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Enantioselective Morita–Baylis–Hillman Reaction of Acrylates with Nitrobenzaldehydes Promoted by the Bifunctional Ferrocene-Based Phosphinothiourea Organocatalysts

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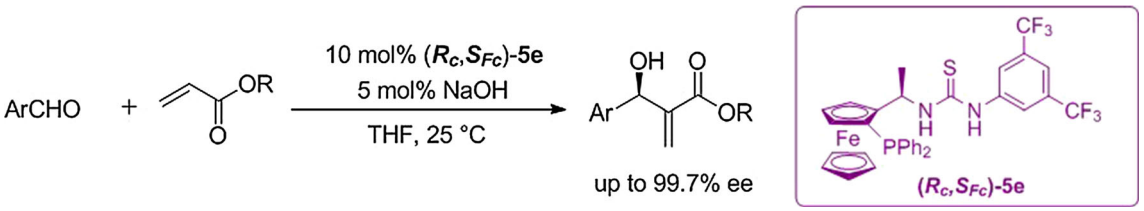
Abstract A series of ferrocene-based bifunctional phosphinothiourea organocatalysts were synthesized and applied to the enantioselective Morita–Baylis–Hillman reaction of acrylates with nitrobenzaldehydes, giving the desired products in up to 99.7 % ee. The strong electron-withdrawing effect of nitro group and hydrogen bonding interactions between the thiourea moiety of catalyst and aldehyde might be crucial during the enantio-controlling process.

Graphical Abstract



Keywords Acrylates · Ferrocene-based · MBH reaction · Nitrobenzaldehyde · Phosphinothiourea

1 Introduction

Chiral phosphines, widely utilized as ligands in asymmetric metal catalysis, have been considered to be the powerful organocatalysts in recent years. Multifunctional chiral phosphines, combination of a highly nucleophilic phosphorus center with the hydrogen bonding units in a catalyst structure bearing a chiral skeleton, can synergistically activate the substrates in an enantio-controlling manner [1–4]. Furthermore, the catalytic activities and asymmetric induction of these multifunctional chiral phosphine can be finely tuned by simply varying the chiral skeleton, the substituents on the phosphorus atom and the hydrogen bond donors. Therefore, multifunctional chiral phosphine

Chuang Li and Peng-Fei Ma have contributed equally to this work.

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organocatalysts have attracted increasing attention and have been successfully applied in asymmetric organocatalytic reactions [5–19].

With a project of developing ferrocene-based chiral catalysts, we recently embarked on exploring novel bifunctional chiral phosphines derived from ferrocene scaffolds [20–29], and demonstrated its effectiveness in the enantioselective intramolecular Morita–Baylis–Hillman (MBH) reaction [25]. Therefore, it is highly desirable to apply them to the more challenging substrates of the MBH reaction.

The enantioselective MBH reaction has been known as an efficient synthetic tool for the formation of carbon–carbon bond, it produces polyfunctional chiral molecules in a single step from simple substrates [30–35]. In the last decade, considerable progress has been made in the asymmetric MBH reaction of enone with aldehydes, aza-MBH reactions and asymmetric intramolecular [36–42]. However, the highly enantioselective MBH reaction between acrylates and aldehydes remains a challenge, and only a few effective chiral catalysts have been applied to this process. The first enantioselective MBH reaction of acrylates and aldehydes was reported by Soai [43], affording corresponding adduct in 9–44 % ee. Then, Hatakeyama [44–46] developed the *β*-ICD/HFIPA (1,1,1,3,3,3-hexafluoroisopropyl acrylate) method, providing desired products with up to 99 % ee (Fig. 1). But when the unactivated acrylates were used, such as methyl acrylate, the enantioselectivities dropped to 8 % ee. Similarly, Rinaldi et al. [47] demonstrated that *β*-ICD derivatives **1** could efficiently promote the enantioselective MBH reaction of electron-deficient acrylates (DMNPA or HFIPA) with aldehydes (up to 99 % ee). Shi et al. [48] also applied *β*-ICD to the MBH reaction of aldehydes with α-naphthyl acrylate to obtain as high as 92 % ee. In Carretero et al. [49] adopt commercial chiral phosphine ligand Mandyphos as organocatalyst in the asymmetric MBH reaction between *p*-nitrobenzaldehyde and benzyl acrylate to obtain corresponding product in 65 % ee. The first example of bifunctional chiral phosphine-catalyzed enantioselective MBH reaction of acrylates with aldehydes was reported by Wu et al. [50–52] in 2009. They synthesized chiral phosphinothioureas (**2** and **3**, Fig. 1) and applied them in the asymmetric MBH reaction of aromatic aldehydes with acrylate, 83 % ee value was obtained. After that, Lu et al. [53] also reported L-threonine-derived phosphinothiourea catalysts **5** for the highly enantioselective MBH reaction between methyl acrylate with aromatic aldehydes (up to 90 % ee). Encouraged by these results, we design bifunctional ferrocene-based phosphinothiourea **(R_C,S_{Fc})-5** (Fig. 2), and examined their efficiency in the asymmetric MBH reaction of acrylates and aldehydes.

