Kinetic resolution via semipinacol rearrangement of α-hydroxy epoxides: a new method for asymmetric synthesis of α-hydroxy epoxides and β-hydroxy ketones containing an α-quaternary carbon

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Abstract—A new method for the enantioselective preparation of β-hydroxy ketones containing a stereogenic quaternary carbon center and tertiary α-hydroxy epoxides has been developed on the basis of kinetic resolution of racemic tertiary α-hydroxy epoxide via semipinacol rearrangement using the chiral catalyst Ti-[(R)/(S)-BINOL]$_2$. The effect of the structure of the migrating group on the enantioselectivity of the reaction is also discussed. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The stereoselective construction of quaternary carbon centers is currently an important subject in organic synthesis.[1] Therefore, developing new methods for the enantioselective construction of quaternary carbon centers is of great interest to research chemists. The preparation of diastereomerically pure tertiary α-hydroxy epoxides is also a challenging problem because the well-known Sharpless Ti-catalyzed asymmetric epoxidation procedure, which is generally highly effective for the preparation of diastereomerically pure primary and secondary α-hydroxy epoxides, is much less efficient in the epoxidation of allylic tertiary alcohols.[2]

When we applied the standard Sharpless epoxidation to allylic tertiary alcohols in the formation of the epoxides **1** and **2** (see Table 2), we observed that the reaction rates were retarded and the reactions occurred with low levels of enantioselectivity. Although Shimazaki et al. obtained enantiomerically pure tertiary α-hydroxy epoxides, the method applied was much more complex.[3]

In our previous work, we have demonstrated a catalytically effective rearrangement of tertiary α-hydroxy epoxides, which is a potential method for the stereocontrolled synthesis of β-hydroxy ketones bearing a quaternary α-carbon center.[4] Within this context, the

discovery that certain Lewis acids can catalyze the rearrangement in an enantioselective fashion prompted us to explore the feasibility of the kinetic resolution of racemic α-hydroxy epoxides using chiral Lewis acid catalysts. We have designed and screened the effective chiral Lewis acid catalysts, Ti-[(R)/(S)-BINOL]$_2$ and we report herein our preliminary experimental results on this subject.[5]

2. Results and discussion

Initially, a series of chiral complexes of (S)-BINOL with Lewis acids, such as TiCl$_2$(O^{i}Pr)$_2$, ZnEt$_2$, TiCl$_4$ etc. were tested using 1,2-epoxycyclohexyldiphenylmethanol **1** as the substrate. The (S)-BINOL-Ti(O^{i}Pr)$_4$ system was found to be the most promising catalyst for the envisaged resolution. To further optimize the experimental conditions, different ratios of (S)-BINOL ligand to Ti(IV), solvents and temperature were tested using **1** as the substrate, and 20 mol% of BINOL-Ti(O^{i}Pr)$_4$ as the catalyst (Scheme 1). The results are summarized in Table 1.
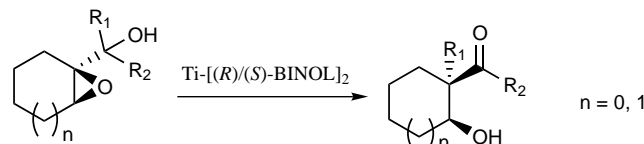
Scheme 1.

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Table 1. Ti-catalyzed kinetic resolution of substrate **1** (1,2-epoxycyclohexyl-diphenylmethanol)

Entry	Catalyst	Solvent	Conv. (%)	Recovered S. M. e.e. (%)	Product e.e. (%)
1	Ti(O^{i}Pr)$_4$/(S)-BINOL[a] (1:1)	PhCH$_3$	53	17	16
2	Ti(O^{i}Pr)$_4$/(S)-BINOL[a] (1:1.5)	PhCH$_3$	57	18	14
3	Ti(O^{i}Pr)$_4$/(S)-BINOL[a] (1:2)	PhCH$_3$	56	30	25
4	Ti(O^{i}Pr)$_4$/(S)-BINOL[a] (1:2.5)	PhCH$_3$	60	35	27
5	Ti(O^{i}Pr)$_4$/(S)-BINOL[a] (1:4)	PhCH$_3$	58	38	31
6	Ti(O^{i}Pr)$_4$/(S)-BINOL[a] (1:2.5)	Et$_2$O	56	30	25
7	Ti(O^{i}Pr)$_4$/(S)-BINOL[a] (1:2.5)	PhH	55	27	24
8	Ti(O^{i}Pr)$_4$/(S)-BINOL[a] (1:2.5)	CH$_2$Cl$_2$	55	29	25
9	Ti(O^{i}Pr)$_4$/(S)-BINOL[b] (1:2.5)	PhCH$_3$	62	93	64
10	Ti(O^{i}Pr)$_4$/(R)-BINOL[b] (1:2.5)	PhCH$_3$	63	94	60

