Difluoromethylation of *O*-, *S*-, *N*-, *C*-Nucleophiles Using Difluoromethyltri(*n*-butyl)ammonium Chloride as a New Difluorocarbene Source†

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Difluoromethyltri(*n*-butyl)ammonium chloride **1** was found to be an effective difluorocarbene reagent for *O*-, *S*-, *N*-, *C*-difluoromethylation under basic conditions. It is particularly remarkable that, when only 1.2 equivalent of reagent **1** was used, the difluoromethylated products were obtained in moderate to excellent yields.

Keywords difluorocarbene, CF_2H group, difluoromethylation, difluoromethyltri(*n*-butyl)ammonium chloride

Introduction

The growing demand for fluorine-containing organic compounds has led to many efforts devoted to the development of efficient fluorination or fluoroalkylation methods.[1] Among various fluorinated moieties, the difluoromethyl (CF_2H) group plays an important role in pharmaceuticals and agrochemicals, because the CF_2H moiety is known to be isosteric to a carbinol (CH_2OH) unit and it could act as a hydrogen donor through hydrogen bonding.[2] Therefore, it has attracted much attention from related chemists and biologists.[3] One of the typical methods of introduction of a difluoromethyl group is relying on difluorocarbene species.[4] Owing to the interaction of the lone pairs of its fluorine substitutes with the carbene center, difluorocarbene is the most stable carbene among dihalocarbenes, and could be captured by nucleophiles directly to give difluoromethylated products under certain conditions.[4] Because of the aforementioned ease in difluoromethylation using difluorocarbene, many precursors of difluorocarbene have been well investigated, such as HCF_2Cl,[5] $ClCF_2COONa$,[6] $ClCF_2COOMe$,[7] $FSO_2CF_2CO_2SiMe_3$ (TFDA),[8] Ph_3P/CF_2Br_2,[9] Zn/CF_2Br_2,[10] and $PhHgCF_3$ (Seyferth reagent).[11] However, methods based on these precursors suffer from several drawbacks such as harsh reaction conditions and the requirement of large excess of reagents, which hampers their wide application. Therefore, a more versatile and nontoxic difluorocarbene reagent is still desired.

As part of our continuing investigation of efficient difluoromethylation reaction, we have described several novel difluorocarbene reagents over the last five years.[12] In particular, $PhCOCF_2Cl$,[12b,12f] $PhSO_2CF_2Cl$[12c,12f] and $PhSO(NTs)CF_2H$[12a] were found to be good difluorocarbene sources for difluoromethylation. More recently, we have shown a remarkable chloride ion-catalyzed generation of difluorocarbene from $TMSCF_2Cl$,[12d] and an efficient sodium iodide-promoted generation of difluorocarbene from $TMSCF_3$.[12e] The latter two reagents were found to be capable of undergoing [2+1] cycloaddition reaction with alkynes and alkenes under non-basic conditions. It has been realized that the reactivity of difluorocarbene is significantly affected by the way that it is generated. In this paper, we wish to report our recent success in developing difluoromethyltri(*n*-butyl)ammonium chloride **1** as a novel difluorocarbene reagent for *O*-, *S*-, *N*-, *C*-difluoromethylations. Although the salt **1** and its analogues were previously prepared with simple synthetic procedures,[13] their application as difluorocarbene reagents has never been reported.

Results and discussion

At the onset of our studies, we examined the difluoromethylation of phenols **2**, by using biphenyl-4-ol **2c** as a model substrate. The results are summarized in Table 1. Sodium hydride (NaH) was used as a base to deprotonate both **2c** and reagent **1**. It turned out that the product yield was sensitive to the reaction solvent. Acetonitrile was found to be a more suitable solvent for this reaction than THF and DMF. It is worth mentioning that the reaction proceeded for 1 and 0.5 h, with temperature ranging from 5 ℃ to r.t.

