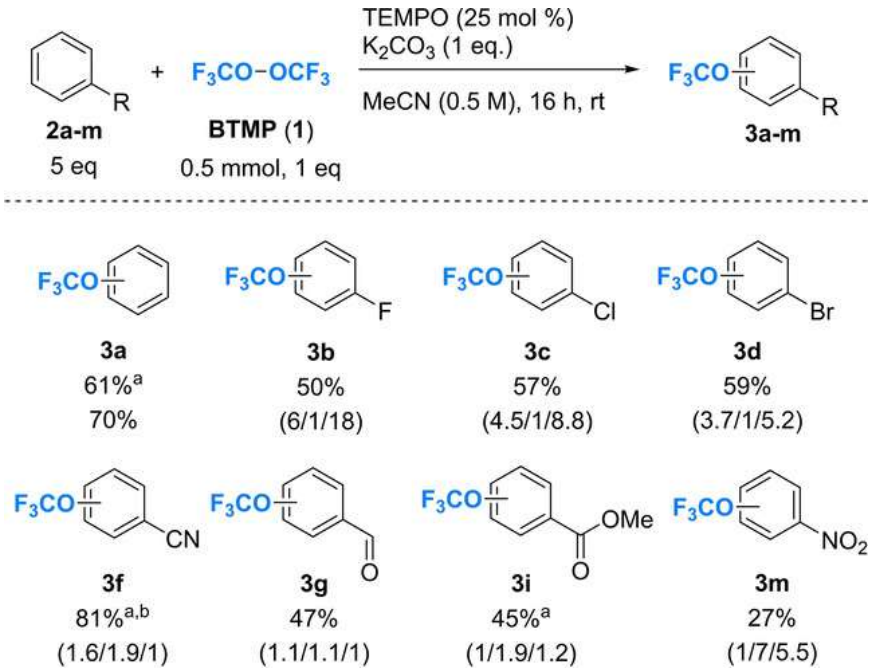


Scheme 2 Scope of the photocatalytic C–H trifluoromethoxylation of arenes using BTMP. ^{19}F NMR yields using $PhCF_3$ as an internal standard, ratio *ortho*-/*meta*-/*para*- determined by ^{19}F NMR shown in brackets. [a]With 0.1 eq. KF.

Having developed a set of efficient photocatalytic conditions, we next sought to investigate alternative approaches for activating BTMP, which do not require light irradiation. While initial results had identified metal salts such as CuCl as suitable stoichiometric activators, we were drawn to the recent report from Ngai and co-workers using catalytic amounts of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as a single electron shuttle with reagent **C**.[6c] TEMPO is significantly less expensive than $[Ru(bpy)_3][PF_6]_2$ while the avoidance of light irradiation brings practical advantages for potential large scale applications.[12] Benzene (**2a**, 5 eq.) and BTMP (1 eq.) were thus reacted with TEMPO (25 mol%) and inexpensive K_2CO_3 (1 eq.) as a basic additive in MeCN (0.5 M) at rt overnight. Analysis of the reaction mixture by ^{19}F NMR revealed the efficient formation of (trifluoromethoxy)benzene **3a** in 70 % yield. Furthermore, the low polarity of TEMPO means that

the benzene substrate can be used as the only solvent, with **3a** being delivered in 61 % ^{19}F NMR yield under neat conditions.

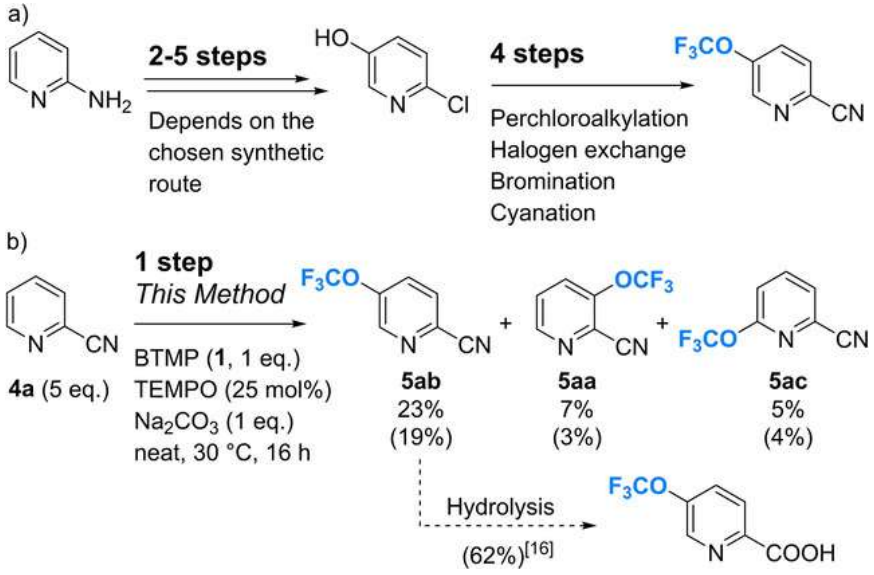
The efficiency of the TEMPO-catalyzed trifluoromethoxylation method with a selection of aromatics is shown in Scheme **3**. As for the photocatalytic reaction, a range of electron-poor and electron-neutral examples could be successfully employed in generally moderate to good yields up to 81 %. While the cyano- and methyl ester-substituted derivatives **3f** and **3i** could also be prepared in good yields under neat conditions (**3f** = 81 %, **3i** = 45 %), other examples reacted more efficiently using MeCN as solvent. In most cases, the yields were similar to those obtained under photocatalytic conditions, although nitrobenzene (**2m**) was less efficiently converted using TEMPO (27 % vs. 54 %). Interestingly, however, significant differences were observed in the regioselectivities of the trifluoromethoxylation reactions under the two sets of conditions. The halogen-substituted arenes **2b**, **2c** and **2d**, for example, exhibited a notably increased preference for the *ortho* and, especially, *para* products under TEMPO catalysis, with this preference increasing in the order **3d** <**3c** <**3b** (i. e. Br < Cl < F). In fact, while the same broad regioselectivity trends were observed under both sets of conditions, TEMPO catalysis led to a higher selectivity for the *para*-(OCF_3)-substituted products with each aromatic substrate tested.



Scheme 3 Scope of the TEMPO-catalyzed C–H trifluoromethoxylation of arenes using BTMP. ^{19}F NMR yields using $PhCF_3$ as an internal standard, ratio *ortho*-/*meta*-/*para*- determined by ^{19}F NMR shown in brackets. [a] TEMPO (5 mol%), no MeCN. [b] Arene (10 eq.).

The observation that different activation modes lead to different product distributions is both potentially synthetically useful and mechanistically interesting as it implies that the regioselectivity is not simply a reflection of the substrate properties. At this stage of the study, we sought to explore BTMP as a practical reagent for the direct synthesis of hitherto under-explored OCF_3-containing building blocks. Given the importance of nitrogen heterocycles in pharmaceuticals, (trifluoromethoxy)pyridines are highly desirable motifs for incorporation into new drug targets. Currently, however, these species are generally accessed via indirect methods. In comparison to benzene derivatives, such approaches entail additional synthetic steps as the (hydroxy)pyridine starting materials required for de novo construction of the OCF_3 moiety are not widely available. Furthermore, the key halex step can only be achieved on α-chloropyridine derivatives using the unattractive fluorinating agent SbF_3.[13] In 2016, the groups of Zou, Wu and Wu reported a trifluoromethylation approach towards trifluoromethoxylated pyridines and pyrimidines. However, the use of the expensive Togni II reagent and the restriction to 2-OCF_3-substituted derivatives limits its applicability for the synthesis of diverse building blocks.[14, 15]

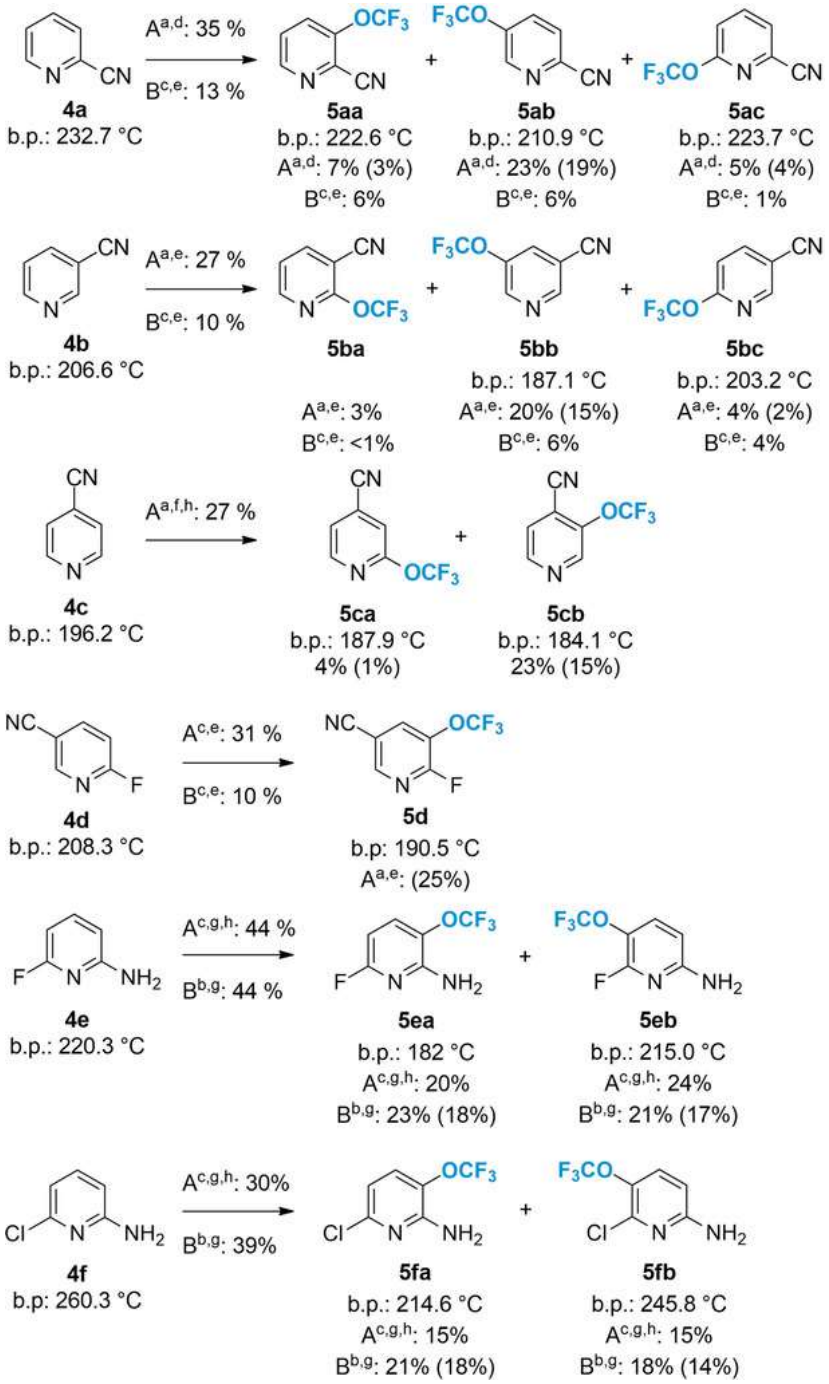
To assess the feasibility of direct C–H trifluoromethoxylation of pyridine building blocks using BTMP, picolinonitrile **4a** was selected as a representative substrate featuring a functional group amenable to subsequent conversion into other useful moieties (e. g. through hydrolysis to a carboxylic acid).



Scheme 4 Synthesis of 5-(trifluoromethoxy)picolinonitrile **5ab**. a) Current approach: multi-step indirect synthesis. b) TEMPO-catalyzed trifluoromethoxylation with BTMP. ^{19}F NMR yields (internal standard=$PhCF_3$), isolated yields in parentheses.

Reacting **4a** with BTMP under the optimized conditions with TEMPO provided the (trifluoromethoxy)pyridine **5a** in a ^{19}F NMR yield of 35 % as a mixture of three regioisomers favoring

the 5-(trifluoromethoxy)picolinonitrile (23 % of **5ab**, Scheme **4**). While the yield is only moderate, the direct synthesis of this species in a single step from **4a** represents a significant improvement on previously reported routes, which involved at least 6 steps from 2-aminopyridine.[16]A selection of further substrates featuring halogen, cyano and amino substituents were then reacted under both sets of optimized conditions and the product distribution was analyzed by ^{19}F NMR and GC-MS (Scheme **5**). In all cases, the desired (trifluoromethoxy)pyridines **5** were obtained in mostly moderate yields with TEMPO catalysis generally proving more efficient. Only with the 2-chloro-5-amino-substituted pyridine **4f** was a higher efficiency observed under photocatalytic conditions with **5f** being produced in 39 % ^{19}F NMR yield (cf. 30 % using TEMPO). To the best of our knowledge, the successful conversion of substrates **4e** and **4f** represents the first time amino substituents have been tolerated in radical trifluoromethoxylation reactions. The more electron deficient pyridine motif likely inhibits undesired direct electron transfer steps, which are thought to take place between electron rich aromatics and OCF_3 reagents.[17] The product regioisomers could be separated from the unreacted substrate and from each other via normal-phase column chromatography while, in no case, were bis(trifluoromethoxy) side-products resulting from double addition observed by GC-MS.[18] As chromatography is unattractive for large scale applications, differential scanning calorimetry (DSC) analysis was performed to assess the potential isolation of each regioisomer by fractional distillation. As shown in Scheme **5**, a significant decrease in the boiling point was observed upon trifluoromethoxylation (up to 45.7 °C for **5fa**), while for most examples, meaningful differences in the boiling points of each product regioisomer were measured (up to 33 °C for **5ea** and **5eb**). These results suggest that radical trifluoromethoxylation with BTMP could prove useful as a practical one-step method for the preparation of (trifluoromethoxy)pyridine building blocks with final product isolation being achieved via well-established and inexpensive distillation techniques.



Scheme 5 C−H Trifluoromethoxylation of pyridines with BTMP. ^{19}F NMR yields, isolated yields in parentheses. A: TEMPO catalysis conditions ((Substrate (5 eq.), BTMP (1 eq., 0.5 mmol), TEMPO (25 mol%), Na_2CO_3 (1 eq.), 16 h, rt, B: photocatalysis conditions (see Scheme **2**). [a] 6 mmol scale. [b] 3 mmol scale. [c] 0.5 mmol scale. [d] neat at 30 °C. [e] in MeCN (2.0 M). [f] in MeCN (0.4 M). [g] in MeCN (0.2 M). [h] 6 h.

In conclusion, BTMP has been employed as a source of $\cdot OCF_3$ radicals in C−H trifluoromethoxylation reactions of aromatic compounds. Using either visible light photoredox catalysis or TEMPO as a catalytic electron shuttle, valuable trifluoromethoxylated arenes could be prepared under mild

conditions, while direct radical trifluoromethoxylation of underexplored pyridine derivatives was achieved. Given the ready availability of BTMP from inexpensive bulk compounds, we believe these methods could serve as useful routes to OCF_3-containing building blocks.

12.3.3 Acknowledgements

The authors thank Dr. Carlo Fasting (FU Berlin) for instruction on advanced chromatographic separation techniques. Financial support from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)-Project-ID 387284271-SFB 1349 (gefördert durch die Deutsche Forschungsgemeinschaft (DFG)-Projektnummer 387284271-SFB 1349), the European Research Council (ERC, HighPotOx-Grant agreement ID: 818862) and the Fonds der chemischen Industrie (FCI, Sachkostenzuschuss) is gratefully acknowledged. We are also very grateful for the continued support of the Solvay company. We would like to acknowledge the assistance of the Core Facility BioSupraMol supported by the DFG. Open access funding enabled and organized by Projekt DEAL.

12.3.4 References

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[11] A discussion of plausible reaction mechanisms is provided in the Supporting Information.

[12] A comparison of commercial prices is provided in the Supporting Information. For a discussion of electron-catalyzed radical reactions, see: A. Studer, D. P. Curran, *Nat. Chem.* **2014**, *6*, 765–773.

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[17] This undesired reaction was previously discussed for anisole by Ngai and co-workers, see the Supporting Information of Ref. [5].

[18] In the reaction of **4c**, 2-fluoro-5-(trifluoromethoxy)isonicotinonitrile was also observed (^{1}H NMR, ^{19}F NMR, GC-MS) as a minor side-product (see the Supporting Information).

12.3.5 Supporting Information

Table of Contents

1 General Information

All reactions with a maximum scale of 1 mmol were conducted in pressure tubes "P26 0001", while reactions on 3 to 6 mmol scale were conducted in pressure tubes "P26 0006" from FengTecEx GmbH. Dry Solvents were prepared by filtering purchased HPLC- or analytical grade solvents trough Aluminium oxide and storing them over activated Molecular sieves (3 or 4 Å) for at least two days. If stated, the experiments were conducted under argon, dry working techniques and/or degassed and/or dry solvents. Blue light irradiation was provided by LED strips (λ_{max} = 440 nm, IP65) purchased from PB Versand GmbH (Type: 5630). A crystallization flask wrapped with the LED strips was used as a light reactor. $Ru(bpy)_3(PF_6)_2$, $Ir(ppy)_3$, $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ ($dF(CF_3)ppy$ = 3,5-difluoro-2-(5-trifluoromethyl)-2-pyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) was prepared according to literature procedures.[16] All other employed compounds were purchased from commercial suppliers and used as received.

1.1 Chromatography

Flash chromatography was performed using the Claricep S-Series Flash columns from Bonna-Agela Technologies Inc. (spherical silica gel, 60 Å, particle size 20-35 µm). A Flash chromatography device of Büchi Labortechnik GmbH was used, consisting of Pump module C-605, UV-Photometer C-635, Control Unit C-620 and Fraction Collector C-660.

1.2 NMR Spectroscopy

NMR spectra were acquired on a JEOL ECX 400 (400 MHz), JEOL ECP 500/ Bruker Avance 500 (500 MHz), Varian INOVA 600 (600 MHz) or a Bruker Avance 700 (700 MHZ) in $CDCl_3$, CD_3CN or ($(CD_3)_2CO$) as a solvent. Chemical shifts (δ) are quoted in ppm downfield of tetramethylsilane. The residual solvent signals were used as references for ^1H and ^{13}C NMR spectra. ^{19}F NMR spectra are not calibrated by an internal reference if deuterated solvent was used. If no deuterated solvent was used for ^{19}F NMR studies the spectra was referenced to the internal standard trifluorotoluene (-63.10 ppm). Coupling constants (*J*) are quoted in Hz. ^{19}F NMR yields were measured using trifluorotoluene as an internal standard with d1=10s, these values are analogous to those reported in the literature.[17] A mixture of **5d** (0.2 mmol) and $PhCF_3$ (0.2 mmol) in MeCN was analyzed using this method and the ^{19}F NMR-Spectra showed identical integral intensities for both compounds (Figure S74).

[16] D. Hanss, J. C. Freys, G. Bernandinelli, O. S. Wenger, *Eur. J. Inorg. Chem.* **2009**, 4850.
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1.3 High Resolution Mass Spectrometry and Gas Chromatography

Mass spectra were obtained on a ESI-FTICR-MS: Ionspec QFT-7 (Agilent/Varian) or on a HR-EI-MS: Waters Autospec Premier with Agilent 7890B GC. Infrared spectra were measured on a JASCO FT/IR-4100 Spectrometer. Characteristic absorption bands are displayed in wavenumbers $\tilde{\nu}$ in cm^{-1} and were analysed with the software Spectral Manager from JASCO.

GC-MS spectra were obtained on an Agilent 5977E MSD with 7820A GC using the Agilent 19091S-433UI HP 5ms Ultra inert column. GC-MS samples were heated from 50 °C to 300 °C at a rate of 20 °C/min with an injection temperature of 280 °C. Analytes were diluted in MeCN.

1.4 Thermogravimetric Analysis – Differential Scanning Calorimetry

DSC spectra were obtained on a DSC 200 with TASC414/3 Controller from Erich NETZSCH GmbH & Co. Holding KG. To prepare the samples, the analyte (1.7 to 2.4 mg) was put into the concavus aluminium pan, which was sealed with a lid (50 μm laser-drilled hole) using the appropriate mechanical press. The necessary equipment was obtained from Erich NETZSCH GmbH & Co. Holding KG (pan and lids, DSC21400A66.050-00), (mechanical press toolkit 6.240.10-85.0.00). Samples were held for 5 minutes at the starting temperature, then heated by 5 K/min or 10 K/min to the final temperature, then held for 10 min at the final temperature and finally cooled down by 10 K/min. This method was adapted from a recommended literature procedure.[18] The accuracy was confirmed by a test measurement of Benzonitrile (Figure S117). It is very important to check the peak shape, because broadened and asymmetric peaks (Figure S119) indicate evaporation of the analyte before the b.p. is reached. This happens when the sample container is insufficiently sealed.

1.5 Synthesis of BTMP

Bis(trifluoromethyl)peroxide was synthesized from elemental fluorine and carbonyl difluoride according to a literature procedure.[19] Suitable materials such as PFA, Teflon, stainless steel, nickel or nickel alloys are required. A stainless steel aperture with a total volume of 3.5 L was pressurized with 600 mbar carbonyl difluoride (5.6 g, 85 mmol) and 400 mbar fluorine (2.2 g, 57 mmol). The mixture was pumped in a continuous flow over silver fluoride at 100 °C for 3 days. The reaction mixture was then passed over aqueous potassium hydroxide solution to deactivate trifluoromethyl hypofluorite, residual fluorine and carbonyl difluoride. The gas obtained was then purified by

[18] K. Jones, R. Seyler, Differential Scanning Calorimetry for Boiling Points and Vapor Pressure, TA Instruments Notes, Rochester, NY, 1994

[19] R.S. Porter, G.H. Cady (United States of America, Secretary of the Navy), US3230264, **1962**

isothermal distillation and bis(trifluoromethyl)peroxide (BTMP, 3.9 g, 23 mmol, 40%) was collected in a liquid nitrogen cooled trap and stored in a stainless steel vessel.

Safety note: ***Caution!*** Extreme caution should be exercised when working with elemental fluorine, carbonyl difluoride and hypofluorites. Beyond their toxic nature, explosions have been reported in the literature during handling of these extremely hazardous compounds in conjunction with easily oxidizable organic matter.

1.6 Working safely with BTMP in trifluoromethoxylation reactions

Although BTMP has been shown to be remarkably stable,[20] appropriate caution should be taken when handling it. Single electron transfer to BTMP results in the formation of the desired •OCF_3 radical and a $^-OCF_3$ anion by-product (see Scheme 1), which will degrade into COF_2 and fluoride. Therefore, pressure tubes containing the reaction mixtures should only be opened in a well-ventilated fumehood and, especially for larger scale reactions, an appropriate quenching procedure for COF_2 should be employed.

Furthermore, care should be taken when mixing BTMP with compounds that could act themselves as single electron transfer reagents. For example, in this study, a stro5ngly exothermic reaction was observed upon reacting BTMP (0.5 mmol) with neat triethylamine (1 mL) with immediate black discolouration and the evolution of self-igniting gas being observed (short-lived flame above the liquid phase).

[20] R. S. Porter, G. H. Cady, *J. Am. Chem. Soc.* **1957**, *79*, 5628-5631.

2 Optimisation for the Trifluoromethoxylation of (Hetero)arenes

2.1 Optimisation of the Photocatalytic Method

A pressure tube was charged with a stir bar, the photocatalyst, additive, solvent and Benzene. The mixture was frozen and degassed using three freeze-pump-thaw cycles. Afterwards $(CF_3O)_2$ was condensed into the tube and the tube was repressurized with argon. The closed tube was gently shaken in a waterbath until the mixture melted and it was then stirred under irradiation from blue LEDs for 16 h. Afterwards, the tube was carefully opened towards the rear side of the fume hood to release over-pressure. The internal standard trifluorotoluene (0.5 mmol) and MeCN (to achieve 0.2 M) was added and the mixture was vigorously shaken. Up to 1 mL of the reaction mixture was filtered through diatomaceous earth and transferred into an NMR-tube for ^{19}F-NMR-Analysis.

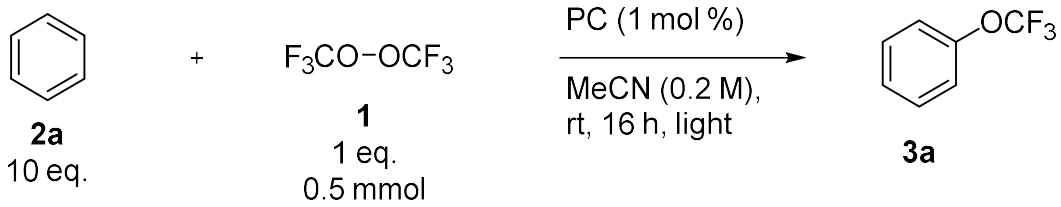


Table S1. Control experiments.

Entry	PC	Light	Yield of 3a[a]
1	$Ru(bpy)_3(PF_6)_2$	Blue LED	48 %
2	-	Blue LED	0 %
3	$Ru(bpy)_3(PF_6)_2$	Dark	3 %

[a] ^{19}F-NMR yields using trifluorotoluene as an internal standard.

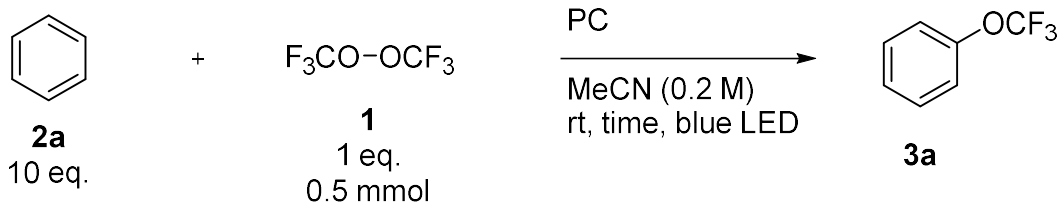


Table S2. Optimization of the photocatalyst, the catalyst loading and reaction time.

Entry	PC	PC mol %	reaction time [h]	Yield of 3a[a]
1	$Ru(bpy)_3(PF_6)_2$	1	16	48 %
2	$Ir(ppy)_3$	1	16	7 %
3	Fluorescein	1	16	<1 %
4	9-Mesityl-10-methylacridinium perchlorate	1	16	<1 %
5	Eosin Y	1	16	0 %
6	$(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$	1	16	8 %
7	$Ru(bpy)_3(PF_6)_2$	0.25	16	18 %
8	$Ru(bpy)_3(PF_6)_2$	0.25	40	15 %
9	$Ru(bpy)_3(PF_6)_2$	2	16	64 %
10	$Ru(bpy)_3(PF_6)_2$	4	16	72 %
11	$Ru(bpy)_3(PF_6)_2$	5	16	69 %
12	$Ru(bpy)_3(PF_6)_2$	6	16	72 %

[a] ^{19}F NMR yields using trifluorotoluene as an internal standard.

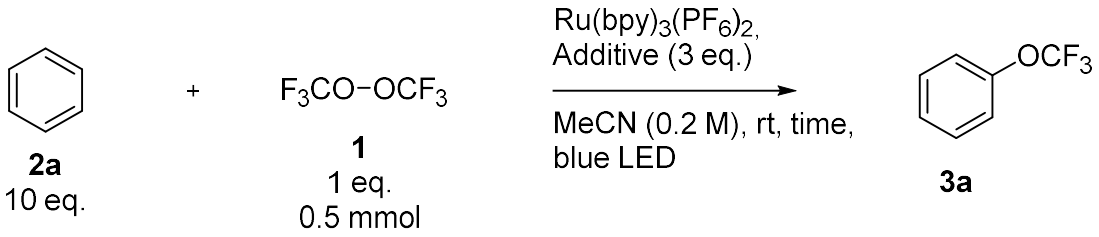


Table S3. Optimization of the photocatalyst loading, additive and reaction time. The formerly used old Blue LEDs were exchanged with a freshly manufactured device of same type and from the same supplier.

Entry	$Ru(bpy)_3(PF_6)_2$ [mol %]	Additive	reaction time [h]	Yield of 3a[a]
1	1	-	40	61 %
2	1	KF	40	74 %
3	1	TMS-Cl	40	24 %
4	1	TMS-Br	40	3 %
5	0.1	KF	16	2 %
6	0.25	KF	16	21 %
7	0.5	KF	16	51 %
8	1	KF	16	82 %
9	1.5	KF	16	86 %
10	2	KF	16	83 %
11	2.5	KF	16	84 %

[a] ^{19}F NMR yields using trifluorotoluene as an internal standard.

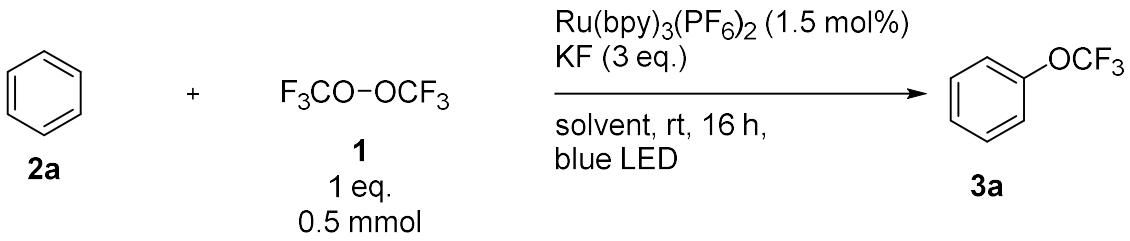


Table S4. Optimization of the Solvent and it's molarity with 10 or 5 equiv. of **2a**.

Entry	Solvent	Solvent Molarity	2a eq.	Yield of 3a[a]
1	MeCN	0.2	10	86 %
2	DMF	0.2	10	3 %
3	THF	0.2	10	9 %
4	Acetone	0.2	10	85 %
5	MeCN	0.5	10	80 %
6	MeCN	1	10	65 %
7	MeCN	0.2	5	78 %
8	MeCN	0.3	5	77 %
9	MeCN	0.5	5	75 %
10	MeCN	0.7	5	70 %
11	MeCN	1	5	61 %
12	MeCN	1.5	5	48 %

[a] ^{19}F NMR yields using trifluorotoluene as an internal standard.

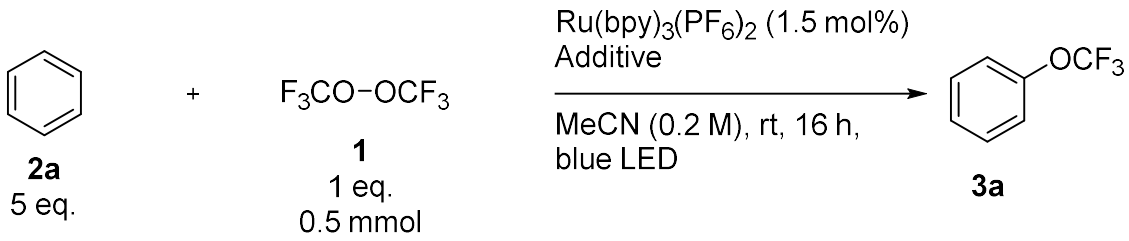


Table S5. Optimization of the additive itself and the additive loading with 5 equivalents of the substrate **2a**.

Entry	Additive	Additive eq.	Yield of 3a[a]
1	-	-	64 %
2	KF	4.5	76 %
3	KF	3	78 %
4	KF	1.5	78 %
5[b]	KF	1.5	76 %
6	KF	1	75 %
7	KF	0.5	75 %
8	KF	0.1	72 %
9[b]	KF	0.1	74 %
10	NaF	3	77 %
11	NaF	1.1	73 %
12	NaF	0.1	69 %
13	CsF	3	74 %
14	NaCl	1.1	44 %

[a] ^{19}F NMR yields using trifluorotoluene as an internal standard. [b] The reaction mixture was not degassed but just frozen with liquid N_2 prior to the addition of BTMP.

2.2 Optimisation of the Cuprous Chloride Method

A pressure tube was charged with a stir bar, CuCl, solvent and Benzene. The mixture was frozen with liquid N_2 and the tube was evacuated. Afterwards $(CF_3O)_2$ (1 eq, 0.5 mmol) was condensed into the tube and the tube was repressurized with argon. The closed tube was gently shaken in a waterbath until the mixture melted and was stirred for 16 h at room temperature. Afterwards, the tube was carefully opened towards the rear side of the fume hood to release over-pressure. The internal standard trifluorotoluene (0.5 mmol) and MeCN (to achieve 0.2 M) was added and the mixture was vigorously shaken. Up to 1 mL of the reaction mixture was filtered through diatomaceous earth and transferred into an NMR-tube for ^{19}F-NMR-Analysis.

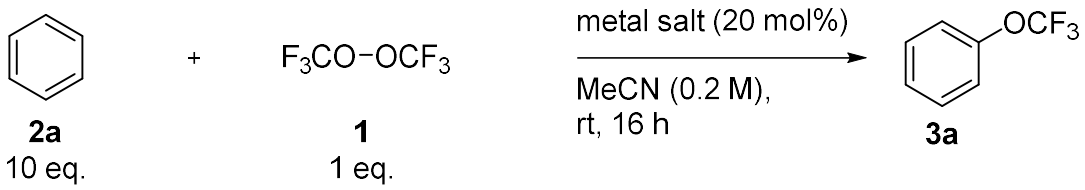
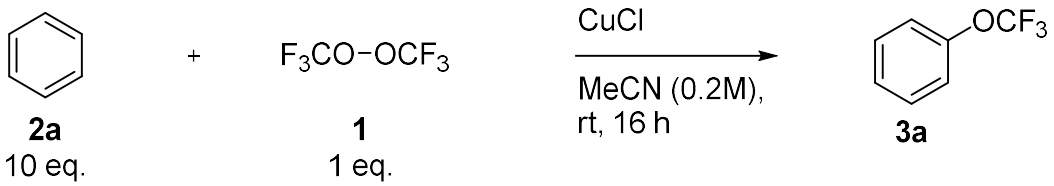


Table S6. Optimisation of the Metal salt, the metal salt loading, control experiments and others.

Entry	Metal salt	Yield of 3a[a]
1	Cu_2O	1 %
2	CuCl	17 %
3	CuBr	5 %
4	CuI	4 %
5	CuSCN	1 %
6	$CuSO_4 \cdot 5\ H_2O$	<1 %
7	$CuCO_3$	1 %
8	$FeSO_4 \cdot 7\ H_2O$	1 %
9	$TiCl_3$	0 %
10	$AlCl_3$	<1 %
11	$Cu(MeCN)_4PF_6$	16 %
12	Ferrocene	2 %
13	$CuCl_2 \cdot 2\ H_2O$	2 %

[a] ^{19}F NMR yields using trifluorotoluene as an internal standard.



2a 10 eq. + $F_3CO-OCF_3$ **1** 1 eq. → **3a**

Table S7. Optimization of CuCl loading.

Entry	CuCl eq.	solvent	Yield of 3a[a]
1	0.2	MeCN	17 %
2	0.4	MeCN	28 %
3	0.6	MeCN	40 %
4	0.8	MeCN	47 %
5	1.0	MeCN	50 %
6	1.0	dry MeCN	52 %
7	1.2	MeCN	46 %
8	1.4	MeCN	38 %

[a] ^{19}F NMR yields using trifluorotoluene as an internal standard.

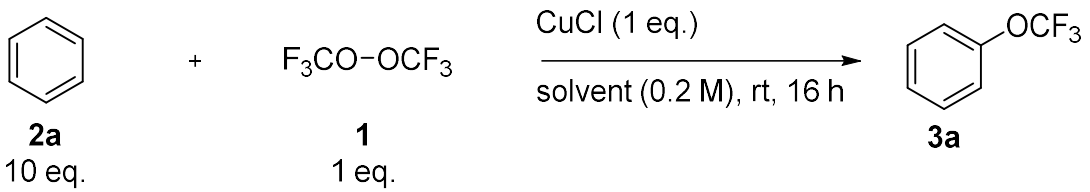


Table S8. Screening of the solvent.

Entry	solvent	Yield of 3a[a]
1	MeCN	50 %
2	DMSO	<1 %
3	Acetone	10 %
4	THF	9 %
5	Diethylether	25 %
6	Ethylacetate	44 %
7	DCM	<1 %

[a] ^{19}F NMR yields using trifluorotoluene as an internal standard.

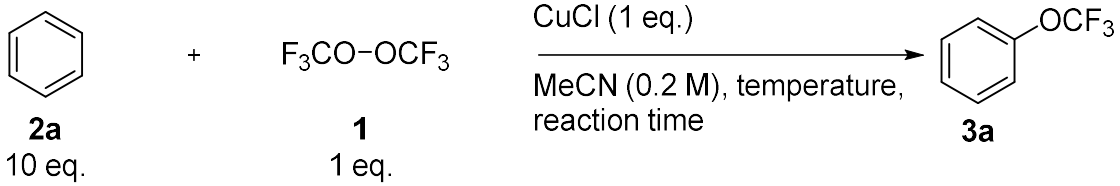


Table S9. Screening of temperature and reaction time.

Entry	temperature	Reaction time [h]	Yield of 3a[a]
1	rt	16	50 %
2	rt	4	45 %
3	0 °C	4	46 %
4	-40 °C	4	33 %

[a] ^{19}F NMR yields using trifluorotoluene as an internal standard.

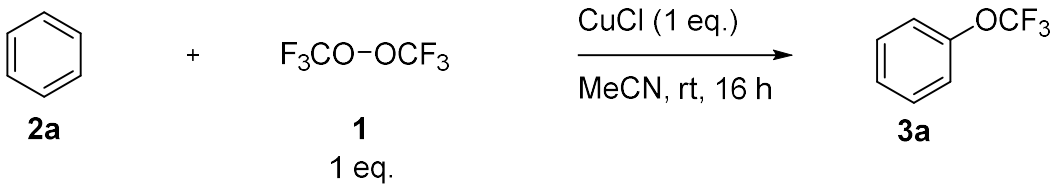


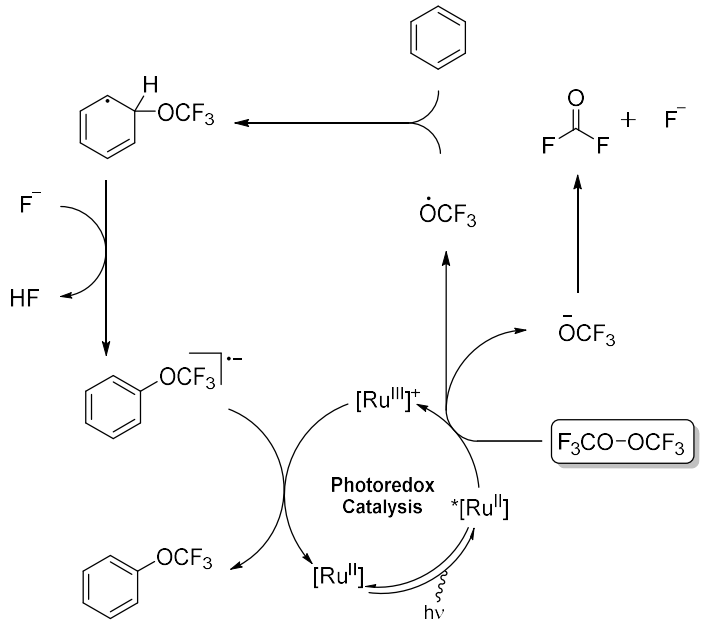
Table S10. Product distribution with different equivalents of substrate and varying solvent concentration.

Entry	Substrate eq.	MeCN Molarity	Yield of 3a[a]
1	10	0.2	50 %
2	10	4.0	52 %
3	5	0.2	40 %
4	5	1.0	47 %
5	5	2.0	55 %
6	5	4.0	53 %
7	5	6.0	54 %
8	5	8.0	42 %

[a] ^{19}F NMR yields using trifluorotoluene as an internal standard.

3 Plausible Mechanisms

Successful trifluoromethoxylation of Benzene was achieved via activation of BTMP through the Photocatalyst $Ru(bpy)_3(PF_6)_2$, the metal salt CuCl and the single electron shuttle TEMPO. Therefore, we conclude that BTMP is activated via SET and subsequently forms the BTMP radical anion. That radical anion will undergo Mesolysis to yield the desired $\bullet OCF_3$ radical and the $^{-}OCF_3$ anion by-product. This by-product is likely to degrade to COF_2 and fluoride. For photocatalyzed reactions we suggest the next steps are insertion of the $\bullet OCF_3$ radical into the (hetero)arene, deprotonation by fluoride or another base and oxidation of the product radical (Scheme 1). Finally, the desired trifluoromethoxyated (hetero)arene is afforded and the photoredox cycle of $Ru(bpy)_3(PF_6)_2$ is completed.



Scheme 1. Possible mechanism for the photocatalyzed trifluoromethoxylation of (hetero)arenes with BTMP.

An analogous mechanism is assumed under TEMPO catalysis, with TEMPO acting as a SET donor to BTMP. It should be noted, however, that with substituted (hetero)arenes differences in the distribution of *ortho*, *meta* and *para* products under photocatalyzed and TEMPO catalyzed conditions are observed. For a survey of the product distribution obtained with Fluorobenzene under TEMPO catalyzed conditions see Table S11. The origins of these differences are not clear but could reflect fundamental differences in the reaction mechanism of each method.

Table S11. A set of mechanistical experiments for the TEMPO catalyzed trifluoromethoxylation of (hetero)arenes with BTMP. Standard conditions are BTMP (0.5 mmol, 1 eq), Fluorobenzene (5 eq), TEMPO (25 mol%), K_2CO_3 (1 eq), MeCN (0.5 M). The shown yields are ^{19}F-NMR yields.

Entry	Changes	Yield[a] of *ortho*- product	Yield[a] of *meta*- product	Yield[a] of *para*- product
1	None	12 %	2 %	36 %
2	Acetone as solvent	11 %	1 %	30 %
3	Neat conditions	6 %	8 %	21 %
4	Neat conditions, 15 eq substrate	6 %	9 %	34 %
5	Neat conditions, 15 eq substrate, Cs_2CO_3 instead of K_2CO_3	6 %	13 %	28 %
6	Neat conditions, 15 eq substrate, TEMPO (1 eq)	13 %	15 %	11 %
7	Neat conditions, Fluorobenzene-d5 as substrate	4 %	7 %	18 %
8	Fluorobenzene-d5 as substrate	8 %	1 %	36 %

[a] ^{19}F NMR yields using trifluorotoluene as an internal standard.

4 Methods for the Trifluoromethoxylation of Hetero(arenes)

4.1 General Method A (Photocatalytic method with KF)

A pressure tube was charged with a stir bar, $Ru(bpy)_3(PF_6)_2$ (1.5 mol%, 0.0075 mmol, 6.5 mg), KF (0.1 eq, 0.05 mmol, 3 mg), MeCN (2.5 mL) and the substrate (5 eq). The mixture was frozen with liquid N_2 and the tube was evacuated. Afterwards $(CF_3O)_2$ (1 eq, 0.5 mmol) was condensed into the tube and the tube was repressurized with argon. The closed tube was gently shaken in a waterbath until the mixture melted and it was then stirred for 16 h at room temperature under irradiation from blue LEDs. Afterwards, the tube was carefully opened towards the rear side of the fume hood to release overpressure.

For reactions on 0.5 mmol scale, the internal standard trifluorotoluene (1 eq, 61 μL) was added and the mixture was vigorously shaken. Up to 1 mL of the reaction mixture was filtered through diatomaceous earth and transferred into an NMR-tube for ^{19}F-NMR-Analysis.

For reactions on 3 mmol scale, the crude was mixed with diethyl ether and sat. $NaHCO_3$ solution. The aqueous phase was extracted with diethyl ether (4 x 20 mL) and the collected organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The internal standard trifluorotoluene (2 mmol, 244 μL) was added and up to 1 mL of the crude reaction mixture was transferred into an NMR-tube for ^{19}F-NMR-Analysis. Afterwards the crude mixture was concentrated *in vacuo*. Part of the crude was dissolved in MeCN for GC-MS analysis.

4.2 General Method B (Photocatalytic method without KF)

As method B but without KF.

4.3 General Method C (Cuprous Chloride method)

A pressure tube was charged with a stir bar, CuCl (1 eq, 0.5 mmol, 49.5 mg), MeCN (0.25 mL) and the substrate (5 eq). The mixture was frozen with liquid N_2 and the tube was evacuated. Afterwards $(CF_3O)_2$ (1 eq, 0.5 mmol) was condensed into the tube and the tube was repressurized with argon. The closed tube was gently shaken in a waterbath until the mixture melted and it was then stirred for 16 h at room temperature. Afterwards the tube was carefully opened towards the rear side of the fume hood to release over-pressure. The internal standard trifluorotoluene (1 eq, 61 μL) and MeCN (to achieve 0.2 M) was added and the mixture was vigorously shaken. Up to 1 mL of the reaction mixture was filtered through diatomaceous earth and transferred into an NMR-tube for ^{19}F-NMR-Analysis.

4.4 General Method D (TEMPO-catalyzed method for Arenes)

A pressure tube was charged with a stir bar, TEMPO (25 mol%, 0.125 mmol, 19.5 mg), K_2CO_3 (1 eq, 0.5 mmol, 69.1 mg), MeCN (0.5 M, 1 mL) and the substrate (5 eq). The mixture was frozen with liquid N_2 and the tube was evacuated. Afterwards $(CF_3O)_2$ (1 eq, 0.5 mmol) was condensed into the tube and the tube was repressurized with argon. The closed tube was gently shaken in a waterbath until the mixture melted and it was then stirred for 16 h at room temperature. Afterwards, the tube was carefully opened towards the rear side of the fume hood to release over-pressure. The internal standard trifluorotoluene (1 eq, 61 μL) and MeCN (to achieve 0.2 M) was added and the mixture was vigorously shaken. Up to 1 mL of the reaction mixture was filtered through diatomaceous earth and transferred into an NMR-tube for ^{19}F-NMR-Analysis.

4.5 General Method E (TEMPO-catalyzed method for Pyridines)

A pressure tube was charged with a stir bar, TEMPO (25 mol%, 0.125 mmol, 19.5 mg), Na_2CO_3 (1 eq, 0.5 mmol, 53 mg), MeCN and the substrate (5 eq). The mixture was frozen with liquid N_2 and the tube was evacuated. Afterwards $(CF_3O)_2$ (1 eq, 0.5 mmol) was condensed into the tube and the tube was repressurized with argon. The closed tube was gently shaken in a waterbath until the mixture melted and it was then stirred for 16 h at room temperature. Afterwards, the tube was carefully opened towards the rear side of the fume hood to release over-pressure.

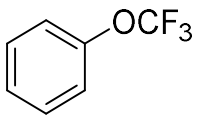
For reaction scales of 0.5 mmol, the internal standard trifluorotoluene (1 eq, 61 μL) and MeCN (to achieve 0.2 M) was added and the mixture was vigorously shaken. Up to 1 mL of the reaction mixture was filtered through diatomaceous earth and transferred into an NMR-tube for ^{19}F-NMR-Analysis.

For reactions on 6 mmol scale, the crude was mixed with diethyl ether and sat. $NaHCO_3$ solution. The aqueous phase was extracted with diethyl ether (3 x 20 mL) and the collected organic phases were dried over Na_2SO_4. The internal standard trifluorotoluene (2 mmol, 244 μL) was added and up to 1 mL of the crude reaction mixture was transferred into an NMR-tube for ^{19}F-NMR-Analysis. Afterwards, the crude mixture was concentrated *in vacuo*. Part of the crude was dissolved in MeCN for GC-MS analysis.

5 Characterization Data for Trifluoromethoxylated (Hetero)arenes

5.1 Characterization Data for Trifluoromethoxylated Arenes

(Trifluoromethoxy)benzene (3a)



The reaction was performed using the general Methods A, B, C, and D with **2a** (5 eq., 2.5 mmol, 223 μL) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method A: ^{19}F NMR Yield = 74 %,

^{19}F-NMR (376 MHz, MeCN) δ = -58.50.

Method B: ^{19}F NMR Yield = 64 %,

^{19}F-NMR (376 MHz, MeCN) δ = -58.49.

Method C: ^{19}F NMR Yield = 55 %,

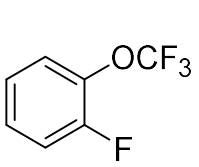
^{19}F-NMR (376 MHz, MeCN) δ = -58.47.

Method D: ^{19}F NMR Yield = 70%

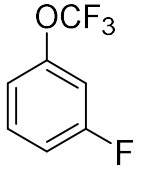
^{19}F-NMR (376 MHz, MeCN) δ = -58.50.

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

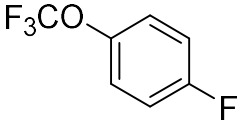
Fluoro(trifluoromethoxy)benzene (3b)



ortho



meta



para

The reaction was performed using the general Methods A, B and D with **2b** (5 eq., 2.5 mmol, 233 μL) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method A: ^{19}F NMR Yield = 58%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -59.60 (d, 5.1 Hz, 3F), -131.31 (m, 1F)

meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.75 (3F), 111.39 (m, 1F).

para **^{19}F-NMR** (376 MHz, MeCN) δ = -59.07 (3F), 116.26 (m, 1F)

r.r = *o : m : p* = 2.5 : 1 : 2.3

Method B: ^{19}F NMR Yield = 58%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -59.58 (d, 5.1 Hz, 3F), -131.32 (m, 1F)

meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.75 (3F), 111.38 (m, 1F).

para **^{19}F-NMR** (376 MHz, MeCN) δ = -59.07 (3F), 116.25 (m, 1F).

r.r = *o : m : p* = 2.1 : 1 : 1.8

Method D: ^{19}F NMR Yield = 50%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -59.61 (m, 3F), -131.34 (m, 1F)

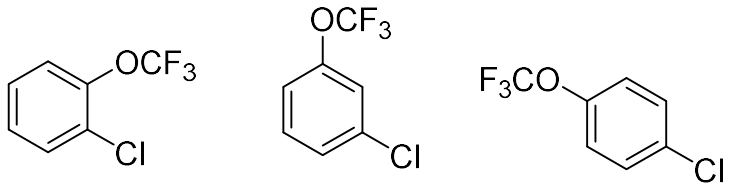
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.75 (3F), -111.40 (m, 1F).

para **^{19}F-NMR** (376 MHz, MeCN) δ = -59.08 (3F), -116.31 (m, 1F).

r.r = *o : m : p* = 6 : 1 : 18

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

Chloro(trifluoromethoxy)benzene (3c)



ortho *meta* *para*

The reaction was performed using the general Methods B and D with **2c** (5 eq., 2.5 mmol, 254 μL) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method B: ^{19}F NMR Yield = 49%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.60.

meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.69.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.84

r.r = *o : m : p* = 1.8 : 1 : 1.3

Method D: ^{19}F NMR Yield = 57%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.60.

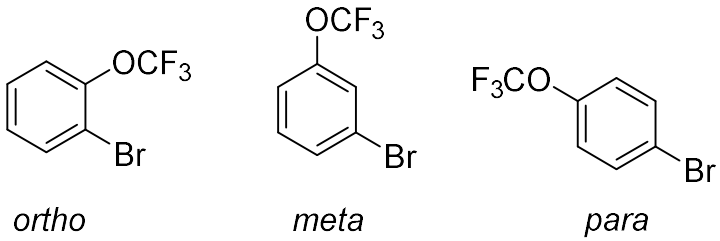
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.69.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.83

r.r = *o : m : p* = 4.5 : 1 : 8.8

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

Bromo(trifluoromethoxy)benzene (3d)



ortho *meta* *para*

The reaction was performed using the general Methods A and D with **2d** (5 eq., 2.5 mmol, 262 μL) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method A: ^{19}F NMR Yield = 60%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.25.

meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.68.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.79.

r.r = *o : m : p* = 2.9 : 1 : 2.1

Method D: ^{19}F NMR Yield = 59%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.26.

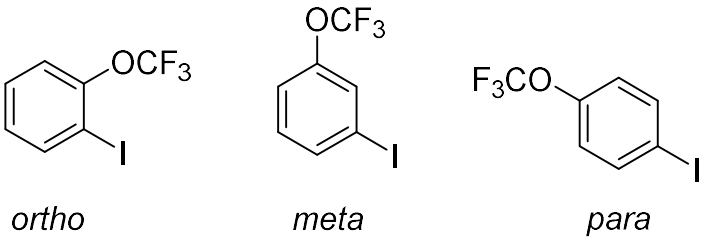
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.68.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.80.

r.r = *o : m : p* = 3.7 : 1 : 5.2

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

Iodo(trifluoromethoxy)benzene (3e)



ortho *meta* *para*

The reaction was performed using the general Methods A and D with **2e** (5 eq., 2.5 mmol, 280 μL) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method A: ^{19}F NMR Yield = 4%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -57.68.

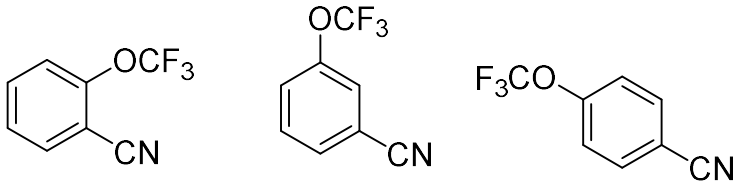
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.62.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.71.

r.r = *o : m : p* = 1 : 1 : 2

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

(Trifluoromethoxy)benzonitrile (3f)



ortho *meta* *para*

The reaction was performed with the general Method A and a modified version of Method D (10 eq. substrate and no solvent) with **2f** (5 eq., 2.5 mmol, 255 μL) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method A: ^{19}F NMR Yield = 69%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.68.

meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.78.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.45.

r.r = *o : m : p* = 2.3 : 1.6 : 1

Method D: ^{19}F NMR Yield = 81%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.68.

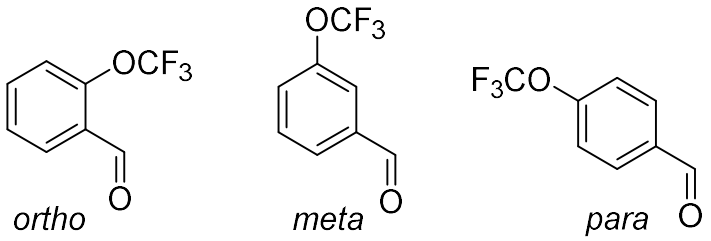
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.77.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.45.

r.r = *o : m : p* = 1.6 : 1.9 : 1

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

(Trifluoromethoxy)benzaldehyde (3g)



The reaction was performed using the generals Method A and D with **2g** (5 eq., 2.5 mmol, 253 μL) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method A: ^{19}F NMR Yield = 60%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.40.

meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.66.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.31.

r.r = *o : m : p* = 2.1 : 1.9 : 1

Method B: ^{19}F NMR Yield = 63%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.40.

meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.65.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.31.

r.r = *o : m : p* = 2.4 : 2.4 : 1

Method D: ^{19}F NMR Yield = 47%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.40.

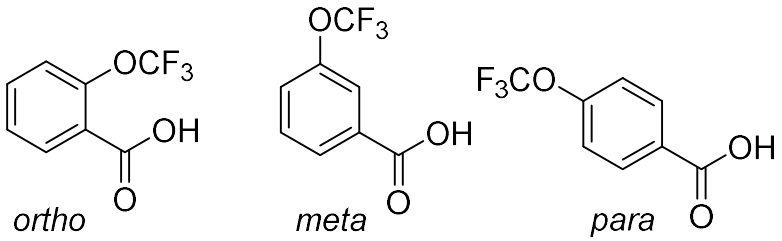
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.66.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.31.

r.r = *o : m : p* = 1.1 : 1.1 : 1

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

(Trifluoromethoxy)benzoic Acid (3h)



The reaction was performed using the generals Method A with **2h** (5 eq., 2.5 mmol, 305 mg) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method A: ^{19}F NMR Yield = 49%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.08.

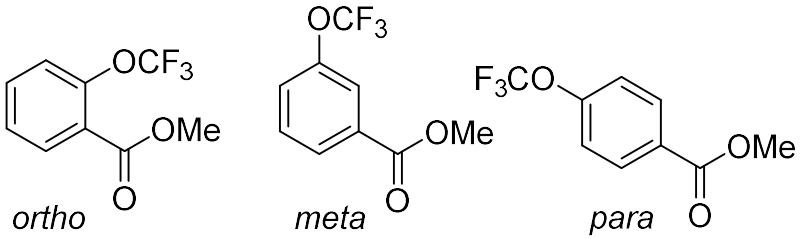
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.65.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.34.

r.r = *o : m : p* = 1.9 : 2 : 1

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

Methyl (trifluoromethoxy)benzoate (3i)



The reaction was performed using general Method A and a modified version of Method D (Tempo (5 mol %, 0.025 mmol, 3.9 mg), no solvent) with **2i** (5 eq., 2.5 mmol, 312 μL) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method A: ^{19}F NMR Yield = 73%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.15.

meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.64.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.35.

r.r = *o : m : p* = 1.8 : 2.1 : 1

Method D: ^{19}F NMR Yield = 45%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.15.

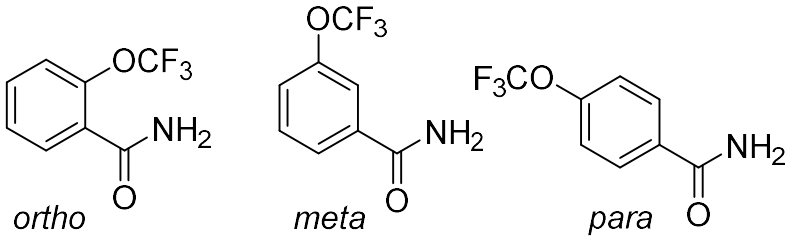
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.64.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.35.

r.r = *o : m : p* = 1 : 1.9 : 1.2

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

(Trifluoromethoxy)benzamide (3j)



The reaction was performed with the general Method B and a modified version of method D (in 2 M MeCN) with **2j** (5 eq., 2.5 mmol, 303 mg) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method B: ^{19}F NMR Yield = 22%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.19.

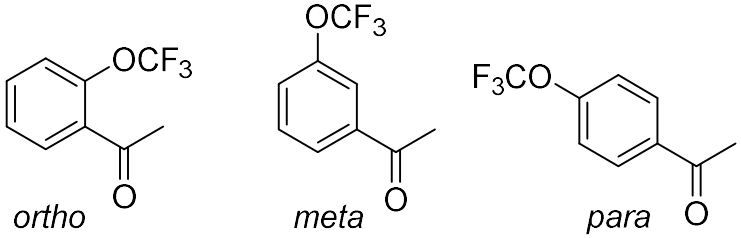
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.56.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.40.

r.r = *o : m : p* = 1 : 2.3 : 2.3

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

1-((Trifluoromethoxy)phenyl) ethan-1-one (3k)



The reaction was performed with the general Methods A, B and D with **2k** (5 eq., 2.5 mmol, 292 μL) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method A: ^{19}F NMR Yield = 70%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -57.84.

meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.59.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.32.

r.r = *o : m : p* = 1.7 : 1.7 : 1

Method B: ^{19}F NMR Yield = 75%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -57.83.

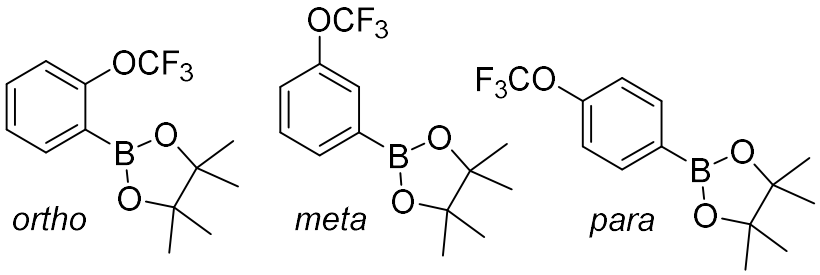
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.59.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.32.

r.r = *o : m : p* = 1.9 : 1.9 : 1

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

4,4,5,5-tetramethyl-2-(trifluoromethoxy)phenyl-1,3,2-dioxaborolane (3l)



The reaction was performed using the general Method B and a modified version of method D (at 30 °C) with **2l** (5 eq., 2.5 mmol, 510 mg) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method B: ^{19}F NMR Yield = 44%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.10.

