

Synthesis and application of L-proline and R-phenylglycine derived organocatalysts for direct asymmetric Michael addition of cyclohexanone to nitroalkenes

Hayriye Nevin NAZIROĞLU¹, Abdulkadir SIRIT^{2,*}

e-mail: asirit42@hotmail.com

¹*Department of Chemistry, Karamanoğlu Mehmetbey University, 70100 Karaman-TURKEY*

²*Department of Chemistry, Konya University, 42099 Konya-TURKEY*

Received: 17.10.2011

Novel R-phenylglycine derived organocatalysts were prepared from the reaction of Cbz-R-phenylglycine with indoline, pyrrolidine, or (S)-(-)-2-(diphenylmethyl)pyrrolidine in 3 steps. The asymmetric Michael addition of cyclohexanone to nitroolefins was investigated using R-phenylglycine derivatives along with L-prolinamides as chiral catalysts. The desired products were obtained in excellent yields with enantioselectivities up to 90% ee and diastereomeric ratio up to 98:2 of the *syn* addition product.

Key Words: Amines, asymmetric catalysis, Michael addition, nitroolefins, organocatalysis

Introduction

Asymmetric synthesis using organocatalysts has been a convenient and highly useful synthetic method for the preparation of enantiomerically pure compounds in the past few years.¹ Operational simplicity and the ready availability and low toxicity of the catalysts, as well as its high efficiencies and selectivities attained in many organocatalytic transformations made this methodology very attractive for the formation of enantiomerically pure compounds.²

The Michael addition is one of the most efficient, atom-economical, and powerful carbon-carbon bond-forming reactions in organic synthesis. The direct asymmetric Michael addition of aldehydes and ketones

*Corresponding author

with nitroalkenes to produce enantiomerically enriched nitroalkanes has been described. These compounds are versatile building blocks owing to the various possible transformations of the nitro functionality into other useful functional groups such as amines, nitrile oxides, ketones, and carboxylic acids.³

Barbas⁴ and List⁵ independently published their pioneering studies on the asymmetric Michael addition reactions using L-proline as the catalyst with good yields but very low enantioselectivities (0%-23% ee). Since then, a variety of organocatalysts have been synthesized and studied for the direct addition of ketones and aldehydes to β -nitrostyrenes. Examples include chiral diamines,⁶ modified L-prolines,⁷ pyrrolidine-based diamines,⁸ chiral guanidines,⁹ urea(thiourea)-based bifunctional organocatalysts,¹⁰ and cinchona alkaloid-based bifunctional organocatalysts.¹¹

Among them, pyrrolidine-based chiral compounds such as chiral pyrrolidinyl triazole,¹² tetrazole,¹³ aminomethylpyrrolidine,¹⁴ 2,2-bipyrrolidine,¹⁵ pyrrolidine-pyridine,¹⁶ pyrrolidine sulfonamide,¹⁷ pyrrolidine-thiourea,¹⁸ diphenylprolinol ethers,¹⁹ ionic liquid supported pyrrolidine-based catalysts,²⁰ and others²¹ were reported to show high catalytic activity and enantioselectivity for asymmetric organic transformations. The rational design and synthesis of an efficient organocatalyst for direct asymmetric Michael addition of ketones and aldehydes to β -nitroalkenes is still receiving considerable attention, although numerous chiral catalysts have been developed for this purpose.

In our previous work,²² we synthesized a series of L-proline-based chiral receptors and investigated their recognition abilities for carboxylic acids by ¹H-NMR spectroscopy. We herein report the synthesis of novel *R*-phenylglycine derived organocatalysts **7-12** and their catalytic properties along with prolinamides **1** and **2** for the enantioselective Michael addition of cyclohexanone with β -nitrostyrenes.

Experimental

General

¹H-NMR spectra were recorded at room temperature on a Varian 400 MHz spectrometer in CDCl₃. Chemical shifts were reported in ppm. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration. The HPLC measurements were carried out on Agilent 1100 equipment connected with a Chiralpak Daicel AD-H column. Analytical TLC was performed using Merck prepared plates (silica gel 60 F254 on aluminum). Flash chromatography separations were performed on Merck Silica Gel 60 (230-400 mesh). All starting materials and reagents used were of standard analytical grade from Fluka, Merck, and Aldrich and were used without further purification. Dichloromethane was dried (CaCl₂), distilled from CaH₂, and stored over molecular sieves. Other commercial grade solvents were distilled, and then stored over molecular sieves. The drying agent employed was anhydrous MgSO₄. The spectra and other data were consistent with the reported values.