2 Results and Discussion

Phosphinothiourea **(R_C,S_{Fc})-5** were conveniently prepared by condensation of aminophosphine **8** with 1.1 equiv of the corresponding isothiocyanate at room temperature (Scheme 1). Compound **8** was prepared from readily accessible (*R*)-Ugi's amine **6** according to published procedures [54]. The catalysts were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and mass spectrometry, in which the structure of **(R_C,S_{Fc})-5e** has been confirmed by X-ray crystal structure analysis [55].

The efficiency of **(R_C,S_{Fc})-5** was first investigated in the MBH reaction of 4-nitrobenzaldehyde **9** with HFIPA **10** in THF at 25 °C. To our delight, catalysts **5a–g** exhibited obvious catalytic activity and enantioselectivity in the reaction (Table 1). The thiourea structure of catalyst affected the enantioselectivities and chemical yields of **11** significantly. Compared with **5a**, the ferrocenylphosphine **8** without a thiourea structure showed very low activity (Table 1, entry 1 vs 8). The aromatic thiourea unit led to higher yields and enantioselectivities than the aliphatic or alicyclic thiourea unit (entries 1–5 vs entries 6 and 7). Furthermore, substituents on the aromatic ring of thiourea unit had a pronounced influence on MBH reaction. The stronger electron-withdrawing group (–CF_3) gave higher ee and yield than others (Table 1, entries 1–3 vs entries 4 and 5). Meanwhile, combining chiral phosphine **8** with the simple phenyl thiourea did not improve the activity under the optimized conditions (Table 1, entry 9), which imply that both the nucleophilic phosphine and the hydrogen bonding donor are indispensable in the structure of catalyst

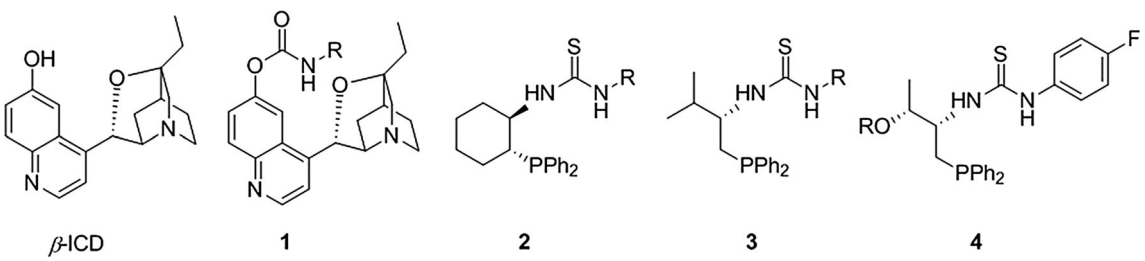


Fig. 1 Effective chiral organocatalysts for the enantioselective MBH reaction of acrylates with aldehydes