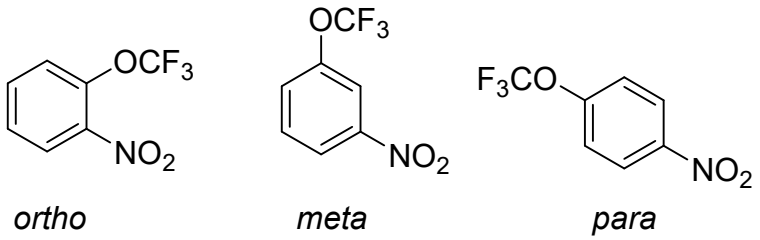
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.42.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.25.

r.r = *o : m : p* = 1.6 : 1.4 : 1

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm). The characterization data agrees with literature values.[17]

Nitro(trifluoromethoxy)benzene (3m)



The reaction was performed using the general Methods A and D with **2m** (5 eq., 2.5 mmol, 256 μL) as the substrate. The reaction mixture was analyzed by ^{19}F-NMR with the use of $PhCF_3$ (1 eq., 61 μL) as internal standard.

Method A: ^{19}F NMR Yield = 54%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.42.

meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.85.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.49.

r.r = *o : m : p* = 1 : 4.2 : 1.5

Method D: ^{19}F NMR Yield = 27%

ortho **^{19}F-NMR** (376 MHz, MeCN) δ = -58.42.

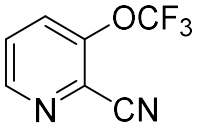
meta **^{19}F-NMR** (376 MHz, MeCN) δ = -58.85.

para **^{19}F-NMR** (376 MHz, MeCN) δ = -58.50.

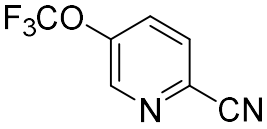
r.r = *o : m : p* = 1 : 7 : 5.5

5.2 Characterization Data for Trifluoromethoxylated Pyridines

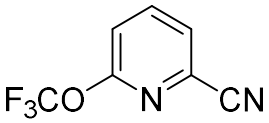
(trifluoromethoxy)picolinonitrile (5a)



5aa



5ab



5ac

The reaction was performed according to the general Method E with **4a** (5 eq., 30 mmol, 3.16 g) as the substrate but under neat conditions at 30 °C. The crude mixture was dissolved in hot Acetone and *n*-Pentane was carefully added until a small dark red phase separated from the main organic phase. The organic layer was separated by decantation. This step was repeated three times to remove the TEMPO related decomposition products. The organic phase was concentrated *in vacuo* and purified via column chromatography in two steps (*n*-Pentane/DCM and *n*-Pentane/MTBE, SiO_2). The products **5aa** (0.2 mmol, 32 mg, 3 %) and **5ab** (1.1 mmol, 210 mg, 19 %) were obtained as colorless oils, while **5ac** (0.2 mmol, 39 mg, 4 %) was obtained as a white solid.

Crude Mixture 5a

Method E (6 mmol, neat conditions, 30 °C):

^{19}F NMR Yield = 35%

3-(trifluoromethoxy)picolinonitrile (5aa): **^{19}F-NMR** (376 MHz, Et_2O) δ = -58.46.

5-(trifluoromethoxy)picolinonitrile (5ab): **^{19}F-NMR** (376 MHz, Et_2O) δ = -58.53.

6-(trifluoromethoxy)picolinonitrile (5ac): **^{19}F-NMR** (376 MHz, Et_2O) δ = -57.31.

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm).

Method B (0.5 mmol, 2 M):

^{19}F NMR Yield = 13%

3-(trifluoromethoxy)picolinonitrile (5aa): **^{19}F-NMR** (376 MHz, MeCN) δ = -58.67.

5-(trifluoromethoxy)picolinonitrile (5ab): **^{19}F-NMR** (376 MHz, MeCN) δ = -58.77.

6-(trifluoromethoxy)picolinonitrile (5ac): **^{19}F-NMR** (376 MHz, MeCN) δ = -57.49.

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm).

3-(trifluoromethoxy)picolinonitrile (5aa)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.67 (d, *J*=4.6, 1H), 7.78 (d, *J*=8.7, 1H), 7.64 (dd, *J*=8.7, 4.6, 1H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -57.70. **^{13}C-NMR** (176 MHz, $CDCl_3$) δ = 148.9, 148.2, 128.8, 128.0, 128.0, 120.2 (q, *J*=263, 263, 263), 113.2. **HRMS (EI)**: m/z calculated for $[C_7H_3F_3N_2O]^+$ ($[M]^+$): 188.0197, measured: 188.0198. **IR (ATR):** ν (cm^{-1}): 3081, 2244, 1794, 1585, 1451, 1440, 1261, 1180, 1109, 1058, 926, 843, 813, 770, 741, 695, 685, 635, 564, 543, 510, 448. **B.p.** = 222.6 °C. **R_f** = 0.42 (*n*-Pentane/DCM**,** 1:1, (v/v)).

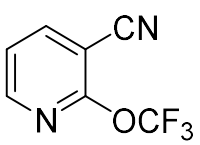
5-(trifluoromethoxy)picolinonitrile (5ab)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.63 (s, 1H), 7.80 (d, *J*=8.6, 1H), 7.70 (d, *J*=8.6, 1H) **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -57.90. **^{13}C-NMR** (176 MHz, $CDCl_3$) δ = 148.0, 144.1, 131.8, 129.7, 128.4, 120.3 (q, *J*=262, 262, 262), 116.3. **HRMS (EI)**: m/z calculated for $[C_7H_3F_3N_2O]^+$ ($[M]^+$): 188.0197, measured: 188.0197. **IR (ATR):** ν (cm^{-1}): 3098, 3069, 2244, 1582, 1469, 1391, 1269, 1258, 1207, 1181, 1127, 1024, 925, 854, 830, 679, 612, 550. **b.p.** = 210.9 °C. **R_f** = 0.52 (*n*-Pentane/DCM**,** 1:1, (v/v)).

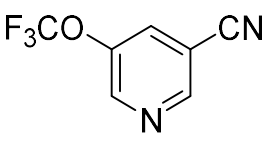
6-(trifluoromethoxy)picolinonitrile (5ac)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.96 (t, *J*=8, 1H), 7.64 (d, *J*=8.0, 1H), 7.24 (d, *J*=8.2, 1H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -56.89. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ = 157.0, 141.4, 131.4, 126.7, 119.9 (q, *J*=263, 263, 263), 117.2, 116.1. **HRMS (EI)**: m/z calculated for $[C_7H_3F_3N_2O]^+$ ($[M]^+$): 188.0197, measured: 188.0172. **IR (ATR):** ν (cm^{-1}): 3102, 3087, 2243, 1591, 1578, 1440, 1430, 1304, 1263, 1244, 1199, 1164, 1149, 1077, 1014, 993, 987, 926, 880, 816, 738, 728, 712, 637, 617, 571, 525, 471. **m.p.** = 40.5 °C. **b.p.** = 223.7 °C. **R_f** = 0.42 (*n*-Pentane/DCM**,** 1:1, (v/v)).

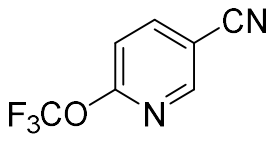
(trifluoromethoxy)nicotinonitrile (5b)



5ba



5bb



5bc

The reaction was performed according to the general Method E with **4b** (5 eq., 30 mmol, 3.16 g) as the substrate and MeCN (2.0 M, 3 mL) as the solvent. The crude mixture was dissolved in hot Acetone and cold *n*-Pentane was added until dark red solids precipitated. The liquid was decanted and concentrated *in vacuo*. The crude mixture was further purified via column chromatography in two steps (*n*-Pentane/DCM and *n*-Pentane/MTBE, SiO_2). The product **5bb** (0.91 mmol, 170 mg,

15 %) was obtained as colorless oil, while **5bc** (0.13 mmol, 25 mg, 2 %) was obtained as white solid. Product **5ba** was isolated together with impurities of MTBE and Et_2O.

Crude Mixture 5b

Method E (6 mmol, 2 M):

^{19}F NMR Yield = 27%

2-(trifluoromethoxy)nicotinonitrile (5ba):**^{19}F-NMR** (376 MHz, Et_2O/MeCN) δ = -56.95.

5-(trifluoromethoxy)nicotinonitrile (5bb):**^{19}F-NMR** (376 MHz, Et_2O/MeCN) δ = -58.75.

6-(trifluoromethoxy)nicotinonitrile (5bc):**^{19}F-NMR** (376 MHz, Et_2O/MeCN) δ = -57.05.

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm).

Method B (0.5 mmol, 2 M):

^{19}F NMR Yield = 10%

2-(trifluoromethoxy)nicotinonitrile (5ba):**^{19}F-NMR** (376 MHz, MeCN) δ = -57.10.

5-(trifluoromethoxy)nicotinonitrile (5bb):**^{19}F-NMR** (376 MHz, MeCN) δ = -59.03.

6-(trifluoromethoxy)nicotinonitrile (5bc):**^{19}F-NMR** (376 MHz, MeCN) δ = -57.22.

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm).

2-(trifluoromethoxy)nicotinonitrile (5ba)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.52 (dd, *J*=4.9, 1.9, 1H), 8.09 (dd, *J*=7.7, 2.0, 1H), 7.36 (dd, *J*=7.7, 5.0, 1H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -56.44. **R_f** = 0.39 (*n*-Pentane/DCM**,** 1:1, (v/v)). The characterization data agrees with literature values.[21]

5-(trifluoromethoxy)nicotinonitrile (5bb)

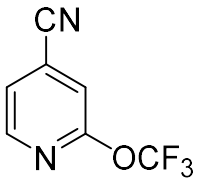
^{1}H-NMR (500 MHz, $CDCl_3$) δ = 8.85 (s, 1H), 8.77 (s, 1H), 7.84 (m, 1H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -58.15. **^{13}C-NMR** (176 MHz, $CDCl_3$) δ = 150.5, 146.6, 145.5, 131.2, 120.3 (q, *J*=261), 115.0, 111.0. **HRMS (EI)**: m/z calculated for $[C_7H_3F_3N_2O]^+$ ($[M]^+$): 188.0197, measured: 188.0198. **IR (ATR):** ν (cm^{-1}): 3075, 2240, 1595, 1572, 1420, 1261, 1200, 1161, 1023, 985, 911, 869, 744, 700, 638, 622, 590, 463. **B.p.** = 187.1 °C. **R_f** = 0.22 (*n*-Pentane/DCM**,** 1:1, (v/v)).

[21] Z. Deng, M. Zhao, F. Wang, P. Tang, *Nature Comm.* **2020**, *11*, 2569.

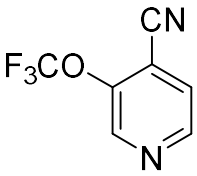
6-(trifluoromethoxy)nicotinonitrile (5bc)

^{1}H-NMR (600 MHz, $CDCl_3$) δ = 8.63 (d, *J*=2.2, 1H), 8.05 (dd, *J*=8.5, 2.3, 1H), 7.12 (d, *J*=8.6, 1H). **^{19}F-NMR** (565 MHz, $CDCl_3$) δ = -56.63. **HRMS (EI)**: m/z calculated for $[C_7H_3F_3N_2O]^+$ ($[M]^+$): 188.0197, measured: 188.0190. **m.p** = 50 °C. **b.p.** = 203.2 °C. **R_f** = 0.47 (*n*-Pentane/DCM**,** 1:1, (v/v)). The characterization data agrees with literature values.[21]

(trifluoromethoxy)isonicotinonitrile (5c)



5ca



5cb

The reaction was performed according to a modified version of Method E (6 h reaction time) with **4c** (5 eq., 30 mmol, 3.16 g) as the substrate and MeCN (0.4 M, 15 mL) as the solvent. The crude mixture was dissolved in hot Acetone and cold *n*-Pentane was added until dark red solids precipitated. The liquid was decanted and concentrated *in vacuo*. The crude mixture was further purified via column chromatography in two steps (*n*-Pentane/DCM and *n*-Pentane/MTBE, SiO_2). The products **5ca** (0,08 mmol, 15 mg, 1 %,) and **5cb** (0.91 mmol, 171 mg, 15 %) were obtained as colorless oils.

Crude Mixture 5c

Method E (6 mmol, 0.4 M, 6 h):

^{19}F NMR Yield = 27%

2-(trifluoromethoxy)isonicotinonitrile (5ca): **^{19}F-NMR** (376 MHz, Et_2O/MeCN) δ = -57.08.

3-(trifluoromethoxy)isonicotinonitrile (5cb): **^{19}F-NMR** (376 MHz, Et_2O/MeCN) δ = -58.76.

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm).

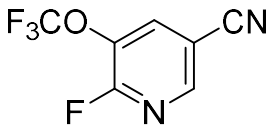
2-(trifluoromethoxy)isonicotinonitrile (5ca)

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 8.52 (d, *J*=5.1, 1H), 7.46 (dd, *J*=5.1, 1.2, 1H), 7.26 (s, 1H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -56.63. **b.p.** = 187.9 °C. **R_f** = 0.37 (*n*-Pentane/DCM**,** 1:1, (v/v)). The characterization data agrees with literature values.[21]

3-(trifluoromethoxy)isonicotinonitrile (5cb)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.82 (s, 1H), 8.76 (d, J=4.9, 1H), 7.64 (d, J=4.9, 1H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -57.98. **^{13}C-NMR** (176 MHz, $CDCl_3$) δ = 148.8, 145.3, 143.7, 126.6, 120.2 (q, J=263), 115.3, 112.2. **HRMS (EI)**: m/z calculated for $[C_7H_3F_3N_2O]^+$ ($[M]^+$): 188.0197, measured: 188.0184. **IR (ATR):** v (cm^{-1}): 3101, 3068, 3040, 2244, 1592, 1487, 1414, 1315, 1263, 1174, 1154, 1055, 924, 844, 829, 773, 737, 657, 626, 581, 542, 495, 457. **b.p.** = 184.1 °C. **R_f** = 0.07 (*n*-Pentane/DCM**,** 1:1, (v/v)).

6-fluoro-5-(trifluoromethoxy)nicotinonitrile (5d)



5d

The reaction was performed according to the general Method E with **4d** (5 eq., 30 mmol, 3.66 g) as the substrate and MeCN (2.0 M, 3 mL) as the solvent. The crude mixture was dissolved in hot Acetone and cold *n*-Pentane was added until dark red solids precipitated. The liquid was decanted and concentrated *in vacuo*. The crude mixture was further purified via column chromatography in two steps (2 x *n*-Pentane/MTBE, SiO_2) and finally with sublimation (50 °C water bath, 0.1 mbar). The product **5d** (1.5 mmol, 310 mg, 25 %) was obtained as white solid.

Crude Mixture 5d

Method E (0.5 mmol, 2 M):

^{19}F NMR Yield = 31%

6-fluoro-5-(trifluoromethoxy)nicotinonitrile (5d): **^{19}F-NMR** (376 MHz, MeCN) δ = -59.63 (d, *J*=4.2, 3F), -74.45 (s br, 1F)

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm).

Method B (0.5 mmol, 2 M):

^{19}F NMR Yield = 10%

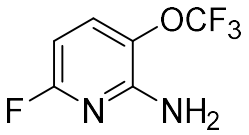
6-fluoro-5-(trifluoromethoxy)nicotinonitrile (5d): **^{19}F-NMR** (376 MHz, MeCN) δ = -59.63 (d, *J*=4.2, 3F), -74.44 (s br, 1F)

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm).

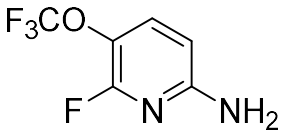
^{1}H-NMR (500 MHz, $CDCl_3$) δ = 8.50 (s, 1H), 8.00 (d, *J*=8.3, 1H). **^{1}H{-^{19}F}-NMR** (400 MHz, $CDCl_3$) δ = 8.50 (d, *J*=2.0, 1H), 8.00 (d, *J*=2.0, 1H).**^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -58.75 (d, *J*=3.8, 3F), -70.24 (s

br, 1F) **^{13}C{-^{1}H}-NMR** (176 MHz, $CDCl_3$) δ = 157.6 (d, *J*=253), 149.4 (d, *J*=16), 136.1, 132.3 (d, *J*=28), 120.3 (q, *J*=263, 263, 263), 114.2, 109.1 (d, *J*=5). **^{13}C{-^{19}F}-NMR** (101 MHz, Chloroform-*d*) δ = 157.6 (dd, *J*=13, 8), 149.4 (dd, *J*=192, 7), 136.0 (dd, *J*=172, 6), 132.3 (dd, *J*=5, 2), 120.3, 114.7 – 113.7 (m), 109.1 (dd, *J*=8, 2). **HRMS (EI)**: m/z calculated for $[C_7H_3F_4N_2O]^+$ ($[M]^+$): 206.0103, measured: 206.0103 **IR (ATR):** ν (cm^{-1}): 3080, 2241, 1586, 1469, 1417, 1303, 1278, 1204, 1170, 1145, 994, 960, 943, 885, 801, 763, 714, 688, 652, 625, 603, 582, 532, 492, 482, 460, 441. **mp** = 32.0 °C. **bp** = 190.5 °C. **R_f** = 0.54 (*n*-Pentane/DCM**,** 1:1, (v/v)).

6-Fluoro-(trifluoromethoxy)pyridin-2-amine (5e)



5ea



5eb

The reaction was performed according to Method B with **4e** (5 eq., 15 mmol, 1.68 g) as the substrate. The crude mixture was filtrated through SiO_2 with DCM, concentrated *in vacuo* and purified via column chromatography in two steps (*n*-Pentane/DCM and *n*-Pentane/MTBE, SiO_2). The products **5ea** (0.54 mmol, 105 mg, 18 %) and **5eb** (0.51 mmol, 99 mg, 17 %) were acquired as white solids.

Crude Mixture 5e

Method B (3 mmol, 0.2 M):

^{19}F NMR Yield = 44%

6-Fluoro-3-(trifluoromethoxy)pyridin-2-amine (5ea):**^{19}F-NMR** (376 MHz, Et_2O/MeCN) δ = -59.30 (s, 3F), -72.25 (s br, 1F).

6-Fluoro-5-(trifluoromethoxy)pyridin-2-amine (5eb):**^{19}F-NMR** (376 MHz, Et_2O/MeCN) δ = -60.56 (d, *J*=4.8, 3F),-85.43 (s br, 1F).

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm).

Method E (0.5 mmol, 0.2 M, 6 h):

^{19}F NMR Yield = 44%

6-Fluoro-3-(trifluoromethoxy)pyridin-2-amine (5ea):**^{19}F-NMR** (376 MHz, MeCN) δ = -59.48 (s, 3F), -72.76 (s br, 1F).

6-Fluoro-5-(trifluoromethoxy)pyridin-2-amine (5eb):**^{19}F-NMR** (376 MHz, MeCN) δ = -60.63 (d, *J*=4.8, 3F),

-85.05 (s br, 1F).

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm).

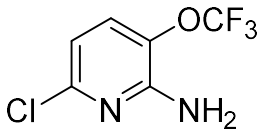
6-Fluoro-3-(trifluoromethoxy)pyridin-2-amine (5ea)

^{1}H-NMR (700 MHz, $CDCl_3$) δ = 7.43 (t, *J*=8.1, 1H), 6.20 (dd, *J*=8.4, 3.2, 1H), 4.93 (s br, 2H). **^{19}F-NMR** (565 MHz, $CDCl_3$) δ = -58.54, -71.35 (s br). **^{13}C-NMR** (176 MHz, $CDCl_3$) δ = 160.4 (d, *J*=239), 150.9 (d, *J*=18), 133.7 (d, *J*=10), 128.2, 121.0 (q, *J*=259), 97.0 (d, *J*=40). **HRMS (EI)**: m/z calculated for $[C_6H_4F_4N_2O]^+$ ($[M]^+$): 196.0260, measured: 196.0242. **IR (ATR):** ν (cm^{-1}): 3519, 3315, 3260, 3239, 3189, 1638, 1611, 1481, 1449, 1253, 1232, 1194, 1153, 1128, 1063, 989, 944, 909 814,793, 753, 666, 620, 600, 581, 540, 508, 459, 449. **m.p.** = 52.4 °C. **b.p.** = 182.0 °C. **R_f** = 0.57 (DCM).

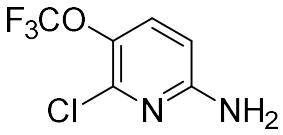
6-Fluoro-5-(trifluoromethoxy)pyridin-2-amine (5eb)

^{1}H-NMR (700 MHz, $CDCl_3$) δ = 7.42 (t, *J*=8.6, 1H), 6.29 (d, *J*=8.6, 1H), 4.64 (s br, 2H). **^{19}F-NMR** (565 MHz, $CDCl_3$) δ = -59.78 (d, *J*=4.8), -83.19 (s br). **^{13}C-NMR** (176 MHz, $CDCl_3$) δ = 155.7 (d, *J*=15), 154.8 (d, *J*=241), 136.2, 121.9 (d, *J*=27), 120.8 (q, *J*=259), 105.1 (d, *J*=5). **HRMS (EI)**: m/z calculated for $[C_6H_4F_4N_2O]^+$ ($[M]^+$): 196.0260, measured: 196.0259. **IR (ATR):** ν (cm^{-1}): 3493, 3316, 3201, 1638, 1613, 1573, 1495, 1425, 1406, 1377, 1297, 1190, 1162, 1117, 1091, 973, 914, 825, 803, 741, 690, 661, 634, 606, 573, 543, 514, 446. **m.p.** = 74.5 °C. **b.p.** = 215.0 °C. **R_f** = 0.44 (DCM).

6-Chloro-(trifluoromethoxy)pyridin-2-amine (5f)



5fa



5fb

The reaction was performed according to Method B with **4f** (5 eq., 15 mmol, 1.93 g) as the substrate. The crude mixture was filtrated through SiO_2 with DCM, concentrated *in vacuo* and purified via column chromatography (*n*-Pentane/DCM, SiO_2), **5fb** was further purified via sublimation (60 °C water bath at 0.1 mbar). The products **5fa** (0.54 mmol, 114 mg, 18 %) and **5fb** (0.42 mmol, 90 mg, 14 %) were obtained as white solids.

Crude Mixture 5f

Method B (3 mmol, 0.2 M):

^{19}F NMR Yield = 39 %

6-Chloro-3-(trifluoromethoxy)pyridin-2-amine (5fa):**^{19}F-NMR** (376 MHz, Et_2O/MeCN) δ = -58.95.

6-Chloro-5-(trifluoromethoxy)pyridin-2-amine (5fb):**^{19}F-NMR** (376 MHz, Et_2O/MeCN) δ = -59.33.

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm).

Method E (0.5 mmol, 0.2 M, 6 h):

^{19}F NMR Yield = 30 %

6-Chloro-3-(trifluoromethoxy)pyridin-2-amine (5fa):**^{19}F-NMR** (376 MHz, Et_2O/MeCN) δ = -59.20.

6-Chloro-5-(trifluoromethoxy)pyridin-2-amine (5fb):**^{19}F-NMR** (376 MHz, Et_2O/MeCN) δ = -59.49.

Internal ^{19}F-NMR Chemical Shift Reference: $PhCF_3$ (-63.10 ppm).

6-Chloro-3-(trifluoromethoxy)pyridin-2-amine (5fa)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.31 (d, *J*=8.3, 1H), 6.63 (d, *J*=8.2, 1H), 5.15 (s, 2H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -58.20. **^{13}C-NMR** (176 MHz, $CDCl_3$) δ = 152.0, 146.9, 131.0, 130.2, 120.9 (q, *J*=260), 113.0. **HRMS (EI)**: m/z calculated for $[C_6H_4ClF_3N_2O]^+$ ($[M]^+$): 211.9964, measured: 211.9974. **IR (ATR):** ν (cm^{-1}): 3508, 3297, 3237, 3167, 3107, 1625, 1593, 1473, 1419, 1251, 1192, 1152, 1118, 1037, 944, 898, 813, 792, 752, 694, 646, 628, 578, 555, 468, 429. **m.p.** = 67.8 °C. **b.p.** = 214.7 °C. **R_f** = 0.48 (DCM).

6-Chloro-5-(trifluoromethoxy)pyridin-2-amine (5fb)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.36 (d, *J*=8.7, 1H), 6.39 (d, *J*=8.7, 1H), 4.84 (s, 2H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ = -58.65. **^{13}C-NMR** (176 MHz, $CDCl_3$) δ = 156.7, 142.7, 133.9, 133.6, 120.8 (q, *J*=259), 107.4. **HRMS (EI)**: m/z calculated for $[C_6H_4ClF_3N_2O]^+$ ($[M]^+$): 211.9964, measured: 211.9976. **IR (ATR):** ν (cm^{-1}): 3486, 3315, 3294, 3253, 1637, 1612, 1482, 1451, 1253, 1232, 1195, 1151, 1128, 1062, 988, 909, 814, 792, 753, 665, 620, 601, 578, 538, 508, 459, 449. **m.p.** = 92.0 °C. **b.p.** = 245.8 °C. **R_f** = 0.31 (DCM).

6 NMR Spectra

6.1 NMR Spectra of Trifluoromethoxylated Arenes

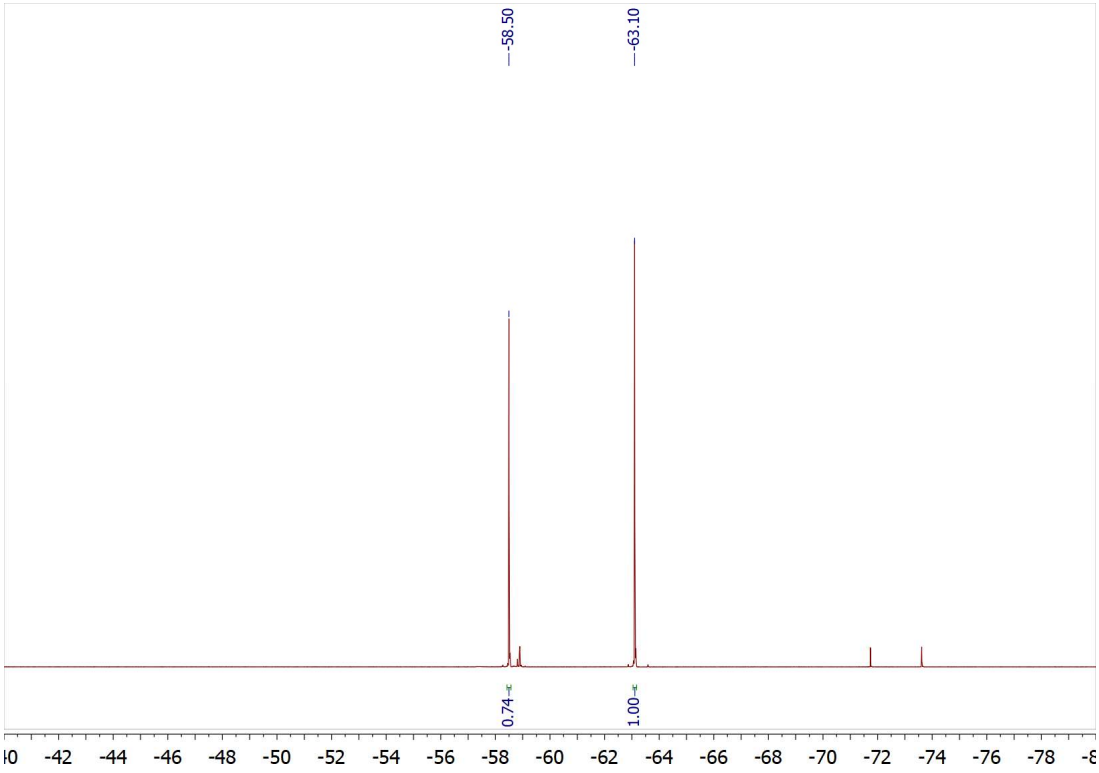


Figure S1. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method A using 1.benzene (**2a**) as substrate.

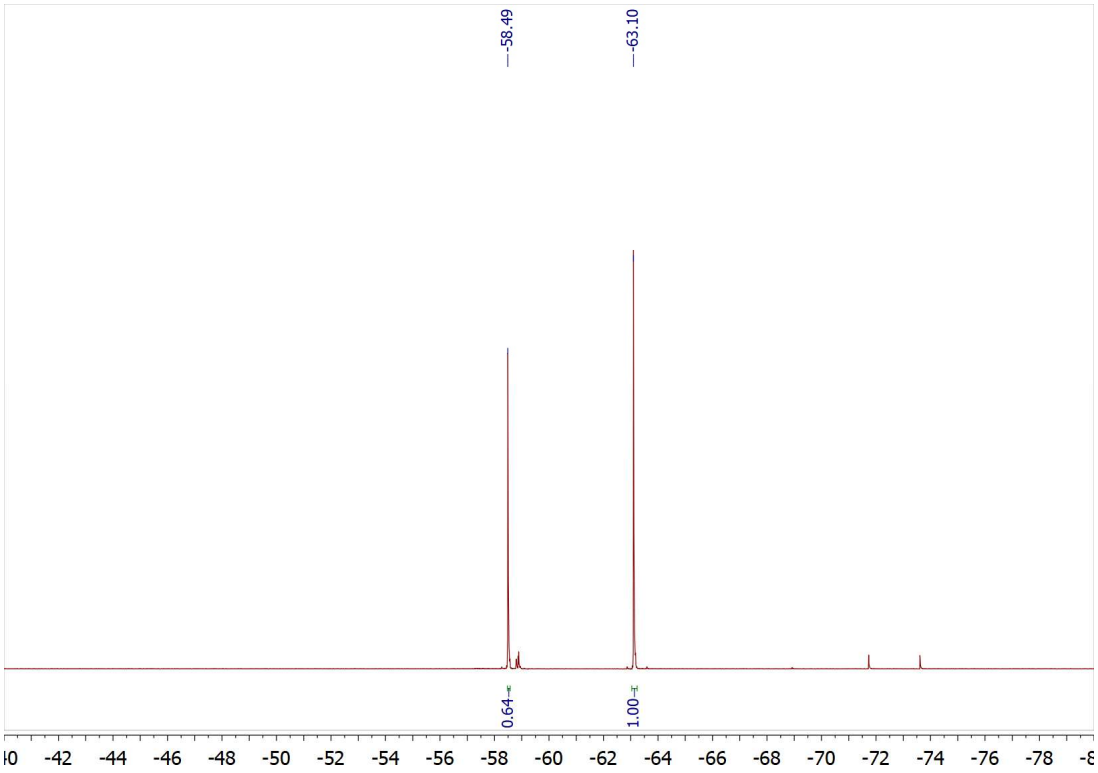


Figure S2. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method B using benzene (**2a**) as substrate.

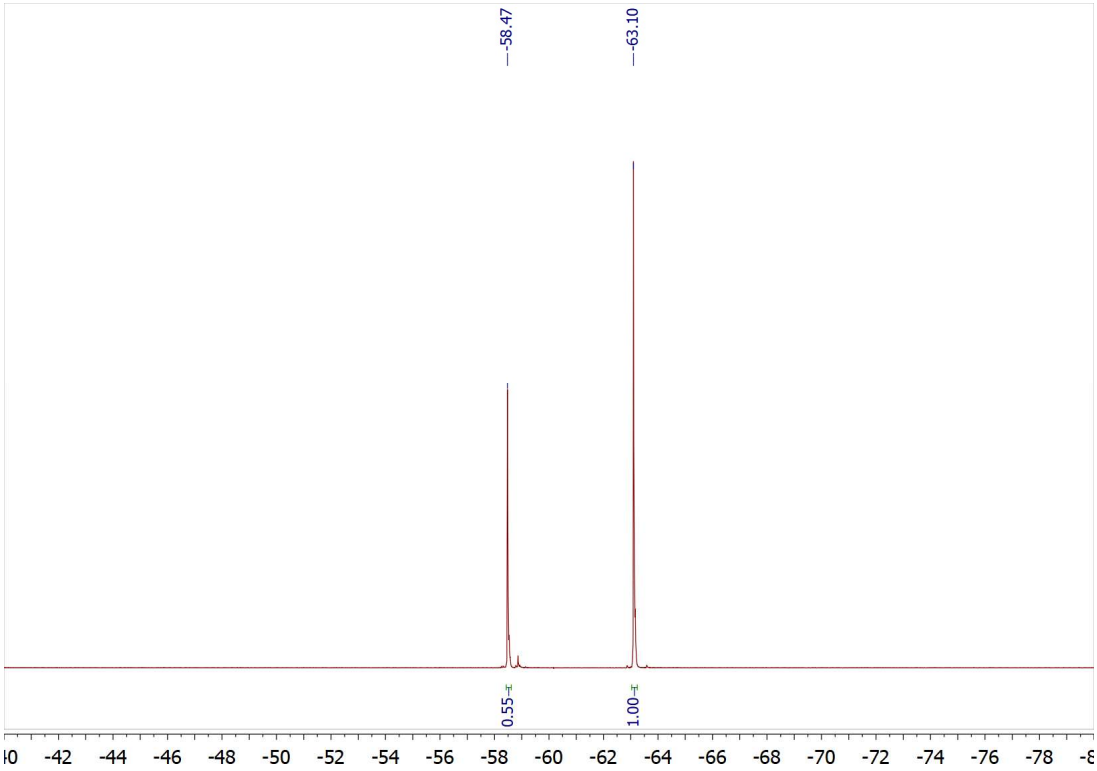


Figure S3. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method C using benzene (**2a**) as substrate.

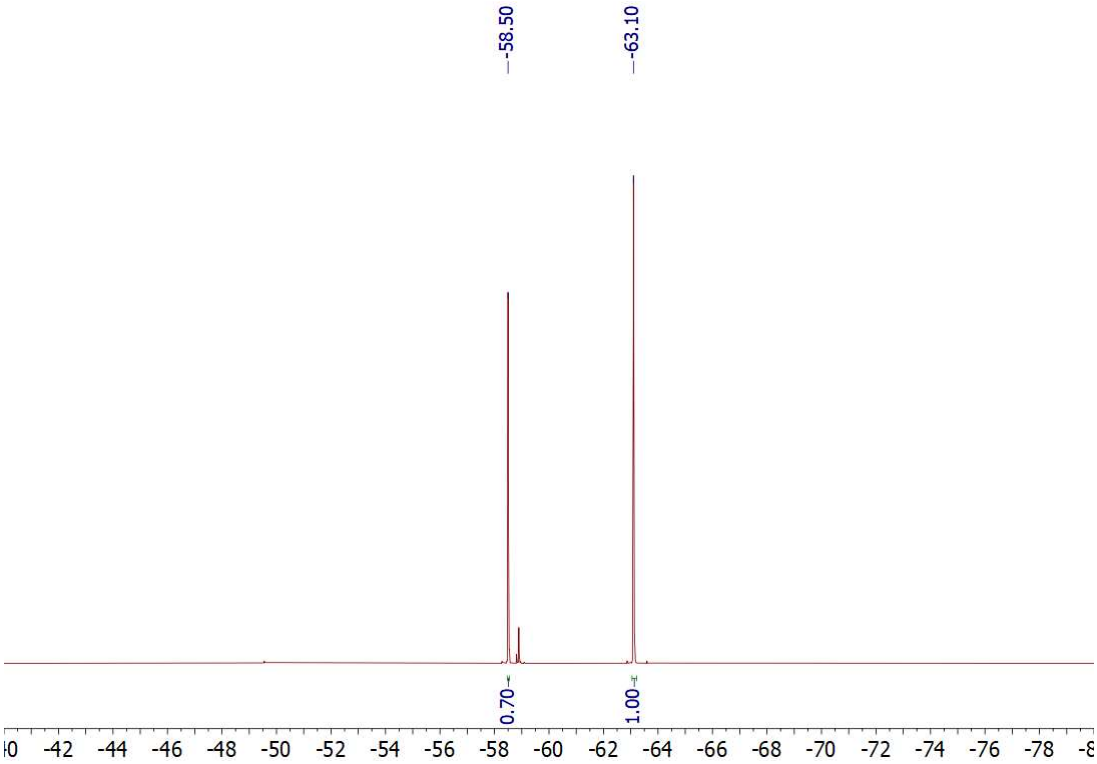


Figure S4. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method D using benzene (**2a**) as substrate.

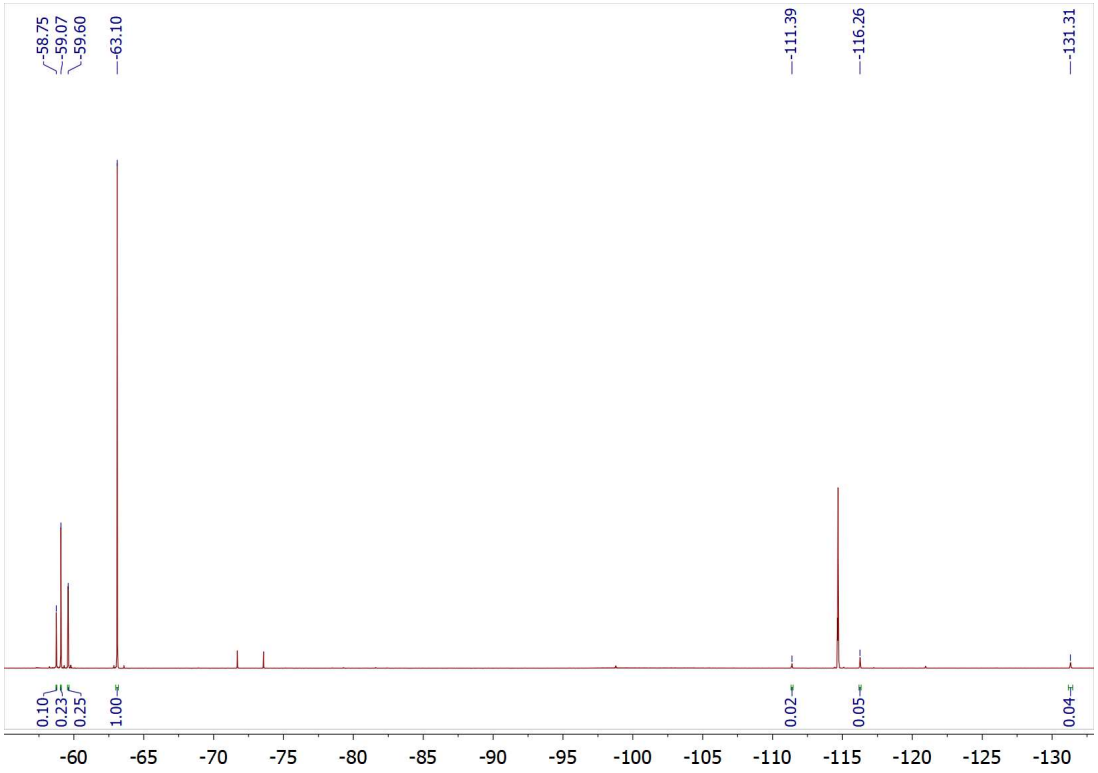


Figure S5. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method A using fluorobenzene (**2b**) as substrate.

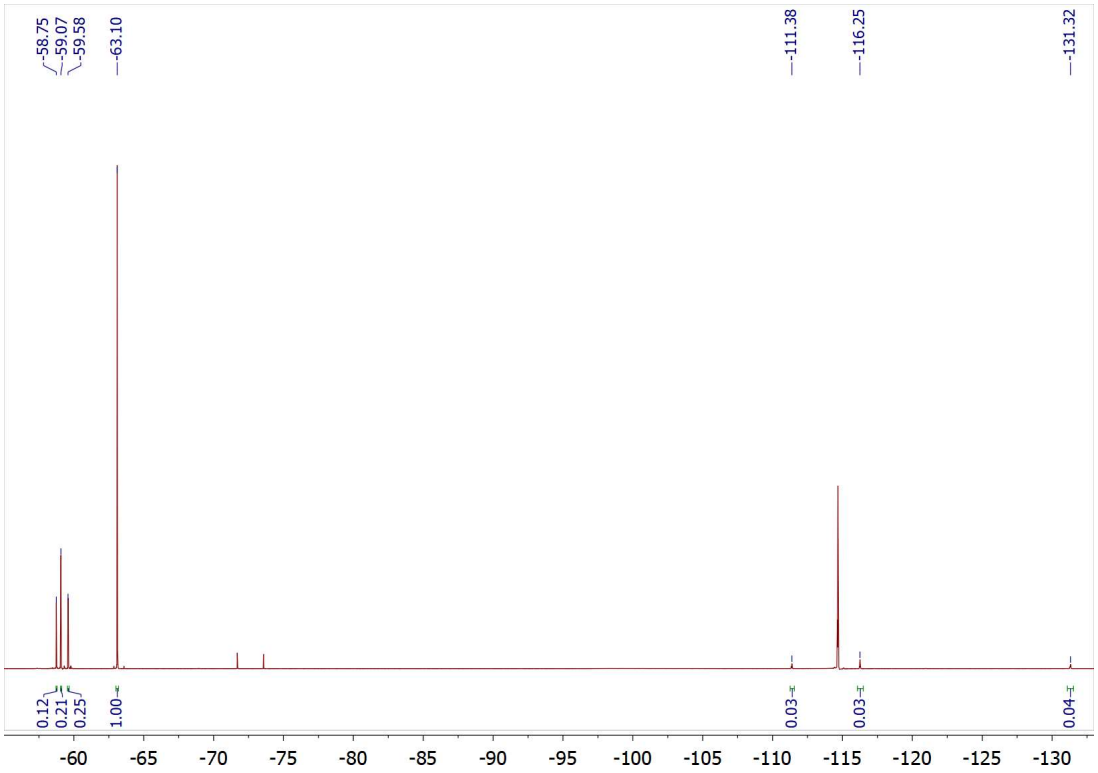


Figure S6. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method B using fluorobenzene (**2b**) as substrate.

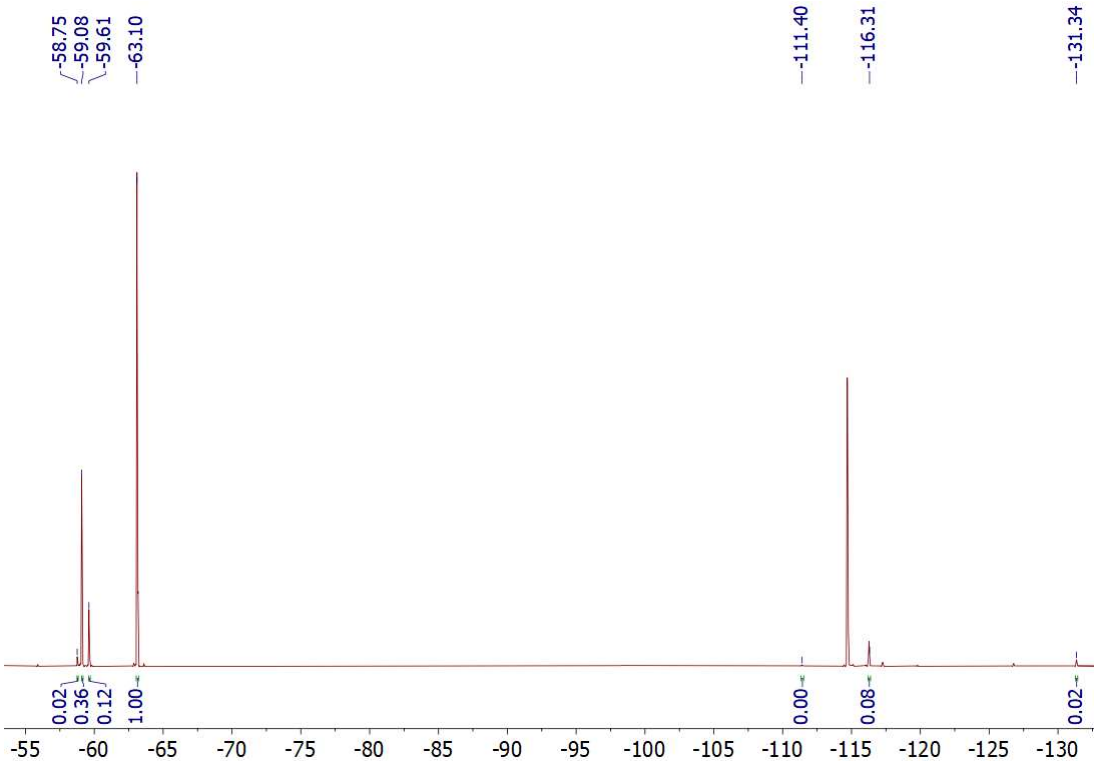


Figure S7. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method D using fluorobenzene (**2b**) as substrate.

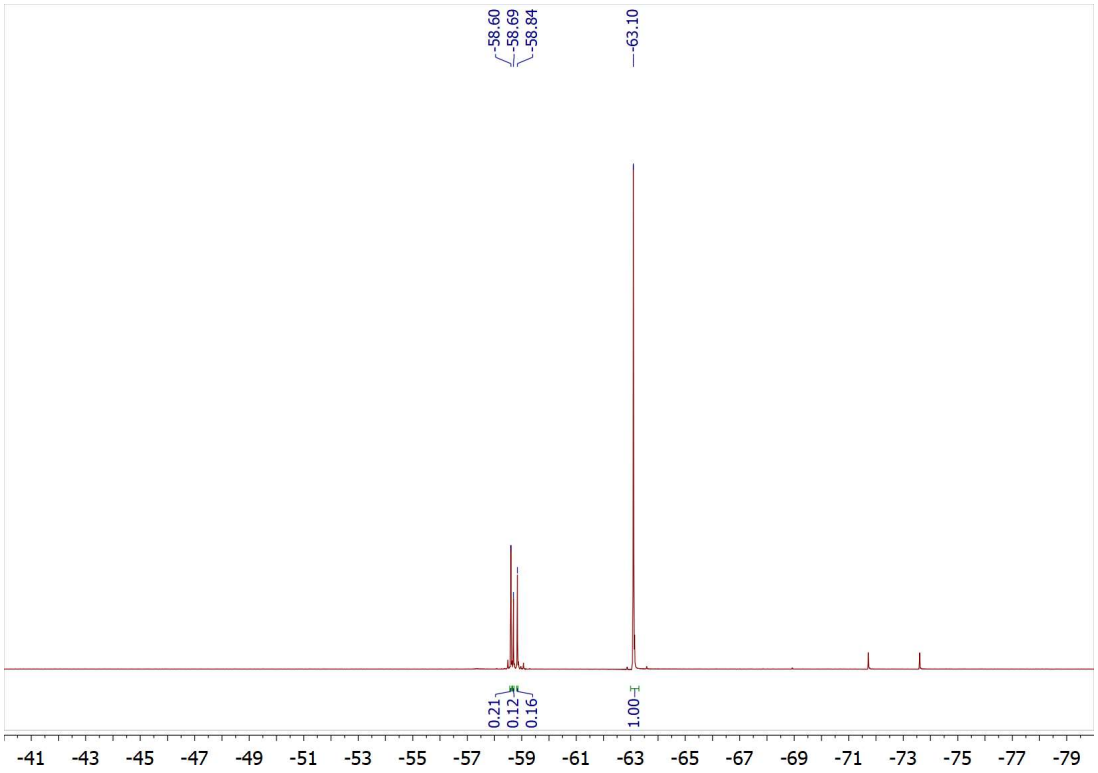


Figure S8. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method D using chlorobenzene (**2c**) as substrate.

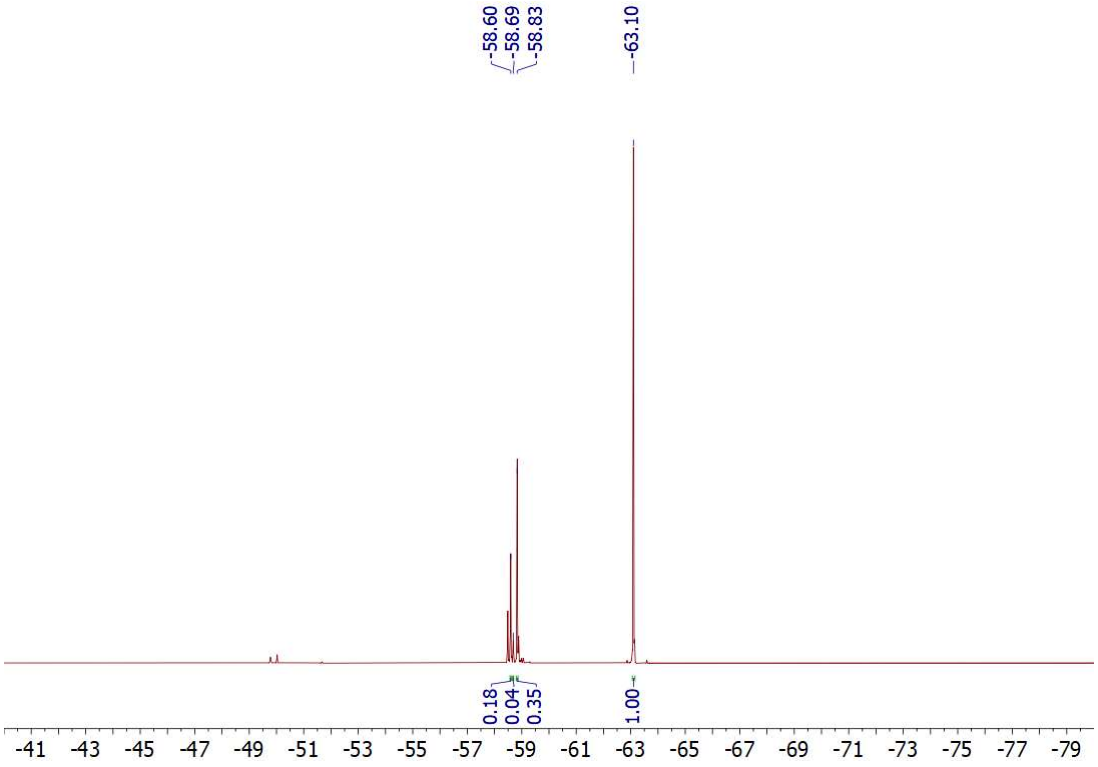


Figure S9. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method D with chlorobenzene (**2c**) as substrate.

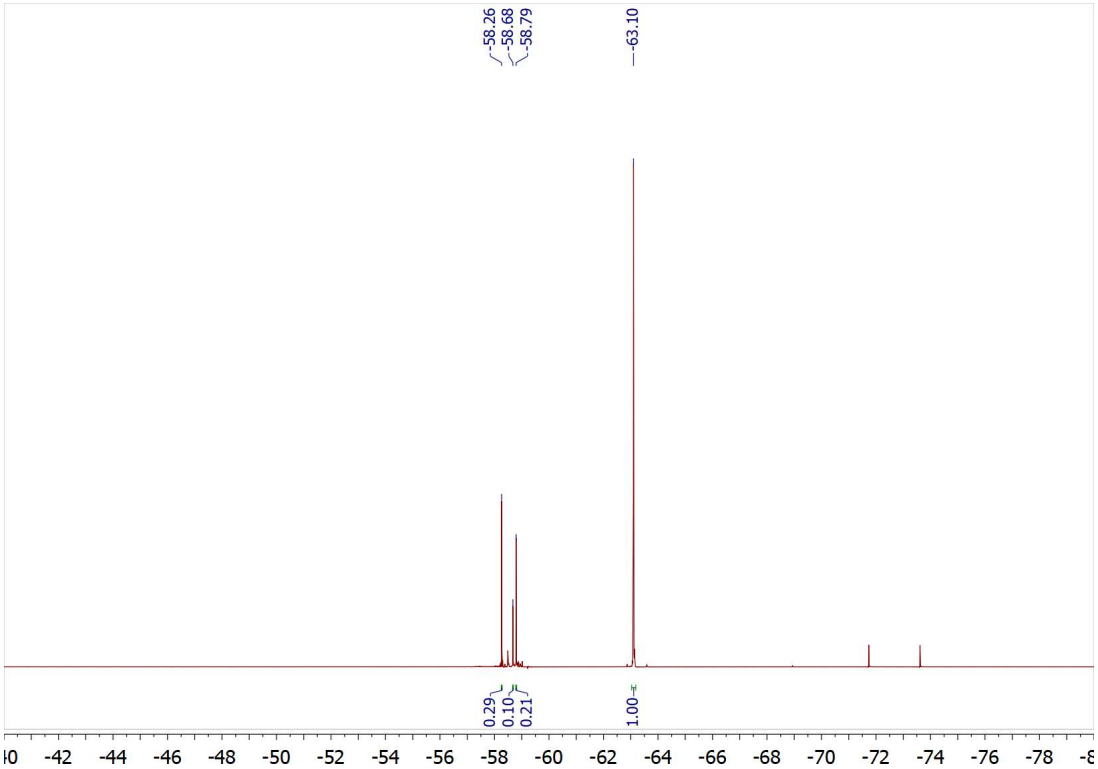


Figure S10. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method A using bromobenzene (**2d**) as substrate.

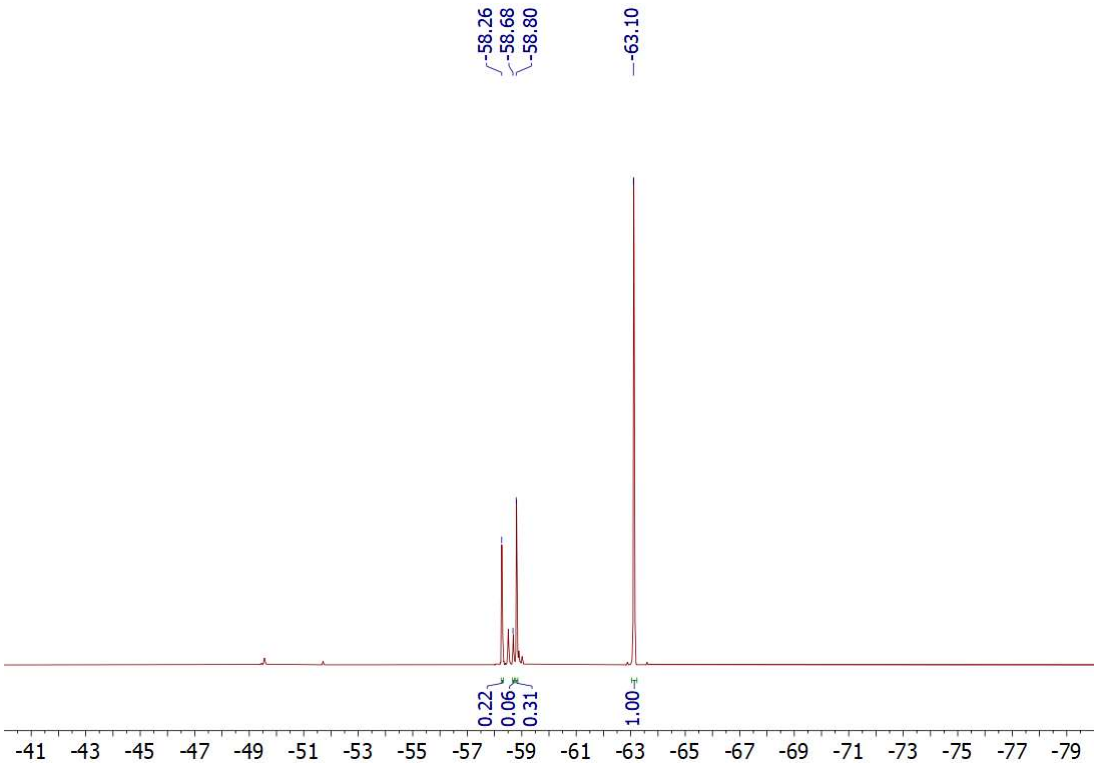


Figure S11. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method D using bromobenzene (**2d**) as substrate.

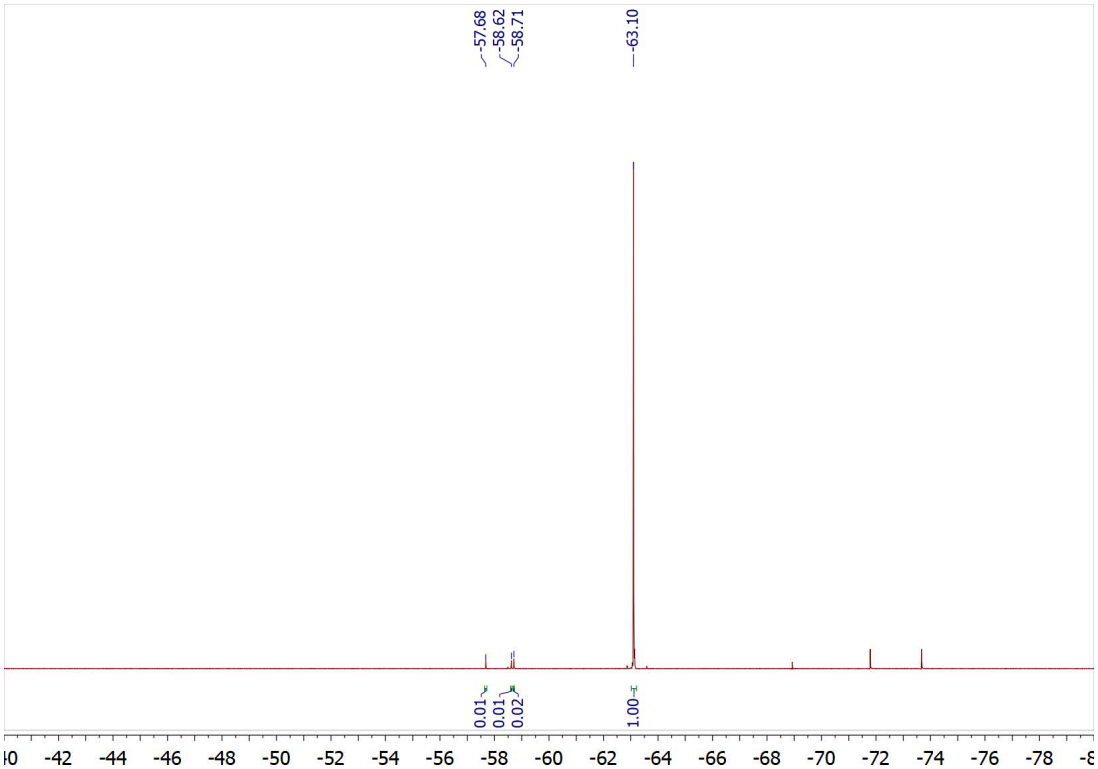


Figure S12. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method A using iodobenzene (**2e**) as substrate.

