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Doubly stereocontrolled asymmetric Michael addition of acetylacetone to nitroolefins promoted by an isosteviol-derived bifunctional thiourea

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ABSTRACT

A novel class of chiral bifunctional thioureas bearing a chiral lipophilic beyerane scaffold and a tertiary amino group was designed and prepared. The thioureas were proven to be effective for catalyzing the doubly stereocontrolled asymmetric Michael addition between acetylacetone and nitroolefins. The corresponding adducts were obtained in high yields (up to 95%) and with good to excellent enantioselectivities (up to 97%). In addition, the reaction of *tert*-butyl acetoacetate and *trans*-β-nitrostyrene also proceeded smoothly with good enantioselectivity.

1. Introduction

Both enantiomers of a chiral compound are often useful and versatile in terms of the pharmaceutical industry and organic synthesis.[1] However, the efficient preparation of both enantiomers of a chiral compound still represents a daunting task, and to the best of our knowledge, the number of examples on effective double asymmetric inductions on metal-free organocatalytic reactions is limited.[2] As a result, developing an effective organocatalytic method to prepare optionally both the enantiomers of chiral compounds is a highly desirable goal.

Over the past few years, bifunctional tertiary amine-thiourea organocatalysts have emerged as new and efficient organocatalysts for asymmetric reactions.[3] Despite their tremendous utility, these organocatalysts are derived from a very limited range of chiral structural scaffolds, including cyclohexane-1,2-diamine,[4] 1,10-binaphthyl-2,20-diamine,[5] and cinchona alkaloids.[6] Therefore, the development of bifunctional tertiary amine-thiourea organocatalysts with novel chiral scaffolds for doubly stereocontrolled asymmetric transformations would be highly desirable.

As part of our continuing interests in natural product[7] and asymmetric catalysis,[8] we have recently reported a novel class of easily prepared, inexpensive, and tunable chiral bifunctional primary amine-thiourea organocatalysts by combining a novel chiral scaffold (isosteviol) and cyclohexane-1,2-diamine, **1a** and **1b**, and their application in doubly stereocontrolled asymmetric Michael additions.[9] Herein we report the discovery that thioureas, **2a** and **2b,** efficiently promote the Michael reaction of acetylacetone and nitroolefins with good levels of enantioselectivity (Fig. 1).

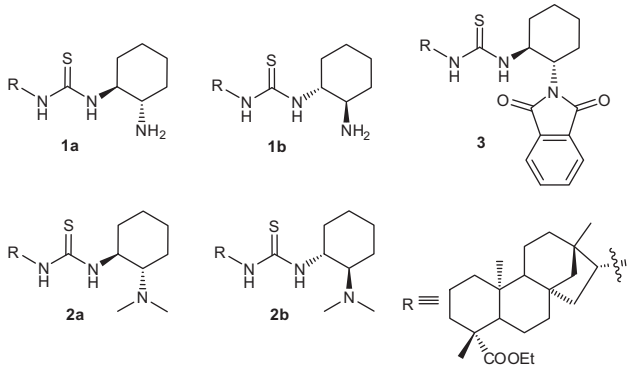

Figure 1. Novel multifunctional thiourea catalysts.

2. Results and discussion

Starting from the commercially available natural product stevioside, isothiocyanate **4** was conveniently prepared.[9] *N*,*N*-Dimethyl cyclohexane-1,2-diamine **5a/5b** was synthesized starting from cyclohexane-1,2-diamine through mono amino protection with phthalic anhydride, N,N-dimethylation, and subsequently deprotection.[10] *N*-Phthaloyl-1,2-diaminocyclohexane **6** was also synthesized. Coupling of compound **4** and **5/6** afforded the desired bifunctional thiourea catalyst **2/3** in good yield (Scheme 1). Following the same procedure, these catalysts could be easily prepared on a gram scale.

With the novel bifunctional thioureas in hand, we initially screened their catalytic activities for asymmetric Michael additions with acetylacetone and *trans*-β-nitrostyrene as the model reaction

