Fluorination

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AgF-Mediated Fluorinative Cross-Coupling of Two Olefins: Facile Access to α-CF_3 Alkenes and β-CF_3 Ketones**

*Bing Gao, Yanchuan Zhao, and Jinbo Hu**

Abstract: *A AgF-mediated fluorination with a concomitant cross-coupling between a gem-difluoroolefin and a non-fluorinated olefin is reported. This highly efficient method provides facile access to both α-CF_3 alkenes and β-CF_3 ketones, which otherwise remain challenging to be directly prepared. The application of this method is further demonstrated by the synthesis of bioactive isoxazoline derivatives. This approach represents a conceptually novel route to trifluoromethylated compounds that combines the in situ generation of the CF_3 moiety and a C–H functionalization in a single reaction system.*

The trifluoromethyl (CF_3) group often significantly alters the acidity, lipophilicity, metabolic stability, and conformation of a molecule; molecules with a trifluoromethyl group are therefore valuable compounds in pharmaceutical chemistry, agrochemistry, and material science.[1] Accordingly, the incorporation of CF_3 group(s) into a target molecule is highly desirable owing to the nearly complete absence of fluorine in naturally occurring organic molecules.[2] To date, research efforts have mainly focused on the direct trifluoromethylation (especially transition-metal-mediated coupling reactions) of prefunctionalized compounds with a set of nucleophilic, electrophilic, or radical trifluoromethyl sources.[3] An alternative route to trifluoromethylated compounds entails the use of CF_3-containing building blocks without the involvement of direct C–CF_3 bond formation.[4] In both cases, the CF_3 groups are already present in the starting materials, and chemists then have to tailor these substrates into the desired compounds. However, there have been rare examples of combining the in situ construction of the CF_3 motif and the functionalization of target molecules by C–C bond formation in a single reaction system. One pioneering work that matches this criterion was reported by Chen and co-workers, who have achieved the copper-mediated trifluoromethylation of aryl halides with methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$).[5a–c] In their system, the reaction of the difluorocarbene with the fluoride anion and CuI to form the "$CuCF_3$" intermediate and the copper-mediated coupling with electrophiles are compatible. Compared to direct trifluoromethylation, this in situ strategy has advantages for the preparation of [^{18}F]CF_3 compounds for PET imaging because of its simple manipulation procedure and excellent efficacy.[5d] Nevertheless, novel methods for the synthesis of trifluoromethylated compounds that are based on similar concepts have rarely been reported since. One major challenge is the in situ generation of the CF_3 motif as nearly all CF_3 moieties currently used are originally obtained by fluorination with harsh reaction conditions.[6]

We envisioned that the *gem*-difluorovinyl group would be an attractive alternative CF_3 precursor. The difluoromethylene carbon atom is electrophilic because of the inductive effect of the fluorine atoms and electron repulsion between the double bond and the fluorine atoms, which facilitates the regioselective nucleophilic fluorination of the *gem*-difluoromethylene carbon atom to afford a CF_3 group.[1a,7] In the past, this α-CF_3 carbanion formed from direct fluoride addition was found to be unstable and would be spontaneously quenched by proton abstraction, making its further functionalization difficult.[7] We have recently found that β,β-difluorostyrene derivatives reacted with AgF to give the fluorinated homocoupling products.[8] Preliminary mechanistic studies implied that an α-CF_3-benzylsilver intermediate, rather than the α-CF_3 carbanion, might be generated although its direct observation failed. Inspired by this result, we settled to explore the concomitant fluorination and intermolecular cross-coupling of a *gem*-difluoroolefin and another reactant as an alternative route to construct more sophisticated CF_3-containing compounds. In this regard, alkenes could be an appealing choice owing to their ready availability and versatile synthetic utility.[9,10] Herein, we disclose our results on using the *gem*-difluorovinyl group as a CF_3 precursor, which is fluorinated to give an α-trifluoromethylated intermediate; subsequent intermolecular alkenyl C–H functionalization affords α-CF_3 alkenes and β-CF_3 ketones (Scheme 1).

