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# Copper-Catalyzed *gem*-Difluoroolefination of Diazo Compounds with $TMSCF_3$ via C−F Bond Cleavage

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*Supporting Information*

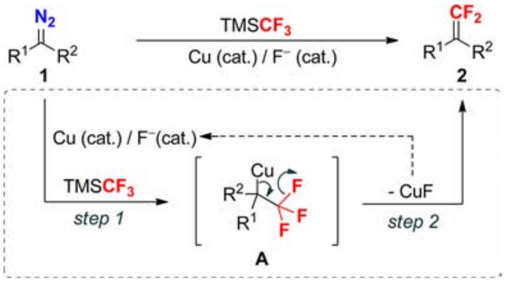
**ABSTRACT:** A novel Cu-catalyzed *gem*-difluoroolefination of diazo compounds is described. This transformation starts from readily available $TMSCF_3$ and diazo compounds, via trifluoromethylation followed by C−F bond cleavage, to afford the desired 1,1-difluoroalkene products.

Fluorine-containing organic molecules often possess elevated reactivity, lipophilicity, and bioactivity compared to their nonfluorinated counterparts.[1] For instance, 1,1-difluoroalkenes are structurally unique organofluorine compounds, which are used as enzyme inhibitors via an addition−elimination mechanism.[2] The *gem*-difluorovinyl functionality is also considered as a bioisostere of the carbonyl group in drug design.[3] The *gem*-difluorovinyl moiety could be converted to other useful fluorinated functionalities such as trifluoromethyl,[4] difluoromethyl,[3] monofluoroalkenyl,[5] and difluoromethylenyl groups.[6] Direct $C{=}CF_2$ double bond construction from aldehydes and ketones,[5,7] pyrolysis of difluoromethylene-containing compounds,[8] and cross-coupling with *gem*-difluorovinyl building blocks[4b,9] are conventional methods for the synthesis of 1,1-difluoroalkenes.

Recently, transition-metal-catalyzed fluorination,[10] fluoroalkylation,[11] and fluoroarylation[12] have attracted much attention in synthetic organic chemistry, owing to the mild reaction conditions and excellent functional-group tolerance in these transition-metal-assisted reactions. However, the transition-metal-mediated $C{=}CF_2$ double bond formation reaction still remains a challenging task. Although the olefin metathesis reaction proved to be a powerful approach for olefin synthesis,[13] its application in the synthesis of fluorinated olefins has been less successful.[14] Grubbs and co-workers attempted the reaction between 1,1-difluoroethene and a ruthenium carbene catalyst, and they found that only a small amount of $\beta,\beta$-difluorostyrene was formed under the stoichiometric reaction conditions.[15] On the other hand, diazo compounds, an important type of carbene precursors, are widely used in olefination reactions;[16] however, there is still a lack of transition-metal-catalyzed efficient *gem*-difluoroolefination of diazo compounds.[17]

Trifluoromethylcopper ($CuCF_3$), which is often pregenerated prior to the desired reactions, is a powerful trifluoromethylating agent.[18] Recently, much effort has been devoted to developing $CuCF_3$-mediated trifluoromethylations with the use of a substoichiometric amount of copper.[19] Previously, we reported a water-promoted and copper-mediated trifluoromethylation of $\alpha$-diazo esters using pregenerated "$CuCF_3$".[20] Under the strictly anhydrous conditions, 1,1-difluoroalkenes could be obtained in moderate yields,[20] which indicates that the 2,2,2-trifluoroethylcopper intermediate (**A**) could undergo $\beta$-fluoride elimination (Scheme 1, $R^2$ = COOR).[21] Based on this finding, we envisaged that a substoichiometric amount of copper might be able to catalyze the *gem*-difluoroolefination of diazo compounds (Scheme 1). However, we quickly realized that two issues have to be considered before a catalytic version of Cu-assisted *gem*-difluoroolefination can be achieved: (a) how to enable **1** to efficiently react with the in situ generated "$CuCF_3$" to give **A** in the presence of only a catalytic amount of Cu(I) (Scheme 1, step 1);[20] and (b) how to facilitate an efficient $\beta$-fluoride elimination of **A** to regenerate the CuF catalyst (Scheme 1, step 2).[21b]

