Supporting Information

Simple proline derivatives as recoverable catalysts for the large-scale stoichiometric aldol reactions

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Experimental

1 General

All chemicals were used as received unless otherwise noted. Reagent grade solvents were distilled prior to use. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25mm silica gel plates visualized with UV light and/or by staining with ethanolic phosphomolybdic acid (PMA) and/or ninhydrin both in ethanol stain. THF was freshly distilled from sodium-benzophenone ketyl radical under an argon atmosphere immediately prior to use. Flash column chromatography was performed on silica gel (200-300mesh). NMR spectra were recorded on 300MHz instrument. Chemical shifts (δ) are given in ppm relative to TMS as the internal reference, coupling constants (J) in Hz. IR spectra were recorded on a spectrometer. Melting points were measured on a digital melting-point apparatus. Mass spectra (MS) were measured with a spectrometer. Analytical high performance liquid chromatography (HPLC) was carried out on Agilent 1200 instrument using Chiralpak AD (4.6mm×250mm), Chiralcel OD-H (4.6mm×250mm) columns. Optical rotations were measured on a JASCO P-1010 Polarimeter at λ=589 nm.

Procedure for the synthesis of (1a–1d)

A 500 ml round bottom flask was charged with CF_3CO_2H (120 mL) and placed in an ice/water bath. Powdered trans-4-hydroxy-L-proine (250 mmol) was added in small portions under vigorous stirring to give a viscous solution. The reaction mixture was stirred for 30 min, and then acyl chloride (375 mmol) was added in one portion. After 30 min of stirring, and then removed from the ice/water bath. The reaction flask was fitted with a loose glass stopper, and the reaction mixture was stirred at room temperature without any external temperature adjustment for 6 h, giving a clear and colorless solution. The reaction flask was then cooled in an ice/water bath, and Et_2O (360 mL) was added under vigorous stirring over a period of 20 min, slowly at first. The resulting white suspension was stirred at 0-5 °C for 15 min after completed addition, and then filtered by vacuum. The crystals were washed with two portions of Et_2O and dried at room temperature for 23 h in a ventilated hood to give direct *O*-acylation proline hydrochloride, and then *O*-acylation proline hydrochloride dissolved in water, added an equivalent amount of triethylamine (Et_3N), the resulting white suspension was stirred at room temperature for 10 min after completed addition, and then filtered by vacuum. The white crystals were washed with two portions of H_2O and dried to give direct *O*-acylation of proline derivative organocatalysts. These essentially pure materials were used for the next step without further purification.

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***O*-3-Phenylpropanoyloxyl-*trans*-4-hydroxy-L- proline (1a)**
White microcrystals, mp: 215–216 °C; isolated yield: 92%; $[\alpha]_D^{20}$ = -19.8 (c= 0.49, MeOH). ^{1}H NMR (300 MHz, DMSO) δ=2.20 (ddd, J=4.9, 10.2 and 14.9 Hz, 1H), 2.30 (dddd, J=1.5, 1.5, 7.8 and 14.9 Hz, 1 H), 2.63–2.68 (m, 2 H), 2,80-2.90 (t, J=7.6 Hz, 2H), 3.22–3.25 (m, 1 H), 3.58(dd, J=4.5 and 13.1 Hz, 1 H), 4.36 (dd, J=8.0 and 10.2 Hz, 1 H), 5.27 (br-s, 1 H), 7.19–7.31 (m, 5H); ^{13}C NMR (75 MHz, DMSO): δ=171.6, 169.4, 140.3, 128.3, 128,2, 126.1, 72.2, 57.5, 50.1, 35.0, 34.1, 29.9; MS (ESI) m/z calcd for ($C_{14}H_{17}NO_4$) 263.29, found 263.51. IR (neat): *v*3500–2600 (broad COOH), 1733, 1680, 1501,1479, 1200, 933cm^{-1}.

