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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 reactions[9] 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,[11b,c] 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-dehydroabietic 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 we[16] 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 provided 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 CH_2Cl_2 with Et_3N 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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† Electronic supplementary information (ESI) available: Experimental details, characterization of all catalysts, NMR spectra, and HPLC spectra of Michael addition products. See DOI: 10.1039/c1ob05442b

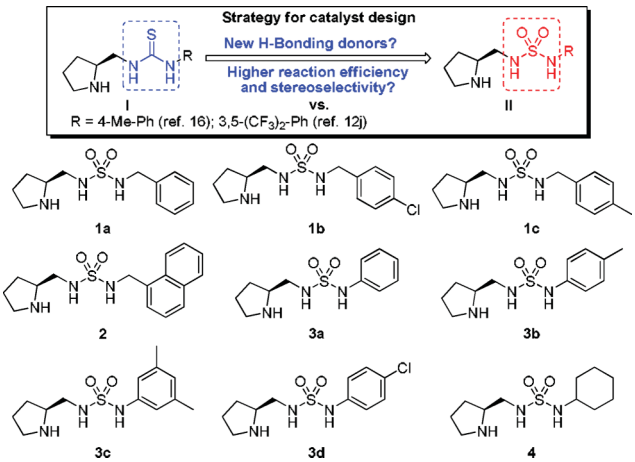
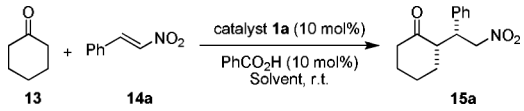


Fig. 1 A new class of pyrrolidinyl-sulfamide catalysts.

sulfamide **9**. Removing the Boc protecting group from nitrogen with TFA/CH_2Cl_2 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 $PhCO_2H$ 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, $CHCl_3$, CH_2Cl_2, DCE, Et_2O, and DMF, and consistently excellent yields and high stereoselectivities were obtained. The use of CH_3CN, 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]

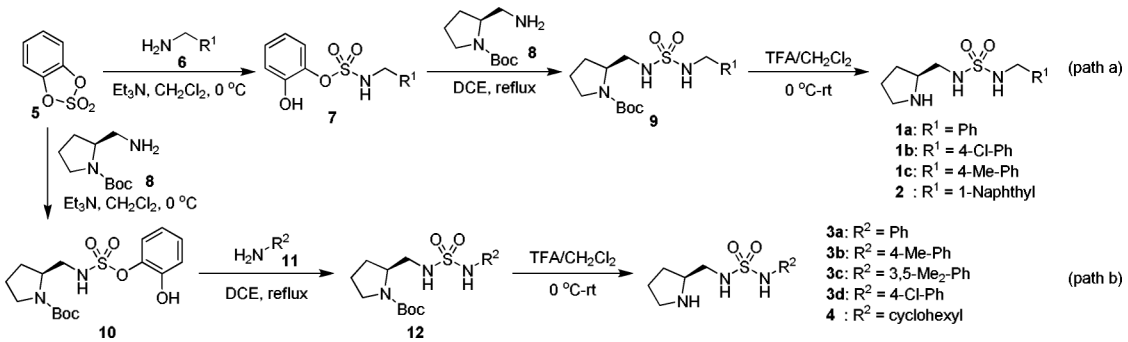


Entry	Solvent	*t*/h	Yield (%)[b]	dr[c]	ee (%)[d]
1	*n*-Hexane	6	94	92/8	84
2	Toluene	22	90	92/8	84
3	$CHCl_3$	22	91	93/7	86
4	CH_2Cl_2	22	92	93/7	85
5	DCE	22	92	92/8	83
6	Et_2O	22	90	94/6	85
7	DMF	22	85	95/5	86
8	CH_3CN	46	33	91/9	80
9	Dioxane	46	31	93/7	80
10	THF	46	43	95/5	82
11	MeOH	22	< 5	—	—
12	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% $PhCO_2H$ in the solvent (0.6 mL) indicated. DCE = 1,2-dichloroethane. [b] Isolated yield for both diastereomers. [c] *Syn*/*anti* ratio was determined by ^{1}H NMR. [d] ee of *syn* diastereomer, determined by chiral HPLC analysis.

