Highly Enantio- and Diastereoselective L-Proline Derived Acetylglucose Amide Catalyzed Aldol Reaction of Ketones to Aldehydes under Solvent-Free Conditions

Xiaoyu Han,*a Yongjiang Wang,a Xikun Gai,a Xiaofei Zeng,*b

a Zhejiang Provincial Key Laboratory for Chemical & Biological Processing Technology of Farm Products, School of Biological and Chemical Engineering, Zhejiang University of Science and Technology, No.318 Liuhe Road, Hangzhou, 310023, P. R. China
E-mail: chemhanxy@zust.edu.cn

b College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, P. R. China
E-mail: chemzxf@hznu.edu.cn

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A. General Information

All the starting materials were obtained from commercial sources and were used without further purification unless otherwise stated. CHCl₃ and CH₂Cl₂ were distilled from CaH₂ prior to use. Optical rotations were measured using a Schmidt + Haensdch polarimeter (Polartronic MH8). ¹H and ¹³C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separations were performed on Merck 60 (0.040-0.063 mm) mesh silica gel. Enantiomeric excesses were determined by HPLC analysis (Daicel Chiralcel AD-H or AS-H column, 25 °C) in comparison with racemic products. The absolute configurations of the products were determined by comparison with compounds previously published.

B. General Procedure for the Synthesis of L-proline D-glucose Derived Catalyst I
(2R,3S,5R,6S)-6-(acetoxymethyl)-3-((E)-4-methoxybenzylideneamino)tetrahydro-2H-pyran-2,4,5-triylyl triacetate (1-3):

To a 50 mL flask, glucose amine hydrochloride (2.16 g, 10.0 mmol) was dissolved in 1M aqueous NaOH solution (200 mL), and then p-anisaldehyde (1.36 g, 1.0 mmol) was added dropwise by syringe at 0 °C. The mixture was stirred at room temperature for 12 h. The product can be obtained as a white solid by filtration of the precipitate formed and dried under reduced pressure, which was used directly for the next step without further purification. To a solution of the crude product from the previous step was dissolved in pyridine (100 mL) and cooled in an ice bath, then acetic anhydride (5.1 mL, 50.0 mmol) was added, the mixture was stirred at room temperature for 48 h. After azeotropic solvent evaporation with toluene, and the resulting was purified by column chromatography on silica gel (hexane/EtOAc = 15:1 to 5:1) to afford product 1-3 in 87% yield (4.05 g) for two steps.

\[
\begin{align*}
\text{AcO} & \quad \text{OAc} \\
\text{PMP} & \quad \text{OAc} \\
\text{N} & \quad \text{OAc}
\end{align*}
\]

1H NMR (400 MHz, CDCl₃): δ 8.17 (s, 1H), 7.67 (d, J = 8.8, 2H), 6.93 (d, J = 8.8, 2H), 5.96 (d, J = 8.4, 1H), 5.44 (t, J = 11.2, 1H), 5.16 (d, J = 11.2, 1H), 4.39 (dd, J₁ = 4.0, J₂ = 12.4, 1H), 4.15 (dd, J₁ = 4.0, J₂ = 12.4, 1H), 4.01-3.97 (m, 1H), 3.86 (s, 3H), 3.46 (d, J = 8.4, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.90 (s, 3H);

13C NMR (100 MHz, CDCl₃): δ 170.8, 170.0, 169.6, 168.9, 164.4, 162.3, 130.3, 128.3, 114.1, 93.2, 73.2, 73.0, 72.8, 68.0, 61.8, 55.4, 20.9, 20.8, 20.7, 20.5

HRMS calcd for C₂₂H₂₃NO₁₀, 465.1635 (M+), found 465.1634;

(2R,3S,5R,6S)-6-(acetoxymethyl)-3-aminotetrahydro-2H-pyran-2,4,5-triylyl triacetate (1-5):

