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The Highly Enantioselective Bifunctional Organocatalysts for the Michael Addition of Cyclohexanone to Titroolefins[1]

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Abstract—A new family of organocatalyst derived from proline has been developed and shown to be an efficient catalyst for asymmetric Michael addition of cyclohexanone to nitroolefins with high diastereo- and enanthio -selectivities. (*syn: anti ratio* up to 99:1, *ee.* up to 95%.). The result of computational studies at the B3LYP/6-31G* level indicate that both the hydrogen bonding and the stereo hindrance play the crucial role in the activation of the nitro alkene and help to discriminate between the two diastereofacial approaches.

Keywords: asymmetric catalysis, Michael addition, proline, DFT

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Organocatalyzed asymmetric carbon-carbon bond-forming reactions have received recently a great deal of attention [1]. The Michael reaction is generally regarded as one of the most efficient and effective transformations in organic synthesis, and studies concerning this reaction have played an important role in the development of modern synthetic organic chemistry [2, 3]. Particularly, Michael addition reactions of nitroolefins with aldehydes and ketones are important methods for the synthesis of synthetically useful γ-nitrocarbonyl compounds, which serve as versatile building blocks for the preparation of complex organic substances. The nitro group in these substances can be readily converted into a variety of new functionalities including amines, nitrile oxides, ketones, and carboxylic acids [4].

Barbas and List independently reported the first organocatalytic addition of ketones to *trans*-β-nitro-styrene with proline as a catalyst with good yields but very low enantioselectivities (0–23% *ee*) [5, 6]. Recent investigations have examined the catalysis of the ketonenitroalkene conjugate addition reaction with derivatives of chiral diamines [7] , amino acids [8], and ionic liquids [9], but a significant amount of effort has been devoted to the modification of the proline motif. Many organocatalysts derived from proline have been investigated [10–27]. Although impressive progress towards improving stereoselectivity and substrate generality has been made, development of simple readily accessible bifunctional systems with improved catalytic activity remains of interest. In 2007, a series of 1,2-amino-alcohol-derived prolinamides **1** as bifunctional catalysts was evaluated for catalyzing the Michael addition, but showed moderate enantioselectivity (~30–80% *ee*) [22]. Herein, we report chiral diamines **2** containing hydroxyl group to catalyze the Michael addition with high diastereoselectivity and enantioselectivity (Fig. 1).

Catalysts **2** were prepared in good to excellent yields from N-Cbz-L-prolinol and the corresponding commercially available β-amino alcohols through the reaction sequence shown in Scheme 1**.**

Firstly, the model Michael reactions of cyclo-hexanone with *trans*-β-nitrostyrene catalyzed by organocatalyst **2a** were examined in various organic solvents and the observed results are summarized in Table 1. When **2a** catalyzed the reaction without protonic acid in different solvents, no Michael addition product was obtained (Table 1 entries 1, 5, 9), however, a quantitative amount of polymerization product was formed quickly in this reaction. Other studies have indicated that amines behave as initiators of polymerization, and Barbas's group have described that addition of Brønsted acids can promote the formation

[1] The text was submitted by the authors in English.

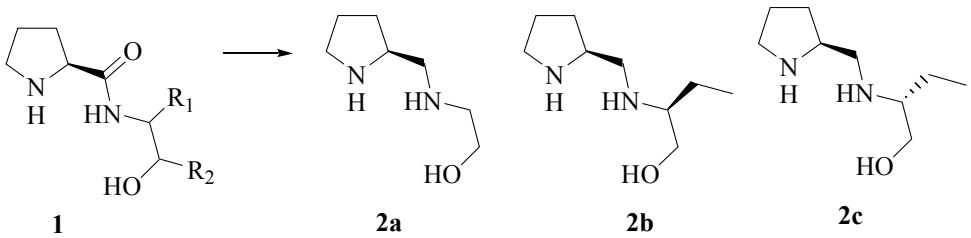


Fig. 1. Organocatalysts for the Michael addition.

of enamine thus inhibiting the polymerization. Therefore, several sulfonic and carboxylic acids were surveyed for their effect on the organocatalyst **2a** catalyzed Michael addition of cyclohexanone to nitrostyrene.

