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A new type of organocatalyst for highly stereoselective Michael addition of ketones to nitroolefins on water

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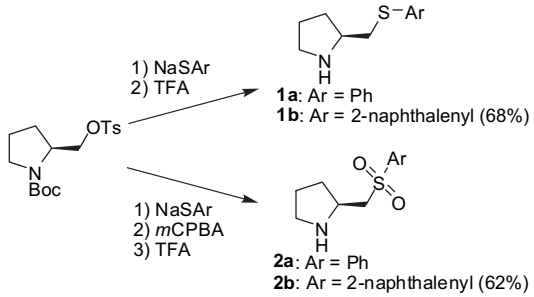
ABSTRACT

(*S*)-2-((Naphthalen-2-ylsulfonyl)methyl)pyrrolidine, prepared in three steps from (*S*)-*N*-Boc-2-[((4-toluenesulfonyl)oxy)methyl]pyrrolidine in 62% overall yield, was used as a new type of organocatalyst bearing a pyrrolidine and a sulfone moiety. It shows very high catalytic activity toward the direct asymmetric Michael reaction of cyclohexanone and nitroolefins. All the corresponding adducts can be furnished in 90–99% yields and with up to 98% ee and over 99:1 dr on water in the presence of this catalyst (15 mol %) without any additive.

1. Introduction

Asymmetric organocatalysis of carbon–carbon bond formation is of importance in organic synthesis.[1] Among all well-developed methods, the asymmetric Michael reaction plays an important role due to its allowance of generation of adducts with high diastereoselectivities as well as high enantioselectivities.[2,3] The most successful development of chiral organocatalysts for the asymmetric Michael reaction includes pyrrolidine-type organocatalysts bearing H-bond functions,[4] bulky groups,[5] salt moieties,[6] and phosphine oxide function.[7] Their further investigation and application are even done by using water as an additive or reaction medium.[8,9] However, to our best knowledge, there are few successful application and study with a pyrrolidine-type organocatalyst bearing a sulfone function in this attractive research field. We suppose that the oxygen of sulfone functionality in combination of protic solvent, such as water, should provide a H-bond interaction to improve not only the reactivity of asymmetric Michael addition but also its stereoselectivity. Herein, we wish to report new types of organocatalysts **1** and **2** starting from easily prepared (*S*)-*N*-Boc-2-[((4-toluenesulfonyl)oxy)methyl]pyrrolidine[10] (Scheme 1) for the asymmetric Michael addition of cyclohexanone (**3a**) and aryl-substituted nitroolefin **4**. Remarkably, the organocatalyst **2b**, which turned out to be the most effective catalyst, can efficiently catalyze the direct asymmetric Michael reaction of cyclohexanone (**3a**) with a range of nitroolefin **4**, giving the corresponding adducts **5** in excellent yields and with excellent enantioselectivities as well as diastereoselectivities on water (Tables 1–3).



Scheme 1. Preparation of organocatalysts **1** and **2** from (*S*)-*N*-Boc-2-[((4-toluenesulfonyl)oxy)methyl]pyrrolidine.

2. Results and discussion

The desired catalyst **1b** was prepared according to the similar procedure of the catalyst **1a** by direct displacement of 4-toluenesulfonate group in (*S*)-*N*-Boc-2-[((4-toluenesulfonyl)oxy)methyl]-pyrrolidine with sodium 2-naphthalenelthiolate (1.2 equiv), followed by deprotection with TFA, in overall 68% yield.[11] Similarly, (*S*)-*N*-Boc-2-[((4-toluenesulfonyl)oxy)methyl]pyrrolidine also underwent the displacement of 4-toluenesulfonate group with sodium 2-naphthalenethiolate (1.2 equiv), followed by oxidation with *m*CPBA and

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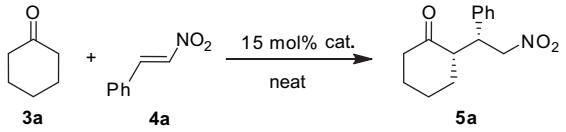
Table 1
Screening of catalysts **1a**, **1b**, **2a** and **2b** for the Michael addition of cyclohexanone (**3a**) to β-nitrostyrene (**4a**)[a]

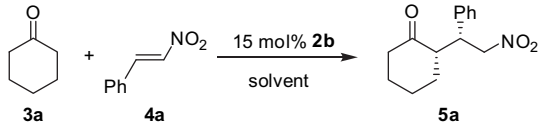


3a **4a** **5a**

Entry	Cat.	Time [h]	Yield[b] [%]	*syn*/*anti*[c]	*ee* [%] *syn*[d]
1	**1a**	1.5	60	92/8	23
2	**1b**	1	97	97/3	65
3	**2a**	2	90	90/10	64
4	**2b**	2.5	97	97/3	94

[a] Unless stated otherwise, the reaction was performed with cyclohexanone (**3a**) (5.0 equiv) and β-nitrostyrene (**4a**) (0.2 mmol) at 27 °C.
[b] Yield of analytically pure isolated product.
[c] Determined by ^{1}H NMR analysis of the crude product.
[d] Determined by HPLC using a Chiralpak AS-H column.

Table 2
Optimization of reaction condition for the Michael addition of cyclohexanone (**3a**) to β-nitrostyrene (**4a**) catalyzed by organocatalyst **2b**[a]



3a **4a** **5a**

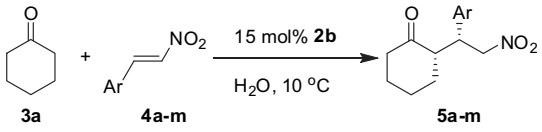
Entry	Solvent	Time [h]	Yield[b] [%]	*syn*/*anti*[c]	*ee* [%] *syn*[d]
1	THF	23	90	99/1	94
2	CH_2Cl_2	29	87	99/1	96
3	Toluene	31	85	97/3	97
4	MeOH	11	98	92/8	91
5	Et_2O	23	92	93/7	97
6	H_2O	2	99	>99/1	97
7[e]	H_2O	4	92	>99/1	97
8[f,g]	H_2O	14	98	>99/1	98

[a] Unless stated otherwise, the reaction was performed with cyclohexanone (**3a**) (5.0 equiv) and β-nitrostyrene (**4a**) (0.2 mmol) in solvent (0.2 mL) at 27 °C.
[b] Yield of analytically pure isolated product.
[c] Determined by ^{1}H NMR analysis of the crude product.
[d] Determined by HPLC using a Chiralpak AS-H column.
[e] 10 mol % **2b** was loaded.
[f] The reaction was performed at 10 °C.
[g] In the presence of 15 mol % **1b**, inferior results on water were obtained (4 h; 97% yield; 88% ee; 87:13 dr) at room temperature and (14 h; 92% yield; 93% ee; 90:10 dr) at 10 °C, respectively.

then deprotection with TFA, furnishing the catalysts **2b** in 62% overall yield (Scheme 1).

