Tetrahedron 67 (2011) 1171–1177

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Pyrrolidine-linker-camphor assembly: bifunctional organocatalysts for efficient Michael addition of cyclohexanone to nitroolefins under neat conditions

Shaik Anwar, Pei-Hsun Lee, Tsai-Yung Chou, Chihliang Chang, Kwunmin Chen *

Department of Chemistry, National Taiwan Normal University, Taipei 116, Taiwan, ROC

ARTICLE INFO

Article history:
Received 27 October 2010
Received in revised form 24 November 2010
Accepted 30 November 2010
Available online 4 December 2010

Keywords:
Michael addition
Nitroolefins
Camphor
Linker
Organocatalysis

ABSTRACT

A simple and convenient strategy was developed to synthesize a new class of pyrrolidinyl–camphor based bifunctional organocatalysts possessing varying functional linkers. Catalytic screening of these camphor–pyrrolidine linked derivatives for asymmetric Michael reaction of cyclohexanone with β-nitrostyrene was carried out. Various aryl- and heteroaryl-nitroolefins, ketones as well as aldehydes gave the corresponding Michael adducts in high chemical yields (up to 95%) and exceptionally high diastereo- (*syn*/*anti* up to 99:1) and enantioselectivity (up to 95%) using catalyst **6** under solvent-free conditions.

1. Introduction

Michael reaction of ketones with nitroolefins represents an unquestionable convenient access to γ-nitroketones, which are valuable building blocks in organic synthesis.[1] The adducts serve as useful precursors for various functionalized organic compounds that are found to be pharmacologically active and can selectively block presynaptic dopamine receptors.[2] Much attention has been directed toward the design and application of organocatalysts recently.[3] Of the developed organocatalysts in asymmetric catalysis,[4] proline and its derivatives have proven to be effective protocols via the enamine catalysis.[5,6] The organocatalytic asymmetric Michael addition of a carbonyl compound with nitroolefins was pioneered by List and Barbas independently.[3h,i] Later on Alexakis[3j] and Kotsuki[3f] have shown that 2,2′-bipyrrolidine and pyrrolidine–pyridine systems could serve as powerful asymmetric catalysts. Most of the organocatalytic reactions require the use of organic solvents, i.e., DMSO, DMF, *i*-PrOH, MeOH, hexanes, toluene, and $CHCl_3$, which are not environmentally friendly. Historically, the metric to measure reaction success has been the chemical yield. Although chemical yields will remain imperative, alternative measures include the 'greenness' of a reaction, or *E* factor,[7a] and the volume productivity.[7b] The *E* factor, introduced by Sheldon, is defined as the ratio of the weight of waste to the weight of product, while the volume productivity is the grams of product per liter of reaction medium. The *E* factor for many pharmaceuticals has been estimated to exceed 100.[7c,d] The largest contributors to the magnitude of *E* factor are organic solvents, many of which are ecologically harmful and require expensive remediation. A pressing challenge facing organic chemists, therefore, is to advance new processes that are not only efficient, selective, and of high yielding but also environmentally friendly.[7e] An alternative strategy to reduce the *E* factor of reactions and their impact on the environment is to conduct the reaction under solvent-free conditions. Among the benefits of solvent-free processes are cost savings, decreased energy consumption, reduced reaction times, and a large reduction in reactor size and capital investment. The study of asymmetric catalysis under solvent-free conditions was inspired by the potential environmental benefits and the economic incentives. In addition, solvent-free Michael addition of cyclohexanone to nitrostyrene is a convenient access to important intermediates in organic synthesis.[8,9] Accordingly considerable efforts have been directed toward the development of organocatalytic systems in solvent-free conditions. Representative catalysts include pyrrolidine based phosphine oxide,[3a] aliphatic-aromatic diamine,[8a] recyclable pyrrolidine systems,[8b,e,f,h] thiourea derivatives,[8d,i] and chiral ionic liquids.[9b–e] Most of the above mentioned catalysts suffer from the limitations of long reaction time, high molecular weight, and tedious catalyst preparation. The development of alternative trivial and eco-friendly organocatalysts for Michael addition is desirable.

* Corresponding author. Tel.: +886 2 7734 6150; fax: +886 2 2932 4249; e-mail address: kchen@ntnu.edu.tw (K. Chen).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.11.093

2. Results and discussion

2.1. Design and preparation of organocatalysts

In this advancing field of organocatalysis, there has always been a high demand for more diverse organocatalysts encompassing the qualities of enhanced stereoselectivity, inert to air as well as water and easy preparation using readily accessible inexpensive starting materials. Over the past few years, we have been actively involved in the development of a series of camphor-based pyrrolidinyl organocatalysts.[10] These pyrrolidine linked camphor assembly have proven efficacies in organocatalytic asymmetric synthesis. The fundamental idea in designing these pyrrolidine–camphor based catalysts relies on the assumption that the pyrrolidine moiety plays a crucial role in enamine formation. The nucleophilic component is accompanied by a rigid bicyclic camphor scaffold that serves as an efficient stereocontrolling element.[11] In addition, with these pyrrolidine–camphor derived organocatalysts available, we would like to study the structure–stereoselectivity relationship. We would like to assess the impact of the linker functionality between the camphor skeleton and the pyrrolidine ring on the stereoselectivity of the reaction.

In these catalytic systems the pyrrolidine structural unit and camphor scaffold were linked with appropriate functionalities, such as amine, amide, and sulfide linkers (Fig. 1). We were interested to see whether the variation in the linker functionality will have an impact on the stereoselectivity of the reaction. We have also presumed that modification in the linker via various functionalities may contribute significantly toward the diastereo- and enantioselectivity of the reaction. Preliminary screening of these pyrrolidinyl–camphor bifunctional organocatalysts led to the conclusion that, the newly designed organocatalyst **6** showed promising results. The reaction of cyclohexanone **7a** with various aryl- and heteroaryl-nitroolefins proceeded smoothly with excellent diastereoselectivities (up to 99:1 *syn*/*anti*) and with good to excellent enantioselectivities (up to 95% ee) during the asymmetric transformation.

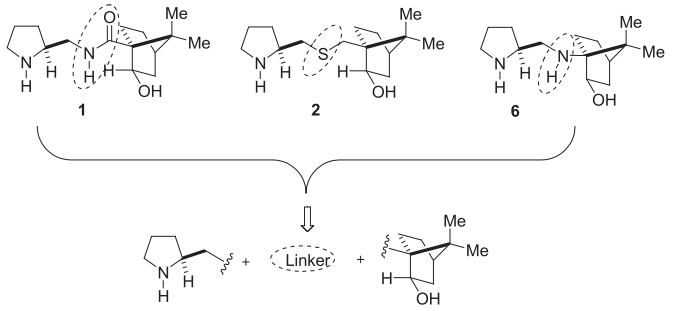


Fig. 1. Structures of various pyrrolidinyl–camphor based organocatalysts.

