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Asymmetric dehydration of β-hydroxy esters and application to the syntheses of flavane derivatives

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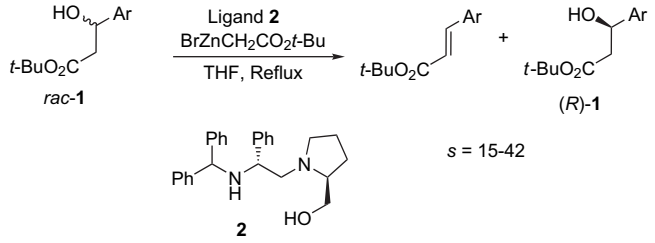
Abstract

Catalytic asymmetric dehydration of β-aryl or alkyl substituted β-hydroxy esters via kinetic resolution has been investigated. A brief survey of 10 different chiral ligands is conducted to examine the effects of chiral ligand structure on selectivity of the dehydration. The kinetic resolution of a variety of *rac*-β-hydroxy *tert*-butyl esters in the presence of prolinol chiral ligand **2** and $BrZnCH_2CO_2$-*t*-Bu can provide highly enantioenriched β-hydroxy esters **14**–**21** with selectivity factors ranging from 11 to 66. Also, application of this asymmetric synthetic methodology to the preparation of enantioenriched flavane derivatives **25**–**29** is demonstrated.

Keywords: Kinetic resolution; Asymmetric syntheses; Chiral catalyst; Flavonoids; Dehydration

1. Introduction

Kinetic resolution of a racemic mixture with a chiral catalyst is presently an area of great importance in organic chemistry.[1] In particular, significant advances have been made recently in nonenzymatic kinetic resolution of alcohols by enantioselective oxidation and acylation.[2,3] Earlier we have been able to introduce first example for the enantioselective catalytic asymmetric dehydration of β-aryl-β-hydroxy esters via kinetic resolution as shown in Scheme 1.[4] The preliminary results of the novel alcohol resolution prompted us to investigate the asymmetric dehydration in more detail. Herein we describe our recent progress to optimize reaction condition with 10 different prolinol chiral ligands and to extend the scope of the methodology to various β-alkyl substituents. Application of this methodology to highly enantioselective preparation of flavane derivatives **25**–**29** is also presented.



Scheme 1.

2. Results and discussion

We have found that chiral ligand **2** is efficient for the asymmetric dehydration of β-aryl-β-hydroxy esters in the presence of excess amount of $BrZnCH_2CO_2$-*t*-Bu as a base. Treatment of racemic β-hydroxy ester **1** (Ar=*p*-MeO-Ph) in the presence of **2** (20 mol %) and $BrZnCH_2CO_2$-*t*-Bu (8 equiv) in anhydrous THF at reflux for 2 h afforded a mixture of *trans*-cinnamate and β-hydroxy ester (*R*)-**1**. At 53% conversion, *trans*-cinnamate was isolated in 43% yield and the unconverted (*R*)-**1** was obtained in 39% yield with 89% ee. In the absence of either ligand **2** or $BrZnCH_2CO_2$-*t*-Bu no elimination occurred at all. It was found that the kinetic resolution worked best when carried out in refluxing THF and the

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elimination of β-hydroxy ester did not proceed at lower temperatures.

Therefore, an investigation was carried out to establish if there was a relationship between the extent of cinnamate formation and enantiopurity of unreacted β-hydroxy ester. We have closely monitored the progress of the reaction in terms of the conversion and enantioselectivity of **1** (Ar=*p*-MeO-Ph) by NMR analysis of crude reaction mixture with 5 mol % of chiral ligand **2**, 8 equiv of $BrZnCH_2CO_2$-*t*-Bu, and hexamethylbenzene as an internal integration standard. The results shown in Figure 1 clearly indicate a direct relationship between dehydration of β-hydroxy ester to cinnamate and enantiomeric excess of the remaining β-hydroxy ester. Figure 1 also shows that the rate of dehydration decreased drastically as they approach 50% conversion. Because of the large difference in reactivities of the two enantiomers of β-hydroxy ester **1** ($s=k_S/k_R=24$, an average of five runs), dehydration will slow as most of (*S*)-**1** is converted to the cinnamate.[5] Consequently, there is a wide range of time during which the reaction can be stopped without compromising the yield of recovered β-hydroxy ester **1**.

