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ARTICLE TYPE

Highly Effective Copper-Mediated *gem*-Difluoromethylenation of Arylboronic Acids

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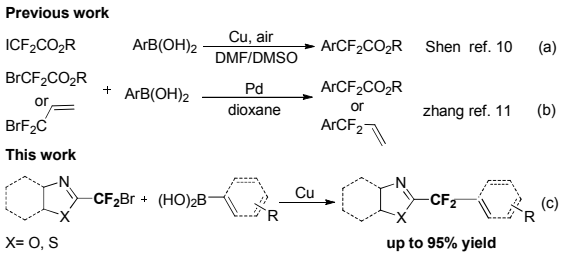
A copper-mediated *gem*-difluoromethylenation of aryl, heteroaryl and vinyl boronic acids with bromodifluoromethylated oxazole or thiazole derivatives has been developed. This novel reaction showed an excellent functional group tolerance and wide substrate scope, providing a facile access to practical application in drug discovery and development.

Due to the unique properties of the difluoromethylene group (CF_2), functionalized difluoromethylated arenes are widely prevalent in biologically active pharmaceuticals, agrochemicals and organic functional materials.[1] Indeed, CF_2 fragment is usually considered as a bioisostere to an ethereal oxygen atom, a carbonyl group,[2] which leads to increased dipole moments, enhanced acidity of its neighboring groups, and conformational changes.[3] As a key component in identical and non-identical twin drugs, the composition of the linkage which acts as a bridge connection of both pharmacophores is priorities to be considered in drug design and innovation.[4] Based on the above understanding, the linker which contains *gem*-difluoromethylene component is proposed to be one of the most valuable linkages for binding two pharmacophores. For example, the A79285 containing a central *gem*-difluoromethylene motif is an excellent inhibitor of HIV-1 aspartic protease.[5] Although significant progresses have been achieved in trifluoromethylation[6] and difluoromethylation[7] of arenes in recent years, mild and efficient strategies for the introduction of a *gem*-difluoromethylene moieties into aromatic compounds have been less explored,[8] due to the shortage of *gem*-difluoromethylene source and the unstability of difluoroalkyl intermediates.

A general approach of introducing difluoromethylene group was on the basis of the transitional metal mediated or catalyzed coupling reaction between aryl halides and difluoroalkyl halides.[9] Compared with traditional methods, cross-coupling reaction of aryl boronic acids with difluoroalkyl halides becomes a "young generation" in the synthesis of difluoromethylation arenes. Therefore, more and more attention has been focused on this promising synthetic strategy. For instance, Shen reported Cu-mediated aerobic difluoroalkylation of arylboronic acids in moderate yields (Scheme 1, a).[10] Recently, Zhang developed a Pd-catalyzed difluoroalkylation of aryl boronic acids with bromodifluoromethylated phosphonate, bromodifluoromethylated carboxylic acid derivatives, and 3-bromo-3,3-difluoropropene (Scheme 1, b).[11] Despite these important advances, most of current strategies for the *gem*-difluoromethylenation are still suffered from one or more limitations, such as the use of expensive Pd-catalysts, unavailable or unstable difluoroalkyl reagents, higher reaction temperature, a limited substrate scope or generality, etc. Hence, it is highly desirable to develop new methods and stable and readily available difluoroalkyl reagents to address these issues. Our group is always interested in functionalization of bromodifluoromethylated oxazole or thiazole analogues,[12] which may be good substrates for the difluoromethylenation reaction. Thus, we describe herein the first example of Cu-mediated *gem*-difluoromethylenation of aryl, heteroaryl and vinyl boronic acids with inexpensive and readily available bromodifluoromethylated heterocyclic compounds as a simple and efficient reaction protocol for practical application in drug discovery and development (Scheme 1, c). This new method proceeds under mild conditions without the need of any additives, and provides a variety of aryldifluoromethylated heterocyclic compounds with high efficiency and excellent functional-group compatibility.

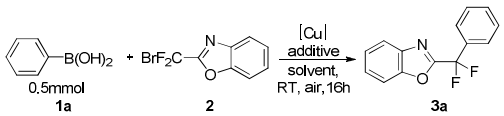


Scheme 1. Preparation of Difluoromethylene Derivatives.

