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Highly asymmetric aldol reaction of cyclohexanone and aromatic aldehydes catalyzed by bifunctional cyclohexane derived thiourea organocatalyst

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ARTICLE INFORMATION

ABSTRACT

Novel two *L*-proline analogues as thiourea organocatalysts were synthesised. The first step comprised of the assembly of a structurally well-defined cyclohexane scaffold with a thiourea moieties and amine functionalities which could constitute a new class of organocatalysts. The second one was the triazole-3-thione analogue. The first one was found to be an efficient catalyst for the direct asymmetric aldol reaction between ketone and aromatic aldehydes. The catalysts exhibited high catalytic activity, diastereoselectivity and excellent enantioselectivity at room temperature with a low loading.

Graphical Abstract

Catalyst 1   Catalyst 2

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Introduction

The most attractive method to produce chiral compounds is a catalytic enantioselective process [1] that provides the compounds with high selectivity and efficiency [2]. In this field, at the end of the last century, the use of transition metal catalysts was the preferred option. Nowadays, organocatalysis is used as the metal free processes [3] and is regarded as an environmentally benign strategy, due to the advantages related to handling, cost, and safety issues.

The growth of metal free small organic molecules, which are useful to catalyze enantioselective reactions, has received much attention in recent years [4]. The intermolecular aldol reaction has been carried out with a successful demonstration of *L*-proline in 2000; spectacular advances have been made using this remarkablly efficient, operationally simple and environmentally benign methodology [5]. Proline and its analogues containing secondary amides [6], thioamides [7], sulfonamides [8], dipeptides [9] and tetrazole [10] have been successfully used for asymmetric synthesis. They have shown powerful utilities in conjugate reaction [11] such as aldol reaction [12], Mannich reaction [13], aza-Diels-Alder reaction [14], Friedel-Crafts reaction [15], Strecker reaction [16], aza-Morita-Baylis-Hillman reaction [17], carbon-heteroatom bond formation [18] etc. [19].

Organocatalytic asymmetric aldol reactions are useful C−C bond-forming reactions with the formation of enamine intermediates and yields aldol products with excellent enantioselectivities [20]. The organic solvents, such as DMSO, DMF, or chloroform are generally used to perform these reactions, under mild conditions. Addition of a small amount of water often accelerates reactions and improves enantioselectivities [21], but it has been shown that the excess of water or aqueous buffer as reaction solvents, has typically resulted with low yield and enantioselectivity [22]. In contrast, aldol reactions which involves an enamine mechanism, in natural Class I aldolase enzymes [23] and aldolase catalytic antibodies [24], that uses an enamine mechanism. In the aldolase antibodies [25], the diminishing contacts between bulk water and the reaction transition states may be critical for high enantioselectivities because the reactions occur in a hydrophobic active site. Nowadays, bifunctional activations have been regarded as an important strategy in asymmetric small molecular catalysis, which simultaneously activates both acceptors and donors, through hydrogen bonding and enamine formation, respectively [26].

Herein, we describe the preliminary results of the aldol reaction, utilizing thiourea organocatalyst bearing a cyclohexane scaffold for catalyzing cyclohexanone (2 equiv) and various aryl aldehydes in DMSO, water solvent.

Experimental

Materials and methods

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20×20 cm, Silica gel 60 F$_{254}$, Merck grade was used for thin layer chromatography to determine the progress of the reaction. The column chromatography was carried out over silica gel (80–120 mesh). Optical rotations were measured on a Polax-2L digital polarimeter. Melting points were determined in open capillary tube and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer in CDCl$_3$ solvent. Mass spectra were taken on Polaris-Q Thermo scintific GC-MS. Enantiomeric purity is determined on PerkinElmer Series 200 HPLC Systems with chiral HPLC and Chiralpak AD-H.
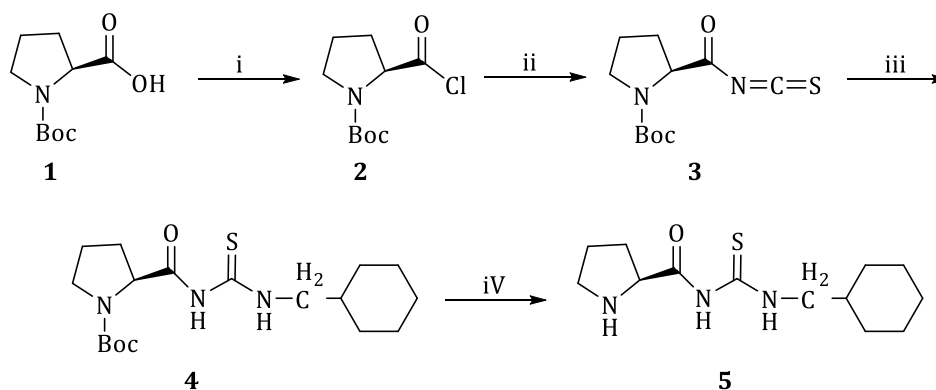
General synthesis procedure for compound (2–5)

