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The enantioselective intramolecular Morita–Baylis–Hillman reaction catalyzed by amino acid-derived phosphinothiourea

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ABSTRACT

A series of chiral bifunctional phosphinothioureas derived from L-amino acids have been developed to promote the enantioselective intramolecular Morita–Baylis–Hillman reaction. The process afforded the cyclic hydroxyl enones with up to 84% ee and good yields under mild conditions.

1. Introduction

The Morita–Baylis–Hillman (MBH) reaction,[1] one of the most fundamental and important processes for construction of C–C bonds and allylic alcohols, has received considerable interest in synthetic organic chemistry. In the last decades, there has been significant progress in developing efficient chiral catalysts for the enantioselective intermolecular MBH reactions.[2] However, the asymmetric intramolecular MBH reaction is in its infancy, only a few reports are known so far.[3] The first enantioselective intramolecular MBH reaction was reported by Fráter's group in 1992, affording the product in 14% ee with 40% yield after a reaction time of 10 days.[3a] Recently Miller and co-workers described an enantioselective intramolecular MBH reaction using a co-catalyst system involving pipecolinic acid and *N*-methylimidazole, the cyclic MBH products were obtained with up to 84% ee.[3b] Hong et al. reported a highly enantioselective intramolecular MBH reaction of hept-2-enedial catalyzed by proline, and the addition of imidazole as co-catalyst resulted in an inversion of enantioselectivity.[3c] Therefore, development of asymmetric version of intramolecular MBH reactions is still a challenge.

In our previous work,[4] we have successfully developed L-valine-derived phosphinothiourea **5a** for the asymmetric Morita–Baylis–Hillman reaction between acrylates and aromatic aldehydes. Accordingly, other bifunctional phosphinothiourea compounds are high efficient in the intermolecular MBH reaction.[5] For these reasons, we thought that it would be of interest to employ phosphinothiourea in the intramolecular Baylis–Hillman reaction. Herein, we report our results on the intramolecular MBH reaction catalyzed by amino acid-derived phosphinothioureas.

2. Results and discussion

The phosphinothioureas **5a**–**f** are easily accessible by condensation of chiral amino-phosphines **4**[6] with 1.1 equiv of the corresponding isothiocyanate in CH_2Cl_2 at room temperature. The amino-phosphines **4** were prepared by degradation of 2-oxazolidinones **3**.[7] Amino alcohols **2**,[8] prepared by reduction of L-amino acids **1**, were converted quantitatively into compounds **3** via the addition with dimethylcarbonate (Scheme 1).

Initially the catalysts **5a**–**f** were examined in the intramolecular MBH reaction of substrate **6a**[9] in CH_2Cl_2 at 25 °C. As shown in Table 1, the chiral scaffold of the organocatalysts significantly affected the enantioselectivity and the chemical yield. The L-phenylalanine-derived catalyst **5c** provided the desired product in higher ee and lower yield than the corresponding phosphinothioureas **5a** and **5b**, which derived from L-valine and L-alanine, respectively (entry 3 vs entries 1 and 2). The thiourea moiety of the catalysts also played an important role in achieving good yield and enantioselectivity. The L-phenylalanine-derived thiourea **5d** bearing strong electron-withdrawing

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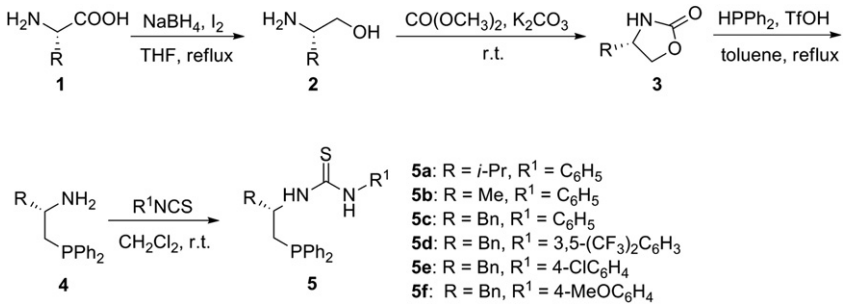
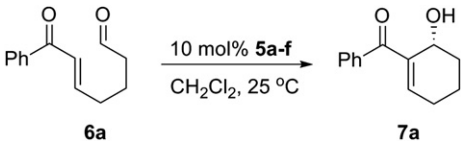