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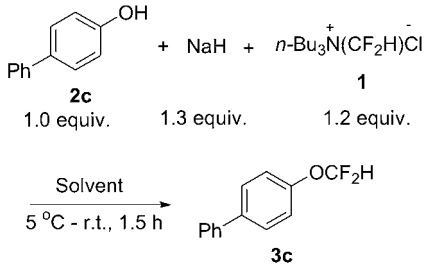
Table 1 Survey of reaction conditions

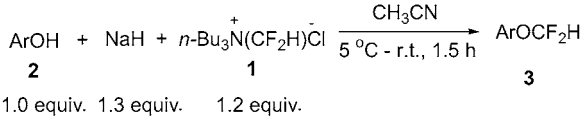


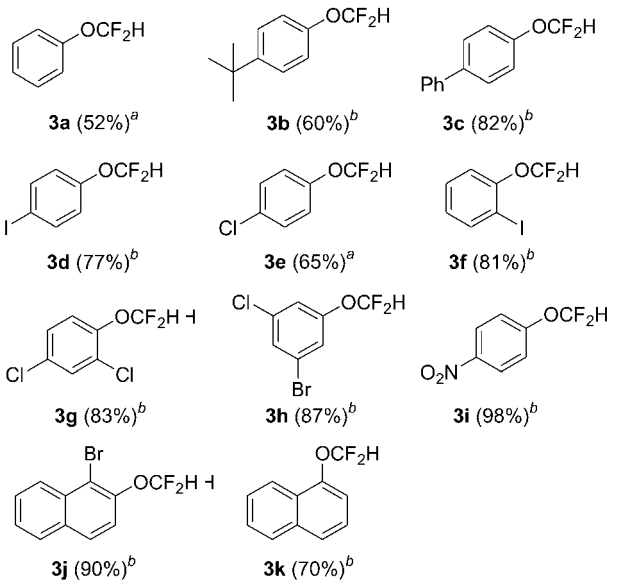
Entry	Solvent	Yielda/%
1	THF	50
2	CH_3CN	85
3	DMF	65

[a] Yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.

With the optimized reaction condition obtained in our examination, we next carefully studied the scope of the *O*-difluoromethylation reaction with reagent **1**. As shown in Table 2, it was found that a wide range of phenol derivatives were readily difluoromethylated in moderate to excellent yields. It was particularly remarkable that phenols with electron-withdrawing groups (**3i**) gave higher yield than electron-donating group (**3b**). In addition, the reaction system also proved to be useful for the difluoromethylation of naphthnols (**3j**, **3k**).

Table 2 *O*-Difluoromethylation with reagent **1**

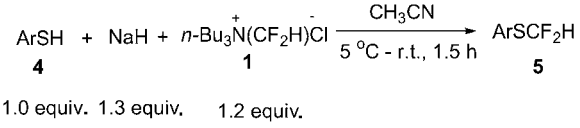


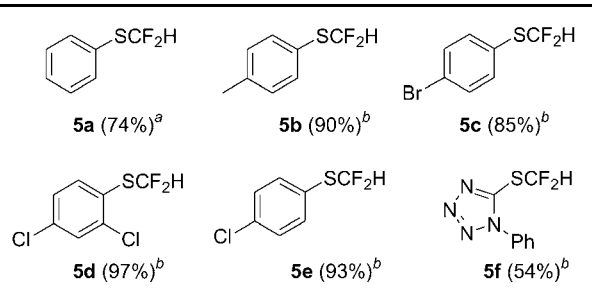


[a] Yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [b] Isolated yield.

Next, we explored the *S*- and *N*-difluoromethylation reaction with reagent **1** by using a similar reaction condition as shown in Table 2. The results in Table 3 show that a range of arylthiols are readily difluoromethylated to give difluoromethyl phenyl sulfide in good to excellent yields (**5a**—**5e**). It turned out that the reaction with heteroarylthiol **4f** could give corresponding product **5f** in moderate yield (54%). Furthermore, a wide range of imidazole derivatives could also be converted to the corresponding difluoromethylated products (Table 4).