[a] This reaction was carried out with the substrate (0.3 mmol) and the catalyst (20 mol%) in sheet (2 mL) at room temperature.
[b] Reaction condition see Ref. 6.

The data shown in Table 1 indicates that the enantioselectivity is highly dependent on the ratio of ligand to metal. The best result was achieved when 2 or more equivalents of (S)-BINOL was used, which induced the highest e.e. values for both the unreacted α-hydroxy epoxide and the β-hydroxy ketone product (e.g. entries 2 and 3). Screening a number of solvents for the reaction showed that completing the reaction in toluene afforded the best overall results (entry 2).

We also found that the presence of trace amounts of 2-propanol, formed in the reaction of Ti(O^{i}Pr)$_4$ with (S)-BINOL, could strongly decrease the enantioselectivity of the reaction. For example, the reactions in entries 1–8 were carried out under standard conditions, while entries 9 and 10 were performed under vacuum to remove any traces of 2-propanol prior to completing the reaction. A possible reason for this lowered enantioselectivity is that 2-propanol inhibits the coordination of the substrate with the Ti-[(S)-BINOL]$_2$ catalyst by associating more favorably with Ti(IV).

In addition, two kinds of BINOL complexes, Ti-[(R)-BINOL]$_2$ and Ti-[(S)-BINOL]$_2$, were shown to give similar *E* values for this catalytic kinetic resolution.[6] Furthermore, the kinetic resolution can be completed at room temperature as it occurs at moderate rate and too low or high temperature would make the reaction too slow or fast. It is worth noting that BINOL can be easily recovered from the column in 80% yield without racemization, which makes the cost of the chiral catalyst less relevant.

Extension of the reaction to different α-hydroxy epoxides afforded the results collected in Table 2. These results indicate that the *E* value is strongly dependent on the migrating group. For example, entries 1 and 2 bearing two aromatic groups gave the highest *E* values of 11.5 and 10, whereas those with only one aromatic group (e.g. entries 3 and 4 and 7–9) gave moderate *E* values of 3.6–6.5. In particular, entry 9 which involved the α-furyl group also showed lower *E* than those above (entries 3, 4, 7 and 8). Substrates containing two benzyl groups (entries 5 and 6), had lower *E* value than those

with one aromatic group (entries 3, 4, 7 and 8). It was a limitation that entry 10 with the aliphatic group gave the lowest *E* value. So it could be seen that the substrate containing aromatic groups give higher *E* values than those containing aliphatic groups. However, at this time we are unclear what the reason for this difference is. Moreover, it is important to note that one or two recrystallizations of many of the recovered α-hydroxy epoxides could raise the enantiomeric purity to ≥99% e.e. (entries 1–9).

The absolute configuration of the (2S,3S)-β-hydroxy ketone obtained from the resolution of α-hydroxy epoxide **1** (entry 1) was investigated by CD spectroscopy of its benzoyl derivative and consisted of deduction from a molecular model. Though we have not examined the stereochemistry of all of the products in Table 2 one by one, we assume that the other products would have the same absolute configuration.
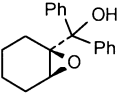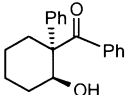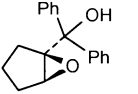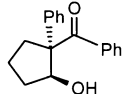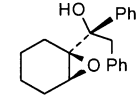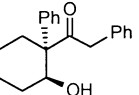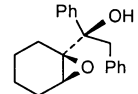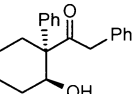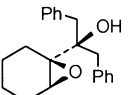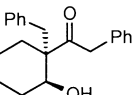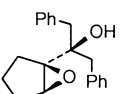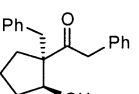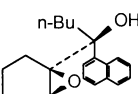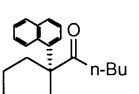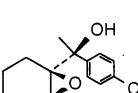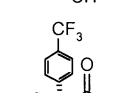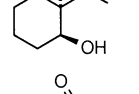
Although the maximum possible yield is 30–40%, the method uses easily accessible racemic starting materials and conversion levels can be manipulated so that completely enantiopure samples of substrate enantiomers are obtained. Further studies on the subject of metal-catalyzed kinetic resolution of α-hydroxy epoxides will focus on the use of different metals and ligands to obtain higher *E* values with different substrates, particularly those containing aliphatic groups.
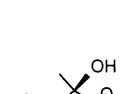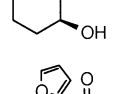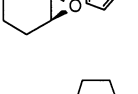
3. Experimental