**Scheme 1. Proposed Cu-Catalyzed *gem*-Difluoroolefination of $\alpha$-Diazo Esters**



Our investigation started with addressing the first issue. Previously, an excess amount of water or CuI was added to enhance the reactivity of pregenerated "$CuCF_3$" to efficiently react with **1**.[20] However, under the catalytic reaction conditions where "$CuCF_3$" was in situ generated from CuI/CsF/$TMSCF_3$ (Scheme 1, step 1), the addition of water jeopardized the desired reaction by protonating the in situ generated "$CF_3^-$" from $TMSCF_3$/CsF. We also examined the possibility of using extra CuI to promote the reaction between **1** and in situ generated "$CuCF_3$". When we conducted Cu-catalyzed *gem*-difluoroolefination with ethyl phenyldiazoacetate (**1a**) as a model substrate using 20 mol % of CuI and 10 mol % of CsF,[22] to our surprise and disappointment, no desired product **2a** was detected, and trifluoromethylated product **2a′** was obtained in 7% yield (eq 1a). After further optimization of the reaction

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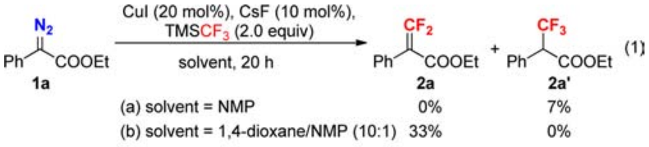
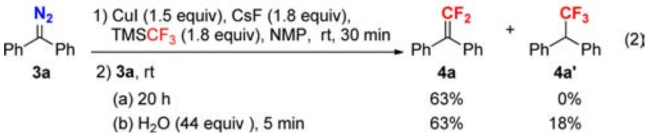




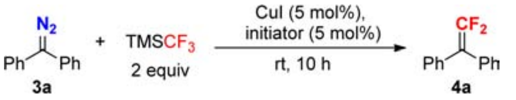
parameters (using 1,4-dioxane/NMP as solvent), **2a** was formed in only 33% yield (eq 1b, for more detailed information, see SI). Thereafter, we envisaged another plausible approach to address the first issue, namely, using a more reactive diazo compound to react with "CuCF$_3$". It is well-known that diaryl diazomethanes possess higher reactivity than $\alpha$-diazo esters.[23] When diphenyl diazomethane (**3a**) was utilized as a substrate and subjected to the pregenerated CuCF$_3$ without adding any promoter (water or CuI), we were delighted to find that 1,1-difluoroalkene **4a** was obtained in 63% yield after 20 h without the formation of any trifluoromethylated product **4a′** (eq 2a). More interestingly, when **3a** was subject to the standard water-promoted trifluoromethylation reaction conditions (44 equiv of water were added),[20] **3a** was consumed in 5 min and **4a** was obtained in 63% yield, with the trifluoromethylation product **4a′** being formed in only 18% yield (eq 2b). These results indicate that **3a** can directly react with unactivated "CuCF$_3$" (from CuI/CsF/TMSCF$_3$), and the resulting 2,2,2-trifluoroethylcopper intermediate **A** (Scheme 1) readily undergoes $\beta$-fluoride elimination to afford 1,1-difluoroalkene **4a** (even in the presence of an excess amount of water!), which nicely address the aforementioned issues.

