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PAPER

Pyrrolidinyl-sulfamide derivatives as a new class of bifunctional organocatalysts for direct asymmetric Michael addition of cyclohexanone to nitroalkenes†

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A series of chiral pyrrolidinyl-sulfamide derivatives have been identified as efficient bifunctional organocatalysts for the direct Michael addition of cyclohexanone to a wide range of nitroalkenes. The desired Michael adducts were obtained in high chemical yields and excellent stereoselectivities (up to 99/1 dr and 95% ee).

Introduction

Recently, organocatalytic asymmetric catalysis has been identified as one of the most powerful and economical approaches to a variety of enantiomerically enriched compounds that are widely used in drug discovery and chemical synthesis.^{1–3} In this scenario, great research efforts have been directed toward the design of environmentally friendly, highly efficient, and selective organocatalysts. As a result, a great number of chiral amine derivatives have been developed for a wide range of asymmetric transformations, especially for the enantioselective functionalization of the carbonyl compounds.^{4–8} Of these reactions, the organocatalytic asymmetric Michael addition reactions⁹ of ketones/aldehydes to nitroalkenes have received much attention because the corresponding adducts, γ -nitrocarbonyl compounds, are synthetically versatile.¹⁰ Stimulated by the seminal works of List^{11a} and Barbas,^{11bc} many efficient and highly selective catalytic systems have been developed for this reaction.^{11–14} Elegant catalysts include Wang's pyrrolidine sulfonamides^{12h} and thiourea-dehydroabiatic amine,^{13k} Barbas' diamines,¹²ⁱ Tang's thiourea-secondary amines,^{12j} Tsogoeva's^{13g,h} and Jacobsen's primary amine-thioureas,¹³ⁱ Takemoto's thiourea-tertiary amine,^{13l} and Chen's pyrrolidinyl-camphor derivatives.^{13t} Among them, those chiral amines based on the thiourea and urea cores dominate the field.¹⁴ Essential to the overwhelming success of thiourea-based catalysts is their capability to form two or more H-bonds with a reaction component. Such H-bonding interactions not only further activate the reactant but also direct it to a well-defined orientation, required for asymmetric induction. Quite recently, the Rawal group firstly developed the (–)-cinchonine-derived squaramide derivatives as highly effective H-bonding

donor catalysts for the conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes.¹⁵ Inspired by these advances, we envisaged that the introduction of new H-bonding donors to the chiral amine scaffold would probably lead to a new class of efficient bifunctional organocatalysts for the asymmetric Michael addition.

The key point for this research was to identify new bifunctional organocatalysts, that are significantly more active than those previously reported, with minimal perturbation of the overall parent catalyst structure. To reach this goal, we evaluated structural modifications of secondary amine-thiourea **I**, a catalyst that we¹⁶ and Tang^{12j} have previously developed for asymmetric Michael additions of cyclohexanone to nitroalkenes. We envisioned that the sulfamide motif, which is a structural relative of (thio)urea, could possibly be introduced to the chiral amine to serve as a versatile core activation unit for bifunctional catalysis (Fig. 1).¹⁷ The sulfamides, such as **II**, are expected to provide stronger acidity of N–H bonds than the corresponding (thio)urea. Notably, Yan *et al.* recently developed a series of primary amine-sulfamide catalysts and successfully applied them to the conjugate addition of aldehydes to nitroalkenes by combination with base additives.¹⁸ As a part of our interest in developing novel and structurally different bifunctional chiral amine organocatalysts,¹⁹ we herein disclose the synthesis of unprecedented pyrrolidinyl-sulfamide catalysts **1–4** and their application to the highly enantioselective direct Michael addition of cyclohexanone to nitroalkenes.

Results and discussion

To access the utility of representative sulfamides for asymmetric catalysis (Fig. 1), several differently substituted chiral pyrrolidinyl-sulfamide derivatives were synthesized by the modification of known procedures.^{18,20} As highlighted in Scheme 1, the preparation of pyrrolidinyl-sulfamides **1a–1c** and **2** with benzyl groups was based on path A. Stirring catechol sulfate **5** with an amine **6** in CH₂Cl₂ with Et₃N as the base promoted the first substitution reaction. Repeating such a process with the (*S*)-2-amino-1-*N*-Boc-pyrrolidine **8**²¹ in refluxing DCE gave rise to the disubstituted

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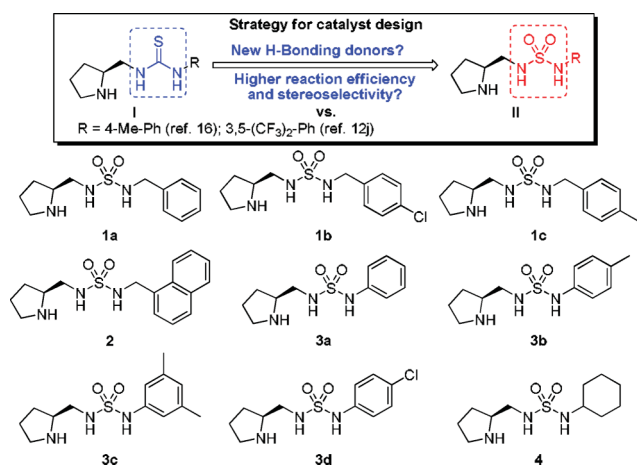


Fig. 1 A new class of pyrrolidinyl-sulfamide catalysts.

sulfamide **9**. Removing the Boc protecting group from nitrogen with TFA/CH₂Cl₂ afforded the target catalysts **1a–1c** and **2** smoothly. The other pyrrolidinyl-sulfamides **3** and **4** bearing aromatic substitution or cyclohexyl group on the nitrogen were also efficiently prepared by a slight change of the substitution sequence (path B). Moreover, the structures of the catalysts **1–4** were fully characterized (see the ESI†). Notably, these catalysts could be easily prepared on gram scales.