***O*-Methacryloyl-*trans*-4-hydroxy-L-proline (1b)**
White microcrystals, mp: 239-242 °C; yield: 85%; $[\alpha]_D^{20}$ = –8.7 (c = 0.138, MeOH). ^{1}H NMR (300 MHz, DMSO) δ =1.88(s, 3H, Me), 2.47 (ddd, 1H, *J* = 15.0 Hz, 10.6 Hz and 4.7 Hz, H-3), 2.70 (ddt, 1H, *J* =14.5 Hz, 7.8 Hz and 1.6 Hz, H-3), 3.65 (dt, 1H, *J* = 13.3 Hz and 1.5 Hz, H-5), 3.74 (dd, 1H, *J* = 13.3 Hz and 4.7 Hz, H-5), 4.65 (dd, 1H, *J* = 10.5 Hz and 7.8 Hz, H-2), 5.52(br-s, 1H, H-4), 5.72 (br-s, 1H, methacrylic H), 6.14 (br-s, 1H, methacrylic H) ppm. ^{13}C NMR (75 MHz, D_2O) δ =16.7, 34.0, 50.6, 58.1, 73.1, 127.3, 134.8, 167.7, 170.6. MS (ESI) m/z calcd for ($C_9H_{13}NO_4$) 199.20, found 199.51. IR (neat):*v* 3101, 2867, 1752, 1716, 1634 cm^{-1}.

***O-trans*-3-Phenylacryloyl-*trans*-4-hydroxy-L-poline (1c)**
White microcrystals, mp: 245-246 °C; yield: 95%; $[\alpha]_D^{20}$ = –10.7 (c = 0.150, MeOH). ^{1}H NMR (300 MHz, DMSO) δ=2.43 (ddd, 1H, *J* = 15.0 Hz, 10.6 Hz and 4.7 Hz, H-3), 2.64 (ddt, 1H, *J* =14.5 Hz, 7.8 Hz and 1.6 Hz, H-3), 3.60 (dt, 1H, *J* = 13.3 Hz and 1.5 Hz, H-5), 3.71 (dd, 1H, *J* = 13.3 Hz and 4.7 Hz, H-5), 4.62 (dd, 1H, *J* = 10.5 Hz and 7.8 Hz, H-2), 5.44 (br-s, 1H, H-4), 6.40 (d, J=16.1Hz, 1H), 7.38-7.54(m, 5H), 7.63 (d, J=16.1Hz, 1H) ppm; ^{13}C NMR (75 MHz, D_2O) δ 34.0, 50.6, 58.0, 72.8, 115.9, 127.9, 128.6, 130.6, 133.2, 146.4, 167.1, 170.4. MS (ESI) m/z calcd for ($C_{14}H_{15}NO_4$) 261.27, found 261.52. IR (neat):*v*3500–2600 (broad COOH), 1741, 1616, 1505,1249, 933cm^{-1}.

***(2S, 4R)*-4-Octanoyloxypyrrolidine-2-carboxylic acid (1d)**
White microcrystals, mp: 225-226 °C; yield: 95%; $[\alpha]_D^{20}$ = –37.1 (c = 0.1, MeOH). ^{1}H NMR (300 MHz, DMSO) δ= 0.80-0.88 (3H, m), 1.25 (8H, br-s), 1.56 (2H, br-s), 2.20-2.31 (3H, m), 2.36-2.45 (1H, m), 3.28-3.41 (1H, m), 3.54-3.67 (1H, m), 4.12 (1H, br-s), 5.27 (1H, br-s) ppm; ^{13}C NMR (75 MHz, D2O) δ14.0, 22.5, 24.6, 28.8, 29.0, 31.5, 33.9, 35.4, 50.2, 59.9, 72.5, 172.7, 173.2. MS (ESI) m/z calcd for (C13H24NO4) 258.17, found 258.32. IR (neat):ν2960, 2929, 1736, 1624, 1577, 1441, 1419, 1383, 1227, 1167 cm-1.

