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ARTICLE

Highly Asymmetric Aldol Reaction of Cyclohexanone and Aromatic Aldehydes Catalyzed by Bifunctional Cyclohexane Derived Thiourea Organocatalyst

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ABSTRACT

Novel two L-proline analogues as thiourea-organocatalysts were synthesized *e.g.*, first is the assembly of a structurally well-defined cyclohexane scaffold with thiourea moieties and amine functionalities could constitute a new class of organocatalysts and second the triazole-3-thione analogue. The first one found to be efficient catalysts 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.

KEYWORDS

Asymmetric synthesis, Thiourea organocatalyst, Aldol reaction.

INTRODUCTION

The most attractive method to produce chiral compounds is a catalytic enantioselective process [1] that gives 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. Now a day, organocatalysis is used as metal-free processes [3] and 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 e useful to catalyze enantioselective reactions, has received h attention in recent years [4]. The intermolecular aldol reaction has been carried out with the successful demonstration of L-proline in 2000; spectacular advances have been made y using this remarkable 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 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] and others [19].

Organocatalytic asymmetric aldol reactions are useful C-C bond-forming reactions with the formation of enamine inter-

mediates and yields aldol products with excellent enantioselectivities [20]. The organic solvents such as DMSO, DMF or $CHCl_3$ are generally used to perform these reactions, under mild conditions. Addition of a small amount of water often accelerates reactions and improves enantioselectivities [10], but it has been shown that excess of water or aqueous buffer as reaction solvents, has typically resulted with low yield and enantioselectivity [21]. In contrast, aldol reactions, which involves an enamine mechanism, in natural Class I aldolase enzymes [22] and aldolase catalytic antibodies [23] that uses an enamine mechanism. In aldolase antibodies [24], indicating 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. Now a day, 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 [25].

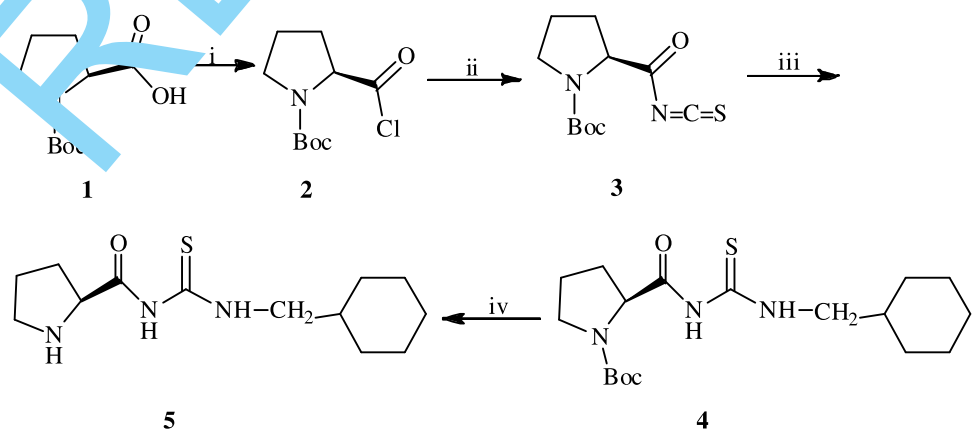
Herein, we describe the preliminary results of aldol reaction, utilizing thiourea organocatalyst bearing a cyclohexane scaffold for catalyzing cyclohexanone (2 equiv.) and various arylaldehydes in DMSO:water solvent.

EXPERIMENTAL

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 cm × 20 cm, Silica gel 60 F_{254}, Merck grade was used for thin layer chromatography to determine progress of 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 capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ solvent. Mass spectra were taken on Polaris-Q Thermoscintific GC-MS. Enantiomeric purity is determined on Perkin-Elmer Series 200 HPLC Systems with chiral HPLC and Chiralpak AD.