Scheme 1. Synthetic route of the amino acid-derived phosphinothioureas.

substituent at phenyl group afforded the desired product in 83% yield and 76% ee, and it was more efficient than the corresponding thioureas **5c**, **5e**, and **5f** (entry 4 vs entries 3, 5, and 6). By comparison, **5d** was the optimum catalyst among the screened phosphinothioureas. The absolute configuration of the intramolecular MBH products is *R*-configuration, which was assigned by comparing the optical rotation value with those reported in the literature.[3b]

Table 1
Screening of the phosphinothioureas for the intramolecular MBH reaction of **6a**[a]



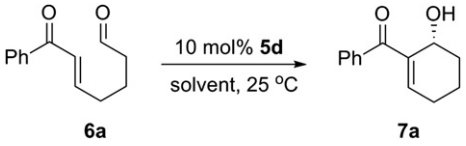
6a **7a**

Entry	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	**5a**	48	73	18
2	**5b**	12	72	16
3	**5c**	60	50	67
4	**5d**	12	83	76[d]
5	**5e**	84	50	65
6	**5f**	84	45	56

[a] The reactions were conducted with 10 mol % of organocatalyst, 0.2 mmol **6a** in 1 mL CH_2Cl_2 (0.2 M) at 25 °C.
[b] Isolated yield.
[c] Determined by HPLC using Chiralcel OD-H column.
[d] $[\alpha]_D^{30}$ +20.0 (*c* 0.30, $CHCl_3$).

Next, the solvents were investigated on this process with **5d** as the organocatalyst (Table 2). In CH_2Cl_2 and $CHCl_3$, the reaction proceeded quickly to provide the corresponding product with good yield and ee (entries 2 and 3). Although the reaction completed within 9 h in EtOH, the enantioselectivity was poor (entry 8). In other screened solvents, the reactions afforded moderate yields (58–73%) and lower enantioselectivities (29–48% ee). Thus CH_2Cl_2 was selected as solvent for further investigation.

Table 2
The effect of the solvents on the intramolecular MBH reaction[a]



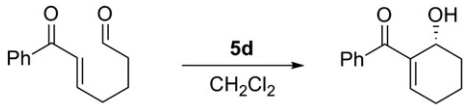
6a **7a**

Entry	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	Toluene	32	70	48
2	$CHCl_3$	13	88	74
3	CH_2Cl_2	13	83	76
4	Ether	32	70	40
5	Ethyl acetate	40	73	45
6	THF	106	58	29
7	Acetone	40	73	40
8	EtOH	9	83	30
9	CH_3CN	32	70	48

[a] The reactions were conducted with 10 mol % **5d**, 0.2 mmol **6a** in 1 mL solvent (0.2 M) at 25 °C.
[b] Isolated yield.
[c] Determined by HPLC using Chiralcel OD-H column.

Furthermore, optimization of other reaction conditions, including the reaction temperature, the substrate concentration and the loading of catalyst were investigated (Table 3). The results indicated that the enantioselectivity was not sensitive to the reaction temperature, and the lower reaction temperature resulted in longer reaction time (entries 1–3). Reducing the substrate concentration from 0.2 M to 0.1 M, the enantioselectivity was decreased by only 2% ee (entry 1 vs entry 4). While the substrate concentration was increased to 0.3 M, the enantioselectivity was reduced obviously (entry 5). The loading of catalyst has a pronounced influence on chemical yield and enantioselectivity (entry 1 vs entries 6 and 7). In the presence of 5 mol % **5d**, the reaction was laggard. Surprisingly, using 20 mol % **5d** led to lower chemical yield due to the side-reaction. The results summarized in Table 3 prompted us to choose the reaction conditions using 10 mol % **5d** in CH_2Cl_2 at 25 °C to probe the scope of the intramolecular MBH reaction.