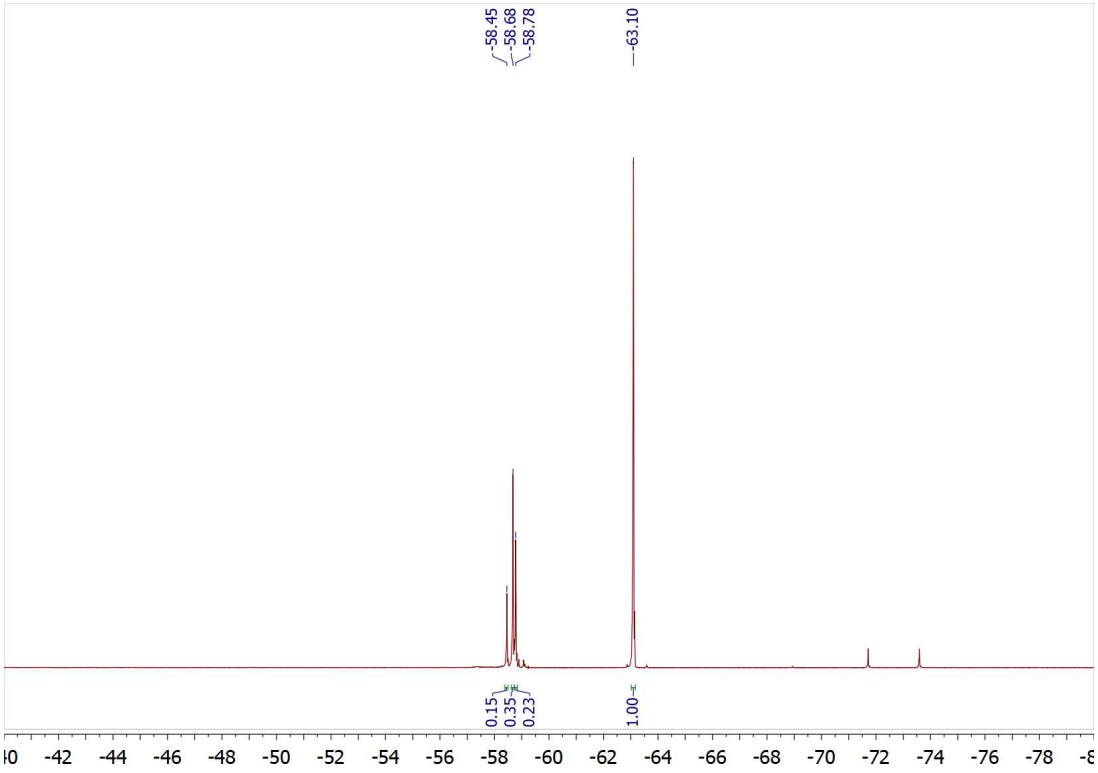


Figure S13. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method A using benzonitrile (**2f**) as substrate.

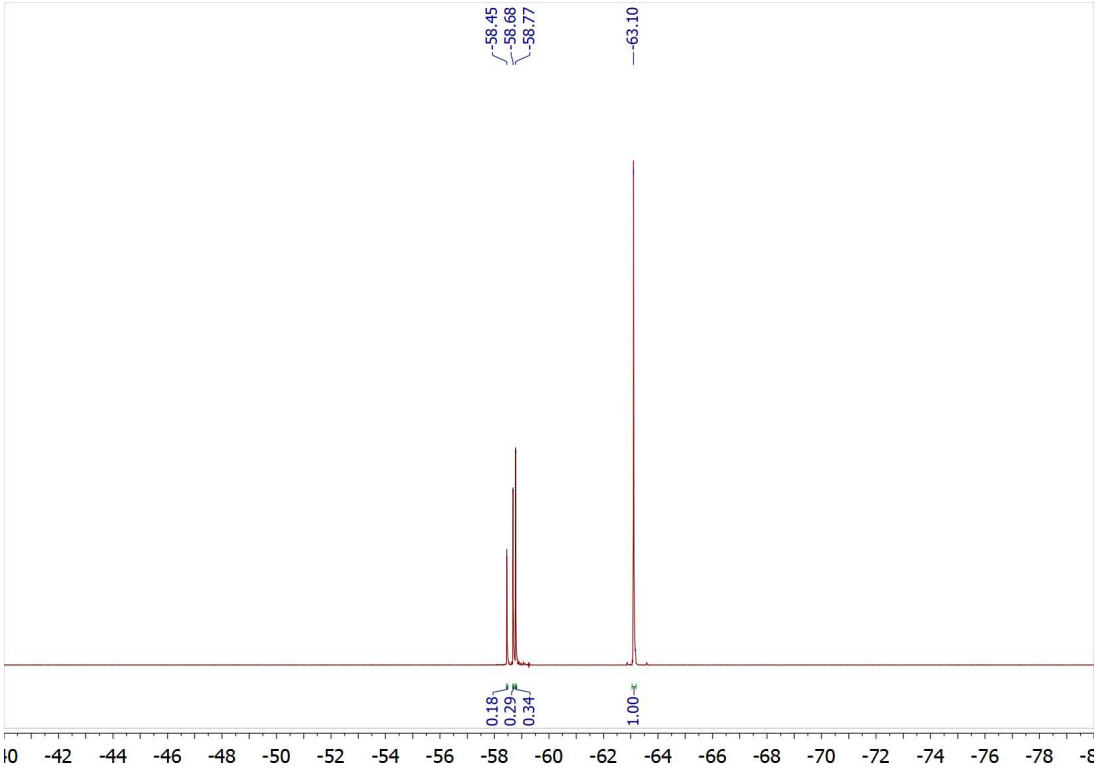


Figure S14. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method D (10 eq, substrate, 5 mol% TEMPO, no solvent) using benzonitrile (**2f**) as substrate.

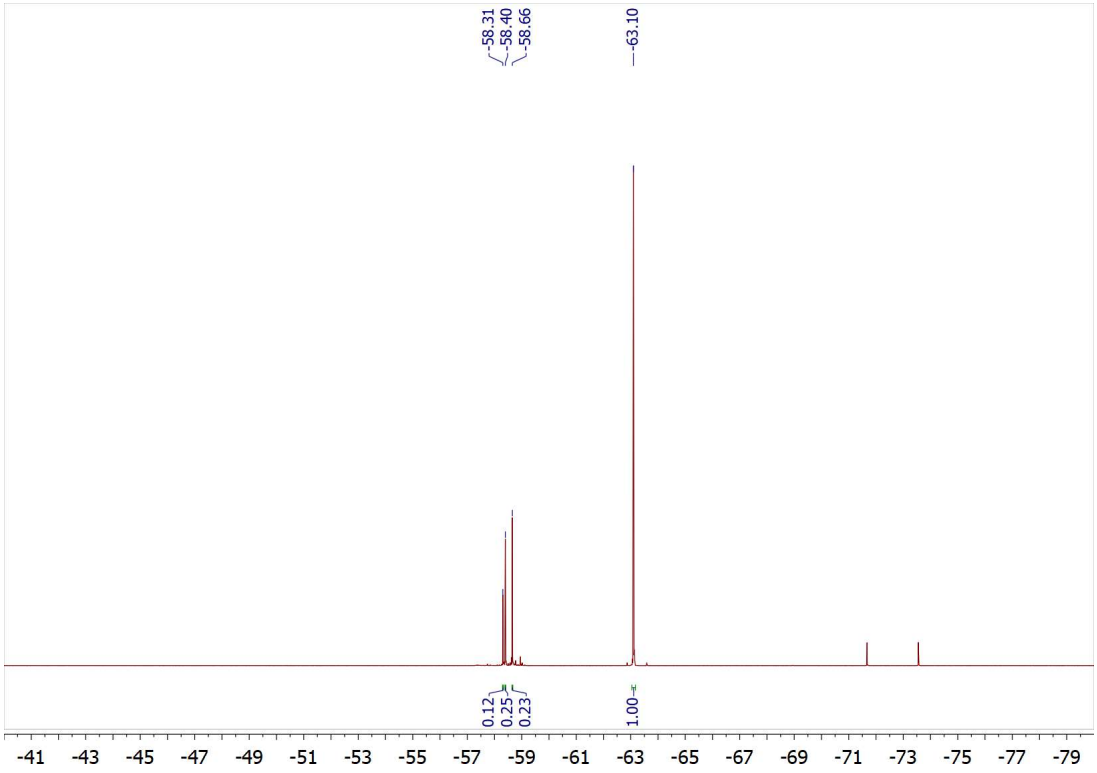


Figure S15. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method A using benzaldehyde (**2g**) as substrate.

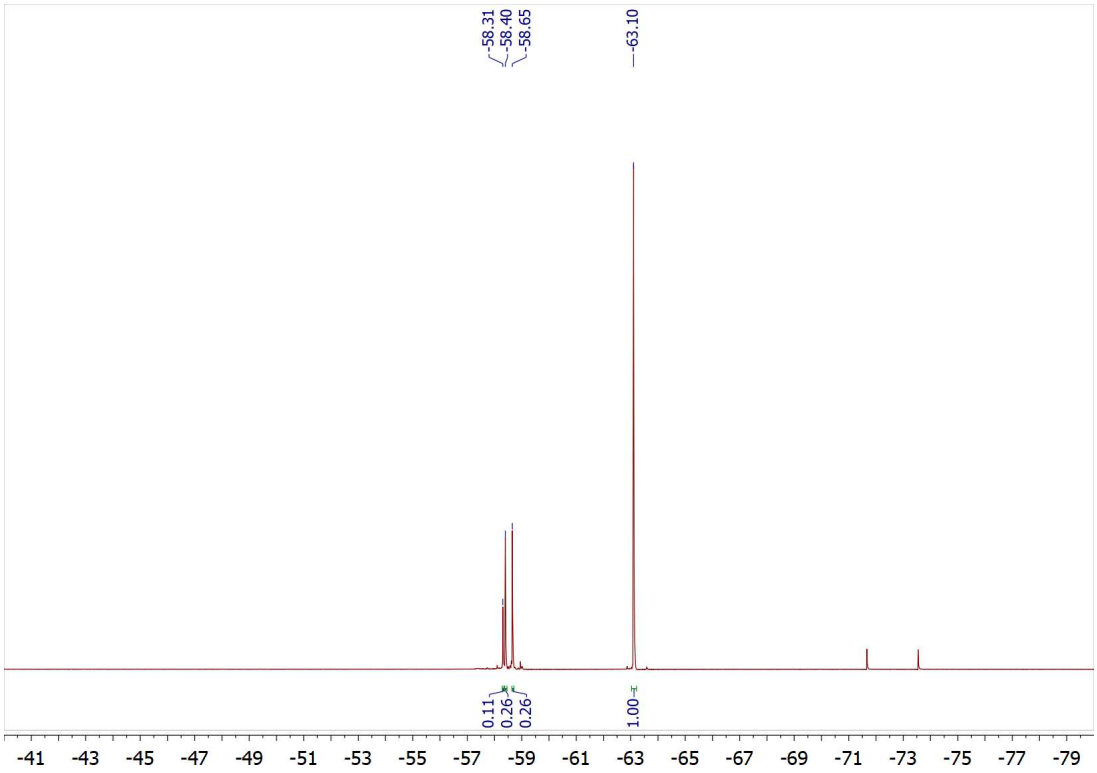


Figure S16. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method B using benzaldehyde (**2g**) as substrate.

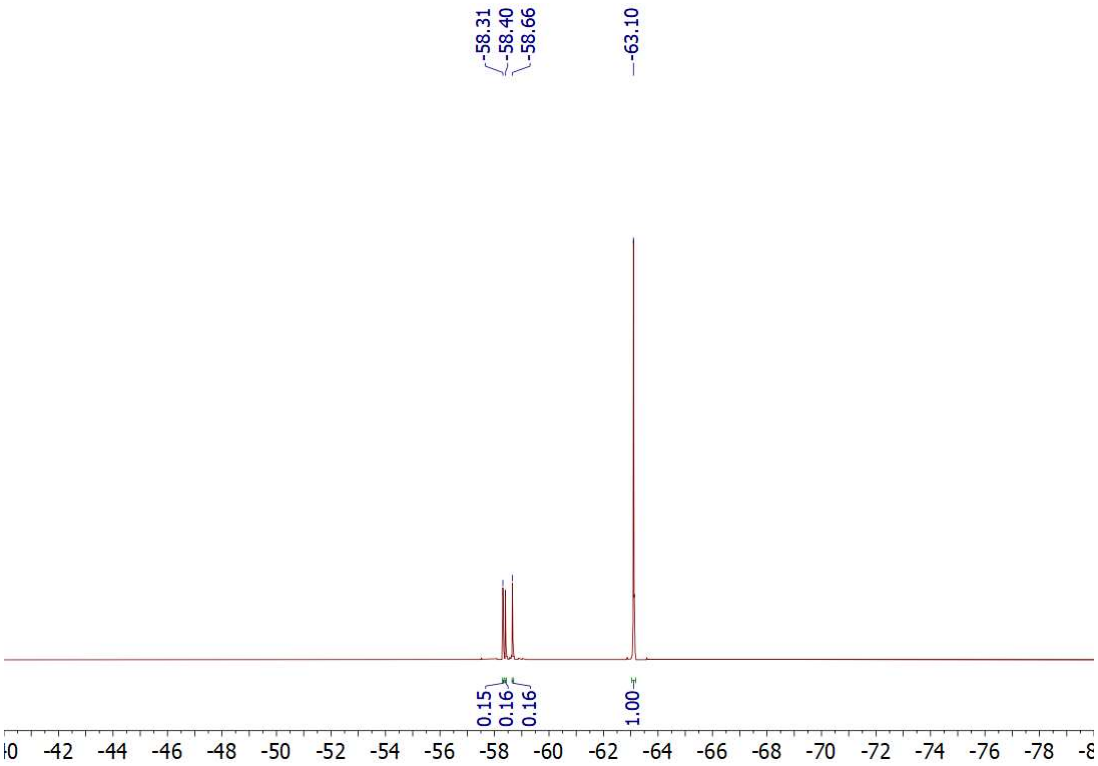


Figure S17. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method D using benzaldehyde (**2g**) as substrate.

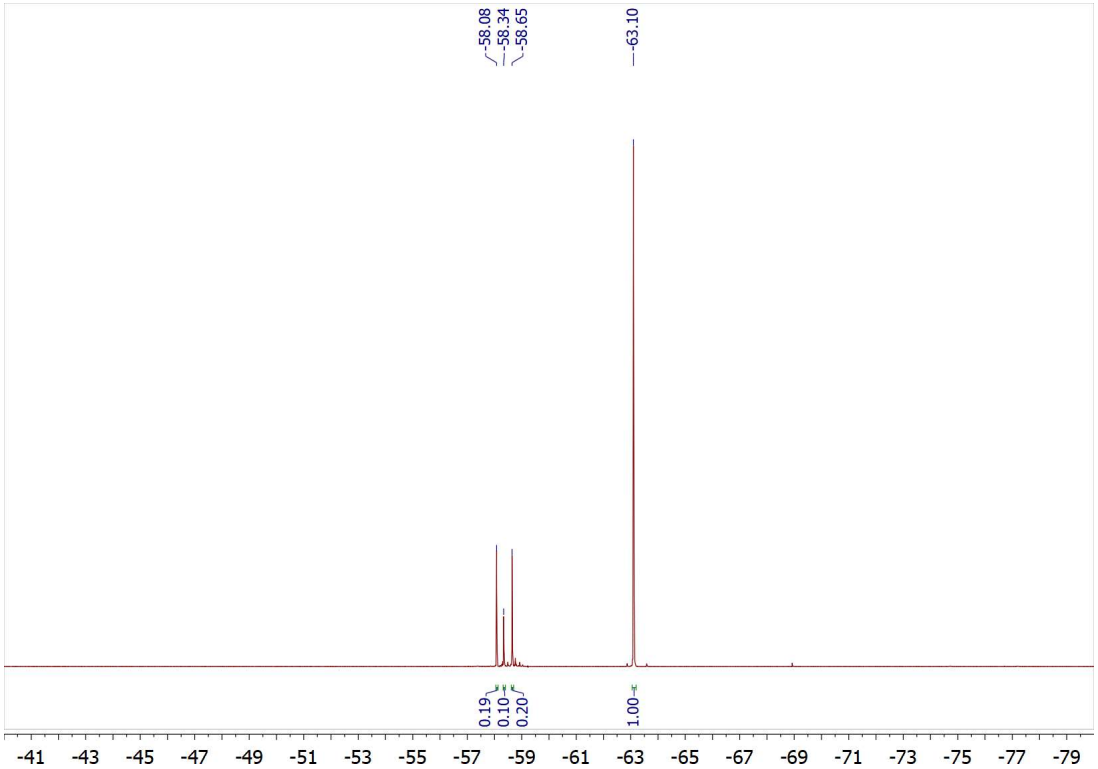


Figure S18. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method A using benzoic acid (**2h**) as substrate.

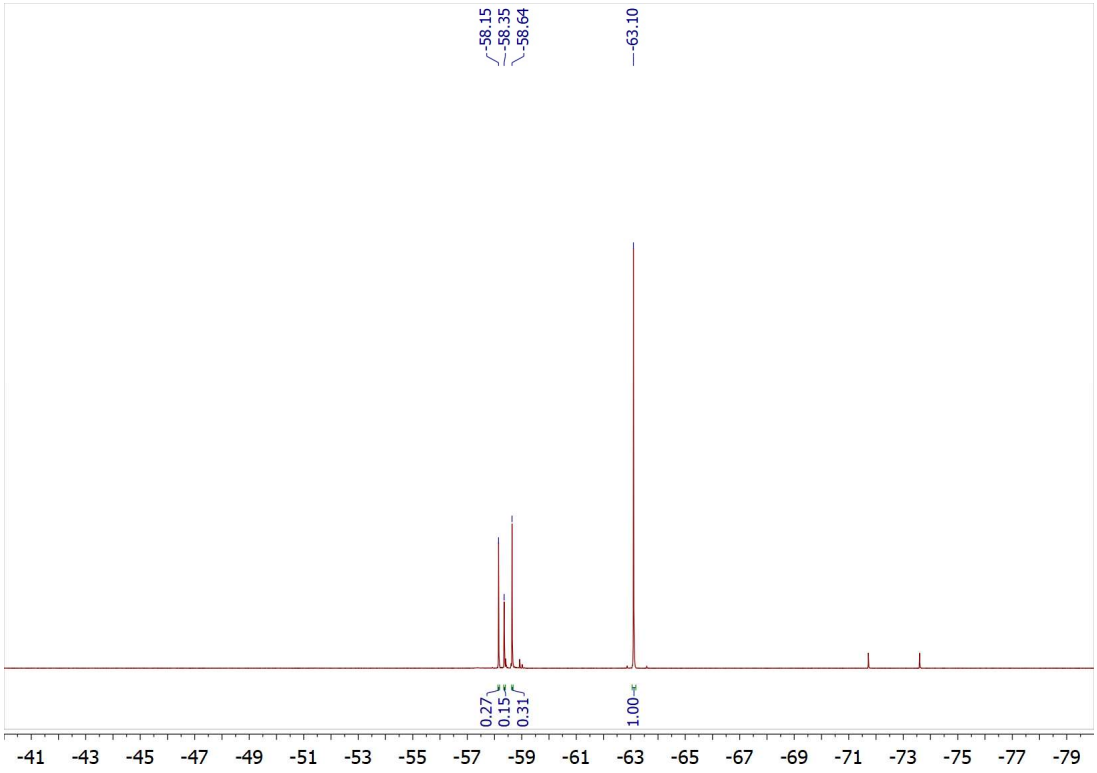


Figure S19. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method A using methyl benzoate (**2i**) as substrate.

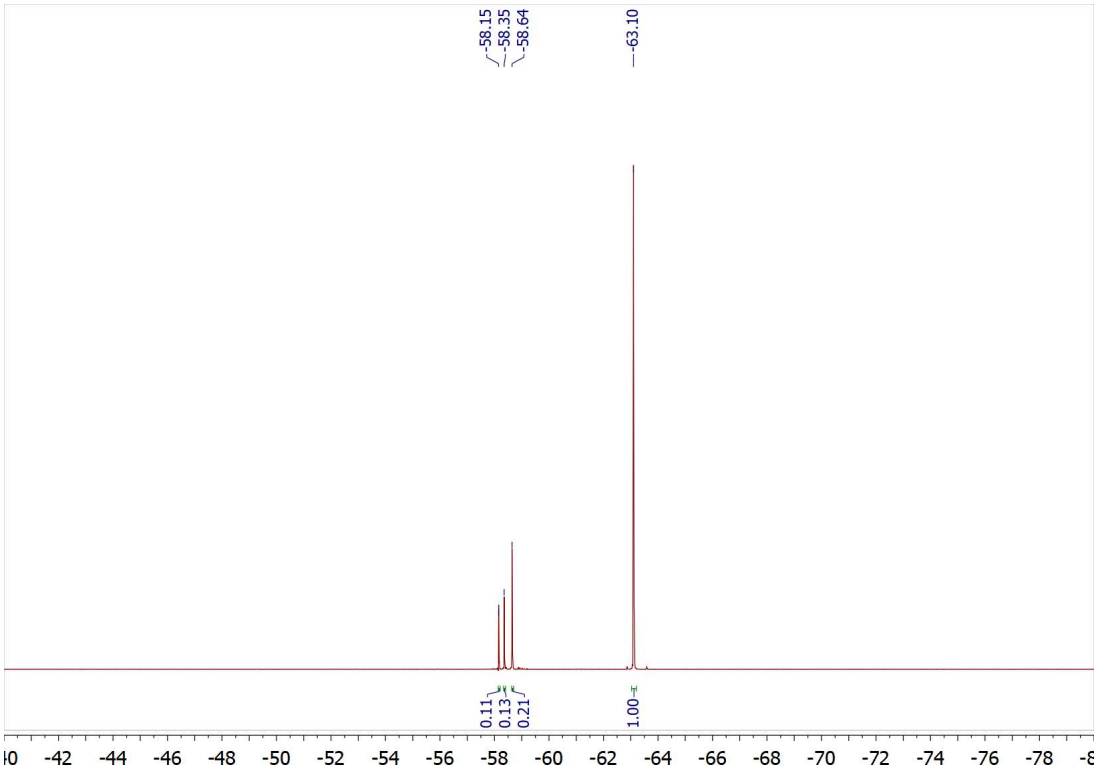


Figure S20. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method D (5 mol% TEMPO, no solvent) using methyl benzoate (**2i**) as substrate.

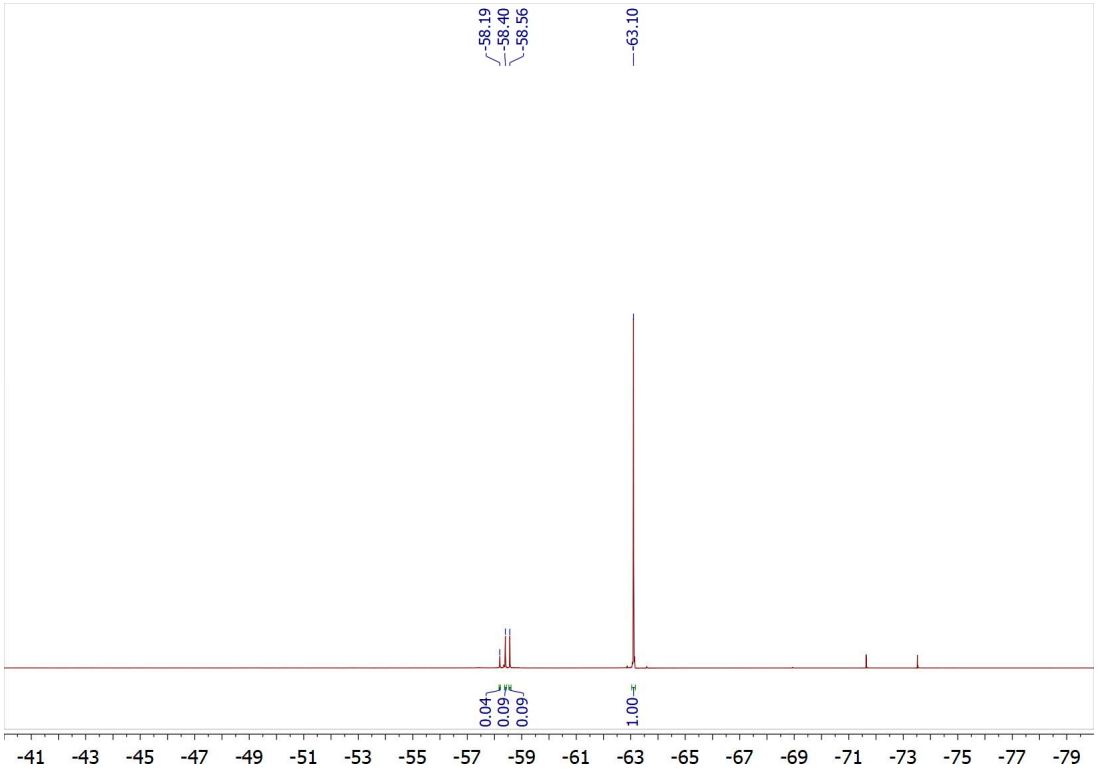


Figure S21. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method B using benzamide (**2j**) as substrate.

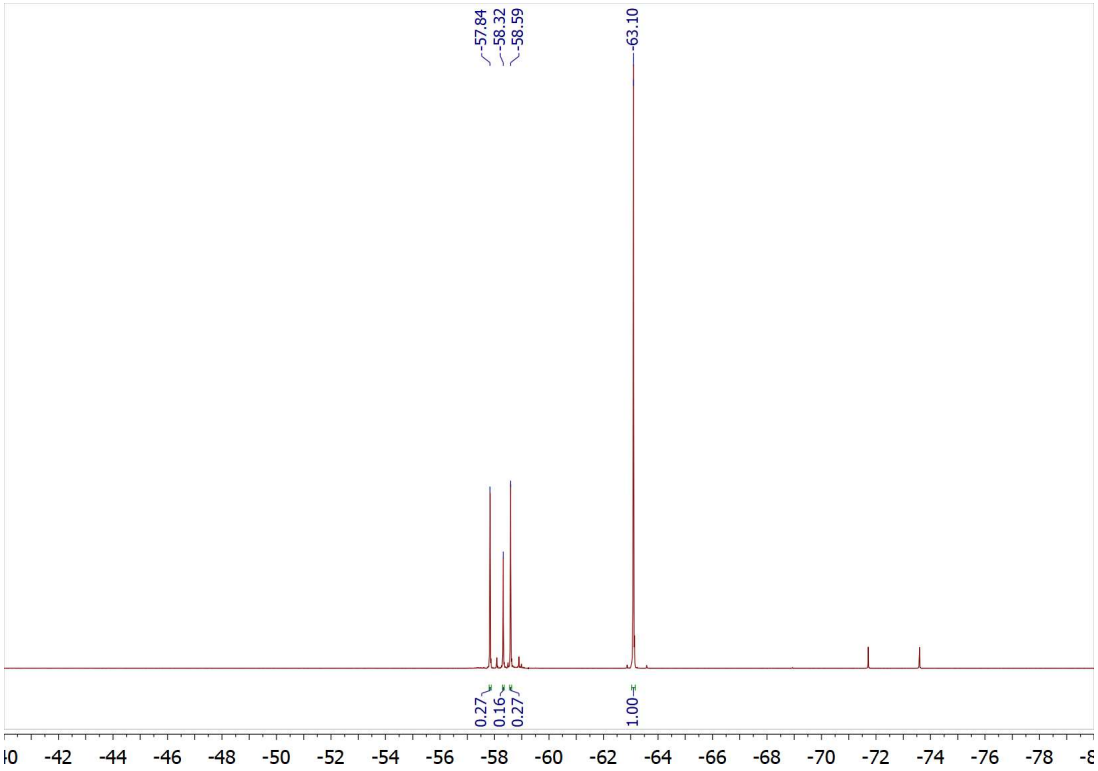


Figure S22. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method A using acetophenone (**2k**) as substrate.

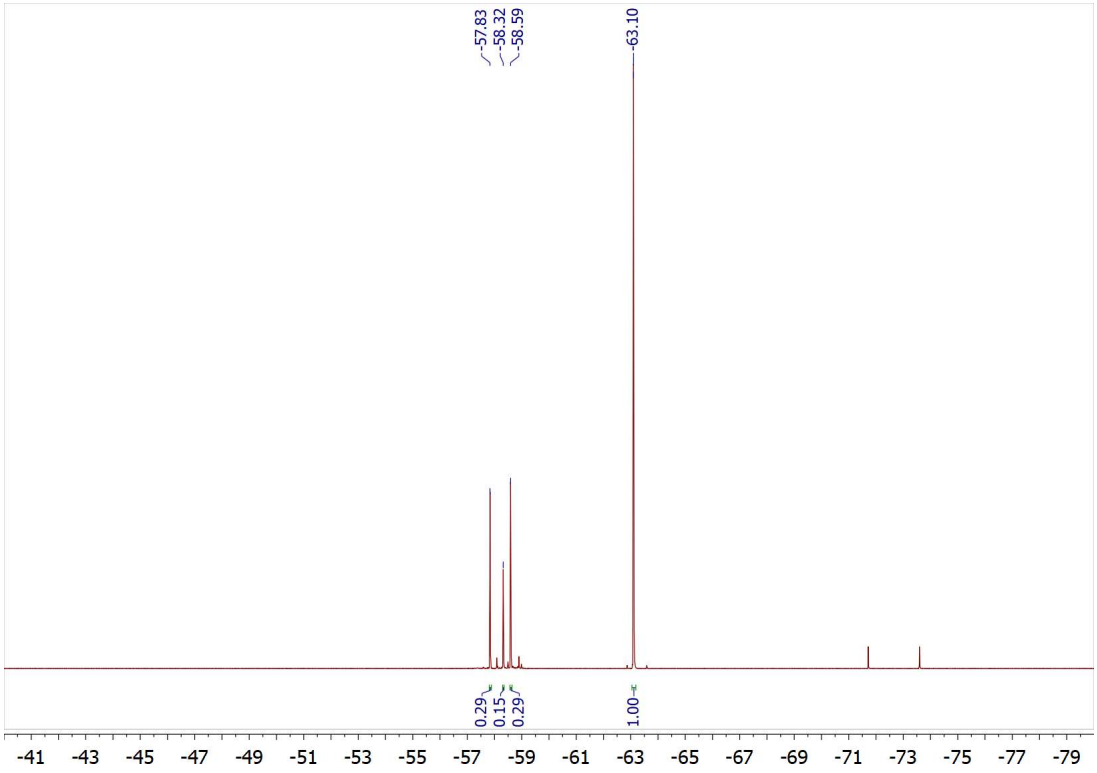


Figure S23. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method B using acetophenone (**2k**) as substrate.

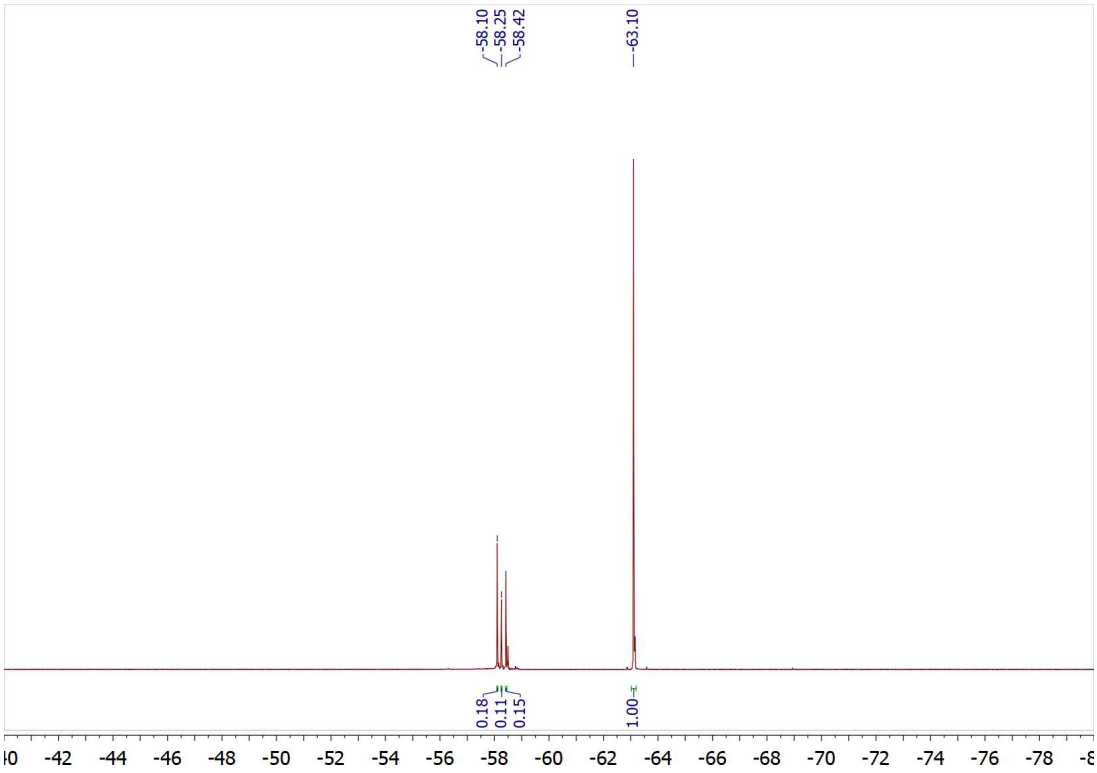


Figure S24. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method B using 4,4,5,5-tetramethyl-2-(trifluoromethoxy)phenyl-1,3,2-dioxaborolane (**2l**) as substrate.

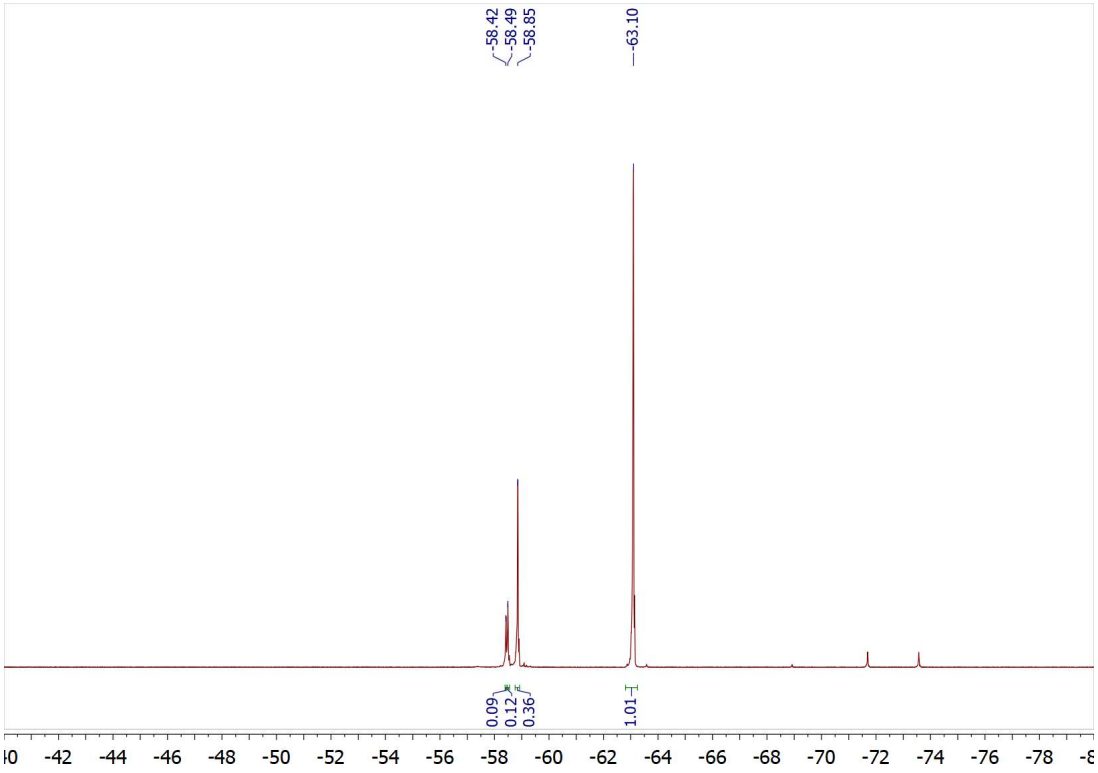


Figure S25. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method A using nitrobenzene (**2m**) as substrate.

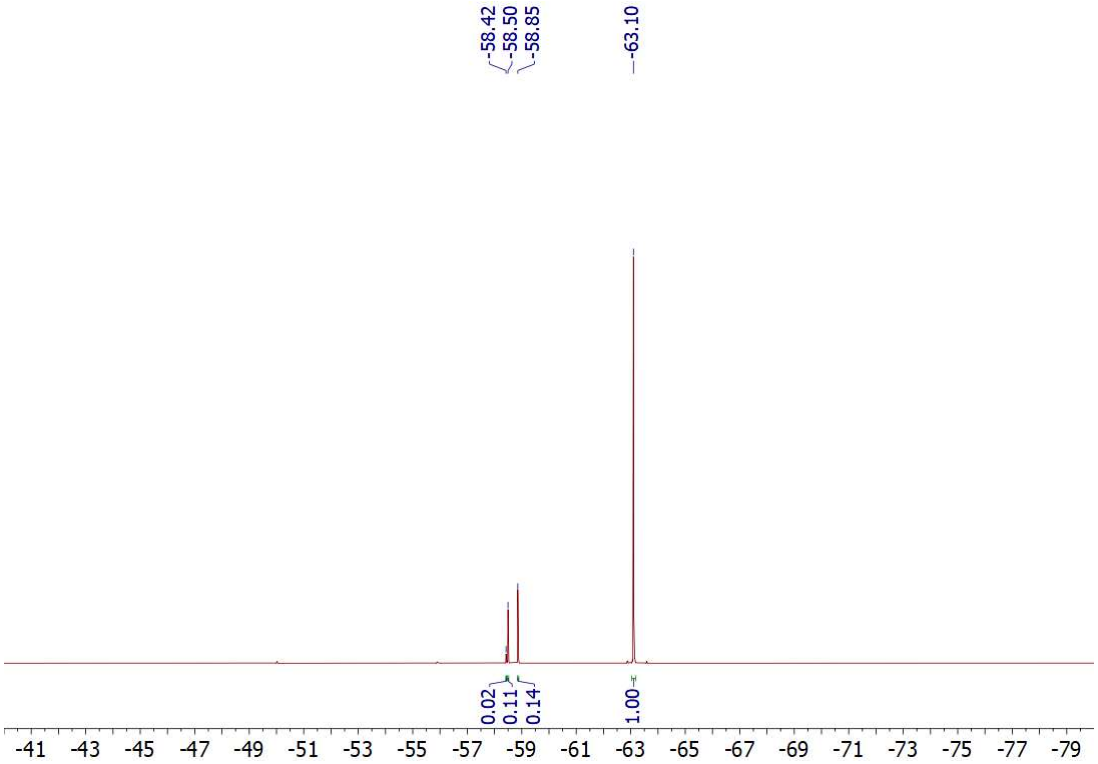


Figure S26. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method D using nitrobenzene (**2m**) as substrate.

6.2 NMR Spectra of Trifluoromethoxylated Pyridines

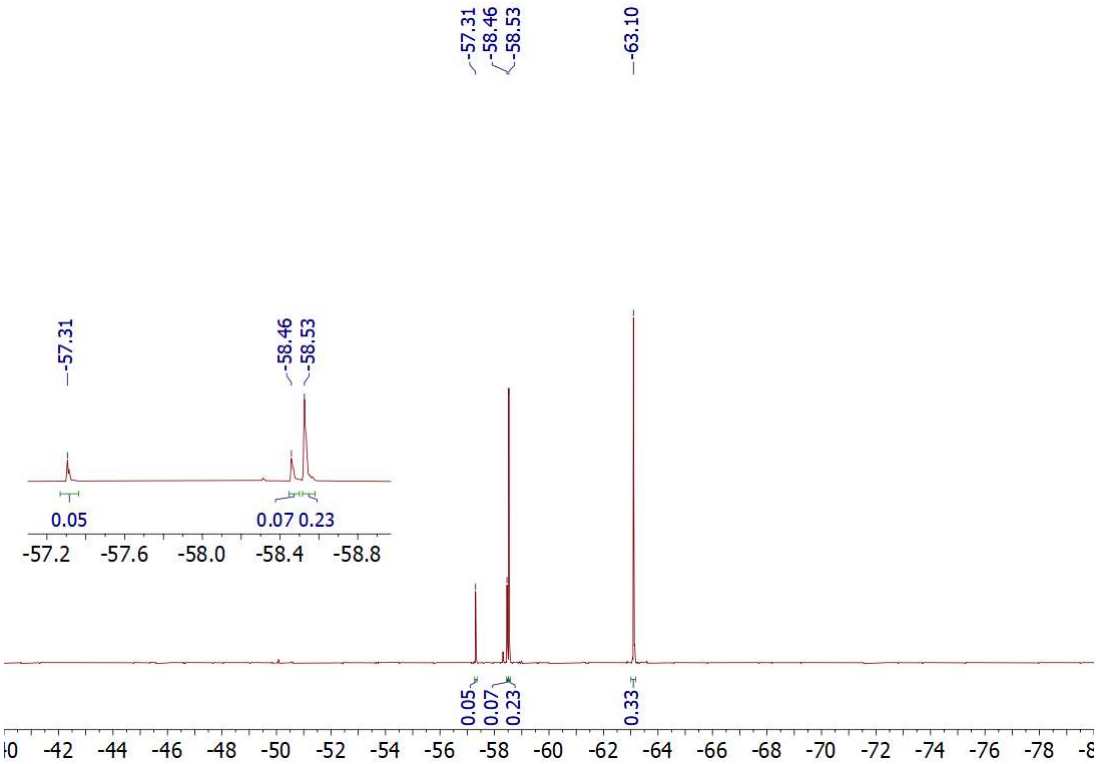


Figure S27. ^{19}F-NMR-Spectrum (376 MHz, Et_2O) of a reaction mixture prepared by modified method E (6 mmol scale, no solvent) using picolinonitrile (**4a**) as substrate and trifluorotoluene (2 mmol) as internal standard.

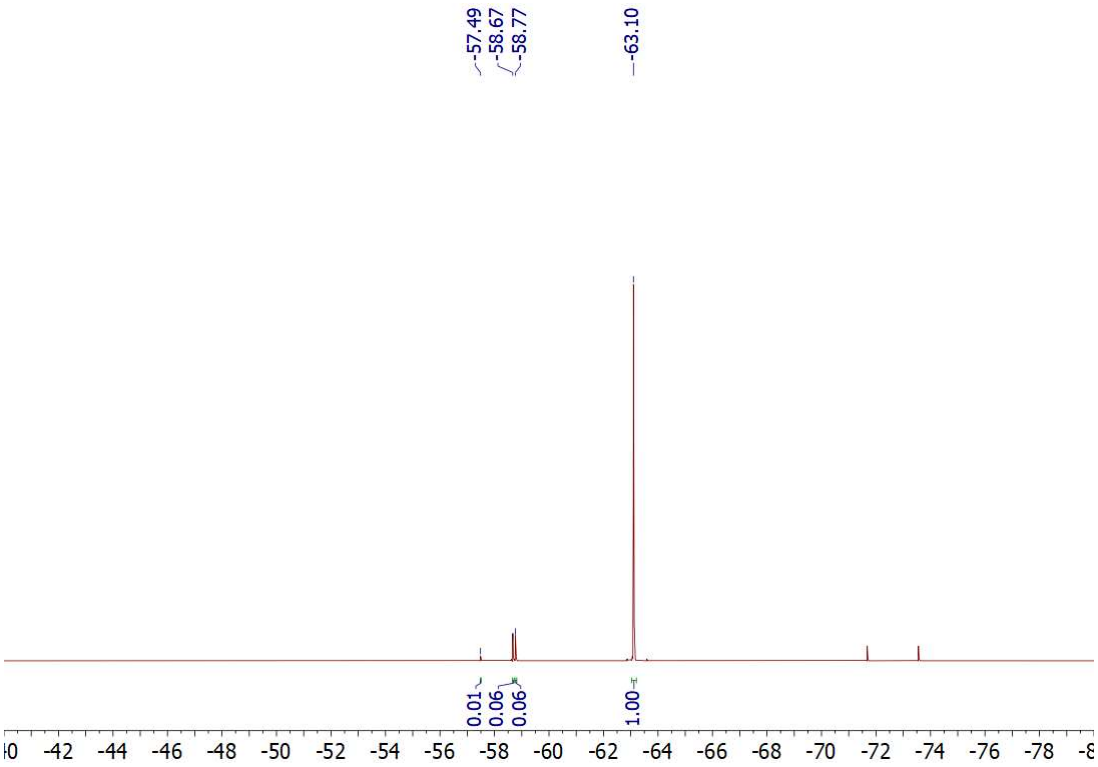


Figure S28. ^{19}F-NMR-Spectrum (376 MHz, Et_2O) of a reaction mixture prepared by method B (0.5 mmol, 2.0 M) using picolinonitrile (**4a**) as substrate and trifluorotoluene (0.5 mmol) as internal standard.

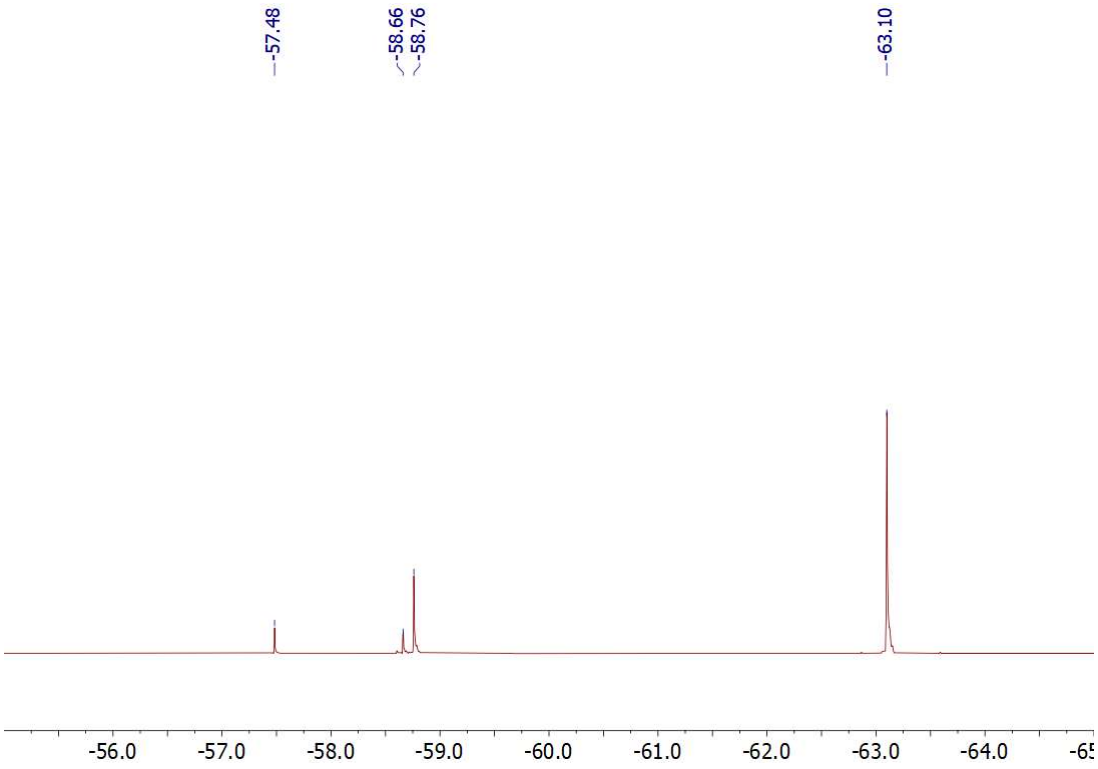


Figure S29. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method E (0.5 mmol scale, no solvent) using picolinonitrile (**4a**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments.

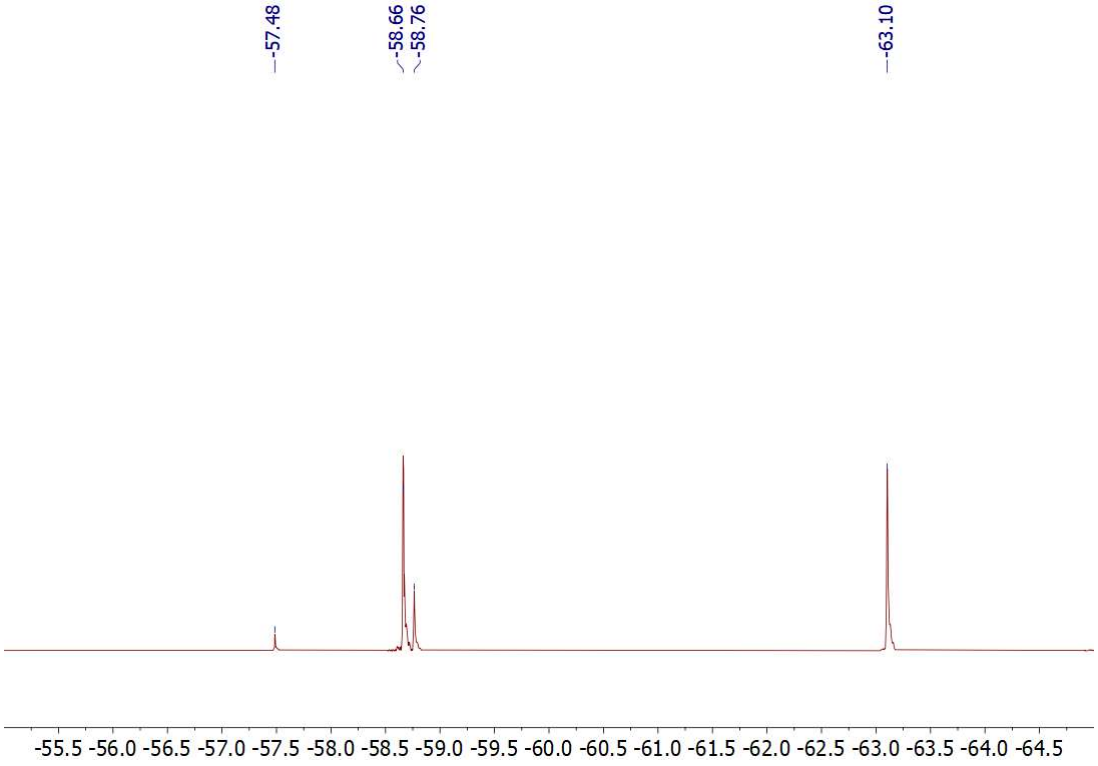


Figure S30. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method E (0.5 mmol scale, no solvent) using picolinonitrile (**4a**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments. Spiked with 3-(trifluoromethoxy)picolinonitrile (**5aa**).

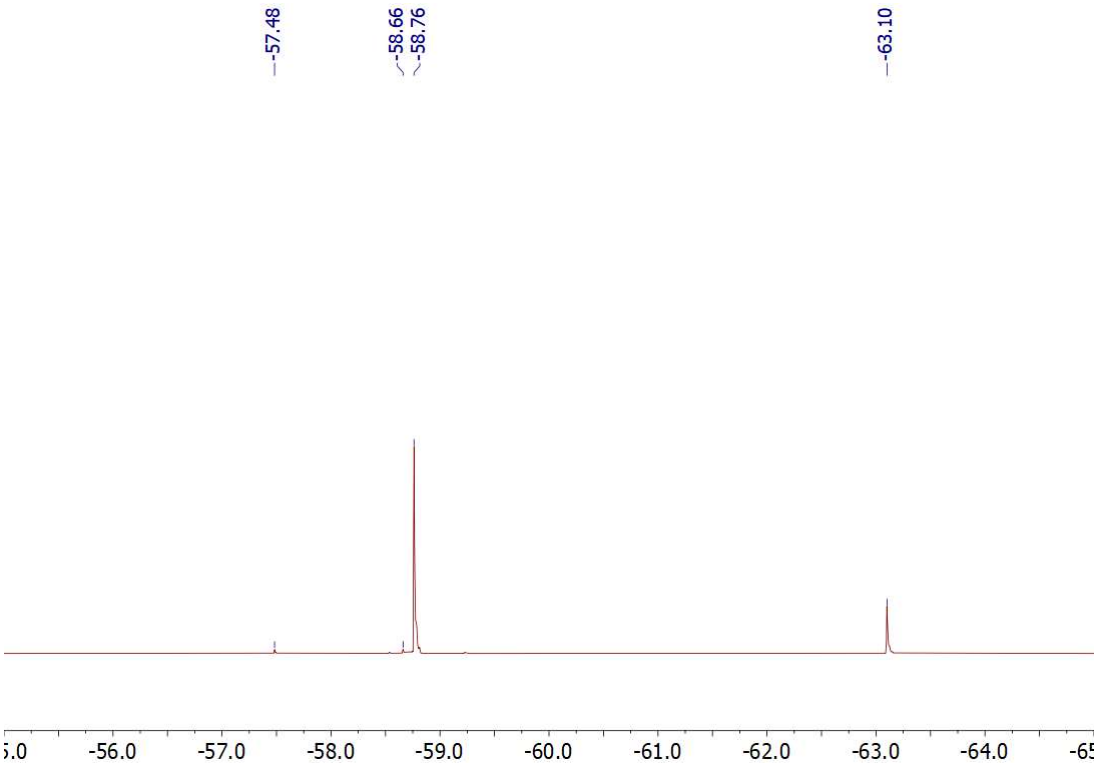


Figure S31. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method E (0.5 mmol scale, no solvent) using picolinonitrile (**4a**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments. Spiked with 5-(trifluoromethoxy)picolinonitrile (**5ab**)

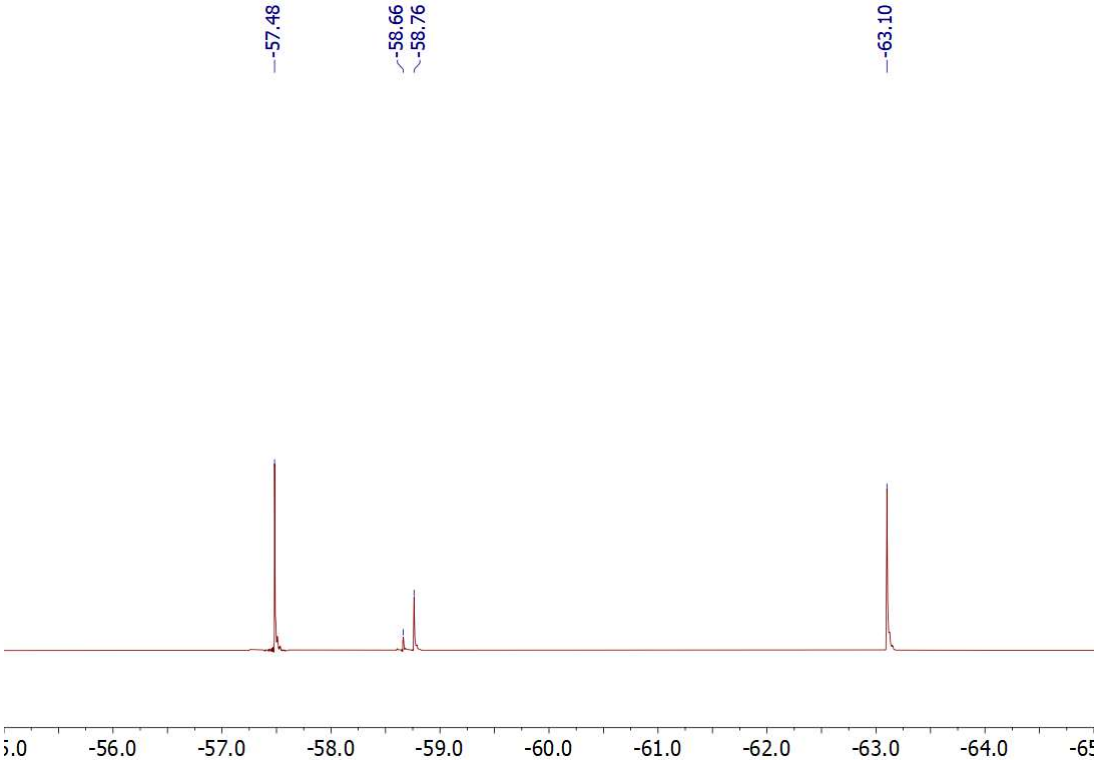


Figure S32. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method E (0.5 mmol scale, no solvent) using picolinonitrile (**4b**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments. Spiked with 6-(trifluoromethoxy)picolinonitrile (**5ac**).

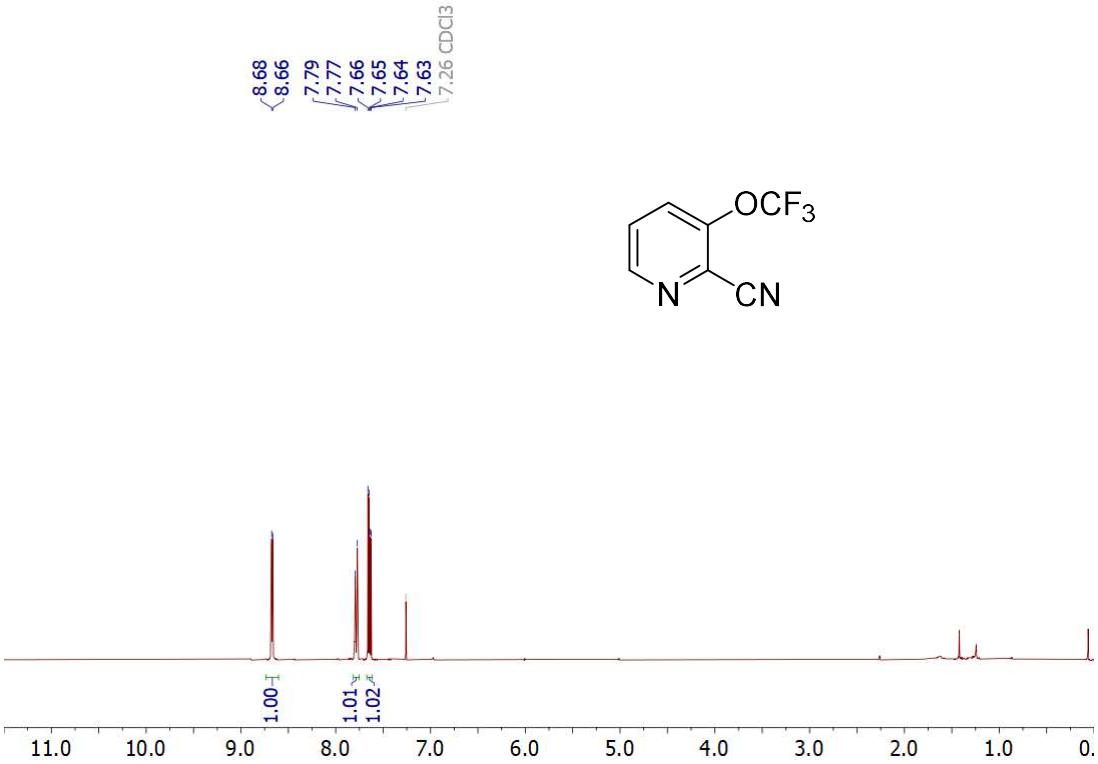


Figure S33. ^{1}H-NMR-Spectrum (400 MHz, $CDCl_3$) of **5aa**.