With success in synthesizing the above mentioned organocatalysts, we chose the Michael addition of cyclohexanone to *trans*-β-nitrostyrene **14a** as the benchmark reaction for examining the catalytic performance of these catalysts (Table 1). To our delight, pyrrolidinyl-sulfamide **1a** could indeed efficiently catalyze the Michael reaction with PhCO₂H as the acidic additive under our previous conditions,¹⁶ giving the corresponding adduct in 94% yield with 92/8 dr and 84% ee (Table 1, entry 1). Encouraged by these preliminary results, we examined the effects of additional solvents on the reaction with **1a** as the catalyst. It was found that the reaction could be performed in a variety of commonly used solvents, such as toluene, CHCl₃, CH₂Cl₂, DCE, Et₂O, and DMF, and consistently excellent yields and high stereoselectivities were obtained. The use of CH₃CN, dioxane, and THF as the reaction media gave the desired adduct **15a** in moderate yield but with good diastereoselectivity and enantioselectivity (Table 1, entries 8–10). In accordance with our previous observation,^{19b} only trace amounts of the Michael adducts were formed in protonic polar

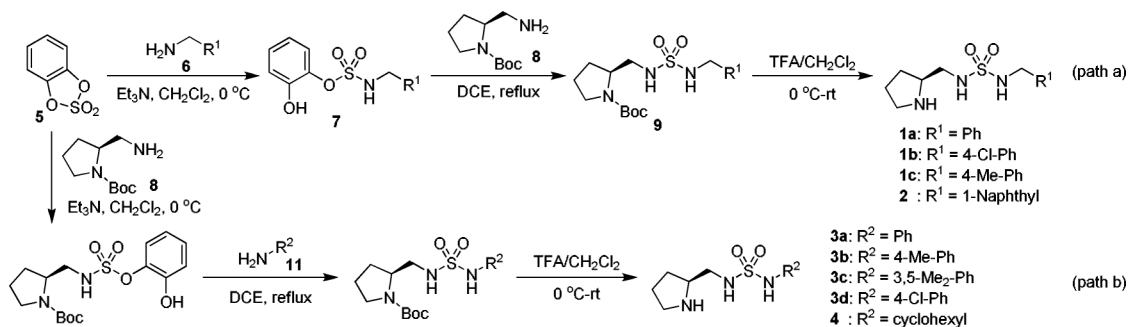
Table 1 Solvent screening for the asymmetric Michael addition of cyclohexanone **13** to *trans*-β-nitrostyrene **14a**^a

Entry	Solvent	<i>t</i> /h	Yield (%) ^b	dr ^c	ee (%) ^d
1	<i>n</i> -Hexane	6	94	92/8	84
2	Toluene	22	90	92/8	84
3	CHCl ₃	22	91	93/7	86
4	CH ₂ Cl ₂	22	92	93/7	85
5	DCE	22	92	92/8	83
6	Et ₂ O	22	90	94/6	85
7	DMF	22	85	95/5	86
8	CH ₃ CN	46	33	91/9	80
9	Dioxane	46	31	93/7	80
10	THF	46	43	95/5	82
11	MeOH	22	< 5	—	—
12	EtOH	22	< 5	—	—

^a Reactions were carried out with cyclohexanone **13** (3.0 mmol), *trans*-β-nitrostyrene **14a** (0.3 mmol) and 10 mol% catalyst **1a** and 10 mol% PhCO₂H in the solvent (0.6 mL) indicated. DCE = 1,2-dichloroethane. ^b Isolated yield for both diastereomers. ^c *Syn/anti* ratio was determined by ¹H NMR. ^d ee of *syn* diastereomer, determined by chiral HPLC analysis.

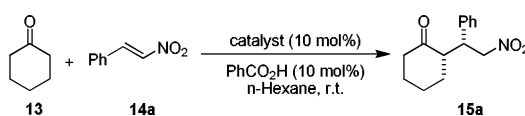
solvents, such as MeOH and EtOH (Table 1, entries 11 and 12). Thus, in terms of the reaction efficiency and stereoselectivity, we chose *n*-hexane as the reaction medium for further optimizations.

As can be seen from the results summarized in Table 2, the catalytic activities and the stereoselectivities of **1b–4** (Fig. 1) were significantly influenced by a subtle change in the sulfamide moiety. An elegant alignment of the steric and electronic properties of the catalyst would determine the reaction efficiency. Among the nine pyrrolidinyl-sulfamide catalysts examined, catalysts **3a** and **3b** were found to give optimal results (Table 1, entries 5 and 6, 95/5 dr, 88% and 89% ee, respectively). Further screenings of other reaction parameters demonstrated that a substantial improvement of the dr and ee to 97/3 and 92% was achieved when the reaction was carried out in a mixture of *n*-hexane and CH₂Cl₂ at –10 °C (Table 1, entry 14). Note that the reaction proceeded well even with 5 mol% of catalyst **3a** without loss of stereoselectivity albeit with a somewhat prolonged reaction time (Table 2, entry 13). Interestingly, the reaction proceeded much more slowly but with comparable dr and ee values in the absence of PhCO₂H (Table 2, entry 15 vs. 5).



Scheme 1 Synthesis of a series of novel pyrrolidinyl-sulfamide catalysts **1–4**.

