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Homochiral bifunctional *L*-prolinamide- and *L*-bis-prolinamide-catalyzed asymmetric aldol reactions performed in wet solvent-free conditions

Gabriela Huelgas[1] | **Ratnasamy Somanathan**[2] | **Julio M. Hernández Pérez**[3] | **Haydee Rojas Cabrera**[1] | **Maximiliano de la Higuera Macías**[1] | **Alejandra Domínguez-Huerta**[1] | **Rocío Sabala**[1] | **Cecilia Anaya de Parrodi**[1]

[1]Departamento de Ciencias Químico Biológicas, Universidad de las Americas Puebla, Cholula, Puebla, Mexico

[2]Centro de Graduados e Investigación en Química, Tecnológico Nacional de México/Instituto Tecnológico de Tijuana, Tijuana, Baja California, Mexico

[3]Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla, Puebla, Mexico

Correspondence
Cecilia Anaya de Parrodi, Universidad de las Américas Puebla, Departamento de Ciencias Químico Biológicas, Santa Catarina Mártir, 72820, Cholula, Puebla, México.
Email: cecilia.anaya@udlap.mx

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Abstract

In this study, the novel bifunctional homochiral thiourea-*L*-prolinamides **1–4**, tertiary amino-*L*-prolinamide **5**, and bis-*L*-prolinamides **6** and **7** were prepared from enantiomerically pure (11*R*,12*R*)-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene **8** and (11*S*,12*S*)-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene ***ent*-8**. Highly enantioselective and diastereoselective aldolic intermolecular reactions (up to 95% enantiomeric excess, 93:7 *anti*/*syn*) between aliphatic ketones (20 equiv) and a range of aromatic aldehydes (1 equiv) were successfully carried out in the presence of water (10 equiv) and monochloroacetic acid (10 mol%), solvent-free conditions, at room temperature over 24 h using organocatalysts **1–7** (5 mol%). Stereoselective induction using density functional theory–based methods was consistent with the experimental data.

KEYWORDS

1,2-diamines, aldol reaction, asymmetric organocatalysis, bifunctional prolinamides, C_2-symmetry axis, stereoselectivity, wet solvent-free

1 | INTRODUCTION

Asymmetric organocatalysis has had a tremendous impact on synthetic organic chemistry since 2000. It is an environmentally benign process that requires no metallic species.[1,2,4,5,14] Several examples exist in the usage of organocatalysts under solvent-free or very concentrated catalytic reaction conditions.[6] The successful use of organocatalysts with water as a solvent or in wet solvent-free conditions has also been reported.[7] Water might play an important role in the transition state of the asymmetric organocatalyzed reactions, through the formation of hydrogen bonds and other noncovalent interactions.[8–10]

Asymmetric C–C bond formation reactions are important in organic synthesis. In particular, there are several reports of the asymmetric aldol reaction between ketones and aldehydes. This reaction produces β-hydroxy-carbonyl compounds with one or more stereogenic centers. These compounds have wide applications as building blocks of complex biologically active molecules.[11–13] List and Barbas reported the aldolic reaction involving an aldehyde and a ketone, catalyzed by chiral proline in DMSO. They reported that proline behaves as a bifunctional organocatalyst, where the proton donor group activates the electrophile, and the amine group activates the nucleophile, through the formation of an enamine. Thus, proline mimicks the natural enzyme aldolase.[14–21]

Since this pioneering work for the aldol reaction, there are other reports of the use of enantiopure bifunctional *L*-prolinamide as organocatalysts, such as **A**, **B**, **C**, and **D** (Figure 1), with moderate to good stereoselectivities and yields. In particular, these prolinamides contain the *trans*-1,2-diaminocyclohexane moiety as backbone.[22–25]

Herein, we synthesized novel homochiral bifunctional *L*-prolinamide organocatalysts **1**–**6** from enantiopure (11*R*,12*R*)-11,12-diamino-9,10-dihydro-9,10-ethanothracene **8**[23,26,27] (Figure 2). We also prepared *L*-prolinamide organocatalyst **7** from enantiopure (11*S*,12*S*)-11,12-diamino-9,10-dihydro-9,10-ethanothracene *ent*-**8** (Scheme 4). We evaluated the novel organocatalysts in the asymmetric aldol reaction in wet solvent-free conditions, and in the presence of chloroacetic acid as additive. Theoretical calculations of the transition state of acetone and *p*-nitrobenzaldehyde with organocatalyst **6** supported the experimental outcome.

2 | EXPERIMENTAL

2.1 | Materials and instruments

All reagents were purchased from commercial suppliers and used without further purification. THF was freshly distilled from a sodium-benzophenone ketyl radical under an argon atmosphere. NMR spectra were recorded on a Bruker 400 MHz spectrometer. The chemical shifts of the peaks in the ^{1}H NMR spectra were referenced to the resonance of tetramethylsilane. The chemical shifts of the peaks in the ^{13}C NMR spectra were referenced to the resonance of the residual solvent. Infrared spectra were recorded on a Bruker Tensor 27 spectrometer. The *ee* values were measured by doing chiral high-performance liquid chromatography (HPLC) purification at room temperature using an Agilent Infinity with an ultraviolet-visible (UV-vis) detector, with Chiralpak AD-H and Chiralcel OD-H columns.

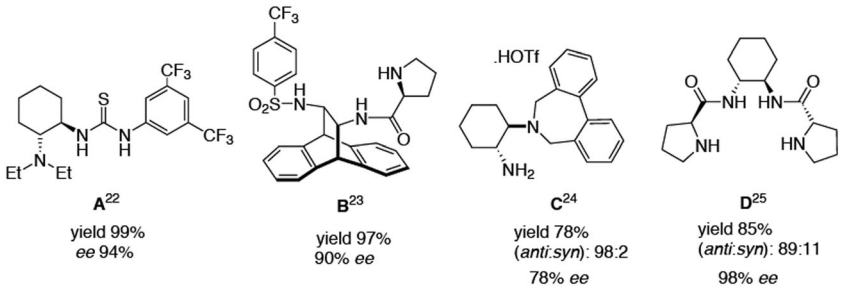


FIGURE 1 Examples of recently synthesized *L*-prolinamide bifunctional organocatalysts used in asymmetric aldol reactions

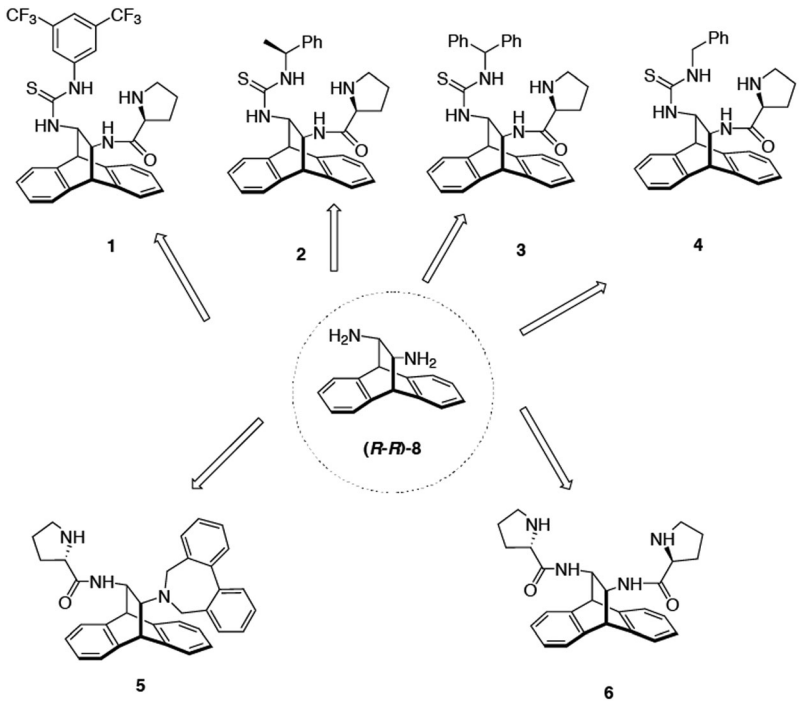


FIGURE 2 Structures of the homochiral bifunctional *L*-prolinamides and *L*-bis-prolinamides **1**–**6**

2.2 | Synthesis

2.2.1 | General procedure for the synthesis of thiourea-L-prolinamides 9–12

(11*R*,12*R*)-11,12-Diamino-9,10-dihydro-9,10-ethanoanthracene **8** (350 mg, 1.48 mmol) and 1.49 mmol of crude (*S*)-1-phenylethyl isothiocyanate, (3,5-trifluoromethyl)phenyl isothiocyanate, di(phenyl) methylene isothiocyanate, or benzylisothiocyanate were dissolved in dichloromethane (10 ml) under a nitrogen atmosphere at 0°C. Triethylamine (0.22 ml, 165 mg) was added to the reaction mixture, which was then stirred at 0°C until the disappearance of the isothiocyanates for ~2 h. The reaction was then quenched by adding water, and the organic phase was first extracted with CH_2Cl_2 (3 × 20 ml), followed by drying over anhydrous sodium sulfate. The solvent was removed at a reduced pressure. Crude amino-thioureas **9–12** were isolated and purified by flash chromatography on silica gel (triethylamine/SiO_2 = 2.0% *v*/*w*, hexanes/ethyl acetate 2:1, *v*/v).

