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Synthesis of Isocyanides by Reacting Primary Amines with Difluorocarbene

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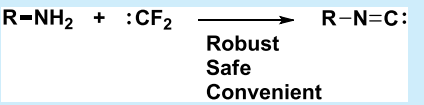
ABSTRACT: A general, convenient, and friendly route for preparing a versatile building block of isocyanides from primary amines is developed. Difluorocarbene, generated in situ from decarboxylation of chlorodifluoroacetate, reacts efficiently with primary amines to produce isocyanides. Various primary amines are well tolerated, including aryl, heteroaryl, benzyl, and alkyl amines, as well as amine residues in amino acids and peptides. Late-stage functionalization of biologically active amines is demonstrated, showing its practical capacity in drug design and peptide modification.



The isocyano group occurs widely in natural products (e.g., terpenoids from marine secondary metabolites), pharmaceuticals, and alkaloids (Figure 1).[1] For example, the first naturally occurring isocyanide compound, xanthocillin, has potent antibiotic properties. Many isocyano-containing terpenoid compounds have broad biological properties, including antibiotic, antifungal, and antineoplastic activities.[1] Isocyanides are also versatile synthetic building blocks that have found diverse applications in organic synthesis,[2] typically in multicomponent reactions,[3] insertion reactions,[4] polymeric materials.[5] and peptides.[6] For instance, Passerini and Ugi reactions are among the most useful and well-known applications using isocyanides to construct molecular complexity. Isocyano is an extraordinary functional group featuring resonances between neutral iminocarbene and the zwitterionic triple bond structures, which imparts it with both nucleophilic and electrophilic properties, as well as radical reactivity under appropriate conditions.

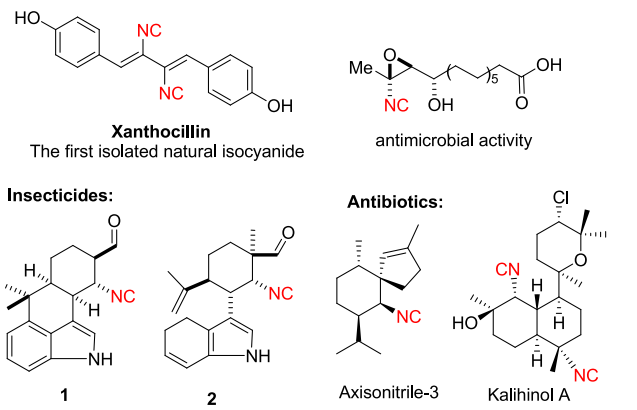


Figure 1. Isocyanide compounds.

The synthesis of isocyanides has received a tremendous amount of interest for centuries, but there is still great space for reaching an ideal solution.[7] More than 100 years ago, Gautier et al. reported the nucleophilic substitution of alkyl iodides with AgCN to give the Ag–isocyanide complex, which, upon treatment with toxic KCN, releases free isocyanides (Scheme 1a).[8] In the same period, Hofmann et al. reported a method using a primary amine, chloroform, and a stoichiometric strong base in the presence of a phase-transfer catalyst (Scheme 1b).[9] These seminal works, however, suffer from a low efficiency, a limited substrate scope, and the use of highly toxic metal cyanides or chloroform, which have greatly impeded their widespread applications.

The Ugi-type dehydration of secondary formamides is the current method of choice for preparing isocyanides (Scheme 1c).[10] The combination of a dehydrating reagent (typically phosgene,[10a] diphosgene,[10b] phosphoryl trichloride,[10c] sulfonyl chloride,[10d] etc.) and a base is required in excess amounts to promote the dehydration. Limitations associated with these types of methods are also noted. First, the need for excess toxic dehydrating reagents raises safety problems and makes it inconvenient in the manipulation and workup, especially for methods involving phosgene analogues, compounds that had been used as deadly chemical weapons. Second, the pregeneration and separation of the formamide precursors are often prerequisite, thereby reducing the step and atom efficiency of the methods and increasing the additional cost of labor and time. Therefore, there are great demands for efficient, safe, and convenient methods for the synthesis of isocyanides.