Organocatalysts **1a** and **1b**, bearing a sulfide function with different aryl groups, showed interesting results in catalytic asymmetric Michael reaction of cyclohexanone (**3a**) with β-nitrostyrene (**4a**) (Table 1, entries 1 and 2). Cyclohexanone (**3a**) (1.0 mmol) reacted with β-nitrostyrene (**4a**) (0.2 mmol) in the presence of the catalyst **1a** (15 mol %) without solvent at 27 °C, giving the desired adduct **5a** in 60% yield with only 23% enantiomeric excess (ee) and 92:8 diastereomeric ratio (dr) within 1.5 h (entry 1). The organocatalyst **1b**, which bears 2-naphthyl group, exhibited remarkable enhancement in reactivity as well as stereoselectivity compared to the catalyst **1a**. Under the same reaction condition, the Michael reaction of cyclohexanone (**3a**) (1.0 mmol) and β-nitrostyrene (**4a**) (0.2 mmol) catalyzed by the catalyst **1b** (15 mol %) was carried out without solvent at 27 °C, providing the desired adduct **5a** in 97% yield with 65% ee and 97:3 dr within 1 h (entry 2). Interestingly, the reactions catalyzed by organocatalysts **2a** and **2b** bearing a sulfone moiety gave superior results (entries 3 and 4). Instead of the catalyst **1a** with a sulfide function, the catalyst **2a** gave the desired adduct **5a** with better reactivity and stereoselectivity (90% yield; 64% ee and 90:10 dr) (entry 3). The organocatalyst **2b**, bearing 2-naphthalenyl group and sulfone functionality, turned out to be the best one in our designed organocatalysts. The desired adduct **5a** was obtained in 97% yield with 94% ee and 97:3 dr within 2.5 h (entry 4).

Table 3
Asymmetric Michael addition of cyclohexanone (**3a**) to nitroolefin **4** catalyzed by organocatalyst **2b**[a]



3a **4a-m** **5a-m**

Entry	Ar	Time [h]	Yield[b] [%]	*syn*/*anti*[c]	*ee*[d] [%]
1	C_6H_5	14	**5a** (98)	>99/1	98
2	1-Naphthyl	18	**5b** (85)	>99/1	94
3	4-$NO_2C_6H_4$	12	**5c** (95)	97/3	92
4	2-$NO_2C_6H_4$	14	**5d** (95)	>99/1	92
5	4-ClC_6H_4	17	**5e** (95)	>99/1	94
6	4-BrC_6H_4	19	**5f** (95)	98/2	96
7	2-BrC_6H_4	20	**5g** (95)	95/5	91
8	2-FC_6H_4	17	**5h** (96)	>99/1	95
9	4-$CH_3C_6H_4$	18	**5i** (96)	>99/1	98
10	2-$CH_3C_6H_4$	20	**5j** (90)	>99/1	95
11	4-$CH_3OC_6H_4$	24	**5k** (89)	>99/1	95
12	2-Furyl	18	**5l** (99)	>99/1	90
13	2-Thienyl	17	**5m** (92)	>99/1	85
14[e]	2-Thienyl	17	**5m** (98)	95/5	90

[a] Unless stated otherwise, the reaction was performed with cyclohexanone (**3a**) (5.0 equiv) and β-nitrostyrene (**4a**) (0.2 mmol) on water (0.2 mL) at 10 °C.
[b] Yield of analytically pure isolated product.
[c] Determined by ^{1}H NMR analysis of the crude product.
[d] Determined by HPLC using a Chiralpak AS-H, AD-H or OD-H column.
[e] The reaction was performed without water at 10 °C.

Further investigation on the reaction condition of the asymmetric Michael addition of cyclohexanone (**3a**) toward β-nitrostyrene (**4a**) catalyzed by organocatalyst **2b** was disclosed in Table 2. The organocatalyst **2b** showed slightly better results in CH_2Cl_2 (96% ee; 99:1 dr) than that in THF (94% ee; 99:1 dr) (Table 2, entries 1 and 2). Even higher enantioselectivity (97% ee) was observed when toluene was used, albeit the diastereoselectivity decreased (97:3 dr) (entry 3). Polar protic organic solvent, such as MeOH, was also examined. The reactivity was enhanced in comparison with other organic solvents, but both of its enantioselectivity and diastereoselectivity dropped (91% ee, 92:8 dr) (entry 4). In Et_2O, the enantioselectivity increased up to 97% ee, although the diastereoselectivity decreased (93:7 dr) (entry 5). Encouraged by the great improvement of reactivity when MeOH was used as solvent compared to other aprotic solvents, water was examined as well. Remarkably, the reaction catalyzed by **2b** on water afforded the adduct **5a** in 2 h with excellent yield and stereoselectivity (99% yield; 97% ee; >99:1 dr) (entry 6). The enantioselectivity and diastereoselectivity remained the same even in the presence of the reduced loading of the catalyst **2b** (10 mol %) (entry 7). The reaction catalyzed by **2b** (15 mol %) took place smoothly with higher enantioselectivity on water within 14 h at 10 °C to provide the adduct **5a** in 98% yield (98% ee; >99:1 dr) (entry 8).

The excellent catalytic ability of the organocatalyst **2b** was confirmed by further studies summarized in Table 3. It showed that various aromatic nitroolefins **4a–m** can react smoothly with cyclohexanone (**3a**) in the presence of the catalyst **2b** (15 mol %) within 24 h, leading to the corresponding adducts **5a–m** in excellent yields and with high stereoselectivies on water. Interestingly, reactions of cyclohexanone (**3a**) and nitroolefins with a *para*-oriented electron-withdrawing or electron-donating substituent in aromatic rings, such as **4f** or **4i**, afforded the corresponding adducts **5f** or **5i** with 96% ee or 98% ee, respectively (Table 3, entries 6 and 9). Inferior enantioselectivies were observed when aromatic nitroolefins, like **4g** or **4j**, had the same substituent as **4f** or **4i** in *ortho*-position, giving the corresponding adducts **5g** or **5i** with 91%

ee or 95% ee, respectively (entries 7 and 10). Heteroaryl substrates, such as **4l** or **4m**, reacted successfully with cyclohexanone (**3a**) yielding the corresponding adducts **5l** or **5m** in 92% or 99% yield, respectively, with excellent diastereoselectivities (>99:1) and high enantioselectivities (**5l**: 90% ee; **5m**: 85% ee) on water within 18 h (entries 12 and 13). The enantioselectivity of the adduct **5m** was improved with 90% ee under neat condition, albeit with the inferior diastereoselectivity (95:5) (entry 14).

