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Copper-Catalyzed Intermolecular Trifluoromethylarylation of Alkenes: Mutual Activation of Arylboronic Acid and CF_3^+ Reagent

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Supporting Information

ABSTRACT: A novel copper-catalyzed intermolecular trifluoromethylarylation of alkenes is developed using less active ether-type Togni's reagent under mild reaction conditions. Various alkenes and diverse arylboronic acids are compatible with these conditions. Preliminary mechanistic studies reveal that a mutual activation process between arylboronic acid and CF_3^+ reagent is essential. In addition, the reaction might involve a rate-determining transmetalation, and the final aryl C−C bond is derived from reductive elimination of the aryl(alkyl)Cu(III) intermediate.

The rich variety of CF_3-containing molecules that occur as pharmaceuticals and agriculture chemicals has inspired considerable interest in the development of new methods for their synthesis.[1] Among them, direct introduction of the CF_3 group into organic compounds is particularly attractive.[2] For instance, copper-catalyzed trifluoromethylation has received much attention for the synthesis of CF_3-containing aromatic and aliphatic compounds.[3,4] In 2012, our group reported the first intramolecular trifluoromethylarylation of activated alkenes using a Pd catalyst to generate a series of CF_3-containing oxindole derivatives.[5] Later, Sodeoka[6] demonstrated that a similar transformation could be achieved using Cu(I)/Togni's reagent. Nevado[7] discovered a Cu-catalyzed intramolecular trifluoromethylarylation of alkenes involving a 1,4-aryl migration and desulfonylation process. Related intramolecular 1,2-aryl migrations were also described by Wu,[8a] Tu,[8b] and Sodeoka.[8c] All those aryl transfers were proposed to follow a radical process. We speculated that, if this arylation could be expanded to an intermolecular process, a large number of vicinal CF_3- and aryl-containing aliphatic compounds could be easily obtained from various simple alkenes. However, a related intermolecular reaction involving coupling of three or more components is much more challenging and remains an underdeveloped process. Here we report a novel Cu-catalyzed intermolecular trifluoromethyl-arylation of alkenes using arylboronic acid as arylation reagent, in which mutual activation of arylboronic acid and CF_3^+ reagent is identified as an essential step. More importantly, preliminary studies reveal that a rate-determining transmetalation is involved, with the final aryl C−C bond derived from reductive elimination of an aryl(alkyl)Cu(III) intermediate, rather than the previously suggested radical pathway.

Based on our group's recent success in developing intermolecular difunctionalization of alkenes,[9] we found that TMSNu (Nu = N_3, CN) acts as a Lewis acid to activate the ether-type Togni's reagent (**2a**) and that the final C−N and C−C bond is derived from an alkyl radical or carbon cation intermediate (top, Scheme 1). In addition, Szabó demonstrated that B_2pin_2 could accelerate the Cu-catalyzed trifluoromethylation of alkenes using Togni's reagent as a CF_3 source.[4p,9c] We envisioned that, similar to TMSNu, arylboronic reagent could also activate the CF_3^+ reagent **2a** to release a CF_3 radical in the presence of a Cu catalyst. Notably, the reaction could simultaneously generate an activated arylboronic reagent, which might react with the above-mentioned alkyl radical or carbon cation intermediate or with a Cu catalyst to form a $C_{alkyl}-C_{aryl}$ bond (bottom, Scheme 1). If so, then a three-component intermolecular reaction might be expected. To test this hypothesis, initial studies were focused on the reaction of styrene **1a** with Togni's reagent **2a** and $PhB(OH)_2$ **3a** in the presence of a Cu catalyst. We are delighted to find that the desired trifluoromethylarylation product **4a** was indeed observed. After extensive screening of different reaction parameters, the optimized reaction conditions were found to provide the desired product **4a** in 76% yield (entry 1, Table 1). Some essential observations: (1) When other CF_3^+ reagents **2b** and **2c** were employed, no reaction occurred (entry 2). (2) PhBPin and $PhBF_3K$ were inactive (entry 3). (3) Other types of arylmetallic reagents, such as $PhSnBu_3$ and $PhSiMe_3$, failed to yield **4a**, and the starting material was recovered quantitatively (entry 4). (4) Both $[Cu(CH_3CN)_4]PF_6$ and $[Cu(CH_3CN)_4]BF_4$ were effective, but CuI and $Cu(OTf)_2$ exhibited lower reactivity, and no reaction occurred in the absence of a Cu catalyst (see Supporting Information (SI)). (5) A slightly lower yield of **4a** was obtained under air, and a significant amount of side product

