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DOI: 10.1039/C8CC03364A

Journal Name

COMMUNICATION

Synthesis of α-CF_3 and α-CF_2H Amines via Aminofluorination of Fluorinated Alkenes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A novel synthesis of α-CF_3 and α-CF_2H amines via the aminofluorination of *gem*-difluoroalkenes and *mono*-fluoroalkenes, respectively, is reported. The method employs Selectfluor as an electrophilic fluorine source and acetonitrile as the nitrogen source. Mechanistic studies revealed a single-electron oxidation/fluorine-abstraction/Ritter-type amination pathway. The protocol allowed the synthesis of a broad range of fluorinated amines including those bearing quaternary carbon centers with good efficiency and functional group tolerance.

The fluorine-containing compounds have found widespread applications in pharmaceuticals, agrochemicals as well as materials.[1] The trifluoromethyl (CF_3) and difluoromethyl (CF_2H) structural motifs have gained particular attention in drug discovery[2] and therefore attracted significant synthetic efforts (Fig. 1).[3] Recently, the *gem*-difluoroalkenes have proved to be useful synthon in organofluorine synthesis[4] via *mono*-defluorinative[5] or fluorine-retentive[6] functionalization reactions. Interestingly, with the judicious employment of additional fluorine source, the fluorine-addition reaction of *gem*-difluoroalkenes also allowed the efficient synthesis of CF_3-containing molecules, which is complementary to the typical trifluoromethylation reaction wherein a CF_3-containing source was used.[7] In 2014, Hu discovered that the reaction of *gem*-difluoroalkene with AgF deliverd a α-trifluoromethylated carbon-centered radical, which could then undergo dimerization reaction[8a] or radical addition reaction to alkenes (Scheme 1a).[8b] The use of a F^- source was found to be able to participate the nucleophilic addition reaction to generate a β-trifluorocarbanion (Scheme 1b). By quenching with a Brønsted acid, the corresponding trifluoroethyl group was formed.[9] Loh and Feng elegantly incorporated this process into the palladium-catalyzed allylation[10] and arylation[11] reaction. In continuation with our interest in the functionalization reactions of *gem*-difluoroalkenes,[5a,5b,5c,12] herein, we reported an unprecedented trifluoromethylation reaction toward the synthesis α-CF_3 amines via the aminofluorination of *gem*-difluoroalkene with a F^+ source (Scheme 1c). A β-trifluorocarbocation, which was trapped by CH_3CN, was believed to be involved in the mechanism. The protocol was also applicable to the aminofluorination of *mono*-fluoroalkenes, leading to the synthesis of α-CF_2H amines in good efficiency.

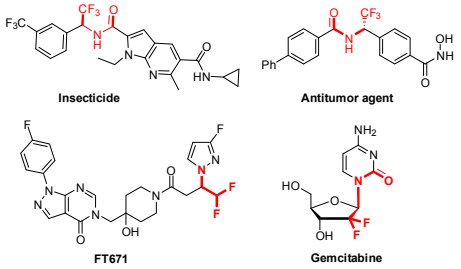
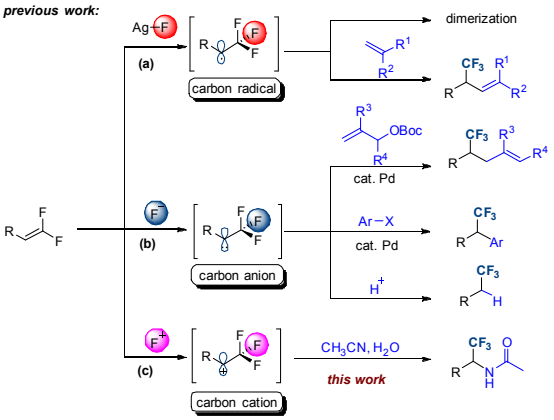


Fig. 1 Representative bioactive α-CF_3 and α-CF_2H amines.