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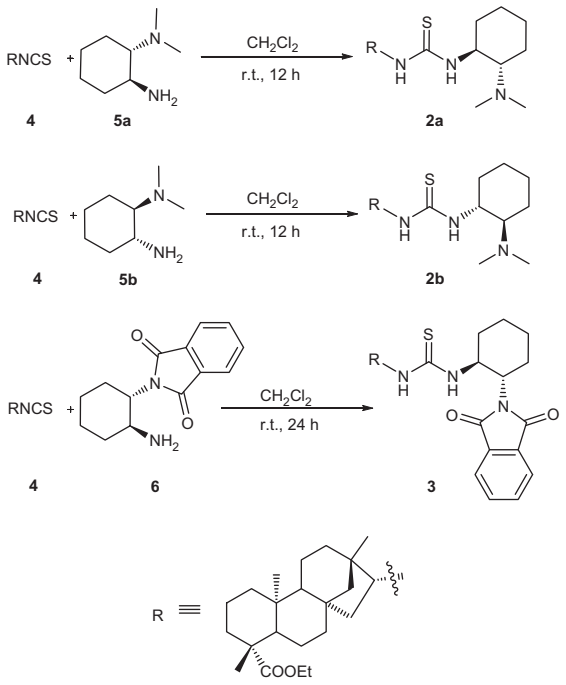
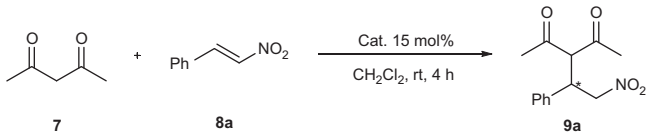


Scheme 1. Synthesis of thiourea-amine multifunctional catalysts.

Table 1
Comparison of catalytic activities of thioureas for the model reaction [a]



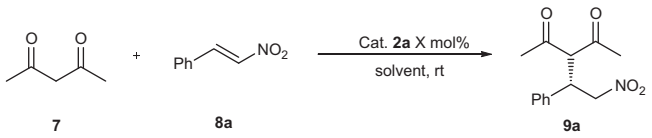
Entry	Catalyst	Yield[b] (%)	Ee[c] (%)
1	**1a**	nr[d]	nd[e]
2	**1b**	nr[d]	nd[e]
3	**2a**	84	85 (*S*)
4	**2b**	83	82 (*R*)
5	**3**	Trace	nd[e]

[a] Unless otherwise specified, all reactions were carried out using *trans*-β-nitrostyrene (0.20 mmol), acetylacetone (0.40 mmol), and 15 mol % of catalyst in 0.5 mL of CH_2Cl_2 at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] No reaction.
[e] Not determined.

(Table 1). The results showed that catalysts **1** and **3** exhibited unobservable activities for the model reaction (Table 1, entries 1, 2, and 5). The newly designed catalysts **2** proved to be the best choice for this asymmetric Michael addition. More importantly, thioureas **2a** and **2b** exhibited a reversed sense of asymmetric induction (Table 1, entry 3 vs entry 4).

In further experiments, other influencing factors, such as solvent, reaction temperature and catalyst loading, were thoroughly investigated employing **2a** as the catalyst. The results are listed in Table 2. Solvent evaluation revealed that both the yield and the enantioselectivity were highly dependent on the solvent. Aprotic solvents such as *n*-hexane, ether, CH_2Cl_2, $CHCl_3$, and toluene gave higher yields and enantioselectivities (Table 2, entries 1–5). When a protic solvent or more polar solvent, such as *i*-PrOH, CH_3CN, were used, both the yield and enantioselectivity decreased remarkably (Table 2, entries 6 and 7). In addition, when an aqueous medium such as H_2O or brine was employed, lower enantioselectivities were obtained (Table 2, entries 8 and 9). This was probably due to the negative effect of the hydrogen bonding interactions between the substrates and the protic solvents, which disturbed the efficient aggregation of the reactants surrounding the bifunctional catalyst. When the Michael reaction was performed without a solvent, it also furnished the product in good yield and enantioselectivity (Table 2, entry 10). A survey of solvents revealed that toluene was the optimal solvent.

Table 2
Optimization of the reaction conditions[a]



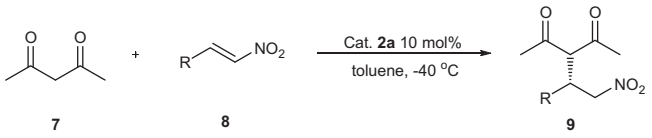
Entry	Solvent	X (mol %)	T (°C)	Time (h)	Yield[b] (%)	Ee[c] (%)
1	Hexane	15	25	2	70	82
2	Ether	15	25	2	74	83
3	CH_2Cl_2	15	25	3	84	85
4	$CHCl_3$	15	25	3	86	87
5	Toluene	15	25	3	88	89
6	CH_3CN	15	25	3	74	59
7	*i*-PrOH	15	25	2	72	67
8	H_2O	15	25	2	68	63
9	Brine	15	25	2	90	72
10[d]	Neat	15	25	2	82	83
11	Toluene	15	0	4	86	90
12	Toluene	15	−40	6	91	94
13	Toluene	15	−60	36	89	92
14	Toluene	10	−40	10	90	94
15	Toluene	5	−40	36	92	90

[a] Unless otherwise specified, all reactions were carried out using *trans*-β-nitrostyrene (0.20 mmol), acetylacetone (0.40 mmol), and 15 mol % of catalyst **2a** in 0.5 mL of solvent at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] 0.80 equiv of acetylacetone were used.

