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Chiral phosphinothiourea-catalyzed asymmetric Morita–Baylis–Hillman reactions of acrylates with aromatic aldehydes

Kui Yuan, Hong-Liang Song, Yinjun Hu, Xin-Yan Wu *

Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Shanghai 200237, China

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ABSTRACT

A series of chiral bifunctional phosphinothioureas were synthesized and applied to the enantioselective Morita–Baylis–Hillman reaction of aromatic aldehydes with acrylates. In the presence of 8 mol % of organocatalyst **2e**, the Baylis–Hillman adducts were obtained in good enantioselectivities and up to 96% yield under mild reaction conditions.

1. Introduction

Recently, the Morita–Baylis–Hillman (MBH) reaction, one of the most useful and popular carbon–carbon bond forming reactions, has attracted much attention due to the atom-economic construction of the multifunctional products.[1] In the last decade, much research effort was concentrated on its efficiency and selectivity, and the asymmetric MBH reaction of enone with aldehydes and aza-MBH reactions have obtained good results.[2,3] However, the identification of an asymmetric MBH reaction of aldehydes with acrylates is still a challenge for organic chemists, and few efficient chiral catalysts have been developed for this process. Among them, Hatakeyama reported the excellent enantioselective MBH reaction of the highly reactive 1,1,1,3,3,3-hexafluoroisopropyl (HFIP) acrylate with aldehydes (up to 99% ee).[4] Shi developed a quinidine-derived chiral amine as organocatalyst for the MBH reactions of aldehydes with (α)-naphthyl acrylate to achieve 92% ee but only 17% yield.[5] Chen and co-workers reported on the use of $La(OTf)_3$ and camphor-derived dimerized ligands to accelerate the MBH reaction of aldehydes with acrylates obtained up to 95% ee and up to 97% yield.[6] While commercially available unactivated acrylates (such as methyl, ethyl or *n*-butyl acrylate) used as Michael donor, fewer successful asymmetric MBH reactions were delevoped.[6,7] Except for some reports of enzyme-catalyzed kinetic resolution of racemic MBH products with poor yields,[1b,2a,8] no other good enantioselectivity has yet been reported by using chiral catalysts. The slow reaction rate (usually several days) and low enantioselectivities are the biggest problems. To the best of our knowledge, the highest enantioselectivity of this kind of MBH reaction catalyzed by organic molecules was 64% ee using chiral *N*-methylprolinol at −10 °C.[7c]

In our previous work, the enantioselective MBH reaction of MVK (methyl vinyl ketone) with *p*-nitrobenzaldehyde catalyzed by **2a** went to completion in 5 min (Fig. 1).[9] Considering the strong reactivity of MVK, we desired to know if better results could be obtained by lowering the reactivity of the Michael donor. To the best of our knowledge, there is no report related to the phosphine-catalyzed enantioselective MBH reaction of acrylates with aldehydes. Herein, we report the first example of a good enantioselective asymmetric MBH reaction of acrylates with aldehydes using chiral bifunctional phosphinothiourea as the catalyst.

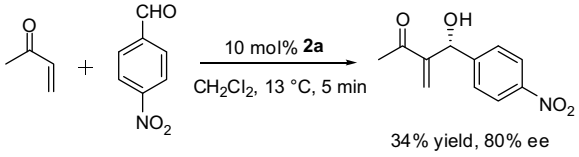

Figure 1. The MBH reaction of MVK with *p*-nitrobenzaldehyde catalyzed by **2a**.

2. Results and discussion

Initially we chose the reaction of *n*-butyl acrylate with *p*-nitrobenzaldehyde as a model reaction, and evaluated the organocatalysts

* Corresponding author. Tel.: +86 21 64252011; fax: +86 21 64252758.
E-mail address: xinyanwu@ecust.edu.cn (X.-Y. Wu).

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2a–**g**, which can be easily synthesized by condensation of (*R*,*R*)-2-amino-1-(diphenylphosphino)-cyclohexane (**1**) with 1.1 equiv of the corresponding isothiocyanate under mild conditions (Fig. 2).[9] The results are summarized in Table 1.

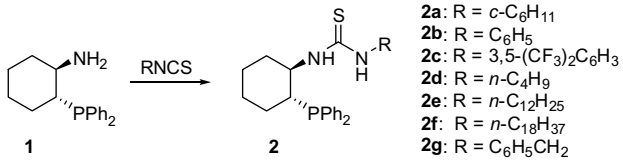
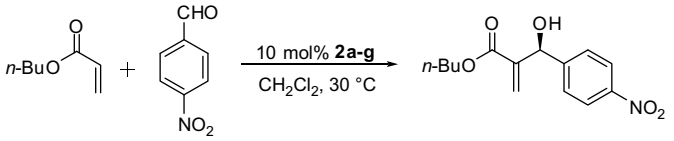


Figure 2. Synthesis of the phosphinothiourea catalysts.