Based on the outcome of our results, we propose that the pyrrolidine ring of the catalyst **2b** first reacts with cyclohexanone (**3a**) to form the resulting enamine. Thereafter, the oxygen atom of the sulfone group, via a H-bond with water, will direct the nitro group so that the resulting enamine can attack the corresponding aryl-substituted nitrolefins **4** from the *Re*-face with opposite orientation of naphthyl group of **2b** to aryl group of **4**, providing the highly enantio- and diastereoselective corresponding adducts **5** (Fig. 1).

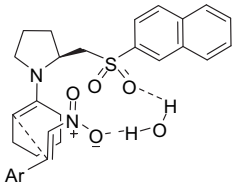
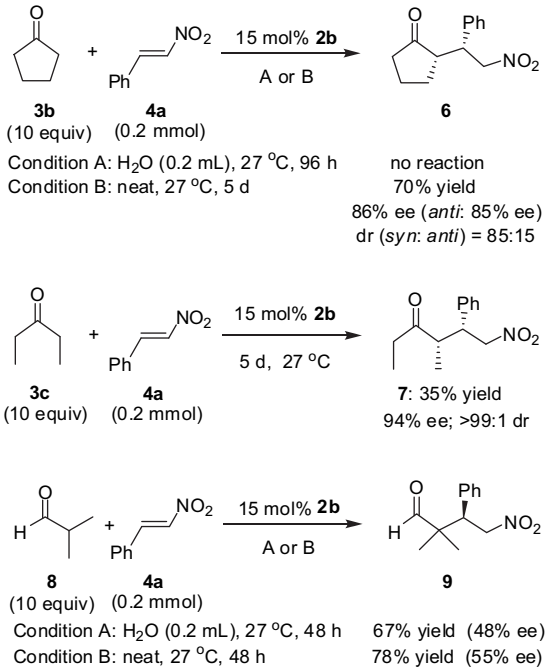


Figure 1. A proposed transition state.

Furthermore, the asymmetric Michael addition of the other cyclic ketone, like cyclopentanone (**3b**), with β-nitrostyrene (**4a**) catalyzed by the organocatalyst **2b** underwent smoothly to afford the adduct **6** in 70% yield with good enantioselectivity and diastereoselectivity (*syn*: 86% ee; *anti*: 85% ee; 85:15 dr) under neat condition (Scheme 2). The expected reaction of cyclopentanone (**3b**), with β-nitrostyrene (**4a**) catalyzed by the organocatalyst **2b** did not occur on water. Surprisingly, acyclic ketone, such as pentan-3-one (**3c**), worked smoothly with β-nitrostyrene (**4a**) in the presence of the organocatalyst **2b**, giving rise to the adduct **7** in 35% yield with 94% ee and over 99:1 dr (Scheme 2). The asymmetric Michael addition of β-nitrostyrene (**4a**) and an aldehyde, like 2-methylpropanal (**8**), catalyzed by the organocatalyst **2b** had also been examined. Its reaction proceeded smoothly on water or in neat condition for 48 h to lead to the adduct **9** in 67% yield with 48% ee or 78% yield with 55% ee, respectively (Scheme 2).



Scheme 2. Asymmetric Michael addition of cyclopentanone (**3b**), pentanone (**3c**) or 2-methylpropanal (**8**) to β-nitrostyrene (**4a**) catalyzed by organocatalyst **2b**.

3. Conclusion

In conclusion, new types of organocatalysts bearing sulfide or sulfone functions (**1** or **2**) were designed and studied for the direct asymmetric Michael addition of cyclohexanone (**3a**) and nitroolefins **4**. The organocatalyst **2b**, bearing a pyrrolidine and a sulfone moiety, showed very high catalytic activity toward the direct asymmetric Michael reaction of cyclohexanone and aromatic nitroolefins to furnish the corresponding adducts[12] in excellent yields and with high stereoselectivities on water in the presence of low loading of this catalyst (15 mol%) without any acidic additive. In addition, this organocatalyst can be easily prepared in a few steps from (*S*)-proline in good yield. Further investigation and application of this potential organocatalyst and its derivatives in other attractive asymmetric organocatalytic reactions are currently underway.

4. Experimental

4.1. General methods

All starting materials were purchased from commercial sources and used without further purification. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H NMR. Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate (0.2 mm thickness). Flash-chromatography was performed using Merck silica gel 60 (70–230 mesh). NMR data were recorded on a 400 MHz NMR spectrometer. The ionization method used was electron impact ionization (EI, 70 eV). Melting points are uncorrected. Enantioselectivities were determined by high performance liquid chromatography (HPLC) analysis employing a Daicel Chiralpak AD-H, OD-H or AS-H column. Optical rotations were measured in $CHCl_3$ on a JASCO co. DIP-1000 Digital polarimeter with a 50 mm cell (*c* given in g/100 mL). Nitroolefins **4** were prepared according to literature procedures.[13] Absolute configuration and spectroscopic data (NMR or HPLC spectra) of the products were determined by comparison with compounds previously published and were given in Supplementary data.[14]

*4.1.1. Preparation of the organocatalysts (S)-2-((naphthalen-2-ylthio)methyl)pyrrolidine (**1b**) and (S)-2-((naphthalen-2-ylsulfonyl)methyl)pyrrolidine (**2b**).*

