Organocatalytic Enantioselective Michael Addition of Malononitrile to Nitroolefins Catalyzed by Bifunctional Thiourea

HAI-MING GUO,[1]* JIAN-GUO LI,[1] GUI-RONG QU,[1] XIAO-MEI ZHANG,[2] AND WEI-CHENG YUAN[2]

[1]*College of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions of Ministry of Education, Henan Normal University, Xinxiang, Henan, People's Republic of China*

[2]*Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province and Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, China*

ABSTRACT A novel enantioselective Michael addition of malononitrile to trans-β-nitroolefins in the presence of bifunctional amine thiourea organocatalyst is developed. The Michael reaction catalyzed by amine thioureas containing both central and axial chiral elements proceeded smoothly and provided the desired adducts with high yields (up to 96% yield) and moderate enantioselectivities (up to 83% enantiomeric excess). *Chirality 23:514–518, 2011.*

KEY WORDS: organocatalysis; Michael addition; malononitrile; nitroolefins; bifunctional thiourea

INTRODUCTION

Michael addition to electron-deficient nitroolefins is one of the important reactions in organic synthesis that provides access to useful functionalized nitroalkanes,[1,2] which are readily converted into other useful compounds such as nitrile oxide,[3,4] amine,[5–7] ketone,[8] carboxylic acid,[9] or other functionalized compounds.[10]

In the last few years, asymmetric organocatalysis has proved to be a practical and powerful tool for the stereoselective preparation of chiral molecules in the field of natural or biologically active compounds.[11–18] Recently, the development of organocatalytic asymmetric Michael addition reactions of nitroolefins has received growing attention.[1] Various organocatalysts activating the nucleophile or the electrophile via formation of covalent bonds or weaker interactions, such as ion pairing hydrogen bonding, have been reported.[11–18] Among them, the development of chiral bifunctional thioureas as powerful hydrogen-bond-donating organocatalysts has rapidly developed[19–21] since Jacobsen and coworkers[22–26] successfully developed an efficient chiral Schiff base-thiourea catalyzed asymmetric Strecker reaction. Takemoto and coworkers[27,28] reported the first example of a thiourea-organocatalyzed asymmetric Michael addition to nitroolefins by tertiary amine thiourea bifunctional catalyst. Primary amine thiourea catalyst developed by Jacobsen and coworkers[29] also demonstrated excellent catalytic activity in the asymmetric Michael addition of ketones to nitroolefins. Ma and coworkers[30,31] reported an efficient organocatalyst for the asymmetric addition of acetophenone to nitroolefins with saccharide-derived bifunctional thiourea. In addition, other type of thiourea catalysts such as cinchona alkaloid-based thioureas,[32–34] pyrrolidine-thioureas,[35,36] and 4-dimethylaminopyridine-thioureas[37] have been found to be useful for Michael addition reactions. Recently, the enantioselective addition reactions of aldehydes and ketones,[38–43] malonate esters,[44,45] β-keto esters,[46,47] and 1,3-diketone[48,49] to nitroolefins have been presented. Moreover, malononitrile and cyanoacetate have been used as Michael donors.[50–54] To the best of our knowledge, addition reactions of malononitrile to nitroolefins catalyzed by bifunctional thiourea have been rarely explored.

EXPERIMENTAL

Melting points are recorded with an XRC-1 micro-melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Brucker-400 and −300 instruments. Proton chemical shifts (δ) are given in ppm relative to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$ or to the residual proton signals of the deuterated solvent CD_3OD. Silica gel (200–300 mesh) (from Qingdao Haiyang Chemical Company) was used for column chromatography. All reactions were monitored by thin layer chromatography. Chiral high performance liquid chromatography (HPLC) analyses were carried out on a Hewlett Packard Series 1100 instrument. High resolution mass spectrometer (HRMS) were obtained in electron impact (EI) mode using a Bruker Esquire 3000 mass spectrometer. Elemental analyses were performed on an EA-1110 instrument. All regents and solvents were purchased from commercial sources and purified commonly before used by standard procedures as specified in Ref. 55.

Synthesis of Chiral Amine Thiourea Catalysts (1)

(*R*)-2,2′-Di(bromomethyl)-1,1′-binaphthyl and phthalic anhydride-monoprotected (1*S*,2*S*)-cyclohexyldiamine were prepared by modified literature procedure.[54,56]

To a solution of primary amine (392 mg, 1 mmol) in dry tetrahydrofuran (5 ml), a solution of 3,5-bis (trifluoromethyl)phenyl isothiocyanate (271 mg, 182 μl, 1 mmol) in dry tetrahydrofuran (5 ml) was added under nitrogen atmosphere. After the mixture was stirred for 12 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the bifunctional thiourea catalyst **1** (white solid, 591 mg, 81% yield).

