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Original article

Direct *N*-*gem*-difluorocyclopropylation of nitro-heterocycles by utilizing *gem*-difluorocyclopropyl tosylate

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ABSTRACT

We have developed an efficient method to achieve *N*-*gem*-difluorocyclopropylation of *N*-heterocycles with the use of *gem*-difluorocyclopropyl tosylate as a building block under mild conditions. *gem*-Difluorocyclopropyl tosylates could be easily prepared on a large scale and exhibit great stability.

1. Introduction

The sharp increase in the number of fluorine-containing pharmaceuticals and agrochemicals clearly demonstrates the exceptional importance of fluorinated compounds [1–5]. As one of the important classes of fluorinated molecules, *gem*-difluorocyclopropanes have attracted much attention due to the unique biological activities of the *gem*-difluorocyclopropyl group [6–16]. As *N*-heterocycles are valuable subunits of many pharmacologically active compounds, the incorporation of *gem*-difluorocyclopropyl moieties into *N*-heterocycles might significantly improve the bioactivities of *N*-heterocycles [8]. Therefore, the synthesis of *gem*-difluorocyclopropyl group substituted *N*-heterocylces continues to be an important goal of organic chemists [17,18]. Traditional method for the preparation of *gem*-difluorocyclopropanes is [2 + 1] cycloaddition of difluorocarbene with alkenes [15–20]. Another largely unexplored approach involves the use of building blocks [12,21–23]. The second approach is very promising because it can construct unique molecules which cannot be easily obtained by [2 + 1] cycloaddition. As a part of our continuing interest in *gem*-difluorocyclopropanes chemistry [24–28], we described the design and synthesis of *gem*-difluorocyclopropane building blocks and the application of them to *N*-*gem*-difluorocyclopropylation of *N*-heterocycles.

The reported *gem*-difluorocyclopropane building blocks include silyl, stannyl, vinyl, and boron substituted *gem*-difluorocyclopropanes (Scheme 1) [12,21–23]. Silyl substituted building blocks could act as anion equivalents in the presence of a catalytic amount of fluoride [21]. Stannyl and vinyl groups are valuable functionalities for transition-metal-catalyzed transformations such as alkene metathesis [22,23]. The homologation of boron substituted *gem*-difluorocyclopropanes with lithium carbenoids and the subsequent oxidation was able to afford a variety of *gem*-difluorocyclopropanes [12]. In this study, we found that *gem*-difluorocyclopropyl tosylate could act as a cation equivalent to achieve *N*-*gem*-difluorocyclopropylation of nitro-heterocylces.

2. Experimental

^{1}H NMR spectra were recorded on a Bruker AM 300 (300 MHz) spectrometer with TMS as an internal standard (negative for upfield). ^{19}F NMR spectra were recorded on a Bruker AM 300 (282 MHz) with $CFCl_3$ as an external standard (negative for upfield). ^{13}C NMR spectra were recorded on a Bruker AM 400 (100 MHz) spectrometer with $CDCl_3$ as an internal standard (negative for upfield). MS and HRMS were recorded on a Hewlett–Packard HP-5989A spectrometer and a Finnigan MAT-8483 mass spectrometer. Elementary analyses were obtained on a Perkin–Elmer 2400 Series II Elemental Analyzer. Infrared spectra were measured with a Perkin–Elmer 983 spectrometer. TLC analysis was performed on silica gel plates, column chromatography over silica gel (mesh 300–400). All solvents for reactions were dried by standard methods.

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Scheme 1. *gem*-Difluorocyclopropane building blocks.

2.1. General procedure for preparation of vinyl sulfonic esters (**1a–c**)

Into anhydrous THF (110 mL), was added *n*-BuLi (2.5 mol/L, 40 mL) under N_2, and the mixture was stirred at 35 °C for 4 h. After being cooled to −78 °C, the solution of sulfonyl chloride (80 mmol) in anhydrous THF (40 mL) was added dropwise in 0.5 h. The resulting mixture was stirred at −78 °C for 1 h and warmed to room temperature and stirred for another 1 h. The reaction system was poured into water (150 mL) and extracted with ether (80 mL × 4). The organic phase was wash with brine, dried over $MgSO_4$, then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give the products **1a–c**.

Vinyl 4-methylbenzenesulfonate **1a**: colorless oil (48%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.78 (d, 2H, J = 8.8 Hz), 7.35 (d, 2H, J = 8.8 Hz), 6.68 (dd, 1H, J = 13.4 Hz, J = 5.8 Hz), 4.89 (dt, 1H, J = 13.4 Hz, J = 2.4 Hz), 4.69 (dt, 1H, J = 5.8 Hz, J = 2.4 Hz) 2.45 (s, 3H).