Herein, we report a general method for the synthesis of isocyanides from feedstock compound primary amines and in situ-generated difluorocarbene (Scheme 1d). The de novo

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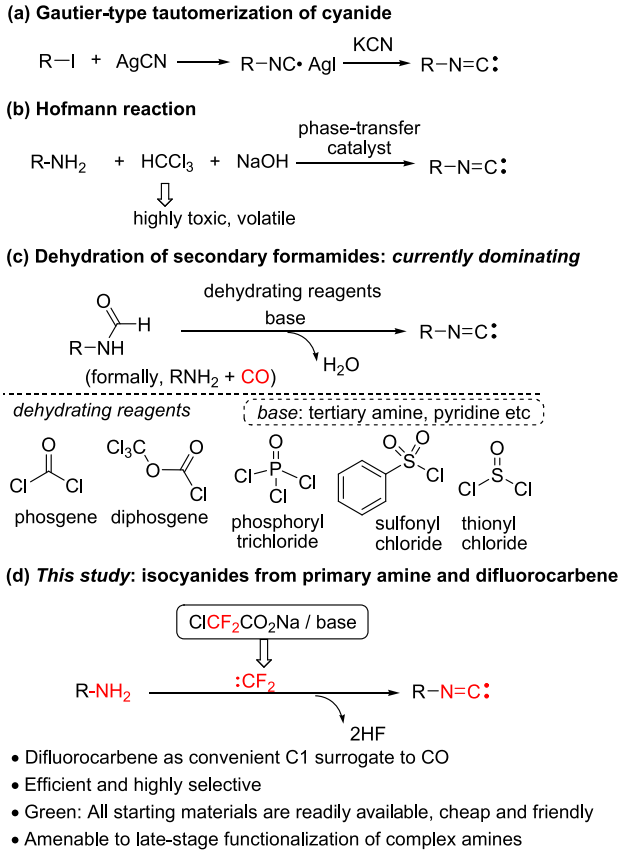
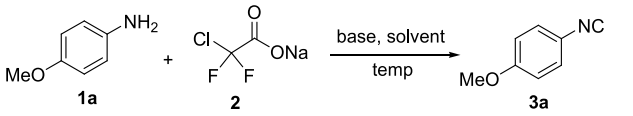
Scheme 1. Strategy for Synthesis of Isocyanides



construction of the isocyano group is enabled by formal extrusion of two molecules of HF, reminiscent of the dehydration method with water extrusion (Scheme 1c). Difluorocarbene thus serves as a novel C1 synthon in our isocyanide synthesis. Difluorocarbene has been emerging as a versatile synthon for preparing various fluorinated compounds in organic synthesis,[11] e.g., in cyclopropanation reactions of alkenes/alkynes,[12] olefination of aldehydes in the presence of PPh_3,[13] and C–H and heteroatom–H insertion reactions.[14] However, the innovative use of difluorocarbene as a convenient and safe C1 synthon is unknown for the synthesis of isocyanides. On the contrary, primary amines, especially anilines, are frequently encountered as a crucial structural motif in many biologically active compounds. Our method therefore paves the way for functionalization and diversification of a large number of biologically relevant primary amines through isocyano group formation. Finally, this method starts with inexpensive and friendly feedstock compounds and occurs by a one-pot convenient and safe operation without needing special safety measures, which are appealing for green, sustainable, and large-scale preparation of isocyanides.

Our study began with the reaction of *p*-methoxyaniline (**1a**) with sodium 2-chlorodifluoroacetate (**2**) in the presence of a base (Table 1). The combination of **2** and a base has been shown to generate difluorocarbene under thermal or photo conditions.[15] The difluorocarbene generated in situ could insert into the thiol S–H bond or alkene double bond, thus producing biologically active ArS-CF_2H or difluoropropane structural motifs. Interestingly, in our study when the in situ-generated difluorocarbene meets aniline **1a**, isocyanide **3a** was produced efficiently and selectively with a characteristic odd