A solution of Boc-*L*-proline (0.1 mol) in anhydrous 1,2-dichloroethane is refluxed for 3 hr with thionyl chloride (0.2 mol). The solvent and the excess thionyl chloride are removed by a reduced pressure distillation. The raw obtained (S)-tert-butyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate (10 mmol) is dissolved in anhydrous acetone (30 mL), is added to a solution of ammonium thiocyanate (10 mmol) in dry acetone and refluxed for 1 hr. The obtained ammonium chloride was removed by filtration and, then, cyclohexylmethyl amine (10 mmol) which has been dissolved in anhydrous acetone is added while stirring. The mixture is heated under reflux for 1 hr. The mixture was extracted with CH$_2$Cl$_2$ (2×20 mL) and, then, the combined organic layer was washed with brine (20 mL) dried over MgSO$_4$, and filtered. The solvent was removed under vacuo. The resulting crude product, i.e. (S)-tert-butyl 2-(amino*N*-(cyclohexylmethyl) methanethio carbamoyl) pyrrolidine-1-carboxylate was dissolved in CH$_2$Cl$_2$ (10 mL) and then, added TFA (2 mL) was added dropwise with stirring for 1 hr at 0 °C. After the consumption of the starting material as indicated by TLC analysis, the reaction mixture was diluted with H$_2$O (10 mL) and the resulting solution was adjusted to pH=~7 with aqueous NaHCO$_3$. The reaction mixture was extracted with CH$_2$Cl$_2$ (2×20 mL), the combined organic layer was washed with brine, dried over MgSO$_4$, filtered, and the solvent was removed in vacuo. The purification of residue by column chromatography (EtOAc/hexane, 1:4) afforded 70–75% of **5** as a yellow solid. Yellowish Solid, mp 132 °C. Optical rotation [α]$^{25}_D$: -60.5° (c 0.4, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.30 (s, 1H, NH), 3.80 (t, 1H), 3.45 (t, 2H), 2.5 (s, 2H), 1.2-1.9 (m, 17H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 184.4, 174.2, 77.25, 77.0, 76.3, 62.0, 49.2, 44.9, 40.0, 37.0, 32.0, 26.8, 22.0. GC-MS: *m/z* 269 (M$^+$). HPLC: 99.00% *ee*. [Enantiomeric purity is determined by chiral HPLC systems using chiral column Whelk-O1 (25 cm×4.6 mm), EtOAc/hexane (80/20), Flow rate 1 mL/min, λ = 254; t$_R$ (minor)=14.2 min, t$_R$ (major)=20 min].
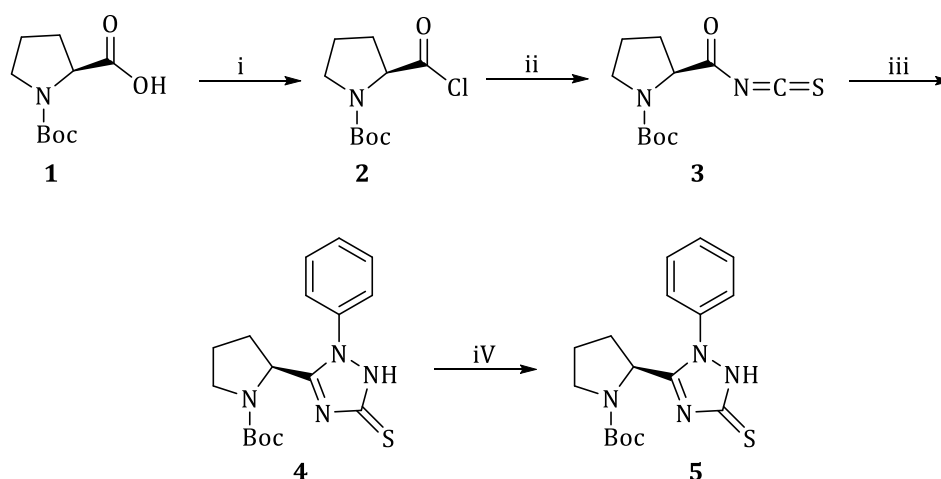
Preparation of 1, 2-dihydro-1-phenyl-5-((S)-pyrrolidin-2-yl)-1, 2, 4-triazole-3-thione (DPPTT) (7)

(S)-tert-butyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate (10 mmol) is dissolved in anhydrous acetonitrile (30 mL), added to a solution of ammonium thiocyanate (10 mmol) and refluxed for 1 hr. The ammonium chloride is removed by filtration and, then, added the solution of phenylhydrazine (10 mmol) is added in acetonitrile. The mixture is heated under reflux for 1 hr. The mixture was extracted with CH_2Cl_2 (2×20 mL) and then, the combined organic layer was washed with brine (20 mL) dried over $MgSO_4$, and filtered. The solvent was removed under vacuo. The resulting crude product, i.e (S)-tert-butyl 2-(2, 5-dihydro-2-phenyl-5-thioxo-1H-1, 2, 4-triazol-3-yl) pyrrolidine-1-carboxylate was dissolved in CH_2Cl_2 (10 mL) and then, TFA (2 mL) was added dropwise with stirring for 1 hr at 0 °C. After the consumption of the starting material, as indicated by TLC analysis, the reaction mixture was diluted with H_2O (10 mL) and the resulting solution was adjusted to pH=~7 with aqueous $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (2×20 mL), the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The purification of residue by column chromatography (EtOAc/hexane, 1:1) afforded 80–85% of **7** as a yellow solid.

