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Direct gem-Difluoromethylenation of sp3-Hybridized Carbon Center through Copper-Mediated Radical/Radical Cross-Coupling for Construction of CH2-CF2 Linkage

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Direct *gem*-Difluoromethylenation of sp^3-Hybridized Carbon Center through Copper-Mediated Radical/Radical Cross-Coupling for Construction of CH_2-CF_2 Linkage

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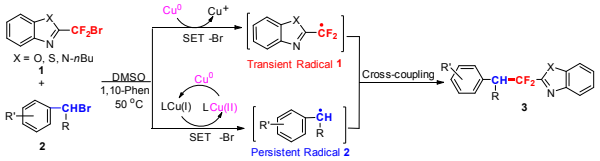
A efficient direct *gem*-difluoromethylenation of sp^3-hybridized carbon center in benzyl bromides using benzo-1,3-azolic (oxa-, thia- or aza-) difluoromethyl bromides for construction of CH_2-CF_2 linkage has been developed through radical/radical C-C cross-coupling via two separate single electron transfer processes (SET) under the promotion of different copper sources.

Introduction of *gem*-difluoromethylene moiety (-CF_2-) into organic molecule to alter its stability, lipophilicity, bioavailability, and biopotency has attracted great attention and has accumulated substantial research results.[1] However, only very few reports involved in research on *gem*-difluoromethylene moiety acting as a part of valuable linkage to conjugate two pharmacophores in twin-drug chemistry, even though the *gem*-difluoromethylene moiety has been proved to be a key alternative structural unit of CH(OH)-linkage in cyclitol and carbohydrate systems.[2] *gem*-Difluoromethylene moiety is known as isosteric and isopolar to an ethereal oxygen atom or a carbonyl group, and is a lipophilic hydrogen bond donors.[3] Furthermore, the transposition of CH_2 into CF_2 can block the metabolic oxidation,[4] and can also lead to the increase inhibition of HIV virus in vitro.[5] On the other hand, the dimethylene linkage has more highly selective inhibition of HIV-1 reverse transcriptase-associated enzyme.[6] Therefore, we envisioned that 1,1-difluoro-dimethylene (CH_2-CF_2) moiety could serve as a linkage to significantly increase affinity twin drug and provide sufficient drug stability during systemic circulation. The key for the efficient construction of the linkage should be the formation of Csp^3-CF_2 bond. Direct coupling of two radicals is a powerful approach for the bond formations.[7] According to Ingold–Fischer persistent radical effect,[8] the simultaneous generation of benzyl radicals (as persistent radicals) and difluoromethylene radicals (as transient radicals) may have great potential for the selective construction of the CH_2-CF_2 bond.

Herein, we would like to report a simple and unique method for construction of CH_2-CF_2 linkage through direct radical/radical cross-coupling *gem*-difluoromethylenation of the C_{sp^3} center of benzyl bromides using readily available benzo-1,3-azolic difluoromethyl bromides[9] promoted by different copper sources *via* two separate single electron transfer (SET) processes to form the C_{sp^3}-CF_2 bonds under mild reaction conditions (Scheme 1).



Scheme 1. Cu-mediated radical/radical cross-coupling for Construction of CH_2-CF_2 Linkages

The *gem*-difluoromethylenation of sp^3 carbon center has been much less studied[10] than their sp^2 counterparts,[11] and is still a great challenge. In our former research, Cu^0-mediated cross-coupling of 1,3-azolic difluoromethyl bromides with aryl halides could efficiently construct C_{sp^2}-CF_2 bonds.[11a] However, the reaction using alkyl halide such as 2-bromomethyl-naphthalene instead of aryl halides, only gave a trace amount of desired C_{sp^3}-CF_2 cross-coupling product **3aa** when **1a** and **2a** was heated at 50 °C (Table 1, entry 1). Thus, further reaction condition screening was carried out using benzo-1,3-oxazolic difluoromethyl bromide (**1a**) with 2-bromomethyl-naphthalene **2a** as the model substrate. Using stoichiometric amounts of $CuBr_2$ or CuBr alone failed to give any desired product **3aa** either (Entries 2 and 3). Encouragingly, the yield can be substantially improved from 5% to 64% by adding 20 mol% of 1,10-phenanthroline into the reaction mixture (Entry5). And amazingly, adding a catalytic amount of $CuBr_2$ to

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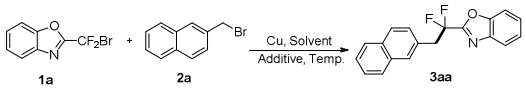
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

the mixture of stoichiometric amount of Cu^0 and halides dramatically increased the yield of the desired product to 85% (Entry 6). Similar results were observed in the reaction where catalytic amount of CuBr was used instead of $CuBr_2$ (Entry 7). These results indicated that $CuBr_2$ and CuBr could be involved in catalytic cycle of the reaction. Considering that $CuBr_2$ is cheaper and more stable than CuBr, we choose $CuBr_2$ as catalyst. DMSO gave the best results among the solvents screened (Entries 14-17). The yield dropped when the reaction was run at 80 °C or room temperature (Entries 10 and 11).

