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Enantioselective Morita-Baylis-Hillman Reaction Organocatalyzed by Glucose-based Phosphinothiourea

Yang, Weihong(杨位红) Sha, Feng(沙风) Zhang, Xin(张鑫)
Yuan, Kui(袁奎) Wu, Xinyan*(伍新燕)

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

A class of bifunctional phosphinothioureas derived from saccharide was developed as new organocatalysts for the enantioselective Morita-Baylis-Hillman reaction between acrylates and aldehydes. With 10 mol% of glucose-based phosphinothiourea **1d**, the allylic alcohols were obtained in up to 96% yield and 83% *ee* under mild reaction conditions.

Keywords asymmetric organocatalysis, Morita-Baylis-Hillman reaction, bifunctional phosphine, chiral phosphinothiourea, acrylate

Introduction

Morita-Baylis-Hillman (MBH) reaction is well known as the coupling between the α-position of an activated alkenes and an sp^2 electrophilic carbon using a suitable catalyst.[1] Its asymmetric version is an important C—C bond-forming avenue to provide enantioenriched allylic alcohols, which are useful building blocks in organic synthesis.[2] Since Hatakeyama[3] developed the first highly enantioselective MBH reaction, great progress has been made in the past decade.[4] Up to date, various chiral organocatalysts, especially bifunctional phosphines,[4e,5] have evolved to promote the highly enantioselective catalytic reactions. However, only a few chiral bifunctional phosphines (Figure 1) are efficient organocatalysts for the asymmetric MBH reaction of acrylates and carbonyl compounds.[6,7] In our previous works, we have developed bifunctional phosphinothioureas derived from (1*R*,2*R*)-2-amino-1-(diphenylphosphino) cyclohexane and natural amino acids, and applied them in the enantioselective MBH reaction between simple acrylates and aromatic aldehydes, providing up to 83% *ee*.[7a,7b,8] Very recently, Lu and coworkers[7d] reported this MBH reaction catalyzed by *L*-threonine-derived phosphine-thiourea, and 69%—90% *ee* with 25%—92% yield were obtained. Therefore, the exploration of highly effective bifunctional phosphine organocatalysts for this enantioselective transform is still in great demand.

It has been proved that incorporating carbohydrate motif to a chiral amino thiourea is a successful approach

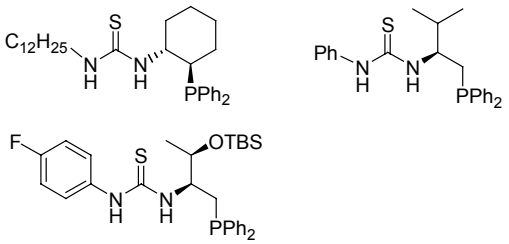

Figure 1 Typical structures of chiral bifunctional phosphinothioureas.

to develop effective organocatalysts. The saccharide-based bifunctional thioureas involving primary amine, secondary amine and tertiary amine are highly efficient organocatalysts for the enantioselective Michael additions between nitroalkenes and carbonyl compounds, such as acetone, acetophenone, cyclohexanone, acetylacetone and malonates.[9] As a part of our continuous efforts to the MBH reaction, we are interested to evaluate whether the chiral phosphinothiourea with additional chiral scaffold such as sugar can be engineered to enhance the catalytic activity as well as enantioselectivity. Therefore, a series of sugar-based phosphinothiourea organocatalysts were designed and prepared to catalyze the asymmetric MBH reaction between acrylate and aldehyde (Figure 2).

