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Ligandless Nickel-Catalyzed *Ortho*-Selective Directed Trifluoromethylthiolation of Aryl Chlorides and Bromides Using $AgSCF_3$

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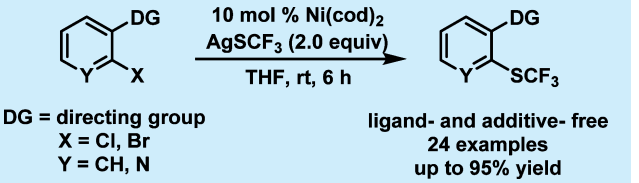
Supporting Information

ABSTRACT: A mild protocol for Ni-catalyzed trifluoromethylthiolation of aryl chlorides and bromides is described herein. The method utilizes $AgSCF_3$ as an easily accessible nucleophilic trifluoromethylthiolating reagent and does not require any ligands or additives. *Ortho*-selectivity is achieved using a variety of directing groups such as imines, pyridines, and oxazolines for 24 examples in up to 95% yield.



Fluorine has become increasingly prevalent in organic compounds; it is present in approximately 50% of all agrochemicals and 25% of pharmaceuticals.[1] Incorporation of fluorine into bioactive molecules can significantly influence their metabolism and physicochemical properties.[2] Despite being the most abundant halogen in the earth's crust, it is present in only about 30 natural products, which has necessitated the development of numerous strategies to synthesize structurally diverse organofluorine compounds.[3] In recent years, the trifluoromethylthio- ($-SCF_3$) group and its oxidized analogues [$S(O)_nCF_3$, $n = 0$, 1, 2] have received notable attention due to their high lipophilicity, electron-withdrawing ability, and bioavailability.[4] Among fluorine-containing motifs, the SCF_3 group possesses the highest lipophilicity (π = 1.44), whereas the SO_2CF_3 group has the strongest electron-withdrawing ability ($\sigma_m = 0.79$, $\sigma_p = 0.93$).[5] In addition, these functional groups can be easily interconverted through redox chemistry, rendering the construction of SCF_3-containing molecules a valuable synthetic target (Figure 1).[4c,6]

Traditional methods to incorporate the $-SCF_3$ group in aryl halides rely upon the fluorination of sulfur-containing substrates either by halogen−fluorine exchange of chloro- or bromomethyl sulfides using a nucleophilic fluoride such as HF, SbF_3, or TREAT·HF,[7] or the trifluoromethylation of thiols using a variety of trifluoromethylating reagents such as biaryltrifluoromethylsulfonium salts (Yagupolskii[8] and Umemoto[9] reagents), hypervalent iodine compounds (Togni's reagent[10]), or silane derivatives (Ruppert−Prakash reagent[11]).

More recently, the direct formation of C−SCF_3 bonds has emerged with the establishment of several strategies involving electrophilic,[12] nucleophilic,[13] and oxidative cross-coupling.[14] Nucleophilic trifluoromethylthiolation offers a direct and efficient approach toward the synthesis of trifluoromethyl aryl sulfides ($ArSCF_3$) (Scheme 1).

These synthetic methods require a readily available and easy-to-use source of trifluoromethylthiolate anions. Early efforts identified a variety of counterions (Cu^{2+}, Ag^+, Cs^+, Me_4N^+, $TDAE^{2+}$) that could stabilize the trifluoromethylthiolate anion.

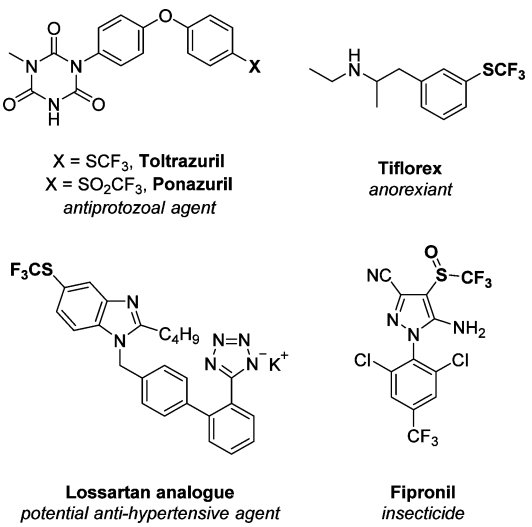


Figure 1. Examples of biologically active compounds containing aromatic SO_nCF_3 (n = 0, 1, 2).