The reaction temperature was found to be an essential factor with regard to the enantioselectivity of this reaction. The stereoselectivity was gradually increased by decreasing the reaction temperature from 25 to −40 °C (Table 2, entries 5, 11 and 12). However, when decreasing the temperature to −60 °C, the reaction time was prolonged and the enantiomeric excess of the reaction reduced slightly (Table 2, entry 13). A decrease in the catalyst loading from 15 to 10 mol % did not affect the enantioselectivity or the yield, although a prolonged reaction time was necessary. When the catalyst loading was reduced to 5 mol %, the enantioselectivity and yield were not significantly affected, but the reaction time was prolonged. Thus, the optimized catalyst loading was chosen as 10 mol %.

Based on all of the above results, a set of acceptable reaction conditions, **7** (0.40 mmol, 2.0 equiv) and **8** (0.20 mmol, 1.0 equiv) in 0.5 mL of toluene with 10 mol % of catalyst **2a** at −40 °C were established. We next investigated the scope and limitations of this asymmetric Michael addition. All the nitrostyrenes bearing either electron-donating or electron-withdrawing substituents on the aromatic ring gave the desired Michael adducts in high yields and enantioselectivities (Table 3, entries 1–8). For 2-nitro-substituted-β-nitro styrene, Zhou's catalyst was not efficient.[4d] However, when our newly designed catalyst was used, the reaction occurred smoothly and afforded the desired product with the best enantioselectivity (97% ee, Table 3, entry 5). With respect to the electron-donating group substituted nitroalkenes, within a longer reaction time, the corresponding adducts were obtained in higher yields and with similar enantioselectivities (Table 3, entries 6–8). Naphthylnitroalkenes **8i/8j** and heteroaromatic nitroalkenes **8k/8l** also gave Michael adducts in good yields and with high

Table 3
Substrate studies of the Michael addition between acetylacetone and nitroolefins promoted by **2a**[a]

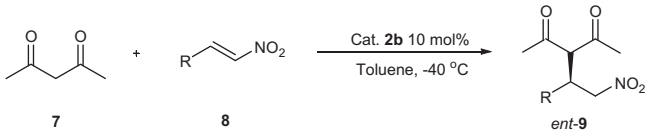


7 8 9

Entry	R		Time (h)	Product	Yield[b] (%)	Ee[c] (%)
1	C_6H_5	**8a**	10	**9a**	91	94
2	4-F-C_6H_4	**8b**	12	**9b**	86	93
3	4-Cl-C_6H_4	**8c**	12	**9c**	89	94
4	4-Br-C_6H_4	**8d**	12	**9d**	84	90
5	2-NO_2-C_6H_4	**8e**	12	**9e**	81	97
6	4-CH_3-C_6H_4	**8f**	24	**9f**	91	93
7	3-OCH_3-C_6H_4	**8g**	24	**9g**	95	95
8	4-OCH_3-C_6H_4	**8h**	24	**9h**	92	96
9	1-Naphthyl	**8i**	48	**9i**	90	92
10	2-Naphthyl	**8j**	48	**9j**	87	94
11	2-Furanyl	**8k**	24	**9k**	91	92
12	5-Cl-2-thienyl	**8l**	24	**9l**	82	95
13	PhCH=CH	**8m**	72	**9m**	79	82
14	*n*-Pr	**8n**	72	—	nr[d]	—
15	$PhCH_2CH_2$	**8o**	72	—	nr[d]	—

[a] Unless otherwise specified, all reactions were carried out using *trans*-β-nitrostyrene (0.20 mmol), acetylacetone (0.40 mmol), and 10 mol % catalyst **2a** in 0.5 mL of toluene at −40 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] No reaction.

Table 4
Substrate studies of the Michael addition between acetylacetone and nitroolefins promoted by **2b**[a]



