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Research Article

Deconstructive Functionalizations of Unstrained Carbon−Nitrogen Cleavage Enabled by Difluorocarbene

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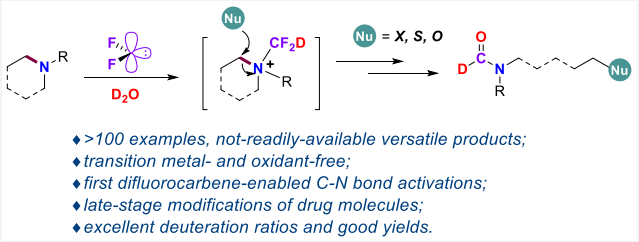
ABSTRACT: Transition-metal- or oxidant-promoted deconstructive functionalizations of noncyclic carbon−nitrogen bonds are well established, usually only leaving one moiety functionalized toward the final product. In contrast, concomitant C- and N-functionalizations via the unstrained C(sp^3)−N bond under metal- and oxidant-free conditions are very rare, which would favorably confer versatility and product diversity. Disclosed herein is the first difluorocarbene-induced deconstructive functionalizations embodying successive C(sp^3)−N bond cleavage of cyclic amines and synchronous functionalization of both constituent atoms which would be preserved in the eventual molecular outputs under transition-metal-free and oxidant-free conditions. Correspondent access to deuterated formamides with ample isotopic incorporation was demonstrated by a switch to heavy water which is conceivably useful in pharmaceutical sciences. The current strategy remarkably administers a very convenient, operationally simple and novel method toward molecular diversity from readily available starting materials. Therefore, we project that these findings would be of broad interest to research endeavors encompassing fluorine chemistry, carbene chemistry, C−N bond activation, as well as medicinal chemistry.



1. INTRODUCTION

The polar disconnection of the C(sp^3)−N bond yields two reactive synthons, the carbon electrophile and nitrogen nucleophile which are versatile precursors of synthetically useful functionalities.[1] A consecutive C(sp^3)−N cleavage−reassembly strategy is therefore prized to derive compounds of heightened structural diversity and complexity in a single step.[2] In biological systems, enzymes mediate C(sp^3)−N bond scission to generate α-amino acids from proteins[3] whereas C−N bond disconnection of tertiary amines is synthetically mediated by transition metals (TMs), oxidants, or the combination of both.[4−6] Atom economy is nonetheless compromised in most cases given that only one entity (either C or N) is functionalized toward the final product while the other converts to sacrificial compounds (Figure 1a).[4,5] The efficiency of these methods is also often predicated on expensive and toxic metals[4,5] or stoichiometric oxidants as in oxidative transformations[6] which generates an equivalent amount of undesired byproducts.[14] Contrarily, concomitant C- and N-functionalization would favorably confer versatility and product diversity.[7−9] Sporadic seminal works only exemplified a confined substrate scope typified by 1,4-diazabicyclo[2.2.2]octane (DABCO) and the quaternary ammonium salts (Figure 1b).[10] The von Braun reaction[11] is also a C−N bond activation reaction, which refers to the treatment of tertiary amines with cyanogen bromide, resulting in a substituted cyanamide. BrCN is called a counter attack reagent, which is a kind of reagent that achieves the two kinds of transformations needed in the reaction to produce the product. In recent years, many chemists have used this strategy to modify tertiary amines; great achievements have been made in both the organic synthesis methodology and total

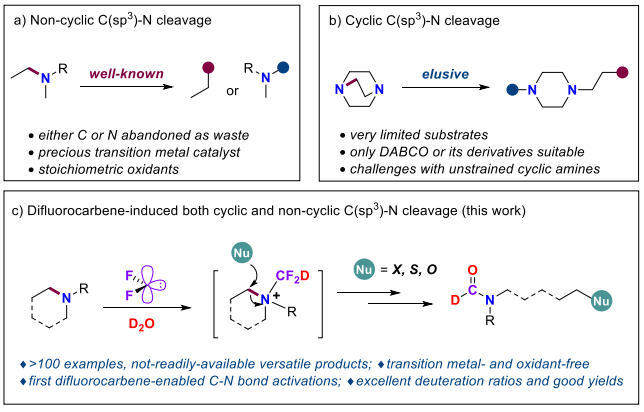


Figure 1. (a) C(sp^3)−N cleavage of noncyclic amines. (b) C(sp^3)−N cleavage of cyclic amines. (c) First difluorocarbene-induced C(sp^3)−N cleavage of various amines (this work).

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synthesis.[12] However, the applications of this strategy have some inherent defects. For example, BrCN has strong hygroscopicity and is sensitive to air and moisture, which limits its applications. Moreover, it can only provide bromine and cyano groups and cannot provide more useful modifications. Given the assortment of tertiary amines readily exploitable, eliminating these limitations and, at the same time, conferring mild reaction conditions, broad substrate scope, as well as good functional group tolerance upon this transformation would be highly appealing.

