SUPPORTING INFORMATION

Title: Use of (S)-5-(2-Methylpyrrolidin-2-yl)-1H-tetrazole as a Novel and Enantioselective Organocatalyst for the Aldol Reaction

Author(s): Sok-Teng (Amy) Tong, Paul W. R. Harris, David Barker, Margaret A. Brimble*

Ref. No.: O200700834
**General Methods.** Reactions were monitored by TLC, using pre-coated silica gel TLC plates obtained from Merck. Flash chromatography was carried out on silica gel (Riedel-de Haën, particle size 0.032-0.063 mm). Reactions that required anhydrous conditions were run under an atmosphere of nitrogen. Evaporation of solvents was carried out at reduced pressure. Dimethyl sulfoxide was distilled over calcium hydride at reduced pressure and acetone was distilled over anhydrous calcium sulfate. Hexane for flash chromatography was distilled before use. HPLC analysis was performed on a Waters Instrument (2487 dual wavelength absorbance detector with a 600 binary HPLC Pump). The chiralpak AD-H column was purchased from Daicel Chemical Industries Ltd. Optical rotations were measured on a Perkin-Elmer 341 polarimeter (λ = 589 nm, 0.1 dm cell). Melting point determinations were performed on an Electrothermal® melting point apparatus. ¹H NMR and ¹³C NMR spectra were recorded on Bruker Avance DRX 300 MHz or 400 MHz spectrometers at ambient temperatures. Chemical shifts δ are expressed in ppm and coupling constants J are reported in Hz. TMS served as internal standard (δ = 0 ppm) for ¹H NMR, and CDCl₃ served as internal standard (δ = 77.0 ppm) for ¹³C NMR. Where CD₃OD was used as the solvent, chemical shifts δ were reported using residual CHD₂OD (δ = 3.30 ppm for ¹H NMR) and CD₃OD (δ = 49.05 ppm for ¹³C NMR) as internal standards, respectively. Infrared spectra were recorded on a Perkin-Elmer spectrum one FT-IR spectrometer.

**Procedure for the synthesis of (S)-α-methylproline 2.**

\[
\begin{align*}
\text{NH} & \quad \text{CO}_2\text{H} \\
\text{H} & \quad \text{Cl}_3\text{CCHOH}_2\text{O} \\
\text{Cl} & \quad \text{CHCl}_3 \\
\text{72%} & \\
\text{1} & \quad \text{Cl}_3\text{CCHOH}_2\text{O} \\
\text{H} & \quad \text{LDA}, \text{CH}_3\text{I} \\
\text{THF} & \quad \text{18} \\
\text{6 N HCl, Dowex 50Wx8} & \quad \text{47% over 2 steps} \\
\text{19} & \quad \text{CH}_3 \\
\text{CO}_2\text{H} & \quad \text{2}
\end{align*}
\]

**(3R,7aS)-3-(Trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one, 18**

Following the known literature procedure, oxazolidinone 18 was obtained as colourless needles (72%). m.p. 109–111 ºC (lit. 107–109 ºC). ¹H NMR (400 MHz, CDCl₃) δ = 1.65–2.30 (m, 4 H, 5-CH₂ and 6-CH₂), 3.08–3.18 (m, 1 H, 4A-H), 3.38–3.50 (m, 1 H, 4B-H), 4.08–4.19 (m, 1 H, 7A-H), 5.16 (s, 1 H, 3-H). ¹H NMR data are consistent with literature values.

