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Communication

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Merging Visible-Light Photocatalysis and Transition-Metal Catalysis in the Copper-Catalyzed Trifluoromethylation of Boronic Acids with CF_3I

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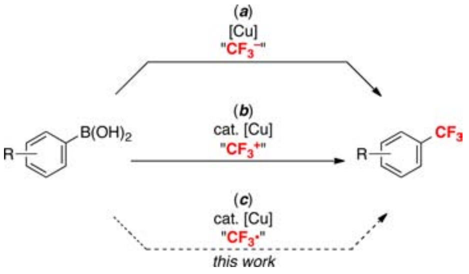
Supporting Information

ABSTRACT: This communication describes the development of a mild method for the cross-coupling of arylboronic acids with CF_3I via the merger of photoredox and Cu catalysis. This method has been applied to the trifluoromethylation of electronically diverse aromatic and heteroaromatic substrates and tolerates many common functional groups.

Trifluoromethyl substituents are widely prevalent in pharmaceuticals and agrochemicals.[1] Thus, the development of mild and versatile synthetic methods for generating carbon−CF_3 bonds has become a field of intense research effort. Over the past three years, a variety of Pd[2,3] and Cu[4,5]-based cross-coupling protocols have been developed for the trifluoromethylation of aryl halides, arylboronic acids, and aromatic carbon−hydrogen bonds. As exemplified in Scheme 1a,b for the Cu-catalyzed trifluoromethylation of boronic acids, these transformations involve “CF_3^-”[4c,e,l,5i] or “CF_3^+”[4f,5d,e] reagents and are generally believed to proceed via nucleophilic or electrophilic transfer of the CF_3 group to the Cu center, respectively. Many of these new methods represent significant progress in comparison to the traditional Swarts reaction,[6] which requires highly reactive fluorinating reagents and harsh conditions.

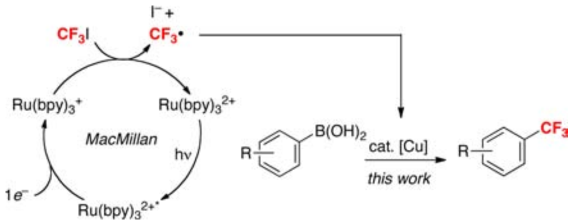
Scheme 1. Cu-Mediated/Catalyzed Trifluoromethylation of Boronic Acids



Despite these important advances, most current strategies for aryl−CF_3 cross-coupling suffer from one or more limitations. In some cases, temperatures greater than 100 °C[2b,3a,b,4d] and/or strong acids or bases (trifluoroacetic acid[3a] or ^{t}BuOK[4j]) are necessary. Other methods require expensive trifluoromethylating reagents [e.g., *S*-(trifluoromethyl)thiophenium salts,[3a,4f,5d] Togni's reagent,[5b,e,g] or $TESCF_3$[3b,5a]]. Finally, many protocols exhibit limited substrate scope/generality.

One attractive approach to begin to address these limitations would be to access alternative and potentially complementary mechanistic manifolds. We reasoned that a radical pathway (Scheme 1c) would be particularly interesting, since $CF_3\cdot$ can be generated under mild, neutral conditions from commercially available and relatively inexpensive CF_3I.[7] In particular, we noted recent reports by MacMillan demonstrating the conversion of CF_3I to $CF_3\cdot$ at room temperature in the presence of a photocatalyst, visible light, and a reductant (Scheme 2).[8] On the basis of this work, we hypothesized that the merger of visible-light photocatalysis (to generate $CF_3\cdot$) with Cu catalysis (to generate reactive Cu−aryl species) (Scheme 2) might provide a mild and general method for the trifluoromethylation of boronic acid derivatives.

Scheme 2. Proposed New Pathway for Radical Trifluoromethylation of Boronic Acids via Cu/Ru Catalysis



Our initial investigations focused on the Cu-catalyzed/Ru-photocatalyzed trifluoromethylation of 1,1′-biphenyl-4-ylboronic acid with CF_3I to form 4-(trifluoromethyl)-1,1′-biphenyl (**1a**). We were delighted to find that Cu/Ru catalysis provided product **1a** in modest to excellent yields under a number of conditions (Table 1). A variety of different bases (to promote transmetalation) and reaction solvents were screened for this reaction [see Table S1 in the Supporting Information (SI)], and the use of K_2CO_3 in *N*,*N*-dimethylformamide (DMF) proved optimal. Cu^I catalysts generally performed better than Cu^{II} salts, and the highest yield of **1a** (76%) was obtained with CuOAc. The optimal conditions were as follows: 1 equiv of boronic acid **1**, 5 equiv of CF_3I, 1 equiv of K_2CO_3, 20 mol % CuOAc, and 1 mol % $Ru(bpy)_3Cl_2{\cdot}6H_2O$ with irradiation from two 26 W household light bulbs. The major side product was 4-

