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Novel ferrocene-based bifunctional amine–thioureas for asymmetric Michael addition of acetylacetone to nitroolefins

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An efficient method was developed to synthesize ferrocene-based bifunctional amine–thioureas bearing multiple hydrogen-bonding donors. Asymmetric Michael addition of acetylacetone to nitroolefins catalyzed by these novel bifunctional catalysts affords the Michael adducts in high yield and moderate to excellent enantioselectivities. Multiple hydrogen-bonds play an important role in accelerating the reaction.

Introduction

Since the pioneering work of Jacobsen,[1] Schreiner[2] and Takemoto,[3] bifunctional amine–thiourea, which incorporates both Lewis/Brøsted acid and base functionalities into a chiral scaffold within the same molecule, has become one of the most versatile catalysts and been successfully used in numerous enantioselective reactions.[4,5] The key to the success of these catalysts is their ability to activate both nucleophilic and electrophilic substrates independently and simultaneously by the discrete functionalities, amine and thiourea, within the same catalyst, and to control their encounter in a well-defined chiral environment.

Ferrocene is a "privileged framework" for the construction of effective chiral ligands in metal catalysis due to its specific and unique geometries (adequate rigidity, steric bulkiness and planar chirality), electronic (redox) properties, easy accessibility and derivatization, as well as stability.[6] Surprisingly, ferrocene-based organocatalysts are rare[7,8] except for the use of the planar chiral DMAP[9] and some chiral ferrocene-based phosphines as nucleophilic organocatalysts.[10] Recently, we reported the first ferrocene-based bifunctional amine–thiourea (R_C,S_{Fc})-**1** (Fig. 1)[11] and demonstrated that, in accord with metal catalysis, ferrocene could be an excellent scaffold for chiral organocatalysts. (R_C,S_{Fc})-**1** is highly enantioselective in the Michael addition of acetylacetone to nitroolefins, giving the enantioselectivity of up to 96% ee, but the catalytic activity is somewhat low.

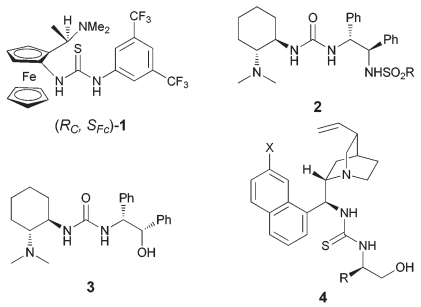

Fig. 1 The structures of chiral amine–thioureas in the literature.

In 2008, Wang elaborately designed the amine–thioureas **2** and **3** with multiple hydrogen-bonding donors (Fig. 1)[12] and proved that multiple hydrogen-bonding donors play a key role in accelerating reactions, improving yields and enantioselectivities. Since then, many amine–thioureas bearing multiple hydrogen bonding donors have been developed and proven to be powerful catalysts for a wide range of asymmetric transformations.[13] Previously, we developed a series of cinchona alkaloid-based bifunctional tertiary amine–thioureas **4** bearing multiple hydrogen-bonding donors (Fig. 1) for highly enantioselective aza-Henry reactions, Michael additions of acetylacetone and acetone to nitroolefins and diethyl malonate to chalcones.[14] In order to improve the catalytic activity, we designed ferrocene-based bifunctional amine–thioureas **5** which bear multiple hydrogen-bonding donors (Fig. 2). We envisioned that, similar to the bifunctional amine–thioureas based on other backbones, multiple hydrogen-bonding donors in the ferrocene-based bifunctional amine–thioureas could also facilitate formation of more hydrogen bonds and thereby might enhance their catalytic activity.

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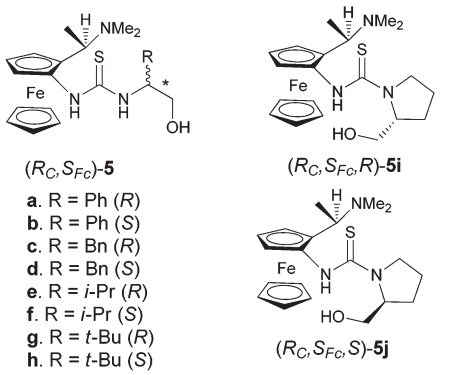
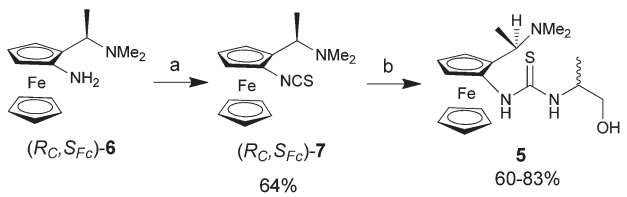


Fig. 2 Ferrocene-based bifunctional amine–thioureas.

