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Enantioselective intramolecular Morita–Baylis–Hillman reaction using chiral bifunctional phosphinothiourea as an organocatalyst

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ABSTRACT

Chiral cyclohexane-based phosphinothioureas were found to be efficient organocatalysts for the enantioselective intramolecular Morita–Baylis–Hillman reaction of ω-formyl-enone. Among the solvents screened, *t*-BuOH was the best one which provided good yield and enantioselectivity. Moreover in the presence of 3 mol % of phosphinothiourea **2b**, the desired products were obtained in good-to-excellent yields with up to 98% ee under mild reaction conditions.

1. Introduction

The Morita–Baylis–Hillman (MBH) reaction is a powerful tool to construct densely functionalized α-methylene-β-hydroxycarbonyl derivatives which could serve as valuable building blocks in organic synthesis.[1] During the past decade, much effort was devoted to promote the efficiency of this reaction.[1,2] In an asymmetric version, various chiral catalysts have been developed for intermolecular MBH reactions.[3] However, the exploration of the enantioselective intramolecular MBH reaction is still a challenge and reports in this area appear scarce. The first enantioselective intramolecular MBH reaction was reported by Fráter in 1992,[4] using (−)-CAMP as a catalyst to provide the corresponding adduct with 14% ee. A major contribution in this area was the accomplishment of a proline-catalyzed intramolecular MBH reaction of hept-2-enedial, providing 98% ee with 74% yield by Hong et al. in 2005.[5] Another enantioselective organocatalytic intramolecular MBH reaction, using pipecolinic acid and *N*-methylimidazole as a cocatalytic system, was developed by Miller with 84% ee.[6] In the field of metal-catalyzed reactions, Gladysz et al. reported the chiral rhenium-containing phosphine (η^5-C_5H_5)Re(NO)(PPh_3)(CH_2PAr_2)-catalyzed intramolecular MBH reaction with 74% ee.[7]

It is well known that a phosphine (PR_3) could activate the Michael acceptor to catalyze the diastereoselective intramolecular MBH reaction,[8] and chiral thiourea derivatives were efficient catalysts for the intermolecular MBH reactions.[3h–k,9] Very recently we have developed a new family of phosphinothioureas derived from amino acids and demonstrated their utility in the asymmetric intramolecular MBH reaction; L-phenylalanine-derived phosphinothiourea **1** could provide the cyclic products with up to 84% ee.[10] We have also found that the cyclohexane-based phosphinothiourea is highly efficient for the intermolecular MBH reaction between enone and aldehyde.[9a] Therefore, we have begun to examine the cyclohexane-based phosphinothiourea **2** for the intramolecular MBH reaction of ω-formyl-enone in order to explore more efficient catalysts (see Fig. 1).

2. Results and discussion

In our previous work, the phosphinothiourea **2a** demonstrated a high efficiency in the enantioselective MBH reaction between aromatic aldehydes with MVK.[9a] Therefore, we initiated our studies with cyclohexane-based phosphinothiourea **2a** (10 mol % catalyst loading) as the catalyst and **3a** as the substrate. The reaction was performed at 25 °C in CH_2Cl_2 and we obtained the MBH product **4a** in 81% yield with poor enantioselectivity (20% ee, Table 1, entry 1). Catalyst screening showed that phosphinothiourea **2b** provided the desired product in nearly quantitative yield with 76% ee (entry 2). Comparatively, amino acid-derived phosphinothiourea **1** could complete this reaction with a shorter time to afford the product with the same enantioselectivity (opposite configuration) but lower yield (entry 8 vs 2). As illustrated in Table 1, compared to the cyclohexane-based organocatalysts with aromatic thioureas, the corresponding organocatalysts bearing aliphatic group at the thiourea moieties provided poor enantioselectivity and a longer time was required to accomplish the reaction (entries 5–7 vs 2–4). Catalyst **2c** containing an electron-rich group at a phenyl ring provided poor yield together with by-products. On the other hand, catalysts containing an electron-deficient substituent at a phenyl group could improve the enantioselectivity (entries 2 and 4 vs 1 and 3). Decreasing the catalyst loading of **2b** to 5 mol % gave the MBH product in 90% yield with 82% ee (entry 9). However, further decreasing the catalyst loading to 3 mol % resulted in an obvious decrease in yield without the enhancement of enantioselectivity (entry 10 vs 9).