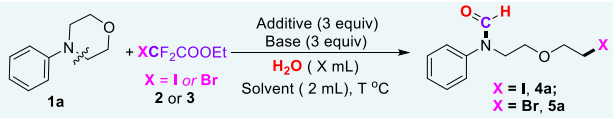
The difluorocarbene species is an exceedingly reactive intermediate possessing high electron deficiency[13] to be used as a robust difluoromethylating reagent[14] or difluoromethylenating reagent.[15] The industrially important tetrafluoroethylene is prepared via dimerization of this species under high temperature.[16] Furthermore, our recent research efforts culminated in the discovery and development of several transformations featuring *in situ* generated difluorocarbene ($:CF_2$) as C1 synthons to assemble various valuable *N*-containing compounds.[17] The synthetic utility of difluorocarbene is nonetheless reckoned to be underexplored considering that *in situ* generation of difluorocarbene is easy under mild conditions from readily accessible starting materials. Grounded in our previous experience,[17] we envisioned capturing the difluorocarbene species to activate and execute C−N bond cleavage in tertiary amines by leveraging the favorable matched electronics between electron-rich tertiary amines and highly electron-deficient difluorocarbene (Figure 1c).[13]

We considered several formidable challenges to realize the titled transformation: (1) surmounting the high bond dissociation energy of C(sp^3)−N without the aid of transition metal and oxidant;[18] (2) the posited interaction between tertiary amines and difluorocarbene as well as the formation of ammonium salt species which found no literature precedence; and (3) chemo- and regioselective cleavage of one single C−N bond.[1] The success of many C−N bond cleavage transformations of tertiary amines resides in the weakened C−N sigma bonds that prime them toward nucleophilic attack when the lone electron pairs are engaged in forming the new N−C bond in ammonium salt. Therefore, if the union of difluorocarbene and tertiary amine indeed generates the hypothesized difluoromethylammonium salt, the stage is set for the occurrence of the proposed reaction. Herein, we report an unprecedented difluorocarbene (derived *in situ* from $BrCF_2COOEt$, ICF_2COOEt, $TMSCF_2H$, and $ClCF_2H$)-induced tertiary amine activation under transition-metal- and oxidant-free conditions. *In situ* decomposition of halodifluoroalkyl reagents simultaneously releases difluorocarbene species and halide anions. While the former forms an ammonium entity with the tertiary amine substrate, the halide performs a nucleophilic attack on the α-carbon to enact C(sp^3)−N bond fission. Interception by an external nucleophile at this stage would further enrich the architectural diversity of products. Consequently, a novel catalyst- and oxidant-free methodology comprising C−N bond cleavage and C−X (X = I, Br, Nu) bond formation is consummated. The instability of the thus-formed difluoromethyl tertiary amines under basic conditions induces their rapid hydrolyses to formamides (Figure 1c). Meanwhile, deuterated formamides with high isotopic incorporation could be procured when interposed by D_2O. The amide bond is one the most important functional motifs in chemistry and biology. Amides feature as prevalent pharmacophores in small-molecule pharmaceuticals. This procedure would allow facile entry to deuterated drugs and late-stage modification of candidates of medicinal importance.[19]

2. RESULTS AND DISCUSSION

Development of Mild Reaction Conditions. The validation of our hypothesis commenced with a model reaction of *N*-phenylmorpholine (**1a**) and ICF_2COOEt (**2a**) with the choice of K_2CO_3 as the base. Compound **4a** embedded with iodo functionality was successfully isolated in 31% yield when the reaction was conducted at 90 °C in CH_3CN (Table 1, entry 1), indicating the feasibility of our conjecture. Mechanistic scrutiny prompted the inclusion of an external iodide ion source to promote C−N bond cleavage by providing a higher iodide concentration in the reaction mixture. This attempt (Table 1, entries 2−5) fruitfully identified ZnI_2 and KI (Table 1, entry 3 or entry 5) as the more competent candidates to deliver **4a** in 79% and 78% yield, respectively. Subscribed to cost and accessibility considerations, KI was opted for subsequent optimization studies. Water was found crucial for the current reaction (Table 1, entries 6−8) where product formation could be significantly enhanced from 63% to 77% (Table 1, entries 7 and 8) when the amount was increased from 0.1 to 0.3 mL. Replacing K_2CO_3 with Na_2CO_3 resulted in a superior result (Table 1, entry 9), yet neither DBU nor $NaHCO_3$ gave better yields (Table 1, entries 10 and 11). CH_3CN was found impeccable given that other solvents such as DMF, acetone, and CH_3OH furnished the titled product in notably inferior