Table 1
Screening of the catalysts for the MBH reaction of *n*-butyl acrylate and *p*-nitrobenzaldehyde[a]



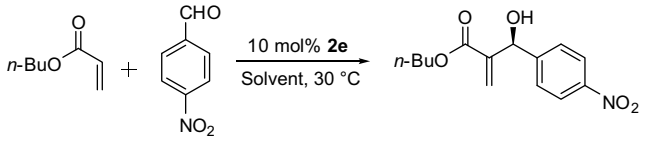
Entry	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a**	5	57	61
2	**2b**	12	47	53
3	**2c**	12	59	43
4	**2d**	5	69	60
5	**2e**	5	80	60
6	**2e**	24	80	60
7	**2f**	5	78	60
8	**2g**	5	80	59

[a] Unless stated otherwise, the reactions were conducted with 10 mol % of organocatalyst, 5 equiv of *n*-butyl acrylate in CH_2Cl_2 (0.2 M) at 30 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC.

We found the thiourea moiety was critical for the MBH reaction in terms of both yield and enantioselectivity. As illustrated in Table 1, the aliphatic thioureas were more effective than the aromatic thioureas, the reaction could complete in a shorter reaction time and provide higher yield and enantioselectivity (entries 1, 4–8 vs entries 2 and 3). The catalyst **2b**, which provided high enantioselectivity for the MBH reaction of MVK with aromatic aldehydes,[9] showed poor reactivity toward this transformation. And the organocatalyst **2e** was proved to be the best catalyst for this reaction and furnished the desired product in 80% yield and 60% ee (entry 5). Further lengthening the carbon chain of the thiourea moiety could not increase the yield and ee (entry 7 vs 5). In addition, the product was found to be stable for long periods of time in the dichloromethane solution (entry 6 vs 5). Comparatively, when MVK was used as Michael donor, longer reaction time afforded lower chemical yield due to the over reaction of the MBH product with MVK.[9] The MBH adduct was (*S*)-configuration, which was assigned by comparing the optical rotation values with those reported in the literatures.[7b,8a]

Next, solvent effects on this reaction using **2e** as the organocatalyst were probed (Table 2). The results indicated that THF was the optimal solvent in which the MBH reaction accomplished in 4 h and afforded nearly quantitative yield and 71% ee. Whether dried or not, using THF as solvent obtained the same results (entries 4 and 5). In general, the presence of water in H-bonding activation catalytic system might lead to a negative effect on the enantioselectivity and conversion. To test the effect of the trace amount of water in THF, distilled H_2O (0.2 vol %) was added to dry THF freshly distilled from Na-benzophenone, the result indicated that the effect could be ignored (entry 6 vs entries 4 and 5). Thus, commercially

Table 2
The effect of the solvents[a]



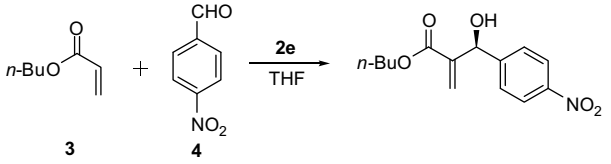
Entry	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	5	80	60
2	$CHCl_3$	5	56	63
3	PhMe	5	54	69
4[d]	THF	4	99	71
5[e]	THF	4	99	71
6[f]	THF	4	97	71
7	Ether	3	94	70
8	1,4-dioxane	5	Trace	n.d.[g]
9	EtOH	5	33	41
10	DMF	5	22	60
11	CH_3CN	5	18	55
12	DMSO	4	78	49

[a] Unless stated otherwise, the reactions were conducted with 10 mol % of organocatalyst **2e**, 5 equiv of *n*-butyl acrylate in the solvent (0.2 M) at 30 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] Dry THF was used.
[e] Commercially available THF was used directly.
[f] Dry THF with 0.2 vol % of H_2O was used.
[g] Not determined.

available THF was directly used for further investigation. In ether, the reaction was accelerated and the product was formed in 94% yield within 3 h (entry 7). However, in the case of 1,4-dioxane, the product was obtained in trace (entry 8). Also, in the polar solvents, such as EtOH, DMF, and MeCN, the product was obtained in less yield and ee (entries 9–11). In DMSO, the product was formed in 78% yield and low ee (entry 12).

Furthermore, other aspects of this reaction such as the reaction temperature, the ratio of **3**/**4**, the loading of the catalyst and additives were investigated (Table 3). The results indicated that the chemical yields were strongly influenced by the reaction temperature without obvious enantioselectivity change. On lowering the reaction temperature from room temperature to −15 °C, the ee

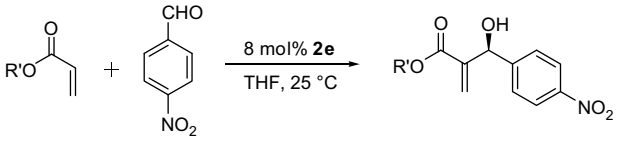
Table 3
Optimization of reaction conditions[a]



Entry	Temp (°C)	**3**/**4**	**2e** (mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	30	5	10	4	99	71
2	25	5	10	5	92	75
3	25	5	8	5	88	76
4	25	5	5	6	83	75
5	25	8	8	5	88	75
6	25	3	8	6	76	75
7	0	5	8	6	43	76
8	−15	5	8	7	31	77
9[d]	25	5	8	5	83	76
10[e]	25	5	8	5	0	n.d.[g]
11[f]	25	5	8	5	72	76

[a] Unless stated otherwise, the reactions were conducted in THF (0.2 M).
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] Added 8 mol % NEt_3.
[e] Added 8 mol % PhCOOH.
[f] Added 10 mg 4 Å MS.
[g] Not determined.