Vinyl 4-nitrobenzenesulfonate **1b**: colorless oil (46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (d, 2H, J = 8.7 Hz), 8.13 (d, 2H, J = 8.7 Hz), 6.66 (dd, 1H, J = 13.3 Hz, J = 5.9 Hz), 4.97 (dd, 1H, J = 13.3 Hz, J = 2.7 Hz), 4.81 (dd, 1H, J = 5.9 Hz, J = 2.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 141.4, 141.2, 129.4, 124.5, 104.1. IR (cm^{-1}): 3105, 3088, 3067, 1638, 1608, 1527, 1404, 1381, 1350, 1306, 1192, 1104, 1086. EI-MS (m/z): 186 (100.00), 165 (10.90), 122 (73.44), 92 (19.41), 76 (33.05), 75 (27.08), 74 (10.26), 50 (22.33). Anal. Calcd. for $C_8H_7NO_5S$: C, 41.92; H, 3.08; N, 6.11. Found: C, 41.90; H, 3.16; N, 6.01.

Vinyl benzenesulfonate **1c**: colorless oil (45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, 2H, J = 7.3 Hz), 7.69 (t, 1H, J = 7.3 Hz), 7.57 (t, 2H, J = 7.3 Hz), 6.62 (dd, 1H, J = 13.7 Hz, J = 6.0 Hz), 4.90 (dd, 1H, J = 13.7 Hz, J = 2.3 Hz), 4.70 (dd, 1H, J = 6.0 Hz, J = 2.3 Hz).

2.2. General procedure for preparation of gem-difluorocyclopropyl sulfonic esters (**2a–c**)

Into the mixture of vinyl sulfonic esters **1a–c** (50 mmol) and NaF (210 mg, 10 mol%) in xylene (5 mL) at 120 °C was added TFDA (75 g, 6 equiv.) dropwise in 2 h. The resulting mixture was then stirred for 2 h at the same temperature. After being cooled to room temperature, the solution was concentrated to remove the solvent. The residue was purified by chromatography on a silica gel to give **2a–c**.

2,2-Difluorocyclopropyl 4′-methylbenzenesulfonate **2a**: colorless oil (78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (dd, 2H, J = 7.7 Hz, J = 2.8 Hz), 7.38 (d, 2H, J = 7.7 Hz), 4.18–4.29 (m, 1H), 2.47 (d, 3H, J = 2.8 Hz), 1.54–1.80 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −132.5 (dm, 1F, J = 170 Hz), −144.9 (ddd, 1F, J = 170 Hz, J = 16.0 Hz, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 132.0, 130.0, 128.2, 107.6 (t, J = 283.1 Hz), 54.5 (dd, J = 16.0 Hz, J = 9.0 Hz), 21.6, 17.9 (t, J = 6.8 Hz). IR (cm^{-1}): 3067, 1930, 1597, 1474, 1368, 1311, 1233, 1196, 1120, 1092, 1018. EI-MS (m/z): 157 (3.72), 156 (13.08), 155 (56.64), 92 (12.83), 91 (100.00), 89 (6.27), 65 (22.80), 63 (5.12). Anal. Calcd. for $C_{10}H_{10}F_2O_3S$: C, 48.38; H, 4.06. Found: C, 48.45; H, 4.21.

2,2-Difluorocyclopropyl 4′-nitrobenzenesulfonate **2b**: colorless solid (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (d, 2H, J = 8.7 Hz), 8.16 (d, 2H, J = 8.7 Hz), 4.34–4.46 (m, 1H), 1.66–1.93 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −132.0 (dm, 1F, J = 171.2 Hz), −144.9 (ddd, 1F, J = 171.2 Hz, J = 14.4 Hz, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 140.8, 129.7, 124.6, 107.3 (t, J = 290.5 Hz), 55.1 (dd, J = 16.3 Hz, J = 9.6 Hz), 18.2 (t, J = 11.4 Hz). IR (cm^{-1}): 3111, 3072, 3023, 2876, 1610, 1539, 1473, 1376, 1349, 1305, 1246, 1202, 1104, 1088, 988. EI-MS (m/z): 187 (31.99), 186 (100.00), 122 (77.93), 77 (58.04), 76 (62.85), 75 (42.23), 65 (42.73), 50 (36.54); Anal. Calcd. for $C_9H_7F_2NO_5S$: C, 38.71; H, 2.53; N, 5.02. Found: C, 38.66; H, 2.70; N, 5.04.