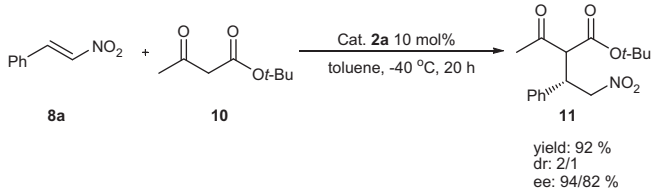
7 8 *ent*-9

Entry	R		Time (h)	Product	Yield[b] (%)	Ee[c] (%)
1	C_6H_5	**8a**	10	*ent*-**9a**	90	86
2	4-F-C_6H_4	**8b**	12	*ent*-**9b**	86	82
3	4-Cl-C_6H_4	**8c**	12	*ent*-**9c**	87	85
4	4-Br-C_6H_4	**8d**	12	*ent*-**9d**	86	83
5	2-NO_2-C_6H_4	**8e**	12	*ent*-**9e**	85	85
6	4-CH_3-C_6H_4	**8f**	24	*ent*-**9f**	94	91
7	3-CH_3O-C_6H_4	**8g**	24	*ent*-**9g**	91	87
8	4-CH_3O-C_6H_4	**8h**	24	*ent*-**9h**	93	85
9	1-Naphthyl	**8i**	48	*ent*-**9i**	90	77
10	2-Naphthyl	**8j**	48	*ent*-**9j**	88	82
11	2-Furanyl	**8k**	24	*ent*-**9k**	90	85
12	5-Cl-2-thienyl	**8l**	24	*ent*-**9l**	84	90
13	PhCH=CH	**8m**	72	*ent*-**9m**	76	79
14	*n*-Pr	**8n**	72	—	nr[d]	—
15	$PhCH_2CH_2$	**8o**	72	—	nr[d]	—

[a] Unless otherwise specified, all reactions were carried out using trans-β-nitrostyrene (0.20 mmol), acetylacetone (0.40 mmol), and 10 mol % of catalyst **2b** in 0.5 mL of toluene at −40 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] No reaction.

enantioselectivities (Table 3, entries 9–12). When the reaction was performed with conjugated nitroalkene **8m**, the yield and enantioselectivity were slightly lower (Table 3, entry 13). However, the reactions of aliphatic nitroolefins **8n** and **8o** were very sluggish under the same condition (Table 3, entries 14 and 15).

When thiourea **2b** was used to catalyze this Michael reaction, the structural inversed products were also obtained with slightly



8a 10 11
8a 12 13

Scheme 2. Asymmetric Michael addition of other nucleophiles to nitroolefin **8a** catalyzed by **2a.**

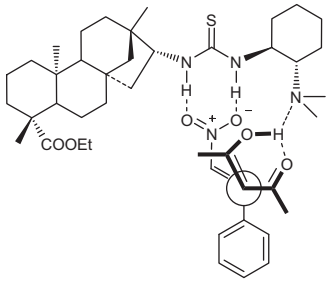


Figure 2. Proposed transition state.

lower enantioselectivities (Table 4). In our earlier work,[9] when primary amine-thioureas **1a** and **1b** were used independently for the asymmetric Michael reaction, nearly the same results with regard to activity and enantioselectivity were obtained. In the case of tertiary amine-thioureas **2a** and **2b**, there were some slight differences, especially with regard to enantioselectivities. Based on our previous theoretical calculations,[9a] we speculated that the conformation of the transition state may generate a slight change when the primary amino group is replaced by a tertiary amino group, causing the enantioselectivity to be slightly lower.

The asymmetric Michael additions of other nucleophiles to nitroolefin **8a** using **2a** as catalyst were also investigated. As shown in Scheme 2, the unsymmetrical 1,3-dicarbonyl compound, *tert*-butyl acetoacetate, also worked well to give the desired products in high yield and with good diastereoselectivity (2/1) and enantioselectivty (94% and 82% ee for the major and the minor diastereomer, respectively). However, in the case of diethyl malonate, no reaction took place.

Although the precise reaction mechanism needs further study, a possible transition state has been proposed based on the observed stereoselectivities of the asymmetric Michael addition of acetylacetone to nitroolefins. In Figure 2, a thiourea moiety of catalyst **2a** interacts through hydrogen bonding with the β-nitro group of the nitroalkene and enhances the electrophilicity of the α-alkene carbon, while the tertiary amine deprotonates an acidic proton of the 2,4-pentandione, generating a ternary complex. The synergistic steric hindrance from the chiral isosteviol moiety of bifunctional catalyst **2a** might be responsible for the increased stereocontrol of the Michael addition reaction. Nevertheless, the precise catalytic mechanism still requires further investigation.

3. Conclusion

In conclusion, we have developed a novel class of chiral bifunctional tertiary amine-thiourea catalysts **2a** and **2b** bearing a chiral

lipophilic beyerane scaffold and a tertiary amino group. The effectiveness of these novel organocatalysts has been demonstrated by catalysis of the doubly stereocontrolled asymmetric Michael reaction of acetylacetone with nitroolefins with good enantioselectivity. More importantly, with the two structurally reversed thioureas as catalysts, the enantiomeric Michael adducts could be obtained predominantly. In addition, the reaction of *tert*-butyl acetoacetate was also effective in obtaining the corresponding adducts with good enantioselectivities, albeit with low diastereoselectivities. Further investigation of these organocatalysts in other asymmetric reactions as well as a more detailed mechanism is currently ongoing in our laboratory.

