SUPPORTING INFORMATION

The smallest organocatalyst in highly enantioselective direct aldol reaction in wet solvent-free conditions

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Experimental Section

**General Methods.** Routine monitoring of reaction was performed by TLC, using pre-coated silica gel TLC plates obtained by E-Merck. All the column chromatographic separations were done by using silica gel (60-120 mesh). Petroleum ether used was of boiling range 60-80 °C. Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were recorded on BRUKER-400 MHz spectrometer. Chemical shifts are expressed in ppm downfield from TMS as internal standard. Infrared (IR) spectra were recorded on a FT-IR spectrometer (Shimadzu). Melting points were measured on a digital melting point apparatus. Analytical high performance liquid chromatography (HPLC) was carried out on (Shimadzu CLASS-VP V6.12 SP5) instrument using Chiralpak AD-H (4.6mm×250mm), Chiralpak Kromasil 5-AmyCoat (4.6 mm×250mm), and Chiralcel OD-H (4.6 mm×250 mm) columns. Optical rotations were measured on a Bellingham+Stanley ADP410 Polarimeter at \(\lambda=589\) nm.
Synthesis of L-proline hydrazide, 1

The following procedure is a partially modified one from the reported procedure in literature.\textsuperscript{1,2} A solution of L-proline (10 mmol, 1.15g) was dissolved in 5 ml of MeOH and was cooled to 0 °C followed by slow addition of 1 mL of acetyl chloride. The mixture was stirred at refluxed for 12 h and then allowed to attain room temperature. The solution was concentrated under reduced pressure. The methyl ester hydrochloride of L-proline so obtained was washed with Et\textsubscript{2}O (2×25 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure to give a crude brownish liquid product (1.57 g, 95%). Then to the crude product in MeOH (9 mL), 98% hydrazine hydrate (8.1 mL) was added drop wise and the mixture was stirred for 24 h. A white precipitate generated was removed by filtration and the filtrate was concentrated under reduced pressure. The yellow oily residue was washed with MeOH (2 x 20 mL) followed by drying under vacuum to give the pure product as a colourless oil (0.99 g, 81%). The \textsuperscript{1}H NMR, \textsuperscript{13}C NMR and IR is consistent with the literature reports.\textsuperscript{2}

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 1.87 (3H, m), 2.22 (1H, m), 3.13 (2H, m), 4.01 (1H, br, s), 4.22 (1H, m), 4.77 (2H, br, s), 8.80 (1H, br, s); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz) \(\delta\) 25.3, 30.8, 45.8, 59.5, 173.1; IR (film, cm\textsuperscript{-1}): 3328 (NH), 3311, 3251, 3153, 3031, 2869, 1741, 1616, 1595, 1446, 1240, 1178, 1087, 894. ESI-MS (m/z): calcd for C\textsubscript{5}H\textsubscript{11}N\textsubscript{3}O [M +H]\textsuperscript{+}: 130.0982; found: 130.0858.
$^1$H NMR Spectrum of L-Proline hydrazide, 1
$^{13}$C NMR Spectrum of L-Proline hydrazide, 1
FT-IR Spectrum of L-Proline hydrazide, 1
ESI-MS Spectrum of L-Proline hydrazide, 1
General procedure for the enantioselective direct aldol reaction.

To a mixture of catalyst 1 (0.1 mmol) and acid additive (0.05 mmol) in water (0.01 mL), ketone (4.0 mmol) was added followed by aromatic aldehyde (1.0 mmol). The resulting mixture was stirred at room temperature, an emulsion was formed. The reaction was monitored by TLC. It was then quenched with 10 mL of saturated NaHCO₃ solution, extracted with EtOAc (3×10 mL), and brine (15 mL), dried over Na₂SO₄. Purification by column chromatography afforded the corresponding pure products as a mixture of syn and anti isomers. The ee of the anti isomers were determined by chiral HPLC analysis.