Results and Discussion

The organocatalysts **1a**—**1f** were easily prepared by condensation of chiral 2-amino-1-(diphenylphosphino)

* E-mail: xinyanwu@ecust.edu.cn; Tel.: 0086-21-64252011; Fax: 0086-21-64252758
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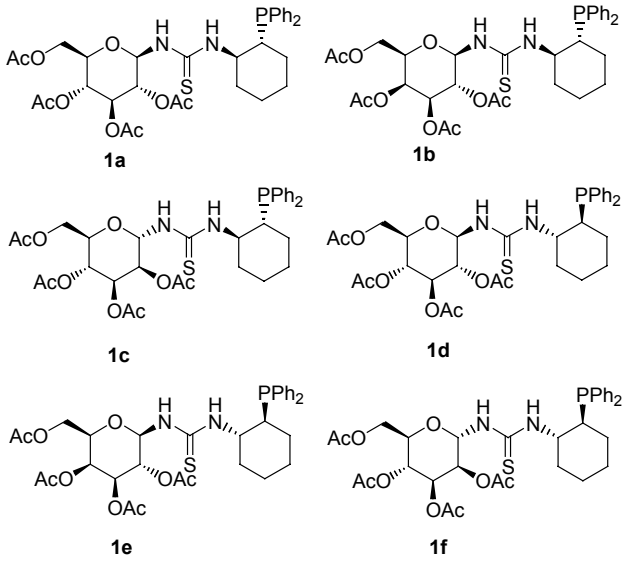


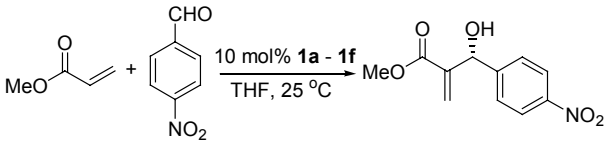
Figure 2 Structures of sugar-based phosphinothioureas.

cyclohexane with the corresponding isothiocyanate derived from different monosaccharide (*D*-glucose, *D*-glactose and *D*-mannose).

Initially, the asymmetric MBH reaction of methyl acrylate and 4-nitrobenzaldehyde in THF at 25 ℃ was selected as a model reaction to evaluate the organocatalysts **1a**—**1f**. The results summarized in Table 1 indicated that the stereoselectivity of the MBH reaction was controlled by the chiral cyclohexane backbone, and the bifunctional phosphinothioureas **1d**—**1f** derived from (1*S*,2*S*)-2-amino-1-(diphenylphosphino)cyclohexane provided higher enantioselectivity than the corresponding diastereoisomers **1a**—**1c** (Entries 4—6 vs. 1—3). Meanwhile, *D*-glucose-based phosphinothioureas **1a** and **1d** exhibited better catalytic activity and enantioselectivity (Entries 1 and 4). It is obvious that phosphinothiourea **1d** was the best catalyst in term of reactivity and enantioselectivity (Entry 4, 90% yield and 79% *ee*), and the results were the same level as our previous reports.[7a,7b] Thus catalyst **1d** was selected for further studies.

Next, the solvent effect on the MBH reaction with 10 mol% organocatalyst **1d** was investigated. The results indicated that the solvent had a significant effect on the reactivity rather than the enantioselectivity (Table 2). When less polar solvents such as toluene, dichloromethane and chloroform were used as reaction media, the MBH reactions were sluggish and resulted in poor chemical yields (27%—35% yield, Entries 1—3). Among the examined solvents, THF and 1,4-dioxane provided excellent chemical yields (Entries 5 and 6), while the use of other aprotic polar solvents led to moderate chemical yields (64%—77% yield, Entries 7—9). In the case of MeOH, the MBH product was obtained in low yield due to the side-reaction, and the enantioselectivity was lower than others. Regarding of both chemical yield and enantioselectivity, THF was selected as solvent for further optimization of reaction conditions.

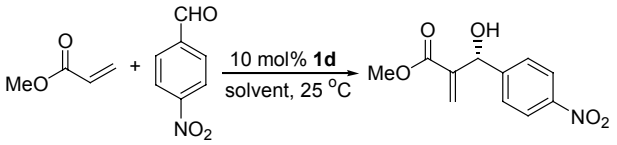
Table 1 Screening of the organocatalysts for the MBH reaction of methyl acrylate and 4-nitrobenzaldehyde[a]



Entry	Catalyst	Time/h	Yield[b]/%	*ee*[c]/%
1	**1a**	8	97	−61
2	**1b**	6	94	−36
3	**1c**	24	41	−60
4	**1d**	24	90	79
5	**1e**	24	49	77
6	**1f**	24	70	73

[a] The reactions were conducted with 10 mol% of organocatalyst, 5 equiv. of methyl acrylate in THF (0.2 mol/L) at 25 ℃. [b] Isolated yields. [c] Determined by chiral HPLC.

