NI-CATALYZED ORTHO-DIRECTED TRIFLUOROMETHYLTHIOLATION OF ARYL CHLORIDES AND BROMIDES

by

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(Vancouver)

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Abstract

This thesis describes a novel method to generate trifluoromethanesulfenyl arene or heteroarene products via Ni-catalyzed ortho-selective C-X (X = Cl or Br) activation. Successful C-X activation requires directing groups, but it is highly selective and allows aryl chlorides to be used and shows an appreciable substrate scope. The protocol tolerates various nitrogen-containing directing groups including imines, pyridines, pyrimidines, amides and oxazolines. The method is also compatible with aryl halides bearing substituents with a wide range of electronic properties, including electron-donating or withdrawing abilities, as well as potentially sensitive functional groups. It also produces trifluoromethylthiolated arenes in good-to-excellent yields at ambient temperatures.
Preface

I have designed, in consultation with my supervisor Dr. Jennifer A. Love, this research project. I have performed nearly all of the experimental work, data collection and analysis, and manuscript preparation.

Any work referred to in the text of this thesis that I did not directly perform has been clearly referenced.

Carol Wu confirmed the reproducibility of this work. She is currently working on a different aspect (i.e. trifluoromethoxylation) of the project.

A version of this thesis is in preparation for publication submission.

Mr. Marshall Lapawa, Mr. Derek Smith, Mr. Marco Yeung of the Department of Chemistry at UBC performed all high-resolution mass spectrometry.
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<table>
<thead>
<tr>
<th>Symbol</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>Angstrom</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift in ppm</td>
</tr>
<tr>
<td>©</td>
<td>Copyright</td>
</tr>
<tr>
<td>°C</td>
<td>Degrees Celcius</td>
</tr>
<tr>
<td>σ</td>
<td>Electron-withdrawing ability</td>
</tr>
<tr>
<td>Π</td>
<td>Lipophilicity</td>
</tr>
<tr>
<td>%</td>
<td>Percentage</td>
</tr>
<tr>
<td>APCI</td>
<td>Atmospheric pressure chemical ionization in mass spectrometry</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>bpy</td>
<td>2,2’-Pyridine</td>
</tr>
<tr>
<td>Brettphos</td>
<td>2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl</td>
</tr>
<tr>
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<tr>
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<tr>
<td>Cy</td>
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</tr>
<tr>
<td>d</td>
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</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>dcpm</td>
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</tr>
<tr>
<td>dd</td>
<td>Doublet of doublet, in NMR spectroscopy</td>
</tr>
<tr>
<td>DG</td>
<td>Directing group</td>
</tr>
<tr>
<td>DMA</td>
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</tr>
<tr>
<td>dmbpy</td>
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</tr>
<tr>
<td>DMF</td>
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</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-Bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dt</td>
<td>Doublet of triplet, in NMR spectroscopy</td>
</tr>
</tbody>
</table>
eq  Equation
equiv.  Equivalence
Et$_3$N  Triethylamine
EtOAc  Ethyl acetate
EtOH  Ethanol
EPR  Electron paramagnetic resonance
hr  Hour
HRMS  High resolution mass spectrometry
Hz  Hertz
i  iso
J  Coupling constant
m  Multiplet, in NMR spectroscopy or meta
M  Metal atom or concentration in molarity
Me  Methyl
MeCN  Acetonitrile
MHz  Megahertz
min  Minute
mmol  Milimole
mol  Mole
m/z  Mass-to-charge ratio, in mass spectrometry
NMR  Nuclear magnetic resonance
'OTf  Trifluoromethanesulfonate
PCy$_3$  Tricyclohexylphosphine
PEt$_3$  Triethylphosphine
Ph  Phenyl
PPh$_3$  Triphenylphosphine
ppm  Part per million, in NMR spectroscopy
q  Quartet, in NMR spectroscopy
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Organic group</td>
</tr>
<tr>
<td>SET</td>
<td>Single-electron-transfer</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>SMe₂</td>
<td>Dimethylsulfide</td>
</tr>
<tr>
<td>Sphos</td>
<td>2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl</td>
</tr>
<tr>
<td>t</td>
<td>Triplet, in MNR spectroscopy</td>
</tr>
<tr>
<td>TASF</td>
<td>Tris(dimethylamino)sulfonium difluorotrimethylsilicate</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>t-BuOH</td>
<td>Tert-butylalcohol</td>
</tr>
<tr>
<td>TEMPO</td>
<td>(2,2,6,6-Tetramethylpiperidin-1-yl)oxy</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TREAT-HF</td>
<td>Triethylamine trihydrofluoride</td>
</tr>
<tr>
<td>X</td>
<td>Halides such as F, Cl, Br, I</td>
</tr>
</tbody>
</table>
Acknowledgements

I would like to thank Dr. Jennifer A. Love for giving me the opportunity to join her research team and to work under her supervisor. I also own her tremendous gratitude for all of her support, guidance and patience over the years.

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I would like to express my appreciation to the undergraduates that I have had the privilege of working with: Gawon Go, Brenda Leong and Carol Wu. I thank you for the hard work and hope you the best in your future.

I would like to thank the various shop and services in the Department of Chemistry at UBC. Without their outstanding services and products, this work would not be possible. I am glad to be in UBC especially the Department of Chemistry.

Lastly, I would like to thank my family including my Mom, Dad, sister, brother and niece for their love and mental supports.
Chapter 1: Introduction

1.1 Overview of bioactive fluorinated compounds and fluorination

Over the past two decades, fluorine-containing molecules have become increasingly prevalent in agrochemical and pharmaceutical sciences. In fact, roughly 35% of current agrochemical compounds contains at least one fluorine atom. Similarly, the number of fluorine-containing drugs on the market has grown to about 25%. Fluorinated compounds exhibit a wide spectrum of biological activities. Representative agrochemicals having C-F bonds include Indoxacarb (insecticide), Thifluzamide (fungicide), and Fluazuron (insecticide) (Figure 1.1). Examples of outstanding fluorinated blockbuster drugs are Lipitor and Crestor (blood cholesterol modulator), Prozac (antidepressant), Prevacid (anti-inflammatory drug) and Ciprobay (antibacterial drug) (Figure 1.2).

![Indoxacarb Insecticide](image1)

![Thifluzamide Fungicide](image2)

![Fluazuron Insecticide](image3)

Figure 1.1 Examples of agrochemicals containing fluorine.
Figure 1.2 Examples of pharmaceuticals containing fluorine.

Incorporation of fluorine into agrochemical and pharmaceutical molecules has become a routine procedure for tuning molecular properties. Addition of fluorine into an organic molecule often results in a significant perturbation of the inherent physiochemical properties of the parent compound, which consequently can give rise to improvements of biological activities.

Fluorine is frequently substituted for hydrogen. Although this replacement alters the steric properties of the compound (van der Waals radius of fluorine is 1.47 Å and hydrogen is 1.20 Å), considerable electrostatic interactions of fluorine with other functional groups in the active site of an enzyme perhaps enhance the binding affinity of the molecule. This consequently results in a boost in potency. In medicinal chemistry, fluorination is well-documented for improving the pharmacokinetic profile of drug candidates. Incorporating fluorine into organic compounds has been a longstanding
procedure to increase metabolic stability of a drug. In particular, replacing aromatic hydrogen with fluorine is an effective strategy to reduce the oxidative degradation of Cytochrome P450. Another well-established influence of fluorination is modulation of trans-membrane bioavailability. Membrane permeability is often elevated when fluorine is introduced into a lead compound. This observation can be explained by the increase of the lipophilicity of a molecule upon fluorination. All of those impressive benefits make fluorination a prolonged interest among scientific communities.

Fluorine is the 13th most common element on the Earth’s crust and it is significantly abundant among the halogens.\(^4\)\(^{,1a}\) Despite those facts, fewer than 50 compounds containing fluorine have been identified in nature.\(^4\) Only a limited number of microorganisms and plants can perform fluorocarbon syntheses.\(^1a\)\(^,4\) Thus, most of the fluoroorganic compounds are obtained from chemical syntheses. Currently, not only a single fluorine atom but also a fluorine-containing group such as CF\(_3\), OCF\(_3\), S(O\(_n\))CF\(_3\) (n = 0,1,2) can be installed into organic substrates.
1.2 Overview of compounds containing trifluoromethanesulfenyl and its analogous moieties

Among fluorinated substituents, the trifluoromethanesulfenyl moiety and its analogous sulfoxides or sulfones, S(O)<sub>n</sub>CF<sub>3</sub> (n = 0,1,2), have received notable attention. In particular, synthetic methods for constructing the SCF<sub>3</sub> motif have rapidly increased (Graph 1.1). In 2014 alone, 35 protocols were developed, accounting for approximately 30% of the reported methods over the past two decades.

**Graph 1.1 Survey of methodologies for incorporation of SCF<sub>3</sub> moiety into organic molecular over the past decades.**

---

*a* Shibata’s review of synthetic methods for trifluoromethylthiolation provides the data up to 2013. Additional information is based on a SciFinder search of the topic. The survey was conducted up to the end of 2014.
Table 1.1 Aromatic substituent constants of selected fluorine-containing moieties.\textsuperscript{5a}

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>CF\textsubscript{3}</th>
<th>OCF\textsubscript{3}</th>
<th>SCF\textsubscript{3}</th>
<th>SOCF\textsubscript{3}</th>
<th>SO\textsubscript{2}CF\textsubscript{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Pi^*)</td>
<td>0.14</td>
<td>0.88</td>
<td>1.04</td>
<td>1.44</td>
<td>-</td>
<td>0.55</td>
</tr>
<tr>
<td>(\sigma_{m^*})</td>
<td>0.34</td>
<td>0.43</td>
<td>0.38</td>
<td>0.40</td>
<td>0.63</td>
<td>0.83</td>
</tr>
<tr>
<td>(\sigma_{p^*})</td>
<td>0.06</td>
<td>0.54</td>
<td>0.35</td>
<td>0.50</td>
<td>0.69</td>
<td>0.96</td>
</tr>
</tbody>
</table>

* lipophilicity was calculated from the partition coefficient of a compound between n-octanol and water
** electron-withdrawing influence, \(m\) is meta-directing, \(p\) is para-directing

Efforts have emerged towards the introduction of the SCF\textsubscript{3} group and its analogs into organic compounds because of their unique physiochemical properties (Table 1.1). As indicated in Table 1.1, SCF\textsubscript{3} possesses the highest lipophilicity \((\Pi = 1.44)\textsuperscript{5a}\) and trifluoromethanesulfonyl (SO\textsubscript{2}CF\textsubscript{3}) has the strongest electron-withdrawing ability \((\sigma_m = 0.83, \sigma_p = 0.96)\textsuperscript{7}\). Compared to a simple fluorination, a more significant perturbation in the electronic and steric properties of the parent compounds is observed when these moieties are incorporated into a molecule. Moreover, since these functionalities can be easily interconverted through redox chemistry,\textsuperscript{5a} tuning of the molecular properties becomes facile. Because of these benefits, the number of biologically active compounds possessing these structural motifs has progressively risen (Figure 1.3).\textsuperscript{8}
Figure 1.3 Examples of biologically active compounds containing aromatic SO\textsubscript{n}CF\textsubscript{3} (n = 0, 1, 2).

1.3 Strategies to synthesize trifluoromethanesulfenyl arenes

Protocols to introduce the SCF\textsubscript{3} moiety and its analogs into organic molecules are numerous and this work has been extensively reviewed.\textsuperscript{5} In the context of this thesis, only relevant synthetic strategies to generate aryl SCF\textsubscript{3} (ArSCF\textsubscript{3}) products will be described.

Incorporation of the SCF\textsubscript{3} group (trifluoromethylthiolation) into arenes is mainly divided into indirect or direct strategies. Indirect installation involves halogen-fluorine exchange or grafting a CF\textsubscript{3} group onto sulfur-containing substrates (i.e., sulfur trifluoromethylation). Three different processes for direct installation are possible, which are categorized as oxidative, electrophilic or nucleophilic trifluoromethylthiolation. Detailed descriptions of each strategy, including its scope and limitations, will be discussed in the following sections.
1.3.1 Indirect incorporation of trifluoromethanesulfenyl moiety

The conventional technique to synthesize ArSCF₃ is fluorination of chloro or bromo methyl sulfides using nucleophilic fluoride sources such as HF or SbF₃ (Scheme 1.1). Although HF is highly available and has a low cost, its high reactivity and corrosiveness limit its usage in a laboratory setting. SbF₃ is easier to handle but its usage in fluorination still requires high temperatures. Recent improvements to the technology involve the replacement of HF by a milder and less corrosive reagent, triethylamine trihydrofluoride (TREAT-HF, Franz’s reagent). However, fluorination by TREAT-HF is promoted by microwave radiation and at elevated temperature. Overall, harsh reaction conditions and toxicity of the fluorinating reagents are the major drawbacks of this technique.

Scheme 1.1 Synthesis of aryl-SCF₃ via halogen-fluorine exchange.

Alternatively, ArSCF₃ can be accessed by the installation of a CF₃ group (trifluoromethylation) into sulfur-containing aromatic compounds. A variety of shelf-stable trifluoromethylating reagents, including the Ruppert-Prakash, Yagupolskii, Umemoto or Togni reagents are able to perform such transformation (Scheme 1.2).
Scheme 1.2 Nucleophilic and electrophilic trifluoromethylation of sulfur-containing arenes.

