Fluorination

AgF-Mediated Fluorinative Cross-Coupling of Two Olefins: Facile Access to α-CF₃ Alkenes and β-CF₃ Ketones

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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-CF₃ alkenes and β-CF₃ 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 CF₃ moiety and a C–H functionalization in a single reaction system.

The trifluoromethyl (CF₃) 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 CF₃ group(s) into a target molecule is highly desirable owing to the nearly complete absence of fluoride 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 CF₃-containing building blocks without the involvement of direct C–CF₃ bond formation.[4] In both cases, the CF₃ 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 CF₃ 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 described the regioselective nucleophilic fluorination of the gem-difluoromethylenecarbonyl carbon atom to afford a CF₃ group.[5a,7] In the past, this α-CF₃ carbanion formed from direct fluoride addition was found to be unstable and would be spontaneously quenched by proton abstraction, making its further functionalization difficult.[6] We have recently found that β,β-difluorostyrene derivatives reacted with AgF to give the fluorinated homo-coupling products.[5b] Preliminary mechanistic studies implied that an α-CF₃-benzylsulfonyl intermediate, rather than the α-CF₃ 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 CF₃-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-difluoro vinyl group as a CF₃ precursor, which is fluorinated to give an α-trifluoromethylated intermediate; subsequent intermolecular alkyl C–H functionalization affords α-CF₃ alkenes and β-CF₃ 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 homo-coupling 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-CF₃ alkene 3aa was formed in 41% (as determined by ¹⁹F 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
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 N₂ atmosphere. Thus product 3aa was obtained in 74% yield (82% ¹⁹F NMR yield) while reagent 1a was fully consumed (Scheme 2).

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.[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 AgBF₄ 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 impact on the outcome of the transformations. For instance, substrate 2e, bearing a proximal methyl group, provided 3ec as the Z/E mixture in relatively low yield. Compared to 2e, which features an electron-deficient p-CF₃ 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 2j also gave a low yield probably because of its poor reactivity.

Owing to their synthetic diversity and feasibility, carbonyl-based synths with a CF₃ substituent have emerged as important intermediates in chemical synthesis.[13d] In recent years.
years, a range of radical, electrophilic, nucleophilic, and organometallic approaches have been developed to incorporate the CF₃ 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-CF₃-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-CF₃ alkenes, we sought to apply our method to the preparation of β-CF₃ 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-CF₃ methoxy-alkenes and 2) the hydrolysis of the newly formed alkenes to release the target β-CF₃ 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]

Selected examples of the β-CF₃ 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 anti-parasitic 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/C₂₉’s asymmetric cyclization method.[17b] As shown in Scheme 4, β-CF₃ 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-CF₃ ketones. For instance, dihydropyrazole 10 was obtained from product 5ba after TEMPO-mediated C–H oxidation (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
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,[3] one plausible mechanistic pathway is proposed in Scheme 6. The synergetic addition of AgF to the gem-difluoroolefin affords an α-CF3-benzylsilver intermediate, which undergoes rapid C–Ag+ bond homolysis in situ to afforded the α-CF3-substituted benzyl radical and silver powder; the non-fluorinated alkene then reacts with the α-CF3 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-CF3 alkene, thus completing a net fluorination/intermolecular alkyl 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 forms the gem-difluoroolefin group into a trifluoromethyl group in step a; 2) as a radical source during C–Ag+ 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.[1]

In summary, we have developed an efficient gem-difluoroolefin fluorination/intermolecular alkyl C–H functionalization cascade reaction. This method provides facile access to α-CF3 alkenes as well as β-CF3 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-difluoroolefin group and silver-mediated alkyl C–H functionalization. Compared with the direct trifluoromethylation or alkylation using CF3-containing reagents, the current strategy may find potential applications in specific areas, for example, for the preparation of 19F-labelled CF3 compounds. Further explorations on the basis of this strategy are underway in our laboratory.

Keywords: alkenes · fluorination · fluorine · ketones · silver

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[2] a) The most abundant natural sources of fluorine are the minerals fluor spar (CaF2) and cryolite (Na3AlF6); b) D. O’Hagan, D. B. Harper, J. Fluorine Chem. 1999, 100, 127–133.


Recently, the silver-mediated methoxycarbonyltetrafluoroethylation of arenes was reported; see: A. Hafner, T. J. Feuerstein, S. Brase, Org. Lett. 2013, 15, 3468–3471.