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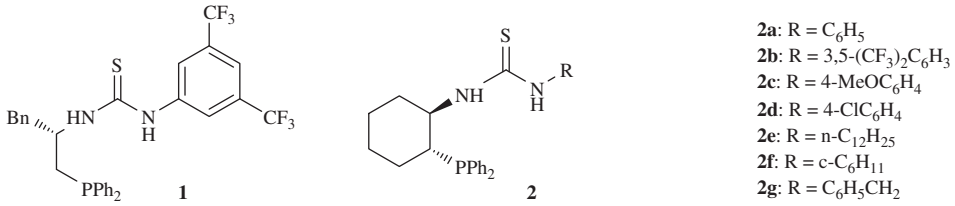
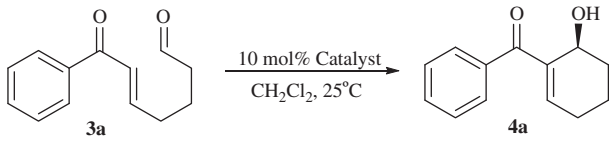


Figure 1. Structures of the phosphinothiourea catalysts.

Table 1
Catalysts screening for the intramolecular MBH reaction of **3a**[a]



Entry	Catalyst	Time (days)	Yield[b] (%)	ee[c] (%)
1	**2a**	4.5	81	20
2	**2b**	1.5	99	76
3	**2c**	1.5	42	25
4	**2d**	1.5	76	49
5	**2e**	4.5	80	26
6	**2f**	4.5	63	36
7	**2g**	4.5	90	20
8	**1**	0.5	83	−76
9[d]	**2b**	3	90	82
10[e]	**2b**	4	59	82

[a] Unless stated otherwise, the reactions were performed with 10 mol % organocatalyst, 0.2 mmol **3a** in 1.0 mL CH_2Cl_2 (0.2 M) at 25 °C.
[b] Isolated yields.
[c] The ee was determined by chiral HPLC, and the absolute configuration was determined by comparison of specific rotation with that of a literature report.[6]
[d] Using 5 mol % **2b** as catalyst.
[e] Using 3 mol % **2b** as catalyst.

Next, 5 mol % of phosphinothiourea **2b** was used to evaluate the effect of solvent on the reaction (Table 2). In non-protic solvents except $CHCl_3$ and CH_2Cl_2, poor yields were obtained and a longer time was required (entries 1–8). Nonpolar solvents such as *n*-hexane and toluene afforded moderate enantioselectivity (entries 1 and 2). The best enantioselectivity was obtained in acetone (91% ee), although the chemical yield was unsatisfactory (64%, entry 6). Comparatively, a rate acceleration was observed in protic solvents, which could act as a shuttle to reduce the proton-transfer energy to activate this reaction.[11] Moreover tertiary alcohols provided better enantioselectivity than secondary and primary alcohols (entries 15 and 16 vs 9–14). Among them, *t*-BuOH afforded the desired adduct in 87% yield with 86% ee within 1.5 days, which was a more suitable solvent in terms of enantioselectivity and yield (entry 15).