Table 1. Optimization of the Reaction Conditions of the Conversion of *N*-Phenylmorpholine (1a)



entry	base	additive	H_2O (X mL)	solvent	T (°C)	yield[a] (%)
1	K_2CO_3		0.5	CH_3CN	90	31[b]
2	K_2CO_3	NaI	0.5	CH_3CN	90	71
3	K_2CO_3	ZnI	0.5	CH_3CN	90	79
4	K_2CO_3	TBAI	0.5	CH_3CN	90	25
5	K_2CO_3	KI	0.5	CH_3CN	90	78
6	K_2CO_3	KI	0.01	CH_3CN	90	trace
7	K_2CO_3	KI	0.1	CH_3CN	90	63
8	K_2CO_3	KI	0.3	CH_3CN	90	77
9	Na_2Co3	KI	0.3	CH_3CN	90	88 (84)[b]
10	DBU	KI	0.3	CH_3CN	90	68
11	$NaHCO_3$	KI	0.3	CH_3CN	90	trace
12	Na_2CO_3	KI	0.3	DMF	90	trace
13	Na_2CO_3	KI	0.3	acetone	90	51
14	Na_2CO_3	KI	0.3	CH_3OH	90	70
15	Na_2CO_3	KI	0.3	CH_3CN	80	75
16	Na_2CO_3	KI	0.3	CH_3CN	100	82
17	Na_2CO_3	KBr	0.3	CH_3CN	90	70[c]

[a]Reaction condition 1: **1a** (0.2 mmol), ICF_2COOEt (**2**, 0.6 mmol), additive (3 equiv), base (3 equiv), H_2O (X mL), solvent (2 mL), for 10 h, N_2; GC yields. [b]Isolated yields. [c]Reaction condition 2: **1a** (0.2 mmol), $BrCF_2COOEt$ (**3**, 0.6 mmol), KBr (3 equiv), Na_2CO_3 (3 equiv), H_2O (0.3 mL), CH_3CN (2 mL) under 90 °C for 10 h, isolated yield. TBAI = tetra-*n*-butylammoniumiodide, DMF = *N*,*N*-dimethylformamide.

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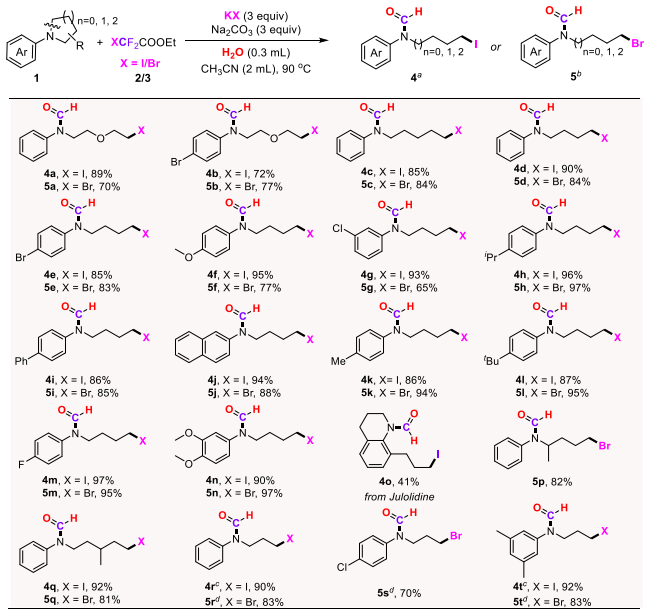
yields (Table 1, entries 12−14). The reaction proceeded most optimally at 90 °C; higher or lower temperature did not further improve the outcomes (Table 1, entries 15 and 16). Exquisitely, the bromide congener of **5a** was formed in 70% yield by switching ICF_2COOEt to $BrCF_2COOEt$ and KI to KBr (Table 1, entry 17). This implied that the more cost-effective $BrCF_2COOEt$ was an adequate alternative of ICF_2COOEt in this transformation to introduce the bromo group as a functional handle in the product.

Substrate Scope of Cyclic Tertiary Amines. With the optimal reaction conditions in hand (Table 1, entries 9 and 17), various tertiary cyclic amines were perused against proton sources (H_2O) with both ICF_2COOEt-KI and $BrCF_2COOEt$-KBr systems (Table 2). Under standard reaction conditions,

Table 2. Substrate Scope of Cyclic Tertiary Amines (H_2O as the Proton Source)[a]



[a]Reaction conditions: **1** (0.2 mmol), ICF_2COOEt (3 equiv), Na_2CO_3 (3 equiv), CH_3CN (2 mL), KI (3 equiv), H_2O (0.3 mL) under N_2 atmosphere at 90 °C for 10 h. [b]**1** (0.2 mmol), $BrCF_2COOEt$ (3 equiv), Na_2CO_3 (3 equiv), CH_3CN (2 mL), KBr (3 equiv), H_2O (0.3 mL) under N_2 atmosphere at 90 °C for 10 h. All yields are isolated yields.