Synthesis of organocatalyst (*S*-*N*-((cyclohexylmethyl)-carbamothioyl)pyrrolidine-2-carboxamide (CCPC) (5): A solution of Boc-L-proline (0.1 mol) in anhydrous 1,2-dichloroethane is refluxed for 3 h with thionyl chloride (0.2 mol). The solvent and the excess thionyl chloride are removed by reduced pressure distillation. The raw obtained (*S*)-*tert*-butyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate (10 mmol) is dissolved in anhydrous acetone (30 mL), added to a solution of ammonium thiocyanate (10 mmol) in dry acetone and refluxed for 1 h. The ammonium chloride obtained, was removed by filtration and cyclohexylmethyl amine (10 mmol) dissolved in anhydrous acetone is added while stirring. The mixture is heated under reflux for 1 h. The mixture was extracted with CH_2Cl_2 (2 × 20 mL) and 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)methanethiocarbamoyl)-pyrrolidine-1-carboxylate was dissolved in CH_2Cl_2 (10 mL) and added trifluoroacetic acid (TFA) (2 mL) dropwise with stirring for 1 h at 0 ºC. After the consumption of the starting material as indicated by TLC analysis, the reaction mixture was diluted with H_2O (20 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* (**Scheme-I**) The purification of residue by column chromatography (EtOAc/hexane, 1:4) afforded 70-75 % of compound **5** as yellowish solid, m.p. 132 ºC. Optical rotation $[\alpha]_{25}^{D}$: -60.5º (c 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (s, 1H, NH), 3.80 (t, 1H), 3.45 (t, 2H), 2.5 (m, 2H), 1.2-1.9 (m, 17H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.4, 174.24, 77.25, 77.04, 76.37, 62.04, 49.25, 44.9, 40.08, 32.00, 32.04, 26.89, 22.01. 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 1.0 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 h. The ammonium chloride is removed by filtration and added the solution of phenyl hydrazine (10 mmol) in acetonitrile. The mixture is heated under reflux for 1 h.The mixture was extracted with CH_2Cl_2 (2 × 20 mL) and 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



Scheme-I: Reaction conditions: i) $SOCl_2$, $C_2H_4Cl_2$, reflux, 3 h; ii) NH_4SCN, acetone, reflux, 1 h; iii) cyclohexylmethanamine, acetone, reflux, 1 h; iv) methylene dichloride (MDC), trifluoroacetic acid (TFA), stirr, 1 h, 70-75 %

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 was added TFA (2 mL) dropwise with stirring for 1 h at 0 ºC. After the consumption of 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* (**Scheme-II**) The purification of residue by column chromatography (EtOAc/hexane, 1:1) afforded 80-85 % of compound **7** as yellow solid. m.p.: 160-162 ºC. Optical rotation $[\alpha]_{20}^{D}$: -80.7 (c 0.42, $CHCl_3$). ^{1}H 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 187.56, 165.78, 140.08, 130.00, 120.03, 114.12, 58.03, 47.01, 28.45, 23.01. 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.

General procedure for aldol reaction: To a mixture of solvent containing *N*,*N*-dimethylformamide (8 mL) and water (2 mL), cyclohexanone (1 mmol) and aromatic aldehyde (0.5 mmol) was added and stirred for few min. Organocatalyst NCCPC (**5**) (0.10 mmol) was added to reaction mixture and stirred at room temperature for 10-12 h. Completion of reaction was indicated by TLC, solvent was removed under vacuum to ob[illegible] crude product. This crude product was partitioned betwe[illegible] ethyl acetate and water. Organic layer was collected and washed with water and brine solution. The combined o[illegible] layer was dried over $MgSO_4$, filtered and the solven[illegible] was re[illegible]oved *in vacuo*, obtained product was purified by c[illegible]mn chr[illegible]atography using silica gel mesh 80-120.