Scheme 1. Toward the synthesis of trifluoromethylated molecules starting from gem-difluoroalkenes

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/x0xx00000x

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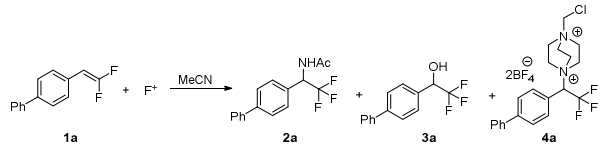
DOI: 10.1039/C8CC03364A

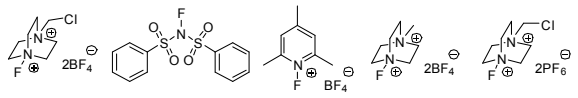
Our reaction design was guided by the fact that Selectfluor is a strong oxidant capable of accepting one electron from olefins to generate the corresponding radical cations, which could further undergo fluorine abstraction to form α-fluorinated carbocations.[13] The reaction of *gem*-difluoroalkenes with Selectfluor would, in principle, provide the carbocation intermediates bearing a α-CF_3 substituent. However, challenges may exist due to the electron-deficient nature of *gem*-difluoroalkenes, which may lead to the single-electron transfer difficult. To test the feasibility of the envisioned process, *gem*-difluoroalkene **1a** was treated with Selectfluor in acetonitrile (Table 1). As expected, the electrophilic fluorination/Ritter-type amidation product α-CF_3 amine **2a** was found, although in low yield (entry 1). Two side products (**3a** and **4a**) were identified to be derived from the competitive nucleophilic attack from H_2O and the reduced amino motif of Selectfluor. We speculated the addition of Brønsted acid might help circumvent these side reactions: first, the Brønsted acid would ionize the alcohol **3a** to regenerate the benzylic cation, offering a second chance for Ritter amination; second, the protonation of the reduced amino motif would eliminate its nucleophilicity, thereby minimizing the formation of **4a**. Indeed, we found that the employment of 2 equivalents of acid gave a better yield of the desired product **2a**, with Tf_2NH being the optimal (entries 2-5). Other F^+ sources were also screened. While NSFI and F-I showed no reactivity (entries 6 and 7), F-II and F-III gave a similar result as Selectfluor (entries 8 and 9). A good yield of 75% was obtained by diluting the reaction mixture to 0.03 M (entries 10-12). Attempts to lower the acid loading resulted in the formation of more **4a**, again, confirming the important role of acid for the reaction (entries 13 and 14).

Table 1. Optimization of the reaction conditions[a]



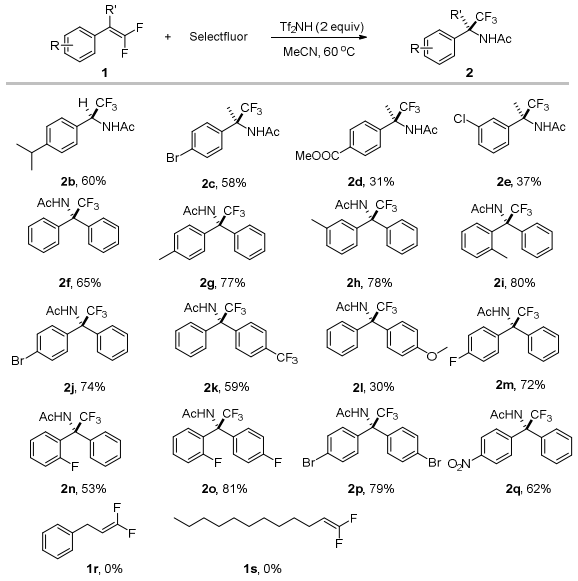
Entry	Additive	F^+ resource	Conc.	Yield (%) 2a/3a/4a
1	None	Selectfluor	0.1	33/6/54
2	TFA (2 equiv)	Selectfluor	0.1	38/5/31
3	H_2SO_4 (2 equiv)	Selectfluor	0.1	51/trace/40
4	TfOH (2 equiv)	Selectfluor	0.1	42/7/50
5	Tf_2NH (2 equiv)	Selectfluor	0.1	45/trace/33
6	Tf_2NH (2 equiv)	NFSI	0.1	0
7	Tf_2NH (2 equiv)	F-I	0.1	0
8	Tf_2NH (2 equiv)	F-II	0.1	47/trace/ND
9	Tf_2NH (2 equiv)	F-III	0.1	45/trace/49
10	Tf_2NH (2 equiv)	Selectfluor	0.2	31/trace/60
11	Tf_2NH (2 equiv)	Selectfluor	0.05	58 /trace/42
12	**Tf_2NH (2 equiv)**	**Selectfluor**	**0.03**	**75/trace/17**
13	Tf_2NH (0.2 equiv)	Selectfluor	0.03	27/trace/54
14	Tf_2NH (1 equiv)	Selectfluor	0.03	38/trace/41