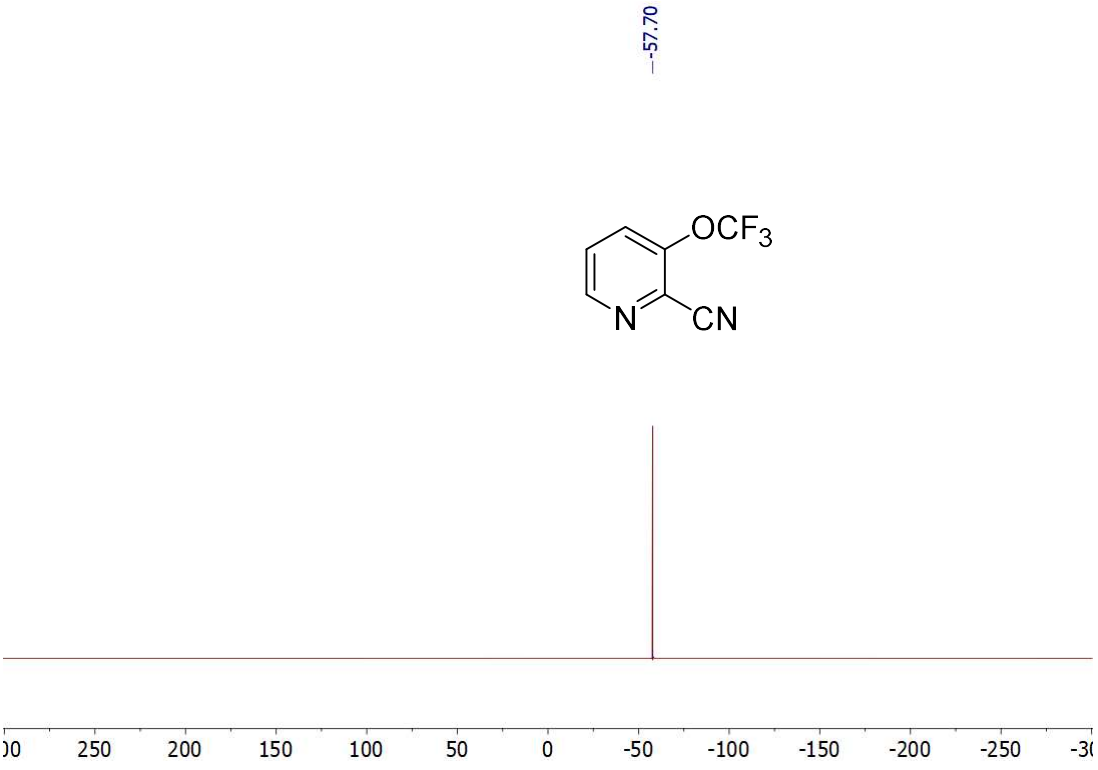


Figure S34. ^{19}F-NMR-Spectrum (376 MHz, $CDCl_3$) of **5aa**.

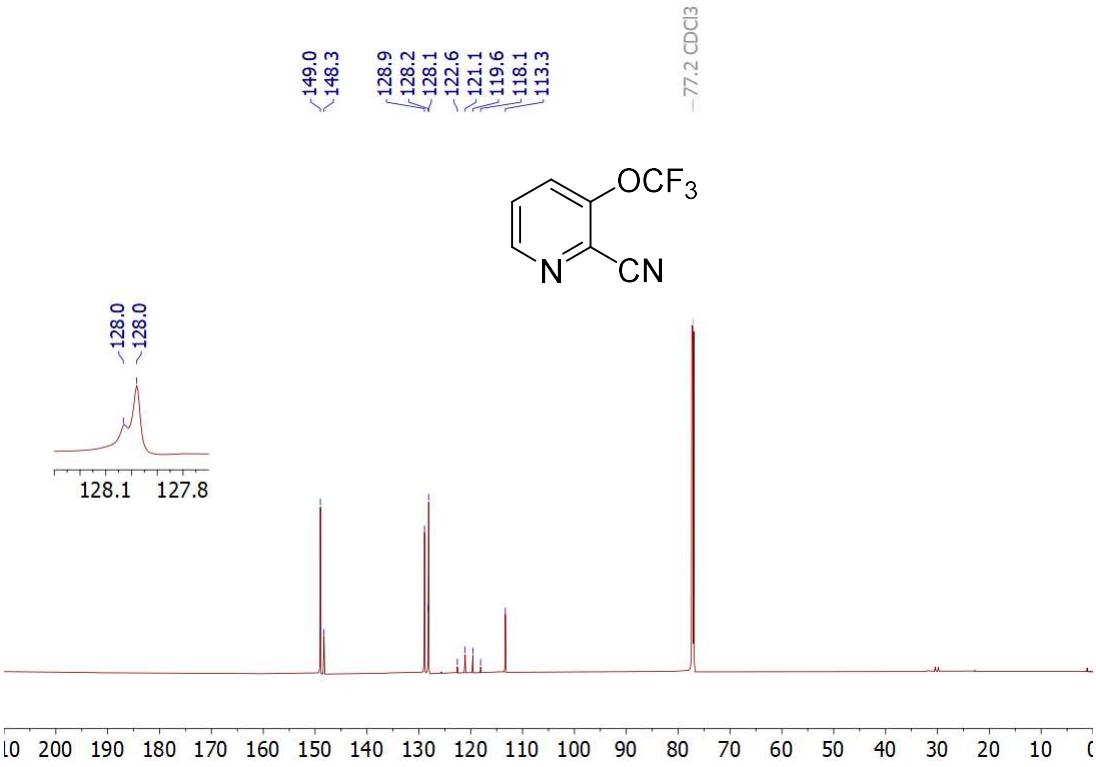


Figure S35. ^{13}C-NMR-Spectrum (176 MHz, $CDCl_3$) of **5aa** .

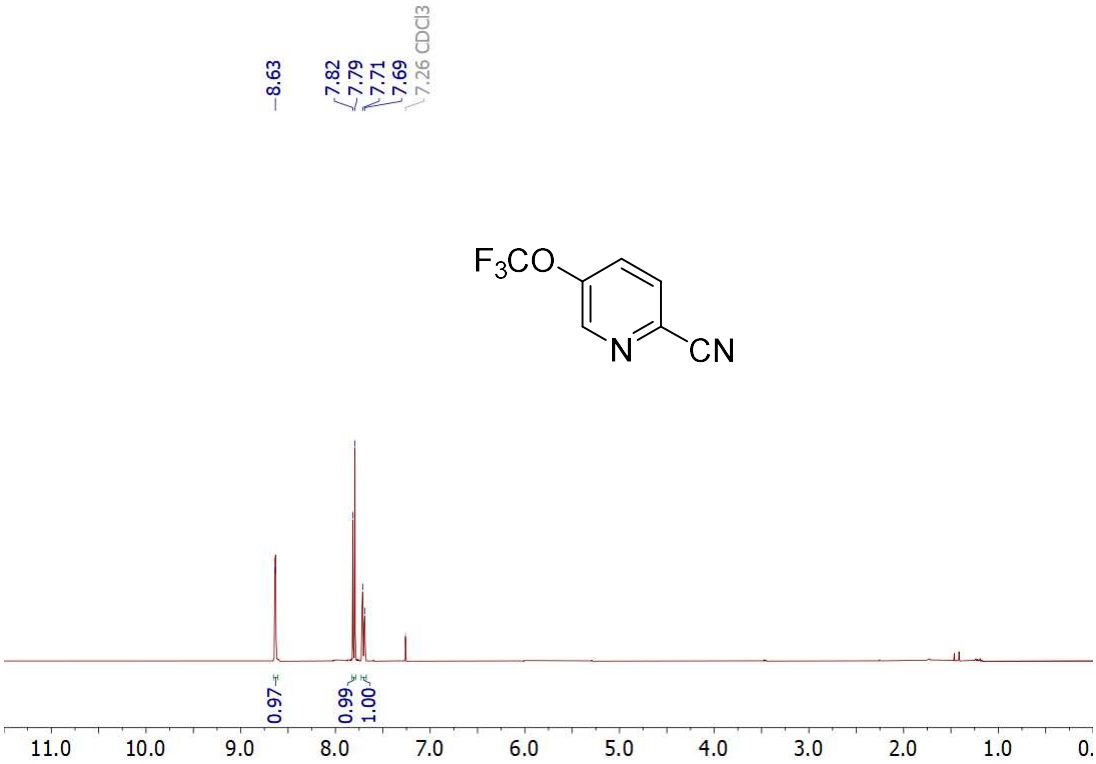


Figure S36. ^{1}H-NMR-Spectrum (400 MHz, $CDCl_3$) of **5ab**.

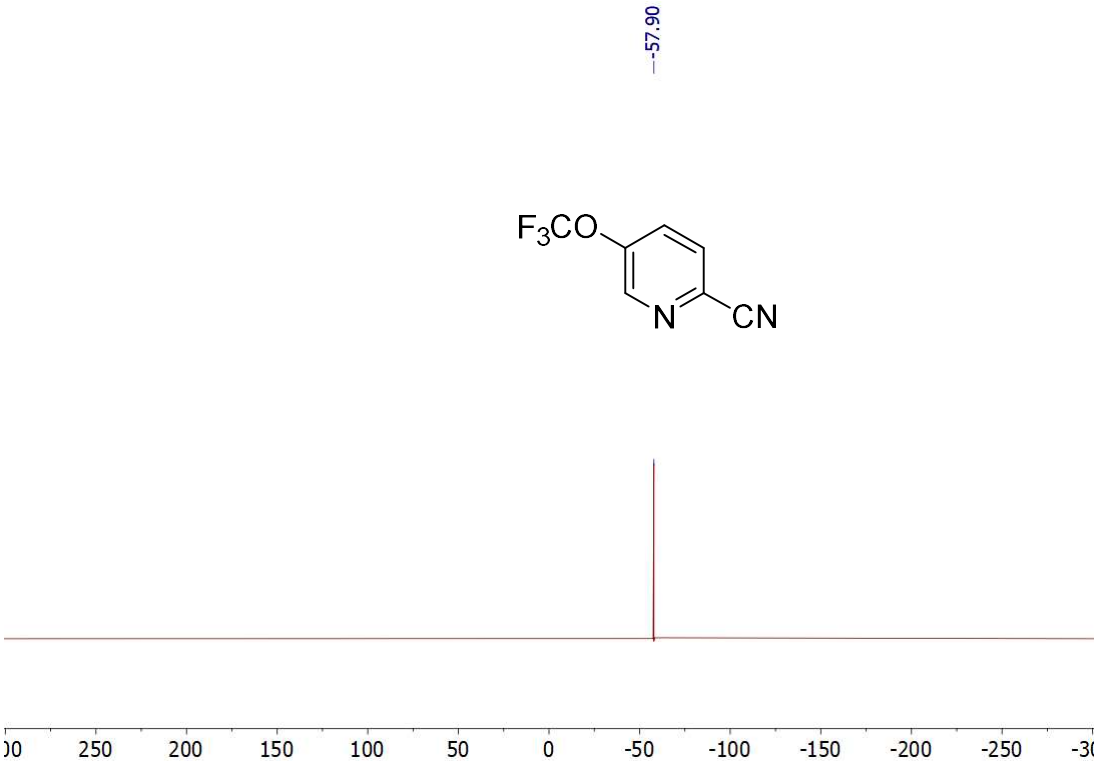


Figure S37. ^{19}F-NMR-Spectrum (376 MHz, $CDCl_3$) of **5ab**.

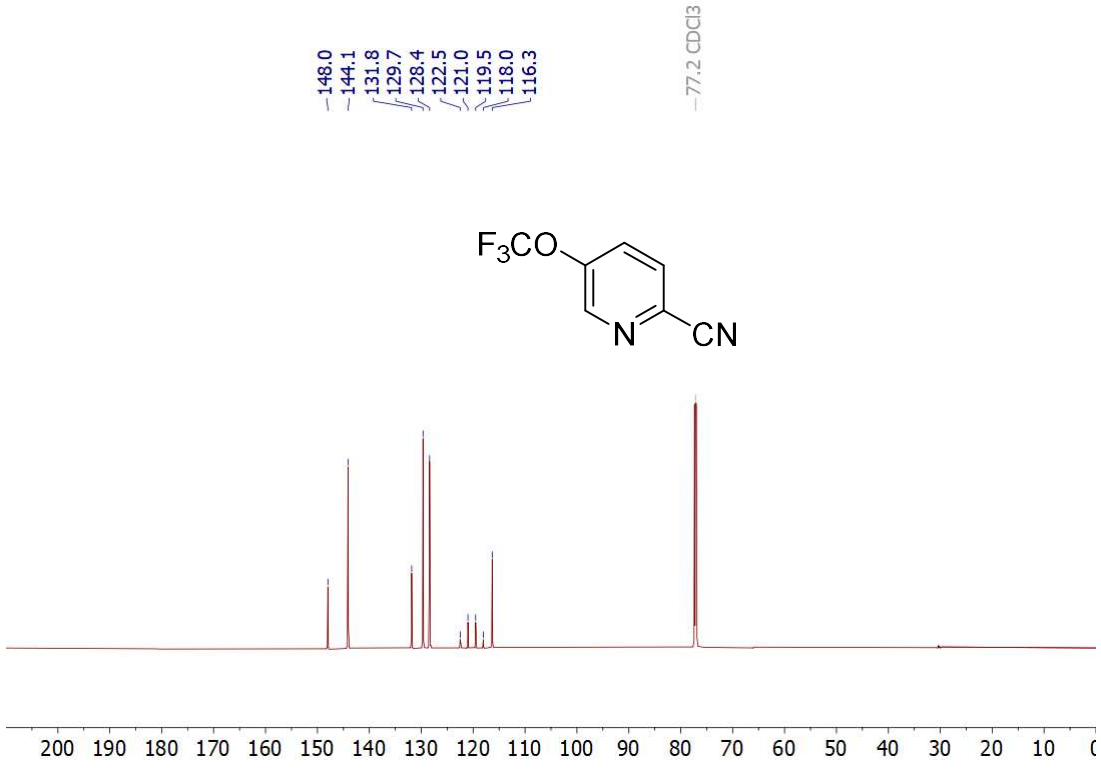


Figure S38. ^{13}C-NMR-Spectrum (176 MHz, $CDCl_3$) of **5ab**.

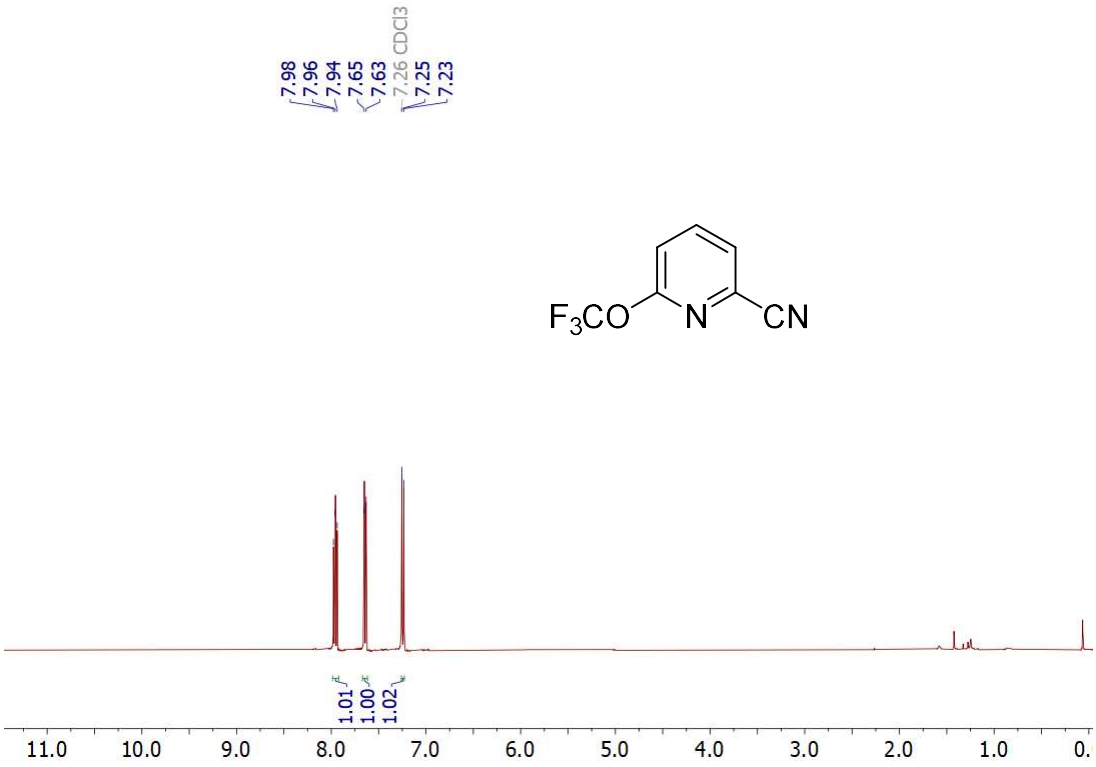


Figure S39. ^{1}H-NMR-Spectrum (400 MHz, $CDCl_3$) of **5ac**.

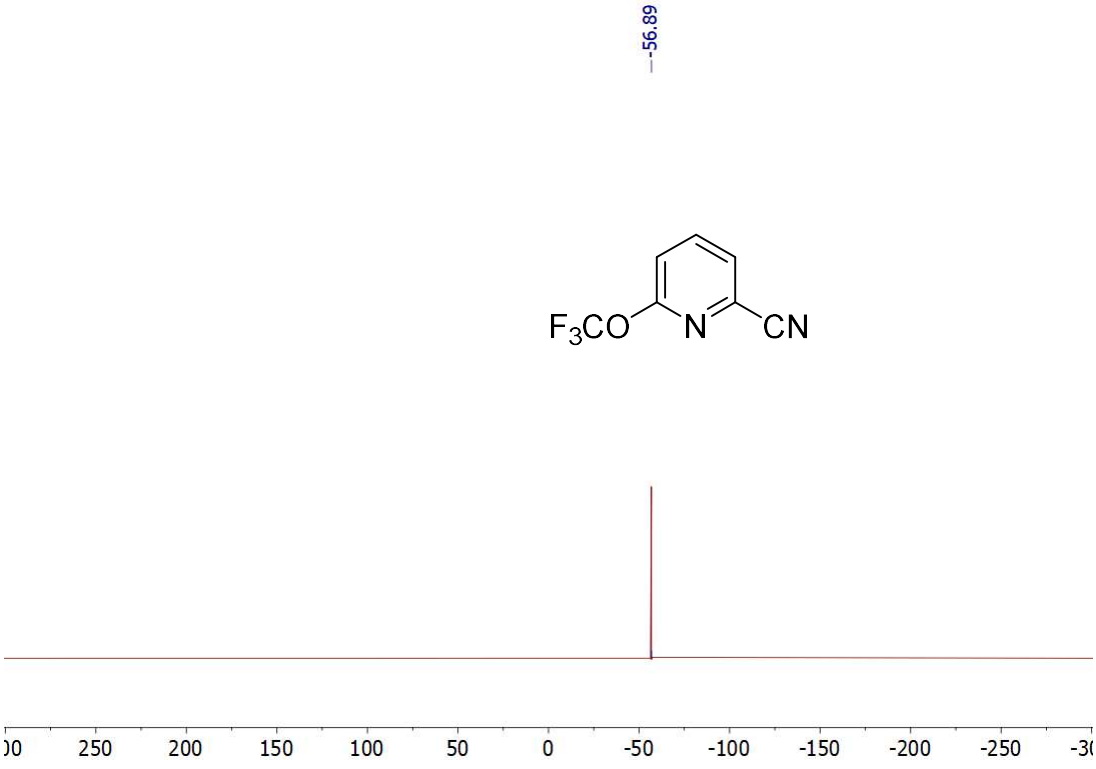


Figure S40. ^{19}F-NMR-Spectrum (376 MHz, $CDCl_3$) of **5ac**.

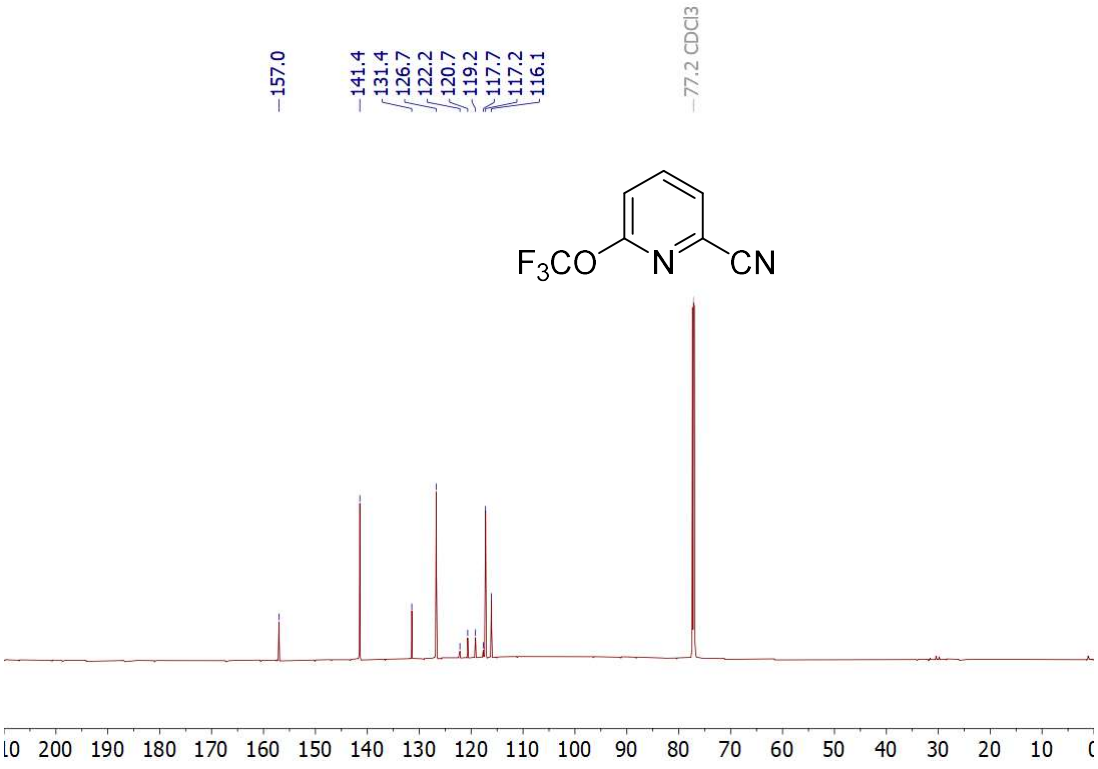


Figure S41. ^{13}C-NMR-Spectrum (176 MHz, $CDCl_3$) of **5ac**.

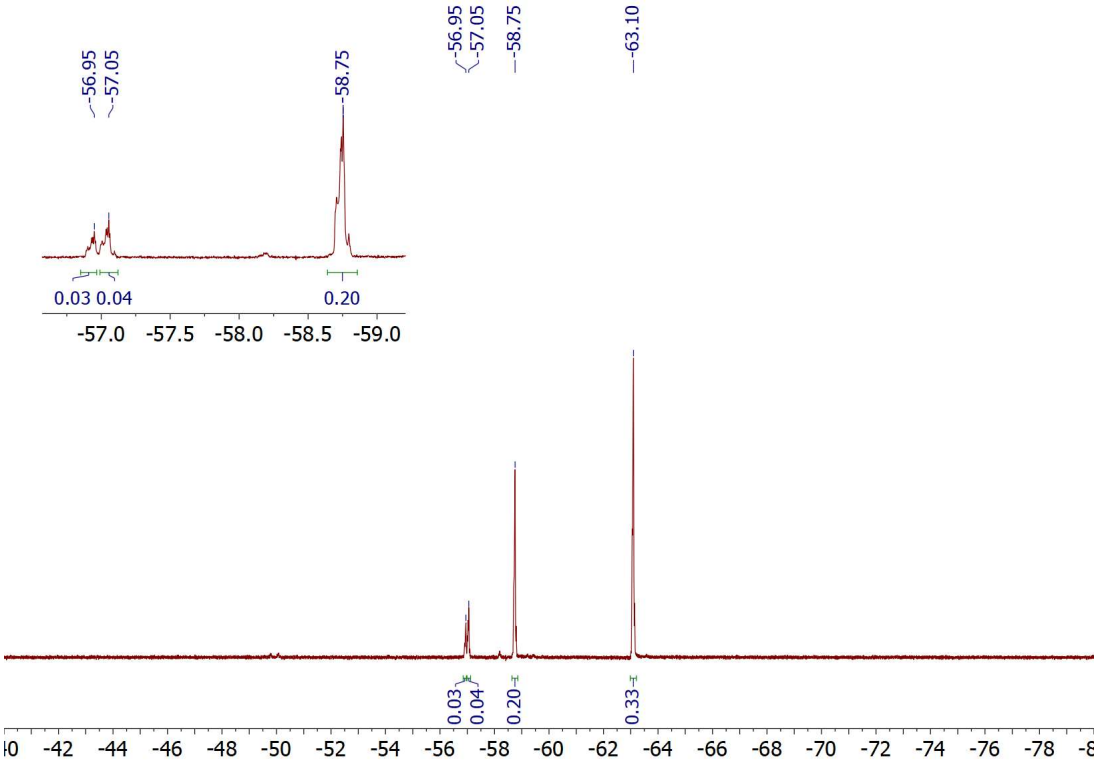


Figure S42. ^{19}F-NMR-Spectrum (376 MHz, Et_2O/MeCN) of a reaction mixture prepared by method E (6 mmol scale, 2.0 M) using nicotinonitrile (**4b**) as substrate and trifluorotoluene (2 mmol) as internal standard.

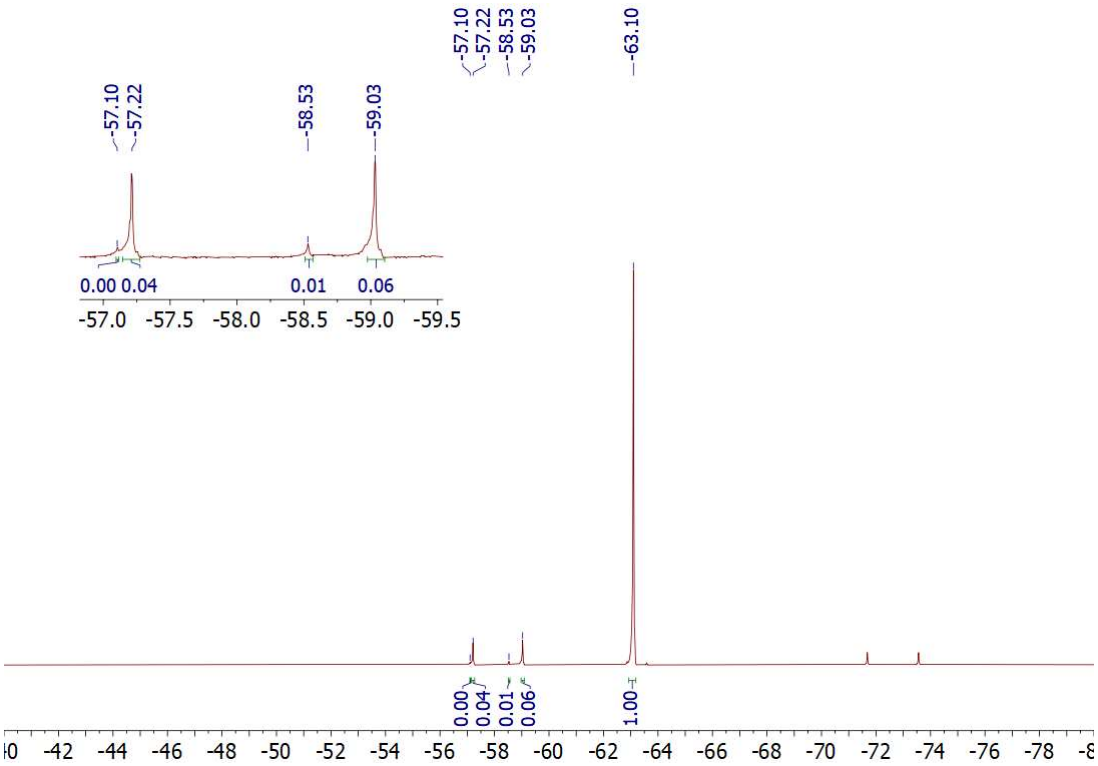


Figure S43. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method B (0.5 mmol, 2.0 M) using nicotinonitrile (**4b**) as substrate and trifluorotoluene (0.5 mmol) as internal standard.

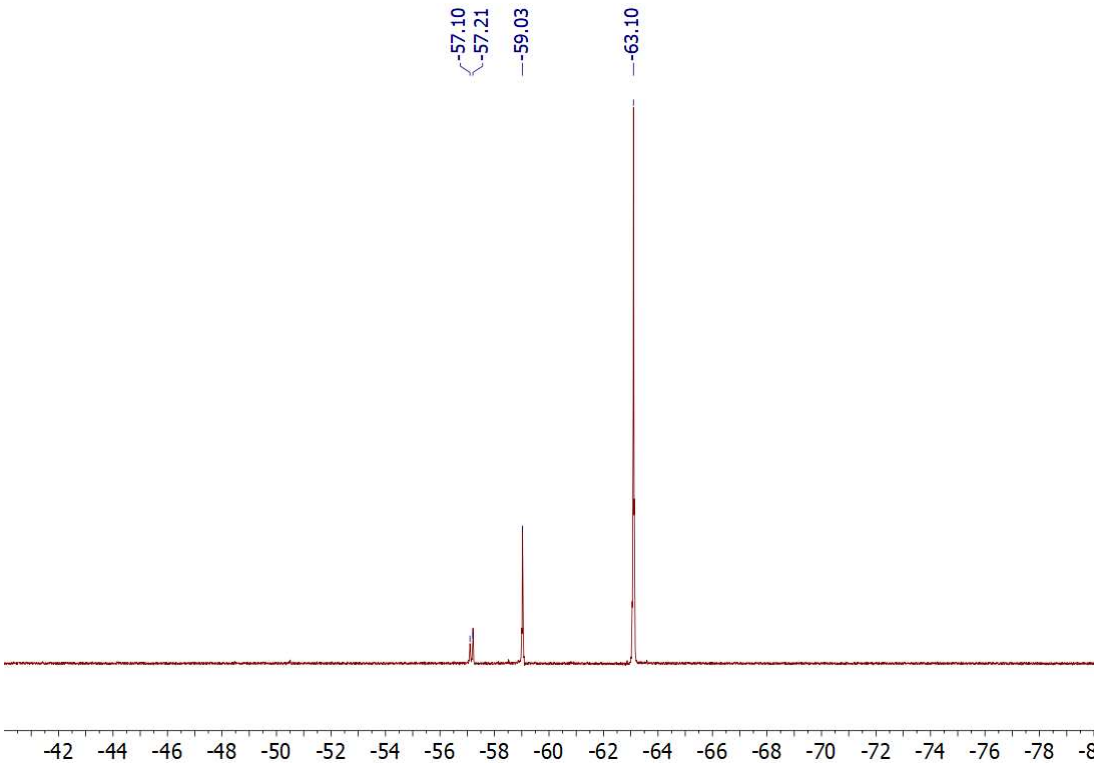


Figure S44. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method E (0.5 mmol scale, 2 M) using nicotinonitrile (**4b**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments.

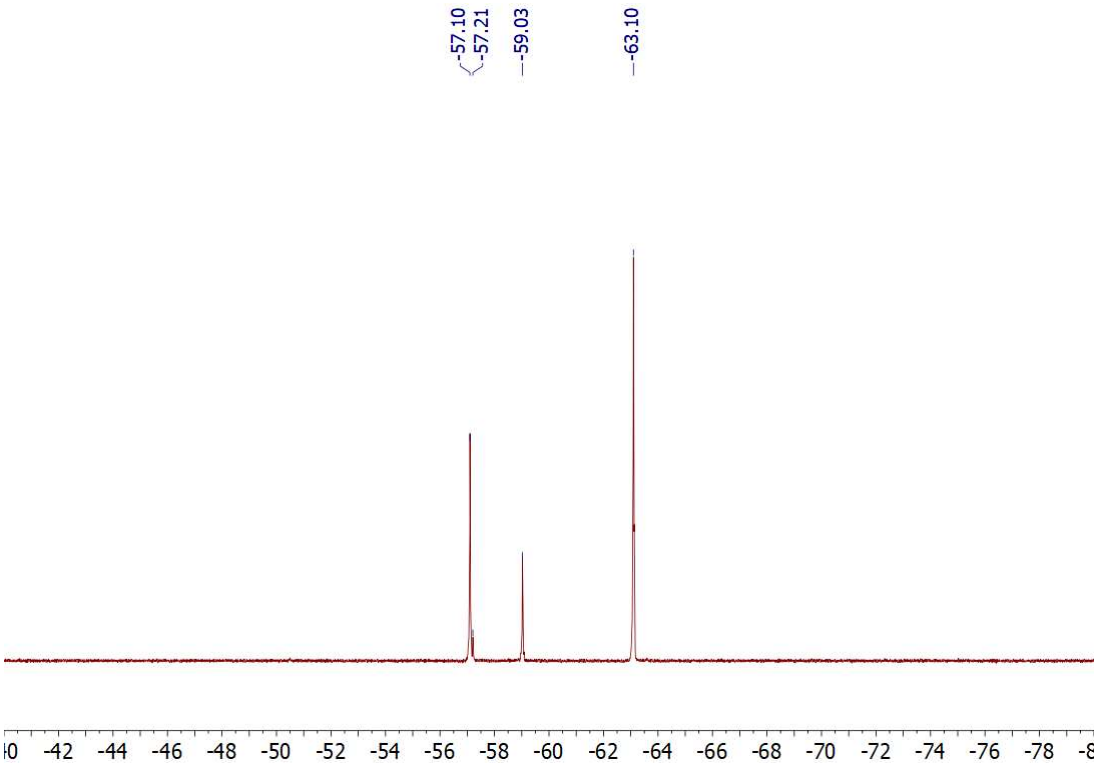


Figure S45. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method E (0.5 mmol scale, 2 M) using nicotinonitrile (**4b**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments. Spiked with 2-(trifluoromethoxy)nicotinonitrile (**5ba**).

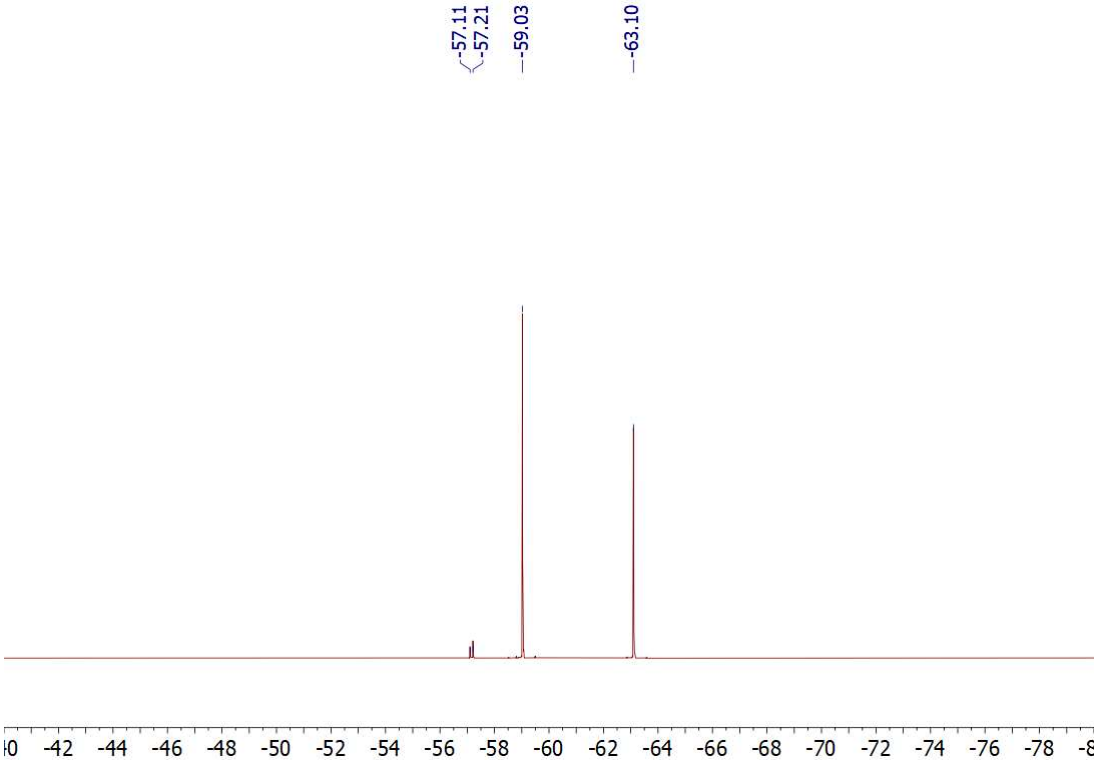


Figure S46. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method E (0.5 mmol scale, 2 M) using nicotinonitrile (**4b**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments. Spiked with 5-(trifluoromethoxy)nicotinonitrile (**5bb**).

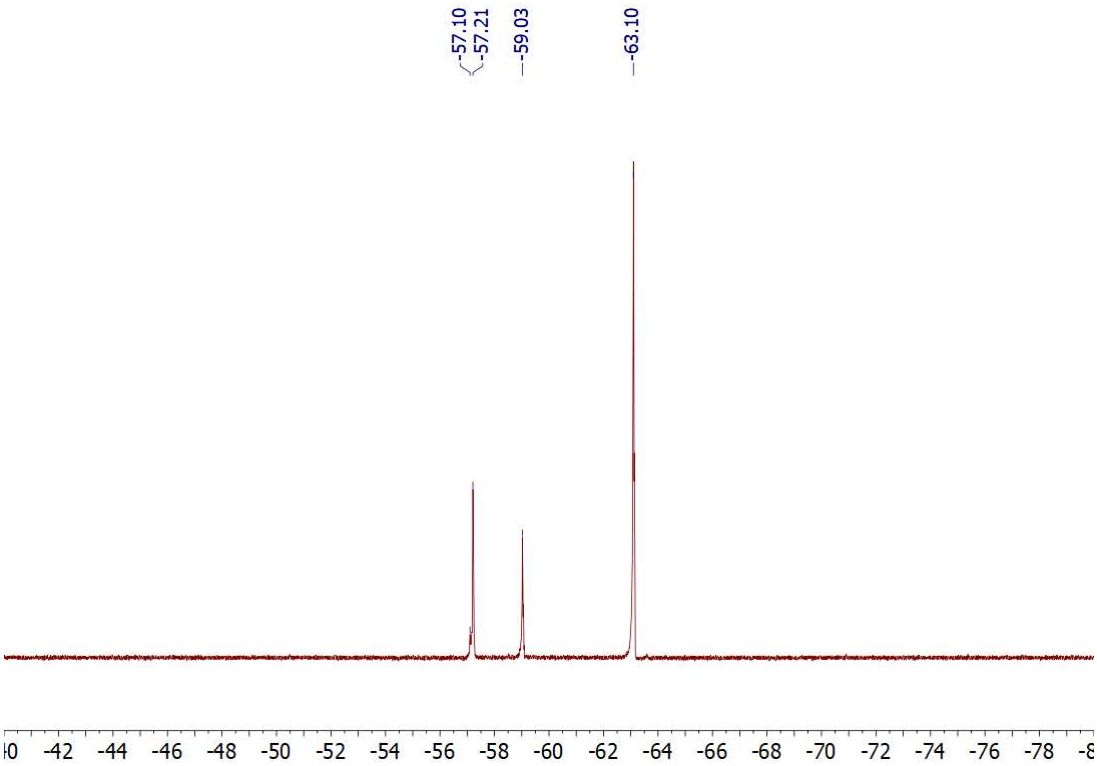


Figure S47. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method E (0.5 mmol scale, 2 M) using nicotinonitrile (**4b**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments. Spiked with 6-(trifluoromethoxy)nicotinonitrile (**5bc**).

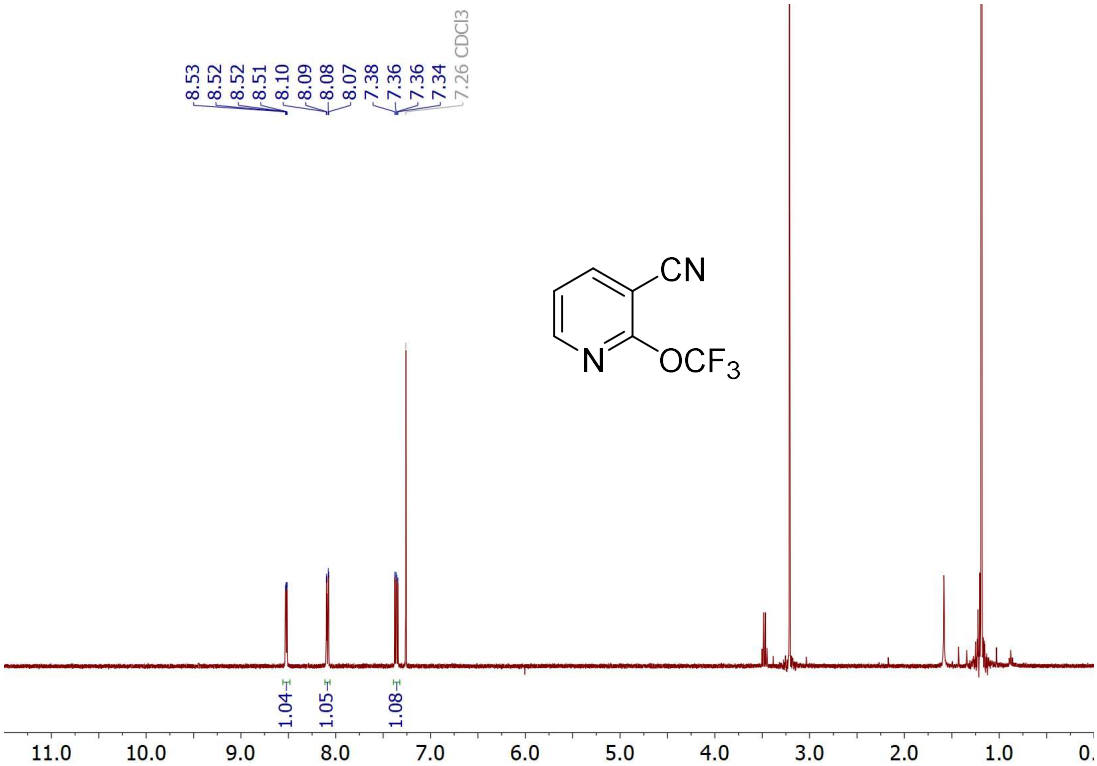


Figure S48. ^{1}H-NMR-Spectrum (400 MHz, $CDCl_3$) of **5ba** with residues of MTBE and Et_2O.

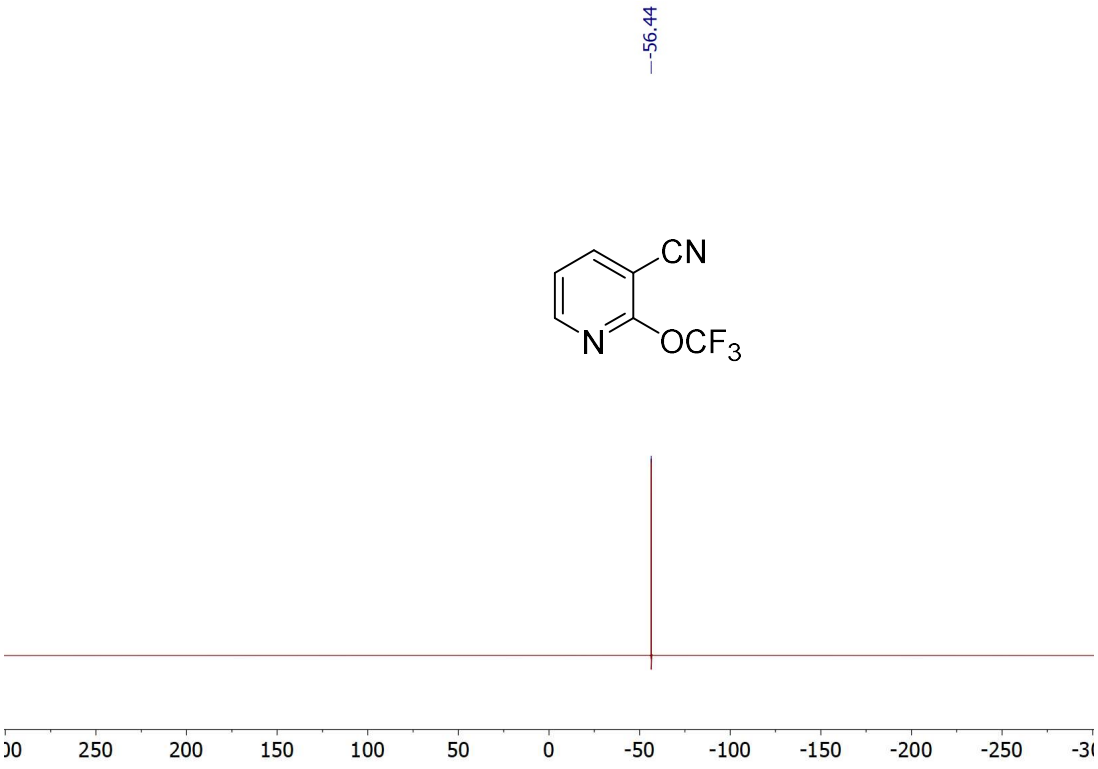


Figure S49. ^{19}F-NMR-Spectrum (376 MHz, $CDCl_3$) of **5ba**.

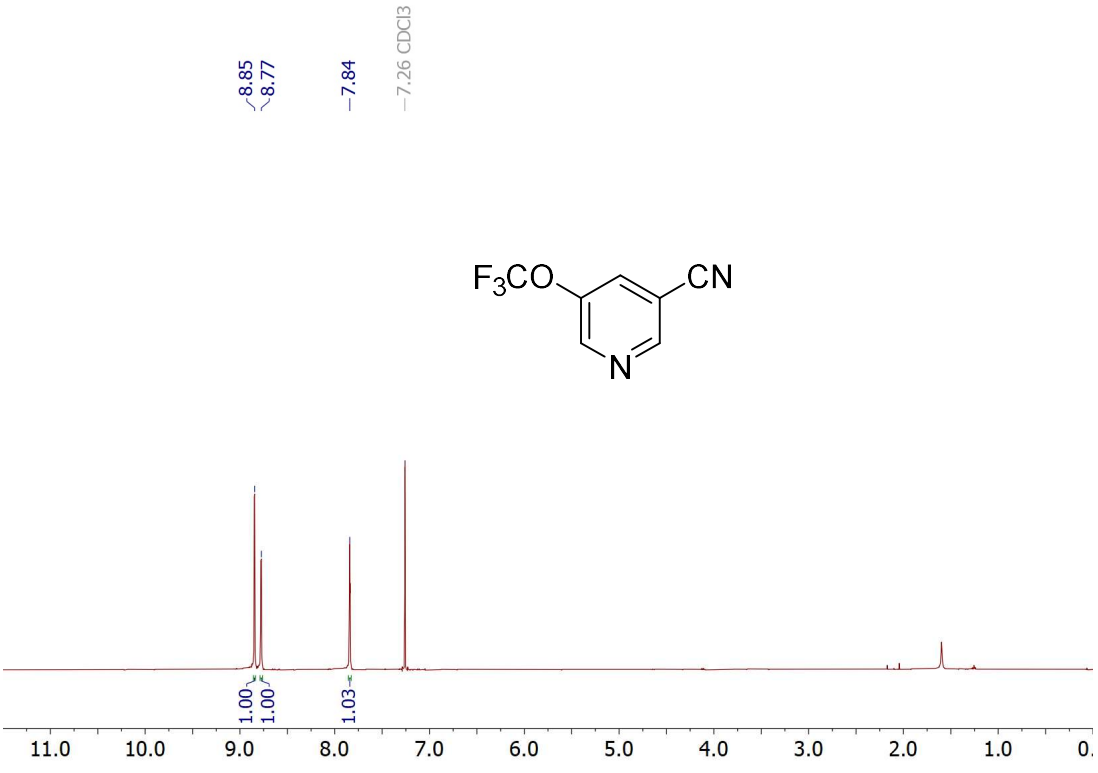


Figure S50. ^{1}H-NMR-Spectrum (500 MHz, $CDCl_3$) of **5bb.**

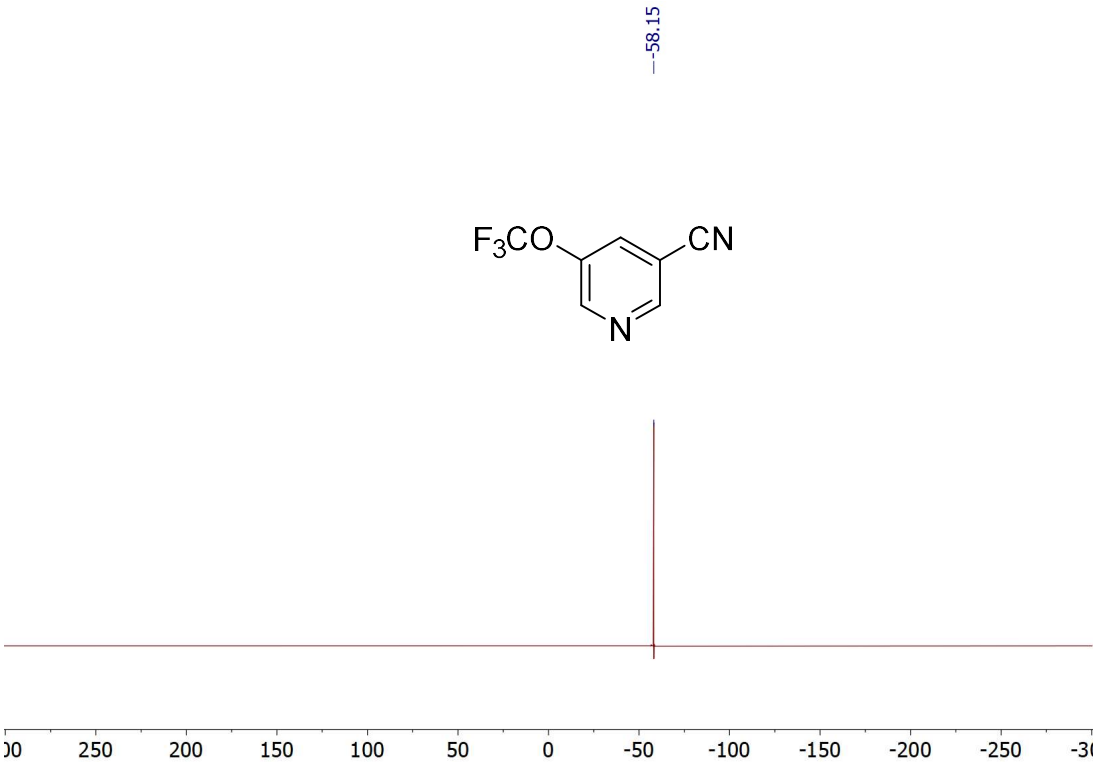


Figure S51. ^{19}F-NMR-Spectrum (376 MHz, $CDCl_3$) of **5bb**.

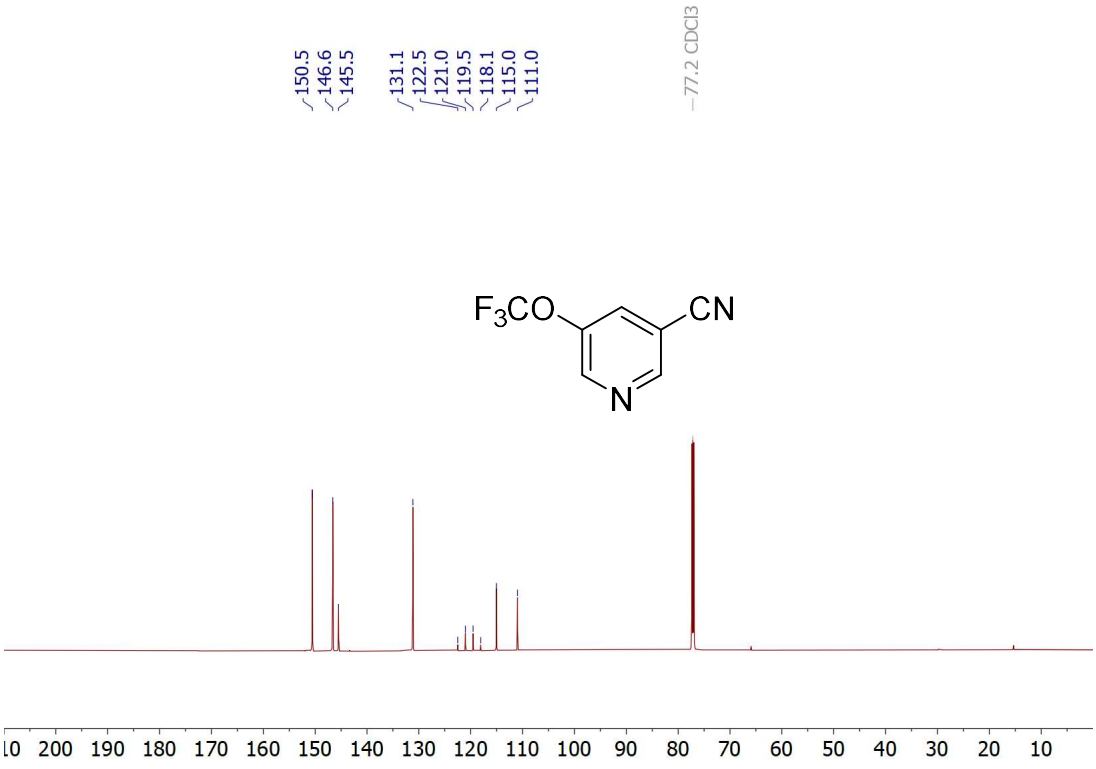


Figure S52. ^{13}C-NMR-Spectrum (176 MHz, $CDCl_3$) of **5bb**.

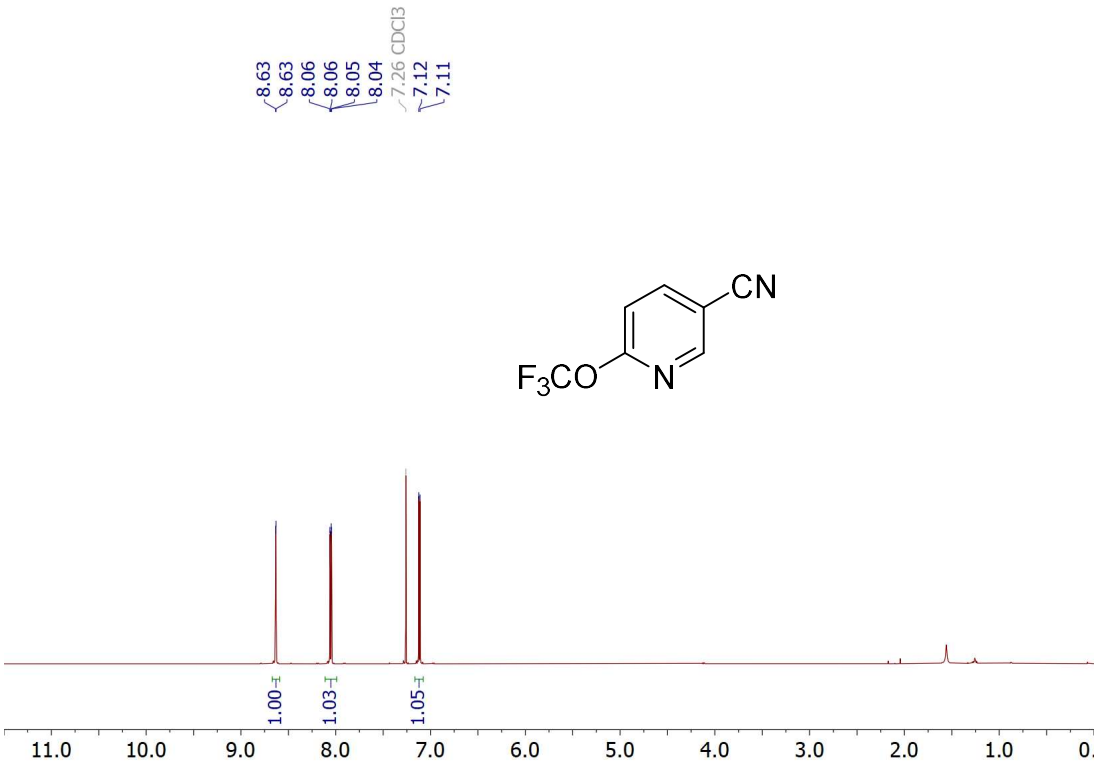


Figure S53. ^{1}H-NMR-Spectrum (600 MHz, $CDCl_3$) of **5bc.**

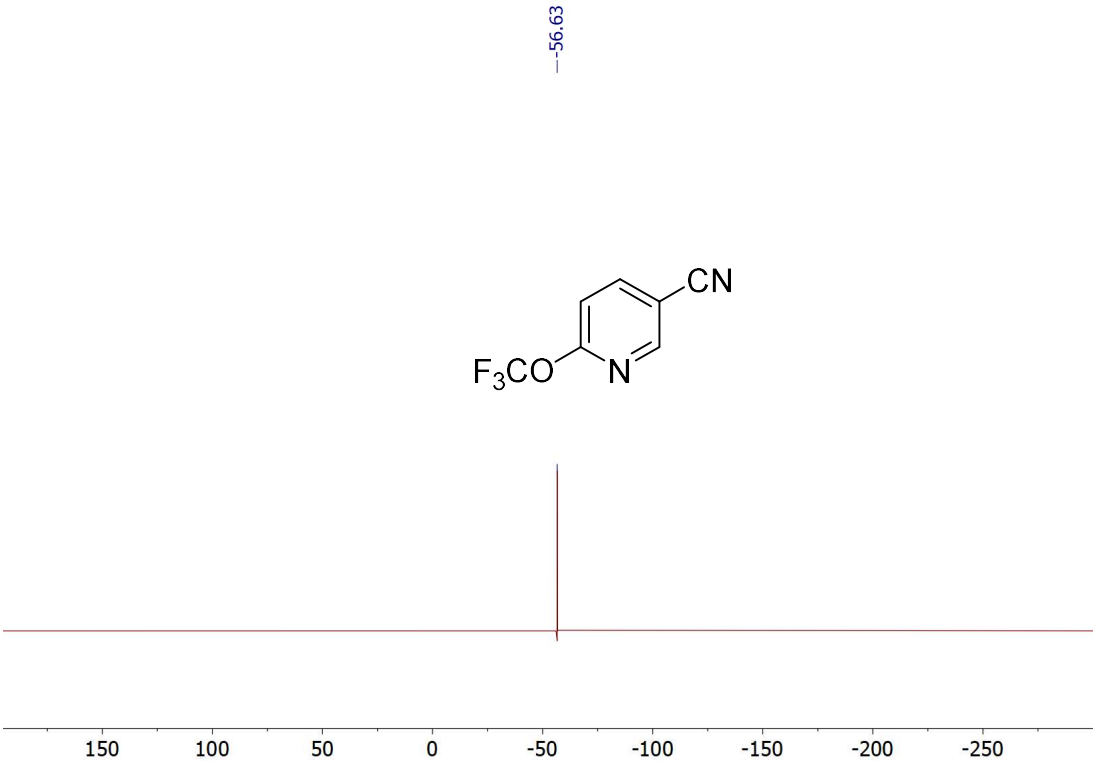


Figure S54. ^{19}F-NMR-Spectrum (565 MHz, $CDCl_3$) of **5bc**.