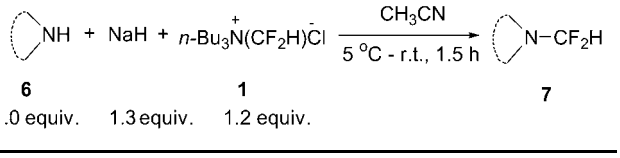
Table 3 *S*-Difluoromethylation with reagent **1**

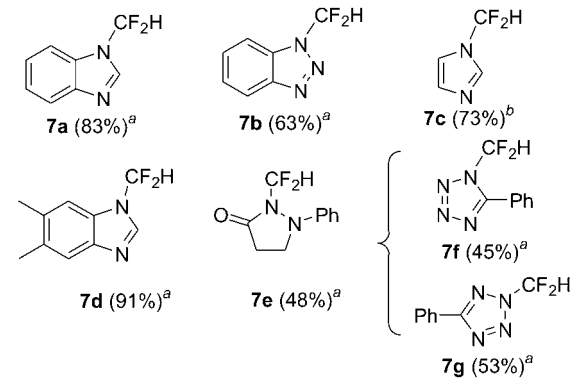




[a] Yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [b] Isolated yield.

Table 4 *N*-Difluoromethylation with reagent **1**





[a] Isolated yield. [b] Yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.

Encouraged by the above results, we continued our efforts towards applying reagent **1** in *C*-difluoromethylation of phenylacetylene derivatives (Table 5). It was found that *n*-butyllithium is a more suitable base than NaH for this reaction. THF was used as a solvent, and the reaction temperature was ranging from −78 ℃ to rt in 6 h. By using this reaction condition, the difluoromethyl substituted alkynes were obtained in satisfactory yields (Table 4).

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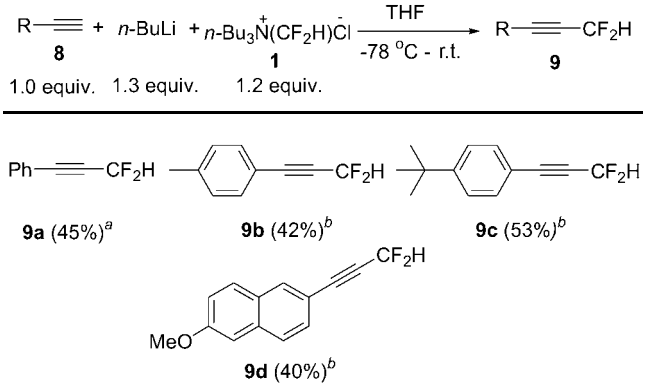
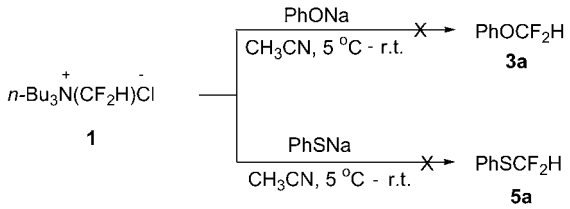
Table 5 *C*-Difluoromethylation with reagent **1**



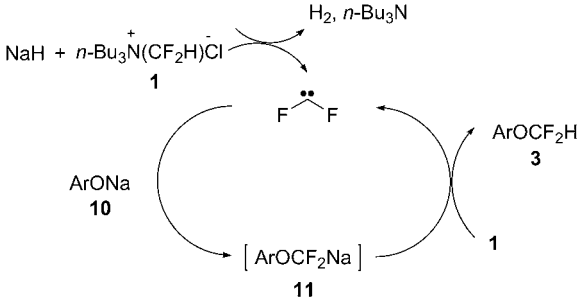
[a] Yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [b] Isolated yield.

To obtain more insights into the reaction mechanism of the current difluoromethylation with reagent **1**, we attempted the reactions between sodium phenolate (sodium thiophenolate) and **1** under the similar reaction conditions (Scheme 1). We found that both reactions did not give the difluoromethylated products **3a** and **5a**, which suggest that our difluoromethylation reactions with **1** do not likely proceed via an S_N2 mechanism. We propose that a difluorocarbene mechanism is involved in this reaction (as depicted in Scheme 2). The slightly excessive NaH (or other strong bases) deprotonates difluoromethyltri(*n*-butyl)ammonium chloride **1**, generating difluorocarbene species, which could be captured by sodium phenolate **10** to give intermediate **11**. Species **11** could act as a base to abstract the proton from **1** to give difluoromethylated ether product **3** and carbanion intermediate **11**, and the latter species goes to the next catalytic cycle (Scheme 2).