**(S)-2-Methylpyrrolidine-2-carboxylic acid, 2**
Following the known literature procedure, oxazolidinone 19 was obtained as crude material which was used directly as follows. Oxazolidinone 19 (7.18 g) was added to HCl (6 N, 77 mL) and the mixture heated at reflux for 1 hour then stirred at room temperature overnight. The black precipitate that formed in the reaction mixture was then removed by filtration. The filtrate was washed with DCM (40 mL × 3) and the dark brown aqueous solution concentrated in vacuo (~60 ºC, 30 mbar) to yield a black oil (8.23 g). The black oil was loaded onto an ion-exchange column (Dowex 50W × 8, 20–50 mesh; 200 g). Deionized water (850 mL) was eluted through the column and the pH of the effluent rose to pH 7. NH₃ solution (3 N, 200 mL) was then eluted through the column after which the hot front reached the outlet. A NH₃ solution (3 N, 700 mL) was then added to completely elute the free acid. All fractions containing the acid (pale yellow spot on TLC with KMnO₄ stain) were combined and evaporated in vacuo to afford a sticky dark brown solid. Further drying (~50 ºC, 4 mmHg) gave a dark brown solid (2.93 g) which was recrystallised with methanol-ether to furnish the title acid as a light brown powder (2.6 g, 47% over two steps). m.p. 310 ºC (lit. [2] 330 ºC); [α]D20 = –69 (c 1.0, MeOH) [lit. [3] [α]DRT = –71.1 to –72.1 (c 1.0, MeOH)]. 1H NMR (400 MHz; D2O) δ = 1.51 (s, 3 H, 2-CH₃), 1.82–1.94 (m, 2 H), 1.94–2.05 (m, 1 H), 2.20–2.34 (m, 1 H), 3.14–3.25 (m, 1 H, 5A-H), 3.25–3.35 (m, 1 H, 5B-H). The 1H NMR data was consistent with literature data.

Procedure for the synthesis of (S)-α–methylproline tetrazole 4.

(S)-1-Benzyl 2-methyl 2-methylpyrrolidine-1,2-dicarboxylate, 6

A solution of ester 6 (578 mg, 2.08 mmol) in 5 N NaOH/MeOH (2:1, 12 mL) was heated at reflux for 2 hours. The mixture was then diluted with water (30 mL) and washed with ether (20 mL). The aqueous phase was acidified to pH 1 with 2 m HCl and extracted with CHCl₃ (35 mL × 3). The combined CHCl₃ extracts were washed with brine (40 mL), dried (MgSO₄) and evaporated to give a crude yellow oil (492 mg). The crude was recrystallised with DCM-hexane to yield the title acid as a colourless solid (263 mg, 87%). m.p. 89–91 ºC (lit. m.p. 121 ºC)[4]. [α]D18 = –7 (c 1.0, MeOH) [lit. [5] [α]D20 = –8.8 (c 1.0, MeOH)]. 1H NMR (400 MHz, CDCl₃) δ = 1.54 and 1.64 (s, 3 H, 2-CH₃), 1.80–2.00 (m, 3 H), 2.20–2.43 (m, 1 H), 3.49–3.72 (m, 2 H, 5A-H and 5B-H), 5.00–5.20 (m, 2 H, PhCH₂CO), 7.20–7.50 (m, 5 H, Ar-H), as an approximately 1:1 mixture of rotamers. The 1H NMR data are consistent with literature values.[4] MS (EI): m/z (%) = 263 (0.015, M +), 218 (0.17, M–CO₂H), 174 (0.18), 91 (1.0, PhCH₂). HMRS calculated for C₁₄H₁₇NO₄ 263.11576, found 263.11551.

(S)-Benzyl 2-carbamoyl-2-methylpyrrolidine-1-carboxylate, 8
To a solution of acid 7 (100 mg, 0.38 mmol) in dry chloroform (32 mL) was added, under nitrogen at 0 °C, triethylamine (0.42 mL, 3.04 mmol) and ethyl chloroformate (0.29 mL, 3.04 mmol). The mixture was stirred at 0 °C for 2 hours and aqueous ammonia solution (28%, 4.94 mL) was added, after which the mixture was stirred for another 3 hours. The aqueous phase was separated and extracted with chloroform (15 mL x 2). The combined organics were washed with cold 5% NaHCO₃ solution (30 mL), dried (MgSO₄) and evaporated to afford a crude yellow oil, which was purified via flash chromatography (99:1 EtOAc/MeOH) to furnish the title amide as a sticky yellow gum (94 mg, 94%).