*(11*R*,12*R*)-11-[(*S*)-1-Phenylethylthiourea]-12-amino-9,10-dihydro-9,10-ethanoanthracene (**9**)*

White solid (78% yield), m.p. 133–135°C. $[\alpha]_D^{20}$ = +62.2 (*c* = 1, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6, 115°C, δ): 1.44 (d, *J* = 7 Hz, 3*H*), 2.80 (b, 4*H*), 3.89 (b, 1*H*), 4.15 (d, *J* = 2.4 Hz, 1*H*), 4.46 (d, *J* = 2.6 Hz, 1*H*), 5.49–5.55 (m, 1*H*), 6.55 (b, 1*H*), 7.12–7.35 (m, 13*H*). ^{13}C NMR (50 MHz, DMSO-d_6, 115°C, δ): 21.5, 48.0, 51.8, 52.3, 59.1, 62.4, 122.3, 122.4, 124.2, 124.4, 124.7, 125.1, 126.7, 137.6, 138.3, 139.8, 141.2, 142.5, 180.2. IR (KBr) υ_{max} 3414, 3361, 3232, 3026, 2928, 2869, 1580, 1529, 1472, 1405, 1377, 1350, 1305, 1230, 1147, 1114, 1082, 1023, 1003 cm^{-1}. HRMS (FAB+) *m*/*z* calcd. for $[C_{25}H_{26}N_3S_1]$: 400.1847, found 400.1855.

*(11*R*,12*R*)-11-[(3,5-Trifluoromethyl)phenylthiourea]-12-amino-9,10-dihydro-9,10-ethanoanthracene (**10**)*

White solid (89% yield), m.p. 125–127°C. $[\alpha]_D^{20}$ = +24.0 (*c* = 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.73 (b, 2*H*), 3.12 (b, 1*H*), 3.38 (b, 1*H*), 4.13 (d, J = 2.0 Hz, 1*H*), 4.30 (d, J = 2.2 Hz, 1*H*), 6.27 (d, J = 5.2 Hz, 1*H*), 7.19–7.60 (m, 9*H*), 8.13 (s, 2*H*), 11.06 (b, 1*H*). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 3, 53.5, 60.2, 63.6, 118.4, 123.2 (q,$^1J_{CF}$ = 273.8 Hz), 123.6, 124.6, 126.8, 127.4, 127.6, 127.8, 132.1, 136.3, 137.6, 140.4, 141.5, 141.7, 180.8. IR (KBr) υ_{max} 3409, 3360, 2926, 1605, 1513, 1471, 1379, 1275, 1172, 1126, 1012 cm^{-1}. HRMS (FAB+) *m*/*z* calcd. for $[C_{25}H_{20}F_6N_3S_1]$: 508.12857, found 508.12821.

*(11*R*,12*R*)-11-[Di(phenyl)methylenethiourea]-12-amino-9,10-dihydro-9,10-ethanoanthracene (**11**)*

White solid (72% yield), m.p. 145–147°C. $[\alpha]_D^{20}$ = +60.5 (*c* = 1, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6, 105°C, δ): 2.78–2.95 (m, 6*H*), 3.91 (b, 1*H*), 4.15 (d, J = 2.4 Hz, 1*H*), 4.51 (d, J = 2.2 Hz, 1*H*), 6.75 (s, 1*H*), 6.84 (d, J = 6.8 Hz, 1*H*), 7.11–7.35 (m, 16*H*). ^{13}C NMR (50 MHz, DMSO-d_6, 105°C, δ): 48.0, 51.8, 59.1, 60.4, 62.6, 122.4, 122.5, 124.2, 124.5, 124.6, 124.7, 125.4, 125.8, 125.9, 126.8, 137.7, 138.4, 139.8, 140.8, 141.0, 141.3, 180.8.IR (KBr) υ_{max} 3415, 3356, 3237, 3028, 2928, 2854, 2117, 1728, 1678, 1580, 1528, 1472, 1402, 1350, 1255, 1225, 1118, 1074, 1027 cm^{-1}. HRMS (FAB+) *m*/*z* calcd. for $[C_{30}H_{28}N_3S_1]$: 462.2004, found 462.2014.

*(11*R*,12*R*)-11-(benzylthiourea)-12-amino-9,10-dihydro-9,10-ethanoanthracene (**12**)*

White solid (70% yield), m.p. 134–136°C. $[\alpha]_D^{20}$ = +58.3 (*c* = 1, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6, 85°C, δ): 3.00 (b, 5*H*), 3.89 (b, 1*H*), 4.14 (d, J = 2.6 Hz, 1*H*), 4.48 (d, J = 2.6 Hz, 1*H*), 4.66 (s, 2*H*), 6.76 (d, J = 7 Hz, 1*H*), 7.10–7.35 (m, 12*H*). ^{13}C NMR (50 MHz, DMSO-d_6, 85°C, δ): 47.0, 48.1, 51.7, 59.0, 62.5, 122.4, 122.5, 124.2, 124.5, 124.6, 124.7, 125.4, 126.0, 126.8, 137.5, 137.7, 138.5, 139.9, 141.3, 181.4. IR (KBr) υ_{max} 3304, 3274, 3115, 3062, 2974, 2946, 2874, 1659, 1531, 1457, 1369, 1345, 1287, 1250, 1162, 1117, 1082, 1028 cm^{-1}. HRMS (FAB+) *m*/*z* calcd. for $[C_{24}H_{24}N_3S_1]$: 386.1691, found 386.1694.

2.2.2 | General procedure for the synthesis of thiourea-L-prolinamides 13–16

A solution of (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (600 mg, 2.76 mmol) and triethylamine (279 mg, 0.384 ml, 2.75 mmol) was prepared in anhydrous THF (50 ml). This solution was then cooled down to 0°C. Ethyl chloroformate (300 mg, 0.264 ml, 2.76 mmol) was then added dropwise, and the resulting solution was stirred for 30 min. A solution of thiourea (2.76 mmol) in anhydrous THF (25 ml) was added to the solution described above, and the solution thus obtained was left stirring for another 4 h at 0°C. The reaction mixture was then filtered, leaving the solvent under reduced pressure. The residue was dissolved in ethyl acetate (60 ml). The organic phase was subjected to successive washes with water, saturated aqueous $NaHCO_3$, and brine. The organic phase was collected, dried over anhydrous sodium sulfate, and concentrated by evaporation under reduced pressure. The product contained in the concentrated solution was purified by column chromatography on silica gel using hexanes/ethyl acetate

(2:1, *v*/v) as an eluent to produce the desired protected prolinamide thioureas **13–16**.

*(11R,12R)-11-[(S)-1-Phenylethylthiourea]-12-[(S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido]-9,10-dihydro-9,10-ethanoanthracene (**13**)*

White solid (78% yield), m.p. 138–140°C. $[\alpha]_D^{20} = -36.9$ (c = 1, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6, 85°C, δ): 1.21 (s, 9*H*), 1.41 (d, J = 6.6 Hz, 3*H*), 1.76–2.00 (m, 4*H*), 3.09 (s, 1*H*), 3.20–3.35 (m, 2*H*), 3.71 (dd, J = 4.2, 2.8 Hz, 1*H*), 4.03–4.06 (m, 1H), 4.36–4.45 (m, 2*H*), 4.69 (d, J = 2.4 Hz, 1*H*), 5.45 (dd, J = 7.8, 7.0 Hz, 1*H*), 6.93 (d, J = 7.8 Hz, 1*H*), 7.09–7.46 (m, 13*H*), 7.56 (d, J = 8.2 Hz, 1*H*). ^{13}C NMR (50 MHz, DMSO-d_6, 85°C, δ): 21.7, 22.8, 27.6, 30.2, 46.0, 48.4, 51.9, 56.2, 58.8, 59.0, 78.0, 123.4, 123.6, 125.2, 125.3, 125.6, 125.6, 125.8, 126.1, 127.6, 139.1, 141.3, 141.6, 143.6, 153.1, 172.0, 181.7. IR (KBr) υ_{max} 3301, 3043, 2973, 2875, 1665, 1525, 1456, 1367, 1249, 1160, 1117, 1086, 1025 cm^{-1}. HRMS (FAB+) *m*/*z* calcd. for $[C_{35}H_{41}N_4O_3S_1]$: 597.2899, found 597.2904.

*(11R,12R)-11-[(3,5-Trifluoromethyl)phenylthiourea])-12-[(S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido]-9,10-dihydro-9,10-ethanoanthracene (**14**)*

White solid (72% yield), m.p. 227–230°C. $[\alpha]_D^{20} = -84.3$ (c = 1, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6, 85°C, δ): 1.14 (s, 9*H*), 1.68–1.79 (m, 3*H*), 2.04–2.31 (m, 3*H*), 3.06–3.23 (m, 3*H*), 4.05–4.23 (m, 2*H*), 4.36 (d, J = 2.2 Hz, 1*H*), 4.67–4.71 (m, 1*H*), 7.16–7.71 (m, 10*H*), 8.02 (s, 1*H*), 8.82 (b, 1*H*). ^{13}C NMR (50 MHz, DMSO-d_6, 85°C, δ): 23.7, 24.4, 24.9, 30.4, 47.3, 48.7, 49.6, 57.4, 59.7, 62.1, 68.4, 80.9, 116.3, 120.7, 122.7 (q,$^1J_{CF}$ = 259.7 Hz), 123.3, 124.9, 125.1, 126.2, 126.7, 126.9, 127.3, 128.5, 130.6, 130.8, 136.9, 138.6, 140.2, 158.5, 171.5, 178.8. IR (KBr) υ_{max} 3308, 3027, 2971, 2929, 2875, 1669, 1522, 1455, 1367, 1287, 1249, 1160, 1116, 1086, 1023 cm^{-1}. HRMS (FAB+) *m*/*z* calcd. for $[C_{35}H_{35}N_4O_3F_6S_1]$: 705.2334, found 705.2334.