At the onset, 2-(2,2-difluorovinyl)naphthalene (**1a**) was chosen as a model substrate to study its reaction with 1,1-diphenylethylene (**2a**). When the reaction was conducted in pyridine (2.0 mL) at 80 °C for six hours [**1a** (0.5 mmol), **2a** (3.0 equiv), AgF(3.0 equiv)], the fluorination and homocoupling process of **1a** was so rapid that no cross-coupling products were detected. The solvents were then carefully screened to circumvent the undesired homo-coupling. Fortunately, α-CF_3 alkene **3aa** was formed in 41 % (as determined by ^{19}F NMR spectroscopy), while 49 % of **1a** did not react, when using 1-methyl-2-pyrrolidinone (NMP) as the solvent under similar reaction conditions. Further screening

[*] Dr. B. Gao, Dr. Y. Zhao, Prof. Dr. J. Hu
Key Laboratory of Organofluorine Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Ling-Ling Road, Shanghai, 200032 (China)
E-mail: jinbohu@sioc.ac.cn

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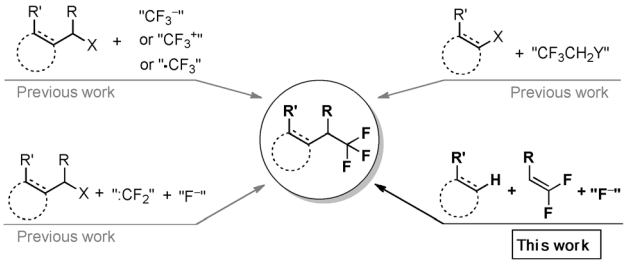
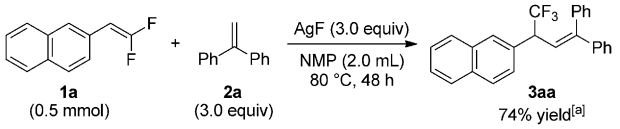


Scheme 1. Combining the formation of a CF_3 moiety and a C–H functionalization process into a single reaction system.

of the additives, the ratio of the reactions, and the reaction time resulted in the optimized reaction conditions: **1a** (0.5 mmol), **2a** (3.0 equiv), and AgF (3.0 equiv) were heated at 80 °C in NMP for 48 hours under N_2 atmosphere. Thus product **3aa** was obtained in 74 % yield (82 % ^{19}F NMR yield) while reagent **1a** was fully consumed (Scheme 2).

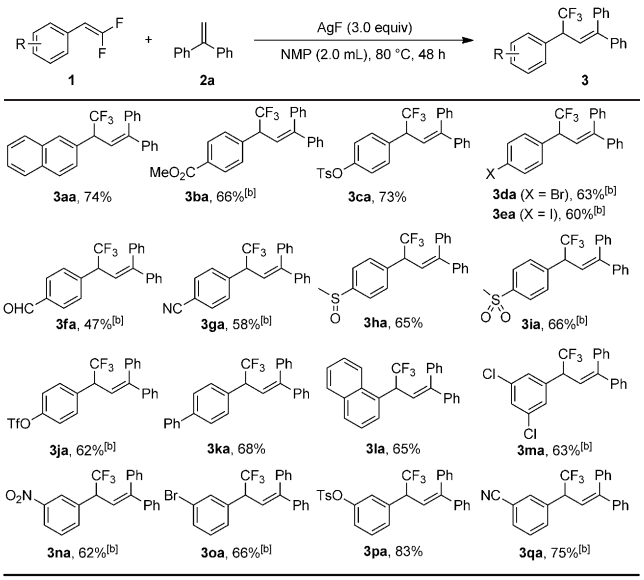


Scheme 2. Optimized reaction conditions for the preparation of α-CF_3 alkenes. [a] Yield determined by ^{19}F NMR spectroscopy: 82%.

As we have recently disclosed an efficient synthetic access to *gem*-difluoroolefins,[11] a series of β,β-difluorostyrene derivatives were subjected to the optimized reaction conditions to undergo the cascade reaction. As shown in Table 1, this method is compatible with a wide range of functional groups, including ester, aldehyde, cyano, sulfoxide, sulfone, and even nitro moieties. Moreover, functional groups that are commonly employed in conventional cross-coupling reactions, such as OTf (**3ja**), OTs (**3ca**, **3pa**), and halogen moieties (Cl, Br, I; **3da**, **3ea**, **3ma**, **3oa**), were also tolerated; the corresponding products should thus be easily modifiable by further transformations.[12] Notably, substrates with electron-withdrawing groups on the aromatic rings were generally more reactive towards AgF, and therefore, the reaction reached completion within eight hours. Meanwhile, using an additional 0.5 equivalents of $AgBF_4$ was beneficial to suppress the hydrofluorination of electron-deficient *gem*-difluoroolefins (**1b**, **1d**–**1g**, **1i**, **1j**, **1m**–**1o**, **1q**). Naphthalene derivative **1l** was also smoothly converted into product **3la** in 65 % yield, indicating the little impact of steric hindrance on the reactivity. It should be mentioned that the fluorination/homo-coupling process of the *gem*-difluoroolefins was minimized to < 3 % in all cases.