Table 1. Optimizations of copper-mediated cross-coupling of **1a** and **2a**

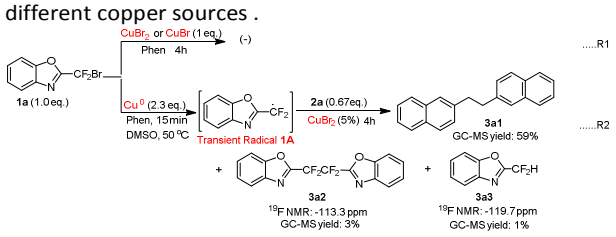


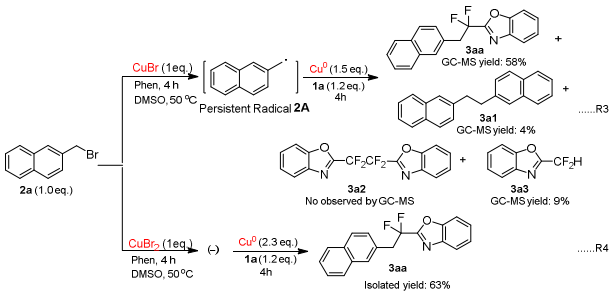
1a 2a 3aa

Entry	Copper source (mol%)	Additive (mol%)[b]	Solvent	Yield(%)[a]
1	Cu^0 (230)	-	DMSO	5
2	CuBr (110)	-	DMSO	0
3	$CuBr_2$ (110)	-	DMSO	0
4	Cu^0 (230), $CuBr_2$ (5)	-	DMSO	39
5	Cu^0 (230)	Phen (20)	DMSO	64
6	Cu^0 (230), $CuBr_2$ (5)	phen (20)	DMSO	85
7	Cu^0 (230), CuBr (5)	phen (20)	DMSO	85
8	Cu^0 (120), CuBr (5)	Phen (20)	DMSO	52
9	Cu^0 (120), CuBr (110)	Phen (20)	DMSO	80
10[c]	Cu^0 (230), $CuBr_2$ (5)	Phen (20)	DMSO	67
11[d]	Cu^0 (230), $CuBr_2$ (5)	Phen (20)	DMSO	46
12	Cu^0 (120), $CuBr_2$ (5)	Phen (20)	DMSO	46
13[e]	Cu^0 (230), $CuBr_2$ (5)	Phen (20)	DMSO	75
14	Cu^0 (230), $CuBr_2$ (5)	Phen (20)	dioxane	NR[f]
15	Cu^0 (230), $CuBr_2$ (5)	Phen (20)	DCM	13
16	Cu^0 (230), $CuBr_2$ (5)	Phen (20)	NMP	69
17	Cu^0 (230), $CuBr_2$ (5)	Phen (20)	MeCN	76

[a] ^{19}F NMR yield using benzotrifluoride as an internal standard, reactions were carried out with molar ratio 1:0.67of **1a**:**2a** in 2 mL solvent at 50 °C for 4 hr. [b] Phen = 1,10-Phenanthroline. [c] at 25 °C. [d] at 80 °C. [e] Reaction lasted 12 hr. [f] NR = No reaction

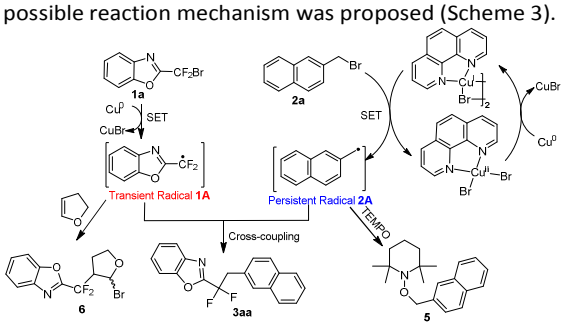
Interestingly, copper sources with the following three combinations work well for the coupling reaction: (a) 2 equiv. of Cu^0 and catalytic amount of $CuBr_2$ (Table 1, entry 6), (b) one equiv. of Cu^0 and one equiv. of CuBr (Entry 9), (c) 2 equiv. of Cu^0 and catalytic amount of CuBr (Entry 7). To understand the role of the different copper sources, and to gain some mechanistic insights into the cross-coupling reaction, the following experiments were conducted and were traced by GC-MS and ^{19}F NMR. Experiments R1 to R4 in Scheme 2 were used to investigate the reactions of reactants **1a** and **2a** with different copper sources .





