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Asymmetric dehydration of β-hydroxy esters via kinetic resolution

Yongtae Kim, Eui Ta Choi, Min Hee Lee and Yong Sun Park*

Department of Chemistry and Bio/Molecular Informatics Center, Konkuk University, Seoul 143-701, Republic of Korea

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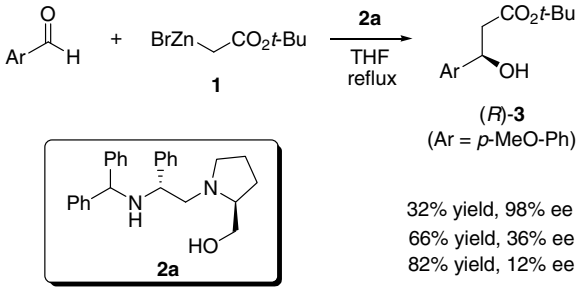
Abstract—Catalytic asymmetric dehydration of β-hydroxy esters via kinetic resolution has been investigated. The kinetic resolution of *rac*-β-hydroxy esters in the presence of prolinol chiral ligand **2a** and $BrZnCH_2CO_2t$-Bu can provide highly enantioenriched β-hydroxy esters **3** and **5**–**11** with selectivity factors ranging from 15 to 42.

The dehydration of alcohol is one of the most fundamental organic transformation for which a large number of catalysts and reagents have been developed.[1] Considering the recent tremendous achievements in the field of asymmetric syntheses, it is surprising that there are few examples of enantioselective dehydration for alcohol resolution, while the enantioselective oxidation and acylation for alcohol resolution have long been the subject of intensive studies.[2–4] Herein we report the first example of highly enantioselective dehydration of β-hydroxy esters via kinetic resolution using organozinc reagent.



Scheme 1.

As a part of our program dealing with the asymmetric syntheses of flavanone derivatives, we previously reported an asymmetric synthetic method for the preparation of β-aryl-β-hydroxy esters with high enantioselectivities. When $BrZnCH_2CO_2t$-Bu (**1**) was added to *p*-anisaldehyde in the presence of prolinol chiral ligand (**2a**), the reaction for 2 h provided β-hydroxy ester (*R*)-**3** in 32% yield with 98% ee along with the corresponding cinnamate.[5] Our continuing investigation have recently found that shorter reactions gave higher yields and lower enantioselectivities as shown in Scheme 1. Reactions for 1 h and 0.5 h produced (*R*)-**3** in 66% yield with 36% ee and in 82% yield with 12% ee, respectively. Based on the observed dependency of enantioselectivity on the yield of **3**, we envisioned that the major source of enantioselection is asymmetric dehydration of the β-hydroxy ester via kinetic resolution, not the enantioselective addition of Reformatsky reagent **1** to the aldehyde.

Initial studies to examine the possibility of the kinetic resolution were carried out under the typical condition with chiral ligand **2a** shown in Scheme 1. When racemic β-hydroxy ester **3** was treated with **2a** (20 mol %) and $BrZnCH_2CO_2t$-Bu (8 equiv) in refuxing THF at a concentration of 0.05 M substrate, we have found that the kinetic resolution of *rac*-**3** proceeded cleanly to allow the isolation of β-hydroxy ester **3** and cinnamate **4** in high yields.[6] As shown in Table 1 and entry 1, at 59% conversion, *trans*-cinnamate **4** was isolated in 43% yield and the unconverted β-hydroxy ester (*R*)-**3** was obtained in 35% yield with 97% ee. Kinetic resolution in asymmetric dehydration favoring (*S*)-**3** proceeded with a selectivity factor (*s*) of 22 (an average of three experiments).[7] The high activity of the catalyst also makes effective resolutions with lower catalyst loading. The kinetic resolution using 10 or 5 mol % of chiral ligand **2a** proceeded with a comparable selectivity factor (entries 2 and 3). However, the dehydration with 3 mol % of

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* Corresponding author. Tel.: +82 2 450 3377; fax: +82 2 3436 5382; e-mail: parkyong@konkuk.ac.kr

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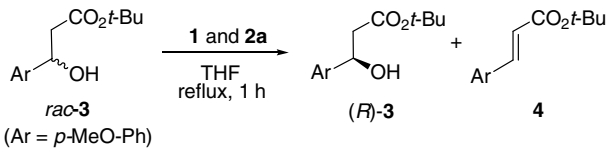
Table 1. Asymmetric dehydration of β-hydroxy ester **3**

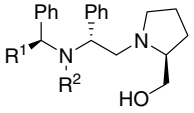


Entry	**1** (equiv)	**2a** (mol %)	Conversion[a] (%)	% ee[b]	s (k_S/k_R) [c]
1	8	20	59	97	22
2	8	10	56	95	25
3	8	5	56	97	24
4	8	3	35	32	7
5	4	10	58	88	14
6	2	5	39	49	12

[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 **3** 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.

chiral ligand **2a** proceeded slowly to give (*R*)-**3** with a lower selectivity factor of 7 (entry 4). In the absence of chiral ligand **2a**, the dehydration did not occur for prolonged reaction time under analogous conditions. Next, we turned our attention to the influence of the organozinc reagent on the enantioselectivity. The use of 4 equiv of $BrZnCH_2CO_2t$-Bu (**1**) in the presence of 10 mol % of chiral ligand **2a** gave lower selectivity (entries 2 and 5). The slow reaction using 2 equiv of **1** produced (*R*)-**3** with a selectivity factor of 12 (entry 6). Also, the reaction using $BrZnCH_2CH_2CH_2(CH_3)_2$ or Et_2Zn instead of $BrZnCH_2CO_2t$-Bu did not provide the elimination product **4** under the same reaction condition. Both nature and amount of organozinc reagent were found to be critical for the enantioselective dehydration of β-hydroxy ester.