model substrate **1a** and the 4-bromo derivative **1b** were converted to respective long-chain iodinated tertiary formamide (**4a**, **4b**) as well as brominated (**5a**, **5b**) in equally good yields. Both six-membered (**1a**−**1c**) and five-membered (**1d**−**1n**) analogues of cyclic tertiary amines were well-suited for this transformation, exhibiting insensitivity toward aryl substitutions (alkyl, alkoxyl, phenoxyl, halo, phenyl, fused, etc.). The corresponding target products (**4c**−**4n** and **5c**−**5n**) were isolated in 65%−97% yields. A drug intermediate, 2,3,6,7-tetrahydro-1*H*,5*H*-benzop[*i*, *j*]quinolizine (**1o**) (or Julolidine), which contains two six-membered cyclic tertiary amines, selectively cleaving one moiety, delivered iodide (**4o**) in 41% yield. Interestingly, for the asymmetric cyclic tertiary amines **1p**, due to the influence of steric hindrance, we can selectively obtain the product **5p** from the less steric hindered side in 82% yield. When 4-methyl-1-phenylpiperidine (**3q**) was subjected to the standard conditions, the target products (**4p** and **5p**) were obtained in 92% and 81% yields. The target product could not be obtained in a satisfactory yield by using both ICF_2COOEt-KI and $BrCF_2COOEt$-KBr systems when we examined four-membered analogues of cyclic tertiary amines. After optimizing the conditions, we found that $TMSCF_2Br$ is a suitable difluorocarbene provider, and the target products can be obtained in good yields from the substrates of four-membered aza-rings (**1r**−**1t**).

Substrate Scope of Noncyclic Tertiary Amines. The exploration of substrate scope ensued by examining the reaction generality against noncyclic tertiary amines (Table 3). Expectedly, these substrates were equipotent to afford formylated products in excellent yields under marginally reoptimized conditions as follows: K_2CO_3 as the base and MeCN as the solvent without any halide salt additives at 90 °C for 10 h under a N_2 atmosphere (see the SI for details).

Employing $BrCF_2COOEt$ as the model reaction partner, varied *para*-substituted *N*,*N*-dimethylanilines (**6a**−**6d**) afforded the corresponding desired products (**7a**−**7d**) in good to excellent yields. Subsequently, *N*,*N*-dimethyl-[1,1′-biphenyl]-4-amines with differing substituents on Ar^2 rings including electron-neutral (**6e**), electron-rich (**6f**−**6h**, **6k**), as well as electron-withdrawing groups (**6i** and **6j**) underwent the current transformation without event to furnish formamides **7e**−**7k** in excellent yields. Diazo functionality in (*E*)-*N*,*N*-dimethyl-4-(phenyldiazenyl)aniline (**6l**) was left unscathed which reacted with commendable efficiency. Heterocycle-containing *N*,*N*-dimethylpyridin-2-amine (**6m**) and aliphatic tertiary amines (**6n**−**6t**), both cyclic and chain amines, led to corresponding products in exemplary yields without event. Interestingly, substrate tethered with two *N*,*N*-dimethylamines (**6u**, **6w**) could undergo selective aza-Arbuzov reaction to deliver mono- or bis-formylated products (**7u**−**7x**) by modulating the proportion of $BrCF_2COOEt$ and tertiary amines. Remarkably, when diphenhydramine (**6y**, antihistamine), cyproheptadine (**6z**, anticoagulant and antiallergic), caulophylline (**6aa**, hypoglycemic), (*R*)-tomoxetine (**6ab**, attention deficit hyperactivity disorder, ADHD), fluoxetine (**6ac**, antidepressant), desloratadine (**6ad**, antiallergic), tropisetron (**6ae**, 5-HT3 receptor antagonists), and amoxapine (**6af**, tricyclic antidepressants) were subjected to the standard conditions, formylated products (**7y**−**7af**) were obtained in 41−90% yields. Importantly, $ClCF_2H$ as the smallest halodifluoroalkyl reagent with wide industrial applications is also a known precursor of difluorocarbene. When treated with various tertiary amines (**6ag**−**6an**), good yields were delightfully mirrored in target products (**7ag**−**7an**) which carry a gamut of functional groups.

To assess the susceptibility of different C−N bonds toward scission, a panel of *N*-substituted tertiary amines was reacted under the standard conditions (Table 4). *N*-Methylanilines with a different *N*-substituent (**6ag**, **6ao**−**6aq**) were first inspected, and the target products (**7ag**, **7ao**−**7aq**) were obtained in 99%, 63%, and 42% yield and a trace amount. When *N*,*N*-dimethylaniline (**6ag**) was studied against different *N*,*N*-disubstituted anilines such as *N*,*N*-diethyl (**6ar**), *N*,*N*-di^{n}propyl (**6as**), and *N*,*N*-di^{n}butyl (**6at**) under the same reaction conditions, only the former two substrates rendered **7ag** and **7ao** in 99% and 32% yield, while the latter two (**6as** and **6at**) could not be processed under our system. Based on these results, we speculated that the bulkier *N*-substituent would incur steric hindrance toward difluorocarbene species, which is reflected in low to nil product yields as the tethering

