Synthetic Methods

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The Trifluoromethylating Sandmeyer Reaction: A Method for Transforming C–N into C–CF_3**

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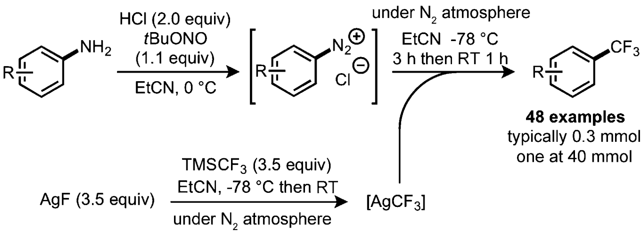
The presence of fluorine-containing substituents can impart favorable properties to organic molecules. On one hand they increase the metabolic stability of important pharmaceutical compounds, thus reducing dosing rates in patients.[1] On the other hand, they can improve switching times and broaden the working temperature ranges in LCD devices.[2] Perhaps even more critical to supporting the basic needs of an ever-growing population,[3] is the use of fluorine substituents to tune the rates and selectivities in agrochemical products,[4] thus leading to both reduced quantities of material required and increasing the reliability and yield of the desired crop per unit area of precious arable land.[5] Owing to these desirable benefits there has been a recent surge in interest to improve the range of methods available for introducing monofluoromethyl, difluoromethyl, and trifluoromethyl appendages to C, O, N, and S atoms, typically through a late-stage coupling or alkylation, and this has also necessitated the development of new reagents for permitting mild transformations.[6] With regard to coupling approaches to achieve trifluoromethylation, it has been demonstrated that C–X (halide), C–B, C–Sn, and even C–H bonds[6] make suitable substrates. Still a number of issues remain to be solved to further improve the methods, and they include reducing the cost of the fluorine reagent, reducing precious metal/ligand loadings, and increasing the generality of the processes. Towards this goal, recently, the scope of potential starting materials has been dramatically increased. The groups of Wang,[7] Gooßen,[8] and Fu[9] have reported the C–N to C–CF_3 transformation using a trifluoromethylating Sandmeyer reaction, as outlined herein.

The general approach seeks to convert an aromatic amine into the requisite diazonium salt before treatment with a suitable metal and trifluoromethyl source. Wang and co-workers reported a protocol that was successfully applied to 48 substrates. The optimized method employs *tert*-butyl nitrite (*t*BuONO) and aqueous hydrochloric acid to generate the aryl diazonium intermediates as chloride salts (as a solution in ethanonitrile). This salt was subsequently treated with 3.5 equivalents of an in situ generated solution of [$AgCF_3$], derived from mixing AgF with the Ruppert–Prakash reagent ($TMSCF_3$) at −78 °C (Scheme 1). Low temperatures were necessary to ensure good conversions and yields, which is likely a result of the relative instability of diazonium chloride salts, however diazo tetrafluoroborate salts, which are considered more stable (and typically isolable) were less reactive under these low-temperature conditions.[10] The reaction procedure tolerates electron-withdrawing and electron-donating groups, vinyl and alkynyl substituents, as well as boronic esters and silyl moieties. Perhaps the most impressive result, however, which proceeds in 83 % yield, is the installation of CF_3, *ortho* to an *i*Pr group, especially when one considers the appropriate steric A values: $CF_3 = 2.1$ kcal mol^{-1} and *i*Pr = 2.15 kcal mol^{-1} (for reference Me = 1.7 kcal mol^{-1} and Et = 1.75 kcal mol^{-1}).[11] With regards to heterocycles, 3-aminopyridine is converted in 10 % yield whereas three examples of indole and one of a benzofuran are converted in moderate to good yields (45–72 %). Mechanistic studies were conducted and strongly suggest that the reaction does not operate by a radical mechanism. The authors hypothesize instead that high-valent silver species mediate an oxidative addition, reductive elimination pathway.



Scheme 1. Sandmeyer-type trifluoromethylation approach as reported by Wang and co-workers.[7] TMS = trimethylsilyl.