Synthesis of catalysts

Chiral catalysts **1** and **2**, shown in Figure 1, were obtained following the literature procedure.²² Compounds **4** **7** and **10** were synthesized according to a procedure reported by Bhuniya et al.²³

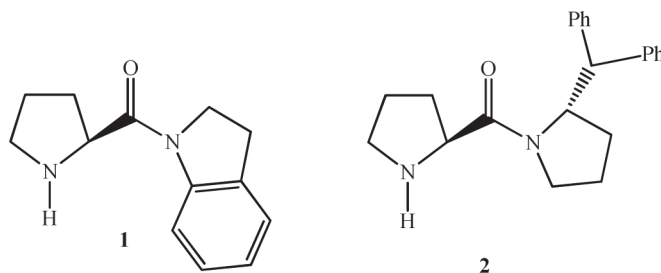


Figure 1. Structure of proline-derived organocatalysts.

General procedure for the synthesis of compounds 5 and 6

N-carbonylbenzyloxy-(*R*)-phenylglycine (0.5 g, 1.75 mmol) was dissolved with stirring in dry dichloromethane (20 mL) in a 50 mL round bottom flask equipped with a dropping funnel. The solution was cooled to -5°C and dicyclohexylcarbodiimide (DCC, 0.36 g, 1.75 mmol) was added slowly in small portions. Appropriate secondary amine (2.23 mmol) was added dropwise to the reaction mixture. After being stirred for 2 h at room temperature the solution was diluted to double its volume with dichloromethane. Urea formed was separated by filtration. The solvent was removed. In order to remove further amounts of urea the residue was dissolved in 20 mL of ethyl acetate and heated to 50°C . The remaining urea was filtered off. This procedure was repeated until no more urea was formed. The solvent was evaporated and the crude products were purified by flash chromatography (*n*-hexane/ethyl acetate, 20:1).

(*R*)-benzyl (2-(indolin-1-yl)-2-oxo-1-phenylethyl)carbamate (5)

Viscous yellow oil. Yield 85%; $\alpha_D^{25} = -143.8$ (*c* 1.05, CHCl_3); IR (KBr) 3395, 3318, 3033, 2955, 1714, 1651 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ (ppm): 2.92-3.04 (m, 1H, CH_2 - pyrrolidine), 3.09-3.20 (m, 1H, CH_2 - pyrrolidine), 3.65-3.74 (m, 1H, CH_2 - pyrrolidine), 4.09-4.20 (m, 1H, CH_2 - pyrrolidine), 5.02-5.18 (AB, $J = 12.4$ Hz, 2H, CH_2ph), 5.59 (d, $J = 7.6$ Hz, 1H, NHCHph), 6.42 (d, $J = 7.6$ Hz, 1H, NH), 7.02- 7.52 (m, 14H, ArH); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ (ppm): 167.92, 155.81, 142.83, 136.97, 136.60, 131.48, 129.43, 128.89, 128.73, 128.38, 128.33, 128.24, 127.84, 124.90, 124.69, 117.55, 60.65, 28.24, 21.32, 14.47; Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_3$ (386.45): C, 74.59%; H, 5.74%; N, 7.25%. Found: C, 74.63%; H, 5.80%; N, 7.20%.

Benzyl ((*R*)-2-((*S*)-2-benzhydrylpyrrolidin-1-yl)-2-oxo-1-phenylethyl)carbamate (6)

Viscous yellow oil. Yield 80%; $\alpha_D^{25} = -159.4$ (*c* 1.05, CHCl_3); IR (KBr) 3300, 3029, 2934, 1713, 1639 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ (ppm): 0.96-1.09 (m, 1H, CH_2 - pyrrolidine), 1.39-1.5 (m, 1H, CH_2 - pyrrolidine), 1.88-1.98 (m, 2H, CH_2 - pyrrolidine), 3.02 (q, $J = 8.1$ Hz, 1H, CH_2 - pyrrolidine), 3.17-3.24 (m, 1H, CH_2 - pyrrolidine), 4.73 (d, $J = 5.4$ Hz, 1H, CH), 4.99 (q, $J = 5.4$ Hz, 1H, CH), 5.04-5.21 (AB, $J = 12.3$ Hz, 2H, CH_2ph), 5.39 (d, $J = 7.6$ Hz, 1H, NHCHph), 6.24 (d, $J = 7.6$ Hz, 1H, NH), 7.14-7.44 (m, 20H, ArH); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ (ppm): 168.27, 155.71, 142.21, 141.68, 137.26, 136.71, 129.98, 129.25, 129.02, 128.74, 128.57, 128.25, 126.99, 126.48, 67.04, 60.91, 57.60, 51.63, 46.50, 27.52, 23.50; Anal. Calcd for $\text{C}_{33}\text{H}_{32}\text{N}_2\text{O}_3$ (504.62): C, 78.55%; H, 6.39%; N, 5.55%. Found: C, 78.60%; H, 6.45%; N, 5.50%.