*(11R,12R)-11-[Di(phenyl)methylenethiourea]12-[(S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido]-9,10-dihydro-9,10-ethanoanthracene (**15**)*

White solid (68% yield), m.p. 147–149°C. $[\alpha]_D^{20} = -15.11$ (c = 1, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6, 85°C, δ): 1.84 (s, 9*H*), 2.00–2.35 (m, 4*H*), 3.61 (ddd, J = 5.8, 2.8, 2.8 Hz, 2*H*), 4.16 (ddd, J = 3.4, 3.2, 1.2 Hz, 1*H*), 4.48 (dd, J = 2.6, 3.0 Hz, 1*H*), 4.78 (d, J = 2.8 Hz, 1*H*), 4.91–5.02 (m, 1*H*), 6.52 (d, J = 7.8 Hz, 1*H*), 6.89 (d, J = 7.0 Hz, 1*H*), 7.0 (d, J = 7.8 Hz, 1*H*), 7.54–7.88 (m, 20*H*). ^{13}C NMR (50 MHz, DMSO-d_6, 85°C, δ): 22.8, 27.5, 30.0, 46.0, 48.1, 48.3, 56.3, 56.5, 58.8, 59.2, 60.1, 78.0, 123.3, 123.5, 123.9, 125.5, 125.6, 125.9, 126.0, 126.3, 126.4, 126.5, 126.7, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.7, 139.0, 139.1, 141.4, 141.5, 141.9, 142.1, 156.1, 171.8, 182.3. IR (KBr) υ_{max} 3301, 3274, 3115, 3061, 2973, 2946, 2874, 1660, 1530, 1456, 1368, 1345, 1288, 1248, 1161, 1116, 1052, 1028 cm^{-1}. HRMS (FAB+) *m*/*z* calcd. for $[C_{40}H_{43}N_4O_3S_1]$: 659.3056, found 659.3064.

*(11R,12R)-11-(Benzylthiourea)-12-[(S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido]-9,10-dihydro-9,10-ethanoanthracene (**16**)*

White solid (70% yield), m.p. 133–135°C. $[\alpha]_D^{20} = -45.8$ (c = 1, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6, 75°C, δ): 1.27 (s, 9*H*), 1.75–1.97 (m, 4*H*), 3.11 (s, 1*H*), 3.31 (dd, J = 5.4, 6.6 Hz, 2*H*), 3.73 (b, 1*H*), 4.07 (d, J = 7.4 Hz, 1*H*), 4.36–4.45 (m, 2*H*), 4.66 (b, 1*H*), 4.72 (d, J = 2.2 Hz, 2*H*), 7.10–7.37 (m, 13*H*), 7.50–7.55 (m, 2*H*). ^{13}C NMR (50 MHz, DMSO-d_6, 75°C, δ): 22.9, 27.7, 30.2, 46.1, 46.7, 48.3, 56.0, 58.8, 59.1, 78.0, 123.5, 123.7, 125.2, 125.4, 125.7, 126.3, 126.4, 126.9, 127.6, 127.8, 138.7, 139.2, 141.3, 141.6, 153.2, 172.0, 182.9. IR (KBr) υ_{max} 3321, 3065, 3026, 2972, 2953, 2930, 2879, 1660, 1526, 1457, 1369, 1344, 1286, 1253, 1161, 1119, 1086, 1054, 1027 cm^{-1}. HRMS (FAB+) *m*/*z* calcd. for $[C_{34}H_{39}N_4O_3S_1]$: 583.2743, found 583.2751.

2.2.3 | General procedure for the synthesis of thiourea-L-prolinamides 1–4

TFA (1 ml) was added to a solution of the protected thiourea-*N*-Boc-*L*-prolinamide (1.0 g) in CH_2Cl_2 (30 ml). The mixture thus obtained was stirred at room temperature for 24 h. The reaction was basified with saturated aqueous $NaHCO_3$ to pH 12.0, and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 ml). The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on deactivated silica gel (triethylamine/SiO_2 = 2.0% *v*/*w*, ethyl acetate 100%) to afford the desired thiourea-*L*-prolinamides **1–4**.

*(11R,12R)-11-[(3,5-Trifluoromethyl)phenylthiourea])-12-[(S)-pyrrolidine-2-carboxamido]-9,10-dihydro-9,10-ethanoanthracene (**1**)*

White solid (82% yield), m.p. 173–175°C. $[\alpha]_D^{20} = -41.4$ (c = 1, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6, 55°C, δ): 1.25–1.87 (m, 6*H*), 2.63–2.74 (m, 1*H*), 3.50 (dd, J = 5.4, 5.0 Hz, 1*H*), 3.86–3.90 (m, 1*H*), 4.38 (d, J = 2.4 Hz, 1*H*), 4.47 (b, 1*H*), 4.65 (d, J = 2.0, 1*H*) 7.20–8.14 (m, 11*H*), 8.29 (s, 1*H*), 9.0 (b, 1*H*). ^{13}C NMR (50 MHz, DMSO-d_6, 55°C, δ): 26.5, 31.1, 47.3, 48.8, 56.8, 60.3, 62.1, 68.4, 116.2, 120.4, 120.2, 122.8 (q,$^1J_{CF}$ = 278.7 Hz), 123.2, 124.5, 124.7, 126.1, 126.4, 126.6, 127.2, 128.5, 130.0, 130.6, 137.0, 139.0, 140.6, 174.6, 178.7. IR (KBr) υ_{max} 3281, 3071, 2951, 2871,

1721, 1647, 1630, 1600, 1515, 1470, 1383, 1335, 1274, 1227, 1172, 1124 cm^{-1}. HRMS (FAB+) *m/z* calcd. for $[C_{30}H_{26}N_4O_1F_6S_1]$: 604.1732, found 604.1740.

*(11*R*,12*R*)-11-[(*S*)-1-Phenylethylthiourea]-12-[(*S*)-pyrrolidine-2-carboxamido]-9,10-dihydro-9,10-ethanoanthracene (**2**)*

White solid (82% yield), m.p. 145–148°C. $[\alpha]_D^{20} = -6.9$ (*c* = 1, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6, 95°C, δ): 1.24 (d, J = 6.6 Hz, 3*H*), 1.42–1.72 (m, 6*H*), 2.80 (b, 2*H*), 3.32 (t, J = 6.0 Hz, 1*H*), 3.55 (b, 1*H*), 4.16–4.23 (m, 2*H*), 4.37 (b, 1*H*), 5.28 (t, J = 6.6 Hz, 1*H*), 6.62 (d, J = 7.8, 1*H*) 7.02–7.22 (m, 13*H*), 7.48 (d, J = 7.8, 1*H*). ^{13}C NMR (50 MHz, DMSO-d_6, 95°C δ): 21.6, 25.0, 29.8, 46.0, 48.4, 48.6, 52.0, 55.9, 59.8, 60.0, 123.5, 123.6, 125.1, 125.3, 125.5, 125.7, 125.8, 126.1, 127.7, 138.8, 138.9, 141.3, 141.4, 143.5, 173.7, 181.8. IR (KBr) υ_{max} 3343, 3083, 2974, 2942, 2877, 1662, 1532, 1451, 1373, 1346, 1287, 1243, 1162, 1114, 1050, 1003 cm^{-1}. HRMS (FAB+) *m/z* calcd. for $[C_{30}H_{33}N_4O_1S_1]$: 497.2375, found 497.2375.

(11*R*,12*R*)-11-[Di(phenyl)methylenethiourea]12-[(*S*)-pyrrolidine-2-carboxamido]-9,10-dihydro-9,10-ethanoan thracene (**3**)

White solid (80% yield), m.p. 135–137°C. $[\alpha]_D^{20} = -39.2$ (*c* = 1, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6, 125°C, δ): 1.27–1.89 (m, 6*H*), 3.21 (b, 2*H*), 3.57–3.83 (m, 3*H*), 4.28–4.70 (m, 2*H*), 5.57 (b, 1*H*), 6.83–7.39 (m, 18*H*), 8.22 (b, 1*H*), 8.43 (b, 1*H*). ^{13}C NMR (50 MHz, DMSO-d_6, 125°C, δ): 24.8, 29.6, 45.9, 48.4, 52.3, 55.8, 56.2, 59.8, 60.3, 123.2, 124.9, 125.1, 125.5, 125.6, 125.6, 126.1, 126.5, 127.2, 127.3, 127.6, 127.7, 127.8, 134.8, 136.9, 139.2, 139.7, 141.6, 150.0, 165.7, 173.4. IR (KBr) V_{max} 3300, 3058, 3026, 2945, 2865, 1647, 1614, 1514, 1455, 1338, 1288, 1226, 1110, 1077, 1028 cm^{-1}. HRMS (FAB+) *m/z* calcd. for $[C_{35}H_{35}N_4O_1S_1]$: 559.2532, found 559.2527.

