# Chiral Lewis Acid Catalyzed Resolution of Racemic Enol Ester Epoxides. Conversion of Both Enantiomers of an Enol Ester Epoxide to the Same Enantiomer of Acyloxy Ketone

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This paper describes an efficient kinetic resolution of racemic enol ester epoxides via a chiral Lewis acid catalyzed rearrangement. Both enantiomerically enriched enol ester epoxides and α-acyloxy ketones can be obtained through this resolution. A positive nonlinear effect is observed in this process. By taking advantage of the mechanistic duality in acid-catalyzed enol ester epoxide rearrangement, we can completely convert a racemic enol ester epoxide into an enantiomerically enriched α-acyloxy ketone by treatment with a catalytic amount of a chiral Lewis acid followed by a catalytic amount of an achiral protic acid.

The rearrangement of enol ester epoxides to α-acyloxy ketones or aldehydes can be promoted by both protic and Lewis acids.[1−3] Studies of such rearrangements with enantiomerically enriched enol ester epoxides have revealed that the rearrangement can proceed either via retention of configuration or inversion by judicious choice of acid catalysts (Scheme 1).[3] The strength of the acid catalyst is an important factor for the stereochemical outcome of the rearrangement, with strong acids favoring retention of configuration and weak acids favoring inversion. Recently, we have shown that a racemic enol ester epoxide can be kinetically resolved to give an enantiomerically enriched epoxide and α-acyloxy ketone when a chiral Lewis acid catalyst is used (Scheme 2).[4] In a further study of this resolution, we observed a positive nonlinear effect. Herein we wish to report our detailed studies on this resolution process.

## Results and Discussion

**BINOL−Ti Catalyzed Kinetic Resolution of Enol Ester Epoxides.** The kinetic resolution of enol ester epoxides started with racemic 1-(benzoyloxy)-1,2-epoxycyclohexane (**1**) as a test substrate (Scheme 3). A variety of chiral Lewis acids were investigated. Chart 1 lists some of the chiral ligands and acids. A wide variety of metals, including $Ti(O^iPr)_4$, $TiF_4$, $Al(O^iPr)_3$, $Zr(OEt)_4$, $Sc(O^iPr)_4$, $SnCl_4$, and $Cu(OAc)_2$, were used with the chiral ligands. With almost every catalyst generated, less than 5% conversion was obtained after the reaction was run for 20 h, except for a BINOL−$Ti(O^iPr)_4$ system,[5] which was found to be the most promising catalyst for the resolution in terms of both reactivity and selectivity. Treating epoxide **1** with 5 mol % [(*R*)-BINOL]$_2$−$Ti(O^iPr)_4$ (**16**) in $Et_2O$ at 0 °C for 0.5 h led to a 52% conversion, as judged by $^1$H 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-(benzoyloxy)cyclohexanone (**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.[5e,6] The solvent study indicated that $Et_2O$ and $CH_2Cl_2$ gave the best overall

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(1) For leading reviews on enol ester epoxide rearrangements see: (a) McDonald, R. N. *Mech. Mol. Migr.* **1971**, *3*, 67. (b) Riehl, J.-J.; Casara, P.; Fourgerousse, A. *C.R. Acad. Sci. Paris, Ser. C* **1974**, *279*, 79.

(2) For examples of acid-catalyzed rearrangements of enol ester epoxides see: (a) Soloway, A. H.; Considine, W. J.; Fukushima, D. K.; Gallagher, T. F. *J. Am. Chem. Soc.* **1954**, *76*, 2941. (b) Leeds, N. S.; Fukushima, D. K.; Gallagher, T. F. *J. Am. Chem. Soc.* **1954**, *76*, 2943. (c) Gardner, P. D. *J. Am. Chem. Soc.* **1956**, *78*, 3421. (d) Johnson, W. S.; Gastambide, B.; Pappo, R. *J. Am. Chem. Soc.* **1957**, *79*, 1991. (e) Nambara, T.; Fishman, J. *J. Org. Chem.* **1962**, *27*, 2131. (f) Rhone, J. R.; Huffman, M. N. *Tetrahedron Lett.* **1965**, 1395. (g) Williamson, K. L.; Coburn, J. I.; Herr, M. F. *J. Org. Chem.* **1967**, *32*, 3934.