Scheme 1



Scheme 2



Conclusions

In conclusion, we have successfully developed a new method for the generation of difluorocarbene by using difluoromethyltri(*n*-butyl)ammonium chloride **1**. We investigated the synthetic applications of salt **1** in the difluoromethylation of *O*-, *S*-, *N*-, *C*-nucleophiles. It is noteworthy that, although only 1.2 equiv. of reagent **1** were used, the yields of difluoromethylated product were still high. Future efforts will focus on preparing difluoromethyltrialkylammonium salts in more environment-friendly ways.

Experimental

^1H NMR spectra were recorded in $CDCl_3$ on a BRUKER AM-300 spectrometer (300 MHz) with TMS as internal standard. ^{19}F NMR spectra were taken on a BRUKER AM-300 spectrometer (300 MHz) using $CFCl_3$ as external standard. IR spectra were obtained with a Nicolet AV-360 spectrometer. Mass spectra were obtained on a mass spectrometer. All the solvents were redistilled before use.

General procedure for difluoromethylation of *O*-, *S*-, *N*-nucleophiles with reagent 1

Under N_2 atmosphere, NaH (60 wt%, 26 mg, 0.65 mmol) was added to a solution of biphenyl-4-ol **2c** (0.85 mg, 0.5 mmol) in dry CH_3CN (3 mL) at 5 ℃. After stiring for 10 min, the reagent **1** (328 mg, 1.2 mmol) was added, then the mixture was gradually warmed to r.t. in 1.5 h. The reaction was quenched by adding 3 mL of water, followed by extraction with ether (15 mL) twice. The organic phase was washed successively with brine, and then dried over with anhydrous $MgSO_4$. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography using a mixture of ethyl acetate and petroleum ether as eluent to give product **3c**.

1-*tert*-Butyl-4-(difluoromethoxy)benzene (3b) Colorless liquid; ^1H NMR δ: 7.38 (d, J=8.9 Hz, 2H), 7.05 (d, J=8.9 Hz, 2H), 6.49 (t, J=74.1 Hz, 1H), 1.31 (s, 9H); ^{19}F NMR δ: −80.4 (d, J=74.4 Hz, 2F); MS (EI) *m/z* (%): 200 (M^+, 17.27), 185 (100.00). The characterization data were consistent with reference.[12c]

4-(Difluoromethoxy)biphenyl (3c) White solid; ^1H NMR δ: 7.55 (t, J=8.1 Hz, 4H), 7.44 (t, J=7.2 Hz, 2H), 7.39—7.30 (m, 1H), 7.19 (d, J=7.8 Hz, 2H), 6.54 (t, J=73.8 Hz, 1H); ^{19}F NMR δ: −80.2 (d, J=73.7 Hz, 2F); MS (EI) *m/z* (%): 220 (M^+, 75.93), 170 (100.00). The characterization data were consistent with reference.[12c]

1-(Difluoromethoxy)-4-iodobenzene (3d) Colorless liquid; ^1H NMR δ: 7.66 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 6.47 (t, J=73.8 Hz, 1H); ^{19}F NMR δ: −80.4 (d, J=73.7 Hz, 2F); MS (EI) *m/z* (%): 270 (M^+, 33.27), 58 (100.00). The characterization data were consistent with reference.[12c]

1-(Difluoromethoxy)-2-iodobenzene (3f) Colorless liquid; ^1H NMR δ: 7.85 (d, J=8.1 Hz, 1H), 7.35 (t,

J=7.8 Hz, 1H), 7.16 (d, J=8.4 Hz, 1H), 6.97 (t, J=73.5 Hz, 1H), 6.52 (t, J=73.2 Hz, 1H); ^{19}F NMR δ: −81.3 (d, J=73.0 Hz, 2F); MS (EI) *m/z* (%): 270 (M^+, 100.00), 220 (70.73), 63 (11.55). The characterization data were consistent with reference.[12c]

