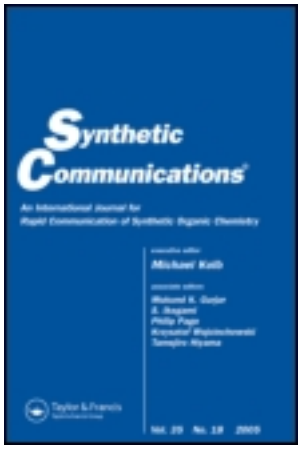

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Enantioselective Organocatalytic Michael Addition of Aliphatic Ketones to Nitrodienes

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ENANTIOSELECTIVE ORGANOCATALYTIC MICHAEL ADDITION OF ALIPHATIC KETONES TO NITRODIENES

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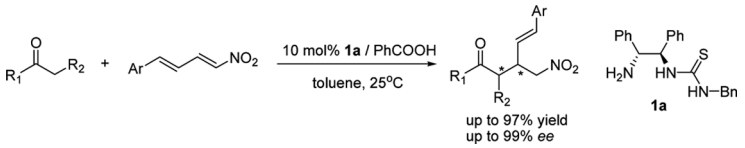
GRAPHICAL ABSTRACT



Abstract *A highly enantioselective Michael addition of aliphatic ketones to nitrodienes has been achieved that is catalyzed by readily available chiral thioureas derived from (1R,2R)-diphenylethane-1,2-diamine. Treatment of ketones with nitrodienes in the presence of 10 mol% thiourea* ***1a*** *and 10 mol% benzoic acid in toluene provided the desired Michael adducts with excellent enantioselectivities (up to 99%* ee*) and modest to excellent yields (up to 97%).*

Keywords Enantioselective organocatalysis; ketone; nitrodiene; nitro-Michael reaction; primary amine-thiourea

INTRODUCTION

The asymmetric Michael reaction of nucleophiles to nitroalkenes is a useful tool for the construction of highly functionalized chiral building blocks.[1] In the past decade, there has been significant progress in developing various efficient chiral organocatalysts for the enantioselective Michael addition of ketones to nitroalkenes.[2] However, the excellent enantioselective Michael addition of acetone to nitroolefins has been seldom reported.[3] Therefore, the development of a highly effective organocatalyst for the asymmetric Michael reaction with acetone as the donor would be desirable.

To the best of our knowledge, only a few studies have related the organocatalytic asymmetric Michael addition of nucleophiles to nitrodienes. Tan et al.[4] and Hayashi's group[5] reported independently a highly diastereo- and enantioselective tandem Michael/Henry reaction using nitrodiene as Michael acceptor. Alexakis

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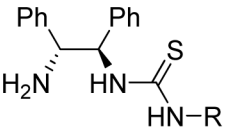
and coworkers[6] presented a successful application of (*S*)-diphenylprolinol silyl ether in the asymmetric Michael addition of aldehydes to nitrodienes. Cheng[7] and Chua[8] with coworkers reported independently the highly enantioselective Michael addition of cyclohexanone to ((1*E*,3*E*)-4-nitrobuta-1,3-dienyl)benzene with *L*-proline derivatives as organocatalysts. We[9] recently succeeded in the asymmetric organocatalyzed Michael addition of aromatic ketones and nitrodienes with chiral primary amine-thiourea.[3a-d,10] Herein, we report the highly enantioselective Michael additions of aliphatic ketones to nitrodienes catalyzed by chiral primary amine-thiourea.

RESULTS AND DISCUSSION

In the initial studies, the chiral bifunctional organocatalysts **1a–h** (Figure 1) were screened in the Michael addition reaction between acetone and nitrodiene **2a**. As illustrated in Table 1, catalyst **1a** provided the desired product **3a** in good yield (75%) with excellent enantioselectivity (94% *ee*, entry 1). The addition of acid such as PhCOOH or AcOH could improve the chemical yield without enantioselectivity variety (entries 2 and 3). The addition of base such as dimethylaminopyridine (DMAP) resulted in a decrease of enantioselectivity (entry 4). The Michael reactions involving other thioureas were investigated in the presence of PhCOOH. The results indicated that the acidity of the N-H of the thiourea group has a strong effect on the catalytic activity and enantioselectivity in the process. Compared to **1a**, catalyst **1b** with a strong electron-withdrawing group gave product **3a** in poor yield and lower enantioselectivity (78% *ee*, entry 5). Thioureas **1c** and **1d** bearing other aryl groups provided similar results as **1b** (entries 6 and 7). The additional chirality in molecule **1e** and **1f** had no positive effect on the enantioselectivity, while the chemical yields declined obviously (entries 8 and 9). Catalyst **1g** with a substituent at the benzyl group afforded the product in lower yield with same enantioselectivity as **1a** (entry 10). Catalyst **1h** bearing *n*-butyl group gave **3a** in good yield (80%), but the enantioselectivity was worse than the others (entry 11).