Results and discussion

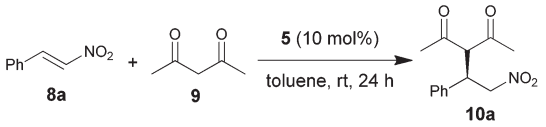
The ferrocene-based bifunctional amine–thioureas **5** are readily synthesized from diamine (R_C,S_{Fc})-**6**[11] (Scheme 1). Thus, reaction of (R_C,S_{Fc})-**6** with CS_2 and DCC gave isothiocyanate (R_C,S_{Fc})-**7** in 64% yield. (R_C,S_{Fc})-**7** was then treated with a chiral β-amino alcohol to afford the corresponding amine–thioureas **5** in 60–83% yields.

Initially, the performance of **5** was evaluated in the model Michael addition of *trans*-β-nitrostyrene **8a** with acetylacetone **9** in the presence of 10 mol% of catalyst at room temperature, and the results are summarized in Table 1. Indeed, introduction of the multiple hydrogen bonding donors in the ferrocene-based bifunctional amine–thioureas significantly enhanced the catalytic activity. The Michael addition of **8a** with **9** was almost complete after 24 h at room temperature using 10 mol% of catalyst **5** (Table 1, entries 1–10), while the prototype catalyst (R_C,S_{Fc})-**1** only gave 33% yield under the same conditions. The configurations of the ferrocenyl moiety in the catalysts play the decisive role in the Michael addition, giving (*R*)-**10a** with (R_C,S_{Fc})-catalysts (entries 1–10). It was shown that all the catalysts have good activity. While the configurations of the ferrocene scaffold are the main governing factors, the configuration of the β-amino alcohol moiety is also important. (R_C,S_{Fc},*R*)-**5(a,c,e,g)** are the catalysts with the matched configurations and (R_C,S_{Fc},*S*)-**5(b,d,f,h)** are the unmatched (entries 1–8). Surprisingly, (R_C,S_{Fc},*S*)-**5j**, derived from (*S*)-prolinol, is the most enantioselective catalyst so far



Scheme 1 Synthesis of ferrocene-based bifunctional amine–thioureas. Reagents and conditions: (a) CS_2, DCC, THF, 0–15 °C, 3 h; then rt, 16 h; (b) β-amino alcohol, THF, rt, 2–4 h.

Table 1 Asymmetric Michael addition of acetylacetone to *trans*-β-nitrostyrene **5**[a]



Entry	Catalyst	Yield[b] (%)	ee[c,d] (%)
1	**5a**	93	41
2	**5b**	87	5
3	**5c**	88	27
4	**5d**	90	3
5	**5e**	82	25
6	**5f**	62	4
7	**5g**	87	28
8	**5h**	81	7
9	**5i**	87	30
10	**5j**	90	80
11	(R_C,S_{Fc})-**1**	33	80

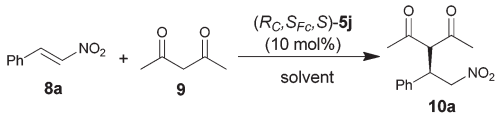
[a] Unless otherwise specified, the reactions were performed with 0.1 mmol of **8a** and 0.2 mmol of **9** in 1.0 mL of toluene for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Absolute configuration was assigned by comparing the optical rotation value with that reported in the literature.

prepared (entries 9 and 10). The results strongly suggest that the determining factors of the catalyst may be the specific combination of prolinol and ferrocene frameworks as well as the matched configurations of prolinol and ferrocene moieties, which make the dimethylamino group and hydrogen-bonding donors (CSNH and OH) in a suitable orientation, although the multiple hydrogen-bonding donors indeed play a key role in accelerating the reaction.

After screening of catalysts, we proceeded to investigate the influence of different experimental parameters, temperature and solvent, in the asymmetric Michael addition reaction using the most effective catalyst (R_C,S_{Fc},*S*)-**5j** and the results are summarized in Table 2. The choice of solvents plays a critical role in the reaction. Reactions in polar solvents afforded the desired Michael adduct (*R*)-**10a** with excellent yields (86–96%) and moderate enantioselectivities (34–67% ee) (Table 2, entries 1–4). Interestingly, more polar solvents, such as CH_3CN and MeOH, increased remarkably the catalytic activity, but gave racemate (entries 5 and 6). Like most Michael additions of acetylacetone to β-nitrostyrene catalyzed by bifunctional amine–thioureas,[11,15] toluene is the best solvent in the reaction (entry 9). Notably, nonpolar cyclohexane improved significantly the activity but decreased the enantioselectivity (entry 7). Lowering the reaction temperature from 25 °C to 0 °C slightly improved the enantioselectivity, and further reducing the temperature was not beneficial for the enantioselectivity (entries 9–13).

