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An exploration of asymmetric Baylis–Hillman reactions catalyzed by quinidine-derived chiral amines

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Abstract—We utilized a reported quinidine-derived chiral amine **1** to catalyze the asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone. The enantioselectivities increase and in some cases, the absolute configuration of the Baylis–Hillman adducts can be inverted by the use of proline or lithium salt additives. The highest ee achieved is 49% with *S* configuration at the newly formed stereogenic centre. When using chiral amine **1** to catalyze the asymmetric Baylis–Hillman reaction of aldehydes with (α)-naphthyl acrylate, ee as high as 92% can be achieved.

1. Introduction

The Baylis–Hillman reaction, notorious for its poor reaction rate, is an important carbon–carbon bond forming process which affords a densely functionalized product.[1] Generally, it is catalyzed by tertiary amines such as DABCO (1,4-diazabicyclic[2,2,2]octane). The asymmetric Baylis–Hillman reaction catalyzed by chiral amines[2] has been explored for many years since the first report from Hirama et al.[3] However, they carried out the reactions under elevated pressure (5–10 kbar). Later, Barrett reported the first asymmetric Baylis–Hillman reaction of arylaldehydes with ethyl vinyl ketone catalyzed by a chiral pyrrolizidine under normal atmospheric pressure in which ee of up to 72% was achieved.[4]

The first breakthrough in the asymmetric Baylis–Hillman reaction was made by Hatakeyama et al. They used a rigid tricyclic quinidine-derived chiral amine **1** to catalyze the asymmetric Baylis–Hillman reaction of aldehydes with the highly reactive 1,1,1,3,3,3-hexafluoroisopropyl acrylate **2** at −55°C (Scheme 1).[5] The ee of the Baylis–Hillman adducts **3** can reach over 91% ee. However, when chiral amine **1** was used to catalyze asymmetric Baylis–Hillman reaction of *p*-nitrobenzaldehyde with methyl acrylate at room temperature, the enantioselectivity of the reaction was rather poor, affording adduct **4** with 8% ee (Scheme 2). In addition, the asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone (MVK) or other nucleophiles has not been examined at all. Herein, we wish to report the full details of asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone (MVK) or (α)-naphthyl acrylate catalyzed by chiral amine **1**. We also disclose some additive effects (proline and lithium salts) on the enantioselectivity of the above Baylis–Hillman reaction.

2. Results and discussion

2.1. The asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone catalyzed by chiral amine 1

We first used quinidine and quinidine derivatives such as $(DHQD)_2PHAL$ and $(DHQD)_2AQN$ to catalyze the asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone under normal atmosphere. However, the desired reaction did not occur at all. Thus, we turned to chiral amine **1**, which bears a more nucleophilic nitrogen atom, as the catalyst (Scheme 3, Table 1). It was delightful to find that, the reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone took place smoothly at −30°C to afford the Baylis–Hillman adduct **5a** in 53% yield. However, the ee achieved was quite low in DMF (7% ee) with *R* configuration[3] (Table 1, entry 1). With *p*-chloro- and *p*-bromobenzaldehyde, the ee values increased to 26 and 25% (*R* configuration[3])

