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Highly enantioselective desymmetrization of *meso*- and prochiral cyclic ketones via organocatalytic Michael reaction

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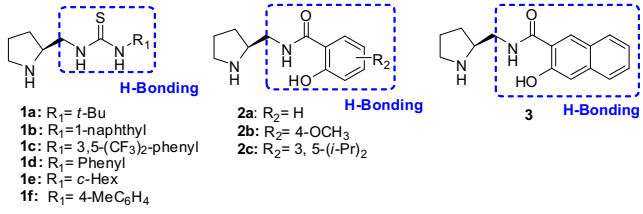
ABSTRACT

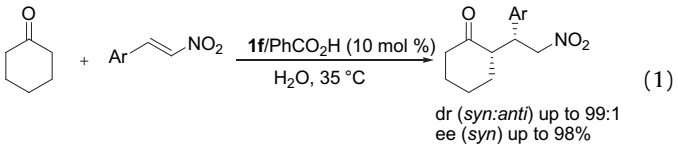
An efficient and novel organocatalyst has been developed for the asymmetric desymmetrization of *meso*- and prochiral ketones by direct Michael addition to nitroolefins. This strategy can afford the desymmetrization products with excellent diastereo- (up to >99:1) and enantioselectivity (up to 96%) in great yields (up to 95%).

1. Introduction

Asymmetric organocatalysis, the use of small chiral organic molecules as catalysts, has become a field of central importance for the stereoselective preparation of chiral, enantioenriched building blocks.[1] In particular, the use of chiral secondary amines exploiting catalytic enamine,[2] iminium ion,[3] SOMO,[4] and dienamine[5] activation modes have proven to be a powerful protocol for stereoselective functionalization of carbonyl compounds. Among the various α-functionalizations of carbonyl compounds, the asymmetric Michael reaction of carbonyl compounds to nitroolefins represents an easy approach to the formation of synthetically useful γ-nitrocarbonyl compounds, which serve as versatile intermediates for the preparation of complex organic targets.[6,7] Accordingly, considerable efforts have been directed toward the development of organocatalytic systems for this transformation. Since the pioneering studies on Michael reaction with proline catalysis by Barbas,[8a] List,[8b] and Enders,[8c] processes promoted by chiral amines have been extensively investigated. Representative catalysts in this area include pyrrolidine diamines,[9] pyrrolidine tetrazole,[10] pyrrolidine–pyridine,[11] pyrrolidine sulfonamide,[12] simple peptides,[13] chiral ionic liquid,[14] amine thiourea derivatives,[15] and cinchona alkaloid.[16] Among them, the bifunctional amine thioureas have been identified as powerful catalysts for Michael addition of nitroolefins due to the efficient activation of nitro group by hydrogen bonding. In the course of our interest in aminocatalysis, especially enamine catalysis using chiral amines bearing hydrogen bonding donors for a diverse range of transformations of carbonyl compounds,[15e–f,17] we have recently discovered a family of pyrrolidine–thiourea based catalysts (1) (Scheme 1). Due to its pyrrolidine backbone and strong activation of nitro group through double hydrogen bonding interaction, these bifunctional organocatalysts showed highly diastereo- and enantioselectivity for the Michael reaction of cyclohexanone with β-nitrostyrenes (Eq. 1).[15e–f] Furthermore, we found that activity and selectivity can be finely tuned by a simple modification of the structural motif of the catalyst.



Scheme 1. Catalysts evaluated in this study.



(1)

On the other hand, new synthetic strategies that facilitate the rapid and efficient construction of complex molecules with multiple stereogenic centers remain a preeminent but challenging goal in modern organic chemistry. Asymmetric desymmetrization (ADS) of prochiral substrates has been considered as one of the most useful accesses to this purpose.[18] Along this line, the ADS of *meso*- and prochiral substrates using enzymatic catalytic[18b,19] and metal catalytic methods[18c,20] have been well documented. Nevertheless, the ADS reaction employing small organic molecule catalysis is still rare. In 2005, Barbas and co-workers reported an ADS of highly substituted *meso*-ketones catalyzed by L-proline[21]; then Hayashi,[22a]

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Rovis,[22b] and co-workers described asymmetric desymmetrization of cyclohexadienones. Very recently, Gong,[23a] Cheng,[23b] and co-workers developed the first organocatalytic ADS of prochiral cyclohexanones by direct aldol and Michael reactions, respectively. While some of these existing strategies have been successful, the development of catalytic, enantioselective methods for the desymmetrization of prochiral ketones with novel and efficient organocatalysts is still highly desirable. As part of our efforts to develop readily tunable organocatalysts of broad utility for chemical transformations, we considered the possibility to extend the hydrogen bonding activation mode to asymmetric desymmetrization of prochiral ketones. We envisaged that the 'tunable' properties of the hydrogen bondings at chiral pyrrolidine–thiourea scaffold (Scheme 1) might remove the symmetry (C4 position) of prochiral ketones by asymmetric Michael reaction. Herein, we present the development of a new bifunctional organocatalyst for desymmetrization of prochiral cyclohexanones via organocatalytic Michael reactions.

