Supporting Information

Highly Enantioselective Direct Aldol Reaction Catalyzed by Proline Based on Calix[4]arene Scaffold in the Presence of Water

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1. General information

All reactions were performed in atmosphere unless noted. The commercially available reagents and solvents were used without further purification unless otherwise noted. Column chromatography was performed with silica gel (200-300 mesh). All yields were given as isolated yields. NMR spectra were recorded on a Bruker DPX 300 MHz spectrometer. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Coupling constants (J values) are reported in Hertz. IR and ESI-MS spectra were measured on Bruker Vector 22 as KBr pellets and Finnigan Mat TSQ 7000 instruments, respectively. Microanalyses were obtained on Perkin-Elmer 240 instruments, and melting points (mp) were determined with a digital electrothermal apparatus without further correction. HPLC was performed on Perkin Elmer LC.


2.1 Synthesis of 1.

DIAD (diisopropyl azodicarboxylate) (0.30 g, 1.5 mmol) was added to a vigorously stirred mixture of 4-tert-butylcalix[4]arene 9 (0.65 g, 1.0 mmol), (2S,4R)-dibenzyl 4-hydroxypyrrolidine-1,2-dicarboxylate 10 (0.39 g, 1.1 mmol), triphenylphosphine (0.39 g, 1.5 mmol) and anhydrous toluene (20 mL). Stirring was continued at 70 °C for 2 h under nitrogen. Then the mixture was cooled to room temperature and concentrated. The residue was purified by a column of silica gel with 5:1 cyclohexane/AcOEt to give Chz and Bn-protected 1 (0.46 g) as a white solid.

To a solution of Cbz and Bn-protected 1 (0.46 g) in Methanol (15 mL) was added palladium
on charcoal catalyst (10%, 70 mg). The mixture was stirred under hydrogen at room temperature for 5 h. After filtration through cellulose and celite to remove the catalyst, the solvent was evaporated under vacuum to give pure 1.

White solid, mp 233-235 °C. Yield: 47%. [α]D26 = +21.6 (c = 1.0, in CHCl3).

1H NMR (300 MHz, DMSO-d6): δ = 1.11 (s, 9H, C(CH3)3), 1.16 (s, 18H, 2 × C(CH3)3), 1.17 (s, 9H, C(CH3)3), 3.34 (d, J = 8.1 Hz, 2H, CH2), 3.40-3.47 (m, 4H, ArCH2Ar), 3.34 (d, J = 12.3 Hz, 2H, NCH2), 4.03-4.09 (m, 4H, ArCH2Ar), 4.37-4.43 (m, 2H, NCHCO + OCH), 4.59 (s, 1H, NH), 6.98-7.22 (m, 8H, ArH).

13C NMR (75 MHz, DMSO-d6): δ = 31.4, 31.7, 32.6, 34.1, 34.3, 36.4, 51.0, 60.5, 84.1, 125.2, 126.1, 126.5, 128.2, 128.4, 130.2, 130.4, 133.6, 133.8, 143.0, 146.4, 148.3, 148.6, 148.9, 150.8, 171.8.

IR (KBr): 3440, 2959, 2869, 1629, 1485, 1364, 1299, 1262, 1204, 1031, 909, 874, 802 cm–1.

Anal. Calcd for C49H63NO6: C, 77.23; H, 8.33; N, 1.84. Found: C, 77.52; H, 8.06; N, 1.65.

ESI-MS: m/z = 762 ([M + 1]+, 8%), 784 ([M + Na]+, 100%).

2.2. Synthesis of 2.

The procedure of the preparation for 2 was the same as 1, only the amount of 10, DIAD, and triphenylphosphine was doubled, respectively.

White solid, mp 261-263 °C. Yield: 78%. [α]D26 = +43.0 (c = 1.0, in CHCl3).

1H NMR (300 MHz, CD3OD): δ = 1.07 (s, 18H, 2 × C(CH3)3), 1.24 (s, 18H, 2 × C(CH3)3), 2.72 (m, 2H, CH2), 2.84-2.90 (m, 2H, CH2), 3.35-3.48 (m, 4H, ArCH2Ar), 3.68-3.74 (m, 2H, NCH2), 4.17-4.38 (m, 8H, NCH2 + ArCH2Ar + OCH), 4.65-4.69 (m, 2H, NCHCO), 5.08 (s, 2H, NH), 7.05-7.16 (m, 8H, ArH).

13C NMR (75 MHz, CDCl3): δ = 30.8, 31.5, 33.7, 51.2, 60.0, 85.1, 124.8, 124.9, 125.5, 125.9, 127.9, 128.0, 128.5, 131.0, 131.1, 131.7, 141.9, 146.5, 149.9, 173.6, 173.7.

IR (KBr): 3448, 2961, 2868, 1632, 1485, 1393, 1362, 1300, 1203, 1124, 1035, 979, 873 cm–1.

