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Highly enantioselective Michael addition of aldehydes to nitroolefins catalyzed by primary amine thiourea organocatalysts

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ABSTRACT

Asymmetric Michael addition reactions of aldehydes to nitroolefins have been successfully initiated by a series of primary amine thiourea bifunctional catalysts, with high enantioselectivities (90–98% ee) and excellent yields (80–96%). The privileged quinine scaffold was found to be essential to the reaction efficiency and enantioselectivity.

1. Introduction

During the past decade, there have been remarkable advances in the development of organocatalysts for enantioselective carbon-carbon bond-forming reactions,[1] particularly for asymmetric Michael addition reactions.[2] In this endeavor, the conjugate addition of ketones/aldehydes to nitroolefins has received extensive attention since the resulting γ-nitro carbonyl compounds are versatile synthetic building blocks, which can be readily converted into, for example, chiral pyrrolidines, γ-amino acids, γ-butyrolactones, and tetrahydropyrans.[3] Stimulated by the seminal reports of chiral amine-catalyzed asymmetric addition of ketones to nitroolefins by List, Barbas and co-workers,[4] several research groups focused on the development of more efficient primary[5] and secondary[6] amine-based catalysts with a critical objective for the improvement of both stereoselectivity and substrate scope. Although extensive studies on conjugate additions of ketones to nitroolefins have been well documented, the reactions with sterically demanding aldehydes, such as α,α-disubstituted aldehydes, have only been explored with very limited success.[5c,n,6q,r,7] Recently, the Jacobsen group successfully applied primary amine thiourea catalysts to Michael addition of racemic α,α-disubstituted aldehydes to β-substituted Michael acceptors, which provided an important design concept for new bifunctional organocatalysts.[7c,d] Despite these elegant works, the search for new organocatalysts that could achieve high reactivity and enantioselectivity for difficult substrates and transformations is still challenging and desirable.

One part of our research is focused on the development of bifunctional organocatalysts for asymmetric organic reactions by the rational combination of privileged chiral scaffolds,[8,9] and we have recently identified chiral amines **1a**,**b** and **2a**,**b** as efficient catalysts for direct aldol reactions of acetones and Michael additions of cyclohexanones, respectively (Fig. 1).[9] These organocatalysts, however, appeared unsuitable for the Michael addition of α,α-disubstituted aldehydes to nitroolefins. While the catalyst **2a** could, for example, promote the Michael addition of isobutyraldehyde [3] to *trans*-β-nitrostyrene **4a** in good yield and enantioselectivity, 4 days were required to reach the full conversion

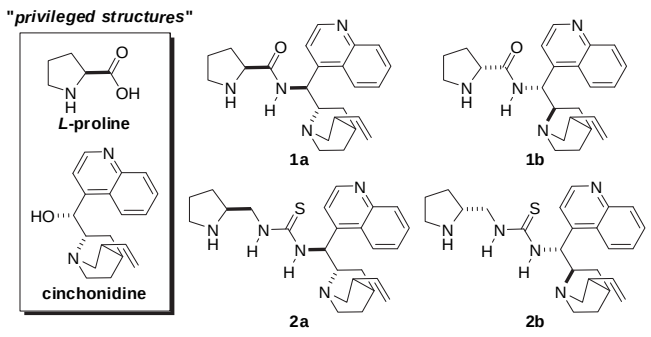

Figure 1. Chiral amine catalysts based on 'rational combination of two privileged chiral backbones into one'.

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(Eq. 1). Inspired by the recent successful use of chiral primary amine thioureas and related tertiary amine thioureas as bifunctional organocatalysts for a wide range of enantioselective reactions,[7c,d,9] we speculated that the strategy, combining two privileged scaffolds into one, may be additionally exploited to design a new class of thiourea/amine catalysts for this reaction. Our current study shows that such combinatorial design of catalyst does indeed work and a series of primary amine thioureas **6**–**9** have proved to be highly efficient and enantioselective for Michael addition of α,α-disubstituted aldehydes to a range of nitroolefins (Fig. 2).

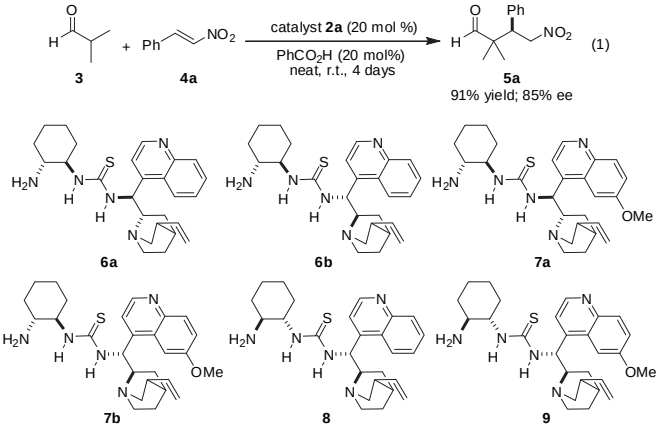
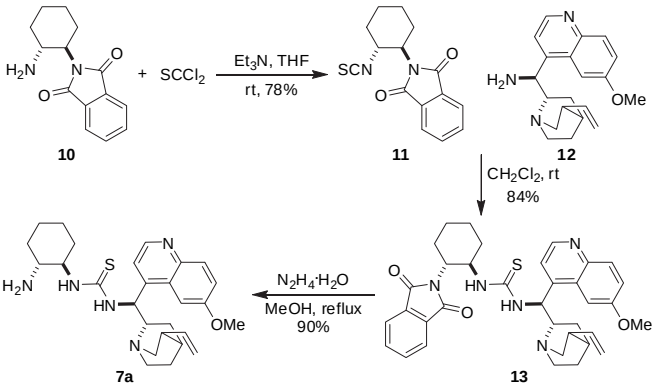


Figure 2. Primary amine thiourea organocatalysts examined.