The organocatalysts **1** and **2** were easily prepared on a gram scale quantities by means of standard protocols developed previously in our laboratory.[10c,e,g] The preparation of the organocatalyst **6** starts with reductive amination of (*S*)-*tert*-butyl 2-formylpyrrolidine-1-carboxylate **3** and aminoketone **4**.[12] The reductive amination was successfully carried out using a mild reducing system of Ti(*i*-PrO)$_4$ and NaBH$_4$. The reaction proceeds through an intermediate titanium(IV) complex, which is either reduced directly or via equilibration of transient iminium species.[13] This synthetic route preparation can be carried out with ease for up to a quantity of 4.0 g without any difficulty. The Boc-protected procatalyst **5** obtained, can be easily deprotected by a known standard protocol using TFA–DCM to inherit the pyrrolidine–camphor based catalyst **6** with a chemical yield of 79% (Scheme 1).

The structure of the newly designed catalyst **6** was fully characterised by IR, ^{1}H, ^{13}C NMR, HRMS analyses and the absolute stereochemistry was further confirmed by a single X-ray structure analysis (Fig. 2).[18]

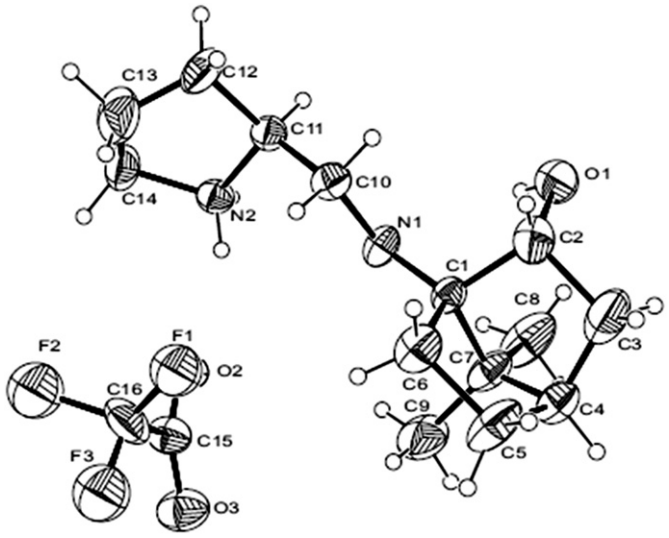


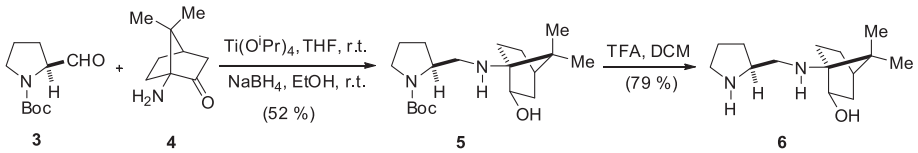
Fig. 2. ORTEP diagram of pyrrolidinyl–camphor based organocatalyst **6** as a TFA salt.

2.2. Screening of organocatalysts and optimization of reaction conditions

Catalytic screening for the previously developed and the newly designed pyrrolidine–camphor based organocatalyst **6** was carried out (Table 1). It was found that organocatalysts **1**, **2**, and **6** catalyzed the reaction of cyclohexanone **7a** with *trans*-β-nitrostyrene **8a** conveniently under neat conditions.

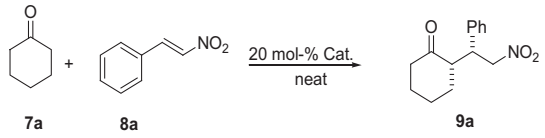
Organocatalyst **1** having an amide linker took about 24 h to give moderate diastereoselectivity (*syn*/*anti*) 79:21 and an enantioselectivity of 57%. Whereas, sulfide linker catalyst **2** took almost 3 days to give a good diastereoselectivity (*syn*/*anti*) 94:6 and an enantioselectivity of 85%. On the other hand, catalyst **6** outperformed the other pyrrolidine–camphor based organocatalysts in terms of reaction rate, chemical yield, and selectivity of the product formation (Table 1, entries 1–3). A very high diastereoselectivity (*syn*/*anti*) 97:3 and an enantioselectivity of 90% was obtained using organocatalyst **6** for Michael addition of cyclohexanone **7a** to *trans*-nitrostyrene **8a** within 14 h.

We next carried out the optimization studies for the reaction of cyclohexanone **7a** with *trans*-β-nitrostyrene **8a** in various solvents (Table 2).



Scheme 1. Synthesis of organocatalyst **6**.

Table 1
Screening of organocatalysts **1**, **2**, and **6** for Michael addition of cyclohexanone **7a** to *trans*-nitrostyrene **8a**[a]

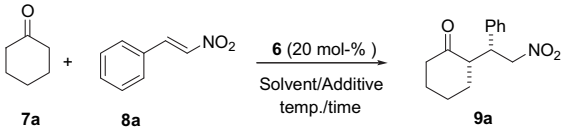


7a **8a** **9a**

Entry	Cat.	Time [h]	Yield[b] [%]	*syn*/*anti*[c]	ee[c] [%]
1	**1**	24	80	79:21	57
2	**2**	72	90	94:6	85
3	**6**	14	95	97:3	90

[a] Unless otherwise noted, all reactions were carried out using **7a** (1.0 mmol, 5.0 equiv) and **8a** (0.2 mmol) in the presence of 20 mol % of catalyst at ambient temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralcel AS-H column).

Table 2
Optimization of reaction conditions for Michael addition of cyclohexanone **7a** to *trans*-nitrostyrene **8a**[a]



7a **8a** **9a**

Entry	Solvent	Additive	Time [h]	Yield[b] [%]	*syn*/*anti*[c]	ee[c] [%]
1	DMSO	—	15	76	96:4	76
2	DMF	—	14	77	97:3	87
3	H_2O	—	240	50	95:5	80
4	$CHCl_3$	—	72	72	95:5	81
5	EtOH	—	12	85	96:4	88
6	Toluene	—	48	58	96:4	87
7	Brine	—	41	78	97:3	85
8	CH_3CN	—	15	86	96:4	86
9	Neat	—	14	95	97:3	90
10	Neat	CH_3COOH	20	96	98:2	89
11	Neat	NaOH	14	94	97:3	91
12	Neat	Et_3N	14	95	98:2	93
13	Neat	EtN(*i*-Pr)$_2$	14	95	98:2	95
14[d]	Neat	EtN(*i*-Pr)$_2$	14	94	99:1	95 (99)[e]

[a] Unless otherwise noted, all reactions were carried out using **7a** (1.0 mmol, 5.0 equiv) and **8a** (0.2 mmol) in the presence of 20 mol % of catalyst at ambient temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralcel AS-H column).
[d] Reaction was carried out at 0 °C.
[e] ee was determined after recrystallisation using CH_2Cl_2/*i*-PrOH.