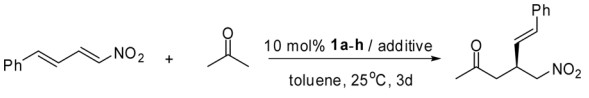
Next we investigated the effects of solvents for this Michael addition using catalyst **1a**. As shown in Table 2, the chemical yields varied significantly in different solvents. In Et_2O, the desired adduct was observed in a moderate yield because of the poor solubility of the nitrodiene **2a** (43%, entry 2). However, in the case of tetrahydrofuran (THF), the product was obtained in trace amounts (entry 7). Moderate yields were obtained using CH_2Cl_2, $CHCl_3$, *i*-PrOH, and *t*-BuOH as solvents (50–70%,



1a R = $C_6H_5CH_2$; **1b** R = 3,5-$(CF_3)_2C_6H_3$;
1c R = C_6H_5; **1d** R = 4-$MeOC_6H_4$;
1e R = (*R*)-CH(Me)C_6H_5; **1f** R = (*S*)-CH(Me)C_6H_5;
1g R = 4-$MeOC_6H_4CH_2$; **1h** R = *n*-Bu

Figure 1. Various chiral primary amine-thiourea organocatalysts.

Table 1. Catalytic asymmetric Michael addition of acetone to nitrodiene **2a**



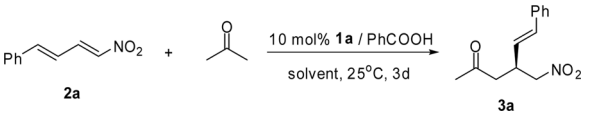
2a **3a**

Entry	Catalyst	Additive	Yield (%)[a]	Ee (%)[b]
1	**1a**	None	75	94
2	**1a**	PhCOOH	85	94
3	**1a**	AcOH	80	94
4	**1a**	DMAP	78	92
5	**1b**	PhCOOH	43	78
6	**1c**	PhCOOH	35	86
7	**1d**	PhCOOH	32	91
8	**1e**	PhCOOH	54	88
9	**1f**	PhCOOH	55	93
10	**1g**	PhCOOH	65	94
11	**1h**	PhCOOH	80	73

[a]Isolated yield after silica-gel column chromatography.
[b]Determined by chiral HPLC analysis (Chiralpak AS-H column, hexane/*i*-PrOH 95:5).

entries 3–6). Surprisely, using EtOH as solvent provided lower chemical yield and enantioselectivity than using other alcohols such as *i*-PrOH and *t*-BuOH (entry 9 vs 5 and 6). Also the product was formed in poor yield in acetone (25%, entry 8). The use of toluene led to the best yield (85%, entry 1). In general, all the screened solvents gave good to excellent enantioselectivities (70–96% *ee*). The greatest enantioselectivity was 96% *ee* with *i*-PrOH as the solvent. Considering both yield and enantioselectivity, toluene was chosen as solvent for further investigation.

Table 2. Effect of solvents on the asymmetric Michael addition of acetone to nitrodiene **2a**



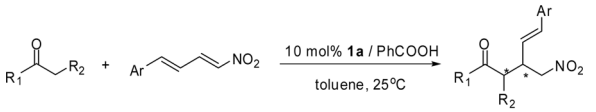
2a **3a**

Entry	Solvent	Yield (%)[a]	Ee (%)[b]
1	Toluene	85	94
2	Et_2O	43	90
3	CH_2Cl_2	70	90
4	$CHCl_3$	50	91
5	*i*-PrOH	68	96
6	*t*-BuOH	70	82
7	THF	5	85
8	Acetone	25	82
9	EtOH	30	70

[a]Isolated yield after silica-gel column chromatography.
[b]Determined by chiral HPLC analysis (Chiralpak AS-H column, hexane/*i*-PrOH 95:5).

Under the optimized reaction conditions, various nitrodienes were examined with acetone as the Michael donor. The results in Table 3 indicated that other nitrodienes with electro-donating or electro-withdrawing substituents on aromatic group were less reactive than nitrodiene **2a** (entries 2–6 vs entry 1), while the enantioselectivity had no obvious change (92–95% *ee*). Because 1-((1*E*,3*E*)-4-nitrobuta-1,3-dienyl)benzene (**2a**) was more reactive, it was then selected to react with other aliphatic ketones. In all the cases except entry 10, the enantioselectivity was excellent (94–99% *ee*). However, all these reactions provided the Michael adducts in low diastereoselectivities (ranging from 83/17 to 69/31). Among the Michael reactions involving cyclic ketones such as cyclohexanone, cyclopentanone, and cycloheptanone as Michael donor, we found that the smaller the ring size, the faster the reaction rate (entries 7–9). The Michael reaction between cyclopentanone and nitrodiene **2a** completed in 24 h with 97% yield and 99% *ee* of the major diastereomer (entry 7), while only a trace amount of desired product was observed with cycloheptanone as Michael donor even after 4 days (entry 9). In contrast to the carbon analogs, lower enantioselectivity (83% *ee*) was obtained for tetrahydropyran-4-one (entry 10). 3-Pentanone was less reactive and afforded the product in poor yield (25%, entry 12). When using 2-butanone as donor, the reaction took place at the more substituted site, presumably because the enamine intermediate formed under thermodynamic control.[11] The adduct was obtained in good yield (75%) and modest diastereoselectivity (83:17) (entry 11). Surprisingly, when the 4-methylpentan-2-one

