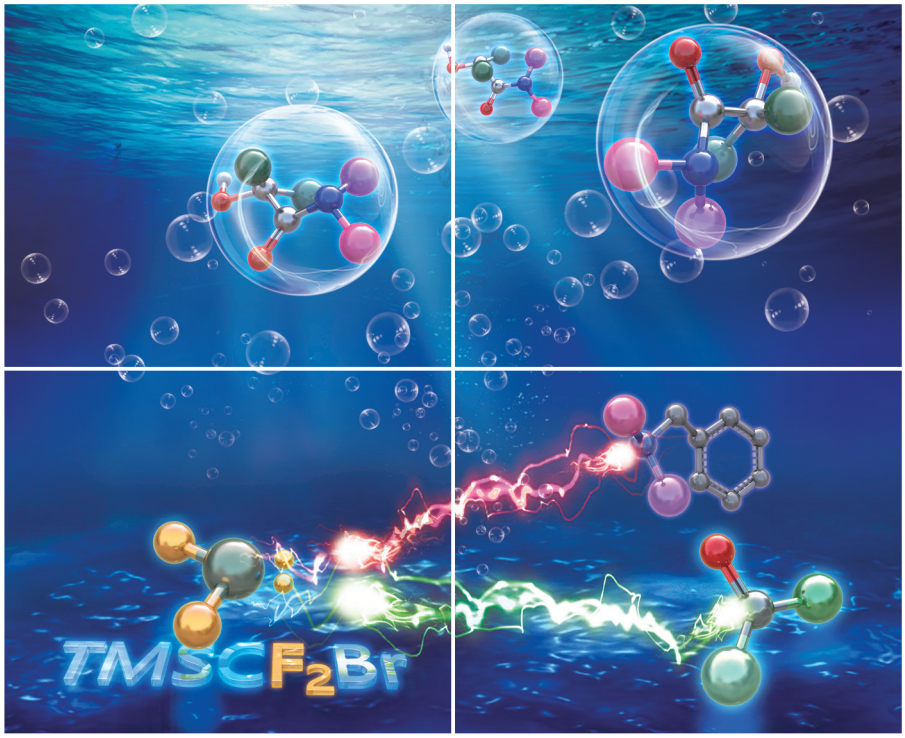
Volume 10 | Number 21 | 7 November 2023

10 YEARS ANNIVERSARY



ORGANIC CHEMISTRY

FRONTIERS

CCS 中国化学会 CHINESE CHEMICAL SOCIETY
SIOC 1950
ROYAL SOCIETY OF CHEMISTRY
rsc.li/frontiers-organic

ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Org. Chem. Front.*, 2023, **10**, 5343

From intramolecular cyclization to intermolecular hydrolysis: $TMSCF_2Br$-enabled carbonylation of aldehydes/ketones and amines to α-hydroxyamides†

An Liu, Shuo Sun, Qiqiang Xie, Rumin Huang, Taige Kong, Chuanfa Ni and Jinbo Hu *

Received 28th May 2023,
Accepted 14th July 2023

DOI: 10.1039/d3qo00665d

rsc.li/frontiers-organic

A metal-free multicomponent strategy has been developed for the synthesis of various α-hydroxyamides *via* carbonylation of aldehydes/ketones and amines enabled by the difluorocarbene reagent $TMSCF_2Br$ (TMS = trimethylsilyl). The TMS-protecting group derived from $TMSCF_2Br$ plays a crucial role in the tunability of the reaction pathways from intramolecular cyclization to intermolecular hydrolysis. The synthetic utility has been demonstrated by the late-stage modification of several drug-related molecules and the highly selective synthesis of ^{18}O-labeled α-hydroxyamides from $H_2{}^{18}O$.

Open Access Article. Published on 15 July 2023. Downloaded on 11/30/2025 5:51:52 AM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Introduction

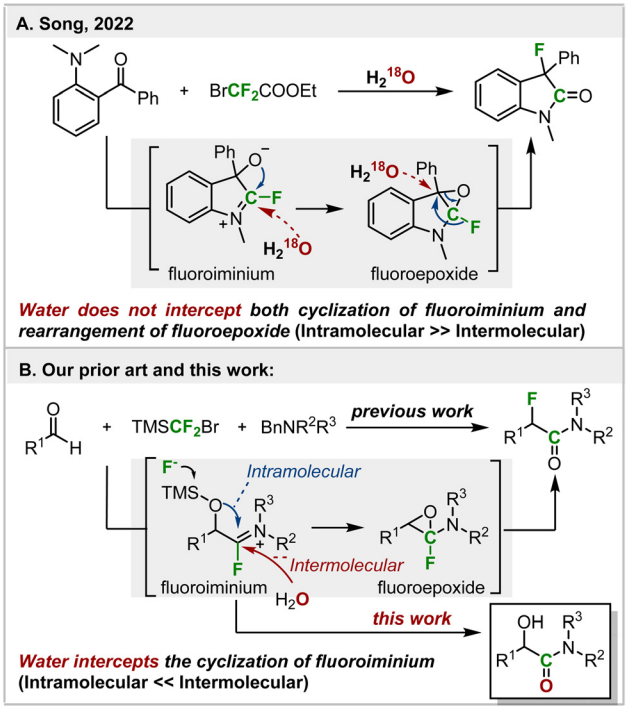
α-Hydroxyamides are found in pharmaceuticals, agrochemicals and natural products, and serve as useful synthetic building blocks.[1] The traditional approaches for the synthesis of α-hydroxyamides require the preparation of α-hydroxy acids, followed by the protection of the hydroxy groups (prior to the condensation with amines) and the final deprotection.[2] And more convenient methods *via* the nucleophilic addition of carbonyl compounds with carbamoyl anions such as carbamoyllithiums,[3] carbamoylsilanes[4] or its equivalent isocyanides[5] for the assembly of α-hydroxyamides have also been well-documented. Even though these established two-component methods have made remarkable progress,[6] they still suffer from multiple-step operations, harsh reaction conditions or limited substrate scope. From a retrosynthetic viewpoint, a three-component method is expected for streamlined access to α-hydroxyamides from abundant carbonyl compounds, suitable carbonyl sources and amines. Indeed, three-component transition-metal-catalyzed carbonylation reactions with simple starting materials and amines have attracted widespread attention owing to the use of CO or CO surrogates as carbonyl sources.[7] And a variety of readily available feedstocks including aryl/vinyl (pseudo)halides,[8] alkenes/alkynes[9] and even nucleophiles[10] (organoboronic acids, organosilanes, C–H activation, *etc.*) have been utilized as starting materials in this area. Surprisingly, carbonyl compounds, which are some of the most abundant feedstocks, have not yet been employed in such three-component reactions for the synthesis of various α-hydroxyamides.

