Nachhaltige Methoden zur Einführung von Fluoralkyl(thio)gruppen

Sandmeyer-Reaktion als moderner Zugang zu fluoralkylierten Aromaten

vom Fachbereich Chemie der Technischen Universität Kaiserslautern

zur Verleihung des akademischen Grades

„Doktor der Naturwissenschaften“

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vorgelegt von

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Für Alex

„Scio, nescio“

Sokrates

Die vorliegende Arbeit wurde im Zeitraum von Oktober 2013 bis Dezember 2016 im Arbeitskreis von Prof. Dr. Lukas J. Gooßen, im Fachbereich Chemie der Technischen Universität Kaiserslautern durchgeführt.

Promotionskommission

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Eidesstattliche Erklärung

Hiermit versichere ich, dass ich die vorliegende Arbeit eigenständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel verwendet, sowie Literaturzitate kenntlich gemacht habe. Kooperationsprojekte sind ausdrücklich als solche gekennzeichnet und die Mitarbeiter genannt. Die Arbeit liegt weder in gleicher noch in ähnlicher Form in einem anderen Prüfungsverfahren vor.

Kaiserslautern, den 13. Januar 2017

_____

(Bilguun Bayarmagnai)

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Abkürzungsverzeichnis

Äquiv.	Äquivalent	*p*-TSA	4-Toluolsulfonsäure
Alk	Alkyl	quant.	quantitativ
Ar	Arylrest	R	organischer Rest
DC	Dünnschichtchromatographie	RT	Raumtemperatur
DFT	Dichtefunktionaltheorie	SET	single electron transfer
DG	Dirigierende Gruppe	t	Zeit
DMF	*N*,*N*-Dimethylformamid	T	Temperatur
DMSO	Dimethylsulfoxid	TFA	Trifluoressigsäure
ee	Enantiomeric excess	TMS	Trimethylsilyl
EI	Elektronenstoßionisation	UV	Ultraviolett
et al.	et alii; und andere		
Et	Ethyl		
GC	Gaschromatographie		
Hal	Halogenid		
HRMS	High Resolution Mass Spectrimetry		
IR	Infrarot		
J	Kopplungskonstante		
Kat.	Katalysator		
L	Ligand		
LM	Lösungsmittel		
M	Metall		
Me	Methyl		
Ph	Phenyl		

Nummerierung der Verbindungen

Die vorliegende Arbeit besteht zu einem großen Teil aus den eigenen wissenschaftlichen Veröffentlichungen. Aufgrund der Vielzahl an Verbindungen in den jeweiligen Veröffentlichungen, wurde auf eine Durchnummerierung verzichtet, um dem Leser eine bessere Übersichtlichkeit zu bieten. Die Verbindungen sind in den jeweiligen Veröffentlichungen bzw. den jeweiligen Kapiteln getrennt voneinander nummeriert. Die analytischen Daten der Verbindungen sind im experimentellen Teil ebenfalls entsprechend den jeweiligen Kapiteln getrennt aufgeführt.

Verallgemeinerte Strukturen in Schemata, die Reaktionsmechanismen und –prinzipien erläutern, wurden nicht nummeriert.

Veröffentlichungen

Die meisten Ergebnisse dieser Arbeit wurden bereits in wissenschaftlichen Fachzeitschriften veröffentlicht:

1. G. Danoun, B. Bayarmagnai, M. F. Grünberg, C. Matheis, E. Risto, L. J. Goossen, *Synth*. **2014**, *17*, 2283─2286: *Sandmeyer Trifluoromethylation*
2. B. Bayarmagnai, C. Matheis, E. Risto, L. J. Goossen, *Ad. Synth. Catal*. **2014**, *356*, 2343─2348: *One-Pot Sandmeyer trifluoromethylation and trifluoromethylthiolation*
3. B. Bayarmagnai, C. Matheis, K. Jouvin, L. J. Goossen, *Angew. Chem. Int. Ed.* **2015**, *127*, 5845─5848: *Synthesis of Difluoromethyl Thioethers from Difluoromethyl Trimethylsilane and Organothiocyanates Generated In situ*
4. B. Exner, B. Bayarmagnai, F. Jia, L. J. Goossen, *Chem. Eur. J.* **2015**, *21*, 17220─17223: *Iron-Catalyzed Decarboxylation of Trifluoroacetate and its Application to the Synthesis of Trifluoromethyl Thioethers* (B. Exner and B. Bayarmagnai contributed equally to this work)
5. C. Matheis, B. Bayarmagnai, K. Jouvin, L. J. Goossen, *Org. Chem. Front*. **2016**, *3*, 949─952: *Convenient Synthesis of Pentafluoroethyl Thioethers via Catalytic Sandmeyer Reaction with a Stable Fluoroalkylthiolation Reagent* (C. Matheis and B. Bayarmagnai contributed equally to this work)
6. B. Exner, B. Bayarmagnai, C. Matheis, L. J. Goossen, **2016**, Manuskript eingereicht, *Synthesis of perfluoroalkyl thioethers from aromatic thiocyanates by iron-catalysed decarboxylative perfluoroalkylation*
7. S. Kovács, B. Bayarmagnai, L. J. Goossen, **2016**, Manuskript in Vorbereitung, *Preparation of electrophilic SCF_3-reagents from nukleophilic tetramethylammonium trifluoromethylthiolate*
8. B. Bayarmagnai, A. Aillerie, S. Kovács, L. J. Goossen, **2016**, Manuskript in Vorbereitung, *New Reagents for Transition Metal Catalyzed Late-Stage Phosphorothioation*

Inhaltsverzeichnis

1 Struktur der Arbeit

Die vorliegende Arbeit wurde in kumulativer Form verfasst. Der Hauptbestandteil diese Arbeit sind fünf eigenständige wissenschaftliche Veröffentlichungen, die sich zu dem Themengebiet der selektiven Fluoralkylgruppeneinführung in organische Moleküle zusammenfassen lassen. Dennoch sind die Eigenschaften der fluorierten Gruppen verschieden, weshalb diese in eigenständigen Unterkapiteln in der Einleitung (Kapitel 2) näher erläutert werden.

Aufgrund der kumulativen Art enthält diese Arbeit englische Originaltexte eigener wissenschaftlicher Veröffentlichungen. Diese wurden mit deutschsprachigen Einführungen in die Thematik jeweils ergänzt.

Im Kapitel 3 sind die grundlegende Aufgabenstellung und die Zielsetzung erläutert. Diese werden im folgenden Kapitel in den einzelnen Projekten detaillierter formuliert und die erhaltenen Ergebnisse nach jeweiliger kurzer Einleitung in die Thematik diskutiert. Die Aufgabenverteilung gemeinsam bearbeiteter Projekte ist ebenfalls in der jeweiligen Einleitung erläutert. Kopien der Manuskripte bereits veröffentlichter Ergebnisse sowie Manuskriptentwürfe sind den betreffenden Abschnitten der Arbeit angefügt. Im Kapitel 5 werden die Ergebnisse kurz zusammengefasst und ein Ausblick auf nächste Arbeiten gegeben.

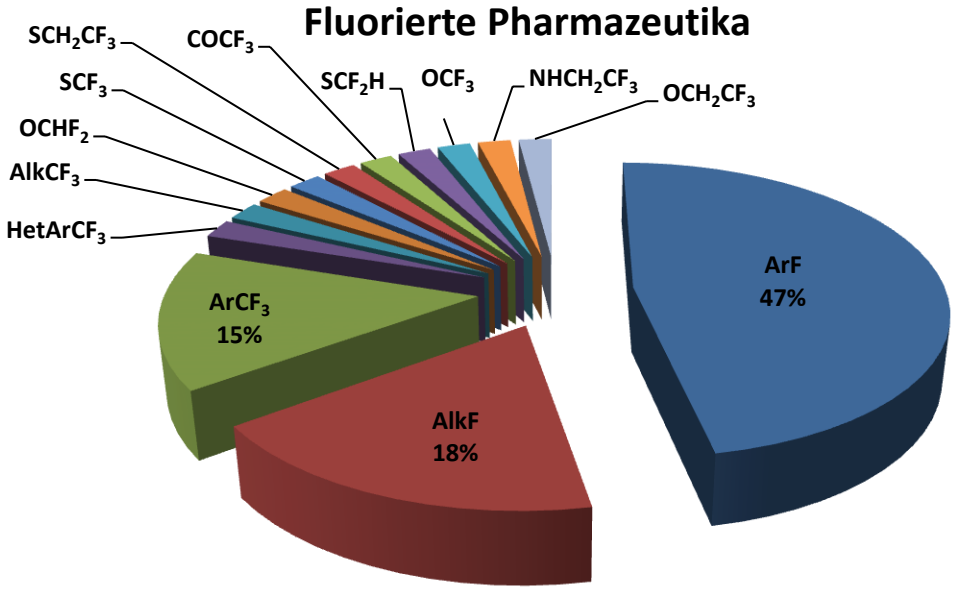
Die experimentellen Daten finden sich am Ende der Arbeit, sortiert nach Projekten, in einem gemeinsamen Kapitel. Diese setzen sich aus den experimentellen Teilen der Veröffentlichungen zusammen und sind zum größten Teil in englischer Sprache.

2 Einleitung

2.1 Eigenschaften und Bedeutung fluoralkylierter Verbindungen

Das Fluoratom, mit der Elektronenkonfiguration [(1s2)(2s2)(2p5)], ist nur geringfügig größer als das kleinste Element Wasserstoff (Van-der-Waals-Radius 1.47 Å vs. 1.20 Å), und mit 3.98 auf der Pauling-Skala das elektronegativste sowie reaktivste Element des Periodensystems. [1] Aufgrund der hohen Reaktivität kommt Fluor in der Natur nur in Verbindungen, am häufigsten in Mineralien wie z.B. Flussspat (CaF_2), vor. Fluorhaltige Naturstoffe sind dagegen sehr selten.[2] Die Tatsache, dass die meisten Organismen Kohlenstoff-Fluorbindungen nicht um-, auf- oder abbauen können, wird gezielt in der Entwicklung von Medikamenten,[3] Pflanzenschutzmitteln[4] und Funktionsmaterialien[5] genutzt. Fluorsubstituenten führen in organischen Molekülen zur starken Bindungspolarisierung und ändern deren physikalische und chemische Eigenschaften. Eine Kohlenstoff-Fluor-Einheit kann sowohl mit polaren funktionellen Gruppen wie Carbonylgruppen und Wasserstoffbrückendonoren als auch mit hydrophoben Resten Wechselwirkungen eingehen. Eine Einführung von Fluorsubstituenten in biologisch aktive Moleküle kann deren Bioverfügbarkeit und metabolische Stabilität steigern. Dabei können die pK_s-Werte der Wirkstoffe so verändert werden, dass diese besser vom Zielorganismus resorbiert werden können.[6] Die Lipophilie der Wirkstoffe kann durch Fluorierung bzw. Fluoralkylierung erhöht werden. Hohe Lipophilie der Wirkstoffe ist aufgrund des verbesserten passiven Transports durch die unpolaren Zellmembranen in der Wirkstoffentwicklung erwünscht. Zusammengefasst lässt sich festhalten, dass eine geschickte Einführung von Fluor und Fluorsubstituenten in Medikamentenkandidaten die Rezeptorbindungsaffinität, Wirksamkeit und Wirkungsdauer rational steuerbar machen kann. Deshalb ist es nicht verwunderlich, dass etwa 40 % aller Agrochemikalien und 25 % aller Arzneimittel in ihrer Struktur Fluoratome enthalten und dieser Trend setzt sich stetig fort.[7,8]

Den Hauptbestandteil fluorierter Wirkstoffe machen aufgrund des erhöhenden Effektes der metabolischen Stabilität einfach fluorierte Aryle und Alkyle aus (Schema 1).[9]



Schema 1. Diversität fluorierter Gruppen in Pharmazeutika.

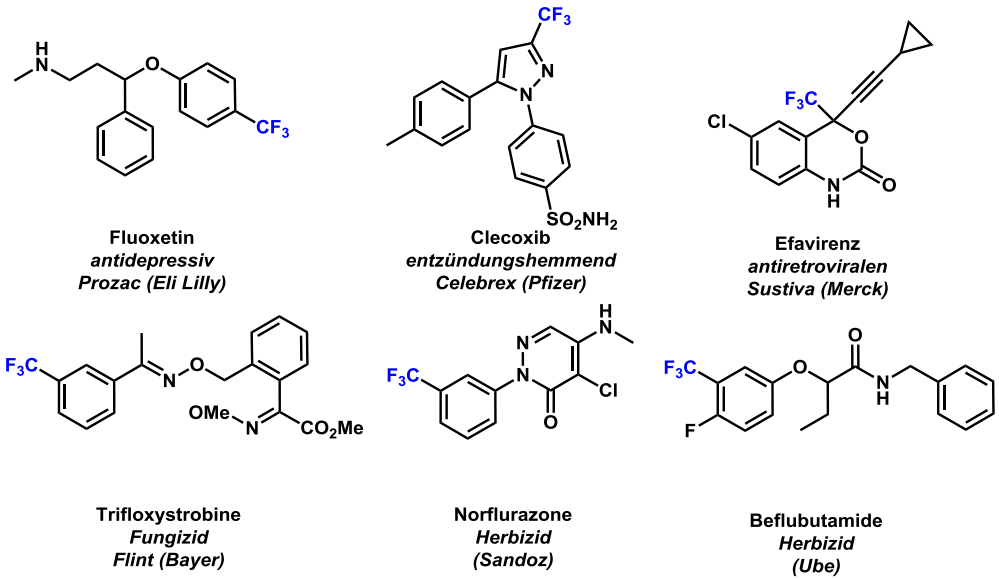
Ein sogenanntes „Fluorine-Scan“ ist in der Wirkstoffentwicklung mittlerweile eine Standardprozedur bei der Fluorsubstituenten wie CF_3, C_2F_5, SCF_3, OCF_3 etc. systematisch eingeführt und auf ihre Wirkung getestet werden.[8] Der Effekt der Bioisosterie (Änderung der biologischen Aktivität ohne die Struktur zu beeinflussen) wird speziell im Bereich des rationalen Wirkstoffdesigns genutzt, um die Wirkung und die Wirkungsdauer zu steuern.

In den folgenden Abschnitten werden die besonderen Eigenschaften und die Einführung von CF_3, SCF_3 und SCF_2H-Gruppen näher erläutert, da die vorliegende Dissertation sich hauptsächlich mit der Einführung dieser Gruppen befasst.

2.1.1 Trifluormethylgruppen

Unter den Fluorsubstituenten erwies sich die Trifluormethylgruppe (CF_3-Gruppe) wegen ihrer besonderen physikalischen und chemischen Eigenschaften als besonders wertvoll für Pharmazeutika,[3] Pflanzenschutzmittel[4] und Funktionsmaterialien.[5] Die CF_3-Gruppe ist geringfügig größer als eine Methylgruppe (Van-der-Waals-Volumen 42.6 $Å^3$ vs. 16.8 $Å^3$) und besitzt eine vergleichbar hohe Elektronegativität von 3.45 auf der Pauling-Skala wie Sauerstoff (3.44) oder Chlor (3.16).[10,11] Die geringe Polarisierbarkeit der CF_3-Gruppe führt zur Erhöhung der Lipophilie der trifluormethylierten Verbindungen.[12] Folglich führt in

einem Wirkstoff der Austausch einer Methyl- oder Methoxygruppe mit einer Trifluormethylgruppe in einem Wirkstoff zu einer verbesserten Bioverfügbarkeit und metabolischen Stabilität, wobei die geringen Größenunterschiede der Substituenten den Enzym-Substrat-Komplex kaum verändern. Ein Beispiel dafür ist die Funktionalisierung des Zytostatikums Epothilon, welches durch eine Trifluormethylierung erhöhte metabolische Stabilität bei vergleichbarer zytotoxischer Wirkung erzielte und anschließend unter dem Namen Fludelon auf den Markt kam.[13] Fluoxetin, Celecoxib, Efavirenz sind weitere Beispiele für trifluormethylierte Arzneimittel und bei den Agrochemikalien sind als weitere Beispiele Beflubutamid, Trifloxystrobine und Norflurazon (Schema 2) zu nennen.[3]



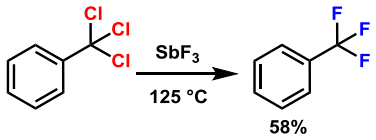
Schema 2. Wirkstoffe mit Trifluormethylgruppen.

In den vergangenen Jahren wurden aufgrund der stetig steigenden Nachfrage an trifluormethylierten Verbindungen zahlreiche innovative Reaktionen und Reagenzien entwickelt, die eine Einführung der CF_3-Gruppe in organische Moleküle in späten Stufen einer Synthese ermöglichten. Diese sollen im nachfolgenden Unterkapitel näher erläutert werden.

2.1.2 Reaktionen und Reagenzien zur Trifluormethylierung

2.1.2.1 Traditionelle Methoden

Traditionelle Methoden zur Synthese von Trifluormethylgruppen sind Fluorierungsreaktionen. Diese basieren auf dem Fluor-Halogen-Austausch am Kohlenstoffatom, welcher bereits zuvor in der Zielstruktur eingeführt wurde. Diese Fluorierungsmethode wurde im Jahre 1898 erstmals am Beispiel von Benzotrichlorid von Swarts beschrieben (Schema 3).[14]



Schema 3. Swarts-Reaktion zur Synthese von Benzotrifluoriden.

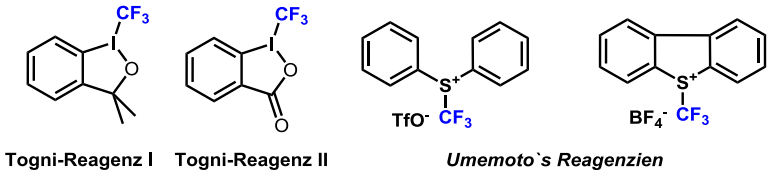
Die Swarts-Reaktion wurde seit ihrer Entdeckung weiterentwickelt und wird noch heute in industriellen Syntheseverfahren genutzt.[15] Allerdings ist diese Methode nur unter sehr harschen Reaktionsbedingungen wie z.B. Reaktionstemperaturen weit über 100 °C, *in situ* Generierung von stark korrosiven Wasserstofffluorid Gasen anwendbar und erfordert dazu entsprechende Reaktorausrüstung. Zudem ist ihre Anwendungbreite durch diese Reaktionsbedingungen an Substratklassen stark beschränkt, weshalb sie ausschließlich am Anfang einer Synthesesequenz eingesetzt wird.

2.1.2.2 Moderne Trifluormethylierung

Aufgrund der starken Nachfrage an trifluormethylierten Verbindungen wurden im letzten Jahrzehnt enorme Fortschritte bei der Entwicklung moderner Methoden zur Trifluormethylierung gemacht. Als Beleg hierfür gelten die mehr als 350 wissenschaftliche Veröffentlichungen seit dem Jahre 2008, die über innovative Verfahren zur Einführung dieser Gruppe berichten.[16] Trifluormethylgruppen werden als eine ganze Einheit regio- und sogar enantioselektiv in hochkomplexe, funktionalisierte organische Moleküle eingeführt, meist übergangsmetallkatalysiert.[17-22] Hierbei erschwert die Bindung der CF_3 Gruppe an die Katalysatormetalle, bedingt durch einerseits einen hohen polaren Anteil, andererseits durch eine Rückbindung der d-Orbitale in die σ* (C─F) Bindungen, den Schritt der reduktiven Eliminierung und stellt eine Herausforderung dar. In den folgenden Abschnitten wird anhand ausgewählter Beispiele der Stand der Forschung vorgestellt.

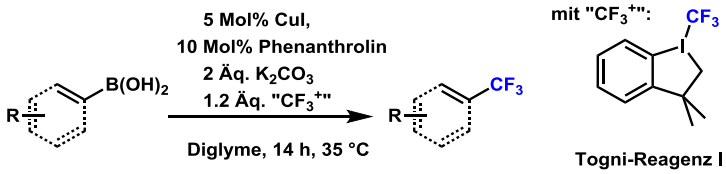
Trifluormethylierung mit elektrophilen Reagenzien

Eine große Bandbreite von Substraten kann mit elektrophilen Trifluormethylierungsreagenzien unter Tolerierung einer Vielzahl an funktionellen Gruppen umgesetzt werden. Besonders im Labormaßstab werden die kristallinen und leicht handhabbaren Reagenzien verwendet und erhielten häufig Trivialnamen wie z.B. die Togni`s Reagenzien oder Umemoto`s Reagenzien. Sie alle haben den großen Nachteil durch die hohen molaren Massen erhebliche Mengen an Abfall zu generieren und sind daher für den industriellen Maßstab zu kosten- und abfallintensiv (Schema 4).



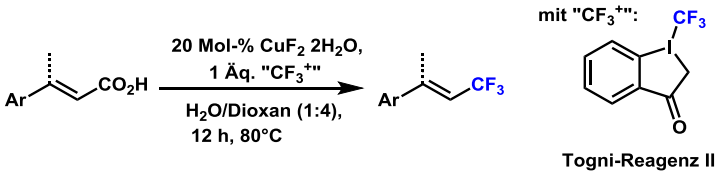
Schema 4. Elektrophile Trifluormethylierungsreagenzien.

Durch den Einsatz dieser Reagenzien wurden zahlreiche Trifluormethylierungsmethoden entwickelt und die Bandbreite der Substratklassen maßgebend erweitert. Sowohl sp, sp^2 als auch sp^3 hybridisierte nukleophile oder radikalische Kohlenstoffzentren können unter optimierten Bedingungen mit diesen elektophilen Reagenzien trifluormethyliert werden.[20] So werden beispielsweise Nukleophile wie Alkenyl- und Arylboronsäuren in Gegenwart eines Kupferkatalysators trifluormethyliert (Schema 5).



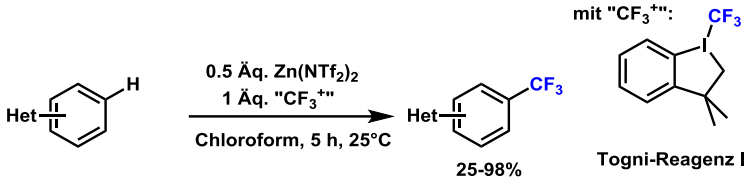
Schema 5. Elektrophile Trifluormethylierung von Aryl- und Alkenylboronsäuren.

α,β-Ungesättigte Carbonsäuren können in einem kupferkatalysierten System unter Decarboxylierung zu trifluormethylierten Alkenen umgesetzt werden, wobei die Trifluormethylquelle zugleich als Oxidatiansmittel dient (Schema 6).[23]



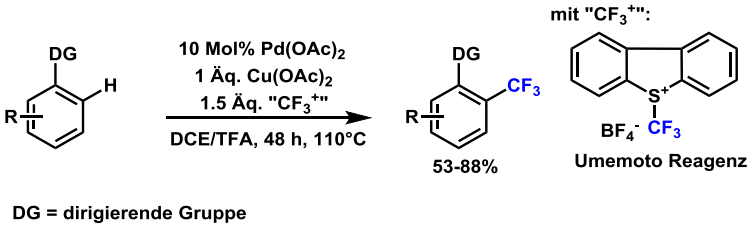
Schema 6. Trifluormethylierung α,β-Ungesättigter Carbonsäuren.

Heteroaromaten können in Gegenwart einer Lewis-Säure wie z.B. Zinkbis(trifluormethylsulfonyl)imid oder Kupferacetat in 2-Position regioselektiv trifluormethyliert werden (Schema 7).[24]



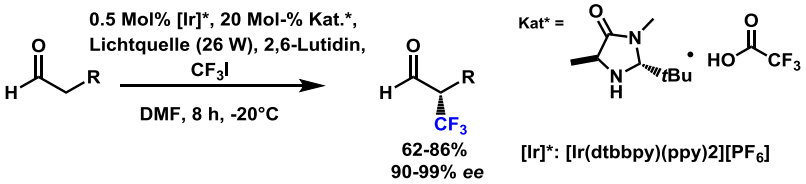
Schema 7. Trifluormethylierung der Heteroaromaten.

Über eine *C-H* Funktionalisierung mittels dirigierender Stickstoffgruppen (DG) können Arene palladiumkatalysiert selektiv trifluormethyliert werden (Schema 8). Ein Vorteil hierbei ist, dass selten eine *ortho.ortho*-Ditrifluormethylierung stattfindet. Der Grund dafür ist höchstwahrscheinlich die sterische Hinderung der CF_3-Gruppe für eine weitere Cyclometallierung.



Schema 8. Trifluormethylierung über *C-H* Funktionalisierung.

Unter Nutzung chiraler Enamine durch Organokatalyse können enantioselektive α-Trifluormethylierungen von Carbonylverbindungen ermöglicht werden. MacMillan und seine Mitarbeiter berichteten über die enantioselektive α-Trifluormethylierung von Aldehyden unter Iridium-Photoredox-Cokatalyse (Schema 9).[25]

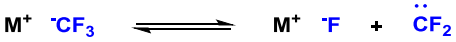


Schema 9. Enantioselektive α-Trifluormethylierung von Aldehyden.

Trifluormethylierung mit nukleophilen Reagenzien

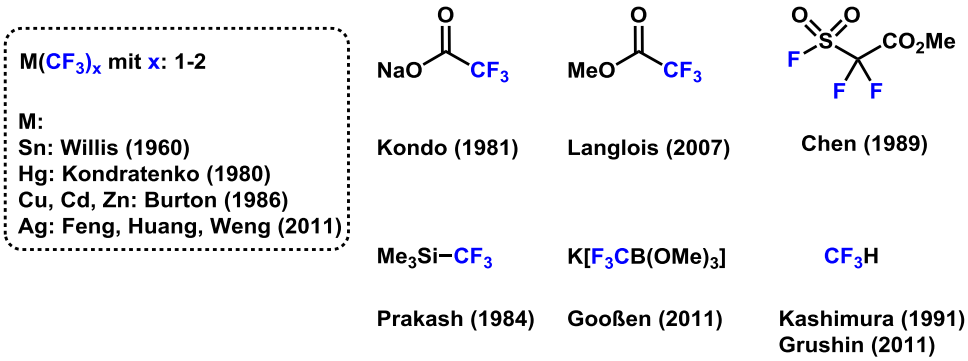
Die nukleophile Trifluormethylierung ist eine breit angewandte Strategie um stabilisierte Trifluormethyl-Anionenäquivalente auf elektrophile Gruppen zu übertragen. Die

Herausforderung dabei ist die Instabilität des Trifluormethylanions und den damit verbundenen Zerfall in Fluorid und Difluorcarben, die sogenannte α-Fluorideliminierung zu kontrollieren (Schema 10).[26]



Schema 10. Zerfallsgleichgewicht des Trifluormethylanions.

Als Pränukleophile werden präformierte Metalltrifluormethylkomplexe aus den Metallen Sn, Hg, Cu, Cd, Zn und Ag[27-31] Trifluomethylacetate,[32,33] $TMSCF_3$,[34] $K(OMe)_3CF_3$,[35] und Fluoroform,[36,37] ein Abfallprodukt der Teflonindustrie, eingesetzt (Schema11).



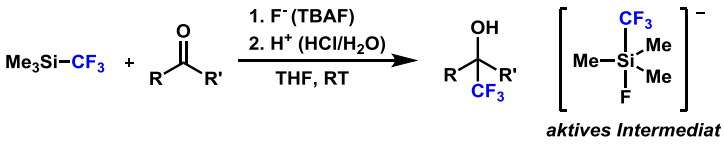
Schema 11. Nukleophile Trifluormethylierungsreagenzien.

Um das instabile CF_3-Anion in der Katalyse zu stabilisieren werden meist Metalle wie z.B. Zink und besonders Kupfer eingesetzt, da diese Metall-CF_3-Komplexe bilden und das Anion so in Lösung stabilisieren, damit es anschließend mit den Elektrophilen weiter reagieren kann. Die Reaktion von Rupperts Reagenz mit Arylhalogeniden zu trifluormethylierten Arenen führten Vicic *et al.* mit preformierten Kupfer-Carbenkomplexen durch. Kondo, Amii, Grushin, Hartwig und Weng leisteten auf diesem Gebiet Pionierarbeiten, in denen diverse Kupfer-CF_3-Komplexe als aktive Katalysatoren identifiziert wurden.[38-42]

$TMSCF_3$ das Rupperts Reagenz

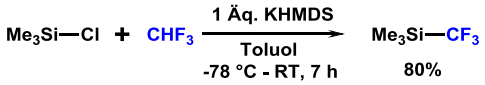
Das von Ruppert *et al.* zuerst beschriebene Trifluoromethylsilan Reagenz[34] wird am häufigsten als nukleophile CF_3-Quelle herangezogen, hierbei wird das Trifluormethylanion unter Zugabe eines Fluoridanions (z.B. Tetrabutylammoniumfluorid oder Kaliumfluorid) in stöchiometrischen Mengen aktiviert (Schema 11, rechts).[43,44] Seit dem ersten Bericht über die Synthese im Jahre 1984,[34] war der synthetische Nutzen des Rupperts Reagenzes bis 1997 zunächst hauptsächlich auf die nukleophile Trifluormethylierung harter Kohlenstoff-

Elektrophile wie z.B. nicht-enolisierbare Aldehyde und Ketone, Lactone, zyklische Anhydride und Azirine (Schema 12) limitiert.[45]



Schema 12. Trifluormethylierung von Carbonylverbindungen.

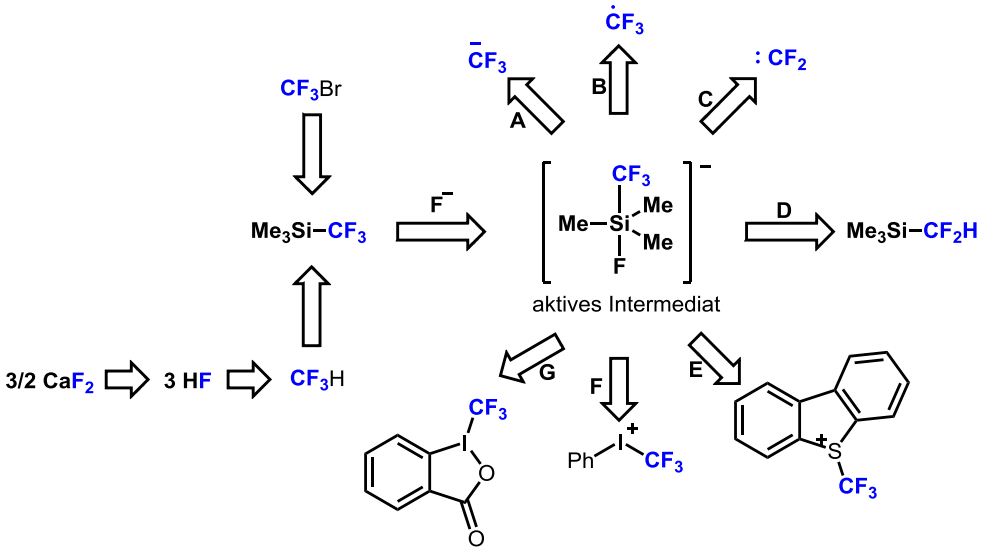
In den letzten Jahren wurden basierend auf den Pionierarbeiten von McLoughlin,[46] Yagupoliskii,[47] Burton,[48] Chambers[49] und Grushin[50] erhebliche Fortschritte in der nukleophilen Trifluormethylierung geleistet. Vor allem mit dem $TMSCF_3$ Reagenz.[44] So werden unter anderem z.B. Arylhalogenide palladiumkatalysiert trifluormethyliert.[51-53],[44] Das Rupperts Reagenz und dessen Einsatz wird immer bedeutender für die organische Synthese seit in der richtungsweisenden Arbeit von Prakash *et al.* gezeigt wurde, dass sich dieses Reagenz aus dem Fluoroform Gas, dem ungenutzten Abfallprodukt der Teflonherstellung, herstellen lässt (Schema 13).[54]



Schema 13. Rupperts Reagenz Synthese aus Fluoroform.

Fluoroform ist zwar nicht ozonschädigend, aber dennoch ein starkes Treibhausgas (15.000-mal stärker als Kohlendioxid), dessen Freisetzung in die Atmosphäre schwere Umweltschäden (sog. „climate bomb“) verursacht. Umso bedeutender ist die Verwertung dieses Gases als wertvolle nachhaltige CF_3-Quelle.

Über die Struktur von $TMSCF_3$ und seinen Derivaten in katalysierten Reaktionen und die entsprechenden Reaktionsmechanismen wurden zahlreiche Studien durchgeführt. Der synthetische Nutzen dieses Reagenzes wurde vom nukleophilen CF_3-Anion (Schema 14, **A**) auf radikalische „$\cdot CF_3$“ (**B**), Difluorcarben-„$:CF_2$“, elektrophile „CF_3^+“ (z.B. Synthese der Togni`s Reagenz **G,** Phenyliodonium-CF_3 oder Umemoto Reagenzien **E**) Quellen oder mittels Reduktion als CF_2H-Quelle erweitert (Schema 14).[44]

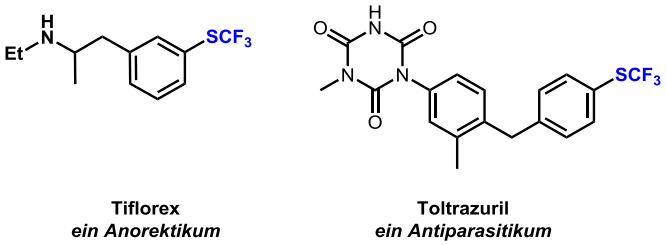


Schema 14. Rupperts Reagenz als nachhaltige, vielfältige CF_3-Quelle.

Als Alternative zur Verwendung ozonschädlicher Interhalogenverbindungen wie z.B. CF_3Br, kann $TMSCF_3$ auch ausgehend von Flussspat als natürliche Fluoridquelle auf nachhaltige Syntheseroute über Fluoroform (CF_3H) hergestellt werden.

2.1.3 Trifluormethylthiolgruppen

Im Vergleich zu den intensiven Forschungen zur Trifluormethylierung gewinnt seit kurzer Zeit die Einführung der weniger erforschtenTrifluormethylthiolgruppe (SCF_3-Gruppe) immer mehr an Bedeutung. Die SCF_3-Gruppe ist eine der lipophilsten Substituenten (Hansch Konstanten für Lipophilie für SCF_3 1.44 vs. für CF_3 0.88)[55] und kann als Substituent in einem Wirkstoff-Kandidaten die Membranpermeabilität signifikant erhöhen und gleichzeitig dessen metabolische Stabilität positiv beeinflussen.[4] Bereits heute sind einige trifluormethylthiolierte Wirkstoffe in Pharmazeutika oder Agrochemikalien, wie z.B. Tiflorex und Toltrazuril, zugelassen und es ist davon auszugehen, dass dieser Trend in naher Zukunft weiter zunimmt (Schema 15).



Tiflorex
ein Anorektikum

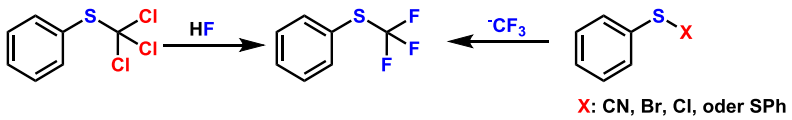
Toltrazuril
ein Antiparasitikum

Schema 15. Wirkstoffe mit Trifluormethylthiolgruppen.

2.1.4 Reaktionen und Reagenzien zur Trifluormethylthiolierung

2.1.4.1 Traditionelle Methoden

Die klassischen Methoden zur Einführung einer SCF_3-Gruppe basieren, ähnlich wie die Swarts-Reaktion, auf dem Fluor-Halogen-Austausch oder Trifluormethylierung am Schwefelzentrum, welches bereits zuvor am Zielmolekül installiert wurde (Schema 16).[56-65] Diese Methoden erfordern jedoch harsche Reaktionsbedingungen und/oder sind auf ihren schwefelhaltigen Ausgangsstoffen beschränkt.



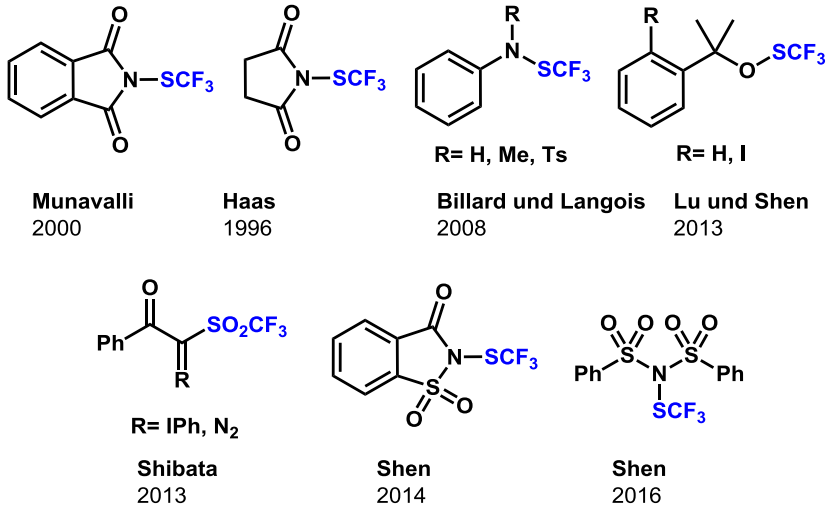
Schema 16. Traditionelle Synthesestrategien der Trifluormethylthiolgruppen.

2.1.4.2 Moderne Trifluormethylthiolierung

Die steigende Nachfrage nach trifluormethylthiolierten Verbindungen führte zwangsläufig zur Entwicklung neuer Reagenzien und Methoden, die eine direkte Einführung von SCF_3-Gruppen als eine ganze Einheit in organische Moleküle erlauben.[66]

Trifluormethylthiolierung mit elektrophilen Reagenzien

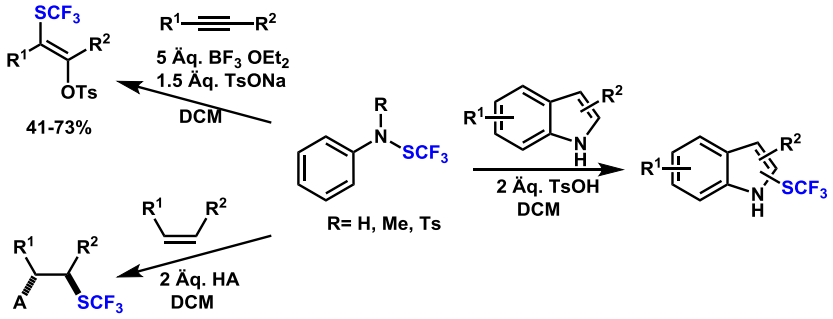
Bis zum Jahre 2009 wurde das Gas CF_3SCl ausschließlich als elektrophiles Trifluormethylierungsreagenz eingesetzt.[66] Die hohe Toxizität des Reagenzes beschränkte dessen Einsatz und führte schließlich zum Verwendungsverbot in der organischen Synthese. In den letzten Jahren wurden zahlreiche Reagenzien unter anderem in den Forschungsgruppen Munavalli, Langlois, Shen etc. entwickelt, welche aus nukleophilen SCF_3-Quellen (hauptsächlich aus Silbertrifluormethylthiolat, $AgSCF_3$ oder Kupfertrifluormethylthiolat $CuSCF_3$) synthetisiert werden (Schema 17).[66]



Schema 17. Elektrophile Trifluormethylthiolierungsreagenzien.

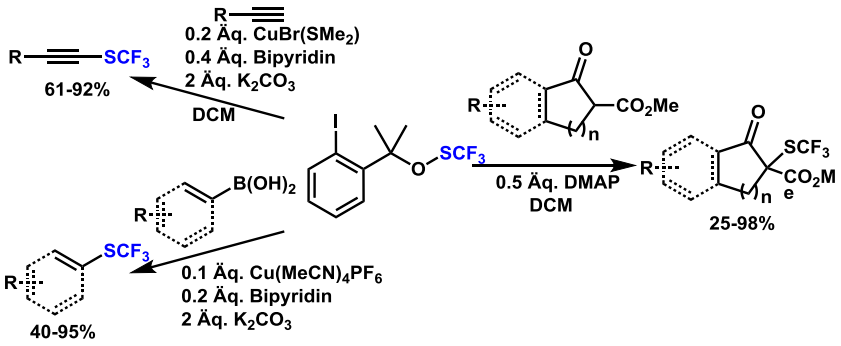
Die Verfügbarkeit dieser Reagenzien führte zu zahlreichen Trifluormethylthiolierungsmethoden und erschuf somit den Zugang zu Verbindungen mit biologisch wertvollen Eigenschaften.

Trifluormethansulfenamide (Billard's Reagenzien) reagieren mit Alkinen und Alkenen unter sauren Bedingungen z.B. in Gegenwart von Brönstedt oder Lewis Säuren (Schema 18).[67] Im Falle der Alkene können regio- und stereoselektive Produkte erhalten werden, was ein Indiz dafür ist, dass diese Additionsreaktion über eine Episulfonium Zwischenstufe verläuft. Indole werden an den C2 oder C3 Positionen mittels direkter elektrophiler aromatischer Substitution trifluormethylthioliert, wobei die Position C3 bevorzugt wird, jedoch erfolgt die Reaktion an C2, wenn C3 substituiert ist.[68]



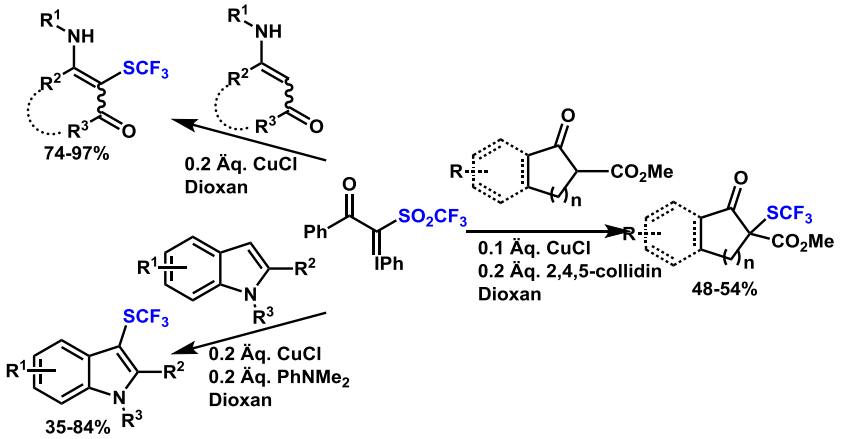
Schema 18. Trifluormethylthiolierung mit Billards Reagenz.

Im Falle terminaler Alkine wird das Shens Reagenz in Gegenwart eines Kupferkatalysators zur Trifluormethylthiolierung eingesetzt (Schema 19).[69]



Schema 19. Trifluormethylthiolierung mit Shens Reagenz.

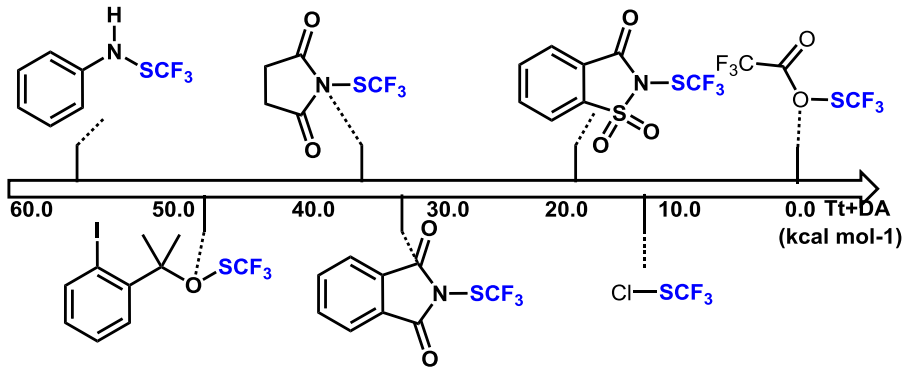
Aryl- und Vinylboronsäuren können mit diesem Reagenz trifluormethylthioliert werden. β-Ketoester können an der α-Position in Gegenwart katalytischer Mengen an Base meistens 4-(Dimethylamino)pyridine (DMAP) trifluormethylthioliert werden.[70]



Schema 20. Trifluormethylthiolierung mit Shibatas Reagenz.

Die Arbeitsgruppe von Shibata berichtete über die Synthese von hypervalenten trifluormethylsulfonylyliden aus Triflon.[71] In Gegenwart von katalytischen Mengen an Kupfer konnte dieses Reagenz zahlreiche Nukleophile wie z.B. β-Enamine und Ketone trifluormethylthiolieren. Des Weiteren wurden Indole an C3 Position und β-Ketoester in α-Position trifluormethylthioliert.[71]

Diese Reagenzien liefern alle „SCF_3^+“, dennoch unterscheiden sie sich in ihrer Reaktivität signifikant. Dazu wurden mechanistische und theoretische Untersuchungen geleistet und eine Auflistung mit steigender „SCF_3-Kation-Donor-Fähigkeit“ (Tt^+DA) erstellt. Diese sollte zur Hilfe der richtigen Reagenzienwahl dienen (Schema 21).[72] Dabei wurde die freie Gibbs-Energie der heterolytischen Spaltung der Y-SCF_3 (Y-Heteroatom der Reagenzien N, O, Cl) in Y-Anion und SCF_3-Kation bei Raumtemperatur berechnet.

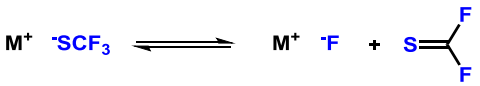


Schema 21. SCF_3-Kation-Donor-Fähigkeiten der Trifluormethylthiolierungsreagenzien.

Während das Billards Reagenz mit 59.7 kcal/mol für stärkere Nukleophile einsetzbar sind, sind Imid Derivative mit ca. 34 kcal/mol wesentlich reaktiver. Das SCF_3-*N*-Saccharin, entwickelt in der Gruppe von Shen, ist am reaktivsten mit 17.9 kcal/mol.[72]

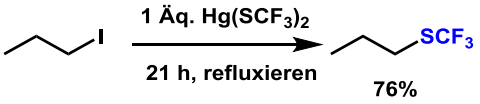
Trifluormethylthiolierung mit nukleophilen Reagenzien

Nukleophile Trifluormethylthiolierungen wurden in den letzten Jahren ebenfalls entwickelt, wobei die Instabilität des SCF_3^--Anions und dessen Zerfall in Difluorthiophosgen und Fluorid, eine Herausforderung darstellt (Schema 21).[73-76]



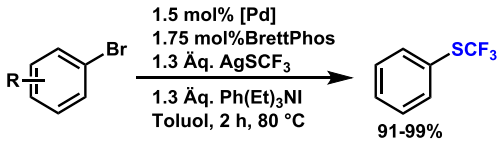
Schema 21. Zerfall des SCF_3^--Anions.

Analog zu den Erfahrungen aus der Trifluormethylierung wurden auch hier stabilisierende Metalle wie Hg^{II}, Ag^{I} und Cu^{I} eingesetzt. Zunächst wurde $Hg(SCF_3)_2$ durch die Reduktion von Bis(trifluormethyl)dilsulfid mit elementarem Quecksilber hergestellt und als präformiertes Trifluormethylthiolierungsreagenz in nukleophile Substitutionsreaktionen eingesetzt (Schema 22).[77]



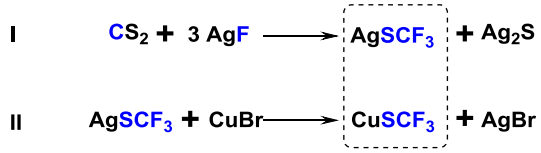
Schema 22. Trifluormethylthiolierung von Alkylhalogeniden.

Aufgrund der hohen Toxizität des Quecksilbers (Hg^{II}) wurden Alternativen $AgSCF_3$ und $CuSCF_3$ untersucht. Im Jahre 2011 berichtete die Forschungsgruppe von Buchwald eine palladiumkatalysierte Methode zur Trifluormethylthiolierung von Arylbromiden mit $AgSCF_3$ (Schema 23).[78]



Schema 23. Trifluormethylthiolierung von Arylbromiden.

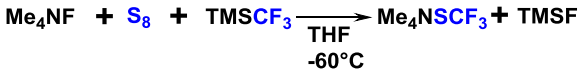
Das $AgSCF_3$ Salz lässt sich aus Kohlenstoffdisulfid (CS_2) und Silberfluorid (AgF) herstellen (Schema 24, **I**). Das Kupfertrifluormethylthiolat ($CuSCF_3$) lässt sich anschließend aus $AgSCF_3$ und Kupferbromid (CuBr) mittels einer Salzmetathese synthetisieren (**II**).[79]



Schema 24. Synthese von Silber- und Kupfertrifluormethylthiolaten.

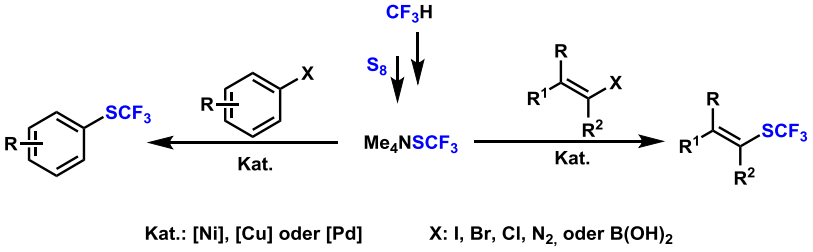
Der große Nachteil dieser Reagenzien ist die teure Herstellung des $AgSCF_3$ Salzes, welches 3 Äquivalente an AgF und den Einsatz von toxischem Kohlenstoffdisulfid erfordert.

Seit kurzem wird das Tetramethylammonium trifluormethylthiolat Salz (Me_4NSCF_3) als alternative nukleophile SCF_3-Quelle eingesetzt. Dieses ist aus dem Rupperts Reagenz $TMSCF_3$, Schwefel und Tetramethylammoniumfluorid leicht herzustellen und stellt eine der momentan günstigsten und nachhaltigen SCF_3-Quellen dar (Schema 25).[80]



Schema 25. Synthese des Tetramethylammonium trifluormethylthiolat Salzes.

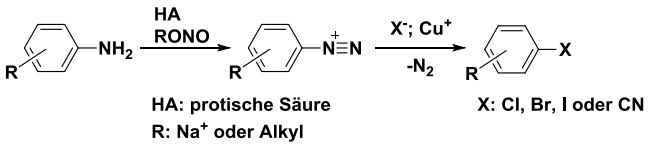
Diverse Elektrophile wie z.B. Vinyliodide, Arylhalogenide und -diazonium Salze konnten in sehr guten Ausbeuten unter milden Reaktionsbedingungen, meist sogar bei Raumtemperatur redoxneutral trifluormethylthioliert werden (Schema 26). Aber auch Nukleophile wie z.B. Aryl- und Vinylboronsäuren können unter oxidativen Bedingungen meist kupferkatalysiert umgesetzt werden.[81-87]



Schema 26. Trifluormethylthiolierung mit Me_4NSCF_3.

2.2 Sandmeyer-Reaktion

Die Sandmeyer-Reaktion, benannt nach ihrem Entdecker Traugott Sandmeyer, ist eine erstmals 1884 beschriebene Methode zur Überführung aromatischer Amine in die Arylhalogenide oder -pseudohalogenide.[88] Aromatische Amine werden zunächst unter sauren Bedingungen zu den entsprechenden Diazoniumsalzen überführt, welche anschließend unter Freisetzung des Stickstoffs in der Lage sind mit diversen Nukleophilen Kreuzkupplungsreaktionen einzugehen.

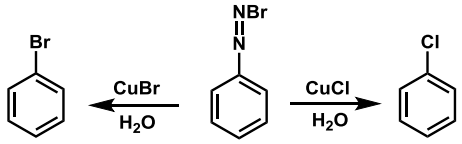


Schema 27. Sandmeyer-Reaktion.

Die zur Herstellung benötigten Anilinderivate sind kommerziell in großer struktureller Vielfalt und recht günstig verfügbar. Weitere Vorteile dieser Transformation sind die hohe Toleranz gegenüber einer Vielzahl funktioneller Gruppen sowie milde Reaktionsbedingungen. Die Sandmeyer-Reaktion zählt zu den bekanntesten Namensreaktionen der organischen Synthesechemie.

2.2.1 Der Mechanismus

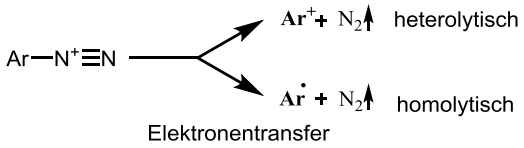
Hantzsch berichtete bereits im Jahre 1895 über die Diazo-Stickstoff-Komplexbildung des Diazoniumsalzes in Gegenwart von Kupferbromid (CuBr) und dessen Zerfall zu Brombenzol bei der Zugabe von Wasser (Schema 28, links)[89] während in Gegenwart von Kupferchlorid Chlorbenzol gebildet wurde (rechts).[90] Dies zeigt, dass das Halogenid, welches die Diazogruppe ersetzt, vom Kupfersalz stammt.



Schema 28. Bromierung und Chlorierung des Phenyldiazoniumbromides.

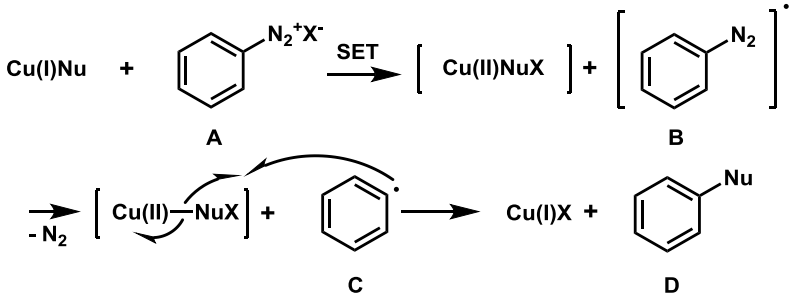
Die Freisetzung des Stickstoffs als Abgangsgruppe kann sowohl heterolytisch als auch homolytisch erfolgen (Schema 29). In Gegenwart eines Kupfersalzes findet ein Einelektrontransfer (SET) vom Kupfer auf die Diazogruppe statt, sodass nach der Dediazonierung ein Arylradikal gebildet wird.[91] In Abwesenheit eines Reduktionsmittels

verläuft die Dediazonierung heterolytisch. Die Triebkraft ist in beiden Prozessen die Bildung des molekularen Stickstoffs.



Schema 29. Dediazonierungen des Diazoniumsalzes.

Die Gruppen um Waters,[92] Kornblum,[93] Knochi,[94] Rüchardt,[95] Bunnet[96] und Zollinger[97] leisteten Pionierarbeiten bei den Untersuchungen zur Dediazonierung und postulierten folgenden Mechanismus (Schema 30). Die Diazogruppe des Salzes **A** wird unter Oxidation von Cu^{+1} zu Cu^{2+} mittels eines SET zum Diazenylradikal (**B**) reduziert. Dieses setzt Stickstoff frei und bildet das Arylradikal (**C**), welches mit dem Gegenanion (Nu = Cl^-, Br^-, CN^-) des Kupfersalzes unter Reduktion des Cu^{2+} zu Cu^+ reagiert.



Schema 30. Der Mechanismus der Sandmeyer Reaktion.

Das Kupfer fungiert dabei sowohl als Elektronendonor als auch –akzeptor. Bei der Einführung von leicht oxidierbaren Nukleophilen wie z. B. Iodid erfolgt die Reaktion ohne Zusatz eines Kupfersalzes. Als mögliche Nebenprodukte entstehen Biaryle und Azoverbindungen, was ebenfalls ein Beweis für radikalische Zwischenstufen ist.

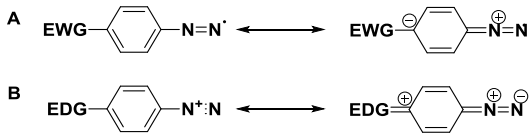
Durch Untersuchungen zur Reduktion auf einer Elektrodenoberfläche zeigten Elofson und Gadallah eine Übersicht über die polarographische Halbstufenreduktionspotentiale ($E_{1/2}$) der Aryldiaziumionen (Tabelle 1).[98]

Tabelle 1. Halbstufenreduktionspotentiale der Aryldiazoniumsalze.

Eintrag	Substituent	$E_{1/2}$ (gegen SCE), V	Eintrag	Substituent	$E_{1/2}$ (gegen SCE), V
1	*p*-NO_2	+0.450	7	*p*-SO_3^-	+0.297
2	*p*-CN	+0.433	8	*p*-H	+0.295
3	*p*-I	+0.383	9	*p*-Me	+0.250
4	*p*-Br	+0.383	10	*p*-OMe	+0.140
5	*p*-Cl	+0.350	11	*p*-$N(Me)_2$	-0.095
6	*p*-CO_2^-	+0.328			

Gemessen in Sulfolan, SCE = saturated calomel electrode, Kalomelektrode, V = Volt, $E_{1/2}$ polarographische Halbstufenreduktionspotentiale.

Elektronenziehende Effekte führten zur Erhöhung der Potentiale (+0.450 V für *p*-NO_2 vs 0.297 V für H). D.h. die Reduktionsreaktion wird durch elektronenziehende Effekte begünstigt (Schema 31). Elektronenreiche Aryldiazoniumsalze (z.B. *p*-$N(Me)_2$ mit -0.095 V) verlangsamen dagegen die Reaktion durch stabilisierende Effekte auf die Diazogruppe.

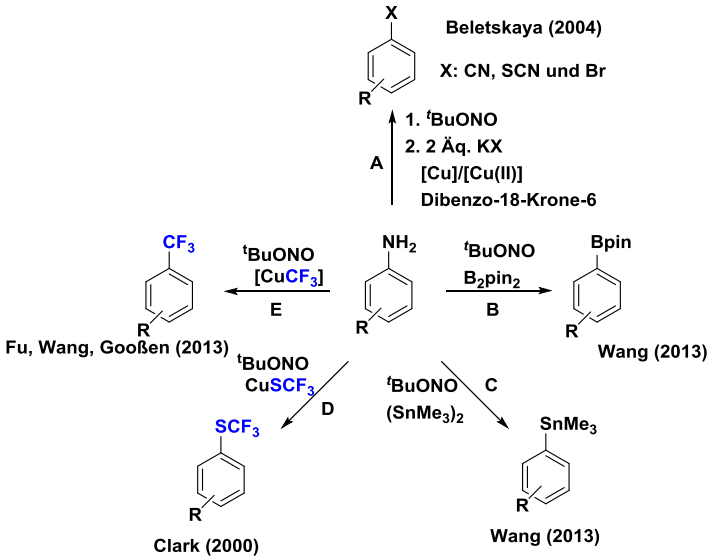


Schema 31. Substituenteneffekte auf die Stabilität der Diazoniumsalze.

2.2.2 Katalytische Sandmeyer-Reaktionen

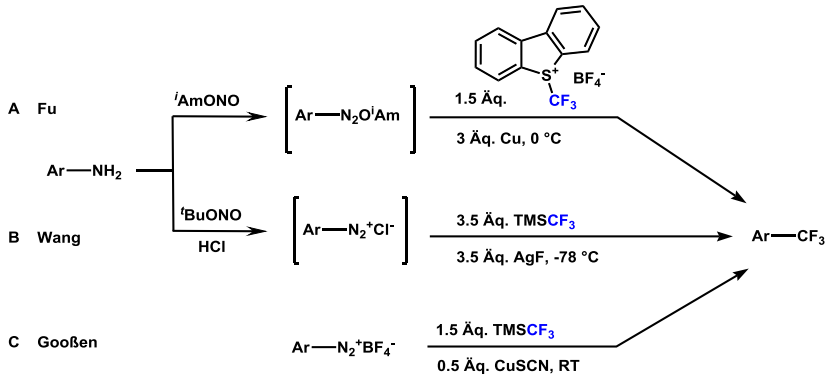
Die Sandmeyer-Reaktion stellt eine nachhaltige Methode zur Einführung von Nukleophilen in aromatische Verbindungen dar. Die hohe Toleranz gegenüber funktionellen Gruppen und die milden Reaktionsbedingungen machen sie- und konzeptionell ähnliche Methoden attraktiv in der organischen Synthese. Weiterhin spart die Nutzung von aromatischen Aminen gegenüber den üblicherweise genutzten Arylhalogeniden mindestens eine Stufe in der Synthesesequenz, i.e. die Sandmeyer-Halogenierung von Diazoniumsalzen. Der einzige Nachteil der Reaktion ist der Einsatz stöchiometrischer Mengen an Kupfer. In den letzten Jahren wurden hier jedoch erhebliche Fortschritte gemacht, sodass die Bromierung, Cyanierung und Thiocyanierung schon mit katalytischen Mengen an Kupfer erfolgen können.[99,100] Dies wurde durch ein effektives Cu(I)/Cu(II)-System (jeweils 10 Mol%) und den Einsatz von Kronenether Liganden, welche stabilisierende Effekte auf die Nukleophile ausüben, ermöglicht (Schema 32, **A**). Das Konzept der Sandmeyer-Reaktion wurde auf

Borylierung (**B**) und Stannylierung (**C**) erweitert.[101,102] Die Trifluormethylthiolierung ausgehend von präformiertem Kupfertrifluormethylthiolat wurde von Clark *et al.* berichtet (**D**), wobei sich die Anwendungsbreite dieser Methode nur auf elektronenarme Aniline und ihre korrespondierenden Aryldiazoniumsalze beschränkte.[103] Dies spricht dafür, dass die Reaktion nicht über die klassische Sandmeyer-Route verläuft, sondern höchstwahrscheinlich über eine nukleophile aromatische Substitution.



Schema 32. Sandmeyer-ähnliche Reaktionen.

In den Forschungsgruppen von Gooßen, Fu und Wang wurden unabhängig voneinander Sandmeyer-analoge Trifluormethylierungsmethoden entwickelt (**E**).[104]



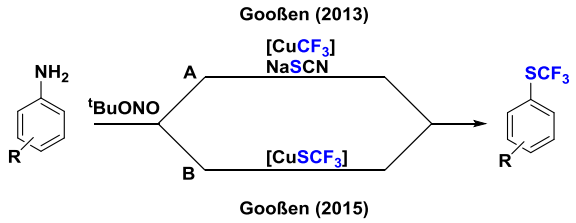
Schema 33. Sandmeyer-Trifluormethylierungen.

Die Methode, entwickelt von Fu und seinen Mitarbeiter, setzte aromatische Amine in Gegenwart von elementarem Kupfer mit elektrophilem CF_3-Reagenz unter oxidativen Bedingungen um (Schema 33, **A**). Wang generierte $AgCF_3$ aus AgF und $TMSCF_3$ und setzte diese mit *in situ* generierten Diazoniumsalzen weiter um (**B**). Im Arbeitskreis von Gooßen

wurde eine direkte Sandmeyer Trifluormethylierungsmethode entwickelt(**C**). $CuCF_3$ wurde aus $TMSCF_3$ und Kupferthiocyanat (CuSCN) *in situ* generiert, welches anschließend mit dem präformierten Diazoniumsalzen umgesetzt wurde. Der klare Vorteil der Methoden von Fu und Wang ist die direkte Umsetzung der Amine in ihre Benzotrifluoride, während die Methode von Gooßen den Einsatz der präformierten Diazoniumsalze erfordert. Der Einsatz von teurem Umemoto`s Reagenz oder überschüssigem Silbersalz machen die Anwendung dieser Methoden allerdings extrem kostspielig.

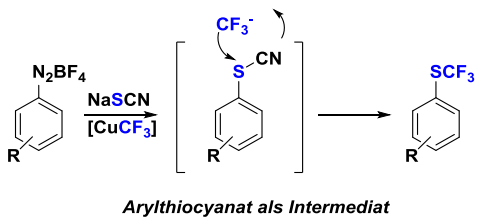
Nach der erfolgreichen Entwicklung der Sandmeyer-ähnlichen Methode zur Trifluormethylierung von Diazoniumsalzen wurde die Einführung der Trifluormethylthiolgruppen in Aryldiazoniumsalze im Arbeitskreis von Gooßen untersucht.

Basierend auf dem Bericht von Clark wurden zwei unterschiedliche Strategien in Erwägung gezogen (Schema 34). Einerseits eine Methode in der die SCF_3-Einheit sequentiell aus unterschiedlichen Reagenzien *in situ* eingeführt (**A**) und zum anderen eine Übertragung der SCF_3-Einheit als Ganzes (**B**).



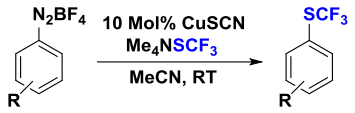
Schema 34. Sandmeyer-ähnliche Trifluormethylthiolierungen.

In der sequentiellen Strategie wird nach der *in situ* Thiocyanierung, das Schwefelzentrum mittels ebenfalls *in situ* generiertem Kupfertrifluormethylat $CuCF_3$ trifluormethyliert (Schema 35). Es werden 50 Mol% Kupferthiocyanat als Katalysator benötigt um die CF_3-Anion vollständig zu stabilisieren. Die Besonderheit dieser Methode ist, dass kommerziell verfügbares, nachhaltig herstellbares Rupperts Reagenz $TMSCF_3$ und günstiges Natriumthiocyanatsalz (NaSCN) bei Raumtemperatur umgesetzt werden. Deshalb eignet sich diese Methode besonders gut für Scale-Up Prozesse.



Schema 35. Sequentielle Sandmeyer-Trifluormethylthiolierungen.

Die direkte Sandmeyer Reaktion verläuft nach dem klassischem Sandmeyer Mechanismus, in dem die Kupfertrifluomethylthiolat Spezies involviert ist (Schema 36). Das Tetramethylammoniumtrifluormethylthiolat Salz (Me_4NSCF_3) reagiert in Gegenwart von 10 Mol% Kupferthiocyanat mit dem Diazoniumsalz. Die Besonderheit dieser Methode ist, dass deutlich weniger Kupfer benötigt wird, da es ausschließlich als ein Einelektronentransfer-Katalysator dient. Diese Methode eignet sich besonders gut für schnelle Screeningreaktionen im Labormaßstab.



Schema 36. Direkte Sandmeyer-Trifluormethylthiolierungen.

2.3 Herausforderungen und offene Probleme

2.3.1 Einsatz der Interhalogenverbindungen als Fluoralkylquelle

Die starke Nachfrage an fluoralkylierten Substraten führte in den letzten Jahren zu einer immensen Entwicklung an Fluoralkylierungsmethoden insbesondere im Bereich der Trifluormethylierung. Zunächst bestand das Hauptaugenmerk der Forschung auf der Synthese der wertvollen fluorierten Substrate ohne dabei die Nachhaltigkeit der Reaktionskonzepte zu berücksichtigen. So wurden hauptsächlich Methoden entwickelt, in denen Interhalogenverbindungen eingesetzt wurden. Insbesondere Fluorchlorkohlenwasserstoffe (FCKW), welche zu den langlebigen, anthropogenen, ozonschädigenden Treibhausgasen gehören. Zwar haben sich die Unterzeichnerstaaten im Montrealer Protokoll verpflichtet, die Emission der ozonzerstörenden Chemikalien zu minimieren, jedoch können Folgeprodukte, die aus FCKWs erzeugt werden, weiterhin verwendet werden.

2.3.2 Fluoroform ein ungenutztes Abfallprodukt der Teflonindustrie

Die Herstellung von Tetrafluorethylen, der Grundbaustein von Teflon, erfordert die Synthese von Chlordifluormethan (CHClF2, HCFC-22, R-22) als Ausgangsverbindung. Diese wird industriell durch Fluorierung von Chloroform mit Flusssäure (HF), in der sog. Swarts-Reaktion, hergestellt. Hierbei entsteht Fluoroform aufgrund der Überfluorierung als Nebenprodukt. Auch wenn der Fluoroformanteil bei diesem Verfahren im Verhältnis zum gewünschten Produkt prozentual gering ist, fallen allein durch die Synthese von HCFC-22 weltweit tausende Tonnen Fluoroform an. Schätzungen zufolge werden bis zum Jahr 2015

über 24.000 Tonnen Fluoroform zirkuliert.[105] Der industrielle Einsatz des Fluoroforms als Synthesebaustein ist im Vergleich zu dessen anfallender Menge nicht annähernd angemessen.

Die geringe Reaktivität des Fluoroforms erschwert dessen umweltgerechte Entsorgung.[106] Nur durch eine vollständige Verbrennung mittels thermischer Oxidation, katalytischer Hydrolyse oder Plasmavergasung ist eine nachhaltige Entsorgung möglich. Die Nachteile dieser Verfahren liegen im hohen Energieverbrauch, der Notwendigkeit von speziellen Materialien, welche bei einer Ofentemperatur von 1200 °C in Gegenwart der stark korrosiver Flusssäure standhalten, dem Einsatz teurer Katalysatoren und der möglichen Erzeugung hochgiftiger Fluorphosgene. Zudem produziert die Neutralisation der Flusssäure große Mengen anorganischer Fluoridsalze.

Es wäre weitaus vorteilhafter, das anfallende Fluoroform als CF_3-Baustein für die organische Synthese nutzbar zu machen. Insbesondere, da letzteres häufig aus eigens dafür erzeugten, ozonschädlichen Fluorhalogenkohlenwasserstoffen hergestellt werden. Angesichts der kontinuierlich steigenden Nachfrage nach fluorierten Wirkstoffen und Funktionsmaterialien ergäbe sich durch die Entwicklung fluoroformbasierter Synthesen zwei entscheidende Vorteile: 1) Die aufwendige Entsorgung von Fluoroformabfällen wäre bei einer Vermarktungsmöglichkeit des Materials nicht mehr notwendig, wodurch auch die Versuchung wegfiele, Produktionskosten durch dessen illegale Freisetzung zu vermindern. 2) Die Produktion von Fluorhalogenkohlenwasserstoffen in Nicht-Montreal-Staaten als Rohstoff für Trifluormethylierungsreagenzien wäre nicht mehr lukrativ.

3 Aufgabenstellung

Das Ziel dieses Dissertationsvorhabens war die rationale Entwicklung umweltfreundlicher atomeffizienter Methoden zur regioselektiven Einführung von Fluoralkyl(thiol)gruppen in organische Moleküle. Anstelle von ozonschädlichen Fluorhalogenkohlenwasserstoffen soll dabei Fluoroform (HFC-23) und dessen Folgeprodukte wie z.B. $TMSCF_3$ oder $KB(OMe)_3CF_3$ als Quelle der Fluoralkylgruppen dienen.

Aufbauend auf meiner Diplomarbeit war das Ziel zunächst die Sandmeyer Fluoralkylierungsmethoden hin zu einem Eintopfverfahren zu optimieren. Dabei war das Ziel die Verwendung von *in situ* diazotierten aromatischen Aminen, die sowohl die Isolierung, als auch die Handhabung der chemisch reaktiven Diazoniumsalze als Zwischenstufe ersparen. Anschließend sollte die Anwendungsbreite bestimmt werden.

Weiterhin lag das Hauptaugenmerk darauf das Sandmeyer–analoge Reaktionskonzept auf weitere wichtige Fluoralkyl(thiol)gruppen, wie beispielsweise CF_2H, SCF_2H, oder SC_2F_5, zu erweitern und im Erfolgsfall die Anwendungsbreite zu bestimmen.

4 Ergebnisse

4.1 Eintopf-Sandmeyer-Reaktion – CF_3 und SCF_3

Das Ziel dieses Teilprojekts bestand in der konsequenten Fortsetzung der Ergebnisse meiner Diplomarbeit zu Sandmeyer-artigen Trilfuormethyl- und Trifluormethylthiolierungen.[104] [107] Im Rahmen dieser Arbeit sollten diese Methoden weiter im Hinblick auf Atomeffizienz und Anwendbarkeit für Scale-Up Prozesse optimiert werden. Dafür sollten Untersuchungen zur *in situ* Generierung der Diazoniumsalze (Diazotierung) erfolgen. Als Testsystem wurde 4-Methoxyanilin in Gegenwart diverser Säuren unter jenen Reaktionsbedingungen umgesetzt, die sich bei den vorherigen Methoden als optimal bewährt hatten.

Die Optimierung des Katalysatorsystems sowie die Untersuchung der Anwendungsbreite dieser Methode erfolgten zu gleichen Teilen mit Herrn C. Matheis. Herr E. Risto unterstütze uns bei der Auftrennung einiger Verbindungen. Das Manuskript verfasste ich zusammen mit Herrn Prof. Dr. L. J. Gooßen, während Herr C. Matheis die analytischen Daten auswertete und die Supporting Information erstellte.

Die Ergebnisse wurden 2014 in den Zeitschriften *Advanced Synthesis and Catalysis* veröffentlicht.[108] Teile dieser Arbeit wurden zusammen mit den vorherigen Ergebnissen zur Sandmeyer-Trifluormethylierung ausgehend von Diazoniumsalzen in der Zeitschrift *Synthesis* zusammengefasst.[109] Dabei unterstützte ich Herrn Dr. G. Danoun, Herrn C. Matheis, Herrn M. F. Grünberg und Herrn Prof. Dr. L. J. Gooßen beim Verfassen des Manuskripts. Kopien der jeweiligen Manuskripte sind angepasst und mit Erlaubnissen der John Wiley & Sons, Inc. Bzw. Thieme nachfolgend beigefügt.

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One-Pot Sandmeyer Trifluoromethylation and Trifluoromethylthiolation

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Abstract: Practical one-pot procedures were developed for both Sandmeyer-type trifluoromethylations and trifluoromethylthiolations. Starting from broadly available (hetero)aromatic amines, various benzotrifluorides were synthesized in high yields *via in situ* diazotization and copper-mediated trifluoromethylation using the inexpensive Ruppert–Prakash trifluoromethylating reagent. In the presence of sodium thiocyanate as a sulfur source, aryl trifluoromethyl thioethers are exclusively formed.

Keywords: anilines; copper; Sandmeyer reaction; trifluoromethylation; trifluoromethylthiolation

Fluorinated residues impart unique chemical and physical properties to organic molecules, including improved metabolic stability, better receptor binding selectivity, higher lipophilicity, and stronger dipole moments compared to their non-fluorinated analogs.[1] In research labs and chemical industry, trifluoromethyl[2] and trifluoromethylthio[3] groups are widely employed and can be found, for example, in the pharmaceuticals celecoxib, dutasteride, fluoxetine, sitagliptin, and tiflorex, the veterinary product toltrazuril and the agrochemicals beflubutamid, diflufenican, norflurazon and vaniliprole (Figure 1).

Traditional approaches to the synthesis of benzotrifluorides[4] and aryl trifluoromethyl thioethers,[5] such as the Swarts reaction, require harsh conditions and display limited substrate scope. McLoughlin, Yagupolskii, Burton, Chambers, Grushin and others have pioneered selective late-stage Cu- and Pd-mediated trifluoromethylation methods.[6] Numerous new protocols have followed that may be subdivided into five types. (i) Cu or Pd complexes mediate the coupling of aryl halides with nucleophilic CF_3-reagents such as Ruppert–Prakash reagent (CF_3SiMe_3),[7] fluoroform,[8] potassium (trifluoromethyl)trimethoxyborate,[9] trifluoroacetate salts[5e,10] methyl trifluoroacetate,[11] or fluorosulfonyldifluoroacetic acid.[12] (ii) Pd catalyzes the C–H trifluoromethylation of arenes, e.g., with Umemoto's reagent[13] or perfluoroalkyl iodides.[14] Under oxidative conditions, heteroarenes undergo C–H trifluoromethylations with nucleophilic trifluoromethylation reagents.[15] (iii) Aryl nucleophiles such as arylboronic acids can be coupled with electrophilic CF_3 sources, for example, Togni's or Umemoto's reagent,[16] or radical reagents, such as trifluoroiodomethane or Langlois' reagent.[17] (iv) Oxidative couplings of aryl nucleophiles, e.g., boronic acids, with nucleophilic CF_3 reagents {CF_3SiMe_3 or $K^+[CF_3B(OMe)_3]^-$} proceed with Cu catalysis.[18] (v) Radical trifluoromethylations of arenes can be performed, for example, with peroxide or Ru initiators.[19]

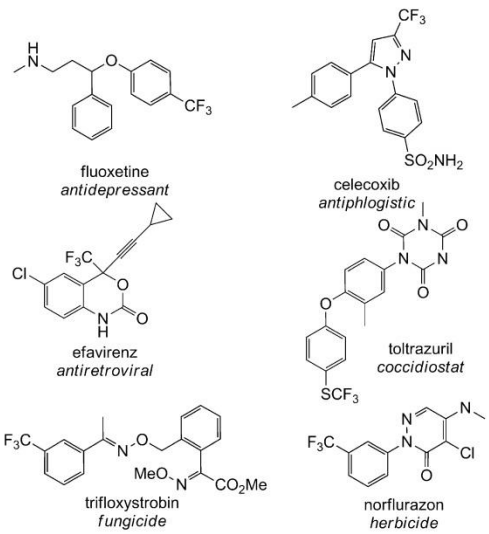
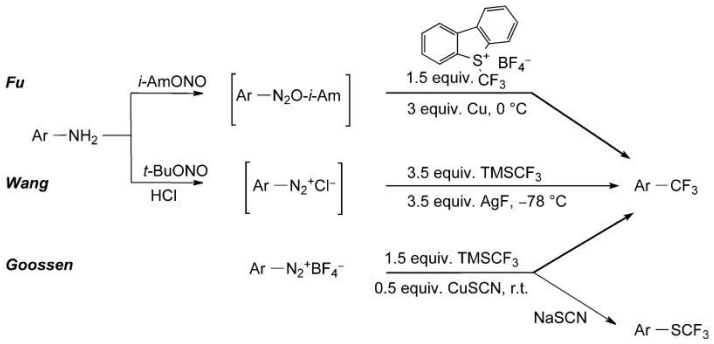


Figure 1. Trifluoromethyl(thiol)ated bioactive substances.



Scheme 1. Sandmeyer-type trifluoromethylations and trifluoromethylthiolations.

Similarly, trifluoromethylthiolations[20] can be divided into (i) electrophilic (e.g., reactions of CF_3-sulfonamides with aryl-Mg or aryl-Li species, Cu-mediated coupling of arylboronic acids with hypervalent iodine-SCF_3 reagents),[21] (ii) nucleophilic (e.g., the Pd-catalyzed trifluoromethylthiolation of aryl halides with $AgSCF_3$, Ni-catalyzed couplings of aryl halides or some electron-poor diazonium salts with Me_4NSCF_3 or $CuSCF_3$),[22] and (iii) radical cross-couplings (e.g., the Cu-mediated *ortho*-trifluoromethylthiolation of benzamides with CF_3S-SCF_3),[23] as well as (iv) oxidative cross-couplings (e.g., of boronic acids with $TMSCF_3$ and S_8).[24]

As an alternative to these methods, Sandmeyer-type trifluoromethylations were almost simultaneously disclosed by Fu,[25] Wang[26] and ourselves[27] (Scheme 1). Their key advantage is that they draw on aromatic amines, widely available in great structural diversity, as the aryl source.[28] In Fu's protocol, the diazonium salts are generated *in situ* by diazotization of the corresponding anilines, and reductively coupled with Umemoto's reagent in the presence of 3 equiv. elemental copper. In Wang's method, diazonium salts are generated from *tert*-butyl nitrite and HCl, and are coupled with excess $AgCF_3$, prepared from AgF at −78 °C. In our method, preformed diazonium tetrafluoroborates are coupled with $TMSCF_3$ in the presence of 0.5 equiv. of copper thiocyanate and 1.5 equiv. cesium carbonate at room temperature to give the corresponding benzotrifluorides. When adding the sulfur source sodium thiocyanate to the reaction mixture, aryl trifluoromethyl thioethers are obtained, which further amplifies the synthetic potential of this reaction concept.[29]

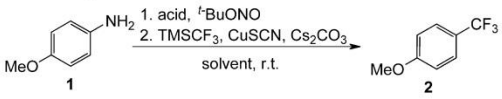
The advantage of the Wang and Fu protocols is that they give high yields even if the diazotization is performed *in situ*. D. L. Browne, who compared the three protocols in a highlight article, views Fu's method as the most straightforward for this reason.[30] However, it is based on the exceedingly expensive Umemoto reagent (47 €/mmol)[31] and calls for overstoichiometric amounts of copper. The advantage of Wang's and our protocols is the use of inexpensive $TMSCF_3$ (0.25 €/mmol).[32] This reagent is also more environmentally benign, since it has been shown to be accessible directly from fluoroform, a by-product in the Teflon production.[33] On the downside, Wang's protocol calls for a large excess of sensitive and costly $AgCF_3$, while our method suffers from the necessity to generate the diazonium salt in an extra step.

