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Prolinethiol Ether Catalysis in an Asymmetric Michael Reaction: Solvent-Free Synthesis of Functionalized Monohaloalkenes

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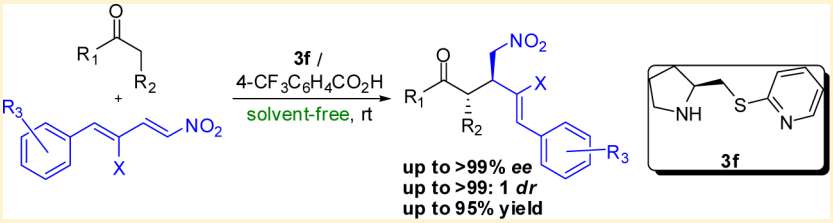
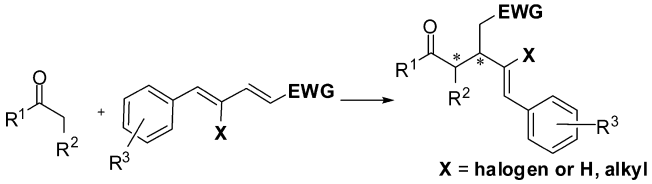
Supporting Information



ABSTRACT: The organocatalytic Michael reaction of ketones with γ-monohalonitrodienes catalyzed by chiral prolinethiol ether under solvent-free conditions was developed. The described method represents a novel approach for accessing highly functionalized monohaloalkenes with α, β-stereocenters of up to >99% ee.

Alkenyl halides are present in a variety of natural products and bioactive compounds.[1] These frameworks are also very important building blocks in the synthesis of many natural products and useful intermediates in organic synthesis.[2] Although several synthetic protocols in the achiral or chiral alkenyl halide synthesis have been well established in recent years,[3] more practical, direct asymmetric reactions of carbonyl compounds with electrophiles containing alkenyl halide for generating highly functionalized monohaloalkenes with α, β-stereocenters were less developed (Scheme 1).

Scheme 1



In the past decades, organocatalysis has gained considerable attention in chemistry as an efficient approach for synthesizing enantiopure molecules under mild, environmentally benign conditions.[4] Furthermore, the absence of any organic solvent in organocatalysis is an ideal synthetic condition for achieving a more efficient and greener process.[5] Present reports mainly focus on the development of the first highly enantioselective, organocatalytic, direct Michael addition of ketones to γ-monohalonitrodienes without solvents to obtain enantioselective monohaloalkenes.

On the basis of these considerations and previous results,[6] the organocatalyzed solvent-free Michael reaction was performed with the addition reaction of cyclohexanone (**1a**) to γ-monobromonitrodiene (**2a**) as a model. Different parameters (Table 1), such as the catalyst and acid additive, were studied. The catalysts L-proline **3a** and L-prolinol **3b** could promote the efficient formation of **5a** with high diastereoselectivities (10:1 dr to 23:1 dr) but modest to good enantioselectivities (30% ee to 83% ee) (entries 1 to 3). The Jørgensen−Hayashi and MacMillan catalysts **3c** and **3d** were almost completely inactive (entries 4 to 5). We speculated that using a multifunctional catalyst capable of simultaneously activating both the substrates **1a** and **2a** might lead to higher catalytic activity and better enantioselectivity. To our delight, the promising chiral prolinethiol ether catalyst **3e** showed better catalytic performance (entry 6). Moreover, chiral prolinethiol ether **3f** was found to be the best catalyst for this reaction, providing **5a** in 98% conversion, 8:1 dr with corresponding 93% and 96% ee after 1 h (entry 7). Next, a series of different organic acid additives **4** was tested. Chiral prolinethiol ether **3f** can catalyze the Michael reaction with different acid additives to obtain **5a** with 88% ee to 94% ee and 8 to 14:1 dr (entries 7−19). 4-$CF_3C_6H_4CO_2H$ (**4i**) proved to be a suitable additive among the screened organic acids. The reduced amounts of catalyst **3f** and additive **4i** to 10 mol % (entry 20) or 5 mol % (entry 21) led to an increase in the reaction time needed to achieve the similar conversions. In

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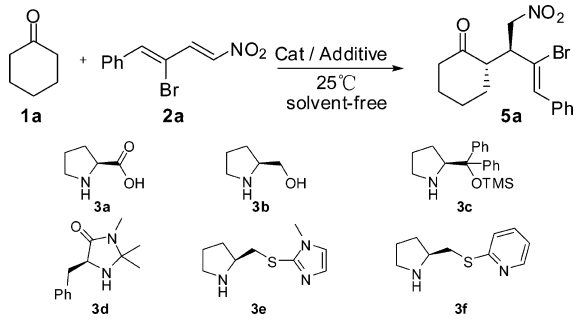
Table 1. Evaluation of Reaction Parameters[a]