\[
\text{[\alpha]_D}^{20} = -25 \quad (c 1.0, \text{MeOH})
\]

\[\delta = 1.53 \text{ and } 1.64 \text{ (s, 3 H, 2-CH}_3\text{, rotamers), 1.72–2.09 \text{ (m, 3 H), 2.09–2.78 (m, 1 H), 3.33–3.78 (m, 2 H, 5A-H and 5B-H), 5.12 (s, 2 H, PhCH}_2\text{), 6.08–6.56 (m, 1 H, NH), 6.83 (br s, 1 H, NH), 7.06–7.60 (m, 5 H, Ar-H), as a mixture of rotamers.} \]

\[\delta = 22.2 \text{ and } 22.5 \text{ (C-4), 38.9 and 41.2 (C-3, rotamers), 48.2 and 48.4 (C-5, rotamers), 65.9 and 70.0 (C-2, rotamers), 66.7 and 66.8 (PhCH}_2\text{, rotamers), 127.5, 127.8, 128.3 (Ar-C), 136.0 and 136.3 (Ar-quat.), 154.4 and 154.7 (C=O carbamate, rotamers), 177.0 and 177.5 (C=O amide, rotamers).} \]

IR (NaCl): v(\text{~}) = 3401 (amide N–H stretching), 2977 (C–H), 2874, 1691 (carbamate, amide C=O stretching), 1606 (amide, N–H bending), 1497 cm⁻¹. MS (CI+, NH₃): m/z (%) = 263 (0.20, M+H), 218 (0.40, M–CONH₂), 174 (0.23), 91 (1.0, PhCH₂). HMRS calculated for C₁₄H₁₉N₂O₃ 263.13957, found 263.13897.

**(S)-Benzyl 2-cyano-2-methylpyrrolidine-1-carboxylate, 9**

**Method 1:**
To a solution of amide 8 (1.09 g, 4.17 mmol) in dimethylformamide (14 mL) was added at 0 °C cyanuric chloride (0.58 g, 3.12 mmol) in one shot. The mixture was stirred for 3 hours, by which time it had turned yellow. Water (30 mL) was added to quench the reaction mixture, and the resultant yellow solution was extracted with EtOAc (30 mL x 3). The combined organics were washed with water (15 mL x 4), dried (MgSO₄) and evaporated to yield the title nitrile as a pale yellow oil (0.97 g, 95%).

\[\text{[\alpha]_D}^{20} = -35.58 \quad (c 2.08, \text{Et}_2\text{O})
\]

\[\delta = 1.67 \text{ and } 1.76 \text{ (s, 3 H, 2-CH}_3\text{, rotamers), 1.85–2.13 \text{ (m, 3 H), 2.41–2.61 (m, 1 H), 3.36–3.55 (m, 1 H, 5A-H), 3.55–3.75 (m, 1 H, 5B-H), 5.06–5.32 (m, 2 H, PhCH}_2\text{), 7.26–7.54 (m, 5 H, Ar-H), as a 3:2 mixture of rotamers.} \]

\[\delta = 22.3 \text{ and } 22.8 \text{ (2-CH}_3\text{, rotamers), 24.2 \text{ and } 25.4 \text{ (C-4, rotamers), 40.3 \text{ and } 41.6 \text{ (C-3, rotamers), 47.3 \text{ and } 48.0 \text{ (C-5, rotamers), 55.1 \text{ and } 55.9 \text{ (C-2, rotamers), 66.9 \text{ and } 67.5 (PhCH}_2\text{, rotamers), 120.7 \text{ (C=N), 127.8, 127.9, 128.1, 128.3 (Ar-C, rotamers), 135.9 (Ar-C quat.), 153.4 (C=O, carbamate), as a 2:1 mixture of rotamers.} \]

IR (NaCl): v(\text{~}) = 2979 (amide N–H stretching), 2874, 1691 (carbamate, amide C=O stretching), 1497 cm⁻¹. MS (EI): m/z (%) = 263 (0.20, M+H), 218 (0.40, M–CONH₂), 174 (0.23), 91 (1.0, PhCH₂). HMRS calculated for C₁₄H₁₉N₂O₂ 244.12118, found 244.12098.