Table 3. Catalytic asymmetric Michael addition of ketones to nitrodienes



3a-m

Entry	R_1	R_2	Ar	Product	Time (d)	dr[a]	Yield (%)[b]	Ee (%)[c]
1	Me	H	C_6H_5	**3a**	3	—	85	94
2	Me	H	4-$NO_2C_6H_4$	**3b**	3	—	62	94
3	Me	H	3-$NO_2C_6H_4$	**3c**	3	—	60	95
4	Me	H	2-$NO_2C_6H_4$	**3d**	3	—	50	95
5	Me	H	2,4-$Cl_2C_6H_3$	**3e**	3	—	42	92
6	Me	H	4-MeC_6H_4	**3f**	3	—	40	94
7	$(CH_2)_3$		C_6H_5	**3g**	1	70:30	97	99
8	$(CH_2)_4$		C_6H_5	**3h**	3	78:22	84	97
9	$(CH_2)_5$		C_6H_5	**3i**	4	n.d.[d]	trace	n.d.[d]
10	$(CH_2)_2O(CH_2)$		C_6H_5	**3j**	3	69:31	90	83
11	Me	Me	C_6H_5	**3k**	3	83:17	75	99
12	Et	Me	C_6H_5	**3l**	4	76:24	25	99
13	*i*-Bu	H	C_6H_5	**3m**	4	—	35	94

[a]The diastereomer ratio was determined by ^{1}H NMR spectroscopy.

[b]Isolated yield after silica-gel column chromatography.

[c]*Ee* values of the major diastereomer, which were determined by chiral HPLC analysis using Chiralpak AD-H, Chiralpak AS-H, or Chiralcel OD-H columns.

[d]Not determined.

was reacted with nitrodiene **2a** under the same conditions, the less hindered methyl group reacted preferentially, giving the product in 35% yield because of poor conversion (entry 13). We assume that the thermodynamic enamine was too hindered to react, so the enamine formed under kinetic condition afforded the methyl adduct. Nevertheless, the reaction rate was very slow because of the low concentration of kinetic enamine in solution.

CONCLUSION

In conclusion, we have developed a highly enantioselective Michael reaction of aliphatic ketones with nitrodienes catalyzed by chiral primary amine thioureas. With 10 mol% of the simple thiourea **1a** in the presence of PhCOOH, the nitro-Michael adducts were obtained in excellent enantioselectivities (92–99% ee) and modest to high yield (40–97%) for most of the tested substrates.

EXPERIMENTAL

Optical rotations were measured on a WZZ-2A digital polarimeter at the wavelength of the sodium D-line (589 nm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 500 or 400 spectrometer using $CDCl_3$ as a solvent. The chemical shifts of ^{1}H NMR spectra were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ, 0.00) and coupling constants (Hz). The chemical shifts of ^{13}C NMR spectra were recorded in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). Infrared (IR) spectra were recorded on Nicolet Magna-IR 550 spectrometer. High-resolution mass spectra (HRMS) were recorded on Micromass GCT spectrometer with electron impact (EI) or electrospray ionization (ESI) resource. High-performance liquid chrometography (HPLC) analysis was performed on a Waters 510 with 2487 detector using Daicel Chiralpak AS-H, Chiralpak AD-H, and Chiralcel OD-H column.

Toluene, THF, and ether were distilled from sodium-benzophenone. Dichloromethane and chloroform were distilled from CaH_2. Ethanol was distilled from magnesium. Various aliphatic ketones were commercially available and used after distillation. Thin-layer chromatography (TLC) was performed on silica gel plates. Column chromatography was performed using silica-gel (300–400 mesh) eluting with ethyl acetate and petroleum ether. Compounds were visualized by ultraviolet (UV) and $KMnO_4$.

General Procedure for the Michael Reaction of Ketone and Nitrodiene

1-((1*R*,2*R*)-2-Amino-1,2-diphenylethyl)-3-benzylthiourea (**1a**) (7.22 mg, 0.02 mmol) and PhCOOH (2.44 mg, 0.02 mmol) were added to a vial containing ketone (1 mmol) and toluene (2 mL) at 25 °C. The mixtures were stirred vigorously for 10 min, and then nitrodiene (0.2 mmol) was added. After the reaction mixture was stirred for the appropriate time (monitored by TLC), the solvent was removed and the residue was purified by column chromatography on silica gel to afford the desired pure product. The diastereomer ratios were determined by ^{1}H NMR spectroscopy. *Ee* values were determined by chiral HPLC analysis.

(*S,E*)-4-(Nitromethyl)-6-phenylhex-5-en-2-one (3a)[12]

Yield: 85%; $[\alpha]_D^{20} = +14.0$ (*c* 0.25, $CHCl_3$); 94% *ee*. Chiral HPLC analysis: Chiralpak AS-H, hexane/*i*-PrOH = 95/5, UV 254 nm, flow rate 1.0 mL/min, $t_R = 27.2$ min (major), 31.4 min (minor); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30–7.22 (m, 4H), 7.20–7.15 (m, 1H), 6.46 (d, $J = 15.8$ Hz, 1H), 6.00 (dd, $J = 15.8$, 8.4 Hz, 1H), 4.54–4.43 (m, 2H), 3.45 (m, 1H), 2.68 (d, $J = 6.4$ Hz, 2H), 2.11 (s, 3H); IR (film, cm^{-1}): ν 2968, 1713, 1548, 1448, 1409, 1369, 1202, 965, 749, 693; HRMS (EI) calcd. for $C_{13}H_{15}NO_3$(M): 233.1052, found: 233.1059.

