DOI: 10.1002/ejoc.200800807

Kinetic Resolution of β-Alkenyl-, β-Alkynyl- and β-Flavenyl-Substituted β-Hydroxy Esters in Asymmetric Dehydration

Min Hee Lee,[a] Eui Ta Choi,[a] Dajung Kim,[a] Yoon Min Lee,[a] and Yong Sun Park*[a]

Keywords: Kinetic resolution / Asymmetric catalysis / Dehydration / Chiral ligands / Flavonoids

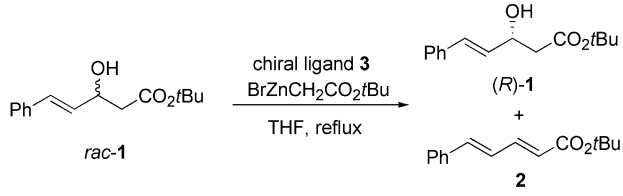
Catalytic asymmetric dehydration of β-alkenyl- or alkynyl-substituted β-hydroxy esters by kinetic resolution has been investigated with five different chiral ligands **3**–**7**. The kinetic resolution of a variety of racemic β-hydroxy *tert*-butyl esters in the presence of a prolinol chiral ligand and $BrZnCH_2CO_2tBu$ provided highly enantio-enriched β-hydroxy esters **9**–**22** with selectivity factors ranging from 11 to 59. In addition, the application of this asymmetric synthetic methodology to the preparation of enantio-enriched flavene derivatives **23**–**29** is demonstrated.

Introduction

The nonenzymatic kinetic resolution of racemic compounds with a chiral catalyst is presently an area of great importance in asymmetric organic synthesis.[1] Highly efficient kinetic resolution in the oxidation and acylation of secondary alcohols has been developed by several research groups.[2,3] We have also explored the catalytic asymmetric dehydration of β-hydroxy esters by kinetic resolution.[4] Although the catalytic dehydration provides a synthetic approach to enantio-enriched β-aryl- and β-styryl-substituted β-hydroxy esters, the substrate scope explored was somewhat limited. Application of this methodology to more complex and highly functionalized β-hydroxy esters and the development of more efficient catalytic systems are desirable. Herein we describe the results of our recent investigation to assess the substrate scope and limitation of the asymmetric dehydration methodology with five different chiral ligands. In addition, the versatility of this kinetic resolution is further demonstrated with β-flavenyl-substituted β-hydroxy esters bearing an additional chiral center.

Results and Discussion

We have previously reported the kinetic resolution of β-hydroxy-β-styryl *tert*-butyl ester **1** in the presence of the D-Phg-L-Pro dipeptide derived chiral ligand **3** and $BrZnCH_2CO_2tBu$[4a] (Scheme 1). When a mixture of racemic β-hydroxy ester **1**, *tert*-butyl bromoacetate (8 equiv.), and chiral ligand **3** (5 mol-%) in THF was added to activated zinc (8 equiv.) in THF and refluxed for 2 h, the reaction provided a mixture of *tert*-butyl (*E*,*E*)-5-phenylpentadienoate (**2**) and β-hydroxy ester (*R*)-**1**. At 55% conversion, pentadienoate **2** was isolated in 40% yield, and the unconverted (*R*)-**1** was obtained in 37% yield with 97% *ee* [selectivity $s = k_S/k_R = 38$].[5] A significantly high enantioselectivity was noted in the elimination of the secondary alcohols with an excess amount of organozinc reagent as base in refluxing THF.



Scheme 1. Asymmetric dehydration of β-hydroxy-β-styryl ester **1**.

To develop a more efficient catalytic system, we initially examined the effect of excess organozinc reagent on the enantioselectivity and conversion, as shown in Figure 1. The dehydration did not proceed with 1 equiv. of $BrZnCH_2CO_2tBu$, and proceeded only slowly in the presence of 2 equiv. of $BrZnCH_2CO_2tBu$ and with low selectivity. Although a comparable conversion was attained with 4 equiv. of $BrZnCH_2CO_2tBu$ in 2 h, the selectivity was much lower than was obtained in the reaction with 8 equiv. of $BrZnCH_2CO_2tBu$. Preliminary results indicate that the selectivity and rate of dehydration is significantly influenced by the amount of $BrZnCH_2CO_2tBu$. Importantly, 8 equiv. of $BrZnCH_2CO_2tBu$ is essential to achieve a highly efficient dehydration, and smaller quantities of $BrZnCH_2CO_2tBu$ gave lower selectivities. When a mixture of β-hydroxy ester **1** and chiral ligand **3** (5 mol-%) in THF was added to preformed $BrZnCH_2CO_2tBu$ in THF (8 equiv.), no significant difference in selectivity or conversion was observed. With $BrZnCH_2CO_2Me$ or $BrZnCH_2CO_2Et$, the dehydration took

[a] Department of Chemistry, Bio/Molecular Informatics Center, Konkuk University,
Seoul 143-701, Korea
Fax: +822-3436-5382
E-mail: parkyong@konkuk.ac.kr

place slowly, and the selectivity was much lower in both cases. The use of $BrZnCH_2CO_2Me$ in the reaction of **1** gave 25% conversion after 10 h and a selectivity value of 10 under the same reaction conditions. When *t*BuLi was used as base in the presence of chiral ligand **3**, the reaction gave the eliminated product **2** with no detectable enantioselectivity. However, the reaction of **1** with Et_2Zn, $BrZnCH_2CH_2CH_2(CH_3)_2$, or *t*BuMgCl did not provide the dehydrated product **2** under the same reaction conditions.

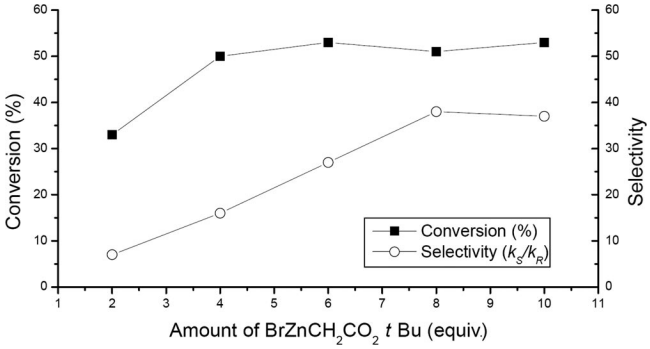
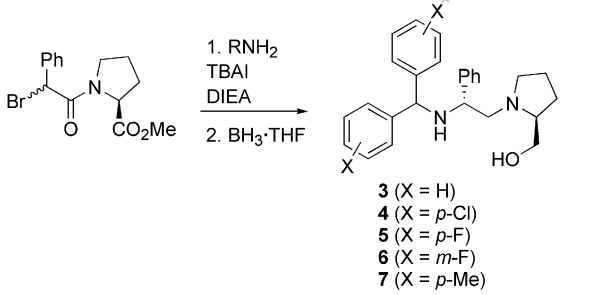


Figure 1. Dependence of converison and selectivity on the amount of $BrZnCH_2CO_2tBu$ used in the reaction of **1** with 5 mol-% of chiral ligand **3** for 2 h in THF.