**Method 2:**
A solution of phosphorus oxychloride (0.18 mL) in dry dichloromethane (0.37 mL) was added at –5 °C under nitrogen to a solution of amide 8 (0.40 g, 1.53 mmol) in pyridine (1.91 mL, 0.024 mol). The mixture was stirred at –5 °C for 5 hours, after which time no starting material was detected by TLC. The mixture was poured onto ice (10 g). The resultant solution was then extracted with ether (12 mL x 3). The combined organics were washed with saturated cupric sulphate solution (20 mL), brine (20 mL) and dried (MgSO₄) and evaporated to give the title nitrile as a pale yellow oil (0.308 g, 83%). The NMR data were identical to those obtained via method 1.

**(S)-Benzyl 2-methyl-2-(1H-tetrazol-5-yl)pyrrolidine-1-carboxylate, 10**
To a solution of triethylamine (0.46 mL, 3.27 mmol) in dry toluene (2 mL), under an atmosphere of nitrogen, was added glacial acetic acid (0.19 mL, 3.27 mmol) and the solution was allowed to stir for two minutes. This solution was then transferred to a round-bottomed flask containing nitrile (9) (200 mg, 0.82 mmol) and sodium azide (0.21 g, 3.27 mmol) was added. The mixture was heated at reflux for 24 hours, after which time no nitrile was detected by TLC. Water (4 mL) was added and the aqueous layer was separated. The organic layer was again extracted with water, and the combined aqueous extracts were treated with 2 M HCl (3 mL). The aqueous mixture was then extracted with EtOAc (10 mL × 3). The combined organic layers were dried (MgSO₄) and evaporated in vacuo to furnish the title tetrazole as a viscous light brown oil (225 mg, 96%). [α]D<sup>18</sup> = –72.30 (c 2.96, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ = 1.88 and 1.90 (s, 3 H, 2-CH₃, rotamers), 1.90–2.92 (m, 4 H, rotamers), 3.54–3.82 (m, 2 H, 5A-H and 5B-H), 4.96 and 5.11 (m, 2 H, PhCH₂, rotamers), 6.85–7.00 and 7.10–7.41 (m, 5 H, Ar-H, rotamers), as a 3:1 mixture of rotamers. ¹³C NMR (100 MHz, CDCl₃) δ = 22.2 and 22.6 (C-4, rotamers), 24.3 and 24.6 (2-CH₃, rotamers), 40.0 and 43.0 (C-3, rotamers), 48.3 and 48.5 (C-5, rotamers), 59.5 and 59.6 (C-2, rotamers), 67.3 and 67.5 (PhCH₂, rotamers), 127.5, 128.0, 128.3, 128.4 (Ar-C, rotamers), 135.1 and 135.7 (Ar-C quat., rotamers), 154.5 and 155.2 (C=O, carbamate, rotamers), 160.0 (CN), as a 3:1 mixture of rotamers. IR (NaCl): ν(~) = 3600–2400, 1702 (carbamate C=O stretching), 1548, 1411, 1354 cm⁻¹. MS (EI): m/z (%) = 287 (0.14, M⁺), 217 (0.07), 201 (0.06), 181 (0.06), 111 (0.12), 91 (1.0, PhCH₂). HMRS calculated for C₄H₇N₅O₂ 287.13822, found 287.13834.