Encouraged by these results, we continued optimizing the reaction conditions, including the substrate concentration, catalyst loading and reaction temperature. As summarized in Table 2, the substrate concentration was reduced from 0.4 M to 0.1 M with an increase of the enantioselectivity from 76% ee to 86% ee (entries 17–19). However, lowering the substrate concentration from 0.1 M to 0.05 M did not have an appreciable effect on enantioselectivity but caused a slight decrease in the chemical yield (entry 20 vs 19). The MBH reaction could be performed with a reduced amount of catalyst loading, where an analogous result (85% ee, 92% yield) was achieved with 3 mol % and 5 mol % of catalyst (entry 21 vs 19), but further lowering of the catalyst loading to 1 mol % led to a pronounced decrease in the yield (entry 22 vs 21). Moreover, the enantioselectivity and yield of the MBH reaction were insensitive to the reaction temperature. Increasing the reaction temperature from 25 °C to 40 °C provided almost the same enantioselectivity (entry 21 vs 23). Therefore, the reaction conditions using 3 mol % of **2b** in *t*-BuOH (0.1 M) at 25 °C were chosen for further investigation.

Under the optimized conditions, the enantioselective intramolecular MBH reaction involving various ω-formyl-enone substrates was investigated. As indicated in Table 3, all the substituted aromatic enones were converted to the corresponding products in 86–98% yields (entries 1–9 and 11–14), except substrate **3j** bearing an *ortho*-methyl group at the phenyl ring (63% yield, entry 10). The substrates **3k–n** with electron-rich substituents could obtain excellent enantioselectivity (entries 11–14 and 90–98% ee). And lower enantioselectivity was observed for the *meta*-substituted substrates compared to their relevant *para*-substituted analogues (entries 4 vs 5, 6 vs 7, and 11 vs 12). However, an *ortho*-substituent at the phenyl group in the cases of substrates **3c** and **3j** had a deleterious effect on enantioselectivity, probably due to the *ortho*-effect (entries 3 and 10). The thiophene analogue **3o** exhibited low reactivity to give the corresponding adducts in 73% yield with 76% ee (entry 15). By comparing the specific rotation values with those reported in the literature,[6] the MBH adducts were assigned an (*S*)-configuration.

The intramolecular MBH reaction of **3p** and **3q** was also investigated under the optimized conditions (Scheme 1). The five-membered ring enone **3p** was converted to the corresponding product **4p** with 42% yield and 89% ee after a reaction time of three days. However, the seven-membered ring precursor **3q** could not be cyclized under the typical conditions even after seven days. The results indicated that six-membered ring products could be easily formed under the typical conditions. This is probably due to the effect of the strain that was generated from cyclization of intermediate to the product.

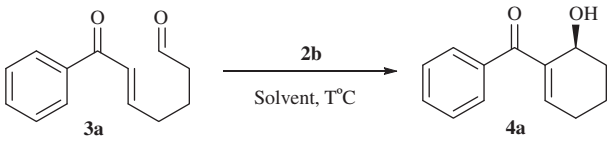
The phosphinothiourea **2b** showed considerable stability toward air oxidation. A single crystal could be obtained from a solution of **2b** in ethyl acetate/*n*-heptane or CH_2Cl_2/*n*-heptane by slow evaporation.[12] The X-ray analysis further confirmed the structure of **2b** (Fig. 2).

According to the above-mentioned experimental results and related reports,[3h–k,9,10] a probable mechanism for the chiral phosphinothiourea-catalyzed intramolecular MBH was proposed (Scheme 2). The thiourea moiety could activate the aldehyde moiety by forming a hydrogen-bond with the oxygen atom of the carbonyl. A nucleophilic addition of the phosphine to the β-position of the Michael acceptor generates an enolate. The cyclohexyl scaffold forces the phosphinoyl-associated enolate to attack the activated carbonyl from the *si*-face to generate the product with an (*S*)-configuration.

3. Conclusion

In summary, the chiral cyclohexane-based phosphinothiourea **2b** was an efficient organocatalyst for the enantioselective intramolecular MBH reaction of ω-formyl-α,β-unsaturated carbonyl compounds; using alcohols as a solvent could promote this reaction. With 3 mol % of **2b** in *t*-BuOH, the intramolecular MBH

Table 2
Reaction condition optimization of the intramolecular MBH reaction of **3a**



