



Fluoroamides Hot Paper

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TMSCF₂Br-Enabled Fluorination–Aminocarbonylation of Aldehydes: Modular Access to α -Fluoroamides

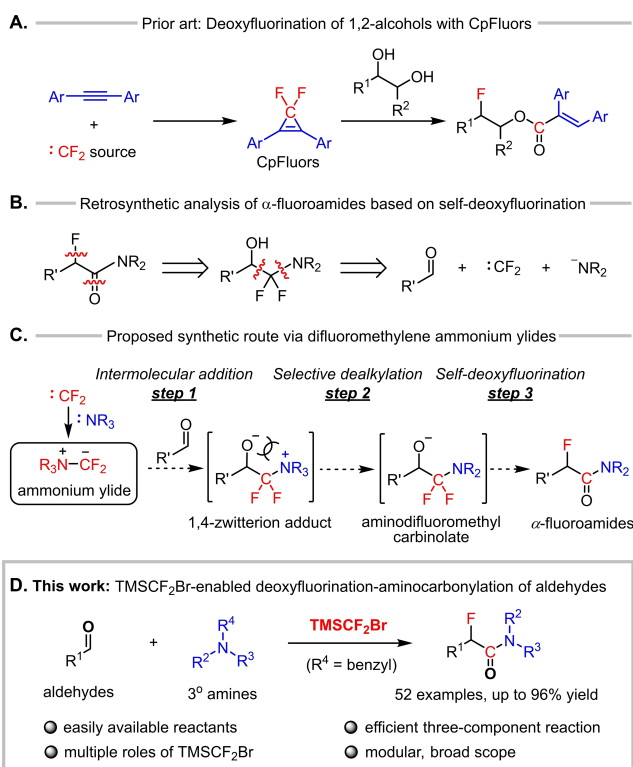
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Abstract: A protocol for the modular assembly of the α -fluoroamide motif has been developed, which provides a practical method for the efficient synthesis of structurally diverse α -fluoroamides from easily available aldehydes and tertiary amines through a three-component fluorination–aminocarbonylation process. The key to the success of this process is taking advantage of the multiple roles of the unique difluorocarbene reagent TMSCF₂Br (TMS = trimethylsilyl). The mechanism of the process involves the 1,2-fluorine and oxygen migrations of the *in situ* formed TMS-protected α -aminodifluoromethyl carbinol intermediates, which represents a new type of deoxyfluorination reaction.

Introduction

Amides are prevalent in nature and can serve as medicinally important compounds.^[1] The introduction of fluorine atoms is an effective way to improve the metabolic stability and other desirable properties of amide-based drug compounds and candidates.^[2] α -Fluoroamides, as an important type of fluorinated amides, are typically synthesized from α -fluorocarboxylic acids and their derivatives via C–N bond formation^[2b,3] or from simple α -fluoroamides via C–C bond formation.^[4] However, these fluorinated precursors are not easily available and have to be individually synthesized via C–F bond formation or from fluorinated building blocks. State-of-the-art methods for the direct synthesis of α -fluoroamides from nonfluorinated precursors via C–F bond formation are also available, including fluorination of aliphatic aldehydes, α -chloro aldehydes or ketenes followed by amide bond formation,^[5] fluorination of enamines followed by oxidation,^[6] α -C–H fluorination of non-fluorinated amides,^[7] and metal-catalyzed fluorination of α -haloamides.^[8] However, these methods rely on multistep synthesis or pre-organized substrates that are derived from various carbonyl compounds. Therefore, a facile method that is suitable for the modular assembly of α -fluoroamides from simple carbonyl compounds and amines via C–N and C–F bond formations in a single process is still lacking.

Difluorocarbene, as a versatile C1 building block, has been extensively exploited for the synthesis of broad scope of structurally diverse organofluorine compounds through various transformations.^[9] However, the use of difluorocarbene for the construction of C–F bonds via deoxyfluorination is rare.^[10] In 2016, we reported the deoxyfluorination of alcohols with 3,3-difluoro-1,2-diarylcyclopropenes (CpFluors) that are derived from difluorocarbene and 1,2-diarylalkynes (Scheme 1A).^[11] Inspired by this work and other known deoxyfluorination of alcohols with α,α -difluoroamine reagents,^[12] we assumed that the self-deoxyfluorination of α -aminodifluoromethyl carbinols^[13] that derived from a one-pot, three-component reaction^[9g,14] of amine nucleophiles, difluorocarbene and carbonyl compounds such as aldehydes might be applicable for the modular synthesis of α -fluoroamides (Scheme 1B), which can be regarded as the fluorination-aminocarbonylation of carbonyl compounds. However, taking into account that competitive N-difluoromethylation or further carbamate reaction^[15] of



Scheme 1. Difluorocarbene-involved fluorination and development of a modular method for the synthesis of α -fluoroamides.

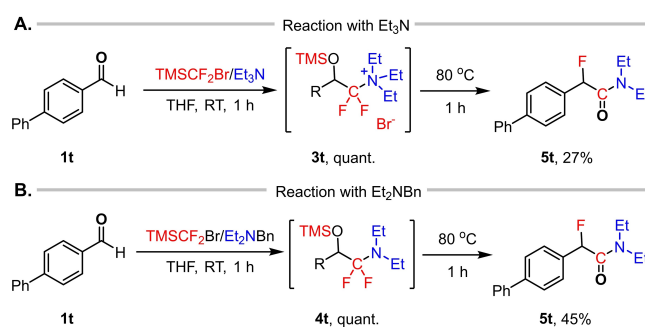
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NH-nucleophiles by difluorocarbene can readily take place to preclude the tandem intermolecular reaction with aldehydes, the difluorocarbene-induced generation of aminodifluoromethyl anion from amines for further nucleophilic addition reaction is challenging.

