(S)-2,2,6,6-Tetramethyl-N-(pyrrolidin-2-ylmethyl)piperidin-4-amine as an efficient organocatalyst for asymmetric Michael addition

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A new organocatalyst derived from proline has been developed and shown to be an efficient catalyst for asymmetric Michael addition reactions of cyclohexanone to nitroolefins with high diastereo- and enantio -selectivities. (*syn: anti* up to 99:1, ee. up to 93%.).

Keywords: asymmetric catalysis, Michael addition, ketones, proline

Recently organocatalysed asymmetric carbon–carbon bond-forming reactions have received a great deal of attention.[1] The Michael reaction is generally regarded as one of the most efficient and effective transformation and studies concerning this reaction have played an important role in the development of modern synthetic organic chemistry.[2] 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 targets. The nitro group in these substances can be readily converted into a variety of new functionalities including amines, nitrile oxides, ketones, and carboxylic acids.[3] Barbas[4] and List[5] independently reported the first organocatalytic addition of ketones to *trans*-β-nitrostyrene with L-proline as the catalyst with good yields but very low enantioselectivities (0–23% ee). Since the preliminary studies, many organocatalysts derived from proline have been reported to exhibit high activities and excellent enantioselectivities for this reaction[6–16]. In previous studies, the sterically bulky property was used as a general strategy for designing the new catalysts[17,18]. We report here (S)-2, 2, 6, 6-tetramethyl-N-(pyrrolidin-2-ylmethyl) piperidin-4-amine **1**, which contains a sterically bulky group, to catalyse the Michael addition with high diastereoselectivity and enantioselectivity (Scheme 1).

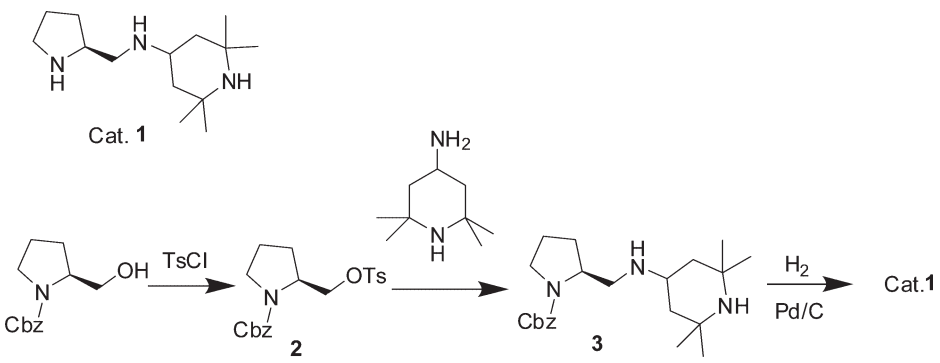
Results and discussion

Catalyst **1** was prepared in good yields from N-Cbz-L-prolinol and the corresponding commercially available 2,2,6,6-tetramethylpiperidin-4-amine through the reaction sequence shown in Scheme 1. Firstly, the model Michael reactions of cyclohexanone with *trans*-β-nitrostyrene catalysed by organocatalyst **1** were examined in various organic solvents and the observed results were summarised in Table 1. When **1** catalysed the reaction without protonic acid in different solvents, we could not obtain the Michael product (Table 1 entries 1, 5 and 9), because a quantitative amount of polymerisation product of 5 was formed quickly under these reaction conditions. Other studies have indicated that amines behave as initiators of polymerisation, Barbas's group have reported that the addition of Brønsted acids can promote the formation of enamines thus inhibit the polymerisation. Several sulfonic and carboxylic acids were surveyed for their effect on the organocatalyst **1** catalysed Michael addition of cyclohexanone **4** to nitrostyrene **5**. As indicated in Table 1, the addition of an acid efficiently improved the reaction. The highest enantioselectivity of 90% and high diastereoselectivity of 96:4 were observed in the presence of 20 mol % TFA for the reaction which was catalysed by **1** in DMSO (Table 1, entry 12).

