Direct Asymmetric Aldol Reaction of Aryl Ketones with Aryl Aldehydes Catalyzed by Chiral BINOL-derived Zincate Catalyst

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Supporting Information

Table of contents

1. General........................................................................................................................................S2
2. Detailed procedure of preparation of ligands \(1a-b\) from (\(S\))- or (\(R\))-BINOL and characterization of the related compounds. ..............................................................................................................S2
3. Typical procedure for catalytic asymmetric direct aldol reactions of aryl methyl ketones with aryl aldehydes........................................................................................................................................S6
4. Characterization of compounds \(5a-5p\)..............................................................................................S6
5. Scheme S2........................................................................................................................................S12
6. Characterization of compounds \(5q-5r\)..............................................................................................S12
7. Spectra of 2,2′-bis(methoxymethy)-1,1′-binaphthol.............................................................................S13
8. Spectrum of \(2b\)....................................................................................................................................S14
9. Spectrum of \(3b\)....................................................................................................................................S15
10. Spectra of \(4b\)......................................................................................................................................S16
11. Spectra of \(1a\)......................................................................................................................................S19
12. Spectra of \(1b\)......................................................................................................................................S21
13. Spectra of \(5a-5r\)................................................................................................................................S23
14. HPLC spectra of compounds \(5a-5r\).................................................................................................S48
15. References.......................................................................................................................................S57
1. General
All reactions were performed under an argon atmosphere and solvents were dried according to the established procedures ahead of use. All reagents were commercial products except of diethyl zinc, which was prepared from Et₂I and activated Zn and was diluted into 1.0 mmol/mL with hexane ahead of use. The reactions were monitored by TLC (thin layer chromatography) method; column and preparative TLC purification were carried out using silica gel. Melting points were uncorrected and recorded on X-4 melting point apparatus. Optical rotations were recorded on a polarimeter. HR-MS were measured with mass spectrometer. ¹H NMR, ¹³C NMR, and HMBC spectra were measured on 400 MHz or 200 MHz spectrometers (NMR in CDCl₃ with TMS as an internal standard) and recorded as ppm. IR spectra were obtained on FT-IR. The ee value determination was carried out using chiral HPLC with OD-H, AS-H or AD-H column.

2. Detailed procedure of preparation of ligands 1a~1b from (S)- or (R)-BINOL and characterization of the related compounds.

**SCHEME S1. Preparation of ligands 1a~1b**

(S)- or (R)-BINOL

\[ \text{NaH/THF, DMF, 0 °C – rt. 94%} \]

(S)- or (R)-BINOL

\[ \text{NaBH₄, EtOH/THF, 0 °C 100%} \]

(S)- or (R)-BINOL

\[ \text{i. MsCl, Et₃N, EtOAc/Tol, 0_°C 91%} \]

(S)- or (R)-BINOL

\[ \text{ii. BrLi, DMF, 0_°C} \]

(S)- or (R)-BINOL

\[ \text{i. (S)-diphenylprolinol, K₂CO₃/DMF, rt. 80%} \]

(S)- or (R)-BINOL

\[ \text{ii. 3N HCl/THF, reflux} \]

(S)- or (R)-BINOL

\[ \text{(S,S,S)-4a or (R,S,S)-1b} \]
2.1 General procedure of preparation of (R)-2,2′-bis(methoxymethyl)-1,1′-binaphthol

To a solution of NaH (60% dispersion in mineral oil, 1.84 g, 46 mmol) in a solution of dry 80 ml THF and 40 ml DMF was added dropwise a solution of 5.90 g (R)-BINOL (20.6 mmol) in 24 ml dry THF at 0 °C. After stirring for 1 h. at room temperature, 6.0 ml chloromethyl methyl ether (MOMCl, 65 mmol) was introduced to the resultant mixture. A white precipitate immediately appeared and the reaction was further stirred for 4 h. at room temperature. Then the reaction was quenched with cold water. Extracted the mixture with ethyl acetate three times, combined the organic layers, washed with little saturated brine, dried with Na₂SO₄, condensed in vacuo. The resultant residue was recrystallized with methanol to give the aimed product as a white crystal. 7.2 g, yield 94%. Mp 103–104 °C; [α]D²⁰ +98 (c 0.9, THF) (Lit.¹ Mp 99–100 °C, [α]D²³ = +94.3 (c 1.1, CHCl₃) for (S)-2,2′-bis(methoxymethyl)-1,1′-binaphthol; ¹H NMR (400 MHz) δ 7.95 (d, J = 9.2 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.34 (t, J = 8.0 Hz, 2H), 7.25–7.20 (m, 2H), 7.15 (d, J = 8.4 Hz, 2H), 5.09 (d, J = 6.8 Hz, 2H), 4.97 (d, J = 6.8 Hz, 2H), 3.14 (s, 6H).

2.2 (S)-2,2′-bis(methoxymethyl)-1,1′-binaphthol.