Fluorinated ylides are common in organofluorine chemistry as reagents or reactive intermediates.^[16] During the last few years, difluoromethylene phosphonium ylides have found wide applications as nucleophilic fluoroalkylation reagents in the transformation of many electrophiles including carbonyl compounds.^[9g,16b,17] In this context, we speculated that the nucleophilic aminodifluoromethylation of carbonyl compounds with difluorocarbene could be tamed by the addition reaction of difluoromethylene ammonium ylides^[18] in-situ generated from tertiary amines and difluorocarbene followed by the selective removal of one alkyl substitute from the quaternary ammonium salt intermediates (Scheme 1C). However, we soon realized that to develop such an efficient protocol, two issues should be addressed: 1) compared to a difluoromethylene phosphonium ylide,^[17d] the stabilization of the 1,4-zwitterion adduct^[19] from a difluoromethylene ammonium ylide and aldehyde (via the formation of a hypervalent nitrogen-involved four-membered ring) is difficult, so a new strategy to stabilize this 1,4-zwitterion adduct to promote the intermolecular addition reaction is required (Scheme 1C, step 1); 2) due to the high stability of quaternary ammonium salts toward most nucleophiles,^[20] selective removal of one *N*-substituent under mild conditions to release the α -aminodifluoromethyl carbinol intermediate is required (Scheme 1C, step 2). Herein, we report our recent success in the development of difluorocarbene-induced modular synthesis of α -fluoroamides from aldehydes and tertiary amines through addressing the aforementioned two issues (Scheme 1D).

Results and Discussion

Our investigation commenced with addressing the first issue. TMSCF₂Br, a mild difluorocarbene reagent introduced by our group in 2011,^[21] has become an important tool for the development of novel difluorocarbene chemistry due to its great versatility in the generation of difluorocarbene.^[9e-g,14,21,22] Of note is that its side product TMSBr can be used as both a Lewis acidic promoter and a source of bromide ion nucleophile. Therefore, we envisioned that TMSCF₂Br would be the difluorocarbene reagent of choice, since TMSBr could capture the in-situ generated 1,4-zwitterion adduct to facilitate the addition reaction, and the released bromide ion could further attack an *N*-alkyl substituent.^[20a] To our delight, we found that difluoromethylene ammonium ylide could be readily generated from TMSCF₂Br/Et₃N and in-situ captured by an aldehyde such as *p*-phenylbenzaldehyde (**1t**) in the absence of any extra initiators (such as TBAB or HMPA) at room temperature (Scheme 2A). The TMS-protected difluorinated quaternary ammonium salt **3t**, characterized by HRMS analysis (see the Supporting Information), was formed in nearly quantitative yield. In contrast, the use of other difluorocarbene reagents



Scheme 2. Preliminary results on the three-component reaction. Conditions: **1t** (0.5 mmol), TMSCF₂Br (0.75 mmol), Et₃N or Et₂NBn (0.75 mmol). R = 4-Ph-C₆H₄. THF = tetrahydrofuran; RT = room temperature.

including BrCF₂CO₂Na, BrCF₂CO₂Et and BrCF₂P(O)(OEt)₂ instead of TMSCF₂Br gave no carbonyl addition product even additional bases were added to activate the difluorocarbene precursors. Interestingly, heating quaternary ammonium salt **3t** in THF at 80 °C for 1 h led to the complete conversion of **3t**, with the desired α -fluoroamide **5t** being formed in 27 % yield. It is clear that dealkylation and subsequent deoxyfluorination of the silyl ether functionality took place under such conditions. However, the yield was somewhat low probably due to the influence of the quaternary ammonium salt **3t** on the C–F bond formation process.

Next, we tested the reactivity of other kinds of amines. Among three amines (Et₂NBn, Et₂NH and BnNH₂), although Et₂NH and BnNH₂ were not suitable amine component, Et₂NBn (**2a**) was found to be as effective as Et₃N in participating the three-component reaction (Scheme 2B). Moreover, when Et₂NBn was employed instead of Et₃N, the TMS-protected (amino)difluoromethyl carbinol intermediate **4t** was formed directly at room temperature (no quaternary ammonium salt intermediate was detected) (see the Supporting Information). These results demonstrate that *N*-benzyl tertiary amines can also participate in the tandem reaction, and the resulting TMS-protected difluorinated quaternary ammonium salt intermediate readily undergoes debenzoylation to reveal the (amino)difluoromethyl carbinol intermediate with high selectivity and high efficiency, which nicely address the aforementioned second issue. Moreover, heating (amino)difluoromethylated intermediate **4t** could afford α -fluoroamide **5t** in higher yield (45 %) than that of quaternary ammonium salt **3t**, which further highlights the advantage of *N*-benzyl tertiary amines as the *N*-nucleophile in three-component modular synthesis of α -fluoroamides.

After confirming the feasibility of our protocol, we then moved to improve the C–F bond formation process by using benzylamine **2a** as the amine component. Initial screening of several common solvents showed that a simple switch of solvent could not increase the yield (see Table S1, entries 1–5). Considering that additives such as KF and Et₃N·3 HF are commonly used to promote the deoxyfluorination of alcohols,^[12] we surveyed the effect of additives on our