Entry	Solvent	**2b** (mol %)	*M* (mol/L)	*T* (°C)	Time (days)	Yield[a] (%)	ee[b] (%)
1	*n*-Hexane	5	0.2	25	3	25	72
2	Toluene	5	0.2	25	3	25	40
3	$CHCl_3$	5	0.2	25	3	88	57
4	CH_2Cl_2	5	0.2	25	3	90	82
5	THF	5	0.2	25	3	10	88
6	Acetone	5	0.2	25	3	64	91
7	CH_3CN	5	0.2	25	3	73	86
8	DMF	5	0.2	25	3	Trace	n.d.[c]
9	MeOH	5	0.2	25	3	70	3
10	EtOH	5	0.2	25	2.5	95	51
11	*n*-PrOH	5	0.2	25	2	75	53
12	*i*-PrOH	5	0.2	25	2	94	77
13	*n*-BuOH	5	0.2	25	2	91	56
14	*i*-BuOH	5	0.2	25	2	86	54
15	*t*-BuOH	5	0.2	25	1.5	87	86
16	*t*-Pentanol	5	0.2	25	2	87	80
17	*t*-BuOH	5	0.4	25	1.5	94	76
18	*t*-BuOH	5	0.3	25	1.5	93	80
19	*t*-BuOH	5	0.1	25	1.5	93	86
20	*t*-BuOH	5	0.05	25	1.5	90	87
21	*t*-BuOH	3	0.1	25	2	92	85
22	*t*-BuOH	1	0.1	25	3	64	85
23	*t*-BuOH	3	0.1	40	1.5	93	84

[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] Not determined.

reaction could be carried out at room temperature to provide the desired products in up to 98% ee and good-to-excellent yields (up to 98%) without special precautions such as an inert atmosphere. Further efforts are currently underway with a focus on designing new bifunctional catalysts to improve the reaction enantioselectivity and extend the substrate scope.

4. Experimental

4.1. General experimental

All commercially available reagents were used without purification and solvents were dried and distilled before use. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 400 spectrometer. Optical rotations were measured on a WZZ-2A digital polarimeter at the wavelength of the sodium D-line (589 nm). IR spectra were recorded on a Nicolet Magna-I 550 spectrometer. High Resolution Mass spectra (HRMS) were recorded on a KE465 LCT Premier/XE spectrometer. X-ray crystallographic data were collected on a Bruker SMART APEX diffractometer at 293 (2) K. HPLC analysis was performed on Waters 510 with 2487 detector using Daicel Chiralpak AS-H, AD-H, or Chiralcel OD-H column.

4.2. General procedure for the asymmetric intramolecular MBH reactions

Phosphinothiourea **2b** (3.3 mg, 0.006 mmol) was added to a solution of aldehyde **3**[8a,13] (0.2 mmol) in dry *t*-BuOH (2.0 mL) at room temperature. The mixture was stirred at the same temperature (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 (SiO_2, eluent: PE/EA/CH_2Cl_2) to afford the intramolecular MBH adduct **4**[14] and the ee value was determined by HPLC analysis with chiral column.

4.2.1. (*S*)-2-Benzoyl-1-hydroxycyclohex-2-ene 4a[6,14]

HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 95/5, flow rate: 0.9 mL/min): t_R = 13.4 min (minor), 16.6 min (major); $[\alpha]_D^{25} = -36.1$ (*c* 0.42, $CHCl_3$, 85% ee).

4.2.2. (*S*)-(6-Hydroxycyclohex-1-enyl)(4-nitrophenyl) methanone 4b

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 6.73 (s, 1H), 4.79 (s, 1H), 3.38 (s, 1H), 2.43–2.25 (m, 2H), 1.98–1.86 (m, 3H), 1.70–1.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.0, 149.5, 149.1, 143.4, 140.3, 130.0, 123.5, 63.3, 29.8, 26.7, 17.3; IR (KBr, cm^{-1}): ν 3425, 2940, 2866, 1652, 1601, 1522, 1350, 1268, 987, 855, 726; HRMS (ESI) calcd for $C_{13}H_{13}NO_4Na$ ([M+Na]$^+$)- 270.0742, found: 270.0750. HPLC analysis (AS-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): t_R = 20.5 min (minor), 44.9 min (major).