[a]1a (0.2 mmol, 1.0 equiv), Selectfluor (0.4 mmol, 2.0 equiv), MeCN, 60 °C, under air, isolated yields. ND: Not detected.



With the optimized reaction conditions in hand (entry 12, Table 1), the generality of the reaction was then explored. *gem*-Difluorostyrenes **1b** bearing electron-donating isopropyl substituent also gave the corresponding product in good yield. Substrates with an additional methyl group also delivered the desired products (**2c-2e**), but accompanied by the formation of minor trifluomethylated alkene byproducts. These byproducts were assumed to be derived from the competitive deprotonation reaction of the benzylic cation intermediate (see Scheme 3). As expected, the diaryl gem-difluoroalkenes were excellent substrates for the reaction. In these cases, a variety of functional groups such as trifluoromethyl (**2k**), methoxy (**2l**), methyl (**2g-2i**), bromo (**2j** and **2p**), fluoro (**2m-2o**), nitro (**2q**) could be well tolerated. Unfortunately, no reaction was found with aliphatic gem-difluoroalkenes (**1r** and **1s**) under the standard reaction conditions.

Table 2. Substrate scope for the synthesis of α-CF_3 amines



With the aminofluorination of *gem*-difluoroalkenes established, we then questioned the feasibility of similar reaction by using *mono*fluoroalkenes as substrate. *Mono*fluoroalkenes are more electron-rich than *gem*-difluoroalkenes and therefore are expected to be more reactive toward aminofluorination. If successful, the reaction

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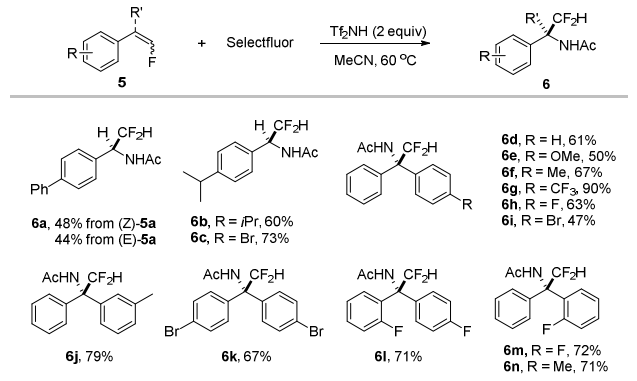
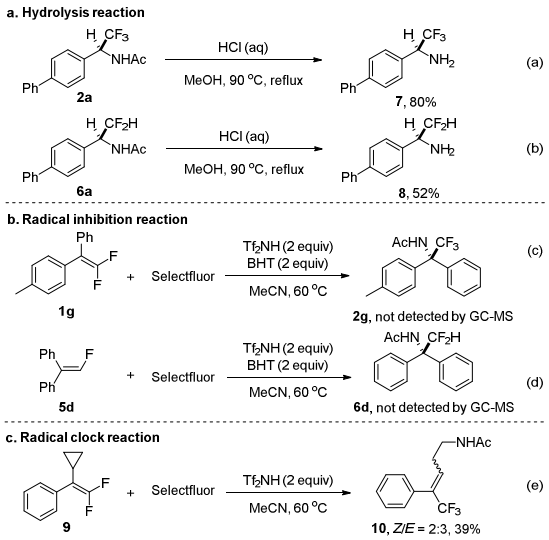
should provide a α-CF_2H amine product, which is also interesting structural motif in medicinal chemistry.[2c,2d,2f] Indeed, the reaction of (***Z***)-**5a** in the above standard reaction provided the desired product 6a in 48% isolated yield (Table 3). The ***E*** type substrate gave a comparable yield. Thus, the mixtures of ***E*** and ***Z*** isomers of *mono*fluoroalkenes were used to investigate the scope. Again, in addition to the aryl *mono*fluoroalkenes (**6a** and **6b**), substrates with additional methyl (**6c**) and aryl group (**6d**-**6n**) were also applicable for aminofluorination, delivering the desired product in moderate to excellent yields.