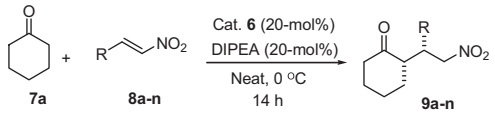
We first examined the reaction with polar aprotic solvents, such as DMSO and DMF. The desired Michael adduct **9a** was obtained with high diastereoselectivity (*syn*/*anti* 96:4) and a moderate stereoselectivity of 76% ee using DMSO (Table 2, entry 1). Whereas, an increase in the diastereo- (*syn*/*anti* 97:3) and enantioselectivity (87% ee) was observed when DMF as solvent (Table 2, entry 2). The use of H_2O as a solvent decreased the reaction rate with a dramatical drop in enantioselectivity, however the diastereoselectivity maintained (Table 2, entry 3). The use of a chlorinated solvent, such as $CHCl_3$ led to a slight increase in reaction rate and enantioselectivity (Table 2, entry 4). Next, the use of a polar protic solvent, such as EtOH showed encouraging results, with an increase in enantioselectivity (88% ee) and a slight increase in diastereoselectivity (*syn*/*anti* 96:4) was also observed (Table 2, entry 5). The reaction proceeded sluggishly when toluene was used in comparison to the use of ethanol, although the stereoselectivity was maintained (Table 2, entry 6). When the reaction was carried out in brine resulted in a drop in enantioselectivity of the Michael adduct **9a** (Table 2, entry 7). Reaction proceeded in CH_3CN failed to improve the stereoselectivity to a greater extent except for the time factor (Table 2, entry 8).

Exclusive screening of various solvents did not show superior results in comparison to reaction carried out in neat conditions (Table 2, entry 9). The addition of a catalytic amount of an acidic additive failed to influence the selectivity of the Michael reaction (Table 2, entry 10). Interestingly, the use of non-nucleophilic organic bases dramatically increased the rate of the reaction in comparison to that of NaOH (Table 2, entries 11–13). For example, when Hunig's base was used as an additive, *trans*-nitrostyrene was readily converted into the desired product with high diastereoselectivity (*syn*/*anti* 98:2) and very high enantioselectivity (95% ee) (Table 2, entry 13). We speculate that the organic bases played a profound role in the enamine formation, in agreement with previous reports.[14] The diastereoselectivity reached a maximum when the reaction temperature was lowered to 0 °C (Table 2, entry 14).

2.3. Substrate generality

Under the optimized conditions, a variety of nitroolefins with different structures were investigated to establish the catalytic ability of the organocatalyst **6** (Table 3).

Table 3
Michael addition of cyclohexanone with nitroolefins catalyzed by **6** under neat conditions[a]



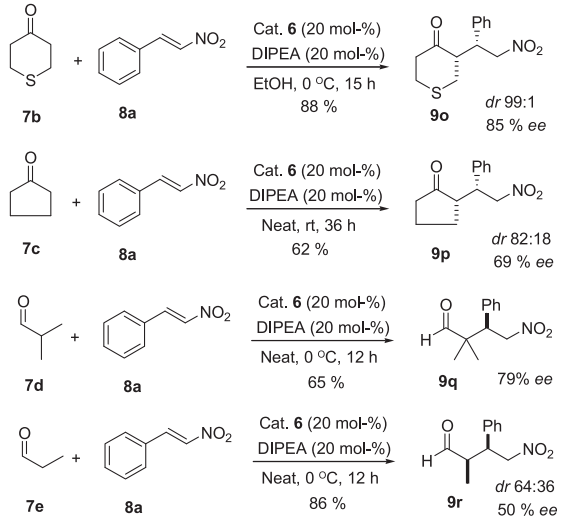
7a **8a-n** **9a-n**

Entry	R	Yield[b] [%]	*syn*/*anti*[c]	ee[c] [%]
1	C_6H_5	**9a** 91	99:1	95
2	2-$MeOC_6H_4$	**9b** 88	97:3	90
3	2-MeC_6H_4	**9c** 89	99:1	91
4	4-MeC_6H_4	**9d** 86	96:4	87
5	4-$MeOC_6H_4$	**9e** 85	96:4	84
6	1-Naphthyl	**9f** 90	97:3	88
7	4-BrC_6H_4	**9g** 80	96:4	86
8	2-Furyl	**9h** 90	91:9	81
9	2-Thienyl	**9i** 88	92:8	84
10	2-$CF_3C_6H_4$	**9j** 95	>99	92
11	2-$NO_2C_6H_4$	**9k** 90	99:1	89
12[d]	2-Naphthyl	**9l** 87	97:3	84
13[d]	4-ClC_6H_4	**9m** 85	95:5	87
14	3,4-(OCH_2O)–C_6H_3	**9n** 92	92:8	71

[a] Unless otherwise noted, all reactions were carried out using **7a** (1.0 mmol, 5.0 equiv) and **8a** (0.2 mmol) in the presence of 20 mol-% of catalyst **6** under neat conditions with 20-mol % of DIPEA at 0 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Reaction was carried out at ambient temperature.

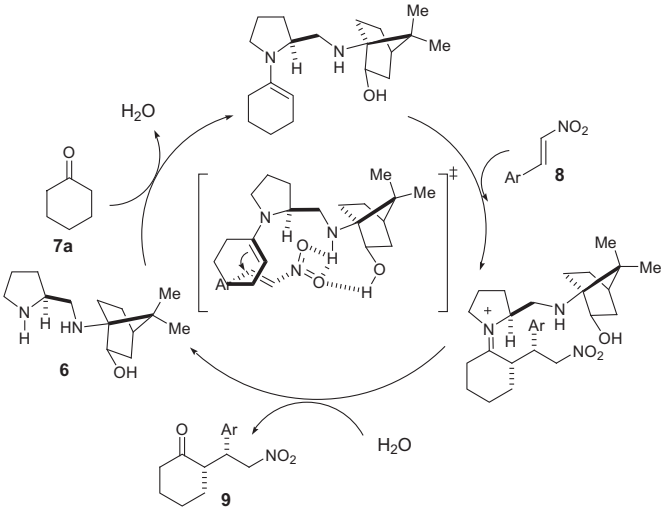
To test the generality of the catalytic system, various aromatic nitroolefins were reacted with cyclohexanone **7a** in the presence of catalyst **6**. The corresponding adducts **9a**–**n** were obtained in high chemical yields and with outstanding diastereoselectivity. The orientation of the substituent on the aryl group slightly influenced the selectivity of the reaction, with *ortho*-substituents performing better over the *para*-substituents (Table 3, entries 2, 3, 10, 11 vs 4, 5, 7, and 13). Nitroolefins with *ortho*-substituted electron donating or withdrawing substituent in an aromatic ring, especially **8c** and **8j**, afforded the corresponding adducts **9c** and **9j** with a high ee of 91% and 92%, respectively (Table 3, entries 3 and 10). Heteroaryl substrates, such as **8h** and **8i** also yielded the corresponding adducts with good selectivity (81% and 84% ee) (Table 3, entries 8 and 9). The substrate **8n** having a [1,3]dioxole substituent provided moderate selectivity, presumably due to steric factors (*syn*/*anti* 92:8, 71% ee) (Table 3, entry 14).

Asymmetric addition of other ketones (**7b** and **7c**) and aldehydes (**7d** and **7e**) to nitrostyrene **8a** using **6** was also investigated (Scheme 2). Tetrahydrothiopyran-4-one **7b** reacted smoothly yielding the desired product **9o**, thereby maintaining excellent stereoselectivities (*syn*/*anti* 99:1, 85% ee). On the other hand cyclopentanone **7c** failed to react at low reaction temperature. A moderate selectivity (*syn*/*anti* 82:18, 69% ee) was obtained when the reaction was carried out at ambient temperature. The use of isobutyraldehyde **7d** furnished the corresponding adduct **9q** with 79% ee in moderate chemical yield (65%). Reaction with propionaldehyde **7e** gave the desired product with a low dr of 64: 36 with an enantioselectivity of 50% ee with the *syn* one.