Under the optimised reaction conditions, the Michael addition of cyclohexanone to a range of nitro-olefins was examined. As show in Table 2, cyclohexanone efficiently underwent Michael reactions with different aryl-substituted nitroolefins to give Michael adducts **6a–g** in high yields with excellent enantio-(85–91% 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 **6b–c** in excellent enantio-(90–93% ee) and diastereoselectivities (*syn/anti* 99/1) (Table 2, entries 2–3). For nitroolefins with electron-deficient groups, the Michael adducts **6d–g** were also obtained in high yields (77–86%) with excellent enantio- (85–90% ee) and diastereoselectivities (*syn/anti* ratio up to 99/1) (Table 2, entries 4–7).

To account for the stereochemical outcome of the Michael reaction, a plausible transition-state model is proposed in Fig. 1. The **R** group occupies a large space to efficiently shield the *si*-face of an enamine double bond, which might be a possible reason for the high stereochemical outcome.

In conclusion, we have designed and prepared a chiral diamine **1**, which effectively catalysed the Michael addition of cyclohexanone to nitroolefins in high yields with excellent diastereo- and enantioselectivity.



Scheme 1 Preparation of organocatalyst **1**.

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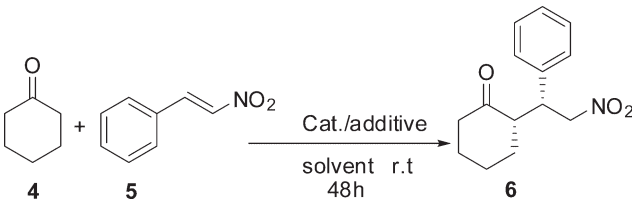
Table 1 Model Michael reaction

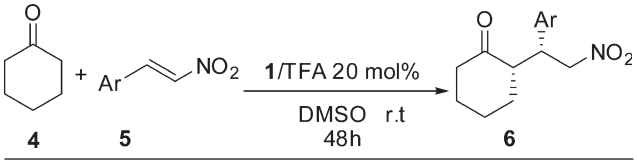


4 5 6

Entry[a]	Catalyst	Solvent	Additive	Yield /%[b]	*syn/anti*[c]	*ee(syn)* /%[d]
1	**1**	MeOH	–	–	–	–
2	**1**	MeOH	PhCOOH	41	92:8	80
3	**1**	MeOH	pTsOH	53	91:9	81
4	**1**	MeOH	TFA	66	98:2	79
5	**1**	DMF	–	–	–	–
6	**1**	DMF	PhCOOH	63	98:2	86
7	**1**	DMF	pTsOH	62	99:1	85
8	**1**	DMF	TFA	79	98:2	87
9	**1**	DMSO	–	–	–	–
10	**1**	DMSO	PhCOOH	76	97:3	88
11	**1**	DMSO	pTsOH	73	98:2	86
12	**1**	DMSO	TFA	85	96:4	90
13	**1**	CH_2Cl_2	TFA	79	95:5	79
14	**1**	Toluene	TFA	72	93:7	84

[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



4 5 6

Entry	Ar	Product	Yield/%	*Syn:anti*	ee/%
1	Ph	**6a**	81	96:4	90
2	4-Me-Ph	**6b**	83	98:2	93
3	4-OMe-Ph	**6c**	76	95:5	90
4	2-Cl-Ph	**6d**	81	98:2	85
5	4-Cl-Ph	**6e**	77	94:6	87
6	2,4-Cl-Ph	**6f**	86	99:1	90
7	2-NO_2-Ph	**6g**	81	93:7	89

[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.

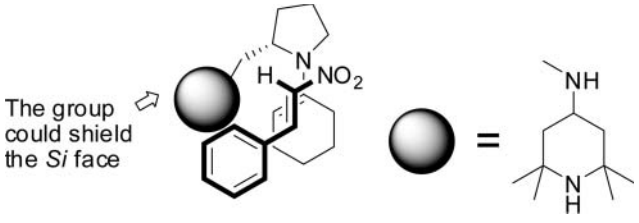


Fig. 1 Proposed transition state.

Experimental

Reagents and solvents were obtained from commercial suppliers. All reactions were carried out under air and monitored by TLC using commercial aluminum-backed silica gel plates. The ultrasonic reactions were performed in ultrasonic cleaner (KQ5200DE, 70W) with frequency of 40 MHz. Melting points were observed on YRT-3 Melting Point Tester and are uncorrected. NMR spectra were recorded on Varian Inova-400/500 MHz NMR spectrometer with TMS as an internal reference. MS were recorded on a LCQ Advanted MAX mass spectrometer. Silica gel (200–300 mesh) was used for the oxidation reactions and column chromatography. HPLC analysis was measured using ChiralPak AS-H column.