The Ruppert-Prakash reagent (TMSCF$_3$) combined with fluoride sources such as tris(dimethylamino)sulfonyl difluorotrimethylsilicate (TASF) or tetra-$n$-butylammonium fluoride (TBAF) was reported as an efficient system for nucleophilic trifluoromethylation of aryl sulfonyl chloride or cyanide (Scheme 1.2 eq. 1).\textsuperscript{11} Despite moderate yields, only a few substrates were described. In addition, the reaction required very low temperatures to suppress the formation of aryl disulfide byproduct.

On the other hand, two different classes of electrophilic trifluoromethylation reagents may also be utilized to obtain ArSCF$_3$: biaryl trifluoromethylsulfonyl salts,
developed by Yagupolskii et al.\textsuperscript{12} and Umemoto et al.\textsuperscript{13} (Scheme 1.2 eq. 2), or hypervalent iodine compounds, synthesized by Togni et al.\textsuperscript{14} (Scheme 1.2 eq. 3). Although sodium aryl thiolates and aryl thiols were converted to the corresponding products in good yields, the downside of this strategy lies in the synthetic procedure of these electrophilic reagents. For instance, the process to synthesize the Umemoto’s reagents requires at least three steps involving the use of ozone-depleting substances such as CF\textsubscript{3}Br or CF\textsubscript{3}I.\textsuperscript{13}

1.3.2 Direct incorporation of trifluoromethanesulfenyl moiety

In spite of the great efforts that have been invested into the indirect approach, the requirement of a sulfur atom in the substrate precursors is inevitable. From this point of view, direct installation of the SCF\textsubscript{3} moiety into aryl compounds would be more efficient to synthesize ArSCF\textsubscript{3}. The SCF\textsubscript{3} group can be synthesized separately prior to react with aryl compounds or it can be generated \textit{in-situ} using one-pot synthetic protocols. Based on the process in which the SCF\textsubscript{3} group is formed, trifluoromethylthiolation can be classified as oxidative, electrophilic and nucleophilic cross-coupling.

1.3.2.1 Oxidative trifluoromethylthiolation

In general, oxidative trifluoromethylthiolation is achieved by cross-coupling of aryl-X (X = halides, boronic acids or diazonium salts) with a trifluoromethylating reagent in the presence of a sulfur source, an oxidant and copper salts (stoichiometric or catalytic amount).\textsuperscript{15} The specific conditions are summarized in Table 1.2
Table 1.2 Summary of oxidative trifluoromethylthiolation of arenes.

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<th>Substrates</th>
<th>Trifluoromethylating reagent</th>
<th>Sulfur source</th>
<th>Oxidant</th>
<th>[Cu]</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aryl-X</td>
<td>FSO$_2$CF$_2$CO$_2$Me</td>
<td>$S_8$</td>
<td>N/A</td>
<td>Stoichiometric Cul</td>
<td>5 examples 41 - 77%</td>
</tr>
<tr>
<td>X = Br, I</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Example 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aryl-X or heterorayl-X</td>
<td>TMSCF$_3$</td>
<td>Na$_2$S$_2$O$_3$</td>
<td>air</td>
<td>Catalytic Cul</td>
<td>21 examples 53 - 92%</td>
</tr>
<tr>
<td>X = Br, I, Cl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Example 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aryl-B(OH)$_2$</td>
<td>TMSCF$_3$</td>
<td>$S_8$</td>
<td>Ag$_2$CO$_3$</td>
<td>Catalytic CuSCN</td>
<td>15 examples 58 - 91%</td>
</tr>
<tr>
<td><strong>Example 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aryl-B(OH)$_2$</td>
<td>CF$_3$CO$_2$Na</td>
<td>$S_8$</td>
<td>Ag$_2$CO$_3$</td>
<td>Catalytic Cul</td>
<td>10 examples 29 - 68%</td>
</tr>
<tr>
<td><strong>Example 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aryl-N$_2$BF$_4$ or heteroaryl-N$_2$BF$_4$</td>
<td>TMSCF$_3$</td>
<td>NaSCN</td>
<td>Cs$_2$CO$_3$</td>
<td>Catalytic CuSCN</td>
<td>22 examples 23 - 98%</td>
</tr>
</tbody>
</table>

Comprehensive investigation of the reaction mechanism has not been yet realized. Two viable pathways are suggested involving 1) initial *in-situ* synthesis of SCF$_3$ then trifluoromethylthiolation of aryl-X or 2) insertion of sulfur atom into aryl-X followed by trifluoromethylation. For simplification, this strategy is classified as oxidative trifluoromethylthiolation. Overall, by utilizing these protocols, good-to-excellent yields of trifluoromethylthiolation products containing sensitive functional groups were obtained (Table 1.2 – examples 1-5). The substrate scope was further extended to heteroaromatic compounds (Table 1.2 – examples 2 and 5).
1.3.2.2 Electrophilic trifluoromethylthiolation

The first electrophilic trifluoromethylthiolating source was trifluoromethansulfenyl chloride ($\text{CF}_3\text{SCl}$).\textsuperscript{16} Due to its gaseous nature and toxicity, protocols employing $\text{CF}_3\text{SCl}$ were not much considered. Consequently, the design of more user-friendly (i.e. safer, less toxic and easier to handle) electrophilic $\text{SCF}_3$ reagents has been extensively researched. The number of new reagents has steadily increased (Scheme 1.3) and their versatility in organic transformation has greatly expanded to accommodate the presence of various functional groups (Table 1.3).

Scheme 1.3 List of electrophilic trifluoromethylthiolation.

### Table 1.3 Scope of electrophilic trifluoromethylthiolation of arenes.

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Example 1</th>
<th>Example 2</th>
<th>Example 3</th>
<th>Example 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{R-MgX}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$X = \text{Cl, Br}$</td>
<td>$2b$</td>
<td>$3$ or $6a$, [Cu]</td>
<td>$2a$, $3$, $4$, $6b$</td>
<td>$5$, [Pd]</td>
</tr>
<tr>
<td>Reagents</td>
<td></td>
<td></td>
<td>Bronsted or Lewis acid</td>
<td></td>
</tr>
<tr>
<td>$\text{DG}$</td>
<td>$4$ examples $70 - 86%$</td>
<td>$19$ examples $40 - 95%$</td>
<td>$17$ examples $32 - 99%$</td>
<td>$17$ examples $47 - 91%$</td>
</tr>
<tr>
<td>DG = pyridine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
For instance, trifluoromethanesulfenyl amine 2b can react with aryl Grignard at ambient temperatures (Table 1.3 example 1).\textsuperscript{17} The Togni reagent -like SCF\textsubscript{3} 3\textsuperscript{18} or trifluoromethanesulfenyl N-phthalimide 6a\textsuperscript{19} can effectively trifluoromethylthiolate aryl boronic acids at mild conditions (Table 1.3 example 2). Yet, catalytic amount of copper salts is necessary for the transformation. Moreover, amine 2a,\textsuperscript{20} 3,\textsuperscript{21} Shibata’s hypervalent iodonium ylide 4\textsuperscript{22} or trifluoromethanesulfenyl saccharin 6b\textsuperscript{23} can functionalize C\textsubscript{3}-H of indoles (Table 1.3 example 3). Nevertheless, the reactions are promoted or catalyzed by a strong Brønsted or Lewis acid. Lastly, C-H activation of pyridine-directed arenes is possible with trifluoromethanesulfenyl N-succinimide 5 by catalytic activity of Pd(CH\textsubscript{3}CN)\textsubscript{4}(OTf)\textsubscript{2} (Table 1.3 example 4).\textsuperscript{24}

Regardless of the diversity observed in the substrate scope of electrophilic trifluoromethylthiolation, the disadvantage of this approach is the synthetic access of these reagents. Amines 2a or 2b are derived from the Ruppert-Prakash reagent, which is a trifluoromethylating reagent. Compounds 3, 5, 6a, and 6b are obtained from nucleophilic trifluoromethylthiolating sources such as AgSCF\textsubscript{3} or CuSCF\textsubscript{3}, whose relevant application in trifluoromethylthiolation is examined in the next section.
1.3.2.3 Nucleophilic trifluoromethylthiolation

Early efforts of nucleophilic trifluoromethylthiolation focused in reagent development. Different trifluoromethylthiolate salts, containing metallic (Cu\(^+\), Hg\(^{2+}\), Ag\(^+\), Cs\(^+\), K\(^+\)) or organic (Me\(_4\)N\(^+\)) counterions, were synthesized\(^{25}\). The initial chemistry of these reagents was limited. Only aryl halides containing multiple electron-withdrawing moieties (i.e. fluoro or nitro groups) were successfully trifluoromethylthiolated. However, in recent years the substrate scope of nucleophilic trifluoromethylthiolation has improved.

One strategy to improve nucleophilic trifluoromethylthiolation is to enhance the reactivity of the reagents. This can be achieved by introducing chelating ligands into the reagents and this work was accomplished by Huang and colleagues (Scheme 1.4).\(^{26}\)

![Scheme 1.4 Stoichiometric use of copper in nucleophilic trifluoromethylthiolation of arenes.](image)

In 2013, they successfully synthesized a series of air stable nitrogen-containing bidentate copper trifluoromethylthiolate complexes that can react with aryl halides. Among these complexes, the bipyridine reagent ((bpy)CuSCF\(_3\)) was the most active and it reacted with aryl iodides and bromides containing both electron-withdrawing or electron-donating functionalities. However, this reagent was inert toward aryl chlorides and the trifluoromethylation reactions were performed at high temperatures.
Another approach to enhance the activity of nucleophilic trifluoromethylthiolating reagents is the addition of transition metal complexes of palladium (Scheme 1.5) or nickel (Scheme 1.6) or salts of copper (Scheme 1.7) into the reaction.

**Scheme 1.5 Palladium-catalyzed nucleophilic trifluoromethylthiolation of aryl bromides.**

Buchwald *et al.* reported the first example of palladium-catalyzed trifluoromethylthiolation of aryl bromides in 2011 (Scheme 1.5).\(^{27}\) In this protocol, silver (I) trifluoromethylthiolate (AgSCF\(_3\)) was shown to be compatible toward numerous aryl and hetero-aryl bromides bearing moieties with both electron-donating and electron-withdrawing influences. A broad substrate scope was established but employment of costly metals and ligands are the main drawbacks of this method.

To circumvent the reaction cost, other researchers have shifted their attention to cheaper metals and ligands. To date, there has been only one reported nucleophilic trifluoromethylthiolating protocol utilizing a nickel source. The system is tetramethylammonium trifluoromethylthiolate (Me\(_4\)NSCF\(_3\)) and Ni(COD)\(_2\), which was described by Vicic *et al.* in 2012 (Scheme 1.6).\(^{28}\) Despite being catalytic in nickel, a narrow substrate scope was presented. Efforts to extend the scope to cheaper aryl chlorides were unsuccessful.
Scheme 1.6 Nickel-catalyzed nucleophilic trifluoromethylthiolation of arenes.

Consecutively, the Vicic group reported another protocol employing Me₄NSCF₃, copper (II) triflate (Cu(OTf)₂) and 4,4'-dimethyl-2,2'-bipyridine (dmbpy) (Scheme 1.7 eq. 1). This methodology described an extension of the substrate scope to aryl boronic acids but it is stoichiometric in both copper salt and dmbpy ligand. Recently, by embracing the ortho-directing strategy, the Liu group established trifluoromethylthiolation of aryl halides with catalytic amount of copper bromide (Scheme 1.7 eq. 2). Although numerous directing groups such as pyridines, amides, imines, oximes, esters and ketones were tolerated, the reaction still suffered from high temperatures and was limited to aryl iodides and bromides.

Scheme 1.7 Copper-catalyzed or facilitated nucleophilic trifluoromethylthiolation of arenes.
1.4 Brief overview of the Love group’s research program

A part of our research program focuses in employing catalytic activity of transition metals to perform relevant organic transformations. A major effort in our group has been interested in the development of platinum- and nickel-based catalysts for aryl fluoride activation. Over the years, a handful of achievements have been reported and those will be discussed in the coming sections.

1.4.1 Platinum-catalyzed methylation or methoxylation of aryl fluorides.

In 2007, our group described the first example of Pt-catalyzed selective C-F activation cross-coupling of aryl fluorides with dimethyl zinc (Scheme 1.8 eq. 1).31 Subsequently, in the later years the cross-coupling partner was further extended to tetramethoxysilane (Scheme 1.8 eq. 2).32

\[
\begin{align*}
\text{R} & \quad \text{F} \quad \text{N} \quad \text{Ph} \\
& \downarrow \\
\text{R} & \quad \text{F} \quad \text{N} \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{N} \quad \text{Ph} \\
& \downarrow \\
\text{F} & \quad \text{N} \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{R} \\
& \downarrow \\
\text{OCF}_3 & \quad \text{R}
\end{align*}
\]

Scheme 1.8 Platinum-catalyzed C-F activation cross-coupling.