entry	cat.	additive	time (h)	conv[b] (%)	dr[c] (*anti*/*syn*)	ee (%)[d] (*anti*/*syn*)
1	**3a**	none	48	78	10:1	34/39
2	**3a**	$C_6H_5CO_2H$ (**4a**)	48	81	23:1	83/50
3	**3b**	$C_6H_5CO_2H$ (**4a**)	48	64	17:1	30/33
4	**3c**	$C_6H_5CO_2H$ (**4a**)	48	<1		
5	**3d**	$C_6H_5CO_2H$ (**4a**)	48	1		
6	**3e**	$C_6H_5CO_2H$ (**4a**)	1	84	6:1	88/82
7	**3f**	$C_6H_5CO_2H$ (**4a**)	1	98	8:1	91/94
8	**3f**	4-$CH_3C_6H_4CO_2H$ (**4b**)	1	98	8:1	93/93
9	**3f**	2-$FC_6H_4CO_2H$ (**4c**)	1	53	9:1	94/93
10	**3f**	4-$FC_6H_4CO_2H$ (**4d**)	1	96	9:1	92/94
11	**3f**	2-$NO_2C_6H_4CO_2H$ (**4e**)	1	87	10:1	91/94
12	**3f**	3-$NO_2C_6H_4CO_2H$ (**4f**)	1	98	8:1	91/94
13	**3f**	4-$NO_2C_6H_4CO_2H$ (**4g**)	1	97	8:1	91/93
14	**3f**	2-$CF_3C_6H_4CO_2H$ (**4h**)	1	97	8:1	94/93
15	**3f**	**4-$CF_3C_6H_4CO_2H$** (**4i**)	**1**	**96**	**10:1**	**92/94**
16	**3f**	CH_3CO_2H (**4j**)	1	98	11:1	91/88
17	**3f**	$C_6H_5CH_2CO_2H$ (**4k**)	1	98	8:1	93/93
18	**3f**	2-$C_{10}H_7CH_2CO_2H$ (**4l**)	1	84	12:1	93/92
19	**3f**	$C_6H_5CHCHCO_2H$ (**4m**)	1	98	14:1	91/87
20[e]	**3f**	**4-$CF_3C_6H_4CO_2H$** (**4i**)	**3**	**98**	**17:1**	**95/95**
21[f]	**3f**	4-$CF_3C_6H_4CO_2H$ (**4i**)	4	92	16:1	95/94

[a]Unless otherwise stated, the reaction was conducted by stirring without a solvent using **1a** (0.65 mmol) and **2a** (0.13 mmol) with 20 mol % of catalyst and 20 mol % of additive at room temperature. [b]Conversion into the product was determined using GC. [c]Determined by chiral phase HPLC. [d]Determined through HPLC analysis on a Chiralcel AS-H. [e]Using 10 mol % of catalyst and 10 mol % of additive. [f]Using 5 mol % of catalyst and 5 mol % of additive.

addition, a slight increase in diastereoselectivities and enantioselectivities was observed.

The reaction scope was determined after the optimal catalytic conditions were obtained. As shown in Table 2, the enantioselectivity of the reaction was minimally affected by the substituents on the cyclic ketone (entries 1−5). Moreover, the substitutions on the aryl of **2** were well tolerated (entries 6 and 7). Cyclopentanone (entry 8) was also well activated as a cyclic substrate. It provided a 57% yield, >99:1 dr, and 95% ee after 168 h. Moderate to high yields (47% to 85%) and high to excellent enantioselectivities (83−92%) of the Michael products were achieved when the acyclic ketones were subjected to this reaction (entries 9−12). Moreover, the asymmetric additions of aliphatic aldehyde to γ-monobromonitrodiene **2a** were also examined (entry 13). The reaction was performed at −10 °C to obtain the desired product **5m** with 93% yield, with 2:1 dr and corresponding >99% and 92% ee.

Of particular note is the addition of 4-methylpentan-2-one or 4-methoxy-4-methylpentan-2-one to γ-monobromonitrodiene **2a** to obtain the Michael products at 38% yield with 87% ee and 43% yield with 93% ee (Scheme 2). The principal issue in these reactions is that the reactions proceed on the sterically less hindered carbon, which is opposite to the other acyclic ketones in Table 2. The balance between steric effects and stability of the enamines derived from catalyst **3f** and ketones presumably favors the terminal Michael product formation.[7]

The investigation on the scope of electrophiles **2** with different substituents on the γ-position of the nitryl showed that nucleophiles bearing substituents can be employed to form the desired adducts in good to high diastereoselectivities and high to excellent enantioselectivities (Table 3, entries 1−4). In addition, the nonsubstituent electrophile **2e** also performed well and produced **5s** at 95% yield with >99:1 dr and 79% ee (Table3, entry 5).

A transition-state model was proposed on the basis of the X-ray crystallographic analysis of the absolute configuration of adduct **5a** (Figure 1). γ-Monohalonitrodiene **2a** was activated well through the positive inducing effect and hydrogen-bonding interaction between the protonated thiopyridine group of **3f** and nitro group of **2a**. Therefore, the enamine formed from **3f** and **1a** attacked the activated **2a** from the *Re* face to afford the major stereoisomer of Michael adduct **5a** with the (*S*,*S*) configuration (TS I). In the case of 4-substituent ketone **1b**, the steric interactions between the enamine activated ketone **1b** and the activated **2a** will make the transition state TS II more stable than TS II′.[8] And the synergistic cooperative activation of