In 2014, our group investigated the rearrangement of fluoroepoxides involving simultaneous cleavage and formation of C–F bonds.[11] More recently, Song and co-workers reported a similar process utilizing fluoroepoxides generated *in situ* from intramolecular tandem reactions of 2-aminoarylketones with difluorocarbene.[12] The 1,2-fluorine migration of fluoroepoxides generated *in situ* from difluorocarbene-involved intermolecular tandem reactions of aldehydes with amines was also accomplished by us.[13] In Song's work, it was found that water had almost no effect on both cyclization of the fluoroiminium intermediate and rearrangement of the fluoroepoxide intermediate (Scheme 1A).[12] In this context, we were interested to explore the possibility of a new nucleophile (such as water, alcohols or other oxygen sources) competitively reacting with the fluoroiminium intermediate,[13] which could change the reaction pathway[14] and bring about a new method for modular access to various α-hydroxyamides (Scheme 1B). We noticed that the intramolecular cyclization of the fluoroiminium intermediate was promoted by external KF in our previous α-fluoroamide system.[13] Furthermore, the addition of KF could facilitate the removal of the TMS-protecting group by the fluoroiminium intermediate, suggesting that the TMS-protecting group somewhat decelerated the intramolecular cyclization of the fluoroiminium intermediate to deliver the fluoroepoxide intermediate. With these in mind, we envisioned that the

Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China. E-mail: jinbohu@sioc.ac.cn

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3qo00665d

Open Access Article. Published on 15 July 2023. Downloaded on 11/30/2025 5:51:52 AM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.



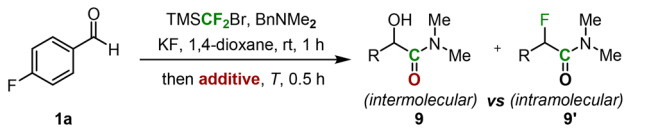
Scheme 1 Reaction design from intramolecular cyclization to intermolecular hydrolysis.

addition of excess water or alcohols (more nucleophilic than water) to our previous α-fluoroamide system with reduced or even no use of KF could switch the intrinsic intramolecular cyclization pathway to the intermolecular reaction pathway, affording the desired α-hydroxyamides.

Results and discussion

We initiated our investigation by comparing the effects of different types of alcohols (more nucleophilic than water) on our previous α-fluoroamide system.[13] When the tertiary alcohol *t*-BuOH was added to this system, the intramolecular pathway involving the fluoroepoxide intermediate could occur along with the formation of **9′** in 29% yield (Table 1, entry 1). Importantly, we found that some of the fluoroiminium intermediate molecules were successfully intercepted by *t*-BuOH albeit without subsequent transformations to afford **9** due to the difficulty of the *t*-Bu–O bond cleavage. Even though the use of the secondary alcohol *i*-PrOH or the primary alcohol MeOH as a nucleophile obviously suppressed the intramolecular cyclization pathway, the desired product **9** could not be observed (Table 1, entries 2 and 3). Benzyl alcohol (BnOH) was therefore considered as a more suitable oxygen source for this reaction due to the easier removal of the benzyl group, and we did obtain the desired α-hydroxyamide **9** in 22% yield with the addition of BnOH (Table 1, entry 4). The reduced use of KF could, as we expected initially, slightly improve the yield of **9** (Table 1, entries 4–6). To our surprise, the use of weakly

Table 1 Optimization of the reaction conditions[a]



Entry	KF (equiv.)	*T* (°C)	Additive	Yield (%) 9	9′
1	4	100	*t*-BuOH	—	29
2	4	100	*i*-PrOH	—	2
3	4	100	MeOH	—	n.d.
4	4	100	BnOH	22	n.d.
5	2	100	BnOH	26	n.d.
6	0	100	BnOH	28	n.d.
7[b]	0	100	H_2O	80	n.d.
8[b,c]	0	rt	H_2O	88	n.d.
9[b,c,d]	0	rt	H_2O	78	n.d.
10[b,c,e]	0	rt	H_2O	69	n.d.

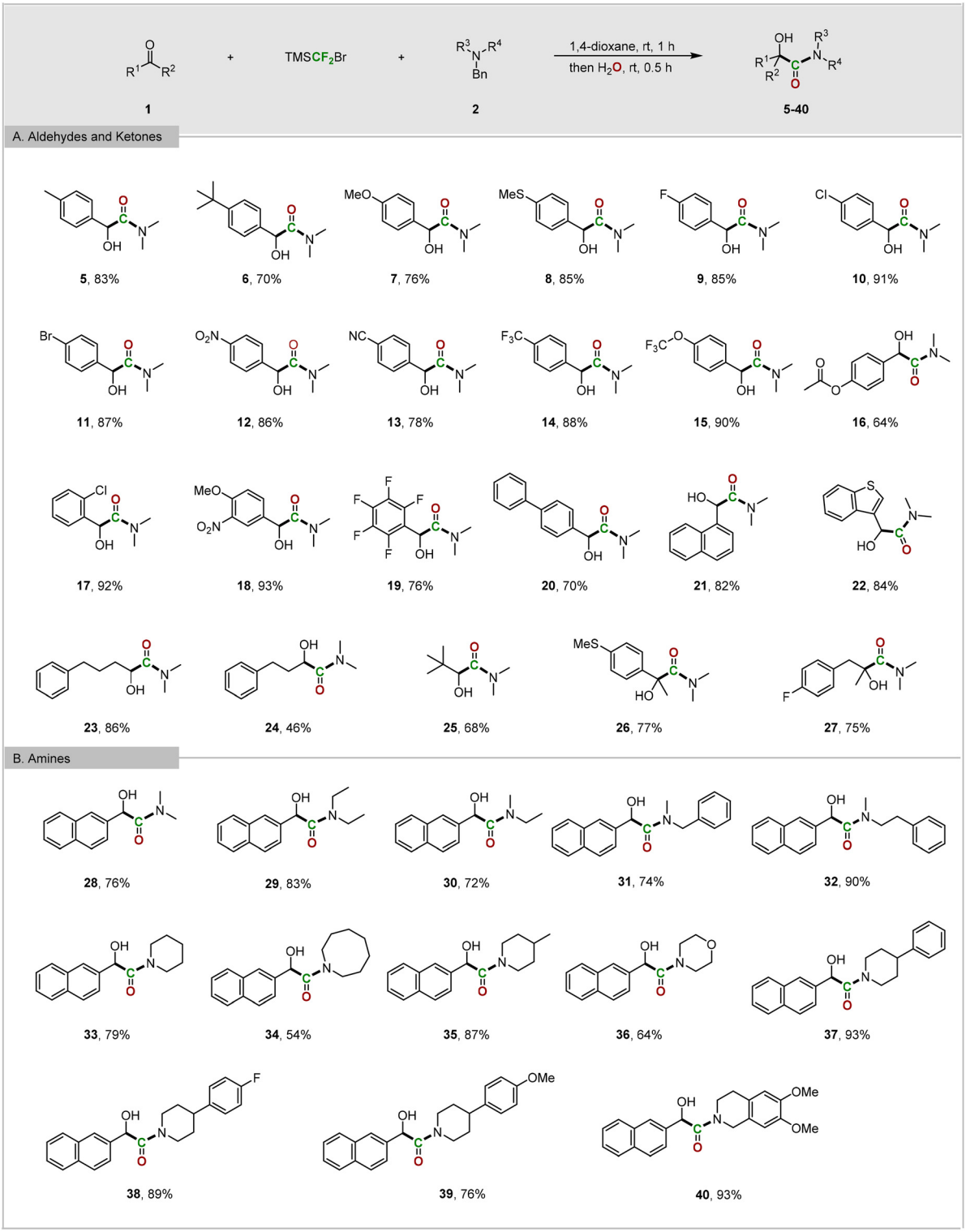
[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), $TMSCF_2Br$ (0.22 mmol, 1.1 equiv.), $BnNMe_2$ (0.22 mmol, 1.1 equiv.), KF, rt, 1 h. Then additive (0.4 mmol, 2.0 equiv.), *T*, 0.5 h. Yields were determined by ^{19}F NMR using 1-fluoronaphthalene as an internal standard. [b] Additive (0.2 mL). [c] $TMSCF_2Br$ (0.4 mmol, 2.0 equiv.), $BnNMe_2$ (0.4 mmol, 2.0 equiv.). [d] THF as solvent. [e] DMF as solvent. n.d. = not detected.