Initially, the chemistry of these reagents was limited to aryl halides bearing multiple electron-withdrawing moieties; however, in recent years, the incorporation of chelating ligands or transition metal complexes has extended the reactivity of trifluoromethylthiolating reagents to substrates bearing electron-donating groups as well as sensitive functional groups.[15] Notwithstanding these significant advances, nucleophilic trifluoromethylthiolation protocols include high reaction temperatures and the use of expensive ligands and are limited to aryl iodides and bromides, which are typically more costly and less commercially available than the analogous chlorides.

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Scheme 1. Transition-Metal-Mediated Nucleophilic Trifluoromethylthiolation of Aryl Halides

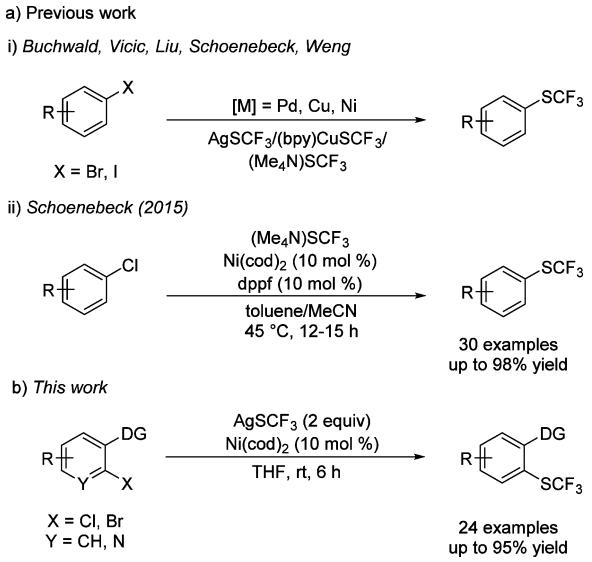
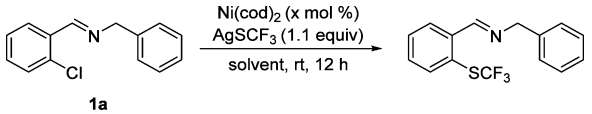


Table 1. Screening Solvent and Catalyst Loading for the Trifluoromethylthiolation of 1a



1a

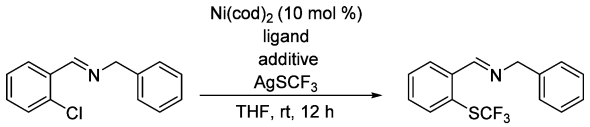
entry	$Ni(cod)_2$ (mol %)	solvent	conversion (%)[a]
1	–	THF	0
2	5	THF	13
3	10	THF	37
4	20	THF	43
5	10	DME	30
6	10	dioxane	12
7	10	MeCN	1

[a]All reactions were performed on a 0.1 mmol scale. Percentages represent conversion based upon the ratio of the imine proton resonances between the product and reactant using ^{1}H NMR spectroscopy and are an average of 2 runs.

Realizing the constraints of these reported methods and inspired by our previous work on *ortho*-selective C−F activation and cross-coupling using nickel,[16] we anticipated that the judicious choice of a directing group would permit the establishment of a new nucleophilic trifluoromethylthiolation protocol that can be extended to aryl chlorides under mild reaction conditions. While the *ortho*-directing strategy has been successful in the trifluoromethylthiolation of arenes via Csp^2−H functionalization, the protocols demand high reaction temperatures and the use of toxic gases.[17] Schoenebeck and co-workers recently reported the first nucleophilic trifluoromethylthiolation of aryl chlorides, without the need for a directing group.[18] This protocol uses $Ni(cod)_2$, $(Me_4N)SCF_3$, and dppf as the ligand at 45 °C. We have found that aryl chlorides and bromides undergo trifluoromethylthiolation at ambient temperature using a ligand- and additive-free Ni catalyst when directing groups are used. We anticipate that our studies will be of particular use when additives, ligands, or higher temperatures are not tolerated.

We initiated our investigation by examining the catalytic activity of $Ni(cod)_2$ toward the reaction between $AgSCF_3$ and *N*-benzyl-1-(2-chlorophenyl)methanimine (**1a**) in different solvents at room temperature (Table 1). $AgSCF_3$ is the primary precursor to several other trifluoromethylthiolating reagents and was chosen as the nucleophile due to its ease of access and stability. Evaluation of product conversion in different solvents revealed THF to be the best solvent for our catalytic system. Aryl trifluoromethylthiolation was not observed in the absence of $Ni(cod)_2$ or in the presence of a Ni(II) precatalyst, suggesting that the catalytic cycle is accessed via a Ni(0) catalytic species. A catalyst loading of 10 mol % (Table 1, entry 3) was considered to be the most suitable despite the highest product conversion with 20 mol % $Ni(cod)_2$ (entry 4), due to an unidentifiable fluorine-containing species that was detected at high $Ni(cod)_2$ loading.