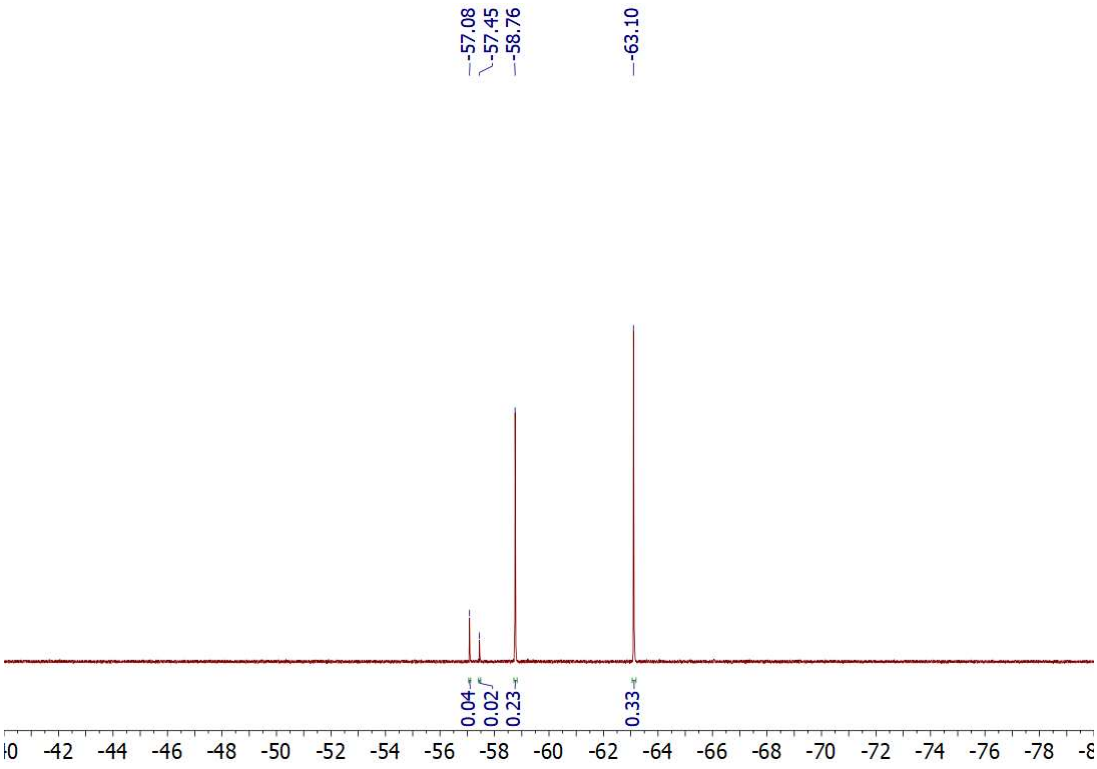


Figure S55. ^{19}F-NMR-Spectrum (376 MHz, Et_2O/MeCN) of a reaction mixture prepared by method E (6 mmol scale, 0.4 M, 6 h reaction time) using isonicotinonitrile (**4c**) as substrate and trifluorotoluene (2 mmol) as internal standard.

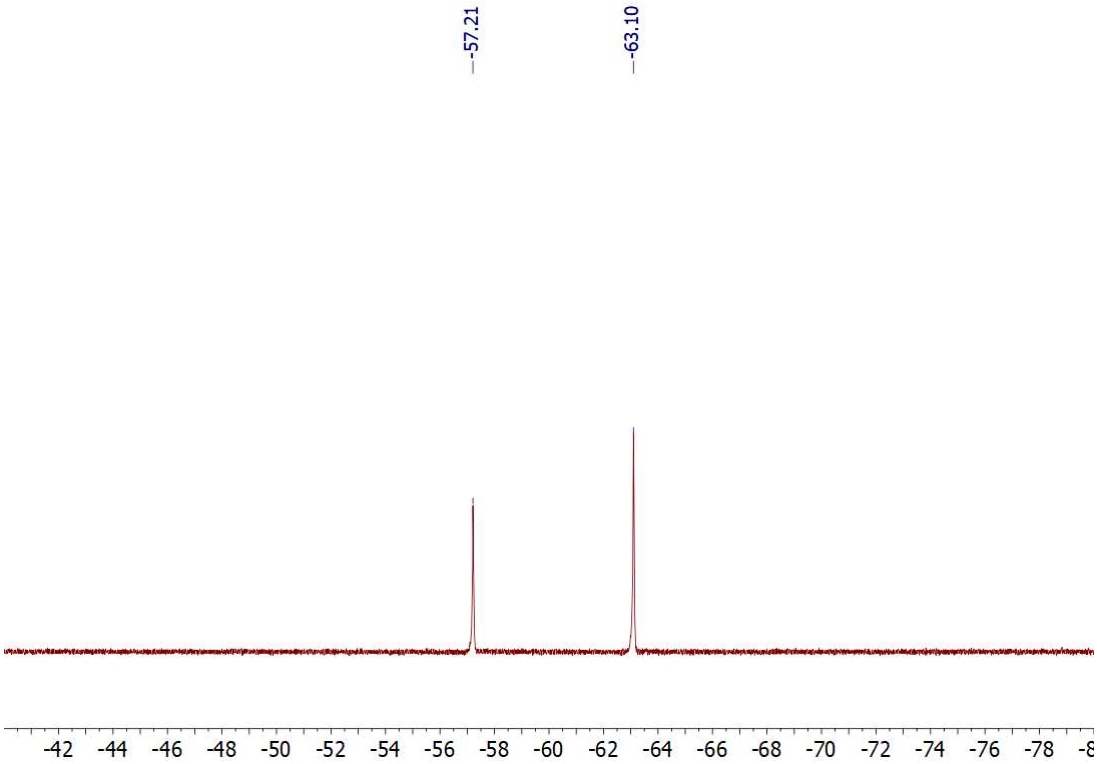


Figure S56. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of 2-(trifluoromethoxy)isonicotinonitrile **(5ca)** and trifluorotoluene in MeCN.

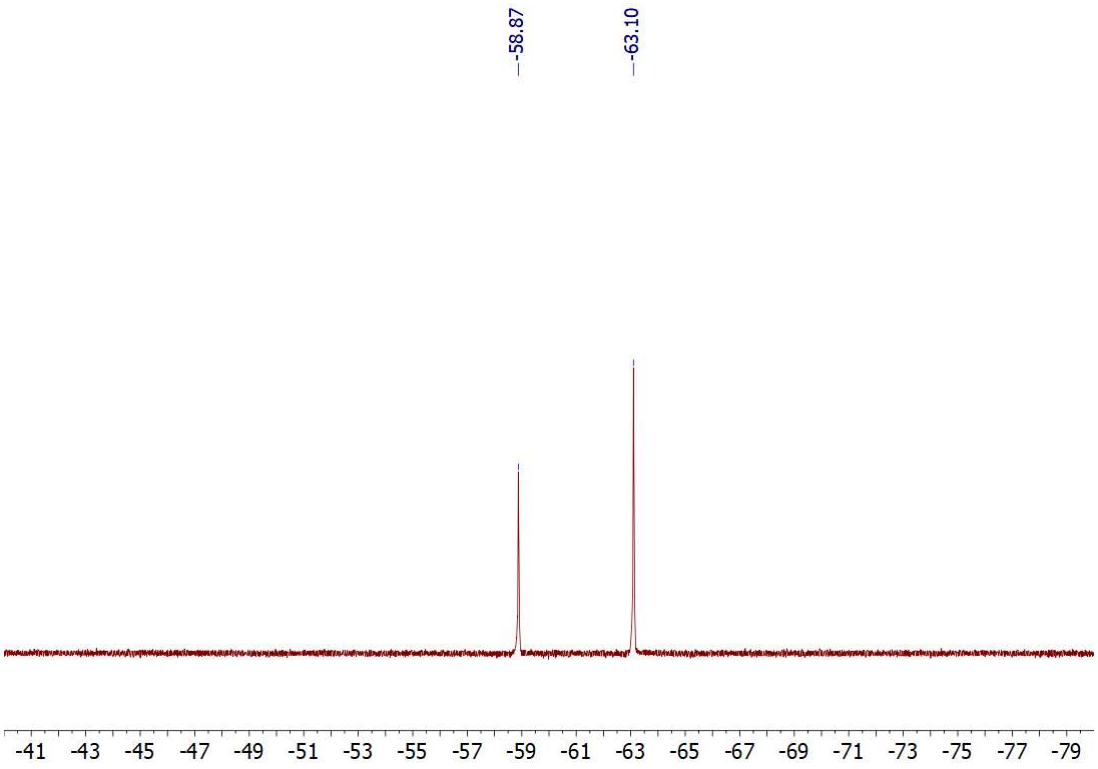


Figure S57. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of 3-(trifluoromethoxy)isonicotinonitrile **(5cb)** and trifluorotoluene in MeCN.

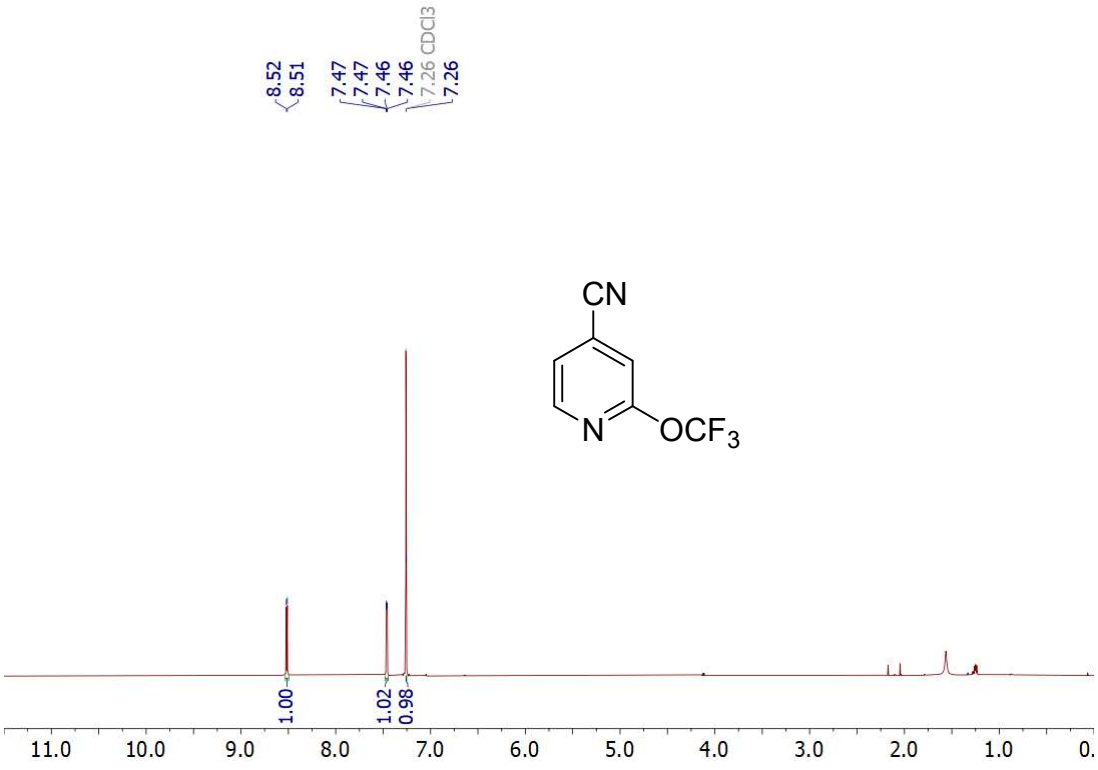


Figure S58. ^{1}H-NMR-Spectrum (500 MHz, $CDCl_3$) of **5ca.**

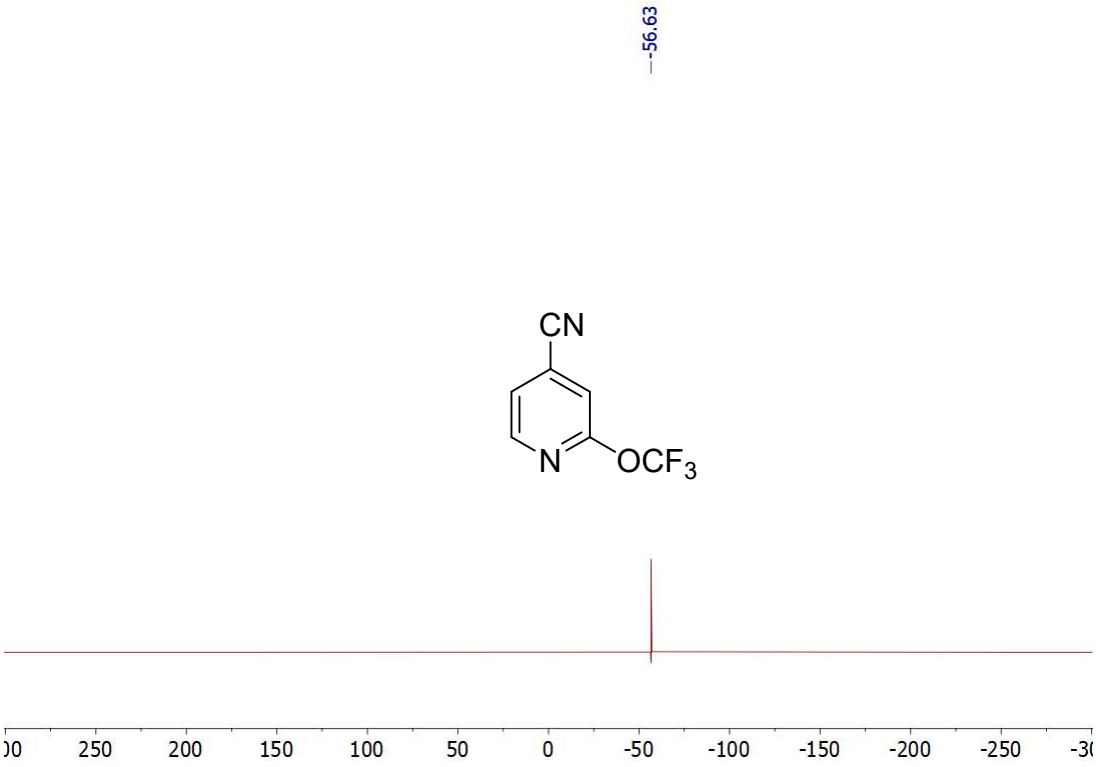


Figure S59. ^{19}F-NMR-Spectrum (376 MHz, $CDCl_3$) of **5ca.**

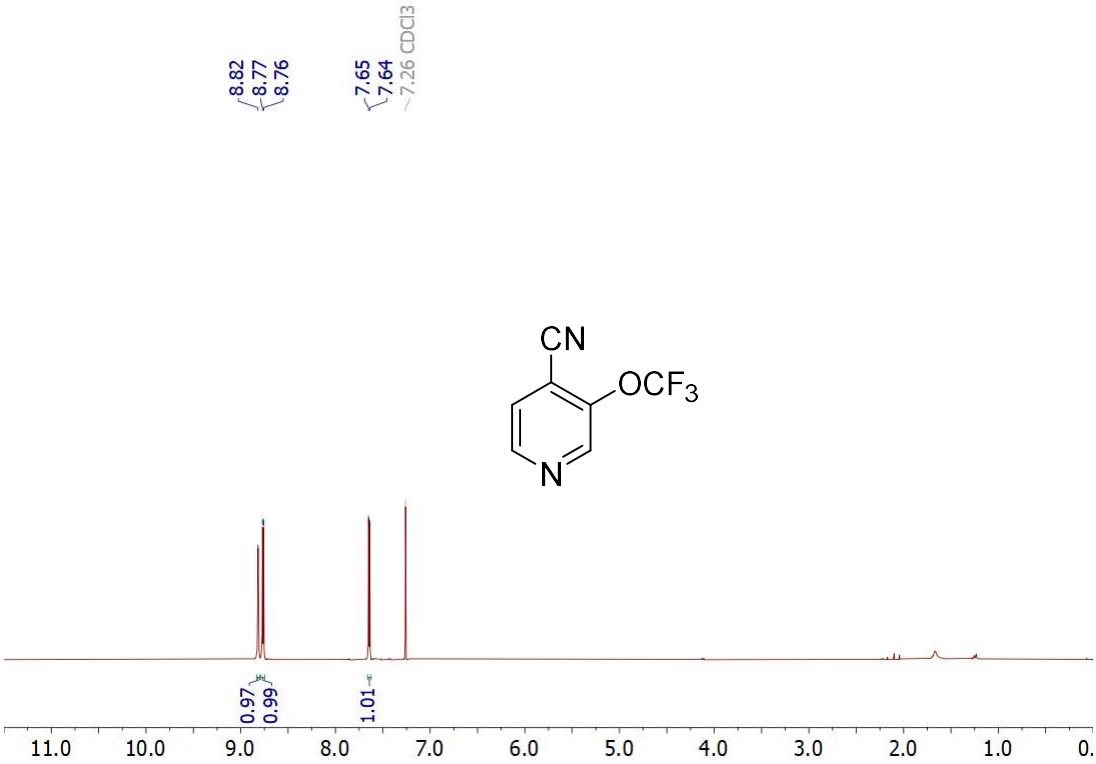


Figure S60. ^{1}H-NMR-Spectrum (400 MHz, $CDCl_3$) of **5cb.**

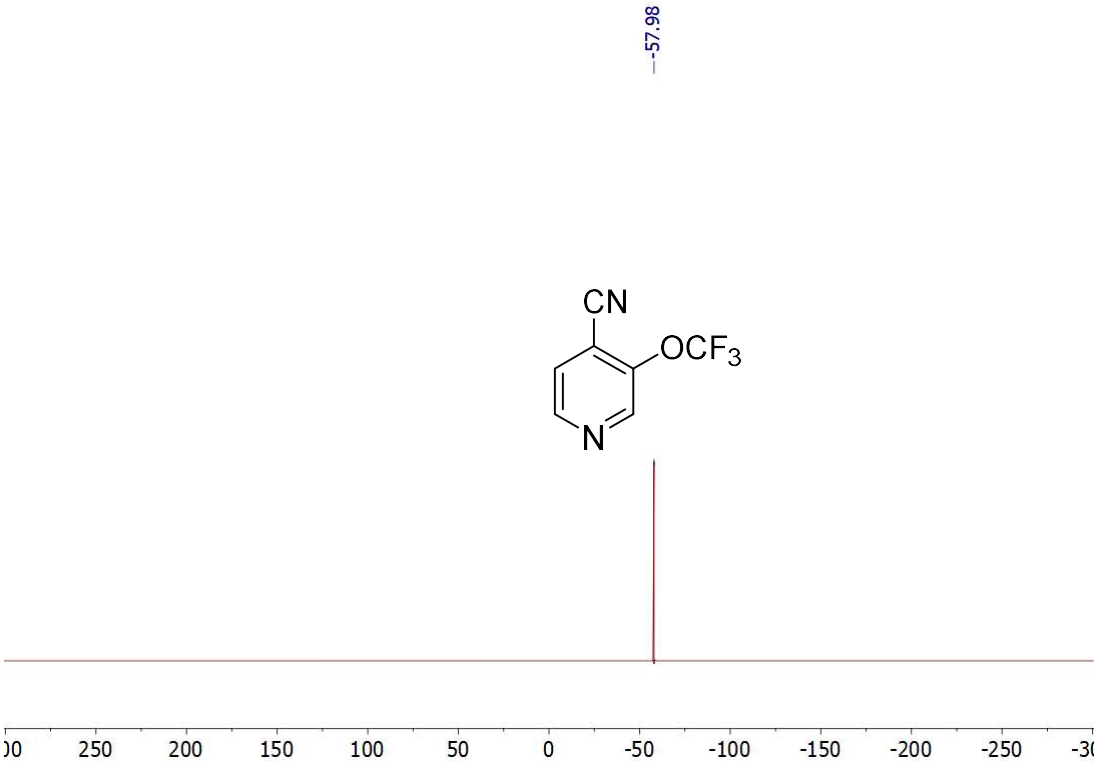


Figure S61. ^{19}F -NMR-Spectrum (376 MHz, $CDCl_3$) of **5cb.**

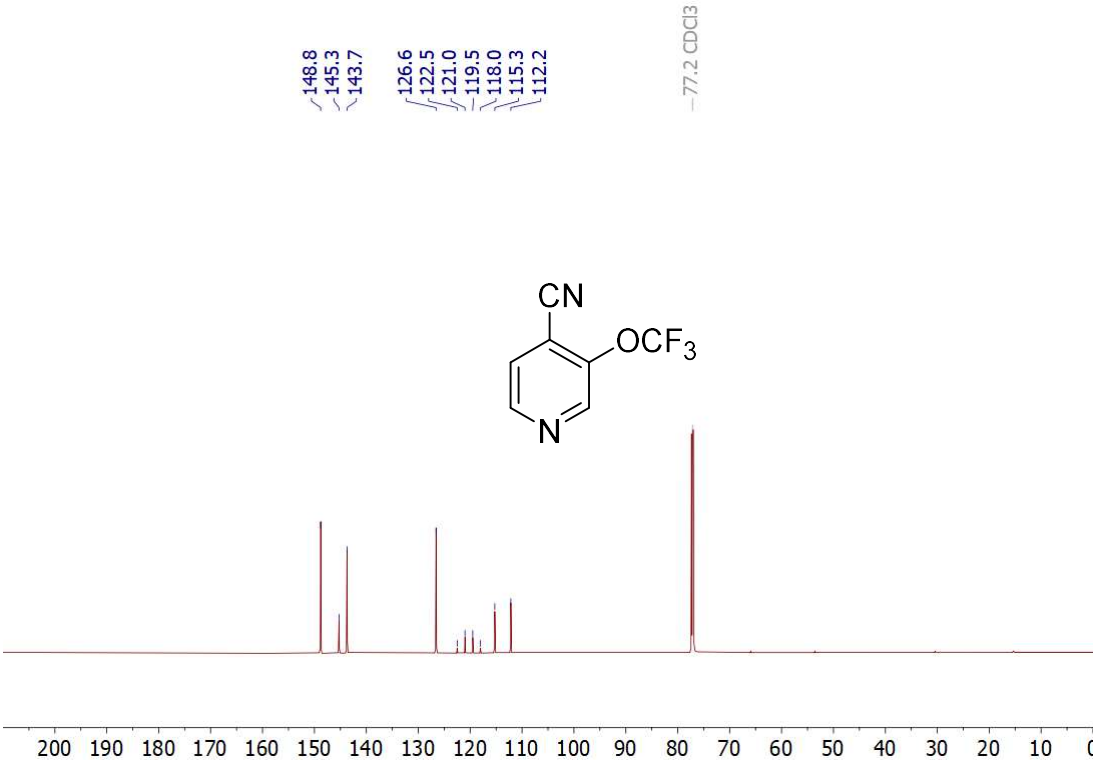


Figure S62. ^{13}C-NMR-Spectrum (176 MHz, $CDCl_3$) of **5cb.**

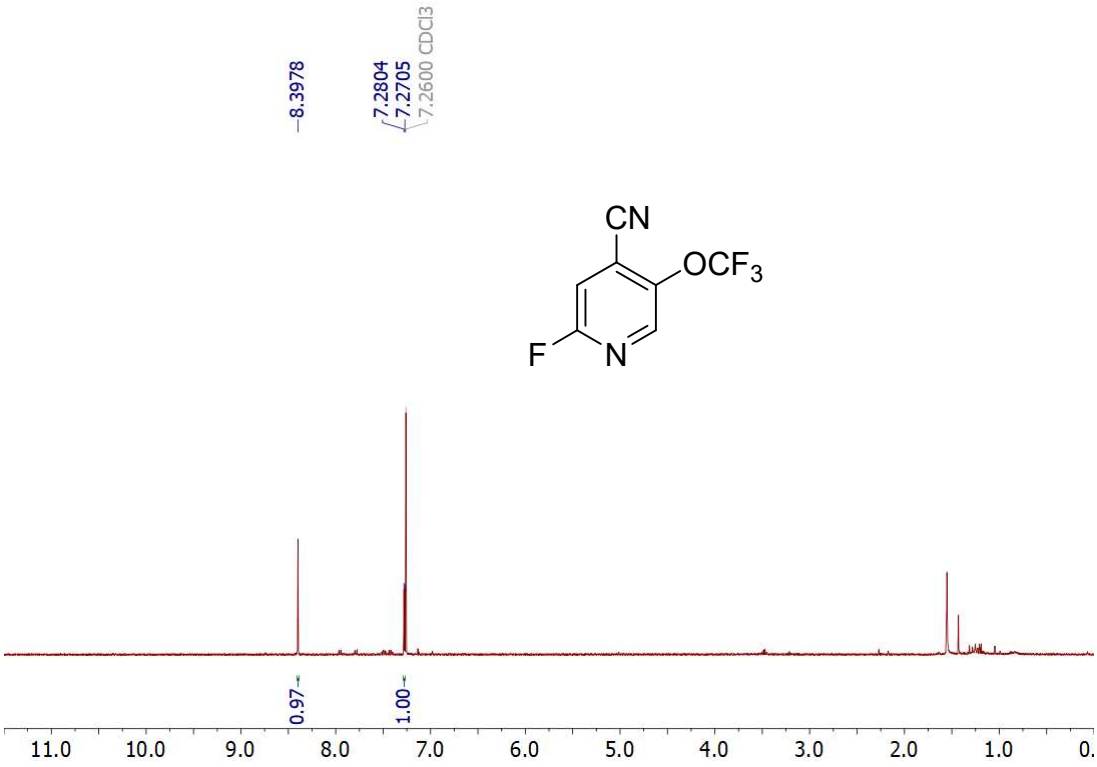


Figure S63. ^{1}H-NMR-Spectrum (400MHz, $CDCl_3$) of the possible sideproduct 2-Fluoro-5-(trifluoromethoxy)isonicotinonitrile from the reaction of **4c** under the conditions of method E (6 mmol, 0.4 M, 6 h reaction time)**.**

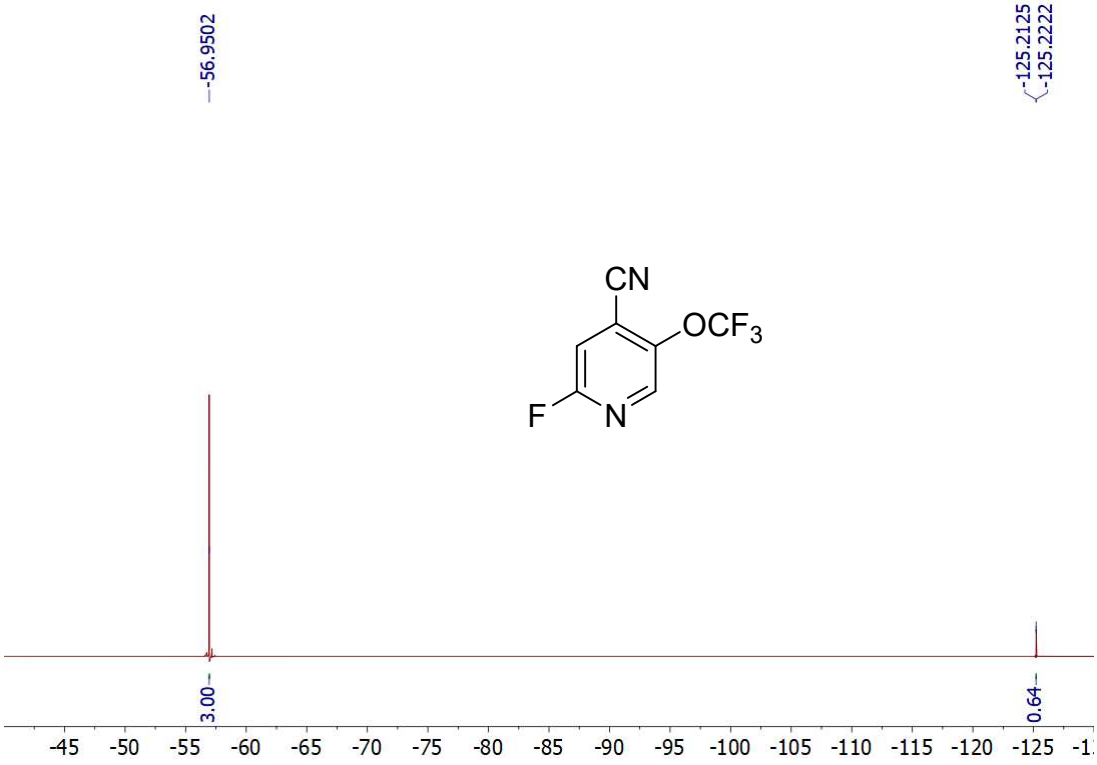


Figure S64. ^{19}F-NMR-Spectrum (376 MHz, $CDCl_3$) of the possible sideproduct 2-Fluoro-5-(trifluoromethoxy)isonicotinonitrile from the reaction of **4c** under the conditions of method E (6 mmol, 0.4 M, 6 h reaction time)**.**

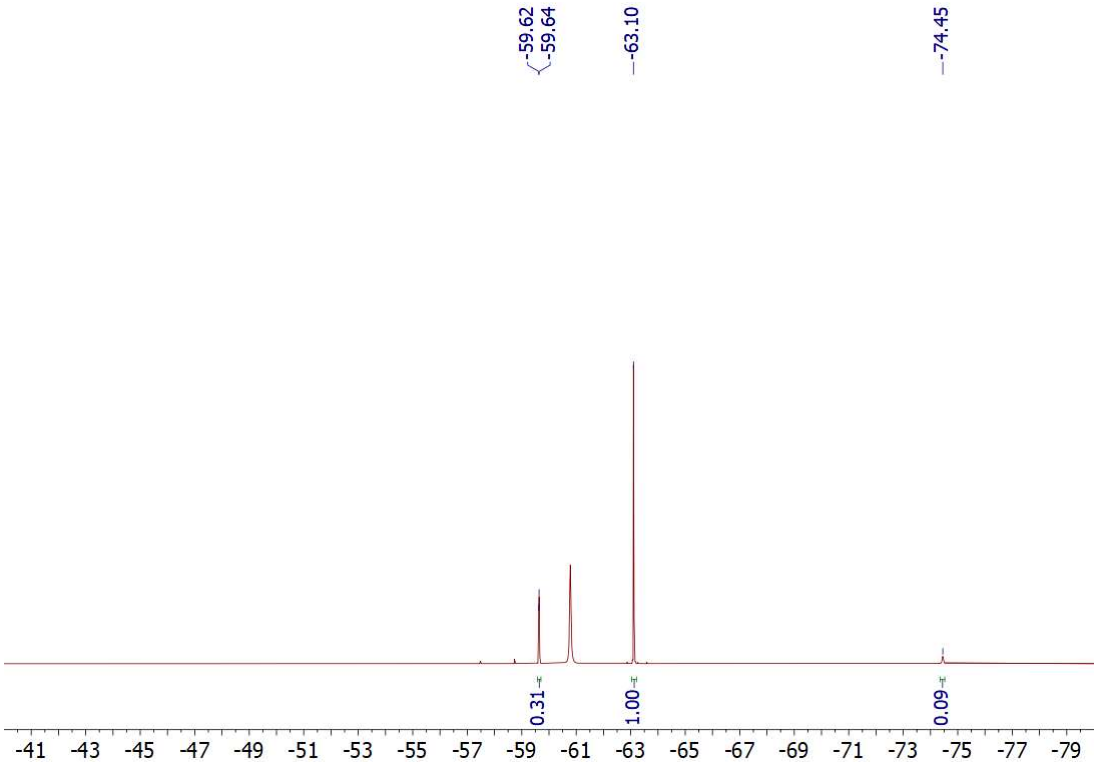


Figure S65. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method E (0.5 mmol scale, 2.0 M) using 6-fluoronicotinonitrile (**4d**) as substrate and trifluorotoluene (0.5 mmol) as internal standard.

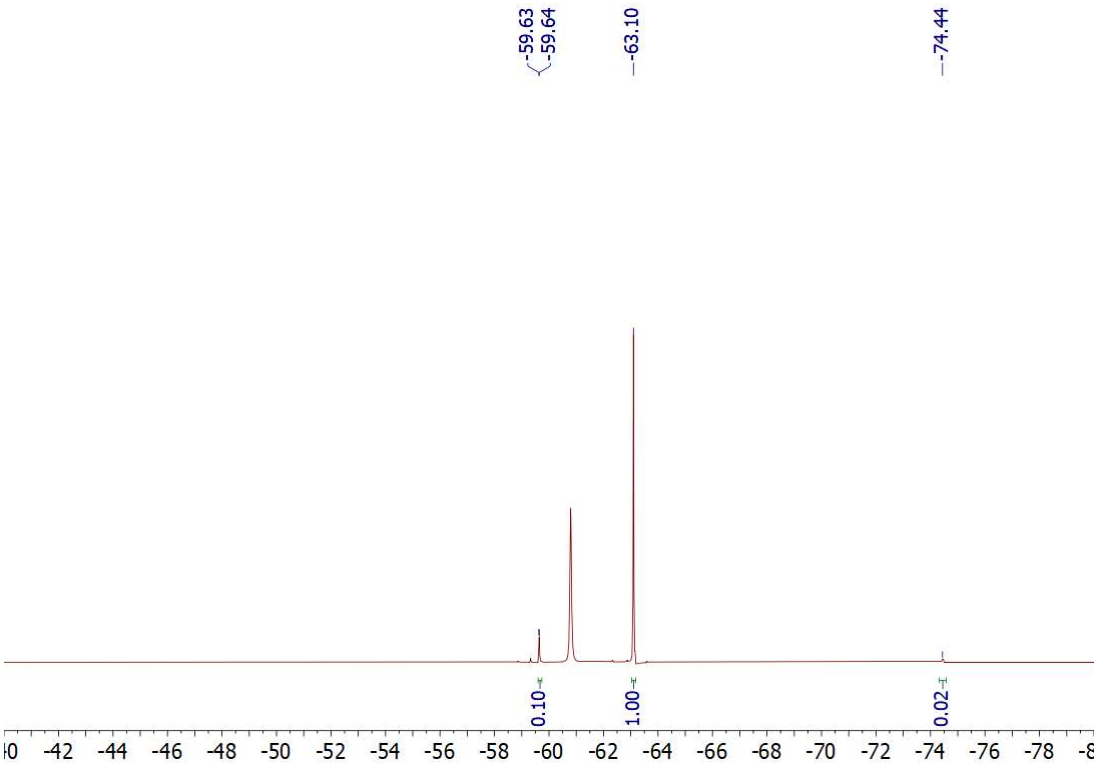


Figure S66. ^{19}F-NMR-Spectrum (376 MHz, Et_2O/MeCN) of a reaction mixture prepared by method B (0.5 mmol scale, 2.0 M) using 6-fluoronicotinonitrile (**4d**) as substrate and trifluorotoluene (0.5 mmol) as internal standard.

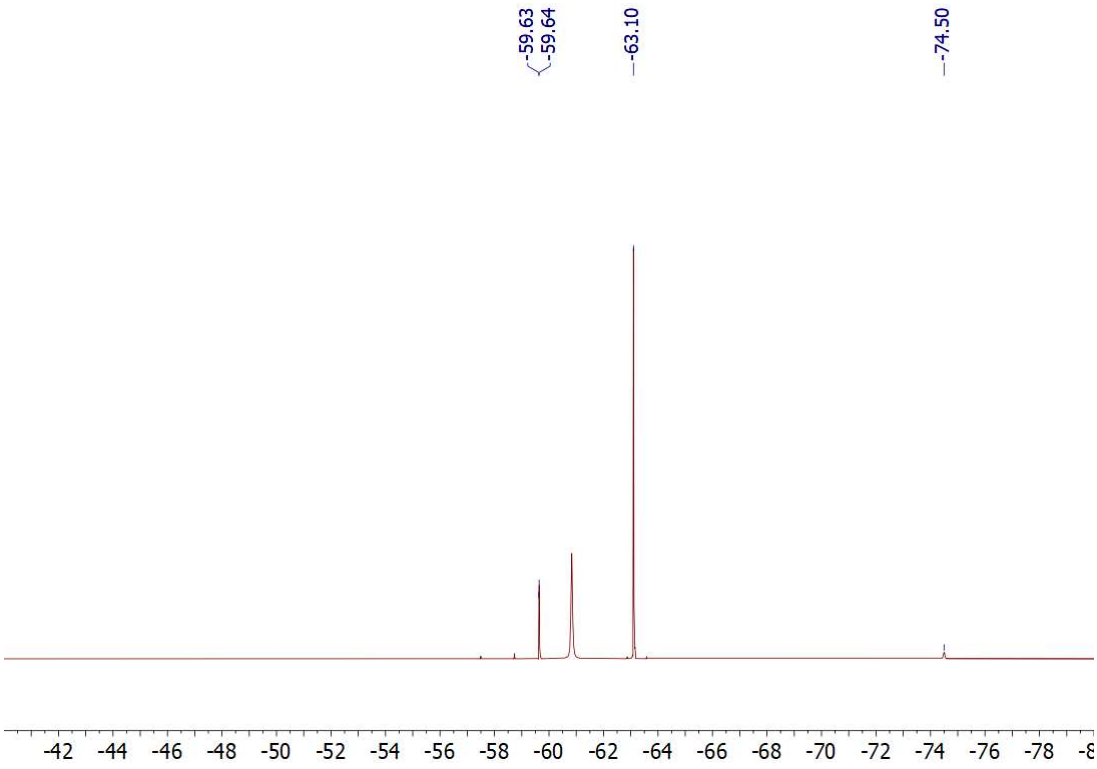


Figure S67. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method E (0.5 mmol scale, 2 M) using 6-fluoronicotinonitrile (**4d**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments.

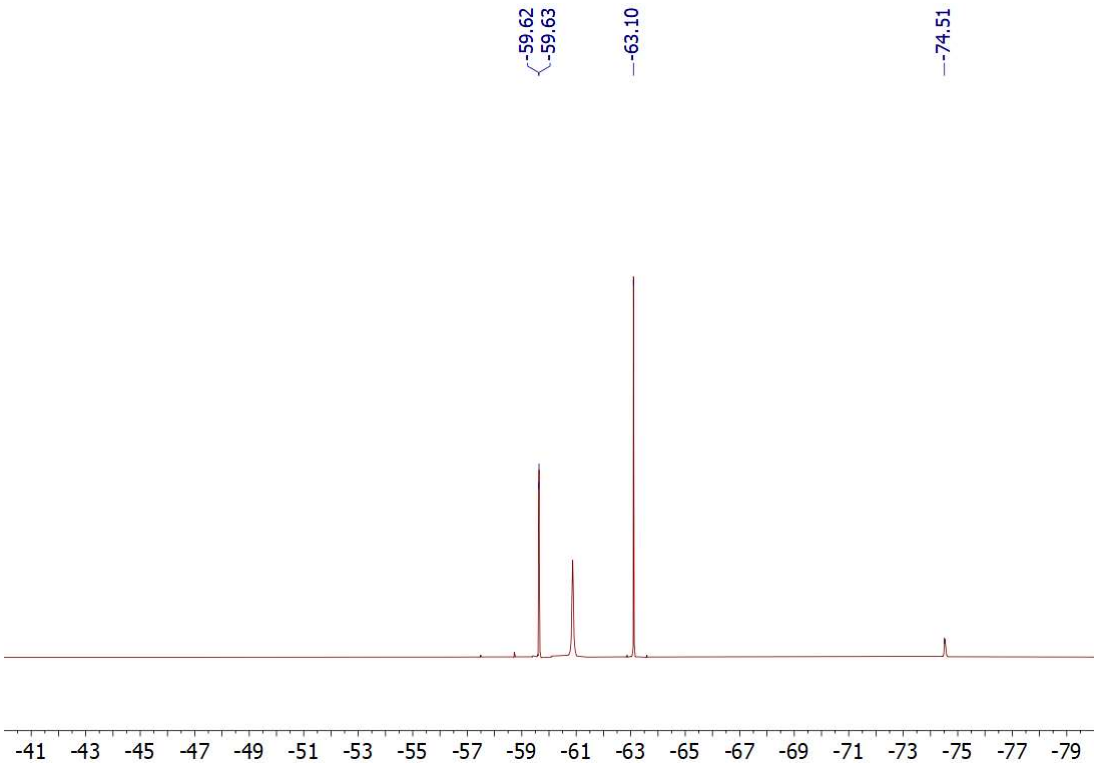


Figure S68. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by modified method E (0.5 mmol scale, 2 M) using 6-fluoronicotinonitrile (**4d**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments. Spiked with 2-Fluoro-5-(trifluoromethoxy)nicotinonitrile (**5d**).

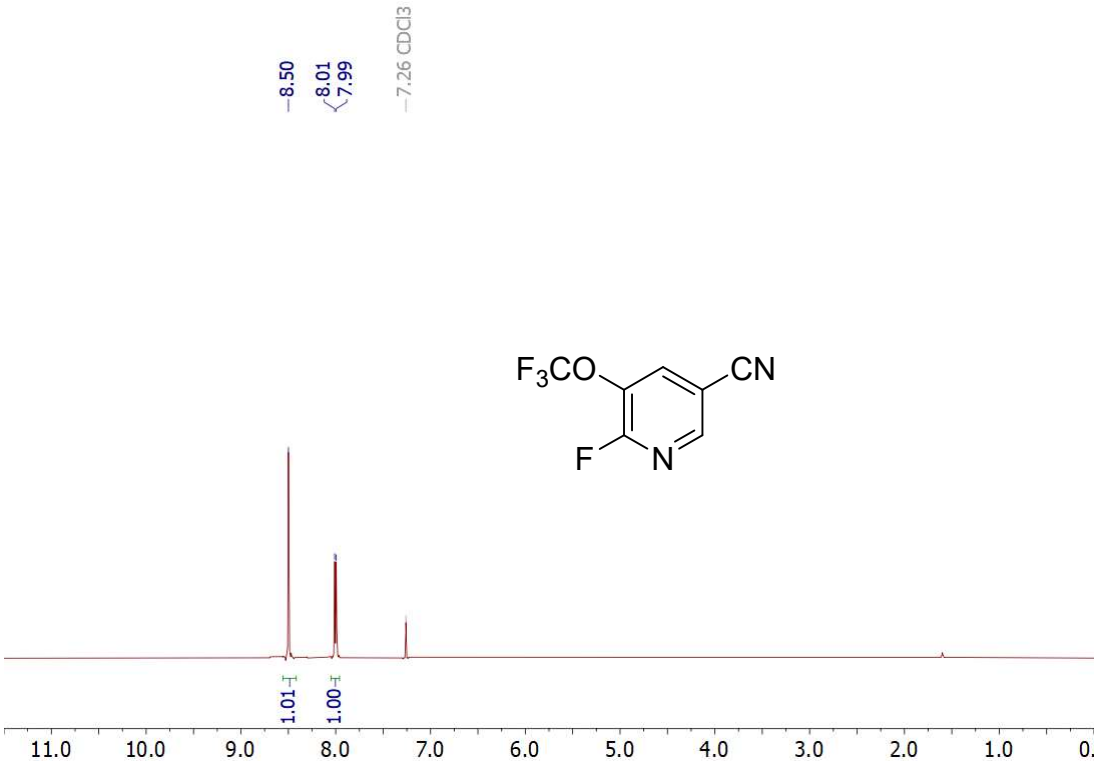


Figure S69. ^{1}H-NMR-Spectrum (500 MHz, $CDCl_3$) of **5d.**

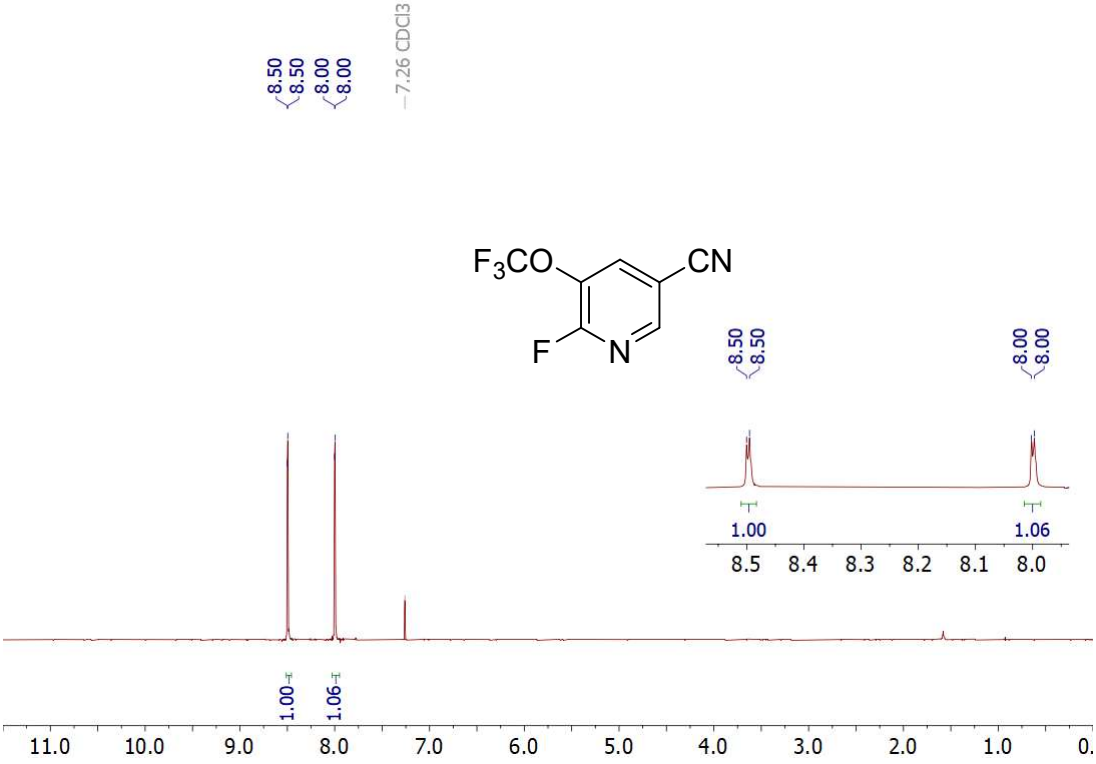


Figure S70. ^{1}H{-^{19}F}-NMR-Spectrum (500 MHz, $CDCl_3$) of **5d.**

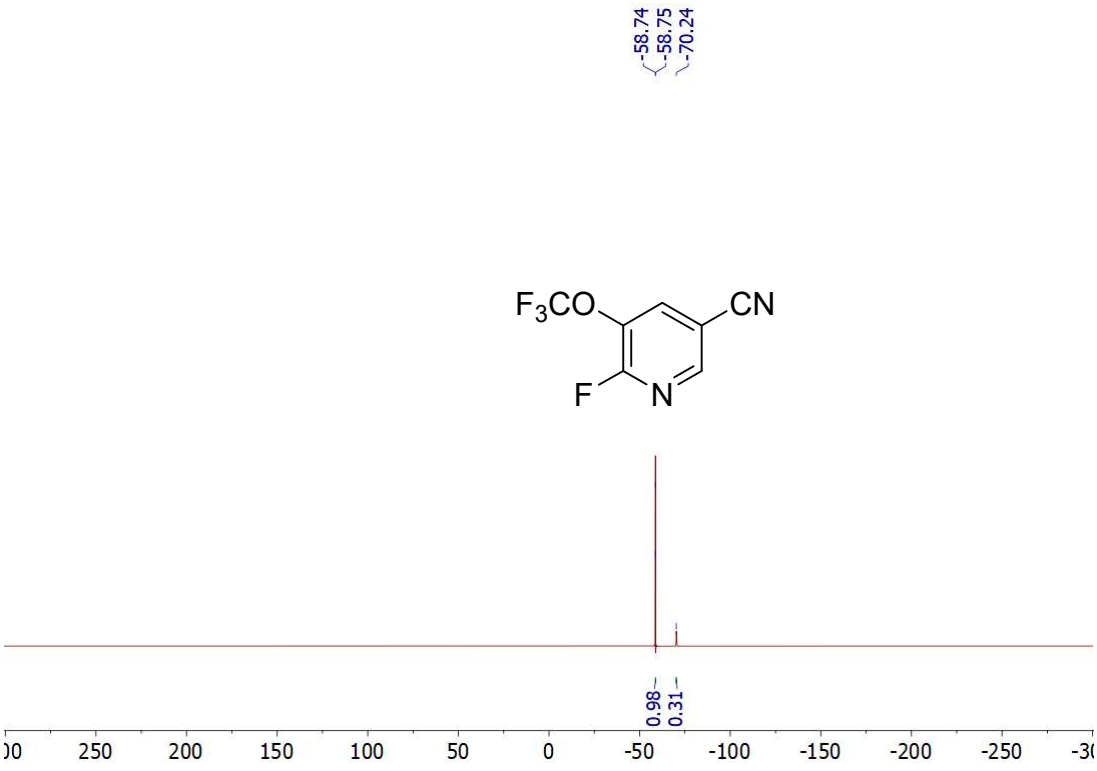


Figure S71. ^{19}F -NMR-Spectrum (376 MHz, $CDCl_3$) of **5d.**

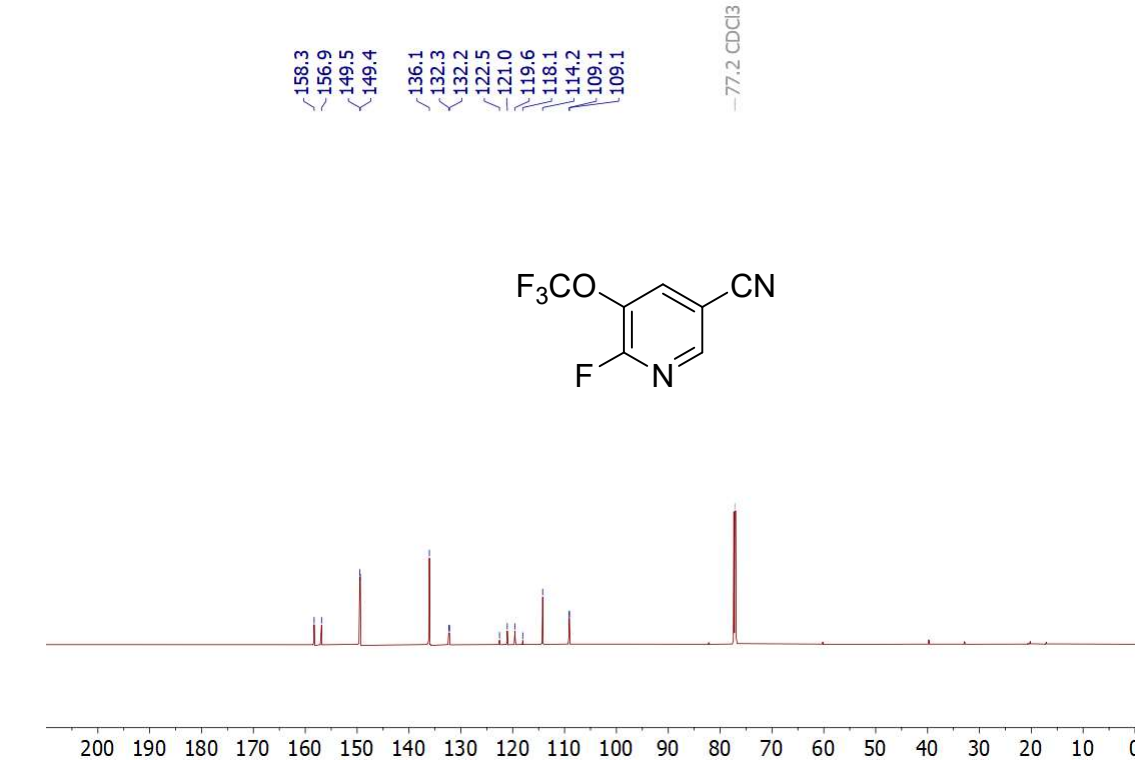


Figure S72. $^{13}C\{^{-1}H\}$-NMR-Spectrum (176 MHz, $CDCl_3$) of **5d.**

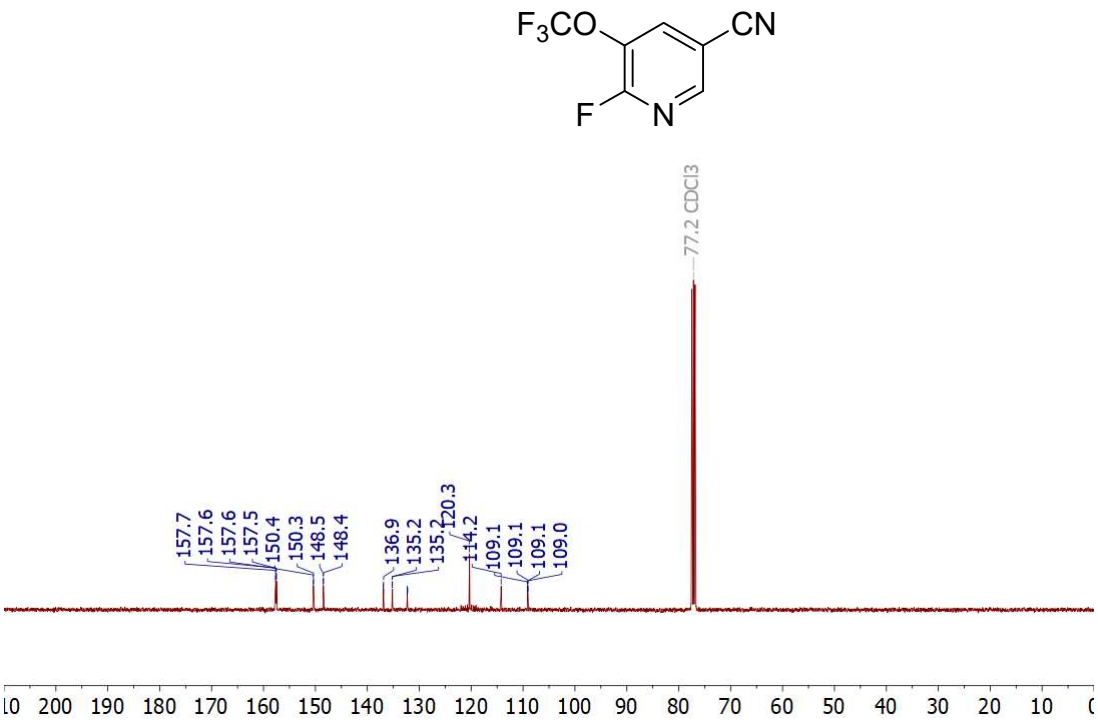


Figure S73. $^{13}C\{^{-19}F\}$-NMR-Spectrum (101 MHz, $CDCl_3$) of **5d.**

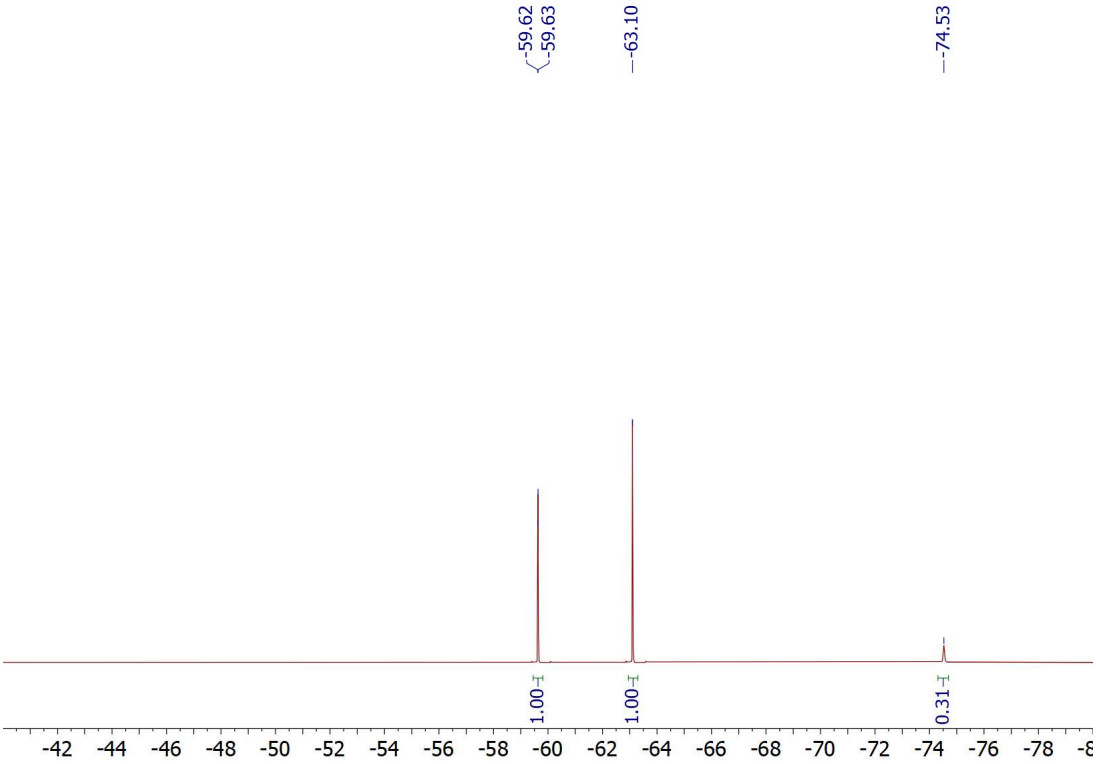


Figure S74. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of **5d** (0.2 mmol) with (trifluoromethoxy)benzene (0.2 mmol).

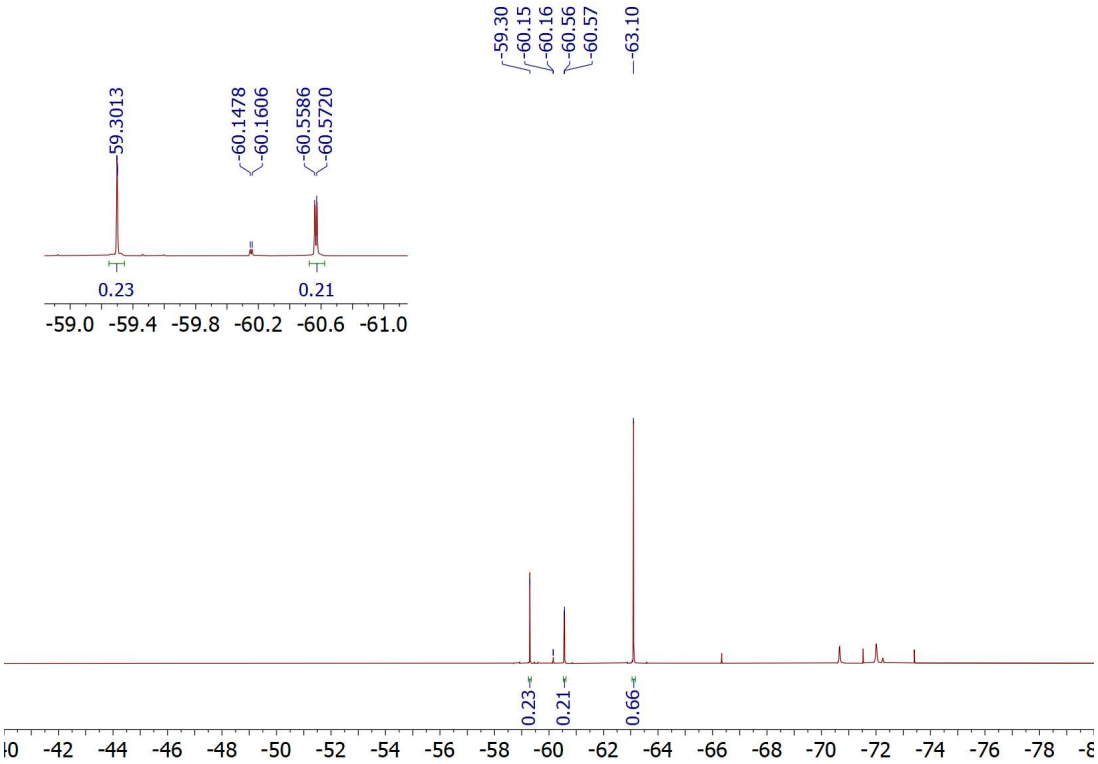


Figure S75. ^{19}F-NMR-Spectrum (376 MHz, Et_2O/MeCN) of a reaction mixture prepared by method B (3 mmol scale) using 6-fluoropyridin-2-amine (**4e**) as substrate and trifluorotoluene (2 mmol) as internal standard.