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(6) The $^1$H NMR showed that all $O^iPr$ groups on Ti had been replaced by BINOL when 2 equiv of BINOL was used per Ti. However, the actual structure of catalytic species responsible for the current resolution is not very clear at the moment.

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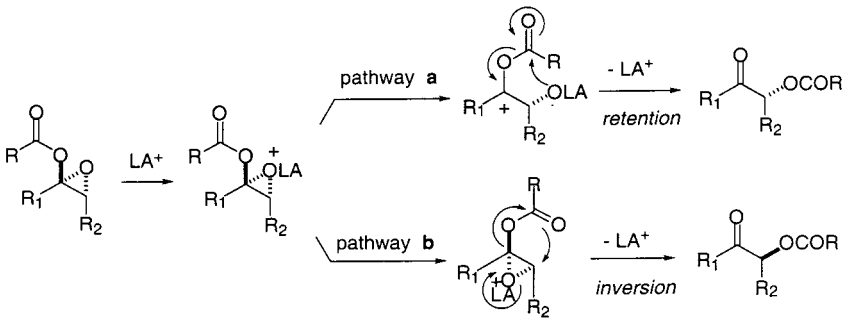
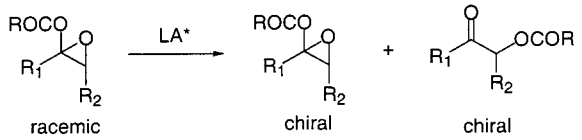
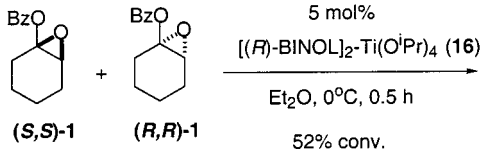
**Scheme 1**




**Scheme 2**




**Scheme 3**



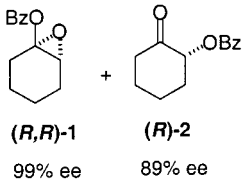
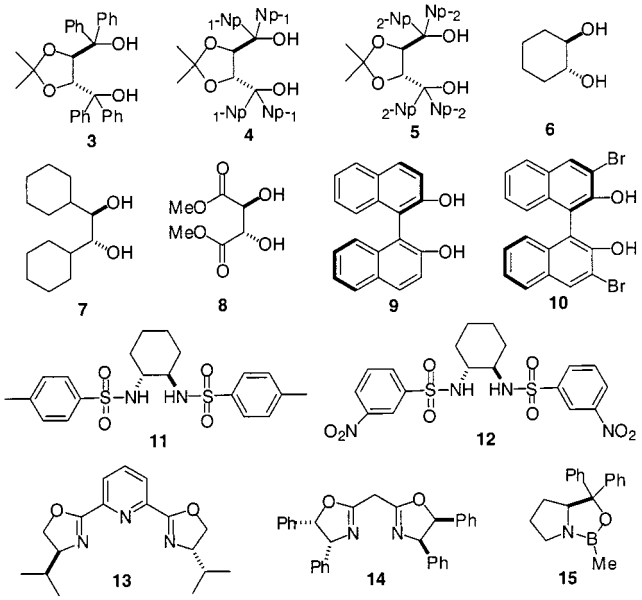




**Chart 1**




results (Table 1). To test the effect of the ester group on the reaction, a number of esters with different steric and electronic properties were investigated. As shown in Table 2 (entries 1−10), good reactivity and selectivity were obtained in all cases except for acetate (entry 10), suggesting that a wide range of esters can be tolerated. This resolution process could also be extended to five-, seven-, and eight-membered-ring systems (Table 2, entries 13−15). 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. However, the current catalyst system is not effective for acyclic epoxides (Table 2, entry 17). Many of these enol ester epoxides can be obtained in high ee by the asymmetric epoxidation of enol esters.[3] However, a distinct feature of current kinetic resolution is that, in principle, extremely high ee's for enol ester epoxides can be obtained by adjusting the reaction conversion.