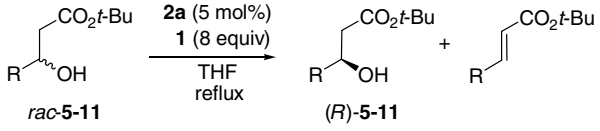
To gain an insight into the effects of chiral ligand and substrate on selectivity, we have conducted a brief survey of different forms for those compounds. Two related prolinol chiral ligands **2b** and **2c** having different *N*-alkyl groups were prepared by the stereoselective nucleophilic substitution of *N*-(α-bromo-α-phenylacetyl)-L-proline ester and subsequent reduction.[5,8] With 8 equiv of **1** and 5 mol % of chiral ligand, the reaction of *N*-(*S*)-1-phenethylated ligand **2b** gave a modest level of selectivity ($s = 5$) relative to **2a**, while *N*,*N*-dibenzylated chiral ligand **2c** produced no elimination product. These investigations indicated that subtle *N*-alkyl group modifications of chiral ligand can lead to substantial variations in reactivity and enantioselection. In order to examine the reactivities of OH protected β-hydroxy esters, we have prepared β-acetoxy and β-trimethylsilyloxy esters of **3**.[9] Both reactions of two modified esters under the analogous condition with chiral ligand **2a** gave no elimination product and the esters are quantitatively recovered. The preliminary results imply that both OH bond of substrate and NH bond of chiral ligand play important roles in the formation of reactive intermediate, which might be formed by action of excess $BrZnCH_2CO_2t$-Bu as a base.



2b ($R^1 = CH_3$, $R^2 = H$)
2c ($R^1 = H$, $R^2 = CH_2Ph$)

We then initiated investigations into the reaction's scope with chiral ligand **2a**. For convenience, most reactions were performed with 5 mol % of **2a** and 8 equiv of $BrZnCH_2CO_2t$-Bu. As shown in Table 2, the kinetic resolution with chiral ligand **2a** provided excellent levels of asymmetric induction with a variety of β-aryl-β-hydroxy esters **5**–**10**. Most reactions reached 53–59% conversion after 1–1.5 h with the selectivities ranging from 15 to 42. Our most impressive results were obtained with β-*p*-phenylphenyl-β-hydroxy ester **7**, affording a k_{rel} of 42 (entry 3). Thus, the unconverted β-hydroxy esters (*R*)-**5**–**10** with 98–93% ee were obtained in 41–32% isolated yields.

Table 2. Asymmetric dehydration of β-hydroxy esters **5**–**11**



Entry	R	Product	Time (h)	Conversion[a] % (% yield)[b]	% ee[c]	s (k_S/k_R)[d]
1	*m*-MeO–Ph	**5**	1.0	55 (39)	95	23
2	*p*-BnO–Ph	**6**	1.0	58 (32)	98	35
3	*p*-Ph–Ph	**7**	1.5	54 (36)	96	42
4	1-Naph	**8**	1.5	59 (32)	93	15
5	*p*-Me–Ph	**9**	1.0	55 (37)	93	28
6	*p*-Cl–Ph	**10**	1.0	57 (33)	98	22
7	(*E*)-PhCH=CH	**11**	1.5	53 (41)	95	31
8	$PhCH_2CH_2$	**12**	2.0	—	—	—

[a] Determined based on the 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] Isolated yields of unconverted substrates.
[c] The ee values of **5**–**11** are determined by CSP-HPLC. Absolute configurations are assigned by the sign of optical rotation of the isolated products.
[d] Selectivity (s) values represent an average of at least two experiments, while conversion and ee value are for specific cases.

The high selectivity and high activity of this catalyst enabled us to successfully perform a resolution of β-hydroxy esters on a multigram scale. Additionally, to our delight, the resolution of β-(*E*)-styryl substituted ester **11** gave a high level of selectivity (entry 7). At present, R is limited to the aryl and styryl groups. When R was an aliphatic group ($R = PhCH_2CH_2$), no dehydration occurred under the same reaction condition and *rac*-**12** was quantitatively recovered (entry 8).

In summary, we have developed the first efficient catalytic method for the asymmetric dehydration of β-hydroxy esters via kinetic resolution. Asymmetric synthesis of β-hydroxy ester by enantioselective dehydration is conceptually novel and may ultimately lead to new catalysts with higher selectivity and broad synthetic utility. Efforts are currently underway to provide detailed mechanistic insight into the catalytic cycle. The methodology of the present work should also be applicable to asymmetric syntheses of flavanone derivatives.

Acknowledgment

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6. *General procedure for asymmetric dehydration reactions*: 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, 0.5 equiv) in THF (5 ml) was slowly added. The mixture was stirred at reflux for 1–1.5 h and then quenched at 0 °C with satd 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 **3** and **5**–**11**. The enantioselectivities were determined by HPLC using Chiralcel OJ–H column for **3** and **5**–**7**; Chiralcel OB–H for **9** and **10**; Chiralcel OD for **8** and **11** (0.5 ml/min, 2-propanol/hexane).
7. 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 **3** and the conversion (*C*) determined by ^1H NMR of reaction mixture using internal standard.
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