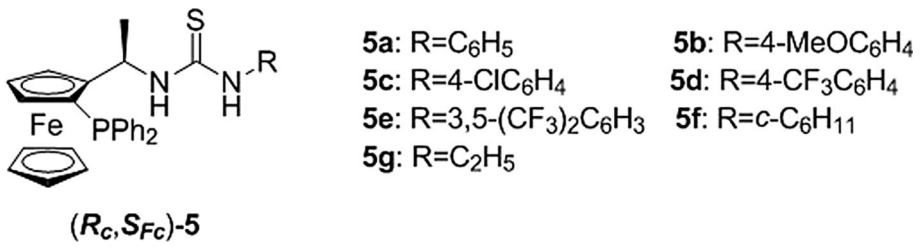
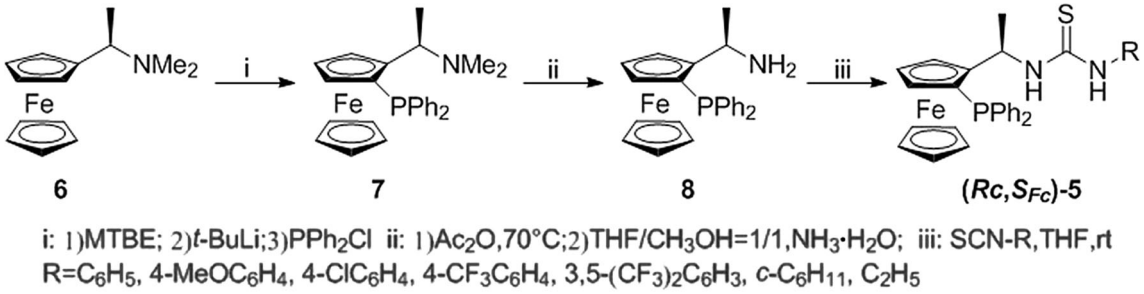
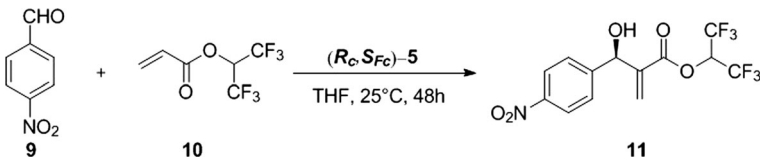


Fig. 2 Bifunctional ferrocenyl phosphinothiourea organocatalysts (R_C,S_{Fc})-**5**



Scheme 1 Synthesis of catalyst (R_C,S_{Fc})-**5**

Table 1 Screening of the catalysts in the MBH reaction of 4-nitrobenzaldehyde with HFIPA



Entry	Catalyst	Yield (%)[a]	ee (%)[b]
1	**5a**	54	43
2	**5b**	50	37
3	**5c**	49	41
4	**5d**	68	50
5	**5e**	65	60
6	**5f**	38	34
7	**5g**	35	25
8	**8**	Trace	n.d.[c]
9	**8**+ phenyl thiourea	Trace	n.d.[c]

The reactions were carried out on a 0.2 mmol scale of aldehyde, with 10 mol% of catalyst **5** (with respect to aldehyde) and 3 equiv of HFIPA in THF (1 mL) at 25 °C for 48 h. The absolute configuration was determined by comparing the specific rotation with the literature value [44]

[a] Isolated yields

[b] Determined by chiral HPLC using Chiralcel OD-H column after the MBH adduct was derivatized [56]

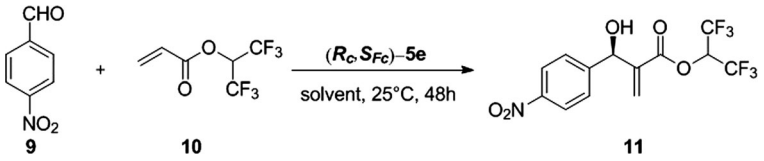
[c] Not determined

for obtaining a high catalytic activity and asymmetric induction.