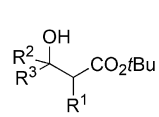
Our previous studies towards the development of an efficient chiral ligand for asymmetric dehydration revealed that the (*S*)-*N*-[(*R*)-2-amino-2-phenylethyl]prolinol skeleton of chiral ligand **3** is the catalytic core structure and the diphenylmethyl substituent is vital for both reactivity and selectivity.[4a] On the basis of these facts, we have attempted to modify the catalytic properties of **3** by introducing different phenyl substituents, such as chlorine, fluorine, and methyl groups, as shown in Scheme 2. The chiral ligands **4**–**7** were prepared according to the synthetic methodology that we recently developed for the asymmetric synthesis of dipeptide analogues.[6] The treatment of two diastereomeric mixtures (ca. 50:50) of *N*-(α-bromo-α-phenylacetyl)-L-proline methyl ester with a corresponding amine nucleophile in the presence of tetrabutylammonium iodide (TBAI) and diisopropylethylamine (DIEA) in CH_2Cl_2 at room temperature gave the D-Phg-L-Pro dipeptide analogues in 45–71% yields with diastereomeric ratios (*dr*s) >95:5. The subsequent reduction with excess BH_3·THF (5 equiv.) in THF furnished chiral ligands **4**–**7** in 53–62% yields by flash column chromatographic separation. We then explored the asymmetric dehydration of β-hydroxy ester **1** as a preliminary evaluation of the catalytic properties of the chiral ligands **4**–**7**. After 2 h at reflux under the standard reaction conditions, the *p*-chloro-, *p*-fluoro-, *m*-fluoro-, and *p*-methyl-substituted ligands **4**–**7** gave selectivity values of 29, 25, 34, and 30, respectively, with 50–55% conversion. In the reactions of β-hydroxy ester **1**, the introduction of a substituent on to the diphenylmethyl group of the ligand in all cases slightly decreased the selectivity without affecting the reactivity.



3 (X = H)
4 (X = *p*-Cl)
5 (X = *p*-F)
6 (X = *m*-F)
7 (X = *p*-Me)

Scheme 2. Asymmetric preparation of chiral ligands **3**–**7**.

To examine the substrate scope of the methodology we carried out the dehydration of various α- and β-substituted β-hydroxy esters **8a**–**g** with chiral ligand **3** (Figure 2). β-Phenethyl-β-hydroxy ester **8a** and β-hydroxy-β-methyl ester **8b** did not undergo dehydration to yield α,β-unsaturated esters, which indicates that the dehydration is not likely to occur if the resulting conjugation does not extend throughout the molecule. Conjugation of the newly formed double bond with both a β-alkenyl group and the carbonyl group stabilizes the α,β-unsaturated product and provides the thermodynamic driving force for the dehydration process. Interestingly, β-phenyl-β-styryl-disubstituted ester **8c**, which is anticipated to exhibit more extended conjugation, did not produce the eliminated product, and the racemic β-hydroxy ester was quantitatively recovered. Also, dehydration of the β-methyl-β-styryl-disubstituted ester **8d** did not occur at all, from which it was concluded that the catalyst system was not suitable for the dehydration of β,β-disubstituted β-hydroxy esters, probably due to the steric bulk associated with the β-position of the substrate. Under the same reaction conditions, the reactions of α-phenyl-substituted ester **8e** (mixture of two diastereomers) and α-methyl-substituted ester **8f** (mixture of two diastereomers) did not produce the corresponding α,β-unsaturated ester. Instead, the two reactions led to β-hydroxy-β-styryl ester **1** and the α,β-unsaturated ester **2**, which might be produced by retro-aldol reactions of **8e** and **8f** and subsequent addition of $BrZnCH_2CO_2tBu$ to cinnamaldehyde. Once again, this dehydration system is not successful for the dehydration of α-phenyl-substituted ester **8g** bearing no β-substituent. Unfortunately, the substrate scope of this asymmetric methodology is limited to β-hydroxy esters with a β-conjugated substituent and no α-substituent.



8a (R^1 = H, R^2 = H, R^3 = CH_2CH_2Ph)
8b (R^1 = H, R^2 = H, R^3 = CH_3)
8c (R^1 = H, R^2 = Ph, R^3 = CH=CHPh)
8d (R^1 = H, R^2 = CH_3, R^3 = CH=CHPh)
8e (R^1 = Ph, R^2 = H, R^3 = CH=CHPh)
8f (R^1 = CH_3, R^2 = H, R^3 = CH=CHPh)
8g (R^1 = Ph, R^2 = H, R^3 = H)

Figure 2. β-Hydroxy esters **8a**–**g** used in the dehydration reactions.

As shown in Table 1, we have investigated the asymmetric dehydration of a variety of β-alkenyl-β-hydroxy esters **9**–**20** bearing a β-substituent and no α-substituent. For conve-

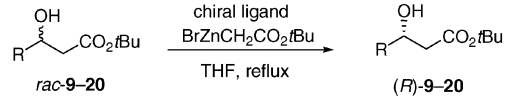
nience, all reactions were performed with 5 mol-% of the chiral ligand and 8 equiv. of $BrZnCH_2CO_2tBu$. The kinetic resolution of the β-(*p*-methoxystyryl)-substituted ester **9** with chiral ligand **3** provided an excellent level of asymmetric induction (s = 58). In an examination of the effects of the modified chiral ligands **4**–**6**, *m*-fluoro-substituted ligand **6** produced a comparable level of selectivity (s = 53) relative to chiral ligand **3**, whereas chiral ligands **4** and **5** produced modest levels of selectivity in the dehydration of β-alkenyl-β-hydroxy esters **9** (Entry 1). On the other hand, in the reactions of **10** and **11**, *p*-chloro-substituted ligand **4** gave slightly higher selectivities than chiral ligand **3** (Entries 2 and 3). With the identification of chiral ligand **3** as generally the most efficient ligand for the asymmetric dehydration of β-alkenyl-β-hydroxy esters, we set out to examine the scope of the asymmetric dehydration with β-alkenyl-substituted esters **12**–**20**. As shown in Entries 4–7, β-alkenyl-β-hydroxy esters **12**–**15** gave high levels of selectivity in the presence of **3** (s = 33–39). We were pleased to observe that excellent selectivities (s = 54–59) were obtained in the kinetic resolution of highly functionalized β-hydroxy esters **16**, **17**, **19**, and **20** (Entries 8, 9, 11, and 12). Curiously, β-(3-furanyl)-substituted ester **18** showed a much lower selectivity (s = 17) with chiral ligand **3** compared with the dehydration of β-(2-furanyl)-substituted ester **17** (Entry 10).

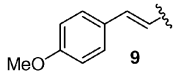
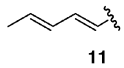
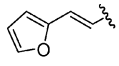
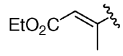
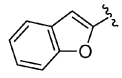
We have also extended the reaction's scope to β-alkynyl-substituted β-hydroxy esters. As shown in Table 2, the kinetic resolution of β-hydroxy-β-propargyl ester **21** provided a selectivity value of 29 with 5 mol-% of chiral ligand **3** and 8 equiv. of $BrZnCH_2CO_2tBu$ (Entry 1). Slightly lower levels of selectivity were observed with chiral ligands **4**, **5**, and **7** (Entries 2–4). In contrast, the kinetic resolution of β-heptynyl-substituted β-hydroxy ester **22** with chiral ligands **3** and **4** gave similar levels of selectivity (Entries 5 and 6).

Given the remarkably high levels of enantioselectivity attainable in the asymmetric dehydration of β-alkenyl- and β-alkynyl-substituted β-hydroxy esters, we evaluated whether β-flavenyl-β-hydroxy esters **23a**–**28a** bearing an additional chiral center might be good substrates for kinetic resolution. The flavene (2-phenyl-2*H*-chromene) structural core is a widespread element in natural flavonoids, and the development of synthetic strategies for highly functionalized flavenes is of considerable interest because a wide range of biological activities associated with the scaffold have been identified.[7] Efficient kinetic resolution in the dehydration of β-flavenyl-β-hydroxy esters bearing an additional chiral center at the 2-position of the flavene framework can allow both unconverted substrate **23a**–**28a** and the eliminated product **23b**–**28b** to be obtained in a highly enantio-enriched form.