4.1.1.1. (S)-N-Boc-2-((naphthalen-2-ylthio)methyl)-pyrrolidine. Sodium hydride (60%) (0.260 g, 6.5 mmol) was pretreated by washing with hexanes in a double-neck round flask. Hexanes were then taken out, and dry THF (7 mL) was added. Thereafter, 2-naphthalenethiol (0.960 g, 6 mmol) was added and stirred at 0 °C for 5 min. A solution of (*S*)-*N*-Boc-2-[((4-toluenesulfonyl)oxy)methyl]pyrrolidine (1.780 g, 5 mmol) in dry THF (10 mL) was then added, and the resulting mixture was heated to reflux for 5 h. The reaction was quenched with water (10 mL), stirred vigorously 0 °C, and then extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash-chromatography (ether/hexanes: 1/20, R_f=0.24), yielded the desired product as a colorless oil (1.300 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.02 (s, 0.5H), 7.84 (s, 0.5H), 7.73–7.71 (m, 3H), 7.51–7.40 (m, 3H), 4,14 (s, 0.5H), 3.96 (s, 0.5H), 3.66 (d, 1H, 12.6 Hz), 3.47–3.33 (m, 2.5H), 2.91–2.76 (m, 1H), 2.00–1.73 (m, 4H), 1.48 (s, 4.5H), 1.43 (s, 4.5H). ^{13}C

NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 154.1, 153.9, 133.8, 133.6, 133.4, 133.2, 131.6, 131.2, 128.1, 128.0, 127.6, 127.3, 126.7, 126.2, 126.1, 125.4, 125.0, 79.2, 78.8, 56.3, 46.8, 46.4, 37.1, 35.3, 29.8, 29.2, 28.2, 23.3, 22.4. MS (70 eV, EI) *m*/*z* (%): 343 (19) [M^+], 174 (48), 170 (45), 115 (41), 114 (92), 70 (100), 57 (85). IR (CH_2Cl_2) $\tilde{\nu}$(cm^{-1}): 2964 (s), 2869 (m), 1625 (m), 1590 (m), 1501 (m), 1458 (w), 1338 (w), 1366 (m), 1195 (w), 1134 (w), 944 (w), 683 (m). HRMS (EI) for $C_{20}H_{25}NO_2S$, (343.1606): found: 343.1603. $[\alpha]_D^{36}$ +6.29 (*c* 10, $CHCl_3$).

*4.1.1.2. (S)-2-((Naphthalen-2-ylthio)methyl)pyrrolidine (**1b**).* To a solution of (*S*)-*N*-Boc-2-((naphthalen-2-ylthio)methyl)-pyrrolidine (0.170 g, 0.5 mmol) in dry CH_2Cl_2 (1.7 mL) was added trifluoroacetic acid (0.37 mL, 5.0 mmol). The resulting mixture was stirred at room temperature for 5 h, followed by removing excess trifluoroacetic acid under reduced pressure. Thereafter, the residue was dissolved in CH_2Cl_2 (25 mL), followed by the addition of water (10 mL) and 1 M $KOH_{(aq)}$(10 ml), extraction with CH_2Cl_2 (10 mL×2). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to provide the desired product as a pale yellow oil (0.100 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.78–7.72 (m, 4H), 7.49–7.40 (m, 3H), 3.30 (quintet, 1H, *J*=6.5 Hz), 3.15–3.06 (m, 2H), 3.05–2.99 (m, 1H), 2.92–2.85 (m, 1H), 2.28 (br s, 1H, NH), 1.99–1.91 (m, 1H), 1.87–1.67 (m, 2H), 1.55–1.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 134.0, 133.7, 131.6, 128.3, 127.6, 127.4, 126.9, 126.8, 126.5, 125.5, 57.5, 46.3, 39.9, 31.1, 25.2. MS (70 eV, EI) *m*/*z* (%):244 (50) [M+H]$^+$, 243 (9) [M^+], 175 (70), 174 (100), 159 (19), 127 (43), 115 (92), 71 (65), 70 (90), 56 (28). IR ($CHCl_3$) $\tilde{\nu}$(cm^{-1}): 3676 (w), 3062 (w), 2922 (m), 1590 (w), 1457 (w), 1218 (m), 909 (m), 782 (w), 620 (m), 565 (m). HRMS (EI) for $C_{15}H_{17}NS$, (243.1082): found: 243.1068. $[\alpha]_D^{36}$ +8.84 (*c* 9.5, $CHCl_3$).

*4.1.1.3. (S)-2-((Naphthalen-2-ylsulfonyl)methyl)pyrrolidine (**2b**).* To a solution of (*S*)-*N*-Boc-2-((naphthalen-2-ylthio)methyl)-pyrrolidine (0.600 g, 1.76 mmol) in dry CH_2Cl_2 (6.2 mL) was added *m*-chloroperoxybenzoic acid (0.840 g, 3.52 mmol). The reaction was stirred at room temperature for 2.5 h, and followed by quenching with saturated $Na_2S_2O_{3(aq)}$(10 mL) and saturated $NaHCO_{3(aq)}$(20 mL) and extracting with CH_2Cl_2 (20 mL×3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to provide (*S*)-*N*-Boc-2-((naphthalen-2-ylsulfonyl)methyl)-pyrrolidine as a white solid (0.580 g, 90%). mp.: 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.50 (s, 1H), 8.03–8.00 (m, 2H), 7.95–7.87 (m, 2H), 7,70–7.63 (m, 2H), 4.13 (m, 1H), 3.97 (d, 0.5H, *J*=13.1 Hz), 3.58 (d, 0.5H, *J*=12.8 Hz), 3.30 (m, 2H), 3.11 (dd, 1H, *J*=13.6, 10.6 Hz), 2.33–2.20 (m, 1H), 2.15–2.00 (m, 1H), 1.90–1.80 (m, 2H), 1.35 (s, 4H), 1.27 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 154.0, 153.6, 136.9, 136.7, 135.3, 132.1, 129.6, 129.3, 129.1, 127.9, 127.8, 127.5, 122.8, 80.3, 80.1, 59.0, 57.5, 52.4, 46.4, 45.8, 30.6, 29.8, 28.3, 23.6, 22.7. MS (70 eV, EI) *m*/*z* (%): 375 (2) [M^+], 319 (19), 302 (41), 274 (88), 211 (38), 183 (78), 141 (29), 127 (97), 84 (58), 70 (91), 57 (100). IR (KBr) $\tilde{\nu}$(cm^{-1}): 3020 (s), 1694 (s), 1683 (s), 1591 (w), 1394 (s), 1302 (s), 1254 (m), 1122 (m), 1071 (w), 964 (w), 900 (w), 864 (w), 661 (w), 636 (w), 522 (w), 473 (w). HRMS (EI) for $C_{20}H_{25}NO_4S$, (375.1504): found: 375.1518. $[\alpha]_D^{36}$ −22.82 (*c* 10, $CHCl_3$).