Table 2 The effect of solvent on the MBH reaction between methyl acrylate and 4-nitrobenzaldehyde[a]



Entry	Solvent	Time/h	Yield[b]/%	*ee*[c]/%
1	Toluene	48	35	76
2	CH_2Cl_2	48	28	70
3	$CHCl_3$	48	27	73
4	Ether	24	62	74
5	THF	24	89	77
6	1,4-Dioxane	24	94	74
7	CH_3CN	24	64	64
8	DMF	18	76	68
9	DMSO	18	77	59
10	CH_3OH	6	42	25

[a] The reactions were conducted with 10 mol% of organocatalyst **1d**, 5 equiv. of methyl acrylate in solvent (0.2 mol/L) at 25 ℃. [b] Isolated yields. [c] Determined by chiral HPLC.

Moreover, the reaction conditions including the ratio of methyl acrylate to 4-nitrobenzaldehyde (**2**/**3**), the reaction temperature, the substrate concentration and the loading of catalyst **1d** were studied. The results summarized in Table 3 indicated that the chemical yield was slightly improved when increasing the amount of methyl acrylate, and the enantioselectivity was changeless (Entries 1—5. The MBH reaction was sensitive to the reaction temperature. The higher temperature resulted in better chemical yield but lower enantioselectivity (Entries 4, 6 and 7). In view of chemical yield and stereoselectivity, the suitable reaction temperature was 25 ℃. When the catalyst loading was reduced to 8 mol%, the reaction rate decreased obviously, and the

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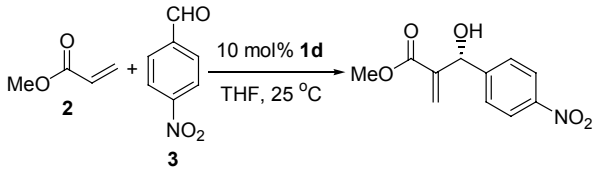
MBH reaction was uncompleted even in 2 d (Entry 8 vs. 4). The lower substrate concentration exhibited positive effect on the enantioselectivity, but the effect on the reactivity was irregular (Entries 9—11 and 4). Among the examined aldehyde concentration, 0.1 mol/L was the optimal one (Entry 10).

Table 3 Further optimization of reaction conditions of MBH reaction[a]



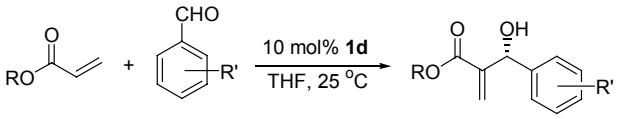
Entry	**2**/**3**	Conc./(mol•L^{-1})	Time/h	Yield[b]/%	*ee*[c]/%
1	2	0.2	24	85	77
2	4	0.2	24	87	77
3	5	0.2	24	89	77
4	6	0.2	24	90	77
5	10	0.2	24	93	77
6[d]	6	0.2	48	63	83
7[e]	6	0.2	24	94	74
8[f]	6	0.2	48	75	77
9	6	0.05	24	78	80
10	6	0.1	28	91	79
11	6	0.3	24	87	78

[a] Unless stated otherwise, the reactions were performed with 10 mol% **1d** in THF at 25 ℃. [b] Isolated yields. [c] Determined by chiral HPLC. [d] The reaction was performed at 0 ℃. [e] The reaction was performed at 40 ℃. [f] The loading of organocatalyst **1d** was 8 mol%.