Table 4
The MBH reaction of different acrylates with *p*-nitrobenzaldehyde by **2e**[a]



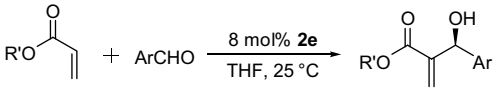
Entry	R′	Time (h)	Yield[b] (%)	ee[c] (%)
1	Me	7	85	76
2	Et	7	92	77
3	*n*-Bu	5	88	76
4	*t*-Bu	8	53	74
5	Bn	7	63	76
6	(α)-Nap	8	32	9

[a] Unless stated otherwise, the reactions were conducted with 8 mol % of organocatalyst **2e**, 5 equiv of acrylate in THF (0.2 M) at 25 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC, and the absolute configuration was determined by comparison of optical rotation with that of literature report.[4,6,7b,8a,10]

value increased just 1% (entry 8 vs 3). The suitable reaction temperature was 25 °C (entries 2 and 3). Using Et_3N, PhCOOH or 4 Å MS as the additive, the catalytic activity of **2e** was also examined. As illustrated in Table 3, Et_3N or 4 Å MS as the additive provided lower yield (83% and 72%) and similar enantioselectivity (76% ee) (entries 9 and 11 vs 3). However, using PhCOOH as additive failed to obtain the product (entry 10). The perfect ratio of **3**/**4** was 5/1. And this reaction could be performed with as low as 5 mol % of catalyst loading (entry 4), where a comparable result (75% ee, 83% yield) was achieved.

Under the optimized conditions (8 mol % of **2e** as catalyst, 5 equiv of acrylate, THF as solvent, 25 °C), the MBH reactions of various acrylates with *p*-nitrobenzaldehyde (**4**) were surveyed to determine the scope of substrates. The results in Table 4 showed that better yield and enantioselectivity were obtained using ethyl acrylate as a Michael donor (92% yield, 77% ee). Surprisingly, (α)-naphthyl acrylate just gave the product in 32% yield and 9% ee in the same reaction conditions and dioxanone was observed as a byproduct.[4]

Table 5
The MBH reactions between various aromatic aldehydes with ethyl acrylate or *n*-butyl acrylate catalyzed by **2e**[a]



Entry	Ar	R′	Time (h)	Yield (%)[b]	ee (%)[c]
1	4-$NO_2C_6H_4$	Et	7	92	77
2	4-$NO_2C_6H_4$	*n*-Bu	5	88	76
3	2-$NO_2C_6H_4$	Et	12	90	35
4	2-$NO_2C_6H_4$	*n*-Bu	12	85	33
5	3-$NO_2C_6H_4$	Et	10	96	77
6	3-$NO_2C_6H_4$	*n*-Bu	10	94	75
7	4-$CF_3C_6H_4$	Et	12	63	71
8	4-$CF_3C_6H_4$	*n*-Bu	12	54	69
9	4-ClC_6H_4	Et	20	37	65
10	4-ClC_6H_4	*n*-Bu	20	36	63
11	2,4-$Cl_2C_6H_3$	Et	20	66	7
12	4-BrC_6H_4	Et	18	36	65
13[d]	C_6H_5	Et	24	24	54
14	2-Furyl	Et	20	42	27

[a] Unless stated otherwise, the reactions were conducted with 8 mol % of organocatalyst **2e**, 5 equiv of acrylate in THF (0.2 M) at 25 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC, and the absolute configuration was determined by comparison of optical rotation with that of literature report.[7c,8a]
[d] 8 mol % NEt_3 was added. Under the typical reaction conditions, no product was detected.

In addition, the reaction could occur with various substituted aromatic aldehydes. As indicated in Table 5, the strong electron-deficient benzaldehydes usually proceeded very quickly to provide the desired products in excellent yields (85–96% yield, entries 1–6) and good enantioselectivities. However *ortho* substitution as in the cases of 2-nitrobenzaldehyde and 2,4-dichlorobenzaldehyde has a deleterious effect on enantioselectivity, with the products being obtained with 35% ee, 33% ee and even 7% ee (entries 3, 4, and 11), respectively. The reaction with non-substituted benzaldehyde and 2-furaldehyde gave relatively poor yields and enantioselectivities due to the low activities (entries 13 and 14).

3. Conclusion

In summary, we have developed the first phosphinothiourea-catalyzed asymmetric MBH reaction between acrylates and aldehydes. It is particularly noteworthy that this new catalytic system is effective for various commercially available acrylates. With 8 mol % of phosphinothiourea **2e**, the Morita–Baylis–Hillman reaction could proceed in 5–24 h under mild conditions and afford the desired products in up to 77% ee and moderate-to-excellent yields (up to 96%).