*(11*R*,12*R*)-11-(Benzylthiourea)-12-[(*S*)-pyrrolidine-2-carboxamido]-9,10-dihydro-9,10-ethanoanthracene (**4**)*

White solid (75% yield), m.p. 147–149°C. $[\alpha]_D^{20} = -31.2$ (*c* = 1, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6, 55°C, δ): 1.32 (b, 2*H*), 1.45–1.92 (m, 4*H*), 2.59–2.76 (m, 2*H*), 3.11 (b, 1*H*), 3.51 (dd, J = 5.2, 5.4 Hz, 1*H*), 3.73–3.80 (m, 1*H*), 4.34 (d, J = 2.6 Hz, 1*H*), 4.38–4.46 (m, 1*H*), 4.59 (d, J = 2.6 Hz, 1*H*), 4.66 (d, J = 5.4 Hz, 1*H*), 7.08–7.42 (m, 13*H*), 7.58 (d, J = 8.2 Hz, 1*H*), 7.71 (t, J = 5.6 Hz, 1*H*). ^{13}C NMR (50 MHz, DMSO-d_6, 55°C δ): 25.4, 30.1, 46.3, 47.0, 48.5, 48.7, 55.7, 59.8, 60.2, 123.7, 123.8, 125.4, 125.5, 125.9, 126.0, 126.6, 127.0, 127.5, 128.0, 138.7, 139.1, 141.4, 141.5, 173.9, 182.8. IR (KBr) υ_{max} 3291, 3069, 2954, 2869, 1651, 1513, 1459, 1342, 1316, 1286, 1227, 1158, 1105, 1056 cm^{-1}. HRMS (FAB+) *m/z* calcd. for $[C_{29}H_{31}N_4O_1S_1]$: 483.2219, found 483.2219.

2.2.4 | General procedure for the synthesis of reaction intermediate 17

A suspension of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoa nthracen-11-amine (*S*)-mandelate salt (1.00 g, 2.60 mmol), 2,2′-bis (bromomethyl)biphenyl (0.88 g, 2.57 mmol), and K_2CO_3 (1.07 g, 7.72 mmol) was prepared in acetonitrile (20 ml). This suspension was then stirred at 85°C for 2 h. After incubation, the mixture was washed with brine (10 ml). The aqueous layer was then extracted with CH_2Cl_2 (30 × 3 ml), and the organic phase was dried over Na_2SO_4 and concentrated.

The concentrated solution thus obtained was subjected to silica gel column chromatography purification using ethyl acetate/hexane (5:1 *v*/v) as an eluent to afford product **17**.

*(11*R*,12*R*)-12-(6,7-Dihydro-5*H*-dibenzo[c,e]azepin)-9,10-dihydro-9,10-ethanoanthracen-11-amine (**17**)*

Yellow solid (71% yield), m.p. 158–160°C. $[\alpha]_D^{20} = +84$ (*c* = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.45 (t, J = 2.7 Hz, 1*H*), 3.21 (t, J = 2.9 Hz, 1*H*), 3.24 (d, J = 3.2 Hz, 2*H*), 3.90 (d, J = 12.1 Hz, 2*H*), 4.06 (d, J = 2.7 Hz, 1*H*), 4.27–4.30 (m, 2*H*), 4.48 (d, J = 2.4 Hz, 1*H*), 7.06–7.23 (m, 16*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 47.5, 52.9, 55.0, 58.4, 62.8, 71.3, 124.5, 124.7, 125.0, 126.2, 126.3, 126.4, 126.5, 127.5, 127.7, 127.7, 127.8, 128.1, 128.2, 129.7, 129.8,129.8, 129.8, 130.7, 135.0, 138.9, 139.0, 139.6, 140.2, 140.2, 141.0, 141.4, 142.0, 142.2. IR-FT (KBr) ν_{max}/cm^{-1}: 3275, 3061, 3019, 2960, 2927, 2869, 2809, 1734, 1450, 1368, 1295, 1192, 1168, 1044, 1192, 1168, 1113, 1021. HRMS-FAB+: *m/z* [M + H] + calcd. for $[C_{30}H_{27}N_2]$: 415.2174, found: 415.2175.

2.2.5 | General procedure for the synthesis of tertiary amino-prolineamide 18

Ethyl chloroformate (0.30 g, 2.76 mmol) was added dropwise to a solution of compound **17** (0.59 g, 2.76 mmol) and triethylamine (0.28 g, 2.76 mmol) in dry CH_2Cl_2 (40 ml) over 15 min under argon at 0°C. The resulting solution was stirred at 0°C for 15 min. A solution of amine (0.95 g, 2.29 mmol) in dry CH_2Cl_2 (10 ml) was then added dropwise. The solution was allowed to warm up to room temperature and then stirred for an additional 5 h. The solution was then washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash chromatography using hexane/ethyl acetate (1:1, *v*/v) as an eluent, to afford the *N*-Boc-protected prolinamide **5**.

*(11R,12R)-[(S)-tert-Butoxycarbonyl-pyrrolidine-2-carboxamido]12-(5H-dibenzo[c,e]azepin)-9,10-dihydro-9,10-ethanoanthracene (**18**)*

White solid (78% yield), m.p. 125–127°C. $[\alpha]_D^{20} = -19.6$ (c = 1, $CHCl_3$ ^{1}H NMR (400 MHz, DMSO-d_6, 90°C δ): 1.00 (s, 9*H*), 1.74–2.00 (m, 7*H*), 2.60 (b, 2*H*), 3.85–4.39 (m, 4*H*), 4.86–5.08 (m, 2*H*), 7.14–7.59 (m, 16*H*), 7.72–7.77 (m, 1*H*). ^{13}C NMR (100 MHz, DMSO-d_6, 90°C δ): 24.0, 33.9, 34.8, 37.9, 41.0, 56.0, 58.4, 59.0, 62.0, 65.9, 68.7, 88.0, 134.1, 134.6, 135.2, 135.4, 135.7, 136.1, 136.3, 136.9, 137.1, 137.2, 137.3, 137.6, 138.1, 138.9, 139.8, 140.1, 140.4, 144.0, 144.3, 149.7, 150.2, 150.3, 150.6, 151.0, 151.1, 151.6, 151.7, 151.8, 163.9, 181.7. IR-FT (KBr) ν_{max}/cm^{-1}: 3648, 3319, 2950, 2925, 2871, 2799, 1675, 1507, 1477, 1456, 1388, 1363, 1312, 1246, 1226, 1158, 1116, 1086, 1025. HRMS-FAB+: m/z [M + H] + calcd. for $[C_{40}H_{42}O_3N_3]$: 612.3226, found: 612.3218.

2.2.6 | General procedure for the synthesis of tertiary amino-prolineamide 5

A solution of *N*-Boc-protected prolinamide **18** (0.6 g, 0.98 mmol) and TFA (0.34 g, 0.23 ml, 2.94 mmol) was prepared in CH_2Cl_2 (5 ml). This solution was then stirred at room temperature for 24 h. An aqueous solution of $NaHCO_3$ was then utilized to adjust the solution's pH to 12. The mixture was diluted with CH_2Cl_2, and the phases were separated. The aqueous layer was extracted with dichloromethane (2 × 100 ml), and the combined organics were washed with a small volume of brine. The organic phase was then dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography on silica gel using methanol/ethyl acetate (1:9, *v*/v) as an eluent, to give the desired product **5**.

*(11R,12R)-12-(6,7-Dihydro-5H-dibenzo[c,e]azepin)-9,10-dihydro-9,10-ethanoanthracen-pyrrolidine-2-carboxamide (**5**)*

Yellow solid (80% yield), m.p. 223–225°C. $[\alpha]_D^{20} = -20.1$ (c = 0.87, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 1.25 (b, 2*H*), 1.77 (t, J = 6.6 Hz, 2*H*), 2.16–2.21 (m, 2*H*), 2.72 (b, 1*H*), 3.0–3.04 (m, 1*H*), 3.33 (d, J = 12.3 Hz, 2*H*), 3.66 (d, J = 12.4 Hz, 3*H*), 3.98 (t, J = 6.2, 1*H*), 4.36 (d, J = 8.4 Hz, 1*H*), 4.44 (b, 1*H*), 4.63 (b, 1*H*), 7.10–7.50 (m, 16*H*). ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 25.9, 30.8, 47.1, 47.5, 49.5, 52.9, 55.0, 60.3, 70.1, 124.8, 125.0, 125.2, 125.6, 126.6, 126.6, 126.8, 127.7, 127.8, 128.4, 130.3, 134.5, 140.0, 140.8, 140.9, 141.3, 141.8, 172.0. IR-FT (KBr) ν_{max}/cm^{-1}: 3372, 3318, 2966, 1602, 1406, 1251, 1197, 1117, 1075, 1043, 937. HRMS-FAB+: m/z [M + H] + calcd. for $[C_{35}H_{34}O_1N_3]$: 512.2702, found: 512.2714.

