Supporting Information

Bimorpholine-mediated Enantioselective Intramolecular and Intermolecular Aldol Condensation

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General methods

Full assignment of ^1H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a 500 MHz instrument. Deuteriosolvent peaks (CHCl_3 $\delta=7.27$, CDCl_3 $\delta=77.00$, CHD_2OD $\delta=3.30$, CD_3OD $\delta=49.00$) were used as chemical shift references. The mass spectra were obtained in GC/MS mode (EI, 70 eV). IR spectra were recorded on FTIR spectrometer. Optical rotations were measured using an automatic digital polarimeter and are reported as follows: $[\alpha]_D^{25}$ (c = g/100 mL, solvent). Gas chromatography was performed using a DB-5 column (25 m x 0.25 mm). Chiral HPLC analyses were performed using Chiralcel OD-H (250 x 4.6 mm), Chiralpak AD-H (250 x 4.6 mm) and Chiralpak AS-H (250 x 4.6 mm) column. Reactions sensitive to oxygen or moisture were conducted under argon atmosphere in flame-dried glassware. Commercial reagents were generally used as received. Petroleum ether used had bp 40-60 °C.

Synthesis of substituted bimorpholines

(3*S*, 3'*S*)-4-Methyl-3,3'-bimorpholine 4a

Title compound was prepared as described earlier.¹

(3*S*, 3'*S*)-4-Isopropyl-3,3'-bimorpholine 4b

Title compound was prepared as described earlier.¹

General method for the organocatalytic intermolecular aldol condensation of aromatic aldehydes and acetone

To a solution of the corresponding aromatic aldehyde **9a-i** (0.3 mmol) in acetone (0.6 mL) was added organocatalyst **6b** (0.09 mmol) and the mixture was stirred at room temperature for an appropriate time (6-10 days). The reaction mixture was treated with brine, extracted with EtOAc or Et₂O (4 x 2 mL) and the combined organic layers were dried over anhydrous Na₂SO₄. After filtration and concentration in vacuum, the crude product **10a-i** was purified by chromatography on silica gel.

(4S)-Hydroxy -4-(4'-nitrophenyl)-butan-2-one 10a²

Yield: 70%; $[\alpha]_D^{22} = -55.7$ ($c = 4.61$, CHCl₃); ee 88%, determined by HPLC (Daicel Chiralpak AD-H, Hex/iPrOH/MeOH 96:4:1), UV 210 nm, flow rate 1.0 mL/min, major: t_R 27.9 min and minor t_R 29.4 min.

(4S)-Hydroxy -4-(2'-nitrophenyl)-butan-2-one 10b^{2b, c, d}

Yield: 77%; $[\alpha]_D^{22} = +142.8$ ($c = 1.97$, CH₂Cl₂); ee 94%, determined by HPLC (Daicel Chiralpak AS-H, Hex/iPrOH 80:20), UV 254 nm, flow rate 0.8 mL/min, major: t_R 13.1 min and minor t_R 19.8 min.

(4S)-Hydroxy -4-(4'-trifluoromethylphenyl)-butan-2-one 10c^{2a}

Yield: 48%; $[\alpha]_D^{22} = -46.9$ ($c = 3.55$, CH₂Cl₂); ee 90%, determined by HPLC (Daicel Chiralpak AD-H, Hex/iPrOH/MeOH 98:2:1), UV 210 nm, flow rate 0.9 mL/min, major: t_R 33.0 min and minor t_R 31.2 min.

(4S)-4-(4'-Chlorophenyl)-4-hydroxybutan-2-one 10d²

Yield: 12%; $[\alpha]_{\text{D}}^{22} = -46.3$ ($c = 0.92$, CH_2Cl_2); ee 88%, determined by HPLC (Daicel Chiralpak AS-H, Hex/iPrOH 90:10), UV 206 nm, flow rate 0.8 mL/min, major: t_{R} 24.0 min and minor t_{R} 19.3 min.

(4S)-4-(2'-Chlorophenyl)-4-hydroxybutan-2-one 10e ^{2a, b, d, e}

Yield: 79%; $[\alpha]_{\text{D}}^{22} = -98.5$ ($c = 1.71$, CH_2Cl_2); ee 89%, determined by HPLC (Daicel Chiralpak AS-H, Hex/iPrOH 90:10), UV 206 nm, flow rate 0.8 mL/min, major: t_{R} 12.0 min and minor t_{R} 16.8 min.