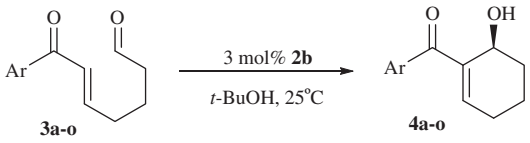
4.2.3. (*S*)-(2-Bromophenyl)(6-hydroxycyclohex-1-enyl) methanone 4c[14]

HPLC analysis (AS-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 1.0 mL/min): t_R = 7.7 min (minor), 17.0 min (major).

4.2.4. (*S*)-(3-Bromophenyl)(6-hydroxycyclohex-1-enyl) methanone 4d[14]

HPLC analysis (AD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 1.0 mL/min): t_R = 13.9 min (minor), 12.2 min (major); $[\alpha]_D^{25} = -8.7$ (*c* 0.23, $CHCl_3$, 63% ee).

Table 3
2b-Catalyzed intramolecular MBH reaction[a]



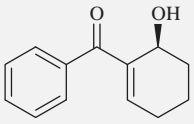
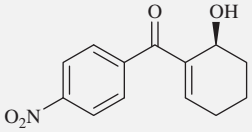
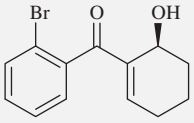
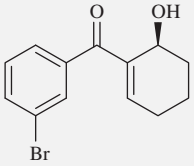
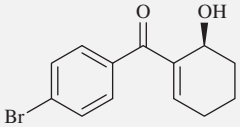
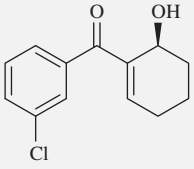
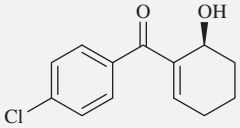
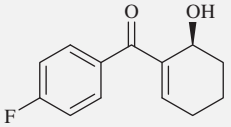
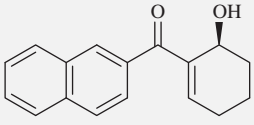
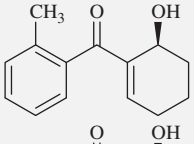
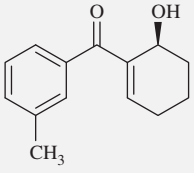
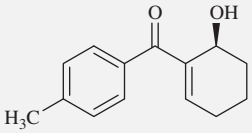
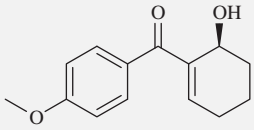
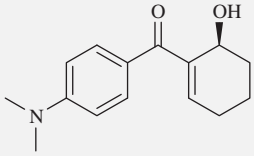
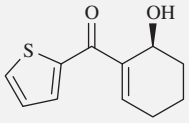
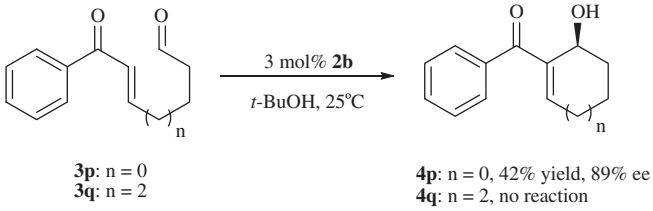
Entry	Product	Time (days)	Yield[b] (%)	ee[c] (%)
1	 **4a**	2	92	85
2	 **4b**	1.5	98	39
3	 **4c**	2	97	16
4	 **4d**	3	92	63
5	 **4e**	2	90	75
6	 **4f**	2.5	95	65
7	 **4g**	2	90	79
8	 **4h**	2	93	83
9	 **4i**	4	92	83
10	 **4j**	5	63	66
11	 **4k**	2.5	96	90

Table 3 (*continued*)

Entry	Product	Time (days)	Yield[b] (%)	ee[c] (%)
12	 **4l**	2.5	90	93
13	 **4m**	4	92	97
14	 **4n**	6	86	98
15	 **4o**	7	73	76

[a] The reactions were conducted with 3 mol % **2b**, 0.2 mmol **3** in 2.0 mL *t*-BuOH (0.1 M) at 25 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC.