4. Experimental

4.1. General methods

Melting points are taken without correction. Optical rotations were measured on a WZZ-2A digital polarimeter at the wavelength of the sodium D-line (598 nm) at 20 °C. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker 500 or 400 spectrometer. ^1H NMR spectra were referenced to tetramethylsilane (δ, 0.00 ppm) using $CDCl_3$ or $(CD_3)_2CO$ as solvent. ^{13}C NMR spectra were referenced to solvent carbons (77.0 ppm for $CDCl_3$, 206.5 ppm for $(CD_3)_2CO$). ^{31}P NMR spectra were referenced to an external H_3PO_4 signal (0.0 ppm). IR spectra were recorded on Nicolet Magna-I 550 spectrometer. High resolution mass spectra (HRMS) were recorded on Micromass GCT spectrometer with Electron Ionization (EI) resource. HPLC analysis was performed on Waters 510 with 2487 detector using Daicel Chiralcel OD-H, Chiralcel OJ, Chiralpak AS-H or Chiralpak AD-H column.

THF was directly used without further purification. And other solvents were purified and dried according to standard methods prior to use. 4-Trifluoromethylbenzaldehyde, 4-chlorobenzaldehyde and benzaldehyde, 2-furaldehyde were freshly distilled while other aldehydes were recrystallized from ethanol.

4.2. General procedure for the synthesis of chiral phosphinothiourea catalysts

To a solution of (*R*,*R*)-1-amino-2-(diphenylphosphino)cyclohexane (**1**)[9,11] (283 mg, 1.0 mmol) in 3.0 mL CH_2Cl_2 was added isothiocyanate (1.1 mmol) at room temperature, and the resulting mixture was stirred at this temperature until the reaction completed (monitoring by TLC). The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate=4/1 or 3/1) to afford the chiral phosphinothiourea compounds (the phosphinothiourea catalysts **2a**–**c** were described in our previous work).[9]

4.2.1. Phosphinothiourea ***2a***. White solid, 65% yield, mp: 98–100 °C; $[\alpha]_D$ −46.0 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): ν 3415, 3064, 2924, 2851, 1644, 1538, 1362, 1064, 608, 559; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.58 (t, 2H, *J*=6.9 Hz), 7.51–7.47 (m, 2H), 7.39–7.33 (m, 6H), 5.26–5.73 (br, 2H), 4.32–3.72 (br, 1H), 2.46–2.43 (m, 1H), 2.36–2.33 (m, 1H), 1.86–1.64 (m, 8H), 1.58–1.56 (m, 1H), 1.43–1.40

(m, 1H), 1.28–0.99(m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 178.52, 136.78 (d, J=13.8 Hz), 134.75 (d, J=15.1 Hz), 133.80 (d, J=20.6 Hz), 132.60 (d, J=19.1 Hz), 128.59, 128.28 (d, J=6.8 Hz), 128.23, 127.92 (d, J=7.5 Hz), 51.63, 40.00 (d, J=13.3 Hz), 32.61, 32.35, 32.18, 27.04, 24.91, 24.15, 23.73; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4): δ −9.39; HRMS (EI) calcd for $C_{25}H_{33}N_2PS$ ($[M]^+$) 424.2102, found: 424.2102.

4.2.2. Phosphinothiourea ***2b***. White solid, 92% yield, mp: 148–149 °C; $[\alpha]_D$ −78.5 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): ν 3374, 3051, 2928, 2852, 1596, 1531, 1496, 1449, 1318, 1258, 1046, 743, 696; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56–7.50 (m, 5H), 7.33–7.23 (m, 9H), 7.13 (d, J=6.4 Hz, 2H), 6.11 (s, 1H), 4.36 (s, 1H), 2.36–2.29 (m, 2H), 1.73–1.70 (m, 2H), 1.58 (s, 1H), 1.38–1.35 (m, 1H), 1.18–1.22 (m, 2H), 1.08–1.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 179.57, 137.29 (d, J=13.0 Hz), 136.73, 135.61, 135.35 (d, J=20.6 Hz), 133.26 (d, J=18.0 Hz), 130.67, 129.70, 129.15 (d, J=5.9 Hz), 128.93 (d, J=5.1 Hz), 128.86, 127.34, 125.41, 57.09 (d, J=15.8 Hz), 41.27 (d, J=16.1 Hz), 34.04, 28.27, 26.18, 25.14; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4): δ −7.73; HRMS (EI) calcd for $C_{25}H_{27}N_2PS$ ($[M]^+$) 418.1633, found: 418.1634.