(*S,E*)-4-(Nitromethyl)-6-(4-nitrophenyl)hex-5-en-2-one (3b)

Yield: 62%; $[\alpha]_D^{20} = +10.8$ (*c* 0.25, $CHCl_3$); 94% *ee*. Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH = 90/10, UV 254 nm, flow rate 1.0 mL/min, $t_R = 82.7$ min (major), 87.6 min (minor); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.09 (d, $J = 8.7$ Hz, 2H), 7.39 (d, $J = 8.7$ Hz, 2H), 6.54 (d, $J = 15.9$ Hz, 1H), 6.22 (dd, $J = 15.9$, 8.6 Hz, 1H), 4.58–4.54 (m, 1H), 4.52–4.48 (m, 1H), 3.51 (m, 1H), 2.73 (d, $J = 6.4$ Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.2, 146.2, 141.5, 130.4, 128.2, 126.0, 123.0, 77.2, 43.6, 35.9, 29.4; IR (film, cm^{-1}): ν 2963, 2923, 2852, 1716, 1552, 1516, 1344, 1261, 1095, 1021, 801, 550; HRMS (EI) calcd. for $C_{13}H_{14}NO_3$(M-NO_2): 232.0974, found: 232.0965.

(*S,E*)-4-(Nitromethyl)-6-(3-nitrophenyl)hex-5-en-2-one (3c)

Yield: 60%; $[\alpha]_D^{20} = +16.0$ (*c* 0.3, $CHCl_3$); 95% *ee*. Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH = 90/10, UV 254 nm, flow rate 1.0 mL/min, $t_R = 55.0$ min (major), 60.4 min (minor); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.12 (s, 1H), 8.03 (d, $J = 8.2$ Hz, 1H), 7.56 (d, $J = 7.7$ Hz, 1H), 7.42 (t, $J = 8.0$, 8.0 Hz, 1H), 6.53 (d, $J = 15.9$ Hz, 1H), 6.18 (dd, $J = 15.9$, 8.6 Hz, 1H), 4.58–4.54 (m, 1H), 4.51–4.47 (m, 1H), 3.52 (m, 1H), 2.72 (d, $J = 6.5$ Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.2, 147.5, 136.9, 131.4, 130.3, 128.8, 128.6, 121.6, 119.9, 77.3, 43.6, 35.8, 29.4; IR (film, cm^{-1}): ν 2922, 1716, 1552, 1528, 1352, 1164, 1076, 971, 734, 676, 552, 472; HRMS (EI) calcd. for $C_{13}H_{14}NO_3$(M-NO_2): 232.0974, found: 232.0951.

(*S,E*)-4-(Nitromethyl)-6-(2-nitrophenyl)hex-5-en-2-one (3d)

Yield: 50%; $[\alpha]_D^{20} = +17.5$ (*c* 0.2, $CHCl_3$); 95% *ee*. Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH = 93/7, UV 254 nm, flow rate 1.0 mL/min, $t_R = 39.2$ min (major), 41.7 min (minor); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.89 (d, $J = 8.0$ Hz, 1H), 7.50 (m, 1H), 7.43 (d, $J = 7.4$ Hz, 1H), 7.35 (m, 1H), 6.94 (d, $J = 15.8$ Hz, 1H), 6.04 (dd, $J = 15.8$, 8.1 Hz, 1H), 4.59–4.50 (m, 2H), 3.51 (m, 1H), 2.75 (d, $J = 6.5$ Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.5, 146.5, 132.4, 131.3, 130.8, 128.1, 128.0, 127.6, 123.6, 77.3, 43.5, 35.6, 29.4; IR (film, cm^{-1}): ν 2921, 1716, 1552, 1471, 1379, 1164, 1101, 1049, 972, 563, 471; HRMS (EI) calcd. for $C_{13}H_{14}NO_3$(M-NO_2): 232.0974, found: 232.0981.

(*S,E*)-6-(2,4-Dichlorophenyl)-4-(nitromethyl)hex-5-en-2-one (3e)

Yield: 42%; $[\alpha]_D^{20} = +15.6$ (*c* 0.4, $CHCl_3$); 93% *ee*. Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH = 93/7, UV 254 nm, flow rate 1.0 mL/min, $t_R = 17.1$ min (major), 18.4 min (minor); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.32–7.29 (m, 2H), 7.12 (d, $J = 6.6$ Hz, 1H), 6.76 (d, $J = 15.9$ Hz, 1H), 6.02 (dd, $J = 15.9$, 8.4 Hz, 1H), 4.57–4.47 (m, 2H), 3.53–3.46 (m, 1H), 2.73 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.4, 133.1, 132.6, 132.0, 128.9, 128.4, 127.6, 126.7, 126.3, 77.3, 43.6, 35.9, 29.4; IR (film, cm^{-1}): ν 2921, 1716, 1552, 1522, 1434, 1346, 1165, 1075, 968, 862, 787, 741; HRMS (EI) calcd. for $C_{13}H_{12}Cl_2O$ (M-NO_2-H): 256.0236, found: 256.0248.