Scheme 2. Reactions of ketones and aldehydes with *trans*-nitrostyrene **8a**.

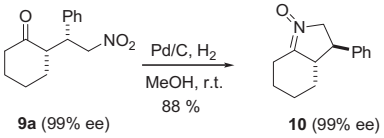
On the basis of the experimental results described above, a catalytic cycle was proposed to account for the high diastereoselectivity and enantioselectivity of the present reaction (Scheme 3).



Scheme 3. Proposed mechanism for **6**-catalyzed Michael addition.

We presume that the pyrrolidine ring first reacts with a carbonyl compound to form a nucleophilic enamine. The rigid and bulky bicyclic camphor moiety selectively shields the approach of the nitrostyrene from the enamine *si*-face.[15] On the other hand, the secondary amine linker plays a vital role in stereochemical outcomes via hydrogen bonding in assistance with the *exo* hydroxyl group (on camphor). Undoubtedly, the observed enantioselectivity points toward the necessity of an amine functionality linker (cat. **6**) in preference to amide (cat. **1**) and sulfide (cat. **2**). The resulting enamine therefore attacks the nitroolefin from the *re*-face to afford the product **9**, which is consistent with the experimental results. On the other hand, more studies are required to elucidate the reaction mechanism for the acylic aldehyde (**7e**), which provided (*R*,*S*)-**9r** as the major product. It can be presumed that the β-nitrostyrene approaches from the less hindered bottom face followed by the attack of nucleophilic enamine from the *si*-face to generate the desired product.

As pointed out earlier γ-nitroketone **9a** is potentially useful and has wide applications in organic synthesis.[1] The preparation of 3-phenyl-hexahydro-2*H*-indole-1-oxide **10** can easily be accessed using **9a** as a starting material (Scheme 4).[16] These are potential synthons for the total synthesis of the montanine-like Amaryllidaceae alkaloids.[17] We reasoned that the γ-nitroketone **9a** should be readily converted to the corresponding nitrone **10**, although this has been previously demonstrated.[8i] Indeed, the hydrogenation of **9a** in the presence of Pd/C furnished the desired nitrone **10** in 88% yield without a loss of stereoselectivity. Likewise, other isomeric products, such as hydroindole and imidazole can also be readily accessed using Michael adduct **9a** as the starting synthon.



Scheme 4. Synthetic utility of γ-nitroketone **9a**.

3. Conclusions

We have developed a new class of pyrrolidinyl–camphor based bifunctional organocatalyst that are capable of catalyzing highly diastereo- and enantioselectivity Michael addition reaction. The catalysts were prepared easily from inexpensive L-proline and camphor structural unit linked via amide, sulfide, and amine-linkers. It is obvious that the distance between pyrrolidine and camphor scaffold is crucial. The two atom distance is better than that of three atom system. The *exo* camphor C2 hydroxy group provided additional H-bond interaction to stabilize the transition model. Catalyst **6** possessing a secondary amine linker has been successfully applied to the asymmetric Michael reaction of cyclohexanone with nitroalkenes with a broad range of aryl- and heteroaryl-substituents. The important features are: (1) high chemical yields are generally obtained, (2) remarkable to high diastereo- and enantioselectivity, and (3) operationally simple reaction conditions. The utility of this organocatalyst is illustrated in the synthesis of an enantiopure nitrone. The current protocol developed complements a related approach to the same products that has recently been reported.[8,9]

4. Experimental section

4.1. General remarks

All reagents were used as purchased from commercial suppliers without additional purification. IR spectra were recorded on a Perkin–Elmer 500 spectrometer. NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Chemical shifts are reported in δ parts per million referenced to an internal TMS standard for ^{1}H NMR and chloroform-*d* (77.0 ppm) for ^{13}C NMR. Optical rotations were measured on a JASCO P-1010 polarimeter. HRMS were recorded on JEOL SX-102A. The X-ray diffraction measurements were carried out at 298 K on

a KAPPA APEX II CCD area detector system equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (λ=0.71073 Å). Routine monitoring of reactions was performed using silica gel, glass-backed TLC plates (Merck Kieselgel 60 F_{254}) and visualized by UV light (254 nm). Solutions were evaporated to dryness under reduced pressure on a rotary evaporator and the residues purified by flash column chromatography on silica gel (230–400 mesh) with the indicated eluents. Air and/or moisture sensitive reactions were performed under the inert atmospheric conditions.

4.2. Synthesis of organocatalyst (6)

A mixture of 1-amino-7,7-dimethylbicyclo[2.2.1]heptan-2-one **4** (3.06 g, 20 mmol), Ti(*i*-PrO)$_4$ (12.0 mL, 40 mmol), and *N*-(*tert*-butoxycarbonyl)prolinal **3** (4.38 g, 22 mmol) in THF (60 mL) was allowed to stir for 12 h at ambient temperature under N_2 atmosphere. $NaBH_4$ (2.28 g, 60 mmol) and absolute EtOH (20 mL) were then added, and the resulting mixture was stirred for an additional 12 h. The reaction mixture was then quenched with H_2O (20 mL), the resulting inorganic precipitate was filtered and washed with EtOAc (50 mL). The organic layer was separated and the remaining aqueous layer was extracted with EtOAc (30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/EtOAc=2:8) to afford the *N*-Boc protected **5** as a pale yellow viscous liquid (3.87 g, 52%). IR (CH_2Cl_2): ν 3431, 2981, 1738, 1660, 1395,1166 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 3.80 (br s, 1H, N–H), 3.70–3.68 (m, 1H), 3.45–3.30 (m, 2H), 2.83–2.75 (m, 1H), 2.06–1.95 (m, 1H), 1.90–1.71 (m, 7H), 1.64–1.58 (m, 2H), 1.50 (s, 9H), 1.32–1.20 (m, 3H), 1.18–1.05 (m, 1H), 1.10 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 162.0, 79.4, 72.8, 68.1, 58.0, 47.7, 46.4, 43.2, 39.4, 29.7, 29.4, 28.5, 27.0, 23.8, 20.3, 19.9. To the above *N*-Boc protected compound **5** (2.0 g, 6 mmol) in 15 mL of CH_2Cl_2 was added TFA (7 mL) at ambient temperature. After stirring for about 19 h and the resulting solution was adjusted to pH ~7 with aqueous NaOH. The reaction mixture was extracted with CH_2Cl_2 (2×20 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The obtained crude residue was dissolved in CH_2Cl_2/hexanes (1:2) and kept for crystallization at ambient temperature to furnish the pure organocatalyst **6** as a white crystal (1.11 g, 79%). Mp 123 °C; $[\alpha]_D^{25}$ −20.5 (*c* 1, $CHCl_3$); IR (CH_2Cl_2): ν 3424, 2934, 1642, 1530 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 5.6 (br s, 3H, N–H, OH), 3.95–3.82 (m, 2H), 3.45–3.38 (m, 1H), 3.30–3.20 (m, 1H), 3.18–3.07 (m, 1H), 3.03–2.95 (m, 1H), 2.18–1.97 (m, 3H), 1.91–1.65 (m, 5H), 1.62–1.55 (m, 1H), 1.31–1.20 (m, 1H), 1.20–1.11 (m, 1H), 1.10 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 73.4, 68.1, 59.8, 47.0, 45.5, 43.1, 42.7, 40.8, 30.9, 28.0, 27.0, 25.3, 20.3, 20.0; HRMS (FAB$^+$) *m*/*z* (M^+): 238.2039 (calcd for $C_{14}H_{26}N_2O$, 238.2045). Crystal data for **6** (as a TFA salt) at 293(2) K: $C_{16}H_{27}F_3N_2O_3$, *M* 352.40, orthorhombic, P_{212121}, *a*=8.7370 (3) Å, *b*=14.0740(5) Å, *c*=14.9440(7) Å, *V*=1837.58(13) Å^3, *Z*=4, λ=0.71073 Å, *D*=1.274 g/cm^3, μ=0.107 mm^{-1}, 3013 reflections, 215 parameters, *R*=0.0855, R_w=0.2633 for all data.