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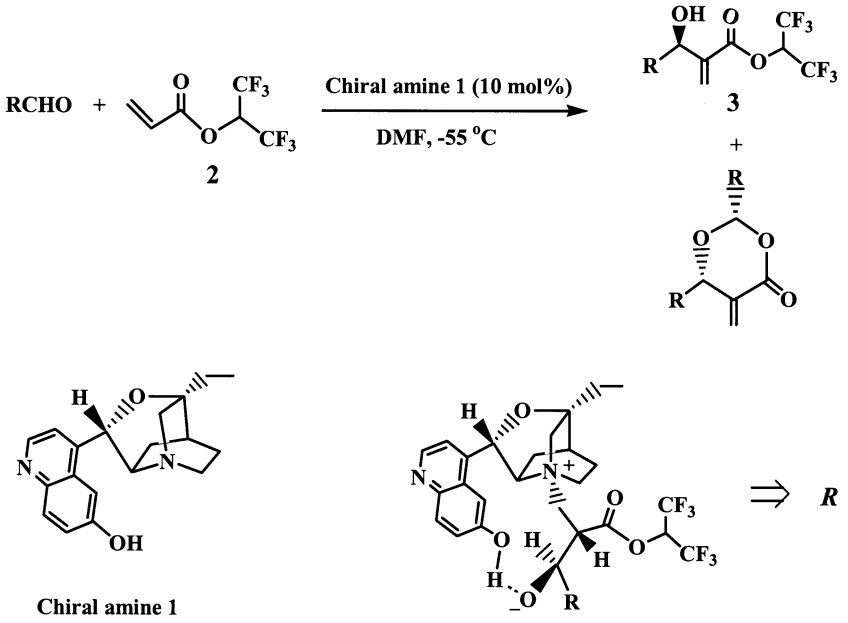
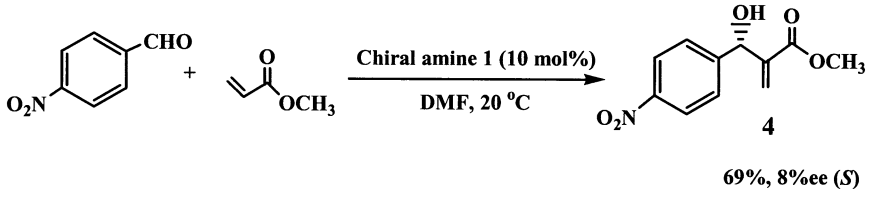
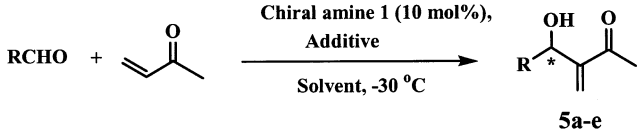


Scheme 1. Asymmetric Baylis–Hillman reaction catalyzed by quinidine-derived chiral amine **1**.



Scheme 2. Chiral amine **1**-catalyzed asymmetric Baylis–Hillman reaction of nitrobenzaldehyde with methyl acrylate at rt.



Scheme 3. Asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone catalyzed by chiral amine **1**.

with THF as the solvent, respectively (Table 1, entries 4, 7). With 3-phenylpropionaldehyde, the ee increased to 49% ee with appreciable isolated yield in 60 h in THF (Table 1, entry 11). However, it was disappointing that in the addition to benzaldehyde, the reaction produced only trace amounts of the corresponding Baylis–Hillman adduct (Table 1, entry 14). This suggests that the substrate can significantly affect the reaction rate and the enantioselectivity of the Baylis–Hillman reaction.

In order to improve the enantioselectivity of the Baylis–Hillman reaction of arylaldehydes with MVK, we tried introducing some additives into the reaction system. According to our previous report,[6] we used chiral amine **1** and proline to co-catalyze the asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone. Because of the high solubility of proline in DMF, we preferred to use DMF as the solvent in reactions where proline was used as the additive. In the presence of D-proline (10 mol%), the Baylis–Hillman reaction of *p*-nitrobenzaldehyde the enantioselectivity was enhanced to 31% ee without inversion of the absolute configuration (Table 1, entry 3). In contrast, the reactions of *p*-chloro- and *p*-bromobenzaldehyde with addition of D-proline, gave the Baylis–Hillman adducts with inverted absolute configurations and higher enantioselectivities compared with the analogous reactions catalyzed only by chiral amine **1** (Table 1, entries 6, 8). It should be noted here that, although 30 mol% D-proline was added into the reaction system (Table 1, entry 6), only part of it can be dissolved in DMF. When adding L-proline, for *p*-chlorobenzaldehyde, the ee was 22% without inversion of the absolute configuration (Table 1, entry 5).

Kobayashi reported that lithium perchlorate ($LiClO_4$) can greatly accelerate the rate of the Baylis–Hillman reaction.[7] We also used chiral amine **1** and lithium salts to co-catalyze this reaction. However, we found that while the addition of lithium salts does not improve the reaction rate in this system, it does have some impact on the observed chiral induction. In the reaction with *p*-bromobenzaldehyde, the ee was enhanced to 49% by addition of 20 mol% lithium perchlorate (Table 1, entry 9). Because of the better solubility of lithium triflate (LiOTf) in THF, we used it in larger amounts as the additive in the asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone (Table 1, entries 10,