In order to unleash the full synthetic potential of this innovative approach, the above drawbacks needed to be overcome and an operationally simple, economically and ecologically advantageous protocol was clearly required. It would be ideal if an *in situ* generation of the diazonium salts from the corresponding anilines could be added to the advantageous features of our initial method (substoichiometric copper, inexpensive trifluoromethylating reagent, room temperature).

Unfortunately, we had been plagued with unsatisfactorily low yields when attempting to generate the diazonium salts *in situ* from various reagents. The acid-free diazotization with *iso*-amyl nitrite, as was successfully employed by Fu et al. in their reductive coupling, was ineffective in our redox-neutral coupling. This can be explained by the formation of the nitrosonium cation requiring acidic conditions,[28] whereas a mild base is essential to generate $CuCF_3$ species from the Ruppert–Prakash reagent.[34]

In search for conditions that would efficiently promote the diazotization step without impeding the formation of $CuCF_3$ intermediates, we chose the reaction of 4-methoxyaniline with the easily available diazotization reagent *tert*-butyl nitrite to systematically investigate the *in situ* diazotization–trifluoromethylation sequence (Table 1). We were delighted to find that a promising yield was obtained in the presence of *p*TSA (entry 1) and trifluoroacetic acid (TFA) (entry 2).

Table 1. Optimization of the reaction conditions.[a]



Entry	Acid[b]	Equiv. Acid	Solvent	Yield of **2** [%]
1	*p*TSA·H_2O	2.0	MeCN	72
2	TFA	2.0	MeCN	70
3	ethereal·HCl	2.0	MeCN	39
4	acetic acid	2.0	MeCN	27
5	MSA	2.0	MeCN	49
6	TCA	2.0	MeCN	58
7	BSA	2.0	MeCN	67
8	*p*TSA	2.0	MeCN	80
9	*p*TSA	1.5	MeCN	98
10	*p*TSA	1.1	MeCN	70
11	TFA	1.5	MeCN	71
12	*p*TSA	1.5	acetone	76
13	*p*TSA	1.5	DMF	56
14	*p*TSA	1.5	DMSO	53

[a] *Conditions*: $TMSCF_3$ (0.75 mmol), CuSCN (0.25 mmol), Cs_2CO_3 (0.75 mmol), acetonitrile (1 mL), 10 min, room temperature, followed by dropwise addition of aromatic amine (0.50 mmol), *tert*-butyl nitrite (0.50 mmol), and acid (1.00 mmol) in acetonitrile (1 mL), 12 h, room temperature. Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard.

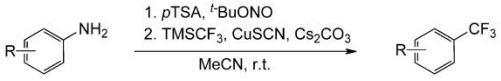
[b] *p*TSA = *para*-toluenesulfonic acid, TFA = trifluoroacetic acid, MSA = methanesulfonic acid, TCA = trichloroacetic acid, BSA = benzenesulfonic acid, TMS = trimethylsilyl.

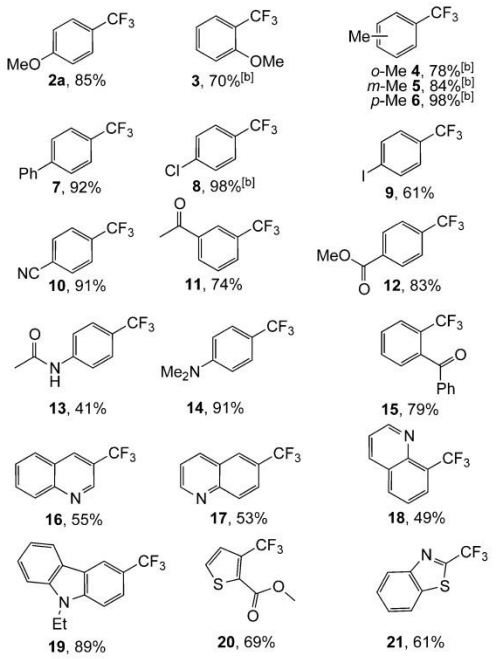
Other acids were less effective (entries 3–7). A step-up in the yields was obtained when anhydrous *p*TSA was used instead of the commonly used monohydrate (entry 8). The amount of acid also strongly influences the reaction outcome. The best results were obtained with 1.5 equivalents, whereas with 1 or 2 equivalents, the yields dropped significantly (entries 8–10). Among the solvents screened, acetonitrile was found to be the most effective (entries 12–14).

In the optimal protocol, 1 equiv. *tert*-butyl nitrite is added to a slurry of aniline **1** and 1.5 equiv. anhydrous *p*TSA in acetonitrile. After the diazotization is complete, the resulting solution is slowly added to a mixture of copper thiocyanate, cesium carbonate and $TMSCF_3$. In this way, the corresponding benzotrifluoride is formed in near quantitative yields within a few hours.

The scope of this convenient one-pot procedure was investigated using diversely substituted aromatic amine substrates (Table 2). A broad range of benzotrifluorides was thus synthesized in good to excellent yields. Both electron-rich and electron-deficient substrates gave similarly high yields, and various functionalities were tolerated, including ester, ether, amino, amido, keto, cyano, and even iodo groups.

Table 2. Substrate scope of the Sandmeyer trifluoromethylation.[a]





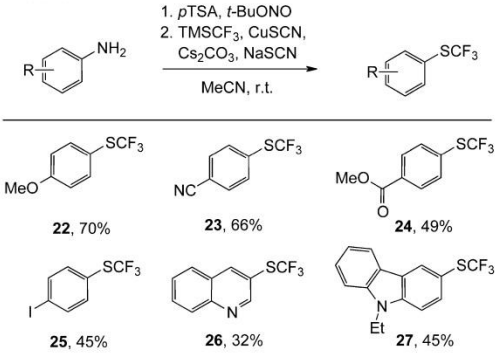
[a] *Conditions*: $TMSCF_3$ (1.50 mmol), CuSCN (0.50 mmol), Cs_2CO_3 (1.50 mmol), acetonitrile (2 mL), 10 min, room temperature, followed by dropwise addition of aromatic amine (1.00 mmol), *tert*-butyl nitrite (1.00 mmol), and *p*TSA (1.50 mmol) in acetonitrile (2 mL), 12 h, room temperature, isolated yields.

[b] Determined by ^{19}F NMR using trifluoroethanol as an internal standard.

Heterocyclic amines were also converted in high yields. Most products were obtained in sufficiently pure form to permit simple isolation. The successful synthesis of **2a** in 81% yield on an 8 mmol scale demonstrates the scalability of the process.

Encouraged by these results, we next investigated whether the *in situ* diazotization could also be combined with our Sandmeyer trifluoromethylthiolation reaction according to the Scheme in Table 3.[29] We thus subsequently added the diazonium salt solution generated from 4-methoxyaniline (**1**) and $TMSCF_3$ to a mixture of copper thiocyanate, cesium carbonate

Table 3. Substrate scope of the Sandmeyer trifluoromethylthiolation.[a]



[a] *Conditions*: NaSCN (1.50 mmol), CuSCN (1.00 mmol), acetonitrile (2 mL), 10 min, room temperature, followed by dropwise addition of aromatic amine (1.00 mmol), *tert*-butyl nitrite (1.00 mmol), and *p*TSA (1.50 mmol) in acetonitrile (2 mL), 15 min. Then addition of Cs_2CO_3 (4.00 mmol) and $TMSCF_3$ (1.50 mmol), 12 h, room temperature, isolated yields.

and sodium thiocyanate. To our delight, the trifluoromethylthiolated product **22** was formed in significant amounts. After careful optimization of the reaction conditions (see the Supporting Information), the yield of this one-pot diazotative trifluoromethylthiolation could be increased to a satisfactory 74% based on the aniline starting material.

In the optimal protocol, 1 equiv. *tert*-butyl nitrite is added to a slurry of aniline **1** and 1.5 equiv. anhydrous *p*TSA in acetonitrile. After the diazotization is complete, the resulting solution is slowly added to a mixture of copper thiocyanate and sodium thiocyanate. Subsequently, cesium carbonate and $TMSCF_3$ are added and the reaction is stirred for 12 h at room temperature. The examples in Table 3 confirm that this straightforward protocol is broadly applicable to the synthesis of (hetero)aryl trifluoromethyl thioethers from aromatic and heteroaromatic amines. It extends even to nitrogen heterocycles and tolerates sensitive iodo and ester groups. The yields were somewhat lower than when starting from diazonium salts, which is due to competing protodediazotation in the thiocyanation step.

In conclusion, straightforward, economically and ecologically advantageous one-pot protocols were developed for both Sandmeyer-type trifluoromethylations and trifluoromethylthiolations. They open up versatile synthetic entries to important substrate classes starting directly from widely available (hetero)aromatic amines and using reagents and solvents straight from commercial suppliers. Future work will be directed at lowering the copper loading by employing stabilizing ligands.

Experimental Section

Synthesis of Benzotrifluorides

An oven-dried 20-mL crimp-cap vessel with Teflon-coated stirrer bar was charged with the amine (1.00 mmol), *para*-toluenesulfonic acid (258 mg, 1.50 mmol) and acetonitrile (2 mL) under nitrogen. *tert*-Butyl nitrite (133 μL, 1.00 mmol) was added dropwise *via* syringe. The resulting solution was stirred at room temperature for 30 min and afterwards added dropwise to a suspension of copper thiocyanate (61.0 mg, 0.50 mmol), cesium carbonate (489 mg, 1.50 mmol) and trifluoromethyltrimethylsilane (240 μL, 1.50 mmol) in acetonitrile (2 mL) that had been stirred at room temperature for 10 min. The resulting suspension was stirred at room temperature for a further 12 h. The resulting mixture was filtered through a short pad of celite (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (2×10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient), yielding the corresponding benzotrifluorides.

Synthesis of Aryl Trifluoromethyl Thioethers

An oven-dried 20-mL crimp-cap vessel with Teflon-coated stirrer bar was charged with the amine (1.00 mmol), *para*-toluenesulfonic acid (258 mg, 1.50 mmol) and acetonitrile (2 mL) under nitrogen. *tert*-Butyl nitrite (133 μL, 1.00 mmol) was added dropwise *via* syringe. The resulting solution was stirred at room temperature for 30 min and afterwards added dropwise to a suspension of copper thiocyanate (123 mg, 1.00 mmol) and sodium thiocyanate (122 mg, 1.50 mmol) in acetonitrile (1 mL). The resulting suspension was stirred at room temperature for 30 min and added to a suspension of cesium carbonate (652 mg, 4.00 mmol) in acetonitrile (1 mL). Finally, trifluoromethyltrimethylsilane (240 μL, 1.50 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The resulting mixture was filtered through a short pad of celite (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (2×10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient), yielding the corresponding aryl trifluoromethyl thioethers.

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References

[1] a) T. Yamazaki, T. Tagauchi, I. Ojima, in: *Fluorine in Medicinal Chemistry and Chemical Biology*, (Ed.: I. Ojima), Wiley-Blackwell, Chichester, **2009**, pp 3–46; b) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; c) L. M. Yagupol'skii, A. Y. Il'chenko, N. V. Kondratenko, *Russ. Chem. Rev.* **1974**, *43*, 32–47.

[2] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

[3] a) A. Harder, A. Haberkorn, *Parasitol Res.* **1989**, *76*, 8–12; b) J. Stetter, F. Lieb, *Angew. Chem.* **2000**, *112*, 1792–1812; *Angew. Chem. Int. Ed.* **2000**, *39*, 1724–1744.

[4] Selected examples for traditional trifluoromethylation methods: a) F. Swarts, *Bull. Acad. R. Belg.* **1892**, *24*, 309–314; b) J. H. Simons, C. J. Lewis, *J. Am. Chem. Soc.* **1938**, *60*, 492–492; c) G. A. Boswell, W. C. Ripka, R. M. Scribner, C. W. Tullock, *Org. React.* **1974**, *21*, 30–44; d) H. Sawada, M. Nakayama, M. Yoshida, T. Yoshida, N. Kamigata, *J. Fluorine Chem.* **1990**, *46*, 423–431.

[5] Selected examples for traditional trifluoromethylthiolation methods: a) N. N. Yarovenko, A. S. Vasileva, *J. Gen. Chem. USSR (Engl. Transl.)* **1958**, *28*, 2537–2539; b) E. A. Nodiff, S. Lipschutz, P. N. Craig, M. Gordon, *J. Org. Chem.* **1960**, *25*, 60–65; c) A. E. Feiring, *J. Org. Chem.* **1979**, *44*, 2907–2910; d) C. Wakselman, M. Tordeux, *J. Org. Chem.* **1985**, *50*, 4047–4051; e) T. Billard, S. Large, B. R. Langlois, *Tetrahedron Lett.* **1997**, *38*, 65–68; f) C. Wakselman, M. Tordeux, J.-L. Clavel, B. R. Langlois, *J. Chem. Soc. Chem. Commun.* **1991**, 993–994; g) B. Quiclet-Sire, R. N. Saicic, S. Z. Zard, *Tetrahedron Lett.* **1996**, *37*, 9057–9058; h) N. Roques, *J. Fluorine Chem.* **2001**, *107*, 311–314; i) G. Blond, T. Billard, B. R. Langlois, *Tetrahedron Lett.* **2001**, *42*, 2473–2475.

[6] Reviews on trifluoromethylations: a) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; c) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744–1754; d) Z. Jin, G. B. Hammond, B. Xu, *Aldrichimica Acta* **2012**, *45*, 67–83; e) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2014**, DOI: 10.1021/cr400473a; copper-mediated trifluoromethylations: f) T. Liu, Q. Shen, *Eur. J. Org. Chem.* **2012**, *2012*, 6679–6687; g) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem.* **2013**, *125*, 8372–8423; *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264.

[7] a) H. Urata, T. Fuchikami, *Tetrahedron Lett.* **1991**, *32*, 91–94; b) G. G. Dubinina, H. Furutachi, D. A. Vicic, *J. Am. Chem. Soc.* **2008**, *130*, 8600–8601; c) G. G. Dubinina, J. Ogikubo, D. A. Vicic, *Organometallics* **2008**, *27*, 6233–6235.

[8] A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *J. Am. Chem. Soc.* **2011**, *133*, 20901–20913.

[9] T. Knauber, F. Arikan, G.-V. Röschenthaler, L. J. Goossen, *Chem. Eur. J.* **2011**, *17*, 2689–2697.

[10] K. A. McReynolds, R. S. Lewis, L. K. G. Ackerman, G. G. Dubinina, W. W. Brennessel, D. A. Vicic, *J. Fluorine Chem.* **2010**, *131*, 1108–1112.

[11] a) B. R. Langlois, N. Roques, *J. Fluorine Chem.* **2007**, *128*, 1318–1325; b) T. Schareina, X.-F. Wu, A. Zapf, A. Cotté, M. Gotta, M. Beller, *Top. Catal.* **2012**, *55*, 426–431.

[12] Q. Y. Chen, S. W. Wu, *J. Chem. Soc. Chem. Commun.* **1989**, 705–706.

[13] X. Wang, L. Truesdale, J. Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3648–3649.

[14] R. N. Loy, M. S. Sanford, *Org. Lett.* **2011**, *13*, 2548–2551.

[15] L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 1298–1304.

[16] a) T. Liu, Q. Shen, *Org. Lett.* **2011**, *13*, 2342–2345; b) J. Xu, D. Luo, B. Xiao, Z. Liu, T. Gong, Y. Fu, L. Liu, *Chem. Commun.* **2011**, *47*, 4300–4302.

[17] a) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2012**, *134*, 9034–9037; b) Y. Ye, S. A. Künzi, M. S. Sanford, *Org. Lett.* **2012**, *14*, 4979–4981.

[18] a) L. Chu, F.-L. Qing, *Org. Lett.* **2010**, *12*, 5060–5063; b) B. A. Khan, A. E. Buba, L. J. Goossen, *Chem. Eur. J.* **2012**, *18*, 1577–1581.

[19] a) B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1991**, *51*, 7525–7528; b) J.-B. Tommasino, A. Brondex, M. Médebielle, M. Thomalla, B. R. Langlois, T. Billard, *Synlett* **2002**, 1697–1699; c) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95–99; d) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224–228.

[20] F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415–2428.

[21] a) F. Baert, J. Colomb, T. Billard, *Angew. Chem.* **2012**, *124*, 10528–10531; *Angew. Chem. Int. Ed.* **2012**, *51*, 10382–10385; b) X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem.* **2013**, *125*, 3620–3620; *Angew. Chem. Int. Ed.* **2013**, *52*, 3457–3460.

[22] a) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 7450–7452; *Angew. Chem. Int. Ed.* **2011**, *50*, 7312–7314; b) C.-P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183–185; c) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem.* **2013**, *125*, 1588–1592; *Angew. Chem. Int. Ed.* **2013**, *52*, 1548–1552; d) D. J. Adams, A. Goddard, J. H. Clark, D. J. Macquarrie, *Chem. Commun.* **2000**, 987–988.

[23] L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237–18240.

[24] a) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem.* **2012**, *124*, 2542–2545; *Angew. Chem. Int. Ed.* **2012**, *51*, 2492–2495; b) C. Chen, L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 12454–12457; c) C.-P. Zhang, D. A. Vicic, *Chem. Asian J.* **2012**, *7*, 1756–1758.

[25] J.-J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z.-J. Liu, X. Lu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 8436–8439.

[26] X. Wang, Y. Xu, F. Mo, G. Ji, D. Qiu, J. Feng, Y. Ye, S. Zhang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 10330–10333.

[27] G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Goossen, *Angew. Chem.* **2013**, *125*, 8130–8133; *Angew. Chem. Int. Ed.* **2013**, *52*, 7972–7975.

[28] a) J. K. Kochi, *J. Am. Chem. Soc.* **1957**, *79*, 2942–2948; b) C. Galli, *Chem. Rev.* **1988**, *88*, 765–792.

[29] G. Danoun, B. Bayarmagnai, M. F. Gruenberg, L. J. Goossen, *Chem. Sci.* **2014**, *5*, 1312–1316.
[30] D. L. Browne, *Angew. Chem.* **2014**, *126*, 1506–1508; *Angew. Chem. Int. Ed.***2014**, *53*, 1482–1484.
[31] Umemeoto's reagent is available from Sigma Aldrich.
[32] $TMSCF_3$ is available from ABCR.
[33] a) G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324–1327; b) S. Large, N. Roques, B. R. Langlois, *J. Org. Chem.* **2000**, *65*, 8848–8856.
[34] G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757–786.

PRACTICAL SYNTHETIC PROCEDURES 2283

Sandmeyer Trifluoromethylation

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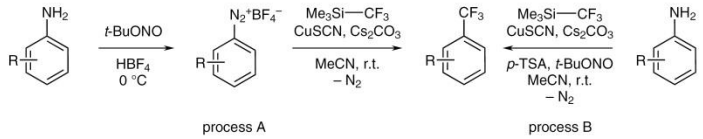
Abstract: A range of benzotrifluorides are conveniently accessible in high yields from widely available (hetero)aromatic amines and the inexpensive trifluoromethylating agent $TMSCF_3$ through a copper-mediated Sandmeyer trifluoromethylation reaction. Two practical procedures are presented. In the first, the diazonium salts are preformed in an extra reaction step, in the second approach the diazotization and the trifluoromethylation are combined into a one-pot procedure.

Key words: anilines, copper, Sandmeyer reaction, trifluoromethylation, diazonium salts



Scheme 1 Sandmeyer trifluoromethylation

Introduction

Trifluoromethyl groups impart unique chemical and physical properties to organic molecules, including improved metabolic stability, better receptor binding selectivity, higher lipophilicity, and stronger dipole moments compared with their nonfluorinated analogues.[1]

Traditional approaches for the synthesis of benzotrifluorides,[2] such as the Swarts reaction, require harsh conditions and display limited substrate scope. Based on pioneering studies by McLoughlin, Yagupolskii, Burton, Chambers, Grushin, and others, various selective copper- and palladium-mediated trifluoromethylation methods have been developed in recent years.[3]

In this context, several Sandmeyer type trifluoromethylations were disclosed almost simultaneously by the groups of Fu,[4] Wang,[5] and us.[6] The reactions are based on aromatic amines, which are widely available in great structural diversity, which is a distinct advantage over other trifluoromethylation methods.[7] Moreover, most chemists are familiar with Sandmeyer reactions since their undergraduate laboratory training and will not hesitate to add such trifluoromethylations to their chemical toolbox. In the new processes, the aniline diazotization and trifluoromethylation steps can optionally be combined into a one-pot process.

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Whereas the protocols developed by Wang and Fu are based on costly Umemoto reagent or preformed $AgCF_3$, our method employs the inexpensive Ruppert–Prakash reagent TMS-CF_3. This reagent has been shown to be accessible directly from fluoroform, which is a byproduct of Teflon production.[8]

Sequential Diazotization / Trifluoromethylation

In this procedure, arenediazonium tetrafluoroborates are synthesized from *tert*-butyl nitrite (2 equiv) and the corresponding amine in aqueous HBF_4 (2 equiv) at 0 °C. After stirring for one hour, diethyl ether is added to precipitate the diazonium salts, which are then isolated by simple filtration.

For their trifluoromethylation, the diazonium salts are dissolved in anhydrous acetonitrile (2 mL) and added dropwise to a solution of copper(I) thiocyanate (0.6 equiv), cesium carbonate (1.5 equiv), and $TMSCF_3$ (1.5 equiv) in acetonitrile (2 mL), and stirring is continued for 12 hours at room temperature. The corresponding benzotrifluorides are obtained in good to excellent yields after aqueous work-up and purification (Table 1, process A). The slow addition is crucial for suppressing both unwanted protodediazotization and the formation of azoarenes and biaryls, which are common byproducts in Sandmeyer reactions. Mechanistic investigations suggest that the actual trifluoromethylation reagent formed in the reaction of copper thiocyanate with TMS-CF_3 and the mild base Cs_2CO_3 is a $[Cu(CF_3)_2]^-$ species.[9] The reason for using copper

thiocyanate is that the anion at the copper competes with CF_3 as the nucleophile in the Sandmeyer reaction. For copper halides, considerable amounts of haloarenes are formed as byproducts, whereas at most trace amounts of arenethiocyanates were observed when starting from copper thiocyanates. Another advantage is the high solubility of this copper precursor in the reaction solvent. The addition of the mild base cesium carbonate facilitates transfer of the CF_3 group from the silane to the copper without affecting the reactivity of the diazonium salts. Due to the hygroscopic character of this base, the reactions are best performed under a dry nitrogen atmosphere to minimize proto-dediazotization.

One-Pot Diazotization / Trifluoromethylation

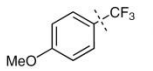
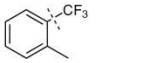
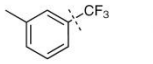
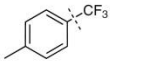
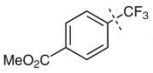
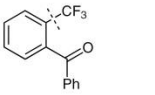
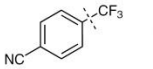
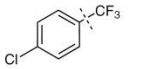
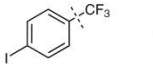
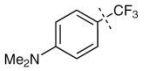
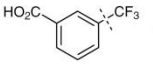
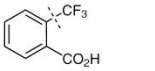
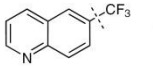
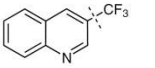
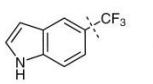
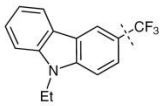
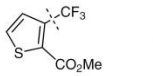
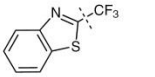
Especially for small-scale reactions and sensitive diazonium salts,[10,11] it may be convenient to diazotize the amine directly in the reaction mixture. This can be done by adding *tert*-butyl nitrite (1 equiv) to a solution of the aniline and anhydrous *p*-toluenesulfonic acid (PTSA; 1.5 equiv) in acetonitrile. The absence of water is crucial, with the monohydrate of the acid already leading to reduced yields. After stirring for 30 minutes at room temperature, the reaction mixture is added to a suspension of CuSCN (0.5 equiv), $TMSCF_3$ (1.5 equiv) and Cs_2CO_3 (1.5 equiv) in acetonitrile, and stirring is continued for 12 hours.[12] This one-pot process gives comparable, sometimes even higher yields than the two-step protocol (Table 1, Process B).

Scope and Limitations

The Sandmeyer trifluoromethylation is widely applicable to various aromatic amines. Due to the mild reaction conditions, common functionalities such as ether, ester, ketone, or cyano groups are tolerated (Table 1, compounds **1**–**7**). Even basic amino groups and free carboxylates are tolerated (compounds **10**–**12**). Various heterocycles, such as quinolines and indole, were also smoothly converted (compounds **13**–**18**). Remarkably, the trifluoromethylation can be performed in the presence of halo-, even iodo-substituents, so that it is orthogonal to many palladium-catalyzed cross-couplings (compounds **8** and **9**). Most products are obtained in pure form after aqueous workup and column chromatography.

In most cases, the isolated yields of both protocols are comparable. For quinolines, diazotization in situ led to the formation of an insoluble precipitate. Even when the precipitate was redissolved by adding acetone (0.5 mL), the yield obtained by using protocol B remained lower than that of the two-step protocol A. For aminoindoles and -benzoic acids, which gave reasonable yields with protocol A, almost no product was formed in the one-pot procedure B. In contrast, aminocarbazole, thiophene, and benzothiazole were successfully converted by using method B only; the difference in outcome in these cases may be caused by the instability of the diazonium salts when isolated. Substrates that lead to even less stable diazonium salts, such as 2-aminopyridines, could not be trifluoromethylated with either protocol.

Table 1 Sandmeyer Trifluoromethylation

Product	Yield (%)[a]	Product	Yield (%)[a]
1 	A: 81 B: 85	**2** 	A: 75[b] B: 78[b]
3 	A: 98[b] B: 84[b]	**4** 	A: 98[b] B: 98[b]
5 	A: 71 B: 83	**6** 	A: 74 B: 79
7 	A: 68 B: 91	**8** 	A: 98[b] B: 98[b]
9 	A: 69 B: 61	**10** 	A: 95 B: 91
11 	A: 73 B: 0	**12** 	A: 87 B: 0
13 	A: 69 B: 53	**14** 	A: 74 B: 55
15 	A: 46 B: 0	**16** 	A: – B: 89
17 	A: – B: 69	**18** 	A: – B: 61

[a] Isolated yield; A: starting from the arenediazonium tetrafluoroborate; B: starting from the aniline.
[b] Yield determined by ^{19}F NMR spectroscopic analysis with trifluoroethanol as internal standard.

Conclusion

The Sandmeyer trifluoromethylation is a useful strategy with which to access benzotrifluorides from readily available starting materials and inexpensive reagents. The reaction is possible either with intermediate isolation of the diazonium salts, or as a one-pot procedure starting from the anilines.

All reactions were performed under a nitrogen atmosphere in dry glassware containing a Teflon-coated stirrer bar. Acetonitrile was dried by heating to reflux over CaH_2 and fractional distillation. All reactions were monitored by GC; spectroscopic yields were determined by ^{19}F NMR spectroscopic analysis with trifluoroethanol as internal standard. GC analyses were carried out on an HP 6890 by using an HP-5 capillary column (Phenyl Methyl Siloxane 30 m × 320 μm × 0.25 μm) with the time program: 2 min at 60 °C, 30 °C/min to 300 °C, 3 min at 300 °C. Column chromatography was performed with an Isco Combi Flash Companion Chromatography System and pre-packed flash columns of silica gel (12 g). NMR spectra were obtained with a Bruker AMX 400 using $CDCl_3$, CD_3OD, or DMSO-d_6 as deuterated solvents, with proton, carbon and fluorine resonances recorded at 400, 101, and 376 MHz, respectively.

The diazonium salts were prepared from the corresponding anilines by following the procedure described below, and were used directly in the next step. All other starting materials were commercially available. All anilines and solvents were purified by distillation or sublimation prior to use. Other chemicals were used without further purification.

Synthesis of Arenediazonium Salts from Anilines; General Procedure

In a 50 mL round-bottom flask, the aniline (10 mmol) was dissolved in a mixture of EtOH (3 mL) and aq HBF_4 (50%, 2.5 mL, 20 mmol), then *tert*-butyl nitrite (2.7 mL, 20 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at r.t. for 1 h, then Et_2O (20 mL) was added to precipitate the arenediazonium tetrafluoroborate, which was filtered off and washed with Et_2O (3 × 10 mL). The arenediazonium tetrafluoroborate was dried in vacuo (10^{-3} mbar) for 10 min, and then used directly without further purification. Some arenediazonium tetrafluoroborates were recrystallized by dissolution in acetone, followed by precipitation by addition of Et_2O.

Two-Pot Synthesis of Benzotrifluorides from Arenediazonium Salts; Procedure A

A 20 mL crimp-cap vessel with Teflon-coated stirrer bar was charged with copper thiocyanide (73.5 mg, 0.60 mmol) and cesium carbonate (489 mg, 1.50 mmol) under an atmosphere of dry nitrogen. MeCN (2 mL) and trifluoromethyl trimethylsilane (240 μL, 1.50 mmol) were added by using a syringe. The resulting suspension was stirred at r.t. for 10 min, then a solution of the arenediazonium tetrafluoroborate (1 mmol) in MeCN (2 mL) was added dropwise by using a syringe. The reaction mixture was stirred at r.t. for 16 h, then filtered through a short pad of Celite (5 g) and rinsed with Et_2O (20 mL). The resulting organic solution was washed with H_2O (3 × 10 mL) and brine (10 mL), then the organic layer was dried over $MgSO_4$, filtered, and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2; pentane–Et_2O gradient), to give the corresponding benzotrifluoride.

One-Pot Synthesis of Benzotrifluorides from Anilines; Procedure B

A 20 mL crimp-cap vessel with Teflon-coated stirrer bar was charged with the amine (1.00 mmol), PTSA (258 mg, 1.50 mmol), and MeCN (2 mL) under nitrogen, and *tert*-butyl nitrite (133 μL, 1.00 mmol) was added dropwise by using a syringe. The resulting solution was stirred at r.t. for 30 min and then added dropwise to a suspension of copper thiocyanate (61.0 mg, 0.50 mmol), cesium carbonate (489 mg, 1.50 mmol), and trifluoromethyl trimethylsilane (240 μL, 1.50 mmol) in MeCN (2 mL), which was prestirred at r.t. for 10 min. The resulting suspension was stirred at r.t. for 12 h, then filtered through a short pad of Celite (5 g) and rinsed with Et_2O (20 mL). The resulting organic solution was washed with H_2O (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2; pentane–Et_2O gradient) to give the corresponding benzotrifluoride.

1-Methoxy-4-(trifluoromethyl)benzene (1)
[CAS Reg. No.: 402-52-8]

Prepared from 4-methoxybenzenediazonium tetrafluoroborate (444 mg, 2.00 mmol) by following Procedure A and isolated as a colorless liquid (286 mg, 1.62 mmol, 81%). The product was also prepared from 4-methoxyaniline (123 mg, 1.00 mmol) by following Procedure B (150 mg, 0.85 mmol, 85%). The spectroscopic data were reported previously.[6,12]

1-Methyl-2-(trifluoromethyl)benzene (2)
[CAS Reg. No.: 5140-17-6]

Prepared from 2-methylbenzenediazonium tetrafluoroborate (103 mg, 0.50 mmol) by following Procedure A (75% yield determined by ^{19}F NMR spectroscopic analysis). The product was also prepared from 2-methylaniline (54 mg, 0.50 mmol) by following Procedure B (78% yield by ^{19}F NMR spectroscopic analysis).[6,12]

1-Methyl-3-(trifluoromethyl)benzene (3)
[CAS Reg. No.: 401-79-6]

Prepared from 3-methylbenzenediazonium tetrafluoroborate (103 mg, 0.50 mmol) by following Procedure A (98% yield as determined by ^{19}F NMR spectroscopic analysis). The product was also prepared from 3-methylaniline (54 mg, 0.50 mmol) by following Procedure B (84% yield by ^{19}F NMR spectroscopic analysis).[6,12]

1-Methyl-4-(trifluoromethyl)benzene (4)
[CAS Reg. No.: 6140-17-6]

Prepared from 4-methylbenzenediazonium tetrafluoroborate (103 mg, 0.50 mmol) by following Procedure A (98% yield as determined by ^{19}F NMR spectroscopic analysis). The product was also prepared from 4-methylaniline (54 mg, 0.50 mmol) by following Procedure B (98% yield by ^{19}F NMR spectroscopic analysis).[6,12]

Methyl 4-(Trifluoromethyl)benzoate (5)
[CAS Reg. No.: 2967-66-0]

Prepared from 4-(methoxycarbonyl)benzenediazonium tetrafluoroborate (250 mg, 1.00 mmol) by following Procedure A and isolated as a colorless liquid (144 mg, 0.71 mmol, 71%). The product was also prepared from methyl 4-aminobenzoate (154 mg, 1.00 mmol) by following Procedure B as a liquid (169 mg, 0.83 mmol, 83%). The spectroscopic data were reported previously.[6,12]

Phenyl[2-(trifluoromethyl)phenyl]methanone (6)
[CAS Reg. No.: 727-99-1]

Prepared from 2-benzoylbenzenediazonium tetrafluoroborate (296 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (184 mg, 0.74 mmol, 74%). The product was also prepared from (2-aminophenyl)(phenyl)methanone (201 mg, 1.00 mmol) by following Procedure B (198 mg, 0.79 mmol, 79%). The spectroscopic data were reported previously.[6,12]

4-(Trifluoromethyl)benzonitrile (7)
[CAS Reg. No.: 455-18-5]

Prepared from 4-cyanobenzenediazonium tetrafluoroborate (108 mg, 0.50 mmol) by following Procedure A and isolated as a colorless solid (58 mg, 0.34 mmol, 68%). The product was also prepared from 4-cyanoaniline (118 mg, 1.00 mmol) by following Procedure B (156 mg, 0.91 mmol, 91%). The spectroscopic data were reported previously.[6,12]

1-Chloro-4-(trifluoromethyl)benzene (8)
[CAS Reg. No.: 98-56-6]

Prepared from 4-chlorobenzenediazonium tetrafluoroborate (113 mg, 0.50 mmol) by following Procedure A (98% yield as determined by ^{19}F NMR spectroscopic analysis). The product was also prepared from 4-chloroaniline (65 mg, 0.50 mmol) by following Procedure B (98% yield by ^{19}F NMR spectroscopic analysis).[6,12]

1-Iodo-4-(trifluoromethyl)benzene (9)
[CAS Reg. No.: 455-13-0]

Prepared from 4-iodobenzenediazonium tetrafluoroborate (649 mg, 2.00 mmol) by following Procedure A and isolated as a light-yellow liquid (373 mg, 1.37 mmol, 69%). The product was also prepared from 4-iodoaniline (221 mg, 1.00 mmol) by following Procedure B (166 mg, 0.61 mmol, 61%). The spectroscopic data were reported previously.[6,12]

***N*,*N*-Dimethyl-4-(trifluoromethyl)aniline (10)**
[CAS Reg. No.: 329-17-9]

Prepared from 4-(dimethylamino)benzenediazonium tetrafluoroborate (470 mg, 2.00 mmol) by following Procedure A and isolated as a colorless solid (358 mg, 1.89 mmol, 95%). The product was also prepared from *N*,*N*-dimethylbenzene-1,4-diamine (140 mg, 1.00 mmol) by following Procedure B (172 mg, 0.91 mmol, 91%). The spectroscopic data were reported previously.[6,12]

3-(Trifluoromethyl)benzoic Acid (11)
[CAS Reg. No.: 454-92-2]

Prepared from 3-carboxybenzenediazonium tetrafluoroborate (236 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (139 mg, 0.73 mmol, 73%). The spectroscopic data were reported previously.[6]

2-(Trifluoromethyl)benzoic Acid (12)
[CAS Reg. No.: 433-97-6]

Prepared from 2-carboxybenzenediazonium tetrafluoroborate (236 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (166 mg, 0.87 mmol, 87%). The spectroscopic data were reported previously.[6]

6-(Trifluoromethyl)quinoline (13)
[CAS Reg. No.: 325-13-3]

Prepared from quinoline-6-diazonium tetrafluoroborate (243 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (136 mg, 0.69 mmol, 69%). The product was also prepared from quinoline-6-amine (147 mg, 1.00 mmol) by following Procedure B (105 mg, 0.53 mmol, 53%). The spectroscopic data were reported previously.[6,12]

3-(Trifluoromethyl)quinoline (14)
[CAS Reg. No.: 25199-76-2]

Prepared from quinoline-3-diazonium tetrafluoroborate (243 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (145 mg, 0.74 mmol, 74%). The product was also prepared from quinolin-3-amine (146 mg, 1.00 mmol) by following procedure B (108 mg, 0.55 mmol, 55%). The spectroscopic data were reported previously.[6,12]

5-(Trifluoromethyl)-1*H*-indole (15)
[CAS Reg. No.: 100846-24-0]

Prepared from 1*H*-indole-5-diazonium tetrafluoroborate (231 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (85 mg, 0.46 mmol, 46%). The spectroscopic data were reported previously.[6]

9-Ethyl-3-(trifluoromethyl)-9*H*-carbazole (16)
Prepared from 9-ethyl-9*H*-carbazol-3-amine (221 mg, 1.00 mmol) by following Procedure B and isolated as a colorless solid (234 mg, 0.89 mmol, 89%). The spectroscopic data were reported previously.[12]

Methyl 3-(Trifluoromethyl)thiophene-2-carboxylate (17)
Prepared from methyl 3-aminothiophene-2-carboxylate (157 mg, 1.00 mmol) by following Procedure B and isolated as a colorless solid (145 mg, 0.69 mmol, 69%). The spectroscopic data were reported previously.[12]

2-(Trifluoromethyl)-1,3-benzothiazole (18)
[CAS Reg. No.: 14468-40-7]

Prepared from 2-amino-benzothiazole (155 mg, 1.00 mmol) by following Procedure B and isolated as a colorless solid (124 mg, 0.61 mmol, 61%). The spectroscopic data were reported previously.[12]

Acknowledgment

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References

(1) (a) Yamazaki, T.; Tagauchi, T.; Ojima, I. In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, **2009**, 3. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Yagupol'skii, L. M.; Il'chenko, A. Y.; Kondratenko, N. V. *Russ. Chem. Rev.* **1974**, *43*, 32.

(2) For selected examples of traditional trifluoromethylation methods, see: (a) Swarts, F. *Bull. Acad. R. Belg.* **1892**, *24*, 309. (b) Simons, J. H.; Lewis, C. J. *J. Am. Chem. Soc.* **1938**, *60*, 492. (c) Boswell, G. A.; Ripka, W. C.; Scribner, R. M.; Tullock, C. W. *Org. React.* **1974**, *21*, 30. (d) Sawada, H.; Nakayama, M.; Yoshida, M.; Yoshida, T.; Kamigata, N. *J. Fluorine Chem.* **1990**, *46*, 423.

(3) For reviews on trifluoromethylations, see: (a) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Asian J.* **2012**, *7*, 1744. (d) Jin, Z.; Hammond, G. B.; Xu, B. *Aldrichimica Acta* **2012**, *45*, 67. For copper-mediated trifluoromethylations, see: (e) Liu, T.; Shen, Q. *Eur. J. Org. Chem.* **2012**, 6679. (f) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214.

(4) Dai, J.-J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z.-J.; Lu, X.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8436.

(5) Wang, X.; Xu, Y.; Mo, F.; Ji, G.; Qiu, D.; Feng, J.; Ye, Y.; Zhang, S.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2013**, *135*, 10330.

(6) Danoun, G.; Bayarmagnai, B.; Grünberg, M. F.; Gooßen, L. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 7972.

(7) (a) Kochi, J. K. *J. Am. Chem. Soc.* **1957**, *79*, 2942. (b) Galli, C. *Chem. Rev.* **1988**, *88*, 765.

(8) (a) Prakash, G. K. S.; Jog, P. V.; Batamack, P. T. D.; Olah, G. A. *Science* **2012**, *338*, 1324. (b) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848.

(9) (a) Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3793. (b) Tomashenko, O. A.; Escudero-Adán, E. C.; Martínez Belmonte, M.; Grushin, V. V. *Angew. Chem. Int. Ed.* **2011**, *50*, 7655. (c) Clark, J. H.; Jones, C. W.; Kybett, A. P.; McClinton, M. A.; Miller, J. M.; Bishop, D.; Blade, R. J. *J. Fluorine Chem.* **1990**, *48*, 249.

(10) (a) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633. (b) Hodgson, H. H. *Chem. Rev.* **1947**, *40*, 251. (c) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622.

(11) Most diazonium salts are reasonably stable in solution. Isolated diazonium salts should be kept cold and treated with appropriate care.

(12) Bayarmagnai, B.; Matheis, C.; Risto, E.; Gooßen, L. J. *Adv. Synth. Catal.* **2014**, *356*, 2343.

4.2 Synthese von Difluormethylthioethern ausgehend von Difluormethyl Trimethylsilan und *in situ* generierten Organothiocyanaten – SCF_2H

Das Ziel dieses Teilprojekts bestand in der Übertragung des Sandmeyer-analogen Trifluormethylthiolierungskonzepts auf die Einführung der Difluormethylthiolgruppe. Dabei erwies sich das Reagenz $TMSCF_2H$, welches aus $TMSCF_3$ mittels einfacher Reduktion erhältlich ist, als erfolgversprechend.[110] Der Mechanismus verläuft dabei analog zu der Sandmeyer Trifluormethylthiolierung über einen *CN-CF_2H*-Austausch der *in situ* generierten Organothiocyanate.

Die ersten mechanistischen Kontrollexperimente mit präformierten Organothiocyanaten bestätigten die Realisierbarkeit dieses Konzepts. Nach der sorgfältigen Optimierung aller Reaktionsparameter wie zum Beispiel Temperatur, Lösemittel, Katalysator etc. lieferte die Testreaktion das gewünschte SCF_2H Produkt in quantitativer Ausbeute. Im Anschluss wurde die Methode mit Unterstützung von Herrn C. Matheis auf ein Eintopfverfahren verfeinert, sodass die Organothiocyanate *in situ* in der Reaktionslösung generiert werden konnten. Die Anwendungsbreit wurde zusätzlich mit der Unterstützung von Herrn Dr. K. Jouvin gemeinsam bestimmt. Hierbei wurden insgesamt 35 bisher unbekannte Substrate synthetisiert und vollständig charakterisiert. Das Manuskript wurde von mir zusammen mit Herrn Prof. Dr. L. J. Gooßen verfasst, während Herr Dr. K. Jouvin und Herr C. Matheis die analytischen Daten auswerteten und die Supporting Information erstellten.

Die Ergebnisse wurden 2015 in der Zeitschrift *Angewandte Chemie Int. Ed.* veröffentlicht.[111] Eine Kopie des Manuskripts ist angepasst und mit Erlaubnis der John Wiley & Sons, Inc. nachfolgend beigefügt.

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Synthetic Methods

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Synthesis of Difluoromethyl Thioethers from Difluoromethyl Trimethylsilane and Organothiocyanates Generated In Situ**

*Bilguun Bayarmagnai, Christian Matheis, Kévin Jouvin, and Lukas J. Goossen**

Abstract: *A copper-CF_2H complex generated in situ from copper thiocyanate and TMS–CF_2H smoothly converts organothiocyanates into valuable difluoromethyl thioethers. This reaction step can be combined with several thiocyanation methods to one-pot protocols, allowing late-stage difluoromethylthiolations of widely available alkyl halides and arenediazonium salts. This strategy enables the introduction of difluoromethylthio groups—a largely unexplored substituent with highly promising properties—into drug-like molecules.*

Close to 40% of marketed agrochemicals and 25% of pharmaceuticals contain fluorine atoms. Fluorine-containing residues are central functionalities in such active substances,[1] because they modulate their metabolic stability, lipophilicity, and bioavailability. So-called "fluorine scans", i.e., systematic derivatizations through the introduction of groups such as CF_3,[2] C_2F_5,[3] SCF_3,[4] and OCF_3,[5] have become standard procedure in drug discovery. New fluorine-containing residues and efficient methods for their introduction into functionalized molecules are, thus, constantly sought.

Trifluoromethyl groups are incorporated into bioactive molecules to enhance their membrane permeability.[1d,6] Recent years have witnessed a tremendous development in trifluoromethylation technology. Efficient benzotrifluoride syntheses that can be employed even at late stages within a synthetic sequence have been disclosed for example, by the groups of Prakash,[7] Grushin,[8] Buchwald,[9] and others.[10]

Lately, there is a shift in focus toward trifluoromethylthio groups, because these are even more effective in inducing lipophilicity and membrane permeability (Hansch constants 1.44 vs. 0.88 for CF_3).[11] Contemporary late-stage trifluoromethylthiolations of arenes employ Pd,[12] Cu,[13] Ni,[14] and Ag[12] catalysts.

Difluoromethyl groups, in contrast, are potent hydrogen donors.[15] They serve as lipophilic and membrane permeability-enhancing isosteric and isopolar analogues to OH and SH groups.[1b,16] Difluoromethylations still face challenges, and only few methods reach the efficiency of the corresponding trifluoromethylations.[17]

With SCF_3 receiving increasing attention as an enhanced version of CF_3 in bioactive molecules, one might expect a similar shift in interest from CF_2H to SCF_2H. Indeed, difluoromethylthio residues were shown to be uniquely effective in the β-lactamase-resistant oxcephalosporin antibiotic Flomoxef sodium (Figure 1). In 2-(difluoro[(4-methylpyrimidin-2-yl)thio]methyl)benzoxazole, the SCF_2 bridge is crucial for its activity against HIV-1, whereas the OCF_2-substituted analogue is inactive.[18]

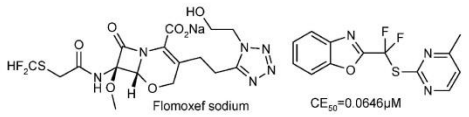
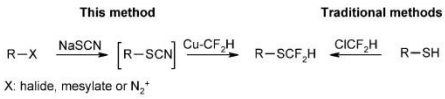


Figure 1. Biologically active α-difluoromethyl thioethers.

The proton in SCF_2H groups is even more acidic than that in CF_2H groups.[19] This underlines the potential of SCF_2H groups as lipophilic OH or NH surrogates. It would be highly desirable to routinely examine SCF_2H substituents during drug discovery. However, no presently available synthetic method is mild and selective enough for their late-stage introduction into drug-like molecules.

Traditional syntheses of SCF_2H moieties are based on the insertion of difluorocarbene into the S–H bond of thiophenols, as first described by Porter et al. in 1957.[20] Originally, the difluorocarbenes were generated from the ozone-depleting chlorodifluoromethane (Scheme 1).[21] The groups of



Scheme 1. Strategies to access difluoromethyl thioethers.

Hu[22] and Dolbier[23] recently utilized TMS–CF_2Br or CF_3H as more environmentally benign CF_2 sources. Thiols and thiophenols can also be difluoromethylated using electrophilic reagents.[24] However, these approaches suffer from the limited availability of thiol substrates, the incompatibility of the strongly basic reaction conditions with sensitive functionalities, and the low selectivity of the CF_2 insertion step.

A method to introduce SCF_2H groups in a single step, using an inexpensive reagent, and substituting a widely available leaving group such as a halide, mesylate, or

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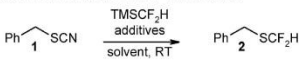
diazotized amino group would be highly desirable. Preformed SCF_3 reagents are laborious to prepare and rather expensive,[12,13,25] and the same limitations must be expected for their presently unknown SCF_2H counterparts. Therefore, we decided to base our difluoromethylthiolation process on a stepwise assembly first of S, introduced by way of an SCN group, then of CF_2H by the in situ conversion of SCN to SCF_2H using a nucleophilic CF_2H source, preferentially TMS–CF_2H, which is easily accessible from the inexpensive Ruppert–Prakash reagent.

Langlois et al.[26] found that SCF_3 groups can be generated from thiocyanates by nucleophilic displacement of the CN group using TMS–CF_3. However, the corresponding reaction between organothiocyanates with TMS–CF_2H has not yet been achieved. Since such a transformation would constitute the pivotal step in our desired synthesis of organodifluoromethyl thioethers, we focused our initial research efforts on this step in isolation. Using the model reaction of benzyl thiocyanate (**1**) with TMS–CF_2H, we investigated a range of reaction conditions, starting with those reported for the analogous trifluoromethylation (TBAF, THF, 0 °C). None of the fluoride sources tested in various solvents promoted the formation of benzyl difluoromethyl sulfide (**2**, Table 1, entries 1–4) in more than trace amounts, confirming that a noncatalyzed introduction of the sensitive CF_2H moiety is not feasible.

Table 1: Optimization of the reaction conditions.[a]

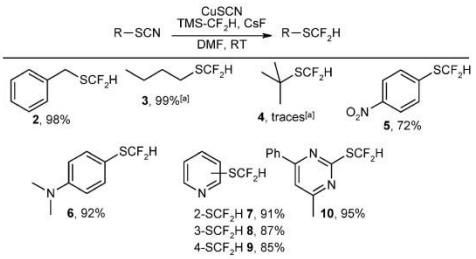


Entry	Additive	Mediator	Solvent	**2** [%][b]
1[c]	TBAF	–	THF	trace
2	CsF	–	THF	0
3	TBAF	–	DMF	trace
4	KF	–	DMF	trace
5	CsF	–	DMF	51
6[d]	CsF	CuSCN	DMF	85
7[e]	CsF	CuSCN	DMF	98

[a] Reaction conditions: 0.5 mmol of benzyl thiocyanate, 1.0 mmol of additive, 1 mL solvent, 1.0 mmol of TMS–CF_2H, RT. [b] Yields were determined by ^{19}F NMR spectroscopy using trifluoroethanol as an internal standard. [c] TMS–CF_2H was added at 0 °C, then the mixture was slowly warmed up to RT. [d] 0.5 mmol of CuSCN. [e] 0.5 mmol of CuSCN and 2.0 mmol of CsF were used.

Systematic investigations of potential mediators identified copper salts, particularly copper thiocyanate, as strong promoters of the desired reaction. NMR investigations showed that Cu–CF_2H is intermediately formed and acts as the actual difluoromethylation reagent (entries 6 and 7).[27] Under optimal conditions, that is, in the presence of CsF and CuSCN in DMF, **1** is converted into benzyl difluoromethyl sulfide (**2**) in quantitative yields within 12 h at room temperature (entry 7).

As illustrated in Scheme 2, the new difluoromethylation protocol extends to aliphatic, aromatic, and heteroaromatic thiocyanates. They include substructures of particular interest, namely a 2-[(difluoromethyl)thio]pyrimidine analogous



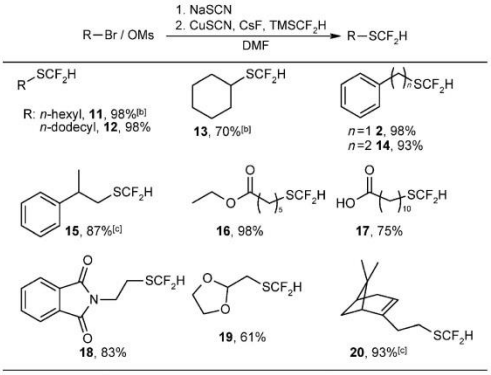
Scheme 2. Cu-mediated difluoromethylation of organothiocyanates. Reaction conditions: 1.0 mmol of organothiocyanate, 1.0 mmol of CuSCN, 4.0 mmol of CsF, 2.0 mmol of TMS–CF_2H in 2 mL of DMF, 12 h, RT. Yields are of isolated products. [a] Yields determined by ^{19}F NMR spectroscopy using trifluoroethanol as an internal standard.

to the above-mentioned anti-HIV-1 agents,[18] and a 2-(difluoromethylthio)pyridine related to the 2-(difluoromethyl)pyridine herbicide thiazopyr.

The discovery of this mild, copper-mediated difluoromethylation of organothiocyanates should be combinable with syntheses of organothiocyanates from various carbon electrophiles, overall leading to one-step synthesis of difluoromethyl thioethers from widely available starting materials. Indeed, upon briefly heating alkyl bromides with sodium thiocyanate in DMF and then adding the difluoromethylation reagent mixture composed of TMS–CF_2H, CsF, and CuSCN, the corresponding alkyl difluoromethyl thioethers were cleanly obtained in high yields and purities.

The scope of this one-pot difluoromethylthiolation is shown in Table 2. Primary and secondary alkyl bromides, as well as mesylates conveniently accessible from ubiquitous

Table 2: One-pot difluoromethylthiolation of alkyl bromides and mesylates.[a]



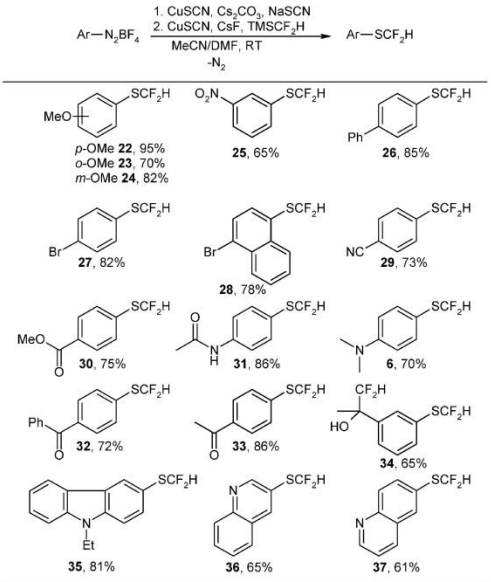
[a] 1.0 mmol of alkyl bromide and 1.2 mmol of NaSCN in 4 mL DMF were heated for 2 h (see SI for detailed conditions). After cooling to RT, 1.0 mmol of CuSCN, 4.0 mmol of CsF, and 2.0 mmol of TMS–CF_2H were added, and stirring continued for 12 h at RT. Yields are of isolated products. [b] Yields determined by ^{19}F NMR spectroscopy using trifluoroethanol as an internal standard. [c] Starting from mesylate.

alcohols, were converted in high yields, and a range of common functionalities was tolerated.

The synthesis of aromatic derivatives by this strategy is limited to strongly activated aryl halides capable of undergoing nucleophilic aromatic thiocyanation. Therefore, we sought another protocol for the C–S bond-forming step capable of converting the entire range of aromatic and heteroaromatic substrates. A Sandmeyer-type approach as recently implemented in several fluoroalkylations of diazonium salts[17b,28] appeared to be promising for a generally applicable synthesis of difluoromethylthio arenes.

To probe the viability of this approach, we treated 4-methoxybenzenediazonium tetrafluoroborate (**21**) with sodium thiocyanate and TMS–CF_2H in the presence of copper thiocyanate (Table 3). The optimal literature conditions for the trifluoromethylthiolation of diazonium salts (Cs_2CO_3, MeCN)[28a] did not yield any of the desired difluoromethylthiolated product (see the Supporting Information, SI). However, upon switching to DMF as the solvent, the arenethiocyanate was fully consumed, and the desired product was detected in modest yield along with anisole, diaryl disulfide, and biaryl byproducts. By careful optimization of the conditions, the yield could be increased to a satisfactory 83% by adding both cesium carbonate and cesium fluoride to the reaction mixture. The carbonate base is required for the Sandmeyer step, and CsF promotes the transfer of CF_2H^- from silicon to copper.[17a,b] The ratio between the two cesium bases has a crucial influence on the yield. Both cesium carbonate and sodium thiocyanate interfere with the difluoromethylation step, so that an excess of these reagents must be avoided. Under optimized conditions, the only remaining byproduct is anisole, which results from competing protodediazotization. Further control experiments showed that the Sandmeyer thiocyanation and the formation of Cu–CF_2H species each require one equivalent of CuSCN.[29]

Table 3: Difluoromethylthiolation of arenediazonium salts.[a]



[a] 1.0 mmol of arenediazonium tetrafluoroborate in 2 mL of MeCN was slowly added to a mixture of 1.0 mmol of CuSCN, 0.75 mmol of Cs_2CO_3, and 1.5 mmol of NaSCN in 2 mL of MeCN, and stirred for 1 h at RT. Then MeCN was evaporated, 1.0 mmol of CuSCN, 4.0 mmol of CsF, and 2.0 mmol of TMS–CF_2H in 4 mL DMF were added, stirring was continued for 12 h at RT. Yields are of isolated products.

DMF was found to be the most effective solvent for the difluoromethylation step,[17a,b] but the Sandmeyer reaction proceeds best in acetonitrile.[30] Near-quantitative yields were achieved only when performing the reaction steps in different solvents. Thus, **21** in MeCN is first added to a mixture of NaSCN, Cs_2CO_3, and CuSCN in MeCN. After stirring for 1 h, the solvent is evaporated, and a solution of CsF, CuSCN, and TMS–CF_2H in DMF is added to the residue. This way, the desired product **22** can be isolated in 95% yield.

Having thus identified a highly efficient protocol, we next investigated its scope. The examples in Table 3 illustrate that diversely substituted arenediazonium tetrafluoroborates are smoothly converted into the corresponding aryl difluoromethyl thioethers in high yields. Electron-rich and electron-deficient substrates give similarly high yields, and various heterocycles such as quinolines and carbazoles are smoothly converted. Common functionalities including ester, ether, keto, amino, cyano, and bromo groups are tolerated. Remarkably, in compound **33**, the acetyl substituent in the *para*-position is left intact whereas the same group in the *meta*-position is converted into the corresponding difluoromethyl alcohol (product **34**). The successful synthesis of **22** in 89% yield on a 10 mmol scale demonstrates the scalability of the process.

Control experiments suggest that the reaction indeed proceeds through a Sandmeyer-type mechanism, as proposed also for related fluoroalkyl(thiol)ations. This copper-mediated radical dediazotative thiocyanation step is followed by nucleophilic displacement of a cyanide group by CF_2H via a $CuCF_2H$ species.

In conclusion, a copper-mediated difluoromethylation of organothiocyanates has opened up new opportunities for the synthesis of difluoromethyl thioethers from widely available substrates such as alkyl halides or (hetero)aryl amines via their diazonium salts. The mild and efficient synthetic approach is suitable for the late-stage functionalization of complex molecules and thus meets the requirements of pharmaceutical and agrochemical research. Many difluoromethyl thioethers have thus become accessible for the first time and may now be screened for biological activity.

Keywords: copper · difluoromethylthiolation · fluorine · Sandmeyer reaction · synthetic methods

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[1] a) *Fluorine-containing Amino Acids* (Eds.: V. P. Kukhar, V. A. Soloshonok), Wiley, Hoboken, **1995**; b) *Fluorine in Medicinal Chemistry and Chemical Biology* (Eds.: I. Ojima), Wiley, Chichester, **2009**; c) *Bioorganic and Medicinal Chemistry of Fluorine* (Eds.: J.-P. Bégué, D. Bonnet-Delpon), Wiley, Hoboken, **2008**; d) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; e) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, 2nd ed., Wiley-VCH, Weinheim, **2013**; f) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.

[2] a) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; c) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744–1754; d) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683–730; e) T. Liu, Q. Shen, *Eur. J. Org. Chem.* **2012**, 6679–6687; f) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264; *Angew. Chem.* **2013**, *125*, 8372–8423.

[3] A. Lishchynskyi, V. V. Grushin, *J. Am. Chem. Soc.* **2013**, *135*, 12584–12587.

[4] F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415–2428.

[5] a) G. L. Trainor, *J. Carbohydr. Chem.* **1985**, *4*, 545–563; b) K. N. Hojczyk, P. Feng, C. Zhan, M.-Y. Ngai, *Angew. Chem. Int. Ed.* **2014**, *53*, 14559–14563; *Angew. Chem.* **2014**, *126*, 14787–14791.

[6] L. M. Yagupol'skii, A. Y. Il'chenko, N. V. Kondratenko, *Russ. Chem. Rev.* **1974**, *43*, 32–47.

[7] a) G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324–1327; b) G. K. S. Prakash, R. Krishnamurti, G. A. Olah, *J. Am. Chem. Soc.* **1989**, *111*, 393–395; c) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757–786.

[8] a) P. Novák, A. Lishchynskyi, V. V. Grushin, *Angew. Chem. Int. Ed.* **2012**, *51*, 7767–7770; *Angew. Chem.* **2012**, *124*, 7887–7890; b) S. Takemoto, V. V. Grushin, *J. Am. Chem. Soc.* **2013**, *135*, 16837–16840; c) A. Lishchynskyi, M. A. Novikov, E. Martin, E. C. Escudero-Adán, P. Novák, V. V. Grushin, *J. Org. Chem.* **2013**, *78*, 11126–11146.

[9] a) A. T. Parsons, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 9120–9123; *Angew. Chem.* **2011**, *123*, 9286–9289; b) T. D. Senecal, A. T. Parsons, S. L. Buchwald, *J. Org. Chem.* **2011**, *76*, 1174–1176; c) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679–1681.

[10] a) H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2011**, *50*, 3793–3798; *Angew. Chem.* **2011**, *123*, 3877–3882; b) N. D. Litvinas, P. S. Fier, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 536–539; *Angew. Chem.* **2012**, *124*, 551–554; c) G. G. Dubinina, H. Furutachi, D. A. Vicic, *J. Am. Chem. Soc.* **2008**, *130*, 8600–8601; d) T. Liu, X. Shao, Y. Wu, Q. Shen, *Angew. Chem. Int. Ed.* **2012**, *51*, 540–543; *Angew. Chem.* **2012**, *124*, 555–558; e) L. Chu, F.-L. Qing, *Org. Lett.* **2010**, *12*, 5060–5063; f) T. Knauber, F. Arikan, G.-V. Röschenthaler, L. J. Gooßen, *Chem. Eur. J.* **2011**, *17*, 2689–2697; g) B. A. Khan, A. E. Buba, L. J. Gooßen, *Chem. Eur. J.* **2012**, *18*, 1577–1581.

[11] C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207–1216.

[12] G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 7312–7314; *Angew. Chem.* **2011**, *123*, 7450–7452.

[13] a) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 1548–1552; *Angew. Chem.* **2013**, *125*, 1588–1592; b) X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457–3460; *Angew. Chem.* **2013**, *125*, 3541–3544; c) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem. Int. Ed.* **2012**, *51*, 2492–2495; *Angew. Chem.* **2012**, *124*, 2542–2545; d) L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237–18240.

[14] C.-P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183–185.

[15] a) Y. Li, J. Hu, *Angew. Chem. Int. Ed.* **2005**, *44*, 5882–5886; *Angew. Chem.* **2005**, *117*, 6032–6036; b) J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.* **1995**, *60*, 1626–1631; c) G. K. S. Prakash, C. Weber, S. Chacko, G. A. Olah, *Org. Lett.* **2007**, *9*, 1863–1866.

[16] a) F. Narjes, K. F. Koehler, U. Koch, B. Gerlach, S. Colarusso, C. Steinkühler, M. Brunetti, S. Altamura, R. De Francesco, V. G. Matassa, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701–704; b) G. K. S. Prakash, M. Mandal, S. Schweizer, N. A. Petasis, G. A. Olah, *J. Org. Chem.* **2002**, *67*, 3718–3723.

[17] a) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 5524–5527; b) C. Matheis, K. Jouvin, L. J. Goossen, *Org. Lett.* **2014**, *16*, 5984–5987; c) Y. Gu, X. Leng, Q. Shen, *Nat. Commun.* **2014**, *5*, 5405; d) G. K. S. Prakash, S. K. Ganesh, J.-P. Jones, A. Kulkarni, K. Masood, J. K. Swabeck, G. A. Olah, *Angew. Chem. Int. Ed.* **2012**, *51*, 12090–12094; *Angew. Chem.* **2012**, *124*, 12256–12260; e) X.-L. Jiang, Z.-H. Chen, X.-H. Xu, F.-L. Qing, *Org. Chem. Front.* **2014**, *1*, 774.

[18] C. R. Burkholder, W. R. Dolbier, M. Médebielle, *J. Fluorine Chem.* **2000**, *102*, 369–376.

[19] For DFT calculations, see the SI. SCF_2H groups can be deprotonated with KOH: J. Hu, *J. Fluorine Chem.* **2009**, *130*, 1130–1139.

[20] J. Hine, J. J. Porter, *J. Am. Chem. Soc.* **1957**, *79*, 5493–5496.

[21] a) R. Van Poucke, R. Pollet, A. De Cat, *Tetrahedron Lett.* **1965**, *6*, 403–406; b) B. R. Langlois, *J. Fluorine Chem.* **1988**, *41*, 247–261.

[22] L. Li, F. Wang, C. Ni, J. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12390–12394; *Angew. Chem.* **2013**, *125*, 12616–12620.

[23] C. S. Thomoson, W. R. Dolbier, *J. Org. Chem.* **2013**, *78*, 8904–8908.

[24] a) W. Zhang, F. Wang, J. Hu, *Org. Lett.* **2009**, *11*, 2109–2112; b) Q.-Y. Chen, S.-W. Wu, *J. Fluorine Chem.* **1989**, *44*, 433–440; c) Y. Zafrani, G. Sod-Moriah, Y. Segall, *Tetrahedron* **2009**, *65*, 5278–5283.

[25] a) R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 1650–1653; *Angew. Chem.* **2014**, *126*, 1676–1679; b) C. Xu, B. Ma, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 9316–9320; *Angew. Chem.* **2014**, *126*, 9470–9474.

[26] T. Billard, S. Large, B. R. Langlois, *Tetrahedron Lett.* **1997**, *38*, 65–68.

[27] R. Eujen, B. Hoge, D. J. Brauer, *J. Organomet. Chem.* **1996**, *519*, 7–20.

[28] a) G. Danoun, B. Bayarmagnai, M. F. Gruenberg, L. J. Goossen, *Chem. Sci.* **2014**, *5*, 1312–1316; b) B. Bayarmagnai, C. Matheis, E. Risto, L. J. Goossen, *Adv. Synth. Catal.* **2014**, *356*, 2343–2348; c) J.-J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z.-J. Liu, X. Lu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 8436–8439; d) X. Wang, Y. Xu, F. Mo, G. Ji, D. Qiu, J. Feng, Y. Ye, S. Zhang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 10330–10333; e) A. Lishchynskyi, G. Berthon, V. V. Grushin, *Chem. Commun.* **2014**, *50*, 10237; f) G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 7972–7975; *Angew. Chem.* **2013**, *125*, 8130–8133; g) G. Danoun, B. Bayarmagnai, M. Grünberg, C. Matheis, E. Risto, L. J. Gooßen, *Synthesis* **2014**, 2283–2286.

[29] See SI. Additional NaSCN or Cs_2CO_3 hinders the difluoromethylation of preformed *p*-methoxyphenyl thiocyanate.

[30] A. Roglans, A. Pla-Quintana, M. Moreno-Mañas, *Chem. Rev.* **2006**, *106*, 4622–4643.

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4.3 Eisenkatalysierte Decarboxylierung von Trifluoracteten – SCF_3

Das Ziel dieses Teilprojekts bestand in der mechanistischen Untersuchung zur Decarboxylierung von Trifluoracetaten. Um Einblicke in den Mechanismus zu erhalten wurde die Decarboxylierung verschiedener Trifluoracetate in Anwesenheit von Eisen- und Kupfermediatoren untersucht. Die Decarboxylierungen sollten an präparativ einfach durchführbaren Testreaktionen durchgeführt werden, in denen die gebildeten Trifluormethylnukleophile auf ein Elektrophil übertragen werden und so eine einfache Analytik der Produkte erlauben. Basierend auf den vorherigen Ergebnissen erwies sich die Umsetzung der Organothiocyanate in ihre korrespondierenden Trifluormethylthioether mittels *CN*-CF_3-Austausches als vielversprechend.

Im Rahmen einer Zusammenarbeit mit Herrn B. Exner konnte ein Verfahren entwickelt werden, in dem Organothiocyanate mittels Decarboxylierung von Trifluoracetatsalzen zu den korrespondierenden, wertvollen Trifluormethylthioethern (SCF_3) umgesetzt werden können. Der eingesetzte Einsenkatalysator ermöglicht die Decarboxylierung von Trifluoracetaten bei 140 °C und formt mit den entstehenden Cyaniden Eisencyanid-Komplexe $[K_4(FeCN_6)_4]$.

Die Optimierungsarbeiten dieser Methode erfolgten zu gleichen Teilen von Herrn B. Exner und mir. Die Anwendungsbreite wurde mit zusätzlicher Unterstützung von Herrn F. Jia gemeinsam bestimmt. Das Manuskript wurde von Herrn B. Exner und mir zusammen mit Herrn Prof. Dr. L. J. Gooßen verfasst. Die Supporting Information wurde von den Herren B. Exner und F. Jia erstellt

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Synthesis Design

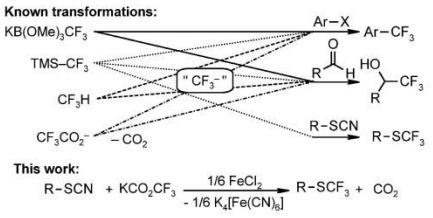
Iron-Catalyzed Decarboxylation of Trifluoroacetate and Its Application to the Synthesis of Trifluoromethyl Thioethers

Benjamin Exner, Bilguun Bayarmagnai, Fan Jia, and Lukas J. Goossen*[a]

Abstract: Nucleophilic CF_3 has been generated by decarboxylation of potassium trifluoroacetate, arguably the most easy-to-handle, inexpensive, and sustainable source of trifluoromethyl groups. Simple iron(II) chloride catalyzes the decarboxylation as well as a subsequent trifluoromethylation of organothiocyanates, resulting in a straightforward synthesis of trifluoromethyl thioethers. The KCN byproduct is absorbed by iron(II) with formation of nontoxic potassium hexacyanoferrate. An analogous trifluoromethylation of aldehydes with trifluoroacetate underlines the synthetic potential of such iron-catalyzed decarboxylative trifluoromethylations.

The development of methods to introduce trifluoromethyl groups into organic molecules is of great importance due to their presence in many top-selling pharmaceuticals, agrochemicals, and functional materials.[1] Fluoroalkyl groups impart desirable properties to drug-like molecules, such as metabolic stability, increased lipophilicity, and stronger dipole moments.[2]

Traditional trifluoromethylation methods often suffer from harsh reaction conditions or the use of aggressive reagents, which confines them to the beginning of a chemical synthesis.[3] The pressing need for late-stage fluoroalkylations in drug discovery has triggered rapid advances in method development over recent years (Scheme 1).



Scheme 1. Nucleophilic trifluoromethylation: reagents and synthetic targets.

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Milestone discoveries in the field of trifluoromethylation chemistry include catalytic couplings of aryl halides or other aryl electrophiles with TMS–CF_3, $KCF_3B(OMe)_3$, or preformed copper- or silver-CF_3 complexes as well as electrophilic C–H functionalizations using the Umemoto or Togni reagents.[4]

The comparatively high cost of these contemporary trifluoromethylation reagents has triggered extensive research on potential alternatives. Grushin[5] and Prakash[6] have recently demonstrated that fluoroform, a byproduct of Teflon production, can be utilized as a source of nucleophilic CF_3. Gaseous fluoroform might one day become the reagent of choice for industrial manufacturing in dedicated plants.

Still, trifluoroacetate salts are the most desirable CF_3 source for other applications, since they are inexpensive ($\ll 1\ \$\,g^{-1}$), stable, and easy-to-handle solids. Kondo, Chambers and others have shown that trifluoroacetate can be decarboxylated and the resulting CF_3 nucleophile transferred to carbon electrophiles such as aryl halides,[7] carbonyl compounds,[8] and disulfides[9] in the presence of stoichiometric amounts of Cu salts at $\geq 160\,^{\circ}C$. Vicic and Buchwald have disclosed contemporary variants of this reaction using NHC complexes or flow reactors.[10] Beller et al. have successfully reduced the Cu loadings to catalytic quantities (20 mol%) by starting from methyl trifluoroacetate.[11] However, these high-temperature reactions have limited scope and tend to give a wide spectrum of byproducts.

Building on our expertise with catalytic decarboxylative couplings,[12] we intensively searched for alternative, efficient concepts for trifluoroacetate decarboxylation and their application to trifluoromethylation reactions. One of our main target products are trifluoromethyl thioethers, because these have recently attracted considerable attention in drug discovery.[1,13] SCF_3 groups are key functionalities in several pharmaceutical and agrochemical products including tiflorex and toltrazuril (Figure 1), and induce even higher lipophilicity and membrane permeability than their CF_3 analogs (Hansch constants 1.44 for SCF_3 vs. 0.88 for CF_3).[14] Traditional syntheses of trifluoromethyl thioethers usually involve chlorination/Cl–F-exchange reactions.[15] Contemporary methods include Ni-,[16] Cu-,[17] or Pd-catalyzed[18] trifluoromethylthiolations of aryl halides, organometallic reagents, or arenes with costly $AgSCF_3$, *N*-(trifluoromethylthio)phthalimide, -saccharin, or -succinimide reagents.[19] Langlois et al. demonstrated that organothiocyanates react with TMS-CF_3 via nucleophilic CN/CF_3 exchange.[20]

We have recently disclosed a trifluoromethyl thioether synthesis through Sandmeyer thiocyanation with concomitant Langlois-type nucleophilic trifluoromethylation of the organothiocyanate intermediate.[21] This synthetic entry is straightfor-

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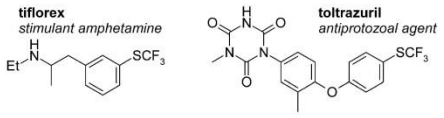
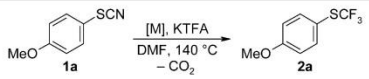


Figure 1. Biologically active trifluoromethyl thioethers.

ward and relatively inexpensive, but would yet vastly improve if the CF_3 nucleophile could be generated from trifluoroacetate rather than TMS–CF_3.

In our search for novel decarboxylation catalysts, we used a model reaction of 4-methoxyphenyl thiocyanate and potassium trifluoroacetate. In the absence of a catalyst, the desired trifluoromethyl thioether **2a** was formed in low quantities by thermal decarboxylation in DMF at 140 °C (Table 1, entry 1). In the presence of stoichiometric amounts of a standard decarboxylation mediator, that is, copper iodide, **2a** was obtained in reasonable yields (entry 2).[8]

Table 1. Optimization of the reaction conditions.[a]



Entry	[M]	**2a** [%][b]
1	–	17
2[c]	CuI	73
3	ZnI_2	80
4	$MnBr_2 \cdot 4H_2O$	14
5	$Fe(OTf)_2$	48
6	$Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$	9
7	$FeCl_3$	51
8	$FeCl_2$	98
9[d]	$FeCl_2$	70
10	$K_4[Fe(CN)_6]$	15

[a] Reaction conditions: 0.5 mmol of 4-methoxyphenyl thiocyanate, 1.5 mL of DMF, 0.6 mmol of KTFA, 0.15 mmol of [M], 140 °C, 16 h. [b] Yields were determined by ^{19}F NMR spectroscopy using 2,2,2-trifluoroethanol as an internal standard. [c] 1 equiv of [M]. [d] 20 mol% $FeCl_2$. KTFA = potassium trifluoroacetate.

A systematic survey of other metal salts revealed that some zinc, manganese and iron salts also display decarboxylation activity (entries 3–8, see also the Supporting Information). Among them, iron(II) chloride is the most effective promoter. Even when employed in catalytic quantities, complete conversion and near-quantitative yields were obtained (entry 8). This was an exciting finding, because iron(II) catalysts[22] are inexpensive and nontoxic, and in this particular reaction, should capture the cyanide byproduct with formation of exceedingly stable, nontoxic potassium hexacyanoferrate(II).[23] Its formation was confirmed by the intense Prussian blue color observed upon addition of $FeCl_3$ to the reaction mixture.

Control experiments with high-purity $FeCl_2$ confirmed that the catalyst is indeed iron(II), rather than a metal contaminant. Because of its dual function as a catalyst and cyanide scavenger, at least 20 mol% $FeCl_2$ are needed to ensure high yields (entry 9). With increasing cyanide concentrations, iron(II) progressively loses its activity, and $K_4[Fe(CN)_6]$ is catalytically inactive (entry 10). Further experiments revealed that water and oxygen hinder the reaction only when present in large quantities, so that special purification of reagents and solvents is not required.

We next investigated the applicability of our iron-catalyzed decarboxylative trifluoromethyl thioether synthesis. The examples in Table 2 show that various organothiocyanates, which are easily accessible from aromatic amines through Sandmeyer reactions,[24] from arylboronic acids via Chan–Lam reactions,[25] or from (hetero)arenes by Friedel–Crafts reactions,[26] were smoothly converted into the corresponding trifluoromethyl thioethers. The decarboxylative trifluoromethylation is applicable to aliphatic, aromatic and heteroaromatic substrates. Common functionalities are tolerated, including ester, ether, keto, amino, hydroxy and even bromo groups. The reaction is particularly effective for electron-rich thiocyanates; electron-deficient derivatives gave somewhat lower yields. This may indicate that the substitution reaction proceeds via a transition state with strongly elongated S–CN bond and a positive partial charge at the sulfur atom which is destabilized by electron-withdrawing substituents. The successful synthesis of **2a** in 96% yield on a multigram scale validates the scalability of the process.

The reaction mechanism was investigated in a series of experiments (Scheme 2). The iron-catalyzed decarboxylative trifluoromethylation of **1a** takes place in the presence of radical scavengers, discounting a radical pathway (1). In contrast, the non-catalyzed background reaction is strongly affected by radical scavengers (2). Because disulfides are known substrates for thermal decarboxylative trifluoromethylations,[19] one might suspect their intermediacy in the iron-catalyzed process. However, the reaction of **1a** with $FeCl_2$ did not result in the formation of disulfides (3). Moreover, the decarboxylative trifluoromethylation of preformed disulfides was not improved by the presence of $FeCl_2$, and was strongly affected by radical scavengers (4).

Our findings suggest that the iron-catalyzed process proceeds via two-electron intermediates and is much more efficient than the thermal decarboxylation observed as a background reaction (Scheme 3). It is not yet clear whether the process indeed involves $FeCF_3$ species or whether Fe^{II} serves to stabilize intermediate DMF-CF_3^- adducts.

If Fe^{II} truly functions as a two-electron catalyst, the decarboxylative trifluoromethylation will potentially extend to a broad range of nucleophilic coupling processes. Indeed, the well-studied thermal trifluoromethylation of aryl aldehydes[8] was also efficiently promoted by iron chloride. Thus, KCO_2CF_3 and the highly functionalized aldehyde **4a** reacted to the corresponding α-trifluoromethyl alcohol in the presence of iron chloride, with yields substantially in excess of those observed for the thermal decarboxylative trifluoromethylation (Scheme 4).

In conclusion, $FeCl_2$ strongly promotes the decarboxylation of trifluoroacetate with formation of CF_3 nucleophiles. This was incorporated as an elemental step into a novel synthesis of val-

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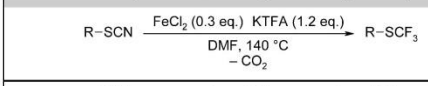
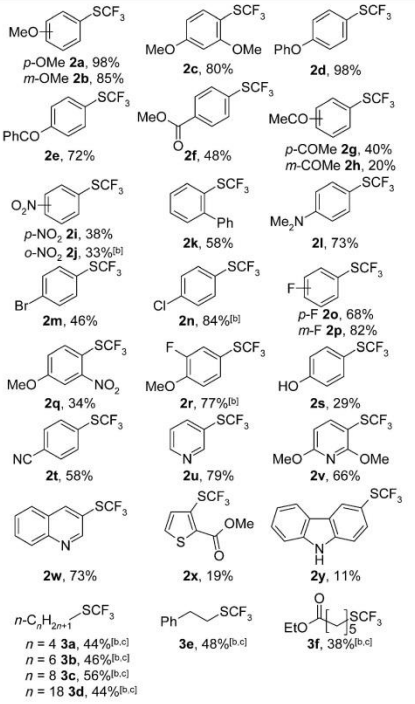
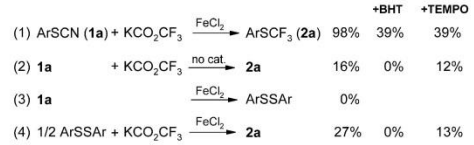
Table 2. Decarboxylative trifluoromethylation of organothiocyanates.[a]

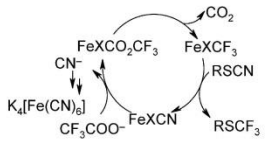




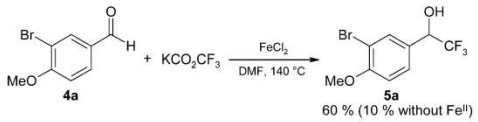
[a] 1.0 mmol of organothiocyanate, 0.3 mmol of $FeCl_2$, 1.2 mmol of KTFA, 3.0 mL of DMF, 140 °C, 16 h. Isolated yields. [b] Yields were determined by ^{19}F NMR spectroscopy using 2,2,2-trifluoroethanol as an internal standard. [c] The aliphatic thiocyanates were generated in situ from 1.0 mmol of the corresponding alkyl bromide and 1.0 mmol NaSCN in 1.5 mL of DMF, 60 °C, 3 h.