Mild reaction conditions were achieved. A wide range of polyfluoroaryl imines with different substitution patterns were methylated or methoxylated in high yields. However, the method only tolerated substrates having a minimum of three electron-withdrawing groups and lacking C-H bonds in the ortho position.
1.4.2 Nickel-catalyzed Negishi and Suzuki-Miyaura cross-coupling

To circumvent the limitations of the Pt-catalyzed C-F activation protocol, alternative Ni sources was investigated. In particular, common Ni sources such as NiCl$_2$(PEt$_3$)$_2$ and Ni(COD)$_2$ were found to be suitable for the desired purposes (Scheme 1.9 and Scheme 1.10).

![Scheme 1.9 Ni-catalyzed C-F activation Negishi cross-coupling.](image)

Moreover, in Negishi cross-coupling, the reactions were carried out in tandem sequence (Scheme 1.9).$^{33}$ The zinc reagents were generated in-situ then consequently subjected to cross-couple with aryl fluorides. Besides, by synthesizing the zinc reagents in-situ, the scope was not limited to only commercially available alkyl zinc reagents. Different alkyl groups ranging from simple straight chains to others bearing more sensitive functional groups were utilized.

![Scheme 1.10 Ni-catalyzed C-F activation Suzuki-Miyaura cross-coupling.](image)
Furthermore, the cross-coupling also included Suzuki-Miyaura reactions (Scheme 1.10). Fluorinated biaryls, one of the highly valuable synthetic targets in the pharmaceutical industry, were obtained in good-to-excellent yields. The reaction went smoothly in anhydrous THF and a variety of aryl or heteroaryl boronic acids were tolerated. Although in both protocols, the selectivity of C-F activation is determined by the presence of an imine directing-group, the imine moiety can be easily hydrolyzed to an aldehyde, providing a site for further synthetic manipulation.

1.5 Project goals

Inspired by the previous work of Pt and Ni-catalyzed ortho-selective C-F activation cross-coupling and realizing the limitations of the metal-catalyzed nucleophilic trifluoromethylthiolation methodologies, we set out to develop a new protocol employing each of these aspects. We envisioned the following requirements to make our method competitive to the reported protocols:

1) *An earth-abundant metal, such as Ni, should be the catalyst.*

2) *The substrate scope should be expanded to include aryl chlorides.*

3) *Requirement # 2 may necessitate the use of a directing group; ideally, conditions will be found that obviate the need for a directing group.*

4) *The reaction should involve user-friendly conditions such as air-stable trifluoromethylthiolating reagent, commonly used solvent, cheap or no ligand and mild-temperature reaction.*
Chapter 2: Results and Discussion

2.1 Introduction

In the following chapter, the development of a Ni-catalyzed protocol for the nucleophilic trifluoromethylthiolation of aryl chlorides and bromides is reported (Scheme 2.1). This is only the second Ni-catalyzed trifluoromethylthiolation reaction and is the only trifluoromethylthiolation reaction that works with a broad range of aryl chlorides. The reaction conditions are ligand- and additive-free. A variety of trifluoromethylthiolated products are obtained in good yields at ambient temperatures. The C-X (X = Cl, Br) activation still requires an ortho directing group; however, a variety of synthetically useful directing groups can be employed. Moreover, the scope of nucleophilic trifluoromethylthiolation is broadened to heteroarenes. The work will be discussed in this chapter.

Scheme 2.1 Summary of our trifluoromethylthiolation protocol.
2.2 Optimization studies

2.2.1 Preliminary evaluation of nucleophilic trifluoromethylthiolation of AgSCF$_3$ and catalytic Ni(COD)$_2$

We initiated our investigation by examining the influence of different catalytic loading of Ni(COD)$_2$ toward the trifluoromethylthiolation of AgSCF$_3$ with (E)-N-benzyl-1-(2-chlorophenyl)methanimine (7a) at ambient temperatures. The results are summarized in Table 2.1. AgSCF$_3$ was chosen because its facile synthesis and stability.$^{25f,27}$ It is also a primary precursor to other trifluoromethylthiolating reagents.$^{18,21,23,24}$ This could possibly The choices of Ni(COD)$_2$ and THF were based on our previous work of Ni-catalyzed Suzuki-Miyaura C$_{aryl}$-C$_{aryl}$ cross-coupling.$^{34}$

Table 2.1 Trifluoromethylthiolation of (E)-N-benzyl-1-(2-chlorophenyl)methanimine and AgSCF$_3$ - Solvent and catalyst loading screening$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>mol % Ni(COD)$_2$</th>
<th>Solvent</th>
<th>Conversion$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>THF</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>5%</td>
<td>THF</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>10%</td>
<td>THF</td>
<td>37%</td>
</tr>
<tr>
<td>4</td>
<td>20%</td>
<td>THF</td>
<td>43%</td>
</tr>
<tr>
<td>5</td>
<td>10%</td>
<td>DME</td>
<td>30%</td>
</tr>
<tr>
<td>6</td>
<td>10%</td>
<td>Dioxane</td>
<td>12%</td>
</tr>
<tr>
<td>7</td>
<td>10%</td>
<td>MeCN</td>
<td>1%</td>
</tr>
</tbody>
</table>

$^a$ All the reactions were performed at 0.1 mmol scale.

$^b$ Percentages represent $^1$H NMR spectroscopy conversion. It is calculated based on the starting-material-to-product ratio of the proton resonance signals arising from the imine group.
Aryl trifluoromethylthiolation was not observed in absence of Ni(COD)$_2$ (Table 2.1 entry 1). The product conversion was highest in 20 mol% loading of Ni(COD)$_2$ (Table 2.1 entry 4). However, the condition of 10 mol% loading of Ni(COD)$_2$ (Table 2.1 entry 3) was more suitable since the presence of unidentified fluorine-containing species were detected at high loading of Ni(COD)$_2$. In addition, we do not observe any apparent C-H activation product. Such a process can be fast and reversible under our reaction conditions and therefore may not be observable if it does not lead to byproduct formation.$^{35}$ We subsequently evaluated the effect of different solvents toward the trifluoromethylthiolation reaction (Table 2.1 entries 5 - 7). THF and DME were found to provide the high yields of all solvents tested and the lowest yield was obtained in MeCN. A possible explanation for the low reaction yield could be the coordination of the solvent to the active catalyst specie. Since THF is commonly used solvent and cheap, it was chosen as the solvent for further investigations.

2.2.2 Additive effect on nucleophilic trifluoromethylthiolation by AgSCF$_3$ and catalytic Ni(COD)$_2$

Encouraged by the preliminary results, we were prompted to optimize the reaction conditions. Our first attempts were to screen for halide salts, which have literature precedence as possible enhancers of trifluoromethylthiolation using AgSCF$_3$.$^{25,27}$
Table 2.2 Influence of additive on nickel-catalyzed trifluoromethylthiolation of \((E)\)-
\(N\)-benzyl-1-(2-chlorophenyl) methanimine and AgSCF\(_3\)\(^\text{a}\)

\[
\begin{array}{ccc}
\text{Entry} & \text{Additive} & \text{Conversion}^b\\
1 & \text{--} & 37\% \\
2 & \text{KI} & 0\% \\
3 & \text{KBr} & 12\% \\
4 & \text{KCl} & 15\% \\
5 & \text{Me}_4\text{NI} & 2\% \\
6 & \text{Me}_4\text{NI} & 14\% \\
7 & \text{Me}_4\text{NCl} & 26\% \\
8 & \text{i-Pr}_4\text{NPF}_6 & 34\% \\
9 & \text{n-Bu}_4\text{NPF}_6 & 50\% \\
\end{array}
\]

\(^a\) All the reactions were performed at 0.1 mmol scale.
\(^b\) Percentages represent \(^1\)H NMR spectroscopy conversion. It is calculated based on the starting-material-to-product ratio of the proton resonance signals arising from the imine group.

In contrast to the other AgSCF\(_3\) system, the reaction yield in our system was diminished by the addition of halide salts (Table 2.2 entries 1 - 6) suggesting that our system perhaps proceeds via a different reaction mechanism. In previous work, Adam and Clark hypothesized that AgSCF\(_3\) reacted with halide salt to form a complex adduct, which was the active species of trifluoromethylthiolation.\(^{25f}\) In particular, K\(^+\)[Ag(SCF\(_3\))I]\(^-\) was proposed as the reactive species for nucleophilic trifluoromethylthiolation of aryl iodides employing a AgSCF\(_3\)/KI system. In addition, they suggested that the stability of the adduct was dependent on the halide ions (i.e. I\(^-\) > Br\(^-\) > Cl\(^-\) > F\(^-\) ). The formation of such complexes, if viable in our system, could potentially suppress the activity of AgSCF\(_3\) toward trifluoromethylthiolation. This
hypothesis is strongly supported by our data. Indeed, aryl trifluoromethylthiolation is more favourable under the conditions where the formation of $M^+ [Ag(SCF_3)X]$ (M = metals, X = halides) is less likely (Table 2.2 entries 2-4 and entries 5 - 7). This observation indicates that in our system AgSCF$_3$ could be the active trifluoromethylating specie not the silver halide complexes suggested by the work of Adam and Clark.

Towards this end, the presence of halide salts suppresses trifluoromethylthiolation but the suppression was less effective in the presence of ammonium halide salts compared to that of potassium halide salts (Table 2.2. entries 4 - 6 vs. entries 1 - 3). Based on Buchwald’s report (i.e. observation of enhanced trifluoromethylthiolation by bulky ammonium iodides),$^{27}$ we rationalized that presence of bulky ammonium salts not containing halides might improve the reaction yield. Indeed, the addition of $n$-Bu$_4$NPF$_6$ boosted the conversion to 50% (Table 2.2. entry 9). An active trifluoromethylthiolating specie, accounting for the increase of yields, might form. It could be the product of salt metathesis of AgSCF$_3$ with $n$-Bu$_4$NPF$_6$. But this hypothesis disagrees with the previous observations of AgSCF$_3$ being the key element of trifluoromethylthiolation. Another possible explanation for the improvement of the reaction yield is that addition of $n$-Bu$_4$NPF$_6$ helps to solubilize the active trifluoromethylthiolating species. A complete picture of the active trifluoromethylthiolating species has not yet been established and will be the subject of further investigation.
2.2.3 Effect of ligand and AgSCF₃ stoichiometry on trifluoromethylthiolation catalyzed by Ni(COD)₂

The next task in our optimization studies involved the evaluation of various ligands. We reasoned that sigma-donor ligands might facilitate the oxidative addition of nickel towards C-Cl bond, which might lead to an increase in the yield. Unfortunately, bidentate nitrogen-based ligands such as neocuproine, phenanthroline, and bipyridine diminished the yield considerably (Table 2.3 entries 1 - 2). Phosphine-based ligands such as SPhos, PPh₃ and PCy₃ fared slightly better (Table 2.3 entries 3 - 6). The use of PCy₃ provided the highest yield but it offered no improvement than without any ligand at all (Table 2.3 entry 6 versus Table 2.2 entry 9). Thus, we proceeded without the use of a ligand.

We then turned our attention to the stoichiometric loading of AgSCF₃. When the amount of AgSCF₃ was increased to 2.0 equivalents, the yield was increased to 83% (Table 2.3 entry 7). We then kept the AgSCF₃ amount constant and screened for the effect of different equivalents of n-Bu₄NPF₆. Interestingly, it was found that the trifluoromethylthiolation yields were independent to the presence of n-Bu₄NPF₆ at high loading of AgSCF₃ (Table 2.3 entries 8 - 10). Curiously, we wanted to determine if the reaction could proceed successfully at high loading AgSCF₃ without the use of nickel pre-catalyst. A reaction between 7a and AgSCF₃ (2.0 equiv.) in the absent of Ni(COD)₂ were performed and no trifluoromethylthiolated product was obtained. This observation confirmed that Ni(COD)₂ plays an essential role in the reaction. Although the optimal conditions require excess loading of AgSCF₃, we decided to pursue subsequent studies in
this direction since the reaction proceeded to desirable yields in an absence of both additives and ligand (Table 2.3 entry10).

Table 2.3 Ligand and AgSCF$_3$ loading effect on nickel-catalyzed trifluoromethylthiolation of (E)-N-benzyl-1-(2-chlorophenyl)methanimine$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>x equiv. AgSCF$_3$</th>
<th>y equiv. n-Bu$_4$NPF$_6$</th>
<th>Ligand</th>
<th>Conversion$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>1.1</td>
<td>Neocuproine</td>
<td>4%</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>1.1</td>
<td>Phenanthroline</td>
<td>12%</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>1.1</td>
<td>Bipy</td>
<td>21%</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>1.1</td>
<td>SPhos</td>
<td>30%</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>1.1</td>
<td>PPh$_3$</td>
<td>32%</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>1.1</td>
<td>PCy$_3$</td>
<td>51%</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>1.1</td>
<td>--</td>
<td>65%</td>
</tr>
<tr>
<td>8</td>
<td>2.0</td>
<td>1.1</td>
<td>--</td>
<td>83%</td>
</tr>
<tr>
<td>9</td>
<td>2.0</td>
<td>1.5</td>
<td>--</td>
<td>84%</td>
</tr>
<tr>
<td>10</td>
<td>2.0</td>
<td>--</td>
<td>--</td>
<td>86%</td>
</tr>
</tbody>
</table>

$^a$ All the reactions were performed at 0.1 mmol scale.

