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β-Isocupreidine–hexafluoroisopropyl acrylate method for asymmetric Baylis–Hillman reactions

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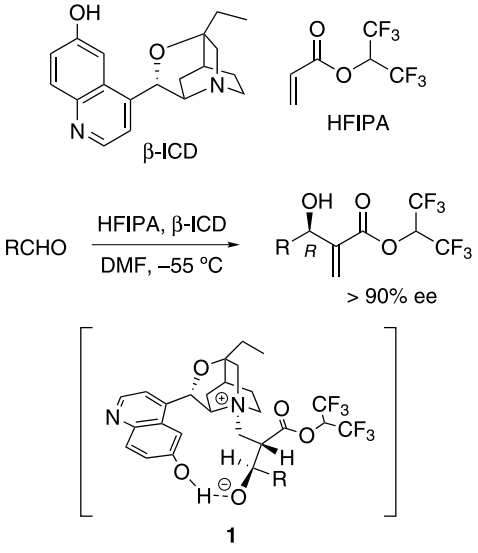
Abstract—Key features of the β-isocupreidine (β-ICD)-catalyzed asymmetric Baylis–Hillman reaction of aldehydes with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) are presented. In addition, an improved method using azeotropically dried β-ICD is described.

1. Introduction

The Morita–Baylis–Hillman reaction has attracted considerable interest due to the fascinating tandem Michael-aldol sequence catalyzed by a Lewis base and the promising utility of the multifunctional products. However, the major problems associated with this reaction are its slow reaction rate and difficulty in realization of a high level of asymmetric induction. This situation has brought about significant progress in rate acceleration as well as asymmetric induction based on various imaginative ideas.[1] Recently, we have developed a highly enantioselective asymmetric Baylis–Hillman reaction of aldehydes[2] as well as imines[3] by use of β-isocupreidine (β-ICD)[4,5] as a chiral Lewis base catalyst and 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) as an activated alkene. In addition, we have successfully demonstrated the synthetic utility of this reaction via syntheses of biologically intriguing natural products.[6] This β-ICD–HFIPA method has remarkable advantages in terms of the high enantioselectivity, the broad applicability, and the availability of both β-ICD and HFIPA. We speculate that hydrogen bonding between the oxy anion and the phenolic OH should play the crucial role during the enantio-controlling event as depicted in **1**.[2]

For the purpose of attaining more mechanistic information about the β-ICD–HFIPA method and seeking a better reaction system, we have investigated asymmetric Baylis–Hillman reactions using various congeners of β-ICD[7] as well as a panel of fluorine-containing acrylates (Scheme 1).



Scheme 1. β-ICD–HFIPA method.

2. Results and discussion

2.1. Preparation of the β-ICD-congeners

In order to investigate the structure-catalytic ability relationship of β-ICD, its seven congeners **2**–**8**[7] were prepared from quinidine (Scheme 2). Hoffmann et al. reported[7b] that treatment of quinidine with 3 equiv of KBr in 85% H_3PO_4 at 100 °C for 3 days produced a mixture of tricyclic ethers **2**, **3**, and **6**. We found that when this reaction

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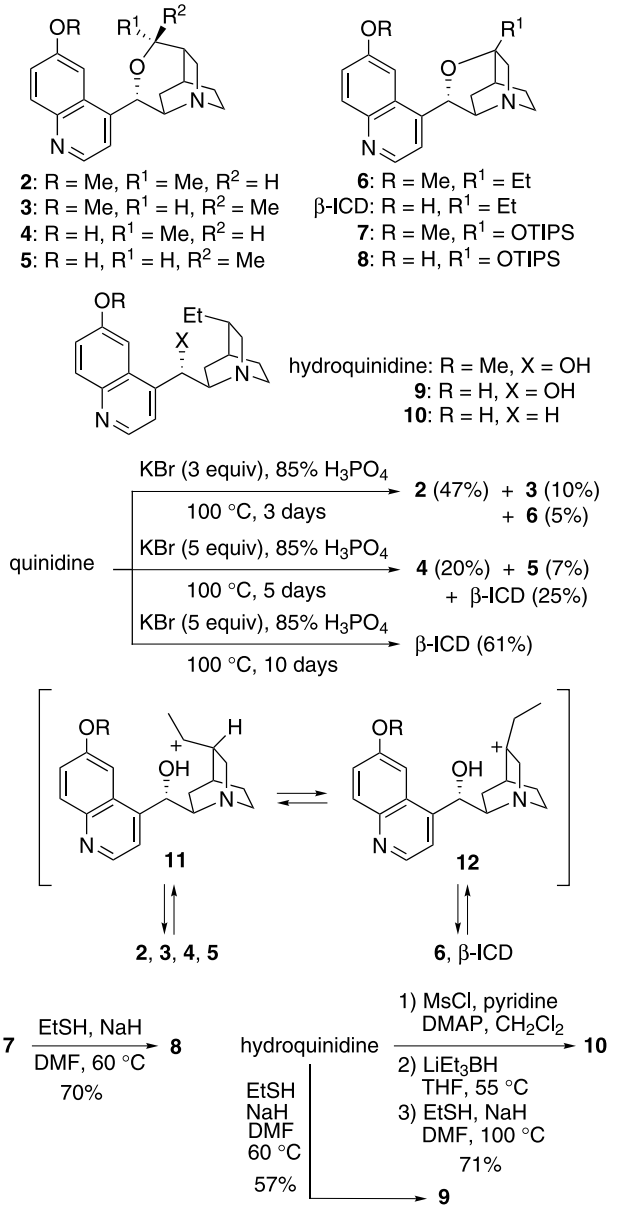
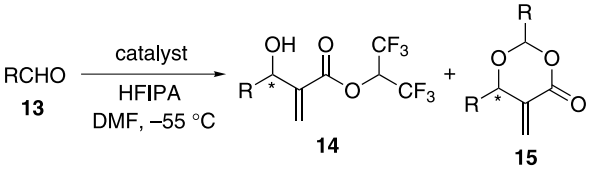


Scheme 2. Preparation of β-ICD-congeners.

was conducted using the increased amount of KBr (5 equiv) for longer reaction time (10 days), demethylation of the methoxy group also occurred together with cycloisomerization of quinidine to give **4**, **5**, and β-ICD in 20, 7, and 25% yields, respectively. In addition, it was gratifyingly found that, under the harsher conditions (KBr (10 equiv), 10 days), β-ICD was directly obtained from quinidine in 61% yield through the equilibration involving **11** and **12**. TIPS ether **8** was prepared by demethylation[8] of the known compound **7**[7b] available from quinidine. Compounds **9** and **10**[9] were also prepared from hydroquinidine.

2.2. Catalytic ability of the β-ICD-congeners

To evaluate the catalytic ability of the β-ICD-congeners, we examined the reaction of *p*-nitrobenzaldehyde with HFIPA using 0.1 equiv of compounds **2**–**10** in DMF at −55 °C (Scheme 3, Table 1). Interestingly, compounds **4**,**5**, and **8** exhibited similar catalytic ability to that of β-ICD (entries 1–4), while compounds **2**, **3**, **6**, **7**, **9**, and **10** were found to be very poor catalysts (entries 9–14). Importantly, the results listed in entries 4–8 indicate that compound **8** is also a useful catalyst for asymmetric Baylis–Hillman reactions of aromatic aldehydes.



Scheme 3. Chiral amine-catalyzed Baylis–Hillman reaction.

