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NHC-catalyzed generation of difluorocarbene and its application to difluoromethylation of oxygen nucleophiles

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ABSTRACT

Controlled generation of difluorocarbene was effected by an NHC catalyst under mild conditions starting from trimethylsilyl 2,2-difluoro-2-fluorosulfonylacetate (TFDA). Cyclohexenones and tetralones were treated with TFDA in the presence of catalytic amounts of *N,N'*-dimesitylimidazolium chloride and sodium carbonate. The ketones were difluoromethylated with the generated difluorocarbene to afford enol difluoromethyl ethers without difluorocyclopropanation. The ethers thus obtained were dehydrogenated with DDQ to furnish aryl difluoromethyl ethers in high yield. Under similar conditions, secondary amides underwent difluoromethylation selectively on the oxygen atom to give difluoromethyl imidates, which allows the formation of 2-difluoromethoxypyridines.

1. Introduction

Difluorocarbene is a synthetically useful species for the introduction of a difluoromethylene group into organic molecules [1]. Since CF_2-containig compounds play crucial roles as pharmaceuticals, agrochemicals, and functional materials [1a,2], advancement in the generation and the utilization of difluorocarbene is desired in contemporary organic synthesis.

To date, three types of methods have been developed for the generation of difluorocarbene (Scheme 1). Pyrolysis has been studied in detail for decades and adopted to generate difluorocarbene (Scheme 1a). Sodium chlorodifluoroacetate ($CClF_2CO_2Na$), which requires a high temperature (typically >120 °C), acts as a representative reagent for this purpose [3–5]. Hexafluoropropyrene oxide (HFPO, >150 °C) [6] and hexafluorocyclopropane (160–170 °C) [7] also work as thermal precursors to difluorocarbene [8,9].

α-Elimination of HCl and its analogous reactions are convenient alternatives for the above-mentioned pyrolysis (Scheme 1b). Chlorodifluoromethane (HCFC-22) is the reagent of choice to release difluorocarbene at relatively low temperatures, although strongly basic conditions are required [10]. Recently, α-eliminations triggered by nucleophilic substitutions on carbonyl group [11] and sulfonyl group [12] are reported [13].

Decomposition of trifluoromethylmetal reagents provides another route to difluorocarbene (Scheme 1c). Phenyl (trifluoromethyl)mercury [14,15] and trimethyl(trifluoromethyl)-stannane [16] in combination with sodium iodide are reported to release difluorocarbene. However, using a stoichiometric amount of toxic reagents should be avoided in large-scale preparations.

As described above, the reported methods for generating difluorocarbene have following drawbacks: (i) high reaction temperatures, (ii) strongly basic conditions, (iii) use of hazardous reagents, and in general, (iv) high loading of reagents. These drawbacks need to be overcome [17].

Trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (TFDA) is a practically useful reagent developed by Dolbier to generate difluorocarbene under mild conditions in a catalytic manner [18]. This reagent releases difluorocarbene in the presence of a fluoride ion (F^-, 1–2 mol%), which is presumed to attack the Si atom of TFDA to promote decomposition (Scheme 2). The generated difluorocarbene is employed in difluorocyclopropanation of alkenes [18,19], alkynes [20], and allenes [21,22].

Although useful, the rapid generation of difluorocarbene from TFDA may cause an overreaction. When alkyl ketones were treated by the TFDA/F^- system, the formed enol difluoromethyl ethers underwent further difluorocyclopropanation with the second molecule of difluorocarbene [23].

To control the reaction, we focused on *N*-heterocyclic carbene (NHC) as an activator of TFDA. NHC is a stable and nucleophilic carbene [24], and acts as an organocatalyst in various synthetic reactions [25]. Note that various NHC-catalyzed cyanosilylations [26], aldol condensations [27], azidations [28], and trifluoromethylations [29] with Si-containing reagents have been reported [30]. Because the reactivity of NHC can be tuned by altering the

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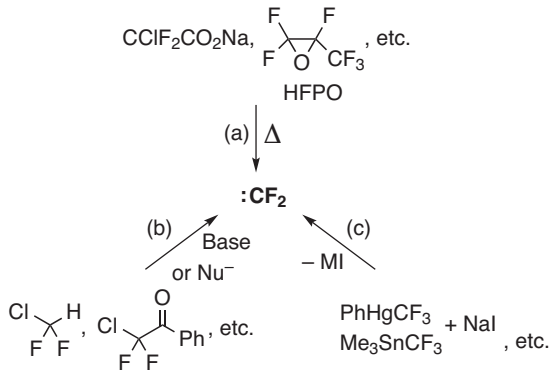


Scheme 1. Conventional methods for difluorocarbene generation.

central heterocyclic core and the substituents on nitrogen, NHC is a promising candidate for the activation of TFDA to regulate the generation of difluorocarbene.

Based on the considerations described above, NHC-catalyzed generation of difluorocarbene from TFDA were examined and applied to difluoromethylation of oxygen nucleophiles. The details of our investigations are described below.

2. Results and discussion

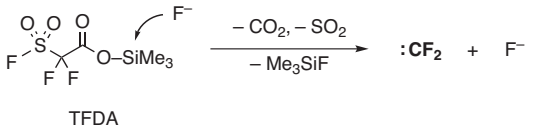
2.1. Reaction conditions

Indan-1-one **1a** was selected as a model substrate for *O*-difluoromethylation and treated with TFDA (2 equiv) in the presence of 1–10 mol% of activators for TFDA. The yields of the produced enol ether **2a** and the undesired overreaction product difluorocyclopropane **3** were determined by ^{19}F NMR spectroscopy. The results of our examination on the activators are summarized in Table 1.

Fluoride ion, the activator originally adopted by Dolbier at 105–120 °C [18b], gave only a 14% yield of **2a** at 80 °C (Entry 1). Other reagents such as DABCO and amine *N*-oxides, which can activate Si-containing reagents [31], were found to be ineffective (Entries 2 and 3).

The difluorocarbene generation proceeded smoothly by using an NHC catalyst. 1,3-Dimesitylimidazolylidene (IMes), generated in situ from 1,3-dimesitylimidazolium chloride (IMes·HCl, 1 and 2 mol%) and sodium carbonate (10 and 20 mol%), gave **2a** in 70% and 74% yield, respectively (Entries 5 and 6). In these cases, only a trace amount of **3** was observed. Note that the enol ether **2a** was stable enough upon standard silica gel chromatography and was isolated in reasonable yield (Entry 6). Reducing the loadings of TFDA from 2 to 1.2 equiv resulted in a diminished yield of **2a** (61%, Entry 7). IMes·HCl alone did not work well (4% of **2a**, Entry 8), which shows the effect of NHC.

It must be mentioned that isolated IMes gave a decreased yield of **2a** (52%) along with a 17% yield of **3** (Entry 9). The rapid generation of difluorocarbene leads to undesired difluorocyclopropanation, even with the NHC catalyst. The use of imidazolinium salt SIMes·HCl, triazolium salt **4**·HBr, and thiazolium salt **5**·HI also resulted in the formation of considerable amounts of difluorocyclopropane **3**, making the reaction less selective (Entries 10–12).



Scheme 2. Generation of difluorocarbene by the TFDA/F$^-$ system.

The use of sodium carbonate with a ratio of 10:1 to IMes·HCl was found to be suitable to achieve a high yield of **2a** (Table 2). When the loading of sodium carbonate was reduced to 2 mol% (Na_2CO_3:IMes·HCl = 1:1), the yield of **2a** decreased to 54% (Entry 1). On the other hand, the 100 mol% loading of sodium carbonate (Na_2CO_3:IMes·HCl = 50:1) also reduced the yield of **2a**, and the undesired **3** was obtained in 32% yield (Entry 3). The use of larger amounts of sodium carbonate also resulted in rapid formation of difluorocarbene, leading to the undesired difluorocyclopropanation reaction of **2a**. Potassium carbonate, potassium *tert*-butoxide, and DBU in place of sodium carbonate gave inferior results (Entries 4–6).