The screen of solvents showed that THF was the optimal one for the reaction (Table 2, entry 3). Although the reaction proceeded quickly in toluene, the enantioselectivity was poor (Table 2, entry 4). In the protonic solvent, such as methanol and ethanol, few MBH product formed (Table 2, entries 8 and 9). In addition, temperatures, substrate ratio and the catalyst loadings were investigated to optimize the reaction (Table 3). The best result was observed at 25 °C, with 5 equiv of acrylate and 10 mol% catalyst with respect to the substrate aldehyde (Table 3, entry 5). Increase of the catalyst loading from 10 mol% to 20 mol% gave no benefit to enantioselectivity (Table 3, entry 5 vs 7).

It is noteworthy that the base additives have a pronounced influence on MBH reaction (Table 4). Except

Table 2 The effect of the solvents on the asymmetric MBH reaction



Entry	Solvent	Yield (%)[a]	ee (%)[b]
1	CH_2Cl_2	56	13
2	$CHCl_3$	48	3
3	THF	65	60
4	Toluene	79	29
5	CH_3CN	53	47
6	DMSO	33	17
7	DMF	48	50
8	MeOH	Trace	n.d.[c]
9	EtOH	Trace	n.d.[c]

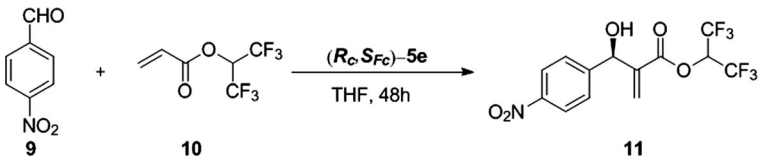
The reactions were carried out on a 0.2 mmol scale of aldehyde, with 10 mol% of catalyst **5e** and 3 equiv of HFIPA in solvent (1 mL) at 25 °C for 48 h

[a] Isolated yields

[b] Determined by chiral HPLC using Chiralcel OD-H column after the MBH adduct was derivatized [56]

[c] Not determined

Table 3 Further optimization of reaction conditions



Entry	**10/9** (mol/mol)	Catalyst loading (mol%)	Temperature (°C)	Yield (%)[a]	ee (%)[b]
1	1/2	10	25	63	39
2	1/1	10	25	64	46
3	2/1	10	25	68	53
4	3/1	10	25	65	60
5	5/1	10	25	72	85
6	5/1	5	25	42	53
7	5/1	20	25	75	85
8	5/1	10	−55	9	20
9	5/1	10	0	45	71
10	5/1	10	10	68	83
11	5/1	10	40	63	80

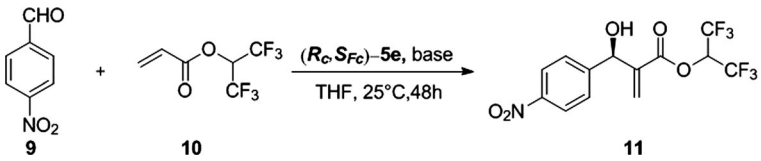
All reactions were carried out on a 0.2 mmol scale of aldehyde in THF(1 mL) for 48 h. The reaction temperature, catalyst loading, molar ratio for 4-nitrobenzaldehyde and HFIPA were changed according to the table

[a] Isolated yields

[b] Determined by chiral HPLC using Chiralcel OD-H column after the MBH adduct was derivatized [56]

for triethylamine, addition of organic base in the reaction gave the corresponding adduct in good yields, but lower enantioselectivities (Table 4, entries 1–5). Interestingly, the inorganic base additives improved both chemical yield and enantioselectivity significantly (Table 4, entries 6–10), and 5 mol% NaOH with respect to the substrate aldehyde gave the best result (Table 4, entry 8). Reducing the amount of sodium hydroxide from 5 to 1 mol% caused a drop in the enantioselectivity and yield (Table 4, entry 10). We speculated that the sodium cation would activate generating zwitterionic intermediates.