Table 1. Chiral amine-catalyzed reaction of aldehydes with HFIPA[a]

Entry	Aldehyde	Catalyst	Time (h)	Yield (%),[b] Config (% ee)[c,d]	
				14	**15**[e]
1	**13a**	β-ICD	1	58, *R* (91)	11, *R* (4)
2	**13a**	**4**	1	59, *R* (89)	19, *R* (38)
3	**13a**	**5**	1	51, *R* (89)	18, *R* (26)
4	**13a**	**8**	7	41, *R* (93)	20, *R* (51)
5	**13b**	**8**	24	68, *R* (98)	0
6	**13c**	**8**	28	71, *R* (95)[f]	0
7	**13g**	**8**	61	25, *R* (100)	20, *R* (17)
8	**13h**	**8**	42	15, *R* (92)	21, *S* (61)
9[g]	**13a**	**2**	6	18, nd[h]	29, *R* (45)
10[g]	**13a**	**3**	6	24, *R* (36)	32, *R* (32)
11[g]	**13a**	**6**	1	74, *R* (10)	7, nd[h]
12	**13a**	**7**	6	2, *R* (3)	9, *R* (11)
13	**13a**	**9**	3	0	26, *R* (4)
14	**13a**	**10**	3	0	27, *R* (2)

[a] Reactions were carried out at −55 °C in DMF (1 M) using **13** (1 equiv), HFIPA (1.3 equiv), and catalyst (0.1 equiv), unless otherwise stated.
[b] Isolated yield.
[c] Determined by comparison of the specific rotation of the corresponding methyl ester with that of the authentic sample obtained by kinetic resolution under Sharpless asymmetric epoxidation conditions.
[d] Determined by HPLC analysis using a chiral column.
[e] *Cis*:*trans*; **15a**: 99:1, **15g**: 70:30, **15h**: 90:10.
[f] Determined by ^{1}H NMR analysis of the *R*- and *S*- MTPA derivatives of the corresponding methyl ester, unless otherwise stated.
[g] HFIPA (3 equiv) was used.
[h] Not determined.

These results suggest that both the rigid tricylic structure and the phenolic OH are indispensable for obtaining a high degree of asymmetric induction as well as the remarkable rate acceleration. As seen in β-ICD,[2] such a cage-like structure is responsible for rate enhancement because it

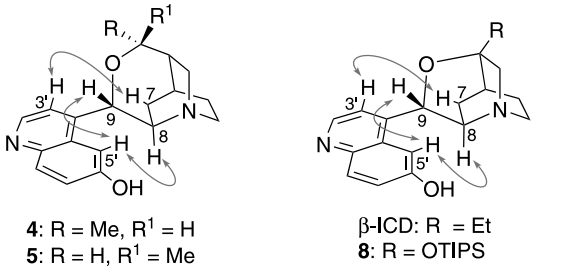


Figure 1. Significant NOE observed in NOESY spectra in DMF-d_7.

renders the quinuclidine moiety more nucleophilic by relieving steric congestion arising from C8–C9 bond rotation. In addition, the tricyclic structure makes the nucleophilic nitrogen face to the phenolic OH as indicated by the NOESY spectra (Fig. 1), so that the oxy anion intermediate stabilized by hydrogen bonding becomes operative resulting in high enantioselectivity as depicted in **1**.[2]

2.3. Improved β-ICD–HFIPA method

During ^{1}H NMR tracing experiments of a 1:1 mixture of β-ICD and HFIPA in DMF-d_7 at −40 °C, we incidentally found that HFIPA was partially hydrolyzed to produce 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and acrylic acid. The employed β-ICD was prepared from quinidine (Scheme 2) and purified by silica gel chromatography using 10% methanol–chloroform as the eluent followed by recrystallization from MeOH–H_2O. The combustion elemental analysis and X-ray analysis[10] of β-ICD thus obtained suggested the molecular formula to be $C_{19}H_{22}N_2O_2\cdot MeOH\cdot H_2O$. We therefore, concluded that the water bound to β-ICD caused the unexpected partial hydrolysis of HFIPA. This finding allowed us to come up with azeotropic removal of the water of β-ICD by repeating evaporation of its THF solution prior to use.

To our surprise, the azeotropically dried β-ICD showed remarkable catalytic activity, in particular, for aromatic aldehydes apart from the very reactive *p*-nitrobenzaldehyde (Scheme 3, Table 2). Thus, benzaldehyde was converted into **14b** in 97% ee in 75% yield, which was previously obtained as 95% ee in 57% yield using the catalyst without azeotropic operation[2] (entries 3, 4). The drying effect was also demonstrated by the reactions of cinnamaldehyde and 2-naphthylaldehyde, which gave the corresponding products in 64% (94% ee) and 82% (97% ee) yields, respectively (entries 5, 6, 9). In addition, even less reactive *p*-methoxybenzaldehyde and 1-naphthylaldehyde were converted to the corresponding adducts with excellent enantioselectivity although the yields were still unsatisfactory (entries 7, 8). These reactions failed under the original conditions using the undried β-ICD. In the case of aliphatic aldehydes, the use of the dried β-ICD exerted little effect on yield and enantioselectivity although the reaction rate increased (entries 10–13). It is important to note that this improved procedure using the dried β-ICD did not work at all for pivalaldehyde (entry 14), thus defining the steric limitation of this method.

Table 2. Improved β-ICD–HFIPA method[a]

Entry	Aldehyde	Catalyst[b]	Time (h)	Yield (%),[c] Config (% ee)[d]	
				14	**15**[e]
1	**13a**	A	1	58, *R* (91)	11, *R* (4)
2	**13a**	B	1.5	57, *R* (95)	17, *R* (49)
3	**13b**	A	48	57, *R* (95)	0
4	**13b**	B	48	75, *R* (97)	0
5[f]	**13c**	A	72	24, *R* (92)	0
6[f]	**13c**	B	4	64, *R* (94)	0
7	**13d**	B	72	27, *R* (95)	0
8	**13e**	B	120	23, *R* (97)	0
9	**13f**	B	58	82, *R* (97)	0
10	**13g**	A	65	21, *R* (100)	29, *R* (53)
11	**13g**	B	17	38, *R* (98)	21, *Racemate*
12	**13h**	A	72	31, *R* (97)	23, *S* (76)
13	**13h**	B	19	36, *R* (99)	22, *S* (65)
14	**13i**	B	72	0	0

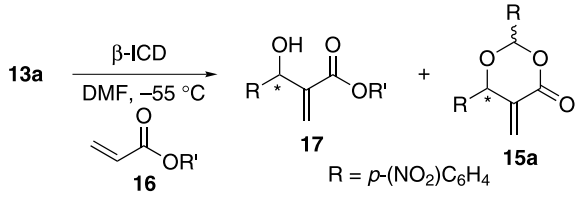
[a] All reactions were carried out at −55 °C in DMF (1 M) using **13** (1 equiv), HFIPA (1.3 equiv), and catalyst (0.1 equiv).
[b] A: undried β-ICD, B: dried β-ICD.
[c] Isolated yield.
[d] Determined in the same manner as noted in Table 1.
[e] *Cis*:*trans*; **15a**: 99:1, **15g**: 70:30, **15h**: 90:10.
[f] Catalyst (0.2 equiv) was used.

The enhanced catalytic activity of the dried β-ICD is ascribed to the prevention of the partial hydrolysis of HFIPA giving two acidic products, acrylic acid (pK_a 4.3[11]) and HFIP (pK_a 9.3[12]). In fact, addition of 10 mol% of acrylic acid completely inhibited the β-ICD-catalyzed reaction of 3-methylbutanal with HFIPA, while HFIP did not affect the reaction significantly. In view of the pK_a value of the phenolic OH of 6-hydroxy quinoline (pK_a 9.3[13]), it is reasonable that HFIP is less influential against β-ICD. It is assumed that, in the case of the less reactive aromatic aldehydes apart from *p*-nitrobenzaldehyde, the reaction rate is comparable with that of hydrolysis of HFIPA and therefore, the reaction is retarded by the generated acrylic acid, which attenuates the catalytic activity of β-ICD by protonation of the nucleophilic nitrogen. On the other hand, *p*-nitrobenzaldehyde reacts with HFIPA so rapidly that the reaction cannot be influenced by moisture contents of β-ICD. It was observed that the procedure using the dried β-ICD is markedly more effective than the previous one for aliphatic aldehydes having moderate reactivity in terms of rate acceleration.