nucleophilic water (instead of benzyl alcohol) dramatically improved the yield of the target product α-hydroxyamide **9** (80%), which was distinctly different from the result reported by the Song group (Table 1, entry 7) (Scheme 1A).[12] Fine tuning of the reaction temperature and the ratio of the reagents brought about further improvement in the yield, and product **9** was obtained in 88% yield (Table 1, entry 8). Next, screening of solvents revealed that 1,4-dioxane remained the optimal choice for this transformation (Table 1, entries 9 and 10). Considering that the synthesis of the desired α-hydroxyamides did not involve the incorporation of fluorine atoms, the use of difluorocarbene might be unnecessary. However, although $TMSCFCl_2$, $TMSCFBr_2$ and $TMSCCl_2Br$ were expected to undergo this tandem reaction as other dihalocarbene precursors,[15] we failed to obtain the desired product. In addition, common difluorocarbene reagents such as $BrCF_2COONa$, $BrCF_2COOEt$ and $BrCF_2CP(O)(OEt)_2$ were also screened, and the desired transformations were not observed even in the presence of activators. To some degree, these failures emphasized the uniqueness of the commercially available $TMSCF_2Br$, which was initially developed by us as a difluorocarbene reagent.[16]

With the optimized conditions in hand, we next turned our attention to evaluating the versatility of this multicomponent tandem reaction (Scheme 2). The synthesis of a variety of aromatic aldehydes featuring diverse electronic and steric properties was first attempted by choosing $TMSCF_2Br$ and *N*,*N*-dimethylbenzylamine as reaction partners, and the corresponding products **5–22** were obtained in good to excellent yields under the standard conditions (Scheme 2A). Various substituents including both electron-donating groups [such as

 This journal is © the Partner Organisations 2023

Open Access Article. Published on 15 July 2023. Downloaded on 11/30/2025 5:51:52 AM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.



Scheme 2 Substrate scope. Reaction conditions: **1** (0.5 mmol, 1.0 equiv.), $TMSCF_2Br$ (1.0 mmol, 2.0 equiv.), **2** (1.0 mmol, 2.0 equiv.), 1,4-dioxane (5 mL), rt, 1 h. Then H_2O (0.5 mL), rt, 0.5 h; isolated yields.

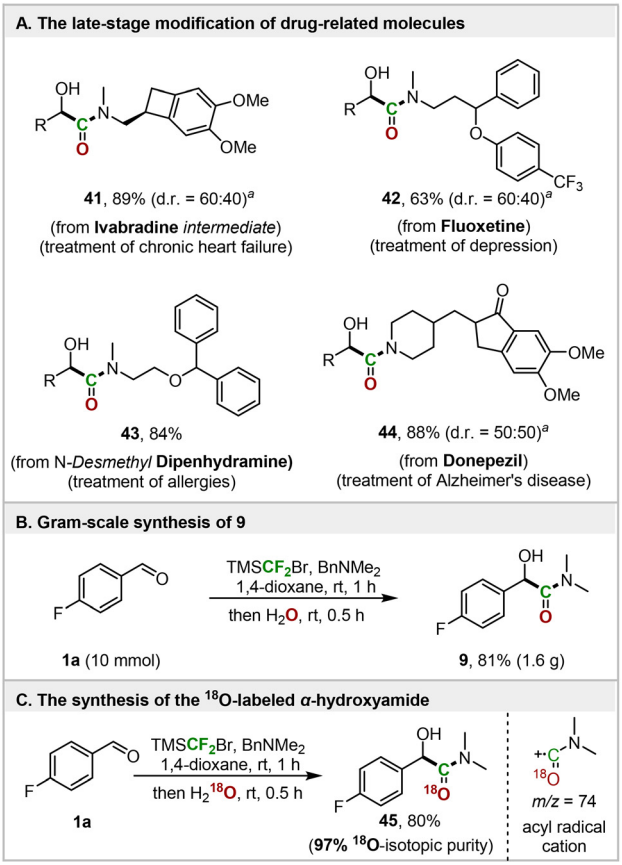
alkyl (**5–6**), ether (**7**) and methylthiol (**8**)] and electron-withdrawing groups [such as halogen (**9–11**), nitro (**12**), cyano (**13**), trifluoromethyl (**14–15**) and ester (**16**)] at the *para* position of the phenyl ring were found to be compatible with the reaction. 2-Chlorobenzaldehyde and 4-chlorobenzaldehyde showed similar reactivity in this transformation with the formation of the corresponding products **17** and **10** in similar yields (92% and 91%, respectively), indicating that the steric hindrance

Open Access Article. Published on 15 July 2023. Downloaded on 11/30/2025 5:51:52 AM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

arising from the *ortho*-substituent did not have much influence on the present reaction. Aldehydes with different substitution patterns participated in this reaction smoothly, although the yield of pentafluorobenzaldehyde (**19**, 76%) was slightly lower than that of 4-methoxy-3-nitrobenzaldehyde (**18**, 93%). Aromatic aldehydes containing extended π-systems including 4-phenylbenzaldehyde, 1-naphthaldehyde and benzo[*b*]thiophene-3-carbaldehyde were also compatible with this reaction, affording the corresponding products **20–22** in 70–84% yields. Notably, this reaction was not limited to aromatic aldehydes, and it was also applicable to both enolizable and non-enolizable alkyl aldehydes (**23–25**). More importantly, unlike our previous work in which ketones failed to provide α-fluoroamides,[13] this new intermolecular hydrolysis system was extended successfully to aromatic and alkyl ketones, giving the corresponding α-hydroxyamides (**26–27**) in good yields.

We subsequently focused on investigating the substrate scope with respect to benzylamines by selecting 2-naphthaldehyde as the model reaction partner (Scheme 2B). A wide range of structurally diverse open-chain and cyclic benzyldialkylamines proved to be suitable starting materials to deliver the desired α-hydroxyamides in good to excellent yields. In the case of open-chain benzylamines, both symmetrical and non-symmetrical dialkyl-substituted benzylamines (such as *N*-benzyl-*N*-ethylethanamine, *N*-benzyl-*N*-methyl-1-phenylmethanamine and others) underwent the multicomponent reaction efficiently, affording the corresponding products (**28–32**) in 72–90% yields. In the case of cyclic benzylamines, compared to 1-benzylpiperidine containing a six-membered ring (**33** *vs.* **34**), 1-benzylazocane containing an eight-membered ring was unfavorable in this reaction and the desired α-hydroxyamide (**34**) was obtained in a moderate yield. Various substituents on the six-membered ring of cyclic benzylamines had no significant effect and their corresponding products (**35–40**) were isolated in 64–93% yields. The nucleophilicity of 4-benzylmorpholine was weakened by the ether group at the β-position of the nitrogen atom, leading to a slightly lower yield of **36** (64%).