Effects of temperature and solvent were examined (Table 3). The reaction of indan-1-one **1a** at 70 °C gave **2a** in 39% yield (Entry 1). The yield of **2a** was improved up to 70% at 80 °C (Entry 2), whereas elevating the temperature to 90 °C showed no further improvement (Entry 3). Thus, NHC is an efficient catalyst that acts at 80 °C. 1,4-Dioxane and 1,1,2,2-tetrachloroethane were not suitable solvents (Entries 4 and 5).

NHC was conclusively found to be a suitable catalyst that can control the rate of difluorocarbene generation from TFDA. By optimizing the NHC catalyst and reaction conditions, indan-1-one **1a** was successfully transformed into the corresponding enol difluoromethyl ether **2a** in a selective manner.

2.2. Mechanism of enol difluoromethyl ether formation

Scheme 3 shows the proposed mechanism for the generation of difluorocarbene and the formation of enol difluoromethyl ethers. IMes, generated from IMes·HCl and sodium carbonate in situ, attacks the Si atom of TFDA. Decomposition of TFDA provides the key difluorocarbene, accompanied by formation of CO_2, SO_2, and fluoride ion. The formed silylimidazolium salt **A** undergoes desilylation with the released fluoride ion to regenerate free IMes. The generated difluorocarbene reacts with **1a** to afford **2a**, presumably via oxycarbenium intermediates [23b].

During the above experiments, tetrafluoroethylene was observed in the ^{19}F NMR spectra of the reaction mixtures (4 ppm vs. C_6F_6) [32]. This suggests that difluorocarbene was actually formed in the reaction medium.

2.3. Synthesis of aryl difluoromethyl ethers

2.3.1. Background and strategy

Aryl difluoromethyl ether units are often found in structures of pharmaceuticals, agrochemicals, and their candidates. For example, pantoprazole is a proton pump inhibitor and is used for a

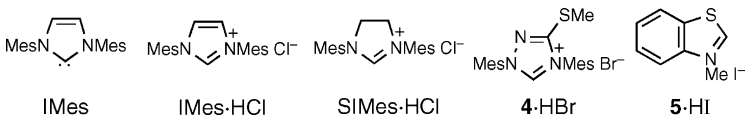
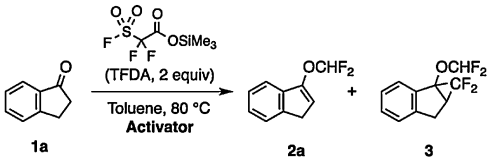


Table 1
NHC-catalyzed generation of difluorocarbene and formation of enol difluoromethyl ethers: effect of activator for TFDA.



Entry	Activator	Time (h)	**2a** (%)[a]	**3** (%)[a]
1	NaF (1 mol%)	4	14	–
2	DABCO (2 mol%)	1	40	<1
3	Pyridine *N*-oxide (10 mol%)	1	Trace	–
4	NMO (10 mol%)	1	5	Trace
5	IMes·HCl (1 mol%), Na_2CO_3 (10 mol%)	0.5	70	–
6	IMes·HCl (2 mol%), Na_2CO_3 (20 mol%)	0.5	74, 72 [b]	Trace
7 [c]	IMes·HCl (2 mol%), Na_2CO_3 (20 mol%)	0.5	61	7
8	IMes·HCl (1 mol%)	4	4	–
9	IMes·(1 mol%)	0.5	52	17
10	SIMes·HCl (2 mol%), Na_2CO_3 (20 mol%)	0.5	54	26
11	**4**·HBr (2 mol%), Na_2CO_3 (20 mol%)	1	46	30
12	**5**·HI (2 mol%), Na_2CO_3 (20 mol%)	1	34	17

DABCO = 1,4-diazabicyclo[2.2.2]octane; NMO = *N*-methylmorpholine *N*-oxide.
[a] ^{19}F NMR yield based on $(CF_3)_2C(p\text{-Tol})_2$.
[b] Isolated yield.
[c] TFDA (1.2 equiv).

short-term treatment of erosion and ulceration of esophagus [33]. Zardaverine is a phosphodiesterase III/IV inhibitor and attracts much attention as a potential therapeutic agent for asthma [34]. Brofluthrinate [35] is an insecticide that acts as a sodium channel modulator [36] (Fig. 1).

To date, aryl difluoromethyl ethers have been synthesized by an electrophilic difluoromethylation of phenols with difluorocarbene [37]. For instance, phenoxides are difluoromethylenated with difluorocarbene, generated by α-elimination of chlorodifluoromethane, to give aryl difluoromethyl ethers after protonation: however, the preparation of the starting phenols is required [10a–c,38,39].

We envisaged developing a new synthetic method for aryl difluoromethyl ethers with substituents by utilizing the above-mentioned selective formation of enol difluoromethyl ethers (Scheme 4): six-membered ketones (cyclohexanone and tetralone derivatives) would be transformed into the corresponding enol difluoromethyl ethers with difluorocarbene, generated by the NHC catalyst. The formed enol difluoromethyl ethers might

Table 2
Effect of base.[a]

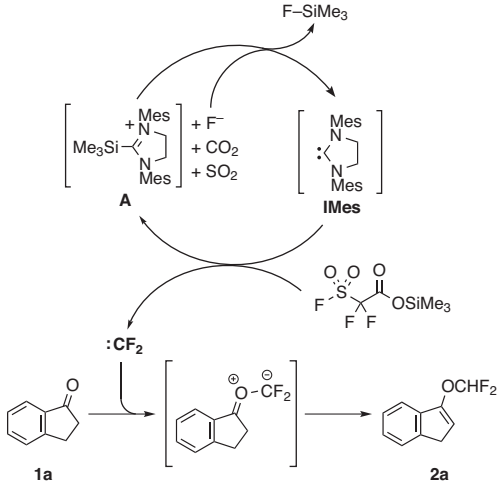
Entry	Base	Time (h)	**2a** (%)[b]	**3** (%)[b]
1	Na_2CO_3 (2 mol%)	0.5	54	–
2[c]	Na_2CO_3 (20 mol%)	0.5	74	Trace
3	Na_2CO_3 (100 mol%)	0.5	40	32
4	K_2CO_3 (20 mol%)	1	37	2
5	*t*-BuOK (20 mol%)	0.5	20	–
6	DBU (2 mol%)	0.5	15	–

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.
[a] **1a**, TFDA (2 equiv), IMes·HCl (2 mol%), base, toluene, 80 °C.
[b] ^{19}F NMR yield based on $(CF_3)_2C(p\text{-Tol})_2$.
[c] Table 1, Entry 6.

Table 3
Effects of solvent and temperature.[a]

Entry	Solvent	Temperature (°C)	Time (h)	**2a** (%)[b]	**3** (%)[b]
1	Toluene	70	2	39	–
2[c]	Toluene	80	0.5	70	–
3	Toluene	90	1	68	Trace
4	1,4-Dioxane	80	1	34	–
5	$CHCl_2CHCl_2$	80	1	23	–

[a] **1a**, TFDA (2 equiv), IMes·HCl (1 mol%), Na_2CO_3 (10 mol%).
[b] ^{19}F NMR yield based on $(CF_3)_2C(p\text{-Tol})_2$.
[c] Table 1, Entry 5.



Scheme 3. Proposed mechanism for CF_2 generation and CHF_2 ether formation.