2,2-Difluorocyclopropyl benzenesulfonate **2c**: colorless oil (75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 2H, J = 7.8 Hz), 7.72 (t, 1H, J = 7.8 Hz), 7.60 (t, 2H, J = 7.8 Hz), 4.20–4.33 (m, 1H), 1.55–1.82 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −132.3 (dm, 1F, J = 171.2 Hz), −144.7 (ddd, 1F, J = 171.2 Hz, J = 15.4 Hz, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 134.6, 129.5, 128.3, 107.5 (t, J = 291.6 Hz), 54.6 (dd, J = 16.2 Hz, J = 9.6 Hz), 18.0 (t, J = 11.0 Hz). IR (cm^{-1}): 3108, 3068, 1586, 1477, 1450, 1378, 1310, 1238, 1192, 1120, 1093, 1010, 986. EI-MS (m/z): 142 (16.28), 141 (54.31), 94 (3.74), 78 (22.45), 77 (100.00), 65 (6.23), 51 (26.12), 50 (7.82); Anal. Calcd. for $C_9H_8F_2O_3S$: C, 46.15; H, 3.44. Found: C, 46.55; H, 3.69.

2.3. General procedure for the N-gem-difluorocyclopropylation of heterocycles (**4a–g**)

Into the suspension of sodium hydride (1 mmol), in anhydrous HMPA (1 mL), under N_2 was added a solution of heterocycles **3a–g** (1 mmol) in anhydrous HMPA (1 mL). The mixture was stirred for 1 h at room temperature. Then the solution of **2a** (1.1 mmol) in anhydrous HMPA (1 mL) was added dropwise in 15 min. The reaction system was stirred until the heterocycle was consumed completely, as detected by TLC. The reaction mixture was poured into water (20 mL) and extracted with ether (15 mL × 3). The organic phase was washed with water (20 mL), dried over $Mg SO_4$, then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give the products **4a–g**.

1-(2,2-Difluorocyclopropyl)-indole **4a**: colorless oil (57%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.62 (d, 1H, J = 7.3 Hz), 7.41 (d, 1H, J = 7.3 Hz), 7.25 (t, 1H, J = 7.3 Hz), 7.15 (t, 1H, J = 7.3 Hz), 7.08 (s, 1H), 6.51 (s, 1H), 3.73–3.91 (m, 1H), 1.81–2.17 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −130.0 (dm, 1F, J = 166.0 Hz), −141.6 (ddd, 1F, J = 166.0 Hz, J = 14.4 Hz, J = 5.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 128.8, 127.4, 122.4, 121.2, 120.5, 110.4 (t, J = 284.2 Hz), 109.9, 102.9, 34.3 (dd, J = 16.6 Hz, J = 9.3 Hz), 18.5 (t, J = 10.7 Hz). IR (cm^{-1}): 3106, 3055, 3018, 2917, 1613, 1517, 1463, 1311, 1232, 1206, 1021, 969. EI-MS (m/z): 193 (M^+, 100.00), 192 (70.43), 172 (48.31), 143 (56.55), 142 (20.51), 129 (16.60), 115 (17.78), 89 (19.52). Anal. Calcd. for $C_{11}H_9F_2N$: C, 68.39; H, 4.70; N, 7.25. Found: C, 68.21; H, 4.54; N, 7.23.

1-(2,2-Difluorocyclopropyl)-2-methyl-indole **4b**: colorless oil (69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, 1H, J = 6.9 Hz), 7.32 (d, 1H, J = 7.3 Hz), 7.01–7.25 (m, 2H), 6.27 (s, 1H), 3.60–3.73 (m, 1H), 2.46 (s, 3H), 1.91–2.28 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −130.8 (dm, 1F, J = 160.9 Hz), −141.6 (ddd, 1F, J = 160.9 Hz, J = 13.4 Hz, J = 5.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 137.4, 128.7, 121.2, 120.2, 120.1, 110.4 (t, J = 282.9 Hz), 109.8, 101.8, 33.1 (dd, J = 16.7 Hz, J = 9.7 Hz), 18.5 (t, J = 10.6 Hz), 12.78. IR (cm^{-1}): 3101, 3017, 2994, 2955, 1608, 1557, 1479, 1462, 1393, 1323, 1312, 1241, 1220, 1027, 965. EI-MS (m/z): 207 (M^+, 100.00), 206 (46.43), 192 (61.53), 186 (49.25), 172 (37.69), 157 (29.01), 156

(45.29), 115 (46.46). Anal. Calcd. for $C_{12}H_{11}F_2N$: C, 69.55; H, 5.35; N, 6.76. Found: C, 69.61; H, 5.47; N, 6.64.