2. Results and discussion

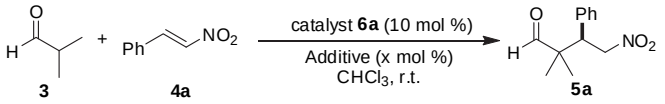
According to our previous method,[9b] organocatalyst **7a** was readily prepared from monoprotected chiral diamine **10** and quinine-derived amine **12** in three steps with good overall yields (Scheme 1).[10] Other primary amine thioureas were also synthesized via this three-step procedure without incident. Notably, the preparation of these catalysts can be easily scaled up on grams. Then, the catalytic performances were examined in the Michael addition reaction of isobutyraldehyde to nitroolefins.



Scheme 1. Synthesis of primary amine thiourea organocatalyst **7a**.

Initially, the Michael addition of isobutyraldehyde to *trans*-β-nitrostyrenes was chosen as the model reaction using **6a** as the catalyst and a variety of additives were examined. As shown in Table 1, additives played an important role on the reaction efficiency and enantioselectivity. For example, without any additive, the use of **6a** only gave a trace amount of the Michael adduct even after 10 days (Table 1, entry 1). With the addition of $PhCO_2H$ as the cocatalyst, moderate yield and ee were obtained albeit with long

Table 1
Effects of the additives on the asymmetric Michael addition of isobutyraldehyde **3** to *trans*-β-nitrostyrene **4a** catalyzed by **6a**[a]



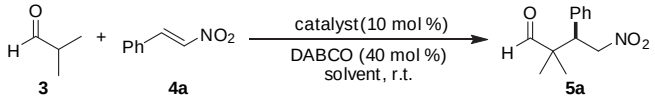
Entry	Additive	x	*T* (h)	Yield[b] (%)	ee[c] (%)
1	—	—	10 days	<10	ND
2	$PhCO_2H$	10	10 days	48	66
3	DIPEA	10	7	90	93
4	Et_3N	10	7	70	94
5	Pyridine	10	7	68	90
6	Imidazole	10	7	91	83
7[d]	TMG	10	5	78	92
8	DMAP	10	5	97	91
9	DABCO	10	5	91	93
10	DMAP	20	8	89	92
11	DMAP	30	8	82	94
12	DMAP	40	8	79	94
13	DABCO	20	8	91	95
14	DABCO	30	8	85	95
15	DABCO	40	8	90	96
16	DABCO	50	8	79	96
17	DABCO	100	8	75	95

[a] Reactions were carried out with isobutyraldehyde **3** (1.5 mmol), *trans*-β-nitrostyrene **4a** (0.5 mmol) and 10 mol % **6a** and x mol % additive in $CHCl_3$ (0.75 mL). ND=Not determined.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] TMG=1,1,3,3-Tetramethylguanidine.

reaction time (Table 1, entry 2). For Michael reactions with chiral amine catalysts, it was found that the nature of base cocatalyst strongly influenced both the reaction activity and the enantioselectivity.[7,5c] Accordingly, the use of different bases was probed. In all cases, the reactions proceeded smoothly in the presence of **6a** while the reactivity and enantioselectivity varied significantly with different bases, such as DIPEA, Et_3N, pyridine, imidazole, TMG, DMAP, and DABCO (Table 1, entries 3–9). For instance, under otherwise identical conditions, replacing $PhCO_2H$ with base DIPEA led to the full conversion of *trans*-β-nitrostyrene **4a** within 7 h and allowed the reaction to proceed at room temperature with 90% yield and 93% ee (Table 1, entry 3). Further investigation indicated that DABCO and DMAP were the best two base additives and therefore were used for other condition optimizations (Table 1, entries 8 and 9). Interestingly, when the ratio of DABCO and catalyst rose to 4:1, the highest reactivity and enantioselectivity could be obtained. Further increase of the amount of DABCO proved less effective. Therefore, an optimal of 4:1 ratio of DABCO/**6a** was used in our subsequent experiments (Table 1, entry 15).

Next, a brief survey of reaction media for this organocatalytic transformation was carried out by the combination of **6a** and DABCO. The yield and enantioselectivity/solvent profile showed that the $CHCl_3$ was the ideal reaction medium (Table 2, entries 1–9). Then, the catalytic performances of the other catalysts were evaluated in $CHCl_3$. It was found that catalysts **6b**–**9** catalyzed this Michael addition efficiently with variant yields and ee. For instance, by the use of **6b**, 80% yield and 96% ee were obtained while almost 2 days were required (Table 2, entry 10). Gratifyingly, we found that **7a** showed the superior ee over **6a** with shorter reaction time. The absolute configuration of the Michael adduct was determined by the chiral diamine backbone. As anticipated, the use of catalysts **8** and **9** (pseudoenantiomers of **6a** and **7a**, respectively), gave the corresponding products with opposite configuration with 80% and 86% ee (Table 2, entries 13 and 14). Interestingly, the addition of 5 equiv of H_2O has no detrimental effect on the enantioselectivity