As indicated in Table 1, the addition of an acid efficiently improved the reaction. All the acids used led to the formation of the Michael addition product. In the presence of an acid the catalyst **2a** generally showed better stereochemical outcome than the reported catalyst **1** [22]. The highest enantioselectivity of 92% and high diastereoselectivity of 96:4 were observed in the presence of 20 mol % TFA for the reaction catalyzed by **2a** in DMSO (Table 1, entry 12).

Under the optimized reaction conditions, the chiral β-amino alcohol derivatives **2b** and **2c** as catalysts were also evaluated for the Michael addition. As show in Table 1, (*S*)- β-amino alcohol derivate **2b** showed slightly higher enantioselectivity (95% *ee*, Table 1, entry 15) than its' diastereoisomer **2c** (93% *ee*, Table 1, entry 16) and **2a**. These results indicated that the chirality of the stereogenic center of the side chain had little effect on the enantioselectivity and diastereoselectivity.

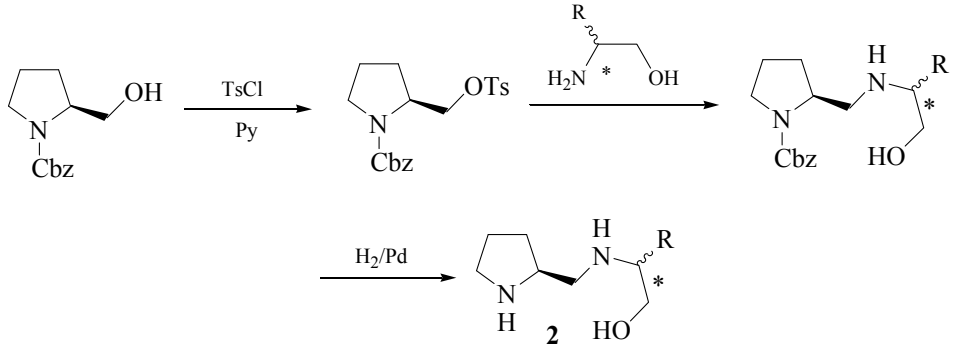
With the catalyst **2b** in hand, the Michael addition of cyclohexanone to a range of nitro-olefins was examined. The results are summarized in Table 2.

As shown in Table 2, cyclohexanone efficiently underwent Michael reactions with different aryl-substituted nitroolefins to give Michael adducts **3a–3h** in high yields with excellent enantio- (91–96% *ee*) and diastereoselectivities (*syn : anti* ratio up to 99 : 1). The results in Table 3 also show that the nature of the substituents on the aryl groups only slightly influences the yields and enatioselectivities. For nitroolefins with electron-rich groups (methyl and methoxy), the reaction proceeded smoothly to afford Michael adducts **3b, 3c** in excellent enantio- (95–97% *ee*) and diastereoselectivities (*syn : anti* ratio = 99 : 1) (Table 2, entries 2–3). For nitroolefins with electron-deficient groups, the Michael adducts **3d–3h** were also obtained in high yields (77–86%) with excellent enantio- (91–95% *ee*) and diastereoselectivities (*syn : anti*ratio up to 99 : 1) (Table 2, entries 4–8).

To account for the stereochemical outcome of the Michael reaction, the plausible transition-state model is proposed in Scheme 2 (Favorable TS). The amine and hydroxy groups were expected to interact by double hydrogen bonding with the nitro group of the electrophile in order to enhance their reactivity as depicted in the TS.

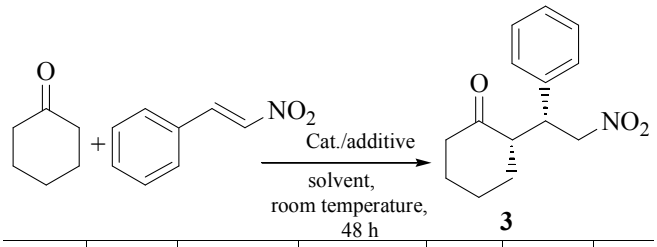
To gain a more detailed understanding of the origin of the high enantio- and diastereoselectivity of the

Scheme 1. Synthesis of bifunctional organocatalysts **2.**



2: R = H (a), R = Et C* (*S*) (**b**), R = Et C* (*R*) (**c**).