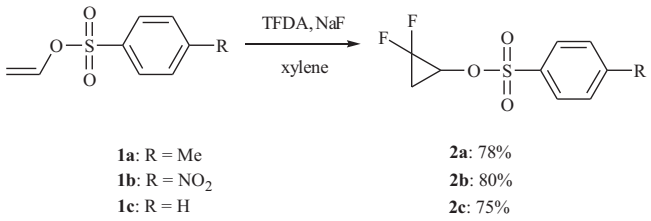
1-(2,2-Difluorocyclopropyl)-3-aceyl-indole **4c**: colorless oil (63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (m, 1H), 7.72 (s, 1H), 7.28–7.45 (m, 3H), 3.84–3.99 (m, 1H), 2.50 (s, 3H), 2.12–2.31 (m, 1H), 1.91–2.01 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −129.8 (dm, 1F, J = 162.9 Hz), −140.9 (ddd, 1F, J = 162.9 Hz, J = 14.5 Hz, J = 6.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.09, 134.2, 126.1, 124.0, 124.0 123.2, 122.8, 118.3, 110.1, 109.5 (t, J = 286.3 Hz), 34.4 (dd, J = 16.6 Hz, J = 9.7 Hz), 27.6, 18.5 (t, J = 11.1 Hz). IR (cm^{-1}): 3133, 3106, 3005, 1639, 1533, 1475, 1460, 1381, 1306, 1229, 1216, 1008, 915. MS (EI) m/z: 235 (M^+, 59.76), 200 (48.11), 192 (74.05), 172 (100.00), 170 (91.98), 115 (38.60), 87 (55.43), 43 (40.09). Anal. Calcd. for $C_{13}H_{11}F_2NO$: C, 66.38; H, 4.71; N, 5.95. Found: C, 66.53; H, 4.90; N, 5.94.

1-(2,2-Difluorocyclopropyl)benzimidazole **4d**: colorless oil (55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.83 (dm, 1H, J = 5.9 Hz), 7.48 (d, 1H, J = 6.8 Hz), 7.29–7.48 (m, 2H), 3.85–4.00 (m, 1H), 2.15–2.35 (m, 1H), 1.93–2.10 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −130.9 (dm, 1F, J = 161.8 Hz), −140.9 (dm, 1F, J = 161.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 142.6, 134.2, 123.8, 122.8, 120.4, 110.0, 109.5 (t, J = 286.9 Hz), 32.3 (dd, J = 16.6 Hz, J = 10.0 Hz), 18.2 (t, J = 11.0 Hz). IR (cm^{-1}): 3093, 3019, 1615, 1497, 1458, 1369, 1315, 1226, 1105, 1023. MS (EI) m/z: 194 (M^+, 100.00), 193 (57.84), 167 (60.84), 144 (36.17), 103 (37.52), 77 (21.50), 76 (48.14), 50 (20.60). Anal. Calcd. for $C_{10}H_8F_2N_2$: C, 61.85; H, 4.15; N, 14.43. Found: C, 61.84; H, 4.44; N, 14.31.

1-(2,2-Difluorocyclopropyl) -6-nitro-benzimidazole **4e**: white solid (54%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–8.79 (m, 4H), 3.95–4.12 (m, 1H), 2.27–2.49 (m, 1H), 1.99–2.18 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −130.3 (dm, 1F, J = 162.9 Hz), −140.9 (dm, 1F, J = 162.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 137.4, 128.7, 121.1, 120.2, 120.0, 110.3 (t, J = 286.3 Hz), 109.7, 33.0 (dd, J = 16.8 Hz, J = 9.4 Hz), 18.5 (t, J = 11.0 Hz). IR (cm^{-1}): 3101, 3014, 1619, 1593, 1517, 1482, 1345, 1308, 1226, 1203, 1063, 1023, 966. MS (EI) m/z: 239 (M^+, 94.16), 222 (100.00), 193 (43.36), 192 (51.91), 173 (39.64), 102 (28.53), 75 (53.67), 74 (26.49). Anal. Calcd. for $C_{10}H_7F_2N_3O_2$: C, 50.22; H, 2.95; N, 17.57. Found: C, 49.96; H, 3.22; N, 17.57.

