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From C_1 to C_3: Copper-Catalyzed *gem*-Bis(trifluoromethyl)olefination of α-Diazo Esters with $TMSCF_3$

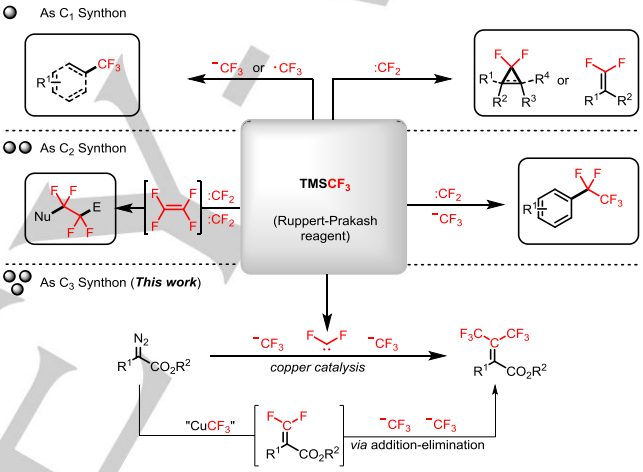
Qian Wang, Chuanfa Ni, Mingyou Hu, Qiqiang Xie, Qinghe Liu, Shitao Pan, and Jinbo Hu*

Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry.

Abstract: We have developed a Cu-catalyzed *gem*-bis(trifluoromethyl)olefination of α-diazo esters using $TMSCF_3$ as the only fluorocarbon source, providing an exquisite method to access *gem*-bis(trifluoromethyl)alkenes. This unprecedented olefination process involves a carbene migratory insertion into "$CuCF_3$" to generate the α-CF_3-substituted organocopper species, which then undergoes β-fluoride elimination and two consecutive addition–elimination processes to give the desired products. The key to this efficient one-pot C_1-to-C_3 synthetic protocol lies in the controllable double CF_3-addditions (over single and triple additions).

Organofluorine compounds have consistently found practical applications in life sciences and materials industry owing to the intriguing properties enabled by the fluorine substituents.[1] In recent years, numerous synthetic methods have been developed to introduce fluorine atoms or fluorinated moieties (such as CH_nF_{3-n} and XCH_nF_{3-n}; n = 0, 1, 2 and X = O, S) into organic compounds. Meanwhile, looming on the horizon are the ever-growing demands for novel structures containing specific moieties such as SF_5 and *gem*-bis(trifluoromethyl)methylene groups.[2] Among them, the *gem*-bis(trifluoromethyl)alkenes are much less prevalent, despite possessing a range of unique biological properties owing to the inductive effect of the geminal trifluoromethyl groups.[1b,c,f,g,3] Indeed, the *gem*-bis(trifluoromethyl)alkenes were found to be effective in preventing pregnancy in warm-blooded animals and used as precursors in the synthesis of fluorinated pyrethroids.[4-5]

However, in spite of these great potentials, there is a dearth of methods available for preparing the *gem*-bis(trifluoromethyl)alkenes.[6-10] Traditional approaches to such alkenes rely on the reactions of gaseous hexafluoroacetone with a phosphorous ylides (or alternatively, phosphonate carbanions),[6] or the reactions of hexafluorinated phosphorus ylide (formed *in situ*) with aldehydes.[7] However, the use of toxic gas and/or the lack of reactivity owing to the short life of the phosphorus ylides, lead to the limitation of the substrate scope and practicality of these methods. In 2001, Qing and co-workers reported the Pd-catalyzed trifluoromethylation of 1,1-dibromo-1-alkenes using $CuCF_3$, affording the trisubstituted *gem*-bis(trifluoromethyl)alkenes.[8] Recently, Cao and co-workers developed a nucleophilic trifluoromethylation of *gem*-difluoroalkenes; however, the process only gave modest overall yields of desired products, with the formation of a mixture of mono(trifluoromethyl)- and bis(trifluoromethyl)alkenes.[9] In general, these reactions suffer from the following drawbacks: 1) difficult to operate; 2) the use of toxic gas; 3) narrow substrate scope; and/or 4) low yields.[6-10] Therefore, the development of new methods for the straightforward and efficient synthesis of *gem*-bis(trifluoromethyl)alkenes is highly desirable.



Scheme 1. The synthetic applications of $TMSCF_3$ as a versatile fluorocarbon source.