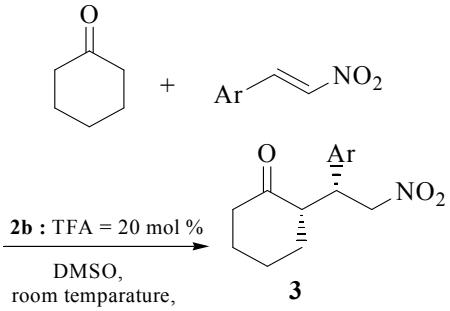
Table 1. Model Michael reaction



Entry[a]	Catalyst	Solvent	Additive	Yield, %[b]	*syn* : *anti* Ratio[c]	*ee* (*syn*)[d]
1	**2a**	MeOH	–	–	–	–
2	**2a**	MeOH	PhCOO	43	93 : 7	84
3	**2a**	MeOH	H	56	95 : 5	83
4	**2a**	MeOH	*p*-TsOH	61	98 : 2	79
5	**2a**	DMF	TFA	–	–	–
6	**2a**	DMF	–	64	98 : 2	90
7	**2a**	DMF	PhCOO	72	99 : 1	91
8	**2a**	DMF	H	69	97 : 3	88
9	**2a**	DMSO	*p*-TsOH	–	–	–
10	**2a**	DMSO	TFA	71	97 : 3	91
11	**2a**	DMSO	–	78	98 : 2	90
12	**2a**	DMSO	PhCOO	86	96 : 4	92
13	**2a**	CH_2Cl_2	H	79	95 : 5	81
14	**2a**	Toluene	*p*-TsOH	72	93 : 7	83
15	**2b**	DMSO	TFA	85	98 : 2	95
16	**2c**	DMSO	TFA	81	97 : 3	93

[a] 10 equiv of ketone, 20 mol % catalyst and 20 mol % additive. [b] Isolated yield. [c] Determined by Chiral HPLC. [d] Determined by Chiral HPLC.

