Asymmetric Dehydration of β-Styryl-β-hydroxy Esters and Application to the Synthesis of a Neoflavonoid

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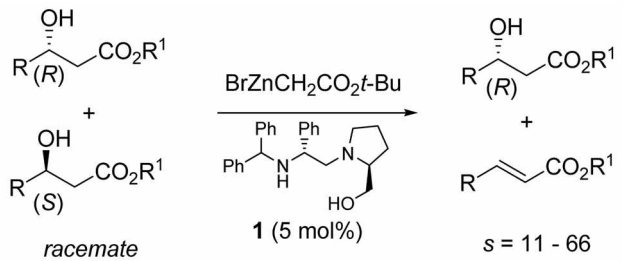
Non-enzymatic kinetic resolution of racemic alcohols with a chiral catalyst is presently an area of great importance in organic chemistry.[1] We have previously reported the first example for the asymmetric dehydration of β-hydroxy esters *via* kinetic resolution using *D*-Phg-*L*-Pro-derived chiral ligand **1** as shown in Scheme 1.[2] The effective kinetic resolution of β-hydroxy esters prompted us to investigate the asymmetric dehydration of β-styryl-β-hydroxy esters in more detail. Herein we describe our recent progress to optimize reaction conditions and to extend the scope of the methodology to various β-styryl substituents. Also, application of this methodology to the preparation of an enantioenriched neoflavonoid is presented.

We have found that chiral ligand **1** is efficient for the asymmetric dehydration of β-hydroxy esters in the presence of excess amount of $BrZnCH_2CO_2t$-Bu as a base. Treatment of racemic β-hydroxy ester **2a** (R^1 = *t*-Bu) with chiral ligand **1** (5 mol%) and $BrZnCH_2CO_2t$-Bu (8 equiv) in anhydrous THF at reflux for 1.5 h afforded a mixture of (*2E,4E*)-5-phenyl-2,4-pentadienoate and β-hydroxy ester (*R*)-**2a**. At 55% conversion, the unconverted (*R*)-**2a** was obtained with 97% ee.[2b] (Table 1, entry 1) Based on the successful results of *t*-butyl ester, our initial investigation has focused on the effect of the alkyl group of the ester. The dehydrations of β-styryl-β-hydroxy methyl ester (**2b**), ethyl ester (**2c**) and isopropyl ester (**2d**) also proceeded with ligand **1** (5 mol%) and $BrZnCH_2CO_2t$-Bu (8 equiv), but the efficiency of the kinetic resolution was lower than the reaction of β-hydroxy *t*-butyl ester (**2a**). Kinetic resolutions of methyl and ethyl esters with 5 mol% of **1** and 8 equiv of $BrZnCH_2CO_2t$-Bu gave much lower selectivities of 3.3 and 3.5, respectively.[3] (entries 2 and 3) Good selectivity (s = 20) was observed in the kinetic resolution of the corresponding isopropyl ester **2d**. (entry 4) Evidently, the efficiency of kinetic resolution is strongly substrate-dependent and subtle steric factors result in highly efficient kinetic resolution of β-hydroxy *t*-butyl ester **2a**.

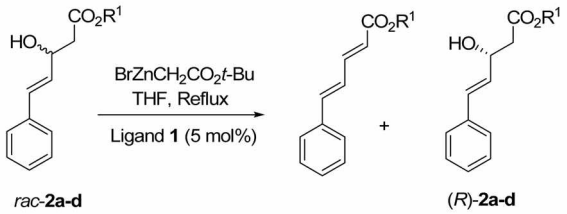


Scheme 1

Next, we tested the possibility of using less amount of base in the reactions of β-styryl-β-hydroxy *t*-butyl esters **2a**, **3** and **4**. The use of 5 equiv of $BrZnCH_2CO_2t$-Bu in the presence of chiral ligand **1** (5 mol%), however, gave lower conversions and lower selectivities compared to the reactions with 8 equiv of $BrZnCH_2CO_2t$-Bu. (Table 2, entries 1-3) The preliminary results indicate that the selectivity and rate of dehydration are substantially influenced by the amount of the base, $BrZnCH_2CO_2t$-Bu. Then we have investigated the reaction's scope with various β-styryl-β-hydroxy *t*-butyl esters and chiral ligand **1**. As shown in entries 4-8, the kinetic resolution of five β-styryl-β-hydroxy esters **5-9** with 5 mol% of **1** and 8 equiv of $BrZnCH_2CO_2t$-Bu provided excellent levels of asymmetric induction. Most reactions reached 55-53% conversion after 1.5-2.5 h with the selectivities ranging from 11 to 48. Our most impressive result was obtained with β-bromostyryl-β-hydroxy ester **9**, affording a k_{rel} of 48. (entry 8)

Two related prolinol chiral ligands **10** and **11** having different *N*-alkyl groups were prepared by the stereoselective nucleophilic substitution of *N*-(α-bromo-α-phenylacetyl)-*L*-proline ester and subsequent reduction.[4] With 8 equiv

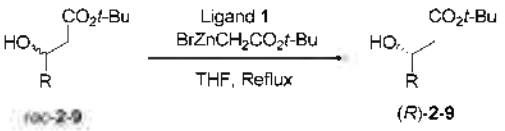
Table 1.