Table 2 Catalyst screening for the asymmetric Michael addition of cyclohexanone **13** to *trans*- β -nitrostyrene **14a**^a

					
Entry	Catalyst	t/h	Yield (%) ^b	dr ^c	ee (%) ^d
1	1a	6	94	92/8	84
2	1b	6	92	92/8	81
3	1c	7	97	93/7	85
4	2	7	92	95/5	88
5	3a	4	94	95/5	88
6	3b	4	95	95/5	89
7	3c	5	95	95/5	87
8	3d	13	92	94/6	88
9	4	20	90	94/6	87
10 ^e	3a	12	96	96/4	90
11 ^e	3b	12	94	96/4	89
12 ^f	3a	12	85	97/3	90
13 ^{f,g}	3a	46	84	97/3	91
14 ^{f,h}	3a	25	89	97/3	92
15 ⁱ	3a	36	38	94/6	88

^a Unless otherwise noted, reactions were carried out with 0.3 mmol of *trans*- β -nitrostyrene **14a**, 3.0 mmol of cyclohexanone **13** in 0.6 mL of *n*-hexane in the presence of 10 mol% of catalyst and 10 mol% of PhCO₂H.

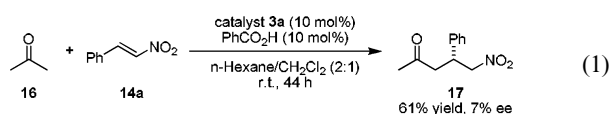
^b Isolated yield for both diastereomers. ^c *Syn/anti* ratio was determined by ¹H NMR. ^d ee of *syn* diastereomer, determined by chiral HPLC analysis.

^e Performed at 0 °C. ^f Performed at -10 °C. ^g With 5 mol% of catalyst **3a**.

^h A mixture of *n*-hexane/CH₂Cl₂ (2 : 1, v/v) was used. ⁱ Without PhCO₂H.

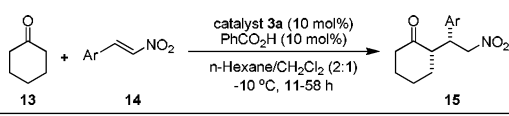
Having identified the optimal catalyst and conditions, we set out to explore the substrate scope with some representative aromatic nitroolefins as highlighted in Table 3. The parent system worked well. A variety of electron-withdrawing and electron-donating groups at the 4- or 2-positions of the aromatic ring of the nitroolefins were also well tolerated, leading to the formation of Michael adducts **15b–k** in high yields with excellent diastereo- (93/7–99/1 dr) and enantioselectivities (85–95% ee) (Table 3, entries 2–11). In the case of 4-methoxyl substituted nitroolefin **14l**, however, only 79% ee was obtained but still with high diastereoselectivity (92/8 dr, Table 3, entry 12). A fused aromatic nitroolefin, such as **14m**, was also successfully employed in this transformation and high yield, dr (98/2), and ee (91%) were obtained. Moreover, heteroaromatic nitroolefin **14n** was a viable substrate (Table 3, entry 14). Unfortunately, the alkyl substituted nitroolefin **14o** proved very sluggish, and no product was observed even after 3 days (Table 3, entry 15). Further structural modification of the catalyst to improve the catalytic activity for alkyl nitroolefins is currently underway in our laboratory.

To further investigate the scope of the new catalyst **3a** for Michael addition, the acyclic acetone **16** was also examined as the donor. The desired product **17** was obtained in 61% isolated yield but with only 7% ee (eqn (1)).



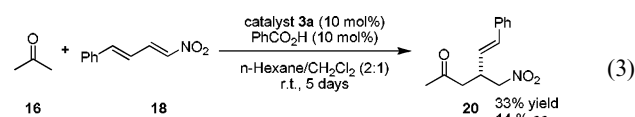
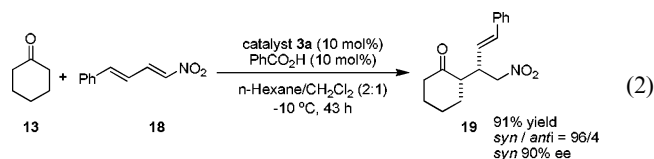
In sharp contrast to the wide utility of *trans*- β -nitrostyrenes in the conjugate addition, the nitrodienees have been less used as Michael acceptors and little progress has been made.²² Recently, Alexakis,^{22a,b} Wu,^{22d} and Ma^{22f} independently succeeded in devel-

Table 3 Asymmetric Michael addition reaction between **13** and **14** catalyzed by catalyst **3a**^a

					
Entry	Nitroolefin, Ar	t/h	Yield (%) ^b	dr ^c	ee (%) ^d
1	Ph (14a)	25	89	97/3	92
2	4-NO ₂ -Ph (14b)	41	90	98/2	94
3	4-F-Ph (14c)	45	89	98/2	93
4	4-Br-Ph (14d)	27	93	97/3	93
5	2-Br-Ph (14e)	15	85	99/1	93
6	4-Cl-Ph (14f)	30	95	97/3	93
7	2-Cl-Ph (14g)	11	94	97/3	93
8	2,4-Cl ₂ -Ph (14h)	22	89	99/1	95
9	4-Me-Ph (14i)	48	91	96/4	88
10	2-MeO-Ph (14j)	15	96	97/3	89
11 ^e	3,4-MeO ₂ -Ph (14k)	27	96	93/7	85
12	4-MeO-Ph (14l)	58	95	92/8	79
13	1-naphthyl (14m)	44	94	98/2	91
14	2-furyl (14n)	25	94	92/8	83
15	cyclohexyl (14o)	72	< 5	—	—

^a Unless otherwise noted, the reactions were carried out with 0.3 mmol of **14**, 3.0 mmol of cyclohexanone **13** in 0.6 mL of *n*-hexane/CH₂Cl₂ (2 : 1, v/v) in the presence of 10 mol% of catalyst **3a** and 10 mol% of PhCO₂H for the indicated time. ^b Isolated yield for both diastereomers. ^c *Syn/anti* ratio was determined by ¹H NMR. ^d ee of *syn* diastereomer, determined by chiral HPLC analysis. ^e Performed at room temperature.

oping highly enantioselective organocatalyzed Michael addition of aldehydes and ketones to nitrodienees. Whereas, the development of efficient organocatalysts for the Michael addition of ketones to nitrodienees is still challenging but desirable. Therefore, we preliminarily examined the feasibility of utilizing nitrodiene **18** as the Michael acceptor with **3a** as the catalyst (eqn (2)). Gratifyingly, the Michael addition proceeded smoothly under the above optimal conditions and afforded the corresponding product **19** in a yield of 91% with 96/4 dr and 90% ee. In addition, the use of acyclic acetone **16** was amenable to the reaction, although the yield and enantioselectivity needs further improvement (eqn (3)).