2.2.7 | General procedure for the synthesis of *N*-Boc-protected *L*-bis-prolinamides 19 and 20

Ethyl chloroformate (0.72 g, 6.6 mmol) was added dropwise to a solution of *N*-Boc-*L*-proline (1.42 g, 6.6 mmol) and triethylamine (0.67 g, 6.6 mmol) in dry CH_2Cl_2 (40 ml) over 15 min under argon at 0°C. The resulting solution was stirred at 0°C for 15 min. Then, a solution of (11*R*,12*R*)-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene (11*R*,12*R*)-**8** or (11*S*,12*S*)-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene (11*S*,12*S*)-**8** in dry CH_2Cl_2 (10 ml) was added to it dropwise. The resulting solution was allowed to warm up to room temperature and then stirred for a further 5 h. The mixture was washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash chromatography using ethyl acetate/methanol (1: 1, *v*/v) as an eluent to afford the desired *N*-Boc-protected bis-prolinamides **19 or 20**.

*(11R,12R)-11,12-Bis[(S)-1-tert-Butoxycarbonyl-pyrrolidine-2-carboxamido]-9,10-dihydro-9,10-ethanoanthracene **(19)***

White solid (82% yield), m.p. 94–96°C. $[\alpha]_D^{20} = -96.5°$ (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6, 90°C δ): 1.29 (s, 18*H*), 1.73–1.96 (m, 8*H*), 3.27–3.37 (m, 4*H*), 3.87 (b, 2*H*), 4.05 (t, J = 4.0 Hz, 2*H*), 4.44 (b, 2*H*), 7.10–7.27 (m, 8*H*), 7.35–7.36 (m, 2*H*). ^{13}C NMR (100 MHz, DMSO-d_6, 90°C δ): 21.7, 27.9, 30.6, 46.2, 47.9, 54.7, 58.9, 78.1, 123.9, 125.3, 125.7, 125.7, 139.7, 141.2, 153.3, 171.9. IR (KBr) ν_{max}/cm^{-1}: 3287, 3044, 2960, 2928, 2886, 1739, 1681, 1653, 1536, 1453, 1416, 1392, 1368, 1329, 1284, 1234,1202, 1159, 1086. HRMS (FAB^+) m/z calcd. for $[C_{36}H_{47}N_4O_6]$: 631.3496, found 631.3503.

*(11S,12S)-11,12-Bis[(S)-1-tert-Butoxycarbonyl-pyrrolidine-2-carboxamido]-9,10-dihydro-9,10-ethanoanthracene **(20)***

White solid (78% yield), m.p. 115–117°C, $[\alpha]_D^{20} = -10.7°$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6, 90°C): δ 1.40 (s, 18*H*), 1.72–1.80 (m, 6*H*), 1.96–2.01 (m, 2*H*), 3.23–3.28 (m, 3*H*), 3.87 (d, *J* = 5.4 Hz, 2*H*), 4.0–4.05 (m, 2*H*) 4.31 (b, 2*H*), 7.13–7.26 (m, 7*H*), 7.34–7.36 (m, 4*H*). ^{13}C NMR (100 MHz, DMSO-d_6, 90°C): δ 22.8, 27.8, 30.5, 46.1, 48.7, 55.2, 59.3, 78.2, 123.6, 123.7, 125.4, 125.6, 125.7, 139.0, 141.7, 153.2, 171.9. IR (KBr) ν_{max}/cm^{-1}: 3415, 3329, 3310, 3293, 2970, 2929, 2872, 1669, 1653, 1507, 1477, 1457, 1363, 1285, 1245, 1227, 1158, 1116, 1087, 1026. HRMS (FAB^+) m/z calcd. for $[C_{36}H_{47}N_4O_6]$: 631.3496, found 631.3503.

2.2.8 | General procedure for the synthesis of *L*-bis-prolinamides 6 and 7

TFA (2 ml) was added to a solution of the protected bis-prolinamides (1.0 g) in CH_2Cl_2 (30 ml). The resulting mixture was stirred for 48 h. The reaction mixture was then rendered basic with saturated aqueous $NaHCO_3$ at pH 12.0 and extracted with CH_2Cl_2 (3 × 20 ml). The organic phase was dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography on deactivated silica gel (triethylamine/SiO_2 = 2.0% *v*/*w*, ethyl acetate 100%), to afford the desired bis-prolinamides **6** and **7**.

*(11*R*,12*R*)-11,12-Bis[(*S*)-prolyl]-9,10-dihydro-9,10-ethanoanthracene-1,2-diamine (**6**)*

White solid (75% yield), m.p. 107–109°C. $[\alpha]_D^{20} = -94°$ (c = 1.5, $CHCl_3$; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.18–1.21 (m, 3*H*), 1.57–1.63 (m, 2*H*), 1.77–1.85 (m, 1*H*), 2.0–2.15 (m, 3*H*), 2.67–2.73 (m, 1*H*), 2.82–2.88 (m, 1*H*), 3.64–3.69 (m, 2*H*), 3.84–3.86 (m, 1*H*) 4.06 (dd, J = 7, 7 Hz, 2*H*), 4.30–4.31 (m, 1*H*), 4.37 (b, 1*H*), 4.58 (d, J = 8.2 Hz, 1*H*), 7.13–7.40 (m, 11*H*). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 26.1, 30.9, 47.2, 49.7, 56.7, 60.6, 124.9, 125.0, 125.7, 126.0, 126.7, 126.8, 126.9, 127.0, 138.9, 139.1, 141.0, 141.1, 156.1, 174.9. IR (KBr) ν_{max} 3287, 3044, 2971, 2873, 1656, 1506, 1461, 1391, 1367, 1284, 1240, 1161, 1118, 1088, 1045 cm^{-1}. HRMS (FAB^+) m/z calcd. for $[C_{26}H_{31}N_4O_2]$: 431.2447, found 431.2447.

*(11*S*,12*S*)-11,12-Bis[(*S*)-prolyl]-9,10-dihydro-9,10-ethanoanthracene-1,2-diamine (**7**)*

White solid (70% yield), m.p. 175–177°C $[\alpha]_D^{20} = +220°$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.63–1.68 (m, 2*H*), 1.90–1.94 (m, 4*H*), 2.07 (b, 4*H*), 2.59–2.65 (m, 2*H*), 2.82–2.88 (m, 2*H*), 3.62 (dd, J = 4.8 Hz, 2*H*), 3.90 (d, J = 9.8 Hz, 2*H*), 4.36 (b, 2*H*), 7.13–7.46 (m, 10*H*). ^{13}C NMR (100 MHz, $CDCl_3$), δ 26.2, 31.0, 47.1, 49.5, 56.2, 60.3, 125.1, 125.6, 126.6, 126.9, 139.3, 140.8, 175.1. IR (KBr) ν_{max} 3297, 3263, 3045, 3021, 2950, 2942, 2864, 2639, 1645, 1636, 1558, 1540, 1506, 1498, 1457, 1464, 1283, 1244, 1167, 1115, 1100, 1061, 1023 cm^{-1}. HRMS (FAB^+) m/z calcd. for $[C_{26}H_{31}N_4O_2]$: 431.2447, found 431.2447.

2.2.9 | General procedure for the aldol reaction of aromatic aldehydes with cyclic ketones

Monochloroacetic acid (10 mol%) and H_2O (10 equiv) were added under stirring to a solution of catalyst **6** (5 mol%). After 5 min, cyclohexanone (20 equiv) and the desired aldehyde (1.0 equiv) were added in succession. The reaction mixture was then stirred at room temperature and monitored by thin-layer chromatography. Upon completion, 3 ml of a saturated solution of NH_4Cl was added. The reaction mixture was then extracted with CH_2Cl_2 (3 × 5 ml). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product was obtained by purification of the concentrated solution by flash chromatography on silica gel using hexane/ethyl acetate (2:1, *v*/v) as an eluent, to afford the desired product. The *ee* values were determined by chiral HPLC analysis, and the configuration was assigned as *R* by comparing the experimental retention time to literature values.[28]

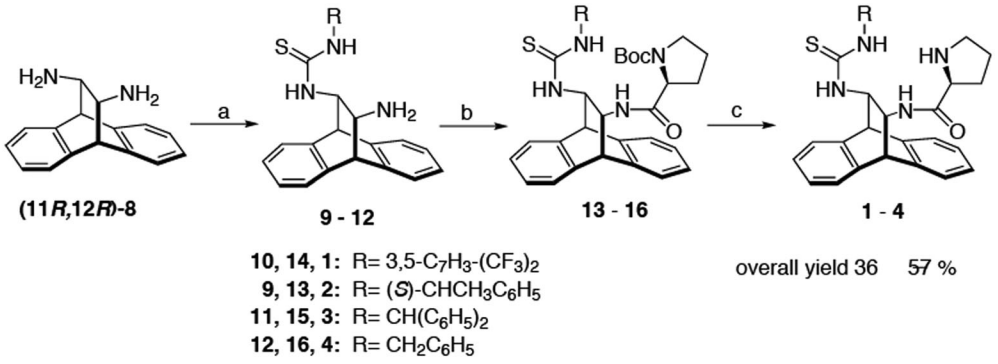
3 | RESULTS AND DISCUSSION

3.1 | Synthesis of catalysts

First, we prepared thiourea-*L*-prolinamides **1–4**, which contain some potentially useful structural features. These structural features such as electron-withdrawing groups and additional chiral centers might influence the stereoselectivity of the reaction. Thiourea group also may contribute to the catalysis of the aldolic reaction, through the formation of hydrogen bonds.[29] Second, tertiary amino-*L*-prolinamide **5** has a bulky substituent, which might favor hydrophobic-hydrophobic interactions. Finally, bis-*L*-prolinamide **6** has a C_2-symmetry axis, which might have beneficial effects in the stereoselectivity of the reaction[30,31] (Figure 2).