Table 2
Screening of the solvents and catalysts **6**–**9**[a]



Entry	Cat.	Solvent	*T* (h)	Yield[b] (%)	ee[c] (%)
1	**6a**	$CHCl_3$	8	90	96
2	**6a**	CH_2Cl_2	9	88	95
3	**6a**	EtOAc	7	85	92
4	**6a**	Toluene	9	80	95
5	**6a**	Et_2O	9	82	92
6	**6a**	THF	24	72	90
7	**6a**	DMF	24	<5	ND
8	**6a**	CH_3CN	24	51	75
9	**6a**	MeOH	24	<5	ND
10	**6b**	$CHCl_3$	45	80	96
11	**7a**	$CHCl_3$	7	88	97
12	**7b**	$CHCl_3$	29	70	92
13	**8**	$CHCl_3$	45	77	−80
14	**9**	$CHCl_3$	45	89	−86
15[d]	**7a**	$CHCl_3$	15	81	97
16[e]	**7a**	$CHCl_3$	15	90	92

[a] Reactions were carried out with isobutyraldehyde **3** (1.5 mmol), *trans*-β-nitrostyrene **4a** (0.5 mmol) and 10 mol % catalyst and 40 mol % DABCO in solvent (0.75 mL). ND=Not determined.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] H_2O (5 equiv) was added.
[e] Compounds **7a** (5 mol %) and 20 mol % of DABCO were used.

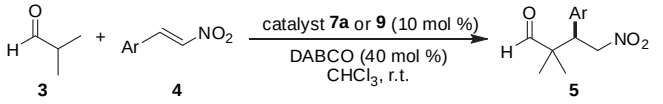
(Table 2, entry 15). And, the reaction still proceeded smoothly when the amount of **7a** was reduced from 10 mol % to 5 mol % giving **5a** in comparable yield but somewhat decreased ee (92%) (Table 2, entry 16 vs entry 11).

With reaction parameters being optimized to a **7a** and DABCO ratio of 1:4 in $CHCl_3$ at room temperature, we next investigated the scope of the Michael addition with a variety of nitroolefins. As highlighted in Table 3, the reaction demonstrated broad applicability with respect to the nitroolefins. A wide range of electron-poor and -rich aromatic nitroolefins with variable substitution patterns reacted well with isobutyraldehyde, affording the corresponding adducts in generally high yields (80–96%) and excellent enantioselectivities (90–98% ee) (Table 3, entries 1–14). Fused aromatic nitroolefins, such as **4n**, could also be successfully used in this reaction and high yield (84%) and excellent ee (95%) were obtained (Table 3, entry 15). Heteroaromatic nitroolefins, such as 2-furyl- and 2-thienyl-nitroolefins, were also well tolerated and gave the products in 97% and 95% ee, respectively (Table 3, entries 16 and 17). Significantly, the opposite enantiomeric Michael adducts can be obtained with comparable high ee when **9**/DABCO was used as the catalytic system under the same conditions (Table 3, entries 18–24). Therefore, our current protocol should be applicable to doubly stereo-controlled asymmetric Michael additions for the synthesis of both enantiomers.[11] However, primary amine thiourea **7a** proved unsuitable for the aliphatic nitroolefin at this stage probably because of the less reactivity.

In addition, we have preliminarily examined the feasibility of using other α,α-disubstituted aldehydes as Michael donors in the presence of **7a**. For example, in the case of 2-phenylpropionaldehydes, excellent diastereomeric ratio of *syn*/*anti* (97:3) was obtained while the ee of major *syn*-isomer was moderate (Eq. 2). Further structural modification of primary amine thiourea catalysts of this type to improve the enantioselectivity is underway in our laboratory.

Although the precise reaction mechanism needs further study, a possible transition state was proposed based on the observed

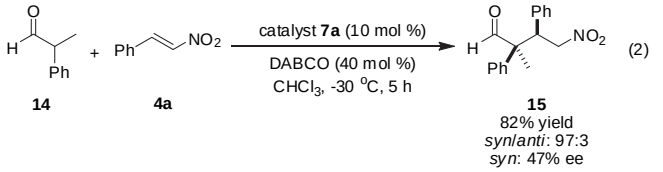
Table 3
Asymmetric Michael addition of isobutyraldehyde **3**–**4** catalyzed by catalyst **7a** and **9**[a]