Enantiomeric purity is determined on PerkinElmer Series 200 HPLC systems with chiral HPLC [Whelk-O1 (25 cm×4.6 mm), EtOAC/hexane (20/80), Flow rate 1.0 mL/min, λ = 254 nm]. Yellowish Solid. mp 160–162 °C. Optical rotation $[\alpha]^{20}_D$: -80.7 (c 0.42, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.70 (s, 1H, NH), 7.20-7.61 (m, 5H), 3.12 (s, 1H), 2.5 (s, 1H), 1.5-1.9 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.5, 165.7, 140, 130, 120, 114.1, 58, 47, 28.4, 23. GC-MS: *m/z* 246 (M+). HPLC: 99.80% *ee*. Enantiomeric purity is determined by chiral HPLC systems using chiral column Whelk-O1 (25 cm×4.6 mm), EtOAc/hexane (80/20), Flow rate 1.0 mL/min, λ = 254; t_R (minor)=10.5 min, t_R (major)=17.8 min].

Scheme 1. Reaction conditions*:* i) $SOCl_2$, 1,2-dichloroethane $C_2H_4Cl_2$, reflux, 3 hr; ii) NH_4SCN, acetone, reflux, 1 hr; iii) Cyclohexylmethanamine, acetone, reflux, 1 hr; iv) Methylene dichloride (MDC), Trifluoroacetic acid (TFA), Stir, 1 hr, 70–75%

Scheme 2. Reaction conditions: i) SOCl$_2$, C$_2$H$_4$Cl$_2$, reflux, 3 hr; ii) NH$_4$SCN, acetonitrile, reflux, 1 hr; iii) C$_6$H$_5$NHNH$_2$, CH$_3$CN, reflux, 1 hr; iv) Methylene dichloride (MDC), Trifluoroacetic acid (TFA), Stir, 1 hr, 80–85%

General procedure for aldol reaction

To a mixture of the solvent containing *N,N*-dimethylformamide (8 mL) and water (2 mL), cyclohexanone (1 mmol) and aromatic aldehyde (0.5 mmol) were added and stirred for few min. Organocatalyst NCCPC **5** (0.10 mmol) was added to the reaction mixture and stirred at room temperature for 10–12 hr. Completion of reaction was indicated by TLC, solvent was removed under vacuum to obtain crude product. This crude product was partitioned between ethyl acetate and water. Organic layer was collected and washed with water and brine solution. The combined organic layer was dried over MgSO$_4$, filtered, and the solvent was removed in vacuo. The obtained product was purified by column chromatography using silica gel mesh 80–120.

*(S)-2-((R)-hydroxy (4-nitrophenyl) methyl) cyclohexanone (**10a**)*

Mp 129-130 °C, Optical rotation [α]$_D$: -49.8 (c 0.45, ethyl acetate). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.15–1.40 (m, 1H), 1.55–1.70 (m, 4H), 1.90–2.1 (m, 1H), 2.15–2.25 (m, 1H), 2.30–2.6 (m, 1H), 2.7–3.00 (m, 1H), 3.7-3.9 (br s, 1H, syn), 4.5-4.7 (br s, 1H anti), 4.8 (d, 1H anti), 5.4 (s, 1H syn), 7.6 (d, 2H), 8.20 (d, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 24.6, 27.5, 30.6, 42.6, 57.1, 73.9, 123.5, 127.8, 147.4, 148.3, 214.6. GC-MS: *m/z* 294 (M$^+$). HPLC: 96% *ee*. [Determined by HPLC (Chiralcel AD, hexane/i-PrOH: 90/10, 0.7 mL min^{-1}), anti: Rt 66.69 (minor), Rt 69.77 (major), syn: Rt 38.71 (minor), Rt 52.62 (major)].

*(S)-2-[(R)-hydroxy (3-nitrophenyl) methyl] cyclohexanone (**10b**)*

White powder**,** Mp: 69-71 °C; Optical rotation $[\alpha]_D$: -72.4 (c 1.35, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.10-8.18 (m, 2H), 7.65 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 4.86 (d, J = 8.4 Hz, 1H), 4.12 (d, J = 2.4 Hz, 1H), 2.53-2.57 (m, 1H), 2.30-2.51 (m, 2H), 2.03-2.12 (m, 1H), 1.80-1.84 (m, 1H), 1.32-1.68 (m, 4H), HPLC: 94% *ee*. [Determined by HPLC (Chiralcel AD-H, hexane/i-PrOH: 92/08, 1.0 mL min^{-1}), anti: Rt 33.94 (minor), Rt 26.05 (major), syn: Rt 23.10 (major), Rt 22.06 (minor)].

*(S)-2-[(R)-hydroxy (2-nitrophenyl) methyl] cyclohexanone (**10c**)*

Mp 116–118 °C. Optical rotation $[\alpha]_D$: -67.5, ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.80 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.20–7.26 (m, 1H), 5.34 (d, J = 7.2 Hz, 1H), 4.07 (br, 1H), 2.71–2.78 (m, 1H), 2.20–2.45 (m, 2H), 2.02–2.12 (m, 1H), 1.52–1.83 (m, 5H). HPLC: 98% *ee*. [Determined by HPLC (Chiralcel AD-H, hexane/i-PrOH: 92/08, 1.0 mL min^{-1}), anti: Rt 66.23 (minor), Rt 71.72 (major), syn: Rt 30.61 (major), Rt 57.35 (minor)].