$^b$ Percentages represent $^1$H NMR spectroscopy conversion. It is calculated based on the starting-material-to-product ratio of the proton resonance signals arising from the imine group.
2.2.4 Evaluation of reaction progress of nucleophilic trifluoromethylthiolation by AgSCF₃ and catalytic Ni(COD)₂

Given the success of our ligand and additive-free conditions, we next set out to monitor the reaction progress of Ni-catalyzed trifluoromethylthiolation of 7a with AgSCF₃ by ¹H NMR spectroscopy (Table 2.4). At each time points, the reaction mixture was sampled. The crude sample was filtered through a Celite plug and washed with chloroform (~ 2-3 mL). The filtrate was then concentrated and re-dissolved in CDCl₃ for ¹H NMR spectroscopy analysis at 25 °C. The product formation was evaluated at 15 minutes, 1, 2, 4, 6, and 8 hours. Maximum conversion was observed after 6 hours. Thus, to obtain optimal yields, all reactions were stopped at least after 6 hours in later studies.

**Table 2.4 Reaction progress of trifluoromethylthiolation of (E)-N-benzyl-1-(2-chlorophenyl)methanimine by AgSCF₃ and catalytic Ni(COD)₂**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 min</td>
<td>9%</td>
</tr>
<tr>
<td>2</td>
<td>1 hr</td>
<td>30%</td>
</tr>
<tr>
<td>3</td>
<td>2 hr</td>
<td>63%</td>
</tr>
<tr>
<td>4</td>
<td>4 hr</td>
<td>86%</td>
</tr>
<tr>
<td>5</td>
<td>6 hr</td>
<td>89%</td>
</tr>
<tr>
<td>6</td>
<td>8 hr</td>
<td>89%</td>
</tr>
</tbody>
</table>

*Percentages represent ¹H NMR spectroscopy conversion. It is calculated based on the starting-material-to-product ratio of the proton resonance signals arising from the imine group.*
2.3 Substrate scope of nucleophilic trifluoromethylthiolation of aryl halides by AgSCF₃ and catalytic Ni(COD)₂

2.3.1 Directing group evaluation

Having narrowed down on optimal conditions, we next studied the effect of various directing group on trifluoromethylthiolation of AgSCF₃ and aryl-X (X = Cl, Br) (Table 2.5). As demonstrated, the imine moiety served as an efficient ortho-directing group for nucleophilic trifluoromethylthiolation (7a, b). Moderate to excellent yields of trifluoromethylthiolated products were also observed with a number of other directing groups bearing nitrogen atom including pyridyl, pyrimidyl, amide and oxazoline (7c-7k). In contrast to nitrogen-containing groups, esters and aldehydes were ineffective as directing groups, presumably as they are not sufficiently electron-donating moieties. In addition, in the absence of the directing group, no product was obtained, even for aryl bromides (7p). These data suggest that a suitable directing group allows for the catalytic trifluoromethylthiolation of aryl chlorides and bromides under mild conditions. Although at present, a directing group is required to achieve Caryl-X activation, most of the tested directing groups are readily amenable to further synthetic manipulation. Moreover, since the nitrogen-based directing group are common structural motifs appeared in biologically active compounds, from the medicinal chemistry point of view, their presence could be an additional benefit. The methodology also tolerated acidic functional groups to a certain extent (7h, 7i, 7l and 7m). It is also worth noting that although Ni complexes are known to break Csp²-S bonds, we did not observe any product decomposition during the reaction course.
Table 2.5 Influence of directing group on Ni-catalyzed trifluoromethylthiolation of AgSCF$_3$ and aryl halides.$^a$

<table>
<thead>
<tr>
<th>DG = Directing group</th>
<th>2.0 equiv. AgSCF$_3$</th>
<th>10 mol % Ni(COD)$_2$</th>
<th>THF, rt, 6-8 hr</th>
</tr>
</thead>
</table>

| $7a$, X = Cl, 72%$^b$ | $7c$, X = Cl, 74% | $7e$, X = Cl, 60% | $7h$, X = Cl, 59% |
| $7b$, X = Br, 80%$^b$ | $7d$, X = Br, 90% | $7f$, X = Cl, 70% | $7i$, X = Br, 84% |
| &nbsp; | &nbsp; | $7g$, X = Br, 95% | &nbsp; |

$7j$, X = Cl, 64% $7l$, X = Cl, <5%$^c$ $7n$, X = Cl, N/R $7p$, X = Br, N/R $7k$, X = Br, 73% $7m$, X = Br, <20%$^c$ $7o$, X = Br, N/R

$^a$ Isolated yield based on an average of two trials of a 0.2 mmol scale.

$^b$ For imine directing substrates, the isolated yield was recorded as yield of the hydrolyzed aldehyde product. See the experimental section for the specific hydrolysis conditions of the imine products.

$^c$ Yield was determined by $^{19}$F{$^1$H} NMR spectroscopy. 3-Fluoro-nitrobenzene was used as internal standard. The delay time for $^{19}$F nuclei was set for 18 seconds.
2.3.2 Limitations of substrate scope

These compelling data prompted us to explore the scope of imine, pyridine and amide directed substrates (Table 2.6). The $\text{C}_\text{aryl}-X$ ($X = \text{Cl, Br}$) activation is highly selective towards the ortho-position. Presence of other halides (F, Br, Cl) at the other position not at the ortho reaction site revealed that trifluoromethylthiolation is only effective at the ortho-position ($8\text{a, b, e, f, j}$). In general, the methodology exhibited good functional group compatibility towards both electron-poor and rich aryl chlorides. However, trifluoromethylthiolation was slightly preferred towards electron-poor arenes ($8\text{c, d, g, h, i}$).

We then further extended the methodology to substrates consisting of N-heterocycles. Comparable yields were obtained for both 2-chloro and 2-bromo nicotinaldehyde ($8\text{k, l}$) while moderate yield was observed for 2-chloro nicotinamide ($8\text{m}$).
Table 2.6 Substrate scope of directed Ni-catalyzed trifluoromethylthiolation of AgSCF$_3$\textsuperscript{a}

<table>
<thead>
<tr>
<th>R</th>
<th>Y</th>
<th>DG</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>N</td>
<td>SCF$_3$</td>
<td>Cl</td>
<td>65%\textsuperscript{b}</td>
</tr>
<tr>
<td>8b</td>
<td>N</td>
<td>SCF$_3$</td>
<td>Cl</td>
<td>50%\textsuperscript{b,c}</td>
</tr>
<tr>
<td>8c</td>
<td>N</td>
<td>SCF$_3$</td>
<td>Cl</td>
<td>65%\textsuperscript{b}</td>
</tr>
<tr>
<td>8d</td>
<td>N</td>
<td>SCF$_3$</td>
<td>Cl</td>
<td>65%\textsuperscript{b}</td>
</tr>
<tr>
<td>8e</td>
<td>Cl</td>
<td>SCF$_3$</td>
<td></td>
<td>73%</td>
</tr>
<tr>
<td>8f</td>
<td>Cl</td>
<td>SCF$_3$</td>
<td></td>
<td>60%</td>
</tr>
<tr>
<td>8g</td>
<td>Cl</td>
<td>SCF$_3$</td>
<td></td>
<td>71%</td>
</tr>
<tr>
<td>8h</td>
<td>Cl</td>
<td>SCF$_3$</td>
<td></td>
<td>87%</td>
</tr>
<tr>
<td>8i</td>
<td>Cl</td>
<td>SCF$_3$</td>
<td></td>
<td>69%</td>
</tr>
<tr>
<td>8j</td>
<td>Cl</td>
<td>SCF$_3$</td>
<td></td>
<td>80%</td>
</tr>
<tr>
<td>8k</td>
<td>Br</td>
<td>SCF$_3$</td>
<td></td>
<td>80%\textsuperscript{b}</td>
</tr>
<tr>
<td>8l</td>
<td>Cl</td>
<td>SCF$_3$</td>
<td></td>
<td>81%\textsuperscript{b}</td>
</tr>
<tr>
<td>8m</td>
<td>Cl</td>
<td>SCF$_3$</td>
<td></td>
<td>43%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yield based on an average of two trials on a 0.2 mmol scale.
\textsuperscript{b} For imine directing substrates, the isolated yield was recorded as yield of the hydrolyzed aldehyde product. See the experimental section for the specific hydrolysis conditions of the imine products.
\textsuperscript{c} Product co-eluted with the starting material. The reported % was the conversion determined by $^1$H NMR spectroscopy. It is based on the ratio of the aldehyde resonance peaks of the product to starting materials.
Chapter 3: Conclusions and Future Directions

3.1 Conclusion

This thesis covers a novel method to generate (hetero) ArSCF$_3$ products via Ni-catalyzed ortho-selective C$_{aryl}$-X ($X = \text{Cl or Br}$) activation under mild conditions. The protocol addresses the key limitations of metal-catalyzed nucleophilic trifluoromethylthiolation of arenes. The reaction is compatible with aryl halides, merely aryl chlorides, bearing substituents with different electronic influences including electron-donating or withdrawing abilities. The trifluoromethylthiolated products are obtained in good-to-excellent yields. The reaction is carried out at ambient temperatures and in ligand- and additive-free conditions. Although directing groups requires for successful C$_{aryl}$-X activation, it is highly selective. This functionalization tolerates various nitrogen-containing groups including imines, pyridines, pyrimidines, amides and oxazolines. It was demonstrated that the imine-directing moiety could be easily hydrolyzed into an aldehyde, providing a potential site for further synthetic manipulation. Nevertheless, mechanistic investigations are underway and are expected to yield insight that will preclude the need for an ortho-directing group. The major disadvantages of our protocol are also addressed including the use of air-sensitive Ni reagent and the excess loading of AgSCF$_3$. Possible studies to improve our protocol are planned. The investigations will be described in subsequent reports.
3.2 Reaction mechanism – possible studies

At this stage, we do not have a mechanistic picture of our Ni-catalyzed nucleophilic trifluoromethylthiolation. Nickel chemistry is more complex compared to that of palladium as a great number of oxidation states including Ni(0), Ni(I), Ni(II), Ni(IV) are more readily available for nickel complexes. This variation of the oxidation states permits a wide range of possible reaction mechanisms including either a single-electron-transfer (SET) process, involving [Ni(0)/(I)], [Ni(I)/(II)], [Ni(II)/(III)] or [Ni(III)/(IV)] or a two-electron redox cycle, involving [Ni(0)/(II)], [Ni(I)/(III)] or [Ni(II)/(IV)]. We here discuss important observations that can help us to outline forthcoming experiments from which a mechanism for our Ni-based protocol is possibly elucidated.

We observed instantaneous colour change of trifluoromethylthiolation reactions from clear to dark brown after the addition of Ni(COD)₂ to mixture of substrates and AgSCF₃. Thus, this could be a suggestion of the presence of a radical species, which may or may not participate in the catalysis. To quickly validate the viability of this hypothesis, the typical radical trapping test can be carried out. This involves the addition of scavenger reagents such as TEMPO or galvinoxyl into the reaction mixture. However, evidence obtained from these experiment is not a sufficient support. To further prove the case, electron paramagnetic resonance (EPR) spectroscopy have to be performed. Nevertheless, we cannot rule out that the mechanistic pathway of our trifluoromethylthiolation method involves a two-electron process. Assuming that it goes by a typical cycle of oxidative addition, transmetalation and reductive elimination, we
can separately study each of the steps by isolating important intermediates from stoichiometric reactions.

We also observed that catalytic amount of Ni(COD)$_2$ provides trifluoromethylthiolation products while Ni(II) source alone cannot initiate the reaction. This suggests that Ni(0) species might actively involve in the catalytic cycle. We can support this hypothesis by proving that successful trifluoromethylthiolation still occurs in conditions of in-situ generation Ni(0) species. Of the reported methods, Ni(0) can be obtained in-situ by reduction of Ni(II) sources by external reductants. These protocols are discussed in details in the following section (Section 3.4).

3.3 Possible role of silver in the reaction mechanism of Ni-catalyzed trifluoromethylthiolation of ortho-directed aryl chlorides.

In our system, the observation of successful trifluoromethylthiolation of aryl chlorides employing AgSCF$_3$ could be an implication that silver is a key element in the reaction mechanism. To evaluate the role of silver in our system, a reaction of 7a and Me$_4$NSCF$_3$ (2.0 equiv.) with 10 mol % catalytic Ni(COD)$_2$ at room temperature was performed. Trifluoromethylthiolation product was observed but the conversion was obtained not in an appreciable percentage (< 5%). This observation suggested that silver is absolutely necessary in our system. Silver ions have also been well-documented for their ability to perform halides abstraction. It could be that in our system high affinity of silver ions to abstract chlorides promotes a viable C-Cl activation by the Ni species, subsequently leading to successful trifluoromethylthiolation. In addition to be an excellent halide abstraction, silver has been known for its ability to involve in radical reaction mechanisms. Although at this stage, we do not have strong evidences to support
that our trifluoromethylthiolation reaction goes by SET process, presence of silver in the system makes SET mechanism become likable. It is possible that a [Ag (0)/(I)] pathway facilitate one-electron redox process of the Nickel pre-catalyst, leading to such successful trifluoromethylthiolation.