To a solution of compound 1-3 (4.05 g, 8.7 mmol) in acetone (50 mL) was cooled to 0 °C, concentrated hydrochloride acid was added carefully to reach pH = 5. The precipitate formed was filtered and washed with acetone and dried, the white solid 1-4 can be obtained and used directly for the next step without further purification. To a stirred solution of the compound 1-4 obtained from the previous step in H₂O (50 mL), powdered sodium acetate (1.31 g, 16.0 mmol) was added. The mixture was stirred for 2 h, and the precipitate
formed was filtered, washed with water and dried under reduced pressure to give compound 1-5 as a white solid which was further purified by column chromatography on silica gel to afford the desired compound 1-5 (1.51 g) in 50% yield for two steps.

\[ \text{1H NMR (400 MHz, CDCl}_3): \delta 5.44 (d, J = 8.8, 1H), 5.06-4.97 (m, 2H), 4.67 (brs, 2H), 4.29 (dd, J_1 = 4.6, J_2 = 12.4, 1H), 4.05 (dd, J_1 = 2.0, J_2 = 12.4, 1H), 3.82-3.78 (m, 1H), 3.00 (t, J = 8.8, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H); \]

\[ \text{13C NMR (100 MHz, CDCl}_3): \delta 170.7, 169.8, 169.3, 95.2, 75.1, 72.7, 68.2, 61.7, 55.0, 21.0, 20.8, 20.7, 20.6. (Some of the 13C peaks represents more than one carbon) \]

HRMS calcd for C_{14}H_{21}NO_9, 347.1216 (M+), found 347.1220.


To a solution of N-Boc L-proline 1-6 (0.65 g, 3.0 mmol) in anhydrous THF (15 mL) was added compound 1-5 (1.04 g, 3.0 mmol) and DCC (0.62 g, 3 mmol), HOBT (0.41 g, 3 mmol) at 0 °C under an ice bath. The reaction mixture was stirred at 0 °C for 1 h, then the reaction was allowed to warm to room temperature and stirred overnight. After the disappearance of the starting material (monitored by TLC), the mixture was filtered, the solvent was removed under vacuo, the residue was purified by column chromatography to give a white solid (1.39 g, 2.55 mmol) in 85% yield. To a solution of the compound (1.39 g, 2.55 mmol mmol) obtained from the previous step, in DCM (10 mL), TFA (3 mL) was added, and the mixture was stirred at room temperature for 2 h. Saturated NaHCO_3 solution was added slowly to quench the reaction, then the mixture was extracted with DCM, washed with brine and water, dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography to give the desired catalyst 1 (1.08 g, 2.42 mmol) as a white solid in 95% yield.
**C. Representative Procedure for the Catalytic Asymmetric Aldol Reaction**

Cyclohexanone (0.2 mmol, 2.0 equiv.), aldehyde (0.1 mmol, 1.0 equiv.) and catalysts 1 (0.01 mmol, 10 mol %) were mixed together at room temperature. The mixture was stirred at room temperature until the disappearance of the aldehyde (checked by TLC). The mixture was diluted with 0.5 mL of DCM, and then was directly purified by column chromatography on silica gel to give the desired optically active aldol product.

**D. Analytical Data of the Aldol Products**

(S)-2-((R)-hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one 4a

![Structure of 4a](image)

The title compound was prepared according to the general procedure, as described above in 99% yield.

HPLC (Chiralpak OD-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): *t*$_{major}$ = 11.77 min, *t*$_{minor}$ = 15.33 min, ee = 97%, [α]$_D^{20}$ = 28.1 (c 1.0, CHCl$_3$); dr 97:3.