Encouraged by these results, we soon examined the catalytic version of the reaction between **3a** and TMSCF$_3$ (Table 1). To our delight, when 5 mol % of CuI and 5 mol % of CsF were applied, **3a** readily underwent *gem*-difluoroolefination to afford **4a** in 85% yield (Table 1, entry 1). When 1,4-dioxane was used as solvent, the reaction was sluggish (entry 2). Further examination revealed that the use of a mixed solvent system of 1,4-dioxane and NMP (entries 1, 3−8) was better than solely using 1,4-dioxane (entry 2) or NMP (entry 9), and the optimal ratio of 1,4-dioxane to NMP was found to be 10:1. When lowering the loading of CsF to 2.5 mol %, the yield decreased sharply (entry 10). However, the yield was also slightly decreased when more CsF (10 mol %) was used (entry 11). Other Lewis base activators for TMSCF$_3$, such as KF, tetrabutylammonium triphenyldifluorosilicate (TBAT), tetramethylammonium fluoride (TMAF), and $^t$BuOK, were found to be inferior to CsF (entries 12−15). CuCl was not as effective as CuI when used to promote the *gem*-difluoroolefination reaction (entry 16). The use of other solvents, such as THF/NMP, DCM/NMP, and toluene/NMP, resulted in lower yields (entries 17−19). It should be noted that, in the absence of either a Cu(I) catalyst or CsF, the reaction was significantly inhibited (entries 20−21).

With the optimized reaction conditions in hand (Table 1, entry 1), we further examined the substrate scope and limitation of this reaction. The reactions with various diaryl diazomethanes proceeded smoothly to give 1,1-difluoroalkenes in moderate to excellent yields (Table 2). The substrates with electron-donating substituents on the arenes (Table 2, **4d**−**4l**) generally gave lower yields. When the reaction temperature was decreased, the reactions with **3e**, **3f**, and **3i** proceeded smoothly to give corresponding products **4e**, **4f**, and **4i**, respectively, in higher yields. However, in the case of bis(4-dimethylamino)-phenyl diazomethane (**3l**), no desired product **4l** was obtained. This might be attributed to the strong electron-donating amino group making the carbenic carbon more electron-rich through p−$\pi$ conjugation and thus difficult to undergo migratory insertion into the Cu-CF$_3$ single bond.[24] On the contrary, those with electron-withdrawing substituents on the arenes generally gave higher yields (Table 2, **4m**−**4x**). It is noteworthy that no aromatic trifluoromethylation occurred in the reactions with substrates bearing a F, Cl, or Br substituent (Table 2, **4m**−**4v**). The reaction was found to be not sensitive to the ortho-, meta-, or para-substituents in the aromatic rings. Note that this reaction represents arguably the most general *gem*-difluoroolefination method for the synthesis of 2,2-diaryl-1,1-difluoroolefins.[5,7−9] When alkyl-substituted diazo compound **3y** was used, the product yield was significantly lower, probably due to the side reactions of the diazo compounds such as self-condensation and 1,2-H shifts.[25]

When TMSCF$_2$CF$_3$ was employed alternatively as a fluoroalkylating reagent, 1,1,1,2-tetrafluoro-3,3-diphenylpropene (**5a**) was obtained in 39% yield (eq 3). The relatively lower yield of **5a** is probably due to the fact that the in situ generated pentafluoroethyl anion (CF$_3$CF$_2$$^-$) readily undergoes $\beta$-fluoride elimination to give tetrafluoroethene (CF$_2$═CF$_2$, detected by $^{19}$F NMR and GC-MS in this case). However, when pregenerated CuCF$_2$CF$_3$ was used, **5a** could be obtained in 70% yield (eq 4).