Scheme 1. Intermolecular Difunctionalization of Alkenes

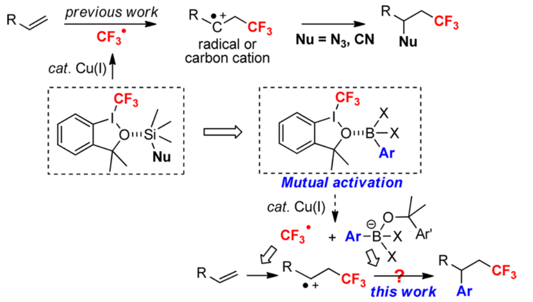

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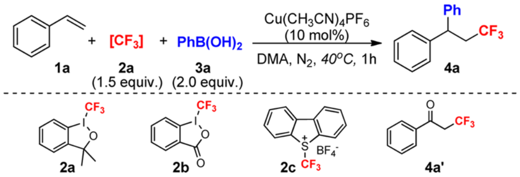
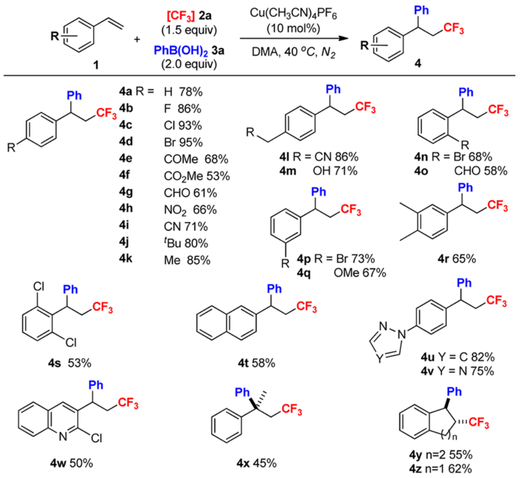
Table 1. Optimization of the Reaction Conditions[a]



entry	reaction conditions	yield **4a** (%)[b]
1	**standard conditions**	**76**
2	**2a** was replaced by **2b** or **2c**	0
3	$PhB(OH)_2$ was replaced by $PhBF_3K$, PhBPin	0
4	$PhB(OH)_2$ was replaced by $PhSiMe_3$, $PhSnBu_3$	0
5	reaction under air	42 (21)[c]
6	reaction under O_2	13 (40)[c]

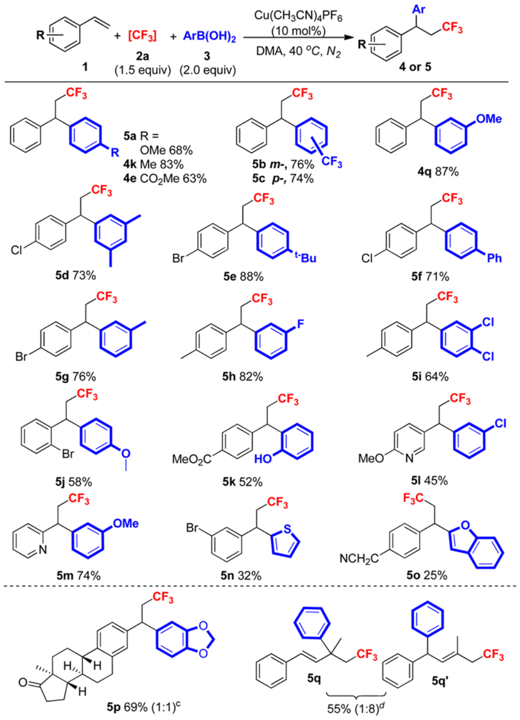
[a] All the reactions were run at 0.1 mmol scale. [b] Yield obtained by ^{19}F NMR with CF_3-DMA as internal standard. [c] Yield of side product **4a′**.

Table 2. Substrate Scope of Styrenes[a,a]



[a] All the reactions were conducted on 0.2 mmol scale. [a] Isolated yields are given.

Table 3. Substrate Scope of Arylboronic Acids[a,b]



[a] All the reactions were conducted on 0.2 mmol scale. [b] Isolated yields are given. [c] Diastereoselectivity. [d] Regioselectivity.

4a′ was observed; less **4a** and more **4a′** were given under O_2 atmosphere (entries 5 and 6).