Table 2. Optimization of Additive, Ligand, and $AgSCF_3$ Loading for the Trifluoromethylthiolation of 1a



1a

entry	$AgSCF_3$ (equiv)	additive (1.1 equiv)	ligand	conversion (%)[a]
1	1.1	KI	–	0
2	1.1	KBr	–	12
3	1.1	KCl	–	15
4	1.1	$(Me_4N)I$	–	2
5	1.1	$(Me_4N)Br$	–	14
6	1.1	$(Me_4N)Cl$	–	26
7	1.1	$(i\text{-}Pr_4N)PF_6$	–	34
8	1.1	$(n\text{-}Bu_4N)PF_6$	–	50
9	1.1	$(n\text{-}Bu_4N)PF_6$	neocuproine	4
10	1.1	$(n\text{-}Bu_4N)PF_6$	phenanthroline	12
11	1.1	$(n\text{-}Bu_4N)PF_6$	bpy	21
12	1.1	$(n\text{-}Bu_4N)PF_6$	SPhos	30
13	1.1	$(n\text{-}Bu_4N)PF_6$	PPh_3	32
14	1.1	$(n\text{-}Bu_4N)PF_6$	PCy_3	51
15	1.5	$(n\text{-}Bu_4N)PF_6$	–	65
16	2.0	$(n\text{-}Bu_4N)PF_6$	–	83
17	2.0	$(n\text{-}Bu_4N)PF_6$[b]	–	84
18	2.0	–	–	86

[a]All reactions were performed on a 0.1 mmol scale. Percentages represent conversion based upon the ratio of the imine proton resonances between the product and reactant using ^{1}H NMR spectroscopy and are an average of 2 runs. [b]1.5 equiv of $(n\text{-}Bu_4N)PF_6$ was used.

Next, we were prompted to explore a variety of ligands and additives, which have been shown to improve the reaction yield, presumably by enhancing the activity of the catalyst and/or the trifluoromethylthiolating reagent (Table 2).

Despite literature precedence for improved yields with the addition of halide salts, there was no observable effect under our conditions (Table 2, entries 1−6). However, the yield increased to 50% upon the addition of $n\text{-}Bu_4PF_6$, which possibly aids in solubilizing the active trifluoromethylthiolating species (entry 8). Notably, the addition of both $n\text{-}Bu_4PF_6$ and bidentate nitrogen-based ligands decreased the yield considerably (entries 9−11). Phosphine-based ligands fared slightly better, but offered no significant improvement than the absence of any ligand (entries 12−14). Increasing the amount of $AgSCF_3$ from 1.1 to 2.0 equiv improved the yield to a respectable 83% (entries 8, 15, and 16). Notably, we discovered that the yields of the trifluoromethylthiolated product were independent of the additive or ligand

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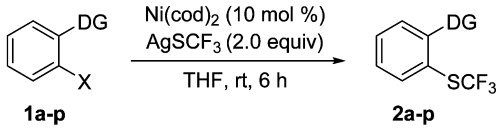
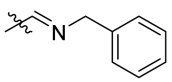
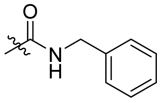
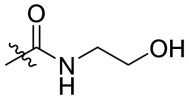
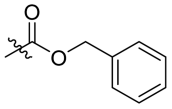
Table 3. Influence of Directing Groups in Ni-Catalyzed Trifluoromethylthiolation Using $AgSCF_3$[a]



1a-p **2a-p**

DG = directing group
X = Cl, Br

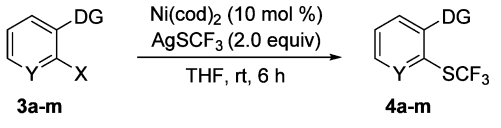
entry	directing group	compound	yield (%)
1		**2a** (X = Cl) **2b** (X = Br)	72 80
2		**2c** (X = Cl) **2d** (X = Br)	74 90
3		**2e** (X = Cl)	60
4		**2f** (X = Cl) **2g** (X = Br)	<5[b] <20[b]
5		**2h** (X = Cl) **2i** (X = Br)	70 95
6		**2j** (X = Cl) **2k** (X = Br)	59 84
7		**2l** (X = Cl) **2m** (X = Br)	64 73
8		**2n** (X = Cl)	N/R
9		**2o** (X = Br)	N/R
10		**2p** (X = Br)	N/R

[a]Isolated yield was based on the average of two trials on a 0.20 mmol scale. For imine directing substrates, the isolated yield is the yield of the aldehyde upon hydrolysis. [b]Yield was determined by ^{19}F NMR spectroscopy; 3-fluoronitrobenzene was used as an internal standard. The delay time for ^{19}F nuclei was set at 18 s. [c]N/R denotes that no reaction occurred.