Table 1. Optimization of the Reaction Conditions[a]



entry	base	solvent	**2** (equiv)[e]	temp (°C)	yield (%)
1	KO*t*-Bu	DMF	2	100	40
2	NaH	DMF	2	100	–
3	$NaHCO_3$	DMF	2	100	–
4	Et_3N	DMF	2	100	64
5	DBU	DMF	2	100	30
6	K_2CO_3	DMF	2	100	70
7[b]	K_2CO_3	DMF	1	100	66
8[c]	K_2CO_3	DMF	1	100	68
9[d]	K_2CO_3	DMF	2	100	52
10	K_2CO_3	DMSO	2	100	30
11	K_2CO_3	toluene	2	100	trace
12	K_2CO_3	NMP	2	100	50
13	K_2CO_3	dioxane	2	100	trace
14	K_2CO_3	DMF	2	80	60
15	K_2CO_3	DMF	2	130	70
16	K_2CO_3	DMF	3	100	69

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), base (0.2 mmol), and solvent (1 mL) for 12 h under N_2. Isolated yield of **3a**. [b]**2** (0.1 mmol), K_2CO_3 (0.1 mmol). [c]**2** (0.1 mmol), K_2CO_3 (0.2 mmol). [d]K_2CO_3 (0.1 mmol). [e]Molar ratio of **2** relative to **1a**.

odor (Table 1, entry 1), rather than the formation of the N-CF_2H product resulting from insertion of CF_2 into the N–H bond. NMR characterization of **3a** features broadened *ortho* protons of the phenyl, and the typical triplet splitting of the carbon resonances of the isocyano and phenyl *ipso*-carbon connected to isocyano. These results verify the coupling of isocyano with the aryl *o*-H and the *ipso*-C. The FT-IR spectrum shows an extremely strong absorption band at 2123 cm^{-1} for **3a**, characteristic of the stretching vibration of the isocyano group.

Having **3a** as the valuable product, we then evaluated a set of conditions aiming to improve the yields, with a focus on the combinatorial effect of the base and the solvent, as well as the temperature effect. Table 1 summarizes some of the experiments screened. The combination of K_2CO_3 and DMF at 100 °C is found to be optimal for this reaction producing **3a** in 70% yield, although other combinations are also good for the promotion of the formation of **3a** (entries 1–6). The amount of 2-chlorodifluoroacetate has a minor effect on the reaction yield, giving slightly higher yields with 2 equiv than with 1 equiv (entries 7 and 8). A further increase in the amount of **2** to 3 equiv could not improve the yield (entry 16). Polar solvents are superior to nonpolar solvents (entries 10–13). Finally, decreasing the temperature to 80 °C led to a significantly lower yield of 60% (entry 14), while the reaction at 130 °C gave the same yield of 70% as at 100 °C (entry 15).

With the optimal conditions in hand, a range of primary amines were studied in this reaction, including aryl/heteroaryl, benzyl, and alkyl amines. As shown in Scheme 2, primary anilines with methoxy, phenoxy, dimethylamino, amide, and even unprotected hydroxyl and amine groups can be tolerated. Generally, electron-rich anilines reacted more efficiently than electron-poor anilines (fluoroaniline and pyridylamines are poor substrates).[16] Primary alkylamines are better and more reactive than anilines because of the more nucleophilic nature