Table 2. Michael reactions of ketones to nitroolefins

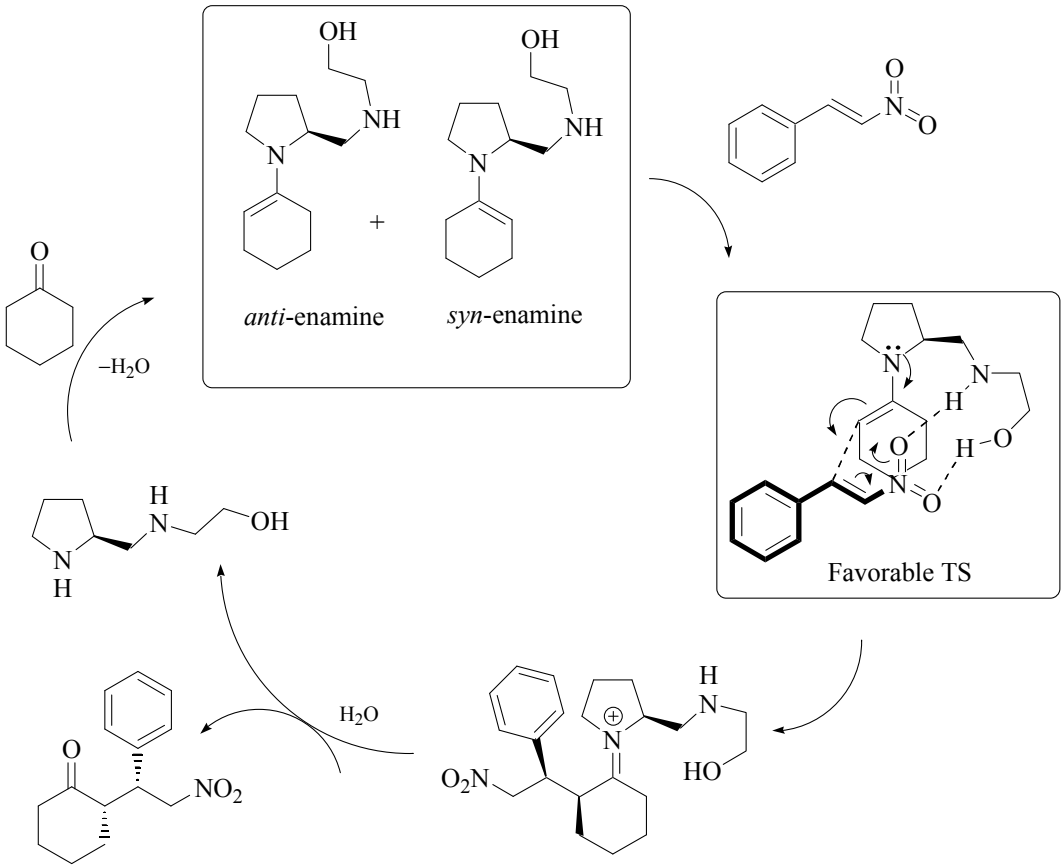


Entry	Ar	Product	Yield, %	*syn* : *anti* Ratio	*ee*, %
1	Ph	**3a**	85	98:2	95
2	4-Me-Ph	**3b**	86	97:3	97
3	4-OMe-Ph	**3c**	74	97:3	95
4	4-Cl-Ph	**3d**	82	99:1	96
5	2-Cl-Ph	**3e**	77	94:6	97
6	2,4-Cl-Ph	**3f**	86	98:2	97
7	4-NO_2-Ph	**3g**	83	93:7	93
8	2-NO_2-Ph	**3h**	85	95:5	91

processes catalyzed by **2**, we have computationally studied the transition states by density functional theory (DFT) at the B3LYP/6-31G* level. Firstly, the enamine formation is assumed to be a fast process thus has no effect on the stereoselectivity of the reaction. Secondly, the final hydrolysis step to recover the catalyst is also believed to be a low-energy barrier step. Therefore, we focused on the study of the transition states involved in the rate-limiting step the nucleophilic attack of the enamines. As shown in Scheme 2, the enamine intermediates can adopt *anti* and *syn* conformations and each of them has two different transition states existing for the approach of the nitropropene to the diastereotopical *Re* and *Si* faces of the enamine, resulting in the formation of four different transition states, two for each enantiomer (Fig. 2). The two transition states arising from the *anti* enamine (TS_A and TS_B) can benefit from hydrogen-bonding activation between the amine NH and the hydroxyl group presented in the prolinamine, and our initial hypothesis was that this interaction might contribute to a lowering in the energy barriers, resulting in faster reaction rates. Meanwhile, reaction through *syn*-enamine conformations would proceed without the help of hydrogen-bonding activation (TS_C and TS_D).

We located the four possible transition states and found that the lowest in energy (7.6 kcal/mol) corresponds to TSA, the one that leads to the experimentally observed *syn*-(2S,3R) enantiomer. According to our initial hypothesis, this result shows that both the amine NH and the hydroxyl group in the catalyst activate the nitroalkene by the concurrence of up to three hydrogen bonds, favouring the approach of the nitro alkene from the *Re* face of the *anti* enamine. The minor enantiomer *syn*-(2*R*, 3*S*) is formed through a *Si* approach of the nitro alkene to the *anti* enamine (TS_B), whose activation energy is 9.1 kcal/mol. As

Scheme 2. The proposed mechanism and transition state.



expected, the activation barriers of the other two transition states for *syn*-enamine (TS_C, TS_D) are much higher than those of their activated counterparts, because they cannot form the hydrogen bond. More detailed parameters are summarized in Table 3.

As shown in Table 3, the reason for the observed stereoselectivity is understandable in view of the hydrogen-bonding differences between TS_A and TS_B. In both cases, three hydrogen bonds formed between the two oxygens of the nitro group and amine NH and hydroxyl group. We can distinguish a strong hydrogen bond (O^3–H···O^1, 1.85 Å), and a weak bond (N^1–H···O^2, 2.65 Å) in TS_A, we also can find the similar intensity bond (O^3–H···O^1, 1.84 Å; N^1–H···O^1, 2.67 Å) in TS_B. But the TS_A shows another strong hydrogen bond (N^1–H···O^1, 2.02 Å) whereas TS_B shows relatively weaker bonds with larger distance for N^1–H···O^2 (2.25 Å). However, according to Alonso group's report [22], the similar hydrogen-bonding effect was also found in the structure of transition states which formed with catalyst **1**, so the hydrogen-bonding effect is not the main reason why catalyst **2** is better than their acid amide analogue **1**.