Table 3
Further optimization of reaction conditions[a]



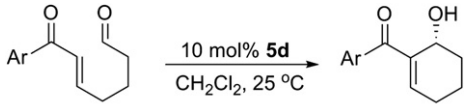
6a **7a**

Entry	Temp (°C)	Concn (mol/L)	**5d** (mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	25	0.2	10	13	83	76
2	0	0.2	10	35	76	71
3	40	0.2	10	13	85	72
4	25	0.1	10	12	80	74
5	25	0.3	10	12	86	60
6	25	0.2	5	108	82	65
7	25	0.2	20	12	69	66

[a] The reactions were conducted in CH_2Cl_2.
[b] Isolated yield.
[c] Determined by HPLC using Chiralcel OD-H column.

Under the established optimal reaction conditions, the scope of the substrates in terms of intramolecular MBH reaction was investigated. As the results summarized in Table 4, the substrates with electron-rich substituent at the *para*-position of phenyl group (entries 1 and 2) could afford better enantioselectivity than those with electron-deficient substituent or without substituent at phenyl group (entries 5–12). In addition, the substrates bearing substituent at the *ortho*-position of phenyl group provided the products in excellent yields with poor enantioselectivity probably due to the *ortho* effect (entries 4 and 9). The thiophene analogue performed the MBH product with reduced yield and enantioselectivity (entry 12).

Table 4
The substrates scope of the intramolecular MBH reaction[a]

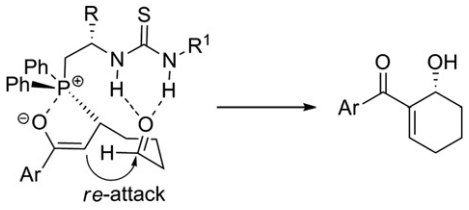


6 7

Entry	Ar	Time (h)	Yield[b] (%)	ee[c] (%)
1	4-MeOC$_6$H$_5$	36	77	84
2	4-MeC$_6$H$_5$	22	79	78
3	3-MeC$_6$H$_5$	24	79	73
4	2-MeC$_6$H$_5$	48	99	45
5	C$_6$H$_5$	13	83	76
6	4-FC$_6$H$_5$	12	76	75
7	4-BrC$_6$H$_5$	12	86	71
8	3-BrC$_6$H$_5$	20	93	66
9	2-BrC$_6$H$_5$	20	100	5
10	4-ClC$_6$H$_5$	12	82	68
11	Naphtha-2-yl	22	85	74
12	Thiophen-2-yl	24	63	59

[a] The reactions were conducted with 10 mol% **5d**, 0.2 mmol **6** in 1 mL CH_2Cl_2 (0.2 M) at 25 °C.
[b] Isolated yield.
[c] Determined by HPLC using Chiralcel OD-H, Chiralpak AS-H or Chiralpak AD-H column.

The proposed mechanism of the phosphinothiourea catalyzed formation of cyclic hydroxyl enones is illustrated in Scheme 2. The phosphine attacks β-position of the Michael acceptor to form an enolate and the thiourea moiety activates the substrates **6** by forming hydrogen-bonds with the aldehyde carbonyl. Then the phosphinoyl associated enolate attacks the activated carbonyl from the *re*-face to give the product in an *R*-configuration.



Scheme 2. Proposed mechanism of phosphinothiourea catalyzed intramolecular MBH reaction.

3. Conclusion

In summary, a series of chiral phosphinothioureas have been synthesized starting from different amino acids, including L-valine, L-alanine, and L-phenylalanine. These bifunctional phosphinothioureas could promote the enantioselective intramolecular MBH reactions of ω-formyl-α,β-unsaturated carbonyl compounds, and the cyclic MBH products were obtained in up to 84% ee with good-to-excellent yields in dichloromethane at room temperature. Further efforts are underway with a focus on improving the reaction enantioselectivity and probing the full scope of this reaction.