Characterization of Bifunctional Thiourea Catalyst 1

Mp 149–151°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.58 (s, 2H), 7.49 (s, 1H), 7.45 (m, 4H),

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*Correspondence to: H.-M. Guo, College of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions of Ministry of Education, Henan Normal University, Xinxiang, Henan, People's Republic of China. Eail: ghm@henannu.edu.cn
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7.39 (d, J = 8.4 Hz, 2H), 7.27–7.25 (m, 2H), 6.72 (br s, 1H), 4.09 (br s, 1H), 3.78–3.72 (m, 2H), 3.62 (d, J = 12.3 Hz, 2H), 2.95 (t, J = 8.4 Hz, 1H), 1.87–1.80 (m, 1H), 1.75–1.71 (m, 3H), 1.37–1.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.8, 141.7, 134.0, 132.2, 130.3, 128.1, 127.4, 126.4, 126.2, 125.1, 124.8, 123.3, 120.6, 117.8, 68.5, 54.7, 32.2, 28.8, 27.1, 27.0, 24.4, 23.7.

General Procedure for Organocatalytic Micheal Addition Reaction

Malononitrile **2** (13.2 mg, 0.2 mmol) was added to a solution of catalyst **1** (6.6 mg, 0.01 mmol, 10 mol %), 4 Å molecular sieve (12–15 mg), and trans-β-nitrostyrene **3a** (14.9 mg, 0.1 mmol) in toluene (1 ml) at −10°C. After 8 h, the resulting mixture was diluted with chloroform (2 ml) and washed with water (10 ml). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvents gave the crude product, which was purified by column chromatography on silica gel (petro ether-ethyl acetate) to afford the desired product **4a** (15.05 mg, 70% yield).

Characterization of Micheal Addition Products

White solid; Mp 54–56°C; HPLC analysis: Daicel Chiralcel AD-H, *n*-Hexane-*i*-PrOH = 85:15, flow rate: 1.0 ml/min, 25°C, UV: λ = 254 nm, *t* (minor) = 11.3 min, *t* (major) = 13.3 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.47 (m, 3H), 7.37–7.35 (m, 2H), 4.95 (m, 2H), 4.44 (d, J = 6.0 Hz, 1H), 4.11–4.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.5, 130.1, 129.6, 127.4, 110.1, 110.0, 74.6, 43.4, 29.4; mass spectrometer (EI, 70 eV): *m/z* (%) = 214.6 (M^+); Anal. calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 60.89; H, 4.31; N, 19.22.

2-(2-Nitro-1-(4-nitrophenyl) ethyl) malononitrile (4b). Yellow solid; Mp 142–144°C; HPLC analysis: Daicel Chiralcel AD-H, *n*-Hexane-*i*-PrOH = 85:15, flow rate: 1.0 ml/min, 25°C, UV: λ = 254 nm, *t* (minor) = 28.1 min, *t* (major) = 34.1 min.

^{1}H NMR (400 MHz, CD_3OD): δ 8.33 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 5.20 (d, J = 7.2 Hz, 1H), 4.53 (d, J = 7.2 Hz, 1H), 3.61 (q, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 150.0, 142.4, 131.0, 125.3, 112.8, 112.6, 76.0, 44.0, 27.6; mass spectrometer (EI, 70 eV): *m/z* (%) = 259.6 (M^+); Anal. calcd for $C_{11}H_8N_4O_4$: C, 50.77; H, 3.10; N, 21.53. Found: C, 50.44; H, 3.22; N, 21.29.

2-(2-Nitro-1-(3-nitrophenyl) ethyl) malononitrile (4c). Light yellow solid; Mp 126–128°C; HPLC analysis: Daicel Chiralcel AD-H, *n*-Hexane-*i*-PrOH = 85:15, flow rate: 1.0 ml/min, 25°C, UV: λ = 254 nm, *t* (minor) = 21.5 min, *t* (major) = 23.2 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38(d, J = 6.8 Hz, 1H), 8.28 (s, 1H), 7.45 (d, J = 7.6 Hz, 2H), 5.02 (m, 2H), 4.51 (d, J = 6 Hz, 1H), 4.27 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 137.6, 135.7, 131.8, 125.5, 124.6, 112.8, 112.7, 76.1, 44.0, 28.1; mass spectrometer (EI, 70 eV): *m/z* (%) = 259.5 (M^+); Anal. calcd for $C_{11}H_8N_4O_4$: C, 50.77; H, 3.10; N, 21.53. Found: C, 50.48; H, 3.05; N, 20.41.

