Trifluoromethylation

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Tamed Arene and Heteroarene Trifluoromethylation

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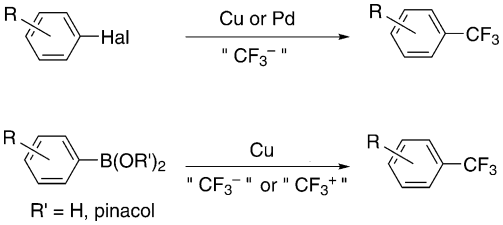
arenes · C–C coupling · C–H activation · fluorine · heterocycles

Although inorganic fluorides are abundant on Earth, nature's ability to incorporate fluorine into life science molecules is extremely poor. Indeed, fluorinated natural products represent only an infinitesimal fraction of all known fluorinated compounds. However, a considerable number of prescribed pharmaceutical agents and drug candidates contain one or more fluorine atoms. Trifluoromethylated arenes and heteroarenes are privileged structural motifs that are routinely evaluated in every new drug-discovery and -development program for fine-tuning of biological properties. Such fluorinated pharmacophores substantially improve catabolic stability, lipophilicity, and transport rate. Classic methods for rapid assembly of CF_3-substituted compounds rely almost exclusively on the commercial availability of CF_3-bearing (hetero)arenes as building blocks that are manufactured by Swarts-type reactions, which is a method without a current industrially feasible alternative. Consequently, new routes to CF_3-(hetero)arenes that are atom-economical, eco-friendly, and appropriate for late-stage functionalization are highly desirable.

In this context, we have recently witnessed an explosion in the number of methods for the late introduction of CF_3 groups into aromatic structures. Two complementary approaches have emerged. The first one is a programmable trifluoromethylation by means of cross-coupling reactions that are catalyzed or mediated by transition metals. This method requires substrate prefunctionalization with halogen or boron substituents. The main advantage of this strategy is regiospecific trifluoromethylation at positions that are not naturally reactive. The second approach bypasses the substrate prefunctionalization step by direct C–H trifluoromethylation at positions of the substrate that are inherently reactive. This permits the late-stage direct trifluoromethylation of biologically active compounds and opens a new avenue in the challenge of drug discovery. These major achievements are indissociable from the use of practical and cheap CF_3 sources, for example, fluoroform (CF_3H), CF_3SO_2Cl, or CF_3SO_2Na. This Highlight discusses the most recent findings in the field.

Since the major breakthrough discovery of the Cu-catalyzed trifluoromethylation of aryl iodides with CF_3SiEt_3 by Amii and co-workers,[1a] considerable advancement has been made in the development of catalytic procedures. Recent accomplishments in the field include: 1) a diversification in sources of CF_3-transferring nucleophilic reagents, such as CF_3SiMe_3,[2] potassium trimethoxytrifluoromethylborate ($CF_3B(OMe)_3K$),[3] as well as the much cheaper CF_3CO_2Na,[4] fluoral hemiaminal,[1b] and CF_3H[5] (Scheme 1, top); 2) the successful Pd^0/Pd^{II} catalyzed cross-coupling



Scheme 1. Programmed trifluoromethylation with prefunctionalized substrates, described by the groups of Amii,[1] Huang,[2] Gooßen,[3] Duan,[4] Daugulis,[5] Buchwald,[6a] and Samant[6b] (top) and of Buchwald,[8a] Qing,[8b,d] and Gooßen[8c] (CF_3^-), and Liu,[9a] Shen,[9b,c] and Xiao[9d,e] (CF_3^+; bottom). Hal = halogen.

trifluoromethylation of aryl chlorides and bromides assisted by bulky phosphorus ligands,[6] thus overcoming the high activation barrier for the reductive elimination step[7] (Scheme 1, top); 3) a broadening of the substrate scope to include widely decorated (hetero)aryl chlorides and bromides,[6] as well as boronic acids and esters.[8,9] The boron derivatives react either by oxidative Chan–Lam-type coupling with nucleophilic CF_3 reagents (CF_3^-)[8] or in the presence of electrophilic CF_3 sources (CF_3^+) such as 3,3-dimethyl-1-trifluoromethyl-1,2-benziodoxole (Togni reagent) or trifluoromethyldibenzothiophenium tetrafluoroborate (Umemoto reagent; Scheme 1, bottom).[9]

In addition to catalytic trifluoromethylations, further discoveries that illustrate the ability of ligands to stabilize Cu^ICF_3 complexes provide synthetic access to well-defined, isolable reagents, that is, N-heterocyclic carbene complexes of copper, (NHC)$CuCF_3$, phosphine- or phenanthroline-stabilized copper reagents, [$(Ph_3P)_3CuCF_3$], [(phen)(PPh_3)-$CuCF_3$], and [(phen)$CuCF_3$] ("Trifluoromethylator"; Scheme 2, top).[10] These trifluoromethylating reagents are all prepared from the costly CF_3SiMe_3 reagent and are used as such for the trifluoromethylation of (hetero)arene halides or boron derivatives. CF_3H is clearly the best feedstock in terms of atom economy; it is cheap and readily available as a side-product of Teflon manufacturing. With this in mind, Grushin

