Rationale Entwicklung neuer nachhaltiger Methoden zur Einführung von Fluoralkyl(thio/seleno)gruppen

dem Fachbereich Chemie der Technischen Universität Kaiserslautern

zur Verleihung des akademischen Grades

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vorgelegt von

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Für meine Familie

Promotionskommission

Vorsitzender: Prof. Dr. Werner Thiel

Berichterstatter: Prof. Dr. Lukas J. Gooßen

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Die vorliegende Arbeit wurde im Zeitraum von Januar 2014 bis April 2017 im Arbeitskreis von Prof. Dr. Lukas J. Gooßen am Fachbereich Chemie der Technischen Universität Kaiserslautern angefertigt.

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 _____   _____

                                                            Christian Matheis

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Veröffentlichungen

Die Ergebnisse dieser Arbeit wurden bereits in wissenschaftlichen Fachzeitschriften veröffentlicht:

1. B. Bayarmagnai, <u>C. Matheis</u>, E. Risto, L. J. Goossen, *Adv. Synth. Catal.* **2014**, *356*, 2343-2348: „*One-Pot Sandmeyer Trifluoromethylation and Trifluoromethylthiolation*".

2. G. Danoun, B. Bayarmagnai, M. F. Grünberg, <u>C. Matheis</u>, E. Risto, L. J. Goossen, *Synthesis* **2014**, *46*, 2283-2286: „*Sandmeyer Trifluoromethylation*".

3. <u>C. Matheis</u>, K. Jouvin, L. J. Goossen, *Org. Lett.* **2014**, *16*, 5984-5987: „*Sandmeyer Difluoromethylation of (Hetero)-Arenediazonium Salts*".

4. B. Bayarmagnai, <u>C. Matheis</u>, K. Jouvin, L. J. Goossen, *Angew. Chem.* **2015**, *127*, 5845-5848; *Angew. Chem. Int. Ed.* **2015**, *54*, 5753-5756: „*Synthesis of Difluoromethyl Thioethers from Difluoromethyl Trimethylsilane and Organothiocyanates Generated in situ*".

5. <u>C. Matheis</u>, M. Wang, T. Krause, L. J. Goossen, *Synlett* **2015**, *26*, 1628-1632: „*Metal-Free Trifluoromethylthiolation of Alkyl Electrophiles via a Cascade of Thiocyanation and Nucleophilic Cyanide-CF₃ Substitution*". **Highlight-Artikel**: *Synform*, **2015**, *09*, A122-A124.

6. K. Jouvin, <u>C. Matheis</u>, L. J. Goossen, *Chem. Eur. J.* **2015**, *21*, 14324-14327: „*Synthesis of Aryl Tri- and Difluoromethyl Thioethers via a C–H-Thiocyanation/Fluoroalkylation Cascade*".

7. <u>C. Matheis</u>, V. Wagner, L. J. Goossen, *Chem. Eur. J.* **2016**, *22*, 79-82: „*Sandmeyer-Type Trifluoromethylthiolation and Trifluoromethylselenolation of (Hetero)Aromatic Amines Catalyzed by Copper*"; **Titelbild**: *Chem. Eur. J.* **2016**, *22*, 1; **Titelprofil**: *Chem. Eur. J.* **2016**, *22*, 11.

8. <u>C. Matheis</u>, 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*".

9. V. Wagner, <u>C. Matheis</u>, *Chem. Unserer Zeit* **2016**, *50*, 222: „*Fluor im Fokus der Forschung - Eine neue Strategie zur Einführung pharmazeutisch wertvoller Fluorgruppen*".

10. <u>C. Matheis</u>, T. Krause, V. Bragoni, L. J. Goossen, *Chem. Eur. J.* **2016**, *22*, 12270-12273: "*Trifluoromethylthiolation and Trifluoromethylselenolation of α-Diazo Esters Catalyzed by Copper*".

11. B. Exner, B. Bayarmagnai, <u>C. Matheis</u>, L. J. Goossen, *J. Fluorine Chem.* **2017**, im Druck, DOI: 10.1016/j.jfluchem.2016.12.006: "*Synthesis of perfluoroalkyl thioethers from aromatic thiocyanates by iron-catalysed decarboxylative perfluoroalkylation*".

Posterpräsentationen und Vorträge

Die Ergebnisse dieser Arbeit wurden von mir bereits auf internationalen Konferenzen vorgestellt:

1. „*Fluorine Days*" in Bordeaux, **2014**: „*Sandmeyer Trifluoromethylthiolation with Sodium Thiocyanate and Ruppert-Prakash Reagent*".

2. „*Fluorine Days*" in Bordeaux, **2014**: „*Sandmeyer Trifluoromethylation of Arenediazonium salts*".

3. „*OMCOS 18*" in Sitges (Barcelona), **2015**: „*Sandmeyer-type Fluoroalkylthiolations*".

4. „*OMCOS 18*" in Sitges (Barcelona), **2015**: „*Sandmeyer-type Fluoroalkylations*".

5. „*BASF - International Summer Course*" in Ludwigshafen, **2015**: „*Sustainable late-stage Fluoroalkyl(thiol)ations*".

6. Kurzvortrag bei dem „*BASF - International Summer Course*" in Ludwigshafen, **2015**: „*Sustainable late-stage Fluoroalkyl(thiol)ations*".

7. Vortrag im iNano Institut in Aarhus, **2016**: "*New Reagents and Reactions for Fluoroalkylations and Fluoroalkylthiolations*".

8. „*RCR-NanoKat Symposium*" in Kaiserslautern, **2016**: "*Sandmeyer-type Fluoroalkylations and Fluoroalkylthiolations*".

Abkürzungsverzeichnis

Ac	Acetyl
Alk	Alkyl
Anal.	Analyse
Äq./Äquiv.	Äquivalente
Ar	Aryl
ATR	Attenuated total reflection
BQ	1,4-Benzochinon
Bipy	2,2′-Bipyridin
Bu	Butyl
Calcd.	Berechnet
Cy	Cyclohexyl
DAST	Diethylaminoschwefeltrifluorid
δ	Chemische Verschiebung
DC	Dünnschichtchromatographie
DFT	Dichtefunktionaltheorie
DG	Dirigierende Gruppe
Diglyme	Diglycoldimethylether
DMF	Dimethylformamid
DMSO	Dimethylsulfoxid
ED_{50}	Effektivdosis bei 50%
ESI	Elektronensprayionisation
Et	Ethyl
et. al.	Und andere
GC	Gaschromatograph
GC-MS	Gekoppelte Gaschromatographie-Massenspektrometrie
Hal	Halogenrest
HPLC	Hochleistungsflüssigkeitschromatographie
HRMS	Hochauflösende Massenspektrometrie
^{i}Am	*Iso*-amyl
IC_{50}	Inhibitorische Konzentration bei 50%
^{i}Pr	*Iso*-propyl
SIPr	1,3-Bis(2,6-diisopropylphenyl)-imidazol-2-yliden
IR	Infrarotspektroskopie
J	Kopplungskonstante
Kat.	Katalysator
KHMDS	Kaliumhexamethyldisilazid

Konz.	Konzentration, Konzentrierte
LM	Lösungsmittel
LogP	Modellmaß für das Verhältnis zwischen Lipophilie und Hydrophilie
m	*Meta*
M	Metall
m.p.	Schmelzpunkt
Me	Methyl
MeCN	Acetonitril
Min.	Minuten
Ms	Mesyl
MS	Massenspektrometrie
neat	Lösungsmittelfrei
NMP	*N*-Methyl-2-pyrrolidon
NMR	Nuclear magnetic resonance
NTS	*N*-Thiocyanatosuccinimid
Nu	Nukleophil
o	*Ortho*
p	*Para*
Ph	Phenylgruppe
Phen	1,10-Phenanthrolin
pKs	Säurekonstante
ppm	Parts per million
p-TSA	*Para*-Toluolsulfonsäure
Quant.	Quantitativ
R	Allgemeiner organischer Rest
RT	Raumtemperatur
SET	Single electron transfer
SIPr	1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-yliden
T	Temperatur
TBAF	Tetrabutylammoniumfluorid
^{t}Bu	*Tert*-Butyl
TEMPO	2,2,6,6-Tetramethylpiperidinyloxyl
Tf	Trifluormethylsulfonyl
TFA	Trifluoressigsäure
THF	Tetrahydrofuran
TM	Trademark
TMS	Trimethylsilyl
Tol	Tolyl
Ts	4-Tolylsulfonyl
X	Allgemeine Abgangsgruppe

Nummerierung der Verbindungen

Die vorliegende Arbeit besteht zu einem großen Teil aus originalen Veröffentlichungstexten, in denen die Verbindungen unabhängig voneinander nummeriert wurden. Diese Nummerierung wurde auch im experimentellen Teil nicht geändert, wodurch Publikationen, getrennt durch die jeweiligen Kapitel, eigenständige, projektbezogenen Ziffern besitzen. Auf sonstige Nummerierungen in der Einleitung sowie im Ergebnisteil wurde gänzlich verzichtet.

Inhaltsverzeichnis

1. Kurzzusammenfassung der Arbeit

Im Rahmen dieser Arbeit wurden neue nachhaltigere Methoden zur gezielten Einführung fluoralkyl(thio/seleno)lierter Substituenten in komplexe organische Moleküle entwickelt. Dafür wurde insbesondere die Sandmeyer-Reaktion als universelles Werkzeug zur Funktionalisierung breit verfügbarer Aniline genutzt (**Schema 1**).
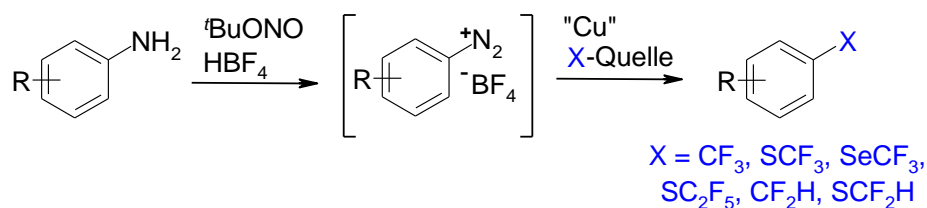
Schema 1. Die Sandmeyer-Reaktion zur Einführung diverser fluorierter Gruppen.

Die entscheidenden Vorteile dieser Technologie sind die milden Reaktionsbedingungen, das breite Substratspektrum und die exzellente Toleranz funktioneller Gruppen, weshalb sie sich selbst für komplexe Verbindungen in einem späten Synthesestadium eignet. Außerdem zeichnen sich die in dieser Arbeit entwickelten Prozesse zur direkten Einführungen von SCF_3-, $SeCF_3$ und SC_2F_5-Gruppen dadurch aus, dass sie mit Kupfermengen von nur 10 mol% zu den seltenen Beispielen katalytischer Sandmeyer-Reaktionen gehören.

Unter ebenso vorteilhaften Reaktionsbedingungen und gleicher katalytischer Kupfermengen konnten auch α-Diazoester, die selbst leicht aus Aminosäuren herstellbar sind, zu den entsprechenden Trifluormethylthio- und Trifluormethylselenoethern umgesetzt werden (**Schema 2**).
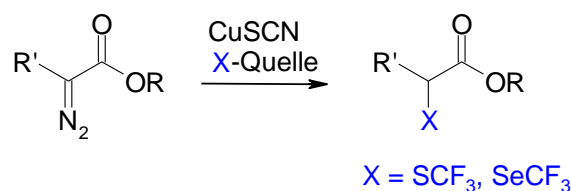
Schema 2. Trifluormethylthio- und Trifluormethylselenolierung von α-Diazoestern.

In weiteren Projekten gelang es, neue Zugänge zu Di- und Trifluormethylthioethern durch das innovative Reaktionskonzept der Thiocyanierung/Fluoralkylierungskaskade zu etablieren.

1

Breit verfügbare Alkylelektrophile wurden hierbei unter milden Reaktionsbedingungen und preiswerten Schwefel- und Fluoralkyl-Quellen di- und trifluormethylthioliert. (**Schema 3**).
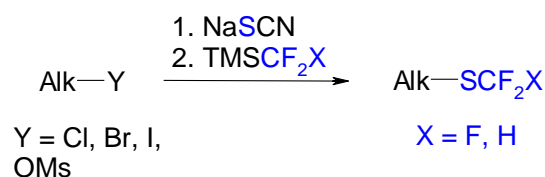
Schema 3. Difluormethylthio- und Trifluormethylthiolierung von Alkylelektrophilen.

Außerdem konnte die Reaktionskaskade auch für regioselektive elektrophile C–H-Fluoralkylthiolierungen elektronenreicher Aromaten mit NTS als nachhaltige elektrophile Schwefelquelle genutzt werden (**Schema 4**).
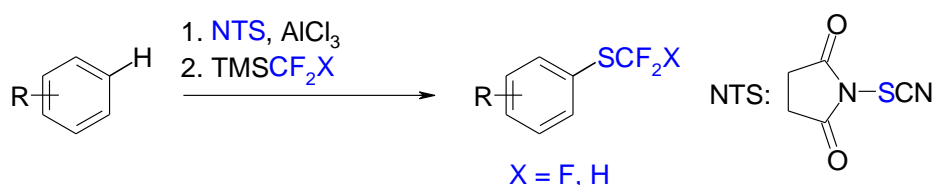
Schema 4. Elektrophile C–H-Difluormethylthio- und Trifluormethylthiolierung.

In allen neuen Verfahren wurden konsequent praktische Fluoralkyl(thio/seleno)-Quellen verwendet, die auf dem nachhaltigen Ruppert-Prakash-Reagenz $TMSCF_3$ basieren. Dies ist ein entscheidender Vorteil gegenüber bekannten Verfahren, die häufig präformierte, instabile Metall-Salze oder teure, hochmolekulare Reagenzien verwenden.

Das große synthetische Potential der neu entwickelten Methoden wurde jeweils anhand zahlreicher funktionalisierter Substrate demonstriert. Darüber hinaus lieferten mechanistische Studien einen näheren Einblick in den Ablauf der Reaktionen.

2

2. Struktur der Arbeit

Die vorliegende Arbeit wurde kumulativ verfasst. Aufgrund dieser Promotionsform enthält die Ausarbeitung elf englische Originaltexte und einen deutschen Highlight-Artikel eigener wissenschaftlicher Veröffentlichungen. Neben den Referenzen in dieser Arbeit gehören auch die Literaturstellen der abgebildeten Publikationen zu den jeweiligen Projekten. Die Beiträge der einzelnen Autoren an den Projekten werden vor den abgebildeten Publikationen beschrieben. Herr Prof. Dr. L. J. Gooßen unterstützte als Betreuer meiner Dissertation alle Arbeiten beratend.

Die Einleitung zeigt die Bedeutung, Eigenschaften und Methoden zur Einführung der in dieser Arbeit dargestellten fluorierten Gruppen. Außerdem wird die Sandmeyer-Reaktion als Schlüsseltechnologie für die entwickelten Funktionalisierungen vorgestellt.

Nach einer allgemeinen Aufgabenstellung werden im Ergebnisteil die einzelnen Projekte kurz beschrieben, die Ziele erläutert und die jeweiligen englischen Originalveröffentlichungen abgebildet.

Der experimentelle Teil enthält die Spezifikationen der eingesetzten Messinstrumente, alle verwendeten Versuchsvorschriften und die Charakterisierung der hergestellten Verbindungen. Das Kapitel wurde teilweise auf Englisch verfasst, da es zum größten Teil aus dem Material der zugehörigen „Supporting Information" der Originalveröffentlichungen besteht.

Im Anschluss daran folgen das Literaturverzeichnis und ein kurzer Lebenslauf.

3. Einleitung

3.1. Fluor und fluorierte Verbindungen

3.1.1. *Allgemeines*

Fluor ist eines der 13 meist vorkommenden Elemente in der Erdkruste, wo es hauptsächlich in den Mineralen Kryolith (Na_3AlF_6), Fluorit (CaF_2) und Fluorapatit ($Ca_5(PO_4)_3F$) gebunden vorliegt.[1] Dennoch wurde das toxische und extrem korrosive elementare Fluor erstmals 1886 von Henri Moissau durch die Elektrolyse einer Kaliumhydrogenfluoridlösung in flüssigem Fluorwasserstoff hergestellt und charakterisiert.[2] Diese bahnbrechende Arbeit des französischen Chemikers wurde 1906 mit dem Chemie-Nobelpreis honoriert. Fluor ist das leichteste Halogen und hat mit der Elektronenkonfiguration $[(1s^2)(2s^3)(2p^5)]$ einen Van-der-Waals-Radius von 1.47 Å, der nur geringfügig größer als der des kleinsten Elements Wasserstoff mit 1.20 Å ist.[3] Außerdem ist es mit 3.98 auf der Pauling-Skala das elektronegativste und reaktivste Element des Periodensystems. Dies lässt sich durch die unbesetzte Elektronenschale und die kurze Bindungslänge von nur 144 ppm erklären, welche zu einer starken Annäherung der freien Elektronenpaare führen und die Bindung extrem abschwächen.[4–6] Folglich ist es so aktiv, dass es mit allen Elementen, außer den Edelgasen Helium und Neon, reagieren kann.[7,8] Fluor wird deshalb als „Superhalogen" angesehen, was verdeutlicht, wie stark dessen Eigenschaften von denen anderer Halogene abweicht (**Tabelle 1**).[9]

Tabelle 1. Ausgewählte Eigenschaften von Fluor im Vergleich zu anderen Elementen.[10]

	H	**F**	Cl	Br	I
Elektronegativität (Pauling)	2.10	**4.00**	3.20	2.80	2.50
Van-der-Waals-Radius (Å)	1.20	**1.47**	1.75	1.85	1.98
C–X Bindungslänge (Å)	1.09	**1.35**	1.77	1.90	2.10
C–X Bindungsdissoziations-energie (kJ/mol)	420	**490**	328	301	218

Kohlenstoff-Fluor-Bindungen weisen eine starke Polarisierung auf und zählen durch den hohen ionischen Bindungsanteil zu den stärksten Bindungen in der organischen Chemie.[11] Dennoch kommen nur sehr wenige Organofluorverbindungen in der Natur vor (**Abbildung 1**).[12–14]
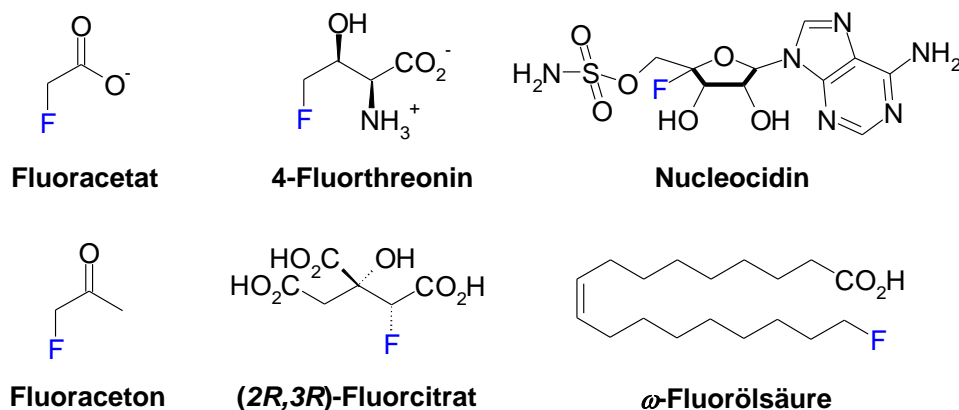
Abbildung 1. Natürlich vorkommende organische Fluorverbindungen.[14]

Diese natürlich vorkommenden fluorhaltigen Verbindungen konnten aus tropischen und subtropischen Pflanzen und zwei Mikroorganismenarten, sogenannten Aktinobakterien, gewonnen werden. Bemerkenswerterweise wurde bislang keine einzige organische Fluorverbindung aus dem Tierreich oder jedweden Organismen aus der maritimen Welt isoliert.[3] Dies lässt sich vor allem durch die geringe Löslichkeit natürlich vorkommender Fluorsalze (Kryolith, Fluorit, Fluorapatit) und der geringen Nukleophilie von Fluor unter neutralen Bedingungen erklären, wodurch es in wässrigen, biologischen Systemen nur schwer verfügbar ist.[15]

Die starke Kohlenstoff-Fluor-Bindung und die damit verbundenen vorteilhaften Eigenschaften stellen einige Gründe dar, weshalb organische Fluorverbindungen besonders attraktiv für diverse Bereiche in der Chemie sind. So werden bei der Entwicklung neuer bioaktiver Moleküle, vor allem in der Agrochemie und pharmazeutischen Chemie, fluorierte Gruppen als Substituenten von Wirkstoffkandidaten routinemäßig getestet.

3.1.2. *Bedeutung von Fluorsubstituenten in bioaktiven Molekülen*

Fluorhaltige Gruppen sind zentrale Bausteine diverser Klassen bioaktiver Moleküle und werden als gängige strukturelle Leitmotive in deren Entwicklung genutzt. Derzeit sind

Fluoratome in etwa 40% aller Agrochemikalien und 25% aller Pharmazeutika auf dem Markt enthalten.[12,15–17] Daraus folgt, dass auch unter den weltweit 20 umsatzstärksten Medikamenten wichtige pharmakologische Wirkstoffe mit Fluorsubstituenten vertreten sind (**Abbildung 2**).[18]

Fluticason
Entzündungshemmer

Rosuvastatin
Cholesterinsenker

Sitagliptin
Antidiabetikum
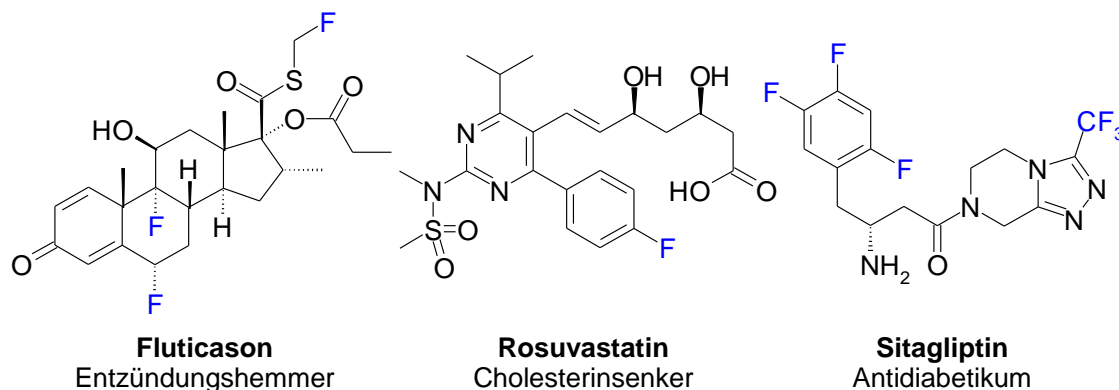
Abbildung 2. Beispiele fluorierter Moleküle aus den meist verkauften Arzneimitteln von 2013.[18]

Durch die Einführung von Fluorsubstituenten werden physikalische und chemische Eigenschaften organischer Verbindungen stark beeinflusst. Insbesondere in der Wirkstoffforschung wird dies routinemäßig genutzt. So werden beispielsweise metabolisch labile Positionen eines Wirkstoffs durch selektive Fluorierung geschützt, um den frühzeitigen Abbau zu verhindern, da C–F-Bindungen gegenüber enzymatischen Spaltungen meist inert sind.[3] Moleküle mit Fluorsubstituenten besitzen dadurch eine besonders hohe thermische und oxidative Stabilität. Ferner kann durch Einbau von Fluorgruppen in Wirkstoffkandidaten die Bioverfügbarkeit gesteigert werden. Beispielsweise lassen sich die pKs-Werte von Verbindungen gezielt verändern, sodass diese deutlich besser vom Zielorganismus resorbiert werden.[16,17] Darüber hinaus wird die Lipophilie gesteigert und dadurch der passive Transport der Wirkstoffe durch die unpolaren Zell-/Lipidmembranen erleichtert.[4,19] Außerdem können Geschwindigkeiten und Selektivitäten der Aufnahme aktiver Verbindungen durch die rationale Einführung fluorierter Gruppen so abgestimmt werden, dass optimale Wirkung bei möglichst kleinster Konzentration des Wirkstoffes erreicht wird.[19]

Bestimmte fluorierte Substituenten können andere funktionelle Gruppen in Wirkstoffkandidaten ersetzen und durch ebendiese nützlichen Eigenschaften die Bioaktivität verbessern, ohne die chemische Struktur signifikant zu ändern. Dieses Verhalten bezeichnet

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man als Bioisosterie - ein Konzept, welches in der heutigen Wirkstoffforschung eine zentrale Rolle einnimmt.

3.2. Das Bioisosterie-Konzept

3.2.1. *Allgemeines*

Die Bioisosterie wurde erstmals von Erlenmeyer in den 1930er Jahren erforscht. In einer Studienreihe zeigte er, dass strukturell verschiedene Verbindungen von biologischen Systemen vergleichbar wahrgenommen werden können.[20–22] Die Begriffsbildung geht schließlich auf Friedmann aus dem Jahr 1951 zurück und setzt sich aus *Biologie* und dem von Langmuir 1919 etablierten Begriff *Isosterie* zusammen.[23,24] Wörtlich übersetzt bedeutet es: „Gleiche biologische Wirkung bei gleicher Gestalt" (isos: gleich, steros Ort, Gestalt). Dies bezieht sich auf pharmakologisch wirksame Verbindungen, die vor allem *in vivo* einen vergleichbaren Effekt erzielen.[25] Bioisostere entstehen dadurch, dass ein Atom oder eine funktionelle Gruppe eines bioaktiven Moleküls mit einem chemisch und physikalisch ähnlichen Atom oder Gruppe ausgetauscht wird. Sie werden generell in klassische Bioisostere, die elektronisch und sterisch sehr ähnlich sind, und nicht-klassische Bioisostere, wesentlich komplexere und elektronisch ungleichere Gruppen, unterteilt (**Abbildung 3**).[26]

Klassische Bioisostere

- **Monovalente Atome/Gruppen:**

D, H
F, H
NH$_2$, OH
RSH, ROH
F, OH, NH$_2$, CH$_3$,
Cl, Br, SH, OH

- **Di-/Trivalente Atome/Gruppen:**

C=C, C=N, C=O, C=S

$-$CH$_2^-$, $-$NH$-$, $-$O$-$

$-$CH=, $-$N=

- **Ring Äquivalente:**
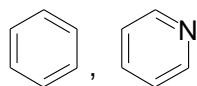
Nicht-klassische Bioisostere

- **Carbonsäure Bioisostere:**
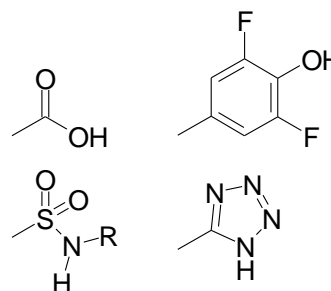
- **Phenol Bioisostere:**
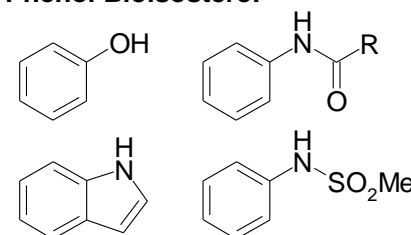
Abbildung 3. Beispiele klassischer und nicht-klassischer Bioisostere.

Das Ziel eines solchen Austausches besteht darin, neue Moleküle mit vergleichbaren bioaktiven Eigenschaften herzustellen. Vorzugsweise sollen dadurch die grundlegenden Eigenschaften der Verbindung insgesamt positiv beeinflusst werden. Besonders im immer kostenintensiveren Wirkstoffdesign ist es wichtig, zielgerichtet nach neuen Kandidaten zu suchen. Dazu trägt vor allem die Bioisosterie als fundamentales Konzept in der Wirkstoffforschung wesentlich bei. Nachdem eine Leitstruktur für eine gewollte bioaktive Funktion gefunden wird, werden routinemäßig bestimmte Strukturen durch ihre Bioisostere ersetzt und untersucht.[26] Dies führt im Optimalfall zu verbesserten Eigenschaften eines Wirkmoleküls. Durch die gezielte Anpassung von Größe, Konformation sowie induktiven und mesomeren Effekten, werden zum Beispiel höhere Affinitäten und Selektivitäten, aber auch eine größere Stabilität erzielt. Es lassen sich aber auch physikochemische Parameter einer Verbindung konsequent beeinflussen. Diese können Lipophilie, Polarität, Elektronendichte, Dynamik und die Löslichkeit betreffen und dadurch die Bioverfügbarkeiten von Verbindungen erhöhen.[27] Aber auch für die Rationalität der Synthese eines Wirkstoffs spielt die Bioisosterie eine wichtige Rolle. Darüber hinaus kann eine bioisostere Substruktur eines komplexen Arzneimittels ein anderes Wirkprofil liefern oder durch andere metabolische Wege abgebaut werden, die zu weniger toxischen Zwischenprodukten führen. Ferner lassen

sich mittels des Bioisosterie-Konzeptes sowohl die Anzahl der Synthesestufen im Verhältnis zur Gesamtausbeute als auch die Entwicklungszeiten bioaktiver Leitstrukturen optimieren.

Der große Einfluss einer bioisosteren Gruppe lässt sich anhand des Analgetikums sowie Entzündungshemmers Aminopyrin, welches 1896 auf den Markt kam, verdeutlichen. 1922 wurden die kanzerogenen Eigenschaften des potenten Wirkstoffs nachgewiesen. Fast 30 Jahre später gelang es der Firma *Roche*, durch die bioisostere Modifikation der Dimethylaminogruppe das kanzerogene Verhalten komplett zu unterdrücken ohne die Bioaktivität zu mindern (**Abbildung 4**).[28]

Aminopyrin
kanzerogen

vs.

Propylphenazon
nicht-kanzerogen
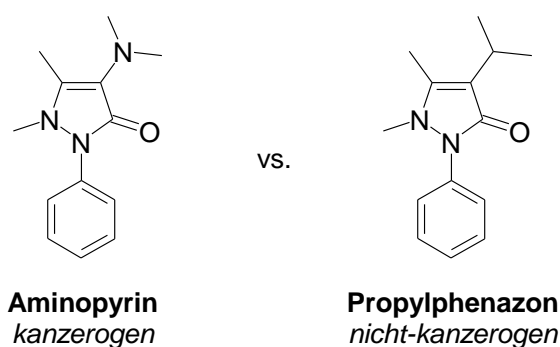
Abbildung 4. Bioisostere Modifikation eines kanzerogenen Wirkstoffs.

Die Bioisosterie wird als ein breit etabliertes und starkes Konzept weiterhin eine wichtige Rolle in der Wirkstoffentwicklung einnehmen.

3.2.2. *Fluorierte Gruppen als Bioisostere*

Fluorierte Gruppen haben eine bedeutende Rolle im Bioisosterie-Konzept.[29,30] Da sich durch deren Einführung die bioaktiven Eigenschaften von Wirkstoffkandidaten einzigartig intensivieren, beziehungsweise gezielt verändern lassen, werden sie besonders häufig als Bioisostere funktioneller Gruppen verwendet. Mittlerweile werden Leitstrukturen systematisch durch fluorierte Gruppen, den sogenannten „Fluorine Scans", in der Wirkstoffforschung modifiziert. Dadurch gelingt es wesentlich potentere Verbindungen als Arzneistoffkandidaten im Vergleich zu ihren nicht-fluorierten Analoga zu identifizieren. Die außergewöhnliche Bedeutung der Fluorine Scans wird nachfolgend kurz anhand von zwei Beispielen erläutert.

Während des Entwicklungsprozesses des Cholesterol-Resorptionshemmers Ezetimib gelang es, den Metabolismus zu toxischen Nebenprodukten, die sogenannte Off-Target Aktivität, der Leitstruktur wesentlich zu verringern. Dafür wurden metabolisch instabile Gruppen beziehungsweise labile Stellen des Moleküls, durch besonders starke C–F-Bindungen strategisch ersetzt. Die relativ kleinen Fluoratome beeinträchtigen die Bindung an das Zielprotein kaum und somit bleibt die ursprüngliche Bioaktivität des Wirkstoffs unverändert (**Abbildung 5**).[31]

Leitstruktur
ED_{50} (Ratte) = 2.00 mg/kg

Ezetimib
ED_{50} (Ratte) = 0.03 mg/kg

Toxizität↓

**Cholesterol-
Resorptionshemmer**
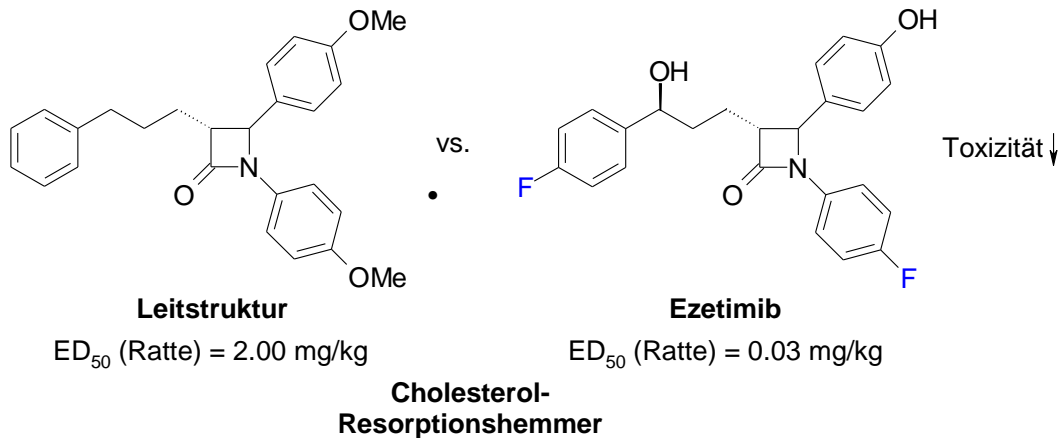
Abbildung 5. Entwicklung des Wirkstoffs Ezetimib durch bioisostere Modifikation.

In einem weiteren Beispiel zeigte sich bei der bioisosteren Modifikation eines Antidiabetikums, dass ein Phenol mit zwei Fluoratomen als lipophileres Bioisoster der Carbonsäuregruppe fungieren kann. Daraus resultierte eine sechsfach höhere Aktivität des Wirkstoffs. Dies basiert einerseits auf der kombinierten Wirkung der positiv polarisierten Hydroxygruppen, die vergleichbare Azidität erzeugen, und andererseits auf der Fähigkeit der Fluoratome, die Carbonylgruppe der Carbonsäure als Wasserstoffbindungsakzeptor nachzuahmen (**Abbildung 6**).[32]
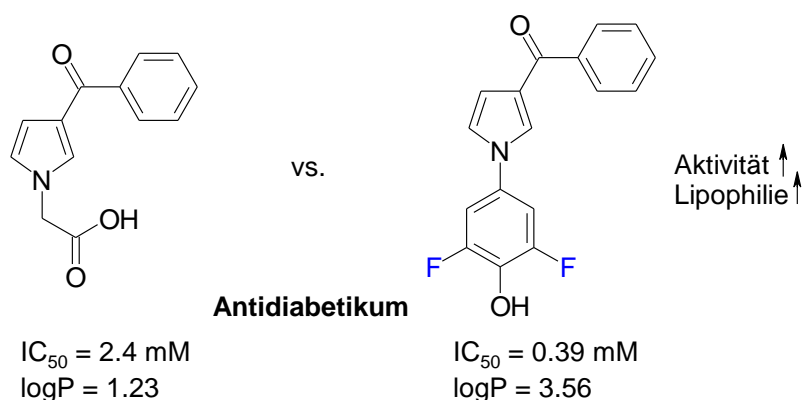
Abbildung 6. Fluorierte Gruppen als Bioisostere zur Steigerung der bioaktiven Wirkung.

Die einzigartigen chemischen und physikalischen Eigenschaften von Fluoratomen haben zu einer raschen Entwicklung verschiedener fluorierter Substituenten geführt, die mittlerweile in der Wirkstoffentwicklung breite Anwendung als Bioisostere von verschiedenen Funktionalitäten finden. Aufgrund der steigenden Nachfrage wurden in den letzten Jahrzehnten viele neue Reaktionen und Reagenzien entwickelt, welche die regio- und stereoselektive Einführung von Fluorsubstituenten selbst in komplexe organische Moleküle ermöglichen.

3.3. Trifluormethylgruppen

3.3.1. *Eigenschaften und Verwendung*

Trifluormethylgruppen erhielten eine große Aufmerksamkeit innerhalb der Fluorsubstituenten und sind besonders wertvoll in unzähligen Pharmazeutika, Pflanzenschutzmitteln und Funktionsmaterialien.[12,15–17,33,34] Dies lässt sich durch den einzigartigen Einfluss auf Wirkstoffkandidaten erklären. Die drei starken C–F-Bindungen führen zu einer hohen Stabilität und durch die elektronenziehenden Fluoratome ist die CF$_3$-Gruppe mit 3.45 auf der Pauling-Skala etwa so elektronegativ wie Sauerstoff mit 3.44.[35] Trifluormethylgruppen erhöhen die Lipophilie von Verbindungen aufgrund ihrer geringen Polarisierbarkeit (Hansch Konstante = 0.88) deutlich.[36] Dadurch wird der passive Transport von Wirkstoffen durch die unpolare Zellmembran immens verbessert.[19] Dabei ist die Trifluormethylgruppe mit einem Van-der-Waals-Radius von 2.7 Å nur geringfügig größer als eine Methylgruppe, die einen Van-der-Waals-Radius von 2.0 Å besitzt.[37] Die

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Bioverfügbarkeit und die metabolische Stabilität des Wirkstoffs wird durch eine eingeführte CF$_3$-Gruppe stark verbessert. Deshalb eignen sie sich als exzellentes Bioisoster einer Methyl- beziehungsweise Methoxygruppe, wobei sich der Enzym-Substrat-Komplex bei bioaktiven Verbindungen wegen der geringen Größenunterschiede der Substituenten kaum verändert.

Aufgrund der genannten beachtlichen Eigenschaften ist es nicht verwunderlich, dass die Trifluormethylgruppe als Schlüsselfunktionalität in einer Vielzahl kommerziell bedeutsamer pharmazeutischer und agrochemischer Wirkstoffe eingesetzt wird (**Abbildung 7**).

Fluoxetin
Antidepressivum

Celecoxib
Entzündungshemmer

Efavirenz
antiretroviraler Arzneistoff

Trifloxystrobin
Fungizid

Norflurazon
Herbizid

Beflubutamid
Herbizid
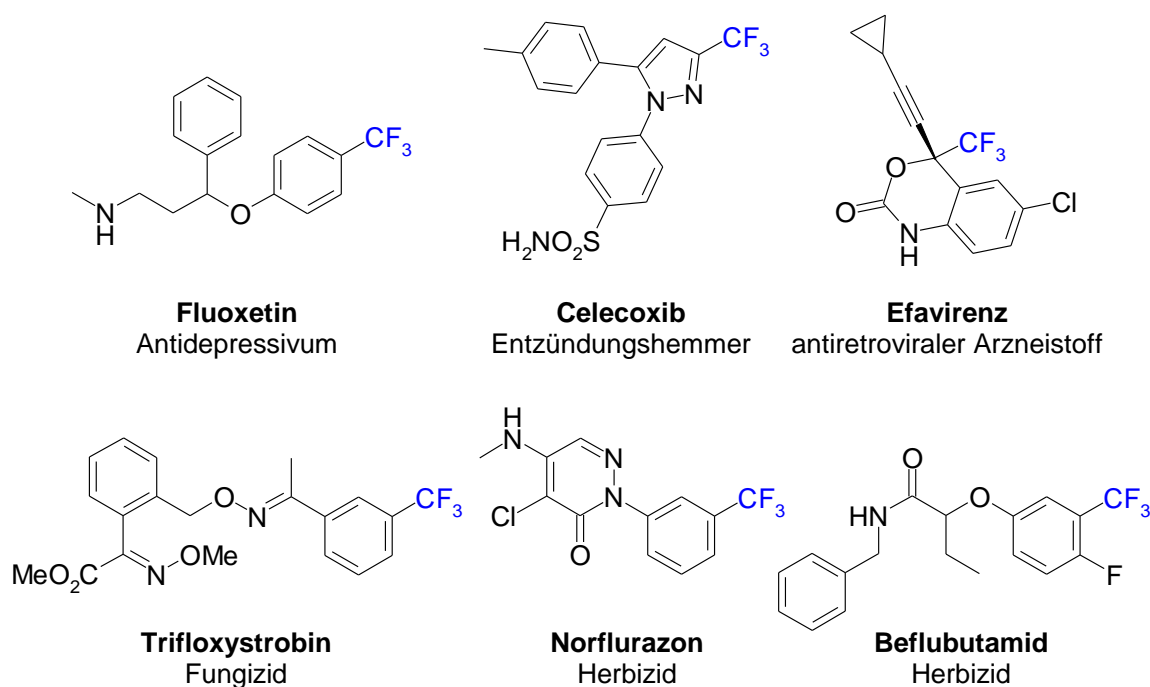
Abbildung 7. Biologisch aktive Moleküle mit CF$_3$-Gruppen.

Fluoxetin, Celecoxib und Efavirenz sind nur einige etablierte Beispiele für potente Arzneimittel mit Trifluormethylgruppen, bei den Agrochemikalien sind beispielsweise Trifloxystrobin, Norflurazon und Beflubutamid zu nennen.[4,12,16,38]

3.3.2. *Einführung von Trifluormethylgruppen*

In den letzten Jahren wurden zunehmend effizientere Reaktionen und Reagenzien zur Trifluormethylierung entwickelt, die die regio- und stereoselektive Einführung von CF$_3$- Gruppen in hochkomplexe organische Moleküle in späten Syntheseschritten ermöglichen. Die meisten Prozesse sind allerdings nach wie vor durch den hohen Preis der CF$_3$-Quelle, der

begrenzten Toleranz funktioneller Gruppen oder der hohen Katalysatorbeladung zu limitiert, um echte Alternativen für synthetische und industrielle Anwendungen darzustellen.

Klassische Methoden zur Synthese trifluormethylierter Verbindungen basieren auf der sogenannten Swarts-Reaktion. Dabei werden durch einen Fluor-Halogen-Austausch an einem bereits vorhandenen Kohlenstoffatom Alkylhalogenide in die entsprechenden Alkylfluoride überführt (**Schema 5**, **A**).[39] Bis heute wird die Swarts-Reaktion zur Trifluormethylierung strukturell einfacher Verbindungen im industriellen Verfahren genutzt.[40] Allerdings erfordert diese Methode raue Reaktionsbedingungen und gefährliche, extrem korrosive Fluorwasserstoffsäure oder Antimon(III)-fluorid, sodass ihr Einsatz nur zu Anfang einer Synthesesequenz möglich ist.

Moderne Übergangsmetall-katalysierte Methoden erlauben eine mildere Einführung von Trifluormethylgruppen in hochfunktionalisierte Startmaterialien. Aufbauend auf den Pionierarbeiten von McLoughlin, Yagupolskii, Burton, Chambers, Grushin und anderen, konnten in den letzten Jahren bedeutende Fortschritte hinsichtlich nachhaltiger Trifluormethylierungen erzielt werden.[10,41–46] Die genauen Reaktionsbedingungen werden in dieser Arbeit aufgrund der Vielfalt unterschiedlicher Protokolle nicht näher vorgestellt. Das Augenmerk soll hier vielmehr auf die Methoden, die Ausgangsstoffe und anschließend detaillierter auf die verwendeten Reagenzien gelegt werden.

Die aktuellen Protokolle lassen sich grob in fünf Kategorien unterteilen (**Schema 5**, **B**-**F**). Hierzu gehört die Kupplung von Arylelektrophilen, beispielsweise Halogenide, mit nukleophilen CF_3-Reagenzien; in der Regel stöchiometrisch eingesetzte Kupfer- oder spezielle Palladium-CF_3-Komplexe (**B**).[47–53] Arylnukleophile, beispielsweise Boronsäuren, können über oxidative Übergangsmetall-katalysierten Kupplungen mit nukleophilen CF_3-Quellen zur Synthese von Benzotrifluoriden verwendet werden (**C**).[54,55] Außerdem können Arylnukleophile mit einer Reihe elektrophiler CF_3-Reagenzien reagieren (**D**).[56,57] Bei C–H-Funktionalisierungen, wie zum Beispiel der *ortho*-Trifluormethylierung donor-substituierter Arenen oder der Kupplung elektronenreicher Aromaten (**E**), werden elektrophile Trifluormethylierungsreagenzien und häufig Palladiumkatalysatoren eingesetzt.[58,59] Es sind aber auch einige C–H-Trifluormethylierungen von Heteroaromaten mit nukleophilen Trifluormethylierungsreagenzien unter oxidativen Bedingungen bekannt.[60] Daneben wurden

radikalische Trifluormethylierungen von Arenen basierend auf Peroxid- oder Rutheniuminitiatoren entwickelt (**F**).[61–63]
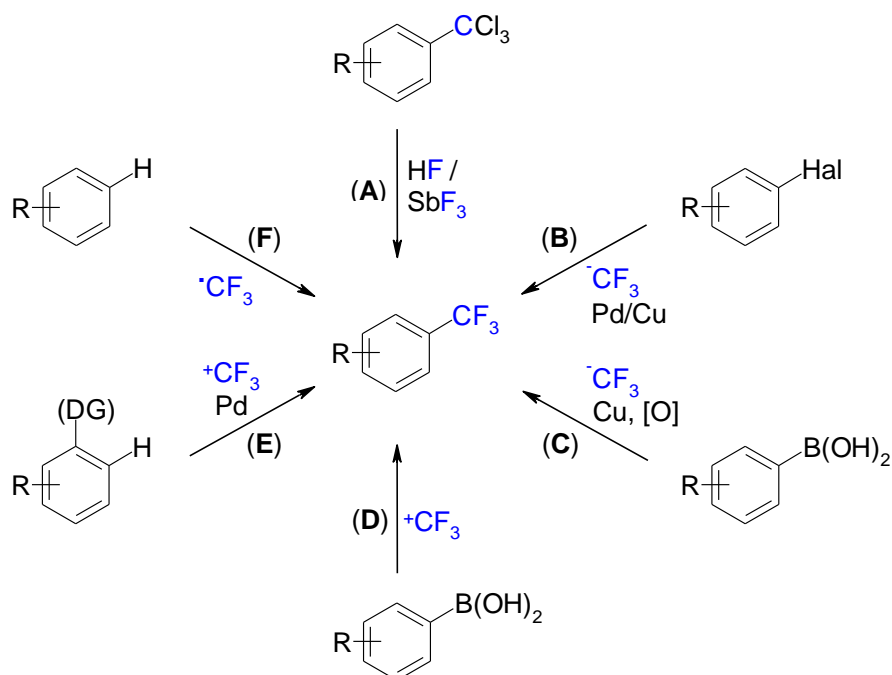
Schema 5. Strategien zur Einführung der Trifluormethylgruppe in Aromaten.

In den letzten Jahren wurden diverse Methoden zur Trifluormethylierung entwickelt, wobei die Nachhaltigkeit dieser Systeme nicht zuletzt durch die Wahl des Trifluormethylierungsmittels bestimmt wird. Für die im **Schema 5** vorgestellten Reaktionsvarianten werden hauptsächlich folgende nukleophile und elektrophile CF$_3$-Quellen, die auch als Vorstufen für radikalische Trifluormethylierungen genutzt werden, verwendet (**Abbildung 8**):

Nukleophile CF$_3$-Quellen:

M(CF$_3$)$_x$ HCF$_3$ F$_3$C—C(=O)OR F$_3$C—S(=O)OR TMSCF$_3$ K[F$_3$CB(OMe)$_3$]

M = Cu, Cd, Zn (**Burton**) (**Kashimiura**) (**Ruppert,** (**Röschenthaler**,
(Phen)Cu (**Hartwig**) **Prakash**) **Gooßen**)
Ag (**Feng, Weng, Huang**) R = Na (**Kondo**) (**Langlois**)
Me (**Langlois**)
Cu (**Vicic, Weng**)

Elektrophile CF$_3$-Quellen:

XCF$_3$

X = I (**Kobayashi**)
Br (**Paratian**)

TfO$^-$ CF$_3$ BF$_4^-$ CF$_3$
(**Yagupolskii**, (**Umemoto**) (**Togni**) (**Shibata**)
Shreeve)
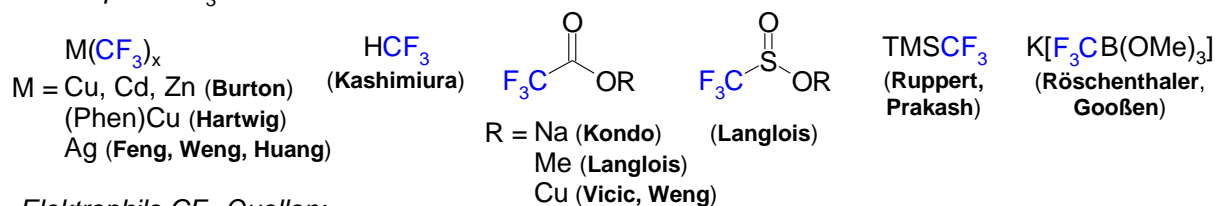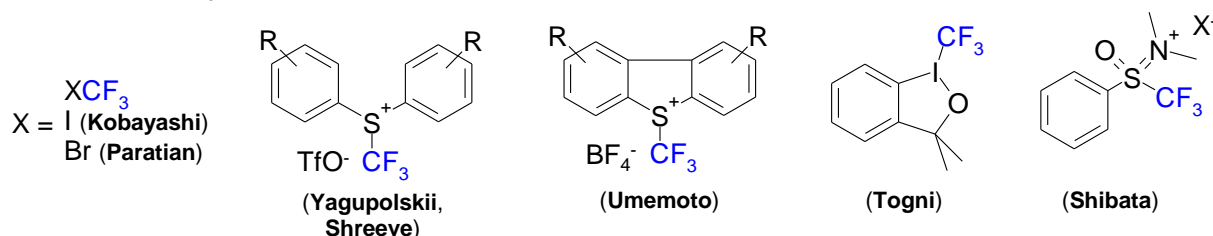
Abbildung 8. Übersicht moderner Trifluormethylierungsreagenzien.

Die Herausforderung bei nukleophilen Trifluormethylierungen liegt besonders in der Instabilität des CF$_3$-Anions. Wenn es nicht als Metall-CF$_3$-Komplex stabilisiert wird, zerfällt das Anion leicht unter α-Fluorideliminierung in ein Fluoridion und ein Difluorcarben. Allerdings wird bei starken Metall-CF$_3$-Bindungen, die reduktive Eliminierung der CF$_3$-Spezies durch den hohen polaren Anteil und die Rückbindung der d-Orbitale in die σ*-(C—F)-Bindungen erschwert. Dennoch wurden für frühe Trifluormethylierungen hauptsächlich präformierte Metall-CF$_3$-Salze aus Kupfer, Silber, Cadmium und Zink verwendet.[64–68] Allerdings sind diese Komplexe extrem instabil, weshalb sie für viele Reaktionen frisch hergestellt und unter striktem Wasser- und Luftausschluss direkt eingesetzt werden müssen. Einzig Hartwigs (Phen)CuCF$_3$-Komplex, der mittlerweile unter dem Namen Trifluoromethylator™ kommerzialisiert wurde, ist bei Raumtemperatur stabil und ermöglicht einfachere Protokolle zur Trifluormethylierung von Arylelektrophilen.[53] Allerdings leidet die Atomökonomität dieser Verfahren aufgrund des großen Liganden zur Stabilisierung des CuCF$_3$-Komplexes. Insgesamt werden für alle Methoden mit Metall-CF$_3$-Komplexen stöchiometrische Mengen an Metall verwendet, weshalb diese Reaktionen vom praktischen Nutzen her begrenzt sind.

Die theoretisch attraktivste CF$_3$-Quelle ist Fluoroform, da es weder toxisch noch ozonschädlich ist und Trifluormethylierungen mit HCF$_3$ atomökonomisch sind.[69] Der größte Vorteil ist, dass es als ein Nebenprodukt der Teflon-Herstellung jährlich im Tonnenmaßstab als Abfall anfällt. Dennoch ist die großtechnische Nutzung als Synthesebaustein

problematisch und im Vergleich zu der anfallenden Menge nicht annähernd angemessen. Dies begründet sich vor allem durch die Limitierungen bei der Prozessoptimierung, da das Gas im Labormaßstab teuer und schwer zu handhaben ist. Deshalb wurde bisher nur von wenigen speziellen und durch starke Basen induzierte Trifluormethylierungen aktivierter Carbonylverbindungen mittels CF_3-Anionen aus Fluoroform berichtet.[70,71]

Neben Fluoroform sind auch Derivate der Trifluoressigsäure ideale Reagenzien zur Trifluormethylierung, da sie preiswert, nicht toxisch sowie atomökonomisch sind und formal nur CO_2 als Nebenprodukt freisetzen. Bislang wurden von Trifluormethylierungen mit Natrium-,[72] Kupfertrifluoracetaten[73,74] und Trifluoressigsäuremethylester berichtet.[75] Allerdings wird häufig ein großer Überschuss dieser Reagenzien benötigt. Außerdem sind sie nur schwer zu aktivieren, wofür häufig hohe Reaktionstemperaturen benötigt werden, die intermediär gebildete Metall-CF_3-Komplexe zur Stabilisierung von CF_3-Anionen nicht tolerieren. Deshalb sind bislang nur wenige effiziente Trifluormethylierungen mit Derivaten der Trifluoressigsäure bekannt.

Ähnlich zu diesen Reagenzien beschrieb Langlois verschiedene CF_3-Sulfinate (F_3CSO_2R), die nach Metall-vermittelter Extrusion von SO_2 nukleophile Trifluormethylierungen ermöglichen.[61,76] Diese Sulfinate können durch den Halogenaustausch der entsprechenden chlorierten Analoga oder ausgehend von ozonschädigenden Interhalogenverbindungen dargestellt werden.

Die am häufigsten verwendete nukleophile CF_3-Quelle ist Trifluormethyltrimethylsilan (TMSCF$_3$), das erstmals von Ruppert im Jahre 1984 synthetisiert wurde.[77] Prakash leistete mit dem vielseitig anwendbarem Reagenz wichtige Pionierarbeiten, weshalb es in der Literatur als Ruppert-Prakash-Reagenz bekannt wurde.[10] TMSCF$_3$ revolutionierte als stabile und einfach handhabbare CF_3-Quelle die Entwicklung neuer effizienter Trifluormethylierungsreaktionen, so wie die wegweisende Palladium-katalysierte Trifluormethylierung von Arylchloriden von Buchwald.[51,78] Allerdings musste das Ruppert-Prakash-Reagenz lange Zeit ausgehend von ozonschädigenden Interhalogenverbindungen dargestellt werden. Erst 2012 konnte Prakash in bahnbrechenden Arbeiten zeigen, dass TMSCF$_3$ einfach aus dem Abfallprodukt Fluoroform zugänglich ist (**Schema 6**).[79] Dadurch gewinnen effektive Trifluormethylierungen mit TMSCF$_3$ erstmals echte industrielle Bedeutung.
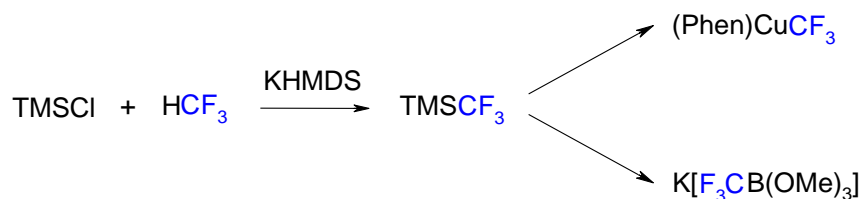
Schema 6. Synthese effizienter nukleophiler CF$_3$-Quellen.

Nachdem Röschenthaler von dem Boratsalz K[F$_3$CB(OMe)$_3$], welches leicht aus TMSCF$_3$, B(OMe)$_3$ und KF zugänglich ist (**Schema 6**), berichtet hatte,[80] erkannte Gooßen dessen großes Potential als eine stabile, leicht handhabbare und vor allem kristalline Alternative zu dem flüssigen Ruppert-Prakash-Reagenz. Tatsächlich gelang die effiziente Trifluormethylierung von Aryliodiden und –boronsäureestern mit katalytischen Kupfermengen.[49,55] Obwohl K[F$_3$CB(OMe)$_3$] eine interessante CF$_3$-Quelle darstellt, konnte es bislang allerdings nur für ausgewählte Trifluormethylierungsreaktionen verwendet werden.

Insgesamt wird deutlich, dass das Ruppert-Prakash-Reagenz die effizienteste nukleophile Trifluormethylquelle darstellt. Es kann preiswert aus Fluoroform hergestellt werden, ist stabil und wird leicht durch die Zugabe von Fluoridionen aktiviert. Aus diesen Gründen wurden bereits viele praktische Trifluormethylierungen mit TMSCF$_3$ ermöglicht.

Neben nukleophilen Reagenzien etablierten sich auch einige elektrophile CF$_3$-Quellen und eröffneten neue Syntheserouten für moderne Trifluormethylierungen.[81] Lange Zeit waren insbesondere die gasförmigen Interhalogenverbindungen BrCF$_3$ (bekannt als Halon 1301) und ICF$_3$ weit verbreitet und als gängige Feuerunterdrückungsmittel leicht verfügbar.[82,83] Allerdings wurden sie im Montreal-Protokoll als extrem ozonschädigend eingestuft und deren Produktion seither in Industrieländern verboten; dennoch werden sie unter strengen Auflagen für Forschungszwecke weiter hergestellt. Obwohl die Anwendung bislang weiter erlaubt wird, sollten moderne Methoden zur Trifluormethylierung auf derartige Interhalogenverbindungen gänzlich verzichten. Deshalb wurden einige hoch aktive Reagenzien entwickelt, die als kristalline und damit vor allem im Labormaßstab leicht handhabbare CF$_3$-Quellen große Entwicklungen eleganter neuer elektrophiler Trifluormethylierungen ermöglichten.[81,84,85] Yagupolskii beschrieb 1984 erstmals ein trifluormethyliertes Diarylsulfoniumsalz (**Schema 7**, **I**), welches erfolgreich zur Trifluormethylierung diverser Arylnukleophile genutzt wurde.[86] Dadurch wurde ein rascher Fortschritt neuer elektrophiler CF$_3$-Quellen initiiert. Umemoto

entwickelte kurz darauf eine zyklische und gespanntere Variante dieses Reagenzes (**II**), welches wesentlich aktiver ist, wodurch effizientere Trifluormethylierungen möglich wurden.[87] Die Aktivität lässt sich ferner genau durch die Wahl der Substituenten auf die Reaktivität der Nukleophile einstellen. Beide Verbindungen müssen allerdings ausgehend von TMSCF$_3$ und 2-Iodbiphenyl aufwendig in mehreren Schritten dargestellt werden. Togni entwickelte 2006 eine neue Klasse elektrophiler, hypervalenter Iodoniumsalze zur einfachen Trifluormethylierung (**III**).[88,89] Allerdings sind diese Reagenzien explosiv, teuer und werden in zwei Schritten aus TMSCF$_3$ und dem entsprechenden Iodoniumchlorid synthetisiert. Shibata berichtete von einem fluorierten Johnson Reagenz als elektrophile CF$_3$-Quelle, das in vier Schritten ausgehend von TMSCF$_3$ und Benzolsulfinsäuremethylester zugänglich ist (**IV**).[90]
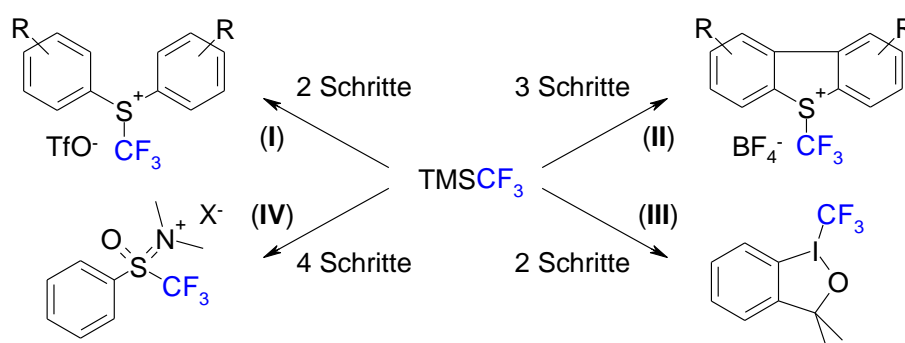
Schema 7. Synthese effizienter elektrophiler CF$_3$-Quellen.

Die größte Einschränkung elektrophiler Reagenzien hinsichtlich einer nachhaltigen Trifluormethylierung ist deren umständliche Synthese. Außerdem besitzen sie relativ hohe molare Massen, wodurch erhebliche Abfallmengen anfallen. Sie sind daher für industrielle Prozesse ungeeignet.

Alle vorgestellten nukleophilen und elektrophilen Reagenzien haben sich zur Trifluormethylierung bewährt und es konnten neue effiziente Protokolle entwickelt werden. Obwohl es einige theoretisch ideale nukleophile CF$_3$-Quellen wie Fluoroform oder Derivate der Trifluoressigsäure gibt, ist deren Anwendung beschränkt, weshalb kaum Methoden mit diesen Reagenzien entwickelt wurden. Abschließend lässt sich das Ruppert-Prakash-Reagenz als effektivste und nachhaltigste CF$_3$-Quelle hervorheben. Die Synthese aus Fluoroform und dessen einfache Handhabbarkeit sind hinsichtlich der Entwicklung neuer nachhaltiger Methoden zur Einführung von Trifluormethylgruppen besonders geeignet.

3.4. Trifluormethylthiogruppen

3.4.1. *Eigenschaften und Verwendung*

In jüngster Zeit verschiebt sich das Interesse zunehmend von Trifluormethyl- auf die analogen Trifluormethylthiogruppen, da sie die Lipophilie von Molekülen noch stärker erhöhen (Hansch-Konstante $SCF_3 = 1.44$ vs. 0.88 für CF_3).[91] Dies resultiert in einer signifikant gesteigerten Membrangängigkeit und Wechselwirkung des Wirkstoffs mit dem Rezeptor sowie einer damit verbundenen erhöhten Wirksamkeit beziehungsweise Wirkungsdauer von pharmakologisch aktiven Molekülen.[4] Dadurch werden geringere Konzentrationen von Wirkstoffen mit Trifluormethylthio- im Vergleich zu Trifluormethylgruppen im Wirkorganismus benötigt.[91]

Aufgrund der im Kapitel 3.3.1 genannten einzigartigen Eigenschaften der Trifluormethylgruppe in Kombination mit der verstärkenden Wirkung der Schwefelbrücke werden Trifluormethylthiogruppen standardmäßig in der Entwicklung neuer Wirkstoffe getestet. Bereits heute sind sie Schlüsselfunktionalitäten in vielen kommerziell etablierten Pharmazeutika und Agrochemikalien (**Abbildung 9**).
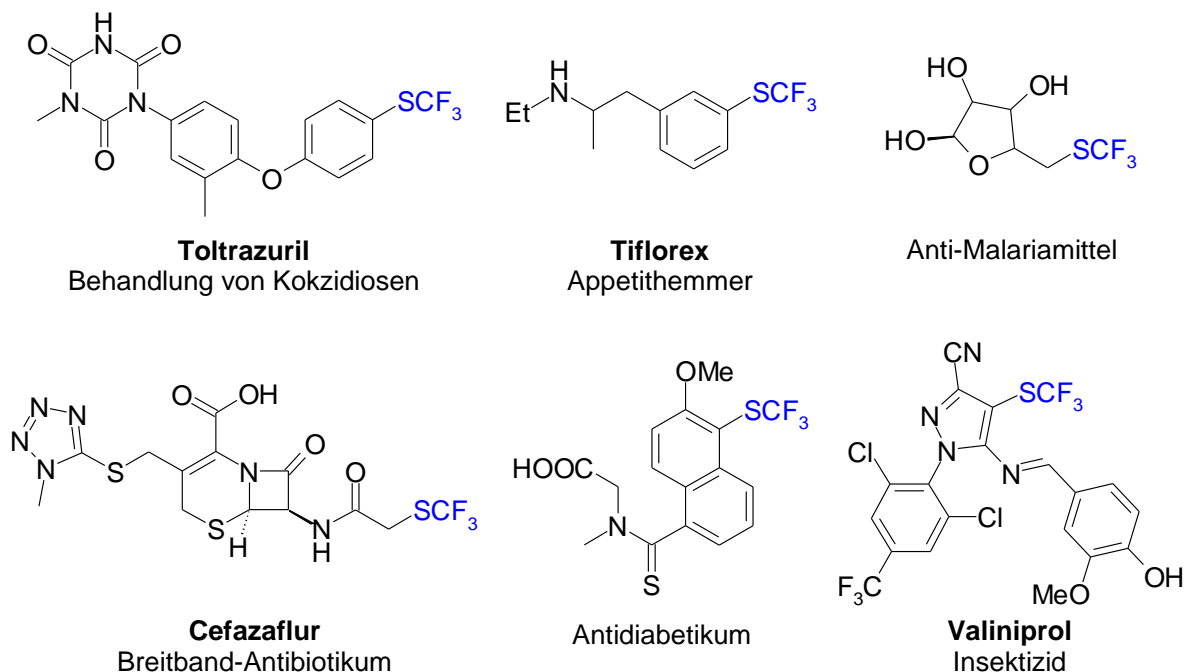

Abbildung 9. Biologisch aktive Moleküle mit SCF_3-Gruppen.

Toltrazazuril, Triflorex, Cefazaflur sind nur einige Beispiele potenter Arzneimittel neben einer Vielzahl weiterer Wirkstoffe mit ausgezeichneten bioaktiven Eigenschaften.[91–93] Valiniprol ist als etabliertes Insektizid bei den Agrochemikalien zu nennen.[94]
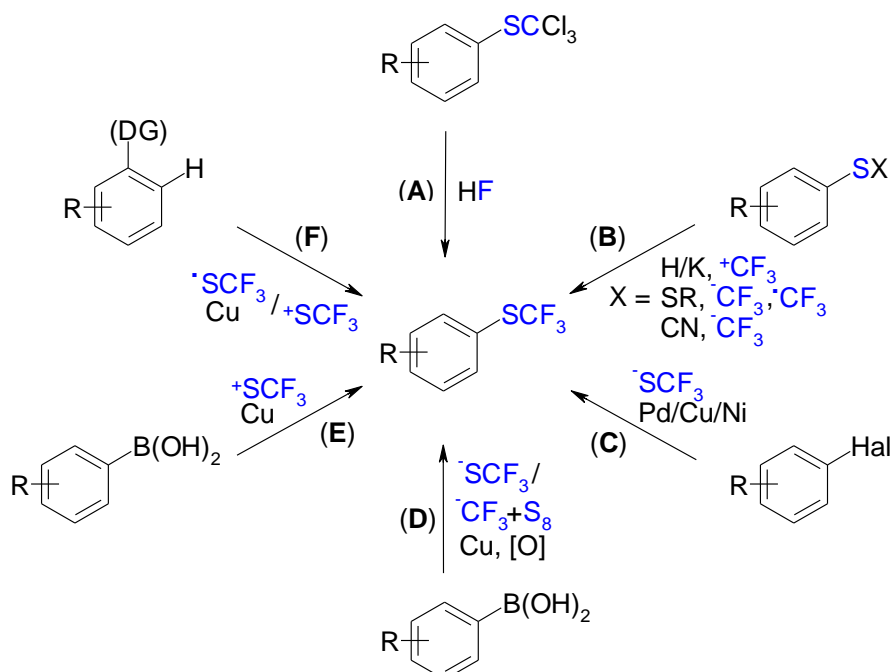
3.4.2. *Einführung von Trifluormethylthiogruppen*

Klassisch werden trifluormethylthiolierte Verbindungen analog zur Swarts-Reaktion über einen Fluor-Halogen-Austausch von Trichlormethylthioethern synthetisiert (**Schema 8**, **A**).[95,96] Außerdem können sie durch Trifluormethylierung schwefelhaltiger Vorstufen, wie beispielsweise Thiole,[97,98] Thiolate,[99] Disulfide[100–103] und Thiocyanate,[104,105] die wiederum in zusätzlichen Schritten synthetisiert werden müssen, dargestellt werden (**B**). Allerdings sind diese Methoden durch raue Reaktionsbedingungen und damit einhergehender geringer Toleranz funktioneller Gruppen und/oder schlechter Verfügbarkeit der schwefelhaltigen Substrate eingeschränkt.

Über moderne Übergangsmetall-katalysierte Methoden können Trifluormethylthiogruppen durch mildere Reaktionsbedingungen in funktionalisierte Startmaterialien mittels präformierter SCF$_3$-Reagenzien übertragen werden.[92,94,106,107] Unterteilt in vier Hauptkategorien, nukleophile (**C**, **D**), elektrophile (**E**) und radikalische (**F**) Funktionalisierungen, werden nachfolgend Trifluormethylthiolierungsreaktionen kurz beschrieben (**Schema 8**). Dabei sollen hauptsächlich die Methoden und Startmaterialien betrachtet werden. Daraufhin werden die verwendeten SCF$_3$-Quellen genauer vorgestellt.

Die Herausforderung nukleophiler Trifluormethylthiolierungen liegt besonders in der Instabilität des SCF$_3$-Anions. Es zerfällt leicht in ein Fluoridion sowie Difluorthiophosgen und muss daher als Metall-SCF$_3$-Komplex oder auch Me$_4$NSCF$_3$ stabilisiert werden. Diese SCF$_3$-Quellen müssen häufig in überstöchiometrischen Mengen zur Palladium-/Kupfer-/Nickel-katalysierten Kupplung mit Arylhalogeniden verwendet werden (**C**).[108–112] Nukleophile Arylboronsäuren können unter oxidativen Bedingungen mit nukleophilen SCF$_3$-Quellen oder elementarem Schwefel und TMSCF$_3$ zur Synthese der korrespondierenden Trifluormethylthioethern reagieren (**D**).[113,114] Beispiele elektrophiler Trifluormethylthiolierungen sind Kupfer-vermittelte Kupplungen von Arylboronsäuren, Palladium-katalysierte *ortho*-C–H-Funktionalisierungen mit Hilfe stickstoffdirigierender Gruppen sowie Lewissäuren-katalysierte Friedel-Crafts-analoge Prozesse elektronenreicher

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Aromaten (**E**, **F**).[115–120] Weitere Beispiele für C–H-Funktionalisierungen sind radikalische oder oxidative *ortho*-Trifluormethylthiolierungen (**F**).[121,122]

Schema 8. Strategien zur Einführung der Trifluormethylthiogruppe in Aromaten.

Trotz der raschen Entwicklung neuer effizienter Methoden zur Trifluormethylthiolierung wird die Nachhaltigkeit dieser Systeme nicht zuletzt durch die Wahl des Trifluormethylthiolierungsmittels bestimmt. Für die im **Schema 8** vorgestellten modernen Methoden zur direkten Trifluormethylthiolierung werden hauptsächlich folgende nukleophile und elektrophile SCF₃-Quellen, die auch als Vorstufen für radikalische Trifluormethylthiolierung genutzt werden, verwendet (**Abbildung 10**):
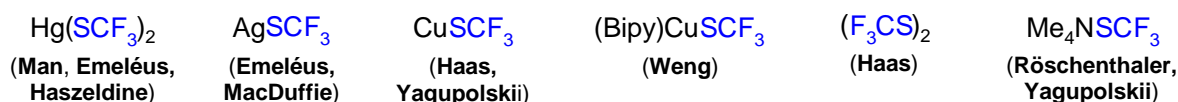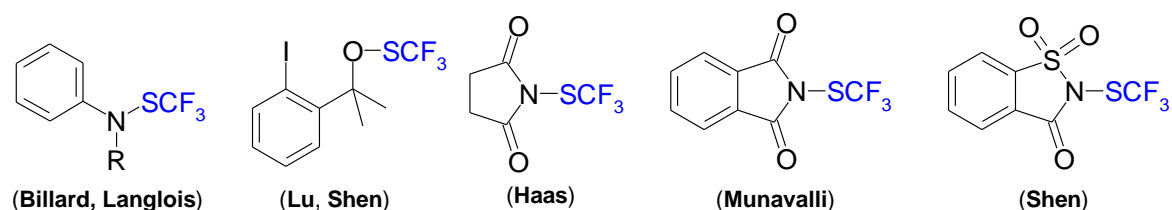
Nukleophile SCF₃ Quellen:

$Hg(SCF_3)_2$ $AgSCF_3$ $CuSCF_3$ $(Bipy)CuSCF_3$ $(F_3CS)_2$ Me_4NSCF_3

(**Man**, **Eméleus**,   (**Eméleus**,   (**Haas**,   (**Weng**)   (**Haas**)   (**Röschenthaler**,
Haszeldine)   **MacDuffie**)   **Yagupolski**i)   **Yagupolskii**)

Elektrophile SCF₃ Quellen:

(**Billard**, **Langlois**)   (**Lu**, **Shen**)   (**Haas**)   (**Munavalli**)   (**Shen**)

Abbildung 10. Übersicht moderner Trifluormethylthiolierungsreagenzien.

Durch die Instabilität des SCF₃-Anions werden hauptsächlich Metall-Komplexe zur nukleophilen Trifluormethylthiolierung diverser Arylelektrophile in überstöchiometrischen Mengen eingesetzt. Bereits 1959 entwickelten Man und Mitarbeiter die erste und über viele Jahre meist genutzte Metall-SCF₃-Verbindung, das extrem korrosive und toxische $Hg(SCF_3)_2$.[123,124] Es wird über ebenso korrosive und toxische Reagenzien durch die Reaktion von HgF₂ mit Kohlenstoffdisulfid oder mittels Reduktion von Bis(trifluormethyl)disulfid mit elementarem Quecksilber hergestellt. Das wesentlich attraktivere AgSCF₃ von Eméleus and Macduff stellte sich als hervorragende Alternative heraus und ermöglichte wesentlich elegantere nukleophile Trifluormethylthiolierungen im Vergleich zu dem bis dahin etablierten Quecksilberanalog.[125] Allerdings ist es nur mäßig luftstabil und wird ausgehend von drei Äquivalenten teuren Silberfluorids und toxischem Kohlenstoffdisulfid synthetisiert, wobei große Mengen anorganischem Salzabfall anfallen (**Schema 9**).
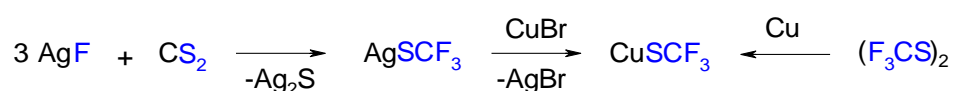
Schema 9. Synthese von AgSCF₃ und CuSCF₃.

Das korrespondierende Kupfer-SCF₃-Salz wird wiederum über eine Salzmetathese ausgehend von AgSCF₃ oder extrem toxischem, gasförmigem Bis(trifluormethyl)disulfid, das selbst auch als nukleophile SCF₃-Quelle verwendet werden kann,[126] hergestellt (**Schema 9**).[127,128] Außerdem ist es deutlich instabiler und muss daher für viele Reaktionen frisch synthetisiert und direkt eingesetzt werden. CuSCF₃ ist nukleophiler als AgSCF₃ und ermöglicht dadurch wesentlich mildere Trifluormethylthiolierungen unaktivierter

Arylelektrophile.[107] 2013 synthetisierten Weng und Mitarbeiter den luftstabilen, Bipyridin-stabilisierten Bipy(CuSCF$_3$)-Komplex ausgehend von TMSCF$_3$ und CuF$_2$.[112] Dieser Komplex ermöglicht analoge, deutlich praktischere Trifluormethylthiolierungen und erlaubte weitere Entwicklungen hinsichtlich milderer Reaktionsbedingungen. Jedoch werden für alle Methoden mit Metall-SCF$_3$-Komplexen stöchiometrische Mengen an Metall verwendet, weshalb die Reaktionen vom praktischen Nutzen her begrenzt sind.

Kürzlich etablierte sich eine wesentlich attraktivere nukleophile SCF$_3$-Quelle. Das hochstabile und einfach handhabbare Tetramethylammoniumtrifluormethylthiolat (Me$_4$NSCF$_3$) wurde erstmals von Röschenthaler und Yagupolskii synthetisiert. Es erlaubte die ersten nachhaltigen nukleophilen Trifluormethylthiolierungen ohne stöchiometrische Metall-Salze.[129,130] Außerdem kann es einfach aus Tetramethylammoniumfluorid, elementarem Schwefel und dem günstigen Ruppert-Prakash-Reagenz TMSCF$_3$ hergestellt werden (**Schema 10**).

$$Me_4NF \ + \ S_8 \ + \ TMSCF_3 \ \xrightarrow{\ -TMSF\ } \ Me_4NSCF_3$$

Schema 10. Synthese von Me$_4$NSCF$_3$.

Neben den nukleophilen haben sich auch einige elektrophile SCF$_3$-Quellen etabliert. Bis vor kurzem wurde fast ausschließlich gasförmiges ClSCF$_3$ zur elektrophilen Trifluomethylthiolierung eingesetzt.[106] Allerdings wurde die Entwicklung neuer Methoden aufgrund der hohen Toxizität des Reagenzes und dem damit einhergehenden Nutzungsverbot in organischen Syntheselaboren komplett gestoppt.[131] Seitdem wurden verschiedene neue Reagenzien als Ersatz für ClSCF$_3$ entwickelt, die nachhaltigere elektrophile Trifluomethylthiolierungen ermöglichen.

Billard und Langlois berichteten von Trifluormethansulfenamiden, die sich als effiziente elektrophile SCF$_3$-Quellen herausstellten und für die Trifluormethylthiolierung unterschiedlichster Nukleophile, hauptsächlich Heterozyklen wie Indole oder Organometallverbindungen, verwendet wurden.[132] Die Synthese gelingt relativ leicht aus Diethylaminoschwefeltrifluorid (DAST), TMSCF$_3$ und den entsprechenden primären oder sekundären aromatischen Aminen (**Schema 11**).
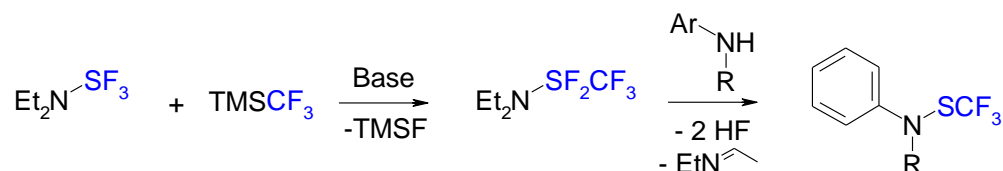
Schema 11. Synthese von Trifluormethansulfenamiden.

Lu und Shen entwickelten eine potente, luft- und feuchtigkeitsbeständige elektrophile SCF₃-Quelle inspiriert von Tognis hypervalentem Iod Reagenz.[116] Anders als zunächst vermutet, handelt es sich dabei nicht um eine zyklische Togni-analoge hypervalente Iodspezies, sondern das SCF₃ ist über ein Sauerstoffatom gebunden.[133] Allerdings muss dieses neue Trifluormethylthiolierungsmittel ausgehend von teurem und instabilem AgSCF₃ und der hypervalenten Iod-Cl Verbindung hergestellt werden (**Schema 12**, **I**). Haas, Munavalli und Shen etablierten eine neue Klasse elektrophiler N–SCF₃-Reagenzien. Dabei zeigten sich vor allem *N*-(Trifluormethylthio)succinimid (**II**),[134] -phthalimid (**III**),[135] -saccharin (**IV**)[118] als breit anwendbare SCF₃-Quellen. Mechanistischen und theoretischen Untersuchungen zufolge ist Saccharin-SCF₃ (**IV**) das reaktivste moderne SCF₃-Reagenz für elektrophile Trifluormethylthiolierungen.[136] Allerdings werden die Reagenzien alle ausgehend von AgSCF₃ oder CuSCF₃ und den entsprechenden N–Cl-Verbindungen hergestellt (**Schema 12**). Unsere Erfahrung zeigte außerdem, dass diese elektrophilen N–SCF₃-Reagenzien in sehr hoher Reinheit eingesetzt werden müssen, da viele Trifluormethylthiolierungen durch Rückstände nicht umgesetzter N–Cl-Verbindungen komplett inhibiert werden.
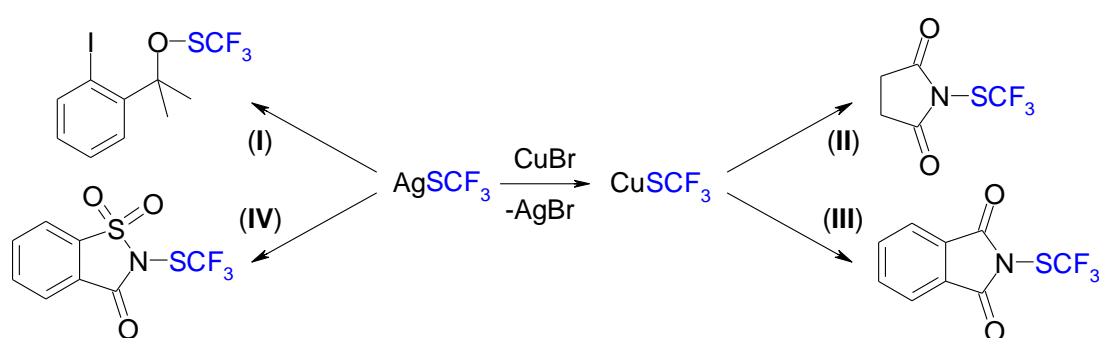
Schema 12. Synthesen von elektrophilen SCF₃-Quellen ausgehen von Ag-/CuSCF₃.

Alle vorgestellten nukleophilen und elektrophilen Reagenzien haben sich für die Trifluormethylthiolierung bewährt und es konnten neue effiziente Zugänge zu der wichtigen

Substanzklasse der Trifluormethylthioethern geschaffen werden. Allerdings sind nukleophile SCF$_3$-Quellen hauptsächlich auf stöchiometrische Metall-SCF$_3$-Komplexe beschränkt und elektrophile Reagenzien müssen aus ebendiesen Metall-SCF$_3$-Komplexen hergestellt werden. Abschließend lässt sich Me$_4$NSCF$_3$ als momentan günstigste und nachhaltigste SCF$_3$-Quelle hervorheben. Die Synthese sowie die intrisischen Eigenschaften dieses Salzes sind besonders attraktiv für die Entwicklung neuer nachhaltiger Methoden zur Einführung von Trifluormethylthiogruppen.

3.5. Difluormethylgruppen

3.5.1. *Eigenschaften und Verwendung*

Difluormethylgruppen besitzen zusätzlich zu den einzigartigen chemischen und physikalischen Gemeinsamkeiten mit einer Trifluormethylgruppe weitere nützliche Eigenschaften. Sie sind potente Wasserstoffdonoren und dienen als membrangängige isostere und isopolare Analoga zu Hydroxy-, Amino-, Thiol- und ähnlichen Gruppen.[137] Demzufolge stellen sie exzellente Bioisotere dieser Funktionalitäten in aktiven Verbindungen dar. Aufgrund dieser idealen Eigenschaften stieg das Interesse an der Difluormethylgruppe enorm. CF$_2$H wird als Schlüsselfunktionalität bereits in vielen pharmazeutischen und agrochemischen Wirkstoffen eingesetzt (**Abbildung 11**).[15,28,138–141]
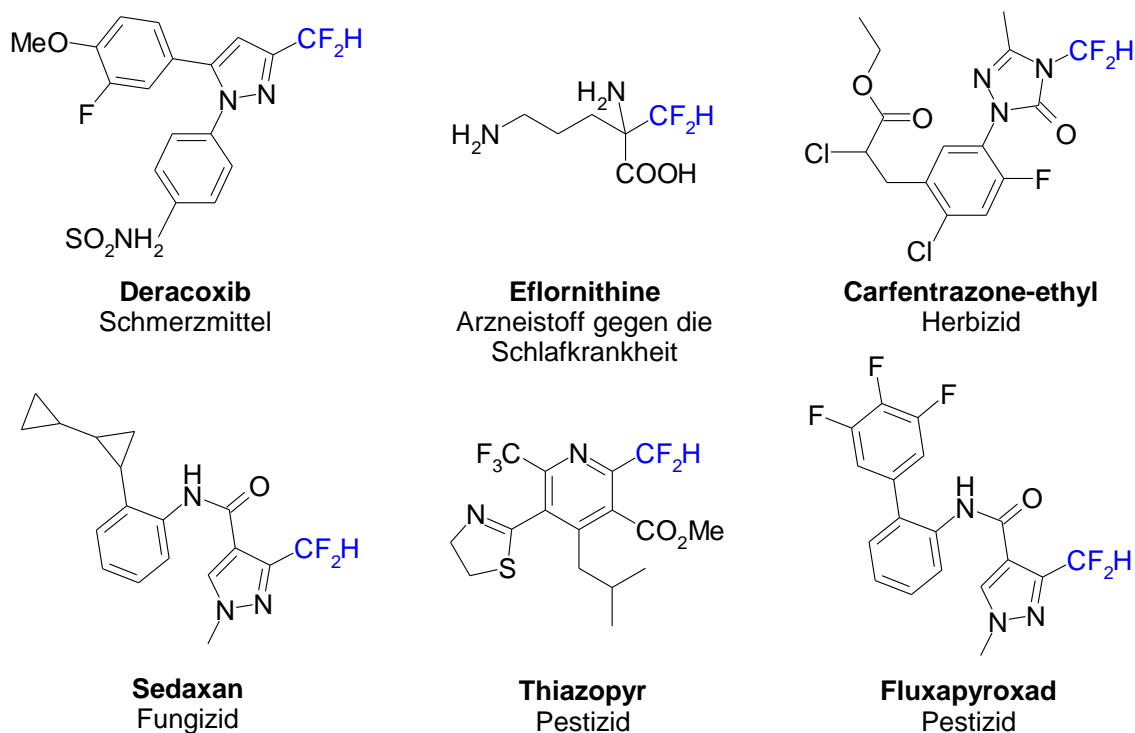
Abbildung 11. Biologisch aktive Moleküle mit CF$_2$H-Gruppen.

Insbesondere difluormethylierte Agrochemikalien, wie beispielsweise Sedaxan, Thiazopyr und Fluxapyroxad, sind als hochwertige sogenannte „Blockbuster", also besonders erfolgreiche und umsatzstarke Wirkstoffe, unter den Nahrungs-und Futtermittelerzeugern weit verbreitet.

3.5.2. *Einführung von Difluormethylgruppen*

Während man große Fortschritte bei der Einführung von Trifluormethylgruppen erzielte, wurde die Einführung von Difluormethylgruppen weitaus weniger untersucht.

Traditionelle Wege beinhalten die Fluorierung benzylischer C–H-Bindungen[142,143] und die deoxo-*gem*-Difluormethylierung von Aldehyden mit SF$_4$ oder Aminoschwefelfluoriden wie DAST oder Deoxofluor.[144,145] Allerdings erfordern diese Methoden harsche Reaktionsbedingungen und sind deshalb nur auf ein beschränktes Substratspektrum anwendbar. Ihr Einsatz ist häufig nur zu Beginn einer Synthesesequenz komplexer Verbindungen möglich. Deshalb wird stetig nach neuen, einfachen Prozessen mit milden Reaktionsbedingungen zur Difluormethylierung von hoch funktionalisierten Molekülen geforscht.[146]

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Moderne Übergangsmetall-katalysierte Difluormethylierungen benötigen im Vergleich zu traditionellen Methoden mildere Reaktionsbedingungen und tolerieren daher viele funktionelle Gruppen. Aufgrund des Mangels an einfach handhabbaren und lagerfähigen Reagenzien wurde jedoch bislang von nur wenigen Beispielen effizienter Difluormethylierungen berichtet. Bei diesen nutzte man folgende CF_2H-Quellen (**Abbildung 12**):

TMSCF_2H MCF_2H nBu$_3$SnCF_2H HF$_2$C–S(O)O–Zn–S(O)O–CF_2H
(**Prakash**)   M = Zn (**Burton**)   (**Prakash**)   (**Baran**)
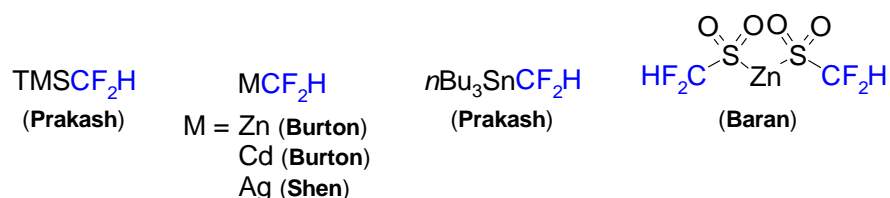   Cd (**Burton**)
               Ag (**Shen**)

Abbildung 12. Übersicht Difluormethylierungsreagenzien.