 Anal. Calcd for C54H70N2O8: C, 74.11; H, 8.06; N, 3.20. Found: C, 74.32; H, 7.86; N, 3.45.

ESI-MS: m/z = 898 ([M + Na]+, 100%).
2.3. Synthesis of 3.

A mixture of Cbz and Bn-protected 1 (0.59 g, 0.6 mmol), K₂CO₃ (0.17 g, 1.2 mmol), KI (0.20 g, 1.2 mmol), and 1-bromobutane (0.49 g, 3.6 mmol) was refluxed in MeCN (30 mL) for 24 h under nitrogen gas. After reaction, the reaction mixture was cooled to room temperature, and the solvent was evaporated. The residue was taken up in CHCl₃ (50 mL), washed with HCl (1M, 2×50 mL), H₂O (2×50 mL), and brine (50 mL), and dried over anhydrous Na₂SO₄. The CHCl₃ was removed in vacuum to give white solid (0.6 g) which was dissolved in MeOH (15 mL). Then palladium on charcoal catalyst (10%, 70 mg) was added, and the mixture was stirred under hydrogen at room temperature for 5 h. After filtration through cellulose and celite to remove the catalyst, the solvent was evaporated under vacuum to give product 3 (0.42 g).

White solid, mp 137-139 °C. Yield: 96%. [α]D²⁷ -6.7 (c = 8.5, in CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 0.82 (s, 9H, C(CH₃)₃), 0.94 (s, 9H, C(CH₃)₃), 1.06 (t, J = 7.2 Hz, 3H, CH₃), 1.25 (s, 9H, C(CH₃)₃), 1.31 (s, 9H, C(CH₃)₃), 1.58-1.72 (m, 2H, CH₂), 1.81-1.98 (m, 2H, CH₂), 2.43-2.52 (m, 1H, CH₂), 2.65-2.82 (m, 1H, CH₂), 3.21-3.34 (m, 2H, ArCH₂Ar), 3.58 (br s, 2H, ArOCH₂), 3.91-3.96 (m, 2H, NCH₂), 4.01-4.28 (m, 4H, ArCH₂Ar), 4.39-4.51 (m, 2H, OCH + NCHCOO), 6.53-6.81 (m, 4H, ArH), 6.98-7.06 (m, 4H, ArH).

¹³C NMR (75 MHz, CDCl₃): δ = 14.0, 19.3, 33.7, 33.8, 34.9, 59.7, 84.0, 124.8, 125.1, 125.3, 125.7, 125.8, 127.0, 127.3, 128.2, 128.4, 131.5, 132.1, 132.2, 141.4, 146.3, 146.8, 149.3, 149.4, 150.2, 173.1.

IR (KBr): 3441, 2960, 2870, 1717, 1635, 1485, 1392, 1362, 1300, 1201, 1123, 1026, 872 cm⁻¹.

Anal. Calcd for C₅₃H₇₁NO₆: C, 77.81; H, 8.75; N, 1.71. Found: C, 77.42; H, 8.96; N, 1.45.

ESI-MS: m/z = 818 ([M + 1]⁺, 23%), 840 ([M + Na]⁺, 100%).


To a solution of Cbz and Bn-protected 1 (0.59 g, 0.6 mmol) in pyridine (10 mL) stirring at 0 °C was added octanoyl chloride (0.59 g, 3.6 mmol) over 5 min. The mixture was stirred for 10 h at room temperature. After reaction, water (70 mL) was added, and the mixture was stirred for 1 h. Then CH₂Cl₂ (80 mL) was added, and the water layer was extracted with additional CH₂Cl₂ (80 mL). The combined organic layer was washed with HCl (1M, 2×50 mL), H₂O (2×50 mL), and brine (50 mL), and dried over anhydrous Na₂SO₄. The CH₂Cl₂ was removed in vacuum to give
white solid (0.5 g) which was dissolved in MeOH (15 mL). Then palladium on charcoal catalyst (10%, 70 mg) was added, and the mixture was stirred under hydrogen at room temperature for 5 h. After filtration through cellulose and celite to remove the catalyst, the solvent was evaporated under vacuum to give product 4 (0.36 g).