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.24 (d, *J* = 12.0, 2H), 7.53 (d, *J* = 12.0, 2H), 4.92 (dd, *J*$_1$ = 4.4, *J*$_2$ = 11.2 , 1H), 4.08 (d, *J* = 4.4, 1H), 2.65-2.54 (m, 3H), 2.51-2.38 (m, 1H), 2.17-2.10 (m, 1H), 1.88-1.83 (m, 1H), 1.72-1.55 (m, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 172.6, 172.0, 170.7, 169.4, 162.3, 92.3, 88.6, 81.4, 81.0, 74.5, 72.8, 71.2, 70.3, 68.1, 61.7, 53.1, 20.8, 20.7, 20.6; (Some of the $^{13}$C peaks represents more than one carbon)

HRMS calc for C$_{19}$H$_{28}$N$_2$O$_{10}$, 444.1744 (M+), found 444.1745;

[α]$_D^{20}$ = −67.2 (c 1.0, CHCl$_3$)
(S)-2-((R)-hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one 4b

The title compound was prepared according to the general procedure, as described above in 96% yield.

HPLC (Chiralpak OD-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, \( \lambda = 254 \) nm): \( t_{\text{major}} = 9.52 \) min, \( t_{\text{minor}} = 12.21 \) min, ee = 99\%, \([\alpha]^{20}_D = 28.4 \) (c 1.0, CHCl\(_3\)); dr 97:3.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 8.22-8.16 \) (m, 2H), 7.68 (d, \( J = 7.4, 1H \)), 7.55 (d, \( J = 7.4, 1H \)), 4.91 (dd, \( J_1 = 2.7, J_2 = 8.2, 1H \)), 4.15 (d, \( J = 2.8, 1H \)), 2.66-2.62 (m, 1H), 2.53-2.38 (m, 2H), 2.14-2.11 (m, 1H), 1.86-1.57 (m, 3H), 1.42-1.38 (m, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta 215.0, 148.3, 143.2, 133.2, 129.3, 122.9, 122.0, 74.0, 57.1, 42.7, 30.7, 27.6, 24.6 \)

HRMS calcd for C\(_{13}\)H\(_{15}\)NO\(_4\), 249.1001 (M+), found 249.1099.

(S)-2-((R)-(3-chlorophenyl)(hydroxy)methyl)cyclohexan-1-one 4c

The title compound was prepared according to the general procedure, as described above in 97% yield.

HPLC (Chiralpak OD-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, \( \lambda = 254 \) nm): \( t_{\text{major}} = 6.48 \) min, \( t_{\text{minor}} = 7.93 \) min, ee = 98\%, \([\alpha]^{20}_D = 17.2 \) (c 1.0, CHCl\(_3\)); dr 99:1.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.35-7.19 \) (m, 4H), 4.77 (dd, \( J_1 = 2.8, J_2 = 8.4, 1H \)), 4.03 (d, \( J = 2.9, 1H \)), 2.63-2.61 (m, 1H), 2.60-2.33 (m, 2H), 2.14-2.06 (m, 1H), 1.84-1.81 (m, 1H), 1.73-1.52 (m, 3H), 1.38-1.27 (m, 2H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta 215.3, 143.1, 134.3, 129.6, 128.0, 127.1, 125.3, 74.3, 57.3, 42.7, 30.8, 27.7, 24.7 \);

HRMS calcd for C\(_{13}\)H\(_{15}\)ClO\(_2\), 238.0761 (M+), found 238.0759.

4-((R)-hydroxy((S)-2-oxocyclohexyl)methyl)benzonitrile 4d
The title compound was prepared according to the general procedure, as described above in 90% yield.

HPLC (Chiralpak OD-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): \( t_{\text{major}} = 11.05 \) min, \( t_{\text{minor}} = 15.36 \) min, ee = 94%, \([\alpha]_D^{20} = 16.0 \) (c 1.0, CHCl$_3$); dr 98:2.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.65 (d, \( J = 8.1 \), 2H), 7.45 (d, \( J = 8.1 \), 2H), 4.84 (dd, \( J_1 = 2.8 \), \( J_2 = 8.3 \), 1H), 4.08 (d, \( J = 2.8 \), 1H), 2.60-2.62 (m, 1H), 2.59-2.32 (m, 2H), 2.14-2.04 (m, 1H), 1.85-1.81 (m, 1H), 1.76-1.51 (m, 3H), 1.41-1.24 (m, 2H);

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 214.8, 146.4, 132.2, 127.8, 118.7, 111.7, 74.2, 57.1, 42.7, 30.7, 27.7, 24.7;

HRMS calcd for C$_{14}$H$_{15}$NO$_2$, 229.1103 (M+), found 229.1105.