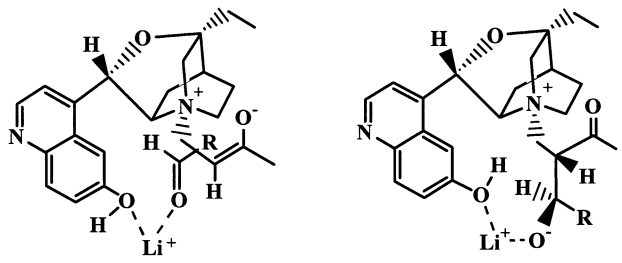
Table 1. Asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone catalyzed by chiral amine **1**

Entry	R	Additive (mol%)	Solvent	Time (h)	Yield (%)[a]	Ee (%)[b]	$[\alpha]_D$[e]	Absolute config.
1	*p*-NO_2Ph	None	DMF	48	53	7[c]	−1.0	*R*
2	*p*-NO_2Ph	L-Proline (10)	DMF	48	61	14[c]	−3.6	*R*
3	*p*-NO_2Ph	D-Proline (10)	DMF	42	88	31[c]	−18.5	*R*
4	*p*-ClPh	None	THF	96	24	17	−4.7	*R*
5	*p*-ClPh	L-Proline (10)	DMF	72	27	22	−6.5	*R*
6	*p*-ClPh	D-Proline (10)	DMF	120	61	26	+7.1	*S*
7	*p*-BrPh	None	THF	96	78	25	+9.2	*R*
8	*p*-BrPh	D-Proline (10)	DMF	60	31	27	−8.8	*S*
9	*p*-BrPh	$LiClO_4$ (20)	THF	72	43	49	+14.9	*R*
10	*p*-BrPh	LiOTf (50)	THF	36	33	42[d]	+12.8	*R*
11	$PhCH_2CH_2$	None	THF	60	69	49	+19.8	*R*
12	$PhCH_2CH_2$	LiOTf (50)	THF	36	69	30	+12.3	*R*
13	$PhCH_2CH_2$	LiOTf (50)	THF	60	44	21[d]	+8.3	*R*
14	Ph	None	THF	72	Trace	–	–	–

[a] Isolated yield.
[b] Determined by Chiral HPLC (Chiralpak AS, Daicel Co.) unless otherwise indicated.
[c] Determined by Chiral HPLC (Chiralpak AD, Daicel Co.).
[d] Determined by comparison of specific rotation values.
[e] Measured in $CHCl_3$ at 20°C.

13). However, for *p*-bromobenzaldehyde, there was no further improvement in the chiral induction on addition of lithium triflate at a level of 50 mol% compared with adding 20 mol% $LiClO_4$ (Table 1, entry 10). While for 3-phenylpropionaldehyde, the enantioselectivity decreased with the addition of lithium salt (Table 1, entries 12, 13). The addition of lithium salts does not change the absolute configuration of the products, c.f. the reactions catalyzed only by chiral amine **1**. However, for benzaldehyde, no reaction occurred at −30°C using chiral amine **1** as the catalyst.

Ikegami and Barrett used BINOL and $NaBF_4$, respectively, to accelerate the rate of the Baylis–Hillman reaction.[4,9] They suggested that BINOL and $NaBF_4$ not only activate the carbonyl group of the aldehyde, but also stabilize the enolate intermediates formed in the process of the Baylis–Hillman reaction. By adding a stoichiometric amount of $NaBF_4$, the enantioselectivities of the asymmetric Baylis–Hillman reactions of aldehydes with ethyl vinyl ketone were enhanced. We think that lithium salts and proline play the same role as $NaBF_4$ or BINOL (Schemes 4 and 5). Lithium can act as a bridge between the carbonyl group of the aldehyde and the phenolic hydroxy group, or stabilize the final Baylis–Hillman reaction step as shown in Scheme 4. This effect can produce a more rigid transition state and consequently, the enantioselectivity can be enhanced.