When racemic 6-chloro-2-(*o*-methoxyphenyl)flavene derivative **23a** was treated with $BrZnCH_2CO_2tBu$ and chiral ligand **3**, the dehydration provided 3-alkenyl-substituted flavene derivative (*R*)-**23b** with 68% *ee* in 42% yield and the unreacted 3-(1′-hydroxyalkyl)flavene derivative (2*S*,1′*R*)-**23a** with 98% *ee* in 30% yield (s = 23), as shown in Table 3, Entry 1.[8] With five different flavenes **24a**–**28a**, the scope of the asymmetric dehydration was explored with chiral ligand

Table 1. Asymmetric dehydration of β-alkenyl-β-hydroxy esters **9**–**20**.

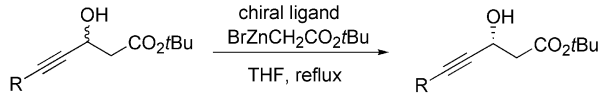


Entry	R	Ligand	Time [h]	Conv.[a] [%]	*ee*[b] [%]	*s*[c] (k_S/k_R)
1	 **9**	**3**	2.5	50	90	58
		4	1.5	50	84	29
		5	1.5	52	80	16
		6	1	51	93	53
2	 **10**	**3**	2.5	51	82	21
		4	1.5	52	90	24
		5	1.5	51	77	16
3	 **11**	**3**	2	57	81	11
		4	1	49	70	13
		5	1	53	68	8
4	 **12**	**3**	1.5	52	91	35
5	 **13**	**3**	2	53	94	39
6	 **14**	**3**	2	52	91	35
7	 **15**	**3**	2.5	50	85	33
8	 **16**	**3**	1.5	53	97	59
9	 **17**	**3**	2	52	95	55
10	 **18**	**3**	1.5	50	76	17
11	 **19**	**3**	1	52	96	54
12	 **20**	**3**	1	52	95	54

[a] Based on the consumption of the starting β-hydroxy ester substrate, as determined by ^1H NMR analysis of characteristic signals directly in the crude mixture with hexamethylbenzene as the internal integration standard. [b] The *ee* values were determined by CSP-HPLC. [c] Selectivity (s) values represent an average of at least two experiments; the conversion and *ee* values are for specific cases.

3. Similar results were obtained with flavenes **25a** and **26a**, whereas poor selectivities were observed with flavenes **24a**, **27a**, and **28a** (Entries 2–6). These limited results suggest that the selectivity is sensitive to the substitution pattern on both aryl rings of the flavene framework. Next, other chiral ligands **4**–**6** were examined to identify a more efficient catalytic system for the dehydration of β-flavenyl-β-hydroxy esters **23a**–**28a**. The reaction of **23a** with *p*-chloro-substituted chiral ligand **4** produced the dehydrated product (*R*)-**23b**

Table 2. Asymmetric dehydration of β-alkynyl-β-hydroxy esters **21** and **22**.



rac-**21**–**22** (*R*)-**21**–**22**

Entry	R	Ligand	Time [h]	Conv.[a] [%]	*ee*[b] [%]	*s*[c]
1	Ph (**21**)	**3**	1.5	55	97	29
2	Ph (**21**)	**4**	1	54	86	18
3	Ph (**21**)	**5**	1	59	97	20
4	Ph (**21**)	**7**	2	58	96	20
5	$CH_3(CH_2)_4$ (**22**)	**3**	1.5	58	97	22
6	$CH_3(CH_2)_4$ (**22**)	**4**	2	55	91	21

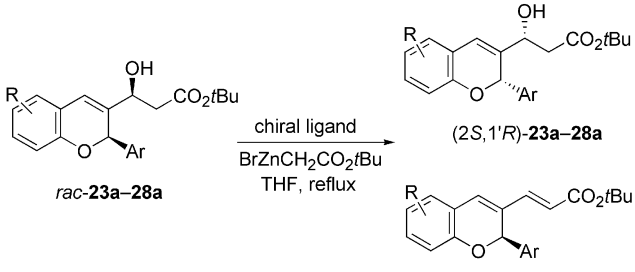
[a] Based on the consumption of the starting β-hydroxy ester substrate, as determined by ^{1}H NMR analysis with hexamethylbenzene as the internal integration standard. [b] The *ee* values were determined by CSP-HPLC. [c] Selectivity ($s = k_S/k_R$) values represent an average of at least two experiments; the conversion and *ee* value are for specific cases.

with a lower selectivity (s = 14; Entry 7) than the reaction with chiral ligand **3**. Furthermore, the chiral ligand **4** gave disappointing results in the dehydration of **24a** and **26a** with much lower selectivities (Entries 8 and 9). On the other hand, *p*-fluoro-substituted chiral ligand **5** exhibited higher selectivities (s = 21–41) than both chiral ligands **3** and **4** with all substrates examined, as shown in Entries 10–15. Exceptionally high efficiency in the kinetic resolution was obtained with 6-methyl-substituted **27a**, affording a selectivity value of 41 (Entry 14). Chiral ligand **6** afforded a similar selectivity in the reaction of **23a** (Entry 16). In addition, the experimental procedure for dehydration was applied to the kinetic resolution of 8-methoxy-2-phenyl-substituted flavene derivative **29**, which is a diastereomeric isomer of **26a**.[8] The reaction of **29** with chiral ligand **5** produced the dehydrated product (*S*)-**26b** in 53% conversion and the unreacted flavene derivative (2*R*,1′*R*)-**29** with 88% *ee* and with a comparable selectivity to that of the diastereomeric isomer **26a**, as shown in Entry 17 (s = 23). These limited results reflect a highly effective discrimination between the (1′*S*) and (1′*R*) chiral centers in the dehydration process, but little effect of the chiral center at the 2-position of the flavene framework. Consequently, the successful asymmetric dehydration of the flavene derivatives **23a**–**28a**,**29** bearing two stereocenters resulted in the isolation of enantioenriched 3-(1′-hydroxyalkyl)- and 3-alkenyl-substituted flavene derivatives.

Conclusions

We have reported the successful catalytic kinetic resolution of β-alkenyl-, β-alkynyl-, and β-(2*H*-3-flavenyl)-substituted β-hydroxy esters in asymmetric dehydration. The en-

Table 3. Asymmetric dehydration of β-flavenyl-β-hydroxy esters **23a**–**28a**,**29**.[a]



rac-**23a**–**28a** (2*S*,1′*R*)-**23a**–**28a** (*R*)-**23b**–**28b**

Entry	Starting material	R	Ar	Ligand	*ee*[b] [%] of **a**	*ee* [%] of **b**	Conv.[c] [%]	*s*[c]
1	**23a**	6-Cl	*o*-$MeOC_6H_4$	**3**	98	68	59	23
2	**24a**	8-MeO	*p*-$MeOC_6H_4$	**3**	30	74	29	9
3	**25a**	H	*o*-$MeOC_6H_4$	**3**	96	70	58	21
4	**26a**	8-MeO	Ph	**3**	89	77	54	22
5	**27a**	6-Me	Ph	**3**	79	73	52	15
6	**28a**	6-Cl	Ph	**3**	50	74	40	11
7	**23a**	6-Cl	*o*-$MeOC_6H_4$	**4**	76	74	51	14
8	**24a**	8-MeO	*p*-$MeOC_6H_4$	**4**	96	32	75	7
9	**26a**	8-MeO	Ph	**4**	88	41	68	6
10	**23a**	6-Cl	*o*-$MeOC_6H_4$	**5**	68	86	44	28
11	**24a**	8-MeO	*p*-$MeOC_6H_4$	**5**	91	75	55	21
12	**25a**	H	*o*-$MeOC_6H_4$	**5**	60	88	41	25
13	**26a**	8-MeO	Ph	**5**	94	74	56	23
14	**27a**	6-Me	Ph	**5**	66	91	42	41
15	**28a**	6-Cl	Ph	**5**	52	87	37	26
16	**23a**	6-Cl	*o*-$MeOC_6H_4$	**6**	96	70	58	21
17	**29**[d]	8-MeO	Ph	**5**	88	77	53	23