General procedure for the synthesis of compounds 8 and 9

A mixture of **5** or **6** (8.8 mmol), cyclohexene (4.36 mL, 53.22 mmol) and 1.4 g of commercial Pd/C (10%) in 110 mL of EtOH was heated under reflux for 2 h in argon, cooled, and filtered over celite. The catalyst was washed with EtOH, and the filtrate and wash liquids were evaporated under reduced pressure. Crude products were purified by flash chromatography.

(*R*)-2-amino-1-(indolin-1-yl)-2-phenylethanone (8)

White solid. Yield 85%; mp 145-146 °C; $\alpha_D^{25} = -20.7$ (*c* 1.05, CHCl₃); IR (KBr) 3362, 3300, 3025, 2931, 1653, 1595 cm⁻¹; ¹H-NMR (CDCl₃): δ (ppm): 2.91 (bs, 2H, NH₂), 2.97-3.09 (m, 2H, CH₂- pyrrolidine), 3.53-3.65 (m, 1H, CH₂- pyrrolidine), 3.96-4.09 (m, 1H, CH₂- pyrrolidine), 4.74 (s, 1H, -CH), 6.93-7.43 (m, 8H, ArH), 8.31 (d, *J* = 8.1 Hz, 1H, ArH); ¹³C-NMR (100 MHz, CDCl₃): δ (ppm): 171.19, 143.18, 140.14, 131.40, 129.51, 128.45, 127.77, 127.75, 124.82, 124.32, 117.40, 59.21, 47.43, 28.22; HRMS (ESI⁺) calcd for C₁₆H₁₆N₂O: 253.3132; found 253.3153.

(*R*)-2-amino-1-((*S*)-2-benzhydrylpyrrolidin-1-yl)-2-phenylethanone (9)

Viscous oil. Yield 65%; $\alpha_D^{25} = -159.6$ (*c* 1.05, CHCl₃); IR (KBr) 3027, 2976, 2881, 1714, 1637 cm⁻¹; ¹H-NMR (CDCl₃): δ (ppm): 1.09-1.19 (m, 1H, CH₂- pyrrolidine), 1.44-1.53 (m, 1H, CH₂- pyrrolidine), 1.91-1.98 (m, 2H, CH₂- pyrrolidine), 2.05 (brs, 2H, NH₂), 3.00-3.22 (m, 2H, CH₂- pyrrolidine), 4.53 (s, 1H, -CH), 4.75 (d, *J* = 5.4 Hz, 1H, -CH), 5.08 (q, *J* = 5.4 Hz, 1H, -CH), 7.19-7.38 (m, 15H, ArH); ¹³C-NMR (100 MHz, CDCl₃): δ (ppm): 171.78, 142.58, 140.9, 130.33, 129.94, 129.07, 128.20, 127.63, 126.91, 60.61, 52.10, 46.26, 30.48, 27.56, 23.57; HRMS (ESI⁺) calcd for C₂₅H₂₆N₂O: 371.4936; found 371.4955.

General procedure for the synthesis of compounds 11 and 12

LiAlH₄ (0.8 g, 20.63 mmol) in dry THF (10 mL) at 20 °C was stirred for a few minutes under a nitrogen atmosphere. The mixture was cooled to 0 °C and compound **8** or **9** (0.98 mmol) in dry THF (10 mL) was added dropwise over 30 min. The mixture was heated under reflux for 8 h and then cooled in an ice bath. Aqueous NaOH (2 M) was added dropwise until a white precipitate of inorganic salts formed. The inorganic salts were removed by filtration and washed with (3 × 20 mL) of THF. The filtrate was dried (MgSO₄) and concentrated under reduced pressure. Crude products were purified by flash chromatography.

(*R*)-2-(indolin-1-yl)-1-phenylethanamine (11)

Viscous yellow oil. Yield 50%; $\alpha_D^{25} = +81.0$ (*c* 1.05, CHCl₃); IR (KBr) 3345, 3284, 3027, 2926, 2847 cm⁻¹; ¹H-NMR (CDCl₃): δ (ppm): δ 2.16 (bs, 2H, NH₂), 2.93-3.04 (m, 1H, CH₂), 3.07-3.17 (m, 2H, CH₂- pyrrolidine), 3.23-3.36 (m, 1H, CH₂), 3.46-3.55 (m, 2H, CH₂- pyrrolidine), 4.28 (dd, 1H, *J*₁ = 4.3 Hz, *J*₂ = 4.3 Hz, CH), 6.56 (d, 1H, *J* = 7.7 Hz, ArH), 6.63-6.72 (m, 1H, ArH), 7.03-7.12 (m, 2H, ArH), 7.24-7.48 (m, 5H, ArH); ¹³C-NMR (100 MHz, CDCl₃): δ (ppm): 151.66, 128.68, 127.64, 127.42, 126.66, 126.34, 126.05, 125.72, 123.45, 116.92, 61.62, 53.68, 28.33, 27.73; HRMS (ESI⁺) calcd for C₁₆H₁₈N₂: 239.3337; found 239.3365.