4. Experimental

4.1. General methods

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). ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker 500 or 400 spectrometer. ^{1}H NMR spectra were referenced to tetramethylsilane (0.00 ppm) using $CDCl_3$ as solvent. ^{13}C NMR spectra were referenced to solvent carbons (77.0 ppm for $CDCl_3$). ^{31}P NMR spectra were referenced to an external H_3PO_4 signal (0.00 ppm). IR spectra were recorded on Nicolet Magna-I 550 spectrometer. High Resolution Mass spectra (HRMS) were recorded on Micromass GCT or KE465 LCT Premier/XE spectrometer. HPLC analysis was performed on Waters 510 with 2487 detector using Daicel Chiralcel OD-H, Chiralpak AS-H or Chiralpak AD-H column.

4.2. General procedure for synthesis of phosphinethiourea catalysts 5a–f

To a solution of amino-phosphine compounds **4**[6] (1.0 mmol) in 2.0 mL CH_2Cl_2 was added isothiocyanate (1.1 mmol) at room temperature, and the corresponding 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) to afford the chiral phosphinothiourea compounds **5a–f**.

4.2.1. L-Valine-derived phosphinothiourea ***5a***.[4] White solid, 60% yield, mp: 54.6–55.7 °C; $[\alpha]_D^{25}$ +32.1 (*c* 0.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.49–7.42 (m, 4H), 7.40–7.35 (t, *J*=7.7 Hz, 2H), 7.34–7.23 (m, 7H), 7.07 (d, *J*=7.7 Hz, 2H), 5.97 (d, *J*=8.5 Hz, 1H), 4.59 (br, 1H), 2.44–2.38 (m, 1H), 2.32–2.24 (m, 1H), 2.17–2.09 (m, 1H), 0.87 (d, *J*=6.8 Hz, 3H), 0.83 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.1, 138.0, 136.2, 133.0 (d, *J*=5.2 Hz), 132.8 (d, *J*=5.2 Hz), 130.0, 128.9, 128.6–128.5 (m), 126.9, 125.1, 58.4 (d, *J*=14.2 Hz), 31.8 (d, *J*=8.6 Hz), 31.2 (d, *J*=13.5 Hz), 18.9, 18.0; ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ −24.49; IR (KBr, cm^{-1}): ν 3229, 3056, 2957, 1598, 1540, 1494, 1043, 565; HRMS (EI) calcd for $C_{24}H_{27}N_2PS$ ([M]$^+$) 406.1633, found: 406.1635.

4.2.2. L-Alanine-derived phosphinothiourea ***5b***. Colorless oil, 72% yield, $[\alpha]_D^{32}$ +50.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (br, 1H), 7.55–7.47 (m, 2H), 7.45–7.27 (m, 10H), 7.28–7.20 (t, *J*=7.6 Hz, 1H), 7.16 (d, *J*=7.6 Hz, 2H), 6.22 (br, 1H), 4.76 (br, 1H), 2.54–2.45 (m, 1H), 2.41–2.32 (m, 1H), 1.30 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 138.3 (d, *J*=11.8 Hz), 137.8 (d, *J*=11.8 Hz), 136.4, 133.0, 132.9, 132.8, 132.7, 130.0, 128.9, 128.8, 128.7–128.2 (m), 126.8, 124.9, 49.6 (d, *J*=16.9 Hz), 36.1 (d, *J*=14.8 Hz), 21.7 (d, *J*=9.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ −24.63; IR (KBr, cm^{-1}): ν 3370, 3208, 3048, 2964, 1595, 1528, 1494, 1478, 1449, 1429, 1318, 1248, 738, 693; HRMS (EI) calcd for $C_{22}H_{23}N_2PS$ ([M]$^+$) 378.1320, found: 378.1321.

