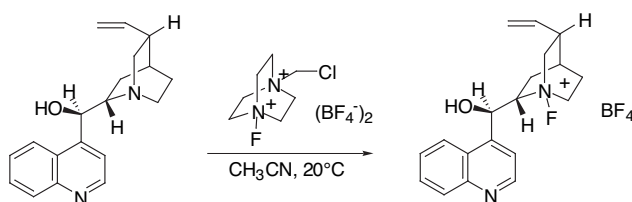


# Design, Synthesis and Evaluation of a Novel Class of Enantioselective Electrophilic Fluorinating Agents: N-Fluoro Ammonium Salts of *Cinchona* Alkaloids (F-CA-BF<sub>4</sub>)

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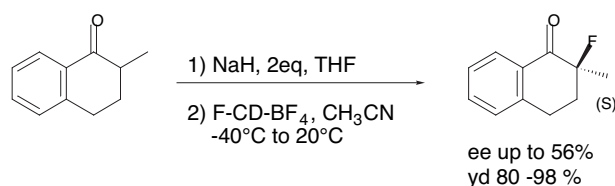
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## Supplementary material



**F-CD-BF<sub>4</sub>:** Selectfluor<sup>TM</sup> (13.6 mmol, 4.82 g) in acetonitrile (30 mL) was slowly added to an equimolar amount of cinchonidine (13.6 mmol, 4 g) in acetonitrile (20 mL). The reaction is exothermic and complete transfer proceeds within 20 min. Acetonitrile was removed under reduced pressure and the resulting white solid was dissolved in the minimum of acetone. To this solution, a dropwise addition of a solution of H<sub>2</sub>SO<sub>4</sub> 96% (10.9 mmol, 1.13 g) in acetone (100 mL) caused the precipitation of 1-chloromethyl-4-hydroxy-1,4-diazoniabicyclo [2.2.2] octane hydrogen sulphate tetrafluoroborate that is recovered by filtration. Addition of diethyl ether to the filtrate caused the precipitation of the N-fluoro cinchonidinium salt. The solid was washed with a 1:1 v/v mixture of diethyl ether and acetone, dried in vacuo and recrystallized by cooling a saturated acetone solution to afford colorless crystals of F-CD-BF<sub>4</sub> (84% yield). <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>) δ 8.98 (d, *J*=4.1 Hz, 1H), 8.13 (d, *J*=8.4 Hz, 1H), 8.05 (d, *J*=8.4 Hz, 1H), 7.90 (d, *J*=4.1 Hz, 1H), 7.83 (app. t, *J*= 7.6 Hz, 1H), 7.70 (app. t, *J*= 7.6 Hz, 1H), 6.68 (bs, 1H), 6.11 (s, OH), 5.94 (m, 1H), 5.25 (d, *J*= 17.2 Hz, 1H), 5.17 (m, 1H), 5.11 (d, *J*= 10.4 Hz, 1H), 4.88-4.69 (m, 2H), 4.54-4.49 (m, 2H), 3.56 (m, 1H), 2.91-2.82 (m, 1H), 2.78-2.74 (m, 1H), 2.63-2.55 (m, 1H), 2.33-2.24 (m, 2H); <sup>13</sup>C NMR (75 MHz, acetone-*d*<sub>6</sub>) δ 150.3, 148.9, 144.5, 136.9, 132.7, 129.8, 127.6, 125.7, 123.9, 120.8, 118.4, 74.9 (d, *J*=9.4 Hz), 68.6 (d, *J*=8.7 Hz), 63.8 (d, *J*=5.8

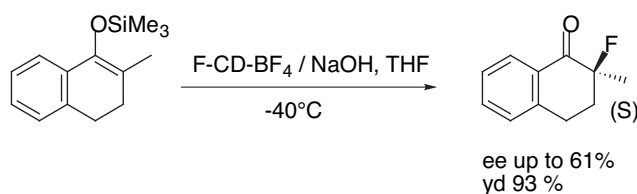
Hz), 59.5 (d,  $J=9.4$  Hz), 43.8 (d,  $J=3.6$  Hz), 28.9 (d,  $J=5.1$  Hz), 27.8 (d,  $J=5.1$  Hz), 24.1 (d,  $J=1.5$  Hz);  $^{19}\text{F}$  NMR (282 MHz, acetone- $d_6$  /  $\text{CFCl}_3$ )  $\delta$  42.2 (1F), -150.4 (4F) ppm; MS (FAB $^+$ ): 313.