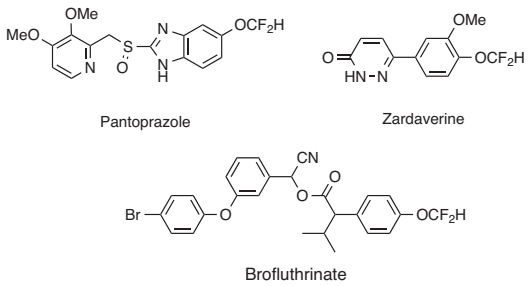
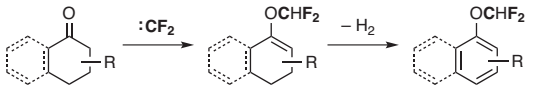


Fig. 1. Examples of bioactive aryl difluoromethyl ethers.



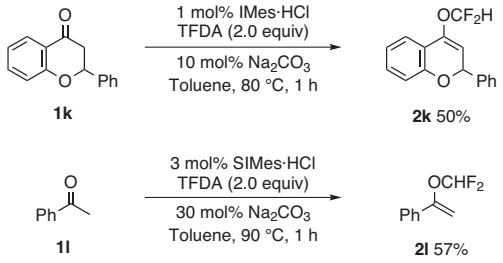
Scheme 4. Synthetic strategy for substituted aryl difluoromethyl ethers.

be readily dehydrogenated to construct a benzene ring, thus targeting aryl difluoromethyl ethers [40]. Commercial and synthetic availability of the cyclohexanone derivatives makes this a practical approach for the synthesis of substituted aryl difluoromethyl ethers.

2.3.2. One-pot synthesis of aryl difluoromethyl ethers

Various aryl difluoromethyl ethers were successfully synthesized from cyclohexenones and tetralones via the expected difluoromethylation–dehydrogenation sequence (Table 4). First, 3-phenylcylclohexenone **1b** was transformed into the corresponding enol difluoromethyl ether **2b** (not shown) by the TFDA/NHC system (Entry 1). The resulting mixture was treated with DDQ (2 equiv) under reflux. Standard chromatographic separation of the products gave biphenyl-3-yl difluoromethyl ether **6b** in 78% yield.

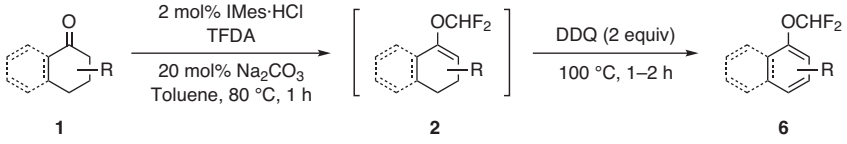
This method was successfully applied to tetralone derivatives, which produced difluoromethyl naphthyl ethers. Not only did parent **1c** give 1-naphthyl ethers **6c** in 81% yield, but also bromo- and chlorotetralones **1d** and **1e** afforded the halogenated naphthyl ethers **6d** and **6e** in 75% and 77% yield, respectively (Entries 2–4). Electron-rich tetralones appeared to be suitable for this reaction: Methyl- and methoxy-substituted tetralones **1f–h** afforded the corresponding naphthyl ethers **6f–h** in 79–91% yield (Entries 5–7). The reaction of β-tetralone **1i** allowed the formation of the corresponding 2-naphthyl ether **6i** in 90% yield (Entry 8). A similar treatment of cyclohexanone **1j** also provided the corresponding biphenyl-4-yl difluoromethyl ether **6j** (Entry 9).

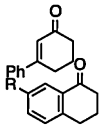
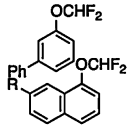
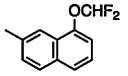
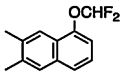
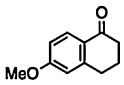
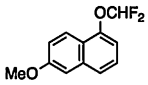
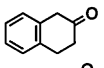
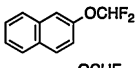
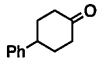
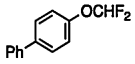


Scheme 5. Synthesis of cyclic and acyclic enol difluoromethyl ethers (^{19}F NMR yield).

Note that the TFDA/NHC system can be applied to the synthesis of other enol difluoromethyl ethers (Scheme 5). Flavanone **1k** was transformed into the corresponding difluoromethoxychromene **2k** in 50% yield. In addition, acetophenone **1l** afforded the corresponding enol ether **2l** in 57% yield in the presence of 3 mol% of SIMes·HCl catayst. It has been reported that the treatment of **1l** by the TFDA/F^- system gives difluorocyclopropanated difluoromethyl ether in 27% yield at 120 °C [23a]. NHC was again found to be an efficient and selective catalyst for the synthesis of enol difluoromethyl ethers. As described above, NHC-catalyzed, controlled generation of difluorocarbene from TFDA has realized a ketone-based one-pot synthesis of aryl difluoromethyl ethers.

Table 4
One-pot synthesis of aryl difluoromethyl ethers.



Entry	1		6		TFDA (equiv)	Temp. (°C)	Yield (%)[a]
1		**1b**		**6b**	2.0	80	78
2		**1c** (R = H)		**6c**	2.0	100	81
3		**1d** (R = Br)		**6d**	1.6	100	75
4		**1e** (R = Cl)		**6e**	1.6	80	77
5		**1f**		**6f**	2.0	100	79
6		**1g**		**6g**	1.2	80	91
7		**1h**		**6h**	1.2	80	86
8[b]		**1i**		**6i**	1.6	100	90
9		**1j**		**6j**	1.6	100	63

DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.
[a] Yield in two steps.
[b] The corresponding enol ether was obtained as a regioisomeric mixture (conjugated:nonconjugated = 88:12, ^{19}F NMR).

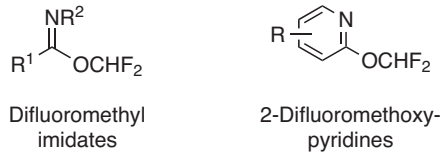
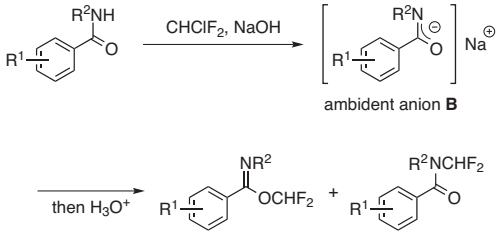
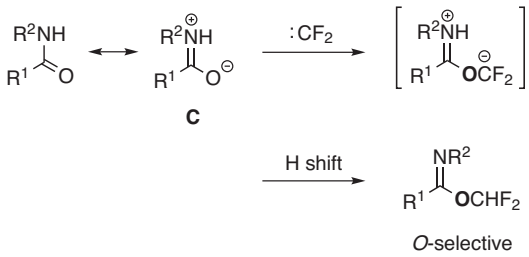


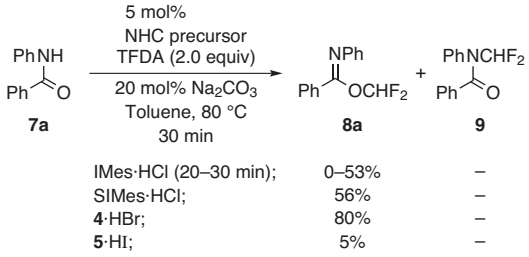
Fig. 2.



Scheme 6. Reported nonselective formation of difluoromethyl imidates under basic conditions.



Scheme 7. Strategy for selective synthesis of difluoromethyl imidates.



Scheme 8. Optimization of NHC precursors in difluoromethyl imidate formation (^{19}F NMR yield).