(*S,E*)-4-(Nitromethyl)-6-p-tolylhex-5-en-2-one (3f)

Yield: 40%; $[\alpha]_D^{20} = +7.0$ (*c* 0.23, $CHCl_3$); 94% *ee*. Chiral HPLC analysis: Chiralpak AS-H, hexane/*i*-PrOH = 90/10, UV 254 nm, flow rate 1.0 mL/min, $t_R = 15.3$ min (major), 18.7 min (minor); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.22 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 6.49 (d, $J = 15.8$ Hz, 1H), 6.02 (dd, $J = 15.8$, 8.6 Hz, 1H), 4.60–4.57 (m, 1H), 4.53–4.50 (m, 1H), 3.51 (m, 1H), 2.74 (d, $J = 6.5$ Hz, 2H), 2.33 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.7, 136.9, 132.3, 132.2, 128.3, 125.3, 124.1, 77.6, 44.0, 36.0, 29.5, 20.2; IR (film, cm^{-1}): ν 2919, 1715, 1550, 1373, 1163, 1027, 967, 567, 482; HRMS (EI) calcd. for $C_{14}H_{17}NO_3$(M): 247.1208, found: 247.1209.

(*E*)-2-(1-Nitro-4-phenylbut-3-en-2-yl)cyclopentanone (3g)

Yield: 97%; dr: 70:30; 99% *ee* for major diastereomer and 99% *ee* for minor diastereomer. Chiral HPLC analysis: Chiralpak AS-H, hexane/*i*-PrOH = 85/15, UV 254 nm, flow rate 1.0 mL/min, $t_R = 10.8$ min (minor diastereomer, minor), 11.6 min (major diastereomer, major), 13.4 min (minor diastereomer, major), 20.8 min (major diastereomer, minor); diastereomer mixtures [dr 70:30 (major diastereomer/minor diastereomer*)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34–7.23 (m, 5H + 2.15H*), 6.54 (d, $J = 15.6$ Hz, 0.43H*), 6.49 (d, $J = 16.0$ Hz, 1H), 5.94 (dd, $J = 15.6$, 9.2 Hz, 1H + 0.43H*), 4.94–4.89 (m, 1H), 4.84–4.74 (m, 0.86H*), 4.58–4.53 (m, 1H), 3.44–3.36 (m, 1H), 3.35–3.30 (m, 0.43H*), 2.44–2.23 (m, 2H + 0.86H*), 2.21–1.97 (m, 3H + 1.29H*), 1.86–1.70 (m, 2H + 0.86H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 219.2, 218.3, 136.1, 136.0, 135.7, 134.7, 128.6(2C), 128.2, 128.1, 126.5(2C), 124.5, 123.8, 77.9, 77.8, 50.2, 49.7, 42.8, 42.0, 39.3, 38.5, 27.4, 26.9, 20.8, 20.5; IR (film, cm^{-1}): ν 2972, 2918, 2881, 1731, 1552, 1383, 964, 741, 691; HRMS (ESI) calcd. for $C_{15}H_{17}NO_3Na$ (M + Na): 282.1106, found: 282.1111.

(*E*)-2-(1-Nitro-4-phenylbut-3-en-2-yl)cyclohexanone (3h)[7,8]

Yield: 84%; dr: 78:22; 97% *ee* for *syn* diastereomer and 90% *ee* for *anti* diastereomer. Chiral HPLC analysis: Chiralpak AS-H, hexane/*i*-PrOH = 80/20, UV 254 nm, flow rate 0.5 mL/min, $t_R = 18.0$ min (*syn*, major), 19.3 min (*anti*, minor), 20.2 min (*anti*, major), 25.7 min (*syn*, minor); diastereomer mixtures [dr 78:22 (*syn*/*anti**)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36–7.21 (m, 5H + 1.4H*), 6.49 (d,

$J = 16.0$ Hz, 1H), 6.48 (d, $J = 16.0$ Hz, 0.28H*), 6.28 (dd, $J = 14.8$, 9.6 Hz, 0.28H*), 6.02 (dd, $J = 16.0$, 9.6 Hz, 1H), 4.71–4.66 (m, 1H + 0.56H*), 4.60–4.55 (m, 1H), 3.39–3.31 (m, 1H), 3.22–3.16 (m, 0.28H*), 2.64–2.51 (m, 1H + 0.28H*), 2.48–2.29 (m, 2H + 0.56H*), 2.21–2.04 (m, 2H + 0.56H*), 1.96–1.86 (m, 1H + 0.28H*), 1.78–1.61 (m, 2H + 0.84H*), 1.51–1.40 (m, 1H).

(*E*)-3-(1-Nitro-4-phenylbut-3-en-2-yl)-tetrahydropyran-4-one (3j)

Yield: 90%; dr: 69:31; 83% *ee* for major diastereomer and 91% *ee* for minor diastereomer. Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH = 90/10, UV 254 nm, flow rate 1.0 mL/min, $t_R = 23.5$ min (minor diastereomer, minor), 25.1 min (minor diastereomer, major), 41.0 min (major diastereomer, major), 56.2 min (major diastereomer, minor); diastereomer mixtures [dr 69:31 (major diastereomer/minor diastereomer*)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35–7.24 (m, 5H + 2.25H*), 6.54 (d, $J = 16.0$ Hz, 1H), 6.48 (d, $J = 16.0$ Hz, 0.45H*), 6.23 (dd, $J = 16.0$, 9.6 Hz, 0.45H*), 5.94 (dd, $J = 15.8$, 9.6 Hz, 1H), 4.77–4.68 (m, 1H + 0.90H*), 4.55–4.50 (m, 1H), 4.23–4.16 (m, 2H + 0.90H*), 3.83–3.53 (m, 2H + 0.90H*), 3.47–3.36 (m, 1H), 3.26–3.13 (m, 0.45H*), 2.89–2.79 (m, 0.45H*), 2.78–2.61 (m, 2H + 0.45H*), 2.53–2.47 (m, 1H), 2.43–2.37 (m, 0.45H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.8, 205.3, 134.9, 134.8, 134.4, 134.3, 127.6 (2C), 127.2 (2C), 125.6, 125.5, 123.0, 122.8, 77.0, 76.9, 70.3, 70.0, 67.8, 67.1, 51.1, 51.0, 42.0, 41.9, 40.0, 38.5; IR (film, cm^{-1}): ν 2991, 2971, 2858, 1702, 1556, 1385, 1232, 1152, 971, 748, 691; HRMS (ESI) calcd. for $C_{15}H_{17}NO_4Na$ (M + Na): 298.1055, found: 298.1056.