Entry	Nitroolefin, Ar	Cat.	5	Yield[b] (%)	ee[c] (%)
1	Ph (**4a**)	**7a**	**5a**	88	97
2	4-NO_2–Ph (**4b**)	**7a**	**5b**	96	96
3	2-NO_2–Ph (**4c**)	**7a**	**5c**	93	92
4	4-F–Ph (**4d**)	**7a**	**5d**	87	95
5	4-Br–Ph (**4e**)	**7a**	**5e**	86	96
6	2-Br–Ph (**4f**)	**7a**	**5f**	91	95
7	4-Cl–Ph (**4g**)	**7a**	**5g**	80	95
8	4-Cl–Ph (**4g**)	**6b**	**5g**	85	98
9	2-Cl–Ph (**4h**)	**7a**	**5h**	86	95
10	4-CF_3–Ph (**4i**)	**7a**	**5i**	85	90
11	4-Me–Ph (**4j**)	**7a**	**5j**	91	96
12	4-MeO–Ph (**4k**)	**7a**	**5k**	95	96
13	2-MeO–Ph (**4l**)	**7a**	**5l**	93	94
14	3,4–$(MeO)_2$–Ph (**4m**)	**7a**	**5m**	93	96
15	1-Naphthyl (**4n**)	**7a**	**5n**	84	95
16	2-Furyl (**4o**)	**7a**	**5o**	95	97
17	2-Thienyl (**4p**)	**7a**	**5p**	92	95
18	4-F–Ph (**4d**)	**9**	**5d**	84	-91
19	4-Br–Ph (**4e**)	**9**	**5e**	85	-91
20	4-Me–Ph (**4j**)	**9**	**5j**	85	-95
21	4-MeO–Ph (**4k**)	**9**	**5k**	86	-93
22	2-MeO–Ph (**4l**)	**9**	**5l**	96	-93
23	2-Furyl (**4o**)	**9**	**5o**	85	−97
24	2-Thienyl (**4p**)	**9**	**5p**	88	−90

[a] Unless otherwise noted, the reactions were carried out with 0.5 mmol of **4**, 1.5 mmol of isobutyraldehyde **3** in 0.75 mL of $CHCl_3$ in the presence of 10 mol % of catalyst **7a** or **9** and 40 mol % of DABCO for the indicated time.
[b] Isolated yield.
[c] Determined by chiral HPLC.

stereoselectivities of asymmetric Michael addition of isobutyraldehyde to nitroolefins (Fig. 3). Mechanistically, the in situ formed enamine in-



termediate between isobutyraldehyde **3** and catalyst **7a** attacked the *Si*-face of nitroolefin **4a** to give the corresponding product (*R*)-**5a**. The beneficial role of the base DABCO may lie in accelerating the tautomerization of imine to the enamine by deprotonation.[7,5c]

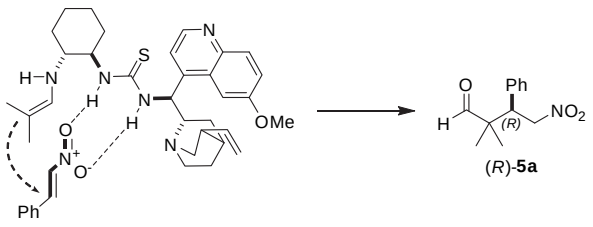


Figure 3. Proposed transition state.

3. Conclusion

In summary, we have developed a highly enantioselective Michael addition of isobutyraldehyde to nitroolefins by the use of

cinchona alkaloid-based bifunctional thiourea catalysts. For most nitroolefins, the designed catalysts exhibited great catalytic efficiency and enantioselectivity (up to 96% yield and 98% ee). Further modification of the catalyst structure for broader substrate scopes and investigation of the capacity of these catalysts toward other asymmetric conjugate addition reactions are in progress.

4. Experimental section

4.1. General methods

Unless otherwise noted, material were purchased from commercial suppliers and used without further purification. Chloroform and dichloromethane were freshly distilled from calcium hydride. Toluene, 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.

^{1}H NMR spectra were recorded on 400 MHz or 600 MHz spectrophotometers. Solvent for NMR is $CDCl_3$, unless the 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 heptalet at 77.0 ppm for $CDCl_3$. The ee values determination was carried out using chiral high-performance liquid chromatography (HPLC) with Daicel Chiracel OD-H and AS-H column and the dr values were determined by 400 MHz ^{1}H NMR.

4.2. General procedure for the michael addition reaction of butyraldehyde 3 to nitroolefin 4 (Table 3)

The organocatalyst **7a** (24.0 mg, 0.05 mmol), DABCO (23.0 mg, 0.20 mmol), and isobutyraldehyde **3** (139 μL, 1.5 mmol) were stirred in 0.75 mL of $CHCl_3$ for 10 min at room temperature. Nitroolefin **4** (0.5 mmol) was then added and the reaction mixture was stirred for 8–48 h. After the complete consumption of the nitroolefin (as monitored by TLC), the 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 adduct. Absolute configurations of the products were determined by comparison of HPLC data with known literatures. Compounds **5a**–**p** and **15** are known.[5]

*4.2.1. Catalyst **6a**.* ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.82–0.87 (m, 1H), 1.15–1.35 (m, 5H), 1.51–1.73 (m, 7H), 1.83–2.08 (m, 3H), 2.30 (s, 1H), 2.41 (br s, 1H), 2.67–2.84 (m, 1H), 3.08–3.31 (m, 3H), 3.45 (br s, 1H), 4.92–5.04 (m, 2H), 5.66–5.74 (m, 1H), 7.50 (d, J=4.4 Hz, 1H), 7.64–7.69 (m, 1H), 7.74 (t, J=7.2 Hz, 1H), 8.13 (d, J=8.4 Hz, 1H), 8.60 (d, J=6.8 Hz, 1H), 8.88 (d, J=4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 25.3, 26.9, 27.0, 28.9, 31.8, 34.5, 38.9, 40.9, 54.8, 55.3, 59.6, 60.5, 64.8, 76.6, 77.3, 114.5, 123.9, 126.5, 126.9, 128.9, 129.7, 129.9, 140.5, 148.1, 149.8, 181.9; MS (EI) m/z 449 (rel intensity) (M^+). Anal. Calcd for $C_{26}H_{35}N_5S$: C, 69.45; H, 7.85; N, 15.57. Found: C, 68.41; H, 7.89; N, 15.52.