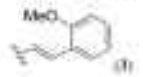
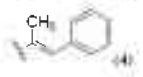
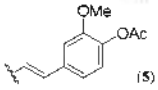
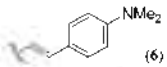
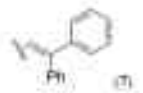
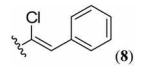
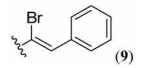


Entry	R^1	Time (h)	Conv. (%)[a]	% ee[b]	*s* (k_S/k_R)[c]
1	*t*-Bu (**2a**)	1.5	55	97	38
2	Me (**2b**)	8.5	61	57	3.3
3	Et (**2c**)	8	65	71	3.5
4	*i*-Pr (**2d**)	1.5	55	92	20

[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 **2a-d** is determined by CSP-HPLC. [c]Selectivity (*s*) values represent an average of at least two experiments, while conversion and ee value are for specific cases.

Table 2.

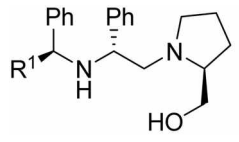


Entry	R	Base (equiv)	Time (h)	Conv.[a] (%)	ee[b] (%)	s[c] (k_S/k_R)
1		8	1	55	97	38
		5	4.5	57	91	16
2		8	1	52	95	66
		5	4.5	54	70	8
3		8	1.5	53	94	42
		5	3	53	74	11
4		8	2.5	55	93	20
5		8	1.5	55	80	11
6		8	1.5	55	93	20
7		8	1.5	55	96	36
8		8	1.5	53	96	48

[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 **2-9** is determined by CSP-HPLC. [c]Selectivity (s) values represent an average of at least two experiments, while conversion and ee value are for specific cases.

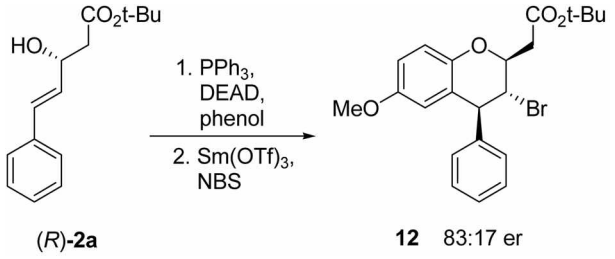
of $BrZnCH_2CO_2t$-Bu and 5 mol% of chiral ligand, the reactions of *N*-benzylated ligand **10** and *N*-(*R*)-1-phenethylated ligand **11** produced lower level of selectivities (s = 7 and 3, respectively) relative to *N*-diphenylmethylated ligand **1**. With 20 mol% of chiral ligand, the reaction with *N*-(*R*)-1-phenethylated ligand **11** gave a selectivity factor of 22, while *N*-benzylated ligand **10** produced a modest level of selectivity (s = 6). These results indicate that subtle *N*-alkyl group modifications of chiral ligand can lead to substantial variations in enantioselection.

To extend the utility of this methodology, we decided to take advantage of the functional groups present in β-styryl-β-hydroxy ester for subsequent synthetic elaboration. In particular, the opportunity to prepare enantioenriched neoflavane (4-phenyl-chromane) derivative **12** was provided



10 (R^1 = H)
11 (R^1 = CH_3)

Figure 1



Scheme 2

from the enantioenriched β-styryl-β-hydroxy esters **2a** as shown in Scheme 2. Certain natural and synthetic neoflavonoids have been reported to show significant biological properties and can be converted into other biologically active flavonoids.[5] When (*R*)-**2a** (93:7 enantiomeric ratio) was treated with *p*-methoxyphenol under standard Mitsunobu inversion condition, the reaction provided the (*S*)-aryl ether in 40% yield. Moderate racemization during Mitsunobu reaction has been observed to give the product with 83:17 er. Subsequent cyclization with $Sm(OTf)_3$ and *N*-bromosuccinimide (NBS) at rt gave 4-phenyl-chromane **12** in 60% yield with 83:17 er.[6] The Lewis acid catalyzed intramolecular bromo-arylation of styryl group is regio- and stereospecific to provide 2,3,4-substituted (*2S,3R,4S*)-**12** as a major stereoisomer.[7]

