Supporting Information
Dry and Wet Prolines for Asymmetric Organic-Solvent-Free Aldehyde-Aldehyde and Aldehyde-Ketone Aldol Reactions

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Typical procedure for the solvent-free cross-aldol reaction between two aldehydes catalyzed by proline
To a mixture of o-chlorobenzaldehyde (45 µL, 0.4 mmol) and L-proline (5 mg, 0.04 mmol) was added propanol (144 µL, 2.0 mmol) successively at 0 °C. After stirring the reaction mixture for 48 hours at that temperature, the reaction mixture was cooled at 0 °C and MeOH (1 mL) and NaBH₄ (76 mg, 2.0 mmol) was added. The reaction mixture was stirred for 1 hour at 0 °C. The reaction was quenched with pH 7.0 phosphate buffer solution and the organic materials were extracted with ethyl acetate three times and the combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated in vacuo after filtration. Purification by preparative thin layer chromatography (ethyl acetate) gave (1R, 2R)-1-(o-chlorophenyl)-2-methylpropane-1,3-diol (72 mg, 0.36 mmol) in 90% yield as the diastereomeric mixture (anti : syn = 12.9 : 1). Enantiometric excess of anti aldol was 96%ee.

(1R, 2R)-1-(o-Chlorophenyl)-2-methylpropane-1,3-diol (1)

1H NMR (400 MHz, CDCl₃): δ 0.81 (3H, t, J = 7.2 Hz), 2.02-2.05 (1H, m), 2.80 (1H, br s), 3.30 (1H, br s), 3.61-3.70 (2H, m), 5.05 (1H, d, J = 6.8 Hz), 7.14 (1H, t, J = 7.6 Hz), 7.22-7.27 (2H, m), 7.50 (1H, d, J = 7.6 Hz);
13C NMR (100 MHz, CDCl₃): δ 13.7, 40.7, 67.1, 76.1, 127.2, 128.1, 128.7, 129.4, 132.5, 140.9;
IR (neat): ν 3357, 2966, 2932, 1572, 1471, 1438, 1034, 754, 703 cm⁻¹;
HRMS(FAB): [M+Na] calcd for [C₁₀H₈ClOHOH]: 223.0504, found: 223.0496;
Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (100:1 hexane:2-propanol, λ=254 nm), 1.2 mL/min; major enantiomer tr = 15.2 min, minor enantiomer tr = 17.2 min, after conversion to the monobenzoyl ester.

(1R, 2R)-1-(p-Trifluoromethylphenyl)-2-methylpropane-1,3-diol (2)

1H NMR (400 MHz, CDCl₃): δ 0.71 (3H, d, J = 7.2 Hz), 1.95-2.06 (1H, m), 2.15-2.32 (2H, m), 4.59 (1H, d, J = 7.6 Hz), 7.43 (2H, d, J = 8.0 Hz), 7.59 (2H, d, J = 8.0 Hz);
13C NMR (100 MHz, CDCl₃): δ 13.7, 41.6, 67.6, 79.8, 125.3, 127.0, 130.2, 147.3;
IR (neat): ν 3349, 2884, 1619, 1419, 1326, 1164, 1126, 1068, 1017, 841 cm⁻¹;
HRMS(FAB): [M+Na] calcd for [C₁₀H₁₃F₂O₂Na]: 257.0760, found: 257.0764;
Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (80:1 hexane:2-propanol, λ=254 nm), 1.0 mL/min; major enantiomer tr = 39.2 min, minor enantiomer tr = 52.8 min, after conversion to the monobenzoyl ester.

(1R, 2R)-1-Phenyl-2-methylpropane-1,3-diol (3)

was known compound.
Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (30:1 hexane:2-propanol, λ=230 nm), 1.0 mL/min; major enantiomer tr = 27.2 min, minor enantiomer tr = 38.6 min, after conversion to the monobenzoyl ester.