2-(1-(4-Chlorophenyl)-2-nitroethyl) malononitrile (4d). White solid; Mp 89–91°C; HPLC analysis: Daicel Chiralcel AD-H, *n*-Hexane-*i*-PrOH = 85:15, flow rate: 1.0 ml/min, 25°C, UV: λ = 254 nm, *t* (minor) = 12.8 min, *t* (major) = 16.3 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 4.94 (m, 2H), 4.43 (d, J = 6.0 Hz, 1H), 4.11–4.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 129.3, 128.2, 109.4, 109.3, 73.8, 42.2, 26.6.; mass spectrometer (EI, 70 eV): *m/z* (%) = 248.7 (M^+); Anal. calcd for $C_{11}H_8ClN_3O_2$: C, 52.92; H, 3.23; N, 16.83. Found: C, 52.53; H, 3.03; N, 16.24.

2-(1-(2-Chlorophenyl)-2-nitroethyl) malononitrile (4e). White solid; Mp 84–86°C; HPLC analysis: Daicel Chiralcel AD-H, *n*-Hexane-*i*-PrOH = 85:15, flow rate: 1.0 ml/min, 25°C, UV: λ = 254 nm, *t* (minor) = 12.5 min, *t* (major) = 17.2 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.556–7.53 (m, 1H), 7.44–7.40 (m, 3H), 5.01 (m, 2H), 4.78 (q, J = 6.8 Hz, 1H), 4.55 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.2, 130.5, 130.2, 128.6, 127.4, 126.8, 109.5, 109.2, 72.9, 38.9, 28.8; mass spectrometer (EI, 70 eV): *m/z* (%) = 248.5 (M^+); Anal. calcd for $C_{11}H_8ClN_3O_2$: C, 52.92; H, 3.23; N, 16.83. Found: C, 52.51; H, 3.43; N, 16.36.

2-(2-Nitro-1-p-tolylethyl) malononitrile (4f). White solid; Mp 99–101°C; HPLC analysis: Daicel Chiralcel AD-H, *n*-Hexane-*i*-PrOH = 85:15, flow rate: 1.0 ml/min, 25 °C, UV: λ = 254 nm, *t* (minor) = 10.7 min, *t* (major) = 13.0 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 728–7.22 (m, 4H), 4.93 (m, 2H), 4.42 (d, J = 6.0 Hz, 1H), 4.07–4.02 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 129.6, 127.8, 126.6, 109.7, 109.6, 74.1, 42.5, 26.8, 20.3; mass spectrometer (EI, 70 eV): *m/z* (%) = 228.7 (M^+); Anal. calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.77; H, 4.84; N, 17.59.

2-(1-(4-Methoxyphenyl)-2-nitroethyl) malononitrile (4g). White solid; Mp 83–85°C; HPLC analysis: Daicel Chiralcel AD-H, *n*-Hexane-*i*-PrOH = 85:15, flow rate: 1.0 ml/min, 25°C, UV: λ = 254 nm, *t* (minor) = 27.6 min, *t* (major) = 29.7 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.92 (m, 2H), 4.40 (d, J = 5.6 Hz, 1H), 4.07–4.02 (m, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 129.0, 123.4, 115.2, 110.6, 110.5, 75.1, 55.4, 43.1, 27.8; mass spectrometer (EI, 70 eV): *m/z* (%) = 244.4 (M^+); Anal. calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.87; H, 4.51; N, 16.17.

2-(1-(2-Methoxyphenyl)-2-nitroethyl) malononitrile (4h). White solid; Mp 90–92°C; HPLC analysis: Daicel Chiralcel AD-H, *n*-Hexane-*i*-PrOH = 85:15, flow rate: 1.0 ml/min, 25°C, UV: λ = 254 nm, *t* (minor) = 10.9 min, *t* (major) = 12.1 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.42 (m, 1H), 7.287–7.26 (m, 1H), 7.07–6.99 (m, 2H), 5.00 (m, 2H), 4.55 (d, J = 8.4 Hz, 1H), 4.45–4.41 (m, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 130.6, 128.7, 120.8, 118.9, 110.7, 110.0, 73.4, 54.8, 39.4, 24.4; mass spectrometer (EI, 70 eV): *m/z* (%) = 244.5 (M^+); Anal. calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.87; H, 4.39; N, 16.19.