(S)-2-((R)-hydroxy(2-methoxyphenyl)methyl)cyclohexan-1-one 4e

The title compound was prepared according to the general procedure, as described above in 91% yield.

HPLC (Chiralpak OD-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): \( t_{\text{major}} = 7.14 \) min, \( t_{\text{minor}} = 8.35 \) min, ee = 97%, \([\alpha]_D^{20} = 3.66 \) (c 1.0, CHCl$_3$); dr 99:1.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.42 (d, \( J = 8.0 \), 1H), 7.40 (t, \( J = 7.6 \), 2H), 7.28 (t, \( J = 8.0 \), 1H), 6.88 (d, \( J = 8.4 \), 1H), 5.28 (dd, \( J_1 = 2.8 \), \( J_2 = 8.4 \), 1H), 3.85 (d, \( J = 4.8 \), 1H), 3.83 (s, 3H), 2.78-2.71 (m, 1H), 2.51-2.32 (m, 2H), 2.08-2.04 (m, 1H), 1.85-1.27 (m, 5H);

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 215.6, 156.7, 129.6, 128.6, 127.8, 120.9, 110.5, 68.6, 57.3, 55.4, 42.6, 30.5, 28.0, 24.7;

HRMS calcd for C$_{14}$H$_{18}$O$_3$, 234.1256 (M+), found 234.1259.

(S)-2-((R)-(2-chlorophenyl)(hydroxy)methyl)cyclohexan-1-one 4f
The title compound was prepared according to the general procedure, as described above in 97% yield.

HPLC (Chiralpak OD-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): \( t_{\text{major}} = 5.81 \text{ min} \), \( t_{\text{minor}} = 6.66 \text{ min} \), ee = 94%, \( [\alpha]_D^{20} = 21.1 \) (c 1.0, CHCl\(_3\)); dr >99:1.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.58-7.55 (m, 1H), 7.35-7.20 (m, 3H), 5.37 (dd, \( J_1 = 3.0 \), \( J_2 = 8.0 \), 1H), 4.06 (d, \( J = 3.0 \), 1H), 2.73-2.68 (m, 1H), 2.66-2.32 (m, 2H), 2.13-2.07 (m, 1H), 1.85-1.82 (m, 1H), 1.75-1.54 (m, 4H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 215.3, 139.1, 133.0, 129.2, 128.8, 128.3, 127.3, 70.4, 57.6, 42.7, 30.4, 27.8, 24.9;

HRMS calcd for C\(_{11}\)H\(_{14}\)ClO\(_2\), 238.0761 (M\(^+\)), found 238.0763.

(S)-2-((R)-hydroxy(3-methoxyphenyl)methyl)cyclohexan-1-one \( \mathbf{4g} \)

The title compound was prepared according to the general procedure, as described above in 89% yield.

HPLC (Chiralpak OD-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): \( t_{\text{major}} = 9.34 \text{ min} \), \( t_{\text{minor}} = 11.34 \text{ min} \), ee = 96%, \( [\alpha]_D^{20} = 6.07 \) (c 1.0, CHCl\(_3\)); dr >99:1.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.26 (t, \( J = 7.6 \), 1H), 6.90-6.83 (m, 3H), 4.77 (d, \( J = 2.0 \), 1H), 3.98 (d, \( J = 2.0 \), 1H), 3.82 (s, 3H), 2.65-2.63 (m, 1H), 2.60-2.32 (m, 2H), 2.12-2.06 (m, 1H), 1.82-1.81 (m, 1H), 1.78-1.50 (m, 3H), 1.36-1.26 (m, 1H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 215.5, 159.7, 142.6, 129.3, 119.5, 113.4, 112.4, 74.7, 57.4, 55.2, 42.7, 30.8, 27.8, 24.7;

HRMS calcd for C\(_{14}\)H\(_{18}\)O\(_3\), 234.1256 (M\(^+\)), found 234.1255.