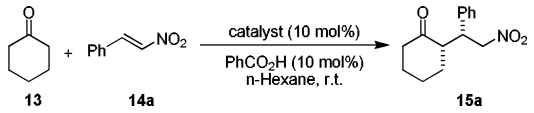
solvents, such as MeOH and EtOH (Table 1, entries 11 and 12). Thus, in terms of the reaction efficiency and stereoselectivity, we chose *n*-hexane as the reaction medium for further optimizations.

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 CH_2Cl_2 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 $PhCO_2H$ (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]

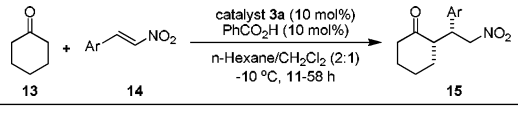


13 14a 15a

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 $PhCO_2H$. [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/CH_2Cl_2 (2 : 1, v/v) was used. [i] Without $PhCO_2H$.

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



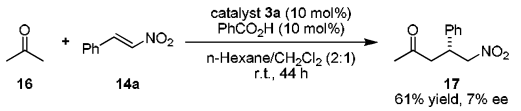
13 14 15

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/CH_2Cl_2 (2 : 1, v/v) in the presence of 10 mol% of catalyst **3a** and 10 mol% of $PhCO_2H$ 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.

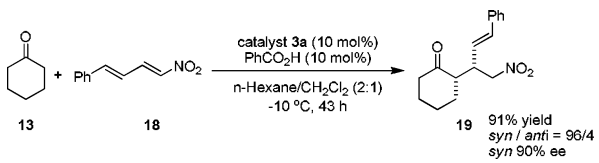
Having identified the optimal catalyst and conditions, we set out to explore the substrate scope with some representative aromatic nitroolefins as highlighted in Table 3. The parent system worked well. A variety of electron-withdrawing and electron-donating groups at the 4- or 2-positions of the aromatic 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 acylic 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)).

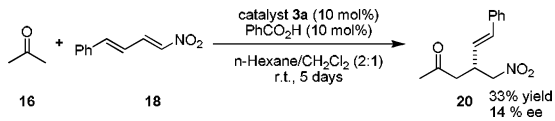


16 14a 17
61% yield, 7% ee (1)

In sharp contrast to the wide utility of *trans*-β-nitrostyrenes in the conjugate addition, the nitrodienes 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 developing highly enantioselective organocatalyzed Michael addition of aldehydes and ketones to nitrodienes. Whereas, the development of efficient organocatalysts for the Michael addition of ketones to nitrodienes 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 acylic acetone **16** was amenable to the reaction, although the yield and enantioselectivity needs further improvement (eqn (3)).



13 18 19 91% yield
syn / *anti* = 96/4
syn 90% ee (2)



16 18 20 33% yield
14 % ee (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**.

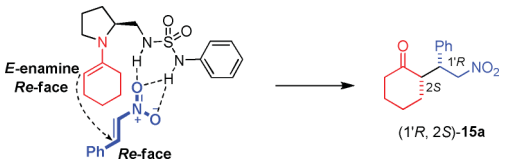


Fig. 2 Proposed transition state.

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. ^{1}H 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 ^{1}H NMR. Organocatalysts **1–4** were prepared according to the modified literature procedure[18–20] from proline-derived amine[21] and commercially available amines.

Catalyst 1a. ^{1}H 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 $C_{12}H_{19}N_3O_2S$ (M+H)$^+$ 270.1276, found 270.1258; $[\alpha]_D^{19.4}$ = +24.9 (c = 1.0, $CHCl_3$).

Catalyst 1b. ^{1}H 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 $C_{12}H_{18}ClN_3O_2S$ (M+H)$^+$ 304.0887, found 304.0879; $[\alpha]_D^{20.5}$ = +18.5 (c = 1.0, CH_3CN).

Catalyst 1c. ^{1}H 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 $C_{13}H_{21}N_3O_2S$ (M+H)$^+$ 284.1433, found 284.1416; $[\alpha]_D^{20.7}$ = +22.4 (c = 1.0, $CHCl_3$).