(4S)-4-(2',4'-Dichlorophenyl)-4-hydroxybutan-2-one 10f ^{2b}

Yield: 74%; $[\alpha]_{\text{D}}^{22} = -91.4$ ($c = 1.58$, CH_2Cl_2); ee 88%, determined by HPLC (Daicel Chiralpak AS-H, Hex/iPrOH 90:10), UV 206 nm, flow rate 0.8 mL/min, major: t_{R} 10.8 min and minor t_{R} 13.4 min.

4-(2'-Chloro-6'-fluorophenyl)-4-hydroxybutan-2-one 10g ^{2e}

Yield: 91%; $[\alpha]_{\text{D}}^{22} = +15.3$ ($c = 3.16$, CH_2Cl_2); ee 88%, determined by HPLC (Daicel Chiralpak AS-H, Hex/iPrOH 90:10), UV 206 nm, flow rate 0.8 mL/min, major: t_{R} 14.4 min and minor t_{R} 17.7 min.

IR (KBr): 3442, 3088, 2923, 1714, 1605, 1577, 1455, 1418, 1361, 1243, 1076, 904, 785, 733 cm^{-1} .

MS (EI): m/z (%) = 198 (7), 181 (80), 159 (100), 139 (13), 123 (17), 121 (18), 95 (18), 58 (61), 43 (62).

HRMS exact mass calculated for $(\text{C}_{10}\text{H}_{10}\text{FO}_2)^+$ requires m/z 181.0663, found m/z 181.0663.

Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{ClFO}_2$ (216.64): C 55.44, H 4.65. Found C 55.11, H 4.56.

(4S)-Hydroxy-4-phenyl-butan-2-one 10h ²

Yield: 18%; $[\alpha]_D^{22} = -52.8$ ($c = 0.39$, CH_2Cl_2); ee 85%, determined by HPLC (Daicel Chiralcel OD-H, Hex/iPrOH 93:7), UV 210 nm, flow rate 1.0 mL/min, major: t_R 12.0 min and minor t_R 12.8 min.

4-Hydroxy-4-(4'-isopropylphenyl)-butan-2-one 10i

Yield: <10%; ee 76%, determined by HPLC (Daicel Chiralpak AD-H, Hex/iPrOH/MeOH 98:2:1), UV 210 nm, flow rate 1.0 mL/min, major: t_R 33.3 min and minor t_R 29.4 min.

MS (EI): m/z (%) = 206 (8), 188 (2), 163 (11), 149 (30), 133 (27), 119 (12), 105 (63), 91 (25), 79 (36), 58 (11), 43 (100).

HRMS exact mass calculated for $(\text{C}_{10}\text{H}_{11}\text{O}_2)^+$ requires m/z 163.0757, found m/z 163.0757 and for $(\text{C}_{13}\text{H}_{18}\text{O}_2)^+$ requires m/z 206.1306, found m/z 206.1321.

^1H and ^{13}C NMR spectra

^1H NMR (CDCl_3 , 500 MHz) spectrum of (3*S*, 3'*S*)-bimorpholine trifluoroacetic acid salt 2a

^{13}C NMR (CDCl_3 , 125 MHz) spectrum of (3*S*, 3'*S*)-bimorpholine trifluoroacetic acid salt 2a

^1H NMR (CDCl_3 , 500 MHz) spectrum of (3*S*, 3'*S*)-4-methyl-3,3'-bimorpholine 4a

¹³C NMR (CDCl₃, 125 MHz) spectrum of (3*S*, 3'*S*)-4-methyl-3,3'-bimorpholine 4a

^1H NMR (CDCl_3 , 500 MHz) spectrum of (3*S*, 3'*S*)-4-isopropyl-3,3'-bimorpholine 4b

¹³C NMR (CDCl₃, 125 MHz) spectrum of (3*S*, 3'*S*)-4-isopropyl-3,3'-bimorpholine 4b

^1H NMR (CDCl_3 , 500 MHz) spectrum of (3*S*, 3'*S*)-4-benzyl-3,3'-bimorpholine 4c