*(S)-2-[(R) -hydroxy (4-cyanophenyl) methyl] cyclohexanone (**10d**)*

Mp 82-83 °C, Optical rotation $[\alpha]_D$: -83.6 (c 0.5, ethyl acetate). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.2–1.4 (m, 1H), 1.6–1.8 (m, 4H), 1.85–2.10 (m, 1H), 2.25–2.30 (m, 1H), 2.5–2.7 (m, 2H), 2.9-3.1 (m, 1H), 3.7 (br s, 1H, syn), 4.50 (br s, 1H, anti), 5.2 (d, 1H, anti), 5.7 (s, 1H, syn), 7.9 (d, 2H), 8.15 (d, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 223.4, 145.3, 134.2, 132.9, 118.5, 113.2, 80.8, 62.9, 43, 30.8, 26.6. GC-MS: *m/z* 229 (M$^+$). HPLC: 90% *ee*. [Determined by HPLC (Chiralcel AD-H, hexane/i-PrOH: 95/05, 1.0 mL min^{-1}), anti: Rt 66.67 (minor), Rt 70.73 (major), syn: Rt 32.62 (major), Rt 58.39 (minor)].

*(S)-2-[(R)-hydroxy (4-fluorophenyl) methyl] cyclohexanone (**10e**)*

Optical rotation $[\alpha]_D$: -62.4 (c 0.35, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.39-1.85 (m, 5H), 1.89-2.19 (m, 1H), 2.24-2.447 (m, 3H), 3.00-3.18 (br s, 1H), 3.84-3.90 (br s, 1H), 4.69-4.71 (d, J = 9 Hz, 1H), 5.24 (s, 1H), 6.92-7.00 (m, 2H), 7.21-7.25 (br s, 2H). HPLC: 92% *ee*. [Determined by HPLC (Chiralcel AD-H, hexane/i-PrOH: 90/10, 0.3 mL min^{-1}), anti: Rt 49.15 (minor), Rt 44.19 (major), syn: Rt 29.28 (major), Rt 33.28 (minor)].

*(S)-2-[(R)-hydroxy (4-chlorophenyl) methyl] cyclohexanone (**10f**)*

Optical rotation $[\alpha]_D$: -58.9 (c 1.00, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.53-1.86 (m, 5H), 1.96-2.07 (m, 1H), 2.33-2.55 (m, 3H), 3.00 (br s, 1H), 3.91 (br s, 1H), 4.71-4.74 (d, J = 9 Hz, 1H), 5.33 (s, 1H), 7.20-7.30 (m, 4H). HPLC: 85% *ee*. [Determined by HPLC (Chiralcel AD-H, hexane/i-PrOH: 90/10, 0.3 mL min^{-1}), anti: Rt 52.77 (minor), Rt 45.71 (major), syn: Rt 29.96 (major), Rt 34.61 (minor)].

*(S)-2-[(R)-hydroxy (4-bromophenyl) methyl] cyclohexanone (**10h**)*

Optical rotation $[\alpha]_D$: -40.3 (c 0.70, CHCl3). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.50-1.87 (m, 5H), 2.05-2.11 (m, 1H), 2.33-2.57 (m, 3H), 3.05 (br s, 1H), 3.93 (br s, 1H), 4.70-4.73 (d, *J* = 9 Hz, 1H), 5.30 (br s, 1H), 7.14-7.18 (m, 2H), 7.42-7.46 (m, 2H). HPLC: 75% *ee*. [Determined by HPLC (Chiralcel AD-H, n-hexane/i-PrOH: 90/10, 0.3 mL min^{-1}), anti: Rt 54.91 (minor), Rt 47.54 (major), syn: Rt 30.13 (major), Rt 35.31 (minor)].

*2-(hydroxy (2-chlorophenyl) methyl) cyclopentanone (**10i**)*

Optical rotation $[\alpha]_D$: -88.2 (c 1.50, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 300 MHz): δ d: 7.65-7.58 (m, 1H), 7.31-7.27 (m, 2H), 7.26-7.119 (m, 1H), 5.32 (d, *J* = 9.0 Hz, 1H), 4.56 (br s, 1H), 2.70-2.35 (m, 3H), 2.07-1.98 (m, 2H), 1.73–1.64 (m, 2H). HPLC: 78% *ee*. [Determined by HPLC (Chiralcel AD-H, hexane/i-PrOH: 95/05, 1.0 mL min^{-1}), anti: Rt 16.73 (minor), Rt 14.8 (major), syn: Rt 10.24 (major), Rt 14.24 (minor)].

*(S)-2-((R)-hydroxy (phenyl) methyl) cyclohexanone (**10j**)*

Optical rotation $[\alpha]_D$: -18.8 (c 0.5, ethyl acetate). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.1-1.5 (m, 1H), 1.8-2.0 (m, 4H), 2.1–2.3 (m, 1H), 2.4–2.6 (m, 2H), 2.7–2.9 (m, 1H), 3.5 (br s, 1H, syn), 4.50 (s, 1H, anti), 5.1 (d, 1H, anti), 5.9 (s, 1H, syn), 7.4-7.6(m, 5H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 24.7, 27.8, 30.8, 42.6, 57.4, 74.7, 127.0, 127.9, 128.3, 140.8, 215.5. GC-MS: *m/z* 204 (M$^+$). HPLC: 65% *ee*. [Determined by HPLC (Chiralcel AD-H, hexane/i-PrOH: 95/5, 0.50 mL min^{-1}), anti: Rt 26.64 (minor), Rt 29.74 (major), syn: Rt 16.90 (major), Rt 19.42 (minor)].