2.4. HFIPA and its related fluorine-containing acrylates as an activated alkene

Table 3 summarizes β-ICD-catalyzed reaction of *p*-nitrobenzaldehyde with a panel of commercially available

Table 3. β-ICD-catalyzed reaction of *p*-nitrobenzaldehyde with fluorine-containing acrylates[a]



a: R' = CH_3, **b**, R' = CH_2CF_3, **c**: R' = $CH_2CF_2CF_3$
d: R' = $CH_2CF_2CF_2CF_3$

Entry	Acrylate	Time (h)	Yield (%),[b] Config (% ee)[c]	
			Ester	**15a**[d]
1[e]	**16a**	36	**17a**: 69, *S* (8)	0
2	**16b**	72	**17b**: 43, *S* (3)	6, *S* (6)
3	**16c**	72	**17c**: 50, *S* (2)	8, *S* (4)
4	**16d**	72	**17d**: 53, (0)	4, *R* (4)
5	HFIPA	1	**14a**: 58, *R* (91)	11, *R* (4)

[a] Reactions were carried out at −55 °C in DMF (0.5 M) using **13a** (1 equiv), acrylate (1.3 equiv), and β-ICD (0.1 equiv).
[b] Isolated yield.
[c] Determined in the same manner as noted in Table 1.
[d] *Cis*:*trans*; **15a**: 99: 1.
[e] The reaction was conducted at 20 °C.

fluorine-containing acrylates **16b–d** and HFIPA as well as methyl acrylate. It was observed that, compared with methyl acrylate, all fluorine-containing acrylates brought about remarkable rate acceleration due to the high electron-withdrawing nature of fluorine atom. It should be stressed that HFIPA having a branched alkoxy group exerts the striking effect both on rate acceleration and enantioselectivity. Other fluorine-containing acrylates **16b–d** having a linear alkoxy group did not induce any appreciable level of enantioselectivity.

3. Summary

In the present work, we proved that both the cage-like tricyclic structure and the phenolic OH of β-ICD as well as the branched structure of HFIPA are necessary for obtaining a high level of asymmetric induction as well as rate acceleration. This fact implies that intermediate **1** stabilized by hydrogen bonding would be responsible for the highly enantioselective production of *R* enriched adducts. In addition, we demonstrated that compound **8** is also able to serve as a chiral catalyst for asymmetric Baylis–Hillman reactions, suggesting that the C3 substituent on the quinuclidine ring exerts little effect on the catalytic ability. It should be highlighted that the azeotropically dried β-ICD was found to display remarkable catalytic ability. By this improved β-ICD–HFIPA method, the aromatic aldehydes except very reactive *p*-nitrobenzaldehyde can be converted into the corresponding Baylis–Hillman adducts in >94%ee without concomitant formation of undesired dioxanones.

4. Experimental

4.1. General

Where appropriate, reactions were performed in flame-dried glassware under an argon atmosphere. All extracts were dried over K_2CO_3 and concentrated by rotary evaporation below 30 °C at ca. 25 Torr unless otherwise noted. Thin-layer chromatography was performed using Merck F-254 TLC plates. Column chromatography was performed employing silica gel 60 (230–400 mesh ASTM, Merk). Commercial reagents and solvents were used as supplied with the following exceptions. Anhydrous tetrahydrofuran (THF) (stabilizer free) was purchased from Kanto Chemical Co., Inc. Dichloromethane (CH_2Cl_2), triethylamine, and *N*,*N*-dimethyformamide (DMF) were distilled from CaH_2. All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-370 polarimeter at ambient temperature. Infrared spectra were measured on a JASCO FT/IR-230 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini 300, JEOL JNM-AL 400, or a Varian Unity plus 500 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) in δ units and coupling constants are given in hertz. TMS was defined as 0 ppm for ^{1}H NMR spectra and the center of the triplet of $CDCl_3$ was also defined as 77.10 ppm for ^{13}C NMR spectra. HRMS (EI) spectra were measured on a JEOL JMS-DX303 or a JEOL JMS-700N.

4.2. Reaction of quinidine with KBr–H_3PO_4

Method A. Quinidine (2.0 g, 6.16 mmol) was added portionwise to a solution of KBr (2.20 g, 18.5 mmol) in 85% H_3PO_4 (30 mL) at room temperature, and the mixture was stirred at 100 °C for 3 days. After being cooled to room temperature, the mixture was added dropwise to an ice-cooled 25% KOH (200 mL). The pH was adjusted to ca. 8 with 25% NH_4OH and extracted with $CHCl_3$. The organic layer was washed with brine, dried over K_2CO_3, and chromatographed (SiO_2, $CHCl_3$/MeOH=9:1–4:1) to give **2** (938 mg, 47%), **3** (199 mg, 10%), and **6** (100 mg, 5%).

Method B. A mixture of quinidine (660 mg, 2.00 mmol), KBr (1.20 g, 10.0 mmol) in 85% H_3PO_4 (10 mL) was heated at 100 °C for 5 days and worked up in the same manner as described in Method A. Purification of the crude material by column chromatography (SiO_2, $CHCl_3$/MeOH=9:1–4:1) gave **4** (124 mg, 20%), **5** (43 mg, 7%), and β-ICD (155 mg, 25%).

Method C. A mixture of quinidine (10.0 g, 30.8 mmol), KBr (36.7 g, 308 mmol) in 85% H_3PO_4 (150 mL) was heated at 100 °C for 10 days and worked up in the same manner as described in Method A. Purification of the crude material by column chromatography (SiO_2, $CHCl_3$/MeOH=9:1–4:1) gave β-ICD (5.85 g, 61%) as a pale yellow amorphous solid, which was spectroscopically pure. β-ICD thus obtained was dissolved in NH_3–MeOH and filtered to remove insoluble precipitates. Concentration of the filtrate gave β-ICD as a crystalline solid, which was recrystallized from MeOH–H_2O to afford colorless needles.

4.2.1. (8*R*,9*S*,10*R*)-10,11-dihydro-9,10-epoxy-6′-methoxycinchonane (2). A pale yellow amorphous solid; $[\alpha]_D^{18}$ +79.2 (*c* 1.06, MeOH); FT-IR (neat) 3369, 2937, 2562, 2206, 1621, 1510, 1232, 1103, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J*=4.5 Hz, 1H), 8.01 (d, *J*=9.0 Hz, 1H), 7.62 (dd, *J*=4.5, 1.0 Hz, 1H), 7.36 (dd, *J*=9.0, 2.5 Hz, 1H), 7.32 (d, *J*=3.0 Hz, 1H), 5.95 (s, 1H), 4.26 (dq, *J*=1.5, 6.5 Hz, 1H), 4.03 (s, 3H), 3.77 (d, *J*=14.0 Hz, 1H), 3.49 (d, *J*=9.0 Hz, 1H), 3.23–3.19 (m, 2H), 2.86–2.82 (m, 1H), 2.45 (ddd, *J*=13.0, 6.0, 2.0 Hz, 1H), 2.38 (ddd, *J*=5.0, 5.0, 5.0 Hz, 1H), 1.85 (dd, *J*=8.0, 5.5 Hz, 1H), 1.74–1.65 (m, 2H), 1.48 (d, *J*=6.5 Hz, 3H), 1.27 (dd, *J*=12.5, 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 147.5, 145.3, 144.2, 131.7, 126.0, 121.6, 117.8, 101.7, 79.1, 72.4, 62.5, 56.6, 51.7, 47.3, 38.8, 25.2, 23.0, 22.3, 20.9; HRMS (EI) calcd for $C_{20}H_{24}N_2O_2$ (M^+): 324.1837, found 324.1840. The spectral data were identical with those reported.[7b]