To a solution of (*S*)-*N*-Boc-2-((naphthalen-2-ylsulfonyl)methyl)-pyrrolidine (0.580 g, 1.55 mmol) in dry CH_2Cl_2 (5.0 mL) was added trifluoroacetic acid (1.2 mL, 15.5 mmol). The resulting mixture was stirred at room temperature for 5 h, followed by removing excess trifluoroacetic acid under reduced pressure. Thereafter, the residue was dissolved in CH_2Cl_2 (25 mL), followed by the addition of water (20 mL) and 1 M $KOH_{(aq)}$(40 mL), extraction with CH_2Cl_2 (20 mL×2). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to provide the desired product **2b** as a pale yellow solid (0.380 g, 90%). mp.: 52–54 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.48 (s, 1H), 7.99–7.95 (m, 2H), 7.91–7.85 (m, 2H), 7,66–7.58 (m, 2H), 3.54 (quintet, 1H, *J*=6.9 Hz), 3.33–3.25 (m, 2H), 3.00–2.94 (m, 1H), 2.89–2.83 (m, 1H), 2.45 (br s, 1H, NH), 1.98–1.89 (m, 1H), 1.80–1.61 (m, 2H), 1.45–1.36 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 136.5, 135.2, 132.0, 129.6, 129.3, 129.2, 127.9, 127.6, 122.5, 61.7, 52.5, 45.8, 31.4, 23.9. MS (70 eV, EI) *m*/*z* (%): 275 (2) [M^+], 274 (7) [M^+−1], 211 (100), 156 (30), 127 (90), 83 (81), 70 (79), 56 (43). IR (KBr) $\tilde{\nu}$(cm^{-1}): 3180 (w), 1298 (s), 1149 (s), 1126 (s), 1073(m), 827 (m), 669 (m), 554 (m), 519 (m), 488 (m). HRMS (EI) for $C_{15}H_{17}NO_2S$, (275.0980): found: 275.0956. $[\alpha]_D^{34}$ +5.94 (*c* 20, $CHCl_3$).

4.2. Typical procedure for addition of 3a, 3b, 3c, or 8 to 4a catalyzed by organocatalyst 1 or 2 (TP 1 for Tables 1 and 3, Scheme 2)

To cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol) was added the organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) at 27 °C. β-Nitrostyrene (**4a**) (30 mg, 0.2 mmol) was added, and the resulting mixture was stirred at 27 °C until the completion of the reaction monitored by TLC (2.5 h) analysis. Purification by flash-chromatography furnished the desired product **5a** as a white solid (48 mg, 97%); 94% ee, determined by HPLC with Chiralpak AS-H column (hexane-IPA=80:20, flow rate=0.5 mL min^{-1}, λ=254 nm): T_R=16.48 min (minor, *syn*), 22.18 min (major, *syn*).

*4.2.1. Synthesis of (S)-2-((R)-2-nitro-1-phenylethyl)-cyclopentanone (**6**).* Prepared according to **TP 1** from the olefin **4a** (30 mg, 0.2 mmol), cyclopentanone (**3b**) (168.3 mg, 10.0 equiv, 2.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) [reaction condition: 27 °C for **5d**]. Purification by flash-chromatography (hexanes/ethyl acetate: 8/1) yielded **6** as a white solid (26 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.34–7.24 (m, 5H, *syn*+*anti*), 7.19–7.15 (m, 3H, *syn*+*anti*), 5.33 (dd, 1H, *J*=12.9, 5.6 Hz, *syn*), 5.02 (d, 2H, *J*=7.7 Hz, *anti*), 4.71 (dd, 1H, *J*=12.8, 9.9 Hz, *syn*), 3.83 (dt, 1H, *J*=7.7, 4.4 Hz, *anti*), 3,69 (dt, 1H, *J*=9.5, 5.5 Hz, *syn*), 2.54–2.49 (m, 1H, *anti*), 2.43–2.24 (m, 3H, *syn*), 2.17–2.08 (m, 2H, *syn*+*anti*), 1.96–1.83 (m, 4H, *syn*+*anti*), 1.76–1.63 (m, 2H, *syn*+*anti*), 1.53–1.43 (m, 2H, *syn*+*anti*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 218.4 (*syn*), 137.7 (*syn*), 137.4 (*anti*), 128.9 (*anti*), 128.8 (*syn*), 128.4 (*anti*), 128.0 (*syn*), 127.9 (*anti*), 127.8 (*syn*), 78.3 (*syn*), 77.2 (*anti*), 51.4 (*anti*), 50.5 (*syn*), 44.2 (*syn*), 44.0 (*anti*), 39.2 (*anti*), 38.6 (*syn*), 28.3 (*syn*), 27.0 (*anti*), 20.5 (*anti*), 20.2 (*syn*). Chiralpak AD-H column (hexane-IPA=90:10, flow rate=0.5 mL min^{-1}, λ=254 nm): T_R=18.01 min (major, *anti*), 20.03 min (minor, *anti*), 21.37 min (minor, *syn*), 27.38 min (major, *syn*), 85% ee (*anti*), 86% ee (*syn*).

*4.2.2. (4S,5R)-4-Methyl-6-nitro-5-phenylhexan-3-one (**7**).* Prepared according to **TP 1** from the olefin **4a** (30 mg, 0.2 mmol), pentan-3-one (**3c**) (172.3 mg, 10.0 equiv, 2.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) [reaction condition: 27 °C for **5d**]. Purification by flash-chromatography (hexanes/ethyl acetate: 12/1) yielded **7** as a colorless liquid (16 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.34–7.26 (m, 3H), 7.16–7.14 (m, 2H), 4.64 (m, 2H), 3.72–3.66 (m, 1H), 2.98 (quart, *J*=7.5 Hz, 1H), 2.5–2.55 (m, 1H), 2.45–2.35 (m, 1H), 1.08–1.05 (m, 3H), 0.97 (d, *J*=7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 213.6, 137.6, 129.0, 127.9, 76.7, 48.3, 46.1, 35.4, 16.3, 7.7 Chiralpak OD-H column (hexane-IPA=97:3, flow rate=0.5 mL min^{-1}, λ=254 nm): T_R=23.94 min (major), 26.96 min (minor): 94% ee $[\alpha]_D^{24}$ −26.25 (*c* 0.5, $CHCl_3$).