(*R*)-2-((*S*)-2-benzhydrylpyrrolidin-1-yl)-1-phenylethanamine (12)

Viscous oil. Yield 51%; $\alpha_D^{25} = -38.3$ (*c* 1.05, CHCl₃); IR (KBr) 3374, 3300, 3059, 3025, 2961, 2792 cm⁻¹; ¹H-NMR (CDCl₃): δ (ppm): 1.55-1.75 (m, 4H, CH₂-pyrrolidine + NH₂), 1.76-1.96 (m, 1H, CH₂), 2.18-2.52 (m, 4H, 2CH₂-pyrrolidine), 3.21-3.25 (m, 1H, CH₂), 3.42-3.47 (m, 1H, CH), 3.79 (dd, 1H, $J_1 = 3.9$ Hz, $J_2 = 3.9$ Hz, CH), 3.99 (d, 1H, $J = 8.3$ Hz, CH), 7.07-7.37 (m, 15H, ArH); ¹³C-NMR (100 MHz, CDCl₃): δ (ppm): 144.33, 143.80, 129.08, 128.63, 128.56, 128.45, 128.38, 126.83, 60.38, 57.81, 54.88, 54.39, 54.30, 30.15, 24.22; HRMS (ESI⁺) calcd for C₂₅H₂₈N₂: 357.5185; found 357.5221.

General procedure for the Michael reaction of cyclohexanone and β -nitrostyrene

To a suspension of catalyst (0.15 equiv) and cyclohexanone (5 equiv) in 0.75 mL of DMSO and water (3 equiv) was added trans- β -nitrostyrene (1 equiv). The resulting mixture was allowed to stir at room temperature, whereupon the reaction was quenched with saturated aqueous ammonium chloride and the aqueous layers were extracted with ethyl acetate. The combined organic layers were dried over MgSO₄, filtered, and evaporated in vacuo and the resulting residue was purified by flash column chromatography using ethyl acetate/hexane (2:1). The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak AD-H). Relative and absolute configurations of the products were determined by comparison with the known ¹H-NMR, ¹³C-NMR, and chiral HPLC analysis.

(*S*)-2-((*R*)-2-nitro-1-phenylethyl)cyclohexanone (13a)

Colourless solid. $\alpha_D^{25} = -27.5$ (*c* 1.2, CHCl₃); mp 128-130 °C; IR (KBr) 3024, 2955, 2865, 1698, 1549, 1444, 1382 cm⁻¹; ¹H-NMR (CDCl₃): δ (ppm): 7.34-7.25 (m, 3H), 7.17 (d, $J = 7.3$ Hz, 2H), 4.94 (dd, $J_1 = 12.4$ Hz, $J_2 = 4.5$ Hz, 1H), 4.64 (dd, $J_1 = 12.3$ Hz, $J_2 = 10$ Hz, 1H), 3.76 (dt, $J_1 = 9.9$ Hz, $J_2 = 4.4$ Hz, 1H), 2.73-2.66 (m, 1H), 2.51-2.46 (m, 1H), 2.43-2.32 (m, 1H), 2.12-2.05 (m, 1H), 1.82-1.70 (m, 4H), 1.29-1.19 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ (ppm): 211.9, 137.7, 128.9, 128.2, 127.8, 78.9, 52.5, 43.9, 42.7, 33.2, 28.5, 25.0; The enantiomeric excess was determined by HPLC column (Daicel Chiralpak AD-H), Hexane:*i*-PrOH 90:10, UV 254 nm, flowrate 1 mL/min, $t_{minor} = 10.0$ min and $t_{major} = 12.8$ min. All the Michael addition products are known compounds. The absolute configuration of the products **13a-g** was determined by comparison with literature data: **13a**,²⁴ **13b**,²⁵ **13c-f**.²⁶

Results and discussion

As shown in Figure 2, the synthesis of novel *R*-phenylglycine derived organocatalysts **7-12** begins with the Cbz-protected *R*-phenylglycine. Treatment of Cbz-*R*-phenylglycine with indoline, pyrrolidine, or (*S*)-(-)-2-(diphenylmethyl)pyrrolidine by a modification of previously reported procedure²⁷ in the presence of dicyclohexylcarbodiimide (DCC) yielded compounds **4-6** in good to excellent (80%-85%) yields. Hydrogenolysis of **4-6** in the presence of 10% Pd/C deprotected the N-Cbz group to provide phenylglycine amides **7-9** in a nearly quantitative yield. The corresponding diamines **10-12** were then prepared by reduction of the *R*-phenylglycine amides **7-9** using excess LiAlH₄ in 50%-51% yields.²⁸