2.4. Synthesis of difluoromethyl imidates

2.4.1. Background and strategy

Difluoromethyl imidate is contained in the structure of 2-difluoromethoxypyridine, which is a motif frequently found in pharmaceuticals and bioactive molecules (Fig. 2) [41,42]. Difluoromethyl imidates have been synthesized by electrophilic *O*-difluoromethylation of secondary amides with difluorocarbene (Scheme 6). However, these difluoromethylations led to only a partial success, which was due to affording a regioisomeric mixture of *O*- and *N*-difluoromethylated products [43]. The poor selectivity is presumably because the *basic* conditions, required for the generation of difluorocarbene, cause deprotonation of the amides. The resulting ambident anion **B** allows formation of not only *O*- but also *N*-difluoromethylation products.

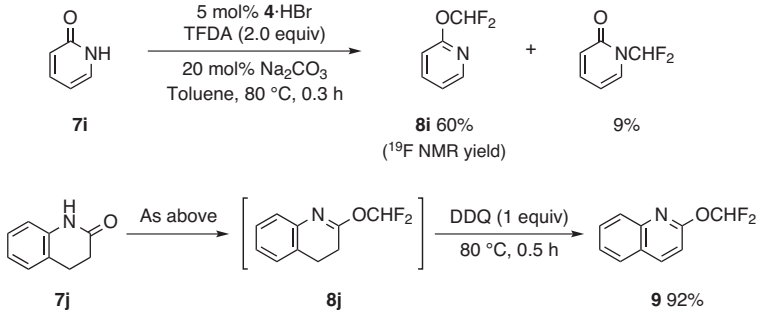
In general, (nondeprotonated) amides undergo alkylations on the oxygen atom because the oxygen center is more nucleophilic than the nitrogen center because of resonance (Scheme 7, **C**). Having the NHC-catalyzed generation of difluorocarbene under *nearly neutral* conditions in hand, we expected *O*-selective difluoromethylation of amides to synthesize difluoromethyl imidates [44].

2.4.2. Selective synthesis of difluoromethyl imidates

We optimized NHC precursors for difluoromethylation of secondary amides (Scheme 8). It was revealed that IMes·HCl was lacking in reproducibility and that triazolium salt **4**·HBr was a suitable catalyst for this purpose [45]. Note that the formation of the undesired tertiary amide **9** was not observed over all the NHC precursors examined as a catalyst.

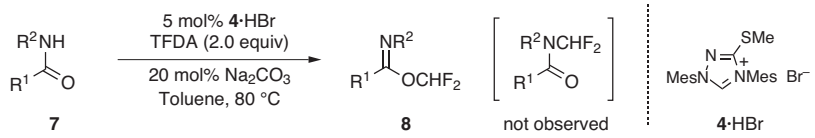
Various difluoromethyl imidates were efficiently synthesized by the triazolium salt-based system (Table 5). Not only benzoic acid-derived amides but also aliphatic acid-derived amides afforded the corresponding imidates in high yield (Entries 1–4): namely, amides **7a–d** gave **8a–d** in 66–81% yield. Electron-donating and -withdrawing group on the *N*-aryl groups did not affect the reaction (Entries 5–8). Although some amount of the imidates decomposed during purification by column chromatography, ^{19}F NMR analysis suggested that substituted anilides **7e–h** gave **8e–h** in 69–83% yield. It must be emphasized that the undesired *N*-difluoromethylated products were not observed by the ^{19}F NMR analysis of the crude mixtures.

This method was successfully applied to the synthesis of 2-difluoromethoxypyridines (Scheme 9). When pyridone **7i** was subjected to the TFDA/NHC system, the desired **8i** was obtained in 60% yield, albeit accompanied by a 9% yield of *N*-difluoromethylated product. The sequential difluoromethylation–dehydrogenation process is also effective for six-membered lactams: 2-difluoromethoxyquinoline **9** was synthesized from dihydroquinolinone **7j** in 92% yield in a one-pot operation.

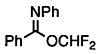
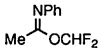
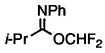
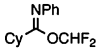
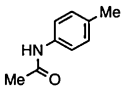
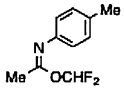
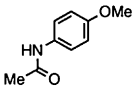
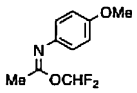
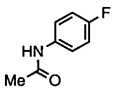
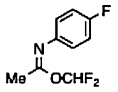
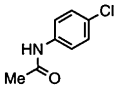
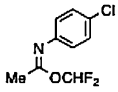


Scheme 9. Synthesis of 2-difluoromethoxypyridines.

Table 5
Selective synthesis of difluoromethyl imidates.



7 8 not observed 4·HBr

Entry	7		Time (h)	8		Yield (%)[a]
1		**7a**	0.5		**8a**	80
2		**7b**	0.4		**8b**	74
3		**7c**	0.4		**8c**	66
4		**7d**	0.3		**8d**	81
5		**7e**	0.3		**8e**	62, 83[b]
6		**7f**	0.3		**8f**	62, 69[b]
7		**7g**	0.4		**8g**	72, 83[b]
8		**7h**	0.3		**8h**	67, 77[b]

[a] Imidates were obtained selectively.
[b] ^{19}F NMR yield based on $(CF_3)_2CTol_2$.

3. Conclusion

We have developed a versatile method for the controlled generation of difluorocarbene from TFDA under mild conditions by using NHC catalyst. Cyclohexenones and tetralones were transformed into enol difluoromethyl ethers without difluorocyclopropanation. The enol ethers obtained were dehydrogenated with DDQ to provide substituted aryl difluoromethyl ethers. Moreover, secondary amides were similarly transformed into difluoromethyl imidates via *O*-selective difluoromethylation, which allows the formation of 2-difluoromethoxypyridines.

4. Experimental

4.1. General information

IR spectra were recorded on Horiba FT-300S spectrometer. NMR spectra were recorded on Bruker Avance 500, Bruker AV600, or Bruker AV400 spectrometers in $CDCl_3$, at 500, 600, or 400 MHz (^1H NMR), at 126, 150, or 100 MHz (^{13}C NMR), and at 470, 565, or 372 MHz (^{19}F NMR). Chemical shift values were given in ppm relative to internal Me_4Si (for ^1H NMR: $\delta = 0.00$), $CDCl_3$ (for ^{13}C NMR: $\delta = 77.0$), and C_6F_6 (for ^{19}F NMR: $\delta = 0.0$) [32]. Mass spectra were taken with JMS-T100GCV spectrometer. Elemental analyses were performed with a YANAKO MT-6 CHN Corder apparatus. TFDA was prepared according to the procedure described by Dolbier [18b]. IMes·HCl and SIMes·HCl were prepared according to the literature [46]. IMes, **4**·HBr, **5**·HI were purchased and used without further purification. All the reactions were conducted under argon. Column chromatography and preparative thin-layer chromatography (PTLC) were performed on silica gel.

4.2. Synthesis of aryl difluoromethyl ethers

4.2.1. Typical procedure for synthesizing aryl difluoromethyl ethers

To a toluene solution (0.4 mL) of IMes·HCl (2.7 mg, 0.0079 mmol), sodium carbonate (8.5 mg, 0.080 mmol), and 6,7-dimethyl-α-tetralone **1g** (70 mg, 0.40 mmol) was added TFDA (100 μL, 0.48 mmol) at room temperature. The reaction mixture was stirred and heated at 80 °C for 1 h. After cooling the resulting mixture to room temperature, DDQ (182 mg, 0.80 mmol) and toluene (2 mL) was added and the mixture was heated at 100 °C for 2 h. Purification by column chromatography (SiO_2, hexane) gave **6g** (82 mg, 91% yield).