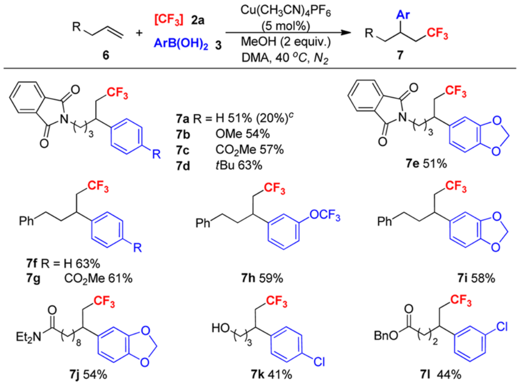
With the optimized reaction conditions in hand, we first examined the substrate scope of the styrenes, and the results are summarized in Table 2. A variety of styrenes bearing monosubstitutents on the aryl ring were initially surveyed. Both electron-donating and -withdrawing groups were compatible with this transformation, and various functional groups, such as halogen, ester, nitro, nitrile, aldehyde, ketone, and hydroxyl, were tolerated to give desired products **4a**–**4q** in moderate to excellent yields. For the styrenes with disubstitutents on the aryl ring, including 2,6-dichlorostyrene, the reactions proceeded smoothly to generate **4r** and **4s** in moderate yields. The reaction of 2-vinylnaphthalene delivered **4t** in 58% yield. The styrenes containing heterocycles were also suitable to produce products **4u**–**4w** in satisfactory yields. Compared with monosubstituted styrenes, 1,1-disubstituted styrenes exhibited slightly lower reactivity to give product **4x** in 45% yield. However, the cyclic styrenes exhibited good reactivities to give products **4y** and **4z** as a single isomer in moderate yields.

Inspired by the above results, we turned our attention to the reactivity of diverse arylboronic acids (Table 3). To our delight, a range of arylboronic acids were suitable to react with various styrenes, and a series of functional groups, such as ether, ester, halides, and CF_3, could survive to give the desired products **5a**–**5m**, **4k**, **4e**, and **4q** in good to excellent yields. Notably, the reaction of $2\text{-}OHC_6H_4B(OH)_2$ proceeded smoothly to produce **5k** in moderate yield. In addition, the reaction of (hetero)-$ArB(OH)_2$ also provided products **5n** and **5o**, albeit in low yields. Finally, an estrone derivative was employed to deliver product **5p** in 69% yield. A conjugated diene substrate was also compatible with this transformation, giving regioisomers **5q** and **5q′** in 55% yield with good regioselectivity (1:8 ratio).

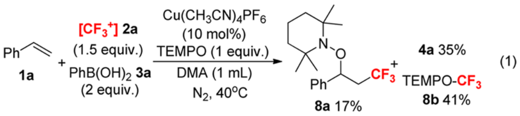
The next investigation focused on the reaction of unactivated alkenes. When aliphatic alkenes **6a** and **2a** were treated under the above optimized reaction conditions, the desired product **7a** was obtained in low yield (~20%) and poor reproducibility. With further screening of the reaction conditions, we were delighted to find that addition of water or alcohol could significantly promote the trifluoromethylarylation reaction and give a reproducible yield. In addition, the amount of Cu catalyst could be reduced to 5 mol %. MeOH was proven to be the best additive to provide product **7a** in moderate yield (51%). With the modified reaction conditions, a series of unactivated alkenes **6** with various $ArB(OH)_2$ **3** could be transformed to the desired products **7a**–**7l** in satisfactory yields (Table 4). It should be noted that the side reaction of allylic C–H trifluoromethylation was hard to inhibit, and the related products were observed in 10–20% yields.[10]

To rationalize this reaction pathway, preliminary mechanistic studies were surveyed. First, the addition of TEMPO could significantly inhibit the trifluoromethylarylation reaction, yielding oxytrifluoromethylated product **8a** and TEMPO–CF_3 adduct **8b** (eq 1). In addition, both reactions of *Z*-**9** and *E*-**9** afforded product **10** with the same diastereoselectivity (5:1), albeit in low yields (eq 2). These results indicated that a CF_3 radical was involved in the reaction, and a benzyl radical species was generated through the addition of CF_3 radical to alkenes.[11]

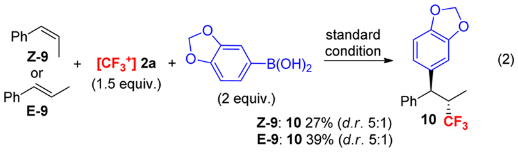
Table 4. Substrate Scope of Unactivated Alkenes[a,b]



[a]All the reactions were conducted in 0.2 mmol scale. [b]Isolated yields are given. [c]Without MeOH.