It was prepared according to the same procedure as its (R)-isomer, yield 95%. Mp 103–104 °C; [α]D²⁰ = –98 (c 0.9, THF) (Lit¹. Mp 99-100 °C, [α]D²³ = –94.3 (c 1.1, CHCl₃); ¹H NMR (400 MHz) δ 7.95 (d, J = 9.2 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.34 (t, J = 8.0 Hz, 2H), 7.25–7.20 (m, 2H), 7.15 (d, J = 8.4 Hz, 2H), 5.09 (d, J = 6.8 Hz, 2H), 4.97 (d, J = 6.8 Hz, 2H), 3.14 (s, 6H).

2.3 General procedure of preparation of (R)-2,2′-bis(methoxymethyl)-3,3′-dicarboxaldehyde (2b).

25 ml n-BuLi (36.8 mmol, 1.5 mmol/ml in hexane) was added dropwise into a solution of 5.01 g (R)-2,2′-bis(methoxymethyl)-1,1′-binaphthol (13.4 mmol) and 8.0 ml TMEDA (53 mmol) in ether (350 ml) at 0 °C, and it was stirred for 1.5 h at the same temperature. Then 5 ml dry DMF (65 mmol) was introduced into and the reaction was stirred for 2 h. Then it was quenched with 1.0 mmol/ml HCl, extracted with ether three times. Combined the organic layers, washed it with saturated NaHCO₃, successively with water, little saturated brine and dried with anhydrous Na₂SO₄, concentrated in vacuo, then purified by column chromatography (Petroleum ether:EtOAc = 5:1) to afford 2b as a yellow solid (4.62 g), yield 80%. Mp 118–119 °C; [α]D²⁰ = +7 (c 0.8, THF) (Lit.² [α]D²⁵ = –5.1 (c 0.777, THF) for (S)-2,2′-bis(methoxymethyl)-3,3′-dicarboxaldehyde); ¹H NMR (400 MHz) δ 10.55 (s, 2H), 8.62 (s, 2H), 8.09 (d, J = 8.0 Hz, 2H), 7.53 (t, J = 8.0 Hz, 2H), 7.43 (t, J = 8.0 Hz, 2H), 7.27–7.22 (m, 2H), 4.74 (d, J = 5.6 Hz, 2H), 4.69 (d, J = 6.4 Hz, 2H), 2.87 (s, 6H).

2.4 (S)-2,2′-bis(methoxymethyl)-3,3′-dicarboxaldehyde (2a).

2a was prepared according to the same procedure of its isomer 2b. Mp 118–119 °C. [α]D²⁰ = –7 (c 0.8, THF) (Lit.² [α]D²⁵ = –5.1 (c 0.777, THF)); ¹H NMR (400 MHz) δ 10.55 (s, 2H), 8.62 (s, 2H), 8.09 (d, J = 8.0 Hz, 2H), 7.53 (t, J = 8.0 Hz, 2H), 7.43 (t, J = 8.0
2.5 General procedure of preparation of (R)-3,3'-bis(hydroxymethyl)-2,2'-bis (methoxymethyl)-1,1'-binaphthol (3b).

At 0 °C, 210 mg NaBH₄ was portionwise added into a stirred solution of 2b of two mixed solvents composed of 55 mL ether and 35 mL EtOH, and then it was stirred for 1 h at the same temperature. After the reaction was completed, it was quenched by addition of dilute aqueous HCl, and then tuned the solution to pH 7.0 or so with saturated NaHCO₃. Removed the organic solvents under reduced pressure. The aqueous phase was extracted with ethyl acetate three times. The ethyl acetate layers were combined, washed with little brine, dried with anhydrous Na₂SO₄, concentrated in vacuo to afford 3b as a colorless thick oil residue. It needn’t be purified and directly used in the next step, yield 100%. [α]₀°D +92.6 (c 2.02, THF) (Lit.² [α]₀°D +92.6 (c 1.638, THF) for (S)-3,3'-bis(hydroxymethyl)-2,2'-bis(methoxymethyl)-1,1'-binaphthol; ¹H NMR (400 MHz) δ 8.03 (s, 2H), 7.92 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.30–7.26 (m, 2H), 7.15 (d, J = 8.8 Hz, 2H), 5.00 (d, J = 12.4 Hz, 2H), 4.84 (d, J = 12.4 Hz, 2H), 4.48–4.44 (m, 4H), 3.22 (s, 6H).

2.6 (S)-3,3'-bis(hydroxymethyl)-2,2'-bis(methoxymethyl)-1,1'-binaphthol (3a).

3a was prepared to the same procedure of its isomer 3b, yield 100%; [α]₀°D +82 (c 2.02, THF) (Lit.² [α]₀°D +92.6 (c 1.638, THF)); ¹H NMR (400 MHz) δ 8.03 (s, 2H), 7.92 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.30–7.26 (m, 2H), 7.15 (d, J = 8.8 Hz, 2H), 5.00 (d, J = 12.4 Hz, 2H), 4.84 (d, J = 12.4 Hz, 2H), 4.48–4.44 (m, 4H), 3.22 (s, 6H).