4.3. General procedure for the Michael addition reaction

The catalyst **6** (9.52 mg, 20 mol %) and DIPEA (7 μL, 20 mol %) were added to cyclohexanone **7a** (104 μL, 1.0 mmol) at 0 °C. The reaction mixture was stirred for 30 min, and then nitroolefin **8** (0.2 mmol) was added. The reaction mixture was stirred to completion at 0 °C for 14 h. After the disappearance of nitroalkene by TLC analysis, the reaction was quenched with brine and extracted with CH_2Cl_2 (2×10 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column silica-gel chromatography (hexanes/ethyl acetate=8:2) to provide Michael product.

*4.3.1. (S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone (**9a**).* Yield 45 mg, 91%. IR (CH_2Cl_2): ν 3008, 2937, 1714, 1553, 1449, 1347 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.34–7.23 (m, 3H), 7.16 (d, *J*=6.9 Hz, 2H), 4.95 (dd, *J*=4.5, 12.6 Hz, 1H), 4.63 (dd, *J*=9.0, 12.3 Hz, 1H), 3.76 (dt, *J*=4.5, 9.9 Hz, 1H), 2.68 (ddd, *J*=8.1, 8.4, 11.7 Hz, 1H), 2.49–2.33 (m, 2H), 2.10–2.04 (m, 1H), 1.79–1.52 (m, 4H), 1.52–1.19 (m, 1H); HPLC: Chiralpak AS-H (hexanes/*i*-PrOH: 90/10, flow rate: 0.8 mL/min, λ=238 nm); retention time: 21.9 min (minor), 32.3 min (major).

*4.3.2. (S)-2-((R)-1-(2-Methoxyphenyl)-2-nitroethyl)cyclohexanone (**9b**).* Yield 49 mg, 88%. IR (CH_2Cl_2): ν 3011, 2941, 1716, 1550, 1442, 1245, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.26 (dd, *J*=1.6, 8.1 Hz, 1H), 7.1 (dd, *J*=1.0, 7.6 Hz, 1H), 6.92–6.88 (m, 2H), 4.88–4.80 (m, 2H), 3.98 (dt, *J*=5.1, 10.3 Hz, 1H), 3.85 (s, 3H), 3.02–2.96 (m, 1H), 2.52–2.47 (m, 1H), 2.43–2.36 (m, 1H), 2.10–2.06 (m, 1H), 1.81–1.77 (m, 1H), 1.71–1.66 (m, 2H), 1.66–1.55 (m, 1H), 1.27–1.21 (m, 1H); HPLC: Chiralpak AS-H (hexanes/*i*-PrOH: 90/10, flow rate: 0.5 mL/min, λ=254 nm); retention time: 30.2 min (minor), 34.7 min (major).

*4.3.3. (S)-2-((R)-2-Nitro-1-(o-tolyl)ethyl)cyclohexanone (**9c**).* Yield 47 mg, 89%. IR (CH_2Cl_2): ν 3013, 2945, 1715, 1550, 1347 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.21–7.11 (m, 4H), 4.95 (dd, *J*=4.4, 12.8 Hz, 1H), 4.63 (dd, *J*=10.4, 12.4 Hz, 1H), 3.68 (dt, *J*=4.0, 10.0 Hz, 1H), 2.67–2.56 (m, 1H), 2.50–2.36 (m, 2H), 2.37 (s, 3H), 2.12–2.09 (m, 1H), 1.77–1.53 (m, 4H), 1.26–1.23 (m, 1H); HPLC: Chiralpak AD-H (hexanes/*i*-PrOH: 90/10, flow rate: 0.5 mL/min, λ=254 nm); retention time: 16.9 min (minor), 24.3 min (major).

*4.3.4. (S)-2-((R)-2-Nitro-1-(p-tolyl)ethyl)cyclohexanone (**9d**).* Yield 45 mg, 86%. IR (CH_2Cl_2): ν 3011, 2940, 1715, 1552, 1349 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.12 (d, *J*=8.0 Hz, 2H), 7.04 (d, *J*=8.0 Hz, 2H), 4.91 (dd, *J*=4.8, 12.4, Hz, 1H), 4.62 (dd, *J*=10.0, 12.4 Hz, 1H), 3.72 (dt, *J*=4.8, 10.0 Hz, 1H), 2.71–2.62 (m, 1H), 2.51–2.32 (m, 2H), 2.31 (s, 3H), 2.12–2.02 (m, 1H), 1.82–1.50 (m, 4H), 1.30–1.18 (m, 1H); HPLC: Chiralpak AS-H (hexanes/*i*-PrOH: 90/10, flow rate: 0.8 mL/min, λ=254 nm); retention time: 14.6 min (minor), 26.1 min (major).

*4.3.5. (S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (**9e**).* Yield 47 mg, 85%. IR (CH_2Cl_2): ν 3011, 2942, 1715, 1552, 1443, 1247, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.09 (d, *J*=8.0 Hz, 2H), 6.86 (d, *J*=8.0 Hz, 2H), 4.91 (dd, *J*=4.5, 12.0 Hz, 1H), 4.60 (dd, *J*=10.1, 12.0 Hz, 1H), 3.80 (s, 3H), 3.72 (dt, *J*=5.2, 10.5 Hz, 1H), 2.69–2.63 (m, 1H), 2.50–2.46 (m, 1H), 2.42–2.36 (m, 1H), 2.10–2.06 (m, 1H), 1.82–1.55 (m, 4H), 1.28–1.21 (m, 1H); Chiralpak AD-H (hexanes/*i*-PrOH: 75/25, flow rate: 0.7 mL/min, λ=238 nm); retention time: 10.8 min (minor), 13.0 min (major).