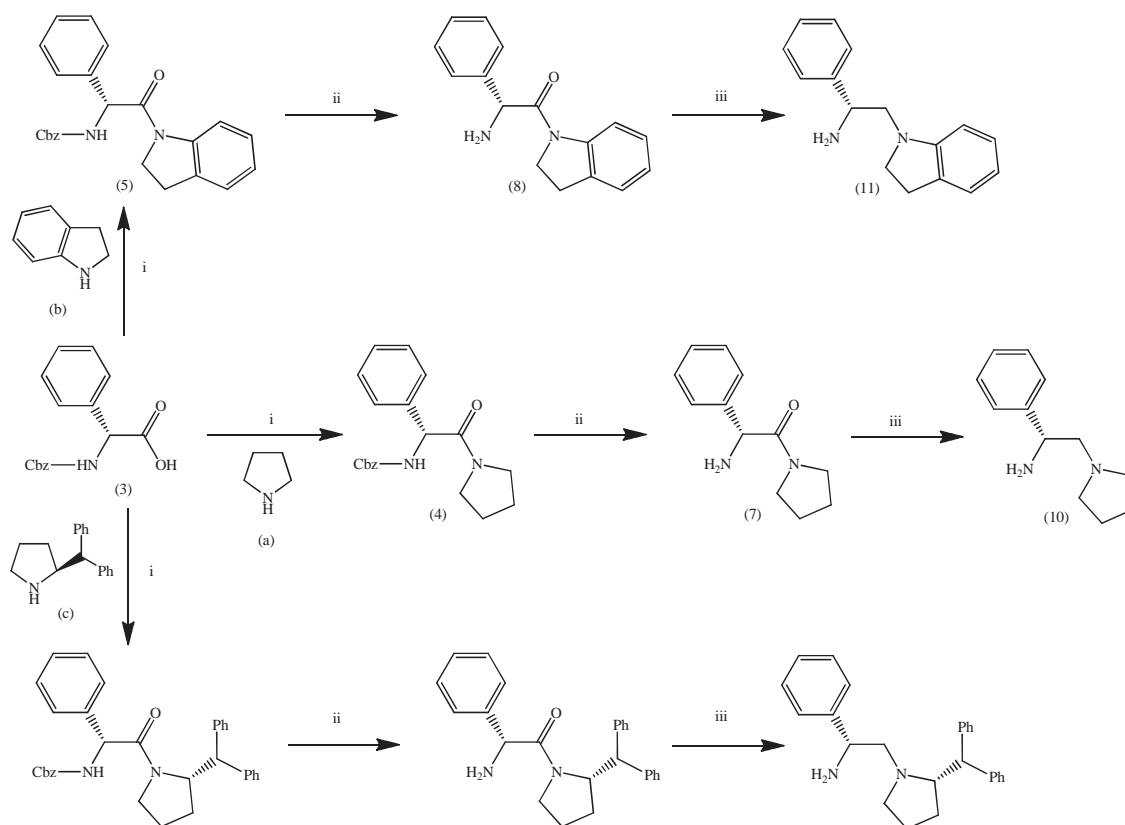


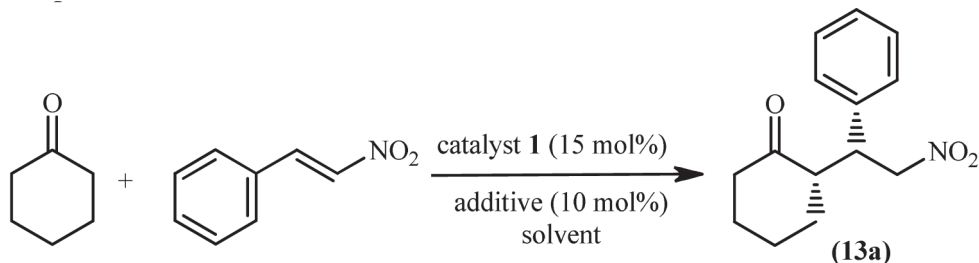
Figure 2. Synthesis of phenylglycine derivatives **3-12**. Reagents and conditions: (i) DCC, CH_2Cl_2 , reflux; (ii) Cyclohexene, Pd/C, EtOH; (iii) LiAlH_4 , THF, reflux.

With *R*-phenylglycine-derived receptors in hand, we then studied the catalytic properties of these receptors for the enantioselective Michael addition of cyclohexanone with β -nitrostyrenes, which is one of the most important C–C bond forming reactions in organic chemistry.