Catalyst 2. ^{1}H 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 $C_{16}H_{21}N_3O_2S$ (M+H)$^+$ 320.1433, found 320.1422; $[\alpha]_D^{20.9}$ = +14.8 (c = 1.0, $CHCl_3$).

Catalyst 3a. ^{1}H 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 $C_{11}H_{17}N_3O_2S$ (M+H)$^+$ 256.1120, found 256.1096; $[\alpha]_D^{20.7}$ = +41.5 (c = 1.0, CH_3CN).

Catalyst 3b. ^{1}H 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 $C_{12}H_{19}N_3O_2S$ (M+H)$^+$ 270.1276, found 270.1253; $[\alpha]_D^{21.0}$ = +45.7 (c = 1.0, CH_3CN).

Catalyst 3c. ^{1}H 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 $C_{13}H_{21}N_3O_2S$ (M+H)$^+$ 284.1433, found 284.1419; $[\alpha]_D^{20.8}$ = +40.3 (c = 1.0, CH_3CN).

Catalyst 3d. ^{1}H 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 $C_{11}H_{16}ClN_3O_2S$ (M+H)$^+$ 290.0730, found 290.0731; $[\alpha]_D^{21.0}$ = +46.1 (c = 1.0, CH_3CN).

Catalyst 4. ^{1}H 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 °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 ^{1}H 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}, λ = 210 nm, 20 °C); t_R (minor) = 9.3 min; t_R (major) = 13.6 min. *syn*/*anti* = 97/3, *syn*: ee = 92%; ^{1}H 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}, λ = 254 nm, 20 °C); t_R (minor) = 13.0 min; t_R (major) = 28.4 min, *syn*/*anti* = 98/2, *syn*: ee = 94%; ^{1}H 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}, λ = 210 nm, 20 °C); t_R (minor) = 19.1 min; t_R (major) = 21.2 min, *syn*/*anti* = 98/2, *syn*: ee = 93%; ^{1}H 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}, λ = 210 nm, 20 °C); t_R (minor) = 13.5 min; t_R (major) = 22.0 min, *syn*/*anti* = 97/3, *syn*: ee = 93%; ^{1}H 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}, λ = 210 nm, 20 °C); t_R (minor) = 8.9 min; t_R (major) = 14.5 min, *syn*/*anti* = 99/1, *syn*: ee = 93%; ^{1}H 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}, λ = 210 nm, 20 °C); t_R (minor) = 12.6 min; t_R (major) = 19.1 min, *syn*/*anti* = 97/3, *syn*: ee = 93%; ^{1}H 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}, λ = 210 nm, 20 °C); t_R (minor) = 14.2 min; t_R (major) = 26.0 min, *syn*/*anti* = 97/3, *syn*: ee = 93%; ^{1}H 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}, λ = 210 nm, 20 °C); t_R (minor) = 9.9 min; t_R (major) = 14.5 min, *syn*/*anti* = 99/1, *syn*: ee = 95%; ^{1}H 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}; λ = 210 nm, 20 °C). t_R (minor) = 15.4 min; t_R (major) = 27.0 min, *syn*/*anti* = 96/4, *syn*: ee = 88%; ^{1}H 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}, λ = 210 nm, 20 °C); t_R (minor) = 15.6 min; t_R (major) = 18.1 min, *syn*/*anti* = 97/3, *syn*: ee = 89%; ^{1}H 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}, λ = 210 nm, 20 °C); t_R (minor) = 13.7 min; t_R (major) = 27.1 min, *syn*/*anti* = 93/7, *syn*: ee = 85%; ^{1}H 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}, λ = 210 nm, 20 °C); t_R (minor) = 11.3 min; t_R (major) = 13.6 min, *syn*/*anti* = 92/8, *syn*: ee = 79%; ^{1}H 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}, λ = 254 nm, 20 °C); t_R (minor) = 11.7 min; t_R (major) = 16.8 min, *syn*/*anti* = 98/2, *syn*: ee = 91%; ^{1}H 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}, λ = 210 nm, 20 °C); t_R (major) = 10.9 min; t_R (minor) = 13.1 min, *syn*/*anti* = 92/8, *syn*: ee = 83%; ^{1}H 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}, λ = 256 nm, 20 °C). t_R (minor) = 15.2 min; t_R (major) = 20.2 min, ee = 7%. ^{1}H 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}, λ = 254 nm, 20 °C). t_R (minor) = 11.5 min; t_R (major) = 18.9 min, *syn*/*anti* = 96/4, *syn*: ee = 90%. ^{1}H 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 (Chirapak 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%. ^{1}H 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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Notes and references