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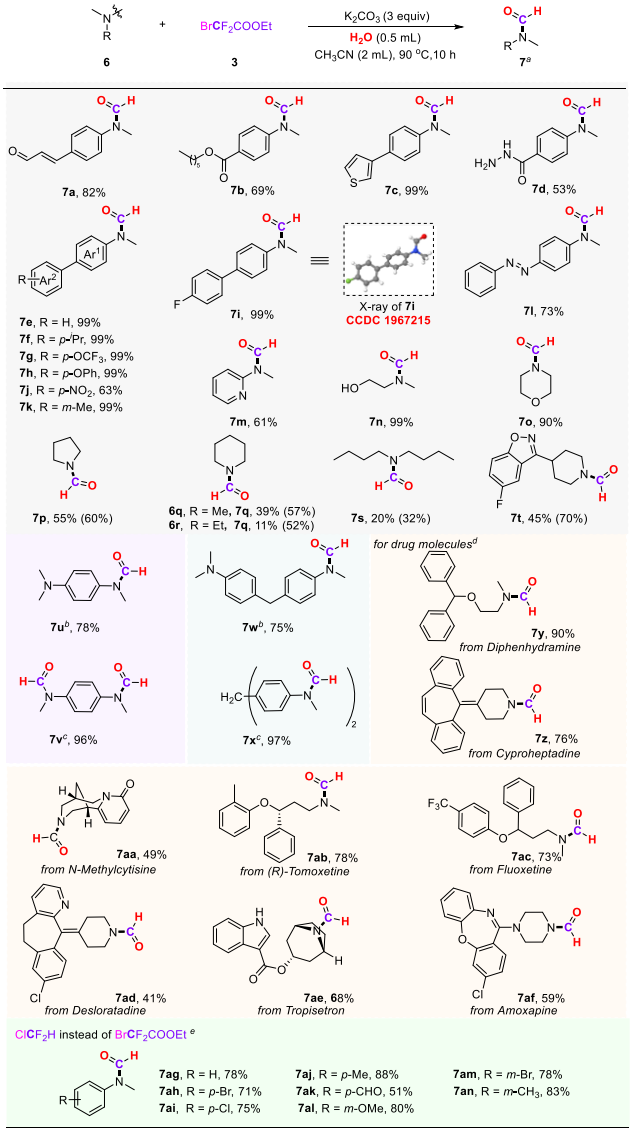
Table 3. Substrate Scope of the Noncyclic Tertiary Amines (H_2O as the Proton Source)[a]

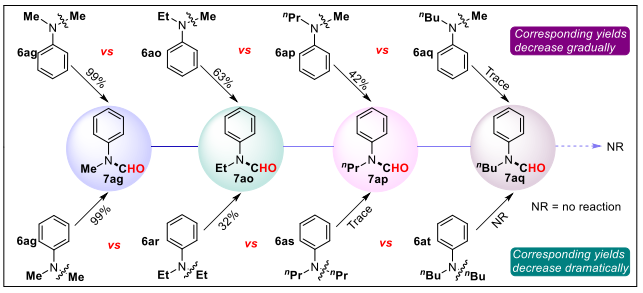


[a]Reaction conditions: **6** (0.2 mmol), **3** (3 equiv.), K_2CO_3 (3 equiv.), CH_3CN (2 mL), H_2O (0.5 mL) under N_2 atmosphere at 90 °C for 10 h. [b]**3** (2.4 equiv.) [c]**3** (4 equiv.), K_2CO_3 (4 equiv.), H_2O (0.7 mL). [d]**6** (0.2 mmol), $BrCF_2COOEt$ (3 equiv.), K_2CO_3 (3 equiv.), CH_3CN (2 mL), CH_3OH (0.5 mL), under N_2 atmosphere at 90 °C for 30 h. [e]**6** (0.1 mmol), $CClF_2H$ (3 equiv.), S_8 (35 mol %), K_2CO_3 (3 equiv.), CH_3CN (2 mL), H_2O (0.5 mL) at 90 °C for 10 h. All yields are the isolated yields, and the numbers in parentheses are the conversion rate of raw materials.

alkyl group gets larger. This imparts chemo- and site-selectivity to the current strategy for selective functionalization in the existence of multiple C−N bonds.

Deuteration Results. Deuterium incorporation as part of isotope labeling has a broad range of applications, including in the investigation of reaction mechanisms and the analysis of drug absorption, distribution, metabolism, and excretion (ADME), as well as in nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry (MS).[20] In 2017, FDA approval for the first deuterated drug, deutetrabenazine (Austedo),[21] has created an urgent demand for synthetic methods that efficiently generate deuterated building blocks.

Table 4. Effect of Substituents on N Atoms[a]



[a]Reaction conditions: **6** (0.2 mmol), $BrCF_2COOEt$ (3 equiv.), K_2CO_3 (3 equiv.), CH_3CN (2 mL), H_2O (0.5 mL) under N_2 atmosphere at 90 °C for 10 h, isolated yield.

Grounded in our current successful formamide formation via C(sp^3)−N bond activation of tertiary amines with H_2O, herein, we invented a mild and generic method for the deuteration of formamides with D_2O, an inexpensive deuterium source. Delightfully, when H_2O was replaced with D_2O under the standard conditions, the yields of the products were barely affected along with excellent deuteration ratios (Table 5). Both cyclic and noncyclic tertiary amines were inspected under the corresponding reaction conditions with either ICF_2COOEt (**a**), $BrCF_2COOEt$ (**b**), or $ClCF_2H$ (**c**) as difluorocarbene sources. Gratifyingly, the corresponding target products (**8a**−**8ao**) were procured in up to 97% yields accompanied by excellent deuteration ratios. Of note, like before, the drug molecule intermediate 2,3,6,7-tetrahydro-1*H*,5*H*-benzop[*i*, *j*]quinolizine (Julolidine) (**1o**) as well as drug molecules diphenhydramine (**6y**) and cyproheptadine (**6z**) were all competent to our systems, and the corresponding deuterated products (**8l**, **8aj**−**8ak**) were obtained in good yields along with excellent deuteration ratios.