4. Experimental section

4.1. General remarks

All reagents were obtained from commercial suppliers without further purification. Commercial grade solvents were dried and purified by standard procedures. Chemicals were used as received unless otherwise noted. Reagent grade solvents were redistilled prior to use. ^{1}H NMR and ^{13}C NMR spectra were collected on a Bruker DPX 400 NMR spectrometer with TMS as internal reference. IR spectra were determined on a Thermo Nicolet IR200 unit. High resolution mass spectra (HRMS) were obtained on a Waters Micromass Q-Tof Micro™ instrument using the ESI technique. Chromatography was performed on silica gel (200–300 mesh). Melting points were determined using aXT5 Apparatus and were uncorrected. Optical rotations were determined on a Perkin Elmer 341 polarimeter. Enantiomeric excess was determined by chiral HPLC at room temperature using Labtech 2006 pump equipped with Labtech UV600 ultra detector with Chiral columns (Chiralcel OD-H, Chiralpak AD-H and AE.LICHROM-AM2–5).

4.2. General procedure for the preparation of catalysts 2 and 3

4.2.1. Catalyst 2

Isothiocyanate **4** (0.778 g, 2.0 mmol) was added to a stirred solution of *N*,*N*-cyclohexane-1,2-diamine **5a/5b** (0.284 g, 2.0 mmol) in dry dichloromethane (25 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude product was purified using column chromatography eluting with $CHCl_3$/MeOH = 50:1.

4.2.2. 1-(Ethyl *ent*-beyeran-19-oate-16-yl)-3-((1*S*,2*S*)-2-(dimethylamino)cyclohexyl) thiourea 2a

White solid; yield: 89%; mp: 95–97 °C; $[\alpha]_D^{20} = -70.8$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.71 (s, 3H, –CH_3), 0.83–0.91 (m, 2H), 0.97 (s, 3H, –CH_3), 0.99–1.12 (m, 4H), 1.17 (s, 3H, –CH_3), 1.25 (t, *J* = 7.2 Hz, 3H), 1.23–1.43 (m, 10H), 1.55–1.90 (m, 13H), 2.16 (d, *J* = 13.6 Hz, 1H), 2.36 (s, 6H, 2–CH_3), 3.82 (m, 1H), 4.00–4.16 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.4, 14.1, 18.9, 21.7, 25.1, 28.9, 32.8, 38.0, 39.9, 41.5, 42.3, 54.0, 55.9, 56.0, 57.1, 59.9, 67.1, 177.6, 182.6; IR (KBr, cm^{-1}): ν 753, 1040, 1095, 1151, 1180, 1232, 1370, 1461, 1531, 1722, 2676, 2847, 2934, 3307, 3440; HRMS: calcd for $C_{31}H_{54}N_3O_2S$ $[M+H]^+$: 532.3937, found 532.3934.

4.2.3. 1-(Ethyl *ent*-beyeran-19-oate-16-yl)-3-((1*R*,2*R*)-2-(dimethylamino)cyclohexyl) thiourea 2b

White solid; yield: 86%; mp: 89–91 °C; $[\alpha]_D^{20} = -149.5$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.72 (s, 3H, –CH_3), 0.83–0.88 (m, 1H), 0.92 (s, 3H, –CH_3), 0.96–1.10 (m, 4H), 1.16 (s, 3H, –CH_3), 1.25 (t, *J* = 7.2 Hz, 3H), 1.23–1.43 (m, 10H), 1.55–1.59 (m, 2H), 1.63–1.73 (m, 6H), 1.78–1.82 (m, 2H), 1.84–1.98 (m, 4H), 2.16 (d, *J* = 12.0 Hz, 1H), 2.40 (s, 6H, 2–CH_3), 3.95 (m, 1H), 4.03–4.14 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.4, 14.1, 18.9, 20.5, 21.7, 22.9, 24.1, 24.4, 25.1, 28.9, 32.8, 34.4, 38.0, 39.9, 40.6, 42.3, 43.7, 54.0, 55.9, 56.0, 57.1, 59.9, 62.3, 67.1, 177.6, 182.6; IR (KBr, cm^{-1}): ν 749, 1029, 1096, 1149, 1180, 1234, 1368, 1466, 1538, 1666, 1720, 2672, 2758, 2849, 2938, 3058, 3281, 3427; HRMS: calcd for $C_{31}H_{54}N_3O_2S$ $[M+H]^+$: 532.3937, found 532.3937.