We synthesized thiourea-*L*-prolinamides **1–4** from the enantiomerically pure diamine (11*R*,12*R*)-**8** in three steps (Scheme 1). First, the 1,2-diamine (11*R*,12*R*)-**8** was made to react in CH_2Cl_2 at 0°C with (*S*)-1-phenylethyl isothiocyanate, (3,5-trifluoromethyl)-phenylisothiocyanate, di(phenyl)methylene isothiocyanate, or benzyl isothiocyanate, to afford monoamino-thioureas **9–12** in good yields (70%–89%). Subsequently, compounds **9–12** reacted with *N*-*tert*-butoxycarbonyl-(*S*)-proline with ethyl chloroformate in anhydrous tetrahydrofuran (THF) at 0°C, to afford thiourea-*N*-Boc-prolinamides **13–16**, in moderate yields (68%–78%). Finally, the removal of the Boc group, with trifluoroacetic acid (TFA) in methylene chloride at room temperature, afforded the deprotection of compounds **13–16**. Thiourea-*L*-prolinamides **1–4** were isolated in good yields (75%–82%). The overall yields of these syntheses were in the range of 36%–57% (Scheme 1).

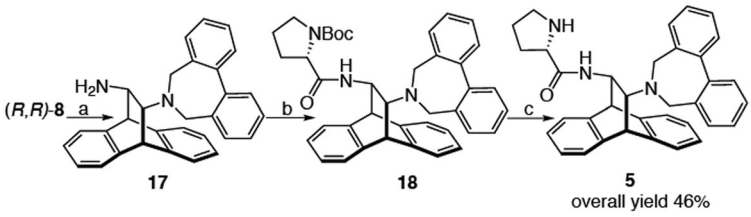
We also synthesized the tertiary amino-*L*-prolinamide **5** (Scheme 2).



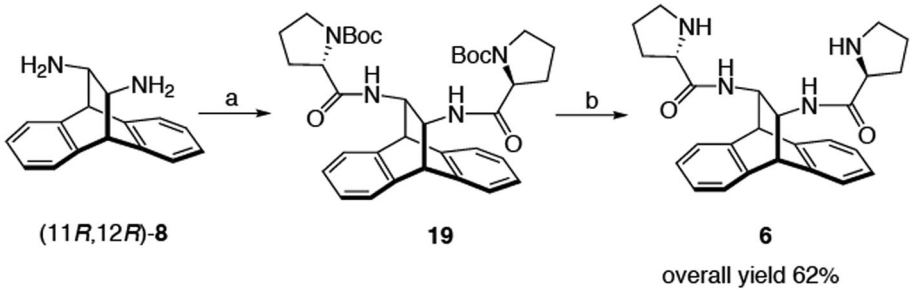
SCHEME 1 Synthesis of the thiourea-*L*-prolinamides **1–4**. Reagents and conditions: (A) isothiocyanate, CH_2Cl_2, 0°C; (B) *N-tert*-butoxycarbonyl-(*S*)-proline, triethylamine, THF, ethyl chloroformate, 0°C, 6 h; (C) TFA, CH_2Cl_2, room temperature, 24 h

The overall process began with the exhaustive amination of (11*R*,12*R*)-**8** with 2,2′-bis (bromomethyl) biphenyl, in the presence of potassium carbonate in acetonitrile under reflux for 2 h. This reaction led to the production of the tertiary amino-amine **17** (73% yield). Compound **17** was then made to react with *N-tert*-butoxycarbonyl-(*S*)-proline, with ethyl chloroformate in anhydrous THF at 0°C, affording the tertiary amino-*N*-Boc-prolinamide **18** (78% yield). Performing a deprotection reaction of compound **18**, with TFA at room temperature, afforded compound **5** (80% yield). The overall yield of organocatalyst **5** was 46%.

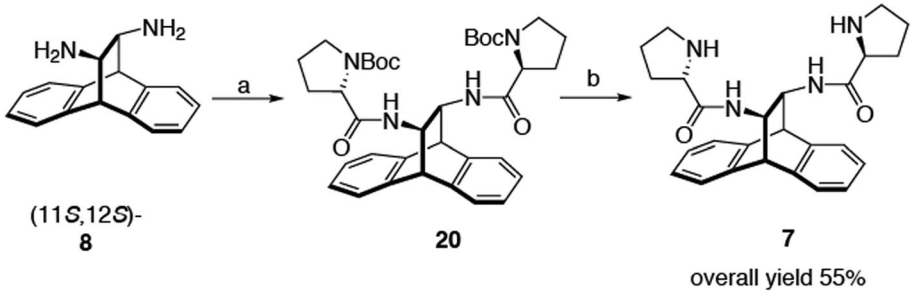
In order to understand the influence of a C_2 axis of symmetry on the stereoselectivity of the reaction, we prepared the bis-prolinamide **6** from the enantiopure diamine (11*R*,12*R*)-**8**. This synthesis was achieved in two steps. First, (11*R*,12*R*)-**8** was made to react with *N-tert*-butoxycarbonyl-(*S*)-proline to produce compound **19**. The *N*-Boc deprotection of compound **19** in the presence of TFA afforded **6**. The overall yield of organocatalyst **6** was 62% (Scheme 3).



SCHEME 2 Synthesis of the tertiary amino-*L*-prolinamide **5**. Reagents and conditions: (A) 2,2′-bis (bromomethyl)biphenyl, K_2CO_3, CH_3CN, reflux, 2 h; (B) *N-tert*-butoxycarbonyl-(*S*)-proline, triethylamine, THF, ethyl chloroformate, 0°C, 6 h; (C) TFA, CH_2Cl_2, room temperature, 24 h



SCHEME 3 Synthesis of bis-prolinamide **6**. Reagents and conditions: (A) *N-tert*-butoxycarbonyl-(*S*)-proline, triethylamine, THF, ethyl chloroformate, 0°C, 6 h; (B) TFA, CH_2Cl_2, room temperature, 24 h

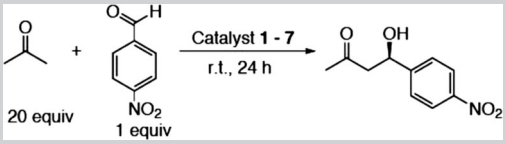


SCHEME 4 Synthesis of bis-prolinamide **7**. Reagents and conditions: (A) *N-tert*-butoxycarbonyl-(*S*)-proline, triethylamine, THF, ethyl chloroformate, 0°C, 6 h; (B) TFA, CH_2Cl_2, room temperature, 24 h

Finally, we prepare the bis-prolinamide **7**, using the enantiomeric diamine (11*S*,12*S*)-**8**, to evaluate the match or mismatch effect of the chiral centers of the two diamines. First, we prepared the *N*-Boc protected bis-prolinamide **20**. Then, the *N*-Boc deprotection of compound **20** in the presence of TFA afforded **7**. The overall yield of organocatalyst **7** was 55% (Scheme 4).

Once all homochiral *L*-prolinamides **1–7** were synthesized, we proceeded to evaluate their activity as organocatalysts in the asymmetric aldol reaction. Table 1

TABLE 1 Optimization of the asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde catalyzed by **1–7**



Entry	Catalyst, mol%	Additive, 10 mol%	Solvent, 0.3 ml	H_2O, equiv	Yield, %[a]	*ee*, %[b]
1	**1 (5)**	None	None	None	54	33 (*R*)
2	**2 (5)**	None	None	None	51	22 (*R*)
3	**3 (5)**	None	None	None	67	40 (*R*)
4	**4 (5)**	None	None	None	65	26 (*R*)
5	**5 (5)**	None	None	None	54	64 (*R*)
6	**6 (5)**	None	None	None	32	53 (*R*)
7	**1 (5)**	None	None	10	60	47 (*R*)
8	**2 (5)**	None	None	10	65	43 (*R*)
9	**3 (5)**	None	None	10	67	43 (*R*)
10	**4 (5)**	None	None	10	61	40 (*R*)
11	**5 (5)**	None	None	10	61	56 (*R*)
12	**6 (5)**	None	None	10	45	44 (*R*)
13	**1 (5)**	$ClCH_2COOH$	None	None	55	74 (*R*)
14	**2 (5)**	$ClCH_2COOH$	None	None	51	58 (*R*)
15	**3 (5)**	$ClCH_2COOH$	None	None	63	68 (*R*)
16	**4 (5)**	$ClCH_2COOH$	None	None	42	60 (*R*)
17	**5 (5)**	$ClCH_2COOH$	None	None	50	67 (*R*)
18	**6 (5)**	$ClCH_2COOH$	None	None	53	72 (*R*)
19	**1 (5)**	$ClCH_2COOH$	None	10	90	88 (*R*)
20	**2 (5)**	$ClCH_2COOH$	None	10	98	73 (*R*)
21	**3 (5)**	$ClCH_2COOH$	None	10	86	76 (*R*)
22	**4 (5)**	$ClCH_2COOH$	None	10	97	78 (*R*)
23	**5 (5)**	$ClCH_2COOH$	None	10	92	90 (*R*)
24	**6 (5)**	$ClCH_2COOH$	None	10	83	84 (*R*)
25	**7 (5)**	$ClCH_2COOH$	None	10	79	56 (*R*)
26	**1 (5)**	$ClCH_2COOH$	CH_2Cl_2	10	98	84 (*R*)
27	**1 (5)**	$ClCH_2COOH$	THF	10	98	76 (*R*)
28	**1 (5)**	$ClCH_2COOH$	CH_3CN	10	96	80 (*R*)
29	**1 (5)**	$ClCH_2COOH$	DMSO	10	92	43 (*R*)
30	**1 (5)**	$ClCH_2COOH$	MeOH	10	74	74 (*R*)
31	**6 (1)**	$ClCH_2COOH$	None	10	31	83 (*R*)
32	**6 (2)**	$ClCH_2COOH$	None	10	63	85 (*R*)
33	**6 (10)**	$ClCH_2COOH$	None	10	92	66 (*R*)

[a]Isolated yield after purification by silica gel column chromatography.