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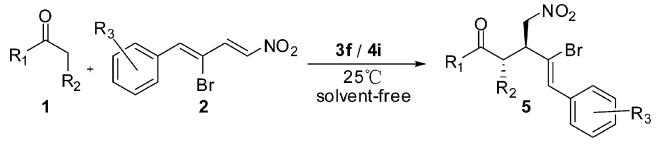
Table 2. Michael Reactions of 1 with 2 by Catalyst 3f under Solvent-Free Conditions[a]



entry	R_1, R_2 (1)	R_3	5	time (h)	yield[b] (%)	dr[c] (*anti*/*syn*)	ee (%)[c] (*anti*/*syn*)
1	$-(CH_2)_4-$ (**1a**)	H	**5a**	2	92	17:1	95/95
2	$-CH_2CH_2CH(Me)CH_2-$ (**1b**)	H	**5b**	2	92	3:1	94/94
3	$-CH_2CH_2CH(Et)CH_2-$ (**1c**)	H	**5c**	2	92	4:1	97/90
4	$-CH_2CH_2OCH_2-$ (**1d**)	H	**5d**	24	90	>99:1	96/–
5	$-CH_2CH_2N(CO_2Et)CH_2-$ (**1e**)	H	**5e**	24	91	2:1	97/83
6	$-CH_2CH_2N(CO_2Et)CH_2-$ (**1f**)	4-Cl	**5f**	24	95	7:1	>99/96
7	$-CH_2CH_2N(CO_2Et)CH_2-$ (**1g**)	4-CF_3	**5g**	24	95	5:1	94/93
8[d]	$-(CH_2)_3-$ (**1h**)	H	**5h**	168	57	>99:1	95/–
9[d]	Me, Me (**1i**)	H	**5i**	48	85	8:1	92/80
10[d]	Et, Me (**1j**)	H	**5j**	120	54	>99:1	98/–
11[d]	Me, $CH_2CH{=}CH_2$ (**1k**)	H	**5k**	120	47	2:1	83/85
12[d]	Me, $(CH_2)_3CH_3$ (**1l**)	H	**5l**	24	60	2:1	88/87
13[d,e]	H, *i*-Pr (**1m**)	H	**5m**	48	93	2:1	>99/92

[a]Unless otherwise stated, the reaction was conducted by stirring without a solvent using **1** (0.65 mmol) and **2** (0.13 mmol) in the presence of **3f** (10 mol % catalyst) and **4i** (10 mol % additive) at room temperature. [b]Isolated yield. [c]Determined by chiral-phase HPLC. [d]Using 20 mol % of catalyst and 20 mol % of additive. [e]Reaction was conducted at −10 °C.

Scheme 2. Further Investigation of the Substrate Scope

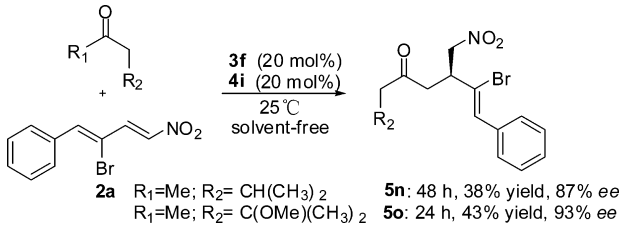
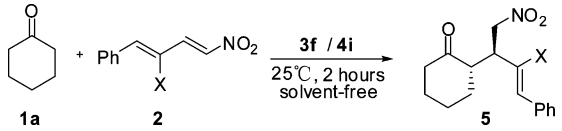


Table 3. Michael Reactions of 1a with 2 by Catalyst 3f under Solvent-Free Conditions for 2 h[a]



entry	X (2/5)	yield[b] (%)	dr[c] (*anti*/*syn*)	ee (%)[c] (*anti*/*syn*)
1	Cl (**2b**/**5p**)	95	17:1	96/87
2	Br (**2a**/**5a**)	92	17:1	95/95
3	I (**2c**/**5q**)	91	3:1	95/93
4	Me (**2d**/**5r**)	90	36:1	92/>99
5	H (**2e**/**5s**)	95	>99:1	79/–

[a]Unless otherwise stated, the reaction was conducted by stirring without a solvent using **1** (0.65 mmol) and **2** (0.13 mmol) in the presence of **3f** (10 mol % catalyst) and **4i** (10 mol % additive) at room temperature. [b]Isolated yields. [c]Determined by chiral-phase HPLC.

both the substrates **1a** and **2a** may explain the excellent performance of the present prolinethiol ether catalytic system.[9]

In conclusion, the first enantioselective, organocatalytic Michael reaction of ketones with γ-monohalonitrodienes under solvent-free conditions was successfully demonstrated. The new reaction sequence provides an easy approach to highly functionalized monohaloalkenes with α,β-stereocenters at 38–95% yields with 2:1 to >99:1 regioselectivities and 79% to >99% enantioselectivities. Further applications of this organocatalytic system are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz, respectively, with TMS as the internal standard. GC–MS experiments were performed on a GC system with a mass selective detector. HRMS data were measured on a LC/TOF-MS with ESI source or GC/TOF-MS with EI source. Column chromatography and flash chromatography experiments were performed on silica gel (200–300 mesh) eluting with ethyl ether and petroleum ether. TLC experiments were carried out on glass-backed silica plates. In each case, enantiomeric ratio was determined on a chiral column in comparison with authentic racemates by chiral HPLC. Chemicals were used without purification as commercially available.