(1)



(2)

Second, compared to the standard reaction conditions, Togni's reagent **2a** was inert in the absence of ArB(OH)$_2$.[12] Thus, it is possible that **2a** was activated by ArB(OH)$_2$ **3**[13] and then reacted with Cu(I) to generate a CF$_3$ radical species. Observation of only one CF$_3$ signal in the mixture of **2a** and **3a** (at −10 °C) suggested a fast equilibrium existed between **2a** with **3a** and **int.I** (**2a·3a**). In addition, the CF$_3$ signal gradually shifted to downfield and broadened with an increase in the amount of PhB(OH)$_2$ (Figure 1, middle). Furthermore, the interaction of electron-poor arylboronic acid (EP-AA **3r**, Figure 1, left) with **2a** was stronger than that of electron-rich arylboronic acid (ER-AA **3c**, Figure 1, right), which means Togni's reagent **2a** with EP-AA should be more reactive with Cu(I) than ER-AA.

Third, we moved our attention to the mechanism of final C−C bond formation. The electronic effect of arylboronic acids and styrenes was evaluated under the standard conditions at 25 °C. As shown in Figure 2A, ER-AA (R = OMe, Me) presented a faster reaction rate than EP-AA (R = Cl, CO$_2$Me). However, no significant electronic effect of styrenes was observed, with a much smaller Hammett ρ-value (−0.087, Figure 2B). In addition, the reaction rate exhibited a saturation dependence on the concentration of PhB(OH)$_2$ and a zero-order dependence on styrene.[10] These observations implied that addition of CF$_3$ radical to styrenes is a fast step to generate alkyl radical **int.III**, and that this species should be involved after the rate-determining step, while ArB(OH)$_2$ should be involved in the rate-determining step or before.

As we originally proposed, if the final C−C bond was derived from the intermediate of the benzyl radical (**int.III**) or benzyl carbon cation (**int.VI**) with ArB(OH)$_2$ (see paths c and d in Scheme 2), the reaction should involve a rate-determining CF$_3$ radical-forming step. If so, then the reaction of EP-AA should be faster since its adduct **int.I** is more reactive (see Figure 1), which is opposite the result in Figure 2A. Thus, these observations indicate that paths c and d (Scheme 2) are less likely.

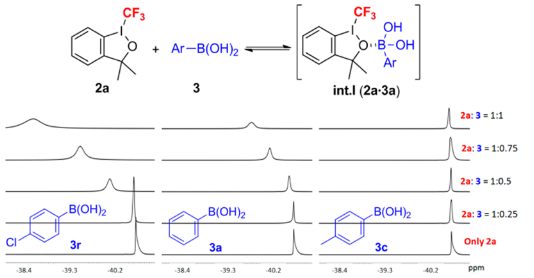


Figure 1. Reactions of **3** and **2a** monitored by ^{19}F NMR.

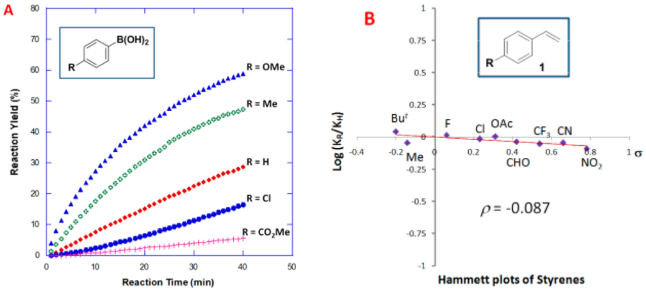
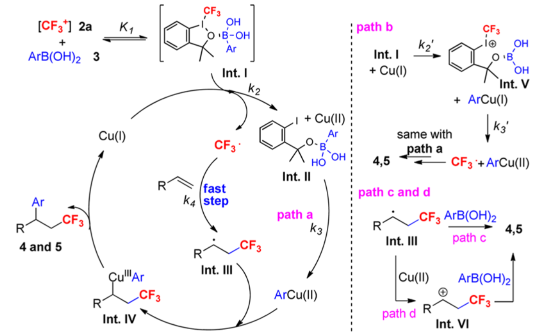


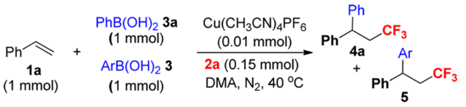
Figure 2. Electron effect of arylboronic acids and styrenes: (A) time course of diverse ArB(OH)$_2$ and (B) Hammett plots of styrenes.