4.2.2. Spectra data of aryl difluoromethyl ethers

*4.2.2.1. 1-Difluoromethoxy-3-phenylbenzene (**6b**).* ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.56–7.59$ (m, 2H), 7.41–7.48 (m, 4H), 7.38 (tt, $J = 7.4$, 2.1 Hz, 1H), 7.34 (s, 1H), 7.10 (dt, $J = 2.4$ Hz, $J = 6.7$ Hz, 1H), 6.57 (t, $^2J_{HF} = 74.0$ Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 151.6$, 143.3, 139.9, 130.1, 128.9, 127.9, 127.1, 124.2, 118.3, 118.1, 116.0 (t, $^1J_{CF} = 258$ Hz). ^{19}F NMR (470 MHz, $CDCl_3$): $\delta = 81.3$ (d, $^2J_{FH} = 74$ Hz, 2F). IR (neat): $\tilde{\nu} =$ 1477, 1196, 1122, 912, 741, 696 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{13}H_{10}F_2O$ ($[M]^+$): 220.0700; found: 220.0689.

*4.2.2.2. 1-Difluoromethoxynaphthalene (**6c**).* ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.18–8.21$ (m, 1H), 7.84–7.88 (m, 1H), 7.70 (d, $J = 8.3$ Hz, 1H), 7.52–7.58 (m, 2H), 7.41 (t, $J = 7.9$ Hz, 1H), 7.19 (d, $J = 7.5$ Hz, 1H), 6.66 (t, $^2J_{HF} = 74.1$ Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 147.4$, 134.7, 127.7, 126.9, 126.6, 126.4, 125.4, 125.3, 121.6, 116.6 (t, $^1J_{CF} = 256$ Hz), 113.7. ^{19}F NMR (470 MHz, $CDCl_3$): $\delta = 81.9$ (d, $^2J_{FH} = 74$ Hz, 2F). IR (neat): $\tilde{\nu} =$ 3059, 1373, 1120, 1051,

771 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{11}H_8F_2O$ ($[M]^+$): 194.0543; found: 194.0548.

*4.2.2.3. 7-Bromo-1-difluoromethoxynaphthalene (**6d**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 8.34 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.62 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.68 (t, $^2J_{HF}$ = 73.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.3, 133.0, 130.4, 129.4, 127.4, 125.8, 125.1, 124.1, 120.9, 116.2 (t, $^1J_{CF}$ = 256 Hz), 114.5. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 81.5 (d, $^2J_{FH}$ = 74 Hz, 2F). IR (neat): $\tilde{\nu}$ = 3062, 1589, 1124, 1049, 823, 742 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{11}H_7{}^{79}BrF_2O$ ($[M]^+$): 271.9648; found: 271.9644.

*4.2.2.4. 7-Chloro-1-difluoromethoxynaphthalene (**6e**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 8.16 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1 H), 7.23 (d, *J* = 7.9 Hz, 1H), 6.68 (t, $^2J_{HF}$ = 73.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.4, 132.8, 132.7, 129.4, 127.9, 127.1, 125.6, 125.1, 120.8, 116.2 (t, $^1J_{CF}$ = 259 Hz), 114.5. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 81.5 (d, $^2J_{FH}$ = 74 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2918, 1593, 1358, 1119, 1032, 822 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{11}H_7{}^{35}ClF_2O$ ($[M]^+$): 228.0154; found: 228.0145

*4.2.2.5. 1-Difluoromethoxy-7-methylnaphthalene (**6f**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.94 (s, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.38 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 6.65 (t, $^2J_{H-F}$ = 74.2 Hz, 1H), 2.55 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 147.0, 136.5, 133.0, 129.2, 127.6, 126.6, 125.1, 124.3, 120.4, 116.6 (t, $^1J_{CF}$ = 257 Hz), 113.8, 22.0. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 82.0 (d, $^2J_{FH}$ = 74 Hz, 2F). IR (neat): $\tilde{\nu}$ = 3062, 1365, 1115, 1032, 822 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{12}H_{10}F_2O$ ($[M]^+$): 208.0700; found: 208.0699.

*4.2.2.6. 1-Difluoromethoxy-6,7-dimethylnaphthalene (**6g**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.91 (s, 1H), 7.61 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.65 (t, $^2J_{HF}$ = 74.4 Hz, 1H), 2.47 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.9, 136.8, 136.6, 133.7, 127.3, 125.1, 124.4 (2C), 120.9, 116.7 (t, $^1J_{CF}$ = 250 Hz), 112.8, 20.4, 20.2. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 82.2 (d, $^2J_{FH}$ = 74 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2920, 1606, 1379, 1122, 1045 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{13}H_{12}F_2O$ ($[M]^+$): 222.0856; found: 222.0865.

*4.2.2.7. 1-Difluoromethoxy-6-methoxynaphthalene (**6h**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 9.2 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.15 (d, *J* = 2.6 Hz, 1H), 7.03 (dd, *J* = 7.7, 1.0 Hz, 1H), 6.65 (t, $^2J_{HF}$ = 74.2 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.4, 147.6, 136.2, 126.1, 124.1, 123.3, 121.6, 119.3, 116.5 (t, $^1J_{CF}$ = 257 Hz), 111.2, 105.7, 55.3. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 82.0 (d, $^2J_{FH}$ = 74 Hz, 2F). IR (neat): $\tilde{\nu}$ = 1635, 1516, 1255, 1171, 1132 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{12}H_{10}F_2O_2$ ($[M]^+$): 224.0649; found: 224.0656.

*4.2.2.8. 2-Difluoromethoxynaphthalene (**6i**).* ^1H NMR (600 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.52 (s, 1H), 7.52 (t, *J* = 9.0 Hz, 1H), 7.45–7.49 (t, *J* = 9.0 Hz, 1H), 7.28 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.63 (t, $^2J_{HF}$ = 73.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 133.8, 131.0, 130.1, 127.8, 127.5, 126.9, 125.7, 119.7, 116.1 (t, $^1J_{CF}$ = 256 Hz), 115.4. ^{19}F NMR (565 MHz, $CDCl_3$): δ = 81.2 (d, $^2J_{FH}$ = 74 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2927, 1255, 1171, 912, 742 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{11}H_8F_2O$ ($[M]^+$): 194.0543; found: 194.0540.

*4.2.2.9. 1-Difluoromethoxy-4-phenylbenzene (**6j**).* ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.60 (m, 4H), 7.44 (t, *J* = 6.8 Hz, 2H), 7.36 (t, *J* = 6.8 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.55 (t, *J* = 74.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.6 (t, $^3J_{CF}$ = 2.7 Hz), 140.1, 138.6, 128.8, 128.5, 127.4, 127.0, 119.8, 115.9 (t, $^1J_{CF}$ = 258 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ = 81.1 (d, $^2J_{FH}$ = 74 Hz, 2F). IR (neat): $\tilde{\nu}$ = 3033, 1487, 1223, 1126, 764 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{13}H_{10}F_2O$ ($[M]^+$): 220.0700; found: 220.0699.

*4.2.2.10. 4-Difluoromethoxy-2-phenylchromene (**2k**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.47 (m, 2H), 7.33–7.42 (m, 4H), 7.21 (dt, *J* = 5.0, 1.5 Hz, 1H), 6.94 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.55 (t, $^2J_{HF}$ = 74.0 Hz, 1H), 6.02 (d, *J* = 3.5 Hz, 1H), 5.29 (d, *J* = 3.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.1, 143.8, 140.2, 131.0, 128.71, 128.67, 126.9, 122.0, 121.2, 117.5, 116.1, 115.3 (t, $^1J_{CF}$ = 260 Hz), 103.7, 77.1. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 80.0 (d, $^2J_{FH}$ = 74 Hz, 2F). IR (neat): $\tilde{\nu}$ = 3033, 1655, 1454, 1122, 756 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{16}H_{12}F_2O_2$ ($[M]^+$): 274.0805; found: 274.0811.

