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Supporting information

A Fundamentally New Approach to Enantioselective Fluorination based on Cinchona Alkaloid Derivatives/Selectfluor Combination

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Reference (11)

A typical experimental procedure for the fluorination of 1a.

A solution of **1a** (40 mg, 0.136 mmol) in MeCN (3ml) was added to DHQB/Selectfluor combination [prepared in situ from DHQB (98%, 78 mg, 0.163 mmol) and Selectfluor (95%, 60 mg, 0.163 mmol) in MeCN (3 ml) stirred in the presence of MS 3Å at room temperature for 1h] at –20 °C under nitrogen atmosphere. After stirring overnight, water was added to the reaction mixture and it was extracted with AcOEt. The organic phase was washed with 5% HCl, sat. $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a crude oil, which was purified by preparative TLC on silica-gel eluting with 20% AcOEt in hexane to give **2a** (32.2 mg, 99%) as a colorless oil. Ee was determined to 89% by HPLC analysis using a Chiralcel OB eluting with 10% isopropanol in hexane. Spectral data for **2a** corresponded to literature value (ref. [6a]).

Fluorination of 1b

Fluorination of **1b** (40 mg, 0.183 mmol), DHQB/Selectfluor combination [prepared in situ from DHQB (98%, 102 mg, 0.215 mmol) and Selectfluor (97%, 78 mg, 0.214 mmol) in MeCN (2 ml) stirred in the presence of MS 3Å at room temperature for 1h] in MeCN (3 ml) at –20 °C gave **2b** (27.9 mg, 93%) as a colorless oil. Ee was determined to 54% by HPLC analysis using a Chiralcel OB eluting with 1% isopropanol in hexane. Spectral data for **2b** corresponded to literature value (ref. [6a]).

Fluorination of 1c

Fluorination of **1c** (40 mg, 0.172 mmol), DHQB/Selectfluor combination [prepared in situ from DHQB (98%, 96 mg, 0.202 mmol) and Selectfluor (97%, 73 mg, 0.200 mmol) in MeCN (2 ml) stirred in the presence of MS 3Å at room temperature for 1h] in MeCN (3 ml) at –20 °C gave **2c** (37.5 mg, 99%) as a colorless oil. Ee was determined to 73% by HPLC analysis using a Chiralcel OB eluting with 1% isopropanol in hexane. Spectral data for **2c** corresponded to literature value (ref. [6a]).

Fluorination of 1d

Fluorination of **1d** (40 mg, 0.172 mmol), DHQB/Selectfluor combination [prepared in situ from DHQB (98%, 96 mg, 0.202 mmol) and Selectfluor (97%, 73 mg, 0.200 mmol) in MeCN (2 ml) stirred in the presence of MS 3Å at room temperature for 1h] in MeCN (3 ml) at –20 °C gave **2d** (29.0 mg, 94%) as a colorless oil. Ee was determined to 42% by HPLC analysis using a Chiralcel OB eluting with 5% isopropanol in hexane. Spectral data for **2d** corresponded to literature value (ref. [6a]).

Fluorination of 1e

Fluorination of **1e** (30 mg, 0.122 mmol), DHQB/Selectfluor combination [prepared in situ from DHQB (98%, 116 mg, 0.244 mmol) and Selectfluor (97%, 67 mg, 0.183 mmol) in MeCN (3 ml) stirred in the presence of MS 3Å at room temperature for 1h] in CH_2Cl_2 (4 ml) at –50 °C gave **2e** (16.7 mg, 71%) as a colorless oil. Ee was determined to 67% by HPLC analysis using a Chiralcel OB eluting with 1% isopropanol in hexane. Spectral data for **2e** corresponded to literature value (ref. [6a]).

Fluorination of 1f

Fluorination of **1f** (40 mg, 0.129 mmol), DHQB/Selectfluor combination [prepared in situ from DHQB (98%, 73 mg, 0.154 mmol) and Selectfluor (97%, 55 mg, 0.151 mmol) in MeCN (2 ml) stirred in the presence of MS 3Å at room temperature for 1h] in MeCN (3 ml) at –20 °C gave **2d** (31.3 mg, 95%) as a colorless oil. Ee was determined to 71% by HPLC analysis using a Chiralcel OB eluting with 10% isopropanol in hexane. Spectral data for **2d** corresponded to literature value (ref. [6a]).