To further demonstrate the utility of this established method and considering the significant roles of amides in pharmaceuticals,[17] we successfully accomplished amide bond linkages for complex molecules by using benzyl derivatives of nitrogen-containing drug-related molecules (Scheme 3A). Ivabradine (for chronic heart failure), fluoxetine (for depression), dipenhydramine (for allergies) and donepezil (for Alzheimer's disease) were transformed smoothly to the corresponding α-hydroxyamide derivatives (**41–44**) in 63–89% yields. And this method could also be scaled up to the gram-scale without much loss of efficiency, as demonstrated by the synthesis of **9** (1.6 g, 81%) (Scheme 3B). Additionally, stable ^{18}O-labeled molecules have been widely applied for isotopic tracing in various fields, and $H_2{}^{18}O$ serves as one of the main ^{18}O sources for their synthesis.[18] In this context, we soon realized that the combination of difluorocarbene and $H_2{}^{18}O$ as the carbonyl equivalent could be utilized for highly selective



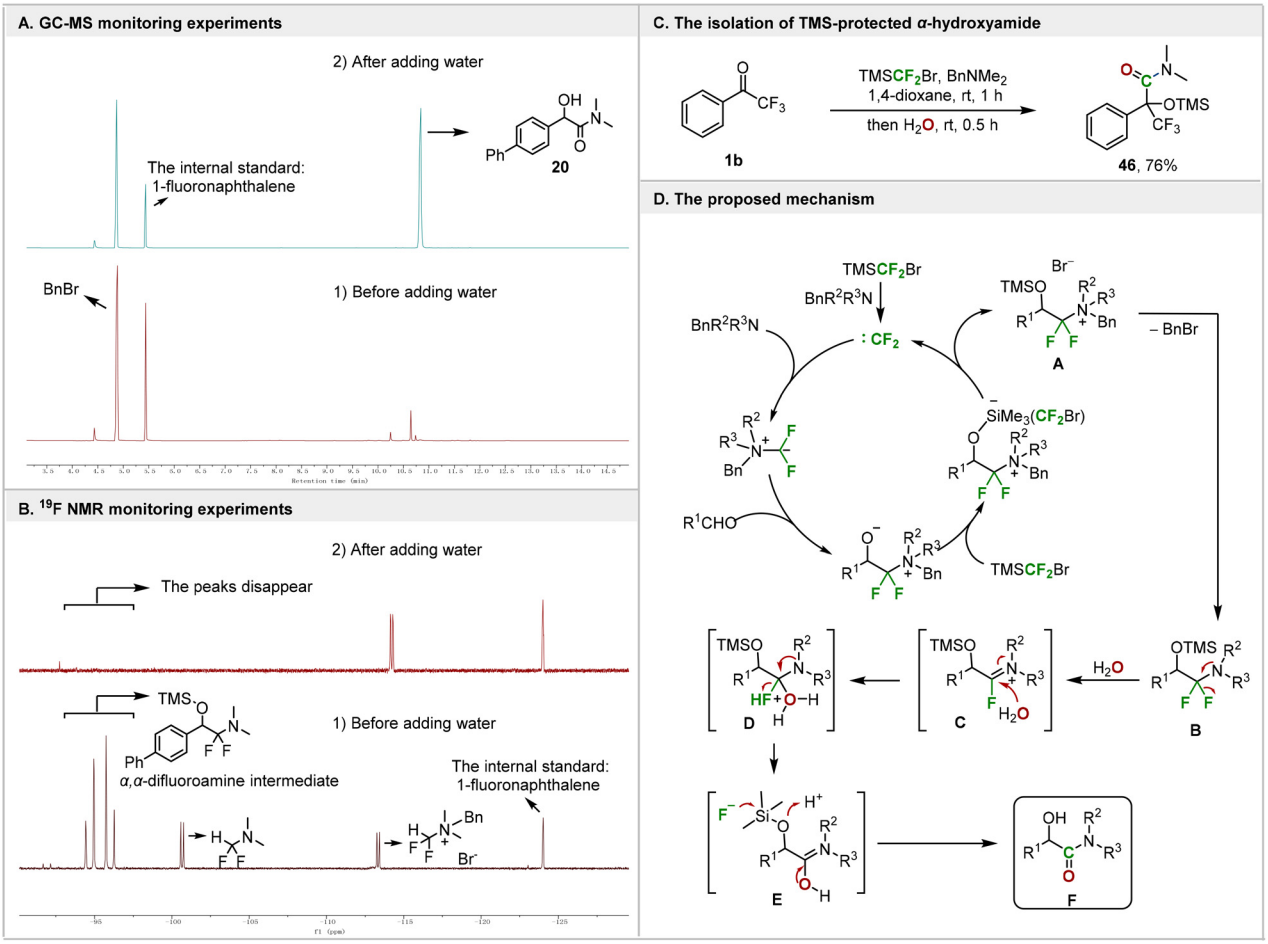
Scheme 3 Synthetic applications (RCHO = 2-naphthaldehyde). For reaction details, see the ESI.† Isolated yields. [a]The diastereoisomer ratio (dr) was determined by HPLC.

access to ^{18}O-labeled α-hydroxyamides with high ^{18}O-isotopic purity. To our delight, we successfully isolated the ^{18}O-labeled α-hydroxyamide **45** in 80% yield (97% ^{18}O-isotopic purity) by using $H_2{}^{18}O$ instead of H_2O under the standard conditions (Scheme 3C).

Notably, the isolation of the ^{18}O-labeled α-hydroxyamide **45** also provides comprehensive insights into the reaction mechanism. The mass spectrometric fragmentation of the ^{18}O-labeled acyl radical cation (m/z = 74) with 97% ^{18}O-isotopic purity confirmed that the ^{18}O-labeling occurred at the carbonyl group rather than the hydroxyl group (Scheme 3B). Meanwhile, this observation demonstrates that water (added to the reaction mixture) intercepts the cyclization process of the fluoroiminium intermediate (leading to the ^{18}O-labeled carbonyl group) rather than the rearrangement of the fluoroepoxide intermediate (leading to the ^{18}O-labeled hydroxyl group), which is consistent with our initial hypothesis. Next, we conducted a series of monitoring experiments by GC-MS (Scheme 4A) and ^{19}F NMR (Scheme 4B) for mechanistic investigations. A large amount of benzyl bromide (Scheme 4A (1)) and the fluorine signal of the α,α-difluoroamine intermediate (Scheme 4B (1)) were observed before water was added to the reaction system. Then the addition of water led to the dis-

 This journal is © the Partner Organisations 2023

Open Access Article. Published on 15 July 2023. Downloaded on 11/30/2025 5:51:52 AM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.



Scheme 4 Mechanistic investigations and the proposed mechanism. For reaction details, see the ESI.†

appearance of the fluorine signal of the α,α-difluoroamine intermediate (Scheme 4B (2)) with the generation of the desired α-hydroxyamide (Scheme 4A (2)). In addition, the TMS-protected α-hydroxyamide **46** was successfully isolated in 76% yield when 2,2,2-trifluoro-1-phenylethan-1-one was subjected to the standard conditions (Scheme 4C), which provided direct evidence that the TMS-protecting group could inhibit the intramolecular cyclization of the fluoroiminium intermediate to give fluoroepoxide (as shown in Scheme 1B). According to these mechanistic investigations and our previous results,[13] a plausible mechanism is outlined in Scheme 4D. The α,α-difluoroammonium intermediate **A**, generated *in situ* from the three-component chain reaction of aldehydes, amines and $TMSCF_2Br$, undergoes debenzylation by the bromide ion, delivering the α,α-difluoroamine intermediate **B**. Then β-fluoride elimination of intermediate **B** leads to the formation of the fluoroiminium intermediate **C**. Given that the TMS-protecting group decelerates the intramolecular cyclization of the fluoroiminium intermediate, intermolecular nucleophilic addition of the fluoroiminium intermediate **C** with water can proceed smoothly. Finally, the desired α-hydroxyamide **F** is afforded with subsequent defluorination and desilylation.