2.7 General procedure of preparation of (R)-3,3'-bis(bromomethyl)-2,2'-bis (methoxymethyl)-1,1'-binaphthol (4b).

To an ice-cooled solution of crude 3b (1.96 g, 4.5 mmol) in toluene (30 mL)/ethyl acetate (30 mL) were successively added Et₃N (5 mL, 36mmol) and MsCl (1.4 mL, 18 mmol). The mixture was stirred at 0 °C for 90 min. The resultant suspension was filtered to remove solid salt Et₃NH⁺Cl⁻ and the solid was washed with ethyl acetate (30 mL). The combined filtrate and washings were cooled to 0 °C and then LiBr (7.82 g, 90 mmol) in DMF (75 mL) were added. The mixture was stirred at room temperature for further 10 min. It was diluted with ether (120 mL) and washed with water (60 mL × 2), 1.0 mmol/L aqueous HCl (30 mL × 2), saturated aqueous NaHCO₃ (30 mL), and saturated brine in succession. Dried over MgSO₄ and evaporated in vacuo to give 3b as a yellow oil (5.568 g, 11.9 mmol, yield 91%) which was pure enough to be used in the next step without further purification. [α]₀°D +36 (c 0.84, THF); IR (KBr) 2924, 2854, 1745, 1460, 1157, 968, 750 cm⁻¹; ¹H NMR (400 MHz) δ 8.09 (s, 2H, Ar-H), 7.88 (d, J = 8.0 Hz, 2H, Ar-H), 7.43 (t, J = 7.8 Hz, 2H, Ar-H), 7.28–7.24 (m, 2H, Ar-H), 7.18–7.15 (m, 2H, Ar-H), 4.89 (d, J = 9.6 Hz, 2H, CH₂Br), 4.85 (d, J = 10.0 Hz, 2H, CH₂Br), 4.67 (d, J = 6.0 Hz, 2H, CH₂), 4.56 (d, J =
5.2 Hz, 2H, CH₂), 2.99 (s, 6H, CH₃); ¹³C NMR (400 MHz) δ 152.3, 134.2, 131.5, 130.6, 129.0, 128.2, 127.3, 126.0, 125.6, 125.3, 99.3, 56.9, 29.3; HRMS calcd for C₂₆H₂₈Br₂N₂O₄ ([M + NH₄⁺]⁺) 576.0380, found 576.0382.

2.8 (S)-3,3′-bis(bromomethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthol (4a).

4a was prepared according to the same procedure of its isomer 4b, [α]D⁺⁰ +36 (c 0.84, THF); IR (KBr) 2924, 2854, 1745, 1460, 1157, 968, 750 cm⁻¹; ¹H NMR (400 MHz) δ 8.09 (s, 2H, Ar-H), 7.88 (d, J = 8.0 Hz, 2H, Ar-H), 7.43 (t, J = 7.8 Hz, 2H, Ar-H), 7.28–7.24 (m, 2H, Ar-H), 7.18–7.15 (m, 2H, Ar-H), 4.89 (d, J = 9.6 Hz, 2H, CH₂Br), 4.85 (d, J = 10.0 Hz, 2H, CH₂Br), 4.67 (d, J = 6.0 Hz, 2H, CH₂), 4.56 (d, J = 5.2 Hz, 2H, CH₂), 2.99 (s, 6H, CH₃); ¹³C NMR (400 MHz) δ 152.3, 134.2, 131.5, 130.6, 129.0, 128.2, 127.3, 126.0, 125.6, 125.3, 99.3, 56.9, 29.3; HRMS calcd for C₂₆H₂₈Br₂N₂O₄ ([M + NH₄⁺]⁺) 576.0380, found 576.0382.

2.9 General procedure of preparation of (R,S,S)-3,3′-bis([N-diphenylprolinol)methyl]-2,2′-bis(methoxymethyl)-1,1′-binaphthol (1b).