Table 4 The effect of base on the asymmetric MBH reaction



Entry	Base	Amount (mol%)	Yield (%)[a]	ee[b] (%)
1	Imidazole	5	81	25
2	DABCO	5	76	10
3	PS	5	71	40
4	DMAP	5	75	0
5	Et_3N	5	72	85
6	$NaHCO_3$	5	76	85
7	Na_2CO_3	5	81	91
8	NaOH	5	85	98
9	t-BuOK	5	82	91
10	NaOH	1	83	91

The reactions were carried out on a 0.2 mmol scale of aldehyde, with 10 mol% of catalyst **5e**, 5 equiv of HFIPA, and base additive in THF (1 mL) at 25 °C for 48 h

PS proton sponge

[a] Isolated yields

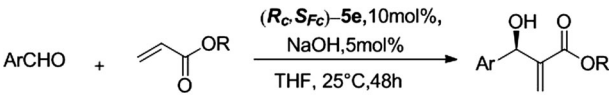
[b] Determined by chiral HPLC using Chiralcel OD-H column after the MBH adduct was derivatized [56]

Encouraged by these results, the substrate scope for **5e**-catalyzed MBH reactions was next investigated. Surprisingly, only nitrobenzaldehyde reacted with acrylate providing the desired products (Table 5). No significant reaction occurred when other aromatic aldehydes were used, such as benzaldehyde, pyridine carboxaldehydes and aromatic aldehydes with other electron withdrawing substituent (4-CF_3, 4-Ms, 4-F, 4-Cl, 2,4-dichloro) or electron donating group (4-Me, 4-^{i}Pr, 4-MeO, 4-OH). We speculate that the strong electron-withdrawing effect of nitro group and hydrogen bonding interactions between the thiourea moiety of catalyst and aldehyde might be crucial during the enantio-controlling process. On the other hand, HFIPA reacted with nitrobenzaldehyde providing higher ee and yield than other acrylates (Table 5, entries 5–8). Further studies focusing on the modification of the catalysts are currently underway.

3 Conclusion

In conclusion, a series of ferrocene-based phosphinothiourea bifunctional organocatalysts have been synthesized and applied to the asymmetric MBH reaction for the first time. The MBH reaction between nitrobenzaldehyde with acrylates catalyzed by **5e** is highly effective, giving the

Table 5 The MBH reactions between nitrobenzaldehyde with different acrylates



12 **13** **14**

Entry	Ar	R	Yield (%)[a]	ee (%)[b]
1	4-$NO_2C_6H_4$(14a)	Me	55	26
2	4-$NO_2C_6H_4$(14b)	Et	53	62
3	4-$NO_2C_6H_4$(14c)	Bn	49	32
4	4-$NO_2C_6H_4$(14d)	*t*-Bu	41	35
5	4-$NO_2C_6H_4$(14e)	$CH(CF_3)_2$	85	98[c]
6	2-$NO_2C_6H_4$(14f)	$CH(CF_3)_2$	45	90[c]
7	3-$NO_2C_6H_4$(14g)	$CH(CF_3)_2$	84	94[c]
8	4-Cl-3-$NO_2C_6H_3$(14h)	$CH(CF_3)_2$	80	99.7[c]

The reactions were carried out on a 0.2 mmol scale of aldehyde, with 10 mol% of catalyst **5e**, 5 equiv of acrylic ester, and 5 mol% of NaOH additive in THF (1 mL) at 25 °C for 48 h. The absolute configuration was determined by comparing the specific rotation with a literature value [44, 50, 51]

[a] Isolated yields

[b] The MBH adduct was determined directly by chiral HPLC using Chiralcel column

[c] Determined by chiral HPLC using Chiralcel OD-H column after the MBH adduct was derivatized [56]

desired products in up to 99.7 % ee and 80 % yield, although the substrate scope is limited.

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56. After the MBH reaction of HFIPA with aromatic aldehyde, the adduct was derivatized by stirred with ethanol (5 mL) and trimethylamine (0.5 mL) for 30 min at 25°C, then the esterified product underwent chiral HPLC determination (for details see SI)