Selective fluoroalkylations via selective assembly of fluorinated carbons have emerged as powerful tools for the synthesis of polyfluorinated compounds.[11,18,19] In this context, the Ruppert-Prakash reagent ($TMSCF_3$), a widely used nucleophilic trifluoromethylating agent, can serve as a versatile precursor for different fluorocarbon moieties in organic synthesis (Scheme 1).[12-19] Over the past few decades, $TMSCF_3$ has been used as a C_1 synthon for nucleophilic CF_3 transfer,[12a,b,g,13] radical CF_3 transfer,[14,15] as well as carbene-type CF_2 transfer (Scheme 1, top).[17] In 2017, we reported the generation and use of tetrafluoroethylene (TFE) in academic laboratories by dimerization of difluorocarbene generated from $TMSCF_3$.[18] More recently, we developed an efficient process for the homologation of fluorocarbon chains from C_1 to C_2, using $TMSCF_3$ as a source of C_2F_5 group for efficient aromatic pentafluoroethylations (Scheme 1, middle).[19] Inspired by these work, we sought to develop a process in which $TMSCF_3$ serves as a precursor for two trifluoromethyl and one difluorocarbene groups, thus achieving an unprecedented C_1-to-C_3 transformation using $TMSCF_3$ as the only

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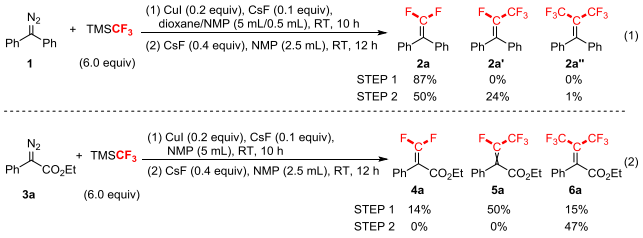
fluorocarbon source (Scheme 1, bottom). Previously, we reported a Cu-mediated trifluoromethylation of α-diazo esters in the presence of water.[20] More recently, we demonstrated that α-CF_3-substituted organocopper species generated from diaryl diazomethanes can undergo a fast β-fluoride elimination under the anhydrous conditions, thus leading to the *gem*-difluoroolefination products.[21] We envisioned that the *in situ* formed *gem*-difluoroalkenes might undergo two successive nucleophilic CF_3-addition/β-fluoride elimination processes in the presence of excess CF_3^-, which not only provides an exquisite and efficient access to *gem*-bis(trifluoromethyl)alkenes, but also represents an unconventional strategy of carbon chain elongation.

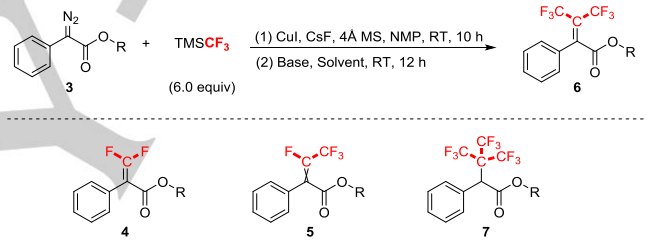


Scheme 2. Initial attempt.

We commenced our investigations with the reaction of diphenyl diazomethane **1** and 6.0 equivalents of $TMSCF_3$ by a two-step procedure (Scheme 2, eq 1). As expected, the *gem*-difluoroalkene **2a** was observed in 87% yield (determined by ^{19}F NMR) after the first step; when CsF (0.4 equiv) was added and stirred for another 12 hours, the desired *gem*-bistrifluoromethylated product **2a''** was formed in only 1% yield, with most *gem*-difluoroalkene **2a** (50%) being unconverted. We attributed this inefficient transformation to the relatively low electrophilicity of **2a**. In our previous *gem*-difluoroolefination reaction, we rationalized that the key point was the use of more reactive diaryldiazomethanes; however, when α-diazo esters was used, the product yield was much lower.[21] Hence, the optimization of reactivity in this chemistry must be achieved by keeping balance between the nucleophilicity of diazo compounds and the electrophilicity of the resultant *gem*-difluoroalkenes. Therefore, ethyl phenyldiazoacetate **3a** was employed as a substrate and subjected to this one-pot procedure (Scheme 2, eq 2). Interestingly, under the optimized reaction conditions (NMP as solvent), the *gem*-difluoroalkene **4a** was observed in only 14% yield, along with the formation of monotrifluoromethylated product **5a** (50%) and the *gem*-bistrifluoromethylated product **6a** (15%) after the first step; **4a** and **5a** disappeared and the yield of **6a** increased to 47% (by ^{19}F NMR) after the reaction!