4.2.3. Phosphinothiourea ***2c***. White solid, 86% yield, mp: 212–214 °C; $[\alpha]_D$ −15.9 (*c* 0.8, CH_2Cl_2); IR (KBr, cm^{-1}): ν 3221, 3054, 2941, 2859, 1548, 1471, 1277, 1137, 1108, 888, 742, 715; ^{1}H NMR ($(CD_3)_2CO$, 400 MHz): δ 8.30 (s, 2H), 7.66 (s, 1H), 7.56 (s, 4H), 7.36–7.32 (m, 5H), 7.28 (d, J=6.8 Hz, 1H), 4.48 (s, 1H), 3.25 (s, 2H), 2.67 (t, J=10.0 Hz, 1H), 2.21–2.18 (m, 1H), 1.86–1.83 (m, 1H), 1.69 (s, 2H), 1.45–1.40 (m, 1H), 1.34–1.27 (m, 2H), 1.04–1.01 (m, 1H); ^{13}C NMR ($(CD_3)_2CO$, 125 MHz): δ 180.51, 143.06, 138.43 (d, J=14.1 Hz), 137.13 (d, J=17.3 Hz), 135.75 (d, J=21.0 Hz), 133.83 (d, J=18.3 Hz), 132.14 (q, J=33.0 Hz), 130.17, 129.52 (d, J=6.0 Hz), 129.39 (d, J=7.5 Hz), 129.12, 125.78, 123.61, 123.26, 117.35, 55.62 (d, J=15.5 Hz), 40.99 (d, J=15.6 Hz), 33.73, 28.72 (d, J=3.6 Hz), 26.30 (d, J=4.0 Hz), 25.63; ^{31}P NMR ($(CD_3)_2CO$, 202 MHz, 85% H_3PO_4): δ −5.08; HRMS (EI) calcd for $C_{27}H_{25}N_2F_6PS$ ($[M]^+$)554.1380, found: 554.1381.

4.2.4. Phosphinothiourea ***2d***. White solid, 70% yield, mp: 76–78 °C; $[\alpha]_D$ −33.0 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): ν 3262, 3072, 2931, 2856, 1546, 1434, 742, 698; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 (t, 2H, J=6.9 Hz), 7.50–7.48 (m, 2H), 7.38–7.33 (m, 6H), 5.56–5.44 (br, 2H), 4.42–3.85 (br, 1H), 3.12–2.83 (br, 1H), 2.43–2.33 (m, 2H), 1.73–1.68 (m, 4H), 1.43–1.35 (m, 3H), 1.34–1.18 (m, 5H), 0.89 (t, 3H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.08, 137.21 (d, J=13.8 Hz), 135.12 (d, J=15.6 Hz), 134.34 (d, J=20.6 Hz), 132.50 (d, J=18.8 Hz), 129.09, 128.73 (d, J=6.6 Hz), 128.63, 128.38 (d, J=7.5 Hz), 55.98, 43.19, 40.52 (d, J=12.8 Hz), 33.56, 30.87, 27.67, 25.42, 24.35, 20.04, 13.79; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4): δ −6.62; HRMS (EI) calcd for $C_{23}H_{31}N_2PS$ ($[M]^+$) 398.1946, found: 398.1945.

4.2.5. Phosphinothiourea ***2e***. Colorless oil, 73% yield, $[\alpha]_D$ −27.5 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): ν 3313, 2926, 2852, 1551, 1493, 1228, 699, 505; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 (t, 2H, J=6.9 Hz), 7.51–7.47 (m, 2H), 7.37–7.32 (m, 6H), 5.86–5.35 (br, 2H), 4.31–3.85 (br, 1H), 3.15–2.72 (br, 1H), 2.43–2.32 (m, 2H), 1.72–1.65 (m, 3H), 1.39–1.37 (m, 3H), 1.30–1.14 (m, 22H), 0.90–0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.05, 137.12 (d, J=13.3 Hz), 135.48 (d, J=14.6 Hz), 134.41 (d, J=20.4 Hz), 132.42 (d, J=18.5 Hz), 129.08, 128.69 (d, J=6.4 Hz), 128.53, 128.35 (d, J=7.5 Hz), 55.18, 43.42, 40.59 (d, J=15.3 Hz), 33.64, 31.91, 29.72, 29.64, 29.60, 29.53, 29.34, 28.86, 27.70, 26.93, 25.49, 24.44, 22.69, 14.14; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4): δ −6.43; HRMS (EI) calcd for $C_{31}H_{47}N_2PS$ ($[M]^+$) 510.3198, found: 510.3200.

4.2.6. Phosphinothiourea ***2f***. Colorless oil, 78% yield, $[\alpha]_D$ −25.5 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): ν 3309, 2924, 2852, 1552, 1494, 1469, 1432, 1258, 1228, 747, 699, 505; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (t, 2H, J=6.8 Hz), 7.54–7.35 (m, 8H), 5.38 (br, 2H), 4.09 (br, 1H), 2.95 (br, 1H), 2.49–2.37 (m, 2H), 1.78–1.69 (m, 3H), 1.48–1.38 (m, 3H), 1.36–1.28 (m, 34H), 0.90 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.06, 137.12 (d, J=13.2 Hz), 134.95 (d, J=14.2 Hz), 134.43 (d, J=20.4 Hz), 132.90 (d, J=18.5 Hz), 129.09, 128.71 (d, J=6.2 Hz), 128.52, 128.35 (d, J=7.5 Hz), 55.88, 43.62, 40.57 (d, J=14.2 Hz), 33.80, 31.94, 29.73, 29.68, 29.64, 29.55, 29.38, 29.35, 28.85, 27.64, 26.95, 25.53, 24.45, 22.70, 14.16; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4): δ −6.25; HRMS (EI) calcd for $C_{37}H_{59}N_2PS$ ($[M]^+$) 594.4137, found: 594.4139.