Typical Experimental Procedure for the Michael Reaction To Achieve Functionalized Monohaloalkenes. Various cyclic ketones **1** (0.65 mmol) and γ-monohalonitrodienes **2** (0.13 mmol) were stirred under solvent-free conditions in the presence of catalyst **3f** (0.013 mmol) and acid **4i** (0.013 mmol) at room temperature. In the case of acyclic ketone or aldehyde substrates, catalyst **3f** (0.026 mmol) and acid **4i** (0.026 mmol) were used at room temperature or −10 °C. The reaction conversion was monitored by GC–MS. After completion, the reaction mixture was washed with water, extracted with EtOAc (3 × 10 mL), dried, and concentrated. The residue was purified by flash chromatography to give the functionalized monohaloalkenes. The enantiomeric ratio was determined by HPLC analysis on a chiral column.

*(S)-2-((S,Z)-3-Bromo-1-nitro-4-phenylbut-3-en-2-yl)cyclohexanone (**5a**).* Yield: 42 mg, 92%; 95% ee (*anti*), 95% ee (*syn*). White solid. Mp: 99–101 °C. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/i-PrOH (85:15) as the eluent. Flow: 1.0 mL/min; UV = 254 nm; t^{anti}_{minor} =17.57 min, t^{anti}_{major} = 25.28 min; t^{syn}_{minor} = 10.67 min, t^{syn}_{major} = 13.91 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7 Hz, 2H), 7.36–7.29 (m, 3H), 6.96 (s, 1H), 4.81–4.78 (m, 1H), 4.62–4.57 (m, 1H), 3.64–3.59 (m, 1H), 2.65–2.59 (m, 1H), 2.59–2.47 (m, 1H), 2.42–2.36 (m, 1H), 2.29–2.24 (m, 1H), 2.17–2.12 (m, 1H), 1.97–1.90 (m, 1H), 1.76–1.66 (m, 2H), 1.44–1.36 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.0, 134.8, 133.7, 129.1 (×2), 128.4, 128.2 (×2), 123.5, 76.3, 50.0, 49.1, 43.0, 33.1, 28.6, 25.2 ppm. GC–MS: *m*/*z* 128, 211, 225, 272 (100), 304, 306.

*(2S,4S)-2-((S,Z)-3-Bromo-1-nitro-4-phenylbut-3-en-2-yl)-4-methylcyclohexanone (**5b**).* Yield: 44 mg, 92%; 94% ee (*anti*), 94% ee (*syn*). White solid. Mp: 108–110 °C. The enantiomeric excess was

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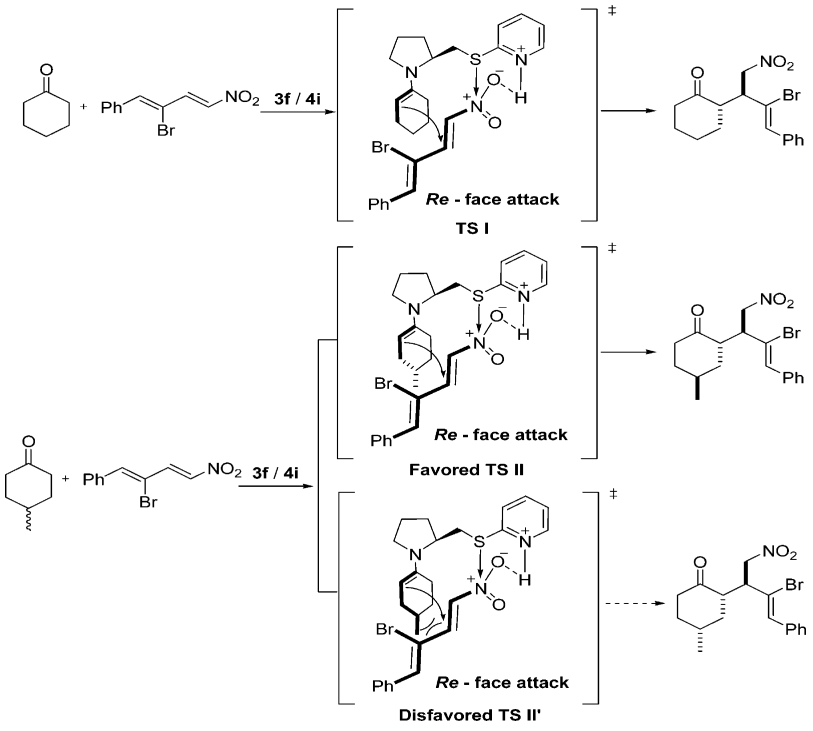

Figure 1. Proposed transition state for the reaction.

determined by HPLC on Daicel Chiralpak AS-H with hexane/*i*-PrOH (90:10) as the eluent. Flow: 1.0 mL/min; UV = 260 nm; t^{anti}_{minor} = 16.49 min, t^{anti}_{major} = 21.98 min; t^{syn}_{minor} = 11.83 min, t^{syn}_{major} = 18.92 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, J = 8.5 Hz, 2H), 7.35−7.27 (m, 3H), 6.97 (s, 1H), 4.74−4.69 (m, 1H), 4.60−4.56 (m, 1H), 4.05−4.01 (m, 1H), 3.06−3.01 (m, 1H), 2.46−2.42 (m, 2H), 2.18−2.14 (m, 1H), 2.11−1.99 (m, 2H),1.46−1.38 (m, 1H), 1.23−1.15 (m, 1H), 1.04 (d, J = 6.5 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.4, 135.2, 132.2, 129.1 (×2), 128.2, 128.1 (×2), 124.1, 75.4, 50.5, 49.9, 41.6, 38.2, 35.8, 32.3, 21.3 ppm. GC−MS: *m*/*z* 128, 225, 239, 286 (100), 318, 320.