[a] All reactions were carried out in refluxing THF for 2–6 h. [b] The *ee* values of **23**–**29** were determined by CSP-HPLC. [c] Determined from the *ee* values of **23a**–**29** and **23b**–**28b**, as given in ref.[5] [d] Flavene derivative **29** is a diastereomer of **26a**.

antio-enriched products contain several functionalities that allow further transformation to more complex molecules. The kinetic resolution in the dehydration reaction is a conceptually new and efficient method for the preparation of highly enantio-enriched β-hydroxy esters, but this method is also prone to limitations. Examples of asymmetric dehydration demonstrated thus far are restricted to β-hydroxy esters bearing a conjugated β-substituent and no α-substituent, and the efficiency of the chiral ligand is strongly substrate-dependent. A challenge for future development is to tailor the chiral ligand for a broader scope of substrates. Further investigations to provide detailed mechanistic insights into the origin of the enantioselectivity and application to the syntheses of biologically interesting molecules are underway.

Experimental Section

General: All reactions were carried out under nitrogen. Chemicals were purchased from Aldrich and Fluka and, unless otherwise noted, were used without further purification. Analytical chiral stationary phase HPLC was performed with a pump system coupled to an absorbance detector (215 nm). Chiral columns (25 cm × 4.6 mm i.d.) with 2-propanol/hexane as mobile phase were used to determine the enantiomeric ratios. ^{1}H and ^{13}C NMR spectra were acquired with a Bruker AV 400 (400 MHz ^{1}H, 100.6 MHz ^{13}C) spectrometer. Mass spectrometric data were acquired at the Korea Basic Science Institute, Mass Spectrometry Laboratory.

General Procedure for the Preparation of Chiral Ligands 4–7: The corresponding diphenylmethylamine (1.2 equiv.), TBAI (1.0 equiv.), and DIEA (1.2 equiv.) were added to a solution of *N*-(α-bromo-α-phenylacetyl)-(*S*)-proline methyl ester in dry CH_2Cl_2 (0.1 M) at room temperature. The resulting reaction mixture was stirred at room temperature for 24 h. The solvent in the mixture was evaporated and the crude product was purified by column chromatography on silica gel. The substituted products were obtained in 45–71% yield with *dr* > 95:5. BH_3·THF (1.0 M, 5.0 equiv.) was added to a solution of the substituted product in THF (0.5 M), and the mixture was refluxed for 12 h. The reaction was quenched by adding MeOH (0.5 mL) under ice/water cooling, and the solvents were evaporated. Aqueous 5% HCl (2 mL) was added to the residue, and the mixture was refluxed for 1 h. The reaction mixture was basified with K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ (5 mL × 3). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic separation on silica gel afforded the chiral ligands **4**–**7** with *dr* > 99:1.

(*S*)-*N*-{(*R*)-2-[Bis(*p*-chlorophenyl)methyl]amino-2-phenylethyl}prolinol (4): A colorless oil was obtained in 41% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34–7.17 (m, 13 H), 4.57 (s, 1 H), 3.68 (dd, *J* = 11.0 and 3.7 Hz, 1 H), 3.57 (dd, *J* = 11.0 and 3.1 Hz, 1 H), 3.47 (dd, *J* = 11.0 and 3.8 Hz, 1 H), 2.95 (m, 1 H), 2.83 (br., 1 H), 2.65 (br., 2 H), 2.41 (dd, *J* = 12.6 and 3.1 Hz, 1 H), 2.15 (m, 1 H), 1.87–1.72 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 142.8, 142.3, 142.2, 133.4, 133.1, 129.5, 129.2, 129.1, 129.0, 128.8, 128.0, 127.7, 65.3, 63.8, 62.8, 62.3, 59.4, 54.6, 27.8, 24.2 ppm. HRMS: calcd. for $C_{26}H_{29}Cl_2N_2O$ [M + 1]$^+$ 455.1657; found 455.1659.

(*S*)-*N*-{(*R*)-2-[Bis(*p*-fluorophenyl)methyl]amino-2-phenylethyl}prolinol (5): A pale-yellow oil was obtained in 32% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34–7.20 (m, 9 H), 7.03 (m, 2 H), 6.92 (m, 2 H), 4.59 (s, 1 H), 3.68 (m, 1 H), 3.57 (m, 1 H), 3.47 (m, 1 H), 2.94 (t, *J* = 12.2 Hz, 1 H), 2.80 (br., 2 H), 2.64 (br., 1 H), 2.41 (d, *J* = 12.6 Hz, 1 H), 2.13 (m, 1 H), 1.85–1.69 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.4 (d, *J* = 244.2 Hz), 162.1 (d, *J* = 243.5 Hz), 142.5, 140.3, 139.6, 129.7 (d, *J* = 7.9 Hz), 129.2 (d, *J* = 7.9 Hz), 129.1, 127.9, 127.8, 115.8 (d, *J* = 21.2 Hz), 115.4 (d, *J* = 21.2 Hz), 65.3, 63.9, 62.8, 62.2, 59.4, 54.6, 27.8, 24.2 ppm. HRMS: calcd. for $C_{26}H_{28}F_2N_2O$ [M]$^+$ 423.2248; found 423.2260.

(*S*)-*N*-{(*R*)-2-[Bis(*m*-fluorophenyl)methyl]amino-2-phenylethyl}prolinol (6): A pale-yellow oil was obtained in 35% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34–6.97 (m, 13 H), 4.60 (s, 1 H), 3.66 (m, 1 H), 3.60 (dd, *J* = 11.0 and 3.1 Hz, 1 H), 3.49 (dd, *J* = 10.9 and 3.9 Hz, 1 H), 2.95–2.80 (m, 4 H), 2.62 (br., 1 H), 2.41 (dd, *J* = 12.5 and 3.1 Hz, 1 H), 2.12 (m, 1 H), 1.87–1.72 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.4 (d, *J* = 244.2 Hz), 163.2 (d, *J* = 244.3 Hz), 146.8, 146.4, 142.4, 130.4 (d, *J* = 7.9 Hz), 130.1 (d, *J* = 7.9 Hz), 129.1, 127.8, 127.7, 123.9 (d, *J* = 2.2 Hz), 123.2 (d, *J* = 2.7 Hz), 114.9 (d, *J* = 21.6 Hz), 114.7 (d, *J* = 22.4 Hz), 114.6 (d, *J* = 21.1 Hz), 114.2 (d, *J* = 21.0 Hz), 65.3, 63.9, 62.8, 62.7, 59.4, 54.6, 27.8, 24.1 ppm. HRMS: calcd. for $C_{26}H_{28}F_2N_2O$ [M]$^+$ 423.2248; found 423.2245.