2-(1-(4-(Dimethylamino) phenyl)-2-nitroethyl) malononitrile (4i). Yellow solid; Mp 84–86°C; HPLC analysis: Daicel Chiralcel AD-H, *n*-Hexane-*i*-PrOH = 85:15, flow rate: 1.0 ml/min, 25°C, UV: λ = 254 nm, *t* (major) = 17.5 min, *t* (minor) = 24.3 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.8 Hz, 1H), 7.47 (s, 1H), 7.18 (d, J = 8.8 Hz, 2H), 4.90 (m, 2H), 4.37 (d, J = 5.6 Hz, 1H), 4.01–3.96 (m, 1H), 2.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 150.4, 132.9, 117.1, 110.0, 109.9, 74.4, 57.6, 39.3, 27.1; mass spectrometer (EI, 70 eV): *m/z* (%) = 257.3 (M^+); Anal. calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 61.38; H, 5.41; N, 20.46.

2-(1-(Furan-2-yl)-2-nitroethyl) malononitrile (4j). Yellow oil; HPLC analysis: Daicel Chiralcel AD-H, *n*-Hexane-*i*-PrOH = 85:15, flow rate: 1.0 ml/min, 25°C, UV: λ = 254 nm, *t* (major) = 14.0 min, *t* (minor) = 16.0 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 6.54 (d, J = 3.2 Hz, 1H), 6.45 (d, J = 3.2 Hz, 1H), 4.93 (d, J = 6.4 Hz, 2H), 4.47 (d, J = 6.0 Hz, 1H), 4.32–4.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 144.5, 111.2, 111.0, 110.2, 110.0, 73.3, 38.2, 25.9; mass spectrometer (EI, 70 eV): *m/z* (%) = 204.7 (M^+); Anal. calcd for $C_9H_7N_3O_3$: C, 52.69; H, 3.44; N, 20.48. Found: C, 52.36; H, 3.46; N, 20.28.

2-(1-Cyclohexyl-2-nitroethyl) malononitrile (4k). Colorless liquid; HPLC analysis: Daicel Chiralcel AD-H, *n*-Hexane-*i*-PrOH = 85:15, flow rate: 1.0 ml/min, 25°C, UV: λ = 254 nm, *t* (major) = 11.7 min, *t* (minor) = 13.3 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63 (m, 2H), 4.26 (d, J = 5.2 Hz, 1H), 2.79–2.73 (m, 1H), 1.87–1.71 (m, 6H), 1.35–1.14 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.5, 110.4, 72.7, 42.3, 37.9, 29.9, 27.9, 25.1, 23.4; mass spectrometer (EI, 70 eV): *m/z* (%) = 220.6 (M^+); Anal. calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.35; H, 6.83; N, 18.36.

RESULTS AND DISCUSSION

The effect of solvents was initially studied for the organocatalytic Michael addition of malononitrile **2** and nitrostyrene **3a** using amine thiourea **1** as the catalyst (Fig. 1 and Table 1). It was found that the reaction performed best in toluene, providing high yield (83%) and moderate enantioselectivity (42%) within 3 h at room temperature (Table 1, entry 1). In other solvents, the adducts were obtained with lower enantioselectivities (Table 1, entries 2–6). However, the enantioselectivity could be increased from 42 to 58% by lowering the reaction temperature to 0°C (entry 7). If the temperature was further decreased, the reaction proceeded with lower enantioselectivity and reaction rate (entry 8).

It is interesting to note that the addition of different activated molecular sieves (MSs) gave different improvements in the enantiomeric excess (*ee*).[57–60] Addition of 5 Å MS did not improve the enantioselectivity (Table 1, entry 11), and 3 Å MS gave the product **4a** with 65% *ee* (Table 1, entry 9). However, the use of 4 Å MS gave the product **4a** with 68% *ee* (Table 1, entry 10). Thus, 4 Å MS was used at −10°C to promote the reaction.