(S)-2-((R)-(4-bromophenyl)(hydroxy)methyl)cyclohexan-1-one \( \mathbf{4h} \)

The title compound was prepared according to the general procedure, as described above in 96% yield.

HPLC (Chiralpak OD-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): \( t_{\text{major}} = 7.59 \text{ min} \), \( t_{\text{minor}} = 9.69 \text{ min} \), ee = 94%, \( [\alpha]_D^{20} = 24.4 \) (c 1.0, CHCl\(_3\)); dr 98:2.
\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta \text{ 7.49 (d, } J = 8.3, \text{ 2H), 7.22 (d, } J = 8.3, \text{ 2H), 4.77 (dd, } J_1 = 3.3, J_2 = 8.9, \text{ 1H), 4.00 (d, } J = 3.3, \text{ 1H), 2.61-2.57 (m, 1H), 2.55-2.33 (m, 2H), 2.14-2.06 (m, 1H), 1.83-1.81 (m, 1H), 1.73-1.51 (m, 3H), 1.36-1.26 (m, 1H).} \]

\[ \text{C NMR (100 MHz, CDCl}_3\text{): } \delta \text{ 215.3, 140.0, 131.5, 128.8, 121.7, 74.2, 57.3, 42.7, 30.8, 27.7, 24.7} \]

\[ \text{HRMS calcd for C}_{13}\text{H}_{15}\text{BrO}_2, 282.0255 (M+)%, found 282.0256.} \]

\[(S)-2-((\text{R})-\text{hydroxy(phenyl)methyl})\text{cyclohexan-1-one 4i} \]

![Diagram of 4i](image)

The title compound was prepared according to the general procedure, as described above in 89% yield.

\[ \text{HPLC (Chiralpak OJ-H, } i-\text{PrOH/hexane = 2/98, flow rate = 1.0 mL/min, } \lambda = 254 \text{ nm): } t_{\text{major}} = 33.11 \text{ min, } t_{\text{minor}} = 38.55 \text{ min, ee } = 90\%, [\alpha]_{D}^{20} = 18.8 (c 1.0, CHCl}_3\text{); dr 97:3.} \]

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta \text{ 7.38-7.30 (m, 5H), 4.80 (dd, } J_1 = 2.8, J_2 = 8.2, \text{ 1H), 4.00 (d, } J = 2.9, \text{ 1H), 2.66-2.60 (m, 1H), 2.50-2.33 (m, 2H), 2.12-2.06 (m, 1H), 1.84-1.52 (m, 3H), 1.36-1.29 (m, 2H).} \]

\[ \text{C NMR (100 MHz, CDCl}_3\text{): } \delta \text{ 215.5, 140.9, 128.3, 127.8, 126.9, 74.6, 57.3, 42.6, 30.7, 27.7, 24.6} \]

\[ \text{HRMS calcd for C}_{13}\text{H}_{16}\text{O}_2, 204.1150 (M+)%, found 204.1149;} \]

\[(S)-2-((\text{R})-\text{hydroxy(2-nitrophenyl)methyl})\text{cyclohexan-1-one 4j} \]

![Diagram of 4j](image)

The title compound was prepared according to the general procedure, as described above in 99% yield.

\[ \text{HPLC (Chiralpak OD-H, } i-\text{PrOH/hexane = 15/85, flow rate = 1.0 mL/min, } \lambda = 254 \text{ nm): } t_{\text{major}} = 7.06 \text{ min, } t_{\text{minor}} = 9.63 \text{ min, ee } = 98\%, [\alpha]_{D}^{20} = 26.1 (c 1.0, CHCl}_3\text{); dr >99:1.} \]