3.4 Possible improvements

Our protocol demonstrates that trifluoromethylthiolation of AgSCF$_3$ is feasible by Ni-based catalysts and its reactivity increases toward readily available and inexpensive aryl chlorides. However, utilization of a Ni(0) source (i.e. Ni(COD)$_2$) is the drawback of the protocol. The manipulation of the catalyst requires an inert-atmospheric glovebox or a Schlenk-line apparatus as it is air-sensitive and thermally unstable. To improve the protocol, we would like to use more stable and easier to handle Ni(II) source. As mentioned, addition of only Ni(II) sources to the reaction mixture did not lead to successful trifluoromethylthiolation. Thus, to utilize Ni(II) sources in our system, they need to be reduced first (i.e. conversion of Ni(II) to Ni(0)). Addition of ligands, bases and presence of solvent are frequently insufficient to reduce Ni(II) to Ni(0) in situ.$^{39}$ Employing external reductants is one of the techniques to generate Ni(0) from Ni(II). The reported modes include addition of zinc dust$^{40}$ or pretreatment of butyllithium$^{41}$ or the Grignard reagent or NaH$^{42}$. However, the activity of AgSCF$_3$ or the stability of the imine-directed aryl halides could be effected by employing these external reductants. To minimize this potential interference, the reaction procedure should be modified. It will be separated into two sequential steps, involving initial reduction of the Ni(II) source with the external reductant followed by the addition of the mixture containing aryl halides and AgSCF$_3$. 
Another disadvantage of our protocol is the excess loading of AgSCF$_3$. Two possible solutions to circumvent this drawback are: 1) re-optimizing the protocol to find a condition such that the loading of AgSCF$_3$ can be stoichiometric or 2) screening for an alternative nucleophilic trifluoromethylthiolating reagent. Firstly, we achieved 50% conversion of 7a to trifluoromethylthiolated product by stoichiometric use of AgSCF$_3$ in the present of $n$-Bu$_4$NPF$_6$. However, this percentage yield is not practical. Additional optimization work in this direction can be a screening study for suitable steric bulk of the ammonium ions. Secondly, we have not fully investigated on the influence of other trifluoromethylthiolating reagents on our Ni-based catalytic system. The nucleophilic trifluoromethylthiolating reagents are numerous (section 1.3.2.3). Of these reagents, two candidates also take an equivalent role as AgSCF$_3$ does in metal-catalyzed nucleophilic trifluoromethylthiolation are CsSCF$_3^{25i}$ or CuSCF$_3^{25a-d}$. Fortunately, these reagents can be obtained by salt metathesis of AgSCF$_3$ with the corresponding halide salts such as CsX or CuX ($X =$ Cl, Br, I, F). These reagents are synthesized and their reactivity with aryl chlorides will be evaluated.
Chapter 4: Experimental Procedure

4.1 General procedures

Manipulation of organometallic compounds was performed using standard Schlenk techniques under an atmosphere of dry nitrogen or in a nitrogen-filled mBraun drybox (O$_2$ < 2 ppm). NMR spectra were recorded on Bruker Avance 300 spectrometer. $^1$H, $^{19}$F{$^1$H} and $^{13}$C{$^1$H} chemical shifts are reported in parts per million and referenced to CDCl$_3$ (7.26 ppm for $^1$H; 77.0 ppm for $^{13}$C), acetone-d$_6$ (2.05 ppm for $^1$H; 29.9 and 206.7 ppm for $^{13}$C) or acetonitrile-d$_3$ (1.94 ppm for $^1$H; 1.4 and 118.7 ppm for $^{13}$C). Coupling constant values were extracted assuming first-order coupling. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q= quartet, m = multiplet. All spectra were obtained at 25°C unless otherwise stated. Mass spectra were recorded on Kratos MS-50 and Waters/Micromass LCT mass spectrometers. 3-Fluoro-nitrobenzene was the internal standard, used to evaluate the reaction yield by $^{19}$F{$^1$H} NMR spectroscopy. The delay time of the quantitative $^{19}$F{$^1$H} NMR spectroscopy experiment was set for 18 seconds and the spectrum offset was set at -75 ppm.

4.2 Materials and methods

Dioxane, MeCN, and DME were dried, distilled over CaH$_2$ and degassed prior to use. Anhydrous THF was obtained from Sigma-Aldrich. It was dried by passing through solvent purification columns and degassed prior to use. All organic reagents and inorganic salts were obtained from commercial sources and used as received. AgSCF$_3$ was prepared by literature procedure.$^{25f,27}$ Me$_4$NSCF$_3$ was obtained by the salt metathesis reaction of AgSCF$_3$ with Me$_4$NBr in acetonitrile. Ni(COD)$_2$ was obtained from Strem
chemicals. NiCl$_2$(PEt$_3$)$_2$, NiCl$_2$(PBu$_3$)$_2$, NiCl$_2$dpme, NiCl$_2$dcpm were synthesized from reactions of NiCl$_2$·6H$_2$O and the corresponding chelating phosphine by adapting reported procedures.$^{43}$ 3-Fluoro-nitrobenzene is analytical pure (> 97%) and purchased from Sigma-Aldrich. Silica gel (silicaflash G60) was purchased from SilliCycle.

4.3 Procedures for preparation of the substrates and their analytical data

4.3.1 Preparation of imine-containing substrates

All imine substrates were prepared from condensation of the necessary benzaldehyde and benzylamine according to a literature procedure on a 2.0 mmol scale.$^{31-34}$ The crude reaction was concentrated and dissolved in pentane. The solution was filtered through a Celite plug and concentrated to remove pentane. The imines were further purified by Kugelrohr distillation to remove excess benzylamine and remaining benzaldehyde. The yields were summarized in Scheme 4.1 below.

![Scheme 4.1 Synthesis summary of imine-containing substrates.](image-url)
### 4.3.2 Preparation of pyridine-containing substrates

All the pyridines were prepared according to a literature procedure on a 2.0 mmol scale (Scheme 4.2).\(^4\)

![Scheme 4.2 Synthesis summary of pyridine-containing substrates.](image)

#### 2-(2-bromophenyl)pyridine:

![Image of 2-(2-bromophenyl)pyridine](image)

Column chromatography (SiO\(_2\), 200-400 mesh, 10% EtOAc in hexanes) gave the desired compound as yellow oil in 50% yield. Analytical data matches previously reported data.\(^5\)

\(^{1}\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.72 (d, \(J = 4.1\) Hz, 1H), 7.75 (dt, \(J = 7.8\) Hz, 1.8 Hz, 1H), 7.68 (dd, \(J = 7.5\) Hz, 1.1 Hz, 1H), 7.60 (d, \(J = 7.8\) Hz, 1H), 7.54 (dd, \(J = 7.8\) Hz, 1.6 Hz 1H), 7.41 (dt, \(J = 7.5\) Hz, 1.1 Hz, 1H), 7.31 - 7.22 (m, 2H). \(^{13}\)C\(^{1}\)H NMR (75 MHz, CDCl\(_3\)): \(\delta\) 158.5 (s), 149.6 (s), 141.4 (s), 136.1 (s), 133.5 (s), 131.6 (s), 129.9 (s), 127.7
(s), 125.0 (s), 122.7 (s), 122.0 (s). HRMS: m/z (APCI) calculated C_{11}H_9BrN [M + H]^+: 233.9918, measured: 233.9917.

2-(2-chlorophenyl)pyridine:

\[
\begin{align*}
\text{N} & \quad \text{Cl} \\
\end{align*}
\]

Column chromatography (SiO\textsubscript{2}, 200-400 mesh, 20% diethyl ether in petroleum ether) gave the desired compound as colourless oil in 51% yield. Analytical data match previously reported data.\textsuperscript{45} \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 8.74 (d, J = 4.8 Hz, 1H), 7.77 (dt, J = 7.3 Hz, 1.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.61 (dd, J = 6.9 Hz, 2.5 Hz, 1H), 7.49 (dd, J = 7.3 Hz, 1.8 Hz, 1H), 7.41 - 7.27 (m, 3H). \textsuperscript{13}C{\textsuperscript{1}H} NMR (75 MHz, CDCl\textsubscript{3}): δ 157.1 (s), 149.8 (s), 139.4 (s), 136.1 (s), 132.4 (s), 131.8 (s), 130.3 (s), 129.8 (s), 127.2 (s), 125.1 (s), 122.6 (s). HRMS: m/z (APCI) calculated C\textsubscript{11}H\textsubscript{9}ClN [M + H]^+: 190.0424, measured: 190.0422.

2-(2,4-dichlorophenyl)pyridine:

\[
\begin{align*}
\text{N} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

Column chromatography (SiO\textsubscript{2}, 200-400 mesh, 10% EtOAc in hexanes) gave the desired compound as white solid in 60% yield. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 8.74 (d, J = 4.1Hz, 1H), 7.78 (t, J = 8.5 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 1.4 Hz, 1H), 7.38 - 7.29 (m, 2H). \textsuperscript{13}C{\textsuperscript{1}H} NMR (75 MHz, CDCl\textsubscript{3}): δ 156.1 (s), 150.0 (s), 138.0 (s), 136.3 (s), 135.1 (s), 133.2 (s), 132.8 (s), 130.2 (s), 127.7 (s), 125.1 (s), 123.0 (s). HRMS: m/z (APCI) calculated C\textsubscript{11}H\textsubscript{8}Cl\textsubscript{2}N [M + H]^+: 224.0034, measured: 224.0033.
2-(2-chloro-4-fluorophenyl)pyridine:

Column chromatography (SiO₂, 200-400 mesh, 10% EtOAc in hexanes) gave the desired compound as yellow solid in 40% yield. ¹H NMR (300 MHz, CDCl₃): δ 8.71 (d, J = 4.8 Hz, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.59 (t, J = 6.2 Hz, 1H), 7.28 (t, J = 5.0 Hz, 1H), 7.22 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 7.08 (dt, J = 8.0 Hz, 2.5 Hz, 1H).

¹³C{¹H} NMR (75 MHz, CDCl₃): δ 164.3 (s), 161.0 (s), 156.2 (s), 149.9 (s), 136.2 (s), 135.8 (s), 133.1 (d, J_C-F = 9 Hz), 125.1 (s), 122.7 (s), 117.6 (d, J_C-F = 25 Hz), 114.7 (d, J_C-F = 21 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -111.92 (s, 1F). HRMS: m/z (APCI) calculated C₁₁H₈ClFN [M + H]⁺: 208.0329, measured: 208.0325.

4-chloro-3-(pyridin-2-yl)benzonitrile:

Column chromatography (SiO₂, 200-400 mesh, 20% EtOAc in hexanes) gave the desired compound as white solid in 42% yield. ¹H NMR (300 MHz, CDCl₃): δ 8.71 (d, J = 5.5 Hz, 1H), 7.92 (s, 1H), 7.80 (td, J = 7.8 Hz, 1.8 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.59 (s, 2H), 7.35 (m, 1H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 154.8 (s), 150.2 (s), 140.7 (s), 137.6 (s), 136.6 (s), 135.6 (s), 128.2 (s), 131.5 (s), 125.1 (s), 123.6 (s), 118.0 (s), 111.7 (s). HRMS: m/z (APCI) calculated C₁₂H₈ClN₂ [M + H]⁺: 215.0376, measured: 215.0379.
**4-chloro-3-(pyridin-2-yl)benzaldehyde:**

Column chromatography (SiO$_2$, 200-400 mesh, 10% EtOAc in hexanes) gave the desired compound as white solid in 50% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.02 (s, 1H), 8.74 (d, J = 4.1 Hz, 1H), 8.11 (s, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.69 - 7.62 (m, 2H), 7.33 (t, J = 7.3 Hz, 1H). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$): $\delta$ 191.1 (s), 155.8 (s), 150.1 (s), 140.3 (s), 138.9 (s), 136.4 (s), 135.4 (s), 133.9 (s), 131.4 (s), 129.7 (s), 125.1 (s), 123.3 (s). HRMS: m/z (APCI) calculated C$_{12}$H$_9$ClNO [M + H]$^+$: 218.0373, measured: 218.0375

**2-(2-chloro-6-methoxyphenyl)pyridine:**

Column chromatography (SiO$_2$, 200-400 mesh, 40% EtOAc in hexanes) gave the desired compound as white solid in 74% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.74 (d, J = 4.8 Hz, 1H), 7.75 (t, J = 7.1 Hz, 1H), 7.33 - 7.26 (m, 3H), 7.10 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 3.71 (s, 3H). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$): $\delta$ 158.4 (s), 155.1 (s), 149.6 (s), 136.2 (s), 134.3 (s), 130.0 (s), 129.2 (s), 125.8 (s), 122.5 (s), 122.0 (s), 109.7 (s), 56.2 (s). HRMS: m/z (APCI) calculated C$_{12}$H$_{11}$ClNO [M + H]$^+$: 220.0529, measured: 220.0528.
5-bromo-2-(2-chlorophenyl)pyridine:

![Chemical structure of 5-bromo-2-(2-chlorophenyl)pyridine]

Column chromatography (SiO$_2$, 200-400 mesh, 10% EtOAc in hexanes) gave the desired compound as white solid in 53% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.78 (d, $J = 2.5$ Hz, 1 H), 7.89 (dd, $J = 8.3$, 2.4 Hz, 1 H), 7.63 - 7.54 (m, 2 H), 7.52 - 7.44 (m, 1 H), 7.41 - 7.30 (m, 2 H). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$): $\delta$ 155.6 (s), 151.0 (s), 138.8 (s), 138.3 (s), 132.4 (s), 131.7 (s), 130.6 (s), 130.3 (s), 127.5 (s), 126.4 (s), 120.2 (s). HRMS: m/z (APCI) calculated C$_{12}$H$_8$BrClN [M + H]$^+$: 267.9529, measured: 267.9525.