*4.2.2. Catalyst **6b**.* ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.82–1.20 (m, 6H), 1.48–1.98 (m, 10H), 2.25–2.36 (m, 1H), 2.83–2.99 (m, 4H), 3.15 (br s, 1H), 5.12–5.15 (m, 2H), 5.81–5.90 (m, 1H), 7.43 (d, J=4.4 Hz, 1H), 7.65 (t, J=7.6 Hz, 1H), 7.75 (t, J=7.6 Hz, 1H), 8.13 (d, J=8.4 Hz, 1H), 8.45 (br s, 1H), 8.90 (d, J=4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 24.3, 24.6, 25.8, 27.1, 28.9, 31.7, 33.6, 38.8, 45.8, 47.2, 48.3, 55.2, 60.5, 77.2, 114.8, 119.6, 124.0, 126.5, 127.0, 129.0, 129.7, 139.6, 148.0, 149.9, 182.3; MS (EI) m/z 449 (rel intensity) (M^+); $C_{26}H_{35}N_5S$: C, 69.45; H, 7.85; N, 15.57. Found: C, 68.40; H, 7.81; N, 15.60.

*4.2.3. Catalyst **7a**.* ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.80–1.05 (m, 2H), 1.22–1.76 (m, 10H), 1.97–2.00 (m, 2H), 2.40–2.41 (m, 1H), 2.78–3.24 (m, 3H), 3.67–3.96 (m, 2H), 4.04 (s, 3H), 4.26 (br s, 1H), 5.01–5.08 (m, 2H), 5.70–5.78 (m, 1H), 5.92 (br s, 1H), 7.38 (dd, J=2.8, 9.6 Hz, 1H), 7.54 (s, 1H), 7.99 (d, J=9.2 Hz, 1H), 8.08 (br s, 1H), 8.76 (d, J=4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 24.5, 25.7, 26.7, 26.9, 32.1, 38.5, 41.7, 45.8, 54.7, 54.9, 55.8, 57.2, 59.6, 77.2, 102.6, 115.0, 119.3, 122.0, 128.1, 131.0, 139.9, 144.4, 147.5, 157.8, 181.5; MS (EI) m/z 479 (rel intensity) (M^+). Anal. Calcd for $C_{27}H_{37}N_5OS$: C, 67.61; H, 7.77; N, 14.60. Found: C, 67.59; H, 7.74; N, 14.65.

*4.2.4. Catalyst **7b**.* ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.89–1.98 (m, 6H), 1.47–1.80 (m, 8H), 2.17–2.36 (m, 4H), 2.86–3.01 (m, 3H), 3.20 (br s, 1H), 5.09–5.19 (m, 2H), 5.84–5.92 (m, 1H), 7.36–7.40 (m, 2H), 7.85 (br s, 1H), 8.01 (d, J=9.2 Hz, 1H), 8.73 (d, J=4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 24.8, 25.9, 27.0, 28.9, 31.5, 33.8, 38.7, 45.7, 46.9, 48.4, 55.4, 60.1, 64.5, 77.2, 102.0, 114.5, 119.4, 122.0, 128.1, 130.8, 139.9, 144.2, 147.2, 157.5, 182.0; MS (EI) m/z 479 (rel intensity) (M^+). Anal. Calcd for $C_{27}H_{37}N_5OS$: C, 67.61; H, 7.77; N, 14.60. Found: C, 67.65; H, 7.79; N, 14.57.

*4.2.5. Catalyst **8**.* ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.82–0.87 (m, 2H), 1.08–1.35 (m, 6H), 1.45–1.72 (m, 6H), 1.81–1.94 (m, 2H), 2.27–2.31 (m, 1H), 2.70–3.04 (m, 4H), 3.38 (s, 1H), 4.23 (br s, 3H), 5.15–5.22 (m, 2H), 5.82–5.90 (m, 1H), 7.54 (d, J=4.4 Hz, 1H), 7.65–7.75 (m, 3H), 8.10 (d, J=8.4 Hz, 1H), 8.60 (br s, 1H), 8.83 (d, J=4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 24.5, 24.8, 25.7, 26.9, 32.0, 34.5, 38.6, 45.7, 46.9, 48.3, 55.3, 60.1, 64.6, 77.2, 114.8, 119.3, 124.2, 126.5, 126.9, 129.0, 129.4, 139.4, 147.9, 149.7, 181.9; MS (EI) m/z 449 (rel intensity) (M^+). Anal. Calcd for $C_{26}H_{35}N_5S$: C, 69.45; H, 7.85; N, 15.57. Found: C, 69.49; H, 7.81; N, 15.61.