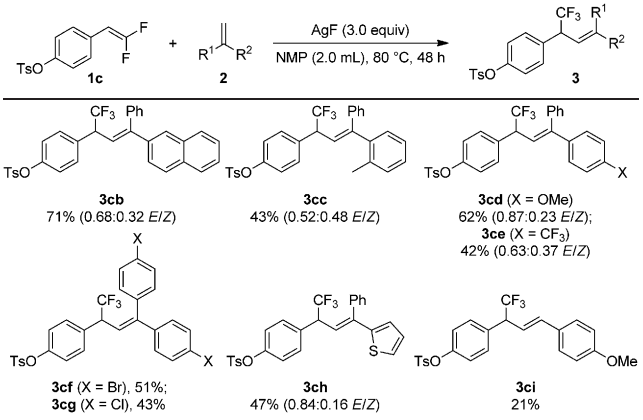
As most of the β,β-difluorostyrene derivatives gave satisfactory results, we also varied the non-fluorinated reaction partners **2** (Table 2). Generally, diaryl ethylenes reacted well with *para*-tosyl β,β-difluorostyrene **1c**, giving the corresponding products in moderate to good yields. Both the steric and electronic properties of the aryl substituents had an

Table 1: Variation of the *gem*-difluoroolefin for the preparation of α-CF_3 alkenes.[a]



[a] Reaction conditions (unless otherwise specified): **1** (0.5 mmol), **2a** (1.5 mmol), AgF (1.5 mmol), NMP (2.0 mL), 80 °C, 48 h. [b] Reaction conditions B: **1** (0.5 mmol), **2a** (1.5 mmol), AgF (1.5 mmol), $AgBF_4$ (0.25 mmol), NMP (2.0 mL), 80 °C, 8 h. Tf = trifluoromethanesulfonyl, Ts = *para*-toluenesulfonyl.

Table 2: Variation of the non-fluorinated alkene for the preparation of α-CF_3 alkenes.[a]



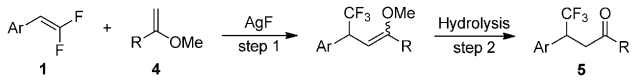
[a] Reaction conditions: **1c** (0.5 mmol), **2** (1.5 mmol), AgF (1.5 mmol), NMP (2.0 mL), 80 °C, 48 h. The absolute configurations were not determined.

impact on the outcome of the transformations. For instance, substrate **2c**, bearing a proximal methyl group, provided **3cc** as the *Z*/*E* mixture in relatively low yield. Compared to **2e**, which features an electron-deficient *p*-CF_3 group, **2d**, with an electron-rich *p*-OMe group, was more reactive and gave the corresponding product in higher yield. A substrate with a heteroaryl moiety (**2h**) and α-methylstyrene could also be converted, albeit less effectively. Monosubstituted alkene **2i** also gave a low yield probably because of its poor reactivity.

Owing to their synthetic diversity and feasibility, carbonyl-based synthons with a CF_3 substituent have emerged as important intermediates in chemical synthesis.[13d] In recent

years, a range of radical, electrophilic, nucleophilic, and organometallic approaches have been developed to incorporate the CF_3 group into carbonyl compounds.[13,14] Whereas most of these efforts succeeded in functionalizing the carbonyl group itself or its α-position, there were only rare advances in developing methods for the synthesis of β-CF_3-substituted carbonyl compounds.[15] The "*direct 1,4-trifluoromethylation to conventional α,β-unsaturated ketones such as chalcone is very tough*";[15b] but this is just one representative challenge.

Encouraged by our aforementioned results on the synthesis of α-CF_3 alkenes, we sought to apply our method to the preparation of β-CF_3 ketones. In this regard, a one-pot procedure was designed and features 1) a concomitant fluorination/cross-coupling process of α-methoxystyrene derivatives with *gem*-difluoroolefins to give α-CF_3 methoxyalkenes and 2) the hydrolysis of the newly formed alkenes to release the target β-CF_3 ketones. To our delight, this method proved to be viable, and the fluorinated cross-coupling product of α-methoxystyrene **4** underwent rapid hydrolysis under acidic conditions to afford the desired ketone **5** (Scheme 3).[16]