Conclusions

In summary, we have described an unprecedented and highly efficient multicomponent strategy for the synthesis of structurally valuable α-hydroxyamides from carbonyls (aldehydes or ketones), amines and the difluorocarbene reagent $TMSCF_2Br$ by switching the reaction pathways of the fluoroiminium intermediate from intramolecular cyclization to intermolecular hydrolysis. The key to the success of this process is that the TMS-protecting group derived from $TMSCF_2Br$ decelerates the intramolecular cyclization of the fluoroiminium intermediate, which utilizes the unique structural advantage of $TMSCF_2Br$. This novel approach shows excellent functional group tolerance thanks to the mild reaction conditions, and all starting materials used in this reaction are commercially available. The late-stage modification of several nitrogen-containing drug-related molecules further demonstrates the utility of rapid construction of complex scaffolds for drug discovery. Significantly, the combination of difluorocarbene and $H_2{}^{18}O$ as the carbonyl equivalent provides a new opportunity for highly selective synthesis of ^{18}O-labeled α-hydroxyamides with high ^{18}O-isotopic purity, which has been largely ignored in organic chemistry.

Open Access Article. Published on 15 July 2023. Downloaded on 11/30/2025 5:51:52 AM. This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Further development of new reactions by intercepting the reaction intermediates (such as **C** in Scheme 4D) in such multi-component systems is underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Key Research and Development Program of China (2021YFF0701700) and the National Natural Science Foundation of China (22271299 and 22261132514).

References

1 (*a*) S. L. Zhang, W. Zhang, Z. Yang, X. Hu and K. Y. Tam, Synthesis and biological evaluation of (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionamides as pyruvate dehydrogenase kinase 1 (PDK1) inhibitors to reduce the growth of cancer cells, *Eur. J. Pharm. Sci.*, 2017, **110**, 87; (*b*) M. Bassetto, S. Ferla, F. Pertusati, S. Kandil, A. D. Westwell, A. Brancale and C. McGuigan, Design and synthesis of novel bicalutamide and enzalutamide derivatives as antiproliferative agents for the treatment of prostate cancer, *Eur. J. Med. Chem.*, 2016, **118**, 230; (*c*) M. R. Wood, K. M. Schirripa, J. J. Kim, S. D. Kuduk, R. K. Chang, C. N. Di Marco, R. M. DiPardo, B. L. Wan, K. L. Murphy, R. W. Ransom, R. S. Chang, M. A. Holahan, J. J. Cook, W. Lemaire, S. D. Mosser, R. A. Bednar, C. Tang, T. Prueksaritanont, A. A. Wallace, Q. Mei, J. Yu, D. L. Bohn, F. C. Clayton, E. D. Adarayn, G. R. Sitko, Y. M. Leonard, R. M. Freidinger, D. J. Pettibone and M. G. Bock, Alpha-hydroxy amides as a novel class of bradykinin B1 selective antagonists, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 716; (*d*) F. Depeint, W. R. Bruce, N. Shangari, R. Mehta and P. J. O'Brien, Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism, *Chem.-Biol. Interact.*, 2006, **163**, 94; (*e*) M. Sani, D. Belotti, R. Giavazzi, W. Panzeri, A. Volonterio and M. Zanda, Synthesis and evaluation of stereopure α-trifluoromethylmalic hydroxamates as inhibitors of matrix metalloproteinases, *Tetrahedron Lett.*, 2004, **45**, 1611; (*f*) H. A. Schenck, P. W. Lenkowski, I. Choudhury-Mukherjee, S. H. Ko, J. P. Stables, M. K. Patel and M. L. Brown, Design, synthesis and evaluation of novel hydroxyamides as orally available anticonvulsants, *Bioorg. Med. Chem.*, 2004, **12**, 979; (*g*) W. Szymanski, M. Zwolinska, S. Klossowski, I. Mlynarczuk-Bialy, L. Bialy, T. Issat, J. Malejczyk and R. Ostaszewski, Synthesis of novel, peptidic kinase inhibitors with cytostatic/cytotoxic activity, *Bioorg. Med. Chem.*, 2014, **22**, 1773.

2 (*a*) S. E. Kelly and T. G. LaCour, A One Pot Procedure for the Synthesis of α-Hydroxyamides from the Corresponding α-Hydroxyacids, *Synth. Commun.*, 1992, **22**, 859; (*b*) J. M. Shin and Y. H. Kim, New facile synthesis of α-hydroxyamides: Intermolecular and intramolecular catalysis in the reaction of α-hydroxycarboxylic acids with *N*-sulfinylamines, *Tetrahedron Lett.*, 1986, **27**, 1921.

3 (*a*) M. A. Ganiek, M. R. Becker, G. Berionni, H. Zipse and P. Knochel, Barbier Continuous Flow Preparation and Reactions of Carbamoyllithiums for Nucleophilic Amidation, *Chem. – Eur. J.*, 2017, **23**, 10280; (*b*) A. Nagaki, Y. Takahashi and J. Yoshida, Generation and Reaction of Carbamoyl Anions in Flow: Applications in the Three-Component Synthesis of Functionalized alpha-Ketoamides, *Angew. Chem., Int. Ed.*, 2016, **55**, 5327; (*c*) N. Kambe, T. Inoue, T. Takeda, S. Fujiwara and N. Sonoda, Generation of carbamoyl- and thiocarbamoyllithium synthons having a hydrogen(s) or an aryl group on the nitrogen and their trapping with carbonyl electrophiles, *J. Am. Chem. Soc.*, 2006, **128**, 12650; (*d*) N. S. Nudelman and G. E. G. Linares, New Insights into the Chemistry of Lithium Carbamoyls: Characterization of an Adduct ($R_2NC(O)CLi(OLi)NR_2$), *J. Org. Chem.*, 2000, **65**, 1629; (*e*) D. J. Ramon and M. Yus, Carbamoyl and Thiocarbamoyl Lithium - a New Route by Naphthalene-Catalyzed Chlorine-Lithium Exchange. Synthesis of Enantiomerically Pure (R)- and (S)-α-Hydroxyketones and Vicinal Diols; Asymmetric Nucleophilic Carbamoylation, *Tetrahedron Lett.*, 1993, **34**, 7115; (*f*) D. Enders and H. Lotter, Synthesis of Enantiomerically Pure(R)- and(S)-α Hydroxyketones and Vicinal Diols; Asymmetric Nucleophilic Carbamoylation, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 795; (*g*) V. Rautenstrauch and M. Joyeux, Carbonylation of Lithium Dialkylamides to Give Carbamoyllithiums, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 83; (*h*) U. Schollkopf and H. Beckhaus, Alpha-Hydroxycarboxamides from N,N-Bis (Methoxymethyl)Carbamoyllithium and Carbonyl-Compounds, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 293.