Scheme 1. The intramolecular MBH reaction of **3p** and **3q**.

4.2.5. (*S*)-(4-Bromophenyl)(6-hydroxycyclohex-1-enyl) methanone 4e[6,14]

HPLC analysis (AD-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 1.0 mL/min): $t_R = 8.8$ min (minor), 15.2 min (major); $[\alpha]_D^{25} = -20.0$ (*c* 0.35, $CHCl_3$, 75% ee).

4.2.6. (*S*)-(3-Chlorophenyl)(6-hydroxycyclohex-1-enyl) methanone 4f

^1H NMR ($CDCl_3$, 400 MHz): δ 7.62 (s, 1H), 7.54–7.50 (m, 2H), 7.38 (t, $J = 8.0$ Hz, 1H), 6.73 (t, $J = 4.0$ Hz, 1H), 4.74 (s, 1H), 3.35 (s, 1H), 2.41–2.23 (m, 2H), 1.97–1.85 (m, 3H), 1.71–1.63 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.3, 147.3, 139.7, 139.2, 134.1, 131.6, 129.3, 128.9, 127.1, 63.4, 29.5, 26.2, 17.1; IR (KBr, cm^{-1}): ν 3441, 2937, 2865, 1644, 1567, 1455, 1248, 1081, 988, 745; HRMS (ESI) calcd for $C_{13}H_{13}O_2ClNa$ ($[M+Na]^+$): 259.0502, found: 259.0518. HPLC analysis (AS-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R = 7.5$ min (minor), 16.3 min (major); $[\alpha]_D^{25} = -16.3$ (*c* 0.40, $CHCl_3$, 65% ee).

4.2.7. (*S*)-(4-Chlorophenyl)(6-hydroxycyclohex-1-enyl) methanone 4g[6,14]

HPLC analysis (AS-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 1.0 mL/min): $t_R = 8.3$ min (minor), 16.4 min (major); $[\alpha]_D^{25} = -21.3$ (*c* 0.46, $CHCl_3$, 79% ee).

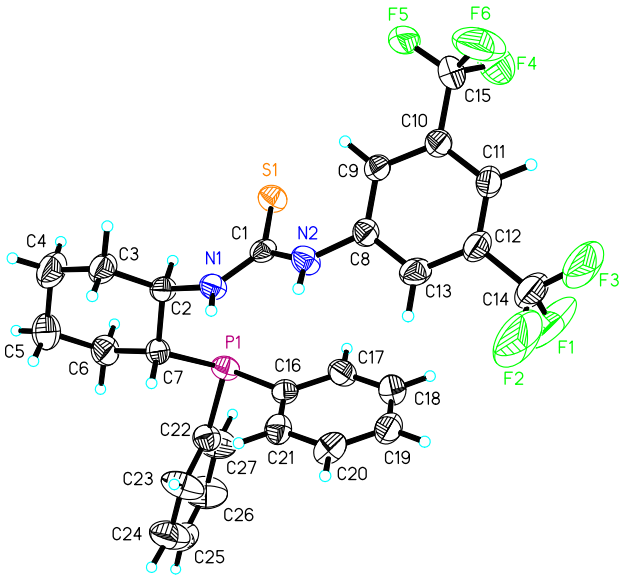


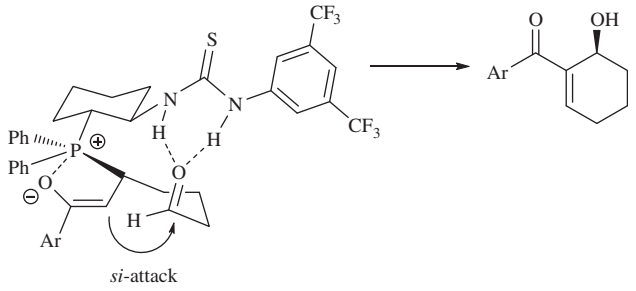
Figure 2. X-ray crystal structure of phosphinothiourea **2b**.