[b]The *ee* value was determined by HPLC using a Chiralcel AS-H column and hexane isopropanol as eluent.

shows the optimized results in the aldol reaction of acetone (20 equiv) and *p*-nitrobenzaldehyde (1 equiv) at room temperature during 24 h, using organocatalysts **1**–**7** in the presence or absence of water, chloroacetic acid, and/or solvent. We observed moderate yields (32%–67%) and enantioselectivities (22%–64%) under solvent free conditions and in absence of chloroacetic acid (Table 1, entries 1–6). Interestingly, addition of 10 equivalents of water to the reaction gave very similar yields (45%–67%), but enantioselectivities were slightly enhanced (40%–56%), compared to solvent free conditions (Table 1, entries 7–12).

We hypothesized that the addition of an organic acid might catalyze the enamine formation more effectively,[32–34] so we added chloroacetic acid (10 mol%) (Table 1, entries 13–18). We observed the best results when chloroacetic acid (10 mol%) and 10 equivalents of water are added (Table 1, entries 19–24), enhancing yields (83%–98%) and improving enantioselectivities (73%–90%). We use organocatalyst **7** affording the aldol product (*R*) but with lower enantiomeric excess (56%) compared to bis-prolinamide **6** (84%) (Table 1, entries 24 and 25). Then, we performed the reaction in the presence of organocatalyst **1** with 0.3 ml of some solvents (CH_2Cl_2, THF, CH_3CN, DMSO, MeOH) affording lower enantiomeric excess (43%–84%, Table 1, entries 26–30), compared to the *ee* with none solvent (88%, Table 1 entry 19). We also used organocatalyst **6** in the presence of water (10 equiv), chloroacetic acid (10 mol%), with catalysts loadings of 1, 2, 5, and 10 mol% (31%–92% yield, 66–85% *ee*, Table 1, entries 24, 31–33). We observed that 5 mol% of catalyst loading gave optimal results (see Table 1, entry 24).

Based on these results, we strongly suggest that water molecule may play an important role in the transition state (Figure 3). The addition of organic acid also enhances the yield and enantioselectivities of the aldol reaction. The addition of several solvents to the reaction does not improve the enantiomeric excess of the aldol reaction.

We hypothesized that introducing two prolinamide rings on the rigid anthracene framework may provide a bifunctional catalyst.[35,36] We assumed that one prolinamide is acting as a proton donor and the other is forming the enamine in the presence of acid as additive (Figure 4).[37–39] We also observed that bis-prolinamide **6**, is the match versus bis-prolinamide **7**, which is the mismatch catalyst.

Interestingly, the cyclohexanone compared to acetone gave better yields (57%–91%), enantioselectivities (78%–91%), and diastereoselectivities (77:23–93:7 *anti*/*syn*) with no additives (Table 2, entries 1–6). Adding both water and chloroacetic acid showed increased yields (86%–97%), enantioselectivities (90%–95%), and diastereoselectivities (85:15–93:7 *anti*/*syn*, Table 2, entries 19–24). Organocatalyst **7** give lower yield, enantioselectivity and diastereoselectivity than **6** (Table 2, entry 25). Finally, we also performed the reaction with organocatayst **6** in the presence of 0.3 ml of toluene, but neither yield nor enantioselectivity or diastereoselectivity were improved (Table 2, entry 26).

Based on these results, we decided to examine the scope of the asymmetric aldol reaction of cyclohexanone. Several substituted aromatic aldehydes (1 equiv) reacted with cyclohexanone (20 equiv) in the optimized conditions, in the presence of organocatalysts **1**, **5**, and **6** (Table 3). Best results were obtained with aldehydes comprising electron-withdrawing groups, such as the trifluoromethyl, cyano, fluoro, chloro, bromo, and 4-pyridinylcarboxy groups. The asymmetric aldol reaction afforded moderate-to-high yields (58%–98%), good-to-high *anti*/*syn* diastereoselectivities (73: 27 to 93: 7), and good-to-high enantioselectivities (77%–94%) (Table 3). Finally, we do the reaction using benzaldehyde with organocatalyst **6** (Table 3, entry 25) observing lower yield, enantio-, and diastereoselectivity compared to other aromatic aldehydes with electron withdrawing groups.

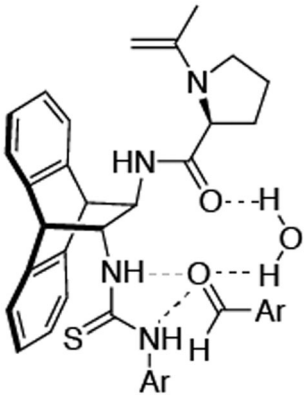


FIGURE 3 Plausible transition state involving water

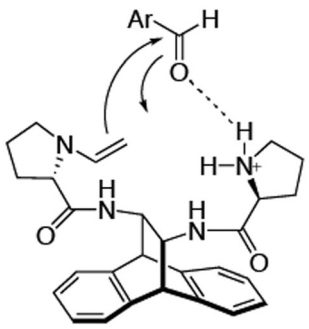
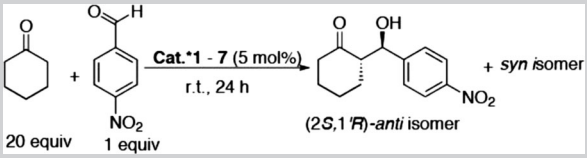


FIGURE 4 Plausible transition state involving acid additive

TABLE 2 Optimization of the asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde catalyzed by **1–7**



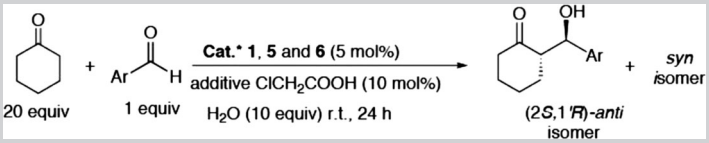
Entry	Catalysts	Additive, 10 mol%	Solvent, 0.3 ml	H_2O, equiv	Yield, %[a]	*anti/syn*[b]	*ee*, %[c]
1	**1**	None	None	None	89	84:16	89 (*R*)
2	**2**	None	None	None	87	78:22	87 (*R*)
3	**3**	None	None	None	86	79:21	86 (*R*)
4	**4**	None	None	None	91	82:18	91 (*R*)
5	**5**	None	None	None	80	77:23	78 (*R*)
6	**6**	None	None	None	57	93:7	87 (*R*)
7	**1**	None	None	10	63	90:10	94 (*R*)
8	**2**	None	None	10	71	67:33	93 (*R*)
9	**3**	None	None	10	73	88:12	89 (*R*)
10	**4**	None	None	10	70	92:8	93 (*R*)
11	**5**	None	None	10	67	92:8	89 (*R*)
12	**6**	None	None	10	56	91:9	96 (*R*)
13	**1**	$ClCH_2COOH$	None	None	65	88:12	86 (*R*)
14	**2**	$ClCH_2COOH$	None	None	52	82:18	83 (*R*)
15	**3**	$ClCH_2COOH$	None	None	58	87:13	91 (*R*)
16	**4**	$ClCH_2COOH$	None	None	67	85:15	74 (*R*)
17	**5**	$ClCH_2COOH$	None	None	72	83:17	85 (*R*)
18	**6**	$ClCH_2COOH$	None	None	80	90:10	89 (*R*)
19	**1**	$ClCH_2COOH$	None	10	90	88:12	95 (*R*)
20	**2**	$ClCH_2COOH$	None	10	98	88:12	92 (*R*)
21	**3**	$ClCH_2COOH$	None	10	94	85:15	93 (*R*)
22	**4**	$ClCH_2COOH$	None	10	86	87:13	94 (*R*)
23	**5**	$ClCH_2COOH$	None	10	98	90:10	90 (*R*)
24	**6**	$ClCH_2COOH$	None	10	97	93:7	93 (*R*)
25	**7**	$ClCH_2COOH$	None	10	90	88:12	92 (*R*)
26	**6**	$ClCH_2COOH$	Toluene	10	64	94:6	89 (*R*)

[a]Isolated yield after purification by silica gel column chromatography.
[b]The diastereomeric ratio was determined by ^{1}H NMR spectroscopy and refers to the *anti*/*syn* ratio.
[c]The *ee* value was determined by HPLC using a Chiralcel AD-H column and hexane isopropanol as an eluent.