(*S*)-2-((*R*)-hydroxy-(4-nitrophen[illegible]methyl)[illegible]clohexanone (10a): m.p. 129-130 ºC; Optic[illegible]tation $[\alpha]^D$: [illegible]8º (c 0.45, ethyl acetate). ^{1}H NMR (300[illegible]Hz, [illegible]CCl_3): δ 1.15-1.40 (m, 1H), 1.55-1.70 (m, 4H), 1.90-2.1 (m, 1H), 2.[illegible]-2.25 (m, 1H), 2.30-2.6 (m, 1H), 2.7-3.00 (m[illegible]H), 3.7-3.9 (br s, [illegible] syn), 4.5-4.7 (br s, 1H anti), 4.8 (d, [illegible] anti), 5[illegible]s, 1H syn), 7.6 (d, 2H), 8.20 (d, 2H). ^{13}C NMR ([illegible]MHz, [illegible]DCl_3): δ 24.6, 27.5, 30.6, 42.6, 57.1, 73.9, 123.5, 127.[illegible]47.4,148.[illegible], 214.6. GC-MS: *m/z* 294 (M^+). HPL[illegible]ee. [De[illegible]min[illegible] by HPLC (Chiralcel AD, *n*-hexane/*i*-[illegible]OH: 9[illegible]10, 0.7[illegible] min^{-1}), *anti*: R_t 66.69 (minor), R_t 6[illegible]7 (mai[illegible] R_t 38.71 (minor), R_t 52.62 (major)].

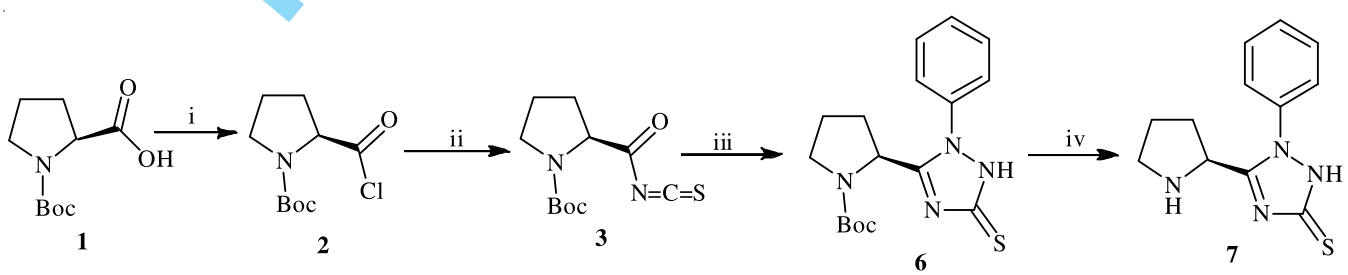
(*S*)-2-[(*R*)-Hydroxy-(3-nitrophenyl)methyl]cyclohexanone (10b): White powder; m.p. 69-71 ºC; Optical rotation $[\alpha]^D$ = -72.4º (c 1.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10-8.18 (m, 2H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 4.86 (d, *J* = 8.4 Hz, 1H), 4.12 (d, *J* = 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, *n*-hexane/*i*-PrOH: 92/08, 1.0 mL min^{-1}), *anti*: R_t 33.94 (minor), R_t 26.05 (major), *syn*: R_t 23.10 (major), R_t 22.06 (minor)].

(S)-2-[(R)-Hydroxy-(2-nitrop[illegible]l)methyl]cyclohexanone (10c): m.p. 116-118 ºC. O[illegible]ical rot[illegible]n $[\alpha]^D$ = -67.5º, ^{1}H NMR (300 MHz, $CDCl_3$): [illegible].80 (d, *J* = [illegible] Hz, 1H), 7.75 (d, *J* = 7.8 Hz,1H), 7.56 (t, *J* = [illegible] Hz, 1H), 7.2[illegible]7.26 (m, 1H), 5.34 (d, *J* = 7.2 Hz, 1H[illegible] 4.07 (d[illegible]1H), 2.[illegible]-2.78(m, 1H), 2.20-2.45 (m, 2H), 2[illegible]2-2.12 (m, 1[illegible]2-1.83 (m, 5H). HPLC: 98 % ee. [D[illegible]ermine[illegible]by HPLC (Chiralcel AD-H, *n*-hexane/*i*-PrOH: 92/0[illegible]1.0[illegible]L min^{-1}) *anti*: R_t 66.23 (minor), R_t 71.72 (mai[illegible]), *syn*: R_t[illegible]61 (m[illegible]r), R_t 57.35 (minor)].