Based on the observed stereochemical outcomes, we proposed a possible transition state for this asymmetric Michael addition (Fig. 2). Mechanistically, the *in situ* formed enamine intermediate between cyclohexanone **13** and catalyst **3a** adopts the *E*-conformation. The sulfamide moiety provides H-bonding interactions with the nitro group, thereby directing the *Re* face of *trans*- β -nitrostyrene to be attacked by the *Re* face of the enamine to give the corresponding preferred *syn* Michael adduct **15a**.

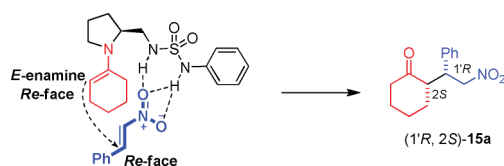


Fig. 2 Proposed transition state.

Conclusions

In conclusion, we have designed and synthesized a new class of chiral pyrrolidinyl-sulfamide derivatives starting from inexpensive proline and amines, which proved to be excellent catalysts for the Michael addition of cyclohexanone to nitroolefins. The reactions proceeded with high yields (85–96%), excellent diastereo- and enantioselectivities (up to 99/1 dr and 95% ee). The modular nature of the synthesis means that a wide range of other chiral amine-sulfamide bifunctional organocatalysts, tuned with regard to the hydrogen-bonding donors as well as the chiral environment, should be readily accessible. Further investigation of these catalysts in other enantioselective transformations and the development of related modified catalysts are ongoing in our laboratory.

Experimental section

General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Dichloromethane and 1,2-dichloroethane were freshly distilled from calcium hydride. Toluene, *n*-hexanes, ethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Reactions were monitored by thin layer chromatography (TLC), and column chromatography purifications were performed using 200–300 mesh silica gel and 200–300 mesh basic aluminum oxide. ^1H NMR spectra were recorded on 400 MHz or 600 MHz spectrophotometer. Solvent for NMR is CDCl_3 or DMSO-d^6 unless otherwise noted. Chemical shifts are reported in delta (δ) units in parts per million (ppm) relative to the singlet (0 ppm) for tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on 100 MHz or 150 MHz. Chemical shifts are reported in ppm relative to the central line of the heptet at 77.0 ppm for CDCl_3 or 39.5 ppm for DMSO-d^6 . The ee value determination was carried out using chiral high-performance liquid chromatography (HPLC) with Daicel Chiracel AD-H, OD-H and AS-H column and the dr values were determined by ^1H NMR. Organocatalysts **1–4** were prepared according to the modified literature procedure^{18–20} from proline-derived amine²¹ and commercially available amines.

Catalyst 1a. ^1H NMR (400 MHz, DMSO-d^6 , TMS): δ 1.26–1.35 (m, 1H), 1.53–1.65 (m, 2H), 1.68–1.76 (m, 1H), 2.67–2.78 (m, 4H), 2.31 (s, 1H), 3.04–3.11 (m, 1H), 4.02 (s, 2H), 7.25–7.34 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d^6): δ 24.7, 28.9, 45.7, 45.8, 47.2, 57.2, 127.0, 127.7, 128.2, 138.5; HRMS (EI): calcd for $\text{C}_{12}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$ (M+H)⁺ 270.1276, found 270.1258; $[\alpha]_{\text{D}}^{20.4} = +24.9$ ($c = 1.0$, CHCl_3).

Catalyst 1b. ^1H NMR (400 MHz, DMSO-d^6 , TMS): δ 1.30–1.39 (m, 1H), 1.57–1.69 (m, 2H), 1.72–1.81 (m, 1H), 2.74–2.85 (m, 4H), 3.11–3.18 (m, 1H), 4.02 (s, 2H), 7.35–7.41 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d^6): δ 24.5, 28.7, 45.0, 45.5, 46.5, 57.3, 128.1, 129.5, 131.5, 137.6; HRMS (EI): calcd for $\text{C}_{12}\text{H}_{18}\text{ClN}_3\text{O}_2\text{S}$ (M+H)⁺ 304.0887, found 304.0879; $[\alpha]_{\text{D}}^{20.5} = +18.5$ ($c = 1.0$, CH_3CN).

Catalyst 1c. ^1H NMR (400 MHz, DMSO-d^6 , TMS): δ 1.23–1.34 (m, 1H), 1.53–1.63 (m, 2H), 1.67–1.76 (m, 1H), 2.28 (s, 3H), 2.67–2.78 (m, 4H), 3.04–3.11 (m, 1H), 3.97 (s, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d^6): δ 20.7, 24.9, 28.9, 45.6, 45.7, 47.2, 57.2, 127.7, 128.7, 135.4, 136.0; HRMS (EI): calcd for $\text{C}_{13}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$ (M+H)⁺ 284.1433, found 284.1416; $[\alpha]_{\text{D}}^{20.7} = +22.4$ ($c = 1.0$, CHCl_3).