*S)-2-[(R)-hydroxy (4-hydroxyphenyl) methyl] cyclohexanone (**10k**)*

White powder, Optical rotation $[\alpha]_D$: -23.5 (c 1.55, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 10.12 (s, 1H) , 7.65 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 4.84 (d, *J* = 8.4 Hz, 1H), 4.07 (s, 1H), 2.47–2.62 (m, 2H), 2.31–2.41 (m, 1H), 2.08–2.15 (m, 1H), 1.81–1.83 (m, 1H), 1.49–1.73 (m, 3H), 1.32–1.41 (m, 1H). HPLC: 72% *ee*. [Determined by HPLC (Chiralcel AD-H, hexane/i-PrOH: 90/10, 0.3 mL min^{-1}), anti: Rt 31.98 (minor), Rt 40.88 (major), syn: Rt 27.33 (major), Rt 23.20 (minor)].

Results and discussion

Here, we describe the synthesis of the new bifunctional thiourea derivatives **5** and **7** and their successful application to the aldol reaction of cyclohexanone and the substituted aromatic aldehydes. The synthesis of organocatalysts **5** and **7** began with (S)-tert-butyl 2-

carbonylpyrrolidine-1-carboxylate **3**, which was readily prepared from the boc-protected *L*-proline **1**. The precursor boc-protected *L*-proline **1** was converted to the (S)-tert-butyl 2-(chlorocarbonyl)-pyrrolidine-1-carboxylate **2** using thionyl chloride as chlorinating reagent and was treated with ammonium thiocyanate in order to afford (S)-tert-butyl 2-carbonylpyrrolidine-1-carboxylate **3**. This was converted to the corresponding (S)-tert-butyl 2-(aminoN-(cyclohexylmethyl) methanethiocarbamoyl) pyrrolidine-1-carboxylate **4** by the addition of cyclohexyl methylamine and refluxing in dry acetone. (S)-tert-butyl2-(2,5-dihydro-2-phenyl-5-thioxo-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate **6** were obtained in one step reaction from (S)-tert-butyl 2-carbonylpyrrolidine-1-carboxylate **3** and phenyl hydrazine. Both boc-protected compounds **4** and **6** was deprotected in methylene dichloride (CH_2Cl_2) using trifluoro aceticacid (TFA) to obtained (S)-*N*-((cyclohexylmethyl)carbamothioyl) pyrrolidine-2-carboxamide (NCCPC) **5** and 1, 2-dihydro-1-phenyl-5-((S)-pyrrolidin-2-yl)-1, 2, 4-triazole-3-thione (DPPTT) **7** with overall 70-85% yield (Scheme 1 and 2).

The structures of the synthesized organocatalysts were confirmed by spectral data. For the organocatalyst **5** ^{1}H NMR spectra showed a singlet at 8.3 ppm indicating the presence of amide proton and confirming the formation of amide group in the catalysts. The signal for proton on nitrogen from proline ring and NH−C=S is observed between 2.5–2.7 ppm in proton NMR. Signal at 3.45 ppm was obtained due to protons of methylene moiety attachéd to cyclohexane ring. The signal for hydrogen attached to chiral carbon was obtained at 3.8 ppm. Similarly, for organocatalyst **7,** ^{1}H NMR spectra showed a singlet at 8.7 ppm which indicates the formation of triazole-thione ring. The signal for proton on nitrogen from proline ring and on chiral carbon was shown at 2.5 and 3.1 ppm, respectively. Further verification of both the organocatalysts was provided by ^{13}C NMR and GC-MS. Enantiomeric purity is determined on PerkinElmer series 200 HPLC systems with chiral HPLC, EtOAc/hexane (80/20), Flow rate 1.0 mL/min, λ = 254 nm which shows enantiomeric purity 99.00% for catalyst NCCPC and 99.80% for DPPTT.

We used both **5** and 7 catalysts for the asymmetric aldol reaction. The bifunctional activations of **5**, which simultaneously activate both acceptors and donors, have recently emerged as an important strategy in asymmetric small molecular catalysis. Generally, thiourea-based catalysts have been widely used due to their strong activation of carbonyl and nitro groups through efficient double hydrogen-bonding interactions. Secondary amine, typically represented by *L*-proline and its structural analogues, is a powerful tool to activate aldehydes and ketones *via* enamine or imine transition state. The secondary amine–thiourea catalysts **5**, synergistically combining thiourea and chiral pyrrolidine with two catalytic sites, have drawn enough attentions to catalyze the aldol reaction of cyclohexanone and the substituted aromatic aldehydes with very high

enantioselectivity. We expected that this bifunctional catalyst could be used to catalyze the asymmetric aldol reaction and reactivity. Enantioselectivity may be enhanced by double activation, mutual stereo-compatibility, and chiral recognition.