As a model reaction, the Michael addition of cyclohexanone to β -nitrostyrene was selected as model substrates in the presence of organocatalysts (15 mol %). We initially focused on solvent effects in the Michael reactions at ambient temperature. Organocatalyst **1** was first examined and high chemical yield (85%) but moderate enantioselectivity (51% ee) was observed in CHCl_3 (Table 1, entry 1) at room temperature, whereas using *i*-PrOH and H_2O resulted in similar yields and enantioselectivities (Table 1, entry 2 and 6). Furthermore, the use of a nonpolar solvent, such as toluene, slightly decreased the reactivity and enantioselectivity (43% ee, Table 1, entry 4). As shown in Table 1, the Michael addition proceeded smoothly in DMSO to afford the desired product in 80% yield with good stereoselectivity (81% ee and 94:6 d.r.) (Table 1, entry 8). It has been reported that the addition of a Brønsted acid and water in the reaction might accelerate the formation of the enamine intermediate and promote the catalytic cycle.²⁹ Despite higher diastereoselectivities being achieved, lower yields and poor enantioselectivities were observed in the presence of various organic acids (PhCOOH, *p*-TsOH or TFA) as additives (Table 1, entries 3, 5, 7, and 10). This may be due to the fact that the protonation of the amine catalyst subsequently hinders the enamine formation. To our delight, the addition of H_2O (3 equiv) slightly improved the reaction yield (90%) as well as significantly improving the enantioselectivity (87% ee) when the

reaction was carried out in DMSO (Table 1, entry 9). When decreased the loading of the catalyst to 10 mol%, a similar yield but lower diastereoselectivity and enantioselectivity was afforded (Table 1, entry 11).

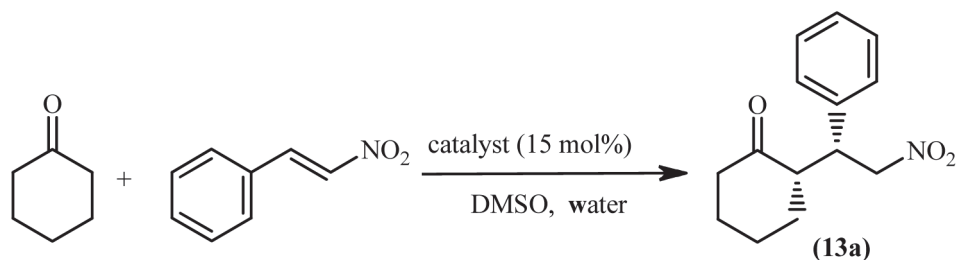
Table 1. Optimization of reaction conditions.



Entry	Solvent	Additive	Time [h]	Yield ^a [%]	d.r. ^b	ee ^c [%]
1	CHCl ₃	None	48	85	92:8	51
2	<i>i</i> -PrOH	None	96	75	94:6	49
3	<i>i</i> -PrOH	TFA	96	70	98:2	41
4	Toluene	None	72	76	91:9	43
5	Toluene	PhCOOH	72	72	93:7	35
6	H ₂ O	None	48	85	96:4	47
7	H ₂ O	<i>p</i> -TsOH	96	78	98:2	39
8	DMSO	None	72	80	94:6	81
9	DMSO-H ₂ O	None	48	90	93:7	87
10	DMSO-H ₂ O	<i>p</i> -TsOH	72	0	n.d. ^d	n.d. ^d
11 ^e	DMSO-H ₂ O	None	56	88	85:15	73

^aYield of isolated product after column chromatography on SiO₂. ^bDiastereomeric ratio, d.r. (*syn/anti*), determined by ¹H-NMR of crude product. ^cDetermined by chiral HPLC analysis (Chiralpak AD-H). The absolute configuration was determined by comparison with literature data. ^dNot determined. ^e10 mol% catalyst was used.

In order to optimize the reaction conditions, the above reaction was studied in the presence of chiral ligands **1**, **2**, **7-12** (15 mol%) and the results are summarized in Table 2. Organocatalysts were able to catalyze the reaction, but the activity and enantioselectivity differed significantly. Among the chiral catalysts examined, prolinamide **1** gave the best results in terms of chemical yield and enantiomeric excess due to the fact that the indoline moiety presumably plays an activating role in the reaction, and contributes to the enantiocontrol. Phenylglycine-derived catalysts **7-12** bearing primary amine groups gave relatively poor to moderate results when the reaction was carried out in DMSO-H₂O. Primary amines **11** and **12** tended to provide the desired products with good enantioselectivity compared with the other phenylglycine-derived organocatalysts. Compound **12** was found to be the best catalyst, giving the product in 88% yield with 76% enantiomeric excess (Table 2, entry 8). This is presumably due to the additional stereogenic center and steric hindrance caused by the presence of the phenyl groups. Not much improvement was observed in either the yield or the enantioselectivity when the reaction temperature was decreased to 0 °C (Table 1, entry 9-10).