Scheme 2. Control experiments performed at 140 °C in DMF.



Scheme 3. Proposed reaction mechanism; X = Cl^-, CN^-, $CF_3CO_2^-$.



Scheme 4. Fe^{II}-catalyzed decarboxylative trifluoromethylation of aldehydes.

uable trifluoromethyl thioethers from easily accessible organothiocyanates, and of α-trifluoromethyl alcohols from aldehydes. Ongoing research is directed towards utilizing trifluoroacetates as a sustainable CF_3^- source in other nucleophilic trifluoromethylation reactions.

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Keywords: decarboxylative couplings · fluorine · iron · trifluoromethylation · synthesis design

[1] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.

[2] a) *Fluorine-Containing Amino Acids* (Eds.: V. P. Kukhar, V. A. Soloshonok), Wiley, Hoboken, **1995**; b) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley, Chichester, **2009**.

[3] J. H. Simons, C. J. Lewis, *J. Am. Chem. Soc.* **1938**, *60*, 492–492.

[4] a) T. Liu, Q. Shen, *Eur. J. Org. Chem.* **2012**, 6679–6687; b) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264; *Angew. Chem.* **2013**, *125*, 8372–8423; c) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; d) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; e) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683–730; f) T. Umemoto, S. Ishihara, *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164; g) J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682.

[5] a) P. Novák, A. Lishchynskyi, V. V. Grushin, *Angew. Chem. Int. Ed.* **2012**, *51*, 7767–7770; *Angew. Chem.* **2012**, *124*, 7887–7890; b) S. Takemoto, V. V. Grushin, *J. Am. Chem. Soc.* **2013**, *135*, 16837–16840; c) A. Lishchynskyi, M. A. Novikov, E. Martin, E. C. Escudero-Adán, P. Novák, V. V. Grushin, *J. Org. Chem.* **2013**, *78*, 11126–11146.

[6] G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324–1327.

[7] a) G. E. Carr, R. D. Chambers, T. F. Holmes, D. G. Parker, *J. Chem. Soc. Perkin Trans. 1* **1988**, 921–926; b) K. Matsui, E. Tobita, M. Ando, K. Kondo, *Chem. Lett.* **1981**, 1719–1720.

[8] a) Y. Chang, C. Cai, *J. Fluor. Chem.* **2005**, *126*, 937–940; b) Y. Chang, C. Cai, *Tetrahedron Lett.* **2005**, *46*, 3161–3164.

[9] a) B. Quiclet-Sire, R. N. Saicic, S. Z. Zard, *Tetrahedron Lett.* **1996**, *37*, 9057–9058; b) N. Roques, *J. Fluor. Chem.* **2001**, *107*, 311–314.

[10] a) K. A. McReynolds, R. S. Lewis, L. K. G. Ackerman, G. G. Dubinina, W. W. Brennessel, D. A. Vicic, *J. Fluor. Chem.* **2010**, *131*, 1108–1112; b) M. Chen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 11628–11631; *Angew. Chem.* **2013**, *125*, 11842–11845.

[11] T. Schareina, X.-F. Wu, A. Zapf, A. Cotté, M. Gotta, M. Beller, *Top. Catal.* **2012**, *55*, 426–431.

[12] a) L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662–664; b) *Topics in Organometallic Chemistry: Inventing Reactions* (Ed.: L. J. Gooßen), Springer, Heidelberg, **2013**; c) B. Song, T. Knauber, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 2954–2958; *Angew. Chem.*

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2013, *125*, 3026 – 3030; d) A. Fromm, C. van Wüllen, D. Hackenberger, L. J. Gooßen, *J. Am. Chem. Soc.* **2014**, *136*, 10007 – 10023.

[13] a) F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415 – 2428; b) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731 – 764.

[14] C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207 – 1216.

[15] E. A. Nodiff, S. Lipschutz, P. N. Craig, M. Gordon, *J. Org. Chem.* **1960**, *25*, 60 – 65.

[16] a) C.-P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183 – 185; b) G. Yin, I. Kalvet, U. Englert, F. Schoenebeck, *J. Am. Chem. Soc.* **2015**, *137*, 4164 – 4172.

[17] a) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 1548 – 1552; *Angew. Chem.* **2013**, *125*, 1588 – 1592; b) X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457 – 3460; *Angew. Chem.* **2013**, *125*, 3541 – 3544; c) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem. Int. Ed.* **2012**, *51*, 2492 – 2495; *Angew. Chem.* **2012**, *124*, 2542 – 2545; d) L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237 – 18240; e) R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 1650 – 1653; *Angew. Chem.* **2014**, *126*, 1676 – 1679; f) C.-P. Zhang, D. A. Vicic, *Chem. Asian J.* **2012**, *7*, 1756 – 1758; g) T. Liu, Q. Shen, *Org. Lett.* **2011**, *13*, 2342 – 2345.

[18] a) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 7312 – 7314; *Angew. Chem.* **2011**, *123*, 7450 – 7452; b) C. Xu, Q. Shen, *Org. Lett.* **2014**, *16*, 2046 – 2049; c) W. Yin, Z. Wang, Y. Huang, *Adv. Synth. Catal.* **2014**, *356*, 2998 – 3006; d) G. Yin, I. Kalvet, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2015**, *54*, 6809 – 6813; *Angew. Chem.* **2015**, *127*, 6913 – 6917.

[19] a) C. Xu, B. Ma, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 9316 – 9320; *Angew. Chem.* **2014**, *126*, 9470 – 9474; b) Q. Wang, Z. Qi, F. Xie, X. Li, *Adv. Synth. Catal.* **2015**, *357*, 355 – 360; c) R. Honeker, J. B. Ernst, F. Glorius, *Chem. Eur. J.* **2015**, *21*, 8047 – 8051; d) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner, H. D. Durst, *Synth. Commun.* **2000**, *30*, 2847 – 2854.

[20] T. Billard, S. Large, B. R. Langlois, *Tetrahedron Lett.* **1997**, *38*, 65 – 68.

[21] a) B. Bayarmagnai, C. Matheis, E. Risto, L. J. Goossen, *Adv. Synth. Catal.* **2014**, *356*, 2343 – 2348; b) K. Jouvin, C. Matheis, L. J. Goossen, *Chem. Eur. J.* **2015**, *21*, 14324 – 14327; c) B. Bayarmagnai, C. Matheis, K. Jouvin, L. J. Goossen, *Angew. Chem. Int. Ed.* **2015**, *54*, 5753 – 5756; *Angew. Chem.* **2015**, *127*, 5845 – 5848; d) C. Matheis, M. Wang, T. Krause, L. J. Goossen, *Synlett* **2015**, *26*, 1628 – 1632.

[22] For iron-catalyzed decarboxylations of other carboxylates, see: a) H.-P. Bi, W.-W. Chen, Y.-M. Liang, C.-J. Li, *Org. Lett.* **2009**, *11*, 3246 – 3249; b) T. Patra, A. Deb, S. Manna, U. Sharma, D. Maiti, *Eur. J. Org. Chem.* **2013**, 5247 – 5250; c) H. Yang, H. Yan, P. Sun, Y. Zhu, L. Lu, D. Liu, G. Rong, J. Mao, *Green Chem.* **2013**, *15*, 976 – 981; d) J. Zhao, H. Fang, J. Han, Y. Pan, *Beilstein J. Org. Chem.* **2013**, *9*, 1718 – 1723; e) J. Zhao, W. Zhou, J. Han, G. Li, Y. Pan, *Tetrahedron Lett.* **2013**, *54*, 6507 – 6510.

[23] LD_{50} of $K_4[Fe(CN)_6]$ 3613 mg kg^{-1} versus KCN 5 mg kg^{-1}, oral, rat.

[24] a) M. Barbero, I. Degani, N. Diulgheroff, S. Dughera, R. Fochi, *Synthesis* **2001**, 0585 – 0590; b) I. P. Beletskaya, A. S. Sigeev, A. S. Peregudov, P. V. Petrovskii, *Mendeleev Commun.* **2006**, *16*, 250 – 251; c) L. Gattermann, W. Haussknecht, L. Gattermann, W. Haussknecht, *Berichte Dtsch. Chem. Ges.* **1890**, *23*, 738 – 739; d) K. Pilgram, D. D. Phillips, *J. Org. Chem.* **1965**, *30*, 2388 – 2392.

[25] N. Sun, H. Zhang, W. Mo, B. Hu, Z. Shen, X. Hu, *Synlett* **2013**, *24*, 1443 – 1447.

[26] a) F. D. Toste, V. d. Stefano, I. W. J. Still, *Synth. Commun.* **1995**, *25*, 1277 – 1286; b) F. D. Toste, I. W. J. Still, *J. Am. Chem. Soc.* **1995**, *117*, 7261 – 7262.

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4.4 Sandmeyer Pentafluoroethylthiolierung - SC_2F_5

Das Ziel dieses Projekts bestand an der konsequenten Fortsetzung der Sandmeyer Trifluormethylthiolierung. Die Erweiterung dieser Methode auf die nächst längere perfluorierte Thioalkylgruppe (SC_2F_5) wurde untersucht. Die vielversprechenden Eigenschaften dieser Gruppe wurden aufgrund fehlender Reagenzien und Methoden vorher nahezu nicht untersucht. Herrn C. Matheis und mir gelang es mittels einer Zusammenarbeit mit der Firma *CF Plus Chemicals* ein neues SC_2F_5-Reagenz, ein Tetramethylammonium Pentafluoroethylthiolat Salz, aus nichtozonschädigenden Fluorkohlenwasserstoffen (TMS-CF_2CF_3) und elementarem Schwefel herzustellen. In ersten Testreaktionen wurde das neue Reagenz in das aus vorangegangenen Arbeiten erarbeitetes Protokoll zur Sandmeyer Trifluormethylthiolierung (SCF_3)[87] übertragen, wodurch das gewünschte Produkt erhalten und die Machbarkeit dieses Ansatzes gezeigt werden konnte. Anschließend wurde die Methode von Herrn C. Matheis und mir vollständig optimiert. Mit Unterstützung von Dr. K. Jouvin wurde die Anwendungsbreite bestimmt. Das Manuskript wurde von mir und Herrn Prof. Dr. L. J. Gooßen verfasst, während Herr C. Matheis die Supporting Information erstellte.

Die Ergebnisse wurden 2016 in der Zeitschrift *Organic Chemistry Frontiers* veröffentlicht.[113] Eine Kopie des Manuskripts ist nachfolgend beigefügt.

ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

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Convenient synthesis of pentafluoroethyl thioethers *via* catalytic Sandmeyer reaction with a stable fluoroalkylthiolation reagent†

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Aromatic and heteroaromatic diazonium salts were smoothly converted into the corresponding pentafluoroethyl thioethers by reaction with $Me_4NSC_2F_5$ in the presence of catalytic amounts of elemental copper. This Sandmeyer-type reaction proceeds at room temperature under mild conditions and is applicable to a wide range of functionalised molecules. It enables the late-stage introduction of pentafluoroethylthio groups, a promising but largely unexplored substituent, into bioactive molecules.

Fluorine-containing groups are of exceptional importance in modern bioactive molecules. Approximately 40% of currently marketed agrochemicals and 25% of pharmaceuticals contain fluorine atoms.[1] The systematic introduction and screening of fluorinated residues has become a standard procedure in drug discovery. Thus, methods for the late-stage introduction of fluorinated substituents into functionalised molecules are highly sought-after. In the past decade, various powerful fluoroalkylation methods have been developed.[2] The attention has recently shifted towards fluoroalkyl thioethers, since the SCF_3 group induces even higher lipophilicity (Hansch constant 1.44 for SCF_3 *vs.* 0.88 for CF_3) and membrane permeability.[3]

Contemporary trifluoromethylthiolation reactions of arenes are based on electrophilic,[4] nucleophilic,[5] radical,[6] or oxidative processes,[7] usually starting from arylboronic acids or aryl halides.

Our contribution to the field of fluoroalkyl(thiol)ations has been the development of several Sandmeyer-type processes.[8] We have demonstrated that a Sandmeyer-thiocyanation followed by a Langlois-type nucleophilic CN/CF_3- or CF_2H-exchange allows the convenient synthesis of fluoroalkylthioethers.[8f,9] For laboratory-scale applications, the use of preformed reagents such as (bpy)CuSCF_3,[10] AgSCF_3 [5a] and Me_4NSCF_3 are more convenient. The bench-stable reagent Me_4NSCF_3 was first synthesised by Roeschenthaler and Yagupolskii[11] and has successfully been employed in trifluoromethylthiolations of vinyl iodides,[12] boronic acids,[7d] aryl halides,[13] aryl triflates,[14] and aryl C–H bonds[15] catalysed by Cu, Ni, or Pd complexes.

In medicinal chemistry, C_2F_5 derivatives have repeatedly been found to exhibit properties that are superior to those of their CF_3 counterparts. Whereas several methods have been reported for the introduction of pentafluoroethyl groups, there are only few reports on the corresponding pentafluoroethylthio compounds.[16] Pentafluoroethyl thioarenes cannot be prepared by classical halogen/fluorine exchange reactions, *e.g.* Swarts-type processes. Traditional syntheses of SC_2F_5 moieties are based on the reaction of C_2F_5 radicals or carbanions with disulfides or thiols.[17] However, these methods suffer from harsh reaction conditions and limited availability of sulfur-containing substrates.

Modern methods suitable for the late-stage introduction of SC_2F_5 groups include the Friedel–Crafts-type reaction of electron-rich arenes with a pentafluoroethyl sulfenamide reagent described by Billard *et al.*[18] and the electrophilic perfluoroalkylthiolation of indoles with perfluoroalkyl sulfinate salts in the presence of stoichiometric copper chloride reported by Zhang *et al.*[19] However, these methods are limited to electron-rich arenes and indoles. A generally applicable, regiospecific method for the introduction of SC_2F_5 groups within a single step, based on widely available substrates and an inexpensive fluoroalkylation reagent, would be highly desirable.

We approached this challenge by investigating Sandmeyer-type pentafluoroethylthiolations (Scheme 1). $Me_4NSC_2F_5$ appeared to be the reagent of choice, because according to a patent by Roeschenthaler, it is easily accessible from tetramethylammonium fluoride, elemental sulfur and $TMSC_2F_5$.[11a,20]

In order to probe the viability of our approach, we treated 4-methoxybenzenediazonium tetrafluoroborate with $Me_4NSC_2F_5$ in the presence of 10 mol% CuSCN in acetonitrile at room temperature, conditions previously optimised for

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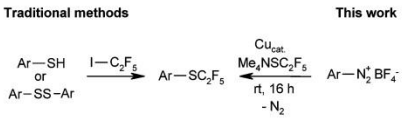
‡These authors contributed equally to this work.



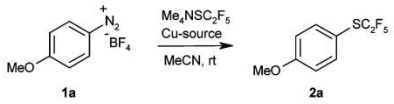
Scheme 1 Syntheses of pentafluoroethyl thioethers.

Sandmeyer trifluoromethylthiolations.[8e] The pentafluoroethyl thioether was indeed observed, albeit in unsatisfactory yield. The main products were 4-methoxyphenyl thiocyanate and the protodediazotisation product anisole (Table 1, entry 1). It soon became clear that $C_2F_5S^-$ is substantially less nucleophilic than SCF_3^-, so that pentafluoroethylthiolation takes place only in reaction media free of other nucleophiles. Thus, most counter-ions of copper(I) precursors led to unwanted side product formation. However, the desired product was formed in high yield in the presence of elemental copper (entries 2–4).

The best results were obtained with 10 mol% of Cu (entries 5–7). This is remarkable, since there are only few examples of Sandmeyer reactions catalytic in copper. The markedly lower nucleophilicity of the pentafluoroethylthio group in comparison to the trifluoromethylthio group is reflected in the increased reaction times; the pentafluoroethylthiolation requires 15 hours to go to completion, whereas Sandmeyer trifluoromethylthiolations occur within less than one hour at room temperature (entry 8).[8e] Without copper, no product formation was observed (entry 9).

Having thus found an effective protocol for the Sandmeyer pentafluoroethylthiolation, we next investigated its scope. Various arenediazonium tetrafluoroborates were smoothly converted into the corresponding pentafluoroethyl thioethers in high yields (Table 2).

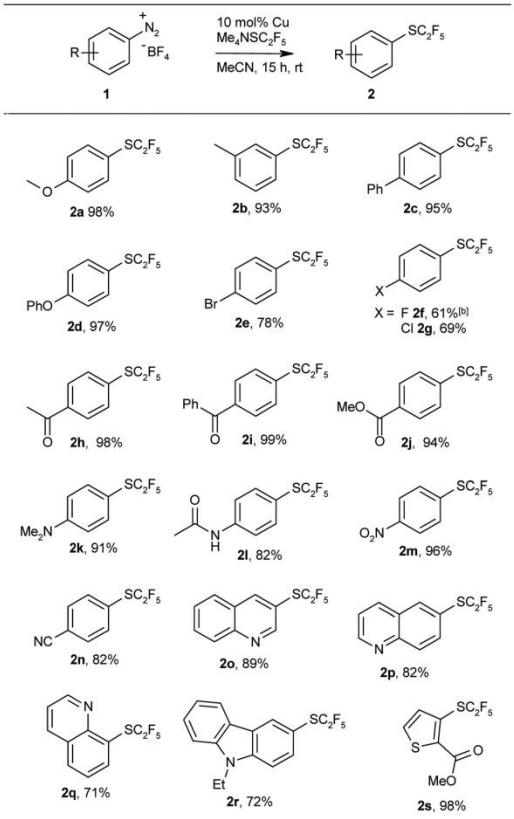
Table 1 Optimisation of the reaction conditions[a]



Entry	Cu-source	Yield **2a** [%]
1	10 mol% CuSCN	70
2	10 mol% CuOAc	15
3	10 mol% CuI	20
4	10 mol% Cu	99
5	5 mol% Cu	62
6	0.5 equiv. Cu	89
7	1.0 equiv. Cu	75
8[b]	1.0 equiv. Cu	12
9	—	0

[a] Reaction conditions: dropwise addition of 0.5 mmol of **1a** in 1 mL acetonitrile to 1.5 equiv. $Me_4NSC_2F_5$ and the copper source in 1 mL acetonitrile, 15 h at room temperature. Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard. [b] 1 h reaction time.

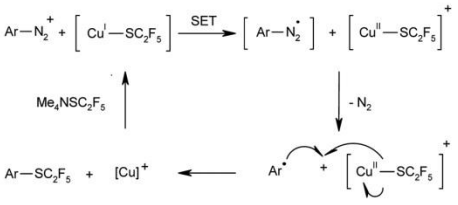
Table 2 Substrate scope of the Sandmeyer pentafluoroethylthiolation[a]



[a] Reaction conditions: dropwise addition of 1.0 mmol of **1** in 2 mL MeCN to 1.5 mmol $Me_4NSC_2F_5$ and 0.1 mmol elemental copper in 2 mL MeCN, 15 h at room temperature. [b] Yields determined by ^{19}F NMR using trifluoroethanol as an internal standard.

Both electron-rich and electron-deficient substrates give similarly high yields, and various functionalities are tolerated including ester, ether, amino, keto, carboxylate, cyano, and even bromo groups. Various heterocycles were also pentafluoroethylthiolated in good yields. These examples clearly demonstrate the utility of the protocol for late-stage pentafluoroethylthiolations of functionalised intermediates. The products are obtained in reasonable purity after simple aqueous workup, and can be further purified by column chromatography.

It is safe to assume that in analogy to classical Sandmeyer halogenations and trifluoromethylthiolations of diazonium salts, the reaction proceeds *via* a single-electron transfer mechanism as depicted in Scheme 2. The use of metallic copper as source of Cu(I) species in these processes is rare but



Scheme 2 Sandmeyer pentafluoroethylthiolation of aromatic amines.

not unprecedented.[8e,21] The addition of radical quenchers such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or *p*-benzoquinone suppressed the reaction, which confirms that the reaction involves radical intermediates. In order to exclude an alternative cationic pathway for extremely electron-poor substrates, analogous control experiments were conducted with 4-nitrobenzenediazonium tetrafluoroborate. In the absence of copper or in the presence of radical trapping reagents no product formation was detected, which supports a Sandmeyer type mechanism even for substrates in which other pathways are conceivable.

Conclusions

The Sandmeyer-type process reported herein allows the straightforward synthesis of pentafluoroethylthiolated compounds from the corresponding aromatic amines. The key advantages of this method are its mild reaction conditions (neutral, room temperature), the use of an inexpensive copper catalyst in only 10 mol% loading, and the exceptional functional group tolerance. As a result, this method is well-suited for the late-stage introduction of pentafluoroethylthio groups into drug-like molecules.

Acknowledgements

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References

1 (*a*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506; (*b*) P. Jeschke, *ChemBioChem*, 2004, **5**, 570–589; (*c*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369.

2 (*a*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475–4521; (*b*) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470–477; (*c*) X.-F. Wu, H. Neumann and M. Beller, *Chem. – Asian J.*, 2012, **7**, 1744–1754; (*d*) T. Liu and Q. Shen, *Eur. J. Org. Chem.*, 2012, 6679–6687; (*e*) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214–8264; (*f*) X. Liu, C. Xu, M. Wang and Q. Liu, *Chem. Rev.*, 2015, **115**, 683–730; (*g*) C. Alonso, E. Martínez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847–1935.

3 (*a*) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani and E. J. Lien, *J. Med. Chem.*, 1973, **16**, 1207–1216; (*b*) F. Toulgoat, S. Alazet and T. Billard, *Eur. J. Org. Chem.*, 2014, 2415–2428.

4 (*a*) A. Tlili and T. Billard, *Angew. Chem., Int. Ed.*, 2013, **52**, 6818–6819; (*b*) X. Shao, X. Wang, T. Yang, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2013, **52**, 3457–3460; (*c*) Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro and N. Shibata, *J. Am. Chem. Soc.*, 2013, **135**, 8782–8785; (*d*) R. Pluta, P. Nikolaienko and M. Rueping, *Angew. Chem., Int. Ed.*, 2014, **53**, 1650–1653; (*e*) C. Xu, B. Ma and Q. Shen, *Angew. Chem., Int. Ed.*, 2014, **53**, 9316–9320.

5 (*a*) G. Teverovskiy, D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 7312–7314; (*b*) C.-P. Zhang and D. A. Vicic, *J. Am. Chem. Soc.*, 2012, **134**, 183–185; (*c*) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan and K.-W. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 1548–1552.

6 L. D. Tran, I. Popov and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237–18240.

7 (*a*) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2012, **51**, 2492–2495; (*b*) C. Chen, L. Chu and F.-L. Qing, *J. Am. Chem. Soc.*, 2012, **134**, 12454–12457; (*c*) C.-P. Zhang and D. A. Vicic, *Chem. – Asian J.*, 2012, **7**, 1756–1758; (*d*) S.-Q. Zhu, X.-H. Xu and F.-L. Qing, *Eur. J. Org. Chem.*, 2014, 4453–4456.

8 (*a*) B. Bayarmagnai, C. Matheis, E. Risto and L. J. Goossen, *Adv. Synth. Catal.*, 2014, **356**, 2343–2348; (*b*) G. Danoun, B. Bayarmagnai, M. Grünberg, C. Matheis, E. Risto and L. Gooßen, *Synthesis*, 2014, 2283–2286; (*c*) C. Matheis, K. Jouvin and L. J. Goossen, *Org. Lett.*, 2014, **16**, 5984–5987; (*d*) B. Bayarmagnai, C. Matheis, K. Jouvin and L. J. Goossen, *Angew. Chem., Int. Ed.*, 2015, **54**, 5753–5756; (*e*) C. Matheis, V. Wagner and L. J. Goossen, *Chem. – Eur. J.*, 2016, **22**, 79–82; (*f*) G. Danoun, B. Bayarmagnai, M. F. Gruenberg and L. J. Goossen, *Chem. Sci.*, 2014, **5**, 1312–1316.

9 (*a*) B. Exner, B. Bayarmagnai, F. Jia and L. J. Goossen, *Chem. – Eur. J.*, 2015, **21**, 17220–17223; (*b*) K. Jouvin, C. Matheis and L. J. Goossen, *Chem. – Eur. J.*, 2015, **21**, 14324–14327; (*c*) C. Matheis, M. Wang, T. Krause and L. Goossen, *Synlett*, 2015, **26**, 1628–1632.

10 (*a*) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan and K.-W. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 1548–1552; (*b*) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2012, **51**, 2492–2495; (*c*) Y. Zhang, K. Gan and Z. Weng, *Org. Process Res. Dev.*, 2016, **20**, 799–802.

11 (*a*) P. Kirsch, G. V. Roeschenthaler, B. Bissky and A. Kolomeitsev, *DE-A1* 10254597, 2003, Merck GmbH;

(*b*) W. Tyrra, D. Naumann, B. Hoge and Y. L. Yagupolskii, *J. Fluorine Chem.*, 2003, **119**, 101–107.
12 M. Rueping, N. Tolstoluzhsky and P. Nikolaienko, *Chem. – Eur. J.*, 2013, **19**, 14043–14046.
13 (*a*) G. Yin, I. Kalvet, U. Englert and F. Schoenebeck, *J. Am. Chem. Soc.*, 2015, **137**, 4164–4172; (*b*) G. Yin, I. Kalvet and F. Schoenebeck, *Angew. Chem., Int. Ed.*, 2015, **54**, 6809–6813; (*c*) Y. Yang, L. Xu, S. Yu, X. Liu, Y. Zhang and D. A. Vicic, *Chem. – Eur. J.*, 2016, **22**, 858–863.
14 A. B. Dürr, G. Yin, I. Kalvet, F. Napoly and F. Schoenebeck, *Chem. Sci.*, 2016, **7**, 1076–1081.
15 C. Xu and Q. Shen, *Org. Lett.*, 2014, **16**, 2046–2049.
16 (*a*) M. Andrzejewska, *Eur. J. Med. Chem.*, 2002, **37**, 973–978; (*b*) A. Johansson, A. Poliakov, E. Åkerblom, K. Wiklund, G. Lindeberg, S. Winiwarter, U. H. Danielson, B. Samuelsson and A. Hallberg, *Bioorg. Med. Chem.*, 2003, **11**, 2551–2568; (*c*) A. Lishchynskyi and V. V. Grushin, *J. Am. Chem. Soc.*, 2013, **135**, 12584–12587.
17 N. Roques, *J. Fluorine Chem.*, 2001, **107**, 311–314.
18 S. Alazet and T. Billard, *Synlett*, 2014, 76–78.
19 L. Jiang, J. Qian, W. Yi, G. Lu, C. Cai and W. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 14965–14969.
20 (*a*) P. Kirsch, *Modern fluoroorganic chemistry: synthesis, reactivity, applications*, Wiley-VCH, Weinheim, 2004, p. 145; (*b*) $Me_4NSC_2F_5$ was commercially available by CF Plus Chemicals s. r. o.
21 (*a*) N. Kornblum, G. D. Cooper and J. E. Taylor, *J. Am. Chem. Soc.*, 1950, **72**, 3013–3021; (*b*) C. Galli, *Chem. Rev.*, 1988, **88**, 765–792.

4.5 Eisenvermittelte Decarboxylierung perfluorierter Carbonsäure Derivate - SR_f

Das Ziel dieses Projekts bestand an der Fortsetzung der Arbeiten zur eisenvermittelten Decarboxylierungen der Trifluoracetate. Nach der erfolgreichen Entwicklung zur decarboxylierenden Trifluormethylierung der Thiocyanate, war es naheliegend Decarboxylierungen weiterer perfluorierten Carbonsäure Derivaten zu untersuchen. Dabei wurde zunächst die Decarboxylierung der Pentafluorpropionate in Anwesenheit von Eisen- und Kupfermediatoren unter denselben Reaktionsbedingungen, die sich für die Decarboxylierung von Trifluoracetaten als optimal erwiesen hatten, untersucht. Die Kontrollexperimente bestätigten die Realisierbarkeit dieser Methode und den analogen mechanistischen Verlauf.

Herr B. Exner entwickelte die Reaktion und optimierte das Katalysatorsystems. Herr B. Exner, Herr C. Matheis und ich synthetisierten diverse Organothiocyanate als Startmaterialien und untersuchten die Anwendungsbreite der Reaktion. Herr B. Exner verfasste das Manuskripts zusammen mit Herrn Prof. Dr. L. J. Gooßen, während Herr C. Matheis und ich die analytischen Daten auswerteten und die Supporting Information erstellten.

Die Ergebnisse wurden 2016 in der Zeitschrift *Journal of Fluorine Chemistry* eingereicht. Eine Kopie des Manuskriptentwurfs ist nachfolgend beigefügt.

Synthesis of perfluoroalkyl thioethers from aromatic thiocyanates by iron-catalysed decarboxylative perfluoroalkylation

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Abstract

Easily available aryl and heteroaryl thiocyanates were converted into the corresponding perfluoroalkyl thioethers *via* decarboxylation of potassium perfluoroalkylcarboxylates, catalysed by the inexpensive and environmentally benign iron(III) chloride.

Keywords: Iron, perfluoroalkylation, perfluoroalkylthiolation, decarboxylative couplings

1. Introduction

The introduction of fluorine-containing groups into organic molecules is of great interest for the development of pharmaceuticals, agrochemicals, and functional materials, since these groups enhance properties such as metabolic stability, lipophilicity and dipole moment.[1–3] Perfluoroalkyl thioethers, in particular, have recently drawn considerable attention in drug discovery because of their higher lipophilicity and membrane permeability compared to the perfluoroalkyl analogues.[4]

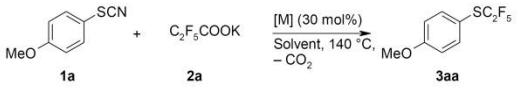
Traditional trifluoromethylation reactions are usually confined to the beginning of a chemical synthesis due to the common use of aggressive reagents under often harsh reaction conditions.[5] This has triggered considerable advances in this field in recent years.[6–9] In contrast, the chemistry of longer-chain substituents such as pentafluoroethyl groups remains somewhat underdeveloped,[10–18] even though their biological activity is greater at times.[19–21] Regardless of the chain length, most methods require fluoroalkylating reagents that are costly, sensitive, waste-intensive and/or arduous to prepare, and that in some cases are banned by the Montreal protocol because of their ozone-depleting properties. Fluorocarbons, such as fluoroform, offer an alternative that circumvents most of these issues, and have successfully been employed.[21–27] They are, however, gaseous up to quite high chain lengths (C_4 for linear compounds[28]) and therefore inconvenient for laboratory use. Furthermore, their immense global warming potentials (GWP, e.g. for CHF_3 it is 14,800 times greater than for CO_2 [29]) are certain to lead to restrictions in their use in the coming years.[30] Perfluoroalkylcarboxylate salts, on the other hand, are solids, easy to store and handle, and release only CO_2. Decarboxylative perfluoroalkylation reactions have been known for several decades, ever since Kondo's pioneering research on the trifluoromethylation of aromatic halides.[31] Several methodologies for the decarboxylative perfluoroalkylation of various electrophiles have since been developed.[32–37] However, almost all of the described processes require overstoichiometric amounts of copper and several equivalents of the corresponding perfluoroalkyl carboxylic acid derivative, exceptions remaining scarce.[38–40]

Based on our experience in fluoroalkylations[41–43] as well as decarboxylative couplings,[44–47] we have recently developed a Langlois-type[48] decarboxylative trifluoromethylation of organothiocyanates catalysed by 30 mol% of iron(II) chloride with 1.2 equivalents of potassium trifluoroacetate, leading to trifluoromethyl thioethers.[49] Literature procedures for the synthesis of thioethers bearing longer perfluoroalkyl chains usually start from thiols or disulfides,[11,16,38,50–52] which is undesirable because of their limited availability. Protocols starting from simple arenes and aromatic amines using preformed reagents have been published only recently by Billard[53] and our own group.[54] In continuation of our work on fluoromethyl(thiol)ations,[55–59] we herein report the synthesis of higher homologues *via* decarboxylative perfluoroalkylation of aryl thiocyanates accessed from aromatic amines by Sandmeyer reaction.

2. Results and discussion

We started the investigations with optimized conditions from our decarboxylative trifluoromethylation. Thus, aryl thiocyanate **1a**, 1.2 equivalents of potassium pentafluoropropionate **2a** and 30 mol% of iron(II) chloride gave the desired product **3aa** in a promising yield of 67% (Table 1, entry 1). A switch to iron(III) chloride or bromide led to quantitative yields (entries 2 and 3). Other Lewis acids as well as CuI gave inferior results, and a control reaction without catalyst also provided substantially lower product yields (entries 4–7). Modifications of the solvent, catalyst loading, or temperature did not improve the outcome (entries 8–12). Besides its good catalytic activity, iron(III) has the additional advantage of capturing the cyanide ion that is released from the thiocyanate as non-toxic hexacyanoferrate(III). (LD_{50} 2970 mg/kg vs. 5 mg/kg for KCN, oral, rat)

Table 1. Optimisation of the reaction conditions[a]



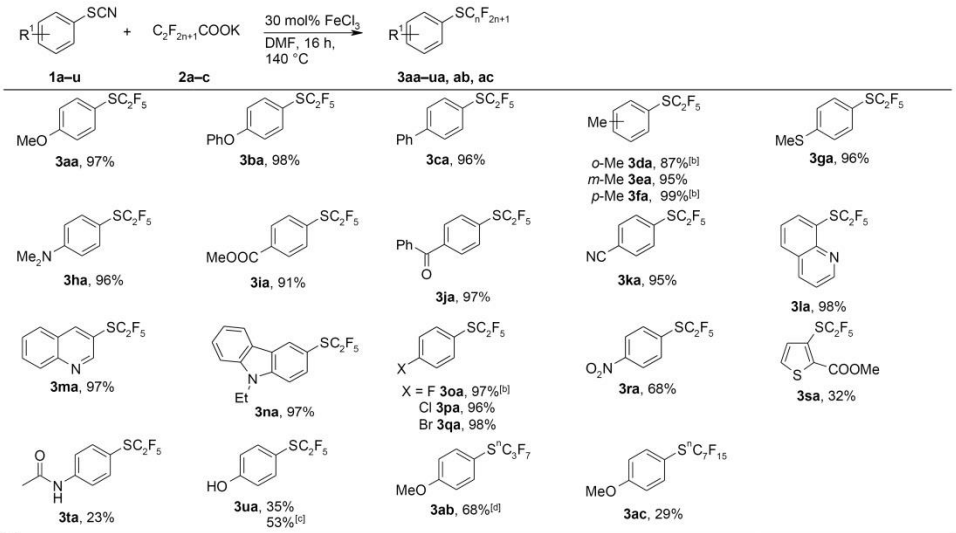
1a **2a** **3aa**

Entry	[M]	Solvent	**3aa** [%]
1	$FeCl_2$	DMF	67
2	$FeCl_3$	DMF	99
3	$FeBr_3$	DMF	99
4	CuI	DMF	81
5	$Sc(OTf)_3$	DMF	16
6	$In(OTf)_3$	DMF	31
7	–	DMF	31
8	$FeCl_3$	NMP	97
9	$FeCl_3$	Me_2SO	89
10	$FeCl_3$	Propylene carbonate	18
11[c]	$FeCl_3$	DMF	81
12[d]	$FeCl_3$	DMF	89

[a] Reaction conditions: 0.30 mmol of 4-methoxyphenyl thiocyanate **1a**, 0.36 mmol of potassium pentafluoropropionate **2a**, 0.09 mmol of [M], 1 mL of solvent, 140 °C, 16 h. [b] Yields were determined by ^{19}F NMR spectroscopy using 2,2,2-trifluoroethanol as an internal standard. [c] Performed at 120 °C. [d] Using 0.20 eq. of $FeCl_3$.

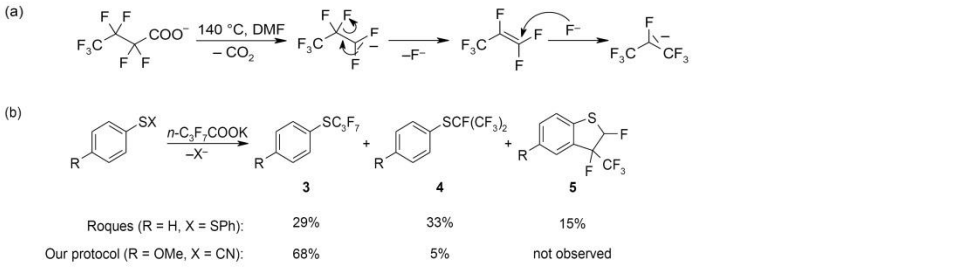
Having thus found the optimal conditions for this reaction, we next investigated its scope (Table 2). Starting materials bearing various functional groups such as ether, thioether, dimethylamino, ester, keto and cyano were smoothly converted into their corresponding SC_2F_5 derivatives (**3aa**–**3kl**). Heterocycles including quinolines (**3la**, **3ma**) and carbazoles (**3na**) were also suitable substrates. The successful conversion of halogeno compounds including chloro (**3pa**) and bromo (**3qa**) derivatives demonstrates that the decarboxylative pentafluoroethylation may be combined with further coupling reactions. *p*-Nitrophenyl thiocyanate gave a moderate product yield (**3ra**), and poor yields were observed starting from thiophene derivatives (**3sa**) or compounds with acidic protons (**3ta**, **3ua**). In the latter case, we hypothesised that the protons led to protodecarboxylation, and the resulting product pentafluoroethane was indeed detected by ^{19}F NMR. This side reaction leaves an insufficient amount of pentafluoropropionate for full conversion, so that we attempted another decarboxylative pentafluoroethylation of the phenol derivative **1u** using 2.2 equivalents of potassium pentafluoropropionate. Indeed, the yield of **3ua** increased from 35 to 53%. The fact that it still remained lower than for most other substrates may be explained by the low electrophilicity of the phenolate ion.

Table 2. Substrate scope of the decarboxylative perfluoroalkylation of arylthiocyanates[a]



[a] Reaction conditions: 2.0 mmol of organothiocyanate **1**, 0.30 mmol of $FeCl_3$, 2.4 mmol of potassium perfluoroalkylcarboxylate **2**, 6.0 mL of DMF, 140 °C, 16 h, isolated yields. [b] The yield was determined by ^{19}F NMR using 2,2,2-trifluoroethanol as an internal standard. [c] 2.2 eq. of potassium pentafluoropropionate were used. [d]The product was contaminated with 5% of the corresponding *iso*-heptafluoropropyl compound as determined by ^{19}F NMR. The yield was adjusted accordingly.

Longer-chain perfluoroalkyl groups were investigated next. With *n*-heptafluorobutyrate, the thioether **3ab** was obtained in 68% yield, along with the corresponding *iso*-heptafluoropropyl side product in ca. 5% yield (determined by ^{19}F NMR). This compares favourably by the work of Roques et al. who got only moderate yields of this product. They rationalized the formation of the unwanted byproduct by a mechanism that involves decarboxylation of the carboxylate to $C_3F_7^-$, followed by elimination and readdition of fluoride leading to rearrangement of the *n*- to the *iso*-heptafluoropropyl anion (Scheme 1a).[38] A second, cyclic byproduct observed by Roques, 2,3-difluoro-5-methoxy-3-(trifluoromethyl)-2,3-dihydro-1-benzothiophene (**5**), was not detected here (Scheme 1b). Interestingly, extending the perfluoroalkyl chain by another four CF_2 units yielded 4-methoxyphenyl perfluoroheptyl thioether **3ac** in 29% yield without any branched side products, as determined by ^{19}F NMR (see the supporting information).



Scheme 1. (a) Origin of side products in decarboxylative heptafluoropropylation and (b) their distribution in the product mixture.

3. Conclusions

The decarboxylative perfluoroalkylation reported herein allows a Langlois-type synthesis of aryl perfluoroalkylthioethers from aryl thiocyanates. Its key advantages are the use of readily available, inexpensive starting materials and an environmentally benign and cheap iron catalyst. Despite the rather high reaction temperatures, the process shows good functional group tolerance, which makes it suitable for the late-stage introduction of perfluoroalkyl chains.

4. Experimental

An oven-dried crimp-cap vessel (20 mL) with stir bar was charged with aryl thiocyanate **1a–u** (2.0 mmol), potassium perfluoroalkylcarboxylate **2a–c** (2.40 mmol), $FeCl_3$ (77.3 mg, 0.60 mmol), and DMF (6 mL). The reaction mixture was stirred for 16 h at 140 °C. The resulting mixture was diluted with diethyl ether (20 mL), then washed with water (20 mL), 20 % (*m*/*m*) aqueous LiCl solution (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated (700 mbar, 40 °C). The residue was purified by flash chromatography (SiO_2, pentane), yielding the perfluoroalkyl thioethers **3aa–3ac**. The yields of particularly volatile compounds were determined by ^{19}F NMR spectroscopy, and their identity by MS.

Acknowledgements

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References

[1] J. Wang, M. Sánchez-Roselló, J.L. Aceña, C. del Pozo, A.E. Sorochinsky, S. Fustero, V.A. Soloshonok, H. Liu, Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011), Chem. Rev. 114 (2014) 2432–2506. doi:10.1021/cr4002879.
[2] P. Jeschke, The Unique Role of Fluorine in the Design of Active Ingredients for Modern Crop Protection, ChemBioChem. 5 (2004) 570–589. doi:10.1002/cbic.200300833.
[3] W.K. Hagmann, The Many Roles for Fluorine in Medicinal Chemistry, J. Med. Chem. 51 (2008) 4359–4369. doi:10.1021/jm800219f.
[4] C. Hansch, A. Leo, S.H. Unger, K.H. Kim, D. Nikaitani, E.J. Lien, Aromatic substituent constants for structure-activity correlations, J. Med. Chem. 16 (1973) 1207–1216. doi:10.1021/jm00269a003.
[5] F. Swarts, Note sur un nouveau dérivé fluoré du carbone, Bull. Acad. R. Belg. (1892) 309–320.
[6] O.A. Tomashenko, V.V. Grushin, Aromatic Trifluoromethylation with Metal Complexes, Chem. Rev. 111 (2011) 4475–4521. doi:10.1021/cr1004293.
[7] T. Furuya, A.S. Kamlet, T. Ritter, Catalysis for fluorination and trifluoromethylation, Nature. 473 (2011) 470–477. doi:10.1038/nature10108.
[8] T. Liang, C.N. Neumann, T. Ritter, Introduction of Fluorine and Fluorine-Containing Functional Groups, Angew. Chem. Int. Ed. 52 (2013) 8214–8264. doi:10.1002/anie.201206566.
[9] X. Liu, C. Xu, M. Wang, Q. Liu, Trifluoromethyltrimethylsilane: Nucleophilic Trifluoromethylation and Beyond, Chem. Rev. 115 (2015) 683–730. doi:10.1021/cr400473a.
[10] P.G. Gassman, N.J. O'Reilly, Pentafluoroethyllithium. Generation and use in synthesis, Tetrahedron Lett. 26 (1985) 5243–5246. doi:10.1016/S0040-4039(00)95005-6.
[11] C. Wakselman, M. Tordeux, Chemistry of halogenoperfluoroalkanes. Synthesis of fluorinated ethers and thioethers via radical or anionic intermediates, J. Org. Chem. 50 (1985) 4047–4051. doi:10.1021/jo00221a017.
[12] P.G. Gassman, N.J. O'Reilly, Nucleophilic addition of the pentafluoroethyl group to aldehydes, ketones, and esters, J. Org. Chem. 52 (1987) 2481–2490. doi:10.1021/jo00388a025.
[13] A.A. Kolomeitsev, A.A. Kadyrov, J. Szczepkowska-Sztolcman, M. Milewska, H. Koroniak, G. Bissky, J.A. Barten, G.-V. Röschenthaler, Perfluoroalkyl borates and boronic esters: new promising partners for Suzuki and Petasis reactions, Tetrahedron Lett. 44 (2003) 8273–8277. doi:10.1016/j.tetlet.2003.09.072.

[14] N.E. Shevchenko, V.G. Nenajdenko, G.-V. Röschenthaler, New method of preparation of C2F5Li and its reactions with cyclic imines and lactims: Synthesis of α-pentafluoroethyl proline, J. Fluor. Chem. 129 (2008) 390–396. doi:10.1016/j.jfluchem.2008.01.013.
[15] R. Krishnamurti, D.R. Bellew, G.K.S. Prakash, Preparation of trifluoromethyl and other perfluoroalkyl compounds with (perfluoroalkyl)trimethylsilanes, J. Org. Chem. 56 (1991) 984–989. doi:10.1021/jo00003a017.
[16] C. Pooput, Dolbier William R., M. Médebielle, Nucleophilic Perfluoroalkylation of Aldehydes, Ketones, Imines, Disulfides, and Diselenides, J. Org. Chem. 71 (2006) 3564–3568. doi:10.1021/jo060250j.
[17] H. Urata, T. Fuchikami, A novel and convenient method for trifluoromethylation of organic halides using CF3SiR'3/KF/Cu(I) system, Tetrahedron Lett. 32 (1991) 91–94. doi:10.1016/S0040-4039(00)71226-3.
[18] Y. Kobayashi, I. Kumadaki, Studies on organic fluorine compounds. Part 27. Abnormal reactions in the trifluoromethylation of aromatic compounds with trifluoromethyl iodide and copper powder, J. Chem. Soc. [Perkin 1]. (1980) 661–664. doi:10.1039/P19800000661.
[19] M. Andrzejewska, L. Yépez-Mulia, R. Cedillo-Rivera, A. Tapia, L. Vilpo, J. Vilpo, Z. Kazimierczuk, Synthesis, antiprotozoal and anticancer activity of substituted 2-trifluoromethyl- and 2-pentafluoroethylbenzimidazoles, Eur. J. Med. Chem. 37 (2002) 973–978. doi:10.1016/S0223-5234(02)01421-6.
[20] A. Johansson, A. Poliakov, E. Åkerblom, K. Wiklund, G. Lindeberg, S. Winiwarter, U.H. Danielson, B. Samuelsson, A. Hallberg, Acyl sulfonamides as potent protease inhibitors of the hepatitis C virus full-Length NS3 (Protease-Helicase/NTPase): A comparative study of different C-terminals, Bioorg. Med. Chem. 11 (2003) 2551–2568. doi:10.1016/S0968-0896(03)00179-2.
[21] A. Lishchynskyi, V.V. Grushin, Cupration of C2F5H: Isolation, Structure, and Synthetic Applications of [K(DMF)2][(t-BuO)Cu(C2F5)]. Highly Efficient Pentafluoroethylation of Unactivated Aryl Bromides, J. Am. Chem. Soc. 135 (2013) 12584–12587. doi:10.1021/ja407017j.
[22] J. Russell, N. Roques, Effective nucleophilic trifluoromethylation with fluoroform and common base, Tetrahedron. 54 (1998) 13771–13782. doi:10.1016/S0040-4020(98)00846-1.
[23] S. Large, N. Roques, B.R. Langlois, Nucleophilic Trifluoromethylation of Carbonyl Compounds and Disulfides with Trifluoromethane and Silicon-Containing Bases, J. Org. Chem. 65 (2000) 8848–8856. doi:10.1021/jo000150s.
[24] A. Zanardi, M.A. Novikov, E. Martin, J. Benet-Buchholz, V.V. Grushin, Direct Cupration of Fluoroform, J. Am. Chem. Soc. 133 (2011) 20901–20913. doi:10.1021/ja2081026.
[25] I. Popov, S. Lindeman, O. Daugulis, Copper-Catalyzed Arylation of 1H-Perfluoroalkanes, J. Am. Chem. Soc. 133 (2011) 9286–9289. doi:10.1021/ja2041942.
[26] G.K.S. Prakash, P.V. Jog, P.T.D. Batamack, G.A. Olah, Taming of Fluoroform: Direct Nucleophilic Trifluoromethylation of Si, B, S, and C Centers, Science. 338 (2012) 1324–1327. doi:10.1126/science.1227859.
[27] A. Lishchynskyi, Z. Mazloomi, V. Grushin, Trifluoromethylation and Pentafluoroethylation of Vinylic Halides with Low-Cost RfH-Derived CuRf (Rf = CF3, C2F5), Synlett. 26 (2014) 45–50. doi:10.1055/s-0034-1379497.
[28] J.D. LaZerte, L.J. Hals, T.S. Reid, G.H. Smith, Pyrolyses of the Salts of the Perfluoro Carboxylic Acids1, J. Am. Chem. Soc. 75 (1953) 4525–4528. doi:10.1021/ja01114a040.
[29] P. Forster, V. Ramaswamy, P. Artaxo, T. Berntsen, R. Betts, D.W. Fahey, J. Haywood, J. Lean, D.C. Lowe, G. Myhre, J. Nganga, R. Prinn, G. Raga, M. Schulz, R. Van Dorland, Changes in Atmospheric Constituents and in Radiative Forcing, in: S. Solomon, D. Qin, M. Manning, Z. Chen, M. Marquis, K.B. Averyt, M. Tignor, H.L. Miller (Eds.), Clim. Change 2007 Phys. Sci. Basis Contrib. Work. Group Fourth Assess. Rep. Intergov. Panel Clim. Change, Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA, 2007. http://www.ipcc.ch/pdf/assessment-report/ar4/wg1/ar4-wg1-chapter2.pdf (accessed October 17, 2016).
[30] Nearly 200 nations agree binding deal to cut greenhouse gases, Reuters. (2016). http://www.reuters.com/article/us-un-climatechange-deal-idUSKBN12F02T (accessed October 17, 2016).
[31] K. Matsui, E. Tobita, M. Ando, K. Kondo, A Convenient Trifluoromethylation of Aromatic Halides with Sodium Trifluoroacetate, Chem. Lett. 10 (1981) 1719–1720. doi:10.1246/cl.1981.1719.
[32] G.E. Carr, R.D. Chambers, T.F. Holmes, D.G. Parker, Sodium perfluoroalkane carboxylates as sources of perfluoroalkyl groups, J. Chem. Soc. [Perkin 1]. (1988) 921–926. doi:10.1039/P19880000921.
[33] Y. Chang, C. Cai, Trifluoromethylation of carbonyl compounds with sodium trifluoroacetate, J. Fluor. Chem. 126 (2005) 937–940. doi:10.1016/j.jfluchem.2005.04.012.
[34] Y. Chang, C. Cai, Sodium trifluoroacetate: an efficient precursor for the trifluoromethylation of aldehydes, Tetrahedron Lett. 46 (2005) 3161–3164. doi:10.1016/j.tetlet.2005.03.072.
[35] B. Quiclet-Sire, R.N. Saicic, S.Z. Zard, A convenient synthesis of trifluoromethyl aryl sulfides, Tetrahedron Lett. 37 (1996) 9057–9058. doi:10.1016/S0040-4039(96)02127-2.
[36] K.A. McReynolds, R.S. Lewis, L.K.G. Ackerman, G.G. Dubinina, W.W. Brennessel, D.A. Vicic, Decarboxylative trifluoromethylation of aryl halides using well-defined copper–trifluoroacetate and –

chlorodifluoroacetate precursors, J. Fluor. Chem. 131 (2010) 1108–1112. doi:10.1016/j.jfluchem.2010.04.005.
[37] M. Chen, S.L. Buchwald, Rapid and Efficient Trifluoromethylation of Aromatic and Heteroaromatic Compounds Using Potassium Trifluoroacetate Enabled by a Flow System, Angew. Chem. Int. Ed. 52 (2013) 11628–11631. doi:10.1002/anie.201306094.
[38] N. Roques, Nucleophilic perfluoroalkylation of diaryldisulfides with perfluorocarboxylate salts, J. Fluor. Chem. 107 (2001) 311–314. doi:10.1016/S0022-1139(00)00374-2.
[39] T. Schareina, X.-F. Wu, A. Zapf, A. Cotté, M. Gotta, M. Beller, Towards a Practical and Efficient Copper-Catalyzed Trifluoromethylation of Aryl Halides, Top. Catal. 55 (2012) 426–431. doi:10.1007/s11244-012-9824-0.
[40] Y. Li, T. Chen, H. Wang, R. Zhang, K. Jin, X. Wang, C. Duan, A Ligand-Free Copper-Catalyzed Decarboxylative Trifluoromethylation of Aryliodides with Sodium Trifluoroacetate Using Ag2O as a Promoter, Synlett. 2011 (2011) 1713–1716. doi:10.1055/s-0030-1260930.
[41] G. Danoun, B. Bayarmagnai, M. Grünberg, C. Matheis, E. Risto, L. Gooßen, Sandmeyer Trifluoromethylation, Synthesis. 46 (2014) 2283–2286. doi:10.1055/s-0034-1378549.
[42] G. Danoun, B. Bayarmagnai, M.F. Gruenberg, L.J. Goossen, Sandmeyer trifluoromethylthiolation of arenediazonium salts with sodium thiocyanate and Ruppert–Prakash reagent, Chem. Sci. 5 (2014) 1312–1316. doi:10.1039/C3SC53076K.
[43] B. Bayarmagnai, C. Matheis, E. Risto, L.J. Goossen, One-Pot Sandmeyer Trifluoromethylation and Trifluoromethylthiolation, Adv. Synth. Catal. 356 (2014) 2343–2348. doi:10.1002/adsc.201400340.
[44] L.J. Gooßen, G. Deng, L.M. Levy, Synthesis of Biaryls via Catalytic Decarboxylative Coupling, Science. 313 (2006) 662–664. doi:10.1126/science.1128684.
[45] L.J. Goossen, ed., Inventing reactions, Springer, Berlin ; New York, 2013.
[46] B. Song, T. Knauber, L.J. Gooßen, Decarboxylative Cross-Coupling of Mesylates Catalyzed by Copper/Palladium Systems with Customized Imidazolyl Phosphine Ligands, Angew. Chem. Int. Ed. 52 (2013) 2954–2958. doi:10.1002/anie.201208025.
[47] A. Fromm, C. van Wüllen, D. Hackenberger, L.J. Gooßen, Mechanism of Cu/Pd-Catalyzed Decarboxylative Cross-Couplings: A DFT Investigation, J. Am. Chem. Soc. 136 (2014) 10007–10023. doi:10.1021/ja503295x.
[48] T. Billard, S. Large, B.R. Langlois, Preparation of trifluoromethyl sulfides or selenides from trifluoromethyl trimethylsilane and thiocyanates or selenocyanates, Tetrahedron Lett. 38 (1997) 65–68. doi:10.1016/S0040-4039(96)02216-2.
[49] B. Exner, B. Bayarmagnai, F. Jia, L.J. Goossen, Iron-Catalyzed Decarboxylation of Trifluoroacetate and Its Application to the Synthesis of Trifluoromethyl Thioethers, Chem. – Eur. J. 21 (2015) 17220–17223. doi:10.1002/chem.201503915.
[50] T. Umemoto, Y. Kuriu, Perfluoroalkylation of Thiols with $R_FI(Ph)OSO_2CF_3$, Chem. Lett. 11 (1982) 65–66. doi:10.1246/cl.1982.65.
[51] F. Sladojevich, E. McNeill, J. Börgel, S.-L. Zheng, T. Ritter, Condensed-Phase, Halogen-Bonded CF3I and C2F5I Adducts for Perfluoroalkylation Reactions, Angew. Chem. Int. Ed. 54 (2015) 3712–3716. doi:10.1002/anie.201410954.
[52] S.M. Sipyagin, V.S. Enshov, S.A. Kashtanov, J.S. Thrasher, 1-Chloro-2,6-dinitro-4-perfluoroalkylthiobenzenes in the Synthesis of Heterocycles, Chem. Heterocycl. Compd. 38 (2002) 1375–1381. doi:10.1023/A:1022138711847.
[53] S. Alazet, T. Billard, Electrophilic Aromatic Trifluoromethylthiolation with the Second Generation of Trifluoromethanesulfenamide, Synlett. 26 (2014) 76–78. doi:10.1055/s-0034-1379501.
[54] C. Matheis, B. Bayarmagnai, K. Jouvin, L.J. Goossen, Convenient synthesis of pentafluoroethyl thioethers via catalytic Sandmeyer reaction with a stable fluoroalkylthiolation reagent, Org Chem Front. 3 (2016) 949–952. doi:10.1039/C6QO00194G.
[55] C. Matheis, K. Jouvin, L.J. Goossen, Sandmeyer Difluoromethylation of (Hetero-)Arenediazonium Salts, Org. Lett. 16 (2014) 5984–5987. doi:10.1021/ol5030037.
[56] B. Bayarmagnai, C. Matheis, K. Jouvin, L.J. Goossen, Synthesis of Difluoromethyl Thioethers from Difluoromethyl Trimethylsilane and Organothiocyanates Generated In Situ, Angew. Chem. Int. Ed. 54 (2015) 5753–5756. doi:10.1002/anie.201500899.
[57] K. Jouvin, C. Matheis, L.J. Goossen, Synthesis of Aryl Tri- and Difluoromethyl Thioethers via a C–H-Thiocyanation/Fluoroalkylation Cascade, Chem. – Eur. J. (2015) 14324-14327. doi:10.1002/chem.201502914.
[58] C. Matheis, T. Krause, V. Bragoni, L.J. Goossen, Trifluoromethylthiolation and Trifluoromethylselenolation of α-Diazo Esters Catalyzed by Copper, Chem. – Eur. J. 22 (2016) 12270–12273. doi:10.1002/chem.201602730.
[59] C. Matheis, V. Wagner, L.J. Goossen, Sandmeyer-Type Trifluoromethylthiolation and Trifluoromethylselenolation of (Hetero)Aromatic Amines Catalyzed by Copper, Chem. – Eur. J. 22 (2016) 79–82. doi:10.1002/chem.201503524.

4.6 Synthese elektrophiler Trifluormethylthiolierungsreagenzien – SCF_3

Das Ziel dieses Projekts bestand darin nachhaltige Synthesen der gängigen elektrophilen Trifluormethylthiolierungsreagenzien zu entwickeln. Diese finden seit kurzer Zeit eine enorme Anwendungsbreite in der organischen Synthese, obwohl deren Herstellungsmethoden noch Optimierungsbedarf hinsichtlich Abfallminimierung und Resourceneffizienz zeigen. Für die Synthese der Reagenzien werden stöchiometrische Mengen Silbertrifluormethylthiolat $AgSCF_3$ eingesetzt, welches wiederum aus überschüssigem Silberfluorid und toxischem Kohlenstoffdisulfid CS_2 hergestellt wird.[114]

Eine Synthesemethode der Reagenzien aus dem günstigen Me_4NSCF_3 sollte eine erheblich nachhaltigere Alternative darstellen. Me_4NSCF_3 ist günstig aus dem Fluoroformderivat $TMSCF_3$, elementarem Schwefel und Tetramethylammoniumfluorid Me_4NF zugängig.

Die Reaktion wurde von mir entwickelt. Herr S. Kovács und ich synthetisierten diverse Reagenzien und untersuchten deren Anwendungsbreite zu gleichen Teilen. Das Manuskript verfasst ich zusammen mit Herrn Prof. Dr. L. J. Gooßen, während Herr S. Kovács die analytischen Daten auswerteten und die Supporting Information erstellte.

Eine Kopie des Manuskriptentwurfes ist nachfolgend beigefügt.

Preparation of electrophilic SCF_3-reagents from nucleophilic tetramethylammonium trifluoromethylthiolate

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ABSTRACT: A straightforward synthetic entry to the principal classes of electrophilic trifluoromethylthiolating agents is presented. It draws on inexpensive, shelf-stable tetramethylammonium trifluoromethylthiolate (Me_4N–SCF_3) as the SCF_3-source in the place of stoichiometric coinage metal-SCF_3 complexes.

Fluorine-containing residues have become central functionalities in drug-like molecules, because they modulate their metabolic stability, lipophilicity, bioavailability and structural configuration.[1 2 3] "Fluorine-scans", i.e. the systematic introduction of groups such as CF_3,[4 5 6 7 8 9] C_2F_5,[10] SCF_3[11] and OCF_3,[12 13] have become a standard tool in drug discovery. Thus, methods for the late-stage introduction of fluorinated substituents into functionalized molecules are highly sought-after. In the past decade, powerful fluoroalkylation methods have been developed. The attention has recently shifted towards fluoroalkyl thioethers, since the SCF_3 group induces even higher lipophilicity (Hansch constant 1.44 for SCF_3 vs. 0.88 for CF_3) and membrane permeability.[14] This is the key factor driving the increasing use of SCF_3 groups or their derivatives as key functionalities of pharmaceutical and agrochemical products, examples of which include toltrazuril, tiflorex and fipronil (Figure 1).

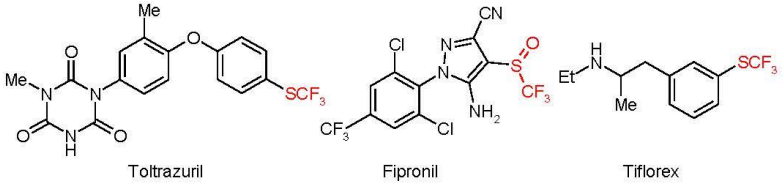
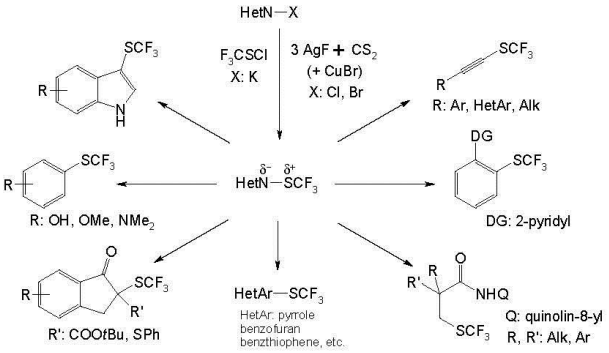


Figure 1. SCF_3-containing drugs and agrochemicals

Traditionally, SCF_3 groups are introduced via halogen-fluorine exchange reactions.[15] The harsh reaction conditions confine such approaches to the construction of simple building blocks.

In recent years, synthetic approaches have been devised that allow the introduction of the SCF_3 group in a single step.[16] Examples are nucleophilic trifluoromethylthiolations of vinyl and aryl halides mediated by copper,[17,18,19,20] palladium,[21] or nickel,[22] as well as Sandmeyer trifluoromethylthiolations.[23 24 25 26]The key advantage of a nucleophilic approach is that inexpensive SCF_3 sources may be used, such as the commercially available, inexpensive $Me_4N–SCF_3$, which is generated from $Me_4N–F$, elemental sulfur and Ruppert-Prakash reagent ($TMS–CF_3$). The latter is sustainably accessible from the waste product fluoroform.[27] Alternatively, SCF_3 may be constructed in situ from SCN and $TMS–CF_3$.[23 24 28 29 30 31] The drawback of nucleophilic trifluoromethylthiolations is that they are based on prefunctionalized substrates.

In comparison, electrophilic methods, many of them catalyzed e.g. by Rh,[32 33] Pd,[34 35] Fe,[36 37] and even Na,[38] allow the direct trifluoromethylthiolation of C–H bonds. Examples are trifluoromethylthiolations of sp-, sp^2- and sp^3- hybridized carbon centers such as terminal alkynes, hetero- or electron-rich arenes, and arenes and alkyl chains with directing groups, e.g. 2-pyridyl or quinoline-8-yl (Scheme 1). These transformations demonstrate the tremendous synthetic potential of electrophilic trifluoromethylthiolations. However, their main disadvantages lie in the difficulty to access suitable trifluoromethylthiolating reagents and the associated cost (Figure 2).



Scheme 1. Opportunities and limitations of electrophilic trifluoromethylthiolations.

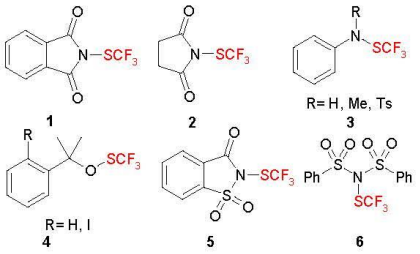


Figure 2. Electrophilic trifluoromethylthiolating reagents (HetN–SCF_3)

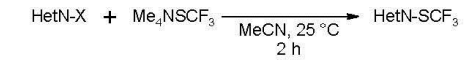
N-(Trifluoromethylthio)phthalimide **1**, disclosed by Munavalli et al., was originally prepared from potassium phthalimide with highly toxic and difficult-to-handle trifluoromethylsulfenyl chloride (CF_3SCl).[39] Alternative syntheses of **1** from *N*-halophthalimides are based on $AgSCF_3$,[4041] which, in turn, is obtained from toxic CS_2 and a large excess of silver fluoride. Shen's succinimide reagent **2**, Buchwald, Shen and Lu's trifluoromethanesulfenates **4**,[42] as well as Shen's SCF_3-saccharin **5** and -dibenzenesulfonimide **6**,[434445] are prepared along the same lines. Billard's anilide **3** is synthesized from TMS–CF_3, dimethylaminosulfur trifluoride (DAST) and aniline.[46] However, its comparatively lower reactivity (SCF_3 cation donating ability 59.7 vs. 33.0 kcal/mol for reagent **1**) leads to a more limited applicability in C–H functionalization.[47]

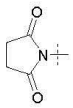
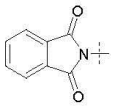
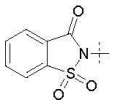
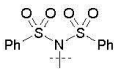
In view of the tremendous progress achieved in electrophilic trifluoromethylthiolation technology, we assessed the development of a sustainable, low-cost synthetic entry to the required SCF_3-reagents to be a top priority, which would improve the practical utility and environmental footprint of this synthetic concept. Me_4N–SCF_3 seemed to be an ideal source of SCF_3, because it is an inexpensive, commercially available raw material that may be sourced from fluoroform, and can easily be stored and handled. This reagent was first synthesized by Röschenthaler[48] and Yagupolskii[49] and has successfully been employed in trifluoromethylthiolations of aryl halides and triflates,[50 51 52 53] vinyl iodides,[54] boronic acids,[55] and diazo compounds.[56 57] In principle, its reaction with haloamides (HetN–X) should lead to the desired HetN–SCF_3 compounds. However, in contrast to silver-based SCF_3-sources, the salt exchange lacks the formation of AgX as central driving force.

After intricate reaction development, we found that the salt exchange equilibrium can still be shifted towards the desired product by performing the reaction in acetonitrile at room temperature. Under

these conditions, the tetramethylammonium halide salt crystallizes from the solution and is thus removed from the equilibrium. This protocol was first optimized for the model reaction of Me_4N–SCF_3 and NBS, then applied to a range of amidic SCF_3 reagents (Table 1). The conversion of Me_4N–SCF_3 to the product was monitored by in situ ^{19}F NMR spectroscopy using 1,4-difluorobenzene as the internal standard, which indicated that the reaction was complete after 2 hours with near-quantitative formation of the target molecule. After filtration, the product solution was free of byproducts, and ready to use in electrophilic trifluoromethylthiolations. Products **1**, **2** and **5** were sufficiently stable for chromatographic purification, leading to good isolated yields. Dibenzenesulfonimide **6** was moisture-sensitive and could not be isolated in the same way. The protocol is applicable not only to HetN–Br, but also to the less costly chloride derivatives.

Table 1. Preparation of electrophilic trifluoromethylthiolating reagents[a]

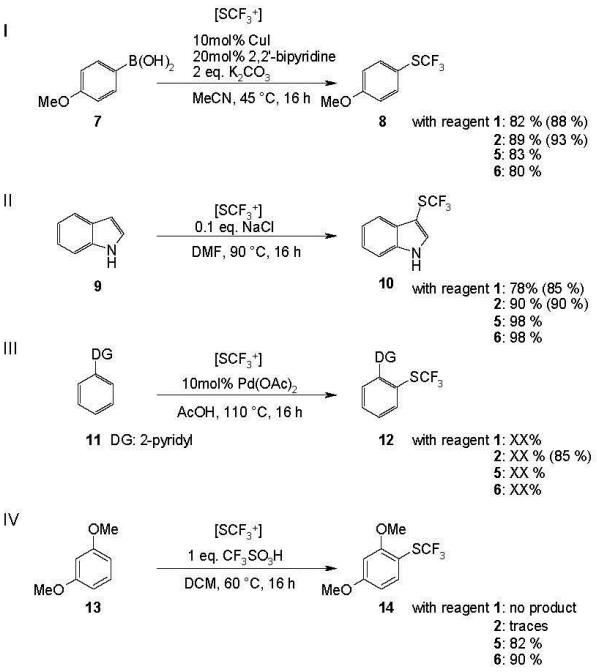


HetN	X	Yield[b] %
	Br	91
	Cl	90
	Br	87
	Cl	85
	Br	85
	Cl	81
	Cl	95[c]

[a]Reaction conditions: 0.55 mmol of Me_4N–SCF_3 in 1 mL of MeCN was slowly added to a solution of 0.5 mmol of HetN–X in 1 mL of MeCN at room temperature for 2 hours, [b] Isolated yield after column chromatography. [c] Yield determined by ^{19}F NMR using 1,4-difluorobenzene as an internal standard.

In order to ascertain the activity of the electrophilic SCF_3-reagents prepared by our method, we applied each filtered HetN–SCF_3 solution in acetonitrile to the trifluoromethylthiolation of standard substrates (Scheme 2).[58] [59] Arylboronic acid **7**, indole **9** and 2-phenylpyridine **11** were

trifluoromethylthiolated in excellent isolated yields. Interestingly, the performance of the succinimide **2** was markedly better than that of the phthalimide **1**. Moreover, we investigated the use of the isolated reagents **1**, **2** and **5** and were pleased to find that comparable yields to the HetN–SCF_3 solutions were obtained.



Scheme 2 Benchmarking the trifluoromethylthiolations with the electrophilic HetN–X reagents as crude solutions; yields for the isolated HetN–X solids in parentheses.

The umpolung of the nucleophilic Me_4N–SCF_3 and the electrophilic trifluoromethylation may also be combined to a one-pot transformation. Thus, the reactions of indole with *in situ* generated SCF_3^+ reagents such as SCF_3-saccharin **5** and -dibenzenesulfonimide **6** gave excellent yields (Scheme 2. III). Reagents **5** and **6** were generated from their corresponding halides (bromide and chloride). Moreover in the case of **5** and **6** no additional chloride catalyst was necessary due to its high reactive nature and *in situ* formation of tetramethylammonium chloride. In addition, 1,3-dimethoxybenzene was trifluoromethylthiolated with *in situ* generated **5** (IV) in high yields. These practical one-pot

procedures combine the synthetic versatility of electrophilic trifluoromethylthiolations with the advantageous use of an inexpensive nucleophilic SCF_3-source.

In summary, an efficient method for the synthesis of electrophilic SCF_3 reagents uses $Me_4N–SCF_3$ as an inexpensive, bench-stable nucleophilic trifluoromethylthiolating reagent. This method is convenient for the preparation of diverse electrophilic trifluoromethylthiolating reagents in near-quantitative yields within a few hours.

EXPERIMENTAL SECTION

General Informations

The reactions were performed in oven-dried glassware containing a Teflon-coated stirrer bar and septum under a nitrogen atmosphere. All reactions were monitored by 19F NMR using 1,4-difluorobenzene as an internal standard. GC analyses were carried out using an HP-5 capillary column (Phenyl methyl siloxane, 30 m × 320 × 0.25, 100/2.3-30-300/3, 2 min at 60 °C, heating rate 30 °C/min, 3 or 10 min at 300 °C). Column chromatography was performed using a Combi Flash Companion-Chromatography-System (Isco-Systems) and Reveleris packed columns (12 g). NMR spectra were recorded on Bruker Avance 400 at ambient temperature using $CDCl_3$ as solvent, with proton, carbon, and fluorine resonances at 400, 101, and 375 MHz respectively.

General procedure for the synthesis of $Me_4N–SCF_3$

Elemental sulfur (1.80 g, 6.64 mmol) was dissolved in THF (300 mL) at room temperature. $TMS–CF_3$ (10.1 mL, 63.7 mmol) was added and the reaction mixture was cooled to -60 °C. Me_4NF (5.00 g, 53.1 mmol) was added in one portion. The reaction mixture was kept at -60 °C for 30 min. and then allowed to warm to room temperature overnight. The resulting solid was filtered and washed with diethyl ether (50-50 mL). $Me_4N–SCF_3$ was isolated as a colourless solid. ^1H NMR (400 MHz, CD_3CN): δ = 3.12 ppm (s, 12H); ^{19}F NMR (375 MHz, CD_3CN): δ = -6.5 ppm; ^{13}C NMR (101 MHz, CD_3CN): δ = 145.1 (q, J = 293.4 Hz), 56.0 ppm.

General procedure for the synthesis of electrophilic SCF_3 reagents

An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with *N*-halo(sulfon)imide derivative (2 mmol), and MeCN (3 mL). $Me_4N–SCF_3$ (385 mg, 2.2 mmol, 1.1 equiv) in MeCN (3 mL) was added dropwise and the reaction mixture was stirred for 2 h at room temperature. Diethyl ether was added and the resulting mixture was filtered through a short pad of celite (5 g). The resulting solution was concentrated and purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate gradient).

N-(Trifluoromethylthio)phthalimide (1)[41]

1 was prepared from *N*-chlorophthalimide (363.2 mg, 2 mmol) following the general procedure. 430 mg (1,74 mmol, 87% yield) were isolated as a white solid, mp. = 116-117 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 5.7, 3.1 Hz, 2 H), 7.81 (dd, J = 5.7, 3.1 Hz, 2 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -48.89 (s, 3 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 135.5, 131.5, 127.9 (q, J = 315.1 Hz), 124.7

ppm. IR (ATR) ν 3099, 2927, 1976, 1791, 1737, 1715, 1610, 1560, 1468, 1345, 1275, 1176, 1105, 1028, 865, 791, 755, 710 cm^{-1}.

_N_-(Trifluoromethylthio)succinimide (2)[41 60]

2 was prepared from _N_-chlorosuccinimide (356 mg, 2 mmol) following the general procedure. 354 mg (1,78 mmol, 89% yield) were isolated as a white solid, mp. = 96-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,96 (s, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -47.99 (s, 3 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 127.7 (q, J = 315.1 Hz), 28.5 ppm. IR (ATR): ν 2951, 1733, 1429, 1294, 1252, 1227, 1095, 1007, 966, 815, 760 cm^{-1}.

2-((Trifluoromethyl)thio)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (5)[43]

6 was prepared from _N_-chlorosaccharin (543.2 mg, 2 mmol) following the general procedure. 447 mg (1,58 mmol, 79% yield) were isolated as a white solid, mp. = 112-113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.5 Hz, 1 H), 7.98-7.92 (m, 2 H), 7.89-7.85 (m, 2 1); ^{19}F NMR (376 MHz, $CDCl_3$) δ -48.97 (s, 3 F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 137.9, 136.4, 135.0, 127.8 (q, J = 316.9 Hz), 126.5, 126,1, 122.0 ppm. IR (ATR): ν 3102, 1762, 1591, 1351, 1173, 1115, 1094, 1057, 938, 748, 675 cm^{-1}.

4-Trifluoromethylthio-anisole (8)

CuI (9.5 mg, 0.05 mmol, 10 mol%), 4-methoxyphenylboronic acid (76 mg, 0.5 mmol, 1 equiv), dry K_2CO_3 (138 mg, 1 mmol, 2.0 equiv), 2,2'-bipyridine (18.8 mg, 0.1 mmol, 20 mol%) and reagent **1** or **2** (110.6 mmol, 1.2 equiv) were placed into an oven-dried crimp-cap vial equipped with a stirring bar. The vial was sealed, evacuated and back-filled with nitrogen (three times). MeCN was added by syringe and reaction mixture was stirred at 45 °C for 16 h. The reaction mixture was cooled to room temperature, diluted with diethyl ether (5 mL), and filtered through a short plug of silica, eluting with additional diethyl ether (50 mL). The filtrate was evaporated and the resulting residue was purified by chromatography (pentane/diethyl ether) to provide the desired product.

The product was obtained as colourless oil (starting from **1**: 91.6 mg, 0.44 mmol, 88% yield, **2**: 96.8 mg, 0.47 mmol 93% yield). $^{1}HNMR$ (400 MHz, $CDCl_3$): δ 7.59 (d, 3 J = 8.8 Hz, 2H), 6.95 (d, 3 J = 8.8 Hz, 2H), 3.85 (s, 3H) ppm; ^{19}F NMR (375 MHz, $CDCl_3$): δ -43.9 ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.8, 138.3 (2C), 129.7 (q, 1 J(C,F) = 308.5 Hz), 115.0 (2C), 114.8 (q, 3 J(C,F) = 1.8 Hz), 55.4 ppm.; IR (neat): ν 3011, 2969, 2946, 2910, 2842, 1593, 1495, 1252, 1104, 1085, 1029, 828 cm^{-1}.

3-((Trifluoromethyl)thio)-1H-indole (10)

An oven-dried crimp-cap vial was filled with sodium chloride (2.9 mg, 0.05 mmol, 10 mol%), indole (0.50 mmol, 1.0 equiv) and reagent **1** or **2** (0.65 mmol, 1.3 equiv.). The vial was sealed, evacuated and back-filled with nitrogen (three times) and 2.5 mL DMF was added. The solution was stirred for 16 h at 90 °C. After the reaction mixture was cooled to room temperature it was poured into 100 ml of water. The aqueous phase was extracted with 3×45 mL of EtOAc. The combined organic phases were washed with 3×40 mL of NaOH (1M, aq.) and 1×50 mL of brine. After drying over Na_2SO_4 and removal of the solvent in vacuo the crude material was purified by flash column chromatography.

The product was obtained as colourless oil (starting from **1**: 91.6 mg, 0.44 mmol, 88% yield, **2**: 96.8 mg, 0.47 mmol 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (br, 1 H), 7.88 - 7.85 (m, 1 H), 7.52 (d, J = 2.7 Hz, 1 H), 7.43-7.40 (m, 1 H), 7.34-7.31 (m, 2 H) ppm; ^{19}F NMR (376 MHz, CDCl3) δ -44.48 (s, 3 F) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.04, 132.82, 129.38, 129.42 (q, J = 310.8 Hz), 123.36, 121.58, 119.24, 111.69, 95.36 ppm. IR (ATR): ν 3406, 3118, 1506, 1546, 1408, 1338, 1281, 1238, 1109, 1009, 748, 582, 502, 464, 424 cm^{-1}.

2-(2-(Trifluoromethylthio)phenyl)pyridine (12)

A 20 mL crimp-cap vial charged with a magnetic bar, $Pd(OAc)_2$ (22.5 mg, 0.05 mmol, 0.1 equiv.), 1-(trifluoromethylthio) -pyrrolidine-2,5-dione (398 mg, 2.0 mmol, 4.0 equiv.) was evacuated under high vacuum and backfilled with nitrogen for three times. Acetic acid (10 mL) and 2-phenylpyridine (72.6 µL, 0.50 mmol, 1.0 equiv.) was then added via syringe. The reaction mixture was stirred at 110 °C for 24 h, and then cooled to room temperature. To the reaction mixture were added H_2O and CH_2Cl_2. The mixture was extracted with CH_2Cl_2 three times, and the combined organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (cyclohexane / ethyl acetate).

The product was obtained as colourless oil (91.6 mg, 0.44 mmol, 88% yield).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 4.0 Hz, 1 H), 7.84 (d, J = 7.8 Hz, 1 H), 7.78 (td, J = 7.8, 1.8 Hz, 1 H), 7.61 (dd, J = 7.8, 1.8 Hz, 1 H), 7.55-7.50 (m, 2 H), 7.46 (td, J = 7.8, 1.8 Hz, 1 H) 7.30 (ddd, J = 7.5, 4.9, 1.2 Hz, 1 H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ -41.72 (s, 3 F) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.60, 148.82, 145.07, 136.18, 135.68, 130.62, 130.04,129.58 (q, J = 310.7 Hz), 129.11, 124.15 (q, J = 2.0 Hz), 124.03, 122.37 ppm. IR: 3060, 2927, 1585, 1571, 1560, 1482, 1465, 1436, 1426, 1297, 1265, 1111, 1080, 1049, 1037, 1023, 991, 793, 755, 689, 632, 619, 565, 497, 460, 406 cm^{-1}.