(*S*)-2-[([illegible]Hydroxy-(4-[illegible]phenyl)methyl]cyclohexanone (10[illegible]): m.p[illegible]2-83 ºC; Optical rotation $[\alpha]^D$: -83.6º (c 0.5, ethyl acetate). [illegible]NMR (300 MHz, $CDCl_3$): δ 1.2-1.4 (m, 1H[illegible].8 (m, 4H), 1.[illegible]-2.10 (m, 1H), 2.25-2.30 (m, 1H), 2[illegible]2.7 (m, 2H), 2.9-3.1(m,1H), 3.7 (br s, 1H, syn), 4.50 (br s, 1[illegible], anti), 5.2 (d, [illegible]H, anti), 5.7 (s, 1H, syn) 7.9 (d, 2H), 8.15 (d, 2[illegible]. ^{13}C NMR ([illegible] MHz, $CDCl_3$): δ 223.49, 145.38, 134.21, 132.[illegible]118.57[illegible]13.29, 80.86, 62.93, 43.01, 30.82, 26.67. GC-MS: *m/z* 229 (M^+). HPLC: 90 % ee. [Determined by HPLC ([illegible]el AD-H, *n*-hexane/*i*-PrOH: 95/05, 1.0 mL min^{-1}), *anti*: [illegible] 66.67 (minor), R_t 70.73 (major), *syn*: R_t 32.62 (major), R_t 58.39 (minor)].

(*S*)-2-[(*R*)-Hydroxy-(4-fluorophenyl)methyl]cyclohexanone (10e): Optical rotation $[\alpha]^D$ = -62.4º (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, *n*-hexane/*i*-PrOH: 90/10, 0.3 mL min^{-1}), *anti*: R_t 49.15 (minor), R_t 44.19 (major), *syn*: R_t 29.28 (major), R_t 33.28 (minor)].

(S)-2-[(*R*)-Hydroxy-(4-chlorophenyl)methyl]cyclohexanone (10f): Optical rotation $[\alpha]^D$ = -58.9º (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, *n*-hexane/*i*-PrOH:



Scheme-II: Reaction conditions: i) $SOCl_2$, $C_2H_4Cl_2$, reflux, 3 h; ii) NH_4SCN, acetonitrile, reflux, 1 h; iii) $C_6H_5NHNH_2$, CH_3CN, reflux, 1 h; iv) methylene dichloride (MDC), Trifluoroacetic acid (TFA), stir, 1 h, 80-85 %

90/10, 0.3 mL min^{-1}), *anti*: R_t 52.77 (minor), R_t 45.71 (major), *syn*: R_t 29.96 (major), R_t 34.61 (minor)].

(*S*)-2-[(*R*)-Hydroxy-(4-bromophenyl)methyl]cyclohexanone (10h): Optical rotation $[\alpha]^D$ = -40.3° (c 0.70, $CHCl_3$). ^1H 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*: R_t 54.91 (minor), R_t 47.54 (major), *syn*: R_t 30.13 (major), R_t 35.31 (minor)].

2-(Hydroxy-(2-chlorophenyl)methyl)cyclopentanone (10i): Optical rotation $[\alpha]^D$ = -88.2° (c 1.50, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ: 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, *n*-hexane/*i*-PrOH: 95/05, 1.0 mL min^{-1}), *anti*: R_t 16.73 (minor), R_t 14.8 (major), *syn*: R_t 10.24 (major), R_t 14.24 (minor)].

(*S*)-2-((*R*)-Hydroxy(phenyl)methyl)cyclohexanone (10j): Optical rotation $[\alpha]^D$: -18.8° (c 0.5, ethyl acetate). ^1H 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, *n*-hexane/*i*-PrOH: 95/5, 0.50 mL min^{-1}), *anti*: R_t 26.[illegible] (minor), R_t 29.74 (major), *syn*: R_t 16.90 (major), R_t 19.42 (minor)].