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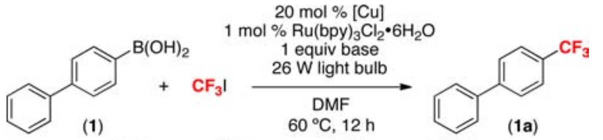
Table 1. Optimization of the Reaction Between 1 and CF_3I[a]



Entry	[Cu]	Base	Yield
1	$Cu(OTf)_2$	K_2CO_3	14%
2	$[Cu(OTf)]_2 \cdot C_6H_6$	K_2CO_3	28%
3	CuI	K_2CO_3	34%
4	Cu	K_2CO_3	40%
5	$Cu(OAc)_2$	K_2CO_3	68%
6	CuOAc	K_2CO_3	76%
7	CuOAc	NaOAc	34%
8	CuOAc	KF	50%
9	CuOAc	none	6%
10[b]	CuOAc	K_2CO_3	1%
11[c]	none	K_2CO_3	3%
12[d]	CuOAc	K_2CO_3	3%

[a] General conditions: substrate (0.05 mmol, 1 equiv), CF_3I (5 equiv), [Cu] (0.2 equiv), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (0.01 equiv), base (1 equiv), DMF (0.17 M in substrate), 60 °C, 12 h, 26 W compact fluorescent light bulb. ^{19}F NMR yields are shown. [b] General conditions, but with no light. [c] General conditions, but with no CuOAc. [d] General conditions, but with no $Ru(bpy)_3Cl_2 \cdot 6H_2O$.

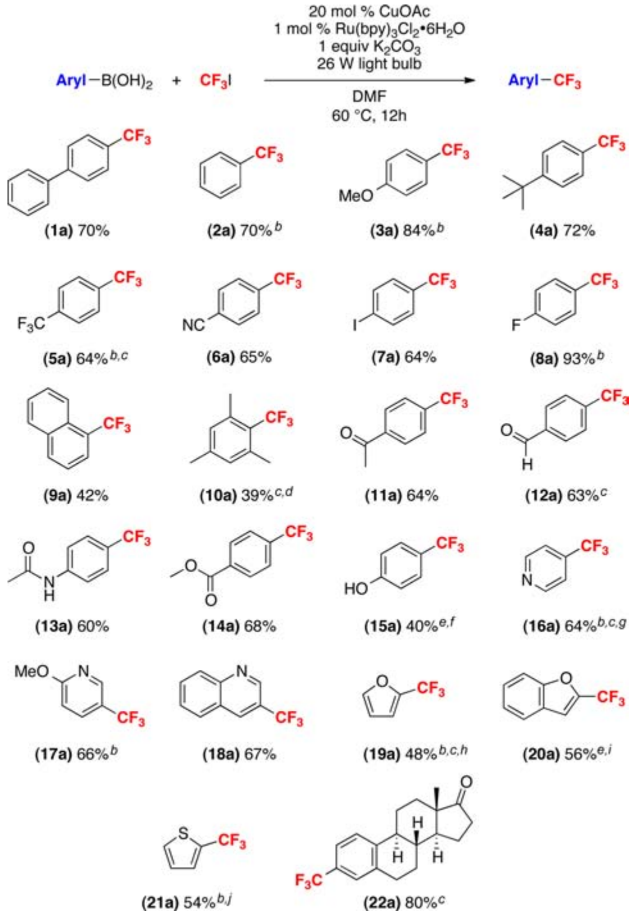
iodo-1,1′-biphenyl (formed in 9% yield under the optimal conditions).

This Cu/Ru-catalyzed coupling between **1** and CF_3I is practical and easily scalable. The reaction in Table 1, entry 6 was performed on a 0.05 mmol scale and provided a 76% yield as determined by ^{19}F NMR spectroscopy and GC−MS. Nearly identical isolated yields (72 and 70%) were obtained on 1 and 5 mmol scales, respectively.