(2,4-Dimethoxyphenyl)(trifluoromethyl)sulfane (14)

The solution of Me_4NSCF_3 in 2 mL DCM was added slowly to the solution of *N*-chlorosaccharin (85.8 mg, 0.55 mmol, 1.1 equiv) and the mixture was stirred at 25 °C for 30 minutes. Then the mixture was added to the solution of 1,3-dimethoxybenzene (65.8 µL, 0.5 mmol, 1 equiv) and CF_3SO_3H (24 µL, 0.5 mmol, 1 equiv) in DCM (6 mL). The mixture was stirred at room temperature for 4 h. The solvent was removed and the residue was purified by flask column chromatography (eluent: pentane: diethyl ether = 100:1) to give (2,4-Dimethoxyphenyl)(trifluoromethyl)sulfane as a colourless liquid (97.7 mg, 0.41 mmol, 82% yield).

^{1}H NMR (400 MHz, CDCl3) δ 7.54 (d, J = 8.8 Hz, 1 H), 6.54-6.50 (m, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -43.66 (s, 3 F) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.88, 162.06, 140.25, 129.56 (q, J = 309.2 Hz), 105.54, 103.18, 99.25, 56.03, 55.54 ppm. IR (ATR): ν 3009, 2944, 2841, 1600, 1575, 1492, 1466, 1438, 1415, 1316, 1304, 1280, 1257, 1213, 1164, 1111, 1072, 1030, 939, 920, 838, 825, 795, 754, 641, 587, 482 cm^{-1}.

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Notes

The authors declare no competing financial interest.

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REFERENCES

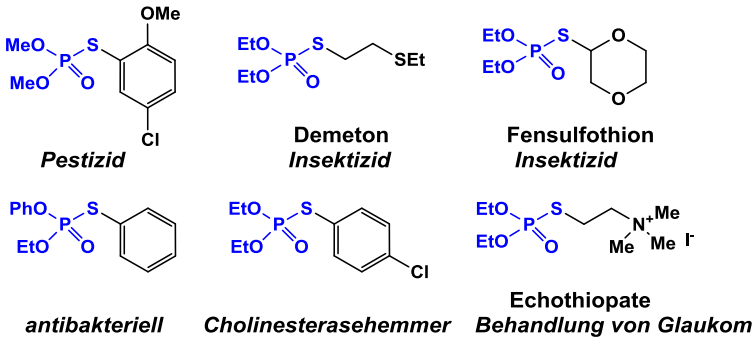
(1) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114* (4), 2432–2506.
(2) Jeschke, P. *ChemBioChem* **2004**, *5* (5), 570–589.
(3) Hagmann, W. K. *J. Med. Chem.* **2008**, *51* (15), 4359–4369.
(4) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111* (8), 4475–4521.
(5) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473* (7348), 470–477.
(6) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52* (32), 8214–8264.
(7) Liu, T.; Shen, Q. *Eur. J. Org. Chem.* **2012**, *2012* (34), 6679–6687.
(8) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. - Asian J.* **2012**, *7* (8), 1744–1754.
(9) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115* (2), 683–730.
(10) Lishchynskyi, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2013**, *135* (34), 12584–12587.
(11) Toulgoat, F.; Alazet, S.; Billard, T. *Eur. J. Org. Chem.* **2014**, *2014* (12), 2415–2428.
(12) Trainor, G. L. *J. Carbohydr. Chem.* **1985**, *4* (4), 545–563.
(13) Hojczyk, K. N.; Feng, P.; Zhan, C.; Ngai, M.-Y. *Angew. Chem. Int. Ed.* **2014**, *53* (52), 14559–14563.
(14) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16* (11), 1207–1216.
(15) Scherer. *Angew. Chem.* **1939**, *52* (27), 457–459.
(16) Barata-Vallejo, S.; Bonesi, S.; Postigo, A. *Org Biomol Chem* **2016**, *14* (30), 7150–7182.
(17) Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K.-W. *Angew. Chem. Int. Ed.* **2013**, *52* (5), 1548–1552.
(18) Shao, X.; Wang, X.; Yang, T.; Lu, L.; Shen, Q. *Angew. Chem. Int. Ed.* **2013**, *52* (12), 3457–3460.
(19) Chen, C.; Xie, Y.; Chu, L.; Wang, R.-W.; Zhang, X.; Qing, F.-L. *Angew. Chem. Int. Ed.* **2012**, *51* (10), 2492–2495.
(20) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134* (44), 18237–18240.
(21) Teverovskiy, G.; Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50* (32), 7312–7314.
(22) Zhang, C.-P.; Vicic, D. A. *J. Am. Chem. Soc.* **2012**, *134* (1), 183–185.
(23) Danoun, G.; Bayarmagnai, B.; Gruenberg, M. F.; Goossen, L. J. *Chem. Sci.* **2014**, *5* (4), 1312.
(24) Bayarmagnai, B.; Matheis, C.; Risto, E.; Goossen, L. J. *Adv. Synth. Catal.* **2014**, *356* (10), 2343–2348.
(25) Danoun, G.; Bayarmagnai, B.; Grünberg, M.; Matheis, C.; Risto, E.; Gooßen, L. *Synthesis* **2014**, *46* (17), 2283–2286.
(26) Matheis, C.; Wagner, V.; Goossen, L. J. *Chem. - Eur. J.* **2016**, *22* (1), 79–82.
(27) Prakash, G. K. S.; Jog, P. V.; Batamack, P. T. D.; Olah, G. A. *Science* **2012**, *338* (6112), 1324–1327.
(28) Jouvin, K.; Matheis, C.; Goossen, L. J. *Chem. - Eur. J.* **2015**, *21* (41), 14324–14327.
(29) Exner, B.; Bayarmagnai, B.; Jia, F.; Goossen, L. J. *Chem. - Eur. J.* **2015**, *21* (48), 17220–17223.
(30) Bayarmagnai, B.; Matheis, C.; Jouvin, K.; Goossen, L. J. *Angew. Chem. Int. Ed.* **2015**, *54* (19), 5753–5756.
(31) Matheis, C.; Wang, M.; Krause, T.; Goossen, L. *Synlett* **2015**, *26* (11), 1628–1632.
(32) Wang, Q.; Xie, F.; Li, X. *J. Org. Chem.* **2015**, *80* (16), 8361–8366.
(33) Luo, P.; Ding, Q.; Ping, Y.; Hu, J. *Org Biomol Chem* **2016**, *14* (10), 2924–2929.
(34) Xu, C.; Shen, Q. *Org. Lett.* **2014**, *16* (7), 2046–2049.
(35) Xiong, H.-Y.; Besset, T.; Cahard, D.; Pannecoucke, X. *J. Org. Chem.* **2015**, *80* (8), 4204–4212.
(36) Wang, Q.; Qi, Z.; Xie, F.; Li, X. *Adv. Synth. Catal.* **2015**, *357* (2-3), 355–360.
(37) Yang, T.; Lu, L.; Shen, Q. *Chem Commun* **2015**, *51* (25), 5479–5481.
(38) Honeker, R.; Ernst, J. B.; Glorius, F. *Chem. - Eur. J.* **2015**, *21* (22), 8047–8051.
(39) Munavalli, S.; Rohrbaugh, D. K.; Rossman, D. I.; Berg, F. J.; Wagner, G. W.; Durst, H. D. *Synth. Commun.* **2000**, *30* (16), 2847–2854.
(40) Pluta, R.; Nikolaienko, P.; Rueping, M. *Angew. Chem. Int. Ed.* **2014**, *53* (6), 1650–1653.
(41) Kang, K.; Xu, C.; Shen, Q. *Org. Chem. Front.* **2014**, *1* (3), 294.
(42) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *J. Org. Chem.* **2015**, *80* (6), 3012–3021.

(43) Xu, C.; Ma, B.; Shen, Q. *Angew. Chem. Int. Ed.* **2014**, *53* (35), 9316–9320.
(44) Zhang, P.; Li, M.; Xue, X.-S.; Xu, C.; Zhao, Q.; Liu, Y.; Wang, H.; Guo, Y.; Lu, L.; Shen, Q. *J. Org. Chem.* **2016**, *81* (17), 7486–7509.
(45) Liu, X.; An, R.; Zhang, X.; Luo, J.; Zhao, X. *Angew. Chem. Int. Ed.* **2016**, *55* (19), 5846–5850.
(46) Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. *J. Org. Chem.* **2008**, *73* (23), 9362–9365.
(47) Li, M.; Guo, J.; Xue, X.-S.; Cheng, J.-P. *Org. Lett.* **2016**, *18* (2), 264–267.
(48)
(49) Tyrra, W.; Naumann, D.; Hoge, B.; Yagupolskii, Y. L. *J. Fluor. Chem.* **2003**, *119* (1), 101–107.
(50) Xu, J.; Mu, X.; Chen, P.; Ye, J.; Liu, G. *Org. Lett.* **2014**, *16* (15), 3942–3945.
(51) Yin, G.; Kalvet, I.; Englert, U.; Schoenebeck, F. *J. Am. Chem. Soc.* **2015**, *137* (12), 4164–4172.
(52) Dürr, A. B.; Yin, G.; Kalvet, I.; Napoly, F.; Schoenebeck, F. *Chem Sci* **2016**, *7* (2), 1076–1081.
(53) Yin, G.; Kalvet, I.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2015**, *54* (23), 6809–6813.
(54) Rueping, M.; Tolstoluzhsky, N.; Nikolaienko, P. *Chem. - Eur. J.* **2013**, *19* (42), 14043–14046.
(55) Zhang, C.-P.; Vicic, D. A. *Chem. - Asian J.* **2012**, *7* (8), 1756–1758.
(56) Matheis, C.; Wagner, V.; Goossen, L. J. *Chem. - Eur. J.* **2016**, *22* (1), 79–82.
(57) Matheis, C.; Krause, T.; Bragoni, V.; Goossen, L. J. *Chem. - Eur. J.* **2016**, *22* (35), 12270–12273.
(58) Honeker, R.; Ernst, J. B.; Glorius, F. *Chem. - Eur. J.* **2015**, *21* (22), 8047–8051.
(59) Kang, K.; Xu, C.; Shen, Q. *Org. Chem. Front.* **2014**, *1* (3), 294.
(60) Haas, A.; Möller, G. *Chem. Ber.* **1996**, *129* (11), 1383–1388.

4.7 Synthese neuer Reagenzien zu übergangsmetallkatalysierten Einführung von Phosphorothioatgruppen – $SP(O)(OMe)_2$

4.7.1 Hintergrund

Organophosphorverbindungen finden aufgrund ihrer besonderen biologischen und physikalischen Eigenschaften eine breite Anwendung in der chemischen, agro-chemischen und medizinischen Industrie.[115] Die Substitution der natürlichen Phosphate durch Phosphonate hat immensen Einfluss auf die metabolische Regulierung, so zeigen beispielsweise phosphorothioatmodifizierte Oligonucleotide zeigen eine deutlich gesteigerte Stabilität gegenüber Nucleasen auf.[116,117] Unter den Phosphonatsubstituenten erwies sich die Phosphorothioatgruppe als besonders wertvoller Grundbaustein für Pharmazeutika und Pestizide in der organischen Synthese (Schema 37).



Schema 37. Biologisch aktive Phosphorothioate.

Traditionelle Methoden zur Einführung dieser Gruppe basieren auf die Additionsreaktion von Sulfenylhalogeniden oder Disulfiden an Phosphiten und erfordern stark basische Reaktionsbedingungen und den Einsatz hochtoxischer, feuchtigkeitsempfindlichen Phosphor- oder Schwefel-Halogenverbindungen.[118,119]

In den letzten Jahren wurden neue Methoden ausgehend von Thiolsubstraten mit Sulfonylchloriden beschrieben.[120-124] Allerdings wurde erst im Jahre 2016 eine halogenfreie, kupferkatalysierte Phosphorothiolierungsmethode ausgehend von Aryl-boronsäuren und –diazoniumsalzen mit elementarem Schwefel und Phosphonat durch die Forschungsgruppe von Zhao beschrieben.[125,126]

Dennoch, Reaktionen und Reagenzien, welche eine regiolselektive Einführung dieser Gruppe als Ganzes erlauben, konnten aufgrund der sensiblen Phosphor-Schwefel-Bindung nicht ermöglicht werden.

4.7.2 Entwicklung neuer Reagenzien zu übergangsmetallkatalysierten Einführung von Phosphorothioatgruppen

Das Ziel des letzten Teilprojekts bestand an der konzeptionellen Übertragung der Reagenziensynthese (**Kap. 4.6**) auf die regioselektive Einführung von Phosphorothioatgruppen (-SP(O)OR_2, mit R: Alkyl) in organische Verbindungen. Das Hauptaugenmerk lag dabei auf der Entwicklung neuer Reagenzien, die die Schwefel-Phosphor-Einheit als Ganzes in späten Stufen einer Synthesesequenz ermöglichen.

Zunächst wurde aufbauend auf den Arbeiten zu Me_4NSCF_3 die Synthese von $Me_4NSP(O)(OMe)_2$ aus Tetramethylammoniumfluorid (TMAF), elementarem Schwefel und Dimethyltrimethylsilylphosphit (TMS-P(O)$(OMe)_2$) untersucht. Nach der erfolgreichen Synthese wurde die Anwendung am Beispiel der kupferkatylisierten Sandmeyer-analogen Reaktion mit Diazoniumsalzen bestimmt. Des Weiteren lieferten die ersten Testreaktionen einer palladiumkatalysierten Umsetzung des Aryliodids vielversprechende Ergebnisse.

Anschließend wurde basierend auf den Erfahrungen aus der Synthese elektrophiler SCF_3-Reagenzien ebenfalls ein elektrophiles SP-Reagenz synthetisiert und seine potenzielle Anwendung mit der Umsetzung von Arylboronsäuren gezeigt.

Diese Methoden ermöglichen zum ersten Mal die Einführung von Phosphorothioategruppen als ganze Einheit unter milden Reaktionsbedingungen und eröffnen komplett neuen Zugang zu der wichtigen Substratklasse. Die Vorteile dieser Sandmeyer Reaktion sind hohe Toleranz gegenüber funktioneller Gruppen und die geringe Katalysatorbeladung (20 mol% Kupferthiocyanat).

Die Synthese der Reagenzien und Reaktionen zur Anwendung wurden von mir entwickelt. Herr Dr. A. Aillerie und Herr Dr. S. Kovács unterstützten mich bei der Bestimmung der Anwendungsbreite. Der Manuskriptentwurf wurde von mir erstellt, während die Herren A. Aillerie und S. Kovács die analytischen Daten auswerteten und die Supporting Information erstellten.

Eine Kopie des Manuskriptentwurfs ist nachfolgend beigefügt.

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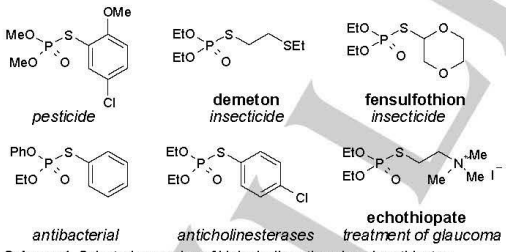
New Reagents for Transition Metal Catalyzed Late-Stage Phosphorothioation

Bilguun Bayarmagnai, Alexandre Aillerie and Lukas J. Goossen*[a]

Abstract: Tetramethylammonium *O,O*-Dimethyl Phosphorothioate is introduced as a new source of $SP(O)(OMe)_2$ nucleophiles in transition metal catalyzed phosphorothioation reactions. The crystalline salt is stable on storage, easy to handle, and can be obtained in nearly quantitatively yields simply mixing $Me_3SiP(O)(OMe)_2$, elemental sulfur and Me_4NF. This is the first easy to prepare and to store one-component nucleophilic phosphorothioation reagent that allows the straightforward phosphorothioation for the late-stage introduction of phosphorothio groups into drug-like molecules under mild conditions.

Organophosphorus compounds have found a wide range of application in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as their neurotoxic activity or the alkylation of DNA and RNA.[1] The use of phosphonates as analogues of natural phosphates represents a systematic approach to metabolic regulation, enhancement or inhibition. Among the phosphate esters, thiophosphate derivatives have proven to be a useful skeleton in organic synthesis as a valuable building block, in pharmaceuticals and pesticides due to its biological and physical properties.[2] [3] [4] [5] [6] [7] [8] [9] [10] Specially *S*-Aryl phosphorothioate represents an important structural element in drug-like molecules. Various well-known pharmaceuticals and agrochemicals contain phosphorothio groups (Scheme 1).[11] [12] [13] [14]



Scheme 1. Selected examples of biologically active phosphorothioates.

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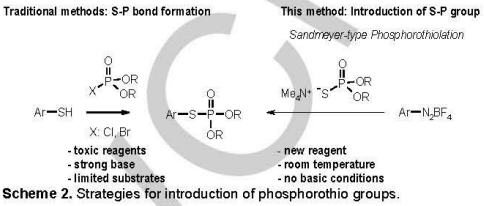
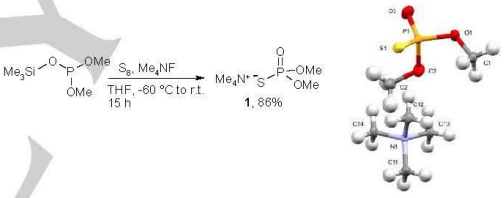
Supporting information for this article is given via a link at the end of the document.



Scheme 2. Strategies for introduction of phosphorothio groups.

However, traditional methods to access phosphorothioates, for example, the Michaelis-Arbuzov-type addition of sulfenyl halides or disulfides to phosphites, typically require strong basic reaction conditions and highly toxic, moisture sensitive $(RO)_2P(O)X$ or RSX and have low substrate scope (Scheme 2).[15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25]



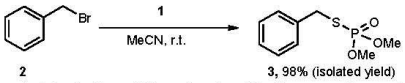
Scheme 3: Synthesis of the new phosphorothiation reagent **1** confirmed by his X-ray structure.

In recent years the synthesis of thiophosphates has attracted much attention and numerous synthetic methods have been developed, usually starting from thiols and sulfonyl chlorides.[26] [27] [28] [29] [30] [31] [32] [33] However, these approaches still suffer from the limited availability of thiol substrates, the incompatibility of the strongly basic or toxic reaction conditions with sensitive functionalities. Very recently substantial progress has been made by groups of Han[34] and Zhao.[35] [36] Han reported a palladium catalyzed dehydrogenative coupling of P(O)H and with thiols to construct *P—S* bond under halogen free conditions. Zhao and co-workers reported copper catalyzed phosphorothioations of arylboronic acids, -diazonium and iodonium salts with elemental sulfur. Due to its low cost, this approach, in which the sulfur and the phosphorous group originate from different reagents, is advantageous particularly for large-scale applications.

However, for efficient laboratory research, a phosphorothioation reagent which contains the fragile *P—S* bond readily installed and allows the straightforward introduction of this valuable functional group into highly functionalized molecules in one step would be highly desirable. Based on our experiences with fluoroalkylthiolations with nucleophilic Me_4NSR_f reagents,[37] [38] we were convinced that a similar strategy should

also allow the synthesis of $Me_4NSP(O)(OMe)_2$ **1** as a new phosphorothioation reagent (Scheme 3).

In order to probe the viability of this approach, we treated tetramethylammonium fluoride, elemental sulfur and dimethyl trimethylsilyl phosphite (TMS–$OP(OMe)_2$) in THF at -60 °C, analogous conditions for the preparation of Me_4NSR_f reagents.[37] Indeed a new single signal on ^{31}P NMR spectroscopy at 56 ppm was exclusively formed and the structure was confirmed by X-Ray analysis. Encouraged by these results in order to probe the introduction of the phosphorothioate group from our new reagent, we decided to investigate the phosphorothioation of benzyl bromide (Scheme 4). Simple nucleophilic substitution gave the desired product in quantitative yield.

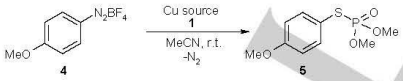


2 **3**, 98% (isolated yield)

Scheme 4. Introduction of the phosphorothioate group by nucleophilic substitution.

After demonstrating the viability of this strategy, we decided to focus our attention on the synthesis of *S*-Aryl phosphorothioates and we treated 4-methoxybenzenediazonium tetrafluoroborate (**4**) with the new reagent (**1**) in the presence of 50 mol% of CuSCN in MeCN at room temperature. The phosphorothioated product was observed in 72% yields, along with the protodediazotization product, anisole (Table 1, entry 1). Then we systematically optimized the reaction conditions for this model reaction. A decisive increase in the yields was obtained when the copper loading was reduced to 20 mol% to result the desired product in 93% yield (entry 3). Other copper catalysts such as copper acetate, copper cyanide or elemental copper gave fewer yields (entries 5-7). Control experiment confirmed that the reaction does not proceed without copper (entry 8).

Table 1. Optimization of the reaction conditions.[a]



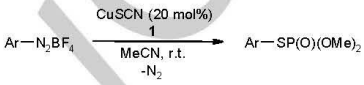
4 **5**

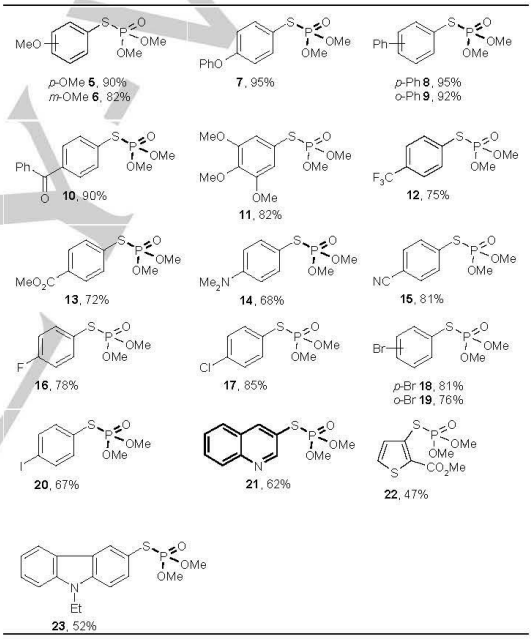
Entry	Cu source	Catalyst Loading [%]	3 [%][b]
1	CuSCN	50	72
2	CuSCN	30	80
3	CuSCN	20	93
4	CuSCN	10	75
5	CuCN	20	69
6	CuOAc	"	74
7	Cu	"	13
8	-	-	0

[a] Reaction conditions: dropwise addition of 0.5 mmol diazonium salt **2** in 1 mL MeCN, to 1.5 mmol $Me_4NSP(O)(OMe)_2$ and copper source in 1 mL MeCN, 15 h, RT. [b] Yields were determined by ^{31}P NMR using triethylphosphate as an internal standard.

Having thus found a convenient protocol for the Sandmeyer phosphorothioation, we next investigated its scope. Various diazonium tetrafluoroborates were smoothly converted into the corresponding thiophosphates in high yields. Both electron-rich and electron-deficient substrates gave similarly high yields. Many common functionalities were tolerated including ester, ether, amino, keto, carboxylate, cyano and even iodo groups. This demonstrates the utility of the new reaction for the late-stage phosphorothioation of complex, highly functionalized intermediates. Various heterocycles including quinoline, carbazole, and thiophene derivatives were also successfully converted.

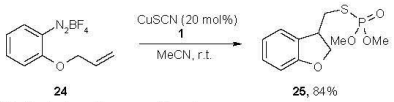
Table 2. Phosphorothioation of arenediazonium salts.[a]





[a] Reaction conditions: 1.0 mmol of arenediazonium tetrafluoroborate in 2 mL of MeCN was slowly added to a mixture of 0.2 mmol of CuSCN, and 1.5 mmol of $Me_4NSP(O)(OMe)_2$ in 2 mL of MeCN, and stirred for 15 h at RT. Isolated yields.

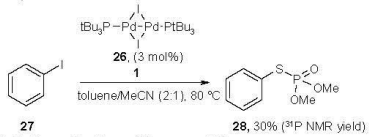
The reaction mechanism was investigated by the addition of radical inhibitors and a radical trapping experiment. When radical quenchers such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or *p*-benzoquinone are present, the reaction is completely suppressed. Moreover, in the phosphorothioation of 2-(allyloxy)diazonium tetrafluoroborate (**24**), the cyclized product (**25**) was obtained (Scheme 5).



24 **25**, 84%

Scheme 5. Radical-capture experiment.

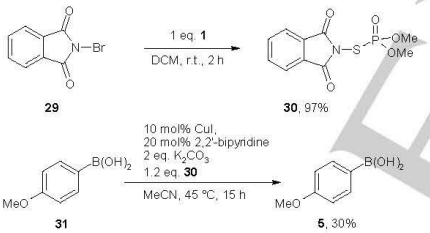
Next, we probed whether this new reagent **1** can also be utilized for other transition metal catalyzed arene phosphorothioation. Already the first few tries showed that aryl iodides can be phosphorothioated when treated with 3 mol% of the Pd^{I}-dimer catalyst **26** in toluene/MeCN (2:1) at 80 °C (Scheme 6).[39]



27 **28**, 30% (^{31}P NMR yield)

Scheme 6: Further utilization of the reagent **1**.

Furthermore, when *N*-Bromophthalimide **29** was treated with the reagent **1** the corresponding phosphorothioated product **30** was obtained in excellent yields. This product could be then utilized as a electrophilic $SP(O)(OMe)_2$-source by treating *p*-methoxyphenylboronic acid **31** in the presence of copper catalyst.



29 **30**, 97%

31 **5**, 30%

Scheme 7: Further utilization of the reagent **1**.

In conclusion, we have described the first easy to prepare and to store one-component nucleophilic phosphorothioation reagent that allows the straightforward introduction of phosphorothio groups into drug-like molecules. The utilization of this reagent has been demonstrated in simple nucleophilic displacement alkyl halides, palladium catalyzed phosphorothioation of aryl iodides, and Sandmeyer-type reactions. The key advantages of the Sandmeyer method are its mild reaction conditions (neutral, room temperature), the use of an inexpensive copper catalyst, and the exceptional group tolerance.

Keywords: phosphorothioation • sulfur • copper • phosphorus • Sandmeyer reaction

[1] R. Engel, *Chem. Rev.* **1977**, *77*, 349–367.
[2] T. S. Kumar, T. Yang, S. Mishra, C. Cronin, S. Chakraborty, J.-B. Shen, B. T. Liang, K. A. Jacobson, *J. Med. Chem.* **2013**, *56*, 902–914.
[3] R. Xie, Q. Zhao, T. Zhang, J. Fang, X. Mei, J. Ning, Y. Tang, *Bioorg. Med. Chem.* **2013**, *21*, 278–282.
[4] M. Noro, S. Fujita, T. Wada, *Org. Lett.* **2013**, *15*, 5948–5951.
[5] S.-W. Rhee, R. P. Iyer, J. E. Coughlin, S. Padmanabhan, J. P. Malerich, M. J. Tanga, *J. Label. Compd. Radiopharm.* **2012**, *55*, 197–200.
[6] M. Fukuoka, S. Shuto, N. Minakawa, Y. Ueno, A. Matsuda, *J. Org. Chem.* **2000**, *65*, 5238–5248.
[7] K. A. Mazzio, K. Okamoto, Z. Li, S. Gutmann, E. Strein, D. S. Ginger, R. Schlaf, C. K. Luscombe, *Chem. Commun.* **2013**, *49*, 1321.
[8] A. M. Lauer, F. Mahmud, J. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 9119–9123.
[9] S. T. Crooke, C. F. Bennett, *Annu. Rev. Pharmacol. Toxicol.* **1996**, *36*, 107–129.
[10] H. Yan, X. Wang, R. KuoLee, W. Chen, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5631–5634.
[11] L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley, New York, **2000**.
[12] L. L. Murdock, T. L. Hopkins, *J. Agric. Food Chem.* **1968**, *16*, 954–958.
[13] P. J. Murphy, Ed. , *Organophosphorus Reagents: A Practical Approach in Chemistry*, Oxford University Press, Oxford ; New York, **2004**.
[14] N.-S. Li, J. K. Frederiksen, J. A. Piccirilli, *Acc. Chem. Res.* **2011**, *44*, 1257–1269.
[15] A. R. Katritzky, R. J. K. Taylor, *Comprehensive Organic Functional Group Transformations II*, Elsevier, Amsterdam; Boston, **2005**.
[16] D. C. Morrison, *J. Am. Chem. Soc.* **1955**, *77*, 181–182.
[17] C. E. Dreef, C. M. Dreef-Tromp, G. A. van der Marel, J. H. van Boom, *Synlett* **1990**, *1990*, 481–483.
[18] L. Du-Dong, C. Da-wei, C. Zhen-Chu, *Synth. Commun.* **1992**, *22*, 2903–2908.
[19] S. Masson, J.-F. Saint-Clair, M. Saquet, *Synthesis* **1993**, *1993*, 485–486.
[20] B. Kaboudin, *Tetrahedron Lett.* **2002**, *43*, 8713–8714.
[21] T. Liu, A. A. Neverov, J. S. W. Tsang, R. S. Brown, *Org. Biomol. Chem.* **2005**, *3*, 1525.
[22] L. Cipolla, C. Redaelli, I. Faria, F. Nicotra, *J. Carbohydr. Chem.* **2006**, *25*, 163–171.
[23] D. S. Panmand, A. D. Tiwari, S. S. Panda, J.-C. M. Monbaliu, L. K. Beagle, A. M. Asiri, C. V. Stevens, P. J. Steel, C. D. Hall, A. R. Katritzky, *Tetrahedron Lett.* **2014**, *55*, 5898–5901.
[24] C. E. Müller, H. J. Roth, *Tetrahedron Lett.* **1990**, *31*, 501–502.
[25] R. G. Harvey, H. I. Jacobson, E. V. Jensen, *J. Am. Chem. Soc.* **1963**, *85*, 1618–1623.
[26] B. Kaboudin, Y. Abedi, J. Kato, T. Yokomatsu, *Synthesis* **2013**, *45*, 2323–2327.
[27] Y.-C. Liu, C.-F. Lee, *Green Chem* **2014**, *16*, 357–364.
[28] J. Bai, X. Cui, H. Wang, Y. Wu, *Chem. Commun.* **2014**, *50*, 8860.
[29] J. Wang, X. Huang, Z. Ni, S. Wang, J. Wu, Y. Pan, *Green Chem* **2015**, *17*, 314–319.
[30] S. Mitra, S. Mukherjee, S. K. Sen, A. Hajra, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2198–2201.
[31] G. Kumaraswamy, R. Raju, *Adv. Synth. Catal.* **2014**, *356*, 2591–2598.
[32] X. Bi, J. Li, F. Meng, H. Wang, J. Xiao, *Tetrahedron* **2016**, *72*, 706–711.
[33] P.-Y. Renard, H. Schwebel, P. Vayron, L. Josien, A. Valleix, C. Mioskowski, *Chem. - Eur. J.* **2002**, *8*, 2910.
[34] Y. Zhu, T. Chen, S. Li, S. Shimada, L.-B. Han, *J. Am. Chem. Soc.* **2016**, *138*, 5825–5828.
[35] J. Xu, L. Zhang, X. Li, Y. Gao, G. Tang, Y. Zhao, *Org. Lett.* **2016**, *18*, 1266–1269.
[36] L. Zhang, P. Zhang, X. Li, J. Xu, G. Tang, Y. Zhao, *J. Org. Chem.* **2016**, *81*, 5588–5594.
[37] C. Matheis, V. Wagner, L. J. Goossen, *Chem. - Eur. J.* **2016**, *22*, 79–82.
[38] C. Matheis, B. Bayarmagnai, K. Jouvin, L. J. Goossen, *Org Chem Front* **2016**, 3, 949-952.
[39] G. Yin, I. Kalvet, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2015**, *54*, 6809–6813.

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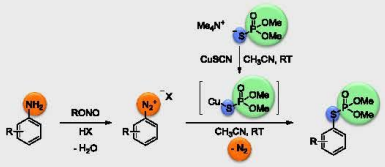
COMMUNICATION



Tetramethylammonium *O,O*-Dimethyl Phosphorothioate is introduced as a new source of $SP(O)(OMe)_2$ nucleophiles in transition metal catalyzed phosphorothioation reactions. This is the first easy to prepare and to store one-component nucleophilic phosphorothioation reagent that allows the straightforward phosphorothioation of highly functionalized molecules.

*Bilguun Bayarmagnai, Alexandre Aillerie, Lukas J. Goossen**

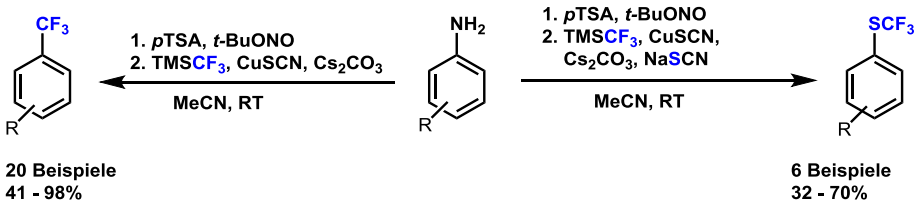
Page No. – Page No.

A New Reagent for Transition Metal Catalyzed Late-Stage Phosphorothioation

5 Zusammenfassung und Ausblick

Im Rahmen dieser Arbeit konnten neue Konzepte zur regioselektiven Einführung von CF_3, SCF_3, und SCF_2H-Gruppen entwickelt und neue konzeptionelle Perspektiven für die Entwicklung nachhaltiger Fluoralkylierungsreaktionen und Reagenzien eröffnet werden.

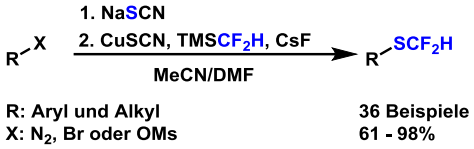
Im ersten Teilprojekt gelang es, praktische Eintopfverfahren zu entwickeln, mit denen Trifluormethyl- und Trifluormethylthiolgruppen selektiv in organische Moleküle eingeführt werden. Der maßgebliche Vorteil dieser Methoden ist, dass breit verfügbare aromatische Amine *in situ* diazotiert und ohne weitere Aufarbeitung weiter umgesetzt werden. Die vorteilhaften Reaktionsbedingungen wie z.B. Katalysatorbeladung, Raumtemperatur, und die hohe Toleranz gegenüber funktionellen Gruppen konnten beibehalten werden (Schema 38).



Schema 38. Eintopf-Sandmeyer-Trifluormethyl(thiol)ierungen.

Ein Ansatzpunkt für weitere Forschungen in diesem Projekt wäre die Reduzierung der substöchiometrischen Katalysatorbeladung bis hin zu katalytischen Mengen. Die Herausforderung dabei ist es die Reaktionsbedingungen so zu optimieren, dass das CF_3-Anion stabil vorliegt ohne am Kupfer gebunden zu sein. Nur dann könnte der Kupferkatalysator als reiner Katalysator dienen und nicht zugleich als CF_3-Stabilisator. Der mögliche Ansatz dazu wären die Untersuchungen von Hilfslösemittel wie z.B. DMF als CF_3-Anionenreservoir oder weiteren Gegenkationen wie z.B. Me_4N^+.

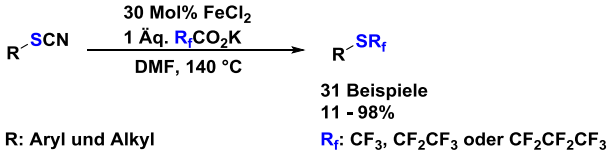
Im nächsten Teilprojekt wurde aufbauend auf dem Konzept der nukleophilen Difluormethylierung der Organothiocyanate Zugang zu wertvollen Difluormethylthioethern ermöglicht. Dabei werden die Organothiocyanate *in situ* in Reaktionslösung aus diversen Aryl- und Alkylhalogeniden und –pseudohalogeniden erzeugt, welche anschließend unter Einsatz von $TMSCF_2H$ difluormethyliert werden konnten (Schema 39). Der entscheidende Vorteil dieser Methode ist der Einsatz der nachhaltigen CF_2H-Quelle, welche aus Fluoroform herstellbar ist.



Schema 39. Synthese der Difluormethyl Thioether.

Weitere Untersuchungen zu dieser Thematik wäre die Synthese nukleophiler und elektrophiler SCF_2H-Reagenzien, die eine direkte Einführung ermöglichen. Die Herausforderung dabei ist ein geeignetes Reaktionsmedium zu finden, in dem das acide Proton der SCF_2H-Gruppe toleriert wird.

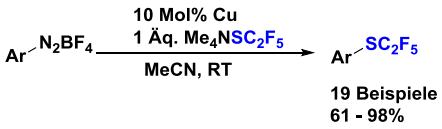
In einem weiteren Teilpojekt erfolgte die Entwicklung eines Verfahrens zur Synthese von Trifluormethylthioethern. Dabei können Organothiocyanate unter Decarboxylierung von Trifluoracetaten in Anwesenheit von Eisenkatalysatoren leicht zu den korrespondierenden, wertvollen Trifluormethylthioethern umgesetzt werden (Schema 40). Die Anwendungsbreite konnte an zahlreichen aromatischen, heteroaromatischen und aliphatischen Organothiocyanaten demonstriert werden. In weiterführenden Arbeiten konnte dieses Reaktionskonzepts auf längerkettige perfluorierte Carboxylate erweitert werden.



Schema 40. Decarboxylierende Perfluoralkylierung der Thiocyanate.

Weitere Untersuchungen auf diesem Gebiet könnten die kupfer- oder eisenkatalysierten Decarboxylierungen von Trifluoracetat in Anwesenheit weiterer Elektrophile wie z.B. terminaler Alkine, Arylboron- oder Benzoesäuren sein. Die Hauptherausforderung dabei ist es ein geeignetes Katalysatorsystem zu entwickeln, welches sowohl die Decarboxylierung der Trifluoracetate als auch die Aktivierung der Elektrophile als Kupplungspartner zur gleichen Zeit vermittelt. Als möglicher Ansatz könnte z.B. eine Umsetzung von terminalen Alkinen mit Trifluoracetaten in Anwesenheit eines Kupferkatalysators getestet werden. In diesem Zusammenhang sollten auch Liganden wie z.B. Phenanthrolin, die sich als gute Stabilisatoren für $CuCF_3$-Komplexe erwiesen haben, in Erwägung gezogen werden.

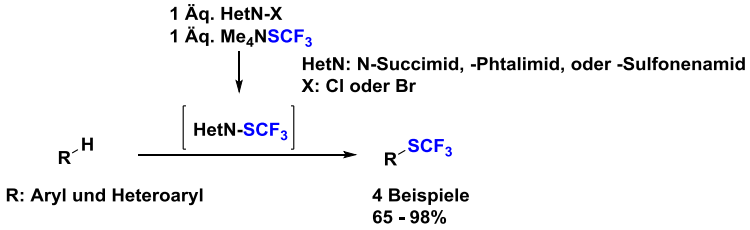
In einem weiteren Teilprojekt wurde die Sandmeyer Pentafluorethylthiolierung mit Aryldiazoniumsalzen ermöglicht. Sie stellt einen weiteren alternativen Zugang zu den pentafluorethylierten Aromaten dar (Schema 41).



Schema 41. Sandmeyer Pentafluorethylthiolierung.

Weitere Untersuchungen beständen in der Entwicklung elektrophiler SC_2F_5-Reagenzien aus diesem Pränukleophil und deren Anwendung.

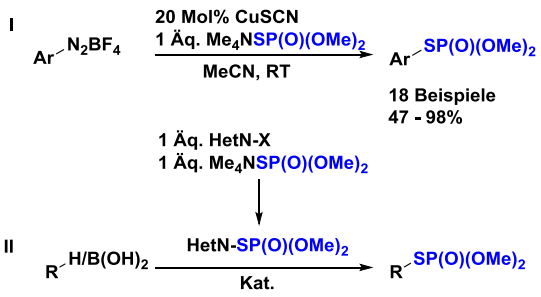
Im darauffolgenden Teilprojekt wurden alternative, nachhaltigere Synthesewege zu den gängigen elektrophilen SCF_3-Reagenzien ausgehend von Me_4NSCF_3 mittels einfacher Salzmetatese realisiert. Besonders erwähnenswert hierbei ist, dass eine *in situ* Generierung dieser sensiblen Reagenzien die komplizierte Handhabung vereinfacht (Schema 42).



Schema 42. C-H Trifluormethylthiolierungen.

Die Resultate dieses Projekts sollten dazu dienen weitere, noch reaktivere SCF_3^+-Reagenzien *in situ* zu generieren, wodurch auch die Funktionalisierung unreaktiver C-H Bindungen ermöglicht werden soll.

Im letzten Teilprojekt wurden sowohl elektrophile als auch nukleophile Reagenzien zur regioselektiven Einführung von Phosphorothioat-Gruppen entwickelt. Die Anwendungsmöglichkeiten wurden anhand kupferkatalysierten Sandmeyer Reaktion von Aryldiazoniumsalzen (Schema 43, **I**), einer palladiumkatalysierten Umsetzung von Aryliodiden und einer kupferkatalysierten Umsetzung von Arylboronsäuren gezeigt (**II**).



Schema 43. Neue Reagenzien und Methoden zur Einführung von SP-Einheiten.

Zusammengefassend wurden in dieser Arbeit nachhaltige Methoden zur regioselektiven Einführung von CF_3, SCF_3, SCF_2H und $SP(O)(OMe)_2$-Gruppen entwickelt. Dabei wurde das Reaktionskonzept der Sandmeyer Reaktion angewandt. Die wesentlichen Vorteile dabei sind der Einsatz geringer Mengen der Kupferkatalysatoren, die milden Reaktionsbedingungen, sowie die hohe Toleranz gegenüber funktioneller Gruppen, wodurch sich diese Verfahren auch besonders in späten Synthesestufen anbietet.

6 Experimenteller Teil

6.1 Verwendete Materialien und Methoden

6.1.1 Chemikalien und Lösungsmittel

Kommerziell verfügbare Chemikalien wurden bei einem Reinheitsgrad von ≥95% direkt eingesetzt oder andernfalls nach Standardverfahren aufgereinigt. Luft- und feuchtigkeitsempfindliche Substanzen wurden mit Standard-Schlenktechniken stets unter einer Stickstoff- oder Argonatmosphäre gelagert und gehandhabt. Flüssige Einsatzstoffe wurden unmittelbar vor der Reaktion mit dem Durchleiten von Argon (20 min) von Sauerstoff befreit. Toluol, 1,4-Dioxan und Mesitylen wurden über Natrium/Benzophenon getrocknet. NMP und DMF wurden durch die azeotrope Destillation mit Toluol von Feuchtigkeitsspuren befreit. Acetonitril, Diglyme und DMSO wurden zunächst über CaH2 refluxiert und anschließend fraktionierend destilliert. Alle Lösungsmittel wurden über Molsieben (3 Å) gelagert, die zuvor im Mikrowellenofen (2 × 2 min, 600 W) erhitzt und im Vakuum (10-3 mbar) abgekühlt wurden. Alle anderen organischen Salze wurden über Nacht bei 60 °C im Vakuum (10-3 mbar) getrocknet. Die anorganischen Salze wurden über Nacht im Vakuum (10-3 mbar) auf 160 °C erhitzt.

6.1.2 Durchführung von Parallelreaktionen

Die Reihenversuche wurden in 20 mL Headspace-Vials für die Gaschromatographie durchgeführt und mit Aluminium-Bördelkappen mit Teflon-beschichteten Butylgummisepten verschlossen. Das Aufheizen der Gefäße erfolgte in 8 cm hohen Aluminiumblöcken mit 7 cm tiefen, zylindrischen Bohrungen vom Durchmesser der Reaktionsgefäße und einer Bohrung für den Temperaturfühler. Der Durchmesser der Heizblöcke entsprach genau dem der Heizplatten gängiger Labor-Magnetrührer.

Zum parallelen Evakuieren und Rückbefüllen mehrerer Reaktionsgefäße wurden Vakuumverteiler verwendet, die an die Schlenk-Linie angeschlossen werden konnten. Diese Verteiler verfügten über jeweils zehn vakuumfeste 3 mm Teflonschläuche mit Adaptern zur Befestigung von Luer-Lock-Spritzennadeln.

Die festen Einsatzstoffe der Reihenversuche wurden an der Luft in die Reaktionsgefäße eingewogen, 20 mm Magnet-Rührkerne zugegeben und mit einer Septumkappe luftdicht verschlossen. Das Einwiegen besonders luft- oder

feuchtigkeitsempfindlicher Substanzen erfolgte in einer Glovebox mit Stickstoff als Inertgas. Die Gefäße wurden in die Bohrungen eines Aluminiumblocks gesteckt und über die Hohlnadeln mit dem Vakuumverteiler verbunden. Die Reaktionsgefäße wurden anschließend dreimal hintereinander evakuiert und mit Stickstoff rückbefüllt. Mit Hilfe von Spritzen wurden die reinen Lösungsmittel, Stammlösungen oder flüssigen Einsatzstoffe durch die Septen hindurch injiziert. Anschließend wurde der Aluminiumblock auf Reaktionstemperatur gebracht und die Hohlnadeln des Vakuumverteilers entfernt.

Nach Ablauf der Reaktionszeit und dem Abkühlen auf Raumtemperatur wurden die Gefäße vorsichtig geöffnet und mit einem geeigneten organischen Lösungsmittel und Wasser verdünnt. Die Phasen wurde mit einer 1 mL Einwegpipette zunächst gut durchmischt und 1.5 mL der organischen Phasen anschließend durch 0.3 mL trockenes Magnesiumsulfat in 2 mL GC-Probengläschen filtriert. Dabei wurden Glaspipetten als Filter verwendet, die mit einem Wattepfropfen versehen waren. Die so vorbereiteten Proben wurden schließlich gaschromatographisch untersucht.

6.1.3 Allgemeine Analytische Methoden

6.1.3.1 Dünnschichtchromatographie

Dünnschichtchromatographische Untersuchungen wurden mit Kieselgel DC-Folien Polygram SIL G/UV254 der Firma Macherey-Nagel durchgeführt. Zur Detektion der Substanzen wurden Fluoreszenzlöschungen bei 254 nm und Fluoreszenzen bei 366 nm genutzt.

6.1.3.2 Säulenchromatographie

Säulenchromatographische Trennungen erfolgten mit einem Combi Flash Companion-Chromatographie-System der Firma Isco-Systems. Als stationäre Phase wurden fertig gepackte RediSep und Grace Reveleris Flashkieselgel-Kartuschen oder Telos Kartuschen mit basischem Aluminiumoxid (0.063–0.200 mm, Aktivitätsstufe I) verwendet.

6.1.3.3 Gaschromatographie

Gaschromatographische Untersuchungen erfolgten mit einem Hewlett Packard 6890 und HP-5-Säulen mit 5% Phenyl-Methyl-Siloxan (30 m × 320 μm × 1.0 μm) der Firmen Agilent, Macherey-Nagel und Perkin Elmer. Dabei betrug die Temperatur des Injektors 220 °C und die des Detektors 330 °C. Das Standardtemperaturprogramm startete mit 2 min bei 60 °C, gefolgt

von einem linearen Temperturanstieg auf 300 °C mit einer Rate von 30 °C/min. Anschließend wurden die 300 °C für weitere 3 min gehalten.

6.1.3.4 Massenspektrometrie

Massenspektren wurden mit einem Varian GC-MS Saturn 2100 T oder einem Agilent GC-MS 5973N System gemessen. Die Ionisierung erfolgte dabei per Elektronenstoß (EI). Hochauflösende Massenspektren wurde mit einem Waters GTC Premier erhalten.

6.1.3.5 Infrarotspektroskopie

Infrarotspektroskopische Messungen erfolgten mit einem Perkin Elmer Fourier Transform Spektrometer oder einem Perkin Elmer Spectrum BX, FT-IR System (He, Ne 633 nm < 0.4 mW). Die Signalintensitäten sind mit vs (very strong), s (strong), m (medium) und w (weak) angegeben.

6.1.3.6 Kernresonanzspektroskopie

Der Großteil der NMR Spektren wurde mit einem Bruker AMX 400 System gemessen. Dabei wurden Benzol-d6, Chloroform-d, Deuteriumoxid, Dioxan-d8, Methanol-d4 und Toluol-d8 als Lösungsmittel und Wasserstoff-, Kohlenstoff-, Fluor- und Phosphorresonanzen von 400 MHz, 101 MHz, 376 MHz bzw. 162 MHz verwendet. Einzelne Messungen erfolgten weiterhin an Bruker FT-NMR DPX 200 und Avance 600 Geräten und sind jeweils als solche gekennzeichnet. Die Auswertung der Spektren erfolgte mit ACD-Labs 12. Die Multiplizität der Signale wird durch die Abkürzungen s = Singulett, d = Dublett, dd = Dublett eines Dubletts, dt = Dublett eines Tripletts, t = Triplett, usw. angegeben. Alle Kopplungskonstanten sind in Hertz angegeben.

6.1.3.7 Elementaranalysen

Die Elementaranalysen wurden mit einem Hanau Elemental Analyzer vario Micro cube durchgeführt. Alle Schmelzpunkte wurden mit einem Mettler FP61 bestimmt.

6.2 One-Pot Sandmeyer Trifluoromethylation and Trifluoromethylthiolation

General Methods

The reactions were performed in oven-dried glassware containing a Teflon-coated stirrer bar and septum under a nitrogen atmosphere. Acetonitrile was dried by refluxing over CaH_2 and subsequent fractionally distillation. Three freeze-pump-thaw cycles were performed before the reagents were mixed. All reactions were monitored by GC and the yields were determined by ^{19}F NMR using trifluoroethanol as internal standard. GC analyses were carried out using a HP-5 capillary column (Phenyl Methyl Siloxane 30 m x 320 x 0.25, 100/2.3-30-300/3) and a time program beginning with 2 min at 60°C followed by 30°C/min ramp to 300°C, then 3 min at this temp. Column chromatography was performed using a Combi Flash Companion-Chromatography-System (Isco-Systems) and Grace Reveleris packed flash columns (12 g). NMR spectra were obtained on a Bruker AMX 400 system using chloroform-d_1, or DMSO-d_6 as deuterated solvents, with proton, carbon and fluorine resonances at 400 MHz, 101 MHz and 151 MHz, respectively. Mass spectral data were acquired on a Varian Saturn 2100 T.

All starting materials were commercially available. All anilines and solvents were purified by distillation or sublimation prior to use. *p*TSA was purified and dried by sublimation prior to use. The other chemicals were used without further purification.

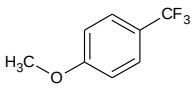
6.2.1 Synthesis of benzotrifluorides

6.2.1.1 Standard procedure for the synthesis of benzotrifluorides from the corresponding aromatic amines

An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with amine (1.00 mmol), p-toluenesulfonic acid (258 mg, 1.50 mmol) and acetonitrile (2 mL) under nitrogen. tert-Butyl nitrite (133 µL, 1.00 mmol) was added dropwise via syringe. The resulting solution was stirred at room temperature for 30 minutes and afterwards added dropwise to a suspension of copper thiocyanate (61.0 mg, 0.50 mmol), caesium carbonate (489 mg, 1.50 mmol) and trifluoromethyltrimethylsilane (240 µL, 1.50 mmol) in acetonitrile (2 mL) that was stirred at room temperature for 10 min. The suspension was stirred at room temperature for 12 h. The resulting mixture was filtered through a short pad of celite (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over

$MgSO_4$, filtered and concentrated (700 mbar, 40°C). The residue was further purified by flash chromatography (SiO2, pentane/diethyl ether gradient), yielding the corresponding benzotrifluorides.

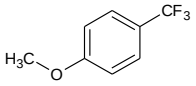
Synthesis of 1-methoxy-4-(trifluoromethyl)benzene (2)



[CAS: 402-52-8]

Compound **2** was prepared following the standard procedure, starting from 4-methoxyaniline (123 mg, 1.00 mmol). After purification, **2** was isolated as colorless liquid (150 mg, 0.85 mmol, 85%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.58 (d, ^3J(H,H) = 8.8 Hz, 2H), 6.98 (d, ^3J(H,H) = 8.8 Hz, 2H), 3.86 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –61.5 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.1, 126.8 (q, ^3J(C,F) = 3.7 Hz, 2C), 124.4 (q, ^1J(C,F) = 271.4 Hz, 1C), 122.9 (q, ^2J(C,F) = 33.0 Hz, 1C), 113.9 (2C), 55.2 ppm.

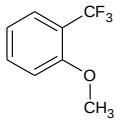
Upscale of 1-methoxy-4-(trifluoromethyl)benzene (2).



[CAS: 402-52-8]

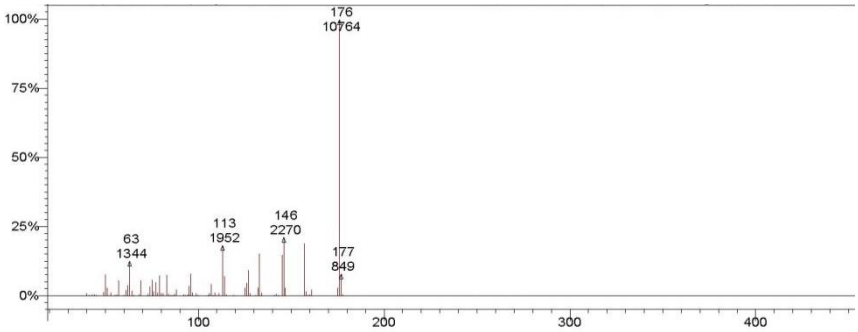
An oven-dried 50 mL flask with Teflon-coated stirrer bar was charged with 4-methoxyaniline (985 mg, 8.00 mmol), *p*-toluenesulfonic acid (2.07 g, 12.0 mmol) and acetonitrile (16 mL) under nitrogen. *tert*-Butyl nitrite (1066 µL, 8.00 mmol) was added dropwise *via* syringe. The resulting solution was stirred at room temperature for 30 minutes and afterwards added dropwise to a suspension of copper thiocyanate (590 mg, 4.00 mmol), caesium carbonate (3.91 g, 12.0 mmol) and trifluoromethyltrimethylsilane (1926 µL, 12.0 mmol) in acetonitrile (16 mL) that was stirred at room temperature for 10 min. The suspension was stirred at room temperature for 12 h. The resulting mixture was filtered through a short pad of celite (40 g) and rinsed with diethyl ether (100 mL). The resulting organic solution was washed with water (2 × 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40°C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient), yielding **2** as colorless liquid (1.14 g, 6.48 mmol, 81%).

Synthesis of 1-methoxy-2-(trifluoromethyl)benzene (3).

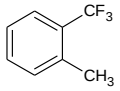


[CAS: 395-48-2]

Compound **3** was prepared following the standard procedure, starting from 2-methoxyaniline (62.0 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36.0 µL, 0.50 mmol) was added to the reaction mixture and the trifluoromethylated product **3** was formed in 70% yield as determined by **^{19}F NMR** spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = –62.8 ppm.

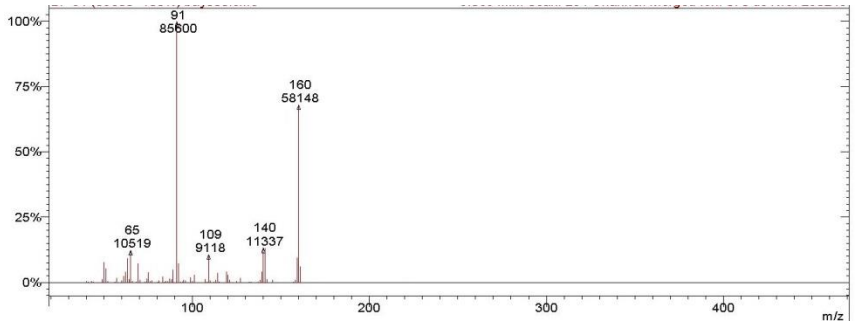


Synthesis of 1-methyl-2-(trifluoromethyl)benzene (4).

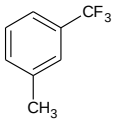


[CAS: 401-79-6]

Compound **4** was prepared following the standard procedure, starting from 2-methylaniline (54.0 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36.0 µL, 0.50 mmol) was added to the reaction mixture and the trifluoromethylated product **4** was formed in 78% yield as determined by **^{19}F NMR** spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = –62.0 ppm.

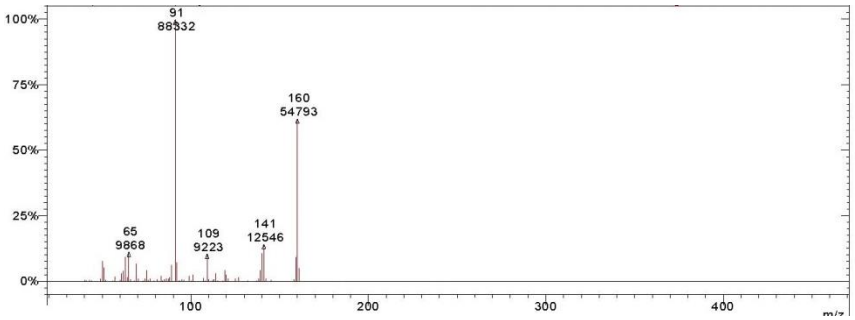


Synthesis of 1-methyl-3-(trifluoromethyl)benzene (5).

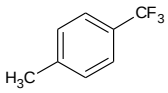


[CAS: 5140-17-6]

Compound **5** was prepared following the standard procedure, starting from 3-methylaniline (54.0 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36.0 µL, 0.50 mmol) was added to the reaction mixture and the trifluoromethylated product **5** was formed in 84% yield as determined by **^{19}F NMR** spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = –63.1 ppm.

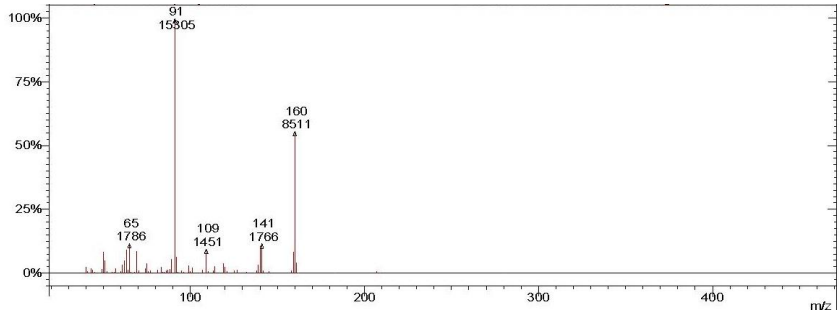


Synthesis of 1-methyl-4-(trifluoromethyl)benzene (6).

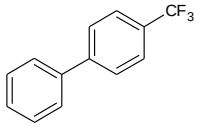


[CAS: 6140-17-6]

Compound **5** was prepared following the standard procedure, starting from 4-methylaniline (54.0 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36.0 µL, 0.50 mmol) was added to the reaction mixture and the trifluoromethylated product **5** was formed in 98% yield as determined by **^{19}F NMR** spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = –62.8 ppm.



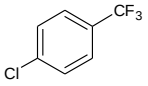
Synthesis of 4-(trifluoromethyl)biphenyl (7)



[CAS: 398-36-7]

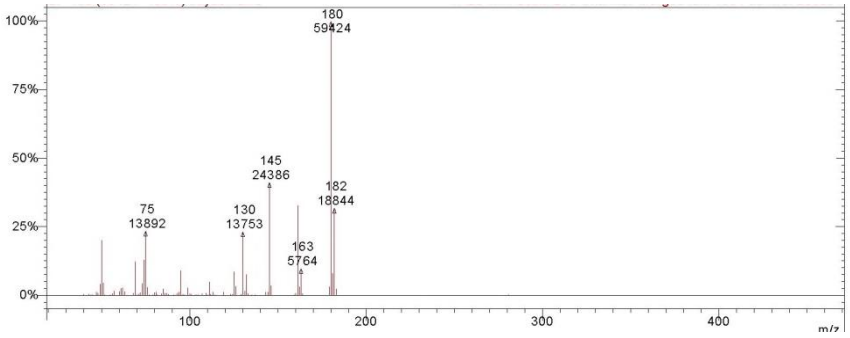
Compound **7** was prepared following the standard procedure, starting from [1,1'-biphenyl]-4-amine (169 mg, 1.00 mmol). After purification, **7** was isolated as colorless solid (204 mg, 0.92 mmol, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.72 (m, 4H), 7.61–7.64 (m, 2H), 7.52–7.50 (m, 2H), 7.48–7.43 ppm (m, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –62.4 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.8, 139.8, 129.3 (q, ^{2}J(C,F) = 32.7 Hz, 1C), 129.0 (2C), 128.2, 127.5 (2C), 127.3 (2C), 125.7 (q, ^{3}J(C,F) = 3.7 Hz, 2C), 124.5 ppm (q, ^{1}J(C,F) = 272.4 Hz, 1C).

Synthesis of 1-chloro-4-(trifluoromethyl)benzene (8)

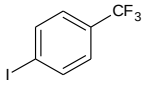


[CAS: 98-56-6]

Compound **8** was prepared following the standard procedure, starting from 4-chloroaniline (65 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36 µL, 0.50 mmol) was added to the reaction mixture and the trifluoromethylated product **8** was formed in 98 % yield as determined by **^{19}F NMR** spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = –63.1 ppm.



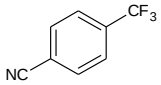
Synthesis of 1-iodo-4-(trifluoromethyl)benzene (9).



[CAS: 455-13-0]

Compound **9** was prepared following the standard procedure, starting from 4-iodoaniline (221 mg, 1.00 mmol). After chromatography, **9** was obtained as colorless liquid (166 mg, 0.61 mmol, 61%) which contained traces of 1,4-diiodobenzene that can be removed by low temperature crystallization from pentane. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85 (d, ^{3}J(H,H) = 8.03 Hz, 2H), 7.36 ppm (d, ^{3}J(H,H) = 8.03 Hz, 2H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –63.0 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 138.0 (2 C), 130.3 (q, ^{2}J(C,F) = 33.1 Hz, 1 C), 126.9 (q, ^{3}J(C,F) = 3.8 Hz, 2 C), 123.8 (q, ^{1}J(C,F) = 272.5 Hz, 1 C), 98.6 ppm (q, J(C,F) = 2.2 Hz, 1C).

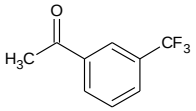
Synthesis of 4-(trifluoromethyl)benzonitrile (10).



[CAS: 455-18-5]

Compound **10** was prepared following the standard procedure, starting from 4-cyanoaniline (118 mg, 1.00 mmol). After purification, **10** was isolated as colorless solid (156 mg, 0.91 mmol, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.82 (d, ^{3}J(H,H) = 8.3 Hz, 2H), 7.77 ppm (d, ^{3}J(H,H) = 8.3 Hz, 2H); **^{19}F NMR** (375 MHz, DMSO-d_6): δ = –63.6 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 134.5 (q, ^{2}J(C,F) = 33.3 Hz, 1C), 132.7 (2C), 126.1 (q, ^{3}J(C,F) = 3.6 Hz, 2C), 123.2 (q, ^{1}J(C,F) = 272.5 Hz, 1C), 117.4, 116.0 ppm (q, J(C,F) = 1.8 Hz, 1C).

Synthesis of 3-(trifluoromethyl)acetophenone (11).

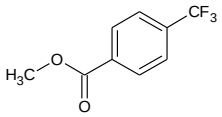


[CAS: 349-76-8]

Compound **11** was prepared following the standard procedure, starting from 1-(3-aminophenyl)ethanone (139 mg, 1.00 mmol). After purification, **11** was isolated as colorless liquid (139 mg, 0.74 mmol, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.22 (s, 1H), 8.15 (d, ^{3}J(H,H) = 8.0 Hz, 1H), 7.84 (d, ^{3}J(H,H) = 7.8 Hz, 1H), 7.63 (t, ^{3}J(H,H) = 7.8 Hz, 1H), 2.66 ppm (s, 3H, CH_3); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –62.8 ppm; **^{13}C NMR** (101 MHz,

$CDCl_3$): δ = 196.6, 137.5, 131.4, 131.2 (q, ^2J(C,F) = 34.5 Hz, 1C), 129.5 (q, ^3J(C,F) = 3.3 Hz, 1C), 129.3, 125.1 (q, ^3J(C,F) = 3.6 Hz, 1C), 123.8 (q, ^1J(C,F) = 272.5 Hz, 1C), 26.6 ppm.

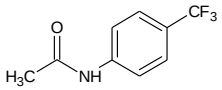
Synthesis of methyl 4-(trifluoromethyl)benzoate (12)



[CAS: 2967-66-0]

Compound **12** was prepared following the standard procedure, starting from methyl 4-aminobenzoate (154 mg, 1.00 mmol). After purification, **12** was isolated as colorless liquid (169 mg, 0.83 mmol, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.17 (d, ^3J(H,H) = 8.1 Hz, 2H), 7.72 (d, ^3J(H,H) = 8.2 Hz, 2H), 3.97 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –63.1 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.9, 134.4 (q, ^2J(C,F) = 32.3 Hz, 1C), 133.3, 130.0 (2C), 125.4 (q, ^3J(C,F) = 3.7 Hz, 2C), 123.6 (q, ^1J(C,F) = 272.9 Hz, 1C), 52.5 ppm.

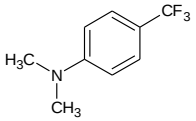
Synthesis of *N*-4[-(trifluoromethyl)phenyl]acetamide (13)



[CAS: 349-97-3]

Compound **13** was prepared following the standard procedure, starting from *N*-(4-aminophenyl)acetamide (158 mg, 1.00 mmol). After purification, **13** was isolated as colorless solid (83 mg, 0.41 mmol, 41%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.64 (d, ^3J(H,H) = 8.5 Hz, 2H), 7.58 (d, ^3J(H,H) = 8.8 Hz, 2H), 7.41 (br. s, 1H), 2.22 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –62.1 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.7, 140.9, 126.3 (q, ^3J(C,F) = 3.7 Hz, 2C), 125.9, 124.1 (q, ^1J(C,F) = 271.4 Hz, 1C), 119.3 (2C), 24.6 ppm.

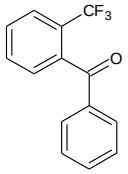
Synthesis of *N*,*N*-dimethyl-4-(trifluoromethyl)aniline (14)



[CAS: 329-17-9]

Compound **14** was prepared following the standard procedure, starting from *N*,*N*-dimethylbenzene-1,4-diamine (140 mg, 1.00 mmol). After purification, **14** was isolated as colorless solid (172 mg, 0.91 mmol, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.49 (d, ^{3}J(H,H) = 8.6 Hz, 2H), 6.72 (d, ^{3}J(H,H) = 8.5 Hz, 2H), 3.03 ppm (s, 6H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –60.8 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.3, 126.3 (q, ^{3}J(C,F) = 3.6 Hz, 2C), 125.1 (q, ^{1}J(C,F) = 270.3 Hz, 1C), 117.4 (q, ^{2}J(C,F) = 32.7 Hz, 1C), 111.1 (2C), 40.1 ppm (2C).

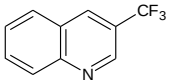
Synthesis of phenyl[2-(trifluoromethyl)phenyl]methanone (15)



[CAS: 727-99-1]

Compound **15** was prepared following the standard procedure, starting from (2-aminophenyl)(phenyl)methanone (201 mg, 1.00 mmol). After purification, **15** was isolated as colorless solid (198 mg, 0.79 mmol, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.80–7.79 (m, 3H), 7.65–7.60 (m, 3H), 7.49–7.47 (m, 2H), 7.45–7.40 ppm (m, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –58.0 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 195.5, 138.3 (q, ^{3}J(C,F) = 1.8 Hz, 1C), 136.3 (q, ^{4}J(C,F) = 1.3 Hz, 1C), 133.8, 131.4, 130.2 (2 C), 130.1, 129.8, 128.5 (2 C), 128.4 (q, ^{2}J(C,F) = 33.1 Hz, 1C), 126.7 (q, ^{3}J(C,F) = 4.5 Hz, 1C), 123.7 ppm (q, ^{1}J(C,F) = 273.4 Hz, 1C).

Synthesis of 3-(trifluoromethyl)quinoline (16)

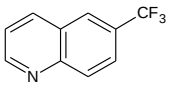


[CAS: 25199-76-2]

Compound **16** was prepared following the standard procedure, starting from quinolin-3-amine (146 mg, 1.00 mmol). Dry acetone (0.50 mL) was added additionally in the diazotization step to improve the solubility. After purification, **16** was isolated as colorless solid (108 mg, 0.55 mmol, 55%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.12 (d, ^{4}J(H,H) = 2.4 Hz, 1H), 8.47 (m, 1H), 8.21 (d, ^{3}J(H,H) = 8.2 Hz, 1H), 7.95 (d, ^{3}J(H,H) = 8.5 Hz, 1H), 7.90–7.86 (m, 1H), 7.71–7.69 ppm (m, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –61.8 ppm; **^{13}C NMR**

(101 MHz, $CDCl_3$): δ = 149.3, 146.1 (q, ^3J(C,F) = 3.6 Hz, 1C), 134.0 (q, ^3J(C,F) = 4.5 Hz, 1C), 131.8, 129.6, 128.6, 128.0, 126.2, 123.2 (q, ^1J(C,F) = 273.4 Hz, 1C), 123.6 ppm (q, ^2J(C,F) = 32.7 Hz, 1C).

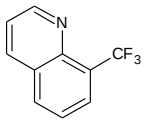
Synthesis of 6-(trifluoromethyl)quinoline (17)



[CAS: 325-13-3]

Compound **17** was prepared following the standard procedure, starting from quinoline-6-amine (147 mg, 1.00 mmol). Dry acetone (0.50 mL) was added additionally in the diazotization step to improve the solubility. After purification, **17** was isolated as colorless solid (105 mg, 0.53 mmol, 53%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.04(d, ^4J(H,H) = 3.0 Hz, 1H), 8.27–8.22 (m, 2H), 8.15 (s, 1H), 7.89 (dd, $^{3,4}J$(H,H) = 9.0, 2.0 Hz, 1H), 7.52 ppm (dd, $^{3,4}J$(H,H) = 8.3, 4.3 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –62.4 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.5, 149.2, 136.9, 130.7, 128.4 (q, ^2J(C,F) = 32.6 Hz, 1C), 127.2, 125.5 (q, ^3J(C,F) = 3.9 Hz, 1C), 125.2 (q, ^3J(C,F) = 2.2 Hz, 1C), 123.9 (q, ^1J(C,F) = 273.2 Hz, 1C), 122.2 ppm.

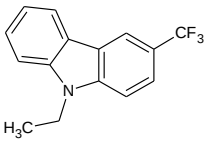
Synthesis of 8-(trifluoromethyl)quinoline (18)



[CAS: 317-57-7]

Compound **18** was prepared following the standard procedure, starting from quinoline-8-amine (144 mg, 1.00 mmol). Dry acetone (0.50 mL) was added additionally in the diazotization step to improve the solubility. After purification, **18** was isolated as colorless solid (97 mg, 0.49 mmol, 49%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.08 (m,1H), 8.22 (m, 1H), 8.08 (d, ^3J(H,H) = 7.3 Hz, 1H), 8.00 (d, ^3J(H,H) = 8.0 Hz, 1H), 7.59 (t, ^3J(H,H) = 8.0 Hz, 1H), 7.51 ppm (m, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –60.2 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.2, 144.7, 136.3, 132.4, 128.7, 127.9 (q, ^3J(C,F) = 5.4 Hz, 1C), 127.6 (q, ^2J(C,F) = 29.4 Hz, 1C), 125.2, 124.4 (q, ^1J(C,F) = 272.9 Hz, 1C), 121.9 ppm.

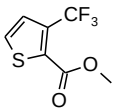
Synthesis of 9-ethyl-3-(trifluoromethyl)-9H-carbazole (19)



[CAS: 1638885-28-5]

Compound **19** was prepared following the standard procedure, starting from 9-ethyl-9*H*-carbazol-3-amine (221 mg, 1.00 mmol). After purification, **19** was isolated as colorless solid (234 mg, 0.89 mmol, 89%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.39 (m, 1H), 8.15 (m, 1H), 7.55 (m, 1H), 7.53 (m, 1H), 7.47 (m, 2H), 7.32 (m, 1H), 4.41 (q, ^{3}J(H,H) = 7.3 Hz, 2H), 1.46 ppm (t, ^{3}J(H,H) = 7.3 Hz, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –59.9 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.3, 140.5, 126.6, 126.1 (q, ^{1}J(C,F) = 270.7 Hz, 1C), 124.0, 122.5 (q, ^{3}J(C,F) = 3.6 Hz, 1C), 122.4 (q, ^{3}J(C,F) = 3.6 Hz, 1C), 120.9 (q, ^{2}J(C,F) = 31.8 Hz, 1C), 120.7, 119.7, 117.9 (q, ^{3}J(C,F) = 3.6 Hz, 1C), 108.9, 108.4, 37.7, 13.8 ppm; **IR** (neat): ν = 3057, 2981, 1603, 1474, 1340, 1269, 1143, 1104, 1051, 904, 804, 748 cm^{-1}; **HRMS** (EI-TOF) calcd for $C_{15}H_{12}F_3N$: 263.0916; found: 263.0915.

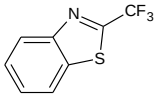
Synthesis of methyl 3-(trifluoromethyl)thiophene-2-carboxylate (20)



[CAS: 1638885-32-1]

Compound **20** was prepared following the standard procedure, starting from methyl 3-aminothiophene-2-carboxylate (157 mg, 1.00 mmol). After purification, **20** was isolated as colorless solid (145 mg, 0.69 mmol, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.54 (d, ^{3}J(H,H) = 5.3, 1H), 7.32 (d, ^{3}J(H,H) = 5.3, 1H), 3.90 (s, 3H) ppm; **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –58.1 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.1, 134.2 (q, ^{2}J(C,F) = 36.3 Hz, 1C), 133.2 (q, ^{3}J(C,F) = 2.7 Hz, 1C), 130.7, 127.7 (q, ^{3}J(C,F) = 3.8 Hz, 1C), 121.2 (q, ^{1}J(C,F) = 271.6 Hz, 1C), 52.6 ppm; **IR** (neat): ν = 3021, 2956, 1734, 1545, 1440, 1398, 1294, 1216, 1153, 1156, 902 cm^{-1}; **HRMS** (EI-TOF) calcd for $C_7H_5F_3O_2S$: 209.9957; found: 209.9958.

Synthesis of 2-(trifluoromethyl)-1,3-benzothiazole (21).

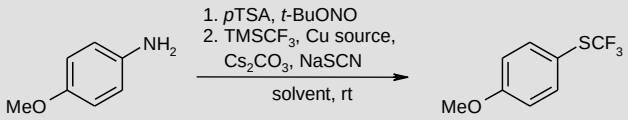


[CAS: 14468-40-7]

Compound **21** was prepared following the standard procedure, starting from 2-amino-benzothiazole (155 mg, 1.00 mmol). After purification, **21** was isolated as colorless solid (124 mg, 0.61 mmol, 61%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.22–8.20 (d, ^{3}J(H,H) = 8.5 Hz, 1H), 8.01–7.99 (d, ^{3}J(H,H) = 8.5 Hz, 1H), 7.64–7.57 ppm (m, 2H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –61.7 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.4 (q, ^{1}J(C,F) = 272.5 Hz, 1C), 152.1, 135.0, 127.5, 127.4, 125.0, 122.0, 119.9 ppm (q, ^{2}J(C,F) = 29.5 Hz, 1C).

Optimization of trifluoromethylthiolation

Table 1. Optimization of the reaction conditions



1 **22**

Entry	Cu source	Cs_2CO_3 [equiv.]	Yield of **22** [%][a]
1[b]	CuSCN	2	15
2	"	"	41
3	"	4	53
4[c]	"	"	74
5[c]	CuCN	"	52
6[c]	CuOAc	"	56
7[c]	$Cu(MeCN)_4BF_4$	"	63

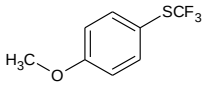
Reaction conditions: 0.75 mmol NaSCN, 0.50 mmol Cu source, Cs_2CO_3, 1 mL MeCN, 10 min, r.t., followed by dropwise addition of 0.50 mmol **1**, 0.50 mmol *t*-BuONO and 0.75 mmol *p*TSA in 1 mL MeCN, 15 min. Then addition of 1.50 mmol $TMSCF_3$, 12 h, r.t. [a] Yields were determined by ***^{19}F NMR*** using trifluoroethanol as internal standard. [b]0.25 mmol Cu source. [c] Addition of Cs_2CO_3 just before adding $TMSCF_3$. *p*TSA = *p*-toluenesulfonic acid, TMS = trimethylsilyl.

6.2.2 Synthesis of aryl trifluoromethyl thioethers

6.2.2.1 Standard procedure for the synthesis of aryl trifluoromethyl thioethers from the corresponding aromatic amines.

An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with amine (1.00 mmol), *p*-toluenesulfonic acid (258 mg, 1.50 mmol) and acetonitrile (2 mL) under nitrogen. *tert*-Butyl nitrite (133 µL, 1.00 mmol) was added dropwise *via* syringe. The resulting solution was stirred at room temperature for 30 minutes and afterwards added dropwise to a suspension of copper thiocyanate (123 mg, 1.00 mmol) and sodium thiocyanate (122 mg, 1.50 mmol) in acetonitrile (1 mL). The suspension was stirred at room temperature for 30 minutes and added to a suspension of caesium carbonate (652 mg, 4.00 mmol) in acetonitrile (1 mL). Finally trifluoromethyltrimethylsilane (240 µL, 1.50 mmol) was added and the reaction mixture was stirred at ambient temperature for 12 h. The resulting mixture was filtered through a short pad of celite (5.00 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40°C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient), yielding the corresponding aryl trifluoromethyl thioethers.

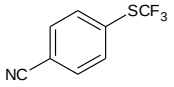
Synthesis of 1-methoxy-4-[(trifluoromethyl)thio]benzene (22)



[CAS: 78914-94-0]

Compound **22** was prepared following the standard procedure, starting from 4-methoxyaniline (123 mg, 1.00 mmol). After purification, **22** was isolated as colorless liquid (146 mg, 0.70 mmol, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.59 (d, ^3J(H,H)=8.8 Hz, 2H), 6.94 (d, ^3J(H,H)=8.8 Hz, 2H), 3.85 ppm (s, 3H); **^{19}F NMR** (151 MHz, $CDCl_3$): δ = –43.9 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.8, 138.3 (2C), 129.7 (q, ^1J(C,F)=308.5 Hz, 1C), 115.0 (2C), 114.8 (q, ^3J(C,F)=1.8 Hz, 1C), 55.4 ppm.

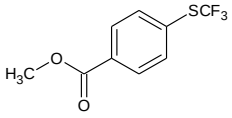
Synthesis of 4-[(trifluoromethyl)thio]benzonitrile (23)



[CAS: 332-26-3]

Compound **23** was prepared following the standard procedure, starting from 4-cyanoaniline (118 mg, 1.00 mmol). After purification, **23** was isolated as colorless liquid (134 mg, 0.66 mmol, 66%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 (d, ^{3}J(H,H)=8.6 Hz, 2H), 7.73 ppm (d, ^{3}J(H,H)=8.6 Hz, 2H); **^{19}F NMR** (151 MHz, $CDCl_3$): δ = –41.5 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ =136.0 (2C), 132.9 (2C), 130.5 (q, ^{3}J(C,F)=1.8 Hz, 1C), 129.1 (q, ^{1}J(C,F)=309.3 Hz, 1C), 117.6, 114.7 ppm.

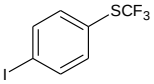
Synthesis of methyl 4-[(trifluoromethyl)thio]benzoate (24)



[CAS: 88489-60-5]

Compound **24** was prepared following the standard procedure, starting from methyl 4-aminobenzoate (154 mg, 1.00 mmol). After purification, **24** was isolated as colorless liquid (116 mg, 0.49 mmol, 49%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.08 (d, ^{3}J(H,H)=8.6 Hz, 2H), 7.72 (d, ^{3}J(H,H)=8.5 Hz, 2H), 3.95 ppm (s, 3H); **^{19}F NMR** (151 MHz, $CDCl_3$): δ = –41.8 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.0, 135.5 (2C), 132.2, 130.4 (2C), 129.9 (q, ^{3}J(C,F)=1.8 Hz, 1C), 129.3 (q, ^{1}J(C,F)=307.9 Hz, 1C), 52.5 ppm.