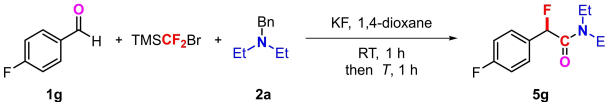
reaction (see Table S1, entries 6–20). To simplify the operation, all additives were added together with the reactants. We found that both the combination of KF/1,4-dioxane and the combination of KHF₂/THF could remarkably enhance the reaction efficiency. To further improve the yield, we used 4-fluorobenzaldehyde (**1g**) as a model reactant (to facilitate the mass balance monitoring), and carefully tuned the parameters of the KF-promoted reaction in 1,4-dioxane with a higher boiling point than THF (Table 1). When the deoxyfluorination of the silyl ether functionality was conducted with 2.0 equiv of KF at 80 °C, increase of the amounts of TMSCF₂Br and **2a** did not improve the yield (Table 1, entries 1–3), and the use of large excess amounts unexpectedly eroded the reaction efficiency significantly (Table 1, entry 3). Thus, we tried the reaction employing only slight excesses of TMSCF₂Br and **2a** (Table 1, entry 4). In this case, although much more aldehyde was remained, a similar yield was obtained (entries 1 and 4), suggesting that reducing the amounts of nucleophilic species other than fluoride is beneficial for the deoxyfluorination of the silyl ether functionality. Based on this molar ratio of reactants, further improvement was observed when the amount of KF was increased to 4.0 equiv and the reaction temperature was elevated to 100 °C (Table 1, entries 5 and 6). However, lowering the temperature led to a much lower yield with incomplete conversion of the intermediate (Table 1, entry 7). It is intriguing to note that the remaining amount of aldehyde also increases as the temperature rises (Table 1, entries 5–7), indicating that the intermediate can undergo retro-addition reaction during its

deoxyfluorination. Moreover, according to the yield of **5g** calculated based on recovered aldehyde, minimizing the amounts of TMSCF₂Br and **2a**, increasing the amount of KF, together with elevating the temperature can largely overwhelm the competitive conversion of aldehyde to other side products (entries 1 and 6). Therefore, to make a full use of the aldehyde, a second addition of TMSCF₂Br and **2a** is necessary. With this in mind, the optimized conditions were ultimately established by adding 1.6 equiv of TMSCF₂Br and 1.6 equiv of **2a** in two portions (Table 1, entry 9). The reaction was first run with 1.0 equiv of each reagent in the presence of 4.0 equiv of KF to generate the intermediate at room temperature. After the full consumption of the intermediate at 100 °C, another 0.6 equiv of TMSCF₂Br and **2a** were added to the reaction mixture to repeat the process. In such a way, α -fluoroamide **5g** was furnished in a good yield, with nearly complete consumption of the starting aldehyde. For comparison, the reaction of Et₃N afforded **5g** in much lower yield (Table 1, entry 10).

With the optimal reaction conditions in hands, we began to explore the reaction scope by varying the aldehyde component in combination with benzylamine **2a**. The reaction is amenable with a wide range of aromatic aldehydes including benzaldehydes (**5a–5v**, **5y** and **5z**), naphthaldehydes (**5w** and **5x**), and oxygen- and sulfur-containing heteroaromatic aldehydes (**5aa–5ac**) (Scheme 3A). Electron-rich and almost electron-neutral aromatic aldehydes were found to react more efficiently than electron deficient ones, as demonstrated by the good to excellent yields of α -fluoroamides **5a–5h**, compared to moderate yield of **5i**. However, the electronic nature of a distal aryl group has little influence on the yields (**5t–5v**). The effect of the position of the monosubstituent on the reaction was small (**5a/5j/5n**, **5d/5k**), although a slight decrease in yield was observed for *ortho*-methylbenzaldehyde (**5n**). Moreover, benzaldehydes with multiple substituents on the *meta*- and *para*-positions also delivered good yield (**5o–5s**). Importantly, the aldehyde scope was not limited to aromatic aldehydes and could be expanded to aliphatic aldehydes (**5ad–5ag**) (Scheme 3B). A series of linear and β -branched primary aliphatic aldehydes proved to be applicable for the reaction, providing the desired α -fluoroamides **5ad–5ag** in moderate to good yields. In addition, cyclic and acyclic secondary alkyl aldehydes were also viable substrates that produced good yields (**5ah–5aj**). However, more sterically hindered tertiary alkyl aldehydes are less efficient, as exemplified by the reaction of pivalaldehyde with only 32 % yield (**5ak**). It is noteworthy that halogen substituents (**5g**, **5h**, **5m**, **5p**, **5s** and **5u**), methylthio substituent (**5y**), acetylene group (**5z**) and alkene group (**5ae**) remained untouched under the reaction conditions, thus allowing further structural elaboration of the so-obtained α -fluoroamides. The practicability of this protocol is demonstrated by the synthesis of **5t** on 10-mmol scale in 76 % yield.

Next, we focused on investigating the scope of benzylamines by employing 4-fluorobenzaldehyde as the aldehyde component (Scheme 3C). The *N*-benzyl tertiary amines could be easily prepared by benzylation of secondary amines with benzyl bromide. Structurally diverse benzyldialkyl-