**Table 1. Solvent Effects on Kinetic Resolution of Epoxide 1**[a]

| entry | solvent | conv, %[b] | recovered SM ee, %[c] | product ee, %[c] |
|---|---|---|---|---|
| 1 | $Et_2O$ | 50 | 95 (*R*) | 87 (*R*) |
| 2 | $^tBuOMe$ | 56 | 89 (*R*) | 69 (*R*) |
| 3 | $^iPr_2O$ | 46 | 86 (*R*) | 90 (*R*) |
| 4 | THF | 6 | 0.5 (*R*) | 13 (*R*) |
| 5 | THP | 4 | 3 (*R*) | 46 (*R*) |
| 6 | $CH_2Cl_2$ | 52 | 94 (*R*) | 86 (*R*) |
| 7 | $CHCl_3$ | 19 | 17 (*R*) | 71 (*R*) |
| 8 | $ClCH_2CH_2Cl$ | 51 | 78 (*R*) | 80 (*R*) |
| 9 | PhH | 22 | 21 (*R*) | 69 (*R*) |

[a] All reactions were carried out with substrate (0.5 mmol) and catalyst (5 mol %) in solvent (3 mL) at 0 °C for 0.5 h. [b] The conversion was determined by $^1H$ NMR of the crude reaction mixture after workup. [c] Enantioselectivity was determined by chiral HPLC (Chiralcel OD).

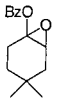
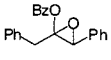
**Nonlinear Effect of the Kinetic Resolution of Enol Ester Epoxides.** Asymmetric amplification has been widely observed in asymmetric catalysis.[7,8] High ee's can be obtained for the reaction products when catalysts with marginal ee's are employed. The nonlinear effects of the BINOL−Ti system for various asymmetric processes have been reported.[5] To gain more insight about the catalyst structure in this resolution, nonlinear effects were then investigated. Table 3 lists the results for the kinetic resolution of 1-(benzoyloxy)-1,2-epoxy-4,4-dimethylcyclohexane (**17**) using the BINOL−Ti catalyst with different ee's. As shown in Table 3, high-resolution efficiency can still be obtained with low ee's of the catalyst, suggesting that some asymmetric amplification exists in this resolution.

Although nonlinear effects have been extensively studied in asymmetric catalysis,[7] such studies for kinetic

(7) For reviews see: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed.* **1991**, *30*, 49. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997. (c) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922.

(8) (a) Ismagilov, R. F. *J. Org. Chem.* **1998**, *63*, 3772. (b) Luukas, T. O.; Girard, C.; Fenwick, D. R.; Kagan, H. B. *J. Am. Chem. Soc.* **1999**, *121*, 9299. (c) Johnson, D. W., Jr.; Singleton, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 9307. (d) Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 545. (e) Kagan, H. B. *Synlett* **2001**, 888.

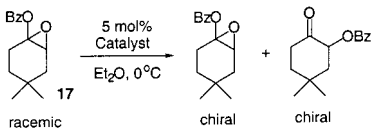
**Table 2. Kinetic Resolution of Enol Ester Epoxides Catalyzed by [(*R*)-BINOL]$_2$−Ti(O$^i$Pr)$_4$[a]**