(entries 16−18). By monitoring reaction progress via ^1H NMR spectroscopy, we observed complete product formation within 6 h, and henceforth all reactions were halted after 6 h.

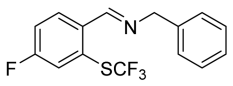
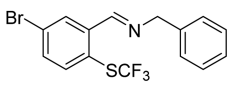
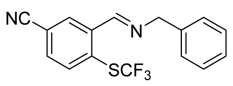
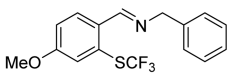
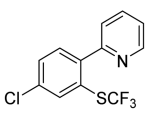
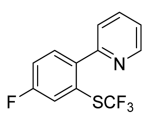
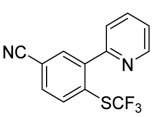
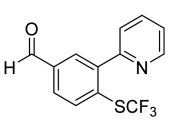
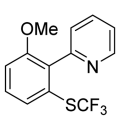
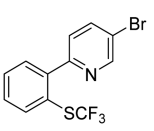
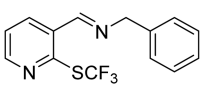
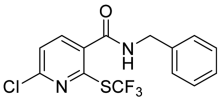
Sequentially, we explored a variety of directing groups for catalytic trifluoromethylthiolation of aryl chlorides and bromides

Table 4. Substrate Scope of Aryl and *N*-Heteroaryl Halides with Imine, Pyridyl, and Amide Directing Groups[a]



3a-m **4a-m**

DG = directing group
X = Cl, Br
Y = CH, N

entry	product	compound	yield (%)
1		**4a** (X = Cl)	65
2		**4b** (X = Cl)	50[b]
3		**4c** (X = Cl)	65
4		**4d** (X = Cl)	40
5		**4e** (X = Cl)	73
6		**4f** (X = Cl)	60
7		**4g** (X = Cl)	71
8		**4h** (X = Cl)	87
9		**4i** (X = Cl)	69
10		**4j** (X = Cl)	80
11		**4k** (X = Cl) **4l** (X = Br)	81 80
12		**4m** (X = Cl)	43

[a]Isolated yield was based on the average of two trials on a 0.20 mmol scale. For imine directing substrates, the isolated yield is the yield of the aldehyde upon hydrolysis. [b]Yield was determined by ^1H NMR spectroscopy due to coelution of product and starting material.

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(Table 3). Moderate to excellent yields of trifluoromethylthiolated products were observed with a variety of directing groups bearing an *ortho*-nitrogen including imine, pyridyl, pyrimidyl, amide, and oxazoline directing groups. In stark contrast, esters and aldehydes were ineffective as directing groups, presumably due to their weaker coordination to Ni.

Acidic groups (Table 3, entries 4 and 6) were tolerated, but only to a certain extent. In the absence of any directing group (entry 10), no product was obtained under the established conditions, even for aryl bromides, emphasizing the need for a directing group under mild conditions. Moreover, such nitrogen-based directing groups are readily amenable to further synthetic manipulation and are also common structural motifs in bioactive compounds. Notably, although Ni(0) complexes are known to activate Csp^2–H and Csp^2–S bonds, we did not observe any side products or product decomposition during the reaction.

Encouraged by our results, we sought to determine the functional group compatibility of the catalytic system. Various aryl chlorides containing potentially reactive functional groups were tested (Table 4). We were pleased to observe that the method is highly selective for substituting *ortho*-chlorides, even in the presence of other halides (entries 1, 2, 5, 6, 10, and 12). The method can also be expanded toward nitrogen-containing heterocycles, with comparable yields observed for 2-chloro- and 2-bromonicotinaldehyde (entry 11) and moderate yields for 2-chloronicotinamide (entry 12).

In summary, we have established a simple protocol for the *ortho*-selective trifluoromethylthiolation of aryl chlorides and bromides using $Ni(cod)_2$ and $AgSCF_3$ under mild reaction conditions, in the absence of any ligand or additive. A range of aryl and heteroaryl halides were converted to the corresponding trifluoromethylaryl sulfides in moderate to excellent yields. Mechanistic investigations, along with the development of a catalytic system that does not require a directing group to activate aryl chlorides selectively, are currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02689.

Full experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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