White solid, mp 157-159 °C. Yield: 75%. \([\alpha]_D^{27} -31.3\) (c = 1.0, in CHCl3).

\[^1\text{H}\ NMR\ (300\ MHz,CDCl}_3\): \(\delta = 0.84\ (s, 9H, C(CH_3)_3), 0.87\ (s, 9H, C(CH_3)_3), 0.91\ (t, J = 7.2\ Hz, 3H, CH_3), 1.27\ (s, 9H, C(CH_3)_3), 1.29-1.31\ (m, 5H, CH_2), 1.32\ (s, 9H, C(CH_3)_3), 1.46-1.51\ (m, 2H, CH_2), 1.60-1.65\ (m, 1H, CH_2), 1.80-1.94\ (m, 2H, CH_2), 2.33\ (t, J = 7.5\ Hz, 2H, OOCCH_2), 2.71-2.93\ (m, 2H, CH_2), 3.23-3.39\ (m, 4H, ArCH_2Ar), 3.76\ (d, J = 13.5\ Hz, 2H, NCH_2), 4.01-4.48\ (m, 4H, ArCH_2Ar), 5.50\ (s, 1H, OH), 5.63\ (s, 1H, OH), 6.57-7.08\ (m, 8H, ArH).

\[^{13}\text{C}\ NMR\ (75\ MHz,CDCl}_3\): \(\delta = 14.1, 22.5, 24.9, 29.0, 29.1, 30.7, 30.8, 31.3, 31.4, 31.6, 33.8, 35.5, 49.0, 59.9, 84.3, 124.8, 125.0, 125.3, 126.0, 126.9, 127.3, 127.6, 127.7, 129.0, 130.7, 131.0, 131.4, 132.0, 141.8, 142.0, 142.2, 147.0, 148.0, 148.3, 149.7, 149.9, 172.0, 173.3, 178.0\).

IR (KBr): 3520, 2957, 2868, 1761, 1634, 1485, 1363, 1301, 1139, 1122, 1037, 873 cm\(^{-1}\).

Anal. Calcd for C\(_{57}\)H\(_{77}\)NO\(_7\): C, 77.08; H, 8.74; N, 1.58. Found: C, 77.34; H, 8.46; N, 1.35.

ESI-MS: \(m/z = 888\ ([M + 1]^+, 26\%), 910\ ([M + Na]^+, 100\%).\)


\[
\begin{align*}
\text{Ar–CHO} + \text{R}_1 \text{R}_2 \text{O} & \quad \xrightarrow{2\ mol\%\ \text{Cat. 1, Water, RT, 2d}} \quad \text{R}_1 \text{R}_2 \text{OH} + \text{syn isomer}
\end{align*}
\]

Catalyst 1 (2 mol %) was added to a suspension of aldehyde (1.0 mmol) and ketone (3.0 mmol) in water (324 µL, 18 mmol) at room temperature. The mixture was allowed to stir for a given time, then ethyl acetate (10 mL) and anhydrous MgSO\(_4\) (0.6 g) were added. After filtration, the solvent was evaporated under vacuum and the crude products were purified by flash chromatography with hexane/ethyl acetate mixture as eluents. The anti/syn ratio (diastereoselectivity) and enantiomeric excess (enantioselectivity) were determined by chiral HPLC analysis.
4. Data of 7 and 8 with HPLC spectra.

Compound 7a\(^5\): Yield: 73%; Ratio \textit{anti}/\textit{syn} = 90:10.

HPLC conditions: Daicel Chiralpak AD-H column, \(\beta\)-PrOH / Hexane = 5:95, flow rate 1.0 mL/min, \(\lambda = 254\) nm, 20 °C.

\textit{anti}-Diastereomer: \(t_R\) (major) = 60.2 min and \(t_R\) (minor) = 43.5 min; 98% ee.

\begin{table}[h]
\begin{tabular}{cccccccc}
\hline
Peak \# & Component Name & Time [min] & Area [\text{nV}\text{sec}] & Height [\text{V}] & Area [%] & Norm. Area [%] & Raw Amount & Adjusted Amount \\
\hline
1 & 30.470 & 37505570.99 & 422761.58 & 8.41 & 8.41 & 37.5056 & 37.5056 \\
2 & 39.042 & 7806421.07 & 68121.62 & 1.75 & 1.75 & 7.8064 & 7.8064 \\
3 & 43.462 & 3505670.93 & 36247.10 & 0.80 & 0.80 & 3.5057 & 3.5057 \\
4 & 60.190 & 3.97e+08 & 1.90e+06 & 89.05 & 89.05 & 397.3517 & 397.3517 \\
\hline
\end{tabular}
\end{table}
Compound 7b: Yield: 63%; Ratio anti/syn = 89: 11.

HPLC conditions: Daicel Chiralpak OD-H column, i-PrOH / Hexane = 5:95, flow rate 1.0 mL/min, \( \lambda = 254 \text{ nm} \), 20 °C.

anti-Diastereomer: \( t_R \) (major) = 15.0 min and \( t_R \) (minor) can not be found; > 99% ee.

racemic-7b
Compound 7c: Yield: 59%; Ratio anti/syn = 66:34.

HPLC conditions: Daicel Chiralpak AD-H column, t-PrOH / Hexane = 5:95, flow rate 1.0 mL/min, λ = 254 nm, 20 °C.

anti-Diastereomer: $t_R$ (major) = 31.5 min and $t_R$ (minor) = 40.5 min; 94% ee.
Compound 7d: Yield: 54%; Ratio anti/syn = 67:33.