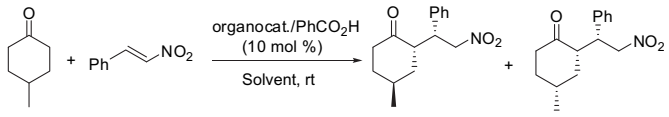
2. Results and discussion

We first screened the ability of this type of organocatalysts (**1a–f**) in the Michael reaction of 4-methylcyclohexanone (**4a**) with β-nitrostyrene (**5a**). The desired Michael adducts were obtained in moderate to good yields with good enantioselectivity (Table 1, entries 1–6). For example, the major isomer **6aa** has 88% ee in the presence of chiral thiourea **1f**. Other diastereoisomers were detected only in trace amounts. Note that the thiourea motif (**1a–f**) has effective impact on the enantioselectivity and rate of the reaction. With this analogy in mind, we synthesized salicylic amides as a new class of organocatalysts and applied them to this desymmetrization process. We further examined the influence of the structure of H-bonding donor on this transformation. We were delighted to find that salicylic amide **2a** efficiently catalyze this reaction, giving the product with comparable enantio- and diastereoselectivity (Table 1, entry 7 vs 6). Then several other analogs of this kind of catalyst were screened in this reaction, the catalyst (**3**) derived from 3-hydroxy-2-naphthoic acid appeared to be the most effective candidate (Table 1, entry 10). Further examination of the solvent effect revealed that CH_2Cl_2 was the suitable one (Table 1, entries 11–16).

With the optimal reaction conditions in hand, the substrate scope of this reaction was next examined. Firstly, a range of nitrostyrenes were tested in the ADS of 4-methylcyclohexanone. As summarized in Table 2, the electronic feature of the substituents has little influence on the reactivity and selectivity; both electron-donating and withdrawing substituents in the aromatic ring of nitrostyrenes are well tolerated in this reaction, providing the products with good to excellent selectivity (Table 2, entries 1–6). Exploring of ketone scope, we found a variety of substituted cyclohexanones were efficiently desymmetrized in this reaction. For these more hindered ketones, the electronic feature of the substituent on nitrostyrenes have obviously effect on the reactivity and selectivity of this reaction. Electron deficient nitrostyrene provided the products with higher selectivity than neutral or electron sufficient ones (Table 2, entries 8 vs 7 and 9, entries 11 vs 10 and 12). It is worthwhile that the desymmetrization of hetero-cyclohexanones can also be realized with excellent diastereoselectivities albeit with moderate enantioselectivities (Table 2, entries 13–16).

To determine the generality of catalyst **3**, we further detect the catalytic activity of **3** in the direct Michael reaction of cyclohexanone with nitrostyrenes. Optimization of the reaction conditions shows that water was the best medium with $PhCO_2H$ as cocatalyst. The loading of the catalyst can even be reduced to 5 mol% (see Supplementary data for details).

Table 1
Optimization of reaction conditions for the ADS of 4-methylcyclohexanone[a]

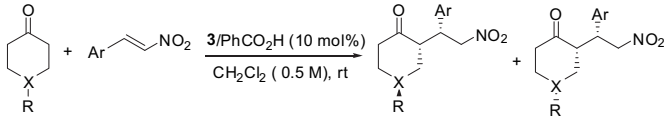


4a 5a 6aa 6aa'

Entry[a]	Cat.	Solvent	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	CH_2Cl_2	24	66	88:12	82
2	**1b**	CH_2Cl_2	32	48	95:5	89
3	**1c**	CH_2Cl_2	32	74	95:5	85
4	**1d**	CH_2Cl_2	36	70	92:8	84
5	**1e**	CH_2Cl_2	24	82	94:6	80
6	**1f**	CH_2Cl_2	32	80	98:2	88
7	**2a**	CH_2Cl_2	12	80	95:5	86
8	**2b**	CH_2Cl_2	29	74	98:2	87
9	**2c**	CH_2Cl_2	29	76	98:2	87
10	**3**	**CH_2Cl_2**	**12**	**78**	**>99:1**	**93**
11	**3**	$CHCl_3$	14	64	99:1	84
12	**3**	THF	17	63	96:4	88
13	**3**	*n*-Hexane	12	69	96:4	86
14	**3**	Toluene	12	79	97:3	82
15[e]	**3**	CH_2Cl_2	20	82	93:7	86
16[f]	**3**	—	20	71	81:19	90

[a] Reactions were run on a scale of 5.0 mmol **4a**, 0.5 mmol **5a**, 10 mol% organocat./$PhCO_2H$.
[b] Isolated yield.
[c] Ratio of **6aa**:**6aa'**, determined by ^1H NMR analysis of the crude products.
[d] Determined by chiral HPLC.
[e] 0.5 mL of CH_2Cl_2 was used.
[f] Neat.