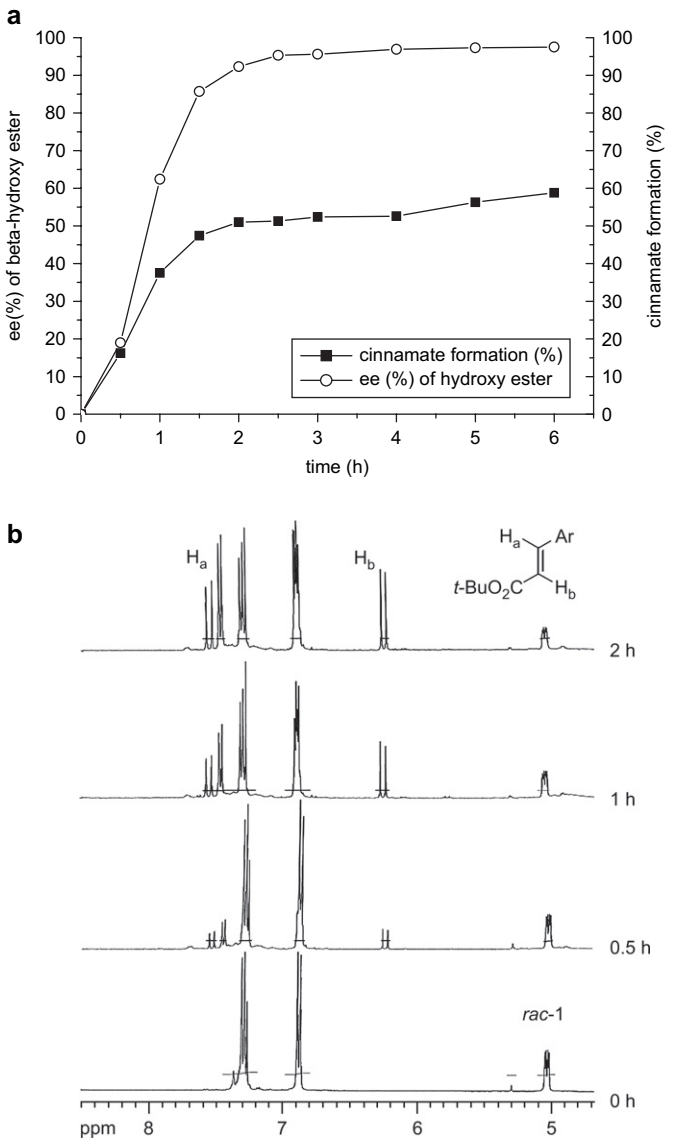


Figure 1. (a) Relationship between cinnamate formation and the enantiopurity of unreacted β-hydroxy ester **1** (Ar=*p*-MeO-Ph). (b) Representative ^1H NMR spectra (400 MHz, $CDCl_3$, 293 K) of the crude reaction mixture after acidic extractive work-up during the dehydration of **1** with 5 mol % of ligand **2** and 8 equiv of $BrZnCH_2CO_2$-*t*-Bu.

During the course of our studies toward the development of the efficient chiral ligand **2** for asymmetric dehydration, we have prepared nine different chiral ligands **5**–**13** as shown in Figure 2. D-Phg-L-Pro dipeptide-derived chiral ligands **5**–**10** were prepared using the methodology, which we have recently developed for asymmetric syntheses of dipeptide

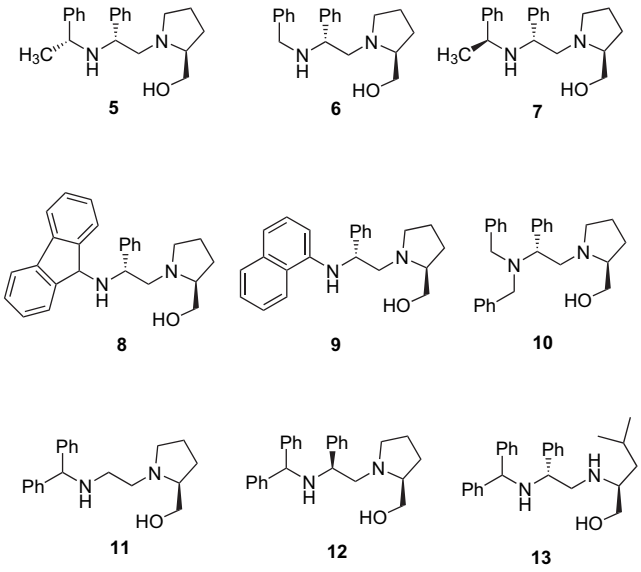
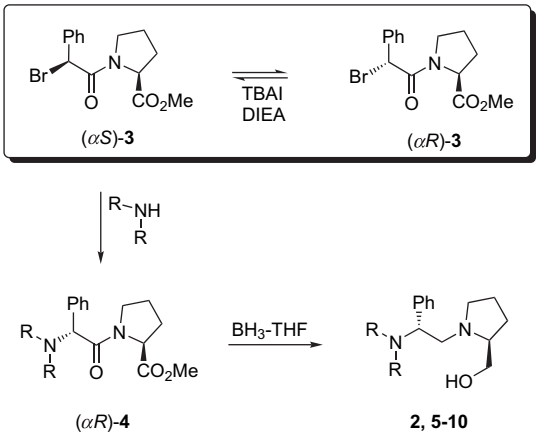


Figure 2.

analogs as shown in Scheme 2.[6] The treatment of two diastereomeric mixtures (ca. 50:50) of *N*-(α-bromo-α-phenylacetyl)-(L)-proline methyl ester **3** with an 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 analogs **4** in 93–40% yields with 99:1–81:19 diastereomeric ratios (drs). The subsequent



Scheme 2.

reduction of **4** using an excess of BH_3–THF (5 equiv) in THF furnished the expected chiral ligands as a mixture of two isomers. In all cases, the optically pure *N*-alkylated (*N*-(*R*)-2-amino-2-phenylethyl)-(*S*)-prolinols **5**–**10** were easily isolated in 70–49% yields by flash column chromatographic separation.

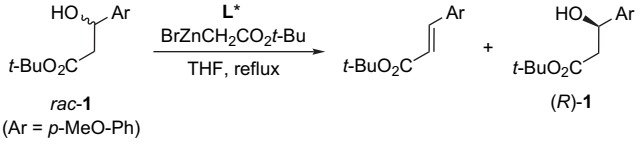
Also, preparation of chiral ligands **11**, **12**, and **13** was successfully achieved by the reduction of corresponding *N*-diphenylmethylene dipeptide derivatives. Treatments of *N*-diphenylmethylene-Gly-L-Pro methyl ester, *N*-diphenylmethylene-L-Phg-L-Pro methyl ester, and *N*-diphenylmethylene-D-Phg-L-Leu methyl ester with BH_3–THF in THF furnished ligands **11**, **12**, and **13** in 78, 82, and 66% yields, respectively.

We then explored asymmetric dehydration reactions as a preliminary evaluation of the catalytic properties of nine chiral ligands **5**–**13**. The results of the kinetic resolution of racemic β-hydroxy ester **1** with chiral ligands **5**–**13** are summarized in Table 1, entries 1–13. With 20 mol % of chiral ligand and 8 equiv of $BrZnCH_2CO_2$-*t*-Bu, the reaction with *N*-(*R*)-1-phenethylated ligand **5** gave a comparable level of selectivity (s=26) relative to *N*-diphenylmethylated ligand **2**, while *N*-benzylated ligand **6** and *N*-(*S*)-1-phenethylated ligand **7** produced modest and poor level of selectivities, respectively (entries 2–4). These results indicate that subtle *N*-alkyl group modifications of D-Phg-L-Pro-derived structure can lead to substantial variations in reactivity and enantioselection. Much lower level of selectivities were observed with chiral ligands **8**–**10**, which have different *N*-alkyl groups such as *N*-fluorenyl, *N*-naphthyl, and *N*,*N*-dibenzyl groups (entries 5–7). To gain an insight into the effect of the phenyl substituent of D-Phg-L-Pro-derived core structure, we have also tested two different prolinol ligands **11** and **12**. Considerable loss of selectivity was observed in both reactions with L-Phg-L-Pro-derived ligand **12** and Gly-L-Pro-derived ligand **11** having no phenyl substituent (entries 8 and 9). Notably, leucine-derived chiral ligand **13** gave no selectivity (entry 10). The brief survey of various chiral ligands shown in Figure 2 indicates that D-Phg-L-Pro dipeptide-derived *N*-(*R*)-aminophenylethyl-(*S*)-prolinol skeleton is catalytic core structure and the other structural component, *N*-benzyl substituent of ligand, has been shown to be vital for both reactivity and selectivity and thus appear to function cooperatively.