Representative procedure for the organocatalytic asymmetric stoichiometric aldol reaction

To a mixture of catalyst **1c** (5.23 mg, 0.02 mmol) and cyclohexanone (0.11 mL, 1 mmol) were added *p*-nitrobenzaldehyde (0.1512 g, 1 mmol) and water (0.8mL). The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate and filtered through silica gel (1 g) to remove the catalyst. The solvent was removed under vacuum to afford the crude product, which was purified by column chromatography (ethyl acetate: hexane=1:10 to 1:2) to afford **2a** as a colorless solid; yield: 246.7 mg (99%);

(*2S, 10R*)-2-[Hydroxy(4-nitrophenyl)methyl]cyclohexan-1-one (2a):[51-54]

Yield 246.2 mg (0.989 mmol, 99%); *anti*/*syn* = 99:1, enantiomeric excess: >99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 20:80; 0.5 mL/min; 20 °C;λ = 254 nm) t_R = 42.5 min (*anti*, major) and t_R = 32.8 min (*anti*, minor).

(2*S*, 10*R*)-2-[Hydroxy(2-nitrophenyl)methyl]cyclohexan-1-one (2b): [51-54]

Yield 245.3 mg (0.985 mmol, 99%); *anti/syn* = 99:1, enantiomeric excess: 99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak OD-H column; *i*-PrOH/hexane = 5:95; 0.5 mL/min; 20 °C; λ= 254 nm) t_R = 41.9 min (*anti*, major) and t_R = 50.7 min (*anti*, minor).

(*2S, 10R*)-2-[Hydroxy(3-nitrophenyl)methyl]cyclohexan-1-one (2c): [51-54]

Yield 241.5 mg (0.97 mmol, 97%); *anti/syn* = 97:3, enantiomeric excess: >99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 20:80; 0.5 mL/min; 20 °C; λ = 254 nm) t_R = 41.9 min (*anti*, major) and t_R = 32.4 min (*anti*, minor).

(*2S, 10R*)-2-[(4-Cyanophenyl)hydroxymethyl]cyclohexan-1-one (2d): [51-54]

Yield 227.0 mg (0.99 mmol, 99%); *anti:syn* = 99:1, enantiomeric excess: 99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 20:80; 0.5 mL/min; 20 °C;λ = 254 nm) t_R = 22.5 min (*anti*, major) and t_R = 18.1 min (*anti*, minor).

(*2S, 10R*)-2-{Hydroxy[4-(trifluoromethyl)methyl]}cyclohexan-1-one (2e): [51-54]

Yield 264.1 mg (0.97 mmol, 97%); anti/syn = 96:4, enantiomeric excess: 99% (anti diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 10:90; 0.5 mL/min, 20 °C, λ = 254 nm) t_R = 34.4 min (anti, major) and t_R = 26.9 min (anti, minor).

(*2S, 10R*)-2-[(4-Bromophenyl)hydroxymethyl]cyclohexan-1-one (2f): [51-54]

Yield 277.5 mg (0.98 mmol, 98%); *anti/syn* = 96:4, enantiomeric excess: 99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 10:90; 0.5 mL/min, 20 °C, λ = 220 nm) t_R = 43.1 min (*anti*, major) and t_R = 35.5 min (*anti*, minor).

(*2S, 10R*)-2-[(4-Chlorophenyl)hydroxymethyl]cyclohexan-1-one (2g): [51-54]

Yield 233.9 mg (0.98 mmol, 98%); *anti/syn* = 97:3, enantiomeric excess: 99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 10:90; 0.5 mL/min, 20 °C, λ = 221 nm) t_R = 39.2 min (*anti*, major) and t_R = 33.4 min (*anti*, minor).

(*2S, 10R*)-2-[(2-Chlorophenyl)hydroxymethyl]cyclohexan-1-one (2h): [51-54]

Yield 227.1 mg (0.96 mmol, 96%); *anti/syn* = 98:2, enantiomeric excess: 99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak OD-H column; *i*-PrOH/hexane = 5:95; 1.0 mL/min, 20 °C, λ= 221 nm) t_R = 9.7 min (*anti*, major) and t_R = 12.3 min (*anti*, minor).