Table 2
ADS of 4-substituted cyclohexanone via asymmetric Michael addition to nitrostyrenes[a]



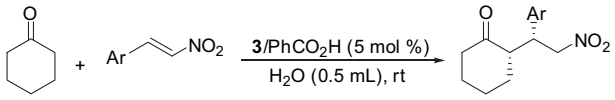
4a-g 5a-f 6aa-ga 6aa'-ga'

Entry[a]	X–R	Ar	Time (h)	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	CH–CH_3(**4a**)	Ph(**5a**)	12	**6aa**	78	>99:1	93
2	CH–CH_3(**4a**)	*p*-F-Ph(**5b**)	10	**6ab**	95	91:9	90
3	CH–CH_3(**4a**)	*p*-Cl-Ph(**5c**)	10	**6ac**	77	98:2	88
4	CH–CH_3(**4a**)	*p*-Br-Ph(**5d**)	10	**6ad**	76	90:10	88
5	CH–CH_3(**4a**)	*p*-Me-Ph(**5e**)	10	**6ae**	90	90:10	74
6	CH–CH_3(**4a**)	*p*-MeO-Ph (**5f**)	10	**6af**	63	99:1	83
7	CH–C_2H_5(**4b**)	Ph(**5a**)	17	**6ba**	59	97:3	83
8	CH–C_2H_5(**4b**)	*p*-F-Ph(**5b**)	10	**6bb**	87	99:1	90
9	CH–C_2H_5(**4b**)	*p*-MeO-Ph (**5f**)	32	**6bf**	90	98:2	77
10	CH–Ph(**4c**)	Ph(**5a**)	23	**6ca**	56	97:3	83
11	CH–Ph(**4c**)	*p*-F-Ph(**5b**)	9	**6cb**	67	94:6	90
12	CH–Ph(**4c**)	*p*-MeO-Ph (**5f**)	23	**6cf**	90	99:1	80
13	C(OCH_2CH_2O) (**4d**)	Ph(**5a**)	34	**6da**	67	90:10	78
14	N-Boc(**4e**)	Ph(**5a**)	40	**6ea**	88	99:1	60
15	S(**4f**)	Ph(**5a**)	10	**6fa**	77	97:3	80
16	O(**4g**)	Ph(**5a**)	48	**6ga**	60	97:3	50

[a] All reactions were carried out under the optimal conditions: 5.0 mmol **4**, 0.5 mmol **5**, 10 mol% **3**/$PhCO_2H$, 1 mL CH_2Cl_2. The absolute configuration of the major product was determined by the comparison of HPLC retention times with those in the literature.[9]
[b] Isolated yield.
[c] Determined by ^1H NMR analysis of the crude products.
[d] Determined by chiral HPLC.

As illustrated in Table 3, catalyst **3** also showed excellent ability in controlling the enantio- and diastereoselectivity of this reaction.

Table 3
Salicylic amide **3** catalyzed asymmetric Michael addition of cyclohexanone with nitrostyrenes in water[a]



4h **5a-j** **6ha-hj**

Entry[a]	Ar	Time (h)	Product	Yield[b] (%)	dr (*syn*:*anti*)[c]	ee[c] (%)
1	Ph(**5a**)	8	**6ha**	83	99:1	96
2	*p*-FPh(**5b**)	10	**6hb**	80	94:6	92
3	*p*-ClPh(**5c**)	13	**6hc**	69	88:12	88
4	*p*-BrPh(**5d**)	11	**6hd**	82	98:2	90
5	*p*-MePh(**5e**)	5	**6he**	93	97:3	94
6	*o*-ClPh(**5f**)	6	**6hf**	89	98:2	93
7	*o*-FPh(**5g**)	11	**6hg**	83	94:6	92
8	*m*-PhOPh(**5h**)	5	**6hh**	74	95:5	86
9	2,4-ClPh(**5i**)	5	**6hi**	80	99:1	92
10	2-Thienyl(**5j**)	6	**6hj**	81	90:10	80

[a] All reactions were run in the presence of **3**/$PhCO_2H$ (5 mol %) on 0.25 mmol scale in 0.5 mL H_2O at rt.
[b] Isolated yield.
[c] Determined by chiral HPLC.

Significant structural variation in the nitrostyrene component can be realized (Table 3). The reaction displays obvious generality and functional-group tolerance. Both electron-donating and withdrawing substrates could be utilized without substantial loss in selectivity (dr up to 99:1, ee up to 96%) and yield (up to 93%). A heteroaromatic nitrostyrene also worked well in this reaction with somewhat lower ee (Table 3, entry 10).

The absolute configuration of the major isomer in the reaction of 4-substituted cyclohexanones with a variety of nitrostyrenes was determined to be (2′*R*,2*S*,4*S*) by comparison of the HPLC data with the known literature.[23b] To explain the excellent selectivity of this reaction, we proposed that the catalytic mode of **3** should be similar to the thiourea catalyst, reported by the Tang[15d] and our groups,[15e,f] respectively. The pyrrolidine motif efficiently activates the ketone via enamine intermediate; meanwhile, the NH of the amide and the adjacent OH presumably provide double hydrogen bond to activate and orientate the nitrostyrenes (Fig. 1).