4.3.3 Preparation of pyrimidine-containing substrates

Pyrimidine-containing substrates were obtained from a modification procedure of the synthesis of the pyridine-containing substrates (Scheme 4.3).$^{46}$

![Scheme 4.3 Synthesis summary of pyrimidine-containing substrates]
2-(2-chlorophenyl)pyrimidine:

Column chromatography (SiO$_2$, 200-400 mesh, 15% EtOAc in hexanes) gave the desired compound as white solid in 53% yield. The $^1$H NMR spectrum match the reported data.$^{46}$

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.88 (d, $J$ = 5.0 Hz, 2 H), 7.78 - 7.67 (m, 1 H), 7.55 - 7.46 (m, 1 H), 7.42 - 7.34 (m, 2 H), 7.29 (t, $J$ = 5.0 Hz, 1 H). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$): $\delta$ 166.0 (s), 159.7 (s), 157.4 (s), 138.0 (s), 133.0 (s), 132.0 (s), 130.8 (s), 127.2 (s), 120.5 (s), 119.7 (s).

4.3.4 Preparation of amide-containing substrates

All amide substrates were prepared from the following general procedure on a 2.0 mmol scale. In a 50 mL round bottom flask containing a Teflon stir bar under nitrogen atmosphere, acyl chloride (2.0 mmol) and triethylamine (5.0 mmol, 2.5 equiv) were added to 25 mL of DCM. To the above solution, a solution of benzylamine (2.2 mmol) in 5 mL of DCM was slowly added. The reaction was left at room temperature overnight. The crude reaction was concentrated and dissolved in 15 mL of ethyl acetate. The solution was washed with 10 mL of KOH (3.0 M). The aqueous layer was re-extracted with 10 mL of ethyl acetate. The combined organic layer was then dried over MgSO$_4$, filtered and concentrated to remove ethyl acetate. The crude was purified by column chromatography. The yields were summarized in Scheme 4.4 below.
Scheme 4.4. Synthesis summary of amide-containing substrates

\[ \text{N-benzyl-2-bromobenzamide:} \]

Column chromatography (SiO\textsubscript{2}, 200-400 mesh, 50% EtOAc in hexanes) gave the desired compound as white solid in 85\% yield. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 7.69 (d, \( J = 9.1 \) Hz, 1H), 7.41 - 7.30 (m, 8H), 6.50 (s, broad, 1H, N-H), 4.67 (d, \( J = 5.7 \) Hz, 2H). \textsuperscript{13}C\{\textsuperscript{1}H\} NMR (75 MHz, CDCl\textsubscript{3}): \( \delta \) 166.8 (s), 138.0 (s), 135.3 (s), 131.6 (s), 130.9 (s), 130.5 (s), 130.4 (s), 190.0 (s), 128.1 (s), 127.9 (s), 127.3 (s), 44.4 (s). HRMS: m/z (APCI) calculated \( C_{14}H_{12}NOBrNa \) [M + Na]\textsuperscript{+}: 312.0000, measured: 312.0000.
**N-benzyl-2-chlorobenzamide:**

![Chemical structure](attachment:image.png)

Column chromatography (SiO$_2$, 200-400 mesh, 50% EtOAc in hexanes) gave the desired compound as white solid in 63% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.59 - 7.26 (m, 9H), 6.41 (s, broad, 1H, N-H), 4.63 (d, $J = 5.7$ Hz, 1H). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$): $\delta$ 167.8 (s), 138.0 (s), 133.7 (s), 131.6 (s), 130.0 (s), 129.0 (s), 120.2 (s), 127.9 (s), 127.8 (s), 119.6 (s), 44.5 (s). HRMS: m/z (APCI) calculated C$_{14}$H$_{12}$NOClNa $[M+Na]^+$: 268.0505, measured: 268.0510.

### 4.3.5 Preparation oxazoline-containing substrates:

Oxazolines were prepared following a two-step literature procedure involving preparation of the amide precursor, through a condensation reaction, followed by cyclization to give the desired oxazoline product. The two-step procedure is outlined in scheme 4.5.$^{47}$

![Scheme 4.5](attachment:scheme.png)

**Scheme 4.5 Synthesis summary of oxazoline-containing substrates.**
2-bromo-N-(2-hydroxyethyl)benzamide:

\[
\begin{align*}
\text{Column chromatography (SiO}_2, \ 200-400 \ \text{mesh}, \ \text{100}\% \ \text{EtOAc}) \ \text{gave the desired compound as white solid in 91}\% \ \text{yield.} \ \ \ & \text{\textsuperscript{1}H NMR (300 MHz, acetonitrile-d\textsubscript{3})}: \ \delta \ 7.62 \ (s, \ J = 8.7 \ \text{Hz}, \ 1\H), \ 7.39 \ - \ 7.28 \ (m, \ 3\H), \ 6.94 \ (s, \ \text{broad}, \ 1\H, \ \text{N-H}), \ 3.62 \ (t, \ J = 5.3 \ \text{Hz}, \ 2\H), \ 3.41 \ (q, \ J = 5.7 \ \text{Hz}, \ 2\H), \ 3.13 \ (s, \ \text{broad}, \ 1\H, \ \text{O-H}). \ \ & \text{\textsuperscript{13}C\textsubscript{\textsuperscript{1}H}} \ \text{NMR (75 MHz, acetonitrile-d\textsubscript{3})}: \ \delta \ 169.5 \ (s), \ 140.2 \ (s), \ 134.3 \ (s), \ 132.3 \ (s), \ 130.1 \ (s), \ 128.9 \ (s), \ 120.3 \ (s), \ 61.9 \ (s), \ 43.6 \ (s). \ \ & \text{HRMS: m/z (APCI) calculated C\textsubscript{9}H\textsubscript{11}BrNO\textsubscript{2} [M + H\textsuperscript{+}]: 243.9973, measured: 243.9973.}
\end{align*}
\]

2-chloro-N-(2-hydroxyethyl)benzamide:

\[
\begin{align*}
\text{Column chromatography (SiO}_2, \ 200-400 \ \text{mesh}, \ \text{100}\% \ \text{EtOAc}) \ \text{gave the desired compound as white solid in 78}\% \ \text{yield.} \ \ & \text{\textsuperscript{1}H NMR (300 MHz, acetonitrile-d\textsubscript{3})}: \ \delta \ 7.46 \ - \ 7.34 \ (m, \ 4\H), \ 7.01 \ (s, \ \text{broad}, \ 1\H, \ \text{N-H}), \ 3.62 \ (q, \ J = 5.5 \ \text{Hz}, \ 2\H), \ 3.41 \ (q, \ J = 5.7 \ \text{Hz}, \ 2\H), \ 3.15 \ (t, \ J = 5.5 \ \text{Hz}, \ 1\H, \ \text{O-H}). \ \ & \text{\textsuperscript{13}C\textsubscript{\textsuperscript{1}H}} \ \text{NMR (75 MHz, Acetonitrile-d\textsubscript{3})}: \ \delta \ 168.5 \ (s), \ 137.8 \ (s), \ 132.3 \ (s), \ 131.6 \ (s), \ 131.1 \ (s), \ 130.3 \ (s), \ 128.4 \ (s), \ 61.9 \ (s), \ 43.6 \ (s). \ \ & \text{HRMS: m/z (APCI) calculated C\textsubscript{9}H\textsubscript{11}ClNO\textsubscript{2} [M + H\textsuperscript{+}]: 200.0478, measured: 200.0478.}
\end{align*}
\]
2-(2-bromophenyl)-4,5-dihydrooxazole:

Column chromatography (SiO$_2$, 200-400 mesh, 50% EtOAc in hexanes) gave the desired compound as white solid in 49% yield. The analytical data match reported data.$^{47}$ $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.72 (dd, $J = 7.5$ Hz, 1.8 Hz, 1H), 7.66 (dd, $J = 7.5$ Hz, 1.1 Hz, 1H), 7.38 – 7.27 (m, 2H), 4.46 (t, $J = 9.4$ Hz, 2H), 4.12 (t, $J = 9.4$ Hz, 2H). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$): $\delta$ 164.2 (s), 134.2 (s), 132.0 (s), 131.7 (s), 130.0 (s), 127.4 (s), 122.1 (s), 68.0 (s), 55.7 (s). HRMS: m/z (APCI) calculated C$_9$H$_9$BrNO [M + H]$^+$: 225.9868, measured: 225.968.

2-(2-chlorophenyl)-4,5-dihydrooxazole:

Column chromatography (SiO$_2$, 200-400 mesh, 50% EtOAc in hexanes) gave the desired compound as white solid in 49% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.77 (dd, $J = 7.5$ Hz, 1.6 Hz, 1H), 7.45 – 7.25 (m, 3H), 4.42 (t, $J = 8.9$ Hz, 2H), 4.11 (t, $J = 8.9$ Hz, 2H). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$): $\delta$ 163.4 (s), 133.7 (s), 131.8 (s), 131.6 (s), 131.0 (s), 127.6 (s), 126.8 (s), 67.7 (s), 55.7 (s). HRMS: m/z (APCI) calculated C$_9$H$_9$ClNO [M + H]$^+$: 182.0373, measured: 182.0374.
4.3.6 Preparation of imidazole-containing substrates

The imidazole-containing substrates were synthesized according to the reported procedures and the synthesis summary is shown below (Scheme 4.6).\textsuperscript{48}

\begin{equation}
\begin{array}{c}
\text{Ph} \\
\text{Br}
\end{array}
\rightarrow
\begin{array}{c}
\text{HN} \\
\text{N}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{X}
\end{array}
\text{Br, Cl}
\text{X}
\text{H}_2
\text{N}
\text{HN}
\begin{array}{c}
\text{Ph} \\
\text{X}
\end{array}
\text{Br, 1.1 equiv.}
\text{H}_2
\text{N}
\text{HN}
\begin{array}{c}
\text{Ph} \\
\text{X}
\end{array}
\text{Br, 3.0 equiv. K}_2\text{CO}_3
\begin{array}{c}
\text{Ph} \\
\text{X}
\end{array}
\text{Br, 1.3 equiv. I}_2
\begin{array}{c}
\text{Ph} \\
\text{X}
\end{array}
\text{Br, t-BuOH, rt, 8 hr}
\begin{array}{c}
\text{HN} \\
\text{N}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{X}
\end{array}
\text{Br, 70%}
\text{Cl, 60%}
\end{equation}

Scheme 4.6 Synthesis summary of imidazole-containing substrates.

2-(2-bromophenyl)-4,5-dihydro-1H-imidazole:

Recrystallization from CHCl\textsubscript{3} and \textit{n}-hexane gave colorless crystals in 70% yield. The analytical data match the reported data but N-H resonance signal was not observed.\textsuperscript{48} \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.65 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 7.59 (dd, J = 7.8, 1.4 Hz, 1H) 7.35 (td, J = 7.8, 1.4 Hz, 1H), 7.26 (td, J = 7.8, 1.8 Hz, 1H), 3.80 (s, 4H). HRMS: m/z (APCI) calculated C\textsubscript{9}H\textsubscript{10}N\textsubscript{2}Br [M]+: 225.0027, measured: 225.0031.

2-(2-chlorophenyl)-4,5-dihydro-1H-imidazole:

Recrystallization from CHCl\textsubscript{3} and \textit{n}-hexane gave colorless crystals in 60% yield. N-H resonance signal was not observed. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.77 (dd, J = 7.3 Hz, 2.1 Hz, 1H), 7.39 (dd, J = 13, 1.8 Hz, 1H), 7.39 – 7.20 (m, 3H), 3.79 (s, 4H). HRMS: m/z (APCI) calculated C\textsubscript{9}H\textsubscript{10}N\textsubscript{2}Cl [M]+: 181.0533, measured: 181.0532.
4.4 General procedure for optimization studies

All the reactions were performed at 0.1 mmol scale and left at ambient temperature overnight. The crude was filtered through a Celite plug and washed with chloroform (2-3 mL). The filtrate was then concentrated down and re-dissolved in CDCl₃ for ¹H NMR spectroscopic analysis. The conversion was calculated based on the ratio between the imine resonance peaks of the product to starting material.

4.5 Procedure for preparation and analytical data of product of Ni-catalyzed trifluoromethylthiolation

All the trifluoromethylthiolation products were prepared by the following procedure. Inside the glovebox, the desired substrate (0.2 mmol), AgSCF₃ (0.4 mmol) and ~ 10 mL of dry THF were added into 20 mL scintillation vial containing a Teflon-coated stir bar. To the above solution, a solution of Ni(COD)₂ in THF (600 µL, 1 mg / 100 µL solution) was added dropwise by micropipette. Instantaneous color change was observed. The solution was left stirred at room temperature for at least 6 hours. During this time, a black brown precipitate was observed. The crude reaction was concentrated by rotary evaporation. Chloroform was added to re-dissolve the residue. The solution was filtered through a Celite plug to remove the solid precipitate. The Celite was rinsed with ~ 2-3 mL of chloroform. The filtered crude solution was then concentrated to dryness by rotary evaporation. The crude material was purified by silica gel chromatography (SiO₂, 200-400 mesh, ethyl acetate - hexane mixture as mobile phase). Specific purification conditions for each substrates are described below. For the ease of purification, imine products were hydrolyzed to aldehydes by adding silica gel (~200 mg) to the filtered crude solution and letting it stirred at room temperature for at least two hour before
concentrating it down to dryness. The reaction completion was determined by TLC. The fused product-silica then was loaded on to a silica column for separation. The other substrates were loaded directly to the silica column. The yields were summarized in Table 2.5 and Table 2.6.