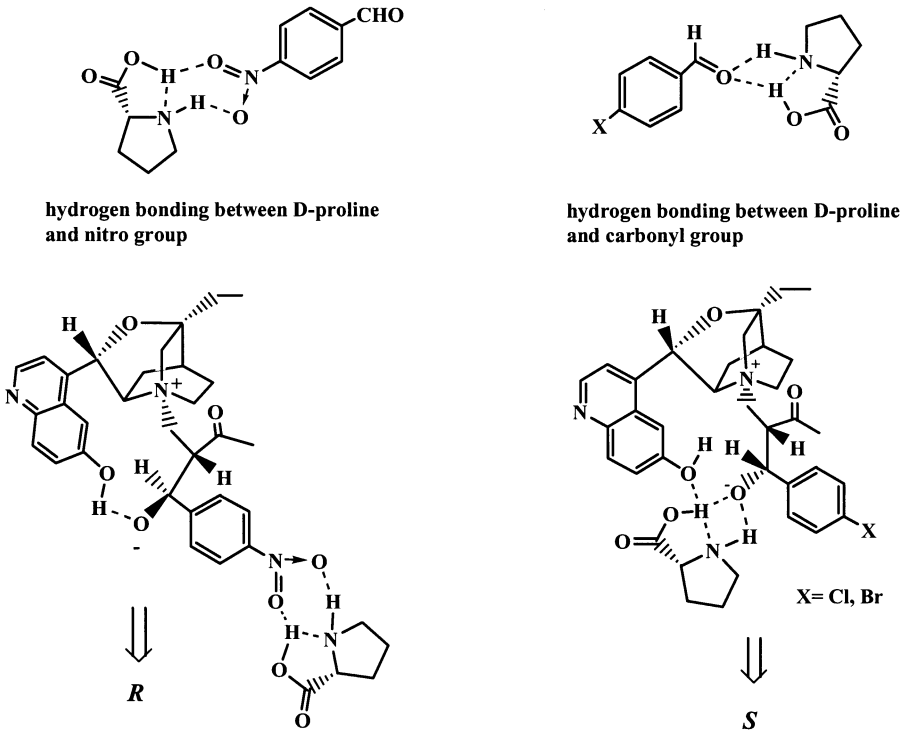
Scheme 4. Possible role of hydrogen or lithium ion in the asymmetric Baylis–Hillman reaction.

The results of using D-proline as an additive can be rationalized by the hydrogen bonds that are formed between proline and the substrate: In the reaction with *p*-nitrobenzaldehyde, the hydrogen bond forms between the nitro- group rather than the carbonyl group, so the absolute configuration of the product is not inverted, as shown in Scheme 5. While in the reactions with *p*-chloro or *p*-bromobenzaldehyde, the hydrogen bond forms between the carbonyl group and D-proline, thus leading to inversion of the absolute configuration (Scheme 5). This is the first example of inversion of the absolute configuration with catalytic additives in the asymmetric Baylis–Hillman reaction. However, because of the affinity of the hydroxyl group or lithium ion for the nucleophilic nitrogen atom of the chiral amine **1**, the reaction rate and enantioselectivity decrease with larger amounts of additive.

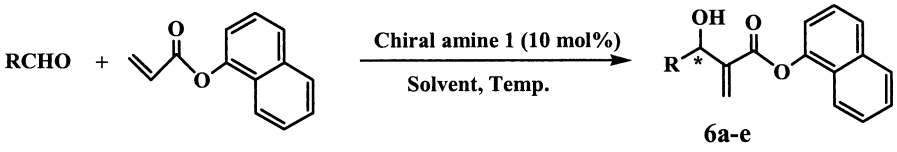
2.2. The asymmetric Baylis–Hillman reaction of aldehydes and (α)-naphthyl acrylate catalyzed by chiral amines

Recently, Chen and his co-workers reported a highly reactive (α)-naphthyl acrylate for the Baylis–Hillman reaction.[8] We then used chiral amine **1** to catalyze asymmetric reaction of aldehydes with (α)-naphthyl acrylate (Scheme 6, Table 2).

We found that THF is the optimal solvent for this reaction (Table 2, entries 1–3). In this reaction system, additives such as proline and lithium salts have no effect on the reaction rate and enantioselectivity. With *p*-nitrobenzaldehyde, the reaction temperature has almost no effect on the chiral induction (Table 1, entries 1, 4, 5). But for other arylaldehydes, when the reactions were carried out at lower temperature (−20°C), the enantioselectivities increased (Table 2,



Scheme 5. The role of D-proline in the asymmetric Baylis–Hillman reaction of arylaldehydes with methyl vinyl ketone catalyzed by chiral amine **1**.



a: R= *p*-$NO_2C_6H_4$, b: R= *p*-ClC_6H_4, c: R= *p*-BrC_6H_4, d: R= $C_6H_5CH_2CH_2$, e: R= C_6H_5.

Scheme 6. Asymmetric Baylis–Hillman reaction of aldehydes with (α)-naphthyl acrylate-catalyzed by chiral amine **1**.