Scheme 2. Proposed Mechanism



Based on the above analysis, an alternative pathway involving ArCu(II) species was proposed to address the final C−C bond formation (paths a and b in Scheme 2): With treatment of activated CF$_3^+$ species **int.I** by Cu(I) catalyst to release CF$_3$ radical, the reaction simultaneously generated a new activated arylboronic acid **int.II** and a Cu(II) species, which could undergo transmetalation to give an ArCu(II) species (path a). The ArCu(II) could then be oxidized by alkyl radical **int.III** to yield a Cu(III) species **int.IV**,[14] which delivers the final product through reductive elimination.[15] Due to the saturation dependence on the concentration of PhB(OH)$_2$ and the lack of dependence on styrene, transmetalation (path a) should be involved as a rate-determining step.[16,17] Another possible pathway involves an initial transmetalation to give ArCu(I) and **int.V**; ArCu(I) would then be oxidized by **int.V** to yield ArCu(II) and release CF$_3$ radical (path b), which can also explain the above observations.

For path a, the reaction of **int.I** of EP-AA with Cu(I) (k_2) is faster, but following the transmetalation step (k_3), ER-AA is favored.[16b] In contrast, both steps (k_2' and k_3') are favored for ER-AA in path b. To differentiate these two possibilities, the competing experiments were conducted, and no significantly different reaction rate was observed for EP-AA and ER-AA (eq 3), which is obviously different from the individual reactions (Figure 2A). A possible reason is that the concentration of **int.II** of EP-AA is higher than that of ER-AA, but the transmetalation of ER-AA (k_3) is faster than that of EP-AA. Thus, the k_3[**int.II**] value of EP-AA is reasonably close to that with ER-AA, resulting in similar yields of **4a** and **5** in a one-pot reaction. This observation is more consistent with path a and against path b.[18]



(3)

Ar = *p*-RC$_6$H$_4$	R = OMe	Me	Cl	CF$_3$	CO$_2$Me
ratio (**5**:**4a**)	1:1.3	1:0.92	1:1.2	1:0.91	1:1.3

In summary, we have developed a novel copper-catalyzed intermolecular trifluoromethylarylation of alkenes under mild reaction conditions. Diverse alkenes and arylboronic acids are compatible with these conditions for efficient synthesis of CF_3-containing diarylmethane derivatives. Preliminary mechanistic studies reveal that the mutual activation process between arylboronic acid and the CF_3^+ reagent is vital to generate the initial CF_3 radical. Transmetalation of $ArB(OH)_2$ to Cu(II) is a key step, and the final C−C bond is derived from a Cu(III) species. Further application and more mechanistic investigation of this process are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. 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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(10) For details, see the SI.

(11) For the side product **4a′** generation (entries 5 and 6, Table 1) from benzyl radical species and O_2, see: Deb, A.; Manna, S.; Modak, A.; Patra, T.; Maity, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 9747.

(12) In the absence of arylboronic acid, no trifluoromethylation of alkenes occurred, and CF_3^+ reagent **2a** was quantitatively recovered.

(13) No significant interaction between ester-type Togni's reagent **2b** with **3a** was observed. For details, see SI.

(14) Oxidation of Cu(II) by alkyl radical to give Cu(III) was also proposed: (a) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034. (b) Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 2555.

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(16) Slow transmetalation of $ArB(OH)_2$ to Cu(II) was also reported: (a) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. Transmetalation of ER-AA with Cu(II) exhibits a faster rate than that of EP-AA: (b) King, A. E.; Ryland, B. L.; Brunold, T. C.; Stahl, S. S. *Organometallics* **2012**, *31*, 7948.

(17) The reaction rate was increased by addition of MeOH. It is possible that adding MeOH could accelerate the transmetalation step; see SI.

(18) A reviewer raised a possible alternative pathway involving initial oxidation of Cu(I) by **int.I** to give $Cu^{III}CF_3$ and subsequent rate-determining transmetalation with $ArB(OH)_2$. The formed $ArCu^{III}CF_3$ complex could further release $ArCu^{II}$ and CF_3 radical; the latter could react with alkenes to generate alkyl radical and recombine with ArCu(II) to generate **int.IV**. For more details, see ref 9c and the SI.