Einfache Difluormethyl-Metallsalze wurden hauptsächlich zur stöchiometrischen Funktionalisierung aktivierter Allyliodide verwendet. Diese Komplexe sind häufig sehr instabil und/oder müssen umständlich ausgehend von ozonschädigenden Interhalogenverbindungen hergestellt werden.[147–149] Baran berichtete von einer radikalischen Difluormethyl-Quelle, $Zn(SO_2CF_2H)_2$, zur Difluormethylierung von Heteroaromaten.[150] Allerdings konnten nur sehr elektronarme Heterocyclen umgesetzt werden und die Methode führte häufig zu einer Mischung verschiedener Regioisomere. Analog zu gängigen Trifluormethylierungen wurden intermediär gebildete Cu–CF_2H Komplexe für effiziente Difluormethylierungen von Aryliodiden genutzt. Neben dem toxischen Zinn-Reagenz von Prakash eignet sich dafür besonders TMSCF_2H, das leicht durch die Reduktion des Ruppert-Prakash-Reagenz TMSCF_3 mit $NaBH_4$ hergestellt werden kann (**Schema 13**).[151–153]

TMSCF_3 $\xrightarrow{\text{NaBH}_4}$ TMSCF_2H
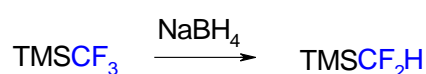
Schema 13. Synthese des Ruppert-Prakash analogen TMSCF_2H.

Unter den gezeigten Difluormethylierungsreagenzien ist vor allem das zuletzt genannte TMSCF_2H besonders attraktiv. Es ist stabil, einfach handhabbar und es werden keine präformierten, stöchiometrischen Metallkomplexe zur Einführung der Difluormethylgruppe benötigt.

3.6. Difluormethylthiogruppen

3.6.1. *Eigenschaften und Verwendung*

Difluormethylthiogruppen sind im Vergleich zu den analogen Trifluormethylthiogruppen weit weniger erforscht. Dennoch sind sie äußerst interessant, da die vorteilhaften Eigenschaften fluorierter Gruppen, die durch die Schwefelbrücke gesteigert werden, und die einzigartige Fähigkeit als bioaktivere, isostere sowie isopolare Analoge zu OH, SH und NH-Gruppen zu wirken, vereint sind.[12] Durch das noch azidere Proton im Vergleich zur CF_2H-Gruppe wird die potenzielle Bioisosterie in Wirkstoffen zu diesen Funktionalitäten weiter gesteigert.[154] Anhand des großen Interesses von SCF_3- und CF_2H-Gruppen in bioaktiven Molekülen würde man eine vergleichbare Anzahl von potenten Wirkstoffen mit SCF_2H-Gruppen erwarten. Obwohl Studien zeigen, dass Difluormethylthiogruppen einzigartig effektiv in einigen Wirkstoffen sind, existieren bislang nur wenige Vertreter auf dem Markt (**Abbildung 13**).[155–157]

Flomoxef-Natrium
Antibiotikum

Pyriprole
Veterinär-Insektizid
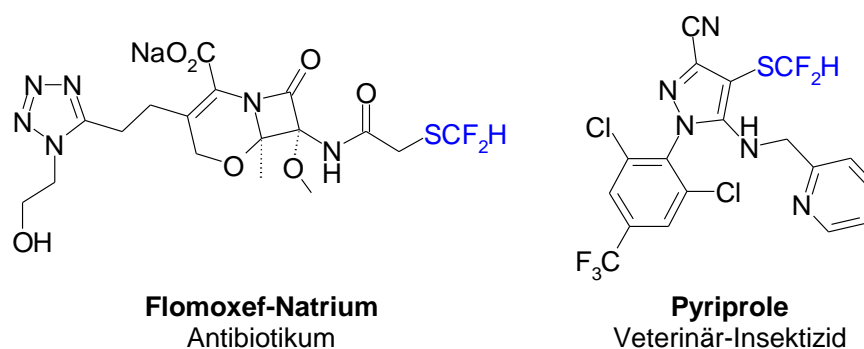
Abbildung 13. Biologisch aktive Moleküle mit SCF_2H-Gruppen.

Difluormethylthiogruppen sind ideale Bioisostere für „Fluorine-Scans" in der Wirkstoffforschung und es wird ein ähnlich großes Wachstum biologisch aktiver Verbindungen mit SCF_2H-Gruppen erwartet. Deshalb ist es besonders wichtig, sie als strukturelles Leitmotiv in der Entwicklung neuer Wirkstoffe routinemäßig zu testen. Allerdings sind bislang kaum synthetische Methoden zur milden, effizienten und selektiven Einführung in hochfunktionalisierte Moleküle in einem späten Synthesestadium bekannt.

3.6.2.   *Einführung von Difluormethylthiogruppen*

Die Einführung von Difluormethylthiogruppen birgt einige Herausforderungen und im Vergleich zu Methoden der entsprechenden Trifluormethylthiolierung gibt es nur wenige Beispiele.[158] Traditionelle Verfahren basieren auf der Insertion von Difluorcarbenen in S–H-Bindungen mit ozonschädlichen Interhalogenverbindungen.[159–161] Des Weiteren können Thiole und deren Derivate durch elektrophile Reagenzien difluormethyliert werden.[162–164] Allerdings sind Thiole nur schlecht und in einem kleinen Substratspektrum verfügbar. Außerdem erfordern diese Methoden stark basische Reaktionsbedingungen, weshalb keine sensiblen funktionellen Gruppen toleriert werden.

Erst durch das Design neuer Reagenzien konnten neue, effizientere Verfahren zur Einführung der SCF_2H-Gruppe entwickelt werden. Bei der Difluormethylthiolierung von Aryl(pseudo)halogeniden, elektronenarmer Heterozyklen und kürzlich auch Aryldiazoniumsalzen haben sich drei SCF_2H-Quellen bewährt (**Abbildung 14**).[158]
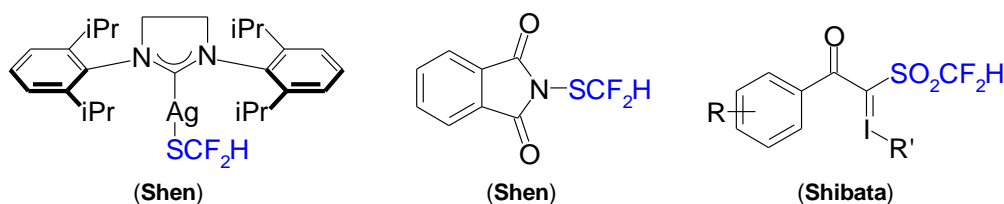

Abbildung 14. Übersicht Difluormethylthiolierungsreagenzien.

Das nukleophile $AgSCF_2H$ Reagenz von Shen ermöglichte effiziente Difluormethylthiolierungen, benötigt allerdings aufgrund der instabilen Metall-SCF_2H Bindung, die zur Eliminierung des Difluorcarbens neigt, sterisch anspruchsvolle NHC-Liganden.[165,166] Außerdem fallen generell teure stöchiometrische Metallabfälle an und es muss aus dem aufwendig herzustellenden analogen CF_2H-Reagenz synthetisiert werden (**Schema 14**). Shen etablierte ferner das stabile, elektrophile Phthalimid-SCF_2H-Reagenz für Difluormethylthiolierungen ohne stöchiometrische Metallsalze.[167] Allerdings kann dieses Reagenz nur ausgehend von $(SIPr)AgCF_2H$ und Phthalimid-SCl, für das wiederum mehrere Synthesestufen notwendig sind, in einer Gesamtausbeute unter 50% dargestellt werden (**Schema 14**).
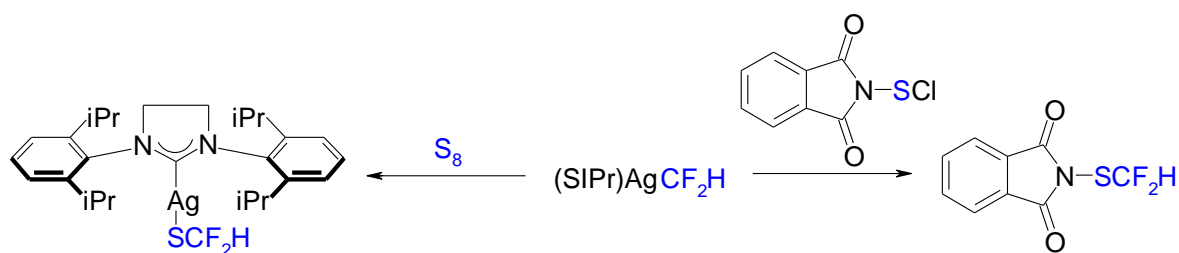
Schema 14. Synthese der SCF$_2$H-Reagenzien von Shen.

Auch das kürzlich veröffentliche elektrophile hypervalente Iodoniumylid von Shibata ist keine echte Verbesserung hinsichtlich nachhaltigeren Difluormethylthiolierungen.[168] Es ist nur mäßig stabil und muss über mehrere Stufen synthetisiert werden (**Schema 15**).
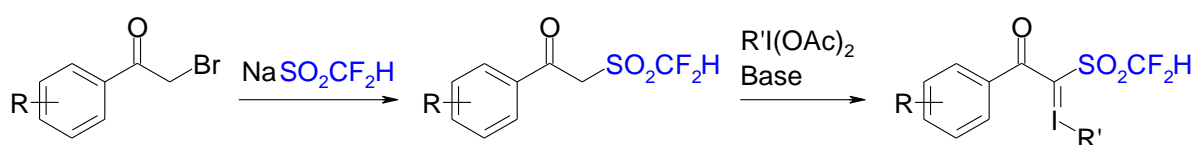
Schema 15. Synthese des hypervalenten Iodoniumylides von Shibata.

Daraus wird deutlich, dass dringend neue, effiziente Wege und Reagenzien zur Einführung der wichtigen Difluormethylthiogruppe benötigt werden. Während Difluormethylierungen von schwefelhaltigen Verbindungen harsche Reaktionsbedingungen benötigen und Startmaterialen nicht in struktureller Vielfalt verfügbar sind, leidet die Nachhaltigkeit direkter Difluormethylthiolierungen insbesondere durch die aufwendig herzustellenden, teuren und/oder instabilen Reagenzien. Außerdem besitzen alle SCF$_2$H-Quellen relativ hohe molare Massen, wodurch erhebliche Abfallmengen anfallen und sie daher für industrielle Prozesse ungeeignet sind. Die Erschließung geeigneter Quellen der Difluormethylthiogruppe stellt weiterhin eine Herausforderung moderner Synthesestrategien dar.

3.7. Die Sandmeyer-Reaktion

3.7.1. *Allgemeines*

Die Sandmeyer-Reaktion, die erstmals vom Schweizer Chemiker Traugott Sandmeyer im Jahre 1884 beschrieben wurde, ist eine bekannte Methode zur effizienten und nachhaltigen Substitution aromatischer Aminogruppen durch Halogenide oder Pseudohalogenide mittels

Diazotierung.[169,170] Diese Entdeckung, mit der sich Sandmeyer mit der nach ihm benannten Namensreaktion in der Chemie verewigte, gelang zufällig bei der eigentlich geplanten Synthese von Phenylacetylen durch Umsetzung von Aryldiazoniumchlorid mit Kupferacetylid, wobei Chlorbenzol als Hauptprodukt gebildet wurde (**Schema 16**).
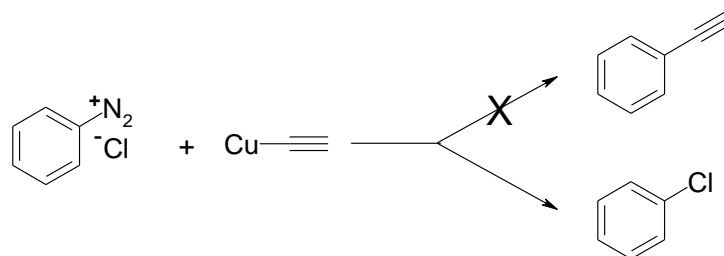
Schema 16. Sandmeyers zufällige Entdeckung - Die erste Sandmeyer-Reaktion.

Mittlerweile gehört die Sandmeyer-Reaktion zu den bekanntesten sowie präparativ bedeutendsten Namensreaktionen der organischen Synthesechemie und ist aufgrund ihrer einfachen Durchführbarkeit im Standardrepertoire jedes Laborchemikers. In der klassischen Sandmeyer-Reaktion wird das Nukleophil mit Hilfe von günstigen Kupfersalzen durch die Dediazotierung aromatischer Diazoniumsalze, wobei molekularer Stickstoff frei wird, übertragen (**Schema 17**).
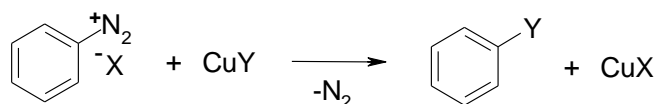
Schema 17. Die Sandmeyer-Reaktion.

Generell werden für Sandmeyer-Reaktionen sehr milde Reaktionsbedingungen benötigt, sie verlaufen meist bei Raumtemperatur in kurzen Reaktionszeiten. Dadurch werden viele funktionelle Gruppen toleriert, wodurch die regioselektive Synthese einiger Aromaten überhaupt erst möglich wird. Es werden beispielsweise Halogenide toleriert, welche die Möglichkeit für weitere Funktionalisierungen bieten. Dennoch ist die Sandmeyer-Reaktion meist orthogonal zu Halogenid-basierten Kreuzkupplungen, was für Reaktionssequenzen aus mehreren Schritten äußerst vorteilhaft ist. Obendrein werden Arylhalogenide, insbesondere die häufig verwendeten Aryliodide, industriell über die Sandmeyer-Reaktion hergestellt. Im Vergleich zur Funktionalisierung von Arylhalogeniden wird dadurch ein synthetischer Schritt gespart.

Die bei der Sandmeyer-Reaktion verwendeten Aryldiazoniumsalze verhalten sich wie Pseudohalogenide mit höherer Reaktivität. Deshalb erfordern sie eine strikte Reaktionskontrolle, um die gewünschten Produkte zu erhalten. Diazoniumsalze können leicht durch die kommerziell in großer struktureller Vielfalt vorkommenden und preiswerten Aniline sowie einer Nitritquelle und einer Säure gebildet werden (**Schema 18**).[171,172]

X = Hal., BF$_4$
Y = Na oder Alkylreste
z. B. ^{t}Bu / ^{i}Am
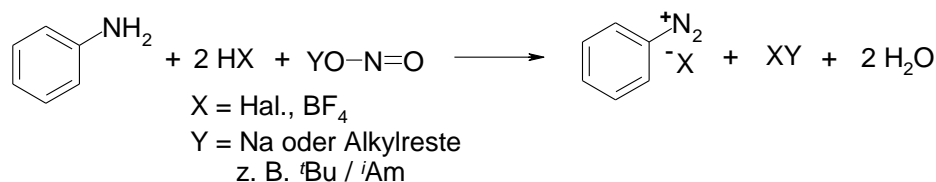
Schema 18. Darstellung von Diazoniumsalzen.

Für die Stabilität des Diazoniumsalzes ist das Gegenion entscheidend, welches durch die Wahl der Säure bestimmt wird. Generell sind die Salze im trockenen Zustand explosiv sowie schlag- und hitzeempfindlich, weshalb sie häufig nicht isoliert, sondern *in situ* generiert und in Folgereaktionen verwendet werden. Lediglich aromatische Salze der Tetrafluorborwasserstoffsäure, Diazoniumtetrafluoroborate, sind stabil, solange sie nach den „Rule of six" mindestens 6 Kohlenstoffatome pro Diazo-Gruppe enthalten.[173,174]

Die Industrie erkannte die entscheidenden Vorteile der Sandmeyer-Reaktion und etablierte sie zur Einführung von Nukleophilen in einem späten Synthesestadium. Ein Beispiel dafür ist die Darstellung des Antibiotikums Garenoxacin, bei der eine wichtige Stufe über eine regioselektive Sandmeyer-Bromierung verläuft, die gleichzeitig viele weitere funktionelle Gruppen toleriert (**Schema 19**).[175]

Garenoxacin
Antibiotikum
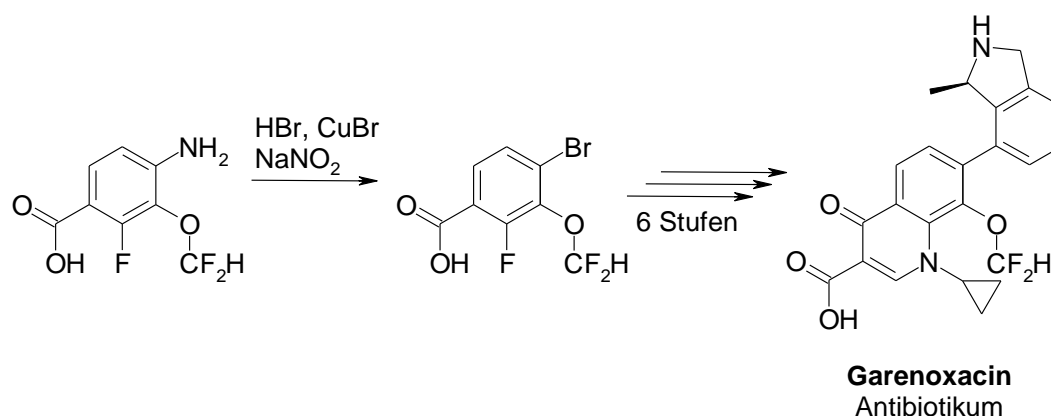
Schema 19. Industrielle Synthese von Garenoxacin über eine Sandmeyer-Reaktion.

3.7.2. *Mechanismus der Sandmeyer-Reaktion*

Seit der Entdeckung vor weit über 100 Jahren wurde der Mechanismus der Sandmeyer-Reaktion noch nicht vollständig aufgeklärt und vielmehr kontrovers diskutiert.[176] Ein wichtiger Beitrag gelang Hantzsch, der zeigen konnte, dass Diazoniumsalze in Gegenwart von Kupfer(I)bromid über die Diazogruppe zunächst komplexieren und bei Zugabe von Wasser zu Brombenzol zerfallen (**Schema 20**).[177]
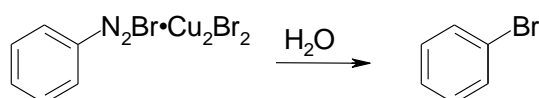
Schema 20. Diazobenzol Kupferbromid-Komplex.

Außerdem konnten Hantzsch und Blagden zeigen, dass das Kupfersalz das Halogenid auf den Aromat überträgt, da in der Reaktion von einem Aryldiazoniumbromid mit Kupferchlorid hauptsächlich das chlorierte Produkt und nic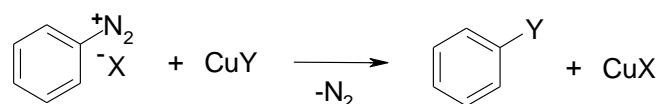ht das bromierte Produkt entsteht. Bestätigt wurden diese Beobachtungen ebenfalls durch die Reaktionen von Aryldiazoniumchlorid/-iodid mit Kupferbromid beziehungsweise Kupfercyanid, in denen jeweils das nukleophile Gegenion des Kupfersalzes übertragen wurde (**Schema 21**).[178]

Schema 21. Übertragung des Nukleophils in der Sandmeyer-Reaktion.

Bereits vor Sandmeyer berichtete Griess, dass die Diazogruppe von Diazoniumsalzen unter Freisetzung von Stickstoff als Abgangsgruppe gegen ein Iodid ausgetauscht werden kann.[179] Ungewöhnlicherweise zeigten Bromide und Chloride eine wesentlich geringere Aktivität als Iodide. Erst durch die Zugabe stöchiometricher Mengen des entsprechenden Kupferhalogenids, der klassischen Sandmeyer-Reaktion, erfolgte die Halogenierung von Diazoniumsalzen. Aufbauend und im Einklang zu den Untersuchungen von Hantzsch und Pray,[177,180,181] postulierten Grieve und Hey im Jahre 1934 erstmals die Bildung eines Arylradikals in der Sandmeyer-Reaktion.[182] Einen weiteren Beitrag zur Aufklärung des Reaktionsmechanismus leistete Waters, der zeigen konnte, dass das Kupfersalz als Reduktionsmittel die homolytische Spaltung des Diazoniumsalzes zu einem Arylradikal und

molekularem Stickstoff initiiert (**Schema 22**). Generell können Diazoniumsalze in Abwesenheit von Reduktionsmitteln auch heterolytisch gespalten werden. Die Triebkraft ist in beiden Prozessen die Bildung molekularen Stickstoffs.
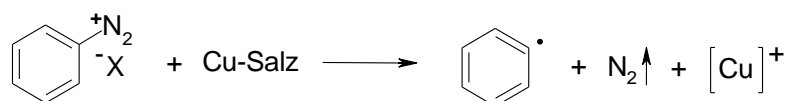
Schema 22. Homolytische Dediazotierung in Gegenwart von Kupfersalzen.

Darauf aufbauend wurde der Mechanismus der homolytischen Dediazotierung der Sandmeyer-Reaktion von vielen Forschern, darunter Waters,[183] Kornblum,[184] Knochi,[185] Rüchardt,[186] Bunnett[187] und Zollinger,[188] ausgiebig untersucht.

Insgesamt wird der Mechanismus der Reaktion wie folgt zusammengefasst (**Schema 23**):
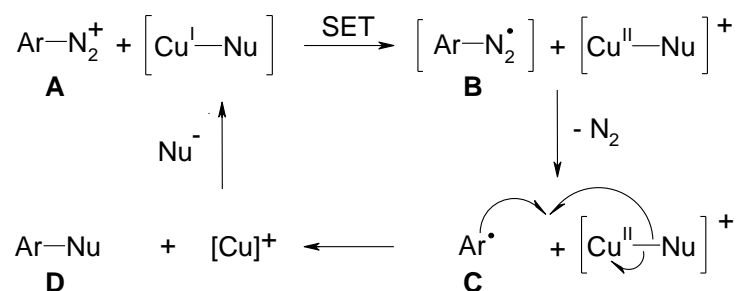
Schema 23. Mechanismus der Sandmeyer-Reaktion.

Das Diazoniumion (**A**) wird unter Oxidation von Cu(I) zu Cu(II) mittels eines Einelektrontransfers[183] (SET = single electron transfer) reduziert und bildet ein Diazenylradikal (**B**). Anschließend wird Stickstoff freigesetzt und das entstandene Arylradikal (**C**) reagiert mit dem Nukleophil des Kupfersalzes unter Reduktion von Cu(II) zu Cu(I) und das Produkt (**D**) entsteht. Das Kupferion ist dabei sowohl Elektronendonor als auch -akzeptor. In katalytischen Sandmeyer-Reaktionen wird darauf der aktive Cu(I)-Nukleophil Komplex wieder gebildet. Allerdings sind bislang nur wenige Beispiele katalytischer Sandmeyer-Reaktionen in der Literatur bekannt.[189,190] Leicht oxidierbare Nukleophile wie beispielsweise Iodidionen, können teilweise ohne Zusatz eines Kupfersalzes eingeführt werden; sie fungieren dabei selbst als Katalysator der Reaktion.

Als Nebenprodukte der Sandmeyer-Reaktion können Phenole durch thermische Hydrolyse, Biaryle und Azoverbindungen durch Homokupplung radikalischer Zwischenstufen, oder die entsprechenden protodediazotierten Produkte entstehen.

3.7.3. *Sandmeyer-Trifluormethylierung*

Erst kürzlich gelang es, die beschriebenen Vorteile der Sandmeyer-Reaktion mit der Einführung der wichtigen Trifluormethylgruppe zu kombinieren. Moderne Methoden waren bislang hauptsächlich auf die Verwendung von Arylhalogeniden oder -boronsäuren beziehungsweise deren Derivate beschränkt oder benötigten harsche Reaktionsbedingungen.[10,41–46] Die Arbeitsgruppen von Fu,[191] Wang[192] und Gooßen[193] entwickelten fast zeitgleich ähnliche Protokolle zur Sandmeyer-Trifluormethylierung (**Schema 24**).
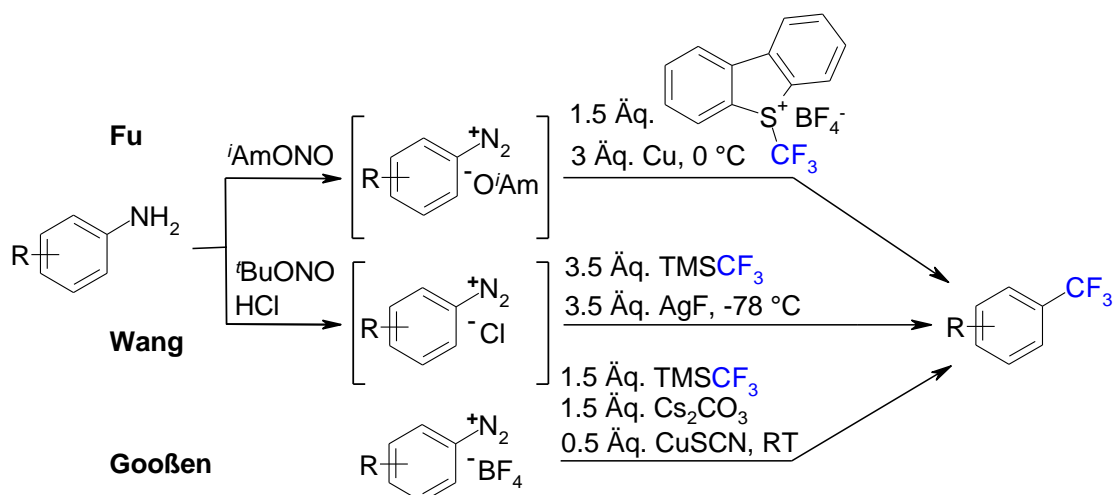
Schema 24. Sandmeyer-Trifluormethylierungen.

Ein Vorteil der Methoden von Fu und Wang ist die *in situ* Bildung des Diazoniumsalzes aus dem entsprechenden Anilin. Allerdings werden in beiden Methoden überstöchiometrische Mengen an Metall, nämlich drei Äquivalente Kupfer beziehungsweise dreieinhalb Äquivalente teures Silberfluorid, benötigt. Außerdem wird in Fus Protokoll teures Umemoto Reagenz und bei Wang große Mengen des Ruppert-Prakash-Reagenz als Trifluormethylquelle eingesetzt. In der Sandmeyer-Trifluormethylierung von Gooßen wird lediglich substöchiometrisches, günstiges Kupfersalz und geringe Mengen des Ruppert-Prakash-

Reagenz benötigt. Allerdings wurden in diesem Verfahren die Diazoniumsalze zunächst präformiert, welches einen weiteren synthetischen Schritt bedeutet.[194]

Mittlerweile konnten Grushin und Mitarbeiter präformiertes CuCF₃, generiert aus Fluoroform (HCF₃), einem Abfallprodukt der Teflonindustrie und damit einer der günstigsten Trifluormethylquellen, in der Sandmeyer-Trifluormethylierung einsetzen.[195]

3.7.4. *Sandmeyer-Trifluormethylthiolierung*

Ähnlich zur Trifluormethylgruppe wurde erst kürzlich die effiziente Sandmeyer-Reaktion zur Einführung der verwandten, hochinteressanten Trifluormethylthiogruppe etabliert. Bislang beschränkten sich moderne Methoden auf die Trifluormethylierung schwefelhaltiger Verbindungen, welche in einem zusätzlichen Schritt hergestellt werden müssen oder die Einführung der SCF₃-Gruppe als Ganzes mittels teurer und/oder instabiler Reagenzien in Aryliodide oder –boronsäuren.[92,94,106,107] Dennoch konnte die Arbeitsgruppe von Clark bereits im Jahre 2000 die prinzipielle Durchführbarkeit einer Trifluormethylthiolierung von Diazoniumsalzen zeigen (**Schema 25**).[196] Allerdings überträgt das stöchiometrisch eingesetzte, umständlich synthetisierte und instabile Trifluormethylthiolierungsreagenz CuSCF₃ nur widerwillig die SCF₃-Gruppe auf wenige elektronarme Diazoniumsalze. Diese Beobachtungen sprechen dafür, dass die Reaktion eher nicht über einen klassischen Sandmeyer-Mechanismus, sondern über eine nukleophile aromatische Substitution verläuft.
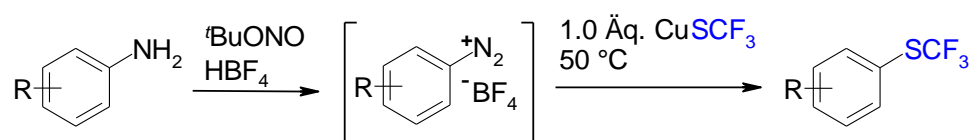
Schema 25. Trifluormethylthiolierung von Anilinen.

Erst 14 Jahre später entwickelten Gooßen und Mitarbeiter ein effizienteres Verfahren zur Synthese von Trifluormethylthioethern ausgehend von Diazoniumsalzen (**Schema 26**).[197]
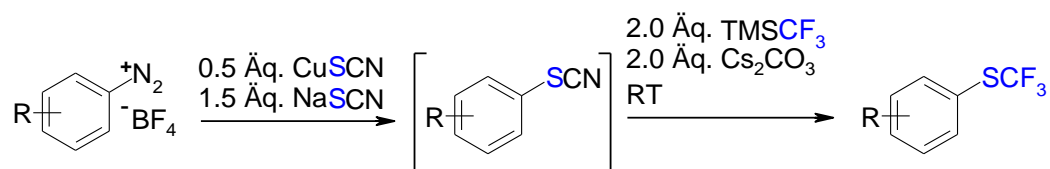
Schema 26. Sandmeyer-Trifluormethylthiolierung.

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Die formale Sandmeyer-Trifluormethylthiolierung wurde dabei durch eine Kaskade aus *in situ* Sandmeyer-Thiocyanierung gefolgt von einem Langlois-Austausch der CN- durch eine CF$_3$-Gruppe ermöglicht.[104] Die Vorteile dieser Methode liegen im Vergleich zu literaturbekannten Trifluormethylthiolierungen vor allem in der guten Verfügbarkeit aromatischer Aniline und im Einsatz günstiger Reagenzien bei milden Reaktionsbedingungen.

4. Aufgabenstellung

Das Ziel dieser Arbeit war die rationale Entwicklung neuer nachhaltiger Methoden zur gezielten Einführung fluoralkyl(thio/seleno)lierter Substituenten in komplexe organische Moleküle. Dabei sollten die bestehenden Probleme der Atomökonomität, Effizienz und Praktikabilität aktueller Verfahren, insbesondere im Hinblick auf die verwendeten Startmaterialien und Quellen der Fluoralkyl(thio/seleno)gruppen, gelöst werden. Die Reaktionsbedingungen sollten jeweils so mild sein, dass sie sich selbst für komplexe Verbindungen in einem späten Synthesestadium eignen. Dafür sollte speziell die Sandmeyer-Reaktion als Basis für neue universell einsetzbare und skalierbare Zugänge zu wichtigen fluorierten Substanzklassen dienen.

Daraus ergeben sich folgende konkrete Aufgabenstellungen:

- Aufbauend auf dem im Arbeitskreis Gooßen etablierten Konzept der Sandmeyer-Trifluormethyl(thiol)ierung sollten neue Kupplungen zur milden Einführung von CF_3-, SCF_3-, SC_2F_5-, $SeCF_3$-, CF_2H- und SCF_2H-Gruppen entwickelt werden. Ein besonders anspruchsvolles Ziel war es dabei, erstmals katalytische Varianten dieser Sandmeyer-Reaktionen zu realisieren.

- Nachhaltigere, regioselektive elektrophile C–H-Fluoralkylthiolierungen elektronenreicher Aromaten sollten durch das Reaktionskonzept der *in situ* Thiocyanierung/Fluoralkylierungskaskade anstelle teurer elektrophiler Reagenzien zugänglich werden.

- In allen neu entwickelten Verfahren sollten konsequent nachhaltige Fluoralkyl(thio/seleno)lierungsreagenzien verwendet werden, die auf dem Ruppert-Prakash-Reagenz $TMSCF_3$ basieren.

- Die Anwendungsbreite der neu entwickelten Methoden sollte anhand zahlreicher funktionalisierter Substrate untersucht werden.

- Mechanistische Studien sollten einen näheren Einblick in den Ablauf der Reaktionen liefern.

5. Ergebnisse und Diskussion

Nachfolgend werden die jeweiligen Ziele und Herausforderungen der einzelnen Projekte kurz beschrieben und thematisch eingeordnet. In jedem Abschnitt werden die zugehörigen wissenschaftlichen Veröffentlichungen abgebildet, die durch die kumulative Promotionsform den Hauptteil des Ergebnis- und Diskussionsteils darstellen. Die entsprechenden Literaturverweise und alle Ergebnisse der experimentellen Arbeiten der Projekte sind in diesen Publikationen aufgeführt.

5.1. Neue Methoden zur Trifluormethylierung

5.1.1. *Eintopf-Sandmeyer-Trifluormethylierung*

Das Ziel dieses Projektes war es, aufbauend auf der zuvor im Arbeitskreis etablierten Sandmeyer-Trifluormethylierung von Diazoniumsalzen[193] ein praktisches Eintopfverfahren durch *in situ* Diazotierung breit verfügbarer Aniline zu entwickeln (**Schema 27**).
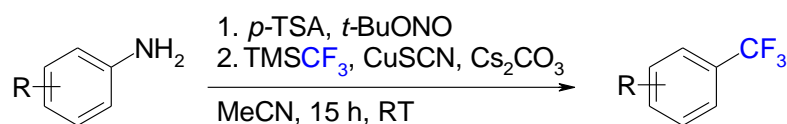
Schema 27. Eintopf-Sandmeyer-Trifluormethylierung.

Dabei sollte insbesondere die Atomeffizienz und die Anwendbarkeit der Methode hinsichtlich der Anforderungen industrieller Prozesse optimiert und das große synthetische Potential verdeutlicht werden. Im Vergleich der Reaktionsbedingungen der Sandmeyer-Trifluormethylierungen von Fu,[191] Wang[192] und unserer Arbeitsgruppe[193] zeigte sich, dass unsere Methode in der Wahl der CF₃-Quelle, des Katalysators und der Reaktionstemperatur deutlich überlegen ist (**Tabelle 2**). Allerdings wurden in diesem Verfahren die Diazoniumsalze in einem zusätzlichen Syntheseschritt präformiert. Dies stellt im direkten Vergleich mit derart ähnlichen Methoden einen ausschlaggebenden Nachteil da.[194] Speziell für instabile Diazoniumsalze könnte es praktisch sein, Aniline in der Reaktionsmischung zu diazotieren und anschließend direkt zu trifluormethylieren.

Tabelle 2. Direkter Vergleich der analogen Sandmeyer-Trifluormethylierungen.

	Eintopf-Verfahren	CF$_3$-Quelle	Katalysator	Temperatur
Fu *et al.*	✓	1.5 Äq. Umemoto's Reagenz	3.0 Äq. Cu	0 - 15°C
Wang *et al.*	✓	3.5 Äq. TMSCF$_3$	3.5 Äq. AgF	-78°C - RT
Gooßen *et al.*	✗	1.5 Äq. TMSCF$_3$	0.6 Äq. CuSCN	RT

Deshalb entwickelten wir ein effizientes Protokoll zur Trifluormethylierung ausgehend von Anilinen. Im Rahmen dieses Vorhabens war es essentiell wichtig, Bedingungen für die *in situ* Diazotierung zu identifizieren, die die darauffolgende Trifluormethylierungsreaktion tolerieren. Die Schwierigkeit bestand zunächst darin, eine geeignete Säure und eine Nitritquelle für den Diazotierungsschritt zu ermitteln. Diese dürfen die intermediär gebildeten, labilen CuCF$_3$-Spezies nicht beeinflussen. Während der umfangreichen Reaktionsoptimierung konnte eine Kombination aus *p*-Toluolsulfonsäure und *t*-Butylnitrit identifiziert werden, die die *in situ* Diazotierung von Anilinen effektiv vermittelt und die Sandmeyer-Trifluormethylierung in hohen Ausbeuten erlaubt. Es zeigte sich, dass die Verwendung von wasserfreier *p*-Toluolsulfonsäure ebenfalls entscheidend ist, da es sonst schnell zu ungewollter Protodediazotierung kommt. Unter den optimalen Reaktionsbedingungen wurde anschließend eine große Anwendungsbreite anhand divers funktionalisierter Aniline demonstriert. Die Ausbeuten der Eintopf-Sandmeyer-Reaktion sind im Vergleich zur ursprünglichen sequentiellen Methode in den meisten Fällen ähnlich hoch, teilweise sogar besser. Außerdem war es mit diesem Verfahren erstmals möglich, Verbindungen wie Thiophen und Benzothiazol, deren Diazoniumsalze labil sind, umzusetzen.

Im weiteren Verlauf wurde die neue Eintopfmethode auf die Sandmeyer-Trifluormethylthiolierung übertragen (**Schema 28**).[197]
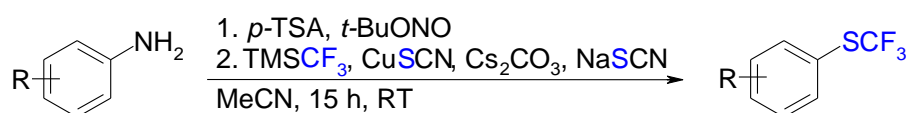
Schema 28. Eintopf-Sandmeyer-Trifluormethylthiolierung.

Das Verfahren erlaubt es, in Gegenwart von Natriumthiocyanat als Schwefelquelle exklusiv die entsprechenden Trifluormethylthioether zu bilden. Die Ausbeuten dieser Reaktion waren geringfügig niedriger, da insgesamt drei Reaktionen, nämlich Diazotierung, Thiocyanierung und Trifluormethylierung, gleichzeitig in einem Reaktionsgefäß stattfinden und sich gegenseitig tolerieren müssen.

Insgesamt konnten effiziente, milde Protokolle zur direkten Sandmeyer-Trifluormethylierung und Trifluormethylthiolierung ausgehend von Anilinen in praktischen Eintopfverfahren entwickelt werden.

Beiträge der Autoren:

Herr B. Bayarmagnai und ich entwickelten die Reaktion, optimierten das Katalysatorsystem und untersuchten die Anwendungsbreite gleichberechtigt. Herr E. Risto unterstützte uns bei der Auftrennung einiger Verbindungen. Das Manuskript verfasste Herr B. Bayarmagnai zusammen mit Herrn Prof. Dr. L. J. Gooßen, während ich die analytischen Daten auswertete und die „Supporting Information" erstellte.

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Advanced Synthesis & Catalysis

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 CF3-reagents such as Ruppert–Prakash reagent (CF3SiMe3),[7] fluoroform,[8] potassium (trifluoromethyl)trimethoxyborate,[9] tri-

fluoroacetate 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 CF3 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 CF3 reagents {CF3SiMe3 or K+[CF3B(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.

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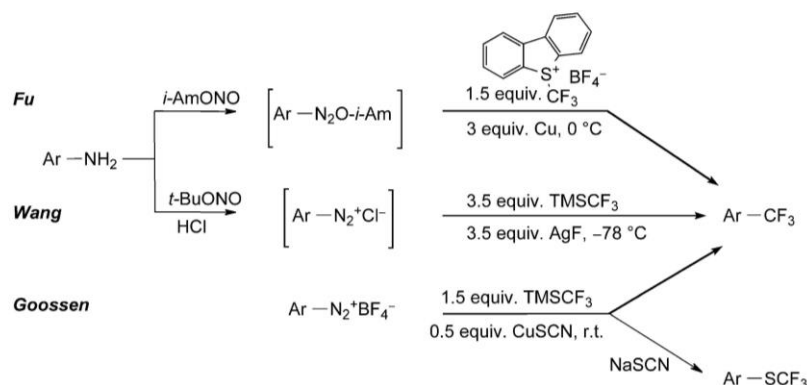
Scheme 1. Sandmeyer-type trifluoromethylations and trifluoromethylthiolations.

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 over-stoichiometric 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).

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Table 1. Optimization of the reaction conditions.[a]
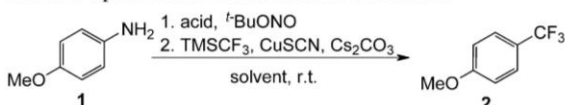
Entry	Acid[b]	Equiv. Acid	Solvent	Yield of **2** [%]
1	pTSA·H$_2$O	2.0	MeCN	72
2	TFA	2.0	MeCN	70
3	ethereal·HCl	2.0	MeCN	39
4	acetic acid	2.0	MeCN	27
5	MSA	2.0	MeCN	49
6	TCA	2.0	MeCN	58
7	BSA	2.0	MeCN	67
8	pTSA	2.0	MeCN	80
9	pTSA	1.5	MeCN	98
10	pTSA	1.1	MeCN	70
11	TFA	1.5	MeCN	71
12	pTSA	1.5	acetone	76
13	pTSA	1.5	DMF	56
14	pTSA	1.5	DMSO	53

[a] *Conditions*: TMSCF$_3$ (0.75 mmol), CuSCN (0.25 mmol), Cs$_2$CO$_3$ (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] pTSA = *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 pTSA 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 pTSA 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.

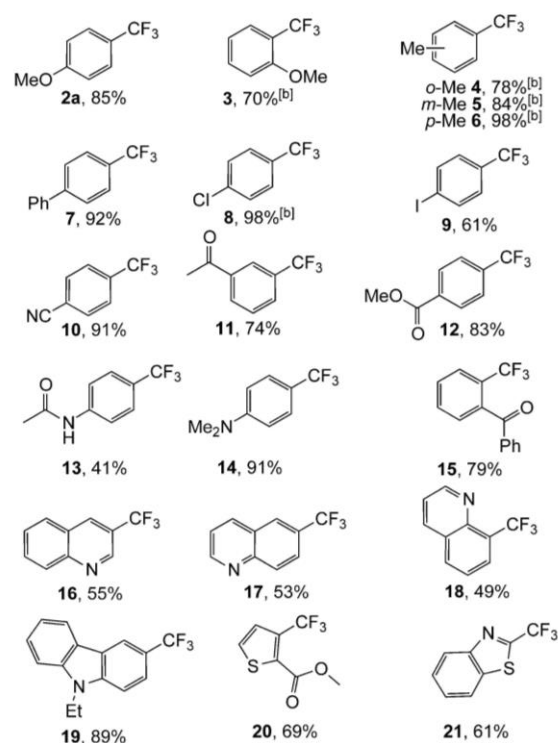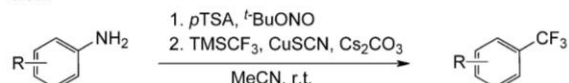**Table 2.** Substrate scope of the Sandmeyer trifluoromethylation.[a]

[a] *Conditions*: TMSCF$_3$ (1.50 mmol), CuSCN (0.50 mmol), Cs$_2$CO$_3$ (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 pTSA (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]

1. pTSA, t-BuONO
2. TMSCF$_3$, CuSCN, Cs$_2$CO$_3$, NaSCN

MeCN, r.t.

22, 70%   **23**, 66%   **24**, 49%

25, 45%   **26**, 32%   **27**, 45%
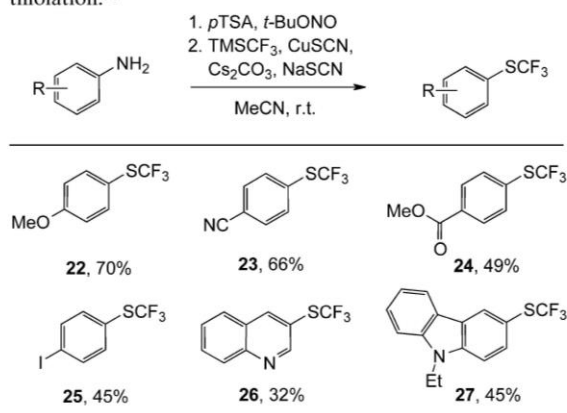
[a] *Conditions*: NaSCN (1.50 mmol), CuSCN (1.00 mmol), acetonitrile (2 mL), 10 min, room temperature, followed by dropwise addition of aromatic amine (1.00 mmol), *tert*-butyl nitrite (1.00 mmol), and pTSA (1.50 mmol) in acetonitrile (2 mL), 15 min. Then addition of Cs$_2$CO$_3$ (4.00 mmol) and TMSCF$_3$ (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 pTSA 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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UPDATES

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Aufgrund der großen Resonanz dieser Publikation und der vorherigen Ergebnisse zur Sandmeyer-Trifluormethylierung ausgehend von Diazoniumsalzen[193] wurden wir darum gebeten, einen „Practical Synthetic Procedure"-Artikel zu verfassen. Darin diskutierten wir beide Methoden ausführlicher, stellten sie gegenüber und beschrieben die experimentelle Vorgehensweise bei der Durchführung der Reaktion.

Beiträge der Autoren:

Herr Dr. G. Danoun, Herr B. Bayarmagnai, Herr M. F. Grünberg und ich verfassten das Manuskript und Herr B. Bayarmagnai, Herr M. F. Grünberg und ich überarbeiteten es zusammen mit Herrn Prof. Dr. L. J. Gooßen.

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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 TMSCF₃ 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
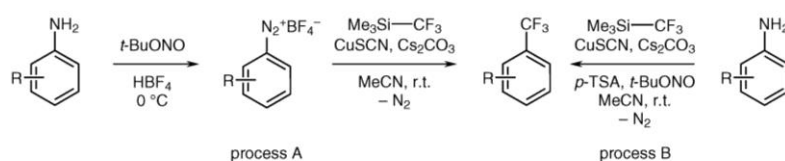
Scheme 1 Sandmeyer trifluoromethylation

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.

Whereas the protocols developed by Wang and Fu are based on costly Umemoto reagent or preformed AgCF₃, our method employs the inexpensive Ruppert–Prakash reagent TMS-CF₃. 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 HBF₄ (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 TMSCF₃ (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 proto-dediazotization 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-CF₃ and the mild base Cs₂CO₃ is a [Cu(CF₃)₂]⁻ species.[9] The reason for using copper

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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).
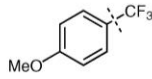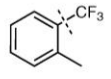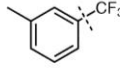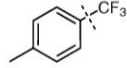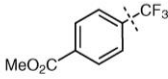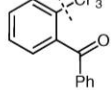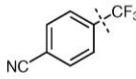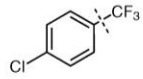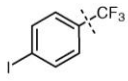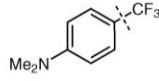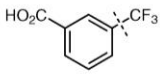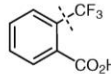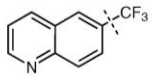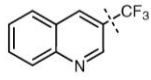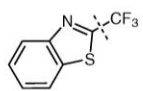
Scope and Limitations

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 benzothi-

azole 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

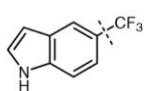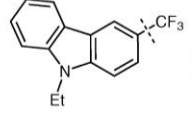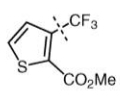| Product		Yield (%)[a]	Product		Yield (%)[a]
1		A: 81 B: 85	**2**		A: 75[b] B: 78[b]
3		A: 98[b] B: 84[b]	**4**		A: 98[b] B: 98[b]
5		A: 71 B: 83	**6**		A: 74 B: 79
7		A: 68 B: 91	**8**		A: 98[b] B: 98[b]
9		A: 69 B: 61	**10**		A: 95 B: 91
11		A: 73 B: 0	**12**		A: 87 B: 0
13		A: 69 B: 53	**14**		A: 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)-1H-indole (15)
[CAS Reg. No.: 100846-24-0]

Prepared from 1H-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)-9H-carbazole (16)

Prepared from 9-ethyl-9H-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]

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5.2. Neue Methoden zur Difluormethylierung

5.2.1. *Sandmeyer-Difluormethylierung*

Um die universelle Anwendbarkeit der von unserem Arbeitskreis etablierten Sandmeyer-Fluoralkylierungen konsequent zu demonstrieren, war das Ziel dieses Projektes, die chemisch und physikalisch einzigartige Difluormethylgruppe unter ähnlich milden Reaktionsbedingungen effizient in Diazoniumsalze einzuführen (**Schema 29**).
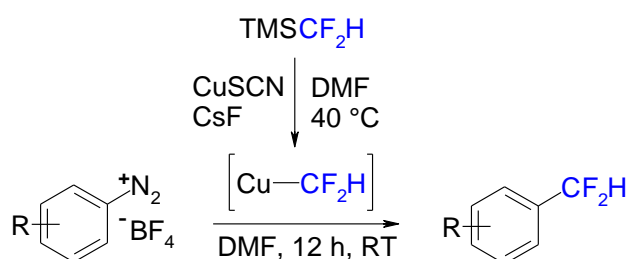
Schema 29. Sandmeyer-Difluormethylierung.

Dieses innovative Verfahren ist den bisherigen Difluormethylierungen teurer Aryliodide deutlich überlegen. Dabei war es besonders wichtig, wie in der wegweisenden Sandmeyer-Trifluormethylierung, ein adäquates nachhaltiges Reagenz zur Übertragung der CF$_2$H-Gruppe zu nutzen. Dafür eignet sich ausschließlich das Ruppert-Prakash analoge TMSCF$_2$H, welches leicht durch die Reduktion von TMSCF$_3$ mit NaBH$_4$ zugänglich ist.[200] Allerdings ist TMSCF$_2$H aufgrund der starken Si–CF$_2$H-Bindung wesentlich unreaktiver als TMSCF$_3$.[201] Ferner zerfallen die intermediär gebildeten Cu–CF$_2$H-Komplexe leicht und müssen durch die bedachte Wahl der Reaktionsbedingungen stabilisiert werden.[147,151,202] Bei den umfassenden Optimierungsreaktionen wurde deutlich, dass die Cu–CF$_2$H-Komplexe unter geringer Wärmezufuhr und in definierter Zeit von 30 Minuten zunächst präformiert werden müssen. Deshalb sind stöchiometrische Mengen des Kupferkatalysators für eine erfolgreiche Sandmeyer-Difluormethylierung unerlässlich. Es zeigte sich sukzessive, dass ausreichende Mengen der gebildeten Cu–CF$_2$H-Spezies bis zur Reaktion nur durch eine Kombination aus DMF als Lösungsmittel und CsF als Aktivator stabilisiert wird. Die Ausbeute sank hingegen bei allen anderen getesteten Lösungsmitteln und Basen drastisch. Die aktive

Katalysatorspezies wurde dann unter Kühlung auf 0°C bis zur Reaktion mit den tropfenweise zugegebenen Diazoniumsalzen konserviert.

Die neu entwickelte Methode zeigte eine große Anwendungsbreite und eröffnet damit einen effizienten, milden Zugang zu der wichtigen Substanzklasse difluormethylierter Verbindungen. Alternativ können die Diazoniumsalze auch *in situ* generiert werden, wobei allerdings etwas geringere Ausbeuten beobachtet wurden. Kontrollexperimente deuten darauf hin, dass die Reaktion tatsächlich über einen klassischen Sandmeyer-Mechanismus verläuft.

Beiträge der Autoren:

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Die Resultate dieses Projektes wurden in *Organic Letters* veröffentlicht, die Publikation für diese Arbeit angepasst und mit Erlaubnis des Verlages beigefügt: "Reprinted (adapted) with permission from C. Matheis, K. Jouvin, L. J. Goossen, *Org. Lett.* **2014**, *16*, 5984-5987: „*Sandmeyer Difluoromethylation of (Hetero)-Arenediazonium Salts*".[203] Copyright 2014 American Chemical Society." Eine separate Lizenz wird von diesem Journal nicht bereitgestellt beziehungsweise benötigt.

Sandmeyer Difluoromethylation of (Hetero-)Arenediazonium Salts

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Ⓢ *Supporting Information*

ABSTRACT: A Sandmeyer-type difluoromethylation process has been developed that allows the straightforward conversion of (hetero-)arenediazonium salts into the corresponding difluoromethyl (hetero-)arenes under mild conditions. The actual difluoromethylating reagent, a difluoromethyl–copper complex, is formed in situ from copper thiocyanate and TMS−CF₂H. The diazonium salts are either preformed or generated in situ from broadly available aromatic amines.
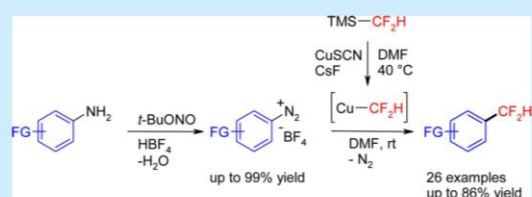
Fluorine-containing residues are central functionalities in pharmaceuticals, agrochemicals, and functional materials.[1] Currently, 30−40% of marketed agrochemicals and about 25% of pharmaceuticals contain fluorine atoms. Whereas perfluoroalkyl chains induce higher lipophilicity and metabolic stability to bioactive substances,[2] the CF_2H group is considered isosteric and isopolar with the hydroxy group.[3] It is weakly acidic and possesses a hydrogen-bond-donating capability comparable to that of OH and NH groups, but the molecule remains more lipophilic. As a result, CF_2H is often a beneficial substitute for such groups in various classes of biologically active compounds. Examples include thiazopyr, fluxapyroxad, deracoxib, eflornithine, pantoprazole, and ZSTK474 (see Figure 1).[1e,4]
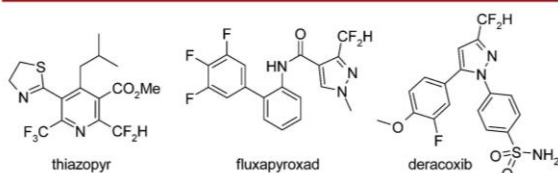

Figure 1. Bioactive molecules containing CF_2H groups.

Traditional approaches to the synthesis of difluoromethyl arenes include the fluorination of benzylic C−H bonds and the deoxo-*gem*-difluoromethylation of aldehydes with SF_4 or aminosulfur trifluorides (e.g., DAST, Deoxofluor).[5] However, these reactions suffer from poor functional group tolerance and harsh reaction conditions.

Methods for the late-stage installation of difluoromethyl groups into functionalized molecules are highly sought-after. However, compared to the tremendous progress made in trifluoromethylation technology,[2a,6] difluoromethylations have met with considerably less success. The advent of easily handled difluoromethylation reagents has sparked new developments in this field. The first type, α-trialkylsilyl difluoroacetate esters, can undergo Cu-catalyzed cross-coupling with aryl iodides, followed by hydrolysis and decarboxylation.[7] The second, difluoromethyl phenyl ketone, can be α-arylated with

aryl bromides or chlorides catalyzed by Pd, followed by ketone cleavage with KOH/H_2O.[8] Both these cleavage steps call for rather harsh conditions.

Baran and co-workers disclosed a radical difluoromethylation of heteroaromatic compounds with zinc difluoromethanesulfinate $Zn(SO_2CF_2H)_2$ that proceeds under mild conditions. Unfortunately, the reaction has a limited scope and usually leads to mixtures of regioisomers.[9]

In view of the high level of efficiency reached in the analogous trifluoromethylations, one would have expected that aryl electrophiles could be difluoromethylated with difluoromethyl copper complexes[6e] generated, e.g., from TMS−CF₂H. This difluoromethylating reagent is easily accessible by reducing the Ruppert−Prakash reagent TMS−CF₃ with $NaBH_4$.[10] However, TMS−CF₂H is substantially less reactive than TMS−CF₃ due to the stronger Si−CF₂H bond.[6e,11] Moreover, Cu−CF₂H complexes easily decompose with formation of 1,1,2,2-tetrafluoroethane and *cis*-difluoroethylene.[6g,12]
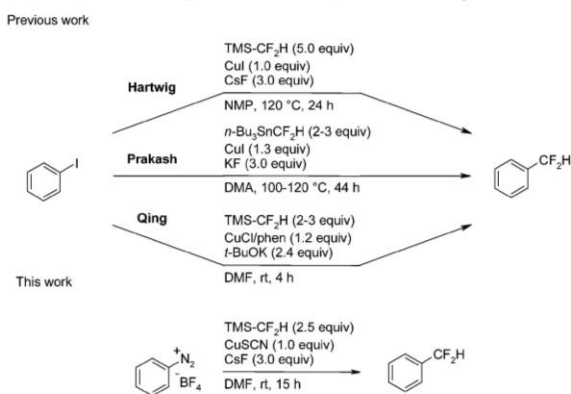
Despite these difficulties, Hartwig et al. have recently disclosed a nucleophilic difluoromethylation of electron-rich aryl and vinyl iodides with Cu−CF₂H complexes generated from excess TMS−CF₂H and copper iodide.[13] Qing and co-workers have extended this method to electron-poor substrates and heteroarenes, reducing the reaction temperature to room temperature and the amount of TMS−CF₂H to 2.5 equiv by introducing phenanthroline as a ligand and using *t*-BuOK as the base (Scheme 1).[14] Prakash et al. have disclosed a similarly efficient protocol based on copper iodide and *n*-Bu₃SnCF₂H. DFT studies revealed that DMF strongly stabilizes the Cu−CF₂H intermediate.[15]

In the context of our work on late-stage trifluoromethylations,[16] we have recently developed Sandmeyer-type[17] trifluoromethylations[18] and trifluoromethylthiolations.[19] An analogous approach would be highly attractive also for the synthesis of difluoromethyl arenes, because it would be based on easily

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Scheme 1. One-Step Difluoromethylation Strategies

Table 1. Optimization of the Reaction Conditions[a]

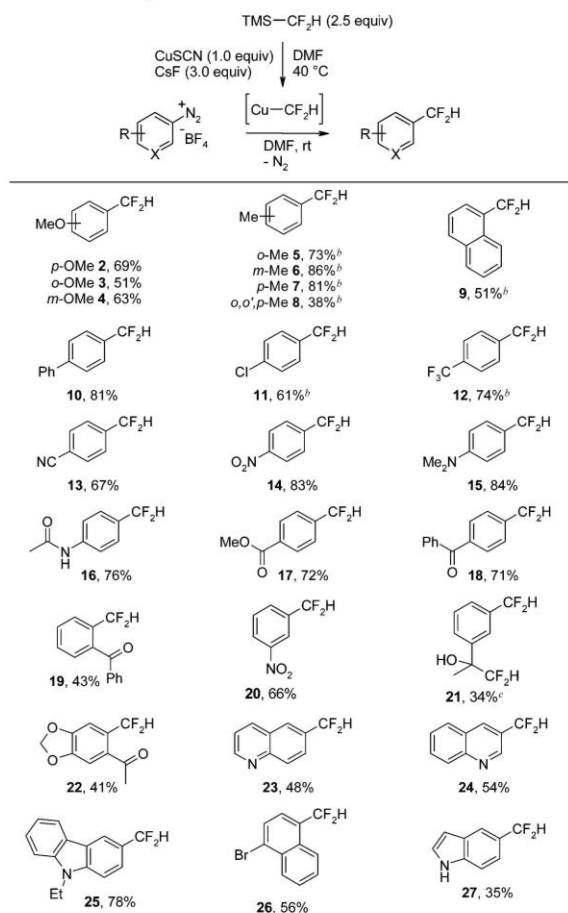| entry	Cu-salt	base	solvent	preform. time/temp	yield (%)
1	CuSCN	Cs_2CO_3	MeCN	0.5 h, rt	<10
2	"	CsF	"	"	26
3	"	KF	"	"	<10
4	"	CsF	NMP	"	15
5	"	"	DMF	"	39
6	CuI	"	"	"	28
7	CuSCN	"	"	0.5 h, 80 °C	46
8	"	"	"	0.5 h, 40 °C	58
9	"	"	"	1 h, 40 °C	73
10[b]	"	"	"	"	71
12[b]	–	"	"	"	0
13[b]	CuSCN	–	"	"	0

[a]Reaction conditions: The Cu reagent was preformed by stirring 2.50 mmol of TMS−CF$_2$H, 0.50 mmol of copper salt, and 1.50 mmol of base in 1 mL of solvent at given temperature and for given time. 0.50 mmol of **1** in 1 mL of solvent was added dropwise at 0 °C and stirred for 12 h at rt. Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard. [b]1.25 mmol TMS−CF$_2$H.

available, inexpensive aryl amines rather than costly aryl iodides (Scheme 1).

However, such a Sandmeyer difluoromethylation may be put into practice only if a suitable Cu−CF$_2$H complex could efficiently be generated from TMS−CF$_2$H and sufficiently be stabilized to enter the reaction pathway outlined in Scheme 2.[18a]

Scheme 2. Mechanistic Sketch for a Sandmeyer Difluoromethylation
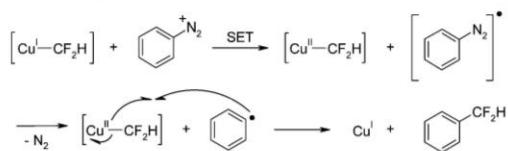
In order to probe the viability of this approach, we chose the reaction of 4-methoxybenzenediazonium tetrafluoroborate (**1**) with TMS−CF$_2$H as a model and applied the conditions that had been most efficient in the corresponding trifluoromethylation. However, the desired product was obtained only in very low yield when slowly adding the diazonium salt to a solution of CuSCN, Cs$_2$CO$_3$, and TMS−CF$_2$H in MeCN that had been prestirred for 30 min at room temperature (Table 1, entry 1). Further investigations revealed that, in comparison to Cu−CF$_3$, the formation of Cu−CF$_2$H species requires stronger bases, which, however, negatively affect the subsequent Sandmeyer process. With fluoride bases, and CsF in particular, the Cu−CF$_2$H preformation step became more efficient, so that the overall yield of the process increased (entries 1−3). Changing the reaction solvent to DMF further increased the yields, which is in agreement with the studies by Prakash et al. that this solvent stabilizes Cu−CF$_2$H species (entries 2, 4, and 5).[15] NMR studies of the mixture of CuSCN, TMS−CF$_2$H, and CsF in DMF confirmed that, under these conditions, Cu−CF$_2$H species are formed in high yields.[20]

Among the copper sources tested, copper thiocyanate gave the best results (entry 5). In contrast, copper iodide, which has been used in difluoromethylations of aryl iodides,[13,15] led to unwanted Sandmeyer halogenation (entry 6).

The decisive parameters turned out to be the Cu−CF$_2$H preformation duration and temperature. In situ NMR studies revealed that this step requires 60 min at 40 °C (entry 9). At

lower temperatures or with shorter reaction times, the reaction does not proceed to completion, and at higher temperatures, the Cu−CF$_2$H species starts to decompose (entries 5, 7, and 8). Accordingly, the highest yield of 73% was obtained when stirring CuSCN, CsF, and TMS−CF$_2$H for 60 min at 40 °C, then cooling down, adding the diazonium salt, and continuing to stir the reaction mixture overnight at room temperature (entry 9). Following this procedure, the amount of TMS−CF$_2$H could be reduced to 2.5 equiv without impacting the reaction outcome (entries 9 and 10).

Control experiments revealed that the reaction does not proceed without either copper or base (entries 12 and 13).

Having thus found an efficient protocol for the Sandmeyer difluoromethylation, we next investigated its scope (Scheme 3). Various difluoromethyl arenes were smoothly synthesized from the corresponding arenediazonium tetrafluoroborates. The products were mostly isolated in pure form and fully characterized. Only for some particularly volatile compounds, the yields could only be determined by ^{19}F NMR, and the identity by mass spectroscopy.

Both electron-withdrawing and -donating substrates gave similarly high yields. However, the reaction seems to be sensitive toward steric hindrance, since *ortho*-substituted products (**3**, **5**, **8**, **19**) were formed in somewhat lower yields than their *para*-substituted analogues (**2**, **7**, **18**). Various common functional groups, such as chloro, trifluoromethyl, cyano, nitro, amino, amido, and even bromo substituents, were tolerated, the latter opening up opportunities for further derivatization. Heteroarene diazonium salts including quino-lines, carbazole, and indole derivatives were also difluoromethy-lated in reasonable yields (**23**, **24**, **25**, **27**). Arenediazonium salts bearing carboxylate or iodo substituents were the sole substrates giving unsatisfactory yields. In each case, large amounts of unwanted protodediazotation products were formed. Diazonium salts bearing keto groups (**18**, **19**, **22**) were selectively difluoromethylated at the arene ring. Protodediazotation was the main side reaction; nucleophilic addition of the difluoromethyl group to the carbonyl group was observed only in traces. Remarkably, the latter reaction took place quantitatively for compound **21**, and the difluoromethyl alcohol was isolated in high yield.[11,21]

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Scheme 3. Scope of the Sandmeyer Difluoromethylation[a]

p-OMe **2**, 69%
o-OMe **3**, 51%
m-OMe **4**, 63%

o-Me **5**, 73%[b]
m-Me **6**, 86%[b]
p-Me **7**, 81%[b]
o,*o*',*p*-Me **8**, 38%[b]

9, 51%[b]

10, 81%

11, 61%[b]

12, 74%[b]

13, 67%

14, 83%

15, 84%

16, 76%

17, 72%

18, 71%

19, 43%

20, 66%

21, 34%[c]

22, 41%

23, 48%

24, 54%

25, 78%

26, 56%

27, 35%

[a]Reaction conditions: The Cu-reagent was preformed by stirring 2.50 mmol of TMS–CF₂H, 1.00 mmol of CuSCN and 3.00 mmol of CsF in 2 mL of DMF at 40 °C for 1 h. 1.00 mmol of Arenediazonium tetrafluoroborate in 2 mL of DMF was added dropwise at 0 °C and stirred for 12 h at rt. Yields of isolated products are given. [b]Yields were determined by ¹⁹F NMR using trifluoroethanol as an internal standard. [c]Starting from 3-acetylbenzenediazonium tetrafluoroborate.

We next probed whether the diazonium salts could also be generated from the corresponding anilines directly in the reaction mixture.[18b] Indeed, when 4-methoxyaniline was diazotized in situ with *tert*-butyl nitrite and the resulting solution added to the preformed Cu–CF₂H species, the desired product was obtained in 45% yield based on the aniline (Scheme 4).

The reaction mechanism was investigated by the addition of radical inhibitors and a radical trapping experiment. When

Scheme 4. One-Pot Diazotization/Difluoromethylation
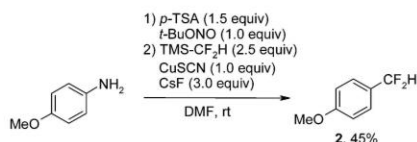
radical quenchers such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or *p*-benzoquinone are present, the reaction is completely suppressed.[22] Moreover, in the difluoromethylation of 2-(allyloxy)diazonium tetrafluoroborate (**28**), the cyclized product **29** was obtained (Scheme 5). These results, which

Scheme 5. Confirmation of Radical Pathway
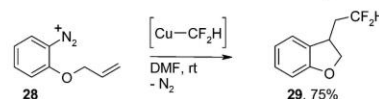
confirm that the reaction proceeds via a radical mechanism, are in good agreement with related studies for other Sandmeyer-type reactions and support the mechanistic outline given in Scheme 2.[18a,19,23]

In conclusion, a Sandmeyer-type difluoromethylation of diazonium salts has been developed that opens up an expedient synthetic entry to valuable difluoromethyl arenes and heteroarenes from easily available aromatic amines. The key advantages of the new process are its mild reaction conditions and the fact that the difluoromethylating reagent can be generated in situ from readily available precursors.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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5.3. Neue Methoden zur Trifluormethylthiolierung und Trifluormethylselenolierung

5.3.1. *Kupfer-katalysierte Sandmeyer-Trifluormethylthiolierung und Trifluormethyl-selenolierung*

Das anspruchsvolle Ziel dieses Projektes war es, eine hocheffiziente Methode zur Darstellung der wichtigen Substanzklasse der Trifluormethylthioether zu erreichen. In diesem Zusammenhang wurde eine katalytische Sandmeyer-Reaktion als universell anwendbare Methode zur Einführung von Trifluormethylthiogruppen ausgehend von leicht verfügbaren und handhabbaren Startmaterialien entwickelt (**Schema 30**).
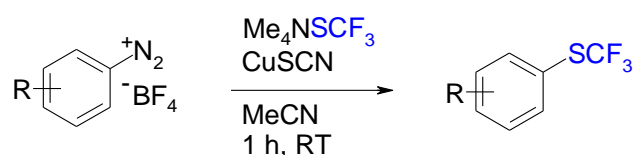
Schema 30. Kupfer-katalysierte Sandmeyer-Trifluormethylthiolierung.

Dafür wurde zunächst Me_4NSCF_3, die momentan günstigste und nachhaltigste SCF_3-Quelle, als geeignetes Reagenz für unsere Konzepte innovativer Sandmeyer-Reaktionen gewählt. In analogen Übergangsmetall-katalysierten Methoden erwies es sich als leistungsfähigstes nukleophiles Trifluormethylthiolierungsmittel von Aryliodiden.[108,110,204] Nach einer ersten Testreaktion aus der Reaktionsmischung von Me_4NSCF_3 und CuSCN stellte sich heraus, dass große Mengen $CuSCF_3$ gebildet werden. Da Clark berichtete, dass stöchiometrisches, präformiertes $CuSCF_3$ nur mit elektronenarmen Diazoniumsalzen in einer nukleophilen Substitution mäßig reagiert, war es zunächst unklar, ob unsere Strategie möglich ist.[196] Dennoch beobachteten wir bereits in einer frühen Experimentenreihe vielversprechende Ergebnisse der postulierten Reaktion. Schließlich konnte sie bis hin zu exzellenten Ausbeuten optimiert werden, indem Reaktionsparameter, wie Lösungsmittel und Mengen der SCF_3-Quelle, angepasst wurden. In folgenden Untersuchungen zeigte sich, dass bereits 10 mol% Kupferthiocyanat die Sandmeyer-Trifluormethylthiolierung innerhalb von nur einer Stunde bei Raumtemperatur effizient vermitteln. Dadurch ist diese Methode eine der wenigen so sehr optimierten Sandmeyer-Reaktionen, die nur katalytische Kupfermengen

benötigen. Die Stärke des Reaktionskonzeptes wurde anhand einer außergewöhnlich großen Anwendungsbreite divers funktionalisierter Verbindungen demonstriert. Darüber hinaus konnte das volle synthetische Potential dieses innovativen Prozesses durch eine *in situ* Diazotierung von Anilinen aufgezeigt werden. Kontrollexperimente deuten darauf hin, dass die Reaktion, im Gegensatz zu der Methode von Clark, tatsächlich über einen klassischen Sandmeyer-Mechanismus verläuft.

In diesem Projekt gelang es außerdem, eine analoge Methode zur direkten Sandmeyer-Trifluormethylselenolierung zu entwickeln (**Schema 31**).
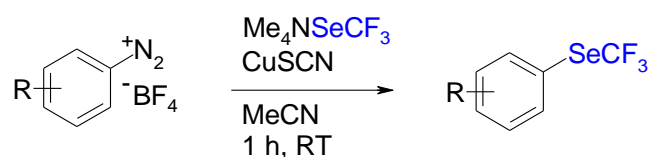
Schema 31. Kupfer-katalysierte Sandmeyer-Trifluormethylselenolierung.

SeCF$_3$-Gruppen besitzen ähnlich einzigartige Eigenschaften wie SCF$_3$ und in den letzten Jahren wurden die therapeutischen und präventiven Effekte auf diverse Krebsarten nachgewiesen.[205–207] Deshalb wuchs kürzlich das Interesse an ihnen deutlich, sodass neue Reaktionen zur Einführung trifluormethylselenolierter Gruppen entwickelt wurden.[208,209] Die Methoden zur Darstellung dieser vielversprechenden Substanzklasse ähneln generell denen der Trifluormethylthiolierung. Sie werden entweder klassisch durch die Trifluormethylierung selenhaltiger Vorstufen, die in zusätzlichen Schritten synthetisiert werden müssen, gebildet,[104,210–212] oder als Ganzes über moderne Übergangsmetall-katalysierte Methoden eingeführt.[213–216] Nachhaltigere, praktischere Zugänge könnten die Einbindung trifluormethylselenolierter Gruppen als gängiges strukturelles Leitmotiv in der Wirkstoffforschung weiter vorantreiben. Aus diesen Gründen wurde das zuvor entwickelte Reaktionskonzept auf die Synthese dieser interessanten Substanzklasse übertragen. Dafür wurde lediglich das entsprechende leicht zugängliche Selenreagenz Me$_4$NSeCF$_3$ in der Kupfer-katalysierten Sandmeyer-Reaktion verwendet, um die korrespondierenden Aryltrifluormethylselenoether ebenso effizient darzustellen. Die Anwendungsbreite dieser Reaktion wurde anhand einiger repräsentativer Substrate mit unterschiedlichen funktionellen Gruppen in hohen Ausbeuten demonstriert.

Beiträge der Autoren:

Frau V. Wagner fertigte unter meiner Betreuung ihre Bachelorarbeit mit dem Thema *„Kupfer-katalysierte direkte Sandmeyer-Trifluormethylthiolierung und Trifluormethylselenolierung*" an. Sie unterstützte mich bei allen praktischen Arbeiten dieses Projektes. Ich entwickelte die Reaktion, wertete die analytischen Daten aus, verfasste die „Supporting Information" sowie das Manuskript und überarbeite letzteres zusammen mit Herrn Prof. Dr. L. J. Gooßen.

Die Resultate dieses Projektes wurden in *Chemistry – A European Journal* als „hot paper" veröffentlicht, die Publikation für diese Arbeit angepasst und mit Erlaubnis des Verlages beigefügt: "Reprinted (adapted) with permission from C. Matheis, V. Wagner, L. J. Goossen, *Chem. Eur. J.* **2016**, *22*, 79-82: „*Sandmeyer-Type Trifluoromethylthiolation and Trifluoromethylselenolation of (Hetero)Aromatic Amines Catalyzed by Copper*".[217] Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim."

▌ **Synthetic Methods** │*Hot Paper*│

Sandmeyer-Type Trifluoromethylthiolation and Trifluoromethylselenolation of (Hetero)Aromatic Amines Catalyzed by Copper

Christian Matheis, Victoria Wagner, and Lukas J. Goossen*[a]

Abstract: Aromatic and heteroaromatic diazonium salts were efficiently converted into the corresponding trifluoromethylthio- or selenoethers by reaction with Me_4NSCF_3 or Me_4NSeCF_3, respectively, in the presence of catalytic amounts of copper thiocyanate. These Sandmeyer-type reactions proceed within one hour at room temperature, are applicable to a wide range of functionalized molecules, and can optionally be combined with the diazotizations into one-pot protocols.

Figure 1. Biologically active trifluoromethyl thioethers.

Fluorine-containing residues are key functionalities in bioactive compounds and present in up to 40% of currently marketed agrochemicals and 25% of pharmaceuticals.[1] Thus, the systematic introduction of fluorinated groups, so called "fluorine scans", has become standard procedure in drug discovery. Hence, new methods for the late-stage introduction of fluorinated moieties into functionalized molecules are highly sought-after. In the last decade, a particular focus was set on CF_3 groups, and various powerful trifluoromethylation methods have been developed.[2] The attention has recently shifted towards trifluoromethyl thioethers, because the SCF_3 group induces an even higher lipophilicity (Hansch constant 1.44 for SCF_3 vs. 0.88 for CF_3) and membrane permeability.[3] Trifluoromethylthio groups are key functionalities in several pharmaceutical and agrochemical products, including tiflorex and toltrazuril (Figure 1).

Traditional strategies for the introduction of SCF_3 groups include the halogen/fluorine exchange of trihalomethyl thioethers with HF or SbF_3,[4] and the trifluoromethylation of sulfur-containing precursors, for example, thiols, disulfides, and thiocyanates.[5,6] However, these methods are limited by substrate availability and/or functional group tolerance. Contemporary trifluoromethylthiolation reactions are based on electrophilic,[7] nucleophilic,[8] radical,[9] or oxidative processes,[10] usually start-
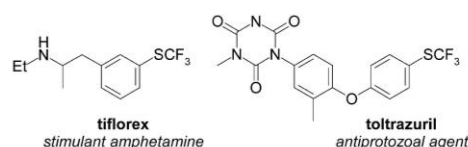
ing from arylboronic acids or aryl halides, or proceed via C—H activation.[9, 11]

Sandmeyer-type trifluoromethylthiolations are advantageous alternatives, because they start from inexpensive and broadly available anilines, use inexpensive copper mediators, and are usually orthogonal to halide-based cross-coupling reactions.

In the course of our research on Sandmeyer-type fluoroalkylations,[12] we have developed a trifluoromethyl thioether synthesis via Sandmeyer thiocyanation followed by Langlois-type nucleophilic CN/CF_3 substitution.[13] Due to its low cost, this two-step approach, in which the sulfur and the CF_3 groups originate from different reagents, is advantageous particularly for large-scale applications. However, on laboratory scale, a Sandmeyer-type trifluoromethylthiolation based on a preformed SCF_3 reagent would be a welcome alternative (Scheme 1). In this context, Me_4NSCF_3 appeared to be the re-
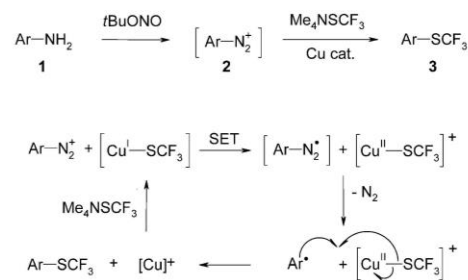
Scheme 1. Sandmeyer trifluoromethylthiolation of aromatic amines.

agent of choice, because it is readily available on preparative scales from tetramethylammonium fluoride, elemental sulfur, and $TMSCF_3$, and can easily be stored and handled. It was first synthesized by Röschenthaler[14] and Yagupolskii and co-worker[15] and has successfully been employed in trifluorome-

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thylthiolations of vinyl iodides,[16] boronic acids,[10c] and aryl halides[8b, 17] catalyzed by Cu, Ni, and Pd complexes.

The feasibility of such a Sandmeyer-type trifluoromethylation with catalytic amounts of copper was unclear, since Clark and co-workers had found that the reaction of arenediazonium salts with stoichiometric amounts of CuSCF$_3$ gives only moderate yields and has a narrow substrate spectrum.[18] Moreover, our two-step trifluoromethylthiolation had been shown to proceed via Cu–SCN rather than Cu–SCF$_3$ intermediates.

To probe the viability of the approach sketched in Scheme 1, we investigated the reaction of 4-methoxybenzenediazonium tetrafluoroborate (2a) with Me$_4$NSCF$_3$ in the presence of several copper salts under various conditions (Table 1).[12a] In the

CuSCN and 1.8 equivalents of Me$_4$NSCF$_3$ in acetonitrile, 3a was formed in 95% yield (Table 1, entry 13).

Having thus identified an effective and convenient protocol for a Sandmeyer-type trifluoromethylthiolation, we next investigated its scope. Diversely substituted aryl trifluoromethyl thioethers were synthesized in high yields from the corresponding arenediazonium tetrafluoroborates (Table 2, Method A).

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

Entry	Solvent	Cu source	Me$_4$NSCF$_3$ [equiv]	Yield 4 [%]
1	MeCN	CuSCN	1.2	64
2	DMF	"	"	22
3	THF	"	"	0
4	MeCN	Cu	"	54
5	"	CuOAc	"	56
6	"	CuI	"	18
7	"	CuSCN	1.5	85
8	"	"	1.8	99
9[b]	"	"	"	99
10[c]	"	"	"	72
11[d]	"	"	"	99
12	"	–	"	0
13[e]	"	CuSCN	"	95

[a] Reaction conditions: dropwise addition of 0.5 mmol diazonium salt 2a in 1 mL solvent to Me$_4$NSCF$_3$ and 0.5 mmol copper source in 1 mL solvent, 15 h at room temperature. Yields were determined by ^{19}F NMR analysis using trifluoroethanol as an internal standard. [b] Cu source (10 mol%). [c] Cu source (5 mol%). [d] 1 h reaction time. [e] 2a was generated in situ.

Table 2. Scope of the Sandmeyer trifluoromethylthiolation.[a]

[a] Method A: dropwise addition of 1.0 mmol diazonium salt (2) in 2 mL MeCN to 1.8 mmol Me$_4$NSCF$_3$ and 0.1 mmol CuSCN in 2 mL MeCN, 1 h at RT. Method B: 2 was generated in situ from 1.0 mmol aromatic amine, 1.0 mmol tert-butyl nitrite and 1.5 mmol p-TSA in 2 mL MeCN. Yields of isolated products. [b] Yields were determined by ^{19}F NMR analysis using trifluoroethanol as standard.

presence of a stoichiometric amount of CuSCN, a promising yield of 64% was obtained at room temperature in acetonitrile (Table 1, entry 1). Other solvents were less effective (Table 1, entries 2 and 3). Of the copper sources tested, CuSCN gave the best yields (entries 4–6). Further investigations revealed that at least 1.8 equivalents of Me$_4$NSCF$_3$ are required to push the reaction to completion (Table 1, entries 7–8). The reaction gave near-quantitative yields within one hour at room temperature even when reducing the amount of CuSCN to 10 mol% (Table 1, entries 9–11). This is remarkable, because most Sandmeyer protocols call for much higher copper loadings. Control experiments confirmed that the reaction does not proceed without copper (Table 1, entry 12).

The diazonium salt can optionally be generated in situ from the corresponding anilines. When 4-methoxyaniline (1a) was treated with p-toluenesulfonic acid and tert-butyl nitrite; and the resulting mixture was added to a solution of 10 mol%

Both electron-withdrawing and electron-donating substrates gave similarly high yields. Various common functionalities are tolerated, such as ether, ester, thio, keto, cyano, amino, nitro, amido, and acetal groups. The reaction is applicable even to halides and carboxylic acids, which opens up opportunities for further derivatization. Heteroarenediazonium salts, including quinoline, carbazole, thiophene, and phthalimide derivatives, were also successfully converted. The scalability of this reaction variant was demonstrated by the synthesis of 3a in 93% on a gram scale.

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The scope of the one-pot diazotization/trifluoromethylthiolation protocol was also investigated with functionalized aromatic and heteroaromatic amines (Table 2, Method B). It was found to be broadly applicable, but the yields were somewhat lower than for the two-step process. A series of experiments was performed to shed some light on the reaction mechanism. The addition of radical quenchers, such as 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) or p-benzoquinone, suppressed the reaction, and with 2-(allyloxy)diazonium tetrafluoroborate (**2ac**) as the substrate, the cyclized product **3ac** was formed exclusively (Scheme 2). A signal at $\delta = -28.0$ ppm in the ^{19}F NMR spectrum
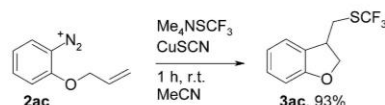
Scheme 2. Radical-capture experiment.

of a mixture of Me$_4$NSCF$_3$ and CuSCN suggests the formation of CuSCF$_3$.[14] Together, these findings support a classical Sandmeyer-type single-electron transfer (SET) mechanism involving aryl radicals (Scheme 1).

Next, we probed whether this reaction concept can also be utilized for the synthesis of trifluoromethyl selenoethers. The SeCF$_3$ moiety imparts similar properties to the SCF$_3$ group,[19] but its introduction can be cumbersome.[6d, 20] Schoenebeck and co-workers recently disclosed an effective Pd-catalyzed trifluoromethylselenolation, which is, however, based on expensive aryl iodides.[19a]

We were pleased to find that by simply replacing Me$_4$NSCF$_3$ with Me$_4$NSeCF$_3$, our Sandmeyer protocol can be turned into an efficient synthesis of trifluoromethyl selenoethers. The scope of this reaction variant is demonstrated by the examples given in Table 3, which include diversely functionalized arenes and heteroarenes.

In conclusion, the Sandmeyer-type processes reported herein open up convenient entries to trifluoromethyl thio- and

selenoethers from easily available aromatic amines. The key advantages of this set of methods are their mild reaction conditions (neutral, 1 h at room temperature), the use of an inexpensive copper catalyst, and the exceptional functional group tolerance. As a result, they are well suited for the late-stage introduction of trifluoromethylthio or -seleno groups into drug-like molecules.

Experimental Section

An oven-dried crimp-cap vessel (20 mL) with stirrer bar was charged with CuSCN (12 mg, 0.10 mmol), Me$_4$NSCF$_3$ (315 mg, 1.80 mmol), and MeCN (2 mL). Then, the diazonium salt **2a–ac** (1 mmol) in MeCN (2 mL) was added dropwise, and the reaction mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with diethyl ether (20 mL), then 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$_2$, pentane/diethyl ether gradient), yielding the aryl trifluoromethyl thioethers **3a–ac**. The yields of particularly volatile compounds were determined by ^{19}F NMR spectroscopy, and their identity by MS.

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Table 3. Scope of the Sandmeyer trifluoromethylselenolation.[a]

[a] Reaction conditions: 1.0 mmol diazonium salt in 2 mL MeCN was added dropwise to a mixture of 1.8 mmol Me$_4$NSeCF$_3$ and 0.1 mmol CuSCN in 2 mL MeCN. The reaction mixture was stirred for 1 h at room temperature. Yields of isolated products are given.

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Aufgrund der überwältigend positiven Gutachterkommentare wurden wir darum gebeten, eine graphische Illustration der entwickelten Reaktion für das Titelbild des Journales zu gestalten. Darin verdeutlichten wir, dass die SCF_3-Gruppe, dargestellt als Dartpfeil, präzise mit der Unterstützung von Kupfer das Ziel, ein Aryldiazoniumsalz, dargestellt als sogenanntes Bulls Eye einer Dartscheibe, trifft.

Beiträge der Autoren:

Ich entwickelte die Idee der graphischen Darstellung der Reaktion als Dartpfeil und -scheibe und gestalte dazu erste einfache Skizzen. Darauf basierend zeichneten Frau V. Wagner mit Frau L. Ruffing das Titelbild per Hand und finalisierten die Zeichnung am Computer.

