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Nickel-Catalyzed Synthesis of Aryl Trifluoromethyl Sulfides at Room Temperature

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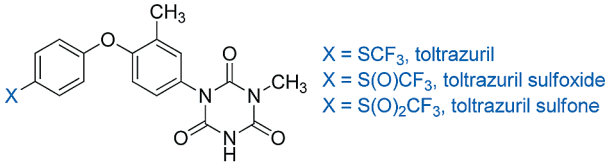
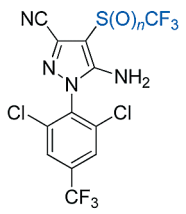
Supporting Information

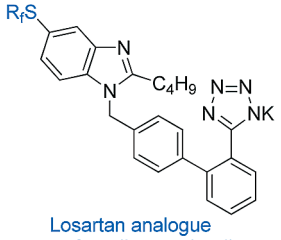
ABSTRACT: Inexpensive nickel–bipyridine complexes were found to be active for the trifluoromethylthiolation of aryl iodides and aryl bromides at room temperature using the convenient $[NMe_4][SCF_3]$ reagent.

The broad-spectrum anticoccidial and antiprotozoal activities of toltrazuril and its sulfoxide and sulfone metabolites[1] and the broad-spectrum insecticide activity of

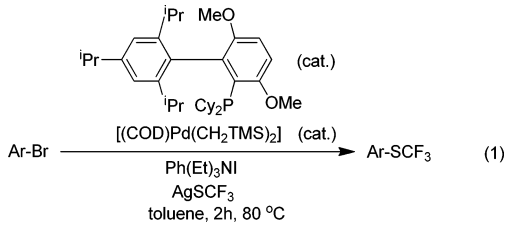




insecticides
(n = 1, Fipronil)



Losartan analogue
(treatment of cardiovascular disease)

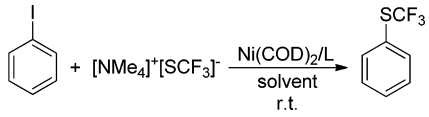


Fipronil have played major roles in rendering the SCF_3 group a privileged functionality that is prominent in the agrochemical and pharmaceutical patent literature. A large number of medicinally active compounds bearing SR_f groups (R_f = perfluoroalkyl) have now been developed, such as the hypertensive agents based on Losartan analogues.[2] This trend of incorporating the SCF_3 pharmacophore in lead compounds is expected to grow as the extremely large Hansch lipophilicity parameter (π = 1.44)[3] for its size makes the SCF_3 group appealing for the design of new molecules capable of crossing lipid membranes.[2]

Novel methods for preparing aryl–SCF_3 molecules from a variety of precursors exist,[2] but unfortunately, the simple and direct attachment of a SCF_3 group to aryl halide substrates has historically been generally limited to electron-poor arenes.[4−7] Although much progress has been made in recent years in metal-catalyzed thioetherification reactions,[8] many of these methods for forming new C_{aryl}–S bonds using aryl halide substrates fail when the nucleophile is trifluoromethyl thiolate.

The state-of-the-art method of incorporating a SCF_3 group into unactivated or electron-rich aryl halides is outlined in eq 1. Buchwald recently found that a wide range of aryl bromides could be converted into aryl trifluoromethyl sulfides through a palladium-catalyzed process employing the hindered BrettPhos ligand.[9] While this method leads to high yields of aryl trifluoromethyl sulfides from aryl iodides and bromides, the combined use of an expensive ligand, an expensive palladium salt, a quaternary amine additive, and a stoichiometric amount of an expensive silver SCF_3 derivative makes such a reaction unattractive for larg-scale commercial use.

Table 1. Conditions for Reaction Optimization[a]



entry	mol % $Ni(COD)_2$	ligand (mol %)	solvent	% yield
1	5	dmbpy (10)	THF	19
2	10	dmbpy (10)	THF	50
3[b]	10	dmbpy (10)	THF	47
4	10	dmbpy (20)	THF	62
5	15	dmbpy (30)	THF	84
6[c]	**15**	**dmbpy (30)**	**THF**	**96**
7	15	dmbpy (30)	toluene	12
8	15	dmbpy (30)	dioxane	25
9	15	dmbpy (30)	DME	70
10	15	bpy (30)	THF	72
11	15	dtbpy (30)	THF	82
12[c]	**15**	**dtbpy (30)**	**THF**	**95**
13	15	phen (30)	THF	2
14	15	terpyridine (30)	THF	0
15	15	none	THF	32
16	0	none	THF	0

[a]All of the reactions were run on a 0.1 mmol scale in 2 mL of solvent for 22 h. The PhI:$[NMe_4][SCF_3]$ molar ratio was 1:1. The yields of $PhSCF_3$ were determined by ^{19}F NMR analysis using trifluoromethylbenzene as an internal standard. [b]The reaction was conducted at 60 °C. [c]1.2 equiv of $[NMe_4][SCF_3]$ was employed in this reaction.