(*E*)-3-Methyl-4-(nitromethyl)-6-phenylhex-5-en-2-one (3k)

Yield: 75%; dr: 83:17; 99% *ee* for major diastereomer; the minor diastereomer was not separated by chiral HPLC. Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH = 90/10, UV 254 nm, flow rate 0.5 mL/min, $t_R = 19.2$ min (minor diastereomer), 20.4 min (major diastereomer, major), 21.9 min (major diastereomer, minor); diastereomer mixtures [dr 83:17 (major diastereomer/minor diastereomer*)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35–7.23 (m, 5H + 1.00H*), 6.53 (d, $J = 15.6$ Hz, 0.20H*), 6.50 (d, $J = 15.6$ Hz, 1H), 6.15 (dd, $J = 15.6$, 9.2 Hz, 1H), 5.97 (dd, $J = 15.8$, 9.6 Hz, 0.20H*), 4.65–4.60 (m, 1H), 4.57–4.49 (m, 1H + 0.40H*), 3.34–3.17 (m, 1H + 0.20H*), 2.87–2.70 (m, 1H + 0.20H*), 2.25 (s, 0.60H*), 2.18 (s, 3H), 1.23 (d, $J = 7.2$ Hz, 3H), 1.19 (d, $J = 7.2$ Hz, 0.60H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.3, 209.0, 135.1(2C), 133.9, 133.8, 127.6(2C), 127.1, 127.0, 125.5(2C), 123.8, 123.7, 77.0, 76.6, 47.1, 46.9, 43.4, 42.6, 28.3, 28.1, 13.9, 13.4; IR (film, cm^{-1}): ν 2985, 2930, 1709, 1544, 1448, 1385, 1168, 1080, 974, 750, 693; HRMS (ESI) calcd. for $C_{14}H_{17}NO_3Na$ (M + Na): 270.1106, found: 270.1108.

(*E*)-4-Methyl-5-(nitromethyl)-7-phenylhept-6-en-3-one (3l)

Yield: 25%; dr: 76:24; 99% *ee* for major diastereomer and 92% *ee* for minor diastereomer. Chiral HPLC analysis: Chiralcel OD-H, hexane/*i*-PrOH = 95/5, UV 254 nm, flow rate 0.5 mL/min, $t_R = 36.4$ min (minor diastereomer, minor), 39.4 min (major diastereomer, minor), 49.7 min (major diastereomer, major), 60.9 min (minor

diastereomer, major); diastereomer mixtures [dr 76:24 (major diastereomer/minor diastereomer*)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38–7.24 (m, 5H + 1.55H*), 6.55 (d, $J = 16.0$ Hz, 0.31H*), 6.51 (d, $J = 16.0$ Hz, 1H), 6.17 (dd, $J = 16.0$, 9.2 Hz, 1H), 5.99 (dd, $J = 15.6$, 9.6 Hz, 0.31H*), 4.67–4.63 (m, 1H), 4.60–4.51 (m, 1H + 0.62H*), 3.37–3.17 (m, 1H + 0.31H*), 2.87–2.76 (m, 1H + 0.31H*), 2.65–2.39 (m, 2H + 0.62H*), 1.23 (d, $J = 7.2$ Hz, 3H), 1.19 (d, $J = 7.2$ Hz, 0.93H*), 1.11 (t, $J = 7.2$ Hz, 0.93H*), 1.05 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.1, 212.7, 136.2(2C), 134.8(2C), 128.6(2C), 128.1, 128.0, 126.5(2C), 125.1(2C), 78.0, 77.6, 47.2, 47.1, 44.5, 43.9, 35.5, 35.2, 15.4, 14.5, 7.7, 7.6; IR (film, cm^{-1}): ν 2978, 2938, 1714, 1548, 1380, 1080, 966, 750, 693; HRMS (ESI) calcd. for $C_{15}H_{19}NO_3Na$ (M + Na): 284.1263, found: 284.1269.