Catalyst 2. ^1H NMR (400 MHz, DMSO-d^6 , TMS): δ 1.10–1.19 (m, 1H), 1.44–1.57 (m, 2H), 1.60–1.68 (m, 1H), 2.54–2.65 (m, 2H), 2.76–2.82 (m, 1H), 2.97–3.01 (m, 1H), 3.04–3.11 (m, 1H), 4.58 (s, 2H), 4.96 (brs, 3H), 7.33–7.37 (m, 1H), 7.42–7.51 (m, 3H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 7.6$ Hz, 1H), 8.07 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d^6): δ 25.0, 28.6, 44.9, 45.6, 46.7, 57.7, 123.4, 125.2, 125.8, 126.3, 126.6, 128.5, 131.1, 132.4, 133.5; HRMS (EI): calcd for $\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$ (M+H)⁺ 320.1433, found 320.1422; $[\alpha]_{\text{D}}^{20.9} = +14.8$ ($c = 1.0$, CHCl_3).

Catalyst 3a. ^1H NMR (400 MHz, DMSO-d^6 , TMS): δ 1.19–1.27 (m, 1H), 1.51–1.66 (m, 3H), 2.67–2.81 (m, 4H), 3.02–3.08 (m, 1H), 6.17 (brs, 2H), 6.98 (t, $J = 7.2$ Hz, 1H), 7.15 (d, $J = 8.0$ Hz, 2H), 7.26 (t, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d^6): δ 24.7, 28.7, 45.5, 47.0, 56.9, 118.0, 122.2, 128.9, 139.1; HRMS (EI): calcd for $\text{C}_{11}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$ (M+H)⁺ 256.1120, found 256.1096; $[\alpha]_{\text{D}}^{20.7} = +41.5$ ($c = 1.0$, CH_3CN).

Catalyst 3b. ^1H NMR (400 MHz, DMSO-d^6 , TMS): δ 1.21–1.29 (m, 1H), 1.49–1.68 (m, 3H), 2.23 (s, 3H), 2.68–2.72 (m, 2H), 2.73–2.80 (m, 2H), 3.02–3.08 (m, 1H), 7.06 (t, $J = 9.6$ Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d^6): δ 20.3, 24.7, 28.7, 45.5, 46.9, 57.0, 118.5, 129.3, 131.3, 136.5; HRMS (EI): calcd for $\text{C}_{12}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$ (M+H)⁺ 270.1276, found 270.1253; $[\alpha]_{\text{D}}^{21.0} = +45.7$ ($c = 1.0$, CH_3CN).

Catalyst 3c. ^1H NMR (400 MHz, CDCl_3 , TMS): δ 1.28–1.36 (m, 1H), 1.61–1.83 (m, 3H), 2.24 (s, 6H), 2.81–2.85 (m, 2H), 2.96 (dd, $J = 8.0$, 13.6 Hz, 1H), 3.15 (dd, $J = 4.4$, 13.2 Hz, 1H), 3.24–3.31 (m, 1H), 5.69 (brs, 3H), 6.70 (s, 1H), 6.79 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 21.2, 25.3, 28.7, 45.9, 46.7, 57.8, 117.3, 125.4, 137.9, 138.8; HRMS (EI): calcd for $\text{C}_{13}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$ (M+H)⁺ 284.1433, found 284.1419; $[\alpha]_{\text{D}}^{20.8} = +40.3$ ($c = 1.0$, CH_3CN).

Catalyst 3d. ^1H NMR (400 MHz, DMSO-d^6 , TMS): δ 1.22–1.29 (m, 1H), 1.51–1.68 (m, 3H), 2.69–2.73 (m, 2H), 2.75–2.82 (m, 2H), 3.04–3.10 (m, 1H), 5.69 (brs, 3H), 7.15 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d^6): δ 24.7, 28.7, 45.5, 46.8, 57.0, 119.5, 125.8, 128.7, 138.5; HRMS (EI): calcd for $\text{C}_{11}\text{H}_{16}\text{ClN}_3\text{O}_2\text{S}$ (M+H)⁺ 290.0730, found 290.0731; $[\alpha]_{\text{D}}^{21.0} = +46.1$ ($c = 1.0$, CH_3CN).

Catalyst 4. ^1H NMR (400 MHz, DMSO-d^6 , TMS): δ 1.05–1.22 (m, 5H), 1.30–1.37 (m, 1H), 1.50–1.85 (m, 8H), 2.69–2.80 (m, 4H), 2.95 (s, 1H), 3.06–3.12 (m, 1H), 6.89 (brs, 1H), 2.95 (s, 1H), 3.06–3.12 (m, 1H), 6.89 (brs, 1H); ^{13}C NMR (100 MHz,

DMSO- d_6): δ 24.7, 24.8, 25.1, 28.9, 33.4, 33.5, 45.7, 47.3, 51.6, 57.2; HRMS (EI): calcd for $C_{11}H_{23}N_3O_2S(M+H)^+$ 262.1589, found 262.1576; $[\alpha]_D^{20.8} = +25.9$ ($c = 1.0$, $CHCl_3$).

