

Communications to the Editor

Complete Conversion of Racemic Enol Ester Epoxides into Optically Active α -Acyloxy Ketones

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






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Enol ester epoxides can rearrange to α -acyloxy ketones or aldehydes under acidic conditions.^{1,2} Both protic and Lewis acids can catalyze this rearrangement.³ In a study of acid-catalyzed rearrangements of enantiomerically enriched enol ester epoxides, we found that this rearrangement operated through two distinct pathways, one with retention of configuration and the other with inversion (Scheme 1).³ Competition between the two pathways depended on the nature of the acid catalyst. The discovery that certain Lewis acids can catalyze the rearrangement in a stereospecific fashion prompted us to explore the feasibility of kinetically resolving a racemic enol ester epoxide using a chiral Lewis acid catalyst (Scheme 2). Herein we report our preliminary studies in this area.

Our studies started with racemic 1-benzoyloxy-1,2-epoxycyclohexane (**1**) as a test substrate (Scheme 3). Among many chiral Lewis acids tested, a BINOL-Ti(OⁱPr)₄ system⁴ was found to be the most promising catalyst for the envisioned resolution. Treating epoxide **1** with 5 mol % [(*R*)-BINOL]₂-Ti(OⁱPr)₄ (**3**) in Et₂O at 0 °C for 0.5 h led to a 52% conversion, as judged by ¹H NMR assay of the crude reaction mixture. Analysis of the unreacted epoxide and the rearranged product using chiral HPLC (Chiralcel OD) revealed a 99% ee for the epoxide and an 89% ee for 2-benzoyloxycyclohexanone (**2**). Both the recovered epoxide and the rearranged ketone were determined to be enriched in the *R* isomer, revealing that the *S* isomer of epoxide **1** had rearranged to the *R* isomer of **2**. Therefore, the rearrangement occurred with inversion of configuration.

Further studies showed that the ratio of ligand to metal was important for both the reactivity and the selectivity. The best results were obtained when 2 equiv or more of BINOL was used per Ti. A solvent study showed that Et₂O and CH₂Cl₂ provided the best overall results. To test the effect of the ester group on the reaction, a number of ester groups with different steric and

Table 1. Kinetic Resolution of Enol Ester Epoxides Catalyzed by [(*R*)-BINOL]₂-Ti(OⁱPr)₄^d

entry	substrate	time (h)	conv. (%) ^b	recov'd S.M.ee (%)	epoxide yield ^c (%)	product ee%	<i>k</i> _{rel} ^d (<i>k</i> _f / <i>k</i> _s)
1 ^e		1.0	50	97 ⁱ (<i>R</i>) ^m	34	90 ⁱ (<i>R</i>) ^o	>100
2	R = <i>p</i> -CH ₃ Ph	0.5	50	99 ^j	34	84 ⁱ (<i>R</i>) ^o	>100
3	R = <i>m</i> -CH ₃ Ph	0.4	53 ^h	97 ^j	36	87 ⁱ	55
4	R = <i>p</i> -ClPh	0.5	52	99 ^j	32	87 ⁱ (<i>R</i>) ^o	>100
5	R = <i>p</i> -NO ₂ Ph	2.2	49	96 ^j	39	96 ⁱ (<i>R</i>) ^o	>100
6	R = 3,5-Me ₂ Ph	0.6	53	99 ^k	35	83 ⁱ	80
7	R = 2,6-Me ₂ Ph	1.7	50	99 ^k	37	90 ⁱ	>100
8	R = 1-Naph.	0.9	52 ^h	98 ^k	33	91 ⁱ	91
9 ^e	R = ^t Bu	0.6	54	97 ^l (<i>R</i>) ^m	22	88 ⁱ (<i>R</i>) ^o	43
10	R = Me	1.2	68	85 ⁱ (<i>R</i>) ^m		48 ⁱ (<i>R</i>) ^o	6
11 ^f		24	51 ^h	98 ^j	33	93 ⁱ	>100
12		3.0	55	99 ^k (<i>R</i>) ^m	33	89 ⁱ (<i>R</i>) ^p	49
13		6.5	54	98 ⁱ (<i>R</i>) ^m	34	80 ⁱ (<i>R</i>) ^q	50
14 ^g		68.5	63	97 ^k (<i>R</i>) ^m	32	71 ^k (<i>R</i>) ^p	14
15		3.0	69	99 ⁱ (<i>R</i>) ⁿ	30	50 ⁱ (<i>R</i>) ⁿ	12
16 ^g		163	58	54 ⁱ		38 ⁱ	4

^a All reactions were carried out with substrate (0.5 mmol) and catalyst (5 mol %) in solvent (2 mL) at 0 °C unless otherwise noted. ^b The conversion was determined by ¹H NMR of the crude reaction mixture after workup. ^c Isolated yield. ^d The relative rate was calculated using the equation $k_{rel} = k_f/k_s = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where *C* is the conversion and *ee* is the percent enantiomeric excess of the recovered starting material.⁸ ^e 2.5 mol % catalyst used. ^f 10 mol % catalyst used. ^g 20 mol % catalyst used. For entry 16, the reaction was carried out at room temperature. ^h The conversion was calculated by applying the ee's of the recovered starting material and the product to the following equation: $ee(\text{SM})/ee(\text{product}) = C/(1 - C)$. ⁱ Enantioselectivity was determined by chiral HPLC (Chiralcel OD). ^j Enantioselectivity was determined by chiral HPLC (Chiralpak AD). ^k Enantioselectivity was determined by chiral HPLC (Chiralcel OJ). ^l Enantioselectivity was determined by ¹H NMR shift analysis with Eu(hfc)₃. ^m The absolute configurations were assigned by comparing the measured optical rotations with those of the epoxides obtained by asymmetric epoxidation.⁹ ⁿ The absolute configurations were assigned by comparing HPLC chromatograms with those of the enol ester epoxide obtained by asymmetric epoxidation⁹ and the α -benzoyloxy ketone obtained from a stereospecific rearrangement of the chiral enol ester epoxide.³ ^o The absolute configurations were determined by comparing the measured optical rotations with those of the authentic samples prepared from commercially available (*R,R*)-1,2-*trans*-cyclohexanediol. ^p The absolute configurations were assigned on the basis of the epoxide configurations and the mechanistic deduction from the transformations of Scheme 4. ^q The absolute configuration was determined by comparing the measured optical rotation with the reported one.³