(*S*)-2-[(*R*)-Hydroxy-(4-Hydroxyphenyl)methyl]cyclohexanone (10k): White powder; Optical rotation [illegible] 23.5° (c 1.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ [illegible]0.12 (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.[illegible]2.41 (m, 1H), 2.08-2.15 (m, 1H), 1.81-1.83 (m, 1H), 1[illegible]-1.73 (m, 1H), 1.32-1.41 (m, 1H). HPLC: 72 % ee. [Determ[illegible]d by HPLC (Chiralcel AD-H, *n*-hexane/*i*-PrOH: 90/10, 0[illegible] mL [illegible]$^{-1}$), *anti*: R_t 31.98 (minor), R_t 40.88 (major), *syn*: R_t 27.33 (major), [illegible]23.20 (minor)].

RESULTS AND DISCUSSION

Herein, we describe[illegible]he sy[illegible]nesis of new bifunctional thiourea derivatives **5** and **7** [illegible]their su[illegible]essful application to aldol reaction o[illegible]cyc[illegible]hexano[illegible]and [illegible]ubstituted aromatic aldehydes.

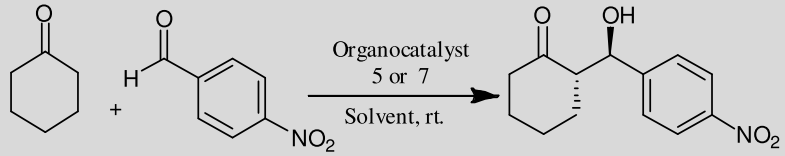
The synth[illegible]is of or[illegible]lysts **5** and **7** began with (*S*)-*tert*-butyl 2-carbo[illegible]l[illegible]rolidine-1-carboxylate (**3**), which was readily prepared fro[illegible]the *Boc*-protected L-proline (**1**). The precursor *Boc*-protected [illegible]proline (**1**) was converted into the (*S*)-*tert*-butyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate (**2**) using thionyl chloride as chlorinating reagent and was treated with ammonium thiocyanate to afford (*S*)-*tert*-butyl 2-carbonyl-pyrrolidine-1-carboxylate (**3**). This was converted into corresponding (*S*)-*tert*-butyl-2-(amino-*N*-(cyclohexylmethyl)-methanethiocarbamoyl)pyrrolidine-1-carboxylate (**4**) by the addition of cyclohexyl methylamine and refluxing in dry acetone. (*S*)-*tert*-butyl-2-(2,5-dihydro-2-phenyl-5-thioxo-1*H*-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (**6**) was 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 using trifluoroacetic acid 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.

The structures of synthesized organocatalysts were confirmed by spectral data. For organocatalyst **5**, ^1H NMR spectra showed a singlet at 8.3 ppm indicates presence of amide proton which confirms formation of amide group in catalysts. The signal for proton on nitrogen from proline ri[illegible]d NH-C=S is observed between 2.5-2.7 ppm in proton N[illegible]R. Sig[illegible]at 3.45 ppm was obtained due to protons of met[illegible]lene moiety a[illegible]ched to cyclohexane ring. The signal for hydr[illegible]en attached [illegible] chiral carbon was obtained at 3.8 ppm. Similar[illegible]for orga[illegible]ocatalyst **7**, ^1H NMR spectra showed [illegible]singlet at 8.7 p[illegible]dicates formation of triazole-thione ri[illegible]. The si[illegible]al for proton on nitrogen from proline ring and [illegible]n chi[illegible]l c[illegible]on was s[illegible]wn at 2.5 and 3.1 ppm, respectively. F[illegible]ther ver[illegible]ation [illegible]both the organocatalysts were provid[illegible]by ^{13}C NMR a[illegible]C-MS. Enantiomeric purity is determ[illegible]ed on [illegible]rkin-Elmer Series 200 HPLC Systems with chiral HPLC, EtOAc[illegible]exane (80/20), Flow rate 1.0 mL /min, λ = [illegible] which shows [illegible]antiomeric purity 99.00 % for catalyst N[illegible]CPC and 99.80 % for DPPTT.

