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N-Heterocyclic Carbene-catalyzed Difluorocarbene Generation and its Application to Aryl Difluoromethyl Ether Synthesis

Kohei Fuchibe, Yuta Koseki, Hisashi Sasagawa, and Junji Ichikawa*
Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8571

(Received July 25, 2011; CL-110621; E-mail: junji@chem.tsukuba.ac.jp)

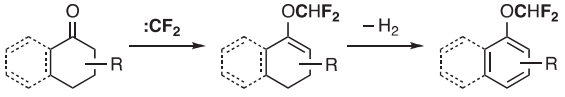
NHC-catalyzed generation of difluorocarbene from trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (TFDA) enables the synthesis of enol difluoromethyl ethers starting from cyclohexenones and tetralones. The resultant enol difluoromethyl ethers were successively dehydrogenated with DDQ to furnish aryl difluoromethyl ethers in good to high yield.

Aryl difluoromethyl ether units are often found in the structures of pharmaceuticals and agrochemicals.[1] One conventional synthesis of aryl difluoromethyl ethers is an electrophilic difluoromethylation of phenols.[2] Phenoxides are difluoromethylenated with difluorocarbene, generated by α-elimination of chlorodifluoromethane, to give aryl difluoromethyl ethers after protonation.[3,4] However, this process requires the preparation of the starting phenols and strongly basic conditions.[5]

Thus, we envisaged developing a new synthetic method for aryl difluoromethyl ethers starting from six-membered cyclic ketones. Difluoromethylation of the ketones would begin with treatment with difluorocarbene. The resultant six-membered enol difluoromethyl ethers might be readily dehydrogenated to construct a benzene ring, thus targeting aryl difluoromethyl ethers (Scheme 1). Commercial and synthetic availability of the cyclohexanone derivatives makes this a practical approach for the synthesis of aryl difluoromethyl ethers.

To this end, generation of difluorocarbene was studied because the reported methods in general require harsh conditions.[6] For example, the strongly basic conditions for the generation of difluorocarbene from chloro- and bromodifluoromethane[7] might cause an aldol-type condensation of ketones. Similarly, the high reaction temperature required to generate difluorocarbene from ClF_2CCO_2Na[8] might give rise to undesired difluorocyclopropanation of the resultant enol difluoromethyl ethers.[9]

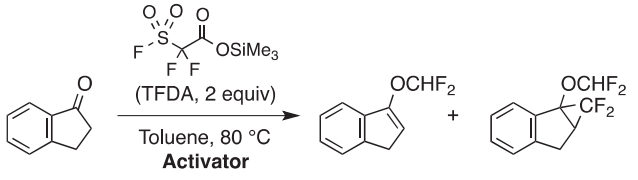
Trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (TFDA) reportedly releases difluorocarbene in the presence of a catalytic amount of fluoride ion, which attacks the Si atom of TFDA to promote its decomposition.[10] However, the treatment of indanones under the TFDA/F^- system did not give indenyl difluoromethyl ethers, but instead yielded 2-fluoronaphthols via overreaction, difluorocyclopropanation.[11] We then focused on using *N*-heterocyclic carbene (NHC)[12] as an activator of TFDA. We expected that NHC might allow the decomposition of TFDA under more controlled conditions.[13]



Scheme 1. Synthetic strategy for aryl difluoromethyl ethers.

The results of our research on the activators for TFDA are summarized in Table 1. Indan-1-one (**1a**) was treated with TFDA (2 equiv) in the presence of 1 to 10 mol % of the activators, and the yield of the desired enol ether **2a** was determined by ^{19}F NMR spectroscopy. Fluoride ion, the activator originally adopted by Dolbier and utilized typically at 105 °C,[10] gave only a 14% yield of **2a** at 80 °C (Entry 1). Other reagents such as DABCO[14] or pyridine *N*-oxide,[15] which can activate Si-containing reagents, were found to be ineffective (Entries 2 and

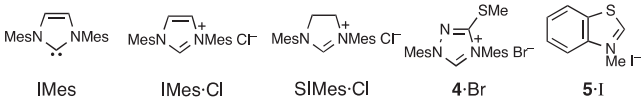
Table 1. NHC-catalyzed generation of difluorocarbene and selective formation of enol difluoromethyl ethers



1a **2a** **3**

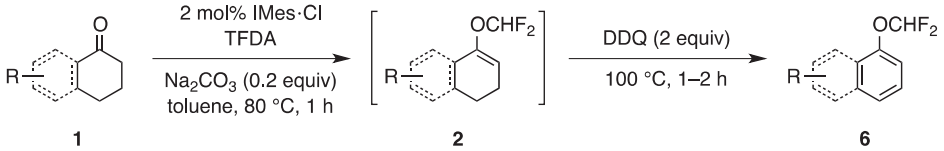
Entry	Activator	Time/h	**2a**/%[a]	**3**/%[a]
1	NaF (1 mol %)	4	14	—
2	DABCO (2 mol %)	1	40	<1
3	Pyridine *N*-oxide (10 mol %)	1	trace	—
4	IMes·Cl (1 mol %) Na_2CO_3 (10 mol %)	0.5	70	—
5	IMes·Cl (2 mol %) Na_2CO_3 (20 mol %)	0.5	74, 72[b]	trace
6[c]	IMes·Cl (2 mol %) Na_2CO_3 (20 mol %)	0.5	61	7
7	IMes·Cl (2 mol %) K_2CO_3 (20 mol %)	1	37	2
8	IMes·Cl (2 mol %) DBU (2 mol %)	0.5	15	—
9	IMes·Cl (2 mol %) *t*-BuOK (20 mol %)	0.5	20	—
10	IMes (1 mol %)	0.5	52	17
11	SIMes·Cl (2 mol %) Na_2CO_3 (20 mol %)	0.5	54	26
12	**4**·Br (2 mol %) Na_2CO_3 (20 mol %)	1	46	30
13	**5**·I (2 mol %) Na_2CO_3 (20 mol %)	1	34	17