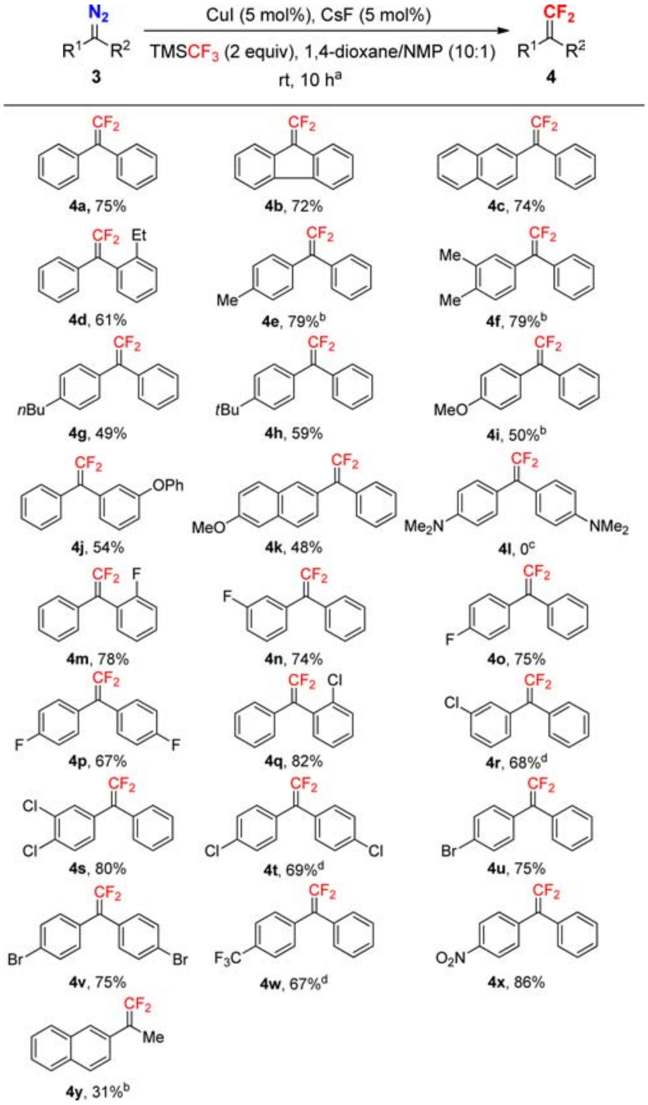
Table 1. Survey of Reaction Conditions



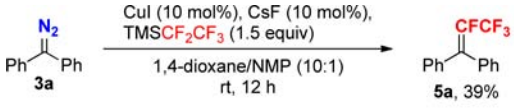
| entry | initiator | solvent | yield (%)[a] |
|---|---|---|---|
| 1 | CsF | 1,4-dioxane/NMP (10:1) | 85 |
| 2 | CsF | 1,4-dioxane | 21 |
| 3 | CsF | 1,4-dioxane/NMP (20:1) | 62 |
| 4 | CsF | 1,4-dioxane/NMP (15:1) | 82 |
| 5 | CsF | 1,4-dioxane/NMP (8:1) | 80 |
| 6 | CsF | 1,4-dioxane/NMP (5:1) | 70 |
| 7 | CsF | 1,4-dioxane/NMP (2:1) | 64 |
| 8 | CsF | 1,4-dioxane/NMP (1:1) | 59 |
| 9 | CsF | NMP | 2 |
| 10 | CsF | 1,4-dioxane/NMP (10:1) | 10[b] |
| 11 | CsF | 1,4-dioxane/NMP (10:1) | 77[c] |
| 12 | KF | 1,4-dioxane/NMP (10:1) | 69 |
| 13 | TBAT | 1,4-dioxane/NMP (10:1) | 47 |
| 14 | TMAF | 1,4-dioxane/NMP (10:1) | 8 |
| 15 | $^t$BuOK | 1,4-dioxane/NMP (10:1) | 50 |
| 16 | CsF | 1,4-dioxane/NMP (10:1) | 64[d] |
| 17 | CsF | THF/NMP (10:1) | 64 |
| 18 | CsF | DCM/NMP (10:1) | 34 |
| 19 | CsF | toluene/NMP (10:1) | 61 |
| 20 | CsF | 1,4-dioxane/NMP (10:1) | <5%[e] |
| 21 | none | 1,4-dioxane/NMP (10:1) | 0 |

[a] The reactions were carried out on 1 mmol scale. The yields were determined by $^{19}$F NMR with PhCF$_3$ as an internal standard. [b] 2.5 mol % of CsF was used. [c] 10 mol % of CsF was used. [d] 5 mol % of CuCl was used as the catalyst. [e] Without a Cu-catalyst.