With the establishment of a set of acceptable reaction conditions: **9** (0.20 mmol, 2.0 equiv.) and **8a** (0.10 mmol, 1.0 equiv.) in 1.0 mL of toluene with 10 mol% of (R_C,S_{Fc},*S*)-**5j** at 0 °C for 24 h (Table 2, entry 11), the scope of substrates was

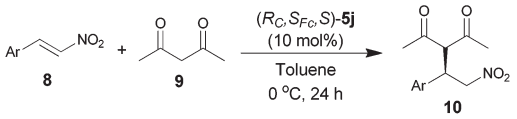
Table 2 Optimization of the reaction conditions for the asymmetric Michael addition of acetylacetone to *trans*-β-nitrostyrene catalyzed by amine–thiourea (R_C,S_{Fc},*S*)-**5j**.[a]



Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	TBME	25	36	96	45
2	THF	25	36	91	59
3	Et_2O	25	16	89	67
4	CH_2Cl_2	25	16	86	34
5	MeOH	25	3	92	0
6	CH_3CN	25	3	93	0
7	Cyclohexane	25	3	87	36
8	Xylene	25	16	76	76
9	Toluene	25	16	89	82
10	Toluene	10	16	90	83
11	Toluene	0	24	92	86
12	Toluene	−10	48	88	85
13	Toluene	−40	60	82	86

[a] The reactions were performed with 0.1 mmol of **8a** and 0.2 mmol of **9** in 1.0 mL of solvent. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Table 3 Asymmetric Michael addition of acetylacetone to *trans*-β-nitrostyrenes catalyzed by amine–thiourea (R_C,S_{Fc},*S*)-**5j**.[a]



Entry	Ar	Product	Yield[b] (%)	ee[c,d] (%)
1	C_6H_5 (**8a**)	**10a**	91	86
2	2-Cl-C_6H_4 (**8b**)	**10b**	89	96
3	2-Br-C_6H_4 (**8c**)	**10c**	93	92
4	2-F-C_6H_4 (**8d**)	**10d**	97	88
5	2,4-Cl_2-C_6H_3 (**8e**)	**10e**	96	93
6	2-MeO-C_6H_4 (**8f**)	**10f**	94	92
7	3-NO_2-C_6H_4 (**8g**)	**10g**	96	94
8	3-Cl-C_6H_4 (**8h**)	**10h**	90	86
9	3-Br-C_6H_4 (**8i**)	**10i**	96	68
10	3-MeO-C_6H_4 (**8j**)	**10j**	95	82
11	4-Cl-C_6H_4 (**8k**)	**10k**	85	74
12	4-Br-C_6H_4 (**8l**)	**10l**	92	80
13	4-F-C_6H_4 (**8m**)	**10m**	97	71
14	4-Me-C_6H_4 (**8n**)	**10n**	91	67
15	4-MeO-C_6H_4 (**8o**)	**10o**	93	77
16	2-Furyl (**8p**)	**10p**	98	86
17	2-Thiophyl (**8q**)	**10q**	98	78
18[e]	2-Cl-C_6H_4 (**8b**)	**10b**	79	96
19[e]	2-Br-C_6H_4 (**8c**)	**10c**	88	91
20[e]	2,4-Cl_2-C_6H_3 (**8e**)	**10e**	90	91

[a] Unless otherwise specified, the reactions conditions: **9** (0.20 mmol, 2.0 equiv.) and **8** (0.10 mmol, 1.0 equiv.) in 1.0 mL of toluene with 10 mol % of (R_C,S_{Fc},*S*)-**5j** at 0 °C for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Absolute configuration was assigned by comparing the optical rotation value with those reported in the literature. [e] Reacted using 5 mol% of (R_C,S_{Fc},*S*)-**5j** at 0 °C for 40 h.

explored. As shown in Table 3, all the *trans*-β-nitrostyrenes bearing either the electron-donating or the electron-withdrawing substituents on the aromatic ring gave the desired Michael adducts in good to excellent yields and enantioselectivities. Normally, higher enantioselectivities were obtained with the *trans*-β-nitrostyrenes having a substituent in the 2-position of the phenylring (Table 3, entries 2–6), and the 2-chloro derivative gave the highest enantioselectivity (97% ee, entry 2). Importantly, lowering of the catalyst loading to 5 mol%, the enantioselectivities (entries 18–20) were still excellent and remained almost untouched.