Das Titelbild wurde in *Chemistry – A European Journal* veröffentlicht, die Publikation für diese Arbeit angepasst und mit Erlaubnis des Verlages beigefügt: "Reprinted (adapted) with permission from C. Matheis, V. Wagner, L. J. Goossen, *Chem. Eur. J.* **2016**, *22*, 1: „*Cover Picture: Sandmeyer-Type Trifluoromethylthiolation and Trifluoromethylselenolation of (Hetero)Aromatic Amines Catalyzed by Copper (Chem. Eur. J. 1/2016)*".[218] Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim."
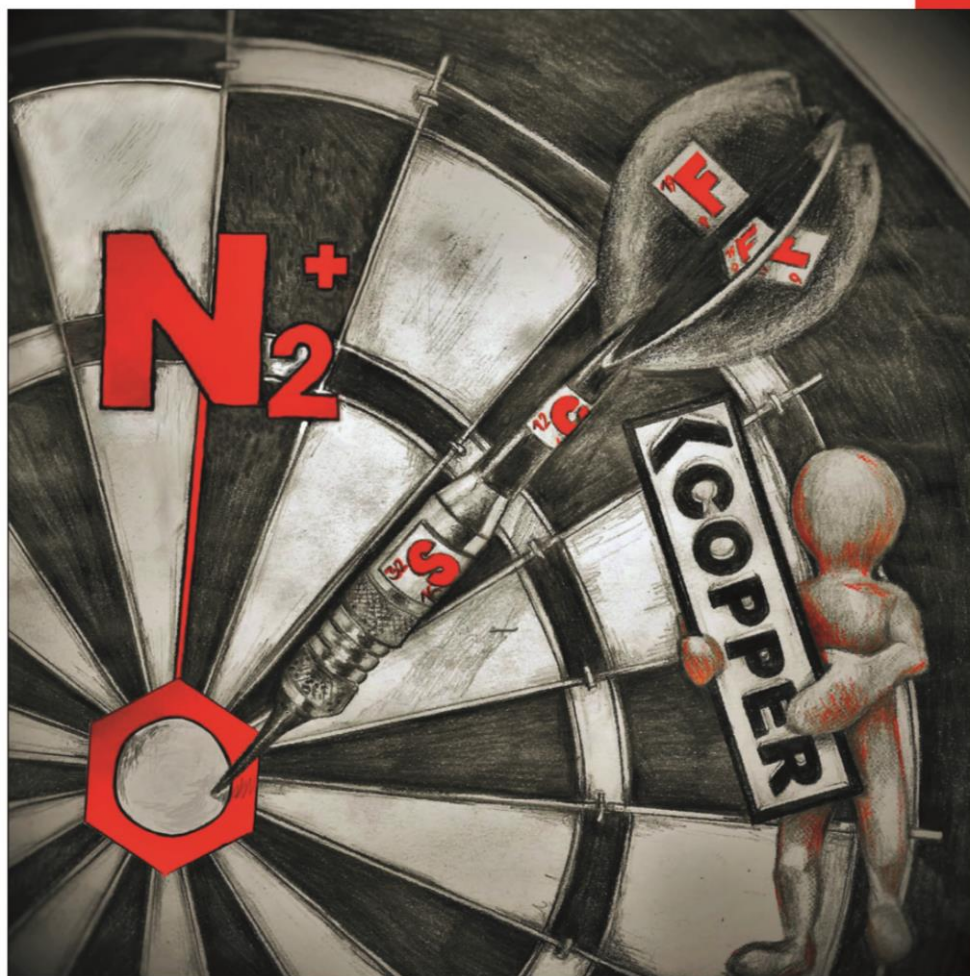
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Front Cover Picture:

L. J. Goossen et al.

Sandmeyer-Type Trifluoromethylthiolation and
Trifluoromethylselenolation of (Hetero)Aromatic Amines
Catalyzed by Copper

Im Zuge der Einladung zur Gestaltung des Titelbildes des Journals wurden wir auch dazu gebeten ein Titelprofil zu verfassen. Darin sollten wir als Frage und Antwort formuliert Hintergrundinformationen zu der entwickelten Reaktion, den Autorenbeiträgen, dem Prozess der Gestaltung des Titelbildes und zu unserer Forschung kurz zusammenfassen.

Beiträge der Autoren:

Ich verfasste das Titelprofil und überarbeite es mit Herrn Prof. Dr. L. J. Gooßen.
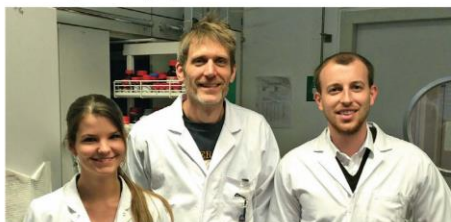
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Sandmeyer-Type Trifluoromethylthiolation and Trifluoromethylselenolation of (Hetero)Aromatic Amines Catalyzed by Copper

From left to right: Victoria Wagner, Lukas J. Goossen and Christian Matheis

TECHNISCHE UNIVERSITÄT KAISERSLAUTERN

Invited for the cover of this issue is the group of Lukas J. Goossen at the Technische Universität Kaiserslautern (Germany). The image depicts the Me_4NSCF_3/Me_4NSeCF_3 reagent—in the form of an arrow—hitting the target benzenediazonium starting material at the center of the dartboard, helped on its way by a copper catalyst. Read the full text of the article at 10.1002/chem.201503524.

What are the most significant results of this study?

The syntheses of trifluoromethyl thio- and selenoethers are usually based on rather complicated processes, often using expensive catalysts. We have now demonstrated that such compounds can be obtained in high yields by a Sandmeyer-type process from easily available aromatic amines and easy to store and handle Me_4NSCF_3/Me_4NSeCF_3. The reactions proceed at room temperature within 1 h and tolerate various functional groups. In contrast to many other Sandmeyer reactions, this process is mediated by a simple, inexpensive copper(I) salt in only 10 mol% loading. The reaction is orthogonal to classical aryl halide based couplings, which is advantageous for multistep reaction sequences.

### How did each team member contribute to the work?

The idea for this reaction first came up in a discussion between Professor Lukas Goossen and Christian Matheis, who's Ph.D. work centers around the development of fluoroalkyl(thiol)ation reactions. Christian had previously developed related fluoroalkylthiolations, in which the sulfur and the fluoroalkyl groups originate from different reagents. In these cases, no formation of $CuSCF_3$ intermediates was observed. Still, it was unclear whether they could be productive intermediates in Sandmeyer trifluoroalkylthiolations if generated another way. Christian suggested reinvestigating this in the context of a bachelor thesis. He supervised the undergraduate student Victoria Wagner during the initial experiments, and after they had turned stoichiometric experiments into an effective trifluoroalkylthiolation method, she spent hard working hours isolating diversely functionalized products to demonstrate the scope of the new process. Coincidently, Professor Goossen received the email notifying him of the acceptance of the manuscript during the oral presentation of her bachelor work, and immediately informed her in front of a considerable audience. Christian and Victoria worked together very efficiently and managed to finish the entire project within the short time of a bachelor project.

Who designed the cover?

Based on an idea by Christian Matheis, Victoria Wagner and her friend Lina Ruffing, a fashion design student, sketched the cover picture by hand and finalized the graphics by computer.

What are the main challenges in your area of research?

The research in the Goossen group is devoted to the development of straightforward transition-metal-catalyzed reactions as alternatives to inconvenient multistep transformations. The derivatization of complex molecules selectively at one specific functional group in the presence of other sensitive functionalities is a major challenge in organic synthesis. In the field of fluoroalkyl(thiol)ation reactions, one of the key challenges is to find scalable protocols that do not require high-tech catalysts and elaborate reagents, but are based on simple chemistry and inexpensive, easy to handle fluoroalkylation reagents—ideally originating from CF_3H or CF_3COOH. Over the last years, the group has disclosed several straightforward methods based on Sandmeyer chemistry. An important goal of this work is to combine nucleophilic trifluoromethylation chemistry with catalytic decarboxylations of CF_3COOH. In another manuscript in this issue, namely "Iron-Catalyzed Decarboxylation of Trifluoroacetate and its Application to the Synthesis of Trifluoromethyl Thioethers" (DOI: 10.1002/chem.201503915), substantial progress in this field is reported.

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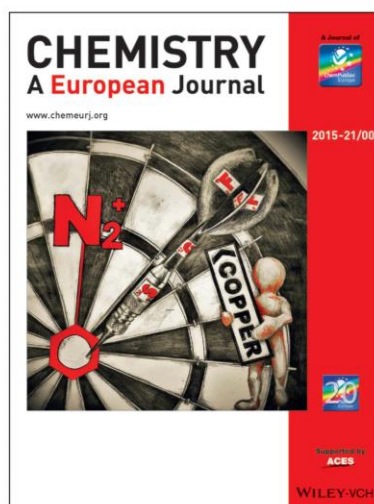
Aufgrund der großen Aufmerksamkeit die der Artikel zur Sandmeyer-Trifluormethythiolierung und -Trifluormethylselenolierung erhalten hatte, wurde Frau V. Wagner auf dem JCF-Frühjahrssymposium 2017 von einer Verlagsmitarbeiterin des „ChiuZ-Storylabs" dazu eingeladen, einen allgemeinverständlichen kurzen Übersichtsartikel zu unserer Forschung zu erstellen.

Beiträge der Autoren:

Frau V. Wagner verfasste die erste Version des Artikels und ich überarbeite ihn anschließend zusammen mit ihr.

Der Highlight Artikel wurde in *Chemie in unserer Zeit* veröffentlicht, die Publikation für diese Arbeit angepasst und mit Erlaubnis des Verlages beigefügt: "Reprinted (adapted) with permission from V. Wagner, C. Matheis, *Chem. Unserer Zeit* **2016**, *50*, 222: „*Fluor im Fokus der Forschung - Eine neue Strategie zur Einführung pharmazeutisch wertvoller Fluorgruppen*".[220] Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim."

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Aus dem ChiuZ-Storylab:

SYNTHESESTRATEGIEN

Fluor im Fokus der Forschung

Eine neue Strategie zur Einführung pharmazeutisch wertvoller Fluorgruppen.

Cefazaflur   Tiflorex   Toltrazuril

Fluorverbindungen als bioaktive Wirkstoffe sind immer weiter auf dem Vormarsch. Bereits 40 % der Agrochemikalien und ein Viertel aller Pharmazeutika enthalten Fluoratome. Fluorierte Gruppen verleihen den Molekülen besonders nützliche Eigenschaften. Sie sorgen dafür, dass Wirkstoffkandidaten besser fettlöslich sind, wodurch der menschliche Körper sie leichter resorbiert und ferner nicht so schnell abbaut. Deshalb werden fluorhaltige Moleküle mittlerweile standardmäßig in der Leitstruktursuche neuer Wirkstoffkandidaten getestet. Insbesondere die Trifluormethyl-Thiogruppe (SCF_3) ist häufig eine wichtige strukturelle Untereinheit von Medikamenten. Beispiele dafür sind Cefazaflur, ein hochwirksames Antibiotikum, Tiflorex, welches als Appetitzügler eingesetzt wird und Toltrazuril zum Behandeln von Kokzidiosen in der Veterinärmedizin.
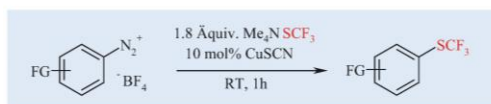
Aufgrund des weiter steigenden Interesses an solchen SCF_3-Verbindungen suchen Forscher nach neuen praktikablen Methoden zur Einführung dieser wichtigen funktionellen Gruppe. Traditionell stellt man Trifluormethyl-Thioverbindungen durch die Übertragung einer Trifluormethylgruppe (CF_3) auf bereits schwefelhaltige Arylverbindungen her. Moderne Methoden übertragen die SCF_3 Gruppe als Ganzes auf Aryhalogenide. Diese setzten aber meistens die Verwendung von teuren Reagenzien oder
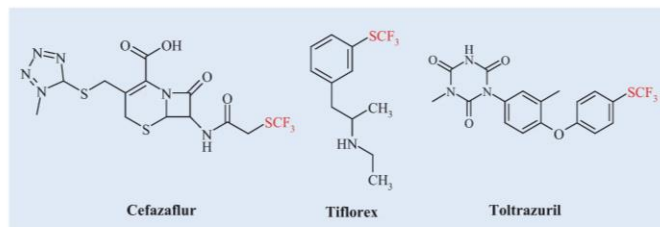
sensiblen Katalysatorsystemen voraus.

Die Arbeitsgruppe von Lukas Gooßen an der TU Kaiserslautern berichtete kürzlich von einer neuen Methode, die einen effektiven Zugang zu fluorierten Thioethern ermöglicht [1]. Bei der Synthese wird in Gegenwart von leicht zugänglichem Me_4NSCF_3 die SCF_3-Gruppe als ganze Einheit über eine Sandmeyer-Reaktion auf aromatische Diazoniumsalze ($R-N_2^+$ mit R=Aromat) übertragen.

Diese Methode zur Darstellung der wichtigen Trifluormethyl-Thioether ist eine von wenigen Beispielen einer Sandmeyer-Reaktion, für die lediglich sehr geringe Mengen des günstigen Kupferkatalysators (10 mol%) benötigt werden. Die Reaktion ist zudem so effizient, dass bereits nach 1 h Reaktionszeit bei Raumtemperatur voller Umsatz erzielt wird. Die milden Reaktionsbedingungen erlauben es, hoch funktionalisierte Moleküle in durchweg sehr guten Ausbeuten umzusetzen. Auch aromatische Aniline, die in großer struktureller Vielfalt günstig und

leicht verfügbar sind, können direkt eingesetzt werden. Diese wurden intermediär in die entsprechenden Diazoniumsalze überführt und im gleichen Reaktionsgefäß zu den SCF_3-Verbindungen umgesetzt. All diese Besonderheiten zeigen deutlich die Stärke des neuen Reaktionskonzeptes.

Es gelang außerdem, eine analoge Methode zur direkten Sandmeyer-Trifluormethylselenolierung zu entwickeln. Dafür wurde das entsprechende Selenreagenz Me_4NSeCF_3 verwendet und unter den gleichen Reaktionsbedingungen mit Aryldiazoniumsalzen umgesetzt. Dadurch konnten erfolgreich Aryltrifluormethyl-Selenoether, eine ebenso vielversprechende Substanzklasse für Wirkstoffkandidaten, dargestellt werden.

[1] C. Matheis, V. Wagner, L. J. Gooßen, *Chem. Eur. J.* **2016**, *22*, 79-82: Sandmeyer-Type Trifluoromethylthiolation and Trifluoromethylselenolation of (Hetero)Aromatic Amines Catalyzed by Copper. DOI: 10.1002/chem.201503524.

Victoria Wagner, Christian Matheis, Kaiserslautern

DIE CHEMISCHEN ELEMENTE NEU ENTDECKEN

Seit Jahresbeginn ist das chemische Periodensystem um vier Elemente reicher und umfasst nun 118 Elemente. Davon kommen 94 in der Natur vor. Von diesen wird jede Woche eines in der diesjährigen Aktuellen Wochenschau der Gesellschaft Deutscher Chemiker (GDCh) vorgestellt.

Arsen beispielsweise kennt jeder als Liebling der Giftmörder, weniger bekannt ist seine Funktion in elektronischen Bauteilen. Oder: Wussten Sie, dass die Fünf-Euro-Banknote dank UV-aktiver Europium-Lumineszenzmaterialien unter UV-Licht strahlt?

Unter www.aktuelle-wochenschau.de warten 52 Geschichten aus der Welt des Periodensystems.

5.3.2. *Kupfer-katalysierte Trifluormethylthiolierung und Trifluormethylselenolierung von α-Diazoestern*

Die Zielsetzung dieses Teilprojektes war es, das hocheffiziente Katalysatorsystem der direkten Sandmeyer-Trifluormethylthiolierung, Me$_4$NSCF$_3$ und katalytische Mengen CuSCN, zur einfachen, milden Funktionalisierung von α-Diazoestern zu nutzen (**Schema 32**).
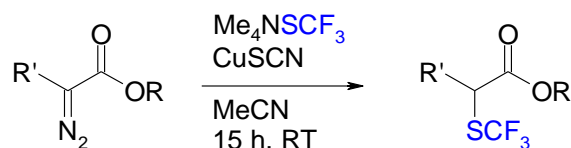
Schema 32. Kupfer-katalysierte Trifluormethylthiolierung von α-Diazoestern.

α-Diazoester sind als breit verfügbare Verbindungen, die beispielsweise leicht aus Aminosäuren hergestellt werden können, ideale Ausgangsstoffe zur Einführung der bedeutenden Trifluormethylthiogruppe. In bereits bekannten ähnlichen Protokollen werden stöchiometrisches präformiertes Cu- oder AgSCF$_3$, die beide aus teurem Silberfluorid hergestellt werden, als SCF$_3$-Quelle eingesetzt (**Schema 33**).[221–223]
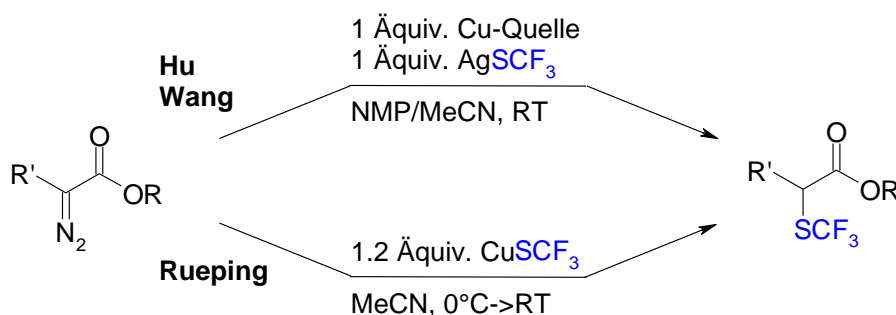
Schema 33. Trifluormethylthiolierungen von α-Diazoestern.

Praktische katalytische Prozesse sind hingegen eines der Hauptziele nachhaltiger Chemie und verbessern das Reaktionskonzept erheblich. Ein weiterer Vorteil ergibt sich daraus, dass Alkyl-substituierte α-Diazoester in Anwesenheit stöchiometrischer Kupfermengen durch Extrusion von Stickstoff und 1,2-Hydridshift zur Bildung von Acrylaten neigen. Dadurch konnten sie in diesen Transformationen nur in geringen Ausbeuten von bis zu 30% dargestellt werden. In unserer Methode hingegen werden nur 10 mol% des preiswerten CuSCN benötigt um *in situ* CuSCF$_3$ aus einfach handhabbaren Me$_4$NSCF$_3$ herzustellen. Dadurch wird diese Nebenreaktion nahezu komplett unterdrückt und die entsprechenden trifluormethylthiolierten

Produkte in hohen Ausbeuten zugänglich macht. Allerdings sind dafür längere Reaktionszeiten nötig, wodurch wiederum Aryl-α-Diazoester zu Homokupplungen bevorzugt gebildet werden. Ein weiterer Nachteil der bekannten Trifluormethylthiolierungen (**Schema 33**) ist, dass die Reaktionen so empfindlich sind, dass die stöchiometrischen Metallsalze häufig frisch hergestellt und direkt verwendet werden müssen. Außerdem können diese Verfahren nur unter striktem Ausschluss von Luft und Feuchtigkeit durchgeführt werden. Dagegen werden in unserem Protokoll Luft und Wasser zu einem gewissen Grad toleriert und Lösungsmittel können direkt ohne Aufreinigungsprozesse verwendet werden. Das innovative Reaktionskonzept zeigte eine außergewöhnlich große Toleranz gegenüber diversen funktionellen Gruppen. Dabei lag der Fokus hauptsächlich auf α-Diazoestern, die aus leicht verfügbaren Aminosäuren zugänglich sind.

Zur Aufklärung des Reaktionsmechanismus wurden einige Kontrollexperimente durchgeführt. Obwohl Radikalfänger, wie TEMPO und *p*-Benzochinon, die Produktbildung komplett unterdrückten, reagierten Substrate, die zu radikalischer Cyclisierung neigen, sogenannte Radikal-Clock Reaktionen, ohne Umlagerungen. Deshalb wurde ein radikalischer Mechanismus ausgeschlossen. Interessanterweise wird im Gegensatz zu den analogen Trifluormethylthiolierungen von α-Diazoestern keine externe Protonenquelle, die nach der eigentlichen Reaktion in einem weiteren Schritt zugefügt wird, benötigt. Deuteriumexperimente deuten darauf hin, dass das Proton nicht aus dem Lösungsmittel, sondern aus dem Tetramethylammoniumion und/oder aus Wasserspuren stammt. Generell zerfallen Diazoverbindungen leicht unter thermischen oder photochemischen Bedingungen und in Anwesenheit von Übergangsmetallen durch die Extrusion von Stickstoff in die entsprechenden Carbene (**Schema 34**). Bei Übergangsmetallen entstehen dadurch die korrespondierenden stabileren Metall-Carbenoide, die die Eigenschaften eines typischen Carbens aufweisen.[224]
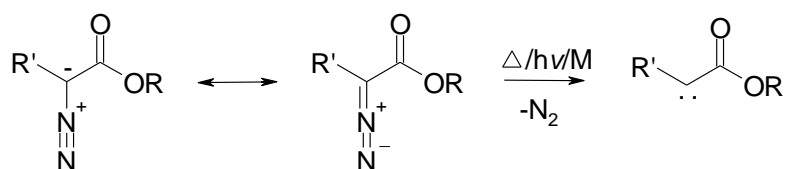

Schema 34. Zerfall von Diazoverbindungen in Carbene.

Auf der Grundlage dieser mechanistischen Untersuchungen formulierten wir einen möglichen Reaktionsmechanismus (**Schema 35**). Zunächst entsteht aus dem α-Diazoester und der *in situ* gebildeten CuSCF₃-Spezies durch Extrusion von Stickstoff ein Kupfercarbenoid. Anschließend erfolgt eine migratorische Insertion, wobei das SCF₃-Anion an das α-Kohlenstoffatom wandert. Durch Protonierung wird das gewünschte trifluormethylthiolierte Produkt gebildet und das Kupferkation kann mit einem weiteren Äquivalent Me₄NSCF₃ die aktive Katalysatorspezies CuSCF₃ bilden.
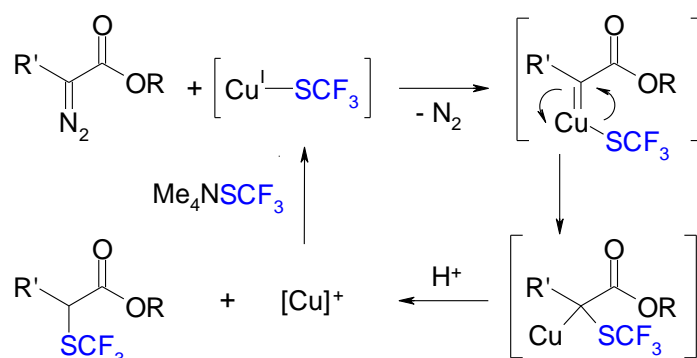
Schema 35. Postulierter Mechanismus der Trifluormethylthiolierungen von α-Diazoestern.

Das Reaktionskonzept konnte außerdem als eine neue, analog effiziente Methode zur Trifluormethylselenolierung von α-Diazoestern angewendet werden (**Schema 36**).
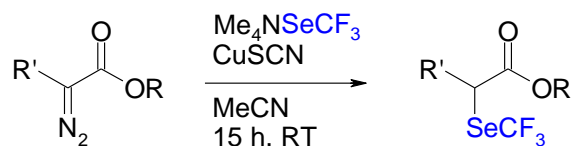
Schema 36. Kupfer-katalysierte Trifluormethylthiolierung von α-Diazoestern.

Dafür wurde lediglich Me₄NSCF₃ durch Me₄NSeCF₃ ersetzt und repräsentative α-Diazoester unter sonst gleichen Reaktionsbedingungen zu den entsprechenden Produkten in hohen Ausbeuten umgesetzt.

Beiträge der Autoren:

Ich entwickelte die Reaktion, optimierte das Katalysatorsystem und untersuchte die Anwendungsbreite. Herr T. Krause und Frau V. Bragoni unterstützten mich bei der Synthese der Diazoverbindungen, bei der Auswertung der analytischen Daten und bei dem Erstellen der „Supporting Information". Frau A.-K. Seitz half wiederum Herrn T. Krause bei den

praktischen Arbeiten, die unter dessen Betreuung ihre Bachelorarbeit mit dem Thema „*Synthese und Verwendung von Diazoverbindungen in Übergangsmetall-katalysierten Funktionalisierungen*" anfertigte. Ich verfasste das Manuskript und überarbeite es zusammen mit Herrn Prof. Dr. L. J. Gooßen.

Die Resultate dieses Projektes wurden in *Chemistry – A European Journal* veröffentlicht, die Publikation für diese Arbeit angepasst und mit Erlaubnis des Verlages beigefügt: "Reprinted (adapted) with permission from C. Matheis, T. Krause, V. Bragoni, L. J. Goossen, *Chem. Eur. J.* **2016**, *22*, 12270-12273: „*Trifluoromethylthiolation and Trifluoromethylselenolation of α-Diazo Esters Catalyzed by Copper*".[225] Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim."

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TERMS AND CONDITIONS

Synthetic Methods

Trifluoromethylthiolation and Trifluoromethylselenolation of α-Diazo Esters Catalyzed by Copper

Christian Matheis, Thilo Krause[+], Valentina Bragoni[+], and Lukas J. Goossen*[a]

Abstract: α-Diazo esters are smoothly converted into the corresponding trifluoromethyl thio- or selenoethers by reaction with Me_4NSCF_3 or Me_4NSeCF_3, respectively, in the presence of catalytic amounts of copper thiocyanate. This straightforward method gives high yields under neutral conditions at room temperature and is applicable to a wide range of functionalized molecules, including diverse α-amino acid derivatives. It is well-suited for the late-stage introduction of trifluoromethylthio or -seleno groups into drug-like molecules.

Figure 1. Biologically active trifluoromethyl thioethers.

Over the past few decades, fluorine-containing moieties have become ubiquitous functionalities in modern bioactive molecules. They are present in close to 40% of currently marketed agrochemicals and 25% of pharmaceuticals.[1] Their systematic evaluation, the so-called "fluorine scan", is routinely performed when refining lead structures in drug discovery. Hence, new methods for the late-stage introduction of fluorinated moieties into complex, functionalized molecules are highly sought-after. Originally, research efforts focused mainly on the development of methods for the introduction of CF_3 groups.[2] Lately, the SCF_3 group has attracted particular attention since it induces an even higher lipophilicity and membrane permeability (Hansch constant 1.44 for SCF_3 vs. 0.88 for CF_3).[3] Trifluoromethylthio groups are present in an increasing number of bioactive molecules, including the antibiotic Cefazaflur, a trifluoromethylthiolated methionine analogue with antimalarial properties, and a ribose derivative with antipneumnonia activity (Figure 1).[4]

Several efficient strategies for the late-stage trifluoromethylthiolation of organic molecules have recently been devised.[5] These are based on electrophilic,[6] nucleophilic,[7] radical,[8] or oxidative processes,[9] usually starting from arylboronic acids or aryl halides, but also from arenes via C–H activation.[10] Our contribution to this emerging field includes the development of Sandmeyer fluoroalkyl- and fluoroalkylthiolations.[11] In this context, we have demonstrated that (hetero-)aromatic
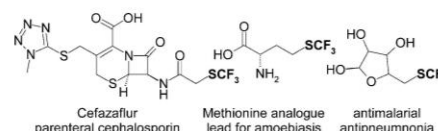
amines can conveniently be converted into aryl trifluoromethylthio ethers by a diazotization/trifluoromethylthiolation sequence using the bench-stable reagent Me_4NSCF_3.[12] This SCF_3 source is readily available from tetramethylammonium fluoride, elemental sulfur, and $TMSCF_3$.[13] Following initial reports by Röschenthaler[14] and Yagupolskii,[15] it has successfully been employed in trifluoromethylthiolations of vinyl iodides,[16] boronic acids,[9c] aryl halides,[7b,17] and triflates[18] mediated by Cu, Ni, and Pd catalysts.

We envisioned that this stable and easy-to-handle reagent might be the key towards enabling a catalytic trifluoromethylation of α-diazo esters (Scheme 1). These substrates are easily
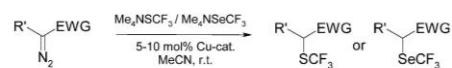
Scheme 1. Catalytic trifluoromethylthiolation/-selenolation of α-diazo esters.

accessible in broad structural diversity from amino acids. Moreover, they can be synthesized from ketones via the Bamford–Stevens reaction or from acetoacetates via a Regitz deprotonation/diazo transfer sequence.[19]

α-Diazo esters have been used as substrates for dediazotative trifluoromethylations, difluoroolefinations,[20] and stoichiometric trifluoromethylthiolations. Wang and Hu and co-workers have disclosed trifluoromethylthiolation processes based on stoichiometric amounts of $AgSCF_3$ and Cu salts.[21] In an analogous synthesis of trifluoromethyl thioethers, Rueping et al. have used preformed $CuSCF_3$.[22] Gouverneur et al. have extended this method from α-diazo esters to 1-(diazo-2,2,2-trifluoroethyl)arenes.[20a] However, in all cases, the stoichiometric use of transition metal salts is unavoidable.

The catalytic use of copper in combination with a stable trifluoromethylthiolation reagent would vastly improve the sustainability and practicability of this reaction concept. Making the decisive transition from stoichiometric reactions based on preformed transition metal–SCF_3 complexes to a catalytic trifluoromethylthiolation process would require a) identifying

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[+] These authors contributed equally.

Supporting information for this article is available on the WWW under
http://dx.doi.org/10.1002/chem.201602730.

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a copper precursor that reacts with Me_4NSCF_3 to form a Cu–SCF_3 complex capable of transferring the SCF_3 moiety to the substrate, and b) sufficiently stabilizing the Cu species liberated during product formation to allow regeneration of the initial Cu–SCF_3 complex (Scheme 2).
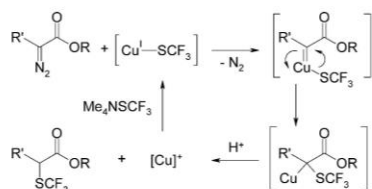
Scheme 2. Proposed mechanism for the Cu-catalyzed trifluoromethylthiolation of α-diazo esters.

To probe the feasibility of our approach, we investigated the reaction of phenylalanine α-diazo ester **1a** with Me_4NSCF_3 in the presence of a range of copper salts under various conditions (Table 1).

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

Entry	Solvent	Cu-source	Me_4NSCF_3 [equiv]	Yield **2a** [%]
1	MeCN	1 equiv CuSCN	1.1	86
2	NMP	1 equiv CuSCN	1.1	37
3	DMF	1 equiv CuSCN	1.1	63
4	MeCN	1 equiv Cu	1.1	6
5	MeCN	1 equiv CuI	1.1	24
6	MeCN	1 equiv CuSCN	1.5	99
7	MeCN	50 mol% CuSCN	1.5	99
8	MeCN	10 mol% CuSCN	1.5	99
9	MeCN	5 mol% CuSCN	1.5	53
10	MeCN	–	1.5	0
11[b]	MeCN	10 mol% CuSCN	1.5	64
12[c]	MeCN	10 mol% CuSCN	1.5	91
13[d]	MeCN	10 mol% CuSCN	1.5	85
14	MeCN	10 mol% CuSCN	1.5	87[e]

[a] Reaction conditions: 0.5 mmol **1a** in 1 mL solvent was added to Me_4NSCF_3 and the Cu-source in 1 mL solvent, and the mixture was stirred for 15 h at room temperature. Yields were determined by ^{19}F NMR spectroscopy using trifluoroethanol as an internal standard. [b] 6 h reaction time. [c] Under air. [d] Standard-grade MeCN. [e] Isolated yield on 10 mmol scale.

After 15 h at room temperature, the trifluoromethyl thioether **2a** was observed in the presence of stoichiometric amounts of CuSCN in acetonitrile, which proves that the first critical step, the generation of a reactive Cu–SCF_3 species, is possible starting from this precursor (entry 1). Other solvents and copper sources were less effective in these stoichiometric experiments (entries 2–5). Near-quantitative yields of the desired
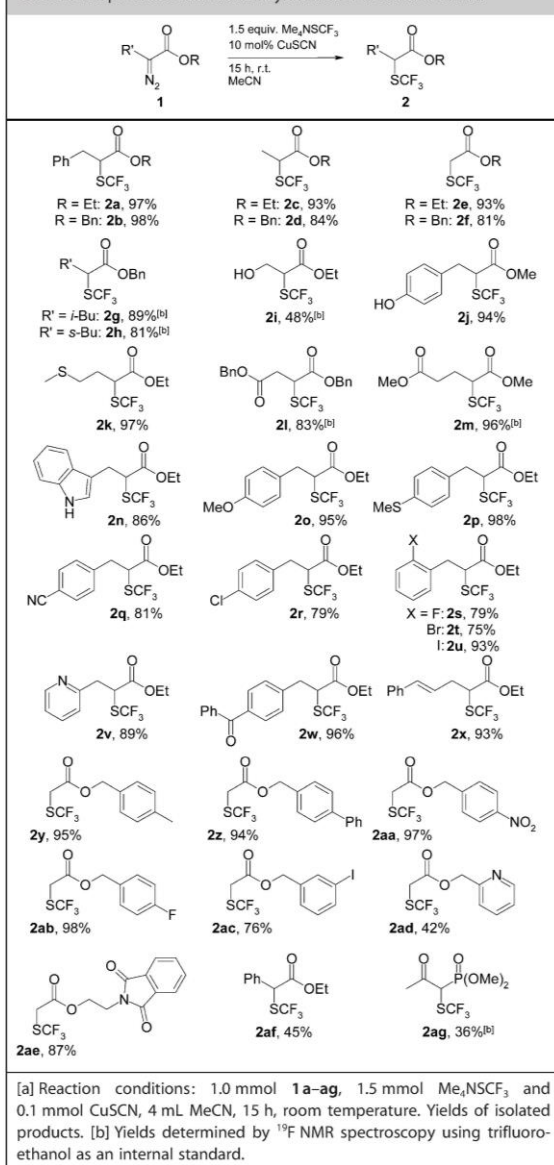
product were obtained when using 1.5 equiv of Me_4NSCF_3 in combination with CuSCN (entry 6). Under these optimized conditions, the copper loading could be reduced to 10 mol% without impacting the yield, and even at 5 mol%, moderate yields were obtained (entries 6–9). This demonstrates that the reactive $CuSCF_3$ species can indeed be regenerated.

Control experiments confirmed that the reaction does not proceed without copper (entry 10) and that several hours of reaction time are required (entry 11). It was found that air and water are tolerated to a certain threshold, so that the reaction can be performed with standard-grade solvents without special precautions (entries 12 and 13). This is a great advantage over the stoichiometric reactions reported in the literature, which had to be set up under rigorous exclusion of air or moisture with freshly prepared reagents.[20a,21,22] The scalability of the process was demonstrated by the high-yielding synthesis of **2a** on gram scale (entry 14).
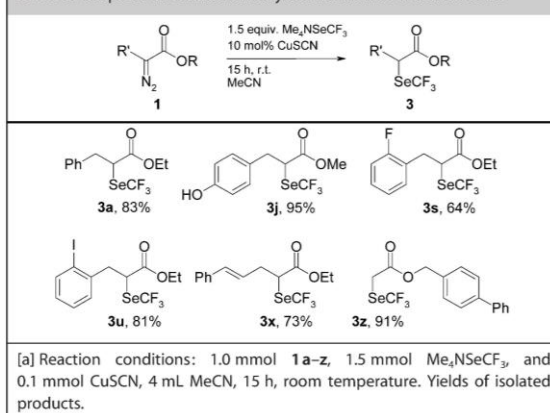
The scope of this straightforward and convenient method for the trifluoromethylthiolation of α-diazo esters is illustrated by the examples in Table 2. A large number of diversely substituted α-diazo esters were smoothly converted into the corresponding trifluoromethyl thioethers in high yields, with a focus on amino acid-derived starting materials. Moreover, various other common functionalities, such as ether, ester, thio, keto, cyano, nitro, and hydroxy groups, are tolerated. Reactive halide substituents remain unchanged in the process, which opens up opportunities for further derivatization. Even α-diazo esters bearing heterocyclic substituents such as indoles, pyridines, and phthalimides, were successfully converted. Aryl α-diazo esters predominantly underwent homo-coupling to the corresponding olefins under the reaction conditions.[23] Phosphoric acid derivatives were also converted, albeit in somewhat lower yields.

A series of experiments was performed to better understand the reaction mechanism (Scheme 2). A signal at $\delta = -28.0$ ppm in the ^{19}F NMR spectrum of a mixture of Me_4NSCF_3 and CuSCN provides evidence for the formation of $CuSCF_3$.[12,14] Based on the findings of Hu and Wang, we excluded a radical pathway.[21] Still, radical quenchers, such as 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) or p-benzoquinone, suppressed the reaction but did not form adducts, pointing to a deactivation of the SCF_3 species.[24] It is interesting that the reaction, which is formally an *ipso* addition of H-SCF_3 to a carbene, does not seem to require a proton source. Deuterium-labeling experiments indicate that the extra proton in the product originates from the tetramethylammonium ion and/or traces of water in the reaction mixture, but not from the solvent (for details see the Supporting Information).

We next probed whether it was possible to extend this reaction concept to trifluoromethylseleno groups. The SeCF_3 moiety should impart similarly beneficial properties as the SCF_3 group, but its introduction is less developed,[12,25] and trifluoromethylselenolations of α-diazo esters are unknown to date. We were pleased to find that by simply replacing Me_4NSCF_3 with Me_4NSeCF_3, various trifluoromethyl selenoethers are accessible in high yields from the corresponding α-diazo esters (Table 3). None of the structures have previously been synthesized.

85

Table 2. Scope of the trifluoromethylthiolation of α-diazo esters.[a]

1.5 equiv. Me₄NSCF₃
10 mol% CuSCN
15 h, r.t.
MeCN

1 → 2

R = Et: **2a**, 97%
R = Bn: **2b**, 98%

R = Et: **2c**, 93%
R = Bn: **2d**, 84%

R = Et: **2e**, 93%
R = Bn: **2f**, 81%

R' = i-Bu: **2g**, 89%[b]
R' = s-Bu: **2h**, 81%[b]

2i, 48%[b]

2j, 94%

2k, 97%

2l, 83%[b]

2m, 96%[b]

2n, 86%

2o, 95%

2p, 98%

2q, 81%

2r, 79%

X = F: **2s**, 79%
Br: **2t**, 75%
I: **2u**, 93%

2v, 89%

2w, 96%

2x, 93%

2y, 95%

2z, 94%

2aa, 97%

2ab, 98%

2ac, 76%

2ad, 42%

2ae, 87%

2af, 45%

2ag, 36%[b]

[a] Reaction conditions: 1.0 mmol **1a–ag**, 1.5 mmol Me₄NSCF₃ and 0.1 mmol CuSCN, 4 mL MeCN, 15 h, room temperature. Yields of isolated products. [b] Yields determined by ¹⁹F NMR spectroscopy using trifluoro-ethanol as an internal standard.

Table 3. Scope of the trifluoromethylselenolation of α-diazo esters.[a]

1.5 equiv. Me₄NSeCF₃
10 mol% CuSCN
15 h, r.t.
MeCN

1 → 3

3a, 83%

3j, 95%

3s, 64%

3u, 81%

3x, 73%

3z, 91%

[a] Reaction conditions: 1.0 mmol **1a–z**, 1.5 mmol Me₄NSeCF₃, and 0.1 mmol CuSCN, 4 mL MeCN, 15 h, room temperature. Yields of isolated products.

Experimental Section

An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with CuSCN (12 mg, 0.10 mmol), Me₄NSCF₃ (262 mg, 1.50 mmol), and MeCN (2 mL). The α-diazo ester **1a–ag** (1 mmol) in MeCN (2 mL) was then added. The reaction mixture was stirred for 15 h at room temperature, then diluted with diethyl ether (20 mL), and washed with water (2×10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered, and concentrated (700 mbar, 40 °C). The residue was purified by flash chromatography (SiO₂, cyclohexane/ethyl acetate gradient), yielding the trifluoromethyl thioethers **2a–ag**.

Acknowledgements

In conclusion, the catalytic trifluoromethylthiolation/trifluoromethylselenolation process reported herein opens up a convenient entry to trifluoromethyl thio- and selenoethers from easily available α-diazo esters. Its key advantages are the operational simplicity, tolerance to air and moisture, use of inexpensive, easy-to-store and handle SCF₃/SeCF₃ sources, mild reaction conditions, and exceptional functional group tolerance. As a result, this method is well-suited for the late-stage derivatization of drug-like molecules.
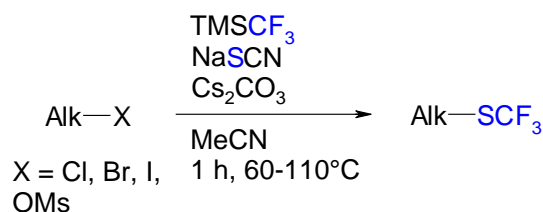
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5.3.3. *Metallfreie Trifluormethylthiolierung von Alkylelektrophilen*

Das Ziel dieses Projektes war die konsequente Fortsetzung der in unserem Arbeitskreis etablierten Kaskade aus *in situ* Thiocyanierung und anschließender Trifluormethylierung,[197] um neue praktische metallfreie Trifluormethylthiolierung breit verfügbarer Alkylelektrophile zu entwickeln (**Schema 37**).

$$\text{Alk}\!-\!\text{X} \quad \xrightarrow[\substack{\text{MeCN} \\ \text{1 h, 60-110°C}}]{\substack{\text{TMSCF}_3 \\ \text{NaSCN} \\ \text{Cs}_2\text{CO}_3}} \quad \text{Alk}\!-\!\text{SCF}_3$$

X = Cl, Br, I, OMs

Schema 37. Metallfreie Trifluormethylthiolierung von Alkylelektrophilen.

Dabei werden in Gegenwart von NaSCN zunächst Alkylthiocyanate aus Alkylelektrophilen generiert und dann unmittelbar in einer unkatalysierten Langlois- CN/CF$_3$-Substitution durch TMSCF$_3$ in die korrespondierenden Trifluormethylthioether überführt. Das Reaktionskonzept, die SCF$_3$-Gruppen aus zwei verschiedenen Quellen einzuführen, erlaubt nachhaltigere Zugänge zu dieser wichtigen Substanzklasse, basierend auf günstigen Startmaterialien und ohne präformierte, stöchiometrische Metall-SCF$_3$-Reagenzien. Im Rahmen der Reaktionsentwicklung war es von essentieller Bedeutung, Bedingungen für beide Teilreaktionen zu finden, die sich gegenseitig tolerieren. Schnell zeigte sich, dass Alkylbromide mit NaSCN bei 60°C bereits in einer Stunde vollständig thiocyaniert werden. Deshalb bestand nun die Herausforderung darin, eine geeignete Base als Aktivator des Ruppert-Prakash-Reagenzes für den CN/CF$_3$-Austausch zu ermitteln. Zunächst zeigte sich, dass TBAF als klassisch verwendete Base für den Langlois-Austausch nur eine geringe Ausbeute liefert. Nach einer umfangreichen Experimentenreihe konnten schließlich Cs$_2$CO$_3$ und MeCN als optimale Kombination identifiziert werden, die sogar bei der direkten Zugabe aller Reagenzien einen vollen Umsatz zeigte. Das große Potential der entwickelten Reaktion wurde außerdem anhand einer außergewöhnlich großen Anwendungsbreite hochfunktionalisierter Alkylelektrophile demonstriert. Bemerkenswerterweise wurden viele Produkte so effizient gebildet, dass häufig nur eine wässrige Aufarbeitung nötig war, um sie analysenrein zu isolieren. Dies unterstreicht weiter den praktischen Nutzen des innovativen Reaktionskonzeptes.

Beiträge der Autoren:

Ich entwickelte die Reaktion, optimierte das Katalysatorsystem und untersuchte die Anwendungsbreite. Frau Dr. M. Wang unterstütze mich bei der Synthese der verwendeten Mesylate und Herr T. Krause half mir bei dem Auswerten der analytischen Daten und bei dem Erstellen der „Supporting Information". Ich verfasste das Manuskript und überarbeitete es zusammen mit Herrn Prof. Dr. L. J. Gooßen.

Die Resultate dieses Projektes wurden in *Synlett* veröffentlicht, die Publikation für diese Arbeit angepasst und mit Erlaubnis des Verlages beigefügt: "Reprinted (adapted) with permission from C. Matheis, M. Wang, T. Krause, L. J. Goossen, *Synlett* **2015**, *26*, 1628-1632: „*Metal-Free Trifluoromethylthiolation of Alkyl Electrophiles via a Cascade of Thiocyanation and Nucleophilic Cyanide-CF₃ Substitution*"[226] Copyright 2015 Georg Thieme Verlag Stuttgart · New York."

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Metal-Free Trifluoromethylthiolation of Alkyl Electrophiles via a Cascade of Thiocyanation and Nucleophilic Cyanide–CF₃ Substitution

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$$ Alk{-}X \xrightarrow[\text{Cs}_2\text{CO}_3]{\text{NaSCN} \quad \text{TMSCF}_3} Alk{-}S{-}CF_3 $$

X = Cl, Br, I, OMs

– simple and environmentally benign system
– one-pot protocol
– 22 examples in high yields

Abstract A straightforward synthesis of alkyl trifluoromethyl thioethers was developed that starts from widely available alkyl halides or mesylates and the inexpensive reagents sodium thiocyanate and trimethyl(trifluoromethyl)silane. The alkyl electrophiles are converted in situ into the corresponding thiocyanates, which react with the nucleophilic Ruppert–Prakash reagent to give the corresponding trifluoromethyl thioethers via a Langlois-type CN–CF₃ substitution. This process enables the efficient introduction of the pharmaceutically meaningful trifluoromethylthio groups into functionalized molecules without the need of metal catalysts or expensive preformed trifluoromethylthiolating agents.

Key words trifluoromethylthiolation, alkyl halides, fluorine, nucleophiles, sulfur

Figure 1 Biologically active alkyl trifluoromethyl thioethers

Around 40% of marketed agrochemicals and 25% of pharmaceuticals contain fluorine atoms. Fluorine-containing residues are central functionalities in bioactive compounds, because they induce higher lipophilicity and metabolic stability.[1] The unique properties of fluorinated groups have led to the development of a range of sustainable concepts for the late-stage introduction of trifluoromethyl groups.[2] In recent years, the focus has shifted towards the corresponding trifluoromethylthio groups,[3] since these enhance the lipophilicity of druglike molecules even more than their trifluoromethylated analog (Hansch constant 1.44 for SCF₃ vs. 0.88 for CF₃).[4] This property improves the bioavailability of drug molecules due to their more effective transport through lipid membranes.[3d,e]

The trifluoromethylthio moiety is a key functionality for example in the antibiotic cefazaflur, in a trifluoromethylthiolated methionine analogue with antimalarial properties, and in a ribose derivative with antipneumnonia activity (Figure 1).[3b,5]
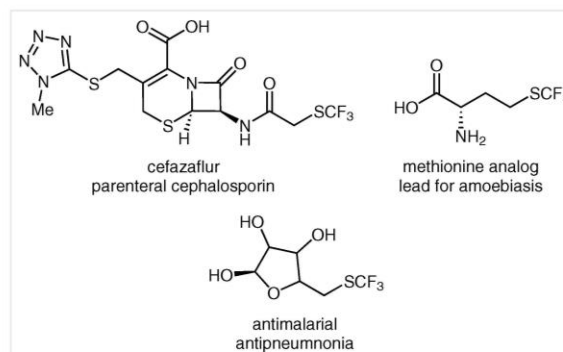
Traditional strategies for the synthesis of trifluoromethylthio groups include halogen–fluorine exchange reactions of trihalomethyl thioethers,[6] as well as the trifluoromethylation of thiols, disulfides, and related compounds.[7] However, these methods are limited by substrate availability. Recently, various methods for the introduction of trifluoromethylthio groups into aromatic substrates via electrophilic,[8] nucleophilic,[9] radical,[10] or oxidative methods have been reported.[11] The synthesis of alkyl trifluoromethyl thioethers is less studied.[3e,12] Contemporary syntheses start from diazo compounds,[13] alcohols,[14] halides,[15] or carboxylic acids[16] or proceed via C–H activation following methods by Tang, Chen, Rüping, or Qing.[17] However, each of these methods calls for preformation of SCF₃ reagents.[18]

Efficient methods for the late-stage introduction of trifluoromethylthio groups into functionalized molecules based on widely available leaving groups and inexpensive, easy-to-use reagents are still highly sought-after.

We envisioned that the nucleophilic displacement of the CN group in thiocyanates by CF$_3$ using TMSCF$_3$, as originally reported by Langlois et al., might be the key towards such a process.[7e] If this transformation could be combined in one pot with a straightforward synthesis of the alkyl thiocyanates from alkyl halides or pseudohalides, the overall protocol would allow accessing valuable trifluoromethyl thioethers without the need for preformed trifluoromethylthiolation reagents (Scheme 1).

Scheme 1 Strategies to access alkyl trifluoromethyl thioethers
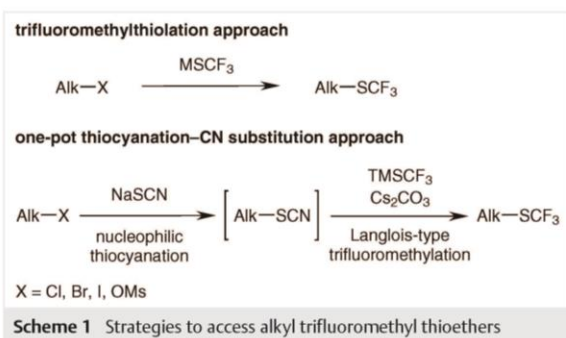
In the context of our work on di- and trifluoromethylation methods,[19] we discovered that for the synthesis of aryl di- and trifluoromethyl thioethers the envisioned approach is viable starting from diazonium salts.[20] However, since the nucleophilic substitution of alkyl halides with thiocyanate salts requires substantially higher temperatures than do Sandmeyer processes, it was doubtful whether the sensitive Ruppert–Prakash reagent would tolerate this initial reaction step.

In order to probe the viability of our projected approach, we started with benzyl bromide (**1**) as a model substrate and investigated its nucleophilic substitution with sodium thiocyanate, with addition of the trifluoromethylating agent TMSCF$_3$ following complete formation of the alkyl thiocyanate (Table 1). In order to combine both steps to a true one-pot procedure, it was crucial to identify solvents and conditions that would be equally effective for both steps.

The nucleophilic substitution of bromide with sodium thiocyanate was found to proceed best in polar aprotic solvents such as DMF. GC analysis revealed that full conversion was reached within one hour at 60 °C. However, when adding TMSCF$_3$ and TBAF, the reagent combination described by Langlois, the trifluoromethylation proceeded rather sluggishly and gave an unsatisfactory 20% yield (Table 1, entry 1). In THF, reported to be the optimal solvent for trifluoromethylations,[7e] the thiocyanation was slower, and the yield of the trifluoromethylation remained low (Table 1, entry 2). This suggests that the sodium bromide released in the thiocyanation step may interfere with the trifluoromethylation step.

Systematic studies revealed that the choice of the base had a profound effect on the reaction outcome (Table 1, entries 3–5). Using Cs$_2$CO$_3$, near-quantitative yields were achieved in the stepwise procedure (Table 1, entry 5). Acetonitrile was found to be the optimal solvent with regard to yield and reaction rate, but DMF and THF can be used as well (Table 1, entry 6). The amounts of base and trifluoromethylation reagent could be reduced to 1.0 equivalent of Cs$_2$CO$_3$ and 1.2 equivalents of TMSCF$_3$, respectively, without affecting the reaction outcome (Table 1, entries 7 and 8).

Table 1 Optimization of the Reaction Conditions[a]

Entry	Base	Solvent	Yield (%)
1	TBAF	DMF	20
2	TBAF	THF	15
3	CsF	DMF	76
4	KF	DMF	80
5	Cs$_2$CO$_3$	DMF	99
6	Cs$_2$CO$_3$	MeCN	99
7[b]	Cs$_2$CO$_3$	MeCN	99
8[b,c]	Cs$_2$CO$_3$	MeCN	99
9[b,d]	Cs$_2$CO$_3$	MeCN	99
10[b,e]	Cs$_2$CO$_3$	MeCN	78
11[b,d,f]	Cs$_2$CO$_3$	MeCN	41

[a] Reaction conditions: benzyl bromide (0.5 mmol) and NaSCN (0.6 mmol) in solvent (1 mL), 60 °C, 1 h, then addition of base (1.0 mmol) and TMSCF$_3$ (1.0 mmol), 15 h, r.t. Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard.
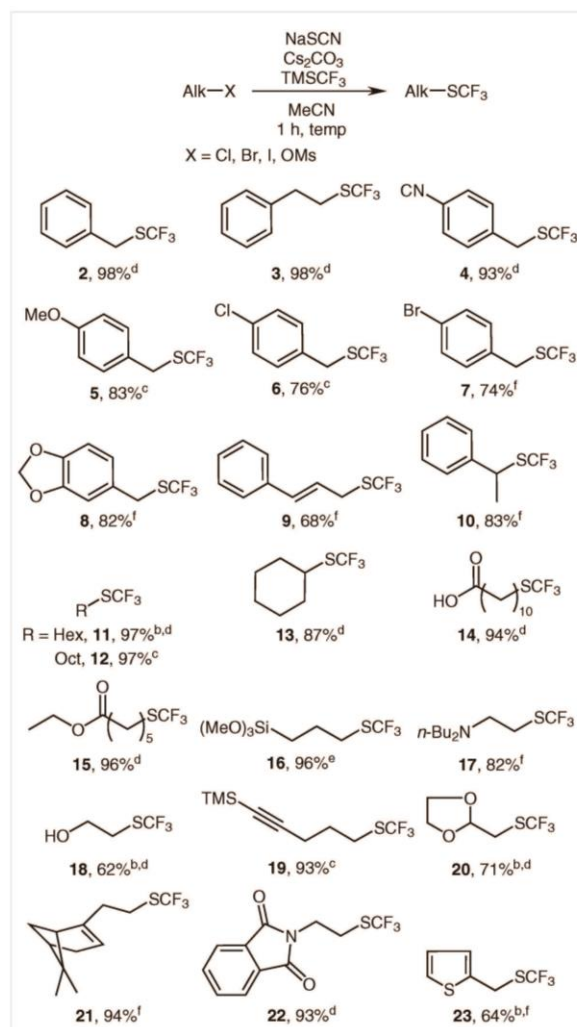[b] 0.5 mmol Cs$_2$CO$_3$.
[c] 0.6 mmol TMSCF$_3$.
[d] All reagents were added at the same time, and the mixture was stirred for 1 h at 60 °C.
[e] 0.25 mmol Cs$_2$CO$_3$.
[f] 0.1 mmol Cs$_2$CO$_3$.

We next probed whether under the optimal conditions the reagents for both steps could directly be combined. To our delight, the desired trifluoromethyl thioether **2** formed in quantitative yield when heating a mixture of **1** with 1.2 equivalents of sodium thiocyanate, 1.0 equivalent of Cs$_2$CO$_3$, and 1.2 equivalents of TMSCF$_3$ in acetonitrile to 60 °C for one hour (Table 1, entry 9). The reaction also proceeds with catalytic amounts of Cs$_2$CO$_3$ (Table 1, entries 10 and 11), since the released cyanate anions are able to desilylate the Ruppert–Prakash reagent as proposed by Langlois.[7e] However, full conversion was only obtained with equimolar amounts.

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Having thus found a convenient and highly efficient trifluoromethylthiolation protocol, we went on to investigate its scope. Diversely substituted alkyl trifluoromethyl thioethers were synthesized in high yields from the corresponding alkyl halides (Scheme 2).[22]

Scheme 2 Trifluoromethylthiolation of alkyl halides and mesylates.
[a] *Reagents and conditions*: alkyl electrophile (1.0 mmol), NaSCN (1.2 mmol), Cs$_2$CO$_3$ (1 mmol), TMSCF$_3$ (1.2 mmol) in MeCN (2 mL), 60–110 °C, 1 h, isolated yields (see Supporting Information). [b] Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard. [c] Starting from alkyl chloride. [d] Starting from alkyl bromide. [e] Starting from alkyl iodide. [f] Starting from alkyl mesylate.

Alkyl mesylates, which are conveniently accessible from ubiquitous alcohols, are also suitable electrophilic precursors. The reaction is applicable to alkyl, benzyl and allyl electrophiles, and common functional groups, such as cyano, ether, carboxylic acid, ester, hydroxy, acetal, and amino

are well-tolerated. In contrast to most metal-mediated trifluoromethylthiolations, chloro- and bromoarene moieties remain intact in this transformation, which opens up opportunities for further derivatization. Terminal alkynes are trimethylsilylated under the reaction conditions, but the TMS group can easily be cleaved by basic workup (**19**).[21]

All products were obtained in reasonable purity after aqueous workup and can be further purified by column chromatography. Compound **2** was isolated in 91% yield on a gram scale, demonstrating the scalability of the process.

In conclusion, a metal-free trifluoromethylthiolation of alkyl electrophiles via a cascade of thiocyanation and nucleophilic CN–CF$_3$ substitution has been developed. The key advantages of this approach, in which the sulfur and the CF$_3$ moiety originate from different sources, are the mild reaction conditions and the use of inexpensive, ready available reagents. As a result, this is suitable both for large-scale applications and late-stage trifluoromethylthiolations in drug discovery.

Acknowledgment

Supporting Information

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(22) **General Procedure for the Trifluoromethylthiolation of Alkyl Thiocyanates Generated in situ**
An oven-dried 20 mL crimp-cap vessel with Teflon-coated stirrer bar was charged with Cs_2CO_3 (652 mg, 1.00 mmol) and NaSCN (100 mg, 1.20 mmol). MeCN (2 mL), $TMSCF_3$ (537 mg, 0.60 mL, 1.20 mmol), and the alkyl halide or mesylate (1.00 mmol) were added via syringe. The suspension was heated to the following temperatures, depending on the leaving group: primary alkyl bromides and iodides 60 °C; secondary alkyl bromides and primary chlorides 90 °C, and alkyl mesylates 110 °C. Stirring was continued until completion of the reaction was determined by GC and GC–MS. The resulting mixture was allowed to cool to r.t., diluted with Et_2O (20 mL), washed with H_2O (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure (700 mbar, 40 °C). Most compounds were obtained in pure form, for products with aromatic substituents the residue was purified by column chromatography (SiOH, Et_2O–pentane gradient).

[(Trifluoromethyl)thio]methylbenzene [CAS No.: 351-60-0] (2)
^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.36 (m, 5 H), 4.15 (s, 2 H) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –41.47 ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.0, 130.6 [q, ^1J(C,F) = 307.0 Hz], 128.9 (2 C), 128.8 (2 C), 128.0, 34.2 [q, ^3J(C,F) = 2.7 Hz] ppm. IR (neat): ν = 2922, 2853, 1463, 1378 cm⁻¹. MS (ion trap, EI, 70 eV): m/z (%) = 192 (23) [M⁺], 91 (100), 69 (13). HRMS (EI-TOF): m/z calcd for $C_8H_7F_3S$: 192.0221; found: 192.0224.

11-[(Trifluoromethyl)thio]undecanoic Acid (14)
^1H NMR (400 MHz, $CDCl_3$): δ = 2.88 (t, ^3J = 7.5 Hz, 2 H), 2.35 (t, ^3J = 7.5 Hz, 2 H), 1.72–1.60 (m, 4 H), 1.44–1.29 ppm (m, 12 H) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –41.3 ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.5, 131.2 [q, ^1J(C,F) = 305.2 Hz], 34.1, 29.83 [q, ^3J(C,F) = 2.4 Hz], 29.34, 29.27, 29.25, 29.1, 29.0, 28.9, 28.5, 24.6 ppm. IR (neat): ν = 2927, 2856, 1709, 1464, 1414, 1113, 938, 756 cm⁻¹. MS (ion trap, EI, 70 eV): m/z (%) = 287 (12) [M⁺ + H], 199 (73), 129 (44), 117 (91), 101 (9), 69 (24). HRMS (EI-TOF): m/z calcd for: $C_{12}H_{21}F_3O_2S$: 286.1214; found: 286.1230.

3-[(Trifluoromethyl)thio]propyltrimethoxysilane (16)
^1H NMR (400 MHz, $CDCl_3$): δ = 3.55 (s, 9 H), 2.88 (t, ^3J = 7.3 Hz, 2 H), 1.79 (qi, ^3J = 7.8 Hz, 2 H), 0.73 (t, ^3J = 8.3 Hz, 2 H) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –41.2 ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 131.2 [q, ^1J(C,F) = 305.9 Hz], 50.5 (3 H), 32.5 [q, ^3J(C,F) = 1.5 Hz], 23.2, 8.3 ppm. IR (neat): ν = 2945, 2843, 1759, 1077, 809, 754 cm⁻¹. MS (ion trap, EI, 70 eV): m/z (%) = 264 (1)

[M⁺], 233 (12), 195 (63), 121 (13), 93 (100). HRMS (EI-TOF): m/z calcd for $C_7H_{15}O_3SiF_3S$: 264.0463; found: 264.0468.

N-{2-[(Trifluoromethyl)thio]ethyl}-N,N-dibutylamine (17)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.30 (t, ^3J = 7.1 Hz, 2 H), 2.74 (t, ^3J = 7.0 Hz, 2 H), 2.42 (t, ^3J = 7.2 Hz, 4 H), 1.43–1.37 (m, 4 H), 1.34–1.28 (m, 4 H), 0.92 (t, ^3J = 7.3 Hz, 6 H) ppm. ^{19}F NMR (375 MHz, CDCl$_3$): δ = –41.4 ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 131.6 [q, ^1J(C,F) = 306.8 Hz], 53.6 (2 C), 52.8, 29.3 (2 C), 28.8, 20.5 (2 C), 14.0 (2 C) ppm. IR (neat): ν = 2959, 2934, 2874, 1739, 1460, 1366, 1217, 1119, 748 cm⁻¹. MS (ion trap, EI, 70 eV): m/z (%) = 257 (3), 214 (44), 172 (66), 142 (100), 58 (41). HRMS (EI-TOF): m/z calcd for $C_{11}H_{22}NF_3S$: 257.1425; found: 257.1420.

1-Trimethylsilyl-5-(trifluoromethyl)thiopent-1-yne (19)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.01 (t, ^3J = 7.1 Hz, 2 H), 2.38 (t, ^3J = 6.8 Hz, 2 H), 1.90 (qi, ^3J = 7.0 Hz, 2 H), 0.15 (s, 9 H) ppm. ^{19}F NMR (375 MHz, CDCl$_3$): δ = –41.1 ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 131.0 [q, ^1J(C,F) = 306.1 Hz], 104.8, 86.2, 28.7 [q, ^3J(C,F) = 1.8 Hz], 28.3, 18.6, 0.0 (3 C) ppm. IR (neat): ν = 2960, 2176, 1685, 1432, 1250, 1107, 838, 758, 699 cm⁻¹. MS (ion trap, EI, 70 eV): m/z (%) = 240 (11) [M⁺], 171 (97), 129 (100). HRMS (EI-TOF): m/z calcd for $C_9H_{15}SiF_3S$: 240.0616; found: 240.0614.

(1R,5S)-[(Trifluoromethyl)thio]-2-{6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl}ethylene (21)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.31 (m, 1 H), 2.93–2.89 (m, 2 H), 2.41–2.38 (m, 1 H), 2.37–2.32 (m, 2 H), 2.26–2.23 (m, 2 H), 2.11–2.09 (m, 1 H), 2.02–1.99 (m, 1 H), 1.29 (s, 3 H), 1.16 (d, ^3J = 8.5 Hz, 1 H), 0.84 (s, 3 H) ppm. ^{19}F NMR (375 MHz, CDCl$_3$): δ = –41.2 ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 145.2, 132.2 [q, ^1J(C,F) = 306.1 Hz], 118.8, 40.6, 38.0, 36.6, 31.6, 31.2, 27.8 [q, ^3J(C,F) = 1.8 Hz], 26.2, 21.1 ppm. IR (neat): ν = 2917, 1434, 1366, 1104, 887, 794, 756 cm⁻¹. MS (ion trap, EI, 70 eV): m/z (%) = 250 (14) [M⁺], 105 (100), 121 (10). HRMS (EI-TOF): m/z calcd for $C_{12}H_{17}F_3S$: 250.1003; found: 250.0987; $[α]_D^{20}$ –25.9 (c 1.00, Et$_2$O).

Aufgrund der großen Aufmerksamkeit, die der Artikel zur metallfreien Trifluormethylthiolierung von Alkylelektrophilen erhalten hatte, wurden wir von den Editoren von *Synform* dazu eingeladen, einen Highlight-Artikel über unsere Arbeit zu schreiben. Darin sollten wir detailliertere Hintergrundinformationen geben wie das Projekt entwickelt worden war, wer dazu beigetragen hatte und wie unser Team zusammengearbeitet hatte. Außerdem sollten wir kurz den Werdegang der einzelnen Autoren vorstellen.

Beiträge der Autoren:

Den Highlight-Artikel verfasste ich und überarbeitete ihn zusammen mit Herrn Prof. Dr. L. J. Gooßen, wonach er von den Editoren des Journals in ein Interviewformat angepasst wurde.

Der Highlight-Artikel zu diesem Projekt wurde in *Synform* veröffentlicht, die Publikation für diese Arbeit angepasst und mit Erlaubnis des Verlages beigefügt: "Dieser Beitrag ist mit Zustimmung des Rechteinhabers aufgrund einer (DFG-geförderten) Allianz- beziehungsweise Nationallizenz frei zugänglich: *Synform*, **2015**, *09*, A122-A124."

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Metal-Free Trifluoromethylthiolation of Alkyl Electrophiles via a Cascade of Thiocyanation and Nucleophilic Cyanide-CF$_3$ Substitution

Fluorine atoms can have profound effects on bioactive molecules. Trifluoromethylthio groups can impart many desirable properties, such as higher metabolic stability and increased lipophilicity. Professor Lukas Goßen at the Kaiserslautern University of Technology (Germany) has been fascinated by these effects since his time at Bayer central research. He commented: "At Bayer, a dedicated team of experts including my later wife provided customized fluorinated building blocks to other synthetic chemists to give them a head start against competitors. The methods they routinely employed required special equipment and substantial experience. In recent years," he continued, "the chemical community has become aware of the importance of fluorinated compounds, and the development of convenient trifluoromethylation reactions that can be employed by synthetic organic chemists without special training is currently one of the most topical fields in method development."

Professor Goßen said: "Our paradigm has always been to base new methods on simple, inexpensive and sustainable raw materials. We are less interested in methods whose use will remain restricted to drug discovery where the cost of reagents does not matter, preferring to provide scalable protocols for use throughout academia and industry. Thus, we deliberately steered away from high-tech catalysts and elaborate reagents and, instead, based our early fluoroalkylation methods on basic Sandmeyer chemistry."

In recent years, the focus of medicinal and agrochemistry has expanded to include fluoroalkylthio groups whose properties often surpass those of the corresponding fluoroalkyl moieties. "Contemporary reports in top journals underline that the introduction of trifluoromethylthio groups is viewed as an unsolved problem that justifies the use of even the most elaborate reagents," said Professor Goßen, adding: "This attracted our interest, and we set out to search for a straightforward synthetic approach for the introduction of fluoroalkylthio groups into functionalized molecules."

When analyzing existing synthetic approaches, Professor Goßen and co-workers came to the conclusion that their complexity and cost arises from the underlying strategy that consists of transferring the SCF$_3$ group as a whole from a preformed reagent. "However, Langlois et al. had demonstrated already in 1997 that SCF$_3$ groups can be generated from thio-

cyanates via nucleophilic displacement of CN by CF$_3$. We immediately realized that this somewhat underappreciated concept might open up straightforward synthetic entries to fluoroalkylthiolated molecules that would not require preformed SCF$_3$ reagents but could be based on the comparably inexpensive Ruppert–Prakash reagent," remarked Professor Goßen.

He continued: "Our reasoning was that if it was possible to introduce thiocyanate groups in the presence of nucleophilic fluoroalkylating reagents, the resulting organothiocyanates could be directly converted into the desired fluoroalkylthio groups." According to Professor Goßen, the key challenge of this approach was to direct the reactivity of the fluoroalkylating reagent exclusively towards the thiocyanate moiety and avoid side reactions between the reagents present in the mixture. With a small team composed of the PhD students Bilguun Bayarmagnai, Matthias Grünberg and Christian Matheis and the postdoctoral researchers Dr. Grégory Danoun and Dr. Kévin Jouvin, they set out to probe the viability of this approach. After many setbacks, the Kaiserslautern based research team finally managed to combine Sandmeyer thiocyanations with Langlois-type trifluoromethylations and novel difluoromethylations and, thus, developed efficient synthetic entries to aryl fluoroalkyl thioethers from readily available arenediazonium salts and inexpensive TMS-fluoroalkanes (*Angew. Chem. Int. Ed.* **2015**, *54*, 5753, *Chem. Sci.* **2014**, *5*, 1312).

Professor Goßen said: "In parallel to this work, we probed whether the synthesis of alkyl thiocyanates via nucleophilic substitution of alkyl halides with NaSCN could also be combined with a trifluoromethylation with TMSCF$_3$. Christian systematically varied the reaction conditions of the thiocyanation and the Langlois trifluoromethylation to identify conditions under which both steps would work well and all reagents would remain stable. For many weeks, he was frustrated by the incompatibility of the two steps, which resulted in unsatisfactory yields. After intricate development efforts, he discovered that with acetonitrile as the solvent and Cs$_2$CO$_3$ as the base, both steps proceeded in high yields when performed individually. Further optimization was required until they could be combined to a one-pot process in which all reagents are added directly at the beginning of the reaction."

The final protocol is easy to use and widely applicable. It allows access to alkyl trifluoromethyl thioethers from widely

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available alkyl halides or mesylates simply by stirring them with sodium thiocyanate, TMS-CF₃ and Cs₂CO₃ in acetonitrile at 60–110°C without the need for transition-metal catalysts.

Professor Goßen revealed that having finally identified an efficient protocol, Christian teamed up with Dr. Minyan Wang and Thilo Krause to investigate its scope. The chromatographic separation of the volatile products from remaining alkyl halide starting materials turned out to be quite tricky. However, they soon found out that the best strategy to overcome their separation problems was to ensure near-quantitative conversions by carefully monitoring the reaction progress. Within a few long working days, they synthesized, isolated

and characterized 22 alkyl trifluoromethyl thioethers bearing various functionalities (Scheme 1).

"The above examples underline that the metal-free cascade of nucleophilic thiocyanation and nucleophilic CN–CF₃ substitution is a powerful tool for the synthesis of alkyl trifluoromethyl thioethers from broadly available alkyl electrophiles. Its key advantages are its simple operation, broad applicability, and tolerance of various functional groups, despite using one of the cheapest sources of trifluoromethyl groups available," said Professor Goßen. He concluded: "We are pleased that our recent fluoroalkylations and fluoroalkylthiolations have been so well received by the chemical com-
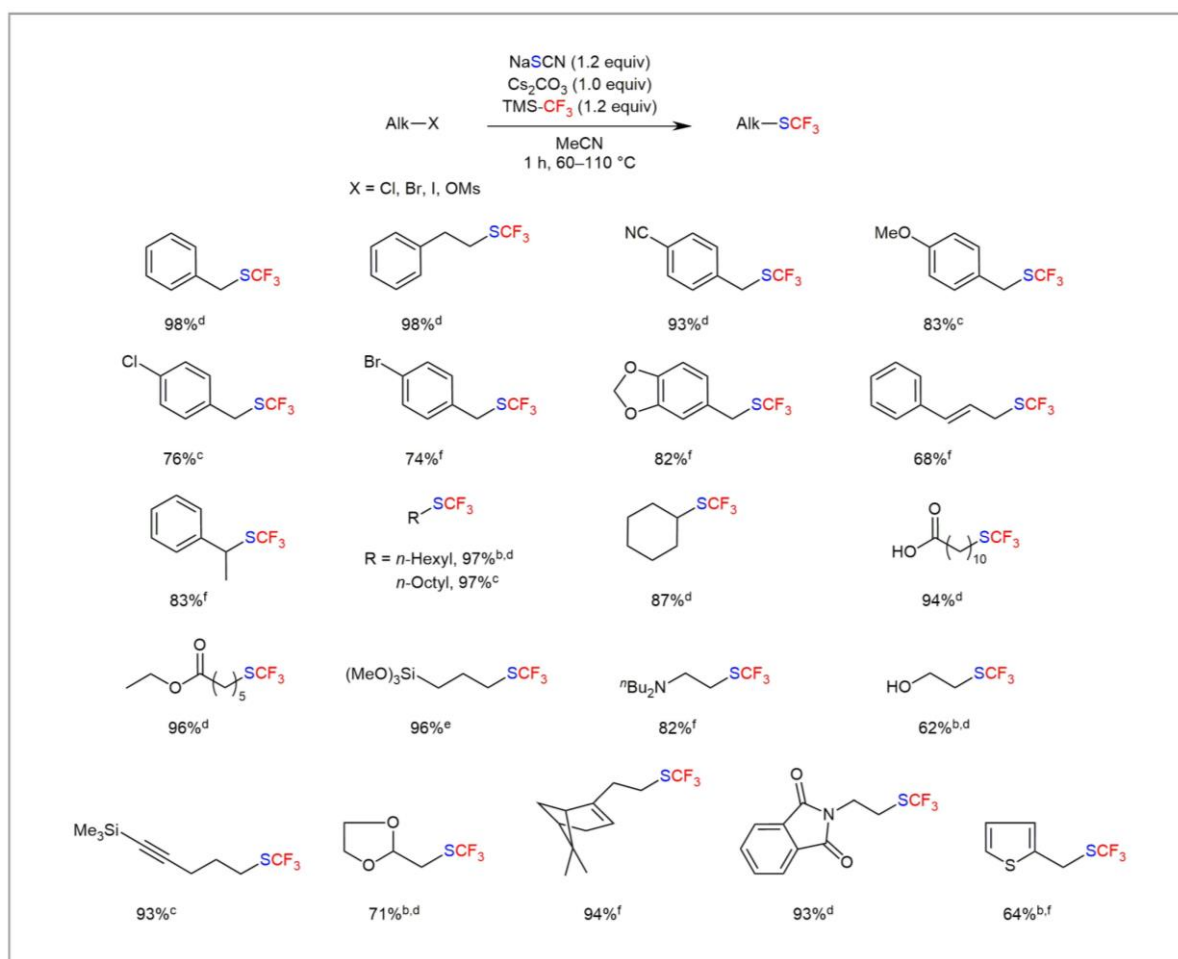
Scheme 1 Trifluoromethylthiolation of alkyl halides and mesylates.[a]
[a] Isolated yields. [b] Yields were determined by 19F NMR using trifluoroethanol as an internal standard. [c] Starting from alkyl chloride. [d] Starting from alkyl bromide. [e] Starting from alkyl iodide. [f] Starting from alkyl mesylate.

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munity, and our 'fluorine guys' cannot wait to apply the experience gained during this work to address some of the many remaining challenges in fluorine chemistry."

Matthes Tande

About the authors

From left: Dr. M. Wang, T. Krause, Prof. Dr. L. Gooßen with his youngest group member Matilda, C. Matheis

Christian Matheis studied Chemistry in Kaiserslautern (Germany) where he received his diploma in 2013 working on new strategies for the formation of C–O bonds. His results were published in Angewandte Chemie as a 'hot paper' and his thesis was awarded within the Springer BestMasters program. After an industrial internship at BASF (Germany) in the lead optimization of agricultural products, he started his Ph.D. work under the supervision of Prof. Gooßen on the development of straightforward methods for the synthesis of fluorinated compounds. Within his first year, he was able to make great contributions to this research area and published several methods for the introduction of fluoroalkyl(thiol)ated groups.

Minyan Wang studied Chemistry at Huazhong University of Science and Technology (P. R. of China). After having received her Bachelor's degree in 2009, she continued her Ph.D. at Zhejiang University (P. R. of China) under the supervision of Professor Shengming Ma, where she worked on the highly selective electrophilic and nucleophilic addition of functionalized allenes. Both her Bachelor and Ph.D. degrees were graded as

excellent. After completing her thesis in 2014, she moved to the TU Kaiserslautern (Germany) for a postdoctoral stay with Professor Gooßen, where she is presently working on the fluorination of organic compounds.

Thilo Krause studied Chemistry at the TU Kaiserslautern (Germany) where he received his diploma in 2013. He is pursuing Ph.D. research under the supervision of Professor Gooßen on the sustainable synthesis of amides from carboxylic acids and amines via in situ generated active esters. In order to gain insights into chemistry in industry, he interrupted his Ph.D. work in April 2014 for a three-month internship in the department of Global Research Agricultural Products at BASF, Ludwigshafen (Germany).

Lukas Gooßen studied chemistry at the Universities of Bielefeld (Germany) and Michigan (USA) and carried out graduate studies at UC Berkeley (USA) with Professor K. Peter C. Vollhardt. He was awarded a Ph.D. in 1997 for his research on N-heterocyclic carbene complexes supervised by Professor Wolfgang A. Herrmann, TU Munich (Germany), and pursued postdoctoral research with Professor K. Barry Sharpless, Scripps Research Institute (USA). He began his professional career as an industrial chemist at Bayer AG (Germany) in 1999, but moved back to academia to the group of Professor Manfred T. Reetz, MPI for Coal Research for his habilitation, and further to RWTH Aachen (Germany). He has been a professor at the TU Kaiserslautern (Germany) since 2005. His research is devoted to the development of novel concepts for C–C and C–heteroatom bond formation. He has authored over 120 publications and 25 patents. Recent awards include the Jochen Block Award of the DECHEMA, the Carl Duisberg Award of the GDCh, the Novartis Young Investigator Award, and the AstraZeneca Award in Organic Chemistry (2008).

5.3.4. *Elektrophile C–H-Trifluormethylthiolierung und Difluormethylthiolierung von Arenen*

In diesem Teilprojekt sollte die zuvor entwickelte Thiocyanierung/Trifluormethylierungskaskade auch für elektrophile C–H-Trifluormethylthiolierungen elektronenreicher Aromate ermöglicht werden (**Schema 38**).
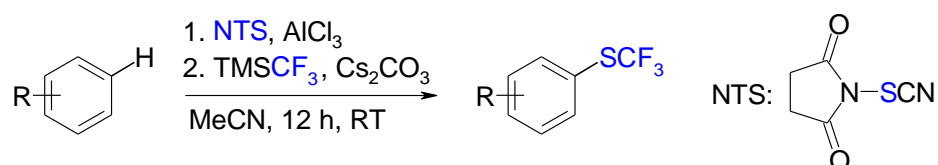
Schema 38. Elektrophile C–H-Trifluormethylthiolierung von Arenen.

Anstelle bekannter Prozesse mit aufwendig herzustellenden, teuren elektrophilen SCF_3-Quellen, eignet sich dieses Reaktionskonzept hervorragend zur nachhaltigeren C–H-Trifluormethylthiolierung von Arenen. Da für die postulierte praktische Kaskade in den vorangehenden Protokollen bereits effiziente Reaktionsbedingungen für die Trifluormethylierung etabliert wurden, sollte zunächst eine günstige elektrophile SCN-Quelle identifiziert werden. Dabei wurde *N*-Thiocyanatosuccinimid (NTS) als optimales Reagenz gewählt, da es einfach aus NaSCN und *N*-Bromsuccinimid zugänglich ist. Außerdem besitzt es die gleiche Struktur wie einige gängige elektrophile SCF_3-Quellen und könnte sich deshalb besonders gut eignen. Im Zuge der ausgiebigen Reaktionsoptimierungen entdeckten wir, dass NTS mit nur 1 mol% $AuCl_3$ oder $AlCl_3$ bei Raumtemperatur die C–H-Thiocyanierung von Anisol tatsächlich effektiv vermittelt. Die Regioselektivität dieser neuen Reaktion ist außergewöhnlich. Während eine analoge Friedel-Crafts Chlorierung von Anisol üblicherweise eine Mischung von *para-* und *ortho*-substituierten Produkten im Verhältnis von 79:21 liefert,[227] beobachteten wir ausschließlich *para*-thiocyaniertes Anisol. Durch die Kombination der zwei Teilreaktionen im gleichen Reaktionsgefäß reagierten die gebildeten Arylthiocyanate in Gegenwart von $TMSCF_3$ und Cs_2CO_3 unmittelbar zu den korrespondierenden Trifluormethylthioethern. Nahezu quantitative Ausbeuten der Reaktionskaskade konnten schließlich mit wahlweise 1 mol% $AuCl_3$ oder 10 mol% des wesentlich günstigeren $AlCl_3$ erreicht werden. Bevor die Anwendungsbreite umfangreichend untersucht wurde, ermittelten wir zunächst bis zu welcher Reaktivität gegenüber

Elektrophilen, beziehungsweise zu welcher Nukleophilie der Arene die entwickelte C–H-Trifluormethylthiolierung möglich ist. Mayr entwickelte dafür ein Verfahren, um den nukleophilen Charakter N von Arenen zu bestimmen und ordnete sie demensprechend ein.[228] Wir untersuchten eine Reihe von Verbindungen, die eine niedrigere Nukleophilie als unser Substrat zur Optimierung der Reaktionsbedingungen aufweist (Anisol mit $N = -1.6$) (**Abbildung 15**). Wir beobachteten schon bei Benzothiophen ($N = -2.5$) eine geringere Produktbildung und auch die Ausbeuten mit Fluoren und Benzofuran (mit je $N = -2.9$) sanken drastisch. Einfache methylsubstituierte Arene, *o*-Xylen ($N = -3.7$) und Toluol ($N = -4.2$), reagierten nicht. Demnach eignet sich die entwickelte elektrophile C–H-Trifluormethylthiolierung für Arene bis zu einer Nukleophilie von $N = -2.5$.
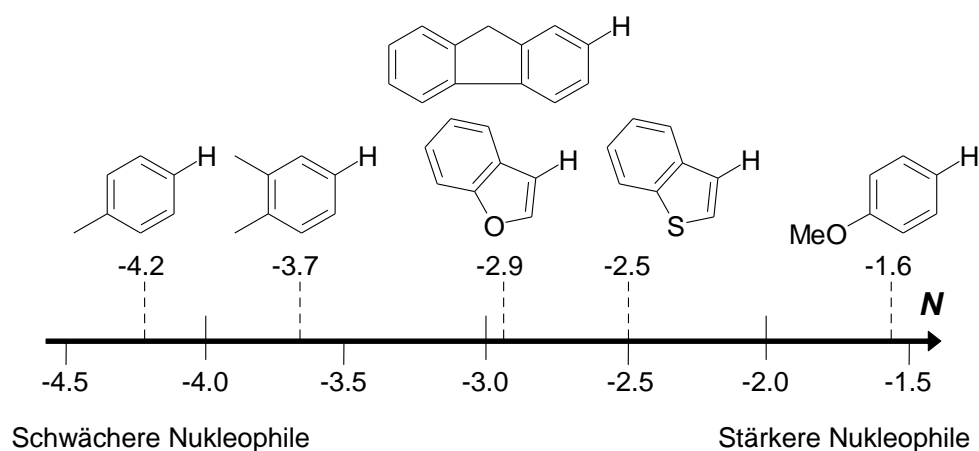
Abbildung 15. Nukleophiler Charakter getesteter Arene.

Mit diesen Ergebnissen konnte nun die vollständige Anwendungsbreite anhand einer großen Zahl divers hochfunktionalisierter Verbindungen mit einem nukleophilen Charakter von $N > -2.5$ demonstriert werden. Alle Reaktionen lieferten bemerkenswerterweise nur ein einziges Regioisomer, was auf die starke Elektrophilie von SCN-Kationen sowie auf sterische Effekte zurückzuführen ist. Außerdem wurden ausschließlich einfach thiocyanierte Produkte beobachtet. Sobald ein Thiocyanat in ein Substrat eingeführt wird, reduziert sich die Nukleophilie drastisch und verhindert damit Mehrfachfunktionalisierungen.

Das Reaktionskonzept wurde außerdem zu einer neuen analogen Methode zur effizienten elektrophilen C–H-Difluormethylthiolierung von Arenen weiterentwickelt (**Schema 39**).
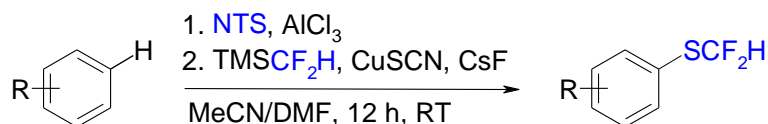
Schema 39. Elektrophile C–H-Difluormethylthiolierung von Arenen.

Besonders wichtig war es, analog zu den vorherigen Erfahrungen aus der Sandmeyer-Difluormethylthiolierung (Kapitel 5.5.1),[229] intermediäre CF$_2$H-Spezies für den CN-Austausch durch die Zugabe von CuSCN und mit CsF als Aktivator sowie DMF als Lösungsmittel zu stabilisieren. Da DMF die Thiocyanierung komplett unterdrückt, wurde zwischen den einzelnen Teilreaktionen ein Lösungsmittelaustausch im Hochvakuum durchgeführt.

Beiträge der Autoren:

Herr Dr. K. Jouvin entwickelte die Reaktion und optimierte zusammen mit mir das Katalysatorsystem. Die Anwendungsbreite und den Reaktionsmechanismus untersuchten wir gleichberechtigt. Herr Dr. K. Jouvin und ich verfassten das Manuskript und ich überarbeitete es zusammen mit Herrn Prof. Dr. L. J. Gooßen. Herr Dr. K. Jouvin und ich interpretierten die analytischen Daten und erstellten gleichberechtigt die „Supporting Information".

Die Resultate dieses Projektes wurden in *Chemistry – A European Journal* als „hot paper" veröffentlicht, die Publikation für diese Arbeit angepasst und mit Erlaubnis des Verlages beigefügt: "Reprinted (adapted) with permission from K. Jouvin, C. Matheis, L. J. Goossen, *Chem. Eur. J.* **2015**, *21*, 14324-14327: „*Synthesis of Aryl Tri- and Difluoromethyl Thioethers via a C–H-Thiocyanation/Fluoroalkylation Cascade*".[230] Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim."

▌ **Synthetic Methods** │*Hot Paper*│

Synthesis of Aryl Tri- and Difluoromethyl Thioethers via a C–H-Thiocyanation/Fluoroalkylation Cascade

Kévin Jouvin, Christian Matheis, and Lukas J. Goossen*[a]

Abstract: An $AlCl_3$-catalyzed C–H thiocyanation was discovered and combined with a Langlois-type trifluoromethylation to afford aryl trifluoromethyl thioethers directly from arenes, N-thiocyanatosuccinimide (NTS) and Ruppert–Prakash reagent. An analogous combination with a copper-mediated difluoromethylation gives access to aryl difluoromethyl thioethers. Both processes proceed with exceptional regioselectivity for the most electron-rich, sterically least hindered position of the arene. The sulfur and fluoroalkyl groups originate from different sources, so that the use of expensive, preformed fluoroalkylthiolation reagents is avoided.

Figure 1. Biologically active trifluoromethyl thioethers.

Presently, 30–40% of marketed agrochemicals and 25% of pharmaceuticals contain fluorine atoms.[1] As a result, the introduction of fluorine residues into organic molecules is a highly topical area. In drug discovery, so called "fluorine scans", that is, systematic derivatizations of lead structures by replacing alkyl, hydroxy-, amino-, or thio-substituents with their bioisosteric fluorinated groups, for example, CF_3,[2] CF_2H,[3] SCF_3[4] or OCF_3,[5] are routinely carried out. This has created a growing demand for technologies for the late-stage introduction of such moieties into functionalized molecules. Powerful methods for the introduction of CF_3 groups have emerged within only a few years.[6]

Lately the focus has somewhat shifted towards SCF_3 groups,[7] which induce an even higher lipophilicity and membrane permeability into bioactive compounds (Hansch constants 1.44 for SCF_3 vs. 0.88 for CF_3).[8] Several bioactive compounds such as Tiflorex, Toltrazuril and a Losartan analogue contain SCF_3 groups as a key functionality (Figure 1).