Inspired by these results, we examined the *gem*-bis(trifluoromethyl)olefination reaction between methyl phenyldiazoacetate and $TMSCF_3$ in the presence of 20 mol% of CuI, 10 mol% of CsF, and 4 Å molecular sieves (MS) in NMP at room temperature. Given the fact that the excess CF_3^- anion may inhibit the reaction between copper species and diazo compounds **3a**,[22] CsF (0.4 equiv) was added as an external additive after the first step to accelerate the consecutive CF_3^- addition. To our disappointment, the desired 1,1-bis(trifluoromethyl)alkene product **6** was obtained in 11% yield, along with formation of perfluorobutylated product **7** in 7% yield (Table 1, entry 1). Changing the ester moiety of diazoacetate from methyl to ethyl group resulted in an increase of 28% in the yield of **6** (Table 1, entry 2). Further studies demonstrated that *the steric hindrance of the ester substituent has a significant effect on the yield and selectivity.* The best result was observed with *tert*-butyl phenyldiazoacetate **3c** (Table 1, entry 4). It is worth noting that when CsF was used as an additive, the *gem*-difluoroalkene **4** and the monotrifluoromethylated product **5** were completely consumed. The use of KF (0.4 equiv) in THF in the second step resulted in a higher yield of **6c** (Table 1, entry 5), indicating that the slow release of CF_3^- is crucial for the desired selectivity. Then several additives were screened (Table 1, entries 6-8). Gratifyingly, the reaction with KHF_2 produced the corresponding **6c** in 59% yield along with the formation of **5c** in 24% yield (Table 1, entry 8). The use of either 0.3 or 0.5 equivalent of KHF_2 was found to be less effective (Table 1, entries 9 and 10). The addition of CuI (0.2 equiv) together with KHF_2 significantly inhibited the formation of **6c** (Table 1, entry 11). Finally, solvent screening revealed that a mixture of NMP and THF (1:1) in the second step was the optimal solvent system (Table 1, entries 12-14). Interestingly, the monotrifluoromethylated product **5c** completely disappeared and the desired product **6c** was observed in moderate yield in the absence of 4 Å MS (Table 1, entry 15).

Table 1. Survey of Reaction Conditions.[a]



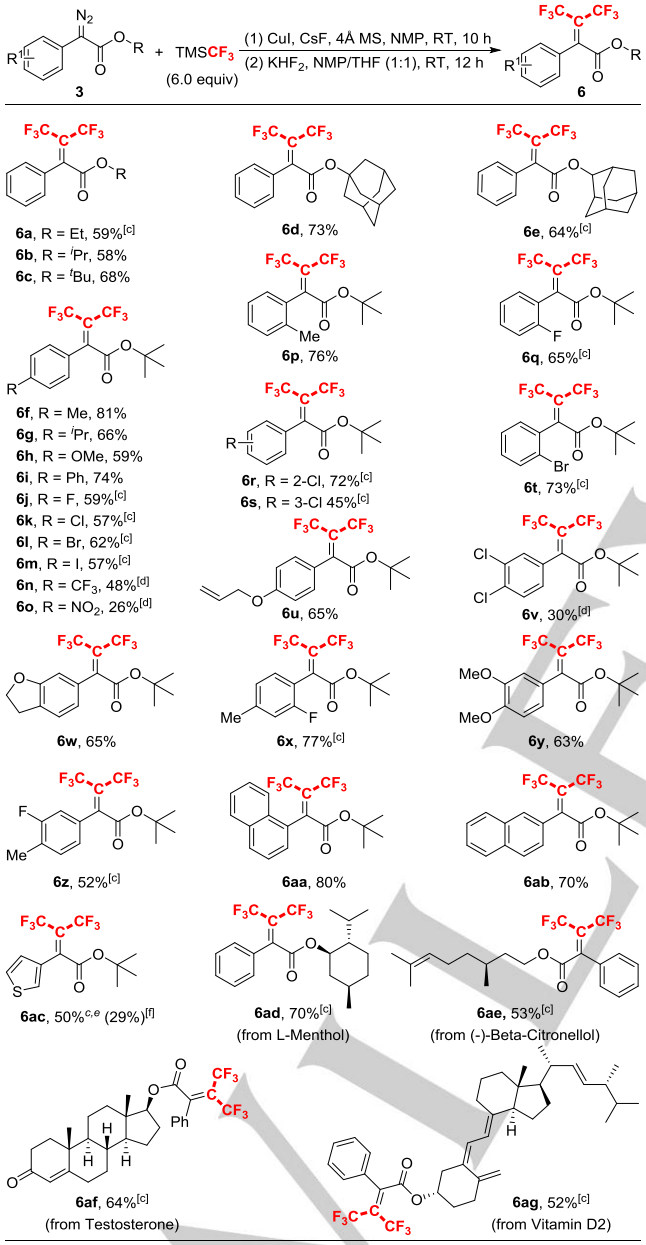
Entry	R	Base	Solvent	Yield (**4/5/6/7**,%)[b]
1	Me	CsF	NMP	0/0/11/7
2	Et	CsF	NMP	0/0/39/5
3	^{i}Pr	CsF	NMP	0/0/51/7
4	^{t}Bu	CsF	NMP	0/0/55/6
5	^{t}Bu	KF	THF	0/0/65/4
6	^{t}Bu	TASF	THF	0/0/44/9
7	^{t}Bu	TMAF	THF	0/12/59/4
8	^{t}Bu	KHF_2	THF	0/24/59/1
9[c]	^{t}Bu	KHF_2	THF	0/55/35/0
10[d]	^{t}Bu	KHF_2	THF	0/13/66/1
11	^{t}Bu	KHF_2/CuI	THF	9/66/11/0
12	^{t}Bu	KHF_2	NMP/THF (1:1)	0/9/**76**/3
13	^{t}Bu	KHF_2	NMP	0/0/55/7
14	^{t}Bu	KHF_2	DMF	0/0/64/4
15[e]	^{t}Bu	KHF_2	NMP/THF (1:1)	0/0/58/7