To a mixture of 0.84 g (R)-4b (1.5 mmol) and 2.1 g anhydrous K₂CO₃ (15 mmol) in 15 mL dry DMF, 0.84 g solid (S)-diphenylprolinol (3.3 mmol) was introduced in one portion at room temperature. The reaction was stirred for 2 h, and it was then quenched with 30 mL water, extracted with ethyl acetate three times, combined the organic layers, washed it with water two times and little saturated brine, condensed in vacuo to give a yellow thick oil. This oil was re-dissolved with 3.0 N HCl (5 mL) in 20 mL THF. The solution was refluxed for 6 h, removed the organic solvents by condensed in vacuo. Added 5.0 mL water, adjusted the solution to pH 10.0 or so with concentrated hydrous ammonia, extracted with ethyl acetate three times, washed the combined ethyl acetate layers successively with water and little saturated brine, dried with anhydrous Na₂SO₄, condensed in vacuo to give a yellow solid. Purification by a silica column afforded the aimed product (R,S,S)-1b as a white solid, 0.98 g, yield 80%. [α]D⁺⁰ +82 (c 5.0, CHCl₃); Mp 119–124°C; IR (KBr) 3509, 2964, 1729, 1446, 1248, 1108, 748, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, J = 7.2Hz, 1H), 7.58–7.51 (m, 5H), 7.37–7.07 (m, 9H), 4.14–4.09 (m, 1H), 3.98 (br, 1H), 3.52 (br, 2H), 3.13–3.10 (m, 1H), 2.54–2.52 (m, 1H), 2.08–2.04 (m, 2H), 1.85 (br, 1H), 1.71 (br, 2H), 1.27–1.23 (m, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 152.3, 128.5, 128.3, 128.1, 127.8, 127.0, 126.6, 125.9, 124.7, 123.3, 114.2, 79.0, 55.5, 29.5, 24.0, 14.2; HRMS calcd for C₅₂H₃₅N₂O₄ ([M + H⁺]⁺) 817.4000, found 817.3999.

2.10 (S,S,S)-3,3′-bis([N-diphenylprolinol)methyl]-2,2′-bis(methoxymethyl)-1,1′-binaphthol (1a).

1a was prepared according to the same procedure of (R,S,S)-1b, yield 80%; [α]D⁺⁰ +10 (c 5.0, CHCl₃); Mp 131–136°C; IR (KBr) 3432, 2954, 1626, 1446, 1251, 748, 701 cm⁻¹; ¹H NMR (400 MHz) δ 7.76(d, J = 7.2 Hz, 1H), 7.58–7.51 (m, 5H), 7.37–7.07 (m, 9H), 4.14–4.09 (m, 1H), 3.98 (br, 1H), 3.52 (br, 2H), 3.13–3.10 (m, 1H), 2.54–2.52 (m, 1H), 2.08–2.04 (m, 2H), 1.85 (br, 1H), 1.71 (br, 2H), 1.27–1.23 (m, 1H); ¹³C NMR (400 MHz) δ 152.2, 146.1, 128.3, 128.1, 127.8, 126.6, 125.9, 124.9,
123.3, 79.0, 58.9, 55.6, 29.3, 24.1; HRMS calcd for C_{56}H_{33}N_{2}O_{4} ([M + H]^+) 817.4000, found 817.3999.

3. Typical procedure for catalytic asymmetric direct aldol reactions of aryl methyl ketones with aryl aldehydes.

Diethyl zinc 0.039 mmol (1.123N in n-hexane) was added dropwise into a solution of 1b (0.02 mmol, 16.35 mg) in 1.0 mL DMF at 0 °C under an argon atmosphere. The mixture was stirred for 40 min, and then 20 mg 4Å molecular seives and triethylamine (0.08 mmol, 11.2 µL) were successively introduced. After 10 min, 0.1 mmol aldehyde and 1.0 mmol ketone were successively added. The reaction was continued for 5 days. Cold diluted hydrous HCl was added dropwise. Extracted the aqueous layer three times with ethyl acetate. The organic layers were combined, washed successively with water and little brine, dried with anhydrous Na_{2}SO_{4}. Filtered out the salt and condensed under reduced pressure. Purification by column chromatography afforded the desired products 5a~5p.


**(R)-3-Hydroxy-1,3-diphenylpropan-1-one (5a).** The title compound was prepared according to the typical procedure, as described above in 61% yield and 70% ee. Mp 50–52.5 °C; [α]_{D}^{20} +60 (c 0.83, CHCl_{3}) (Lit. 3 [α]_{D}^{20} −85.3 (c 1.3, CHCl_{3}) for (S) enantiomer); 1H NMR (200 MHz) δ 7.95 (d, J = 7.0 Hz, 2H), 7.59–7.25 (m, 8H), 5.35 (t, J = 6.0 Hz, 1H), 3.37 (d, J = 6.0 Hz, 2H); enantiomeric excess was determined by HPLC with a OD-H column (hexane:2-propanol 85:15), 0.8 mL/min, major enantiomer t_{R} = 13.1 min, minor enantiomer t_{S} = 11.8 min.

**(R)-3-Hydroxy-3-naphthyl-1-phenylpropan-1-one (5b).** The title compound was prepared according to the typical procedure, as described above in 63% yield and 73% ee. Mp 94–96 °C; [α]_{D}^{20} +113 (c 1.28, CHCl_{3}); 1H NMR (200 MHz) δ 7.98–7.95 (m, 6H), 7.56–7.45 (m, 6H), 6.15 (dd, J_{1} = 3.4 Hz, J_{2} = 8.4 Hz, 1H), 3.68 (br, 1H),
3.54–3.39 (m, 2H); enantiomeric excess was determined by HPLC with a OD-H column (hexane:2-propanol 85:15), 0.8 mL/min, major enantiomer $t_R = 18.4$ min, minor enantiomer $t_S = 13.8$ min.