A typical experimental procedure for the fluorination of 4a.

A solution of **4a** (50 mg, 0.246 mmol) in CH_2Cl_2 (4 ml) was added to DHQDA/Selectfluor combination [prepared in situ from DHQDA (181 mg, 0.491 mmol) and Selectfluor (95%, 138 mg, 0.390 mmol) in MeCN (3 ml) in the presence of MS 3Å at room temperature for 1h] at –80 °C under nitrogen atmosphere. After stirring for 2 h, water was added to the reaction mixture and extracted with AcOEt. The work-up similar to the fluorination of **1a** gave **3a** (43.5 mg, 80%) as a colorless oil. Ee was determined to 87% by HPLC analysis using a Chiralcel OB eluting with 1% ethanol in hexane. Spectral data for **3a** corresponded to literature value (ref. [14b]).

Fluorination of 4b

Fluorination of **4b** (20 mg, 0.0893 mmol) with DHQDA/Selectfluor combination [prepared in situ from DHQDA (66 mg, 0.177 mmol) and Selectfluor (97%, 49 mg, 0.134 mmol) in MeCN (3 ml) in the presence of MS 3Å at room temperature for 1h] in CH_2Cl_2 (4 ml) at –80 °C gave **3b** (18.7 mg, 87%) as colorless crystals. Ee was determined to 76% by HPLC analysis using a Chiralpak AD eluting with 2% ethanol in hexane. Spectral data for **3b** corresponded to literature value (ref. [15]).

Fluorination of 4c

Fluorination of **4c** (50 mg, 0.265 mmol) with DHQDA/Selectfluor combination [prepared in situ from DHQDA (195 mg, 0.529 mmol) and Selectfluor (97%, 145 mg, 0.397 mmol) in MeCN (3 ml) in the presence of MS 3Å at room temperature for 1h] in CH_2Cl_2 (4 ml) at –80 °C gave **3c** (44.2 mg, 81%) as a colorless oil. Ee was determined to 83% by HPLC analysis using a Chiralcel OJ eluting with 1% isopropanol in hexane. Spectral data for **4c** corresponded to literature value (ref. [16] and Takeuchi, Y., Itoh, N., Satoh, T., Koizumi, T., Yamaguchi, K, *J. Org. Chem.* **1993**, *58*, 1812—1820.).

Fluorination of 4d

Fluorination of **4d** (20 mg, 0.0921 mmol) with DHQDA/Selectfluor combination [prepared in situ from DHQDA (68 mg, 0.184 mmol) and Selectfluor (97%, 51 mg, 0.138 mmol) in MeCN (3 ml) in the presence of MS 3Å at room temperature for 1h] in CH_2Cl_2 (4 ml) at –80 °C gave **3d** (17.5 mg, 81%) as a colorless oil. Ee was determined to 76% by HPLC analysis using a Chiralpak AS eluting with 1% isopropanol in hexane. ^{1}H NMR δ 7.36—7.57 (m, 2H, ArH), 7.32—7.35 (m, 2H, ArH), 3.90 (s, 3H, OMe), 2.95 (m, 1H, C<u>H</u>Me$_2$), 2.52 (d, J = 6.83 Hz, 6H, <u>Me</u>$_2$CH). ^{19}F NMR δ –144.3 (s).