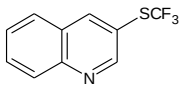
Synthesis of 1-iodo-4-[(trifluoromethyl)thio]benzene (25)



[CAS: 372-15-6]

Compound **25** was prepared following the standard procedure, starting from 4-iodoaniline (221 mg, 1.00 mmol). After chromatography, **25** was obtained as colorless liquid (137 mg, 0.45 mmol, 45%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 (m, 2H), 7.23 ppm (m, 2H); **^{19}F NMR** (151 MHz, $CDCl_3$): δ = –42.6 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 138.7 (2C), 137.7 (2C), 129.2 (q, ^{1}J(C,F)=308.7 Hz, 1C), 124.1 (q, ^{3}J(C,F)=1.8 Hz, 1C), 98.0 ppm.

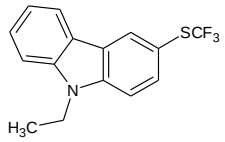
Synthesis of 3-[(trifluoromethyl)thio]quinoline (26)



[CAS: 1333415-90-9]

Compound **26** was prepared following the standard procedure, starting from quinolin-3-amine (146 mg, 1.00 mmol). Dry acetone (0.50 mL) was added additionally in the diazotization step to improve the solubility. After purification, **26** was isolated as colorless solid (73 mg, 0.32 mmol, 32%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.07 (m, 1H), 8.54 (d, ^{4}J(H,H)=1.8 Hz, 1H), 8.17 (m, 1H), 7.85 (m, 2H), 7.65 ppm (m, 1H); **^{19}F NMR** (151 MHz, $CDCl_3$): δ = –42.3 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.5, 148.4, 144.7, 131.6, 129.6, 129.3 (q, ^{1}J(C,F)=308.8 Hz, 1C), 128.1, 127.8, 127.7, 118.3 ppm (q, ^{3}J(C,F)=1.8 Hz, 1C).

Synthesis of 9-ethyl-3-[(trifluoromethyl)thio]-9*H*-carbazole (27)



[CAS: 1639370-01-6]

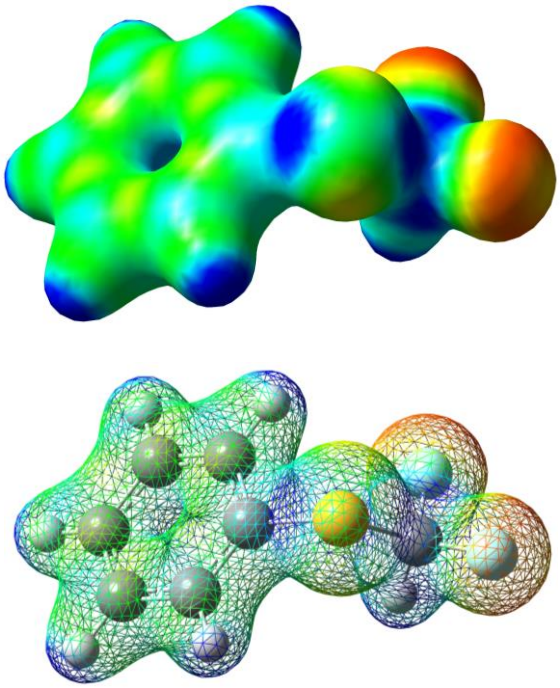
Compound **27** was prepared following the standard procedure, starting from 9-ethyl-9*H*-carbazol-3-amine (221 mg, 1.00 mmol). After purification, **27** was isolated as colorless solid (133 mg, 0.45 mmol, 45%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.40 (d, ^{4}J(H,H)=1.8 Hz, 1H), 8.13 (d, ^{3}J(H,H)=7.6 Hz, 1H), 7.74 (dd, $^{3,4}J$(H,H)=8.2, 1.8 Hz, 1H), 7.53 (m, 1H), 7.45 (d, ^{3}J(H,H)=8.3 Hz, 1H), 7.43 (d, ^{3}J(H,H)=8.5 Hz, 1H), 7.31 (d, $^{3,4}J$(H,H)=7.5, 0.9 Hz, 1H), 4.40 (q, ^{3}J(H,H)=7.1 Hz, 2H), 1.47 ppm (t, ^{3}J(H,H)=7.1 Hz, 3H); **^{19}F NMR** (151 MHz, $CDCl_3$): δ = –44.1 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.1, 140.3, 133.7, 130.0 (q, ^{1}J(C,F)=309.3 Hz, 1C), 129.6, 126.6, 123.9, 122.2, 120.7, 119.8, 112.5 (q, ^{3}J(C,F)=1.8 Hz, 1C), 109.2, 108.9, 37.8, 13.8 ppm; **HRMS** (EI-TOF) calcd for $C_{15}H_{12}N_1F_3{}^{32}S$: 295.0637; found: 295.0636.

6.3 Synthesis of Difluoromethyl Thioethers from Difluoromethyl Trimethylsilane and Organothiocyanates Generated *in situ*

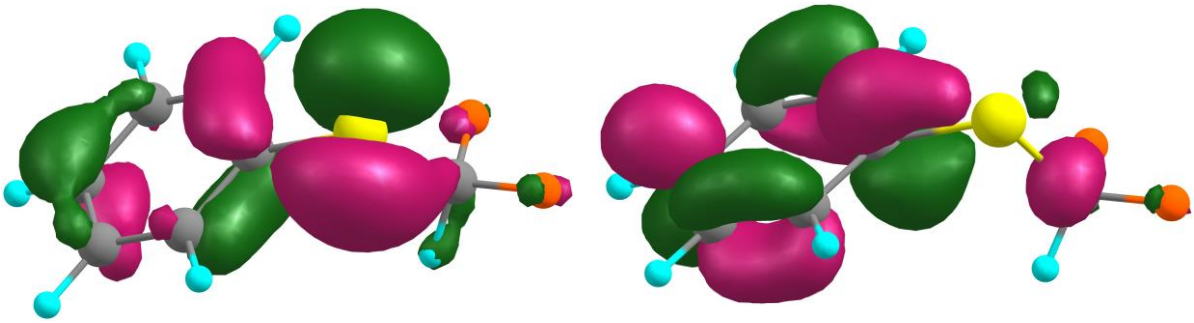
6.3.1 DFT Calculations

Level of calculations: **M06-2X/6-311+G(d,p)**

1) Electrostatic potential plot (isodensity = 0.02 electron/bohr^3).

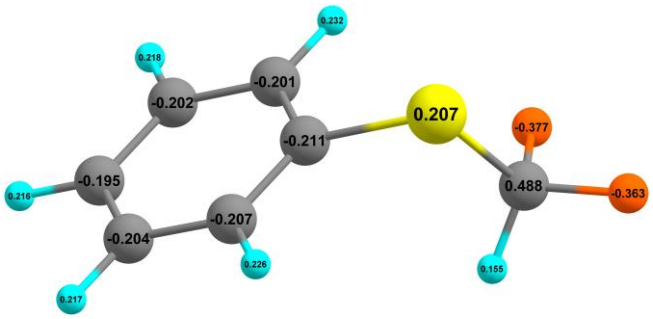


2) Frontier molecular orbitals (isodensity = 0.05 electron/bohr^3).



$PhSCF_2H$_HOMO **$PhSCF_2H$_LUMO**

3) Natural charge



4) The calculated pKa values:

$PhSCF_2H$ = **35.2**

$PhCF_2H$ = **42.2**

5) Cartesian coordinate

$PhSCF_2H$

16

XYZ

C	-0.50740	0.76425	0.48637
C	0.85009	0.73317	0.78482
C	1.64721	1.83810	0.48605
C	1.08430	2.97593	-0.09028
C	-0.27773	3.00494	-0.37206
C	-1.07212	1.89912	-0.08828
H	-1.12566	-0.09627	0.71186
H	1.29675	-0.14018	1.24371
H	1.71294	3.82970	-0.31271
H	-0.71547	3.89055	-0.81669
H	-2.13194	1.92226	-0.31187
S	3.39346	1.82190	0.87349
C	3.90643	0.69719	-0.45469
H	3.49641	0.99545	-1.41979
F	3.52408	-0.57862	-0.20667
F	5.25430	0.70596	-0.50641

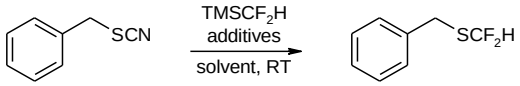
General Methods

The reactions were performed in oven-dried glassware containing a Teflon-coated stirrer bar and septum under a nitrogen atmosphere. Dimethylformamid and acetonitrile were dried by refluxing over CaH_2 and subsequent fractionally distillation. All reactions were monitored by GC and the yields were determined by **^{19}F NMR** using trifluoroethanol as internal standard. GC analyses were carried out using a HP-5 capillary column (Phenyl Methyl Siloxane 30 m x 320 x 0.25) and a time program beginning with 2 min at 60 °C followed by 30 °C/min ramp to 300 °C, then 3 min at this temp. Column chromatography was performed using a Combi Flash Companion-Chromatography-System (Isco-Systems) and Grace Reveleris packed flash columns (12 g). NMR spectra were obtained on a Bruker AMX 400 system using chloroform-d_1 as deuterated solvent, with proton, carbon and fluorine resonances at 400 MHz, 101 MHz and 375 MHz, respectively. Mass spectral data were acquired on a Varian Saturn 2100 T. Optical rotations were recorded on a Jasco P-2000 polarimeter at 589 nm and reported as follows: $[\alpha]_D^{20}$, concentration (*c* in g/100 mL), and solvent.

The diazonium salts were prepared from the corresponding anilines following the procedure below and were directly used. $TMSCF_2H$ was prepared from $TMSCF_3$ following the procedure below and was directly used. All other starting materials were commercially available. CsF was dried for 24 h at 200 °C in $1x10^{-3}$ mbar. The other chemicals were used without further purification.

6.3.2 Detailed Screening Experiments

Table 1. Optimization of the reaction conditions.[a]

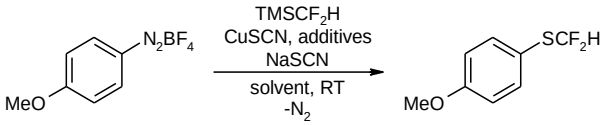


1 **2**

Entry	Additive	Mediator	Solvent	Yield of 2 [%][b]
1[c]	TBAF	-	THF	trace
2	CsF	-	"	0
3	TBAF	-	DMF	trace
4	KF	-	"	trace
5	CsF	-	"	51
6[d]	"	CuSCN	"	85
7[e]	"	"	"	98
8[e]	"	CuI	"	90
9[e]	"	CuCl	"	82
10[e]		Cu	"	61
11[e]	"	CuO	"	76
12[e]	"	CuSCN	THF	trace
13[e]	"	"	NMP	85
14[e,f]	"	"	DMF	73
15[e,g]	"	"	"	80

*[a] Reaction conditions: 0.5 mmol of benzyl thiocyanate, 1.0 mmol of additive, 1 mL solvent, 1.0 mmol of TMS–CF_2H, RT. [b] Yields were determined by **^{19}F NMR** using trifluoroethanol as an internal standard. [c] TMS–CF_2H was added at 0 °C, then slowly warm up to RT. [d] 1.0 mmol of CuSCN. [e] 1.0 mmol of CuSCN and 2.0 mmol of CsF were used. [f] In the presence of 0.5 mmol TEMPO. [g] In the presence of 0.5 mmol p-benzochinone.*

Table 2. Optimization of the reaction conditions.[a]

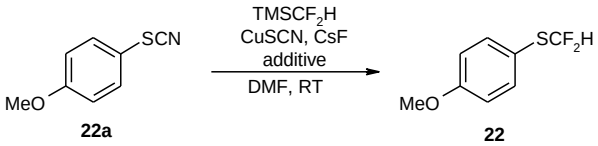


21 **22**

Entry	Additive 1	Additive 2	Solvent	Yield of 22 [%][b]
1	Cs_2CO_3	-	MeCN	0
2	"	-	DMF	15
3[c]	"	CsF	"	25
4[d]	"	"	"	50
5[e]	"	"	"	83
6	-	"	DMF	0
7[f]	"	"	MeCN/DMF	98

*[a] Reaction conditions: 1.0 mmol of CuSCN, 0.5 mmol of Cs_2CO_3, 0.75 mmol of NaSCN, 1 mL solvent, RT, dropwise addition of 0.5 mmol of **21** in 1 mL solvent, then 1.0 mmol of TMS–CF_2H. [b] Yields were determined by **^{19}F NMR** using trifluoroethanol as an internal standard. [c] 1.5 mmol of both cesium bases. [d] 1.0 mmol of CsF [e] 2.0 mmol of CsF. [f] 0.5 mmol of CuSCN, 0.35 mmol Cs_2CO_3, 0.75 mmol NaSCN, 1 mL MeCN, dropwise addition of 0.5 mmol of **21** in 1 mL MeCN, 1 h. Then evaporation of the solvent, addition of 0.5 mmol of CuSCN, 2.0 mmol of CsF, 1.0 mmol of TMS–CF_2H in 1 mL DMF, RT, 12 h.*

Table 3. Interference of Cs_2CO_3 or NaSCN on the difluoromethlation step.[a]



22a **22**

Entry	Additive	Yield of 22 [%][b]
1	-	98
2	Cs_2CO_3	77
3	NaSCN	82

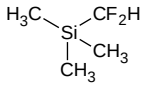
*[a] Reaction conditions: 0.5 mmol of **22a**, 0.5 mmol of CuSCN, 2.0 mmol of CsF, 0.5 mmol of additive, 1.0 mmol of TMS–CF_2H in 1 mL DMF, RT, 12 h. [b] Yields were determined by ^{19}**F NMR** using trifluoroethanol as an internal standard.*

6.3.3 Synthesis of Starting Materials

6.3.3.1 Synthesis of arenediazonium tetrafluoroborates

The aniline (10 mmol) was dissolved in a mixture of absolute ethanol (3 mL) and an aqueous solution of HBF_4 (50%, 2.5 mL, 20 mmol) and *tert*-butyl nitrite (2.7 mL, 20 mmol) was added dropwise to the solution at 0 °C. The reaction was stirred at room temperature for 1 h and diethyl ether (20 mL) was added to precipitate the arenediazonium tetrafluoroborate that was filtered off and washed with diethyl ether (3 × 10 mL). The arenediazonium tetrafluoroborate was dried in vacuo (10^{-3} mbar) for 10 minutes and was then directly used without further purification.

6.3.3.2 Synthesis of difluoromethyltrimethylsilane

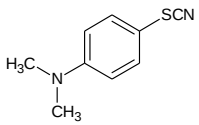


[CAS: 65864-64-4]

Following the literature procedure, trifluoromethyltrimethylsilane (22.3 mL, 139 mmol) was added dropwise to the stirred suspension of sodium borohydride (1.79 g, 46 mmol) in 40 mL of dry diglyme at 10 °C. The reaction mixture was stirred 12 h at room temperature and afterwards difluoromethyltrimethylsilane was isolated by distillation (b.p. 65-66 °C) as a colorless liquid (15.6 mL, 97 mmol, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.86 (t, *J* = 46.2 Hz, 1H), 0.18 ppm (s, 9H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –139.5.6 ppm (d, *J* = 46.3 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 123.9 (t, ^{1}J(C,F) = 253.9 Hz), -5.5 (3C) ppm.

6.3.3.3 Synthesis of thiocyanated compounds

Synthesis of 4-(dimethylamino)benzenethiocyanate

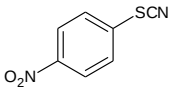


[CAS: 7152-80-9]

Copper thiocyanate (610 mg, 5.00 mmol), sodium thiocyanate (620 mg, 7.50 mmol) and cesium carbonate (1.14 g, 3.50 mmol) was dissolved in MeCN (10 mL). Afterwards a solution of the 4-(dimethylamino)benzenediazonium tetrafluoroborate (1.18 g, 5.00 mmol) in MeCN (10 mL) and was added dropwise via syringe. The suspension was stirred at room temperature

for 1 h. The resulting mixture was filtered through a short pad of silica (20 g) and rinsed with diethyl ether (100 mL). The resulting organic solution was washed with water (2 × 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient) and 4-(dimethylamino)benzenethiocyanate was isolated as a yellow solid (757 mg, 4.25 mmol, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 9.1 Hz, 2H), 6.68 (d, *J* = 9.0 Hz, 2H), 3.01 ppm (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.6, 134.5 (2C), 113.1 (2C), 112.6, 106.4, 40.1 (2C) ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 178 [M^+] (100), 152 (30), 145 (47), 118 (13); **HRMS** (EI-TOF) calcd for $C_9H_{10}N_2S$: 178.0565; found: 178.0567.

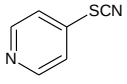
Synthesis of 4-nitrobenzenethiocyanate



[CAS: 2137-92-0]

Copper thiocyanate (610 mg, 5.00 mmol), sodium thiocyanate (620 mg, 7.50 mmol) and cesium carbonate (1.14 g, 3.50 mmol) was dissolved in MeCN (10 mL). Afterwards a solution of the 4-nitrobenzenediazonium tetrafluoroborate (1.19 g, 5.00 mmol) in MeCN (10 mL) and was added dropwise via syringe. The suspension was stirred at room temperature for 1 h. The resulting mixture was filtered through a short pad of silica (20 g) and rinsed with diethyl ether (100 mL). The resulting organic solution was washed with water (2 × 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient) and 4-nitrobenzenethiocyanate was isolated as a yellow solid (738 mg, 4.10 mmol, 82%). **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 9.0 Hz, 2H), 7.68 ppm (d, *J* = 9.1 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.0, 133.4, 128.7 (2C), 125.1 (2C), 108.1 ppm.

Synthesis of 4-thiocyanatopyridine

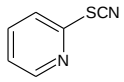


[CAS: 2637-36-7]

Following the literature procedure, 4-aminopyridine [CAS: 504-24-5] (2.00 g, 21.2 mmol) was dissolved in a mixture of conc. H_2SO_4 (6 mL) and water (24 mL) and a solution of

sodium nitrite (1.00 g, 14.5 mmol) in water (20 mL) was added at 0 °C dropwise. Afterwards a solution of potassium thiocyanate (2.00 g, 20.0 mmol) in water (5 mL) and copper thiocyanate (500 mg, 4.07 mmol) was added. The reaction mixture was stirred at room temperature for 5 h and neutralized with sodium carbonate. Diethyl ether was added and the resulting organic solution was washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient) and 4-thiocyanatopyridine was isolated as yellow oil (1.47 g, 9.12 mmol, 43%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 6.0 Hz, 2H), 7.40 ppm (d, *J* = 6.0 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 150.7 (2C), 136.7, 121.5 (2C), 107.3 ppm; **IR** (neat): ν = 3048, 2160, 1570, 1455, 1415, 1022, 757, 707 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 136 [M^+] (100), 109 (40), 78 (34); **HRMS** (EI-TOF) calcd for $C_6H_4N_2S$: 136.0095; found: 136.0091.

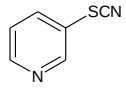
Synthesis of 2-thiocyanatopyridine



[CAS: 2637-35-6]

Following the literature procedure, 2-aminopyridine [CAS: 504-29-0] (10.0 g, 105 mmol) and sodium nitrite (8.00 g, 116 mmol) were dissolved in water (40 mL) and a solution of acetic acid (6 mL) in water (20 mL) was added dropwise at 0 °C. The solution was stirred for 10 min at 0 °C and potassium thiocyanate (45.0 g, 454 mmol) in water (25 mL) and copper thiocyanate (12.9 g, 105 mmol) was added. The reaction mixture was stirred at room temperature for 17 h and neutralized with sodium carbonate. Diethyl ether was added and the resulting organic solution was washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient) and 2-thiocyanatopyridine was isolated as yellow oil (2.54 g, 15.8 mmol, 15%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 4.8 Hz, 1H), 7.78 (td, *J* = 8.0, 1.9 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.29 ppm (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 150.5, 150.0, 138.5, 122.7, 122.0, 109.0 ppm; **IR** (neat): ν = 3054, 2161, 1574, 1563, 1449, 1419, 1118, 1082, 1044, 988, 757, 715 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 136 [M^+] (100), 78 (100); **HRMS** (EI-TOF) calcd for $C_6H_4N_2S$: 136.0095; found: 136.0090.

Synthesis of 3-thiocyanatopyridine



[CAS: 2645-25-2]

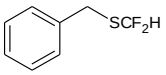
Following the literature procedure, 3-aminopyridine [CAS: 462-08-8] (7.50 g, 79.0 mmol) was dissolved in a mixture of conc. H_2SO_4 (14 mL) and water (50 mL) and sodium nitrite (5.77 g, 83.6 mmol) in water (25 mL) was added dropwise. Afterwards a solution of potassium thiocyanate (8.75 g, 88.2 mmol) in water (25 mL) and copper thiocyanate (9.69 g, 78.9 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and neutralized with sodium carbonate. Diethyl ether was added and the resulting organic solution was washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient) and 3-thiocyanatopyridine was isolated as yellow oil (5.09 g, 31.6 mmol, 40%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.76 (d, J = 1.9 Hz, 1H), 8.67 (d, J = 4.9 Hz, 1H), 7.93 (m, 1H), 7.62 ppm (dd, J = 8.1, 4.9 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 150.6, 150.4, 137.9, 124.8, 122.5, 109.2 ppm; **IR** (neat): ν = 3043, 2159, 1568, 1466, 1412, 1327, 1192, 1107, 1014, 796, 751, 698 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 136 [M^+] (100), 111 (12), 109 (41), 92 (10), 78 (45); **HRMS** (EI-TOF) calcd for $C_6H_4N_2S$: 136.0095; found: 136.0088.

6.3.4 Synthesis of difluoromethyl thioethers starting from the corresponding organo thiocyanates

6.3.4.1 Standard procedure 1

An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with the organo thiocyanate (1.00 mmol), copper thiocyanate (122 mg, 1.00 mmol), cesium fluoride (608 mg, 4.00 mmol) and DMF (4 mL). Difluoromethyltrimethylsilane (245 mg, 2.00 mmol) was added and the suspension was stirred at room temperature for 12 h. The resulting mixture was filtered through a short pad of silica (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). After evaporation of the solvent, the corresponding difluoromethyl thioether was generally obtained pure (in some cases a second filtration through a short pad of silica removed the trace amount of impurities).

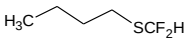
Synthesis of [(difluoromethyl)thio]-methylbenzene (2).



[CAS: 68965-44-6]

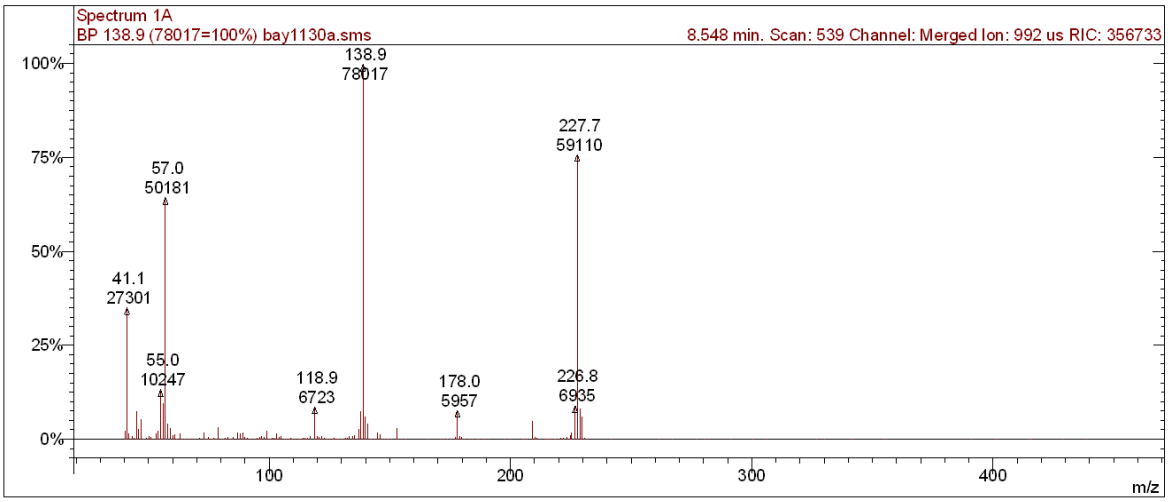
Compound **2** was prepared following the standard procedure 1, starting from (bromomethyl)benzene [CAS: 100-39-0] (171 mg, 1.00 mmol). After purification, **2** was isolated as colorless oil (171 mg, 0.98 mmol, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.32 (m, 5H), 6.75 (t, J = 56.6 Hz, 1H), 4.04 ppm (s, 2H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –94.4 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 136.2, 128.9 (2C), 128.8 (2C), 127.6, 120.2 (t, ^1J(C,F) = 272.9 Hz), 31.7 ppm (t, ^3J(C,F) = 3.6 Hz); **IR** (neat): ν = 3032, 1739, 1496, 1455, 1366, 1323, 1217, 1056, 1018, 754, 703 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 174 [M^+] (65), 92 (10), 91 (100); **HRMS** (EI-TOF) calcd for $C_8H_8F_2S$: 174.0315; found: 174.0314.

Synthesis of 1-[(difluoromethyl)thio]-butane (3).

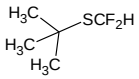


[CAS: 1809138-51-9]

Compound **3** was prepared following the standard procedure 1, starting from butylthiocyanate [CAS: 628-83-1] (83 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36 µL, 0.50 mmol) was added to the reaction mixture and product **3** was formed in 99% yield as determined by **^{19}F NMR** spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = –93.7 ppm (d, J = 55.9 Hz).



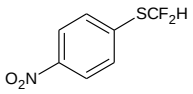
Synthesis of 1-[(difluoromethyl)thio]-2-methyl-propane (4).



[CAS: 68965-47-9]

Compound **4** was prepared following the standard procedure 1, starting from 2-thiocyano-2-methyl-propane [CAS: 37985-18-5], that was synthesized via nukleophilic substitution of 2-iodo-2-methyl-propane [CAS: 558-17-8] (92 mg, 0.50 mmol) by sodium thiocyanate (50 mg, 0.60 mmol) in DMF (1 mL) and used without further purification. After the reaction, trifluoroethanol as internal standard (36 µL, 0.50 mmol) was added to the reaction mixture and product **4** was formed in trace amounts (<10%) as determined by **^{19}F NMR** spectroscopic analysis. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = –92.5 ppm (d, J = 57.2 Hz).

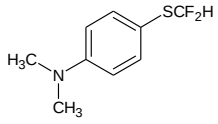
Synthesis of 1-[(difluoromethyl)thio]-4-nitrobenzene (5)



[CAS: 24933-57-1]

Compound **5** was prepared following the standard procedure 1, starting from 4-nitrobenzenethiocyanate [CAS: 2137-92-0] (180 mg, 1.00 mmol). After purification, **5** was isolated as colorless oil (148 mg, 0.72 mmol, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.24 (d, ^{3}J(H,H) = 8.9 Hz, 2H), 7.73 (d, ^{3}J(H,H) = 8.9 Hz, 2H), 6.96 ppm (t, J = 55.8 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.2 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.2, 134.2 (t, ^{3}J(C,F) = 3.3 Hz), 134.3 (2C), 124.1 (2C), 119.6 ppm (t, ^{1}J(C,F) = 276.6 Hz); **IR** (neat): ν = 2971, 1739, 1600, 1517, 1344, 1217, 1035, 852, 763, 739, 684 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 205 [M^+] (100), 175 (75), 155 (38), 125 (37), 124 (86), 108 (33), 80 (16); **HRMS** (EI-TOF) calcd for $C_7H_5NO_2F_2S$: 205.0009; found: 205.0002.

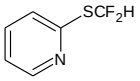
Synthesis of *N*,*N*-dimethyl-4-[(difluoromethyl)thio]aniline (6)



[CAS: 1808089-13-5]

Compound **6** was prepared following the standard procedure 1, starting from 4-(dimethylamino)benzenethiocyanate [CAS: 7152-80-9] (178 mg, 1.00 mmol). After purification, **6** was isolated as yellow oil (187 mg, 0.92 mmol, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.43 (d, ^{3}J(H,H) = 9.0 Hz, 2H), 6.71 (t, J = 57.6 Hz, 1H), 6.68 (d, ^{3}J(H,H) = 9.0 Hz, 2H), 3.00 ppm (s, 6H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –92.6 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.4, 137.3 (2C), 121.4 (t, ^{1}J(C,F) = 274.8 Hz), 112.5 (2C), 109.8 (t, ^{3}J(C,F) = 2.7 Hz), 40.1 ppm (2C); **IR** (neat): ν = 2971, 1739, 1593, 1508, 1445, 1365, 1218, 1197, 1060, 1028, 815, 769, 751 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 203 [M^+] (52), 153 (15), 152 (100), 136 (13); **HRMS** (EI-TOF) calcd for $C_9H_{11}NF_2S$: 203.0580; found: 203.0571.

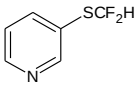
Synthesis of 2-[(difluoromethyl)thio]pyridine (7)



[CAS: 250690-59-6]

Compound **7** was prepared following the standard procedure 1, starting from 2-thiocyanatopyridine [CAS: 2637-35-6] (136 mg, 1.00 mmol). After purification, **7** was isolated as a slightly yellow oil (147 mg, 0.91 mmol, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.50 (d, ^3J(H,H) = 4.8 Hz, 1H), 7.71 (t, J = 56.3 Hz, 1H), 7.62 (dt, ^3J(H,H) = 7.8, 1.6 Hz, 1H), 7.28 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.16 ppm (dd, ^3J(H,H) = 7.6, 4.9 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –96.2 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 153.2 (t, ^3J(C,F) = 3.6 Hz), 150.1, 137.1, 124.3 (t, ^3J(C,F) = 2.3 Hz), 121.7, 121.3 ppm (t, ^1J(C,F) = 271.3 Hz); **IR** (neat): ν = 3002, 1739, 1578, 1562, 1455, 1419, 1284, 1127, 1042, 989, 790, 757, 720 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 161 [M^+] (100), 111 (65), 79 (47), 67 (14); **HRMS** (EI-TOF) calcd for $C_6H_5NF_2S$: 161.0111; found: 161.0114.

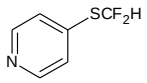
Synthesis of 3-[(difluoromethyl)thio]pyridine (8)



[CAS: 1809138-52-0]

Compound **8** was prepared following the standard procedure 1, starting from 3-thiocyanatopyridine [CAS: 2645-25-2] (136 mg, 1.00 mmol). After purification, **8** was isolated as a slightly yellow oil (140 mg, 0.87 mmol, 87%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.80 (s, 1 H), 8.67 (d, ^3J(H,H) = 4.8 Hz, 1H), 7.95 (d, ^3J(H,H) = 7.9 Hz, 1H), 7.37 (dd, ^3J(H,H) = 7.9, 4.8 Hz, 1H), 6.86 ppm (t, J = 56.3 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.4 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.0, 150.6, 142.9, 132.9, 122.9, 119.6 ppm (t, ^1J(C,F) = 276.6 Hz); **IR** (neat): ν = 3041, 1738, 1570, 1467, 1407, 1320, 1299, 1063, 1031, 1016, 808, 783, 753, 724, 703 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 161 [M^+] (100), 111 (51), 110 (27), 83 (17); **HRMS** (EI-TOF) calcd for $C_6H_5NF_2S$: 161.0111; found: 161.0104.

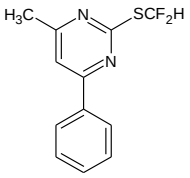
Synthesis of 4-[(difluoromethyl)thio]pyridine (9)



[CAS: 1809138-53-1]

Compound **9** was prepared following the standard procedure 1, starting from 4-thiocyanatopyridine [CAS: 2637-36-7] (136 mg, 1.00 mmol). After purification, **9** was isolated as yellow oil (137 mg, 0.85 mmol, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.59 (s, 2H), 7.40 (d, ^{3}J(H,H) = 4.8 Hz, 2H), 6.99 ppm (t, J = 55.8 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.1 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 150.2 (2C), 138.4 (t, ^{3}J(C,F) = 3.0 Hz), 126.3 (2C), 119.7 ppm (t, ^{1}J(C,F) = 276.1 Hz); **IR** (neat): ν = 3041, 1738, 1574, 1545, 1486, 1408, 1299, 1217, 1033, 809, 787, 756, 706 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 161 [M^+] (100), 111 (50); **HRMS** (EI-TOF) calcd for $C_6H_5NF_2S$: 161.0111; found: 161.0111.

Synthesis of 2-[(difluoromethyl)thio]-4-methyl-6-phenylpyrimidine (10)



[CAS: 1809138-54-2]

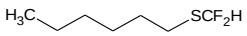
Compound **10** was prepared following the standard procedure 1, starting from 4-methyl-6-phenyl-2-pyrimidinyl thiocyanate [CAS: 55055-29-3] (227 mg, 1.00 mmol). After purification, **10** was isolated as green oil (239 mg, 0.95 mmol, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.04 (m, 2H), 7.94 (t, J = 56.0 Hz, 1H), 7.51 (m, 3H), 7.35 (s, 1H), 2.55 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –99.0 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 186.8, 167.1 (t, ^{3}J(C,F) = 5.8 Hz), 164.3, 135.7, 131.4, 129.0 (2C), 127.2 (2C), 121.0 (t, ^{1}J(C,F) = 269.8 Hz), 113.3, 24.2 ppm; **IR** (neat): ν = 2971, 1739, 1574, 1523, 1353, 1257, 1206, 1044, 914, 834, 783, 753, 689 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 252 [M^+] (19), 201 (25), 170 (100); **HRMS** (EI-TOF) calcd for $C_{12}H_{10}N_2F_2S$: 252.0533; found: 252.0532.

6.3.5 Synthesis of difluoromethyl thioethers starting from the corresponding bromides or mesylates

6.3.5.1 Standard procedure 2

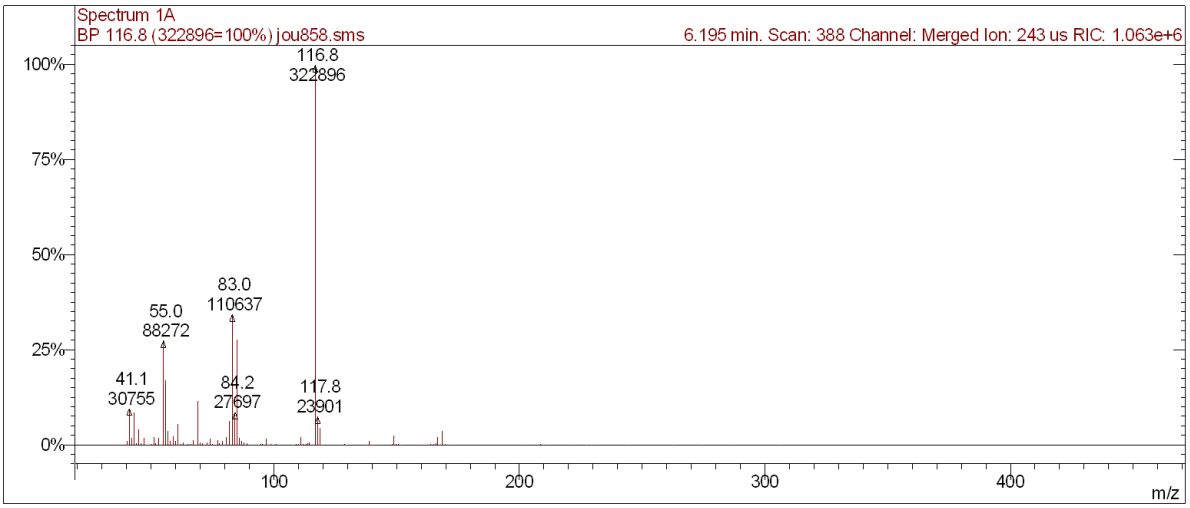
An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with sodium thiocyanate (100 mg, 1.20 mmol), DMF (2 mL) and the bromide or mesylate starting material (mesylates were obtained from the corresponding alcohol via classical mesylation reaction, after a short extraction with DCM, water and brine the mesylates were used without further purification). (1.00 mmol) was added via syringe. The suspension was heated under stirring until completion of the reaction, followed by GC and GC-MS (following temperatures were required depending on the leaving group: primary alkylbromides: 60 °C; secondary alkylbromides 110 °C and primary alkylmesylates: 80-90 °C). Afterwards the reaction mixture was charged with copper thiocyanate (122 mg, 1.00 mmol), cesium fluoride (608 mg, 4.00 mmol) and difluoromethyltrimethylsilane (245 mg, 2.00 mmol) and the suspension was stirred at room temperature for 12 h. The resulting mixture was filtered through a short pad of silica (5 g) and rinsed with diethyl ether (20 mL). The organic solution was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). After evaporation of the solvent, the corresponding difluoromethyl thioether was generally obtained pure (in some cases a second filtration through a short pad of silica removed the trace amount of impurities).

Synthesis of 1-[(difluoromethyl)thio]-hexane (11)

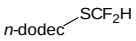


[CAS: 1809138-55-3]

Compound **11** was prepared following the standard procedure 2, starting from 1-bromohexane [CAS: 111-25-1] (82 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36 µL, 0.50 mmol) was added to the reaction mixture and product **11** was formed in 98% yield as determined by **^{19}F NMR** spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = –92.7 ppm (d, J = 57.2 Hz).



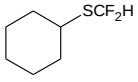
Synthesis of 1-[(difluoromethyl)thio]-dodecane (12)



[CAS: 1191279-61-4]

Compound **12** was prepared following the standard procedure 2, starting from 1-bromododecane [CAS: 143-15-7] (249 mg, 1.00 mmol). After purification, **12** was isolated as slightly yellow oil (246 mg, 0.98 mmol, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.81 (t, *J* = 56.5 Hz, 1H), 2.80 (d, ^{3}J(H,H) = 7.5 Hz, 2H), 1.67 (q, ^{3}J(H,H) = 7.5 Hz, 2H), 1.40 (q, ^{3}J(H,H) = 7.4 Hz, 2H), 1.27 (m, 16H), 0.89 ppm (t, ^{3}J(H,H) = 6.8 Hz, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –92.7 ppm (d, *J* = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 120.8 (t, ^{1}J(C,F) = 271.8 Hz), 31.9, 30.1, 29.6 (2C), 29.5, 29.4, 29.3, 29.0, 28.7, 27.2 (t, ^{3}J(C,F) = 2.9 Hz), 22.7, 14.1 ppm; **IR** (neat): ν = 2924, 2854, 1738, 1466, 1282, 1168, 1021, 771, 721 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 202 (29), 201 (100), 139 (10), 97 (24), 83 (24), 69 (27); **HRMS** (EI-TOF) calcd for $C_{13}H_{26}F_2S$: 251.1645; found: 251.1626.

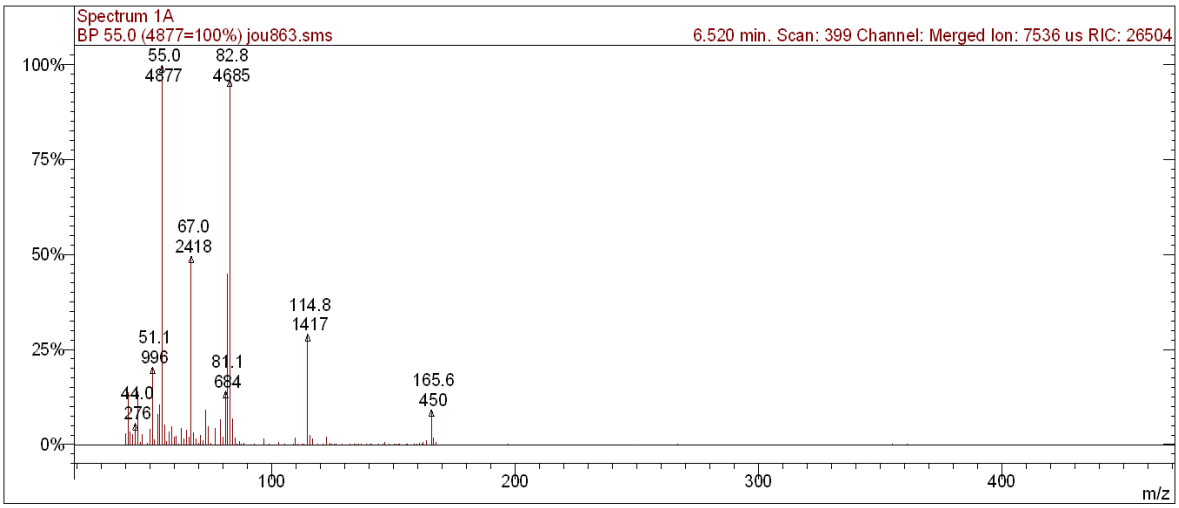
Synthesis of [(difluoromethyl)thio]-cyclohexane (13)



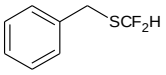
[CAS: 1809138-56-4]

Compound **13** was prepared following the standard procedure 2, starting from bromocyclohexane [CAS: 108-85-0] (81 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36 µL, 0.50 mmol) was added to the reaction mixture and product **13** was

formed in 70% yield as determined by **^{19}F NMR** spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = –92.4 ppm (d, J = 55.9 Hz).



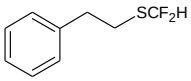
Synthesis of [(difluoromethyl)thio]-methylbenzene (2)



[CAS: 68965-44-6]

Compound **2** was prepared following the standard procedure 2, starting from (bromomethyl)benzene [CAS: 100-39-0] (171 mg, 1.00 mmol). After purification, **2** was isolated as colorless oil (171 mg, 0.98 mmol, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.32 (m, 5H), 6.75 (t, J = 56.6 Hz, 1H), 4.04 ppm (s, 2H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –94.4 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 136.2, 128.9 (2C), 128.8 (2C), 127.6, 120.2 (t, ^{1}J(C,F) = 272.9 Hz), 31.7 ppm (t, ^{3}J(C,F) = 3.6 Hz); **IR** (neat): ν = 3032, 1739, 1496, 1455, 1366, 1323, 1217, 1056, 1018, 754, 703 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 174 [M^+] (65), 92 (10), 91 (100); **HRMS** (EI-TOF) calcd for $C_8H_8F_2S$: 174.0315; found: 174.0314.

Synthesis of [(difluoromethyl)thio]-ethylbenzene (14)

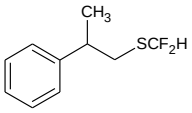


[CAS: 1809138-57-5]

Compound **14** was prepared following the standard procedure 2, starting from (2-bromoethyl)benzene [CAS: 103-63-9] (184 mg, 1.00 mmol). After purification, **14** was

isolated as colorless oil (175 mg, 0.93 mmol, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.36 (m, 2H), 7.29 (m, 1H), 7.25 (m, 2H), 6.80 (t, *J* = 56.2 Hz, 1H), 3.05 ppm (m, 4H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –92.7 ppm (d, *J* = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 139.5, 128.6 (2C), 128.5 (2C), 126.7, 120.6 (t, ^1J(C,F) = 272.9 Hz), 36.7, 28.5 ppm (t, ^3J(C,F) = 2.7 Hz); **IR** (neat): ν = 3030, 1604, 1497, 1455, 1323, 1056, 1010, 798, 773, 745, 697 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 188 [M^+] (45), 91 (100); **HRMS** (EI-TOF) calcd for $C_9H_{10}F_2S$: 188.0471; found: 188.0461.

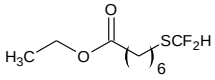
Synthesis of [(difluoromethyl)thio]-2-phenylpropylene (15)



[CAS: 112028-29-2]

Compound **15** was prepared following the standard procedure 2, starting from 2-Phenyl-1-propanol [CAS: 1123-85-9] (136 mg, 1.00 mmol). After purification, **15** was isolated as colorless oil (176 mg, 0.87 mmol, 87%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.36 (m, 2H), 7.26 (m, 3H), 6.70 (t, *J* = 56.5 Hz, 1H), 3.05 (m, 3H), 1.41 ppm (d, ^3J = 6.7 Hz, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –92.8 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 114.5, 128.6 (2C), 127.0 (2C), 126.9, 120.5 (t, ^1J(C,F) = 272.4 Hz), 40.4, 35.0 (t, ^3J(C,F) = 2.7 Hz), 20.8 ppm; **IR** (neat): ν = 2967, 1494, 1453, 1328, 1049, 1011, 783, 760, 697 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 166 [M^+] (11), 83 (100); **HRMS** (EI-TOF) calcd for $C_{10}H_{12}F_2S$: 202.0628; found: 202.0619.

Synthesis of 6-[(difluoromethyl)thio]-hexanoic acid-ethyl ester (16)

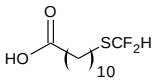


[CAS: 1809138-59-7]

Compound **16** was prepared following the standard procedure 2, starting from 6-bromo-hexanoic acid-ethyl ester [CAS: 25542-62-5] (223 mg, 1.00 mmol). After purification, **16** was isolated as orange oil (222 mg, 0.98 mmol, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.80 (t, *J* = 56.3 Hz, 1H), 4.13 (q, ^3J = 7.2 Hz, 2H), 2.80 (t, ^3J = 7.4 Hz, 2H), 2.31 (t, ^3J = 7.4 Hz, 2H), 1.67 (m, 4H), 1.44 (m, 2H), 1.26 ppm (t, ^3J = 7.2 Hz, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –92.7 ppm (d, *J* = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.5, 120.7 (t,

^{1}J(C,F) = 271.9 Hz), 60.3, 34.1, 29.8, 28.1, 26.9 (t, ^{3}J(C,F) = 3.3 Hz), 24.3, 14.2 ppm; **IR** (neat): ν = 2939, 1730, 1463, 1374, 1259, 1180, 1016, 770 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 206 (33), 186 (30), 181 (100), 171 (17), 143 (60), 129 (68), 101 (48), 97 (41), 88 (53), 69 (42); **HRMS** (EI-TOF) calcd for $C_9H_{16}O_2F_2S$: 226.0839; found: 226.0858.

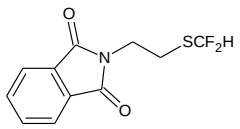
Synthesis of [(difluoromethyl)thio]-undecanoic acid (17)



[CAS: 1809138-60-0]

Compound **17** was prepared following the standard procedure 2, but with the double amounts of copper thiocyanate, cesium fluoride and $TMSCF_2H$, starting from 11-Bromoundecanoic acid [CAS: 2834-05-1] (265 mg, 1.00 mmol). After purification, **17** was isolated as yellow oil (201 mg, 0.75 mmol, 75%) but contained traces of impurities. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.81 (t, *J* = 56.5 Hz, 1H), 2.80 (d, ^{3}J = 7.4 Hz, 2H), 2.36 (d, ^{3}J = 7.4 Hz, 2H), 1.65 (m, 4H), 1.39 (m, 2H), 1.29 ppm (s, 10H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –92.7 ppm (d, *J* = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 179.9, 120.8 (t, ^{1}J(C,F) = 271.9 Hz), 34.0, 30.1, 29.3, 29.3, 29.2, 29.0, 29.0, 28.6, 27.2 (t, ^{3}J(C,F) = 2.9 Hz), 24.6 ppm; **IR** (neat): ν = 2926, 2855, 1738, 1708, 1366, 1217, 1056, 1019, 771 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 247 [M^+, -H, -HF] (12), 228 (10), 215 (95), 181 (26), 113 (30), 99 (27), 98 (72), 87 (95), 73 (36), 69 (100), 55 (73); **HRMS** (EI-TOF) calcd for Fragment 1 [M^+, -H, -HF]: $C_{12}H_{20}FO_2S$: 247.1168; found: 247.1160, calcd for Fragment 2 [-2HF]: $C_{12}H_{20}O_2S$: 228.1184; found: 228.1172, calcd for Fragment 3 [-CF_2H]: $C_{11}H_{19}O_2S$: 215.1106; found: 215.1086.

Synthesis of 2-[2-[(difluoromethyl)thio]ethyl]-1*H*-isoindole-1,3(2H)-dione (18)

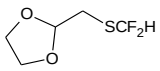


[CAS: 1809138-61-1]

Compound **18** was prepared following the standard procedure 2, starting from 2-(2-bromoethyl)-1*H*-isoindole-1,3(2*H*)-dione [CAS: 574-98-1] (254 mg, 1.00 mmol). After purification, **18** was isolated as colorless solid (213 mg, 0.83 mmol, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.86 (m, 2H), 7.74 (m, 2H), 6.85 (t, *J* = 56.1 Hz, 1H), 3.98 (d,

^{3}J = 7.0 Hz, 2H), 3.13 ppm (d, ^{3}J = 7.0 Hz, 2H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –92.78 ppm (d, *J* = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.0 (2C), 134.2 (2C), 131.8 (2C), 123.4 (2C), 120.0 (t, ^{1}J(C,F) = 273.8 Hz), 37.8, 25.4 ppm (t, ^{3}J(C,F) = 3.2 Hz); **IR** (neat): ν = 2995, 2951, 1769, 1706, 1471, 1438, 1396, 1331, 1047, 999, 940, 862, 769, 714 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 175 (15), 161 (11), 160 (100), 148 (11); m.p.: 59-60 °C; **HRMS** (EI-TOF) calcd for $C_{11}H_9NO_2F_2S$: 257.0322; found: 257.0320.

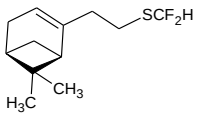
Synthesis of [(difluoromethyl)thio]-methyl-1,3-dioxolane (19)



[CAS: 1809138-62-2]

Compound **19** was prepared following the standard procedure 2, starting from 2-Bromomethyl-1,3-dioxolane [CAS: 4360-63-8] (167mg, 1.00 mmol) with traces of impurities. After purification, **19** was isolated as slightly yellow oil (104 mg, 0.61 mmol, 61%) but contained traces of impurities. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.97 (t, *J* = 57.4 Hz, 1H), 5.16 (t, ^{3}J = 4.1 Hz, 1H), 4.05 (m, 2H), 3.94 (m, 2H), 2.99 (d, ^{3}J = 4.0 Hz, 2H),; **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –93.4 ppm (d, *J* = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 120.5 (t, ^{1}J(C,F) = 272.5 Hz), 102.9, 65.5 (2C), 31.2 ppm (t, ^{3}J(C,F) = 2.9 Hz); **IR** (neat): ν = 2970, 1739, 1366, 1229, 1217, 1137, 1060, 1014, 980, 831, 778, 738 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 96 (34), 73 (100); **HRMS** (EI-TOF) calcd for $C_5H_8F_2O_2S$: 169.0135; found: 169.0126.

Synthesis of [(difluoromethyl)thio]-2-(6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl)ethylene (20)



[CAS: 1809138-63-3]

Compound **20** was prepared following the standard procedure 2, starting from 2-methanesulfonate-6,6-dimethyl-(1R,5S)-Bicyclo[3.1.1]-hept-2-ene-2-ethanol [CAS:107667-90-3] (166 mg, 1.00 mmol). After purification, **20** was isolated as slightly yellow oil (216 mg, 0.93 mmol, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.82 (t, *J* = 56.4 Hz, 1H), 5.30 (m, 1H), 2.83 (m, 2H), 2.39 (m, 1H), 2.32 (m, 2H), 2.24 (m, 2H), 2.10 (m, 1H), 2.02 (m, 1H), 1.29 (s, 3H), 1.16 (d, ^{3}J = 8.5 Hz, 1H), 0.84 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$):

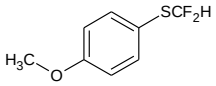
δ = –92.7 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 145.7, 120.7 (t, ^1J(C,F) = 272.1 Hz), 118.3, 45.5, 40.7, 38.0, 37.4, 31.6, 31.2, 26.2, 25.1 (t, ^3J(C,F) = 3.3 Hz), 21.2 ppm; **IR** (neat): ν = 2917, 1469, 1433, 1324, 1060, 1020, 772 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 232 [M^+] (49), 188 (100), 105 (54); **HRMS** (EI-TOF) calcd for $C_{12}H_{18}F_2S$: 232.1097; found: 232.1099; $[\alpha]_D^{20}$ -29 (c 1.14, $CHCl_3$).

6.3.6 Synthesis of difluoromethyl thioethers from the corresponding arenediazonium salts

6.3.6.1 Standard procedure 3

An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with copper thiocyanate (122 mg, 1.00 mmol) sodium thiocyanate (124 mg, 1.50 mmol) and cesium carbonate (228 mg, 0.70 mmol) in MeCN (2 mL). Afterwards a solution of the arenediazonium tetrafluoroborate (1.00 mmol) in MeCN (2 mL) and was added dropwise via syringe. The suspension was stirred at room temperature for 1 h. After a short filtration through a short pad of silica the solvent was evaporated and the vessel was charged with copper thiocyanate (122 mg, 1.00 mmol), cesium fluoride (608 mg, 4.00 mmol) and DMF (4 mL). Difluoromethyltrimethylsilane (245 mg, 2.00 mmol) was added and the suspension was stirred at room temperature for 12 h. The resulting mixture was filtered through a short pad of silica (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient), yielding the corresponding aryl difluoromethyl thioethers.

Synthesis of 1-[(difluoromethyl)thio]-4-methoxybenzene (22)

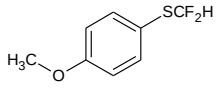


[CAS: 81931-98-8]

Compound **22** was prepared following the standard procedure 3, starting from 4-methoxybenzenediazonium tetrafluoroborate (**21**) [CAS: 459-64-3] (222 mg, 1.00 mmol). After purification, **22** was isolated as colorless oil (181 mg, 0.95 mmol, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.56 (d, ^3J = 8.9 Hz, 2H), 6.94 (d, ^3J = 8.9 Hz, 2H), 6.80 (t, J = 57.1 Hz, 1H), 3.82 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –92.2 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.1, 137.4 (2C), 121.0 (t, ^1J(C,F) = 274.6 Hz), 115.9 (t, ^3J(C,F) = 3.3 Hz), 114.8 (2C), 55.0 ppm; **IR** (neat): ν = 2971, 1739, 1592, 1494, 1463, 1366, 1290, 1247, 1175, 1063, 1027, 829, 800, 755, 711 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 190 [M^+] (57), 187 (18), 154 (28), 139 (100), 124 (21), 96

(17), 95 (18), 77 (10), 70 (13), 69 (13), 63 (13); **HRMS** (EI-TOF) calcd for $C_8H_8OF_2S$: 190.0264; found: 190.0270.

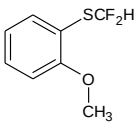
Upscale of 1-[(difluoromethyl)thio]-4-methoxybenzene (22)



[CAS: 81931-98-8]

An oven-dried 100 mL flask with Teflon-coated stirrer bar was charged with copper thiocyanate (1.22 g, 10.0 mmol) sodium thiocyanate (1.22 g, 10.0 mmol) and cesium carbonate (2.28 g, 7.00 mmol) in MeCN (20 mL). Afterwards a solution of 4-methoxybenzenediazonium tetrafluoroborate (**21**) [CAS: 459-64-3] (2.22 g, 10.0 mmol) in MeCN (20 mL) and was added dropwise via syringe. The suspension was stirred at room temperature for 1 h. After a short filtration through a short pad of silica the solvent was evaporated and the vessel was charged with copper thiocyanate (1.22 g, 10.0 mmol), cesium fluoride (6.08 g, 40.0 mmol) and DMF (40 mL). Difluoromethyltrimethylsilane (2.45 g, 20.0 mmol) was added and the suspension was stirred at room temperature for 12 h. The resulting mixture was filtered through a short pad of silica (50 g) and rinsed with diethyl ether (100 mL). The resulting organic solution was washed with water (2 × 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient), and **22** was isolated as colorless oil (1.69 g, 8.90 mmol, 89%).

Synthesis of 1-[(difluoromethyl)thio]-2-methoxybenzene (23)

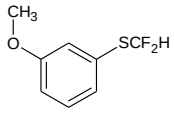


[CAS: 1097193-02-6]

Compound **23** was prepared following the standard procedure 3, starting from 2-methoxybenzenediazonium tetrafluoroborate [CAS: 395-48-2] (222 mg, 1.00 mmol). After purification, **23** was isolated as colorless oil (133 mg, 0.70 mmol, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.54 (m, 1H), 7.41 (m, 1H), 6.98 (m, 2H), 6.95 (t, *J* = 58.0 Hz, 1H), 3.92 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –92.6 ppm (d, *J* = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.4, 136.6, 131.5, 121.3, 120.6 (t, ^1J(C,F) = 274.3 Hz), 114.8 (t, ^3J(C,F) = 3.6 Hz), 111.4, 56.0 ppm; **IR** (neat): ν = 2970, 1739, 1586, 1479, 1433, 1292, 1276,

1248, 1058, 1017, 802, 750, 685 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 190 [M^+] (100), 157 (20), 140 (58), 125 (16); **HRMS** (EI-TOF) calcd for $C_8H_8OF_2S$: 190.0264; found: 190.0263.

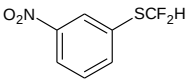
Synthesis of 1-[(difluoromethyl)thio]-3-methoxybenzene (24)



[CAS: 1333375-76-0]

Compound **24** was prepared following the standard procedure 3, starting from 3-methoxybenzenediazonium tetrafluoroborate[i] (222 mg, 1.00 mmol). After purification, **24** was isolated as colorless oil (156 mg, 0.82 mmol, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.31 (t, ^3J = 7.9 Hz, 1H), 7.18 (d, ^3J = 7.7 Hz, 1H), 7.12 (m, 1H), 6.97 (m, 1H), 6.86 (t, J = 57.0 Hz, 1H), 3.83 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.1 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.9, 130.1, 127.2, 127.1 (t, ^3J = 3.3 Hz), 121.1 (t, ^1J(C,F) = 274.7 Hz), 120.1, 115.8, 55.4 ppm; **IR** (neat): ν = 2965, 1739, 1591, 1577, 1480, 1425, 1316, 1285, 1248, 1233, 1064, 1030, 860, 795, 754, 686 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 190 [M^+] (20), 140 (13), 139 (35), 111 (33), 109 (24); **HRMS** (EI-TOF) calcd for $C_8H_8OF_2S$: 190.0264; found: 190.0269.

Synthesis of 1-[(difluoromethyl)thio]-3-nitrobenzene (25).

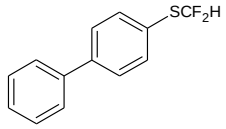


[CAS: 24933-39-9]

Compound **25** was prepared following the standard procedure 3, starting from 3-nitrobenzenediazonium tetrafluoroborate [CAS: 586-36-7] (237 mg, 1.00 mmol). After purification, **25** was isolated as colorless oil (133 mg, 0.65 mmol, 65%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.46 (t, ^3J(H,H) = 1.9 Hz, 1H), 8.30 (m, 1H), 7.93 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.62 (t, ^3J(H,H) = 8.0 Hz, 1H), 6.92 ppm (t, J = 56.0 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.5 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.4, 141.0, 130.1, 129.8, 128.1.5 (t, ^3J(C,F) = 2.7 Hz), 124.6, 119.6 ppm (t, ^1J(C,F) = 277.0 Hz); **IR** (neat): ν = 3088, 1739, 1528, 1341, 1318, 1296, 1063, 1032, 876, 807, 761, 729, 672 cm^{-1}; **MS** (Ion trap, EI, 70

eV): m/z (%) = 205 [M^+] (100), 175 (15), 159 (14), 155 (68), 139 (12), 109 (17), 108 (46), 95 (12); **HRMS** (EI-TOF) calcd for $C_7H_5NO_2F_2S$: 205.0009; found: 205.0003.

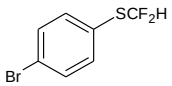
Synthesis of 4-[(difluoromethyl)thio]-1,1'-biphenyl (26)



[CAS: 207974-77-4]

Compound **26** was prepared following the standard procedure 3, starting from [1,1'-biphenyl]-4-diazonium tetrafluoroborate[ii] (267 mg, 1.00 mmol). After purification, **26** was isolated as white solid (201 mg, 0.85 mmol, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.67 (m, 2H), 7.61 (m, 4H), 7.48 (m, 2H), 7.41 (m, 1H), 6.88 ppm (t, J = 56.9 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.3 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.8, 139.8, 135.7, 128.9 (2C), 128.0 (2C), 127.9 (2C), 127.1 (2C), 124.7 (t, ^3J(C,F) = 3.1 Hz), 120.9 ppm (t, ^1J(C,F) = 275.2 Hz); **IR** (neat): ν = 3027, 1739, 1593, 1479, 1397, 1322, 1310, 1058, 1018, 968, 920, 835, 762, 747, 718, 699, 656 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 237 [M^++H] (13), 236 (83), 186 (41), 185 (100), 184 (30), 152 (32); m.p.: 56-57 °C; **HRMS** (EI-TOF) calcd for $C_{13}H_{10}F_2S$: 236.0471; found: 236.0474.

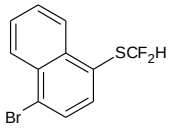
Synthesis of 1-bromo-4-[(difluoromethyl)thio] benzene (27)



[CAS: 4837-14-3]

Compound **27** was prepared following the standard procedure 3, starting from 4-bromobenzenediazonium tetrafluoroborate [CAS: 673-40-5] (271 mg, 1.00 mmol). After purification, **27** was isolated as colorless oil (195 mg, 0.82 mmol, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.53 (m, 2H), 7.45 (m, 2H), 6.99 ppm (t, J = 56.6 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.6 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 136.9 (2C), 132.5 (2C), 124.8 (t, ^3J(C,F) = 3.3 Hz), 124.7, 120.2 ppm (t, ^1J(C,F) = 275.7 Hz); **IR** (neat): ν = 3083, 1910, 1739, 1646, 1561, 1472, 1385, 1065, 1044, 1007, 964, 886, 867, 816, 758, 729 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 240 [M^+] (80), 238 (81), 190 (76), 189 (36), 188 (77), 187 (35), 109 (24), 108 (100), 82 (14), 63 (12); **HRMS** (EI-TOF) calcd for $C_7H_5F_2SBr$: 237.9263; found: 237.9259.

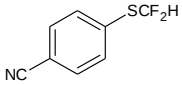
Synthesis of 1-bromo-4-[(difluoromethyl)thio]naphthalene (28)



[CAS: 1809138-64-4]

Compound **28** was prepared following the standard procedure 3, starting from 4-bromonaphthalen-1-yldiazonium tetrafluoroborate [CAS: 341-89-9] (321 mg, 1.00 mmol). After purification, **28** was isolated as colorless oil (225 mg, 0.78 mmol, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.55 (m, 1H), 8.32 (m, 1H), 7.82 (d, ^{3}J(H,H) = 7.9 Hz, 1H), 7.74 (d, ^{3}J(H,H) = 7.8 Hz, 1H), 7.69 (m, 2H), 6.83 ppm (t, J = 56.8 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –90.9 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 136.3, 136.2, 132.7, 129.7, 128.2, 128.0, 127.9, 126.7, 124.5, 123.4 (t, ^{3}J(C,F) = 2.7 Hz), 120.7 ppm (t, ^{1}J(C,F) = 276.1 Hz); **IR** (neat): ν = 3072, 1578, 1496, 1369, 1317, 1295, 1069, 1039, 976, 877, 828, 759 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 291 [M^{+}+H] (12), 290 (100), 289 (13), 288 (100), 240 (26), 239 (82), 238 (27), 237 (78), 193 (10), 159 (28), 158 (97), 126 (12), 115 (12), 114 (23), 113 (13); **HRMS** (EI-TOF) calcd for $C_{11}H_7F_2SBr$: 287.9420; found: 287.9434.

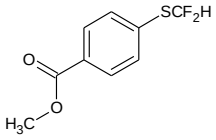
Synthesis of 4-[(difluoromethyl)thio]benzonitrile (29)



[CAS: 4837-25-6]

Compound **29** was prepared following the standard procedure 3, starting from 4-cyanobenzenediazonium tetrafluoroborate [CAS: 2252-32-6] (217 mg, 1.00 mmol). After purification, **29** was isolated as colorless oil (135 mg, 0.73 mmol, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.65 (s, 4H), 6.92 ppm (t, J = 55.8 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.2 (d, J = 55.9 Hz) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 134.4 (2C), 132.7 (t, ^{3}J(C,F) = 2.7 Hz), 132.6 (2C), 119.7 (t, ^{1}J(C,F) = 276.6 Hz), 117.9, 113.2 ppm; **IR** (neat): ν = 2927, 2231, 1738, 1594, 1486, 1370, 1299, 1217, 1064, 1036, 1018, 833, 791, 777, 754 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 185 [M^{+}] (69), 135 (100), 134 (22); **HRMS** (EI-TOF) calcd for $C_8H_5NF_2S$: 185.0111; found: 185.0102.

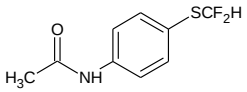
Synthesis of methyl 4-[(difluoromethyl)thio]benzoate (30)



[CAS: 1458640-72-6]

Compound **30** was prepared following the standard procedure 3, starting from 4-(methoxycarbonyl)benzenediazonium tetrafluoroborate (222 mg, 1.00 mmol). After purification, **30** was isolated as colorless oil (164 mg, 0.75 mmol, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.04 (d, ^{3}J(H,H) = 8.4 Hz, 2H), 7.62 (d, ^{3}J(H,H) = 8.4 Hz, 2H), 6.90 (t, J = 56.5 Hz, 1H), 3.93 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.1 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.2, 134.0 (2C), 132.2 (t, ^{3}J(C,F) = 2.7 Hz), 131.0, 130.3 (2C), 120.3 (t, ^{1}J(C,F) = 275.7 Hz), 52.4 ppm; **IR** (neat): ν = 2955, 1720, 1597, 1436, 1400, 1273, 1180, 1110, 1064, 1031, 1016, 964, 855, 828, 793, 748, 720, 691 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 218 [M^+] (70), 187 (100), 182 (46), 168 (21), 151 (63), 139 (10), 137 (58), 136 (13), 109 (12), 108 (21); **HRMS** (EI-TOF) calcd for $C_9H_8O_2F_2S$: 218.0213; found: 218.0202.

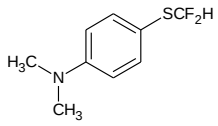
Synthesis of methyl 4-[(difluoromethyl)thio]acetanilide (31)



[CAS: 24933-63-9]

Compound **31** was prepared following the standard procedure 3, starting from 4-acetamidobenzenediazonium tetrafluoroborate [CAS: 19089-87-3] (249 mg, 1.00 mmol). After purification, **31** was isolated as colorless solid (187 mg, 0.86 mmol, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.54 (m, 4H), 6.78 (t, J = 57.0 Hz, 1H), 2.20 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.8 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.6, 139.6, 136.6 (2C), 120.8 (t, ^{1}J(C,F) = 275.2 Hz), 120.2 (2C), 24.7 ppm; **IR** (neat): ν = 3253, 3185, 3112, 1737, 1664, 1609, 1590, 1532, 1492, 1399, 1371, 1317, 1292, 1262, 1025, 969, 835, 758 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 217 [M^+] (64), 175 (52), 125 (18), 124 (100); m.p.: 133-134 °C; **HRMS** (EI-TOF) calcd for $C_9H_9NOF_2S$: 217.0373; found: 217.0384.

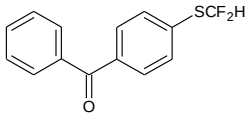
Synthesis of *N*,*N*-dimethyl-4-[(difluoromethyl)thio]aniline (6)



[CAS: 1808089-13-5]

Compound **6** was also prepared following the standard procedure 3, starting from 4-(dimethylamino)benzenediazonium tetrafluoroborate [CAS: 24564-52-1] (235 mg, 1.00 mmol). After purification, **6** was isolated as yellow oil (142 mg, 0.70 mmol, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.43 (d, ^{3}J(H,H) = 9.0 Hz, 2H), 6.71 (t, J = 57.6 Hz, 1H), 6.68 (d, ^{3}J(H,H) = 9.0 Hz, 2H), 3.00 ppm (s, 6H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –92.6 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.4, 137.3 (2C), 121.4 (t, ^{1}J(C,F) = 274.8 Hz), 112.5 (2C), 109.8 (t, ^{3}J(C,F) = 2.7 Hz), 40.1 ppm (2C); **IR** (neat): ν = 2971, 1739, 1593, 1508, 1445, 1365, 1218, 1197, 1060, 1028, 815, 769, 751 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 203 [M^+] (52), 153 (15), 152 (100), 136 (13); **HRMS** (EI-TOF) calcd for $C_9H_{11}NF_2S$: 203.0580; found: 203.0571.

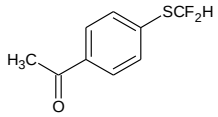
Synthesis of (4-[(difluoromethyl)thio]phenyl)(phenyl)methanone (32)



[CAS: 1779524-54-7]

Compound **32** was prepared following the standard procedure 3, starting from 4-benzoylbenzenediazonium tetrafluoroborate [CAS: 32785-41-4] (296 mg, 1.00 mmol). After purification, **32** was isolated as colorless oil (190 mg, 0.72 mmol, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 (m, 4H), 7.68 (m, 2H), 7.63 (m, 1H), 7.51 (m, 2H), 6.94 ppm (t, J = 56.4 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.0 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 195.7, 138.3, 137.0, 134.0 (2C), 132.8, 131.4 (t, ^{3}J(C,F) = 2.9 Hz), 130.7 (2C), 130.0 (2C), 128.4 (2C), 120.3 ppm (t, ^{1}J(C,F) = 275.8 Hz); **IR** (neat): ν = 3062, 1738, 1656, 1592, 1447, 1397, 1317, 1305, 1277, 1063, 1029, 937, 922, 846, 795, 760, 729, 696, 662 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 265 [M^++H] (20), 264 (100), 214 (33), 187 (87), 181 (14), 137 (51), 109 (11), 108 (13), 105 (84), 77 (39); **HRMS** (EI-TOF) calcd for $C_{14}H_{10}OF_2S$: 264.0420; found: 264.0412.

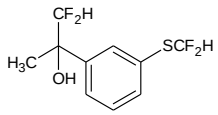
Synthesis of 1-[4-[(difluoromethyl)thio]phenyl]ethanone (33)



[CAS: 145326-60-9]

Compound **33** was prepared following the standard procedure 3, starting from 4-acetylbenzenediazonium tetrafluoroborate [CAS: 350-47-0] (234 mg, 1.00 mmol). After purification, **33** was isolated as colorless oil (174 mg, 0.86 mmol, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.96 (d, ^{3}J(H,H) = 8.4 Hz, 2H), 7.66 (d, ^{3}J(H,H) = 8.4 Hz, 2H), 6.99 (t, J = 56.3 Hz, 1H), 2.62 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.1 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 197.2, 137.5, 134.2 (2C), 132.4 (t, ^{3}J(C,F) = 2.7 Hz), 129.0 (2C), 120.2 (t, ^{1}J(C,F) = 275.6 Hz), 26.7 ppm; **IR** (neat): ν = 2970, 1736, 1683, 1593, 1396, 1358, 1260, 1028, 957, 826, 792, 766, 751, 719 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 202 [M^{+}] (51), 187 (100), 137 (35), 136 (10), 108 (13); **HRMS** (EI-TOF) calcd for $C_9H_8OF_2S$: 202.0264; found: 202.0258.

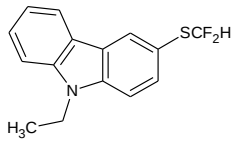
Synthesis of 2-(3-[(difluoromethyl)thio]phenyl)-1,1-difluoropropan-2-ol (34)



[CAS: 1809138-65-5]

Compound **34** was prepared following the standard procedure 3, starting from 3-acetylbenzenediazonium tetrafluoroborate**Fehler! Textmarke nicht definiert.** (234 mg, 1.00 mmol). After purification, **34** was isolated as colorless oil (165 mg, 0.65 mmol, 65%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.76 (s, 1H), 7.58 (m, 2H), 7.43 (m, 1H), 6.85 (t, J = 56.8 Hz, 1H), 5.71 (t, J = 56.4 Hz, 1H), 1.68 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.4 ppm (d, J = 55.8 Hz), –130.0 ppm (qd, ^{1}J = 277.9 Hz, ^{2}J = 54.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.7, 134.9, 132.7, 129.3, 127.4, 126.4 (t, ^{3}J(C,F) = 6.2 Hz), 120.8 (t, ^{1}J(C,F) = 275.2 Hz), 116.6 (t, ^{1}J(C,F) = 247.2 Hz), 74.0 (t, ^{2}J(C,F) = 21.5 Hz), 22.4 ppm (t, ^{3}J(C,F) = 2.2 Hz); **IR** (neat): ν = 3409, 1736, 1661, 1475, 1416, 1386, 1321, 1297, 1043, 958, 902, 803, 753, 699 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 254 [M^{+}] (29), 204 (12), 203 (100), 183 (13), 163 (29); **HRMS** (EI-TOF) calcd for $C_{10}H_{10}OF_4S$: 254.0388; found: 254.0387.

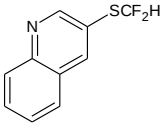
Synthesis of 9-ethyl-3-[(difluoromethyl)thio]-9H-carbazole (35)



[CAS: 1779524-74-1]

Compound **35** was prepared following the standard procedure 3, starting from 9-ethyl-9*H*-carbazol-3-diazonium tetrafluoroborate (309 mg, 1.00 mmol). After purification, **35** was isolated as colorless oil (224 mg, 0.81 mmol, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.36 (d, ^{3}J(H,H) = 1.6 Hz, 1H), 8.13 (d, ^{3}J(H,H) = 7.8 Hz, 1H), 7.68 (m, 1H), 7.53 (m, 1H), 7.43 (d, ^{3}J(H,H) = 8.3 Hz, 2H), 7.30 (m, 1H), 6.86 (t, J = 57.4 Hz, 1H), 4.38 (q, ^{3}J(H,H) = 7.2 Hz, 2H), 1.46 ppm (t, ^{3}J(H,H) = 7.2 Hz, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –92.1 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.6, 140.3, 132.3, 128.9, 126.4, 123.9, 122.2, 121.5 (t, ^{1}J(C,F) = 274.6 Hz), 120.6, 119.6, 113.9 (t, ^{3}J(C,F) = 3.1 Hz), 109.2, 108.8, 37.7, 13.8 ppm; **IR** (neat): ν = 2972, 1739, 1590, 1473, 1455, 1380, 1330, 1269, 1231, 1057, 1022, 888, 806, 747, 727 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 278 [M^{+}+H] (13), 277 (72), 262 (15), 227 (32), 226 (100), 212 (26), 211 (17), 198 (10); **HRMS** (EI-TOF) calcd for $C_{15}H_{13}NF_2S$: 277.0737; found: 277.0747.

Synthesis of 3-[(difluoromethyl)thio]quinoline (36)

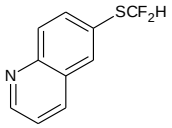


[CAS: 1779524-71-8]

Compound **36** was prepared following the standard procedure 3, starting from quinoline-3-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **36** was isolated as colorless oil (137 mg, 0.65 mmol, 65%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.01 (s, 1H), 8.48 (d, ^{3}J(H,H) = 2.0 Hz, 1H), 8.16 (d, ^{3}J(H,H) = 8.5 Hz, 1H), 7.86 (d, ^{3}J(H,H) = 8.2 Hz, 1H), 7.82 (m, 1H), 7.64 (m, 1H), 6.91 ppm (t, J = 56.3 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.3 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.5, 148.0, 143.7, 131.1, 129.5, 127.9, 127.6, 119.8 (t, ^{1}J(C,F) = 276.9 Hz), 119.4 ppm; **IR** (neat): ν = 2926, 1738, 1489, 1356, 1317, 1297, 1064, 1034, 957, 911, 864, 783, 766 cm^{-1}; **MS** (Ion trap, EI, 70 eV):

m/z (%) = 212 [M^++H] (12), 211 (100), 161 (54), 160 (65), 133 (13), 116 (11), 89 (27); **HRMS** (EI-TOF) calcd for $C_{10}H_7NF_2S$: 211.0267; found: 211.0269.

Synthesis of 6-[(difluoromethyl)thio]quinoline (37)



[CAS: 1779524-70-7]

Compound **37** was prepared following the standard procedure 3, starting from quinoline-6-diazonium tetrafluoroborate[iii] (243 mg, 1.00 mmol). After purification, **37** was isolated as colorless oil (129 mg, 0.61 mmol, 61%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.98 (m, 1H), 8.14 (m, 3H), 7.85 (m, 1H), 7.47 (m, 1H), 6.94 ppm (t, J = 56.6 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –91.3 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.8, 148.3, 136.0, 135.1, 135.0, 130.6, 128.4, 124.4 (t, ^3J(C,F) = 2.7 Hz), 122.0, 120.6 ppm (t, ^1J(C,F) = 275.7 Hz); **IR** (neat): ν = 3039, 1590, 1567, 1489, 1348, 1316, 1187, 1059, 1025, 945, 890, 864, 834, 792, 766, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 212 [M^++H] (12), 211 (100), 162 (10), 161, (64), 160 (72), 117 (14), 116 (27), 89 (14); **HRMS** (EI-TOF) calcd for $C_{10}H_7NF_2S$: 211.0267; found: 211.0260.

6.4 Iron-Catalyzed Decarboxylation of Trifluoroacetate and its Application to the Synthesis of Trifluoromethyl Thioethers

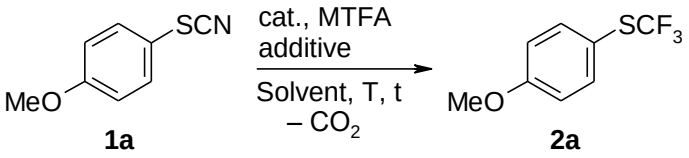
General Methods

All reactions were performed in oven-dried glassware containing a Teflon-coated stir bar and sealed by a septum under a nitrogen atmosphere. Acetonitrile and DMF were dried by refluxing over CaH_2 and subsequent fractional distillation. The yields were determined by ^{19}F NMR spectroscopy using 2,2,2-trifluoroethanol as the internal standard. GC analyses were carried out using a HP-5 capillary column (phenyl pethyl siloxane 30 m × 320 µm × 0.25 µm, 100/2.3-30-300/3) and a time program beginning with 2 min at 60 °C followed by a 30 °C·min^{-1} ramp to 300 °C, then 3 min at this temperature. Column chromatography was performed using a *CombiFlash* Companion chromatography system (Isco Systems) and Grace Reveleris packed flash columns (12 g). NMR spectra were obtained on a Bruker AMX 400 system using chloroform-*d* as deuterated solvent, with proton, carbon and fluorine resonances at 400 MHz, 101 MHz and 376 MHz, respectively. Mass spectral data were acquired on a Varian Saturn 2100 T.

The diazonium salts were prepared from the corresponding anilines following the procedures below and were directly used. The aryl thiocyanates were prepared following the procedures below from the corresponding diazonium salts or the corresponding simple arenes. All other starting materials were commercially available. All solvents were purified by distillation prior to use. The other chemicals were used without further purification.

6.4.1 Optimization of the Reaction Conditions

Table 1: Optimization of the reaction conditions for the iron-catalyzed decarboxylative trifluoromethylation of 4-methoxyphenyl thiocyanate (**1a**) yielding 1-methoxy-4-[trifluoromethyl)thio]benzene (**2a**).