(*E*)-2-Methyl-6-(nitromethyl)-8-phenyloct-7-en-4-one (3m)

Yield: 35%; $[\alpha]_D^{20} = +12.9$ (*c* 0.35, $CHCl_3$); 94% *ee*. Chiral HPLC analysis: Chiralpak AD-H, hexane/*i*-PrOH = 90/10, UV 254 nm, flow rate 0.5 mL/min, $t_R = 17.6$ min (major), 18.4 min (minor); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.26–7.16 (m, 5H), 6.46 (d, $J = 16.0$ Hz, 1H), 6.00 (dd, $J = 15.8$, 8.8 Hz, 1H), 4.55–4.43 (m, 2H), 3.52–3.43 (m, 1H), 2.63 (d, $J = 6.8$ Hz, 2H), 2.24 (d, $J = 7.2$ Hz, 2H), 2.11–2.04 (m, 1H), 0.84 (d, $J = 6.4$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.8, 135.2, 132.3, 127.6, 127.0, 125.4(2C), 77.6, 51.3, 43.5, 36.0, 23.5, 21.5; IR (film, cm^{-1}): ν 2961, 1713, 1548, 1380, 1262, 1021, 966, 750, 693; HRMS (ESI) calcd. for $C_{16}H_{21}NO_3$ Na (M + Na): 298.1419, found: 298.1412.

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REFERENCES

1. For reviews of organocatalytic asymmetric nitro-Michael addition, see (a) Almasi, D.; Alonso, D. A.; Najera, C. Organocatalytic asymmetric conjugate additions. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; (b) Tsogoeva, S. B. Recent advances in asymmetric organocatalytic 1,4-conjugate additions. *Eur. J. Org. Chem.* **2007**, 1701–1716; (c) Sulzer-Mosse, S.; Alexakis, A. Chiral amine as organocatalysts for asymmetric conjugate addition to nitroolefins and vinyl sulfones via enamine activation. *Chem. Commun.* **2007**, 3123–3135.
2. For recent papers of ketones involved in nitro-Michael addition, see (a) Tan, B.; Zeng, X.; Lu, Y.; Chua, P. J.; Zhong, G. Rational design of organocatalyst: Highly stereoselective Michael addition of cyclic ketones to nitroolefins. *Org. Lett.* **2009**, *11*, 1927–1930; (b) Ni, B.; Zhang, Q.; Dhungana, K.; Headley, A. D. Ionic liquid-supported (ILS) (*S*)-pyrrolidine sulfonamide, a recyclable organocatalyst for the highly enantioselective Michael addition to nitroolefins. *Org. Lett.* **2009**, *11*, 1037–1040; (c) Wang, C.; Yu, C.; Liu, C.; Peng, Y. 4-Trifluoromethanesulfonamidyl prolinol *tert*-butyldiphenylsilyl ether as a highly efficient bifunctional organocatalyst for Michael addition of ketones and aldehydes to nitroolefins. *Tetrahedron Lett.* **2009**, *50*, 2363–2366; (d) Tsandi, E.; Kokotos, C. G.; Kousidou, S.;

Ragoussis, V.; Kokotos, G. Sulfonamides of homoproline and dipeptides as organocatalysts for Michael and Aldol reactions. *Tetrahedron* **2009**, *65*, 1444–1449; (e) Luo, S.; Li, J.; Zhang, L.; Xu, H.; Cheng, J.-P. Noncovalently supported heterogeneous chiral amine catalysts for asymmetric direct Aldol and Michael addition reactions. *Chem. Eur. J.* **2008**, *14*, 1273–1281; (f) Xu, D.-Q.; Yue, H.-D.; Luo, S.-P.; Xia, A.-B.; Zhang, S.; Xu, Z.-Y. A chiral thioureido acid as an effective additive for enantioselective organocatalytic Michael additions of nitroolefins. *Org. Biomol. Chem.* **2008**, *6*, 2054–2057; (g) Xu, D.-Q.; Wang, L.-P.; Luo, S.-P.; Wang, Y.-F.; Zhang, S.; Xu, Z.-Y. 2-[(Imidazolylthio)methyl]pyrrolidine as a trifunctional organocatalyst for the highly asymmetric Michael addition of ketones to nitroolefins. *Eur. J. Org. Chem.* **2008**, 1049–1053; (h) Li, P.; Wang, L.; Wang, M.; Zhang, Y. Polymer-immobilized pyrrolidine-based chiral ionic liquids as recyclable organocatalysts for asymmetric Michael additions to nitrostyrenes under solvent-free reaction conditions. *Eur. J. Org. Chem.* **2008**, 1157–1160; (i) Chandrasekhar, S.; Tiwari, B.; Parida, B. B.; Reddy, C. R. Chiral pyrrolidine-triazole conjugate catalyst for asymmetric Michael and Aldol reactions. *Tetrahedron: Asymmetry*, **2008**, *19*, 495–499; (j) Zhao, Y.-B.; Zhang, L.-W.; Wu, L.-Y.; Zhong, X.; Li, R.; Ma, J.-T. Silica-supported pyrrolidine-triazole, an insoluble, recyclable organocatalyst for the enantioselective Michael addition of ketones to nitroalkenes. *Tetrahedron: Asymmetry*, **2008**, *19*, 1352–1355; (k) Lv, G.; Jin, R.; Mai, W.; Gao, L. Highly efficient and recoverable dendritic organocatalyst from click chemistry for the asymmetric Michael addition of ketones to nitroolefins without the use of organic solvent. *Tetrahedron: Asymmetry* **2008**, *19*, 2568–2572 (l) Yacob, Z.; Shah, J.; Leisyner, J.; Liebscher, J. (*S*)-Pyrrolidin-2-ylmethyl-1,2,3-triazolium salts: Ionic liquid–supported organocatalysts for enantioselective Michael addition to β-nitrostyrenes. *Synlett*, **2008**, *15*, 2342–2344; (m) Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Li, Y.-J. Xiao, W.-J. Michael additions in water of ketones to nitroolefins catalyzed by readily tunable and bifunctional pyrrolidine-thiourea organocatalysts. *Tetrahedron Lett.* **2007**, *48*, 21–24; (n) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. Pyrrolidine-thiourea as a bifunctional organocatalyst: Highly enantioselective Michael addition of cyclohexanone to nitroolefins. *Org. Lett.* **2006**, *6*, 2901–2904; (o) Cao, Y.-J.; Lu, H.-H.; Lai, Y.-Y.; Lu, L.-Q.; Xiao, W.-J. An effective bifunctional thiourea catalyst for highly enantio- and diastereoselective Michael addition of cyclohexanone to nitroolefins. *Synthesis* **2006**, 3795–3800.