**(S)-2-fluoro-2-methyl-3,4-dihydro-2H-naphthalen-1-one:** 2-methyl-1-tetralone (0.5 mmol, 80.1 mg) was added to a suspension of NaH 95% (1.1 mmol, 27.8 mg) in THF (5 mL, distilled from Na $^\circ$ ) and stirred at room temperature under Ar for 15 min. The reaction temperature is then lowered to -40°C and F-CD-BF<sub>4</sub> (0.6 mmol, 240.1 mg) in acetonitrile (1.5 mL) was slowly added in 2 h. The mixture was stirred at -40°C for 5 h and then quenched at 20°C with water and diethyl ether (4 mL). The two phases were separated, and the combined organic phases were dried over MgSO<sub>4</sub>. Concentration *in vacuo* and purification by chromatography (silica gel, heptane/diethyl ether) afforded (S)-2-fluoro-2-methyl-3,4-dihydro-2H-naphthalen-1-one (98% yield, 50% ee determined by HPLC analysis using a Chiralcel OB-column (10% *i*PrOH-hexane, 1 mL/min,  $\lambda=254\text{nm}$ , retention time: *R* (minor) 9.7 min, *S* (major) 15.4 min)).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (d,  $J=7.5$  Hz, 1H), 7.45 (dt,  $J=7.5$ , 1.2 Hz, 1H), 7.27 (app. t,  $J=7.5$  Hz, 1H), 7.20 (d,  $J=7.5$  Hz, 1H), 3.06 (dt,  $J=17.4$ , 5.4 Hz, 1H), 2.95 (ddd,  $J=17.4$ , 9.2, 5.1 Hz, 1H), 2.38 (m, 1H), 2.21 (m, 1H), 1.52 (d,  $J=21.9$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  194.8 (d,  $J=18.4$  Hz), 143.3, 134.5, 130.9, 129.2, 128.8, 128.5, 94.2 (d,  $J=179.5$  Hz), 35.3 (d,  $J=22.9$  Hz), 26.5 (d,  $J=9.4$  Hz), 21.2 (d,  $J=25.4$  Hz);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$  /  $\text{CFCl}_3$ )  $\delta$  -152.8 (qdd,  $J=22.1$ , 16.6, 9.2 Hz).

**Spectroscopic characterization and ee determination for:** 2-Benzyl-2-fluoro-3,4-dihydro-2H-naphthalen-1-one (96% yield, 42% ee determined by HPLC analysis using a Chiralcel OJ-column (5% *i*PrOH-heptane, 1.5 mL/min,  $\lambda=254\text{nm}$ , retention time: 15.5 and 17.9 min)).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.12 (d,  $J=7.8$  Hz, 1H), 7.02-7.58 (m, 8H), 3.36 (dd,  $J=17.4$ , 14.7 Hz, 1H), 3.06-3.17 (m, 3H), 2.13-2.35 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  194.4, 143.2, 135.0, 134.6, 131.4, 130.9, 129.2, 128.8, 128.2, 127.6, 127.4, 95.6 (d,  $J=184.6$  Hz), 39.8 (d,  $J=23.0$  Hz), 31.8 (d,  $J=22.6$  Hz), 26.4 (d,  $J=9.7$  Hz);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$  /  $\text{CFCl}_3$ )  $\delta$  -158.0 (dddd,  $J=31.4$ , 16.6, 16.4, 5.5 Hz). 1-Fluoro-2-oxo-cyclopentanecarboxylic acid ethyl ester (98% yield, 40% ee determined by GC analysis using a

Chiraldex column type G-TA(20 m x 0.25 mm; 65°C during 2 min then 5°C/min to 160°C; retention time: 14.7 (minor) and 14.85 (major)). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.25 (q, *J*=7.1 Hz, 2H), 2.14-2.66 (m, 6H), 1.30 (t, *J*=7.1 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 208.1, 168.0, 95.0 (d, *J*=199.8 Hz), 62.7, 36.1, 34.3 (d, *J*=21 Hz), 19.5, 18.4; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub> / CFCl<sub>3</sub>) δ -164.5 (t, *J*=20.2 Hz). 2-Fluoro-1-oxo-indan-2-carboxylic acid methyl ester (95% yield, 36% ee determined by HPLC analysis using a Chiralcel OD-column (12% *i*PrOH-hexane, 1 mL/min, λ=254nm, retention time: 15.4 and 17.9 min. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.86 (d, *J*=7.8 Hz, 1H), 7.75 (app. t, *J*=7.2 Hz, 1H), 7.52 (m, 2H), 3.83 (s, 3H), 3.88-3.62 (m, 1H), 3.46 (dd, *J*= 15.3, 17.7 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 195.5 (d, *J*=17.9 Hz), 168.1 (d, *J*=27.8 Hz), 151.3, 137.2, 133.6, 129.1, 127.0, 126.1, 95.1 (d, *J*=201.5 Hz), 53.7, 38.6 (d, *J*=24.6 Hz); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub> / CFCl<sub>3</sub>) δ -165.0 (dd, *J*=23, 11 Hz).



**Experimental procedure.** To a suspension of F-CD-BF<sub>4</sub> (0.325 mmol, 130.1 mg) in THF (1 mL) was added NaOH 6N (0.6 mmol, 100 μL) at 20°C. After stirring 10 min the solution became limpid and the temperature was lowered to -40°C. The trimethylsilyl enol ether of 2-methyl-1-tetralone (0.225 mmol, 52.3 mg) in THF (1 mL) was added over a period of 2h. The mixture was stirred at -40°C for 20h and quenched at -40°C with water and diethyl ether (4 mL). The two phases were separated, and the combined organic phases were dried over MgSO<sub>4</sub>. Concentration *in vacuo* and purification by chromatography (silica gel, heptane/diethyl ether) afforded the fluorinated product.