With the optimized reaction conditions in hand (10 mol% **1d**, 6 equiv. of acrylate, THF as solvent, 25 ℃), the substrate scope was surveyed (Table 4). Except the bulky *t*-butyl acrylate, the MBH reaction of alkyl acrylates with 4-nitrobenzaldehyde exhibited similar level of enantioselectivities and chemical yields (Entries 1—4 vs. 5). However, the catalytic system was inefficient for aryl acrylate, and the chemical yield of MBH adducts was poor (Entries 6 and 7). Therefore, methyl, butyl and benzyl acrylates were applied as nucleophiles to investigate the substrate scope of aldehydes. In general, the benzaldehydes bearing strong electron-withdrawing group provided good yields (Entries 1—4 and 8—16), and less active aromatic aldehydes gave low yields (Entries 17—21). Regarding the stereoselectivity, except using 2-substituted benzaldehyde as electrophile (Entries 11 — 13), moderate-to-good enantioselectivities were achieved (68%—83% *ee*).

The absolute configurations of the MBH reaction products were assigned as *R*-configuration by comparison of the optical rotation with that of literature report.[3,7,10] The possible mechanism for the asymmetric MBH reaction is as similar as that in our pervious work.[7b,8b] The proposed transition state is illustrated in

Table 4 The MBH reactions of different arcylates and aldehydes catalyzed by **1d**[a]



Entry	R	R'	Time/h	Yield[b]/%	*ee*[c]/%
1	Me	4-NO_2	28	91	79
2	Et	4-NO_2	24	90	75
3	*n*-Bu	4-NO_2	24	96	76
4	Bn	4-NO_2	24	96	83
5	*t*-Bu	4-NO_2	51	35	29
6	1-naphthyl	4-NO_2	51	7	48
7	Ph	4-NO_2	51	6	73
8	Me	3-NO_2	48	89	79
9	*n*-Bu	3-NO_2	24	91	77
10	Bn	3-NO_2	24	90	81
11	Me	2-NO_2	48	68	72
12	*n*-Bu	2-NO_2	24	77	50
13	Bn	2-NO_2	24	69	52
14	Me	4-CF_3	48	41	77
15	*n*-Bu	4-CF_3	48	80	70
16	Bn	4-CF_3	48	51	77
17	*n*-Bu	4-Br	48	25	72
18	Me	4-Cl	48	31	69
19	*n*-Bu	4-Cl	48	23	72
20	Me	H	96	7	68
21	*n*-Bu	H	96	9	70

[a] The reactions were performed with 10 mol% of **1d** and 6 equiv. of acrylate in THF (0.1 mol/L) at 25 ℃. [b] Isolated yields. [c] Determined by chiral HPLC.

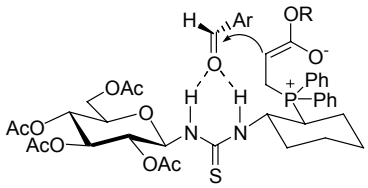


Figure 3 Proposed transition state.

Figure 3. The thiourea scaffold of the bifunctional organocatalyst forms hydrogen-bond with the aldehyde carbonyl, and the chiral cyclohexyl backbone causes the phosphinoyl associated enolate to attack the activated carbonyl from the *si*-face to provide the product in the *R*-configuration.

Conclusions

In summary, we developed a new class of chiral bifunctional organocatalysts derived from *trans*-2-amino-1-(diphenylphosphino)cyclohexane and saccharide, which showed good catalytic activity and enantio-selectivity in the asymmetric Morita-Baylis-Hillman reaction between alkyl acrylates and aromatic aldehydes.

Further efforts are underway with a focus on expanding the application of these bifunctional phosphinothiourea organocatalyts to other useful transformations.

Experimental

General Information

Melting points were taken without correction. Optical rotations were measured on a WZZ-2A digital polarimeter at the wavelength of the sodium D-line (589 nm) at 20 ℃. NMR spectra were recorded on Bruker 400 spectrometer. Chemical shifts (δ) of ^{1}H NMR and ^{13}C NMR spectra were recorded relative to tetramethylsilane (δ 0.00). Chemical shifts of ^{31}P NMR spectra were reported and referenced to 85% H_3PO_4 (δ 0.0). IR spectra were recorded on Nicolet Magna-I 550 spectrometer. High Resolution Mass spectra (HRMS) were recorded on Micromass GCT spectrometer with Electron Ionization resource. HPLC analysis was performed on Waters equipment with 2487 detector using Daicel Chiralcel OD-H column, Chiralpak AS-H or AD-H column.