N-(2,2-Difluorocyclopropyl)phthalimide **4f**: white solid (65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.92 (m, 2H), 7.72–7.79 (m, 2H), 3.22–3.32 (m, 1H), 2.02–2.24(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −134.0 (dm, 1F, J = 163.3 Hz), −142.7 (dm, 1F, J = 163.3 Hz).

1-(2,2-Difluorocyclopropyl)benzotriazole **4g**: colorless oil (60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, 1H, J = 8.1 Hz), 7.63 (d, 1H, J = 8.1 Hz), 7.56 (dd, 1H, J = 8.1 Hz, J = 6.9 Hz), 7.41 (dd, 1H, J = 8.1 Hz, J = 6.9 Hz), 4.22–4.39 (m, 1H), 2.58–2.77 (m, 1H), 2.33–2.52 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −131.2 (dm, 1F, J = 162.8 Hz), −141.9 (ddd, 1F, J = 162.8 Hz, J = 13.5 Hz, J = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 133.6, 127.8, 124.1, 119.8, 108.9, 108.5 (t, J = 285.6 Hz), 34.7 (dd, J = 16.9 Hz, J = 10.3 Hz), 18.5 (t, J = 11.2 Hz). IR (cm^{-1}): 3109, 3029, 1614, 1495, 1478, 1454, 1316, 1233, 1178, 1099, 1021, 1008, 978. EI-MS (m/z): 166 (35.83), 148 (28.73), 140 (23.56), 103 (73.87), 173 (39.64), 91 (24.60), 76 (100.00), 50 (32.81). Anal. Cald. for $C_9H_7F_2N_3$: C, 55.39; H, 3.62; N, 21.53. Found: C, 55.22; H, 3.69; N, 21.45.

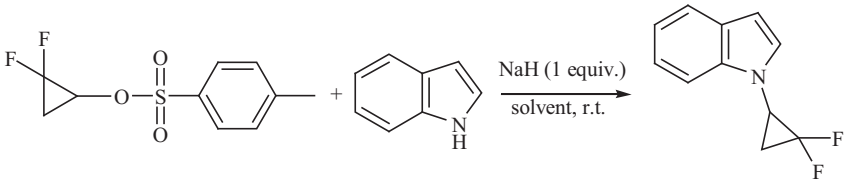


Scheme 2. The synthesis of *gem*-difluorocyclopropyl sulfonic esters.

3. Results and discussion

As tosylate was an excellent leaving group, we assumed *gem*-difluorocyclopropyl sulfonic esters could be used for direct *N*-difluorocyclopylation *via* simple nucleophilic substitution. So the initial effort was directed towards the synthesis of these building blocks. Fortunately, *gem*-difluorocyclopropyl sulfonic esters (**2a**–**c**) could be easily obtained by *gem*-difluorocyclopropanation of vinyl sulfonic esters **1a–c** with trimethylsilyl fluorosulfonyldifluoroacetate (TFDA), which has proved to be an efficient difluorocarbene reagent (Scheme 2) [19,20]. Slow addition of TFDA to vinyl sulfonic esters in xylene with a catalytic amount of NaF gave *gem*-difluorocyclopyl tosylates in moderate to good yields. The desired products **2a–c** could be prepared in gram scale and are stable to air and water.

Table 1
Optimization of reaction conditions for *N*-difluorocyclopopylation of heterocycles.[a]



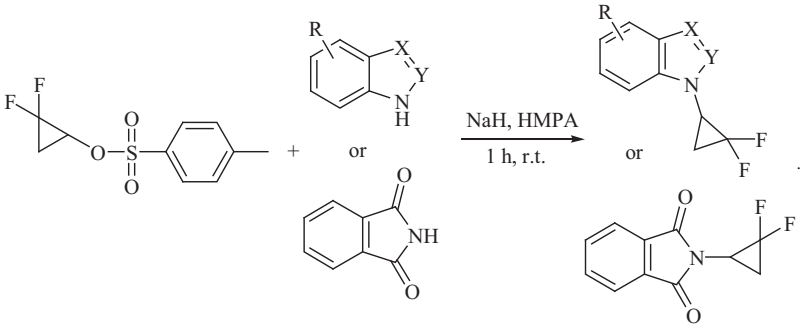
Entry	Solvent	**2a**:**3a**[b]	Time (h)	Yield (%)[c]
1	HMPA	1.0:1	1	47
2	HMPA	1.1:1	1	51
3	HMPA	1.2:1	1	51
4	HMPA	1.1:1	1.5	51
5	DMF	1.1:1	1	51
6	DMSO	1.1:1	1	51
7	THF	1.1:1	1	ND
8[d]	HMPA	1.1:1	1	58