4.2.2. (8*R*,9*S*,10*S*)-10,11-dihydro-9,10-epoxy-6′-methoxycinchonane (3). A pale yellow amorphous solid; $[\alpha]_D^{17}$ +60.4 (*c* 1.02, MeOH); FT-IR (neat) 3350, 2931, 2459, 2210, 1622, 1508, 1471, 1232, 1136, 1076, 1030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J*=5.0 Hz, 1H), 8.01 (d, *J*=9.0 Hz, 1H), 7.58 (dd, *J*=4.5, 1.0 Hz, 1H), 7.35, (dd, *J*=9.0, 2.5 Hz, 1H), 7.24 (d, *J*=2.5 Hz, 1H), 6.03 (s, 1H), 4.70 (dq, *J*=1.0, 6.5 Hz, 1H), 3.96 (s, 3H), 3.79, (d, *J*=14.0 Hz, 1H), 3.42 (d, *J*=9.5 Hz, 1H), 3.08 (dd, *J*=13.0, 8.5 Hz, 1H), 2.87 (dd, *J*=12.5, 8.5 Hz, 1H), 2.83–2.76 (m, 1H), 2.24 (ddd, *J*=13.0, 5.5, 2.5 Hz, 1H), 2.11 (ddd, *J*=5.5, 5.5, 5.5 Hz, 1H), 1.83–1.80 (m, 1H), 1.74–1.70 (m, 1H),

1.60–1.53 (m, 1H), 1.32 (d, J=6.5 Hz, 3H), 1.23 (ddd, J=13.5, 9.5, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 147.5, 146.7, 144.1, 131.6, 126.1, 121.4, 118.2, 101.4, 75.7, 74.1, 60.1, 56.1, 47.3, 44.9, 39.6, 26.5, 24.9, 22.9, 22.1; HRMS (EI) calcd for $C_{20}H_{24}N_2O_2$ (M^+): 324.1837, found 324.1838. The spectral data were identical with those reported.[7b]

4.2.3. (8*R*,9*S*,10*R*)-10,11-dihydro-9,10-epoxy-6′-hydroxycinchonane (4). A pale yellow amorphous solid; $[\alpha]_D^{17}$ +114.0 (*c* 1.00, MeOH); FT-IR (neat) 3200–2600, 2939, 2567, 1620, 1508, 1468, 1232, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J=4.5 Hz, 1H), 7.94 (d, J=9 Hz, 1H), 7.86 (d, J=2.5 Hz, 1H), 7.55 (dd, J=4.5, 1.0 Hz, 1H), 7.24 (dd, J=9.0, 2.5 Hz, 1H), 5.92 (s, 1H), 4.23 (q, J=6.5 Hz, 1H), 3.73 (d, J=13.5 Hz, 1H), 3.47 (d, J=8.0 Hz, 1H), 3.25–3.18 (m, 2H), 2.92–2.87 (m, 1H), 2.51 (ddd, J=13.0, 6.0, 1.5 Hz, 1H), 2.42 (m, 1H), 1.88 (dd, J=9.0, 5.5 Hz, 1H), 1.79–1.70 (m, 2H), 1.48 (d, J=6.5 Hz, 3H), 1.28 (dd, J=13.0, 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 146.9, 144.7, 143.3, 131.5, 125.9, 121.9, 117.3, 105.7, 79.0, 72.1, 62.6, 51.0, 47.0, 39.0, 25.2, 22.8, 22.2, 20.9; HRMS (EI) calcd for $C_{19}H_{22}N_2O_2$ (M^+): 310.1681, found 310.1683. The spectral data were identical with those reported.[7b]

4.2.4. (8*R*,9*S*,10*S*)-10,11-dihydro-9,10-epoxy-6′-hydroxycinchonane (5). A pale yellow amorphous solid; $[\alpha]_D^{18}$ +47.8 (*c* 1.06, MeOH); FT-IR (neat) 3100–2500, 2929, 1842, 1618, 1510, 1469, 1236, 1138, 1092, 910, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J=4.5 Hz, 1H), 7.95 (d, J=9.0 Hz, 1H), 7.93 (dd, J=3.0, 1.0 Hz, 1H), 7.54, (d, J=4.5 Hz, 1H), 7.24 (dd, J=9.0, 3.0 Hz, 1H), 6.02 (s, 1H), 4.69 (dq, J=7.0, 1.5 Hz, 1H), 3.81, (d, J=14.0 Hz, 1H), 3.36 (d, J=8.5 Hz, 1H), 3.14 (dd, J=12.5, 9.5 Hz, 1H), 2.93 (dd, J=14.0, 9.0 Hz, 1H), 2.83–2.77 (m, 1H), 2.34 (ddd, J=13.0, 6.0, 2.0 Hz, 1H), 2.18 (ddd, J=6.0, 6.0, 6.0 Hz, 1H), 1.87 (dd, J=9.0, 6.0 Hz, 3H), 1.79–1.73 (m, 1H), 1.66–1.61 (m, 1H), 1.30 (d, J=7.0 Hz, 3H), 1.26 (dd, J=13.0, 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 146.8, 146.2, 143.3, 131.3, 126.6, 122.3, 117.9, 106.3, 75.5, 73.0, 60.4, 47.0, 44.5, 39.6, 26.5, 25.1, 22.5, 22.6; HRMS (EI) calcd for $C_{19}H_{22}N_2O_2$ (M^+): 310.1681, found 310.1691. The spectral data were identical with those reported.[7b]

4.2.5. (3*R*,8*R*,9*S*)-10,11-dihydro-3,9-epoxy-6′-methoxycinchonane (6). A pale yellow amorphous solid; $[\alpha]_D^{19}$ −8.2 (*c* 1.02, MeOH); FT-IR (neat) 3350, 2966, 2517, 1622, 1508, 1232, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, J=4.5 Hz, 1H), 8.03 (d, J=9.0 Hz, 1H), 7.73 (dd, J=4.5, 1.0 Hz, 1H), 7.35 (dd, J=9.0, 2.5 Hz, 1H), 7.16 (d, J=3.0 Hz, 1H), 5.94 (s, 1H), 3.96 (s, 3H), 3.55 (d, J=13.5 Hz, 1H), 3.48 (d, J=6.0 Hz, 1H), 3.02–3.00 (m, 2H), 2.68 (d, J=14.0 Hz, 1H), 2.14 (dd, J=5.5, 5.0 Hz, 1H), 1.77 (ddd, J=13.0, 6.5, 2.5 Hz, 1H), 1.70–1.64 (m, 1H), 1.66 (q, J=7.5 Hz, 2H), 1.54–1.49 (m, 1H), 1.27 (dd, J=13.5, 6.5 Hz, 1H), 1.04 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 147.6, 144.0, 142.3, 131.7, 126.4, 121.6, 119.3, 100.5, 77.1, 73.0, 56.2, 55.9, 54.7, 46.7, 32.9, 27.4, 24.2, 23.5, 7.3; HRMS (EI) calcd for $C_{20}H_{24}N_2O_2$ (M^+): 324.1838, found 324.1827. The spectral data were identical with those reported.[7b]

4.2.6. (3*R*,8*R*,9*S*)-10,11-dihydro-3,9-epoxy-6′-hydroxycinchonane (β-ICD). Colorless needles; mp 258–259 °C; $[\alpha]_D^{22}$ +8.6 (*c* 1.00, MeOH); FT-IR (neat) 3400–3200, 2962, 2713, 1620, 1508, 1469, 1280, 1240, 1012, 858 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, J=4.5 Hz, 1H), 7.99 (br s, 1H), 7.97 (d, J=9.0 Hz, 1H), 7.57 (dd, J=4.5, 1.0 Hz, 1H), 7.24 (dd, J=9.0, 2.5 Hz, 1H), 6.00 (s, 1H), 3.68 (d, J=13.5 Hz, 1H), 3.46 (d, J=6.0 Hz, 1H), 3.19 (dd, J=13.0, 8.5 Hz, 1H), 3.09–3.03 (m, 1H), 2.77 (d, J=14.0 Hz, 1H), 2.21–2.19 (m, 1H), 1.87 (ddd, J=13.0, 6.5, 2.0 Hz, 1H), 1.79–1.73 (m, 1H), 1.69 (dq, J=3.5, 7.5 Hz, 2H), 1.63–1.58 (m, 1H), 1.24 (dd, J=13.6, 1.0 Hz, 1H), 1.04 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 146.7, 143.0, 142.2, 131.3, 127.0, 122.3, 119.1, 105.2, 77.0, 72.7, 56.0 54.0, 46.4, 32.7, 27.4, 23.5, 23.3, 7.3; HRMS (EI) calcd for $C_{19}H_{22}N_2O_2$ (M^+): 310.1681, found 310.1691. Anal. Calcd for $C_{19}H_{22}N_2O_2\cdot CH_3OH\cdot H_2O$: C 66.64, H 7.83, N 7.77; found C 66.51, H 7.50, N 7.58.