As shown in Table 3, the *Re* face arrangement of the reactant complex has a lower energy (1.8 kcal/mol) than its si counterpart. This higher energy of RC_{si} is more likely due to the stereo hindrance, in which C^3 methylene group is much closer to C^4 methylene group than in the re counterpart as displayed in Fig. 3. This is evidenced by the corresponding C^3–H···H–C^4 distance of 2.0 Å (in RC_{si}) and 2.36 Å (in RC_{re}) as listed in Table 3. The similar stereo hindrance effect can be found in the transition state structures (TS_A and TS_B) displayed in Fig. 3 and Table 3, the C^3–H···H–C^4 distance in TS_A (2.13 Å) is farther than TS_B (1.99 Å). We suggest the difference of stereo hindrance between TS_A and TS_B is another important beneficial to improve the stereo-selectivity. In comparison, the steric effect is not found in transition states which formed with acid-amide analogue **1** due to their C^4 carbonyl is a plane group [22]. In summary, these results of DFT study suggested that the stereo-

Table 3. Activation energies[a] and interatomic distances for the transition states calculated at the B3LYP/6-31G* level

State	Energy, kcal/mol	E_a, kJ/mol	Distances, Å					
			C^1–C^2	O^3–H···O^1	N^1–H···O^1	N^1–H···O^2	C^3···C^4	C^3–H···H–C^4
Reactant complex	0.0	–	4.00	1.92	2.80	2.43	3.46	2.36
TS_A	7.6	7.6	2.19	1.85	2.02	2.65	3.46	2.13
TS_C	11.4	11.4	2.01	–	–	–	–	–
RC_{si}	5.8	–	3.53	1.99	2.95	2.16	3.24	2.00
TS_B	14.9	9.1	2.06	1.84	2.68	2.25	3.22	1.99
TS_D	21.3	15.5	2.03	–	–	–	–	–

[a] Energies calculated at the B3LYP/6-31G*+ZPVE level.

hindrance effect (C^3 methylene–C^4 methylene) is the main reason why the amine-catalysts are better than their acid amine analogue.

In summary, a new family of organocatalysts which can be used to promote asymmetric Michael addition reactions of cyclohexanone to nitroolefins in high efficiency has been developed. Computational studies at the B3LYP/6-31G* level have been conducted on a model reaction, confirming the initial hypothesis that hydrogen bonding plays a crucial role in the activation of the nitro alkene and helping to distinguish between two diastereofacial approaches. The computationally favored transition state TS_A presents the strongest hydrogen bonds and, in accordance with the experimental results, leads to the observed major *syn*-(2*S*,3*R*) enantiomer. On the other hand, the preference of the *re* reaction path in ketone reactions seems to originate from the stereo hindrance between the bulky β-amino alcohol group in the catalyst and an alkyl group in the enamine intermediate. These results provide valuable insight into the mechanisms of asymmetric organocatalysis and might help the design of new and more efficient organocatalysts.