Traditional approaches for the introduction of SCF_3 group are based on halogen exchange from aryl trichloromethyl thioethers using HF or SbF_3, the so-called Swarts reaction,[9] which is inexpensive but has a rather low functional group tolerance. Modern trifluoromethylthiolation reactions suitable for late-stage derivatizations are based on preformed nucleophilic, electrophilic or radical SCF_3 reagents in combination with tran-

sition metal catalysts, for example, Ni,[10] Cu[11] or Pd complexes.[12] The seminal report by Shen et al. on the trifluoromethylthiolation of electron-rich arenes with N-trifluoromethylthiosaccharin[13] has triggered substantial efforts to synthesize aryl trifluoromethyl thioethers by electrophilic C–H functionalization.[14] However, the drawback of this approach is the high cost of the reagents, which are synthesized from expensive Ag^I fluoride or toxic and corrosive CF_3SCl gas (Figure 2).[11a,e, 13, 15]
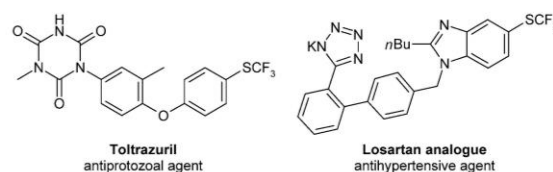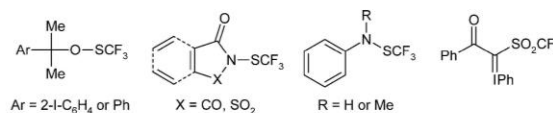
Figure 2. Examples of electrophilic trifluoromethylthiolation reagents.

A potential alternative to introducing SCF_3 as a whole from a preformed reagent is its stepwise assembly at the target molecule. This can be achieved in a straightforward fashion by first introducing an SCN group and then replacing the CN group by the CF_3 group though a Langlois-type nucleophilic substitution.[16]

We have recently shown that nucleophilic thiocyanations of alkyl halides or Sandmeyer thiocyanations of aryldiazonium salts can be combined with Langlois-type exchange reactions into convenient one-pot procedures.[17] These allow the conversion of various electrophiles into di- and trifluoromethylthiolated compounds using simple thiocyanate salts in combination with inexpensive fluoroalkylation reagents. We envisioned that a similar stepwise assembly might enable inexpensive and straightforward di- and trifluoroalkylthiolations of aromatic C–H bonds (Scheme 1). If electrophilic C–H thiocyanations based on easily accessible, stable reagents could be combined with an exchange of CN for CF_3 or CF_2H, di- and trifluoromethyl thioethers would become accessible from simple arenes rather than prefunctionalized substrates or expensive reagents.

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    http://dx.doi.org/10.1002/chem.201502914.
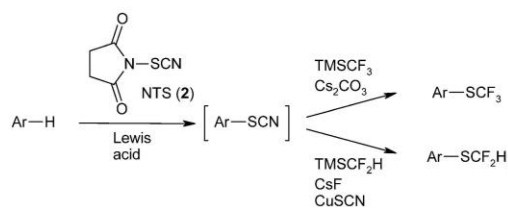
Scheme 1. Electrophilic trifluoromethylthiolations via a C−H thiocyanation/fluoroalkylation cascade.

We considered N-thiocyanatosuccinimide (NTS) to be the electrophilic reagent of choice, because it is readily available from N-bromosuccinimide (NBS) and NaSCN.[18] So far, it has been used only in the thiocyanation of thiols[18] and N-acyl imides.[19] Still et al. have shown that Friedel–Crafts thiocyanation of electron-rich compounds is possible with NTS formed in situ in MeOH or AcOH.[20] Unfortunately, these conditions are incompatible with common fluoroalkylation reagents.

To identify conditions that promote both the C−H thiocyanation and the CN/CF$_3$ exchange, we systematically investigated catalysts, solvents and temperatures for the one-pot reaction of anisole (1) with NTS (2) and TMS-CF$_3$ (Table 1).

When subjecting 1 and 2 to the conditions reported by Still et al. (AcOH, 60 °C) the aryl thiocyanate was formed in high yields, but subsequent addition of TMS-CF$_3$ and Cs$_2$CO$_3$ did not afford the desired trifluoromethyl thioether 4 (entry 1).[21] Further studies confirmed that protic solvents and Brønsted acids are incompatible with the trifluoromethylation step (entries 1 and 2). However, we discovered that the C−H thiocyanation

can alternatively be performed with 1% AuCl$_3$ as a catalyst in dichloroethane,[22] and that these conditions permit the subsequent trifluoromethylation to give 4 in moderate yields along with residual thiocyanate (entry 3). A decisive step-up in the yield of this two-step process was achieved by switching to MeCN as the solvent (entries 4–7). Further studies revealed that the transformation was catalyzed not only by gold but also by inexpensive Lewis acids, and AlCl$_3$ in particular (entry 8). After increasing the catalyst loading to 10 mol%, full conversion was reached after 12 h at RT (entry 9). ZrCl$_4$ displayed similarly high activity, other Lewis acids less so (entries 10–12). Without Lewis acid, no conversion was observed (entry 14). The regioselectivity is remarkable. Whereas Friedel–Crafts chlorination of anisole usually provides a para/ortho ratio of 79:21,[23] the thiocyanation gives the para-substituted product exclusively.

Because the activity of the Friedel–Crafts catalysts is diminished by Cs$_2$CO$_3$, TBAF or other TMS-CF$_3$ activators but the AlCl$_3$ catalyst does not affect the trifluoromethylation, the process is best performed stepwise in one pot. First, the arene is allowed to react at RT for 12 h with one equivalent of NTS (2) in the presence of 10% AlCl$_3$ in MeCN. TMS-CF$_3$ and Cs$_2$CO$_3$ are then added, and the reaction is stirred for another 2 h (entry 13).

Next, we investigated the scope of the trifluoromethylthiolation, extending the trifluoromethylation time to 16 h to ensure full conversion even of less reactive substrates (Table 2). Mayr has introduced the nucleophilicity parameter N to classify arenes with regard to their reactivity with electrophiles.[24] We determined that arenes with an N above a threshold of −2.5 are suitable for the C−H thiocyanation step. Thus, benzothiophene (N = −2.5) and fluorene (N = −2.9) gave reasonable yields, whereas o-xylene (N = −3.7) or toluene (N = −4.2) did not react. Various electron-rich arenes and heteroarenes with N > −2.5 were converted to the aryl trifluoromethyl thioethers in high yields. Functionalities including alkyloxy, hydroxy, ketal and amino groups are well tolerated. Sterically demanding substrates, unprotected phenols, indoles and carbazoles, and even a pyridine were smoothly converted. Aniline gave a surprisingly low yield, although the thiocyanation proceeded well. In contrast, both reaction steps were effective for N-methyl aniline. Bromo- and iodo-substituents remain intact, which opens up opportunities for further derivatization.

In all reactions, monothiocyanation was exclusively observed, which is understandable because the thiocyanate substituent reduces the nucleophilicity of arenes (Hammett constants for SCN: $\sigma_m = 0.51$, $\sigma_p = 0.52$).[25] Only a single regioisomer was formed for all substrates. This degree of selectivity is exceptional for electrophilic aromatic substitutions, and is linked to the strong electrophilicity of the SCN moiety.[26]

The scalability of the reaction was demonstrated by the high-yielding synthesis of 4 on a gram scale. The same strategy was successfully applied also to the synthesis of difluoromethyl thioethers, which are hard to access by other means.[17a,27] Mechanistically, the CN/CF$_2$H exchange is more complex, since this sensitive nucleophile can be transferred only with a stabilizing copper mediator that requires DMF to be active.[17a,28] After

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

Entry	Solvent	Catalyst	T, t	Conv. 1 [%]	Yield 4 [%]
1	AcOH	–	60 °C, 3 d	80	0
2	MeOH	–	60 °C, 3 d	0	0
3	DCE	1% AuCl$_3$	25 °C, 3 d	100	48
4	dioxane	1% AuCl$_3$	25 °C, 3 d	0	0
5	DMF	1% AuCl$_3$	25 °C, 3 d	0	0
6	THF	1% AuCl$_3$	25 °C, 3 d	0	0
7	MeCN	1% AuCl$_3$	25 °C, 3 d	100	94
8	MeCN	1% AlCl$_3$	25 °C, 1 d	90	86
9	MeCN	10% AlCl$_3$	25 °C, 12 h	100	99
10	MeCN	10% ZrCl$_4$	25 °C, 12 h	100	98
11	MeCN	10% FeCl$_3$	25 °C, 12 h	95	78
12	MeCN	10% BF$_3$·Et$_2$O	25 °C, 12 h	80	54
13[b]	MeCN	10% AlCl$_3$	25 °C, 12 h	100	99
14	MeCN	–	25 °C, 12 h	0	0

[a] Reaction conditions: 0.5 mmol of anisole (1), the catalyst, and 0.5 mmol of NTS (2) in 1 mL of solvent were stirred at given temperature for the given amount of time. Then, 1.0 mmol of Cs$_2$CO$_3$ and 1.0 mmol of TMS-CF$_3$ were added and the reaction mixture was stirred at RT for 12 h. Conversion of 1 was determined by GC, the yield of 4 by ^{19}F NMR spectroscopy using 1 equivalent of trifluoroethanol as internal standard; [b] 2 h for the Langlois exchange.

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Table 2. Trifluoromethylthiolation of electron-rich arenes.[a]

$$\text{Ar-H} \xrightarrow[\text{MeCN}]{\substack{1.\ \text{NTS (2), AlCl}_3 \\ 2.\ \text{TMSCF}_3,\ \text{Cs}_2\text{CO}_3}} \text{Ar-SCF}_3$$

4, 97%
8 mmol scale: 93%

5, 0%

6, 18%[b][c]

7, 42%

m-Me 8, 94%
o-Me 9, 95%

10, 88%[c]

11, 73%

12, 92%

13, 98%

14, 99%

15, 97%

16, 41%

17, 84%

18, 78%[b]

19, 70%[b]

20, 98%

21, 63%

22, 65%

23, 94%

24, 43%[b]

25, 53%[b]

26, 95%

27, 23%[c]

28, 76%[c]

[a] 1.0 mmol NTS, 0.1 mmol of AlCl$_3$, 2 mL MeCN, 1.0 mmol of arene, RT, 12 h. Then, 2.0 mmol of Cs$_2$CO$_3$, 2.0 mmol of TMS-CF$_3$, RT, overnight. Isolated yields. [b] The thiocyanation step was performed at 60 °C. [c] Yield determinate by ^{19}F NMR spectroscopy using 1 equivalent of trifluoroethanol as standard.

Table 3. Difluoromethylthiolation of electron-rich arenes.[a]

$$\text{Ar-H} \xrightarrow[\text{MeCN/DMF, RT}]{\substack{1.\ \text{NTS (2), AlCl}_3 \\ 2.\ \text{TMSCF}_2\text{H, CuSCN, CsF}}} \text{Ar-SCF}_2\text{H}$$

29, 79%

30, 63%

31, 59%

32, 88%

33, 69%

34, 53%

[a] 1.0 mmol NTS, 0.1 mmol of AlCl$_3$, 2 mL MeCN, 1.0 mmol of arene, RT, 12 h. Then, MeCN is exchanged for 2 mL of DMF; 1.0 mmol of CuSCN, 4.0 mmol of CsF, 2.0 mmol of TMS-CF$_2$H, RT, overnight. Isolated yields.

Table 3. These include ethers, phenols, anilines, pyridine and indole derivatives.

In conclusion, one-pot, two-step C–H thiocyanation/fluoroalkylation processes were developed that open up convenient entries to di- and trifluoromethyl thioethers starting from electron-rich arenes, an inexpensive thiocyanate source and TMS-CF$_3$ or TMS-CF$_2$H. The C–H functionalization proceeds exclusively at the most electron-rich, sterically least hindered position of the arene.

Experimental Section

Standard procedure for the synthesis of trifluoromethylthio ethers

An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with NTS (156 mg, 1.00 mmol), AlCl$_3$ (13.3 mg, 0.10 mmol), the arene (1.00 mmol) and MeCN (2 mL). After stirring at the given reaction temperature for 12 h, Cs$_2$CO$_3$ (652 mg, 2.00 mmol) and TMS-CF$_3$ (287 mg, 2.00 mmol) was added and the reaction mixture was stirred at RT for 16 h. 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$_2$, pentane/diethyl ether gradient), yielding the aryl trifluoromethyl thioethers. The yields of particularly volatile compounds were determined by ^{19}F NMR spectroscopy, and their identity by mass spectroscopy.

intricate tuning of all reaction parameters, we obtained an efficient difluoromethylthiolation protocol (see the Supporting Information for details), using anisole as the model substrate. The Friedel–Crafts thiocyanation step requires a maximum of 12 h at RT in the presence of NTS (**2**) and 10 mol % of AlCl$_3$. For the subsequent difluoromethylation, acetonitrile was exchanged for DMF, followed by addition of copper thiocyanate, excess cesium fluoride and TMS-CF$_2$H.

The scope of the difluoromethylthiolation is similar to the trifluoromethylthiolation but the yields are somewhat lower throughout, as demonstrated by the selected examples in

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5.4. Neue Methoden zur Pentafluorethylthiolierung

Im Gegensatz zu C_2F_5-Gruppen, die in der Wirkstoffforschung wiederholt bessere Eigenschaften als die kürzeren CF_3-Analoge aufweisen, wurden SC_2F_5-Gruppen bislang nahezu nicht erforscht. Dies lässt sich insbesondere durch den Mangel an entsprechenden Reagenzien und die wenigen effizienten Methoden erklären. Pentafluorethylthiolierte Moleküle können nämlich nicht über einen klassischen Fluor-Halogen-Austausch dargestellt werden; es entstehen lediglich komplexe Mischungen aus unvollständig fluorierten Verbindungen. Die einzige Methode zur Pentafluorethylierung schwefelhaltiger Vorstufen erfordert ozonschädliche Interhalogenverbindungen und raue Reaktionsbedingungen, weshalb sie in der Anwendungsbreite und Verfügbarkeit der Substrate stark eingeschränkt ist.[231] Modernere Methoden beschränken sich auf elektrophile Funktionalisierungen elektronenreicher Aromate und Indole.[232,233] Mögliche vorteilhaftere nukleophile Pentafluorethylthiolierungen sind hingegen nicht bekannt. Nachhaltige und besonders praktische Konzepte zur Einführung von SC_2F_5-Gruppen in komplexe organische Moleküle könnten diese interessante Substanzklasse als gängiges strukturelles Leitmotiv in der Wirkstoffforschung etablieren.

5.4.1. *Kupfer-katalysierte Sandmeyer-Pentafluorethylthiolierung*

Das Ziel dieses Projektes war es, die vorgestellten Kupfer-katalysierten Sandmeyer-Trifluormethylthiolierungen zur praktischen Einführung längerer Pentafluorethylgruppen unter milden Reaktionsbedingungen konsequent weiterzuentwickeln (**Schema 40**).
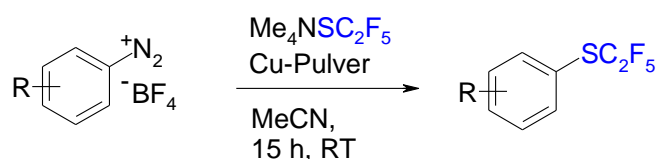
Schema 40. Kupfer-katalysierte Sandmeyer-Pentafluorethylthiolierung.

In Kollaboration mit der Firma *CF Plus Chemicals* wurde dafür zunächst ein Syntheseweg für das SC_2F_5-Reagenz $Me_4NSC_2F_5$, analog zu Me_4NSCF_3, aus $TMSC_2F_5$, Me_4NF und elementarem Schwefel entwickelt. Bislang wurde die Herstellung dieser Verbindung einzig in einem Patent von Röschenthaler ausgehend von ozonschädigenden Fluorkohlenwasserstoffen

beschrieben.[129] Da *CF Plus Chemicals* auf die Auftragssynthese fluorierter Chemikalien spezialisiert ist, Spezialequipment besitzt und Zugänge zu dem im Labormaßstab teurem TMSC$_2$F$_5$ hat, wurde das Reagenz dort hergestellt und analysiert. Mit diesem SC$_2$F$_5$-Reagenz konnte in unseren Laboren dann bereits in den ersten Testreaktionen die prinzipielle Durchführbarkeit der postulierten Kupfer-katalysierten Sandmeyer-Pentafluorethylthiolierung gezeigt und aromatische SC$_2$F$_5$-Verbindungen erstmals mit Me$_4$NSC$_2$F$_5$ dargestellt werden. Allerdings beobachteten wir in der Reaktionsoptimierung deutlich geringere Ausbeuten als in unseren analogen Sandmeyer-Reaktionen. Stattdessen wurden die Diazoniumsalze protodediazotiert oder durch den bewährten Kupferkatalysator CuSCN thiocyaniert. Auch bei anderen Kupfer(I)katalysatoren wurden die nukleophilen Gegenionen stets ungewollt eingeführt. Dies resultiert aus dem erkennbar geringeren nukleophilen Charakter des SC$_2$F$_5$-Anions im Vergleich zu SCF$_3$, weshalb die Sandmeyer-Pentafluorethylthiolierung wesentlich langsamer verläuft. Erst bei der Verwendung elementaren Kupfers, also in einem Reaktionsmedium ohne konkurrierende Nukleophile, konnte voller Umsatz zu den gewünschten Pentafluorethylthioethern erreicht werden. Dies ist eines der wenigen Beispiele von Sandmeyer-Reaktionen, die sowohl von katalytischen Mengen als auch von elementarem Kupfer vermittelt werden. Die entwickelte Methode zeigte eine große Anwendungsbreite anhand divers substituierter Diazoniumsalze und eröffnet damit einen effizienten, milden Zugang zu einer neuen, potenziell wichtigen Substanzklasse.

Beiträge der Autoren:

Herr B. Bayarmagnai und ich entwickelten die Reaktion, optimierten das Katalysatorsystem und untersuchten die Anwendungsbreite gleichberechtigt. Herr K. Jouvin unterstütze uns bei der Optimierung des Katalysatorsystems und bei der Auftrennung der Verbindungen. Herrn B. Bayarmagnai verfasste das Manuskript zusammen mit Herrn Prof. Dr. L. J. Gooßen, während ich die analytischen Daten auswertete und die „Supporting Information" erstellte.

Die Resultate dieses Projektes wurden in *Organic Chemistry Frontiers* veröffentlicht, die Publikation für diese Arbeit angepasst und mit Erlaubnis des Verlages beigefügt: "Reproduced and adapted from Ref.: C. Matheis, B. Bayarmagnai, K. Jouvin, L. J. Goossen, *Orc. Chem. Front.* **2016**, *3*, 949-952: „*Convenient Synthesis of Pentafluoroethyl Thioethers via Catalytic Sandmeyer Reaction with a Stable Fluoroalkylthiolation Reagent*" with permission from The Royal Society of Chemistry".[234] Eine separate Lizenz wird von diesem Journal nicht bereitgestellt beziehungsweise benötigt.

RESEARCH ARTICLE

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 fluoroalkyl-thioethers.[8f,9] For laboratory-scale applications, the use of pre-formed 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 Yagu-polskii[11] and has successfully been employed in trifluoro-methylthiolations 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 dis-ulfides or thiols.[17] However, these methods suffer from harsh reaction conditions and limited availability of sulfur-contain-ing substrates.

Modern methods suitable for the late-stage introduction of SC_2F_5 groups include the Friedel–Crafts-type reaction of elec-tron-rich arenes with a pentafluoroethyl sulfenamide reagent described by Billard *et al.*[18] and the electrophilic perfluoroalkyl-thiolation 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 fluoroalkyla-tion 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 tetra-methylammonium 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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Traditional methods   **This work**
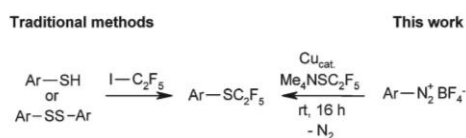
Scheme 1 Syntheses of pentafluoroethyl thioethers.

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(ı) 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$_4$NSC$_2$F$_5$ 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]
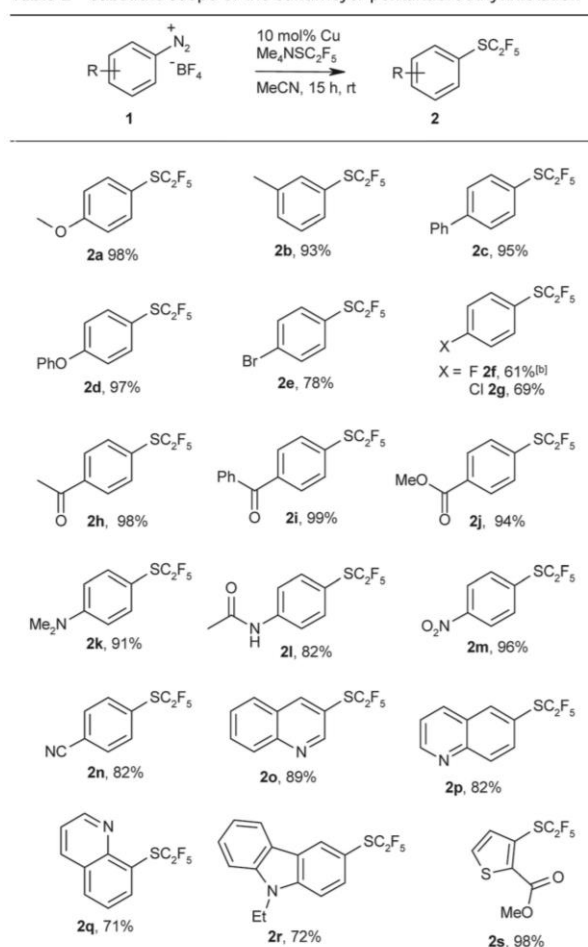
[a] Reaction conditions: dropwise addition of 1.0 mmol of **1** in 2 mL MeCN to 1.5 mmol Me$_4$NSC$_2$F$_5$ and 0.1 mmol elemental copper in 2 mL MeCN, 15 h at room temperature. [b] Yields determined by ^{19}F NMR using trifluoroethanol as an internal standard.

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(ı) species in these processes is rare but

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$$Ar-N_2^+ + \left[Cu^I-SC_2F_5\right] \xrightarrow{SET} \left[Ar-N_2^{\bullet}\right] + \left[Cu^{II}-SC_2F_5\right]^+$$

$$Me_4NSC_2F_5 \uparrow \qquad \downarrow -N_2$$

$$Ar-SC_2F_5 + [Cu]^+ \longleftarrow Ar^{\bullet} + \left[Cu^{II}-SC_2F_5\right]^+$$
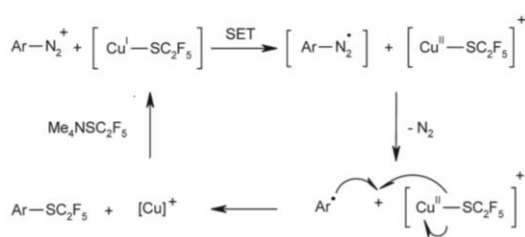
Scheme 2 Sandmeyer pentafluoroethylthiolation of aromatic amines.

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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5.4.2. *Eisen-katalysierte decarboxylierende Synthese von Pentafluorethylthioethern*

Das Ziel dieses Forschungsvorhabens war es, die zuvor im Arbeitskreis etablierte Eisen-katalysierte Decarboxylierung von Trifluoracetaten zur Trifluormethylierung von Organothiocyaten weiterzuentwickeln.[235] In diesem Protokoll decarboxyliert das Trifluoracetat am Eisenkatalysator unter Bildung einer nukleophilen Trifluormethylspezies. Dadurch konnte eine der preiswertesten und nachhaltigsten Trifluormethylquellen, da lediglich CO_2 als Abfallprodukt frei wird, zur Überführung von SCN in SCF_3-Gruppen genutzt werden. Nun sollten durch höhere Homologe perfluorierter Acetate praktische analoge Zugänge zu Pentafluorethylthioethern geschaffen werden (**Schema 41**).
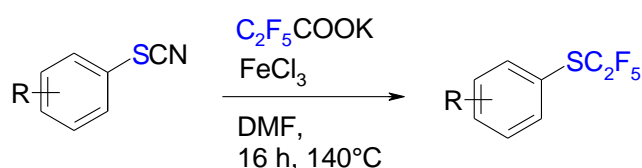
Schema 41. Eisen-katalysierte decarboxylierende Synthese von Pentafluorethylthioethern.

Unter den etablierten Reaktionsbedingungen wurde zunächst ein Eisenkatalysator identifiziert, der sich optimal für die decarboxylierende Synthese von Pentafluorethylthioethern eignet. Umweltverträgliches und günstiges $FeCl_3$ vermittelt die Decarboxylierung von Pentafluorethylacetaten effizient und bindet die entstehenden Cyanide zu ungiftigem $[K_4(FeCN_6)_4]$. Durch dieses Reaktionskonzept gelang die Synthese divers funktionalisierter Pentafluorethylthioether in hohen Ausbeuten. Ferner konnten auch höhere Homologe perfluorierter Acetate erfolgreich umgesetzt werden. Mechanistische Studien unterstützen die Annahme, dass es sich um eine Decarboxylierung unter Bildung einer nukleophilen Perfluoralkylspezies handelt.

Beiträge der Autoren:

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

Die Resultate dieses Projektes wurden im *Journal of Fluorine Chemistry* veröffentlicht, die Publikation für diese Arbeit angepasst und mit Erlaubnis des Verlages beigefügt: "Reproduced from Ref.: B. Exner, B. Bayarmagnai, C. Matheis, L. J. Goossen, *J. Fluorine Chem.* **2017**, im Druck, DOI: 10.1016/j.jfluchem.2016.12.006*:* „ *Synthesis of perfluoroalkyl thioethers from aromatic thiocyanates by iron-catalysed decarboxylative perfluoroalkylation*" with permission from Elsevier."[236]

Short Communication

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.

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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. This greenhouse gas is problematic when released in huge quantities by cars and power plants, but in chemical production it is one of the least harmful byproducts. 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 or the catalyst loading did not improve the outcome (entries 8–11), and performing the reaction at a decreased temperature of 120 °C led to a substantially lower yield (entry 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).

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$_2$F$_5$ 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. The successful synthesis of **3aa** in 89% yield on a 5 mmol scale demonstrates the scalability of the process.

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$_3$F$_7^-$, 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).

To elucidate the reaction mechanism, one equivalent of the radical scavenger 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) was added to several reactions using different metal salts as the catalyst. The fact that the reactions were not completely suppressed speaks against a radical mechanism for all these mediators. In another control experiment, the decarboxylation was performed in the presence of benzaldehyde leading to the formation of 2,2,3,3,3-pentafluoro-1-phenylpropan-1-ol in a yield of 43%. This supports a pathway via a nucleophilic perfluoroalkyl species (see SI) [60].

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–3ua**, **3ab** and **3ac**. The yields of particularly volatile compounds were determined by ^{19}F NMR spectroscopy, and their identity by MS.

Acknowledgements

Table 1
Optimisation of the reaction conditions.[a]

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$_2$SO	89
10	FeCl$_3$	Propylene carbonate	18
11[c]	FeCl$_3$	DMF	89
12[d]	FeCl$_3$	DMF	81

[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] Using 0.20 eq. of FeCl$_3$.
[d] At 120 °C.

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

| 1a–u | 2a–c | 30 mol% FeCl₃ DMF, 16 h, 140 °C | 3aa–ua, ab, ac |

3aa, 97%

3ba, 98%

3ca, 96%

o-Me 3da, 87%[b]
m-Me 3ea, 95%
p-Me 3fa, 99%[b]

3ga, 96%

3ha, 96%

3ia, 91%

3ja, 97%

3ka, 95%

3la, 98%

3ma, 97%

3na, 97%

X = F 3oa, 97%[b]
Cl 3pa, 96%
Br 3qa, 98%

3ra, 68%

3sa, 32%

3ta, 23%

3ua, 35%
53%[c]

3ab, 68%[d]

3ac, 29%
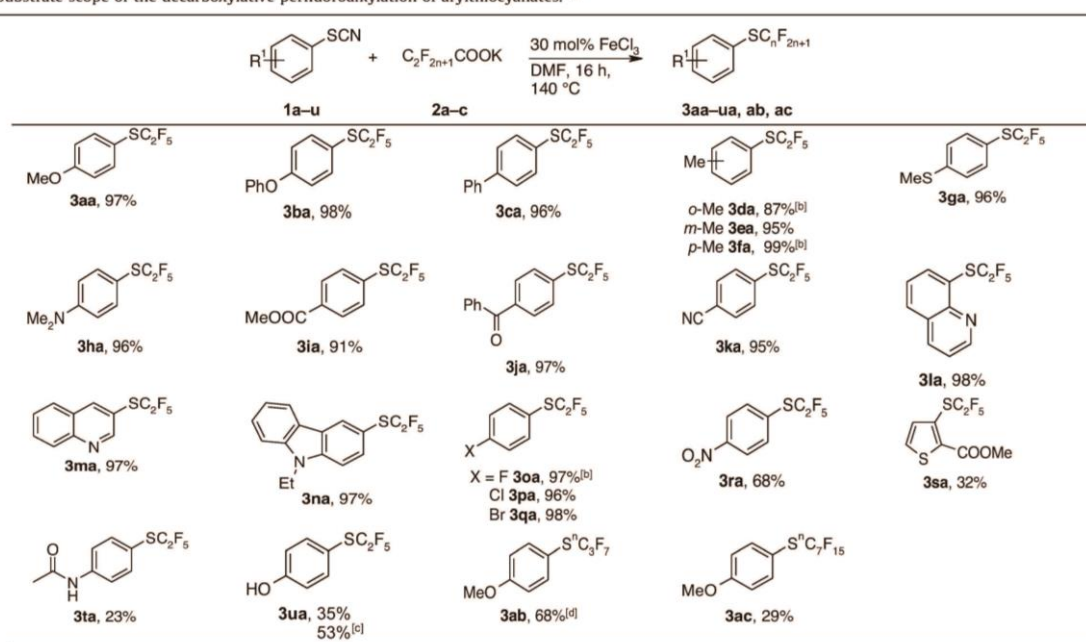
[a] Reaction conditions: 2.0 mmol of organothiocyanate **1**, 0.30 mmol of FeCl₃, 2.4 mmol of potassium perfluoroalkylcarboxylate **2**, 6.0 mL of DMF, 140 °C, 16 h, isolated yields.
[b] The yield was determined by ^{19}F NMR using 2,2,2-trifluoroethanol as an internal standard.
[c] 2.2 eq. of potassium 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.

(a)

(b)

		3	**4**	**5**
Roques (R = H, X = SPh):		29%	33%	15%
Our protocol (R = OMe, X = CN):		68%	5%	not observed
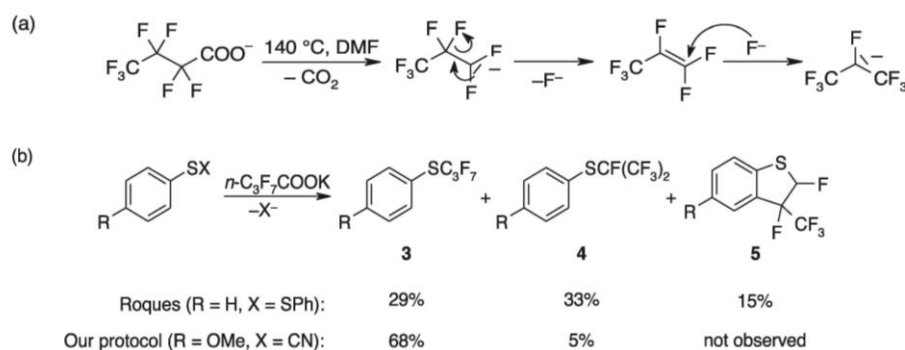
Scheme 1. (a) Origin of side products in decarboxylative heptafluoropropylation and (b) their distribution in the product mixture.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2016.12.006.

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5.5. Neue Methoden zur Difluormethylthiolierung

5.5.1. *Difluormethylthiolierung in situ generierter Organothiocyanate*

Das Ziel dieses Projektes bestand darin, die im Arbeitskreis etablierte Thiocyanierung/Trifluormethylierungskaskade systematisch weiterzuentwickeln, um neue praktische Methoden zur milden, effizienten und selektiven Einführung von weit weniger erforschten Difluormethylthiogruppen zu schaffen (**Schema 42**, **Schema 43**, **Schema 44**).

Allerdings wurde ein Langlois-analoger CN/CF$_2$H-Austausch bisher nicht beschrieben, weshalb dieser Schritt zunächst separat betrachtet wurde (**Schema 42**).

$$R-SCN \xrightarrow[\substack{DMF \\ 12 \text{ h, RT}}]{\substack{TMSCF_2H \\ CuSCN \\ CsF}} R-SCF_2H$$
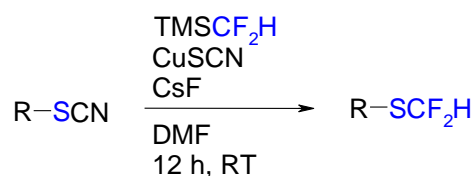
Schema 42. Difluormethylthiolierung präformierter Organothiocyanate.

Dafür setzten wir präformierte Organothiocyanate unter den etablierten Langlois-analogen Reaktionsbedingungen um. Jedoch wurden so nur Spuren der gewünschten difluormethylthiolierten Produkte detektiert. Diese Ergebnisse kamen nicht unerwartet, da schon in den ausgiebigen Untersuchungen zu der Sandmeyer-Difluormethylierung deutlich wurde, dass es unerlässlich ist, intermediäre labile CF$_2$H-Spezies durch geeignete Reaktionsbedingungen zu stabilisieren.[203] Mit der zuvor entwickelten Kombination aus CsF als Aktivator und DMF als Lösungsmittel gelang es tatsächlich, die entsprechenden Produkte in moderaten Ausbeuten darzustellen. Dennoch zeigte sich in weiteren umfangreichen Optimierungsreaktionen, dass der CN/CF$_2$H-Substitutionsschritt zwar unkatalysiert möglich ist, aber nur durch Kupferkatalysatoren effizient vermittelt wird.

Diese Erkenntnisse wurden nun auf eine Kaskade aus *in situ* Thiocyanierung und unmittelbar anschließender Difluormethylierung breit verfügbarer Alkylelektrophile erfolgreich übertragen (**Schema 43**).
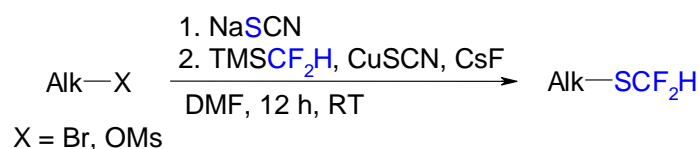
Schema 43. Difluormethylthiolierung von Alkylelektrophilen.

Besonders wichtig war es auch, aromatische Difluormethylthioether durch unsere etablierten milden Sandmeyer-Reaktionen mittels einer Thiocyanierung/Difluormethylierungskaskade effizient zugänglich zu machen (**Schema 44**).
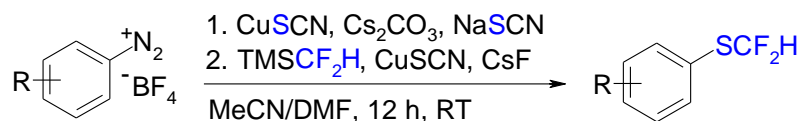
Schema 44. Sandmeyer-Difluormethylthiolierung.

Allerdings wurden unter den gegebenen Bedingungen der jeweiligen Teilreaktion weder in MeCN noch in DMF zufriedenstellende Ausbeuten beobachtet. Während DMF die vorangehende Thiocyanierung limitiert, inhibiert MeCN den CN/CF$_2$H-Austausch komplett. Indessen zeigten vielversprechende Kontrollexperimente, dass sich die verwendeten Reagenzien des Thiocyanierungsschrittes in der Difluormethylierung, genau wie umgekehrt, untereinander tolerieren. Demnach war es notwendig, die Lösungsmittel während der einzelnen Teilprozesse auszutauschen, was nach der vollständigen Thiocyanierung im Hochvakuum gelang. Anschließend wurden TMSCF$_2$H, CsF und weiteres CuSCN zusammen mit DMF zu der Reaktionsmischung gegeben, um die gewünschten Difluormethylthioether in nahezu quantitativen Ausbeuten zu erhalten.

Insgesamt konnte die Stärke des Reaktionskonzeptes der Thiocyanierung/Difluormethylierungskaskade anhand zahlreicher divers substituierter Substrate demonstriert werden. Viele der dargestellten Produkte waren bislang nicht bekannt und konnten erstmals synthetisiert sowie vollständig charakterisiert werden. Dadurch konnten innovative, effiziente Methoden zur Difluormethylthiolierung gängiger Startmaterialien geschaffen werden, die nun als mögliches strukturelles Leitmotiv in ihrer biologischen Wirkung untersucht werden können.

Beachtenswert ist hierbei, dass zum Zeitpunkt der Veröffentlichung dieser Ergebnisse noch keine Prozesse zur Einführung von SCF$_2$H-Gruppen ausgehend von breit verfügbaren

Startmaterialen wie Halogeniden, Mesylaten oder Diazoniumsalzen bekannt waren. Außerdem existierten noch keine SCF$_3$-analogen SCF$_2$H-Reagenzien. Obwohl mittlerweile neue Reagenzien und Verfahren entwickelt wurden, sind unsere Methoden zur Difluormethylthiolierung *in situ* generierter Thiocyanate diesen bis heute überlegen.

Beiträge der Autoren:

Herr B. Bayarmagnai und ich entwickelten die Reaktion. Zusammen mit Herrn Dr. K. Jouvin wurde das Katalysatorsystem optimiert sowie die Anwendungsbreite untersucht. Das Manuskript verfasste Herrn B. Bayarmagnai zusammen mit Herrn Prof. Dr. L. J. Gooßen, während Herr Dr. K. Jouvin und ich gleichberechtigt die analytischen Daten auswerteten und ich außerdem die „Supporting Information" erstellte.

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Synthetic Methods

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]
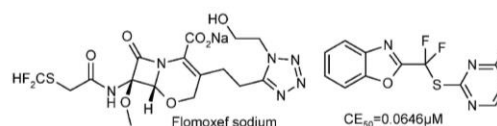
Figure 1. Biologically active α-difluoromethyl thioethers.

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
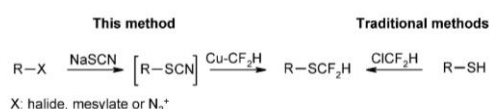
Scheme 1. Strategies to access difluoromethyl thioethers.

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 SCF₃ reagents are laborious to prepare and rather expensive,[12,13,25] and the same limitations must be expected for their presently unknown SCF₂H 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 CF₂H by the in situ conversion of SCN to SCF₂H using a nucleophilic CF₂H source, preferentially TMS–CF₂H, which is easily accessible from the inexpensive Ruppert–Prakash reagent.

Langlois et al.[26] found that SCF₃ groups can be generated from thiocyanates by nucleophilic displacement of the CN group using TMS–CF₃. However, the corresponding reaction between organothiocyanates with TMS–CF₂H 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–CF₂H, 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 CF₂H 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–CF₂H, RT. [b] Yields were determined by ¹⁹F NMR spectroscopy using trifluoroethanol as an internal standard. [c] TMS–CF₂H 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–CF₂H 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
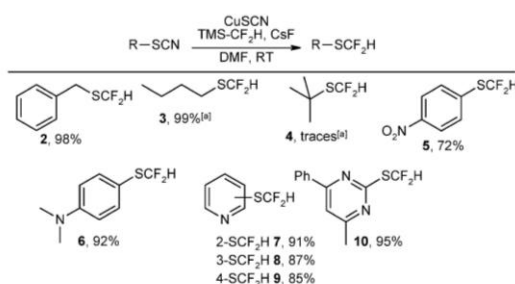
Scheme 2. Cu-mediated difluoromethylation of organothiocyanates. Reaction conditions: 1.0 mmol of organothiocyanate, 1.0 mmol of CuSCN, 4.0 mmol of CsF, 2.0 mmol of TMS–CF₂H in 2 mL of DMF, 12 h, RT. Yields are of isolated products. [a] Yields determined by ¹⁹F NMR spectroscopy using trifluoroethanol 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–CF₂H, 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]
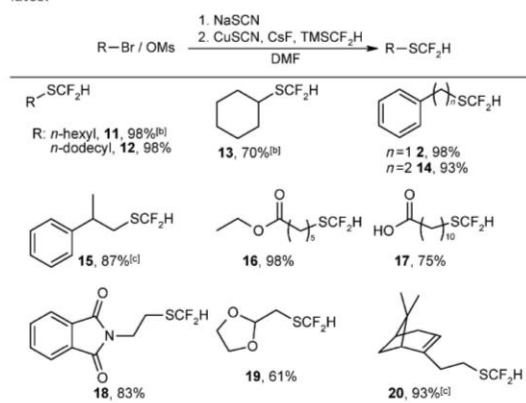
[a] 1.0 mmol of alkyl bromide and 1.2 mmol of NaSCN in 4 mL DMF were heated for 2 h (see SI for detailed conditions). After cooling to RT, 1.0 mmol of CuSCN, 4.0 mmol of CsF, and 2.0 mmol of TMS–CF₂H were added, and stirring continued for 12 h at RT. Yields are of isolated products. [b] Yields determined by ¹⁹F NMR spectroscopy using trifluoroethanol as an internal standard. [c] Starting from mesylate.

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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$_2$H in the presence of copper thiocyanate (Table 3). The optimal literature condi-

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$_2$CO$_3$, 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$_2$H in 4 mL DMF were added, stirring was continued for 12 h at RT. Yields are of isolated products.

tions for the trifluoromethylthiolation of diazonium salts (Cs$_2$CO$_3$, 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$_2$H$^-$ 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$_2$H species each require one equivalent of CuSCN.[29]

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$_2$CO$_3$, and CuSCN in MeCN. After stirring for 1 h, the solvent is evaporated, and a solution of CsF, CuSCN, and TMS–CF$_2$H 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$_2$H via a CuCF$_2$H 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.

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6. Zusammenfassung und Ausblick

Im Rahmen dieser Arbeit wurden neue nachhaltigere Methoden zur gezielten Einführung fluoralkyl(thio/seleno)lierter Substituenten in komplexe organische Moleküle entwickelt. Dafür konnte insbesondere die Sandmeyer-Reaktion als universelles Werkzeug zur milden Funktionalisierung breit verfügbarer Aniline genutzt werden. In allen neuen Verfahren wurden konsequent praktische Fluoralkyl(thio/seleno)-Quellen verwendet, die auf dem nachhaltigen Ruppert-Prakash-Reagenz TMSCF$_3$ basieren, das wiederum aus dem Abfallprodukt Fluoroform herstellbar ist. Die Stärke der innovativen Reaktionskonzepte wurde anhand zahlreicher hochfunktionalisierter Substrate demonstriert, die in durchweg hohen Ausbeuten umgesetzt werden konnten. Konkreter wurden dabei folgende vielseitig einsetzbare Zugänge zu wichtigen Substanzklassen fluoralkyl(thio/seleno)lierter Verbindungen geschaffen:

In den ersten Arbeiten konnte durch eine einfache und kostengünstige Eintopf-Sandmeyer-Reaktion Trifluormethylgruppen selektiv in organische Moleküle eingeführt werden. Entscheidend war dabei, dass die breit verfügbaren Aniline *in situ* diazotiert werden und anschließend ohne weitere Aufarbeitung in der wegweisenden Sandmeyer-Trifluormethylierung reagieren (**Schema 45**).
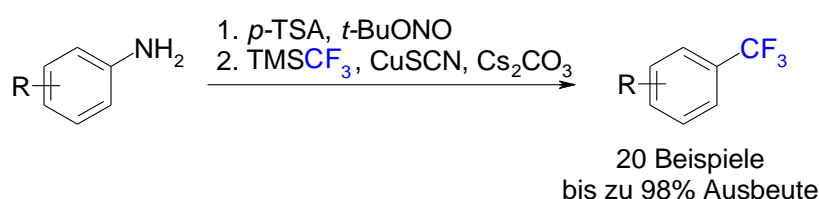
Schema 45. Sandmeyer-Trifluormethylierung von Anilinen.

Nachfolgende Arbeiten erweiterten dieses innovative Reaktionskonzept zur milden Einführung hochinteressanter Difluormethylgruppen. Ausschlaggebend für den Erfolg des Projektes war es, die intermediär gebildeten Cu–CF$_2$H-Komplexe zunächst mit DMF und CsF zu stabilisieren und diese anschließend mit aromatischen Diazoniumsalzen zu den entsprechenden difluormethylierten Verbindungen umzusetzen (**Schema 46**).

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TMSCF$_2$H

CuSCN
CsF

$\left[\text{Cu}\!-\!\text{CF}_2\text{H}\right]$

R⟨Ar⟩$^{+}$N$_2$ $^{-}$BF$_4$ → R⟨Ar⟩CF$_2$H

27 Beispiele
bis zu 86% Ausbeute
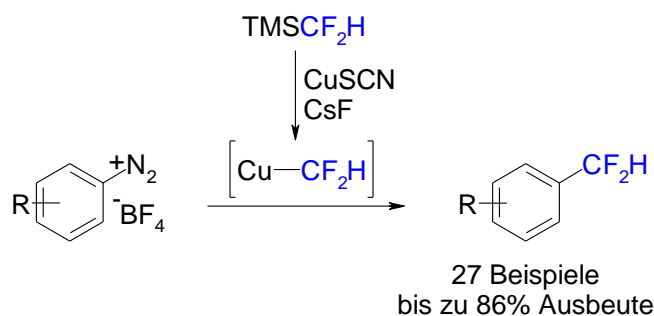
Schema 46. Sandmeyer-Difluormethylierung.

In weiteren Projekten zur Einführung von Trifluormethylthiogruppen konnten verschiedene neue praktische Zugänge zu dieser wichtigen Substanzklasse geschaffen werden (**Schema 47**).

(V)
24 Beispiele
bis zu 99% Ausbeute

1. NTS AlCl$_3$ 2. TMSCF$_3$ Cs$_2$CO$_3$

TMSCF$_3$
NaSCN
Cs$_2$CO$_3$

Alk—X   X = Cl, Br, I, OMs

(IV)
22 Beispiele
bis zu 98% Ausbeute

R⟨Ar⟩NH$_2$ 1. *p*-TSA, *t*-BuONO   2. TMSCF$_3$, CuSCN Cs$_2$CO$_3$, NaSCN → R–SCF$_3$

(I)
6 Beispiele
bis zu 70% Ausbeute

Me$_4$NSCF$_3$
CuSCN

Me$_4$NSCF$_3$
CuSCN

(II)
28 Beispiele
bis zu 99% Ausbeute

R⟨Ar⟩$^{+}$N$_2$ $^{-}$BF$_4$

präformiert oder in situ generiert

R'—C(=O)OR mit N$_2$

(III)
33 Beispiele
bis zu 98% Ausbeute

Schema 47. Übersicht der entwickelten Trifluormethylthiolierungen.

Die *in situ* Diazotierung breit verfügbarer Aniline, wie sie bereits in der Eintopf-Sandmeyer-Trifluormethylierung realisiert werden konnte, war auch auf die Sandmeyer-Thiocyanierung/Trifluormethylierungskaskade übertragbar (**I**). Sie erwies sich als eine

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praktische Route zur Darstellung von Trifluormethylthioethern, die auch instabile Diazoniumsalze toleriert.

Eine neue wegweisende Einführung von SCF$_3$-Gruppen gelang durch die Kupfer-katalysierte Sandmeyer-Trifluormethylthiolierung mit Me$_4$NSCF$_3$ (**II**). Diese Methode ist im Gegensatz zu etablierten Sandmeyer-Reaktionen so effizient, dass bereits 10 mol% CuSCN die Reaktion innerhalb von nur einer Stunde bei Raumtemperatur vermittelt.

Das gleiche fortschrittliche Katalysatorsystem wurde auch für die Trifluormethylthiolierung von α-Diazoestern genutzt (**III**). Dadurch konnten die leicht aus Aminosäuren herstellbaren Substrate einfach und, im Gegensatz zu den in der Literatur beschriebenen Verfahren, in einzigartiger Anwendungsbreite zu den entsprechenden Trifluormethylthioethern umgesetzt werden.

In einem weiteren Teilprojekt konnte die etablierte Kaskade aus *in situ* Thiocyanierung mit NaSCN und anschließender Trifluormethylierung mit TMSCF$_3$ auch für eine praktische, metallfreie Trifluormethylthiolierung breit verfügbarer Alkylelektrophile genutzt werden (**IV**). Diese Reaktion ist nahezu quantitativ, sodass häufig eine einfache wässrige Aufarbeitung ausreichte, um die Produkte analysenrein zu isolieren.

Schließlich gelang es ebenfalls, diese Thiocyanierung/Trifluormethylierungskaskade auf elektrophile C–H-Trifluormethylthiolierungen elektronenreicher Aromate zu übertragen (**V**). Die entwickelte Methode benötigt milde Reaktionbedingungen, katalytische Mengen preiswertes AlCl$_3$ und besitzt eine außergewöhnlich hohe Regioselektivität. Im Vergleich zu bekannten direkten elektrophilen Trifluormethylthiolierungen ist dieses Verfahren besonders vorteilhaft, da *N*-Thiocyanatosuccinimid (NTS) und TMSCF$_3$ als günstige und leicht handhabbare Reagenzien anstelle teurer und instabiler elektrophiler SCF$_3$-Quellen eingesetzt werden.

Neben SCF$_3$- konnten auch SeCF$_3$-Gruppen, eine neue potenzielle Leitstruktur in der Wirkstoffforschung, durch das entwickelte innovative Katalysatorsystem der Kupfer-katalysierten Trifluormethylthiolierungen in Diazoniumsalze und α-Diazoester praktisch eingeführt werden. Dafür wurde lediglich Me$_4$NSCF$_3$ durch Me$_4$NSeCF$_3$ ersetzt und repräsentative Verbindungen unter sonst gleichen Reaktionsbedingungen zu den entsprechenden Trifluormethylselenoethern in hohen Ausbeuten umgesetzt (**Schema 48**).
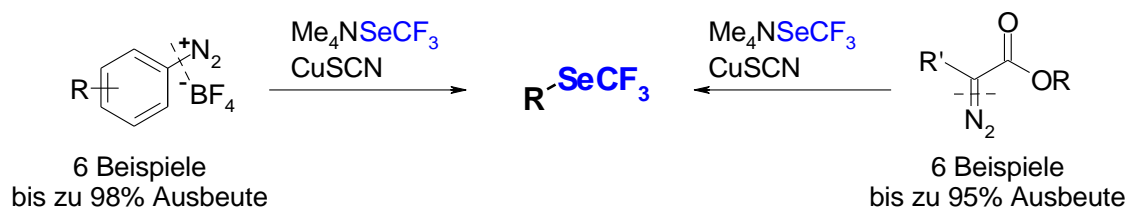
Schema 48. Übersicht der entwickelten Trifluormethylselenolierungen.

In weiteren Projekten wurde die Einführung von Pentafluorethylthiosubstituenten, eine interessante Substanzklasse, für die kaum Synthesewege bekannt sind, untersucht. In einer konsequenten Weiterentwicklung der Kupfer-katalysierten Verfahren wurde diese funktionelle Gruppe unter milden Reaktionsbedingungen in Gegenwart katalytischer Mengen elementaren Kupfers in Diazoniumsalze eingeführt (**Schema 49**, links). Außerdem konnten Organothiocyanate unter Decarboxylierung pentafluorethylierter Acetate in Anwesenheit von Eisenkatalysatoren praktisch zu den korrespondierenden Pentafluorethylthioethern umgesetzt werden (**Schema 49**, rechts). Damit wurde eine der preiswertesten und nachhaltigsten Pentafluorethylquellen zur Überführung von SCN- in SC_2F_5-Gruppen genutzt, in der lediglich CO_2 als Abfallprodukt freigesetzt wird.
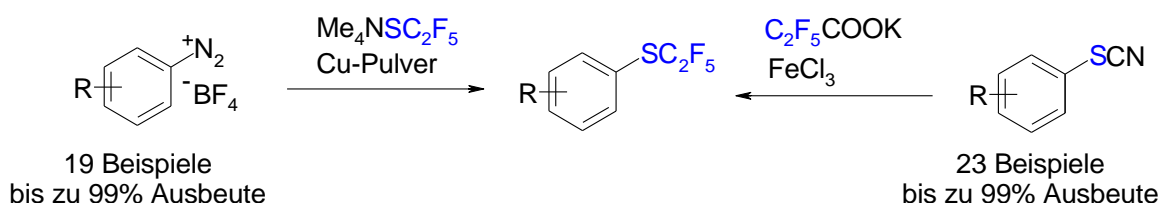
Schema 49. Übersicht der entwickelten Perfluoralkylthiolierungen.

Aufgrund der einzigartig vielversprechenden Eigenschaften der SCF_2H-Gruppe als potenziell gängiges strukturelles Leitmotiv in der Wirkstoffforschung entwickelten wir neue Wege zur Darstellung von Difluormethylthioethern (**Schema 50**). Da zu diesem Zeitpunkt noch keine Methoden zur Einführung der Difluormethylthiogruppe ausgehend von breit verfügbaren Startmaterialen bekannt waren, kombinierten wir die Erkenntnisse aus der Difluormethylierung und den Thiocyanierung/Trifluormethylierungskaskaden.
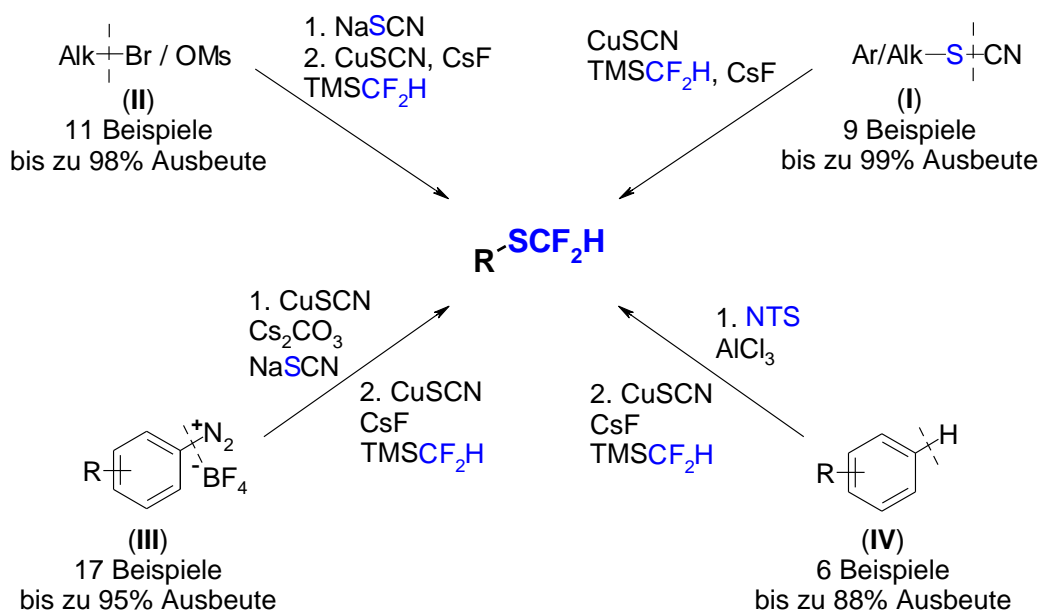
Schema 50. Übersicht der entwickelten Difluormethylthiolierungen.

Zunächst wurden geeignete Reaktionsbedingungen identifiziert, die den bisher unbekannten Langlois-artigen CN/CF$_2$H Austausch ermöglichen (**I**). Dabei war es von essentieller Bedeutung, mit Kupfer, CsF und DMF intermediäre CF$_2$H-Spezies zu stabilisieren. Anschließend wurden Methoden entwickelt, die diesen neuen Austausch auch in einer Thiocyanierung/Difluormethylierungskaskade tolerieren. Dabei wurden Organothiocyanate *in situ* aus diversen Alkylelektrophilen (**II**) sowie über die Sandmeyer-Reaktion aus Aryldiazoniumsalzen (**III**) erzeugt und in die entsprechenden Difluormethylthioether überführt. Schließlich konnte die Reaktionssequenz auch für elektrophile C–H-Difluormethylthiolierungen elektronenreicher Aromate demonstriert werden (**IV**).

Insgesamt wurden eine Reihe innovativer Methoden zur Darstellung einzigartig wichtiger fluorierter Substituenten erforscht. Insbesondere die Sandmeyer-Reaktion konnte zur praktischen Einführung von CF$_3$-, SCF$_3$-, SC$_2$F$_5$-, SeCF$_3$- und sogar CF$_2$H- sowie SCF$_2$H-Gruppen etabliert werden. Die wesentlichen Vorteile dieser Reaktion sind die milden Reaktionsbedingungen sowie die hohe Toleranz gegenüber funktionellen Gruppen, weshalb sie sich selbst für komplexe Verbindungen in einem späten Synthesestadium eignet. Die Chancen, die sich durch diese Technologien ergeben könnten, sind klar erkennbar, obwohl die Reaktionen noch im Prototypenstadium sind. Trotzdem ist die Reaktionsentwicklung so weit

fortgeschritten, dass für die Einführung von SCF_3-, SC_2F_5- und $SeCF_3$-Gruppen Kupfer in katalytischen Mengen von nur 10 mol% eingesetzt werden kann.

Aufbauend auf den vorgestellten Arbeiten ergeben sich Möglichkeiten, die neuen Reaktionskonzepte hinsichtlich ihrer industriellen Anwendbarkeit weiterzuentwickeln.

Ein wichtiges Ziel ist hierbei, die Katalysatorbeladung der Sandmeyer-Reaktionen noch weiter zu reduzieren. Dies liegt in der Kalkulation industrieller Prozesse begründet, bei denen die rückstandlose Entfernung großer Kupfermengen häufig als einzelner Syntheseschritt gezählt wird. Im Rahmen der Projekte dieser Arbeit konnten wir durch systematische Reihenversuche sehr viele Erfahrungen auf dem Gebiet der Sandmeyer-Reaktion sammeln. Mit diesen umfangreichen Daten ausgestattet könnte es gelingen, das lange ungelöste Problem zur Verwendung katalytischer Kupfermengen in Sandmeyer-Reaktionen insgesamt zu lösen. Neben den erfolgreich entwickelten Protokollen mit 10 mol% Kupfer konnten in Stichversuchen auch mit 5 mol% Ausbeuten von über 70% erreicht werden. Außerdem hat sich in den katalytischen Reaktionen mit elementarem Kupfer gezeigt, dass in der obligatorischen Reaktionszeit dieses Protokolls von 15 Stunden die geringen Mengen an Kupfer immer noch aktiv waren und die Reaktion vermittelten. Dies bedeutet, wenn ein weiteres Nukleophil in dieser Zeit auf das Kupferkation nach der nukleophilen Funktionalisierung übertragen wird, dann verliert auch über diese Dauer die Katalysatorspezies seine Aktivität nicht. Diese Ergebnisse sind ein wichtiger Ansatz für weitere Optimierungen, um die Katalysatorbeladung weiter zu verringern. Führte man diese Entwicklungen konsequent weiter, könnten die Erkenntnisse auf vielerlei Anwendungen der Sandmeyer-Reaktion übertragen werden.

Ein weiterer Ansatz für die Katalysatoroptimierung der vorgestellten Sandmeyer-Prozesse ist es, intermediäre Fluoralkylanionen ohne Kupfer zu stabilisieren. Normant,[70] Roques[71] und Langlois[237] zeigten, dass DMF als CF_3-Anionenreservoir für Trifluormethylierungen ohne Metall fungiert. Daher ist eine Kombination aus katalytischem Kupfer einzig für den Einelektronentransfer der Sandmeyer-Reaktion und einem geeigneten Reservoir für instabile Fluoralkylanionen ein weiterer vielversprechender Ausgangspunkt.

7. Experimenteller Teil

7.1. Anmerkungen

Dieser Teil der Arbeit besteht hauptsächlich aus den englischen „Supporting Information" der Originalveröffentlichungen.

Alle dargestellten Produkte wurden vollständig durch die gängigen analytischen Methoden charakterisiert. Die analytischen Daten bekannter Verbindungen wurden zusätzlich mit denen aus der Literatur verglichen und damit überprüft. Viele dieser Produkte wurden durch die neu entwickelten Verfahren erstmals dargestellt und erhielten daraufhin eine CAS-Nummer. Die Ausbeuten einiger weniger, besonders flüchtiger Verbindungen wurden mittels ^{19}F-NMR und deren Identität mittels GC-MS bestimmt.

Alle NMR-Spektren der synthetisierten Verbindungen dieser Arbeit sind in den „Supporting Information" der jeweiligen Publikationen abgebildet und auf den Onlineportalen der Journale frei verfügbar.

7.2. Allgemeine Arbeitstechniken

7.2.1. *Chemikalien und Lösungsmittel*

Kommerziell verfügbare Chemikalien wurden bei einem Reinheitsgrad von ≥95% direkt eingesetzt oder andernfalls nach Standardverfahren aufgereinigt.[238] Luft− und feuchtigkeitsempfindliche Substanzen wurden mit Standard−Schlenktechniken stets unter einer Stickstoff− oder Argonatmosphäre gelagert und gehandhabt. Die verwendeten Lösungsmittel wurden nach Standardverfahren getrocknet und über Molsieben (Porengröße 3 Å), die zuvor im Mikrowellenofen (2 × 2 min, 600 W) erhitzt und im Ölpumpenvakuum (10^{-3} mbar) abgekühlt wurden, unter Stickstoffatmosphäre gelagert.[238] Generell wurden Feststoffe an der Luft eingewogen, im Ölpumpenvakuum ($< 10^{-3}$ mbar) von Luft und Feuchtigkeit befreit und anschließend die Reaktionsapparatur mit Stickstoff rückbefüllt.

Reaktionen, die unter Schutzatmosphäre durchgeführt wurden, sind als solche gekennzeichnet.

7.2.2. *Durchführung von Parallelreaktionen*

Alle Reaktionen der Reihenversuche wurden in 20 mL Headspace−Vials für die Gaschromatographie durchgeführt und mit Aluminium−Bördelkappen mit Teflon−beschichteten Butylgummisepten verschlossen. Diese Bördelkappen waren zur Sicherheit mit Perforationen versehen, die bei einem Überdruck von mehr als 0.5 bar ausreißen und dadurch das Platzen der Gefäße verhindern. Die Reaktionsgefäße wurden zur Temperierung in 8 cm hohe zylindrische Aluminiumblöcke, die mit 7 cm tiefen Bohrungen und einer weiteren Bohrung zur Aufnahme eines Temperaturfühlers versehen waren, versenkt. Die Aluminiumblöcke entsprachen dem Durchmesser der Heizplatten von gängigen Labor-Magnetrührern. Speziell angefertigte Vakuumverteiler wurden zum gleichzeitigen Evakuieren und Rückfüllen der Reaktionsgefäße für den Anschluss an die Schlenk-Linie benutzt. Dazu wurden zehn vakuumfeste 3 mm breite Teflonschläuche an ein mit Bohrungen versehenes Stahlrohr angebracht, die jeweils mit Adaptern zur Aufnahme von Luer-Lock-Spritzennadeln verbunden waren. Die Vakuumverteiler konnten über einen Anschluss am Stahlrohr mit der Schlenk-Linie verbunden werden.

Zur Durchführung der Katalyse-Reihenversuche wurden die festen Reaktanden an der Luft in die Reaktionsgefäße eingewogen, 20 mm teflonbeschichtete Magnetrührkerne hinzugegeben und mit einer Septumkappe luftdicht verschlossen. Danach wurden die Gefäße in den Bohrungen des Aluminium-Blocks versenkt und über Kanülen, die durch die Septumkappen gestochen wurden, mit der Vakuumlinie verbunden. Zur Erzeugung einer Sauerstoffatmosphäre wurden alle Reaktionsgefäße gleichzeitig dreimal hintereinander evakuiert und mit Sauerstoff rückbefüllt. Mit Hilfe von Spritzen wurden flüssige Reagenzien und Lösungsmittel durch die Septen eingespritzt. Anschließend wurden alle Reaktionsgefäße von der Vakuumlinie getrennt und der Aluminiumblock auf Reaktionstemperatur erhitzt, wobei sich alle angegebenen Temperaturen auf die Temperaturen des Heizblocks beziehen, welche erfahrungsgemäß ±2°C von den Temperaturen in den Reaktionsgefäßen abweichen. Die Reaktionsgefäße wurden nun bei der entsprechenden Temperatur mit circa 600 Umdrehungen pro Minute gerührt. Nach dem Ablauf der Reaktionszeit und dem

Abkühlen der Gefäße wurde der interne Standard injiziert, worauf die Reaktionsgefäße geschüttelt und geöffnet wurden.

Zur GC-Analyse wurde 0.25 mL der Reaktionsmischungen mit Einwegpipetten in 10 mL Rollrandgefäße überführt, in die vorher 2 mL Ethylacetat und 2 mL destilliertes Wasser gegeben wurde. Die Phasen wurden mit der Einwegpipette gut durchmischt und eine Phasentrennung abgewartet. Jeweils die organische Phase wurde über 0.30 mL wasserfreiem Magnesiumsulfat in ein 2 mL GC-Probenglas filtriert. Dabei wurden Einwegpipetten als Filter verwendet, die mit einem Wattepfropfen versehen waren. Der Responsefaktor in Bezug auf den internen Standard wurde experimentell durch eine bekannte Menge des Produktes bestimmt.

Zur Bestimmung der Ausbeute mittels ^{19}F-NMR wurden 2 mL Ethylacetat in die Reaktionsgefäße hinzugeben und 0.75 mL der Reaktionsmischungen durch Einwegpipetten mit einem Wattepfropfen direkt in ein NMR-Röhrchen gefiltert. Anschließend wurde ein verschlossenes Glasröhrchen, das mit DMSO-d_6 befüllt war, in das NMR-Röhrchen gegeben und die Ausbeute der Reaktionen durch Integration des Produktes im Vergleich zum internen Standard ermittelt.

Durch die neu entwickelten Versuchsapparaturen war es möglich, Reihenversuche in einem Bruchteil der Zeit, die bei der Verwendung von Standardtechniken erforderlich gewesen wäre, durchzuführen. Nur durch die Anwendung dieser Parallelisierungstechniken und durch die Verwendung eines elektronischen Laborjournals[239] war es möglich, die für die Entwicklung der neuen Methoden benötigte Zahl an Experimenten innerhalb kurzer Zeit durchzuführen und rechnergestützt auszuwerten.

7.2.3. *Analytische Methoden*

7.2.3.1. *Dünnschichtchromatographie*

Zur Durchführung der Dünnschichtchromatographie wurden Kieselgel DC–Folien *Polygram SIL G/UV254* der Firma *Macherey–Nagel* verwendet. Zur Detektion der Substanzen wurden Fluoreszenzlöschungen bei 254 nm oder Anfärbereagenzien wie KMnO$_4$-Lösung (3 g KMnO$_4$, 20 g K$_2$CO$_3$, 15 g NaOH, 300 mL Wasser) und schwefelsaures *p*-Anisaldehyd (10 mL *p*-Anisaldehyd, 10 mL konz. H$_2$SO$_4$, 200 mL EtOH) genutzt.

7.2.3.2.   Säulenchromatographische Methoden

Zur Isolierung der meisten Produkte wurde das *Combi Flash Companion-Chromatographie-System* der Firma *Isco-Systems* und gepackte Kieselgelsäulen (12, 24 oder 40 g) der Firma *GRACE* oder der Firma *TELOS* verwendet.

7.2.3.3.   Gaschromatographie

Zur gaschromatographischen Analyse wurde ein *Hewlett Packard 6890* Chromatograph verwendet. Die Trennung gelang mit einer HP-5-Säule mit 5 % Phenyl-Methyl-Siloxan (30 m × 320 μm × 0.25 μm) der Firma *Agilent*. Als Trägergas diente Stickstoff mit einer Flussrate von 44 mL·min^{-1}. Die Injektortemperatur betrug 220°C. Zur Analyse der Proben wurde ein Temperaturprogramm mit einer Starttemperatur von 60°C (2 min) und einem linearen Temperaturanstieg auf 300°C (30°C·min^{-1}) als Endtemperatur (3 min) verwendet.

7.2.3.4.   Massenspektrometrie (GC-MS)

Die Massenspektren wurden mit einem *GC-MS Saturn 2100T* der Firma *Varian* oder an einem *GC–MS 5973N* System der Firma *Agilent* durchgeführt. Die angegebenen Intensitäten beziehen sich auf das Verhältnis zum intensivsten Peak. Für Fragmente mit einer Isotopenverteilung ist jeweils nur der intensivste Peak eines Isotopomers aufgeführt.

7.2.3.5.   Hochauflösende Massenspektrometrie (HRMS)

Die hochauflösenden Massenspektren wurden in der Analytikabteilung im Fachbereich Chemie mit einem *GCT Premier* der Firma *Waters* gemessen.

7.2.3.6.   Infrarotspektroskopie

Zur Messung der Infrarotspektren wurde ein Fourier-Transform-Infrarotspektrometer (FT-IR) der Firma *Perkin Elmer,* mit einem *Universal ATR Accessory* (UATR) verwendet. Alle Messungen erfolgten gegen Luft als Hintergrund in einem Bereich von 4000 bis 400 cm^{-1}.

7.2.3.7. Kernresonanzspektroskopie

^{1}H-NMR, breitband-entkoppelte ^{13}C-NMR und ^{19}F-NMR Messungen wurden bei Raumtemperatur an dem *FT-NMR DPX 400* der Firma *Bruker* aufgenommen. Dabei wurden Chloroform-d$_1$, DMSO-d$_6$ und Methanol−d$_4$ als Lösungsmittel und Wasserstoff−, Kohlenstoff−, Fluorresonanzen von 400 MHz, 101 MHz bzw. 376 MHz verwendet. Die chemischen Verschiebungen der Signale sind in Einheiten der δ-Skala angegeben [ppm]. Als interner Standard dienten die Resonanzsignale der Restprotonen in den ^{1}H-Spektren bzw. die entsprechenden Resonanzsignale bei ^{13}C-Spektren.[240] Die Multiplizität der Signale wird durch folgende Abkürzungen wiedergegeben: s = Singulett, d = Dublett, dd = Dublett eines Dubletts, dt = Dublett eines Tripletts, t = Triplett, q = Quartett, m = Multiplett, usw. Die Kopplungskonstanten *J* sind in Hertz [Hz] angegeben. Mit *ACD-Labs 12.0* (Advanced Chemistry Development Inc.) wurden die Rohdaten eingelesen und ausgewertet.

7.2.3.8. Polarimetrie

Zur Messung des Drehwertes α wurde ein *Jasco P-2000* Polarimeter verwendet. Die Messungen erfolgten gegen Chloroform als Hintergrund, welches als Lösungsmittel verwendet wurde.

7.2.3.9. Schmelzpunktbestimmung

Alle Schmelzpunkte wurden mit einem *Mettler FP61* bestimmt.

7.3. One-Pot Sandmeyer-Trifluoromethylation and Trifluoromethylthiolation

7.3.1. *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 375 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.

7.3.2. *Synthesis of Benzotrifluorides from the corresponding Aromatic Amines*
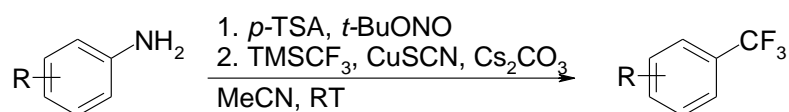
Standard procedure: An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with amine (1.00 mmol), *p*-toluenesulfonic acid (258 mg, 1.50 mmol) and acetonitrile (2 mL) under nitrogen. *t*-butyl nitrite (133 µL, 1.00 mmol) was added dropwise *via* syringe. The resulting solution 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 (SiO$_2$, pentane/diethyl ether gradient), yielding the corresponding benzotrifluorides.

7.3.2.1. Synthesis of 1-methoxy-4-(trifluoromethyl)benzene (2)
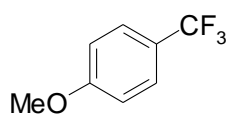
[CAS: 402-52-8]

Compound **2** was prepared following the standard procedure, starting from 4-methoxyaniline (123 mg, 1.00 mmol). After purification, **2** was isolated as colorless oil (150 mg, 0.85 mmol, 85%).

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

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. *t*-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 oil (1.14 g, 6.48 mmol, 81%).

¹H NMR (400 MHz, CDCl₃): 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); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −61.5 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 162.1, 126.8 (q, ^3J(C,F) = 3.7 Hz, 2C), 124.4 (q, ^1J(C,F) = 271.4 Hz), 122.9 (q, ^2J(C,F) = 33.0 Hz), 113.9 (2C), 55.2 ppm; **IR** (ATR): ν = 2963, 1616, 1521, 1328, 1260, 1161, 1110, 836, 600 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 176 [M^+] (68), 157 (100), 146 (75), 145 (77), 113 (89), 83 (43), 63 (67); **HRMS** (EI-TOF) calcd for C₈H₇F₃O: 176.0449; found: 176.0448.

7.3.2.2.   *Synthesis of 1-methoxy-2-(trifluoromethyl)benzene (3)*
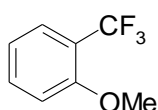
[CAS: 395-48-2]

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 ¹⁹F NMR spectroscopic analysis and confirmed by GC-MS analytics.

¹⁹F NMR (375 MHz, DMSO-d_6): δ = −62.8 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 176 [M^+] (9), 175 (100), 156 (8), 132 (8), 126 (8), 113 (9), 112 (10).

7.3.2.3.   *Synthesis of 1-methyl-2-(trifluoromethyl)benzene (4)*
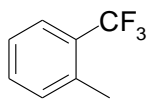
[CAS: 401-79-6]

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 ¹⁹F NMR spectroscopic analysis and confirmed by GC-MS analytics.

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¹⁹F NMR (375 MHz, DMSO-d_6): δ = −62.0 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 160 [M^+] (8), 159 (100), 140 (13), 139 (10), 108 (9), 91 (12), 64 (8).

7.3.2.4. Synthesis of 1-methyl-3-(trifluoromethyl)benzene (5)
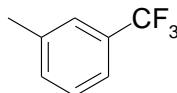
[CAS: 5140-17-6]

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 ¹⁹F NMR spectroscopic analysis and confirmed by GC-MS analytics.

¹⁹F NMR (375 MHz, DMSO-d_6): δ = −63.1 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 160 [M^+] (46), 91 (100), 69 (17), 65 (16), 44 (14), 43 (23), 40 (18).

7.3.2.5. Synthesis of 1-methyl-4-(trifluoromethyl)benzene (6)
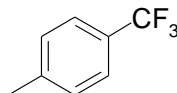
[CAS: 6140-17-6]

Compound **6** 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 **6** was formed in 98% yield as determined by ¹⁹F NMR spectroscopic analysis and confirmed by GC-MS analytics.

¹⁹F NMR (375 MHz, DMSO-d_6): δ = −62.8 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 160 [M^+] (81), 159 (10), 141 (12), 109 (9), 91 (100), 69 (8), 65 (10).

7.3.2.6. Synthesis of 4-(trifluoromethyl)biphenyl (7)
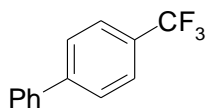
[CAS: 398-36-7]

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%).

m.p.: 69–70°C; **^{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, ^2J(C,F) = 32.7 Hz), 129.0 (2C), 128.2, 127.5 (2C), 127.3 (2C), 125.7 (q, ^3J(C,F) = 3.7 Hz, 2C), 124.5 ppm (q, ^1J(C,F) = 272.4 Hz); **IR** (ATR): ν = 1614 (w), 1327 (m), 1273 (m), 1112 (vs), 1073 (s), 843 (s), 767 (s), 727 (vs), 689 cm^{-1} (s); **MS** (Ion trap, EI, 70 eV): m/z (%) = 223 [M^+] (14), 222 (100), 203 (5), 153 (9), 152 (11), 69 (5), 50 (6); **HRMS** (EI-TOF) calcd for C$_{13}$H$_9$F$_3$: 222.0656; found: 222.0657.

7.3.2.7. Synthesis of 1-chloro-4-(trifluoromethyl)benzene (8)
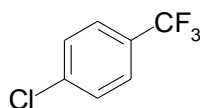
[CAS: 98-56-6]

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; **MS** (Ion trap, EI, 70 eV): m/z (%) = 182 [M^+] (32), 180 [M^+] (100), 161 (33), 145 (41), 130 (23), 75 (23), 50 (20).

7.3.2.8. Synthesis of 1-iodo-4-(trifluoromethyl)benzene (9)
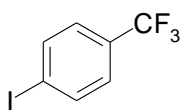
[CAS: 455-13-0]

Compound **9** was prepared following the standard procedure, starting from 4-iodoaniline (221 mg, 1.00 mmol). After chromatography, **9** was obtained as colorless oil (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, ^3J(H,H) = 8.03 Hz, 2H), 7.36 ppm (d, ^3J(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, ^2J(C,F) = 33.1 Hz, 1 C), 126.9 (q, ^3J(C,F) = 3.8 Hz, 2 C), 123.8 (q, ^1J(C,F) = 272.5 Hz, 1 C), 98.6 ppm (q, J(C,F) = 2.2 Hz); **IR** (ATR): ν = 2958, 1579, 1483, 1229, 1160, 1011, 822 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 272 [M^+] (7), 271 (100), 252 (3), 145 (2), 144 (7), 143 (3), 75 (3); **HRMS** (EI-TOF) calcd for C$_7$H$_4$F$_3$I: 271.9310; found: 271.9303.

7.3.2.9. Synthesis of 4-(trifluoromethyl)benzonitrile (10)
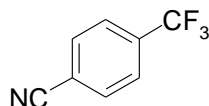
[CAS: 455-18-5]

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%).

m.p.: 38–39°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.82 (d, ^3J(H,H) = 8.3 Hz, 2H), 7.77 ppm (d, ^3J(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, ^2J(C,F) = 33.3 Hz), 132.7 (2C), 126.1 (q, ^3J(C,F) = 3.6 Hz, 2C), 123.2 (q, ^1J(C,F) = 272.5 Hz), 117.4, 116.0 ppm (q, J(C,F) = 1.8 Hz); **IR** (ATR): ν = 3108, 2235, 1623, 1412, 1321, 1175, 1069, 846 cm^{-1}; **MS** (Ion trap, EI,

70 eV): m/z (%) = 171 $[M^+]$ (9), 170 (100), 152 (23), 121 (32), 75 (11), 69 (10), 50 (13); **HRMS** (EI-TOF) calcd for $C_8H_4F_3N$: 171.0296; found: 171.0299.

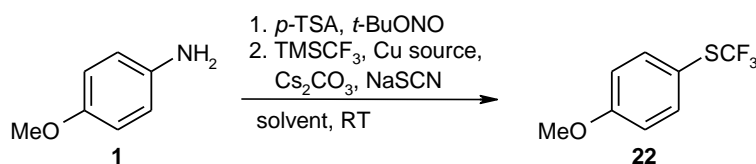### 7.3.2.10. *Synthesis of 3-(trifluoromethyl)acetophenone (11)*
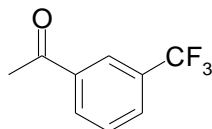
[CAS: 349-76-8]

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 oil (139 mg, 0.74 mmol, 74%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.22 (s, 1H), 8.15 (d, ^3J(H,H) = 8.0 Hz, 1H), 7.84 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.63 (t, ^3J(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), 129.5 (q, ^3J(C,F) = 3.3 Hz), 129.3, 125.1 (q, ^3J(C,F) = 3.6 Hz), 123.8 (q, ^1J(C,F) = 272.5 Hz), 26.6 ppm; **IR** (ATR): ν = 2923, 1694, 1607, 1563, 1333, 1245, 1127, 1071, 805 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 188 $[M^+]$ (9), 173 (33), 169 (24), 145 (100), 75 (21), 50 (22), 43 (38); **HRMS** (EI-TOF) calcd for $C_9H_7F_3O$: 188.0449; found: 188.0446.

7.3.2.11. *Synthesis of methyl 4-(trifluoromethyl)benzoate (12)*
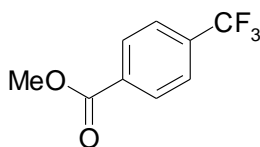
[CAS: 2967-66-0]

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 oil (169 mg, 0.83 mmol, 83%).

¹H NMR (400 MHz, CDCl₃): 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); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −63.1 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 165.9, 134.4 (q, ^2J(C,F) = 32.3 Hz), 133.3, 130.0 (2C), 125.4 (q, ^3J(C,F) = 3.7 Hz, 2C), 123.6 (q, ^1J(C,F) = 272.9 Hz), 52.5 ppm; **IR** (ATR): ν = 2956, 1740, 1435, 1314, 1142, 1054, 769 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 204 [M^+] (11), 203 (11), 185 (17), 174 (9), 173 (100), 145 (32), 75 (7); **HRMS** (EI-TOF) calcd for C₉H₇F₃O₂: 204.0398; found: 204.0395.

7.3.2.12. Synthesis of N-4[-(trifluoromethyl)phenyl]acetamide (13)
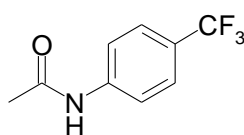
[CAS: 349-97-3]

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%).

m.p.: 150–151°C; **¹H NMR** (400 MHz, CDCl₃): 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); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −62.1 ppm; **¹³C NMR** (101 MHz, CDCl₃): 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), 119.3 (2C), 24.6 ppm; **IR** (ATR): ν = 3319, 1673, 1602, 1529, 1408, 1317, 1111, 1068, 833, 677 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 203 [M^+] (9), 202 (62), 183 (9), 160 (100), 110 (15), 44 (10), 43 (33); **HRMS** (EI-TOF) calcd for C₉H₈F₃NO: 203.0558; found: 203.0557.

7.3.2.13. Synthesis of N,N-dimethyl-4-(trifluoromethyl)aniline (14)
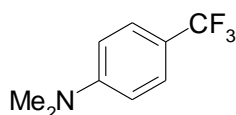
[CAS: 329-17-9]

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%).

m.p.: 69–70°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.49 (d, ^3J(H,H) = 8.6 Hz, 2H), 6.72 (d, ^3J(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, ^3J(C,F) = 3.6 Hz, 2C), 125.1 (q, ^1J(C,F) = 270.3 Hz), 117.4 (q, ^2J(C,F) = 32.7 Hz), 111.1 (2C), 40.1 ppm (2C); **IR** (ATR): ν = 1615, 1535, 1324, 1232, 1195, 1156, 1094, 1064, 940, 816 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 189 [M^+] (43), 188 (100), 172 (11), 170 (7), 145 (8), 119 (8), 118 (10); **HRMS** (EI-TOF) calcd for C$_9$H$_{10}$F$_3$N: 189.0765; found: 189.0753.

7.3.2.14. *Synthesis of phenyl[2-(trifluoromethyl)phenyl]methanone (15)*
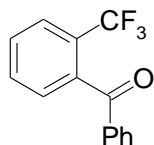
[CAS: 727-99-1]

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%).

m.p.: 60–61°C; **^{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, ^3J(C,F) = 1.8 Hz), 136.3 (q, ^4J(C,F) = 1.3 Hz), 133.8, 131.4, 130.2 (2 C), 130.1, 129.8, 128.5 (2 C), 128.4 (q, ^2J(C,F) = 33.1 Hz), 126.7 (q, ^3J(C,F) = 4.5 Hz), 123.7 ppm (q, ^1J(C,F) = 273.4 Hz); **IR** (ATR): ν = 3010, 1600, 1429, 1329, 1162, 1081, 814 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 250 [M^+] (18), 249 (100), 145 (31), 105 (17), 77 (86), 51 (37), 50 (30); **HRMS** (EI-TOF) calcd for C$_{14}$H$_9$F$_3$O: 250.0605; found: 250.0617.

7.3.2.15. Synthesis of 3-(trifluoromethyl)quinoline (16)
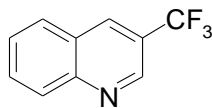
[CAS: 25199-76-2]

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%).

m.p.: 42–43°C; **^{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, ^{3}J(C,F) = 3.6 Hz), 134.0 (q, ^{3}J(C,F) = 4.5 Hz), 131.8, 129.6, 128.6, 128.0, 126.2, 123.2 (q, ^{1}J(C,F) = 273.4 Hz), 123.6 ppm (q, ^{2}J(C,F) = 32.7 Hz); **IR** (ATR): ν = 1739, 1601, 1575, 1466, 1337, 1297, 1260, 1195, 1144, 1106, 1062, 1032, 901, 840, 800, 671 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 198 [M^+] (15), 197 (100), 178 (13), 177 (11), 176 (11), 147 (12), 128 (14); **HRMS** (EI-TOF) calcd for C$_{10}$H$_6$F$_3$N: 197.0452; found: 197.0452.

### 7.3.2.16. Synthesis of 6-(trifluoromethyl)quinoline (17)
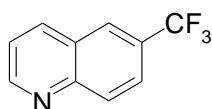
[CAS: 325-13-3]

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, ^{4}J(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), 127.2, 125.5 (q, ^3J(C,F) = 3.9 Hz), 125.2 (q, ^3J(C,F) = 2.2 Hz), 123.9 (q, ^1J(C,F) = 273.2 Hz), 122.2 ppm; **IR** (ATR): ν = 1466, 1429, 1337, 1144, 1123, 1106, 1062, 840 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 197 [M^+] (70), 196 (43), 178 (59), 147 (100), 128 (40), 75 (45), 50 (48); **HRMS** (EI-TOF) calcd for C$_{10}$H$_6$F$_3$N: 197.0452; found: 197.0446.

7.3.2.17. Synthesis of 8-(trifluoromethyl)quinoline (18)
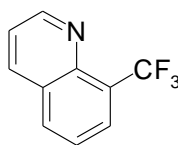
[CAS: 317-57-7]

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 to improve the solubility. After purification, **18** was isolated as colorless solid (97 mg, 0.49 mmol, 49%).

m.p.: 64−65°C; **^{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), 127.6 (q, ^2J(C,F) = 29.4 Hz), 125.2, 124.4 (q, ^1J(C,F) = 272.9 Hz), 121.9 ppm; **IR** (ATR): ν = 1331, 1294, 1205, 1141, 1117, 1067, 981, 831, 797, 767 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 197 [M^+] (100), 178 (23), 177 (21), 147 (41), 75 (13), 69 (15), 50 (14); **HRMS** (EI-TOF) calcd for C$_{10}$H$_6$F$_3$N: 197.0452; found: 197.0444.

7.3.2.18. Synthesis of 9-ethyl-3-(trifluoromethyl)-9H-carbazole (19)
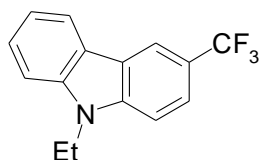
[CAS: 1638885-28-5]

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, ^3J(H,H) = 7.3 Hz, 2H), 1.46 ppm (t, ^3J(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, ^1J(C,F) = 270.7 Hz), 124.0, 122.5 (q, ^3J(C,F) = 3.6 Hz), 122.4 (q, ^3J(C,F) = 3.6 Hz), 120.9 (q, ^2J(C,F) = 31.8 Hz), 120.7, 119.7, 117.9 (q, ^3J(C,F) = 3.6 Hz), 108.9, 108.4, 37.7, 13.8 ppm; **IR** (ATR): ν = 3057, 2981, 1603, 1474, 1340, 1269, 1143, 1104, 1051, 904, 804, 748 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 263 [M^+] (38), 249 (15), 248 (100), 195 (57), 180 (45), 152 (9), 43 (12); **HRMS** (EI-TOF) calcd for C$_{15}$H$_{12}$F$_3$N: 263.0916; found: 263.0915.