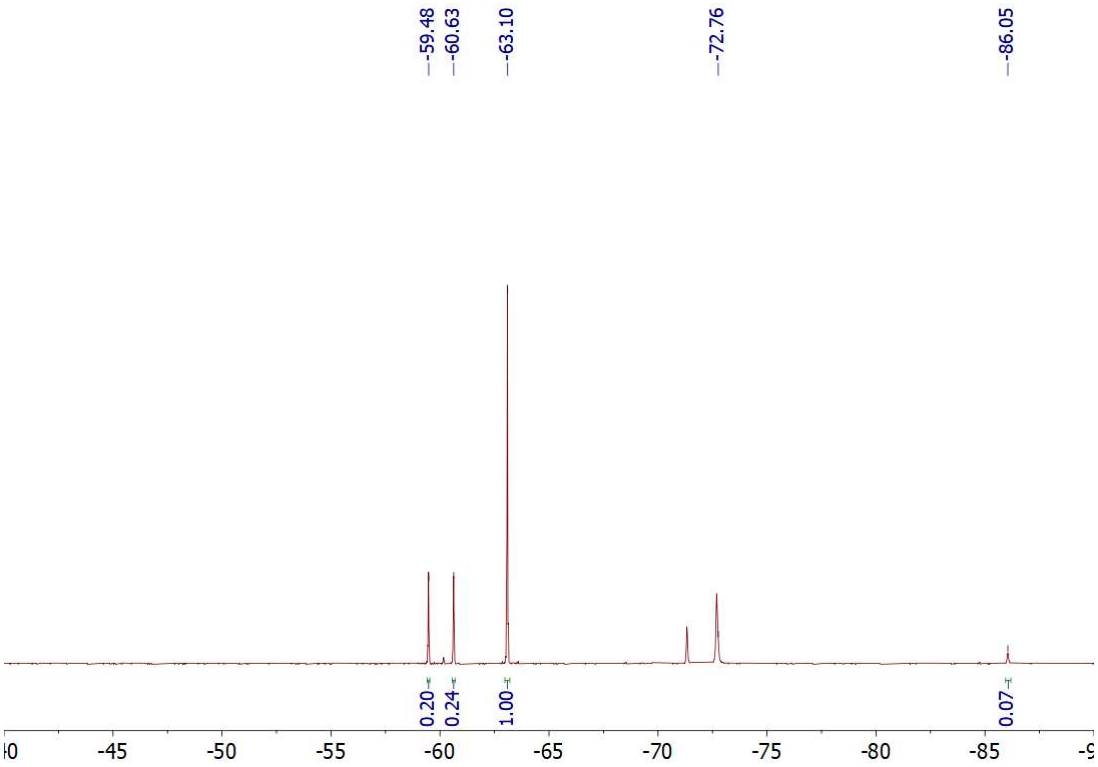


Figure S76. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method E (0.5 mmol scale, MeCN 0.2 M, 6 h reaction time) using 6-fluoropyridin-2-amine (**4e**) as substrate and trifluorotoluene (0.5 mmol) as internal standard.

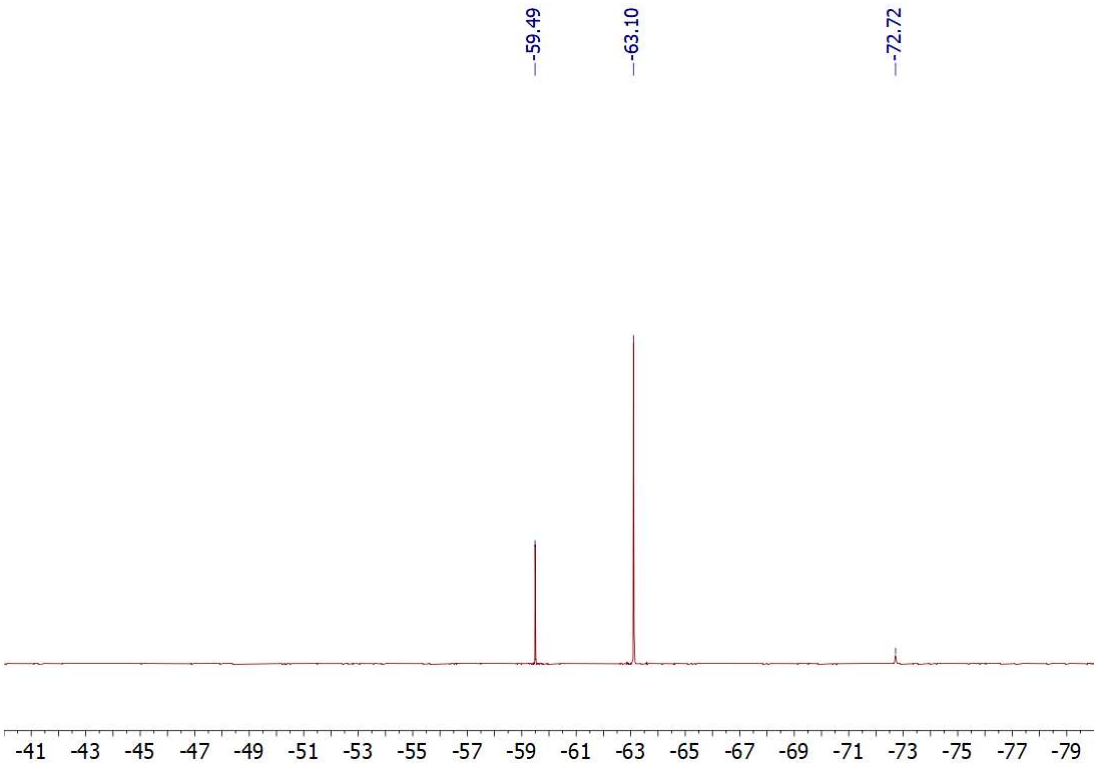


Figure S77. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of 6-Fluoro-3-(trifluoromethoxy)pyridin-2-amine (**5ea**) and trifluorotoluene in MeCN.

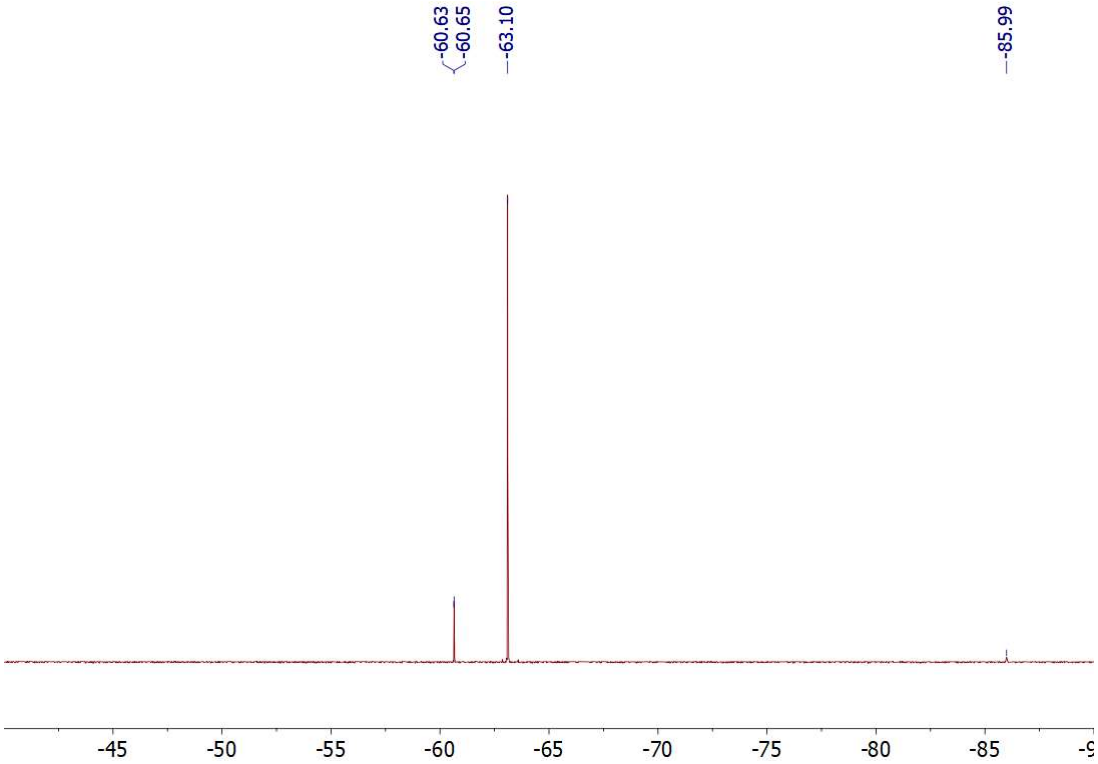


Figure S78. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of 6-Fluoro-5-(trifluoromethoxy)pyridin-2-amine (**5eb**) and trifluorotoluene in MeCN.

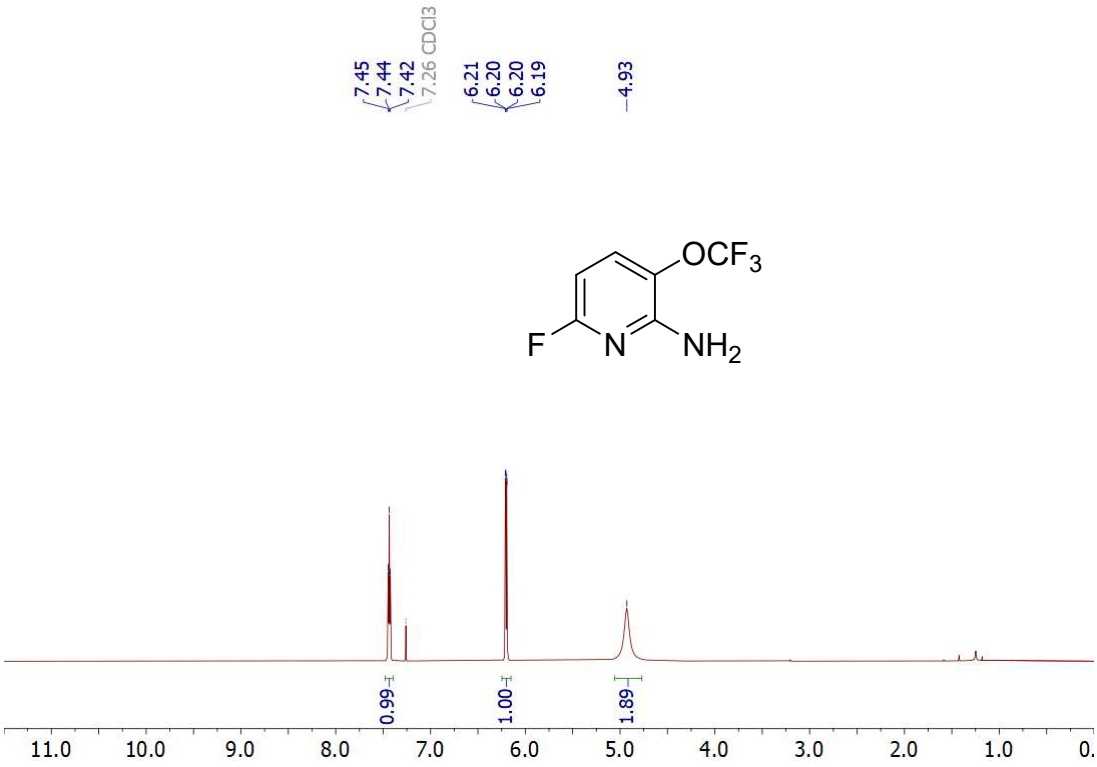


Figure S79. ^{1}H-NMR-Spectrum (700 MHz, $CDCl_3$) of **5ea.**

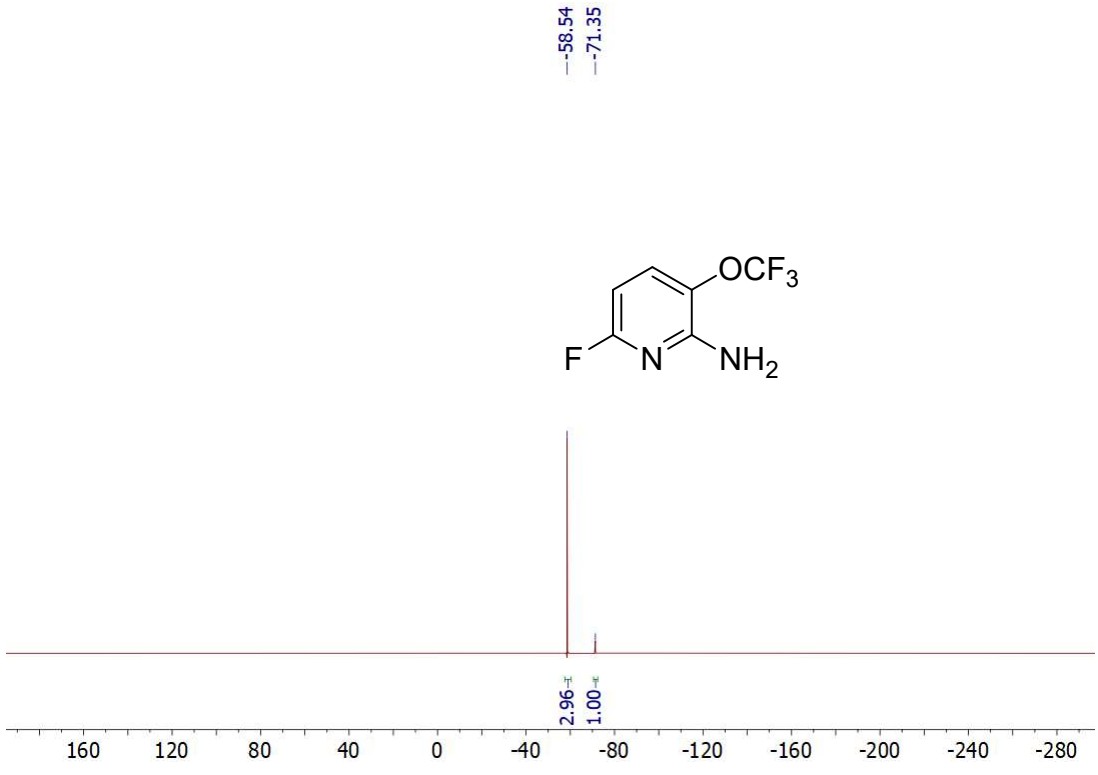


Figure S80. ^{19}F-NMR-Spectrum (565 MHz, $CDCl_3$) of **5ea.**

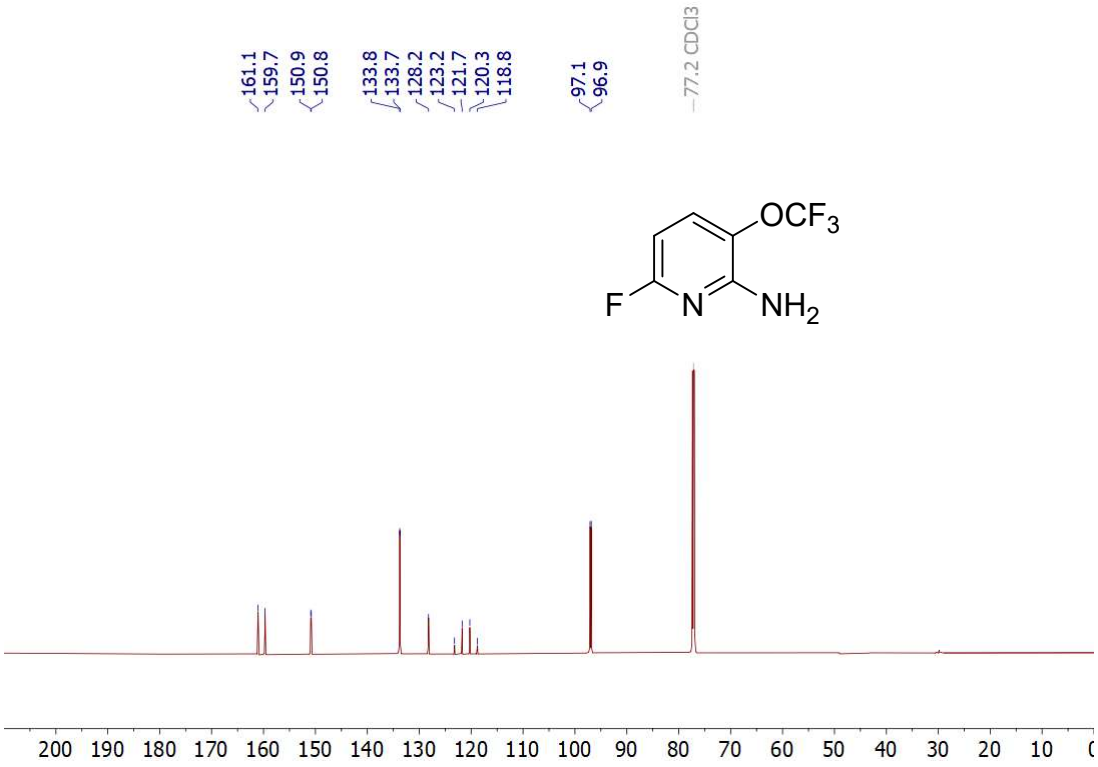


Figure S81. ^{13}C-NMR-Spectrum (176 MHz, $CDCl_3$) of **5ea.**

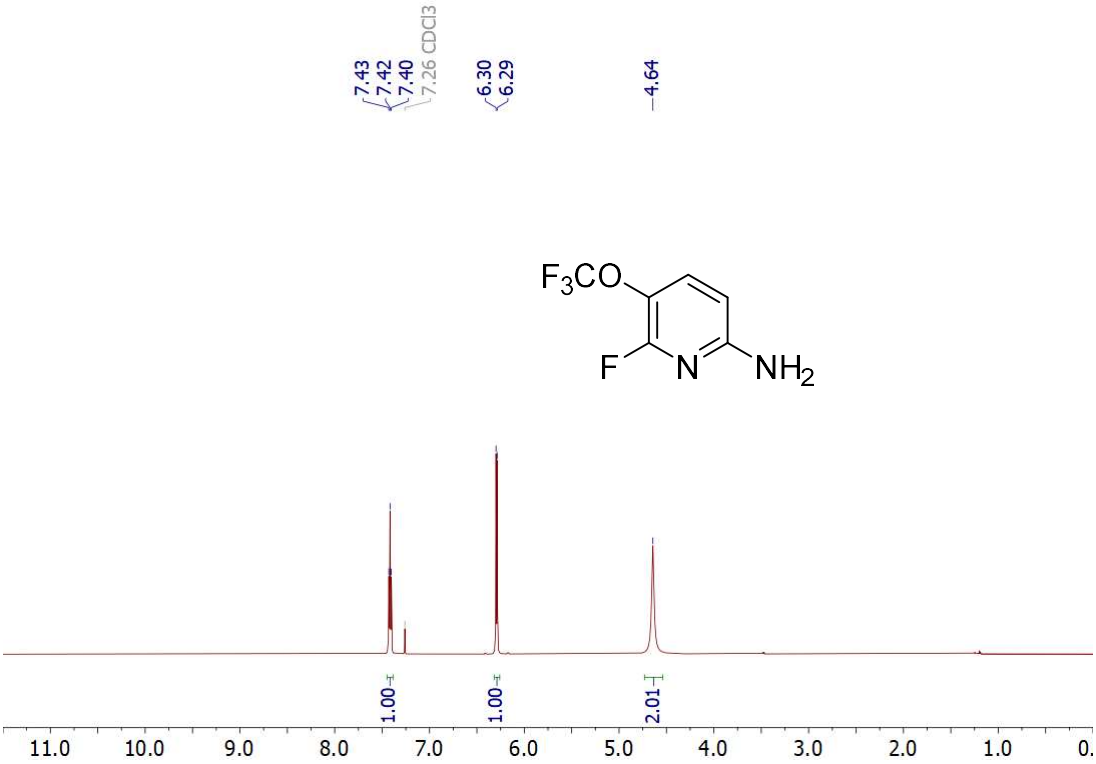


Figure S82. ^{1}H-NMR-Spectrum (700 MHz, $CDCl_3$) of **5eb.**

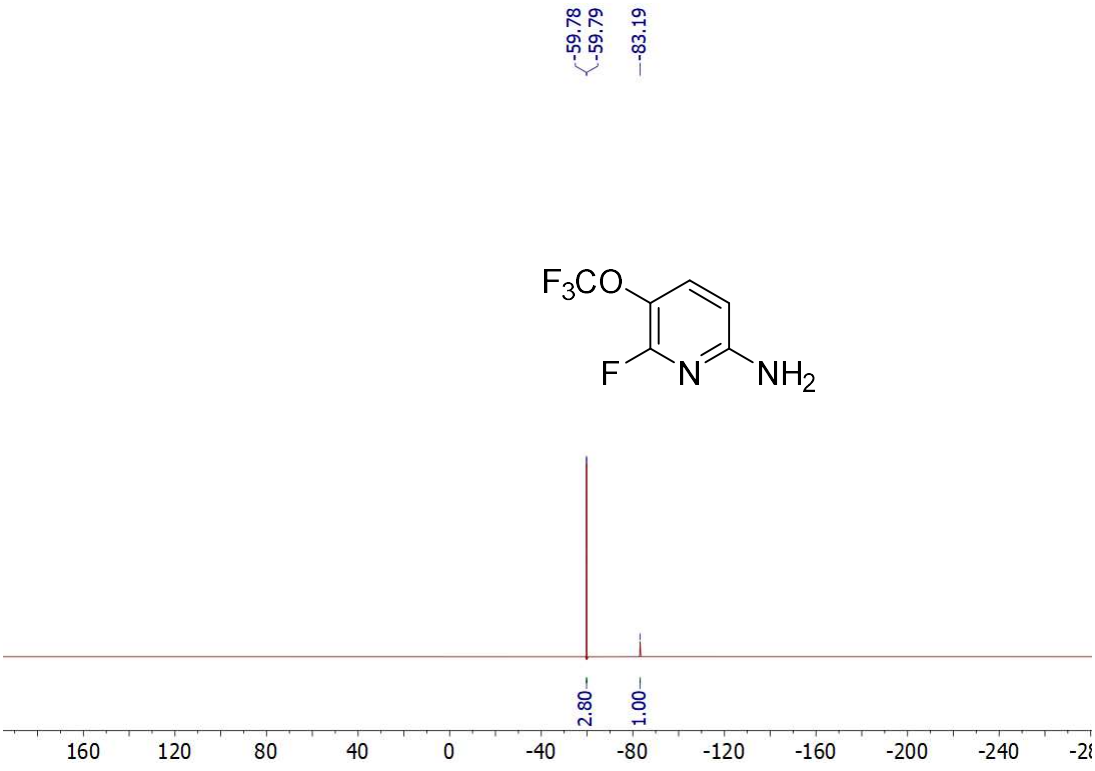


Figure S83. ^{19}F-NMR-Spectrum (565 MHz, $CDCl_3$) of **5eb.**

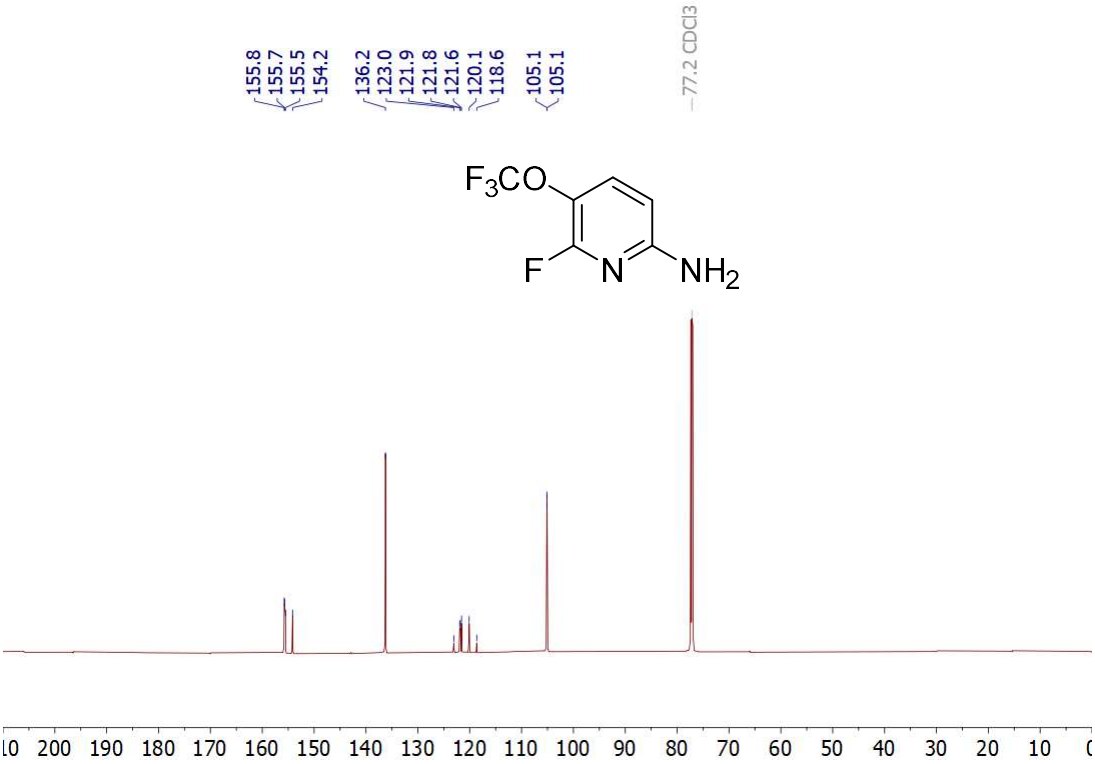


Figure S84. ^{13}C-NMR-Spectrum (176 MHz, $CDCl_3$) of **5eb.**

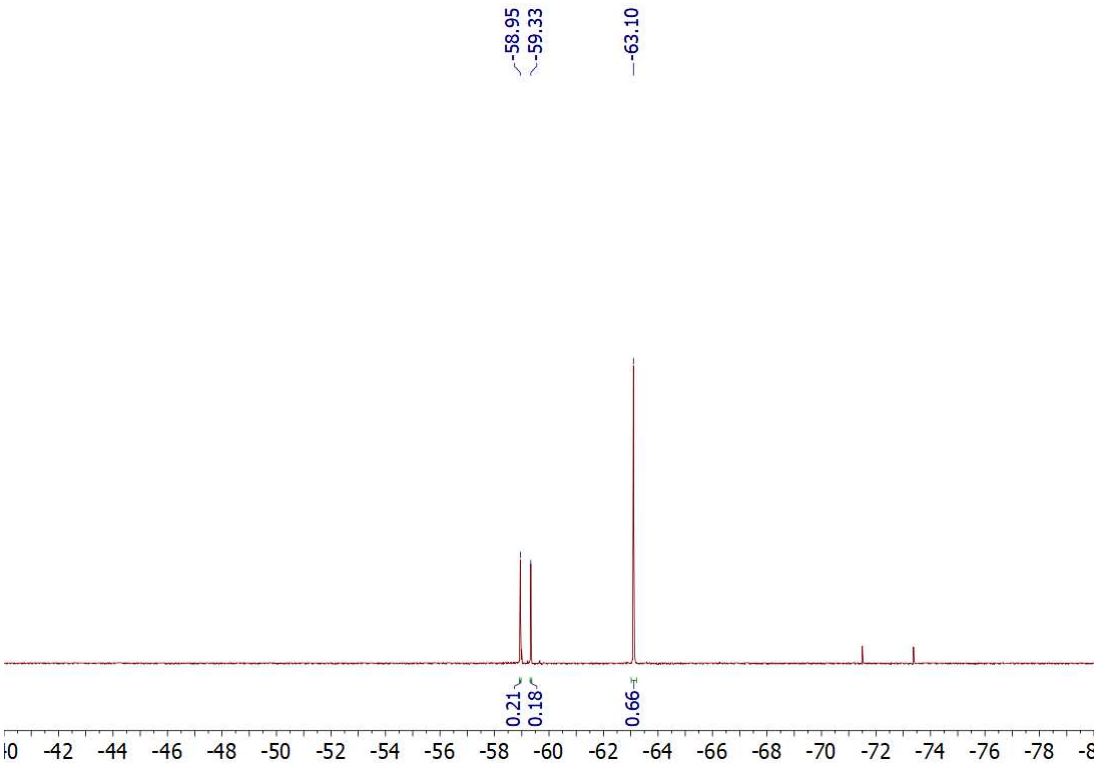


Figure S85. ^{19}F-NMR-Spectrum (376 MHz, Et_2O/MeCN) of a reaction mixture prepared by method B (3 mmol scale) using 6-chloropyridin-2-amine (**4f**) as substrate and trifluorotoluene (2 mmol) as internal standard.

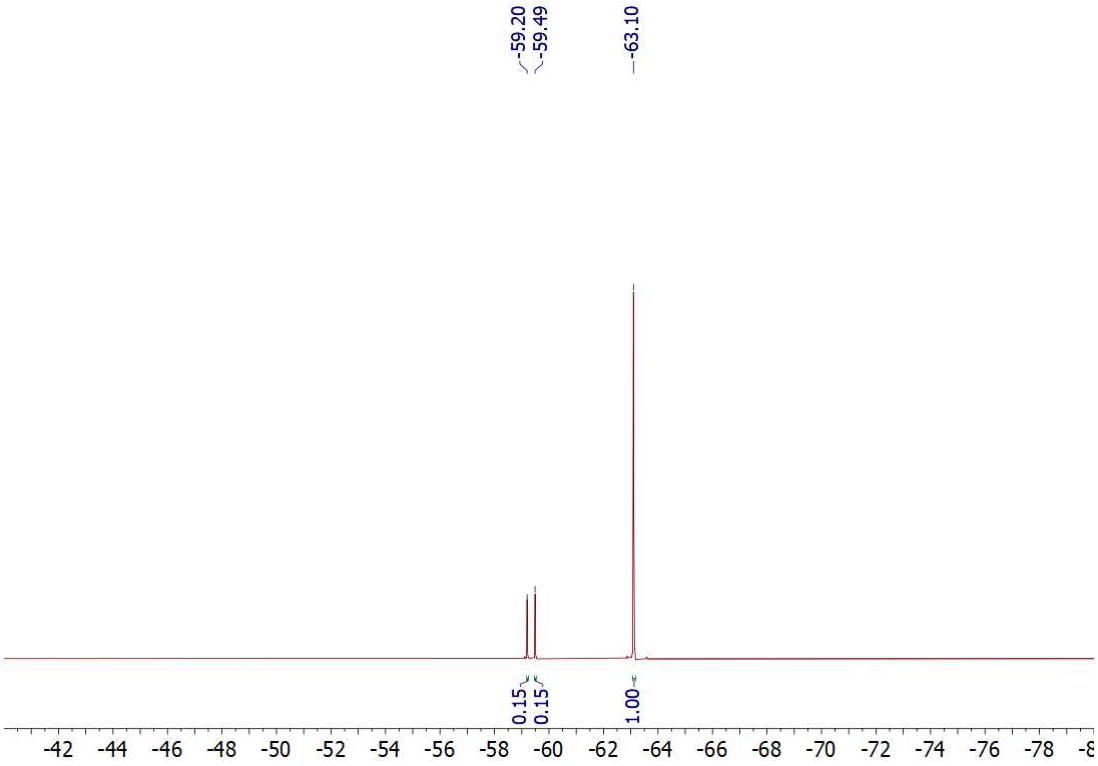


Figure S86. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method E (0.5 mmol scale, 0.2 M, 6 h reaction time) using 6-chloropyridin-2-amine (**4f**) as substrate and trifluorotoluene (0.5 mmol) as internal standard.

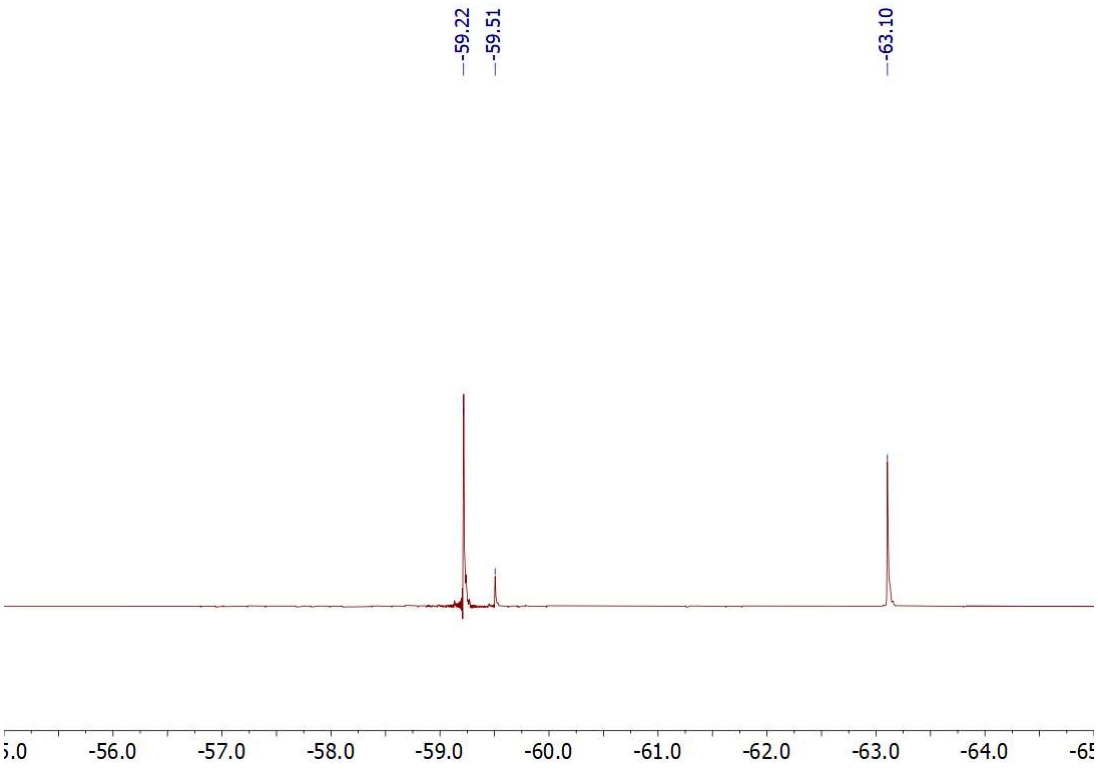


Figure S87. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method E (0.5 mmol, 0.2 M, 6 h reaction time) using 6-chloropyridin-2-amine (**4f**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments. Spiked with 6-Chloro-3-(trifluoromethoxy)pyridin-2-amine (**5fa**).

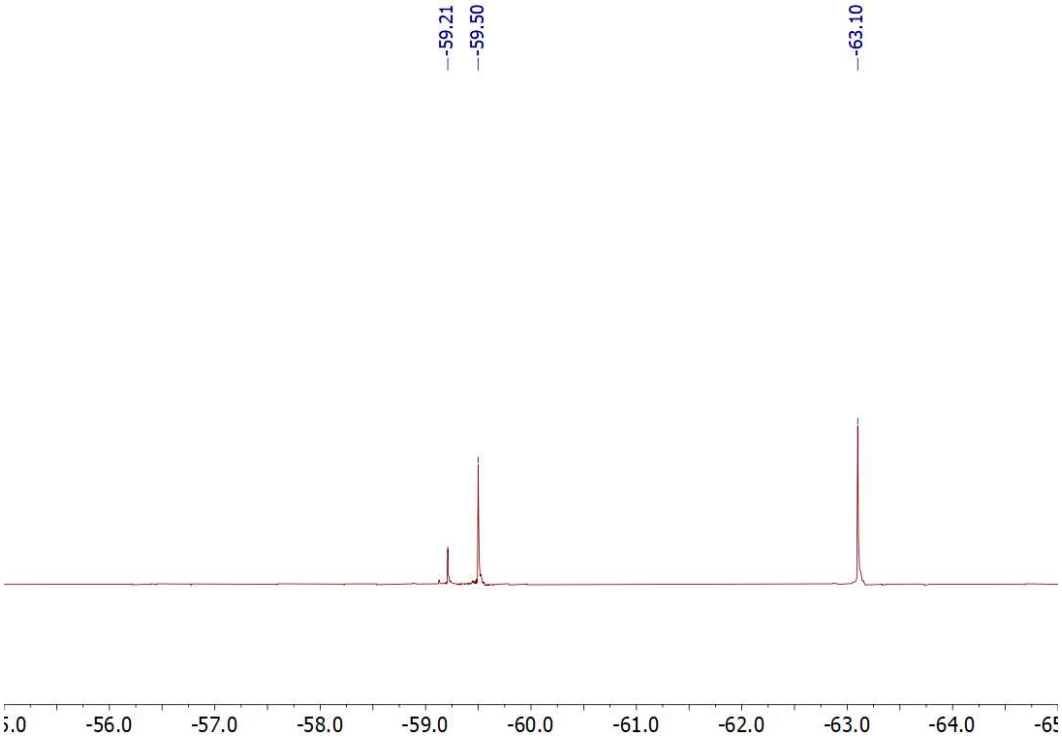


Figure S88. ^{19}F-NMR-Spectrum (376 MHz, MeCN) of a reaction mixture prepared by method E (0.5 mmol, 0.2 M, 6 h reaction time) using 6-chloropyridin-2-amine (**4f**) as substrate and trifluorotoluene as internal standard. Remeasured for spiking experiments. Spiked with 6-Chloro-5-(trifluoromethoxy)pyridin-2-amine (**5fb**).

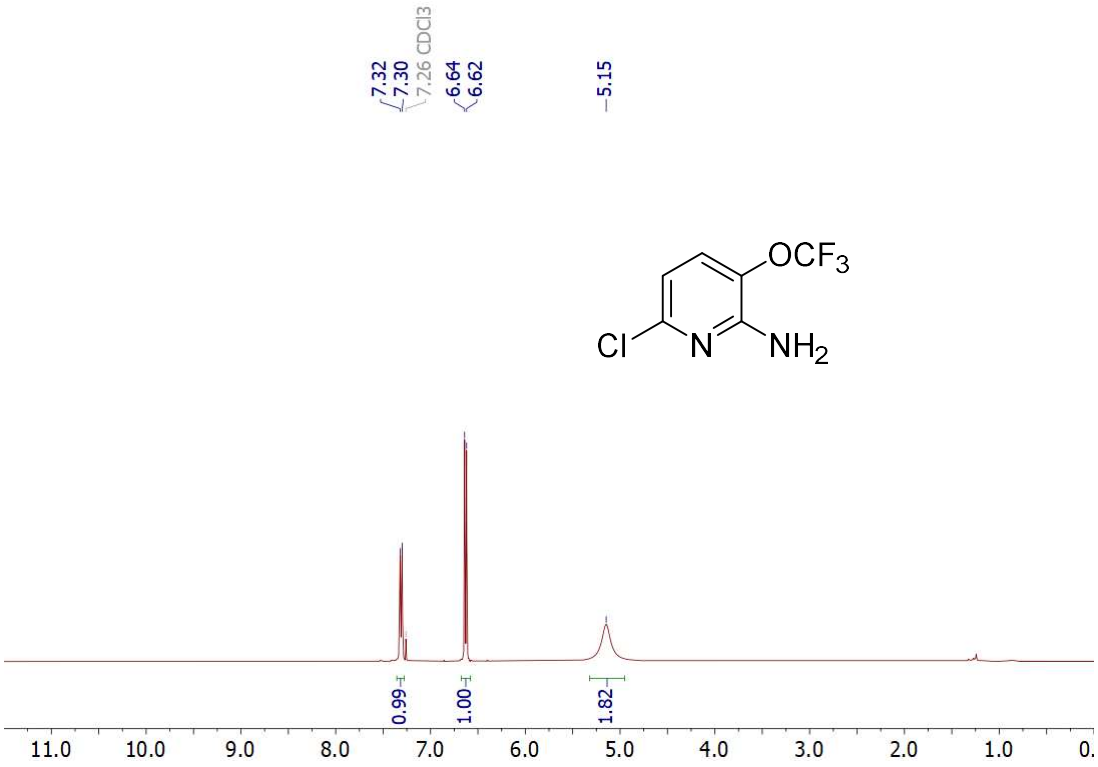


Figure S89. ^{1}H-NMR-Spectrum (400 MHz, $CDCl_3$) of **5fa.**

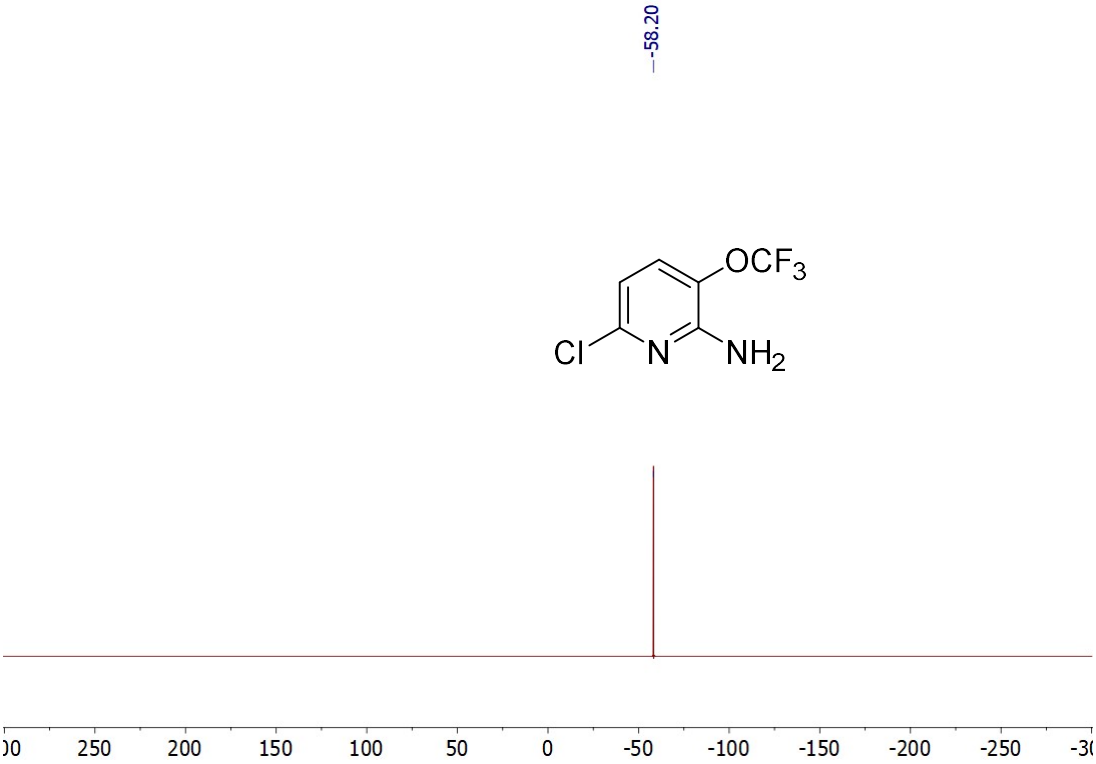


Figure S90. ^{19}F-NMR-Spectrum (376 MHz, $CDCl_3$) of **5fa.**

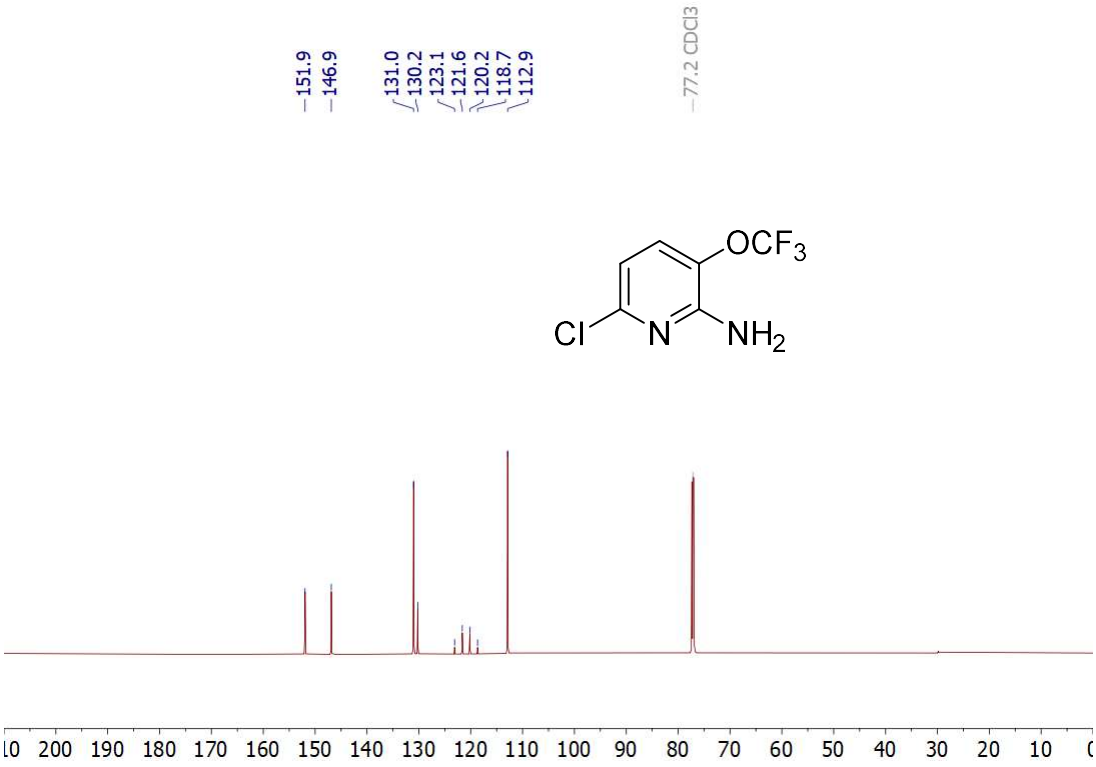


Figure S91. ^{13}C-NMR-Spectrum (176 MHz, $CDCl_3$) of **5fa.**

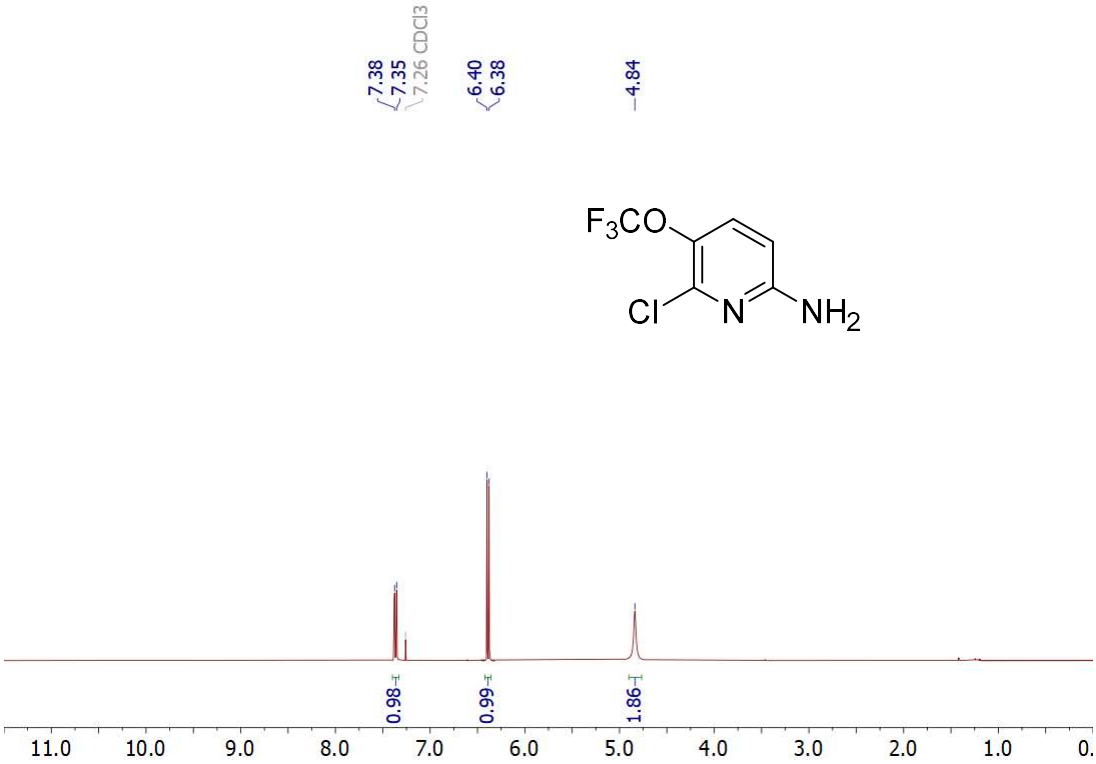


Figure S92. ^{1}H-NMR-Spectrum (400 MHz, $CDCl_3$) of **5fb.**

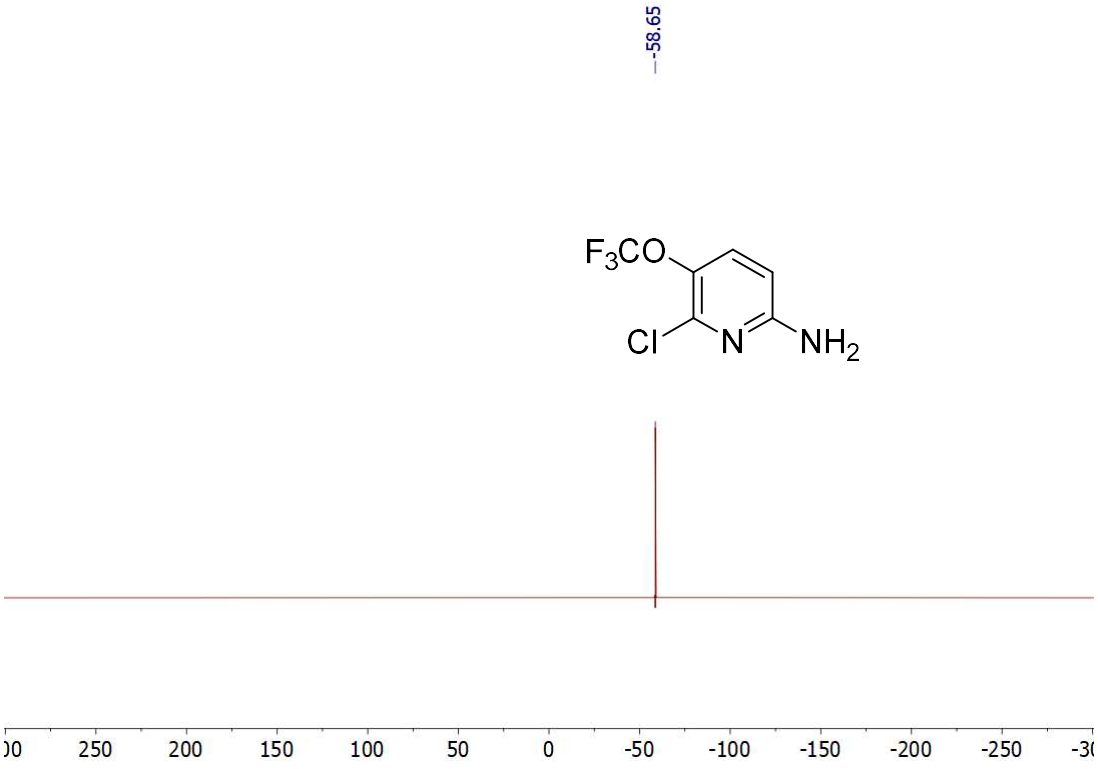


Figure S93. ^{19}F-NMR-Spectrum (376 MHz, $CDCl_3$) of **5fb.**

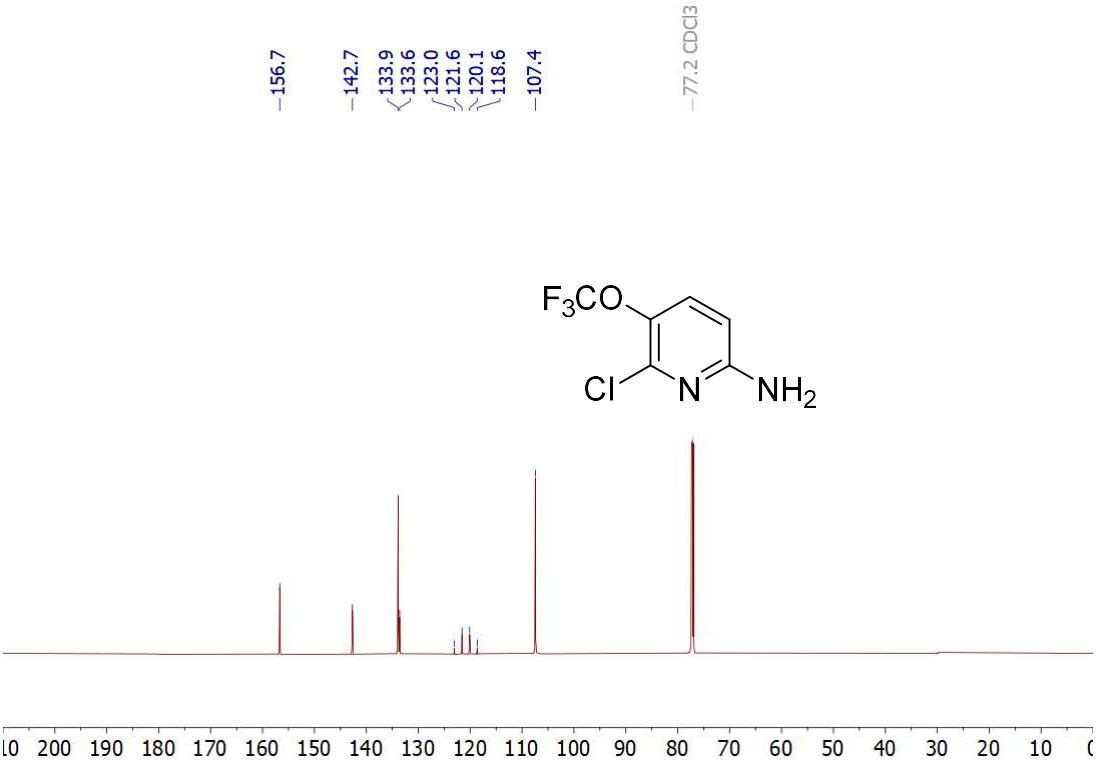


Figure S94. ^{13}C-NMR-Spectrum (176 MHz, $CDCl_3$) of **5fb.**

7 GC-MS and HR-MS Spectra

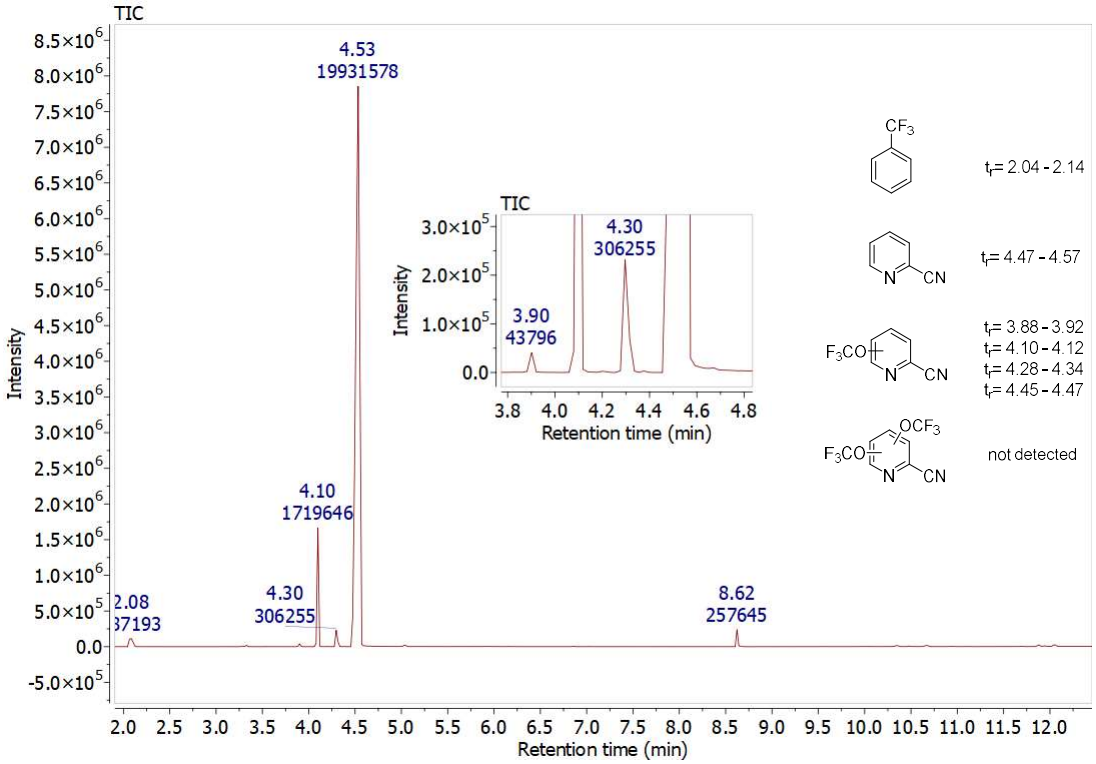


Figure S95. GC-MS spectrum of a reaction mixture prepared by modified method E (6 mmol scale, no solvent) using picolinonitrile (**4a**) as substrate.

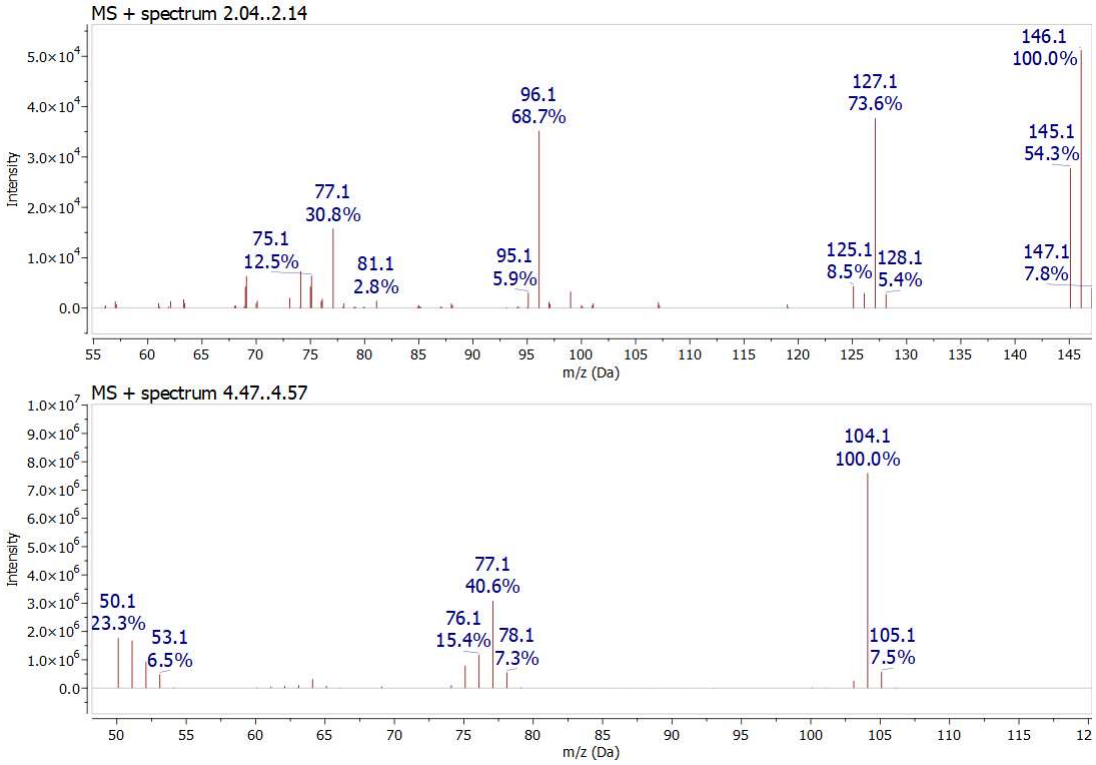


Figure S96. GC-MS spectra of a reaction mixture, prepared by modified method E (6 mmol scale, no solvent) using picolinonitrile (**4a**) as substrate, showing trifluorotoluene (t_r = 2.04 – 2.14) and picolinonitrile (t_r = 4.47 – 4.57).