Representative procedure for the asymmetric Michael reaction of nitroolefin **14a** with cyclohexanone **13** (Table 3, entry 1)

The organocatalyst **3a** (7.7 mg, 0.03 mmol), $PhCO_2H$ (3.7 mg, 0.03 mmol) and cyclohexanone **13** (0.32 mL, 3.0 mmol) were stirred in 0.6 mL of *n*-hexane/ CH_2Cl_2 (2 : 1, v/v) for 20 min at $-10^\circ C$. The *trans*- β -styrene **14a** (45.0 mg, 0.3 mmol) was then added and the reaction mixture was stirred for 25 h. After the complete consumption of **14a** (as monitored by TLC), the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate (4 : 1 to 2 : 1)) to give the corresponding pure Michael product **13a** (110.0 mg, 89%) as a white solid. Relative and absolute configurations of the products were determined by comparison of 1H NMR, ^{13}C NMR spectra and HPLC data with the known literature. Compounds **15a–o**, **17**, **19**, and **20** are known.^{12,19,22}

2-(2-Nitro-1-phenylethyl)cyclohexanone (15a), (Table 3, entry 1). 89% yield; the ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 75 : 25, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm, $20^\circ C$); t_R (minor) = 9.3 min; t_R (major) = 13.6 min. *syn/anti* = 97/3, *syn*: ee = 92%; 1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.17–1.27 (m, 1H), 1.50–1.79 (m, 4H), 2.03–2.11 (m, 1H), 2.34–2.41 (m, 1H), 2.44–2.49 (m, 1H), 2.65–2.71 (m, 1H), 3.71–3.79 (m, 1H), 4.62 (dd, $J = 10.0$, 12.8 Hz, 1H), 4.94 (dd, $J = 4.4$, 12.4 Hz, 1H), 7.15–7.17 (m, 2H), 7.23–7.27 (m, 1H), 7.29–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 28.4, 33.1, 42.6, 43.8, 52.3, 78.8, 127.6, 128.0, 128.8, 137.6, 211.9.

2-(2-Nitro-1-(4-nitrophenyl)ethyl)cyclohexanone (15b), (Table 3, entry 2). 90% yield; the ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 75 : 25, flow rate 1.0 mL min $^{-1}$, $\lambda = 254$ nm, $20^\circ C$); t_R (minor) = 13.0 min; t_R (major) = 28.4 min, *syn/anti* = 98/2, *syn*: ee = 94%; 1H NMR (600 MHz, $CDCl_3$, TMS): δ 1.24–1.30 (m, 1H), 1.57–1.71 (m, 4H), 1.81–1.84 (m, 1H), 2.11–2.13 (m, 1H), 2.36–2.42 (m, 1H), 2.48–2.50 (m, 1H), 2.70–2.75 (m, 1H), 3.91–3.95 (m, 1H), 4.70 (dd, $J = 10.8$, 12.6 Hz, 1H), 5.00 (dd, $J = 4.2$, 13.2 Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 2H), 8.20 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 28.1, 33.0, 42.5, 43.6, 52.0, 77.9, 123.9, 129.2, 145.5, 147.2, 210.8.

2-(1-(4-Fluorophenyl)-2-nitroethyl)cyclohexanone (15c), (Table 3, entry 3). 89% yield; the ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 95 : 5, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm, $20^\circ C$); t_R (minor) = 19.1 min; t_R (major) = 21.2 min, *syn/anti* = 98/2, *syn*: ee = 93%; 1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.16–1.26 (m, 1H), 1.54–1.86 (m, 4H), 2.05–2.11 (m, 1H), 2.31–2.47 (m, 2H), 2.62–2.69 (m, 1H), 3.74–3.80 (m, 1H), 4.58 (dd, $J = 10.0$, 12.8 Hz, 1H), 4.95 (dd, $J = 4.8$, 12.4 Hz, 1H), 7.01 (t, $J = 8.8$ Hz, 2H), 7.14–7.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 28.3, 33.0, 42.6, 43.1, 52.3, 78.7, 115.6, 115.8, 129.6, 129.7, 133.3, 133.4, 160.7, 163.1, 211.6.

2-(1-(4-Bromophenyl)-2-nitroethyl)cyclohexanone (15d), (Table 3, entry 4). 93% yield; the ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 90 : 10, flow rate 1.0 mL min $^{-1}$,

$\lambda = 210$ nm, $20^\circ C$); t_R (minor) = 13.5 min; t_R (major) = 22.0 min, *syn/anti* = 97/3, *syn*: ee = 93%; 1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.16–1.26 (m, 1H), 1.53–1.79 (m, 4H), 2.05–2.11 (m, 1H), 2.32–2.47 (m, 2H), 2.61–2.68 (m, 1H), 3.72–3.78 (m, 1H), 4.59 (dd, $J = 10.4$, 12.4 Hz, 1H), 4.94 (dd, $J = 4.4$, 12.8 Hz, 1H), 7.06 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 28.3, 33.0, 42.6, 43.2, 52.1, 78.4, 121.5, 129.8, 131.9, 136.7, 211.4.

2-(1-(2-Bromophenyl)-2-nitroethyl)cyclohexanone (15e), (Table 3, entry 5). 85% yield; the ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 85 : 15, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm, $20^\circ C$); t_R (minor) = 8.9 min; t_R (major) = 14.5 min, *syn/anti* = 99/1, *syn*: ee = 93%; 1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.33–1.41 (m, 1H), 1.53–1.83 (m, 4H), 2.06–2.12 (m, 1H), 2.31–2.48 (m, 2H), 2.88 (s, 1H), 4.32 (d, $J = 8.0$ Hz, 1H), 4.89 (d, $J = 5.6$ Hz, 2H), 7.10–7.14 (m, 1H), 7.21–7.23 (m, 1H), 7.27–7.31 (m, 1H), 7.57 (dd, $J = 1.2$, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 28.4, 32.8, 42.7, 52.0, 77.3, 125.2, 127.9, 128.9, 133.5, 137.1, 211.5.

2-(1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (15f), (Table 3, entry 6). 95% yield; the ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 90 : 10, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm, $20^\circ C$); t_R (minor) = 12.6 min; t_R (major) = 19.1 min, *syn/anti* = 97/3, *syn*: ee = 93%; 1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.16–1.26 (m, 1H), 1.49–1.79 (m, 4H), 2.05–2.10 (m, 1H), 2.31–2.47 (m, 2H), 2.61–2.68 (m, 1H), 3.73–3.79 (m, 1H), 4.57 (dd, $J = 10.4$, 12.4 Hz, 1H), 4.95 (dd, $J = 4.4$, 12.8 Hz, 1H), 7.12 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 28.3, 33.0, 42.6, 43.2, 52.1, 78.4, 128.9, 129.4, 133.3, 136.1, 211.5.