(R)-3-Hydroxy-3-(2-naphthyl)-1-phenylpropan-1-one (5c). The title compound was prepared according to the typical procedure, as described above in 70% yield and 72% ee. Mp 82–84 °C; $[\alpha]_D^{20} +20$ (c 3.0, CHCl$_3$); $^1$H NMR (200 MHz) $\delta$ 7.99–7.84 (m, 6H), 7.56–7.46 (m, 6H), 5.52 (t, $J = 6.0$ Hz, 1H), 3.70 (br, 1H), 3.46 (d, $J = 5.7$ Hz, 2H); enantiomeric excess was determined by HPLC with a OD-H column (hexane:2-propanol 85:15), 0.8 mL/min, major enantiomer $t_R = 22.5$ min, minor enantiomer $t_S = 20.1$ min.

(R)-3-Hydroxy-3-(2-methoxyphenyl)-1-phenylpropan-1-one (5d). The title compound was prepared according to the typical procedure, as described above in 65% yield and 59% ee. Mp 67–69 °C; $[\alpha]_D^{20} +59$ (c 2.96, CHCl$_3$); FT-IR (KBr) 3525, 1671, 1596, 1496, 1458, 1400, 1325, 1254, 1215, 1027, 752, 691, 563, 508 cm$^{-1}$; $^1$H NMR (200 MHz) $\delta$ 7.98 (d, $J = 2.8$ Hz, 2H), 7.57–7.42 (m, 4H), 7.23–7.19 (m, 1H), 7.22–6.99 (m, 1H), 6.88 (d, $J = 8.2$ Hz, 1H), 5.60 (dd, $J_1 = 2.7$ Hz, $J_2 = 9.0$Hz, 1H), 3.84 (s, 3H), 3.52 (dd, $J_1 = 2.8$ Hz, $J_2 = 17.4$ Hz, 1H), 3.24 (dd, $J_1 = 9.1$ Hz, $J_2 = 17.4$ Hz, 1H); $^{13}$C NMR (200 MHz) $\delta$ 200.6, 155.7, 136.8, 133.4, 131.1, 128.6, 128.3, 128.2, 126.5, 120.9, 110.2, 65.6, 55.3, 45.8; enantiomeric excess was determined by HPLC with a AS-H column (hexane:2-propanol 85:15), $\lambda =254$ nm, 0.8 mL/min, major enantiomer $t_R = 18.9$ min, minor enantiomer $t_S = 13.0$ min.
(R)-3-Hydroxy-3-(3-methoxyphenyl)-1-phenylpropan-1-one (5e). The title compound was prepared according to the typical procedure, as described above in 70% yield and 61% ee. Mp 39–42 °C; [α]_D^{20} +36 (c 1.06, CHCl_3); FT-IR (KBr) 3521, 1675, 1598, 1323, 1257, 1214, 1156, 1042, 798, 755, 689, 556 cm⁻¹; ^1^H NMR (200 MHz) δ 7.97 (d, _J_ = 1.6 Hz, 2H), 7.59–7.43 (m, 3H), 7.26 (d, _J_ = 1.0 Hz, 1H), 7.21 (d, _J_ = 1.1 Hz, 2H), 6.87–6.71 (m, 1H), 5.33 (t, _J_ = 6.0 Hz, 1H), 3.83 (s, 3H), 3.37 (d, _J_ = 6.2 Hz, 2H); ^1^C NMR (200 MHz) δ 200.1, 159.9, 144.7, 136.6, 133.6, 129.6, 128.7, 128.1, 118.0, 113.2, 111.2, 70.0, 55.3, 47.4; enantiomeric excess was determined by HPLC with a AS-H column (hexane:2-propanol 90:10), 1mL/min, major enantiomer _t_R_ = 27.7 min, minor enantiomer _t_S_ = 22.8 min.

(R)-3-Hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (5f) The title compound was prepared according to the typical procedure, as described above in 22% yield and 32% ee. Mp 44–46 °C; [α]_D^{20} +53 (c 0.94, CHCl_3); ^1^H NMR (200 MHz) δ 7.96 (d, _J_ = 7.0 Hz, 2H), 7.59–7.26 (m, 5H), 6.91 (d, _J_ = 8.7 Hz, 2H), 5.30 (t, _J_ = 6.0 Hz, 1H), 3.82 (s, 3H), 3.36 (d, _J_ = 5.8 Hz, 2H); enantiomeric excess was determined by HPLC with a AS-H column (hexane:2-propanol 80:20), 1mL/min, major enantiomer _t_R_ = 20.2 min, minor enantiomer _t_S_ = 18.8 min.