The high selectivities obtained with chiral ligands **2**, **5**, and **6** prompted us to test the possibility of lowering the ligand loading of them. As shown in entries 11–13, with 5 mol % of ligand loading, the selectivity dropped sharply with chiral ligands **5** and **6**, while the selectivity did not change significantly with chiral ligand **2** showing the superior reactivity of the catalyst of ligand **2**. However, further decreasing ligand loading to 3 mol % of **2** was not satisfactory with a selectivity of 11 (entry 14). When the reaction was carried out with 1 mol % of ligand **2**, only 4% conversion was observed after 4 h. Taking reactivity and selectivity into account, 5 mol % of ligand **2** was deemed to be the best for dehydration and it was used for the subsequent investigations. Next, the influence of the organozinc reagent on enantioselectivtity was investigated. The use of 4 or 2 equiv of $BrZnCH_2CO_2$-*t*-Bu in the presence of 5 mol % of chiral ligand **2** gave lower conversions and lower selectivities after 6 h (entries 16 and 17). The preliminary results indicate that the selectivity and rate of dehydration is substantially influenced by the amount of the base, $BrZnCH_2CO_2$-*t*-Bu.

Next, we initiated investigations into the reaction's scope with various β-hydroxy *tert*-butyl esters and chiral ligand **2**. For convenience, most reactions were performed with 5 mol % of **2** and 8 equiv of $BrZnCH_2CO_2$-*t*-Bu. As shown in Table 2, the kinetic resolution with chiral ligand **2** provided excellent levels of asymmetric induction with three β-aryl-β-hydroxy esters **14**–**16**. Most reactions reached 55–57% conversion after 1–1.5 h with the selectivities ranging from 19 to 28. Thus, the unconverted β-hydroxy esters (*R*)-**14**–**16** with 93–98% ee were obtained in 40–32% isolated yields. The high selectivity and high activity of this catalyst enabled us to successfully perform a resolution of β-hydroxy esters **14**–**16** on a multigram scale, which have been used in asymmetric syntheses of flavane derivatives **25**–**29** as shown in Scheme 3. Additionally, the resolutions of β-vinyl substituted ester **17** and β-pentadienyl substituted ester **18** gave a high level of selectivities (entries 4 and 5). Higher selectivities were observed in the kinetic resolution of β-(*E*)-styryl substituted β-hydroxy esters **19**–**21** (entries 6–8). Our most impressive results were obtained with β-*o*-methoxystyryl β-hydroxy ester **20**, affording a k_{rel} of 66 (entry 7). When R was an aliphatic group (R=CH_3 or $PhCH_2CH_2$), no

Table 1



rac-**1** (Ar = *p*-MeO-Ph) (*R*)-**1**

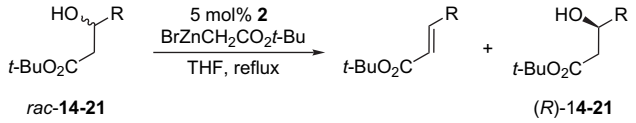
Entry	Ligand (mol %)	BrZnR (equiv)	Time (h)	Conv.[a] (%)	% ee[b]	s (k_S/k_R)[c]
1	**2** (20)	8	2	53	89	22
2	**5** (20)	8	3	51	87	26
3	**6** (20)	8	0.5	47	68	13
4	**7** (20)	8	2	44	37	5
5	**8** (20)	8	4	53	59	5
6	**9** (20)	8	6	46	18	2
7	**10** (20)	8	20	39	4	1.2
8	**11** (20)	8	0.5	50	65	6
9	**12** (20)	8	20	39	28	4
10	**13** (20)	8	3	56	12	1.3
11	**2** (5)	8	1	56	97	24
12	**6** (5)	8	2	26	18	4
13	**7** (5)	8	2	51	58	6
14	**2** (3)	8	2	51	72	11
15	**2** (1)	8	4	4	—	—
16	**2** (5)	4	6	38	51	17
17	**2** (5)	2	6	21	20	11

[a] Determined based on consumption of starting β-hydroxy ester substrate by ^{1}H NMR analysis of characteristic signals directly on the crude mixture with hexamethylbenzene as an internal integration standard.

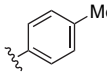
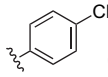
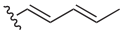
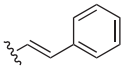
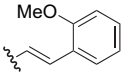
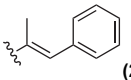
[b] The % ee of **1** is determined by CSP-HPLC.

[c] Selectivity (s) values represent an average of at least three experiments, while conversion and ee value are for specific cases.

Table 2



rac-**14-21** (*R*)-**14-21**

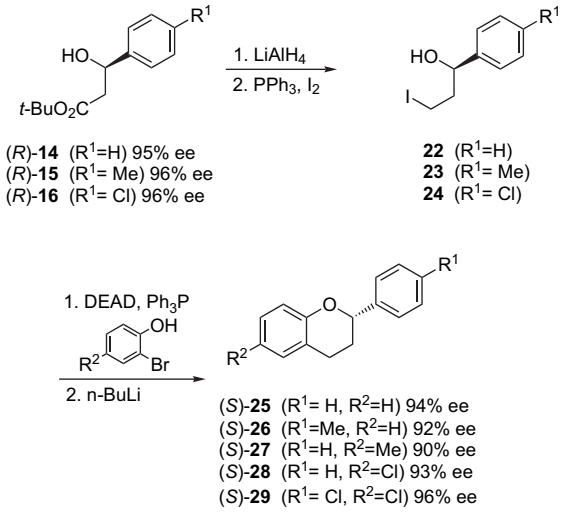
Entry	R	Time (h)	Conv.[a] (%)	% ee[b]	s (k_S/k_R)[c]
1	 **(14)**	1.5	57	93	19
2	 **(15)**	1	55	93	28
3	 **(16)**	1	57	98	22
4	 **(17)**	5	62	97	20
5	 **(18)**	4	57	81	11
6	 **(19)**	1.5	55	97	38
7	 **(20)**	1	52	95	66
8	 **(21)**	1.5	53	94	42

[a] Determined based on consumption of starting β-hydroxy ester substrate by ^{1}H NMR analysis of characteristic signals directly on the crude mixture with hexamethylbenzene as an internal standard.