Synthesis of catalyst **1**

A stirred solution of Cbz- protected (S)-prolinol 5.5 g (0.023 mol) in pyridine 20mL was cooled to 0 °C. Then a solution of TsCl 3.2 g (0.028 mol) in CH_2Cl_2 (20 mL) was added dropwise to the above solution. After allowing the reaction temperature to rise to r. t., the reaction mixture was stirred for 18 h. The mixture was diluted with water (50 mL) and then the resulted mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with 1M HCl solution (25 mL×2) and brine (20 mL×2) then dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the Cbz-protected (S)-prolinol tosylate **2**. (7.3 g, 99 % yield). Then the tosylate **2** was dissolved in 2,2,6,6-tetramethylpiperidin-4-amine (10 mL). The reaction mixture was stirred at 50 °C for 24 h. The excess amine was recovered by vacuum distillation and the residue was chromatographed to give the intermediate **3**. The crude product was dissolved in EtOH (20mL) and the 0.1 g Pd/C (10%) was added. The reaction mixture was stirred at r.t under 1atm H_2 overnight. The Pd/C was filtered and the solution was concentrated *in vacuo*. The residue was purified by flash chromatograhy on silica gel to give the desired product **1**.

(S)-2,2,6,6-Tetramethyl-N-(pyrrolidin-2-ylmethyl)piperidin-4-amine (**1**): Yellow oil, $[\alpha]_D^{rt}$ = +33.4o (1.0, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.80–0.87(2H, m), .09(6H, s), 1.16(6H, s), 1.28–1.36 (1H, m), 1.69–1.88(7H, m), 2.49–2.53(1H, m), 2.67(1H, dd, J_1 = 4.5H 1z, J_2 = 11.5Hz), 2.84–2.91(3H, m), 3.17–3.22(1H, m).^{13}C NMR (125 MHz, CDCl3) δ: 25.97, 28.88, 28.90, 35.26, 35.28, 46.38, 46.41, 46.70, 50.27, 51.27, 52.17, 58.89. HRMS (ESI) Calcd for [M+H]+: $C_{14}H_{30}N_3$, *m/z* 240.2434; found 240.2440.

Michael addition; general procedure

Cyclohexanone (5 mmol) was added to a solution of the amine catalyst **1** (0.1 mmol), TFA (0.1 mmol) and the nitroalkene (0.5 mmol) in DMSO (2 mL) and the solution was stirred at room temperature for 24 h except when noted otherwise. The solution was then concentrated at room 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, 1N HCl, dried (Na_2SO_4) and concentrated to give the crude product which was purified by flash chromatography on silica gel. Compounds **6a–g** reported in Table 2 (entries 1–8) are known in literature and our spectroscopic data are in agreement with published data[19].

(S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone (**6a**): ^{1}H NMR (500 MHz, CDCl3) δ 1.10–1.23 (1H, m), 1.43–1.73 (4H, m), 1.97–2.05 (1H, m), 2.26–2.45 (2H, m), 2.57–2.66 (1H, m), 3.65–3.73 (1H, m), 4.56 (1H, dd, *J* 12.5, 9.9 Hz), 4.87 (1H, dd, *J* = 12.5, 4.5 Hz), 7.07–7.28 (5H, m); The enantiomeric excess was determined by chiral HPLC with a Chiralpack AS-H column at 238nm (hexane:2-propanol 90:10), 0.7 mL min^{-1}; t_r = 24.1min (minor), 34.5 min (major).

(S)-2-((R)-2-Nitro-1-p-tolylethyl)cyclohexanone (**6b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20–1.28 (1H, m), 1.57–1.81 (4H, m), 2.03–2.11 (1H, m), 2.32 (3H, s), 2.36–2.42 (1H, m), 2.46–2.50 (1H, m), 2.64–2.70 (1H, m), 3.70–3.75 (1H, m), 4.59–4.63 (1H, m), 4.90–4.94 (1H, m), 7.04 (2H, d, *J* = 8.0 Hz), 7.12 (2H, d, *J* = 8.0 Hz). The enantiomeric excess was determined by chiral HPLC with a Chiralpack AS-H column at 238nm hexane: 2-propanol (90:10), 0.7 mL min^{-1}; t_r = 16.7min (minor), 29.6 min (major).