(R)-3-(2-Chlorophenyl)-3-hydroxy-1-phenylpropan-1-one (5g). The title compound was prepared according to the typical procedure, as described above in 97% yield and 54% ee. Mp 82–84 °C; [α]_D^{20} +61 (c 4.3, CHCl_3); FT-IR (KBr) 3526, 1669, 1400, 1207, 755, 689, 550 cm⁻¹; ^1^H NMR (200 MHz) δ 7.97 (d, _J_ = 7.0 Hz, 2H), 7.73 (d, _J_ = 7.5 Hz, 1H), 7.60–7.23 (m, 6H), 5.69 (dd, _J_1 = 2.0 Hz, _J_2 = 9.5 Hz, 1H), 3.58(dd, _J_1 = 2.2 Hz, _J_2 = 17.8 Hz, 1H), 3.15 (dd, _J_1 = 9.5 Hz, _J_2 = 17.8 Hz, 1H); ^1^C NMR (200 MHz) δ 200.3, 140.3, 136.5, 133.7, 131.2, 129.3, 128.7, 128.6, 128.2, 127.3, 66.8, 45.4; enantiomeric excess was determined by HPLC with a AS-H column (hexane:2-propanol 90:10), 1mL/min, major enantiomer _t_R_ = 15.1 min, minor enantiomer _t_S_ = 10.8 min.
(R)-3-(3-Chlorophenyl)-3-hydroxy-1-phenylpropan-1-one (5i). The title compound was prepared according to the typical procedure, as described above in 65% yield and 64% ee. Mp 101–102 °C; [α]_D^20 +42 (c 2.0, CHCl₃); FT-IR (KBr) 3467, 1672, 1527, 1350, 1211, 136.5, 133.8, 133.3, 128.7, 128.6, 128.1, 127.2, 69.4, 47.2; enantiomeric excess was determined by HPLC with a AD-H column (hexane:2-propanol 90:10), 1mL/min, major enantiomer t_R = 17.3 min, minor enantiomer t_S = 14.9 min.

(R)-3-Hydroxy-3-(3-nitrophenyl)-1-phenylpropan-1-one (5j). The title compound was prepared according to the typical procedure, as described above in 74% yield and 57% ee. Mp 85–87 °C; [α]_D^20 +84 (c 2.48, CHCl₃); FT-IR (KBr) 3510, 1672, 1527, 1350, 1211, 1073, 759, 688, 512 cm⁻¹; ^1H NMR (200 MHz) δ 8.33 (s, 1H), 8.10–8.19 (m, 1H), 7.98–7.93 (m, 2H), 7.78 (d, J = 2.2 Hz, 1H), 7.62–7.45 (m, 4H), 5.48–5.42 (dd, J₁ = 4.0 Hz, J₂ = 8.0 Hz, 1H), 3.80 (br, 1H), 3.43–3.37 (m, 2H); ^13C NMR (125 MHz) δ 199.6, 148.5, 145.1, 136.2, 134.0, 131.9, 129.5, 128.8, 128.2, 122.6, 120.9, 69.1, 47.0; enantiomeric excess was determined by HPLC with a AS-H column
(hexane:2-propanol 95:5), 1mL/min, major enantiomer $t_R = 56.7$ min, minor enantiomer $t_S = 62.9$ min.

(R)-3-Hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one (5k). The title compound was prepared according to the typical procedure, as described above in 75% yield and 46% ee. Mp 115–116 °C; $[\alpha]_D^{20} +27$ (c 2.88, CHCl$_3$); $^1$H NMR (200 MHz) $\delta$ 8.23 (d, $J = 8.8$ Hz, 2H), 7.95 (d, $J = 7.0$ Hz, 2H), 7.66–7.48 (m, 5H), 5.49–5.43 (dd, $J_1 = 4.1$ Hz, $J_2 = 7.9$Hz, 1H), 3.79 (br, 1H), 3.40–3.35 (m, 2H); enantiomeric excess was determined by HPLC with a AD-H column (hexane:2-propanol 80:20), 1mL/min, major enantiomer $t_R = 17.0$ min, minor enantiomer $t_S = 14.3$ min.

(R)-3-Hydroxy-3-(3-methylphenyl)-1-phenylpropan-1-one (5l). The title compound was prepared according to the typical procedure, as described above in 43% yield and 50% ee. $[\alpha]_D^{20} +35$ (c 1.7, CHCl$_3$); $^1$H NMR (400 MHz) $\delta$ 7.96 (d, $J = 7.6$ Hz, 2H), 7.59 (t, $J = 7.6$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 2H), 7.29–7.21 (m, 3H), 7.12 (d, $J = 7.2$ Hz, 1H), 5.32 (t, $J = 6.0$ Hz, 1H), 3.60 (br, 1H), 3.37 (d, $J = 5.6$ Hz, 2H); enantiomeric excess was determined by HPLC with a OD-H column (hexane:2-propanol 85:15), 0.8 mL/min, major enantiomer $t_R = 12.3$ min, minor enantiomer $t_S = 11.0$ min.