[b] The % ee of **14**–**21** is determined by CSP-HPLC.

[c] Selectivity (s) values represent an average of at least three experiments, while conversion and ee value are for specific cases.

dehydration occurred under the same reaction condition and racemic β-hydroxy ester was quantitatively recovered. These results imply that the primary driving force for dehydration is the formation of a double bond, which is conjugated with both the carbonyl group and R group.



Scheme 3.

The dehydration of β-hydroxy isopropyl or ethyl ester also proceeded with ligand **2** and $BrZnCH_2CO_2$-*t*-Bu, but the efficiency of the kinetic resolution was lower than the reaction of β-hydroxy *tert*-butyl ester. Kinetic resolutions of β-(*p*-methoxyphenyl)-β-hydroxy isopropyl and ethyl esters with 5 mol % of **2** and 8 equiv of $BrZnCH_2CO_2$-*t*-Bu gave lower selectivities of 9 and 10, respectively. When using β-hydroxy esters, which have an α-substituent or two β-substituents as substrates, no dehydration occurred under the same reaction condition. Evidently, the efficiency of kinetic resolution is strongly substrate-dependent. Subtle steric and electronic factors result in efficient kinetic resolution of β-hydroxy *tert*-butyl ester.

To extend the utility of this methodology, we decided to take advantage of the functional groups present in β-aryl-β-hydroxy ester for subsequent synthetic elaboration. In particular, the opportunity to prepare enantioenriched flavane derivatives **25**–**29** was provided from the enantioenriched β-aryl-β-hydroxy esters **14**–**16** as shown in Scheme 3. Reduction of **14**–**16** (95–96% ee) with $LiAlH_4$ provided the corresponding 1,3-diols and subsequent selective iodination of primary alcohols gave 3-iodo-propanols **22**–**24** in 68–50% yields over the two steps. When **22**–**24** were treated with a phenol under standard Mitsunobu inversion condition, the reaction provided the (*S*)-aryl ethers in 87–77% yields. After the addition of 2 equiv of *n*-butyl lithium to the aryl ether in THF at 0 °C, the reaction was allowed to warm to room temperature.[7] Under these conditions, the bromine–lithium exchange of the aryl bromide and subsequent cyclization gave (*S*)-chromans **25**–**29** in 67–55% yields with 90–96% ee. The sign of rotation and optical purities of **25**–**29** confirmed that the Mitsunobu reaction occurred with inversion and the four-step transformation from enantioenriched **14**–**16** proceeded without significant racemization.

3. Conclusion

We have developed conceptually novel enantioselective dehydration of β-hydroxy esters via kinetic resolution. This study introduces D-Phg-L-Pro dipeptide-derived *N*-(*R*)-aminophenylethyl-(*S*)-prolinol ligand for asymmetric dehydration and may ultimately lead to new dehydration catalysts with higher selectivity and broad synthetic utility. In addition, we have established the applicability of this method as exemplified by the preparation of enantioenriched flavane derivatives. While the effective chiral catalyst for dehydration was found in this work, the substrate scope is still quite limited and the precise structure of the zinc enolate–chiral ligand complex is unclear. Further studies to resolve them as well as to show more synthetic utility are now in progress.

4. Experimental

*4.1. General procedure for the preparation of chiral ligands **2** and **5**–**10***

To a solution of *N*-(α-bromo-α-phenylacetyl) (*S*)-proline methyl ester in dry CH_2Cl_2 (0.1 M) at room temperature

were added an amine (1.2 equiv), TBAI (1.0 equiv), and DIEA (1.2 equiv). The resulting reaction mixture was stirred at room temperature for 24 h. The solvent in mixture was evaporated and the crude product was purified by column chromatography on silica gel. The substituted products were obtained in 85% yield with 99:1 dr (with benzhydrylamine), 43% yield with 90:10 dr (with (*R*)-α-methylbenzylamine), in 89% yield with 81:19 dr (with benzylamine), in 40% yield with 81:19 dr (with (*S*)-α-methylbenzylamine), in 79% yield with 91:9 dr (with 9-fluorenamine), in 80% yield with 85:15 dr (with 1-naphthylamine), and in 93% yield with 99:1 dr (with dibenzylamine), respectively.[6] To a solution of product in THF (0.5 M) was added BH_3–THF (1.0 M, 5.0 equiv), 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 ligands with >99:1 dr.

*4.1.1. N-((R)-N-Diphenylmethyl-2-amino-2-phenylethyl)-(S)-prolinol (**2**)*

A colorless oil was obtained in 70% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.31–7.11 (m, 15H), 4.62 (s, 1H), 3.60 (m, 2H), 3.45 (dd, *J*=11.0 and 4.0 Hz, 1H), 3.12 (br, 1H), 2.94 (t, *J*=12.1 Hz, 1H), 2.77 (m, 1H), 2.54 (m, 1H), 2.34 (dd, *J*=12.5 and 3.2 Hz, 1H), 2.04 (m, 1H), 1.80–1.63 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 140.5, 138.6, 129.6, 129.3, 128.7, 128.5, 127.7, 127.4, 65.4, 62.8, 61.4, 57.1, 55.1, 54.5, 28.3, 24.4. Anal. Calcd for $C_{26}H_{30}N_2O$: C, 80.79; H, 7.82; N, 7.25. Found: C, 80.77; H, 8.00; N, 7.51. $[\alpha]_D^{20}$ −75.5 (*c* 0.1, $CHCl_3$).

