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# Formation of C–SCF$_3$ Bonds through Direct Trifluoromethylthiolation[**]

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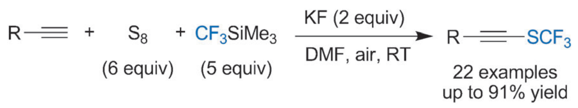
homogeneous catalysis · cross-coupling · C–S coupling · fluorine · trifluoromethylthiolation

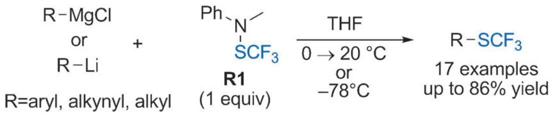
For a long time, the SCF$_3$ moiety has attracted the interest of chemists because of its intrinsic properties, including its high lipophilicity.[1] However, until recently, the direct introduction of the SCF$_3$ group into organic molecules has been poorly investigated, favoring indirect strategies, including the trifluoromethylation of sulfur compounds or the formation of a CF$_3$ moiety from a precursor group that was already present in the molecule by halogen–fluorine exchange reactions.[2] The development of new methods for the formation of C–SCF$_3$ bonds has very recently attracted the interest of several research groups. The most general and efficient methods for the attachment of SCF$_3$ groups to carbon centers are highlighted herein.

A transition-metal-free oxidative trifluoromethylthiolation of alkynes was presented by Qing and co-workers (Scheme 1).[3] The reaction of elemental sulfur with the Ruppert–Prakash reagent (CF$_3$SiMe$_3$) generated the "CF$_3$S$^-$" species[2f,g] in situ, and allowed the formation of the C–SCF$_3$ bond at room temperature under air. This system supplies the products with good to excellent yields and exhibits a broad tolerance toward electron-rich and electron-poor aryl acetylene derivatives.



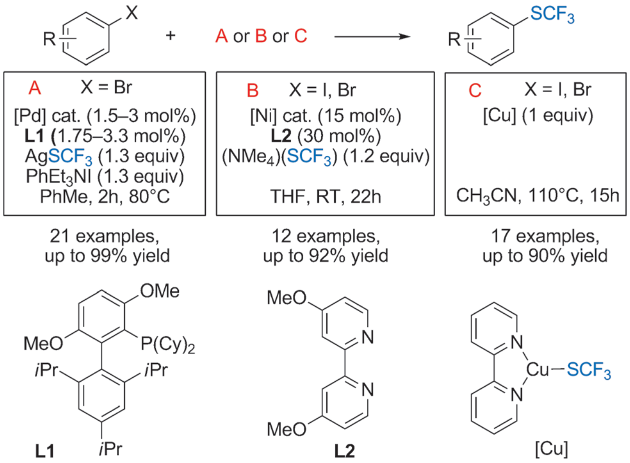
***Scheme 1.*** Trifluoromethylthiolation of alkynes.

Recently, reagent **R1**, which is an air- and moisture-stable reagent, was successfully synthesized and used for the trifluoromethylthiolation of Grignard or Lithium reagents with good to excellent yields (Scheme 2).[4]



***Scheme 2.*** Trifluoromethylthiolation with reagent **R1**.

In 2011, Buchwald and co-workers reported a general and convenient method for the trifluoromethylthiolation of aryl halides by employing the less-stable reagent AgSCF$_3$.[5] This example, once again, demonstrated the versatility of the Buchwald biaryl ligands in combination with palladium precatalysts. The developed system was tolerant toward electron-rich as well as electron-poor aryl bromides and gave the products with excellent yields (Scheme 3, A). Heterocyclic bromides were also successfully coupled, but required higher catalyst loadings. Another sensitive and less stable CF$_3$S$^-$ source ((NMe$_4$)(SCF$_3$)) was recently used by Zhang and Vicic.[6] This system uses quite a high catalyst loading based on nickel (15 mol %) and the commercially available bipyridine-type ligand **L2** (30 mol %). While moderate to