*4.2.2.11. 1-Difluoromethoxystyrene (**2l**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.61 (m, 2H), 7.36–7.39 (m, 3H), 6.53 (t, *J* = 74.0 Hz, 1H), 5.13 (d, *J* = 3.4 Hz, 1H), 4.74 (d, *J* = 3.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.3, 133.6, 129.4, 128.5, 125.3, 115.8 (t, $^1J_{CF}$ = 258 Hz), 93.0. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 80.3 (d, $^2J_{FH}$ = 74 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2927, 1635, 1126, 1047, 771 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_9H_8F_2O$ ($[M]^+$): 170.0543; found: 170.0542.

4.3. Synthesis of difluoromethyl imidates

4.3.1. Typical procedure for synthesizing difluoromethyl imidates

To a toluene solution (1.5 mL) of **4**·HBr (3.4 mg, 0.0098 mmol), sodium carbonate (4.2 mg, 0.040 mmol), and *N*-phenylcyclohexanecarboxamide **7d** (39 mg, 0.19 mmol) was added TFDA (75 μL, 0.38 mmol) at room temperature. The reaction mixture was stirred and heated at 80 °C for 20 min. After cooling the resulting mixture to room temperature, aquaus NaOH was added to quench the reaction. Extraction with dichloromethane and purification by column chromatography (SiO_2, hexane:AcOEt = 50:1, 0 °C) gave **8d** (39 mg, 81% yield).

4.3.2. Spectra data of difluoromethyl imidates

*4.3.2.1. Difluoromethyl N-phenyl-1-phenylmethanimidate (**8a**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (t, $^2J_{HF}$ = 72.8 Hz, 1H, broad), 7.38 (t, *J* = 7.5 Hz, 2H), 7.22–7.29 (m, 5H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.4 (broad), 146.0, 131.2, 129.5, 129.2, 128.2, 123.9, 120.9, 113.6 (t, $^1J_{CF}$ = 255 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ = 70.8 (d, $^2J_{FH}$ = 73 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2929, 1687, 1267, 1113, 912, 744 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{14}H_{11}F_2NO$ ($[M]^+$): 247.0809; Found: 247.0812.

*4.3.2.2. Difluoromethyl N-phenylethan-1-imidate (**8b**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (t, $^2J_{HF}$ = 72.1 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 2H), 1.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.3, 146.3, 129.2, 124.1, 120.5, 113.0 (t, $^1J_{CF}$ = 255 Hz), 15.6. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 71.0 (d, $^2J_{FH}$ = 72 Hz, 2F). IR (neat): $\tilde{\nu}$ = 1701, 1238, 1105, 1086, 912 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_9H_9F_2NO$ ($[M]^+$): 185.0652; found: 185.0653.

*4.3.2.3. Difluoromethyl N-phenyl-2-methylpropan-1-imidate (**8c**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (t, $^2J_{HF}$ = 72.6 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 2.72 (septet, *J* = 6.5 Hz, 1H), 1.14 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.0, 146.2, 129.2, 123.8, 120.3, 113.4 (t, $^1J_{CF}$ = 254 Hz), 28.6, 19.2. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 70.3 (d, $^2J_{FH}$ = 73 Hz, 2F).

IR (neat): $\tilde{\nu}$ = 2978, 1695, 1244, 1109, 912 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{11}H_{13}F_2NO$ ($[M]^+$): 213.0965; Found: 213.0968.

*4.3.2.4. Difluoromethyl N-pheny-1-cyclohexylmethanimidate (**8d**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31 (t, $^2J_{HF}$ = 72.6 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 2.37–2.42 (m, 1H), 1.68–1.74 (m, 4H), 1.57–1.65 (m, 3H), 1.15–1.23 (m, 1H), 1.07–1.13 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.2, 146.1, 129.2, 123.7, 120.4, 113.4 (t, $^1J_{CF}$ = 254 Hz), 38.4, 29.0, 25.4, 25.2. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 70.5 (d, $^2J_{FH}$ = 73 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2935, 1697, 1238, 1124, 912 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{14}H_{17}F_2NO$ ($[M]^+$): 253.1278; found: 253.1282.

*4.3.2.5. Difluoromethyl N-(p-tolyl)ethan-1-imidate (**8e**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (t, $^2J_{HF}$ = 72.3 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.68 (d, *J* = 7.8 Hz, 2H), 2.32 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.2, 143.7, 133.6, 129.7, 120.4, 113.0 (t, $^1J_{CF}$ = 255 Hz), 20.8, 15.5. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 71.1 (d, $^2J_{FH}$ = 72 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2925, 1699, 1508, 1230, 1065 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{10}H_{11}F_2NO$ ($[M]^+$): 199.0809; Found: 199.0808.

*4.3.2.6. Difluoromethyl N-(p-methoxyphenyl)ethan-1-imidate (**8f**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (t, $^2J_{HF}$ = 72.4 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.4, 156.4, 139.5, 121.6, 114.4, 113.0 (t, $^1J_{CF}$ = 255 Hz), 55.4, 15.5. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 70.6 (d, $^2J_{FH}$ = 72 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2956, 1699, 1506, 1230, 1103 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{10}H_{11}F_2NO_2$ ($[M]^+$): 215.0758; Found: 215.0760.

*4.3.2.7. Difluoromethyl N-(p-fluorophenyl)ethan-1-imidate (**8g**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.34 (t, $^2J_{HF}$ = 72.1 Hz, 1H), 7.02 (dd, $^3J_{HF}$ = *J* = 8.5 Hz, 2H), 6.74 (dd, $^4J_{HF}$ = 4.0 Hz, *J* = 8.5 Hz, 2H), 1.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.7 (d, $^1J_{CF}$ = 242 Hz), 157.9, 142.4 (d, $^3J_{CF}$ = 3 Hz), 121.9, 115.4 (d, $^2J_{CF}$ = 23 Hz), 112.9 (t, $^1J_{CF}$ = 255 Hz), 15.6. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 70.5 (d, $^2J_{FH}$ = 72 Hz, 2F), 42.0 (tt, $^3J_{FH}$ = 8.5 Hz, $^4J_{FH}$ = 4.0 Hz, 1F). IR (neat): $\tilde{\nu}$ = 1705, 1506, 1240, 1109, 914 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_9H_8F_3NO$ ($[M]^+$): 203.0558; found: 203.0553.

*4.3.2.8. Difluoromethyl N-(p-chlorophenyl)ethanimidate (**8h**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (t, $^2J_{HF}$ = 72.0 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 1.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.8, 144.9, 129.6, 129.3, 121.9, 112.9 (t, $^1J_{CF}$ = 256 Hz), 15.6. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 70.4 (d, $^2J_{FH}$ = 72 Hz, 2F). IR (neat): $\tilde{\nu}$ = 1703, 1240, 1136, 1088, 914 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_9H_8{}^{35}ClF_2NO$ ($[M]^+$): 219.0262; found: 219.0260.

*4.3.2.9. 2-Difluoromethoxypyridine (**8i**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 8.20 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.48 (t, $^2J_{HF}$ = 73.5 Hz, 1H), 7.10 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.1, 147.0, 140.0, 120.0, 114.0 (t, $^1J_{CF}$ = 255 Hz), 111.5. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 72.8 (d, $^2J_{FH}$ = 74 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2925, 1261, 1219, 1099, 773 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_6H_5F_2NO$ ($[M]^+$): 145.0339; found: 145.0341.