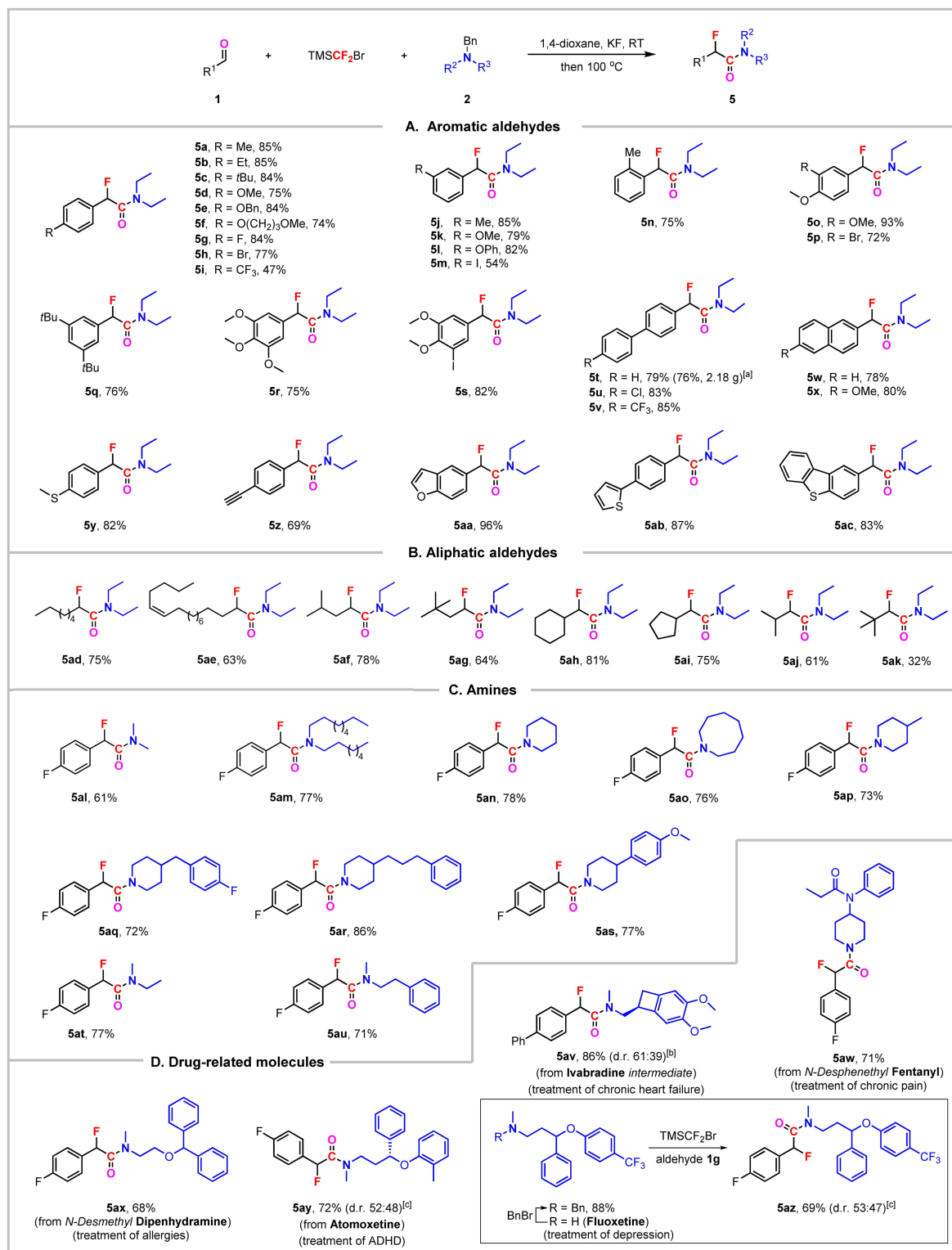
Table 1: Optimization of reaction conditions for the synthesis of α -fluoroamides.^[a]



Entry	1g /TMSCF ₂ Br/ 2a /KF	T [°C]	Yield [%] ^[b]	Recovery yield [%] ^[b]
1	1.0:1.5:1.5:2.0	80	45 (49)	8
2	1.0:2.0:2.0:2.0	80	44 (47)	7
3	1.0:4.0:4.0:2.0	80	27 (29)	7
4	1.0:1.1:1.1:2.0	80	45 (54)	16
5	1.0:1.1:1.1:4.0	80	53 (64)	17
6	1.0:1.1:1.1:4.0	100	61 (78)	22
7	1.0:1.1:1.1:4.0	50	6 (7)	11
8	1.0:1.5:1.5:4.0 ^[c]	100	79 (> 79)	trace
9	1.0:1.6:1.6:4.0 ^[c]	100	80 (> 80)	trace
10 ^[d]	1.0:1.6:1.6:4.0 ^[c]	100	56 (62)	9

[a] Unless otherwise noted, reactions were performed using **1g** (0.5 mmol, 1.0 equiv), TMSCF₂Br/**2a** = 1:1, 1,4-dioxane (5 mL).

[b] Yields of **5g** and recovery yields of **1g** were determined by ¹⁹F NMR spectroscopy analysis using 1-fluoronaphthalene as an internal standard. Yields of **5g** based on recovered starting material **1g** are given in the parentheses. [c] The molar ratio given refers to the molar ratio of all the reactants/reagents used. Reaction conditions: **1g** (0.5 mmol, 1.0 equiv), **2a** (1.0 equiv), TMSCF₂Br (1.0 equiv), KF (4.0 equiv), 1,4-dioxane (5 mL), RT, 1 h; then 100 °C, 1 h; after cooling to room temperature, the rest of **2a** and TMSCF₂Br were added into the reaction mixture, RT, 0.5 h; then 100 °C, 0.5 h. [d] Using NEt₃ instead of **2a**.