7.3.2.19.   *Synthesis of methyl 3-(trifluoromethyl)thiophene-2-carboxylate (20)*
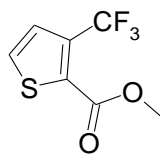
[CAS: 1638885-32-1]

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, ^3J(H,H) = 5.3, 1H), 7.32 (d, ^3J(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, ^2J(C,F) = 36.3 Hz), 133.2 (q, ^3J(C,F) = 2.7 Hz), 130.7, 127.7 (q, ^3J(C,F) = 3.8 Hz), 121.2 (q, ^1J(C,F) = 271.6 Hz), 52.6 ppm; **IR** (ATR): ν = 3021, 2956, 1734, 1545, 1440, 1398, 1294, 1216, 1153, 1156, 902 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 210 [M^+] (39), 191 (17), 179 (100), 178 (36), 176 (18), 175 (14), 151 (22); **HRMS** (EI-TOF) calcd for C$_7$H$_5$F$_3$O$_2$S: 209.9957; found: 209.9958.

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7.3.2.20. Synthesis of 2-(trifluoromethyl)-1,3-benzothiazole (21)
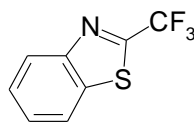
[CAS: 14468-40-7]

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, ^3J(H,H) = 8.5 Hz, 1H), 8.01–7.99 (d, ^3J(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, ^1J(C,F) = 272.5 Hz), 152.1, 135.0, 127.5, 127.4, 125.0, 122.0, 119.9 ppm (q, ^2J(C,F) = 29.5 Hz); **IR** (ATR): ν = 3068, 1796, 1706, 1625, 1598, 1492, 1439, 1103, 944, 850 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 203 [M^+] (100), 153 (25), 108 (18), 69 (38), 44 (19), 40 (33).

7.3.3. Optimization of the Trifluoromethylthiolation

Tabelle 3. Optimization of the reaction conditions.

Entry	Cu source	Cs$_2$CO$_3$ [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)$_4$BF$_4$	"	63

Reaction conditions: 0.75 mmol NaSCN, 0.50 mmol Cu source, Cs$_2$CO$_3$, 1 mL MeCN, 10 min, RT, 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, RT [a]Yields were determined by ^{19}F NMR using trifluoroethanol as internal standard. [b]0.25 mmol Cu source. [c]Addition of Cs$_2$CO$_3$ just before adding TMSCF$_3$.

7.3.4. Synthesis of Aryl Trifluoromethyl Thioethers from the corresponding Aromatic Amines
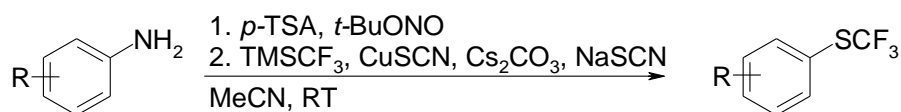
Standard procedure: An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with amine (1.00 mmol), *p*-toluenesulfonic acid (258 mg, 1.50 mmol) and acetonitrile (2 mL) under nitrogen. *t*-butyl nitrite (133 μL, 1.00 mmol) was added dropwise *via* syringe. The resulting solution 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.

7.3.4.1. Synthesis of 4-methoxy-1-[(trifluoromethyl)thio]benzene (22)
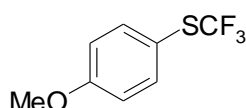
[CAS: 78914-94-0]

Compound **22** was prepared following the standard procedure, starting from 4-methoxyaniline (123 mg, 1.00 mmol). After purification, **22** was isolated as colorless oil (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** (375 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), 115.0 (2C), 114.8 (q,

^3J(C,F)=1.8 Hz), 55.4 ppm; **IR** (ATR): ν = 3011, 2969, 2946, 2910, 2842, 1593, 1495, 1252, 1104, 1085, 1029, 828 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 208 [M^+] (10), 207 (100), 138 (75), 123 (10), 95 (14), 69 (9), 68 (25); **HRMS** (EI-TOF) calcd for C$_8$H$_7$F$_3$OS: 208.0170; found: 208.0172.

7.3.4.2. *Synthesis of 4-[(trifluoromethyl)thio]benzonitrile (23)*
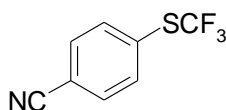
[CAS: 332-26-3]

Compound **23** was prepared following the standard procedure, starting from 4-cyanoaniline (118 mg, 1.00 mmol). After purification, **23** was isolated as colorless oil (134 mg, 0.66 mmol, 66%).

m.p.: 41–42°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.78 (d, ^3J(H,H)=8.6 Hz, 2H), 7.73 ppm (d, ^3J(H,H)=8.6 Hz, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.5 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ =136.0 (2C), 132.9 (2C), 130.5 (q, ^3J(C,F)=1.8 Hz), 129.1 (q, ^1J(C,F)=309.3 Hz), 117.6, 114.7 ppm; **IR** (ATR): ν = 2231, 1488, 1404, 1159, 1116, 1083, 1019, 834 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 203 [M^+] (15), 184 (15), 135 (9), 134 (100), 106 (12), 90 (23), 69 (43); **HRMS** (EI-TOF) calcd for C$_8$H$_4$F$_3$NS: 203.0017; found: 203.0019.

7.3.4.3. *Synthesis of methyl 4-[(trifluoromethyl)thio]benzoate (24)*
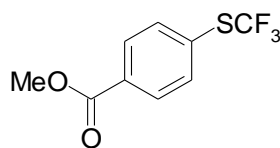
[CAS: 88489-60-5]

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 oil (116 mg, 0.49 mmol, 49%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.08 (d, ^3J(H,H)=8.6 Hz, 2H), 7.72 (d, ^3J(H,H)=8.5 Hz, 2H), 3.95 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.8 ppm; **^{13}C NMR** (101 MHz,

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CDCl$_3$): δ = 166.0, 135.5 (2C), 132.2, 130.4 (2C), 129.9 (q, ^3J(C,F)=1.8 Hz), 129.3 (q, ^1J(C,F)=307.9 Hz), 52.5 ppm; **IR** (ATR): ν = 3071, 3028, 3002, 2956, 2909, 1726, 1597, 1436, 1273, 1101, 1079, 1016, 964, 855, 762 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 235 [M^+] (91), 206 (9), 205 (100), 176 (7), 108 (11), 69 (18), 63 (7); **HRMS** (EI-TOF) calcd for C$_9$H$_7$F$_3$O$_2$S: 236.0119; found: 236.0116.

7.3.4.4.   *Synthesis of 1-iodo-4-[(trifluoromethyl)thio]benzene (25)*
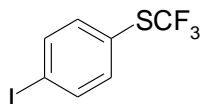
[CAS: 372-15-6]

Compound **25** was prepared following the standard procedure, starting from 4-iodoaniline (221 mg, 1.00 mmol). After chromatography, **25** was obtained as colorless oil (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** (375 MHz, CDCl$_3$): δ = −42.6 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 138.7 (2C), 137.7 (2C), 129.2 (q, ^1J(C,F)=308.7 Hz), 124.1 (q, ^3J(C,F)=1.8 Hz), 98.0 ppm; **IR** (ATR): ν = 3061, 3002, 2955, 2924, 2854, 1567, 1471, 1382, 1156, 1109, 1078, 1004, 995, 812, 755, 699 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 304 [M^+] (9), 303 (100), 235 (11), 127 (3), 108 (13), 82 (3), 69 (9); **HRMS** (EI-TOF) calcd for C$_7$H$_4$F$_3$IS: 303.9030; found: 303.9030.

7.3.4.5.   *Synthesis of 3-[(trifluoromethyl)thio]quinoline (26)*
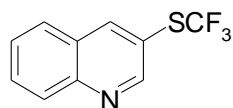
[CAS: 1333415-90-9]

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%).

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1H NMR (400 MHz, CDCl₃): δ = 9.07 (m, 1H), 8.54 (d, ^4J(H,H)=1.8 Hz, 1H), 8.17 (m, 1H), 7.85 (m, 2H), 7.65 ppm (m, 1H); **19F NMR** (375 MHz, CDCl₃): δ = −42.3 ppm; **13C NMR** (101 MHz, CDCl₃): δ = 154.5, 148.4, 144.7, 131.6, 129.6, 129.3 (q, ^1J(C,F)=308.8 Hz), 128.1, 127.8, 127.7, 118.3 ppm (q, ^3J(C,F)=1.8 Hz); **IR** (ATR): ν = 1489, 1158, 1132, 1116, 1106, 1070, 894, 836, 794, 754 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 229 [M^+] (100), 160 (37), 133 (9), 116 (7), 89 (20), 69 (11), 63 (6); **HRMS** (EI-TOF) calcd for C₁₀H₆F₃NS: 229.0173; found: 229.0172.

7.3.4.6. *Synthesis of 9-ethyl-3-[(trifluoromethyl)thio]-9H-carbazole (27)*
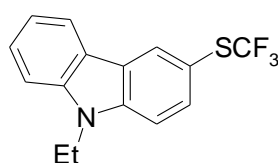
[CAS: 1639370-01-6]

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%).

1H NMR (400 MHz, CDCl₃): δ = 8.40 (d, ^4J(H,H)=1.8 Hz, 1H), 8.13 (d, ^3J(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, ^3J(H,H)=8.3 Hz, 1H), 7.43 (d, ^3J(H,H)=8.5 Hz, 1H), 7.31 (d, $^{3,4}J$(H,H)=7.5, 0.9 Hz, 1H), 4.40 (q, ^3J(H,H)=7.1 Hz, 2H), 1.47 ppm (t, ^3J(H,H)=7.1 Hz, 3H); **19F NMR** (375 MHz, CDCl₃): δ = −44.1 ppm; **13C NMR** (101 MHz, CDCl₃): δ = 141.1, 140.3, 133.7, 130.0 (q, ^1J(C,F)=309.3 Hz), 129.6, 126.6, 123.9, 122.2, 120.7, 119.8, 112.5 (q, ^3J(C,F)=1.8 Hz), 109.2, 108.9, 37.8, 13.8 ppm; **IR** (ATR): ν = 2975, 1475, 1449, 1234, 1134, 1124, 1108, 744, 722, 604 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 296 (6), 295 (100) [M^+], 226 (47); **HRMS** (EI-TOF) calcd for C₁₅H₁₂N₁F₃³²S: 295.0637; found: 295.0636.

7.4. Sandmeyer Difluoromethylation of (Hetero-)Arenediazonium Salts

7.4.1. *General Methods*

The reactions were performed in oven-dried glassware containing a Teflon-coated stirrer bar and septum under a nitrogen atmosphere. Dimethylformamide 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) 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 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.

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. All the anilines and solvents were purified by distillation or sublimation prior to use. CsF was dried for 24 h at 200°C in $1x10^{-3}$ mbar. The other chemicals were used without further purification.

7.4.2. *Synthesis of Starting Materials*

7.4.2.1. *Synthesis of arenediazonium tetrafluoroborates*
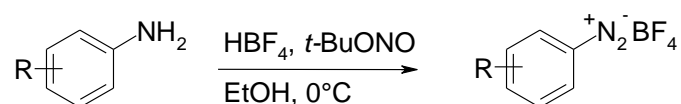
In a 50 mL round-bottom flask, the aniline (10 mmol) was dissolved in a mixture of absolute ethanol (3 mL) and an aqueous solution of HBF_4 (50%, 2.5 mL, 20 mmol) and *t*-

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 ($3 \times$ 10 mL). The arenediazonium tetrafluoroborate was dried in vacuo (10^{-3} mbar) for 10 minutes and was then directly used without further purification.

7.4.2.2. *Synthesis of difluoromethyltrimethylsilane[200]*

$$Me_3Si\text{—}CF_2H$$

[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 as colorless oil (15.6 mL, 97 mmol, 71%).

b.p.: 65-66°C; **^{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, ^1J(C,F) = 253.9 Hz), -5.5 (3C) ppm.

7.4.3. *Synthesis of Difluoromethylarenes from the corresponding Arenediazonium Salts*
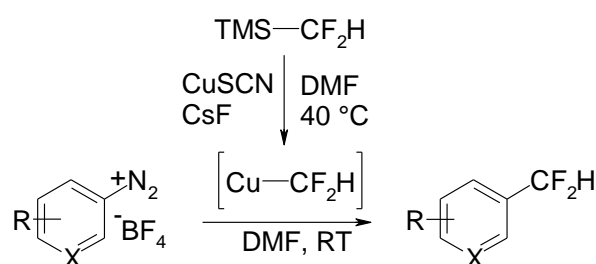
Standard procedure: An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with copper thiocyanate (122 mg, 1.00 mmol) and caesium fluoride (456 mg, 3.00 mmol) in DMF (2 mL) and difluoromethyltrimethylsilane (311 mg, 2.50 mmol) was added dropwise at 0°C. The resulting suspension was stirred at 40°C for 60 min and a solution of the arenediazonium tetrafluoroborate (1.00 mmol) in DMF (2 mL) was added dropwise via

syringe at 0°C. 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 (SiO_2, pentane/diethyl ether gradient), yielding the corresponding difluoromethylarenes.

### 7.4.3.1.   Synthesis of 1-(difluoromethyl)-4-methoxybenzene (2)
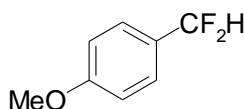
[CAS: 658-17-3]

Compound **2** was prepared following the standard procedure, starting from 4-methoxybenzenediazonium tetrafluoroborate (222 mg, 1.00 mmol). After purification, **2** was isolated as colorless oil (109 mg, 0.69 mmol, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, ^3J = 8.7 Hz, 2H), 6.96 (d, ^3J = 8.8 Hz, 2H), 6.61 (t, J = 56.8 Hz, 1H), 3.85 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): δ = −108.1 ppm (d, J = 57.1 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.2, 126.9 (t, ^3J(C,F) = 6.4 Hz, 2C), 126.7 (t, ^2J(C,F) = 22.7 Hz), 114.7 (t, ^1J(C,F) = 237.5 Hz), 113.8 (2C), 55.1 ppm; **IR** (ATR): ν = 2962, 2845, 1610, 1498, 1468, 1386, 1290, 1256, 1059, 1025, 755 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 158 [M^+] (100), 157 (46), 139 (23), 127 (15), 108 (16); **HRMS** (EI-TOF) calcd for $C_8H_8OF_2$: 158.0543; found: 158.0545.

7.4.3.2.   Synthesis of 1-(difluoromethyl)-2-methoxybenzene (3)
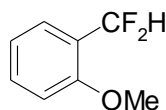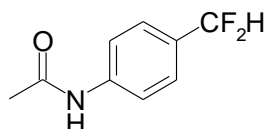

[CAS: 1366392-20-2]

Compound **3** was prepared following the standard procedure, starting from 2-methoxybenzenediazonium tetrafluoroborate (222 mg, 1.00 mmol). After purification, **3** was isolated as colorless oil (81 mg, 0.51 mmol, 51%).

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1H NMR (400 MHz, CDCl$_3$): δ = 7.58 (d, ^3J = 7.7 Hz, 1H), 7.44 (t, ^3J = 8.0 Hz, 1H), 7.04 (t, ^3J = 7.5 Hz, 1H), 6.97 (t, J = 55.7 Hz, 1H), 6.95 (d, ^3J = 8.6 Hz, 1H), 3.88 ppm (s, 3H); **19F NMR** (375 MHz, CDCl$_3$): δ = −115.4 ppm (d, J = 55.6 Hz); **13C NMR** (101 MHz, CDCl$_3$): δ = 157.2, 131.9, 126.2 (t, ^3J(C,F) = 6.0 Hz), 126.6 (t, ^2J(C,F) = 22.7 Hz), 120.5, 111.6 (t, ^1J(C,F) = 235.2 Hz), 110.8, 55.6 ppm; **IR** (ATR): ν = 2962, 2845, 1610, 1498, 1468, 1386, 1290, 1256, 1059, 1025, 755 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 159 [M^++H] (10), 158 (100), 143 (33), 139 (23), 127 (16), 109 (13); **HRMS** (EI-TOF) calcd for C$_8$H$_8$OF$_2$: 158.0543; found: 158.0539.

### 7.4.3.3.   Synthesis of 1-(difluoromethyl)-3-methoxybenzene (4)
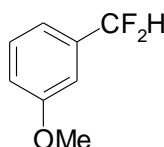
[CAS: 403648-71-5]

Compound **4** was prepared following the standard procedure, starting from 3-methoxybenzenediazonium tetrafluoroborate (222 mg, 1.00 mmol). After purification, **4** was isolated as colorless oil (100 mg, 0.63 mmol, 63%).

1H NMR (400 MHz, CDCl$_3$): δ = 7.38 (t, ^3J = 7.9 Hz, 1H), 7.10 (d, ^3J = 7.7 Hz, 1H), 7.05 (s, 1H), 7.03 (d, ^3J = 7.5 Hz, 1H), 6.63 (t, J = 56.4 Hz, 1H), 3.85 ppm (s, 3H); **19F NMR** (375 MHz, CDCl$_3$): δ = −110.6 ppm (d, J = 55.9 Hz); **13C NMR** (101 MHz, CDCl$_3$): δ = 159.8, 135.7 (t, ^2J(C,F) = 22.3 Hz), 129.9, 117.8 (t, ^3J = 6.6 Hz), 116.6 (t, ^3J(C,F) = 1.8 Hz), 114.6 (t, ^1J(C,F) = 238.8 Hz), 110.6 (t, ^3J = 5.9 Hz), 55.4 ppm; **IR** (ATR): ν = 2962, 2845, 1610, 1498, 1468, 1386, 1290, 1256, 1059, 1025, 755 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 158 [M^+] (100), 139 (13), 128 (12), 127 (45), 115 (12), 109 (11), 108 (11), 95 (34), 77 (11), 75 (11), 63 (10), 51 (11); **HRMS** (EI-TOF) calcd for C$_8$H$_7$OF$_2$: 157.0465; found: 157.0455.

7.4.3.4. Synthesis of 1-(difluoromethyl)-2-methylbenzene (5)
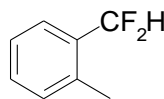
[CAS: 1222556-60-6]

Compound **5** was prepared following the standard procedure, starting from 2-methylbenzenediazonium tetrafluoroborate (103 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36 μL, 0.50 mmol) was added to the reaction mixture and the difluoromethylated product **5** was formed in 73% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}**F NMR** (375 MHz, DMSO-d_6): δ = −114.0 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 142 [M^+] (76), 123 (10), 122 (15), 91 (100), 65 (17), 51 (14), 50 (11).

7.4.3.5. Synthesis of 1-(difluoromethyl)-3-methylbenzene (6)
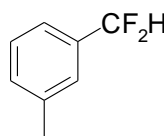
[CAS: 705-46-4]

Compound **6** was prepared following the standard procedure, starting from 3-methylbenzenediazonium tetrafluoroborate (103 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36 μL, 0.50 mmol) was added to the reaction mixture and the difluoromethylated product **6** was formed in 86% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}**F NMR** (375 MHz, DMSO-d_6): δ = −110.9 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 1412 [M^+] (69), 141 (12), 127 (17), 101 (9), 91 (100), 65 (17), 51 (14).

7.4.3.6. Synthesis of 1-(difluoromethyl)-4-methylbenzene (7)
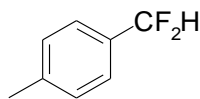
[CAS: 66865-75-6]

Compound **7** was prepared following the standard procedure, starting from 4-methylbenzenediazonium tetrafluoroborate (103 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36 µL, 0.50 mmol) was added to the reaction mixture and the difluoromethylated product **7** was formed in 81% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}**F NMR** (375 MHz, DMSO-d_6): δ = −110.6 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 142 [M^+] (51), 1401 (13), 127 (19), 91 (100), 65 (14), 51 (14), 50 (9).

7.4.3.7. Synthesis of 2-(difluoromethyl)-1,3,5-trimethylbenzene (8)
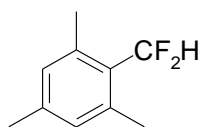
[CAS: 103383-72-8]

Compound **8** was prepared following the standard procedure, starting from 1,3,5-trimethylbenzenediazonium tetrafluoroborate (117 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36 µL, 0.50 mmol) was added to the reaction mixture and the difluoromethylated product **8** was formed in 38% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}**F NMR** (375 MHz, DMSO-d_6): δ = −111.9 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 170 [M^+] (100), 155 (17), 150 (15), 119 (85), 91 (18), 51 (12).

7.4.3.8. Synthesis of 1-(difluoromethyl)naphthalene (9)
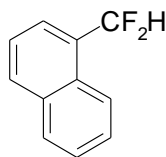

[CAS: 53731-26-3]

Compound **9** was prepared following the standard procedure, starting from α-naphthyldiazonium tetrafluoroborate (121 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36 µL, 0.50 mmol) was added to the reaction mixture and the difluoromethylated product **9** was formed in 51% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}**F NMR** (375 MHz, DMSO-d_6): δ = −111.7 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 178 [M^+] (100), 177 (85), 128 (73).

7.4.3.9. Synthesis of 4-(difluoromethyl)-1,1'-biphenyl (10)
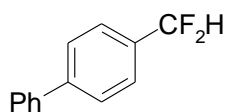
[CAS: 139219-68-4]

Compound **10** was prepared following the standard procedure, starting from [1,1'-biphenyl]-4-diazonium tetrafluoroborate (267 mg, 1.00 mmol). After purification, **10** was isolated as white solid (165 mg, 0.81 mmol, 81%).

m.p.: 69-70°C; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 7.70 (m, 2H), 7.61 (m, 4H), 7.48 (m, 2H), 7.41 (m, 1H), 6.72 ppm (t, J = 56.2 Hz, 1H); ^{19}**F NMR** (375 MHz, CDCl$_3$): δ = −110.3 ppm (d, J = 57.2 Hz); ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 143.7, 140.2, 133.2 (t, ^2J(C,F) = 22.7 Hz), 128.9 (2C), 127.9 (2C), 127.4 (2C), 127.2 (2C), 126.0 (t, ^3J(C,F) = 5.8 Hz), 114.7 ppm (t, ^1J(C,F) = 238.4 Hz); **IR** (ATR): ν = 3060, 3037, 2966, 1614, 1487, 1412, 1376, 1315, 1223, 1199, 1072, 1021, 1006, 838, 764, 738, 691 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 204 [M^+] (100), 203 (28); **HRMS** (EI-TOF) calcd for C$_{13}$H$_9$F$_2$: 203.0672; found: 203.0667.

7.4.3.10. Synthesis of 1-chloro-4-(difluoromethyl)benzene (11)
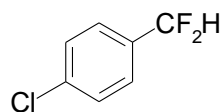
[CAS: 43141-66-8]

Compound **11** was prepared following the standard procedure, starting from 4-chlorobenzenediazonium tetrafluoroborate (118 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36 µL, 0.50 mmol) was added to the reaction mixture and the difluoromethylated product **11** was formed in 61% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (375 MHz, DMSO-d_6): $\delta = -111.2$ ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 164 [M^+] (20), 162 (59), 161 (25), 127 (100), 75 (18), 51 (21), 50 (22).

7.4.3.11. Synthesis of 1-(difluoromethyl)-4-(trifluoromethyl)benzene (12)
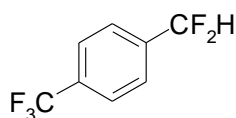
[CAS: 2251-82-3]

Compound **12** was prepared following the standard procedure, starting from 4-(trifluoromethyl)benzenediazonium tetrafluoroborate (130 mg, 0.50 mmol). After the reaction, trifluoroethanol as internal standard (36 µL, 0.50 mmol) was added to the reaction mixture and the difluoromethylated product **12** was formed in 74% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (375 MHz, DMSO-d_6): $\delta = -113.1$ ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 196 [M^+] (100), 195 (18), 177 (31), 145 (18), 127 (94), 51 (15), 50 (13).

7.4.3.12.   Synthesis of 4-(difluoromethyl)benzonitrile (13)
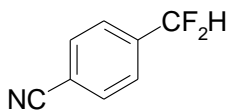
[CAS: 55805-10-2]

Compound **13** was prepared following the standard procedure, starting from 4-cyanobenzenediazonium tetrafluoroborate (217 mg, 1.00 mmol). After purification, **13** was isolated as colorless oil (103 mg, 0.67 mmol, 67%).

^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.78$ (d, ^3J(H,H) = 7.9 Hz, 2H), 7.65 (d, ^3J(H,H) = 8.0 Hz, 2H), 6.70 ppm (t, $J = 55.8$ Hz, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): $\delta = -113.2$ (d, $J = 55.9$ Hz) ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): $\delta = 138.5$ (t, ^2J(C,F) = 22.7 Hz), 132.6 (2C), 126.4 (t, ^3J(C,F) = 6.4 Hz, 2C), 117.9, 114.8, 113.3 ppm (t, ^1J(C,F) = 240.7 Hz); **IR** (ATR): $\nu = 2962, 2845, 1610, 1498, 1468, 1386, 1290, 1256, 1059, 1025, 755$ cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 154 [M^++H] (14), 153 (88), 152 (100), 134 (17), 103 (59), 102 (13), 76 (18), 75 (18), 51 (21), 50 (18); **HRMS** (EI-TOF) calcd for C$_8$H$_5$NF$_2$: 153.0390; found: 153.0384.

### 7.4.3.13.   Synthesis of 1-(difluoromethyl)-4-nitrobenzene (14)
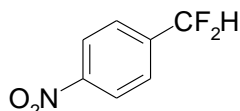
[CAS: 29848-57-5]

Compound **14** was prepared following the standard procedure, starting from 4-nitrobenzenediazonium tetrafluoroborate (237 mg, 1.00 mmol). After purification, **14** was isolated as light yellow oil (144 mg, 0.83 mmol, 83%).

^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.34$ (d, ^3J(H,H) = 8.9 Hz, 2H), 7.73 (d, ^3J(H,H) = 8.3 Hz, 2H), 6.75 ppm (t, $J = 55.8$ Hz, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): $\delta = -112.9$ ppm (d, $J = 55.9$ Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): $\delta = 149.3, 140.2$ (t, ^2J(C,F) = 22.7 Hz), 126.8 (t, ^3J(C,F) = 5.9 Hz, 2C), 124.0 (2C), 113.0 ppm (t,

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[^1J(C,F) = 240.9 Hz); **IR** (ATR): ν = 3096, 2970, 1533, 1484, 1349, 1219, 1100, 1031, 940, 901, 808, 740, 707 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 174 [M^++H] (17), 173 (100), 157 (31), 154 (15), 143 (30), 127 (68), 115 (25), 107 (33), 101 (34), 95 (10), 77 (29), 75 (10), 57 (10), 51 (15), 50 (16), 46 (12); **HRMS** (EI-TOF) calcd for $C_7H_4NO_2F_2$: 172.0210; found: 172.0207.

7.4.3.14. Synthesis of N,N-dimethyl-4-(difluoromethyl)aniline (15)
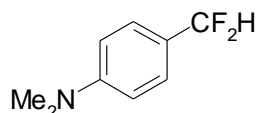
[CAS: 705-39-5]

Compound **15** was prepared following the standard procedure, starting from 4-(dimethylamino)benzenediazonium tetrafluoroborate (235 mg, 1.00 mmol). After the aqueous workup and evaporation of the solvent, the resulting suspension was taken up in pentane and filtered. After evaporation of the pentane the crude mixture was purified by kugelrohr distillation and **15** was isolated as red solid (144 mg, 0.84 mmol, 84%).

m.p.: 57-58°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.38 (d, ^3J(H,H) = 8.8 Hz, 2H), 6.74 (d, ^3J(H,H) = 8.8 Hz, 2H), 6.58 (t, J = 57.1 Hz, 1H), 3.01 ppm (s, 6H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −106.6 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 151.9, 126.7 (t, ^3J(C,F) = 5.5 Hz, 2C), 121.7 (t, ^2J(C,F) = 22.7 Hz), 111.7 (t, ^1J(C,F) = 236.2 Hz), 111.6 (2C), 40.2 ppm (2C); **IR** (ATR): ν = 2911, 2820, 1660, 1591, 1529, 1363, 1310, 1230, 1163, 1050, 987, 936, 813, 726 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 172 [M^++H] (18), 171 (61), 170 (100), 118 (11); **HRMS** (EI-TOF) calcd for $C_9H_{10}F_2N$: 170.0781; found: 170.0774.

7.4.3.15. Synthesis of methyl 4-(difluoromethyl)acetanilide (16)

[CAS: 29848-60-0]

Compound **17** was prepared following the standard procedure, starting from 4-acetamidobenzenediazonium tetrafluoroborate (249 mg, 1.00 mmol). After column chromatography, **16** and the protodediazotated compound were separated by precipitation of **16** from pentane and chloroform as colorless solid (141 mg, 0.76 mmol, 76%).

m.p.: 149-150°C; **^{1}H NMR** (400 MHz, MeOD-d$_4$): δ = 7.67 (d, ^3J(H,H) = 8.6 Hz, 2H), 7.46 (d, ^3J(H,H) = 8.5 Hz, 2H), 6.69 (t, J = 56.6 Hz, 1H), 2.13 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −109.7 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, MeOD-d$_4$): δ = 172.0, 142.4, 131.6 (t, ^2J(C,F) = 22.7 Hz, 2C), 127.5 (t, ^3J(C,F) = 6.4 Hz, 2C), 120.9 (2C), 116.4 (t, ^1J(C,F) = 236.2 Hz), 24.1 ppm; **IR** (ATR): ν = 3267, 3203, 3137, 3083, 2972, 2872, 1670, 1609, 1545, 1520, 1413, 1374, 1324, 1270, 1219, 1065, 1014, 845, 807, 759 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 186 [M^++H] (29), 185 (100), 143 (90), 142 (45), 124 (14), 93 (27), 43 (25); **HRMS** (EI-TOF) calcd for C$_9$H$_9$NOF$_2$: 185.0652; found: 185.0647.

7.4.3.16. Synthesis of methyl 4-(difluoromethyl)benzoate (17)
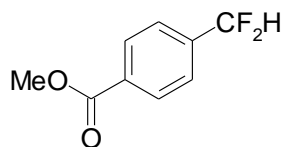
[CAS: 444915-76-8]

Compound **17** was prepared following the standard procedure, starting from 4-(methoxycarbonyl)benzenediazonium tetrafluoroborate (222 mg, 1.00 mmol). After purification, **17** was isolated as colorless solid (134 mg, 0.72 mmol, 72%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.13 (d, ^3J(H,H) = 8.4 Hz, 2H), 7.60 (d, ^3J(H,H) = 8.2 Hz, 2H), 6.70 (t, J = 56.1 Hz, 1H), 3.95 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −113.3 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 166.2, 138.4 (t, ^2J(C,F) = 21.8 Hz), 132.3, 130.0 (2C), 125.6 (t, ^3J(C,F) = 5.8 Hz, 2C), 114.0 (t, ^1J(C,F) = 239.8 Hz), 52.4 ppm; **IR** (ATR): ν = 3011, 2959, 2854, 1721, 1582, 1440, 1371, 1279, 1216, 1112, 1072, 1014, 958, 850, 770 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 186 [M^+] (12), 155 (100), 127 (33); **HRMS** (EI-TOF) calcd for C$_9$H$_8$O$_2$F$_2$: 186.0492; found: 186.0484.

7.4.3.17. Synthesis of (4-(difluoromethyl)phenyl)(phenyl)methanone (18)
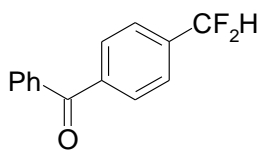
[CAS: 64747-73-5]

Compound **18** was prepared following the standard procedure, starting from 4-benzoylbenzenediazonium tetrafluoroborate (296 mg, 1.00 mmol). After purification, **18** was isolated as yellow oil (164 mg, 0.71 mmol, 71%).

**^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.89 (d, ^3J(H,H) = 8.4 Hz, 2H), 7.82–7.80 (m, 2H), 7.66–7.63 (m, 3H), 7.53–7.49 (m, 2H), 6.74 ppm (t, J = 56.2 Hz, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −112.0 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 195.9, 139.7, 137.8 (t, ^2J(C,F) = 22.4 Hz), 137.0, 132.9 (2C), 130.2 (2C), 130.1 (2C), 128.4 (2C), 125.6 (t, ^3J(C,F) = 5.9 Hz), 114.0 ppm (t, ^1J(C,F) = 239.8 Hz); **IR** (ATR): ν = 3063, 2971, 1649, 1597, 1418, 1369, 1309, 1278, 1217, 1122, 1070, 1016, 974, 939, 922, 841, 791, 748, 693, 658 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 233 [M^++H] (20), 232 (65), 181 (17), 155 (46), 127 (24), 105 (100), 77 (36), 51 (23), 50 (14); **HRMS** (EI-TOF) calcd for C$_{14}$H$_{10}$OF$_2$: 232.0700; found: 232.0701.

### 7.4.3.18. Synthesis of (2-(difluoromethyl)phenyl)(phenyl)methanone (19)
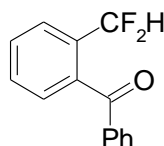
[CAS: 1188475-55-9]

Compound **19** was prepared following the standard procedure, starting from 2-benzoylbenzenediazonium tetrafluoroborate (296 mg, 1.00 mmol). After purification, **19** was isolated as yellow oil (100 mg, 0.43 mmol, 43%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.84–7.81 (m, 3H), 7.65–7.62 (m, 2H), 7.49–7.47 (m, 4H), 7.07 ppm (t, J = 55.8 Hz, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −112.3 ppm (d,

$J = 55.5$ Hz); **¹³C NMR** (101 MHz, CDCl₃): δ = 196.6, 137.3 (t, ^3J(C,F) = 5.1 Hz), 137.0, 134.0 (t, ^2J(C,F) = 22.3 Hz), 133.6, 131.0, 130.3 (2C), 129.7, 129.4, 128.5 (2C), 126.2 (t, ^3J(C,F) = 7.0 Hz), 112.3 ppm (t, ^1J(C,F) = 238.4 Hz); **IR** (ATR): ν = 3063, 2970, 1649, 1597, 1418, 1368, 1309, 1277, 1216, 1122, 1070, 1016, 974, 939, 922, 842, 791, 748, 693, 658 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 233 [M^++H] (100), 231 (10), 213 (41), 212 (80), 211 (18), 155 (46), 127 (24), 107 (12), 105 (95), 77 (12), 51 (10); **HRMS** (EI-TOF) calcd for C₁₄H₁₀OF₂: 232.0700; found: 232.0711.

7.4.3.19. *Synthesis of 1-(difluoromethyl)-3-nitrobenzene (20)*
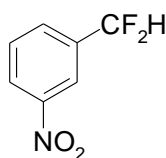
[CAS: 403-25-8]

Compound **20** was prepared following the standard procedure, starting from 3-nitrobenzenediazonium tetrafluoroborate (237 mg, 1.00 mmol). After purification, **20** was isolated as light yellow oil (114 mg, 0.66 mmol, 66%).

¹H NMR (400 MHz, CDCl₃): δ = 8.41 (s, 1H), 8.37 (m, 1H), 7.88 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.70 (t, ^3J(H,H) = 8.0 Hz, 1H), 6.76 ppm (t, $J = 55.9$ Hz, 1H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −112.1 ppm (d, $J = 55.9$ Hz); **¹³C NMR** (101 MHz, CDCl₃): δ = 148.3, 136.1 (t, ^2J(C,F) = 23.6 Hz), 131.5 (t, ^3J(C,F) = 5.5 Hz), 130.1, 125.6, 121.0 (t, ^3J(C,F) = 6.4 Hz), 113.1 ppm (t, ^1J(C,F) = 241.1 Hz); **IR** (ATR): ν = 3096, 2970, 1533, 1484, 1349, 1219, 1100, 1031, 940, 901, 808, 740, 707 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 173 [M^+] (100), 157 (14), 154 (21), 143 (39), 127 (78), 115 (11), 107 (29), 101 (32), 95 (13), 77 (30), 75 (13), 63 (10), 57 (14), 51 (21), 50 (22), 46 (15); **HRMS** (EI-TOF) calcd for C₇H₅NO₂F₂: 173.0288; found: 173.0281.

7.4.3.20. Synthesis of 2-(3-(difluoromethyl)phenyl)-1,1-difluoropropan-2-ol (21)
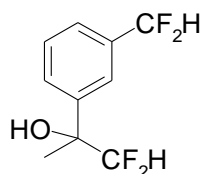
[CAS: 1637371-43-7]

Compound **21** was prepared following the standard procedure, starting from 3-acetylbenzenediazonium tetrafluoroborate (234 mg, 1.00 mmol). After purification, **21** was isolated as colorless oil (75 mg, 0.34 mmol, 34%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.70 (s, 1H), 7.65-7.63 (m, 1H), 7.51-7.49 (m, 2H), 6.68 (t, J = 56.3 Hz, 1H), 5.72 (t, J = 56.3 Hz, 1H), 1.69 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −110.7 ppm (d, J = 55.9 Hz), −129.9 ppm (qd, ^1J = 277.9 Hz, ^2J = 55.9 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 141.0, 134.6 (t, ^2J(C,F) = 22.4 Hz), 128.9, 128.2, 125.3 (t, ^3J(C,F) = 6.2 Hz), 123.1 (t, ^3J(C,F) = 6.2 Hz), 116.6 (t, ^1J(C,F) = 249.4 Hz), 114.6 (t, ^1J(C,F) = 238.6 Hz), 74.1 (t, ^2J(C,F) = 22.0 Hz), 22.5 ppm (t, ^3J(C,F) = 2.2 Hz); **IR** (ATR): ν = 3441, 2989, 1448, 1372, 1167, 1053, 805, 705 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 171 [M^++H] (100), 43 (61); **HRMS** (EI-TOF) calcd for C$_{10}$H$_9$OF$_4$: 221.0590; found: 221.0588.

7.4.3.21. Synthesis of 1-(6-(difluoromethyl)benzo[d][1,3]dioxol-5-yl)ethanone (22)
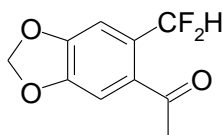
[CAS: 1637371-44-8]

Compound **22** was prepared following the standard procedure, starting from 6-acetylbenzo[d][1,3]dioxole-5-diazonium tetrafluoroborate (278 mg, 1.00 mmol). After purification, **22** was isolated as light yellow solid (88 mg, 0.41 mmol, 41%).

m.p.: 70-71°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.33 (t, J = 55.6 Hz, 1H), 7.29 (s, 1H), 7.28 (s, 1H), 6.12 (s, 2H), 2.58 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −111.2 ppm

(d, $J = 55.9$ Hz); ^{13}**C NMR** (101 MHz, CDCl$_3$): $\delta = 198.2$, 150.9, 148.9, 131.0, 130.5, 111.6 (t, ^1J(C,F) = 237.8 Hz), 109.7, 106.8 (t, ^3J(C,F) = 8.8 Hz), 102.5, 28.8 ppm; **IR** (ATR): $\nu = 2916$, 1683, 1617, 1509, 1493, 1392, 1363, 1266, 1241, 1116, 1068, 1036, 882 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 214 [M^+] (71), 159 (100), 171 (23), 115 (13), 63 (13); **HRMS** (EI-TOF) calcd for C$_{10}$H$_8$O$_3$F$_2$: 214.0442; found: 214.0440.

7.4.3.22.   *Synthesis of 6-(difluoromethyl)quinoline (23)*
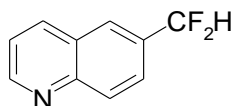
[CAS: 1416806-01-3]

Compound **23** was prepared following the standard procedure, starting from quinoline-6-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **23** was isolated as light yellow oil (86 mg, 0.48 mmol, 48%).

^{1}**H NMR** (400 MHz, CDCl$_3$): $\delta = 9.00$ (s, 1H), 8.22 (t, ^3J(H,H) = 9.2 Hz, 2H), 8.00 (s, 1H), 7.84 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.51-7.47 (m, 1H), 6.84 ppm (t, $J = 56.2$ Hz, 1H); ^{19}**F NMR** (375 MHz, CDCl$_3$): $\delta = -111.4$ ppm (d, $J = 55.9$ Hz); ^{13}**C NMR** (101 MHz, CDCl$_3$): $\delta = 151.8$, 148.9, 136.6, 132.4 (t, ^2J(C,F) = 22.3 Hz), 130.5, 127.5, 125.8 (t, ^3J(C,F) = 5.5 Hz), 125.7, 121.9, 114.4 ppm (t, ^1J(C,F) = 239.4 Hz); **IR** (ATR): $\nu = 2989$, 2870, 1635, 1599, 1506, 1472, 1398, 1353, 1321, 1168, 1121, 1085, 1070, 1028, 895, 841, 794 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 180 [M^++H] (17), 179 (100), 178 (31), 129 (36), 51 (11); **HRMS** (EI-TOF) calcd for C$_{10}$H$_7$NF$_2$: 179.0547; found: 179.0539.

7.4.3.23.   *Synthesis of 3-(difluoromethyl)quinoline (24)*
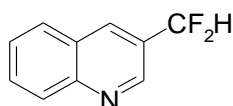
[CAS: 1186195-11-8]

Compound **24** was prepared following the standard procedure, starting from quinoline-3-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **24** was isolated as yellow oil (97 mg, 0.54 mmol, 54%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.05 (s, 1H), 8.34 (s, 1H), 8.19 (d, ^3J(H,H) = 8.4 Hz, 1H), 7.92 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.86–7.82 (m, 1H), 7.67–7.63 ppm (m, 1H), 6.91 ppm (t, J = 55.8 Hz, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −111.6 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 148.9, 147.1 (t, ^3J(C,F) = 5.5 Hz), 134.0 (t, ^3J(C,F) = 6.4 Hz), 131.1, 129.4, 128.4, 127.7, 127.2, 126.9, 113.6 ppm (t, ^1J(C,F) = 239.4 Hz); **IR** (ATR): ν = 2989, 2870, 1635, 1599, 1506, 1471, 1398, 1353, 1321, 1168, 1121, 1085, 1069, 1028, 895, 841, 794 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 180 [M^++H] (64), 179 (100), 178 (24), 129 (27), 101 (10), 51 (10); **HRMS** (EI-TOF) calcd for C$_{10}$H$_7$NF$_2$: 179.0547; found: 179.0537.

7.4.3.24. *Synthesis of 9-ethyl-3-(difluoromethyl)-9H-carbazole (25)*
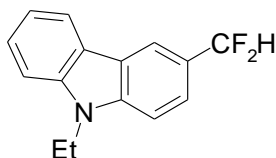
[CAS: 1637371-45-9]

Compound **25** was prepared following the standard procedure, starting from 9-ethyl-9*H*-carbazol-3- diazonium tetrafluoroborate (309 mg, 1.00 mmol). After purification, **25** was isolated as yellow oil (191 mg, 0.78 mmol, 78%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.27 (s, 1H), 8.14 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.62 (d, ^3J(H,H) = 8.5 Hz, 1H), 7.53 (m, 1H), 7.46 (m, 2H), 7.30 (m, 1H), 6.87 (t, J = 57.0 Hz, 1H), 4.40 (q, ^3J(H,H) = 7.3 Hz, 2H), 1.46 ppm (t, ^3J(H,H) = 7.3 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −106.7 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 141.0, 140.4, 126.3, 125.0 (t, ^2J(C,F) = 22.3 Hz), 122.9 (t, ^3J(C,F) = 5.5 Hz), 122.7 (t, ^3J(C,F) = 3.6 Hz), 120.6, 119.4, 118.2, 118.2, 115.9 (t, ^1J(C,F) = 237.1 Hz), 108.8, 108.6, 37.7, 13.8 ppm; **IR** (ATR): ν = 2976, 2873, 1603, 1472, 1373, 1348, 1334, 1232, 1189, 1126, 1058, 1003, 890, 808, 770, 749, 730, 719 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 246 [M^++H] (14), 245 (79), 231 (15), 230 (100); **HRMS** (EI-TOF) calcd for C$_{15}$H$_{13}$NF$_2$: 245.1016; found: 245.1017.

7.4.3.25. Synthesis of 1-bromo-4-(difluoromethyl)naphthalene (26)
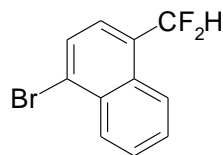
[CAS: 1261672-09-6]

Compound **26** was prepared following the standard procedure, starting from 4-bromonaphthalen-1-yldiazonium tetrafluoroborate (321 mg, 1.00 mmol). After purification, **26** was isolated as orange oil (144 mg, 0.56 mmol, 56%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.36 (m, 1H), 8.17 (m, 1H), 7.85 (d, ^3J(H,H) = 7.7 Hz, 1H), 7.68 (m, 2H), 7.56 (d, ^3J(H,H) = 7.7 Hz, 1H), 7.13 ppm (t, J = 56.2 Hz, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −112.2 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 132.2, 130.8 (t, ^3J(C,F) = 1.4 Hz), 129.4 (t, ^2J(C,F) = 21.4 Hz), 128.9, 128.1, 128.0, 127.8, 126.7, 124.9 (t, ^3J(C,F) = 9.1 Hz), 123.9, 114.7 ppm (t, ^1J(C,F) = 238.9 Hz); **IR** (ATR): ν = 2962, 2845, 1610, 1498, 1468, 1386, 1290, 1256, 1059, 1025, 755 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 233 [M^++H] (100), 231 (10), 213 (41), 212 (80), 211 (18), 155 (46), 127 (24), 107 (12), 105 (95), 77 (12), 51 (10); **HRMS** (EI-TOF) calcd for C$_{11}$H$_7$F$_2$Br: 255.9699; found: 255.9710.

### 7.4.3.26. Synthesis of 5-(difluoromethyl)-1H-indole (27)
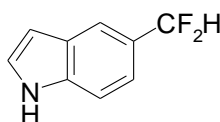
[CAS: 1547144-47-7]

Compound **27** was prepared following the standard procedure, starting from 1H-indole-5-diazonium tetrafluoroborate (231 mg, 1.00 mmol). After purification, **27** was isolated as colorless oil (59 mg, 0.35 mmol, 35%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.32 (s, 1H), 7.81 (s, 1H), 7.48 (d, ^3J(H,H) = 8.4 Hz, 1H), 7.37 (d, ^3J(H,H) = 8.4 Hz, 1H), 7.30 (t, ^3J(H,H) = 2.8 Hz, 1H), 6.77 (t, J = 56.9 Hz, 1H),

6.64 ppm (m, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): $\delta = -105.9$ ppm (d, $J = 57.2$ Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): $\delta = 136.8$, 127.4, 126.2 (t, $^2J(C,F) = 22.0$ Hz), 125.4, 119.1 (t, $^3J(C,F) = 5.1$ Hz), 118.8 (t, $^3J(C,F) = 6.9$ Hz), 116.1 (t, $^1J(C,F) = 237.0$ Hz), 111.4, 103.3 ppm; **IR** (ATR): $\nu = 3416$, 2971, 1382, 1325, 1230, 1217, 1076, 1001, 901, 820, 772, 741 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 168 [M^+] (12), 167 (100), 166 (77), 148 (30), 119 (10), 117 (30), 89 (17), 63 (15), 51 (13), 50 (12); **HRMS** (EI-TOF) calcd for C$_9$H$_7$NF$_2$: 167.0547; found: 167.0551.

7.4.3.27.   *Synthesis of 3-(2,2-difluoroethyl)-2,3-dihydrobenzofuran (29)*
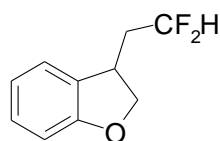
[CAS: 1565823-37-1]

Compound **29** was prepared following the standard procedure, starting from 2-(allyloxy)benzenediazonium salt (248 mg, 1.00 mmol). After purification, **29** was isolated as colorless oil (138 mg, 0.75 mmol, 75%).

^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.17$ (m, 2H), 6.90 (t, $^3J(H,H) = 7.4$ Hz, 1H), 6.84 (d, $^3J(H,H) = 7.8$ Hz, 1H), 5.97 (tdd, $^3J = 56.1$, 4.6 and 3.6 Hz, 1H), 4.72 (t, $^3J(H,H) = 9.0$ Hz, 1H), 4.29 (dd, $^3J = 9.0$ and 6.9 Hz, 1H), 3.73 (m, 1H), 2.36 (m, 1H), 2.14 ppm (m, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): $\delta = -116.1$ ppm (qm, $J = 284.7$ Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): $\delta = 159.7$, 128.8 (2C), 124.1, 120.7, 116.0 (t, $^1J(C,F) = 239.5$ Hz), 109.9, 76.6, 38.7 (t, $^2J(C,F) = 20.5$ Hz), 36.1 ppm (t, $^3J(C,F) = 4.8$ Hz); **IR** (ATR): $\nu = 2978$, 2893, 1598, 1482, 1461, 1234, 1122, 1075, 1017, 961, 844, 748 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 185 [$M^+ + H$] (11), 184 (88), 119 (100), 91 (43); **HRMS** (EI-TOF) calcd for C$_{10}$H$_9$OF$_2$: 183.0621; found: 183.0612.

7.4.3.28. *One-pot procedure*
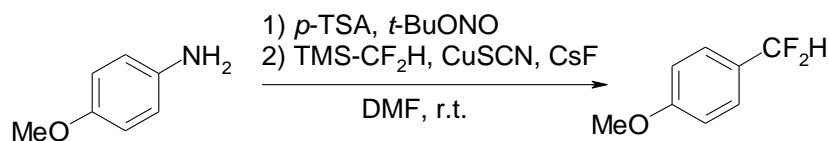
An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with 4-methoxyaniline (62 mg, 0.50 mmol), *p*-toluenesulfonic acid (129 mg, 0.75 mmol) and DMF (1 mL) under nitrogen. *t*-butyl nitrite (67 µL, 0.50 mmol) was added dropwise via syringe. The resulting solution was stirred at room temperature for 30 minutes. An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with copper thiocyanate (61 mg, 0.50 mmol) and caesium fluoride (228 mg, 1.50 mmol) in DMF (1 mL) and difluoromethyltrimethylsilane (156 mg, 1.25 mmol) was added dropwise at 0°C. The resulting suspension was stirred at 40°C for 60 min. Afterwards the solution of the generated diazonium salt was added dropwise via syringe at 0°C. The suspension was stirred at room temperature for 12 h.

7.5. Sandmeyer-Type Trifluoromethylthiolation and Trifluoro-methylselenolation of (Hetero)Aromatic Amines

7.5.1. *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, acetone-d_6 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.

7.5.2. *Synthesis of Starting Materials*

7.5.2.1. *Synthesis of arene diazonium tetrafluoroborates*
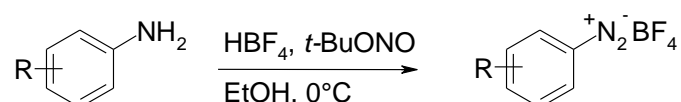
In a 50 mL round-bottom flask, the aniline (10 mmol) was dissolved in a mixture of absolute ethanol (3 mL) and an aqueous solution of HBF_4 (50%, 2.5 mL, 20 mmol) and *t*-butyl nitrite (2.7 mL, 20 mmol) was added dropwise to the solution at 0°C. The reaction was stirred at room temperature for 1 h and 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.

7.5.2.2.   Synthesis of Me$_4$NSCF$_3$[110]
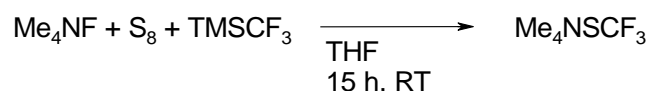
$$Me_4NF + S_8 + TMSCF_3 \xrightarrow[\substack{THF \\ 15\ h,\ RT}]{} Me_4NSCF_3$$

Elemental sulfur (1.80 g, 6.64 mmol) was dissolved in THF (300 mL) at room temperature. TMSCF$_3$ (10.1 mL, 63.7 mmol) was added and the reaction mixture was cooled to −60°C and afterwards Me$_4$NF (5.00 g, 53.1 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 Diethylether and Me$_4$NSCF$_3$ was isolated as colorless solid.

^{1}H NMR (400 MHz, CD$_3$CN): δ = 3.12 ppm (s, 12H); **^{19}F NMR** (375 MHz, CD$_3$CN): δ = −6.5 ppm; **^{13}C NMR** (101 MHz, CD$_3$CN): δ = 145.1 (q, ^1J(C,F) = 293.4 Hz), 56.0 ppm (4C).

7.5.2.3.   Synthesis of red selenium[213]

Grey selenium (3.40 g, 43.1 mmol) was added to conc. sulfuric acid (180 mL) and the reaction mixture was stirred at 180°C for 6 h. The solution was filtered onto ice (400 mL) and the resulting solution left to recrystallize at 4°C overnight. The mixture was then filtered and the obtained red solid was washed with cold water (3 x 50 mL) and acetone (3 x 50 mL). The resulting red powder was then dried in vacuo to yield Se$_8$.

7.5.2.4.   Synthesis of Me$_4$NSeCF$_3$[213]
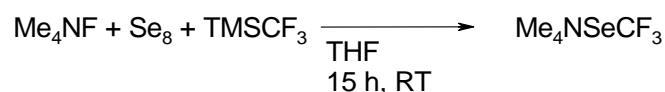
$$Me_4NF + Se_8 + TMSCF_3 \xrightarrow[\substack{THF \\ 15\ h,\ RT}]{} Me_4NSeCF_3$$

TMSCF$_3$ (1.72 mL, 10.8 mmol) was added to activated molecular sieves (100 g) in anhydrous 1,2-dimethoxyethane (200 mL). The reaction mixture was stirred at −60°C for 15 min before red Se$_8$ (711 mg, 1.13 mmol) was added and the reaction mixture stirred another 15 min. Then, Me$_4$NF (600 mg, 6.38 mmol) was added and stirred for 1 h at −58°C. The reaction mixture was allowed to warm room temperature and stirred for a further 24 h in darkness. The suspension was filtered through a plug of celite and the remaining black solid was washed with anhydrous 1,2-dimethoxyethane (2 x 20 mL). The residue was then

extracted with acetonitrile (3 x 50 mL). Then, the solvent was evaporated and the crude product was dissolved in acetonitrile (20 mL) and THF (200 mL) was added. The resulting solid was filtered, washed with THF and dried to yield Me_4NSeCF_3 as white solid.

^{1}H NMR (400 MHz, acetone-d_6): $\delta = 3.50$ ppm (s, 12H); **^{19}F NMR** (375 MHz, acetone-d_6): $\delta = -6.5$ ppm; **^{13}C NMR** (101 MHz, acetone-d_6): $\delta = 133.1$ (q, ^1J(C,F) = 323.3 Hz), 56.1 ppm (4C).

7.5.3. *Synthesis of Trifluoromethyl thioethers from the corresponding Arenediazonium Salts*
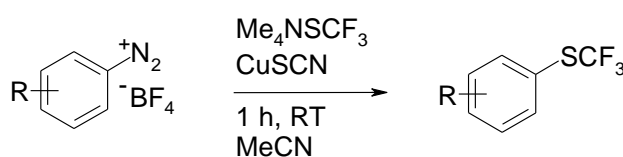
Standard procedure A: An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with CuSCN (12.0 mg, 0.10 mmol), Me_4NSCF_3 (315 mg, 1.80 mmol) and MeCN (2 mL). Then, the arenediazonium salt (1.00 mmol) in MeCN (2 mL) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. 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, pentane / diethyl ether gradient), yielding the aryl trifluoromethyl thioethers. The yields of particularly volatile compounds were determined by ^{19}F NMR, and their identity by mass spectroscopy.

7.5.3.1. *Synthesis of 1-methoxy-4-[(trifluoromethyl)thio]benzene (3a)*

[CAS: 78914-94-0]

Compound **3a** was prepared following the standard procedure, starting from 4-methoxybenzenediazonium tetrafluoroborate (222 mg, 1.00 mmol). After purification, **3a** was isolated as colorless oil (202 mg, 0.97 mmol, 97%).

¹H NMR (400 MHz, CDCl₃): δ = 7.59 (d, ^3J = 8.8 Hz, 2H), 6.95 (d, ^3J = 8.8 Hz, 2H), 3.85 ppm (s, 3H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −43.9 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 161.8, 138.3 (2C), 129.7 (q, ^1J(C,F) = 308.5 Hz), 115.0 (2C), 114.8 (q, ^3J(C,F) = 1.8 Hz), 55.4 ppm; **IR** (ATR): ν = 3011, 2969, 2946, 2910, 2842, 1593, 1495, 1252, 1104, 1085, 1029, 828 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 208 [M^+] (86), 139 (100); **HRMS** (EI-TOF) calcd. for C₈H₇F₃OS: 208.0170; found: 208.0171.

7.5.3.2.   Synthesis of 1-methoxy-2-[(trifluoromethyl)thio]benzene (3b)
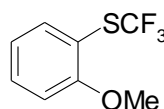
[CAS: 75168-99-9]

Compound **3b** was prepared following the standard procedure, starting from 2-methoxybenzenediazonium tetrafluoroborate (222 mg, 1.00 mmol). After purification, **3b** was isolated as colorless oil (200 mg, 0.96 mmol, 96%).

**¹H NMR** (400 MHz, CDCl₃): δ = 7.63 (m, 1H), 7.47 (m, 1H), 7.00 (m, 2H), 3.92 ppm (s, 3H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −42.4 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 160.5, 138.5, 132.9, 129.6 (q, ^1J(C,F) = 308.8 Hz), 121.2, 112.4 (q, ^3J(C,F) = 1.8 Hz), 111.7, 56.0 ppm; **IR** (ATR): ν = 3071, 3012, 2944, 1739, 1587, 1479, 1466, 1435, 1278, 1253, 1100, 1062, 1024, 799, 750 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 208 [M^+] (100), 111 (18); **HRMS** (EI-TOF) calcd. for C₈H₇F₃OS: 208.0170; found: 208.0170.

7.5.3.3.   Synthesis of 1-methoxy-3-[(trifluoromethyl)thio]benzene (3c)
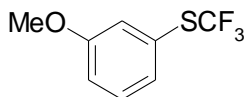
[CAS: 97675-15-5]

Compound **3c** was prepared following the standard procedure, starting from 3-methoxybenzenediazonium tetrafluoroborate (222 mg, 1.00 mmol). After purification, **3c** was isolated as colorless oil (175 mg, 0.84 mmol, 84%).

¹H NMR (400 MHz, CDCl₃): δ = 7.32 (t, ^3J = 8.0 Hz, 1H), 7.23 (d, ^3J = 7.8 Hz, 1H), 7.18 (s, 1H), 7.01 (dd, ^3J = 8.3, 1.8 Hz, 1H), 3.82 ppm(s, 3H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −42.6 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 159.9, 130.1, 129.6 (q, ^1J(C,F) = 307.9 Hz), 128.4, 125.2 (q, ^3J(C,F) = 1.8 Hz), 121.2, 116.8, 55.4 ppm; **IR** (ATR): ν = 3045, 2925, 2855, 1739, 1366, 1229, 1217, 1206, 1092 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 208 [M^+] (100), 139 (20); **HRMS** (EI-TOF) calcd. for C₈H₇F₃OS: 208.0170; found: 208.0152.

### 7.5.3.4. *Synthesis of 4-[(trifluoromethyl)thio]toluene (3d)*
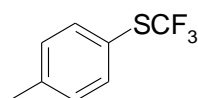
[CAS: 352-68-1]

Compound **3d** was prepared following the standard procedure, starting from 4-methylbenzenediazonium tetrafluoroborate (103 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 trifluoromethylthiolated product **3d** was formed in 91% yield as determined by ¹⁹F NMR spectroscopic analysis and confirmed by GC-MS analytics.

¹⁹F NMR (375 MHz, DMSO-d_6): δ = −45.8 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 192 [M^+] (100), 123 (66), 91 (26), 79 (17), 77 (20), 69 (28), 45 (26).

7.5.3.5. *Synthesis of 2-[(trifluoromethyl)thio]toluene (3e)*
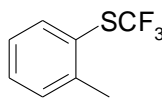
[CAS: 1736-75-0]

Compound **3e** was prepared following the standard procedure, starting from 2-methylbenzenediazonium tetrafluoroborate (103 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 trifluoromethylthiolated product **3e** was formed in 99% yield as determined by ¹⁹F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (375 MHz, DMSO-d_6): δ = −44.3 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 192 [M^+] (100), 123 (60), 91 (10), 77 (16), 69 (26), 51 (10), 45 (57).

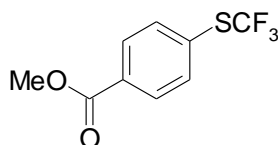### 7.5.3.6. *Synthesis of 3-[trifluoromethyl)thio]toluene (3f)*
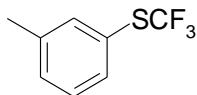
[CAS: 705-46-4]

Compound **3f** was prepared following the standard procedure, starting from 3-methylbenzenediazonium tetrafluoroborate (103 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 trifluoromethylthiolated product **3f** was formed in 82% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (375 MHz, DMSO-d_6): δ = −43.6 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 192 [M^+] (100), 123 (45), 91 (34), 79 (12), 77 (16), 69 (27), 45 (30).

7.5.3.7. *Synthesis of 4-[(trifluoromethyl)thio]biphenyl (3g)*
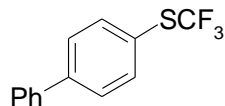
[CAS: 177551-63-2]

Compound **3g** was prepared following the standard procedure, starting from [1,1-biphenyl]-4-diazonium tetrafluoroborate (268 mg, 1.00 mmol). After purification, **3g** was isolated as colorless solid (239 mg, 0.94 mmol, 94%).

m.p.: 41-42°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.74 (d, ^3J = 8.3 Hz, 2H), 7.99-7.60 (m, 4H), 7.49 (t, ^3J = 7.4 Hz, 2H), 7.41 ppm (t, ^3J = 7.4 Hz, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −42.7 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 143.8, 139.7, 136.7 (2C), 129.6 (q, ^1J(C,F) = 307.9 Hz), 129.0 (2C), 128.1 (2C), 127.9, 127.2 (2C), 123.0 ppm (q, ^3J(C,F) = 1.8 Hz); **IR** (ATR): ν = 1477, 1395, 1123, 1105, 1080, 836, 759, 715, 689 cm^{-1};

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MS (Ion trap, EI, 70 eV): m/z (%) = 255 [M^+] (13), 254 (100), 186 (9), 185 (66), 184 (15), 152 (15), 69 (17); **HRMS** (EI-TOF) calcd. for $C_{13}H_9F_3S$: 254.0377; found: 254.0386.

### 7.5.3.8. Synthesis of 1-phenoxy-4-[(trifluoromethyl)thio]benzene (3h)
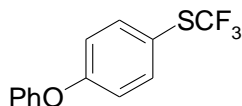
[CAS: 1333415-80-7]
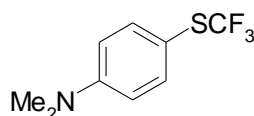
Compound **3h** was prepared following the standard procedure, starting from 4-phenoxybenzenediazonium tetrafluoroborate (284 mg, 1.00 mmol). After purification, **3h** was isolated as colorless oil (265 mg, 0.98 mmol, 98%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.61 (d, ^3J = 7.3 Hz, 2H), 7.41 (t, ^3J = 7.8 Hz, 2H), 7.21 (t, ^3J = 7.3 Hz, 1H), 7.08 (d, ^3J = 7.3 Hz, 2H), 7.01 ppm (d, ^3J = 8.3 Hz, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −43.5 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 160.6, 155.8, 138.5, 130.2 (2C), 129.7 (q, ^1J(C,F) = 308.1 Hz), 124.7 (2C), 120.2 (2C), 118.8 (2C), 117.4 ppm (q, ^3J(C,F) = 2.2 Hz); **IR** (ATR): ν = 307855, 1739, 1583, 1487, 1366, 1244, 1117, 870, 756 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 270 [M^+] (100), 204 (20); **HRMS** (EI-TOF) calcd. for $C_{13}H_9F_3OS$: 270.0326; found: 270.0330.

7.5.3.9. Synthesis of 1-fluoro-4-[(trifluoromethyl)thio]benzene (3i)
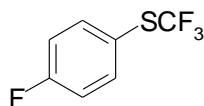
[CAS: 940-76-1]

Compound **3i** was prepared following the standard procedure, starting from 4-fluoro-diazonium 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 trifluoromethylthiolated product **3i** was formed in 55% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

¹⁹F NMR (375 MHz, DMSO-d_6): δ = −42.1 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 196 [M^+] (92), 177 (12), 128 (7), 127 (100), 83 (44), 69 (23), 57 (14).

7.5.3.10. Synthesis of 1-chloro-4-[(trifluoromethyl)thio]benzene (3j)
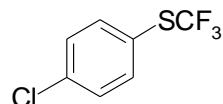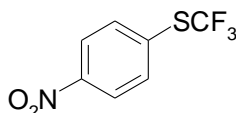

[CAS: 407-16-9]

Compound **3j** was prepared following the standard procedure, starting from 4-chlorobenzenediazonium tetrafluoroborate (113 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 trifluoromethylthiolated product **3j** was formed in 76% yield as determined by ¹⁹F NMR spectroscopic analysis and confirmed by GC-MS analytics.

¹⁹F NMR (375 MHz, DMSO-d_6): δ = −42.8 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 212 [M^+] (100), 145 (29), 143 (72), 108 (42), 69 (32), 50 (10).

### 7.5.3.11. Synthesis of 1-bromo-4-[(trifluoromethyl)thio]benzene (3k)
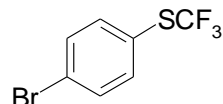
[CAS: 333-47-1]

Compound **3k** was prepared following the standard procedure, starting from 4-bromobenzenediazonium tetrafluoroborate (271 mg, 1.00 mmol). After purification, **3k** was isolated as colorless oil (193 mg, 0.75 mmol, 75%).

¹H NMR (400 MHz, CDCl₃): δ = 7.58 (d, ^3J = 8.5 Hz, 2H), 7.53 ppm (d, ^3J = 8.5 Hz, 2H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −42.8 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 137.7 (2C), 132.8 (2C), 129.2 (q, ^1J(C,F) = 308.1 Hz), 126.0, 123.5 ppm (q, ^3J(C,F) = 1.8 Hz); **IR** (ATR): ν = 3078, 3002, 2954, 2923, 1588, 1432, 1272, 1104, 1010, 954, 860, 826, 755, 687 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 257 [M^+] (100), 256 (99); **HRMS** (EI-TOF) calcd. for C₇H₄BrF₃S: 257.9149; found: 257.9139.

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7.5.3.12. Synthesis of 1-iodo-4-[(trifluoromethyl)thio]benzene (3l)
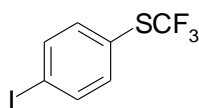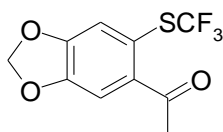

[CAS: 372-15-6]

Compound **3l** was prepared following the standard procedure, starting from 4-iodobenzenediazonium tetrafluoroborate (318 mg, 1.00 mmol). After purification, **3l** was isolated as colorless oil (283 mg, 0.93 mmol, 93%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.63 (d, ^3J = 8.3 Hz, 2H), 7.23 ppm (d, ^3J = 8.5 Hz, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −42.6 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ=138.7 (2C), 137.7 (2C), 129.1 (q, ^1J(C,F) = 308.8 Hz), 124.1 (q, ^3J(C,F) = 1.8 Hz), 98.0 ppm; **IR** (ATR): ν = 3061, 3002, 2955, 2924, 2854, 1567, 1471, 1382, 1156, 1109, 1078, 1004, 995, 812, 755, 699 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 304 [M^+] (9), 303 (100), 235 (11), 127 (3), 108 (13), 82 (3), 69 (9); **HRMS** (EI-TOF) calcd. for C$_7$H$_4$F$_3$IS: 303.9030; found. 303.9030.

7.5.3.13. Synthesis of 1-(methylthio)-4-[(trifluoromethyl)thio]benzene (3m)
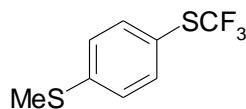
[CAS: 2262-08-0]

Compound **3m** was prepared following the standard procedure, starting from 4-(methylthio)benzenediazonium tetrafluoroborate (238 mg, 1.00 mmol). After purification, **3m** was isolated as colorless oil (215 mg, 0.96 mmol, 96%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.54 (d, ^3J = 8.5 Hz, 2H), 7.24 (d, ^3J = 8.5 Hz, 2H), 2.49 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −43.3 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 143.3, 136.6 (2C), 129.5 (q, ^1J(C,F) = 307.9 Hz), 126.3 (2C), 119.7 (q, ^3J(C,F) = 1.8 Hz), 14.9 ppm; **IR** (ATR): ν = 3021, 2967, 2925, 1738, 1577, 1479, 1438, 1114, 1089, 1011, 968, 812, 754 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 223 [M^+] (100), 155 (43); **HRMS** (EI-TOF) calcd. for C$_8$H$_7$F$_3$S$_2$: 223.9941; found: 223.9940.

### 7.5.3.14.   Synthesis of 4-[(trifluoromethyl)thio]acetophenone (3n)
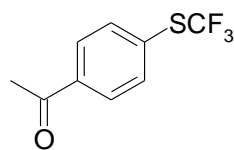
[CAS: 713-67-7]

Compound **3n** was prepared following the standard procedure, starting from 4-acetylbenzenediazonium tetrafluoroborate (234 mg, 1.00 mmol). After purification, **3n** was isolated as colorless oil (194 mg, 0.88 mmol, 88%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.99 (d, ^3J = 8.3 Hz, 2H), 7.75 (d, ^3J = 8.3 Hz, 2H), 2.63 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.8 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 197.1, 138.5, 135.7 (2C), 130.0 (q, ^3J(C,F) = 1.8 Hz), 129.2 (q, ^1J(C,F) = 308.3 Hz), 129.1 (2C), 26.7 ppm; **IR** (ATR): ν = 3065, 3006, 2958, 2918, 2850, 1736, 1689, 1593, 1397, 1359, 1260, 1114, 958, 828 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 220 [M^+] (10), 206 (10), 205 (100), 136 (8), 108 (10), 69 (13), 42 (11); **HRMS** (EI-TOF) calcd. for C$_9$H$_7$F$_3$OS: 220.0170; found: 220.0162.

7.5.3.15.   Synthesis of 4-[(trifluoromethyl)thio]benzophenone (3o)
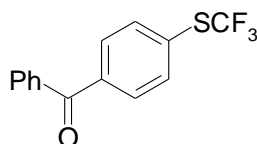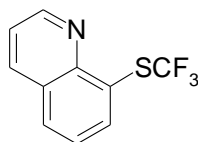

[CAS: 41830-99-3]

Compound **3o** was prepared following the standard procedure, starting from 4-benzoylbenzenediazonium tetrafluoroborate (296 mg, 1.00 mmol). After purification, **3o** was isolated as colorless solid (259 mg, 0.92 mmol, 92%).

m.p.: 44-45°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.85-7.76 (m, 6H), 7.63 (t, ^3J = 7.5 Hz, 1H), 7.51 ppm (t, ^3J = 7.5 Hz, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.8 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 195.6, 139.6, 136.9, 135.6 (2C), 133.1, 130.8 (2C), 130.2 (2C), 129.5 (q, ^1J(C,F) = 308.8 Hz), 129.2 (q, ^3J(C,F) = 1.8 Hz), 128.6 (2C) ppm; **IR** (ATR): ν = 1652,

1590, 1280, 1142, 1108, 1080, 924, 847, 792, 730, 696, 664 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 283 [M^+] (6), 281 (100), 204 (35), 108 (7), 77 (18), 68 (8), 50 (9); **HRMS** (EI-TOF) calcd. for C$_{14}$H$_9$F$_3$OS: 282.0326; found: 282.0338.

### 7.5.3.16. Synthesis of 4-[(trifluoromethyl)thio]benzoic acid (3p)
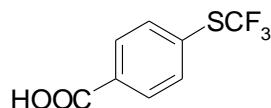
[CAS: 330-17-6]

Compound **3p** was prepared following the standard procedure, starting from 4-carboxybenzenediazonium tetrafluoroborate (236 mg, 1.00 mmol). After purification, **3p** was isolated as colorless solid (198 mg, 0.89 mmol, 89%).

m.p.: 159-160°C; **^{1}H NMR** (400 MHz, CD$_3$CN): δ = 8.07 (d, ^3J = 8.3 Hz, 2H), 7.79 ppm (d, ^3J = 8.0 Hz, 2H); **^{19}F NMR** (375 MHz, CD$_3$CN): δ = −43.0 ppm; **^{13}C NMR** (101 MHz, CD$_3$CN): δ = 167.0, 136.9 (2C), 133.6, 131.7 (2C), 130.7 (q, ^1J(C,F) = 307.0 Hz), 130.3 ppm (q, ^3J(C,F) = 1.8 Hz); **IR** (ATR): ν = 3457, 3018, 2971, 1739, 1366, 1217 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 222 [M^+] (100), 205 (45); **HRMS** (EI-TOF) calcd. for C$_8$H$_5$F$_3$O$_2$S: 221.9962; found: 221.9953.

7.5.3.17. Synthesis of methyl-4-[(trifluoromethyl)thio]benzoate (3q)

[CAS: 88489-60-5]

Compound **3q** was prepared following the standard procedure, starting from 4-(methoxycarbonyl)benzenediazonium tetrafluoroborate (250 mg, 1.00 mmol). After purification, **3q** was isolated as colorless oil (210 mg, 0.89 mmol, 89%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.08 (d, ^3J = 8.5 Hz, 2H), 7.72 (d, ^3J = 8.3 Hz, 2H), 3.94 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.9 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 166.2, 135.7 (2C), 132.3, 130.6 (2C), 130.0 (q, ^3J(C,F) = 1.8 Hz), 129.4 (q,

^1J(C,F) = 307.9 Hz), 52.6 ppm; **IR** (ATR): ν = 3071, 3028, 3002, 2956, 2909, 1726, 1597, 1436, 1273, 1101, 1079, 1016, 964, 855, 762 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 235 [M^+] (91), 206 (9), 205 (100), 176 (7), 108 (11), 69 (18), 63 (7); **HRMS** (EI-TOF) calcd. for C$_9$H$_7$F$_3$O$_2$S: 236.0119; found: 236.0116.

7.5.3.18. *Synthesis of 4-[(trifluoromethyl)thio]benzonitrile (3r)*
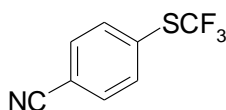
[CAS: 332-26-3]

Compound **3r** was prepared following the standard procedure, starting from 4-cyanobenzenediazonium tetrafluoroborate (217 mg, 1.00 mmol). After purification, **3r** was isolated as colorless oil (171mg, 0.84 mmol, 84%).

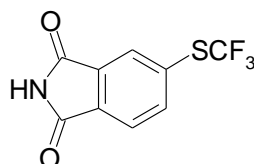**^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.78 (d, ^3J = 8.6 Hz, 2H), 7.73 ppm (d, ^3J = 8.6 Hz, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.5 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ =136.0 (2C), 132.9 (2C), 130.5 (q, ^3J(C,F) = 1.8 Hz), 129.1 (q, ^1J(C,F) = 309.3 Hz), 117.6, 114.7 ppm; **IR** (ATR): ν = 2231, 1488, 1404, 1159, 1116, 1083, 1019, 834 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 203 [M^+] (15), 184 (15), 135 (9), 134 (100), 106 (12), 90 (23), 69 (43); **HRMS** (EI-TOF) calcd. for C$_8$H$_4$F$_3$NS: 203.0017; found: 203.0019.

7.5.3.19. *Synthesis of N,N-dimethyl-4-[(trifluoromethyl)thio]aniline (3s)*

[CAS: 2677-71-6]

Compound **3s** was prepared following the standard procedure, starting from 4-(dimethylamino)benzenediazonium tetrafluoroborate (235 mg, 1.00 mmol). After purification, **3s** was isolated as colorless oil (212 mg, 0.96 mmol, 96%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.49 (d, ^3J = 9.0 Hz, 2H), 6.69 (d, ^3J = 9.0 Hz, 2H), 3.02 ppm (s, 6H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −44.7 ppm; **^{13}C NMR** (101 MHz,

CDCl$_3$): δ = 151.9, 137.9 (2C), 129.8 (q, ^1J(C,F) = 308.8 Hz), 112.3 (2C), 108.3 (q, ^3J(C,F) = 2.7 Hz), 40.1 (2C) ppm; **IR** (ATR): ν = 3003, 2999, 1608, 1490, 1306. 1094, 979, 820, 785 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 222 [M^+] (14), 221 (100), 220 (7), 152 (57), 151 (8), 108 (7), 69 (8); **HRMS** (EI-TOF) calcd. for C$_9$H$_{10}$F$_3$NS: 221.0486; found: 221.0488.

7.5.3.20.   Synthesis of 1-nitro-4-[(trifluoromethyl)thio]benzene (3t)

[CAS: 403-66-7]

Compound **3t** was prepared following the standard procedure, starting from 4-nitrobenzenediazonium tetrafluoroborate (237 mg, 1.00 mmol). After purification, **3t** was isolated as colorless oil (221 mg, 0.97 mmol, 97%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.29 (d, ^3J = 8.8 Hz, 2H), 7.84 ppm (d, ^3J = 8.8 Hz, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.3 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 149.1, 136.1 (2C), 132.5 (q, ^3J(C,F) = 1.8 Hz), 128.9 (q, ^1J(C,F) = 308.8 Hz), 124.4 (2C) ppm; **IR** (ATR): ν = = 3104, 2845, 2162, 1923, 1602, 1578, 1514, 1475, 1340, 1279, 1189, 1107, 1082, 1009, 956, 842, 736, 700, 674 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$_7$H$_4$F$_3$NO$_2$S: 222.9915; found: 222.9917.

### 7.5.3.21.   Synthesis of N-[4-[(trifluoromethyl)thio]phenyl]acetamide (3u)
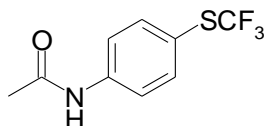
[CAS: 351-81-5]

Compound **3u** was prepared following the standard procedure, starting from 4-(acetylamino)benzenediazonium tetrafluoroborate (249 mg, 1.00 mmol). After purification, **3u** was isolated as colorless solid (200 mg, 0.85 mmol, 85%).

m.p.: 188-189°C; **¹H NMR** (400 MHz, CD$_3$OD): δ = 7.70 (d, ^3J = 8.8 Hz, 2H), 7.61 (d, ^3J = 8.8 Hz, 2H), 2.14 ppm (s, 3H); **¹⁹F NMR** (375 MHz, CD$_3$OD): δ = –45.4 ppm; **¹³C NMR** (101 MHz, CD$_3$OD): δ = 272.1, 143.2, 138.6 (2C), 131.3 (q, ^1J(C,F) = 308.8 Hz), 121.6 (2C), 119.1 (q, ^3J(C,F) = 1.8 Hz), 24.1 ppm; **IR** (ATR): ν = 3457, 3018, 2971, 1738, 1366, 1229, 1217 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 235 [M^+] (88), 124 (100); **HRMS** (EI-TOF) calcd. for C$_9$H$_8$F$_3$NOS: 235.0279; found: 235.0274.

7.5.3.22.   *Synthesis of 1-[6-[(trifluoromethyl)thio]-1,3-benzodioxol-5-yl]ethanone (3v)*

[CAS: 1620284-96-9]

Compound **3v** was prepared following the standard procedure, starting from 6-acetyl-1,3-benzodioxole-5-diazonium tetrafluoroborate (278 mg, 1.00 mmol). After purification, **3v** was isolated as colorless solid (246 mg, 0.93 mmol, 93%).

m.p.: 115°C; **¹H NMR** (400 MHz, CDCl$_3$): δ = 7.18 (s, 2H), 6.11 (s, 2H), 2.58 ppm (s, 3H); **¹⁹F NMR** (375 MHz, CDCl$_3$): δ = –42.2 ppm; **¹³C NMR** (101 MHz, CDCl$_3$): δ = 198.5, 150.6, 148.4, 135.8, 129.5 (q, ^1J(C,F) = 309.7 Hz), 120.7 (q, ^3J(C,F) = 2.3 Hz), 112.8, 109.3, 102.7, 29.2 ppm; **IR** (ATR): ν = 3015, 2970, 2947, 1739, 1658, 1366, 1217, 1112 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 264 [M^+] (40), 195 (100); **HRMS** (EI-TOF) calcd. for C$_{10}$H$_7$F$_3$O$_3$S: 264.0068; found: 264.0045.

7.5.3.23.   *Synthesis of 3-[(trifluoromethyl)thio]quinoline (3w)*
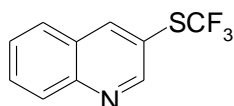
[CAS: 1333415-90-9]

Compound **3w** was prepared following the standard procedure, starting from quinoline-3-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **3w** was isolated as colorless oil (195 mg, 0.85 mmol, 85%).

¹H NMR (400 MHz, CDCl₃): δ = 9.03 (d, ^3J = 2.3 Hz, 1H), 8.50 (d, ^3J = 2.0 Hz, 1H), 8.15 (d, ^3J = 8.5 Hz, 1H), 7.85-7.80 (m, 2H), 7.64-7.60 ppm (m, 1H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −42.3 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 154.5, 148.3, 144.7, 131.6, 129.5, 129.1 (q, ^1J(C,F) = 308.8 Hz), 128.0, 127.7, 127.7, 118.2 ppm (q, ^3J(C,F) = 1.8 Hz); **IR** (ATR): ν = 1489, 1158, 1132, 1116, 1106, 1070, 894, 836, 794, 754 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 229 [M^+] (100), 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.

7.5.3.24. Synthesis of 6-[(trifluoromethyl)thio]quinoline (3x)
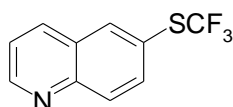
[CAS: 1639369-99-5]

Compound **3x** was prepared following the standard procedure, starting from quinoline-6-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **3x** was isolated as colorless oil (197 mg, 0.86 mmol, 86%).

¹H NMR (400 MHz, CDCl₃): δ = 9.01 (s, 1H), 8.18-8.13 (m, 3H), 7.59 (dd, ^3J = 8.8, 1.5 Hz, 1H), 7.51-7.45 ppm (m, 1H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −42.3 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 152.2, 148.6, 136.7, 136.2, 135.4, 130.9, 129.5 (q, ^1J(C,F) = 308.8 Hz), 128.3, 122.7 (q, ^3J(C,F) = 1.8 Hz) 122.1 ppm; **IR** (ATR): ν = 3045, 29251489, 1158, 1132, 1116, 1106, 1070, 894, 836, 794, 754 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 230 (5), 229 [M^+] (100), 160 (46); **HRMS** (EI-TOF) calcd. for $C_{10}H_6NF_3S$: 229.0168; found: 229.0165.

7.5.3.25. Synthesis of 8-[(trifluoromethyl)thio]quinoline (3y)

[CAS: 1639370-00-5]

Compound **3y** was prepared following the standard procedure, starting from quinoline-8-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **3y** was isolated as colorless oil (179 mg, 0.78 mmol, 78%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.03 (dd, ^3J = 4.0, 1.5 Hz, 1H), 8.21 (dd, ^3J = 8.3, 1.8 Hz, 1H), 8.09 (d, ^3J = 7.5 Hz, 1H), 7.89 (dd, ^3J = 8.3, 1.3 Hz, 1H), 7.59 (t, ^3J = 7.5 Hz, 1H), 7.50 ppm (dd, ^3J = 8.3, 4.3 Hz, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.1 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 150.7, 146.7, 136.6, 134.0, 129.9 (q, ^1J(C,F) = 308.8 Hz), 129.6, 128.8, 126.9 (q, ^3J(C,F) = 1.8 Hz), 126.6, 122.1 ppm; **IR** (ATR): ν = 1607, 1595, 1491, 1459, 1306, 1108, 980, 822, 788, 756 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 230 (5), 229 [M^+] (100), 160 (48); **HRMS** (EI-TOF) calcd. for C$_{10}$H$_6$NF$_3$S: 229.0166; found: 229.0168.

7.5.3.26. Synthesis of 9-ethyl-3-[(trifluoromethyl)thio]-9H-carbazole (3z)
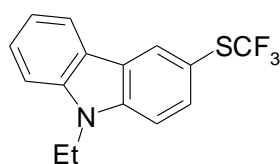
[CAS: 1639370-01-6]

Compound **3z** was prepared following the standard procedure, starting from 9-ethyl-9*H*-carbazol-3-diazonium tetrafluoroborate (309 mg, 1.00 mmol). After purification, **3z** was isolated as colorless solid (245 mg, 0.83 mmol, 83%).

m.p.: 72°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.43 (s, 1H), 8.14 (d, ^3J = 7.8 Hz, 1H), 7.75 (d, ^3J = 8.5 Hz, 1H), 7.56 (t, ^3J = 7.0 Hz, 1H), 7.43 (t, ^3J = 8.5 Hz, 2H), 7.33 (t, ^3J = 7.0 Hz, 1H), 4.35 (q, ^3J = 7.3 Hz, 2H), 1.46 ppm (t, ^3J = 7.3 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −44.0 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 141.0, 140.3, 133.7, 130.0 (q, ^1J(C,F) = 308.8 Hz), 129.5, 126.6, 123.8, 122.1, 120.6, 119.7, 112.4 (q, ^3J(C,F) = 1.8 Hz), 109.2, 108.8, 37.6, 13.7 ppm; **IR** (ATR): ν = 2975, 1475, 1449, 1234, 1134, 1124, 1108, 744, 722, 604 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 296 (6), 295 (100) [M^+], 226 (47); **HRMS** (EI-TOF) calcd. for C$_{15}$H$_{12}$NF$_3$S: 295.0637; found: 295.0636.

7.5.3.27. Synthesis of methyl-3-[(trifluoromethyl)thio]thiophene-2-carboxylate (3aa)
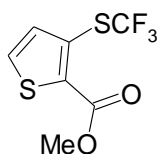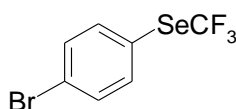

[CAS: 1639370-02-7]

Compound **3aa** was prepared following the standard procedure, starting from 2-(methoxycarbonyl)thiophene-3-diazonium tetrafluoroborate (256 mg, 1.00 mmol). After purification, **3aa** was isolated as colorless oil (165 mg, 0.68 mmol, 68%).

¹H NMR (400 MHz, CDCl₃): δ = 7.60 (d, ^3J = 5.5 Hz, 1H), 7.26 (m, 1H), 3.92 ppm (s, 3H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −42.4 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 161.8, 131.7, 130.6 (q, ^3J(C,F) = 2.2 Hz), 129.4 (q, ^1J(C,F) = 308.8 Hz), 129.3 (q, ^3J(C,F) = 2.2 Hz), 128.4 (q, ^3J(C,F) = 2.2 Hz), 52.5 ppm; **IR** (ATR): ν = 3105, 2957, 1701, 1501, 1439, 1407, 1274, 1152, 1136, 1106 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 243 (10), 241 (100) [M^+]; **HRMS** (EI-TOF) calcd. for C₇H₅F₃O₂S₂: 241.9675; found: 241.9678.

7.5.3.28. Synthesis of 2,3-dihydro-1,3-dioxo-1H-Isoindole-5-[(trifluoromethyl)thio]-benzene (3ab)

[CAS: 1821280-30-1]

Compound **3ab** was prepared following the standard procedure, starting from 2,3-dihydro-1,3-dioxo-1*H*-Isoindole-5-diazonium tetrafluoroborate (261 mg, 1.00 mmol). After purification, **3ab** was isolated as colorless solid (183 mg, 0.74 mmol, 74%) along with traces of protodediazotated side product.

m.p.: 143-144°C; **¹H NMR** (400 MHz, CDCl₃): δ = 8.55 (br.s, 1H), 8.15 (s, 1H), 8.05 (dd, ^3J = 7.8, 1.5 Hz, 1H), 7.95 ppm (d, ^3J = 7.8 Hz, 1H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −41.5 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 167.0, 166.8, 141.3, 134.1, 133.6, 132.2 (q,

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^3J(C,F) = 1.8 Hz), 130.4, 128.9 (q, ^1J(C,F) = 308.8 Hz), 124.5 ppm; **IR** (ATR): ν = 3223, 3069, 2775, 1769, 1718, 1699, 1611, 1420, 1350, 1295, 1177, 1100, 1041, 864, 741 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 247 [M^+] (100), 203 (27); **HRMS** (EI-TOF) calcd. for $C_9H_4F_3NO_2S$: 246.9915; found: 246.9907.