(2S,4S)-2-((S,Z)-3-Bromo-1-nitro-4-phenylbut-3-en-2-yl)-4-ethylcyclohexanone (**5c**). Yield: 45 mg, 92%; 97% ee (*anti*), 90% ee (*syn*). White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/*i*-PrOH (99:1) as the eluent. Flow: 0.5 mL/min; UV = 256 nm; t^{anti}_{minor} = 83.49 min, t^{anti}_{major} = 73.08 min; t^{syn}_{minor} = 68.57 min, t^{syn}_{major} = 59.22 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 7.5 Hz, 2H), 7.38−7.31 (m, 3H), 6.99 (s, 1H), 4.65−4.4.63 (m, 2H), 3.65−3.57 (m, 1H), 2.73−2.68 (m, 1H), 2.53−2.48 (m, 1H), 2.44−2.39 (m, 1H), 2.00−1.91 (m, 2H), 1.86−1.71 (m, 3H), 1.58−1.50 (m, 2H), 0.99−0.96 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.0, 134.7, 134.0, 129.1 (×2), 128.5, 128.2 (×2), 123.1, 76.4, 49.1, 46.5, 39.0, 35.5, 33.9, 32.0, 25.6, 12.2 ppm. GC−MS: *m*/*z* 128, 239, 253, 300 (100), 332, 334.

(R)-3-((S,Z)-3-Bromo-1-nitro-4-phenylbut-3-en-2-yl)dihydro-2H-pyran-4(3H)-one (**5d**). Yield: 41 mg, 90%; 96% ee (*anti*); White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/i-PrOH (85:15) as the eluent. Flow: 1.0 mL/min; UV = 254 nm; t^{anti}_{minor} = 62.78 min, t^{anti}_{major} =32.72 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, J = 7.0 Hz, 2H), 7.94−7.31 (m, 3H), 6.99 (s, 1H), 4.82−4.79 (m, 1H), 4.70−4.65 (m, 1H), 4.26−4.23 (m, 2H), 3.82−3.77 (m, 1H), 3.72−3.67 (m, 1H), 3.54−3.49 (m, 1H), 2.90−2.84 (m, 1H), 2.73−2.67 (m, 1H), 2.56−2.52 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.6, 134.4, 134.3, 129.0 (×2), 128.7, 128.3 (×2), 121.5, 76.0, 71.3, 69.1, 50.4, 46.5, 43.2 ppm. GC−MS: *m*/*z* 128, 183 (100), 213, 227, 274, 306, 308.

(R)-Ethyl 3-((S,Z)-3-Bromo-1-nitro-4-phenylbut-3-en-2-yl)-4-oxopiperidine-1-carboxylate (**5e**). Yield: 50 mg, 91%; 97% ee (*anti*), 83% ee (*syn*). White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/*i*-PrOH (80:20) as the eluent. Flow: 1.0 mL/min; UV = 256 nm; t^{anti}_{minor} =25.08 min, t^{anti}_{major} =12.68 min; t^{syn}_{minor} = 21.96 min, t^{syn}_{major} = 50.18 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 7.0 Hz, 2H), 7.38−7.33 (m, 3H), 7.00 (s, 1H), 4.81−4.78 (m, 1H), 4.69−4.64 (m, 1H), 4.46−4.29 (m, 2H), 4.25−4.15 (m, 2H), 3.69−3.64 (m, 1H), 3.37−3.21 (m, 1H), 3.03−2.98 (m, 1H), 2.77 (s, 1H), 2.62−2.50 (m, 2H), 1.27−1.26 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.4, 155.2, 134.5, 134.5, 129.1 (×2), 128.7, 128.3 (×2), 121.7, 76.038, 62.2, 49.5, 47.6, 47.2, 44.4, 41.9, 14.9 ppm.

(R)-Ethyl 3-((S,Z)-3-Bromo-1-nitro-4-phenylbut-3-en-2-yl)-4-oxopiperidine-1-carboxylate (**5f**). Yield: 56 mg, 95%; 99.9% ee (*anti*), 96% ee (*syn*). White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/*i*-PrOH (80:20) as the eluent. Flow: 1.0 mL/min; UV = 254 nm; t^{anti}_{minor} = 30.46 min, t^{anti}_{major} = 54.83 min; t^{syn}_{minor} = 33.75 min, t^{syn}_{major} = 25.44 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 6.95 (s, 1H), 4.81−4.79 (m, 1H), 4.67−4.62 (m, 1H), 4.41−4.15 (m, 4H), 3.68−3.63 (m, 1H), 3.29 (s, 1H), 3.02−2.98 (m, 1H), 2.76 (s, 1H), 3.61−2.49 (m, 2H), 1.32−1.27 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.2, 155.1, 134.5, 133.4, 132.9, 130.4 (×2), 128.5 (×2), 122.6, 76.0, 62.2, 49.4, 47.6, 47.2, 44.0, 41.9, 14.6 ppm.