4.2.7. (3*R*,8*R*,9*S*)-3-triisopropylsilyloxy-3,9-epoxy-6′-hydroxy-10,11-dinorcinconane (8). NaH (60% in mineral oil; 2.00 g, 50.1 mmol) was washed with hexane, dried, and suspended in DMF (40 mL). Ethanethiol (8.17 μL, 110.3 mmol) was added dropwise to the suspension over 20 min with cooling in an ice bath, and the mixture was stirred at room temperature for 10 min. A solution of **7**[7b] (2.35 g, 5.01 mmol) in DMF (35 mL) was added at room temperature and the mixture was heated at 60 °C for 12 h. The reaction mixture was allowed to cool to room temperature, quenched with saturated NH_4Cl, and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography (SiO_2 75 g, $CHCl_3$/MeOH=10:1), followed by lyophilization gave **8** (1.59 g, 70%) as a pale yellow amorphous solid; $[\alpha]_D^{23}$ −18.6 (*c* 1.35, $CHCl_3$); FT-IR (neat) 3600–2300, 1622, 1468, 1348, 1238, 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J=8.0 Hz, 1H), 8.11 (br s, 1H), 7.97 (d, J=12.0 Hz, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.23 (dd, J=4.0, 12.0 Hz, 1H), 6.13 (s, 1H), 3.82 (d, J=12.0 Hz, 1H), 3.41 (d, J=8.0 Hz, 1H), 3.31–3.21 (m, 1H), 3.10–2.98 (m, 1H), 2.94 (d, J=8.0 Hz, 1 H), 2.36 (m, 1H), 2.14–1.97 (m, 2H), 1.69 (m, 1H), 1.32–0.98 (m, 22H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 146.4, 142.7, 140.8, 130.8, 126.7, 121.6, 118.5, 106.1, 99.2, 73.7, 55.9, 55.9, 46.1, 37.4, 24.4, 22.8, 17.9, 17.8, 12.8; HRMS (EI) calcd for $C_{26}H_{38}N_2O_3Si$ (M^+): 454.2651, found 454.2644.

4.2.8. (3*R*,8*R*,9*S*)-10,11-dihydro-3,6′-dihydroxycinchonane (9). NaH (60% in mineral oil; 122 mg, 3.06 mmol) was washed with hexane, dried, and suspended in DMF (2 mL). Ethanethiol (500 μL, 6.75 mmol) was added dropwise to the suspension, and the mixture was stirred at room temperature for 10 min. To this mixture was added a solution of hydroquinidine (100 mg, 0.31 mmol) in DMF (3 mL), and stirring was continued at room temperature for 1 h and at 100 °C for 20 h. The reaction mixture was allowed to cool to room temperature, acidified with 1 M HCl, and extracted with CH_2Cl_2. The aqueous layers were adjusted to pH 8 with 25% aqueous ammonia and extracted with CH_2Cl_2. Combined extracts were washed with brine, dried over K_2CO_3, and concentrated. Purification of the residue by column chromatography (SiO_2 deactivated by

exposure to MeOH and Et_3N, 10 g, $CHCl_3$/MeOH=10:1), followed by lyophilization gave **9** (55 mg, 57%) as a colorless amorphous solid; $[\alpha]_D^{20}$ +250.1 (*c* 1.03, MeOH); FT-IR (neat) 3130–2636, 2944, 1616, 1466, 1234 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.57 (d, *J*=4.5 Hz, 1H), 7.88 (d, *J*=9.3 Hz, 1H), 7.61, (d, *J*=4.5 Hz, 1H), 7.31 (dd, *J*=9.0, 2.7 Hz, 1H), 7.22 (d, *J*=2.7 Hz, 1H), 5.56 (d, *J*=2.7 Hz, 1H), 3.41–3.35 (m, 1H), 3.10–3.01 (m, 1H), 2.99–2.85 (m, 2H), 2.85–2.75 (m, 1H), 2.18–2.11 (m, 1H), 1.72 (br s, 1H), 1.60–1.47 (m, 5H), 1.08–0.99 (m, 1H), 0.93 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 158.7, 149.4, 147.1, 143.7, 131.3, 128.4, 123.7, 119.6, 105.1, 72.0, 60.7, 51.8, 50.9, 38.3, 27.5, 27.4, 26.0, 20.7, 12.3; HRMS (EI) calcd for $C_{19}H_{24}N_2O_2$ (M^+): 312.1838, found 312.1853.

4.2.9. (3*R*,8*R*)-10,11-dihydro-3,6′-methoxycinchonane (10). To an ice-cooled solution of hydroquinidine (1.20 g, 3.68 mmol) in CH_2Cl_2 (5 mL) were added 4-DMAP (45 mg, 0.34 mmol), pyridine (0.89 mL, 11.0 mmol) and methanesulfonyl chloride (0.57 mL, 7.35 mmol), and the mixture was stirred at room temperature for 3 days. The mixture was diluted with $CHCl_3$, washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 30 g, $CHCl_3$/MeOH=20:1) gave the corresponding mesylate (1.20 g, 81%). To a solution of the mesylate in THF (10 mL) was added dropwise lithium triethylborohydride (1 M in THF, 5.9 mL, 5.92 mmol) at −70 °C. The mixture was allowed to slowly warm to −55 °C, and stirred at that temperature for 3 days. The reaction mixture was acidified with 1 M HCl, and extracted with $CHCl_3$. The aqueous layers were adjusted to pH 8 with 25% NH_4OH and extracted with $CHCl_3$. The combined extracts were washed with brine, dried over K_2CO_3, and concentrated. Purification of the residue by column chromatography (SiO_2 25 g, $CHCl_3$/MeOH=20:1) gave **10** (673 mg, 73%) as a pale yellow amorphous solid; $[\alpha]_D^{18}$ +117.8 (*c* 1.02, MeOH); FT-IR (neat) 3371, 2937, 2868, 1622, 1510, 1466, 1234, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J*=4.5 Hz, 1H), 8.01 (d, *J*=9.5 Hz, 1H), 7.37 (dd, *J*=9.0, 2.5 Hz, 1H), 7.33, (d, *J*=2.5 Hz, 1H), 7.23 (d, *J*=4.5 Hz, 1H), 3.97 (s, 3H), 3.49–3.47 (m, 1H), 3.18 (dt, *J*=14, 8.5 Hz, 1H), 3.07 (dd, *J*=13.5, 9.5 Hz, 1H), 3.01 (dd, *J*=14, 9.5 Hz, 1H), 2.99–2.89 (m, 1H), 2.70 (ddd, *J*=13.5, 7.5, 2.5 Hz, 1H), 1.69 (br s, 1H), 1.60–1.44 (m, 4H), 1.47 (q, *J*=7.5 Hz, 2H), 1.42–1.36 (m, 1H), 0.94 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 147.3, 144.3, 143.6, 132.5, 128.5, 121.7, 121.3, 101.5, 55.5, 55.5, 49.2, 49.2, 37.4, 37.2, 27.9, 26.9, 25.9, 25.6, 11.9; HRMS (EI) calcd for $C_{20}H_{26}N_2O$ (M^+): 310.2045, found 310.2048.