1 For selected reviews on organocatalysis, see: (*a*) A. Berkessel and H. Gröger, Ed., *Asymmetric Organocatalysis; From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, Germany, 2005; (*b*) P. I. Dalko, Ed., *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, Germany, 2007; (*c*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*d*) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719; (*e*) B. List and J. W. Yang, *Science*, 2006, **313**, 1584; (*f*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*g*) M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, *Drug Discovery Today*, 2007, **12**, 8; (*h*) H. Pellissier, *Tetrahedron*, 2007, **63**, 9267; (*i*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304; (*j*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*,

2008, **47**, 4638; (*k*) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178; (*l*) M. Bella and T. Gasperi, *Synthesis*, 2009, 1583; (*m*) D. Enders, C. Wang and J. X. Liebich, *Chem.–Eur. J.*, 2009, **15**, 11058; (*n*) Y. Sohtome and K. Nagasawa, *Synlett*, 2010, 1; (*o*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (*p*) B. List, Ed., *Asymmetric Organocatalysis (Topics in Current Chemistry Volume 291)*, Springer-Verlag Berlin Heidelberg, 2010; (*q*) H. Pellissier, *Recent Developments in Asymmetric Organocatalysis*, Royal Society of Chemistry, 2010.

2 For special issues on asymmetric organocatalysis, see: (*a*) K. N. Houk and B. List (guest editors), *Acc. Chem. Res.*, 2004, **37**(issue 8); (*b*) B. List and C. Bolm (guest editors), *Adv. Synth. Catal.*, 2004, **346**(issues 9–10); (*c*) B. List (guest editor), *Chem. Rev.*, 2007, **107**(issue 12); (*d*) E. N. Jacobsen and D. W. C. MacMillan (guest editors), *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20618.

3 A. Thayer, *Chem. Eng. News*, 2005, **83**, 40.

4 For selected reviews on asymmetric aminocatalysis, see: (*a*) B. List, *Chem. Commun.*, 2006, 819; (*b*) C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2008, **47**, 42; (*c*) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138; (*d*) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178; (*e*) P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 1360; (*f*) H. Yang and R. G. Carter, *Synlett*, 2010, 2827.

5 For reviews on chiral amines as enamine catalysts, see: (*a*) B. List, *Acc. Chem. Res.*, 2004, **37**, 548; (*b*) W. Notz, F. Tanaka and C. F. Barbas III, *Acc. Chem. Res.*, 2004, **37**, 580; (*c*) G. Guillena and D. J. Ramón, *Tetrahedron: Asymmetry*, 2006, **17**, 1465; (*d*) M. Marigo and K. A. Jørgensen, *Chem. Commun.*, 2006, 2001; (*e*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471, and references therein.

6 For excellent reviews on iminium catalysis, see: (*a*) G. Lelais and D. W. C. MacMillan, *Aldrichimica Acta*, 2006, **39**, 79; (*b*) A. Erkkilä, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416.

7 For a review on enamine-SOMO catalysis, see: (*a*) S. Bertelsen, M. Nielsen and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 7356; For selected examples, see: (*b*) T. D. Beeson, A. Mastracchio, J. Hong, K. Ashton and D. W. C. MacMillan, *Science*, 2007, **316**, 582; (*c*) H. Jang, J. Hong and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2007, **129**, 7004; (*d*) M. P. Sibi and M. Hasegawa, *J. Am. Chem. Soc.*, 2007, **129**, 4124; (*e*) D. Nicewicz and D. W. C. MacMillan, *Science*, 2008, **322**, 77; (*f*) H. Kim and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2008, **130**, 398.