4.2.3. L-Phenylalanine-derived phosphinothiourea ***5c***. White solid, 68% yield, mp: 45.8–46.9 °C; $[\alpha]_D^{31}$ +20.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.51–7.43 (m, 2H), 7.40–7.26 (m, 10H), 7.25–7.14 (m, 4H), 7.08 (d, *J*=6.5 Hz, 2H), 6.90 (d, *J*=7.6 Hz, 2H), 5.96 (d, *J*=7.0 Hz, 1H), 4.59–4.55 (m, 1H), 3.20–2.59 (m, 2H), 2.37 (d, *J*=6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 138.1–137.8 (m), 137.4, 136.2, 133.1–132.8 (m), 130.0, 129.5, 128.9, 128.7, 128.6, 126.9, 126.7, 125.1, 54.2 (d, *J*=15.9 Hz), 40.6 (d, *J*=8.7 Hz), 33.1 (d, *J*=14.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ −24.51; IR (KBr, cm^{-1}): ν 3373, 3195, 3053, 3025, 2932, 1595, 1529, 1494, 1451, 1432, 1309, 1244, 733, 699; HRMS (EI) calcd for $C_{28}H_{27}N_2PS$ ([M]$^+$) 454.1633, found: 454.1634.

4.2.4. L-Phenylalanine-derived phosphinothiourea ***5d***. White solid, 75% yield, mp: 109.6–111.0 °C; $[\alpha]_D^{31}$ +8.3 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (br, 1H), 7.68 (s, 1H), 7.60 (s, 2H), 7.48–7.35 (m, 4H), 7.35–7.23 (m, 9H), 7.19 (d, *J*=6.8 Hz, 2H), 6.37 (br, 1H), 4.95 (br, 1H), 3.29–2.95 (m, 2H), 2.66–2.49 (m, 1H), 2.46–2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 138.7, 137.6, 137.5, 137.1, 136.9, 136.8, 132.9, 132.8, 132.7, 132.6, 129.3, 129.1, 129.0, 128.7 (d,

J=7.2 Hz), 127.0, 124.2, 123.9, 121.5, 119.2, 54.7, 40.9, 32.9; ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ −25.19; IR (KBr, cm^{-1}): ν 3212, 3035, 1540, 1496, 1471, 1455, 1384, 1335, 1289, 1176, 1127, 737, 695; HRMS (EI) calcd for $C_{30}H_{25}F_6N_2PS$ ($[M]^+$) 590.1380, found: 590.1385.

4.2.5. L-Phenylalanine-derived phosphinothiourea ***5e***. White solid, 60% yield, mp: 53.1–54.7 °C; $[\alpha]_D^{31}$ +29.5 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (br, 1H), 7.54–7.44 (m, 2H), 7.44–7.36 (m, 2H), 7.36–7.28 (m, 6H), 7.28–7.23 (m, 5H), 7.15 (d, J=6.8 Hz, 2H), 6.90 (d, J=8.4 Hz, 2H), 6.06 (br, 1H), 4.95 (br, 1H), 3.17–2.99 (m, 2H), 2.53–2.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 138.0–137.6 (m), 137.3, 134.8, 133.0, 132.9, 132.8, 132.7, 132.2, 130.0, 129.5, 128.9, 128.8–128.4 (m), 126.8, 126.3, 54.3 (d, J=15.5 Hz), 40.6 (d, J=8.5 Hz), 33.5 (d, J=14.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ −24.66; IR (KBr, cm^{-1}): ν 3371, 3265, 3054, 2917, 1521, 1489, 1456, 1430, 1093, 737, 695; HRMS (EI) calcd for $C_{28}H_{26}ClN_2PS$ ($[M]^+$) 488.1243, found: 488.1245.