4 (*a*) P. Zhang, S. Han and J. Chen, Efficient Synthesis of β-Keto-α-hydroxy Secondary (Primary) Amides by Selective Aminocarbonylation of Vicinal Diketones Using Carbamoylsilane as an Amide Source, *Chin. J. Org. Chem.*, 2020, **40**, 1737; (*b*) P. Zhang, W. Chen, H. Feng and J. Chen, Synthesis of 3-Hydroxy-3-heterocyclebutylamide Derivatives Using Carbamoylsilanes as an Amide Source, *Chin. J. Org. Chem.*, 2019, **39**, 3560; (*c*) W. Li, S. Han, Y. Lui and J. Chen, Synthesis of α-Alkoxycarbonyl-α-siloxyamides by the Reaction of a Carbamoylsilane with α-Ketoesters, *Chin. J. Org. Chem.*, 2017, **37**, 2423; (*d*) Y. Yao, W. Tong and J. Chen, *a*-Hydroxy amides from carbamoylsilane and aldehydes, *Mendeleev Commun.*, 2014, **24**, 176; (*e*) F. Ma and J. Chen, Novel Method for Synthesis of Unsymmetrical α-Organyl-α-hydroxymalonamide Derivatives, *Huaxue Xuebao*, 2013, **71**, 1118; (*f*) R. F. Cunico, alpha-siloxyamides from a carbamoylsilane and carbonyl compounds, *Tetrahedron Lett.*, 2002, **43**, 355.

 This journal is © the Partner Organisations 2023

Open Access Article. Published on 15 July 2023. Downloaded on 11/30/2025 5:51:52 AM. This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

5 (*a*) L. A. Martinho, T. P. F. Rosalba and C. K. Z. Andrade, Passerini Reaction to Access α-Hydroxy Amides by Facile Decarbonylation/Decarboxylation of Oxalic Acid, *Eur. J. Org. Chem.*, 2022, e202201199; (*b*) L. B. Gaied, N. Fincias, J. Garrec and L. E. Kaïm, 5-endo-dig Cyclization of O-Propargyl Mandelic Acid Amides towards 2,5-Dihydrofurans, *Eur. J. Org. Chem.*, 2019, 7656; (*c*) M. Serafini, A. Griglio, E. Oberto, T. Pirali and G. C. Tron, The use of 2-hydroxymethyl benzoic acid as an effective water surrogate in the Passerini reaction: A straightforward access to α-hydroxyamides, *Tetrahedron Lett.*, 2017, **58**, 4786; (*d*) Y. Prapurna, K. Lingaswamy, D. Mohan and P. Krishna, Indium(III) Chloride Promoted Highly Efficient Tandem Rearrangement–α-Addition Strategy towards the Synthesis of α-Hydroxyamides, *Synlett*, 2016, 1693; (*e*) T. Yamada, T. Hirose, S. Ōmura and T. Sunazuka, Organocatalytic α-Addition of Isocyanides to Aldehydes, *Eur. J. Org. Chem.*, 2015, 296; (*f*) B. Alcaide, P. Almendros, C. Aragoncillo, R. Callejo and M. P. Ruiz, Organocatalyzed three-component Ugi and Passerini reactions of 4-oxoazetidine-2-carbaldehydes and azetidine-2,3-diones. Application to the synthesis of gamma-lactams and gamma-lactones, *J. Org. Chem.*, 2013, **78**, 10154; (*g*) J. S. Kumar, S. C. Jonnalagadda and V. R. Mereddy, An Efficient Boric Acid Mediated Preparation of alpha-Hydroxyamides, *Tetrahedron Lett.*, 2010, **51**, 779; (*h*) R. Frey, S. G. Galbraith, S. Guelfi, C. Lamberth and M. Zeller, First examples of a highly stereoselective Passerini reaction: A new access to enantiopure mandelamides, *Synlett*, 2003, 1536; (*i*) S. E. Denmark and Y. Fan, The first catalytic, asymmetric alpha-additions of isocyanides. Lewis-base-catalyzed, enantioselective Passerini-type reactions, *J. Am. Chem. Soc.*, 2003, **125**, 7825; (*j*) T. Carofiglio, C. Floriani, A. Chiesi-Villa and C. Rizzoli, Nonorganometallic pathway of the Passerini reaction assisted by titanium tetrachloride, *Organometallics*, 2002, **10**, 1659.

6 Some methods involving the transformations of functionalized amides have also been developed. For selected examples, see: (*a*) C. Wu, B. Hu, H. Liu, J. Jiang and J. Kim, Arginine-Catalyzed Henry Reaction of α-Keto Amides with Nitromethane on Water, *ChemistrySelect*, 2022, **7**, e202104433; (*b*) A. K. Ghosh, A. J. Basu, C. S. Hsu and M. Yadav, Asymmetric 1,2-Carbamoyl Rearrangement of Lithiated Chiral Oxazolidine Carbamates and Diastereoselective Synthesis of alpha-Hydroxy Amides, *Chem. – Eur. J.*, 2022, **28**, e202200941; (*c*) C. Sun, Y. Yu, X. Zhang, Y. Liu, C. Sun, G. Kai, L. Shi and H. Li, Transition-metal-free decarbonylative alkylation towards N-aryl α-hydroxy amides via triple C–C bond cleavages and their selective deuteration, *Org. Chem. Front.*, 2021, **8**, 4814; (*d*) F. Tang, Y. Yao, Y. J. Xu and C. D. Lu, Diastereoselective Aza-Mislow-Evans Rearrangement of N-Acyl tert-Butanesulfinamides into alpha-Sulfenyloxy Carboxamides, *Angew. Chem., Int. Ed.*, 2018, **57**, 15583; (*e*) G. Kumar, A. Muthukumar and G. Sekar, A Mild and Chemoselective Hydrosilylation of α-Keto Amides by Using a Cs_2CO_3/PMHS/2-MeTHF System, *Eur. J. Org. Chem.*, 2017, 4883; (*f*) G. Gu, T. Yang, O. Yu, H. Qian, J. Wang, J. Wen, L. Dang and X. Zhang, Enantioselective Iridium-Catalyzed Hydrogenation of alpha-Keto Amides to alpha-Hydroxy Amides, *Org. Lett.*, 2017, **19**, 5920; (*g*) K. D. James and N. N. Ekwuribe, A two-step synthesis of the anti-cancer drug (*R*,*S*)-bicalutamide, *Synthesis*, 2002, 850.

7 For selected reviews, see: (*a*) J.-B. Xia, Y.-L. Li and Z.-Y. Gu, Transition-Metal-Catalyzed Intermolecular C–H Carbonylation toward Amides, *Synlett*, 2021, 7; (*b*) J. B. Peng, F. P. Wu and X. F. Wu, First-Row Transition-Metal-Catalyzed Carbonylative Transformations of Carbon Electrophiles, *Chem. Rev.*, 2019, **119**, 2090; (*c*) J.-B. Peng, H.-Q. Geng and X.-F. Wu, The Chemistry of CO: Carbonylation, *Chem*, 2019, **5**, 526; (*d*) X.-F. Wu, J.-B. Peng and X. Qi, Recent Achievements in Carbonylation Reactions: A Personal Account, *Synlett*, 2016, 175; (*e*) R. Franke, D. Selent and A. Borner, Applied hydroformylation, *Chem. Rev.*, 2012, **112**, 5675; (*f*) A. Brennfuhrer, H. Neumann and M. Beller, Palladium-catalyzed carbonylation reactions of aryl halides and related compounds, *Angew. Chem., Int. Ed.*, 2009, **48**, 4114; (*g*) S. D. Friis, A. T. Lindhardt and T. Skrydstrup, The Development and Application of Two-Chamber Reactors and Carbon Monoxide Precursors for Safe Carbonylation Reactions, *Acc. Chem. Res.*, 2016, **49**, 594; (*h*) P. Gautam and B. M. Bhanage, Recent advances in the transition metal catalyzed carbonylation of alkynes, arenes and aryl halides using CO surrogates, *Catal. Sci. Technol.*, 2015, **5**, 4663; (*i*) L. Wu, Q. Liu, R. Jackstell and M. Beller, Carbonylations of alkenes with CO surrogates, *Angew. Chem., Int. Ed.*, 2014, **53**, 6310; (*j*) T. Morimoto and K. Kakiuchi, Evolution of carbonylation catalysis: no need for carbon monoxide, *Angew. Chem., Int. Ed.*, 2004, **43**, 5580.