HPLC data for chiral aldol products

(2S,1′R)-2-[Hydroxy(4-nitrophenyl)methyl]cyclohexan-1-one (2a).³

![2a]

The spectroscopic NMR data are in agreement with the previously reported ones.³ The enantiomeric excess of this sample was determined to be 97% by chiral HPLC analysis (Chiralpak Kromasil 5-CelluCoat, hexanes/iPrOH 95/5), flow rate = 1.0 mL/min; λ = 254 nm; tᵣ (major)=24.5 min, tᵣ (minor)=34.9 min.

(2S,1′R)-2-[Hydroxy(3-nitrophenyl)methyl]cyclohexan-1-one (2b).⁴

![2b]

The spectroscopic NMR data are in agreement with the previously reported ones.⁴ The enantiomeric excess of this sample was determined to be 98% by chiral HPLC analysis
Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (15:85), flow rate = 0.5 mL/min; 
$\lambda = 254$ nm; $t_R$ (major) = 20.7 min, $t_R$ (minor) = 27.9 min.

$(2S,1'R)$-2-[Hydroxy(2-nitrophenyl)methyl]cyclohexan-1-one (2c).\(^3\)

![2c]

The spectroscopic NMR data are in agreement with the previously reported ones.\(^3\) The enantiomeric excess of this sample was determined to be 88% by chiral HPLC analysis.

Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (15:85), flow rate = 0.5 mL/min; 
$\lambda = 254$ nm; $t_R$ (major) = 17.5 min, $t_R$ (minor) = 20.0 min.

$(2S,1'R)$-2-[Hydroxy(2-fluorophenyl)methyl]cyclohexan-1-one (2d).\(^5\)

![2d]

The spectroscopic NMR data are in agreement with the previously reported ones.\(^5\) The enantiomeric excess of this sample was determined to be 68% by chiral HPLC analysis.

Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (05:95), Flow rate: 0.5 mL/min; 
$\lambda = 254$ nm; $t_R$ (major) = 16.2 min, $t_R$ (minor) = 20.7 min.

$(2S,1'R)$-2-[Hydroxy(3-fluorophenyl)methyl]cyclohexan-1-one (2e).

![2e]
The spectroscopic NMR data are in agreement with the previously reported ones. The enantiomeric excess of this sample was determined to be 32% by chiral HPLC analysis Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (05:95), Flow rate: 0.5 mL/min; \( \lambda = 254 \, \text{nm} \); \( t_R \) (minor) = 16.5 min, \( t_R \) (major) = 18.5 min.

\( (2S,1'R)-2-[\text{Hydroxy}(2\text{-methoxyphenyl})\text{methyl}]\text{cyclohexan-1-one (2f).}^6 \)

![2f](image)

The spectroscopic NMR data are in agreement with the previously reported ones.\(^6\) The enantiomeric excess of this sample was determined to be 89% by chiral HPLC analysis Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (05:95), Flow rate: 0.5 mL/min; \( \lambda = 254 \, \text{nm} \); \( t_R \) (major) = 24.8 min, \( t_R \) (minor) = 28.8 min.

\( (2S,1'R)-2-[\text{Hydroxy}(2\text{-chlorophenyl})\text{methyl}]\text{cyclohexan-1-one (2g).}^3 \)

![2g](image)

The spectroscopic NMR data are in agreement with the previously reported ones.\(^3\) The enantiomeric excess of this sample was determined to be 64% by chiral HPLC analysis Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (05:95), Flow rate: 0.5 mL/min; \( \lambda = 254 \, \text{nm} \); \( t_R \) (major) = 12.1 min, \( t_R \) (minor) = 17.0 min.
(2S,1'R)-2-[Hydroxy(3-chlorophenyl)methyl]cyclohexan-1-one (2h).\(^3\)

![Structure of 2h]

The spectroscopic NMR data are in agreement with the previously reported ones.\(^3\) The enantiomeric excess of this sample was determined to be 46% by chiral HPLC analysis Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (05:95), Flow rate: 0.5 mL/min; \(\lambda = 254 \text{ nm}; \ t_R \text{(major)} = 19.2 \text{ min}, \ t_R \text{(minor)} = 21.0 \text{ min}.\)