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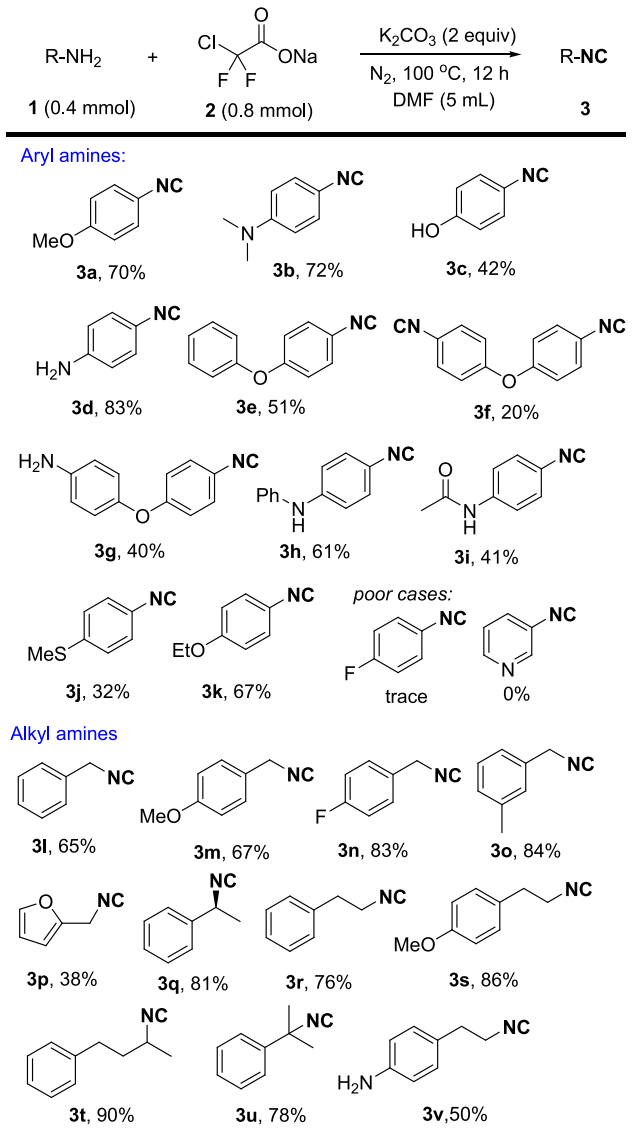
Scheme 2. Substrate Scope of Primary Amines[a]

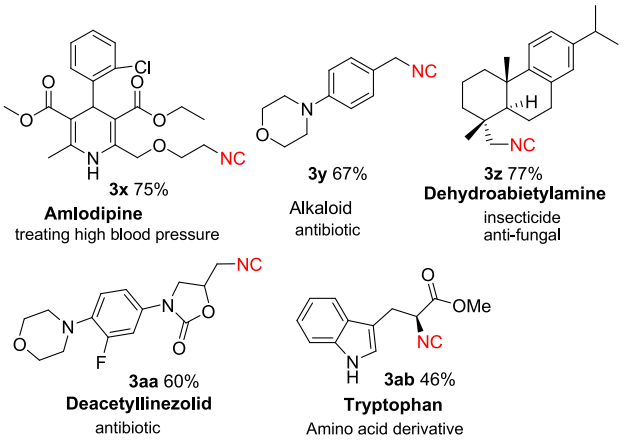


[a]Reaction conditions: **1** (0.4 mmol), **2** (0.8 mmol), K_2CO_3 (0.8 mmol), and DMF (5 mL) stirred at 100 °C for 12 h under N_2. Isolated yields. **2** (1 equiv) is used to show the chemoselectivity in the case of **3v**.

of aliphatic amines. This is exemplified by the case of **2v** (*p*-2-aminoethylaniline) that selectively produces **3v** from preferred conversion of alkylamine and with the aniline group remaining intact. These electronic effects suggest the involvement of a crucial step of nucleophilic attack of amine on the electrophilic difluorocarbene. In addition to the linear primary amines, branched primary amines with tertiary and quaternary α-carbon are also excellent substrates for giving the desired products (**3q**, **3t**, and **3u**). It is noteworthy that this method allows stereoretentive transformation of the amine group in asymmetric α-branched amines, generating asymmetric isocyanide **3q** with a tertiary α-branched center. This is complementary to the current nucleophilic substitution methods in which inversion or partial loss of configuration is observed for the α-carbon.[7d] Such asymmetric isocyanides are expected to be valuable in a range of asymmetric applications, e.g., in the synthesis of asymmetric amides and peptides.[1] Finally, a secondary amine, for instance, diphenylamine, was not reactive. The tolerance of phenylamino group in **3h** shows the high chemoselectivity of this reaction toward primary amines.