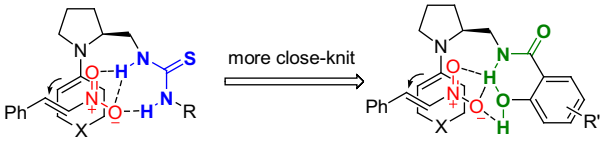


Figure 1. Improvement on of H-bonding interaction model.

3. Conclusions

In summary, we have developed a new bifunctional catalyst for the desymmetrization of prochiral cyclohexanone by direct Michael reaction. The optimal organocatalyst (**3**), which is readily accessible from commercially available material, tolerates a range of 4-substituted cyclohexanones and nitrostyrenes and provide for the desired products with three newly generated stereogenic centers in high yields and with excellent diastereo- and enantioselectivities. The extension of substrate scope and application of this catalyst in other reactions are ongoing in our laboratory.

4. Experimental section

4.1. General remarks

Unless otherwise noted, material were purchased from commercial suppliers and used without further purification. Dichloromethane and trichloromethane were freshly distilled from calcium hydride. Hexane and ethyl acetate for flash column chromatography were distilled before use. Flash column chromatography was performed using 200–300 mesh silica gel. Infrared spectra were recorded on a Perkin–Elmer PE-983 spectrometer as KBr film with absorption in cm^{-1}. ^1H NMR spectra were recorded on Varian Mercury 400 (400 MHz) spectrophotometers. Chemical shifts are reported in parts per million from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s=single, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on Varian Mercury 400 (100 MHz) with complete proton decoupling spectrophotometers ($CDCl_3$: 77.0 ppm). Chiral HPLC was performed on Agilent 1100 series with chiral columns (Chiralpak AS, AD, OD, and OJ columns (Daicel Chemical Ind., Ltd)). Elementary analysis was taken on a Vario EL III elementary analysis instrument. Mass spectra analysis was performed on API 200 LC/MS system (Applied Biosystems Co. Ltd).

4.2. General procedures for preparation of thiourea catalysts 2a–c and 3

3-Hydroxy-2-naphthoic acid (1.26 g, 6.7 mmol) was dissolved in 10 mL THF. The mixture was cooled to 0 °C. Then DCC (1.39 g 6.7 mmol) and HOBt (0.91 g, 6.7 mmol) were added into this solution. And *N*-Boc-(*S*)-2-aminomethylpyrrolidine (1.0 g, 5 mmol, prepared according to the known procedure in five steps from L-proline[10]) was introduced into the solution by dropwise at 0 °C. After the addition was completed, the mixture was allowed to warm to room temperature and stirred for an appropriate time (monitored by TLC, petroleum ether/ethyl acetate=3:1). When the reaction was completed, the solvent was removed under reduced pressure. The residue was directly subjected to the next step —dissolved in a mixture of TFA/CH_2Cl_2=1:4 (20 mL) and stirred for 2 h at room temperature. The mixture was basified with concentrated ammonia solution and extracted with CH_2Cl_2 (3×30 mL). After the removal of the solvent under reduced pressure, the residue was purified through flash column chromatography on silica gel (eluent, ethyl acetate/methanol=1:1) to yield **3** as a yellow solid in 70% yield.

*4.2.1. Catalyst **2a**.* The title compound was prepared according to the typical procedure, as described above in 78% yield. White solid. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.56–7.54 (m, 1H), 7.34–7.27 (m, 1H), 6.91–6.78 (br s, 2H), 3.59–3.56 (m, 1H), 3.46–3.43 (m, 1H), 3.30–3.25 (m, 1H), 2.98–2.94 (m, 2H), 1.94–1.74 (m, 3H), 1.49–1.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 169.3, 154.2, 135.9, 134.3, 126.5, 118.2, 109.5, 60.2, 45.2, 40.5, 33.6, 24.0. Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.37; H, 7.43; N, 12.70. MS: *m*/*z*, 220.1.

*4.2.2. Catalyst **2b**.* The title compound was prepared according to the typical procedure, as described above in 78% yield. White solid. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 9.65 (br s, 1H), 8.37 (s, 1H), 7.54 (d, *J*=7.2 Hz, 1H), 6.38–6.34 (m, 2H), 3.83 (s, 1H), 3.75 (s, 3H), 3.64 (s, 1H), 3.24 (s, 2H), 2.08–1.75 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 171.4, 164.6, 162.9, 128.5, 107.0, 106.8, 101.4, 60.6, 55.3, 45.3, 40.5, 27.3, 23.9. Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.11; H, 7.23; N, 11.05. MS: *m*/*z*, 250.1.