(*2S, 10R*)-2-(Hydroxy-(4-fluor-phenyl)methyl) cyclohexan-1-one (2i): [51-54]

Yield 215.6 mg (0.97 mmol, 97%); *anti/syn* = 93:7, enantiomeric excess: >99% (*anti* diastereomer) determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 5:95; flow rate 1.0 mL/min, 20 °C, λ=221 nm; t_R = 28.3 min (anti, major), t_R = 24.7 min (anti, minor)).

(*2S, 10R*)-2-[Hydroxy(4-methoxyphenyl)methyl]cyclohexan-1-one (2j): [51-54]

Yield 229.5 mg (0.98 mmol, 98%); *anti/syn* = 96:4, enantiomeric excess: 99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 10:90; 0.8 mL/min, 20 °C, λ = 221 nm) t_R = 32.5 min (*anti*, major) and t_R = 30.8 min (*anti*, minor).

(*2S, 10R*)-2-[Hydroxy(3-methoxyphenyl)methyl]cyclohexan-1-one (2k): [51-54]

Yield 229.5 mg (0.98 mmol, 98%); *anti/syn* = 96:4, enantiomeric excess: 99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 10:90; 0.5 mL/min, 20 °C, λ = 221 nm) t_R = 56.3 min (*anti*, major) and t_R = 51.1 min (*anti*, minor).

(*2S, 10R*)-2-[Hydroxy(2-naphthyl)methyl]cyclohexan-1-one (2l): [51-54]

Yield 249.2 mg (0.98 mmol, 98%); *anti/syn* = 97:3, enantiomeric excess: >99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak OD-H column; *i*-PrOH/hexane = 10:90; 1.0 mL/min, 20 °C, λ = 221 nm) t_R = 15.7 min (*anti*, major) and t_R = 22.2 min (*anti*, minor).

(*2S, 10R*)-2-[Hydroxy(1-naphthyl)methyl]cyclohexan-1-one (2m): [51-54]

Yield 244.1 mg (0.96 mmol, 96%); *anti/syn* = 98:2, enantiomeric excess: 99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 5:95; 1.0 mL/min, 20 °C, λ= 254 nm) t_R = 45.9 min (*anti*, major) and t_R = 36.7 min (*anti*, minor).

(*2S, 10R*)-2-[Hydroxy(phenyl)methyl]cyclohexan-1-one (2n): [51-54]

Yield 171.6 mg (0.84 mmol, 84%); *anti/syn* = 98:2, enantiomeric excess: 98% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak OD-H column; *i*-PrOH/hexane = 10:90; 0.5 mL/min, 20 °C, λ =220 nm) t_R = 19.6 min (*anti*, major) and t_R = 30.6 min (*anti*, minor).

(*2S, 10R*)-2-[Hydroxy(4-nitrophenyl)methyl]cyclopentan-1-one (2o): [51-54]

Yield 232.9 mg (0.99 mmol, 99%); *anti/syn* = 78:22, enantiomeric excess: 98% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 5:95; 1.0 mL/min, 20 °C, λ= 254 nm) t_R = 58.4 min (*anti*, major) and t_R = 55.4 min (*anti*, minor); tR = 30.8 min (*syn*, major) and tR = 43.9 min (*syn*, minor).

(*2S, 10R*)-2-[Hydroxy(2-nitrophenyl)methyl]cyclopentan-1-one (2p): [51-54]

Yield 230.5 mg (0.98 mmol, 98 %); *anti/syn* = 85:15, enantiomeric excess: 99% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak OD-H column; *i*-PrOH/hexane = 5:95; 1.0 mL/min, 20 °C, λ= 254 nm) t_R = 39.8 min (*anti*, major) and t_R = 43.2 min (*anti*, minor).