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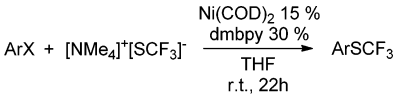
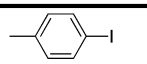
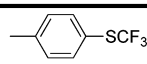
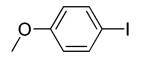
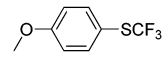
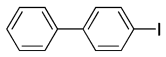
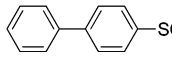
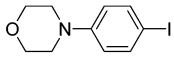
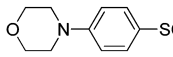
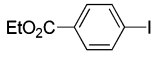
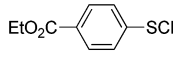
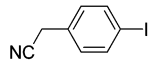
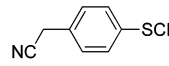
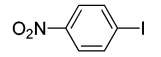
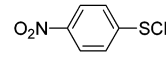
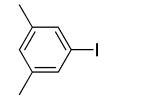
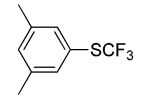
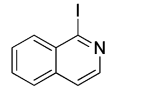
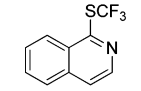
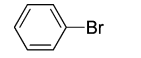
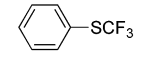
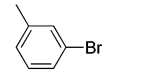
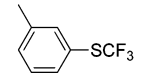
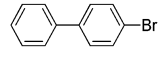
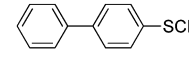
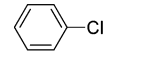
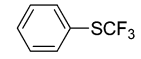
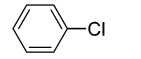
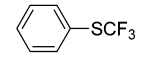
Table 2. Exploration of Substrate Scope[a,b]



Entry	ArX	Ar-SCF_3	% Yield
1			90
2			90 (89)
3			92 (92)
4			91 (88)
5			45
6			47
7[c]			0
8			83 (77)
9			55
10[d]			65
11			37
12			64
13[d]			0
14[e]			0

[a]All of the reactions were run on a 0.1 mmol scale in 2 mL of solvent, except entries 9 and 10. The ArX:$[NMe_4][SCF_3]$ molar ratio was 1:1.2. The yields of $ArSCF_3$ were determined by ^{19}F NMR analysis using trifluoromethylbenzene as an internal standard. [b]Isolated yields for reactions run on a 0.2 mmol scale in 4 mL of THF are shown in parentheses. [c]The reaction was conducted at r.t. and at 60 °C. Neither run afforded product. [d]Addition of NaI or KI in these reactions resulted in no formation of $ArSCF_3$. [e]The reaction was conducted under solvent-free conditions, and 60 equiv of PhCl was employed. TMEDA was also investigated as a ligand, but same result was found.

The employment of $AgSCF_3$ in the protocol outlined in eq 1 was necessitated by the fact that many convenient SCF_3 salts are thermally unstable. Important work by Clark suggested that the cheaper and more soluble $[NMe_4][SCF_3]$ reagent decomposes at low temperatures (reportedly even at 0 °C) in acetonitrile.[7] Tyrra and Naumann, however, noted that the thermal instability of $[NMe_4][SCF_3]$ may be related to methods of preparation.[10] We found that in our hands, $[NMe_4][SCF_3]$ persists in dry nonprotic solvents such as THF at temperatures up to 60 °C. However, in cross-coupling screens, the reagent was found to be quite sensitive to transition metals and often readily decomposed before any appreciable couplings were observed.

The apparent constraint that any transition-metal-catalyzed method for preparing aryl trifluoromethyl sulfides using the less expensive SCF_3 salts must be realized under extremely mild conditions led us to focus our attention on nickel. The bipyridine nickel system, in particular, became an attractive starting point because the low-valent [(bpy)Ni] fragment is known to activate aryl chlorides, aryl bromides, and aryl iodides at room temperature,[11] producing intermediates that are known to be active in cross-coupling catalysis.[12]

Table 1 highlights selected examples of our initial screens and follow-up optimizations. The highly soluble bipyridine derivatives 4,4′-dimethoxybipyridine (dmbpy) and 4,4′-di-*tert*-butylbipyridine (dtbpy) afforded product in nearly quantitative yields (Table 1, entries 6 and 12). The catalyst loadings were relatively high at 15%, but these loadings are mitigated by the inexpensive combination of all the reagents employed in the reaction mixture. The more soluble bipyridine ligands outperformed unsubstituted bipyridine (Table 1, entry 10), affording over 12% higher yields. Other polypyridine architectures such as 1,10-phenanthroline (phen; Table 1, entry 13) and 2,2′:6′,2″-terpyridine (Table 1, entry 14) were ineffective and gave yields lower than $Ni(COD)_2$ alone (Table 1, entry 15).

Table 2 shows that the nickel catalyst can be used to incorporate the SCF_3 functionality effectively in a variety of aryl halides. Interestingly, the present system works better for electron-rich aryl halides than it does for electron-poor ones (Table 2, entries 1−7). This reactivity complements the chemistry exhibited by copper[4,5] and silver,[6] which are known to be more active toward the trifluoromethylthiolation of electron-poor arenes. Remarkably, successful perfluorothioetherification reactions were observed even for aryl bromides at room temperature, albeit in slightly lower yields than for the aryl iodides (Table 2, entries 10−12). Aryl chlorides were unreactive toward the nickel-catalyzed process. Aryl chlorides were also shown to be unreactive in the Buchwald system.[9] The result in Table 1, entry 15 demonstrates that other ligands besides diimines may promote reactivity, and we are currently investigating which ligands show promise for aryl chloride trifluoromethylthiolations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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