(2S,1'R)-2-[Hydroxy(4-chlorophenyl)methyl]cyclohexan-1-one (2i).\(^3\)

![Structure of 2i]

The spectroscopic NMR data are in agreement with the previously reported ones.\(^3\) The enantiomeric excess of this sample was determined to be 91% by chiral HPLC analysis Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (10:90), Flow rate: 0.5 mL/min; \(\lambda = 254 \text{ nm}; \ t_R \text{(major)} = 16.5 \text{ min}, \ t_R \text{(minor)} = 18.8 \text{ min}.\)

(2S,1'R)-2-[Hydroxy(4-methylphenyl)methyl]cyclohexan-1-one (2j).\(^4\)

![Structure of 2j]

The spectroscopic NMR data are in agreement with the previously reported ones.\(^4\) The enantiomeric excess of this sample was determined to be 49% by chiral HPLC analysis Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (3:97), Flow rate: 0.5 mL/min;
\[ \lambda = 254 \text{ nm}; t_R (\text{major}) = 14.2 \text{ min}, t_R (\text{minor}) = 18.6 \text{ min}. \]

\((2S, 1'R)-2-[\text{Hydroxy(naphthalen}-1-yl)methyl]\text{cyclohexan-1-one (2k).}^4\)

\[
\begin{align*}
\text{2k} & \\
& \\
\end{align*}
\]

The spectroscopic NMR data are in agreement with the previously reported ones.$^4$ The enantiomeric excess of this sample was determined to be 44% by chiral HPLC analysis Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (3:97), Flow rate: 0.5 mL/min; \[ \lambda = 254 \text{ nm}; t_R (\text{major}) = 16.2 \text{ min}, t_R (\text{minor}) = 23.5 \text{ min}. \]

\((2S, 1'R)-2-[\text{Hydroxy(naphthalen}-2-yl)methyl]\text{cyclohexan-1-one (2l).}^4\)

\[
\begin{align*}
\text{2l} & \\
& \\
\end{align*}
\]

The spectroscopic NMR data are in agreement with the previously reported ones.$^4$ The enantiomeric excess of this sample was determined to be 61% by chiral HPLC analysis Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (10:90), Flow rate: 0.5 mL/min; \[ \lambda = 254 \text{ nm}; t_R (\text{major}) = 26.4 \text{ min}, t_R (\text{minor}) = 33.4 \text{ min}. \]

\((2S, 1'R)-2-[\text{Hydroxy(4-trifluoromethylphenyl)methyl]}\text{cyclohexan-1-one (2m).}^4\)

\[
\begin{align*}
\text{2m} & \\
& \\
\end{align*}
\]
The spectroscopic NMR data are in agreement with the previously reported ones. The enantiomeric excess of this sample was determined to be 80% by chiral HPLC analysis Chiralcel OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (20:80), Flow rate: 0.5 mL/min; λ = 254 nm; t_R (major) = 19.3 min, t_R (minor) = 21.4 min.

(4R)-4-Hydroxy-p-nitrophenylbutan-2-one (3a).

The spectroscopic NMR data are in agreement with the previously reported ones. The enantiomeric excess of this sample was determined to be 98% by chiral HPLC analysis Chiralcel-OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (8.5:91.5), Flow rate: 0.7 mL/min; λ = 254 nm; t_R (major) = 38.2 min, t_R (minor) = 45.0 min.

(2S,1'R)-2-[Hydroxy(4-nitrophenyl)methyl]cyclopentan-1-one (3b).