4.2.4. 1-(Ethyl *ent*-beyeran-19-oate-16-yl)-3-((1*S*,2*S*)-2-(*N*-phthaloylamino)cyclohexyl) thiourea 3

White solid; yield: 71%; mp: 150–152 °C; $[\alpha]_D^{20} = +12.1$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.66 (s, 3H, –CH_3), 0.78–0.88 (m, 5H), 0.94–1.08 (m, 5H), 1.17 (s, 3H, –CH_3), 1.28 (t, *J* = 7.2 Hz, 3H), 1.26–1.43 (m, 8H), 1.49–1.58 (m, 6H), 1.69 (s, 2H), 1.81–1.89 (m, 6H), 2.17 (d, *J* = 13.2 Hz, 1H), 2.28 (s, 1H), 3.97–4.02 (m, 1H), 4.10–4.15 (m, 2H), 5.89 (s, 1H), 7.68–7.76 (m, 4H); ^{13}C NMR(100 MHz, $CHCl_3$): δ 13.4, 14.1, 14.2, 18.9, 20.4, 21.1, 21.6, 24.7, 25.0, 25.3, 28.9, 33.3, 38.0, 39.9, 41.3, 43.6, 55.7, 57.0, 59.9, 60.4, 123.2, 131.8, 134.0, 168.9, 171.2, 177.5, 181.7; IR (KBr, cm^{-1}): ν 718, 869, 974, 1092, 1153, 1233, 1332, 1373, 1467, 1539, 1613, 1713, 1769, 2848, 2938, 3066, 3352; HRMS: calcd for $C_{37}H_{52}N_3O_4S$ $[M+H]^+$: 634.3679, found 634.3672.

4.3. Typical procedure for the Michael addition

Acetylacetone **7** (0.40 mmol) was added to a mixture of catalyst **2** (11 mg, 10 mol %) and the corresponding nitroolefin **8** (0.20 mmol) in toluene (0.5 mL). The reaction mixture was stirred at −40 °C for the required time. After the nitroolefin was consumed by TLC analysis, the reaction mixture was subjected to thin layer chromatography on silica gel (ethyl acetate/petroleum ether) to afford the pure product. The enantiomeric excess of the products was determined by chiral HPLC analysis using Chiral columns.

4.3.1. (*S*)-3-(2-Nitro-1-phenylethyl)pentane-2,4-dione 9a[4d]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.94 (s, 3H), 2.29 (s, 3H), 4.22–4.28 (m, 1H), 4.38 (d, 1H, *J* = 10.8 Hz), 4.59–4.68 (m, 2H), 7.18–7.20 (m, 2H), 7.27–7.35 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 29.6, 30.5, 42.8, 70.7, 78.2, 127.9, 128.6, 129.3, 136.0, 201.0, 201.8. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 90/10, flow rate = 0.7 mL/min, wavelength = 210 nm): R_t = 18.2 min (major), 25.6 min (minor).

4.3.2. (*S*)-3-[1-(4-Fluorophenyl)-2-nitroethyl]pentane-2,4-dione 9b[6g]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.96 (s, 3H), 2.29 (s, 3H), 4.22–4.27 (m, 1H), 4.33 (d, 1H, *J* = 10.4 Hz), 4.61 (d, 2H, *J* = 6.4 Hz), 7.00–7.05 (m, 2H), 7.16–7.20 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 29.7, 30.4, 42.1, 70.7, 78.1, 116.4, 129.8, 131.8, 161.3, 163.7, 200.8, 201.5. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 90/10, flow rate = 0.7 mL/min, wavelength = 210 nm): R_t = 22.6 min (major), 47.2 min (minor).

4.3.3. (*S*)-3-[1-(4-Chlorophenyl)-2-nitroethyl]pentane-2,4-dione 9c[4d]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.98 (s, 3H), 2.30 (s, 3H), 4.20–4.26 (m, 1H), 4.33 (d, 1H, *J* = 10.8 Hz), 4.59–4.62 (m, 2H), 7.14 (d, 2H, *J* = 8.4 Hz), 7.31 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 29.7, 30.5, 42.1, 70.5, 77.9, 129.3, 129.6, 134.6, 200.6, 201.4. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 80/20, flow rate = 0.6 mL/min, wavelength = 210 nm): R_t = 16.5 min (major), 44.6 min (minor).

4.3.4. (*S*)-3-[1-(4-Bromophenyl)-2-nitroethyl]pentane-2,4-dione 9d[6g]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.98 (s, 3H), 2.29 (s, 3H), 4.19–4.25 (m, 1H), 4.33 (d, 1H, *J* = 10.4 Hz), 4.1 (d, 2H, *J* = 6.0 Hz), 7.08

(d, 2H, J = 8.4 Hz), 7.46 (d, 2H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 29.7, 30.5, 42.2, 70.4, 77.8, 122.7, 129.7, 132.5, 135.1, 200.6, 201.4. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 85/15, flow rate = 0.6 mL/min, wavelength = 210 nm): R_t = 21.4 min (major), 74.6 min (minor).