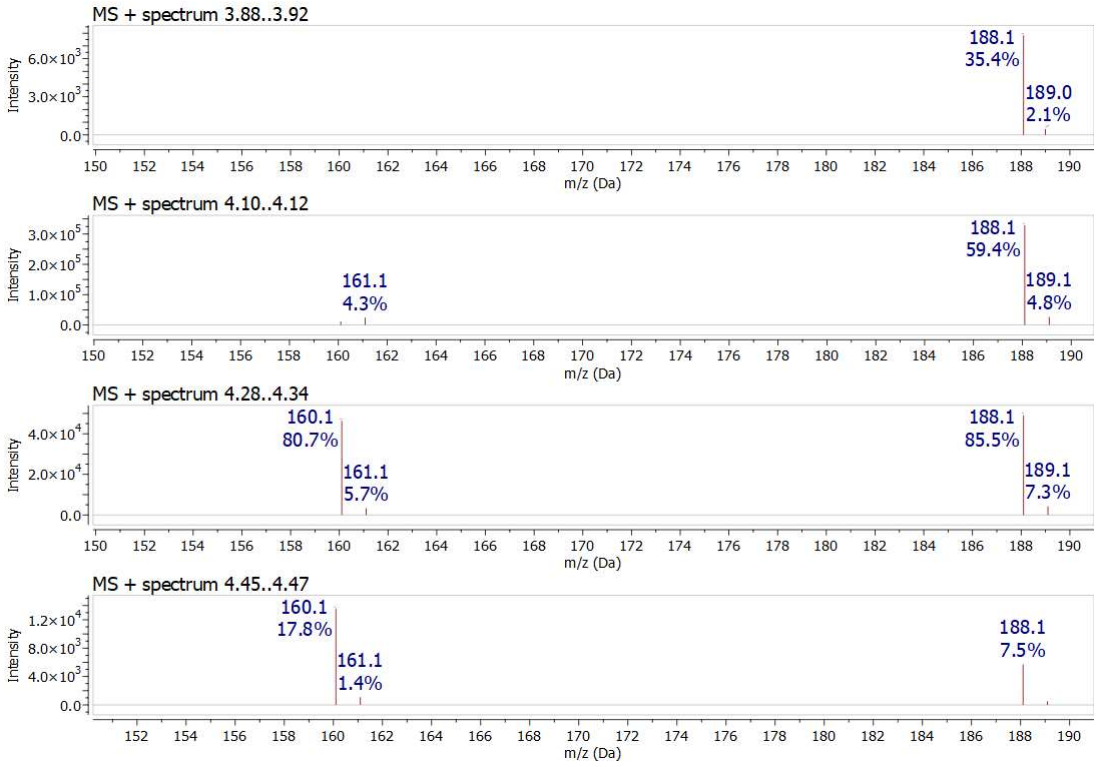


Figure S97. GC-MS spectra of a reaction mixture, prepared by modified method E (6 mmol scale, no solvent) using picolinonitrile (**4a**) as substrate, showing 4 distinct (trifluoromethoxy)picolinonitriles (t_r = 3.88 – 3.92, 4.10 – 4.12, 4.28 – 4.34, 4.45 – 4.47).

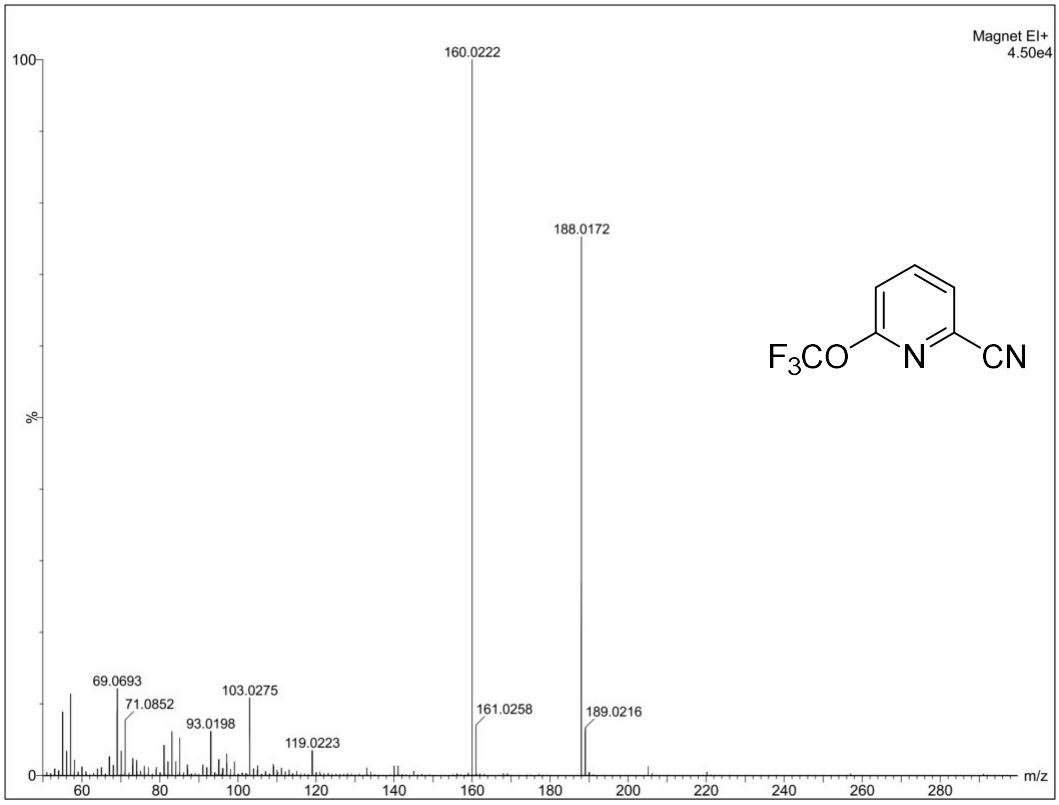


Figure S98. HRMS-EI spectrum of **5ac**.

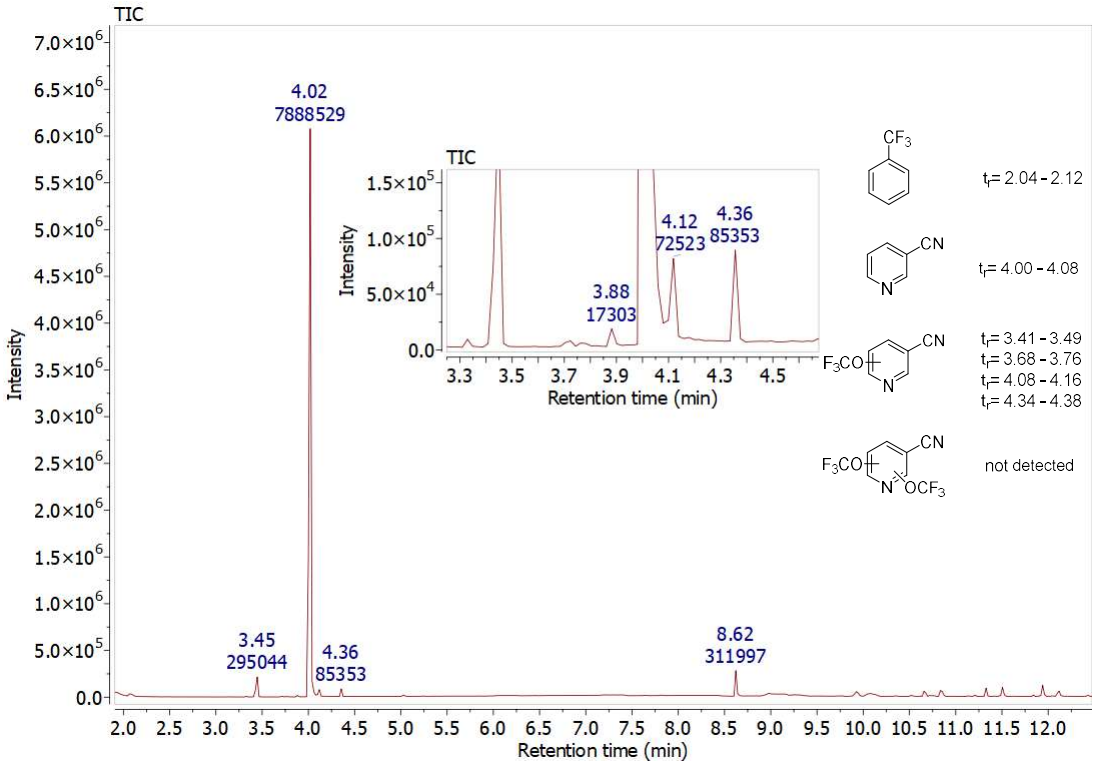


Figure S99. GC-MS spectrum of a reaction mixture prepared by method E (6 mmol scale, 2.0 M) using nicotinonitrile (**4b**) as substrate.

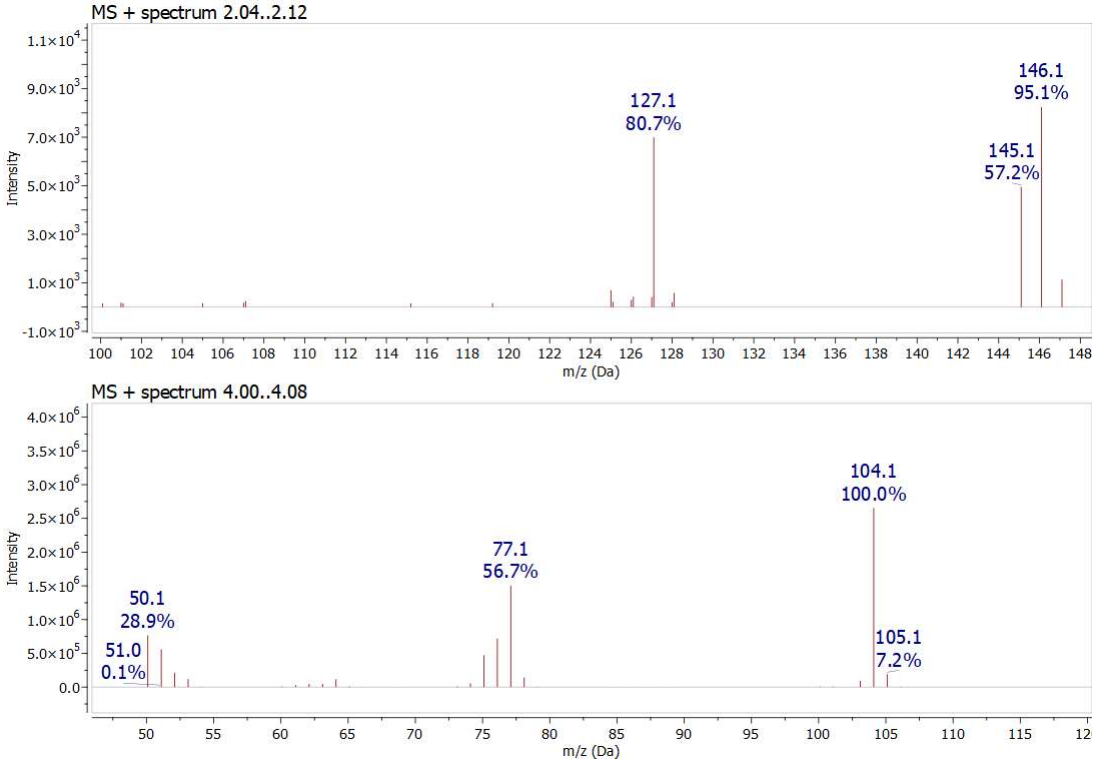


Figure S100. GC-MS spectra of a reaction mixture, prepared by method E (6 mmol scale, 2.0 M) using nicotinonitrile (**4b**) as substrate, showing trifluorotoluene (t_r = 2.04 – 2.12) and nicotinonitrile (t_r = 4.00 – 4.08).

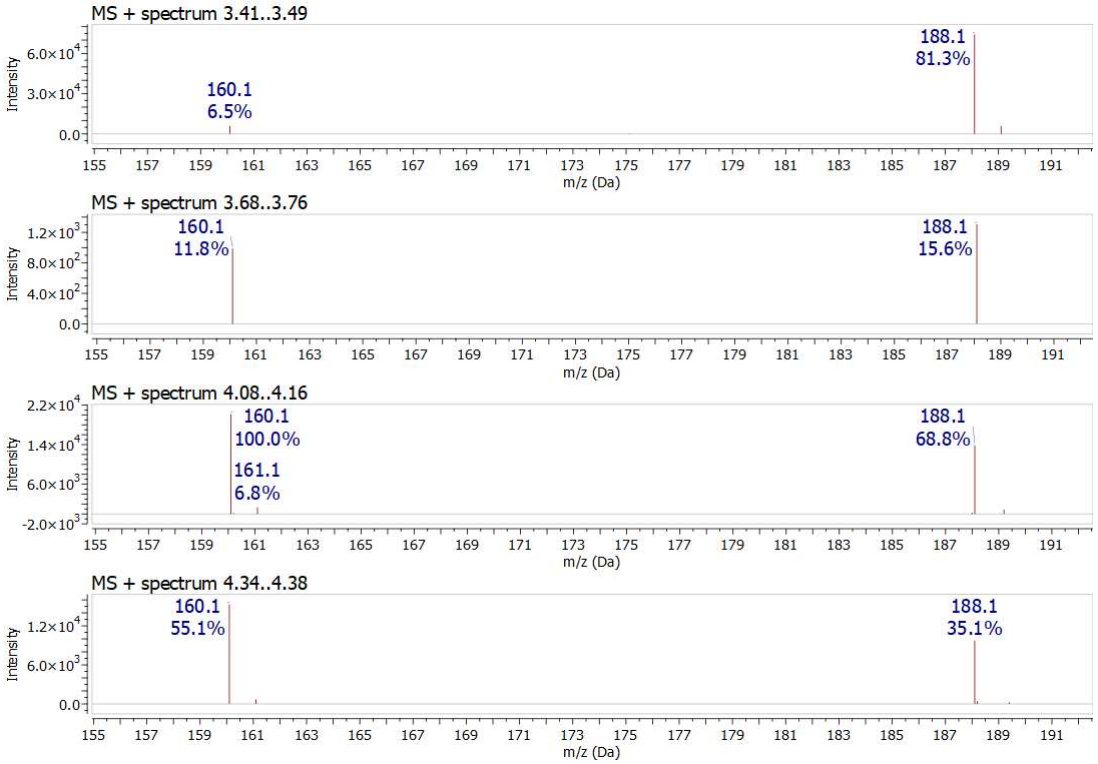


Figure S101. GC-MS spectra of a reaction mixture, prepared by method E (6 mmol scale, 2.0 M) using nicotinonitrile (**4b**) as substrate, showing 4 distinct (trifluoromethoxy)nicotinonitriles (t_r = 3.41 – 3.49, 3.68 – 3.76, 4.08 – 4.16, 4.34 – 4.38).

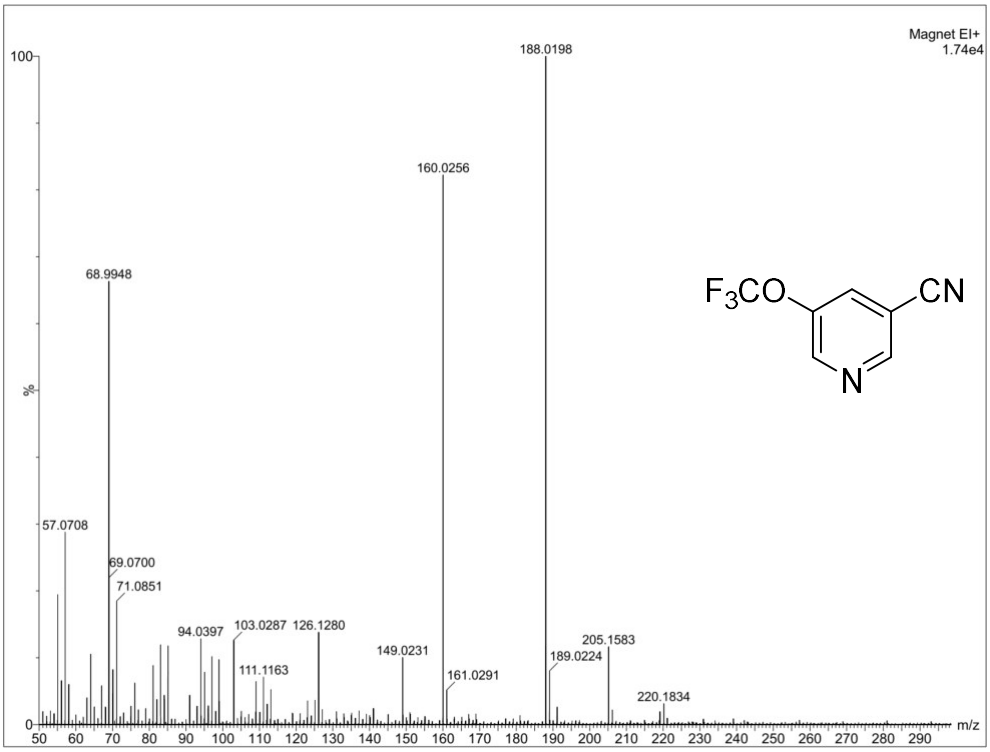


Figure S102. HRMS-EI spectrum of **5bb**.

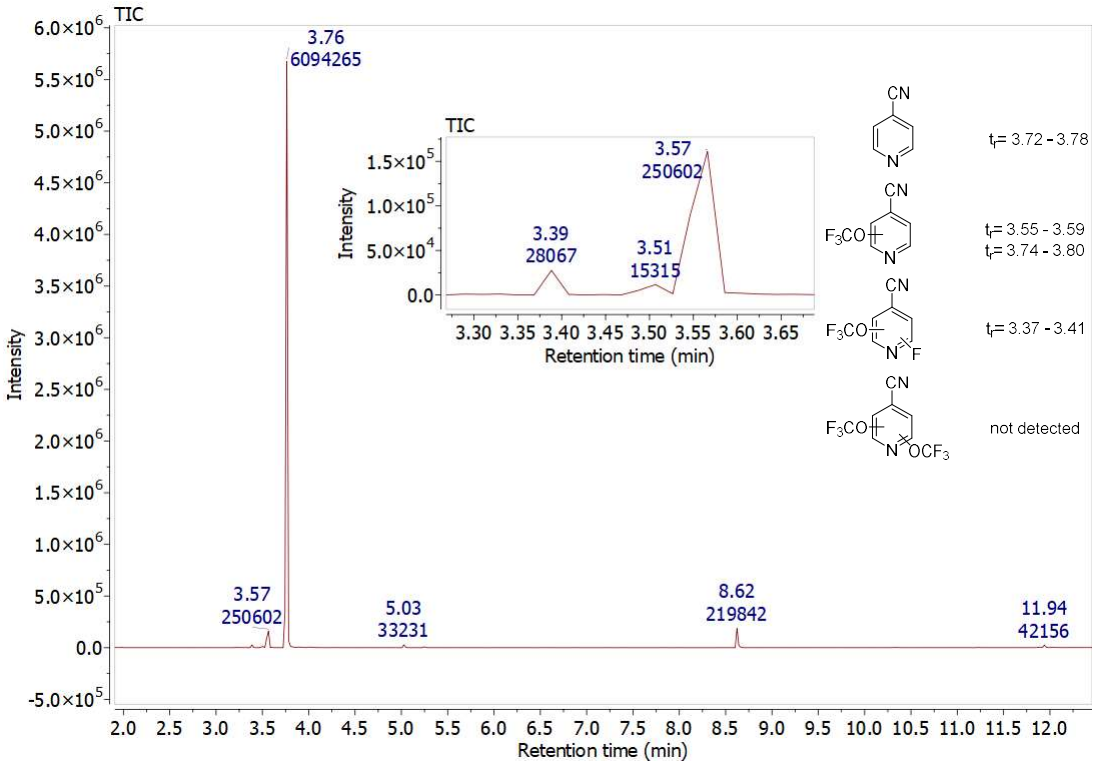


Figure S103. GC-MS spectrum of a reaction mixture prepared by method E (6 mmol scale, 0.4 M, 6 h reaction time) using isonicotinonitrile (**4c**) as substrate.

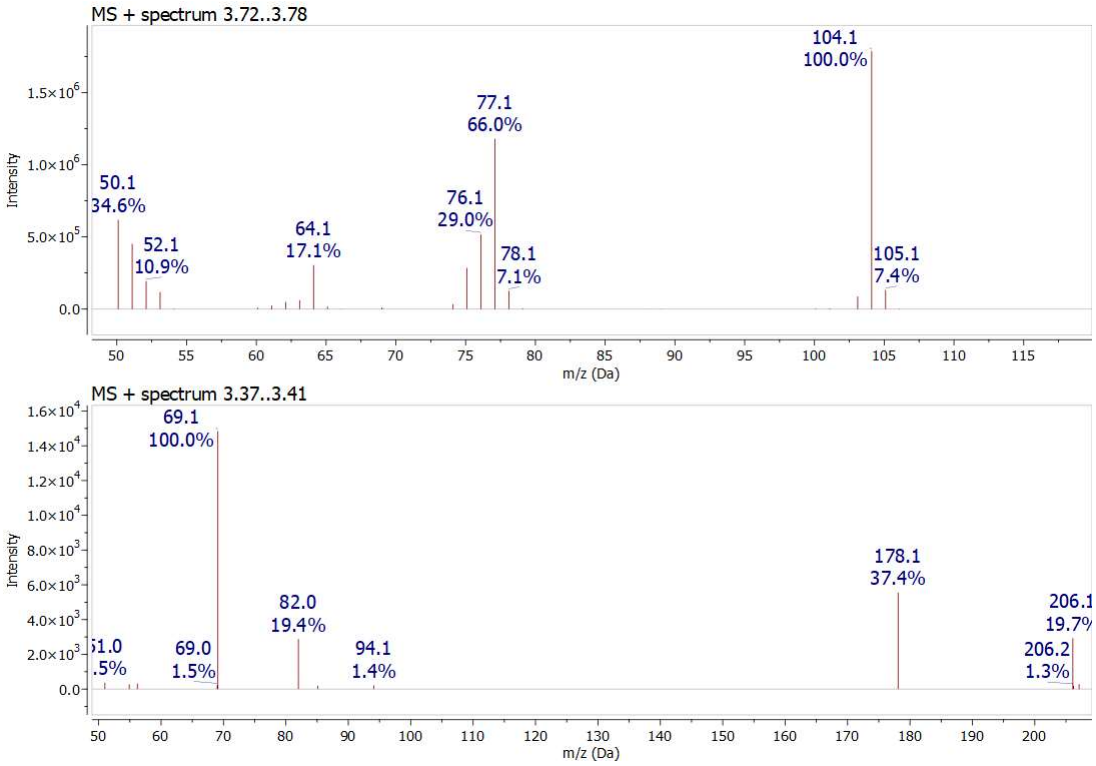


Figure S104. GC-MS spectra of a reaction mixture, prepared by method E (6 mmol scale, 0.4 M, 6 h reaction time) using isonicotinonitrile (**4c**) as substrate, showing 2-fluoro-5-(trifluoromethoxy)isonicotinonitrile (t_r = 3.37 – 3.41) and isonicotinonitrile (t_r = 3.72 – 3.78).

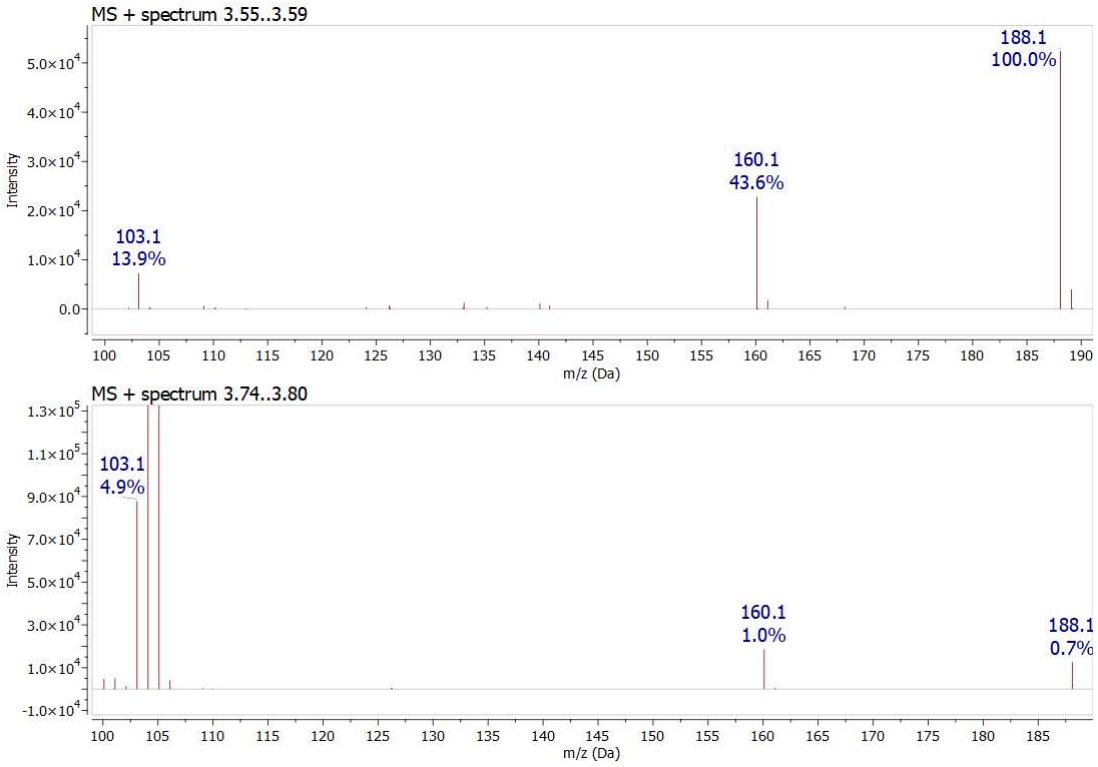


Figure S105. GC-MS spectra of a reaction mixture, prepared by by method E (6 mmol scale, 0.4 M, 6 h reaction time) using isonicotinonitrile (**4c**) as substrate, showing 2 distinct (trifluoromethoxy)isonicotinonitriles (t_r = 3.55 – 3.59, 3.74 – 3.80)

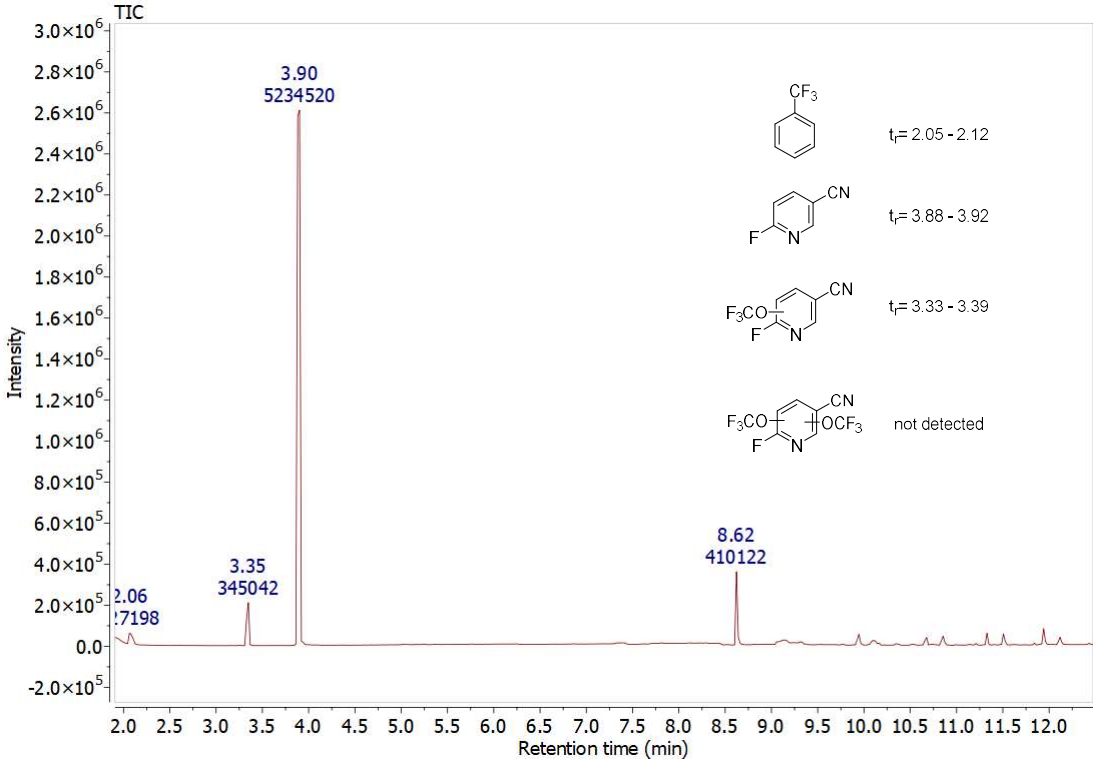


Figure S106. GC-MS spectrum of a reaction mixture prepared by method E (6 mmol scale, 2.0 M) using 6-fluoronicotinonitrile (**4d**) as substrate.

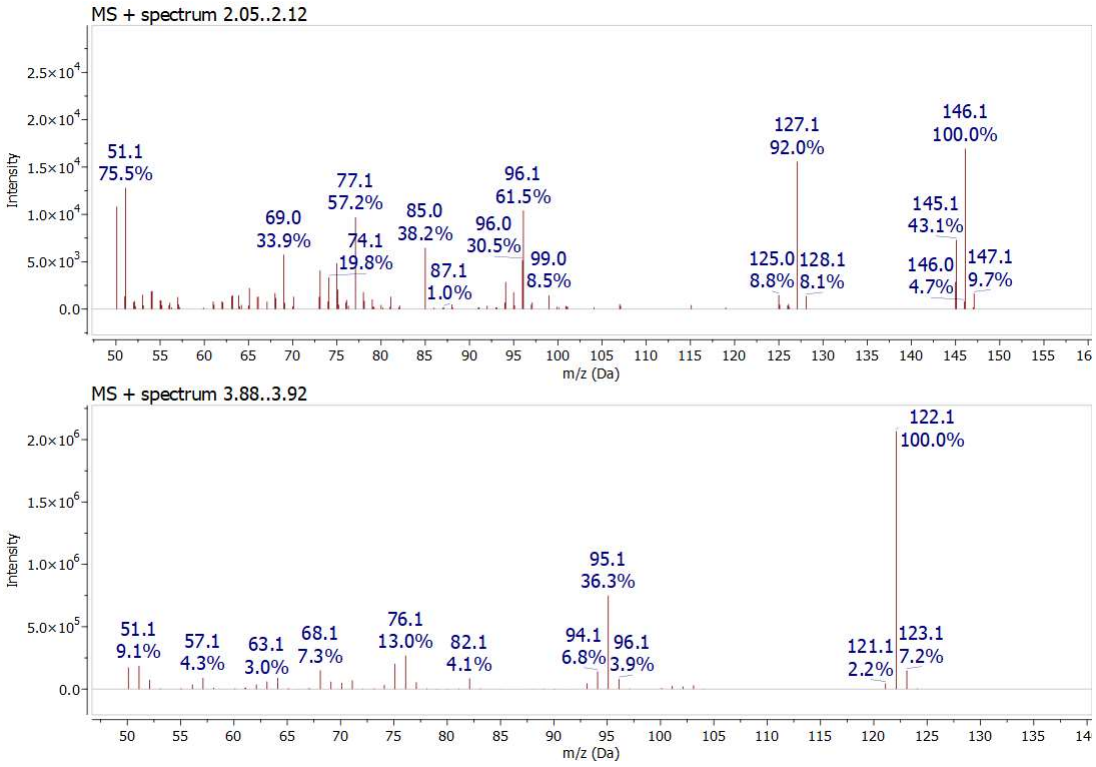


Figure S107. GC-MS spectra of a reaction mixture, prepared by method E (6 mmol scale, 2.0 M) using 6-fluoronicotinonitrile (**4d**) as substrate, showing trifluorotoluene (t_r = 2.05 – 2.12) and 6-fluoronicotinonitrile (t_r = 3.88 – 3.92).

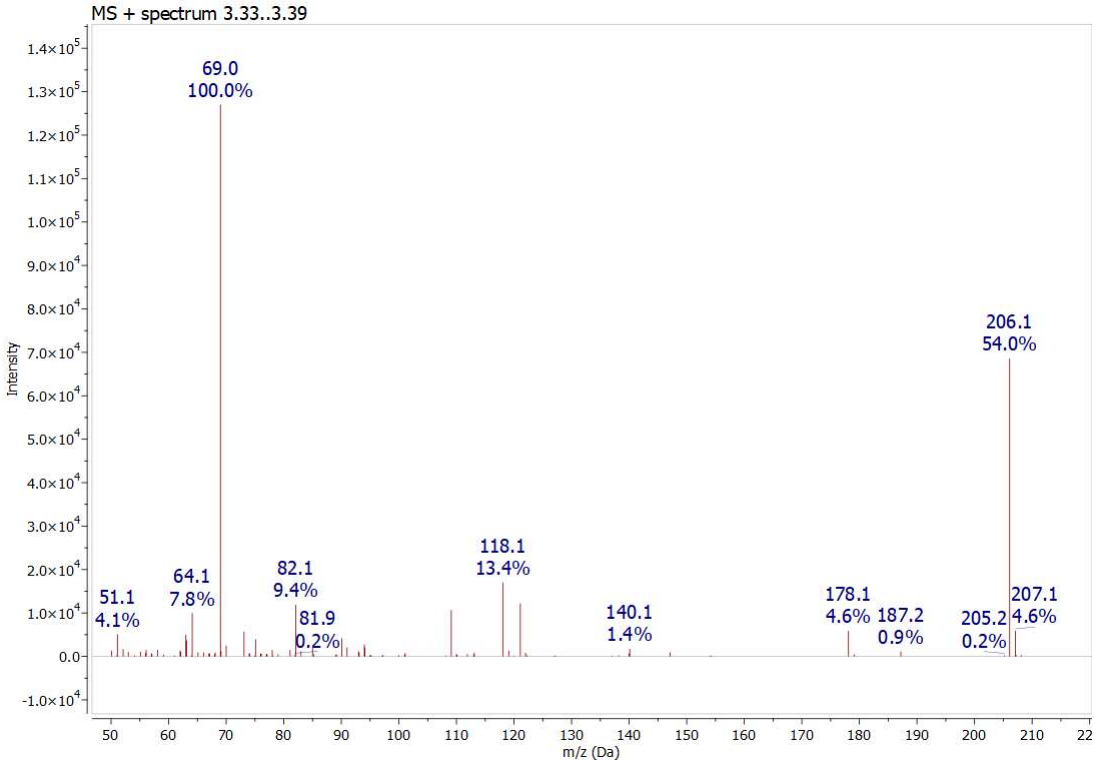


Figure S108. GC-MS spectrum of a reaction mixture, prepared by method E (6 mmol scale, 2.0 M) using 6-fluoronicotinonitrile (**4d**) as substrate, showing 6-fluoro-5-(trifluoromethoxy)nicotinonitrile (t_r = 3.33 – 3.39).

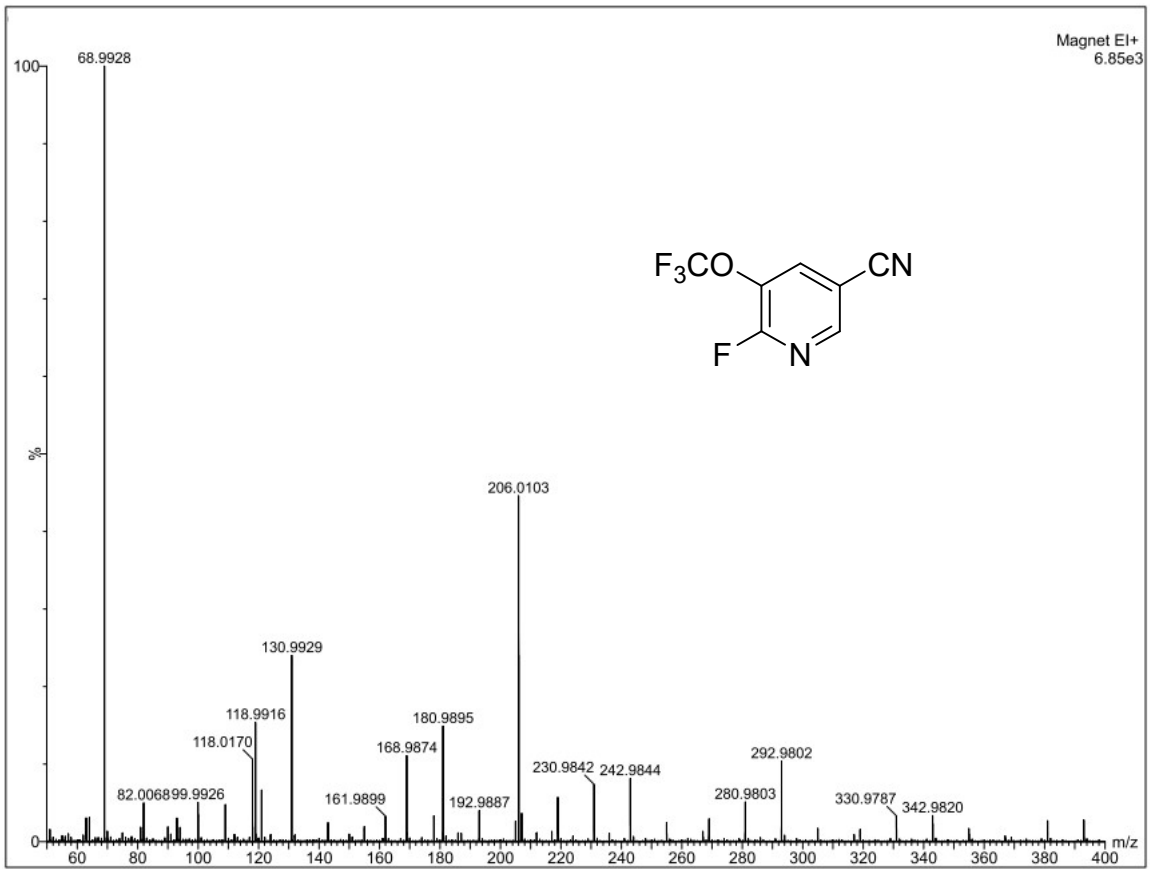


Figure S109. HRMS-EI spectrum of **5d**.

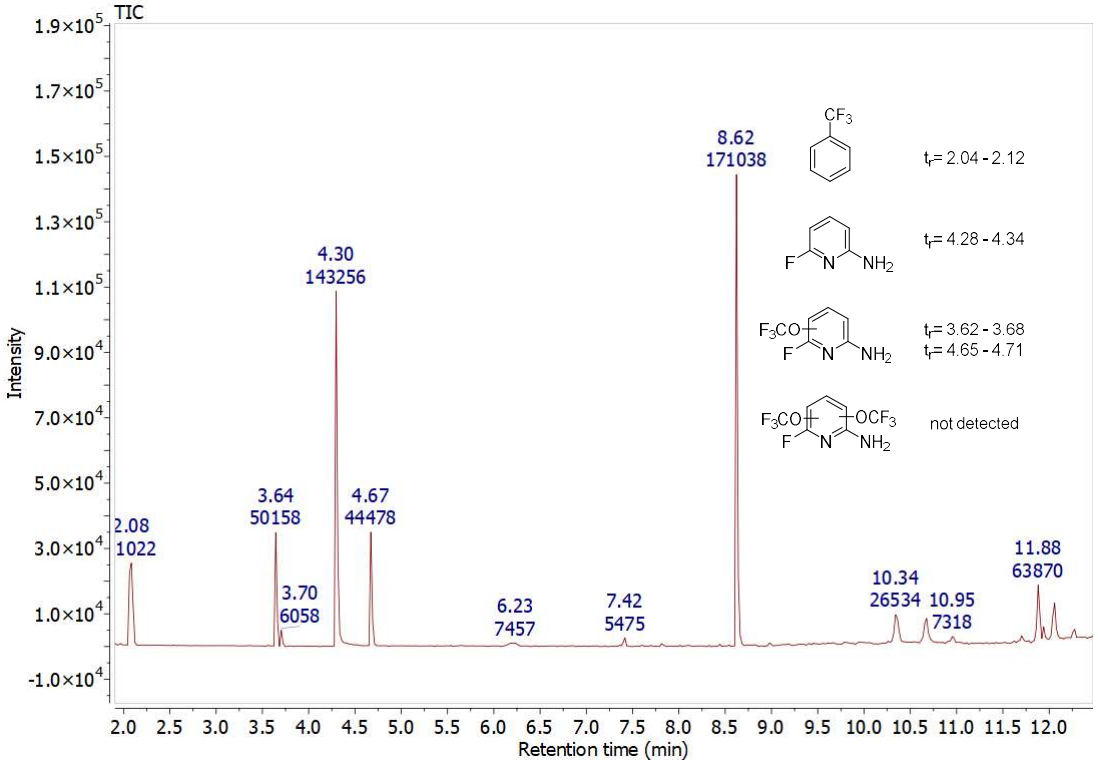


Figure S110. GC-MS spectrum of a reaction mixture prepared by method B (3 mmol scale, 0.2 M, 6 h reaction time) using 6-fluoropyridin-2-amine (**4e**) as substrate.

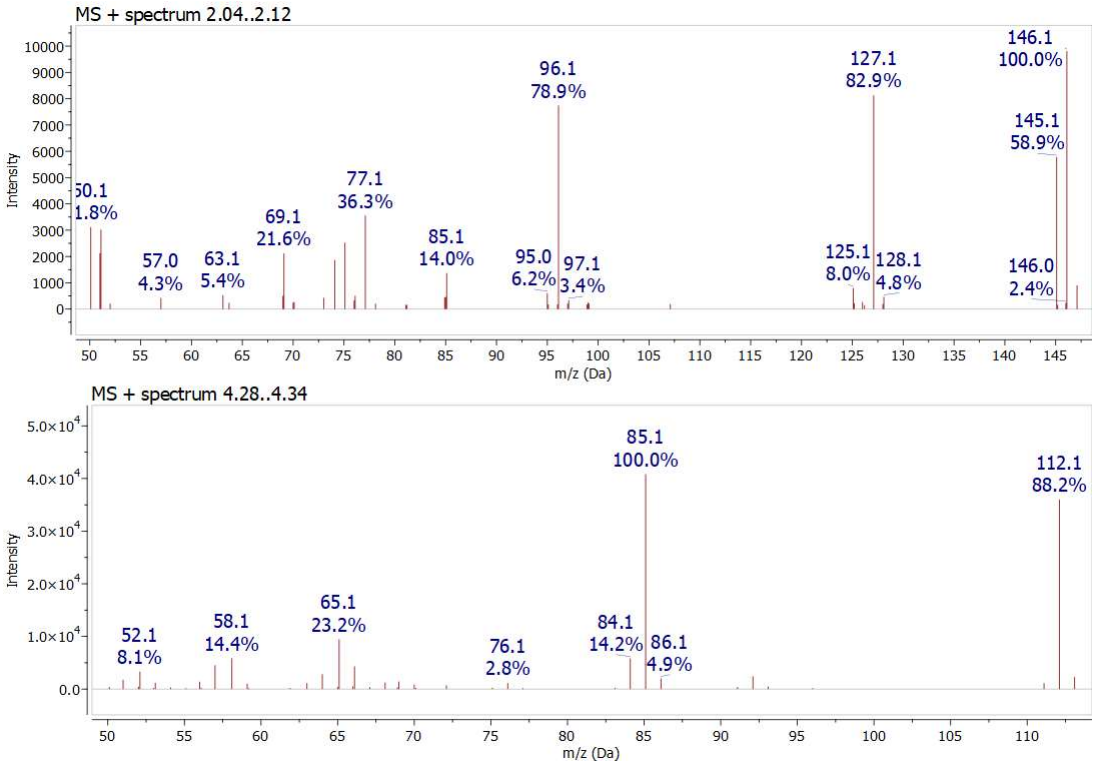


Figure S111. GC-MS spectra of a reaction mixture, prepared by method B (3 mmol scale, 0.2 M, 6 h reaction time) using 6-fluoropyridin-2-amine (**4e**) as substrate, showing trifluorotoluene (t_r = 2.04 – 2.12) and 6-fluoropyridin-2-amine (t_r = 4.28 – 4.34).

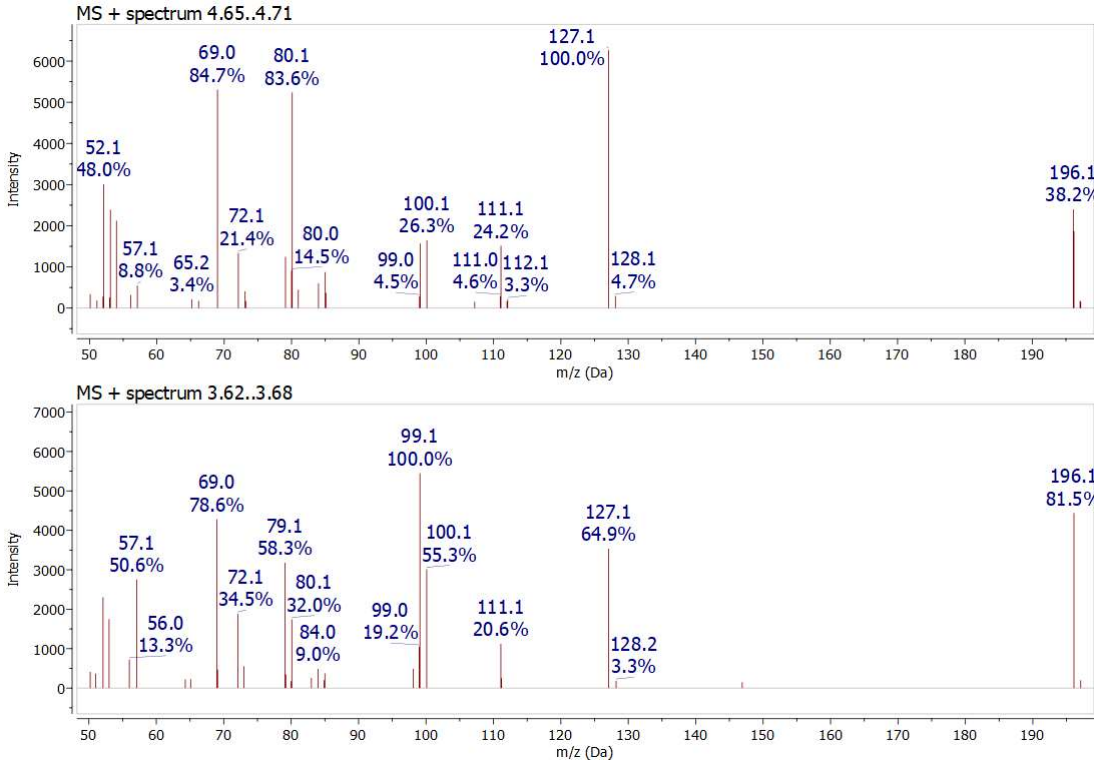


Figure S112. GC-MS spectra of a reaction mixture, prepared by method B (3 mmol scale, 0.2 M) using 6-fluoropyridin-2-amine (**4e**) as substrate, showing two distinct 6-fluoro(trifluoromethoxy)pyridin-2-amines (t_r = 3.62 – 3.68, 4.65 – 4.71).

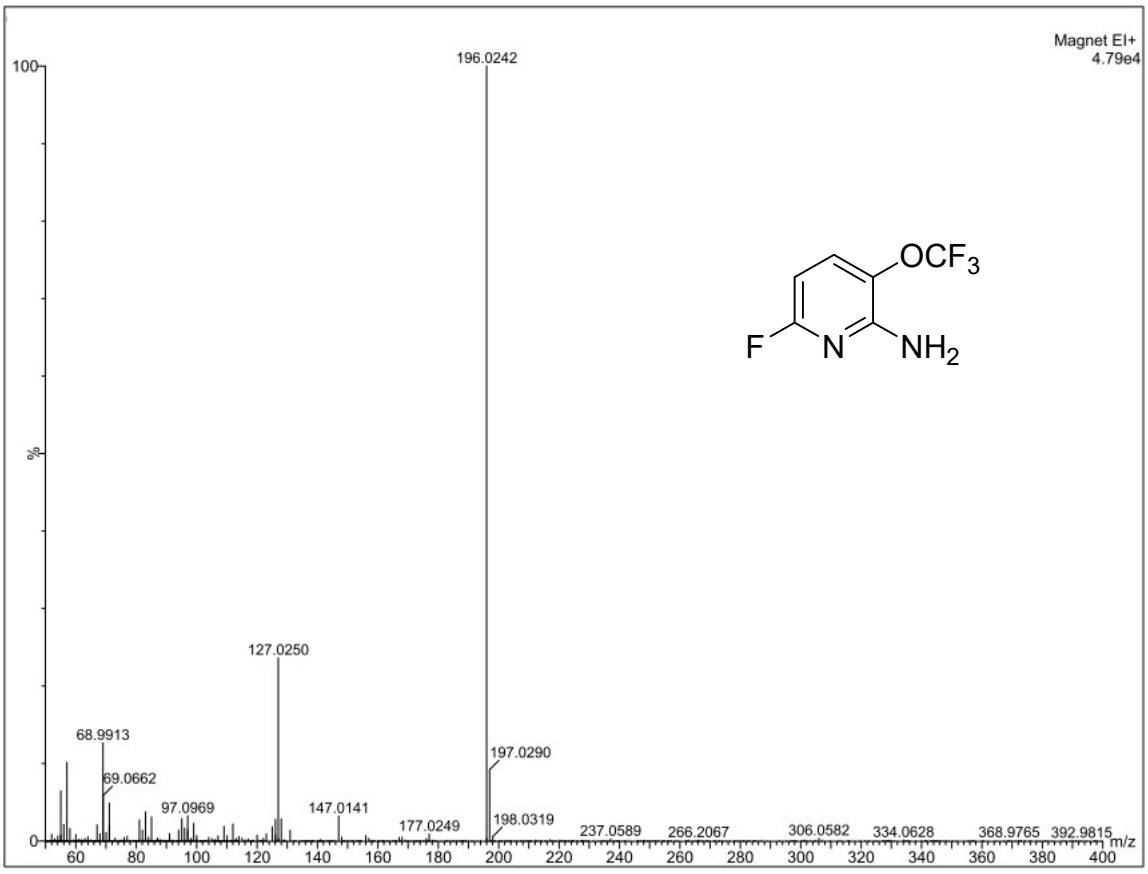


Figure S113. HRMS-EI spectrum of **5ea**.

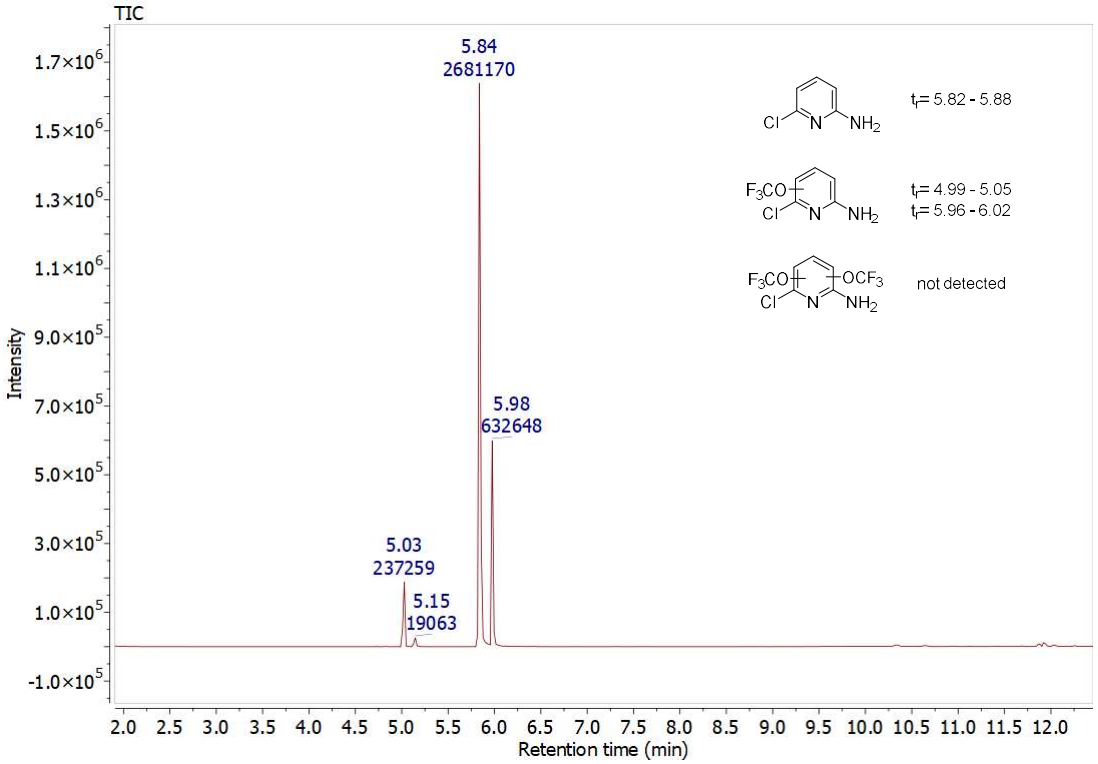


Figure S114. GC-MS spectrum of a reaction mixture prepared by method B (3 mmol scale, 0.2 M, 6 h reaction time) using 6-chloropyridin-2-amine (**4f**) as substrate.

Figure S115. GC-MS spectra of a reaction mixture, prepared by method B (3 mmol scale, 0.2 M) using 6-chloropyridin-2-amine (**4f**) as substrate, showing 6-chloropyridin-2-amine (t_r = 2.04 – 2.12) and two distinct 6-Chloro(trifluoromethoxy)pyridin-2-amines (t_r = 4.99 – 5.05. 5.96 – 6.02).

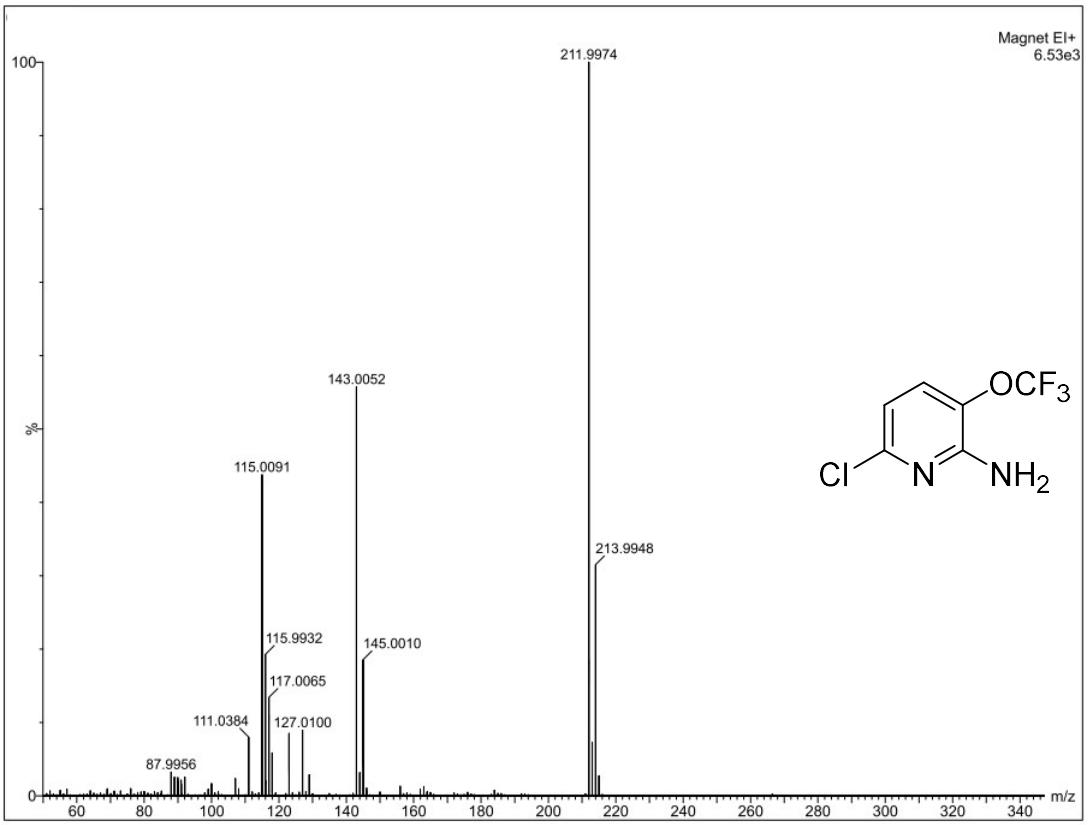


Figure S116. HRMS-EI spectrum of **5fa**.