Toluene, ether and 1,4-dioxane were freshly distilled from sodium-benzophenone. Dichloromethane, chloroform and acetonitrile were distilled from CaH_2. DMF and DMSO were dried over CaH_2 and distilled under reduced pressure. Methanol was distilled from magnesium. Thin-layer chromatography (TLC) was performed on pre-coated silica gel plate. Column chromatography was performed using silica gel (300—400 mesh) eluting with ethyl acetate and petroleum ether.

General procedure for the synthesis of catalysts 1a—1f

To a solution of (*R*,*R*)- or (*S*,*S*)-1-amino-2-(diphenylphosphino)cyclohexane (283 mg, 1.0 mmol) in 3.0 mL CH_2Cl_2 was added the corresponding sugar-derived isothiocyanate (428 mg, 1.1 mmol) at room temperature, and the resulting mixture was stirred at this temperature until the reaction completed (monitored by TLC). Then, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (2∶1, petroleum ether∶ethyl acetate) to afford the saccharide-based phosphinothiourea compounds **1a**—**1f**.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(3-((1*R*,2*R*)-2-(diphenylphosphino)cyclohexyl)thioureido)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (1a) 92% yield, white solid, m.p. 93—95 ℃; $[\alpha]_D^{20}$ −16.3 (*c* 0.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.65—7.62 (m, 2H), 7.52—7.35 (m, 8H), 5.82 (br, 2H), 5.26 (t, *J*=9.0 Hz, 1H), 5.02 (t, *J*=9.8 Hz, 1H), 4.84—4.80 (m, 1H), 4.58—4.25 (m, 2H), 4.16—4.12 (m, 1H), 3.67 (br, 1H), 2.43—2.31 (m, 2H), 2.15 (s, 3H), 2.08—2.04 (m, 9H), 1.74—1.71 (m, 4H), 1.47—1.14 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 181.8, 171.2, 170.6, 169.9, 169.7, 137.2, 135.0 (d, *J*=15.0 Hz), 134.3 (d, *J*=20.6 Hz), 133.2 (d, *J*=19.3 Hz), 129.1, 128.9 (d, *J*=6.7 Hz), 128.8, 128.4 (d, *J*=7.5 Hz), 82.0, 73.0, 72.5, 70.7, 68.4, 62.1, 56.7, 40.6, 33.0, 27.8, 25.5, 24.3, 20.9, 20.8, 20.6, 20.5; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4) δ: −5.68; IR (KBr) *v*: 3432, 3071, 2933, 2855, 1754, 1633, 1533, 1434, 1368, 1229, 1038, 908, 745, 699 cm^{-1}; HRMS (EI) calcd for $C_{33}H_{41}N_2O_9PS$ ($[M]^+$) 672.2270, found 672.2271.

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(3-((1*R*,2*R*)-2-(diphenylphosphino)cyclohexyl)thioureido)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (1b) 90% yield, white solid, m.p. 105—107 ℃; $[\alpha]_D^{20}$ −16.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68—7.64 (m, 2H), 7.49—7.35 (m, 8H), 5.92 (br, 2H), 5.40 (s, 1H), 5.02 (s, 2H), 4.32 (br, 1H), 4.16—4.08 (m, 2H), 3.81 (s, 1H), 2.44—2.33 (m, 2H), 2.17—2.12 (m, 9H), 2.01 (s, 3H), 1.77—1.66 (m, 4H), 1.48—1.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 181.8, 171.4, 170.4, 170.2, 169.9, 135.0 (d, *J*=14.5 Hz), 134.4 (d, *J*=20.7 Hz), 133.1 (d, *J*=18.9 Hz), 129.1, 129.0 (d, *J*=6.5 Hz), 128.7, 128.4 (d, *J*=7.5 Hz), 82.3, 71.8, 70.7, 68.2, 67.2, 61.5, 56.9, 40.6, 33.3, 27.9, 25.7, 24.5, 20.9, 20.8, 20.7, 20.6; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4) δ: −5.36; IR (KBr) *v*: 3373, 3053, 2932, 2855, 1751, 1533, 1434, 1370, 1229, 1084, 1052, 955, 745, 699 cm^{-1}; HRMS (EI) calcd for $C_{33}H_{41}N_2O_9PS$ ($[M]^+$) 672.2270, found 672.2254.