This system could be extrapolated to a three-component reaction with thiols as extraneous nucleophiles (Table 6). The C(sp^3)−S bond plays a pivotal role in modern organic synthesis, natural products, and pharmaceuticals. Clinical trials demonstrated that the introduction of C(sp^3)−S moieties could improve their biological activities, such as antitumor, anti-inflammatory, and immunomodulatory properties.[22] Besides that, the C(sp^3)−S bond can also be found in the natural amino acid, such as cysteine, and facilitate the metabolism process of the related protein in the organism.[23] Then, we introduce a sulfur-containing nucleophilic reagent, which could directly assemble the C(sp^3)−S bond through direct C−N difunctionalization. Relevant optimization efforts utilizing 1-phenylpyrrolidine (**1d**), $BrCF_2COOEt$ (**3**), and thiol **9** as model substrates (see the SI for details) concluded the optimal conditions herewith: Na_2CO_3 as the base and KBr as an additive in CH_3CN at 90 °C for a 10 h reaction. As shown in Table 6, both aromatic (**9a**−**9f**) and aliphatic thiols (**9g**−**9j**) were auspiciously coupled onto formamide products in moderate to excellent yields. Except the substrate **1d**, the four-membered (**1r**) and six-membered (**1c**) analogues of cyclic tertiary amines were well-suited for this transformation, rendering the corresponding products **10k**−**10l** and **10m** in excellent yields (Table 6). Phenol acted as an equally fitting nucleophile for this three-component reaction with 1-phenylpyrrolidine (**1d**) and $BrCF_2COOEt$ (**3**) to afford *N*-(4-phenoxybutyl)-*N*-phenylformamide (**12**) in excellent yield with DMF as the cosolvent.

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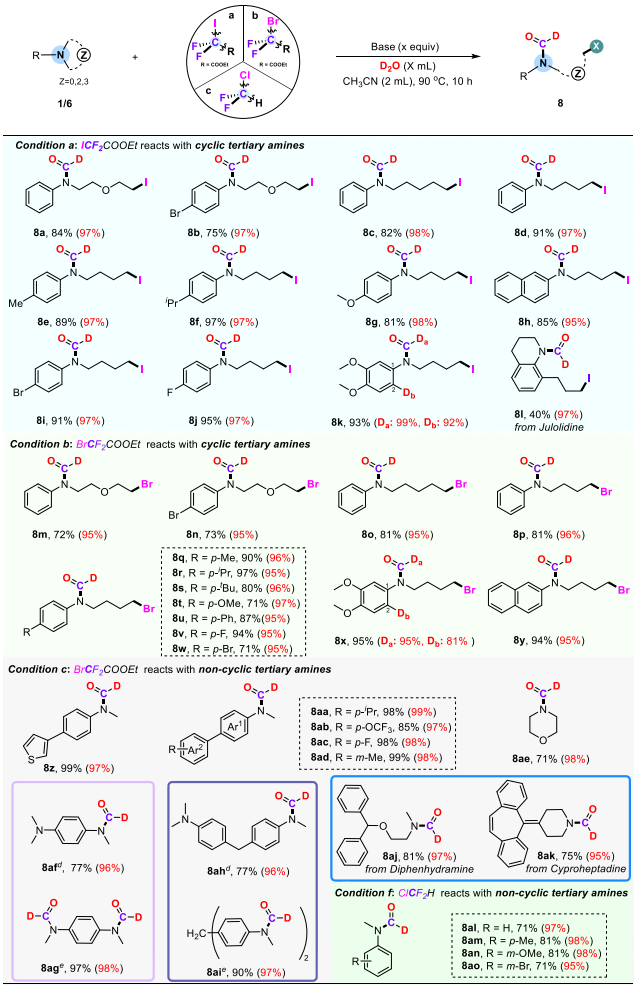
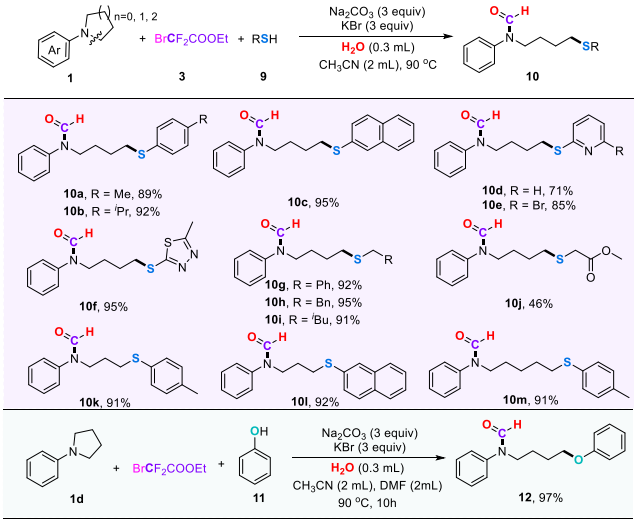
Table 5. Deuteration with D_2O as the Deuterium Source



