Trifluoromethylation

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Fluoroform-Derived $CuCF_3$ for Low-Cost, Simple, Efficient, and Safe Trifluoromethylation of Aryl Boronic Acids in Air**

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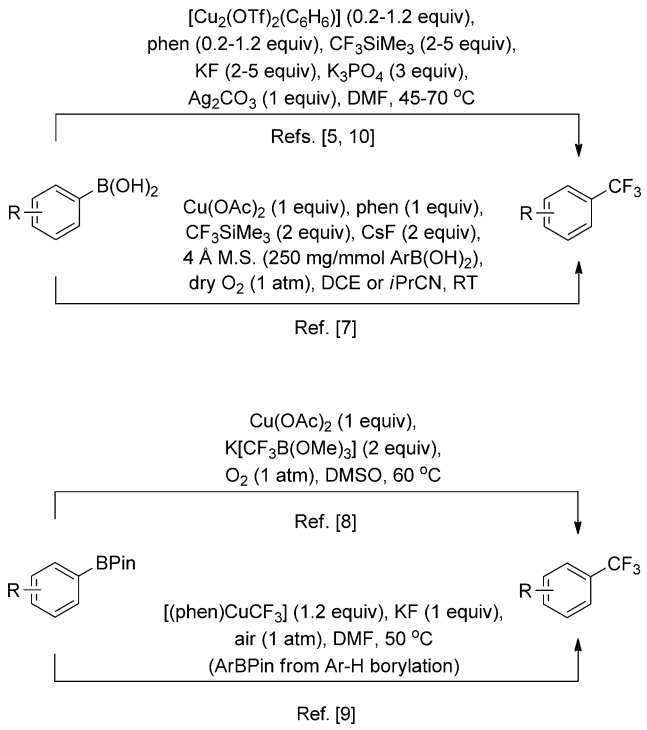
Aromatic compounds bearing one or more CF_3 groups on the ring are important intermediates and building blocks for the synthesis of numerous modern pharmaceuticals, highly efficient crop-protection agents, and specialty materials.[1] Trifluoromethylated aromatic compounds are currently manufactured by exhaustive chlorination of a methyl group on the aromatic ring, followed by the Swarts reaction of the resultant $ArCCl_3$ with HF.[2] This process shows low functional-group tolerance and is ecologically unfriendly as it involves aggressive and hazardous materials (Cl_2, HF) and generates large quantities of chlorine waste (HCl).

A broader-scope, benign alternative to the Swarts reaction-based process is the direct introduction of a CF_3 group into the desired position on the aromatic ring.[3] While aromatic electrophiles have been widely used for this purpose since the original pioneering work by McLoughlin and Thrower in the 1960s,[4] nucelophilic aromatic coupling partners are seldom employed in the synthesis of trifluoromethylarenes. In 2010, Chu and Qing[5] reported the first example of oxidative trifluoromethylation of aryl boronic acids with Ruppert's reagent CF_3SiMe_3 using the Chan–Lam[6] methodology. The reaction smoothly occurred in high yield for a variety of aryl boronic acids in the presence of semicatalytic quantities of $[CuOTf]_2{\cdot}C_6H_6$, 1,10-phenanthroline (phen), CF_3SiMe_3 (5 equiv), KF, K_3PO_4, and Ag_2CO_3 as an oxidant in DMF at 45 °C. Almost simultaneously, Senecal, Parsons, and Buchwald[7] described a similar, yet more economical method, using only a twofold excess of CF_3SiMe_3 and dry O_2 in place of the silver salt. Most recently, aryl boronic acids and aryl boronates were oxidatively trifluoromethylated with $K[CF_3B(OMe)_3]/Cu(OAc)_2$,[8] with $[(phen)CuCF_3]$,[9] and also using CF_3SiMe_3 in the presence of catalytic quantities of Cu/phen.[10] A summary of these reactions is presented in Scheme 1. Alternatively, aryl boronic acids and boronates can be trifluoromethylated with electrophilic CF_3 sources, such as sulfonium salts[11,12] and Togni's reagent,[13–15] in the absence of an oxidant and in the presence of catalytic amounts of Cu and a ligand.

The aforementioned methods[5,7–14] offer good opportunities for the synthesis of benzotrifluorides for medicinal chemistry and agrochemical discovery research. Applications on a larger scale are unlikely, however, despite the fact that aryl boronic acids are manufactured and used in significant quantities in a variety of industrial processes.[16] Let alone the necessity to use silver salts,[5,10] molecular sieves,[7] pure oxygen,[7,8] phen,[5,7,9,10] and other ligands,[11] the key problem with scaling up all of the reported trifluoromethylation reactions of boronic acids and their derivatives is the high cost of the CF_3 sources involved. The electrophilic reagents used for this transformation[11–14] are particularly expensive. All other reactions employ, directly or indirectly,[17] Ruppert's reagent, which is incomparably cheaper but still cost-prohibitive for applications on a larger scale.