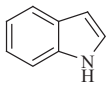
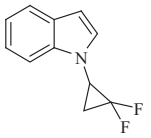
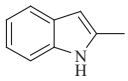
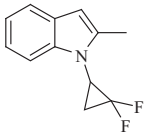
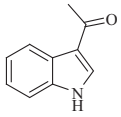
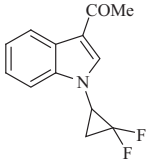
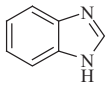
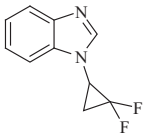
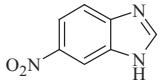
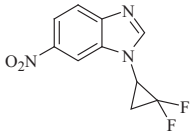
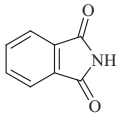
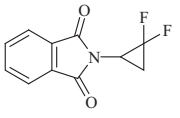
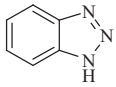
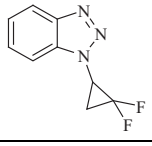
[a] Reaction conditions: **2a** solution (1 mL solvent) was added into the reaction system of indole (1 mmol) and NaH (1 mmol) in solvent (1 mL) at r.t.
[b] Molar ratio.
[c] Determined by ^{19}F NMR with the use of trifluoromethyl benzene as internal standard.
[d] The addition of **2a** solution was completed in 15 min.

With these reagents in hand, we next explored *N-gem*-difluorocyclopropylation of indole (**3a**) with **2a**. We believed the reaction would proceed via the S_N2 process instead of S_N1, because the strong destabilization effect of β-fluorine and strain energy makes it hard to form a cation intermediate of cyclopropane. One of the issues for this nucleophilic substitution is the regioselectivity of indole, because the C_3- position is also very reactive towards electrophiles. The problem could be solved by the addition of **2a** solution into indole anion, which is generated from the reaction of indole with strong base. The other issue is the decomposition of **2a** in the presence of strong base due to deprotonation followed by β-fluorine elimination. The decomposition should be able to be suppressed if the base is used without excess.

Indeed, this transformation in HMPA could give the desired product with excellent regioselectivity at room temperature with 1 equiv. of sodium hydride (Table 1, entry 1). The further screening of the ratio of substrates and reaction time (entries 2–4) showed that

Table 2
gem-Difluorocyclopropylation of heterocycles.[a]



Entry	Substrate (**3a–3g**)	Product	**4**, yields (%)[b]
1			**4a**, 57
2			**4b**, 69
3			**4c**, 63
4			**4d**, 55
5			**4e**, 54
6			**4f**, 65
7[c]			**4g**, 60

[a] Reaction conditions: **2a** (1.1 mmol), *N*-heterocycle (1 mmol) and NaH (1 mmol) in HMPA (1 mL) at r.t.
[b] Isolated yields.
[c] Reaction was performed at 80 °C.

reasonable yield could be obtained with the use of 1.1 equiv. of **2a**, the conversion of which was completed in 1 h (entry 2). Highly polar solvent is favorable for the reaction (entries 5 and 6), but a less polar solvent resulted in no expected product (entry 7). It was found that the yield was increased slightly by slowing down the addition rate of **2a** solution (entry 8).

The scope of substrates was explored (Table 2) under the optimized reaction conditions (Table 1, entry 8). Irrespective of whether the indole was substituted by an electron-withdrawing or an electron-donating group, the conversion occurred smoothly to give the desired *gem*-difluorocyclopropylation product in moderate yields (Table 2, entries 1–3). Similar results were obtained in the case of benzimidazoles (entries 4 and 5). Phthalimide could also be converted well into the expected product (entry 6). For benzotriazole, the reaction needs a higher temperature in order to get a reasonable yield due to the low nucleophilic ability of the corresponding anion (entry 7).

4. Conclusion

In summary, we have designed and synthesized some *gem*-difluorocyclopropane building blocks, *gem*-difluorocyclopropyl tosylates. The tosylate could act as a cation equivalent to achieve *N*-*gem*-difluorocyclopropylation of *N*-heterocycles under mild conditions. Further application of these building blocks into *gem*-difluorocyclopropylation of other compounds is currently under investigation in our laboratory.

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