Scheme 2. Stepwise experiments of cross-coupling *gem*-difluoromethylenation

The reactions of the substrate **1a** with CuBr or $CuBr_2$ alone hardly happened (Scheme 2, R1). However, the reaction mixture of **1a** with copper powder only revealed very weak signals at -113.3 and -119.7 ppm (**3a2** and **3a3**) after 15 min by ^{19}F NMR. It clearly showed that **1a** was consumed completely during 15 min. When **2a** and $CuBr_2$ were added to the above reaction mixture, no cross-coupling product **3aa** was generated after stirring for 4h, only homo-coupling products **3a1** and **3a2** were observed in 59% and 3% yield, respectively, and 1% of **3a3** was found by GC-MS (R2). Strangely, no new major fluorine-containing products were traced by TLC or ^{19}F NMR. These observation suggested that **1a** could be quickly transformed by Cu^0 alone into free radical **1A**,[11a] which has a short lifetime (transient radical) and easily decomposes in the absence of **2a.** On the other hand, we found that **2a** could react with 1 equiv of CuBr with 1,10-phenanthroline as ligand, which confirmed by TLC analysis. When **1a** and Cu^0 was added to the above reaction mixture after stirring for 4 h, the reaction provided product **3aa** in 58% yield along with very small amount of **3a1** and **3a2,** no **3a3** was found (R3) by GC-MS analysis. But **2a** could not react with $CuBr_2$ alone (R4). These observations imply that benzyl radical **2A** has longer lifetime (persistent radical, only partly decomposes in 4 hours according to R3) than radical **1A**. Thus, once radical **1A** was produced in the second step of R3, it immediately coupled with benzyl radical **2A** generated in the first step to obtain cross-coupling product. According to the above results, we inferred that Cu^0 selectively react with substrate **1** first, while benzyl bromide reacted preferentially with CuBr (reactant or generated by $CuBr_2$ reacting with Cu^0 *in situ*) using 1,10-phenanthroline as ligand. From the experimental facts, the possible reaction mechanism was proposed (Scheme 3).



Scheme 3. Possible mechanistic pathway

The coupling reaction proceeded via two separate single electron transfer (SET) processes. one SET from Cu^0 to substrate **1** to form a radical anion, which generates transient radical **1A** upon the loss of halide,[11a] the other SET from the electron-rich copper(I) complex to benzyl bromide to form a neutral persistent benzylic radical **2A** and copper(II) complex. The copper(II) complex is reduced back to copper(I) complex by Cu^0. Then persistent radical **2A** couples with the transient radical **1A** to afford the desired cross-coupling products in highly selective according to the persistent radical effect.[8]

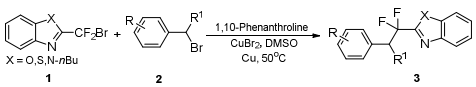
To prove the existence of radical intermediates, the TEMPO trapping reaction was carried out.[12] One equiv of TEMPO was reacted with benzyl bromide (**2a**) in the presence of stoichiometric Cu^0 and catalytic amount of $CuBr_2$ using 1,10-phenanthroline as ligand in DMSO. The TEMPO trapped complex **5** was isolated in 64% yield. The other copper source combinations could also provide the complex **5** (Table S1 in the supporting information). The results support the formation of benzylic radical species **2A**. Furthermore, when TEMPO was added in the standard reaction system (Table 1, entry 6), the *gem*-difluoromethylenation reaction was significantly suppressed and TEMPO trapped complex **5** was formed in 5% isolated yield. However, the adduct of TEMPO with **1a** was not detected on the basis of ^{19}F NMR analysis. Nevertheless, evidence of the formation of 1,3-oxazolic difluoromethyl radical **1A** was found by the observation of radical adduct **6** in the reaction of 2,3-dihydrofuran with substrate **1a** in the presence of copper powder in DMSO by ^{19}F NMR and GC-MS analysis (Scheme S1 in the supporting information).[13] Thus, the *gem*-difluoromethylenation of sp^3-hybridized carbon center was demonstrated to be a radical/radical cross-coupling process.