The spectroscopic NMR data are in agreement with the previously reported ones. The enantiomeric excess of this sample was determined to be >99.9% by chiral HPLC analysis Chiralpak Kromasil-5AmyCoat (254 × 4.6), Mobile phase: IPA:Pet Ether (10:90), Flow rate : 1 mL/min; λ = 265 nm; t_R (minor) = 20.0 min, t_R (major) = 21.5 min.
References:


2a (Racemic) (HPLC Conditions: Chiralpak Kromasil 5-CelluCoat, hexanes/iPrOH 95/5), flow rate = 0.7 mL/min; $\lambda = 254$ nm)

2a (Chiral HPLC done under conditions mentioned in the above experimental section)
2b (Racemic) (HPLC conditions: Chiralcel OD-H (250 x 4.6 mm), IPA:n-Hexane (15:85), flow rate = 0.7 mL/min; λ = 254 nm)

2b (Chiral HPLC done under conditions mentioned in the above experimental section)
2c (Racemic) (HPLC conditions: Chiralcel OD-H (250 x 4.6 mm), IPA:n-Hexane (10:90), flow rate = 0.7 mL/min; $\lambda = 254$ nm)

![HPLC graph and table data]

2c  (Chiral HPLC done under conditions mentioned in the above experimental section)
2d (Racemic) **(HPLC conditions):** Chiralcel OD-H (250 x 4.6 mm), IPA:n-Hexane (05:95), Flow rate: 0.7 ml/min; \( \lambda = 254 \text{ nm} \); \( t_R \) (major) = 12.2 min, \( t_R \) (minor) = 16.3 min.)

2d  (Chiral HPLC done under conditions mentioned in the above experimental section)
2e (Racemic) (HPLC conditions: Chiralcel OD-H (250 x 4.6 mm), IPA:n-Hexane (05:95), Flow rate: 0.7 ml/min; $\lambda = 254$ nm)

2e (Chiral HPLC done under conditions mentioned in the above experimental section)
2f (Racemic) (HPLC conditions: Chiralcel OD-H (250 x 4.6 mm), IPA:n-Hexane (05:95), Flow rate: 0.7 ml/min; λ = 254 nm)

![Chiral HPLC done under conditions mentioned in the above experimental section)](image)

2f (Chiral HPLC done under conditions mentioned in the above experimental section)
**2g (Racemic) (HPLC conditions):** Chiralcel OD-H (250 x 4.6 mm), IPA:n-Hexane (05:95), Flow rate: 0.7 ml/min; $\lambda = 254$ nm

Chiral HPLC done under conditions mentioned in the above experimental section.

![Chemical structure of 2g](image)

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<tr>
<th>Retention Time</th>
<th>C Area</th>
<th>Area %</th>
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<td>12.150</td>
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<td><strong>8436293</strong></td>
<td><strong>100.000</strong></td>
<td></td>
</tr>
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</table>
2h (Racemic) (HPLC conditions: Chiralcel OD-H (250 x 4.6 mm), IPA:n-Hexane (05:95), Flow rate: 0.7 ml/min; λ = 254 nm)

2h (Chiral HPLC done under conditions mentioned in the above experimental section)
2i (Racemic) **(HPLC conditions:** Chiralcel OD-H (250 x 4.6 mm), IPA:n-Hexane (15:85), Flow rate: 0.7 ml/min; \( \lambda = 254 \text{ nm} \))

![Chiral HPLC chromatogram](image)

**2i** (Chiral HPLC done under conditions mentioned in the above experimental section)
**2j (Racemic) (HPLC conditions):** Chiralcel OD-H (250 x 4.6 mm), IPA:n-Hexane (3:97), Flow rate: 1 ml/min; $\lambda = 254$ nm

![HPLC Chromatogram](image)

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**2j** (Chiral HPLC done under conditions mentioned in the above experimental section)

![Chemical Structure](image)

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<td>18.675</td>
<td>5958510</td>
<td>25.632</td>
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<td><strong>Totals</strong></td>
<td><strong>23245963</strong></td>
<td><strong>100.000</strong></td>
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</table>
2k (Racemic) (HPLC conditions: Chiralcel OD-H (250 x 4.6 mm), IPA:n-Hexane (3:97), Flow rate: 1 ml/min; λ = 254 nm)