Conclusions

In summary, a series of ferrocene-based bifunctional amine–thioureas bearing multiple hydrogen-bonding donors were synthesized starting from the ferrocene-based isothiocyanate. Incorporation of the multiple hydrogen-bonding donors into the ferrocene amine indeed significantly enhanced the activity of the Michael addition reactions between acetylacetone with *trans*-β-nitrostyrenes. The spatial arrangement of β-amino alcohol moieties has significant influence on the enantioselectivity. The determined factors of the catalyst may be the specific combination of prolinol and ferrocene frameworks as well as the matched configurations of prolinol and ferrocene moieties, which make the dimethylamino group and hydrogen-bonding donors (CSNH and OH) in a suitable orientation. Further work in our lab is ongoing to disclose the structure–reactivity–enantioselectivity relationship in order to develop more efficient organocatalysts based on ferrocene templates.

Experimental

General methods

All the reactions were carried out in oven dried reaction flasks under an argon atmosphere and also the solvents and reagents were transferred using oven-dried syringes at ambient temperature. TLC was performed on Merck silica gel aluminum sheets using UV as a visualizing agent. The solvents were removed under reduced pressure. The columns were packed as slurry of silica gel in hexane and ethyl acetate solvent mixture. ^{1}H NMR and ^{13}C NMR spectra were recorded on an Avance (400 MHz or 600 MHz) spectrometer. The following abbreviations were used to explain multiplicities: s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet). The enantiomeric excess (ee) values of chiral adducts were recorded by using a high performance liquid chromatography (HPLC) system using a chiralcel AD-H column (0.46 cm Ø × 10 cm). Mass spectra were noted by electrospray ionization mass spectrometry (ESI-MS). All reactions were performed under an argon atmosphere with freshly distilled and dried solvents and the solvents were distilled using the standard procedures. Unless otherwise noted, the reagents were obtained from Aldrich, Alfa Aesar, and TCI, and used without further purification.

General procedure for the synthesis of (R_C,S_{Fc})-7

In a 25 mL round-bottomed flask, compound (R_C,S_{Fc})-**6** 272 mg (1 mmol) was taken and then dissolved in freshly distilled anhydrous THF (1.5 mL). The mixture was cooled to −10 °C, and CS_2 (363 μl, 6 mmol) and DCC (194 mg, 1 mmol mL^{-1} in THF) were slowly added. The mixture was slowly warmed to the room temperature within 2–3 h and stirred overnight at room temperature. After completion of the reaction, the reaction mixture was concentrated under vacuum and the residue was purified by column chromatography on silica gel (300–400 mesh, PE–EA–Et_3N = 1 : 1 : 0.05) to give a yellow solid (R_C,S_{Fc})-**7** 200 mg, yield 64%; mp: 74.9–75.6 °C; $[\alpha]_D^{25}$ = −166 (c = 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.45 (s, 1H), 4.24 (s, 5H), 4.08 (s, 2H), 3.80 (q, J = 6.8 Hz, 1H), 2.12 (s, 6H), 1.52 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 133.04, 85.32, 84.80, 70.57, 65.52, 65.17, 64.52, 55.77, 40.79, 15.90 ppm.

General procedure for syntheses of compounds 5a–5j

The β-amino alcohol (0.23 mmol) was dissolved in 1 mL of THF. The mixture was cooled to 0 °C, and (R_C,S_{Fc})-**7** (72 mg, 0.23 mmol, in THF 0.12 mmol mL^{-1}) was slowly added. The mixture was slowly warmed to the room temperature with stirring within 2–3 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under vacuum and the residue was purified by column chromatography on silica gel (300–400 mesh, PE–EA–Et_3N = 2 : 1: 0.05 to PE–EA–Et_3N = 1 : 3 : 0.05) to give the catalysts **5a–5h**.

Catalyst 5a. Yellow solid; yield 83%; mp: 136.8–137.9 °C; $[\alpha]_D^{25}$ = −342 (c = 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 7.91 (s, 1H), 7.43 (d, J = 7.7 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.29 (m, 1H), 5.80 (s, 1H), 4.26 (s, 1H), 4.19–4.14 (m, 2H), 4.14–4.11 (m, 1H), 4.11–3.81 (m, 8H), 2.13 (s, 6H), 1.25 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ: 180.63, 138.81, 128.93, 127.98, 127.18, 92.94, 85.07, 69.85, 65.74, 64.64, 64.12, 60.17, 59.29, 56.93, 39.16, 7.42 ppm; ESI-MS: Calcd for $C_{23}H_{29}FeN_3OS$ $(M + H)^+$ 452.1459; found 452.1469.