(R)-3-(2-Furyl)-3-hydroxy-1-phenylpropan-1-one (5m). The title compound was prepared according to the typical procedure, as described above in 45% yield and 80% ee. Mp 78–79 °C; $[\alpha]_D^{20} +44$ (c 1.6, CHCl$_3$); $^1$H NMR (400 MHz) $\delta$ 7.99 (d, $J = 8.0$ Hz, 2H), 7.63–7.59 (m, 1H), 7.51–7.47 (m, 2H), 7.40 (s, 1H), 6.36–6.35 (m, 2H), 5.37 (dd, $J_1 = 2.8$ Hz, $J_2 = 8.8$ Hz, 1H), 3.60 (dd, $J_1 = 8.4$ Hz, $J_2 = 17.8$ Hz, 1H), 3.48 (dd, $J_1 = 2.8$ Hz, $J_2 = 17.6$ Hz, 1H); enantiomeric excess was determined by HPLC with a OD-H column (hexane:2-propanol 90:10), 0.8 mL/min, major enantiomer $t_R = 29.6$ min, minor enantiomer $t_S = 27.6$ min.
(R)-3-Hydroxy-1-phenyl-3-(2-thienyl)propan-1-one (5n). The title compound was prepared according to the typical procedure, as described above in 31% yield and 69% ee. Mp 60–61 °C; [α]D<sup>20</sup> +264 (c 1.02, CHCl₃); ¹H NMR (400 MHz) δ 7.97 (d, J = 7.6 Hz, 2H), 7.62–7.59 (m, 1H), 7.50–7.46 (m, 2H), 7.28–7.26 (m, 1H), 7.04–6.98 (m, 2H), 5.62–5.59 (t, J <sub>1</sub> = 6.0 Hz, J <sub>2</sub> = 5.6 Hz, 1H), 3.78 (s, 1H), 3.52–3.50 (m, 2H); enantiomeric excess was determined by HPLC with a AS-H column (hexane:2-propanol 90:10), 1.0 ml/min, major enantiomer t<sub>R</sub> = 22.6 min, minor enantiomer t<sub>S</sub> = 15.9 min.

(R)-3-Hydroxy-1-naphthyl-3-phenylpropan-1-one (5o). The title compound was prepared according to the typical procedure, as described above in 65% yield and 54% ee. Mp 116–117 °C; [α]D<sup>20</sup> +49 (c 3.0, CHCl₃); ¹H NMR (200 MHz) δ 8.68 (d, J = 8.6 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.86–7.82 (m, 3H), 7.62–7.35 (m, 8H), 5.43–5.37 (dd, J <sub>1</sub> = 4.1 Hz, J <sub>2</sub> = 8.2 Hz, 1H), 3.60 (s, 1H), 3.48–3.33 (m, 2H); ¹³C NMR (200 MHz) δ 203.0, 143.0, 135.1, 133.9, 133.3, 130.0, 128.5, 128.4, 128.3, 128.1, 127.6, 126.5, 125.7, 124.2, 70.4, 50.4; enantiomeric excess was determined by HPLC with a AS-H column (hexane:2-propanol 85:15), 1 mL/min, major enantiomer t<sub>R</sub> = 15.5 min, minor enantiomer t<sub>S</sub> = 13.5 min.

(R)-3-Hydroxy-1-(2-naphthyl)-3-phenylpropan-1-one (5p). The title compound was prepared according to the typical procedure, as described above in 57% yield and 59% ee. Mp 106–107 °C; [α]D<sup>20</sup> +45 (c 4.0, CHCl₃); ¹H NMR (200 MHz) δ 8.45 (s, 1H), 8.02–7.85 (m, 3H), 7.62–7.35 (m, 8H), 5.41 (t, J = 6.0 Hz, 1H), 3.51 (d, J = 6.0 Hz, 2H); enantiomeric excess was determined by HPLC with a OD-H column (hexane:2-propanol 85:15), 0.8 mL/min, major enantiomer t<sub>R</sub> = 24.5 min, minor enantiomer t<sub>S</sub> = 16.4 min.
5. Scheme S2.

SCHEME S2. Direct asymmetric aldol reaction of acetophenone with alkyl aldehydes

\[ R \text{CHO} + \text{MeO} + \text{Et}_2Zn(40\%), \text{Et}_3N(80\%) \rightarrow \text{R} = \text{i-Bu} \]

20 mg 4Å MS, DMF, 0°C, 5 days

5q: \[ R = \text{i-Bu} \]