We initially focused on the *gem*-difluoromethylenation of phenylboronic acid **1a** with bromodifluoromethylated benzoxazole **2**. Reaction conditions were evaluated to optimize the cross-coupling *gem*-difluoromethylenation (Table 1). It was found that **1a** and **2** were treated with CuI at room temperature for 16 h in NMP to give the desired cross-coupling *gem*-difluoromethylenated product **3** in 20% yield based on the ^{19}F NMR and LC-MS analysis (Table 1, entry 2). After switching Cu salts from CuX (X =I, Br, Cl) to CuX_2 (X =Br, OAc, CO_2CF_3), the yield of **3** was improved to 49% (Table 1, entries 3-8). Fortunately, product **3** was enhanced to 82% yield when Cu^0 powder (2.0 equiv) was added to the reaction mixture. The solvent effects in this reaction were also examined. It was found that the reaction could be carried out in DMF, DMSO or NMP, in

which NMP was proved to be the best (Table 1, entries 9-14). Notably, the yield of the reaction was significantly decreased and no new signals could be detected by ^{19}F NMR, indicating that there was no new fluorine-containing Cu complex formed when bipy or phen was added to this reaction (ESI, Table S1). The addition of phosphine ligands such as Ph_3P, DPPP, or DPPF, was also ineffective. Further investigation of the influence of the bases on the reaction indicated that the reactions were completely shut down, when the base, such as KOAc, Na_2CO_3, Cs_2CO_3 or *t*-BuOK, was employed. A quick screening of reactant ratio revealed that **1a**:**2**:Cu = 1:3:3 was an ideal ratio of reactants in the formation of **3a** (97% by ^{19}F NMR, entry 15). In addition, the N_2 atmosphere has a negative effect on this *gem*-difluoromethylenation reaction, affording **3a** in a slightly lower ^{19}F NMR yield of 81% (entry 16).