7.5.3.29. *Synthesis of 3-(((trifluoromethyl)thio)methyl)-2,3-dihydrobenzofuran (3ac)*
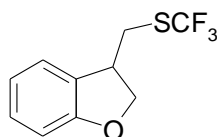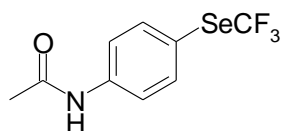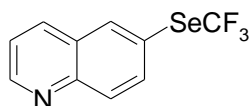

[CAS: 1821280-31-2]

Compound **3ac** was prepared following the standard procedure, starting from 2-(allyloxy)diazonium tetrafluoroborate (248 mg, 1.00 mmol). After purification, **3ac** was isolated as colorless oil (218 mg, 0.93 mmol, 93%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.28 (d, ^3J = 7.3 Hz, 1H); 7.20 (t, ^3J = 8.0 Hz, 1H); 6.91 (t, ^3J = 7.3 Hz, 1H); 6.84 (d, ^3J = 8.0 Hz, 1H); 4.67 (t, ^3J = 9.3 Hz, 1H); 4.43 (dd, ^3J = 9.3, 5.2 Hz, 1H), 3.74 (m, 1H), 3.24 (m, 1H), 3.03 ppm (m, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.7 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 159.9, 130.9 (q, ^1J(C,F) = 306.1 Hz), 129.4, 127.9, 124.6, 120.8, 110.1, 75.5, 41.8, 34.1 ppm; **IR** (ATR): ν = 3015, 2970, 2947, 1597, 1482, 1322, 1265, 1234, 1149, 1096, 967, 844, 748 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 234 [M^+] (40), 119 (100), 91 (70), 69 (10), 65 (10); **HRMS** (EI-TOF) calcd. for $C_{10}H_9F_3OS$:; 234.0326 found: 234.0326.

7.5.4. *Synthesis of Trifluoromethyl Thioethers from the corresponding Aromatic Amines*
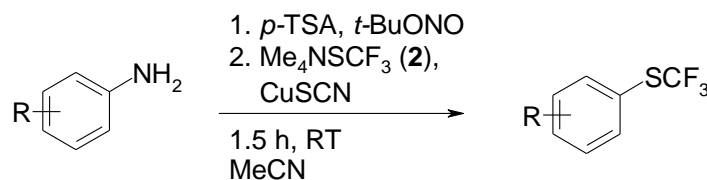
Standard procedure B: An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with aromatic amine (1.00 mmol) and *p*-TSA (262 mg, 1.50 mmol) in MeCN (2 mL), *t*-butyl nitrite (0.12 mL, 1.0 mmol) was added dropwise and the solution was stirred for 0.5 h

at room temperature. The reaction mixture was added dropwise to a 20 mL crimp-cap vessel with stirrer bar, that was charged with CuSCN (12 mg, 0.10 mmol), Me$_4$NSCF$_3$ (315 mg, 1.80 mmol) and MeCN (2 mL). The reaction mixture was stirred for 1 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$_2$, pentane / diethyl ether gradient), yielding the aryl trifluoromethyl thioethers.

7.5.4.1.   Synthesis of 1-methoxy-4-[(trifluoromethyl)thio]benzene (3a)
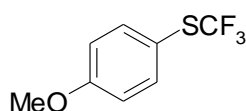
[CAS: 78914-94-0].

Compound **3a** was prepared following the standard procedure, starting from 4-methoxyaniline (123 mg, 1.00 mmol). After purification, **3a** was isolated as colorless oil (189 mg, 0.91 mmol, 91%). The analytical data matched the one already reported in this document.

7.5.4.2.   Synthesis of 4-[(trifluoromethyl)thio]biphenyl (3g)
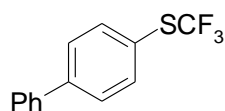
[CAS: 177551-63-2]

Compound **3g** was prepared following the standard procedure, starting from [1,1'-biphenyl]-4-amine (169 mg, 1.00 mmol). After purification, **3g** was isolated as colorless solid (198 mg, 0.78 mmol, 78%). The analytical data matched the one already reported in this document.

7.5.4.3.   Synthesis of methyl-4-[(trifluoromethyl)thio]benzoate (3q)
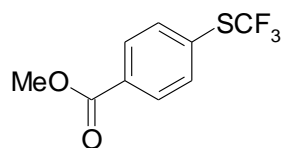
[CAS: 88489-60-5]

Compound **3q** was prepared following the standard procedure, starting from methyl 4-aminobenzoate (154 mg, 1.00 mmol). After purification, **3q** was isolated as colorless oil (210 mg, 0.89 mmol, 89%). The analytical data matched the one already reported in this document.

7.5.4.4.   Synthesis of N,N-dimethyl-4-[(trifluoromethyl)thio]aniline (3s)
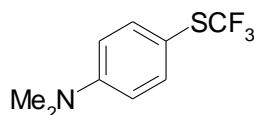
[CAS: 2677-71-6]

Compound **3s** was prepared following the standard procedure, starting from *N,N*-dimethylbenzene-1,4-diamine (140 mg, 1.00 mmol). After purification, **3s** was isolated as colorless oil (135 mg, 0.61 mmol, 61%). The analytical data matched the one already reported in this document.

7.5.4.5.   Synthesis of N-[4-[(trifluoromethyl)thio]phenyl]acetamide (3u)
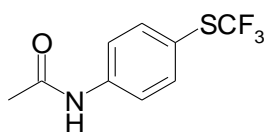
[CAS: 351-81-5]

Compound **3u** was prepared following the standard procedure, starting from *N*-(4-aminophenyl)acetamide (158 mg, 1.00 mmol). After purification, **3u** was isolated as colorless solid (61 mg, 0.26 mmol, 26%). The analytical data matched the one already reported in this document.

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7.5.4.6. Synthesis of 3-[(trifluoromethyl)thio]quinoline (3w)
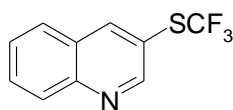
[CAS: 1333415-90-9]

Compound **3w** was prepared following the standard procedure, starting from quinolin-3-amine (146 mg, 1.00 mmol). After purification, **3w** was isolated as colorless oil (181 mg, 0.79 mmol, 79%). The analytical data matched the one already reported in this document.

7.5.5. Synthesis of Trifluoromethyl Selenoethers from the corresponding Arenediazonium Salts
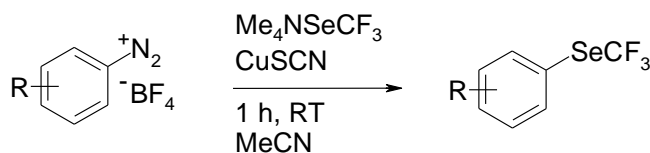
Standard procedure: An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with CuSCN (12.0 mg, 0.10 mmol), Me$_4$NSeCF$_3$ (400 mg, 1.80 mmol) and MeCN (2 mL). Then, the arenediazonium salt (1.00 mmol) in MeCN (2 mL) was added dropwise and the reaction mixture was stirred for 1h at room temperature. 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$_2$, pentane / diethyl ether gradient), yielding the corresponding aryl trifluoromethyl selenoethers.

7.5.5.1. Synthesis of 1-methoxy-4-[(trifluoromethyl)seleno]benzene (4a)

[CAS: 21506-10-5]

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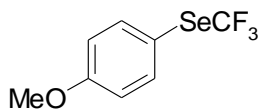
Compound **4a** was prepared following the standard procedure, starting from 4-methoxybenzenediazonium tetrafluoroborate (222 mg, 1.00 mmol). After purification, **4a** was isolated as colorless oil (249 mg, 0.98 mmol, 98%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.67 (d, ^3J = 8.8 Hz, 2H), 6.92 (d, ^3J = 8.8 Hz, 2H), 3.84 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −37.2 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 161.4, 138.9 (2 C), 122.5 (q, ^1J(C,F) = 333.3 Hz), 115.2 (2C), 112.9 (q, ^3J(C,F) = 1.8 Hz), 55.3 ppm; **IR** (ATR): ν = 2956, 2921, 2851, 1738, 1591, 1492, 1365, 1258, 1091, 1024, 820, 795 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 256 [M^+] (66), 187 (100); **HRMS** (EI-TOF) calcd. for C$_8$H$_7$F$_3$OSe: 255.9614; found: 255.9618.

7.5.5.2. *Synthesis of 1-bromo-4-[(trifluoromethyl)seleno]benzene (4b)*

[CAS: 21506-09-2]

Compound **4b** was prepared following the standard procedure, starting from 4-bromobenzenediazonium tetrafluoroborate (271 mg, 1.00 mmol). After purification, **4b** was isolated as colorless oil (258 mg, 0.85 mmol, 85%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.61 (d, ^3J = 8.5 Hz, 2H), 7.54 ppm (d, ^3J = 8.5 Hz, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −36.0 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 138.5 (2C), 132.9 (2C), 125.5, 122.2 (q, ^1J(C,F) = 333.3 Hz), 121.2 ppm (q, ^3J(C,F) = 1.8 Hz); **IR** (ATR): ν = 3049, 3073, 2954, 2924, 2854, 1894, 1738, 1470, 1384, 1144, 1007, 809 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 303 [M^+] (93), 235 (100); **HRMS** (EI-TOF) calcd. for C$_7$H$_4$BrF$_3$Se: 303.8601; found: 303.8601.

7.5.5.3. *Synthesis of 1-nitro-4-[(trifluoromethyl)seleno]benzene (4c)*

[CAS: 21506-11-6]

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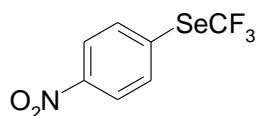
Compound **4c** was prepared following the standard procedure, starting from 4-nitrobenzenediazonium tetrafluoroborate (237 mg, 1.00 mmol). After purification, **4c** was isolated as colorless oil (221 mg, 0.82 mmol, 82%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.24 (d, ^3J = 8.8 Hz, 2H), 7.92 ppm (d, ^3J = 8.8 Hz, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −34.8 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 148.9, 137.0 (2C), 130.4 (q, ^3J(C,F) = 1.8 Hz), 124.3 (2C), 122.2 ppm (q, ^1J(C,F) = 333.3 Hz); **IR** (ATR): ν = 3102, 3031, 2990, 2971, 2869, 1600, 1521, 1348, 1278, 1129, 1092, 1062, 1012, 848. 739 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 271 [M^+] (100), 241 (59), 172 (66); **HRMS** (EI-TOF) calcd. for C$_7$H$_4$F$_3$NO$_2$Se: 270.9359; found: 270.9351.

7.5.5.4. Synthesis of N-[4-[(trifluoromethyl)seleno]phenyl]acetamide (4d)

[CAS: 5172-98-5]

Compound **4d** was prepared following the standard procedure, starting from from 4-(acetylamino)benzenediazonium tetrafluoroborate (249 mg, 1.00 mmol). After purification, **4d** was isolated as colorless solid (271 mg, 0.96 mmol, 96%).

m.p.: 188-189°C; **^{1}H NMR** (400 MHz, CD$_3$OD): δ = 6.11-6.09 (m, 4H), 0.57 ppm (s, 3H); **^{19}F NMR** (375 MHz, CD$_3$OD): δ = −38.8 ppm; **^{13}C NMR** (101 MHz, CD$_3$OD): δ = 172.1, 142.6, 139.2 (2C), 124.2 (q, ^1J(C,F) = 333.4 Hz), 121.8 (2C), 117.7, 24.1 ppm; **IR** (ATR): ν = 3301, 3255, 3113, 2970, 2395, 1738, 1655, 1492, 1317, 1231, 1184, 1105, 1092, 1072, 980, 824, 733 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 283 [M^+] (52), 172 (100); **HRMS** (EI-TOF) calcd. for C$_9$H$_8$F$_3$NOSe: 282.9723; found: 282.9747.

7.5.5.5. Synthesis of 6-[(trifluoromethyl)seleno]-quinoline (4e)

[CAS: 1821280-32-3]

Compound **4e** was prepared following the standard procedure, starting from quinoline-6-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **4e** was isolated as colorless oil (190 mg, 0.69 mmol, 69%).

¹H NMR (400 MHz, CDCl₃): δ = 8.98 (dd, ^3J = 4.3, 1.5 Hz, 1H), 8.24 (d, ^3J = 2.0 Hz, 1H), 8.16 (d, ^3J = 8.3 Hz, 1H), 8.11 (d, ^3J = 8.8 Hz, 1H), 7.99 (dd, ^3J = 8.8, 1.8 Hz, 1H), 7.48-7.45 ppm (m, 1H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −35.6 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 152.0, 148.3, 137.2, 136.4, 136.1, 130.8, 128.5, 122.4 (q, ^1J(C,F) = 333.3 Hz), 122.0, 120.7 ppm (q, ^3J(C,F) = 1.8 Hz); **IR** (ATR): ν = 3038, 2935, 1614, 1586, 1488, 1345, 1119, 1089, 1076, 1059, 941, 832, 793 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 277 [M^+] (86), 208 (100); **HRMS** (EI-TOF) calcd. for C₁₀H₆F₃NSe: 276.9618; found: 276.9610.

7.5.5.6.   Synthesis of 9-ethyl-3-[(trifluoromethyl)seleno]-9H-carbazole (4f)
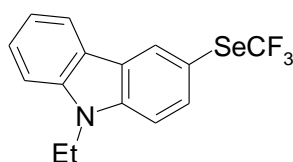
[CAS: 1821280-33-4]

Compound **4f** was prepared following the standard procedure, starting from 9-ethyl-9*H*-carbazol-3-diazonium tetrafluoroborate (309 mg, 1.00 mmol). After purification, **4f** was isolated as colorless solid (332 mg, 0.97 mmol, 97%).

m.p.: 89-90°C; **¹H NMR** (400 MHz, CDCl₃): δ = 8.49 (d, ^3J = 1.5 Hz, 1H), 8.13 (d, ^3J = 7.5 Hz, 1H), 7.82 (dd, ^3J = 8.5, 1.5 Hz, 1H), 7.53 (t, ^3J = 8.3 Hz, 1H), 7.46-7.41 (m, 2H), 7.30 (t, ^3J = 7.9 Hz, 1H), 4.39 (q, ^3J = 7.3 Hz, 2H), 8.49 ppm (t, ^3J = 7.3 Hz, 3H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −37.3 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 140.7, 140.2, 134.4, 130.2, 126.5, 124.1, 122.7 (q, ^1J(C,F) = 333.3 Hz), 122.2, 120.7, 119.7, 110.9, 109.4, 108.8, 37.7, 13.8; **IR** (ATR): ν = 3051, 2977, 2936, 1587, 1467, 1448, 1330, 1230, 1084, 888, 806, 746 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 343 [M^+] (68), 274 (100), 272 (62); **HRMS** (EI-TOF) calcd. for C₁₅H₁₂F₃NSe: 343.0087; found: 343.0091.

7.6. Trifluoromethylthiolation and Trifluoromethylselenolation of α-Diazo Esters Catalyzed by Copper

7.6.1. *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. 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 $\times$ 320 $\times$ 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 temperature. 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, acetone-d_6 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.

7.6.2. *Mechanistic Investigations*

Tabelle 4. Mechanistic Investigations.[a]
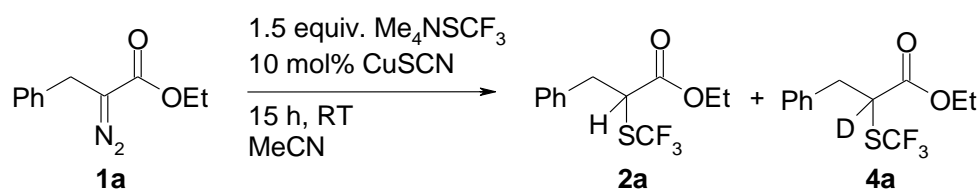
Entry	Changed Conditions	Yield 2a [%]	Yield 4a [%]
1	Molecular sieves as additives	61	-
2	1 equiv. H_2O as additive	60	-
3	44 equiv. H_2O as additive	14	-
4	1 equiv. D_2O as additive	11	43
5	MeCN-d_3 as solvent	81	-

6	Addtition of MeOD after 15h	99	-
7	Addtition of D$_2$O after 15h	99	-
8	1.5 equiv. TEMPO as additive	trace	-
9	1.5 equiv. *p*-benzoquinone as additive	trace	-

[a] Reaction conditions: addition of 0.5 mmol α-diazo ester **1a** in 1 mL MeCN to 1.5 equiv. Me$_4$NSCF$_3$ and 0.05 mmol CuSCN in 1 mL MeCN, 15 h at room temperature. Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard. Deuteration grade was determined by GC-MS.

7.6.3. *Synthesis of Starting Materials*

7.6.3.1. *Synthesis of Me$_4$NSCF$_3$[110]*
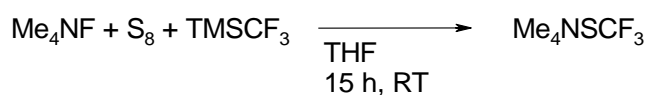
$$Me_4NF + S_8 + TMSCF_3 \xrightarrow[\text{15 h, RT}]{\text{THF}} Me_4NSCF_3$$

Elemental sulfur (1.80 g, 6.64 mmol) was dissolved in THF (300 mL) at room temperature. TMSCF$_3$ (10.1 mL, 63.7 mmol) was added and the reaction mixture was cooled to −60°C and afterwards Me$_4$NF (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 diethylether to give the desired product Me$_4$NSCF$_3$ as a white solid.

^{1}H NMR (400 MHz, CD$_3$CN): δ = 3.12 ppm (s, 12H); **^{19}F NMR** (375 MHz, CD$_3$CN): δ = −6.5 ppm; **^{13}C NMR** (101 MHz, CD$_3$CN): δ = 145.1 (q, ^1J(C,F) = 293.4 Hz), 56.0 ppm (4C).

7.6.3.2. *Synthesis of red selenium[213]*

Grey selenium (3.40 g, 43.1 mmol) was added to conc. sulfuric acid (180 mL) and the reaction mixture was stirred at 180°C for 6 h. The solution was filtered onto ice (400 mL) and the resulting solution left to recrystallize at 4°C overnight. The mixture was then filtered and the obtained red solid was washed with cold water (3 × 50 mL) and acetone (3 × 50 mL). The resulting red powder was then dried under reduced pressure to yield Se$_8$.

7.6.3.3. Synthesis of Me$_4$NSeCF$_3$[213]
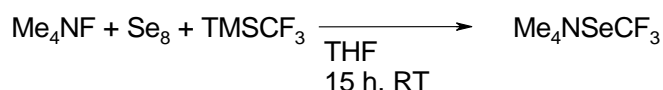
$$\text{Me}_4\text{NF} + \text{Se}_8 + \text{TMSCF}_3 \xrightarrow[\text{15 h, RT}]{\text{THF}} \text{Me}_4\text{NSeCF}_3$$

TMSCF$_3$ (1.72 mL, 10.8 mmol) was added to activated molecular sieves (100 g) in anhydrous 1,2-dimethoxyethane (200 mL). The reaction mixture was stirred at −60°C for 15 min before Se$_8$ (711 mg, 1.13 mmol) was added and the reaction mixture stirred for another 15 min. Then, Me$_4$NF (600 mg, 6.38 mmol) was added and stirred for 1 h at −58°C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h in darkness. The suspension was filtered through a plug of celite and the remaining black solid was washed with anhydrous 1,2-dimethoxyethane (2 × 20 mL). The residue was extracted with acetonitrile (3 × 50 mL) and the solvent evaporated. The crude product was dissolved in acetonitrile (20 mL) and THF (200 mL) was added. The resulting precipitate was filtered, washed with THF (3 × 50 mL) and dried under reduced pressure to yield Me$_4$NSeCF$_3$ as a white solid.

^{1}H NMR (400 MHz, acetone-d$_6$): δ = 3.50 ppm (s, 12H); **^{19}F NMR** (375 MHz, acetone-d$_6$): δ = −6.5 ppm; **^{13}C NMR** (101 MHz, acetone-d$_6$): δ = 133.1 (q, ^1J(C,F) = 323.3 Hz), 56.1 ppm (4C).

7.6.4. Synthesis of α-Diazo Esters

General information: Hydrochloride salts were extracted prior to use with NEt$_3$ (5 equiv.), water and ethyl acetate. The organic phase was dried over MgSO$_4$ and concentrated under reduced pressure.

Standard procedure 1:[223]
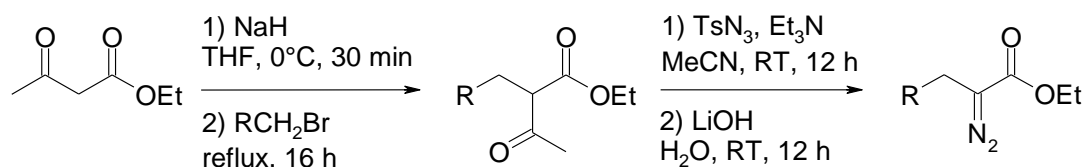
To a suspension of NaH (720 mg, 30.0 mmol; 60% dispersion in mineral oil) in THF (15 mL) at 0°C, a solution of ethyl acetoacetate (3.80 mL, 3.90 g, 30.0 mmol) in THF (10 mL) was added dropwise under vigorous stirring. After warming to room temperature, a

solution of the corresponding benzyl halide (20.0 mmol) in THF (10 mL) was added and the resulting solution refluxed for 16 h. After cooling to room temperature, the mixture was quenched with saturated NH$_4$Cl solution (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over MgSO$_4$, the solvent removed under reduced pressure and if necessary the residue purified by column chromatography (SiO$_2$, cyclohexane/ethyl acetate gradient).

The obtained material was then dissolved with tosyl azide (1.2 equiv.) in MeCN (40 mL). To this, a solution of NEt$_3$ (1.5 equiv.) in MeCN (10 mL) was added in one portion, and the resulting mixture was stirred for 12 h at room temperature. Then a solution of LiOH (5 equiv.) in water (20 mL) was added, and the resulting mixture was stirred for 12 h. The mixture was extracted with Et$_2$O (3 × 30 mL), the combined organic layers washed with brine (30 mL) and dried over MgSO$_4$. After concentrating the mixture under reduced pressure, the residue was purified by column chromatography (SiO$_2$, cyclohexane/ethyl acetate gradient).

Standard procedure 2:[241]
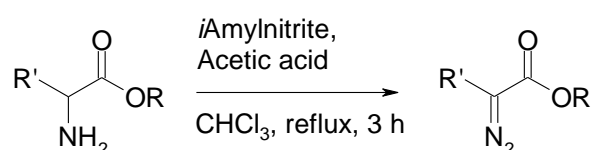
A solution of the amino acid ester (10.0 mmol), isoamyl nitrite (12.0 mmol) and acetic acid (1.00 mmol) in chloroform (80 mL) was refluxed for 3 h. The mixture was diluted with ethyl acetate (100 mL) and washed with saturated NaHCO$_3$ solution (3 × 40 mL). The organic layer was dried over MgSO$_4$, concentrated under reduced pressure and if necessary the residue purified by column chromatography (SiO$_2$, cyclohexane/ethyl acetate gradient).

Standard procedure 3:[242]
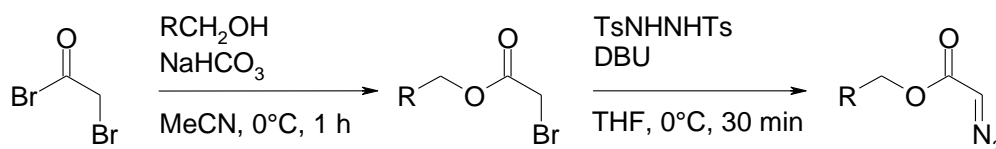
To a suspension of NaHCO$_3$ (30.0 mmol) and the benzyl alcohol (10.0 mmol) in MeCN (60 mL) cooled to 0°C, a solution of bromo acetyl bromide (14.0 mmol) in MeCN (10 mL) was added dropwise over a period of 10 min. After 1 h of stirring at room temperature, water

(100 mL) was added and the mixture extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. In most cases, the material obtained was directly used in the next step. If necessary, the crude product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate gradient).

The obtained material was added to a solution of *N,N'*-ditosyl hydrazine (1.50 equiv.) in THF (70 mL) and cooled to 0°C. To this mixture, a solution of DBU (4.00 equiv.) in THF (10 mL) was added dropwise over a period of 5 min. After stirring for 30 min at room temperature, the mixture is diluted with Et_2O (100 mL) and washed with saturated $NaHCO_3$ solution (70 mL). The organic layer is dried over $MgSO_4$ and concentrated under reduced pressure. If necessary, the crude product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate gradient).

Note: In many cases, the quaternary carbon bearing the diazo function and the quaternary carbon bearing the ester function could not be observed by NMR spectroscopy. Moreover, the diazo function decomposed during the ionization process of the HRMS; only [M$^+$-(N$_2$)] fragments were detected. Nevertheless, the authenticity was confirmed by their bright yellow color, the characteristic IR-band at 2070-2100 cm^{-1} and by ^{1}H NMR according to literature procedures.

### 7.6.4.1.   *Synthesis of 2-diazo-3-phenylpropanoic acid ethyl ester (1a)*
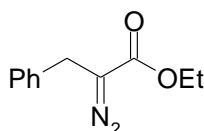
[CAS No.: 15626-54-7]

Compound **1a** was prepared following the standard procedure 2, starting from L-phenylalanine ethyl ester. After purification, **1a** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.22-7.39 (m, 5H), 4.26 (q, ^3J = 7.3 Hz, 2H), 3.64 (s, 2H), 1.29 ppm (t, ^3J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 137.2, 128.7 (2C), 128.3 (2C), 127.0, 29.3, 22.6, 14.4 ppm; **IR** (ATR): ν = 2981, 2081, 1684, 1496, 1455, 1370, 1331, 1300, 1265, 1173, 1101, 1020, 866, 737, 698 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 176 [*M$^+$-(N$_2$)*]

(55), 148 (22), 131 (100), 103 (67); **HRMS** (EI-TOF) calcd. for $C_{11}H_{12}O_2$: 176.0837; found: 176.0842 [M^+-(N_2)].

7.6.4.2. Synthesis of 2-diazo-3-phenylpropanoic acid benzyl ester (1b)
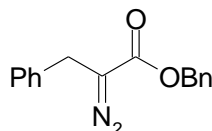
[CAS No.: 126191-07-9]

Compound **1b** was prepared following the standard procedure 2, starting from L-phenylalanine benzyl ester. After purification, **1b** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.16-7.43 (m, 10H), 5.23 (s, 2H), 3.64 ppm (s, 2H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 137.1, 136.0, 128.8 (2C), 128.5, 128.3, 128.2, 128.0 (2C), 127.1, 66.5, 41.7, 29.3 ppm; **IR** (ATR): ν = 3031, 2957, 2082, 1685, 1497, 1455, 1382, 1334, 1296, 1263, 1172, 1097, 965, 911, 734, 695 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 238 [M^+-(N_2)] (5), 191 (100), 177 (20), 146 (30), 131 (37), 91 (46); **HRMS** (EI-TOF) calcd. for $C_{16}H_{14}O_2$: 238.0994; found: 238.0978 [M^+-(N_2)].

7.6.4.3. Synthesis of 2-diazopropanoic acid ethyl ester (1c)
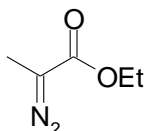
[CAS No.: 6111-99-5]

Compound **1c** was prepared analogously to the standard procedure 3, starting from DL-2-bromopropanoic acid ethyl ester. After purification, **1c** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 4.05 (q, ^3J = 7.3 Hz, 2H), 2.39 (s, 3H), 1.11 ppm (t, ^3J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 166.3, 62.2, 21.7, 13.9 ppm; **IR** (ATR): ν = 2959, 2873, 2078, 1689, 1370, 1321, 1219, 1135, 1073, 861, 740, 652 cm^{-1}.
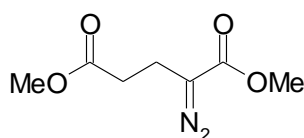
7.6.4.4.   Synthesis of 2-diazopropanoic acid benzyl ester (1d)
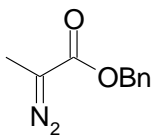
[CAS No.: 55895-92-6]

Compound **1d** was prepared following the standard procedure 2, starting from L-alanine benzyl ester. After purification, **1d** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.40-7.32 (m, 5H), 5.22 (s, 2H), 1.99 ppm (s, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 136.1, 128.5, 128.2 (2C), 128.0 (2C), 66.3, 8.5 ppm; **IR** (ATR): ν = 2918, 2876, 2075, 1683, 1384, 1303, 1117, 730, 695 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 162 [M^+-(N_2)] (69), 117 (71), 107 (29), 91 (100), 77 (34); **HRMS** (EI-TOF) calcd. for C$_{10}$H$_{10}$O$_2$: 162.0681; found: 162.0689 [M^+-(N_2)].

7.6.4.5.   Synthesis of 2-diazoacetic acid ethyl ester (1e)
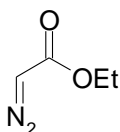
[CAS No.: 623-73-4]

Compound **1e** was prepared analogously to the standard procedure 3, starting from bromoacetic acid ethyl ester. After purification, **1e** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 4.74 (s, 1H), 4.14 (q, ^3J = 7.3 Hz, 2H), 1.20 ppm (t, ^3J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 162.5, 61.1, 14.5 ppm; **IR** (ATR): ν = 2958, 2873, 2079, 1689, 1371, 1321, 1219, 1135, 1071, 1019, 670, 650 cm^{-1}.

### 7.6.4.6.   Synthesis of 2-diazoacetic acid benzyl ester (1f)
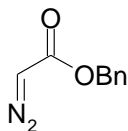
[CAS No.: 52267-51-3]

Compound **1f** was prepared following the standard procedure 2, starting from glycine benzyl ester. After purification, **1f** was isolated as yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ = 7.30-7.43 (m, 5H), 5.21 (s, 2H) 4.81 ppm (s, 1H); **¹³C NMR** (101 MHz, CDCl₃): δ = 135.8, 128.6 (2C), 128.3 (2C), 128.2, 66.5 ppm; **IR** (ATR): ν = 2874, 2077, 1683, 1498, 1303, 1116, 987, 910, 731, 696 cm⁻¹.

7.6.4.7. *Synthesis of 2-diazo-4-methylpentanoic acid benzyl ester (1g)*
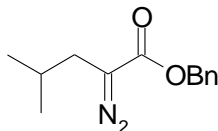
[CAS No.: 54684-79-6]

Compound **1g** was prepared following the standard procedure 2, starting from L-leucine benzyl ester. After purification, **1g** was isolated as yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ = 7.36-7.42 (m, 5H), 5.22 (s, 2H), 2.20 (d, ³*J* = 7.3 Hz, 2H), 1.84 (m, 1H), 0.97 ppm (d, ³*J* = 6.8 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃): δ = 136.2, 128.5, 128.4, 128.1, 127.9, 127.8, 72.1, 32.2, 28.0, 21.8 ppm (2C); **IR** (ATR): ν = 2959, 2871, 2077, 1687, 1456, 1382, 1320, 1217, 1129, 1066, 735, 695 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 204 [*M⁺-(N₂)*] (4), 161 (32), 148 (23), 107 (5), 97 (77), 91 (100); **HRMS** (EI-TOF) calcd. for C₁₃H₁₆O₂: 204.1150; found: 204.1146 [*M⁺-(N₂)*].

7.6.4.8. *Synthesis of (3S)-2-diazo-3-methylpentanoic acid benzyl ester (1h)*
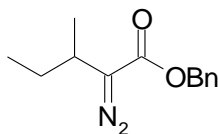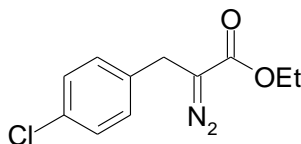

[CAS No.: 1160845-75-9]

Compound **1h** was prepared following the standard procedure 2, starting from L-isoleucine benzyl ester. After purification, **1h** was isolated as yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ = 7.34-7.40 (m, 5H), 5.22 (s, 2H), 2.51-2.58 (m, 1H), 1.43-1.53 (m, 2H), 1.15 (d, ³*J* = 7.0 Hz, 3H), 0.94 ppm (t, ³*J* = 7.4 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃): δ = 136.2, 128.5 (2C), 128.1, 127.9 (2C), 66.2, 29.9, 27.8, 18.1, 11.6 ppm; **IR** (ATR): ν = 2965, 2932,

2876, 2077, 1687, 1381, 1353, 1280, 1238, 1142, 1070, 738, 695 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 204 [M^+-(N_2)] (3), 113 (22), 97 (49), 91 (100); **HRMS** (EI-TOF) calcd. for C$_{13}$H$_{16}$O$_2$: 204.1150; found: 204.1146 [M^+-(N_2)].

7.6.4.9.   Synthesis of 2-diazo-3-hydroxypropanoic acid ethyl ester (1i)
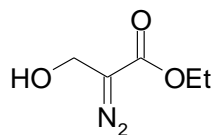
[CAS No. 81077-09-0]

Compound **1i** was prepared following the standard procedure 2, starting from L-serine ethyl ester. After purification, **1i** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 4.50 (br. s, 2H), 4.19-4.32 (m, 2H), 1.18-1.37 ppm (m, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 61.2, 41.6, 14.4 ppm; **IR** (ATR): ν = 3410, 2957, 2872, 2096, 1741, 1692, 1373, 1294, 1198, 1126, 1051, 1023, 744 cm^{-1}.

7.6.4.10.   Synthesis of 2-diazo-3-(4-hydroxyphenyl)propanoic acid methyl ester (1j)
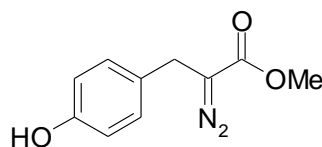
[CAS No.: 35047-20-2]

Compound **1j** was prepared following the standard procedure 2, starting from L-tyrosine methyl ester. After purification, **1j** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 10.59 (br. s, 1H), 7.97 (d, ^3J = 2.3 Hz, 1H), 7.51 (dd, ^3J = 8.5, 2.3 Hz, 1H), 7.13 (d, ^3J = 8.5 Hz, 1H), 6.77-7.07 (m, 1H), 3.80 (s, 3H), 3.63 ppm (s, 2H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 154.2, 137.7, 133.3, 129.8, 124.1, 120.6, 115.3, 52.2, 38.3 ppm; **IR** (ATR): ν = 3377, 2956, 2080, 1655, 1613, 1514, 1437, 1193, 1169, 1114, 834, 736 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 178 [M^+-(N_2)] (75), 147 (100), 119 (27); **HRMS** (EI-TOF) calcd. for C$_{10}$H$_{10}$O$_3$: 178.0630; found: 178.0618 [M^+-(N_2)].

7.6.4.11.   Synthesis of 2-diazo-4-(methylthio)butanoic acid ethyl ester (1k)
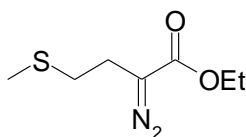
[CAS No.: 1251853-51-6]

Compound **1k** was prepared following the standard procedure 2, starting from L-methionine ethyl ester. After purification, **1k** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 4.22 (m, 2H), 2.64-2.71 (m, 2H), 2.55-2.61 (m, 2H), 2.11-2.14 (m, 3H), 1.27 ppm (m, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 60.8, 32.8, 23.8, 15.3, 14.4 ppm; **IR** (ATR): ν = 2981, 2918, 2079, 1680, 1370, 1332, 1302, 1280, 1155, 1099, 1024, 958, 869, 737 cm^{-1}.

7.6.4.12.   Synthesis of 2-diazo-1,4-butanedioic acid dibenzyl ester (1l)
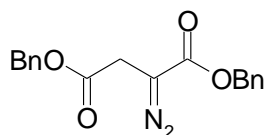
[CAS No.: 1979189-38-2]

Compound **1l** was prepared following the standard procedure 2, starting from L-aspartic acid dibenzyl ester. After purification, **1l** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.40-7.33 (m, 10H), 5.23 (s, 2H), 5.18 (s, 2H), 3.40 ppm (s, 2H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 169.4 (2C), 135.8, 135.2, 128.6 (2C), 128.5 (2C), 128.5, 128.3 (2C), 128.3, 128.1, 67.3 (2C), 26.9 ppm; **IR** (ATR): ν = 2984, 2092, 1738, 1686, 1498, 1456, 1381, 1304, 1170, 1105, 968, 905, 735, 695 cm^{-1}.

7.6.4.13.   Synthesis of 2-diazo-1,5-pentanedioic acid dimethyl ester (1m)

[CAS No.: 81077-05-6]

Compound **1m** was prepared following the standard procedure 2, starting from L-glutamic acid dimethyl ester. After purification, **1m** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 3.76 (s, 3H), 3.70 (s, 3H), 2.56-2.63 ppm (m, 4H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 172.9, 51.9, 51.8, 32.1, 19.5 ppm; **IR** (ATR): ν = 3114, 2967, 2107, 1685, 1395, 1352, 1298, 1239, 1160, 1032, 739 cm^{-1}.

7.6.4.14. Synthesis of 2-diazo-1H-Indole-3-propanoic acid ethyl ester (1n)
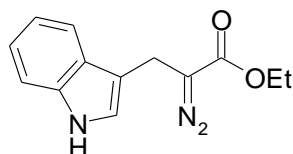
[CAS No.: 136035-29-5]

Compound **1n** was prepared following the standard procedure 2, starting from L-tryptophan ethyl ester. After purification, **1n** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.14 (br. s, 1H), 7.63 (d, ^3J = 7.8 Hz, 1H), 7.38 (d, ^3J = 8.0 Hz, 1H), 7.20-7.26 (m, 1H), 7.13-7.19 (m, 1H), 7.10 (d, ^3J = 2.0 Hz, 1H), 4.28 (q, ^3J = 7.3 Hz, 2H), 3.82 (s, 2H), 1.30 ppm (t, ^3J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 136.4, 126.8, 122.6, 122.4, 119.7, 118.8, 111.2, 111.1, 60.5, 19.5, 14.5 ppm; **IR** (ATR): ν = 3353, 2982, 2080, 1663, 1457, 1371, 1332, 1249, 1177, 1097, 738 cm^{-1}.

7.6.4.15. Synthesis of 2-diazo-3-(4-methoxyphenyl)propanoic acid ethyl ester (1o)
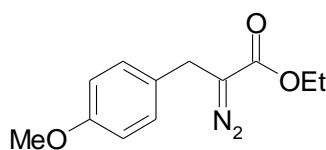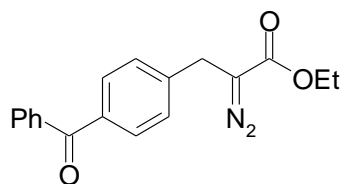

[CAS No.: 51507-20-1]

Compound **1o** was prepared following the standard procedure 1, starting from 4-methoxy benzyl bromide. After purification, **1o** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.16 (m, 2H), 6.85 (m, 2H), 4.24 (q, ^3J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.57 (s, 2H), 1.28 ppm (t, ^3J = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 158.7, 129.5 (2C), 129.2, 114.2 (2C), 60.9, 55.3, 28.5, 14.5 ppm; **IR** (ATR): ν = 2980, 2837, 2078, 1683, 1512, 1464,

212

1370, 1301, 1245, 1170, 1095, 1031, 809, 730 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 206 [M^{+}-(N_2)] (100), 178 (12), 161 (82), 134 (50), 89 (24).

7.6.4.16. *Synthesis of 2-diazo-3-(4-thiomethylphenyl)propanoic acid ethyl ester (1p)*
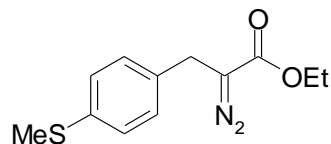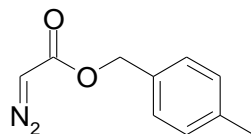

[CAS No.: 1979189-40-6]

Compound **1p** was prepared following the standard procedure 1, starting from from 4-thiomethyl benzyl bromide. After purification, **1p** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.14-7.25 (m, 4H), 4.25 (q, ^3J = 7.3 Hz, 2H), 3.59 (s, 2H), 2.45-2.52 (m, 3H), 1.29 ppm t, (^3J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 137.1, 134.1, 128.8 (2C), 127.0 (2C), 60.9, 28.9, 15.9, 14.5 ppm; **IR** (ATR): ν = 2980, 2078, 1682, 1369, 1331, 1297, 1259, 1170, 1091, 1016, 970, 796, 652 cm^{-1}.

### 7.6.4.17. *Synthesis of 2-diazo-3-(4-cyanophenyl)propanoic acid ethyl ester (1q)*
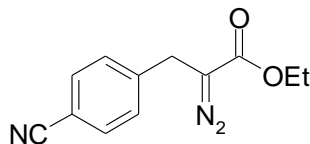
[CAS No.: 1979189-41-7]

Compound **1q** was prepared following the standard procedure 1, starting from 4-cyano benzyl bromide. After purification, **1q** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.62 (m, 2H), 7.37 (m, 2H), 4.25 (q, ^3J = 7.2 Hz, 2H), 3.68 (s, 2H), 1.28 ppm (t, ^3J = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 143.1, 132.6, 129.0, 118.7, 111.1, 61.2, 29.7, 14.5 ppm; **IR** (ATR): ν = 2981, 2229, 2082, 1683, 1608, 1465, 1371, 1269, 1172, 1099, 1018, 816, 752 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 201 [M^{+}-(N_2)] (13), 156 (100); **HRMS** (EI-TOF) calcd. for C$_{12}$H$_{11}$NO$_2$: 201.0790; found: 201.0789 [M^{+}-(N_2)].

7.6.4.18. Synthesis of 2-diazo-3-(4-chlorophenyl)propanoic acid ethyl ester (1r)
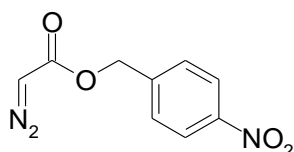

[CAS No.: 874162-66-0]

Compound **1r** was prepared following the standard procedure 1, starting from 4-chloro benzyl chloride. After purification, **1r** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.28-7.34 (d, ^3J = 8.3 Hz, 2H), 7.19 (d, ^3J = 8.3 Hz, 2H), 4.25 (q, ^3J = 7.1 Hz, 2H), 3.61 (s, 2H), 1.29 ppm (t, ^3J = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 135.8, 132.9, 129.7 (2C), 128.9 (2C), 61.0, 28.8, 14.5 ppm; **IR** (ATR): ν = 2980, 2080, 1683, 1491, 1370, 1297, 1172, 1091), 1015, 797, 744, 650 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 212/210 [M^+-(N_2)] (11/33), 167/165 (30/100).

7.6.4.19. Synthesis of 2-diazo-3-(2-fluorophenyl)propanoic acid ethyl ester (1s)
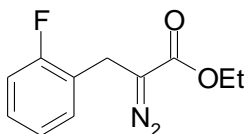
[CAS No.: 1403620-60-9]

Compound **1s** was prepared following the standard procedure 1, starting from 2-fluorobenzyl chloride. After purification, **1s** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.18-7.35 (m, 2H), 7.00-7.17 (m, 2H), 4.23 (q, ^3J = 7.1 Hz, 2H), 3.66 (s, 2H), 1.28 ppm (t, ^3J = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 161.2 (d, ^1J(C,F) = 245 Hz), 130.7 (d, ^3J(C,F) = 5.2 Hz), 128.9 (d, ^3J(C,F) = 8.2 Hz), 124.4 (d, ^2J(C,F) = 15.4 Hz), 124.3 (d, ^4J(C,F) = 3.6 Hz), 115.4 (d, ^2J(C,F) = 21.8 Hz), 60.9, 23.3 (d, ^3J(C,F) = 3.6 Hz) 14.4 ppm; **IR** (ATR): ν = 2981, 2086, 1687, 1492, 1372, 1229, 1173, 1112, 1019, 754 cm^{-1}.

7.6.4.20. Synthesis of 2-diazo-3-(2-bromophenyl)propanoic acid ethyl ester (1t)
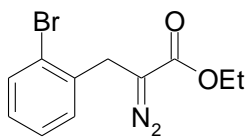
[CAS No.: 1821042-84-5]

Compound **1t** was prepared following the standard procedure 1, starting from 2-bromo benzyl bromide. After purification, **1t** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.57 (m, 1H), 7.35 (m, 1H), 7.28 (m, 1H), 7.13 (m, 1H), 4.23 (q, ^3J = 7.2 Hz, 2H), 3.75 (s, 2H), 1.27 ppm (t, ^3J = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 136.7, 133.0, 130.9, 128.8, 127.6, 124.3, 60.9, 30.0, 14.5 ppm; **IR** (ATR): ν = 3054, 2981, 2082, 1683, 1569, 1469, 1440, 1370, 1337, 1275, 1172, 1126, 1095, 1024, 868, 740 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 257/253 [M^+-(N_2)] (3/3), 175 (33), 147 (100), 102 (32); **HRMS** (EI-TOF) calcd. for C$_{11}$H$_{11}$O$_2$^{79}Br: 253.9942; found: 253.9964 [M^+-(N_2)]; calcd. for C$_{11}$H$_{11}$O$_2$^{81}Br: 255.9922; found: 255.9946 [M^+-(N_2)].

### 7.6.4.21. Synthesis of 2-diazo-3-(2-iodo-phenyl)propanoic acid ethyl ester (1u)
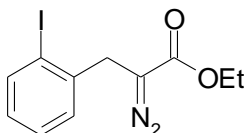
[CAS No.: 1979189-42-8]

Compound **1u** was prepared following the standard procedure 1, starting from 2-iodo benzyl bromide. After purification, **1u** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.82-7.88 (m, 1H), 7.28-7.36 (m, 2H), 6.92-6.99 (m, 1H), 4.25 (q, ^3J = 7.2 Hz, 2H), 3.76 (s, 2H), 1.28 ppm (t, ^3J = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 139.9, 139.7, 130.0, 128.9, 128.5, 100.0, 60.9, 34.3, 14.5 ppm; **IR** (ATR): ν = 2978, 2082, 1684, 1437, 1369, 1336, 1304, 1260, 1171, 1093, 1011, 739 cm^{-1}.

7.6.4.22. *Synthesis of 2-diazo-3-(2-pyridinyl)propanoic acid ethyl ester (1v)*
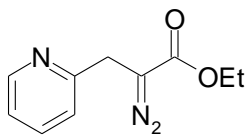
[CAS No.: 1979189-43-9]
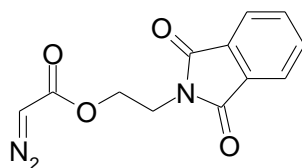
Compound **1v** was prepared following the standard procedure 1, starting from 2-picolylchloride. After purification, **1v** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.56 (s, 2H), 7.18-7.16 (m, 2H), 4.24 (q, ^3J = 7.3 Hz, 2H), 3.62 (s, 2H), 1.27 ppm (t, ^3J = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 157.7, 149.6, 136.7, 122.6, 122.0, 60.9, 31.6, 14.5 ppm; **IR** (ATR): ν = 2982, 2088, 1715, 1687, 1598, 1561, 1446, 1416, 1370, 1298, 1178, 1110, 1029, 992, 855, 816, 741, 654 cm^{-1}.

7.6.4.23. *Synthesis of 2-diazo-3-(4-benzoylphenyl)propanoic acid ethyl ester (1w)*

[CAS No.: 1979189-44-0]

Compound **1w** was prepared following the standard procedure 1, starting from 4-(bromomethyl)benzophenone. After purification, **1w** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.76-7.83 (m, 4H), 7.56-7.62 (m, 1H), 7.45-7.52 (m, 2H), 7.37 (d, ^3J = 8.3 Hz, 2H), 4.26 (q, ^3J = 7.1 Hz, 2H), 3.72 (s, 2H), 1.29 ppm (t, ^3J = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 196.2, 142.3, 137.5, 136.4, 132.4, 130.6 (2C), 130.0 (2C), 128.2 (2C), 128.2 (2C), 61.1, 29.4, 26.9, 14.5 ppm; **IR** (ATR): ν = 2979, 2081, 1686, 1656, 1606, 1370, 1309, 1275, 1173, 1097, 924, 784, 736, 699 cm^{-1}.

7.6.4.24.   Synthesis of (4E)-2-diazo-5-phenyl-4-pentenoic acid ethyl ester (1x)
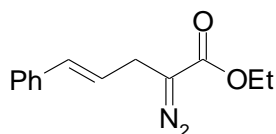
[CAS No.: 1403620-68-7]

Compound **1x** was prepared following the standard procedure 1, starting from cinnamyl chloride. After purification, **1x** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.41-7.20 (m, 5H), 6.51 (dt, ^3J = 15.7, ^4J = 1.5 Hz, 1H), 6.21 (dt, ^3J = 15.7, 6.8 Hz, 1H), 4.26 (q, ^3J = 7.2 Hz, 2H), 3.22 (dd, ^3J = 6.8, ^4J = 1.5 Hz, 2H), 1.30 ppm (t, ^3J = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 136.6, 132.7, 128.6 (2C), 127.6, 126.3 (2C), 124.0, 60.9, 28.7, 14.5 ppm; **IR** (ATR): ν = 2978, 2082, 1684, 1565, 1369, 1336, 1304, 1171, 1093, 1011, 739 cm^{-1}.

7.6.4.25.   Synthesis of 2-diazoacetic acid 4-methylbenzyl ester (1y)

[CAS No.: 1979189-45-1]

Compound **1y** was prepared following the standard procedure 3, starting from 4-methylbenzyl alcohol. After purification, **1y** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.16-7.22 (m, 2H), 7.07-7.14 (m, 2H), 5.08 (s, 2H), 4.70 (br. s. 1H), 2.28 ppm (s, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 138.2, 132.8, 129.2 (2C), 128.4 (2C), 66.4, 21.2 ppm; **IR** (ATR): ν = 3107, 2105, 1686, 1518, 1385, 1349, 1233, 1170, 1013, 803, 737 cm^{-1}.

7.6.4.26.   Synthesis of biphenyl-4-ylmethyl 2-diazoacetate (1z)
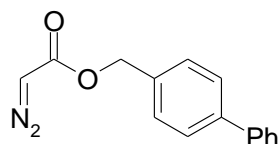
[CAS No.: 1979189-46-2]

Compound **1z** was prepared following the standard procedure 3, starting from 4-biphenylmethanol. After purification, **1z** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.60-7.66 (m, 4H), 7.44-7.51 (m, 4H), 7.37-7.42 (m, 1H), 5.28 (s, 2H), 4.84 ppm (br. s, 1H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 141.2, 140.6, 134.8, 128.7 (2C), 128.7 (2C), 127.4, 127.3 (2C), 127.1 (2C), 66.2 ppm; **IR** (ATR): ν = 3114, 3031, 2099, 1665, 1484, 1386, 1333, 1229, 1014, 825, 759, 731, 691 cm^{-1}.

7.6.4.27. Synthesis of 2-diazoacetic acid 4-nitrobenzyl ester (1aa)

[CAS No.: 84899-07-0]

Compound **1aa** was prepared following the standard procedure 3, starting from 4-nitrobenzyl alcohol. After purification, **1aa** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.19 (m, ^3J = 8.8 Hz, 2H), 7.50 (m, ^3J = 8.8 Hz, 2H), 5.27 (s, 2H), 4.89 ppm (br. s, 1H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 147.5, 143.2, 128.1, 123.6, 64.7 ppm; **IR** (ATR): ν = 2989, 2398, 2095, 1694, 1593, 1497, 1373, 1324, 1301, 1238, 1166, 1112, 1040, 844, 750, 686, 650 cm^{-1}.

7.6.4.28. Synthesis of 2-diazoacetic acid 4-fluorobenzyl ester (1ab)
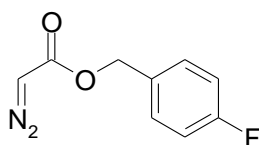
[CAS No.: 1979189-47-3]

Compound **1ab** was prepared following the standard procedure 3, starting from 4-fluorobenzyl alcohol. After purification, **1ab** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.35 (m, 2H), 7.00-7.11 (m, 2H), 5.16 (s, 2H), 4.80 ppm (br. s, 1H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 162.6 (d, ^1J(C,F) = 246.5 Hz), 131.7 (d, ^4J(C,F) = 3.7 Hz), 130.2 (d,

^3J(C,F) = 8.8 Hz, 2C), 115.5 (d, ^2J(C,F) = 21.3 Hz, 2C), 65.7 ppm; **IR** (ATR): ν = 3118, 7958, 2109, 1687, 1606, 1511, 1386, 1351, 1223, 1177, 1155, 1012, 823, 738 cm^{-1}.

7.6.4.29.   Synthesis of 2-diazoacetic acid 3-iodobenzyl ester (1ac)
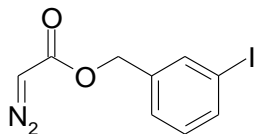
[CAS No.: 1979189-48-4]

Compound **1ac** was prepared following the standard procedure 3, starting from 3-iodobenzyl alcohol. After purification, **1ac** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.63-7.73 (m, 2H), 7.33 (d, ^3J = 7.8 Hz, 1H), 7.11 (t, ^3J = 7.8 Hz, 1H), 5.14 (s, 2H), 4.83 ppm (br. s, 1H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 138.1, 137.3, 136.9, 130.3, 127.3, 94.3, 65.3 ppm; **IR** (ATR): ν = 3109, 2110, 1682, 1566, 1383, 1348, 1155, 996, 771, 738, 684, 655 cm^{-1}.

7.6.4.30.   Synthesis of 2-diazoacetic acid 2-pyridinylmethyl ester (1ad)
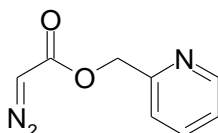
[CAS No.: 1438843-09-4]

Compound **1ad** was prepared following the standard procedure 3, starting from 2-hydroxymethyl pyridine. After purification, **1ad** was isolated as yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.60 (d, ^3J = 3.7 Hz, 1H), 7.71 (dt, ^3J = 7.8, 1.8 Hz, 1H), 7.35 (d, ^3J = 8.7 Hz, 1H), 8.60 (t, ^3J = 7.3 Hz, 1H), 5.32 (s, 2H), 4.89 ppm (s, 1H); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 136.8, 125.5, 123.7, 122.9, 121.7, 67.0 ppm; **IR** (ATR): ν = 2981, 2090, 1716, 1692, 1598, 1416, 1370, 1313, 1179, 1111, 818, 680, 653 cm^{-1}.

7.6.4.31. Synthesis of 2-diazoacetic acid 2-(1,3-dioxoisoindolin-2-yl)ethyl ester (1ae)

[CAS No.: 1979189-49-5]

Compound **1ae** was prepared following the standard procedure 3, starting from *N*-(2-hydroxyethyl)phthalimid. After purification, **1ae** was isolated as yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ = 7.79-7.98 (m, 2H), 7.65-7.79 (m, 2H), 4.72 (br. s, 1H), 4.39 (t, ³*J* = 5.3 Hz, 2H), 3.97 ppm (t, ³*J* = 5.3 Hz, 2H); **¹³C NMR** (101 MHz, CDCl₃): δ = 168.0 (2C), 134.0 (2C), 131.9 (2C), 123.3 (2C), 61.9, 37.1 ppm; **IR** (ATR): ν = 3116, 2113, 1688, 1607, 1517, 1385, 1341, 1233, 1148, 1109, 1013, 960, 841, 738, 692 cm⁻¹.

7.6.4.32. Synthesis of 2-diazophenylacetic acid ethyl ester (1af)[223]
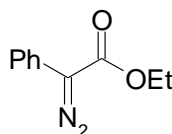
[CAS No.: 22065-57-2]

At room temperature, a solution of 1,8-diazabicyclo-[5.4.0]-undec-7-ene (2.28 g, 15.0 mmol) in anhydrous acetonitrile (10 mL) was added dropwise to a solution of ethyl phenyl acetate (1.64 g, 10.0 mmol) and *p*-toluenesulfonyl azide (2.37 g, 12.0 mmol, 1.20 equiv.) in anhydrous acetonitrile (50 mL). Then the reaction mixture was stirred at room temperature for 15 hours. The purification followed the standard procedure 1 and yielded **1af** as yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ = 7.45-7.59 (m, 2H), 7.37-7.45 (m, 2H), 7.17-7.22 (m, 1H), 4.35 (q, ³*J* = 7.1 Hz, 2H), 1.36 ppm (t, ³*J* = 7.1 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃): δ = 165.2, 128.9 (2C), 125.7, 125.6, 123.9 (2C), 61.0, 14.5 ppm; **IR** (ATR): ν = 2981, 2079, 1698, 1499, 1370, 1337, 1242, 1149, 1048, 1027, 752, 690, 666 cm⁻¹.

7.6.5. Synthesis of Trifluoromethyl Thioethers from the corresponding α-Diazo Esters
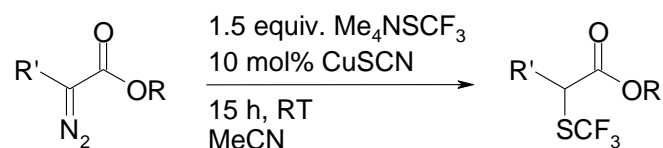
Standard procedure: An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with CuSCN (12.0 mg, 0.10 mmol), Me_4NSCF_3 (262 mg, 1.50 mmol) and MeCN (2 mL). Then, α-diazo ester **1a-ag** (1.00 mmol) in MeCN (2 mL) was added dropwise and the reaction mixture was stirred for 15 h at room temperature. 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 trifluoromethyl thioethers **2a-ag**. The yields of a few compounds were determined by ^{19}F NMR, and their identity confirmed by mass spectroscopy.

7.6.5.1. Synthesis of 2-[(trifluoromethyl)thio]-3-phenylpropanoic acid ethyl ester (2a)
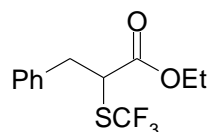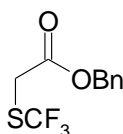

[CAS No.: 1584158-30-4]

Compound **2a** was prepared following the standard procedure, starting from 2-diazo-3-phenylpropanoic acid ethyl ester (**1a**, 204 mg, 1.00 mmol). After purification, **2a** was isolated as colorless oil (270 mg, 0.97 mmol, 97%).

Upscale of 2-[(trifluoromethyl)thio]-3-phenylpropanoic acid ethyl ester (2a)

An oven-dried 50 mL flask with Teflon-coated stirrer bar was charged with copper thiocyanate (123 mg, 1.00 mmol) and Me_4NSCF_3 (2.63 g, 15.0 mmol) in MeCN (10 mL). To this, a solution of 2-diazo-3-phenylpropanoic acid ethyl ester (**1a**, 2.04 g, 10.0 mmol) in MeCN (10 mL) was added in one portion at room temperature. The suspension was stirred at room temperature for 15 h. The 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

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(2 × 50 mL) and brine (50 mL). The organic layer was dried over MgSO₄, filtered and concentrated (700 mbar, 40°C). The residue was further purified by flash chromatography (SiO₂, cyclohexane/ethyl acetate gradient), and **2a** was isolated as colorless oil (2.53 g, 9.10 mmol, 91%).

^{1}H NMR (400 MHz, CDCl₃): δ = 7.29-7.21 (m, 3H), 7.16-7.14 (m, 2H), 4.12-4.04 (m, 2H), 3.98 (dd, ^3J = 6.5, 2.8 Hz, 1H), 3.15 (m, 2H), 1.12 ppm (t, ^3J = 7.2 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl₃): δ = −40.5 ppm; **^{13}C NMR** (101 MHz, CDCl₃): δ = 170.3, 136.1, 130.1 (q, ^1J(C,F) = 306.7 Hz), 129.1 (2C), 128.7 (2C), 127.4, 62.0, 47.5 (q, ^3J(C,F) = 1.8 Hz), 38.3, 13.8 ppm; **IR** (ATR): ν = 3460, 2971, 1740, 1497, 1455, 1370, 1229, 1217, 1159, 1109, 1033, 912, 748, 698 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 205 [M^+-($C_3H_5O_2$)] (4), 177 (28), 91 (100); **HRMS** (EI-TOF) calcd. for C₉H₉F₃S: 205.0299; found: 205.0301 [M^+-($C_3H_5O_2$)].

7.6.5.2. Synthesis of 2-[(trifluoromethyl)thio]-3-phenylpropanoic acid benzyl ester (2b)
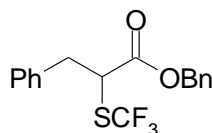
[CAS No.: 1979189-50-8]

Compound **2b** was prepared following the standard procedure, starting from 2-diazo-3-phenylpropanoic acid benzyl ester (**1b**, 266 mg, 1.00 mmol). After purification, **2b** was isolated as colorless oil (333 mg, 0.98 mmol, 98%). **^{1}H NMR** (400 MHz, CDCl₃): δ = 7.26-7.25 (m, 3H), 7.21-7.19 (m, 3H), 7.13-7.11 (m, 2H), 7.08-7.06 (m, 2H), 5.02 (dd, ^3J = 12.0, 3.8 Hz, 2H), 4.01 (dd, ^3J = 6.3, 3.0 Hz, 1H), 3.19-3.06 ppm (m, 2H); **^{19}F NMR** (375 MHz, CDCl₃): δ = −40.4 ppm; **^{13}C NMR** (101 MHz, CDCl₃): δ = 170.1, 135.9, 134.8, 130.0 (q, ^1J(C,F) = 306.5 Hz), 129.1 (2C), 128.7 (2C), 128.6 (2C), 128.5, 128.3 (2C), 67.7, 47.5 (q, ^3J(C,F) = 1.8 Hz), 38.2 ppm; **IR** (ATR): ν = 3031, 2970, 2949, 1739, 1498, 1456, 1366, 1217, 1151, 1099, 976, 743, 695 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 339 [M^+] (1), 193 (15), 161 (42), 91 (100), 65 (20); **HRMS** (EI-TOF) calcd. for C₉H₈F₃S: 205.0293; found: 205.0285 [M^+-(COOBn)].

7.6.5.3.   Synthesis of 2-[(trifluoromethyl)thio]propanoic acid ethyl ester (2c)
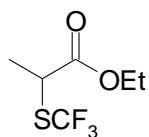

[CAS No.: 84132-15-0]

Compound **2c** was prepared following the standard procedure, starting from 2-diazopropanoic acid ethyl ester (**1c**, 128 mg, 1.00 mmol). After purification, **2c** was isolated as colorless oil (168 mg, 0.83 mmol, 83%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 4.29-4.17 (m, 2H), 3.93 (q, $^3J = 7.3$ Hz, 1H), 1.60 (q, $^3J = 7.3$ Hz, 3H), 1.30 ppm (t, $^3J = 7.0$ Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.6 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 171.1, 130.1 (q, ^1J(C,F) = 307.0 Hz), 62.1, 41.3 (q, ^3J(C,F) = 1.8 Hz), 18.3, 13.9 ppm; **IR** (ATR): ν = 3003, 2971, 2948, 1739, 1367, 1217, 1106, 1073, 861, 652 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 202 [M^+] (9), 129 (100); **HRMS** (EI-TOF) calcd. for C$_6$H$_9$O$_2$F$_3$S: 202.0275; found: 202.0283.

### 7.6.5.4.   Synthesis of 2-[(trifluoromethyl)thio]-propanoic acid benzyl ester (2d)
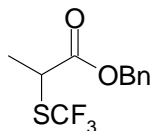
[CAS No.: 1979189-51-9]

Compound **2d** was prepared following the standard procedure, starting from 2-diazopropanoic acid benzyl ester (**1d**, 190 mg, 1.00 mmol). After purification, **2d** was isolated as colorless oil (222 mg, 0.84 mmol, 84%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.42-7.27 (m, 5H), 5.21 (dd, $^3J = 12.3$, 1.8 Hz, 2H), 4.00 (q, $^3J = 7.3$ Hz, 1H), 1.63 ppm (d, $^3J = 7.3$ Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.5 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 170.9, 135.0, 130.1 (q, ^1J(C,F) = 307.9 Hz), 128.6 (2C), 128.5, 128.3 (2C), 67.8, 41.5 (q, ^3J(C,F) = 1.8 Hz), 18.3 ppm; **IR** (ATR): ν = 3006, 2971, 1739, 1366, 1217, 1104, 752, 696 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 264 [M^+] (5), 129 (11), 91 (100); **HRMS** (EI-TOF) calcd. for C$_{11}$H$_{11}$O$_2$F$_3$S: 264.0432; found: 264.0411.

7.6.5.5. Synthesis of 2-[(trifluoromethyl)thio]acetic acid ethyl ester (2e)
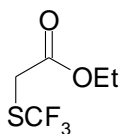
[CAS No.: 65540-51-4]

Compound **2e** was prepared following the standard procedure, starting from 2-diazoacetic acid ethyl ester (**1e**, 114 mg, 1.00 mmol). After purification, **2e** was isolated as colorless oil (175 mg, 0.93 mmol, 93%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 4.24 (q, ^3J = 7.0 Hz, 2H), 3.66 (s, 2H), 1.30 ppm (t, ^3J = 7.0 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −42.3 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 167.6, 130.1 (q, ^1J(C,F) = 307.0 Hz), 62.3, 31.9 (q, ^3J(C,F) = 2.7 Hz), 13.9 ppm; **IR** (ATR): ν = 2989, 1740, 1453, 1371, 1321, 1246, 1102, 1068, 1019, 860, 799, 757 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 188 [M^+] (17), 143 (13), 115 (100); **HRMS** (EI-TOF) calcd. for C$_5$H$_7$F$_3$O$_2$S: 188.0119; found: 188.0126.

7.6.5.6. Synthesis of 2-[(trifluoromethyl)thio]acetic acid benzyl ester (2f)

[CAS No.: 1481718-86-8]

Compound **2f** was prepared following the standard procedure, starting from 2-diazoacetic acid ethyl ester (**1f**, 176 mg, 1.00 mmol). After purification, **2f** was isolated as colorless oil (203 mg, 0.81 mmol, 81%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.43-7.38 (m, 5H), 5.23 (s, 2H), 3.72 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −42.2 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 167.4, 134.8, 130.0 (q, ^1J(C,F) = 307.0 Hz), 128.6 (2C), 128.4 (2C), 128.3, 68.0, 31.8 ppm (q, ^3J(C,F) = 2.7 Hz); **IR** (ATR): ν = 3015, 2970, 2949, 1739, 1366, 1217, 1099, 964, 739, 695 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 250 [M^+] (16), 108 (10), 91 (100), 65 (11); **HRMS** (EI-TOF) calcd. for C$_{10}$H$_9$O$_2$F$_3$S: 250.0275; found:250.0255.

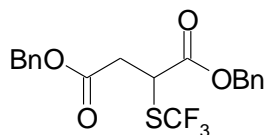### 7.6.5.7. Synthesis of 2-[(trifluoromethyl)thio]-4-methylpentanoic acid benzyl ester (2g)
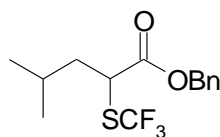
[CAS No.: 1979189-52-0]

Compound **2g** was prepared following the standard procedure, starting from 2-[(trifluoromethyl)thio]-4-methylpentanoic acid benzyl ester (**1g**, 116 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 trifluoromethylthiolated product **2g** was formed in 89% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = −41.3 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 306 [M^+] (3), 171 (14), 91 (100), 69 (19); **HRMS** (EI-TOF) calcd. for $C_{14}H_{17}O_2F_3S$: 306.0901; found: 306.0898.

7.6.5.8. Synthesis of (3S)-2-[(trifluoromethyl)thio]-3-methylpentanoic acid benzyl ester (2h)
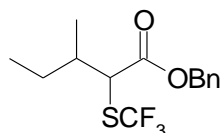
[CAS No.: 1979189-53-1]

Compound **2h** was prepared following the standard procedure, starting from (3*S*)-2-diazo-3-methylpentanoic acid benzyl ester (**1h**, 116 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 trifluoromethylthiolated product **2h** was formed in 81% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = −41.2 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 306 [M^+] (1), 161 (30), 133 (12), 91 (100), 65 (28), 41 (17).
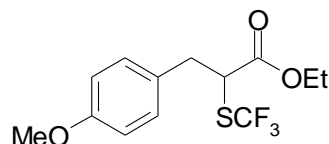
7.6.5.9. Synthesis of 2-[(trifluoromethyl)thio]-3-hydroxypropanoic acid ethyl ester (2i)
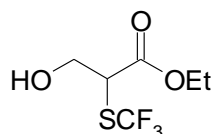
[CAS No.: 1979189-54-2]

Compound **2i** was prepared following the standard procedure, starting from 2-diazo-3-hydroxypropanoic acid ethyl ester (**1i**, 144 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 trifluoromethylthiolated product **2i** was formed in 48% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = −41.4 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 218 [M^+] (13), 70 (100), 55 (50), 43 (64).

7.6.5.10. Synthesis of 2-[(trifluoromethyl)thio]-3-(4-hydroxyphenyl)propanoic acid methyl ester (2j)
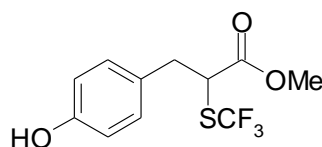
[CAS No.: 1979189-55-3]

Compound **2j** was prepared following the standard procedure, starting from 2-diazo-3-(4-hydroxyphenyl)propanoic acid methyl ester (**1j**, 206 mg, 1.00 mmol). After purification, **2j** was isolated as colorless oil (263 mg, 0.94 mmol, 94%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.29 (d, ^3J = 8.5 Hz, 2H), 7.17 (d, ^3J = 8.5 Hz, 2H), 4.04 (dd, ^3J = 6.3, 2.8 Hz, 1H), 3.69 (s, 3H), 3.31-3.16 ppm (m, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.5 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 170.5, 152.7, 134.8, 130.4 (2C), 129.9 (q, ^1J(C,F) = 307.0 Hz), 122.1 (2C), 52.9, 47.2 (q, ^3J(C,F) = 1.8 Hz), 37.7 ppm; **IR** (ATR): ν = 3007, 2970, 2950, 1739, 1507, 1438, 1366, 1273, 1217, 1183, 1157, 1105, 1017, 987, 846, 822 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 280 [M^+] (1), 179 (24), 147 (16), 107(100), 82 (49), 63 (13); **HRMS** (EI-TOF) calcd. for C$_{11}$H$_{11}$O$_3$F$_3$S: 280.0381; found: 280.0386.

7.6.5.11. Synthesis of 2-[(trifluoromethyl)thio]-4-(methylthio)butanoic acid ethyl ester (2k)
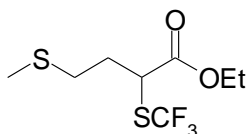
[CAS No.: 1979189-56-4]

Compound **2k** was prepared following the standard procedure, starting from 2-diazo-4-(methylthio)butanoic acid ethyl ester (**1k**, 188 mg, 1.00 mmol). After purification, **2k** was isolated as yellow oil (254 mg, 0.97 mmol, 97%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 4.28-4.21 (m, 2H), 3.99 (t, ^3J = 7.3 Hz, 1H), 2.60 (dt, ^3J = 7.5, 1.8 Hz, 2H), 2.25 (sxt, ^3J = 7.0 Hz, 1H), 2.11 (sxt, ^3J = 7.0 Hz, 1H), 2.10 (s, 3H), 1.30 ppm (t, ^3J = 7.2 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.3 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 170.4, 130.0 (q, ^1J(C,F) = 307.5 Hz), 62.2, 45.0, 31.0, 30.8, 15.2, 13.9 ppm; **IR** (ATR): ν = 2957, 2929, 1736, 1249, 1162, 1111, 1028, 656 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 262 [M^+] (12), 193 (100), 188 (23), 160 (29); **HRMS** (EI-TOF) calcd. for C$_8$H$_{13}$F$_3$O$_2$S$_2$: 262.0309; found: 262.0292.

7.6.5.12. Synthesis of 2-[(trifluoromethyl)thio]-butanedioic acid 1,4-bis(phenylmethyl) ester (2l)

[CAS No.: 1979189-57-5]

Compound **2l** was prepared following the standard procedure, starting from 2-diazo-butanedioic acid 1,4-bis(phenylmethyl) ester (**1l**, 162 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 trifluoromethylthiolated product **2l** was formed in 83% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = −41.3 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 180.0 (7), 106.8 (82), 92.0 (13), 91.0 (100), 79.1 (15), 77.0 (8), 65.0 (22).

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7.6.5.13. Synthesis of 2-[(trifluoromethyl)thio]-1,5-pentanedioic acid dimethyl ester (2m)
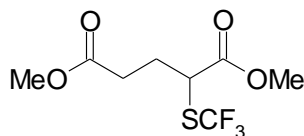
[CAS No.: 1979189-58-6]

Compound **2m** was prepared following the standard procedure, starting from 2-diazo-1,5-pentanedioic acid dimethyl ester (**1m**, 186 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 trifluoromethylthiolated product **2m** was formed in 96% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = −40.6 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 260 [M^+] (5), 227 (88), 201 (20), 181 (15), 159 (23), 141 (32), 131 (100), 115 (44).

7.6.5.14. Synthesis of 2-[(trifluoromethyl)thio]-1H-Indole-3-propanoic acid ethyl ester (2n)
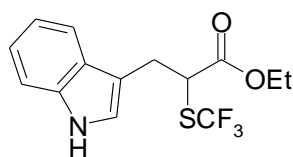
[CAS No.: 1979189-59-7]

Compound **2n** was prepared following the standard procedure, starting from 2-diazo-1H-Indole-3-propanoic acid ethyl ester (**1n**, 243 mg, 1.00 mmol). After purification, **2n** was isolated as colorless oil (273 mg, 0.86 mmol, 86%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.10 (s, 1H), 7.59 (d, ^3J = 8.0 Hz, 1H), 7.38 (d, ^3J = 8.0 Hz, 1H), 7.23 (dt, ^3J = 7.0, 1.3 Hz, 1H), 7.17 (dt, ^3J = 8.0, 1.0 Hz, 1H), 7.08 (d, ^3J = 2.3 Hz, 1H), 4.18-4.05 (m, 3H), 3.49-3.31 (m, 2H), 1.15 ppm (t, ^3J = 7.2 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.3 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 170.8, 136.0, 130.2 (q, ^1J(C,F) = 307.4 Hz), 126.9, 123.1, 122.4, 119.8, 118.4, 111.3, 110.7, 61.9, 46.8 (q, ^3J(C,F) = 1.5 Hz), 28.4, 13.8 ppm; **IR** (ATR): ν = 3413, 2984, 1729, 1457, 1157, 1106, 1030, 741 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z

(%) = 317 [M^+] (17), 215 (30), 142 (28), 130 (100), 81 (27); **HRMS** (EI-TOF) calcd. for C$_{14}$H$_{14}$F$_3$O$_2$SN: 317.0697; found: 317.0690.
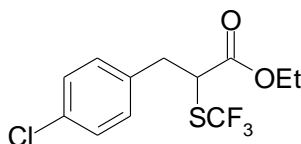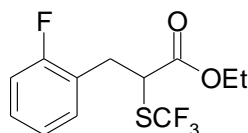
7.6.5.15. Synthesis of 2-[(trifluoromethyl)thio]-3-(4-methoxyphenyl)propanoic acid ethyl ester (2o)

[CAS No.: 1979189-60-0]

Compound **2o** was prepared following the standard procedure, starting from 2-diazo-3-(4-methoxyphenyl)propanoic acid ethyl ester (**1o**, 234 mg, 1.00 mmol). After purification, **2o** was isolated as colorless oil (293 mg, 0.95 mmol, 95%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.12 (d, ^3J = 8.5 Hz, 2H), 6.85 (d, ^3J = 8.5 Hz, 2H), 4.14 (m, 2H), 3.99 (dd, ^3J = 6.5, 2.8 Hz, 1H), 3.79 (s, 3H), 3.13 (m, 2H), 1.19 ppm (t, ^3J = 7.3 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.5 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 170.3, 158.9, 130.1 (2C), 130.1 (q, ^1J(C,F) = 307.4 Hz), 128.0, 114.0 (2C), 61.9, 55.2, 47.7 (q, ^3J(C,F) = 1.8 Hz), 37.4, 13.8 ppm; **IR** (ATR): ν = 2991, 2971, 1740, 1515, 1371, 1249, 1157, 1107, 1036 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 308 [M^+] (4), 207 (16), 161 (14), 121 (100); **HRMS** (EI-TOF) calcd. for C$_{13}$H$_{15}$O$_3$F$_3$S: 308.0694; found: 308.0677.

7.6.5.16. Synthesis of 2-[(trifluoromethyl)thio]-3-(4-thiomethylphenyl)propanoic acid ethyl ester (2p)
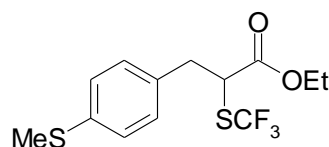
[CAS No.: 1979189-61-1]

Compound **2p** was prepared following the standard procedure, starting from 2-diazo-3-(4-thiomethylphenyl)propanoic acid ethyl ester (**1p**, 250 mg, 1.00 mmol). After purification, **2p** was isolated as yellow oil (317 mg, 0.98 mmol, 98%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.20 (d, ^3J = 8.3 Hz, 2H), 7.12 (d, ^3J = 8.3 Hz, 2H), 4.20-4.08 (m, 2H), 4.01-3.97 (m, 1H), 3.15

(dq, $^3J = 13.8, 9.3$ Hz, 2H), 2.47 (s, 3H), 1.19 ppm (t, $^3J = 7.2$ Hz, 3H); ^{19}**F NMR** (375 MHz, CDCl$_3$): δ = −40.4 ppm; ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 170.1, 137.7, 132.8, 130.0 (q, ^1J(C,F) = 307.5 Hz), 129.5 (2C), 126.6 (2C), 62.0, 47.4 (q, ^3J(C,F) = 1.8 Hz), 37.6, 15.7, 13.8 ppm; **IR** (ATR): ν = 2986, 1737, 1496, 1442, 1261, 1234, 1154, 1098, 1032, 1017, 9869, 805, 758 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 324 [M^+] (15), 223 (20), 117 (17), 137 (100), 122 (10); **HRMS** (EI-TOF) calcd. for C$_{13}$H$_{15}$F$_3$O$_2$S$_2$: 324.0466; found: 324.0471.
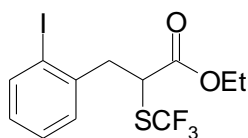
7.6.5.17. Synthesis of 2-[(trifluoromethyl)thio]-3-(4-cyanophenyl)propanoic acid ethyl ester (2q)
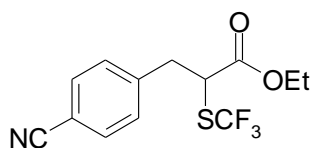
[CAS No.: 1979189-62-2]

Compound **2q** was prepared following the standard procedure, starting from 2-diazo-3-(4-cyanophenyl)propanoic acid ethyl ester (**1q**, 186 mg, 1.00 mmol). After purification, **2q** was isolated as colorless oil (246 mg, 0.81 mmol, 81%). ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 7.62 (d, $^3J = 8.3$ Hz, 2H), 7.33 (d, $^3J = 8.3$ Hz, 2H), 4.20-4.11 (m, 2H), 4.02-3.98 (m, 1H), 3.34-3.17 (m, 2H), 1.19 ppm (t, $^3J = 7.3$ Hz, 3H); ^{19}**F NMR** (375 MHz, CDCl$_3$): δ = −40.3 ppm; ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 169.6, 141.5, 132.4 (2C), 129.8 (q, ^1J(C,F) = 307.0 Hz), 130.0 (2C), 118.5, 111.5, 62.3, 45.8 (q, ^3J(C,F) = 1.8 Hz), 38.1, 13.8 ppm; **IR** (ATR): ν = 2991, 2970, 2231, 1738, 1609, 1371, 1217, 1010, 1023, 853, 655 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 230 [M^+-(C$_3$H$_5$O$_2$)] (9), 202 (100), 174 (62), 156 (40), 116 (70); **HRMS** (EI-TOF) calcd. for C$_{10}$H$_7$NF$_3$S: 230.0251; found: 230.0264 [M^+-(C$_3$H$_5$O$_2$)].

7.6.5.18. Synthesis of 2-[(trifluoromethyl)thio]-3-(4-chlorophenyl)propanoic acid ethyl ester (2r)
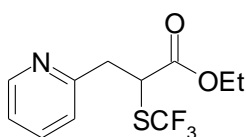

[CAS No.: 1979189-63-3]

Compound **2r** was prepared following the standard procedure, starting from 2-diazo-3-(4-chlorophenyl)propanoic acid ethyl ester (**1r**, 238 mg, 1.00 mmol). After purification, **2r** was isolated as colorless oil (247 mg, 0.79 mmol, 79%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.29 (d, ^3J = 8.5 Hz, 2H), 7.14 (d, ^3J = 8.5 Hz, 2H), 4.21-4.10 (m, 2H), 3.98 (dd, ^3J = 6.5, 2.8 Hz, 1H), 3.24-3.09 (m, 2H), 1.20 ppm (t, ^3J = 7.3 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.4 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 170.0, 134.5, 133.4, 130.5 (2C), 128.8 (2C), 130.0 (q, ^1J(C,F) = 307.4 Hz), 62.1, 47.7 (q, ^3J(C,F) = 1.8 Hz), 37.6, 13.8 ppm; **IR** (ATR): ν = 2971, 1739, 1494, 1371, 1217, 1098, 1016, 809, 758 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 238 [M^+-(C$_3$H$_5$O$_2$)] (2), 211 (67), 165 (21), 127 (26), 125 (100); **HRMS** (EI-TOF) calcd. for C$_9$H$_7$F$_3$^{35}ClS: 238.9909; found: 238.9894 [M^+-(C$_3$H$_5$O$_2$)].
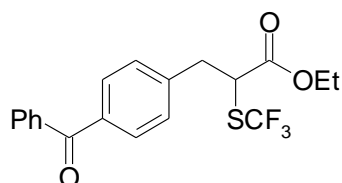
7.6.5.19. *Synthesis of 2-[(trifluoromethyl)thio]-3-(2-fluorophenyl)propanoic acid ethyl ester (2s)*

[CAS No.: 1979189-64-4]

Compound **2s** was prepared following the standard procedure, starting from 2-diazo-3-(2-fluorophenyl)propanoic acid ethyl ester (**1s**, 222 mg, 1.00 mmol). After purification, **2s** was isolated as colorless oil (234 mg, 0.79 mmol, 79%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.30-7.25 (m, 1H), 7.19 (dt, ^3J = 7.5, 1.5 Hz, 1H), 7.11-7.04 (m, 2H), 4.20-4.11 (m, 1H), 4.09 (t, ^3J = 8.0 Hz, 2H), 3.24 (d, ^3J = 7.8 Hz, 2H), 1.18 ppm (t, ^3J = 7.2 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.5, −117.5 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 170.1, 161.3 (d, ^1J(C,F) = 246.0 Hz), 131.5 (d, ^3J(C,F) = 4.5 Hz), 130.0 (q, ^1J(C,F) = 307.0 Hz), 129.4 (d, ^3J(C,F) = 8.2 Hz), 124.2 (d, ^4J(C,F) = 3.6 Hz), 123.2 (d, ^2J(C,F) = 15.4 Hz), 115.5 (d, ^2J(C,F) = 21.8 Hz), 62.0, 40.1, 32.2, 13.8 ppm; **IR** (ATR): ν = 2989, 1739, 1494, 1271, 1232, 1158, 1010, 1032, 755 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 296 [M^+] (5), 223 (14), 195 (92), 167 (30), 149 (25), 109 (100); **HRMS** (EI-TOF) calcd. for C$_{12}$H$_{12}$F$_4$O$_2$S: 296.0494; found: 296.0492.

7.6.5.20. Synthesis of 2-[(trifluoromethyl)thio]-3-(2-bromophenyl)propanoic acid ethyl ester (2t)
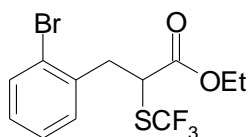
[CAS No.: 1979189-65-5]

Compound **2t** was prepared following the standard procedure, starting from 2-diazo-3-(2-bromophenyl)propanoic acid ethyl ester (**1t**, 283 mg, 1.00 mmol). After purification, **2t** was isolated as colorless oil (268 mg, 0.75 mmol, 75%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.62 (d, ^3J = 7.0 Hz, 1H), 7.32-7.25 (m, 2H), 7.21-7.17 (m, 1H), 4.27-4.23 (m, 1H), 4.22-4.13 (m, 2H), 3.42-3.21 (m, 2H), 1.21 ppm (t, ^3J = 7.0 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.2 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 170.1, 135.6, 133.1, 131.7, 130.0 (q, ^1J(C,F) = 307.9 Hz), 129.2, 127.5, 124.6, 62.0, 45.4 (q, ^3J(C,F) = 1.8 Hz), 38.7, 13.8 ppm; **IR** (ATR): ν = 2971, 1739, 1444, 1371, 1217, 1154, 1102, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 282 [M^+-($C_3H_5O_2$)] (9), 277 [M^+-(Br)] (100), 255 (42), 230 (2), 215 (2), 209 (18), 184 (4), 169 (68); **HRMS** (EI-TOF) calcd. for C$_9$H$_7$^{79}BrF$_3$S: 282.9404; found: 282.9405 [M^+-($C_3H_5O_2$)]; calcd. for C$_{12}$H$_{12}$F$_3$O$_2$S: 277.0516; found: 277.0494 [M^+-(Br)].

7.6.5.21. Synthesis of 2-[(trifluoromethyl)thio]-3-(2-iodophenyl)propanoic acid ethyl ester (2u)
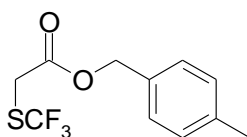

[CAS No.: 1979189-66-6]

Compound **2u** was prepared following the standard procedure, starting from 2-diazo-3-(2-iodo-phenyl)propanoic acid ethyl ester (**1u**, 330 mg, 1.00 mmol). After purification, **2u** was isolated as colorless oil (376 mg, 0.93 mmol, 93%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.85 (dd, ^3J = 8.0, 1.3 Hz, 1H), 7.31-7.27 (m, 1H), 7.21 (dd, ^3J = 7.8, 1.8 Hz, 1H), 6.97 (dt, ^3J = 7.5, 1.8 Hz, 1H), 4.21-4.09 (m, 3H), 3.30 (dq, ^3J = 13.8, 9.5 Hz, 2H), 1.18 ppm (t,

$^3J = 7.2$ Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.0 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 170.0, 139.9, 138.9, 130.9, 130.0 (q, ^1J(C,F) = 307.4 Hz), 129.2, 128.4, 100.3, 62.0, 45.6 (q, ^3J(C,F) = 1.8 Hz), 42.8, 13.8 ppm; **IR** (ATR): ν = 2986, 1738, 1565, 1468, 1441, 1370, 1290, 1261, 1155, 1098, 1034, 1012, 856, 748, 717 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 404 [M^+] (7), 303 (25), 277 (100), 217 (81), 135 (52); **HRMS** (EI-TOF) calcd. for C$_{12}$H$_{12}$F$_3$O$_2$SI: 403.9555; found: 403.9572.