(2*R*,3*R*,4*S*,5*S*,6*S*)-2-(Acetoxymethyl)-6-(3-((1*R*,2*R*)-2-(diphenylphosphino)cyclohexyl)thioureido)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (1c) 90% yield, white solid, m.p. 101—103 ℃; $[\alpha]_D^{20}$ +17.6 (*c* 0.85, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.51—7.29 (m, 10H), 7.18 (br, 1H), 6.61 (s, 1H), 5.40—5.35 (m, 3H), 5.29—5.26 (m, 1H), 4.29—4.16 (m, 4H), 2.37—2.34 (m, 2H), 2.20 (s, 3H), 2.05—2.02 (m, 9H), 1.90—1.65 (m, 3H), 1.32—1.22 (m, 3H), 0.94 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 182.4, 170.4, 170.3, 170.0, 169.6, 135.6 (d, *J*=11.2 Hz), 135.0 (d, *J*=20.3 Hz), 133.8 (d, *J*=15.7 Hz), 132.1 (d, *J*=16.3 Hz), 129.2, 128.5 (d, *J*=5.2 Hz), 128.2 (d, *J*=7.5 Hz), 128.0, 81.4, 69.2, 68.8, 68.6, 65.3, 61.3 (d, *J*=7.6 Hz), 55.2 (d, *J*=13.7 Hz), 40.2, 33.5, 27.1, 25.5, 24.3, 20.9, 20.8, 20.7, 20.6; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4) δ: −6.86; IR (KBr) *v*: 3432, 2932, 2854, 1751, 1538, 1434, 1369, 1227, 1054, 745, 699 cm^{-1}; HRMS (EI) calcd for $C_{33}H_{41}N_2O_9PS$ ($[M]^+$) 672.2270, found 672.2271.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(3-((1*S*,2*S*)-2-(diphenylphosphino)cyclohexyl)thioureido)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (1d) 92% yield, white solid, m.p. 93—95 ℃; $[\alpha]_D^{20}$ +35.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.47—7.36 (m, 10H), 6.14 (br, 2H), 5.83 (t, *J*=8.8 Hz, 1H), 5.37 (t, *J*=9.6 Hz, 1H), 5.11 (t, *J*=9.8 Hz, 1H), 4.90 (br, 1H), 4.38 (d, *J*=10.4 Hz, 1H), 4.15 (d, *J*=11.2 Hz, 1H), 3.87 (d, *J*=10.0 Hz, 1H), 2.33 (br, 1H), 2.07—2.03 (m, 12H), 1.86—1.64 (m, 5H), 1.38—1.26 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 182.4, 171.1, 170.8, 169.9, 169.8, 134.7 (d, *J*=20.5 Hz), 134.3 (d, *J*=8.9 Hz), 133.6 (d, *J*=8.0 Hz), 132.4, 129.8 (d, *J*=11.6 Hz),

129.3 (d, J=12.1 Hz), 128.6, 128.3, 81.8, 73.8, 73.3, 70.7, 68.3, 61.8, 54.5, 40.4, 33.0, 27.0, 26.0, 24.1, 20.8, 20.7, 20.6, 20.5; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4) δ: −6.14; IR (KBr) v: 3364, 3053, 2933, 2855, 1752, 1539, 1434, 1368, 1229, 1038, 745, 699 cm^{-1}; HRMS (EI) calcd for $C_{33}H_{41}N_2O_9PS$ ([M]$^+$) 672.2270, found 672.2268.