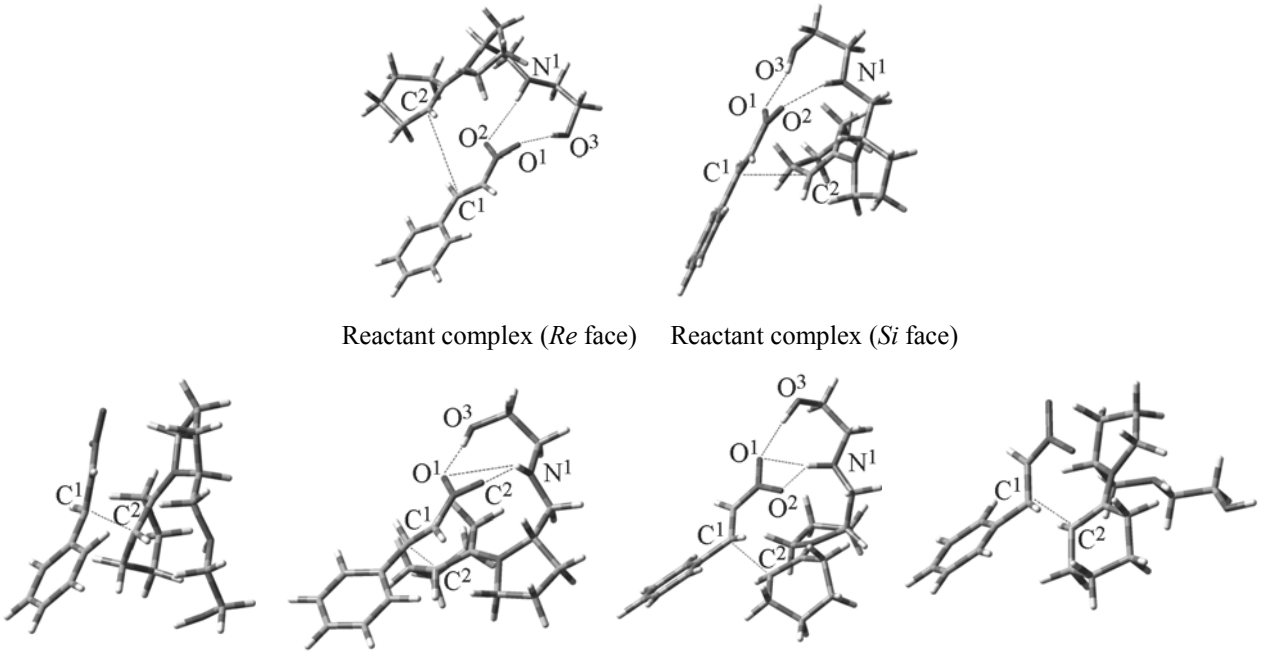
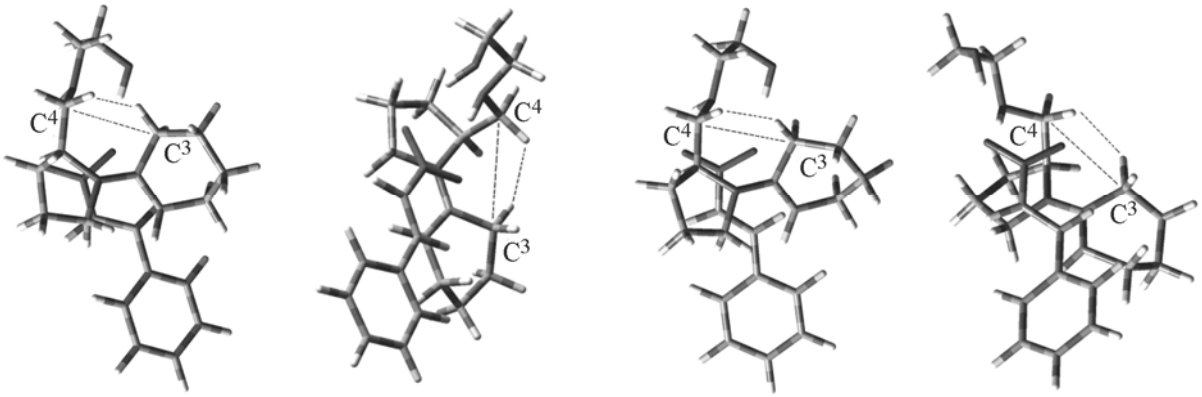


Fig. 2. Transition-state geometries and activation energies for the reaction between **4** and **5**, calculated at B3LYP/6-31G* level.



RC_{re} RC_{si} TS_A TS_B

Fig. 3. Stereo hindrance of reactant complexes and transition states.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Varian -500 instrument. Chemical shifts reported in ppm down field from Me_4S as internal standard. Mass spectra were recorded using electrospray ionization (ESI) on LCQ Advanted MAX Mass instruments. Optical rotations were tested on a WZZ-3 polarimeter using 10mL cell with a 1 dm path length and Autopol II polarimeter using 1 mL cell with a 1 dm path length. HPLC analysis was performed using ChiralPak AS-H column.

Commercial reagents were used without further purification. Analytical thin layer chromatography was performed on 0.20 mm silica gel plates and silica gel (200–300 mesh) was used for flash chromatography. Both were purchased from Qingdao Haiyang Chem. Company, Ltd.

Synthesis of catalyst 2 *(general procedure).* To a stirred solution of 5.5g (0.023 mol) Cbz- protected (*S*)-prolinol in 20 mL of pyridine a solution of 3.2 g (0.028 mol) TsCl in 20 mL of CH_2Cl_2 was added dropwise at 0°C. The reaction mixture was allowed to warm to room temperature and was stirred for further 18 h. The mixture was diluted with 50 mL of water, then the resulted mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers was washed with 1M HCl solution (2 × 25 mL) and brine (2 × 20 mL) then dried over anhydrous Na_2SO_4 and concentrated in vacuum to give the Cbz-protected (*S*)-prolinol tosylate (7.3 g, 99% yield). Then the tosylate was dissolved in 10 mL of corresponding β-amino alcohol. The reaction mixture was stirred at 50°C for 24 h. The excess amide was removed by vacuum distillation and the residue was chromatographed to give corresponding Cbz derivative. The crude product was dissolved in EtOH (20 mL) and 0.1 g of Pd/C (10%) was added. The reaction mixture was stirred at room temperature under H_2 (1 atm) overnight. Pd/C was filtered off and the solution was concentrated in vacuum. The residue was purified by flash chromatograhy on silica gel to give the desired product **2.**