4.2.7. Phosphinothiourea ***2g***. White solid, 91% yield, mp: 63–65 °C; $[\alpha]_D$ −18.8 (*c* 0.85, CH_2Cl_2); IR (KBr, cm^{-1}): ν 3419, 3062, 2927, 2853, 2361, 1541, 1496, 1480, 1433, 1373, 1262, 1050, 742, 697, 509; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57–7.47 (m, 4H), 7.37–7.29 (m, 9H), 7.23–7.22 (m, 2H), 5.19–5.78 (br, 1H), 3.78–4.39 (br, 3H), 2.46–2.37 (m, 1H), 2.31–2.28 (m, 1H), 1.75–1.61 (m, 4H), 1.47–1.39 (m, 1H), 1.30–1.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.38, 136.98 (d, J=12.4 Hz), 135.02 (d, J=14.9 Hz), 134.36 (d, J=20.4 Hz), 132.50 (d, J=18.7 Hz), 129.13, 128.77, 128.72, 128.67, 128.39 (d, J=7.6 Hz), 127.75, 127.66, 55.51, 47.75, 40.40 (d, J=14.1 Hz), 33.10, 27.28, 25.16, 24.17; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4): δ −6.66; HRMS (EI) calcd for $C_{23}H_{31}N_2PS$ ($[M]^+$) 432.1789, found: 432.1788.

4.3. General procedure for the Morita–Baylis–Hillman reaction

To a solution of the organocatalyst **2e** (0.016 mmol) in THF (1.0 mL) was added acrylate (1.0 mmol) at 25 °C. After 10 min stirring at this temperature, aromatic aldehyde (0.2 mmol) was added. The reaction mixture was stirred at 25 °C (monitoring by TLC). After the reaction was completed, the solvent was removed under reduced pressure and the residue was purified by a flash column chromatography to afford the Baylis–Hillman adduct and the ee value was determined by HPLC analysis with chiral column.

4.3.1. Methyl (S)-2-[hydroxy-(4-nitro-phenyl)-methyl]-acrylate.[4,7b] 85% yield, 76% ee, $[\alpha]_D$ +54.4 (*c* 0.34, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.22 (d, J=8.7 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 6.40 (s, 1H), 5.87 (s, 1H), 5.64 (d, J=6.2 Hz, 1H), 3.75 (s, 3H), 3.27 (d, J=6.2 Hz, 1H); HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=95/5, flow rate: 1.0 mL/min): t_R=38.22 min (major), 33.70 min (minor).

4.3.2. Ethyl (S)-2-[hydroxy-(4-nitro-phenyl)-methyl]-acrylate.[8a] 92% yield, 77% ee, $[\alpha]_D$ +60.3 (*c* 0.39, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.21 (d, J=8.7 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 6.40 (s, 1H), 5.85 (s, 1H), 5.63 (d, J=6.3 Hz, 1H), 4.20 (q, J=7.1 Hz, 2H), 3.35 (d, J=6.3 Hz, 1H), 1.27 (t, J=7.1 Hz, 3H); HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=95/5, flow rate: 1.0 mL/min): t_R=29.63 min (major), 26.51 min (minor).

4.3.3. n-Butyl (S)-2-[hydroxy-(4-nitro-phenyl)-methyl]-acrylate.[7b,12] 88% yield, 76% ee, $[\alpha]_D$ +54.8 (*c* 0.46, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, J=8.4 Hz, 2H), 7.58 (d, J=8.4 Hz, 2H), 6.40 (s, 1H), 5.85 (s, 1H), 5.63 (d, J=6.4 Hz, 1H), 4.15 (t, J=6.8 Hz, 2H), 3.32 (d, J=6.4 Hz, 1H), 1.66–1.58 (m, 2H), 1.39–1.30 (m, 2H), 0.92 (t, J=7.6 Hz, 3H); HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=96/4, flow rate: 1.0 mL/min): t_R=22.18 min (major), 24.26 min (minor).

4.3.4. tert-Butyl (S)-2-[hydroxy-(4-nitro-phenyl)-methyl]-acrylate.[10] 53% yield, 74% ee, $[\alpha]_D$ +38.9 (*c* 0.18, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.21 (d, J=8.7 Hz, 2H), 7.57 (d, J=8.5 Hz, 2H), 6.31 (s, 1H), 5.75 (s, 1H), 5.57 (d, J=6.6 Hz, 1H), 3.45 (d, J=6.6 Hz, 1H), 1.43 (s, 9H); HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-

propanol=90/10, flow rate: 1.0 mL/min): t_R=9.45 min (major), 11.49 min (minor).