***Scheme 3.*** Transition-metal-catalyzed trifluoromethylthiolation of aryl halides.

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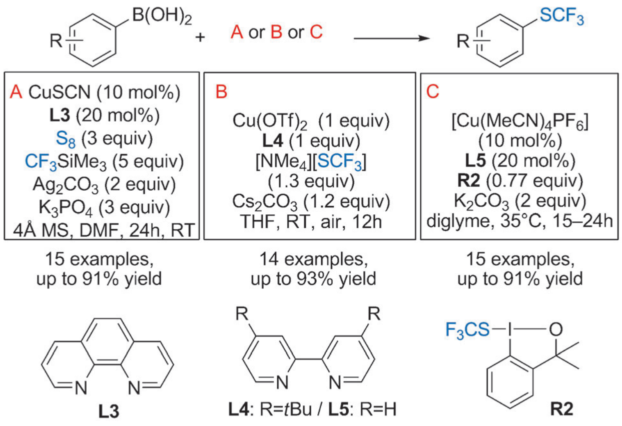
very good yields were obtained with aryl iodides and bromides as starting materials, the developed method does not exhibit a broad substrate scope. It is worth noting that the reactions were performed at room temperature (Scheme 3, B). Finally, a series of discrete and air-stable copper trifluoromethylthiolate complexes were successfully applied under stoichiometric conditions for the nucleophilic trifluoromethylthiolation of aryl iodides that were substituted with electron-donating or electron-withdrawing groups (Scheme 3, C).[7] Only one example of an aryl bromide substituted with a strong electron-withdrawing group (*o*-nitro) was presented. Heterocyclic aryl iodides and bromides also showed interesting reactivity. The reactions were carried out in acetonitrile at 110 °C.

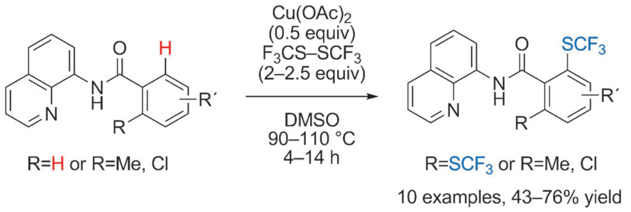
More recently, new methods have emerged based on the use of copper catalysts and aryl boronic acids as starting materials. The first oxidative trifluoromethylthiolation of an aryl boronic acid was reported by Qing and co-workers.[8] The use of the Ruppert–Prakash reagent ($CF_3SiMe_3$) in combination with sulfur ($S_8$) allowed the synthesis of $ArSCF_3$ in good to excellent yield, independent from the nature of the starting materials. The reactions were carried out with silver carbonate as oxidant in DMF at room temperature (Scheme 4, A).

The highly advantageous use of air as oxidant was successfully employed by Zhang and Vicic.[9] The corresponding products were obtained in good to excellent yields, regardless of whether the aryl or vinyl boronic derivatives were substituted with electron-withdrawing or electron-donating groups. It is worth noting that in this case stoichiometric amounts of copper and ligand (**L4**) were required (Scheme 4, B).

Finally, the group of Lu and Shen developed an air- and moisture-stable hypervalent iodine reagent (**R2**) inspired from the Togni reagent.[10] This reagent was successfully applied for the trifluoromethylthiolation of aryl and vinyl boronic derivatives with good to excellent yields at 35 °C (Scheme 4, C). Furthermore, the system showed a broad substrate scope. The novel reagent **R2** was also successfully applied to the copper-catalyzed trifluoromethylthiolation of alkynes as well as to the metal-free trifluoromethylthiolation of β-ketoesters.



***Scheme 4.*** Cu-catalyzed trifluoromethylthiolation of aryl boronic acids.



***Scheme 5.*** Trifluoromethylthiolation through the direct functionalization of C–H bonds.

Very recently, Daugulis and co-workers reported one example for a single or double trifluoromethylthiolation through the direct functionalization of C–H bonds of arenes (Scheme 5).[11] Although a high catalyst loading of the environmentally and economically friendly copper acetate was required, a good reactivity was observed with both electron-withdrawing and electron-donating groups and also heterocyclic arenes. Moreover, the catalyst system is highly tolerant toward halides (F, Cl, Br).

The new systems for trifluoromethylthiolation highlighted herein show a high potential, though several challenges need to be addressed. In the case of cross-coupling reactions, more efficient catalysts are needed with regard to turnover number and turnover frequency; a wider range of (hetero)aryl halides, especially chlorides and sulfonates, should become substrates; and finally milder reaction conditions are needed.

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