Under the optimized reaction conditions (Table 1, entry 6), the scope of benzyl bromides **2** and benzo-1,3-azolic difluoromethyl bromides **1** were examined, and the representative results are illustrated in Table 2. The reactions were compatible with both electron-donating (Table 2, entry 3) and electron-withdrawing groups (Entries 4-12) on the aryl rings of primary benzyl bromides **2**. Electron-deficient benzyl bromides (Entries 4 and 10) gave much higher yields. *o*- and *p*-Nitrobenzyl bromides (Entries 4 and 6) gave better results than *m*-nitrobenzyl bromides (Entry 5). 2-(Bromomethyl)naphthalene (**2a**) afforded **3aa** in 85% yield (Entry 1), and 2-bromomethyl-1,3-dichloro-benzene also provided **3ao** in 88% yield under the same reaction conditions (Entry 15). On the other hand, this methodology is also suited for the smaller steric hindrance secondary benzyl bromide (**2p**) (Entry 16).[14] However, the larger steric hindrance secondary benzyl bromide (**2s**) hardly provided the desired product **3as** (Entry 19).

This cross-coupling process is tolerant to a variety of functional groups attached to benzylbromides, such as ester, cyano, nitro, carbonyl groups, ether and halides, which provides opportunities for further transformations. It is noteworthy that the bromine on the aromatic ring is also compatible with the copper-mediated reaction conditions (Entry 14). Heterocyclic aromatic methyl bromide (Entry 17) could also serve as suitable coupling partners. Chloromethyl benzene is not reactive enough in this cross-coupling process (Entry 20).

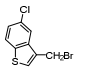
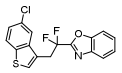
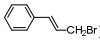
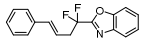
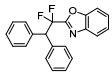
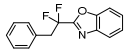
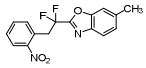
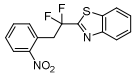
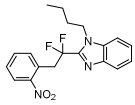
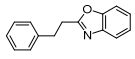
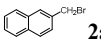
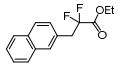
To further demonstrate the utility of this protocol, other 1,3-azolic difluoromethyl bromides such as 2-bromodifluoromethyl-6-methyl-benzoxazole (**1a'**), 2-bromodifluoromethyl-benzothiazole (**1b**), *N*-alkyl-2-bromodifluoromethyl-benzoimidazole (**1c**) were examined for the coupling with *o*-nitrobenzyl bromide. The *gem*-difluoromethylenation all worked well (Entries 21-23). However, if the transient radical source 1,3-oxazolic difluoromethyl bromide **1a** was replaced with 2-bromomethyl-benzooxazole (Entry 24) or ethyl bromodifluoroacetate (Entry 25), the yield became much lower, thus the remarkable reaction characteristics of *gem*-difluoromethylene building block could mainly attribute to the unique π-conjugated aryl-fused 1,3-oxazolic moiety and the special role of the fluorine atoms.

Table 2. Copper-mediated *gem*-difluoromethylenation of **2**



1 2 3

Entr	Substrate **2**	Products **3**	Yields [a]
1	**2a**	**3aa**	85
2	**2b**	**3ab**	52
3	**2c**	**3ac**	50
4	**2d**	**3ad**	92
5	**2e**	**3ae**	45
6	**2f**	**3af**	91
7	**2g**	**3ag**	77
8	**2h**	**3ah**	49
9	**2i**	**3ai**	89
10	**2j**	**3aj**	94
11	**2k**	**3ak**	88
12	**2l**	**3al**	76
13	**2m**	**3am**	46
14	**2n**	**3an**	63
15	**2o**	**3ao**	88
16	**2p**	**3ap**	30

17		**2q**		**3aq**	77
18		**2r**		**3ar**	20
19		**2s**		**3as**	Trace[b]
20		**2t**		**3at**	Trace[b]
21		**2d**		**3a'd**	85
22		**2d**		**3bd**	85
23		**2d**		**3cd**	66
24		**2d**		**9**	Trace
25		**2a**		**10**	34

[a] Isolated yield. [b] ^{19}F NMR yield using benzotrifluoride as an internal standard.

In conclusion, a copper-mediated *gem*-difluoromethylenation of sp^3-hybridized carbon center to form C_{sp^3}-CF_2 bonds *via* radical/radical C-C cross-coupling for constructing CH_2-CF_2 linkage has been developed. The method is tolerant of a wide range of functional groups and provides the *gem*-difluoromethylene compounds in good to excellent yields under mild reaction condition. The mechanism study showed that the coupling reaction proceeds through two separate single electron transfer (SET) processes promoted by different copper sources, and the desired products are derived from the cross-coupling of two carbon radicals. This copper-mediated *gem*-difluoromethylenated cross-coupling method could provide a new synthetic strategy for drug design and innovation.

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