*4.1.2. N-[(R)-N-((R)-1-Phenylethyl)-2-amino-2-phenylethyl]-(S)-prolinol (**5**)*

A pale yellow oil was obtained in 63% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.33–7.16 (m, 10H), 3.84 (dd, *J*=10.5 and 3.4 Hz, 1H), 3.78 (q, *J*=6.5 Hz, 1H), 3.61 (dd, *J*=11.0 and 3.4 Hz, 1H), 3.41 (dd, *J*=11.0 and 4.9 Hz, 1H), 3.21 (m, 1H), 3.00 (br, 1H), 2.97 (dd, *J*=12.7 and 10.8 Hz, 1H), 2.68 (m, 1H), 2.52 (dd, *J*=12.8 and 3.5 Hz, 1H), 2.36 (q, *J*=8.2 Hz, 1H), 1.90–1.60 (m, 4H), 1.36 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 146.4, 143.4, 128.8, 128.7, 127.6, 127.5, 127.1, 127.0, 65.8, 64.8, 63.6, 60.5, 55.8, 55.3, 27.9, 24.6, 22.5. HRMS calcd for $C_{21}H_{29}N_2O$ (M^++1): 325.2280, found: 325.2309.

*4.1.3. N-((R)-N-Benzyl-2-amino-2-phenylethyl)-(S)-prolinol (**6**)*

A colorless oil was obtained in 69% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.39–7.25 (m, 10H), 3.75 (m, 2H), 3.63 (dd, *J*=11.1 and 3.5 Hz, 1H), 3.51 (d, *J*=13.6 Hz, 1H), 3.42 (dd, *J*=11.1 and 4.2 Hz, 1H), 3.01 (m, 1H), 2.92 (dd, *J*=11.3 and 12.3 Hz, 1H), 2.76 (br, 1H), 2.62 (m, 1H), 2.43 (dd, *J*=12.5 and 3.5 Hz, 1H), 2.23 (m, 1H), 1.89–1.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 142.7, 140.9, 128.9, 128.8, 128.5, 127.9, 127.8, 127.3, 65.7, 64.3, 63.2, 61.2, 54.8, 51.7, 27.7, 24.2. HRMS calcd for $C_{20}H_{27}N_2O$ (M^++1): 311.2123, found: 311.2149.

*4.1.4. N-[(R)-N-((S)-1-Phenylethyl)-2-amino-2-phenylethyl]-(S)-prolinol (**7**)*

A pale yellow oil was obtained in 49% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.33–7.17 (m, 10H), 3.67 (dd, *J*=11.1 and 3.7 Hz, 1H), 3.50 (m, 2H), 3.41 (dd, *J*=11.2 and 3.1 Hz, 1H), 3.30 (br, 1H), 2.90 (t, 1H), 2.74 (m, 1H), 2.60 (m, 1H), 2.30 (dd, *J*=12.5 and 3.1 Hz, 1H), 2.05 (m, 1H), 1.90–1.60 (m, 4H), 1.33 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 145.8, 143.0, 128.9, 128.8, 127.9, 127.7, 127.3, 127.0, 65.5, 64.2, 62.9, 59.1, 55.2, 54.6, 27.8, 25.0, 24.2. HRMS calcd for $C_{21}H_{29}N_2O$ (M^++1): 325.2280, found: 325.2251. $[\alpha]_D^{20}$ −125.5 (*c* 0.1, $CHCl_3$).

*4.1.5. N-[(R)-N-(9H-Fluoren-9-yl)-2-amino-2-phenylethyl]-(S)-prolinol (**8**)*

A colorless oil was obtained in 66% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.63–7.13 (m, 13H), 4.73 (s, 1H), 4.24 (dd, *J*=10.8 and 3.6 Hz, 1H), 3.58 (dd, *J*=11.1 and 3.5 Hz, 1H), 3.34 (dd, *J*=11.1 and 3.6 Hz, 1H), 2.98 (m, 4H), 2.57 (m, 1H), 2.43 (dd, *J*=12.5 and 3.5 Hz, 1H), 2.25 (m, 1H), 1.83–1.50 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 147.2, 146.8, 142.9, 141.0, 140.6, 128.9, 128.4, 128.2, 128.1, 127.8, 127.7, 127.3, 125.9, 125.8, 120.3, 119.9, 65.7, 64.4, 63.7, 61.0, 59.8, 54.7, 27.6, 24.2. HRMS calcd for $C_{26}H_{29}N_2O$ (M^++1): 385.2280, found: 385.2254.

*4.1.6. N-[(R)-N-(1-Naphthyl)-2-amino-2-phenylethyl]-(S)-prolinol (**9**)*

A colorless oil was obtained in 57% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.05–7.10 (m, 11H), 6.27 (d, *J*=8.0 Hz, 1H), 5.80 (br, 1H), 4.43 (dd, *J*=11.2 and 3.6 Hz, 1H), 3.73 (dd, *J*=10.8 and 4.0 Hz, 1H), 3.58 (dd, *J*=10.7 and 2.8 Hz, 1H), 3.07 (m, 2H), 2.66 (m, 2H), 2.31 (m, 2H), 1.95–1.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 143.7, 142.8, 134.7, 129.2, 129.1, 127.8, 127.0, 126.8, 126.2, 125.5, 124.8, 120.7, 118.1, 107.2, 65.4, 63.8, 63.2, 58.0, 54.3, 27.9, 24.2. HRMS calcd for $C_{23}H_{27}N_2O$ (M^++1): 347.2123, found: 347.2107.

*4.1.7. N-((R)-N,N-Dibenzyl-2-amino-2-phenylethyl)-(S)-prolinol (**10**)*

A colorless oil was obtained in 68% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.42–7.18 (m, 15H), 3.89 (m, 1H), 3.87 (d, *J*=13.6 Hz, 2H), 3.57 (dd, *J*=10.7 and 3.5 Hz, 1H), 3.40 (dd, *J*=12.8 and 8.7 Hz, 1H), 3.32 (dd, *J*=10.7 and 2.1 Hz, 1H), 3.15 (d, *J*=13.6 Hz, 2H), 2.80 (br, 1H), 2.79 (m, 1H), 2.62 (dd, *J*=12.8 and 5.5 Hz, 1H), 2.56 (m, 1H), 2.03 (q, *J*=8.6 Hz, 1H), 1.81–1.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 144.8, 144.2, 142.9, 129.0, 128.9, 128.7, 128.4, 127.9, 127.8, 127.7, 127.5, 127.1, 65.3, 64.0, 63.5, 62.9, 59.3, 54.6, 27.9, 24.2. Anal. Calcd for $C_{27}H_{32}N_2O$: C, 80.96;

H, 8.05; N, 6.99. Found: C, 80.83; H, 8.04; N, 6.89. $[\alpha]_D^{20}$ −93.8 (*c* 0.1, $CHCl_3$).