Late-stage functionalization of complex biologically active amines is enabled by this method, including some pharmaceuticals and an amine residue in amino acids (Scheme 3). Thus, primary amines **2x** (Amlodipine, pharmaceutical for

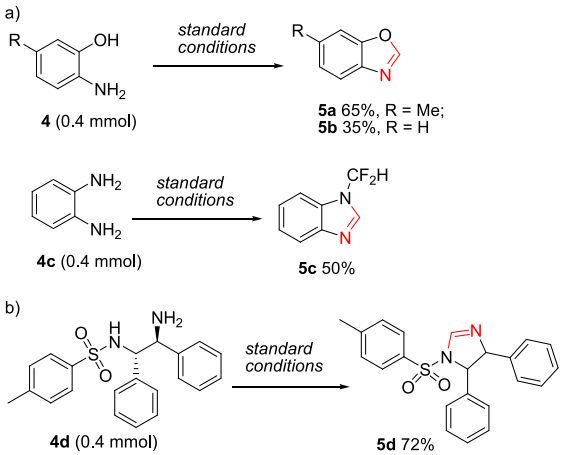
Scheme 3. Late-Stage Functionalization of Complex Biologically Active Amines and an Amine Residue in Amino Acids



the treatment of high blood pressure), **2y** (alkaloid), **2z** (Dehydroabietylamine, widely used as an insecticide, anti-fungal agent, etc.), and **2aa** (Linezolid derivative, antibiotic) can be facilely and selectively converted to their isocyanide derivatives **3x**, **3y**, **3z**, and **3aa**, respectively, in good yields. Moreover, the amino group in tryptophan ester **2ab** can be transformed into the isocyano group (**3ab**), providing a reactive handle that allows diversification of amino acids and peptides.

Furthermore, this method can be used to prepare N,O- and N,N-heteroarenes with an unusual methide incorporation using difluorocarbene (Scheme 4). For anilines with an *o*-hydroxy or -amino, heteroarenes **5a**−**5c** could be obtained arising probably from cascade isocyanide formation/insertion of the isocyano into the *o*-O−H or N−H bond. Interestingly,

Scheme 4. Synthesis of N,O- and N,N-Heteroarenes Using Difluorocarbene



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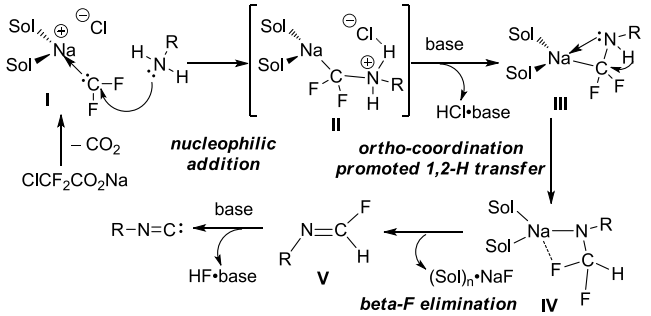
the benzimidazole obtained can be further difluoromethylated to give **5c** resulting from insertion of a second difluorocarbene into the N−H bond of benzimidazole. Interestingly, 1,2-ethylenediamine **4d** with a more flexible backbone can efficiently produce an *N*-tosyl dihydroimidazole **5d** in a similar way.

With various isocyanides in hand, their application in conventional four-component Ugi reaction of isocyanides, carboxylic acids, benzaldehydes, and amines, and in a modified three-component variant of isocyanides, amino acids, and benzaldehydes, produces a number of highly functionalized amides and peptoids (see the Supporting Information).

A plausible mechanism for isocyanide formation is suggested in Scheme 5. A difluorocarbene−sodium complex **I** is initially

Scheme 5. Probable Mechanism



generated from decarboxylation of sodium chlorodifluoroacetate.[15] Due to the enhanced electrophilic nature of difluorocarbene in **I** by metal coordination, nucleophilic addition of amines to **I** gives transient intermediate **II**, which upon base-promoted HCl dissociation produces a key α-aminodifluoromethyl intermediate **III** (Scheme 5).[17] In complex **III**, the presence of an α-amino *ortho*-coordinating to a metal center facilitates 1,2-proton transfer from nitrogen to an adjacent carbanion, thereby giving metal−amide complex **IV** with adjacent fluoride coordination. Now, elimination of β-fluoride from complex **IV** produces imine **V** with the release of solvated NaF. Finally, base-promoted elimination of HF from imine **V** is known to give isocyanides.[18]