We used bo[illegible]5 and **7** catalysts for asymmetric aldol reaction. D[illegible]to the bifun[illegible]onal activations of **5**, which simultaneously activ[illegible]both a[illegible]eptors and donors, have recently emerged as an important strategy in asymmetric small molecular catalysis. G[illegible]lly, thiourea-based catalysts have been widely used due [illegible]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 substituted aromatic aldehydes with 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 stereocompatibility and chiral recognition.

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** (Table-1). The probe substrate was treated with a catalytical amount of **5** and **7** (10 mol %) in water to give the desired product with 45 and 36 % yield in 20 and 25 h. 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, entry 1and 2). The formation of additional hydrogen bonding due to N-H protons of thiourea moiety in **5**, which 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, entry 1, 3, 5, 7). This may due to enhanced additional hydrogen bonding by thiourea moiety, which activates the electrophile by double hydrogen

TABLE-1
DIASTEREO- AND ENANTIOSELECTIVE ALDOL REACTION OF CYCLOHEXANONE AND 4-NITROBENZALDEHYDE CATALYZED BY ORGANOCATALYSTS NCCPC **5** & DPPTT **7** IN VARIOUS SOLVENTS (10 mL) AT AMBIENT TEMPERATURE[a]



9 **8a** **10a**

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	*anti/syn* ratio[c]	*anti ee*[d]
1	NCCPC	Water	20	45	82/18	55
2	DPPTT	Water	25	36	8 /20	50
3	NCCPC	Chloroform	22	20	4/16	35
4	DPPTT	Chloroform	28	-	77/23	22
5	NCCPC	Dimethyl sulfoxide	18	60	/12	70
6	DPPTT	Dimethyl sulfoxide	20	43	85/1	68
7	NCCPC	N,N-Dimethyl formamide	15	70	90/10	74
8	DPPTT	N,N-Dimethyl formamide	18	55	89/11	72
9	NCCPC	DMF:Water (90:10)	14	75	91/09	85
10	DPPTT	DMF:Water (90:10)	15		68/	80
11	NCCPC	DMF:Water (80:20)	12.5	95	9 /2	96
12	NCCPC	DMF:Water (70:30)	16		/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, mmol), and 10 mol % organocatalysts (5 & 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.

bonding. Low chemical yields and moderate selectivities were observed, when organocatalyst **7** was used in respective solvents (Table-1, entry 2, 4, 6). No desired product was obtained when organocatalyst **7** was used in chloroform. This demonstrated the vital role of 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. When a solvent polarity increases by incorporating DMSO as solvent into the aldol reaction (Table-1, entry 5, 6), slight improvements in selectivity were observed when organocatalysts **5** was used in DMF:water co-solvent (Table-1, entry 9). It was observed that the better yield obtained when organocatalyst **7** used in DMF:water system than above used solvent but decreases selectivity.

From all the observations, it was found that organocatalyst **5** is more efficient than **7** due to additional hydrogen bonding, which enhances the electrophilic character of aldehydes. By screening both the organocatalysts using these conditions, it was observed that the anti aldol products dominated with the newly generated absolute stereochemistry to be (2R, 1′S). The assignment of absolute configuration (2R, 1′S) of anti-aldol product is determined on the bases of the literature reports [20,26-28]. By analyzing the preliminary data obtained, it is evident that the presence of bifunctional group is crucial for the catalytical reaction. Attention was also paid to DMF:water system effect of organ catalysts **5** under similar reaction conditions. Surprisingly, reasonable to excellent yield and stereoselectivity was 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 used with DMF.