Table 2. Screening of new chiral catalysts for asymmetric addition of cyclohexanone to trans- β -nitrostyrene.

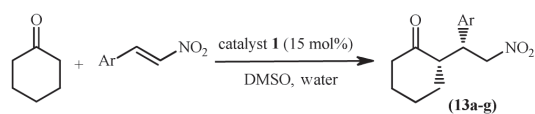
Entry	Catalyst	Time [h]	Yield ^a [%]	d.r. ^b	ee ^c [%]
1	1	48	90	93:7	87
2	2	72	88	83:17	56
3	7	56	86	96:4	14
4	8	72	85	97:3	13
5	9	56	82	92:8	8
6	10	72	84	95:5	39
7	11	48	80	91:9	53
8	12	72	88	91:9	76
9	1 ^d	72	85	90:10	85
10	12 ^d	96	75	85:15	72

^aYield of isolated product after column chromatography on SiO₂. ^bDiastereomeric ratio, d.r. (*syn/anti*), determined by ¹H-NMR of crude product. ^cDetermined by chiral HPLC analysis (Chiralpak AD-H). The absolute configuration was determined by comparison with literature data. ^dThe reaction was performed at 0 °C.

With the optimal reaction conditions realized, we further proceeded to examine a variety of nitroalkenes reacting with cyclohexanone to establish the general utility of this asymmetric transformation (Table 3). All reactions were performed in DMSO-H₂O in the presence of 15 mol% of catalyst **1**. Various aromatic substituted nitroalkenes reacted well with cyclohexanone donor to give the desired Michael products (**13a-g**) with 86%-92% yields and different enantioselectivities (Table 3, entries 1-7).

The introduction of various electron-withdrawing or electron-donating groups on the aromatic ring of the nitroolefine did not affect enantioselectivities or yields (86%-92%, Table 3, entries 1-4), with the sole exception of the highest enantioselectivity achieved with aromatic nitroolefine bearing an electron-withdrawing substituent (Table 3, entry 7).

The stereoselectivities can be explained by a plausible transition model proposed originally by Seebach and Golinski³⁰ as shown in Figure 3. In this model, the pyrrolidine moiety of the catalyst **2** reacts with cyclohexanone to form a nucleophilic enamine and the carbonyl oxygen directs the nitro group through hydrogen bonding via a hydrogen bond with H₂O to organize a favorable transition model. The attack of this enamine on the *Re*-face of the nitrostyrene leads to the formation of the observed major enantiomer of the *syn* diastereomer.

Table 3. Catalytic asymmetric Michael addition of cyclohexanone to different aromatic nitroolefines under optimized conditions.


Entry	Product	Time [h]	Yield ^a [%]	d.r. ^b	ee ^c [%]
1		48	90	93:7	87
2		56	88	92:8	43
3		48	86	96:4	50
4		72	92	75:25	75
5		56	88	94:6	55
6		72	86	93:7	35
7		48	88	91:9	90

^aYield of isolated product after column chromatography on SiO₂. ^bDiastereomeric ratio, d.r. (*syn/anti*), determined by ¹H-NMR of crude product. ^c Determined by chiral HPLC analysis (Chiralpak AD-H). The absolute configuration was determined by comparison with literature data.

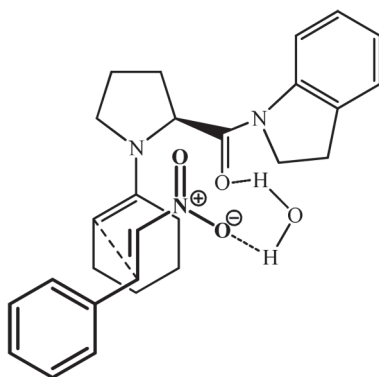


Figure 3. Proposed transition state.

Conclusion

The phenylglycine-based chiral receptors **7-12** were synthesized from commercially available *R*-phenylglycine conveniently. The Michael addition of cyclohexanone to nitroolefins was investigated using *R*-phenylglycine derivatives along with L-prolinamides as chiral catalysts. Among them, organocatalysts **1** and **12** gave the best results in terms of chemical yield and enantiomeric excess. Further studies of the catalytic system in other asymmetric C–C bond forming processes are currently underway.

Acknowledgments

We are grateful for the grants from the Scientific and Technological Research Council of Turkey (TÜBİTAK–109T167) and the Research Foundation of Selçuk University (BAP–09201134).