Scheme 1. Reported oxidative trifluoromethylation reactions of aryl boronic acids and boronates (DCE = 1,2-dichloroethane, M.S. = molecular sieves; Pin = pinacolyl).

A novel reaction of direct cupration of low-cost fluoroform (CHF_3) has recently been discovered in our laboratories (Scheme 2).[18] This reaction employs only inexpensive reagents (CuCl, *t*BuOK) and cleanly occurs at ambient temperature to furnish $CuCF_3$ in up to over 90% yield. While these fluoroform-derived $CuCF_3$ reagents have already been shown[18] to efficiently trifluoromethylate various electrophiles, reactions with nucleophilic substrates, such as aryl

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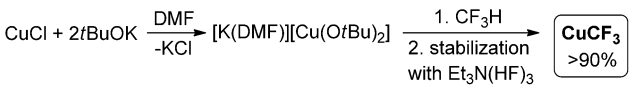
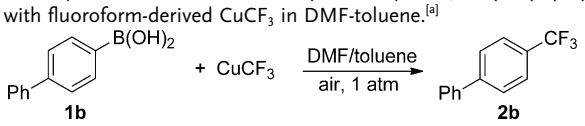


Scheme 2. Direct synthesis of $CuCF_3$ from fluoroform.[18]

boronic acids, have not been reported. Moreover, considering the available literature data,[5,7–14] it was impossible to predict whether the "ligandless" fluoroform-derived $CuCF_3$ would efficiently trifluoromethylate aryl boronic acids in air, the cheapest and most readily available oxidant, and in the absence of costly ligands and promoters/additives.

It was encouraging to find that our $Et_3N{\cdot}3\,HF$-stabilized[19] $CuCF_3$ reagent[18] in DMF reacted with $PhB(OH)_2$ (**1a**) in air to give $PhCF_3$ (**2a**) in up to 99% yield. It was noticed however, that when the reaction was run in an open vessel at $\geq 50\,°C$, the volatile product could be partially lost because of evaporation. Therefore, for optimization studies (Table 1), **1a** was replaced with its less-volatile analogue *p*-$PhC_6H_4B(OH)_2$ (**1b**) to eliminate the evaporation problem and thus ensure accurate yield determination. First it was found that additional purification[20] of **1b** did not affect the yield of **2b**; hence in all subsequent experiments, **1b** was used as received from the commercial source. The reaction was originally carried out by adding, at vigorous stirring, a $CuCF_3$ solution in DMF (0.36–0.41 mol L^{-1}) to **1b** in air at room temperature. As the trifluoromethylation proceeded, the reaction mixture turned viscous. Pre-mixing **1b** with toluene prior to $CuCF_3$ addition was found to have no effect on the yield and selectivity (Table 1, entries 3 and 4), yet facilitated monitoring the reaction by TLC. No bibenzyl was produced in the presence of toluene, which ruled out involvement of free radicals. Although with 1.2 and 1.5 equivalents of $CuCF_3$ **2b** was produced in high yields (89% and 93%, respectively; Table 1, entries 1 and 2), the conversion of **1b** was incomplete. When 2 equivalents of $CuCF_3$ were used, full conversion was achieved (entry 3). Raising the temperature speeded up the reaction but lowered its selectivity. While at room temperature biphenyl, the side-product from deborylation of **1b** (see below), was formed in only small amounts (1–2%), at 35 and 50 °C the yield of Ph_2 was 7% and 11%, respectively (entries 5 and 6). Full details of the optimization studies are provided in the Supporting Information.

Table 1: Optimization of trifluoromethylation of *p*-$PhC_6H_4B(OH)_2$ (**1b**) in air with fluoroform-derived $CuCF_3$ in DMF-toluene.[a]