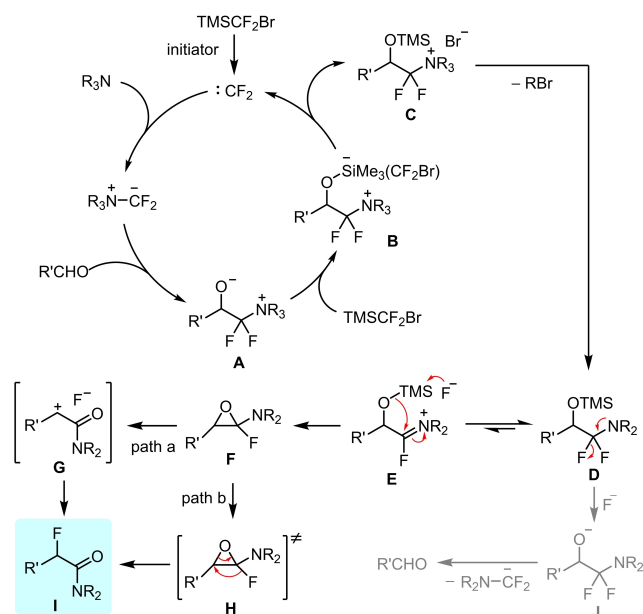


Scheme 3. Substrate scope. Reaction conditions: **1** (0.5 mmol, 1.0 equiv), **2** (0.8 mmol, 1.6 equiv), TMSCF₂Br (0.8 mmol, 1.6 equiv), KF (2.0 mmol, 4.0 equiv), 1,4-dioxane (5 mL). The reaction was performed by first reacting **1** (0.5 mmol), **2** (0.5 mmol), TMSCF₂Br (0.5 mmol) and KF (2.0 mmol) in 1,4-dioxane at RT for 1 h, then at 100 °C for 1 h. After cooling to RT, a second portion of **2** (0.3 mmol) and TMSCF₂Br (0.3 mmol) were added, and the mixture was allowed to react at RT for 0.5 h, then 100 °C for 0.5 h. Yields given refer to isolated yields of product **5**. [a] Performed on 10-mmol scale. [b] The diastereoisomer ratio (d.r.) was determined by ¹⁹F NMR spectroscopy analysis (see the Supporting Information). [c] The d.r. was determined by HPLC (see the Supporting Information).

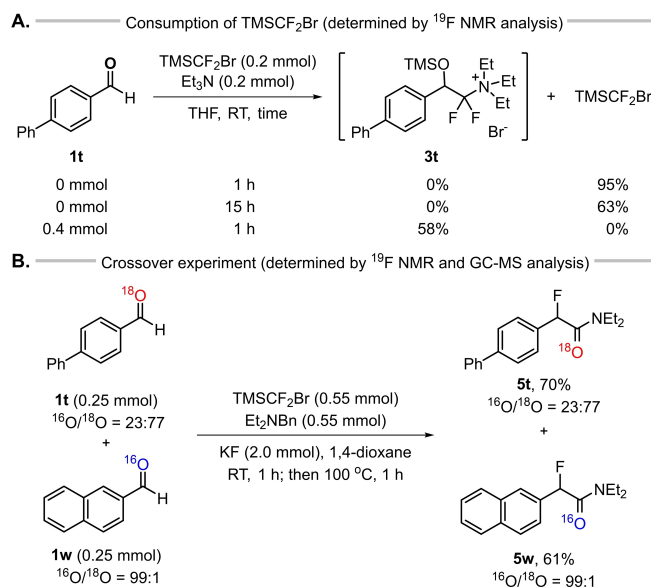
amines (**5al–5au**), including long chain ones (**5am**) and cyclic ones (**5an–5as**), could accomplish the desired transformation similarly to benzylamine **2a**, constituting an efficient and unprecedented method for α -fluoroacylation of secondary amines. In the cases of cyclic amines, no ring-opening products were detected, which is consistent with the good leaving ability of the benzyl group in the ammonium salt intermediate. Amines bearing non-symmetrical substituents on the nitrogen atom, such as *N*-benzyl-*N*-methylethanamine and *N*-benzyl-*N*-methyl-2-phenylethan-1-amine, also led to α -fluoroamides in good yields (**5at** and **5au**). With the consideration that the amine group is one of the most frequently found functional groups in an armory of marketed drugs,^[23] we investigated the modification of several secondary amine-containing drug molecules and drug intermediates (Scheme 3D). Using the *N*-benzyl derivatives, the intermediate of Ivabradine (treatment of chronic heart failure) (**5av**), *N*-desphenethyl Fentanyl (treatment of chronic pain) (**5aw**), *N*-desmethyl Diphenhydramine (treatment of allergies) (**5ax**), Atomoxetine (treatment of attention deficit hyperactivity disorder, ADHD) (**5ay**), and Fluoxetine (treatment of depression) (**5az**) were easily converted to their α -fluoroamide analogues. An example for utilizing this protocol to convert secondary amines to α -fluoroamides is showcased with the synthesis of **5az**.

Our proposed mechanism for the three-component reaction is outlined in Scheme 4. Initially, under the activation of a nucleophilic activator (such as KF, adventitious water/ R_3N , and trace carboxylic acid/ R_3N), $TMSCF_2Br$ is activated to release difluorocarbene, which reacts with R_3N to form the difluoromethylene ammonium ylide $R_3N^+-CF_2^-$. This ylide participates in nucleophilic addition to the aldehyde $R'CHO$, affording the 1,4-zwitterion adduct **A**. The reaction of intermediate **A** with $TMSCF_2Br$ provides the instable pentacoordinate silicate intermediate **B**, which

readily undergoes F_2C-Si and F_2C-Br bond cleavage, liberating TMS-protected quaternary ammonium salt intermediate **C** and difluorocarbene. The predominance of a difluorocarbene-involved chain reaction pathway is evidenced by the remarkably faster consumption of $TMSCF_2Br$ in the presence of aldehyde compared to that in the absence of aldehyde (Scheme 5A). Subsequently, intermediate **C** is dealkylated by bromide ion to give the α -aminodifluoromethyl carbinol intermediate **D**. Because intermediate **D** could undergo transformation in the absence of an extra fluoride salt (see Scheme 2B), it is reasonable to propose that one of the C–F bonds of intermediate **D** is first activated to form the fluoroiminium intermediate **E**.^[24] Then its desilylation by the in-situ released fluoride ion followed by cyclization generates the fluoroepoxide intermediate **F**. In this process, the external addition of fluoride salt can facilitate the removal of the TMS-protecting group from **C** to promote the formation of **F**. According to our previous report on the rearrangement of fluoroepoxides,^[25] the 1,2-fluorine migration of intermediate **F** via either a tight ion pair intermediate **G** (path a) or a concerted transition state **H** (path b) finally delivers the target α -fluoroamide **I**. However, during the desilylation of intermediate **E**, intermediate **D** could also be competitively desilylated to some extent, thus leading to the regeneration of the aldehyde via the retro-aldol-type reaction of intermediate **J**. Therefore, a portionwise addition of $TMSCF_2Br$ and R_3N is beneficial for improving the conversion of aldehydes. To probe the possibility of intermolecular deoxyfluorination of intermediate **D**, we conducted the crossover experiment by using two structurally different aldehydes with similar reactivity, of which one is ^{18}O -labeled, and the other is non-labeled (^{16}O -aldehyde). As shown in Scheme 5B, the reaction of ^{18}O -labeled aldehyde **1t** and non-labeled aldehyde **1w** resulted in no-crossover of the ^{18}O -label, and vice versa (see the Supporting Information). These results suggest that the