(*S*)-2-(Pyrrolidin-2-ylmethylamino)ethanol (2a). Yield 73.1%, $[\alpha]_D$ = +13.4° (1.0 MeOH) ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.24–1.27 m (1H), 1.62–1.69 m (2H), 1.79–1.81 m (1H), 2.44–2.48 m (1H), 2.67 m (2H) 2.82–2.83 m (2H), 3.16 m (1H), 3.37 m (3H) 3.49–3.56 m (2H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.82, 29.87, 46.50, 51.91, 54.63, 58.51, 60.72. Mass spectrum: *m/z* 145.3158. Calculated: *M* 145.3147.

(*S*)-2-[(*S*)-pyrrolidin-2-ylmethylamino]butan-1-ol (2b). Yield 75.6%, $[\alpha]_D$ = +17.3° (1.1 MeOH) ^1H NMR spectrum ($CDCl_3$) δ, ppm: 0.87 t (3H, J = 7.5 Hz), 1.22–1.44 m (3H), 1.64–1.88 m (3H), 2.48–2.61 m (3H), 2.89 t (2H, J = 6.5 Hz), 3.20–3.30 m (5H), 3.52–3.55 d.d (1H, J_1 = 4.0 Hz, J_2 = 11.0 Hz) ^{13}C NMR spectrum ($CDCl_3$) δ_C, ppm: 10.78, 24.47, 25.89, 29.72, 46.46, 51.03, 59.02, 60.72, 63.10. Mass spectrum: *m/z* 173.4201. Calculated: *M* 173.4123.

(*R*)-2-[(*S*)-Pyrrolidin-2-ylmethylamino]butan-1-ol (2c). Yield 72.4%, $[\alpha]_D$ = +37.8° (1.0, MeOH) ^1H NMR spectrum ($CDCl_3$) δ, ppm: 0.89 t (3H, J = 7.5 Hz), 1.33–1.43 m (3H), 1.66–1.92 m (3H), 2.44–2.60 m (2H), 2.74dd (1H, J_1 = 4.0 Hz, J_2 = 12 Hz), 2.91–2.93 m (2H), 3.22–3.32 m (2H), 3.54–3.62 m (2H). ^{13}C NMR spectrum ($CDCl_3$) δ_C, ppm: 10.82, 24.66, 25.89,

29.69, 46.46, 51.67, 59.32, 61.12, 63.31. Mass spectrum: *m/z* 173.4148. Calculated: *M* 173.4123.

General experimental procedure for the Michael addition. To a solution of the amine catalyst (0.1 mmol), *p*-toluene sulfonic acid monohydrate (0.1 mmol) and the nitroalkene (0.5 mmol) in DMF (2 mL) was added cyclohexanone (5 mmol), and the solution was stirred at ambient temperature for 24 h except when noted otherwise. The solution was then concentrated at ambient temperature under reduced pressure and the residue was purified by flash column chromatography on silica gel. Alternatively, ethyl acetate (10 volumes) was added and the solution was washed with water, 1 N HCl, dried (Na_2SO_4) and concentrated to give the crude product which was purified by flash chromatography on silica gel.

The relative configurations of the products (*syn*- and *anti*-) were determined by comparison of HPLC data with those reported in the literature. The absolute configurations of the product and the e.e. were determined by comparison of HPLC retention times with those reported in the literature. The enantiomeric excess for products **3a–3g** was determined by chiral HPLC on a Chiralpack AS-H column (UV detection at 238 nm, hexane : 2-propanol = 90 : 10, as eluent, 0.7 mL/min).

(*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]cyclohexanone (3a). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10–1.23 m (1H), 1.43–1.73 m(4H), 1.97–2.05 m (1H), 2.26–2.45 m (2H), 2.57–2.66 m (1H), 3.65–3.73 m (1H), 4.56 d.d (1H, J = 12.5, 9.9 Hz), 4.87 d.d (1H, J = 12.5, 4.5 Hz), 7.07–7.28 m (5H). HPLC : t_r = 24.1 min (minor), 34.5 min (major).