[a] Conditions: **3** (0.5 mmol),$TMSCF_3$ (6.0 equiv), CuI (0.2 equiv), CsF (0.1 equiv), and 4Å MS (50 mg), NMP (2.5 mL), RT, 10 h under argon atmosphere; base (0.4 equiv), solvent (2.5 mL), RT, 12 h under Ar. [b] Yields were determined by ^{19}F NMR with $PhOCF_3$ as internal standard. [c] KHF_2 (0.3 equiv). [d] KHF_2 (0.5 equiv). [e] In the absence of 4Å MS.

With the optimal conditions established (Table 1, entry 12), the scope of α-diazo esters for the reaction was investigated. As summarized in Table 2, a variety of aryl diazo esters reacted smoothly with $TMSCF_3$ to give the corresponding bistrifluoromethylated products in moderate to good yields. Aryl diazo esters with electron-withdrawing groups on the aromatic ring required higher loading of copper catalyst to achieve moderate to good yields; this can be ascribed to the relatively low reactivity of the substrates or the higher electrophilicity of the resulting *gem*-difluoroalkenes, which might participate in several competi-

tive reactions in the presence of excess CF_3^- species. However, highly electron-deficient substrates afforded lower yields even though a stoichiometric amount of copper was used (**6o**, **6v**). The reaction also showed a remarkable steric effect; the yields of substrates bearing various ester moieties increased along with the increase of the steric hindrance of the ester alkyl group (**6a**-**6e**). Ethyl phenyldiazoacetate **3a** also underwent this reaction by increasing the loading of CuI to accelerate the formation of *gem*-difluoroalkene, providing product **6a** in 59% yield.

Table 2. Scope of the *gem*-Bis(trifluoromethyl)olefination Reaction.[a,b]

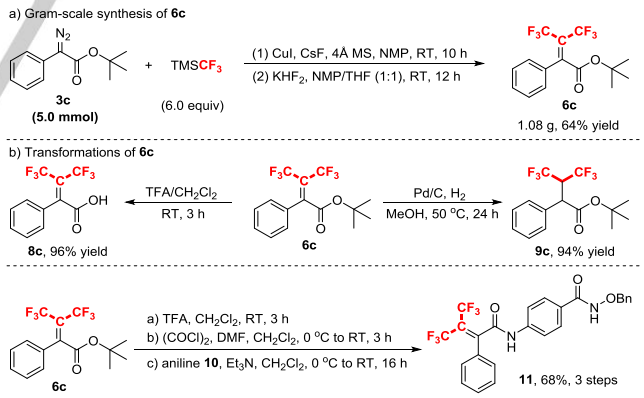


[a] Reaction conditions: **3** (0.5 mmol), $TMSCF_3$ (6.0 equiv), CuI (0.2 equiv), CsF (0.1 equiv), 4Å MS (50 mg), NMP (2.5 mL), RT, 10 h under argon atmosphere; Then KHF_2 (0.4 equiv), NMP/THF (1.25 mL/1.25 mL), rt, 12 h under argon atmosphere. [b] Isolated yield. [c] CuI (0.4 equiv), CsF (0.2 equiv) and KHF_2 (0.6 equiv) were used. [d] CuI (1.0 equiv), CsF (0.5 equiv) and KHF_2 (0.7 equiv) were used. [e] ^{19}F NMR yield with $PhOCF_3$ as an internal standard. [f] The monotrifluoromethylated product **5ac** was obtained in 29% ^{19}F NMR yield.