Thus, we focus our subsequent investigations on the effect of catalyst concentration in DMF:water (80:20) co-solvent. After determination of appropriate solvent combination we studied effect of catalyst concentration on the reaction, 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. As after 20 h, yield obtained was 70 % giving diastereoselectivity (85/15) and 55 % ee for anti isomer. On increasing concentration to 10 mol %, reaction time was reduced to 12.5 h from 20 h. Raised quantity also enhanced yield (95 %) with improved diastereoselectivity (98/02 dr) and 96 % ee for major anti-isomer was observed. Further increase in concentration of catalyst to 15 mol % and 20 mol % showed 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 optimized conditions for aldol reaction with 10 mol % 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)

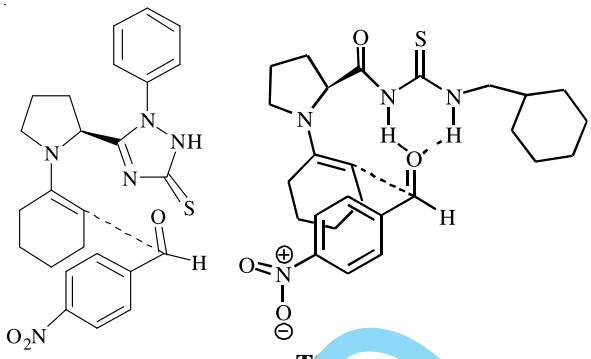
Entry	Catalyst (mol %)	Time (h)	Yield[a] (%)	*anti/syn* ratio[b]	*anti ee*[c] (%)
1	5	20	70	85/15	55
2	10	12.5	95	98/02	96
4	15	14	80	80/20	82
5	20	15	76	72/18	74

[a]Isolated yield; [b]Determined by ^{1}H NMR; [c]Determined by chiral HPLC analysis.

Substrate generality: The substrate generality of this aldol reaction using cyclohexanone, catalyzed by **5** with a series of aromatic aldehydes was examined under optimum reaction conditions. In most cases, anti-aldol products with high to

excellent diastereo- and enantioselectivities were obtained. The reaction rate of aldol reaction depended upon the nature of substituent on the aromatic group. Excellent diasteroselectivity 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 but diminished reactivity 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 anti-product were observed, for electron-donating substituent acceptor aldehydes, 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, entries 5). The reactivity for aldehydes with electron-donating substituent′s and 4-halobenzaldehydes was considerably decreased. This may be depend upon the nature of less reactivity of aldehydes having electron donating and 4-halo substituent group on the aromatic ring.

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 by using **7**, aldol reaction facilitated only with the pyrrolidine-activated ketone by the formation of an enamine intermediate (TS 1). The additional hydrogen-bonding interaction between the aldehyde carbonyl and the thiourea moiety should be favourable in activating the aldehyde acceptor and facilitating the aldol reaction, while pyrrolidine activated the ketone by the formation of an enamine intermediate using **5** as in TS 2 (Fig. 1).



TS 1 TS 2

Fig. 1. Proposed transition state model for aldol reaction

Conclusion

A novel cyclohexane scaffold with a thiourea moiety (NCCPC) and triazole-3-thione analog (DCCPC) derived from L-proline, have been obtained *via* a simple synthesis. The catalytic performance of resultant stereogenic products for the direct asymmetric aldol reactions of ketones and aromatic aldehydes has been established. 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) have excellent enantioselectivities, high yields and excellent diastereoselectivities with small dosages of catalyst (10 mol %) in the absence of additives. The high efficiency of 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 aldehyde carbonyl and thiourea moiety, which should be favourable in activating the aldehyde acceptor and facilitating the aldol reaction.

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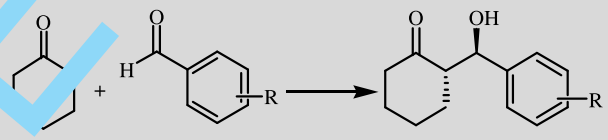
TABLE-3
REACTION OF CYCLOHEXANONE AND VARIOUS AROMATIC ALDEHYDES



9 **8 (a-l)** **10 (a-l)**

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.

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