3.1. General

^{1}H and ^{13}C NMR data were recorded in CDCl$_3$ solution with Brucker AM-400 MHz spectrometers. The chemical shifts are reported in ppm relative to TMS or CDCl$_3$. Column chromatographs were generally performed on silica gel (200–300 mesh) eluting with petroleum ether and EtOAc. Enantiomeric excesses were determined by Agilent 1100 HPLC fitted with Daicel Chiralcel OD, OJ, Daicel Chiralpak AS, AD (4.6×250 mm).

Table 2. Kinetic resolution of α-hydroxy epoxides catalyzed by Ti-[(R)-BINOL]$_2$

Entry	Substrate	Product	Time (h)	Conv. (%)	Recovered S. M. ee (%)	Product e.e. (%)	E^e (K$_f$/K$_s$)
1	**1**[a]		2	63	94	60	11.5
2	**2**[a]		2.5	62	90	61	10
3	**3**[b]		3	64	82	48	6.5
4	**4**[b]		3	65	80	47	5.8
5	**5**[b]		70	69	71	34	3.8
6	**6**[b]		80	69	70	32	3.7
7	**7**[b]		4	65	79	46	5.7
8	**8**[c]		5	67	77	41	4.8
9	**9**[c]		5	64	61	39	3.6
10	**10**[d]		3.5	69	51	24	2.5

Recrystallization conditions: [a] hexane [b] hexane and EtOAc [c] hexane, -20 °C.

[d] 40 mol% catalyst used.

[e] The relative rate was calculated using the equation $E = K_f/K_s = \ln[(1-C)(1-e.e.)]/\ln[(1-C)(1+e.e.)]$, where C is the conversion and e.e. is the percent enantiomeric excess of the recovered starting material.[6]

3.2. General procedures for kinetic resolution

NOTE: The reaction is moisture sensitive and needs to be carried out under rigorously anhydrous conditions.

To a solution of (S)-BINOL (42.9 mg, 0.15 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added a solution of Ti(O^{i}Pr)$_4$ (18.2 μL, 17.3 mg, 0.06 mmol). Upon stirring at room temperature for 10–14 h, the reaction mixture was concentrated and dried using a vacuum pump (ca. 2 h). The catalyst was then dissolved in PhCH$_3$ (1 mL). To this solution was added a solution of racemic 1,2-epoxycyclohexyl-diphenylmethanol (84 mg, 0.3 mmol) in PhCH$_3$ (0.5 mL). After stirring 2 h, the reaction

mixture was quenched with saturated $NaHCO_3$ solution (3 mL) and poured into a mixture of ether (10 mL) and saturated $NaHCO_3$ solution (5 mL). The organic layer was washed with water and brine, dried (Na_2SO_4) (ca. 10 min), and rapidly filtered through a plug of silica gel (pre-treated with Et_3N in petroleum ether and thoroughly washed with petroleum ether to remove Et_3N before use). The silica gel was washed with Et_2O. The combined ether solutions were concentrated to give a mixture of 1,2-epoxycyclohexyl-diphenylmethanol and 2-benzoyl-2-phenylcyclohexan-1-ol. After a sample was taken for determination of the conversion and e.e. the mixture was purified by silica gel chromatography (silica gel was pre-treated with Et_3N) using petroleum ether–EtOAc as eluent to afford a white solid (31 mg), then recrystallized from hexane.

Acknowledgements

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