4.5.1 Trifluoromethylthiolated products containing an aldehyde group

2-((trifluoromethyl)thio)benzaldehyde:

![Chemical Structure](image)

Column chromatography (SiO$_2$, 200-400 mesh, 5% EtOAc in hexanes) gave the desired compound as a white solid. The analytical data match the reported data.$^{30}$ $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.60 (s, 1H), 8.07-8.04 (m, 1H), 7.81-7.78 (m, 1H), 7.71-7.63 (m, 2H). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$): $\delta$ 190.8 (s), 137.8 (s), 137.8 (s), 134.5 (s), 131.4 (s), 130.0 (s), 128.9 (q, $J_{C-F}$ = 309 Hz), 127.7 (s). $^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ -42.53 (s, 3F).

4-fluoro-2-((trifluoromethyl)thio)benzaldehyde:

![Chemical Structure](image)

Column chromatography (SiO$_2$, 200-400 mesh, 2% EtOAc in hexanes) gave the desired compound as colourless oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.46 (s, 1H), 8.08 (dd, $J = 8.7$ Hz, $J = 2.7$ Hz, 1H), 7.50 (dd, $J = 8.5$ Hz, $J = 2.3$ Hz, 1H), 7.34 (td, $J = 8.0$ Hz, $J = 2.5$ Hz, 1H). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$): $\delta$ 189.3 (s), 167.0 (s), 163.6 (s), 134.0 (s), 133.0 (d, $J_{C-F}$ = 10 Hz), 128.7 (q, $J_{C-F}$ = 309 Hz), 123.6 (d, $J_{C-F}$ = 23 Hz), 118.5 (d, $J_{C-F}$ = 22 Hz). $^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ -42.20 (s, 3F), -101.33 (s, 1F).
3-formyl-4-((trifluoromethyl)thio)benzonitrile:

Column chromatography (SiO₂, 200-400 mesh, 2% EtOAc in hexanes) gave the desired compound as colourless oil. ¹H NMR (300 MHz, CDCl₃): δ 10.46 (s, 1H), 8.28 (s, 1H), 7.92 (s, 2H). ¹⁹F NMR (282 MHz, CDCl₃): δ -41.00 (s, 3F).

4-methoxy-2-((trifluoromethyl)thio)benzaldehyde:

Column chromatography (SiO₂, 200-400 mesh, 5% EtOAc in hexanes) gave the desired compound as yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 10.43 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 7.13 (dd, J = 8.2 Hz, J = 2.5 Hz, 1H), 3.93 (s, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 189.7 (s), 163.9 (s), 132.2 (s), 130.9 (s), 129.9 (s), 128.9 (q, Jₐₓ₋ₐₓ = 309 Hz), 122.1 (s), 116.6 (s), 55.9 (s). ¹⁹F NMR (282 MHz, CDCl₃): δ -42.28 (s, 3F).

2-((trifluoromethyl)thio)nicotinaldehyde:

Column chromatography (SiO₂, 200-400 mesh, 20% EtOAc in hexanes) gave the desired compound as colourless oil. The analytical data match the reported data. ³¹H NMR (300 MHz, CDCl₃): δ 10.18 (s, 1H), 8.76 (dd, J = 4.8 Hz, J = 1.8 Hz, 1H), 8.18 (dd, J = 7.8 Hz, J = 1.8 Hz, 1H), 7.46 (dd, J = 7.8, J = 3.0 Hz, 1H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ
190.2 (s), 153.7 (s), 140.7 (s), 129.7 (s), 128.5 (q, \( J_{CF} = 310\) Hz), 122.3 (s). \(^{19}\)F NMR (282 MHz, CDCl\(_3\)): \( \delta \) -40.65 (s, 3F).

### 4.5.2 Trifluoromethylthiolated products containing a pyridine group

**2-(2-((trifluoromethyl)thio)phenyl)pyridine:**

![Pyridine with trifluoromethylthio group](image)

Column chromatography (SiO\(_2\), 200-400 mesh, 15% EtOAc in hexanes) gave the desired compound as yellow oil. The data match the reported data. \(^{24,30}\) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 8.68 (d, \( J = 4.9\) Hz, 1H), 7.82 (d, \( J = 7.7\) Hz, 1H), 7.75 (dt, \( J = 7.7\) Hz, \( J = 1.8\) Hz, 1H), 7.59 (d, \( J = 7.4\) Hz, 1H), 7.51 (t, \( J = 8.0, 2\)H), 7.43 (t, \( J = 7.4\) Hz, 1H), 7.26 (t, \( J = 6.7\) Hz, 1H). \(^{13}\)C\{\(^1\)H\} NMR (75 MHz, CDCl\(_3\)): \( \delta \) 157.6 (s), 148.8 (s), 145.1 (s), 136.1 (s), 135.7 (s), 130.6 (s), 130.0 (s), 129.6 (q, \( J_{CF} = 309\) Hz), 129.1 (s), 124.2 (s), 124.0 (s), 122.3 (s). \(^{19}\)F NMR (282 MHz, CDCl\(_3\)): \( \delta \) -42.11 (s, 3F). HRMS: m/z (APCI) calculated C\(_{12}\)H\(_9\)F\(_3\)NS [M + H]\(^+\): 256.0408, measured: 256.0404.

**2-(4-chloro-2-((trifluoromethyl)thio)phenyl)pyridine:**

![Pyridine with chloro and trifluoromethylthio group](image)

Column chromatography (SiO\(_2\), 200-400 mesh, 10% EtOAc in hexanes) gave the desired compound as colourless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 8.71 (d, \( J = 4.8\) Hz, 1H), 7.83 (s, 1H), 7.78 (d, \( J = 7.8\) Hz, 1H), 7.58-7.48 (m, 3H), 7.32 (t, \( J = 5.9\) Hz, 1H). \(^{13}\)C\{\(^1\)H\} NMR (75 MHz, CDCl\(_3\)): \( \delta \) 156.4 (s), 148.9 (s), 143.0 (s), 136.4 (s), 134.8 (s), 134.5 (s), 131.5 (s), 130.0 (s), 129.3 (q, \( J_{CF} = 309\) Hz), 126.2 (s), 123.8 (s), 122.6 (s). \(^{19}\)F NMR
(282 MHz, CDCl₃): δ -41.87 (s, 3F). HRMS: m/z (APCI) calculated C₁₂H₈ClF₃NS [M + H]⁺: 290.0018, measured: 290.0015.

**2-(4-fluoro-2-((trifluoromethyl)thio)phenyl)pyridine:**

![Structure](image)

Column chromatography (SiO₂, 200-400 mesh, 10% EtOAc in hexanes) gave the desired compound as colourless oil. ¹H NMR (300 MHz, CDCl₃): δ 8.69 (d, J = 4.6 Hz, 1H), 7.79 (t, J = 7.5 Hz, 1H), 7.62-7.49 (m, 3H), 7.31 (d, J = 7.3 Hz, 1H), 7.21 (dt, J = 8.2 Hz, J = 2.5 Hz, 1H). ¹³C {¹H} NMR (75 MHz, CDCl₃): δ 163.8 (s), 160.5 (s), 156.6 (s), 148.8 (s), 140.5 (s), 136.4 (s), 131.9 (d, J_C-F = 8 Hz), 129.4 (q, J_C-F = 309 Hz), 123.8 (s), 122.5 (s), 121.4 (d, J_C-F = 25 Hz), 116.9 (d, J_C-F = 21 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -41.67 (s, 3F), -111.78 (s, 1F). HRMS: m/z (APCI) calculated C₁₂H₈F₄NS [M + H]⁺: 274.0314, measured: 274.0310.

**3-(pyridin-2-yl)-4-((trifluoromethyl)thio)benzonitrile:**

![Structure](image)

Column chromatography (SiO₂, 200-400 mesh, 10% EtOAc in hexanes) gave the desired compound as colourless oil. ¹H NMR (300 MHz, CDCl₃): δ 8.71 (d, J = 3.0 Hz, 1H), 7.92-7.81 (m, 3H), 7.70 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.3 Hz, 1H). ¹³C {¹H} NMR (75 MHz, CDCl₃): δ 155.1 (s), 148.9 (s), 143.8 (s), 136.9 (s), 133.5 (s), 133.4 (s), 131.9 (s), 129.1 (q, J_C-F = 310 Hz), 123.4 (s), 123.3 (s), 117.5 (s), 112.9 (s). ¹⁹F NMR (282 MHz, CDCl₃): δ -41.27 (s, 3F). HRMS: m/z (APCI) calculated C₁₃H₈F₃N₂S [M + H]⁺: 281.0360, measured: 281.0360.
3-(pyridin-2-yl)-4-((trifluoromethyl)thio)benzaldehyde:

![Chemical Structure](image)

Column chromatography (SiO$_2$, 200-400 mesh, 10% EtOAc in hexanes) gave the desired compound as colourless oil. $^1$H NMR (300 MHz, CDCl$_3$): δ 10.06 (s, 1H), 8.70 (d, J = 4.3 Hz, 1H), 8.09 (s, 1H), 7.98-7.89 (m, 2H), 7.83 (t, J = 7.5 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 5.9 Hz, 1H). $^{13}$C {$^1$H} NMR (75 MHz, CDCl$_3$): δ 190.8 (s), 156.0 (s), 148.7 (s), 143.5 (s), 136.8 (s), 136.1 (s), 133.4 (s), 133.1 (s), 130.7 (s), 129.5 (s), 129.2 (q, J$_{C-F}$ = 309 Hz), 123.4 (s), 123.0 (s). $^{19}$F NMR (282 MHz, CDCl$_3$): δ -41.29 (s, 3F).

HRMS: m/z (APCI) calculated C$_{13}$H$_9$F$_3$NOS [M + H]$^+$: 284.0357, measured: 284.0353.

2-(2-methoxy-6-((trifluoromethyl)thio)phenyl)pyridine:

![Chemical Structure](image)

Column chromatography (SiO$_2$, 200-400 mesh, 30% EtOAc in hexanes) gave the desired compound as colourless oil. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.72 (d, J = 4.6 Hz, 1H), 7.77 (dt, J = 7.8 Hz, J = 1.8Hz, 1H), 7.45-7.38 (m, 3H), 7.30 (t, J = 7.5 Hz, 1H), 7.19-7.08 (m, 1H), 3.76 (s, 3H). $^{13}$C {$^1$H} NMR (75 MHz, CDCl$_3$): δ 157.6 (s), 155.0 (s), 148.9 (s), 135.7 (s), 135.6 (s), 135.0 (s), 129.7 (s), 129.5 (q, J$_{C-F}$ = 309 Hz), 127.7 (s), 125.7 (s), 122.3 (s), 112.9 (s), 56.9 (s). $^{19}$F NMR (282 MHz, CDCl$_3$): δ -42.04 (s, 3F). HRMS: m/z (APCI) calculated C$_{13}$H$_{11}$F$_3$NOS [M + H]$^+$: 286.0513, measured: 286.0512.
**5-bromo-2-(2-((trifluoromethyl)thio)phenyl)pyridine:**

![Chemical structure](image)

Column chromatography (SiO₂, 200-400 mesh, 10% EtOAc in hexanes) gave the desired compound as colourless oil. ¹H NMR (300 MHz, CDCl₃): δ 8.76 (d, J = 2.1 Hz, 1H), 7.91 (dd, J = 8.5 Hz, 2.3 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.60-7.41 (m, 4H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 156.1 (s), 150.0 (s), 144.2 (s), 138.8 (s), 136.3 (s), 130.6 (s), 130.4 (s), 129.5 (s), 129.5 (q, J_C-F = 309 Hz), 125.4 (s), 123.91 (s), 120.0 (s). ¹⁹F NMR (282 MHz, CDCl₃): δ -42.12 (s, 3F). HRMS: m/z (APCI) calculated C₁₂H₈BrF₃NS [M + H]⁺: 333.9513, measured: 333.9516.