Table 1. Optimization of reaction conditions

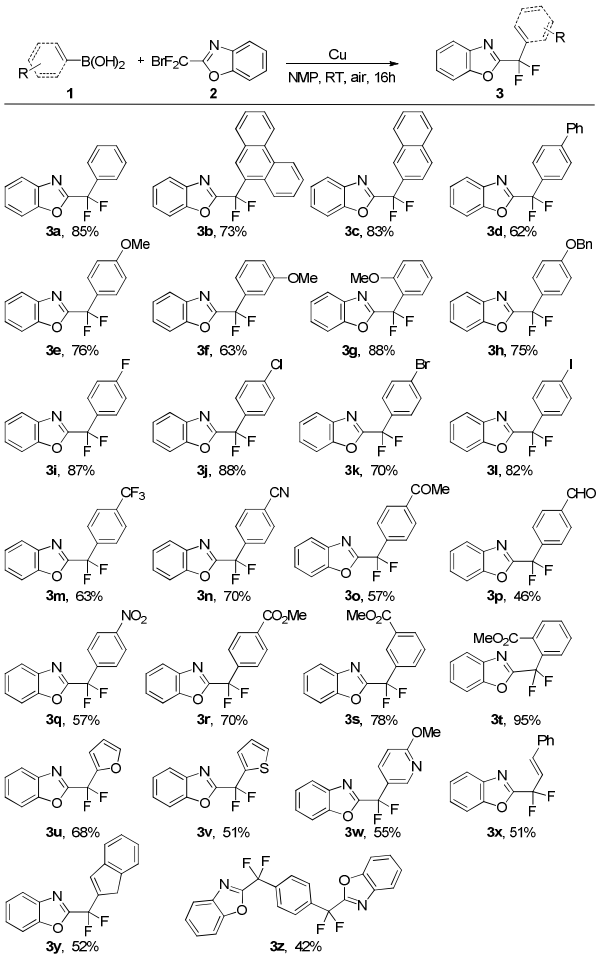


Entry	[**Cu**]	**1a**:**2**:[**Cu**]	Solvent	Yield(%)[a]
1	Cu_2O	1:2:1	NMP	0
2	CuI	1:2:1	NMP	20
3	CuBr	1:2:1	NMP	49
4	CuCl	1:2:1	NMP	38
5	Cu(OTf)*1/2Ph	1:2:1	NMP	32
6	$CuBr_2$	1:2:1	NMP	0
7	$Cu(OAc)_2$	1:2:1	NMP	40
8	$Cu(CO_2CF_3)_2$	1:2:1	NMP	8
9	Cu	1:2:1	NMP	56
10	Cu	1:2:2	NMP	82
11	Cu	1:2:2	DMF	77
12	Cu	1:2:2	DMSO	72
13	Cu	1:2:2	DCM	0
14	Cu	1:2:2	CH_3CN	0
15	**Cu**	**1:3:3**	**NMP**	**97(85[b])**
16	Cu	1:3:3	NMP	81[c]

[a] ^{19}F NMR Yields; [b] Isolated Yields; [c] Under N_2.

With the optimized reaction conditions in hand, the scope of the *gem*-difluoromethylenation with a number of arylboronic acids was investigated (Table 2). A wide range of arylboronic acids were readily converted into the corresponding *gem*-difluoromethylenation arenes in moderate to excellent yields. The results were almost independent of substituents type and position on the aromatic ring (**3e-3g**, **3r-3t**). Arylboronic acids containing electron-donating groups were readily converted into the corresponding products in moderate to good yields (**3e**-**3h**). While, substrates with electron-withdrawing groups, such as trifluoromethyl (**3m**), cyano (**3n**), acetyl (**3o**), formyl (**3p**), nitro (**3q**), and ester (**3r**-**3t**), gave the corresponding *gem*-difluoromethylenated arenes in moderate to excellent yields. Carbonyl groups such as ketone, ester, and aldehyde (**3o**-**3t**) could be survived, although the conventional nucleophilic fluoroalkylation attack generally occurred in carbonyl carbon. Importantly, the halogenated arylboronic acids were always almost quantitative into the corresponding difluoromethylated products, whereas a substitution of the corresponding halide was never or rarely observed (**3i-3l**). This situation is remarkable, because most common difluoromethylation reactions substitute halides, especially iodides.[9] Therefore, the new transformation shows a reaction pathway that is orthogonal to common routes. Interestingly, the heterocyclic arylboronic acids and vinyl boronic acids could be successfully *gem*-difluoromethylenated to afford products in moderate yields (**3u**-**3y**). It is particularly noteworthy that the 1,4-phenylenediboronic acid was a suitable substrate for transformation to afford bis-difluoromethylenated product (**3z**).

Table 2. Scope of *gem*-difluoromethylenated arylboronic acids with **2**.[a]



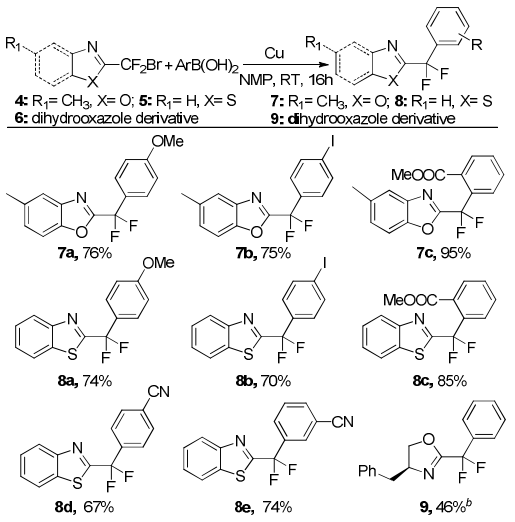
[a] Isolated Yields.

Bromodifluoromethylated oxazolic and thiazolic derivatives **4**-**6** were also applied in this cross-coupling reaction, which proceeded smoothly to afford the *gem*-difluoromethylenated arenes in good to excellent yields (Table 3). Methyl-substituted bromodifluoromethylated benzoxazole **4** was converted into the corresponding *gem*-difluoromethylenated arenes **7a-7c** in 75%-95% yields. Bromodifluoromethylated benzothiazole was also a suitable substrate, providing compounds **8a-8e** in good yields. Interestingly, the bromodifluoromethylated dihydrooxazole derivative **6** afforded **9** in synthetically useful yield. It is noteworthy that dihydrooxazoles have important applications in the design of drug molecules and chiral catalysts. Thus, this method provided a convenient and facile rout for such valuable building blocks. However, 2-(bromodifluoro-methyl)-1-butyl-benzoimidazole was ineffective under the optimized conditions.