In conclusion, an efficient, convenient, and safe method for the facile synthesis of isocyanides from primary amines and in situ difluorocarbene, which serves as a convenient and green C1 synthon, is developed. This method is amenable to various primary amines and can be used in late-stage functionalization of complex biologically active amines, and amine residues in amino acids and peptides. It also provides a new route to N,O- and N,N-heteroarenes via methide incorporation using difluorocarbene. This method paves the way to various applications involving isocyanides and may also stimulate future efforts exploiting difluorocarbene as a convenient C1 source.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03472.

Experimental details and spectroscopic characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Isocyanide compounds: (a) Schnermann, M. J.; Shenvi, R. A. *Nat. Prod. Rep.* **2015**, *32*, 543−577. (b) Hagadone, M. R.; Scheuer, P. J.; Holm, A. *J. Am. Chem. Soc.* **1984**, *106*, 2447−2448. (c) Emsermann, J.; Kauhl, U.; Opatz, T. *Mar. Drugs* **2016**, *14*, 16.

(2) For isocyanide chemistry, see: (a) Ugi, I. *Isonitrile Chemistry*; Academic Press: New York, 1971. (b) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698−2779. (c) Lygin, A. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094−9124. (d) Nenajdenko, V., Ed. *Isocyanide Chemistry. Applications in Synthesis and Material Science*; Wiley-VCH: New York, 2012.

(3) For multicomponent reactions of isocyanides, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (b) Zhu, J. P. *Eur. J. Org. Chem.* **2003**, *2003*, 1133−1144. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89. (d) Nair, V.; Rajesh, C.; Vinod, A.; Bindu, U. S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899−907.

(4) For insertion of isocyanides, see: (a) Lang, S. *Chem. Soc. Rev.* **2013**, *42*, 4867−4880. (b) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7084−7097. (c) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257−5269.

(5) For polymeric materials, see: (a) Kouwer, P. H. J.; Koepf, M.; Le Sage, V. A. A.; Jaspers, M.; van Buul, A. M.; Eksteen-Akeroyd, Z. H.; Woltinge, T.; Schwartz, E.; Kitto, H. J.; Hoogenboom, R.; Picken, S. J.; Nolte, R. J. M.; Mendes, E.; Rowan, A. E. *Nature* **2013**, *493*, 651−655. (b) Schwartz, E.; Koepf, M.; Kitto, H. J.; Nolte, R. J. M.; Rowan, A. E. *Polym. Chem.* **2011**, *2*, 33−47.

(6) For peptides, see: Wilson, R. M.; Stockdill, J. L.; Wu, X.; Li, X.; Vadola, P. A.; Park, P. K.; Wang, P.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2834−2848.

(7) For examples of methods for the synthesis of isocyanides, see: (a) Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, *4*, 400−402. (b) Gokel, G. W.; Widera, R. P.; Weber, W. P. *Org. Synth.* **1976**, *55*, 96. (c) Kitano, Y.; Chiba, K.; Tada, M. *Synthesis* **2001**, *3*, 437−443. (d) Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. *Nature* **2013**, *501*, 195−199. (e) Waibel, K. A.; Nickisch, R.; Mohl, N.; Seim, R.; Meier, M. A. R. *Green Chem.* **2020**, *22*, 933−941. (f) Zhang, W.; Lin, J.-H.; Zhang, P.; Xiao, J.-C. *Chem. Commun.* **2020**, *56*, 6221−6224.

(8) Gautier reaction: (a) Gautier, A. *Justus Liebigs Ann. Chem.* **1868**, *146*, 119−124. (b) Gautier, A. *Justus Liebigs Ann. Chem.* **1867**, *142*, 289−294.

(9) For the Hofmann reaction, see: (a) Hofmann, A. W. *Justus Liebigs Ann. Chem.* **1867**, *144*, 114−120. (b) Weber, W. P.; Gokel, G. W.; Ugi, I. K. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 530−531.