Table 1. Diastereo and enantioselective aldol reaction of cyclohexanone and 4-nitrobenzaldehyde catalyzed by organocatalysts NCCPC **5** and DPPTT **7** in various solvents (10 mL) at ambient temperature[a]

Entry	Catalyst	Solvent	Time (hr)	Yield[b] (%)	*anti/syn* ratio[c]	*anti ee[d]*
1	NCCPC	Water	20	45	82/18	55
2	DPPTT	Water	25	36	80/20	50
3	NCCPC	Chloroform	22	20	84/16	35
4	DPPTT	Chloroform	28	-	77/23	22
5	NCCPC	Dimethyl sulfoxide	18	60	88/12	70
6	DPPTT	Dimethyl sulfoxide	20	43	85/15	68
7	NCCPC	N,N-Dimethylformamide	15	70	90/10	74
8	DPPTT	N,N-Dimethylformamide	18	55	89/11	72
9	NCCPC	DMF:Water (90:10)	14	75	91/09	85
10	DPPTT	DMF:Water (90:10)	15	71	68/32	80
11	NCCPC	DMF:Water (80:20)	12.5	95	98/02	96
12	NCCPC	DMF:Water (70:30)	16	66	87/13	90
13	NCCPC	DMF:Water (60:40)	20	46	88/12	78
14	NCCPC	DMF:Water (50:50)	27	30	70/30	75

[a] All reactions were carried out using 4-nitrobenzaldehyde (75.5 mg, 0.5 mmol), cyclohexanone (0.1 mL, 1 mmol), and 10 mol% organocatalysts (**5** and **7**)

[b] Isolated yield

[c] Determined by analysis of the crude products with ^{1}H NMR

[d] Anti-product % of ee was determined by Chiralpak AD-H

Screening of organocatalysts and optimization of reaction conditions

As a model study, we explored the aldol reaction using cyclohexanone and 4-nitrobenzaldehyde in the presence of the organocatalysts **5** and **7** in (Table 1). The probe substrate was treated with a catalytical amount of 5 and **7** (10 mol%) in water in order to give the desired product with 45 and 36% yield in 20 and 25 hr. The anti-products were obtained with a reasonable diastereoisomeric ratio (anti/syn, 82:18 and 80:20), with 55 and 50% enantiomeric excess (Table 1, entries 1 and 2). The formation of additional hydrogen bonding due to N−H protons of thiourea moiety in **5** resulted in an increase in chemical yield and enantioselectivity (Table 1, entry 1). An appreciable increase in reactivity was achieved, when a thiourea-derived *L*-proline catalyst **5** was used (Table 1, entries 1, 3, 5 and 7). This may be due to the enhanced additional hydrogen bonding by thiourea moiety, which activates the electrophile by double hydrogen bonding. Low chemical yields and moderate selectivities were observed, when organocatalyst **7** was used in respective solvents (Table 1, entries 2, 4 and 6). No desired product was obtained when organocatalyst **7** was used in chloroform. This demonstrated the vital role of the polarity of solvent to increase the electrophilicity of 4-nitrobenzaldehyde in the aldol reaction (Table 1, entry 4). The reaction proceeded smoothly to afford the anti-aldol product with a 75% yield and good stereoselectivities. The solvent polarity was increased by incorporating DMSO and DMF solvents into the aldol reaction (Table 1, entries 5, 6, 7 and 8), while slight improvements in selectivity were observed when organocatalyst **5** was used in DMF: water co-solvent (Table 1, entry 9). It was observed that, a better yield was obtained, when organocatalyst **7** was used in DMF.

From all the observations, it was found that organocatalyst **5** is more efficient than **7** due to the additional hydrogen bonding, which enhances the electrophilic character of aldehydes. By screening both of the the organocatalysts using these conditions, it was observed that the anti-aldol products were dominated by the newly generated absolute stereochemistry (2R, 1`S). The assignment of the absolute configuration (2R, 1`S) of anti-aldol product is determined on the bases of the literature reports [27–30]. By analyzing the preliminary obtained data, it is evident that the presence of the bifunctional group is crucial for the catalytical reaction. Attention was also paid to the DMF: water system effect of organ catalysts **5** under similar reaction conditions. Surprisingly, reasonable to excellent yield and stereoselectivity were obtained when DMF: water system used in the ratio of 80:20 (Table 1, entry 11). Reactivity, yield and stereoselectivity were considerably decreased with the organocatalysts **5** when excess of water was used with DMF.

Thus, we focused our subsequent investigations on the effect of catalyst concentration in DMF: water (80:20) co-solvent. After determination of appropriate solvent combination, we studied the effect of catalyst concentration on the reaction, the obtained results are shown in Table 2. The reaction showed drop in diastereoselectivity and enantioselectivity with increase in quantity of the

catalyst. Catalyst loading of 5 mol% was found to be inadequate to catalyze the reaction. After 20 hours, the obtained yield was 70% giving diastereoselectivity (85/15) and 55% *ee* for anti isomer. On increasing the concentration to 10 mol%, reaction time was reduced to 12.5 hours from 20 hours. Raised quantity also enhanced the yield (95%) with an improved diastereoselectivity (98/02 dr) and 96% *ee* for the major anti isomer. Further increase in concentration of the catalyst to 15 mole% and 20 mole% showed the decreased yield (80% and 76%) and diastereoselectivity (80/20 and 72/18 respectively) with enantioselectivity (80% and 74% for major isomer respectively). Entry 2 shows the optimized conditions for aldol reaction with 10 mole% organocatalyst **5** and solvent *N,N*-dimethylformamide: water in proportion 80:20.
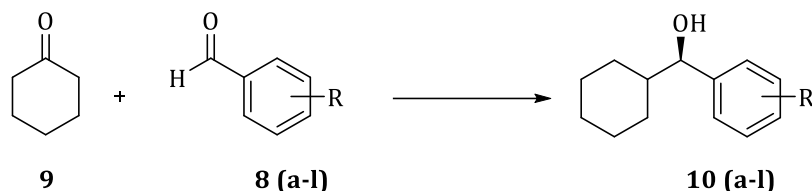
Table 2. Effect of catalyst concentration NCCPC **5** in solvent DMF: water (80:20)