| entry | substrate | time (h) | conv. (%)[b] | recov'd S.M.ee (%) | epoxide yield[c] (%) | product ee% | $k_{rel}$[d] ($k_f/k_s$) |
|---|---|---|---|---|---|---|---|
| |  | | | | | | |
| 1[e] | R = Ph | 1.0 | 50 | 97[i] (*R*)[m] | 34 | 90[i] (*R*)[o] | >100 |
| 2 | R = *p*-$CH_3$Ph | 0.5 | 50 | 99[j] | 34 | 84[j] (*R*)[o] | >100 |
| 3 | R = *m*-$CH_3$Ph | 0.4 | 53[h] | 97[j] | 36 | 87[j] | 55 |
| 4 | R = *p*-ClPh | 0.5 | 52 | 99[j] | 32 | 87[j] (*R*)[o] | >100 |
| 5 | R = *p*-$NO_2$Ph | 2.2 | 49 | 96[j] | 39 | 96[j] (*R*)[o] | >100 |
| 6 | R = 3,5-$Me_2$Ph | 0.6 | 53 | 99[k] | 35 | 83[j] | 80 |
| 7 | R = 2,6-$Me_2$Ph | 1.7 | 50 | 99[k] | 37 | 90[j] | >100 |
| 8 | R = 1-Napth. | 0.9 | 52[h] | 98[k] | 33 | 91[j] | 91 |
| 9[e] | R = $^t$Bu | 0.6 | 54 | 97[l] (*R*)[m] | 22 | 88[l] (*R*)[o] | 43 |
| 10 | R = Me | 1.2 | 68 | 85[j] (*R*)[m] | -- | 48[j] (*R*)[o] | 6 |
| 11 |  | 2.0 | 54 | 99[j] | 40 | 91[j] | 61 |
| 12[f] |  | 24 | 51[h] | 98[j] | 33 | 93[i] | >100 |
| 13 |  | 3.5 | 55 | 99[k] (*R*)[m] | 33 | 89[i] (*R*)[p] | 49 |
| 14 |  | 6.5 | 54 | 98[i] (*R*)[m] | 34 | 80[i] (*R*)[q] | 50 |
| 15[g] |  | 68.5 | 63 | 97[k] (*R*)[m] | 32 | 71[k] (*R*)[p] | 14 |
| 16 |  | 3.0 | 69 | 99[i] (*R*)[n] | 30 | 50[i] (*R*)[n] | 12 |
| 17[g] |  | 163 | 58 | 54[i] | -- | 38[j] | 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 $^1$H 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 fractional enantiomeric excess of the recovered starting material.[13] [e] 2.5 mol % catalyst used. [f] 10 mol % catalyst used. [g] 20 mol % catalyst used. For entry 17, 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(SM)/ee(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 $^1$H NMR shift analysis with Eu(hfc)$_3$. [m] The absolute configurations were assigned by comparing the measured optical rotations with the epoxides obtained by asymmetric epoxidation.[3] [n] The absolute configurations were assigned by comparing HPLC chromatograms with the enol ester epoxide obtained by asymmetric epoxidation[3] 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 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 5. [q] The absolute configuration was determined by comparing the measured optical rotation with the reported one.[3]

resolutions are relatively few. A nonlinear effect for the kinetic resolution of sulfoxides was reported by Uemura and co-workers in 1993.[5h] In their studies, the positive nonlinear effect was illustrated by the plots of the ee of the sulfoxide and $k_{rel}$ ($k_f/k_s$) versus the ee of BINOL. Recently, various mathematical analyses for the kinetic resolution using enantioimpure catalysts have been reported by Ismagilov, Kagan, Singleton, and Blackmond.[8] For example, in the model presented by Johnson and Singleton, a plot of DKEE versus the ee of the catalyst is used, where DKEE stands for differential kinetic enantiomeric enhancement (DKEE = $(k_{rel} - 1)/(k_{rel} + 1)$). The nonlinear effect is defined for a process if DKEE does not vary linearly with the ee of the catalyst. This model was then applied to the kinetic resolution of enol ester epoxide **17**. As shown in Figure 1, a positive nonlinear effect was indeed displayed when the DKEE was plotted against the ee of the catalyst. A similar effect was also observed for two additional substrates, 1-(benzoyloxy)-1,2-epoxycyclohexane and 1-(benzoyloxy)-1,2-

**Table 3. Studies of the Nonlinear Effect of the Kinetic Resolution of Enol Ester Epoxide 17 Catalyzed by $(BINOL)_2-Ti(O^iPr)_4$[a]**




| entry | catalyst ee, % | conv, %[b] | recovered SM ee, %[c] | product ee, %[c] | $k_{rel}$ |
|---|---|---|---|---|---|
| 1 | 100 | 52 | 98 | 92 | 91 |
| 2 | 90 | 54 | 99 | 84 | 61 |
| 3 | 70 | 54 | 98 | 87 | 50 |
| 4 | 50 | 56 | 95 | 72 | 25 |
| 5 | 40 | 57 | 93 | 68 | 19 |
| 6 | 30 | 69 | 92 | 40 | 7 |
| 7 | 20 | 65 | 68 | 33 | 4 |
| 8 | 10 | 82 | 42 | 10 | 2 |
| 9 | 0 | 67 | 0 | 0 | 1 |

[a] All reactions were carried out with substrate (0.25 mmol) and catalyst (5 mol %) in solvent (1 mL) at 0 °C. The BINOL ligand with different ee's was prepared by mixing (*R*)-BINOL with (±)-BINOL. The ligand to metal ratio was 2.2:1. [b] The conversion was determined by $^1H$ NMR of the crude reaction mixture after workup. [c] Enantioselectivity was determined by chiral HPLC (Chiralpak AD).