Fluorination of 4e

Fluorination of **4e** (40 mg, 0.196 mmol) with DHQDA/Selectfluor combination [prepared in situ from DHQDA (144 mg, 0.392 mmol) and Selectfluor (97%, 107 mg, 0.294 mmol) in MeCN (3 ml) in the presence of MS 3Å at room temperature for 1h] in CH_2Cl_2 (4 ml) at –80 °C gave **3e** (38.7 mg, 89%) as a colorless oil. Ee was determined to 78% by HPLC analysis using a Chiralcel OJ eluting with 1% isopropanol in hexane. ^{1}H NMR δ 7.82 (m, 1H, ArH), 7.71 (m, 1H, ArH), 7.48 (m, 2H, ArH), 4.28 (q, J = 7.1 Hz, 2H, C<u>H</u>$_2$Me), 3.80 (dd, J = 11.6, 17.7Hz, 1H, C<u>H</u>HAr), 3.43 (dd, J = 23.3, 17.8 Hz, 1H, CH<u>H</u>Ar), 1.26 (t, J = 7.2 Hz, 3H, Me). ^{19}F NMR δ –164.9 (dd, J = 12.0, 23.5 Hz)

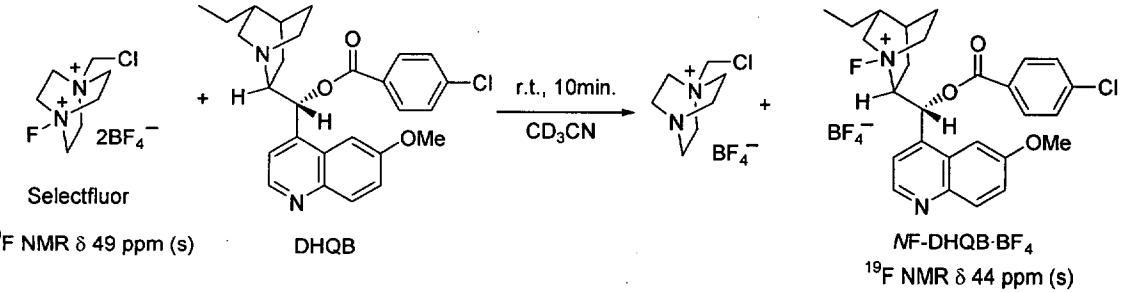
Fluorination of 4f

Fluorination of **4f** (30 mg, 0.146 mmol) with DHQDA/Selectfluor combination [prepared in situ from DHQDA (107 mg, 0.292 mmol) and Selectfluor (95%, 81 mg, 0.218 mmol) in MeCN (3 ml) in the presence of MS 3Å at room temperature for 1h] in CH_2Cl_2 (4 ml) at –80 °C gave **3f** (30.1 mg, 92%) as a colorless oil. Ee was determined to 80% by HPLC analysis using a Chiralcel OJ eluting with 10% isopropanol in hexane. ^{1}H NMR δ 7.74 (m, 2H, ArH), 7.25 (m, 2H, ArH), 4.35 (qd, J = 7.3, 1.2 Hz, 2H, CH_2), 1.31 (t, J = 7.2 Hz, 3H, Me). ^{19}F NMR δ –127.43 (s).

Reference (18)