In summary, we have developed asymmetric dehydration of various β-styryl-β-hydroxy esters *via* kinetic resolution. The present results indicate that the stereoselectivity is significantly influenced by the alkyl group of the ester and amount of $BrZnCH_2CO_2t$-Bu. Best results of the kinetic resolution have been obtained with 5 mol% of chiral ligand **1** and 8 equiv of the base in refluxing THF. In addition, we have established the applicability of this method as exemplified by the asymmetric synthesis of a 2,3,4-substituted chromane. The finding for the efficient preparation of **12** suggests that many kinds of neoflavonoids can be synthesized in the same way.

Experimental

General procedure for asymmetric dehydration reactions of 2-9. 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%), *t*-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 **2-9**.

***t*-Butyl (3*R*,4*E*)-3-hydroxy-5-phenyl-4-pentenoate (2a).**

The product was recovered in 37% yield based on 55% conversion. The analytical data is in accordance with the lit.[8a] ^{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*).

Methyl (3*R*,4*E*)-3-hydroxy-5-phenyl-4-pentenoate (2b). The product was recovered in 29% yield based on 61% conversion. The analytical data is in accordance with the lit.[8b] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.34-7.18 (m, 5H), 6.61 (d, J = 16.0 Hz, 1H), 6.21 (dd, J = 16.0 and 6.2 Hz, 1H), 4.71 (br, 1H), 3.65 (s, 3H), 2.64 (m, 2H); CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 57% ee, 29.0 min (*R*), 40.6 min (*S*).

Ethyl (3*R*,4*E*)-3-hydroxy-5-phenyl-4-pentenoate (2c). The product was recovered in 25% yield based on 65% conversion. The analytical data is in accordance with the lit.[8c] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35-7.18 (m, 5H), 6.62 (d, J = 16.0 Hz, 1H), 6.21 (dd, J = 16.0 and 6.1 Hz, 1H), 4.71 (br, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.57 (d, J = 4.5 Hz, 1H), 2.63 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H); CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 71% ee, 24.3 min (*R*), 35.1 min (*S*).

Isopropyl (3*R*,4*E*)-3-hydroxy-5-phenyl-4-pentenoate (2d). The product was recovered in 37% yield based on 55% conversion. The analytical data is in accordance with the lit.[8d] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.36-7.20 (m, 5H), 6.62 (d, J = 16.0 Hz, 1H), 6.21 (dd, J = 16.0 and 6.0 Hz, 1H), 5.06 (m, 1H), 4.69 (br, 1H), 3.34 (d, J = 4.4 Hz, 1H), 2.58 (m, 2H), 1.24 (d, J = 6.4 Hz, 6H); CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 92% ee, 19.7 min (*R*), 30.2 min (*S*).

***t*-Butyl (3*R*,4*E*)-3-hydroxy-5-(2-methoxyphenyl)-4-pentenoate (3).** The product was recovered in 35% yield based on 52% conversion. The analytical data is in accordance with the lit.[8b] ^{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); 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*).

***t*-Butyl (3*R*,4*E*)-3-hydroxy-4-methyl-5-phenyl-4-pentenoate (4).** The product was recovered in 34% yield based on 53% conversion. The analytical data is in accordance with the lit.[8b] ^{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*).

***t*-Butyl (3*R*,4*E*)-3-hydroxy-5-(4-acetoxy-3-methoxyphenyl)-4-pentenoate (5).** The product was recovered in 38% yield based on 55% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz) 6.93 (m, 3H), 6.60 (d, J = 15.9 Hz, 1H), 6.15 (dd, J = 16.0 and 6.0 Hz, 1H), 4.66 (br, 1H), 3.83 (s, 3H), 3.34 (d, J = 4.2 Hz, 1H), 2.55 (m, 2H), 2.30 (s, 3H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.0, 169.4, 151.5, 139.4, 136.1, 131.0, 130.2, 123.2, 119.6, 110.6, 81.9, 69.2, 56.2, 42.9, 28.5, 21.0; CSP-HPLC (Chiralcel OD column; 20% 2-propanol in hexane; 0.5 mL/min): 93% ee, 31.1 min (*R*), 22.5 min (*S*).