4.3.5. Benzyl (S)-2-[hydroxy-(4-nitro-phenyl)-methyl]-acrylate.[6] 63% yield, 76% ee, $[\alpha]_D$ +40.4 (*c* 0.26, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, *J*=8.6 Hz, 2H), 7.56 (d, *J*=8.6 Hz, 2H), 7.37–7.35 (m, 3H), 7.30–7.28 (m, 2H), 6.47 (s, 1H), 5.92 (s, 1H), 5.66 (d, *J*=6.0 Hz, 1H), 5.18 (s, 2H), 3.24 (d, *J*=6.0 Hz, 1H); HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=18.09 min (major), 20.62 min (minor).

4.3.6. α-Naphthyl (S)-2-[hydroxy-(4-nitro-phenyl)-methyl]-acrylate.[6] 32% yield, 9% ee; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.18 (d, *J*=8.7 Hz, 2H), 7.80 (d, *J*=8.2 Hz, 1H), 7.69 (d, *J*=8.2 Hz, 1H,), 7.61 (d, *J*=8.6 Hz, 2H), 7.50 (d, *J*=8.3 Hz, 1H), 7.39 (m, 3H), 7.11 (d, *J*=7.5 Hz, 1H), 6.78 (s, 1H), 6.14 (s, 1H), 5.76 (s, 1H), 2.29 (br, 1H); HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=20.97 min (major), 18.69 min (minor).

4.3.7. Ethyl 2-[hydroxy-(2-nitro-phenyl)-methyl]-acrylate.[7c] 90% yield, 35% ee, $[\alpha]_D$ +100.0 (*c* 0.60, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (d, *J*=8.1 Hz, 1H), 7.75 (d, *J*=7.8 Hz, 1H), 7.67–7.64 (m, 1H), 7.49–7.46 (m, 1H), 6.38 (s, 1H), 6.19 (s, 1H), 5.74 (s, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 3.43 (s, 1H), 1.22 (t, *J*=7.1 Hz, 3H); HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=10.39 min (major), 14.61 min (minor).

4.3.8. n-Butyl (S)-2-[hydroxy-(2-nitro-phenyl)-methyl]-acrylate.[13] 85% yield, 33% ee, $[\alpha]_D$ +71.6 (*c* 0.44, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (d, *J*=8.1 Hz, 1H), 7.74 (d, *J*=7.7 Hz, 1H), 7.66–7.63 (m, 1H), 7.49–7.46 (m, 1H), 6.39 (s, 1H), 6.17 (s, 1H), 5.76 (s, 1H), 4.16–4.07 (m, 2H), 3.43 (s, 1H), 1.59–1.53 (m, 2H), 1.33–1.24 (m, 2H), 0.89 (t, *J*=7.4 Hz, 3H); HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=8.58min (major), 12.43 min (minor).

4.3.9. Ethyl (S)-2-[hydroxy-(3-nitro-phenyl)-methyl]-acrylate.[8a] 96% yield, 77% ee, $[\alpha]_D$ +64.4 (*c* 0.45, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.27 (s, 1H), 8.16 (dd, *J*=1.0 and 8.1 Hz, 1H), 7.76 (d, *J*=7.7 Hz, 1H), 7.52 (t, *J*=7.9 Hz, 1H), 6.42 (s, 1H), 5.89 (s, 1H), 5.63 (d, *J*=6.2 Hz, 1H), 4.20 (q, *J*=7.1 Hz, 2H), 3.33 (d, *J*=6.2 Hz, 1H), 1.27 (t, *J*=7.1 Hz, 3H); HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=95/5, flow rate: 0.8 mL/min): t_R=28.06 min (major), 25.98 min (minor).

4.3.10. n-Butyl (S)-2-[hydroxy-(3-nitro-phenyl)-methyl]-acrylate.[14] 94% yield, 75% ee, $[\alpha]_D$ +48.8 (*c* 0.43, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.27 (s, 1H), 8.15 (dd, *J*=1.0 and 8.1 Hz, 1H), 7.75 (d, *J*=7.7 Hz, 1H), 7.53 (t, *J*=8.0 Hz, 1H), 6.41 (s, 1H), 5.89 (s, 1H), 5.63 (d, *J*=6.3 Hz, 1H), 4.14 (t, *J*=6.4 Hz, 2H), 3.34 (d, *J*=6.3 Hz, 1H), 1.64–1.58 (m, 2H), 1.37–1.28 (m, 2H), 0.90 (t, *J*=7.4 Hz, 3H); HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=10.17 min (major), 11.20 min (minor).

4.3.11. Ethyl (S)-2-[hydroxy-(4-trifluoromethyl-phenyl)-methyl]-acrylate.[14] 63% yield, 71% ee, $[\alpha]_D$ +26.9 (*c* 0.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 (d, *J*=8.2 Hz, 2H), 7.51 (d, *J*=8.2 Hz, 2H), 6.37 (s, 1H), 5.82 (s, 1H), 5.60 (s, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 3.25 (br, 1H), 1.26 (t, *J*=7.1 Hz, 3H); HPLC analysis (OD-H column, λ=220 nm, eluent: hexane/2-propanol=95/5, flow rate: 0.8 mL/min): t_R=11.77 min (major), 10.64 min (minor).