(*2S, 10R*)-2-[Hydroxy(3-nitrophenyl)methyl]cyclopentan-1-one (2q): [51-54]

Yield 232.9 mg (0.99 mmol, 99%); *anti/syn* = 69:31, enantiomeric excess: 97% (*anti* diastereomer) determined by HPLC (Daicel Chiralpak AD-H column; *i*-PrOH/hexane = 8:92; 1.0 mL/min, 20 °C, λ= 254 nm) tR = 29.4 min (*anti*, major) and tR = 43.3 min (*anti*, minor).

((2S,4S)-2-((R)-Hydroxy(4-nitrophenyl)methyl)-4-methylcyclohexan-1-one (2r): [51-54]

Yield 260.6 mg (0.99 mmol, 99%); *anti/syn* = 97:3, enantiomeric excess: >99% (*anti* diastereomer) determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 1.0 mL/min, 20 °C, λ= 254 nm; t_R = 36.3 min (*anti*, major), t_R = 41.3 min (*anti*, minor)).

(2S,4S)-2-((R)-Hydroxy(2-nitrophenyl)methyl)-4-methylcyclohexan-1-one (2s): [51-54]

Yield 260.6 mg (0.99 mmol, 99%); *anti/syn* = 99:1, enantiomeric excess: 99% (*anti* diastereomer) determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 20 °C, λ= 254 nm; t_R = 63.4 min (*anti*, major), t_R = 46.5 min (*anti*, minor)).

(*2S, 4S*)-2-((R)-Hydroxy(2-nitrophenyl)methyl)-4-methylcyclohexan-1-one (2t): [51-54]

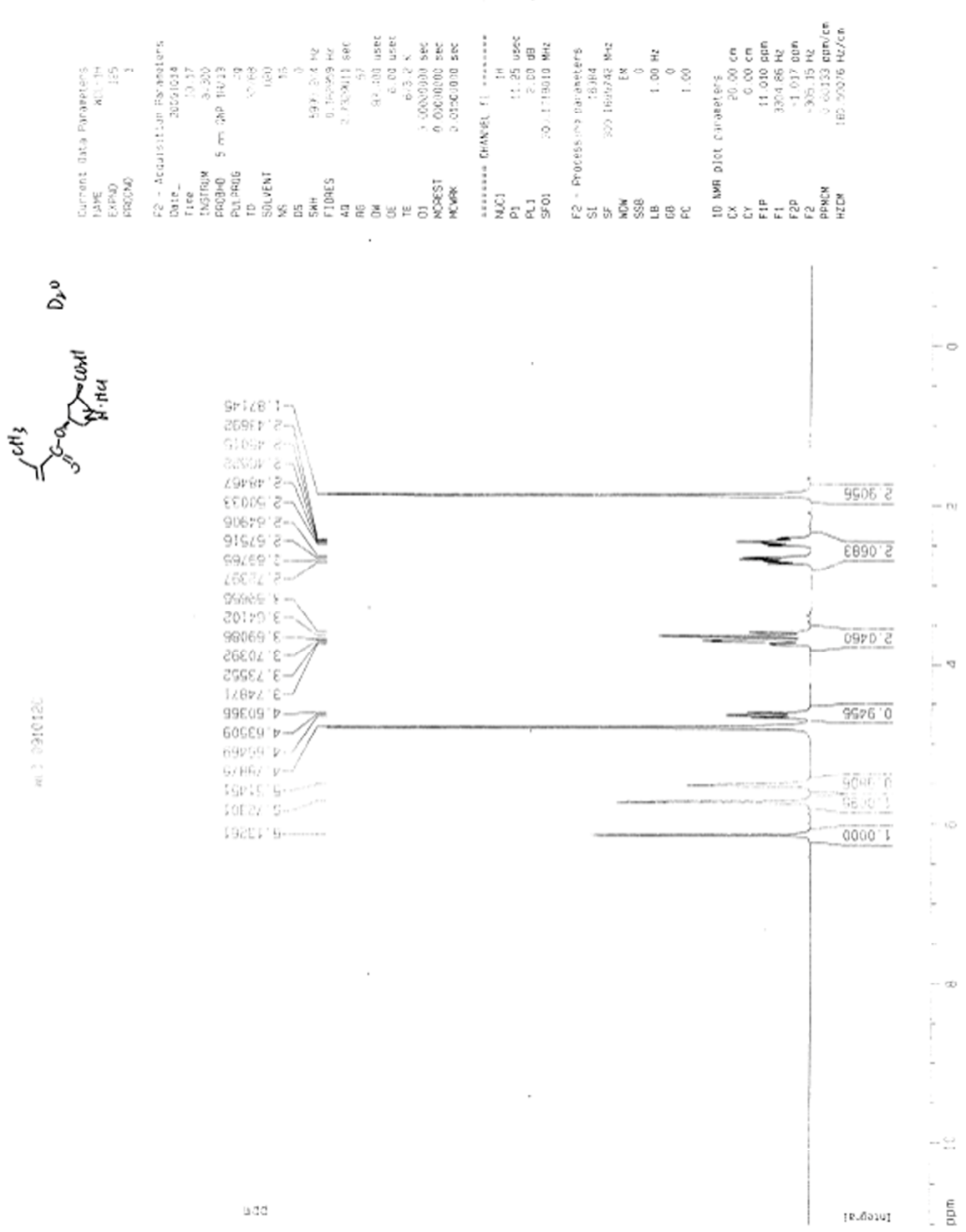
Yield 260.6 mg (0.99 mmol, 99%); *anti/syn* = 96:4, enantiomeric excess: 99% (*anti* diastereomer) determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.8 mL/min, 20 °C, λ= 254 nm; t_R = 32.5 min (*anti*, major), t_R = 34.7 min (*anti*, minor)).