4.3. General procedure for asymmetric Baylis–Hillman reactions

To a solution of aldehyde **13** (1.0 mmol) and the chiral amine catalyst (0.1 mmol) in DMF (1 mL) at −55 °C was added HFIPA or **16** (1.3 mmol). After stirring at −55 °C for the indicated time in Tables 1–3, the reaction was quenched by the addition of 0.1 M HCl (3 mL). The reaction mixture was extracted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated, and chromatographed (SiO_2, solvent system: EtOAc/hexane).

Dried β-ICD. β-ICD (0.1 mmol) was dissolved into THF (2 mL) and the solution was evaporated by rotary evaporation at room temperature. After repeating this operation three times, the resulting amorphous solid was dried under vacuum at room temperature for 10 min.

4.4. Conversion of 14 and 15 into the corresponding methyl ester for the determination of their optical purity

A mixture of **14** or **15** (1.0 mmol) and triethylamine (0.7 mL) in MeOH (7 mL) was stirred at room temperature for 30 min and the reaction was quenched by the addition of Dowex 50 (H^+ form). The reaction mixture was filtered, concentrated, and chromatographed (SiO_2, solvent system: EtOAc/hexane). The optical purity of the methyl ester was determined by HPLC analysis using a chiral column.

4.4.1. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate (14a). A colorless oil (95% ee); $[\alpha]_D^{24}$ −40.9 (*c* 0.87, $CHCl_3$); FT-IR (neat) 3533, 1751, 1525, 1352, 1286, 1232, 1120, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J*=8.7 Hz, 2H), 7.58 (d, *J*=8.7 Hz, 2H), 6.66 (s, 1H), 6.27 (s, 1H), 5.80–5.74 (m, 2H), 2.47 (d, *J*=4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 147.9, 147.5, 139.2, 130.9, 127.6, 123.9, 120.3 (q, $^1J_{C,F}$=281 Hz), 71.8, 66.9 (hept, $^2J_{C,F}$=34.2 Hz); HRMS (EI) calcd for $C_{13}H_9NO_5F_6$ (M^+): 373.0385, found 373.0389.

4.4.2. (2*R*,6*R*)-2,6-di(4-nitrophenyl)-5-methylene-1,3-dioxan-4-one (15a). A colorless oil (49% ee); $[\alpha]_D^{25}$ +3.2 (*c* 0.57, $CHCl_3$); FT-IR (neat) 3082, 2862, 1741, 1523, 1348, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J*=8.7 Hz, 2H), 8.31 (d, *J*=8.7 Hz, 2H), 7.79 (d, *J*=8.7 Hz, 2H), 7.64 (d, *J*=8.7 Hz, 2H), 6.74 (d, *J*=2.7 Hz, 1H), 6.62 (s, 1H), 5.92 (br s, 1H), 5.42 (d, *J*=2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 149.0, 148.6, 144.2, 141.1, 135.2, 130.6, 128.8, 127.5, 124.3, 123.9, 99.5, 80.4; HRMS (EI) calcd for $C_{17}H_{12}N_2O_7$ (M^+): 356.0644, found 356.0663.

4.4.3. Methyl (*R*)-3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate (methyl ester obtained from 14a). A colorless oil (95% ee); $[\alpha]_D^{23}$ −85.6 (*c* 0.54, MeOH); FT-IR (neat) 3427, 2962, 1751, 1387, 1232, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (dd, *J*=6.9, 1.8 Hz, 2H), 7.58 (d, *J*=6.9 Hz, 2H), 6.40 (s, 1H), 5.87 (s, 1H), 5.64 (d, *J*=6.3 Hz, 1H), 3.75 (s, 3H), 3.30 (d, *J*=6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 147.8, 146.0, 127.9, 123.5, 71.5, 58.4, 53.0, 50.0; HRMS (EI) calcd for $C_{11}H_{11}NO_6$ (M^+): 253.0586, found 253.0578. HPLC conditions: Daicel Chiralcel OJ, 2-propanol/hexane 1:10 (0.5 mL/min), t_R=29.0 min (*R*) and 32.4 min (*S*).

4.4.4. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-2-methylene-3-phenylpropanoate (14b). A colorless oil (97% ee); $[\alpha]_D^{19}$ −51.1 (*c* 1.04, $CHCl_3$); FT-IR (neat) 3375, 2970, 1755, 1387, 1298, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.30 (m, 5H), 6.60 (s, 1H), 6.24 (s, 1H), 5.75 (hept, *J*=6.0 Hz, 1H), 5.63 (br s, 1H), 2.45 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 140.5, 140.0, 129.6, 128.8, 128.5, 126.8, 120.4 (q, $^1J_{C,F}$=305.6 Hz), 72.6, 66.8 (hept,

$^{2}J_{C,F}$=35.3 Hz); HRMS (EI) calcd for $C_{13}H_{10}NO_5F_6$ (M^+): 328.0534, found 328.0538.

4.4.5. Methyl (*R*)-3-hydroxy-2-methylene-3-phenylpropanoate (methyl ester obtained from 14b). A colorless oil (95% ee); $[\alpha]_D^{20}$ −124.6 (*c* 1.30, MeOH); {lit.[14] $[\alpha]_D^{18}$ −111.1 (*c* 1.11, MeOH)}; FT-IR (neat) 3363, 3032, 2952, 1704, 1496, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 6.34 (s, 1H), 5.84 (s, 1H), 5.57 (d, *J*= 5.4 Hz, 1H), 3.73 (s, 3H), 3.02 (d, *J*=5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 142.1, 141.3, 128.5, 127.9, 126.6, 126.1, 73.3, 52.0; HRMS (EI) calcd for $C_{11}H_{12}O_5$ (M^+): 192.0786, found 192.0788. HPLC conditions: Daicel Chiralcel OJ, 2-propanol/hexane 1:5 (0.5 mL/min), t_R= 26.4 min (*R*) and 32.4 min (*S*).

4.4.6. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*E*,*R*)-3-hydroxy-2-methylene-5-phenyl-4-pentenoate (14c). A colorless oil (94% ee); $[\alpha]_D^{26}$ −39.1 (*c* 0.95, $CHCl_3$); FT-IR (neat) 3390, 3032, 2970, 1754, 1664, 1633, 1387, 1290, 1126, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.23 (m, 5H), 6.69 (d, *J*=15.9 Hz, 1H), 6.55 (s, 1H), 6.26 (s, 1H), 6.24 (dd, *J*=15.9, 6.6 Hz, 1H), 5.85 (hept, *J*= 6.0 Hz, 1H), 5.22 (d, *J*=6.6 Hz, 1H), 2.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 139.3, 136.1, 132.8, 129.7, 128.7, 128.3, 128.2, 126.8, 120.5 (q, $^{1}J_{C,F}$=281 Hz), 71.3, 66.8 (hept, $^{2}J_{C,F}$=34 Hz); HRMS (EI) calcd for $C_{15}H_{12}NO_5F_6$ (M^+): 354.0691, found 354.0675.

4.4.7. Methyl (*E*,*R*)-3-hydroxy-2-methylene-5-phenyl-4-pentenoate (methyl ester obtained from 14c). A colorless oil (94% ee); $[\alpha]_D^{22}$ +12.5 (*c* 0.56, $CHCl_3$); FT-IR (neat) 3442, 3028, 2952, 1718, 1631, 1440, 1277, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.20 (m, 5H), 6.67 (d, *J*= 16.0 Hz, 1H), 6.36 (dd, *J*=16.0, 6.3 Hz, 1H), 6.30 (s, 1H), 5.92 (s, 1H), 5.13 (dd, *J*=6.3, 6.3 Hz, 1H), 3.79 (s, 3H), 3.02 (d, *J*=6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 141.3, 136.5, 131.6, 129.3, 128.6, 127.9, 126.7, 126.0, 72.2, 52.1; HRMS (EI) calcd for $C_{13}H_{14}O_5$ (M^+): 218.0943, found 218.0951. HPLC conditions: Daicel Chiralcel OD, 2-propanol/hexane 1:10 (0.5 mL/min), t_R= 26.4 min (*R*) and 29.3 min (*S*).