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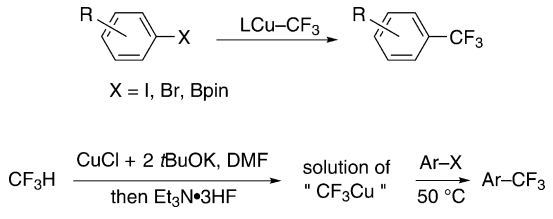
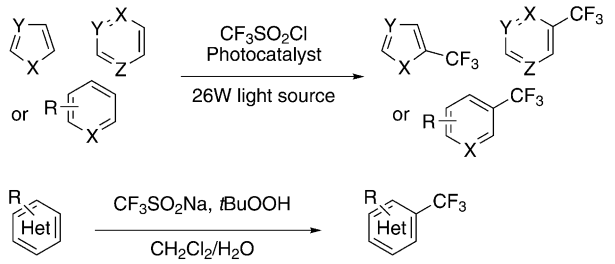


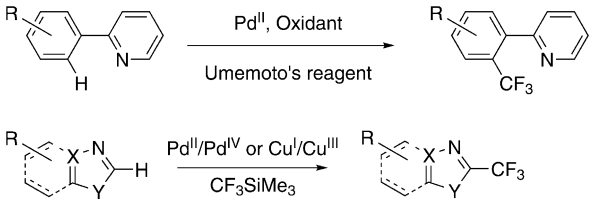
Scheme 2. Trifluoromethylation of arenes with well-defined sources of $CuCF_3$, described by the groups of Vicic,[10a] Grushin,[10b] and Hartwig,[10c,d] (top) and of Grushin[11] (bottom). Bpin = pinacolylboryl.



Scheme 4. C–H radical trifluoromethylation of (hetero)arenes according to Nagib and MacMillan[14] (top) and Baran et al.[15] (bottom).

and co-workers described the direct cupration of CF_3H with a combination of CuCl and *t*BuOK in dimethylformamide (DMF). The stabilized $CuCF_3$ solution was used in a series of trifluoromethylation reactions. Noteworthy, no additional ligand (e.g. phenanthroline) is required and C_2F_5 side-products are not detected (Scheme 2, bottom).[11]

Although powerful methods have been developed, programmed trifluoromethylation suffers from the need for preactivated substrates. However, for some substrates, prefunctionalization is not required and site-selective C–H trifluoromethylation is now possible. Yu and co-workers described a remarkable C–H activation process in the Pd-catalyzed *ortho*-trifluoromethylation of 2-pyridyl arenes with the electrophilic Umemoto reagent (Scheme 3, top).[12] Liu and co-workers and Chu and Qing, respectively, reported the Pd- and Cu-catalyzed oxidative trifluoromethylation of indoles at the C2 position and of heteroarenes that contain an acidic C–H bond by direct C–H activation (Scheme 3, bottom).[13]



Scheme 3. C–H trifluoromethylation, described by the groups of Yu[12] (top) and Liu[13a] and Qing[13b] (bottom).

A recurring problem is that most of the CF_3 sources are expensive and not favorable for industrial applications. The groups of MacMillan and Baran tackled this drawback guided by the same leitmotif: late trifluoromethylations with practical and cheap trifluoromethyl sources. They developed a very promising alternative called "innate trifluoromethylation", which consists of the direct functionalization of the inherently reactive positions of the substrates. Nagib and MacMillan described a mild, visible-light-induced C–H trifluoromethylation of nonfunctionalized (hetero)arenes by using CF_3SO_2Cl, a practical, accessible, and cheap source of CF_3 radicals, in the presence of a Ru- or Ir-based photocatalyst (Scheme 4, top).[14] The electron-deficient CF_3 radical that is generated from the photoredox catalytic cycle selectively reacts at the most electron-rich position of the (hetero)arene. A myriad of 5- and 6-membered heterocycles as well as arenes that contain a wide range of ring substituents have been regioselectively functionalized at 23 °C.

Another remarkable advance was made by Baran and co-workers by means of CF_3 radicals that are generated from CF_3SO_2Na, a benchtop-stable and inexpensive solid, in the presence of peroxides as radical initiators without the use of a metal (Scheme 4, bottom).[15] Different classes of heterocycles have been used in the reaction and the method is tolerant of many functional groups. Mixtures of regioisomers are often obtained and solvent-mediated regiocontrol operates, which allows the innate substrate reactivity to be tuned. These two radical trifluoromethylation approaches are extremely beneficial for medicinal chemistry because they maximize chemical diversity at the last stage of drug synthesis. The versatility of these approaches was illustrated by subjecting common pharmaceutical agents to the trifluoromethylation protocol. Examples include the direct installation of a CF_3 group into the cholesterol-lowering drug Lipitor (Atorvastatin),[14] the anti-inflammatory Ibuprofen,[14] the anaesthetic and antiarrhythmic Lidocaine,[14] and Chantix (varenicline), which is prescribed to treat smoking addiction.[15] Even though some of these transformations are nonselective and require the separation of regioisomers, this method gives straightforward access to drug analogues and is a very promising example of late-stage functionalization.

Research in the area of (hetero)arene trifluoromethylation has strongly intensified. The major achievements in late-stage installation of a CF_3 group into advanced intermediates and current pharmaceuticals should dramatically accelerate the discovery of new drugs. Robust protocols as well as eco-friendly and low-cost CF_3 sources should allow a rapid transfer of the technology to the industrial sector. However, high-yielding and site-selective direct trifluoromethylation, as well as better prediction of reactivity remain challenging and merit further investigation.

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