*4.3.2.10. 2-Difluoromethoxyquinoline (**9**).* ^1H NMR (500 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.77 (dd, *J* = 7.7, 3.0 Hz, 1H), 7.74 (t, $^2J_{HF}$ = 72.7 Hz, 1H), 7.68 (ddd, *J* = 7.7, 7.7, 3.0 Hz, 1H), 7.48 (ddd, *J* = 7.7, 7.7, 3.0 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.3, 145.5, 140.5, 130.3, 127.8, 127.6, 126.1, 125.7, 113.9 (t, $^1J_{CF}$ = 255 Hz), 111.8. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 72.1 (d, $^2J_{FH}$ = 73 Hz, 2F). IR (neat): $\tilde{\nu}$ = 1604, 1311, 1232, 1065, 912 cm^{-1}. HRMS (70 eV, EI): *m/z* calcd. for $C_{10}H_7F_2NO$ ($[M]^+$): 195.0496; found: 195.0496.

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References

[1] (a) M. Hudlický, A.E. Pavlath (Eds.), Chemistry of Organic Fluorine Compounds II: A Critical Review, American Chemical Society, Washington, 1995;
(b) D.L.S. Brahms, W.P. Dailey, Chem. Rev. 96 (1996) 1585–1632;
(c) W.R. Dolbier Jr., M.A. Battiste, Chem. Rev. 103 (2003) 1071–1098.
[2] (a) T. Hiyama, Organofluorine Compounds: Chemistry and Applications, Springer, Berlin, 2000;
(b) P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, Wiley-VCH, VeinHeim, 2004;
(c) K. Uneyama, Organofluorine Chemistry, Blackwell, Oxford, 2006;
(d) J.-P. Bégué, D. Bonnet-Delpon, Bioorganic and Medicinal Chemistry of Fluorine, Wiley, Hoboken, 2008.
[3] (a) J.M. Birchall, G.E. Cross, R.N. Haszeldine, Proc. Chem. Soc. (1960), 81–81;
(b) L.H. Knox, E. Velarde, S. Berger, D. Cuadriello, P.W. Landis, A.D. Cross, J. Am. Chem. Soc. 85 (1963) 1851–1858;
(c) C. Beard, N.H. Dyson, J.H. Fried, Tetrahedron Lett. 7 (1966) 3281–3286;
(d) P.D. O'Shea, C.-y. Chen, W. Chen, P. Dagneau, L.F. Frey, E.J.J. Grabowski, K.M. Marcantonio, R.A. Reamer, L. Tan, R.D. Tillyer, A. Roy, X. Wang, D. Zhao, J. Org. Chem. 70 (2005) 3021–3030;
(e) D. Babin, F. Pilorge, L.M. Delbarre, J.P. Demoute, Tetrahedron 51 (1995) 9603–9610.
[4] K. Oshiro, Y. Morimoto, H. Amii, Synthesis (2010) 2080–2084 (Recently, Amii has reported a generation of difluorocarbene from sodium bromodifluoroacetate with low reagent loadings).
[5] Y. Chang, C. Cai, Chem. Lett. 34 (2005) 1440–1441.
[6] (a) P.B. Sargeant, J. Org. Chem. 35 (1970) 678–682;
(b) H. Millauer, W. Schwertfeger, G. Siegemund, Angew. Chem. Int. Ed. 24 (1985) 161–179.
[7] (a) J.M. Birchall, R.N. Haszeldine, D.W. Roberts, Chem. Commun. (1967) 287–288;
(b) J.M. Birchall, R. Fields, R.N. Haszeldine, R.J. McLean, J. Fluorine Chem. 15 (1980) 487–495.
[8] (a) R.A. Mitsch, J. Heterocycl. Chem. 1 (1964) 271–274;
(b) R.A. Mitsch, J. Am. Chem. Soc. 87 (1965) 758–761 (For thermal generation of difluorocarbene from difluoroazirine).
[9] (a) R.A. Mitsch, J. Heterocycl. Chem. 1 (1964) 59–60;
(b) R.A. Moss, L. Wang, K. Krogh-Jespersen, J. Am. Chem. Soc. 131 (2009) 2128–2130 (For photolytic generation of difluorocarbene from difluoroazirine).
[10] (a) T.G. Miller, J.W. Thanassi, J. Org. Chem. 25 (1960) 2009–2012;
(b) B.R. Langlois, J. Fluorine Chem. 41 (1988) 247–261;
(c) A. Fuss, V. Koch, Synthesis (1990) 604–608;
(d) T.Y. Shen, S. Lucas, L.H. Sarett, Tetrahedron Lett. 2 (1961) 43–47;
(e) A. Fuss, V. Koch, Synthesis (1990) 681–685.
[11] (a) L. Zhang, J. Zheng, J. Hu, J. Org. Chem. 71 (2006) 9845–9848;
(b) G. Guerrini, G. Ciciani, F. Bruni, S. Selleri, C. Guarino, F. Melani, M. Montali, S. Daniele, C. Martini, C. Ghelardini, M. Norcini, S. Ciattini, A. Costanzo, J. Med. Chem. 53 (2010) 7532–7548.
[12] (a) J. Zheng, Y. Li, L. Zhang, J. Hu, G.J. Meuzelaar, H.-J. Federsel, Chem. Commun. (2007) 5149–5151;
(b) W. Zhang, F. Wang, J. Hu, Org. Lett. 11 (2009) 2109–2112;
(c) Y. Zafrani, G. Sod-Moriah, Y. Segall, Tetrahedron 65 (2009) 5278–5283.
[13] G.K.S. Prakash, Z. Zhang, F. Wang, C. Ni, G.A. Olah, J. Fluorine Chem. 132 (2011) 792–798.
[14] (a) D. Seyferth, J.Y.-P. Mui, M.E. Gordon, J.M. Burlitch, J. Am. Chem. Soc. 87 (1965) 681–682;
(b) D. Seyferth, S.P. Hopper, K.V. Darragh, J. Am. Chem. Soc. 91 (1969) 6536–6537;
(c) D. Seyferth, S.P. Hopper, J. Org. Chem. 37 (1972) 4070–4075.
[15] I. Nowak, M.J. Robins, Org. Lett. 7 (2005) 721–724.
[16] D. Seyferth, H. Dertouzos, R. Suzuki, J.Y.-P. Mui, J. Org. Chem. 32 (1967) 2980–2984.
[17] (a) D.J. Burton, D.G. Naae, J. Am. Chem. Soc. 95 (1973) 8467–8468 (Burton and Dolbier reported practical methods for the generation of difluorocarbene that proceed at room temperature);
(b) W.R. Dolbier Jr., H. Wojtowicz, C.R. Burkholder, J. Org. Chem. 55 (1990) 5420–5422;
(c) Y. Bessard, U. Müller, M. Schlosser, Tetrahedron 46 (1990) 5213–5221.
[18] (a) F. Tian, V. Kruger, O. Bautista, J.-X. Duan, A.-R. Li, W.R. Dolbier Jr., Q.-Y. Chen, Org. Lett. 2 (2000) 563–564;
(b) W.R. Dolbier Jr., F. Tian, J.-X. Duan, A.-R. Li, S. Ait-Mohand, O. Bautista, S. Buathong, J.M. Baker, J. Crawford, P. Anselme, X.H. Cai, A. Modzelewska, H. Koroniak, M.A. Battiste, Q.-Y. Chen, J. Fluorine Chem. 125 (2004) 459–469.
[19] T. Itoh, N. Ishida, K. Mitsukura, K. Uneyama, J. Fluorine Chem. 112 (2001) 63–68.