(S)-5-(2-Methylpyrrolidin-2-yl)-1H-tetrazole, 4

To a solution of tetrazole (652 mg, 2.269 mmol) in HOAc/H₂O (9:1, 25 mL) was added 10% palladium on charcoal (65.2 mg). The mixture was placed under an H₂ atmosphere and stirred for 72 hours. The mixture was then filtered through a pad of celite and the pad washed with methanol. The volatiles were removed in vacuo and the remaining brown solution was azeotroped with acetonitrile to yield a cream solid which was recrystallised using methanol-ether to afford the title tetrazole as a colourless solid (308 mg, 89%). m.p. = 238–240 °C. [α]D<sup>18</sup> = –8 (c 1.0, CH₃OH). ¹H NMR (400 MHz, CD₃OD) δ = 1.82 (s, 3 H, 2-CH₃), 2.05–2.28 (m, 3 H), 2.52–2.65 (m, 1 H), 3.39–3.52 (m, 2 H, 5A-H and 5B-H). ¹³C NMR (100 MHz, CD₃OD) 22.6 (C-4) and 23.4 (2-CH₃), 37.0 (C-3), 44.5 (C-5), 64.4 (C-2), 162.7 (CN). IR (NaCl): ν(~) = 3347 (b), 2112 (b), 1646 (b), 1381 cm⁻¹. MS (EI): m/z (%) = 153 (0.08, M⁺), 138 (0.07, M–CH₃), 110 (0.23, M–HN₃), 84 (0.34, M–CN₄H), 43 (1.0, HN₃⁺). HMRS calculated for C₆H₁₁N₅ 153.10145, found 153.10164.

General procedure for the enantioselective direct aldol reaction catalysed by α–methylproline tetrazole 4.

A. Under anhydrous conditions

A clean, dry round-bottomed flask was charged α–methylproline tetrazole 4 (7.66 mg, 0.05 mmol) and the flask flushed with nitrogen and placed under an atmosphere of nitrogen. Anhydrous dimethyl sulfoxide (2 mL) was added via syringe followed by freshly distilled acetone (0.5 mL). The mixture was stirred for 5 minutes. The aldehyde (0.25 mmol) was then added in one shot. The mixture was stirred at room temperature for the reported number of hours. The mixture was quenched with saturated ammonium chloride (1 mL), after which it became warm. The mixture was diluted with water (5 mL) and transferred to a separating funnel where it was extracted with EtOAc or ether until no more product was detected in the aqueous phase by TLC. The combined organics were dried (MgSO₄) and evaporated in vacuo to furnish a crude brown liquid, which was purified via flash chromatography (hexane/EtOAc) to provide the aldol adduct.

B. Under ambient conditions

To a solution of α–methylproline tetrazole 4 (7.66 mg, 0.05 mmol) in dimethyl sulfoxide (2 mL) acetone (0.5 mL) was added. The mixture was stirred for 5 minutes, after which time aldehyde (0.25 mmol) was added in one shot. The mixture was stirred at room temperature for the reported number of hours. The mixture was quenched with saturated ammonium chloride (1 mL), after which it became warm. The mixture was diluted with water (5 mL) and transferred to a separating funnel where it was extracted with EtOAc or ether until no more product was detected in the aqueous phase by TLC. The combined organics were dried (MgSO₄) and evaporated in vacuo to furnish a crude brown liquid, which was purified via flash chromatography (hexane/EtOAc) to provide the aldol adduct.

4-Hydroxy-4-(4-nitrophenyl)butan-2-one, 16a
The $^1$H NMR data was consistent with literature values. The product was obtained in 88% ee. The optical purity was determined via the synthesis of the corresponding Mosher ester (see below). $[\alpha]_{D}^{23} +37.5 \ (c \ 0.48, \ CHCl_3) \ \text{[lit.]}^{[7]} \ (99\% \ ee); \ [\alpha]_{D}^{22} +66.2 \ (c \ 0.5, \ CHCl_3)$. 

4-(2-Chlorophenyl)-4-hydroxybutan-2-one, 16b

The $^1$H NMR data was consistent with literature values. The product was obtained in 90% ee. The optical purity was determined by HPLC using a solvent system of 95:5 hexane/isopropanol; flow rate 0.5 mL/min; $t_R = 24.94 \ \text{min} \ (R), \ 27.27 \ \text{min} \ (S)$. $[\alpha]_{D}^{23} 86.7 \ (c \ 0.6, \ CHCl_3) \ \text{[lit.]}^{[7]} \ (96\% \ ee); \ [\alpha]_{D}^{22} +101.7 \ (c \ 0.58, \ CHCl_3)$. 