(10) For the Ugi-type method, see: (a) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 472−484. (phosgene) (b) Skorna, G.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 259−260. (disphosgene) (c) Ugi, I.; Meyr, R. *Chem. Ber.* **1960**, *93*, 239. (phophoryl chloride) (d) Hertler, W. R.; Corey, E. J. *J. Org. Chem.* **1958**, *23*, 1221−1222. (sulfonyl chloride)

(11) For CF_2 carbene chemistry, see: (a) Brothers, P. J.; Roper, W. R. *Chem. Rev.* **1988**, *88*, 1293. (b) Brahms, D. L. S.; Dailey, W. P. *Chem. Rev.* **1996**, *96*, 1585. (c) Dolbier, W. R.; Battiste, M. A. *Chem. Rev.* **2003**, *103*, 1071. (d) Dilman, A. D.; Levin, V. V. *Acc. Chem. Res.* **2018**, *51*, 1272. (e) Ni, C.; Hu, J. *Synthesis* **2014**, *46*, 842. (f) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465. (g) Ni, C.; Hu, J. *Chem. Soc. Rev.* **2016**, *45*, 5441. (h) Yerien, D. E.; Barata-Vallejo, S.; Postigo, A. *Chem. - Eur. J.* **2017**, *23*, 14676. (i) Zhang, X.; Cao, S. *Tetrahedron Lett.* **2017**, *58*, 375.

(12) For the reaction with alkenes or alkynes, see: (a) Li, L.; Wang, F.; Ni, C.; Hu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12390. (b) Wang, F.; Zhang, W.; Zhu, J.; Li, H.; Huang, K.-W.; Hu, J. *Chem. Commun.* **2011**, *47*, 2411.

(13) For the reaction with ArCHO, see: (a) Fuqua, S. A.; Duncan, W. G.; Silverstein, R. M. *J. Org. Chem.* **1965**, *30*, 1027. (b) Krishnamoorthy, S.; Kothandaraman, J.; Saldana, J.; Prakash, G. K. S. *Eur. J. Org. Chem.* **2016**, *2016*, 4965. (c) Thomoson, C. S.; Martinez, H.; Dolbier, W. R. *J. Fluorine Chem.* **2013**, *150*, 53. (d) Wang, F.; Li, L.; Ni, C.; Hu, J. *Beilstein J. Org. Chem.* **2014**, *10*, 344.

(14) For selected examples of difluoromethylation of Nu−H, see: (a) Zhang, W.; Wang, F.; Hu, J. *Org. Lett.* **2009**, *11*, 2109. (b) Deng, X.-Y.; Lin, J.-H.; Zheng, J.; Xiao, J.-C. *Chem. Commun.* **2015**, *51*, 8805. (c) Li, L.; Wang, F.; Ni, C.; Hu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12390. (d) Wang, F.; Huang, W.; Hu, J. *Chin. J. Chem.* **2011**, *29*, 2717.

(15) For the $BrCF_2CO_2Na$ salt as a CF_2 source, see: (a) MacNeil, J. G.; Burton, D. J. *J. Fluorine Chem.* **1991**, *55*, 225. (b) Mehta, V. P.; Greaney, M. F. *Org. Lett.* **2013**, *15*, 5036−5039. (c) Feng, W.; Zhang, X.-G. *Chem. Commun.* **2019**, *55*, 1144−1147.

(16) Several other substrates were also examined, including the active basic residues adenine, guanine, and cytosine in the DNA/RNA strand, but were ineffective due to the poor solubility or the electron-deficient nature of the amine group.

(17) For the proposal of alkaline metal reactivity, see: (a) Toutov, A. A.; Liu, W.-B.; Betz, K. N.; Fedorov, A.; Stoltz, B. M.; Grubbs, R. H. *Nature* **2015**, *518*, 80−84. (b) Liu, W. B.; et al. *J. Am. Chem. Soc.* **2017**, *139*, 6867−6879.

(18) Porcheddu, A.; Giacomelli, G.; Salaris, M. *J. Org. Chem.* **2005**, *70*, 2361−2363.

https://dx.doi.org/10.1021/acs.orglett.0c03472
Org. Lett. XXXX, XXX, XXX−XXX