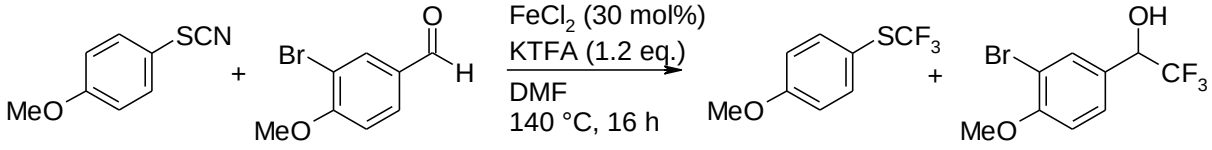
1a **2a**

Entry	MTFA (eq.)	cat. (eq.)	additive (eq.)	solvent (mL)	Yield of **2a** / %
1	KTFA (1.2)	–	–	DMF	17
2	“	CuI (1.0)	–	“	73
3	KTFA (1.0)	“	–	“	53
4	KTFA (1.5)	“	–	“	75
5	“	ZnI_2 (0.3)	–	“	83
6	“	$Zn(CN)_2$ (0.3)	–	“	78
7	“	$MnSO_4•H_2O$ (0.1)	–	“	14
8	“	$MnBr_2•4H_2O$ (0.1)	–	“	11
9	“	$Fe(CO)_5$(0.3)	–	“	50
10	“	$FeCl_3$(0.3)	–	“	51
11	“	$Fe(OTf)_2$ (0.1)	–	“	50
12	“	$Fe(NH_4)_2(SO_4)_2•6\ H_2O$ (0.1)	–	“	4
13	“	$FeCl_2$ (0.3)	–	“	99
14	“	$FeCl_2$ (0.25)	–	“	79
15	“	$FeCl_2$ (0.2)	–	“	70
16	“	$FeCl_2$ (0.15)	–	“	59
17	“	$FeCl_2$ (0.1)	–	“	45
18	“	“	NaF (1.0)	“	46
19	“	“	LiF(1.0)	“	48
20	“	“	Na_2CO_3 (0.5)	“	39
21	“	“	NaH (0.5)	“	8
22	“	$FeCl_2$ (0.3)	–	DMSO	76
23	“	“	–	NMP	74
24	“	“	–	mesitylene	0
25	“	“	–	*y*-butyrolactone	38
26	“	“	–	DMAc	77
27	“	“	–	propylene carbonate	37
28	“	“	–	sulfolane	59
29	“	$FeCl_2$ (0.1)	–	diglyme	22
30	“	“	–	ethylene glycol	0
31	“	$FeCl_2$ (0.3)	Water (0.5)	DMF	traces
32[h]	“	“	–	DMF	17
33	“	“	BHT (1.0)	“	39
34[i]	“	“	–	“	98
35[j]	“	“	–	“	98
36[k]	“	“	–	“	0

*[a] Reaction conditions: 0.5 mmol of 4-methoxyphenyl thiocyanate **1a**, solvent (1.5 mL), additive, MTFA, cat., 16 h, at 140 °C. Yields were determined by **^{19}F NMR** using 2,2,2-trifluoroethanol as an internal standard. [a] 1 mL solvent. [b] 2 mL solvent. [c] Reaction time was 2 h. [d] Reaction time was 4 h. [e] Temperature was 120 °C. [f] Temperature was 100 °C. [g] Reaction time was 64 h. [h] Under O_2 atmosphere. [i] Using $FeCl_2$ of high purity (99.998%). [j] All chemicals were used as received from the commercial supplier without any purification. [k] Starting from thiophenol.*

6.4.2 Additional control experiments

6.4.2.1 Competition experiment between organo thiocyanate and alydehyde



1a	**4a**		**2a**	**5a**
1 eq.	1 eq.		61%	20%

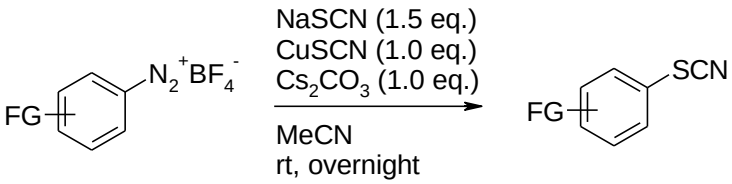
Reaction conditions: 0.5 mmol of 4-methoxyphenyl thiocyanate **1a**, 0.5 mmol of 3-bromo-4-methoxybenzaldehyde **4a**, DMF (1.5 mL), 0.6 mmol of KTFA, 0.15 mmol of $FeCl_2$, 16 h, at 140 °C. Yields were determined by **^{19}F NMR** using 2,2,2-trifluoroethanol as an internal standard.

Synthesis of arenediazonium tetrafluoroborates

In a 50 mL round-bottomed flask, the aniline (10 mmol) was dissolved in a mixture of absolute ethanol (3 mL) and an aqueous solution of HBF_4 (50%, 2.5 mL, 20 mmol). Afterwards *tert*-butyl nitrite (2.7 mL, 20 mmol) was added dropwise to the solution at 0 °C. The reaction was stirred at room temperature for 1 h, followed by the addition of diethyl ether (20 mL) to precipitate the arenediazonium tetrafluoroborate that was then filtered off and washed with diethyl ether (3 × 10 mL). After it had been dried in vacuo (10^{-3} mbar) for 10 minutes, it was directly used without further purification.

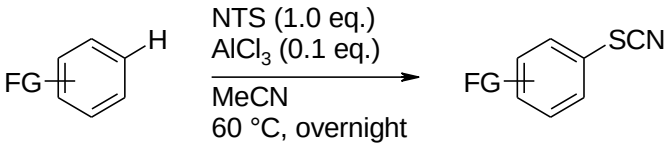
6.4.3 Synthesis of aryl thiocyanates

6.4.3.1 Procedure A, starting from the corresponding arenediazonium tetrafluoroborates



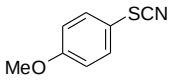
Cesium carbonate (1 eq.), sodium thiocyanate (1.5 eq.), and copper(I) thiocyanate (1 eq.) were suspended in acetonitrile (0.67 M). To this suspension was added dropwise a solution of the arenediazonium salt (1 eq.) in acetonitrile (0.40 M), and the resulting mixture was stirred overnight. Afterwards diethyl ether (30 mL) was added and the precipitate was filtered off. The filtrate was washed with water (2 × 30 mL) and the organic layer was dried with magnesium sulfate. The product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate gradient).

6.4.3.2 Procedure B, starting from the corresponding simple arenes



The corresponding arene (1 eq.), aluminium chloride (0.1 eq.), and *N*-thiocyanatosuccinimide (1 eq.) were dissolved in acetonitrile (0.6 M) and heated to 60 °C overnight. Afterwards diethyl ether (30 mL) was added and the precipitate was filtered off. The filtrate was washed with water (2 × 30 mL) and the organic layer was dried with magnesium sulfate. The product was purified by column chromatography (ethyl acetate/cyclohexane gradient).

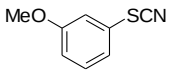
Synthesis of 4-methoxyphenyl thiocyanate (1a)



[CAS: 5285-90-5]

Compound **1a** was prepared following procedure **A** starting from Cs_2CO_3 (6.52 g, 20.0 mmol), NaSCN (2.48 g, 30.0 mmol), CuSCN (2.46 g, 20.0 mmol), and 4-methoxybenzenediazonium tetrafluoroborate [CAS: 459-64-3] (4.44 g, 20.0 mmol). After purification, **1a** was obtained as yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.50 (m, 2 H), 6.94 (m, 2 H), 3.82 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.4, 133.9, 115.9, 113.9, 111.7, 55.6 ppm; **IR** (neat): $\tilde{\nu}$ = 2942 (w), 2838 (w), 2155 (w), 1590 (m), 1493 (vs), 1460 (w), 1295 (m), 1248 (vs), 1175 (m), 1025 (s), 825 (s), 679 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 166 (23), 165 (100) [M^+], 150 (57), 122 (34), 95 (11), 69 (13), 63 (14).

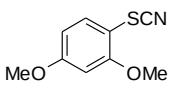
Synthesis of 3-methoxyphenyl thiocyanate (1b)



[CAS: 14372-67-9]

Compound **1b** was prepared following procedure **A** starting from Cs_2CO_3 (3.26 g, 10.0 mmol), NaSCN (1.24 g, 15.0 mmol), CuSCN (1.23 g, 10.0 mmol), and 3-methoxybenzenediazonium tetrafluoroborate [CAS: 660-42-4] (2.22 g, 10.0 mmol). After purification, **1b** was obtained as orange liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 8.2 Hz, 1 H), 7.08 (m, 1 H), 7.04 (t, *J* = 2.1 Hz, 1 H), 6.93 (m, 1 H), 3.83 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.7, 131.1, 125.3, 122.0, 115.6, 115.1, 110.5, 55.6 ppm; **IR** (neat): $\tilde{\nu}$ = 2939 (w), 2837 (w), 2157 (w), 1591 (vs), 1479 (vs), 1428 (m), 1287 (m), 1235 (vs), 1162 (w), 1032 (vs), 991 (w), 853 (m), 770 (vs), 681 (vs) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 166 (13), 165 (100) [M^+], 150 (44), 122 (19), 92 (12), 77 (16), 63 (19); **HRMS** (EI-TOF) calcd. for C_8H_7NOS: 165.0248; found: 165.0253.

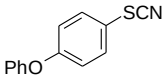
Synthesis of 2,4-dimethoxyphenyl thiocyanate (1c)



[CAS: 186047-37-0]

Compound **1c** was prepared following procedure **B** starting from $AlCl_3$ (66.7 mg, 500 µmol), *N*-thiocyanatosuccinimide (780 mg, 5.00 mmol) and 1,3-dimethoxybenzene (690 mg, 5.00 mmol). After purification, **1c** was obtained as yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.8 Hz, 1 H), 6.54 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.51 (d, *J* = 2.5 Hz, 1 H), 3.91 (s, 3 H), 3.83 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.2, 159.2, 134.0, 111.5, 106.3, 102.6, 99.7, 56.3, 55.8 ppm; **IR** (neat): $\tilde{\nu}$ = 2942 (w), 2839 (w), 2155 (w), 1575 (m), 1489 (m), 1456 (m), 1409 (w), 1306 (m), 1283 (m), 1209 (vs), 1162 (s), 1068 (m), 1023 (s), 916 (w), 825 (m), 792 (m), 650 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 197 (7), 196 (27), 195 (100) [M^+], 180 (23), 169 (8), 152 (25), 69 (7); **HRMS** (EI-TOF) calcd. for $C_9H_9NO_2S$: 195.0354; found: 195.0360.

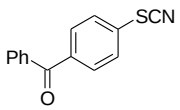
Synthesis of 4-phenoxyphenyl thiocyanate (1d)



[CAS: 96460-69-4]

Compound **1d** was prepared following procedure **A** starting from Cs_2CO_3 (3.26 g, 10.0 mmol), NaSCN (1.24 g, 15.0 mmol), CuSCN (1.23 g, 10.0 mmol), and 4-phenoxybenzenediazonium tetrafluoroborate [CAS: 330-87-0] (2.84 g, 10.0 mmol). After purification, **1d** was obtained as orange liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.52 (m, 2 H), 7.40 (m, 2 H), 7.20 (tt, *J* = 7.4, 1.1 Hz, 1 H), 7.04 ppm (m, 4 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.7, 155.7, 133.5, 130.2, 124.7, 119.9, 119.7, 116.6, 111.2 ppm; **IR** (neat): $\tilde{\nu}$ = 3065 (w), 2156 (w), 1580 (m), 1481 (vs), 1234 (vs), 1167 (m), 1071 (w), 1008 (w), 868 (m), 830 (m), 794 (w), 753 (s), 691 (s) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 228 (18), 227 (100) [M^+], 198 (9), 109 (16), 77 (16), 51 (17), 50 (10); **HRMS** (EI-TOF) calcd. for $C_{13}H_9NOS$: 227.0405; found: 227.0405.

Synthesis of 4-benzoylphenyl thiocyanate (1e)

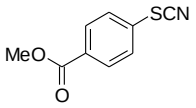


[CAS: 107508-42-9]

Compound **1e** was prepared following procedure **A** starting from Cs_2CO_3 (2.28 g, 7.00 mmol), NaSCN (869 mg, 10.5 mmol), CuSCN (860 mg, 7.00 mmol), and 4-benzoylbenzenediazonium tetrafluoroborate [CAS: 38246-74-1] (2.07 g, 7.00 mmol). After

purification, **1e** was obtained as orange solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85 (m, 2 H), 7.76 (m, 2 H), 7.61 (m, 3 H), 7.49 ppm (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 195.2, 138.3, 136.9, 133.2, 131.6, 130.1, 129.8, 128.7, 128.6, 109.3 ppm; **IR** (neat): $\tilde{\nu}$ = 3058 (w) 2159 (w), 1655 (s), 1587 (m), 1447 (w), 1398 (w), 1315 (m), 1271 (s), 1177 (w), 1149 (w), 1078 (w), 1013 (w), 921 (s), 840 (m), 788 (m), 727 (s), 695 (vs), 659 (vs) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 240 (22), 239 (100) [M^+], 162 (36), 105 (62), 77 (30), 51 (15), 50 (13); **HRMS** (EI-TOF) calcd. for $C_{14}H_9NOS$: 239.0405; found: 239.0420; **m.p.**: 44–45 °C.

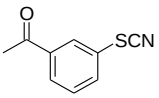
Synthesis of methyl 4-thiocyanatobenzoate (1f)



[CAS: 1879-22-7]

Compound 1f was prepared following procedure A starting from Cs2CO3 (1.42 g, 4.36 mmol), NaSCN (541 mg, 6.54 mmol), CuSCN (536 mg, 4.36 mmol), and 4-methoxycarbonylbenzenediazonium tetrafluoroborate [CAS: 1879-22-7] (1.09 g, 4.36 mmol). After purification, 1f was obtained as pale orange solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.09 (m, 2 H), 7.56 (m, 2 H), 3.94 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.9, 131.3, 131.0, 130.5, 128.5, 109.2, 52.6 ppm; **IR** (neat): $\tilde{\nu}$ = 2953 (w), 2156 (w), 1707 (s), 1596 (w), 1434 (m), 1402 (w), 1277 (vs), 1178 (w), 1107 (s), 1012 (m), 961 (w), 846 (w), 827 (w), 755 (vs), 683 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 194 (9), 193 (76) [M^+], 163 (10), 162 (100), 134 (18), 63 (8), 50 (9); **HRMS** (EI-TOF) calcd. for $C_9H_7NO_2S$: 193.0198; found: 193.0208; **m.p.**: 61 °C.

Synthesis of 3-acetylphenyl thiocyanate (1g)

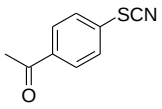


[CAS: 14428-55-8]

Compound **1g** was prepared following procedure **A** starting from Cs_2CO_3 (1.63 g, 5.00 mmol), NaSCN (620 mg, 7.50 mmol), CuSCN (614 mg, 5.00 mmol), and 3-acetylbenzenediazonium tetrafluoroborate [CAS: 59206-56-4] (1.17 g, 5.00 mmol). After purification, **1g** was obtained as yellowish liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.08 (m, 1 H), 7.98 (m, 1 H), 7.74 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.57 (t, *J* = 7.8 Hz, 1 H), 2.63 ppm (s,

3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 196.4, 138.8, 134.1, 130.8, 129.7, 129.5, 125.8, 110.0, 26.8 ppm; **IR** (neat): $\tilde{\nu}$ = 3063 (w), 2922 (w), 2158 (w), 1685 (s), 1571 (w), 1420 (m), 1356 (m), 1249 (vs), 1072 (w), 997 (w), 959 (w), 899 (w), 787 (m), 682 (s) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 177 (41) [M^+], 163 (11), 162 (100), 134 (23), 63 (7), 50 (8), 43 (12); **HRMS** (EI-TOF) calcd. for C_9H_7NOS: 177.0248; found: 177.0260.

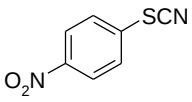
Synthesis of 4-acetylphenyl thiocyanate (1h)



[CAS: 14428-56-9]

Compound **1h** was prepared following procedure **A** starting from Cs_2CO_3 (1.63 g, 5.00 mmol), NaSCN (620 mg, 7.50 mmol), CuSCN (614 mg, 5.00 mmol), and 4-acetylbenzenediazonium tetrafluoroborate [CAS: 1820-80-0] (1.17 g, 5.00 mmol). After purification, **1h** was obtained as colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.00 (m, 2 H), 7.58 (m, 2 H), 2.62 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 196.7, 137.4, 130.7, 130.0, 128.6, 109.2, 26.8 ppm; **IR** (neat): $\tilde{\nu}$ = 3095 (w), 2158 (w), 1685 (m), 1585 (m), 1486 (w), 1425 (w), 1395 (m), 1359 (m), 1260 (s), 1187 (m), 1125 (w), 1087 (m), 1005 (m), 960 (m), 811 (vs), 757 (m), 708 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 177 (33) [M^+], 163 (10), 162 (100), 134 (20), 63 (8), 50 (7), 43 (8); **HRMS** (EI-TOF) calcd. for C_9H_7NOS: 177.0248; found: 177.0254; **m.p.**: 80 °C.

Synthesis of 4-nitrophenyl thiocyanate (1i)

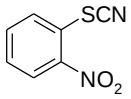


[CAS: 3226-41-3]

Compound **1i** was prepared following procedure **A** starting from Cs_2CO_3 (1.96 g, 6.00 mmol), NaSCN (745 mg, 7.50 mmol), CuSCN (737 mg, 6.00 mmol), and 4-nitrobenzenediazonium tetrafluoroborate [CAS: 456-27-9] (1.42 g, 6.00 mmol). After purification, **1i** was obtained as pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.30 (m, 2 H), 7.67 ppm (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.1, 133.5, 128.8, 125.2, 108.2 ppm; **IR** (neat): $\tilde{\nu}$ = 3104 (w), 2845 (w), 2162 (w), 1923 (w), 1602 (w), 1578 (m), 1514 (s), 1475 (m), 1340 (vs), 1279 (m), 1189 (w), 1107 (m), 1082 (m), 1009 (m), 956 (w), 842 (vs),

736 (vs), 700 (w), 674 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 180 (100) [M^+], 150 (79), 134 (26), 122 (37), 90 (26), 63 (28), 50 (21); **HRMS** (EI-TOF) calcd. for $C_7H_4N_2O_2S$: 179.9993; found: 180.0002; **m.p.**: 132 °C.

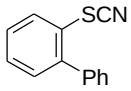
Synthesis of 2-nitrophenyl thiocyanate (1j)



[CAS: 2769-30-4]

Compound 1j was prepared following procedure A starting from Cs2CO3 (3.26 g, 10.0 mmol), NaSCN (1.24 g, 15.0 mmol), CuSCN (1.23 g, 10.0 mmol), and 2-nitrobenzenediazonium tetrafluoroborate [CAS: 365-33-3] (2.37 g, 10.0 mmol). After purification, 1j was obtained as beige solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.41 (dd, *J* = 8.3, 1.5 Hz, 1 H), 8.06 (dd, *J* = 8.2, 1.1 Hz, 1 H), 7.81 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1 H), 7.58 ppm (ddd, *J* = 8.3, 7.3, 1.1 Hz, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 135.2, 129.2, 129.0, 126.7, 126.5, 110.3 ppm; **IR** (neat): $\tilde{\nu}$ = 3100 (w), 2159 (w), 1592 (w), 1568 (m), 1509 (m), 1456 (m), 1331 (vs), 1261 (m), 1152 (m), 1113 (m), 1041 (m), 959 (w), 856 (s), 784 (s), 728 (vs), 654 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 181 (17), 180 (100) [M^+], 154 (18), 116 (41), 90 (21), 69 (17), 63 (25); **HRMS** (EI-TOF) calcd. for $C_7H_4N_2O_2S$: 179.9993; found: 180.0007; **m.p.**: 129 °C.

Synthesis of [1,1'-biphenyl]-2-yl thiocyanate (1k)

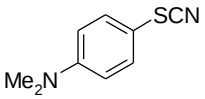


[CAS: 99847-58-2]

Compound **1k** was prepared following procedure **A** starting from Cs_2CO_3 (1.63 g, 5.00 mmol), NaSCN (620 mg, 7.50 mmol), CuSCN (614 mg, 5.00 mmol), and [1,1'-biphenyl]-2-diazonium tetrafluoroborate [CAS: 318-13-8] (1.34 g, 5.00 mmol). After purification, **1k** was obtained as yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.79 (m, 1 H), 7.47 (m, 5 H), 7.35 ppm (m, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.5, 138.6, 131.2, 129.6, 129.3, 129.2, 128.9, 128.7, 124.2, 110.9 ppm; **IR** (neat): $\tilde{\nu}$ = 3056 (w), 2156 (w), 1587 (w), 1464 (m), 1429 (w), 1256 (w), 1074 (w), 1032 (w), 1008 (w), 918 (w), 746 (vs), 699 (vs), 675 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 212 (19), 211 (100) [M^+],

210 (19), 185 (14), 184 (87), 152 (12), 50 (10); **HRMS** (EI-TOF) calcd. for $C_{13}H_9NS$: 211.0463; found: 211.0456.

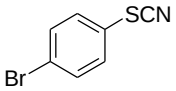
Synthesis of 4-(dimethylamino)phenyl thiocyanate (1l)



[CAS: 7152-80-9]

Compound **1l** was prepared following procedure **A** starting from Cs_2CO_3 (3.26 g, 10.0 mmol), NaSCN (1.24 g, 15.0 mmol), CuSCN (1.23 g, 10.0 mmol), and 4-(dimethylamino)benzenediazonium tetrafluoroborate [CAS: 33271-82-8] (2.35 g, 10.0 mmol). After purification, **1l** was obtained as orange solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.42 (m, 2 H), 6.68 (m, 2 H), 3.00 ppm (s, 6 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.8, 134.6, 113.3, 112.7, 106.7, 40.3 ppm; **IR** (neat): $\tilde{\nu}$ = 2906 (w), 2808 (w), 2143 (m), 1884 (w), 1753 (w), 1586 (m), 1508 (m), 1439 (m), 1367 (m), 1230 (m), 1198 (m), 1073 (m), 989 (m), 946 (m), 805 (vs), 762 (w), 708 (w), 665 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 179 (21), 178 (99) [M^+], 177 (100), 162 (15), 161 (15), 118 (13), 63 (9); **HRMS** (EI-TOF) calcd. for $C_9H_{10}N_2S$: 178.0565; found: 178.0567; **m.p.**: 71–72 °C.

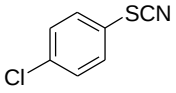
Synthesis of 4-bromophenyl thiocyanate (1m)



[CAS: 3226-41-3]

Compound **1m** was prepared following procedure **A** starting from Cs_2CO_3 (1.63 g, 5.00 mmol), NaSCN (620 mg, 7.50 mmol), CuSCN (614 mg, 5.00 mmol), and 4-bromobenzenediazonium tetrafluoroborate [CAS: 673-40-5] (1.35 g, 5.00 mmol). After purification, **1m** was obtained as pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.57 (m, 2 H), 7.40 ppm (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 133.5, 131.7, 124.3, 123.5, 110.0 ppm; **IR** (neat): $\tilde{\nu}$ = 3081 (w), 2164 (m), 1889 (w), 1625 (w), 1471 (vs), 1390 (m), 1262 (w), 1112 (w), 1068 (m), 1004 (vs), 957 (w), 800 (vs), 720 (m), 694 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 215 (79) [M^+(^{81}Br)], 213 (67) [M^+(^{79}Br)], 134 (100), 75 (15), 69 (11), 63 (11), 50 (22); **HRMS** (EI-TOF) calcd. for $C_7H_4{}^{79}BrNS$: 212.9248; found: 212.9258; **m.p.**: 53 °C.

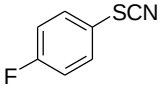
Synthesis of 4-chlorophenyl thiocyanate (1n)



[CAS: 3226-37-7]

Compound **1n** was prepared following procedure **A** starting from Cs_2CO_3 (3.26 g, 10.0 mmol), NaSCN (1.24 g, 15.0 mmol), CuSCN (1.23 g, 10.0 mmol), and 4-chlorobenzenediazonium tetrafluoroborate [CAS: 673-41-6] (2.26 g, 10.0 mmol). After purification, **1n** was obtained as yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.43 (m, 2 H), 7.37 ppm (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 136.0, 131.3, 130.3, 122.7, 109.9 ppm; **IR** (neat): $\tilde{\nu}$ = 3086 (w), 2158 (w), 1572 (w), 1475 (vs), 1391 (m), 1089 (vs), 1010 (vs), 814 (vs), 741 (w), 701 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 171 (38), 170 (19), 169 (100) [M^+], 134 (33), 108 (11), 75 (11), 69 (11); **HRMS** (EI-TOF) calcd. for $C_7H_4{}^{35}ClNS$: 168.9753; found: 168.9755.

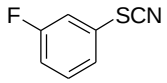
Synthesis of 4-fluorophenyl thiocyanate (1o)



[CAS: 2924-02-9]

Compound 1o was prepared following procedure A starting from Cs_2CO_3 (1.63 g, 5.00 mmol), NaSCN (620 mg, 7.50 mmol), CuSCN (614 mg, 5.00 mmol), and 4-fluorobenzenediazonium tetrafluoroborate [CAS: 1820-80-0] (1.05 g, 5.00 mmol). After purification, 1o was obtained as yellowish liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.54 (m, 2 H), 7.13 ppm (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.7 (d, *J* = 252.5 Hz), 133.3 (d, *J* = 9.1 Hz), 119.3 (d, *J* = 3.6 Hz), 117.6 (d, *J* = 22.7 Hz), 110.6 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –109.6 ppm; **IR** (neat): $\tilde{\nu}$ = 3099 (w), 2158 (w), 1590 (m), 1489 (vs), 1401 (w), 1229 (s), 1160 (m), 1080 (w), 1012 (w), 827 (vs), 705 (w), 684 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 154 (32), 153 (100) [M^+], 133 (22), 127 (12), 126 (24), 83 (11), 69 (14); **HRMS** (EI-TOF) calcd. for C_7H_4FNS: 153.0048; found: 153.0037.

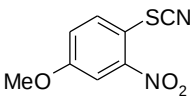
Synthesis of 3-fluorophenyl thiocyanate (1p)



[CAS: 2402-01-9]

Compound **1p** was prepared following procedure **A** starting from Cs_2CO_3 (3.26 g, 10.0 mmol), NaSCN (1.24 g, 15.0 mmol), CuSCN (1.23 g, 10.0 mmol), and 3-fluorobenzenediazonium tetrafluoroborate [CAS: 1996-38-9] (2.10 g, 10.0 mmol). After purification, **1p** was obtained as yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.41 (td, *J* = 8.2, 5.8 Hz, 1 H), 7.29 (m, 1 H), 7.24 (dt, *J* = 8.3, 2.1 Hz, 1 H), 7.10 ppm (tdd, *J* = 8.3, 2.5, 0.9 Hz, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.0 (d, *J* = 253 Hz), 131.7 (d, *J* = 8.2 Hz), 126.4 (d, *J* = 8.2 Hz), 125.3 (d, *J* = 3.6 Hz), 116.9 (d, *J* = 24.5 Hz), 116.8 (d, *J* = 20.9 Hz), 109.6 ppm (s); **IR** (neat): $\tilde{\nu}$ = 3070 (w), 2160 (w), 1590 (s), 1475 (vs), 1428 (m), 1268 (m), 1221 (s), 1160 (w), 1087 (w), 1066 (w), 1001 (w), 873 (vs), 776 (vs), 672 (vs), 522 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 153 (100) [M^+], 133 (23), 126 (29), 109 (18), 95 (20), 83 (16), 75 (33); **HRMS** (EI-TOF) calcd. for C_7H_4FNS: 153.0048; found: 153.0047.

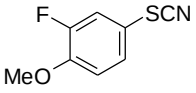
Synthesis of 2-nitro-4-methoxyphenyl thiocyanate (1q)



[CAS: 59607-71-5]

Compound **1q** was prepared following procedure **A** starting from Cs_2CO_3 (3.26 g, 10.0 mmol), NaSCN (1.24 g, 15.0 mmol), CuSCN (1.23 g, 10.0 mmol), and 2-nitro-4-methoxybenzenediazonium tetrafluoroborate [CAS: 33271-82-8] (2.67 g, 10.0 mmol). After purification, **1q** was obtained as yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.8 Hz, 1 H), 7.86 (d, *J* = 3.0 Hz, 1 H), 7.35 (dd, *J* = 8.9, 2.9 Hz, 1 H), 3.93 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.1, 145.6, 130.1, 123.1, 116.3, 110.8, 110.7, 56.4 ppm; **IR** (neat): $\tilde{\nu}$ = 3099 (w), 3078 (w), 2162 (w), 1608 (w), 1517 (vs), 1473 (s), 1434 (w), 1339 (m), 1280 (vs), 1239 (vs), 1187 (m), 1106 (m), 1049 (m), 1024 (s), 911 (m), 885 (s), 820 (vs), 756 (m), 688 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 210 (100) [M^+], 184 (19), 168 (20), 131 (14), 121 (11), 120 (21), 63 (12); **HRMS** (EI-TOF) calcd. for $C_8H_6N_2O_3S$: 210.0099; found: 210.0108; **m.p.**: 128–129 °C.

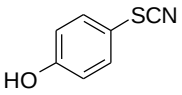
Synthesis of 3-fluoro-4-methoxyphenyl thiocyanate (1r)



[CAS: 89818-26-8]

Compound **1r** was prepared following procedure **A** starting from Cs_2CO_3 (652 mg, 2.00 mmol), NaSCN (248 mg, 3.00 mmol), CuSCN (246 mg, 2.00 mmol), and 3-fluoro-4-methoxybenzenediazonium tetrafluoroborate (479 mg, 2.00 mmol). After purification, **1r** was obtained as yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.33 (m, 1 H), 7.31 (m, 1 H), 7.01 (m, 1 H), 3.92 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.6 (d, *J* = 253 Hz), 149.9 (d, *J* = 10.0 Hz), 128.6 (d, *J* = 3.6 Hz), 119.8 (d, *J* = 20.0 Hz), 114.6 (d, *J* = 2.7 Hz), 114.4 (d, *J* = 7.3 Hz), 110.9 (s), 56.6 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –130.6 ppm; **IR** (neat): $\tilde{\nu}$ = 2940 (w), 2847 (w), 2155 (m), 2016 (w), 1880 (w), 1603 (w), 1505 (vs), 1468 (m), 1442 (s), 1414 (m), 1316 (m), 1273 (s), 1212 (vs), 1182 (s), 1136 (vs), 1079 (m), 1014 (vs), 872 (s), 817 (vs), 762 (vs), 715 (w), 684 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 184 (19), 183 (100) [M^+], 168 (66), 140 (28), 113 (10), 69 (11), 63 (9); **HRMS** (EI-TOF) calcd. for C_8H_6FNOS: 183.0154; found: 183.0166; **m.p.**: 48–49 °C.

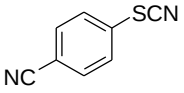
Synthesis of 4-hydroxyphenyl thiocyanate (1s)



[CAS: 3774-52-5]

Compound **1s** was prepared following procedure **B** starting from $AlCl_3$ (66.7 mg, 500 µmol), *N*-thiocyanatosuccinimide (781 mg, 5.00 mmol) and phenol (471 mg, 5.00 mmol). After purification, **1s** was obtained as colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.44 (m, 2 H), 6.88 (m, 2 H), 6.04 ppm (s, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 158.1, 134.4, 117.6, 113.3, 112.4 ppm; **IR** (neat): $\tilde{\nu}$ = 3363 (s), 3062 (w), 2152 (s), 1870 (w), 1597 (m), 1580 (vs), 1494 (vs), 1463 (w), 1426 (m), 1348 (m), 1282 (vs), 1207 (vs), 1167 (s), 1099 (m), 957 (w), 829 (vs), 804 (s), 711 (w), 679 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 151 (100) [M^+], 123 (38), 122 (13), 96 (48), 69 (17), 65 (14), 53 (13); **HRMS** (EI-TOF) calcd. for C_7H_5NOS: 151.0092; found: 151.0091; **m.p.**: 61–62 °C.

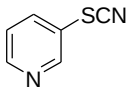
Synthesis of 4-cyanophenyl thiocyanate (1t)



[CAS: 122148-91-8]

Compound **1t** was prepared following procedure **A** starting from Cs_2CO_3 (1.96 g, 6.00 mmol), NaSCN (745 mg, 9.00 mmol), CuSCN (737 g, 6.00 mmol), and 4-cyanobenzenediazonium tetrafluoroborate [CAS: 2252-32-6] (1.30 g, 6.00 mmol). After purification, **1t** was obtained as light-yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.73 (m, 2 H), 7.61 ppm (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 133.7, 131.5, 128.9, 117.6, 113.2, 108.3 ppm; **IR** (neat): $\tilde{\nu}$ = 3090 (w), 2227 (m), 2163 (w), 1917 (w), 1592 (m), 1487 (m), 1402 (m), 1279 (w), 1255 (w), 1181 (w), 1079 (m), 1017 (w), 952 (w), 820 (vs), 774 (w), 696 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 161 (13), 160 (100) [M^+], 133 (45), 116 (20), 102 (20), 75 (18), 50 (12); **HRMS** (EI-TOF) calcd. for $C_8H_4N_2S$: 160.0095; found: 160.0109; **m.p.**: 127–128 °C.

Synthesis of 3-pyridinyl thiocyanate (1u)

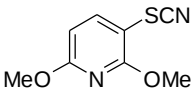


[CAS: 2645-25-2]

3-Aminopyridine (7.50 g, 78.9 mmol) was dissolved in a mixture of concentrated sulfuric acid (13.6 mL) and water (50 mL), and a solution of sodium nitrite (5.77 g, 83.6 mmol) in water (25 mL) was added. To this mixture potassium thiocyanate (8.75 g, 88.2 mmol) and copper(I) thiocyanate (9.69 g, 78.9 mmol), dissolved in water (25 mL), were added and the resulting mixture was stirred for 1 h. Sodium carbonate solution was added until a basic pH was reached and the solution was extracted with diethyl ether (4 × 50 mL). The organic phase was dried with magnesium sulfate. After purification by column chromatography (cyclohexane/ethyl acetate gradient), **1u** was obtained as yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.75 (d, *J* = 2.0 Hz, 1 H), 8.67 (m, 1 H), 7.92 (m, 1 H), 7.41 ppm (m, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 150.8, 150.5, 138.1, 125.0, 122.6, 109.3 ppm; **IR** (neat): $\tilde{\nu}$ = 3045 (w), 2159 (w), 1568 (w), 1466 (w), 1412 (m), 1327 (w), 1192 (w), 1107 (w), 1014 (s), 796 (m), 698 (vs) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 138 (10), 137 (81), 136 (100)

[M^+], 110 (9), 109 (53), 78 (15), 51 (18); **HRMS** (EI-TOF) calcd. for $C_6H_4N_2S$: 136.0095; found: 136.0088.

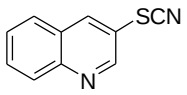
Synthesis of 2,6-dimethoxypyridin-3-yl thiocyanate (1v)



[CAS: 1821240-60-1]

Compound **1v** was prepared following procedure **B** starting from $AlCl_3$ (40.0 mg, 300 µmol), *N*-thiocyanatosuccinimide (469 mg, 3.00 mmol) and 2,6-dimethylpyridine (331 mg, 3.00 mmol). After purification, **1v** was obtained as colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.3 Hz, 1 H), 6.39 (d, *J* = 8.3 Hz,1 H), 4.05 (s, 3 H), 3.95 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.1, 161.4, 144.9, 110.9, 103.7, 95.4, 54.6, 54.2 ppm; **IR** (neat): $\tilde{\nu}$ = 3095 (w), 2980 (w), 2955 (w), 2926 (w), 2855 (w), 2150 (w), 1735 (w), 1568 (vs), 1465 (s), 1411 (m), 1374 (m), 1323 (vs), 1270 (s), 1239 (vs), 1193 (m), 1128 (m), 1064 (m), 1006 (vs), 955 (m), 817 (s), 760 (s), 725 (m), 700 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 197 (20), 196 (100) [M^+], 181 (14), 167 (15), 153 (16), 96 (15), 69 (13); **HRMS** (EI-TOF) calcd. for $C_8H_8N_2O_2S$: 196.0306; found: 196.0305; **m.p.**: 69–70 °C.

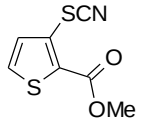
Synthesis of 3-quinolinyl thiocyanate (1w)



[CAS: 2645-26-3]

Compound **1w** was prepared following procedure **A** starting from Cs_2CO_3 (995 mg, 3.05 mmol), NaSCN (378 mg, 4.57 mmol), CuSCN (375 mg, 3.05 mmol), and 3-quinolinediazonium tetrafluoroborate (741 mg, 3.05 mmol). After purification, **1w** was obtained as colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.96 (s, 1 H), 8.42 (d, *J* = 2.5 Hz, 1 H), 8.15 (d, *J* = 8.5 Hz, 1 H), 7.84 (m, 2 H), 7.66 ppm (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 149.8, 147.9, 138.5, 131.6, 129.8, 128.5, 128.1, 127.8, 120.1, 109.5 ppm; **IR** (neat): $\tilde{\nu}$ = 3031 (w), 2153 (w), 1977 (w), 1847 (w), 1713 (w), 1615 (w), 1564 (w), 1490 (m), 1455 (w), 1361 (m), 1330 (w), 1254 (w), 1197 (w), 1128 (w), 1082 (w), 950 (m), 911 (s), 865 (w), 780 (m), 745 (vs) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 187 (17), 186 (100) [M^+], 159 (13), 142 (28), 128 (13), 101 (15), 89 (11); **HRMS** (EI-TOF) calcd. for $C_{10}H_6N_2S$: 186.0252; found: 186.0253; **m.p.**: 59-60 °C.

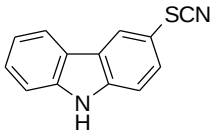
Synthesis of methyl-3-thiocyanatothiophene-2-carboxylate (1x)



[CAS: 1369794-51-3]

Compound **1x** was prepared following procedure **A** starting from Cs_2CO_3 (3.26 g, 10.0 mmol), NaSCN (1.24 g, 15.0 mmol), CuSCN (1.23 g, 10.0 mmol), and 2-(methoxycarbonyl)-3-thiophenediazonium tetrafluoroborate [CAS: 100421-50-9] (2.56 g, 10.0 mmol). After purification, **1x** was obtained as colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 5.3 Hz, 1 H); 7.28 (d, *J* = 5.3 Hz, 1 H), 3.88 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.1, 132.6, 130.1, 128.0, 125.1, 110.5, 52.7 ppm; **IR** (neat): $\tilde{\nu}$ = 3123 (w), 2952 (w), 2158 (w), 1689 (s), 1505 (m), 1437 (s), 1409 (m), 1357 (w), 1275 (s), 1191 (w), 1100 (m), 966 (w), 891 (m), 793 (w), 765 (vs), 737 (m), 665 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 201 (10), 199 (100) [M^+], 168 (76), 142 (28), 96 (16), 69 (17), 45 (11); **HRMS** (EI-TOF) calcd. for $C_7H_5NO_2S$: 198.9762; found: 198.9757; **m.p.**: 115 °C.

Synthesis of 9*H*-carbazol-3-yl thiocyanate (1y)



[CAS: 40604-35-1]

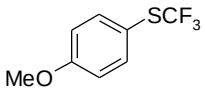
Compound **1y** was prepared following procedure **B** starting from $AlCl_3$ (66.7 mg, 500 µmol), *N*-thiocyanatosuccinimide (781 mg, 5.00 mmol) and 9*H*-carbazole (880 mg, 5.00 mmol). After purification, **1y** was obtained as colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 7.59 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.47 (m, 3 H), 7.30 ppm (ddd, *J* = 8.0, 6.2, 1.9 Hz, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.3, 140.0, 129.8, 127.3, 125.4, 125.0, 122.3, 120.8, 120.6, 112.7, 112.4 (2 C), 111.2 ppm; **IR** (neat): $\tilde{\nu}$ = 3412 (m), 3069 (w), 2151 (m), 1894 (w), 1710 (w), 1595 (w), 1491 (w), 1449 (m), 1386 (w), 1318 (w), 1275 (m), 1236 (m), 1199 (w), 1153 (w), 1132 (w), 1005 (w), 939 (w), 890 (w), 844 (w), 815 (s), 754 (vs), 733 (s) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 225 (17), 224 (100) [M^+], 223 (7), 198 (5), 192 (21); **HRMS** (EI-TOF) calcd. for $C_{13}H_8N_2S$: 224.0408; found: 224.0409; **m.p.**: 146–147 °C.

6.4.4 Synthesis of aryl trifluoromethyl thioethers

6.4.4.1 Standard procedure for the synthesis of aryl trifluoromethyl thioethers from the corresponding aryl thiocyanates

An oven-dried 20 mL crimp cap vessel with PTFE-coated stir bar was charged with anhydrous iron chloride (38.8 mg, 300 µmol), potassium trifluoroacetate (186 mg, 1.20 mmol), and the corresponding aryl thiocyanate (1.00 mmol) and was then brought under an atmosphere of dry nitrogen. DMF (3.00 mL) was added *via* syringe and the reaction mixture was heated to 140 °C for 16 h. Afterwards it was diluted with diethyl ether (20 mL), filtered through a short pad of silica and washed with a 1 M solution of lithium chloride in water (2 × 50 mL). The organic phase was dried with magnesium sulfate and the crude product purified by column chromatography (SiO_2, pentane/diethyl ether gradient).

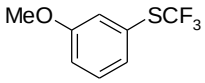
1-methoxy-4-[trifluoromethyl)thio]benzene (2a)



[CAS: 78914-94-0]

Compound **2a** was prepared following the standard procedure starting from 4-(dimethylamino)phenyl thiocyanate (**1a**, 165 mg, 1.00 mmol). After purification, **2a** was isolated as colorless liquid (204 mg, 980 µmol, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 3.85 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.8 (s), 138.3 (s), 129.6 (q, *J* = 308 Hz), 115.0 (s), 114.8 (q, *J* = 1.8 Hz), 55.4 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –44.0 ppm; **IR** (neat): $\tilde{\nu}$ = 3012 (w), 2946 (w), 2843 (w), 1592 (m), 1494 (m), 1463 (w), 1294 (w), 1252 (m), 1104 (vs), 1029 (s), 828 (s), 799 (w), 755 (w), 650 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 208 (10) [M^+], 207 (100), 138 (75), 123 (10), 95 (14), 69 (9), 68 (25); **HRMS** (EI-TOF) calcd. for $C_9H_{10}F_3NS$: 208.0170; found: 208.0171.

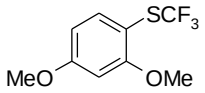
Synthesis of 1-methoxy-3-[trifluoromethyl)thio]benzene (2b)



[CAS: 97675-15-5]

Compound **2b** was prepared following the standard procedure starting from 3-methoxyphenyl thiocyanate (**1b**, 165 mg, 1.00 mmol). After purification, **2b** was isolated as colorless oil (177 mg, 852 µmol, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.9 Hz, 1 H), 7.24 (d, *J* = 7.8 Hz, 1 H), 7.18 (t, *J* = 2 Hz, 1 H), 7.02 (ddd, *J* = 8.3, 2.5, 1.0 Hz, 1 H), 3.83 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.1 (s), 130.3 (s), 129.8 (q, *J* = 308.1 Hz), 128.6 (s), 125.4 (q, *J* = 2.2 Hz), 121.3 (s), 117.0 (s), 55.6 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –42.6 ppm; **IR** (neat): $\tilde{\nu}$ = 3014 (w), 2970 (w), 2924 (w), 2853 (w), 1739 (vs), 1366 (m), 1229 (m), 1217 (m), 1206 (m), 1092 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 208 (10), 207 (100) [M^+], 138 (36), 123 (19), 95 (16), 94 (20), 68 (21); **HRMS** (EI-TOF) calcd. for $C_8H_7F_3OS$: 208.0170; found: 208.0188.

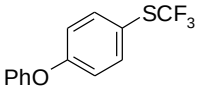
Synthesis of 2,4-dimethoxy-1-[(trifluoromethyl)thio]benzene (2c)



[CAS: 66476-29-7]

Compound **2c** was prepared following the standard procedure starting from 2,4-dimethoxyphenyl thiocyanate (**1c**, 195 mg, 1.00 mmol). After purification, **2c** was isolated as colorless oil (177 mg, 745 µmol, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.8 Hz, 1 H), 6.52 (m, 2 H), 3.88 (s, 3 H), 3.84 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.1 (s), 162.2 (s), 140.4 (s), 129.7 (q, *J* = 309 Hz), 105.7 (s), 103.4 (q, *J* = 2.2 Hz), 99.4 (s), 56.2 (s), 55.7 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –44.7 ppm; **IR** (neat): $\tilde{\nu}$ = 2945 (w), 2842 (w), 1739 (w), 1584 (m), 1574 (m), 1492 (w), 1464 (w), 1415 (w), 1303 (m), 1211 (s), 1099 (vs), 1070 (vs), 1027 (s), 938 (w), 824 (m), 794 (w), 754 (w), 650 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 238 (11), 237 (100) [M^+], 169 (44), 141 (26), 123 (19), 94 (15), 69 (14); **HRMS** (EI-TOF) calcd. for $C_9H_9F_3O_2S$: 238.0275; found: 238.0288.

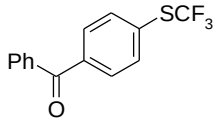
Synthesis of 1-phenoxy-4-[(trifluoromethyl)thio]benzene (2d)



[CAS: 1333415-80-7]

Compound **2d** was prepared following the standard procedure starting from 4-phenoxyphenyl thiocyanate (**1q**, 227 mg, 1.00 mmol). After purification, **2d** was isolated as colorless oil (265 mg, 982 µmol, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.61 (m, 2 H), 7.41 (m, 2 H), 7.20 (m, 1 H), 7.09 (2 H), 7.01 ppm (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.6 (s), 155.8 (s), 138.5 (s) 130.2 (s), 129.7 (q, *J* = 308 Hz), 124.7 (s), 120.2 (s), 118.8 (s), 117.4 ppm (q, *J* = 2.2 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –44.5 ppm; **IR** (neat): $\tilde{\nu}$ = 3043 (w), 1582 (m), 1485 (s), 1241 (s), 1111 (vs), 1081 (vs), 1011 (w), 869 (m), 834 (m), 797 (w), 754 (s), 691 (s) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 271 (16), 270 (100) [M^+], 201 (50), 129 (11), 77 (15), 69 (12), 51 (13); **HRMS** (EI-TOF) calcd. for $C_{13}H_9F_3OS$: 270.0326; found: 270.0320.

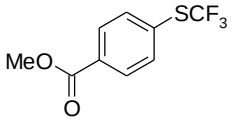
Synthesis of phenyl[4-[(trifluoromethyl)thio]phenyl]methanone (2e)



[CAS: 41830-99-3]

Compound **2e** was prepared following the standard procedure starting from 2-benzoylphenyl thiocyanate (**1e**, 239 mg, 1.00 mmol). After purification, **2e** was isolated as colorless solid (182 mg, 643 µmol, 64 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.80 (m, 6 H), 7.62 (m, 1 H), 7.50 ppm (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 195.7 (s), 139.6 (s), 136.9 (s), 135.6 (s), 133.1 (s), 130.8 (s), 130.2 (s), 129.5 (q, *J* = 308 Hz), 129.3 (q, *J* = 2.0 Hz), 128.6 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –42.9 ppm; **IR** (neat): $\tilde{\nu}$ = 3067 (w), 2971 (w), 1738 (w), 1652 (m), 1590 (w), 1448 (w), 1397 (w), 1307 (w), 1280 (w), 1108 (vs), 1080 (s), 1014 (m), 971 (w), 924 (m), 847 (m), 792 (m), 756 (m), 730 (m), 696 (s), 664 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 283 (19), 282 (91) [M^+], 205 (91), 108 (15), 105 (100), 77 (29), 51 (16); **HRMS** (EI-TOF) calcd. for $C_{14}H_9F_3OS$: 282.0326; found: 282.0317; **m.p.**: 69.0 °C.

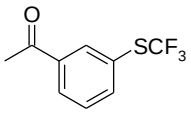
Synthesis of methyl-4-[(trifluoromethyl)thio]benzoate (2f)



[CAS: 88489-60-5]

Compound **2f** was prepared following the standard procedure starting from methyl-4-thiocyanato benzoate (**1f**, 193 mg, 500 µmol). After purification, **2f** was isolated as colorless oil (99.9 mg, 423 µmol, 42%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.06 (m, 2 H), 7.70 (m, 2 H), 3.93 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.1 (s), 135.7 (s), 132.3 (s), 130.5 (s), 130.5 (q, *J* = 2.2 Hz), 129.4 (q, *J* = 308 Hz), 52.6 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –43.0 ppm; **IR** (neat): $\tilde{\nu}$ = 2955 (w), 1726 (s), 1597 (w), 1436 (w), 1399 (w), 1273 (s), 1101 (vs), 1079 (vs), 1016 (m), 964 (w), 856 (w), 827 (w), 763 (s), 725 (w), 692 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 236 (10), 235 (93) [M^+], 206 (9), 205 (100), 177 (8), 108 (10), 69 (18); **HRMS** (EI-TOF) calcd. for $C_9H_7F_3O_2S$: 236.0119; found: 236.0123.

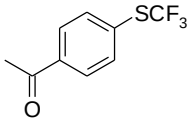
Synthesis of 1-[3-[(trifluoromethyl)thio]phenyl]ethanone (2g)



[CAS: 56773-33-2]

Compound **2g** was prepared following the standard procedure starting from 3-acetylphenyl thiocyanate (**1g**, 177 mg, 1.00 mmol). After purification, **2g** was isolated as colorless oil (87.2 mg, 396 µmol, 40%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.23 (t, *J* = 2 Hz, 1 H), 8.07 (dt, *J* = 7.8, 1.5 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 7.55 (t, *J* = 7.8 Hz, 1 H), 2.63 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 196.7 (s), 140.6 (s), 138.4 (s), 136.2 (s), 130.7 (s), 130.0 (s), 129.5 (q, *J* = 308 Hz), 125.6 ppm (q, *J* = 2.2 Hz), 26.8 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –43.5 ppm; **IR** (neat): $\tilde{\nu}$ = 2918 (w), 2848 (w), 1689 (m), 1593 (w), 1564 (w), 1431 (w), 1397 (w), 1360 (w), 1259 (m), 1115 (vs), 1086 (vs), 1014 (w), 958 (w), 828 (w), 757 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 220.0 (26) [M^+], 205.1 (100), 177.1 (17), 108.1 (12), 69.0 (15), 43.1 (10); **HRMS** (EI-TOF) calcd. for $C_9H_7F_3OS$: 220.0170; found: 220.0154.

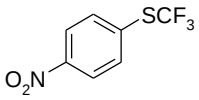
Synthesis of 1-[4-[(trifluoromethyl)thio]phenyl]ethanone (2h)



[CAS: 713-67-7]

Compound **2h** was prepared following the standard procedure starting from 4-acetylphenyl thiocyanate (**1h**, 177 mg, 1.00 mmol). After purification, **2h** was isolated as colorless oil (40.7 mg, 185 µmol, 19%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.98 (m, 2 H), 7.74 (m, 2 H), 2.62 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 197.2 (s), 138.6 (s), 135.9 (s), 130.2 (q, *J* = 2.2 Hz), 129.4 (q, *J* = 308 Hz), 129.2 (s), 26.8 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –43.1 ppm; **IR** (neat): $\tilde{\nu}$ = 2917 (w), 1689 (m), 1593 (w), 1397 (w), 1359 (w), 1260 (m), 1115 (vs), 1085 (vs), 1014 (w), 958 (w), 828 (w), 757 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 220 (19) [M^+], 206 (10), 205 (100), 177 (10), 136 (11), 108 (11), 69 (15); **HRMS** (EI-TOF) calcd. for $C_9H_7F_3OS$: 220.0170; found: 220.0164.

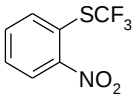
Synthesis of 1-nitro-4-[(trifluoromethyl)thio]benzene (2i)



[CAS: 403-66-7]

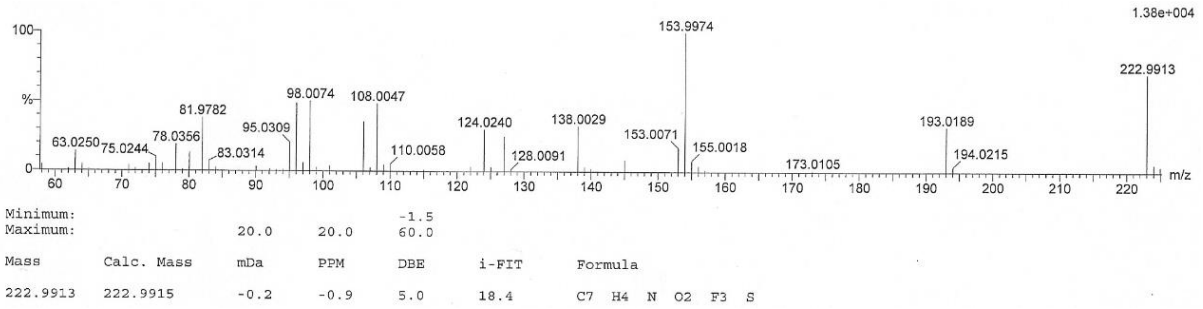
Compound **2i** was prepared following the standard procedure starting from 4-nitrophenyl thiocyanate (**1i**, 180 mg, 1.00 mmol). After purification, **2i** was obtained as yellow oil (69.6 mg, 312 µmol, 31%) **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.27 (m, 2 H), 7.83 ppm (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 149.3 (s), 136.3 (s), 132.9 (q, *J* = 2.2 Hz), 129.2 (q, *J* = 309 Hz), 124.7 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –42.6 ppm; **IR** (neat): $\tilde{\nu}$ = 2946 (w), 2843 (w), 1592 (m), 1494 (m), 1463 (w), 1294 (w), 1252 (m), 1104 (vs), 1029 (s), 828 (s), 799 (w), 755 (w), 650 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 223 (100) [M^+], 193 (42), 165 (13), 108 (17), 95 (10), 69 (31), 63 (13); **HRMS** (EI-TOF) calcd. for $C_7H_4F_3NO_2S$: 222.9915; found: 222.9917.

Synthesis of 1-nitro-2-[(trifluoromethyl)thio]benzene (2j)

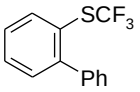


[CAS: 1644-87-7]

Compound **2j** was prepared following the standard procedure starting from 3-quinolyl thiocyanate (**1j**, 180 mg, 1.00 mmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36 µL, 500 µmol) was added to the reaction mixture. **2j** was formed in 33% yield as determined by ^{19}F spectroscopic analysis and confirmed by GC-**HRMS** analytics. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –42.4 ppm; **HRMS** (EI-TOF) calcd. for $C_7H_4F_3NO_2S$: 222.9915; found: 222.9913.



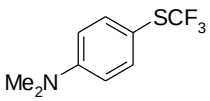
Synthesis of 2-[(trifluoromethyl)thio]-1,1'-biphenyl (2k)



[CAS: 129922-51-6]

Compound **2k** was prepared following the standard procedure starting from (1,1'-biphenyl)-2-yl thiocyanate (**1k**, 211 mg, 1.00 mmol). After purification, **2k** was isolated as yellow liquid (138 mg, 543 µmol, 54%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.0 Hz, 1 H), 7.53 (m, 1 H), 7.43 (m, 5 H), 7.32 ppm (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.0 (s), 140.4 (s), 137.3 (s), 131.4 (s), 130.8 (s), 129.8 (s), 129.7 (q, *J* = 308 Hz), 128.4 (s), 128.1 (s), 127.8 (s), 123.4 ppm (q, *J* = 2.0 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –43.0 ppm; **IR** (neat): $\tilde{\nu}$ = 3061 (w), 1588 (w), 1465 (w), 1100 (vs), 1072 (s), 1036 (m), 1008 (w), 756 (s), 749 (s), 698 (s) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 254 (100) [M^+], 186 (15), 185 (94), 184 (88), 152 (17), 139 (14), 69 (24); **HRMS** (EI-TOF) calcd. for $C_{13}H_9F_3S$: 254.0377; found: 254.0378.

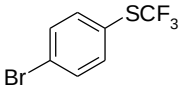
Synthesis of *N*,*N*-dimethyl-4-[(trifluoromethyl)thio]benzeneamine (2l)



[CAS: 2677-71-6]

Compound **2l** was prepared following the standard procedure starting from 4-(dimethylamino)phenyl thiocyanate (**1l**, 178 mg, 1.00 mmol). After purification, **2l** was isolated as colorless liquid (154 mg, 694 µmol, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.48 (m, 2 H), 6.68 (m, 2 H), 3.01 ppm (s, 6 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.0 (s), 138.1 (s), 130.0 (q, *J* = 308 Hz), 112.5, 108.5 (q, *J* = 2.2 Hz), 40.2 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –45.7 ppm; **IR** (neat): $\tilde{\nu}$ = 3003 (w), 2999 (w), 1596 (w), 1490 (w), 1462 (w), 1381 (w), 1306 (w), 1095 (vs), 979 (m), 820 (m), 785 (s), 754 (m), 658 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 222 (15), 221 (100) [M^+], 220 (13), 152 (81), 151 (11), 136 (9), 108 (10); **HRMS** (EI-TOF) calcd. for $C_9H_{10}F_3NS$: 221.0486; found: 221.0473.

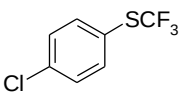
Synthesis of 1-bromo-4-[(trilfluoromethyl)thio]benzene (2m)



[CAS: 333-47-1]

Compound **2m** was prepared following the standard procedure starting from 4-bromophenyl thiocyanate (**1m**, 214 mg, 1.00 mmol). After purification, **2m** was isolated as colorless liquid (119 mg, 463 µmol, 46%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.56 (m, 2 H), 7.52 ppm (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 137.9 (s), 133.0 (s), 129.3 (q, *J* = 308 Hz), 126.2 (s), 123.5 ppm (q, *J* = 2.2 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –43.8 ppm; **IR** (neat): $\tilde{\nu}$ = 2927 (w), 1642 (w), 1564 (w), 1474 (w), 1388 (w), 1112 (vs), 1080 (vs), 1009 (s), 817 (s), 756 (w), 732 (w), 702 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 258 (100) [M^+], 256 (90), 189 (35), 187 (34), 108 (53), 69 (33), 63 (12); **HRMS** (EI-TOF) calcd. for $C_7H_4{}^{79}BrF_3S$: 255.9169; found: 255.9179.

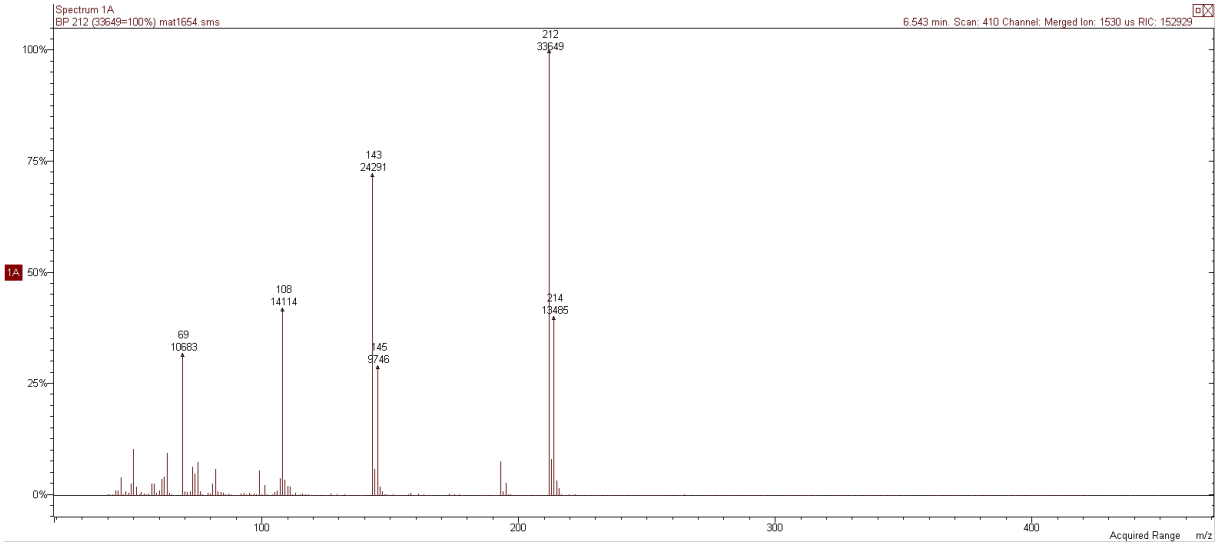
Synthesis of 1-chloro-4-[(trifluoromethyl)thio]benzene (2n)



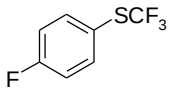
[CAS: 407-16-9]

Compound **2n** was prepared following the standard procedure starting from 4-chlorophenyl thiocyanate (**1n**, 84.8 mg, 500 µmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36 µL, 500 µmol) was added to the reaction mixture. **2n** was formed in

80% yield as determined by ^{19}F spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –43.9 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 214 (40), 212 (100) [M^+], 145 (29), 143 (72), 108 (42), 69 (32), 50 (10).

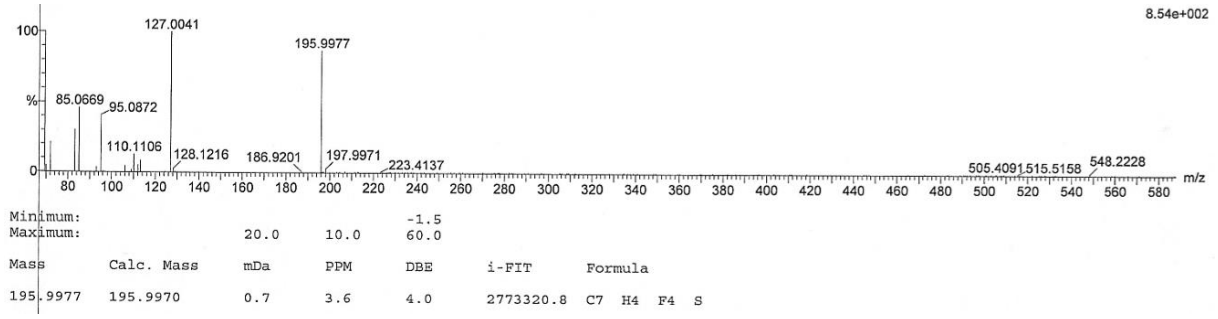


Synthesis of 1-fluoro-4-[(trifluoromethyl)thio]benzene (2o)

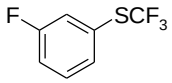


[CAS: 940-76-1]

Compound **2o** was prepared following the standard procedure starting from 4-fluorophenyl thiocyanate (**1o**, 76.6 mg, 500 µmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36 µL, 500 µmol) was added to the reaction mixture. **2o** was formed in 63% yield as determined by ^{19}F spectroscopic analysis and confirmed by GC-**HRMS** analytics. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –43.6, –108.8 ppm; **HRMS** (EI-TOF) calcd. for $C_7H_4F_4S$: 195.9970; found: 195.9977.

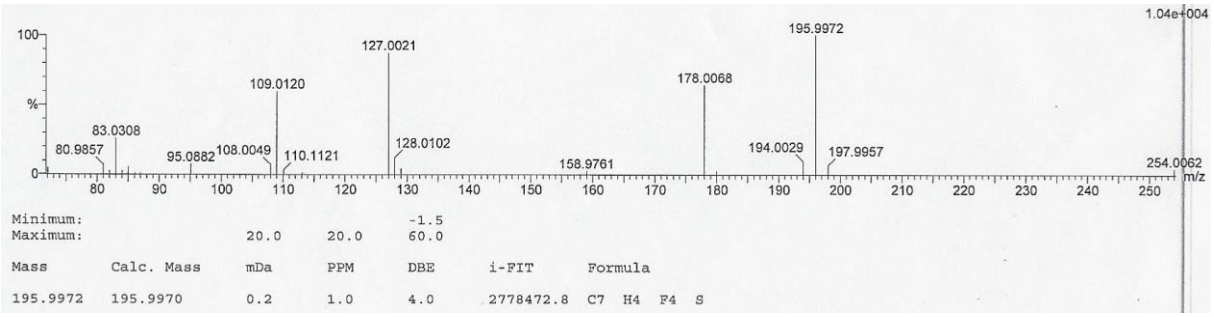


Synthesis of 1-fluoro-3-[(trifluoromethyl)thio]benzene (2p)

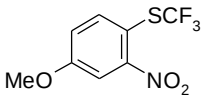


[CAS: 940-19-2]

Compound **2p** was prepared following the standard procedure starting from 3-fluorophenyl thiocyanate (**1p**, 76.6 mg, 500 µmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36 µL, 500 µmol) was added to the reaction mixture. **2p** was formed in 82% yield as determined by ^{19}F spectroscopic analysis and confirmed by GC-**HRMS** analytics. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –43.5, –112.0 ppm; **HRMS** (EI-TOF) calcd. for $C_7H_4F_4S$: 195.9970; found: 195.9972.



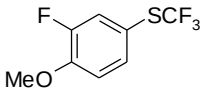
Synthesis of 4-methoxy-2-nitro-1-[(trifluormethyl)thio]benzene (2q)



[CAS: 959144-33-3]

Compound **2q** was prepared following the standard procedure starting from 4-methoxy-2-nitrophenyl thiocyanate (**1q**, 210 mg, 1.00 mmol). After purification, **2q** was isolated as yellow oil (86.1 mg, 340 µmol, 34%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.8 Hz, 1 H), 7.46 (d, *J* = 2.8 Hz, 1 H), 7.17 (dd, *J* = 8.9, 2.9 Hz, 1 H), 3.91 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.5 (s), 153.3 (s), 137.2 (q, *J* = 1.5 Hz), 129.0 (q, *J* = 310 Hz), 119.5 (s), 111.1 (q, *J* = 2.4 Hz), 110.6 (s), 56.3 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –43.4 ppm; **IR** (neat): $\tilde{\nu}$ = 2944 (w), 1602 (w), 1534 (m), 1485 (w), 1356 (w), 1303 (m), 1273 (w), 1237 (m), 1126 (s), 1092 (vs), 1052 (m), 1023 (m), 911 (w), 859 (w), 801 (m), 755 (m), 676 (w), 655 (w) cm^{-1} **MS** (Ion trap, EI, 70 eV): m/z (%) = 253 (89) [M^+], 184 (100), 136 (39), 128 (46), 126 (48), 123 (52), 69 (49); **HRMS** (EI-TOF) calcd. for $C_8H_6F_3NO_3S$: 253.0020; found: 253.0026.

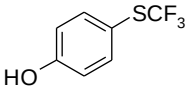
Synthesis of 2-fluoro-1-methoxy-4-[(trifluoromethyl)thio]benzene (2r)



[CAS: 1821240-73-6]

Compound **2r** was prepared following the standard procedure starting from 3-fluoro-4-methoxyphenyl thiocyanate (**1r**, 183 mg, 1.00 mmol). After purification, **2r** was obtained as colorless liquid (174 mg, 768 µmol, 77%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.40 (m, 2 H), 6.99 (t, *J* = 8.7 Hz, 1 H), 3.93 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.0 (d, *J* = 251 Hz), 150.5 (d, *J* = 11.0 Hz), 133.7 (d, *J* = 3.7 Hz), 129.5 (q, *J* = 308 Hz), 124.1 (d, *J* = 19.8 Hz), 115.2 (m), 113.7 (d, *J* = 2.2 Hz), 55.4 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –44.7, –133.8 ppm; **IR** (neat): $\tilde{\nu}$ = 2938 (w), 1602 (w), 1507 (m), 1465 (w), 1444 (w), 1410 (w), 1307 (w), 1272 (m), 1217 (w), 1098 (vs), 1024 (m), 898 (w), 875 (w), 809 (m), 761 (m), 652 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 227 (10) [M^+], 226 (100), 157 (73), 142 (13), 114 (11), 95 (11), 69 (25); **HRMS** (EI-TOF) calcd. for $C_8H_6F_4OS$: 226.0075; found: 226.0086.

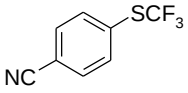
Synthesis of 4-[(trifluoromethyl)thio]phenol (2s)



[CAS: 461-84-7]

Compound **2s** was prepared following the standard procedure starting from 4-fluorophenyl thiocyanate (**1s**, 151 mg, 1.00 µmol). After purification, **2s** was obtained as colorless solid (57.1 mg, 294 µmol, 29%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.54 (m, 2 H), 6.88 (m, 2 H), 5.70 ppm (s, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 158.0 (s), 138.7 (s), 129.7 (q, *J* = 308 Hz), 116.7 (s), 115.4 ppm (q, *J* = 2.4 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –45.3 ppm; **IR** (neat): $\tilde{\nu}$ = 3221 (m), 3021 (w), 2971 (w), 1739 (w), 1584 (m), 1494 (m), 1437 (w), 1365 (w), 1228 (m), 1109 (vs), 1086 (vs), 1011 (m), 827 (s), 755 (m), 708 (w), 650 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 194 (100) [M^+], 125 (76), 97 (28), 81 (15), 69 (31), 53 (17), 45 (11); **HRMS** (EI-TOF) calcd. for $C_7H_5F_3OS$: 194.0013; found: 194.0010; **m.p.**: 58–59 °C.

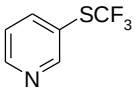
Synthesis of 4-[(trifluoromethyl)thio]benzonitrile (2t)



[CAS: 332-26-3]

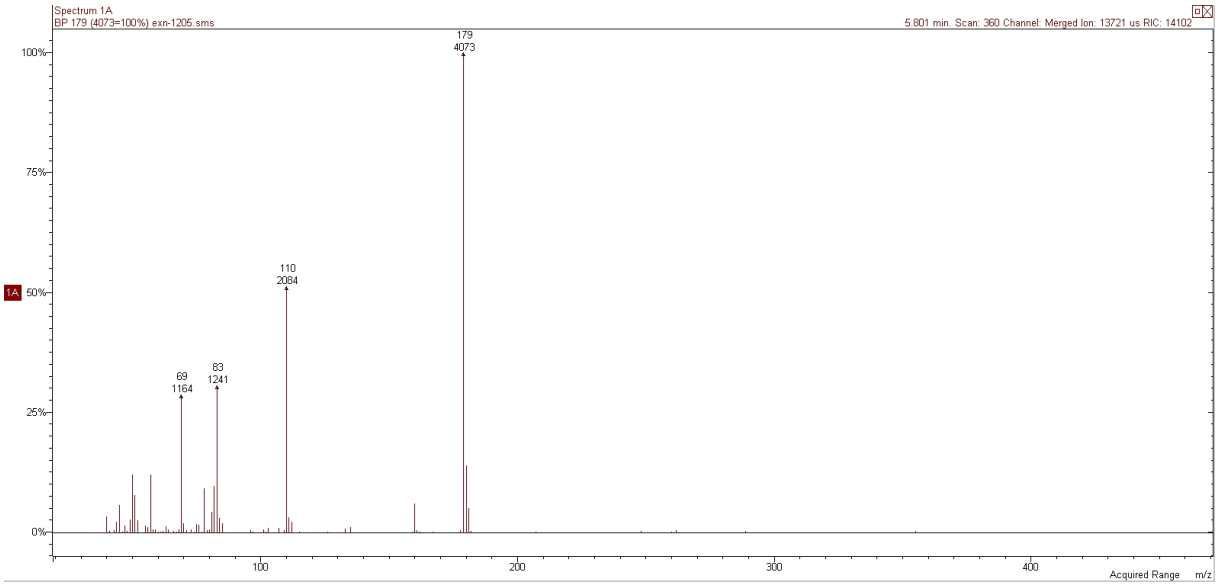
Compound **2t** was prepared following the standard procedure starting from 3-quinolyl thiocyanate (**1w**, 160 mg, 1.00 mmol). After purification, **2t** was obtained as colorless oil (117 mg, 578 µmol, 58%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.73 ppm (m, 4 H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 136.1 (s), 133.0 (s), 130.6 (q, J = 2.1 Hz), 129.1 (q, J = 309 Hz), 117.7 (s), 114.8 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –42.8 ppm; **IR** (neat): $\tilde{\nu}$ = 3093 (w), 3069 (w), 3043 (w), 2231 (w), 1927 (w), 1594 (w), 1488 (w), 1404 (w), 1306 (w), 1277 (w), 1116 (vs), 1019 (m), 961 (w), 834 (m), 756 (w), 719 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 203 (15) [M^+], 184 (15), 135 (9), 134 (100), 106 (12), 90 (23), 69 (43); **HRMS** (EI-TOF) calcd. for $C_8H_4F_3NS$: 203.0017; found: 203.0019.

Synthesis of 3-[(trifluoromethyl)thio]pyridine (2u)

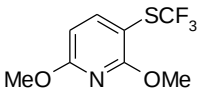


[CAS: 58313-26-1]

Compound **2u** was prepared following the standard procedure starting from 3-pyridyl thiocyanate (**1u**, 68.1 mg, 500 µmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36 µL, 500 µmol) was added to the reaction mixture. **2u** was formed in 79% yield as determined by ^{19}F spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –43.6 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 180 (16), 179 (100) [M^+], 110 (49), 83 (34), 69 (29), 57 (11), 50 (18).



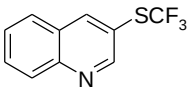
Synthesis of 2,6-dimethoxy-3-[(trifluoromethyl)thio]pyridine (2v)



[CAS: 58313-26-1]

Compound **2v** was prepared following the standard procedure starting from 2,6-dimethoxypyridin-3-yl thiocyanate (**1v**, 196 mg, 1.00 mmol). After purification, **2v** was obtained as colorless oil (147 mg, 616 µmol, 62%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.3 Hz, 1 H), 6.36 (d, 8.0 Hz, 1 H), 4.02 (s, 3 H), 3.96 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.6 (s), 164.2 (s), 150.2 (s), 129.6 (q, *J* = 310 Hz), 103.1 (s), 96.0 (q, *J* = 2.1 Hz), 54.4 (s), 54.0 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –44.7 ppm; **IR** (neat): $\tilde{\nu}$ = 2956 (w), 1570 (s), 1466 (m), 1414 (m), 1376 (s), 1324 (s), 1267 (w), 1240 (m), 1099 (vs), 1068 (s), 1010 (s), 956 (w), 811 (m), 753 (m), 728 (w), 692 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 239.0 (100) [M^+], 169.9 (58), 139.9 (18), 125.0 (11), 86.0 (11), 69.0 (19); **HRMS** (EI-TOF) calcd. for $C_7H_5F_3O_2S_2$: 239.0228; found: 239.0227.

Synthesis of 3-[(trifluoromethyl)thio]quinoline (2w)

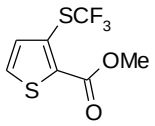


[CAS: 1333415-90-9]

Compound **2w** was prepared following the standard procedure starting from 3-quinolyl thiocyanate (**1w**, 186 mg, 1.00 mmol). After purification, **2w** was obtained as colorless oil

(168 mg, 731 µmol, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.02 (d, *J* = 2.2 Hz, 1 H), 8.50 (d, *J* = 2.0 Hz, 1 H), 8.14 (m, 1 H), 7.81 (m, 2 H), 7.61 ppm (m, 1 H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.6 (s), 148.4 (s), 144.7 (s), 131.7 (s), 129.5 (s), 129.2 (q, *J* = 309 Hz), 128.1 (s), 127.8 (s, 2C), 118.2 ppm (q, *J* = 1.8 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –43.6 ppm; **IR** (neat): $\tilde{\nu}$ = 3063 (w), 2928 (w), 1619 (w), 1567 (w), 1489 (w), 1357 (w), 1321 (w), 1100 (vs), 956 (m), 911 (w), 863 (w), 783 (m), 749 (s), 650 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 229 (100) [M^+], 160 (37), 133 (9), 116 (7), 89 (20), 69 (11), 63 (6); **HRMS** (EI-TOF) calcd. for $C_{10}H_6F_3NS$: 229.0173; found: 229.0172.

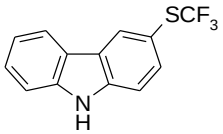
Synthesis of methyl-3-[(trifluoromethyl)thio]thiophene-2-carboxylate (2x)



[CAS: 1639370-02-7]

Compound **2x** was prepared following the standard procedure starting from methyl-3-thiocyanatothiophene-2-carboxylate (**1x**, 199 mg, 1.00 mmol). After purification, **2x** was obtained as colorless oil (46.1 mg, 190 µmol, 19%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 5.3 Hz, 1 H), 7.25 (m, 1 H), 3.91 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.9 (s), 131.9 (s), 130.8 (q, *J* = 2.2 Hz), 129.5 (q, *J* = 309 Hz), 129.4 (q, *J* = 2.2 Hz), 128.6 (q, *J* = 1.7 Hz), 52.7 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –42.4 ppm; **IR** (neat): $\tilde{\nu}$ = 2956 (w), 1701 (m), 1504 (w), 1438 (m), 1406 (m), 1268 (m), 1082 (vs), 973 (w), 894 (m), 793 (w), 767 (s), 721 (w) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 241.8 (100) [M^+], 210.9 (70), 173.0 (69), 142.0 (25), 68.9 (40), 45.0 (11); **HRMS** (EI-TOF) calcd. for $C_7H_5F_3O_2S_2$: 241.9683; found: 241.9695.

Synthesis of 3-[(trifluoromethyl)thio]-9*H*-carbazole (2y)



[CAS: 1808089-09-9]

Compound **2y** was prepared following the standard procedure starting from 9*H*-carbazol-3-yl thiocyanate (**1y**, 224 mg, 1.00 mmol). After purification, **2y** was obtained as colorless solid (29.4 mg, 110 µmol, 11%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 1.3 Hz, 1 H),

8.14 (s, 1 H), 8.09 (dd, J = 7.8, 0.8 Hz, 1 H), 7.68 (dd, J = 8.5, 1.9 Hz, 1 H), 7.49 (ddd, J = 8.2, 7.1, 1.1 Hz, 1 H), 7.41 (m, 2 H), 7.31 ppm (ddd, J = 7.9, 7.0, 1.0 Hz, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.7 (s), 139.8 (s), 134.0 (s), 129.9 (q, J = 308 Hz), 129.6 (s), 126.9 (s), 124.4 (s), 122.5 (s), 120.6 (s), 120.4 (s), 113.5 (q, J = 2.0 Hz), 111.4 (s), 110.9 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –45.1 ppm; **IR** (neat): $\tilde{\nu}$ = 3385 (m), 2970 (w), 1894 (w), 1739 (m), 1598 (w), 1491 (w), 1454 (m), 1366 (w), 1276 (w), 1231 (m), 1149 (m), 1101 (vs), 894 (w), 815 (m), 754 (s) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 267.2 (100) [M^+], 198.0 (78), 154.2 (14), 69.0 (15); **HRMS** (EI-TOF) calcd. for $C_{13}H_8F_3NS$: 267.0327; found: 267.0330; **m.p.**: 146–147 °C.

6.4.4.2 Upscaling of the synthesis of 1-methoxy-4-[trifluoromethyl)thio]benzene (2a)

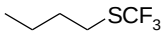
Potassium trifluoroacetate (5.64 g, 36.4 mmol) and iron(II) chloride (1.18 g, 9.09 mmol) were weighed into a three-neck flask with reflux condenser and magnetic stir bar that was afterwards brought under an atmosphere of nitrogen. DMF (90 mL) and Synthesis of 4-methoxyphenyl thiocyanate **(1a)** were added *via* syringe through a septum and the mixture was stirred for 16 h at 140 °C. After the reaction was completed, pentane (200 mL) and a 1 M lithium chloride solution (100 mL) were added. The organic layer was separated and dried over magnesium sulfate. The solvent was removed using a vigreux column (water bath at 45 °C). The remaining crude product was purified by a manual column (SiO_2, pentane/diethyl ether). After removing the solvent, **2a** was obtained as colorless liquid (6.05 g, 29.1 mmol, 96%). The analytical data matched the one previously reported in this paper.