electronic properties were investigated. As shown in Table 1 (entries 1–10), good reactivity and selectivity were obtained in all cases except for acetate (entry 10), suggesting that a wide range of ester groups can be tolerated.

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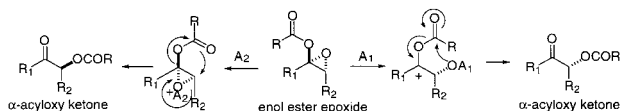
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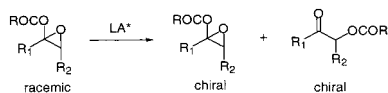
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(4) For leading references on BINOL-Ti catalyzed asymmetric processes, see: (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940. (b) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. (c) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (d) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (e) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363. (f) Faller, J. W.; Sams, D. W. I.; Liu, X. *J. Am. Chem. Soc.* **1996**, *118*, 1217. (g) Gauthier, D. R., Jr.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363.

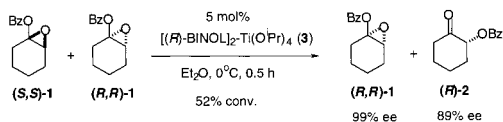
Scheme 1



Scheme 2



Scheme 3

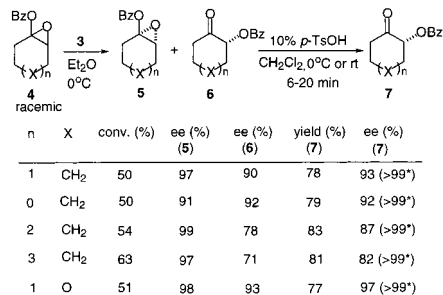


Encouraged by the result obtained for the six-membered ring epoxides (Table 1, entries 1–11), we prepared and investigated a number of other enol ester epoxides to probe their behavior under the current catalyst conditions. As shown in Table 1, this resolution process could be extended to five-, seven-, and eight-membered ring systems (Table 1, entries 12–14). In all these cases, the recovered enol ester epoxides could be obtained with high ee's, and the pure epoxides could be isolated in reasonable yields. Compared to the other ring systems, the eight-membered system was substantially less reactive, requiring more catalyst and a longer reaction time. In contrast to the cyclic epoxides, the current catalyst system is not effective for acyclic epoxides (Table 1, entry 16).

As discussed above (Scheme 3), the rearrangements occurred with inversion of configuration. As a result, the remaining epoxide and the rearranged α -acyloxy ketone had the same configuration at C₂. It was envisioned that the remaining epoxide might be further converted into the rearranged α -acyloxy ketone using an achiral acid which would catalyze the rearrangement with retention of configuration.³ This could then provide a high yield (>50%) of enantiomerically enriched α -acyloxy ketone. To test this hypothesis, **1** was again used as a substrate. After the resolution reaction was quenched at the desired conversion, the chiral catalyst was removed by a rapid filtration through a plug of silica gel. The resulting mixture was subsequently treated with 10% *p*-TsOH at room temperature for 20 min,⁵ at which time the epoxide was completely consumed, and the 2-benzoyloxycyclohexanone was then isolated in 78% overall yield with 93% ee (Scheme 4)! The ee could be further enhanced to >99% by a single recrystallization from Et₂O. As shown in Scheme 4, this sequential process could also be extended to other substrates. *The overall result is that a racemic enol ester epoxide can be completely converted into an enantiomerically enriched α -acyloxy*

(5) In the case of the five-membered ring, the transformation was carried out at 0 °C for 6 min. Higher temperature and longer reaction time could lead to partial racemization of 2-benzoyloxycyclopentanone.

Scheme 4



* the ee's after recrystallization

*ketone using a catalytic amount of a chiral Lewis acid, followed by a catalytic amount of an achiral acid.*⁶

In summary, we have shown that the kinetic resolution of racemic enol ester epoxides using a chiral Lewis acid catalyst is feasible. High resolution efficiency was obtained for a number of cyclic systems. Both enantiomerically enriched enol ester epoxides and α -acyloxy ketones could be obtained through this resolution. By taking advantage of the mechanistic duality of the acid-catalyzed enol ester epoxide rearrangement, a racemic enol ester epoxide can be completely converted into an enantiomerically enriched α -acyloxy ketone by sequential treatment with a catalytic amount of a chiral Lewis acid and a catalytic amount of an achiral acid.⁷ Future efforts will be devoted to further understanding the difference between cyclic and acyclic epoxides and searching for effective catalysts for acyclic systems.

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Supporting Information Available: Characterization of enol ester epoxides and α -acyloxy ketones along with the NMR spectral and HPLC data for the determination of the enantiomeric excess of these compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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