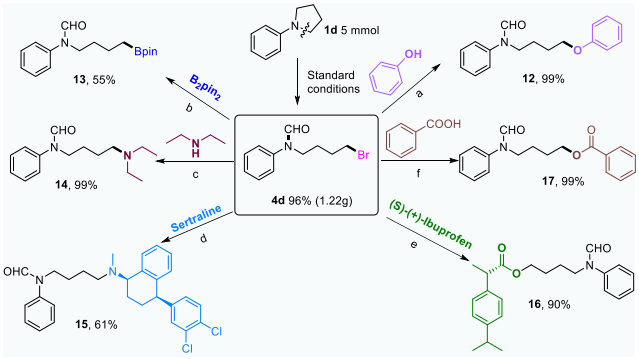
[a]Reaction condition: **1** (0.2 mmol), ICF_2COOEt (3 equiv.), Na_2CO_3 (3 equiv.), CH_3CN (2 mL), KI (3 equiv.), D_2O (0.3 mL) under N_2 atmosphere at 90 °C for 10 h. [b]**1** (0.2 mmol), $BrCF_2COOEt$ (3 equiv.), Na_2CO_3 (3 equiv.), CH_3CN (2 mL), KBr (3 equiv.), D_2O (0.3 mL) under N_2 atmosphere at 90 °C for 10 h. [c]**6** (0.2 mmol), $BrCF_2COOEt$ (3 equiv.), K_2CO_3 (3 equiv.), CH_3CN (2 mL), D_2O (0.5 mL) under N_2 atmosphere at 90 °C for 10 h, isolated yield. [d]**3** (2.4 equiv.). [e]**3** (4 equiv.), K_2CO_3 (4 equiv.), D_2O (0.7 mL). [f]**6** (0.1 mmol), $CClF_2H$ (3 equiv.), S_8 (35 mmol %), K_2CO_3 (3 equiv.), CH_3CN (2 mL), D_2O (0.5 mL) at 90 °C for 10 h. All yields are the isolated yields, and the numbers in parentheses are the deuteration ratios of the corresponding deuterated products.

Synthetic Elaborations. Under standard conditions, product **4d** was scalably prepared from tertiary amine **1d** in excellent yields (96%). Having sufficient **4d** compound at our disposal, structural elaborations were performed (Figure 2). Alkylboronic ester (**13**) was readily obtained in 55% yield from **4d** and B_2pin_2,[24] which is amenable toward chemical modifications through various coupling protocols. **4d** readily reacted with diethylamine, phenol,[25] and benzoic acid in DMF to furnish 1,4-diamine compounds (**14**), *N*-(4-phenoxybutyl)-*N*-phenylformamide (**12**), and 4-(*N*-phenylformamido) butyl benzoate (**17**) in 99% yield. For complex drug molecules, such as sertraline and (*S*)-(+)-ibuprofen, they can achieve their late-stage modification products **15** and **16** with **4d** under mild conditions.

Table 6. Substrate Scope of the External Nucleophiles[a]



[a]Reaction conditions: **1d** (0.2 mmol), **3** (3 equiv.), **9** (3 equiv.), Na_2CO_3 (3 equiv.), CH_3CN (2 mL), KBr (3 equiv.), H_2O (0.3 mL) under air atmosphere 90 °C for 10 h, isolated yield.



Conditions: (a) phenol (1.2 equiv), K_2CO_3 (3 equiv), DMF (2 mL), CH_3OH (0.5 mL), 90 °C, 10 h. (b) B_2pin_2 (3 equiv), CuI (2.5 mol %), PPh_3 (3.3 mol %), LiOMe (3 equiv), CH_3CN (2 mL), rt, 18 h. (c) diethylamine (1.2 equiv), K_2CO_3 (3 equiv), DMF (2 mL), 90 °C,10 h. (d) Sertraline (1.2 equiv), K_2CO_3 (3 equiv), CH_3CN (2 mL), 90 °C,18 h. (e) (S)-(+)-Ibuprofen (1.2 equiv), K_2CO_3 (3 equiv), DMF (2 mL), 90 °C, 20 h. (f) benzoic acid (1.2 equiv), K_2CO_3 (3 equiv), DMF (2 mL), 90 °C, 10 h.

Figure 2. Synthetic applications.