### 4.5.3 Trifluoromethylthiolated products containing a pyrimidine group

**2-(2-((trifluoromethyl)thio)phenyl)pyrimidine:**

![Chemical structure](image)

Column chromatography (SiO₂, 200-400 mesh, 10% EtOAc in hexanes) gave the desired compound as colourless oil. The analytical data is similar to the reported data. The literature data were obtained by ¹H NMR 400 MHz. ¹H NMR (300 MHz, CDCl₃): δ 8.87 (d, J = 5.0 Hz, 2H), 8.09-8.06 (m, 1H), 7.83 (t, J = 4.6 Hz, 1H), 7.54-7.47 (m, 2H), 7.28 (t, J = 5.0 Hz, 1H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 165.2 (s), 157.0 (s), 141.3 (s), 133.4 (s), 131.5 (s), 130.7 (s), 130.1 (q, J_C-F = 309 Hz), 129.3 (s), 127.0 (s), 119.5 (s). ¹⁹F NMR (282 MHz, CDCl₃): δ -41.77 (s, 3F). HRMS: m/z (APCI) calculated C₁₁H₈N₂F₃S [M + H]⁺: 257.0360, measured: 257.0355.
4.5.4 Trifluoromethylthiolated products containing an amide group

N-benzyl-2-((trifluoromethyl)thio)benzamide:

Column chromatography (SiO₂, 200-400 mesh, 30% EtOAc in hexanes) gave the desired compound as white solid. ¹H NMR (300 MHz, CDCl₃): δ 7.75 (t, J = 4.1 Hz, 1H), 7.58 (t, J = 4.8 Hz, 1H), 7.52-7.47 (m, 2H), 7.38-7.31 (m 5H), 6.31 (s, broad, 1H, N-H), 4.65 (d, J = 5.7 Hz, 2H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 167.4 (s), 141.7 (s), 137.5 (s), 136.7 (s), 130.8 (s), 130.6 (s), 129.4 (q, J_C-F = 310 Hz), 128.8 (s), 128.3 (s), 128.0 (s), 127.7 (s), 44.3 (s). ¹⁹F NMR (282 MHz, CDCl₃): δ -42.11 (s, 3F). HRMS: m/z (APCI) calculated C₁₅H₁₂F₃NOSNa [M + Na]⁺: 334.0489, measured: 334.0487.

N-benzyl-6-chloro-2-((trifluoromethyl)thio)nicotinamide:

Column chromatography (SiO₂, 200-400 mesh, 95% EtOAc in hexanes) gave the desired compound as white solid. ¹H NMR (300 MHz, acetone-d₆): δ 8.62 (s, broad, 1H, N-H), 8.29 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.37-7.21 (m, 5H), 4.57 (d, J = 5.7 Hz, 2H). ¹³C{¹H} NMR (75 MHz, acetone-d₆): δ 165.8 (s), 155.2 (s), 153.1 (s), 139.9 (s), 139.8 (s), 130.4 (q, J_C-F = 309 Hz), 129.8 (s), 129.1 (s), 128.2 (s), 123.2 (s), 44.8 (s). ¹⁹F NMR (282 MHz, Acetone-d₆): δ -42.76 (s, 3F). HRMS: m/z (APCI) calculated C₁₄H₁₀ClF₃N₂OSNa [M + Na]⁺: 369.0052, measured: 369.0049.
N-(2-hydroxyethyl)-2-((trifluoromethyl)thio)benzamide:

\[
\begin{align*}
\text{SiO}_2, \ 200-400 & \text{ mesh, 95\% EtOAc in hexanes} \text{ gave the desired compound as white solid.} \\
^1H \text{ NMR (300 MHz, CDCl}_3\) & : \delta 7.71 (t, J = 5.0 Hz, 1H), 7.52 (t, J = 4.1 Hz, 1H), 7.48-7.41 (m, 2H), 6.77 (s, broad, 1H, N-H), 3.75 (t, J = 5.0 Hz, 2H), 3.53 (dd, J = 10.0 Hz, J = 5.0 Hz, 2H), 3.06 (s, broad, 1H, O-H). \ \\
^{13}C\{^1H\} \text{ NMR (75 MHz, CDCl}_3\) & : \delta 168.5 (s), 141.4 (s), 136.5 (s), 130.8 (s), 130.5 (s), 129.4 (q, J_{C-F} = 309 Hz), 128.3 (s), 122.7 (s), 61.5 (s), 42.6 (s). \ \\
^{19}F \text{ NMR (282 MHz, CDCl}_3\) & : \delta -42.14 (s, 3F). \ \\
\text{HRMS: m/z (APCI) calculated } & C_{10}H_{10}F_{3}NO_2SNa [M + Na]^+ : 288.0282, \text{ measured: 288.0282.} \\
\end{align*}
\]

4.5.5 Trifluoromethylthiolated products containing an oxazoline group

2-(2-((trifluoromethyl)thio)phenyl)-4,5-dihydrooxazole:

\[
\begin{align*}
\text{SiO}_2, \ 200-400 & \text{ mesh, 50\% EtOAc in hexanes} \text{ gave the desired compound as colourless oil.} \\
^1H \text{ NMR (300 MHz, CDCl}_3\) & : \delta 7.81 (d, J = 7.3 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.48-7.37 (m, 2H), 4.42 (t, J = 9.4 Hz, 2H), 4.11 (t, J = 9.4 Hz, 2H). \ \\
^{13}C\{^1H\} \text{ NMR (75 MHz, CDCl}_3\) & : \delta 163.1 (s), 132.4 (s), 131.1 (s), 130.4 (s), 130.0 (s), 129.5 (q, J_{C-F} = 309 Hz), 128.5 (s), 67.6 (s), 55.3 (s). \ \\
^{19}F \text{ NMR (282 MHz, CDCl}_3\) & : \delta -41.82 (s, 3F). \ \\
\text{HRMS: m/z (APCI) calculated } & [M]^+ : 248.0357, \text{ measured: 248.0354.} \\
\end{align*}
\]
References


6) The statistic is based on the Shibta’s review and a Scifinder search on the topics. The survey was conducted up to the end of 2014.


39) Only one example has been reported where Ni(II) as a pre-catalyst was reduced to Ni(0) by PR₃ (R = Ph, Cl, or Oi-Pr) for C-C cross coupling: Leadbeater, N. E. *J. Org. Chem.* **2001**, *66*, 7593.


Appendices

A. Trifluoromethylthiolated arenes containing aldehydes

2-((trifluoromethyl)thio)benzaldehyde:
$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):
$^{19}\text{F NMR (282 MHz, 25} \, ^{\circ}\text{C CDCl}_3):}$

![Chemical Shift (ppm)]

$\text{SCF}_3$
$^{13}$C{$^1$H} NMR (75 MHz, 25 °C, CDCl$_3$):

Starred resonances are the coupling between $^{13}$C nuclei and $^{19}$F nuclei of SCF$_3$ moiety.
4-fluoro-2-((trifluoromethyl)thio)benzaldehyde:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

![1H NMR spectrum](image1)

$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):

![19F NMR spectrum](image2)
$^{13}$C{$_1^1$H} NMR (75 MHz, 25°C, CDCl$_3$):

Starred resonances are the coupling between $^{13}$C nuclei and $^{19}$F nuclei of SCF$_3$ moiety
3-formyl-4-((trifluoromethyl)thio)benzonitrile:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):
4-methoxy-2-((trifluoromethyl)thio)benzaldehyde:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):
$^{13}\text{C}\{^{1}\text{H}\}$ NMR (75 MHz, 25 °C, CDCl$_3$):

Starred resonances are the coupling between $^{13}\text{C}$ nuclei and $^{19}\text{F}$ nuclei of SCF$_3$ moiety
2-((trifluoromethyl)thio)nicotinaldehyde:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

$^9$F NMR (282 MHz, 25 °C, CDCl$_3$):
$^{13}$C $^{1}$H NMR (75 MHz, 25 °C, CDCl$_3$):

Starred resonances are the coupling between $^{13}$C nuclei and $^{19}$F nuclei of SCF$_3$ moiety
B. Trifluoromethylthiolated arenes containing pyridines

2-(2-((trifluoromethyl)thio)phenyl)pyridine:
$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

![Chemical Structure]
$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):

[Chemical Shift (ppm) graph]
$^{13}\text{C}\{^1\text{H}\}$ NMR (75MHz, 25°C, CDCl$_3$):

Starred resonances are the coupling between $^{13}\text{C}$ nuclei and $^{19}\text{F}$ nuclei of SCF$_3$ moiety. One of the quartet resonance was not observed.
2-(4-chloro-2-((trifluoromethyl)thio)phenyl)pyridine:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

$^{19}$F NMR (282 MHz, CDCl$_3$):
$^{13}$C{$^1$H} NMR (75MHz, 25 $^\circ$C, CDCl$_3$):

Starred resonances are the coupling between $^{13}$C nuclei and $^{19}$F nuclei of SCF$_3$ moiety.
2-(4-fluoro-2-((trifluoromethyl)thio)phenyl)pyridine:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

![NMR spectrum](image)

$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):

![NMR spectrum](image)
$^{13}$C-$^1$H NMR (75 MHz, 25 °C, CDCl$_3$):

Starred resonances are the coupling between $^{13}$C nuclei and $^{19}$F nuclei of SCF$_3$ moiety.
3-(pyridin-2-yl)-4-((trifluoromethyl)thio)benzonitrile:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):
$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, 25 °C, CDCl$_3$):

Starred resonances are the coupling between $^{13}\text{C}$ nuclei and $^{19}\text{F}$ nuclei of SCF$_3$ moiety.
3-(pyridin-2-yl)-4-((trifluoromethyl)thio)benzaldehyde:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):
\(^{13}\text{C} \{^1\text{H}\} \text{ NMR (75 MHz, 25} \, ^\circ\text{C, CDCl}_3):\]

Starred resonances are the coupling between \(^{13}\text{C}\) nuclei and \(^{19}\text{F}\) nuclei of SCF\(_3\) moiety. One of the quartet resonance was not observed.
2-(2-methoxy-6-((trifluoromethyl)thio)phenyl)pyridine:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

![NMR spectrum of 2-(2-methoxy-6-((trifluoromethyl)thio)phenyl)pyridine](image)

$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):

![NMR spectrum of 2-(2-methoxy-6-((trifluoromethyl)thio)phenyl)pyridine](image)
$^{13}$C–H NMR (75 MHz, 25 °C, CDCl$_3$):

Starred resonances are the coupling between $^{13}$C nuclei and $^{19}$F nuclei of SCF$_3$ moiety
5-bromo-2-(2-((trifluoromethyl)thio)phenyl)pyridine:

${}^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):
$^{13}$C{$^{1}$H} NMR (75 MHz, 25 °C, CDCl$_3$):

Starred resonances are the coupling between $^{13}$C nuclei and $^{19}$F nuclei of SCF$_3$ moiety
C. Trifluoromethylthiolated arenes containing pyrimidines:

2-(2-((trifluoromethyl)thio)phenyl)pyrimidine:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):
$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):
$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, 25 °C, CDCl$_3$):

Starred resonances are the coupling between $^{13}\text{C}$ nuclei and $^{19}\text{F}$ nuclei of SCF$_3$ moiety.
D. Trifluoromethylthiolated arenes containing amides

N-benzyl-2-((trifluoromethyl)thio)benzamide:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):

![NMR Spectrum]
$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):
$^{13}$C \{${}^1$H\} NMR (75 MHz, 25 °C, CDCl$_3$):

Starred resonances are the coupling between $^{13}$C nuclei and $^{19}$F nuclei of SCF$_3$ moiety
N-benzyl-6-chloro-2-((trifluoromethyl)thio)nicotinamide:

$^1$H NMR (300 MHz, 25 °C, acetone-d$_6$):

\[
\begin{align*}
\text{Chemical Shift (ppm)} & \\
\end{align*}
\]

$^{19}$F NMR (282 MHz, 25 °C, acetone-d$_6$):

\[
\begin{align*}
\text{Chemical Shift (ppm)} & \\
\end{align*}
\]
$^{13}$C\{$^1$H\} NMR (75 MHz, 25 °C, acetone-d$_6$):

Starred resonances are the coupling between $^{13}$C nuclei and $^{19}$F nuclei of SCF$_3$ moiety
N-(2-hydroxyethyl)-2-((trifluoromethyl)thio)benzamide:

\[^1\text{H}\] NMR (300 MHz, 25 °C, CDCl\textsubscript{3}): 

\[
\begin{array}{c}
\text{Chemical Shift (ppm)}
\end{array}
\]

\[
\begin{array}{c}
0.98 \\
2.09 \\
2.07 \\
1.01 \\
2.00 \\
0.98 \\
0.99 \\
0.99
\end{array}
\]

\[
\begin{array}{c}
3.06 \\
3.51 \\
3.53 \\
3.54 \\
3.56 \\
3.73 \\
3.75 \\
3.77
\end{array}
\]

\[
\begin{array}{c}
6.77 \\
7.41 \\
7.43 \\
7.45 \\
7.46 \\
7.51 \\
7.52 \\
7.69 \\
7.71 \\
7.72
\end{array}
\]

\[19\text{F}\] NMR (282 MHz, 25 °C, CDCl\textsubscript{3}): 

\[
\begin{array}{c}
\text{Chemical Shift (ppm)}
\end{array}
\]

\[
\begin{array}{c}
-42.14
\end{array}
\]
$^{13}$C $^1$H NMR (75 MHz, 25 °C, CDCl₃):

Starred resonances are the coupling between $^{13}$C nuclei and $^{19}$F nuclei of SCF₃ moiety
E. Trifluoromethylthiolated arenes containing oxazolines

2-(2-((trifluoromethyl)thio)phenyl)-4,5-dihydrooxazole:

$^1$H NMR (300 MHz, 25 °C, CDCl$_3$):
$^{19}$F NMR (282 MHz, 25 °C, CDCl$_3$):
$^{13}$C $^1$H NMR (75 MHz, 25 °C, CDCl$_3$):

Starred resonances are the coupling between $^{13}$C nuclei and $^{19}$F nuclei of SCF$_3$ moiety.