2k (Chiral HPLC done under conditions mentioned in the above experimental section)
**2l (Racemic) (HPLC conditions):** Chiralcel OD-H (250 x 4.6 mm), IPA:n-Hexane (10:90), Flow rate: 0.7 ml/min; $\lambda = 254$ nm

![HPLC Chromatogram](image)

**Retention Time** | **C Area**       | **Area %**
-------------------|------------------|-----------
18.692            | 27382960         | 50.208    |
23.308            | 27155710         | 49.792    |
**Totals**         | 54538670         | 100.000   |

**2l (Chiral HPLC done under conditions mentioned in the above experimental section)**

![Structural Formula](image)

**Detector A - 1 (254nm)**

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<th>Area %</th>
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</table>
2m (Racemic) (HPLC conditions: Chiralcel OD-H (250 x 4.6 mm), Mobile phase: IPA:n-Hexane (20:80), Flow rate: 0.5 ml/min; λ = 254 nm)

![Chiral HPLC chromatogram](image1)

<table>
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<tr>
<th>Retention Time</th>
<th>C Area</th>
<th>Area %</th>
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</table>

2m (Chiral HPLC done under conditions mentioned in the above experimental section)

![Chemical structure](image2)

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<td>21.458</td>
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</table>
3a (Racemic) (HPLC conditions mentioned above)

![Graph with retention time and peaks]

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Retention Time</th>
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<td>45.000</td>
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</table>

3a (Chiral) (Same HPLC conditions like racemic mentioned above)

![Chemical structure of 3a]

![Graph with retention time and peaks]

<table>
<thead>
<tr>
<th>Pk #</th>
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3b (Racemic) (HPLC conditions mentioned above)

<table>
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</table>

Totals | 1355998 | 100.000 |

3b (Chiral) (Same HPLC conditions like racemic mentioned above)

Detector A - 1 (265nm)

<table>
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<td>21.550</td>
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Totals | 1273155 | 100.000 |
Table 2

Effect of the acid additives in the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone catalyzed by 1

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (pkₐ)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>anti/syn (%)</th>
<th>ee (%)</th>
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</thead>
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<tr>
<td>1</td>
<td>PTSA (-2.8)</td>
<td>72</td>
<td>99</td>
<td>93/7</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>Methane sulfonic acid (-1.9)</td>
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<td>85</td>
<td>81/19</td>
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</tr>
<tr>
<td>3</td>
<td>TFA (0.23)</td>
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<td>84/16</td>
<td>88</td>
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<tr>
<td>4</td>
<td>Picric acid (0.38)</td>
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<td>97</td>
<td>84/16</td>
<td>97</td>
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<tr>
<td>5</td>
<td>L-Tartaric acid (2.89)</td>
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<td>93</td>
<td>80/20</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>Citric acid (3.14)</td>
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<td>87</td>
<td>89/11</td>
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</tr>
<tr>
<td>7</td>
<td>4-Nitrobenzoic acid (3.41)</td>
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<td>95</td>
<td>86/14</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>2,4-dinitrophenol (4.11)</td>
<td>17</td>
<td>96</td>
<td>84/16</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>Benzoic acid (4.2)</td>
<td>36</td>
<td>91</td>
<td>82/18</td>
<td>86</td>
</tr>
<tr>
<td>10</td>
<td>Adipic acid (4.43)</td>
<td>48</td>
<td>88</td>
<td>82/18</td>
<td>66</td>
</tr>
<tr>
<td>11</td>
<td>Oleic acid (9.85)</td>
<td>22</td>
<td>97</td>
<td>80/20</td>
<td>76</td>
</tr>
<tr>
<td>12</td>
<td>Stearic acid (10.15)</td>
<td>18</td>
<td>87</td>
<td>78/22</td>
<td>76</td>
</tr>
</tbody>
</table>

*Isolated yield after purification by column chromatography. *Diastereomer ratios (anti/syn) were determined by ¹H NMR spectrum of the crude product mixture. *Determined by chiral HPLC analysis.