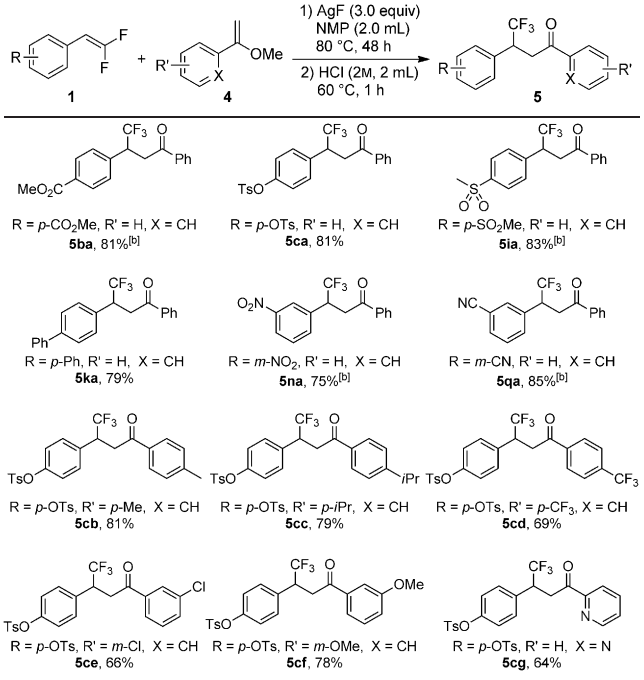


Scheme 3. Preparation of β-CF_3 ketones through fluorination and cross-coupling. Optimized reaction conditions: step 1: **1** (0.5 mmol), **4** (3.0 equiv), AgF (3.0 equiv), NMP (2.0 mL), 80 °C, 48 h; step 2: HCl (2.0 M, 2.0 mL), 60 °C, 1 h.

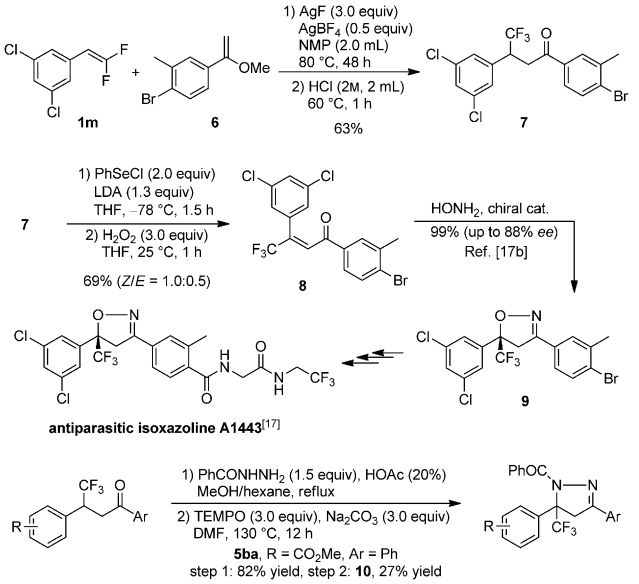
Selected examples of the β-CF_3 ketone synthesis are summarized in Table 3. This strategy was applicable to a variety of *gem*-difluoroolefins and α-methoxystyrene derivatives under the optimized reaction conditions, giving the desired products in excellent overall yields, and tolerated various functional groups. The hydrolysis process was sufficiently mild to leave the ester, tosyl, sulfonyl, nitro, and cyano groups intact. Electron-deficient α-methoxystyrene derivatives afforded lower yields than electron-rich ones (**4b**–**4d**). It is noteworthy that a heteroaryl substrate, namely 2-(1-methoxyvinyl)pyridine (**4g**), could also be converted into the corresponding ketone with satisfactory yield.

Structurally unique 3,5-diaryl-5-(trifluoromethyl)-2-isoxazoline derivatives, for which more than 20000 variants with similar skeletons have been reported, have been approved as useful pest-control reagents. A1443 exhibits excellent antiparasitic activity against cat fleas and dog tick.[17] The stereoselective synthesis of its key precursor **9** could be readily realized by employing our method in combination with Shibata's asymmetric cyclization method.[17b] As shown in Scheme 4, β-CF_3 ketone **7** was prepared in 63% yield with our method and subsequently transformed into intermediate **8** in 69% yield. Thereafter, **8** could be further converted into **9** with excellent yield and high *ee*. Heterocyclic analogues of A1443 were also available from the corresponding β-CF_3 ketones. For instance, dihydropyrazole **10** was obtained from product **5ba** after TEMPO-mediated C–H oxidation

Table 3: Substrate scope of the preparation of β-CF_3 ketones.[a]