4.4.8. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropanoate (14d). A pale yellow oil (95% ee); $[\alpha]_D^{20}$ −60.6 (*c* 1.44, $CHCl_3$); FT-IR (neat) 3475, 2966, 1763, 1616, 1514, 1304, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J*= 8.4 Hz, 2H), 6.88 (d, *J*=8.1 Hz, 2H), 6.58 (t, *J*=0.8 Hz, 1H), 6.26 (dd, *J*=1.5, 0.6 Hz, 1H), 5.75 (hept, *J*=6.1 Hz, 1H), 5.58 (d, *J*=4.2 Hz, 1H), 3.80 (s, 3H), 2.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 159.7, 140.1, 132.7, 129.1, 128.2, 120.4, (q, $^{1}J_{C,F}$=280.1 Hz), 114.1, 72.1, 66.6 (hept, $^{2}J_{C,F}$=34.7 Hz), 55.3; HRMS (EI) calcd for $C_{14}H_{12}F_6O_4$ (M^+): 358.0632, found 358.0639.

4.4.9. Methyl (*R*)-3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropanoate (methyl ester obtained from 14d). A pale yellow oil (95% ee); $[\alpha]_D^{22}$ −112.2 (*c* 0.54, $CHCl_3$); FT-IR (neat) 3512, 2951, 2841, 1712, 1506, 1444, 1242, 1144, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J*=9.0 Hz, 2H), 6.87 (d, *J*=9.0 Hz, 2H), 6.32 (s, 1H), 5.86 (s, 1H), 5.52 (d, *J*=5.1 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 1H), 2.82 (d, *J*=5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 159.3, 142.2, 133.5, 128.0, 125.7, 113.9, 72.8, 55.3, 52.0; HRMS (EI) calcd for $C_{12}H_{14}O_4$ (M^+): 222.0892, found 222.0892. HPLC conditions: Daicel Chiralcel OJ, 2-propanol/hexane 1:5 (0.5 mL/min), t_R= 53.3 min (*R*) and 70.3 min (*S*).

4.4.10. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-2-methylene-3-(naphthalen-1-yl)propanoate (14e). A colorless oil (97% ee); $[\alpha]_D^{23}$ −42.4 (*c* 1.65, $CHCl_3$); FT-IR (neat) 3433, 2969, 1718, 1441, 1286, 1151, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J*= 9.0 Hz, 1H), 7.89–7.81 (m, 2H), 7.55–7.42 (m, 4H), 6.61 (s, 1H), 6.39 (br d, *J*=3.9 Hz, 1H), 6.03 (s, 1H), 5.79 (hept, *J*= 6.0 Hz, 1H), 2.68 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 140.0, 136.1, 134.3, 131.1, 130.9, 129.6, 129.2, 126.9, 126.3, 120.7 (q, $^{1}J_{C,F}$=280 Hz), 69.2, 67.2 (hept, $^{2}J_{C,F}$=35.3 Hz); HRMS (EI) calcd for $C_{17}H_{12}F_6O_3$ (M^+): 378.0690, found 378.0698.

4.4.11. Methyl (*R*)-3-hydroxy-2-methylene-3-(naphthalen-1-yl)propanoate (methyl ester obtained from 14e). A pale yellow oil (97% ee); $[\alpha]_D^{23}$ −46.3 (*c* 0.83, $CHCl_3$); FT-IR (neat) 3433, 1718, 1441, 1286, 1151, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00–7.97 (m, 1H), 7.87–7.79 (m, 2H), 7.62 (d, *J*=6.9 Hz, 1H), 7.51–7.44 (m, 3H), 6.36 (br s, 1H), 6.34 (s, 1H), 5.57 (s, 1H), 3.76 (s, 3H), 3.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 141.8, 136.4, 133.7, 130.7, 128.7, 128.5, 127.1, 126.1, 125.5, 125.3, 124.4, 123.7, 69.2, 52.1; HRMS (EI) calcd for $C_{15}H_{14}O_3$ (M^+): 242.0943, found 242.0936. HPLC conditions: Daicel Chiralcel OJ–H, 2-propanol/hexane 1:2 (0.5 mL/min), t_R=27.6 min (*R*) and 57.8 min (*S*).

4.4.12. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-2-methylene-3-(naphthalen-2-yl)propanoate (14f). A colorless oil (97% ee); $[\alpha]_D^{26}$ −72.8 (*c* 1.04, $CHCl_3$); FT-IR (neat) 3388, 1755, 1385, 1238, 1120, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86–7.73 (m, 4H), 7.54–7.44 (m, 3H), 6.64 (s, 1H), 6.27 (s, H), 5.80 (d, *J*=4.8 Hz, 1H), 5.75 (hept, *J*=6.0 Hz, 1H), 2.58 (d, *J*=4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 139.8, 137.7, 133.3, 130.0, 128.7, 128.2, 127.8, 126.5, 126.1, 124.3, 120.4 (q, $^{1}J_{C,F}$= 279.7 Hz), 72.7, 66.7 (hept, $^{2}J_{C,F}$=35.3 Hz); HRMS calcd for $C_{17}H_{12}F_6O_3$ (M^+): 378.0690, found 378.0696.

4.4.13. Methyl (*R*)-3-hydroxy-2-methylene-3-(naphthalen-2-yl)propanoate (methyl ester obtained from 14f). A colorless solid (97% ee); $[\alpha]_D^{21}$ −31.1 (*c* 0.68, $CHCl_3$); FT-IR (neat) 3448, 2950, 1716, 1441, 1277, 1151, 1043, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86–7.81 (m, 4H), 7.49–7.45 (m, 3H), 6.38 (t, *J*=0.9 Hz, 1H), 5.88 (t, *J*=0.9 Hz, 1H), 5.74 (d, *J*=5.1 Hz, 1H), 3.72 (s, 3H), 3.14 (d, *J*=5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 141.9, 138.6, 133.3, 133.1, 128.3, 128.2, 127.7, 126.4, 126.2, 126.1, 125.6, 124.6, 73.4, 73.3, 52.1; HRMS (EI) calcd for $C_{15}H_{14}O_3$ (M^+): 242.0943, found 242.0947. HPLC conditions: Daicel Chiralcel OJ, 2-propanol/hexane 1:5 (1.0 mL/min), t_R=52.8 min (*R*) and 62.9 min (*S*).

4.4.14. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-2-methylene-5-phenylpentanoate (14g). A colorless oil

(98% ee); $[\alpha]_D^{22}$ +11.5 (*c* 1.41, $CHCl_3$); FT-IR (neat) 3427, 2962, 1751, 1387, 1232, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.24 (m, 2H), 7.22–7.17 (m, 3H), 6.49 (s, 1H), 6.15 (s, 1H), 5.85 (hept, J=6.0 Hz, 1H), 4.52 (dd, J=3.6, 4.2 Hz, 1H), 2.85–2.66 (m, 2H), 2.24 (br s, 1H), 2.08–1.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 142.2, 140.6, 129.2, 128.6, 128.5, 126.2, 120.5 (q, $^1J_{C,F}$=282.3 Hz), 70.1, 66.7 (hept, $^2J_{C,F}$=34.7 Hz), 37.8, 32.0; HRMS (EI) calcd for $C_{15}H_{14}F_6O_3$ (M^+): 356.0847, found 356.0863.