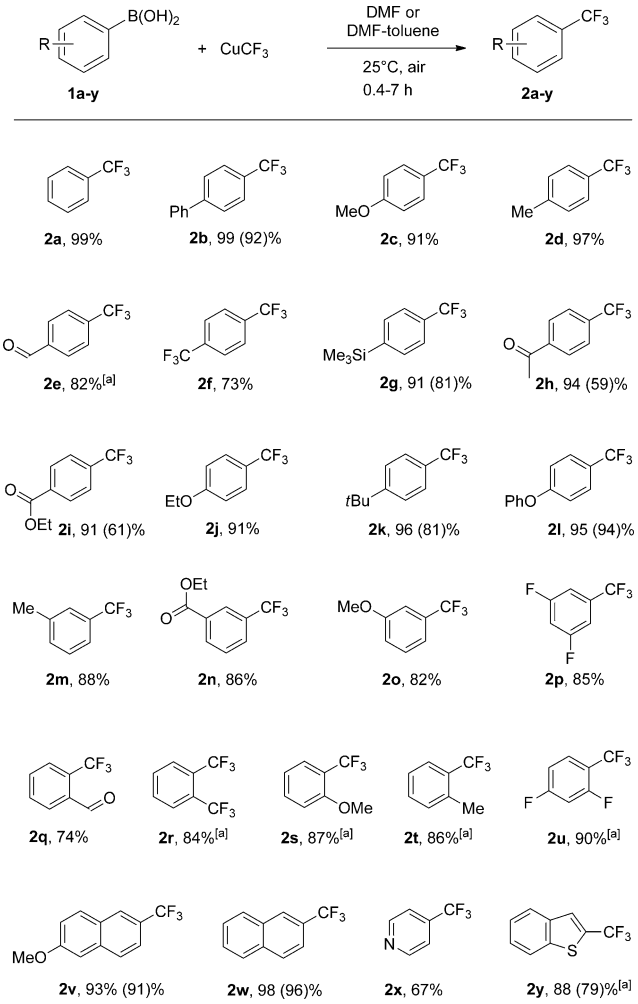


Entry	$CuCF_3$ [equiv]	*T* [°C]	*t* [h]	Conversion [TLC]	Yield of Ph_2 [%]	Yield of **2b** [%]
1	1.2	25	0.5	<100%	1	89
2	1.5	25	0.5	<100%	2	93
3	2	25	0.5	full	1	98
4[b]	2	25	0.5	full	1	99
5	2	35	0.5	full	7	80
6	2	50	0.25	full	11	74

[a] Yields of **2b** were determined by ^{19}F NMR spectroscopy with an internal standard. Yields of biphenyl were determined by GC-MS with calibration. Reaction conditions: phenylboronic acid (0.5 mmol), toluene (5 mL), fluoroform-derived $CuCF_3$ in DMF in open air. [b] In the absence of toluene.

Having identified the optimum reaction conditions (Table 1), we proceeded to explore the scope and limitations of the method. Results of these studies are summarized in Scheme 3. A twofold excess of the trifluoromethylating reagent was employed in the experiments with all of the boronic acids to ensure full conversion and highest possible yield (see above). The use of 2 equiv of the $CuCF_3$ is justified by its low cost and the obvious reality that independent optimization of the $CuCF_3$ to substrate ratio would be needed for each particular boronic acid in a potentially practicable process.

As can be seen from Scheme 3, the reaction occurs smoothly at room temperature, reaching completion within 0.4–7 h. The method has a broad scope and tolerates various functionalities, including not only simple alkyl or aryl groups



Scheme 3. Trifluoromethylation of aryl boronic acids (0.5–1.0 mmol) with fluoroform-derived $CuCF_3$ (2 equiv) in air. See the Supporting Information for details. Yields were determined by ^{19}F NMR spectroscopy with an internal standard. Yields of isolated products are shown in parentheses. [a] At 0 °C.

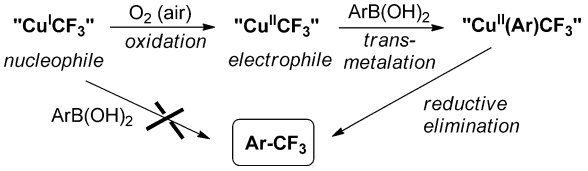
(**2b**, **2d**, **2k**, **2m**, **2t**) but also alkoxy and aryloxy (**2c**, **2j**, **2l**, **2o**, **2s**, **2v**), carbalkoxy (**2i**, **2n**), silyl (**2g**), and even formyl (**2e**, **2q**) groups. (Note that previous attempts to trifluoromethylate aryl boronic acids bearing an aldehyde function have been unsuccessful.[7]) Also important is the fact that like the *para* and *meta* isomers, *ortho*-substituted $ArB(OH)_2$ are smoothly trifluoromethylated in good (74%, **2q**) to excellent (90%, **2u**) yield. On the whole, the yields (Scheme 3) are noticeably higher than those previously reported[5,7–10] for oxidative trifluoromethylation of aryl boronic acids and boronate esters. For some substrates it was beneficial to perform the reaction at 0°C rather than at room temperature. Thus, at 0°C, **2e**, **2r**, **2s**, **2t**, **2u**, and **2y** were formed in noticeably higher yield and the side formation of the corresponding deborylation product was minimized. This effect was particularly well-pronounced for the trifluoromethylation of **1y**. At 25°C, the yield of **2y** was 77% and considerable quantities (up to 15–20%) of benzothiophene side product were produced, whereas at 0°C the reaction furnished **2y** in 88% yield and only about 3% of benzothiophene. Overall, the trifluoromethylation reaction exhibits excellent selectivity, as manifested by the yields of around 90% and higher for over two-thirds of the substrates explored (Scheme 3).