4-Hydroxy-4-(4-methoxyphenyl)butan-2-one, 16c

The $^1$H NMR data was consistent with literature values. The product was obtained in 85% ee. The optical purity was determined by HPLC using a solvent system of 95:5 hexane/isopropanol; flow rate 0.5 mL/min; $t_R = 52.87 \ \text{min} \ (R), \ 60.81 \ \text{min} \ (S)$. $[\alpha]_{D}^{23} +30.0 \ (c \ 0.4, \ CHCl_3) \ \text{[lit.]}^{[10]} \ (67\% \ ee); \ [\alpha]_{D}^{16} +25.51 \ (c \ 0.24, \ CHCl_3)$. 

4-(4-Bromophenyl)-4-hydroxybutan-2-one, 16d

The $^1$H NMR data was consistent with literature values. The product was obtained in 87% ee. The optical purity was determined by HPLC using a solvent system of 93:7 hexane/isopropanol; flow rate 0.5 mL/min; $t_R = 38.46 \ \text{min} \ (R), \ 41.12 \ \text{min} \ (S)$. $[\alpha]_{D}^{23} +50.9 \ (c \ 0.57, \ CHCl_3) \ \text{[lit.]}^{[8]} \ (90\% \ ee); \ [\alpha]_{D}^{18} +53.3 \ (CHCl_3)$. 

N-(4-(1-Hydroxy-3-oxobutyl)phenyl)acetamide, 16e

$^1$H NMR (300 MHz, CDCl$_3$) $\delta = 2.17 \ (s, \ 3 \ H), \ 2.20 \ (s, \ 3 \ H), \ 2.73–2.93 \ (m, \ 2 \ H), \ 3.29 \ (br \ s, \ 1 \ H), \ 5.00–5.19 \ (m, \ 1 \ H), \ 7.30 \ (d, \ J = 8.5 \ Hz, \ 2 \ H), \ 7.47 \ (d, \ J = 8.5 \ Hz, \ 2 \ H)$. The product was obtained in 70% ee. The optical purity was determined by HPLC using a solvent system of 90:10 hexane/isopropanol; flow rate 0.5 mL/min; $t_R = 100.40 \ \text{min} \ (R), \ 108.86 \ \text{min} \ (S)$. $[\alpha]_{D}^{23} +15.9 \ (c \ 0.44, \ CHCl_3) \ \text{[lit.]}^{[6]} \ (69\% \ ee); \ [\alpha]_{D}^{16} +12.5 \ (c \ 1, \ CHCl_3)$. 

4-Hydroxy-4-(naphthalen-2-yl)butan-2-one, 16f
The $^1$H NMR data was consistent with literature values.\textsuperscript{(6)} The product was obtained in 81\% ee. The optical purity was determined by HPLC using a solvent system of 95.5 hexane/isopropanol; flow rate 0.5 mL/min; $t_R = 94.46$ min ($R$), 109.57 min ($S$). $[\alpha]_D^{23} + 40.0$ ($c$ 0.5, CHCl$_3$) [lit.\textsuperscript{(11)} (74\% ee); $[\alpha]_D^{20} + 34.8$ ($c$ 0.525, CHCl$_3$)].

4-Hydroxy-4-phenylbutan-2-one, 16g

The $^1$H NMR data was consistent with literature values.\textsuperscript{(8)} The product was obtained in 80\% ee. The optical purity was determined by HPLC using a solvent system of 93.7 hexane/isopropanol; flow rate 0.5 mL/min; $t_R = 39.13$ min ($R$), 42.51 min ($S$). $[\alpha]_D^{23} + 31.1$ ($c$ 0.45, CHCl$_3$) [lit.\textsuperscript{(12)} (96\% ee); $[\alpha]_D^{20} + 59.7$ ($c$ 1.7, CHCl$_3$)].