(*S*)-*N*-{(*R*)-2-[Bis(*p*-methylphenyl)methyl]amino-2-phenylethyl}prolinol (7): A colorless oil was obtained in 39% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.03 (m, 13 H), 4.56 (s, 1 H), 3.68 (dd, *J* = 11.1 and 3.6 Hz, 1 H), 3.63 (dd, *J* = 11.0 and 3.2 Hz, 1 H), 3.47 (dd, *J* = 11.1 and 4.0 Hz, 1 H), 3.05 (br., 2 H), 2.97 (t, *J* = 12.1 Hz, 1 H), 2.83 (m, 1 H), 2.62 (m, 1 H), 2.40 (dd, *J* = 12.6 and 3.2 Hz, 1 H), 2.33 (s, 3 H), 2.26 (s, 3 H), 2.13 (m, 1 H), 1.72–1.69 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 142.9, 142.1, 141.2, 136.8, 136.6, 129.6, 129.3, 129.0, 128.1, 127.9, 127.7, 127.6, 65.5, 63.9, 62.9, 59.3, 54.6, 53.9, 27.8, 24.2, 21.5, 21.4 ppm. HRMS: calcd. for $C_{28}H_{34}N_2O$ [M]$^+$ 415.2749; found 415.2768.

General Procedure for Asymmetric Dehydration: Chlorotrimethylsilane (0.5 equiv.) was added to a suspension of zinc metal (8 equiv.) in anhydrous THF (5 mL). After the mixture had been heated at reflux for 40 min, a solution of the chiral ligand (5 mol-%), *tert*-butyl bromoacetate (8 equiv.), and racemic β-hydroxy ester in THF was slowly added. The mixture was stirred at reflux for 2–6 h and then quenched with a saturated NH_4Cl aqueous solution. The resulting mixture was extracted with CH_2Cl_2 (5 mL × 2), and the combined extracts were washed with brine. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography to give the enantio-enriched products.

***tert*-Butyl (3*R*,4*E*)-3-Hydroxy-5-(*p*-methoxyphenyl)-4-pentenoate (9):** The product was recovered in 37% yield based on 50% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.26 (d, *J* = 8.6 Hz, 1 H), 6.81 (d, *J* = 8.6 Hz, 1 H), 6.54 (d, *J* = 16.0 Hz, 1 H), 6.05 (dd, *J* = 16.0 and 6.4 Hz, 1 H), 4.63 (m, 1 H), 3.75 (s, 3 H), 3.60 (br., 1 H), 2.53 (d, *J* = 6.7 Hz, 2 H), 1.44 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.9, 159.6, 130.4, 129.7, 128.6, 128.1, 114.3, 81.6, 69.6, 55.6, 43.3, 28.5 ppm. $C_{16}H_{22}O_4$ (278.4): calcd. C 69.04, H 7.97; found C 69.12, H 7.79. CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 90% *ee*; 17.0 min (major enantiomer), 18.8 min (minor enantiomer).

***tert*-Butyl (*R*)-3-Hydroxy-4-pentenoate (10):** The product was recovered in 41% yield based on 51% conversion. The analytical data is in accordance with that in the literature.[4a] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.88 (m, 1 H), 5.31 (m, 1 H), 5.13 (m, 1 H), 4.49 (br., 1 H), 3.54 (br., 1 H), 2.44 (m, 2 H), 1.47 (s, 9 H) ppm. CSP-HPLC: β-hydroxy ester **10** was converted into the *O*-(3,5-dini-

trobenzoyl) derivative for better chromatographic analysis (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 82% *ee*; 22.2 min (major enantiomer), 33.5 min (minor enantiomer).

***tert*-Butyl (3*R*,4*E*,6*E*)-3-Hydroxy-4,6-octadienoate (11):** The product was recovered in 35% yield based on 57% conversion. The analytical data is in accordance with that in the literature.[4a] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.22 (dd, J = 16.1 and 10.4 Hz, 1 H), 6.02 (m, 1 H), 5.70 (m, 1 H), 5.55 (dd, J = 15.3 and 6.4 Hz, 1 H), 4.50 (br., 1 H), 3.20 (br., 1 H), 2.46 (m, 2 H), 1.74 (d, J = 5.9 Hz, 3 H), 1.45 (s, 9 H) ppm. CSP-HPLC (Chiralcel O*J*-H column; 5% 2-propanol in hexane; 0.5 mL/min): 81% *ee*; 15.5 min (major enantiomer), 14.5 min (minor enantiomer).

***tert*-Butyl (3*R*,4*E*)-3-Hydroxy-4-hexenoate (12):** The product was recovered in 39% yield based on 52% conversion. The analytical data is in accordance with that in the literature.[9] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.69 (m, 1 H), 5.48 (m, 1 H), 4.42 (m, 1 H), 3.61 (br., 1 H), 2.42 (m, 2 H), 1.63 (d, J = 6.5 Hz, 3 H), 1.45 (s, 9 H) ppm. CSP-HPLC: β-Hydroxy ester **12** was converted into the *O*-(3,5-dinitrobenzoyl) derivative for better chromatographic analysis (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 91% *ee*; 35.5 min (major enantiomer), 47.5 min (minor enantiomer).

***tert*-Butyl (3*R*,4*E*)-3-Hydroxy-4-methyl-4-hexenoate (13):** The product was recovered in 39% yield based on 53% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.10 (m, 1 H), 4.63 (m, 1 H), 3.28 (br., 1 H), 2.38 (dd, J = 15.5 and 8.1 Hz, 1 H), 2.26 (dd, J = 15.5 and 4.9 Hz, 1 H), 1.63 (s, 3 H), 1.61 (s, 3 H), 1.37 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.8, 135.3, 126.6, 81.0, 65.5, 43.4, 28.3, 25.9, 18.4 ppm. $C_{11}H_{20}O_3$ (200.3): calcd. C 65.97, H 10.07; found C 65.97, H 10.00. CSP-HPLC: β-hydroxy ester **13** was converted into the *O*-(3,5-dinitrobenzoyl) derivative for better chromatographic analysis (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 94% *ee*; 24.1 min (major enantiomer), 33.8 min (minor enantiomer).

***tert*-Butyl (*R*)-3-(1-Cyclohexen-1-yl)-3-hydroxypropanoate (14):** The product was recovered in 41% yield based on 52% conversion. The analytical data is in accordance with that in the literature.[9] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.71 (br., 1 H), 4.33 (m, 1 H), 3.18 (d, J = 4.0 Hz, 1 H), 2.45 (m, 2 H), 2.02 (m, 4 H), 1.61 (m, 4 H), 1.45 (s, 9 H) ppm. CSP-HPLC: β-hydroxy ester **14** was converted into the *O*-(3,5-dinitrobenzoyl) derivative for better chromatographic analysis (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 91% *ee*; 26.7 min (major enantiomer), 43.9 min (minor enantiomer).

***tert*-Butyl (*R*)-5-(2-Furanyl)-3-hydroxy-4-pentenoate (15):** The product was recovered in 38% yield based on 50% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (s, 1 H), 6.49–6.12 (m, 4 H), 4.64 (m, 1 H), 3.60 (br., 1 H), 2.51 (m, 2 H), 1.45 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.8, 152.6, 142.3, 129.3, 119.0, 111.7, 108.6, 81.7, 68.8, 43.0, 28.4 ppm. $C_{13}H_{18}O_4$ (238.3): calcd. C 65.53, H 7.61; found C 65.47, H 7.59. CSP-HPLC (Chiralcel OD column; 2% 2-propanol in hexane; 0.5 mL/min): 85% *ee*; 36.5 min (major enantiomer), 39.9 min (minor enantiomer).