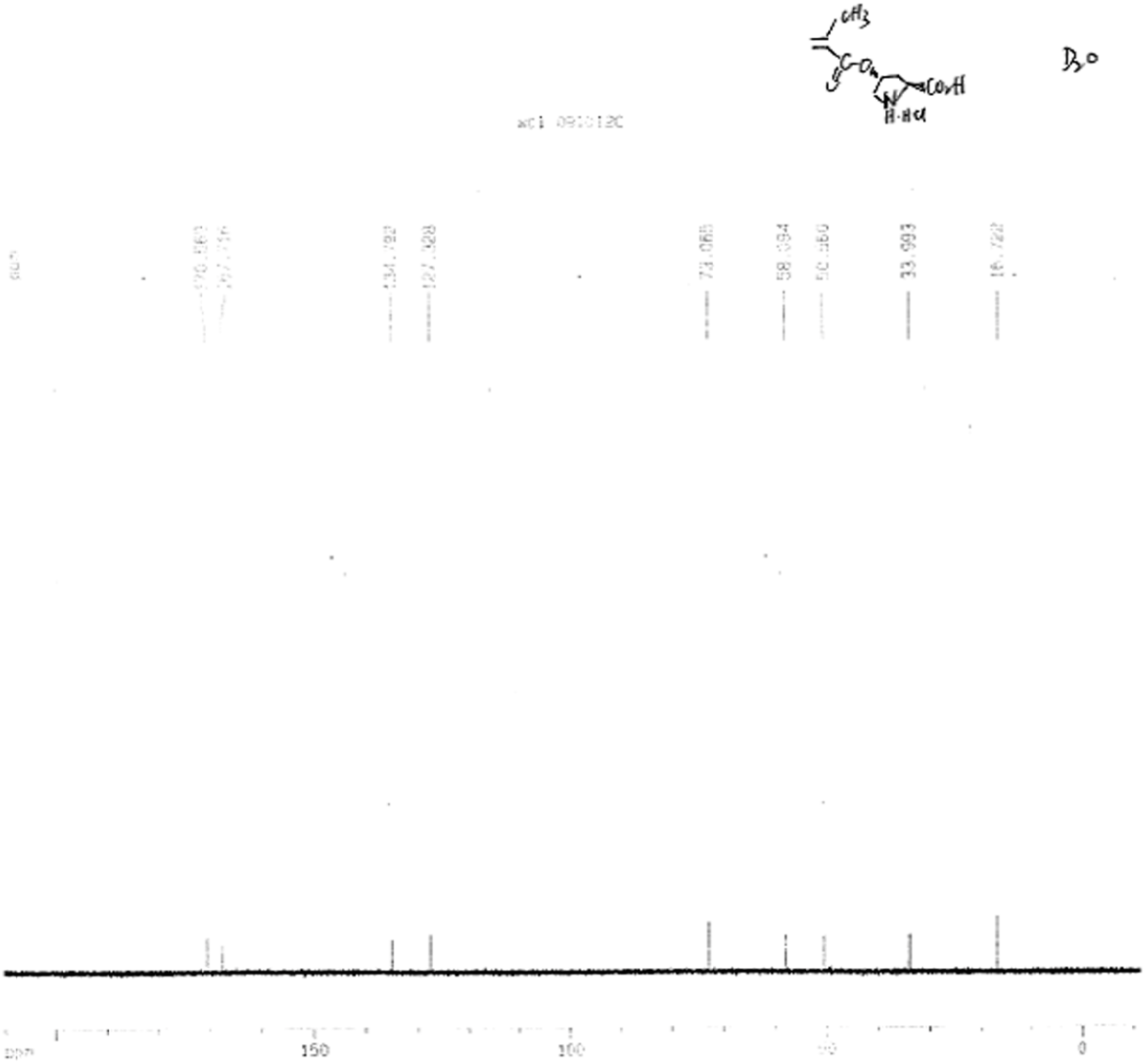
Representative procedure for the organocatalytic asymmetric stoichiometric aldol reaction