8 DSC Data and Spectra

Table S12. Data of conducted DSC measurements with benzonitrile and substrates **4a-f**. In case of repeated measurements with different samples from the same substance (Entries 2-3, 4-5, 9-10), b.p. deviations of 0.4 °C, 0.6 °C, and 0.1 °C were observed.

entry	compound	sample mass [mg]	m.p. [°C]	m.p. lit [°C]	b.p. [°C]	b.p. lit [°C]
1	Benzonitrile	2.06	-	-	190.8	190 [22]
2	**4a**	2.24	25.7	27.0 – 27.5 [23]	232.7	222 – 227 [23]
3	**4a**	2.04	-	27.0 – 27.5 [23]	233.1	222 – 227 [23]
4	**4b**	2.17	49.8	50 – 51 [24]	206.6	205 – 208 [24]
5	**4b**	2.19	-	50 – 51 [24]	207.2	205 – 208 [24]
6	**4c**	2.38	77.9	77 – 81 [25]	196.2	196 [25]
7	**4d**	2.17	52.6	51 – 52 [26]	208.3	-
8	**4e**	2.26	58.4	58 – 62 [27]	220.3	-
9	**4f**	2.30	70.6	72 – 73.5 [28]	260.3	-
10	**4f**	2.17	70.7	72 – 73.5 [28]	260.4	-

[22] H. Eshghi, Z. Gordi, *Phosphorus, Sulfur and Silicon* **2005**, *180*, 619-623

[23] I.M. Robinson, G.J. Janz (Canadian Industries Ltd.), US2494204A, **1945**

[24] P.C. Teague, W.A. Short, *Org. Synth.* **1953**, *33*, 52

[25] 4-Cyanopyridine, MSDS ALFAAA10286, Kandel, Germany, February 04, 2021

[26] 5-Cyano-2-fluoropyridine, MSDS ALFAAH64278, Kandel, Germany, March 10, 2021

[27] 2-Amino-6-fluoropyridine, MSDS ALFAAH30629, Kandel, Germany, February 26, 2021

[28] 2-Amino-6-chloropyridine, MSDS ALFAAL19836, Kandel, Germany, January 05, 2021

Table S13. Data of conducted DSC measurements with products **5aa-fb**.

entry	**compound**	**sample mass [mg]**	**m.p. [°C]**	**b.p. [°C]**
1	**5aa**	2.11	-	222.6
2	**5ab**	2.12	-	210.9
3	**5ac**	2.25	40.5	223.7
4	**5bb**	2.18	-	187.1
5	**5bc**	2.07	50.0	203.2
6	**5ca**	1.70	-	187.9
7	**5cb**	2.31	-	184.1
8	**5d**	2.24	32.0	190.5
9	**5ea**	2.16	52.4	182.0
10	**5eb**	2.07	74.5	215.0
11	**5fa**	2.25	67.8	214.6
12	**5fb**	2.05	92.0	245.8

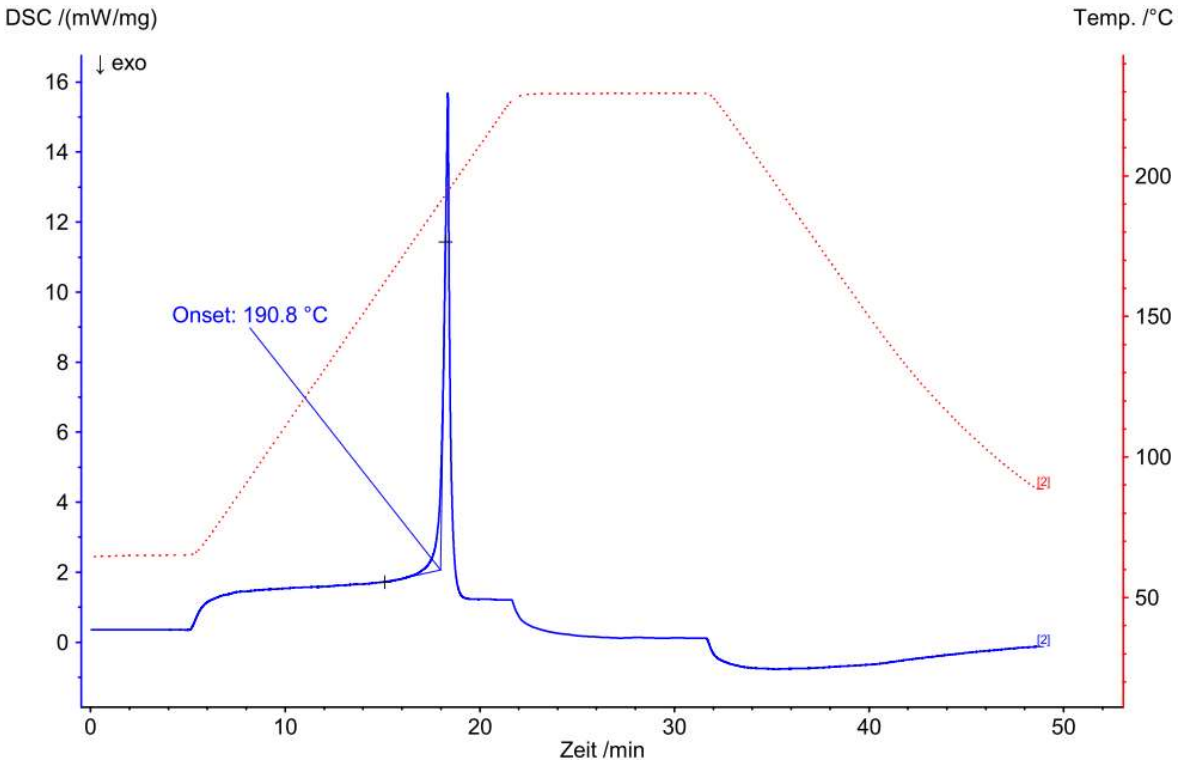


Figure S117. DSC Spectrum of benzonitrile.

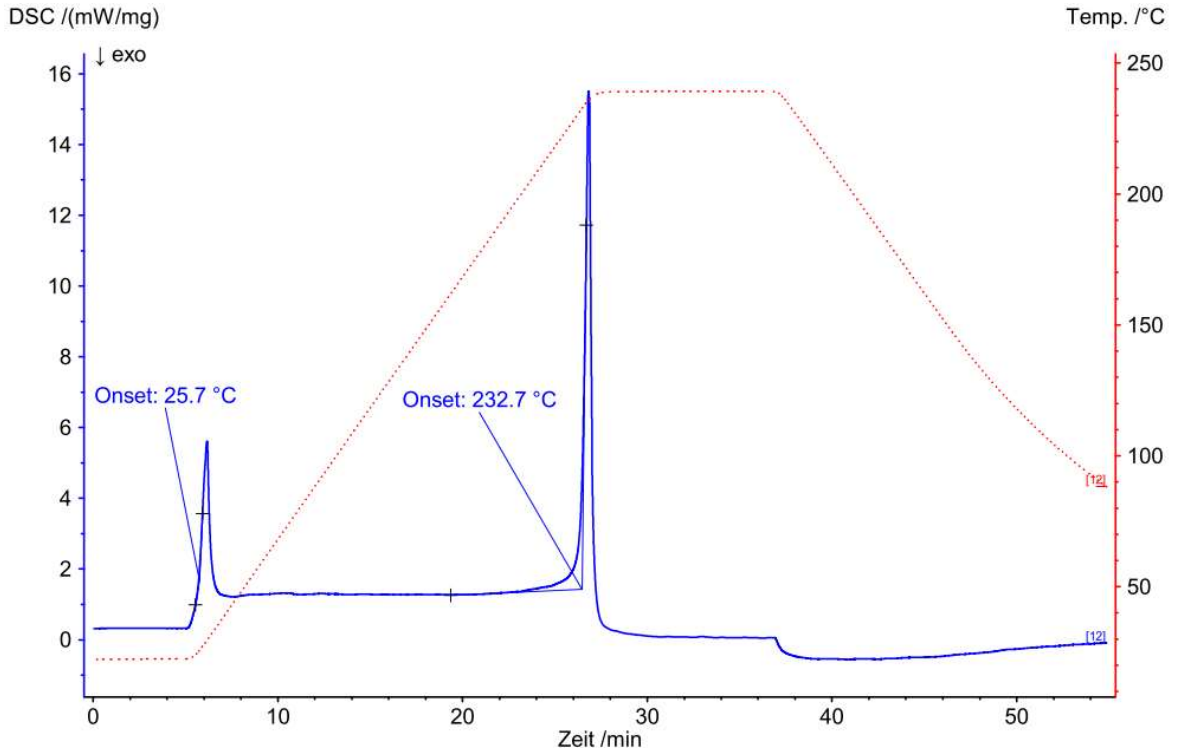


Figure S118. DSC Spectrum of **4a**.

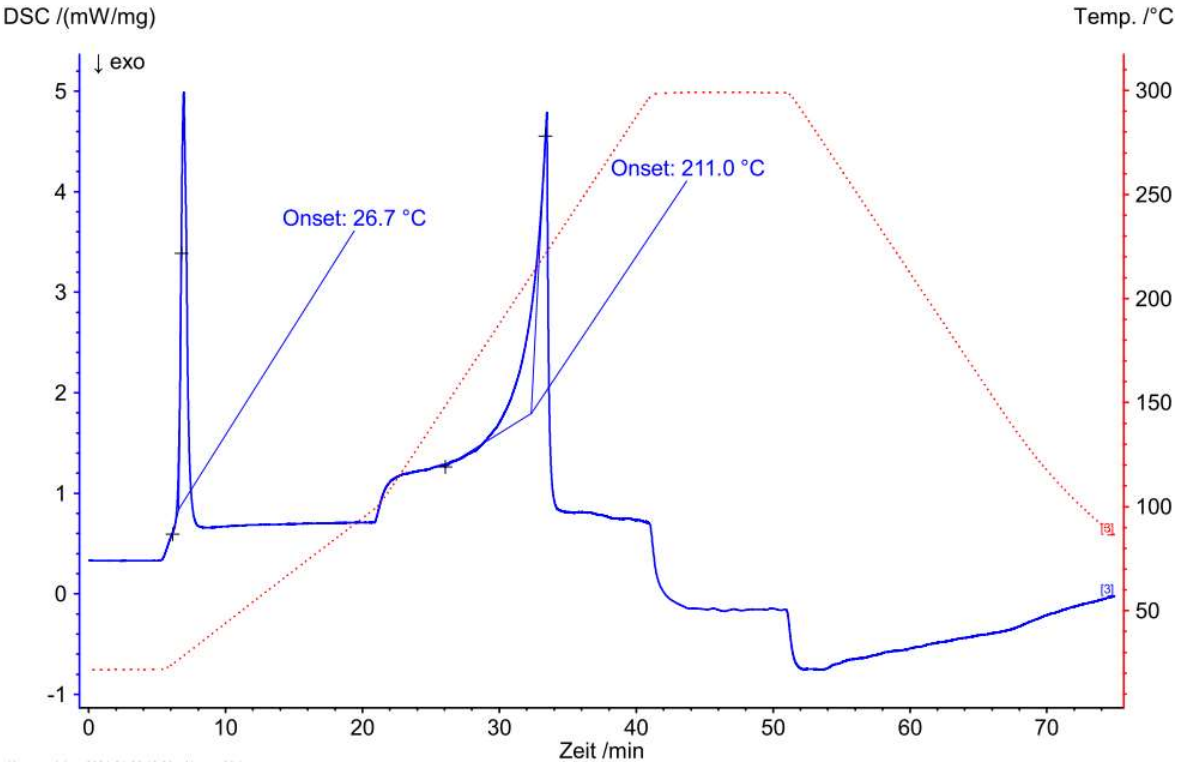


Figure S119. DSC Spectrum of **4a** using an insufficiently sealed pan.

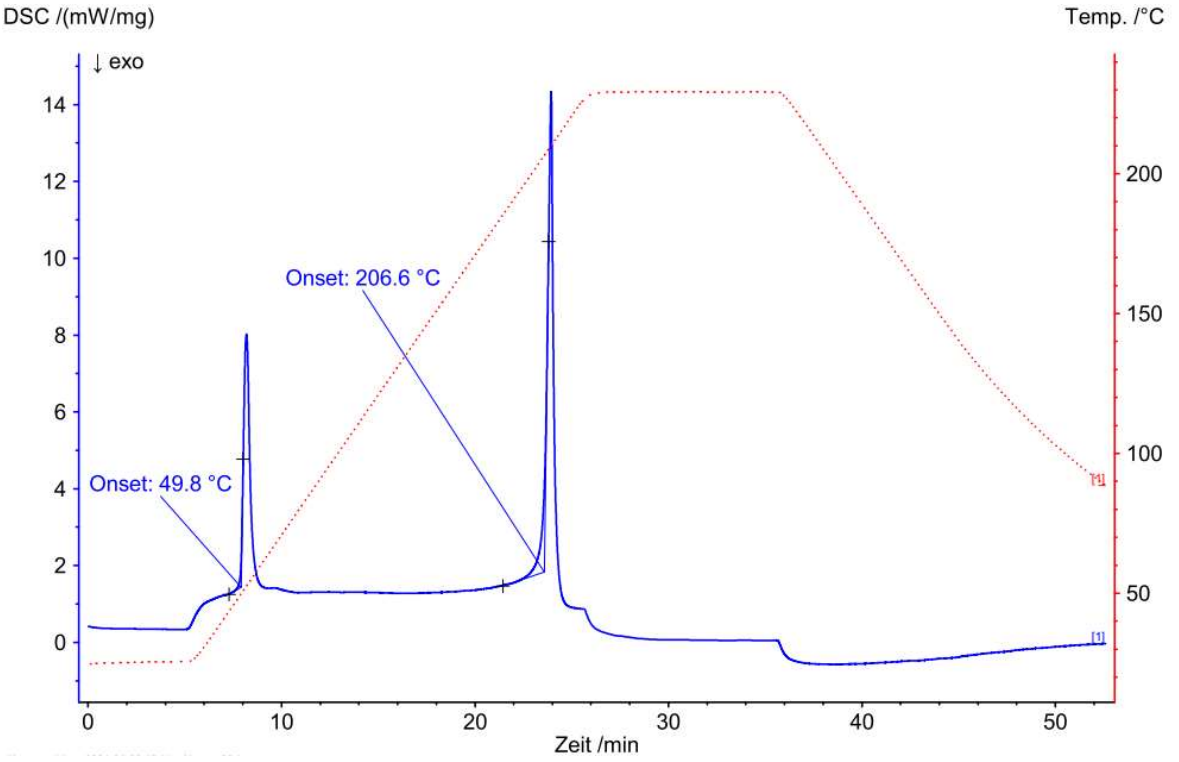


Figure S120. DSC Spectrum of **4b**.

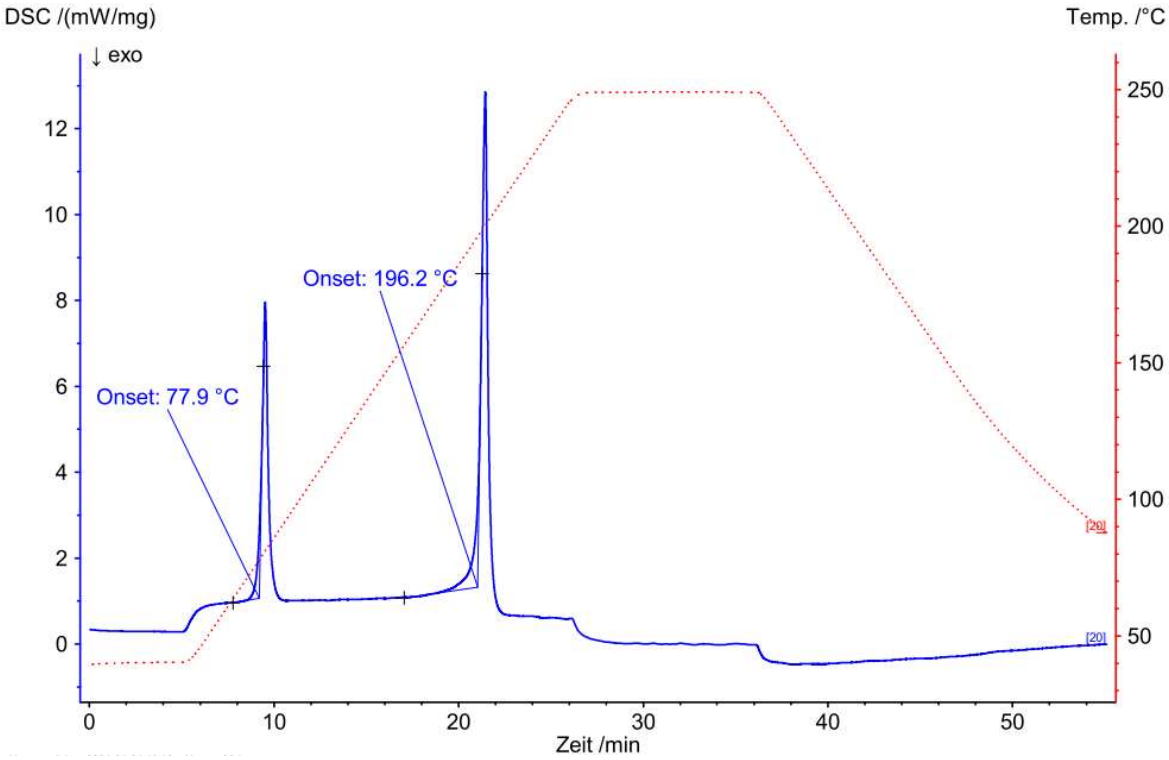


Figure S121. DSC Spectrum of **4c**.

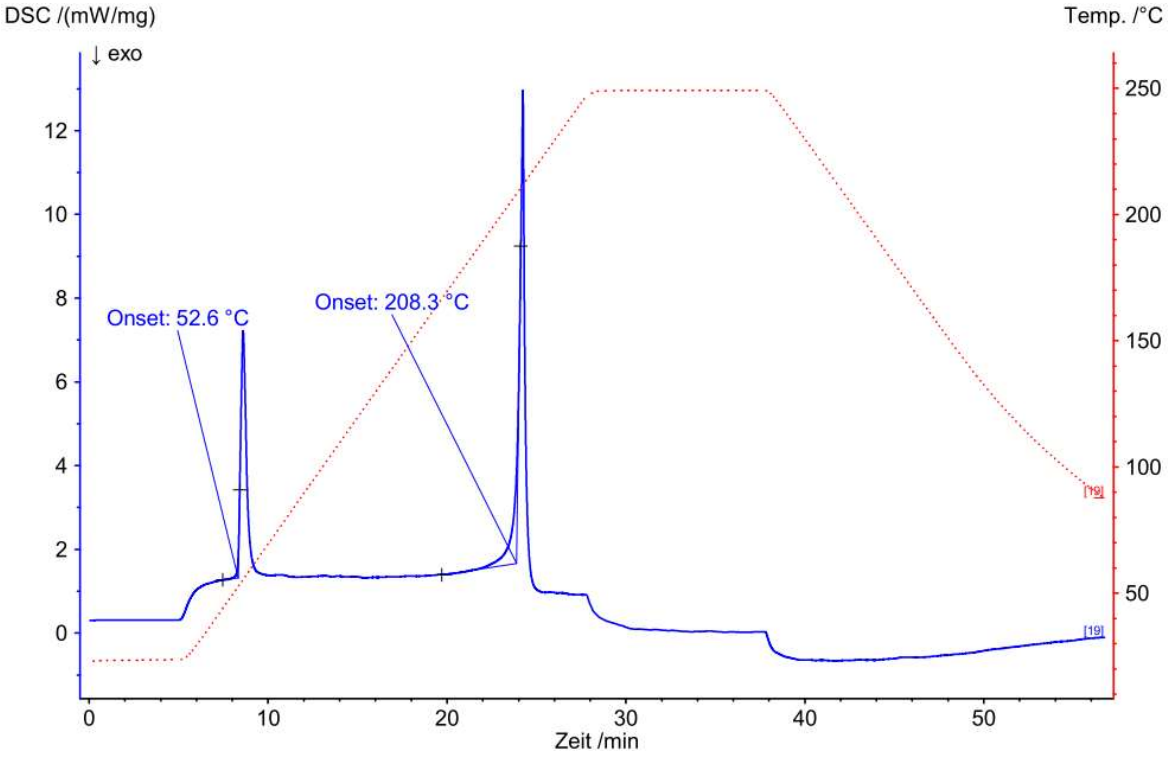


Figure S122. DSC Spectrum of **4d**.

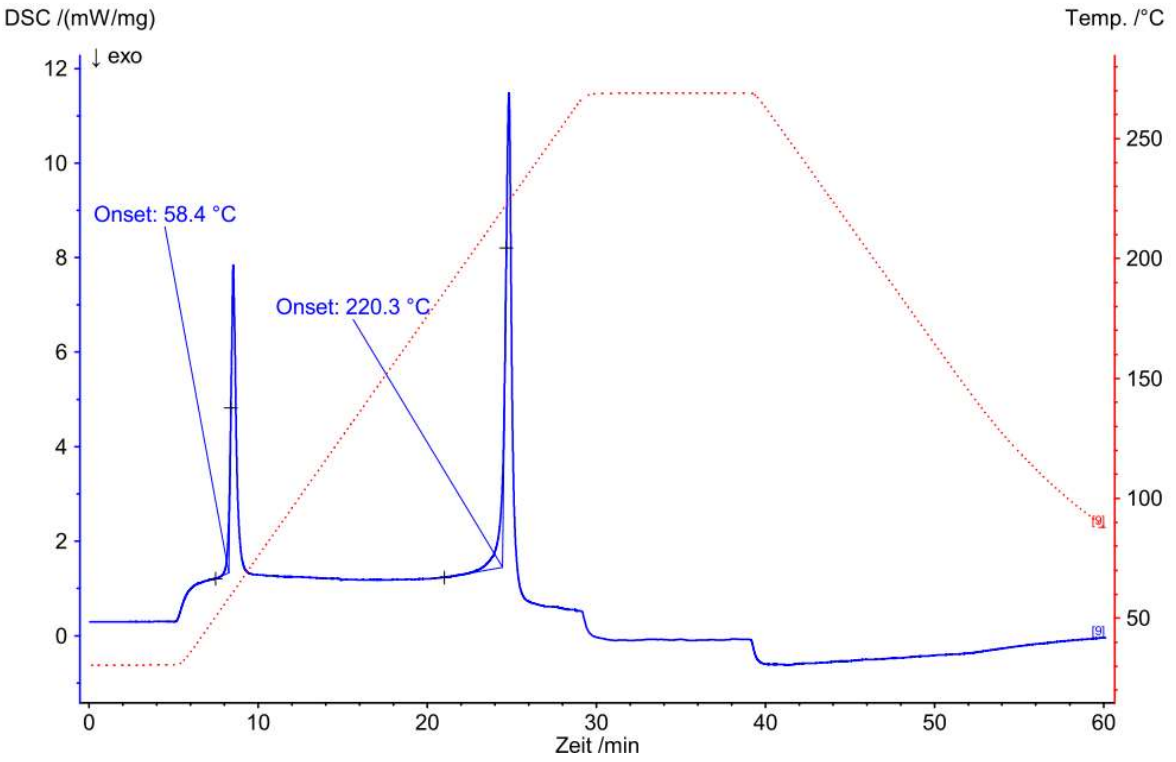


Figure S123. DSC Spectrum of **4e**.

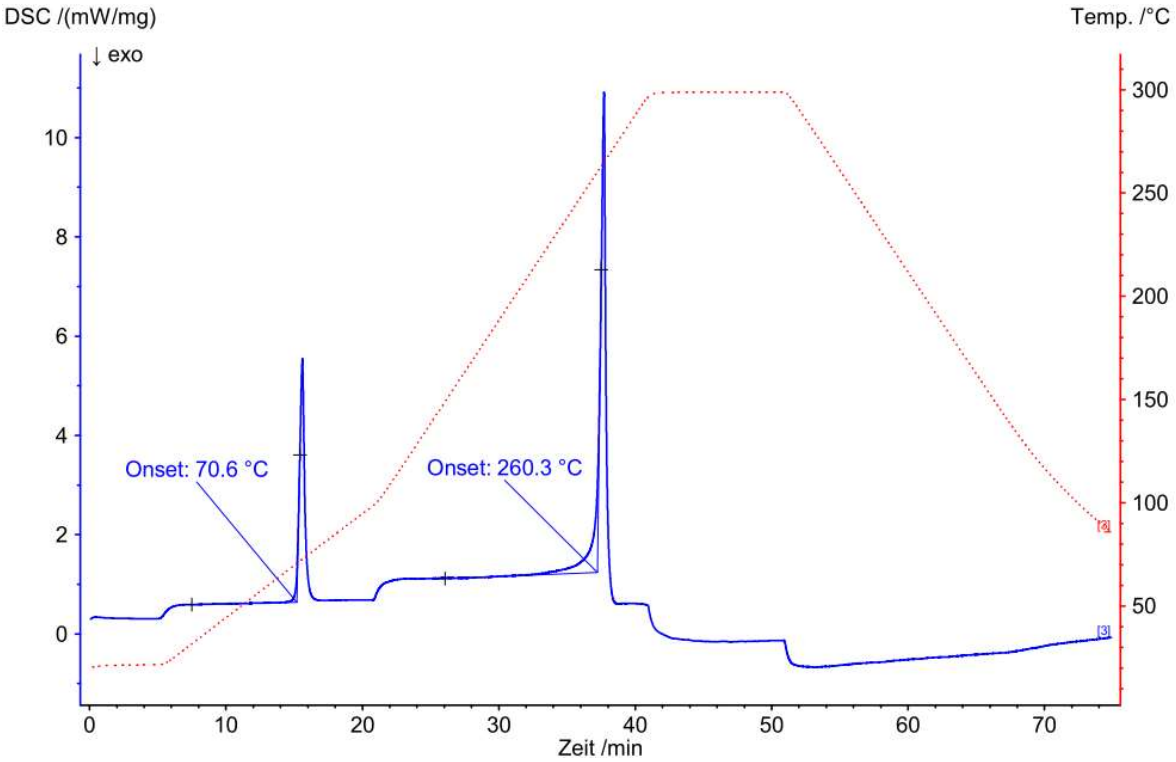


Figure S124. DSC Spectrum of **4f.**

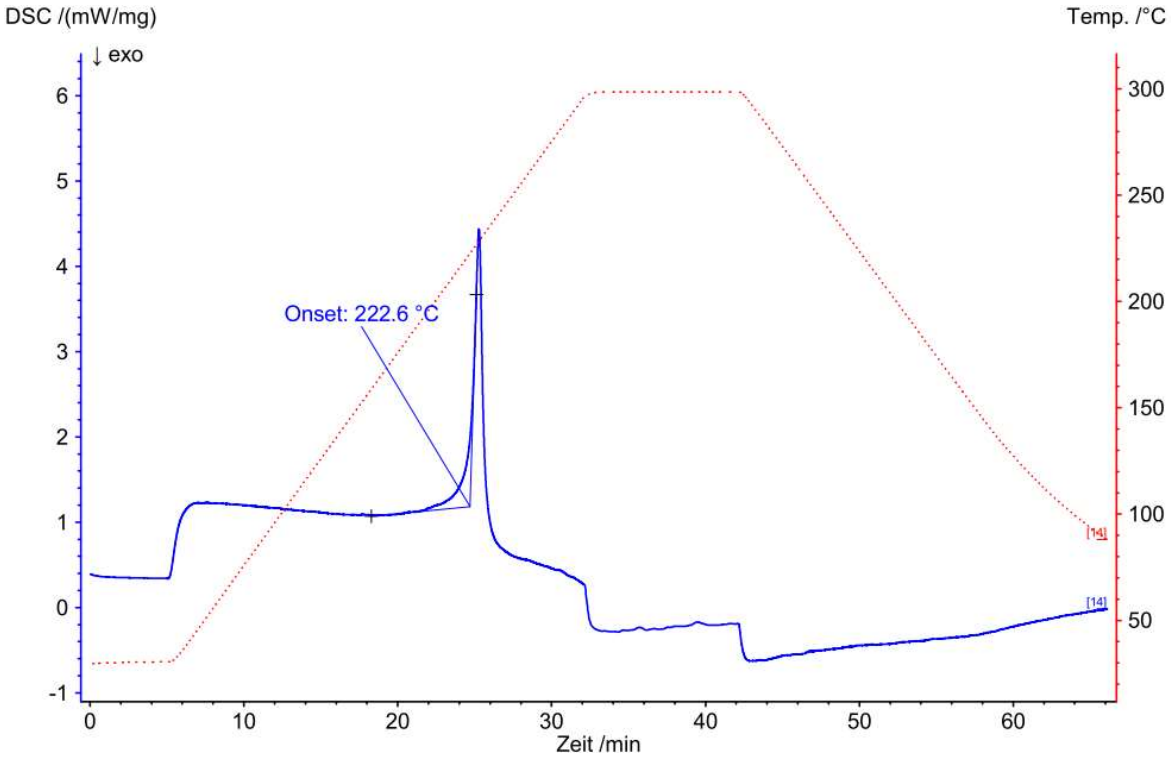


Figure S125. DSC Spectrum of **5aa**.

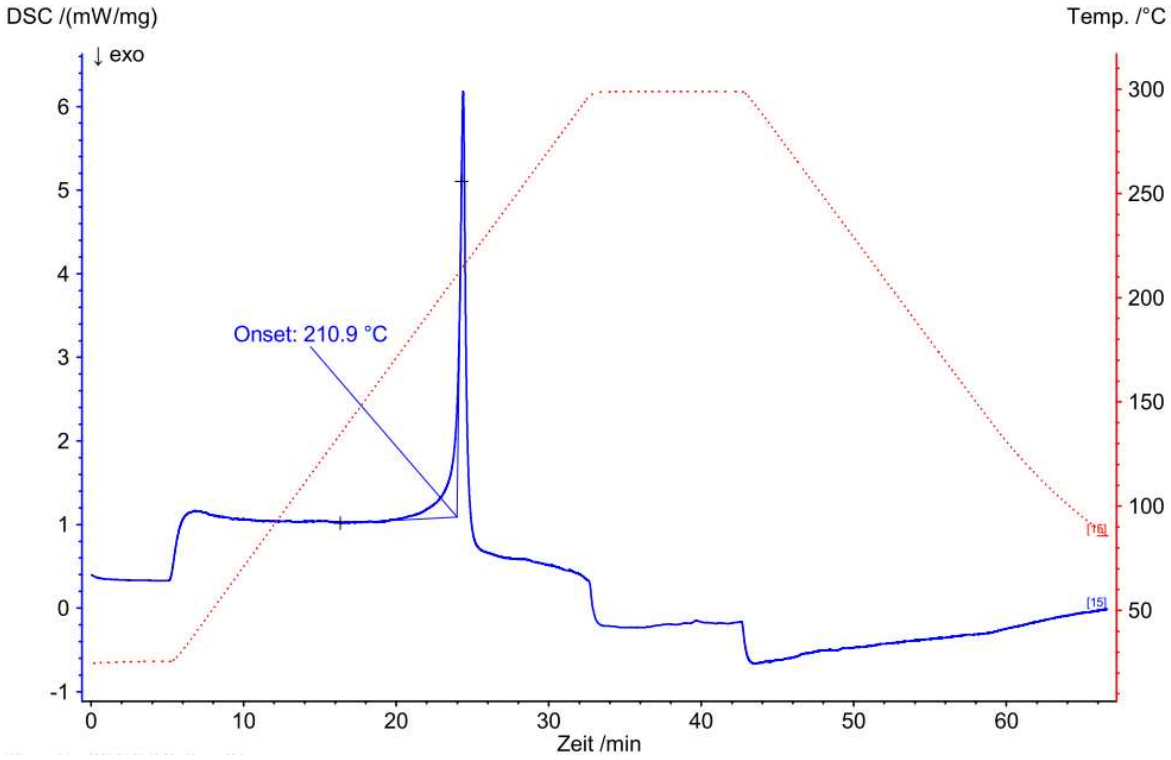


Figure S126. DSC Spectrum of **5ab**.

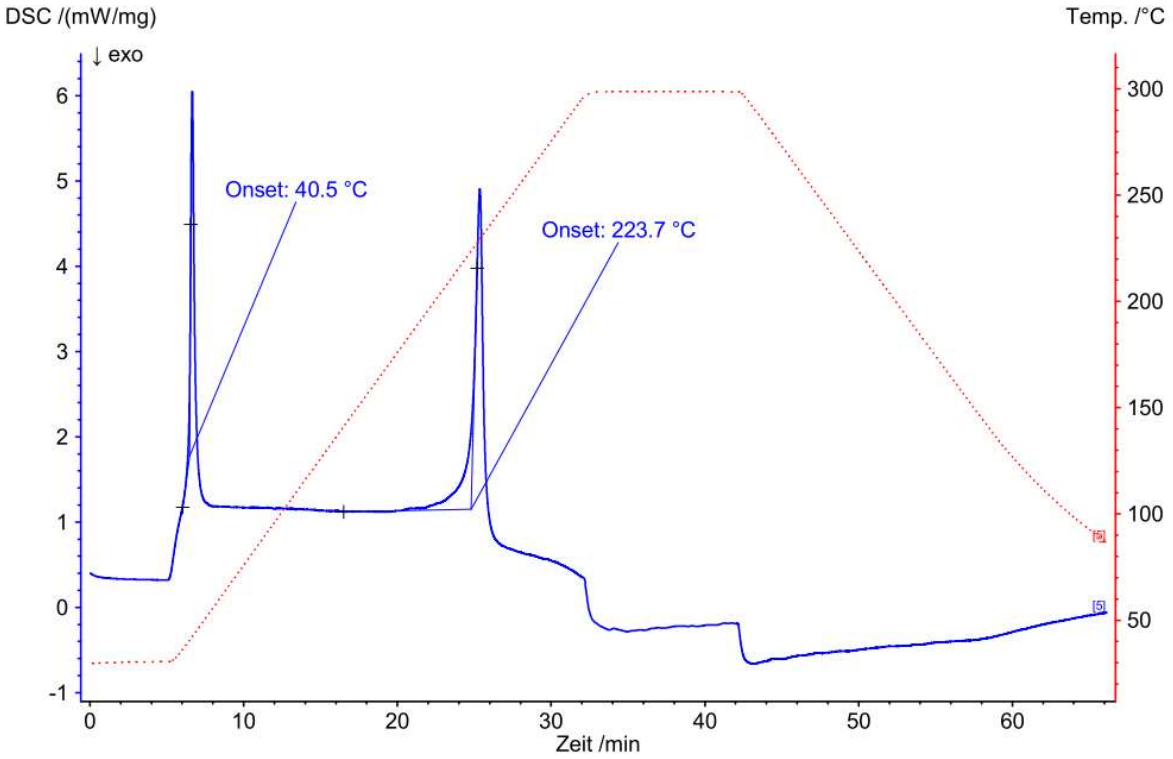


Figure S127. DSC Spectrum of **5ac**.

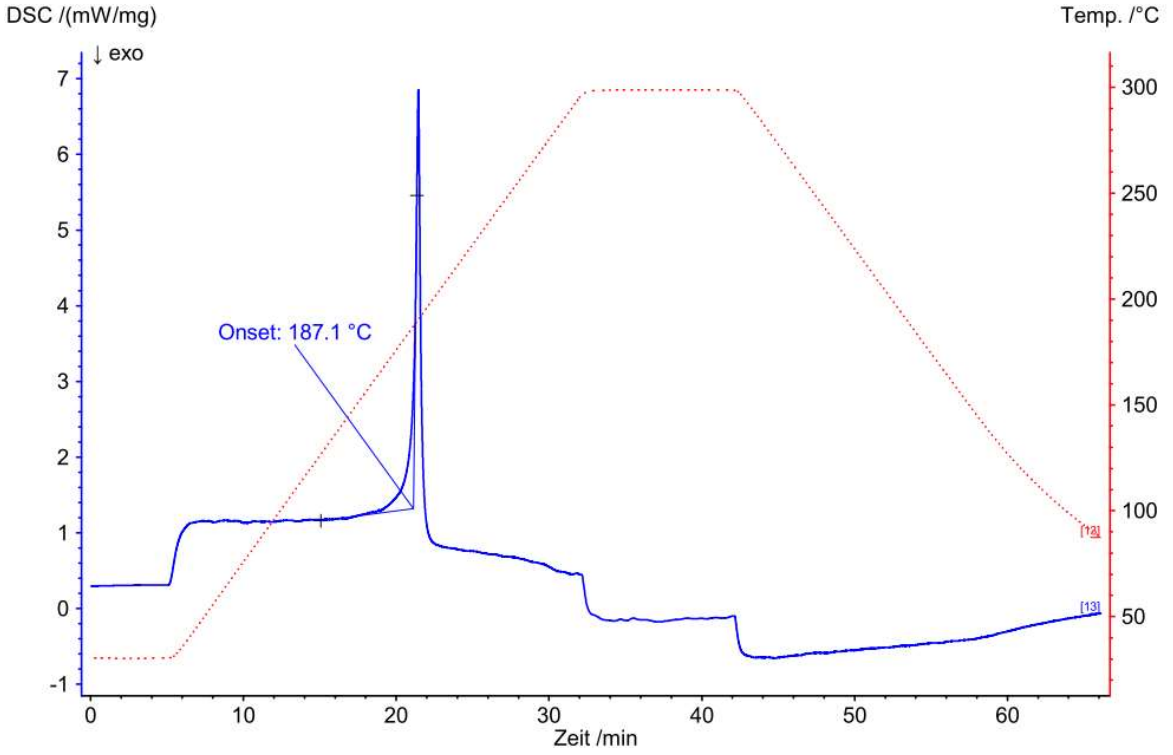


Figure S128. DSC Spectrum of **5bb**.

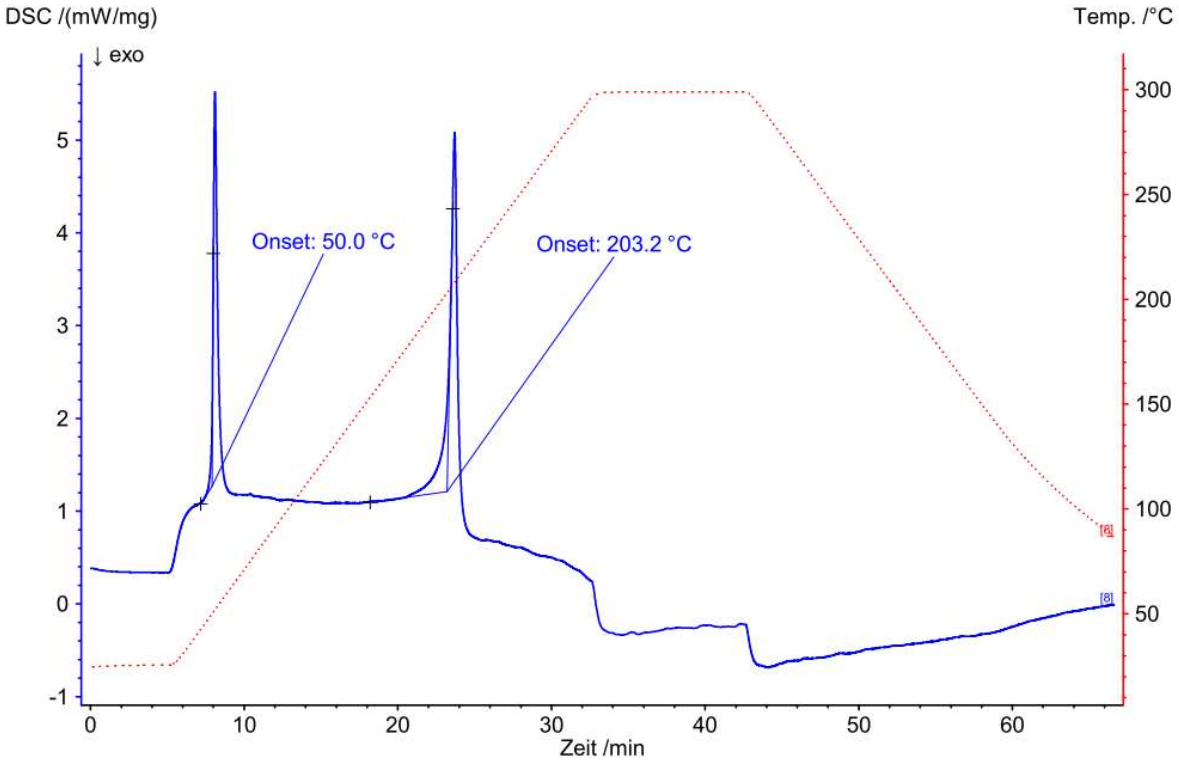


Figure S129. DSC Spectrum of **5bc**.

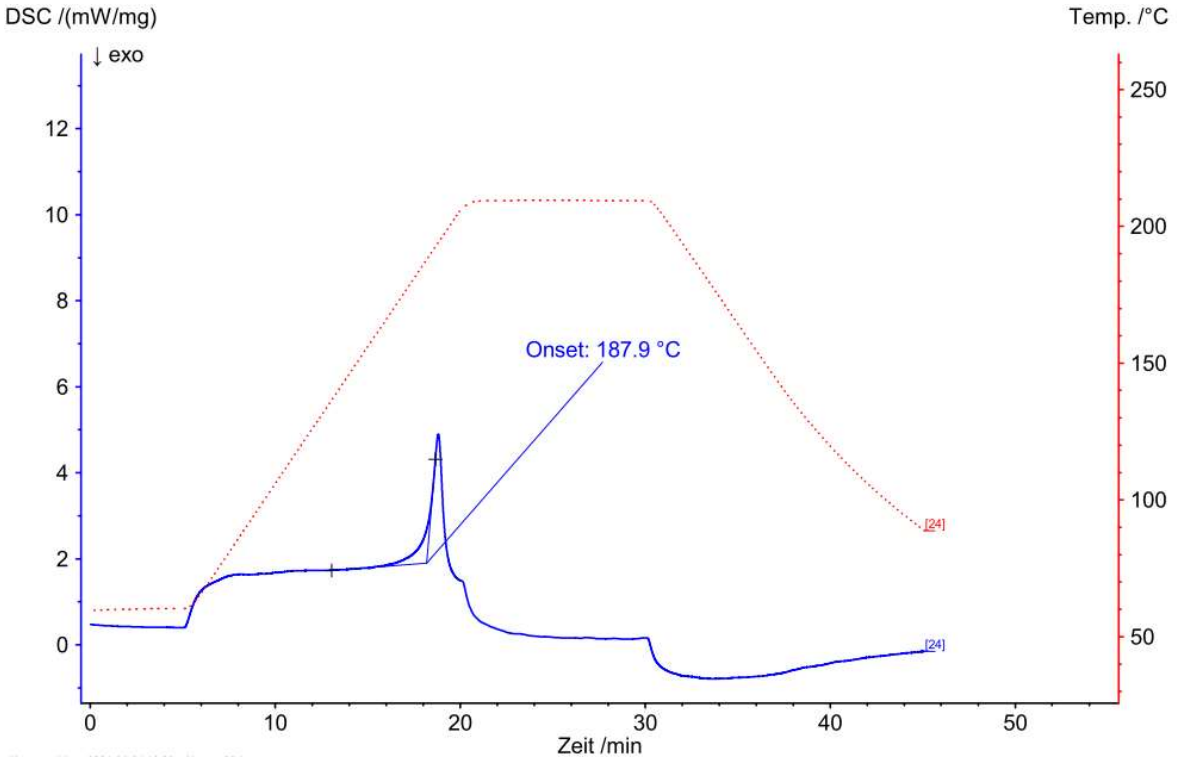


Figure S130. DSC Spectrum of **5ca**.

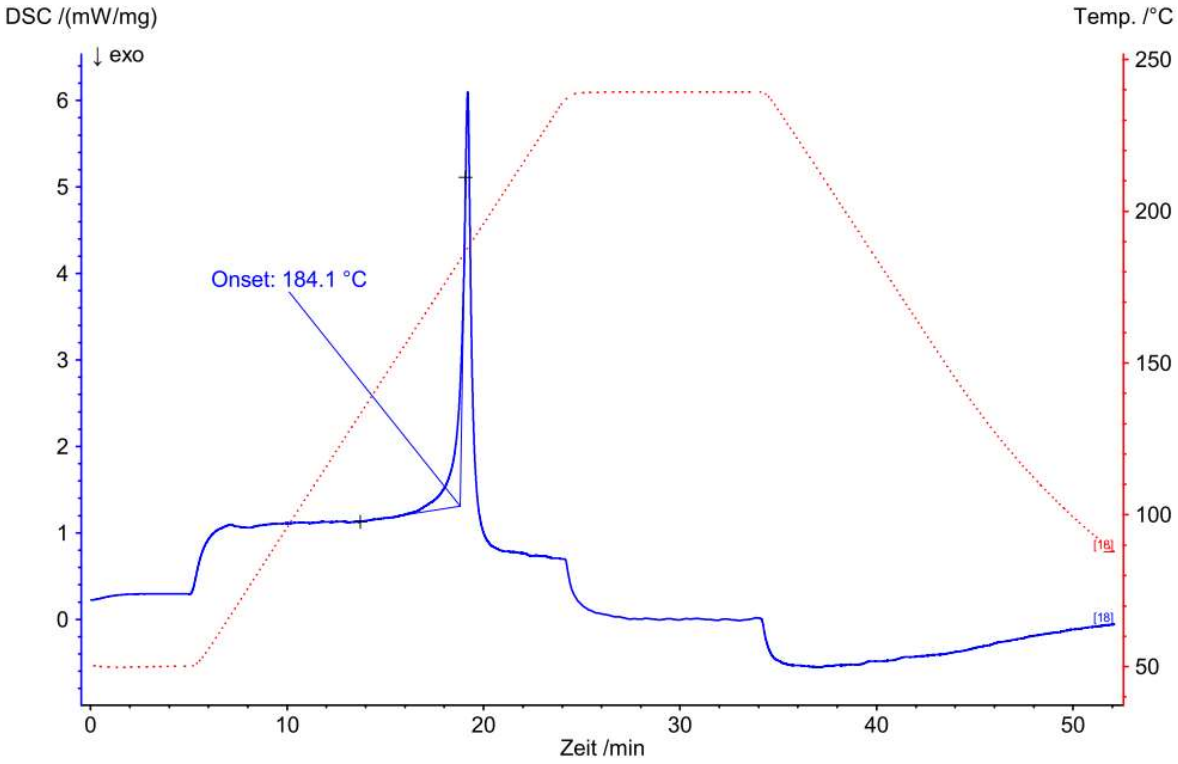


Figure S131. DSC Spectrum of **5cb**.

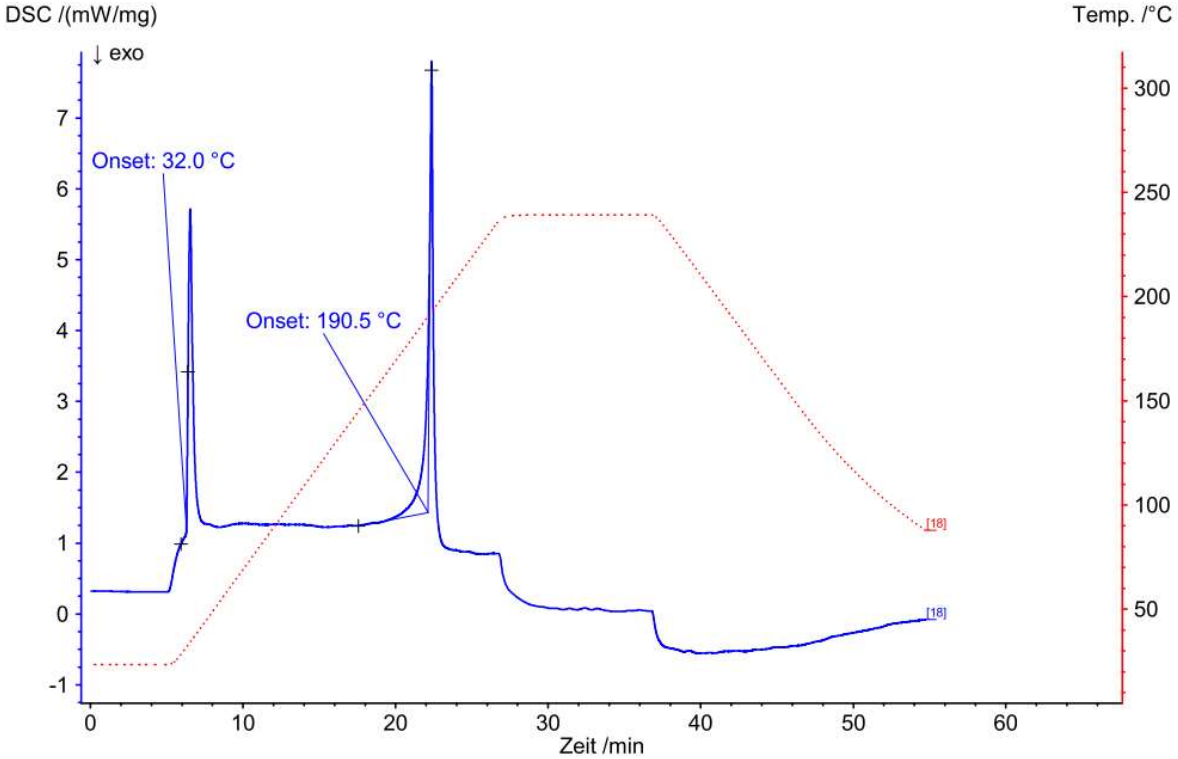


Figure S132. DSC Spectrum of **5d**.

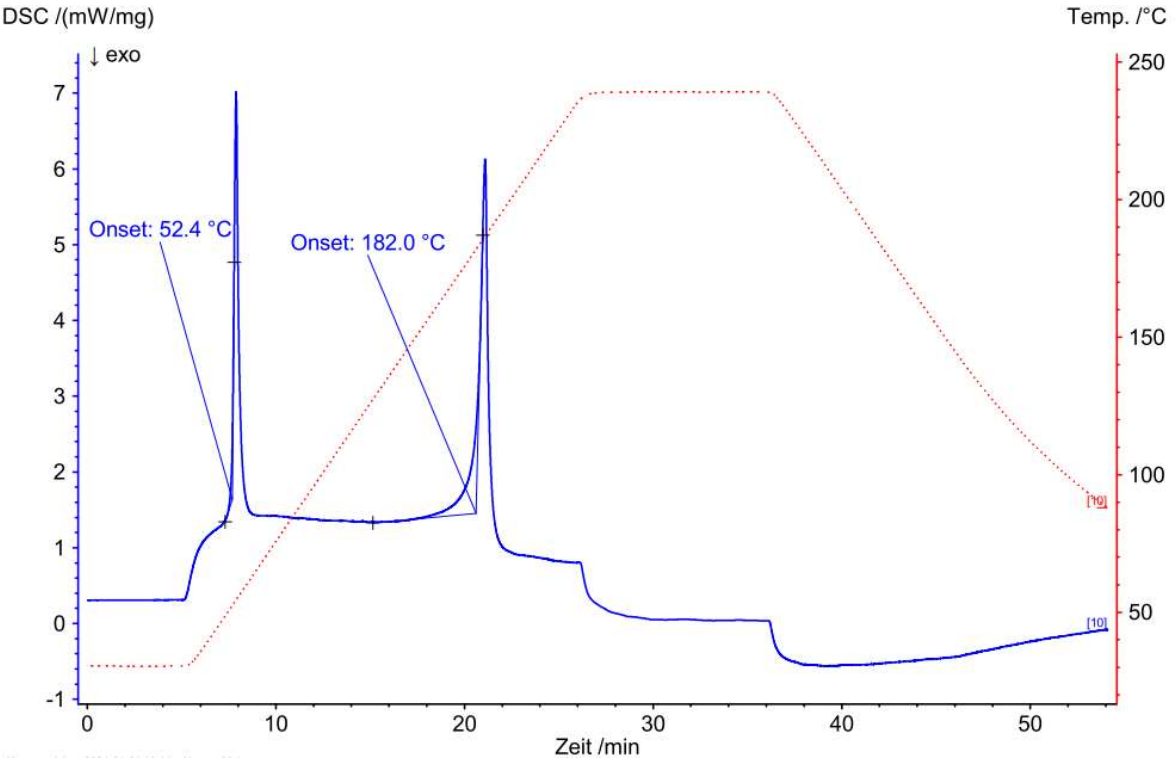


Figure S133. DSC Spectrum of **5ea**.

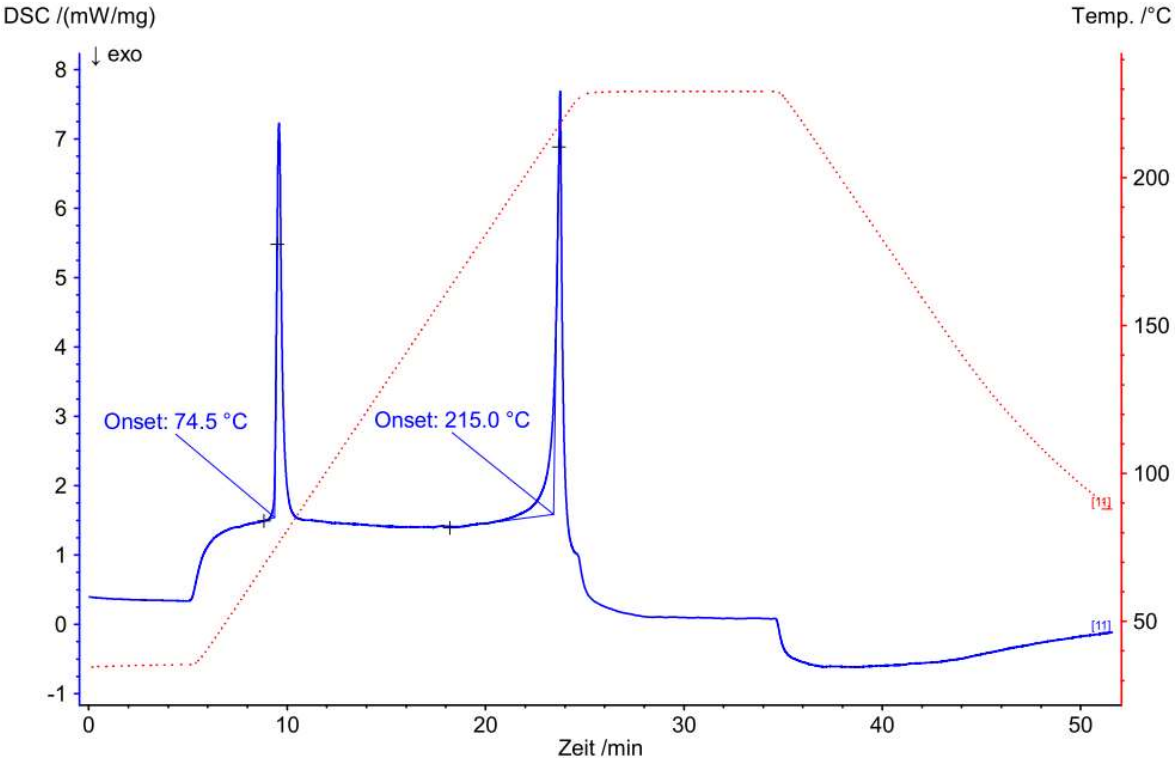


Figure S134. DSC Spectrum of **5eb**.

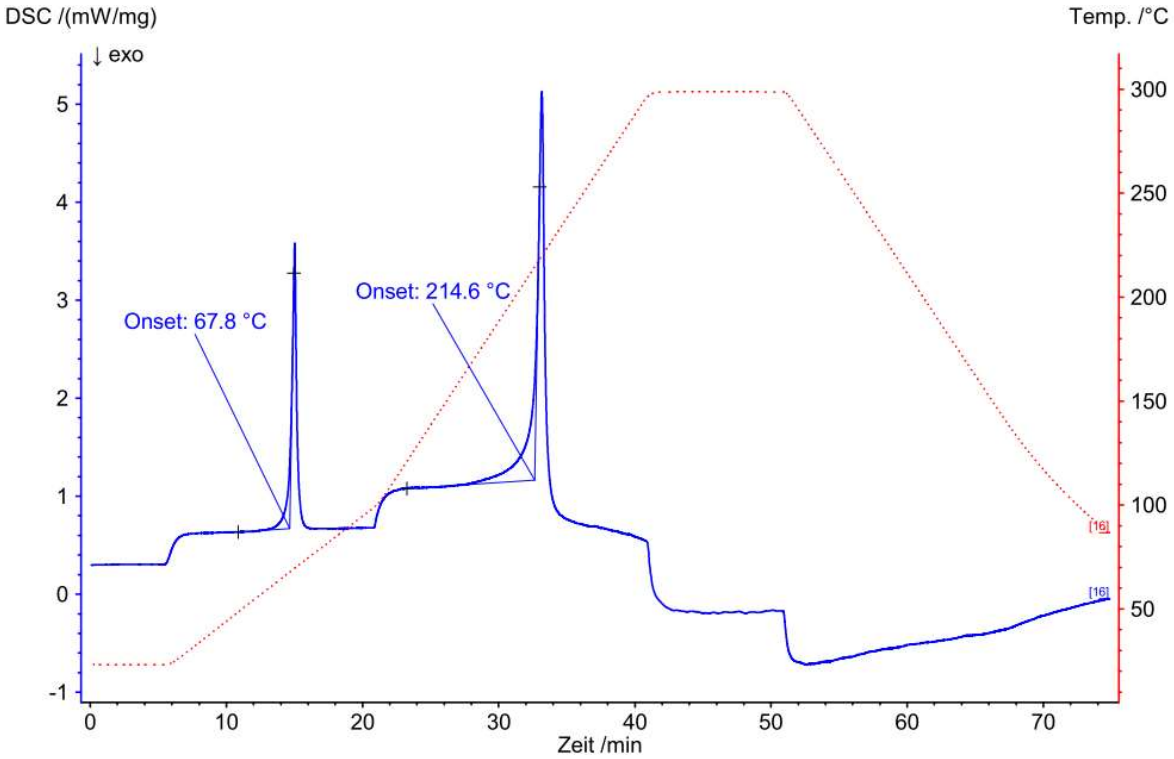


Figure S135. DSC Spectrum of **5fa**.

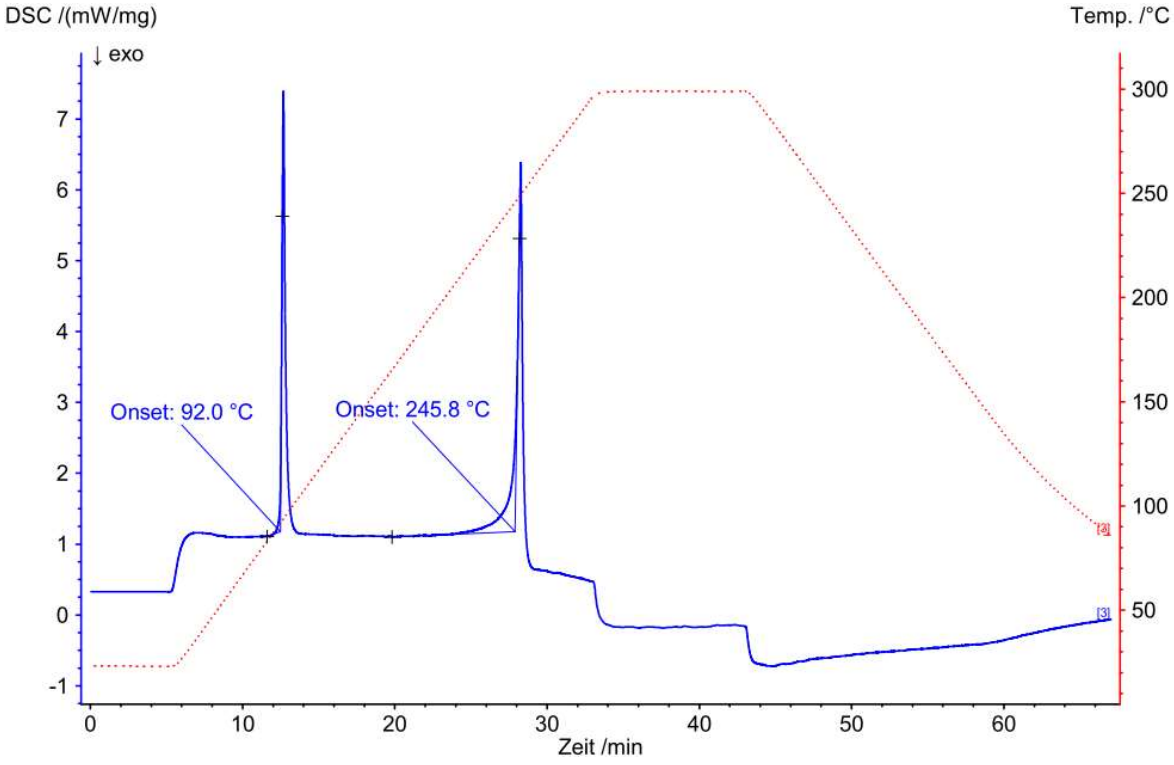


Figure S136. DSC Spectrum of **5fb**.

9 Commercial supplier data for selected Pyridines and TEMPO

Table S14. Collection of results from a Scifinder search. In each case, the largest quantity for the lowest available price was chosen. The search result was furthermore verified on the vendor's webpage.

Entry	Pyridine	Date of Search	Supplier	Largest Quantity [g]	Lowest Price [US$]	[US$/g]
1	2-Aminopyridine	11.04.2021 17:00	3B Scientific (Wuhan)	50.000	1.700	0.034
2	2-Cyanopyridine	11.04.2021 17:10	Aaron Chemicals	1.000	45	0.045
3	6-chloropyridin-3-ol	11.04.2021 17:30	AOBChem	1.000	1129	1.13
4	5-(Trifluoromethoxy)-2-pyridinecarbonitrile	11.04.2021 17:44	Abovchem	5	2090	418
5	5-(Trifluoromethoxy)-picolinic acid	11.04.2021 17:49	1click chemistry	10	4530	453
6	5-(Trifluoromethoxy)-pyridin-2-yl)methan-amine	11.04.2021 18:05	BLDpharm	1	1018	1018
7	TEMPO	29.04.2021 21:00	Aaron Chemicals	1000	161	0.16