The absolute stereochemistry of the aldol 3 was determined by the chiral HPLC analysis by comparing the retention time of the present aldol product with that synthesized by L-proline in DMF by MacMillan’s
was known compound.  

Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (100:1 hexane:2-propanol), 0.5 mL/min; major enantiomer tr = 42.4 min, minor enantiomer tr = 47.8 min, after conversion to the monobenzoyl ester.

The absolute stereochemistry of the aldols 1, 2, 4 were assumed by the chiral HPLC analysis by comparing the retention time of the present aldol product with that synthesized by L-proline in DMF by MacMillan’s procedure.

4,4-Dimethoxy-2-benzylbutane-1,3-diol (diastereomeric mixture (anti : syn = 3.3 : 1)) (5)

\[ \text{H NMR (400 MHz, CDCl}_3\): } \delta 1.61-1.82 (3H, m), 1.85-1.91 (1H, m), 2.03-2.12 (2H, m), 2.28-2.39 (2H, m), 2.65-2.70 (1H, m), 3.17 (1H, d, J = 7.6 Hz), 3.39 (3H, s), 3.43 (3H, s), 3.58-3.62 (1H, m), 4.47 (1H, d, J = 5.6 Hz);  

\[ \text{IR (neat): v 3499, 2937, 2864, 2833, 1704, 1450, 1191, 1123, 1078, 972 cm}^{-1}; \]

HRMS (FAB): [M+Na] calcd for [C\(_{16}\)H\(_{35}\)O\(_{5}\)Na]: 263.1254, found: 263.1248;  

Enantiomeric excess of major anti isomer was determined by HPLC with a Chiralpak IA column (50:1 hexane:2-propanol, \( \lambda = 254 \text{ nm} \)), 1.0 mL/min; major enantiomer tr = 21.2 min, minor enantiomer tr = 19.6 min after conversion to the monobenzoyl ester.

**Typical procedure of cross-aldol reaction between dimethoxyacetaldehyde and another aldehyde catalyzed by proline in the presence of water**  

To a mixture of 60 wt% aqueous solution of dimethoxyacetaldehyde (60 \( \mu \)L, 0.4 mmol), L-proline (9 mg, 0.08 mmol) and was added 2,2-dimethyl-1,3-dioxan-5-one (238 \( \mu \)L, 2.0 mmol) successively at room temperature. After stirring the reaction mixture for 16 hours at that temperature. The reaction was quenched with pH 7.0 phosphate buffer solution and the organic materials were extracted with ethyl acetate three times and the combined organic extracts were dried over anhydrous Na\(_2\)SO\(_4\), and concentrated in vacuo after filtration. Purification by silicagel column chromatography (ethyl acetate:hexane=1:5 ~ 1:1) gave (4R, 1’R)-4-(1’-hydroxy-2’-2’-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-5-one (44 mg, 0.19 mmol) in 47% yield.

(2R, 1’R)-2-(1’-Hydroxy-2’-2’-dimethoxyethyl)-cyclohexan-1-one (6)

\[ \text{H NMR (400 MHz, CDCl}_3\): } \delta 1.61-1.82 (3H, m), 1.85-1.91 (1H, m), 2.03-2.12 (2H, m), 2.28-2.39 (2H, m), 2.65-2.70 (1H, m), 3.17 (1H, d, J = 7.6 Hz), 3.39 (3H, s), 3.43 (3H, s), 3.58-3.62 (1H, m), 4.47 (1H, d, J = 5.6 Hz);  

\[ \text{IR (neat): v 3499, 2937, 2864, 2833, 1704, 1450, 1191, 1123, 1078, 972 cm}^{-1}; \]

HRMS (FAB): [M+Na] calcd for [C\(_{16}\)H\(_{35}\)O\(_{5}\)Na]: 225.1097, found: 225.1089;  

Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (100:1 hexane:2-propanol, \( \lambda = 254 \text{ nm} \)), 1.0 mL/min; major enantiomer tr = 7.3 min, minor enantiomer tr = 6.8 min, after conversion to the monobenzoyl ester.