4.2.8. (*S*)-(4-Fluorophenyl)(6-hydroxycyclohex-1-enyl) methanone 4h[14]

HPLC analysis (AD-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.8 mL/min): $t_R = 18.2$ min (minor), 16.2 min (major); $[\alpha]_D^{25} = -31.8$ (*c* 0.33, $CHCl_3$, 83% ee).

4.2.9. (*S*)-(6-Hydroxycyclohex-1-enyl)(naphthalen-2-yl) methanone 4i[14]

HPLC analysis (OD-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 95/5, flow rate: 1.0 mL/min): $t_R = 13.2$ min (minor), 17.0 min (major); $[\alpha]_D^{25} = -36.8$ (*c* 0.38, $CHCl_3$, 83% ee).



Scheme 2. Proposed transition state.

4.2.10. (*S*)-(6-Hydroxycyclohex-1-enyl)(o-tolyl)methanone 4j[6,14]

HPLC analysis (AS-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R = 6.4$ min (minor), 12.7 min (major); $[\alpha]_D^{25} = -7.6$ (*c* 0.46, $CHCl_3$, 66% ee).

4.2.11. (*S*)-(6-Hydroxycyclohex-1-enyl)(m-tolyl)methanone 4k[14]

HPLC analysis (AS-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.9 mL/min): $t_R = 7.0$ min (minor), 17.2 min (major); $[\alpha]_D^{25} = -32.0$ (*c* 0.39, $CHCl_3$, 90% ee).

4.2.12. (*S*)-(6-Hydroxycyclohex-1-enyl)(p-tolyl)methanone 4l[7,14]

HPLC analysis (AD-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 1.0 mL/min): $t_R = 15.3$ min (minor), 17.1 min (major); $[\alpha]_D^{25} = -48.6$ (*c* 0.36, $CHCl_3$, 93% ee).

4.2.13. (*S*)-(6-Hydroxycyclohex-1-enyl)(4-methoxyphenyl) methanone 4m[14]

HPLC analysis (AS-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 1.0 mL/min): $t_R = 14.9$ min (minor), 40.1 min (major); $[\alpha]_D^{25} = -51.0$ (*c* 0.31, $CHCl_3$, 97% ee).

4.2.14. (*S*)-(4-(Dimethylamino)phenyl)(6-hydroxycyclohex-1-enyl)methanone 4n[14]

HPLC analysis (OD-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 0.8 mL/min): $t_R = 19.4$ min (minor), 16.9 min (major); $[\alpha]_D^{25} = -55.2$ (*c* 0.30, $CHCl_3$, 98% ee).

4.2.15. (*S*)-(6-Hydroxycyclohex-1-enyl)(thiophen-2-yl) methanone 4o[6,14]

HPLC analysis (OD-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 95/5, flow rate: 1.0 mL/min): $t_R = 18.5$ min (minor), 16.7 min (major); $[\alpha]_D^{25} = -40.4$ (*c* 0.26, $CHCl_3$, 76% ee).

4.2.16. (*S*)-(5-Hydroxycyclopent-1-enyl)(phenyl)methanone 4p[9a]

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.78–7.76 (m, 2H), 7.59–7.55 (m, 1H), 7.46 (t, $J = 7.6$ Hz, 2H), 6.72 (t, $J = 2.8$ Hz, 1H), 5.30 (s, 1H), 3.21 (br s, 1H), 2.83–2.74 (m, 1H), 2.59–2.34 (m, 2H), 1.97–1.90 (m, 1H); HPLC analysis (AS-H column, $\lambda = 254$ nm, eluent: *n*-hexane/*i*-propanol = 90/10, flow rate: 1.0 mL/min): $t_R = 7.5$ min (minor), 16.3 min (major).

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12. Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 753478. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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14. The analytical data of the intramolecular MBH products **4** could be found in our recent publication; see Ref. 10.