(S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (**6c**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19–1.28 (1H, m), 1.57–1.82 (4H, m), 2.05–2.11 (1H, m), 2.36–2.42 (1H, m), 2.46–2.50 (1H, m), 2.62–2.68 (1H, m), 3.69–3.74 (1H, m), 3.79 (3H, s), 4.57–4.61 (1H, m), 4.90–4.93 (1H, m), 6.84 (2H, d, *J* = 8.5 Hz), 7.06 (2H, d, *J* = 8.5 Hz). The enantiomeric excess was determined by chiral HPLC with a Chiralpack AS-H column at 238nm (hexane: 2-propanol 90:10), 0.7 mL min^{-1}; t_r = 42.2min (minor), 68.6 min (major).

(S)-2-((R)-1-(2-Chlorophenyl)-2-nitroethyl)cyclohexanone (**6d**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30–1.38 (1H, m), 1.59–1.85 (4H, m), 2.09–2.14 (1H, m), 2.37–2.43 (1H, m), 2.47–2.51 (1H, m), 2.90–2.97 (1H, m), 4.27–4.31 (1H, m), 4.87–4.94 (2H, m), 7.20–7.25 (3H, m), 7.38–7.39 (1H, m). The enantiomeric excess was determined by chiral HPLC with a Chiralpack AS-H column at 238nm (hexane:2-propanol 90:10), 0.7 mL min^{-1}; t_r = 20.2min (minor), 27.7 min (major).

(S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (**6e**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19–1.28 (1H, m), 1.57–1.83 (4H, m), 2.08–2.13 (1H, m), 2.35–2.42 (1H, m), 2.46–2.51 (1H, m), 2.63–2.68 (1H, m), 3.74–3.79 (1H, m), 4.59–4.63 (1H, m), 4.92–4.96 (1H, m), 7.11–7.14 (2H, m), 7.29–7.32 (2H, m). The enantiomeric excess was

determined by chiral HPLC with a Chiralpack AS-H column at 238nm (hexane:2-propanol 90:10), 0.7 mL min^{-1}; t_r = 21.1min (minor), 35.1 min (major)

(S)-2-((R)-1-(2,4-Dichlorophenyl)-2-nitroethyl)cyclohexanone (**6f**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30–1.38 (1H, m), 1.60–1.86 (4H, m), 2.10–2.15 (1H, m), 2.35–2.42 (1H, m), 2.46–2.51 (1H, m), 2.84–2.92 (1H, m), 4.11–4.24 (1H, m), 4.86–4.92 (2H, m), 7.17 (1H, d, J = 8.0 Hz), 7.23 (1H, dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz), 7.41 (1H, d, J = 2.0 Hz). The enantiomeric excess was determined by chiral HPLC with a Chiralpack AS-H column at 238nm (hexane:2-propanol 90:10), 0.7 mL min^{-1}; t_r = 16.5min (minor), 25.1 min (major)

(S)-2-((R)-2-Nitro-1-(2-nitrophenyl)ethyl)cyclohexanone (**6g**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19–1.28 (1H, m), 1.57–1.82 (4H, m), 2.05–2.11 (1H, m), 2.36–2.42 (1H, m), 2.46–2.50 (1H, m), 2.62–2.68 (1H, m), 3.69–3.74 (1H, m), 3.79 (3H, s), 4.57–4.61 (1H, m), 4.90–4.93 (1H, m), 6.84 (2H, d, J = 8.5 Hz), 7.06 (2H, d, J = 8.5 Hz). The enantiomeric excess was determined by chiral HPLC with a Chiralpack AS-H column at 238nm (hexane:2-propanol 93:7), 0.7 mL min^{-1}; t_r = 37.4min (minor), 78.6 min (major).

Received 2 April 2012; accepted 27 April 2012
Paper 1201242 doi: 10.3184/174751912X13383120111261
Published online: 8 August 2012

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