4.3.5. (*S*)-3-(2-Nitro-1-(2-nitrophenyl)ethyl)pentane-2,4-dione 9e[6c]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.14 (s, 3H), 2.32 (s, 3H), 4.68 (d, 1H, J = 8.8 Hz), 4.74 (dt, 1H, J = 8.0, 6.8 Hz), 4.84 (dd, 1H, J = 13.6, 3.6 Hz), 4.97 (dd, 1H, J = 13.2, 7.2 Hz), 7.36 (d, 1H, J = 7.6 Hz), 7.49 (t, 1H, J = 8.0 Hz), 7.59 (t, 1H, J = 7.6 Hz), 7.93 (d, 1H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 29.4, 31.3, 37.1, 69.1, 76.6, 125.6, 129.2, 129.4, 131.2, 133.5, 149.8, 200.6, 201.6. HPLC analysis (Chiralcel OD-H column, *i*-propanol/hexane = 90/10, flow rate = 0.7 mL/min, wavelength = 210 nm): R_t = 71.6 min (major), 92.2 min (minor).

4.3.6. (*S*)-3-[1-(4-Methylphenyl)-2-nitroethyl]pentane-2,4-dione 9f[4d]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.97 (s, 3H), 2.29 (s, 3H), 3.78 (s, 3H), 4.19–4.24 (m, 1H), 4.37 (d, 1H, J = 10.8 Hz), 4.61–4.63 (m, 2H), 6.72–6.83 (m, 3H), 7.22–7.27 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 29.6, 30.5, 42.8, 55.2, 70.6, 78.1, 113.6, 114.1, 119.9, 130.4, 137.6, 160.1, 201.0, 201.8. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 85/15, flow rate = 0.65 mL/min, wavelength = 210 nm): R_t = 16.9 min (major), 22.4 min (minor).

4.3.7. (*S*)-3-[1-(3-Methoxyphenyl)-2-nitroethyl]pentane-2,4-dione 9g[4d]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.97 (s, 3H), 2.29 (s, 3H), 3.78 (s, 3H), 4.19–4.24 (m, 1H), 4.37 (d, 1H, J = 10.8 Hz), 4.60–4.67 (m, 2H), 7.16 (t, 1H, J = 2.0 Hz), 6.76 (d, 1H, J = 7.6 Hz), 6.81 (dd, 2H, J = 2.0, 8.0 Hz), 7.24 (t, 1H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 29.7, 30.5, 42.8, 55.2, 70.6, 78.1, 113.6, 114.2, 119.9, 130.4, 137.6, 160.1, 201.0, 201.8. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 85/15, flow rate = 0.5 mL/min, wavelength = 210 nm): R_t = 21.3 min (major), 28.0 min (minor).

4.3.8. (*S*)-3-[1-(4-Methoxyphenyl)-2-nitroethyl]pentane-2,4-dione 9h[4d]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.94 (s, 3H), 2.29 (s, 3H), 3.77 (s, 3H), 4.18–4.23 (m, 1H), 4.33 (d, 1H, J = 10.8 Hz), 4.59 (d, 2H, J = 6.4 Hz), 6.84 (d, 2H, J = 8.4 Hz), 7.10 (d, 2H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 29.5, 30.4, 42.1, 55.2, 70.9, 78.5, 114.7, 127.6, 129.1, 159.5, 201.2, 201.9. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 85/15, flow rate = 0.65 mL/min, wavelength = 210 nm): R_t = 21.2 min (major), 33.4 min (minor).

4.3.9. (*S*)-3-[1-(Naphthalen-1-yl)-2-nitroethyl]pentane-2,4-dione 9i[4d]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.86 (s, 3H), 2.31 (s, 3H), 4.69–4.75 (m, 2H), 4.81 (dd, 1H, J = 12.0, 8.4 Hz), 5.20 (m, 1H), 7.27 (d, 1H, J = 7.2 Hz), 7.40 (t, 1H, J = 7.6 Hz), 7.54 (t, 1H, J = 7.2 Hz), 7.63 (dt, 1H, J = 7.6, 1.2 Hz), 7.80 (d, 1H, J = 8.0 Hz), 8.17 (d, 1H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 28.7, 31.1, 36.3, 70.4, 77.8, 121.9, 124.8, 125.3, 126.3, 127.4, 129.2, 129.5, 130.8, 131.9, 134.3, 200.8, 202.4. HPLC analysis (AE.LICHROM-AM2–5 column, *i*-propanol/hexane = 40/1, flow rate = 0.8 mL/min, wavelength = 210 nm): R_t = 109.2 min (major), 149.8 min (minor).