Scheme 4. Proposed mechanism.



Scheme 5. Mechanistic investigations.

transformation of intermediate **D** is more likely to proceed through an intramolecular process, which is distinctly different from the general mechanism of the deoxyfluorination of alcohols with α,α -difluoroamine reagents.^[12,24]

Conclusion

In summary, we have developed an operationally simple fluorination-aminocarbonylation strategy for the synthesis of α -fluoroamides from easily available aldehydes, *N*-benzyl tertiary amines and TMSCF₂Br. This multicomponent protocol combines C–F bond formation and amide bond formation in one process and allows for the convenient preparation of a broad scope of structurally diverse α -fluoroamides that are otherwise difficult to obtain in such a modular manner. The process involves the addition of difluoromethylene ammonium ylides to aldehydes and the 1,2-fluorine and oxygen migrations of TMS-protected α -aminodifluoromethyl carbinol intermediates. The TMSCF₂Br reagent is the key to the success of the process, which not only serves as the source of difluorocarbene to generate the ylides, but also is the promoter of the addition, as well as the bromide source for releasing the TMS-protected α -aminodifluoromethyl carbinol intermediates from the corresponding quaternary ammonium salt intermediates. Since triethylamine could also undergo the reaction, we believe that this protocol is promising for the employment of tertiary amines other than the *N*-benzyl-substituted ones as the amine component. Further applications of difluoromethylene onium ylides derived from TMSCF₂Br are under way in our laboratory.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Amide • Aminocarbonylation • Ammonium ylide • Difluorocarbene • Fluorination

- [1] *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science* (Eds.: A. Greenberg, C. M. Breneman, J. F. Liebman), Wiley, New York, **2000**.
- [2] a) J. Clayden, *Nature* **2019**, 573, 37; b) T. L. Marcha, M. R. Johnston, P. J. Duggan, J. Gardiner, *Chem. Biodiversity* **2012**, 9, 2410; c) C. R. S. Briggs, D. O'Hagan, J. A. K. Howard, D. S. Yufit, *J. Fluorine Chem.* **2003**, 119, 9.
- [3] For examples, a) J. Saadi, H. Wennemers, *Nat. Chem.* **2016**, 8, 276; b) L. Brewitz, F. A. Arteaga, L. Yin, K. Alagiri, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2015**, 137, 15929; c) V. Peddie, R. J. Butcher, W. T. Robinson, M. C. J. Wilce, D. A. K. Traore, A. D. Abell, *Chem. Eur. J.* **2012**, 18, 6655; d) D. S. Reddy, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.* **2008**, 47, 164; *Angew. Chem.* **2008**, 120, 170; e) K. Tenza, J. S. Northen, D. O'Hagan, A. M. Z. Slawin, *Beilstein J. Org. Chem.* **2005**, 1, 13.
- [4] For examples, see: a) Y.-J. Yu, F.-L. Zhang, T.-Y. Peng, C.-L. Wang, J. Cheng, C. Chen, K. N. Houk, Y.-F. Wang, *Science* **2021**, 371, 1232; b) Z.-T. He, X. Jiang, J. F. Hartwig, *J. Am. Chem. Soc.* **2019**, 141, 13066; c) E. Gupta, R. Kant, K. Mohanan, *Org. Lett.* **2017**, 19, 6016; d) A. G. Myers, J. K. Barbay, B. Zhong, *J. Am. Chem. Soc.* **2001**, 123, 7207.
- [5] a) X. Dong, W. Yang, W. Hu, J. Sun, *Angew. Chem. Int. Ed.* **2015**, 54, 660; *Angew. Chem.* **2015**, 127, 670; b) F. Buckingham, A. K. Kirjavainen, S. Forsback, A. Krzyczmonik, T. Keller, I. M. Newington, M. Glaser, S. K. Luthra, O. Solin, V. Gouverneur, *Angew. Chem. Int. Ed.* **2015**, 54, 13366; *Angew. Chem.* **2015**, 127, 13564; c) P. Wheeler, H. U. Vora, T. Rovis, *Chem. Sci.* **2013**, 4, 1674; d) S. Y. Lee, S. Neufeind, G. C. Fu, *J. Am. Chem. Soc.* **2014**, 136, 8899; e) D. H. Paull, M. T. Scerba, E. Alden-Danforth, L. R. Widger, T. Lectka, *J. Am. Chem. Soc.* **2008**, 130, 17260.
- [6] T. Honjo, R. J. Phipps, V. Rauniyar, F. D. Toste, *Angew. Chem. Int. Ed.* **2012**, 51, 9684; *Angew. Chem.* **2012**, 124, 9822.
- [7] For examples, see: a) K. Ishihara, K. Nishimura, K. Yamakawa, *Angew. Chem. Int. Ed.* **2020**, 59, 17641; *Angew. Chem.* **2020**, 132, 17794; b) P. Adler, C. J. Teskey, D. Kaiser, M. Holy, H. H. Sitte, N. Maulide, *Nat. Chem.* **2019**, 11, 329; c) T. Suzuki, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed.* **2007**, 46, 5435; *Angew. Chem.* **2007**, 119, 5531.
- [8] a) T. Nishikata, S. Ishida, R. Fujimoto, *Angew. Chem. Int. Ed.* **2016**, 55, 10008; *Angew. Chem.* **2016**, 128, 10162; b) S. Mizuta, K. Kitamura, A. Kitagawa, T. Yamaguchi, T. Ishikawa, *Chem. Eur. J.* **2021**, 27, 5930.
- [9] For reviews, see: a) D. L. S. Brahm, W. P. Dailey, *Chem. Rev.* **1996**, 96, 1585; b) W. R. Dolbier Jr., M. A. Battiste, *Chem. Rev.* **2003**, 103, 1071; c) M. Fedoryński, *Chem. Rev.* **2003**, 103, 1099; d) C. Ni, J. Hu, *Synthesis* **2014**, 46, 842; e) W. Zhang, Y. Wang, *Tetrahedron Lett.* **2018**, 59, 1301; f) X. Wang, X. Wang, J. Wang, *Tetrahedron* **2019**, 75, 949; g) A. D. Dilman, V. V. Levin, *Acc. Chem. Res.* **2018**, 51, 1272; h) X. Ma, Q. Song, *Chem. Soc. Rev.* **2020**, 49, 9197; i) W. Zhou, W.-J. Pan, J. Chen, M. Zhang, J.-H. Lin, W. Cao, J.-C. Xiao, *Chem. Commun.* **2021**, 57, 9316.
- [10] a) K. Morimoto, K. Makino, G. Sakata, *J. Fluorine Chem.* **1992**, 59, 417; b) C.-M. Hu, F.-L. Qing, C.-X. Shen, *J. Chem. Soc. Perkin Trans. 1* **1993**, 335; c) G. Zhang, Q. Shi, M. Hou, K. Yang, S. Wang, S. Wang, W. Li, C. Li, J. Qiu, H. Xu, L. Zhou, C. Wang, S.-J. Li, Y. Lan, Q. Song, *CCS Chem.* **2021**, 3, 1613.
- [11] a) L. Li, C. Ni, F. Wang, J. Hu, *Nat. Commun.* **2016**, 7, 13320; b) X. Wang, F. Wang, F. Huang, C. Ni, J. Hu, *Org. Lett.* **2021**, 23, 1764.
- [12] For reviews, see: a) "Fluoroolefin-Amine Adduct Deoxofluorination": V. Petrov in *Fluorination. Synthetic Organofluorine Chemistry* (Eds.: J. Hu, T. Umemoto), Springer, Singapore, **2020**; b) " α,α -Difluorobenzyamines Deoxofluorination": L. Li,