2,4-Dichloro-1-(difluoromethoxy)benzene (3g) Colorless liquid; ^{1}H NMR δ: 7.48—7.42 (m, 1H), 7.29—7.15 (m, 2H), 6.52 (t, J=72.7 Hz, 1H); ^{19}F NMR δ: −82.1 (d, J=73.4 Hz, 2F); MS (EI) *m/z* (%): 212 (M^+, 32.96), 162 (100.00). The characterization data were consistent with reference.[12c]

1-Bromo-3-chloro-5-(difluoromethoxy)benzene (3h) Colorless liquid; ^{1}H NMR δ: 7.38 (s, 1H), 7.22 (s, 1H), 7.10 (s, 1H), 6.50 (t, J=72.7 Hz, 1H); ^{19}F NMR δ: −81.7 (d, J=72.8 Hz, 2F); MS (EI) *m/z* (%): 256 (M^+, 52.78), 208 (100.00), 206 (79.56). The characterization data were consistent with reference.[12c]

1-(Difluoromethoxy)-4-nitrobenzene (3i) Light yellow liquid; ^{1}H NMR δ: 8.28 (d, J=9.0 Hz, 2H), 7.26 (d, J=9.0 Hz, 2H), 6.64 (t, J=72.1 Hz, 1H); ^{19}F NMR δ: −81.8 (d, J=72.3 Hz, 2F); MS (EI) *m/z* (%): 189 (100.00), 109 (91.91). The characterization data were consistent with reference.[12c]

1-Bromo-2-(difluoromethoxy)naphthalene (3j) White solid; ^{1}H NMR δ: 8.28 (d, J=8.4 Hz, 1H), 7.88—7.80 (m, 2H), 7.68—7.49 (m, 2H), 7.43—7.37 (m, 1H), 6.63 (t, J=73.7 Hz, 1H); ^{19}F NMR δ: −80.1 (d, J=73.8 Hz, 2F); MS (EI) *m/z* (%): 272 (M^+, 78.09), 222 (100.00). The characterization data were consistent with reference.[12f]

1-(Difluoromethoxy)naphthalene (3k) Colorless liquid; ^{1}H NMR δ: 8.24—8.17 (m, 1H), 7.89—7.82 (m, 1H), 7.70 (d, J=8.4 Hz, 1H), 7.60—7.39 (m, 3H), 7.22—7.15 (m, 1H), 6.66 (t, J=74.1 Hz, 1H); ^{19}F NMR δ: −79.1 (d, J=74.0 Hz, 2F); MS (EI) *m/z* (%): 194 (M^+, 72.21), 144 (100.00), 115 (93.41). The characterization data were consistent with reference.[12c]

(Difluoromethyl)(*p*-tolyl)sulfane (5b) Colorless liquid; ^{1}H NMR δ: 7.47 (d, J=8.4 Hz, 2H), 7.20 (d, J=7.8 Hz, 2H), 6.78 (t, J=57.0 Hz, 1H), 2.37 (s, 3H); ^{19}F NMR δ: −91.6 (d, J=56.8 Hz, 2F); MS (EI) *m/z* (%): 174 (M^+, 78.51), 108 (100.00), 124 (62.13). The characterization data were consistent with reference.[14]

(4-Bromophenyl)(difluoromethyl)sulfane (5c) Colorless liquid; ^{1}H NMR δ: 7.58—7.49 (m, 2H), 7.49—7.41 (m, 2H), 7.00 (t, J=56.4 Hz, 1H); ^{19}F NMR δ: −91.6 (d, J=56.7 Hz, 2F); MS (EI) *m/z* (%): 238 (M^+, 62.83), 108 (100.00), 240 (62.93), 188 (50.99). The characterization data were consistent with reference.[15]

(2,4-Dichlorophenyl)(difluoromethyl)sulfane (5d) Colorless liquid; ^{1}H NMR δ: 7.63—7.52 (m, 2H), 7.32—7.25 (m, 1H), 6.87 (t, J=57.3 Hz, 1H); ^{19}F NMR δ: −91.4 (d, J=56.9 Hz, 2F); ^{13}C NMR δ: 139.6, 137.6, 136.9, 130.3, 127.9, 124.3, 119.8 (t, J=276.2 Hz); IR (film) ν: 1569, 1549, 1456, 1371, 1298, 1077, 1033, 871, 816, 755, 557 cm^{-1}; MS (EI) *m/z* (%): 228 (M^+, 73.70), 178 (100.00); HRMS (EI) calcd for $C_7H_4Cl_2F_2O_2S$ 227.9379, found 227.9381. Anal. calcd for $C_7H_4Cl_2F_2O_2S$: C 36.70, H 1.76; found C 36.45, H 1.79.