4.3.12. n-Butyl (S)-2-[hydroxy-(4-trifluoromethyl-phenyl)-methyl]-acrylate.[14] 54% yield, 69% ee; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, *J*=8.2 Hz, 2H), 7.51 (d, *J*=8.2 Hz, 2H), 6.37 (s, 1H), 5.82 (s, 1H), 5.59 (d, *J*=6.0 Hz, 1H), 4.14 (t, *J*=6.6 Hz, 2H), 3.32 (d, *J*=6.0 Hz, 1H), 1.62–1.58 (m, 2H), 1.36–1.29 (m, 2H), 0.90 (t, *J*=7.4 Hz, 3H); HPLC analysis (OD-H column, λ=220 nm, eluent: hexane/2-propanol=99/1, flow rate: 1.0 mL/min): t_R=23.71 min (major), 21.23 min (minor).

4.3.13. Ethyl (S)-2-[hydroxy-(4-chloro-phenyl)-methyl]-acrylate.[7c] 37% yield, 65% ee; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (s, 4H), 6.34 (s, 1H), 5.80 (s, 1H), 5.53 (d, *J*=5.7 Hz, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 3.21 (d, *J*=5.7 Hz, 1H), 1.26 (t, *J*=7.1 Hz, 3H); HPLC analysis (OD-H column, λ=220 nm, eluent: hexane/2-propanol=97/3, flow rate: 1.0 mL/min): t_R=15.41 min (major), 13.90 min (minor).

4.3.14. n-Butyl (S)-2-[hydroxy-(4-chloro-phenyl)-methyl]-acrylate.[15] 36% yield, 63% ee; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (s, 4H), 6.34 (s, 1H), 5.80 (s, 1H), 5.53 (d, *J*=5.7 Hz, 1H), 4.13 (t, *J*=6.6 Hz, 2H), 3.92 (d, *J*=5.7 Hz, 1H), 1.63–1.58 (m, 2H), 1.35–1.29 (m, 2H), 0.91 (t, *J*=7.4 Hz, 3H); HPLC analysis (AS-H column, λ=220 nm, eluent: hexane/2-propanol=97/3, flow rate: 0.8 mL/min): t_R=14.07 min (major), 15.21 min (minor).

4.3.15. Ethyl (S)-2-[hydroxy-(2,4-dichloro-phenyl)-methyl]-acrylate.[13] 66% yield, 7% ee; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52 (d, *J*=8.4 Hz, 1H), 7.39 (d, *J*=1.6 Hz, 1H), 7.30 (dd, *J*=1.6 and 8.4 Hz, 1H), 6.34 (s, 1H), 5.92 (d, *J*=4.5 Hz, 1H), 5.57 (s, 1H), 4.23 (q, *J*=7.1 Hz, 2H), 3.32 (d, *J*=4.5 Hz, 1H), 1.29 (t, *J*=7.1 Hz, 3H); HPLC analysis (OD-H column, λ=220 nm, eluent: hexane/2-propanol=95/5, flow rate: 1.0 mL/min): t_R=9.71 min (major), 7.77 min (minor).

4.3.16. Ethyl (S)-2-[hydroxy-(4-bromo-phenyl)-methyl]-acrylate.[7c] 36% yield, 65% ee, $[\alpha]_D$ +17.6 (*c* 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H), 6.34 (s, 1H), 5.80 (s, 1H), 5.51 (d, *J*=5.8 Hz, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 3.21 (d, *J*=5.8 Hz, 1H), 1.26 (t, *J*=7.1 Hz, 3H); HPLC analysis (OD-H column, λ=220 nm, eluent: hexane/2-propanol=95/5, flow rate: 0.8 mL/min): t_R=13.96 min (major), 12.870 min (minor).

4.3.17. Ethyl (S)-2-[hydroxy-phenyl-methyl]-acrylate.[16] 24% yield, 54% ee; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39–7.27 (m, 5H), 6.34 (s, 1H), 5.81 (s, 1H), 5.57 (d, *J*=5.5 Hz, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 3.48 (d, *J*=5.5 Hz, 1H), 1.24 (t, *J*=7.1 Hz, 3H); HPLC analysis (OJ column, λ=220 nm, eluent: hexane/2-propanol=90/10, flow rate: 0.8 mL/min): t_R=21.93 min (major), 17.79 min (minor).

4.3.18. Ethyl (S)-2-[hydroxy-(2-furfuryl)-methyl]-acrylate.[12] 42% yield, 27% ee; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 (s, 1H), 6.37 (s, 1H), 6.35–6.34 (m, 1H), 6.27 (d, *J*=3.2 Hz, 1H), 5.92 (s, 1H), 5.59 (s, 1H), 4.22 (q, *J*=7.1 Hz, 2H), 3.41 (s, 1H), 1.28 (t, *J*=7.1 Hz, 3H); HPLC analysis (OD-H column, λ=220 nm, eluent: hexane/2-propanol=90/10, flow rate: 0.8 mL/min): t_R=9.62 min (major), 11.31 min (minor).

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Supplementary data

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