3. (a) Tsogoeva, S. B.; Wei, S.-W. Highly enantioselective addition of ketones to nitroolefins catalyzed by new thiourea-amine bifunctional organocatalysts. *Chem. Commun.* **2006**, 1451–1453; (b) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. Chiral thiourea-based bifunctional organocatalysts in the asymmetric nitro-Michael addition: A joint experimental-theoretical study. *Adv. Synth. Catal.* **2006**, *348*, 826–832; (c) Wei, S.-W.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. New highly enantioselective thiourea-based bifunctional organocatalysts for nitro-Michael addition reactions. *Catal. Today* **2007**, *121*, 151–157; (d) Huang, H.; Jacobsen, E. N. Highly enantioselective direct conjugate addition of ketones to nitroalkenes promoted by a chiral primary amine-thiourea catalyst. *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171; (e) Mandal, T.; Zhao, C.-G. Modularly designed organocatalytic assemblies for direct nitro-Michael addition reactions. *Angew. Chem. Int. Ed.* **2008**, *47*, 7714–7717; (f) Yang, Z.; Liu, J.; Liu, X.; Wang, Z.; Feng, X.; Su, Z.; Hu, C. Highly efficient amine organocatalysts based on bispidine for the asymmetric Michael addition of ketones to nitroolefins. *Adv. Synth. Catal.* **2008**, *350*, 2001–2006.
4. Tan, B.; Chua, P.; Li, Y.; Zhong, G. Organocatalytic asymmetric tandem Michael–Henry reactions: A highly stereoselective synthesis of multifunctionalized cyclohexanes with two quaternary stereocenters. *Org. Lett.* **2008**, *10*, 2437–2440.
5. Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. Diphenylprolinol silyl ether as a catalyst in an enantioselective, catalytic, tandem Michael/Henry reaction for the control of four stereocenters. *Angew. Chem. Int. Ed.* **2007**, *46*, 4922–4925.

6. Belot, S.; Massaro, A.; Tenti, A.; Mordini, A.; Alexakis, A. Enantioselective organocatalytic conjugate addition of aldehydes to nitrodienes. *Org. Lett.* **2008**, *10*, 4557–4560.
7. Cheng, D.; Bao, W. Enantioselective Michael addition of nitroolefins and cyclohexanones catalyzed by novel pyrrolidine-thiourea bifunctional catalysts with two chiral centers. *Lett. Org. Chem.* **2008**, *5*, 342–345.
8. (a) Chua, P. J.; Tan, B.; Zeng, X.; Zhong, G. *L*-Prolinol as a highly enantioselective catalyst for Michael addition of cyclohexanone to nitroolefins. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3915–3918; (b) Zeng, X.; Zhong, G. Prolinol sulfinyl ester derivatives: Organocatalytic Michael addition of ketones to nitroolefins under neat conditions. *Synthesis* **2009**, *9*, 1545–1550.
9. For recent reviews concerning bifunctional thiourea organocatalysis, see (a) Zhang, Z.; Schreiner, P. R. (Thio)urea organocatalysis—What can be learnt from anion recognition? *Chem. Soc. Rev.* **2009**, *38*, 1187–1198; (b) Connon, S. J. The design of novel, synthetically useful (thio)urea-based organocatalysts. *Synlett* **2009**, 354–376; (c) Connon, S. J. Asymmetric catalysis with bifunctional cinchona alkaloid-based urea and thiourea organocatalysts. *Chem. Commun.* **2008**, 2499–2510; (d) Yu, X.; Wang, W. Hydrogen-bond-mediated asymmetric catalysis. *Chem. Asian J.* **2008**, *3*, 516–532.
10. He, T.; Qian, J.-Y.; Song, H.-L.; Wu, X.-Y. Enantioselective organocatalytic conjugate addition of aromatic ketones to nitrodienes. *Synlett* **2009**, 3195–3197.
11. Alexakis, A.; Andrey, O. Diamine-catalyzed asymmetric Michael addition of aldehydes and ketones to nitrostyrene. *Org. Lett.* **2002**, *4*, 3611–3614.
12. Mei, K.; Jin, M.; Zhang, S.; Li, P.; Liu, W.; Chen, X.; Xue, F.; Duan, W.; Wang, W. Simple cyclohexanediamine-derived primary amine thiourea catalyzed highly enantioselective conjugate addition of nitroalkanes to enones. *Org. Lett.* **2009**, *11*, 2864–2867.