(4-Chlorophenyl)(difluoromethyl)sulfane (5e) Colorless liquid; ^{1}H NMR δ: 7.52 (d, J=8.4 Hz, 2H), 7.37 (t, J=8.4 Hz, 2H), 6.81 (d, J=56.7 Hz, 1H); ^{19}F NMR δ: −91.7 (d, J=57.0 Hz, 2F); MS (EI) *m/z* (%): 196 (M^+, 100.00), 181 (72.76), 195 (47.50). The characterization data were consistent with reference.[16]

5-(Difluoromethylthio)-1-phenyl-1*H*-tetrazole (5f) Colorless liquid; ^{1}H NMR δ: 7.15—6.74 (m, 6H); ^{19}F NMR δ: −91.9 (d, J=55.8 Hz, 2F); MS (EI) *m/z* (%): 217 (M^+, 40.04), 167 (100.00), 108 (30.77). The characterization data were consistent with reference.[12a]

1-(Difluoromethyl)-1*H*-benzo[*d*]imidazole (7a) Light yellow liquid; ^{1}H NMR δ: 8.14 (s, 1H), 7.90—7.80 (m, 1H), 7.67—7.57 (m, 1H), 7.56—7.11 (m, 3H); ^{19}F NMR δ: −92.9 (d, J=60.1 Hz, 2F); MS (EI) *m/z* (%): 168 (M^+, 100.00), 118 (62.21). The characterization data were consistent with reference.[12a]

1-(Difluoromethyl)-1*H*-benzo[*d*][1,2,3]triazole (7b) Light yellow liquid; ^{1}H NMR δ: 8.18—8.11 (m, 1H), 8.06—7.60 (m, 3H), 7.55—7.47 (m, 1H); ^{19}F NMR δ: −96.4 (d, J=59.0 Hz, 2F); MS (ESI) *m/z*: 170.2 ($M+H^+$). The characterization data were consistent with reference.[12a]

1-(Difluoromethyl)-5,6-dimethyl-1*H*-benzo[*d*]-imidazole (7d) Colorless liquid; ^{1}H NMR δ: 8.00 (s, 1H), 7.59 (s, 1H), 7.51—7.00 (m, 2H), 2.40 (s, 3H), 2.38 (s, 3H); ^{19}F NMR δ: −93.5 (d, J=61.1 Hz, 2F); MS (EI) *m/z* (%): 196 (M^+, 100.00), 181 (72.76), 195 (47.50). The characterization data were consistent with reference.[12a]

2-(Difluoromethyl)-1-phenylpyrazolidin-3-one (7e) Light yellow liquid; ^{1}H NMR δ: 7.39—6.81 (m, 6H), 3.83 (t, J=10.2 Hz, 2H), 3.02 (t, J=9.6 Hz, 2H); ^{19}F NMR δ: −87.1 (d, J=72.4 Hz, 2F); MS (EI) *m/z* (%): 169 (M^+, 34.72), 91 (100.00), 64 (23.27). The characterization data were consistent with reference.[12a]

1-(Difluoromethyl)-5-phenyl-1*H*-tetrazole (7f) Light yellow liquid; ^{1}H NMR δ: 7.93—7.79 (m, 2H), 7.72—7.45 (m, 4H); ^{19}F NMR δ: −94.8 (d, J=57.8 Hz, 2F); MS (EI) *m/z* (%): 196 (M^+, 46.70), 118 (100.00), 89 (29.16). The characterization data were consistent with reference.[12a]

2-(Difluoromethyl)-5-phenyl-2*H*-tetrazole (7g) Light yellow liquid; ^{1}H NMR δ: 8.28—8.17 (m, 2H), 7.90—7.46 (m, 4H); ^{19}F NMR δ: −98.2 (d, J=57.5 Hz, 2F); MS (EI) *m/z* (%): 196 (M^+, 4.66), 168 (100.00), 89 (67.24). The characterization data were consistent with reference.[12a]