4.3. Typical procedure for addition of 3a, 3b, or 8 to 4a–m catalyzed by 2b (TP 2 for Tables 2 and 3, Scheme 2)

To cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol) was added the organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) and then 0.2 mL H_2O at 10 °C. β-Nitrostyrene (**4a**) (30 mg, 0.2 mmol) was added, and the resulting mixture was stirred at 10 °C until the completion of the

reaction monitored by TLC analysis (14 h). The reaction mixture was extracted with ethyl acetate (3×10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (hexanes/ethyl acetate: 10/1) furnished the desired product **5a** as a white solid (49 mg, 98%); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.34–7.24 (m, 3H), 7.16 (d, 2H, J=7.0 Hz), 4.95 (dd, 1H, J=4.5, 12.5 Hz), 4.63 (dd, 1H, J=10.0, 12.4 Hz), 3.76 (dt, 1H, J=10.2, 4.7 Hz), 2.68 (m, 1H), 2.38 (m, 2H), 2.10–2.04 (m, 1H), 1.77–1.58 (m, 4H), 1.26–1.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 211.8, 137.7, 128.8, 128.1, 127.6, 78.8, 52.4, 43.8, 42.6, 33.1, 28.4, 24.9. Chiralpak AS-H column (hexane-IPA=80:20, flow rate=0.5 mL min^{-1}, λ=254 nm): T_R=16.48 min (minor, *syn*), 22.18 min (major, *syn*), 98% ee $[\alpha]_D^{24}$ −20.52 (*c* 1, $CHCl_3$).

*4.3.1. (S)-2-((R)-(1-Naphthalen-1-yl)-2-nitroethyl) cyclohexanone (**5b**).* Prepared according to **TP 2** from the olefin **4b** (40 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 18 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 10/1) yielded **5b** as a white solid (49 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.17 (br s, 1H), 7.86 (d, 1H, J=8.0 Hz), 7.78 (d, 1H, J=8.2 Hz), 7.58–7.44 (m, 3H), 7.38 (d, 1H, J=7.0 Hz), 5.07 (dd, 1H, J=12.6, 4.4 Hz), 4.92 (br t, 1H, J=12.5 Hz), 4.77 (br s, 1H), 2.87 (br s, 1H) 2.49–2.41 (m, 2H), 2.08–2.06 (m, 1H), 1.69–1.50 (m, 4H), 1.27–1.23 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 212.2, 134.6 (br s), 134.0 (br s), 132.4 (br s), 129.1 (br s), 128.2 (br s), 126.6, 125.9, 125.3, 123.6 (br s), 122.8, 78.7, 53.8 (br s), 42.9, 36.8 (br s), 33.3, 28.7, 25.3. Chiralpak AS-H column (hexane-IPA=80:20, flow rate=0.5 mL min^{-1}, λ=254 nm): T_R=22.09 min (minor, *syn*), 30.81 min (major, *syn*), 94% ee $[\alpha]_D^{24}$ −90.48 (*c* 1, $CHCl_3$).

*4.3.2. (S)-2-((R)-1-(4-Nitrophenyl)-2-nitroethyl)-cyclohexanone (**5c**).* Prepared according to **TP 2** from the olefin **4c** (39 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 12 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 8/1) yielded **5c** as a pale yellow solid (56 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.17 (d, 2H, J=8.6 Hz), 7.39 (d, 2H, J=8.6 Hz), 4.98 (dd, 1H, J=13.1, 4.4 Hz), 4.68 (dd, 1H, J=13.0, 10.3 Hz), 3.92 (dt, 1H, J=4.4, 9.9 Hz), 2.75–2.68 (m, 1H), 2.48–2.44 (m, 1H), 2.41–2.33 (m, 1H), 2.12–2.07 (m, 1H), 1.81–1.76 (m, 1H), 1.71–1.53 (m, 3H), 1.30–1.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 210.8, 147.4, 145.6, 129.3, 124.0, 77.9, 52.1, 43.7, 42.6, 33.1, 28.2, 25.0. Chiralpak AD-H column (hexane-IPA=80:20, flow rate=0.5 mL min^{-1}, λ=254 nm): T_R=31.41 min (minor, *syn*), 65.39 min (major, *syn*), 92% ee $[\alpha]_D^{24}$ −101.21 (*c* 1.2, $CHCl_3$).

*4.3.3. (S)-2-((R)-1-(2-Nitrophenyl)-2-nitroethyl)-cyclohexanone (**5d**).* Prepared according to **TP 2** from the olefin **4d** (39 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 14 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 8/1) yielded **5d** as a white solid (56 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.80 (d, 1H, J=8.6 Hz), 7.58 (t, 1H, J=7.5 Hz), 7.46–7.40 (m, 2H), 4.93–4.82 (m, 2H), 4.35–4.33 (m, 1H), 2.93–2.85 (m, 1H), 2.43–2.32 (m, 2H), 2.12–2.08 (m, 1H), 1.83–1.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 211.0, 150.8, 133.1, 132.8, 129.2, 128.5, 124.9, 77.7, 52.2, 42.7, 38.6, 33.1, 28.3, 25.3. Chiralpak AD-H column (hexane-IPA=85:15, flow rate=1.0 mL min^{-1}, λ=254 nm): T_R=15.71 min (minor, *syn*), 23.94 min (major, *syn*), 92% ee $[\alpha]_D^{24}$ −85.24 (*c* 1.3, $CHCl_3$).

*4.3.4. (S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl)-cyclohexanone (**5e**).* Prepared according to **TP 2** from the olefin **4e** (37 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 17 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 10/1) yielded **5e** as a white solid (54 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.29 (d, 2H, J=8.4 Hz), 7.11 (d, 2H, J=8.4 Hz), 4.92 (dd, 1H, J=12.6, 4.6 Hz), 4.60 (dd, 1H, J=12.6, 10.0 Hz), 3.75 (dt, 1H, J=9.9, 4.8 Hz), 2.68–2.61 (m, 1H), 2.49–2.33 (m, 2H), 2.12–2.05 (m, 1H), 1.82–1.51 (m, 4H), 1.28–1.17 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 211.4, 136.3, 133.6, 129.5, 129.1, 78.6, 52.4, 43.4, 42.7, 33.1, 28.4, 25.0. Chiralpak AS-H column (hexane-IPA=80:20, flow rate=0.5 mL min^{-1}, λ=254 nm): T_R=17.23 min (minor, *syn*), 25.44 min (major, *syn*), 94% ee $[\alpha]_D^{24}$ −26.24 (*c* 1.2, $CHCl_3$).