4.2.6. L-Phenylalanine-derived phosphinothiourea ***5f***. White solid, 65% yield, mp: 59.1–60.4 °C; $[\alpha]_D^{31}$ +23.5 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (br, 1H), 7.54–7.44 (m, 2H), 7.44–7.34 (m, 2H), 7.34–7.26 (m, 6H), 7.26–7.15 (m, 3H), 7.11 (d, J=6.8 Hz, 2H), 6.90 (d, J=8.4 Hz, 2H), 6.83 (d, J=8.4 Hz, 2H), 5.89 (br, 1H), 4.93 (br, 1H), 3.79 (s, 3H), 3.13–2.94 (m, 2H), 2.40 (d, J=6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0, 158.7, 138.4–137.7 (m), 137.3, 133.1, 132.9 (d, J=5.8 Hz), 132.7, 129.5, 128.8 (d, J=2.1 Hz), 128.7–128.4 (m), 127.6, 126.6, 115.1, 55.6, 54.0 (d, J=16.0 Hz), 40.5 (d, J=8.7 Hz), 33.1 (d, J=14.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4): δ −24.67; IR (KBr, cm^{-1}): ν 3368, 3190, 3054, 2959, 2830, 1608, 1509, 1430, 1239, 1164, 1027, 740, 702; HRMS (EI) calcd for $C_{29}H_{29}N_2OPS$ ($[M]^+$) 484.1738, found: 484.1736.

4.3. General procedure for the intramolecular MBH reaction

To a solution of phosphinothiourea **5d** (0.02 mmol, 11 mg) in CH_2Cl_2 (1.0 mL) was added substrates **6** (0.2 mmol) at 25 °C. The reaction mixture was stirred at 25 °C until the reaction completed (monitoring by TLC). The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography to afford the intramolecular Baylis–Hillman adducts. The ee values were determined by HPLC analysis with a chiral column.

4.3.1. (R)-(6-Hydroxycyclohex-1-enyl)(phenyl) methanone.[9] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J=7.2 Hz, 2H), 7.54 (t, J=7.2 Hz, 1H), 7.44 (t, J=7.2 Hz, 2H), 6.73 (t, J=4.0 Hz, 1H), 4.74 (d, J=1.2 Hz, 1H), 3.51 (d, J=1.2 Hz, 1H), 2.39–2.22 (m, 2H), 1.97–1.84 (m, 3H), 1.69–1.66 (m, 1H). HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=95/5, flow rate: 1.0 mL/min): t_R=9.9 min (major), 11.8 min (minor); $[\alpha]_D^{30}$ +20.0 (c 0.30, $CHCl_3$, 76% ee).

4.3.2. (R)-(6-Hydroxycyclohex-1-enyl)(4-methoxyphenyl)-methanone. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J=8.8 Hz, 2H), 6.94 (d, J=8.8 Hz, 2H), 6.66 (t, J=4.0 Hz, 1H), 4.71 (s, 1H), 3.88 (s, 3H), 3.60 (br s, 1H), 2.39–2.22 (m, 2H), 1.95–1.85 (m, 3H), 1.69–1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 163.0, 144.7, 139.8, 131.8, 130.2, 113.5, 64.2, 55.4, 29.8, 26.2, 17.4; IR (KBr, cm^{-1}): ν 3440, 2936, 1635, 1599, 1509, 1257, 1173, 1028, 767; HRMS (ESI) calcd for $C_{14}H_{16}O_3Na$ ($[M+Na]^+$): 255.0997, found: 255.0992. HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=12.0 min (major), 29.1 min (minor); $[\alpha]_D^{30}$ +57.5 (c 0.20, $CHCl_3$, 84% ee).

4.3.3. (R)-(6-Hydroxycyclohex-1-enyl)(4-tolyl)methanone.[10] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J=8.0 Hz, 2H), 7.25 (d, J=7.6 Hz, 2H), 6.71 (t, J=4.0 Hz, 1H), 4.73 (s, 1H), 2.91 (br s, 1H), 2.42 (s, 3H), 2.40–2.22 (m, 2H), 1.97–1.85 (m, 3H), 1.70–1.63 (m, 1H). HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=14.7 min (major), 16.1 min (minor); $[\alpha]_D^{30}$ +42.3 (c 0.26, $CHCl_3$, 78% ee).