¹³C NMR (CDCl₃, 125 MHz) spectrum of (3*S*, 3'*S*)-4-benzyl-3,3'-bimorpholine 4c

¹H NMR (CDCl₃, 500 MHz) spectrum of (3*S*, 3'*S*)-2-(3,3'-bimorpholin-4-ylmethyl)phenol 4d

^{13}C NMR (CDCl_3 , 125 MHz) spectrum of (3*S*,3'*S*)-2-(3,3'-bimorpholin-4-ylmethyl)phenol 4d

^1H NMR (CDCl_3 , 500 MHz) spectrum of (3*S*, 3'*S*)-4-phenyl-3,3'-bimorpholine 4e

^{13}C NMR (CDCl_3 , 125 MHz) spectrum of (3*S*, 3'*S*)-4-phenyl-3,3'-bimorpholine 4e

^1H NMR (CDCl_3 , 500 MHz) spectrum of (3*S*, 3'*S*)-4-methyl-3,3'-bimorpholine trifluoroacetic acid salt 5a

^{13}C NMR (CDCl_3 , 125 MHz) spectrum of (3*S*, 3'*S*)-4-methyl-3,3'-bimorpholine trifluoroacetic acid salt 5a

^1H NMR (CDCl_3 , 500 MHz) spectrum of (3*S*, 3'*S*)-4-isopropyl-3,3'-bimorpholine trifluoroacetic acid salt **5b**

^{13}C NMR (CDCl_3 , 125 MHz) spectrum of (3*S*, 3'*S*)-4-isopropyl-3,3'-bimorpholine trifluoroacetic acid salt **5b**

^1H NMR (CDCl_3 , 500 MHz) spectrum of (3*S*, 3'*S*)-4-benzyl-3,3'-bimorpholine trifluoroacetic acid salt **5c**

^{13}C NMR (CDCl_3 , 125 MHz) spectrum of (3*S*, 3'*S*)-4-benzyl-3,3'-bimorpholine trifluoroacetic acid salt **5c**

^1H NMR (CDCl_3 , 500 MHz) spectrum of (3*S*, 3'*S*)-2-(3,3'-bimorpholin-4-ylmethyl)phenol trifluoroacetic acid salt **5d**

¹³C NMR (CDCl₃, 125 MHz) spectrum of (3*S*, 3'*S*)-2-(3,3'-bimorpholin-4-ylmethyl)phenol trifluoroacetic acid salt **5d**

^1H NMR (CDCl_3 , 500 MHz) spectrum of (3*S*, 3'*S*)-4-phenyl-3,3'-bimorpholine trifluoroacetic acid salt **5e**

^{13}C NMR (CDCl_3 , 125 MHz) spectrum of (3*S*, 3'*S*)-4-phenyl-3,3'-bimorpholine trifluoroacetic acid salt **5e**

^1H NMR (CDCl_3 , 500 MHz) spectrum of (3*S*, 3'*S*)-4-isopropyl-3,3'-bimorpholine trifluoromethanesulfonic acid salt **6b**

^{13}C NMR (CDCl_3 , 125 MHz) spectrum of (3*S*, 3'*S*)-4-isopropyl-3,3'-bimorpholine trifluoromethanesulfonic acid salt **6b**

^1H NMR (CDCl_3 , 500 MHz) and ^{13}C NMR (CDCl_3 , 125 MHz) spectrum of aldol product 10a

¹H NMR (CDCl₃, 500 MHz) spectrum of aldol product 10b

¹³C NMR (CDCl₃, 125 MHz) spectrum of aldol product 10b

¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectrum of aldol product 10c

^1H NMR (CDCl_3 , 500 MHz) and ^{13}C NMR (CDCl_3 , 125 MHz) spectrum of aldol product 10d

^1H NMR (CDCl_3 , 500 MHz) and ^{13}C NMR (CDCl_3 , 125 MHz) spectrum of aldol product 10e

¹H NMR (CDCl₃, 500 MHz) spectrum of aldol product 10f

¹³C NMR (CDCl₃, 125 MHz) spectrum of aldol product 10f

¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectrum of aldol product 10g

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