*4.3.5. (S)-2-((R)-1-(4-Bromophenyl)-2-nitroethyl)-cyclohexanone (**5f**).* Prepared according to **TP 2** from the olefin **4f** (46 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 19 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 10/1) yielded **5f** as a white solid (62 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.43 (d, 2H, J=8.3 Hz), 7.05 (d, 2H, J=8.3 Hz), 4.92 (dd, 1H, J=12.6, 4.5 Hz), 4.58 (dd, 1H, J=12.5, 10.2 Hz), 3.73 (dt, 1H, J=10, 4.4 Hz), 2.50–2.34 (m, 2H), 2.15–2.05 (m, 1H), 1.83–1.57 (m, 4H), 1.28–1.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 211.4, 136.8, 132.0, 129.9, 121.6, 78.4, 52.3, 43.4, 42.7, 33.1, 28.3, 25.0. Chiralpak AD-H column (hexane-IPA=80:20, flow rate=0.5 mL min^{-1}, λ=254 nm): T_R=19.47 min (minor, *syn*), 29.13 min (major, *syn*), 96% ee $[\alpha]_D^{24}$ −20.26 (*c* 1, $CHCl_3$).

*4.3.6. (S)-2-((R)-1-(2-Bromophenyl)-2-nitroethyl)-cyclohexanone (**5g**).* Prepared according to **TP 2** from the olefin **4g** (46 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 20 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 10/1) yielded **5g** as a white solid (62 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.56 (d, 1H, J=7.9 Hz), 7.28 (t, 1H, J=7.4 Hz), 7.21 (d, 1H, J=7.4 Hz), 7.11 (t, 1H, J=7.4 Hz), 4.88 (d, 2H, J=6.0 Hz), 4.31–4.27 (m, 1H), 2.88 (br m, 1H), 2.47–2.33 (m, 2H), 2.10–2.06 (m, 1H), 1.82–1.53 (m, 4H), 1.43–1.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 211.5, 137.2, 133.6, 129.0, 127.9, 125.3, 77.3, 52.1, 42.8, 33.0, 28.5, 26.7, 25.2. Chiralpak AD-H column (hexane-IPA=96:4, flow rate=0.5 mL min^{-1}, λ=254 nm): T_R=31.92 min (minor, *syn*), 47.70 min (major, *syn*), 91% ee $[\alpha]_D^{24}$ −40.25 (*c* 1, $CHCl_3$).

*4.3.7. (S)-2-((R)-1-(2-Fluorophenyl)-2-nitroethyl)-cyclohexanone (**5h**).* Prepared according to **TP 2** from the olefin **4h** (33 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 14 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 10/1) yielded **5h** as a white solid (51 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.30–7.24 (m, 1H), 7.21–7.17 (m, 1H), 7.11–7.03 (m, 2H), 4.94 (dd, 1H, J=12.6, 4.3 Hz), 4.72 (dd, 1H, J=12.5, 10.2 Hz), 4.00 (dt, 1H, J=10.2, 4.4 Hz), 2.89–2.82 (m, 1H), 2.51–2.36 (m, 2H), 2.13–2.07 (m, 1H), 1.82–1.56 (m, 4H), 1.31–1.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 211.5, 161.2 (d, J=245 Hz), 130.9 (d, J=4 Hz), 129.5 (d, J=8 Hz), 124.6 (d, J=4 Hz), 124.5 (d, J=6 Hz), 115.9 (d, J=23 Hz), 77.4 (d, J=2 Hz), 50.9 (d, J=1.5 Hz), 42.7, 39.8, 33.2, 28.4, 25.1. Chiralpak OD-H column (hexane-IPA=98:2, flow rate=0.4 mL min^{-1}, λ=254 nm): T_R=39.85 min (minor, *syn*), 43.24 min (major, *syn*), 95% ee $[\alpha]_D^{24}$ −34.64 (*c* 1.3, $CHCl_3$).

*4.3.8. (S)-2-((R)-2-Nitro-1-p-tolylethyl)cyclohexanone (**5i**).* Prepared according to **TP 2** from the olefin **4i** (33 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst

2b (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 18 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 10/1) yielded **5i** as a white solid (50 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.12 (d, 2H, J=7.0 Hz), 7.04 (d, 2H, J=7.0 Hz), 4.91 (d, 1H, J=12.4 Hz), 4.60 (t, 1H, J=11.1 Hz), 3.71 (t, 1H, J=9.8 Hz), 2.67–2.63 (m,1H), 2.48–2.37 (m, 2H), 2.31 (s, 3H), 2.08–2.05 (m, 1H), 1.78–1.51 (m, 4H), 1.27–1.18 (m,1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 212.0, 137.4, 134.6, 129.6, 128.0, 79.0, 52.5, 43.5, 42.7, 33.1, 28.5, 25.0, 21.0. Chiralpak AD-H column (hexane-IPA=96:4, flow rate=0.5 mL min^{-1}, λ=254 nm) T_R=27.64 min (minor, *syn*), 35.32 min (major, *syn*), 98% ee $[\alpha]_D^{24}$ −28.28 (*c* 1, $CHCl_3$).

*4.3.9. (S)-2-((R)-1-(2-Methylphenyl)-2-nitroethyl)-cyclohexanone (**5j**).* Prepared according to **TP 2** from the olefin **4j** (33 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 20 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 10/1) yielded **5j** as a colorless liquid (43 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.19–7.1 (m, 4H), 4.99 (dd, 1H, J=12.6, 4.4 Hz), 4.60 (dd, 1H, J=12.6, 10.2 Hz), 4.12 (dt, 1H, J=10.2, 4.4 Hz), 2.67–2.56 (m, 1H), 2.50–2.36 (m, 2H), 2.37 (s, 3H), 2.12–2.09 (m, 1H), 1.73–1.54 (m, 4H), 1.26–1.21 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 212.2, 137.4, 136.4, 131.0, 127.2, 126.7, 125.7, 78.7, 53.4, 42.9, 38.3, 32.9, 28.7, 25.3, 19.9. Chiralpak AS-H column (hexane-IPA=80:20, flow rate=0.5 mL min^{-1}, λ=254 nm): T_R=14.09 min (minor, *syn*), 18.82 min (major, *syn*), 95% ee $[\alpha]_D^{24}$ −32.21 (*c* 1.3, $CHCl_3$).