Catalyst 5b. Yellow solid; yield 81%; mp: 137.1–137.9 °C; $[\alpha]_D^{25}$ = −530 (c = 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.81 (s, 1H), 8.05 (s, 1H), 7.43 (m, 4H), 7.34 (m, 1H), 5.91 (s, 1H), 4.23 (m, 6H), 4.18 (m, 2H), 4.11–4.05 (m, 3H), 3.99 (m, 1H), 2.07 (s, 6H), 1.23 (d, J = 6.0 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ: 179.88, 138.70, 128.99, 127.90, 127.03, 93.80, 84.37, 69.88, 66.12, 64.40, 63.79, 60.35, 57.42, 39.45, 38.66, 6.98 ppm; ESI-MS: Calcd for $C_{23}H_{29}FeN_3OS$ $(M + H)^+$ 452.1459; found 452.1457.

Catalyst 5c. Yellow solid; yield 80%; mp: 147.0–147.5 °C; $[\alpha]_D^{25}$ = −346 (c = 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.30 (s, 1H), 7.80 (d, J = 6.2 Hz, 1H), 7.28–7.24 (m, 5H), 4.79 (s, 1H), 4.17 (m, 6H), 4.15 (m, 1H), 4.02–3.98 (m, 2H), 3.79 (dd, J = 10.8, 3.3 Hz, 1H), 3.63 (dd, J = 10.8, 3.8 Hz, 1H), 3.06 (dd, J = 13.3, 5.9 Hz, 1H), 2.93 (dd, J = 13.3, 9.0 Hz, 1H), 2.13 (s, 6H), 1.25 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ: 180.23, 137.84, 129.38, 128.52, 126.45, 92.70, 85.49, 69.98, 64.64, 64.19, 62.69, 60.07, 57.91, 56.77, 39.26, 36.64, 7.59 ppm; ESI-MS: Calcd for $C_{24}H_{31}FeN_3OS$ $(M + H)^+$ 466.1615; found 466.1612.

Catalyst 5d. Yellow solid; yield 80%; mp: 146.0–146.8 °C; $[\alpha]_D^{25}$ = −606 (c = 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.74 (s, 1H), 7.58 (s, 1H), 7.43–7.29 (m, 5H), 5.03 (s, 1H), 4.15 (m, 6H), 4.11–4.01 (m, 1H), 3.95 (dd, J = 10.8, 3.5 Hz, 1H), 3.90 (dd, J = 10.8, 3.5 Hz, 1H), 3.74 (dd, J = 11.0, 5.2 Hz, 2H), 3.13 (dt, J = 13.6, 6.5 Hz, 2H), 2.12 (s, 6H), 1.21 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 179.15, 137.62, 129.37, 128.74, 126.79, 93.38, 83.85, 69.76, 64.32, 63.85, 63.61, 60.41, 57.56, 57.44, 39.11, 36.97, 7.00 ppm; ESI-MS: Calcd for $C_{24}H_{31}FeN_3OS$ $(M + H)^+$ 466.1615; found 466.1613.

Catalyst 5e. yellow solid; yield 79%; mp: 147.0–147.6 °C; $[\alpha]_D^{25}$ = −164 (c = 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.82 (s, 1H), 7.51 (s, 1H), 4.24 (d, J = 6.8 Hz, 2H), 4.11 (m, 6H), 4.01 (s, 1H), 3.88 (s, 1H), 3.78 (dd, J = 11.1, 2.9 Hz, 1H), 3.62 (dd, J = 11.1, 5.1 Hz, 1H), 2.09 (s, 6H), 1.85–1.70 (m, 1H), 1.23 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 182.65, 167.61, 130.92, 128.85, 70.08, 64.97, 64.66, 63.47, 62.53, 56.10, 39.39, 29.69, 19.59, 13.73 ppm; ESI-MS: Calcd for $C_{20}H_{31}FeN_3OS$ $(M + H)^+$ 418.1615; found 418.1616.

Catalyst 5f. Yellow pulp; yield 60%; $[\alpha]_D^{25}$ = −372 (c = 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.91 (s, 1H), 7.44 (s, 1H), 4.65 (s, 1H), 4.24 (s, 5H), 4.19 (s, 1H), 4.01 (m, 4H), 3.81 (dd, J = 10.9, 7.3 Hz, 1H), 2.16 (s, 6H), 2.08 (m, 1H), 1.25 (d, J = 6.7 Hz, 3H), 1.14 (d, J = 4.1 Hz, 3H), 1.10 (d, J = 5.8 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.72, 132.32, 130.92, 128.84, 69.90, 65.56, 64.37, 62.41, 57.66, 39.09, 30.57, 29.88, 19.67, 13.72 ppm; ESI-MS Calcd for $C_{20}H_{31}FeN_3OS$ $(M + H)^+$ 418.1615; found 418.1614.