*4.2.3. Catalyst **2c**.* The title compound was prepared according to the typical procedure, as described above in 78% yield. White solid. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.55 (br s, 1H), 7.33 (d, *J*=2.0 Hz, 1H), 7.21 (s, 1H), 3.84–3.68 (m, 2H), 3.63–3.60 (m, 2H), 3.37–3.30 (m, 1H), 3.18–3.13 (m, 2H), 2.85–2.78 (m, 1H), 2.08–1.70 (m, 4H),

1.22 (d, J=6.8 Hz, 6H), 1.20 (d, J=6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 172.2, 157.2, 138.9, 137.3, 129.5, 121.2, 112.5, 60.2, 45.2, 40.5, 33.6, 27.7, 26.6, 24.1, 24.0, 22.4. Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 70.94; H, 9.14; N, 9.08. MS: m/z, 304.0.

4.2.4. Catalyst ***3****.* The title compound was prepared according to the typical procedure, as described above in 78% yield. White solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.12 (s, 1H), 7.67–7.60 (m, 2H), 7.44–7.41 (m, 1H), 7.25–7.20 (m, 2H), 4.19 (br s, 3H), 3.64–3.35 (m, 3H), 3.06–3.00 (m, 2H), 2.02–1.86 (m, 3H), 1.52–1.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 169.4, 158.9, 137.0, 130.7, 128.9, 127.7, 126.1, 120.3, 112.3, 59.5, 45.7, 42.7, 42.6, 28.7, 24.9. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.74; H, 6.14; N, 9.88. MS: m/z, 270.3.

4.3. General procedure for the Michael addition (Table 2)

Catalyst (0.05 mmol), $PhCO_2H$ (0.05 mmol), and 10 equiv cyclohexanone were dissolved in 1 mL CH_2Cl_2. After the mixture was stirred for 15 min at room temperature, the corresponding nitroolefin (0.5 mmol) was added and the mixture was stirred for an appropriate time (monitored by TLC, petroleum ether/ethyl acetate=5:1). The reaction mixture was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=20:1–5:1) to gain the desired product as oil or solid. Relative and absolute configurations of the products were determined by comparison with the known ^{1}H NMR, ^{13}C NMR, and chiral HPLC analysis.

*4.3.1. (2S,4S)-4-Methyl-2-((R)-2-nitro-1-phenylethyl)cyclohexanone (****6aa****).* The title compound was prepared according to the typical procedure, as described above in 78% yield. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.56–7.16 (m, 5H), 4.70 (dd, J=4.6, 12.7 Hz, 1H), 4.61 (dd, J=10.1, 12.6 Hz, 1H), 3.84–3.77 (m, 1H), 2.76–2.70 (m, 1H), 2.52–2.49 (m, 2H), 2.08–1.97 (m, 1H), 1.67–1.39 (m, 4H), 0.97 (d, J=6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 212.9, 137.2, 128.9, 128.6, 128.2, 128.1, 127.9, 79.0, 52.7, 49.9, 43.9, 38.4, 34.3, 26.4, 19.2. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.90; H, 7.15; N, 5.35. MS: m/z, 261.1. HPLC (Chiralpak AS-H, i-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=230 nm): t_{minor}=18.1 min, t_{major}=36.9 min; ee=93%. R_f=0.36 (petroleum ether/ethyl acetate=5:1).

*4.3.2. (2S,4S)-2-((R)-1-(4-Fluorophenyl)-2-nitroethyl)-4-methylcyclohexanone (****6ab****).* The title compound was prepared according to the typical procedure, as described above in 95% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.36–7.02 (m, 5H), 4.97–4.67 (m, 2H), 4.34–3.95 (m, 1H), 2.95–2.87 (m, 1H), 2.52–2.35 (m, 2H), 2.07–1.88 (m, 2H), 1.73–1.59 (m, 4H), 1.03–0.97 (m, 3H), 0.88–0.86 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 212.5, 162.4, 159.9, 130.5, 129.7, 124.7, 124.3, 115.9, 77.6, 51.5, 47.9, 39.7, 38.3, 34.1, 26.6, 18.9. Anal. Calcd for $C_{15}H_{18}FNO_3$: C, 64.50; H, 6.50; N, 5.01. Found: C, 64.58; H, 6.43; N, 5.07. MS: m/z, 279.0. HPLC (Chiralpak AD-H+OD-H, i-propanol/hexane=5:95, flow rate 1.0 mL/min, λ=230 nm): t_{minor}=29.6 min, t_{major}=33.0 min; ee=90%. R_f=0.44 (petroleum ether/ethyl acetate=5:1).

*4.3.3. (2S,4S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl)-4-methylcyclohexanone (****6ac****).* The title compound was prepared according to the typical procedure, as described above in 77% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.39–7.34 (m, 2H), 7.29–7.20 (m, 2H), 5.02–4.63 (m, 2H), 4.02–3.80 (m, 1H), 2.87–2.75 (m, 1H), 2.54–2.41 (m, 2H), 2.11–1.96 (m, 2H), 1.74–1.33 (m, 2H), 1.17–1.14 (m, 1H), 1.03 (d, J=6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 210.4, 136.8, 133.2, 129.8, 128.8, 78.5, 52.5, 42.5, 41.4, 37.9, 35.1, 31.9, 21.1. Anal. Calcd for $C_{15}H_{18}ClNO_3$: C, 60.91; H, 6.13; N, 4.74. Found: C, 60.88; H, 6.09; N, 4.76. MS: m/z, 259.0. HPLC (Chiralpak AD-H, i-propanol/hexane=2:98, flow rate 1.0 mL/min, λ=230 nm): t_{minor}=35.1 min, t_{major}=40.0 min; ee=88%. R_f=0.63 (petroleum ether/ethyl acetate=5:1).