***tert*-Butyl (*R*)-5-(Ethoxycarbonyl)-3-hydroxy-4-methyl-4-pentenoate (16):** The product was recovered in 39% yield based on 53% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.02 (s, 1 H), 4.45 (m, 1 H), 4.16 (q, J = 7.0 Hz, 2 H), 3.49 (d, J = 3.8 Hz, 1 H), 2.56 (dd, J = 16.0 and 3.2 Hz, 1 H), 2.42 (dd, J = 16.1 and 9.0 Hz, 1 H), 2.12 (s, 3 H), 1.46 (s, 9 H), 1.27 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.9, 167.1, 157.9, 116.0, 82.2, 72.8, 60.1, 41.1, 28.4, 15.5, 14.6 ppm. $C_{12}H_{20}O_5$ (244.3): calcd. C 59.00, H 8.25; found C 58.77, H 8.43. CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 97% *ee*; 0.9 min (major enantiomer), 10.1 min (minor enantiomer).

***tert*-Butyl (*R*)-3-(2-Furanyl)-3-hydroxypropanoate (17):** The product was recovered in 39% yield based on 52% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (s, 1 H), 6.31–6.24 (m, 2 H), 5.06 (m, 1 H), 3.78 (br., 1 H), 2.75 (m, 2 H), 1.44 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.4, 155.6, 142.3, 110.5, 106.4, 81.7, 64.6, 41.4, 28.3 ppm. $C_{11}H_{16}O_4$ (212.2): calcd. C 62.25, H 7.60; found C 62.20, H 7.52. CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 95% *ee*; 12.4 min (major enantiomer), 10.9 min (minor enantiomer).

***tert*-Butyl (*R*)-3-(3-Furanyl)-3-hydroxypropanoate (18):** The product was recovered in 39% yield based on 50% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37 (m, 2 H), 6.39 (s, 1 H), 5.04 (m, 1 H), 3.78 (d, J = 4.4 Hz, 1 H), 2.65 (m, 2 H), 1.45 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.0, 143.6, 139.4, 128.0, 108.9, 81.9, 63.9, 43.4, 28.4 ppm. $C_{11}H_{16}O_4$ (212.2): calcd. C 62.25, H 7.60; found C 62.24, H 7.77. CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 76% *ee*; 11.4 min (major enantiomer), 10.5 min (minor enantiomer).

***tert*-Butyl (*R*)-3-Hydroxy-3-(2-thiophenyl)propanoate (19):** The product was recovered in 30% yield based on 52% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.20 (d, J = 4.6 Hz, 1 H), 6.92 (m, 2 H), 5.27 (m, 1 H), 3.90 (d, J = 4.6 Hz, 1 H), 2.73 (m, 2 H), 1.43 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.5, 147.2, 127.0, 125.0, 123.9, 81.9, 67.0, 44.7, 28.4 ppm. $C_{11}H_{16}O_3S$ (228.3): calcd. C 57.87, H 7.06, S 14.04; found C 57.85, H 6.89, S 13.68. CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 96% *ee*; 12.8 min (major enantiomer), 11.6 min (minor enantiomer).

***tert*-Butyl (*R*)-3-(2-Benzofuranyl)-3-hydroxypropanoate (20):** The product was recovered in 37% yield based on 52% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.50–7.16 (m, 4 H), 6.61 (s, 1 H), 5.20 (m, 1 H), 3.90 (d, J = 5.4 Hz, 1 H), 2.85 (d, J = 6.3 Hz, 2 H), 1.43 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.6, 158.3, 155.2, 128.5, 124.6, 123.2, 121.5, 111.6, 103.2, 82.1, 65.3, 41.4, 28.5 ppm. $C_{15}H_{18}O_4$ (262.3): calcd. C 68.68, H 6.92; found C 68.68, H 6.99. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 95% *ee*; 24.9 min (major enantiomer), 28.7 min (minor enantiomer).

***tert*-Butyl (*R*)-3-Hydroxy-5-phenyl-4-pentynoate (21):** The product was recovered in 35% yield based on 55% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42–7.26 (m, 5 H), 4.93 (m, 1 H), 3.45 (d, J = 6.3 Hz, 1 H), 2.75 (d, J = 6.0 Hz, 2 H), 1.48 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.0, 132.1, 128.8, 128.6, 122.9, 89.0, 85.2, 82.1, 59.8, 43.6, 28.5 ppm. $C_{15}H_{18}O_3$ (246.3): calcd. C 73.15, H 7.37; found C 73.19, H 7.17. CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 97% *ee*; 13.1 min (major enantiomer), 18.9 min (minor enantiomer).

***tert*-Butyl (*R*)-3-Hydroxy-4-decynoate (22):** The product was recovered in 30% yield based on 58% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.68 (m, 1 H), 3.28 (d, J = 6.0 Hz, 1 H), 2.62 (d, J = 6.0 Hz, 2 H), 2.18 (m, 2 H), 1.51–1.30 (m, 6 H), 1.47 (s, 9 H), 0.89 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.3, 86.0, 81.8, 79.9, 59.5, 43.8, 31.3, 28.6, 28.4, 22.5, 19.0, 14.3 ppm. $C_{14}H_{24}O_3$ (240.3): calcd. C 69.96, H 10.07; found C 69.93, H 9.77. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 96% *ee*; 20.6 min (major enantiomer), 23.7 min (minor enantiomer).

***tert*-Butyl (*R*)-3-[(*S*)-6-Chloro-2-(*o*-methoxyphenyl)-2*H*-chromen-3-yl]-3-hydroxypropanoate (23a):** The product was recovered in 30% yield based on 59% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.27–7.19 (m, 2 H), 7.02–6.82 (m, 4 H), 6.60 (m, 2 H), 6.48 (s, 1 H), 4.43 (m, 1 H), 3.89 (s, 3 H), 3.21 (d, J = 4.8 Hz, 1 H), 2.43 (m, 2 H), 1.42 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.9, 157.2, 151.1, 137.7, 130.7, 129.3, 129.0, 126.5, 126.4, 126.0, 123.5, 121.1, 119.7, 118.0, 111.7, 82.1, 71.4, 70.9, 68.3, 56.3, 41.0, 28.5 ppm. HRMS: calcd. for $C_{23}H_{25}ClO_5$ $[M]^+$ 416.1391; found 416.1383. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 98% *ee*; 70.0 min (major enantiomer), 63.5 min (minor enantiomer).

***tert*-Butyl 3-[(*R*)-6-Chloro-2-(*o*-methoxyphenyl)-2*H*-chromen-3-yl]-propenoate (23b):** The product was recovered in 42% yield based on 59% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29–6.62 (m, 10 H), 5.61 (d, J = 16.0 Hz, 1 H), 3.96 (s, 3 H), 1.48 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.3, 157.1, 151.7, 140.9, 132.1, 131.0, 130.7, 129.5, 128.7, 127.2, 126.4, 125.7, 123.4, 121.3, 121.1, 118.4, 111.6, 81.0, 70.4, 56.2, 28.5 ppm. HRMS: calcd. for $C_{23}H_{23}ClO_4$ $[M]^+$ 398.1285; found 398.1286. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 68% *ee*; 39.3 min (major enantiomer), 42.8 min (minor enantiomer).

***tert*-Butyl (*R*)-3-Hydroxy-3-[(*S*)-2-(*p*-methoxyphenyl)-8-methoxy-2*H*-chromen-3-yl]propanoate (24a):** The product was recovered in 36% yield based on 55% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36 (d, J = 11.4 Hz, 2 H), 6.81–6.69 (m, 5 H), 6.61 (s, 1 H), 5.97 (s, 1 H), 4.47 (m, 1 H), 3.77 (s, 3 H), 3.73 (s, 3 H), 3.23 (br., 1 H), 2.47 (m, 2 H), 1.42 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.1, 160.3, 148.6, 141.4, 136.6, 131.3, 129.7, 122.9, 121.1, 120.0, 119.6, 114.3, 113.3, 82.1, 77.1, 68.5, 56.7, 55.6, 41.2, 28.5 ppm. HRMS: calcd. for $C_{24}H_{28}O_6$[M]$^+$ 412.1886; found 412.1876. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 91% *ee*; 74.2 min (major enantiomer), 90.9 min (minor enantiomer).