Catalyst 5g. Yellow pulp; yield 67%; $[\alpha]_D^{25}$ = −44 (c = 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.52 (s, 1H), 7.06 (s, 1H), 4.38 (m, 2H), 4.20 (s, 5H), 4.15 (d, J = 2.3 Hz, 1H), 3.89–3.84 (m, 2H), 3.57–3.47 (m, 2H), 2.16 (s, 6H), 1.34 (d, J = 6.4 Hz, 3H), 0.85 (s, 9H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ: 184.77, 90.78, 88.97, 70.24, 65.31, 64.93, 62.21, 41.99, 39.76, 34.00, 27.01, 23.38, 14.09, 11.11 ppm; ESI-MS: Calcd for $C_{21}H_{33}FeN_3OS$ $(M + H)^+$ 432.1772; found 432.1767.

Catalyst 5h. Yellow pulp; yield 70%; $[\alpha]_D^{25}$ = −236 (c = 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.12 (s, 1H), 7.32 (s, 1H), 4.90 (s, 1H), 4.24 (s, 5H), 4.07 (s, 2H), 4.01 (s, 1H), 3.89 (d, J = 12.4 Hz, 1H), 3.74 (t, J = 10.3 Hz, 1H), 3.55 (d, J = 5.0 Hz, 1H), 2.17 (s, 6H), 1.27 (d, J = 14.4 Hz, 3H), 1.14 (s, 9H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 128.85, 130.09, 128.85, 69.91, 65.31, 64.42, 42.01, 39.24, 34.20, 30.16, 27.54, 23.38, 14.09, 11.12 ppm; ESI-MS: Calcd for $C_{21}H_{33}FeN_3OS$ $(M + H)^+$ 432.1772; found 432.1769.

Catalyst 5i. Yellow solid; yield 73%; mp: 86.9–87.4 °C; $[\alpha]_D^{25}$ = −690 (c = 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.67 (s, 1H), 5.62 (s, 1H), 5.44 (s, 1H), 4.93 (s, 1H), 4.38 (m, 1H), 4.18 (s, 5H), 3.97 (d, J = 1.6 Hz, 2H), 3.84–3.77 (m, 2H), 3.51 (s, 2H), 2.19–2.16 (s, 6H), 2.11–2.05 (m, 3H), 1.87 (m, 1H), 1.28 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.62, 142.51, 99.19, 79.30, 70.09, 62.89, 62.69, 59.03, 46.08, 38.87, 29.68,

28.18, 24.21, 14.83, 11.01 ppm; ESI-MS: Calcd for $C_{20}H_{29}FeN_3OS$ $(M + H)^+$ 416.1459; found 416.1454.

Catalyst 5j. Yellow solid; yield 77%; mp: 106.1–107.0 °C; $[\alpha]_D^{25} = -840$ (c = 0.1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ: 9.76 (s, 1H), 5.47 (s, 1H), 4.98 (s, 1H), 4.33–4.30 (m, 1H), 4.17 (s, 5H), 3.95 (d, J = 2.3 Hz, 2H), 3.80 (m, 2H), 3.46 (s, 2H), 2.15 (s, 6H), 2.09 (m, 3H), 1.86–1.83 (m, 1H), 1.25 (d, J = 4.9 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.37, 131.36, 129.06, 79.44, 70.06, 62.70, 62.58, 59.11, 38.90, 30.58, 29.70, 28.16, 24.28, 19.18, 13.72 ppm; ESI-MS: Calcd for $C_{20}H_{29}FeN_3OS$ $(M + H)^+$ 416.1459; found 416.1455.

General procedure for the Michael reaction of nitrostyrenes with acetylacetone

A mixture of the β-nitrostyrenes (0.125 mmol), catalyst **5j** (0.01 mmol) in anhydrous PhMe (1 mL) was stirred at 0 °C for 5–10 min. Acetylacetone (27 μl, 0.25 mmol) was then added and stirred at the same temperature for 24 h. After the reaction was completed, excess PhMe was removed under reduced pressure and the residue was purified by column chromatography on silica gel (300–400 mesh, PE–EA = 3 : 1 to PE–EA = 1 : 1) to afford the product **10a–10q**.

(*R*)-3-(2-Nitro-1-phenylethyl)-pentane-2,4-dione (10a). White solid; yield 91%, 86% ee. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.31 (s, 2H), 7.19 (d, J = 7.5 Hz, 2H), 4.67–4.61 (m, 2H), 4.37 (d, J = 10.7 Hz, 1H), 4.24 (dd, J = 10.8, 7.0 Hz, 1H), 2.29 (s, 3H), 1.94 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 90 : 10, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 15.3 min [minor, (*S*)], t_R = 20.5 min [major, (*R*)].