Table 3. Substrate scope for the synthesis of α-CF_2H amines

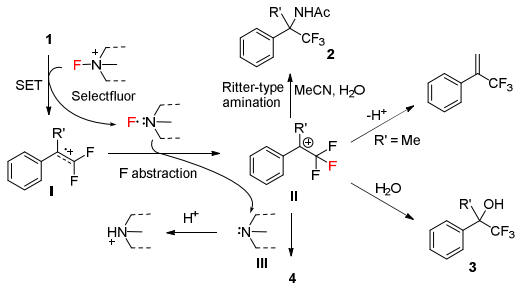


The acetyl group in **2a** and **6a** could be removed under acidic conditions to give the free α-CF_3 amine **7** and α-CF_2H amine **8** in good yields (Scheme 2a and 2b), which offered good opportunities for further elaboration on the nitrogen atom. To verify our mechanistic hypothesis, experimental studies were conducted. Both of the aminofluorination reactions were inhibited by radical scavenger BHT (Scheme 2c and 2d). In addition, the ring opening product **10** was observed when cyclopropyl-substituted substrate **9** was employed. These results suggested the involvement of a radical in the mechanism.



Scheme 2. Derivatization of products and mechanistic studies

Based on the above experimental results and literature precedents,[13] the following mechanism was proposed. The aminofluorination reactions of *gem*-difluoroalkenes and monofluoroalkene were believed to share a similar mechanism. Initially, the strong oxidizing property of Selectfluor leads to a single electron oxidation of *gem*-difluoroalkene to form an alkene radical cation **I**. This species would then undergo an in-cage regioselective fluorine atom abstraction from the reduced Selectfluor, providing a benzylic cation **II** and the corresponding tertiary amine **III**. The nucleophilic attack of the **III** forms the sideproduct **4**. Alternatively, a Ritter-type amination gives desired aminofluorination product **2**. The presence of water in the reaction mixture also leads to the generation of alcohol **3**. With a methyl group substituted, a deprotonation reaction can occur to furnish a trifluoromethylated alkene. The acid employed might protonate amine **III**, thereby minimizing the formation of **4**.



Scheme 3. Mechanistic proposals

In conclusion, a facile synthesis of α-CF_3 and α-CF_2H amine was developed via the aminofluorination of *gem*-difluoroalkenes and *mono*fluoroalkenes, respectively. The protocol employs Selectfluor as the fluorine source and acetonitrile as the nitrogen source. Mechanistic studies pointed out that a single-electron-transfer is involved in the mechanism. Broad substrate scope and generally good yield were observed. Given the importance of nitrogen groups in bioactive compounds, this novel synthesis of fluoroamines is expected to find application in medicinal chemistry.

Acknowledgement

Financial support from the National Natural Science Foundation of China (21472250), the Key Project of Chinese National Programs for Fundamental Research and Development (2016YFA0602900), the National Science and Technology Major Project of the Ministry of Science and Technology of China (2018ZX09735010), and the "1000-Youth Talents Plan" are gratefully acknowledged.

Conflicts of interest

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There are no conflicts to declare.

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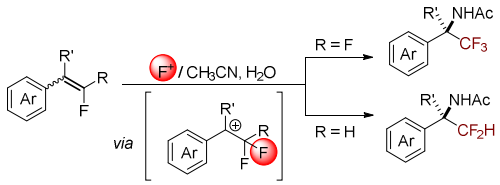

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