*4.3.10. (S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (**5k**).* Prepared according to **TP 2** from the olefin **4k** (36 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 24 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 10/1) yielded **5k** as a white solid (48 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.08 (d, 2H, J=8.6 Hz), 6.84 (d, 2H, J=8.6 Hz), 4.90 (dd, 1H, J=12.3, 4.5 Hz), 4.58 (dd, 1H, J=12.3, 9.9 Hz), 3.78 (s, 3H), 3.71 (dt, 1H, J=4.6, 9.8 Hz), 2.68–2.61 (m, 1H), 2.50–2.44 (m, 1H), 2.41–2.34 (m, 1H), 2.10–2.04 (m, 1H), 1.81–1.56 (m, 4H), 1.28–1.18 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 212.0, 159.0, 129.5, 129.2, 114.3, 79.1, 55.2, 52.7, 43.2, 42.7, 33.1, 28.5, 25.0. Chiralpak AD-H column (hexane-IPA=85:15, flow rate=1.0 mL min^{-1}, λ=254 nm): T_R=28.76 min (minor, *syn*), 37.67 min (major, *syn*), 95% ee $[\alpha]_D^{24}$ −18.25 (*c* 1, $CHCl_3$).

*4.3.11. (S)-2-((S)-1-(Furan-2-yl)-2-nitroethyl)-cyclohexanone (**5l**).* Prepared according to **TP 2** from the olefin **4l** (28 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 18 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 12/1) yielded **5l** as a white solid (48 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.32 (m, 1H), 6.26 (s, 1H), 6.16 (s, 1H), 4.79–4.62 (m, 2H), 3.96 (dt, J=4, 8.6 Hz, 1H), 2.73–2.70 (m, 1H), 2.45–2.32 (m, 2H), 2.14–2.04 (m, 1H), 1.81–1.60 (m, 4H), 1.28–1.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 210.8, 150.9, 142.2, 110.2, 108.9, 76.6, 51.0, 42.4, 37.5, 32.3, 28.1, 25.0. Chiralpak AD-H column (hexane-IPA=95:5, flow rate=0.5 mL min^{-1}, λ=254 nm): T_R=32.44 min (major, *syn*), 41.32 min (minor, *syn*), 90% ee $[\alpha]_D^{24}$ −12.36 (*c* 1, $CHCl_3$).

*4.3.12. (S)-2-((S)-1-(Thiophen-2-yl)-2-nitroethyl)cyclohexanone (**5m**).* Prepared according to **TP 2** from the olefin **4m** (31 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition: 10 °C for 17 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 12/1) yielded **5m** as a colorless solid (45 mg, 92%) (Table 3, entry 13). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.20 (d, 1H, J=4.9 Hz), 6.91 (dd, 1H, J=4.9, 3.5 Hz), 6.85 (d, 1H, J=3 Hz), 4.87 (dd, 1H, J=12.6, 4.7 Hz), 4.63 (dd, 1H, J=12.6, 9.5 Hz), 4.11 (dt, 1H, J=4.6, 9.6 Hz), 2.72–2.67 (m, 1H), 2.50–2.46 (m, 1H), 2.42–2.36 (m, 1H), 2.13–2.06 (m, 1H), 1.87–1.81 (m, 2H), 1.63–1.61 (m, 2H), 1.29–1.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 211.1, 140.5, 126.8, 126.5, 124.9, 79.1, 53.3, 42.5, 39.3, 32.7, 28.2, 25.3. Chiralpak AD-H column (hexane-IPA=95:5, flow rate=1.0 mL min^{-1}, λ=254 nm), T_R=19.88 min (minor, *syn*), 22.61 min (major, *syn*), 85% ee. Prepared according to **TP 1** from the olefin **4m** (31 mg, 0.2 mmol), cyclohexanone (**3a**) (98 mg, 5.0 equiv, 1.0 mmol), and organocatalyst **2b** (8.2 mg, 0.15 equiv, 0.03 mmol) [reaction condition: 10 °C for 17 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 12/1) yielded **5m** as a colorless solid (50 mg, 98%) (Table 3, entry 14). Chiralpak AD-H column (hexane-IPA=95:5, flow rate=1.0 mL min^{-1}, λ=254 nm): T_R=18.63 min (minor, *syn*), 21.11 min (major, *syn*), 90% ee $[\alpha]_D^{24}$ −34.21 (*c* 1.1, $CHCl_3$).

*4.3.13. (R)-2,2-Dimethyl-4-nitro-3-phenylbutanal (**9**).* Prepared according to **TP 2** from the olefin **4a** (30 mg, 0.2 mmol), 2-methylpropanal (**8**) (144 mg, 10.0 equiv, 2.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) on water (0.2 mL) [reaction condition A: 27 °C for 48 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 12/1) yielded **9** as a colorless liquid (30 mg, 67%) (Scheme 2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 9.53 (s, 1H), 7.35–7.29 (m, 3H), 7.21–7.18 (m, 2H), 4.85 (dd, J=13.0, 11.4 Hz, 1H), 4.69 (dd, J=13.0, 4.2 Hz, 1H), 3.78 (dd, J=11.2, 4.2 Hz, 1H), 1.13 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 204.2, 135.4, 129.0, 128.7, 128.1, 76.3, 48.5, 48.2, 21.7, 18.9. Chiralpak OD-H column (hexane-IPA=80:20, flow rate=0.8 mL min^{-1}, λ=254 nm): T_R=13.21 min (major), 18.12 min (minor): 48% ee.

Prepared according to **TP 1** from the olefin **4a** (30 mg, 0.2 mmol), 2-methylpropanal (**8**) (144 mg, 10.0 equiv, 2.0 mmol), and organocatalyst **2b** (8.2 mg, 15 mol %, 0.03 mmol) [reaction condition B: 27 °C for 48 h]. Purification by flash-chromatography (hexanes/ethyl acetate: 12/1) yielded **9** as a colorless liquid (35 mg, 78%). Chiralpak OD-H column (hexane-IPA=80:20, flow rate=0.8 mL min^{-1}, λ=254 nm): T_R=13.21 min (major), 18.12 min (minor): 55% ee $[\alpha]_D^{24}$ +6.52 (*c* 1, $CHCl_3$).

4.4. Typical procedure for addition of 3a to 4a catalyzed by 2b (TP 3 for Table 2)

To a solution of cyclohexanone (**3a**) (1.0 mmol, 5.0 equiv) in THF, CH_2Cl_2, toluene, MeOH, or Et_2O (1 M) was added the organocatalyst **1b** (15 mol %) at 27 °C. β-Nitrostyrene (**4a**) (0.2 mmol) was added, and the resulting mixture was stirred at 27 °C until the completion of the reaction monitored by TLC analysis. Purification by flash-chromatography furnished the desired product **5a**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2009.11.093.

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