8 For recent examples, see: (*a*) F. Zhao, H. J. Ai and X. F. Wu, Copper-Catalyzed Substrate-Controlled Carbonylative Synthesis of alpha-Keto Amides and Amides from Alkyl Halides, *Angew. Chem., Int. Ed.*, 2022, **61**, e202200062; (*b*) A. M. Veatch, S. Liu and E. J. Alexanian, Cobalt-Catalyzed Deaminative Amino- and Alkoxycarbonylation of Aryl Trialkylammonium Salts Promoted by Visible Light, *Angew. Chem., Int. Ed.*, 2022, **61**, e202210772; (*c*) Z. Qi, S. S. Li, L. Li, Q. Qin, L. M. Yang, Y. K. Liang, Y. Kang, X. Z. Zhang, A. J. Ma and J. B. Peng, Palladium Catalyzed Cascade Azidation/Carbonylation of Aryl Halides with Sodium Azide for the Synthesis of Amides, *Chem. – Asian J.*, 2021, **16**, 503; (*d*) J. M. Orduna, G. Dominguez and J. Perez-Castells, Cobalt catalysed aminocarbonylation of thiols in batch and flow for the preparation of amides, *RSC Adv.*, 2021, **11**, 30398; (*e*) N. Pálinkás, G. Mikle, A. Aranyi, A. Péter and L. Kollár, Synthesis of Axially Chiral Carboxamides via Aminocarbonylation of Aryl and Vinyl Iodides with 2,2′-Diamino-1,1-binaphthalene in the Presence of Palladium Catalysts, *ChemistrySelect*, 2020, **5**, 11048; (*f*) S. Zhang, H. Neumann and M. Beller, Pd-Catalyzed Carbonylation of Vinyl Triflates To Afford alpha,

Open Access Article. Published on 15 July 2023. Downloaded on 11/30/2025 5:51:52 AM. This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

beta-Unsaturated Aldehydes, Esters, and Amides under Mild Conditions, *Org. Lett.*, 2019, **21**, 3528; (*g*) B. T. Sargent and E. J. Alexanian, Cobalt-Catalyzed Aminocarbonylation of Alkyl Tosylates: Stereospecific Synthesis of Amides, *Angew. Chem., Int. Ed.*, 2019, **58**, 9533; (*h*) P. Szuroczki, B. Boros and L. Kollár, Efficient synthesis of alkynyl amides via aminocarbonylation of iodoalkynes, *Tetrahedron*, 2018, **74**, 6129; (*i*) F. Messa, S. Perrone, M. Capua, F. Tolomeo, L. Troisi, V. Capriati and A. Salomone, Towards a sustainable synthesis of amides: chemoselective palladium-catalysed aminocarbonylation of aryl iodides in deep eutectic solvents, *Chem. Commun.*, 2018, **54**, 8100; (*j*) Y. Li, F. Zhu, Z. Wang, J. Rabeah, A. Brückner and X.-F. Wu, Practical and General Manganese-Catalyzed Carbonylative Coupling of Alkyl Iodides with Amides, *ChemCatChem*, 2017, **9**, 915.

9 For recent examples, see: (*a*) S. Byun, A. O. Farah, H. R. Wise, A. Katchmar, P. H. Cheong and K. A. Scheidt, Enantioselective Copper-Catalyzed Borylative Amidation of Allenes, *J. Am. Chem. Soc.*, 2022, **144**, 22850; (*b*) Y. H. Yao, H. Y. Yang, M. Chen, F. Wu, X. X. Xu and Z. H. Guan, Asymmetric Markovnikov Hydroaminocarbonylation of Alkenes Enabled by Palladium-Monodentate Phosphoramidite Catalysis, *J. Am. Chem. Soc.*, 2021, **143**, 85; (*c*) H. Y. Yang, Y. H. Yao, M. Chen, Z. H. Ren and Z. H. Guan, Palladium-Catalyzed Markovnikov Hydroaminocarbonylation of 1,1-Disubstituted and 1,1,2-Trisubstituted Alkenes for Formation of Amides with Quaternary Carbon, *J. Am. Chem. Soc.*, 2021, **143**, 7298; (*d*) Y. Yuan, F. P. Wu, C. Schunemann, J. Holz, P. C. J. Kamer and X. F. Wu, Copper-Catalyzed Carbonylative Hydroamidation of Styrenes to Branched Amides, *Angew. Chem., Int. Ed.*, 2020, **59**, 22441; (*e*) X. Zhou, G. Zhang, B. Gao and H. Huang, Palladium-Catalyzed Hydrocarbonylative C-N Coupling of Alkenes with Amides, *Org. Lett.*, 2018, **20**, 2208; (*f*) S. Liu, H. Wang, X. Dai and F. Shi, Organic ligand-free carbonylation reactions with unsupported bulk Pd as catalyst, *Green Chem.*, 2018, **20**, 3457; (*g*) L. J. Cheng and N. P. Mankad, Cu-Catalyzed Hydrocarbonylative C-C Coupling of Terminal Alkynes with Alkyl Iodides, *J. Am. Chem. Soc.*, 2017, **139**, 10200.