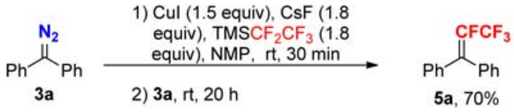
**Table 2. Cu-Catalyzed *gem*-Difluoroolefination of Diazo Compound 3**



[a] All reactions were performed by using 1.0 mmol of **3**, 0.05 mmol of CuI and CsF unless otherwise noted. The yields referred to isolated yields. [b] The reaction was performed at the melting point of the mixed solvent (6 °C). [c] The yield was determined by $^{19}$F NMR with $PhCF_3$ as an internal standard. [d] The reaction was performed on 2.0 mmol scale with 0.1 mmol of CuI and CsF.



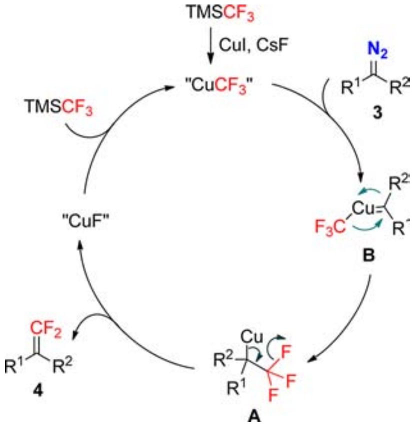
(3)



(4)

Based on the aforementioned results, we propose a plausible mechanism for the Cu-catalyzed *gem*-difluoroolefination of diazo compounds (Scheme 2). $TMSCF_3$ first reacts with CuI and CsF to generate $CuCF_3$, and the latter species reacts with diazo compound **3** to form Cu-carbene intermediate **B**. Intermediate **B** undergoes carbene migratory insertion into the Cu−$CF_3$ single bond to give intermediate **A**.[20] Then the species **A** undergoes a fast *β*-fluoride elimination to give *gem*-difluoroolefin product **4** and CuF, and CuF further reacts with $TMSCF_3$ to regenerate $CuCF_3$ (Scheme 2).

**Scheme 2. Proposed Mechanism of Cu-Catalyzed *gem*-Difluoroolefintion of Diazo Compounds**



In summary, we have developed a novel Cu-catalyzed *gem*-difluoroolefination of diazo compounds. This new synthetic protocol enables the efficient preparation of a variety of structurally diverse 1,1-difluoroalkenes, which promises to find applications in medicinal chemistry and materials science related fields. It was found that, even without the activation by water or CuI,[20] the "$CuCF_3$" species (generated from CuI/CsF/$TMSCF_3$) could still directly react with diaryl diazomethanes. Furthermore, the resulting 1,1-diaryl-2,2,2-trifluoroethylcopper intermediate **A** underwent facile *β*-fluoride elimination to give 1,1-difluoroalkene. Not only do these two important factors facilitate an efficient Cu(I)-catalyzed *gem*-difluoroolefination process, they also provide intriguing new insights into the unique reaction between "$CuCF_3$" and diazo compounds.[20] Moreover, this olefination process provides a proof of concept for the use of *β*-fluoride (or other leaving groups) elimination to realize a catalytic olefination via a Cu-carbene intermediate.[26] Further exploration of this new synthetic protocol is currently underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental procedures and characterization for all new compounds. This information 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.

## ■ ACKNOWLEDGMENTS

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(22) The reason for the ratio CuI/CsF = 2/1 is that 1 equiv of CuI is expected to prepare "$CuCF_3$", and the other equivalent is to activate "$CuCF_3$" to form highly reactive "$CuCF_3$".

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