4.3.4. (R)-(6-Hydroxycyclohex-1-enyl)(3-tolyl)methanone. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.43 (m, 2H), 7.36–7.30 (m, 2H), 6.73 (t, J=4.0 Hz, 1H), 4.74 (d, J=2.4 Hz, 1H), 3.51 (d, J=2.4 Hz, 1H), 2.41 (s, 3H), 2.39–2.20 (m, 2H), 1.97–1.82 (m, 3H), 1.69–1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5, 146.8, 140.1, 138.0, 137.8, 132.7, 129.7, 128.0, 126.5, 63.9, 29.8, 26.3, 21.3, 17.4; IR (KBr, cm^{-1}): ν 3448, 2934, 2864, 1636, 1601, 1420, 1277, 1201, 1056, 986, 756; HRMS (ESI) calcd for $C_{14}H_{16}O_2Na$ ($[M+Na]^+$): 239.1048, found: 239.1046. HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 0.9 mL/min): t_R=7.1 min (major), 23.1 min (minor).

4.3.5. (R)-(6-Hydroxycyclohex-1-enyl)(2-tolyl)methanone.[3b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.32 (m, 1H), 7.24–7.19 (m, 3H), 6.60 (t, J=4.0 Hz, 1H), 4.79 (s, 1H), 3.51 (s, 1H), 2.31 (s, 3H), 2.34–2.15 (m, 2H), 1.92–1.80 (m, 3H), 1.67–1.61 (m, 1H). HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 0.9 mL/min): t_R=6.4 min (major), 12.6 min (minor); $[\alpha]_D^{27}$ +13.3 (c 0.30, $CHCl_3$, 45% ee).

4.3.6. (R)-(4-Fluorophenyl)(6-hydroxycyclohex-1-enyl)methanone. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.70 (m, 2H), 7.13 (t, J=8.4 Hz, 2H), 6.70 (t, J=4.0 Hz, 1H), 4.74 (s, 1H), 3.42 (s, 1H), 2.41–2.23 (m, 2H), 1.97–1.86 (m, 3H), 1.71–1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 165.1 (d, J=251.8 Hz), 146.3, 140.0, 133.9 (d, J=3.2 Hz), 131.8 (d, J=8.9 Hz), 115.3 (d, J=21.7 Hz), 63.9, 29.8, 26.3, 17.4; IR (KBr, cm^{-1}): ν 3440, 2940, 2859, 1645, 1598, 1506, 1271, 1228, 987, 767; HRMS (ESI) calcd for $C_{13}H_{13}O_2FNa$ ($[M+Na]^+$): 243.0797, found: 243.0801. HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 0.8 mL/min): t_R=12.7 min (minor), 14.0 min (major); $[\alpha]_D^{30}$ +25.0 (c 0.32, $CHCl_3$, 75% ee).

4.3.7. (R)-(4-Bromophenyl)(6-hydroxycyclohex-1-enyl)methanone.[3b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J=8.4 Hz, 2H), 7.54 (d, J=8.4 Hz, 2H), 6.71 (t, J=4.0 Hz, 1H), 4.75 (s, 1H), 2.57 (br s, 1H), 2.40–2.23 (m, 2H), 1.98–1.83 (m, 3H), 1.71–1.63 (m, 1H). HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=19.4 min (minor), 22.7 min (major); $[\alpha]_D^{30}$ +16.7 (c 0.24, $CHCl_3$, 71% ee).