*4.3.6. (S)-2-((R)-1-(Naphthalen-1-yl)-2-nitroethyl)cyclohexanone (**9f**).* Yield 54 mg, 90%. IR (CH_2Cl_2): ν 3009, 2936, 1715, 1552, 1447, 1346, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.16 (br s, 1H), 7.85 (d, *J*=7.7 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.56–7.43 (m, 3H), 7.37 (d, *J*=7.3, Hz, 1H), 5.06 (dd, *J*=4.5, 12.5 Hz, 1H), 4.73 (m, 1H), 4.75–4.71 (m, 1H), 2.86 (br s, 1H), 2.52–2.48 (m, 1H), 2.44–2.37 (m, 1H), 2.09–2.04 (m, 1H), 1.76–1.60 (m, 3H), 1.58–1.47 (m, 1H), 1.29–1.21 (m, 1H); HPLC: Chiralpak AS-H (hexanes/*i*-PrOH: 70/30, flow rate: 0.7 mL/min, λ=238 nm); retention time: 15.9 min (minor), 23.5 min (major).

*4.3.7. (S)-2-((R)-1-(4-Bromophenyl)-2-nitroethyl)cyclohexanone (**9g**).* Yield 52 mg, 80%. IR (CH_2Cl_2): ν 3008, 2937, 1714, 1553, 1449, 1347, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.46 (d, *J*=8.4 Hz, 2H), 7.06 (d, *J*=8.4 Hz, 2H), 4.94 (dd, *J*=5.2, 12.4 Hz, 1H),

4.61 (dd, J=9.6, 12.4 Hz, 1H), 3.75 (dt, J=4.4, 10.0 Hz, 1H), 2.69–2.60 (m, 1H), 2.51–2.32 (m, 2H), 2.15–2.05 (m, 1H), 1.83–1.57 (m, 4H), 1.26–1.22 (m, 1H); HPLC: Chiralpak AD-H (hexanes/*i*-PrOH: 80/20, flow rate: 0.5 mL/min, λ=254 nm); retention time: 15.9 min (minor), 23.3 min (major).

*4.3.8. (S)-2-((S)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (**9h**).* Yield 43 mg, 90%. IR (CH_2Cl_2): ν 3077, 2937, 1714, 1553, 1449, 1347, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.36 (m, 1H), 6.30–6.28 (m, 1H), 6.19 (m, 1H), 4.82 (dd, J=4.8, 12.4 Hz, 1H), 4.68 (dd, J=9.2, 12.4 Hz, 1H), 4.00 (dt, J=4.8, 9.2 Hz, 1H), 2.80–2.72 (m, 1H), 2.48–2.47 (m, 1H), 2.40–2.33 (m, 1H), 2.18–2.09 (m, 1H), 1.89–1.60 (m, 4H), 1.35–1.26 (m, 1H); HPLC: Chiralpak AS-H (hexanes/*i*-PrOH: 85/15, flow rate: 0.5 mL/min, λ=230 nm); retention time: 27.9 min (minor), 32.2 min (major).

*4.3.9. (S)-2-((S)-2-Nitro-1-(thiophen-2-yl) ethyl) cyclohexanone (**9i**).* Yield 45 mg, 88%. IR (CH_2Cl_2): ν 3070, 2937, 1714, 1553, 1449, 1347, 925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.23 (d, J=5.1 Hz, 1H), 6.94 (dd, J=3.0, 5.1 Hz, 1H), 6.88 (d, J=3.2 Hz, 1H), 4.90 (dd, J=4.1, 13.0 Hz, 1H), 4.67 (dd, J=9.1, 13.0 Hz, 1H), 4.14 (dt, J=4.1, 9.1 Hz, 1H), 2.72–2.67 (m, 1H), 2.50–2.46 (m, 1H), 2.42–2.36 (m, 1H), 2.13–2.10 (m, 1H), 1.96–1.90 (m, 1H), 1.88–1.85 (m, 1H), 1.73–1.56 (m, 2H), 1.38–1.24 (m, 1H); HPLC: Chiralpak AS-H (hexanes/*i*-PrOH: 90/10, flow rate: 1.0 mL/min, λ=254 nm); retention time: 18.2 min (minor), 24.3 min (major).

*4.3.10. (S)-2-((R)-2-Nitro-1-(2-(trifluoromethyl) phenyl) ethyl) cyclohexanone (**9j**).* 60 mg, 95% yield. IR (CH_2Cl_2): ν 3013, 2945, 1714, 1550, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.71 (d, J=7.5 Hz, 1H), 7.57 (t, J=7.5 Hz, 1H), 7.41 (t, J=7.5 Hz, 1H), 7.39 (d, J=7.5 Hz, 1H), 5.05 (dd, J=7.0, 12.0 Hz, 1H), 4.77 (dd, J=3.7, 12.0 Hz, 1H), 4.12–4.07 (m, 1H), 3.05–3.0 (m, 1H), 2.53–2.41 (m, 2H), 2.17–2.11 (m, 1H), 1.83–1.78 (m, 1H), 1.76–1.64 (m, 2H), 1.64–1.55 (m, 1H), 1.38–1.28 (m, 1H); HPLC: Chiralpak AD-H (hexanes/*i*-PrOH: 90/10, flow rate: 0.5 mL/min, λ=254 nm); retention time: 12.8 min (minor), 19.7 min (major).

*4.3.11. (S)-2-((R)-2-Nitro-1-(2-nitrophenyl)ethyl)cyclohexanone (**9k**).* Yield 54 mg, 90%. IR (CH_2Cl_2): ν 3008, 2937, 1714, 1553, 1449, 1347, 852, 793 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.84 (d, J=8.0 Hz, 1H), 7.59 (t, J=8.0 Hz, 1H), 7.48–7.42 (m, 2H), 4.98–4.87 (m, 2H), 4.32 (dt, J=4.8, 8.8 Hz, 1H), 2.99–2.91 (m, 1H), 2.52–2.32 (m, 2H), 2.16–2.08 (m, 1H), 1.88–1.78 (m, 2H), 1.72–1.40 (m, 4H); HPLC: Chiralpak AD-H (hexanes/*i*-PrOH: 95/5, flow rate: 1.0 mL/min, λ=238 nm); retention time: 32.3 min (minor), 54.6 min (major).

*4.3.12. (S)-2-((R)-1-(Naphthalen-2-yl)-2-nitroethyl)cyclohexanone (**9l**).* Yield 52 mg, 87%. IR (CH_2Cl_2): ν 3008, 2937, 1714, 1553, 1449, 1347, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.82–7.78 (m, 2H), 7.63 (s, 1H), 7.50–7.45 (m, 2H), 7.28 (dd, J=2.0, 8.5 Hz, 2H), 5.01 (dd, J=12.0, 4.7 Hz, 1H), 4.74 (dd, J=10.0, 12.0 Hz, 1H), 3.95 (dt, J=4.7, 10.0 Hz, 1H), 2.81–2.75 (m, 1H), 2.52–2.48 (m, 1H), 2.44–2.37 (m, 1H), 2.10–2.04 (m, 1H), 1.78–1.65 (m, 3H), 1.61–1.53 (m, 1H), 1.31–1.23 (m, 1H); HPLC: Chiralpak AS-H (hexanes/*i*-PrOH: 50/50, flow rate: 0.7 mL/min, λ=254 nm); retention time: 10.4 min (minor), 21.1 min (major).