[20] (a) W. Xu, Q.-Y. Chen, J. Org. Chem. 67 (2002) 9421–9427;
(b) Z.-L. Cheng, Q.-Y. Chen, Synlett (2006) 478–480;
(c) X.-C. Hang, W.-P. Gu, Q.-Y. Chen, J.-C. Xiao, Tetrahedron 65 (2009) 6320–6324.
[21] Z.-L. Cheng, J.-C. Xiao, C. Liu, Q.-Y. Chen, Eur. J. Org. Chem. (2006) 5581–5587.
[22] (a) M. Rapp, X. Cai, W. Xu, W.R. Dolbier Jr., S.F. Wnuk, J. Fluorine Chem. 130 (2009) 321–328;
(b) W. Xu, K.A. Abboud, I. Ghiviriga, W.R. Dolbier Jr., M. Rapp, S.F. Wnuk, Org. Lett. 8 (2006) 5549–5551.
[23] (a) X. Cai, Y. Zhai, I. Ghiviriga, K.A. Abboud, W.R. Dolbier Jr., J. Org. Chem. 69 (2004) 4210–4215;
(b) X. Cai, K. Wu, W.R. Dolbier Jr., J. Fluorine Chem. 126 (2005) 479–482.
[24] (a) S.P. Nolan (Ed.), N-Heterocyclic Carbenes in Synthesis, Wiley-VCH, Weinheim, 2006;
(b) N. Marion, S. Díez-González, S.P. Nolan, Angew. Chem. Int. Ed. 46 (2007) 2988–3000;
(c) D. Enders, O. Niemeier, A. Henseler, Chem. Rev. 107 (2007) 5606–5655 (For reviews on NHC catalyst).
[25] (a) G.A. Grasa, T. Güveli, R. Singh, S.P. Nolan, J. Org. Chem. 68 (2003) 2812–2819;
(b) Y.-K. Liu, R. Li, L. Yue, B.-J. Li, Y.-C. Chen, Y. Wu, L.-S. Ding, Org. Lett. 8 (2006) 1521–1524;
(c) H. Takikawa, K. Suzuki, Org. Lett. 9 (2007) 2713–2716;
(d) Y. Kayaki, M. Yamamoto, T. Ikariya, Angew. Chem. Int. Ed. 48 (2009) 4194–4197;
(e) J.M. O'Brien, A.H. Hoveyda, J. Am. Chem. Soc. 133 (2011) 7712–7715 (For recent cataytic reactions using NHC as an organocatalyst).
[26] (a) J.J. Song, F. Gallou, J.T. Reeves, Z. Tan, N.K. Yee, C.H. Senanayake, J. Org. Chem. 71 (2006) 1273–1276;
(b) Y. Fukuda, Y. Maeda, S. Ishii, K. Kondo, T. Aoyama, Synthesis (2006) 589–590;
(c) T. Kano, K. Sasaki, T. Konishi, H. Mii, K. Maruoka, Tetrahedron Lett. 47 (2006) 4615–4618;
(d) Y. Suzuki, M.D.A. Bakar, K. Muramatsu, M. Sato, Tetrahedron 62 (2006) 4227–4231.
[27] J.J. Song, Z. Tan, J.T. Reeves, N.K. Yee, C.H. Senanayake, Org. Lett. 9 (2007) 1013–1016.
[28] J. Wu, X. Sun, S. Ye, W. Sun, Tetrahedron Lett. 47 (2006) 4813–4816.
[29] J.J. Song, Z. Tan, J.T. Reeves, F. Gallou, N.K. Yee, C.H. Senanayake, Org. Lett. 7 (2005) 2193–2196.
[30] T.E. Reynolds, C.A. Stern, K.A. Scheidt, Org. Lett. 9 (2007) 2581–2584.
[31] (a) S.-K. Tian, R. Hong, L. Deng, J. Am. Chem. Soc. 125 (2003) 9900–9901;
(b) S. Soo Kim, G. Rajagopal, D. Won Kim, D. Ho Song, Synth. Commun. 34 (2004) 2973–2980;
(c) N. Takenaka, R.S. Sarangthem, B. Captain, Angew. Chem. Int. Ed. 47 (2008) 9708–9710.
[32] 1,1,1,3,3,3-Hexafluoro-2,2-di(*p*-tolyl)propane (δ 97.9 vs. C_6F_6) was used as an internal standard.
[33] B. Kohl, E. Sturm, J. Senn-Bilfinger, W.A. Simon, U. Krueger, H. Schaefer, G. Rainer, V. Figala, K. Klemm, J. Med. Chem. 35 (1992) 1049–1057.
[34] J.C. Kips, G.F. Joos, R.A. Peleman, R.A. Pauwels, Clin. Exp. Allergy 23 (1993) 518–523.
[35] G. Sun, W. Jin, L. Zuo, H. Xie, PCT Int. Appl. WO 9518790, 1995.
[36] P. Kirsch, M. Bremer, Angew. Chem. Int. Ed. 39 (2000) 4216–4235.
[37] (a) F. Leroux, P. Jeschke, M. Schlosser, Chem. Rev. 105 (2005) 827–856;
(b) J. Hu, W. Zhang, F. Wang, Chem. Commun. (2009) 7465–7478;
(c) B. Manteau, S. Pazenok, J.-P. Vors, F.R. Leroux, J. Fluorine Chem. 131 (2010) 140–158.
[38] (a) Q.-Y. Chen, S.-W. Wu, J. Fluorine Chem. 44 (1989) 433–440;
(b) S.V. Pasenok, Y.L. Yagupolskii, W. Tyrra, D. Naumann, Z. Anorg, Allg. Chem. 625 (1999) 831–833;
(c) J.Z. Ho, C.S. Elmore, M.A. Wallace, D. Yao, M.P. Braun, D.C. Dean, D.G. Melillo, C.-y. Chen, Helv. Chim. Acta 88 (2005) 1040–1047 (and Refs. [3d,11,12]), (For other syntheses of aryl difluoromethyl ethers from phenols and difluorocarbene).
[39] (a) S. Stavber, Z. Koren, M. Zupan, Synlett (1994) 265–266;
(b) Y. Hagooly, O. Cohen, S. Rozen, Tetrahedron Lett. 50 (2009) 392–394 (For the synthesis of aryl difluoromethyl ethers without using difluorocarbene).
[40] K. Fuchibe, Y. Koseki, H. Sasagawa, J. Ichikawa, Chem. Lett. 40 (2011) 1189–1191.
[41] R.A. Hartz, V.T. Ahuja, X. Zhuo, R.J. Mattson, D.J. Denhart, J.A. Deskus, V.M. Vrudhula, S. Pan, J.L. Ditta, Y.-Z. Shu, J.E. Grace, K.A. Lentz, S. Lelas, Y.-W. Li, T.F. Molski, S. Krishnananthan, H. Wong, J. Qian-Cutrone, R. Schartman, R. Denton, N.J. Lodge, R. Zaczek, J.E. Macor, J.J. Bronson, J. Med. Chem. 52 (2009) 7653–7668.
[42] I. Kmentova, H.S. Sutherland, B.D. Palmer, A. Blaser, S.G. Franzblau, B. Wan, Y. Wang, Z. Ma, W.A. Denny, A.M. Thompson, J. Med. Chem. 53 (2010) 8421–8439.
[43] (a) E. Nawrot, A. Jonczyk, J. Fluorine Chem. 127 (2006) 943–947;
(b) J.P. Chupp, D.M. Hemmerly, J.J. Freeman, J. Org. Chem. 58 (1993) 245–248.
[44] *O*-difluoromethylation of benzamides of adenine nucleosides by TFDA/F^- system was described by Dolbier (See Ref. [22a]).
[45] We found that quaternary ammonium bromides also promote the decomposition of TFDA, albeit less effective than NHC.
[46] A.J. Arduengo, R. Krafczyk, R. Schmutzler, H.A. Craig, J.R. Goerlich, W.J. Marshall, M. Unverzagt, Tetrahedron 55 (1999) 14523–14534.