8 For recent examples on dienamine catalysis, see: (*a*) B. Hong, M. Wu, H. Tseng and J. Liao, *Org. Lett.*, 2006, **8**, 2217; (*b*) S. Bertelsen, M. Marigo, S. Brandes, P. Dinir and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2006, **128**, 12973; (*c*) R. M. de Figueiredo, R. Fröhlich and M. Christmann, *Angew. Chem., Int. Ed.*, 2008, **47**, 1450; (*d*) B.-C. Hong, M.-F. Wu, H. C. Tseng, G.-F. Huang, C.-F. Su and J.-H. Liao, *J. Org. Chem.*, 2007, **72**, 8459; (*e*) E. Marqués-López, R. P. Herrera, T. Marks, W. C. Jacobs, D. Könning, R. M. de Figueiredo and M. Christmann, *Org. Lett.*, 2009, **11**, 4116; (*f*) B. Han, Z.-Q. He, J.-L. Li, R. Li, K. Jiang, T.-Y. Liu and Y.-C. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, 5474; (*g*) B. Han, Y.-C. Xiao, Z.-Q. He and Y.-C. Chen, *Org. Lett.*, 2009, **11**, 4660.

9 For recent reviews on asymmetric 1,4-conjugate addition reactions, see: (*a*) O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, 1877; (*b*) S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, 1701; (*c*) J. L. Vicario, D. Badía and L. Carillo, *Synthesis*, 2007, 2065; (*d*) D. Almasi, D. A. Alonso and C. Nájera, *Tetrahedron: Asymmetry*, 2007, **18**, 299; (*e*) S. Sulzer-Mosse and A. Alexakis, *Chem. Commun.*, 2007, 3123; (*f*) D. Enders, C. Wang and J. X. Liebich, *Chem.–Eur. J.*, 2009, **15**, 11058; (*g*) D. Roca-Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero and P. Merino, *Tetrahedron: Asymmetry*, 2010, **21**, 2561.

10 (*a*) G. Calderari and D. Seebach, *Helv. Chim. Acta*, 1995, **58**, 1592; (*b*) M. P. Sibi and S. Manyem, *Tetrahedron*, 2000, **56**, 8033; (*c*) N. Ono, *The Nitro Group in Organic Synthesis*Wiley-VCH, New York, 2001; (*d*) J. Christoffers and A. Baro, *Angew. Chem., Int. Ed.*, 2003, **42**, 1688; (*e*) C. Czekelius and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2005, **44**, 612.

11 For proline-catalyzed Michael addition reactions, see: (*a*) B. List, P. Pojarliev and H. J. Martin, *Org. Lett.*, 2001, **3**, 2423; (*b*) J. M. Betancort, K. Sakthivel, R. Thayumanavan and C. F. Barbas III, *Tetrahedron Lett.*, 2001, **42**, 4441; (*c*) J. M. Betancort and C. F. Barbas III, *Org. Lett.*, 2001, **3**, 3737; (*d*) S. Hanessian and V. Pham, *Org. Lett.*, 2000, **2**, 2975; (*e*) D. Enders and A. Seki, *Synlett*, 2002, 26; (*f*) Y.-G. Chi and S. H. Gellman, *Org. Lett.*, 2005, **7**, 4253; (*g*) S. Mossé and A. Alexakis, *Org. Lett.*, 2005, **7**, 4361; (*h*) C. E. T. Mitchell, A. J. A. Cobb and S. V. Ley, *Synlett*, 2005, 611; (*i*) L. Planas, J. Perand-Viret and J. Royer, *Tetrahedron: Asymmetry*, 2004, **15**, 2399.