*4.3.13. (S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (**9m**).* Yield 47 mg, 85%. IR (CH_2Cl_2): ν 3009, 2937, 1714, 1553, 1448, 1348, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.31 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 4.96 (dd, J=4.8, 12.8 Hz, 1H), 4.62 (dd, J=10.0, 12.8 Hz, 1H), 3.78 (dt, J=4.4, 10.0 Hz, 1H), 2.69–2.60 (m, 1H), 2.51–2.34 (m, 2H), 2.15–2.05 (m, 1H), 1.83–1.52 (m, 4H), 1.28–1.23 (m, 1H); HPLC: Chiralpak AS-H (hexanes/*i*-PrOH: 90/10, flow rate: 1.0 mL/min, λ=254 nm); retention time: 10.4 min (minor), 21.1 min (major).

*4.3.14. (S)-2-((R)-1-(Benzo[d] [1,3]dioxol-5-yl)-2-nitroethyl) cyclohexanone (**9n**).* Yield 54 mg, 92%. IR (CH_2Cl_2): ν 3008, 2941, 1716, 1552, 1440, 1245, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.74 (d, J=7.8 Hz, 1H), 6.64 (s, 1H), 6.62 (d, J=7.8 Hz, 1H), 5.96 (s, 2H), 4.90 (dd, J=4.5, 12.3 Hz, 1H), 4.55 (dd, J=10.2, 12.0 Hz, 1H), 3.68 (dt, J=4.2, 9.9 Hz, 1H), 2.65–2.56 (m, 1H), 2.52–2.33 (m, 2H), 2.15–2.05 (m, 1H), 1.83–1.59 (m, 4H), 1.31–1.18 (m, 1H); HPLC: Chiralpak AD-H (hexanes/*i*-PrOH: 95/5, flow rate: 0.7 mL/min, λ=214 nm); retention time: 35.5 min (minor), 37.9 min (major).

*4.3.15. (S)-3-((R)-2-Nitro-1-phenylethyl) dihydro-2H-thiopyran-4 (3H)-one (**9o**).* Yield 47 mg, 88%. IR (CH_2Cl_2): ν 3008, 2937, 1714, 1553, 1449, 1347, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.40–7.32 (m, 3H), 7.22 (d, J=7.6 Hz, 2H), 4.76 (dd, J=4.4, 12.4 Hz, 1H), 4.63 (dd, J=10.0, 12.8 Hz, 1H), 4.01 (dt, J=4.4, 10.0 Hz, 1H), 3.11–2.99 (m, 3H), 2.92–2.82 (m, 2H), 2.66–2.62 (m, 1H), 2.48 (dd, J=9.2, 13.6 Hz, 1H); HPLC: Chiralpak AS-H (hexanes/*i*-PrOH: 80/20, flow rate: 1.0 mL/min, λ=210 nm); retention time: 18.6 min (minor), 25.3 min (major).

*4.3.16. (S)-2-((R)-2-Nitro-1-phenylethyl)cyclopentanone (**9p**).* Yield 29 mg, 62%. IR (CH_2Cl_2): ν 3008, 2937, 1751, 1553, 1449, 1347 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.34–7.23 (m, 3H), 7.20–7.15 (m, 2H), 5.37–5.30 (m, 1H), 4.71 (dd, J=10.2, 12.6 Hz, 1H), 3.76–3.65 (m, 1H), 2.44–2.31 (m, 2H), 2.19–2.06 (m, 1H), 1.94–1.83 (m, 2H), 1.76–1.66 (m, 1H), 1.55–1.41 (m, 1H); HPLC: Chiralpak AD-H (hexanes/*i*-PrOH: 90/10, flow rate: 0.5 mL/min, λ=254 nm); retention time: 19.7 min (minor), 28.2 min (major).

*4.3.17. (R)-2,2-Dimethyl-4-nitro-3-phenylbutanal (**9q**).* Yield 29 mg, 65%. IR (CH_2Cl_2): ν 3008, 2977, 1723, 1604, 1555, 1447, 1345 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 9.49 (s, 1H), 7.34–7.29 (m, 1H), 7.28–7.22 (m, 2H), 7.22–7.15 (m, 2H), 4.85 (dd, J=11.3, 13.1 Hz, 1H), 4.69 (dd, J=4.2, 13.1 Hz, 1H), 3.78 (dd, J=4.2, 11.3 Hz, 1H), 1.12 (s, 3H), 0.96 (s, 3H); HPLC: Chiralcel OD-H (hexanes/*i*-PrOH: 80/20, flow rate: 0.8 mL/min, λ=254 nm); retention time: 15.0 min (major), 20.8 min (minor).

*4.3.18. (2R,3S)-2-Methyl-4-nitro-3-phenylbutanal (**9r**).* Yield 36 mg, 86%. IR (CH_2Cl_2): ν 3008, 2977, 1724, 1601, 1553, 1449, 1347 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 9.72 (d, J=1.5 Hz, 1H), 7.36–7.29 (m, 3H), 7.17–7.16 (m, 2H), 4.80 (dd, J=5.5, 12.9 Hz, 1H), 4.69 (dd, J=9.2, 12.9 Hz, 1H), 3.81 (ddd, J=5.5, 9.2, 9.2 Hz, 1H), 2.80–2.75 (m, 1H), 1.01 (d, J=7.4 Hz, 3H); HPLC: Chiralcel OD-H (hexanes/*i*-PrOH: 90/10, flow rate: 1.0 mL/min, λ=254 nm); retention time: 26.7 min (major), 19.6 min (minor).

4.4. Synthesis of nitrone (10)

A suspension of Pd/C (8 mg) and **9a** (50 mg) in MeOH (5 mL) was stirred at ambient temperature under hydrogen atmosphere. After being stirred for 12 h, the mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash column silica-gel chromatography (chloroform/methanol=9:1) to provide the desired product **10** (38 mg, 88% yield). IR (CH_2Cl_2): ν 3009, 2981, 2857, 1615, 1253, 1175, 765, 704 cm-1; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.30–7.25 (m, 2H), 7.21–7.15 (m, 3H), 4.23–4.04 (m, 2H), 3.19–3.01 (m, 2H), 2.73 (m, 1H), 2.05–1.87 (m, 3H), 1.77 (m, 1H), 1.33–1.14 (m, 3H); HPLC: Chiralpak AD-H (hexanes/*i*-PrOH: 90/10,

flow rate: 0.6 mL/min, λ=238 nm); retention time: 19.1 min (major), 24.7 min (minor).

Acknowledgements

We thank the National Science Council of the Republic of China (NSC 99-2113-M-003-002-MY3 and NSC 99-2119-M-003-001-MY2) and National Taiwan Normal University (99T3030-5 and 99-D) for financial support of this work. Our gratitude goes to the Academic Paper Editing Clinic at NTNU, and to the National Center for High-Performance Computing for providing us with computer time and facilities.

Supplementary data

This material includes spectral data for catalyst **6** and chiral-phase HPLC data for various Michael adducts **9a**–**r** as well as **10**. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.11.093.