To a mixture of catalyst **1c** (5.23 mg, 0.02 mmol) and cyclohexanone (0.11 mL, 1 mmol) were added *p*-nitrobenzaldehyde (0.1512 g, 1 mmol) and water (0.8mL). The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate and filtered through silica gel (1 g) to remove the catalyst. The solvent was removed under vacuum to afford the crude product, which was purified by column chromatography (ethyl acetate: hexane=1:10 to 1:2) to afford **2a** as a colorless solid; yield: 246.7 mg (99%);

Procedure for Catalyst Recovery: To a mixture of catalyst **1c** (1.046 g, 4 mmol) and cyclohexanone (200 mmol), were added 4-chlorobenzaldehyde (28.114 g, 200 mmol) and water (160 mL). The mixturewas stirred at room temperature as specified in **Table 5**. The reaction mixture was quenched with aqueous HCl (4 mmol, 6 mol/L) and then diluted with diethyl ether (200 mL) and the reaction mixture was vigorous stirred for 5 min. The reaction mixture was placed in an ethanol bath for 1 h (–20 °C), then the organic layer was concentrated in vacuo to afford the crude aldol product, which was purified by column chromatography (ethyl acetate/hexane= 1:10 to 1:2). To the catalyst 1f, which remained in the acidic aqueous layer, was added triethylamine (4 mmol), and the resulting white suspension was stirred at room temperature for 10 min after addition, and then filtered under vacuum. The white crystals of **1c** could be recycled to catalyze the aldol reaction without adding any new catalyst.

General procedure for large-scale stoichiometric aldol reactions: To a mixture of catalyst **1c** (2.092 g, 8 mmol) and ketone (400 mmol), were added aromatic aldehyde (400 mmol) and water (320 mL). The resulting mixture was stirred at room temperature and the reaction was monitored by TLC. The reaction was then quenched with saturated NH_4Cl (60 mL), extracted with EtOAc (3×150 mL), and dried with Na_2SO_4. Purification by flash chromatography afforded the corresponding pure products.