HPLC conditions: Daicel Chiralpak AD-H column, i-PrOH / Hexane = 10:90, flow rate 0.5 mL/min, $\lambda$ = 254 nm, 20 °C.

anti-Diastereomer: $t_R$ (major) = 24.1 min and $t_R$ (minor) = 20.4 min; 96% ee.
Compound 7e: Yield: 63%; Ratio anti/syn = 68:32.

HPLC conditions: Daicel Chiralpak AS-H column, i-PrOH / Hexane = 10:90, flow rate 0.5 mL/min, λ = 254 nm, 20 °C.

anti-Diastereomer: $t_R$ (major) = 38.5 min and $t_R$ (minor) = 45.1 min; 74% ee.

racemic-7e
Compound 7f: Yield: 50%; Ratio anti/syn = 55:45.

HPLC conditions: Daicel Chiralpak AD-H column, i-PrOH / Hexane = 5:95, flow rate 0.5 mL/min, λ = 220 nm, 16 °C.

anti-Diastereomer: τR (major) = 36.3 min and τR (minor) = 31.4 min; 97% ee.

HPLC REPORT

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τR = 36.3 min and 31.4 min; 97% ee.
Compound 7g\(^7\): Yield: 37%; Ratio \textit{anti}:/\textit{syn} = 54:46.

HPLC conditions: Daicel Chiralpak AS-H column, \(i\)-PrOH / Hexane = 10:90, flow rate 0.5 mL/min, \(\lambda = 254\) nm, 24 °C.

\textit{anti}-Diastereomer: \(t_R\) (major) = 27.3 min and \(t_R\) (minor) = 25.2 min; 63% ee.

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**HPLC REPORT**

| Peak | Component | Time [min] | Area [\(\mu\)V\(\times\)sec] | Height [V] | Area [%] | Norm. Area [%] | Raw Amount | Adjusted Amount |
|------|-----------|------------|-----------------------------|------------|---------|---------------|------------|----------------|}
| 1    |           | 17.533     | 4915561.85 191401.77 38.35 38.35 | 4.9136     | 4.9136 |
| 2    |           | 19.595     | 926996.15 251411.07 7.24 7.24 | 0.9270     | 0.9270 |
| 3    |           | 25.155     | 1256530.42 37080.09 10.14 10.14 | 1.2895     | 1.2895 |
| 4    |           | 27.302     | 567225.39 102597.76 44.28 44.28 | 5.6723     | 5.6723 |

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Missing Component Report
Component: Expected Retention (Calibration File)

All components were found

ANALYZED BY  

DATE
Compound 7h: Yield: 71%; Ratio \textit{anti/syn} = 50:50.

HPLC conditions: Daicel Chiralpak AD-H column, \textit{i}-PrOH / Hexane = 10:90, flow rate 0.5 mL/min, \( \lambda = 254 \) nm, 21 °C.

\textit{syn}-Diastereomer: \( t_R \) (major) = 16.5 min and \( t_R \) (minor) = 19.4 min; 95% ee.

\textit{anti}-Diastereomer: \( t_R \) (major) = 29.1 min and \( t_R \) (minor) = 25.5 min; 81% ee.
Compound 7i: Yield: 23%; Ratio \( \text{anti}/\text{syn} = 12:88 \).

HPLC conditions: Daicel Chiralpak AD-H column, \( \text{i-PrOH} / \text{Hexane} = 10:90 \), flow rate 1.0 mL/min, \( \lambda = 254 \text{ nm} \), 20 °C.

\( \text{syn-Diastereomer: } t_R \) (major) = 5.5 min and \( t_R \) (minor) = 8.9 min; 83% ee.
Compound 8: Yield: > 99%; Ratio anti/syn = 32:68.

HPLC conditions: Daicel Chiralpak AS-H column, i-PrOH / Hexane = 15:85, flow rate 0.8 mL/min, λ = 254 nm, 20 °C.

syn-Diastereomer: $t_R$ (major) = 26.0 min and $t_R$ (minor) = 70.7 min; 99% ee.

anti-Diastereomer: $t_R$ (major) = 37.9 min and $t_R$ (minor) = 59.1 min; > 99% ee.
5. $^1$H NMR, $^{13}$C NMR, IR, and ESI-MS spectra of 1–4.

5.1. $^1$H NMR, $^{13}$C NMR, IR, and ESI-MS spectra of 1.
5.2. $^1$H NMR, $^{13}$C NMR, IR, and ESI-MS spectra of 2.
5.3 $^1$H NMR, $^{13}$C NMR, IR, and ESI-MS spectra of 3.
5.4 $^1$H NMR, $^{13}$C NMR, IR, and ESI-MS spectra of 4.
References