12 For representative examples of proline-derived organocatalysts, see: (*a*) A. Alexakis and O. Andrey, *Org. Lett.*, 2002, **4**, 3611; (*b*) N. Mase, R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Org. Lett.*, 2004, **6**, 2527; (*c*) T. Ishii, S. Fujioka, Y. Sekiguchi and H. Kotsuki, *J. Am. Chem. Soc.*, 2004, **126**, 9558; (*d*) J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Synthesis*, 2004, 1509; (*e*) O. Andrey, A. Alexakis, A. Tomassini and G. Bernardinelli, *Adv. Synth. Catal.*, 2004, **346**, 1147; (*f*) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw and S. V. Ley, *Chem. Commun.*, 2004, 1808; (*g*) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold and S. V. Ley, *Org. Biomol. Chem.*, 2005, **3**, 84; (*h*) W. Wang, J. Wang and H. Li, *Angew. Chem., Int. Ed.*, 2005, **44**, 1369; (*i*) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2006, **128**, 4966; (*j*) C.-L. Cao, M.-C. Ye, X.-L. Sun and Y. Tang, *Org. Lett.*, 2006, **8**, 2901; (*k*) E. Reyes, J. L. Vicario, D. Badia and L. Carrillo, *Org. Lett.*, 2006, **8**, 6135; (*l*) J. Wang, H. Li, B. Lou, L. Zu, H. Guo and W. Wang, *Chem.–Eur. J.*, 2006, **12**, 4321; (*m*) S. V. Pansare and K. Pandya, *J. Am. Chem. Soc.*, 2006, **128**, 9624; (*n*) Vishnumaya and V. K. Singh, *Org. Lett.*, 2007, **9**, 1117; (*o*) B. Ni, Q. Zhang and A. D. Headley, *Tetrahedron: Asymmetry*, 2007, **18**, 1443; (*p*) D.-Q. Xu, L.-P. Wang, S.-P. Luo, Y.-F. Wang, S. Zhang and Z.-Y. Xu, *Eur. J. Org. Chem.*, 2008, 1049; (*q*) B.-K. Ni, Q.-Y. Zhang, K. Dhungana and A. D. Headley, *Org. Lett.*, 2009, **11**, 1037; (*r*) C. Chang, S.-H. Li, R. J. Reddy and K. Chen, *Adv. Synth. Catal.*, 2009, **351**, 1273; (*s*) R. J. Reddy, H.-H. Kuan, T.-Y. Chou and K. Chen, *Chem.–Eur. J.*, 2009, **15**, 9294; (*t*) M. Wiesner, M. Neuberger and H. Wennemers, *Chem.–Eur. J.*, 2009, **15**, 10103; (*u*) S.-L. Zhu, S.-Y. Yu and D.-W. Ma, *Angew. Chem., Int. Ed.*, 2008, **47**, 545; (*v*) D.-Z. Xu, S.-S. Shi, Y.-J. Liu and Y.-M. Wang, *Tetrahedron*, 2009, **65**, 9344; (*w*) S. Saha, S. Seth and J. N. Moorthy, *Tetrahedron Lett.*, 2010, **51**, 5281; (*x*) X.-Y. Cao, J.-C. Zheng, Y.-X. Lia, Z.-C. Shua, X.-L. Sun, B.-Q. Wang and Y. Tang, *Tetrahedron*, 2010, **66**, 9703; (*y*) J. Agarwal and R. K. Peddinti, *Tetrahedron Lett.*, 2011, **52**, 117; (*z*) D.-F. Lu, Y.-F. Gong and W.-Z. Wang, *Adv. Synth. Catal.*, 2010, **352**, 644; (*aa*) M. Yoshida, A. Sato and S. Hara, *Org. Biomol. Chem.*, 2010, **8**, 3031.