- J. Hu in *Fluorination. Synthetic Organofluorine Chemistry* (Eds.: J. Hu, T. Umemoto), Springer, Singapore, **2020**; c) "PhenoFluor, PhenoFluorMix, and AlkylFluor": T. Ritter, J. Chen in *Encyclopedia of Reagents for Organic Synthesis* (Eds.: A. B. Charette, J. W. Bode, T. Rovis, R. A. Shenvi), Wiley, Hoboken, **2021**.
- [13] The synthesis of heteroaryl-*N*-difluoromethyl carbinols via nucleophilic addition of heteroaryl-*N*-difluoromethyl anions, generated via debromination, deprotonation and desilylation, to carbonyl compounds is known; however, the corresponding carbinols are stable and reluctant to undergo self-deoxyfluorination, see: a) L. M. Yagupolskii, D. V. Feduk, *Tetrahedron Lett.* **2000**, 41, 2265; b) G. Bissky, V. I. Staninets, A. A. Kolomeitsev, G.-V. Rösenthaller, *Synlett* **2001**, 374; c) G. Bissky, G.-V. Rösenthaller, E. Lork, J. Barten, M. Médebielle, V. Staninets, A. A. Kolomeitsev, *J. Fluorine Chem.* **2001**, 109, 173; d) J. Y. Chai, H. Cha, H. B. Kim, D. Y. Chi, *Tetrahedron* **2020**, 76, 131370.
- [14] For recent examples, see: a) Q. Xie, Z. Zhu, C. Ni, J. Hu, *Org. Lett.* **2019**, 21, 9138; b) T. Mita, Y. Harabuchi, S. Maeda, *Chem. Sci.* **2020**, 11, 7569; c) H. Hayashi, H. Takano, H. Katsuyama, Y. Harabuchi, S. Maeda, T. Mita, *Chem. Eur. J.* **2021**, 27, 10040.
- [15] For examples, see: a) A. Polley, G. Bairy, P. Das, R. Jana, *Adv. Synth. Catal.* **2018**, 360, 4161; b) V. P. Mehta, M. F. Greaney, *Org. Lett.* **2013**, 15, 5036; c) W. Zhang, F. Wang, J. Hu, *Org. Lett.* **2009**, 11, 2109; d) X. Ma, S. Deng, Q. Song, *Org. Chem. Front.* **2018**, 5, 3505; e) Y.-X. Si, P.-F. Zhu, S.-L. Zhang, *Org. Lett.* **2020**, 22, 9086.
- [16] For reviews, see: a) D. J. Burton, Z.-Y. Yang, W. Qiu, *Chem. Rev.* **1996**, 96, 1641; b) J.-H. Lin, J.-C. Xiao, *Acc. Chem. Res.* **2020**, 53, 1498.
- [17] For examples, see: a) F. Wang, L. Li, C. Ni, J. Hu, *Beilstein J. Org. Chem.* **2014**, 10, 344; b) V. V. Levin, A. L. Trifonov, A. A. Zemtsov, M. I. Struchkova, D. E. Arkhipov, A. D. Dilman, *Org. Lett.* **2014**, 16, 6256; c) V. O. Smirnov, A. D. Volodin, A. A. Korlyukov, A. D. Dilman, *Angew. Chem. Int. Ed.* **2020**, 59, 12428; *Angew. Chem.* **2020**, 132, 12528; d) W. C. Fu, T. F. Jamison, *Angew. Chem. Int. Ed.* **2020**, 59, 13885; *Angew. Chem.* **2020**, 132, 13989; e) A. L. Trifonov, A. D. Dilman, *Org. Lett.* **2021**, 23, 6977.
- [18] The adducts of difluoromethylene azomethine ylides (1,3-dipoles) with carbonyl groups are not suitable for further self-deoxyfluorination, see: a) M. S. Novikov, A. F. Khlebnikov, A. Krebs, R. R. Kostikov, *Eur. J. Org. Chem.* **1998**, 133; b) M. S. Novikov, A. F. Khlebnikov, E. S. Sidorina, R. R. Kostikov, *J. Chem. Soc. Perkin Trans. 1* **2000**, 231; c) M. S. Novikov, I. V. Voznyi, A. F. Khlebnikov, J. Kopf, R. R. Kostikov, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1628; d) I. V. Voznyi, M. S. Novikov, A. F. Khlebnikov, J. Kopf, R. R. Kostikov, *Russ. J. Org. Chem.