(2R, 1’R)-2-(1’-Hydroxy-2’-2’-dimethoxyethyl)-cyclopentan-1-one (7)

\[ \text{H NMR (600 MHz, CDCl}_3\): } \delta 1.73-1.81 (1H, m), 1.87-1.94 (1H, m), 2.01-2.09 (1H, m), 2.11-2.22 (2H, m), 2.28-2.36 (1H, m), 2.40-2.44 (1H, m), 3.02 (1H, d, J = 1.6 Hz), 3.46 (3H, s), 3.47 (3H, s), 3.76-3.78 (1H, m), 4.61 (1H, d, J = 4.4 Hz);  

S2
Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (30:1 hexane:2-propanol, λ=220 nm); 1.0 mL/min; major enantiomer tr = 15.4 min, minor enantiomer tr = 17.8 min.

(4R, 1'R)-4-(1'-'Hydroxy-2',2'-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-5-one
was known compound.
Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (30:1 hexane:2-propanol), 1 mL/min; major enantiomer tr = 19.3 min, minor enantiomer tr = 27.5 min, after conversion to the 3,5-dinitrobenzoylester.
The absolute stereochemistry of the aldol 8 was determined by the chiral HPLC analysis by comparing the retention time of the 3,5-dinitrobenzoylester of the present aldol product with that synthesized by L-proline in DMF by Barbas’s procedure.

The absolute stereochemistry of the aldols 5, 6, 7 were assumed by the chiral HPLC analysis by comparing the retention time of the 3,5-dinitrobenzoylester of the present aldols product with that synthesized by L-proline in DMF by Barbas’s procedure.

**Typical procedure of cross-aldol reaction between aldehyde and ketone catalyzed by proline in the presence of water**

To a mixture of o-chlorobenzaldehyde (45 µL, 0.4 mmol), L-proline (14 mg, 0.12 mmol) and water (22 µL, 1.2 mmol) was added cyclohexanone (123 µL, 1.2 mmol) successively at room temperature. After stirring the reaction mixture for 72 hours at that temperature, the reaction was quenched with pH 7.0 phosphate buffer solution and the organic materials were extracted with ethyl acetate three times and the combined organic extracts were dried over anhydrous Na2SO4 and concentrated in vacuo after filtration. Purification by preparative thin layer chromatography (ethyl acetate) gave (2S, 1'R)-2-(hydroxy-o-chlorophenylmethyl) cyclohexan-1-one (67 mg, 0.28 mmol) in 70% yield as the diastereomeric mixture (anti : syn = 12.5 : 1). Enantiomeric excess of anti aldol was 97%ee.

(2S, 1’R)-2-(Hydroxy-o-chlorophenylmethyl)cyclohexan-1-one
was known compound.
Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (100:1 hexane:2-propanol, λ= 220 nm), 1.0 mL/min; major enantiomer tr = 14.2 min, minor enantiomer tr = 16.5 min.

(2S, 1’R)-2-(Hydroxy-o-chlorophenylmethyl)cyclopentan-1-one
1H NMR (400 MHz, CDCl3): δ 1.64-1.78 (3H, m), 1.93-2.07 (1H, m), 2.22-2.35 (1H, m), 2.36-2.52 (2H, m), 4.47 (1H, d, J=1.2 Hz), 5.29 (1H, br d, J=9.3 Hz), 7.15-7.23 (1H, m), 7.26-7.36 (2H, m), 7.52 (1H, m);
13C NMR (100 MHz, CDCl3): δ 20.5, 26.4, 38.7, 55.6, 70.4, 127.4, 128.4, 128.9, 129.3, 132.5, 139.2, 222.8;
IR (neat): ν 3447, 2965, 1735, 1695, 1440, 1402, 1156, 1024, 749 cm⁻¹;
Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (100:1 hexane:2-propanol, λ= 220 nm), 1.0 mL/min; major enantiomer tr = 28.2 min, minor enantiomer tr = 37.8 min.
(2S, 1′R)-2-(Hydroxy-p-nitrophenylmethyl)cyclohexan-1-one

was known compound. Melting point: 98.0-98.5 °C; Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (10:1 hexane:2-propanol, λ = 254 nm), 1.0 mL/min; major enantiomer tr = 10.3 min, minor enantiomer tr = 12.3 min.