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta \text{ 7.83-7.73 (m, 2H), 7.64-7.58 (m, 1H), 7.43-7.38 (m, 1H), 5.42 (d, } J = 9.6, \text{ 1H), 4.10 (s, 1H), 2.78-2.70 (m, 1H), 2.45-2.26 (m, 2H), 2.11-2.01 (m, 1H), 1.84-1.54 (m, 5H).} \]

\[ \text{C NMR (100 MHz, CDCl}_3\text{): } \delta \text{ 214.9, 148.7, 136.6, 133.1, 129.0, 128.4, 124.1, 69.7, 57.3, 42.8, 31.1, 27.8, 25.0} \]

\[ \text{HRMS calcd for C}_{13}\text{H}_{15}\text{NO}_4, 249.1001 (M+)%, found 249.1005.} \]
(S)-2-((R)-(4-chlorophenyl)(hydroxy)methyl)cyclohexan-1-one 4k

The title compound was prepared according to the general procedure, as described above in 96% yield.

HPLC (Chiralpak OD-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, \( \lambda = 254 \) nm): \( t_{major} = 7.06 \) min, \( t_{minor} = 9.63 \) min, ee = 95%, [\( \alpha \)]\(_{D}^{20} \) = 16.8 (c 1.0, CHCl\(_3\)); dr 98:2.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.34 (d, \( J = 8.0 \), 2H), 7.27 (d, \( J = 8.0 \), 2H), 4.78 (dd, \( J_1 = 2.8 \), \( J_2 = 8.0 \), 1H), 4.01 (d, \( J = 2.8 \), 1H), 2.61-2.48 (m, 2H), 2.41-2.33 (m, 1H), 2.14-2.06 (m, 1H), 1.83-1.81 (m, 1H), 1.72-1.51 (m, 3H), 1.36-1.26 (m, 1H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 215.3, 139.5, 133.6, 128.6, 128.4, 74.1, 57.4, 42.7, 30.8, 27.7, 24.7

HRMS calcd for C\(_{13}\)H\(_{15}\)ClO\(_2\), 238.0761 (M\(^+\)), found 238.0765.

(S)-2-((R)-hydroxy(4-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one 4l

The title compound was prepared according to the general procedure, as described above in 98% yield.

HPLC (Chiralpak OD-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, \( \lambda = 254 \) nm): \( t_{major} = 6.51 \) min, \( t_{minor} = 8.05 \) min, ee = 97%, [\( \alpha \)]\(_{D}^{20} \) = 34.6 (c 1.0, CHCl\(_3\)); dr 99:1.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.62 (d, \( J = 8.1 \), 2H), 7.46 (d, \( J = 8.1 \), 2H), 4.86 (dd, \( J_1 = 2.8 \), \( J_2 = 8.2 \), 1H), 4.06 (d, \( J = 2.8 \), 1H), 2.64-2.58 (m, 1H), 2.53-2.33 (m, 2H), 2.15-2.06 (m, 1H), 1.84-1.56 (m, 3H), 1.46-1.29 (m, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 215.1, 145.0, 130.2, 127.3, 122.7, 74.3, 57.3, 42.7, 30.8, 27.7, 24.7

HRMS calcd for C\(_{14}\)H\(_{15}\)F\(_3\)O\(_2\), 272.1024 (M\(^+\)), found 272.1023.

(S)-2-((R)-hydroxy(2-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one 4m
The title compound was prepared according to the general procedure, as described above in 93% yield.

HPLC (Chiralpak OD-H, i-ProOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): t_major = 5.35 min, t_minor = 8.89 min, ee = 99%, [α]_D^20 = 36.3 (c 1.0, CHCl_3); dr >99:1.