Table 2. Asymmetric Baylis–Hillman reaction of aldehydes with (α)-naphthyl acrylate catalyzed by chiral amine **1**

Entry	R	Temp. (°C)	Solvent	Time (h)	Yield (%)[a]	E.e. (%)[b]	Absolute config.
1	*p*-$NO_2C_6H_4$	rt	THF	24	71	40	*R*
2	*p*-$NO_2C_6H_4$	rt	DMF	24	53	33	*R*
3	*p*-$NO_2C_6H_4$	rt	CH_3CN	24	27	8	*R*
4	*p*-$NO_2C_6H_4$	0	THF	48	68	40	*R*
5	*p*-$NO_2C_6H_4$	−20	THF	48	61	41	*R*
6	*p*-BrC_6H_4	rt	THF	48	47	34	*R*
7	*p*-BrC_6H_4	−20	THF	48	50	51	*R*
8	*p*-ClC_6H_4	rt	THF	48	42	26	*R*
9	*p*-ClC_6H_4	−20	THF	48	48	45	*R*
10	C_6H_5	rt	THF	72	30	16	*R*
11	C_6H_5	−20	THF	96	33	33	*R*
12	$PhCH_2CH_2$	rt	THF	72	50[c]	70	*R*
13	$PhCH_2CH_2$	−20	THF	120	17[d]	92	*R*
14	$PhCH_2CH_2$	−20	DMF	48	60[e]	23	*R*

[a] Isolated yield.
[b] Determined by Chiral AD.
[c] For **7**: yield 23%, ee 10%.
[d] For **7**: yield 59%, ee 20%.
[e] For **7**: yield 20%, ee 4%.

entries 6–11). In particular, with 3-phenylpropionaldehyde, the ee can reach 70% in 50% yield at room temperature using THF as solvent (Table 2, entry 12). We found that in the Baylis–Hillman reaction of 3-phenylpropionaldehyde with (α)-naphthyl acrylate using THF as the solvent, dioxanone **7** was also formed at the same time with ee of 10% (Scheme 7). In this case when the reaction was carried out at −20°C, the ee increased greatly to 92%. This is the highest ee achieved so far, besides 1,1,1,3,3,3-hexafluoroisopropyl acrylate **2** for the traditional Baylis–Hillman reaction using aldehyde substrates. However, the yield was only 17% after prolonged reaction time and dioxanone **7** was formed as the major product with 20% ee. At −20°C using DMF as the solvent, the yield can reach 60%, but the ee is only 23% (Table 2, entry 14). In this case, it was found that the enantioselectivity increased in accordance with the formation of large amount of dioxanone **7**. We believe that chiral amine **1** can catalyze an in situ kinetic resolution of the Baylis–Hillman adduct of 3-phenylpropionaldehyde with (α)-naphthyl acrylate by the formation of dioxanone **7** (4–20% ee, Table 2. entry 12–14) to produce the Baylis–Hillman adduct with higher ee.

In conclusion, we have used chiral amine **1** to catalyze the asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone or (α)-naphthyl acrylate. Ees of up to 49 and 92% have been achieved, respectively. Some interesting effects of additives have been disclosed in this paper. However, this catalytic asymmetric reaction is highly dependant on the substrate, including the aldehyde and the Michael acceptor. Careful examination of the reaction conditions for each substrate is required. Efforts are underway to elucidate the mechanistic details of this interesting asymmetric reaction and to disclose the scope and limitations of this method. Further research into the chiral amine **1**-catalyzed asymmetric Baylis–Hillman reaction is ongoing.

3. Experimental

3.1. General methods

^{1}H NMR was measured on Bruker AM300 (300 MHz), the internal standard was TMS; MS was measured on HP-5989; HRMS (EI) was measured on Finnigan MA$^+$; IR was measured on Perkin–Elmer 983. Elemental analysis was measured on Italian Carlo-Erba 110. The optical rotation was measured on Perkin–Elmer 241 MC at 20°C. Chiral amine **1** was prepared according to the reported procedure.[5]