13 For selected other chiral amine-catalyzed Michael addition reactions, see: (*a*) N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370; (*b*) N. Halland, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2002, **67**, 8331; (*c*) T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2003, **125**, 12672; (*d*) N. Halland, T. Hansen and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2003, **42**, 4955; (*e*) P. Melchiorre and K. A. Jørgensen, *J. Org. Chem.*, 2003, **68**, 4151; (*f*) H. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc.*, 2004, **126**, 9906; (*g*) S. B. Tsogeva and S.-W. Wei, *Chem. Commun.*, 2006, 1451; (*h*) S.-W. Wei, D. A. Yalalov, S. B. Tsogoeva and S. Schmata, *Catal. Today*, 2007, **121**, 151; (*i*) H.-B. Huang and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2006, **128**, 7170; (*j*) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu and J.-P. Cheng, *Angew. Chem., Int. Ed.*, 2006, **45**, 3093; (*k*) C. G. Kokotos and G. Kokotos, *Adv. Synth. Catal.*, 2009, **351**, 1355; (*l*) T. Inokuma, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2006, **128**, 9413; (*m*) X.-X. Jiang, Y.-F. Zhang, A. S. C. Chan and R. Wang, *Org. Lett.*, 2009, **11**, 153; (*n*) Y. Hayashi, H. Gotoh, T. Hayasi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, **44**, 4212; (*o*) C. Palomo, S. Vera, A. Mielgo and E. Gómez-Bengoa, *Angew. Chem., Int. Ed.*, 2006, **45**, 5984; (*p*) M. Lombardo, M. Chiarucci, A. Quintavalla and C. Trombini, *Adv. Synth. Catal.*, 2009, **351**, 2801; (*q*) K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li and J.-A. Ma, *Org. Lett.*, 2007, **9**, 923; (*r*) A. Lu, P. Gao, Y. Wu, Y. Wang, Z. Zhou and C.-C. Tang, *Org. Biomol. Chem.*, 2009, **7**, 3141; (*s*) M. Freund, S. Schenker and S. B. Tsogoeva, *Org. Biomol. Chem.*, 2009, **7**, 4279; (*t*) Y.-F. Ting, C. Chang, R. J. Reddy, D. R. Magar and K. Chen, *Chem.–Eur. J.*, 2010, **16**, 7030; (*u*) F. Yu, Z.-C. Jin, H.-C. Huang, T.-T. Ye, X.-M. Liang and J.-X. Ye, *Org. Biomol. Chem.*, 2010, **8**, 4767; (*v*) R. Husmann, M. Jörres, G. Raabe and C. Bolm, *Chem.–Eur. J.*, 2010, **16**, 12549; (*w*) A. M. Flock, A. Krebs and C. Bolm, *Synlett*, 2010, 1219; (*x*) T. C. Nugent, M. Shoaib and A. Shoaib, *Org. Biomol. Chem.*, 2011, **9**, 52.

14 For recent reviews of thiourea and urea catalysis, see: (*a*) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289; (*b*) T. Akiyama, J. Itoh and K. Fuchibe, *Adv. Synth. Catal.*, 2006, **348**, 999; (*c*) S. J. Connon, *Chem.–Eur. J.*, 2006, **12**, 5418; (*d*) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (*e*) Y. Takemoto and H. Miyabe, *Chimia*, 2007, **61**, 269; (*f*) W. Yu and W. Wang, *Chem.–Asian J.*, 2008, **3**, 516; (*g*) H. Miyabe and Y. Takemoto, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 785; (*h*) S. J. Connon,

Synlett, 2009, 354. For the seminal paper, see: (*i*) M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 4901.

15 (*a*) J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc.*, 2008, **130**, 14416. For other related work with squaramides, see: (*b*) V. B. Gondi, K. Hagihara and V. H. Rawal, *Chem. Commun.*, 2010, **46**, 904; (*c*) H. Konishi, T. Y. Lam, J. P. Malerich and V. H. Rawal, *Org. Lett.*, 2010, **12**, 2028; (*d*) Y. Qian, G.-Y. Ma, A.-F. Lv, H.-L. Zhu, J. Zhao and V. H. Rawal, *Chem. Commun.*, 2010, **46**, 3004; (*e*) Y. Zhu, J. P. Malerich and V. H. Rawal, *Angew. Chem. Int. Ed.*, 2010, **49**, 153.

16 (*a*) Y.-J. Cao, H.-H. Lu, Y.-Y. Lai, L.-Q. Lu and W.-J. Xiao, *Synthesis*, 2006, 3795; (*b*) Y.-J. Cao, Y.-Y. Lai, X. Wang and W.-J. Xiao, *Tetrahedron Lett.*, 2007, **48**, 21.