4-(4-Chlorophenyl)-4-hydroxybutan-2-one, 16h

The $^1$H NMR data was consistent with literature values.\textsuperscript{(8)} The product was obtained in 86\% ee. The optical purity was determined by HPLC using a solvent system of 96.4 hexane/isopropanol; flow rate 0.5 mL/min; $t_R = 42.03$ min ($R$), 45.77 min ($S$). $[\alpha]_D^{23} + 73.0$ ($c$ 0.49, CHCl$_3$) [lit.\textsuperscript{(12)} (83\% ee); $[\alpha]_D^{27} + 53.5$ ($c$ 1.0, CHCl$_3$)].

4-Hydroxy-4-(2-nitrophenyl)butan-2-one, 16i

The $^1$H NMR data was consistent with literature values.\textsuperscript{(13)} The product was obtained in 91\% ee. The optical purity was determined by HPLC using a solvent system of 97.3 hexane/isopropanol; flow rate 0.5 mL/min; $t_R = 80.84$ min ($R$), 84.87 min ($S$). $[\alpha]_D^{23} - 141.0$ ($c$ 0.546, CHCl$_3$) [lit.\textsuperscript{(12)} (75\% ee); $[\alpha]_D^{27} - 108.2$ ($c$ 1.2, CHCl$_3$)].

4-Hydroxy-4-(3-nitrophenyl)butan-2-one, 16j

The $^1$H NMR data was consistent with literature values.\textsuperscript{(8)} The product was obtained in 90\% ee. The optical purity was determined by HPLC using a solvent system of 97.3 hexane/isopropanol; flow rate 0.5 mL/min; $t_R = 120.49$ min ($R$), 129.38 min ($S$). $[\alpha]_D^{23} + 65.9$ ($c$ 0.44, CHCl$_3$) [lit.\textsuperscript{(8)} (87\% ee); $[\alpha]_D^{20} + 62.1$ (CHCl$_3$)].

Procedures for the synthesis of the Mosher ester of adduct 16a.
To a solution of (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (15.11 mg, 0.065 mmol) in dry dichloromethane (0.3 mL) was added aldol adduct 16a (9 mg, 0.043 mmol) and DMAP (1.05 mg, 0.0086 mmol). The mixture was stirred and cooled to 0 °C and dicyclohexylcarbodiimide (22.18 mg, 0.11 mmol) was added. The mixture was stirred overnight, at room temperature, after which time the TLC indicated complete consumption of the starting material. The reaction mixture was filtered, the filtrate was then evaporated in vacuo, the residue dissolved in ether (4 mL). The solution was washed with 0.5 N HCl (2 mL × 2), saturated NaHCO₃ (2 mL × 2), dried (MgSO₄) and evaporated to yield the Mosher ester as a yellow residue which was directly subjected to ¹H NMR analysis: ¹H NMR (400 MHz; CDCl₃) δ = 2.09 and 2.17 (s, 3 H, CH₃), 2.80 (dd, J = 3.8, 17.8 Hz, 1 H, CH₂), 3.20 (dd, J = 9.4, 17.8 Hz, 1 H, CH₂), 3.51 (s, 3H, OMe), 6.41 (dd, J = 4.0, 9.2 Hz, 1 H, CH) and 6.5 (dd, CH), 7.29–7.41 (m, 5 H, Ph-H), 7.70 (d, J = 9.0 Hz, 1 H, ArNO₂-H), 8.16 (d, J = 8.6 Hz, 2 H, ArNO₂-H), 8.26 (d, J = 9.0 Hz, 1 H, ArNO₂-H).

Reaction profile of the aldol reaction between acetone and aldehyde 11 catalysed by α-methylproline tetrazole 4 at 35 °C, determined by ¹H NMR studies.

References:
AcOH
16f
Mosher ester of adduct 16a

88% ee
16f

9.63%

90.37%
90.17%

9.83%

16g