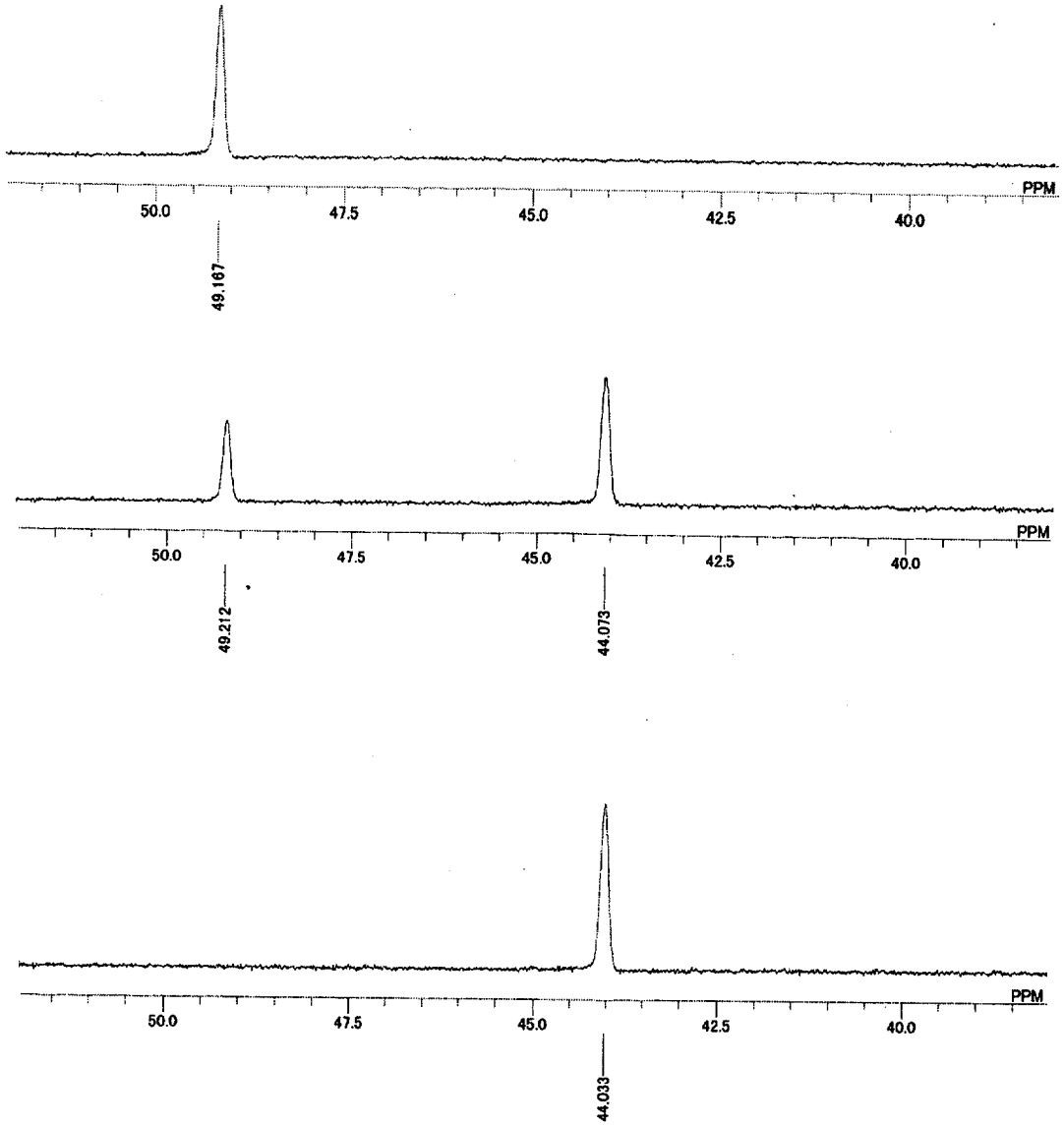
NMR Studies of the DHQB/Selectfluor Combination

This structure of the species produced by the DHQB/Selectfluor combination was examined by ^{19}F NMR spectroscopy ($CFCl_3$ was used as a reference). The 254 MHz ^{19}F NMR spectrum of Selectfluor in CD_3CN at room temperature showed a singlet peak at 49 ppm due to fluorine originated from the *N*-F, whereas the spectrum of DHQB/Selectfluor (0.5:1) combination in CD_3CN gave two singlet peaks at 49 ppm and 44 ppm. As we expected, the signal at 49 ppm disappeared completely with the addition of DHQB (0.1—1.0 equiv). Thus, the ^{19}F NMR spectrum of DHQB/Selectfluor (1:1) combination showed only a singlet peak at 44 ppm. The characteristic signal at 44 ppm clearly confirmed a new *N*-F structure over that of a reactive species. These initial NMR spectroscopic studies strongly support the proposed structure of *N*F-DHQB·BF_4 in solution, although further investigation for this structure is necessary.



Scheme. Transfer-fluorination of DHQB (0.1 —1.0equiv) with Selectfluor (1.0 equiv) in CD_3CN.

(Also see Figure on the next page)



Figure

The 254 MHz ^{19}F NMR spectrum of Selectfluor and the combination in CD_3CN.

Top: Downfield region of the ^{19}F NMR spectrum of Selectfluor in CD_3CN.

Middle: The same region after the addition 0.5 equiv. of DHQB.

Bottom: The same region after the addition 1.0 equiv. of DHQB, leading to the quantitative formation of *N*F-DHQB·BF_4.