6.4.5 Synthesis of alkyl trifluoromethyl thioethers

6.4.5.1 Standard procedure for the synthesis of alkyl trifluoromethyl thioethers from the corresponding alkyl bromides

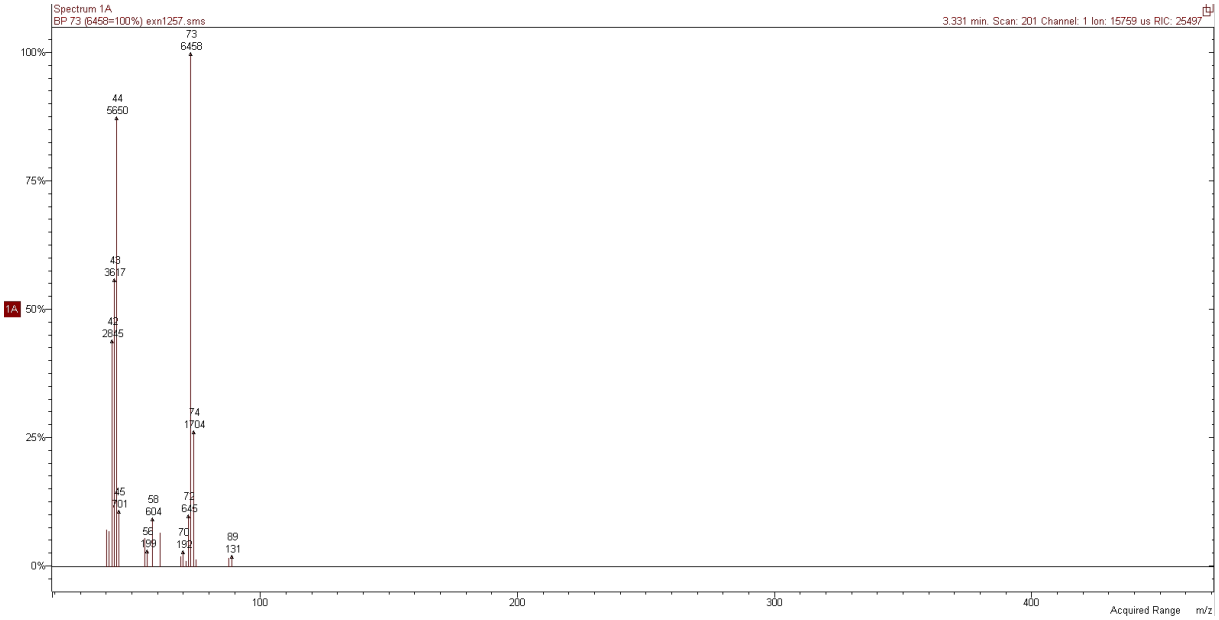
An oven-dried 20 mL crimp cap vessel with PTFE-coated stir bar was charged with anhydrous sodium thiocyanate (41.4 mg, 500 µmol) and was brought under an atmosphere of dry nitrogen. DMF (1.50 mL) and the alkyl bromide (500 µmol) were added *via* syringe and the mixture was stirred at 60 °C for 3 h. Afterwards the mixture was added to iron chloride (19.4 mg, 150 µmol) and potassium trifluoroacetate (93.1 mg, 600 µmol), that had been brought under an atmosphere of dry nitrogen, *via* syringe. The reaction mixture was heated to 140 °C for 16 h.

Synthesis of 1-[(trifluoromethyl)thio]butane (3a)

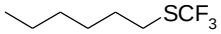


[CAS: 7412-26-2]

Compound **3a** was prepared following the standard procedure starting from 1-bromobutane (69.2 mg, 54.5 µL, 500 µmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36 µL, 500 µmol) was added to the reaction mixture. **3a** was formed in 44% yield as determined by ^{19}F spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –42.0 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 89 (2) [$(M–CF_3)^+$], 73 (100), 58 (9), 44 (87).

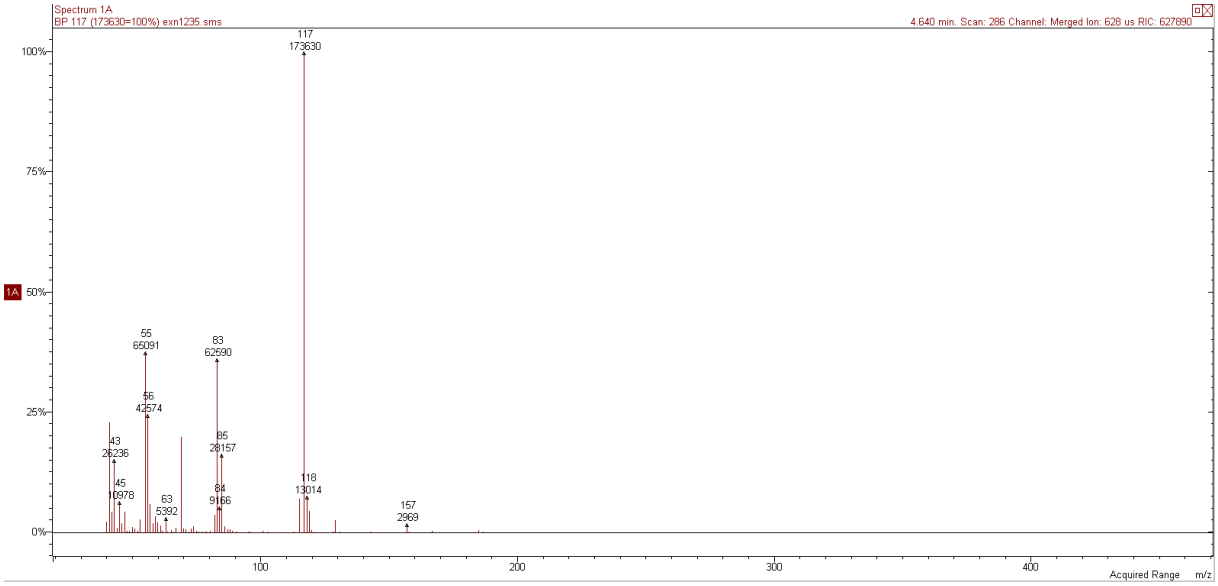


Synthesis of 1-[(trifluoromethyl)thio]hexane (3b)

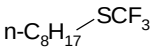


[CAS: 59529-76-9]

Compound **3b** was prepared following the standard procedure starting from 1-bromohexane (84.2 mg, 62.5 µL, 500 µmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36 µL, 500 µmol) was added to the reaction mixture. **3b** was formed in 46% yield as determined by ^{19}F spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –42.0 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 117 (100) [$(M–CF_3)^+$], 83 (38), 69 (22), 56 (25), 55 (41), 43 (15), 41 (25).

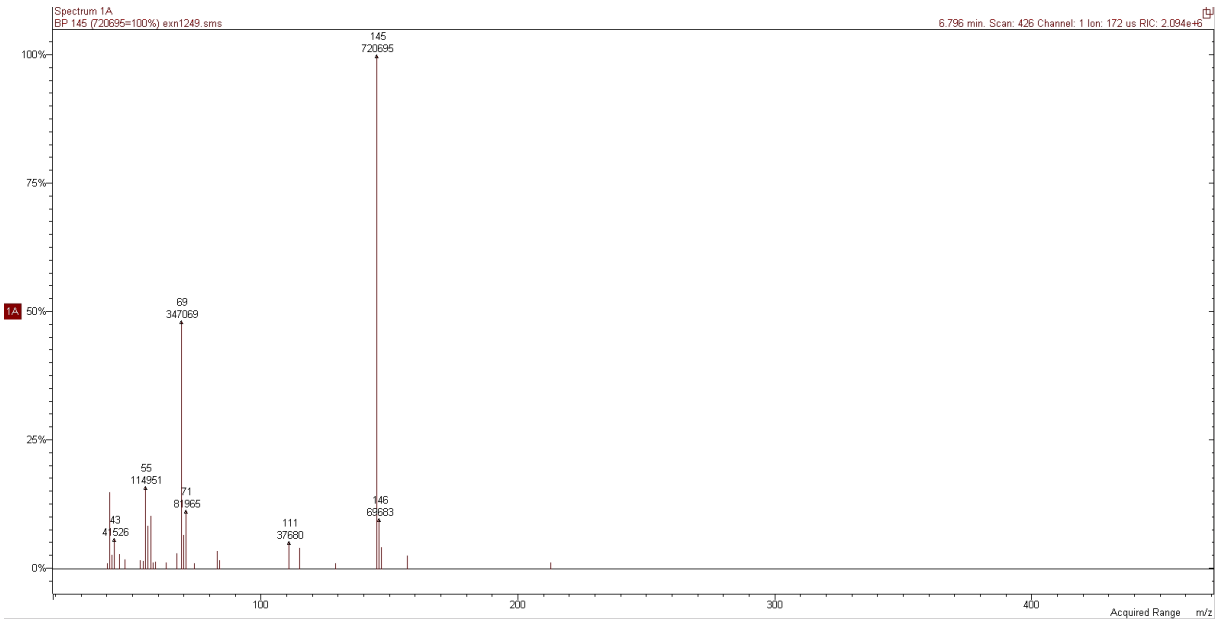


Synthesis of 1-[(trifluoromethyl)thio]octane (3c)

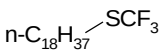


[CAS: 134776-65-1]

Compound **3c** was prepared following the standard procedure starting from 1-bromooctane (97.5 mg, 87.9 µL, 500 µmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36 µL, 500 µmol) was added to the reaction mixture. **3c** was formed in 55% yield as determined by ^{19}F spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –42.0 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 146 (10), 145 (100) [$(M–CF_3)^+$], 69 (50), 56 (8), 55 (16), 41 (18).

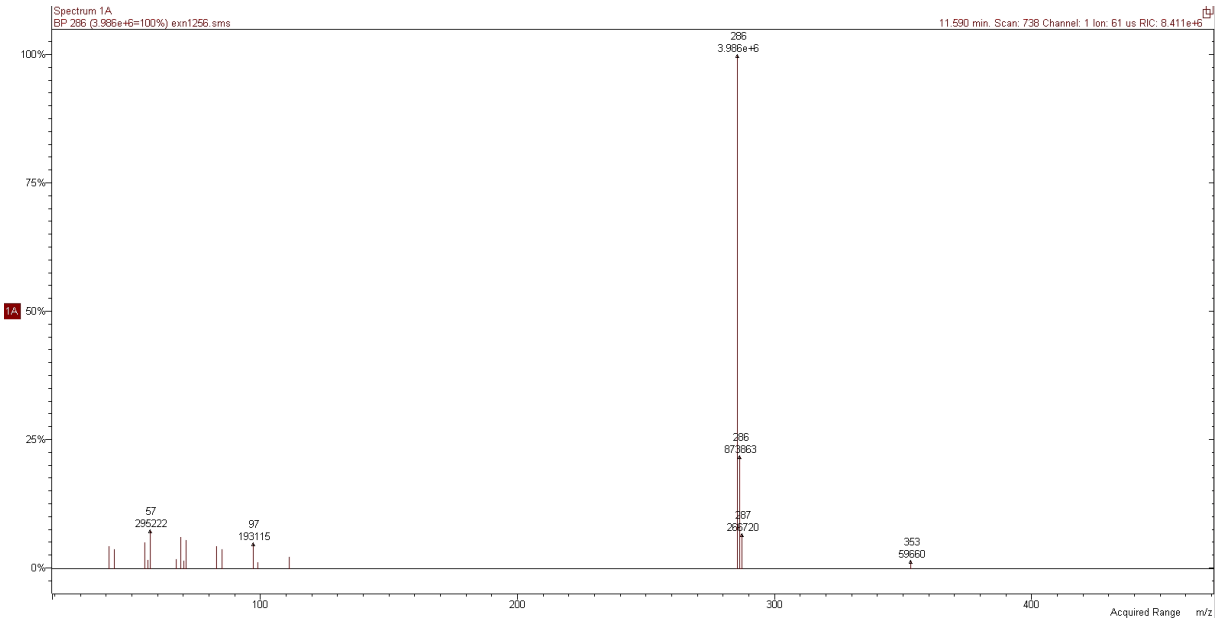


Synthesis of 1-[(trifluoromethyl)thio]octadecane (3d)

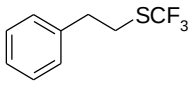


[CAS: 1821240-74-7]

Compound **3d** was prepared following the standard procedure starting from 1-bromooctadecane (172 mg, 176 µL, 500 µmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36 µL, 500 µmol) was added to the reaction mixture. **3d** was formed in 46% yield as determined by ^{19}F spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –42.0 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 286 (20), 285 (100) [(M–CF_3)$^+$], 69 (7), 57 (7), 55 (7), 41 (7).

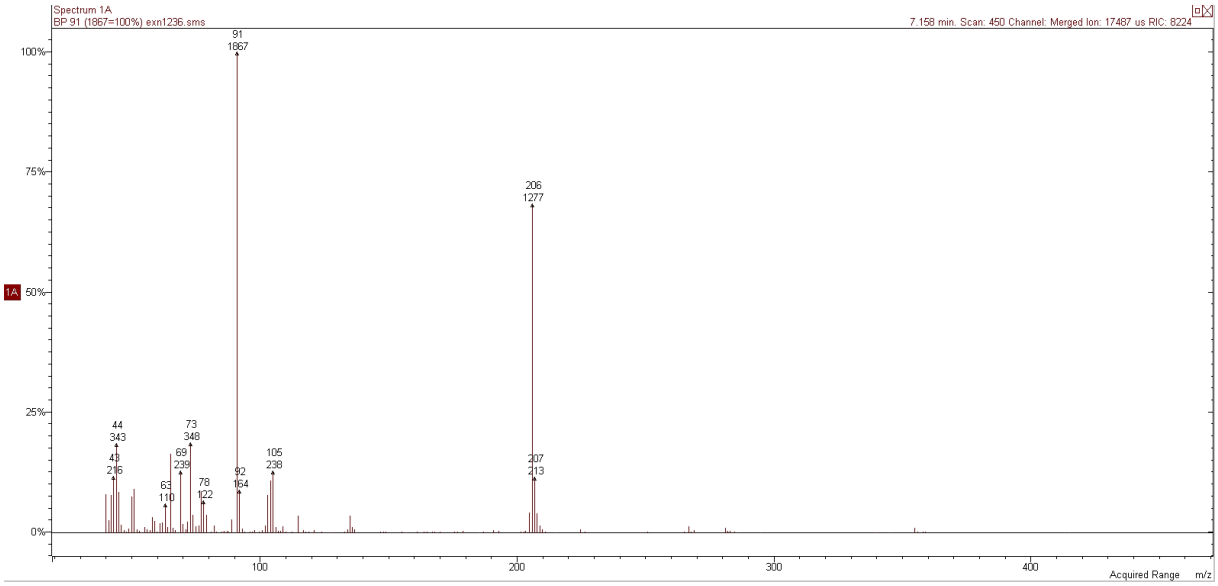


Synthesis of [2-[(trifluoromethyl)thio]ethyl]benzene (3e)

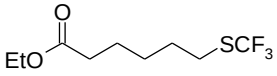


[CAS: 361182-15-2]

Compound **3e** was prepared following the standard procedure starting from (2-bromoethyl)benzene (94.4 mg, 69.7 µL, 500 µmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36 µL, 500 µmol) was added to the reaction mixture. **3e** was formed in 48% yield as determined by ^{19}F spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –41.8 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 206 (64) [M^+], 105 (12), 104 (8), 92 (8), 91 (100), 69 (9), 65 (16).



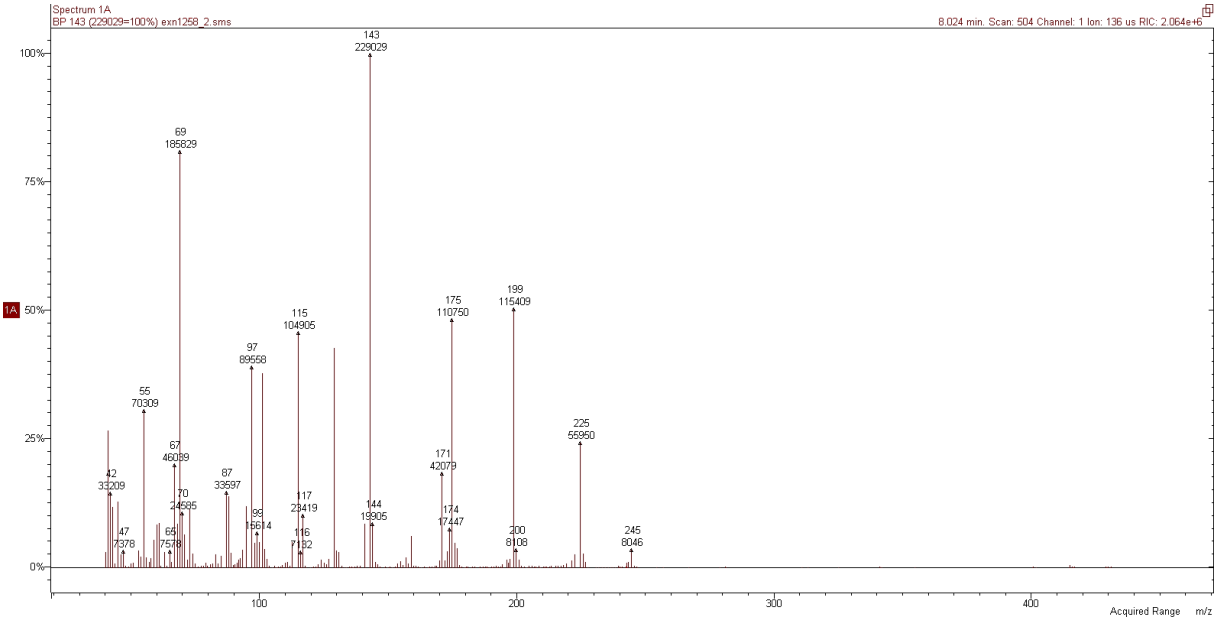
Synthesis of ethyl-6-[(trifluoromethyl)thio]hexanoate (3f)



[CAS: 1620061-36-0]

Compound **3f** was prepared following the standard procedure starting from 1-bromooctadecane (172 mg, 176 µL, 500 µmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36 µL, 500 µmol) was added to the reaction mixture. **3f** was formed in 38% yield as determined by ^{19}F spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –41.9 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 245 (4)

[$(M+H)^+$], 225 (24), 199 (50), 175 (48), 143 (100), 129 (43), 115 (46), 97 (39), 69 (81).

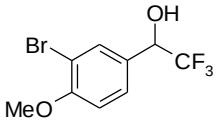


6.4.6 Synthesis of α-(trifluoromethyl)-2-arenemethanols

6.4.6.1 Standard procedure for the synthesis of α-(trifluoromethyl)-2-arenemethanols from the corresponding aldehydes

An oven-dried 20 mL crimp cap vessel with PTFE-coated stir bar was charged with anhydrous iron chloride (77.6 mg, 600 µmol), potassium trifluoroacetate (373 mg, 2.40 mmol), and the corresponding aldehyde (2.00 mmol) and was then brought under an atmosphere of dry nitrogen. DMF (6.00 mL) was added *via* syringe and the reaction mixture was heated to 140 °C for 6 h. Afterwards it was diluted with diethyl ether (20 mL), filtered through a short pad of silica and washed with a saturated solution of sodium hydrogencarbonate in water (2 × 50 mL). The organic phase was dried with magnesium sulfate and the crude product purified by column chromatography (SiO_2, cyclohexane/ethyl acetate gradient).

Synthesis of α-(trifluoromethyl)-3-bromo-4-methoxybenzenemethanol (5a)



[CAS: 1249929-52-9]

Compound **5a** was prepared following the standard procedure starting from 3-bromo-4-methoxybenzaldehyde (439 mg, 2.00 mmol). After purification, **5a** was obtained as yellow oil

(342 mg, 1.20 mmol, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 2.3 Hz, 1 H), 7.38 (dd, *J* = 8.5, 2.0 Hz, 1 H), 6.92 (d, *J* = 8.5 Hz, 1 H), 4.93 (q, *J* = 6.5 Hz, 1 H), 3.92 ppm (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.9 (s), 132.5 (s), 127.9 (s), 124.2 (q, *J* = 282 Hz) 112.0 (s), 111.8 (s), 71.9 (q, *J* = 32.3 Hz), 56.5 ppm (s); **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –77.4 ppm; **IR** (neat): $\tilde{\nu}$ = 3451 (w), 2948 (w), 2944 (w), 1606 (w), 1498 (m), 1463 (w), 1442 (w), 1408 (w), 1255 (s), 1166 (s), 1121 (vs), 1052 (s), 1018 (m), 888 (w), 810 (m), 780 (w), 723 (w), 700 (w), 671 (m) cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 286 (63) [M^+], 284 (64), 217 (100), 215 (82), 108 (77), 78 (11), 65 (10).

6.5 Convenient Synthesis of Pentafluoroethyl Thioethers via Catalytic Sandmeyer Reaction with a Stable Fluoroalkylthiolation Reagent

General Methods

The reactions were performed in oven-dried glassware containing a Teflon-coated stirrer bar and septum under a nitrogen atmosphere. Acetonitrile were dried by refluxing over CaH_2 and subsequent fractionally distillation. All reactions were monitored by GC and the yields were determined by ^{19}F NMR using trifluoroethanol as internal standard. GC analyses were carried out using a HP-5 capillary column (Phenyl Methyl Siloxane 30 m x 320 x 0.25) and a time program beginning with 2 min at 60 °C followed by 30 °C/min ramp to 300 °C, then 3 min at this temp. Column chromatography was performed using a Combi Flash Companion-Chromatography-System (Isco-Systems) and Grace Reveleris packed flash columns (12 g). NMR spectra were obtained on a Bruker AMX 400 system using chloroform-d_1, acetonitrile-d_3 or methanol-d_4 as deuterated solvents, with proton, carbon and fluorine resonances at 400 MHz, 101 MHz and 375 MHz, respectively. Mass spectral data were acquired on a Varian Saturn 2100 T.

All commercially available starting materials were used without further purification. $Me_4NSC_2F_5$ was commercially available by CF Plus Chemicals s. r. o.

6.5.1 Synthesis of Starting Materials

Synthesis of arene diazonium tetrafluoroborates

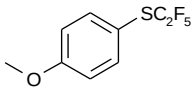
In a 50 mL round-bottom flask, the aniline (10 mmol) was dissolved in a mixture of absolute ethanol (3 mL) and an aqueous solution of HBF_4 (50%, 2.5 mL, 20 mmol) and *tert*-butyl nitrite (2.7 mL, 20 mmol) was added dropwise to the solution at 0 °C. The reaction was stirred at room temperature for 1 h and diethyl ether (20 mL) was added to precipitate the arenediazonium tetrafluoroborate that was filtered off and washed with diethyl ether (3 × 10 mL). The arenediazonium tetrafluoroborate was dried in vacuo (10^{-3} mbar) for 10 minutes and was then directly used without further purification.

6.5.1.1 Synthesis of pentafluoroethyl thioethers from arenediazonium salts

Standard procedure

An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with Cu (6.4 mg, 0.10 mmol), $Me_4NSC_2F_5$ (338 mg, 1.50 mmol) and MeCN (2 mL). Then, the arenediazonium salt (1.00 mmol) in MeCN (2 mL) was added dropwise and the reaction mixture was stirred for 15 h at room temperature. The resulting mixture was diluted with diethyl ether (20 mL). The organic solution was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was purified by flash chromatography (SiO_2, cyclohexane / ethyl acetate gradient), yielding the aryl pentafluoroethyl thioethers. The yields of particularly volatile compounds were determined by ^{19}F NMR, and their identity by mass spectroscopy.

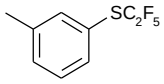
Synthesis of 1-methoxy-4-[(pentafluoroethyl)thio]benzene (2a)



[CAS: 1955495-78-9]

Compound **2a** was prepared following the standard procedure, starting from 4-methoxybenzenediazonium tetrafluoroborate (222 mg, 1.00 mmol). After purification, **2a** was isolated as colorless oil (253 mg, 0.98 mmol, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.57 (d, ^3J = 8.8 Hz, 2H), 6.94 (d, ^3J = 8.8 Hz, 2H), 3.85 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.5 (t, J = 4.1 Hz, 3F), –92.8 ppm (q, J = 4.1 Hz, 2F); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.0, 139.0 (2C), 115.0 (2C), 113.1 (t, ^3J(C,F) = 2.7 Hz), 120.0 (qt, ^1J(C,F) = 287.0 Hz, ^2J(C,F) = 40.3 Hz), 118.8 (tq, ^1J(C,F) = 286.1 Hz, ^2J(C,F) = 37.0 Hz), 55.4 ppm; **IR** (neat): ν= 2934, 2842, 1593, 1495, 1293, 1252, 1205, 1102, 1087, 1030, 956, 828, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 258 [M^+] (73), 139 (100), 123 (11), 96 (14); **HRMS** (EI-TOF) calcd. for $C_9H_7F_5OS$: 258.0138; found: 258.0143.

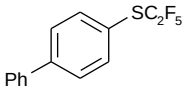
Synthesis of 1-methyl-3-[(pentafluoroethyl)thio]benzene (2b)



[CAS: 1955495-79-0]

Compound **2b** was prepared following the standard procedure, starting from 3-methylbenzenediazonium tetrafluoroborate (206 mg, 1.00 mmol). After purification, **2b** was isolated as colorless oil (225 mg, 0.93 mmol, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.49-7.47 (m, 2H), 7.33-7.32 (m, 2H), 2.41 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.5 (t, *J* = 4.1 Hz, 3F), –91.0 ppm (q, *J* = 3.8 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 139.5, 137.7, 134.2, 131.8, 129.2, 122.4 (t, ^{3}J(C,F) = 2.7 Hz), 120.2 (qt, ^{1}J(C,F) = 288.4 Hz, ^{2}J(C,F) = 40.0 Hz), 118.8 (tq, ^{1}J(C,F) = 286.8 Hz, ^{2}J(C,F) = 36.8 Hz), 21.1 ppm; **IR** (neat): ν= 3053, 2929, 1595, 1477, 1330, 1203, 1095, 957, 780, 750, 691 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 242 [M^+] (100), 173 (12), 123 (67), 91 (14); **HRMS** (EI-TOF) calcd. for $C_9H_7F_5S$: 242.0189; found: 242.0183.

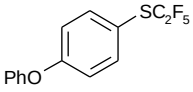
Synthesis of 4-[(pentafluoroethyl)thio]-1,1'-biphenyl (2c)



[CAS No.: 933673-37-1]

Compound **2c** was prepared following the standard procedure, starting from [1,1-biphenyl]-4-diazonium tetrafluoroborate (268 mg, 1.00 mmol). After purification, **2c** was isolated as colorless solid (289 mg, 0.95 mmol, 95%). **m.p.**: 60-61°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.80-7.78 (m, 2H), 7.70-7.66 (m, 4H), 7.56-7.45 ppm (m, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.4 (t, *J* = 3.8 Hz, 3F), –91.7 ppm (s, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.1, 139.6, 137.6, 129.0 (2C), 128.2 (2C), 128.1 (2C), 127.2 (2C), 121.4, 120.5 (qt, ^{1}J(C,F) = 288.4 Hz, ^{2}J(C,F) = 39.9 Hz), 118.9 ppm (tq, ^{1}J(C,F) = 287.0 Hz, ^{2}J(C,F) = 37.1 Hz); **IR** (neat): ν= 3033, 1478, 1333, 1200, 1100, 960, 836, 760, 688 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 304 [M^+] (100), 190 (19), 188 (59), 185 (85), 152 (44); **HRMS** (EI-TOF) calcd. for $C_{14}H_9F_5S$: 304.0345; found: 304.0368.

Synthesis of 1-phenoxy-4-[(pentafluoroethyl)thio]benzene (2d)

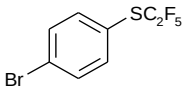


[CAS: 1955495-80-3]

Compound **2d** was prepared following the standard procedure, starting from 4-phenoxybenzenediazonium tetrafluoroborate (284 mg, 1.00 mmol). After purification, **2d** was

isolated as colorless oil (311 mg, 0.97 mmol, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.60 (d, ^3J = 8.8 Hz, 2H), 7.42 (t, ^3J = 8.0 Hz, 2H), 7.22 (t, ^3J = 7.5 Hz, 1H), 7.09 (d, ^3J = 8.5 Hz, 2H), 7.01 ppm (d, ^3J = 8.8 Hz, 2H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.4 (t, J = 3.8 Hz, 3F), –92.5 ppm (q, J = 4.1 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.6, 155.5, 139.0 (2C), 130.1 (2C), 124.6, 120.1 (2C), 120.0 (tq, ^1J(C,F) = 286.1 Hz, ^2J(C,F) = 36.3 Hz), 118.5 (2C), 118.7 (qt, ^1J(C,F) = 288.8 Hz, ^2J(C,F) = 40.4 Hz), 115.5 ppm (t, ^3J(C,F) = 3.2 Hz); **IR** (neat): ν= 3043, 1582, 1485, 1331, 1242, 1200, 1085, 957, 869, 833, 749, 691 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 320 [M^+] (94), 201 (100), 129 (16), 77 (23); **HRMS** (EI-TOF) calcd. for $C_{14}H_9F_5OS$: 320.0294; found: 320.0279.

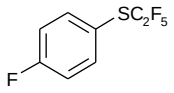
Synthesis of 1-bromo-4-[(pentafluoroethyl)thio]-benzene (2e)



[CAS No.: 782491-17-2]

Compound **2e** was prepared following the standard procedure, starting from 4-bromobenzenediazonium tetrafluoroborate (271 mg, 1.00 mmol). After purification, **2e** was isolated as colorless oil (239 mg, 0.78 mmol, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.58-7.51 ppm (m, 4H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.7 (t, J = 4.1 Hz, 3F), –92.0 ppm (q, J = 4.1 Hz, 2F); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.6 (2C), 132.8 (2C), 126.4, 121.9 (t, ^3J(C,F) = 2.7 Hz), 120.0 (qt, ^1J(C,F) = 288.8 Hz, ^2J(C,F) = 40.9 Hz), 118.7 ppm (tq, ^1J(C,F) = 286.6 Hz, ^2J(C,F) = 36.8 Hz); **IR** (neat): ν= 3023, 1569, 1475, 1388, 1331, 1204, 1103, 1012, 954, 817, 749, 731 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 305 [M^+] (100), 189 (72), 171 (11), 108 (52); **HRMS** (EI-TOF) calcd. for $C_8H_4F_5S^{79}Br$: 305.9137; found: 305.9154.

Synthesis of 1-fluoro-4-[(pentafluoroethyl)thio]-benzene (2f)

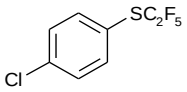


[CAS No.: 75220-65-4]

Compound **2f** was prepared following the standard procedure, starting from 4-fluorodiazonium tetrafluoroborate (105 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36.0 µL, 0.50 mmol) was added to the reaction mixture and the

pentafluoroethylthiolated product **2f** was formed in 61% yield as determined by **^{19}F NMR** spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –85.7 (t, *J* = 3.6 Hz, 3F), –92.1 ppm (q, *J* = 4.1 Hz, 2F); **MS** (Ion trap, EI, 70 eV): m/z (%) = 245.9 [M^+] (100), 177.0 (9), 127.0 (92), 83.0 (44), 75.0 (9), 68.9 (23), 57.0 (15).

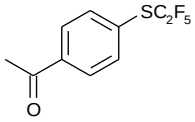
Synthesis of 1-chloro-4-[(pentafluoroethyl)thio]-benzene (2g)



[CAS No.: 782491-17-2]

Compound **2g** was prepared following the standard procedure, starting from 4-chlorobenzenediazonium tetrafluoroborate (226 mg, 1.00 mmol). After purification, **2g** was isolated as colorless oil (181 mg, 0.69 mmol, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.59 (d, ^{3}J = 8.5 Hz, 2H), 7.41 ppm (d, ^{3}J = 8.8 Hz, 2H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.5 (t, *J* = 3.8 Hz, 3F), –92.0 ppm (q, *J* = 4.1 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 138.4 (2C), 138.0, 129.8 (2C), 121.2 (t, ^{3}J(C,F) = 3.2 Hz), 120.2 (qt, ^{1}J(C,F) = 288.8 Hz, ^{2}J(C,F) = 40.3 Hz), 119.1 ppm (tq, ^{1}J(C,F) = 287.0 Hz, ^{2}J(C,F) = 36.3 Hz); **IR** (neat): ν= 3045, 2925, 2855, 1575, 1478, 1331, 1204, 1088, 957, 822, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 261 [M^+] (100), 145 (31), 143 (82), 108 (32); **HRMS** (EI-TOF) calcd. for $C_8H_4F_5{}^{35}ClS$: 261.9642; found: 261.9633.

Synthesis of 4-[(pentafluoroethyl)thio]acetophenone (2h)

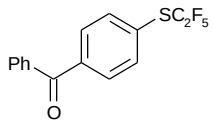


[CAS No.: 1328939-62-3]

Compound **2h** was prepared following the standard procedure, starting from 4-acetylbenzenediazonium tetrafluoroborate (234 mg, 1.00 mmol). After purification, **2h** was isolated as colorless oil (264 mg, 0.98 mmol, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.99 (d, ^{3}J = 7.0 Hz, 2H), 7.76 (d, ^{3}J = 7.0 Hz, 2H), 2.64 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.5 (t, *J* = 4.1 Hz, 3F), –91.2 ppm (q, *J* = 3.8 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 197.0, 138.7, 136.9 (2C), 128.9 (2C), 128.4 (t, ^{3}J(C,F) = 2.7 Hz), 120.3 (qt, ^{1}J(C,F) = 289.7 Hz, ^{2}J(C,F) = 40.8 Hz), 118.6 (tq, ^{1}J(C,F) = 286.5 Hz, ^{2}J(C,F) = 36.4 Hz), 26.7 ppm; **IR** (neat): ν= 3015, 2971, 1690, 1365, 1207, 1104, 954, 827, 750 cm^{-1}; **MS** (Ion

trap, EI, 70 eV): m/z (%) = 270 [M^+] (39), 255 (100), 136 (9); **HRMS** (EI-TOF) calcd. for $C_{10}H_7F_5OS$: 270.0138; found: 270.0132.

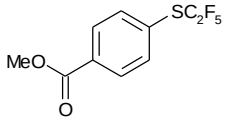
Synthesis of 4-[(pentafluoroethyl)thio]benzophenone (2i)



[CAS: 1955495-81-4]

Compound **2i** was prepared following the standard procedure, starting from 4-benzoylbenzenediazonium tetrafluoroborate (296 mg, 1.00 mmol). After purification, **2i** was isolated as colorless solid (309 mg, 0.99 mmol, 99%). m.p.: 56-57°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.88-7.77 (m, 6H), 7.64 (t, ^3J = 7.5 Hz, 1H), 7.52 ppm (t, ^3J = 7.5 Hz, 2H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.4 (t, J = 3.8 Hz, 3F), –91.1 ppm (q, J = 4.1 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 195.6, 139.7, 136.7, 136.7, 133.0, 130.6, 130.1, 128.5, 127.4 (t, ^3J(C,F) = 2.7 Hz), 120.0 (qt, ^1J(C,F) = 289.7 Hz, ^2J(C,F) = 41.0 Hz), 118.6 ppm (tq, ^1J(C,F) = 286.6 Hz, ^2J(C,F) = 36.8 Hz); **IR** (neat): ν= 2929, 1650, 1592, 1448, 1304, 1199, 1103, 961, 850, 791, 730, 694 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 332 [M^+] (100), 254 (28), 108 (6); **HRMS** (EI-TOF) calcd. for $C_{15}H_9F_5OS$: 332.0296; found: 332.0288.

Synthesis of methyl-4-[(pentafluoroethyl)thio]benzoate (2j)

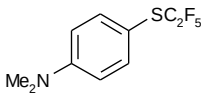


[CAS: 1955495-82-5]

Compound **2j** was prepared following the standard procedure, starting from 4-(methoxycarbonyl)benzenediazonium tetrafluoroborate (250 mg, 1.00 mmol). After purification, **2j** was isolated as colorless oil (269 mg, 0.94 mmol, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.08 (d, ^3J = 8.2 Hz, 2H), 7.73 (d, ^3J = 8.0 Hz, 2H), 3.95 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.5 (t, J = 3.8 Hz, 3F), –91.2 ppm (q, J = 4.1 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.0, 136.7 (2C), 132.5, 130.3 (2C), 128.2 (t, ^3J(C,F) = 2.7 Hz), 120.0 (qt, ^1J(C,F) = 289.7 Hz, ^2J(C,F) = 40.9 Hz), 118.6 (tq, ^1J(C,F) = 286.6 Hz, ^2J(C,F) = 36.3 Hz), 52.5 ppm; **IR** (neat): ν= 2925, 1713, 1438, 1282, 1214, 1106, 961,

764 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 286 [M^+] (56), 154 (100), 135 (17), 108 (15); **HRMS** (EI-TOF) calcd. for $C_{10}H_7F_5O_2S$: 286.0087; found: 286.0105.

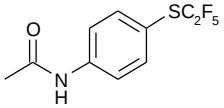
Synthesis of *N,N*-dimethyl-4-[(pentafluoroethyl)thio]benzenamine (2k)



[CAS: 1955495-83-6]

Compound **2k** was prepared following the standard procedure, starting from 4-(dimethylamino)benzenediazonium tetrafluoroborate (235 mg, 1.00 mmol). After purification, **2k** was isolated as colorless oil (247 mg, 0.91 mmol, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.52-7.50 (m, 2H), 6.72-6.69 (m, 2H), 3.04 ppm (s, 6H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.4 (t, *J* = 4.1 Hz, 3F), –93.5 ppm (q, *J* = 4.1 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.1, 138.6 (2C), 120.3 (qt, ^1J(C,F) = 287.9 Hz, ^2J(C,F) = 39.9 Hz), 120.0 (tq, ^1J(C,F) = 286.1 Hz, ^2J(C,F) = 37.2 Hz), 112.2 (2C), 106.3 (t, ^3J(C,F) = 2.7 Hz), 39.9 (2C) ppm; **IR** (neat): ν= 2896, 1593, 1509, 1446, 1365, 1329, 1193, 1086, 955, 810, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 271 [M^+] (19), 257 (38), 152 (49), 138 (100), 109 (26), 104 (20), 82 (29), 62 (40); **HRMS** (EI-TOF) calcd. for $C_{10}H_{10}F_5NS$: 271.0454; found: 271.0450.

Synthesis of *N*-[4-[(pentafluoroethyl)thio]phenyl]acetamide (2l)

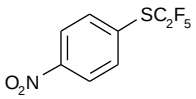


[CAS: 1955495-84-7]

Compound **2l** was prepared following the standard procedure, starting from 4-(acetylamino)benzenediazonium tetrafluoroborate (249 mg, 1.00 mmol). After purification, **2l** was isolated as slightly yellow solid (234 mg, 0.82 mmol, 82%). **m.p.**: 137-138°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.60 (s, 4H), 2.21 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.4 (t, *J* = 4.1 Hz, 3F), –92.3 ppm (q, *J* = 4.1 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.1, 143.4, 139.3 (2C), 121.6 (2C), 121.5 (qt, ^1J(C,F) = 286.8 Hz, ^2J(C,F) = 40.1 Hz), 120.4 (tq, ^1J(C,F) = 285.9 Hz, ^2J(C,F) = 37.1 Hz), 117.3 (t, ^3J(C,F) = 2.9 Hz), 24.1 ppm; **IR** (neat): ν= 3456, 3018, 2975, 1738, 1368, 1229, 1217 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) =

285 [M^+] (40), 243 (35), 124 (100); **HRMS** (EI-TOF) calcd. for $C_{10}H_8NF_5OS$: 285.0247; found: 285.0254.

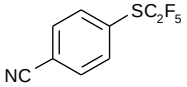
Synthesis of 4-[(pentafluoroethyl)thio]nitrobenzene (2m)



[CAS: 106854-75-5]

Compound **2m** was prepared following the standard procedure, starting from 4-nitrobenzenediazonium tetrafluoroborate (237 mg, 1.00 mmol). After purification, **2m** was isolated as slightly yellow oil (262 mg, 0.96 mmol, 96%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.29 (d, ^3J = 8.8 Hz, 2H), 7.86 ppm (d, ^3J = 8.8 Hz, 2H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.5 (t, J = 3.8 Hz, 3F), –90.8 ppm (q, J = 3.8 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 149.4, 137.5 (2C), 130.8 (t, ^3J(C,F) = 2.7 Hz), 124.2 (2C), 120.0 (qt, ^1J(C,F) = 290.5 Hz, ^2J(C,F) = 41.1 Hz), 118.4 ppm (tq, ^1J(C,F) = 286.5 Hz, ^2J(C,F) = 36.0 Hz); **IR** (neat): ν= 3459, 3003, 2971, 1602, 1524, 1347, 1207, 1103, 956, 851, 750, 729, 685 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 272 [M^+] (56), 243 (98), 206 (12), 124 (100), 108 (30), 96 (12), 80 (21); **HRMS** (EI-TOF) calcd. for $C_8H_4NF_5O_2S$: 272.9883; found: 272.9897.

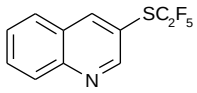
Synthesis of 4-[(pentafluoroethyl)thio]benzonitrile (2n)



[CAS: 1955495-85-8]

Compound **2n** was prepared following the standard procedure, starting from 4-cyanobenzenediazonium tetrafluoroborate (217 mg, 1.00 mmol). After purification, **2n** was isolated as colorless solid (208 mg, 0.82 mmol, 82%). **m.p.**: 45-46°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.79 (d, ^3J = 8.3 Hz, 2H), 7.73 ppm (d, ^3J = 8.8 Hz, 2H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.5 (t, J = 3.4 Hz, 3F), –91.0 ppm (q, J = 3.8 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 137.2 (2C), 132.8 (2C), 128.9 (t, ^3J(C,F) = 2.7 Hz), 120.0 (qt, ^1J(C,F) = 290.6 Hz, ^2J(C,F) = 40.9 Hz), 118.4 (tq, ^1J(C,F) = 287.0 Hz, ^2J(C,F) = 36.3 Hz), 117.5, 115.0 ppm; **IR** (neat): ν= 3073, 3039, 2232, 1487, 1318, 1202, 1092, 959, 851, 830, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 253 [M^+] (100), 184 (69), 134 (94), 102 (13), 90 (16); **HRMS** (EI-TOF) calcd. for $C_9H_4NF_5S$: 252.9985; found: 252.9991.

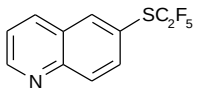
Synthesis of 3-[(pentafluoroethyl)thio]quinoline (2o)



[CAS: 1955495-86-9]

Compound **2o** was prepared following the standard procedure, starting from quinoline-3-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **2o** was isolated as colorless solid (249 mg, 0.89 mmol, 89%). **m.p.**: 35-36°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.00 (s, 1H), 8.49 (s, 1H), 8.14 (d, ^{3}J = 8.5 Hz, 1H), 7.84-7.79 (m, 2H), 8.19 ppm (t, ^{3}J = 7.5 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.5 (t, J = 4.1 Hz, 3F), –91.4 ppm (q, J = 4.1 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.9, 148.4, 145.5, 131.7, 129.5, 128.0, 127.7, 119.6, 120.3 (qt, ^{1}J(C,F) = 289.6 Hz, ^{2}J(C,F) = 40.6 Hz), 118.6 (tq, ^{1}J(C,F) = 286.1 Hz, ^{2}J(C,F) = 36.3 Hz), 116.7 ppm (t, ^{3}J(C,F) = 2.9 Hz); **IR** (neat): ν= 3031, 1972, 1617, 1565, 1489, 1321, 1199, 1090, 948, 786, 748 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 279 [M^+] (87), 160 (100), 116 (14), 89 (31); **HRMS** (EI-TOF) calcd. for $C_{11}H_6NF_5S$: 279.0141; found: 279.0145.

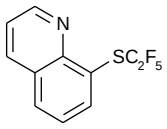
Synthesis of 6-[(pentafluoroethyl)thio]quinoline (2p)



[CAS: 1955495-87-0]

Compound **2p** was prepared following the standard procedure, starting from quinoline-6-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **2p** was isolated as colorless oil (229 mg, 0.82 mmol, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.01 (dd, ^{3}J = 4.3, 1.8 Hz, 1H), 8.19 (d, ^{3}J = 8.8 Hz, 2H), 8.14 (d, ^{3}J = 8.8 Hz, 1H), 7.89 (dd, ^{3}J = 8.8, 1.8 Hz, 1H), 7.48 ppm (dd, ^{3}J = 8.5, 4.3 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.4 (t, J = 3.8 Hz, 3F), –91.5 ppm (q, J = 4.1 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.4, 148.7, 137.7, 136.2, 136.1, 130.8, 128.3, 122.1, 121.1 (t, ^{3}J(C,F) = 2.9 Hz), 120.2 (qt, ^{1}J(C,F) = 289.0 Hz, ^{2}J(C,F) = 40.6 Hz), 118.6 ppm (tq, ^{1}J(C,F) = 286.8 Hz, ^{2}J(C,F) = 36.7 Hz); **IR** (neat): ν= 3037, 1591, 1488, 1331, 1202, 1095, 959, 835, 794, 749, 660 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 279 [M^+] (88), 160 (100), 116 (23); **HRMS** (EI-TOF) calcd. for $C_{11}H_6NF_5S$: 279.0141; found: 279.0130.

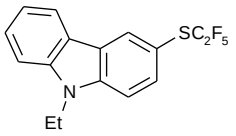
Synthesis of 8-[(pentafluoroethyl)thio]quinoline (2q)



[CAS: 1955495-88-1]

Compound **2q** was prepared following the standard procedure, starting from quinoline-8-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **2q** was isolated as colorless oil (198 mg, 0.71 mmol, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.07 (dd, ^{3}J = 4.3, 1.8 Hz, 1H), 8.21 (dd, ^{3}J = 8.3, 1.5 Hz, 1H), 8.15 (d, ^{3}J = 7.3 Hz, 1H), 7.94 (dd, ^{3}J = 8.0, 1.3 Hz, 1H), 7.58 (t, ^{3}J = 7.8 Hz, 1H), 7.50 ppm (dd, ^{3}J = 8.3, 4.3 Hz, 1H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.6 (t, J = 4.1 Hz, 3F), –91.0 ppm (q, J = 4.1 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.2, 147.9, 137.5, 136.5, 130.9, 130.0, 126.4, 124.3, 122.0, 120.3 (qt, ^{1}J(C,F) = 290.3 Hz, ^{2}J(C,F) = 40.6 Hz), 118.7 ppm (tq, ^{1}J(C,F) = 286.6 Hz, ^{2}J(C,F) = 36.8 Hz); **IR** (neat): ν= 3065, 1596, 1493, 1328, 1204, 1093, 950, 826, 787, 750, 660 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 279 [M^{+}] (80), 160 (100), 116 (15); **HRMS** (EI-TOF) calcd. for $C_{11}H_6NF_5S$: 279.0141; found: 279.0134.

Synthesis of 9-ethyl-3-[(pentafluoroethyl)thio]-9H-carbazole (2r)



[CAS: 1955495-89-2]

Compound **2r** was prepared following the standard procedure, starting from 9-ethyl-9*H*-carbazol-3-diazonium tetrafluoroborate (309 mg, 1.00 mmol). After purification, **2r** was isolated as colorless solid (249 mg, 0.72 mmol, 72%). **m.p.**: 64-65°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.40 (s, 1H), 8.14 (d, ^{3}J = 7.8 Hz, 1H), 7.73 (dd, ^{3}J = 8.5, 1.8 Hz, 1H), 7.55 (dt, ^{3}J = 7.7, 1.1 Hz, 1H), 7.44 (t, ^{3}J = 8.8 Hz, 2H), 7.32 (t, ^{3}J = 7.8 Hz, 1H), 4.38 (q, ^{3}J = 7.3 Hz, 2H), 1.47 ppm (t, ^{3}J = 7.3 Hz, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.2 (t, J = 4.1 Hz, 3F), –92.7 ppm (q, J = 3.6 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.1, 140.3, 134.3, 130.2, 126.6, 123.9, 122.2, 120.7, 120.2 (qt, ^{1}J(C,F) = 287.9 Hz, ^{2}J(C,F) = 40.0 Hz), 119.8, 118.8 (tq, ^{1}J(C,F) = 287.0 Hz, ^{2}J(C,F) = 37.2 Hz), 110.7 (t, ^{3}J(C,F) = 3.1 Hz), 109.2, 108.9, 37.7, 13.8 ppm; **IR** (neat): ν= 3055, 2975, 1588, 1474, 1330, 1200, 1074, 958, 884, 798, 742,

654 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 345 [M^+] (54), 330 (12), 226 (100), 211 (27), 197 (14), 167 (16); **HRMS** (EI-TOF) calcd. for $C_{16}H_{12}NF_5S$: 345.0611; found: 345.0616.

Synthesis of methyl-3-[(pentafluoroethyl)thio]thiophene-2-carboxylate (2s)

[CAS: 1955495-90-5]

Compound **2s** was prepared following the standard procedure, starting from 2-(methoxycarbonyl)thiophene-3-diazonium tetrafluoroborate (256 mg, 1.00 mmol). After purification, **2s** was isolated as colorless oil (286 mg, 0.98 mmol, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.59 (d, ^3J = 5.3 Hz, 1H), 7.30 (d, ^3J = 5.3 Hz, 1H), 3.92 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = –82.8 (t, J = 4.1 Hz, 3F), –91.2 ppm (q, J = 4.1 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.3, 132.6, 132.2 (t, ^3J(C,F) = 2.7 Hz), 131.0, 126.6 (t, ^3J(C,F) = 1.8 Hz), 120.3 (qt, ^1J(C,F) = 291.9 Hz, ^2J(C,F) = 41.3 Hz), 118.1 (tq, ^1J(C,F) = 287.0 Hz, ^2J(C,F) = 35.8 Hz), 52.5 ppm; **IR** (neat): ν= 2955, 1709, 1502, 1439, 1266, 1204, 1075, 958, 893, 793, 768, 750 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 291 [M^+] (95), 261 (52), 172 (100), 142 (43), 114 (20); **HRMS** (EI-TOF) calcd. for $C_8H_5F_5O_2S_2$: 291.9651; found: 291.9675.

6.6 Synthesis of perfluoroalkyl thioethers by iron-catalysed decarboxylation of potassium perfluorocarboxylates

6.6.1 Formation of pentafluoroethane through the protodecarboxylation of potassium pentafluoropropionate with starting materials containing acidic protons

The reactions were performed in a 0.50 mmol scale using the optimised reaction conditions with 2,2,2-trifluoroethanol as an internal standard. After the reaction, the mixture was diluted with ethyl acetate (3 mL) and the mixture was filtered through a short pad of celite directly into an NMR tube. Although small quantities of pentafluoroethane[127] were also formed in the control reaction with a starting material without acidic protons, probably originating from traces of water (**1a**, Figure S1), the amount increases considerably for compounds containing them (**1t+u**, Figures S2 and S3).

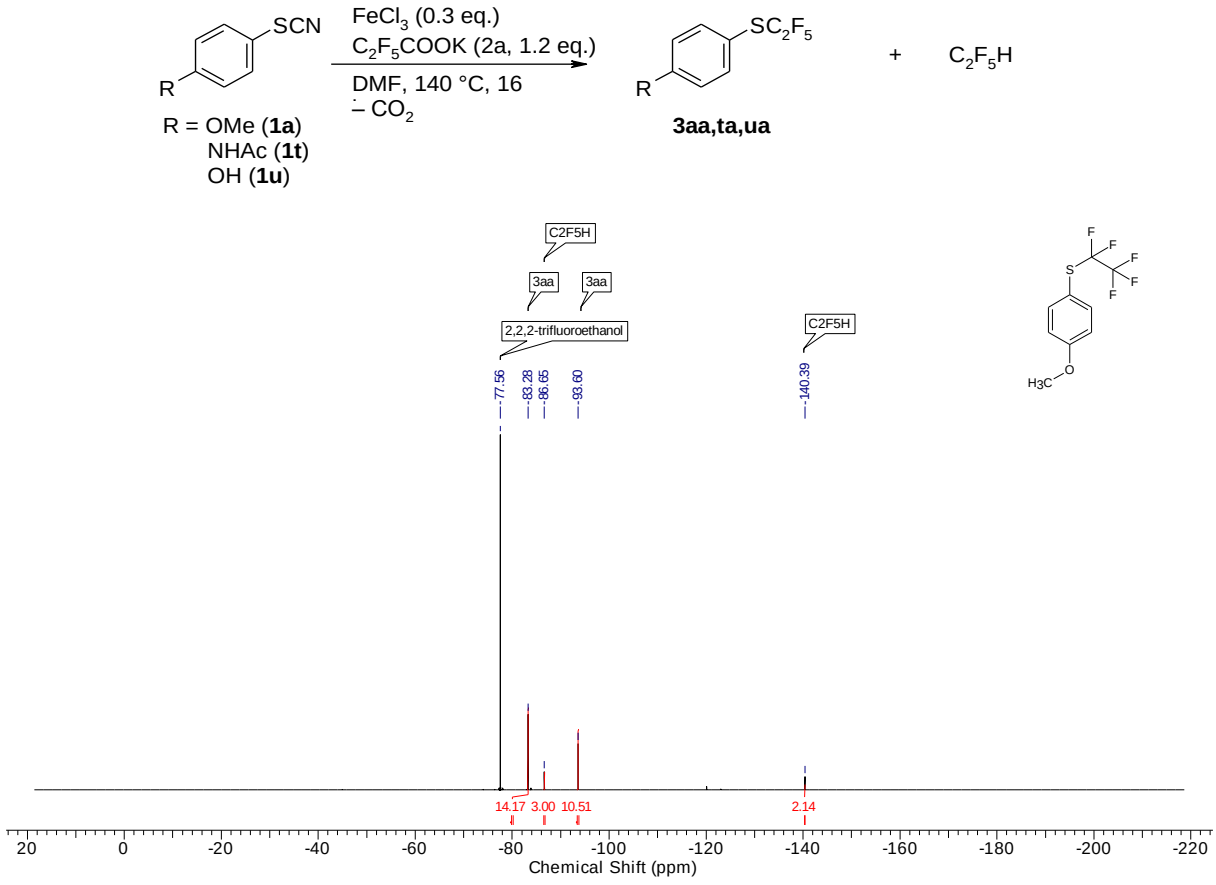


Figure S 1: ^{19}F spectrum of the reaction mixture starting from **1a**.

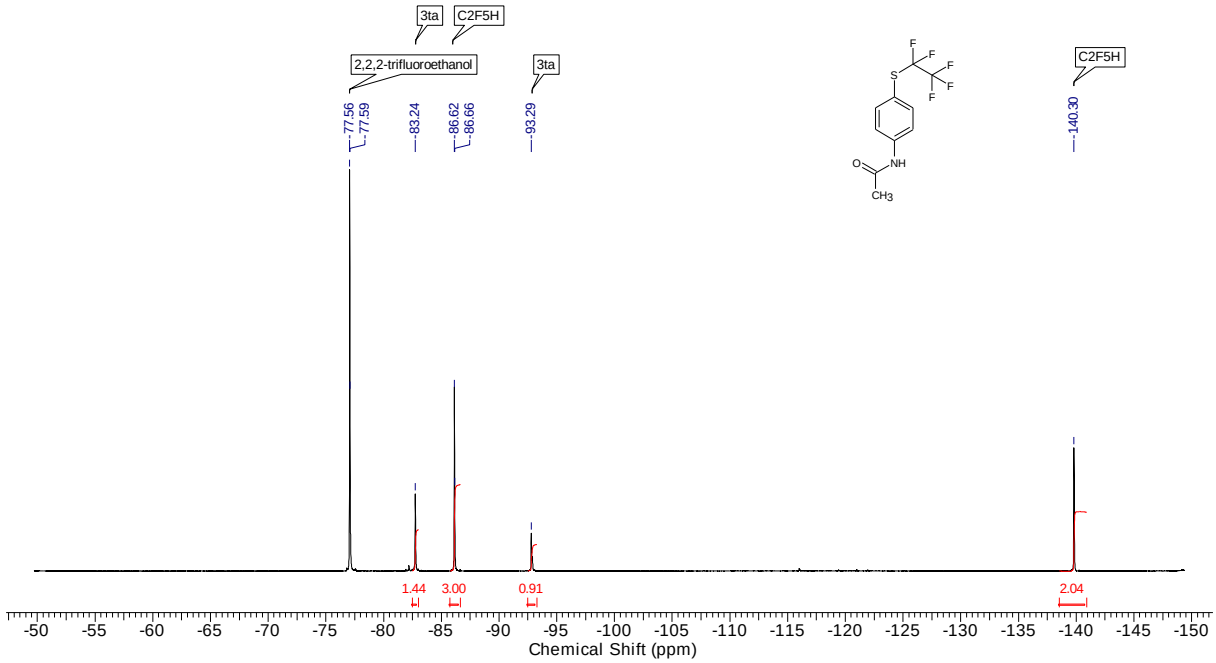


Figure S 2: ^{19}F spectrum of the reaction mixture starting from **1t**.

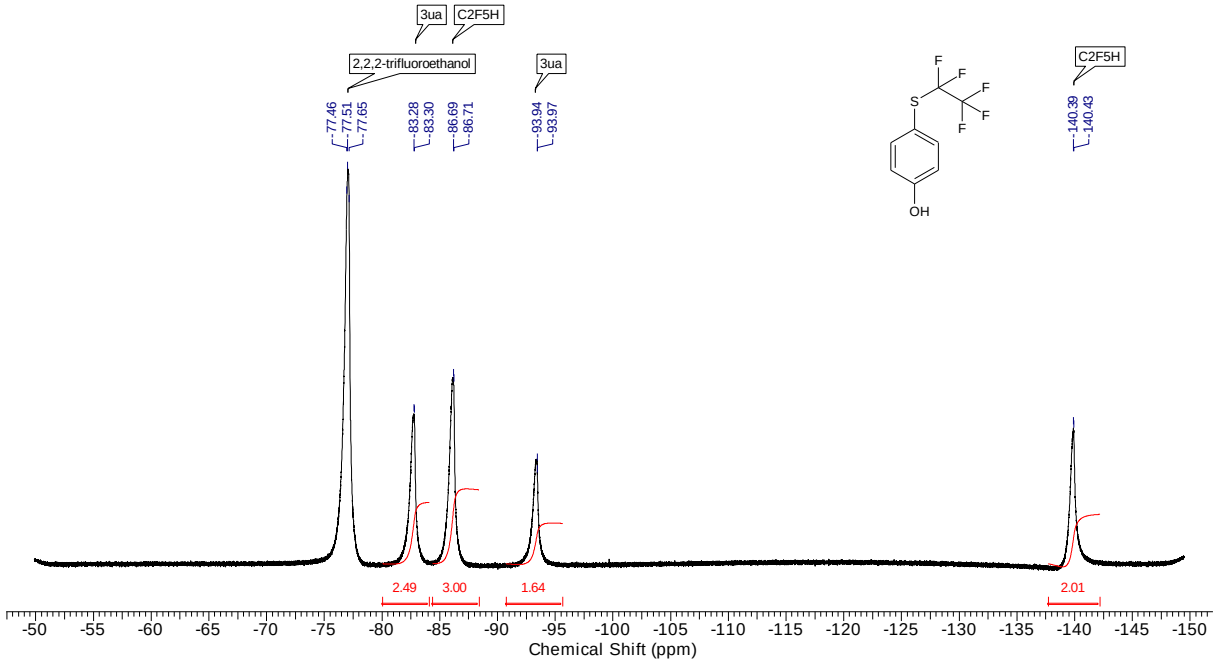


Figure S 3: ^{19}F spectrum of the reaction mixture starting from **1u**.

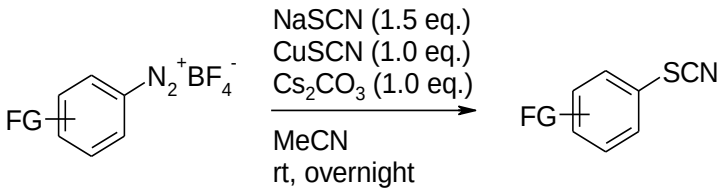
6.6.2 Synthesis of Starting Materials

Synthesis of arene diazonium tetrafluoroborates

In a 50 mL round-bottomed flask, the aniline (20 mmol) was dissolved in a mixture of absolute ethanol (20 mL) and an aqueous solution of HBF_4 (50%, 5.0 mL, 40 mmol). Afterwards *tert*-butyl nitrite (4.8 mL, 40 mmol) was added dropwise to the solution at 0 °C. The reaction was stirred at room temperature for 1 h, followed by the addition of diethyl ether (50 mL) to precipitate the arenediazonium tetrafluoroborate that was then filtered off and washed with diethyl ether (3 × 20 mL). After it had been dried in vacuo (10^{-3} mbar) for 10 minutes, it was directly used without further purification.

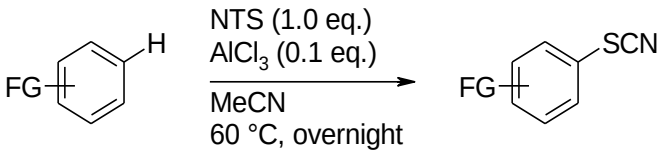
6.6.2.1 Synthesis of aryl thiocyanates

Procedure A, starting from the corresponding arenediazonium tetrafluoroborates:



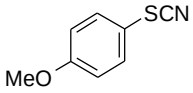
Caesium carbonate (1.0 eq.), sodium thiocyanate (1.5 eq.), and copper(I) thiocyanate (1.0 eq.) were suspended in acetonitrile (0.67 M), and the mixture was cooled to 0 °C. To this suspension was added dropwise a solution of the arenediazonium salt (1.0 –1.2 eq.) in acetonitrile (0.40 M), and the resulting mixture was first stirred for 1 h at 0 °C and then overnight at room temperature. Afterwards diethyl ether (30 mL) was added and the precipitate was filtered off. The filtrate was washed with water (2 × 30 mL) and the organic layer was dried with magnesium sulphate. The product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate gradient).

Procedure B, starting from the corresponding simple arenes:



The corresponding arene (1.0 eq.), aluminium chloride (0.1 eq.), and *N*-thiocyanatosuccinimide (1.0 eq.) were dissolved in acetonitrile (0.6 M) and heated to 60 °C overnight. Afterwards diethyl ether (30 mL) was added and the precipitate was filtered off. The filtrate was washed with water (2 × 30 mL) and the organic layer was dried with magnesium sulphate. The product was purified by column chromatography (ethyl acetate/cyclohexane gradient).[128]

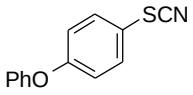
Synthesis of 4-methoxyphenyl thiocyanate (1a)



[CAS: 5285-90-5]

Compound **1a** was prepared following procedure **A** starting from Cs_2CO_3 (14.4 g, 44.3 mmol), NaSCN (5.50 g, 66.4 mmol), CuSCN (5.44 g, 44.3 mmol), and 4-methoxybenzenediazonium tetrafluoroborate [CAS: 459-64-3] (16.9 g, 53.2 mmol). After purification, **1a** was obtained as yellow liquid. The analytical data matched the one reported previously.[129]

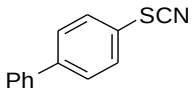
Synthesis of 4-phenoxyphenyl thiocyanate (1b)



[CAS: 96460-69-4]

Compound **1b** was prepared following procedure **A** starting from Cs_2CO_3 (4.83 g, 14.8 mmol), NaSCN (1.84 g, 22.2 mmol), CuSCN (1.82 g, 14.8 mmol), and 4-phenoxybenzenediazonium tetrafluoroborate [CAS: 330-87-0] (5.04 g, 17.8 mmol). After purification, **1b** was obtained as orange liquid. The analytical data matched the one reported previously.[129]

Synthesis of [1,1'-biphenyl]-4-yl thiocyanate (1c)

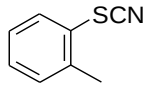


[CAS: 99847-27-5]

Compound **1c** was prepared following procedure **A** starting from Cs_2CO_3 (2.61 g, 8.01 mmol), NaSCN (994 mg, 12.0 mmol), CuSCN (984 mg, 8.01 mmol), and [1,1'-biphenyl]-4-diazonium tetrafluoroborate [CAS: 52053-64-2] (2.17 g, 8.09 mmol). After purification, **1c** was obtained as orange solid.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.68–7.56 (m, 6H), 7.51–7.37 ppm (m, 3H); **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 143.0, 139.5, 127.1, 130.8, 129.2, 129.0, 128.3, 127.3, 123.1, 111.4 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 211 (100) [M^+], 210 (53), 183 (12), 152 (18), 102 (7), 74 (6), 50 (11); **m.p.:** 80–81 °C.

Synthesis of 2-methylphenyl thiocyanate (1d)

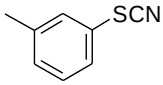


[CAS: 5285-88-1]

Compound **1d** was prepared following procedure **A** starting from Cs_2CO_3 (5.19 g, 15.9 mmol), NaSCN (1.97 g, 23.9 mmol), CuSCN (1.95 g, 15.9 mmol), and 2-methylbenzenediazonium tetrafluoroborate [CAS: 2093-46-1] (3.93 g, 19.1 mmol). After purification, **1d** was obtained as yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.36–7.24 (m, 3H), 2.47 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 139.4, 132.0, 131.5, 130.3, 127.9, 123.7, 110.6, 20.5 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 149 (100) [M^+], 122 (41), 121 (60), 91 (15), 89 (15), 65 (23), 63 (15); **HRMS** (EI-TOF) calcd. for C_8H_7NS: 149.0299; found: 149.0307.

Synthesis of 3-methylphenyl thiocyanate (1e)

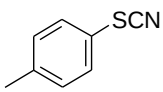


[CAS: 5285-89-2]

Compound **1e** was prepared following procedure **A** starting from Cs_2CO_3 (4.89 g, 15.0 mmol), NaSCN (1.86 g, 22.5 mmol), CuSCN (1.84 g, 15.0 mmol), and 3-methylbenzenediazonium tetrafluoroborate [CAS: 1422-76-0] (3.71 g, 18.0 mmol). After purification, **1e** was obtained as yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 7.31 (m, 2H), 7.21 (m, 1H), 2.38 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.6, 130.6, 130.5, 130.1, 127.2, 124.1, 110.9, 21.4 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 150 (13), 149 (100) [M^+], 148 (13), 116 (72), 91 (33), 65 (21), 63 (11).

Synthesis of 4-methylphenyl thiocyanate (1f)

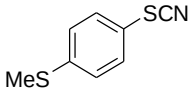


[CAS: 5285-74-5]

Compound **1f** was prepared following procedure **A** starting from Cs_2CO_3 (5.09 g, 15.6 mmol), NaSCN (1.94 g, 23.4 mmol), CuSCN (1.92 g, 15.6 mmol), and 4-methylbenzenediazonium tetrafluoroborate [CAS: 459-44-9] (3.85 g, 18.7 mmol). After purification, **1f** was obtained as yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 2H), 7.23 (m, 2H), 2.37 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.4, 131.1, 130.8, 120.6, 111.2, 21.3 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 150 (11), 149 (100) [M^+], 116 (51), 91 (58), 89 (12), 65 (24), 63 (12); **HRMS** (EI-TOF) calcd. for C_8H_7NS: 149.0299; found: 149.0302.[130]

Synthesis of 4-(methylthio)phenyl thiocyanate (1g)

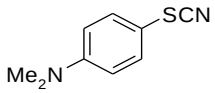


[CAS: 5285-91-6]

Compound **1g** was prepared following procedure **A** starting from Cs_2CO_3 (5.25 g, 16.1 mmol), NaSCN (2.00 g, 24.2 mmol), CuSCN (1.98 g, 16.1 mmol), and 4-(methylthio)benzenediazonium tetrafluoroborate [CAS: 69209-17-2] (4.60 g, 19.3 mmol). After purification, **1g** was obtained as red liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (m, 2H), 7.23 (m, 2H) 2.46 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.1, 131.2, 127.1, 119.2, 110.8, 15.1 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 182 (16), 181 (100) [M^+], 166 (61), 135 (12), 108 (19), 69 (16), 45 (21); **HRMS** (EI-TOF) calcd. for $C_8H_7F_3OS$: 180.0020; found: 180.0018.

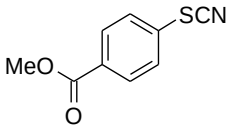
Synthesis of 4-(dimethylamino)phenyl thiocyanate (1h)



[CAS: 7152-80-9]

Compound **1h** was prepared following procedure **A** starting from Cs_2CO_3 (2.62 g, 8.02 mmol), NaSCN (995 mg, 12.0 mmol), CuSCN (985 mg, 8.02 mmol), and 4-(dimethylamino)benzenediazonium tetrafluoroborate [CAS: 33271-82-8] (2.17 g, 9.22 mmol). After purification, **1h** was obtained as orange solid. The analytical data matched the one reported previously.[129]

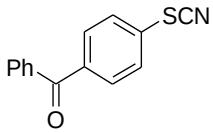
Synthesis of methyl 4-thiocyanatobenzoate (1i)



[CAS: 1879-22-7]

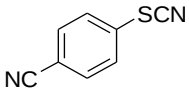
Compound **1i** was prepared following procedure **A** starting from Cs_2CO_3 (2.62 g, 8.03 mmol), NaSCN (996 mg, 12.0 mmol), CuSCN (987 mg, 8.03 mmol), and 4-methoxycarbonylbenzenediazonium tetrafluoroborate [CAS: 1879-22-7] (8.67 g, 8.67 mmol). After purification, **1i** was obtained as pale orange solid. The analytical data matched the one reported previously.

Synthesis of 4-benzoylphenyl thiocyanate (1j)



Compound **1j** was prepared following procedure **A** starting from Cs_2CO_3 (5.38 g, 16.5 mmol), NaSCN (2.05 g, 24.8 mmol), CuSCN (2.03 g, 16.5 mmol), and 4-benzoylbenzenediazonium tetrafluoroborate [CAS: 38246-74-1] (5.87 g, 19.8 mmol). After purification, **1j** was obtained as orange solid. The analytical data matched the one reported previously.[129]

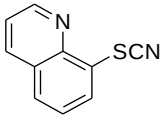
Synthesis of 4-cyanophenyl thiocyanate (1k)



[CAS: 122148-91-8]

Compound **1k** was prepared following procedure **A** starting from Cs_2CO_3 (2.61 g, 8.00 mmol), NaSCN (993 mg, 12.0 mmol), CuSCN (983 g, 8.00 mmol), and 4-cyanobenzenediazonium tetrafluoroborate [CAS: 2252-32-6] (1.74 g, 8.00 mmol). After purification, **1k** was obtained as light-yellow solid. The analytical data matched the one reported previously.[129]

Synthesis of 8-quinolinyl thiocyanate (1l)

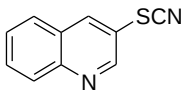


[CAS: 16671-93-5]

Compound **1l** was prepared following procedure **A** starting from Cs_2CO_3 (4.89 g, 15.0 mmol), NaSCN (1.86 g, 22.5 mmol), CuSCN (1.84 g, 15.0 mmol), and 8-quinolinediazonium tetrafluoroborate [CAS: 27388-19-8] (4.37 g, 18.0 mmol). After purification, **1l** was obtained as colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.90 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.23 (dd, *J* = 8.4, 1.9 Hz, 1H), 8.05 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.82 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.63 (t, *J* = 7.9 Hz, 1H), 7.54 ppm (dd, *J* = 8.3, 4.3 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 150.1, 144.2, 136.5, 128.5, 127.7, 127.5, 127.4, 126.6, 122.8, 111.4 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 188 (6), 187 (21), 186 (100) [M^+], 159 (11), 142 (38), 3640 (9), 2414 (6); **m.p.:** 90–91 °C.

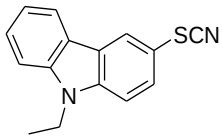
Synthesis of 3-quinolinyl thiocyanate (1m)



[CAS: 2645-26-3]

Compound **1m** was prepared following procedure **A** starting from Cs_2CO_3 (2.91 g, 8.92 mmol), NaSCN (1.11 g, 13.4 mmol), CuSCN (1.10 g, 8.92 mmol), and 3-quinolinediazonium tetrafluoroborate (2.17 g, 8.92 mmol). After purification, **1m** was obtained as colourless solid. The analytical data matched the one reported previously.[129]

Synthesis of 9-ethyl-9*H*-carbazol-3-yl thiocyanate (1n)

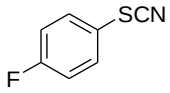


Compound **1n** was prepared following procedure **A** starting from Cs_2CO_3 (2.29 g, 7.01 mmol), NaSCN (870 mg, 10.5 mmol), CuSCN (861 mg, 7.01 mmol), and 9-ethyl-9*H*-carbazol-3-diazonium tetrafluoroborate [CAS: 115771-91-0] (2.17 g, 7.01 mmol). After purification, **1n** was obtained as orange solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 1.5 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.53 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 4.10 (q, 7.2 Hz, 2H), 1.30 ppm (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.0 (2 signals), 123.1, 126.6, 124.9, 123.9, 121.4, 120.4, 119.6, 112.4, 110.8, 109.8, 108.7, 37.3,

13.5 ppm; **IR** (neat): $\tilde{\nu}$ = 3050, 2973, 2147, 1619, 1588, 1492, 1467, 1450, 1379, 1347, 1321, 1287, 1276, 1232, 1149, 1126, 1089, 1057, 1022, 942, 898, 799, 785, 741, 723, 685 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 253 (11), 252 (65) [M^+], 238 (18), 237 (100), 179 (18).

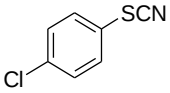
Synthesis of 4-fluorophenyl thiocyanate (1o)



[CAS: 2924-02-9]

Compound **1o** was prepared following procedure **A** starting from Cs_2CO_3 (5.35 g, 16.4 mmol), NaSCN (2.04 g, 24.6 mmol), CuSCN (2.01 g, 16.4 mmol), and 4-fluorobenzenediazonium tetrafluoroborate [CAS: 159-45-0] (3.73 g, 15.7 mmol). After purification, **1o** was obtained as yellow liquid. The analytical data matched the one reported previously.[129]

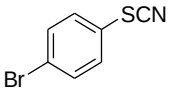
Synthesis of 4-chlorophenyl thiocyanate (1p)



[CAS: 3226-37-7]

Compound **1p** was prepared following procedure **A** starting from Cs_2CO_3 (4.57 g, 14.0 mmol), NaSCN (1.74 g, 21.0 mmol), CuSCN (1.72 g, 14.0 mmol), and 4-chlorobenzenediazonium tetrafluoroborate [CAS: 673-41-6] (3.80 g, 16.8 mmol). After purification, **1p** was obtained as yellow liquid. The analytical data matched the one reported previously.[129]

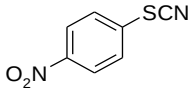
Synthesis of 4-bromophenyl thiocyanate (1q)



[CAS: 3226-41-3]

Compound **1q** was prepared following procedure **A** starting from Cs_2CO_3 (2.61 g, 8.00 mmol), NaSCN (993 mg, 12.0 mmol), CuSCN (983 mg, 8.00 mmol), and 4-bromobenzenediazonium tetrafluoroborate [CAS: 673-40-5] (2.17 g, 8.00 mmol). After purification, **1q** was obtained as pale yellow solid. The analytical data matched the one reported previously.[129]

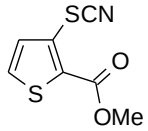
Synthesis of 4-nitrophenyl thiocyanate (1r)



[CAS: 3226-41-3]

Compound **1ir** was prepared following procedure **A** starting from Cs_2CO_3 (4.27 g, 13.1 mmol), NaSCN (16.3 g, 19.7 mmol), CuSCN (16.1 g, 13.1 mmol), and 4-nitrobenzenediazonium tetrafluoroborate [CAS: 456-27-9] (3.73 g, 15.7 mmol). After purification, **1ir** was obtained as pale yellow solid. The analytical data matched the one reported previously.[129]

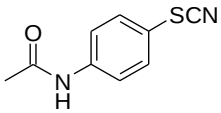
Synthesis of methyl-3-thiocyanatothiophene-2-carboxylate (1s)



[CAS: 1369794-51-3]

Compound **1s** was prepared following procedure **A** starting from Cs_2CO_3 (5.41 g, 16.6 mmol), NaSCN (2.06 g, 24.9 mmol), CuSCN (2.04 g, 16.6 mmol), and 2-(methoxycarbonyl)-3-thiophenediazonium tetrafluoroborate [CAS: 100421-50-9] (5.09 g, 19.9 mmol). After purification, **1s** was obtained as colourless solid. The analytical data matched the one reported previously.[129]

Synthesis of 4-(acetylamino)phenyl thiocyanate (1t)



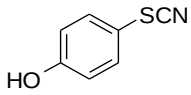
[CAS: 3321-94-6]

Compound **1t** was prepared following procedure **A** starting from Cs_2CO_3 (2.60 g, 7.98 mmol), NaSCN (990 mg, 12.0 mmol), CuSCN (980 mg, 7.98 mmol), and 4-(acetylamino)benzenediazonium tetrafluoroborate [CAS: 332-39-8] (2.17 g, 8.70 mmol). After purification, **1t** was obtained as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, 8.5 Hz, 2H), 7.50 (m, 2H), 7.36 (s, 1H), 2.20 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.5, 139.7, 132.1, 121.0, 118.1, 111.0, 24.7 ppm; **IR** (neat): $\tilde{\nu}$ = 3246, 3176, 3105, 3052, 2151, 1667, 1608, 1585, 1529, 1490, 1477,

1394, 1366, 1314, 1262, 1175, 1086, 1009, 967, 828, 756, 715, 706, 675 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 193 (13), 192 (40) [M^+], 151 (10), 150 (100), 123 (11), 118 (11), 43 (16).

Synthesis of 4-hydroxyphenyl thiocyanate (1u)



[CAS: 3774-52-5]

Compound **1u** was prepared following procedure **B** starting from $AlCl_3$ (133 mg, 1.00 mmol), *N*-thiocyanatosuccinimide (3.12 g, 20.0 mmol) and phenol (941 mg, 10.0 mmol). After purification, **1u** was obtained as colourless solid. The analytical data matched the one reported previously.[129]

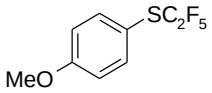
6.6.3 Synthesis of potassium carboxylates

Potassium *tert*-butoxid (1.0 eq.) was dissolved in ethanol (4 M) and the corresponding acid (1 eq.) was added dropwise, either pure for liquid acids or dissolved in a small amount of ethanol for solid ones. After stirring the solution for 1 h, the solvent was removed under reduced pressure (50 mbar, 40 °C) and diethyl ether (50 mL) was added. The solid was filtered off, washed with diethyl ether (3 × 20 mL) and dried under vacuum.

6.6.4 Synthesis of pentafluoroethyl thioethers from aryl thiocyanates

Standard procedure: An oven-dried 20 mL crimp-cap vessel with stir bar was charged with the potassium carboxylate (2.40 mmol), the aryl thiocyanate (2.00 mmol), iron(III) chloride (97.3 mg, 0.60 mmol) and DMF (6 mL). The reaction mixture was stirred for 16 h at 140 °C. To prevent the crimp cap from flying off, the upper half of the vessel was cooled with water and the evolving CO_2 pressure was released through a bubbler. After the reaction, the mixture was diluted with diethyl ether (20 mL), and subsequently washed with 20% (*m*/*m*) aq. LiCl solution (20 mL), water (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate gradient), yielding the aryl pentafluoroethyl thioethers. The yields of particularly volatile compounds were determined by ^{19}F NMR, and their identity by mass spectroscopy.

Synthesis of 1-methoxy-4-[(pentafluoroethyl)thio]benzene (3aa)

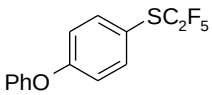


[CAS: 1955495-78-9]

Compound **3aa** was prepared following the standard procedure, starting from Synthesis of **4-methoxyphenyl thiocyanate (1a)** (**1a,** 330 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3aa** was isolated as colourless oil (501 mg, 1.94 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (m, 2H), 6.93 (m, 2H), 3.84 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.2, 139.1, 120.2 (tq, *J* = 288.0, 40.0 Hz), 119.0 (qt, *J* = 285.7, 37.2 Hz), 115.1, 113.2 (t, *J* = 3.2 Hz), 55.5 ppm; **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –83.3 (t, *J* = 4.1 Hz, 3F), –93.6 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 2971, 2947, 1740, 1594, 1574, 1496, 1464, 1443, 1366, 1333, 1294, 1254, 1206, 1175, 1104, 1088, 1032, 960, 829, 800, 750, 652 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 259 (10), 258 (100) [M$^+$], 140 (8), 139 (87), 96 (10), 95 (15), 69 (15); **HRMS** (EI-TOF) calcd. for $C_9H_7F_5OS$: 258.0138; found: 258.0143.