4.3.10. (*S*)-3-[1-(Naphthalen-2-yl)-2-nitroethyl]pentane-2,4-dione 9j

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.94 (s, 3H), 2.31 (s, 3H), 4.39–4.45 (m, 1H), 4.50 (d, 1H, J = 10.8 Hz), 4.67–4.77 (m, 2H), 7.30 (dd, 1H, J = 8.8, 1.6 Hz), 7.47–7.51 (m, 2H), 7.65 (d, 1H, J = 1.2 Hz), 7.77–7.84 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 29.6, 30.5, 42.9, 70.7, 78.2, 125.0, 126.7, 126.8, 127.5, 127.7, 128.0, 129.4, 133.0, 133.3, 201.0, 201.8. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 15/1, flow rate = 0.7 mL/min, wavelength = 210 nm): R_t = 40.6 min (major), 54.3 min (minor).

4.3.11. (*R*)-3-[1-(Furan-2-yl)-2-nitroethyl]pentane-2,4-dione 9k[4d]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.09 (s, 3H), 2.28 (s, 3H), 4.33–4.41 (m, 2H), 4.67 (d, 2H, J = 5.6 Hz), 6.18 (d, 1H, J = 3.6 Hz), 6.31 (dd, 1H, J = 3.2, 2.0 Hz), 7.36 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 29.3, 30.7, 36.6, 67.9, 75.8, 108.9, 110.8, 142.9, 149.4, 200.8, 201.5. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 40/1, flow rate = 0.75 mL/min, wavelength = 210 nm): R_t = 35.2 min (major), 44.8 min (minor).

4.3.12. (*R*)-3-(1-(5-Chlorothiophen-2-yl)-2-nitroethyl)pentane-2,4-dione 9l

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (s, 6H), 1.47 (s, 3H), 2.06 (s, 1H), 2.31 (s, 2H), 3.92 (d, 0.3H, J = 9.6 Hz), 4.01 (d, 0.7H, J = 10.4 Hz), 4.66–4.76 (m, 1.4H), 4.79–4.89 (m, 0.7H), 7.20–7.22 (m, 2H), 7.27–7.33 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 27.4, 27.8, 29.7, 30.1, 42.3, 42.5, 62.7, 63.0, 82.9, 83.5, 128.0, 128.2, 128.3, 128.8, 129.1, 136.6, 165.8, 166.6, 200.6, 201.4. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 95/5, flow rate = 0.7 mL/min, wavelength = 215 nm): major diastereomer: R_t = 14.4 min (major), 20.3 min (minor); minor diastereomer: 22.2 min (minor), 41.6 min (major)

4.3.13. (*R*)-3-[(*E*)-1-Nitro-4-phenylbut-3-en-2-yl)pentane-2,4-dione 9m[4d]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.21 (s, 3H), 2.28 (s, 3H), 3.70–3.77 (m, 1H), 4.06 (d, 1H, J = 9.2 Hz), 4.52–4.59 (m, 2H), 6.02 (dd, 1H, J = 16.0, 9.6 Hz), 6.55 (d, 1H, J = 16.0 Hz), 7.25–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): 30.0, 30.6, 40.9, 69.1, 77.4, 123.1, 126.6, 128.5, 128.7, 135.6, 201.6, 201.9. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 90/10, flow rate = 0.7 mL/min, wavelength = 210 nm): R_t = 20.3 min (major), 26.0 min (minor).

4.3.14. (3*S*)-*tert*-Butyl 2-acetyl-4-nitro-3-phenylbutanoate 11[11]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (s, 6H), 1.47 (s, 3H), 2.06 (s, 1H), 2.31 (s, 2H), 3.92 (d, 0.3H, J = 9.6 Hz), 4.01 (d, 0.7H, J = 10.4 Hz), 4.11–4.22 (m, 1H), 4.66–4.76 (m, 1.4H), 4.79–4.89 (m, 0.7H), 7.20–7.22 (m, 2H), 7.27–7.33 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 27.4, 27.8, 29.7, 30.1, 42.3, 42.5, 62.7, 63.0, 82.9, 83.5, 128.0, 128.2, 128.3, 128.8, 129.1, 136.6, 165.8, 166.6, 200.6, 201.4. HPLC analysis (Chiralpak AD-H column, *i*-propanol/hexane = 95/5, flow rate = 0.7 mL/min, wavelength = 215 nm): the major diastereomer: R_t = 14.4 min (major), 20.3 min (minor); the minor diastereomer: 22.2 min (minor), 41.6 min (major).

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