3.2. Typical procedure of asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone catalyzed by chiral amine 1

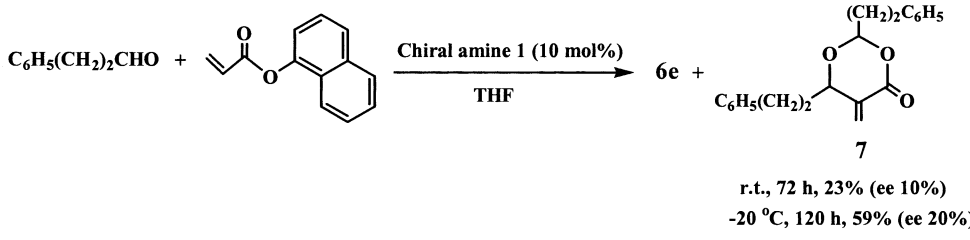
To a Schlenk tube was added the aldehyde (0.3 mmol), methyl vinyl ketone (0.6 mmol), the chiral amine **1** (9.6 mg, 0.03 mmol), an additive if necessary and the solvent (0.3 mL) as indicated in Table 1. The reaction was carried out at −30°C. After usual work-up, the residue was subjected to flash chromatography on silica gel to give the pure product. The ee was determined by chiral HPLC (Chiralpak AS and Chiralpak AD, Daicel Co.).

3.2.1. 3-(Hydroxy-(4-nitrophenyl)methyl)-but-3-en-2-one, 5a. This is a known compound. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.36 (3H, s, Me), 3.26 (1H, br. s, OH), 5.68 (1H, s), 6.05 (1H, s), 6.28 (1H, s), 7.56 (2H, d, J 8.6, Ar), 8.19 (2H, d, J 8.6, Ar). The ee value was determined by chiral AD (eluent: ^{i}PrOH/n-hexane = 5/95, v/v);
$[\alpha]_D = -1.0$ (c 0.49, $CHCl_3$), ee = 7%.
$[\alpha]_D = -3.6$ (c 0.46, $CHCl_3$), ee = 14%.
$[\alpha]_D = -18.5$ (c 1.38, $CHCl_3$), ee = 31%.

3.2.2. 3-(Hydroxy-(4-chlorophenyl)methyl)]-but-3-en-2-one, 5b. This is a known compound. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.34 (3H, s), 3.21 (1H, br. s., OH), 5.58 (1H, s, CH), 5.98 (1H, s), 6.20 (1H, s), 7.32 (4H, s, Ar). The ee value was determined by chiral AS (eluent: ^{i}PrOH/n-hexane = 10/90, v/v);
$[\alpha]_D = -4.7$ (c 1.00, $CHCl_3$), ee = 17%.
$[\alpha]_D = -6.5$ (c 0.54, $CHCl_3$), ee = 22%.
$[\alpha]_D = +7.1$ (c 0.66, $CHCl_3$), ee = 26%.

3.2.3. 3-(Hydroxy-(4-bromophenyl)methyl)-but-3-en-2-one, 5c. This is a known compound. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.33 (3H, s, CH_3), 3.17 (1H, d, J 4.8, OH), 5.55 (1H, d, J 4.8), 5.97 (1H, s), 6.19 (1H, s), 7.22 (2H, d, J 8.5), 7.45 (1H, d, J 8.5). The ee value was determined by chiral AS (eluent: ^{i}PrOH/n-hexane = 10/90, v/v);
$[\alpha]_D = +9.2$ (c 1.7, $CHCl_3$), ee = 25%.
$[\alpha]_D = -8.8$ (c 1.0, $CHCl_3$), ee = 27%.
$[\alpha]_D = +14.9$ (c 0.45, $CHCl_3$), ee = 49%.
$[\alpha]_D = +12.8$ (c 0.60, $CHCl_3$), ee = 42%.

3.2.4. 4-Hydroxy-3-methylene-6-phenylhexa-2-one, 5d. This is a known compound. ^{1}H NMR (300 MHz,



Scheme 7. Asymmetric Baylis–Hillman reaction of 3-phenylpropylaldehyde with (α)-naphthyl acrylate-cataylyzed by chiral amine **1**.

$CDCl_3$, TMS): δ 1.89–1.96 (2H, m, CH_2), 2.37 (3H, s, CH_3), 2.77–2.84 (2H, m, CH_2), 4.40–4.50 (1H, m, CH), 6.01 (1H, s), 6.11 (1H, s), 7.13–7.21 (3H, m, Ar), 7.24–7.32 (2H, m, Ar). The ee value was determined by chiral AS (eluent: ^{i}PrOH/*n*-hexane = 10/90, v/v);
$[\alpha]_D$ = +19.8 (*c* 0.86, $CHCl_3$), ee = 49%.
$[\alpha]_D$ = +12.3 (*c* 0.82, $CHCl_3$), ee = 30%.
$[\alpha]_D$ = +8.3 (*c* 0.71, $CHCl_3$), ee = 21%.