4.2. General procedure for the preparation of chiral ligands **11**–**13**

To a solution of *N*-diphenylmethylene dipeptide methyl ester in THF (0.5 M) was added BH_3–THF (1.0 M, 5.0 equiv), and the mixture was refluxed for 12–24 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 ligands **11**–**13**.

4.2.1. N-(N-Diphenylmethyl-2-aminoethyl)-(*S*)-prolinol (**11**)

A pale yellow oil was obtained in 78% yield from *N*-diphenylmethylene-Gly-L-Pro methyl ester. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.40–7.18 (m, 10H), 4.82 (s, 1H), 3.64 (dd, *J*=11.1 and 3.6 Hz, 1H), 3.43 (m, 2H), 3.10 (m, 1H), 2.97 (m, 1H), 2.72 (m, 3H), 2.49 (m, 1H), 2.28 (m, 1H), 1.84–1.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 144.4, 144.2, 129.0, 128.9, 127.7, 127.6, 127.3, 127.4, 68.0, 65.9, 64.0, 55.4, 55.1, 47.0, 27.9, 24.2. HRMS calcd for $C_{20}H_{27}N_2O$ (M^++1): 311.2123, found: 311.2118.

4.2.2. N-((*S*)-N-Diphenylmethyl-2-amino-2-phenylethyl)-(*S*)-prolinol (**12**)

A pale yellow oil was obtained in 82% yield from *N*-diphenylmethylene-L-Phg-L-Pro methyl ester. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.40–7.16 (m, 15H), 4.66 (s, 1H), 3.64 (m, 1H), 3.40 (dd, *J*=11.1 and 3.9 Hz, 1H), 3.21 (dd, *J*=11.0 and 4.2 Hz, 1H), 3.03 (dd, *J*=12.8 and 7.7 Hz, 1H), 2.92 (br, 1H), 2.80–2.60 (m, 4H), 2.24 (m, 1H), 1.73–1.51 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 144.9, 143.6, 143.2, 129.0, 128.9, 128.8, 128.1, 127.7, 127.6, 127.5, 127.4, 127.3, 66.1, 64.2, 64.0, 62.8, 60.2, 56.4. Anal. Calcd for $C_{26}H_{30}N_2O$: C, 80.79; H, 7.82; N, 7.25. Found: C, 80.67; H, 7.86; N, 7.23.

4.2.3. N-((*R*)-N-Diphenylmethyl-2-amino-2-phenylethyl)-(*S*)-leucinol (**13**)

A pale yellow oil was obtained in 66% yield from *N*-diphenylmethylene-D-Phg-L-Leu methyl ester. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35–7.13 (m, 15H), 4.64 (s, 1H), 3.60 (dd, *J*=7.8 and 5.5 Hz, 1H), 3.53 (dd, *J*=10.6 and 3.8 Hz, 1H), 3.19 (dd, *J*=10.6 and 6.5 Hz, 1H), 2.83 (m, 1H), 2.77 (m, 1H), 2.60 (m, 1H), 1.52 (m, 1H), 1.22 (m, 1H), 1.13 (m, 1H), 0.83 (d, *J*=6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 144.9, 143.6, 142.7, 129.0, 128.9, 128.8, 128.2, 127.9, 127.7, 127.6, 127.4, 127.3, 64.0, 63.8, 60.9, 57.3, 53.8, 41.5, 25.3, 23.4, 23.1. HRMS calcd for $C_{27}H_{35}N_2O$ (M^++1): 403.2749, found: 403.2718.

4.3. General procedure for asymmetric dehydration reactions of **1** and **14**–**21**

Trimethylchlorosilane (0.3 equiv) was added to a suspension of zinc metal (8.0 equiv) in anhydrous THF (5 mL). After the mixture was refluxed for 40 min, the heating was stopped, and a solution of ligand (5 mol %), *tert*-butyl bromoacetate (8.0 equiv) and racemic β-hydroxy ester (0.5 mmol, 1.0 equiv), and hexamethylbenzene (internal standard, 0.3–0.5 equiv) in THF (5 mL) was slowly added. The mixture was stirred at reflux for 1–5 h and then quenched with saturated NH_4Cl solution. The resulting mixture was extracted with methylene chloride (3×5 mL) and the combined extracts were washed with brine. The solvents were removed under reduced pressure and the residue purified by flash column chromatography to give enantioenriched β-hydroxy esters **1** and **14**–**21**.

4.3.1. tert-Butyl (*R*)-3-(4-methoxyphenyl)-3-hydroxypropanoate (**1**)

The product was recovered in 35% yield based on 56% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.26 (d, *J*=8.4 Hz, 2H), 6.85 (d, *J*=8.4 Hz, 2H), 5.00 (br, 1H), 3.76 (s, 3H), 3.51 (br, 1H), 2.61 (m, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.2, 159.5, 135.4, 127.4, 114.2, 81.7, 70.4, 55.6, 44.8, 28.5. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.56; H, 7.87. $[\alpha]_D^{20}$ +28.0 (*c* 0.15, $CHCl_3$); CSP-HPLC (Chiralcel OJ-H column; 5% 2-propanol in hexane; 0.5 mL/min): 97% ee, 33.3 min (*R*), 30.7 min (*S*).

4.3.2. tert-Butyl (*R*)-3-phenyl-3-hydroxypropanoate (**14**)

The product was recovered in 32% yield based on 57% conversion. The analytical data is in accordance with the literature.[8a] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35–7.22 (m, 5H), 5.05 (br, 1H), 3.57 (br, 1H), 2.62 (m, 2H), 1.38 (s, 9H). $[\alpha]_D^{20}$ +7.8 (*c* 0.05, $CHCl_3$); CSP-HPLC; *tert*-butyl ester **14** was converted to methyl ester for better chromatographic separation (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 93% ee, 26.8 min (*R*), 19.0 min (*S*).