(*S*)-2-[(*R*)-2-Nitro-1-p-tolylethyl]cyclohexanone (3b). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20–1.28 m (1H), 1.57–1.81 m (4H), 2.03–2.11 m (1H), 2.32 s (3H), 2.36–2.42 m (1H), 2.46–2.50 m (1H), 2.64–2.70 m (1H), 3.70–3.75 m (1H), 4.59–4.63 m (1H), 4.90–4.94 m (1H), 7.04 d (2H, J = 8.0 Hz), 7.12 d (2H, J = 8.0 Hz). HPLC: t_r = 16.7 min (minor), 29.6 min (major).

(*S*)-2-[(*R*)-1-(4-Methoxyphenyl)-2-nitroethyl]-cyclohexanone (3c). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.19–1.28 m (1H), 1.57–1.82 m (4H), 2.05–2.11 m (1H), 2.36–2.42 m (1H), 2.46–2.50 m (1H), 2.62–2.68 m (1H), 3.69–3.74 m (1H), 3.79 s (3H), 4.57–4.61 m (1H), 4.90–4.93 m (1H), 6.84 d (2H, J = 8.5 Hz), 7.06 d (2H, J = 8.5 Hz). HPLC: t_r = 42.2 min (minor), 68.6 min (major).

(*S*)-2-[(*R*)-1-(2-Chlorophenyl)-2-nitroethyl]-cyclohexanone (3d). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30–1.38 m (1H), 1.59–1.85 m(4H), 2.09–2.14 m (1H), 2.37–2.43 m (1H), 2.47–2.51 m (1H), 2.90–2.97 m (1H), 4.27–4.31 m (1H), 4.87–4.94 m (2H), 7.20–7.25 m (3H), 7.38–7.39 m (1H). HPLC: t_r = 20.2 min (minor), 27.7 min (major).

(*S*)-2-[(*R*)-1-(4-Chlorophenyl)-2-nitroethyl]-cyclohexanone (3e). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.19–1.28 m (1H), 1.57–1.83 m(4H), 2.08–2.13 m (1H), 2.35–2.42 m (1H), 2.46–2.51 m (1H), 2.63–2.68 m (1H), 3.74–3.79 m (1H), 4.59–4.63 m (1H), 4.92–4.96 m (1H), 7.11–7.14 m (2H), 7.29–7.32 m (2H). HPLC: t_r = 21.1 min (minor), 35.1 min (major)

(*S*)-2-[(*R*)-1-(2,4-Dichlorophenyl)-2-nitroethyl]-cyclohexanone (3f): ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30–1.38 m (1H), 1.60–1.86 m (4H), 2.10–2.15 m (1H), 2.35–2.42 m (1H), 2.46–2.51 m (1H), 2.84–2.92 m (1H), 4.11–4.24 m (1H), 4.86–4.92 m (2H), 7.17 d (1H, J = 8.0 Hz), 7.23 d.d (1H, J_1 = 8.0 Hz, J_2 = 2.0 Hz), 7.41 d (1H, J = 2.0 Hz). HPLC: t_r = 16.5 min (minor), 25.1 min (major)

(*S*)-2-[(*R*)-2-Nitro-1-(2-nitrophenyl)ethyl]-cyclohexanone (3g). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.19–1.28 m (1H), 1.57–1.82 m (4H), 2.05–2.11 m (1H), 2.36–2.42 m (1H), 2.46–2.50 m (1H), 2.62–2.68 m (1H), 3.69–3.74 m (1H), 3.79 s (3H), 4.57–4.61 m (1H), 4.90–4.93 m (1H), 6.84 d (2H, J = 8.5 Hz), 7.06 d (2H, J = 8.5 Hz). HPLC: t_r = 37.4 min (minor), 78.6 min (major).

Computational methods. DFT calculations were carried out with Gaussian 09 package [28]. The transition structure were fully optimized by B3LYP [29–31] method using 6-31G* basis set and have been confirmed to be a transition state geometry by the harmonic frequencies calculations at the same level of theory. The transition state was verified by the existence of imaginary frequency and the connectivity between the reactant and transition sate confirmed by intrinsic reaction coordinate (IRC) calculation [32].

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