*4.3.4. (2S,4S)-2-((R)-1-(4-Bromophenyl)-2-nitroethyl)-4-methylcyclohexanone (****6ad****).* The title compound was prepared according to the typical procedure, as described above in 76% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.49–7.05 (m, 4H), 4.98–4.54 (m, 2H), 3.93–3.71 (m, 1H), 2.79–2.69 (m, 1H), 2.54–2.30 (m, 2H), 2.06–1.86 (m, 2H), 1.68–1.62 (m, 2H), 1.49–1.26 (m, 1H), 1.01–0.97 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 210.7, 137.6, 130.5, 121.8, 77.7, 52.8, 43.1, 41.9, 38.4, 35.5, 32.3, 21.5. Anal. Calcd for $C_{15}H_{18}BrNO_3$: C, 52.96; H, 5.83; N, 4.12. Found: C, 52.90; H, 5.91; N, 4.04. MS: m/z, 339.1. HPLC (Chiralpak AD-H, i-propanol/hexane=5:95, flow rate 1.0 mL/min, λ =230 nm): t_{minor}=33.3 min, t_{major}=36.7 min; ee=88%. R_f=0.75 (petroleum ether/ethyl acetate=5:1).

*4.3.5. (2S,4S)-4-Methyl-2-((R)-2-nitro-1-p-tolylethyl)cyclohexanone (****6ae****).* The title compound was prepared according to the typical procedure, as described above in 90% yield. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.15–7.04 (m, 4H), 4.67 (dd, J=4.6, 12.6 Hz, 1H), 4.57 (dd, J=12.4, 12.8 Hz, 1H), 2.77–2.67 (m, 1H), 2.54–2.36 (m, 2H), 2.31 (s, 3H), 2.08–1.91 (m, 2H), 1.63–1.60 (m, 1H), 1.50–1.34 (m, 2H), 0.96 (d, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 213.0, 137.6, 134.0, 129.8, 129.5, 127.9, 127.7, 79.1, 50.1, 43.7, 38.4, 34.3, 26.4, 21.0, 20.9, 19.4. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.85; H, 7.52; N, 5.01. MS: m/z, 275.1. HPLC (Chiralpak OD-H, i-propanol/hexane=1:99, flow rate 1.0 mL/min, λ=230 nm): t_{minor}=25.3 min, t_{major}=26.7 min; ee=74%. R_f=0.60 (petroleum ether/ethyl acetate=5:1).

*4.3.6. (2S,4S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)-4-methylcyclohexanone (****6af****).* The title compound was prepared according to the typical procedure, as described above in 63% yield. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.19–7.07 (m, 2H), 6.88–6.83 (m, 2H), 4.83 (dd, J=6, 9.2 Hz, 1H), 4.60 (m, 1H), 3.94–3.73 (m, 4H), 2.78–2.64 (m, 1H), 2.51–2.33 (m, 2H), 2.05–1.96 (m, 2H), 1.74–1.08 (m, 3H), 0.97 (d, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 213.1, 158.7, 130.1, 129.4, 129.1, 128.9, 114.3, 79.2, 55.1, 43.3, 38.5, 31.9, 26.4, 21.2. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.90; H, 7.35; N, 4.73. MS: m/z, 291.0 HPLC (Chiralpak AD-H+OD-H, i-propanol/hexane=5:95, flow rate 1.0 mL/min, λ=230 nm): t_{minor}=53.3 min, t_{major}=55.5 min; ee=83%. R_f=0.40 (petroleum ether/ethyl acetate=5:1).

*4.3.7. (2S,4S)-4-Ethyl-2-((R)-1-(4-fluorophenyl)-2-nitroethyl)cyclohexanone (****6bb****).* The title compound was prepared according to the typical procedure, as described above in 87% yield. Light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.31–7.05 (m, 4H), 4.77 (dd, J=4.8, 12.8 Hz, 1H), 4.70 (dd, J=9.9, 12.9 Hz, 1H), 4.06–4.00 (m, 1H), 2.90–2.84 (m, 1H), 2.50–2.43 (m, 2H), 1.99–1.93 (m, 1H), 1.75–1.70 (m, 2H), 1.48–1.29 (m, 4H), 0.80 (t, J=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 212.7, 130.6, 129.8, 129.7, 124.7, 116.1, 115.1, 78.8, 55.8, 48.0, 39.7, 35.6, 33.5, 25.7, 11.7. Anal. Calcd for $C_{16}H_{20}FNO_3$: C, 65.51; H, 6.87; N, 4.78. Found: C, 65.48; H, 6.87; N, 4.71. MS: m/z, 293.0. HPLC (Chiralpak AD-H+OD-H, i-propanol/hexane=5:95, flow rate 1.0 mL/min, λ=230 nm): t_{minor}=31.2 min, t_{major}=39.2 min; ee=90%. R_f=0.84 (petroleum ether/ethyl acetate=5:1).