4.3.8. (R)-(3-Bromophenyl)(6-hydroxycyclohex-1-enyl)methanone. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.66 (d, J=8.0 Hz, 1H), 7.57 (d, J=8.0 Hz, 1H), 7.32 (t, J=8.0 Hz, 1H), 6.73 (t, J=4.0 Hz, 1H), 4.74 (s, 1H), 3.37 (s, 1H), 2.42–2.23 (m, 2H), 1.97–1.81 (m, 3H), 1.69–1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 147.7, 140.0, 139.7, 134.8, 132.0, 129.8, 127.8, 122.4, 63.7, 29.7, 26.5, 17.4; IR (KBr, cm^{-1}): ν 3446, 2925, 2855, 1652, 1636, 1418, 1078; HRMS (ESI) calcd for $C_{13}H_{13}O_2BrNa$ ($[M+Na]^+$): 302.9997, found: 302.9983. HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=11.9 min (minor), 13.5 min (major); $[\alpha]_D^{28}$ +11.3 (c 0.40, $CHCl_3$, 66% ee).

4.3.9. (R)-(2-Bromophenyl)(6-hydroxycyclohex-1-enyl)methanone. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J=8.0 Hz, 1H), 7.38–7.24 (m, 3H), 6.60 (t, J=4.0 Hz, 1H), 4.80 (t, J=4.4 Hz, 1H), 3.33 (s, 1H), 2.35–2.15 (m, 2H), 1.96–1.71 (m, 3H), 1.70–1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 150.4, 140.6, 140.2, 133.0, 130.9, 128.6, 127.0, 119.4, 63.0, 29.7, 26.8, 17.4; IR (KBr, cm^{-1}): ν 3446, 2939, 2859, 1653, 1634, 1429, 1287, 1056, 986, 767. HRMS (ESI) calcd for $C_{13}H_{13}O_2BrNa$ ($[M+Na]^+$): 302.9997, found: 303.0005. HPLC

analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=7.9 min (major), 17.2 min (minor).

4.3.10. (R)-(4-Chlorophenyl)(6-hydroxycyclohex-1-enyl)methanone.[3b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J=8.4 Hz, 2H), 7.43 (d, J=8.4 Hz, 2H), 6.71 (t, J=4.0 Hz, 1H), 4.74 (s, 1H), 2.51 (br s, 1H), 2.42–2.24 (m, 2H), 1.98–1.88 (m, 3H), 1.71–1.64 (m, 1H). HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=7.3 min (major), 12.4 min (minor); $[\alpha]_D^{30}$ +23.3 (*c* 0.30, $CHCl_3$, 68% ee).

4.3.11. (R)-(6-Hydroxycyclohex-1-enyl)(naphthalen-2-yl)methanone. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.96–7.89 (m, 3H), 7.79–7.77 (m, 1H), 7.62–7.55 (m, 2H), 6.81 (t, J=4.0 Hz, 1H), 4.82 (s, 1H), 3.54 (s, 1H), 2.43–2.27 (m, 2H), 2.03–1.87 (m, 3H), 1.74–1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 146.6, 140.3, 135.1, 135.0, 132.2, 130.6, 129.2, 128.2, 128.1, 127.8, 126.8, 125.4, 64.0, 29.9, 26.4, 17.5; IR (KBr, cm^{-1}): ν 3441, 2937, 1635, 1456, 1354, 1283, 1231, 1056, 989, 762; HRMS (ESI) calcd for $C_{17}H_{17}O_2$ ($[M+H]^+$): 253.1229, found: 253.1214. HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=95/5, flow rate: 1.0 mL/min): t_R=13.5 min (major), 17.4 min (minor); $[\alpha]_D^{30}$ +31.4 (*c* 0.35, $CHCl_3$, 74% ee).

4.3.12. (R)-(6-Hydroxycyclohex-1-enyl)(thiophen-2-yl)methanone.[3b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J=4.8 Hz, 1H), 7.63 (d, J=2.8 Hz, 1H), 7.15–7.12 (m, 1H), 6.96 (t, J=4.0 Hz, 1H), 4.69 (s, 1H), 2.70 (s, 1H), 2.43–2.25 (m, 2H), 1.98–1.80 (m, 3H), 1.72–1.65 (m, 1H). HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=9.5 min (major), 17.0 min (minor); $[\alpha]_D^{30}$ +33.3 (*c* 0.24, $CHCl_3$, 59% ee).

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