***tert*-Butyl 3-[(*R*)-2-(*p*-Methoxyphenyl)-8-methoxy-2*H*-chromen-3-yl]-propenoate (24b):** The product was recovered in 45% yield based on 55% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (m, 3 H), 6.94 (s, 1 H), 6.81 (m, 5 H), 6.11 (s, 1 H), 5.61 (d, J = 15.9 Hz, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 1.46 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.5, 160.4, 148.8, 142.1, 141.7, 131.0, 130.9, 130.2, 129.5, 123.1, 121.6, 120.6, 120.3, 114.4, 114.3, 81.0, 76.3, 56.7, 55.6, 28.5 ppm. HRMS: calcd. for $C_{24}H_{26}O_5$ $[M]^+$ 394.1780; found 394.1781. CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 75% *ee*; 17.7 min (major enantiomer), 20.1 min (minor enantiomer).

***tert*-Butyl (*R*)-3-Hydroxy-3-[(*S*)-2-(*o*-methoxyphenyl)-2*H*-chromen-3-yl]propanoate (25a):** The product was recovered in 35% yield based on 58% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.25 (m, 2 H), 7.04 (m, 2 H), 6.91 (d, J = 8.4 Hz, 1 H), 6.82 (m, 2 H), 6.68 (m, 2 H), 6.49 (s, 1 H), 4.42 (m, 1 H), 3.90 (s, 3 H), 3.10 (d, J = 4.8 Hz, 1 H), 2.46 (m, 2 H), 1.41 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.0, 157.2, 152.6, 136.3, 130.5, 129.8, 129.1, 127.2, 127.1, 122.1, 121.4, 121.1, 120.7, 116.7, 111.6, 81.9, 70.6, 68.5, 56.3, 41.1, 28.5 ppm. $C_{23}H_{26}O_5$ (382.5): calcd. C 72.23, H 6.85; found C 72.31, H 6.67. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 96% *ee*; 40.9 min (major enantiomer), 51.8 min (minor enantiomer).

***tert*-Butyl 3-[(*R*)-2-(*o*-Methoxyphenyl)-2*H*-chromen-3-yl]propenoate (25b):** The product was recovered in 41% yield based on 58% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.27–6.65 (m, 11 H), 5.58 (d, J = 16.0 Hz, 1 H), 3.97 (s, 3 H), 1.45 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.6, 157.1, 153.2, 141.5, 131.2, 131.0, 130.9, 130.7, 128.8, 127.9, 126.3, 122.1, 121.7, 121.1, 120.3, 117.1, 111.5, 80.8, 70.1, 56.2, 28.5 ppm. HRMS: calcd. for $C_{23}H_{24}O_4$ $[M]^+$ 364.1675; found 364.1666. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 70% *ee*; 29.6 min (major enantiomer), 14.2 min (minor enantiomer).

***tert*-Butyl (*R*)-3-Hydroxy-3-[(*S*)-8-methoxy-2-phenyl-2*H*-chromen-3-yl]propanoate (26a):** The product was recovered in 35% yield based on 54% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44–7.26 (m, 5 H), 6.83–6.69 (m, 3 H), 6.60 (s, 1 H), 6.05 (s, 1 H), 4.47 (m, 1 H), 3.72 (s, 3 H), 3.21 (d, J = 4.8 Hz, 1 H), 2.52 (m, 2 H), 1.42 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.1, 148.5, 141.5, 139.2, 136.4, 129.1, 129.0, 128.2, 122.7, 121.2, 120.1, 119.6, 113.4, 82.1, 77.1, 68.3, 56.7, 41.0, 28.5 ppm. $C_{23}H_{26}O_5$ (382.5): C 72.23, H 6.85; found C 72.18, H 6.89. CSP-HPLC (Chiralcel-OD column; 10% 2-propanol in hexane; 0.5 mL/min): 89% *ee*; 52.0 min (major enantiomer), 37.4 min (minor enantiomer).

***tert*-Butyl 3-[(*R*)-8-Methoxy-2-phenyl-2*H*-chromen-3-yl]propenoate (26b):** The product was recovered in 41% yield based on 54% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43–7.26 (m, 6 H), 6.95 (s, 1 H), 6.80 (m, 3 H), 6.16 (s, 1 H), 5.64 (d, J = 16.0 Hz, 1 H), 3.76 (s, 3 H), 1.47 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.5, 148.8, 142.1, 141.8, 138.1, 131.1, 130.8, 129.2, 129.0, 128.0, 123.1, 121.7, 120.7, 120.4, 114.4, 81.0, 76.5, 56.7, 28.5 ppm. HRMS: calcd. for $C_{23}H_{24}O_4$ $[M]^+$ 364.1675; found 364.1681. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 77% *ee*; 24.4 min (major enantiomer), 21.7 min (minor enantiomer).

***tert*-Butyl (*R*)-3-Hydroxy-3-[(*S*)-6-methyl-2-phenyl-2*H*-chromen-3-yl]propanoate (27a):** The product was recovered in 33% yield based on 52% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.39–7.26 (m, 5 H), 6.85 (m, 2 H), 6.58 (d, J = 8.0 Hz, 1 H), 6.55 (s, 1 H), 5.96 (s, 1 H), 4.43 (m, 1 H), 3.17 (d, J = 4.9 Hz, 1 H), 2.50 (m, 2 H), 2.24 (s, 3 H), 1.43 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.1, 150.2, 139.4, 136.3, 130.7, 130.5, 129.1, 129.0, 128.2, 127.6, 121.6, 120.3, 116.3, 82.1, 77.6, 68.2, 40.9, 28.5, 21.0 ppm. $C_{23}H_{26}O_4$ (366.5): C 75.38, H 7.15; found C 75.33, H 6.98. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 79% *ee*; 27.9 min (major enantiomer), 32.4 min (minor enantiomer).

***tert*-Butyl 3-[(*R*)-6-Methyl-2-phenyl-2*H*-chromen-3-yl]propenoate (27b):** The product was recovered in 41% yield based on 52% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.39–7.26 (m, 6 H), 6.91 (m, 3 H), 6.64 (m, 1 H), 6.03 (s, 1 H), 5.59 (d, J = 15.9 Hz, 1 H), 2.23 (s, 3 H), 1.46 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.6, 150.8, 141.9, 138.3, 132.0, 131.4, 131.2, 130.7, 129.1, 129.0, 128.4, 128.1, 122.1, 120.3, 116.9, 81.0, 76.5, 28.5, 20.9 ppm. HRMS: calcd. for $C_{23}H_{24}O_3$ $[M]^+$ 348.1725; found 348.1728. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 73% *ee*; 14.2 min (major enantiomer), 19.5 min (minor enantiomer).

***tert*-Butyl (*R*)-3-[(*S*)-6-Chloro-2-phenyl-2*H*-chromen-3-yl]-3-hydroxypropanoate (28a):** The product was recovered in 44% yield based on 37% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.30 (m, 5 H), 7.00 (m, 2 H), 6.61 (d, J = 8.2 Hz, 1 H), 6.54 (s, 1 H), 5.96 (s, 1 H), 4.42 (m, 1 H), 3.29 (d, J = 4.8 Hz, 1 H), 2.49 (m, 2 H), 1.43 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.0, 150.9, 138.8, 137.8, 129.5, 129.4, 129.2, 128.2, 126.6, 126.2, 123.3, 119.3, 117.9, 82.3, 77.9, 68.0, 40.7, 28.5 ppm. $C_{22}H_{23}ClO_4$ (386.9): C 68.30, H 5.99; found C 68.50, H 5.75. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 52% *ee*; 34.2 min (major enantiomer), 38.1 min (minor enantiomer).