7.6.5.22. *Synthesis of 2-[(trifluoromethyl)thio]-3-(2-pyridinyl)propanoic acid ethyl ester (2v)*

[CAS No.: 1979189-67-7]

Compound **2v** was prepared following the standard procedure, starting from 2-diazo-3-(2-pyridinyl)propanoic acid ethyl ester (**1v**, 205 mg, 1.00 mmol). After purification, **2v** was isolated as yellow oil (249 mg, 0.89 mmol, 89%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.53 (dd, ^3J = 5.8, 1.5 Hz, 1H), 7.62 (dt, ^3J = 7.5, 1.8 Hz, 1H), 7.18-7.15 (m, 2H), 4.42-4.39 (m, 1H), 4.22-4.14 (m, 2H), 3.39 (dq, ^3J = 14.8, 8.5 Hz, 2H), 1.21 ppm (t, ^3J = 7.2 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.3 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 170.4, 156.2, 149.4, 136.5, 130.1 (q, ^1J(C,F) = 307.9 Hz), 123.7, 122.1, 61.9, 45.2 (q, ^3J(C,F) = 2.7 Hz), 39.7, 13.8 ppm; **IR** (ATR): ν = 2929, 1711, 1594, 1482, 1440, 1347, 1207, 1154, 1107, 1053, 1015, 801, 760 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 234 [M^+] (7), 210 (100), 182 (15), 136 (84), 93 (19); **HRMS** (EI-TOF) calcd. for C$_9$H$_7$F$_3$ONS: 234.0200; found: 234.0198.

7.6.5.23. Synthesis of 2-[(trifluoromethyl)thio]-3-(4-benzoylphenyl)propanoic acid ethyl ester (2w)

[CAS No.: 1979189-68-8]

Compound **2w** was prepared following the standard procedure, starting from 2-diazo-3-(4-benzoylphenyl)propanoic acid ethyl ester (**1w**, 308 mg, 1.00 mmol). After purification, **2w** was isolated as colorless (367 mg, 0.96 mmol, 96%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.79-7.76 (m, 4H); 7.60 (tt, ^3J = 7.5, 2.0 Hz, 1H), 7.49 (t, ^3J = 7.5 Hz, 2H), 7.33 (d, ^3J = 8.3 Hz, 2H), 4.21-4.13 (m, 2H), 4.09-4.05 (m, 1H), 3.28 (dq, ^3J = 14.1, 9.0 Hz, 2H), 1.21 ppm (t, ^3J = 7.0 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.3 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 196.1, 169.9, 140.8, 137.4, 136.7, 132.5, 130.4 (2C), 129.9 (q, ^1J(C,F) = 307.4 Hz), 129.9 (2C), 129.1 (2C), 128.3 (2C), 62.2, 47.1 (q, ^3J(C,F) = 1.8 Hz), 38.1, 13.8 ppm; **IR** (ATR): ν = 2990, 1738, 1658, 1608, 1580, 1317, 1276, 1152, 1101, 1028, 938, 923, 758, 735, 698 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 309 [M^+-$(COOC_2H_5)$] (5), 281 (100), 253 (21), 1996 (19), 166 (36), 131 (7), 105 (36); **HRMS** (EI-TOF) calcd. for C$_{16}$H$_{12}$F$_3$OS: 309.0561; found: 309.0563 [M^+-$(COOC_2H_5)$].

7.6.5.24. Synthesis of (4E)-2-[(trifluoromethyl)thio]-5-phenyl-4-pentenoic acid ethyl ester (2x)
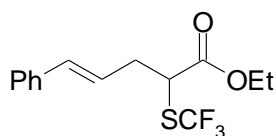
[CAS No.: 1979189-69-9]

Compound **2x** was prepared following the standard procedure, starting from (4E)-2-diazo-5-phenyl-4-pentenoic acid ethyl ester (**1x**, 230 mg, 1.00 mmol). After purification, **2x** was isolated as colorless oil (283 mg, 0.93 mmol, 93%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.32-

234

7.25 (m, 4H), 7.20 (tt, ^3J = 6.8, 1.8 Hz, 1H), 7.49 (d, ^3J = 15.9 Hz, 1H), 6.12-6.05 (m, 1H), 4.22-4.15 (m, 2H), 3.92-3.88 (m, 1H), 2.84-2.69 (m, 2H), 1.23 ppm (t, ^3J = 7.2 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = –40.4 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 170.2, 135.5, 134.4, 130.1 (q, ^1J(C,F) = 307.4 Hz), 128.6 (2C), 127.7, 136.2 (2C), 123.4, 62.1, 46.3 (q, ^3J(C,F) = 1.8 Hz), 35.6, 14.0 ppm; **IR** (ATR): ν = 2989, 1739, 1449, 1262, 1158, 1108, 1030, 966, 859, 758, 744, 693 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 304 [M^+] (20), 203 (88), 157 (60), 129 (44), 117 (100); **HRMS** (EI-TOF) calcd. for C$_{14}$H$_{15}$F$_3$O$_2$S: 304.0745; found: 304.0739.

7.6.5.25. *Synthesis of 2-[(trifluoromethyl)thio]acetic acid 4-methylbenzyl ester (2y)*
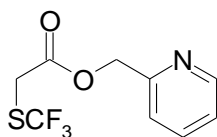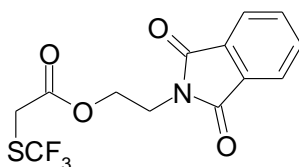

[CAS No.: 1979189-70-2]

Compound **2y** was prepared following the standard procedure, starting from 2-diazo acetic acid 4-methylbenzyl ester (**1y**, 190 mg, 1.00 mmol). After purification, **2y** was isolated as colorless solid (251 mg, 0.95 mmol, 95%). **m.p.**: 45-46°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.28 (d, ^3J = 7.8 Hz, 2H), 7.21 (d, ^3J = 7.8 Hz, 2H), 5.18 (s, 2H), 3.70 (s, 2H), 2.38 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = –42.3 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 167.5, 138.6, 131.8, 130.1 (q, ^1J(C,F) = 307.0 Hz), 129.3 (2C), 128.6 (2C), 70.0, 31.8 (q, ^3J(C,F) = 1.8 Hz), 21.2 ppm; **IR** (ATR): ν = 2970, 1740, 1519, 1298, 1218, 1104, 963, 808 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 264 [M^+] (20), 115 (9), 105 (100), 77 (10); **HRMS** (EI-TOF) calcd. for C$_{11}$H$_{11}$F$_3$O$_2$S: 264.0432; found: 264.0423.

7.6.5.26. *Synthesis of 2-[(trifluoromethyl)thio]acetic acid 4-phenylbenzyl ester (2z)*
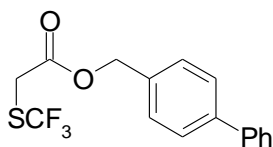
[CAS No.: 1979189-71-3]

Compound **2z** was prepared following the standard procedure, starting from biphenyl-4-ylmethyl 2-diazoacetate (**1z**, 252 mg, 1.00 mmol). After purification, **2z** was isolated as colorless oil (306 mg, 0.94 mmol, 94%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.65-7.61 (m, 4H), 7.50-7.46 (m, 4H), 7.41-7.38 (m, 1H), 5.28 (s, 2H), 3.75 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −42.2 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 167.5, 141.7, 140.5, 133.7, 130.1 (q, ^1J(C,F) = 307.0 Hz), 129.0 (2C), 128.8 (2C), 127.6, 127.4 (2C), 127.1 (2C), 67.7, 31.8 ppm (q, ^3J(C,F) = 2.7 Hz); **IR** (ATR): ν = 3033, 1739, 1488, 1298, 1266, 1099, 1008, 967, 823, 757, 696 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 326 [M^+] (19), 167 (100), 152 (16); **HRMS** (EI-TOF) calcd. for C$_{16}$H$_{13}$F$_3$O$_2$S: 326.0588; found: 326.0569.

7.6.5.27. *Synthesis of 2-[(trifluoromethyl)thio]acetic acid 4-nitrobenzyl ester (2aa)*
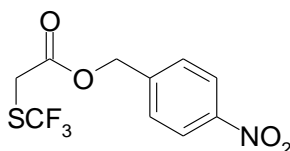
[CAS No.: 1979189-72-4]

Compound **2aa** was prepared following the standard procedure, starting from 2-diazoacetic acid 4-nitrobenzyl ester (**1aa**, 221 mg, 1.00 mmol). After purification, **2aa** was isolated as yellow oil (286 mg, 0.97 mmol, 97%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.25 (d, ^3J = 8.5 Hz, 2H), 7.54 (d, ^3J = 8.5 Hz, 2H), 5.31 (s, 2H), 3.75 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −42.2 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 167.3, 147.9, 141.9, 129.9 (q, ^1J(C,F) = 307.0 Hz), 128.6 (2C), 123.9 (2C), 66.3, 31.6 ppm (q, ^3J(C,F) = 1.8 Hz); **IR** (ATR): ν = 2989, 2096, 1693, 1593, 1497, 1373, 1323, 1301, 1238, 1167, 1039, 844, 750 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 295 [M^+] (7), 153 (12), 136 (100), 115 (34); **HRMS** (EI-TOF) calcd. for C$_{10}$H$_8$F$_3$O$_4$SN: 295.0126; found: 295.0123.

7.6.5.28. *Synthesis of 2-[(trifluoromethyl)thio]acetic acid 4-fluorobenzyl ester (2ab)*

[CAS No.: 1979189-73-5]

236
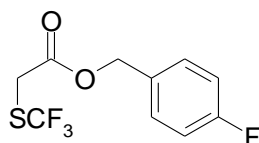
Compound **2ab** was prepared following the standard procedure, starting from 2-diazo acetic acid 4-fluorobenzyl ester (**1ab**, 194 mg, 1.00 mmol). After purification, **2ab** was isolated as colorless oil (263 mg, 0.98 mmol, 98%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.36 (m, 2H), 7.07 (m, 2H), 5.18 (s, 2H), 3.70 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −42.3, −112.8 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 167.4, 162.9 (d, ^1J(C,F) = 248.0 Hz), 130.7 (d, ^4J(C,F) = 2.7 Hz), 130.5 (d, ^3J(C,F) = 8.2 Hz, 2C), 130.0 (q, ^1J(C,F) = 307.0 Hz), 115.6 (d, ^2J(C,F) = 21.8 Hz, 2C), 67.2, 31.7 ppm (q, ^3J(C,F) = 2.7 Hz); **IR** (ATR): ν = 2953, 2174, 2137, 1743, 1607, 1514, 1376, 1299, 1227, 1107, 970, 854, 827, 757 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 268 [M^+] (6), 115 (6), 109 (100); **HRMS** (EI-TOF) calcd. for C$_{10}$H$_8$F$_4$O$_2$S: 268.0181; found: 268.0180.

7.6.5.29. *Synthesis of 2-[(trifluoromethyl)thio]acetic acid 3-iodobenzyl ester (2ac)*
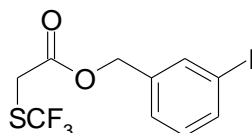
[CAS No.: 1979189-74-6]

Compound **2ac** was prepared following the standard procedure, starting from 2-diazoacetic acid 3-iodobenzyl ester (**1ac**, 302 mg, 1.00 mmol). After purification, **2ac** was isolated as colorless oil (286 mg, 0.76 mmol, 76%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.73 (s, 1H), 7.69 (d, ^3J = 8.0 Hz, 1H), 7.34 (d, ^3J = 7.3 Hz, 1H), 7.12 (t, ^3J = 7.0 Hz, 1H), 5.14 (s, 2H), 3.72 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −42.2 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 167.3, 137.7, 137.2, 137.0, 130.3, 130.0 (q, ^1J(C,F) = 307.0 Hz), 127.5, 94.3, 66.8, 31.7 ppm (q, ^3J(C,F) = 2.9 Hz); **IR** (ATR): ν = 2970, 1740, 1568, 1372, 1297, 1217, 1098, 997, 973, 773, 657 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 376 [M^+] (31), 234 (100), 232 (52), 216 (70), 127 (25), 82 (50); **HRMS** (EI-TOF) calcd. for C$_{10}$H$_8$F$_3$O$_2$SI: 375.9242; found: 375.9254.

7.6.5.30.   *Synthesis of 2-[(trifluoromethyl)thio]acetic acid 2-pyridinylmethyl ester (2ad)*

[CAS No.: 1979189-75-7]

Compound **2ad** was prepared following the standard procedure, starting from 2-diazo acetic acid 2-pyridinylmethyl ester (**1ad**, 177 mg, 1.00 mmol). After purification, **2ad** was isolated as yellow oil (106 mg, 0.42 mmol, 42%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.61 (d, ^3J = 4.5 Hz, 1H), 7.73 (dt, ^3J = 7.8, 1.8 Hz, 1H), 7.37 (d, ^3J = 7.8 Hz, 1H), 7.27 (t, ^3J = 5.8 Hz, 1H), 5.32 (s, 2H), 3.78 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −42.2 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 167.4, 154.6, 149.6, 136.9, 130.0 (q, ^1J(C,F) = 307.0 Hz), 123.2, 122.0, 68.3, 31.7 ppm (q, ^3J(C,F) = 2.7 Hz); **IR** (ATR): ν = 1973, 1742, 1595, 1439, 1372, 1218, 1108, 757 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 251 [M^+] (2), 182 (43), 136 (25), 115 (30), 108 (50), 92 (100); **HRMS** (EI-TOF) calcd. for C$_9$H$_8$F$_3$NO$_2$S: 251.0228; found: 251.0225.

7.6.5.31.   *Synthesis of 2-[(trifluoromethyl)thio]acetic acid 2-(1,3-dioxoisoindolin-2-yl)ethyl ester (2ae)*

[CAS No.: 1979189-76-8]

Compound **2ae** was prepared following the standard procedure, starting from 2-diazoacetic acid 2-(1,3-dioxoisoindolin-2-yl)ethyl ester (**1ae**, 259 mg, 1.00 mmol). After purification, **2ae** was isolated as colorless oil (290 mg, 0.87 mmol, 87%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.89-7.85 (m, 2H), 7.77-7.73 (m, 2H), 4.43 (t, ^3J = 5.2 Hz, 2H), 4.00 (t, ^3J = 5.2 Hz, 2H), 3.66 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −42.4 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 168.1 (2C), 167.5, 134.2 (2C), 131.8 (2C), 130.0 (q, ^1J(C,F) = 307.0 Hz), 123.4

(2C), 63.3, 36.6, 31.6 ppm (q, ^3J(C,F) = 1.8 Hz); **IR** (ATR): ν = 2970, 1710, 1393, 1367, 1305, 1106, 720 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 333 [M^+] (2), 173 (48), 160 (100), 115 (16); **HRMS** (EI-TOF) calcd. for C$_{13}$H$_{10}$F$_3$NO$_4$S: 333.0283; found: 333.0292.

7.6.5.32. *Synthesis of 2-[(trifluoromethyl)thio]phenylacetic acid ethyl ester (2af)*
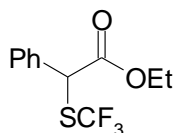
[CAS No.: 1584158-10-0]

Compound **2af** was prepared following the standard procedure, starting from 2-diazophenylacetic acid ethyl ester (**1af**, 190 mg, 1.00 mmol). After purification, **2af** was isolated as colorless oil (119 mg, 0.45 mmol, 45%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.48-7.45 (m, 2H), 7.41-7.36 (m, 3H), 5.06 (s, 1H), 4.34-4.15 (m, 2H), 1.27 ppm (t, ^3J = 7.0 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.1 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 169.0, 134.0, 129.8 (q, ^1J(C,F) = 307.9 Hz), 129.1 (2C), 129.0, 128.2 (2C), 62.6, 51.4 (q, ^3J(C,F) = 1.8 Hz), 13.9 ppm; **IR** (ATR): ν = 2992, 2971, 1738, 1368, 1217, 1151, 1104, 1023, 757, 724, 694 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 264 [M^+] (6), 191 (100), 122 (17), 121 (21); **HRMS** (EI-TOF) calcd. for C$_{11}$H$_{11}$O$_2$F$_3$S: 264.0432; found: 264.0424.

7.6.5.33. *Synthesis of [1-(trifluoromethylthio)-2-oxopropyl]phosphonic acid dimethyl ester (2ag)*
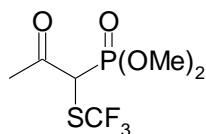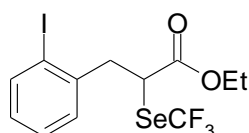

[CAS No.: 1979189-77-9]

Compound **2ag** was prepared following the standard procedure, starting from *P*-(1-diazo-2-oxopropyl)phosphonic acid dimethyl ester (**1ag**, 96 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 trifluoromethylthiolated product **2ag** was formed in 36% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics. **^{19}F NMR** (375 MHz,

DMSO-d_6): δ = −45.1 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 266 [M^+] (6), 197 (22), 174 (44), 91 (100), 65 (40).

7.6.6. *Synthesis of the Trifluoromethyl Selenoether from the corresponding α-Diazo Esters*
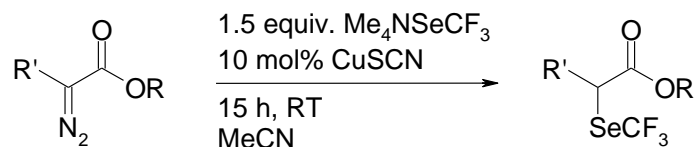
Standard procedure: An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with CuSCN (12.0 mg, 0.10 mmol), Me$_4$NSeCF$_3$ (333 mg, 1.50 mmol) and MeCN (2 mL). Then, α-diazo ester **1a-z** (1.00 mmol) in MeCN (2 mL) was added dropwise and the reaction mixture was stirred for 15 h at room 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 trifluoromethyl selenoethers **3a-z**.

### 7.6.6.1. *Synthesis of 2-[(trifluoromethyl)seleno]-3-phenylpropanoic acid ethyl ester (3a)*
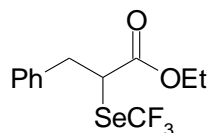
[CAS No.: 1979189-78-0]

Compound **3a** was prepared following the standard procedure, starting from 2-diazo-3-phenylpropanoic acid ethyl ester (**1a**, 204 mg, 1.00 mmol). After purification, **3a** was isolated as colorless oil (270 mg, 0.83 mmol, 83%). **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.34-7.20 (m, 5H), 4.20-4.06 (m, 3H), 3.39-3.22 (m, 2H), 1.18 ppm (t, ^3J = 7.2 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −33.4 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 171.0, 137.1, 128.9 (2C), 128.7 (2C), 127.3, 122.5 (q, ^1J(C,F) = 332.4 Hz), 61.8, 43.1, 38.6, 13.8 ppm; **IR** (ATR): ν = 2992, 2971, 1740, 1371, 1217, 1159, 1109, 699 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 326 [M^+] (1), 177 (99), 149 (16), 131 (100), 103 (20), 91 (31), 77 (10); **HRMS** (EI-

TOF) calcd. for $C_{11}H_9O_2Se$: 252.9768; found: 252.9782 [M^+-(CF_3)]; calcd. for $C_{11}H_{13}O_2$: 177.0916; found: 177.0907 [M^+-(SeCF_3)]; calcd. for $C_9H_8F_3Se$: 252.9743; found: 252.9782 [M^+-(COOEt)].

7.6.6.2. Synthesis of 2-[(trifluoromethyl)seleno]-3-(4-hydroxyphenyl)propanoic acid methyl ester (3j)
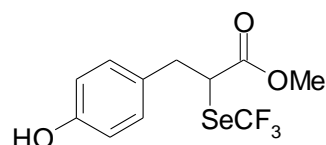
[CAS No.: 1979189-79-1]

Compound **3j** was prepared following the standard procedure, starting from 2-diazo-3-(4-hydroxyphenyl)propanoic acid methyl ester (**1j**, 206 mg, 1.00 mmol). After purification, **3j** was isolated as colorless oil (310 mg, 0.95 mmol, 95%). ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 7.05 (d, ^3J = 8.3 Hz, 2H), 6.76 (d, ^3J = 8.3 Hz, 2H), 5.82 (s, 1H), 4.11-4.07 (m, 1H), 3.70 (s, 3H), 3.22 ppm (dq, ^3J = 14.1, 10.0 Hz, 2H); ^{19}**F NMR** (375 MHz, CDCl$_3$): δ = −33.4 ppm; ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 172.0, 155.0, 130.1 (2C), 129.0, 122.4 (q, ^1J(C,F) = 332.4 Hz), 115.6 (2C), 52.9, 43.0, 37.6 ppm; **IR** (ATR): ν = 3320, 1721, 1614, 1515, 1440, 1350, 1229, 1121, 1088, 832, 803, 761, 739 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 327 [M^+] (1), 179 (64), 147 (51), 130 (20) 107 (100); **HRMS** (EI-TOF) calcd. for $C_{11}H_{11}F_3O_3Se$: 327.9825; found: 327.9818.

7.6.6.3. Synthesis of 2-[(trifluoromethyl)seleno]-3-(2-fluorophenyl)propanoic acid ethyl ester (3s)
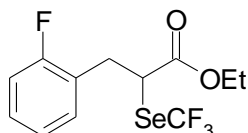
[CAS No.: 1979189-80-4]

Compound **3s** was prepared following the standard procedure, starting from 2-diazo-3-(2-fluorophenyl)propanoic acid ethyl ester (**1s**, 222 mg, 1.00 mmol). After purification, **3s** was isolated as colorless oil (219 mg, 0.64 mmol, 64%). ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 7.29-

7.19 (m, 2H), 7.10-7.03 (m, 2H), 4.18-4.11 (m, 3H), 3.36-3.34 (m, 2H), 1.21-1.16 ppm (m, 3H); ^{19}**F NMR** (375 MHz, CDCl$_3$): δ = −33.4, −117.6 ppm; ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 170.9, 161.2 (d, ^{1}J(C,F) = 246.1 Hz), 131.4 (d, ^{3}J(C,F) = 4.5 Hz), 129.2 (d, ^{3}J(C,F) = 8.2 Hz), 124.2 (d, ^{4}J(C,F) = 3.6 Hz), 124.2 (d, ^{2}J(C,F) = 16.3 Hz), 122.4 (q, ^{1}J(C,F) = 331.5 Hz), 115.5 (d, ^{2}J(C,F) = 21.8 Hz), 61.9, 41.7, 32.5, 13.8 ppm; **IR** (ATR): ν = 2973, 1734, 1587, 1494, 1456, 1372, 1232, 1130, 1095, 910, 858, 757 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 271 (11), 195 (100), 167 (51), 149 (60), 122 (68), 101 (21); **HRMS** (EI-TOF) calcd. for C$_9$H$_7$F$_4$Se: 270.9649; found: 270.9659 [*M$^+$-(COOEt)*].

7.6.6.4. Synthesis of 2-[(trifluoromethyl)seleno]-3-(2-iodophenyl)propanoic acid ethyl ester (3u)

[CAS No.: 1979189-81-5]

Compound **3u** was prepared following the standard procedure, starting from 2-diazo-3-(2-iodo-phenyl)propanoic acid ethyl ester (**1u**, 330 mg, 1.00 mmol). After purification, **3u** was isolated as colorless oil (365 mg, 0.81 mmol, 81%). ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 7.85 (dd, ^{3}J = 8.0, 1.0 Hz, 1H), 7.31-7.22 (m, 2H), 6.96 (dt, ^{3}J = 7.8, 2.0 Hz, 1H), 4.26-4.22 (m, 1H), 4.19-4.08 (m, 2H), 3.41 (dq, ^{3}J = 14.1, 10.0 Hz, 2H), 1.19 ppm (t, ^{3}J = 7.1 Hz, 3H); ^{19}**F NMR** (375 MHz, CDCl$_3$): δ = −32.8 ppm; ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 170.8, 140.0, 139.8, 130.8, 129.1, 128.4, 122.5 (q, ^{1}J(C,F) = 332.4 Hz), 100.3, 61.9, 43.0, 41.2, 13.8 ppm; **IR** (ATR): ν = 2981, 1709, 1636, 1462, 1435, 1368, 1313, 1263, 1179, 1036, 1014, 974, 907, 761, 729, 650 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 406 (1), 378 (5), 325 (100), 256 (65), 216 (51), 147 (24), 127 (23); **HRMS** (EI-TOF) calcd. for C$_{10}$H$_7$F$_3$ISe: 406.8659; found: 406.8684 [*M$^+$-(OEt)*]; calcd. for C$_{12}$H$_{12}$F$_3$O$_2$Se: 324.9955; found: 324.9953 [*M$^+$-(I)*].

7.6.6.5. Synthesis of (4E)-2-[(trifluoromethyl)seleno]-5-phenyl-4-pentenoic acid ethyl ester (3x)
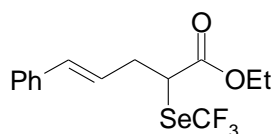
[CAS No.: 1979189-82-6]

Compound **3x** was prepared following the standard procedure, starting from (4E)-2-diazo-5-phenyl-4-pentenoic acid ethyl ester (**1x**, 230 mg, 1.00 mmol). After purification, **3x** was isolated as colorless oil (256 mg, 0.73 mmol, 73%) along with traces of impurities. ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 7.37-7.30 (m, 4H), 7.27-7.24 (m, 1H), 6.52 (d, ^3J = 15.8 Hz, 1H), 6.21-6.14 (m, 1H), 4.29-4.28 (m, 2H), 4.06-4.02 (m, 1H), 2.98-2.85 (m, 2H), 1.28 ppm (t, ^3J = 7.1 Hz, 3H); ^{19}**F NMR** (375 MHz, CDCl$_3$): δ = −33.3 ppm; ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 171.1, 136.6, 134.1, 128.6 (2C), 127.7, 126.3 (2C), 124.4, 122.4 (q, ^1J(C,F) = 331.5 Hz), 62.0, 42.0, 35.8, 13.9 ppm; **IR** (ATR): ν = 2979, 1733, 1495, 1450, 1371, 1129, 1094, 967, 740, 694 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 352 (1), 203 (94), 175 (22), 157 (100), 129 (78), 117 (70), 115 (50), 91 (44); **HRMS** (EI-TOF) calcd. for C$_{14}$H$_{15}$F$_3$O$_2$Se: 352.0189; found: 352.0182.

7.6.6.6. Synthesis of 2-[(trifluoromethyl)seleno]acetic acid 4-phenylbenzyl ester (3z)
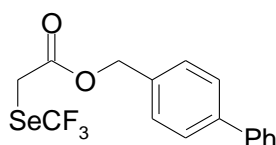
[CAS No.: 1979189-83-7]

Compound **3z** was prepared following the standard procedure, starting from biphenyl-4-ylmethyl 2-diazoacetate (**1z**, 252 mg, 1.00 mmol). After purification, **3z** was isolated as colorless oil (339 mg, 0.91 mmol, 91%). ^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 7.63-7.60 (m, 4H), 7.48-7.45 (m, 4H), 7.36 (t, ^3J = 7.3 Hz, 1H), 5.25 (s, 2H), 3.75 ppm (s, 2H); ^{19}**F NMR** (375 MHz, CDCl$_3$): δ = −34.9 ppm; ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 168.7, 141.6, 140.5, 133.8, 128.9 (2C), 128.8 (2C), 127.5, 127.4 (2C), 127.1 (2C), 122.1 (q, ^1J(C,F) = 330.9 Hz),

67.7, 24.9 ppm (q, ^3J(C,F) = 2.2 Hz); **IR** (ATR): ν = 3036, 1737, 1488, 1408, 1269, 1093, 971, 824, 762, 739, 699 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 375 (7), 184 (11), 181 (59), 167 (100), 152 (65); **HRMS** (EI-TOF) calcd. for C$_{16}$H$_{13}$F$_3$O$_2$Se: 374.0033; found: 374.0041.

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7.7. Metal-Free Trifluoromethylthiolation of Alkyl Electrophiles via a Cascade of Thiocyanation and Nucleophilic Cyanide-CF₃-Substitution

7.7.1. *General Methods*

The reactions were performed in oven-dried glassware containing a Teflon-coated stirrer bar and septum under a nitrogen atmosphere. Dimethylformamide 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-d₁ 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.

Unless otherwise noted the commercial available bromides and chlorides were used without further purification.

7.7.2. *Synthesis of Starting Materials*

7.7.2.1. *Synthesis of Mesylates[243]*
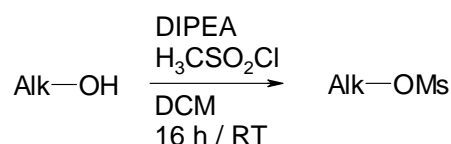
Mesylates were synthesized from the corresponding alcohols by classical procedures: A solution of the alcohol (1.00 mmol) and *N*-ethyldiisopropylamine (DIPEA) (1.6 mmol, 211 mg, 0.27 mL) in dry DCM (10 mL) under inert atmosphere was cooled to 0°C. To this a solution of methanesulfonyl chloride (1.50 mmol, 175 mg, 0.12 mL) in dry DCM (5 mL) was added dropwise over a period of 30 minutes. After complete addition, the resulting solution was allowed to warm to 25°C and stirred for 16 h. The mixture was washed with ice water (5x20 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure to yield the crude product that was used without further purification.

7.7.3. *Synthesis of Trifluoromethyl Thioethers starting from the corresponding Bromides or Mesylates*

$$Alk-X \xrightarrow[\substack{MeCN \\ 1\,h\,/\,T}]{\substack{NaSCN \\ Cs_2CO_3 \\ TMS\text{-}CF_3}} Alk-SCF_3$$

$$X = Cl, Br, I, OMs$$
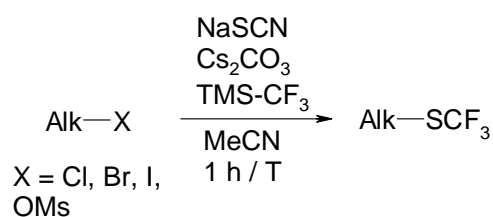
Standard procedure: An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with cesium carbonate (652 mg, 1.00 mmol) and sodium thiocyanate (100 mg, 1.20 mmol). After exchanging the atmosphere three times with nitrogen, MeCN (2 mL), $TMSCF_3$ (537 mg, 0.60 mL, 1.20 mmol) and the alkyl halide or mesylate (1.00 mmol) were added *via* syringe. The suspension was heated under stirring until completion of the reaction was determined by GC and GC-MS (following temperatures were required depending on the leaving group: primary alkyl bromides and -iodides 60°C; secondary alkyl bromides and primary -chlorides 90°C and alkyl mesylates 110°C). After the reaction time the resulting mixture was diluted with Et_2O (20 mL), and washed with water (2×10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure (700 mbar, 40°C). Most compounds were obtained in pure form, for aromatic substituted compounds the residue was purified with column chromatography (SiOH, Et_2O/pentane gradient).

7.7.3.1. Synthesis of [(trifluoromethyl)thio]methylbenzene (2)
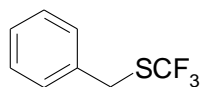
[CAS: 351-60-0]

Compound **2** was prepared following the standard procedure, starting from (bromomethyl)benzene (171 mg, 1.00 mmol) and heating at 60°C. After purification, **2** was isolated as pale yellow oil (188 mg, 0.98 mmol, 98%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.38-7.36 (m, 5H), 4.15 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.47 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 135.0, 130.6 (q, ^1J(C,F) = 307.0 Hz), 128.9 (2C), 128.8 (2C), 128.0, 34.2 ppm (q, ^3J(C,F) = 2.7 Hz); **IR** (ATR): ν = 2922, 2853, 1463, 1378 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 192 [M^+] (23), 91 (100), 69 (13); **HRMS** (EI-TOF) calcd for C$_8$H$_7$F$_3$S: 192.0221; found: 192.0224.

7.7.3.2. Synthesis of [(trifluoromethyl)thio]ethylbenzene (3)
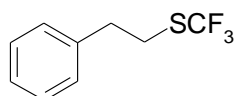
[CAS: 361182-15-2]

Compound **3** was prepared following the standard procedure, starting from (2-bromoethyl)benzene (185 mg, 1.00 mmol) and heating at 60°C. After purification, **3** was isolated as colorless oil (202 mg, 0.98 mmol, 98%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.40-7.36 (m, 2H), 7.33-7.29 (m, 1H), 7.27-7.25 (m, 2H), 3.18 (t, ^3J = 7.6 Hz, 2H), 3.05 ppm (t, ^3J = 7.5 Hz, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.0 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 138.9, 131.1 (q, ^1J(C,F) = 306.1 Hz), 128.7 (2C), 128.5 (2C), 126.9, 36.0, 31.9 ppm (q, ^3J(C,F) = 2.7 Hz); **IR** (ATR): ν = 1739, 1498, 1455, 1366, 1109, 749, 697 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 206 [M^+] (100), 105 (30), 91 (84); **HRMS** (EI-TOF) calcd for C$_9$H$_9$F$_3$S: 206.0377; found: 206.0373.

7.7.3.3. *Synthesis of 4-[(trifluoromethyl)thio]methylbenzonitrile (4)*
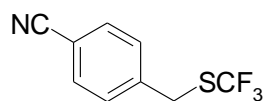
[CAS: 251926-46-2]

Compound **4** was prepared following the standard procedure, starting from 4-cyanobenzylbromide (196 mg, 1.00 mmol) and heating at 60°C. After purification, **4** was isolated as colorless oil (202 mg, 0.93 mmol, 93%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.66 (d, ^3J = 8.5 Hz, 2H), 7.48 (d, ^3J = 8.3 Hz, 2H), 4.14 (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.3 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 140.9, 132.6 (2C), 130.3 (q, ^1J(C,F) = 307.9 Hz), 129.6 (2C), 118.4, 112.0, 33.8 (q, ^3J(C,F) = 2.2 Hz); **IR** (ATR): ν = 2232, 1610, 1505, 1415, 1107, 844, 757 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 217 [M^+] (30), 116 (100), 69 (12), 89 (17); **HRMS** (EI-TOF) calcd for C$_9$H$_6$F$_3$NS: 217.0173; found: 217.0174.

7.7.3.4. *Synthesis of 1-methoxy-4-[(trifluoromethyl)thio]methylbenzene (5)*
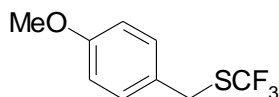
[CAS: 1612253-29-8]

Compound **5** was prepared following the standard procedure, starting from 4-methoxybenzylchloride (157 mg, 1.00 mmol) and heating at 90°C. After purification, **5** was isolated as colorless oil (184 mg, 0.83 mmol, 83%).

**^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.28 (d, ^3J = 8.5 Hz, 2H), 6.89 (d, ^3J = 8.5 Hz, 2H), 4.11 (s, 2H), 3.82 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.6 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 159.3, 130.6 (q, ^1J(C,F) = 307.0 Hz), 130.2 (2C), 126.7, 114.2 (2C), 55.3, 33.8 ppm (q, ^3J(C,F) = 2.4 Hz); **IR** (ATR): ν = 1739, 1612, 1514, 1304, 1249, 1110, 1035, 832, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 222 [M^+] (22), 121 (100); **HRMS** (EI-TOF) calcd for C$_9$H$_9$F$_3$OS: 222.0326; found: 222.0328.

7.7.3.5. Synthesis of 4-[(trifluoromethyl)thio]methyl-1-chlorobenzene (6)
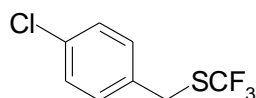
[CAS: 185315-59-7]

Compound **6** was prepared following the standard procedure, starting from 4-chlorobenzylchloride (161 mg, 1.00 mmol) and heating at 90°C. After purification, **6** was isolated as yellow oil (172 mg, 0.76 mmol, 76%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.35-7.28 (m, 4H), 4.09 (m, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.5 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 133.9, 133.7, 130.2 (2C), 130.5 (q, ^1J(C,F) = 307.0 Hz), 129.0 (2C), 35.6 ppm (q, ^3J(C,F) = 2.7 Hz); **IR** (ATR): ν = 1739, 1492, 1112, 1016, 833, 757 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 226 [M^+H] (32), 125 (100), 89 (12), 69 (5); **HRMS** (EI-TOF) calcd for C$_8$H$_6$ClF$_3$S: 225.9831; found: 225.9817; cald for C$_7$H$_6$^{37}Cl (M+ -[SCF$_3$]): 127.0129, found: 127.0126.

7.7.3.6. Synthesis of 4-[(trifluoromethyl)thio]methyl-1-bromobenzene (7)
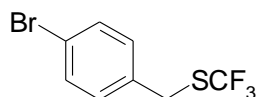
[CAS: 1612253-26-5]

Compound **7** was prepared following the standard procedure, starting from 1-bromo-4-[(methylsulfonyl)methyl]benzene (265 mg, 1.00 mmol) and heating at 90°C. After purification, **7** was isolated as colorless oil (201 mg, 0.74 mmol, 74%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.49 (d, ^3J = 8.3 Hz, 2H), 7.23 (d, ^3J = 8.3 Hz, 2H), 4.07 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.5 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 134.2, 132.0 (2C), 130.5 (2C), 130.4 (q, ^1J(C,F) = 307.0 Hz), 122.0, 33.6 ppm (q, ^3J(C,F) = 2.7 Hz); **IR** (ATR): ν = 1489, 1113, 1013, 832, 757 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 272 [M^+] (37), 171 (100), 90 (22), 69 (15); **HRMS** (EI-TOF) calcd for C$_8$H$_6$^{81}BrF$_3$S: 271.9305; found: 271.9284.

7.7.3.7. Synthesis of 5-[(trifluoromethyl)thio]methyl-benzo[d][1,3]dioxole (8)
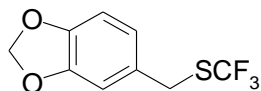
[CAS: 1242101-29-6]

Compound **8** was prepared following the standard procedure, starting from 5-[(methylsulfonyl)methyl]-1,3-benzodioxole (230 mg, 1.00 mmol) and heating at 90°C. After purification, **8** was isolated as colorless oil (194 mg, 0.82 mmol, 82%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.84 (s, 1H), 6.82-6.76 (m, 2H), 5.98 (s, 2H), 4.07 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.6 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 148.0, 147.4, 130.6 (q, ^1J(C,F) = 307.0 Hz), 128.5, 122.4, 109.2, 108.4, 101.3, 34.3 ppm (q, ^3J(C,F) = 2.7 Hz); **IR** (ATR): ν = 1490, 1446, 1363, 1247, 1096, 1038, 927, 813, 756 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 236 [M^+] (67), 135 (100), 69 (4); **HRMS** (EI-TOF) calcd for C$_9$H$_7$O$_2$F$_3$S: 236.0119; found: 236.0118.

7.7.3.8. Synthesis of (E)-[(trifluoromethyl)thio]prop-1-en-1-ylbenzene (9)
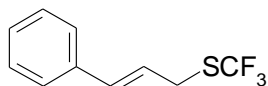
[CAS: 1464149-40-3]

Compound **9** was prepared following the standard procedure, starting from (1E)-(3-(methylsulfonyl)prop-1-en-1-yl)benzene (212 mg, 1.00 mmol) and heating at 90°C. After purification, **9** was isolated as colorless oil (148 mg, 0.68 mmol, 68%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.70-7.28 (m, 5H), 6.60 (d, ^3J = 15.7 Hz, 1H), 6.27-6.20 (m, 1H), 3.73 ppm (d, ^3J = 8.3 Hz, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.8 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 136.1, 134.3, 128.7 (2C), 128.1, 126.5 (2C), 123.0, 32.7 ppm (q, ^3J(C,F) = 2.4 Hz); **IR** (ATR): ν = 2969, 2923, 2857, 1739, 1366, 1217, 1115 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 218 [M^+] (24), 117 (100), 115 (49), 69 (14); **HRMS** (EI-TOF) calcd for C$_{10}$H$_9$F$_3$S: 218.0377; found: 218.0368.

7.7.3.9. Synthesis of (1S)-1-(trifluoromethyl)thio-1-phenylethane (10)
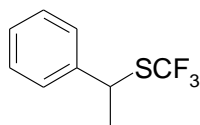
[CAS: 1774371-15-1]

Compound **10** was prepared following the standard procedure, starting from, (*1S*)-methylsulfonyl-1-phenylethyl ester (153 mg, 1.00 mmol) and heating at 90°C. After purification, **10** was isolated as colorless oil (171 mg, 0.83 mmol, 83%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.37-7.36 (m, 4H), 7.34-7.28 (m, 1H), 4.54 (q, ^3J = 7.0 Hz, 1H), 1.75 ppm (d, ^3J = 7.2 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −40.2 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 141.3, 133.5 (q, ^1J(C,F) = 307.0 Hz), 128.8 (2C), 128.0, 127.0 (2C), 44.5 (q, ^3J(C,F) = 1.8 Hz), 23.2 ppm; **IR** (ATR): ν = 3059, 3025, 2962, 2926, 2869, 1600, 1493, 1451, 1373, 1115, 1011, 965, 743, 697 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 105 (100); **HRMS** (EI-TOF) calcd for C$_9$H$_9$F$_3$S: 206.0377; found: 206.0381; $[\alpha]_D^{20}$ 0.00 (c 1.00, Et$_2$O).

7.7.3.10. Synthesis of 1-[(trifluoromethyl)thio]hexane (11)
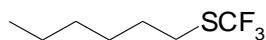
[CAS: 59529-76-9]

Compound **11** was prepared following the standard procedure, starting from 1-bromohexane (165 mg, 1.00 mmol) and heating at 60°C. After the reaction, trifluoroethanol as internal standard (72 μL, 1.00 mmol) was added to the reaction mixture and product **11** was formed in 97% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (375 MHz, DMSO-d_6): δ = −41.2 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 117 (100), 83 (35), 69 (24), 56 (23), 55 (40), 43 (15), 41 (25).

7.7.3.11. Synthesis of [(trifluoromethyl)thio]octane (12)
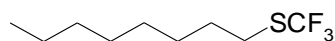
[CAS: 134776-65-1]

Compound **12** was prepared following the standard procedure, starting from 1-chlorooctane (149 mg, 1.00 mmol) and heating at 90°C. After purification, **12** was isolated as pale yellow oil (208 mg, 0.97 mmol, 97%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.88 (t, ^{3}J = 7.4 Hz, 2H), 1.7 (qi, ^{3}J = 7.5 Hz, 2H), 1.41 (qi, ^{3}J = 7.5 Hz, 2H), 1.35-1.25 (m, 8H), 0.90 (t, ^{3}J = 6.9 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.4 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 131.2 (q, ^{1}J(C,F) = 307.9 Hz), 31.8, 29.9 (q, ^{3}J(C,F) = 1.8 Hz), 29.4, 29.1, 29.0, 28.5, 22.6, 14.0; **IR** (ATR): ν = 2927, 2857, 1466, 1150, 1107, 756, 723 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 213 [M^{+}-H] (5), 145 (100), 71 (23), 69 (50); **HRMS** (EI-TOF) calcd for C$_9$H$_{17}$F$_3$S: 214.1003; found: 214.0996.

7.7.3.12. Synthesis of [(trifluoromethyl)thio]cyclohexane (13)
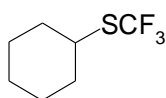
[CAS: 6476-52-4]

Compound **13** was prepared following the standard procedure, starting from bromocyclohexane (162 mg, 1.00 mmol) and heating at 110°C. After the reaction, trifluoroethanol (72 µL, 1.00 mmol) was added as internal standard to the reaction mixture. Product **13** was formed in 87% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (375 MHz, DMSO-d_6): δ = −40.3 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 184 [M^{+}] (1), 115 (17), 83 (100), 67 (12), 55 (40).

7.7.3.13. Synthesis of 11-[(trifluoromethyl)thio]undecanoic acid (14)
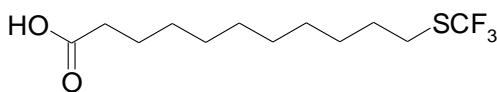
[CAS: 1774371-16-2]

Compound **14** was prepared following the standard procedure, starting from 11-bromoundecanoic acid (265 mg, 1.00 mmol) and heating at 60°C. After purification, **14** was isolated as colorless oil (269 mg, 0.94 mmol, 94%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.88 (t, ^3J = 7.5 Hz, 2H), 2.35 (t, ^3J = 7.5 Hz, 2H), 1.72-1.60 (m, 4H), 1.44-1.29 ppm (m, 12H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.3 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 180.5, 131.2 (q, ^1J(C,F) = 305.2 Hz), 34.1, 29.83 (q, ^3J(C,F) = 2.4 Hz), 29.34, 29.27, 29.25, 29.1, 29.0, 28.9, 28.5, 24.6 ppm; **IR** (ATR): ν = 2927, 2856, 1709, 1464, 1414, 1113, 938, 756 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 287 [M^++H] (12), 199 (73), 129 (44), 117 (91), 101 (9), 69 (24); **HRMS** (EI-TOF) calcd for: C$_{12}$H$_{21}$F$_3$O$_2$S: 286.1214; found: 286.1230.

7.7.3.14. Synthesis of 6-[(trifluoromethyl)thio]-hexanoic acid ethyl ester (15)
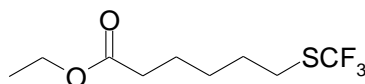

[CAS: 1620061-36-0]

Compound **15** was prepared following the standard procedure, starting from 6-bromo-hexanoic acid ethyl ester (223 mg, 1.00 mmol) and heating at 60°C. After purification, **15** was isolated as yellow oil (234 mg, 0.96 mmol, 96%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 4.12 (q, ^3J = 7.0 Hz, 2H), 2.88 (t, ^3J = 7.3 Hz, 2H), 2.31 (t, ^3J = 7.3 Hz, 2H), 1.75-1.62 (m, 4H), 1.48-1.40 (m, 2H), 1.25 ppm (t, ^3J = 7.0 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.2 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 179.4, 131.1 (q, ^1J(C,F) = 306.1 Hz), 60.3, 34.0, 29.6 (q, ^3J(C,F) = 2.2 Hz), 29.1, 27.9, 24.2, 14.2 ppm; **IR** (ATR): ν = 2942, 1734, 1464, 1374, 1110, 756 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 246

[M^+] (31), 225 (45), 175 (28), 143 (100), 129 (14), 69 (14); **HRMS** (EI-TOF) calcd for $C_9H_{15}O_2F_3S$: 244.0745; found: 244.0741.

7.7.3.15. *Synthesis of 3-[(trifluoromethyl)thio]propyltrimethoxysilane (16)*
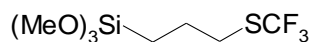
[CAS: 1774371-17-3]

Compound **16** was prepared following the standard procedure, starting from (3-iodopropyl)trimethoxysilane (290 mg, 1.00 mmol) and heating at 60°C. After purification, **16** was isolated as yellow oil (253 mg, 0.96 mmol, 96%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.55 (s, 9H), 2.88 (t, ^3J = 7.3 Hz, 2H), 1.79 (qi, ^3J = 7.8 Hz, 2H), 0.73 (t, ^3J = 8.3 Hz, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.2 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 131.2 (q, ^1J(C,F) = 305.9 Hz), 50.5 (3H), 32.5 (q, ^3J(C,F) = 1.5 Hz), 23.2, 8.3; **IR** (ATR): ν = 2945, 2843, 1759, 1077, 809, 754 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 264 [M^+] (1), 233 (12), 195 (63), 121 (13), 93 (100); **HRMS** (EI-TOF) calcd for $C_7H_{15}O_3SiF_3S$: 264.0463; found: 264.0468.

7.7.3.16. *Synthesis of N-{2-[(trifluoromethyl)thio]ethyl}-N,N-dibutylamine (17)*
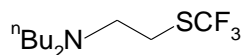
[CAS: 1774371-18-4]

Compound **17** was prepared following the standard procedure, starting from *N*-(2-(methylsulfonyl)ethyl)dibutylamine (251 mg, 1.00 mmol) and heating at 90°C. After purification *via* Kugelrohrdistillation, **17** was isolated as pale yellow oil (211 mg, 0.82 mmol, 82%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.30 (t, ^3J = 7.1 Hz, 2H), 2.74 (t, ^3J = 7.0 Hz, 2H), 2.42 (t, ^3J = 7.2 Hz, 4H), 1.43-1.37 (m, 4H), 1.34-1.28 (m, 4H), 0.92 ppm (t, ^3J = 7.3 Hz, 6H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.4 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 131.6 (q, ^1J(C,F) = 306.8 Hz), 53.6 (2C), 52.8, 29.3 (2C), 28.8, 20.5 (2C), 14.0 ppm (2C); **IR** (ATR): ν = 2959, 2934, 2874, 1739, 1460, 1366, 1217, 1119, 748 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z

(%) = 257 (3), 214 (44), 172 (66), 142 (100), 100 (), 58 (41); **HRMS** (EI-TOF) calcd for $C_{11}H_{22}NF_3S$: 257.1425; found: 257.1420.

7.7.3.17. *Synthesis of 2-[(trifluoromethyl)thio]ethanol (18)*
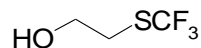
[CAS: 307337-29-7]

Compound **18** was prepared following the standard procedure, starting from 2-bromoethanol (125 mg, 1.00 mmol) and heating at 60°C. After the reaction, trifluoroethanol (72 µL, 1.00 mmol) was added as internal standard to the reaction mixture. Product **18** was formed in 62% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}**F NMR** (375 MHz, DMSO-d_6): δ = −42.0 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 147 [MH^+] (10); 129 (11), 128 (100), 115 (4).

7.7.3.18. *Synthesis of 1-trimethylsilyl-5-(trifluoromethyl)thiopent-1-yne (19)*
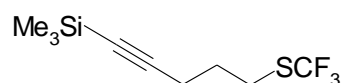
[CAS: 1774371-19-5]

Compound **19** was prepared following the standard procedure, starting from 5-chloro-1-pentyne (103 mg, 1.00 mmol) and heating at 90°C. After purification, **19** was isolated as slightly yellow oil (224 mg, 0.93 mmol, 93%).

^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 3.01 (t, ^3J = 7.1 Hz, 2H), 2.38 (t, ^3J = 6.8 Hz, 2H), 1.90 (qi, ^3J = 7.0 Hz, 2H), 0.15 ppm (s, 9H); ^{19}**F NMR** (375 MHz, CDCl$_3$): δ = −41.1 ppm; ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 131.0 (q, ^1J(C,F) = 306.1 Hz), 104.8, 86.2, 28.7 (q, ^3J(C,F) = 1.8 Hz), 28.3, 18.6, 0.0 ppm (3C); **IR** (ATR): ν = 2960, 2176, 1685, 1432, 1250, 1107, 838, 758, 699 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 240 [M^+] (11), 171 (97), 129 (100); **HRMS** (EI-TOF) calcd for $C_9H_{15}SiF_3S$: 240.0616; found: 240.0614.

7.7.3.19.   Synthesis of [(trifluoromethyl)thio]methyl-1,3-dioxolane (20)
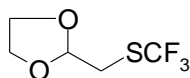
[CAS: 1774371-20-8]

Compound **20** was prepared following the standard procedure, starting from 2-Bromomethyl-1,3-dioxolane (167 mg, 1.00 mmol) and heating at 60°C. After the reaction, trifluoroethanol (72 µL, 1.00 mmol) was added as internal standard to the reaction mixture. Product **20** was formed in 71% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}**F NMR** (375 MHz, DMSO-d_6): δ = −42.7 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 188 [M^+] (100), 144 (96), 69 (26), 58 (27).

7.7.3.20.   Synthesis of (1R,5S)-[(trifluoromethyl)thio]-2-(6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl)ethylene (21)
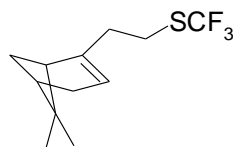
[CAS: 1774371-21-9]

Compound **21** was prepared following the standard procedure, starting from (*1R,5S*)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene-2-(2-methanesulfonate)-ethanol) (244 mg, 1.00 mmol) and heating at 90°C. After purification, **21** was isolated as yellow oil (235 mg, 0.94 mmol, 94%).

^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 5.31 (m, 1H), 2.93-2.89 (m, 2H), 2.41-2.38 (m, 1H), 2.37-2.32 (m, 2H), 2.26-2.23 (m, 2H), 2.11-2.09 (m, 1H), 2.02-1.99 (m, 1H), 1.29 (s, 3H), 1.16 (d, ^3J = 8.5 Hz, 1H), 0.84 ppm (s, 3H); ^{19}**F NMR** (375 MHz, CDCl$_3$): δ = −41.2 ppm; ^{13}**C NMR** (101 MHz, CDCl$_3$): δ = 145.2, 132.2 (q, ^1J(C,F) = 306.1 Hz), 118.8, 40.6, 38.0, 36.6, 31.6, 31.2, 27.8 (q, ^3J(C,F) = 1.8 Hz), 26.2, 21.1 ppm; **IR** (ATR): ν = 2917, 1434, 1366, 1104, 887, 794, 756 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 250 [M^+] (14), 105 (100), 121

(10); **HRMS** (EI-TOF) calcd for $C_{12}H_{17}F_3S$: 250.1003; found: 250.0987; $[\alpha]_D^{20}$ -25.9 (c 1.00, Et_2O).

7.7.3.21. Synthesis of 2-{2-[(trifluoromethyl)thio]ethyl}-1H-isoindole-1,3(2H)-dione (22)
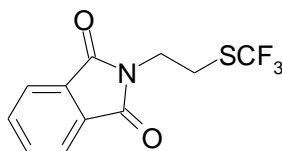
[CAS: 1408279-16-2]

Compound **22** was prepared following the standard procedure, starting from 2-(2-bromoethyl)-1*H*-isoindole-1,3(2*H*)-dione (254 mg, 1.00 mmol) and heating at 60°C. After purification, **22** was isolated as colorless oil (256 mg, 0.93 mmol, 93%).

¹H NMR (400 MHz, CDCl₃): δ = 7.88-8.84 (m, 2H), 7.76-7.72 (m, 2H), 4.00 (t, ^3J = 7.0 Hz, 2H), 3.20 ppm (t, ^3J = 7.0 Hz, 2H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −41.0 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 167.8 (2C), 134.2 (2C), 131.7 (2C), 130.6 (q, ^1J(C,F) = 307.0 Hz), 123.5 (2C), 37.3, 27.8 ppm; **IR** (ATR): ν = 1775, 1711, 1468, 1441, 1399, 1361, 1263, 1086, 984, 866, 754, 714 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 275 [M^+] (15), 160 (100), 133 (9), 104 (4); **HRMS** (EI-TOF) calcd for $C_{11}H_8NO_2F_3S$: 275.0228; found: 275.0223.

7.7.3.22. Synthesis of 2-[(trifluoromethyl)thio]methylthiophene (23)
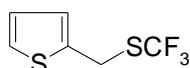
[CAS: 1612253-23-2]

Compound **23** was prepared following the standard procedure, starting from 2-thienylmethyl mesylate (153 mg, 1.00 mmol) and heating at 110°C. After the reaction, trifluoroethanol (72 µL, 1.00 mmol) was added as internal standard to the reaction mixture. Product **23** was formed in 64% yield as determined by ¹⁹F NMR spectroscopic analysis and confirmed by GC-MS analytics.

¹⁹F NMR (375 MHz, DMSO-*d*₆): δ = −41.7 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 198 [*M*⁺] (15), 97 (100, 69 (17).

7.8. Synthesis of Aryl Tri- and Difluoromethyl Thioethers via a C–H-Thiocyanation / Fluoroalkylation Cascade

7.8.1. *General Methods*

The reactions were performed in oven-dried glassware containing a Teflon-coated stirrer bar and septum under a nitrogen atmosphere. Dimethylformamide 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.

7.8.2. *Optimization of the C–H-Thiocyanation / Difluoromethylation Cascade*

Tabelle 5. Optimization of the reaction conditions.[a]
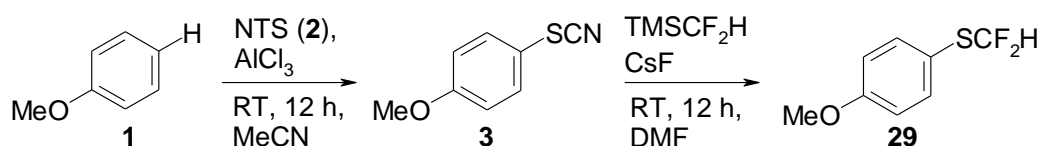
Entry	Solvent change from MeCN to DMF	Yield 29
1	No evaporation, a solution of preformed $CuCF_2H$ in DMF is added	trace
2	No evaporation, DMF is added followed by reagents	trace
3	Addition of DMF followed by evaporation of MeCN	52%
4	Small work up with Et_2O	81%
5	Filtration over a plug of silica and evaporation MeCN	79%
6	Evaporation of MeCN followed by addition of DMF	80%

[a] To a mixture of 1.0 mmol NTS and 0.1 mmol of $AlCl_3$ in 2 mL MeCN was added 1.0 mmol of arene and the mixture is stirred at RT for 12 h. Then, the solvent is changed and 1.0 mmol of CuSCN and 4.0 mmol of CsF were introduced followed by 2 mL of DMF and 2.0 mmol of $TMSCF_2H$, finally the mixture is stirred at RT overnight. Yields were determined by ^{19}F NMR using 1 equiv. of trifluoroethanol as internal standard.

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7.8.3. *Synthesis of Starting Materials*

7.8.3.1. *Synthesis of difluoromethyltrimethylsilane[200]*

$$Me_3Si\!-\!CF_2H$$

[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 as colorless oil (15.6 mL, 97 mmol, 71%).

b.p.: 65-66°C; **^{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.

7.8.4. *Synthesis of Trifluoromethyl Thioethers from the corresponding Arenes*
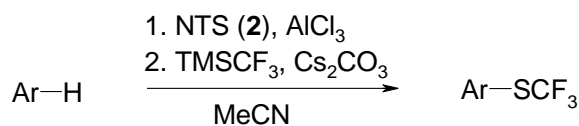
$$Ar\!-\!H \xrightarrow[\text{MeCN}]{\substack{\text{1. NTS (2), AlCl}_3 \\ \text{2. TMSCF}_3\text{, Cs}_2\text{CO}_3}} Ar\!-\!SCF_3$$

Standard procedure: An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with *N*-thiocyanatosuccinimide (**2**, 156 mg, 1.00 mmol), aluminium chloride (13.3 mg, 0.10 mmol), the starting material (1.00 mmol) and acetonitrile (2 mL). After stirring at the given reaction temperature for 12 h Cs$_2$CO$_3$ (652 mg, 2.00 mmol) and TMSCF$_3$ (287 mg, 2.00 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The resulting mixture was 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). The residue was further purified by flash chromatography (SiO$_2$, pentane/diethyl ether gradient), yielding the corresponding aryl trifluoromethyl thioethers.

### 7.8.4.1. Synthesis of 1-methoxy-4-[(trifluoromethyl)thio]benzene (4)
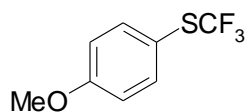

[CAS: 78914-94-0]

Compound **4** was prepared following the standard procedure, starting from methoxybenzene (114 mg, 1.00 mmol) at room temperature. After purification, **4** was isolated as colorless oil (202 mg, 0.97 mmol, 97%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.59 (d, ^3J = 8.8 Hz, 2H), 6.95 (d, ^3J = 8.8 Hz, 2H), 3.85 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −44.0 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 161.8, 138.3 (2C), 129.7 (q, ^1J(C,F) = 308.5 Hz), 115.0 (2C), 114.8 (q, ^3J(C,F) = 1.8 Hz), 55.4 ppm; **IR** (ATR): ν = 3011, 2969, 2946, 2910, 2842, 1593, 1495, 1252, 1104, 1085, 1029, 828 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 208 [M^+] (86), 139 (100); **HRMS** (EI-TOF) calcd for C$_8$H$_7$F$_3$OS: 208.0170; found: 208.0171.

7.8.4.2. Synthesis of 3-[(trifluoromethyl)thio]-9H-fluorene (6)
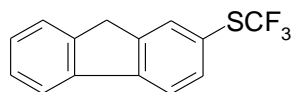
[CAS: 1333415-84-1]

Compound **6** was prepared following the standard procedure, starting from 9H-fluorene (83 mg, 0.50 mmol) at 60°C. After the reaction, trifluoroethanol as internal standard (36.0 μL, 0.50 mmol) was added to the reaction mixture and the trifluoromethylthiolated product **6** was formed in 18% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (375 MHz, DMSO-d_6): δ = −44.1 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 167 (13), 166 (100), 165 (100), 164 (11), 82 (13), 63 (11), 50 (14).

7.8.4.3. Synthesis of 3-[(trifluoromethyl)thio]-benzo[b]thiophene (7)
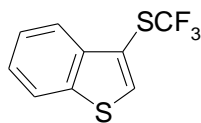
[CAS: 1333415-87-4]

Compound **7** was prepared following the standard procedure, starting from Benzo[*b*]thiophene (134.2 mg, 1.00 mmol) at room temperature. After purification, **7** was isolated as colorless oil (98 mg, 0.42 mmol, 42%).

1H NMR (400 MHz, CDCl$_3$): δ = 8.05 (d, ^3J = 8.0 Hz, 1H), 8.00 (s, 1H), 7.91 (d, ^3J = 8.0 Hz, 1H), 7.55-7.51 (m, 1H), 7.49-7.44 ppm (m, 1H); **19F NMR** (375 MHz, CDCl$_3$): δ = −42.6 ppm; **13C NMR** (101 MHz, CDCl$_3$): δ = 139.4, 139.4, 137.9, 129.0 (q, ^1J(C,F) = 309.7 Hz), 125.4, 125.3, 122.9, 122.8, 115.2 ppm (q, ^3J(C,F) = 1.8 Hz); **IR** (ATR): ν = 3072, 3031, 1456, 1422, 1106, 908, 838, 755, 731 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 234 [M^+] (92), 166 (10), 165 (100), 121 (44), 69 (21); **HRMS** (EI-TOF) calcd for C$_9$H$_5$F$_3$S$_2$: 233.9785; found: 233.9782.

7.8.4.4. Synthesis of 1-methoxy-2-methyl-4-[(trifluoromethyl)thio]benzene (8)
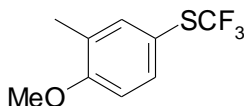
[CAS: 1357624-60-2]

Compound **8** was prepared following the standard procedure, starting from 1-methoxy-2-methylbenzene (122 mg, 1.00 mmol) at room temperature. After purification, **8** was isolated as colorless oil (209 mg, 0.94 mmol, 94%).

1H NMR (400 MHz, CDCl$_3$): δ = 7.48 (d, ^3J = 8.5 Hz, 1H), 7.43 (s, 1H), 6.85 (d, ^3J = 8.3 Hz, 1H), 3.87 (s, 3H), 2.24 ppm (s, 3H); **19F NMR** (375 MHz, CDCl$_3$): δ = −43.9 ppm; **13C NMR** (101 MHz, CDCl$_3$): δ = 160.0, 138.6, 135.9, 129.7 (q, ^1J(C,F) = 307.9 Hz), 128.2, 114.1 (q, ^3J(C,F) = 1.8 Hz), 110.5, 55.4, 16.1 ppm; **IR** (ATR): ν = 3009, 2966, 2942, 2842, 1596, 1241, 1099, 1063, 1033, 806 cm^{-1}; **MS** (Ion trap, EI,

70 eV): m/z (%) = 222 [M^+] (100), 153 (83); **HRMS** (EI-TOF) calcd for $C_9H_9F_3OS$: 222.0326; found: 222.0330.

7.8.4.5.   Synthesis of 4-methoxy-2-methyl-1-[(trifluoromethyl)thio]benzene (9)
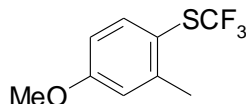
[CAS: 1686143-46-3]

Compound **9** was prepared following the standard procedure, starting from 1-methoxy-3-methylbenzene (122 mg, 1.00 mmol) at room temperature. After purification, **9** was isolated as colorless oil (211 mg, 0.95 mmol, 95%).

**^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.58 (d, ^3J = 8.5 Hz, 1H), 6.87 (s, 1H), 6.78 (dd, ^3J = 8.5, 3.0 Hz, 1H), 3.83 (s, 3H), 2.53 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −43.5 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 162.0, 146.0, 140.0, 129.8 (q, ^1J(C,F) = 308.8 Hz), 116.5, 114.5 (q, ^3J(C,F) = 1.8 Hz), 112.4, 55.3, 21.5 ppm; **IR** (ATR): ν = 3009, 2970, 2945, 2843, 1494, 1251, 1105, 1091, 1030, 809 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 222 [M^+] (91), 153 (100); **HRMS** (EI-TOF) calcd for $C_9H_9F_3OS$: 222.0326; found: 222.0327.

7.8.4.6.   Synthesis of 1,3,5-trimethyl-2-[(trifluoromethyl)thio]benzene (10)
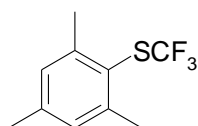
[CAS: 103548-34-1]

Compound **10** was prepared following the standard procedure, starting from 1,3,5-Trimethylbenzene (60 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 trifluoromethylthiolated product **10** was formed in 88% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (375 MHz, DMSO-d_6): δ = −43.1 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 220 [M^+] (100), 151 (87), 107 (34), 105 (29), 91 (21), 69 (23), 45 (21).

7.8.4.7. Synthesis of 1-methoxy-4-methyl-2-[(trifluoromethyl)thio]benzene (11)
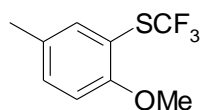
[CAS: 1357624-60-2]

Compound **11** was prepared following the standard procedure, starting from 1-methoxy-4-methylbenzene (122 mg, 1.00 mmol) at room temperature. After purification, **11** was isolated as colorless oil (162 mg, 0.73 mmol, 73%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.43 (s, 1H), 7.28-7.25 (m, 1H), 6.88 (d, ^3J = 8.3 Hz, 1H), 3.89 (s, 3H), 2.32 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −42.4 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 158.5, 138.8, 133.4, 130.6, 129.6 (q, ^1J(C,F) = 308.8 Hz), 111.8 (q, ^3J(C,F) = 1.8 Hz), 111.6, 56.1, 20.1 ppm; **IR** (ATR): ν = 3009, 2966, 2942, 2842, 1596, 1482, 1297, 1241, 1099, 1063, 1033, 806 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 222 [M^+] (100), 153 (48); **HRMS** (EI-TOF) calcd for C$_9$H$_9$F$_3$OS: 222.0326; found: 222.0329.

7.8.4.8. Synthesis of 5-[(trifluoromethyl)thio]- 1,3-benzodioxole (12)
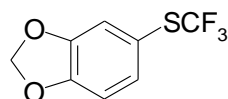
[CAS: 1677706-17-0]

Compound **12** was prepared following the standard procedure, starting from 1,3-benzodioxole (122 mg, 1.00 mmol) at room temperature. After purification, **12** was isolated as colorless oil (204 mg, 0.92 mmol, 92%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.18 (m, 1H), 7.11 (s, 1H), 6.84 (d, ^3J = 8.0 Hz, 1H), 6.0 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −43.9 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 150.3, 148.3, 131.6, 129.5 (q, ^1J(C,F) = 307.9 Hz), 116.2, 115.9 (q, ^3J(C,F) = 1.8 Hz), 109.0, 101.9 ppm; **IR** (ATR): ν = 3079, 3017, 2971, 2903, 2841, 1480, 1471, 1238, 1114, 1094, 1036, 935, 808 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 223 [M^+] (11), 222 (100); **HRMS** (EI-TOF) calcd for C$_8$H$_5$F$_3$O$_2$S: 221.9962; found: 221.9966.

7.8.4.9. Synthesis of 2,4-dimethoxy-1-[(trifluoromethyl)thio]benzene (13)
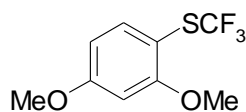
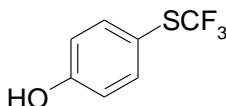[CAS: 66476-29-7]

Compound **13** was prepared following the standard procedure, starting from 1,3-dimethoxybenzene (138 mg, 1.00 mmol) at room temperature. After purification, **13** was isolated as colorless oil (233 mg, 0.98 mmol, 98%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.54 (d, ^3J = 9.0 Hz, 1H), 6.54-6.51 (m, 2H), 3.88 (s, 3H), 3.84 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −43.7 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 163.9, 162.1, 140.2, 129.6 (q, ^1J(C,F) = 309.7 Hz), 105.6, 103.1 (q, ^3J(C,F) = 1.8 Hz), 99.2, 55.9, 55.4 ppm; **IR** (ATR): ν = 3010, 2970, 2945, 2842, 1592, 1574, 1464, 1211, 1099, 1070, 1027, 824 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 238 [M^+] (100), 169 (53); **HRMS** (EI-TOF) calcd for C$_9$H$_9$F$_3$O$_2$S: 238.0275; found: 238.0278.

7.8.4.10. Synthesis of 1-(phenylmethoxy)-4-[(trifluoromethyl)thio]benzene (14)
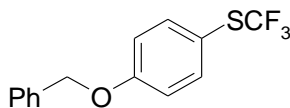

[CAS: 1373406-47-3]

Compound **14** was prepared following the standard procedure, starting from phenoxymethylbenzene (184 mg, 1.00 mmol) at room temperature. After purification, **14** was isolated as colorless solid (281 mg, 0.99 mmol, 99%).

m.p.: 51-52°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.60 (d, ^3J = 8.8 Hz, 2H), 7.46-7.35 (m, 5H), 7.02 (d, ^3J = 8.8 Hz, 2H), 5.10 ppm (s, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −43.8 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 161.0, 138.3 (2C), 136.2, 129.6 (q, ^1J(C,F) = 307.9 Hz), 128.7 (2C), 128.3, 127.5 (2C), 115.8 (2C), 115.1 (q, ^3J(C,F) = 1.8 Hz), 70.2 ppm; **IR** (ATR): ν = 3091, 3035, 2971, 2941, 2889, 1592, 1492, 1242, 1132, 1109, 1084, 1004, 750, 699 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 284 [M^+] (36), 91 (100); **HRMS** (EI-TOF) calcd for C$_{14}$H$_{11}$F$_3$OS: 284.0483; found: 284.0483.

7.8.4.11. Synthesis of 2-methoxy-1-[(trifluoromethyl)thio]naphthalene (15)
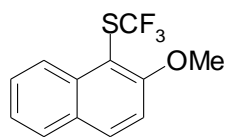
[CAS: 1808089-04-4]

Compound **15** was prepared following the standard procedure, starting from 2-methoxynaphtalene (158 mg, 1.00 mmol) at room temperature. After purification, **15** was isolated as colorless solid (250 mg, 0.97 mmol, 97%).

m.p.: 58-59°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.55 (d, ^3J = 8.5 Hz, 1H), 8.03 (d, ^3J = 9.0 Hz, 1H), 7.82 (d, ^3J = 8.0 Hz, 1H), 7.64 (t, ^3J = 8.3 Hz, 1H), 7.44 (t, ^3J = 7.8 Hz, 1H), 7.35 (d, ^3J = 9.0 Hz, 1H), 4.06 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −41.8 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 160.6, 136.9, 134.2, 129.6 (q, ^1J(C,F) = 310.6 Hz), 129.3, 128.3, 128.2, 125.0, 124.3, 113.0, 105.2 (q, ^3J(C,F) = 1.8 Hz), 56.8 ppm; **IR** (ATR): ν = 3091, 3064, 2981, 2952, 2895, 2851, 1507, 1470, 1271, 1249, 1138, 1092, 1064, 1023, 812, 752 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 258 [M^+] (100), 115 (43); **HRMS** (EI-TOF) calcd for C$_{12}$H$_9$F$_3$OS: 258.0326; found: 258.0320.

7.8.4.12. Synthesis of [4-[(trifluoromethyl)thio](methoxymethoxy)benzene (16)
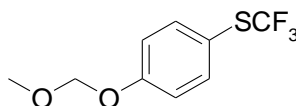
[CAS: 1808089-05-5]

Compound **16** was prepared following the standard procedure, starting from (methoxymethoxy)benzene (138 mg, 1.00 mmol) at room temperature. After purification, **16** was isolated as colorless oil (98 mg, 0.41 mmol, 41%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.58 (d, ^3J = 8.8 Hz, 2H), 7.08 (d, ^3J = 9.0 Hz, 2H), 5.21 (s, 2H), 3.49 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −43.7 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 159.5, 138.2 (2C), 129.6 (q, ^1J(C,F) = 308.1 Hz), 117.1 (2C), 116.2 (q, ^3J(C,F) = 2.2 Hz), 94.2, 56.2 ppm; **IR** (ATR): ν = 3015, 2968, 2941, 2912, 2841, 1592,

1501, 1252, 1104, 1084, 1028, 830 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 238 [M^+] (100), 125 (45); **HRMS** (EI-TOF) calcd for $C_9H_9F_3O_2S$: 238.0280; found: 238.0275.

7.8.4.13. *Synthesis of 1-hydroxy-4-[(trifluoromethyl)thio]benzene (17)*
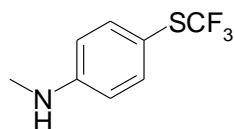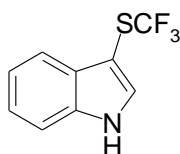

[CAS: 461-84-7]

Compound **17** was prepared following the standard procedure, starting from phenol (94 mg, 1.00 mmol) at room temperature. After purification, **17** was isolated as colorless solid (163 mg, 0.84 mmol, 84%).

m.p.: 58-59°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.55 (d, ^3J = 8.5 Hz, 2H), 6.89 (d, ^3J = 8.8 Hz, 2H), 5.71 ppm (s, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −43.9 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 157.9, 138.6 (2C), 129.6 (q, ^1J(C,F) = 307.9 Hz), 116.5 (2C), 115.2 ppm (q, ^3J(C,F) = 2.7 Hz); **IR** (ATR): ν = 3222, 1739, 1584, 1494, 1437, 1365, 1228, 1109, 1086, 1011, 827 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 194 [M^+] (95), 125 (100); **HRMS** (EI-TOF) calcd for $C_7H_5F_3OS$: 194.0013; found: 194.0010.

7.8.4.14. *Synthesis of 3-bromo-1-methoxy-4-[(trifluoromethyl)thio]benzene (18)*
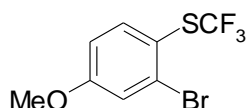
[CAS: 1808089-06-6]

Compound **18** was prepared following the standard procedure, starting from 3-bromoanisole (187 mg, 1.00 mmol) and heating at 60°C. After purification, **18** was isolated as colorless oil (224 mg, 0.78 mmol, 78%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.64 (d, ^3J = 8.5 Hz, 1H), 7.22 (d, ^3J = 2.7 Hz, 1H), 6.85 (dd, ^3J = 8.5, 2.7 Hz, 1H), 3.79 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −43.2 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 162.3, 139.9, 132.5, 129.3 (q, ^1J(C,F) = 309.7 Hz), 119.4, 116.4 (q, ^3J(C,F) = 2.7 Hz), 114.4, 55.7 ppm; **IR** (ATR): ν = 3014, 2970, 2942, 2841, 1587,

267

1558, 1477, 1437, 1291, 1228, 1118, 856, 845 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 288 [M^+] (81), 219 (100); **HRMS** (EI-TOF) calcd for C$_8$H$_6$BrF$_3$OS: 287.9254; found: 287.9266.

7.8.4.15. *Synthesis of 2-iodo-1-methoxy-4-[(trifluoromethyl)thio]benzene (19)*
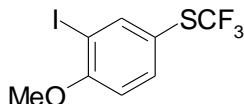
[CAS: 1808089-07-7]

Compound **19** was prepared following the standard procedure, starting from 2-iodoanisole (234 mg, 1.00 mmol) and heating at 60°C. After purification, **19** was isolated as colorless oil (234 mg, 0.70 mmol, 70%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.06 (d, ^3J = 2.3 Hz, 1H), 7.62 (dd, ^3J = 8.5, 2.0 Hz, 1H), 6.84 (d, ^3J = 8.5 Hz, 1H), 3.92 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −43.6 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 160.4, 146.9, 138.2, 129.4 (q, ^1J(C,F) = 308.8 Hz), 116.5 (q, ^3J(C,F) = 2.7 Hz), 111.1, 86.3, 56.5 ppm; **IR** (ATR): ν = 3061, 3015, 2971, 2940, 2841, 1587, 1477, 1470, 1291, 1228, 1118, 1092, 1031, 845 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 334 [M^+] (100), 265 (62); **HRMS** (EI-TOF) calcd for C$_8$H$_6$F$_3$IOS: 333.9136; found: 333.9132.

7.8.4.16. *Synthesis of N,N-dimethyl-4-[(trifluoromethyl)thio]benzenamine (20)*
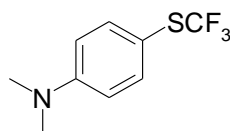
[CAS: 2677-71-6]

Compound **20** was prepared following the standard procedure, starting from *N,N*-dimethylphenylamine (121 mg, 1.00 mmol) at room temperature. After purification, **20** was isolated as colorless oil (217 mg, 0.98 mmol, 98%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.48 (d, ^3J = 8.8 Hz, 2H), 6.68 (d, ^3J = 8.8 Hz, 2H), 3.02 ppm (s, 6H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −44.7 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 151.9, 137.9 (2C), 129.8 (q, ^1J(C,F) = 308.8 Hz), 112.3 (2C), 108.3 (q,

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^3J(C,F) = 2.7 Hz), 40.1 (2C) ppm; **IR** (ATR): ν = 3095, 2896, 2864, 2818, 1593, 1509, 1363, 1104, 1089, 810 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 221 [M^+] (22), 152 (100); **HRMS** (EI-TOF) calcd for $C_9H_{10}F_3NS$: 221.0486; found: 221.0484.

7.8.4.17.   Synthesis of N-methyl-4-[(trifluoromethyl)thio]benzenamine (21)

[CAS: 66476-46-8]

Compound **21** was prepared following the standard procedure, starting from *N*-methylaniline (107 mg, 1.00 mmol) at room temperature. After purification, **21** was isolated as colorless oil (130 mg, 0.63 mmol, 63%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.45 (d, ^3J = 8.7 Hz, 2H), 6.59 (d, ^3J = 8.7 Hz, 2H), 4.06 (br. s, 1H), 2.87 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −44.7 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 151.3, 138.2 (2C), 129.8 (q, ^1J(C,F) = 308.8 Hz), 112.6 (2C), 109.3, 30.2 ppm (q, ^3J(C,F) = 1.8 Hz); **IR** (ATR): ν = 3433, 2937, 2823, 1599, 1512, 1327, 1107, 1089, 819 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 207 [M^+] (70), 138 (100); **HRMS** (EI-TOF) calcd for $C_8H_8F_3NS$: 207.0332; found: 207.0330.

7.8.4.18.   Synthesis of 3-[(trifluoromethyl)thio]-1H-indole (22)

[CAS: 62665-49-0]

Compound **22** was prepared following the standard procedure, starting from indole (117 mg, 1.00 mmol) at room temperature. After purification, **22** was isolated as colorless oil (141 mg, 0.65 mmol, 65%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.50 (br.s, 1H), 7.84 (m, 1H), 7.55 (d, ^3J = 2.8 Hz, 1H), 7.46-7.42 (m, 1H), 7.35-7.29 ppm (m, 2H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −44.6 ppm;

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¹³C NMR (101 MHz, CDCl₃): δ = 136.0, 132.8, 129.4, 129.4 (q, ¹*J*(C,F) = 309.9 Hz), 123.4, 121.6, 119.3, 111.7, 95.5 ppm (q, ³*J*(C,F) = 2.7 Hz); **IR** (ATR): ν = 3405, 3119, 3063, 1456, 1408, 1092, 1008, 741 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 217 [*M*⁺] (74), 148 (100); **HRMS** (EI-TOF) calcd for C₉H₆F₃NS: 217.0173; found: 217.0170.

### 7.8.4.19. *Synthesis of 1-[(4-methylphenyl)sulfonyl]-3-[(trifluoromethyl)thio]indole (23)*
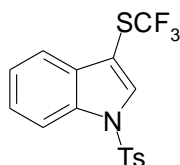
[CAS: 1808089-08-8]

Compound **23** was prepared following the standard procedure, starting from 1-[(4-methylphenyl)sulfonyl]-indole (271 mg, 1.00 mmol) at room temperature. After purification, **23** was isolated as colorless oil (349 mg, 0.94 mmol, 94%).

¹H NMR (400 MHz, CDCl₃): δ = 7.99 (d, ³*J* = 8.0 Hz, 1H), 7.97 (s, 1H), 7.82 (d, ³*J* = 8.5 Hz, 2H), 7.72 (d, ³*J* = 7.5 Hz, 1H), 7.43-7.34 (m, 2H), 7.28 (d, ³*J* = 8.5 Hz, 2H), 2.37 ppm (s, 3H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −43.2 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 145.8, 134.7, 134.6, 133.9, 131.2, 130.2 (2C), 128.9 (q, ¹*J*(C,F) = 309.7 Hz), 127.1 (2C), 125.7, 124.3, 120.1, 113.6, 103.1 (q, ³*J*(C,F) = 2.7 Hz), 21.6 ppm; **IR** (ATR): ν = 3138, 3068, 3032, 2971, 2928, 1445, 1374, 1366, 1176, 1121, 1089, 1049, 1018, 744, 662 cm⁻¹; **MS** (Ion trap, EI, 70 eV): m/z (%) = 371 [*M*⁺] (88), 216 (100); **HRMS** (EI-TOF) calcd for C₁₆H₁₂F₃NO₂S₂: 371.0262; found: 371.0255.

7.8.4.20. *Synthesis of 3-methyl-2-[(trifluoromethyl)thio]-1H-indole (24)*
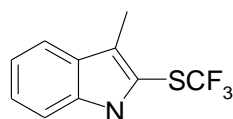
[CAS: 1045823-07-1]

Compound **24** was prepared following the standard procedure, starting from 3-methylindole (131 mg, 1.00 mmol) and heating at 60°C. After purification, **24** was isolated as colorless solid (99 mg, 0.43 mmol, 43%).

m.p.: 132-133°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.13 (br. s, 1H), 7.63 (d, ^3J = 8.8 Hz, 1H), 7.39-7.31 (m, 2H), 7.19 (m, 1H), 2.47 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = –43.1 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 137.3, 128.7 (q, ^1J(C,F) = 311.5 Hz), 127.9, 124.8, 123.7, 120.2, 120.0, 113.0 (q, ^3J(C,F) = 2.7 Hz), 111.1, 9.4 ppm; **IR** (ATR): ν = 3395, 3082, 2971, 2930, 2863, 1132, 1122, 1105, 748 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 231 [M^+] (87), 162 (100); **HRMS** (EI-TOF) calcd for C$_{10}$H$_8$F$_3$NS: 231.0330; found: 231.0334.

7.8.4.21. *Synthesis of 3-[(trifluoromethyl)thio]-9H-Carbazol (25)*
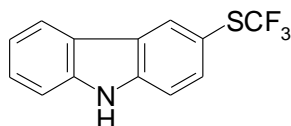
[CAS: 1808089-09-9]

Compound **25** was prepared following the standard procedure, starting from carbazole (167 mg, 1.00 mmol) and heating at 60°C. After purification, **25** was isolated as colorless solid (141 mg, 0.53 mmol, 53%).

m.p.: 146-147°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 8.39 (s, 1H), 8.15 (br. s, 1H), 8.10 (d, ^3J = 8.3 Hz, 1H), 7.69 (dd, J = 8.3, 1.8 Hz 1H), 7.52-7.48 (m, 1H), 7.44-7.40 (m, 2H), 7.34-7.30 ppm (m, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = –44.0 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 140.6, 139.7, 133.9, 129.9 (q, ^1J(C,F) = 308.1 Hz), 129.5, 126.8, 124.3, 122.5, 120.6, 120.3, 113.4 (q, ^3J(C,F) = 2.2 Hz), 111.4, 110.9 ppm; **IR** (ATR): ν = 3386, 1739, 1598, 1454, 1366, 1231, 1101, 815, 754 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 267 [M^+] (74), 198 (100); **HRMS** (EI-TOF) calcd for C$_{13}$H$_8$F$_3$NS: 267.0327; found: 267.0330.

7.8.4.22. Synthesis of 2,6-dimethoxy-3-[(trifluoromethyl)thio)]pyridine (26)
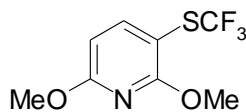
[CAS: 1808089-10-2]

Compound **26** was prepared following the standard procedure, starting from 2,6-dimethoxypyridine (139 mg, 1.00 mmol) at room temperature. After purification, **26** was isolated as colorless oil (227 mg, 0.95 mmol, 95%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.74 (d, ^3J = 8.3 Hz, 1H), 6.36 (d, ^3J = 8.3 Hz, 1H), 4.02 (s, 3H), 3.96 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −43.8 ppm; **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 165.5, 164.1, 150.0, 129.4, 102.9 (q, ^1J(C,F) = 309.2 Hz), 95.9 (q, ^3J(C,F) = 1.8 Hz), 54.2, 53.8 ppm; **IR** (ATR): ν = 2990, 2957, 2901, 2873, 1583, 1570, 1376, 1324, 1099, 1068, 1029, 1010, 811 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 239 [M^+] (100), 170 (72); **HRMS** (EI-TOF) calcd for C$_8$H$_8$F$_3$NO$_2$S: 239.0228; found: 239.0227.

7.8.4.23. Synthesis of 4-[(trifluoromethyl)thio]-1H-pyrazole (27)
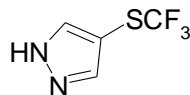
[CAS: 1808089-11-3]

Compound **27** was prepared following the standard procedure, starting from pyrazole (68 mg, 1.00 mmol) at room temperature. After the reaction, trifluoroethanol as internal standard (36.0 μL, 0.50 mmol) was added to the reaction mixture and the trifluoromethylthiolated product **27** was formed in 23% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (375 MHz, DMSO-d_6): δ = −46.7 ppm.

7.8.4.24. *Synthesis of 3-[(trifluoromethyl)thio]thiophene (28)*
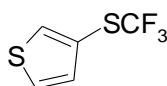
[CAS: 86369-94-0]

Compound **28** was prepared following the standard procedure, starting from thiophene (42 mg, 0.50 mmol) at room temperature. After the reaction, trifluoroethanol as internal standard (36.0 µL, 0.50 mmol) was added to the reaction mixture and the trifluoromethylthiolated product **28** was formed in 76% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics.

^{19}F NMR (375 MHz, DMSO-d_6): δ = −46.5 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 141 (100), 115 (12), 114 (10), 97 (10), 71 (38), 69 (13).

7.8.5. *Synthesis of Difluoromethyl Thioethers from the corresponding Arenes*
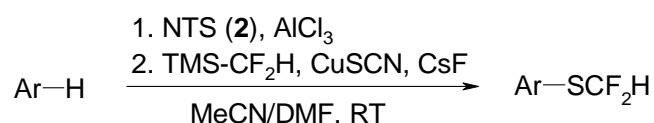
$$\text{Ar−H} \xrightarrow[\text{MeCN/DMF, RT}]{\substack{\text{1. NTS (2), AlCl}_3 \\ \text{2. TMS-CF}_2\text{H, CuSCN, CsF}}} \text{Ar−SCF}_2\text{H}$$

Standard procedure: An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with *N*-thiocyanatosuccinimide (156 mg, 1.00 mmol), aluminium chloride (13.3 mg, 0.10 mmol), the starting material (1.00 mmol) and acetonitrile (2 mL). After stirring at the given reaction temperature for 12 h the solvent was evaporated, CuSCN (123 mg, 1.00 mmol), CsF (608 mg, 4.00 mmol) and DMF (2 mL) were added. Afterwards TMSCF$_2$H (251 mg, 2.00 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The resulting mixture was 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). The residue was further purified by flash chromatography (SiO$_2$, pentane/diethyl ether gradient), yielding the corresponding aryl trifluoromethyl thioethers.