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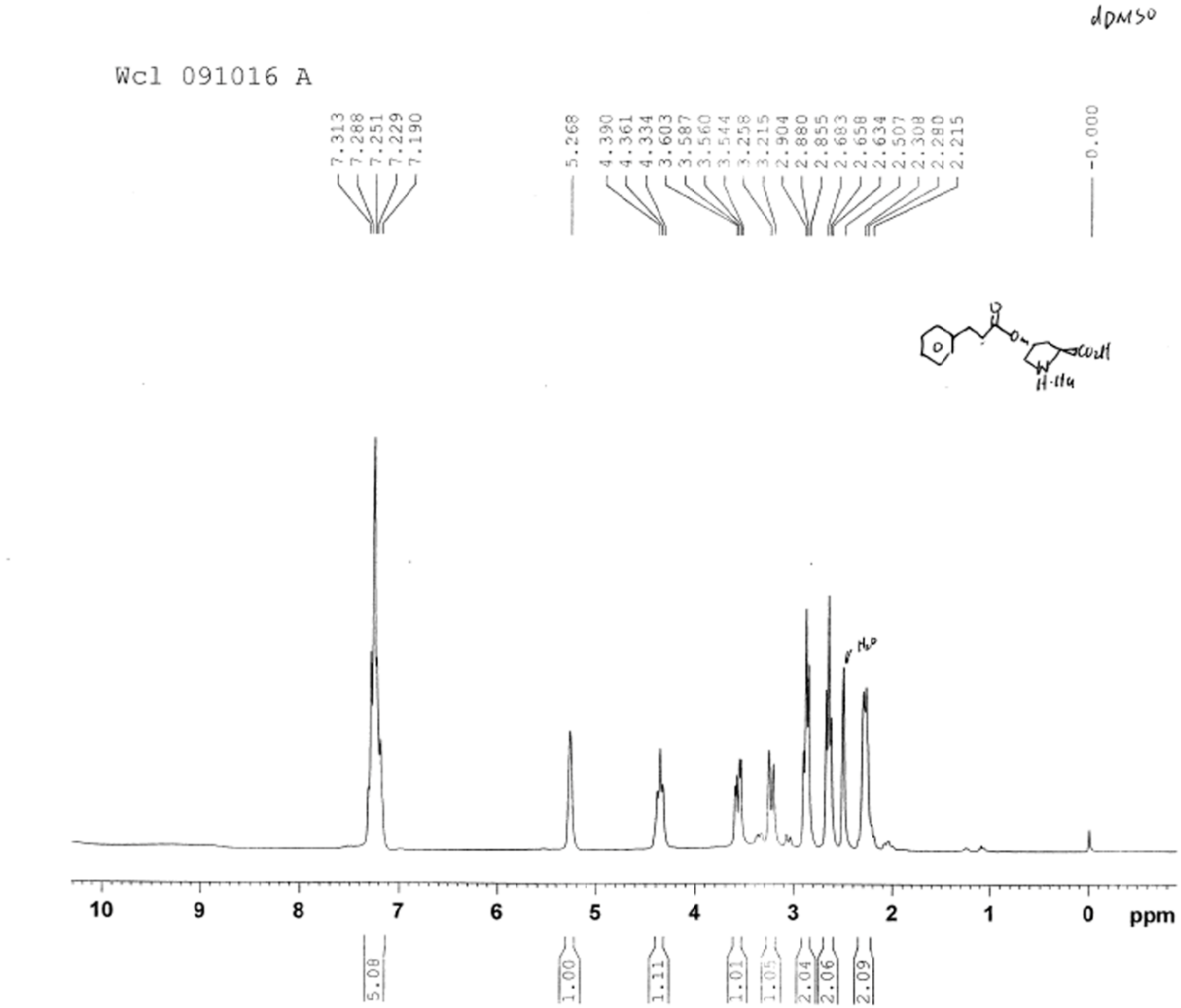

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