4.3.3. tert-Butyl (*R*)-3-(4-methylphenyl)-3-hydroxypropanoate (**15**)

The product was recovered in 40% yield based on 55% conversion. The analytical data is in accordance with the literature.[8b] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.23 (d, *J*=8.1 Hz, 2H), 7.11 (d, *J*=8.1 Hz, 2H), 5.01 (m, 1H), 3.51 (br, 1H), 2.67–2.54 (m, 2H), 2.31 (s, 3H), 1.43 (s, 9H); CSP-HPLC (Chiralcel OB-H column; 5% 2-propanol in hexane; 0.5 mL/min): 93% ee, 10.8 min (*R*), 12.8 min (*S*).

4.3.4. tert-Butyl (*R*)-3-(4-chlorophenyl)-3-hydroxypropanoate (**16**)

The product was recovered in 37% yield based on 57% conversion. The analytical data is in accordance with the literature.[8c] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.29 (m, 4H), 5.03 (m, 1H), 3.68 (m, 3H), 2.61 (m, 2H), 1.44 (s, 9H). $[\alpha]_D^{20}$ +13.8 (*c* 0.18, $CHCl_3$); CSP-HPLC (Chiralcel OB-H column; 5%

2-propanol in hexane; 0.5 mL/min): 98% ee, 11.5 min (*R*), 13.2 min (*S*).

4.3.5. tert-Butyl (R)-3-hydroxy-4-pentenoate (17)

The product was recovered in 31% yield based on 62% conversion. The analytical data is in accordance with the literature.[8d] ^{1}H NMR ($CDCl_3$, 400 MHz) 5.88 (m, 1H), 5.31 (m, 1H), 5.13 (m, 1H), 4.49 (br, 1H), 3.54 (br, 1H), 2.44 (m, 2H), 1.47 (s, 9H); CSP-HPLC; β-hydroxy ester **17** was converted to *O*-(3,5-dimethoxyphenyl)derivative (Chiralcel OJ-H column; 5% 2-propanol in hexane; 0.5 mL/min): 97% ee, 11.5 min (*R*), 12.4 min (*S*).

4.3.6. tert-Butyl (3R,4E,6E)-3-hydroxy-4,6-octadienoate (18)

The product was recovered in 35% yield based on 57% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz) 6.22 (dd, J=16.1 and 10.4 Hz, 1H), 6.02 (m, 1H), 5.70 (m, 1H), 5.55 (dd, J=15.3 and 6.4 Hz, 1H), 4.50 (br, 1H), 3.20 (br, 1H), 2.46 (m, 2H), 1.74 (d, J=5.9 Hz, 3H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.0, 131.4, 131.1, 130.9, 130.5, 81.7, 69.2, 43.0, 28.5, 18.4. HRMS calcd for $C_{12}H_{21}O_3$ (M^+): 212.1412, found: 212.1405; CSP-HPLC (Chiralcel OJ-H column; 5% 2-propanol in hexane; 0.5 mL/min): 81% ee, 15.5 min (*R*), 14.5 min (*S*).

4.3.7. tert-Butyl (3R,4E)-3-hydroxy-5-phenyl-4-pentenoate (19)

The product was recovered in 37% yield based on 55% conversion. The analytical data is in accordance with the literature.[8c] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.23 (m, 5H), 6.62 (d, J=16.0 Hz, 1H), 6.18 (dd, J=17.0 and 6.0 Hz, 1H), 4.66 (br, 1H), 3.44 (d, J=3.8 Hz, 1H), 2.54 (m, 2H), 1.45 (s, 9H). $[\alpha]_D^{20}$ +7.2 (*c* 0.12, $CHCl_3$); CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 97% ee, 17.4 min (*R*), 25.9 min (*S*).

4.3.8. tert-Butyl (3R,4E)-3-hydroxy-5-(2-methoxyphenyl)-4-pentenoate (20)

The product was recovered in 38% yield based on 52% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.40 (d, J=7.6 Hz, 1H), 7.21 (m, 1H), 6.88 (m, 3H), 6.22 (dd, J=16.1 and 6.0 Hz, 1H), 4.68 (br, 1H), 3.82 (s, 3H), 3.18 (d, J=4.0 Hz, 1H), 2.57 (m, 2H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.1, 157.2, 131.3, 129.2, 127.4, 126.0, 121.0, 111.3, 81.7, 69.9, 55.8, 43.1, 28.5. HRMS calcd for $C_{16}H_{22}O_4$ (M^+): 278.1518, found: 278.1518; CSP-HPLC (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min): 95% ee, 21.4 min (*R*), 17.4 min (*S*).

4.3.9. tert-Butyl (3R,4E)-3-hydroxy-4-methyl-5-phenyl-4-pentenoate (21)

The product was recovered in 34% yield based on 53% conversion. The analytical data is in accordance with the literature.[8a] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.24 (m, 5H), 6.59 (s, 1H), 4.55 (br, 1H), 3.22 (d, J=3.6 Hz, 1H), 2.58 (d, J=6.4 Hz, 2H), 1.88 (s, 3H), 1.47 (s, 9H); CSP-HPLC (Chiralcel OJ-H column; 5% 2-propanol in hexane; 0.5 mL/min): 94% ee, 20.5 min (*R*), 14.8 min (*S*).

4.4. General procedure for the preparation of 22–24

From the reactions of racemic β-hydroxy esters **14**, **15**, and **16** (10.0 mmol) under the standard asymmetric dehydration condition described in Section 4.3, enantioenriched **14**, **15**, and **16** were obtained with 95% ee (32% yield at 60% conversion), 96% ee (30% yield at 62% conversion), and 96% ee (30% yield at 63% conversion), respectively. After the addition of $LiAlH_4$ (1.5 equiv) to enantioenriched β-hydroxy esters **14–16** in THF, the mixture was stirred at rt for 1 h and then quenched with EtOAc and 10% HCl. Extractive work-up and flash chromatography gave 1,3-diols in 85–79% yields. To a stirred solution of a 1,3-diol (1.0 equiv) in benzene was added imidazole (1.0 equiv), PPh_3 (2.0 equiv), and iodine (2.0 equiv). After stirring for 1 h, saturated sodium thiosulfate solution and EtOAc were added. The resulting mixture was extracted with ethyl acetate (3×5 mL) and the combined extracts were washed with brine. The solvents were removed under reduced pressure and the residue purified by flash column chromatography to give 3-iodo-1-propanols **22–24**.