Entry	Catalyst (mole %)	Time (hr)	Yield[a] (%)	*anti/syn* ratio[b]	*anti ee*[c] (%)
1	5	20	70	85/15	55
2	10	12.5	95	98/02	96
3	15	14	80	80/20	82
4	20	15	76	72/18	74

Substrate generality

The substrate generality of this aldol reaction using cyclohexanone, and catalyzed by **5** with a series of aromatic aldehydes, was examined under optimum reaction conditions (Scheme 3). In most cases, anti-aldol products with high to excellent diastereo and enantioselectivities were obtained. The reaction rate of aldol reaction depended on the nature of the substituent on the aromatic group. Excellent diastereoselectivity and enantioselectivity were observed when 2-nitrobenzaldehyde was employed as the acceptor due to more inductive effect while the use of 3-nitrobenzaldehyde resulted in a decrease in both the reactivities and selectivities (Table 3, entries 3 and 2). Admirable enantioselectivity was observed when 4-cyanobenzaldehyde was used (Table 3, entry 4). The chemical yield was further decreased to 65% when benzaldehyde was used (Table 3, entry 10). High enantioselectivities of the anti-product were observed, for the electron-donating substituent acceptor aldehydes, the reactivity decreased noticeably as expected (Table 3, entries 6-8, 10 and 11). High to excellent diastereo and enantioselectivities were obtained, when the reaction with 4-fluorobenzaldehyde was catalyzed by organocatalysts **5** in the presence of DMF: water with chemical yields of only 50% (Table 3, entry 5). The reactivity for aldehydes with el electron-donating substituents and 4-halobenzaldehydes was considerably decreased. This may be

depending on the nature of less reactivity of aldehydes having electron-donating and 4-halosubstituent group on the aromatic ring.

Scheme 3. Reaction conditions: i) NCCPC (5), DMF-Water (80:20), 12–14 hr, 60-98% *ee*

Table 3. Reaction of cyclohexanone and various aromatic aldehydes

Entry	R	Time (h)	Product	Yield[a] (%)	*anti/syn* ratio[b]	*anti ee*[c] (%)	$[\alpha]_D$[d]
1	4-NO$_2$	12.5	10a	95	98/2	96	-49.8
2	3-NO$_2$	13.00	10b	90	90/10	94	-72.4
3	2-NO$_2$	12.00	10c	94	99/1	98	-67.5
4	4-CN	13.00	10d	75	85/15	90	-83.6
5	4-F	13.50	10e	50	98/2	92	-62.4
6	2-Br	14.00	10f	78	75/25	80	-52.7
7	4-Cl	13.50	10g	82	80/20	85	-58.9
8	4-Br	13.00	10h	87	82/18	75	-40.3
9	2-Cl	13.00	10i	79	70/30	78	-88.2
10	H	12.50	10j	65	60/40	65	-18.8
11	4-OH	13.50	10k	85	65/35	72	-23.5
12	4-OCH$_3$	14.00	10l	86	68/32	60	-35.6

[a] Isolated yield

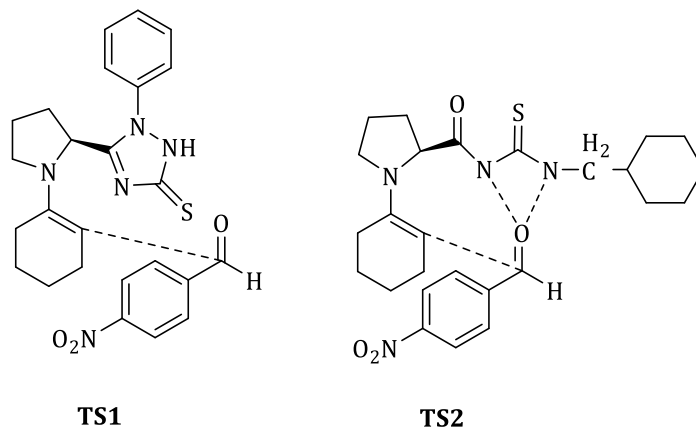[b] Determined by ^{1}H NMR

[c] Determined by chiral HPLC analysis

[d] Optical rotation determined at 27 °C in ethyl acetate

Plausible mechanism of aldol reaction

Based on the experimental results, we proposed the catalytic process in a plausible bifunctional catalytic mechanism. When the reaction was carried out using **7** aldol reaction, it was only facilitated with the pyrrrolidine activated ketone by the formation of an enamine intermediate (T.S.1). The additional hydrogen bonding interaction between the aldehyde carbonyl and the thiourea moiety should be favorable in activating the aldehyde acceptor and facilitating the aldol

reaction, while the pyrrolidine activated the ketone by the formation of an enamine intermediate using **5** as in (T.S.2) (Scheme 4).