(2S, 1′R)-2-(Hydroxy-p-trifluoromethylphenylmethyl)cyclohexan-1-one

1H NMR (400 MHz, CDCl3): δ 1.24-1.37 (1H, m), 1.48-1.70 (3H, m), 1.77-1.82 (1H, m), 2.09 (1H, ddd, J = 3.2, 6.0, 12.8 Hz), 2.34 (1H, ddt, J = 0.8, 6.0, 13.6 Hz), 2.44-2.50 (1H, m), 2.54-2.61 (1H, m), 3.99 (1H, br s), 4.83 (1H, d, J = 8.8 Hz), 7.42 (2H, d, J = 8.0 Hz), 7.59 (2H, d, J = 8.0 Hz);

13C NMR (100 MHz, CDCl3): δ 24.7, 27.7, 30.7, 42.7, 57.2, 74.3, 123.2, 125.3, 127.4, 130.1, 144.9, 215.2;

IR (KBr): ν 3752, 3361, 2948, 2910, 1700, 1328, 1170, 1138, 1109, 845 cm⁻¹;

HRMS (FAB): [M+Na] calcd for [C16H13F3O2Na]: 295.0916, found: 295.0907; [α]D25 = –35.2 (c 1.00, MeOH), >99% ee for anti;

Melting point: 86.5-87.0 °C; Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (10:1 hexane:2-propanol, λ = 254 nm), 1.0 mL/min; major enantiomer tr = 12.9 min, minor enantiomer tr = 9.5 min.

The absolute stereochemistry of the aldols 9, 10, 11, 12 were assumed by the chiral HPLC analysis by comparing the retention time of the present aldol products with that synthesized by Barbas’s procedure.

Procedure of cross-aldol reaction catalyzed by proline in the presence of water without using any organic solvent (in the case of aldol product was oil)

To a mixture of p-chlorobenzaldehyde (7.9 mL, 70 mmol), L-proline (2.42 g, 21 mmol) and water (3.8 mL) was added cyclopentanone (30.9 mL, 350 mmol) successively at room temperature. After stirring the reaction mixture for 25 hours at that temperature, water (40 mL) and brine (20 mL) were added to the reaction mixture, which was stirred for 10 minutes. After removal of aqueous phase, bulb to bulb distillation of the organic residue at 140 °C under 0.8 mmHg gave (2S, 1′R)-2-(hydroxy-p-chlorophenylmethyl)cyclohexan-1-one (11.7 g, 52.1 mmol) in 75% yield as the diastereomeric mixture (anti : syn = 1.7 : 1). Enantiomeric excess of anti aldol was >99% ee.

Procedure of cross-aldol reaction catalyzed by proline in the presence of water without using any organic solvent (in the case of aldol product was crystal)

To a mixture of p-trifluoromethylbenzaldehyde (8.6 mL, 57.4 mmol), L-proline (1.98 g, 17.2 mmol) and water (3.1 mL) was added cyclohexanone (29.6 mL, 287 mmol) successively at room temperature. After stirring the reaction mixture for 96 hours at that temperature, organic phase was washed with water (50 mL) three times to remove proline and the organic phase was concentrated in vacuo. Purification by recrystallization from cyclohexane (57.6 mL) gave (2S, 1′R)-2-(hydroxy-p-trifluoromethylphenylmethyl)cyclohexan-1-one (11.4 g, 41.8 mmol) in 73% yield (anti : syn = >20 : 1). Enantiomeric excess of anti aldol was >99% ee.

References
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