7.8.5.1. Synthesis of 1-[(difluoromethyl)thio]-4-methoxybenzene (29)
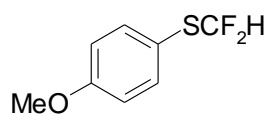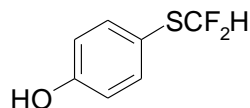

[CAS: 81931-98-8]

Compound **29** was prepared following the standard procedure, starting from methoxybenzene (108 mg, 1.00 mmol) at room temperature. After purification, **29** was isolated as colorless oil (150 mg, 0.79 mmol, 79%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.53 (d, ^3J = 8.8 Hz, 2H), 6.92 (d, ^3J = 8.8 Hz, 2H), 6.76 (t, J = 57.1 Hz, 1H), 3.84 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 = 161.2, 137.6 (2C), 120.9 (t, ^1J(C,F) = 275.1 Hz), 116.1 (t, ^3J(C,F) = 3.3 Hz), 114.9 (2C), 55.4 ppm; **IR** (ATR): ν = 2970, 2841, 1738, 1592, 1494, 1290, 1247, 1174, 1024, 829, 755 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 190 [M^+] (75), 139 (100); **HRMS** (EI-TOF) calcd for C$_8$H$_8$F$_2$OS: 190.0271; found: 190.0264.

7.8.5.2. Synthesis of 1-(phenylmethoxy)-4-[(difluoromethyl)thio]benzene (30)
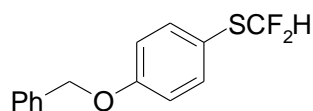
[CAS: 1808089-12-4]

Compound **30** was prepared following the standard procedure, starting from phenoxymethylbenzene (184 mg, 1.00 mmol) at room temperature. After purification, **30** was isolated as colorless oil (168 mg, 0.63 mmol, 63%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.54 (d, ^3J = 8.8 Hz, 2H), 7.47-7.36 (m, 5H), 7.01 (d, ^3J = 8.8 Hz, 2H), 6.77 (t, J = 57.1 Hz, 1H), 5.10 (s, 2H) ppm; **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −92.1 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 160.3, 137.6, 136.3, 128.7, 128.2, 127.5, 120.9 (t, ^1J(C,F) = 275.2 Hz), 116.4 (t, ^3J(C,F) = 3.2 Hz), 115.8, 70.1 ppm; **IR** (ATR): ν = 3035, 1593, 1493, 1455, 1382, 1288, 1242, 1174, 1064, 1024, 908, 829, 733,

696 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 266 [M^+] (17), 91 (100); **HRMS** (EI-TOF) calcd for C$_{14}$H$_{12}$F$_2$OS: 266.0573; found: 266.0577.

7.8.5.3. *Synthesis of 4-[(difluoromethyl)thio]phenol (31)*
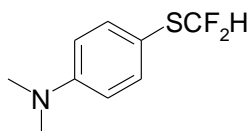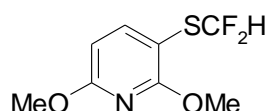

[CAS: 1179181-83-9]

Compound **31** was prepared following the standard procedure, starting from phenol (94 mg, 1.00 mmol) at room temperature. After purification, **31** was isolated as colorless oil (104 mg, 0.59 mmol, 59%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.48 (d, ^3J = 8.5 Hz, 2H), 6.86 (d, ^3J = 8.5 Hz, 2H), 6.76 (t, J = 57.1 Hz, 1H), 5.36 (s, 1H) ppm; **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −92.3 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 157.2, 137.9 (2C), 120.9 (t, ^1J(C,F) = 275.2 Hz), 116.4 (t, ^3J(C,F) = 3.6 Hz), 116.4 (2C) ppm; **IR** (ATR): ν = 3327, 2962, 1600, 1584, 1497, 1431, 1322, 1308, 1261, 1222, 1100, 1055, 1021, 831, 764 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 176 [M^+] (100), 125 (89); **HRMS** (EI-TOF) calcd for C$_7$H$_6$F$_2$OS: 176.0108; found: 176.0107.

7.8.5.4. *Synthesis of N,N-dimethyl-[4-[(difluoromethyl)thio]benzene (32)*
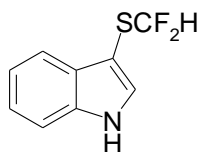

[CAS: 1808089-13-5]

Compound **32** was prepared following the standard procedure, starting from *N,N*-dimethylphenylamine (121 mg, 1.00 mmol) at room temperature. After purification, **32** was isolated as colorless oil (178 mg, 0.88 mmol, 88%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.44 (d, ^3J = 9.0 Hz, 2H), 6.71 (t, J = 57.6 Hz, 1H), 6.68 (d, ^3J = 8.8 Hz, 2H), 3.00 ppm (s, 6H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −92.6 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 151.4, 137.3 (2C), 121.4 (t,

^1J(C,F) = 274.7 Hz), 112.5 (2C), 109.9 (t, ^3J(C,F) = 3.2 Hz), 40.1 ppm (2C); **IR** (ATR): ν = 2893, 2814, 1592, 1507, 1445, 1359, 1195, 1058, 1023, 945, 813, 749 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 203 [M^+] (51), 152 (100); **HRMS** (EI-TOF) calcd for $C_9H_{11}F_2NS$: 203.0581; found: 203.0580.

7.8.5.5. Synthesis of 2,6-dimethoxy-[(difluoromethyl)thio]pyridine (33)

[CAS: 1808089-14-6]

Compound **33** was prepared following the standard procedure, starting from 2,6-dimethoxypyridine (139 mg, 1.00 mmol) at room temperature. After purification, **33** was isolated as colorless oil (152 mg, 0.69 mmol, 69%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.70 (d, ^3J = 8.0 Hz, 1H), 6.80 (t, J = 57.2 Hz, 1H), 6.35 (d, ^3J = 8.3 Hz, 1H), 4.02 (s, 3H), 3.95 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −93.4 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 164.7, 163.2, 149.2, 120.1 (t, ^1J(C,F) = 275.8 Hz), 102.6, 97.6 (t, ^3J(C,F) = 3.7 Hz), 54.2, 53.9 ppm; **IR** (ATR): ν = 2989, 2954, 1739, 1585, 1465, 1415, 1378, 1323, 1266, 1234, 1217, 1075, 1031, 1013, 814 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 221 [M^+] (100), 170 (94); **HRMS** (EI-TOF) calcd for $C_8H_9F_2NO_2S$: 221.0316; found: 221.0322.

7.8.5.6. Synthesis of 3-[(difluoromethyl)thiol]-1H-indole (34)

[CAS: 1805773-38-9]

Compound **34** was prepared following the standard procedure, starting from indole (118 mg, 1.00 mmol) at room temperature. After purification, **34** was isolated as colorless oil (105 mg, 0.53 mmol, 53%).

¹H NMR (400 MHz, CDCl$_3$): δ = 8.34 (br. s, 1H), 7.88-7.86 (m, 1H), 7.42-7.39 (m, 2H), 7.36-7.31 (m, 2H), 6.73 ppm (t, J = 57.5 Hz, 1H); **¹⁹F NMR** (375 MHz, CDCl$_3$): δ = −92.1 ppm (d, J = 57.2 Hz); **¹³C NMR** (101 MHz, CDCl$_3$): δ = 136.0, 131.9, 129.6, 123.2, 121.2, 121.0 (t, ^1J(C,F) = 275.8 Hz), 119.2, 111.6, 96.3 (t, ^3J(C,F) = 3.9 Hz) ppm; **IR** (ATR): ν = 3461, 3404, 2971, 1739, 1506, 1455, 1408, 1316, 1237, 1059, 1024, 1008, 742 cm^{-1}; **MS** (Ion trap, EI, 70 eV): m/z (%) = 199 [M^+] (61), 148 (100); **HRMS** (EI-TOF) calcd for C$_9$H$_7$F$_2$NS: 199.0261; found: 199.0267.

7.9. Convenient Synthesis of Pentafluoroethyl Thioethers via Catalytic Sandmeyer Reaction with a Stable Fluoroalkylthiolation Reagent

7.9.1. *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.

7.9.2. *Synthesis of Starting Materials*

7.9.2.1. *Synthesis of arene diazonium tetrafluoroborates*
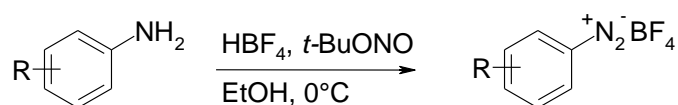
In a 50 mL round-bottom flask, the aniline (10 mmol) was dissolved in a mixture of absolute ethanol (3 mL) and an aqueous solution of HBF$_4$ (50%, 2.5 mL, 20 mmol) and *t*-butyl nitrite (2.7 mL, 20 mmol) was added dropwise to the solution at 0°C. The reaction was stirred at room temperature for 1 h and diethyl ether (20 mL) was added to precipitate the arenediazonium tetrafluoroborate that was filtered off and washed with diethyl ether (3 ×
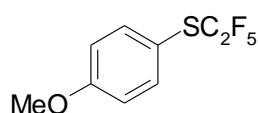
10 mL). The arenediazonium tetrafluoroborate was dried in vacuo (10^{-3} mbar) for 10 minutes and was then directly used without further purification.

7.9.3. *Synthesis of Pentafluoroethyl Thioethers from the corresponding Arenediazonium Salts*
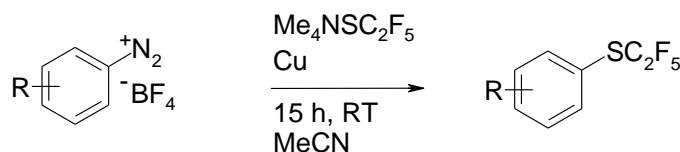
Standard procedure: An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with Cu (6.4 mg, 0.10 mmol), $Me_4NSC_2F_5$ (338 mg, 1.50 mmol) and MeCN (2 mL). Then, the arenediazonium salt (1.00 mmol) in MeCN (2 mL) was added dropwise and the reaction mixture was stirred for 15 h at room temperature. 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.

### 7.9.3.1. *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%).

^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.57$ (d, $^3J = 8.8$ Hz, 2H), 6.94 (d, $^3J = 8.8$ Hz, 2H), 3.85 ppm (s, 3H); **^{19}F NMR** (375 MHz, $CDCl_3$): $\delta = -82.5$ (t, $J = 4.1$ Hz, 3F), -92.8 ppm (q, $J = 4.1$ Hz, 2F); **^{13}C NMR** (101 MHz, $CDCl_3$): $\delta = 162.0$, 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,

279

^1J(C,F) = 286.1 Hz, ^2J(C,F) = 37.0 Hz), 55.4 ppm; **IR** (ATR): 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$_9$H$_7$F$_5$OS: 258.0138; found: 258.0143.

7.9.3.2. Synthesis of 1-methyl-3-[(pentafluoroethyl)thio]benzene (2b)
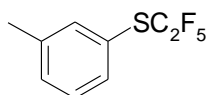
[CAS: 1955495-79-0]

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, ^3J(C,F) = 2.7 Hz), 120.2 (qt, ^1J(C,F) = 288.4 Hz, ^2J(C,F) = 40.0 Hz), 118.8 (tq, ^1J(C,F) = 286.8 Hz, ^2J(C,F) = 36.8 Hz), 21.1 ppm; **IR** (ATR): 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$_9$H$_7$F$_5$S: 242.0189; found: 242.0183.

### 7.9.3.3. Synthesis of 4-[(pentafluoroethyl)thio]-1,1'-biphenyl (2c)
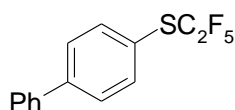
[CAS: 933673-37-1]

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, ^1J(C,F) = 288.4 Hz, ^2J(C,F) = 39.9 Hz), 118.9 ppm (tq, ^1J(C,F) = 287.0 Hz, ^2J(C,F) = 37.1 Hz); **IR** (ATR): 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$_9$F$_5$S: 304.0345; found: 304.0368.

7.9.3.4. *Synthesis of 1-phenoxy-4-[(pentafluoroethyl)thio]benzene (2d)*
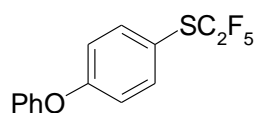
[CAS: 1955495-80-3]

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** (ATR): 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$_9$F$_5$OS: 320.0294; found: 320.0279.

### 7.9.3.5. Synthesis of 1-bromo-4-[(pentafluoroethyl)thio]-benzene (2e)
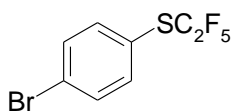
[CAS No.: 782491-17-2]

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** (ATR): 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$_8$H$_4$F$_5$S^{79}Br: 305.9137; found: 305.9154.

7.9.3.6. Synthesis of 1-fluoro-4-[(pentafluoroethyl)thio]-benzene (2f)
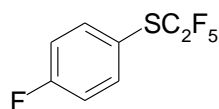
[CAS No.: 75220-65-4]

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).

### 7.9.3.7. Synthesis of 1-chloro-4-[(pentafluoroethyl)thio]-benzene (2g)
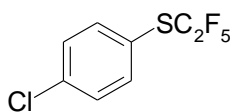
[CAS No.: 65538-02-5]

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, ^3J = 8.5 Hz, 2H), 7.41 ppm (d, ^3J = 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, ^3J(C,F) = 3.2 Hz), 120.2 (qt, ^1J(C,F) = 288.8 Hz, ^2J(C,F) = 40.3 Hz), 119.1 ppm (tq, ^1J(C,F) = 287.0 Hz, ^2J(C,F) = 36.3 Hz); **IR** (ATR): 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$_8$H$_4$F$_5$^{35}ClS: 261.9642; found: 261.9633.

7.9.3.8. Synthesis of 4-[(pentafluoroethyl)thio]acetophenone (2h)
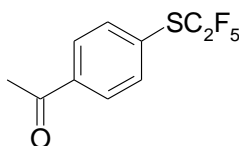
[CAS No.: 1328939-62-3]

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, ^3J = 7.0 Hz, 2H), 7.76 (d, ^3J = 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, ^3J(C,F) = 2.7 Hz), 120.3 (qt, ^1J(C,F) = 289.7 Hz, ^2J(C,F) = 40.8 Hz), 118.6 (tq, ^1J(C,F) = 286.5 Hz, ^2J(C,F) = 36.4 Hz), 26.7 ppm; **IR** (ATR): ν = 3015, 2971, 1690, 1365,

283

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$_7$F$_5$OS: 270.0138; found: 270.0132.

### 7.9.3.9. *Synthesis of 4-[(pentafluoroethyl)thio]benzophenone (2i)*
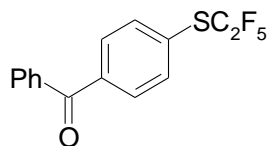
[CAS: 1955495-81-4]

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** (ATR): 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$_9$F$_5$OS: 332.0296; found: 332.0288.

7.9.3.10. *Synthesis of methyl-4-[(pentafluoroethyl)thio]benzoate (2j)*
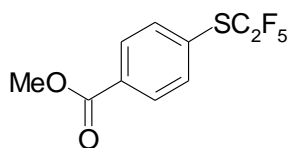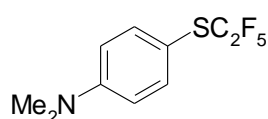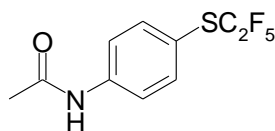

[CAS: 1955495-82-5]

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%).

¹H NMR (400 MHz, CDCl₃): δ = 8.08 (d, ^3J = 8.2 Hz, 2H), 7.73 (d, ^3J = 8.0 Hz, 2H), 3.95 ppm (s, 3H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −82.5 (t, J = 3.8 Hz, 3F), −91.2 ppm (q, J = 4.1 Hz, 2F); **¹³C NMR** (101 MHz, CDCl₃): 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** (ATR): 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 C₁₀H₇F₅O₂S: 286.0087; found: 286.0105.

7.9.3.11. 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%).

¹H NMR (400 MHz, CDCl₃): δ = 7.52-7.50 (m, 2H), 6.72-6.69 (m, 2H), 3.04 ppm (s, 6H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −82.4 (t, J = 4.1 Hz, 3F), −93.5 ppm (q, J = 4.1 Hz, 2F); **¹³C NMR** (101 MHz, CDCl₃): 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** (ATR): 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 C₁₀H₁₀F₅NS: 271.0454; found: 271.0450.

### 7.9.3.12. 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; **¹H NMR** (400 MHz, CDCl₃): δ = 7.60 (s, 4H), 2.21 ppm (s, 3H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −82.4 (t, J = 4.1 Hz, 3F), −92.3 ppm (q, J = 4.1 Hz, 2F); **¹³C NMR** (101 MHz, CDCl₃): 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** (ATR): 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 C₁₀H₈NF₅OS: 285.0247; found: 285.0254.

7.9.3.13. *Synthesis of 4-[(pentafluoroethyl)thio]nitrobenzene (2m)*
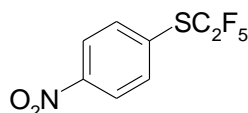
[CAS: 106854-75-5]

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%).

¹H NMR (400 MHz, CDCl₃): δ = 8.29 (d, ^3J = 8.8 Hz, 2H), 7.86 ppm (d, ^3J = 8.8 Hz, 2H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −82.5 (t, J = 3.8 Hz, 3F), −90.8 ppm (q, J = 3.8 Hz, 2F); **¹³C NMR** (101 MHz, CDCl₃): 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** (ATR): 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 C₈H₄NF₅O₂S: 272.9883; found: 272.9897.

7.9.3.14. Synthesis of 4-[(pentafluoroethyl)thio]benzonitrile (2n)
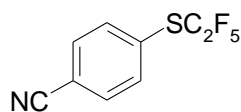
[CAS: 1955495-85-8]

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** (ATR): 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$_9$H$_4$NF$_5$S: 252.9985; found: 252.9991.

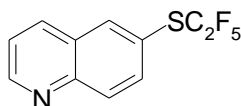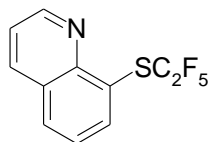### 7.9.3.15. Synthesis of 3-[(pentafluoroethyl)thio]quinoline (2o)
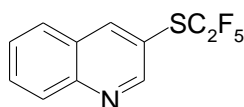
[CAS: 1955495-86-9]

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, ^3J = 8.5 Hz, 1H), 7.84-7.79 (m, 2H), 8.19 ppm (t, ^3J = 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,

^1J(C,F) = 289.6 Hz, ^2J(C,F) = 40.6 Hz), 118.6 (tq, ^1J(C,F) = 286.1 Hz, ^2J(C,F) = 36.3 Hz), 116.7 ppm (t, ^3J(C,F) = 2.9 Hz); **IR** (ATR): 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.

7.9.3.16.   *Synthesis of 6-[(pentafluoroethyl)thio]quinoline (2p)*
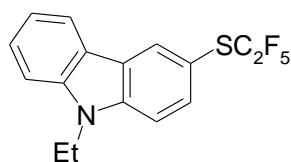

[CAS: 1955495-87-0]

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, ^3J = 4.3, 1.8 Hz, 1H), 8.19 (d, ^3J = 8.8 Hz, 2H), 8.14 (d, ^3J = 8.8 Hz, 1H), 7.89 (dd, ^3J = 8.8, 1.8 Hz, 1H), 7.48 ppm (dd, ^3J = 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, ^3J(C,F) = 2.9 Hz), 120.2 (qt, ^1J(C,F) = 289.0 Hz, ^2J(C,F) = 40.6 Hz), 118.6 ppm (tq, ^1J(C,F) = 286.8 Hz, ^2J(C,F) = 36.7 Hz); **IR** (ATR): 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.

7.9.3.17.   *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%).

¹H NMR (400 MHz, CDCl₃): δ = 9.07 (dd, ³J = 4.3, 1.8 Hz, 1H), 8.21 (dd, ³J = 8.3, 1.5 Hz, 1H), 8.15 (d, ³J = 7.3 Hz, 1H), 7.94 (dd, ³J = 8.0, 1.3 Hz, 1H), 7.58 (t, ³J = 7.8 Hz, 1H), 7.50 ppm (dd, ³J = 8.3, 4.3 Hz, 1H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −82.6 (t, J = 4.1 Hz, 3F), −91.0 ppm (q, J = 4.1 Hz, 2F); **¹³C NMR** (101 MHz, CDCl₃): δ = 151.2, 147.9, 137.5, 136.5, 130.9, 130.0, 126.4, 124.3, 122.0, 120.3 (qt, ¹J(C,F) = 290.3 Hz, ²J(C,F) = 40.6 Hz), 118.7 ppm (tq, ¹J(C,F) = 286.6 Hz, ²J(C,F) = 36.8 Hz); **IR** (ATR): 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 C₁₁H₆NF₅S: 279.0141; found: 279.0134.

7.9.3.18. *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; **¹H NMR** (400 MHz, CDCl₃): δ = 8.40 (s, 1H), 8.14 (d, ³J = 7.8 Hz, 1H), 7.73 (dd, ³J = 8.5, 1.8 Hz, 1H), 7.55 (dt, ³J = 7.7, 1.1 Hz, 1H), 7.44 (t, ³J = 8.8 Hz, 2H), 7.32 (t, ³J = 7.8 Hz, 1H), 4.38 (q, ³J = 7.3 Hz, 2H), 1.47 ppm (t, ³J = 7.3 Hz, 3H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −82.2 (t, J = 4.1 Hz, 3F), −92.7 ppm (q, J = 3.6 Hz, 2F); **¹³C NMR** (101 MHz, CDCl₃): δ = 141.1, 140.3, 134.3, 130.2, 126.6, 123.9, 122.2, 120.7, 120.2 (qt, ¹J(C,F) = 287.9 Hz, ²J(C,F) = 40.0 Hz), 119.8, 118.8 (tq, ¹J(C,F) = 287.0 Hz, ²J(C,F) = 37.2 Hz), 110.7 (t, ³J(C,F) = 3.1 Hz), 109.2, 108.9, 37.7, 13.8 ppm; **IR** (ATR): 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 C₁₆H₁₂NF₅S: 345.0611; found: 345.0616.

7.9.3.19. 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** (ATR): 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$_8$H$_5$F$_5$O$_2$S$_2$: 291.9651; found: 291.9675.

7.10. Synthesis of Perfluoroalkyl Thioethers from Aromatic Thiocyanates by Iron-Catalysed Decarboxylative Perfluoroalkylation

7.10.1. *General Methods*

All reactions were performed in oven-dried glassware that contained a Teflon-coated stir bar and was 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 methyl 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 and 40 g, respectively). NMR spectra were obtained on a Bruker AMX 400 system using chloroform-*d* or methanol-*d₄* as deuterated solvents, with proton, carbon and fluorine resonances at 400 MHz, 101 MHz and 377 MHz, respectively. The shifts were referenced using the respective solvent (residual) signals. 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. The potassium carboxylates were prepared from the corresponding free acid following the procedure below. All other starting materials were commercially available. All solvents were purified by distillation prior to use. The other chemicals were used without further purification.

7.10.2. *Detailed Screening Experiments*

Tabelle 6. Optimization of the reaction conditions.[a]
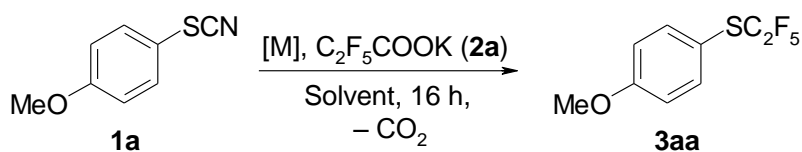
Entry	[M] (eq.)	T/°C	Solvent	Yield of 3aa/%
1	FeCl$_2$ (0.3)	140	DMF	67
2	CuI (0.3)	140	DMF	81
3	FeCl$_3$ (0.3)	140	DMF	99
4	FeBr$_3$ (0.3)	140	DMF	99
5	FeF$_3$ (0.3)	140	DMF	41
6	Fe(acac)$_3$ (0.3)	140	DMF	2
7	Fe (0.3)	140	DMF	42
8	Fe(CO)$_5$ (0.3)	140	DMF	19
9	Fe(OTf)$_2$ (0.3)	140	DMF	60
10	Sc(OTf)$_3$ (0.3)	140	DMF	16
11	In(OTf)$_3$ (0.3)	140	DMF	31
12	Mg(OTf)$_2$ (0.3)	140	DMF	27
13	K(OTf) (0.3)	140	DMF	16
14	Bi(OTf)$_3$ (0.3)	140	DMF	3
15	Zn(OTf)$_2$ (0.3)	140	DMF	20
16	Cu(OTf)$_2$ (0.3)	140	DMF	29
17	AlCl$_3$ (0.3)	140	DMF	40
18	MsOH (0.3)	140	DMF	24
19	FeCl$_3$ (0.2)	140	DMF	81
20	FeCl$_3$ (0.1)	140	DMF	49
21	FeCl$_3$ (0.3)	130	DMF	95
22	FeCl$_3$ (0.3)	120	DMF	81
23	FeCl$_3$ (0.3)	100	DMF	21
24	FeCl$_3$ (0.3)	140	NMP	97
25	FeCl$_3$ (0.3)	140	Propylene carbonate	19

| 26 | FeCl$_3$ (0.3) | 140 | Sulfolane | 48 |
| 27 | FeCl$_3$ (0.3) | 140 | DMSO | 89 |

[a] Reaction conditions: 0.30 mmol of 4-methoxyphenyl thiocyanate (**1a**), 0.36 mmol of potassium pentafluoropropionate (**2a**), [M], 1 mL of solvent, T, 16 h. [b] Yields were determined by ^{19}F NMR spectroscopy using 2,2,2-trifluoroethanol as an internal standard.

7.10.3. *Formation of Pentafluoroethane with Starting Materials containing Acidic Protons*
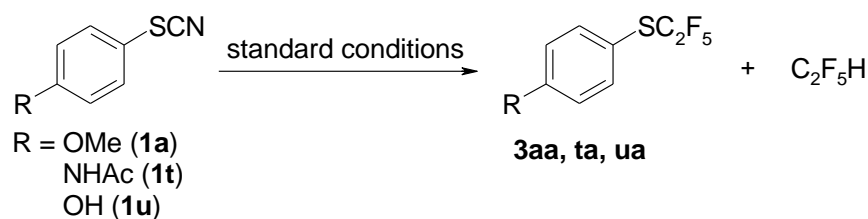
The reactions were performed in a 0.50 mmol scale using the optimised reaction conditions with 2,2,2-trifluoroethanol as an internal standard. After the reaction, the mixture was diluted with ethyl acetate (3 mL) and the mixture was filtered through a short pad of celite directly into an NMR tube. Although small quantities of pentafluoroethane were also formed in the control reaction with a starting material without acidic protons, probably originating from traces of water (**1a**), the amount increases considerably for compounds containing them (**1t+u**).[244]

7.10.4. *Synthesis of Starting Materials*

7.10.4.1. *Synthesis of arene diazonium tetrafluoroborates*
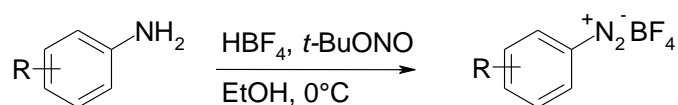
In a 50 mL round-bottom flask, the aniline (10 mmol) was dissolved in a mixture of absolute ethanol (3 mL) and an aqueous solution of HBF$_4$ (50%, 2.5 mL, 20 mmol) and *t*-butyl nitrite (2.7 mL, 20 mmol) was added dropwise to the solution at 0°C. The reaction was stirred at room temperature for 1 h 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.

7.10.4.2. Synthesis of potassium carboxylates

Potassium *tert*-butoxid (1.0 eq.) was dissolved in ethanol (4 M) and the corresponding acid (1.0 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.

7.10.5. Synthesis of Aryl Thiocyanates
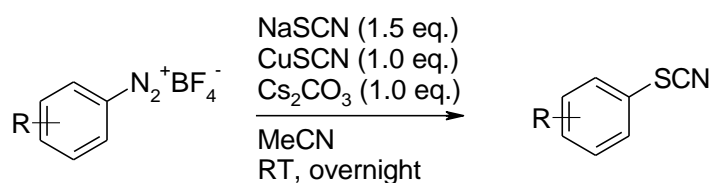
Procedure A, starting from the corresponding arenediazonium tetrafluoroborates: Caesium carbonate (1.0 eq.), sodium thiocyanate (1.5 eq.), and copper(I) thiocyanate (1.0 eq.) were suspended in acetonitrile (0.67 M), and the mixture was cooled to 0°C. To this suspension was added dropwise a solution of 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).
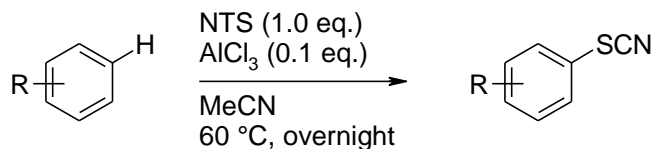
Procedure B, starting from the corresponding simple arenes: The corresponding arene (1.0 eq.), aluminium chloride (0.1 eq.), and *N*-thiocyanatosuccinimide (1.0 eq.) were dissolved in acetonitrile (0.6 M) and heated to 60°C overnight. Afterwards diethyl ether (30 mL) was added and the precipitate was filtered off. The filtrate was washed with water

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(2 × 30 mL) and the organic layer was dried with magnesium sulphate. The product was purified by column chromatography (ethyl acetate/cyclohexane gradient).

### 7.10.5.1. *Synthesis of 4-methoxyphenyl thiocyanate (1a)*
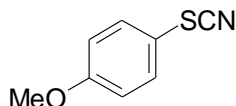
[CAS: 5285-90-5]

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 (16.9 g, 53.2 mmol). After purification, **1a** was obtained as yellow liquid. The analytical data matched the one reported previously.[235]

7.10.5.2. *Synthesis of 4-phenoxyphenyl thiocyanate (1b)*
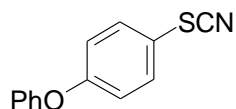
[CAS: 96460-69-4]

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 (5.04 g, 17.8 mmol). After purification, **1b** was obtained as orange liquid. The analytical data matched the one reported previously.[235]

7.10.5.3. *Synthesis of [1,1'-biphenyl]-4-yl thiocyanate (1c)*
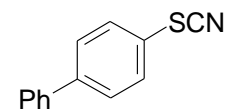
[CAS: 99847-27-5]

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 (2.17 g, 8.09 mmol). After purification, **1c** was obtained as orange solid.

m.p.: 80-81°C, **^{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).

7.10.5.4. *Synthesis of 2-methylphenyl thiocyanate (1d)*
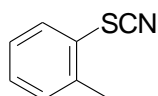
[CAS: 5285-88-1]

Compound 1d was prepared following procedure **A** starting from Cs$_2$CO$_3$ (5.19 g, 15.9 mmol), NaSCN (1.97 g, 23.9 mmol), CuSCN (1.95 g, 15.9 mmol), and 2-methylbenzenediazonium tetrafluoroborate (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$_8$H$_7$NS: 149.0299; found: 149.0307.

### 7.10.5.5. *Synthesis of 3-methylphenyl thiocyanate (1e)*
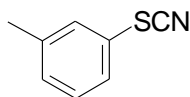
[CAS: 5285-89-2]

Compound 1e was prepared following procedure **A** starting from Cs$_2$CO$_3$ (4.89 g, 15.0 mmol), NaSCN (1.86 g, 22.5 mmol), CuSCN (1.84 g, 15.0 mmol), and 3-methylbenzenediazonium tetrafluoroborate (3.71 g, 18.0 mmol). After purification, 1e was obtained as yellow liquid.

¹H NMR (400 MHz, CDCl₃): δ = 7.34 (s, 1H), 7.31 (m, 2H), 7.21 (m, 1H), 2.38 ppm (s, 3H); **¹³C NMR** (101 MHz, CDCl₃): 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).

### 7.10.5.6. Synthesis of 4-methylphenyl thiocyanate (1f)
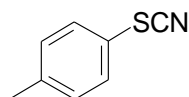
[CAS: 5285-74-5]

Compound 1f was prepared following procedure **A** starting from Cs₂CO₃ (5.09 g, 15.6 mmol), NaSCN (1.94 g, 23.4 mmol), CuSCN (1.92 g, 15.6 mmol), and 4-methylbenzenediazonium tetrafluoroborate (3.85 g, 18.7 mmol). After purification, 1f was obtained as yellow liquid.[245]

¹H NMR (400 MHz, CDCl₃): δ = 7.42 (m, 2H), 7.23 (m, 2H), 2.37 ppm (s, 3H); **¹³C NMR** (101 MHz, CDCl₃): 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 C₈H₇NS: 149.0299; found: 149.0302.

### 7.10.5.7. Synthesis of 4-(methylthio)phenyl thiocyanate (1g)
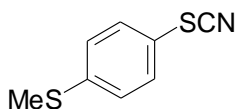
[CAS: 5285-91-6]

Compound **1g** was prepared following procedure **A** starting from Cs₂CO₃ (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 (4.60 g, 19.3 mmol). After purification, **1g** was obtained as red liquid.

¹H NMR (400 MHz, CDCl₃): δ = 7.41 (m, 2H), 7.23 (m, 2H) 2.46 ppm (s, 3H); **¹³C NMR** (101 MHz, CDCl₃): 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.
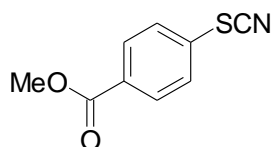
7.10.5.8. *Synthesis of 4-(dimethylamino)phenyl thiocyanate (1h)*
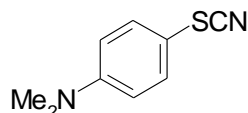
[CAS: 7152-80-9]

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 (2.17 g, 9.22 mmol). After purification, **1h** was obtained as orange solid. The analytical data matched the one reported previously.[235]

7.10.5.9. *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 (2.17 g, 8.67 mmol). After purification, **1i** was obtained as pale orange solid. The analytical data matched the one reported previously.[235]

7.10.5.10. *Synthesis of 4-benzoylphenyl thiocyanate (1j)*
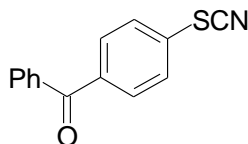
Compound **1j** was prepared following procedure **A** starting from Cs_2CO_3 (5.38 g, 16.5 mmol), NaSCN (2.05 g, 24.8 mmol), CuSCN (2.03 g, 16.5 mmol), and 4-

benzoylbenzenediazonium tetrafluoroborate (5.87 g, 19.8 mmol). After purification, **1j** was obtained as orange solid. The analytical data matched the one reported previously.[235]

7.10.5.11. *Synthesis of 4-cyanophenyl thiocyanate (1k)*
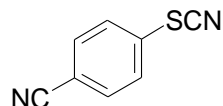
[CAS: 122148-91-8]

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 (1.74 g, 8.00 mmol). After purification, **1k** was obtained as light-yellow solid. The analytical data matched the one reported previously.[235]

### 7.10.5.12. *Synthesis of 8-quinolinyl thiocyanate (1l)*
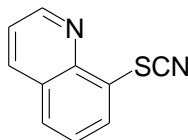
[CAS: 16671-93-5]

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 (4.37 g, 18.0 mmol). After purification, **1l** was obtained as colourless solid.

m.p.: 90-91°C, **^{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).

7.10.5.13. Synthesis of 3-quinolinyl thiocyanate (1m)
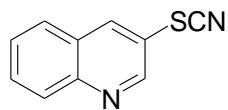

[CAS: 2645-26-3]

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.[235]

### 7.10.5.14. Synthesis of 9-ethyl-9H-carbazol-3-yl thiocyanate (1n)
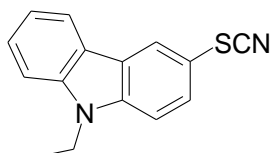
Compound **1n** was prepared following procedure **A** starting from Cs_2CO_3 (2.29 g, 7.01 mmol), NaSCN (870 mg, 10.5 mmol), CuSCN (861 mg, 7.01 mmol), and 9-ethyl-9*H*-carbazol-3-diazonium tetrafluoroborate (2.17 g, 7.01 mmol). After purification, **1n** was obtained as orange solid.

1H NMR (400 MHz, CDCl₃): 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); **13C NMR** (101 MHz, CDCl₃): 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** (ATR): ν = 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).

### 7.10.5.15. Synthesis of 4-fluorophenyl thiocyanate (1o)
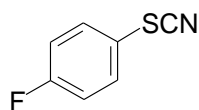
[CAS: 2924-02-9]

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 (3.73 g, 15.7 mmol). After purification, **1o** was obtained as yellow liquid. The analytical data matched the one reported previously.[235]

### 7.10.5.16. Synthesis of 4-chlorophenyl thiocyanate (1p)
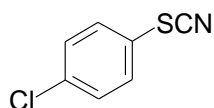
[CAS: 3226-37-7]

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 (3.80 g, 16.8 mmol). After purification, **1p** was obtained as yellow liquid. The analytical data matched the one reported previously.[235]

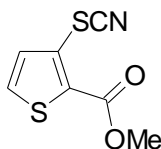### 7.10.5.17. Synthesis of 4-bromophenyl thiocyanate (1q)
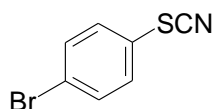
[CAS: 3226-41-3]

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 (2.17 g, 8.00 mmol). After purification, **1q** was obtained as pale yellow solid. The analytical data matched the one reported previously.[235]

### 7.10.5.18. Synthesis of 4-nitrophenyl thiocyanate (1r)
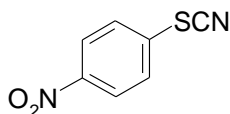
[CAS: 3226-41-3]

Compound **1r** 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 (3.73 g, 15.7 mmol). After purification, **1r** was obtained as pale yellow solid. The analytical data matched the one reported previously.[235]

7.10.5.19. 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 (5.09 g, 19.9 mmol). After purification, **1s** was obtained as colourless solid. The analytical data matched the one reported previously.[235]

### 7.10.5.20. Synthesis of 4-(acetylamino)phenyl thiocyanate (1t)
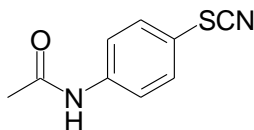
[CAS: 3321-94-6]

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 (2.17 g, 8.70 mmol). After purification, **1t** was obtained as yellow solid.

¹H NMR (400 MHz, CDCl₃): δ = 7.61 (d, 8.5 Hz, 2H), 7.50 (m, 2H), 7.36 (s, 1H), 2.20 ppm (s, 3H); **¹³C NMR** (101 MHz, CDCl₃): δ = 168.5, 139.7, 132.1, 121.0, 118.1, 111.0, 24.7 ppm; **IR** (ATR): ν = 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).

7.10.5.21. Synthesis of 4-hydroxyphenyl thiocyanate (1u)
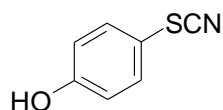
[CAS: 3774-52-5]

Compound **1u** was prepared following procedure **B** starting from AlCl₃ (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.[235]

7.10.6. Synthesis of Perfluoroalkyl Thioethers from the corresponding Aryl Thiocyanates
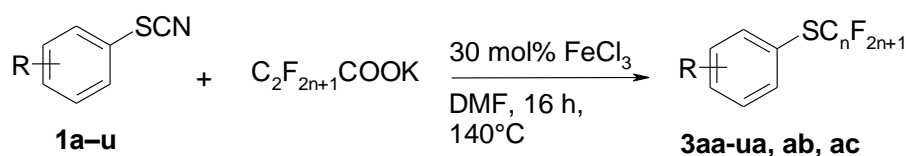
Standard procedure: An oven-dried 20 mL crimp-cap vessel with stir bar was charged with the potassium carboxylate (2.40 mmol), the aryl thiocyanate (2.00 mmol), iron(III) chloride (97.3 mg, 0.60 mmol) and DMF (6 mL). The reaction mixture was stirred for 16 h at 140°C. To prevent the crimp cap from flying off, the upper half of the vessel was cooled with water and the evolving CO₂ 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.

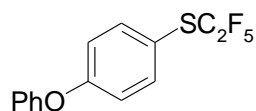### 7.10.6.1. Synthesis of 1-methoxy-4-[(pentafluoroethyl)thio]benzene (3aa)
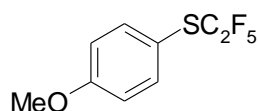
[CAS: 1955495-78-9]

Compound **3aa** was prepared following the standard procedure, starting from 4-methoxyphenyl thiocyanate (**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** (ATR): ν = 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$_9$H$_7$F$_5$OS: 258.0138; found: 258.0143.

### 7.10.6.2. Synthesis of 1-phenoxy-4-[(pentafluoroethyl)thio]benzene (3ba)

[CAS: 1955495-80-3]

Compound **3ba** was prepared following the standard procedure, starting from 4-methoxyphenyl thiocyanate (**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** (ATR): ν = 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$_9$F$_5$OS: 320.0294; found: 320.0279.

### 7.10.6.3.   *Synthesis of 4-[(pentafluoroethyl)thio]-1,1'-biphenyl (3ca)*
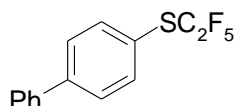
[CAS: 933673-37-1]

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%).

m.p.: 60-61°C, **^{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** (ATR): ν = 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$_9$F$_5$S: 304.0345; found: 304.0368.

7.10.6.4. Synthesis of 1-methyl-2-[(pentafluoroethyl)thio]benzene (3da)
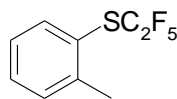
Compound **3da** was prepared following the standard procedure, starting from 2-methylphenyl thiocyanate (**1d**, 74.6 mg, 0.50 mmol) and potassium pentafluoropropionate (**2a**, 222 mg, 0.60 mmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36.0 µL, 0.50 mmol) was added to the 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): $\delta = -82.7$ (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).

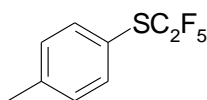### 7.10.6.5. Synthesis of 1-methyl-3-[(pentafluoroethyl)thio]benzene (3ea)
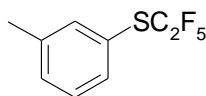
[CAS: 1955495-79-0]

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$_3$): $\delta = 7.50$–7.47 (m, 2H), 7.33–7.32 (m, 2H), 2.40 ppm (s, 3H); ^{13}**C NMR** (101 MHz, CDCl$_3$): $\delta = 139.6$, 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$_3$): $\delta = -82.4$ (t, $J = 4.1$ Hz, 3F), -91.7 ppm (q, $J = 3.6$ Hz, 2F); **IR** (ATR): $\nu = 3053$, 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$_9$H$_7$F$_5$S: 242.0189; found: 242.0183.

### 7.10.6.6. 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): $\delta = -82.4$ (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).

7.10.6.7. Synthesis of 1-methylthio-4-[(pentafluoroethyl)thio]benzene (3ga)
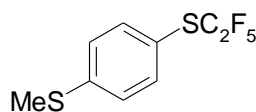
Compound **3ga** was prepared following the standard procedure, starting from 4-methylthiophenyl thiocyanate (**1g**, 363 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3ga** was isolated as colourless oil (527 mg, 1.92 mmol, 96%).

^{1}**H NMR** (400 MHz, CDCl$_3$): $\delta = 7.54–7.51$ (m, 2H), 7.24–7.21 (m, 2H), 2.48 ppm (s, 3H); ^{13}**C NMR** (101 MHz, CDCl$_3$): $\delta = 143.8$, 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$_3$): $\delta = -82.3$ (t, $J = 3.4$ Hz, 3F), -92.2 ppm (q, $J = 3.2$ Hz, 2F); **IR** (ATR): $\nu = 2925$, 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$_9$H$_7$F$_5$S$_2$: 273.9909; found: 273.9910.

7.10.6.8. Synthesis of N,N-dimethyl-4-[(pentafluoroethyl)thio]benzenamine (3ha)
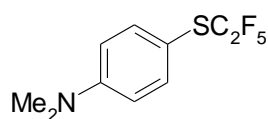
[CAS: 1955495-83-6]

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%).

¹H NMR (400 MHz, CDCl₃): δ = 7.51–7.47 (m, 2H), 6.71–6.67 (m, 2H), 3.02 ppm (s, 6H); **¹³C NMR** (101 MHz, CDCl₃): 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; **¹⁹F NMR** (377 MHz, CDCl₃): δ = −82.3 (t, J = 3.7 Hz, 3F), −93.3 ppm (q, J = 4.0 Hz, 2F); **IR** (ATR): ν = 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.

7.10.6.9. Synthesis of methyl-4-[(pentafluoroethyl)thio]benzoate (3ia)
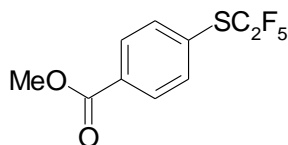
[CAS: 1955495-82-5]

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%).

¹H NMR (400 MHz, CDCl₃): δ = 8.07 (m, 2H), 7.72 (m, 2H), 3.94 ppm (s, 3H); **¹⁹F NMR** (377 MHz, CDCl₃): δ = −82.3 (t, J = 3.4 Hz, 3F), −91.0 ppm (q, J = 3.6 Hz, 2F); **¹³C NMR** (101 MHz, CDCl₃): 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** (ATR): $\nu = 2954$, 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.

7.10.6.10. Synthesis of 4-[(pentafluoroethyl)thio]benzophenone (3ja)
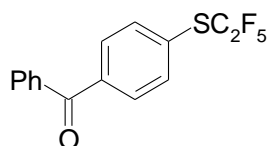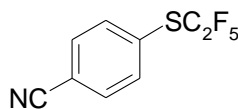

[CAS: 1955495-81-4]

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%).

m.p.: 56-57°C, **¹H NMR** (400 MHz, CDCl$_3$): $\delta = 7.87–7.76$ (m, 6H), 7.65–7.61 (m, 1H), 7.53–7.49 ppm (m, 2H); **¹³C NMR** (101 MHz, CDCl$_3$): $\delta = 195.7$, 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); **¹⁹F NMR** (377 MHz, CDCl$_3$): $\delta = -82.4$ (t, $J = 3.4$ Hz, 3F), -91.1 ppm (q, $J = 3.6$ Hz, 2F); **IR** (ATR): $\nu = 2929$, 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.

### 7.10.6.11. 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%).

m.p.: 45-46°C, **^{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** (ATR): ν = 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$_9$H$_4$NF$_5$S: 252.9985; found: 252.9991.

7.10.6.12.   Synthesis of 8-[(pentafluoroethyl)thio]quinoline (3la)
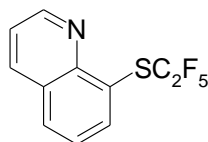
[CAS: 1955495-88-1]

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** (ATR): ν = 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$_6$NF$_5$S: 279.0141; found: 279.0134.

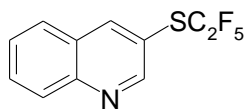### 7.10.6.13. Synthesis of 3-[(pentafluoroethyl)thio]quinoline (3ma)

[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%).

m.p.: 35-36°C, **^{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** (ATR): ν = 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$_6$NF$_5$S: 279.0141; found: 279.0145.

7.10.6.14. Synthesis of 9-ethyl-3-[(pentafluoroethyl)thio]-9H-carbazole (3na)
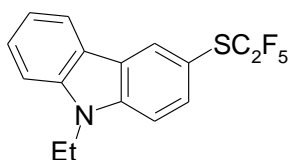
Compound **3na** was prepared following the standard procedure, starting from 9-ethyl-9H-carbazol-3-yl thiocyanate (**1n**, 505 mg, 2.00 mmol) and potassium pentafluoropropionate (**2a**, 485 mg, 2.40 mmol). After purification, **3na** was isolated as colourless solid (670 mg, 1.94 mmol, 97%).

m.p.: 64-65°C, **^{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

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(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** (ATR): ν = 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$_5$S: 345.0611; found: 345.0616.

7.10.6.15. *Synthesis of 1-fluoro-4-[(pentafluoroethyl)thio]-benzene (3oa)*

[CAS: 75220-65-4]
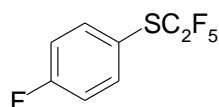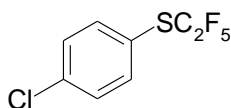
Compound **3oa** was prepared following the standard procedure, starting from 4-fluorophenyl thiocyanate (**1o**, 76.6 mg, 0.50 mmol) and potassium pentafluoropropionate (**2a**, 222 mg, 0.60 mmol). After the reaction, 2,2,2-trifluoroethanol as internal standard (36.0 μL, 0.50 mmol) was added to the 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 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).

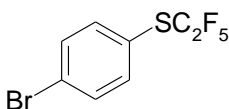### 7.10.6.16. *Synthesis of 1-chloro-4-[(pentafluoroethyl)thio]-benzene (3pa)*

[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** is 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** (ATR): ν = 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$_8$H$_4$F$_5$^{35}ClS: 261.9642; found: 261.9633.

7.10.6.17. Synthesis of 1-bromo-4-[(pentafluoroethyl)thio]-benzene (3qa)
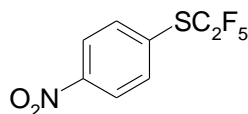

[CAS: 782491-17-2]

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** (ATR): ν = 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$_8$H$_4$F$_5$S^{79}Br: 305.9137; found: 305.9154.

7.10.6.18. 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** (ATR): ν = 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$_8$H$_4$NF$_5$O$_2$S: 272.9883; found: 272.9897.

7.10.6.19. Synthesis of methyl-3-[(pentafluoroethyl)thio]thiophene-2-carboxylate (3sa)
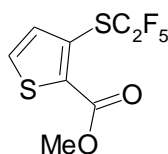
[CAS: 1955495-90-5]

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 (ATR): ν = 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$_8$H$_5$F$_5$O$_2$S$_2$: 291.9651; found: 291.9675.

7.10.6.20.   *Synthesis of N-[4-[(pentafluoroethyl)thio]phenyl]acetamide (3ta)*
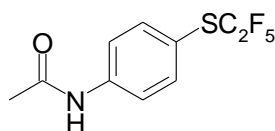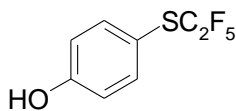

[CAS: 1955495-84-7]

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%).

m.p.: 137-138°C, **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 7.59 (s, 4H), 2.20 ppm (s, 3H); **^{13}C NMR** (101 MHz, CD$_3$OD): 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** (ATR): ν = 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$_8$NF$_5$OS: 285.0247; found: 285.0254.

### 7.10.6.21.   *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%).

¹H NMR (400 MHz, CDCl₃): δ = 7.52 (m, 2H), 6.88 (m, 2H), 6.04 ppm (s, 1H); **¹³C NMR** (101 MHz, CDCl₃): 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); **¹⁹F NMR** (377 MHz, CDCl₃): δ = −82.3 (t, J = 3.4 Hz, 3F), −92.7 ppm (q, J = 3.6 Hz, 2F); **IR** (ATR): ν = 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); **HRMS** (EI-TOF) calcd. for $C_8H_5F_5OS$: 243.9981; found: 243.9969.

7.10.6.22. *Synthesis of 1-methoxy-4-[(heptafluoropropyl)thio]benzene (3ab)*
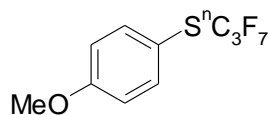
[CAS: 166392-12-7]

Compound **3ab** was prepared following the standard procedure, starting from 4-methoxyphenyl thiocyanate (**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%).

¹H NMR (400 MHz, CDCl₃): δ = 7.59–7.55 (m, 2H), 6.95–6.92 (m, 2H), 3.84 ppm (s, 3H); **¹³C NMR** (101 MHz, CDCl₃): 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; **¹⁹F NMR** (377 MHz, CDCl₃): 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** (ATR): ν = 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); **HRMS** (EI-TOF) calcd. for $C_{10}H_7F_7OS$: 308.0106; found: 308.0096.

7.10.6.23. Synthesis of 1-methoxy-4-[(1-trifluoromethyl-1,2,2,2-tetrafluoroethyl)thio]benzene
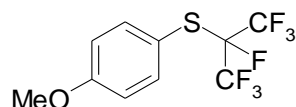
Due to very similar physical properties, the side product could not be separated from **3ba**. Therefore and because of the comparatively low quantities in which the side product was present in the sample, a full characterisation proved difficult. In the ^{1}H NMR, the shifts of the compounds seem to 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).

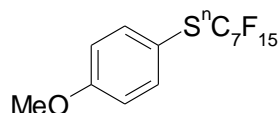### 7.10.6.24. Synthesis of 1-methoxy-4-[(perfluoroheptyl)thio]benzene (3ac)

Compound **3ac** was prepared following the standard procedure, starting from 4-methoxyphenyl thiocyanate (**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, −

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121.0, −121.7, −122.4, −125.9 ppm; **IR** (ATR): ν = 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$_7$F$_{15}$OS: 507.9978; found: 507.9968.

7.11. Synthesis of Difluoromethyl Thioethers from Difluoromethyl Trimethylsilane and Organothiocyanates Generated in situ
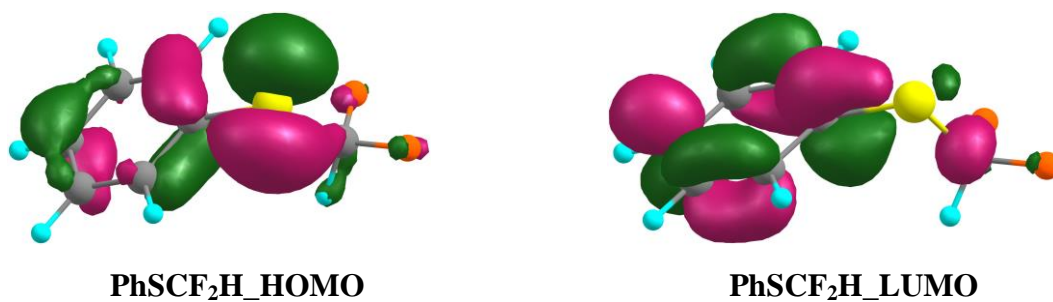
7.11.1. *DFT Calculations*

Level of calculations: **M06-2X/6-311+G(d,p)**
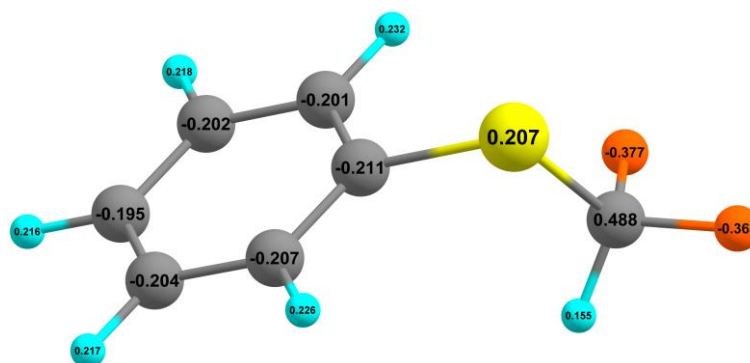
1) Electrostatic potential plot (isodensity = 0.02 electron/bohr^3)

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

PhSCF$_2$H_HOMO   **PhSCF$_2$H_LUMO**

3) Natural charge

4) The calculated pKa values

PhSCF$_2$H = **35.2**

PhCF$_2$H = **42.2**

5) Cartesian coordinate

PhSCF$_2$H

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

7.11.2. *General Methods*

The reactions were performed in oven-dried glassware containing a Teflon-coated stirrer bar and septum under a nitrogen atmosphere. Dimethylformamide 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$_2$H 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 1×10^{-3} mbar. The other chemicals were used without further purification.

7.11.3. *Detailed Screening Experiments*

Tabelle 7. Optimization of the reaction conditions.[a]
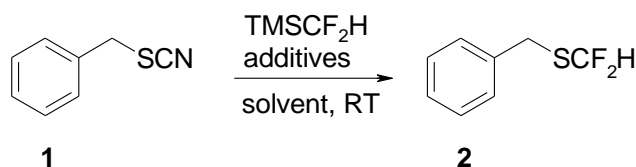
Entry	Additive	Mediator	Solvent	Yield of 2 [%][b]
1[c]	TBAF	-	THF	trace
2	CsF	-	"	0
3	TBAF	-	DMF	trace
4	KF	-	"	trace
5	CsF	-	"	51
6[d]	"	CuSCN	"	85
7[e]	"	"	"	98
8[e]	"	CuI	"	90

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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$_2$H, RT. [b] Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard. [c] TMS–CF$_2$H 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.

Tabelle 8. Optimization of the reaction conditions.[a]
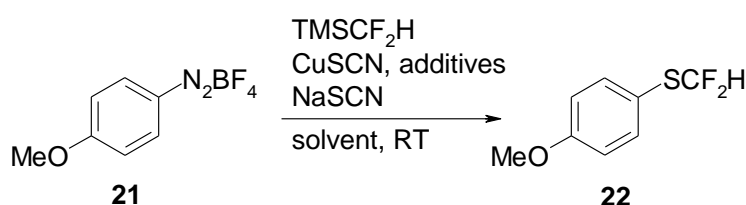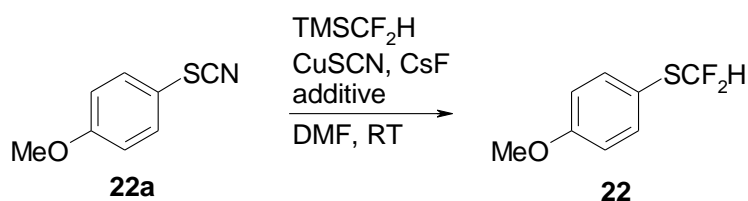

Entry	Additive 1	Additive 2	Solvent	Yield of 22 [%][b]
1	Cs$_2$CO$_3$	-	MeCN	0
2	"	-	DMF	15
3[c]	"	CsF	"	25
4[d]	"	"	"	50
5[e]	"	"	"	83
6	-	"	DMF	0
7[f]	"	"	MeCN/DMF	98

[a] Reaction conditions: 1.0 mmol of CuSCN, 0.5 mmol of Cs$_2$CO$_3$, 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$_2$H. [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$_2$CO$_3$, 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$_2$H in 1 mL DMF, RT, 12 h.

Tabelle 9. Interference of Cs_2CO_3 or NaSCN on the difluoromethylation step.[a]

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.

7.11.4. *Synthesis of Starting Materials*

7.11.4.1. *Synthesis of arenediazonium tetrafluoroborates*
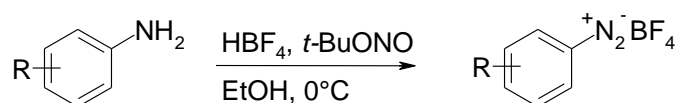
The aniline (10 mmol) was dissolved in a mixture of absolute ethanol (3 mL) and an aqueous solution of HBF_4 (50%, 2.5 mL, 20 mmol) and *t*-butyl nitrite (2.7 mL, 20 mmol) was added dropwise to the solution at 0°C. The reaction was stirred at room temperature for 1 h and diethyl ether (20 mL) was added 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.

7.11.4.2. *Synthesis of difluoromethyltrimethylsilane[200]*

$$Me_3Si{-}CF_2H$$

[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 as colorless oil (15.6 mL, 97 mmol, 71%).

b.p.: 65-66°C; **^{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, ^1J(C,F) = 253.9 Hz), -5.5 (3C) ppm.

7.11.4.3. *Synthesis of 4-(dimethylamino)benzenethiocyanate*[246]
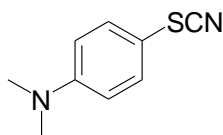
[CAS: 7152-80-9]

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 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$_9$H$_{10}$N$_2$S: 178.0565; found: 178.0567.

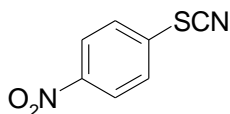### 7.11.4.4. Synthesis of 4-nitrobenzenethiocyanate

[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 yellow solid (738 mg, 4.10 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.31$ (d, $J = 9.0$ Hz, 2H), 7.68 ppm (d, $J = 9.1$ Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): $\delta = 148.0$, 133.4, 128.7 (2C), 125.1 (2C), 108.1 ppm.

7.11.4.5. Synthesis of 4-thiocyanatopyridine[247]
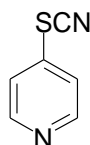
[CAS: 2637-36-7]

Following the literature procedure, 4-aminopyridine (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** (ATR): 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$_6$H$_4$N$_2$S: 136.0095; found: 136.0091.

7.11.4.6.   Synthesis of 2-thiocyanatopyridine[247]
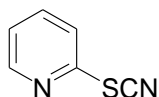
[CAS: 2637-35-6]

Following the literature procedure, 2-aminopyridine (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** (ATR): 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.

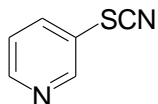### 7.11.4.7. *Synthesis of 3-thiocyanatopyridine[247]*

[CAS: 2645-25-2]

Following the literature procedure, 3-aminopyridine (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** (ATR): 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.
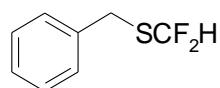
7.11.5. *Synthesis of Difluoromethyl Thioethers starting from the corresponding Thiocyanates*
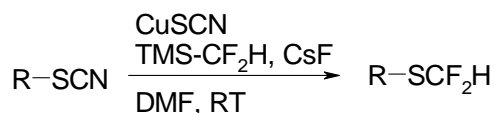
Standard procedure 1: An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with the organo thiocyanate (1.00 mmol), copper thiocyanate (122 mg,

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).

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

[CAS: 68965-44-6]

Compound **2** was prepared following the standard procedure 1, starting from (bromomethyl)benzene (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** (ATR): 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$_8$H$_8$F$_2$S: 174.0315; found: 174.0314.

### 7.11.5.2. Synthesis of 1-[(difluoromethyl)thio]-butane (3)
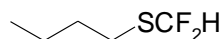
[CAS: 1809138-51-9]

Compound **3** was prepared following the standard procedure 1, starting from butylthiocyanate (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); **MS** (Ion trap, EI, 70 eV): m/z (%) = 139 [M^+] (70), 130 (41), 95 (31), 57 (100), 55 (43), 41 (67).

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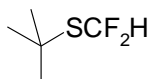

[CAS: 68965-47-9]

Compound **4** was prepared following the standard procedure 1, starting from 2-thiocyano-2-methyl-propane, that was synthesized via nucleophilic substitution of 2-iodo-2-methyl-propane (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); **MS** (Ion trap, EI, 70 eV): m/z (%) = 119 (57), 97 (100), 83 (22), 67 (19), 56.9 (96).

7.11.5.4. *Synthesis of 1-[(difluoromethyl)thio]-4-nitrobenzene (5)*
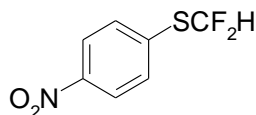
[CAS: 24933-57-1]

Compound **5** was prepared following the standard procedure 1, starting from 4-nitrobenzenethiocyanate (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, ^3J(H,H) = 8.9 Hz, 2H), 7.73 (d, ^3J(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,

^3J(C,F) = 3.3 Hz), 134.3 (2C), 124.1 (2C), 119.6 ppm (t, ^1J(C,F) = 276.6 Hz); **IR** (ATR): 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$_7$H$_5$NO$_2$F$_2$S: 205.0009; found: 205.0002.

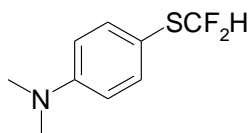### 7.11.5.5. *Synthesis of N,N-dimethyl-4-[(difluoromethyl)thio]aniline (6)*

[CAS: 1808089-13-5]

Compound **6** was prepared following the standard procedure 1, starting from 4-(dimethylamino)benzenethiocyanate (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, ^3J(H,H) = 9.0 Hz, 2H), 6.71 (t, J = 57.6 Hz, 1H), 6.68 (d, ^3J(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, ^1J(C,F) = 274.8 Hz), 112.5 (2C), 109.8 (t, ^3J(C,F) = 2.7 Hz), 40.1 ppm (2C); **IR** (ATR): 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$_9$H$_{11}$NF$_2$S: 203.0580; found: 203.0571.

7.11.5.6. *Synthesis of 2-[(difluoromethyl)thio]pyridine (7)*
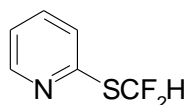
[CAS: 250690-59-6]

Compound **7** was prepared following the standard procedure 1, starting from 2-thiocyanatopyridine (136 mg, 1.00 mmol). After purification, **7** was isolated as slightly yellow oil (147 mg, 0.91 mmol, 91%).

¹H NMR (400 MHz, CDCl₃): 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); **¹⁹F NMR** (375 MHz, CDCl₃): δ = –96.2 ppm (d, J = 57.2 Hz); **¹³C NMR** (101 MHz, CDCl₃): 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** (ATR): 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 C₆H₅NF₂S: 161.0111; found: 161.0114.
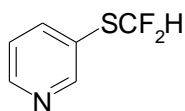
7.11.5.7. *Synthesis of 3-[(difluoromethyl)thio]pyridine (8)*

[CAS: 1809138-52-0]

Compound **8** was prepared following the standard procedure 1, starting from 3-thiocyanatopyridine (136 mg, 1.00 mmol). After purification, **8** was isolated as slightly yellow oil (140 mg, 0.87 mmol, 87%).

¹H NMR (400 MHz, CDCl₃): 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); **¹⁹F NMR** (375 MHz, CDCl₃): δ = –91.4 ppm (d, J = 55.9 Hz); **¹³C NMR** (101 MHz, CDCl₃): δ = 155.0, 150.6, 142.9, 132.9, 122.9, 119.6 ppm (t, ¹J(C,F) = 276.6 Hz); **IR** (ATR): 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 C₆H₅NF₂S: 161.0111; found: 161.0104.

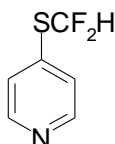### 7.11.5.8. *Synthesis of 4-[(difluoromethyl)thio]pyridine (9)*

[CAS: 1809138-53-1]

Compound **9** was prepared following the standard procedure 1, starting from 4-thiocyanatopyridine (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, ^3J(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, ^3J(C,F) = 3.0 Hz), 126.3 (2C), 119.7 ppm (t, ^1J(C,F) = 276.1 Hz); **IR** (ATR): 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$_6$H$_5$NF$_2$S: 161.0111; found: 161.0111.

7.11.5.9. *Synthesis of 2-[(difluoromethyl)thio]-4-methyl-6-phenylpyrimidine (10)*
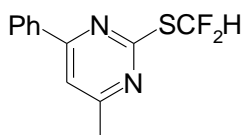
[CAS: 1809138-54-2]

Compound **10** was prepared following the standard procedure 1, starting from 4-methyl-6-phenyl-2-pyrimidinyl thiocyanate (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, ^3J(C,F) = 5.8 Hz), 164.3, 135.7, 131.4, 129.0 (2C), 127.2 (2C), 121.0 (t, ^1J(C,F) = 269.8 Hz), 113.3, 24.2 ppm; **IR** (ATR): 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$_2$F$_2$S: 252.0533; found: 252.0532.

7.11.6. *Synthesis of Difluoromethyl Thioethers starting from the corresponding Bromides or Mesylates*

$$\text{R-Br / OMs} \xrightarrow[\text{DMF}]{\substack{\text{1. NaSCN} \\ \text{2. CuSCN, CsF, TMSCF}_2\text{H}}} \text{R-SCF}_2\text{H}$$
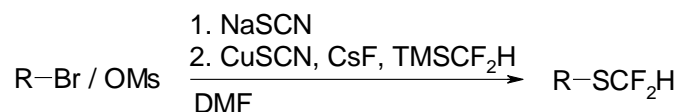
Standard procedure 2: An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with sodium thiocyanate (100 mg, 1.20 mmol), DMF (2 mL) and the bromide or mesylate starting material (mesylates were obtained from the corresponding alcohol via classical mesylation reaction,[243] after 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).

7.11.6.1. *Synthesis of 1-[(difluoromethyl)thio]-hexane (11)*
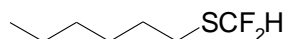
[CAS: 1809138-55-3]

Compound **11** was prepared following the standard procedure 2, starting from 1-bromohexane (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); **MS** (Ion trap, EI, 70 eV): m/z (%) = 116 (85), 87 (63), 85 (43), 56 (49), 55 (49), 43 (97), 41 (100).

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

[CAS: 1191279-61-4]

Compound **12** was prepared following the standard procedure 2, starting from 1-bromododecane (249 mg, 1.00 mmol). After purification, **12** was isolated as slightly yellow oil (246 mg, 0.98 mmol, 98%).
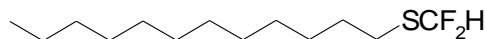
^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.81 (t, J = 56.5 Hz, 1H), 2.80 (d, ^3J(H,H) = 7.5 Hz, 2H), 1.67 (q, ^3J(H,H) = 7.5 Hz, 2H), 1.40 (q, ^3J(H,H) = 7.4 Hz, 2H), 1.27 (m, 16H), 0.89 ppm (t, ^3J(H,H) = 6.8 Hz, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −92.7 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 120.8 (t, ^1J(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, ^3J(C,F) = 2.9 Hz), 22.7, 14.1 ppm; **IR** (ATR): 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$_2$S: 251.1645; found: 251.1626.

7.11.6.3. *Synthesis of [(difluoromethyl)thio]-cyclohexane (13)*

[CAS: 1809138-56-4]

Compound **13** was prepared following the standard procedure 2, starting from bromocyclohexane (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); **MS** (Ion trap, EI, 70 eV): m/z (%) = 83 (55), 82 (18), 67 (13), 58 (11), 55 (100), 41 (12).

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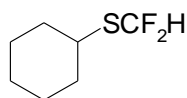### 7.11.6.4. Synthesis of [(difluoromethyl)thio]-methylbenzene (2)

[CAS: 68965-44-6]

Compound **2** was prepared following the standard procedure 2, starting from (bromomethyl)benzene (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** (ATR): 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$_8$H$_8$F$_2$S: 174.0315; found: 174.0314.

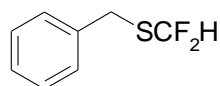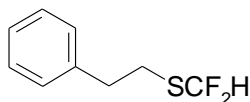### 7.11.6.5. Synthesis of [(difluoromethyl)thio]-ethylbenzene (14)

[CAS: 1809138-57-5]

Compound **14** was prepared following the standard procedure 2, starting from (2-bromoethyl)benzene (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** (ATR): 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$_9$H$_{10}$F$_2$S: 188.0471; found: 188.0461.

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7.11.6.6. 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 (136 mg, 1.00 mmol). After purification, **15** was isolated as colorless oil (176 mg, 0.87 mmol, 87%).
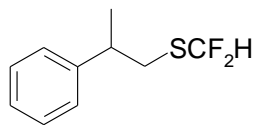
¹H NMR (400 MHz, CDCl₃): δ = 7.36 (m, 2H), 7.26 (m, 3H), 6.70 (t, *J* = 56.5 Hz, 1H), 3.05 (m, 3H), 1.41 ppm (d, ³*J* = 6.7 Hz, 3H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −92.8 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 114.5, 128.6 (2C), 127.0 (2C), 126.9, 120.5 (t, ¹*J*(C,F) = 272.4 Hz), 40.4, 35.0 (t, ³*J*(C,F) = 2.7 Hz), 20.8 ppm; **IR** (ATR): 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 C₁₀H₁₂F₂S: 202.0628; found: 202.0619.

7.11.6.7. Synthesis of 6-[(difluoromethyl)thio]-hexanoic acid-ethyl ester (16)
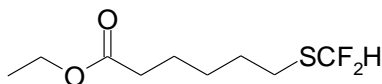
[CAS: 1809138-59-7]

Compound **16** was prepared following the standard procedure 2, starting from 6-bromo-hexanoic acid-ethyl ester (223 mg, 1.00 mmol). After purification, **16** was isolated as orange oil (222 mg, 0.98 mmol, 98%).

¹H NMR (400 MHz, CDCl₃): δ = 6.80 (t, *J* = 56.3 Hz, 1H), 4.13 (q, ³*J* = 7.2 Hz, 2H), 2.80 (t, ³*J* = 7.4 Hz, 2H), 2.31 (t, ³*J* = 7.4 Hz, 2H), 1.67 (m, 4H), 1.44 (m, 2H), 1.26 ppm (t, ³*J* = 7.2 Hz, 3H); **¹⁹F NMR** (375 MHz, CDCl₃): δ = −92.7 ppm (d, *J* = 55.9 Hz); **¹³C NMR** (101 MHz, CDCl₃): 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** (ATR): 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.

7.11.6.8. *Synthesis of [(difluoromethyl)thio]-undecanoic acid (17)*
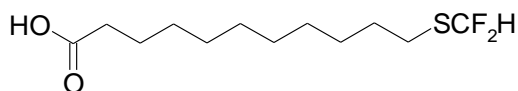
[CAS: 1809138-60-0]

Compound **17** was prepared following the standard procedure 2, but with the double amounts of copper thiocyanate, cesium fluoride and TMSCF$_2$H, starting from 11-Bromoundecanoic acid (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, ^3J = 7.4 Hz, 2H), 2.36 (d, ^3J = 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, ^1J(C,F) = 271.9 Hz), 34.0, 30.1, 29.3, 29.3, 29.2, 29.0, 29.0, 28.6, 27.2 (t, ^3J(C,F) = 2.9 Hz), 24.6 ppm; **IR** (ATR): 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$_2$H]: $C_{11}H_{19}O_2S$: 215.1106; found: 215.1086.

7.11.6.9. *Synthesis of 2-[2-[(difluoromethyl)thio]ethyl]-1H-isoindole-1,3(2H)-dione (18)*
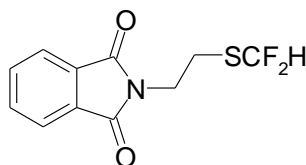
[CAS: 1809138-61-1]

Compound **18** was prepared following the standard procedure 2, starting from 2-(2-bromoethyl)-1*H*-isoindole-1,3(2*H*)-dione (254 mg, 1.00 mmol). After purification, **18** was isolated as colorless solid (213 mg, 0.83 mmol, 83%).

m.p.: 59-60°C; **^{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, $^3J = 7.0$ Hz, 2H), 3.13 ppm (d, $^3J = 7.0$ 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, ^1J(C,F) = 273.8 Hz), 37.8, 25.4 ppm (t, ^3J(C,F) = 3.2 Hz); **IR** (ATR): 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); **HRMS** (EI-TOF) calcd for C$_{11}$H$_9$NO$_2$F$_2$S: 257.0322; found: 257.0320.

7.11.6.10. *Synthesis of [(difluoromethyl)thio]-methyl-1,3-dioxolane (19)*
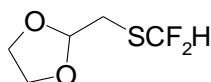
[CAS: 1809138-62-2]

Compound **19** was prepared following the standard procedure 2, starting from 2-Bromomethyl-1,3-dioxolane (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, $^3J = 4.1$ Hz, 1H), 4.05 (m, 2H), 3.94 (m, 2H), 2.99 (d, $^3J = 4.0$ 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, ^1J(C,F) = 272.5 Hz), 102.9, 65.5 (2C), 31.2 ppm (t, ^3J(C,F) = 2.9 Hz); **IR** (ATR): 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$_5$H$_8$F$_2$O$_2$S: 169.0135; found: 169.0126.

7.11.6.11. Synthesis of [(difluoromethyl)thio]-2-(6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl)ethylene (20)
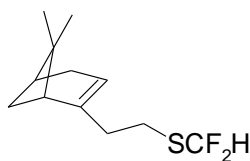
[CAS: 1809138-63-3]

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 (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, ^3J = 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** (ATR): 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$_2$S: 232.1097; found: 232.1099; $[\alpha]_D^{20}$ -29 (c 1.14, CHCl$_3$).

7.11.7. Synthesis of Difluoromethyl Thioethers from the corresponding Arenediazonium Salts
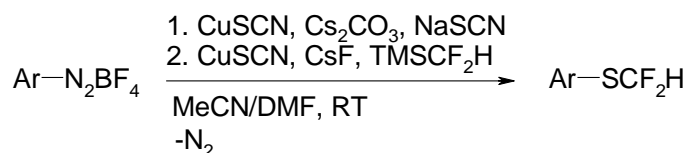
Standard procedure 3: An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with copper thiocyanate (122 mg, 1.00 mmol) sodium thiocyanate (124 mg, 1.50 mmol) and cesium carbonate (228 mg, 0.70 mmol) in MeCN (2 mL). Afterwards a solution of the arenediazonium tetrafluoroborate (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.

7.11.7.1. Synthesis of 1-[(difluoromethyl)thio]-4-methoxybenzene (22)
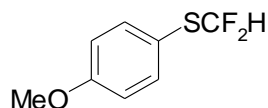
[CAS: 81931-98-8]

Compound **22** was prepared following the standard procedure 3, starting from 4-methoxybenzenediazonium tetrafluoroborate (**21**) (222 mg, 1.00 mmol). After purification, **22** was isolated as colorless oil (181 mg, 0.95 mmol, 95%).

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

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**) (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%).

^{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** (ATR): 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$_8$H$_8$OF$_2$S: 190.0264; found: 190.0270.

7.11.7.2. *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 (222 mg, 1.00 mmol). After purification, **23** was isolated as colorless oil (133 mg, 0.70 mmol, 70%).
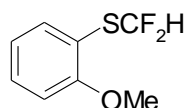
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.54 (m, 1H), 7.41 (m, 1H), 6.98 (m, 2H), 6.95 (t, J = 58.0 Hz, 1H), 3.92 ppm (s, 3H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −92.6 ppm (d, J = 57.2 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 159.4, 136.6, 131.5, 121.3, 120.6 (t, ^1J(C,F) = 274.3 Hz), 114.8 (t, ^3J(C,F) = 3.6 Hz), 111.4, 56.0 ppm; **IR** (ATR): 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$_8$H$_8$OF$_2$S: 190.0264; found: 190.0263.

7.11.7.3.   Synthesis of 1-[(difluoromethyl)thio]-3-methoxybenzene (24)
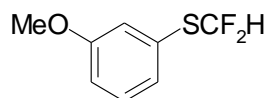
[CAS: 1333375-76-0]

Compound **24** was prepared following the standard procedure 3, starting from 3-methoxybenzenediazonium tetrafluoroborate (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** (ATR): 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$_8$H$_8$OF$_2$S: 190.0264; found: 190.0269.

7.11.7.4.   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 (237 mg, 1.00 mmol). After purification, **25** was isolated as colorless oil (133 mg, 0.65 mmol, 65%).
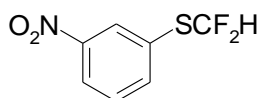
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.46 (t, ^3J(H,H) = 1.9 Hz, 1H), 8.30 (m, 1H), 7.93 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.62 (t, ^3J(H,H) = 8.0 Hz, 1H), 6.92 ppm (t, J = 56.0 Hz, 1H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −91.5 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 148.4, 141.0, 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** (ATR): 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

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(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.

7.11.7.5. *Synthesis of 4-[(difluoromethyl)thio]-1,1'-biphenyl (26)*
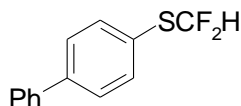
[CAS: 207974-77-4]

Compound **26** was prepared following the standard procedure 3, starting from [1,1'-biphenyl]-4-diazonium tetrafluoroborate (267 mg, 1.00 mmol). After purification, **26** was isolated as white solid (201 mg, 0.85 mmol, 85%).

m.p.: 56-57°C; **^{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** (ATR): 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); **HRMS** (EI-TOF) calcd for $C_{13}H_{10}F_2S$: 236.0471; found: 236.0474.

### 7.11.7.6. *Synthesis of 1-bromo-4-[(difluoromethyl)thio] benzene (27)*
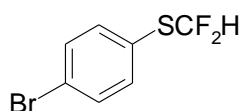
[CAS: 4837-14-3]

Compound **27** was prepared following the standard procedure 3, starting from 4-bromobenzenediazonium tetrafluoroborate (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** (ATR): 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$_7$H$_5$F$_2$SBr: 237.9263; found: 237.9259.

### 7.11.7.7. *Synthesis of 1-bromo-4-[(difluoromethyl)thio]naphthalene (28)*
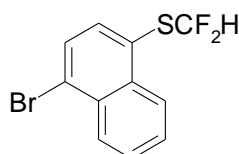
[CAS: 1809138-64-4]

Compound **28** was prepared following the standard procedure 3, starting from 4-bromonaphthalen-1-yldiazonium tetrafluoroborate (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, ^3J(H,H) = 7.9 Hz, 1H), 7.74 (d, ^3J(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, ^3J(C,F) = 2.7 Hz), 120.7 ppm (t, ^1J(C,F) = 276.1 Hz); **IR** (ATR): 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$_7$F$_2$SBr: 287.9420; found: 287.9434.

### 7.11.7.8. *Synthesis of 4-[(difluoromethyl)thio]benzonitrile (29)*
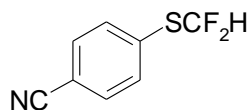
[CAS: 4837-25-6]

Compound **29** was prepared following the standard procedure 3, starting from 4-cyanobenzenediazonium tetrafluoroborate (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, ^3J(C,F) = 2.7 Hz), 132.6 (2C), 119.7 (t, ^1J(C,F) = 276.6 Hz), 117.9, 113.2 ppm; **IR** (ATR): 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$_8$H$_5$NF$_2$S: 185.0111; found: 185.0102.

7.11.7.9.   *Synthesis of methyl 4-[(difluoromethyl)thio]benzoate (30)*
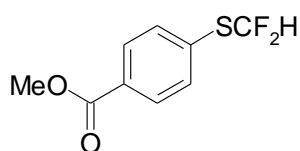
[CAS: 1458640-72-6]

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, ^3J(H,H) = 8.4 Hz, 2H), 7.62 (d, ^3J(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, ^3J(C,F) = 2.7 Hz), 131.0, 130.3 (2C), 120.3 (t, ^1J(C,F) = 275.7 Hz), 52.4 ppm; **IR** (ATR): 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$_9$H$_8$O$_2$F$_2$S: 218.0213; found: 218.0202.

### 7.11.7.10. Synthesis of methyl 4-[(difluoromethyl)thio]acetanilide (31)
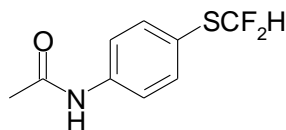
[CAS: 24933-63-9]

Compound **31** was prepared following the standard procedure 3, starting from 4-acetamidobenzenediazonium tetrafluoroborate (249 mg, 1.00 mmol). After purification, **31** was isolated as colorless solid (187 mg, 0.86 mmol, 86%).

m.p.: 133-134°C; **^{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, ^1J(C,F) = 275.2 Hz), 120.2 (2C), 24.7 ppm; **IR** (ATR): 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); **HRMS** (EI-TOF) calcd for C$_9$H$_9$NOF$_2$S: 217.0373; found: 217.0384.

7.11.7.11. 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 (235 mg, 1.00 mmol). After purification, **6** was isolated as yellow oil (142 mg, 0.70 mmol, 70%).
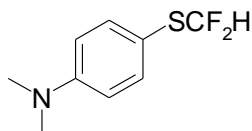
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.43 (d, ^3J(H,H) = 9.0 Hz, 2H), 6.71 (t, J = 57.6 Hz, 1H), 6.68 (d, ^3J(H,H) = 9.0 Hz, 2H), 3.00 ppm (s, 6H); **^{19}F NMR** (375 MHz, CDCl$_3$): δ = −92.6 ppm (d, J = 55.9 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 151.4, 137.3 (2C), 121.4 (t, ^1J(C,F) = 274.8 Hz), 112.5 (2C), 109.8 (t, ^3J(C,F) = 2.7 Hz), 40.1 ppm (2C); **IR** (ATR): 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.

7.11.7.12. 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 (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, ^3J(C,F) = 2.9 Hz), 130.7 (2C), 130.0 (2C), 128.4 (2C), 120.3 ppm (t, ^1J(C,F) = 275.8 Hz); **IR** (ATR): 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.

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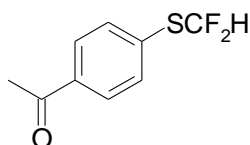
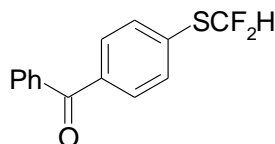

[CAS: 145326-60-9]

Compound **33** was prepared following the standard procedure 3, starting from 4-acetylbenzenediazonium tetrafluoroborate (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, ^3J(H,H) = 8.4 Hz, 2H), 7.66 (d, ^3J(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, ^3J(C,F) = 2.7 Hz), 129.0 (2C), 120.2 (t, ^1J(C,F) = 275.6 Hz), 26.7 ppm; **IR** (ATR): 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$_9$H$_8$OF$_2$S: 202.0264; found: 202.0258.

### 7.11.7.14. *Synthesis of 2-(3-[(difluoromethyl)thio]phenyl)-1,1-difluoropropan-2-ol (34)*
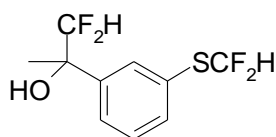
[CAS: 1809138-65-5]

Compound **34** was prepared following the standard procedure 3, starting from 3-acetylbenzenediazonium tetrafluoroborate (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, ^1J = 277.9 Hz, ^2J = 54.5 Hz); **^{13}C NMR** (101 MHz, CDCl$_3$): δ = 141.7, 134.9, 132.7, 129.3, 127.4, 126.4 (t, ^3J(C,F) = 6.2 Hz), 120.8 (t, ^1J(C,F) = 275.2 Hz), 116.6 (t, ^1J(C,F) = 247.2 Hz), 74.0 (t, ^2J(C,F) = 21.5 Hz), 22.4 ppm (t, ^3J(C,F) = 2.2 Hz); **IR** (ATR): 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$_4$S: 254.0388; found: 254.0387.

7.11.7.15. Synthesis of 9-ethyl-3-[(difluoromethyl)thio]-9H-carbazole (35)
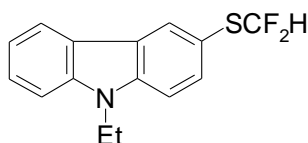
[CAS: 1779524-74-1]

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, ^3J(H,H) = 1.6 Hz, 1H), 8.13 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.68 (m, 1H), 7.53 (m, 1H), 7.43 (d, ^3J(H,H) = 8.3 Hz, 2H), 7.30 (m, 1H), 6.86 (t, J = 57.4 Hz, 1H), 4.38 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.46 ppm (t, ^3J(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, ^1J(C,F) = 274.6 Hz), 120.6, 119.6, 113.9 (t, ^3J(C,F) = 3.1 Hz), 109.2, 108.8, 37.7, 13.8 ppm; **IR** (ATR): 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), 227 (32), 226 (100), 212 (26), 211 (17), 198 (10); **HRMS** (EI-TOF) calcd for C$_{15}$H$_{13}$NF$_2$S: 277.0737; found: 277.0747.

7.11.7.16. Synthesis of 3-[(difluoromethyl)thio]quinoline (36)
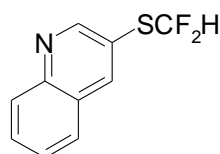
[CAS: 1779524-71-8]

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, ^3J(H,H) = 2.0 Hz, 1H), 8.16 (d, ^3J(H,H) = 8.5 Hz, 1H), 7.86 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.82 (m, 1H), 7.64 (m, 1H), 6.91 ppm

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(t, $J = 56.3$ Hz, 1H); ¹⁹**F NMR** (375 MHz, CDCl₃): δ = −91.3 ppm (d, $J = 57.2$ Hz); ¹³**C NMR** (101 MHz, CDCl₃): δ = 154.5, 148.0, 143.7, 131.1, 129.5, 127.9, 127.6, 119.8 (t, $^1J(C,F) = 276.9$ Hz), 119.4 ppm; **IR** (ATR): 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 C₁₀H₇NF₂S: 211.0267; found: 211.0269.

7.11.7.17. *Synthesis of 6-[(difluoromethyl)thio]quinoline (37)*
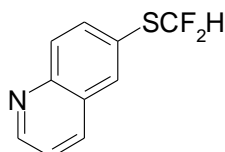
[CAS: 1779524-70-7]

Compound **37** was prepared following the standard procedure 3, starting from quinoline-6-diazonium tetrafluoroborate (243 mg, 1.00 mmol). After purification, **37** was isolated as colorless oil (129 mg, 0.61 mmol, 61%).

¹**H NMR** (400 MHz, CDCl₃): 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, CDCl₃): δ = −91.3 ppm (d, $J = 57.2$ Hz); ¹³**C NMR** (101 MHz, CDCl₃): 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** (ATR): 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 C₁₀H₇NF₂S: 211.0267; found: 211.0260.

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