2-(1-(2-Chlorophenyl)-2-nitroethyl)cyclohexanone (15g), (Table 3, entry 7). 94% yield; the ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 95 : 5, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm, $20^\circ C$); t_R (minor) = 14.2 min; t_R (major) = 26.0 min, *syn/anti* = 97/3, *syn*: ee = 93%; 1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.28–1.37 (m, 1H), 1.57–1.87 (m, 4H), 2.06–2.11 (m, 1H), 2.31–2.48 (m, 2H), 2.86–2.92 (m, 1H), 4.28–4.34 (m, 1H), 4.84–4.94 (m, 2H), 7.18–7.24 (m, 3H), 7.37 (dd, $J = 0.8$, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 28.4, 32.8, 40.7, 42.6, 51.5, 77.1, 127.2, 128.7, 129.2, 130.1, 134.3, 135.3, 211.6.

2-(1-(2,4-Dichlorophenyl)-2-nitroethyl)cyclohexanone (15h), (Table 3, entry 8). 89% yield; the ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 90 : 10, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm, $20^\circ C$); t_R (minor) = 9.9 min; t_R (major) = 14.5 min, *syn/anti* = 99/1, *syn*: ee = 95%; 1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.29–1.38 (m, 1H), 1.57–1.83 (m, 4H), 2.08–2.13 (m, 1H), 2.32–2.48 (m, 2H), 2.82–2.89 (m, 1H), 4.23–4.29 (m, 1H), 4.82–4.93 (m, 2H), 7.18–7.25 (m, 2H), 7.40 (t, $J = 1.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 28.5, 33.0, 40.5, 42.8, 51.6, 77.4, 127.7, 130.1, 134.0, 134.2, 135.3, 211.4.

2-(2-Nitro-1-*p*-tolylethyl)cyclohexanone (15i), (Table 3, entry 9). 91% yield; the ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 90 : 10, flow rate 0.8 mL min $^{-1}$; $\lambda = 210$ nm, $20^\circ C$). t_R (minor) = 15.4 min; t_R (major) = 27.0 min, *syn/anti* = 96/4, *syn*: ee = 88%; 1H NMR (600 MHz, $CDCl_3$, TMS): δ 1.19–1.26 (m, 1H), 1.53–1.59 (m, 1H), 1.64–1.79 (m, 3H), 2.05–2.09 (m, 1H),

2.31 (s, 3H), 2.35–2.40 (m, 1H), 2.45–2.48 (m, 1H), 2.64–2.68 (m, 1H), 3.69–3.73 (m, 1H), 4.60 (dd, $J = 10.2, 12.0$ Hz, 1H), 4.92 (dd, $J = 4.8, 12.6$ Hz, 1H), 7.04 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.9, 24.8, 28.4, 33.1, 42.6, 43.4, 52.3, 78.9, 127.8, 129.4, 134.4, 137.2, 212.0.

2-(1-(2-Methoxyphenyl)-2-nitroethyl)cyclohexanone (15j), (Table 3, entry 10). 96% yield; the ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm, 20 °C); t_R (minor) = 15.6 min; t_R (major) = 18.1 min, *syn/anti* = 97/3, *syn*: ee = 89%; ^1H NMR (400 MHz, CDCl_3 , TMS): δ 1.14–1.24 (m, 1H), 1.54–1.68 (m, 3H), 1.71–1.77 (m, 1H), 2.04–2.08 (m, 1H), 2.34–2.47 (m, 2H), 2.94–3.01 (m, 1H), 3.83 (s, 3H), 3.92–3.98 (m, 1H), 4.79–4.87 (m, 2H), 6.87 (t, $J = 7.6$ Hz, 2H), 7.08 (t, $J = 6.0$ Hz, 1H), 7.21–7.27 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 25.0, 28.4, 33.1, 41.2, 42.6, 50.3, 55.2, 77.3, 110.8, 120.7, 125.1, 128.7, 130.8, 157.4, 212.5.

2-(1-(3,4-dimethoxyphenyl)-2-nitroethyl)cyclohexanone (15k), (Table 3, entry 11). 96% yield; the ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm, 20 °C); t_R (minor) = 13.7 min; t_R (major) = 27.1 min, *syn/anti* = 93/7, *syn*: ee = 85%; ^1H NMR (400 MHz, CDCl_3 , TMS): δ 1.19–1.29 (m, 1H), 1.55–1.80 (m, 4H), 2.04–2.09 (m, 1H), 2.31–2.47 (m, 2H), 2.62–2.68 (m, 1H), 3.67–3.73 (m, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 4.60 (dd, $J = 10.4, 12.4$ Hz, 1H), 4.92 (dd, $J = 4.4, 12.4$ Hz, 1H), 6.68–6.72 (m, 2H), 6.81 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 24.8, 28.3, 32.9, 42.5, 43.4, 52.4, 55.6, 55.7, 78.8, 111.1, 111.2, 119.9, 129.9, 148.1, 148.8, 211.9.

2-(1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (15l), (Table 3, entry 12). 95% yield; the ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 75:25, flow rate 0.7 mL min $^{-1}$, $\lambda = 210$ nm, 20 °C); t_R (minor) = 11.3 min; t_R (major) = 13.6 min, *syn/anti* = 92/8, *syn*: ee = 79%; ^1H NMR (400 MHz, CDCl_3 , TMS): δ 1.16–1.28 (m, 1H), 1.50–1.78 (m, 4H), 2.03–2.09 (m, 1H), 2.33–2.47 (m, 2H), 2.61–2.67 (m, 1H), 3.68–3.74 (m, 1H), 3.76 (s, 3H), 4.56 (dd, $J = 10.4, 12.0$ Hz, 1H), 4.92 (dd, $J = 4.8, 12.4$ Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 2H), 7.08 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 24.8, 28.4, 33.0, 42.6, 43.0, 52.4, 55.0, 78.9, 114.1, 129.0, 129.3, 158.8, 212.0.