References and notes

1. Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894.
2. (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1–18; (b) Svensson, K.A.I. PCT Int. Appl. WO 9218475, 1992.
3. For some selected references, see: (a) Tan, B.; Zeng, X.; Lu, Y.; Chua, P. J.; Zhong, G. *Org. Lett.* **2009**, *11*, 1927–1930; (b) Wang, C.; Yu, C.; Liu, C.; Peng, Y. *Tetrahedron Lett.* **2009**, *50*, 2363–2366; (c) Vishnuyama; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117–1119; (d) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; (e) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624–9625; (f) Ishii, T.; Fujuoka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559; (g) Liu, F.; Wang, S.; Wang, N.; Peng, Y. *Synlett* **2007**, *15*, 2415–2419; (h) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423–2425; (i) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441–4444; (j) Aleaxakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611–3614; (k) Syu, S.-E.; Kao, T.-T.; Lin, W. *Tetrahedron* **2010**, *66*, 891–897; (l) Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Li, Y.-J.; Xioa, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21–24; (m) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539–7542.
4. For selected references, see: (a) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496; (b) Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526–533; (c) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621–631; (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (e) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724.
5. (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557; (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591; (c) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975–978; (d) List, B. *Tetrahedron* **2002**, *58*, 5573–5590; (e) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529–532.
6. (a) Chen, J.-R.; Lu, H.-H.; Li, X.-Y.; Cheng, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543–4545; (b) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289; (c) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028–16029; (d) Itagaki, N.; Kimura, M.; Sugahara, T.; Iwabuchi, Y. *Org. Lett.* **2005**, *7*, 4185–4188; (e) Tokuda, O.; Kano, T.; Gao, W.-G.; Ikemoto, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5103–5105; (f) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408–16409; (g) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586–3588; (h) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321–5323; (i) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215; (j) Terakado, D.; Takano, M.; Oriyama, T. *Chem. Lett.* **2005**, *34*, 962–963.
7. (a) Sheldon, R. A. *Chem. Ind.* **1992**, 903–906; (b) Jacobsen, E. N.; Finney, N. S. *Chem. Biol.* **1994**, *1*, 85–90; (c) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159–2169; (d) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246; (e) DeSimone, J. M. *Science* **2002**, *297*, 799–803.
8. (a) Miao, S.; Bai, J.; Yang, J.; Zhang, Y. *Chirality.* **2010**, *22*, 855–862; (b) Liu, J.; Li, P.; Zhang, Y.; Ren, K.; Wang, L.; Wang, G. *Chirality* **2010**, *22*, 432–441; (c) Chua, P. J.; Tan, B.; Xeng, X.; Zhong, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3915–3918; (d) Lu, A.; Gao, P.; Wu, Y.; Wang, Y.; Zhou, Z.; Tang, C. *Org. Biomol. Chem.* **2009**, *7*, 3141–3147; (e) Zhao, Y.-B.; Zhang, L.-W.; Wu, L.-Y.; Xong, X.; Li, R.; Ma, J.-T. *Tetrahedron: Asymmetry* **2008**, *19*, 1352–1355; (f) Lv, G.; Jin, R.; Mai, W.; Gao, L. *Tetrahedron: Asymmetry* **2008**, *19*, 2568–2572; (g) Chandrasekhar, S.; Tiwari, B.; Parida, B. B.; Reddy, ch. R. *Tetrahedron: Asymmetry* **2008**, *19*, 495–499; (h) Miao, T.; Wang, L. *Tetrahedron Lett.* **2008**, *49*, 2173–2176; (i) Cao, C. L.; Ye, M. C.; Sun, X. L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901–2904.
9. (a) Ni, B.; Zhang, Q.; Dhungana, K.; Headley, A. D. *Org. Lett.* **2009**, *11*, 1037–1040; (b) Ni, B.; Zhang, Q.; Headley, A. D. *Tetrahedron Lett.* **2008**, *49*, 1249–1252; (c) Li, P.; Wang, L.; Zhang, Y.; Wang, G. *Tetrahedron* **2008**, *64*, 7633–7638; (d) Wu, L.-Y.; Yan, Z.-Y.; Xie, Y.-X.; Niu, Y.-N.; Liang, Y.-M. *Tetrahedron: Asymmetry* **2007**, *18*, 2086–2090; (e) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093–3097; (f) Kotrusz, P.; Toma, S.; Schmalz, H.-G.; Adler, A. *Eur. J. Org. Chem.* **2004**, 1577–1583.
10. (a) Tzeng, Z.-H.; Chen, H.-Y.; Huang, C.-T.; Chen, K. *Tetrahedron Lett.* **2008**, *49*, 4134–4137; (b) Tzeng, Z.-H.; Chen, H.-Y.; Reddy, R. J.; Huang, C.-T.; Chen, K. *Tetrahedron* **2009**, *65*, 2879–2888; (c) Chang, C.; Li, S.-H.; Reddy, R. J.; Chen, K. *Adv. Synth. Catal.* **2009**, *351*, 1273–1278; (d) Reddy, R. J.; Kuan, H.-H.; Chou, T.-Y.; Chen, K. *Chem.—Eur. J.* **2009**, *15*, 9294–9298; (e) Liu, P.-M.; Chang, C.; Reddy, R. J.; Ting, Y.-F.; Kuan, H.-H.; Chen, K. *Eur. J. Org. Chem.* **2010**, 42–46; (f) Magar, D. R.; Chang, C.; Ting, Y.-F.; Chen, K. *Eur. J. Org. Chem.* **2010**, 2060–2066; (g) Ting, Y.-F.; Chang, C.; Reddy, R. J.; Magar, D. R.; Chen, K. *Chem.—Eur. J.* **2010**, 7030–7038.
11. Camphor-based catalysts for various asymmetric transformations, see: (a) Aggarwal, V. K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9964–9965; (b) Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* **2004**, *6*, 1193–1195; (c) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 5473–5475; (d) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141–4144; (e) Langlois, Y.; Petit, A.; Remy, P.; Scherrmann, M.-C.; Kouklovsky, C. *Tetrahedron Lett.* **2008**, *49*, 5576–5579; (f) He, H.; Pei, B.-J.; Chou, H.-H.; Tian, T.; Chan, W.-H.; Lee, A. W. M. *Org. Lett.* **2008**, *10*, 2421–2424.
12. Braslau, R.; Kuhn, H.; Burrill, L. C., II; Lanham, K.; Stenland, C. J. *Tetrahedron Lett.* **1996**, *37*, 7933–7936.
13. (a) Kumpaty, H. J.; Bhattacharyya, S.; Rehr, E. W.; Gonzalez, A. M. *Synthesis* **2006**, 2206–2210; (b) Dalai, M.; Periasamy, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1247–1253.
14. (a) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317–328; (b) Amedjkouh, M. *Tetrahedron: Asymmetry* **2007**, *18*, 390–395.
15. (a) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413–1423; (b) Seebach, D.; Missbach, M.; Calderari, G.; Eberele, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625–7638.
16. Sanchez, I. H.; Larraza, M. I.; Rojas, I.; Brena, F. K.; Flores, H. J. *Heterocycles* **1985**, *23*, 3033–3039.
17. (a) Fugantic, C. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, NY, 1975; Vol. 15, pp 83–164; (b) Sainsbury, M. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Coffey, S., Ed.; Elsevier Scientific: Amsterdam, 1977; Vol. 4, Part B, Chapter 10.
18. Detailed X-ray crystallographic data is available from the CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK for organocatalyst **6** as a TFA salt (CCDC No. 796818).