New reagents and catalysts for substituting organics with trifluoromethyl groups

Professor Robert H Crabtree
Yale Chemistry Department, New Haven, CT

Introduction

A selection of previous studies in this area are analyzed in detail in this article. The requirements of the pharmaceutical and agrochemical communities have led to the development of several useful techniques for synthesizing CF₃ groups. The successful strategies covered are mostly mediated by Cu or Pd, either catalytically or via organometallic intermediates.

The CF₃ sources used include CF₃SiEt₃/KF, electrophilic CF₃ sources such as Umemoto’s reagent, and even lower-cost reagents such as CF₃COOH or CF₃H. One of the most attractive syntheses generates •CF₃ radicals from t-BuOOH and CF₃SO₂Na, which can then attack a variety of substrate heterocycles at their most nucleophilic site, with reasonable selectivity. The site for reaction can be further defined by the addition of a boronic acid group to the reagent.

The CF₃ group has several attractive features—not only is it one of the most electron-drawing known, but it also confers great chemical robustness. Since it occurs in such multibillion dollar pharmaceuticals as Celebrex, Sustiva and Prozac, as well as in numerous agrochemicals and synthetic materials, improved syntheses are eagerly sought. Recent advances in organometallic chemistry and catalysis have made some of these structures more easily available.

Fluorine is an ornery element in that it inverts the properties of the rest of the molecule relative to the standard organic analogue, so syntheses that work fine for standard organics mostly fail here. Organometallics have been key contributors to improving the situation, but it is still hard to find suitable combinations of CF₃ donor reagent, catalyst and substrate for high efficiency and selectivity.

Cu and Pd are the two elements that have worked best so far, Cu being specially prized for its low cost and low toxicity. A key advance was conversion of the previous stoichiometric Cu-mediated coupling of CF₃SiEt₃/KF and ArI to give CF₃Ar into a catalytic procedure by complexing the Cu(I) catalyst 1:1 with the N,N’ chelate, phenanthroline. With 10% catalyst loading, yields of 43-99% were seen at 60°C over 24 hours. A later move to the much cheaper CF₃COOH as CF₃ donor required Ag₂O as an additive and a much higher temperature, 130°C was also needed to drive the decarboxylation. A particularly cheap reagent, CF₃H can be converted to “CuCF₃” with CuCl and t-BuOK in DMF; the resulting organometallic trifluoromethylates a number of iodoarenes stoichiometrically in good to quantitative yield (Figure 1).
Palladium coupling of RX with ArY \([X = \text{B(OH)}_2, \text{SnMe}_3 \text{ etc; \ Y = halide}]\) is normally a reliable Ar-R bond forming strategy that fails for \(R = \text{CF}_3\). This is in part because PdII-CF\(_3\) bonds are unusually strong as a result of Pd(d\(_\pi\)) to C-F(\(\sigma^*\)) \(\pi\) bonding and thus Pd\(^0\) catalysts often fail to give the required last step of the cycle, reductive elimination (RE) of the product, ArCF\(_3\). One counter to this problem is oxidation of the intermediate [LnPdAr(CF\(_3\))] \((L = \text{ancillary ligands})\) complex to Pd\(^{IV}\), expected to weaken the \(\pi\) bonding component and facilitate RE. Indeed, Sanford and coworkers identified well-defined Pd\(^{II}\) and Pd\(^{IV}\) complexes that show precisely this effect (Equation 1, bipy' = di-t-butyl-2,2'-dipyridyl).\(^5\) Liu and coworkers\(^6\) developed a catalytic version for the trifluoromethylation of indoles by this type of reaction using Phl(OAc)\(_2\) as the stoichiometric oxidant.

Another way to persuade Pd catalysis to work is to avoid the situation in equation 1 where the ligand occupies two sites. Buchwald and coworkers\(^7\) equipped Pd with ligands \((1: \text{R}_1 = \text{OMe}, \text{R}_2 = \text{R}_3 = \text{i-Pr}; \text{or R}_1 = \text{OMe}, \text{R}_2 = \text{i-PrO}, \text{R}_3 = \text{H})\) that are bulky enough to prevent the formation of a bis-ligand complex. The resulting 1:1 LPd species are not only more reactive in the ArCl oxidative addition step, but also in the RE product-forming step. With CF\(_3\)SiEt\(_3\)/KF as "CF\(_3\)" donor, ArI was not required because even the much cheaper ArCl substrates were effective partners. In dioxane at 120-140°C over 6-20 hours, good to excellent yields were seen from a variety of ArCl, although protic substrates (e.g. ROH, R\(_2\)NH) failed; Figure 2 shows a selection of products formed in this way.

Electrophilic CF\(_3\) sources are also useful in certain circumstances, e.g. Umemoto’s reagent, \(^2\) can be activated by a Pd/Cu catalyst to functionalize a variety of 2-pyridyl arenes via CH activation, directed by binding of the Pd to the pyridyl nitrogen prior to the CH activation step (Equation 2); functional group tolerance was not as wide as might have been hoped, however.\(^8\)

Metal mediation is not always required, however, as in the following radical reaction. In favorable cases, the electrophilic \(\bullet\text{CF}_3\) radical, easily generated from the cheap starting materials, t-BuOOH and CF\(_3\)SO\(_2\)Na at ambient temperature in aqueous solution, can attack with modest to good selectivity at the most nucleophilic site of a substrate heterocycle to introduce the CF\(_3\) group via a C-H activation. The products from nicotine, melatonin, caffeine, and allopurinol are illustrated as examples in Figure 3.\(^9\)

Where the desired site of reaction in the molecule has low intrinsic reactivity or where a mixture is formed, a boronic acid group can be usefully incorporated into the reagent to define the site for reaction. Sanford and coworkers\(^10\) have identified conditions that permit introduction of the CF\(_3\) group in this way (Equation 3). The Cu presumably traps the \(\bullet\text{CF}_3\) radical to suppress free radical C-H trifluoromethylation so that trifluoromethylation of the C-B bond always wins out. The procedure is insensitive to impurities, has broad functional group tolerance and operates at room temperature.
Moving to the synthesis of sp³ C-CF₃ bonds, asymmetric catalysis has been the main focus of activity. By combining an organocatalyst with Togni’s electrophilic CF₃ donor (3), Allen and MacMillan¹¹ developed an effective reaction of this type (Equation 5).

Only a few years ago, this area was little understood, but the requirements¹² of the pharmaceutical and agrochemical communities has led to the development of a wide variety of useful techniques, some with quite broad applicability. We can now look forward to better mechanistic understanding as well as more commercial applications in future.

References

Professor Robert H Crabtree

Bob Crabtree, educated at New College, Oxford with Malcolm Green, did his Ph.D. with Joseph Chatt, University of Sussex. He then spent four years in Paris with Hugh Felkin at the CNRS, Gif. At Yale since 1977, he is now Whitehead Professor.

He has been ACS and RSC organometallic chemistry awardee, Baylor Medallist, Mond lecturer, Kosolapoff awardee, Stauffer Lecturer, has chaired the ACS Inorganic Division and is the author of an organometallic textbook. Early work on catalytic alkane C-H activation and functionalization was followed by work on H² complexes, dihydrogen bonding, and catalysis for green and energy chemistry. His organometallic textbook and homogeneous hydrogenation catalyst are both widely used.

He is an American Chemical Society Fellow and a Fellow of the American Academy.