(*R*)-3-[1-(2-Chlorophenyl)-2-nitroethyl]-pentane-2,4-dione (10b). White solid; yield 89%, 96% ee; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.49–7.43 (m, 1H), 7.29–7.26 (m, 2H), 7.20–7.15 (m, 1H), 4.86 (dd, J = 12.2, 6.7 Hz, 1H), 4.77 (m, 1H), 4.68 (dd, J = 12.2, 3.9 Hz, 1H), 4.62 (d, J = 9.9 Hz, 1H), 2.31 (s, 3H), 2.06 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 98 : 2, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 28.7 min [minor, (*S*)], t_R = 31.6 min [major, (*R*)].

(*R*)-3-[1-(2-Bromophenyl)-2-nitroethyl]-pentane-2,4-dione (10c). White solid; yield 93%, 92% ee; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.25–7.10 (m, 2H), 4.85 (dd, J = 12.1, 6.3 Hz, 1H), 4.78–4.73 (m, 1H), 4.68 (dd, J = 12.2, 3.9 Hz, 1H), 4.62 (d, J = 9.7 Hz, 1H), 2.31 (s, 3H), 2.06 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 98 : 2, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 30.7 min [minor, (*S*)], t_R = 33.7 min [major, (*R*)].

(*R*)-3-[1-(4-Fluorophenyl)-2-nitroethyl]-pentane-2,4-dione (10d). White solid; yield 97%, 88% ee; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.29 (m, 1H), 7.19 (dd, J = 11.2, 3.9 Hz, 1H), 7.16–7.12 (m, 1H), 7.11–7.05 (m, 1H), 4.79–4.72 (m, 1H), 4.69–4.62 (m, 1H), 4.50 (m, 2H), 2.32 (s, 3H), 2.04 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 90 : 10, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 15.8 min [minor, (*S*)], t_R = 18.2 min [major, (*R*)].

(*R*)-3-[1-(2,4-Dichlorophenyl)-2-nitroethyl]-pentane-2,4-dione (10e). Colorless oil; yield 96%, 93% ee; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.48 (d, J = 2.1 Hz, 1H), 7.25 (dd, J = 8.4, 2.1 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 4.85 (dd, J = 12.3, 6.5 Hz, 1H), 4.69 (m, 2H), 4.57 (d, J = 9.8 Hz, 1H), 2.32 (s, 3H), 2.08 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.61, 200.54, 135.12, 134.52, 132.09, 130.51, 130.20, 128.01, 75.98, 68.83, 28.58 ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 90 : 10, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 15.1 min [minor, (*S*)], t_R = 18.9 min [major, (*R*)].

(*R*)-3-[1-(2-Methoxyphenyl)-2-nitroethyl]-pentane-2,4-dione (10f). White solid; yield 94%; 92% ee. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26 (s, 1H), 7.12–7.01 (m, 1H), 6.94–6.84 (m, 2H), 4.78 (dd, J = 12.1, 7.8 Hz, 1H), 4.64–4.55 (m, 2H), 4.49 (ddd, J = 10.9, 7.8, 4.3 Hz, 1H), 3.89 (s, 3H), 2.28 (s, 3H), 1.94 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 98 : 2, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 37.5 min [minor, (*S*)], t_R = 40.8 min [major, (*R*)].

(*R*)-3-[1-(3-Nitrophenyl)-2-nitroethyl]-pentane-2,4-dione (10g). White solid; yield 96%, 94% ee; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.11 (d, J = 7.4 Hz, 1H), 8.05 (s, 1H), 7.49 (s, 1H), 7.46 (dd, J = 14.1, 7.6 Hz, 1H), 4.64 (dd, J = 12.9, 7.9 Hz, 1H), 4.60 (t, J = 6.5 Hz, 1H), 4.36 (d, J = 10.5 Hz, 1H), 4.35–4.30 (m, 1H), 2.28 (s, 3H), 1.98 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 90 : 10, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 32.8 min [minor, (*S*)], t_R = 34.5 min [major, (*R*)].

(*R*)-3-[1-(3-Chlorophenyl)-2-nitroethyl]-pentane-2,4-dione (10h). White solid; yield 90%, 86% ee; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.29–7.26 (m, 3H), 7.08 (d, J = 6.0 Hz, 1H), 4.63 (t, J = 6.0 Hz, 2H), 4.35 (d, J = 10.6 Hz, 1H), 4.26–4.20 (m, 1H), 2.30 (s, 3H), 2.00 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 93 : 7, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 19.4 min [minor, (*S*)], t_R = 22.0 min [major, (*R*)].