A variety of control reactions were conducted to establish the role of each component of the reaction mixture. As shown in Table 1, entries 10−12, when light, CuOAc, or $Ru(bpy)_3Cl_2 \cdot 6H_2O$ was excluded under otherwise identical conditions, ≤3% yield of **1a** was obtained.[9] These results clearly indicate the necessity that all three components be present to achieve high yields under these conditions, consistent with the major pathway to **1a** proceeding via dual Cu/Ru catalysis (see below). The iodinated side product 4-iodo-1,1′-biphenyl was also subjected to the reaction conditions to establish whether it is an intermediate in the boronic acid trifluoromethylation process. A <2% yield of the aryl−CF_3 product was formed, strongly suggesting that the major pathway to **1a** does not involve an iodinated intermediate. Finally, the reactivity of boronic acid substrate **1** was investigated under conditions reported by Baran and MacMillan to promote C−H trifluoromethylation reactions via in situ generation of $CF_3\cdot$.[10] In both cases, a <2% yield of **1a** was observed. These results indicate that **1a** is not formed by the direct reaction of $CF_3\cdot$ with the boronic acid.

This transformation was next applied to a variety of different aryl- and heteroarylboronic acid derivatives. The representative examples shown in Scheme 3 were selected to highlight not only the broad scope but also the limitations of this method.[11] Aromatic boronic acids bearing either electron-donating (*tert*-butyl, methoxy) or electron-withdrawing (cyano, trifluoromethyl, fluoro, methyl ester) substituents underwent trifluoromethylation in high yield. A variety of different potentially reactive functional groups (aromatic alcohols, ketones, aldehydes, esters, and amides) were quite well-tolerated. A boronic acid embedded in the estrone framework underwent trifluoromethylation to generate **22a** in 80% isolated yield. Most remarkably, 4-iodophenylboronic acid underwent selective trifluoromethylation to form **7a**, leaving the aryl iodide intact for subsequent functionalization. This demonstrates the complementarity of this method to many other Cu-catalyzed trifluoromethylation protocols.[5a,c,f] Furthermore, it provides additional evidence against the possibility of aryl iodide intermediates in this transformation.

Scheme 3. Substrate Scope for Cu/Ru-Catalyzed Trifluoromethylation of Boronic Acids[a]



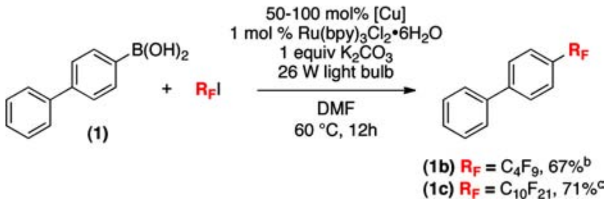
[a] General conditions: substrate (1 equiv), CF_3I (5 equiv), [Cu] (0.2 equiv), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (0.01 equiv), K_2CO_3 (1 equiv), DMF (0.17 M in substrate), 60 °C, 12 h, 26 W compact fluorescent light bulb. Isolated yields (≥95% purity) are shown, unless otherwise noted. [b] ^{19}F NMR yield. [c] 0.5 equiv of CuOAc. [d] Isolated as a 1:1 mixture with inseparable protodeboronated product. [e] 0.1 equiv of CuOAc. [f] Isolated as a 10:1 mixture with inseparable protodeboronated product. [g] 3 equiv of CF_3I. [h] Reaction run at 70 °C. [i] Reaction run at 40 °C. [j] 0.05 equiv of CuOAc.

The use of sterically hindered substrates such as 1-naphthyl- and 2,4,6-trimethylphenylboronic acid is typically challenging for copper-mediated cross-coupling reactions.[12] As shown in Scheme 3, similar effects were seen in the current transformation, with products **9a** and **10a** being formed in modest yields (42 and 39%, respectively). In these cases, competing protodeboronation was problematic, and the major side products were naphthalene and mesitylene, respectively.

Heteroaromatic substrates are of particular relevance to the pharmaceutical and agrochemical industries because of the prevalence of heteroarenes in biologically active compounds.[13] Boronic acids derived from pyridine, quinoline, furan, and thiophene all underwent trifluoromethylation in modest to good yields.[10] In some of these cases, modification of the catalyst loading and/or reaction temperature was needed to achieve the optimal yield. Importantly, with all of these substrates, trifluoromethylation of the boronic acid moiety outcompeted uncatalyzed C−H trifluoromethylation of the heterocycle with $CF_3\cdot$. Thus, this method provides an attractive route for the site-selective installation of CF_3 substituents into these scaffolds.