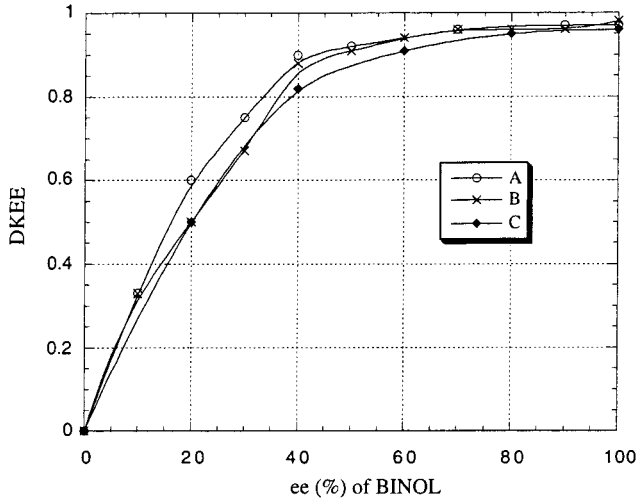
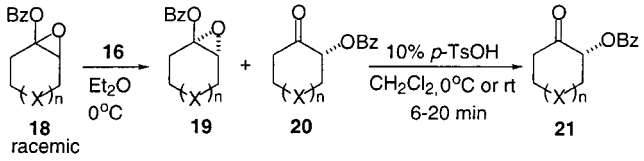



**Figure 1.** Plot of DKEE against ee (%) of BINOL: (A) 1-(benzoyloxy)-1,2-epoxy-4,4-dimethylcyclohexane; (B) 1-(benzoyloxy)-1,2-epoxycyclohexane; (C) 1-(benzoyloxy)-1,2-epoxycycloheptane.

epoxycycloheptane (Figure 1). These nonlinear effects suggest that the active catalyst contains two or more BINOL ligands.[9]

**Complete Conversion of Racemic Enol Ester Epoxides into Optically Active α-Acyloxy Ketones.** In the current kinetic resolution, the remaining epoxide and the rearranged α-acyloxy ketone had the same configuration at $C_2$, since the rearrangement of the enol ester epoxide occurred with inversion of configuration (Scheme 3). It would be possible that a high yield (>50%) of enantiomerically enriched α-acyloxy ketone could be obtained if the proper achiral acid is used to convert the remaining epoxide into the α-acyloxy ketone with retention of configuration.[3] This hypothesis was tested with 1-(benzoyloxy)-1,2-epoxycyclohexane (**1**). 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,[10] at which time the epoxide was completely consumed and the 2-(benzoyloxy)cyclohexanone 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 $Et_2O$. 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 ketone using a catalytic amount of a chiral Lewis acid followed by a catalytic amount of an achiral protic acid.[11]

**Scheme 4**




| n | X | conv. (%) | ee (%) (**19**) | ee (%) (**20**) | yield (%) (**21**) | ee (%) (**21**) |
|---|---|---|---|---|---|---|
| 1 | $CH_2$ | 50 | 97 | 90 | 78 | 93 (>99*) |
| 0 | $CH_2$ | 50 | 91 | 92 | 79 | 92 (>99*) |
| 2 | $CH_2$ | 54 | 99 | 78 | 83 | 87 (>99*) |
| 3 | $CH_2$ | 63 | 97 | 71 | 81 | 82 (>99*) |
| 1 | O | 51 | 98 | 93 | 77 | 97 (>99*) |

* the ee's after recrystallization

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 can be obtained. A positive nonlinear effect was observed in this resolution, suggesting that multiple ligands are

(9) Caution needs to be taken with regard to this nonlinear effect due to the possible kinetic partitioning effect (for a detailed discussion, see ref 8d).

(10) 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-(benzoyloxy)cyclopentanone.