*4.3.8. (2S,4S)-4-Ethyl-2-((R)-1-(4-methoxyphenyl)-2-nitroethyl)cyclohexanone (****6bf****).* The title compound was prepared according to the typical procedure, as described above in 90% yield. Light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.10–7.08 (m, 2H),

6.88–6.83 (m, 2H), 4.68 (dd, J=12.0, 12.0 Hz, 1H), 4.60 (dd, J=16.0, 24.0 Hz, 1H), 3.78 (s, 3H), 2.70–2.58 (m, 1H), 2.50–2.43 (m, 2H), 1.99–1.93 (m, 1H), 1.73–1.61 (m, 2H), 1.48–1.29 (m, 4H), 0.80 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 213.2, 159.0, 128.9, 128.8, 114.3, 79.2, 55.1, 50.2, 43.3, 38.6, 35.2, 33.3, 32.1, 26.3, 11.8. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.65; H, 7.52; N, 4.62. MS: m/z, 305.2. HPLC (Chiralpak OD-H, i-propanol/hexane=5:95, flow rate 1.0 mL/min, λ=230 nm): t_{minor}=29.3 min, t_{major}=35.7 min; ee=77%. R_f=0.60 (petroleum ether/ethyl acetate=5:1).

*4.3.9. (2S,4S)-2-((R)-2-Nitro-1-phenylethyl)-4-phenylcyclohexanone (**6ca**).* The title compound was prepared according to the typical procedure, as described above in 56% yield. White solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.37–7.31 (m, 2H), 7.30–7.26 (m, 3H), 7.24–7.20 (m, 3H), 7.11–7.10 (m, 2H), 4.64 (dd, J=12.0, 16.0 Hz, 1H), 4.58 (dd, J=8.0, 12.0 Hz, 1H), 4.12–3.92 (m, 1H), 3.20–3.14 (m, 1H), 2.75–2.70 (m, 2H), 2.60–2.54 (m, 1H), 2.27–2.13 (m, 2H), 1.96–1.89 (m, 1H), 1.76–1.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 212.3, 143.0, 136.7, 129.2, 128.6, 128.2, 127.9, 126.6, 126.4, 79.0, 51.4, 44.0, 38.9, 36.8, 32.6, 29.6. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.32; H, 6.51; N, 4.27. MS: m/z, 323.0. HPLC (Chiralpak AS-H, i-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=230 nm): t_{minor}=29.1 min, t_{major}=46.2 min; ee=83%. R_f=0.68 (petroleum ether/ethyl acetate=5:1).

*4.3.10. (2S,4S)-2-((R)-1-(4-Fluorophenyl)-2-nitroethyl)-4-phenylcyclohexanone (**6cb**).* The title compound was prepared according to the typical procedure, as described above in 67% yield. White solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.34–7.07 (m, 9H), 4.94–4.67 (m, 2H), 4.43–4.22 (m, 1H), 3.22–3.17 (m, 1H), 3.11–3.05 (m, 1H), 2.89–2.70 (m, 1H), 2.59–2.53 (m, 1H), 2.25–2.22 (m, 2H), 2.00–1.93 (m, 1H), 1.93–1.62 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 212.0, 162.4, 159.9, 143.0, 130.0, 129.9, 129.8, 128.6, 126.5, 126.4, 124.9, 116.3, 77.4, 50.1, 43.4, 39.9, 38.9, 36.8, 32.4, 29.6. Anal. Calcd for $C_{20}H_{20}FNO_3$: C, 70.37; H, 5.91; N, 4.10. Found: C, 70.29; H, 5.88; N, 4.16. MS: m/z, 341.0. HPLC (Chiralpak AD-H=OD-H, i-propanol/hexane=5:95, flow rate 1.0 mL/min, λ=230 nm): t_{minor}=53.0 min, t_{major}=67.1 min; ee=90%. R_f=0.50 (petroleum ether/ethyl acetate=5:1).

*4.3.11. (2S,4S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)-4-phenylcyclohexanone (**6cf**).* The title compound was prepared according to the typical procedure, as described above in 90% yield. White solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.30–7.25 (m, 2H), 7.22–7.11 (m, 5H), 6.88–6.86 (m, 2H), 4.60 (dd, J=12.8, 12.8 Hz, 1H), 4.53 (dd, J=12.8, 12.8 Hz, 1H), 3.93–3.88 (m, 1H), 3.78 (s, 3H), 3.17–3.14 (m, 1H), 2.78–2.59 (m, 2H), 2.59–2.53 (m, 1H), 2.23–2.15 (m, 2H), 1.97–1.90 (m, 1H), 1.75–1.69 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 213.2, 159.9, 143.8, 129.6, 129.3, 129.0, 127.3, 115.3, 79.9, 55.9, 52.3, 44.1, 37.5, 36.9, 33.4. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.20; H, 6.44; N, 3.94. MS: m/z, 353.2. HPLC (Chiralpak AD-H+OD-H, i-propanol/hexane=15:85, flow rate 1.0 mL/min, λ=230 nm): t_{minor}=47.4 min, t_{major}=66.0 min; ee=80%. R_f=0.47 (petroleum ether/ethyl acetate=5:1).