The oxazoles are useful equivalents of protected acid[13] and therefore can be easily converted to various functional groups, such as formyl (CHO), carbonyl (C=O), ester (CO_2R), etc.[14] We believe that this versatility makes difluoromethylenated oxazoles

useful in the synthesis of new CF_2 building units. To demonstrate this synthetic potential, we tested the transformation of **3d** to 2-([1,1'-biphenyl]-4-yl)-2,2-difluoroacetic acid with zinc chloride in 14% HCl/EtOH at 80 °C, affording 65% yield (ESI, S16). Difluoroacetic acid group is known as an important precursor for the construction of difluoromethyl[7b] or trifluoromethyl group.[15] Therefore, this new strategy can be applied to the synthesis of a large number of fluorine-containing drug candidates.

Table 3. *gem*-Difluoromethylenated of arylboronic acids wih **4**-**6**.[a]

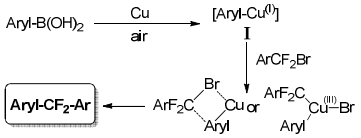


[a] Isolated Yields; [b] 50°C under N_2 atmosphere.

It has previously been shown that a Cu^0 can initiate the generation of radicals from difluoroalkyl halides through single electron transfer (SET).[9d] To identify whether a radical pathway is involved in the Cu-mediated transformation, several experiments were conducted (ESI, Table S2). Experimental studies showed that the yields of the Cu-mediated *gem*-difluoromethylenation of phenylboronic acid were almost identical in the presence or absence of ambient light. Furthermore, the addition of hydroquinone, a known radical inhibitor, and 1,4-dinitrobenzene, an electron-transfer scavenger, had a negligible impact on the yield of reactions under air atmosphere. These results suggest against a purely free radical pathway.

The unique effectiveness of Cu in this reaction is mechanistically intriguing. Therefore, we carried out a few control reactions to probe for the possible mechanism. First, activated Cu powder was reacted with **2** in NMP under air. No new product was detected by ^{19}F NMR and reactant **2** was fully recovered. This result indicated that [$ArCF_2Cu$] is not formed in the aforementioned reaction. When we applied a stoichiometric amount of $PhB(OH)_2$ with Cu powder, a biphenyl product was afforded in 76% yield, suggesting that [PhCu] intermediates play an important role in the reaction.[16] To our delight, the desired product **3a** was observed in 23% yield when a coupling reaction was conducted by treating **2** with [PhCu] prepared according to a procedure reported by Costa. [17]

On the basis of these observations, the proposed reaction mechanisms were depicted in Scheme 2. Arylboronic acid is first converted to [Aryl-Cu^I] intermediate in the presence of Cu powder and air. This cuprate of aryl copper species could either react with **2** by oxidative addition to form a $Cu^{III}(ArCF_2)(Aryl)$ species, followed by reductive elimination to give Aryl–CF_2–Ar, or directly initiate an S_N2-type substitution (or σ-bond metathesis) reaction at the CF_2 center to release the desired product **3**. There was also a possibility that [Cu^I] participates in the same reaction (Table 1, entry 3).



Scheme 2. Plausible mechanistic pathways.

In summary, we have disclosed a first example of a simple and highly efficient Cu-mediated *gem*-difluoromethylenation of a variety of aryl, heteroaryl and vinyl boronic acids with inexpensive bromodifluoromethylated heterocyclic compounds. The transformations were performed in air at room temperature without the need for sealed reaction vessels and, importantly, a ligand, a base, or an additive was not necessary. The remarkable functional group tolerance and a wide substrate scope means that this reaction will find wide applications in various drugs discovery and development. Ongoing studies are focused on probing the mechanism and developing related Cu-catalyzed *gem*-difluoromethylenation transformations.

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Notes and references

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