Related conditions could also be applied to analogous perfluoroalkylation reactions. This is a significant advantage of the current method, since perfluoroalkyl analogues of other common trifluoromethylating reagents [e.g., R_3SiCF_3, *S*-(trifluoromethyl)thiophenium salts, or Togni's reagent] are expensive and/or not commercially available. As shown in Scheme 4, perfluorobutyl and perfluorodecyl iodides reacted with **1** to afford products **1b** and **1c**, respectively, in good yields under the Cu/Ru-catalyzed conditions.

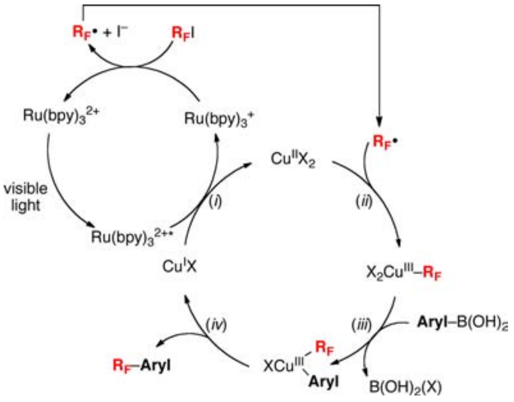
Scheme 4. Cu/Ru-Catalyzed Perfluoroalkylation of 1[a]



[a]General conditions: substrate (1 equiv), CuOAc (0.5−1 equiv), $Ru(bpy)_3Cl_2\cdot 6H_2O$ (0.01 equiv), K_2CO_3 (1 equiv), DMF (0.17 M in substrate), 60 °C, 12 h, 26 W compact fluorescent light bulb. Isolated yields are shown. [b]5 equiv of C_4F_9I, 0.5 equiv of CuOAc. [c]1.2 equiv of $C_{10}F_{21}I$, 1 equiv of CuOAc.

While a detailed mechanistic picture of this transformation remains to be elucidated, a possible set of catalytic cycles is shown in Scheme 5. In this sequence, photoexcitation of $Ru(bpy)_3^{2+}$ to $Ru(bpy)_3^{2+*}$ is followed by one-electron reduction by Cu^I to generate $Ru(bpy)_3^+$ and Cu^{II}.[14] Reduction of CF_3I by $Ru(bpy)_3^+$ then affords $CF_3\cdot$ and I^-. Notably, literature reduction potential data indicate that both of these reactions should be thermodynamically favorable (Figure S1 in the SI). The $CF_3\cdot$ could then react with Cu^{II} to generate a $Cu^{III}(CF_3)$ intermediate. Subsequent base-promoted transmetalation between Cu^{III} and the arylboronic acid would afford $Cu^{III}(aryl)(CF_3)$, which could undergo aryl−CF_3 bond-forming reductive elimination to release the organic product and regenerate the Cu^I catalyst.[15]

Scheme 5. Possible Mechanism for Cu/Ru-Catalyzed Trifluoromethylation of Boronic Acids



In summary, this communication describes a mild and general approach for the Cu-catalyzed/Ru-photocatalyzed trifluoromethylation and perfluoroalkylation of arylboronic acids. This method takes advantage of visible-light photoredox catalysis to generate $R_F\cdot$ under mild conditions and merges it with copper-catalyzed arylboronic acid functionalization. The combination has enabled the trifluoromethylation of a wide variety of aromatic and heteroaromatic substrates bearing many common functional groups. This transformation demonstrates the feasibility of achieving Cu-catalyzed trifluoromethylation via a radical pathway. Furthermore, it represents a new example of combining organometallic and photoredox catalysis to achieve synthetically useful organic transformations.[16]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) Reactions between some electron-deficient substrates and CF_3I showed yields of ~20% for the trifluoromethylated products in the absence of Ru catalyst. See the SI for more details.

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(11) The trifluoromethylated products that are liquids were isolated via Kugelrohr distillation. This isolation procedure typically afforded ≥95% pure products (contaminated with traces of protodeboronated material). In many cases (e.g., **6a**, **9a**, **18a**, **20a**), >98% pure products could be obtained via subsequent careful purification by column chromatography, albeit in reduced yields. See the SI for full details.

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(14) The observation that Cu^I salts generally perform better than Cu^{II} salts in this transformation is consistent with this proposal.

(15) The order of steps ii and iii in Scheme 5 could also potentially be reversed. Without detailed evidence about the resting state of the Cu catalyst, we cannot draw definitive conclusions about the Cu species most likely to react with $CF_3\cdot$.

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