4.4.15. (6*R*)-2,6-Diphenethyl-5-methylene-1,3-dioxan-4-one (15g) (70:30 *cis*/*trans*-mixture). A colorless oil; FT-IR (neat) 3028, 2931, 1730, 1446, 1379, 1234, 1161, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (m, 4H), 7.23–7.17 (m, 10H), 6.49–6.47 (m, 1H), 5.58 (d, J=2.1 Hz, 0.7H), 5.54 (d, J=2.1 Hz, 0.3H), 5.45 (t, J=5.1 Hz, 0.3H), 5.27 (d, J=5.1 Hz, 0.7H), 4.71–4.67 (m, 0.3H), 4.51–4.46 (m, 0.7H), 2.93–2.65 (m, 4H), 2.22–1.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 140.9, 140.6, 140.5, 136.8, 136.0, 128.7, 128.6, 128.5, 128.4, 126.8, 126.4, 126.2, 125.7, 101.1, 96.4, 77.5, 77.1, 76.7, 76.5, 74.2, 36.6, 35.8, 35.6, 35.3, 31.4, 30.8, 29.4, 29.3; HRMS (EI) calcd for $C_{21}H_{22}O_3$ (M^+): 322.1569, found 322.1567.

4.4.16. Methyl (*R*)-3-hydroxy-2-methylene-5-phenylpentanoate (methyl ester obtained from 14g). A colorless oil (98% ee); $[\alpha]_D^{22}$ +28.1 (*c* 0.83, $CHCl_3$); FT-IR (neat) 3487, 3024, 2947, 1720, 1631, 1444, 1149, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.15 (m, 5H), 6.24–6.23 (m, 1H), 5.81 (t, J=0.9 Hz, 1H), 4.45–4.39 (m, 1H), 3.76 (s, 3H), 2.87–2.64 (m, 3H), 2.01–1.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 142.2, 141.7, 128.5, 128.5, 126.0, 125.4, 71.2, 52.0, 37.7, 32.1; HRMS (EI) calcd for $C_{15}H_{16}O_3$ (M^+): 220.1099, found 220.1123. HPLC conditions: Daicel Chiralcel OD–H, 2-propanol/hexane 1:5 (0.5 mL/min), t_R=13.0 min (*R*), t_R=15.8 min (*S*).

4.4.17. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-cyclohexyl-3-hydroxy-2-methylenepropanoate (14h). A colorless oil (99% ee); $[\alpha]_D^{24}$ −2.6 (*c* 1.00, $CHCl_3$); FT-IR (neat) 3419, 2935, 2857, 1749, 1647, 1387, 1365, 1294, 1124 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 6.07 (s, 1H), 5.84 (hept, J=6.0 Hz, 1H), 4.26 (dd, J=6.3, 6.3 Hz, 1H), 2.04 (d, J=6.9 Hz, 1H), 1.92–1.50 (m, 6H), 1.32–0.94 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 139.6, 129.9, 120.5 (q, $^1J_{C,F}$=281.2 Hz), 75.8, 66.7 (hept, $^2J_{C,F}$=35.3 Hz), 42.7, 29.8, 27.8, 26.4, 26.2, 26.0; HRMS (EI) calcd for $C_{13}H_{16}O_5F_6$ (M^+): 334.1003, found 334.0993.

4.4.18. (2*S*,6*S*)-dicyclohexyl-5-methylene-1,3-dioxan-4-one (15h) (90:10 *cis*/*trans*-mixture). A colorless oil; FT-IR (neat) 2929, 2854, 1739, 1631, 1201 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (d, J=2.4 Hz, 1H), 5.53 (d, J=1.8 Hz, 1H), 4.98 (d, J=5.1 Hz, 1H), 4.43 (m, 1H), 1.88–1.62 (m, 12H), 1.38–1.18 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 136.7, 125.0, 103.6, 81.5, 43.6, 41.7, 29.0, 26.6, 26.4, 26.4, 26.3, 26.3, 26.2, 26.0, 25.6, 26.5; HRMS (EI) calcd for $C_{17}H_{26}O_3$ (M^+): 278.1882, found 278.1880.

4.4.19. Methyl (*R*)-3-cyclohexyl-3-hydroxy-2-methylenepropanoate (methyl ester obtained from 14h). A colorless oil (99% ee); $[\alpha]_D^{24}$ −8.1 (*c* 0.93, $CHCl_3$); FT-IR (neat) 3448, 2929, 2852, 1718, 1628, 1440, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.25 (d, J=1.2 Hz, 1H), 5.73 (d, J=1.2 Hz, 1H), 4.06 (dd, J=7.8, 7.8 Hz, 1H), 3.78 (s, 3H), 2.56 (d, J=8.4 Hz, 1H), 1.97 (m, 1H), 1.79–1.50 (m, 5H), 1.29–0.91 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 141.1, 126.2, 77.1, 51.9, 42.4, 30.0, 28.3, 26.4, 26.1, 26.0; HRMS (EI) calcd for $C_{11}H_{18}O_5$ (M^+): 198.1256, found 198.1264. HPLC conditions: Daicel Chiralcel OD, 2-propanol/hexane 1:50 (0.5 mL/min), t_R=21 min (*R*) and 26 min (*S*).

4.4.20. 1,1,1-Trifluoroethyl 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate (17b). A pale yellow oil; FT-IR (neat) 3523, 1734, 1522, 1348, 1282, 1173, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J=9.0 Hz, 2H), 7.58 (d, J=9.0 Hz, 2H), 6.55 (d, J=0.6 Hz, 1H), 6.10 (s, 1H), 5.96 (d, J=5.1 Hz, 1H), 4.50 (dq, J=1.5, 8.1 Hz, 2H), 2.94 (dd, J=4.5, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 148.2, 147.5, 140.1, 129.0, 127.6, 123.7, 122.7 (q, $^1J_{C,F}$=275.5 Hz), 71.9, 60.7 (q, $^2J_{C,F}$=36.5 Hz); HRMS calcd for $C_{12}H_{10}NO_5F_3$ (M^+): 305.0511, found 305.0529.

4.4.21. 1,1,1,2,2-Pentafluoropropyl 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate (17c). A pale yellow oil; FT-IR (neat) 3523, 1734, 1603, 1523, 1348, 1271, 1207, 1149, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J=9.0 Hz, 2H), 7.58 (d, J=9.0 Hz, 2H), 6.53 (s, 1H), 6.10 (s, 1H), 5.69 (d, J=5.4 Hz, 1H), 4.58 (dt, J=0.9, 12.6 Hz, 2H), 2.94 (dd, J=5.4, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 148.2, 147.6, 140.0, 129.0, 127.6, 123.7, 118.4 (dt, 2 $J_{C,F}$=34.0 Hz, $^1J_{C,F}$=283 Hz), 111.9 (dt, $^1J_{C,F}$=254.0 Hz, $^2J_{C,F}$=38.0 Hz), 71.9, 59.6 (t, $^2J_{C,F}$=28.5 Hz); HRMS calcd for $C_{13}H_{10}NO_5F_5$ (M^+): 355.0479, found 355.0490.

4.4.22. 1,1,1,2,2,3,3-Heptafluorobutyl 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate (17d). A pale yellow oil; FT-IR (neat) 3529, 1736, 1604, 1525, 1404, 1350, 1236, 1136, 1059, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J=9.0 Hz, 2H), 7.58 (d, J=9.0 Hz, 2H), 6.53 (s, 1H), 6.10 (d, J=0.9 Hz, 1H), 5.69 (d, J=5.4 Hz, 1H), 4.62 (td, J=13.2, 1.5 Hz, 2H), 2.94 (d, J=6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 148.1, 147.7, 140.1, 129.1, 127.6, 123.8, 117.5 (dt, $^2J_{C,F}$=33.0 Hz, $^1J_{C,F}$=285.7 Hz), 113.8 (dd, $^1J_{C,F}$=254.9 Hz, $^2J_{C,F}$=30.7 Hz), 108.6 (m), 72.1, 59.8 (t, $^2J_{C,F}$=27.3 Hz); HRMS calcd for $C_{14}H_{10}NO_5F_7$ (M^+): 405.0447, found 405.0454.

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