The reactions listed in Scheme 3 were run on a 0.5 mmol scale for yield determination by ^{19}F NMR spectroscopy with an internal standard and on a 1.0 mmol scale for isolation that was performed for less volatile products **2b**, **2g**, **2h**, **2i**, **2k**, **2l**, **2v**, **2w**, and **2y**. To demonstrate further scalability, the synthesis of **2w** was carried out with 10 mmols of 2-naphthylboronic acid **1w**. In this experiment, 2-trifluoromethylnaphthalene (**2w**) was successfully prepared and isolated in an amount of 1.85 g (91% yield).

Other salient features of the method are as follows:

- The reaction employs aryl boronic acids that are more atom-economical and readily available than the corresponding boronate esters. However, aryl boronic acids are prone to undergo facile protodeborylation under the reaction conditions used in the previously reported procedures.[5,7,8] This highly undesired side-process could be reduced by using dry O_2 in the presence of molecular sieves[7] or by diverting to pinacol boronate esters as the substrate.[8] In favorable contrast, our method, despite employing aryl boronic acids and non-dried air as the oxidant, does not suffer significantly from the protodeborylation. With a handful of exceptions, only small quantities (< 5%, if any) of the corresponding arenes were observed (GC-MS) in all of the reactions carried out at room temperature.[21] For the trifluoromethylation of **1e**, **1r**, **1s**, **1t**, **1u**, and **1y** that proceeds less selectively at ambient temperature, the side deborylation process can be largely minimized by performing the reaction at 0°C (see above). Indeed, the isolated trifluoromethylated products **2b**, **2g**, **2h**, **2i**, **2k**, **2l**, **2v**, **2w**, and **2y** were all found to be 95–99% pure by ^1H and ^{19}F NMR spectroscopy and GC-MS data.
- Importantly, no *tert*-butoxylation of $ArB(OH)_2$ was observed in the reaction, despite the fact that the $CuCF_3$ reagent solutions always contain *t*BuOH from the preparation step.[18]
- The lack of necessity to use costly Ruppert's reagent as the CF_3 source, especially in excess (see above and Ref. [17]) by far overwhelms the issue of employing Cu in stoichiometric amounts. Note that all of the reported oxidative trifluoromethylation methods also use copper in stoichiometric[7–9] or at best semicatalytic (20–60%)[5,10] quantities.
- Ligands such as phen are conventionally used in large amounts[5,7,9,10] for the reported oxidative trifluoromethylation reactions, thus adding considerably to the cost and lowering the overall atom economy of the reaction. In contrast, the reactions employing fluoroform-derived $CuCF_3$ smoothly occur in the absence of any extra ligands/additives.

Although the mechanism of the Chan–Lam reaction is not fully understood,[6,22] evidence has been presented for its non-radical character.[6] This conclusion accords with the lack of signs of involvement of free radicals in our reaction (see above). The trifluoromethylation is most likely initiated by air oxidation of the air-sensitive[18] Cu^ICF_3 reagent to a $Cu^{II}CF_3$ species that, being much more electrophilic, undergoes transmetalation with $ArB(OH)_2$, as shown in the simplified mechanism presented in Scheme 4. Reductive elimination of



Scheme 4. Proposed simplified mechanism for trifluoromethylation of aryl boronic acids with fluoroform-derived $CuCF_3$.

$ArCF_3$ from the resultant $Cu^{II}(Ar)CF_3$ intermediate would complete the transformation, although involvement of Cu^{III} and polynuclear species should not be ruled out.[6,22] Significantly however, the transmetalation, which is possibly[22a] the rate-limiting step of the entire process, might be facilitated by the CF_3 ligand. The latter has been shown to promote nucleophile-aided transmetalation reactions, likely because of its stabilization of the d orbitals on the metal in addition to strong electron donation.[3a,23]

In conclusion, we have demonstrated, for the first time, that low-cost fluoroform-derived $CuCF_3$ reagents[18] readily trifluoromethylate aryl boronic acids. The reaction smoothly occurs at room temperature (and even below) and 1 atm of air as the oxidant to give the corresponding benzotrifluorides in excellent yield (up to 99%) and with high selectivity. The method exhibits unprecedentedly high functional-group tolerance for a variety of substrates bearing substituents in the *ortho*, *meta*, and *para* positions; even aryl boronic acids with formyl groups on the ring have been successfully trifluoromethylated in 74–82% yield. Importantly, use of additional ligands, costly oxidants (Ag^I), drying agents, and pure O_2 is not needed, which makes the reaction not only synthetically useful and inexpensive, but also advantageously simple and safe to run.

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