3.3. Typical procedure for the asymmetric Baylis–Hillman reaction of aldehydes with (α)-naphthyl acrylate catalyzed by chiral amine 1

To a Schlenk tube was added aldehyde (0.3 mmol), (α)-naphthyl acrylate (59.4 mg, 0.3 mmol), chiral amine **1** (9.6 mg, 0.03 mmol) and 0.3 mL solvent. The reaction was carried out at the temperature as indicated in Table 2. After completion, CH_2Cl_2 (8 mL) was added and washed wish water (2×5 mL). The organic layer was dried over anhydrous Na_2SO_4. After the evaporation of CH_2Cl_2 under reduced pressure, the residue was subjected to flash chromatography to give the product. The ee was determined by HPLC analysis using Chiralpak AD (Daicel Co.).

3.3.1. 2-(Hydroxy-(4-nitrophenyl)methyl)-acrylic acid-naphthalen-1-yl ester, 6a. IR (KBr): *v* 1736 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 3.73 (1H, br., OH), 5.81 (1H, d, *J* 4.5), 6.21 (1H, s), 6.84 (1H, s), 7.18 (1H, d, *J* 8.0), 7.35–7.54 (3H, m), 7.55 (1H, d, *J* 8.0), 7.65 (2H, d, *J* 8.6), 7.75 (1H, d, *J* 8.5), 7.86 (1H, d, *J* 8.0), 8.26 (2H, d, *J* 8.6); MS (EI) *m*/*z*: 198 (M^+−151), 161 (3.80), 144 (100.00), 115 (35.46); HRMS (EI) *m*/*z*: 349.0961 (M^+), $C_{20}H_{15}NO_5$ requires 349.0950. The ee was determined by HPLC analysis using a Chiral AD column (eluent: ^{i}PrOH/*n*-hexane = 10/90, v/v);
$[\alpha]_D$ = −6.4 (*c* 1.00, $CHCl_3$), ee = 40%.
$[\alpha]_D$ = −7.3 (*c* 0.60, $CHCl_3$), ee = 33%.
$[\alpha]_D$ = −1.9 (*c* 0.90, $CHCl_3$), ee = 27%.
$[\alpha]_D$ = −6.2 (*c* 0.90, $CHCl_3$), ee = 40%.
$[\alpha]_D$ = −6.5 (*c* 0.90, $CHCl_3$), ee = 41%.

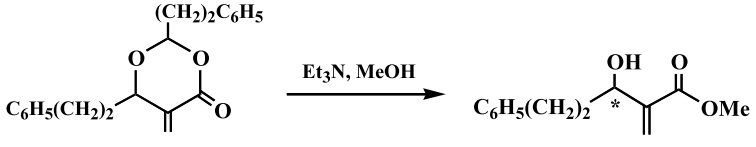
3.3.2. 2-(Hydroxy-(4-chlorophenyl)methyl)-acrylic acid-naphthalen-1-yl ester, 6b. IR (KBr): *v* 1736 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.99 (1H, d, *J* 4.8), 5.74 (1H, d, *J* 4.7), 6.20 (1H, s), 6.79 (1H, s), 7.18 (1H, d, *J* 7.4), 7.37–7.53 (8H, m), 7.76 (1H, d, *J* 8.3), 7.87 (1H, d, *J* 7.8); MS (EI) *m*/*z*: 321 (M^+−17), 144 (100.00), 115 (41.98). Elemental analysis: Found C, 70.85; H, 4.59%. $C_{20}H_{15}ClO_3$ requires C, 70.90; H, 4.46%. The ee value was determined by Chiral AD (eluent: ^{i}PrOH/*n*-hexane = 20/80, v/v);
$[\alpha]_D$ = −10.6 (*c* 0.43, $CHCl_3$), ee = 26%.
$[\alpha]_D$ = −17.5 (*c* 0.48, $CHCl_3$), ee = 45%.