(R)-Ethyl 3-((S,Z)-3-Bromo-1-nitro-4-(4-(trifluoromethyl)phenyl)-but-3-en-2-yl)-4-oxopiperidine-1-carboxylate (**5g**). Yield: 60 mg, 95%; 94% ee (*anti*), 93% ee (*syn*). White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/*i*-PrOH (80:20) as the eluent. Flow: 1.0 mL/min; UV = 256 nm; t^{anti}_{minor} = 19.81 min, t^{anti}_{major} = 17.38 min; t^{syn}_{minor} = 32.42 min, t^{syn}_{major} = 26.38 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.62 (s, 4H), 7.04 (s, 1H), 4.85−4.80 (m, 1H), 4.68−4.64 (m, 1H), 4.45−4.42 (m, 1H), 4.26−4.10 (m, 3H), 3.71−3.66 (m, 1H), 3.44−3.20 (m, 1H), 3.10−2.99 (m, 1H), 2.77 (s, 1H), 2.63−2.51 (m, 2H), 1.33−1.25 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.1, 155.1, 138.1, 133.4, 132.3, 129.4 (×4), 125.3 (×2), 75.9, 62.3, 49.4, 47.6, 47.2, 44.4, 41.9, 14.6 ppm.

(S)-2-((S,Z)-3-Bromo-1-nitro-4-phenylbut-3-en-2-yl)-cyclopentanone (**5h**). Yield: 25 mg, 57%; 95% ee (*anti*). White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/*i*-PrOH (90:10) as the eluent. Flow: 1.0 mL/min; UV = 240 nm; t^{anti}_{minor} = 46.09 min, t^{anti}_{major} = 40.58 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 7.0 Hz, 2H), 7.37−7.30

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(m, 3H), 6.94 (s, 1H), 5.47−5.44 (m, 1H), 4.76−4.72 (m, 1H), 3.36−3.31 (m, 1H), 2.46−2.40 (m, 1H), 2.36−2.22 (m, 3H), 2.09−2.04 (m, 1H), 1.88−1.77 (m, 1H), 1.73−1.65 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 218.5, 134.6, 133.7, 129.1 (×2), 128.6, 128.2 (×2), 123.8, 75.5, 50.2, 47.8, 38.8, 28.9, 20.1 ppm. GC−MS: *m*/*z* 128, 169, 211, 258 (100), 290, 292.

*(3S,4S,Z)-5-Bromo-3-methyl-4-(nitromethyl)-6-phenylhex-5-en-2-one (**5i**).* Yield: 36 mg, 85%; 92% ee (*anti*), 80% ee (*syn*). Colorless oil. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/*i*-PrOH (90:10) as the eluent. Flow: 1.0 mL/min; UV = 272 nm; t^{anti}_{minor} = 40.81 min, t^{anti}_{major} = 21.93 min; t^{syn}_{minor} = 19.80 min, t^{syn}_{major} = 25.09 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.0 Hz, 2H), 7.37−7.30 (m, 3H), 7.00 (s, 1H), 4.66−4.61 (m, 1H), 4.43−4.40 (m, 1H), 3.60−3.56 (m, 1H), 2.91−2.84 (m, 1H), 2.27 (s, 3H), 1.25−1.22 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.5, 134.7, 133.9, 129.1 (×2), 128.5, 128.2 (×2), 123.2, 76.2, 50.7, 46.9, 29.3 15.8 ppm. GC−MS: *m*/*z* 97, 128, 185, 199, 246 (100), 278, 280.

*(4S,5S,Z)-6-Bromo-4-methyl-5-(nitromethyl)-7-phenylhept-6-en-3-one (**5j**).* Yield: 24 mg, 54%; 98% ee (*anti*), >99% ee (*syn*). Colorless oil. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (95:5) as the eluent. Flow: 1.0 mL/min; UV = 254 nm; t^{anti}_{minor} = 10.85 min, t^{anti}_{major} = 12.08 min; t^{syn}_{major} = 10.16 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.0 Hz, 2H), 7.37−7.30 (m, 3H), 7.01 (s, 1H), 4.65−4.61 (m, 1H), 4.36−4.33 (m, 1H), 3.63−3.38 (m, 1H), 2.92−2.85 (m, 1H), 2.74−2.66 (m, 1H), 2.47−2.39 (m, 1H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.3, 134.8, 133.8, 129.1 (×2), 128.5, 128.2 (×2), 123.3, 76.2, 50.9, 46.0, 35.6, 16.2, 7.8 ppm. GC−MS: *m*/*z* 128, 199, 213, 260 (100), 292, 294.

*(3S,4S,Z)-3-Allyl-5-bromo-4-(nitromethyl)-6-phenylhex-5-en-2-one (**5k**).* Yield: 21 mg, 47%; 83% ee (*anti*), 85% ee (*syn*). White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/*i*-PrOH (90:10) as the eluent. Flow: 1.0 mL/min; UV = 276 nm; t^{anti}_{minor} = 9.61 min, t^{anti}_{major} = 13.33 min; t^{syn}_{minor} = 16.05 min, t^{syn}_{major} = 18.29 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.0 Hz, 2H), 7.37−7.30 (m, 3H), 6.98 (s, 1H), 5.71−5.63 (m, 1H), 5.14−5.09 (m, 2H), 4.66−4.62 (m, 1H), 4.41−4.39 (m, 1H), 3.66−3.61 (m, 1H), 3.02−2.97 (m, 1H), 2.55−2.50 (m, 1H), 2.41−2.35 (m, 1H), 2.24 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.8, 134.6, 134.3, 132.5, 129.1 (×2), 128.6, 128.2 (×2), 122.6, 119.1, 76.2, 51.5, 49.2, 34.1, 31.0 ppm. GC−MS: *m*/*z* 128, 211, 225, 272 (100), 304, 306.