17 Sulfamides have been investigated in self-assembly, see: (*a*) B. Gong, C. Zheng, E. Skrzypczak-Jankun, Y.-F. Yan and J.-H. Zhang, *J. Am. Chem. Soc.*, 1998, **120**, 11194; (*b*) B. Gong, C. Zheng, E. Skrzypczak-Jankun, Y.-F. Yan and J.-H. Zhang, *Org. Lett.*, 2000, **2**, 3273; the sulfamide functional groups are also found in a number of marketed and investigational drugs, see: (*c*) C.-X. Guo, L.-M. Dong, S. Kephart and X.-J. Hou, *Tetrahedron Lett.*, 2010, **51**, 2909, and references therein.

18 (*a*) X.-J. Zhang, S.-P. Liu, X.-M. Li, M. Yan and A. S. C. Chan, *Chem. Commun.*, 2009, 833; (*b*) S.-P. Liu, X.-J. Zhang, J.-H. Lao and A. S. C. Chan, *ARKIVOC*, 2009, 268; (*c*) X.-J. Zhang, S.-P. Liu, J.-H. Lao, G.-J. Du, M. Yan and A. S. C. Chan, *Tetrahedron: Asymmetry*, 2009, **20**, 1451; (*d*) J.-H. Lao, X.-J. Zhang, J.-J. Wang, X.-M. Li, M. Yan and H.-B. Luo, *Tetrahedron: Asymmetry*, 2009, **20**, 2818.

19 (*a*) J.-R. Chen, Y.-Y. Lai, H.-H. Lu, X.-F. Wang and W.-J. Xiao, *Tetrahedron*, 2009, **65**, 9238; (*b*) J.-R. Chen, Y.-J. Cao, Y.-Q. Zou, F. Tan, L. Fu, X.-Y. Zhu and W.-J. Xiao, *Org. Biomol. Chem.*, 2010, **8**, 1275; (*c*) J.-R. Chen, Y.-Q. Zou, L. Fu, F. Ren, F. Tan and W.-J. Xiao, *Tetrahedron*, 2010, **66**, 5367; (*d*) J.-R. Chen, H.-H. Lu, X.-Y. Li, L. Cheng, J. Wan and W.-J. Xiao, *Org. Lett.*, 2005, **7**, 4543; (*e*) J.-R. Chen, X.-Y. Li, X.-N. Xing and W.-J. Xiao, *J. Org. Chem.*, 2006, **71**, 8198; (*f*) J.-R. Chen, X.-P. Liu, X.-Y. Zhu, L. Li, Y.-F. Qiao, J.-M. Zhang and W.-J. Xiao, *Tetrahedron*, 2007, **63**, 10437; (*g*) J.-R. Chen, X.-L. An, X.-Y. Zhu, X.-F. Wang and W.-J. Xiao, *J. Org. Chem.*, 2008, **73**, 6006.

20 (*a*) G. E. Dubois and R. A. Stephenson, *J. Org. Chem.*, 1980, **45**, 5371; (*b*) G. E. DuBois, *J. Org. Chem.*, 1980, **45**, 5373; see also ref. 17c.

21 N. Dahlin, A. Bøgevig and H. Adolfsson, *Adv. Synth. Catal.*, 2004, **346**, 1101.

22 (*a*) S. Belot, A. Massaro, A. Tenti, A. Mordini and A. Alexakis, *Org. Lett.*, 2008, **10**, 4557; (*b*) S. Belot, A. Quintard, A. Alexakis and N. Krause, *Adv. Synth. Catal.*, 2010, **352**, 667; (*c*) For other related work with, see: B. Tan, X. Zhang, P. J. Chua and G.-F. Zhong, *Chem. Commun.*, 2009, 779; (*d*) T.-X. He, J.-Y. Qian, H.-L. Song and X.-Y. Wu, *Synlett*, 2009, 3195; (*e*) Z.-B. Li, S.-P. Luo, Y. Guo, A.-B. Xia and D.-Q. Xu, *Org. Biomol. Chem.*, 2010, **8**, 2505; (*f*) H. Ma, K. Liu, F.-G. Zhang, Ch.-L. Zhu, J. Nie and J.-A. Ma, *J. Org. Chem.*, 2010, **75**, 1402.