We also decided to examine the scope of the asymmetric aldol reaction using other carbocyclic and heterocyclic ketones (20 equiv) and *p*-nitrobenzaldehyde (1 equiv) in the presence of organocatalyst **6** (see Table 4, entries 1–4). We observed the corresponding *anti*-aldol products in moderate-to-good yields (63%–91%), enantioselectivities (68%–87%), and diastereoselectivities (*anti*:*syn* = 65:35–97:3). To assign the stereochemical outcomes, we compared the products with those reported in the literature.[28]

We calculated the transition state (TS) structure for the reaction of *p*-nitrobenzaldehyde and acetone catalyzed by **6**. All calculations were performed using the Gaussian09 program package,[40] and the relevant chemical structures were visualize using the Chemcraft 1.6 program.[41] We employed the density functional theory at the B3LYP/6–31 + G(d,p) level with the CPCM (conductor-like polarizable continuum model) to describe the solvent effect; importantly, water was considered as the solvent. The energies of structure corresponding to energy

TABLE 3 Performance of organocatalysts **1**, **5**, and **6** in the asymmetric aldol reaction of cyclohexanone and different aromatic aldehydes



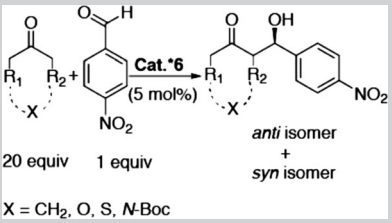
Entry	Aldehyde	Catalyst	Yield, %[a]	*anti/syn*[b]	*ee*%[c]
1	3-Nitrobenzaldehyde	**1**	76	92:8	81 (*R*)
2		**5**	96	58:42	82 (*R*)
3		**6**	74	96:4	91 (*R*)
4	2-Nitrobenzaldehyde	**1**	87	86:14	90 (*R*)
5		**5**	58	85:15	77 (*R*)
6		**6**	97	94:6	90 (*R*)
7	4-Trifluoromethylbenzaldehyde	**1**	97	97:3	94 (*R*)
8		**5**	97	86:14	90 (*R*)
9		**6**	98	95:5	93 (*R*)
10	4-Cyanobenzaldehyde	**1**	95	86:14	93 (*R*)
11		**5**	85	96:4	84 (*R*)
12		**6**	90	90:10	94 (*R*)
13	4-Fluorobenzaldehyde	**1**	95	80:20	93 (*R*)
14		**5**	80	77:23	81 (*R*)
15		**6**	98	94:6	92 (*R*)
16	4-Chlorobenzaldehyde	**1**	76	77:23	94 (*R*)
17		**5**	68	83:17	85 (*R*)
18		**6**	75	93:7	93 (*R*)
19	4-Bromobenzaldehyde	**1**	58	92:8	91 (*R*)
20		**5**	90	88:12	86 (*R*)
21		**6**	75	95:5	92 (*R*)
22	4-(4-Pyridyl)benzaldehyde	**1**	95	73:27	93(*R*)
23		**5**	90	83:17	87 (*R*)
24		**6**	94	84:16	94 (*R*)
25	Benzaldehyde	**6**	80	80:20	88 (*R*)

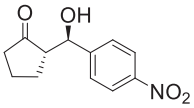
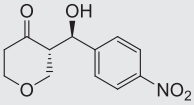
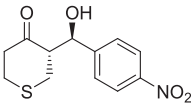
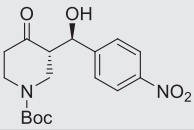
[a]Isolated yield after purification by silica gel column chromatography.
[b]The diastereomeric ratio was determined by ^{1}H NMR spectroscopy and refers to the *anti*/*syn* ratio.
[c]The *ee* value was determined by HPLC using a Chiralcel AD-H column and hexane isopropanol as an eluent.

minima and transition state structure were validated by subsequent frequency calculations carried out at the same level of theory. All minima corresponded to real frequencies, whereas transition states rendered one imaginary frequency each. The transition state structure was identified through the intrinsic reaction coordinate method. The Gibbs energy of the transition state was calculated within the standard harmonic-oscillator, rigid-rotor model.

The energy of the transition state of the reaction catalyzed by compound **6** corresponded to the formation of the *R* aldol (Figure 5). The carbonyl group of benzaldehyde is hydrogen bonded to the prolinamide moiety ($O_1\cdots H_1$ distance typical of weak hydrogen bonding interactions 1.780 Å), whereas the new carbon-carbon bond begins to be formed ($C_1\cdots C_2$ distance of 1.952 Å). The attack of the enamine occurs on the *Re* face of the carbonyl group of *p*-nitrobenzaldehyde. It is activated by the NH of the prolinamide moiety, which involves the diamine (11*R*,12*R*)-**8**-derived compound **6**. The results of these calculations are in agreement with the observed product stereoselectivities, which confirms that the reaction outcome depends only on the proline itself.

TABLE 4 Scope of the asymmetric aldol reaction between 4-nitrobenzadehyde and different ketones in the presence of organocatalyst **6**



Entry	Product	Yield, %[a]	*anti/syn*[b]	*ee*, %[c]
1		76	65:35	77 (*R*)
2		73	94:6	83 (*R*)
3		63	97:3	87 (*R*)
4		91	96:4	68 (*R*)

[a]Isolated yield after purification by silica gel column chromatography.
[b]The diastereomeric ratio was determined by ^{1}H NMR spectroscopy.
and refers to the *anti*/*syn* ratio.
[c]The *ee* value was determined by HPLC using a Chiralcel AD-H column and hexane isopropanol as an eluent.

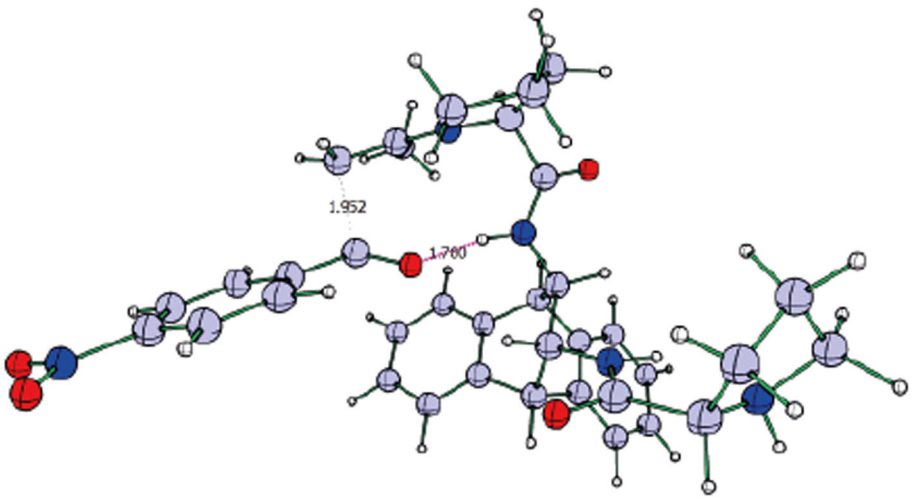


FIGURE 5 Computed structure of the proposed transition state TS1 of the asymmetric aldol reaction involving 4-nitrobenzaldehyde as a reagent and compound **6** as catalyst

4 | CONCLUSION

In this study, the syntheses of novel homochiral bifunctional *L*-prolinamides **1–5** and *L*-bis-prolinamides **6** and **7** were reported. Compounds **1–6** were prepared from the enantiomerically pure diamine (11*R*,12*R*)-**8**. *L*-bis-prolinamide **7** was obtained with the enantiomeric diamine (11*S*,12*S*)-**8**. Organocatalyst **6** was obtained in only two steps and in good overall yield. The catalytic activities of these compounds were evaluated in asymmetric aldol reactions performed in water (10 equiv) at room temperature, with catalyst loading of 5 mol%, in the presence of monochloroacetic acid (10 mol%) over 24 h, and under wet solvent-free conditions. Notably, all organocatalysts are stable and can be stored for several months at room temperature without any significant

observable decomposition. In particular, very good results were obtained with the optimized reaction conditions in the presence of organocatalyst **6**, that is, in the reaction of cyclohexanone with 4-nitrobenzaldehyde yield of 97%, diastereoselectivity of *anti*/*syn* = 93: 7, and an *ee* value of 95%.

This result led us to the conclusion that the rigid backbone of compound (11*R*,12*R*)-**8**, which contains the *trans*-1,2-diamino-cyclohexane moiety, and the stereocenter of *L*-proline determined the stereochemistry of the reaction product. The occurrence of hydrogen bonding interactions due to the addition of 10 equivalents of water between the aldehyde and *L*-proline moiety are observed. Besides, the addition of monochloracetic acid facilitates the enamine formation. The attack of the enamine occurs on the *Re* face of the aldehyde the carbonyl group as shown in the theoretical calculation of the transition state. Studies focusing on the use of organocatalysts **1–7** in other asymmetric reactions whereby carbon-carbon bonds are formed are currently underway.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available in the supporting information of this article or are available from the corresponding author upon reasonable request.

ORCID

Ratnasamy Somanathan https://orcid.org/0000-0003-1220-082X
Cecilia Anaya de Parrodi https://orcid.org/0000-0001-5619-2513

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efficient large-scale asymmetric direct aldol reactions. *Tetrahedron: Asymmetry*. 2011;22:840-850.
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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