(*R*)-3-[1-(2-Bromophenyl)-2-nitroethyl]-pentane-2,4-dione (10i). White solid; yield 96%; 68% ee; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.45 (dd, J = 7.9, 0.7 Hz, 1H), 7.38 (s, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 4.68–4.62 (m, 2H), 4.36 (d, J = 10.6 Hz, 1H), 4.23 (ddd, J = 10.8, 7.6, 5.0 Hz, 1H), 2.32 (s, 3H), 2.02 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 93 : 7, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 25.1 min [minor, (*S*)], t_R = 27.8 min [major, (*R*)].

(*R*)-3-[1-(3-Methoxyphenyl)-2-nitroethyl]-pentane-2,4-dione (10j). Colorless oil; yield 95%; 82% ee; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26 (m, 1H), 6.84 (d, J = 8.3 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.73 (s, 1H), 4.72–4.59 (m, 2H), 4.39 (d, J = 10.9 Hz, 1H), 4.27–4.18 (m, 1H), 3.80 (s, 3H), 2.32 (s, 3H), 1.99 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 90 : 10, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 19.6 min [minor, (*S*)], t_R = 26.2 min [major, (*R*)].

(*R*)-3-[1-(4-Chlorophenyl)-2-nitroethyl]-pentane-2,4-dione (10k). White solid; yield 85%; 74% ee; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 4.70–4.59 (m, 2H), 4.35 (d, J = 10.7 Hz, 1H), 4.29–4.21 (m, 1H), 2.32 (s, 3H), 2.00 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 85 : 15, flow rate = 0.7 mL

min^{-1}, wavelength = 210 nm): t_R = 15.7 min [minor, (*S*)], t_R = 41.5 min [major, (*R*)].

(*R*)-3-[1-(4-Bromophenyl)-2-nitroethyl]-pentane-2,4-dione (10l). White solid; yield 92%; 80% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 4.67–4.60 (m, 2H), 4.35 (d, J = 10.7 Hz, 1H), 4.27–4.19 (m, 1H), 2.32 (s, 3H), 2.00 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 85 : 15, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 15.1 min [minor, (*S*)], t_R = 49.2 min [major, (*R*)].

(*R*)-3-[1-(2-Fluorophenyl)-2-nitroethyl]-pentane-2,4-dione (10m). White solid; yield 97%; 71% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23–7.17 (m, 2H), 7.08–7.01 (m, 2H), 4.67–4.59 (m, 2H), 4.36 (d, J = 10.8 Hz, 1H), 4.30–4.22 (m, 1H), 2.32 (s, 3H), 1.99 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 90 : 10, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 20.8 min [minor, (*S*)], t_R = 41.6 min [major, (*R*)].

(*R*)-3-[1-(4-Methylphenyl)-2-nitroethyl]-pentane-2,4-dione (10n). White solid; yield 91%; 67% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 4.62 (m, 2H), 4.38 (d, J = 10.9 Hz, 1H), 4.26–4.19 (m, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 1.96 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 90 : 10, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 15.4 min [minor, (*S*)], t_R = 25.5 min [major, (*R*)].

(*R*)-3-[1-(3-Methoxyphenyl)-2-nitroethyl]-pentane-2,4-dione (10o). White solid; yield 93%; 77% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.61 (m, 2H), 4.35 (d, J = 10.9 Hz, 1H), 4.27–4.17 (m, 1H), 3.80 (s, 3H), 2.31 (s, 3H), 1.96 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 90 : 10, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 23.2 min [minor, (*S*)], t_R = 36.4 min [major, (*R*)].

(*S*)-3-[1-Furyl-2-nitroethyl]-pentane-2, 4-dione (10p). Colorless oil; yield 98%; 86% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (s, 1H), 6.32 (dd, J = 3.2, 1.9 Hz, 1H), 6.20 (d, J = 3.3 Hz, 1H), 4.68 (d, J = 5.4 Hz, 2H), 4.41 (d, J = 9.8 Hz, 1H), 4.39–4.33 (m, 1H), 2.30 (s, 3H), 2.10 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 90 : 10, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 16.9 min [minor, (*R*)], t_R = 20.1 min [major, (*S*)].

(*S*)-3-[1-Thienyl-2-nitroethyl]-pentane-2,4-dione (10q). Light yellow color solid; yield 98%, 78% ee; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.24 (d, J = 5.0 Hz, 1H), 7.00–6.92 (m, 1H), 6.89 (d, J = 3.2 Hz, 1H), 4.66 (d, J = 6.1 Hz, 2H), 4.55 (dt, J = 11.6, 6.0 Hz, 1H), 4.41 (d, J = 10.2 Hz, 1H), 2.30 (s, 3H), 2.08 (s, 3H) ppm; HPLC analysis (Chiralpak AD-H column, hexane–2-propanol = 90 : 10, flow rate = 0.7 mL min^{-1}, wavelength = 210 nm): t_R = 20.2 min [minor, (*R*)], t_R = 27.8 min [major, (*S*)].

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