*(S)-3-((S,Z)-3-Bromo-1-nitro-4-phenylbut-3-en-2-yl)heptan-2-one (**5l**).* Yield: 29 mg, 60%; 88% ee (*anti*), 87% ee (*syn*). White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/*i*-PrOH (85:15) as the eluent. Flow: 1.0 mL/min; UV = 248 nm; t^{anti}_{minor} = 7.53 min, t^{anti}_{major} = 9.47 min; t^{syn}_{minor} = 10.92 min, t^{syn}_{major} = 13.59 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.0 Hz, 2H), 7.37−7.30 (m, 3H), 6.99 (s, 1H), 4.67−4.63 (m, 1H), 4.37−4.34 (m, 1H), 3.65−3.61 (m, 1H), 2.93−2.89 (m, 1H), 2.26 (s, 3H), 1.72−1.66 (m, 2H), 1.31−1.26 (m, 4H), 0.87 (t, *J* = 7 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.8, 134.8, 133.8, 129.0 (×2), 128.5, 128.2 (×2), 123.2, 76.3, 52.0, 49.5, 30.6, 29.5, 27.7, 22.7, 13.8 ppm. GC−MS: *m*/*z* 128, 227, 242, 288 (100), 320, 322.

*(2S,3S,Z)-4-Bromo-2-isopropyl-3-(nitromethyl)-5-phenylpent-4-enal (**5m**).* Yield: 41 mg, 93%; >99% ee (*anti*), 92% ee (*syn*). Colorless oil. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/*i*-PrOH (85:15) as the eluent. Flow: 1.0 mL/min; UV = 254 nm; t^{anti}_{major} = 14.63 min; t^{syn}_{minor} = 12.87 min, t^{syn}_{major} = 11.75 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.53 (d, *J* = 7.0 Hz, 2H), 7.36−7.30 (m, 3H), 7.00 (s, 1H), 4.63−4.59 (m, 1H), 4.53−4.49 (m, 1H), 3.79−3.74 (m, 1H), 2.78−2.75 (m, 1H), 2.22−2.16 (m, 1H), 1.26 (d, *J* = 7.5 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.2, 134.6, 134.0, 129.1 (×2), 128.6, 128.2 (×2), 122.9, 76.3, 56.1, 47.0, 28.2, 21.9, 16.7 ppm. GC−MS: *m*/*z* 91, 129 (100), 171, 199, 260.

*(S,Z)-7-Bromo-2-methyl-6-(nitromethyl)-8-phenyloct-7-en-4-one (**5n**).* Yield: 17 mg, 38%; 87% ee. Colorless oil. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/*i*-PrOH (90:10) as the eluent. Flow: 1.0 mL/min; UV = 254 nm; t_{minor} = 12.45 min, t_{major} = 16.41 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.0 Hz, 2H), 7.35−7.28 (m, 3H), 7.03 (s, 1H), 4.67−4.63 (m, 1H), 4.56−4.52 (m, 1H), 3.96−3.91 (m, 1H), 2.96−2.91 (m, 1H), 2.62−2.58 (m, 1H), 2.37−2.29 (m, 2H), 2.19−2.12 (m, 1H), 0.92−0.91 (m, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.6, 134.8, 132.6, 129.0 (×2), 128.4, 128.2 (×2), 123.8, 77.2, 52.3, 44.4, 43.7, 24.6, 22.6, 22.5 ppm. GC−MS: *m*/*z* 128 (100), 227, 274.

*(S,Z)-7-Bromo-2-methoxy-2-methyl-6-(nitromethyl)-8-phenyloct-7-en-4-one (**5o**).* Yield: 21 mg, 43%; 93% ee. Colorless oil. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/*i*-PrOH (85:15) as the eluent. Flow: 1.0 mL/min; UV = 254 nm; t_{minor} = 10.92 min, t_{major} = 14.09 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.0 Hz, 2H), 7.38−7.28 (m, 3H), 7.03 (s, 1H), 4.66−4.62 (m, 1H), 4.54−4.50 (m, 1H), 3.96−3.91 (m, 1H), 3.21 (s, 3H), 3.05−3.00 (m, 1H), 2.79−2.74 (m, 1H), 2.62−2.54 (m, 2H), 1.24 (s, 3H), 1.23 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.1, 135.0, 132.4, 129.0 (×2), 128.3, 128.1 (×2), 124.2, 77.2, 74.7, 53.8, 49.4, 45.6, 44.3, 24.8, 24.6 ppm. GC−MS: *m*/*z* 128 (100), 211, 249, 272, 304.