*4.2.6. Catalyst **9**.* ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.88–0.99 (m, 2H), 1.06–1.13 (m, 2H), 1.20–1.34 (m, 4H), 1.47–1.74 (m, 8H), 1.92–2.01 (m, 2H), 2.27–2.33 (m, 1H), 2.74–2.92 (m, 3H), 3.17 (s, 1H), 3.39 (br s, 1H), 4.03 (br s, 1H), 4.04 (s, 3H), 5.11–5.31 (m, 2H), 5.83–5.92 (m, 1H), 7.39 (dd, J=2.4, 9.2 Hz, 1H), 7.46 (d, J=4.4 Hz, 1H), 7.97 (d, J=9.2 Hz, 1H), 8.67 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 25.1, 25.2, 26.0, 26.8, 32.1, 34.4, 38.6, 45.9, 47.0, 48.4, 55.0, 55.5, 60.0, 77.2, 102.1, 114.6, 119.2, 122.1, 128.1, 130.9, 139.7, 144.2, 147.2, 157.6, 181.9; MS (EI) m/z 479 (rel intensity) (M^+). Anal. Calcd for $C_{27}H_{37}N_5OS$: C, 67.61; H, 7.77; N, 14.60. Found: C, 67.64; H, 7.74; N, 14.64.

*4.2.7. (R)-2,2-Dimethyl-4-nitro-3-phenylbutanal (**5a**), (Table 3, entry 1).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 80:20, flow rate 0.8 mL/min, λ=210 nm, 20 °C). t_R (major)=18.3 min; t_R (minor)=26.8 min, ee=97%. ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ 1.01 (s, 3H), 1.14 (s, 3H), 3.78 (dd, J=3.0, 10.8 Hz, 1H), 4.69 (dd, J=3.6, 13.2 Hz, 1H), 4.85 (t, J=12.6 Hz, 1H), 7.20 (d, J=7.2 Hz, 2H), 7.29–7.34 (m, 3H), 9.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 21.4, 48.1, 76.1, 127.9, 128.5, 128.9, 135.1, 204.2.

*4.2.8. (R)-2,2-Dimethyl-4-nitro-3-(4-nitrophenyl) butanal (**5b**), (Table 3, entry 2).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 65:35, flow rate 1.0 mL/min, λ=254 nm, 20 °C). t_R (major)=15.6 min; t_R (minor)=25.7 min, ee=96%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.04 (s, 3H), 1.17 (s, 3H), 3.96 (dd, J=3.6, 11.6 Hz, 1H), 4.79 (dd, J=4.0, 13.6 Hz, 1H), 4.95 (dd, J=11.6, 13.2 Hz, 1H), 7.46 (d, J=8.8 Hz, 2H), 8.21 (d, J=8.8 Hz, 2H), 9.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 21.7, 47.7, 48.0, 75.6, 123.6, 130.0, 143.3, 147.4, 203.1.

*4.2.9. (R)-2,2-Dimethyl-4-nitro-3-(2-nitrophenyl) butanal (**5c**), (Table 3, entry 3).* The ee was determined by HPLC (Chiralpak OD

column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, λ=254 nm, 20 °C). t_R (major)=10.4 min; t_R (minor)=30.5 min, ee=92%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.12 (s, 3H), 1.21 (s, 3H), 4.69 (dd, *J*=3.6, 11.6 Hz, 1H), 4.77 (dd, *J*=4.0, 14.0 Hz, 1H), 4.94 (dd, *J*=11.2, 13.6 Hz, 1H), 7.45–7.49 (m, 1H), 7.53 (dd, *J*=1.2, 8.0 Hz, 1H), 7.61–7.65 (m, 1H), 7.84 (dd, *J*=1.6, 8.4 Hz, 1H), 9.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 21.2, 40.3, 48.6, 76.2, 125.1, 128.7, 128.8, 130.9, 132.8, 151.2, 203.3.

*4.2.10. (R)-2,2-Dimethyl-4-nitro-3-(4-fluorophenyl) butanal (**5d**), (Table 3, entry 4).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 75:25, flow rate 0.8 mL/min, λ=210 nm, 20 °C). t_R (major)=12.6 min; t_R (minor)=23.3 min, ee=95%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.98 (s, 3H), 1.11 (s, 3H), 3.79 (dd, *J*=4.0, 11.6 Hz, 1H), 4.69 (dd, *J*=4.0, 12.8 Hz, 1H), 4.83 (dd, *J*=11.6, 13.2 Hz, 1H), 7.02 (t, *J*=8.8 Hz, 2H), 7.19 (dd, *J*=5.2, 8.4 Hz, 2H), 9.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 21.4, 47.4, 48.0, 76.1, 115.4, 115.6, 130.5, 130.6, 131.0, 131.1, 160.9, 163.4, 204.0.

*4.2.11. (R)-2,2-Dimethyl-4-nitro-3-(4-bromophenyl) butanal (**5e**), (Table 3, entry 5).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 75:25, flow rate 0.8 mL/min, λ=210 nm, 20 °C). t_R (major)=16.7 min; t_R (minor)=26.4 min, ee=96%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.99 (s, 3H), 1.11 (s, 3H), 3.76 (dd, *J*=4.4, 11.6 Hz, 1H), 4.69 (dd, *J*=4.0, 13.2 Hz, 1H), 4.82 (dd, *J*=11.6, 13.2 Hz, 1H), 7.09 (d, *J*=8.4 Hz, 2H), 7.46 (d, *J*=8.4 Hz, 2H), 9.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 21.6, 47.6, 48.0, 75.9, 122.1, 130.6, 131.7, 134.4, 203.7.