To evaluate the generality of the reaction, a wide range of nitroalkenes bearing electron-donating, electron-withdrawing, electron-neutral, heteroaromatic, or alkyl groups were investigated (Table 2). The substituent at different position of the aromatic ring of nitrostyrenes exhibited a strong impact on the enantioselectivity. For example, the use of 4-NO_2-trans-β-nitrostyrene led to a higher enantioselectivity (Table 2, entry 2) when compared with 3-NO_2-trans-β-nitrostyrene (Table 2, entry 3). Moreover, steric hindrance on ortho-methoxy substrate **3h** provided a high yield (96%) and good enantioselectivity (80% *ee*). Likewise, the employment of ortho-chloro substituent **3e** obtained moderate enantioselectivity (Table 2, entry 5). However, para-chloro substituent **3d** as electron-withdrawing groups resulted in a marked loss of enantioselectivity (Table 2, entry 4). As for other nitroolefin substrates, the introduction of either an electron-donating or electron-neutral aryl group at the para-position of aromatic ring or heterocyclic group favored the reaction. The corresponding conjugate addition products were obtained with moderate enantioselectivities (Table 2, entries 6, 7, and 10). In addition, the substrate of cyclohexyl **3k** also afforded the product with an alkyl nitroolefin with high enantioselectivity (Table 2, entry 11). Although the enantioselectivity of some products is not so high, this is the first example of enantioselective Michael addition of malononitrile to nitroolefins.

CONCLUSION

In summary, we have presented the first addition reaction of malononitrile to nitroolefins catalyzed by amine thiourea organocatalyst with high yields and moderate to high enantioselectivities. Moreover, 4 Å MS was found to have positive effects on the reaction. Modification of these organocatalysts and their use in other asymmetric reactions is underway in our laboratory.

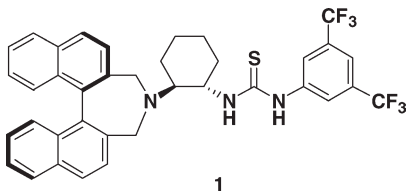
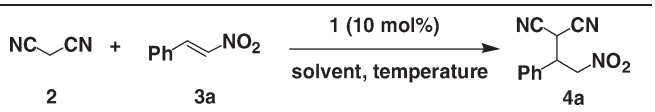


Fig. 1. Bifunctional amine thiourea catalyst **1**.

TABLE 1. Screening of different reaction solvents and temperatures for the addition of malononitrile 2 to nitrostyrene 3a using catalyst 1[a]

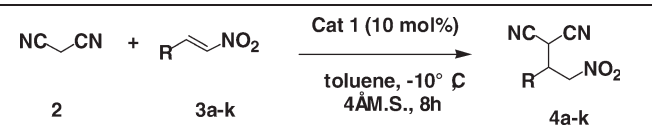


2 3a 4a

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	Toluene	25	3	83	42
2	CH_2Cl_2	25	3	80	29
3	Xylene	25	3	77	41
4	Mesitylene	25	3	80	42
5	Et_2O	25	3	74	17
6	THF	25	3	72	28
7	Toluene	0	6	73	58
8	Toluene	−10	8	71	54
9[d]	Toluene	−10	8	80	65
10[e]	Toluene	−10	8	70	68
11[f]	Toluene	−10	8	71	55

[a]Experimental conditions (unless stated otherwise): a mixture of **2** (0.2 mmol), **3a** (0.1 mmol), and catalyst **1** (10 mol %) in solvent (1 ml) was performed at room temperature.
[b]Isolated yields.
[c]Determined by chiral HPLC analysis.
[d]3 Å molecular sieve was used.
[e]4 Å molecular sieve was used.
[f]5 Å molecular sieve was used.

TABLE 2. Organocatalytic enantioselective addition of malononitrile to various nitroolefins catalyzed by amine thioureas[a]



2 3a-k 4a-k

Entry	R	Yield (%)[b]	*ee* (%)[c]
1	Ph (**3a**)	70	68
2	4-NO_2-C_6H_4 (**3b**)	77	83
3	3-NO_2-C_6H_4 (**3c**)	57	47
4	4-Cl-C_6H_4 (**3d**)	67	43
5	2-Cl-C_6H_4 (**3e**)	94	64
6	4-CH_3-C_6H_4 (**3f**)	87	66
7	4-CH_3O-C_6H_4 (**3g**)	90	50
8	2-CH_3O-C_6H_4 (**3h**)	96	80
9	4-N$(CH_3)_2$-C_6H_4 (**3i**)	85	43
10	Furyl (**3j**)	59	62
11[d]	Cyclohexyl (**3k**)	93	82

[a]Experimental conditions (unless stated otherwise): a mixture of **2** (0.2 mmol), **3a** (0.1 mmol), 4 Å molecular sieve (MS) (12 mg), and catalyst **1** (10 mol %) in toluene (1 ml) was performed.
[b]Isolated yields.
[c]Determined by chiral HPLC analysis.
[d]The reaction mixture was consumed completely for 44 h.

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