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(3-((1*S*,2*S*)-2-(diphenylphosphino)cyclohexyl)thioureido)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (1e) 87% yield, white solid, m.p. 110—112 ℃; $[\alpha]_D^{20}$ +55.0 (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.48—7.36 (m, 10H), 6.26 (br, 2H), 5.77 (s, 1H), 5.47 (s, 1H), 5.22—5.13 (m, 2H), 4.18—4.07 (m, 3H), 2.34 (br s, 1H), 2.18 (s, 3H), 2.05—2.01 (m, 9H), 1.86—1.64 (m, 5H), 1.31—1.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 181.9, 171.5, 170.5, 170.1, 169.8, 136.3 (d, J=9.2 Hz), 134.8 (d, J=20.3 Hz), 134.4 (d, J=16.9 Hz), 132.4 (d, J=14.5 Hz), 129.2, 128.6, 128.3, 128.2, 83.3, 72.4, 70.9, 68.5, 67.3, 61.2, 54.5, 40.5, 33.2, 27.2, 25.4, 24.2, 20.9, 20.8, 20.7, 20.6; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4) δ: −6.26; IR (KBr) v: 3374, 3053, 2933, 2856, 1751, 1539, 1434, 1370, 1227, 1083, 1052, 744, 699 cm^{-1}; HRMS (EI) calcd for $C_{33}H_{41}N_2O_9PS$ ([M]$^+$) 672.2270, found 672.2274.

(2*R*,3*R*,4*S*,5*S*,6*S*)-2-(Acetoxymethyl)-6-(3-((1*S*,2*S*)-2-(diphenylphosphino)cyclohexyl)thioureido)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (1f) 90% yield, white solid, m.p. 107—109 ℃; $[\alpha]_D^{20}$ +51.5 (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.62 (t, J=7.2 Hz, 2H), 7.54—7.48 (m, 2H), 7.36—7.30 (m, 5H), 7.28—7.23 (m, 1H), 6.55 (d, J=8.4 Hz, 1H), 6.32 (br s, 1H), 5.23—5.18 (m, 2H), 5.11—5.08 (m, 1H), 4.46 (s, 1H), 4.26—4.12 (m, 3H), 4.01—3.98 (m, 1H), 2.46—2.41 (m, 1H), 2.31—2.28 (m, 1H), 2.20 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.78—1.73 (m, 3H), 1.48—1.38 (m, 1H), 1.31—1.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 181.7, 170.6, 170.2, 169.7, 169.5, 137.6 (d, J=13.8 Hz), 135.6 (d, J=15.0 Hz), 134.4 (d, J=20.9 Hz), 133.1 (d, J=19.2 Hz), 129.0, 128.5 (d, J=6.6 Hz), 128.4, 128.3 (d, J=7.7 Hz), 80.3, 69.1, 68.7, 67.9, 65.7, 62.2, 57.2 (d, J=17.5 Hz), 40.7 (d, J=15.5 Hz), 33.5, 28.0, 25.6, 24.7, 20.9, 20.8, 20.7, 20.7; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4) δ: −5.84; IR (KBr) v: 3356, 2932, 2854, 1751, 1539, 1434, 1368, 1225, 1055, 744, 699 cm^{-1}; HRMS (EI) calcd for $C_{33}H_{41}N_2O_9PS$ ([M]$^+$) 672.2270, found 672.2274.

General procedure for the asymmetric Morita-Baylis-Hillman reaction

To a solution of the glucose-based phosphinothiourea **1d** (0.03 mmol) in THF (3.0 mL) was added the acrylate (1.8 mmol) at 25 ℃. After stirring for 10 min at this temperature, the aldehyde (0.3 mmol) was added. Then the resulting mixture was stirred at 25 ℃ until the reaction was completed (monitored by TLC). After removing the solvent under reduced pressure, the residue was purified by flash column chromatography to afford the desired product, and the *ee* value was determined by HPLC analysis with a chiral column.

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(Lu, Y.)