***t*-Butyl (3*R*,4*E*)-3-hydroxy-5-(4-*N*,*N*-dimethylaminophenyl)-4-pentenoate (6).** The product was recovered in 32% yield based on 55% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.25 (d, J = 8.8 Hz, 2H), 6.66 (d, J = 8.8 Hz, 2H), 6.53 (d, J = 15.9 Hz, 1H), 6.00 (dd, J = 15.9 and 6.5 Hz, 1H), 4.63 (br, 1H), 3.06 (br, 1H), 2.95 (s, 6H), 2.54 (m, 2H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.2, 150.6, 131.2, 127.9, 126.2, 125.4, 112.8, 81.7, 69.9, 43.2, 40.9, 28.5; CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 80% ee, 22.0 min (*R*), 25.0 min (*S*).

***t*-Butyl (3*R*,4*E*)-3-hydroxy-5,5-diphenyl-4-pentenoate (7).** The product was recovered in 32% yield based on 55% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.40-7.21 (m, 10H), 6.06 (d, J = 9.2 Hz, 1H), 4.55 (m, 1H), 3.18 (d, J = 4.0 Hz, 1H), 2.52 (m, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.1, 144.6, 142.1, 139.5, 130.1, 129.3, 128.7, 128.6, 128.1, 128.0, 81.9, 66.6, 42.9, 28.5; CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 93% ee, 11.2 min (*R*), 14.4 min (*S*).

***t*-Butyl (3*R*,4*Z*)-4-chloro-3-hydroxy-5-phenyl-4-pentenoate (8).** The product was recovered in 35% yield based on 55% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.61-7.25 (m, 5H), 6.88 (s, 1H), 4.70 (m, 1H), 3.70 (d, J = 5.0 Hz, 1H), 2.78 (dd, J = 16.1 and 4.0 Hz, 1H), 2.68 (dd, J = 16.0 and 8.2 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.8, 134.6, 134.1, 129.7, 128.6, 128.5, 125.4, 82.2, 73.1, 41.3, 28.5; CSP-HPLC (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min): 96% ee, 15.6 min (*R*), 13.6 min (*S*).

***t*-Butyl (3*R*,4*Z*)-4-bromo-3-hydroxy-5-phenyl-4-pentenoate (9).** The product was recovered in 35% yield based on 53% conversion. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.58-7.25 (m, 5H), 7.17 (s, 1H), 4.72 (m, 1H), 3.88 (m, 1H), 2.78 (dd, J = 15.8 and 3.7 Hz, 1H), 2.68 (dd, J = 15.8 and 8.1 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.6, 135.5, 129.5, 128.8, 128.6, 127.6, 82.2, 74.2, 41.9, 28.4; CSP-HPLC (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min): 96% ee, 18.1 min (*R*), 15.2 min (*S*).

3-Bromo-2-*t*-butoxycarbonylmethyl-6-methoxy-4-phenyl-chromane (12). To a stirred solution of PPh_3 (1.5 equiv) and DEAD (1.5 equiv) in THF at 0 °C was added a solution of *p*-methoxyphenol (2 equiv) and *β*-hydroxy ester **2a** (1.0 equiv, 93:7 er) 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 40% yield.[2b] For intramolecular cyclization, a solution of *O*-phenyl derivative of **2a** (1.0 equiv) in THF was added to a solution of $Sm(OTf)_3$ (10 mol%) and *N*-bromosuccinimide (NBS, 1.1 equiv) in THF at rt. The mixture was stirred for 12 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 4-phenyl-chromane **12** in 60% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.34-7.18 (m, 5H), 6.77 (d, J = 9.2 Hz, 1H), 6.69 (m, 1H), 6.13 (d, J = 2.8 Hz, 1H), 4.58 (m, 1H), 4.40 (d, J = 10.3 Hz, 1H), 4.30 (dd, J = 10.3 and 10.3 Hz, 1H), 3.56 (s, 3H), 3.17 (dd, J = 15.4 and 3.4 Hz, 1H), 2.67 (dd, J = 15.4 and 8.5 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.0, 154.6, 148.6, 142.2, 129.6, 129.1, 128.0, 126.0, 117.7, 114.8, 114.5, 81.5, 77.3, 56.4, 56.0, 53.8, 41.5, 28.6; CSP-HPLC (Chiralcel AD-H column; 5% 2-propanol in hexane; 0.5 mL/min): 83:17 er, 22.5 min (*2S,3R,4S*), 20.9 min (*2R,3S,4R*).

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References and Notes

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3. The selectivity factor (s) was estimated using the equation, $s = k_S/k_R = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$, where ee is the enantiomeric excess of unconverted β-hydroxy ester and the conversion (C) determined by ^{1}H NMR of reaction mixture using internal standard.
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