TS1   **TS2**

Scheme 4. Proposed transition state model for aldol reaction

Conclusion

A novel cyclohexane scaffold with a thiourea moiety (NCCPC) and triazole-3-thione analogue (DCCPC) derived from *L*-proline, has been obtained *via* a simple synthesis. The catalytic performance of the resultant synthetic products for the direct asymmetric aldol reactions of ketones and aromatic aldehydes has been evaluated. It has been found that both thiourea organocatalyst and triazole-3-thione are efficient for the aldol reactions under investigation. But, it was observed that cyclohexane scaffold, with a thiourea moiety (NCCPC), has excellent enantioselectivities, high yields and excellent diastereoselectivities with small dosages of catalyst (10 mol%) in the absence of additives. The high efficiency of the thiourea catalysts (NCCPC) could be attributed to the double activation and water compatibility. The double activation is through enamine intermediate and additional hydrogen-bonding interaction between the aldehyde carbonyl and the thiourea moiety, which should be favorable in activating the aldehyde acceptor and facilitating the aldol reaction.

Acknowledgments

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1]. Jacobsen E.N., Pfaltz A., Yamamoto H. Comprehensive Asymmetric Catalysis; Springer: Berlin, 1999; p 1178

[2]. Trost B.M. *Science*, 1991, **254**:1471

[3]. Kocovsky P., Malkov A.V. *Tetrahedron*, 2006, **62**:255

[4]. Dalko P.I., Moisan L. *Angew. Chem. Int. Ed.*, 2004, **4**:5138

[5]. List B., Lerner R.A., Barbas III C.F. *J. Am. Chem. Soc.*, 2000, **122**:2395

[6]. Jia Y.N., Wu F.C., Ma X., Zhu G.J., Da C.S. *Tetrahedron Lett.*, 2009, **50**:3059

[7]. Almasi D., Alonso D.A., Najera C. *Adv. Synth. Catal.*, 2008, **350**:2467

[8]. Yang H., Carter R.G. *Org. Lett.*, 2008, **10**:4649

[9]. Shi L.X., Sun Q., Ge Z.M., Zhu Y.Q., Cheng T.M., Li R.T. *Synlett.*, 2004, 2215

[10]. Torii H., Nakadai M., Ishihara K., Saito S., Yamamoto H. *Angew. Chem. Int. Ed.*, 2004, **43**:1983

[11]. McCooey S.H., Connon S.J. *Org. Lett.*, 2007, **9**:599

[12]. Xu X.Y., Wang Y.Z., Gong L.Z. *Org. Lett.*, 2007, **9**:4247

[13]. Hashimoto T., Maruoka K. *J. Am. Chem. Soc.*, 2007, **129**:10054

[14]. He M., Struble J.R., Bode J.W. *J. Am. Chem. Soc.*, 2006, **128**:8418

[15]. Li H., Wang Y. Q. Deng L. *Org. Lett.*, 2006, **8**:4063

[16]. Sigman M.S., Vachal P., Jacobsen E.N. *Angew. Chem. Int. Ed.*, 2000, **39**:1279

[17]. Wang J., Li H., Yu X., Zu L., Wang W. *Org. Lett.,* 2005, **7**:4293

[18]. Sibi M.P., Hasegawa M. *J. Am. Chem. Soc.*, 2007, **129**:4124

[19]. Mizuta S., Shibata N., Akiti S., Fujimoto H., Nakamura S., Toru T. *Org. Lett.*, 2007, **9**:3707

[20]. Sakthivel K., Notz W., Bui T., Barbas C.F. *J. Am. Chem. Soc.*, 2001, **123**:5260

[21]. Torii H., Nakadai M., Ishihara K., Saito S., Yamamoto H. *Angew. Chem. Int. Ed.*, 2004, **43**:1983

[22]. Peng Y.Y., Ding Q.P., Li Z., Wang P.G., Cheng J.P. *Tetrahedron Lett.*, 2003, **44**:3871

[23]. Heine A., Desantis G., Luz J.G., Mitchell M., Wong C.H., Wilson I.A. *Science*, 2001, **294**:369

[24]. Green M.M., Wittcoff H.A. Organic Chemistry Principles and Industrial Practice; Wiley-VCH: Weinheim, Germany, 2003; p 249

[25]. Zhu X., Tanaka F., Hu Y., Heine A., Fuller R., Zhong G., Olson A.J., Lerner R.A., Barbas III C.F., Wilson A. *J. Mol. Biology*, 2004, **343**:1269

[26]. McCooey S.H., Connon S.J. *Angew. Chem.*, 2005, **44**:6367

[27]. Chen J.R., Lu H.H., Li X.Y., Cheng L., Wan J., Xiao W.J. *Org. Lett.*, 2005, **7**:4543

[28]. Mase N., Nakai Y., Ohara N., Yoda H., Takabe K., Tanaka F., Barbas C.F. *J. Am. Chem. Soc.*, 2006, **128**:734

[29]. Sakthivel K., Notz W., Bui T., Barbas C.F. *J. Am. Chem. Soc.*, 2001, **123**:5260

[30]. Tzeng Z.H., Chen H.Y., Reddy R.J., Huang C.T., Chen K. *Tetrahedron*, 2009, **65**:2879