* **2004**, 40, 199; e) M. S. Novikov, A. A. Amer, A. F. Khlebnikov, *Tetrahedron Lett.* **2006**, 47, 639; f) K. A. Khistiaev, M. S. Novikov, A. F. Khlebnikov, J. Magull, *Tetrahedron Lett.* **2008**, 49, 1237; g) M. S. Novikov, A. F. Khlebnikov, K. A. Khistiaev, I. Magull, *Russ. Chem. Bull. Int. Ed.* **2008**, 57, 1070; h) K. R. Gaisina, A. F. Khlebnikov, M. S. Novikov, *Org. Biomol. Chem.* **2017**, 15, 4579.
- [19] The intramolecular addition reaction can readily take place without further stabilizing the 1,4-zwitterion adducts (see Ref. [10c]); however, the reported reaction conditions are not applicable for three-component synthesis of α -fluoroamides.
- [20] The removal of one of the *N*-substituents from quaternary ammonium salts with nucleophiles usually proceeds under harsh conditions, for examples, see: a) Y. Kim, J. Heo, D. Kim, S. Chang, S. Seo, *Nat. Commun.* **2020**, 11, 4761; b) J. Su, X. Ma, Z. Ou, Q. Song, *ACS Cent. Sci.* **2020**, 6, 1819; c) J. Su, X. Hu, H. Huang, Y. Guo, Q. Song, *Nat. Commun.* **2021**, 12, 4986; d) H. Sheng, J. Su, X. Li, X. Li, Q. Song, *Org. Lett.* **2021**, 23, 7781.
- [21] a) F. Wang, W. Zhang, J. Zhu, H. Li, K.-W. Huang, J. Hu, *Chem. Commun.* **2011**, 47, 2411; b) L. Li, F. Wang, C. Ni, J. Hu, *Angew. Chem. Int. Ed.* **2013**, 52, 12390; *Angew. Chem.* **2013**, 125, 12616; c) Q. Xie, C. Ni, R. Zhang, L. Li, J. Rong, J. Hu, *Angew. Chem. Int. Ed.* **2017**, 56, 3206; *Angew. Chem.* **2017**, 129, 3254; d) Q. Xie, Z. Zhu, L. Li, C. Ni, J. Hu, *Angew. Chem. Int. Ed.* **2019**, 58, 6405; *Angew. Chem.* **2019**, 131, 6471; e) R. Zhang, Q. Li, Q. Xie, C. Ni, J. Hu, *Chem. Eur. J.* **2021**, 27, 17773–17779.
- [22] For recent examples, see: a) Ref. [17e]; b) Y. Jia, Y. Yuan, J. Huang, Z.-X. Jiang, Z. Yang, *Org. Lett.* **2021**, 23, 2670; c) R.-Y. Yang, H. Wang, B. Xu, *Chem. Commun.* **2021**, 57, 4831; d) Z. Zhu, V. Krishnamurti, X. Ispizua-Rodriguez, C. Barrett, G. K. S. Prakash, *Org. Lett.* **2021**, 23, 6494; e) Ref. [20a]; f) X. Liu, D. Du, S. Li, X. Wang, C. Xu, M. Wang, *Adv. Synth. Catal.* **2020**, 362, 5135; g) R. Zhang, Z. Zhang, K. Wang, J. Wang, *J. Org. Chem.* **2020**, 85, 9791; h) R. Zhang, Z. Zhang, Q. Zhou, L. Yu, J. Wang, *Angew. Chem. Int. Ed.* **2019**, 58, 5744; *Angew. Chem.* **2019**, 131, 5800; i) J. Wang, E. Tokunaga, N. Shibata, *Chem. Commun.* **2018**, 54, 8881.
- [23] J. P. Krise, R. Oliyai, *Prodrugs of Amines in: Prodrugs. Biotechnology: Pharmaceutical Aspects, Vol. V* (Eds.: V. J. Stella, R. T. Borchardt, M. J. Hageman, R. Oliyai, H. Maag, J. W. Tilley), Springer, New York, **2007**, pp. 801–831.
- [24] B. Commare, E. Schmitt, F. Aribi, A. Panossian, J.-P. Vors, S. Pazenok, F. R. Leroux, *Molecules* **2017**, 22, 977.
- [25] T. Luo, R. Zhang, W. Zhang, X. Shen, T. Umemoto, J. Hu, *Org. Lett.* **2014**, 16, 888.

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