3.3.3. 2-(Hydroxy-(4-bromophenyl)methyl)-acrylic acid-naphthalen-1-yl ester, 6c. IR (KBr): *v* 1736 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.94 (1H, d, *J* 5.5), 5.71 (1H, d, *J* 5.5), 6.17 (1H, s), 6.77 (1H, s), 7.16 (1H, dd, *J* 7.8, 1.0), 7.36 (2H, d, *J* 6.6), 7.37–7.50 (4H, m), 7.53 (1H, d, *J* 6.6), 7.74 (1H, d, *J* 8.1), 7.85 (1H, d, *J* 8.1); MS (EI) *m*/*z*: 382 (M^+), 239 (2.24), 185 (4.92), 160 (12.62), 144 (100.00). Elemental analysis: found C, 62.60; H, 4.03%. $C_{20}H_{15}BrO_3$ requires: C, 62.68%; H, 3.95%. The ee value was determined by chiral AD (eluent: ^{i}PrOH/*n*-hexane = 20/80, v/v);
$[\alpha]_D$ = −12.0 (*c* 0.69, $CHCl_3$), ee = 34%.
$[\alpha]_D$ = −18.0 (*c* 0.71, $CHCl_3$), ee = 51%.

3.3.4. 2-(Hydroxy-4-phenylmethyl)-acrylic acid-naphthalen-1-yl ester, 6d. IR (neat): *v* 1736 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.88 (1H, d, *J* 4.2), 5.78 (1H, d, *J* 4.2), 6.20 (1H, s), 6.77 (1H, s), 7.15 (1H, d, *J* 7.5), 7.30–7.60 (9H, m), 7.73 (1H, d, *J* 8.1), 7.84 (1H, d, *J* 8.1); MS (EI) *m*/*z*: 304 (M^+), 198 (2.80), 144 (100.00), 115 (61.64); HRMS (EI) *m*/*z*: 304.1134, $C_{20}H_{15}NO_5$ requires 304.1099. The ee value was determined by HPLC analysis using a chiral AD column (eluent: ^{i}PrOH/*n*-hexane = 20/80, v/v);
$[\alpha]_D$ = −4.2 (*c* 0.79, $CHCl_3$), ee = 16%.
$[\alpha]_D$ = −15.8 (*c* 0.40, $CHCl_3$), ee = 33%.

3.3.5. 3-Hydroxy-2-methylene-5-phenyl-pentanoic acid-naphthalen-1-yl ester, 6e. IR (neat): *v* 1731 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.00–2.12 (2H, m, CH_2), 2.63 (1H, d, *J* 5.8), 2.76–2.82 (1H, m), 2.84–2.91 (1H, m), 4.61 (1H, m, CH), 6.13 (1H, s), 6.71 (1H, s), 7.10–7.37 (6H, m), 7.40–7.55 (3H, m), 7.70–7.82 (2H, m), 7.83–7.90 (1H, m); MS (EI) *m*/*z*: 315 (M^+−17), 198 (7.42), 144 (100.00), 115 (39.28), 91 (49.46); HRMS (EI) *m*/*z*: 332.1412 (M^+), $C_{22}H_{20}O_3$ requires 332.1412. The ee value was determined by chiral AD (eluent: ^{i}PrOH/*n*-hexane = 20/80, v/v);
$[\alpha]_D$ = +8.5 (*c* 1.30, $CHCl_3$), ee = 70%.
$[\alpha]_D$ = +2.7 (*c* 1.00, $CHCl_3$), ee = 23%.
$[\alpha]_D$ = +10.9 (*c* 0.80, $CHCl_3$), ee = 92%.

3.3.6. 5-Methylene-2,6-diphenylethyl-[1,3]-dioxan-4-one, 7. This is a known compound. $[\alpha]_D$ = −1.2 (*c* 1.0, $CHCl_3$), ee = 10%. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.98–2.20 (4H, m), 2.72–2.90 (4H, m), 4.47–4.51 (1H, m), 5.28 (1H, t, *J* 5.1), 5.59 (1H, s), 6.49 (1H, s), 7.10–7.26 (5H, m, Ar), 7.27–7.40 (5H, m, Ar). The spectral data are consistent with those reported in literature.[10] The ee of **7** was determined by the method reported by Hatakeyama.[5] Namely, conversion of **7** to the corresponding methyl ester for determination of the ee by chiral HPLC (chiralcel OD, eluent: ^{i}PrOH/*n*-hexane = 10/90, v/v).



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