6. Characterization of 5q-5r.

(R)-3-Hydroxy-5-methyl-1-phenylhexan-1-one (5q). The title compound was prepared according to the typical procedure of aryl ketones and aryl aldehydes, as described above in 22% yield and 44% ee. \([\alpha]_D^{20} + 29 (c 0.84, \text{CHCl}_3)\), (Lit.\(^4 \) \([\alpha]_D^{25} + 55.5 (c 4.07, \text{CHCl}_3)\) for \( R \) enantiomer); \(^1\)H NMR (400 MHz) \( \delta \) 7.96(d, \( J = 7.2 \) Hz, 2H), 7.60 (t, \( J = 7.2 \) Hz, 1H), 7.48 (t, \( J = 7.6 \) Hz, 2H), 4.35−4.29 (m, 1H), 3.16 (dd, \( J_1 = 2.8 \) Hz, \( J_2 = 17.4 \) Hz, 1H), 3.04 (dd, \( J_1 = 8.8 \), \( J_2 = 17.8 \) Hz, 1H), 1.91−1.85 (m, 1H), 1.64−1.57 (m, 1H), 1.29−1.22 (m, 1H), 0.96 (dd, \( J_1 = 3.2 \) Hz, \( J_2 = 6.8 \) Hz, 6H); enantiomeric excess was determined by HPLC with a OD-H column (hexane:2-propanol 85:15), 0.8 mL/min, major enantiomer \( t_R = 7.458 \) min, minor enantiomer \( t_S = 6.053 \) min.

(R)-3-Hydroxy-1-phenylhexan-1-one (5r). The title compound was prepared according to the typical procedure of aryl ketones and aryl aldehydes, as described above in 21% yield and 39% ee. \([\alpha]_D^{20} + 24 (c 0.76, \text{CHCl}_3)\), (Lit.\(^4 \) \([\alpha]_D^{25} + 31.9 (c 0.75, \text{CHCl}_3)\) for \( R \) enantiomer); \(^1\)H NMR (400 MHz) \( \delta \) 7.97 (d, \( J = 7.2 \) Hz, 2H), 7.60 (t, \( J = 7.6 \) Hz, 1H), 7.48 (t, \( J = 7.6 \) Hz, 2H), 4.24−4.22 (m, 1H), 3.18 (dd, \( J = 2.8 \) Hz, 17.6 Hz, 1H), 3.05 (dd, \( J_1 = 4.4 \) Hz, \( J_2 = 17.6 \) Hz, 1H), 1.65−1.43 (m, 4H), 0.97 (t, \( J = 7.2 \) Hz, 3H); enantiomeric excess was determined by HPLC with a OD-H column (hexane:2-propanol 85:15), 0.8 mL/min, major enantiomer \( t_R = 7.445 \) min, minor enantiomer \( t_S = 6.220 \) min.
7. $^1$H NMR of (R)-2,2'-bis(methoxymethyl)-1,1'-binaphthol (400 MHz, CDCl$_3$).
8. Spectra of compounds 2b.

$^1$H NMR of compound 2b (400 MHz, CDCl$_3$).
9. Spectra of compounds 3b.

$^1$H NMR of compound 3b (400 MHz, CDCl$_3$).
10. Spectra of compounds 4b.

$^1$H NMR of compound 4b (400 MHz, CDCl$_3$).
$^{13}$C NMR of compound 4b (400 MHz, CDCl$_3$).
HMBC of compound 4b (400 MHz, CDCl3)
11. Spectra of compounds 1a.

$^1$H NMR of compound 1a (400 MHz, CDCl$_3$).
$^{13}$C NMR of compound 1a (400 MHz, CDCl$_3$).
12. Spectra of compounds 1b.

$^1$H NMR of compound 1b (400 MHz, CDCl$_3$).
$^{13}$C NMR of compound 1b (400 MHz, CDCl$_3$).
13. Spectra of compounds 5a~5r.

$^1$H NMR of compound 5a (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5b (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5c (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5d (200 MHz, CDCl$_3$).
$^{13}$C NMR of compound 5d (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5e (200 MHz, CDCl$_3$).
$^{13}$C NMR of compound 5e (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5f (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5g (200 MHz, CDCl$_3$).
$^{13}$C NMR of compound 5g (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5h (200 MHz, CDCl$_3$).
$^{13}$C NMR of compound 5h (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5i (200 MHz, CDCl$_3$).
$^{13}$C NMR of compound 5i (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5j (200 MHz, CDCl$_3$).
\(^{13}\)C NMR of compound 5j (200 MHz, CDCl\(_3\)).
$^1$H NMR of compound 5k (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5l (400 MHz, CDCl$_3$).
$^1$H NMR of compound 5m (400 MHz, CDCl$_3$).
$^1$H NMR of compound 5n (400 MHz, CDCl$_3$).
$^1$H NMR of compound 50 (200 MHz, CDCl$_3$).
$^{13}$C NMR of compound 5o (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5p (200 MHz, CDCl$_3$).
$^1$H NMR of compound 5q (200 MHz, CDCl$_3$)
$^1$H NMR of compound 5r (200 MHz, CDCl$_3$)
14. HPLC spectra of 5a–5r.
5g

5g racemate

5h

5h racemate
15. References.