*4.3.12. (S)-7-((R)-2-Nitro-1-phenylethyl)-1,4-dioxaspiro[4.5]decan-8-one (**6da**).* The title compound was prepared according to the typical procedure, as described above in 67% yield. White solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.33–7.15 (m, 5H), 4.96–4.58 (m, 2H), 3.97–3.84 (m, 4H), 3.09–3.02 (m, 1H), 2.74–2.62 (m, 1H), 2.47–2.42 (m, 1H), 2.05–1.93 (m, 2H), 1.69–1.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 210.3, 137.1, 128.9, 128.4, 128.1, 127.8, 106.9, 78.8, 64.7, 64.4, 48.0, 43.3, 39.2, 38.5, 34.9. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.87; H, 6.33; N, 4.61. MS: m/z, 305.0. HPLC (Chiralpak AS-H, i-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=230 nm): t_{minor}=29.6 min, t_{major}=50.4 min; ee=78%. R_f=0.33 (petroleum ether/ethyl acetate=4:1).

*4.3.13. (S)-3-((R)-2-Nitro-1-phenylethyl)dihydro-2H-thiopyran-4(3H)-one (**6fa**).* The title compound was prepared according to the typical procedure, as described above in 77% yield. White solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.37–7.29 (m, 3H), 7.25–7.19 (m, 2H), 4.76–4.60 (m, 2H), 4.01–3.95 (m, 1H), 3.08–2.93 (m, 3H), 2.88–2.75 (m, 3H), 2.63–2.59 (m, 1H), 2.48–2.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 209.4, 136.4, 129.2, 128.2, 128.1, 78.5, 54.9, 44.5, 43.4, 35.0, 31.5. Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.55; H, 5.70; N, 5.28. Found: C, 58.73; H, 5.81; N, 5.24. HPLC (Chiralpak As-H, i-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=15.66 min, t_{major}=20.00 min; ee=80%. R_f=0.45 (petroleum ether/ethyl acetate=4:1).

*4.3.14. (R)-3-((R)-2-Nitro-1-phenylethyl)dihydro-2H-pyran-4(3H)-one (**6ga**).* The title compound was prepared according to the typical procedure, as described above in 60% yield. White solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.35–7.17 (m, 5H), 4.93 (dd, J=4.0 Hz, 1H), 4.63 (dd, J=10 Hz, 1H), 4.12–4.11 (m, 1H), 3.83–3.66 (m, 3H), 3.28–3.23 (m, 1H), 2.87 (m, 1H), 2.65–2.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 207.3, 136.2, 129.1, 128.2, 127.8, 78.6, 71.5, 68.9, 53.2, 44.5, 42.9, 41.2. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.73; H, 5.97; N, 5.34. HPLC (Chiralpak AD-H, i-propanol/hexane=15:85, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=14.5 min, t_{major}=28.1 min; ee=50%. R_f=0.50 (petroleum ether/ethyl acetate=4:1).

*4.3.15. (R)-tert-Butyl 3-((R)-2-nitro-1-phenylethyl)-4-oxopiperidine-1-carboxylate (**6ea**).* The title compound was prepared according to the typical procedure, as described above in 88% yield. White solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.36–7.19 (m, 5H), 4.94 (dd, J=4.8, 12.4 Hz, 1H), 4.63 (dd, J=9.6, 12.0 Hz, 1H), 4.21 (s, 1H), 3.79 (s, 1H), 3.19 (s, 2H), 2.79–2.68 (m, 2H), 2.59–2.46 (m, 2H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 208.3, 154.0, 136.4, 129.1, 128.2, 80.7, 78.8, 51.9, 48.1, 44.2, 41.8, 41.7, 28.2. Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 61.97; H, 6.96; N, 8.02. HPLC (Chiralpak AD-H, i-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=13.4 min, t_{major}=15.2 min; ee=60%. R_f=0.50 (petroleum ether/ethyl acetate=5:1).

4.4. General procedure for the Michael addition in water (Table 3)

Catalyst **3** (0.025 mmol), $PhCO_2H$ (0.025 mmol), and 10 equiv cyclohexanone were dissolved in 0.5 mL H_2O. After the mixture was stirred for 15 min at 35 °C, the corresponding nitroolefin (0.25 mmol) was added and the mixture was stirred for an appropriate time (monitored by TLC, petroleum ether/ethyl acetate=4:1). The reaction mixture was then extracted with CH_2Cl_2, and the resulting residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=20:1–5:1) to gain the desired product as a white solid. Relative and absolute configurations of the products were determined by comparison with the known ^{1}H NMR, ^{13}C NMR, and chiral HPLC analysis. Compounds **6ha–6hj** are known.[10]

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.09.005.

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