***tert*-Butyl 3-[(*R*)-6-Chloro-2-phenyl-2*H*-chromen-3-yl]propenoate (28b):** The product was recovered in 29% yield based on 37% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (m, 6 H), 7.06 (m, 2 H), 6.90 (s, 1 H), 6.67 (d, J = 8.6 Hz, 1 H), 6.06 (s, 1 H), 5.63 (d, J = 16.0 Hz, 1 H), 1.46 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.2, 151.4, 141.1, 137.6, 131.8, 130.8, 129.7, 129.5, 129.2, 128.1, 127.3, 126.7, 123.6, 121.6, 118.5, 81.2, 76.8, 28.5 ppm. HRMS: calcd. for $C_{22}H_{21}ClO_3$ $[M]^+$ 368.1179; found 368.1182. CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 87% *ee*; 22.0 min (major enantiomer), 44.0 min (minor enantiomer).

***tert*-Butyl (*R*)-3-Hydroxy-3-[(*R*)-8-methoxy-2-phenyl-2*H*-chromen-3-yl]propanoate (29):** The product was recovered in 35% yield based on 53% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49–7.26 (m, 5 H), 6.82–6.71 (m, 3 H), 5.85 (s, 1 H), 4.43 (m, 1 H), 3.72 (s, 3 H), 3.34 (d, J = 3.9 Hz, 1 H), 2.55 (dd, J = 16.3 and 3.0 Hz, 1 H), 2.41 (dd, J = 16.3 and 8.8 Hz, 1 H), 1.43 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.1, 148.5, 141.6, 138.9, 136.7, 129.3, 129.1, 128.4, 122.9, 121.3, 120.3, 119.6, 113.3, 82.3, 77.1, 68.4, 56.7, 41.5, 28.5 ppm. $C_{23}H_{26}O_5$ (382.5): C 72.23, H 6.85; found C 72.18, H 6.89. CSP-HPLC (Chiralpak-AD-H column; 10% 2-propanol in hexane; 0.5 mL/min): 88% *ee*; 52.2 min (major enantiomer), 43.2 min (minor enantiomer).

Acknowledgments

This work was supported by a grant from the Korea Research Foundation (KRF-2006-005-J03402).

[1] a) D. E. J. E. Robinson, S. D. Bull, *Tetrahedron: Asymmetry* **2003**, *14*, 1407–1446; b) J. M. Keith, J. F. Larrow, E. N. Jacobson, *Adv. Synth. Catal.* **2001**, *343*, 5–26.

[2] For recent reviews on asymmetric oxidation, see: a) M. Wills, *Angew. Chem. Int. Ed.* **2008**, *47*, 4264–4267; b) S. Arita, T. Koike, Y. Kayaki, T. Ikariya, *Angew. Chem. Int. Ed.* **2008**, *47*, 2447–2449; c) T. Chen, J.-J. Jiang, Q. Xu, M. Shi, *Org. Lett.* **2007**, *9*, 865–868; d) J. A. Mueller, A. Cowell, B. D. Chandler, M. S. Sigman, *J. Am. Chem. Soc.* **2005**, *127*, 14817–14824; e) R. M. Trend, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 4482–4483; f) A. T. Radosevich, C. Musich, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 1090–1091.

[3] For recent reviews on asymmetric acylation, see: a) C. Mazet, S. Roseblade, V. Köhler, A. Pfaltz, *Org. Lett.* **2006**, *8*, 1879–1882; b) V. B. Birman, H. Jiang, *Org. Lett.* **2005**, *7*, 3445–3447; c) S. Yamada, T. Misono, Y. Iwai, *Tetrahedron Lett.* **2005**, *46*, 2239–2242; d) Y. Suzuki, K. Yamauchi, K. Muramatsu, M. Sato, *Chem. Commun.* **2004**, 2770–2771; e) E. Vedejs, O. Daugulis, *J. Am. Chem. Soc.* **2003**, *125*, 4166–4173; f) B. Tao, J. C. Ruble, D. A. Hoic, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 5091–5092.

[4] a) E. T. Choi, M. H. Lee, Y. Kim, Y. S. Park, *Tetrahedron* **2008**, *64*, 1515–1522; b) Y. Kim, E. T. Choi, M. H. Lee, Y. S. Park, *Tetrahedron Lett.* **2007**, *48*, 2833–2835; c) E.-k. Shin, H. J. Kim, Y. Kim, Y. Kim, Y. S. Park, *Tetrahedron Lett.* **2006**, *47*, 1933–1935.

[5] The selectivity factor (s) was estimated by using the equation $s = k_S/k_R = \ln[(1 - C)(1 - ee_s)]/\ln[(1 - C)(1 + ee_s)]$, where ee_s is the enantiomeric excess of unconverted β-hydroxy esters and C is the conversion determined by ^{1}H NMR analysis of the reaction mixture using hexamethylbenzene as an internal standard for **1** and **9**–**22**. For the reactions of **23a**–**28a** and **29** the conversion (C) was calculated by using the equation $C = 100 \times ee_s/(ee_s + ee_p)$, where ee_p is the enantiomeric excess of the eliminated product. H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249–330.

[6] a) J.-y. Chang, E.-k. Shin, H. J. Kim, Y. Kim, Y. S. Park, *Tetrahedron* **2005**, *61*, 2743–2750; b) J. Nam, J.-y. Chang, E.-k. Shin, H. J. Kim, Y. Kim, S. Jang, Y. S. Park, *Tetrahedron* **2004**, *60*, 6311–6318.

[7] a) Y. Satoh, J. L. Stanton, A. J. Hutchison, A. H. Libby, T. J. Kowalski, W. H. Lee, D. H. White, E. F. Kimble, *J. Med. Chem.* **1993**, *36*, 3580–3594; b) J.-F. Cheng, A. Ishikawa, Y. Ono, T. Arrhenius, A. Nadzan, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3647–3650; c) K. Hajela, J. Pandey, A. Dwivedy, J. D. Dhar, S. Sarkhel, P. R. Maulik, D. Velumurugan, *Bioorg. Med. Chem.* **1999**, *7*, 2083–2090; d) N. Ishizuka, K.-i. Matsumura, J. Kikuchi, H. Nakai, *Bioorg. Med. Chem.* **2002**, *10*, 3965–3972; e) O. F. Funk, V. Kettmann, J. Drimal, T. Langer, *J. Med. Chem.* **2004**, *47*, 2750–2760; f) N. Ishizuka, K.-i. Matsumura, K. Sakai, M. Fujimoto, S.-i. Mihara, T. Yamamori, *J. Med. Chem.* **2002**, *45*, 2041–2055.

[8] Racemic β-flavenyl-β-hydroxy esters **23a**–**28a** have been prepared by the substrate-controlled diastereoselective addition of a Reformatsky reagent to flavene-3-carbaldehyde with $dr \approx$ 90:10. M. H. Lee, E. T. Choi, Y. M. Lee, D. Kim, Y. S. Park, *Bull. Korean Chem. Soc.* **2008**, *29*, 1299–1300. The major diastereomers **23a**–**28a** were separated from minor diastereomers by column chromatography on silica gel and subjected to asymmetric dehydration.

[9] J.-F. Lavallée, C. Spino, R. Ruel, K. T. Hogan, P. Deslongchamps, *Can. J. Chem.* **1992**, *70*, 1406–1426.

Received: August 21, 2008
Published Online: October 13, 2008