Gooßen and colleagues report a copper-mediated trifluoromethylating Sandmeyer reaction. In their case however, the more stable diazonium tetrafluoroborate salts are preformed and isolated before being subjected to the trifluoromethylating conditions. The Ruppert–Prakash reagent is again used as the CF_3 source, and is premixed with copper(I) thiocyanate and cesium carbonate for 10 minutes before addition of the diazonium salt (Scheme 2). Similarly, the reaction conditions are tolerant of electron-rich, electron-poor, ester, amino, keto, carboxylate, cyano, and even iodo

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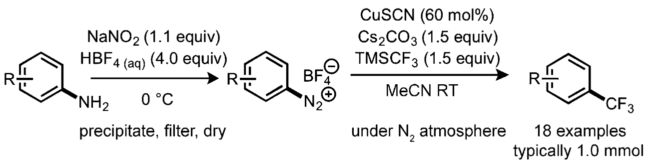
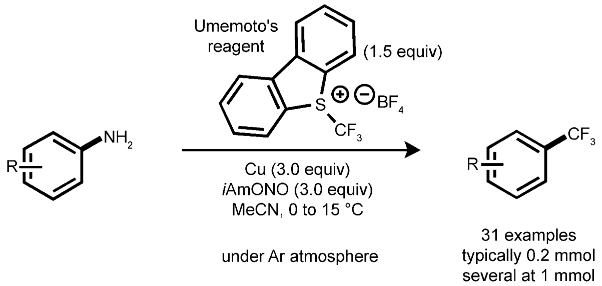


Scheme 2. Sandmeyer-type trifluoromethylation approach as reported by Gooßen and co-workers.[8]

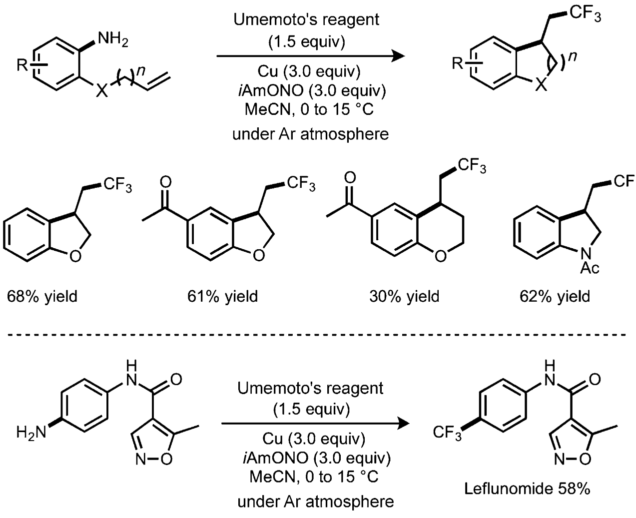
substituents. The latter being particularly interesting as it demonstrates the true complimentarity of this process to existing C–X trifluoromethylation cross-coupling methods. Four heterocyclic examples are reported, three of which are quinoline and one indole, and these provide the trifluoromethyl derivatives in moderate to good yield (46–74%). It is presumed by Gooßen et al. that the reaction proceeds by a radical process, which is in line with other Sandmeyer halogenation reactions.

The group of Fu report a copper-powder-mediated version of the reaction, thus employing Umemoto's reagent as the CF_3 source. Here isoamyl nitrite (*i*AmONO) was used to effect the in situ diazotization reaction (Scheme 3). The scope of this newly discovered process is good, and tolerates electron-donating (ether, thioether and amide), electron-withdrawing (nitro, ester, ketone, and azo), alkenyl, alkynyl, hydroxy, and bromide substituents. Transformation of C_{Ar}–N bonds into pendant C_{Ar}–CF_3 bonds was demonstrated successfully for quinolines, pyridines, and pyrazoles (a total of eight heterocyclic examples). Across the 31 (hetero)aromatic examples, reaction yields ranged from 32 to 89%.



Scheme 3. Sandmeyer-type trifluoromethylation approach as reported by Fu and co-workers.[9]

Interestingly, mechanistic studies, such as observation of the intramolecular trapping of a pendant alkene, ESR phenomena, and ^{19}F NMR data highlighting a $CuCF_3$ species, all support a radical pathway. This information was used to access a number of interesting trifluoromethylated bicyclic scaffolds by an intramolecular radical cyclization with subsequent intermolecular radical combination of trifluoromethyl and *exo*-methylene radicals (Scheme 4). Lastly, the method was applied to a new preparation of leflunomide, an antirheumatic drug (Scheme 4).



Scheme 4. Sandmeyer-type radical cyclization/trifluoromethylation and preparation of leflunomide as reported by Fu and co-workers.[9]

In conclusion, the presented methods permit a significantly broadened scope of starting substrates which can be used to introduce a CF_3 substituent. The methods show good tolerance to a range of appended functionalities and are even effective in sterically demanding instances, thus highlighting them as a useful tool for late-stage trifluoromethylation. The reported methods offer excellent complementarity to existing carbon–halide functionalization processes and are likely to permit access to compounds that were not previously available. Of the three methods, the protocol described by Fu and colleagues appears to be the most straightforward, as a one-pot operation employing reagents and solvents straight from commercial suppliers. Improvements for the future could be made both in the amount of the metal loading and the nature of the CF_3-containing reagent.

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