*(S)-2-((S,Z)-3-Chloro-1-nitro-4-phenylbut-3-en-2-yl)cyclohexanone (**5p**).* Yield: 38 mg, 95%; 96% ee(anti), 87% ee(syn). White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (99:1) as the eluent. Flow: 1.0 mL/min; UV = 268 nm; t^{anti}_{minor} = 54.19 min, t^{anti}_{major} = 49.84 min; t^{syn}_{minor} = 73.45 min, t^{syn}_{major} = 60.18 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.0 Hz, 2H), 7.36−7.28 (m, 3H), 6.66 (s, 1H), 4.81−4.78 (m, 1H), 4.61−4.57 (m, 1H), 3.71−3.66 (m, 1H), 2.66−2.60 (m, 1H), 2.49−2.47 (m, 1H), 2.42−2.35 (m, 1H), 2.26−2.22 (m, 1H), 2.17−2.12 (m, 1H), 1.93−1.91 (m, 1H), 1.73−1.68 (m, 2H), 1.46−1.37 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.1, 133.7, 130.5, 129.5(×2), 129.3, 128.4(×2), 128.3, 75.7, 49.4, 48.2, 42.9, 33.0, 28.6, 25.2 ppm. GC−MS: *m*/*z* 115, 129(100), 163, 225, 272, 307, 309. HRMS: (EI+) *m*/*z* calcd for $[C_{16}H_{18}ClNO_3]^+$ 307.0987, found 307.0975.

*(S)-2-((S,Z)-3-Iodo-1-nitro-4-phenylbut-3-en-2-yl)cyclohexanone (**5q**).* Yield 47 mg, 91%; 95% ee (*anti*), 93% ee (*syn*). White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AS-H with hexane/*i*-PrOH (85:15) as the eluent. Flow: 1.0 mL/min; UV = 280 nm; t^{anti}_{minor} = 13.97 min, t^{anti}_{major} = 20.12 min; t^{syn}_{minor} = 9.67 min, t^{syn}_{major} = 12.16 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39−7.30 (m, 5H), 7.01 (s, 1H), 4.79−4.76 (m, 1H), 4.55−4.51 (m, 1H), 3.20−3.15 (m, 1H), 2.58−2.52 (m, 1H), 2.50−2.47 (m, 1H), 2.44−2.36 (m, 1H), 2.28−2.23 (m, 1H), 2.18−2.13 (m, 1H), 1.95−1.93 (m, 1H), 1.75−1.70 (m, 2H), 1.41−1.32 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.9, 140.0, 128.6 (×2), 128.3, 128.1 (×2), 127.8, 105.7, 77.5, 51.0, 50.0, 43.1, 33.3, 28.7, 25.3 ppm. GC−MS: *m*/*z* 128, 211, 225, 272 (100).

*(S)-2-((R,E)-3-Methyl-1-nitro-4-phenylbut-3-en-2-yl)cyclohexanone (**5r**).* Yield: 33 mg, 90%; 92% ee (*anti*), >99% ee (*syn*). White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (85:15) as the eluent. Flow: 1.0 mL/min; UV = 272 nm; t^{anti}_{minor} = 10.67, t^{anti}_{major} = 12.16 min, t^{syn}_{major} = 11.40 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.28 (m, 2H), 7.21−7.18 (m, 3H), 6.39 (m, 1H), 4.84−4.80 (m, 1H), 4.43−4.39 (m, 1H), 3.36−3.31 (m, 1H), 2.51−2.43 (m, 2H), 2.39−2.33 (m, 1H), 2.09−2.03 (m, 2H), 1.89−86 (m, 1H), 1.80 (s, 3H), 1.76−1.60 (m, 2H), 1.47−1.39 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.8, 137.0, 133.0, 131.3, 129.0 (×2), 128.1 (×2), 126.8, 77.0, 50.0, 48.1, 42.7, 33.0, 28.5, 25.0, 14.0 ppm; GC−MS: *m*/*z* 129, 143(100), 240, 287. HRMS: (EI+) *m*/*z* calcd for $[C_{17}H_{21}NO_3]^+$ 287.1521, found 287.1531.

*(S)-2-((S,E)-1-Nitro-4-phenylbut-3-en-2-yl)cyclohexanone (**5s**).* Yield: 34 mg, 95%, 79% ee (*anti*). White solid. The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/*i*-PrOH (85:15) as the eluent. Flow: 1.0 mL/min; UV = 250 nm; t^{anti}_{minor} = 18.44, t^{anti}_{major} = 13.76 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.26 (m, 4H), 7.25−7.20(m, 1H), 6.47 (d, *J* = 15.5 Hz, 1H), 6.03−5.98 (m, 1H), 4.67−4.63 (m, 1H), 4.54−4.50 (m, 1H), 3.37−3.31 (m, 1H), 2.53−2.48 (m, 1H), 2.42−2.39 (m, 1H), 2.35−

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2.29 (m, 1H), 2.15−2.11 (m, 1H), 2.07−2.02 (m, 1H), 1.87−1.85 (m, 1H), 1.68−1.59 (m, 2H), 1.46−1.37 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.2, 136.4, 134.3, 128.6 (×2), 127.9, 126.4 (×2), 125.9, 78.1, 51.7, 42.6, 41.9, 32.5, 28.1, 25.0 ppm. GC−MS: m/z 129 (100), 197, 226, 273. HRMS: (EI+) m/z calcd for $[C_{16}H_{19}NO_3]^+$ 273.1365, found 273.1362.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra, HPLC analysis of the products, as well as X-ray structures of compounds **5a** and **5b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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