4.4.1. (R)-3-Iodo-1-phenyl-1-propanol (22)

A pale yellow oil was obtained in 62% overall yield. The analytical data is in accordance with the literature.[8e] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.38–7.25 (m, 5H), 4.79 (m, 1H), 3.29 (m, 1H), 3.16 (m, 1H), 2.21 (m, 2H), 2.10 (d, J=3.4 Hz, 2H).

4.4.2. (R)-3-Iodo-1-(4-methylphenyl)-1-propanol (23)

A pale yellow oil was obtained in 50% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.23 (d, J=7.9 Hz, 2H), 7.15 (d, J=7.9 Hz, 2H), 4.73 (m, 1H), 3.27 (m, 1H), 3.13 (m, 1H), 2.33 (s, 3H), 2.18 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 140.9, 138.1, 129.8, 126.2, 74.4, 42.7, 21.6, 3.2. Anal. Calcd for $C_{10}H_{13}IO$: C, 43.50; H, 4.75. Found: C, 43.43; H, 4.84.

4.4.3. (R)-3-Iodo-1-(4-chlorophenyl)-1-propanol (24)

A pale yellow oil was obtained in 68% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35–7.26 (m, 5H), 4.80 (m, 1H), 3.29 (m, 1H), 3.15 (m, 1H), 2.21–2.11 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 142.4, 134.0, 129.2, 127.6, 73.9, 42.6, 2.7. Anal. Calcd for $C_9H_{10}ClIO$: C, 36.45; H, 3.40. Found: C, 36.49; H, 3.46.

4.5. General procedure for the preparation of 25–29

To a stirred solution of PPh_3 (1.5 equiv) and DIAD (1.5 equiv) in THF at 0 °C was added a solution of 2-bromophenol (2 equiv) and iodopropanols **22–24** (1.0 equiv) in THF. After stirring for 2 h at 0 °C, the reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash chromatography to obtain *O*-phenyl derivatives in 87–77% yields. For intramolecular cyclization, a solution of *O*-phenyl derivatives (1.0 equiv) in THF was added

dropwise to a stirred solution of *n*-BuLi (2.5 M in hexane, 1 equiv) in THF at 0 °C. After an additional *n*-BuLi (1 equiv) was introduced, the reaction mixture was slowly warmed to room temperature. After stirring at rt for 3 h, the reaction was quenched by pouring into saturated aqueous ammonium chloride. The resulting mixture was extracted with methylene chloride (3×5 mL) and the combined extracts were washed with brine. The solvents were removed under reduced pressure and the residue purified by flash column chromatography to give flavane derivatives **25**–**29**.

*4.5.1. (S)-3,4-Dihydro-2-phenyl-2H-1-benzopyran (**25**)*

A white solid was obtained in 57% overall yield. The analytical data is in accordance with the literature.[7a] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.43–7.31 (m, 5H), 7.12 (m, 2H), 6.90 (m, 2H), 5.06 (dd, J=10.1 and 2.4 Hz, 1H), 2.98 (m, 1H), 2.80 (m, 1H), 2.20 (m, 1H), 2.10 (m, 1H). $[\alpha]_D^{20}$ −10.6 (*c* 0.06, $CHCl_3$); CSP-HPLC (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min): 94% ee, 23.4 min (*S*), 17.3 min (*R*).

*4.5.2. (S)-3,4-Dihydro-2-(4-methylphenyl)-2H-1-benzopyran (**26**)*

A pale yellow oil was obtained in 48% overall yield. The analytical data is in accordance with the literature.[8f] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.31 (d, J=8.0 Hz, 2H), 7.23–7.06 (m, 4H), 6.91–6.83 (m, 2H), 5.02 (dd, J=10.0 and 2.0 Hz, 1H), 2.97 (m, 1H), 2.80 (m, 1H), 2.35 (s, 3H), 2.18 (m, 1H), 2.10 (m, 1H); CSP-HPLC (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min): 92% ee, 26.8 min (*S*), 18.3 min (*R*).

*4.5.3. (S)-6-Methyl-3,4-dihydro-2-phenyl-2H-1-benzopyran (**27**)*

A pale yellow oil was obtained in 45% overall yield. The analytical data is in accordance with the literature.[7a] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.43–7.31 (m, 5H), 6.93–6.80 (m, 3H), 5.02 (dd, J=10.0 and 2.3 Hz, 1H), 2.95 (m, 1H), 2.76 (m, 1H), 2.27 (s, 3H), 2.18 (m, 1H), 2.09 (m, 1H); CSP-HPLC (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min): 90% ee, 23.9 min (*S*), 17.1 min (*R*).

*4.5.4. (S)-6-Chloro-3,4-dihydro-2-phenyl-2H-1-benzopyran (**28**)*

A white solid was obtained in 52% overall yield. The analytical data is in accordance with the literature.[7a] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.40–7.26 (m, 5H), 7.08–6.82 (m, 3H), 5.04 (dd, J=10.0 and 2.4 Hz, 1H), 2.92 (m, 1H), 2.75 (m, 1H), 2.20 (m, 1H), 2.08 (m, 1H); CSP-HPLC (Chiralcel OJ-H column; 5% 2-propanol in hexane; 0.5 mL/min): 93% ee, 33.9 min (*S*), 18.3 min (*R*).

*4.5.5. (S)-6-Chloro-3,4-dihydro-2-(4-chlorophenyl)-2H-1-benzopyran (**29**)*

A pale yellow oil was obtained in 46% overall yield. The analytical data is in accordance with the literature.[7a] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.37–7.28 (m, 4H), 7.07 (m, 2H), 6.80 (d, J=8.4 Hz, 1H), 4.97 (dd, J=10.1 and 1.8 Hz, 1H), 2.88 (m, 1H), 2.72 (m, 1H), 2.15 (m, 1H), 1.97 (m, 1H). $[\alpha]_D^{20}$ −7.8 (*c* 0.16, $CHCl_3$); CSP-HPLC (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min): 96% ee, 22.4 min (*S*), 14.2 min (*R*).

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