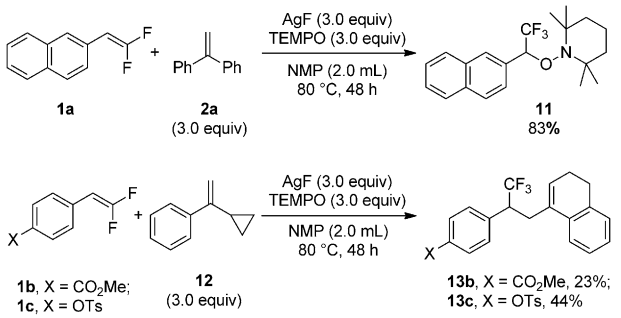
[a] Reaction conditions (unless otherwise specified): **1** (0.5 mmol), **4** (1.5 mmol), AgF (1.5 mmol), NMP (2.0 mL), 80 °C, 48 h; then HCl (2 M, 2 mL), 60 °C, 1 h. [b] Reaction conditions B: **1** (0.5 mmol), **4** (1.5 mmol), AgF (1.5 mmol), $AgBF_4$ (0.25 mmol), NMP (2.0 mL), 80 °C, 8 h; then HCl (2 M, 2 mL), 60 °C, 1 h.



Scheme 4. Synthesis of bioactive compounds. LDA = lithium diisopropylamide.

(TEMPO = 2,2,6,6-tetramethyl-1-oxylpiperidine).[18] These results further highlight the practical utility of our method.

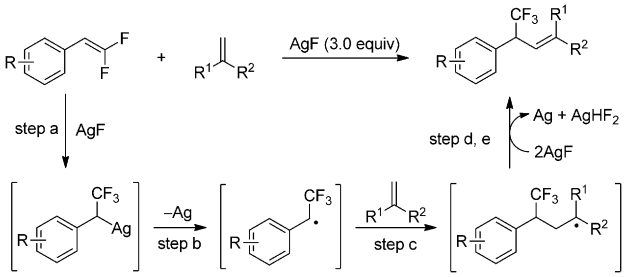
To gain mechanistic insights into the present reaction, the following experiments were performed (Scheme 5). When 3.0 equivalents of TEMPO, a radical scavenger, were added to the reaction system, the cross-coupling between **1a** and **2a**



Scheme 5. Mechanistic studies.

was completely inhibited, and the radical trapping adduct **11** was obtained in 83% yield. Furthermore, when (1-cyclopropylvinyl)benzene was subjected to the standard reaction conditions with **1b** and **1c**, the homoallylic trifluoromethylated alkenes **13b** and **13c**, respectively, were isolated as the major products. They were likely the result of the ring opening of the cyclopropane motif followed by intramolecular addition of the carbon radical to the phenyl ring.[19]

On the basis of these findings and our previous results,[8] one plausible mechanistic pathway is proposed in Scheme 6. The synergetic addition of AgF to the *gem*-difluoroolefin



Scheme 6. Proposed reaction mechanism.

affords an α-CF_3-benzylsilver intermediate, which undergoes rapid C–Ag^I bond homolysis in situ to afforded the α-CF_3-substituted benzyl radical and silver powder; the non-fluorinated alkene then reacts with the α-CF_3 benzyl radical to form a new carbon-centered radical. The resulting carbon radical is oxidized to a carbocation with AgF, followed by rapid deprotonation to give the α-CF_3 alkene, thus completing a net fluorination/intermolecular alkenyl C–H functionalization reaction. It should be noted that AgF is essential and plays at least four different roles in the reaction: It acts 1) as a fluorination reagent that transforms the *gem*-difluorovinyl group into a trifluoromethyl group in step a; 2) as a radical source during C–Ag^I bond homolysis in step b; 3) as an oxidant to convert the carbon radical into a carbocation in step d; and 4) as a base to regenerate the double bond by removing the proton in step e.[8,20]

In summary, we have developed an efficient *gem*-difluoroolefin fluorination/intermolecular alkenyl C–H functionalization cascade reaction. This method provides facile access to α-CF_3 alkenes as well as to β-CF_3 ketones, which are otherwise difficult to prepare in a one-pot process. This reaction represents a conceptually novel route for the synthesis of trifluoromethylated compounds that combines the in situ formation of a trifluoromethyl moiety from a *gem*-difluorovinyl group and silver-mediated alkenyl C–H functionalization. Compared with the direct trifluoromethylation or alkylation using CF_3-containing reagents, the current strategy may find potential applications in specific areas, for example, for the preparation of ^{18}F-labelled CF_3 compounds. Further explorations on the basis of this strategy are underway in our laboratory.

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