In addition, the *ortho*-substituted α-diazo esters gave higher yield, probably owing to the steric hindrance (**6p** and **6q, 6r, 6t**).

The *tert*-butyl α-aryl α-diazoacetates substituted with a variety of functional groups such as alkyl (**6f**, **6g**), alkoxy (**6h**, **6w**), phenyl (**6i**), halogen (**6j**-**6m** and **6q**-**6t**), trifluoromethyl (**6n**), and allyloxy (**6u**) were well tolerated under standard conditions. It is noteworthy that no aromatic trifluoromethylation product was found (**6l** and **6m, 6t**), providing a platform for further elaboration through aromatic cross-coupling strategies. The olefination of α-diazo esters bearing an alkene also worked well under the standard reaction conditions, and no cyclopropanation product was detected (**6u** and **6ae, 6ag**). To our delight, naphthalene and thiophene were also amenable to this process, providing the corresponding 1,1-bis(trifluoromethyl)alkenes in moderate to good yields (**6aa** and **6ab**, **6ac**). It should be noted that **6ac** was obtained along with minor amounts of inseparable monotrifluoromethylated product **5ac** ascribing to the electron-rich thiophene ring. In a final demonstration of the practicability of this *gem*-bis(trifluoromethyl)olefination protocol, several naturally existing alcohols could also be readily converted to the corresponding diazo compounds and applied to this reaction (**6ad**-**6ag**), providing an effective approach for the late stage functionalization of complex natural products.

To evaluate the synthetic potential of this unprecedented *gem*-bis(trifluoromethyl)olefination method, gram-scale synthesis and other synthetic applications were carried out (Scheme 3). The reaction of **3c** was easily scaled up to 5.0 mmol with only a slight decrease in yield. The 1,1-bis(trifluoromethyl)alkene **6c** can be readily converted to carboxylic acid derivative **8c** in the presence of trifluoroacetic acid (TFA). In addition, the double bond in compound **6c** could be hydrogenated to deliver α-hexafluoroisopropyl ester **9c**. Furthermore, we applied this process in the synthesis of a hexafluorinated analog of a histone deacetylase (HDAC) inhibitor.[23] The treatment of the acid (generated from **6c** with $(COCl)_2$) furnished the corresponding acyl chloride, which was converted to amide **11** in 68% overall yield.



Scheme 3. Gram-scale synthesis and other elaborations.

In summary, the first Cu-catalyzed *gem*-bis(trifluoromethyl) olefination of α-diazo esters has been developed, using $TMSCF_3$ as the sole fluorocarbon source. This one-pot process, involving four successive steps (carbene migratory insertion, β-fluoride elimination, and two consecutive addition–elimination steps) in an efficient manner, represents a novel protocol of carbon chain elongation from C_1 to C_3. This copper-catalyzed one-pot multi-step process not only showcases the unique reactivity of organofluorine compounds, it also promises to find applications in

developing new pharmaceuticals, agrochemicals, and functional materials.

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Keywords: copper • *gem*-bis(trifluoromethyl)olefination • α-diazo esters • trifluoromethyltrimethylsilane • chain elongation

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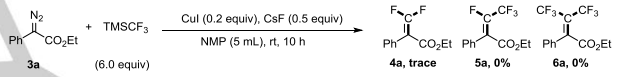
[22] The reaction was completely suppressed in the presence of excess CF_3^- species by adding CsF (0.5 equiv) in one portion:



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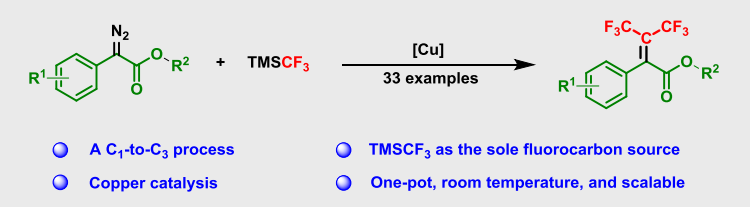

Controllable chain growth: A copper-catalyzed one-pot C_1-to-C_3 process enables the conversion of α-diazo esters to 1,1-bis(trifluoromethyl)alkenes using $TMSCF_3$ as the sole fluorocarbon source.

*Qian Wang, Chuanfa Ni, Mingyou Hu, Qiqiang Xie, Qinghe Liu, Shitao Pan, and Jinbo Hu**

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From C_1 to C_3: Copper-Catalyzed *gem*-Bis(trifluoromethyl)olefination of *α*-Diazo Esters with $TMSCF_3$