*4.2.12. (R)-2,2-Dimethyl-4-nitro-3-(2-bromophenyl) butanal (**5f**), (Table 3, entry 6).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 65:35, flow rate 1.0 mL/min, λ=210 nm, 20 °C). t_R (major)=9.9 min; t_R (minor)=27.1 min, ee=95%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.07 (s, 3H), 1.16 (s, 3H), 4.62 (dd, *J*=4.0, 11.2 Hz, 1H), 4.72 (dd, *J*=4.0, 13.6 Hz, 1H), 4.83 (dd, *J*=11.6, 13.2 Hz, 1H), 7.12–7.16 (m, 1H), 7.27–7.34 (m, 2H), 7.60 (d, *J*=8.0 Hz, 1H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 20.7, 44.9, 48.9, 76.2, 126.8, 127.7, 128.2, 129.3, 133.7, 135.3, 203.7.

*4.2.13. (R)-2,2-Dimethyl-4-nitro-3-(4-chlorophenyl) butanal (**5g**), (Table 3, entry 7).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 75:25, flow rate 0.8 mL/min, λ=210 nm, 20 °C). t_R (major)=14.7 min; t_R (minor)=24.9 min, ee=95%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.98 (s, 3H), 1.10 (s, 3H), 3.78 (dd, *J*=4.0, 11.6 Hz, 1H), 4.69 (dd, *J*=4.4, 13.2 Hz, 1H), 4.82 (dd, *J*=11.2, 12.8 Hz, 1H), 7.16 (d, *J*=8.4 Hz, 2H), 7.30 (d, *J*=8.4 Hz, 2H), 9.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 21.4, 47.5, 48.0, 75.9, 128.7, 130.2, 133.8, 133.9, 203.8.

*4.2.14. (R)-2,2-Dimethyl-4-nitro-3-(2-chlorophenyl) butanal (**5h**), (Table 3, entry 9).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 65:35, flow rate 1.0 mL/min, λ=210 nm, 20 °C). t_R (major)=9.0 min; t_R (minor)=24.6 min, ee=95%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.05 (s, 3H), 1.15 (s, 3H), 4.63 (dd, *J*=4.0, 11.6 Hz, 1H), 4.73 (dd, *J*=4.0, 13.2 Hz, 1H), 4.84 (t, *J*=11.6 Hz, 1H), 7.20–7.29 (m, 3H), 7.41 (dd, *J*=1.6, 8.0 Hz, 2H), 9.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 20.6, 42.1, 48.9, 76.0, 127.0, 128.1, 129.0, 130.2, 133.5, 135.6, 203.7.

*4.2.15. (R)-2,2-Dimethyl-4-nitro-3-(4-trifluoromethylphenyl) butanal (**5i**), (Table 3, entry 10).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 75:25, flow rate 0.8 mL/min, λ=210 nm, 20 °C). t_R (major)=12.3 min; t_R (minor)=21.8 min, ee=90%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.01 (s, 3H), 1.14 (s, 3H), 3.88 (dd, *J*=4.0, 11.6 Hz, 1H), 4.74 (dd, *J*=4.4, 13.2 Hz, 1H), 4.89 (dd, *J*=11.6, 13.6 Hz, 1H), 7.36 (d, *J*=8.0 Hz, 2H), 7.60 (d, *J*=8.4 Hz, 2H), 9.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 21.7, 48.0, 48.1, 75.8, 125.6, 129.5, 129.7, 130.1, 130.4, 139.7, 203.5.

*4.2.16. (R)-2,2-Dimethyl-4-nitro-3-(4-methylphenyl) butanal (**5j**), (Table 3, entry 11).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 75:25, flow rate 0.8 mL/min; λ=210 nm, 20 °C). t_R (major)=13.1 min; t_R (minor)=19.4 min, ee=96%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.97 (s, 3H), 1.10 (s, 3H), 2.30 (s, 3H), 3.74 (dd, *J*=4.0, 11.2 Hz, 1H), 4.66 (dd, *J*=4.4, 12.8 Hz, 1H), 4.82 (dd, *J*=11.6, 12.8 Hz, 1H), 7.07 (d, *J*=8.4 Hz, 2H), 7.12 (d, *J*=8.4 Hz, 2H), 9.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 20.8, 21.3, 47.8, 48.0, 76.2, 128.7, 129.2, 132.0, 137.6, 204.3.

*4.2.17. (R)-2,2-Dimethyl-4-nitro-3-(4-methoxylphenyl) butanal (**5k**), (Table 3, entry 12).* The ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 75:25, flow rate 1.0 mL/min, λ=210 nm, 20 °C). t_R (major)=12.7 min; t_R (minor)=20.4 min, ee=96%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.98 (s, 3H), 1.11 (s, 3H), 3.73 (dd, *J*=4.4, 11.6 Hz, 1H), 3.77 (s, 3H), 4.66 (dd, *J*=4.4, 12.8 Hz, 1H), 4.81 (dd, *J*=11.6, 12.8 Hz, 1H), 6.85 (d, *J*=8.8 Hz, 2H), 7.11 (d, *J*=8.4 Hz, 2H), 9.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 21.3, 47.5, 48.2, 55.0, 76.3, 113.9, 126.8, 129.9, 159.0, 204.4.

*4.2.18. (R)-2,2-Dimethyl-4-nitro-3-(2-methoxylphenyl) butanal (**5l**), (Table 3, entry 13).* The ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 75:25, flow rate 0.8 mL/min, λ=210 nm, 20 °C). t_R (major)=10.5 min; t_R (minor)=17.1 min, ee=94%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.03 (s, 3H), 1.08 (s, 3H), 3.79 (s, 3H), 4.22 (s, 1H), 4.72 (dd, *J*=4.4, 12.8 Hz, 1H), 4.90 (dd, *J*=10.8, 12.8 Hz, 1H), 6.87 (d, *J*=8.4 Hz, 1H), 6.92 (t, *J*=7.6 Hz, 1H), 7.12 (dd, *J*=1.6, 7.6 Hz, 1H), 7.23–7.27 (m, 1H), 9.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 20.7, 42.6, 48.2, 55.1, 75.6, 111.1, 120.5, 123.8, 129.1, 129.4, 157.1, 204.0.