General procedure for difluoromethylation of *C*-nucleophiles with reagent 1

Under N_2 atmosphere, the compound **8b** (116 mg, 1.0 mmol) was stirred in dry THF (3 mL) at 0 ℃, then added butyllithium (2.5 mol/L, 0.52 mL, 1.3 mmol) using a syringe. After stirring for 30 min, reagent **1** (328 mg, 1.2 mmol) was added at −78 ℃, then the mixture was gradually warmed to r.t. in 8 h. The reaction was

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quenched by adding 3 mL of water. Then NH_3 (25 wt%, 1 mL), $AgNO_3$ (338 mg, 2.0 mmol) and Et_2O (4 mL) were added to the solution. After stirring for 1 h, the mixture was extracted with ether (20 mL). The organic phase was washed successively with brine, and then dried over with anhydrous $MgSO_4$. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography using a mixture of ethyl acetate and petroleum ether as eluent to give product **9b**.

1-(3,3-Difluoroprop-1-ynyl)-4-methylbenzene (9b) Colorless liquid; ^{1}H NMR δ: 7.41 (d, J=8.1 Hz, 2H), 7.17 (t, J=7.5 Hz, 2H), 6.41 (d, J=55.2 Hz, 1H), 2.37 (s, 3H); ^{19}F NMR δ: −104.9 (d, J=54.7 Hz, 2F); MS (EI) *m/z* (%): 166 (M^+, 100.00), 115 (74.28), 151 (40.44). The characterization data were consistent with reference.[12a]

1-*tert*-Butyl-4-(3,3-difluoroprop-1-ynyl)benzene (9c) Colorless liquid; ^{1}H NMR δ: 7.51—7.31 (m, 4H), 6.41 (t, J=54.9 Hz, 1H), 1.31 (s, 9H); ^{19}F NMR δ: −104.8 (d, J=56.1 Hz, 2F); ^{13}C NMR δ: 153.7, 132.0 (t, J=3.0 Hz), 125.6, 125.3, 104.4 (t, J=230.2 Hz), 88.8 (t, J=7.2 Hz), 79.3 (t, J=33.5 Hz), 35.0, 31.1; IR (film) ν: 3305, 2965, 2907, 2253, 2226, 1667, 1606, 1505, 1463, 1375, 1267, 1087, 1039, 974, 836, 773, 672, 565 cm^{-1}; MS (EI) *m/z* (%): 208 (M^+, 23.70), 193 (100.00), 165 (30.81); HRMS (EI) calcd for $C_{13}H_{14}F_2$ 208.1064, found 208.1065.

2-(3,3-Difluoroprop-1-ynyl)-6-methoxynaphthalene (9d) White solid; m.p. 73 ℃; ^{1}H NMR δ: 7.99 (s, 1H), 7.77—7.65 (m, 2H), 7.49 (d, J=8.4 Hz, 1H), 7.23—7.07 (m, 2H), 6.46 (d, J=55.5 Hz, 1H), 3.93 (s, 3H); ^{19}F NMR δ: −104.7 (d, J=54.4 Hz, 2F); ^{13}C NMR δ: 159.1, 135.1, 132.8 (t, J=2.8 Hz), 129.6, 128.5 (t, J=2.2 Hz), 128.2, 127.1, 119.9, 114.6 (t, J=3.3 Hz), 105.9, 104.4 (t, J=230.3 Hz), 89.2 (t, J=7.1 Hz), 79.5 (t, J=33.5 Hz), 55.4; IR (film) ν: 2963, 2937, 2847, 2271, 2229, 1626, 1600, 1497, 1486, 1439, 1379, 1272, 1255, 1201, 1165, 1126, 1090, 1025, 954, 915, 854, 824, 747, 665, 477 cm^{-1}; MS (EI) *m/z* (%): 232 (M^+, 100.00), 189 (48.68); HRMS (EI) calcd for $C_{14}H_{10}F_2O$ 232.0700, found 230.0703.

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