2-(1-(Naphthalen-1-yl)-2-nitroethyl)cyclohexanone (15m), (Table 3, entry 13). 94% yield; the ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 50:50, flow rate 0.7 mL min $^{-1}$, $\lambda = 254$ nm, 20 °C); t_R (minor) = 11.7 min; t_R (major) = 16.8 min, *syn/anti* = 98/2, *syn*: ee = 91%; ^1H NMR (400 MHz, CDCl_3 , TMS): δ 1.14–1.24 (m, 1H), 1.38–1.47 (m, 1H), 1.54–1.62 (m, 3H), 1.98–2.03 (m, 1H), 2.30–2.33 (m, 1H), 2.43–2.46 (m, 1H), 2.80 (s, 1H), 4.77 (s, 1H), 4.86 (t, $J = 12.0$ Hz, 1H), 5.06 (dd, $J = 3.6, 12.8$ Hz, 1H), 7.34–7.48 (m, 4H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 8.17 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 25.0, 28.5, 33.1, 36.5, 42.7, 53.6, 78.5, 122.6, 123.4, 125.2, 125.7, 126.4, 127.9, 128.8, 132.3, 133.7, 134.5, 212.2.

2-(1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (15n), (Table 3, entry 14). 94% yield; the ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL min $^{-1}$, $\lambda =$

210 nm, 20 °C); t_R (major) = 10.9 min; t_R (minor) = 13.1 min, *syn/anti* = 92/8, *syn*: ee = 83%; ^1H NMR (400 MHz, CDCl_3 , TMS): δ 1.15–1.25 (m, 1H), 1.50–1.59 (m, 2H), 1.64–1.77 (m, 2H), 1.98–2.05 (m, 1H), 2.25–2.38 (m, 2H), 2.64–2.71 (m, 1H), 3.86–3.92 (m, 1H), 4.58 (dd, $J = 9.6, 12.4$ Hz, 1H), 4.71 (dd, $J = 4.4, 12.8$ Hz, 1H), 6.10 (d, $J = 3.2$ Hz, 1H), 6.20 (dd, $J = 1.6, 3.2$ Hz, 1H), 7.27 (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 24.9, 28.0, 32.3, 37.3, 42.4, 50.9, 76.5, 108.7, 110.1, 142.1, 150.8, 210.8.

5-Nitro-4-phenylpentan-2-one (17), (eqn (1)). 61% yield; the ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 75:25, flow rate 1.0 mL min $^{-1}$, $\lambda = 256$ nm, 20 °C). t_R (minor) = 15.2 min; t_R (major) = 20.2 min, ee = 7%. ^1H NMR (400 MHz, CDCl_3 , TMS): δ 2.12 (s, 3H), 2.91 (d, $J = 4.0$ Hz, 2H), 3.97–4.04 (m, 1H), 4.59 (dd, $J = 8.0, 12.0$ Hz, 1H), 4.69 (dd, $J = 8.0, 12.0$ Hz, 1H), 7.21–7.23 (m, 2H), 7.28–7.35 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 30.3, 38.9, 46.0, 79.3, 127.3, 127.8, 128.9, 138.7, 205.4.

(E)-2-(1-Nitro-4-phenylbut-3-en-2-yl)cyclohexanone (19), (eqn (2)). 91% yield; the ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 85:15, flow rate 1.0 mL min $^{-1}$, $\lambda = 254$ nm, 20 °C). t_R (minor) = 11.5 min; t_R (major) = 18.9 min, *syn/anti* = 96/4, *syn*: ee = 90%. ^1H NMR (400 MHz, CDCl_3 , TMS): δ 1.37–1.47 (m, 1H), 1.59–1.71 (m, 2H), 1.83–1.89 (m, 1H), 2.03–2.17 (m, 2H), 2.29–2.45 (m, 2H), 2.48–2.55 (m, 1H), 3.30–3.38 (m, 1H), 4.53 (dd, $J = 8.8, 12.0$ Hz, 1H), 4.66 (dd, $J = 4.8, 12.0$ Hz, 1H), 6.00 (dd, $J = 9.6, 15.6$ Hz, 1H), 6.47 (d, $J = 15.6$ Hz, 1H), 7.20–7.24 (m, 1H), 7.25–7.34 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 24.9, 27.9, 32.4, 41.7, 42.5, 51.4, 77.9, 125.5, 126.3, 127.7, 128.4, 134.2, 136.1, 211.1.

4-Nitromethyl-6-phenylhex-5-en-2-one (20), (eqn (3)). 33% yield; the ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 80:20, 254 nm, 20 °C). t_R (minor) = 20.6 min; t_R (major) = 22.5 min, ee = 14%. ^1H NMR (400 MHz, CDCl_3 , TMS): δ 2.18 (s, 3H), 2.74 (d, $J = 4.0$ Hz, 2H), 3.48–3.57 (m, 1H), 4.51 (dd, $J = 8.0, 12.0$ Hz, 1H), 4.59 (dd, $J = 8.0, 12.0$ Hz, 1H), 6.07 (q, $J = 8.0$ Hz, 1H), 6.53 (d, $J = 16.0$ Hz, 1H), 7.23–7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 30.4, 36.9, 44.8, 78.5, 126.1, 126.3, 127.9, 128.5, 133.3, 136.0, 205.6.

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