Synthesis of 1-phenoxy-4-[(pentafluoroethyl)thio]benzene (3ba)

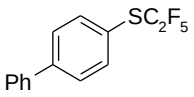


[CAS: 1955495-80-3]

Compound **3ba** was prepared following the standard procedure, starting from Synthesis of **4-methoxyphenyl thiocyanate (1a)** (**1b,** 455 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ba** was isolated as colourless oil (628 mg, 1.96 mmol, 98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (m, 2H), 7.40 (m, 2H), 7.21 (t, 1H), 7.08 (m, 2H), 7.00 ppm (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.7, 155.7, 139.2, 130.2, 124.8, 120.3, 120.2 (tq, *J* = 289.1, 38.6 Hz), 118.9 (qt, *J* = 288.5, 38.5 Hz) 118.7, 115.6 ppm (t, *J* = 3.2 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.3 (t, *J* = 3.4 Hz, 3F), –92.5 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3043, 1582, 1485, 1331, 1242, 1200, 1085, 957, 869, 833, 749, 691 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 321 (16), 320 (100) [M^+], 202 (8), 201 (53), 129 (9), 77 (13), 51 (10); **HRMS** (EI-TOF) calcd. for $C_{14}H_9F_5OS$: 320.0294; found: 320.0279.

Synthesis of 4-[(pentafluoroethyl)thio]-1,1'-biphenyl (3ca)

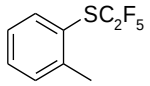


[CAS: 933673-37-1]

Compound **3ca** was prepared following the standard procedure, starting from [1,1'-biphenyl]-4-yl thiocyanate (**1c**, 423 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ca** was isolated as colourless solid (584 mg, 1.92 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.77 (m, 2H), 7.69–7.65 (m, 4H), 7.56–7.51 (m, 2H), 7.49–7.44 ppm (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.2, 139.7, 137.7, 129.1, 128.4, 128.2, 127.4, 121.6 (t, *J* = 2.6 Hz), 120.4 (tq, *J* = 288.9, 40.4 Hz), 119.0 ppm (qt, *J* = 286.5, 37.1 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.3 (t, *J* = 3.4 Hz, 3F), –91.7 ppm (q, J = 4.1 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3033, 1479, 1333, 1200, 1086, 961, 836, 751, 717, 688 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 305 (17), 304 (100) [M^+], 186 (8), 185 (54), 184 (10), 152 (11), 69 (9); **HRMS** (EI-TOF) calcd. for $C_{14}H_9F_5S$: 304.0345; found: 304.0368; **m.p.**: 60–61 °C.

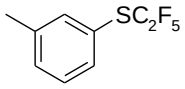
Synthesis of 1-methyl-2-[(pentafluoroethyl)thio]benzene (3da)



Compound **3da** was prepared following the standard procedure, starting from 2-methylphenyl thiocyanate (**1d**, 74.6 mg, 0.50 mmol) and potassium pentafluoropropionate (**2a**, 222 mg, 0.60 mmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36.0 µL, 0.50 mmol) was added to the reaction mixture. The pentafluoroethylthioether **3da** was formed in 87% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (377 MHz, DMF/EtOAc): δ = –82.7 (t, *J* = 3.4 Hz, 3F), –91.2 ppm (q, *J* = 3.6 Hz, 2F); **MS** (Ion trap, EI, 70 eV): m/z (%) = 243 (9), 242 (100) [M^+], 123 (62), 91 (7), 77 (11), 69 (15), 45 (45).

Synthesis of 1-methyl-3-[(pentafluoroethyl)thio]benzene (3ea)

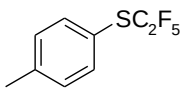


[CAS: 1955495-79-0]

Compound **3ea** was prepared following the standard procedure, starting from 3-methylphenyl thiocyanate (**1e**, 298 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ea** was isolated as colourless oil (460 mg, 1.90 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.47 (m, 2H), 7.33–7.32 (m, 2H), 2.40 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 139.6, 137.9, 134.4, 132.0, 129.4, 122.6 (t, *J* = 2.7 Hz), 120.4 (tq, *J* = 288.6, 40.2 Hz), 119.0 (qt, *J* = 286.5, 36.8 Hz) 21.2 ppm; **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.4 (t, *J* = 4.1 Hz, 3F), –91.7 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3053, 2929, 1595, 1478, 1318, 1202, 1096, 958, 780, 750, 692, 650 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 242 (100) [M^+], 173 (14), 123 (41), 91 (11), 77 (11), 69 (15), 45 (27); **HRMS** (EI-TOF) calcd. for $C_9H_7F_5S$: 242.0189; found: 242.0183.

Synthesis of 1-methyl-2-[(pentafluoroethyl)thio]benzene (3fa)

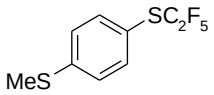


[CAS: 159597-07-6]

Compound **3fa** was prepared following the standard procedure, starting from 4-methylphenyl thiocyanate (**1f**, 74.6 mg, 0.50 mmol) and potassium pentafluoropropionate (**2a**, 222 mg, 0.60 mmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36.0 µL, 0.50 mmol) was added to the reaction mixture. The pentafluoroethylthioether **3fa** was formed in 99% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (377 MHz, DMF/EtOAc): δ = –82.4 (t, *J* = 3.4 Hz, 3F), –92.0 ppm (q, *J* = 3.6 Hz, 2F); **MS** (Ion trap, EI, 70 eV): m/z (%) = 243 (10), 242 (100) [M$^+$], 123 (71), 79 (13), 77 (11), 69 (16), 45 (23).

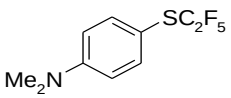
Synthesis of 1-methylthio-4-[(pentafluoroethyl)thio]benzene (3ga)



Compound **3ga** was prepared following the standard procedure, starting from 4-methylthiophenyl thiocyanate (**1g**, 363 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ga** was isolated as colourless oil (527 mg, 1.92 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.51 (m, 2H), 7.24–7.21 (m, 2H), 2.48 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 143.8, 137.6, 126.3, 120.2 (tq, *J* = 288.5, 40.6 Hz), 118.9 (qt, *J* = 286.5, 36.8 Hz), 118.1 (t, *J* = 2.9 Hz), 15.0 ppm; **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.3 (t, *J* = 3.4 Hz, 3F), –92.2 ppm (q, *J* = 3.2 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 2925, 1578, 1479, 1439, 1393, 1331, 1320, 1203, 1089, 1014, 955, 812, 749, 720, 707 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 276 (10), 275 (11), 274 (100) [M$^+$], 155 (69), 140 (8), 69 (16), 45 (8); **HRMS** (EI-TOF) calcd. for $C_9H_7F_5S_2$: 273.9909; found: 273.9910.

Synthesis of *N*,*N*-dimethyl-4-[(pentafluoroethyl)thio]benzenamine (3ha)



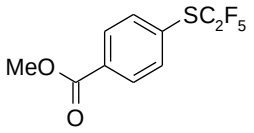
[CAS: 1955495-83-6]

Compound **3ha** was prepared following the standard procedure, starting from 4-(dimethylamino)phenyl thiocyanate (**1h**, 357 mg, 2.00 mmol) and potassium

pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ha** was isolated as colourless oil (521 mg, 1.92 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.47 (m, 2H), 6.71–6.67 (m, 2H), 3.02 ppm (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.1, 138.7, 120.2 (tq, *J* = 287.0, 39.8 Hz), 119.1 (qt, *J* = 286.4, 37.5 Hz), 112.4, 106.5 (t, *J* = 3.3 Hz), 40.1 ppm; **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.3 (t, *J* = 3.7 Hz, 3F), –93.3 ppm (q, *J* = 4.0 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 2895, 1594, 1509, 1447, 1365, 1330, 1194, 1086, 956, 811, 749, 650 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 271 [M^+] (19), 257 (38), 152 (49), 138 (100), 109 (26), 104 (20), 82 (29), 62 (40); **HRMS** (EI-TOF) calcd. for $C_{10}H_{10}F_5NS$: 271.0454; found: 271.0450.

Synthesis of methyl-4-[(pentafluoroethyl)thio]benzoate (3ia)

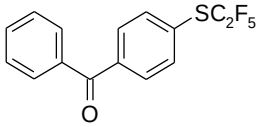


[CAS: 1955495-82-5]

Compound **3ia** was prepared following the standard procedure, starting from 4-thiocyanatobenzoate (**1i**, 386 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ia** was isolated as colourless oil (521 mg, 1.82 mmol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (m, 2H), 7.72 (m, 2H), 3.94 ppm (s, 3H); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.3 (t, *J* = 3.4 Hz, 3F), –91.0 ppm (q, *J* = 3.6 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.2, 136.9, 132.6, 130.5, 128.4 (t, *J* = 2.7 Hz), 120.2 (tq, *J* = 289.8, 41.1 Hz), 118.7 (qt, *J* = 287.0, 36.5 Hz), 52.6 ppm**;** **IR** (neat): $\tilde{\nu}$ = 2954, 1731, 1599, 1438, 1332, 1284, 1214, 1107, 962, 764 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 287 (8) [M^+], 286 (67), 256 (10), 255 (100), 136 (17), 108 (11), 69 (12); **HRMS** (EI-TOF) calcd. for $C_{10}H_7F_5O_2S$: 286.0087; found: 286.0105.

Synthesis of 4-[(pentafluoroethyl)thio]benzophenone (3ja)

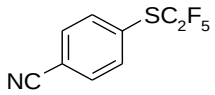


[CAS: 1955495-81-4]

Compound **3ja** was prepared following the standard procedure, starting from 4-benzoylphenyl thiocyanate (**1j**, 479 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ja** was isolated as colourless solid (645 mg, 1.94 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.76 (m, 6H), 7.65–7.61 (m, 1H), 7.53–7.49 ppm (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 195.7, 139.9, 136.7, 136.9, 136.8, 133.2, 130.7, 130.2, 128.7, 127.6 (t, *J* = 2.7 Hz), 120.3 (tq, *J* = 289.5, 41.3 Hz), 118.8 ppm (qt, *J* = 286.7, 36.7 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.4 (t, *J* = 3.4 Hz, 3F), –91.1 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 2929, 1651, 1597, 1449, 1396, 1375, 1334, 1280, 1201, 1105, 961, 925, 849, 792, 752, 731, 695, 663 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 333 (18), 332 (100) [M^+], 255 (38), 105 (49), 77 (24) 51 (12), 50 (10); **HRMS** (EI-TOF) calcd. for $C_{15}H_9F_5OS$: 332.0296; found: 332.0288; **m.p.**: 56–57°C.

Synthesis of 4-[(pentafluoroethyl)thio]benzonitrile (3ka)

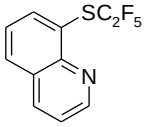


[CAS: 1955495-85-8]

Compound **3ka** was prepared following the standard procedure, starting from 4-cyanophenyl thiocyanate (**1k**, 320 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ka** was isolated as colourless solid (481 mg, 0.82 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.76 (m, 2H), 7.74–7.70 ppm (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 137.4, 133.0, 129.1 (t, *J* = 2.7 Hz), 120.1 (tq, *J* = 290.6, 41.0 Hz), 118.6 (qt, *J* = 286.5, 36.1 Hz), 117.7, 115.2 ppm; **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.5 (t, *J* = 3.4 Hz, 3F), –90.9 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3074, 3041, 2233, 1487, 1309, 1209, 1099, 960, 831, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 254 (11), 253 (100) [M^+], 184 (60), 134 (42), 90 (12), 69 (20), 63 (14); **HRMS** (EI-TOF) calcd. for $C_9H_4NF_5S$: 252.9985; found: 252.9991; **m.p.**: 45–46 °C.

Synthesis of 8-[(pentafluoroethyl)thio]quinoline (3la)

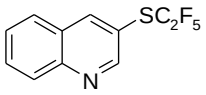


[CAS: 1955495-88-1]

Compound **3la** was prepared following the standard procedure, starting from quinoline-8-yl thiocyanate (**1l**, 372 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3la** was isolated as colourless oil (547 mg, 1.96 mmol, 98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.15 (d, *J* = 7.3 Hz, 1H), 7.94 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.50 ppm (dd, *J* = 8.3, 4.3 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.3, 148.1, 137.7, 136.7, 131.1, 129.2, 126.6, 124.5 (t, *J* = 1.8 Hz), 122.2, 120.9 (tq, *J* = 290.3, 40.2 Hz), 118.8 ppm (qt, *J* = 286.7, 36.5 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.7 (t, *J* = 4.1 Hz, 3F), –91.1 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3065, 1597, 1493, 1462, 1329, 1204, 1094, 956, 827, 788, 750, 661 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 280 (13), 279 (100) [M^+], 160 (55), 116 (20), 89 (11), 69 (12); **HRMS** (EI-TOF) calcd. for $C_{11}H_6NF_5S$: 279.0141; found: 279.0134.

Synthesis of 3-[(pentafluoroethyl)thio]quinoline (3ma)

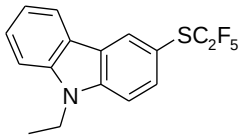


[CAS: 1955495-86-9]

Compound **3ma** was prepared following the standard procedure, starting from quinoline-3-yl thiocyanate (**1m**, 372 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ma** was isolated as colourless solid (542 mg, 1.94 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99 (s, 1H), 8.47 (d, *J* = 5.0 Hz, 1H), 8.12 (dd, *J* = 7.8, 2.9 Hz, 1H), 7.82–7.76 (m, 2H), 7.58 ppm (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.0, 148.5, 145.6, 131.8, 129.6, 128.2, 127.9, 120.0 (tq, *J* = 289.9, 40.8 Hz), 118.7 (qt, *J* = 286.5, 36.6 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.4 (t, *J* = 4.1 Hz, 3F), –91.3 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3031, 1956, 1856, 1738, 1617, 1565, 1490, 1322, 1197, 1090, 948, 912, 787, 748, 658 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 280 (13), 279 (100) [M^+], 160 (43), 133 (10), 116 (8), 89 (20), 69 (10); **HRMS** (EI-TOF) calcd. for $C_{11}H_6NF_5S$: 279.0141; found: 279.0145. **m.p.**: 35–36 °C.

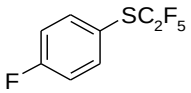
Synthesis of 9-ethyl-3-[(pentafluoroethyl)thio]-9*H*-carbazole (3na)



Compound **3na** was prepared following the standard procedure, starting from 9-ethyl-9*H*-carbazol-3-yl thiocyanate (**1n**, 505 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3na** was isolated as colourless solid (670 mg, 1.94 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 1.5 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.72 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.54 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1H), 7.44 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.42 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.31 (ddd, *J* = 7.8, 7.2, 1.0 Hz, 1H), 4.36 (q, *J* = 7.3 Hz, 2H), 1.47 ppm (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.3, 140.5, 134.5, 130.4, 126.8, 124.1, 122.3, 120.8, 120.4 (tq, *J* = 287.4, 40.1 Hz), 120.0, 119.1 (qt, *J* = 286.4, 37.1 Hz), 110.8 (t, *J* = 3.2 Hz), 109.3, 109.0, 37.9, 13.9 ppm; **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.2 (t, *J* = 3.4 Hz, 3F), –92.7 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3055, 2974, 1625, 1588, 1475, 1331, 1201, 1074, 959, 884, 799, 742, 654 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 347 (6), 346 (18), 345 (100) [M^+], 330 (6), 227 (8), 226 (50), 211 (7), 119 (3), 69 (6); **HRMS** (EI-TOF) calcd. for $C_{16}H_{12}NF_5S$: 345.0611; found: 345.0616; **m.p.**: 64–65°C.

Synthesis of 1-fluoro-4-[(pentafluoroethyl)thio]-benzene (3oa)

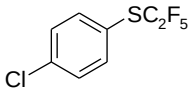


[CAS: 75220-65-4]

Compound **3oa** was prepared following the standard procedure, starting from 4-fluorophenyl thiocyanate (**1o**, 76.6 mg, 0.50 mmol) and potassium pentafluoropropionate (**2a**, 222 mg, 0.60 mmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36.0 µL, 0.50 mmol) was added to the reaction mixture and the pentafluoroethylthiolated product **3oa** was formed in 97% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F{^{1}H} NMR (377 MHz, EtOAc/DMF 3:1): δ = –82.3 (t, *J* = 3.4 Hz, 3F), –92.1 ppm (q, *J* = 3.2 Hz, 2F), 108.6 ppm (s, 1F); **MS** (Ion trap, EI, 70 eV): m/z (%) = 246 (100) [M^+], 177 (9), 127 (92), 83 (44), 75 (9), 69 (23), 57 (15).

Synthesis of 1-chloro-4-[(pentafluoroethyl)thio]-benzene (3pa)

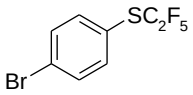


[CAS: 782491-17-2]

Compound **3pa** was prepared following the standard procedure, starting from 4-chlorophenyl thiocyanate (**1p**, 339 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3pa** was isolated as colourless oil (504 mg, 1.92 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.58 (m, 2H), 7.42–7.79 ppm (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 138.6, 138.2, 129.9, 121.4 (t, *J* = 2.7 Hz), 120.1 (tq, *J* = 289.1, 40.6 Hz), 118.8 ppm (qt, *J* = 286.4, 36.8 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.4 (t, *J* = 3.4 Hz, 3F), –92.0 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3045, 2925, 2855, 1576, 1478, 1394, 1332, 1203, 1089, 958, 823, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 264 (38) [M^+(^{37}Cl)], 262 (100) [M^+(^{35}Cl)], 145 (26), 143 (67), 108 (32), 73 (11), 69 (24); **HRMS** (EI-TOF) calcd. for $C_8H_4F_5{}^{35}ClS$: 261.9642; found: 261.9633.

Synthesis of 1-bromo-4-[(pentafluoroethyl)thio]-benzene (3qa)

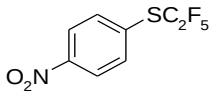


[CAS: 782491-17-2]

Compound **3qa** was prepared following the standard procedure, starting from 4-bromophenyl thiocyanate (**1q**, 428 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3qa** was isolated as colourless oil (614 mg, 1.96 mmol, 98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.55 (m, 2H), 7.53–7.50 ppm (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 138.7, 132.9, 126.5, 122.0 (t, *J* = 3.2 Hz), 120.1 (tq, *J* = 289.1, 40.6 Hz), 118.9 ppm (qt, *J* = 286.4, 36.7 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –83.3 (t, *J* = 3.2 Hz, 3F), –92.6 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3023, 1569, 1475, 1389, 1331, 1204, 1103, 1012, 957, 818, 750, 731 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 308 (100) [M^+(^{81}Br)], 306 (85) [M^+(^{79}Br)], 189 (43), 187 (39), 108 (44), 69 (27), 50 (13); **HRMS** (EI-TOF) calcd. for $C_8H_4F_5S^{79}Br$: 305.9137; found: 305.9154.

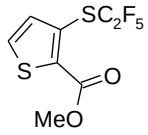
Synthesis of 4-[(pentafluoroethyl)thio]nitrobenzene (3ra)



Compound **3ra** was prepared following the standard procedure, starting from 4-nitrophenyl thiocyanate (**1r**, 407 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ra** was isolated as slightly yellow oil (372 mg, 1.36 mmol, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (m, 2H), 7.85 ppm (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 149.6, 137.6, 131.0 (t, *J* = 2.6 Hz), 124.4, 120.1 (tq, *J* = 291.0, 41.0 Hz), 118.6 ppm (qt, *J* = 286.7, 36.2 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –83.6 (t, *J* = 3.4 Hz, 3F), –92.0 ppm (q, *J* = 3.5 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3459, 3002, 2970, 1603, 1524, 1348, 1207, 1103, 957, 851, 751, 730, 686 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 273 (100) [M^+], 243 (38), 215 (10), 108 (16), 82 (10), 69 (23), 50 (10); **HRMS** (EI-TOF) calcd. for $C_8H_4NF_5O_2S$: 272.9883; found: 272.9897.

Synthesis of methyl-3-[(pentafluoroethyl)thio]thiophene-2-carboxylate (3sa)

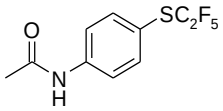


[CAS: 1955495-90-5]

Compound **3sa** was prepared following the standard procedure, starting from methyl-3-thiocyanatothiophene-2-carboxylate (**1s**, 399 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3sa** was isolated as colourless oil (187 mg, 0.64 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 5.3 Hz, 1H), 7.30 (dt, *J* = 5.3, 1.3 Hz, 1H), 3.91 ppm (s, 3H); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.7 (t, *J* = 4.1 Hz, 3F), –91.2 ppm (q, *J* = 3.4 Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.5, 132.8, 132.3 (t, *J* = 2.7 Hz), 131.2, 126.8 (t, *J* = 1.8 Hz), 120.6 (tq, *J* = 291.4, 40.8 Hz), 118.6 (qt, *J* = 286.9, 35.8 Hz), 52.6 ppm; **IR** (neat): $\tilde{\nu}$ = 2955, 1708, 1502, 1439, 1407, 1266, 1204, 1076, 959, 894, 793, 768, 750, 723 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 293 (11), 292 (100) [M^+], 261 (37), 173 (63), 143 (19), 142 (18), 69 (25); **HRMS** (EI-TOF) calcd. for $C_8H_5F_5O_2S_2$: 291.9651; found: 291.9675.

Synthesis of *N*-[4-[(pentafluoroethyl)thio]phenyl]acetamide (3ta)

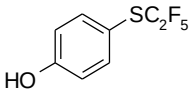


[CAS: 1955495-84-7]

Compound **3ta** was prepared following the standard procedure, starting from 4-(acetylamino)phenyl thiocyanate (**1t**, 384 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ta** was isolated as slightly yellow solid (131 mg, 0.46 mmol, 23%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 4H), 2.20 ppm (s, 3H); **^{13}C NMR** (101 MHz, CD_3OD): δ = 172.0, 143.3, 139.2, 121.5 (tq, *J* = 287.1, 40.0 Hz), 121.4, 120.2 (qt, *J* = 285.6, 37.1 Hz), 117.1 (t, *J* = 2.9 Hz), 24.0 ppm; **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.3 (t, *J* = 4.1 Hz, 3F), –92.2 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3457, 3018, 2974, 1739, 1369, 1229, 1218 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 285 (100) [M^+], 243 (68), 124 (81), 69 (14), 44 (15), 43 (37), 40 (15); **HRMS** (EI-TOF) calcd. for $C_{10}H_8NF_5OS$: 285.0247; found: 285.0254; **m.p.:** 137–138°C.

Synthesis of 4-[(pentafluoroethyl)thio]phenol (3ua)

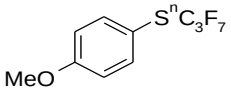


[CAS: 1639457-49-0]

Compound **3ua** was prepared following the standard procedure, starting from 4-hydroxyphenyl thiocyanate (**1u**, 302 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 889 mg, 4.40 mmol). After purification, **3ua** was isolated as colourless liquid (259 mg, 1.06 mmol, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (m, 2H), 6.88 (m, 2H), 6.04 ppm (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 158.5, 139.4, 166.7, 133.4 (t, *J* = 3.3 Hz), 120.1 (tq, *J* = 288.2, 40.0 Hz), 109.2 (qt, *J* = 286.6, 36.8 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –82.3 (t, *J* = 3.4 Hz, 3F), –92.7 ppm (q, *J* = 3.6 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3343, 1702, 1602, 1586, 1496, 1437, 1379, 1332, 1319, 1261, 1201, 1172, 1101, 1087, 1045, 958, 831, 750, 727, 646 cm^{-1}**MS** (Ion trap, EI, 70 eV): m/z (%) = 245 (9), 244 (100) [M^+], 125 (76), 97 (22), 81 (11), 69 (22), 53 (16).

Synthesis of 1-methoxy-4-[(heptafluoropropyl)thio]benzene (3ab)

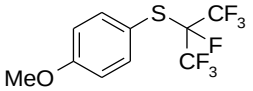


[CAS: 166392-12-7]

Compound **3ab** was prepared following the standard procedure, starting from Synthesis of **4-methoxyphenyl thiocyanate (1a)** (**1a,** 330 mg, 2.00 mmol) and potassium heptafluorobutyrate (**2b**, 605 mg, 2.40 mmol). After purification, **3ab** was isolated as colourless oil (419 mg, 1.36 mmol, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.55 (m, 2H), 6.95–6.92 (m, 2H), 3.84 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.3, 139.3, 122.4 (tt, *J* = 289.0, 33.3 Hz), 118.0 (qtt, *J* = 288.0, 35.4, 2.0 Hz) 115.1, 113.1 (t, *J* = 3.2 Hz), 111.8 (tqt, *J* = 265.1, 36.9, 2.1 Hz), 55.5 ppm; **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –80.0 (t, *J* = 9.5 Hz, 3F), –88.4 (qt, *J* = 8.9, 4.3 Hz, 2F), –123.5 ppm (t, *J* = 4.1 Hz, 2F); **IR** (neat): $\tilde{\nu}$ = 3023, 2950, 1908, 1495, 1252, 1205, 1174, 1108, 1030, 919, 851, 828, 741, 682 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 309 (13), 308 (100) [M$^+$], 140 (8), 139 (97), 96 (11), 95 (14), 69 (23).

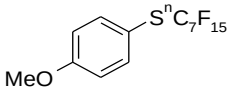
Branched side product in the synthesis of 1-methoxy-4-[(pentafluoropropyl)thio]benzene (3ba), 1-methoxy-4-[(1-trifluoromethyl-1,2,2,2-tetrafluoroethyl)thio]benzene



Due to very similar physical properties, the side product could not be separated from **3ba**. Therefore and because of the comparatively low quantities in which the side product was present in the sample, a full characterisation proved difficult. In the ^{1}H NMR, the shifts of the compounds seem to be too similar to identify individual signals. In the ^{13}C NMR, only the shifts of the methoxy group and the aromatic carbons *ipso*, *ortho* and *meta* to it could be determined, as the C–F coupling causes all other signals to have a very low intensity and therefore to disappear in the noise.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.4, 139.5, 115.1, 55.5 ppm; **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –73.6 (d, *J* = 12.3 Hz, 6F), –157.6 ppm (sept, *J* = 11.4 Hz, 1F); **MS** (Ion trap, EI, 70 eV): m/z (%) = 309 (11), 308 (91) [M$^+$], 139 (100), 124 (8), 95 (16), 69 (21), 63 (7), 45 (5).

Synthesis of 1-methoxy-4-[(perfluoroheptyl)thio]benzene (3ac)



Compound **3ac** was prepared following the standard procedure, starting from Synthesis of **4-methoxyphenyl thiocyanate (1a)** (**1a,** 330 mg, 2.00 mmol) and potassium perfluoroheptanoate (**2c**, 1.09 g, 2.40 mmol). After purification, **3ac** was isolated as colourless oil (295 mg, 0.58 mmol, 29%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.57 (m, 2H), 6.96–6.92 (m, 2H), 3.83 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.3, 139.4, 125.8 (tt, J = 268.8, 41.3 Hz), 123.1 (tt, J = 290.6, 34.2 Hz), 117.4 (qt, J = 288.2, 33.1 Hz), 115.1, 113.3 (t, J = 3.2 Hz), 111.7 (tt, J = 287.1, 39.4 Hz), 111.2 (tq, J = 272.2, 32.3 Hz), 110.5 (tt, J = 271.5, 32.2 Hz), 108.5 (tt, J = 270.1, 38.9 Hz), 55.4 ppm; **^{19}F NMR** (377 MHz, $CDCl_3$): δ = –80.6, –87.5, –118.9, –121.0, –121.7, –122.4, –125.9 ppm; **IR** (neat): $\tilde{\nu}$ = 2847, 1594, 1574, 1497, 1466, 1444, 1411, 1367, 1295, 1236, 1197, 1174, 1145, 1103, 1063, 1033, 986, 973, 874, 830, 802, 777, 763, 745, 736, 723, 702, 670 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 509 (14), 508 (90) [M^+], 489 (12), 140 (9), 139 (100), 95 (11), 69 (18); **HRMS** (EI-TOF) calcd. for $C_{14}H_7F_{15}OS$: 507.9978; found: 507.9968.

6.7 New Reagents for Transition Metal Catalyzed Late-Stage Phosphorothioation

Synthesis of Starting Materials

Synthesis of arene diazonium tetrafluoroborates

In a 100 mL round-bottom flask, the aniline (25 mmol) was dissolved in a mixture of absolute ethanol (25 mL) and an aqueous solution of HBF_4 (50%, 6.23 mL, 50 mmol) and *tert*-butyl nitrite (6.7 mL, 50 mmol) was added dropwise to the solution at 0 °C. The reaction was stirred at room temperature for 1 h and diethyl ether (20 mL) was added to precipitate the arenediazonium tetrafluoroborate that was filtered off and washed with diethyl ether (3 × 20 mL). The arenediazonium tetrafluoroborate was dried in vacuo (10^{-3} mbar) for 10 minutes and was then directly used without further purification.

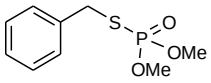
Synthesis of Tetramethylammonium *O,O*-Dimethyl Phosphorothioate (1)

In an oven-dried 500 mL round-bottom flask with stirrer bar, elemental sulfur (0.64 g, 2.5 mmol) was dissolved in THF (160 mL) at room temperature under nitrogen atmosphere. Dimethyltrimethylphosphite (4.73 mL, 24 mmol) was added and the reaction mixture was cooled to −60 °C and afterwards Me_4NF (1.86 g, 20 mmol) was added in one portion. The reaction mixture was kept at −60 °C for ca. 30 min and then allowed to warm to room temperature overnight. The resulting solid was filtered, washed with diethyl ether and **1** was isolated as a white hydroscopic solid (3.7 g, 17.2 mmol, 86%). A solution of **1** in a mixture cyclohexane/acetone was cooled to -20°C to afford colorless prism crystals. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.44 (s, 3H), 3.41 (s, 3H), 3.18 (s, 12H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 56.6 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 118.4, 56.0, 52.3; **IR** (neat): ν = 3014, 2942, 2836, 2364, 1493, 1463, 1167, 1067, 1028, 949, 739, 626, 586, 552, 524 cm^{-1}; **ESI-MS** (+MS): *m/z*: 289.17 $[2M\text{-}((CH_3)_2O_3PS)]^+$, 74.10 $[M\text{-}((CH_3)_2O_3PS)]^+$; ESI-MS (-MS): *m/z*: 356.05 $[2M\text{-}((CH_3)_4N)]^-$, 140.98 $[M\text{-}((CH_3)_4N)]^-$; **Crystal Data** for $C_6H_{18}NO_3PS$ (M = 215.24 $g.mol^{-1}$): orthorhombic, space group $Pca2_1$ (no. 29), a = 14.1490(4) Å, b = 11.2214(3) Å, c = 13.8446(3) Å, V = 2198.13(10) $Å^3$, Z = 8, T = 112(6) K, μ(CuKα) = 3.816 mm^{-1}, *Dcalc* = 1.301 g/cm^3, 11823 reflections measured (7.878° ≤ 2Θ ≤ 152.504°), 4166 unique (R_{int} = 0.0201, R_{sigma} = 0.0218) which were used in all calculations. The final R_1 was 0.0245 (I > 2σ(I)) and wR_2 was 0.0661 (all data).

Synthesis of *S*-Aryl Phosphorothioates from arenediazonium salts

Standard procedure: An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with CuSCN (24.6 mg, 0.20 mmol), **1** (323 mg, 1.50 mmol) in MeCN (2 mL). Then, the arenediazonium salt (1.00 mmol) in MeCN (2 mL) was added dropwise and the reaction mixture was stirred for 15 h at room temperature. The resulting mixture was diluted with diethyl ether (20 mL). The organic solution was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was purified by flash chromatography (SiO_2, cyclohexane / ethyl acetate gradient), yielding the *S*-Aryl Phosphorothioate.

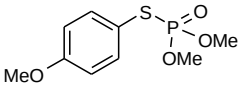
Synthesis of *O,O*-Dimethyl *S*-(benzyl) phosphorothioate (3)



[CAS: 7205-16-5]

An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with CuSCN (24.6 mg, 0.20 mmol), **1** (323 mg, 1.50 mmol) and MeCN (2 mL). Then, benzyl bromide **2** (1.00 mmol) in MeCN (2 mL) was added dropwise and the reaction mixture was stirred for 15 h at room temperature. The resulting mixture was diluted with diethyl ether (20 mL). The organic solution was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was purified by flash chromatography (SiO_2, cyclohexane / ethyl acetate gradient), yielding the *S*-Benzyl Phosphorothioate **3**, isolated as colorless oil (227.7 mg, 0.98 mmol, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.34-7.21 (m, 5H), 4.01-3.95 (m, 2H), 3.66-3.60 (m, 6H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 30.2 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 137.1 (d, ^3J = 4.5 Hz), 128.6 (2C), 128.4 (2C), 127.4, 53.3 (d, ^3J = 5.4 Hz, 2C), 34.5 (d, ^3J = 3.7 Hz), **IR** (neat): ν = 2952, 2850, 1497, 1456, 1257, 1181, 1009, 826, 767, 698, 670 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 234.0 [M^{2+}] (14), 232.0 (93), 199.0 (11), 122.9 (42), 121.0 (11), 109.8 (26), 91.0 (100), 79.0 (17); **HRMS** (EI-TOF) calcd. for $C_9H_{13}O_3PS$: 232.0323; found: 232.0314.

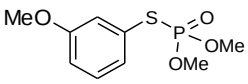
Synthesis of *O,O*-Dimethyl *S*-(4-methoxyphenyl) phosphorothioate (5)



[CAS: 1335244-09-1]

Compound **5** was prepared following the standard procedure, starting from 4-methoxybenzenediazonium tetrafluoroborate **2** (222 mg, 1.00 mmol). After purification, **5** was isolated as pale yellow oil (223.4 mg, 0.90 mmol, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.47 (d, ^{3}J = 8.8 Hz, 2H), 6.89 (d, ^{3}J = 8.8 Hz, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80 ppm (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 26.9 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.6 (d, ^{3}J = 3.6 Hz), 136.3 (d, ^{3}J = 4.5 Hz, 2C), 116.0 (d, ^{3}J = 7.3 Hz), 115.1 (d, ^{3}J = 1.8 Hz, 2C), 55.3, 54.2 ppm (d, ^{3}J = 6.4 Hz, 2C); **IR** (neat): ν = 2954, 2850, 1591, 1494, 1461, 1290, 1244, 1174, 1011, 826, 789, 759 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 249.0 [M^+] (14), 248.1 (100), 139.0 (22), 125.0 (8), 121.0 (11), 109.1 (27), 79.1 (9); **HRMS** (EI-TOF) calcd. for $C_9H_{13}O_4PS$: 248.0272; found: 248.0277.

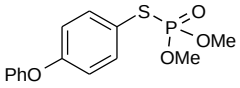
Synthesis of *O,O*-Dimethyl *S*-(3-methoxyphenyl) phosphorothioate (6)



[CAS: 1335244-10-4]

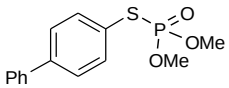
Compound **6** was prepared following the standard procedure, starting from 3-methoxybenzenediazonium tetrafluoroborate (222 mg, 1.00 mmol). After purification, **6** was isolated as pale yellow oil (203.6 mg, 0.82 mmol, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.27 (t, ^{3}J = 8.0 Hz, 1H), 7.16-7.13 (m, 1H), 7.12 (q, ^{3}J = 2.0 Hz, 1H), 6.93-6.90 (m, 1H), 3.85 (s, 3H), 3.82 ppm (s, 6H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 26.1 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.9 (d, ^{3}J = 1.8 Hz), 130.1 (d, ^{3}J = 1.8 Hz), 126.9 (d, ^{3}J = 7.3 Hz), 126.6 (d, ^{3}J = 5.4 Hz), 119.8 (d, ^{3}J = 4.5 Hz), 115.1 (d, ^{3}J = 3.1 Hz), 55.4, 54.3 ppm (d, ^{3}J = 5.4 Hz, 2C); **IR** (neat): ν = 2955, 1737, 1590, 1479, 1231, 1182, 1008, 828, 758, 686 cm^{-1}; MS (Ion trap, EI, 70 eV): *m/z* (%): 249.2 [M^+] (15), 248.3 (100), 121.2 (27), 120.3 (12), 109.2 (38), 79.1 (14); HRMS (EI-TOF) calcd. for $C_9H_{13}O_4PS$: 248.0272; found: 248.0265.

Synthesis of *O,O*-Dimethyl *S*-(4-phenoxyphenyl) phosphorothioate (7)



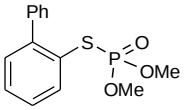
Compound **7** was prepared following the standard procedure, starting from 4-phenoxybenzenediazonium tetrafluoroborate (284 mg, 1.00 mmol). After purification, **7** was isolated as pale yellow oil (294.8 mg, 0.95 mmol, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.50-7.47 (m, 2H), 7.36 (t, ^{3}J = 8.0 Hz, 2H), 7.15 (t, ^{3}J = 7.3 Hz, 2H), 7.15 (d, ^{3}J = 7.8 Hz, 1H), 6.95 (d, ^{3}J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.80 ppm (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 26.4 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.8 (d, ^{3}J = 3.6 Hz), 155.8, 136.2 (d, ^{3}J = 4.5 Hz, 2C), 129.9 (2C), 124.1, 119.7 (2C), 118.8 (d, ^{3}J = 2.7 Hz, 2C),118.7 (d, ^{3}J = 8.2 Hz), 54.2 ppm (d, ^{3}J = 6.4 Hz, 2C); **IR** (neat): ν = 2953, 2850, 1581, 1483, 1233, 1166, 1007, 868, 828, 788, 753, 693 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 311.1 [M^{+}] (20), 310.2 (100), 201.3 (10), 183.3 (8), 109.1 (24), 77.0 (9), 51.0 (8); **HRMS** (EI-TOF) calcd. for $C_{14}H_{15}O_4PS$: 310.0429; found: 310.0419.

Synthesis of *O,O*-Dimethyl *S*-[1,1'-biphenyl]-4-yl phosphorothioate (8)



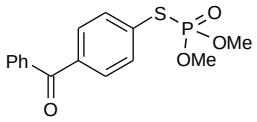
Compound **8** was prepared following the standard procedure, starting from [1,1'-biphenyl]-4-diazonium tetrafluoroborate (268 mg, 1.00 mmol). After purification, **8** was isolated as white crystalline solid (279.6 mg, 0.95 mmol, 95%); **m. p.** 61.1°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.65-7.63 (m, 2H), 7.59-7.57 (m, 4H), 7.48-7.44 (m, 2H), 7.40-7.36 (m, 1H), 3.88 (s, 3H), 3.85 ppm (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 26.2 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.1 (d, ^{3}J = 3.6 Hz), 139.8, 134.9 (d, ^{3}J = 5.5 Hz, 2C), 128.9 (2C), 128.1 (d, ^{3}J = 2.7 Hz, 2C), 127.8, 127.1 (2C), 124.7 (d, ^{3}J = 7.3 Hz), 54.3 ppm (d, ^{3}J = 6.4 Hz, 2C); **IR** (neat): ν = 2952, 2850, 2340, 1738, 1594, 1479, 1448, 1256, 1179, 1005, 827, 791, 755, 696 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 295.1 [M^{+}] (18), 294.1 (100), 185.1 (21), 109.0 (26); **HRMS** (EI-TOF) calcd. for $C_{14}H_{15}O_3PS$: 294.0480; found: 294.0490.

Synthesis of *O,O*-Dimethyl S-[1,1'-biphenyl]-2-yl) phosphorothioate (9)



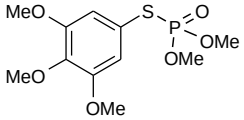
Compound **9** was prepared following the standard procedure, starting from [1,1'-biphenyl]-2-diazonium tetrafluoroborate (268 mg, 1.00 mmol). After purification, **9** was isolated as colorless crystals (270.8 mg, 0.92 mmol, 92%); **m. p.** 73.5°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.80-7.78 (m, 1H), 7.46-7.42 (m, 5H), 7.40-7.34 (m, 3H), 3.54 (s, 3H), 3.51 ppm (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 25.8 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 146.5 (d, ^{3}J = 5.4 Hz), 140.4, 136.6 (d, ^{3}J = 3.6 Hz), 131.1 (d, ^{3}J = 2.7 Hz), 129.9 (2C), 128.9 (dd, ^{1}J = 124.4 Hz, ^{3}J = 2.7 Hz, 2C), 127.8 (2C), 127.4, 124.3 (d, ^{3}J = 7.3 Hz), 53.9 ppm (d, ^{3}J = 5.4 Hz, 2C); **IR** (neat): ν = 2947, 2852, 2353, 1886, 1738, 1586, 1447, 1250, 1188, 1061, 1002, 836, 796, 755, 702, 677 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 295.1 [M^+] (18), 294.2 (100), 185.2 (22), 184.4 (94), 109.2 (11), 79.2 (8); **HRMS** (EI-TOF) calcd. for $C_{14}H_{15}O_3PS$: 294.0480; found: 294.0481.

Synthesis of *O,O*-Dimethyl *S*-(4-benzoylphenyl) phosphorothioate (10)



Compound **10** was prepared following the standard procedure, starting from 4-(benzoyl)-benzenediazonium tetrafluoroborate (296 mg, 1.00 mmol). After purification, **10** was isolated as colorless oil (290.1 mg, 0.90 mmol, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.80-7.76 (m, 4H), 7.70-7.67 (m, 2H), 7.63-7.59 (m, 1H), 7.51-7.47 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 24.9 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 195.6, 137.8 (d, ^{3}J = 2.7 Hz), 136.9, 133.8 (d, ^{3}J = 5.5 Hz), 132.7, 131.6 (d, ^{3}J = 7.3 Hz), 130.7 (d, ^{3}J = 1.8 Hz), 130.0 (2C), 128.4 (2C), 54.4 ppm (d, ^{3}J = 6.4 Hz, 2C); **IR** (neat): ν = 2954, 2851, 1738, 1656, 1590, 1447, 1396, 1256, 1178, 1011, 923, 830, 791, 762, 731, 697, 662 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 229.2 (17), 228.2 (100), 181.3 (7), 151.2 (61), 105.2 (12), 77.2 (24); **HRMS** (EI-TOF) calcd. for $C_{15}H_{15}O_4PS$: 322.0429; found: 322.0424.

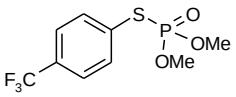
Synthesis of *O,O*-Dimethyl *S*-(3,4,5-trimethoxyphenyl) phosphorothioate (11)



Compound **11** was prepared following the standard procedure, starting from 3,4,5-trimethoxybenzenediazonium tetrafluoroborate (282 mg, 1.00 mmol). After purification, **11** was isolated as white crystalline solid (252.8 mg, 0.82 mmol, 82%); **m. p.** 78.7°C. **^{1}H NMR**

(400 MHz, $CDCl_3$): δ = 6.77-6.75 (m, 2H), 3.83-3.78 (m, 15H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 26.2 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 153.3 (d, ^3J = 2.7 Hz, 2C), 139.0 (d, ^3J = 3.6 Hz), 119.9 (d, ^3J = 7.3 Hz), 111.7 (d, ^3J = 5.5 Hz, 2C), 60.7, 56.1 (2C), 54.3 ppm (d, ^3J = 6.4 Hz); **IR** (neat): ν = 2953, 2839, 2144, 1992, 1738, 1582, 1498, 1458, 1408, 1305, 1255, 1230, 1124, 998, 871, 824, 794, 772, 653 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 309.2 [M^+] (10), 308.2 (70), 294.3 (11), 293.5 (100), 125.2 (30), 109.2 (11), 79.1 (8); **HRMS** (EI-TOF) calcd. for $C_{11}H_{17}O_6PS$: 308.0483; found: 308.0475.

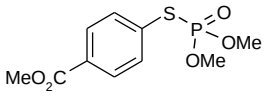
Synthesis of *O,O*-Dimethyl *S*-(4-(trifluoromethyl)phenyl) phosphorothioate (12)



[CAS: 1519014-89-1]

Compound **12** was prepared following the standard procedure, starting from 4-(trifluoromethyl)-benzenediazonium tetrafluoroborate (260 mg, 1.00 mmol). After purification, **12** was isolated as colorless oil (214.7 mg, 0.75 mmol, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.71 (d, ^3J = 7.8 Hz, 2H), 7.61 (d, ^3J = 8.8 Hz, 2H), 3.87 (s, 3H), 3.84 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = -62.9 ppm; **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 24.7 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 134.4 (d, ^3J = 5.5 Hz, 2C), 131.3, 131.1 (d, ^3J = 24.5 Hz), 126.2 (d, ^3J = 1.8 Hz, 2C), 123.7 (d, ^1J = 272.5 Hz), 54.5 ppm (d, ^3J = 6.4 Hz, 2C); **IR** (neat): ν = 2956, 1608, 1450, 1401, 1322, 1262, 1166, 1124, 1062, 1009, 831, 794, 763, 702 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 287.0 [M^+] (10), 285.9 (96), 267.0 (19), 177.0 (17), 157.9 (18), 127.0 (13), 109.0 (100), 108.0 (12), 78.9 (29); **HRMS** (EI-TOF) calcd. for $C_9H_{10}F_3O_3PS$: 286.0040; found: 286.0041.

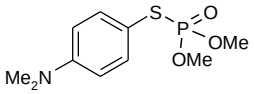
Synthesis of Methyl 4-((dimethoxyphosphoryl)thio)benzoate (13)



Compound **13** was prepared following the standard procedure, starting from 4-(methoxycarbonyl)-benzenediazonium tetrafluoroborate (250 mg, 1.00 mmol). After purification, **13** was isolated as pale yellow oil (198.9 mg, 0.72 mmol, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.02 (d, ^3J = 8.3 Hz, 2H), 6.66-6.64 (m, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 3.83 ppm (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 24.9 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.3, 133.9 (d, ^3J = 5.4 Hz, 2C), 132.3 (d, ^3J = 7.3 Hz), 130.6 (d, ^3J = 2.7 Hz),

130.4 (d, ^3J = 1.8 Hz, 2C), 54.4 (d, ^3J = 5.4 Hz, 2C), 52.4 ppm; **IR** (neat): ν = 2954, 1720, 1596, 1436, 1398, 1258, 1178, 1109, 1009, 855, 827, 791, 758, 692 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 276.0 (100), 245.1 (29), 215.9 (15), 149.0 (23), 136.0 (20), 109.0 (59), 78.9 (19); **HRMS** (EI-TOF) calcd. for $C_{10}H_{13}O_5PS$: 276.0221; found: 276.0222.

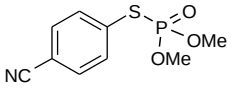
Synthesis of *O,O*-Dimethyl *S*-(4-(dimethylamino)phenyl) phosphorothioate (14)



[CAS: 91010-15-0]

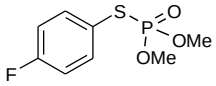
Compound **14** was prepared following the standard procedure, starting from 4-(dimethylamino)-benzenediazonium tetrafluoroborate (235 mg, 1.00 mmol). After purification, **14** was isolated as an orange oil (177.7 mg, 0.68 mmol, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.38-7.36 (m, 2H), 6.66-6.64 (m, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.98 ppm (s, 6H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 27.7 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 150.9 (d, ^3J = 2.7 Hz), 136.0 (d, ^3J = 4.5 Hz, 2C), 112.8 (d, ^3J = 2.7 Hz, 2C), 109.5 (d, ^3J = 8.2 Hz), 54.1 (d, ^3J = 6.4 Hz, 2C), 40.2 ppm (2C); **IR** (neat): ν = 2952, 1593, 1505, 1444, 1358, 1249, 1195, 1172, 1010, 944, 813, 792, 757 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 262.1 [M^+] (14), 261.1 (100), 152.0 (50); **HRMS** (EI-TOF) calcd. for $C_{10}H_{16}NO_3PS$: 261.0589; found: 261.0581.

Synthesis of *O,O*-Dimethyl *S*-(4-cyanophenyl) phosphorothioate (15)



Compound **15** was prepared following the standard procedure, starting from 4-cyanobenzenediazonium tetrafluoroborate (217 mg, 1.00 mmol). After purification, **15** was isolated as pale yellow oil (197.0 mg, 0.81 mmol, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.71-7.69 (m, 2H), 7.65-7.63 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 23.9 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 134.3 (d, ^3J = 5.4 Hz, 2C), 133.2 (d, ^3J = 7.3 Hz), 132.7 (d, ^3J = 1.8 Hz, 2C), 117.9, 112.7 (d, ^3J = 2.7 Hz), 54.6 ppm (d, ^3J = 6.4 Hz, 2C); **IR** (neat): ν = 2956, 2231, 1594, 1486, 1458, 1399, 1257, 1181, 1011, 830, 792, 760 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 244.0 [M^+] (21), 243.0 (67), 133.9 (12), 109.0 (100), 78.9 (18), 63.0 (9), 47.0 (11); **HRMS** (EI-TOF) calcd. for $C_9H_{10}NO_3PS$: 243.0119; found: 243.0109.

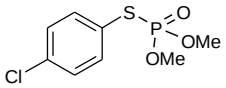
Synthesis of *O,O*-Dimethyl *S*-(4-fluorophenyl) phosphorothioate (16)



[CAS: 4163-76-2]

Compound **16** was prepared following the standard procedure, starting from 4-fluorobenzenediazonium tetrafluoroborate (210 mg, 1.00 mmol). After purification, **16** was isolated as colorless oil (184.2 mg, 0.78 mmol, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.57-7.51 (m, 2H), 7.06 (t, ^{3}J = 8.3 Hz, 2H), 3.83 (s, 3H), 3.80 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = -111.3 ppm (d, J = 5.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 25.9 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.4 (dd, ^{1}J = 250.7 Hz, ^{3}J = 2.7 Hz), 136.7 (dd, ^{3}J = 8.2 Hz, ^{3}J = 4.5 Hz, 2C), 120.1 (dd, ^{3}J = 7.3, 3.6 Hz), 116.7 (dd, ^{3}J = 21.8, 2.7 Hz, 2C), 54.3 ppm (d, ^{3}J = 5.4 Hz, 2C); **IR** (neat): ν = 2956, 2852, 2369, 1737, 1590, 1490, 1462, 1256, 1225, 1159, 1007, 829, 763 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 235.9 (29), 222.0 (100), 221.2 (42), 109.0 (29), 83.0 (44), 75.0 (37), 57.0 (26); **HRMS** (EI-TOF) calcd. for $C_8H_{10}FO_3PS$: 236.0072; found: 236.0081.

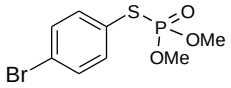
Synthesis of *O,O*-Dimethyl *S*-(4-chlorophenyl) phosphorothioate (17)



[CAS: 3309-87-3]

Compound **17** was prepared following the standard procedure, starting from 4-chlorobenzenediazonium tetrafluoroborate (226.4 mg, 1.00 mmol). After purification, **17** was isolated as pale yellow oil (214.8 mg, 0.85 mmol, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.50-7.45 (m, 2H), 7.34-7.29 (m, 2H), 3.83-3.78 ppm (m, 6H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 25.5 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 135.7 (d, ^{3}J = 4.5 Hz, 2C), 135.6 (d, ^{3}J = 2.7 Hz), 129.6 (d, ^{3}J = 2.7 Hz, 2C), 124.4 (d, ^{3}J = 7.3 Hz), 54.3 ppm (d, ^{3}J = 5.4 Hz, 2C); **IR** (neat): ν = 2955, 2851, 1573, 1476, 1392, 1256, 1179, 1091, 1007, 819, 792, 758 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 253.9 [M^{+}] (37), 252.8 (16), 251.9 (100), 125.0 (25), 109.0 (92), 108.0 (27), 78.9 (15); **HRMS** (EI-TOF) calcd. for $C_8H_{10}O_3PS^{35}Cl$: 251.9777; found: 251.9773; HRMS (EI-TOF) calcd. for $C_8H_{10}O_3PS^{37}Cl$: 253.9747; found: 253.9762.

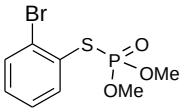
Synthesis of *O,O*-Dimethyl *S*-(4-bromophenyl) phosphorothioate (18)



[CAS: 1616795-45-9]

Compound **18** was prepared following the standard procedure, starting from 4-bromobenzenediazonium tetrafluoroborate (270.8 mg, 1.00 mmol). After purification, **18** was isolated as pale yellow oil (240.7 mg, 0.81 mmol, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.51-7.48 (m, 2H), 7.45-7.41 (m, 2H), 3.84 (s, 3H), 3.81 ppm (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 25.3 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 136.0 (d, ^{3}J = 4.5 Hz, 2C), 132.6 (d, ^{3}J = 1.8 Hz, 2C), 125.2 (d, ^{3}J = 7.3 Hz), 123.9 (d, ^{3}J = 3.6 Hz), 54.4 ppm (d, ^{3}J = 6.4 Hz, 2C); **IR** (neat): ν = 2953, 2850, 1565, 1474, 1387, 1256, 1179, 1003, 815, 790, 761 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 298.0 [M^+] (78), 296.0 (72), 169.0 (12), 109.0 (100), 108.0 (26), 78.9 (23), 47.0 (15); **HRMS** (EI-TOF) calcd. for $C_8H_{10}O_3PS^{79}Br$: 295.9272; found: 295.9280; **HRMS** (EI-TOF) calcd. for $C_8H_{10}O_3PS^{81}Br$: 297.9251; found: 297.9258.

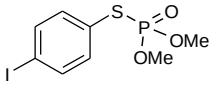
Synthesis of *O,O*-Dimethyl *S*-(2-bromophenyl) phosphorothioate (19)



[CAS: 1519014-90-4]

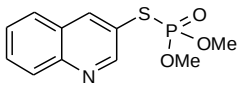
Compound **19** was prepared following the standard procedure, starting from 2-bromobenzenediazonium tetrafluoroborate (271 mg, 1.00 mmol). After purification, **19** was isolated as pale yellow oil (225.8 mg, 0.76 mmol, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.77 (dt, ^{3}J = 7.8, 2.0 Hz, 1H), 7.66 (dt, ^{3}J = 8.0, 1.0 Hz, 1H), 7.35-7.30 (m, 1H), 7.25-7.20 (m, 1H), 3.89 (s, 3H), 3.86 ppm (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 24.7 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 136.7 (d, ^{3}J = 3.7 Hz), 136.7 (d, ^{3}J = 3.7 Hz), 133.7 (d, ^{3}J = 2.2 Hz), 130.5 (d, ^{3}J = 2.9 Hz), 128.7 (d, ^{3}J = 7.3 Hz), 128.2 (d, ^{3}J = 2.9 Hz), 128.0 (d, ^{3}J = 6.6 Hz), 54.5 ppm (d, ^{3}J = 5.9 Hz, 2C) ; **IR** (neat): ν = 2954, 2850, 1738, 1561, 1449, 1250, 1181, 1005, 830, 792, 751 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 218.0 [M^+-*Br*] (9), 217.1 (100), 202.2 (11), 109.1 (20), 79.1 (11); **HRMS** (EI-TOF) calcd. for $C_8H_{10}O_3PS^{79}Br$: 295.9272; found: 295.9266; **HRMS** (EI-TOF) calcd. for $C_8H_{10}O_3PS^{81}Br$: 297.9251; found: 297.9231.

Synthesis of *O,O*-Dimethyl *S*-(4-iodophenyl) phosphorothioate (20)



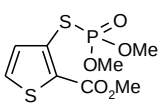
Compound **20** was prepared following the standard procedure, starting from 4-iodobenzenediazonium tetrafluoroborate (318 mg, 1.00 mmol). After purification, **20** was isolated as colorless liquid (230.6 mg, 0.67 mmol, 67%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.47 (d, ^3J = 8.3 Hz, 2H), 7.08 (dd, ^3J = 8.5, 2.0 Hz, 2H), 3.63 (s, 3H), 3.60 ppm (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 25.2 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 138.5, 138.5, 130.1, 130.0, 126.0 (d, ^3J = 7.3 Hz), 95.5 (d, ^3J = 4.5 Hz), 54.3 ppm (d, ^3J = 6.4 Hz, 2C); **IR** (neat): ν = 2952, 2849, 1737, 1567, 1471, 1382, 1252, 1179, 1000, 810, 788, 755, 716 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 344.9 [M^+] (10), 344.0 (100), 217.2 (11), 109.0 (38), 108.1 (10), 79.1 (10); **HRMS** (EI-TOF) calcd. for $C_8H_{10}O_3PSI$: 243.9133; found: 243.9145.

Synthesis of O,*O*-Dimethyl *S*-(quinolin-3-yl) phosphorothioate (21)



Compound **21** was prepared following the standard procedure, starting from quinoline-3-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **21** was isolated as colorless oil (166.9 mg, 0.62 mmol, 62%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.94 (s, 1H), 8.42 (t, ^3J = 2.5 Hz, 1H), 8.10 (d, ^3J = 8.3 Hz, 1H), 7.81 (d, ^3J = 8.6, 1H), 7.77 (t, ^3J = 7.8 Hz, 1H), 7.59 (t, ^3J = 8.0 Hz, 1H), 3.88 (s, 3H), 3.85 ppm (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 25.0 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 153.6, (d, ^3J = 3.6 Hz), 147.4 (d, ^3J = 2.7 Hz), 142.2 (d, ^3J = 6.4 Hz), 130.8, 129.3, 128.0, 127.7, 127.5, 120.3 (d, ^3J = 7.3 Hz), 54.5, 54.5; **IR** (neat): ν = 2953, 2850, 1618, 1567, 1490, 1455, 1357, 1254, 1181, 1008, 954, 909, 830, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 269.8 [M^+] (15), 268.7 (100), 174.8 (25), 159.9 (8), 108.8 (34), 88.9 (19), 78.8 (12); **HRMS** (EI-TOF) calcd. for $C_{11}H_{12}NO_3PS$: 269.0276; found: 269.0291.

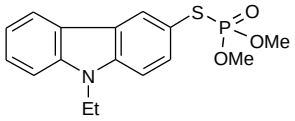
Synthesis of Methyl 3-((dimethoxyphosphoryl)thio)thiophene-2-carboxylate (22)



Compound **22** was prepared following the standard procedure, starting from 2-(methoxycarbonyl)-thiophene-3-diazonium tetrafluoroborate (256 mg, 1.00 mmol). After

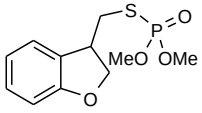
purification, **22** was isolated as pale yellow oil (132.7 mg, 0.47 mmol, 47%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.52 (d, ^{3}J = 5.3 Hz, 1H), 7.44 (dd, ^{3}J = 5.3, 1.0 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.84 ppm (s, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 24.2 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.6, 131.8 (d, ^{3}J = 4.5 Hz), 130.9 (d, ^{3}J = 1.8 Hz), 130.0 (d, ^{3}J = 5.5 Hz), 129.7 (d, ^{3}J = 7.3 Hz), 54.5 (d, ^{3}J = 5.5 Hz, 2C), 52.3 ppm; **IR** (neat): ν = 2954, 1705, 1499, 1437, 1404, 1354, 1240, 1182, 1075, 1008, 891, 832, 762, 662 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 283.0 [M^{+}] (17), 281.9 (100), 251.1 (26), 156.0 (30), 143.0 (16), 142.0 (19), 109.1 (39); **HRMS** (EI-TOF) calcd. for $C_8H_{11}O_5PS_2$: 281.9786; found: 281.9799.

Synthesis of *O,O*-Dimethyl *S*-(9-ethyl-9*H*-carbazol-3-yl) phosphorothioate (23)



Compound **23** was prepared following the standard procedure, starting from 9-ethyl-9*H*-carbazole-3-diazonium tetrafluoroborate (309 mg, 1.00 mmol). After purification, **23** was isolated as colorless crystals (174.4 mg, 0.52 mmol, 52%); **m. p.** 105.3°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.28 (t, ^{3}J = 2.0 Hz, 1H), 8.10 (dt, ^{3}J = 7.8, 1.0 Hz, 1H), 7.63 (dt, ^{3}J = 8.5, 1.0 Hz, 1H), 7.53-749 (m, 1H), 7.43-7.37 (m, 2H), 7.29-7.25 (m, 1H), 4.35 (q, ^{3}J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 1.43 ppm (t, ^{3}J = 7.3, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 27.4 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.2, 140.1 (d, ^{3}J = 2.1 Hz), 132.1 (d, ^{3}J = 3.7 Hz), 127.5 (d, ^{3}J = 5.1 Hz), 126.3, 123.9 (d, ^{3}J = 2.9 Hz), 122.1, 120.5, 119.4, 113.6 (d, ^{3}J = 7.3 Hz), 109.4 (d, ^{3}J = 2.1 Hz), 108.7, 54.2 (d, ^{3}J = 6.6 Hz, 2C), 37.6, 13.7 ppm; **IR** (neat): ν = 2954, 2339, 1737, 1623, 1590, 1471, 1449, 1381, 1348, 1316, 1253, 1178, 1147, 1009, 881, 798, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 242.1 (12), 241.0 (94), 226.0 (100), 211.1 (24), 197.1 (11), 167.0 (20); **HRMS** (EI-TOF) calcd. for $C_{16}H_{18}NO_3PS$: 335.0745; found: 335.0737.

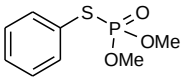
Synthesis of *O,O*-Dimethyl *S*-((2,3-dihydrobenzofuran-3-yl)methyl) phosphorothioate (25)



Compound **25** was prepared following the standard procedure, starting from 2-(allyloxy)-benzenediazonium tetrafluoroborate **25** (248 mg, 1.00 mmol). After purification, **23** was

isolated as pale yellow oil (230.4 mg, 0.84 mmol, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.27 (d, ^{3}J = 7.3 Hz, 1H), 7.16 (t, ^{3}J = 7.5 Hz, 1H), 6.87 (dt, ^{3}J = 7.5, 1.0 Hz, 1H), 6.79 (d, ^{3}J = 8.0 Hz, 1H), 4.66-4.61 (m, 1H), 4.41 (ddd, ^{3}J = 9.4, 5.1, 1.3 Hz, 1H), 3.81-3.73 (m, 7H), 3.18 (tdd, ^{3}J = 13.1, 5.5, 0.9 Hz, 1H), 3.05-2.95 ppm (m, 1H); **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 30.5 ppm; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.9, 129.1, 128.1, 124.6, 120.5, 109.8, 75.4, 53.8 (d, ^{3}J = 6.4 Hz, 2C), 42.7 (d, ^{3}J = 5.4 Hz), 34.8 ppm (d, ^{3}J = 3.6 Hz); IR (neat): ν = 2953, 1739, 1597, 1482, 1231, 1181, 1012, 966, 827, 748 cm^{-1}; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 265.0 (13), 264.0 (69), 144.0 (14), 132.0 (100), 131.1 (81), 115.0 (18), 91.0 (67), 89.1 (11), 77 (30); **HRMS** (EI-TOF) calcd. for $C_{11}H_{13}O_4PS$ [M^+ - *2H*]: 272.0272; found: 272.0278.

Synthesis of *O,O*-Dimethyl *S*-phenyl phosphorothioate (28)



[CAS: 4237-00-7]

An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with Pd^{I}-dimer catalyst **24** (13.1 mg, 0.015 mmol), **1** (161 mg, 0.75 mmol), iodobenzene **25** (57 µL, 0.5 mmol) in Toluene/MeCN (2:1, 2 mL) and the reaction mixture was stirred for 15 h at 80°C. The resulting mixture was diluted with diethyl ether (20 mL). The organic solution was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C) to afford the crude product **28**. **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 26.4 ppm, 30% NMR yield; **MS** (Ion trap, EI, 70 eV): *m/z* (%): 218.9 [M^+] (6), 217.9 (34), 186.0 (100), 185.0 (71), 184.2 (30), 108.9 (31), 77.0 (17), 65.0 (31), 51.0 (43).

Crystallographic data for 1

Experimental

X-ray diffraction data were collected by using a Rigaku Oxford Diffraction SuperNova, Single source at offset, Altlas as detector with SuperNova (Cu) X-ray Source and CuKα radiation (λ = 1.54178 Å). Single colourless prism crystal of $C_6H_{18}NO_3PS$ (**1**) was selected and was mounted on a 'multiwire proportional' diffractometer with perfluoropolyalkyl ether, viscosity 1800 cSt (ABCR) as cryoprotectant and then flashfrozen in a nitrogen-gas stream at 112 K. The temperature of the crystal was maintained at the selected value (112 K) by means of an Oxford Instruments Cryjet XL cooling device to within an accuracy of ±1 K. Using

Olex2, the structure was solved with the Superflip structure solution program using Charge Flipping and refined with the ShelXL refinement package using Least Squares minimization. The crystal data collection and refinement parameters are given in Table S1.

CCDC 1497456 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via https://summary.ccdc.cam.ac.uk/structure-summary-form.

Crystal structure determination of 1

Table 1 Crystal data and structure refinement for **1**.

Identification code	**$Me_4NSP(O)(OMe)_2$**
Empirical formula	$C_6H_{18}NO_3PS$
Formula weight	215.24
Temperature/K	112(6)
Crystal system	orthorhombic
Space group	$Pca2_1$
a/Å	14.1490(4)
b/Å	11.2214(3)
c/Å	13.8446(3)
α/°	90
β/°	90
γ/°	90
Volume/$Å^3$	2198.13(10)
Z	8
$\rho_{calc}g/cm^3$	1.301
μ/mm^{-1}	3.816
F(000)	928.0
Crystal size/mm^3	0.11 × 0.1 × 0.07
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.878 to 152.504
Index ranges	$-16 \leq h \leq 17$, $-13 \leq k \leq 13$, $-17 \leq l \leq 17$
Reflections collected	11823
Independent reflections	4166 [R_{int} = 0.0201, R_{sigma} = 0.0218]
Data/restraints/parameter	4166/1/229

s

Goodness-of-fit on F^2	1.065
Final R indexes [I>=2σ (I)]	R_1 = 0.0245, wR_2 = 0.0657
Final R indexes [all data]	R_1 = 0.0250, wR_2 = 0.0661
Largest diff. peak/hole / e $Å^{-3}$	0.42/-0.27
Flack parameter	0.018(8)

7 Lebenslauf

Persönliche Angaben

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8 Literaturverzeichnis

[1] J. H. Holloway, *J. Fluor. Chem.* **1986**, *33*, 149–158.
[2] D. O'Hagan, D. B. Harper, *J. Fluor. Chem.* **1999**, *100*, 127–133.
[3] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem Soc Rev* **2008**, *37*, 320–330.
[4] P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589.
[5] P. Kirsch, M. Bremer, *Angew. Chem.* **2000**, *39*, 4216–4235.
[6] M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, et al., *ChemMedChem* **2007**, *2*, 1100–1115.
[7] K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.
[8] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.
[9] J. M. Brown, V. Gouverneur, *Angew. Chem. Int. Ed.* **2009**, *48*, 8610–8614.
[10] D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320–1367.
[11] J. E. Huheey, *J. Phys. Chem.* **1965**, *69*, 3284–3291.
[12] N. Muller, *J. Pharm. Sci.* **1986**, *75*, 987–991.
[13] A. Rivkin, K. Biswas, T.-C. Chou, S. J. Danishefsky, *Org. Lett.* **2002**, *4*, 4081–4084.
[14] F. Swarts, *Bull. Acad. R. Belg.* **1892**, *24*, 309.
[15] H. Schroeder, R. Rätz, W. Schnabel, H. Ulrich, E. Kober, C. Grundmann, *J. Org. Chem.* **1962**, *27*, 2589–2592.
[16] G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324–1327.
[17] O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521.
[18] T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477.
[19] T. Liu, Q. Shen, *Eur. J. Org. Chem.* **2012**, *2012*, 6679–6687.
[20] T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264.
[21] X.-F. Wu, H. Neumann, M. Beller, *Chem. - Asian J.* **2012**, *7*, 1744–1754.
[22] X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683–730.
[23] Z. He, T. Luo, M. Hu, Y. Cao, J. Hu, *Angew. Chem. Int. Ed.* **2012**, *51*, 3944–3947.
[24] M. S. Wiehn, E. V. Vinogradova, A. Togni, *J. Fluor. Chem.* **2010**, *131*, 951–957.
[25] D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877.
[26] M. Schlosser, Ed. , *Organometallics in Synthesis: Third Manual*, Wiley, Hoboken, New Jersey, **2013**.
[27] H. C. Clark, C. J. Willis, *J. Am. Chem. Soc.* **1960**, *82*, 1888–1891.
[28] N. V. Kondratenko, E. P. Vechirko, L. M. Yagupolskii, *Synthesis* **1980**, *1980*, 932–933.
[29] D. M. Wiemers, D. J. Burton, *J. Am. Chem. Soc.* **1986**, *108*, 832–834.
[30] D. J. Burton, D. M. Wiemers, *J. Am. Chem. Soc.* **1985**, *107*, 5014–5015.
[31] Z. Weng, R. Lee, W. Jia, Y. Yuan, W. Wang, X. Feng, K.-W. Huang, *Organometallics* **2011**, *30*, 3229–3232.
[32] K. Matsui, E. Tobita, M. Ando, K. Kondo, *Chem. Lett.* **1981**, *10*, 1719–1720.
[33] B. R. Langlois, N. Roques, *J. Fluor. Chem.* **2007**, *128*, 1318–1325.
[34] I. Ruppert, K. Schlich, W. Volbach, *Tetrahedron Lett.* **1984**, *25*, 2195–2198.
[35] T. Knauber, F. Arikan, G.-V. Röschenthaler, L. J. Gooßen, *Chem. - Eur. J.* **2011**, *17*, 2689–2697.
[36] T. Shono, M. Ishifune, T. Okada, S. Kashimura, *J. Org. Chem.* **1991**, *56*, 2–4.

[37] A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *J. Am. Chem. Soc.* **2011**, *133*, 20901–20913.
[38] G. G. Dubinina, H. Furutachi, D. A. Vicic, *J. Am. Chem. Soc.* **2008**, *130*, 8600–8601.
[39] M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909.
[40] H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2011**, *50*, 3793–3798.
[41] Z. Weng, R. Lee, W. Jia, Y. Yuan, W. Wang, X. Feng, K.-W. Huang, *Organometallics* **2011**, *30*, 3229–3232.
[42] G. G. Dubinina, J. Ogikubo, D. A. Vicic, *Organometallics* **2008**, *27*, 6233–6235.
[43] H. Urata, T. Fuchikami, *Tetrahedron Lett.* **1991**, *32*, 91–94.
[44] X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683–730.
[45] G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757–786.
[46] V. C. R. Mcloughlin, J. Thrower, *Tetrahedron* **1969**, *25*, 5921–5940.
[47] N. V. Kondratenko, E. P. Vechirko, L. M. Yagupolskii, *Synthesis* **1980**, *1980*, 932–933.
[48] D. M. Wiemers, D. J. Burton, *J. Am. Chem. Soc.* **1986**, *108*, 832–834.
[49] G. E. Carr, R. D. Chambers, T. F. Holmes, D. G. Parker, *J. Chem. Soc. [Perkin 1]* **1988**, 921.
[50] V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.* **2006**, *128*, 12644–12645.
[51] G. G. Dubinina, J. Ogikubo, D. A. Vicic, *Organometallics* **2008**, *27*, 6233–6235.
[52] H. Urata, T. Fuchikami, *Tetrahedron Lett.* **1991**, *32*, 91–94.
[53] G. G. Dubinina, H. Furutachi, D. A. Vicic, *J. Am. Chem. Soc.* **2008**, *130*, 8600–8601.
[54] G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324–1327.
[55] A. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525–616.
[56] Scherer, *Angew. Chem.* **1939**, *52*, 457–459.
[57] B. Quiclet-Sire, R. N. Saicic, S. Z. Zard, *Tetrahedron Lett.* **1996**, *37*, 9057–9058.
[58] V. Soloshonok, V. Kukhar, Y. Pustovit, V. Nazaretian, *Synlett* **1992**, *1992*, 657–658.
[59] C. Wakselman, M. Tordeux, *J. Org. Chem.* **1985**, *50*, 4047–4051.
[60] G. Blond, T. Billard, B. . Langlois, *Tetrahedron Lett.* **2001**, *42*, 2473–2475.
[61] C. Pooput, W. R. Dolbier,, M. Médebielle, *J. Org. Chem.* **2006**, *71*, 3564–3568.
[62] S. Large, N. Roques, B. R. Langlois, *J. Org. Chem.* **2000**, *65*, 8848–8856.
[63] V. I. Popov, V. N. Boiko, L. M. Yagupolskii, *J. Fluor. Chem.* **1982**, *21*, 365–369.
[64] B. Langlois, D. Montègre, N. Roidot, *J. Fluor. Chem.* **1994**, *68*, 63–66.
[65] T. Billard, N. Roques, B. R. Langlois, *J. Org. Chem.* **1999**, *64*, 3813–3820.
[66] F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, *2014*, 2415–2428.
[67] A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *Angew. Chem. Int. Ed.* **2009**, *48*, 8551–8555.
[68] A. Ferry, T. Billard, E. Bacqué, B. R. Langlois, *J. Fluor. Chem.* **2012**, *134*, 160–163.
[69] X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457–3460.
[70] X. Wang, T. Yang, X. Cheng, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 12860–12864.
[71] Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shibata, *J. Am. Chem. Soc.* **2013**, *135*, 8782–8785.
[72] M. Li, J. Guo, X.-S. Xue, J.-P. Cheng, *Org. Lett.* **2016**, *18*, 264–267.
[73] D. J. Adams, J. H. Clark, P. A. Heath, L. B. Hansen, V. C. Sanders, S. J. Tavener, *J. Fluor. Chem.* **2000**, *101*, 187–191.
[74] J. H. Clark, S. J. Tavener, *J. Fluor. Chem.* **1997**, *85*, 169–172.
[75] W. Dmowski, A. Haas, *J. Chem. Soc. [Perkin 1]* **1987**, 2119.

[76] S. J. Tavener, D. J. Adams, J. H. Clark, *J. Fluor. Chem.* **1999**, *95*, 171–176.
[77] E. H. Man, D. D. Coffman, E. L. Muetterties, *J. Am. Chem. Soc.* **1959**, *81*, 3575–3577.
[78] G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 7312–7314.
[79] R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 1650–1653.
[80] W. Tyrra, D. Naumann, B. Hoge, Y. L. Yagupolskii, *J. Fluor. Chem.* **2003**, *119*, 101–107.
[81] C.-P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183–185.
[82] G. Yin, I. Kalvet, U. Englert, F. Schoenebeck, *J. Am. Chem. Soc.* **2015**, *137*, 4164–4172.
[83] M. Rueping, N. Tolstoluzhsky, P. Nikolaienko, *Chem. - Eur. J.* **2013**, *19*, 14043–14046.
[84] C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem. Int. Ed.* **2012**, *51*, 2492–2495.
[85] Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 1548–1552.
[86] C. Matheis, K. Jouvin, L. J. Goossen, *Org. Lett.* **2014**, *16*, 5984–5987.
[87] C. Matheis, V. Wagner, L. J. Goossen, *Chem. - Eur. J.* **2016**, *22*, 79–82.
[88] T. Sandmeyer, *Dtsch. Chem. Ber.* **1884**, *17*, 1633-1635.
[89] A. Hantzsch, *Ber.* **1895**, *28*, 1751.
[90] A. Hantzsch, G. W. Blagden, *Ber.* **1900**, *33*, 2544.
[91] W. S. M. Grieve, D. H. Hey, *J. Chem. Soc. Resumed* **1934**, 1797.
[92] W. A. Waters, *J. Chem. Soc. Resumed* **1942**, 266.
[93] N. Kornblum, G. D. Cooper, J. E. Taylor, *J. Am. Chem. Soc.* **1950**, *72*, 3013–3021.
[94] J. K. Kochi, *J. Am. Chem. Soc.* **1957**, *79*, 2942–2948.
[95] C. Rüchardt, E. Merz, B. Freudenberg, H.-J. Opgenorth, C. C. Tan, R. Werner, *Spec. Publ.-Chem. Soc.* **1970**, *24*, 51.
[96] J. F. Bunnett, C. Yijima, *J. Org. Chem.* **1977**, *42*, 639–643.
[97] H. Zollinger, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 141–150.
[98] R. M. Elofson, F. F. Gadallah, *J. Org. Chem.* **1969**, *34*, 854–857.
[99] I. Beletskaya, A. Sigeev, A. Peregudov, P. Petrovskii, *Synthesis* **2007**, *2007*, 2534–2538.
[100] I. P. Beletskaya, A. S. Sigeev, A. S. Peregudov, P. V. Petrovskii, *J. Organomet. Chem.* **2004**, *689*, 3810–3812.
[101] D. Qiu, L. Jin, Z. Zheng, H. Meng, F. Mo, X. Wang, Y. Zhang, J. Wang, *J. Org. Chem.* **2013**, *78*, 1923–1933.
[102] D. Qiu, H. Meng, L. Jin, S. Wang, S. Tang, X. Wang, F. Mo, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 11581–11584.
[103] D. J. Adams, A. Goddard, J. H. Clark, D. J. Macquarrie, *Chem. Commun.* **2000**, 987–988.
[104] G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 7972–7975.
[105] *Incineration of HFC-23 Waste Streams for Abatement of Emissions from HCFC-22 Production*, http://cdm.unfccc.int/methodologies/Background_240305.pdf, abgerufen am 15.09.2016.
[106] W. Han, Y. Li, H. Tang, H. Liu, *J. Fluor. Chem.* **2012**, *140*, 7–16.
[107] G. Danoun, B. Bayarmagnai, M. F. Gruenberg, L. J. Goossen, *Chem. Sci.* **2014**, *5*, 1312.
[108] B. Bayarmagnai, C. Matheis, E. Risto, L. J. Goossen, *Adv. Synth. Catal.* **2014**, *356*, 2343–2348.

[109] G. Danoun, B. Bayarmagnai, M. Grünberg, C. Matheis, E. Risto, L. Gooßen, *Synthesis* **2014**, *46*, 2283–2286.
[110] P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 5524–5527.
[111] B. Bayarmagnai, C. Matheis, K. Jouvin, L. J. Goossen, *Angew. Chem. Int. Ed.* **2015**, *54*, 5753–5756.
[112] B. Exner, B. Bayarmagnai, F. Jia, L. J. Goossen, *Chem. - Eur. J.* **2015**, *21*, 17220–17223.
[113] C. Matheis, B. Bayarmagnai, K. Jouvin, L. J. Goossen, *Org Chem Front* **2016**, *3*, 949–952.
[114] K. Kang, C. Xu, Q. Shen, *Org. Chem. Front.* **2014**, *1*, 294.
[115] R. Engel, *Chem. Rev.* **1977**, *77*, 349–367.
[116] T. S. Kumar, T. Yang, S. Mishra, C. Cronin, S. Chakraborty, J.-B. Shen, B. T. Liang, K. A. Jacobson, *J. Med. Chem.* **2013**, *56*, 902–914.
[117] R. Xie, Q. Zhao, T. Zhang, J. Fang, X. Mei, J. Ning, Y. Tang, *Bioorg. Med. Chem.* **2013**, *21*, 278–282.
[118] D. C. Morrison, *J. Am. Chem. Soc.* **1955**, *77*, 181–182.
[119] R. G. Harvey, H. I. Jacobson, E. V. Jensen, *J. Am. Chem. Soc.* **1963**, *85*, 1618–1623.
[120] B. Kaboudin, Y. Abedi, J. Kato, T. Yokomatsu, *Synthesis* **2013**, *45*, 2323–2327.
[121] Y.-C. Liu, C.-F. Lee, *Green Chem* **2014**, *16*, 357–364.
[122] J. Bai, X. Cui, H. Wang, Y. Wu, *Chem. Commun.* **2014**, *50*, 8860.
[123] S. Mitra, S. Mukherjee, S. K. Sen, A. Hajra, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2198–2201.
[124] P.-Y. Renard, H. Schwebel, P. Vayron, L. Josien, A. Valleix, C. Mioskowski, *Chem. - Eur. J.* **2002**, *8*, 2910.
[125] J. Xu, L. Zhang, X. Li, Y. Gao, G. Tang, Y. Zhao, *Org. Lett.* **2016**, *18*, 1266–1269.
[126] L. Zhang, P. Zhang, X. Li, J. Xu, G. Tang, Y. Zhao, *J. Org. Chem.* **2016**, *81*, 5588–5594.
[127] A. Foris, *Magn. Reson. Chem.* **2004**, *42*, 534–555.
[128] K. Jouvin, C. Matheis, L. J. Goossen, *Chem. – Eur. J.* **2015**, *21*, 14324-14327.
[129] B. Exner, B. Bayarmagnai, F. Jia, L. J. Goossen, *Chem. – Eur. J.* **2015**, *21*, 17220–17223.
[130] M. Hosseini-Sarvari, M. Tavakolian, *J. Chem. Res.* **2008**, *2008*, 318–321.