10 For selected examples, see: (*a*) L. Ren, X. Li and N. Jiao, Dioxygen-Promoted Pd-Catalyzed Aminocarbonylation of Organoboronic Acids with Amines and CO: A Direct Approach to Tertiary Amides, *Org. Lett.*, 2016, **18**, 5852; (*b*) J. Zhang, Y. Hou, Y. Ma and M. Szostak, Synthesis of Amides by Mild Palladium-Catalyzed Aminocarbonylation of Arylsilanes with Amines Enabled by Copper(II) Fluoride, *J. Org. Chem.*, 2019, **84**, 338; (*c*) L. C. Wang, B. Chen and X. F. Wu, Cobalt-Catalyzed Direct Aminocarbonylation of Ethers: Efficient Access to alpha-Amide Substituted Ether Derivatives, *Angew. Chem., Int. Ed.*, 2022, **61**, e202203797; (*d*) N. V. Shvydkiy, T. N. Petrushina and D. S. Perekalin, Cyclobutadiene Rhodium Complexes as Catalysts for the Synthesis of Amides from Electron-rich Arenes, Tosyl Azide and CO, *ChemCatChem*, 2021, **13**, 2873; (*e*) T. Carny, R. Rocaboy, A. Clemenceau and O. Baudoin, Synthesis of Amides and Esters by Palladium (0)-Catalyzed Carbonylative C(sp^3)-H Activation, *Angew. Chem., Int. Ed.*, 2020, **59**, 18980; (*f*) S. W. Yuan, H. Han, Y. L. Li, X. Wu, X. Bao, Z. Y. Gu and J. B. Xia, Intermolecular C-H Amidation of (Hetero)arenes to Produce Amides through Rhodium-Catalyzed Carbonylation of Nitrene Intermediates, *Angew. Chem., Int. Ed.*, 2019, **58**, 8887; (*g*) Q. Xing, H. Lv, C. Xia and F. Li, Palladium-catalyzed intermolecular carbonylative cross-coupling of heteroaryl C(sp^2)-H bonds with amines: an efficient strategy for oxidative aminocarbonylation of azoles, *Chem. Commun.*, 2017, **53**, 6914; (*h*) P. Williamson, A. Galvan and M. J. Gaunt, Cobalt-catalysed C-H carbonylative cyclisation of aliphatic amides, *Chem. Sci.*, 2017, **8**, 2588; (*i*) Y. Q. Jiang, Z. Y. Gu, Y. Chen and J. B. Xia, Pd-Catalyzed Amidation of Silyl Enol Ethers With CO and Azides via an Isocyanate Intermediate, *Asian J. Org. Chem.*, 2021, **10**, 1704; (*j*) Z. Y. Gu, J. Chen and J. B. Xia, Pd-catalyzed amidation of 1,3-diketones with CO and azides via a nitrene intermediate, *Chem. Commun.*, 2020, **56**, 11437.

11 T. Luo, R. Zhang, W. Zhang, X. Shen, T. Umemoto and J. Hu, Divergent rearrangements of cyclopropyl-substituted fluoroepoxides involving C-F bond cleavage and formation, *Org. Lett.*, 2014, **16**, 888.

12 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 and Q. Song, Atom Recombination of Difluorocarbene Enables 3-Fluorinated Oxindoles from 2-Aminoarylketones, *CCS Chem.*, 2022, **4**, 1671.

13 A. Liu, C. Ni, Q. Xie and J. Hu, $TMSCF_2Br$-Enabled Fluorination-Aminocarbonylation of Aldehydes: Modular Access to alpha-Fluoroamides, *Angew. Chem., Int. Ed.*, 2022, **61**, e202115467.

14 In fact, we have successfully switched the conversion of the α,α-difluoroammonium intermediate in a previous α-fluoroamide system to furnish valuable 2,2-difluoroenolsilyl ethers by employing trimethylamine instead of benzylamines, and this process has been utilized for the new design of controllable single and double difluoromethylene formal insertions into C–H bonds of aldehydes. For details, see: A. Liu, C. Ni, Q. Xie and J. Hu, Transition-Metal-Free Controllable Single and Double Difluoromethylene Formal Insertions into C-H Bonds of Aldehydes with $TMSCF_2Br$, *Angew. Chem., Int. Ed.*, 2023, **62**, e202217088.

15 (*a*) D. Chen, Z. Fan, L. Huang, K. Gao, P. Xiao, C. Ni and J. Hu, TMSCFX2 (X = Cl, Br) as halofluorocarbene sources for the synthesis of halofluorocyclopropanes, *Chem. Commun.*, 2021, **57**, 319; (*b*) D. S. Lee, M. J. Duran-Pena, L. Burroughs and S. Woodward, Efficient Preparation of $TMSCCl_2Br$ and Its Use in Dichlorocyclopropanation of Electron-Deficient Alkenes, *Chem. – Eur. J.*, 2016, **22**, 7609.

16 For representative work in our group, see: (*a*) F. Wang, W. Zhang, J. Zhu, H. Li, K. W. Huang and J. Hu, Chloride ion-catalyzed generation of difluorocarbene for efficient preparation of gem-difluorinated cyclopropenes and cyclo-

 This journal is © the Partner Organisations 2023

Open Access Article. Published on 15 July 2023. Downloaded on 11/30/2025 5:51:52 AM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

propanes, *Chem. Commun.*, 2011, **47**, 2411; (*b*) L. Li, F. Wang, C. Ni and J. Hu, Synthesis of gem-difluorocyclopropa(e)nes and O-, S-, N-, and P-difluoromethylated compounds with $TMSCF_2Br$, *Angew. Chem., Int. Ed.*, 2013, **52**, 12390; (*c*) Q. Xie, C. Ni, R. Zhang, L. Li, J. Rong and J. Hu, Efficient Difluoromethylation of Alcohols Using $TMSCF_2Br$ as a Unique and Practical Difluorocarbene Reagent under Mild Conditions, *Angew. Chem., Int. Ed.*, 2017, **56**, 3206; (*d*) Q. Xie, Z. Zhu, L. Li, C. Ni and J. Hu, A General Protocol for C-H Difluoromethylation of Carbon Acids with $TMSCF_2Br$, *Angew. Chem., Int. Ed.*, 2019, **58**, 6405; (*e*) X. Wang, S. Pan, Q. Luo, Q. Wang, C. Ni and J. Hu, Controllable Single and Double Difluoromethylene Insertions into C-Cu Bonds: Copper-Mediated Tetrafluoroethylation and Hexafluoropropylation of Aryl Iodides with $TMSCF_2H$ and $TMSCF_2Br$, *J. Am. Chem. Soc.*, 2022, **144**, 12202; (*f*) Ref. 13 and 14.

17 *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*, ed. A. Greenberg, C. M. Breneman and J. F. Liebman, John Wiley & Sons, 2000.

18 For selected papers, see: (*a*) S. P. Mirza, A. S. Greene and M. Olivier, ^{18}O labeling over a coffee break: a rapid strategy for quantitative proteomics, *J. Proteome Res.*, 2008, **7**, 3042; (*b*) M. Miyagi and K. C. Rao, Proteolytic ^{18}O-labeling strategies for quantitative proteomics, *Mass Spectrom. Rev.*, 2007, **26**, 121; (*c*) B. D. Halligan, R. Y. Slyper, S. N. Twigger, W. Hicks, M. Olivier and A. S. Greene, ZoomQuant: an application for the quantitation of stable isotope labeled peptides, *J. Am. Soc. Mass Spectrom.*, 2005, **16**, 302; (*d*) Y. Yang, B. Han, F. Dong, J. Lv, H. Lu, Y. Sun, Z. Lei, Z. Yang and H. Ma, A Cost-Effective Way to Produce Gram-Scale ^{18}O-Labeled Aromatic Aldehydes, *Org. Lett.*, 2022, **24**, 4409; (*e*) J. Yu, J. H. Lin, D. Yu, R. Du and J. C. Xiao, Oxidation of difluorocarbene and subsequent trifluoromethoxylation, *Nat. Commun.*, 2019, **10**, 5362; (*f*) J. Hu, Y. Yang, Z. Lou, C. Ni and J. Hu, Fluoro-Hydroxylation of gem-Difluoroalkenes: Synthesis of ^{18}O-labeled α-CF_3, *Chin. J. Chem.*, 2018, **36**, 1202; (*g*) Y. Kawanishi, Y. Suzuki and A. Miyazawa, Efficient ^{16}O–^{18}O isotope exchange reactions of carbonyl compounds in aqueous organic solvents catalyzed by acidic resin, *Chem. Eng. J.*, 2011, **167**, 531.