References

1. (a) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138-5175.
2. Chua, P. J.; Tan, B.; Zeng, X.; Zhong, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3915-3918.
3. (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877-1894; (b) Li, P.; Wang, L.; Wang, M.; Zhang, Y. *Eur. J. Org. Chem.* **2008**, 1157-1160.
4. Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267.
5. List, B.; Pojarliev, P.; Martin, H. *J. Org. Lett.* **2001**, *3*, 2423-2425.
6. (a) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559-2561; (b) Mosse, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559-2562.
7. Gu, L. Q.; Zhao, G. *Adv. Synth. Catal.* **2007**, *349*, 1629-1632.

8. (a) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2006**, *128*, 4966-4967; (b) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624-9625; (c) Vishnumaya, Singh, V. *Org. Lett.* **2007**, *9*, 1117-1119.
9. Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454-1455.
10. (a) Wang, J.; Li, H.; Duan, W. H.; Zu, L. S.; Wang, W. *Org. Lett.* **2005**, *7*, 4713-4716; (b) Tsogoeva, S. B.; Wei, S. W. *Chem. Commun.* **2006**, 1451-1453; (c) Lalonde, M. P.; Chen, Y. G.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 6366-6370.
11. (a) Li, H. M.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906-9907; (b) Ye, J. X.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481-4483.
12. (a) Luo, S.; Xu, H.; Mi, X.; Li, J.; Zheng, X.; Cheng, J. P. *J. Org. Chem.* **2006**, *71*, 9244-9247; (b) Yan, Z. Y.; Niu, Y. N.; Wei, H. L.; Wu, L. Y.; Zhao, Y. B.; Liang, Y. M. *Tetrahedron: Asymmetry* **2006**, *17*, 3288-3293.
13. (a) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84-96; (b) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611-614.
14. (a) Betancort, J. M.; Barbas, C. F. III. *Org. Lett.* **2001**, *3*, 3737-3740; (b) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F. III. *Org. Lett.* **2004**, *6*, 2527-2530; (c) Zhu, M. K.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491-493.
15. (a) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147-1168; (b) Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123-3135.
16. Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558-9559.
17. (a) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369-1371; (b) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077-3079; (c) Ni, B.; Zhang, Q.; Headley, A. D. *Tetrahedron: Asymmetry* **2007**, *18*, 1443-1447.
18. (a) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170-7171; (b) Cao, C. L.; Ye, M. C.; Sun, X. L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901-2904; (c) Cao, Y. J.; Lai, Y. Y.; Wang, X.; Li, Y. J.; Xiao, W. J. *Tetrahedron Lett.* **2007**, *48*, 21-24.
19. (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215; (b) García-García, P.; Ladépeche, A.; Halder, R.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 4719-4721; (c) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 4722-4724; (d) Zheng, Z.; Perkins, B. J.; Ni, B. *J. Am. Chem. Soc.* **2010**, *132*, 50-51; (e) Wu, J.; Ni, B.; Headley, A. D. *Org. Lett.* **2009**, *11*, 3354-3356.
20. (a) Meciarova, M.; Toma, S.; Sebesta, R. *Tetrahedron: Asymmetry* **2009**, *20*, 2403-2406; (b) Yacob, Z.; Shah, J.; Leistner, J.; Liebscher, J. *Synlett* **2008**, *15*, 2342-2344.
21. (a) Laars, M.; Ausmees, K.; Uudsemaa, M.; Tamm, T.; Kanger, T.; Lopp, M. *J. Org. Chem.* **2009**, *74*, 3772-3775; (b) Reddy, R. J.; Kuan, H. H.; Chou, T. Y.; Chen, K. *Chem. Eur. J.* **2009**, *15*, 9294-9298.
22. Naziroglu, H. N.; Durmaz, M.; Bozkurt S.; Sirit, A. *Chirality*, **2011**, *23*, 463-571.
23. Bhuniya, D.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1996**, *61*, 6108-6113.
24. Li, P.; Wang L.; Zhang Y.; Wang G. *Tetrahedron* **2008**, *64*, 7633-7638.
25. Syu, S.; Kao, T.; Lin, W. *Tetrahedron* **2010**, *66*, 891-897.

26. Alza, E.; Cambeiro, X. C.; Jimeno C.; Pericàs, M. A. *Org. Lett.* **2007**, *9*, 3717-3720.
27. Kobayashi, S.; Horibe, M. *Chem. Eur. J.* **1997**, *3*, 1472-1481.
28. Terakado, D.; Oriyama, T. *Org. Synth.* **2006**, *83*, 70-79.
29. Zhang, Q.; Ni, B.; Headley, A. D. *Tetrahedron* **2008**, *64*, 5091-5097.
30. Seebach, D.; Golinski, J. *Helv. Chim. Acta*, **1981**, *64*, 1413-1423.