^1^H NMR (400 MHz, CDCl_3): δ 7.74-7.60 (m, 3H), 7.44-7.40 (m, 1H), 5.32 (d, J = 8.7, 1H), 4.04 (d, J = 2.8, 1H), 2.80-2.73 (m, 1H), 2.53-2.35 (m, 2H), 2.13-2.08 (m, 1H), 1.80-1.52 (m, 3H), 1.46-1.27 (m, 2H).

^13^C NMR (100 MHz, CDCl_3): δ 215.0, 140.0, 132.5, 128.5, 127.9, 125.5, 122.8, 69.0, 57.7, 42.7, 30.3, 27.7, 24.9

HRMS calcd for C_{14}H_{15}F_3O_2, 272.1024 (M+), found 272.1024.

(S)-2-((R)-hydroxy(thiophen-3-yl)methyl)cyclohexan-1-one 4n

The title compound was prepared according to the general procedure, as described above in 70% yield.

HPLC (Chiralpak OD-H, i-ProOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): t_major = 6.93 min, t_minor = 8.40 min, ee = 95%, [α]_D^20 = 12.5 (c 1.0, CHCl_3); dr 97:3.

^1^H NMR (400 MHz, CDCl_3): δ 7.74-7.60 (m, 3H), 7.44-7.40 (m, 1H), 5.32 (d, J = 8.7, 1H), 4.04 (d, J = 2.8, 1H), 2.80-2.73 (m, 1H), 2.53-2.35 (m, 2H), 2.13-2.08 (m, 1H), 1.80-1.52 (m, 3H), 1.46-1.27 (m, 2H).

^13^C NMR (100 MHz, CDCl_3): δ 215.0, 144.6, 126.3, 125.2, 125.1, 70.8, 57.9, 42.6, 30.9, 27.8, 24.7

HRMS calcd for C_{11}H_{14}O_2S, 210.0715 (M+), found 210.0715.

(S)-2-((R)-hydroxy(phenyl)methyl)cyclopentan-1-one 4o

The title compound was prepared according to the general procedure, as described above in 91% yield.

HPLC (Chiralpak AD-H, i-ProOH/hexane = 5/95, flow rate = 1.0 mL/min, λ = 254 nm): t_major = 56.18 min, t_minor = 54.22 min, ee = 91%, dr 98:2.

^1^H NMR (400 MHz,CDCl_3) d 8.21 (2H, d, J = 8.8 Hz), 7.52 (2H, d, J = 8.8 Hz), 5.42 (1H, s), 4.84 (1H, d, J = 9.2 Hz),
4.76 (1H, brs), 2.69 (1H, brs), 2.52-2.18 (3H, m), 2.15-1.83 (2H, m), 1.78-1.55 (2H, m); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 214.6, 213.4, 149.2, 147.9, 147.4, 147.3, 127.2, 126.5, 123.0, 122.9, 73.5, 69.8, 57.0, 56.3, 42.5, 30.2, 27.7, 25.5, 24.6, 24.3;

HRMS calcd for C$_{12}$H$_{14}$O$_2$, 190.0225 (M+) found 190.0221.

(R)-4-hydroxy-4-phenylbutan-2-one 4p

![Structure of 4p]

The title compound was prepared according to the general procedure, as described above in 93% yield as a colorless oil.

HPLC (Chiralpak AS-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): $t_{\text{major}}$ = 42.78 min, $t_{\text{minor}}$ = 32.69 min, ee = 88%, $[\alpha]_{D}^{20}$ = 26.4 (c 1.0, CHCl$_3$);

$^1$HNMR (400 MHz, CDCl$_3$) δ 8.20 (2H, d, $J$ = 7.0 Hz), 7.52 (2H, d, $J$ = 7.0 Hz), 5.25 (1H, m), 3.56 (1H, brs), 3.01-2.71 (2H, m), 2.21 (3H, s); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 208.6, 149.9, 147.4, 126.4, 123.8, 68.9, 51.5, 30.7;

HRMS calcd for C$_{10}$H$_{12}$O$_2$, 164.0132 (M+) found 164.0123.