Mechanistic Investigation. Mechanistic insights on the current reaction were gathered via several control experiments (Figure 3). Smooth reactions were observed in the presence of radical scavengers (TEMPO, BHT, and 1,1-diphenylethylene) to produce **4d** in 77%, 79%, and 82% yields, respectively, which could possibly rule out an operating radical process (Figure 3, eq 1). When carbene trapping reagents, namely, 2-aminopyridine **15** and aniline **17**, were added individually into this system, the formation of *N*-(difluoromethyl)pyridin-2-amine **16** (detected by GC-MS) and the formylated product **18** in 91% yield alongside a trace amount of **4d** attested to the intermediacy of difluorocarbene species (Figure 3, eqs 2 and 3). For a comprehensive understanding of reactions with thiol substrates, several control experiments were carried out: cotreatment of **1d** with $BrCF_2COOEt$ in the absence of KBr did not yield product **5d**, while in standard conditions with 3 equiv of KBr, the product **5d** was procured in 84% yield (Figure 3, eq 4). When **5d** was exposed to 4-methylbenzenethiol **9a** under basic conditions, the long-chain thioether **10a** was obtained in near-quantitative yield (Figure 3, eq 5). However, when 4-methylbenzenethiol **9a** was directly added to

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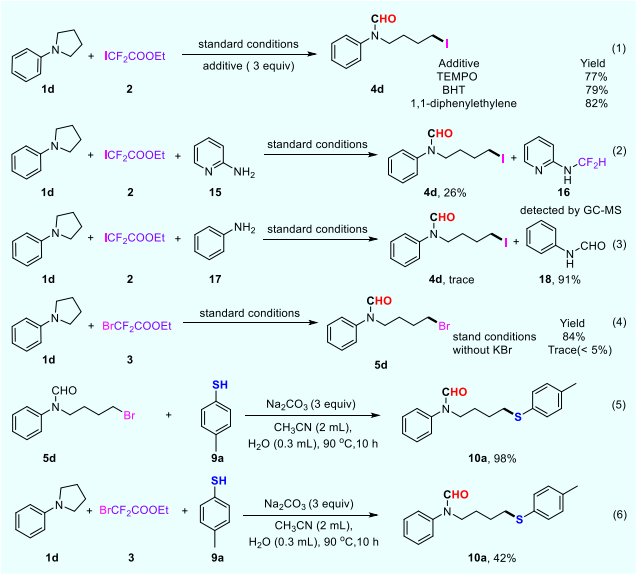

Figure 3. Control experiment of these transformations.

the mixture of substrate **1d** and $BrCF_2COOEt$ under the standard conditions without KBr, only 42% of **10a** was observed (Figure 3, eq 6). These results implied that thiols should directly attack the activated carbon of the C−N bond leading to the product **10a**. Nonetheless, an alternate pathway that involves the prior formation of **5d** followed by nucleophilic substitution of thiol could not be exclusively refuted.

Proposed Mechanism. Grounded in these empirical data, a proposed mechanism is depicted in Figure 4. Difluorocarbene ($:CF_2$) should first be unmasked from halodifluoroalkyl reagents (ICF_2COOEt, $BrCF_2COOEt$, or $ClCF_2H$) in the presence of the base. Tertiary amine **A** then reacts with the *in situ* generated $:CF_2$ species to deliver ammonium salt **B** under basic conditions. Internal (X^-) or external nucleophiles (X^-, S^-, or O^-) attack the α carbon of ammonium salt **B** to render intermediate **C** via C−N bond cleavage. Upon C−F bond scission in intermediate **C**, complex **D** could be hydrolyzed through two different pathways (via complex **E** or **F**) to generate the target molecule.[17a]

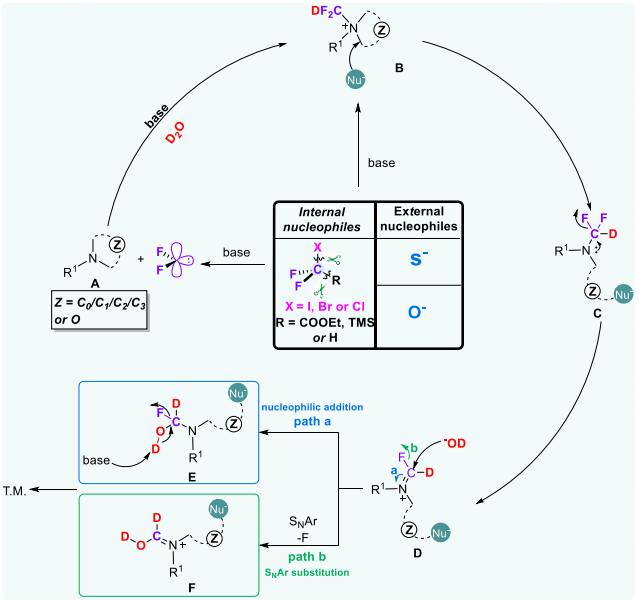

Figure 4. Proposed mechanism.

3. DISCUSSION

A new deconstructive halogenation reaction that features C−N bond cleavage of various tertiary amines has been developed with *in situ* generated difluorocarbene as an activating reagent. The long-chain halogen-containing amide compounds prepared via this strategy were inaccessible by any previously known protocols. Densely functionalized formamides and the deuterated congeners were assembled from simple amine building blocks in one-pot reactions without any metal catalyst or oxidant. Further investigations to extend the reaction scope and applications of this process are currently in progress.

Safety Statement. No unexpected or unusually high safety hazards were encountered.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscentsci.0c00779.

Experimental details of synthetic procedures and methods and X-ray data (PDF)

Crystallographic data for **7i** (CIF)

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Notes

The authors declare no competing financial interest.

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