*4.2.19. (R)-2,2-Dimethyl-4-nitro-3-(3,4-dimethoxylphenyl) butanal (**5m**), (Table 3, entry 14).* The ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 65:35, flow rate 1.0 mL/min, λ=210 nm, 20 °C). t_R (minor)=14.6 min; t_R (major)=17.9 min, ee=96%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.02 (s, 3H), 1.14 (s, 3H), 3.72 (dd, *J*=4.0, 11.6 Hz, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 4.67 (dd, *J*=4.0, 12.8 Hz, 1H), 4.83 (t, *J*=11.6 Hz, 1H), 6.68 (s, 1H), 6.75 (dd, *J*=2.0 Hz, 1H), 6.82 (d, *J*=8.4 Hz, 1H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 21.5, 48.1, 48.2, 55.7, 55.8, 76.4, 110.8, 112.2, 120.9, 127.4, 148.5, 148.6, 204.4.

*4.2.20. (R)- 2,2-Dimethyl-4-nitro-3-(2-naphthyl)butanal (**5n**), (Table 3, entry 15).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 65:35, flow rate 1.0 mL/min, λ=254 nm, 20 °C). t_R (major)=17.1 min; t_R (minor)=29.3 min, ee=95%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.90 (s, 3H), 1.15 (s, 3H), 4.83 (dd, *J*=12.4, 22.4 Hz, 1H), 4.94 (d, *J*=12.4 Hz, 1H), 4.99 (d, *J*=10.8 Hz, 1H), 7.39–7.58 (m, 4H), 7.78 (d, *J*=7.6 Hz, 1H), 7.84 (d, *J*=8.0 Hz, 1H), 8.22 (d, *J*=8.4 Hz, 1H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 21.5, 39.9, 48.9, 76.6, 122.9, 124.7, 124.8, 125.8, 126.6, 128.6, 128.9, 132.0, 132.7, 133.8, 204.4.

*4.2.21. (R)- 2,2-Dimethyl-4-nitro-3-(2-furyl)butanal (**5o**), (Table 3, entry 16).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 75:25, flow rate 0.8 mL/min, λ=210 nm, 20 °C). t_R (major)=10.3 min; t_R (minor)=17.2 min, ee=97%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.03 (s, 3H), 1.17 (s, 3H), 3.93 (dd, *J*=4.0, 11.2 Hz, 1H), 4.59 (dd, *J*=4.0, 12.8 Hz, 1H), 4.76 (dd, *J*=11.2, 12.8 Hz, 1H), 6.22 (d, *J*=3.2 Hz, 1H), 6.31 (dd, *J*=4.0, 5.2 Hz, 1H), 7.37 (d, *J*=1.6 Hz, 1H), 9.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 20.9, 42.0, 48.0, 74.7, 109.4, 110.2, 142.6, 149.6, 203.4.

*4.2.22. (R)-2,2-Dimethyl-4-nitro-3-(2-thienyl)butanal (**5p**), (Table 3, entry 17).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 75:25, flow rate 0.8 mL/min, λ=210 nm, 20 °C). t_R (major)=14.0 min; t_R (minor)=23.9 min, ee=95%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.07 (s, 3H), 1.20 (s, 3H), 4.14 (dd, *J*=4.0,

10.8 Hz, 1H), 4.66 (dd, *J*=4.0, 12.8 Hz, 1H), 4.73 (dd, *J*=10.8, 13.2 Hz, 1H), 6.92 (dd, *J*=1.2, 3.6 Hz, 1H), 6.96 (dd, *J*=3.6, 5.2 Hz, 1H), 7.24 (dd, *J*=1.2, 5.2 Hz, 1H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 21.4, 43.7, 48.2, 76.6, 125.4, 126.8, 127.7, 137.6, 203.6.

*4.2.23. (2S,3R)-2-Methyl-4-nitro-2,3-diphenylbutanal (**15**), (Eq. 2).* The ee was determined by HPLC (Chiralpak OD column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ=210 nm, 20 °C). t_R (minor)=22.0 min; t_R (major)=30.5 min, *syn*/*anti*=97:3, *syn*: ee=47%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.48 (s, 3H), 4.20 (dd, *J*=4.0, 11.6 Hz, 1H), 4.84 (dd, *J*=3.6, 12.8 Hz, 1H), 5.00 (dd, *J*=11.6, 13.2 Hz, 1H), 6.90–6.92 (m, 2H), 7.02–7.04 (m, 2H), 7.08–7.11 (m, 2H), 7.23–7.30 (m, 4H), 9.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 49.3, 56.4, 76.0, 127.1, 127.4, 127.9, 128.0, 128.1, 128.8, 129.5, 135.2, 136.9, 200.9.

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Supplementary data

Experimental details, characterization of all catalysts, NMR spectra, and HPLC spectra of Michael addition products. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.056. This data include MOL files and InChIKeys of the most important compounds described in this article.

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