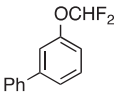
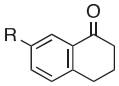
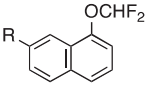
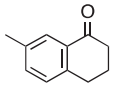
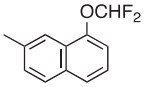
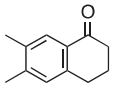
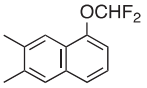
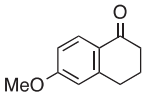
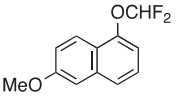
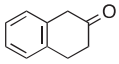
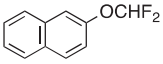
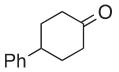
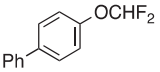
[a] ^{19}F NMR yield based on $(CF_3)_2C(p\text{-Tol})_2$. [b] Isolated yield. [c] TFDA 1.2 equiv.



IMes IMes·Cl SIMes·Cl **4**·Br **5**·I

Table 2. 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

[a]Yield in two steps. [b]The corresponding enol ether **2i** was obtained as a regioisomeric mixture (conjugated:nonconjugated = 88:12, ^{19}F NMR).

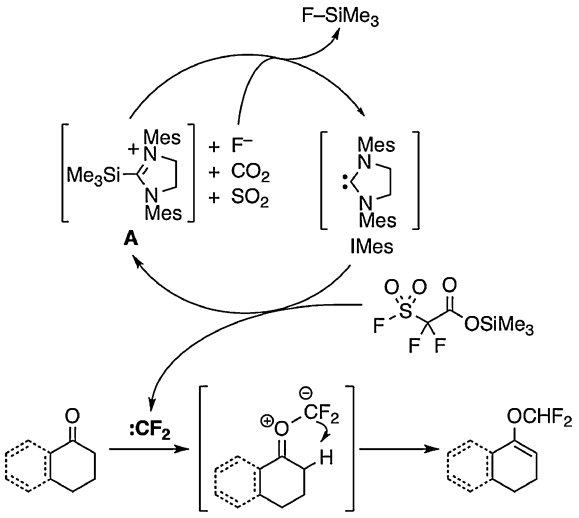
3). Note that the difluorocarbene generation proceeded smoothly with the use of NHC as a catalyst. 1,3-Dimesitylimidazolylidene (IMes), generated in situ from 1,3-dimesitylimidazolium chloride (IMes·Cl, 1 and 2 mol %) and sodium carbonate, gave **2a** in 70% and 74% yield, respectively (Entries 4 and 5). Reducing the loadings of TFDA from 2 to 1.2 equiv resulted in a diminished yield of **2a** (Entry 6). The use of potassium carbonate, DBU, and potassium *tert*-butoxide in place of sodium carbonate, gave inferior results (Entries 7–9). Note that isolated IMes gave a decreased yield of **2a** (52%) along with a 17% yield of **3** (Entry 10). This suggests that considerably rapid generation of difluorocarbene leads to undesired difluorocyclopropanation. Use of imidazolinium and related salts also resulted in the formation of considerable amounts of difluorocyclopropane **3**, making the reaction less selective (Entries 11–13).

Various aryl difluoromethyl ethers were successfully synthesized from six-membered ketones via the difluoromethylation–dehydrogenation sequence (Table 2).[16] Enol difluoromethyl ether **2b** was formed from 3-phenylcyclohexenone (**1b**) under 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**–**1h** afforded the corresponding naphthyl ethers **6f**–**6h** 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).[17]

Scheme 2 shows the proposed catalytic cycle for difluorocarbene generation and mechanism for the formation of enol difluoromethyl ethers. IMes, generated in situ from IMes·Cl and sodium carbonate, attacks the Si atom of TFDA. The decomposition of TFDA forms the key species, difluorocarbene,[18] accompanied by the formation of silylimidazolium salt **A**, CO_2, SO_2, and a fluoride ion. Salt **A** is desilylated by the released fluoride ion to regenerate free IMes. The generated difluorocarbene reacts with ketones to afford the corresponding enol ethers, presumably via oxycarbenium intermediates.[11b]

In summary, we have developed an NHC-catalyzed method for the generation of difluorocarbene from TFDA under mild conditions. Cyclohexenones and tetralones were transformed into enol difluoromethyl ethers, which were in turn dehydrogenated with DDQ to give aryl difluoromethyl ethers in good to high yield.[19]



Scheme 2. Proposed catalytic cycle for $:CF_2$ generation and mechanism for the formation of CHF_2 ethers.

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16 **Typical procedure**. To a toluene solution (0.4 mL) of IMes·Cl (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) as a colorless liquid.

17 Acetophenone afforded the corresponding α-difluoromethoxystyrene in 57% yield (^{19}F NMR) in the presence of 3 mol % of SIMes·Cl catalyst.

18 ^{19}F NMR analysis of crude mixtures suggested that tetrafluoroethylene is generated in the reaction medium.

19 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