(11) For examples of synthesis of enantiomerically enriched hydroxy ketones and their derivatives see: (a) Enders, D.; Bhushan, V. *Tetrahedron Lett.* **1988**, *29*, 2437. (b) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679. (c) DeNinno, M. P.; Perner, R. J.; Lijewski, L. *Tetrahedron Lett.* **1990**, *31*, 7415. (d) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. (e) Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 5067. (f) Reddy, D. R.; Thornton, E. R. *J. Chem. Soc., Chem. Commun.* **1992**, 172. (g) Duh, T.-H.; Wang, Y.-F.; Wu, M.-J. *Tetrahedron: Asymmetry* **1993**, *4*, 1793. (h) D'Accolti, L.; Detomaso, A.; Fusco, C.; Rosa, A.; Curci, R. *J. Org. Chem.* **1993**, *58*, 3600. (i) Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669. (j) Gala, D.; DiBenedetto, D. J.; Clark, J. E.; Murphy, B. L.; Schumacher, D. P.; Steinman, M. *Tetrahedron Lett.* **1996**, *37*, 611. (k) Adam, W.; Diaz, M. T.; Fell, R. T.; Saha-Moller, C. R. *Tetrahedron: Asymmetry* **1996**, *7*, 2207. (l) Fududa, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4389. (m) Naemura, K.; Wakebe, T.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 2585. (n) Adam, W.; Fell, R. T.; Stegmann, V. R.; Saha-Moller, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 708. (o) Adam, W.; Fell, R. T.; Saha-Moller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1998**, *9*, 397. (p) Kajiro, H.; Mitamura, S−i.; Mori, A.; Hiyama, T. *Tetrahedron: Asymmetry* **1998**, *9*, 907. (q) Demir, A. S.; Hamamci, H.; Tanyeli, C.; Akhmedov, I. M.; Doganel, F. *Tetrahedron: Asymmetry* **1998**, *9*, 1673. (r) Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1999**, *40*, 1689. (s) Adam, W.; Saha-Moller, C. R.; Zhao, C.-G. *J. Org. Chem.* **1999**, *64*, 7492.

interacting with the Lewis acid. These results are also supported by observation that a 2/1 ligand/metal ratio gave the best results. 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 protic acid.[12]

## Experimental Section

The general experimental information is similar to those recently described.[14]

**Representative Procedures for Kinetic Resolution. A. Preparation of Enantiomerically Enriched Enol Ester Epoxide.** (Note: the reaction is moisture sensitive and needs to be carried out under rigorously anhydrous conditions.) To a solution of (*R*)-(+)-binaphthol (7.9 mg, 0.0275 mmol) in $CH_2Cl_2$ (0.5 mL) was added a solution of $Ti(O^iPr)_4$ (3.8 uL, 3.6 mg, 0.0125 mmol) in $CH_2Cl_2$ (0.5 mL). After it was stirred at room temperature for 5−10 h, the reaction mixture was concentrated and dried using a vacuum pump (ca. 0.5 h). The catalyst was then dissolved in $Et_2O$ (1 mL) and cooled in an ice bath. To this was added a solution of racemic 1-(benzoyloxy)-1,2-epoxycyclohexane (0.109 g, 0.5 mmol) in $Et_2O$ (1 mL). After it was stirred at 0 °C for 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ (4 mL) and poured into a mixture of ether (20 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was washed with water and brine, dried ($Na_2SO_4$) (ca. 10 min), and then rapidly filtered through a plug of silica gel (ca. 10 g) (pretreated with 5% $Et_3N$ in hexane and washed thoroughly with hexane to remove $Et_3N$ before use). The silica gel was further washed with $Et_2O$ (10 mL). The combined ether solutions were concentrated to give a mixture of (*R*)-1-(benzoyloxy)-1,2-epoxycyclohexane and (*R*)-2-(benzoyloxy)cyclohexanone. After a sample was taken for the determination of the conversion and ee's, the mixture was purified by flash chromatography (silica gel was pretreated with 5% $Et_3N$) using hexane−$CH_2Cl_2$−EtOAc (84:10:6) as eluent to afford (*R*)-1-(benzoyloxy)-1,2-epoxycyclohexane as a colorless oil (0.0365 g, 34% yield, 97% ee) (Table 2, entry 1) (Note: for the isolation of the enol ester epoxides, $Et_3N$ is used to buffer the silica gel to prevent any decomposition and rearrangement of the epoxides. Under these isolation conditions, the α-acyloxy ketones undergo partial racemization. Therefore, a better way to prepare these α-acyloxy ketones is through kinetic resolution, followed by conversion, as illustrated in the following procedure.)

**B. Preparation of Enantiomerically Enriched α-Acyloxy Ketone.** (Note: the reaction is moisture sensitive and needs to be carried out under rigorously anhydrous conditions.) To a solution of (*R*)-(+)-binaphthol (7.9 mg, 0.0275 mmol) in $CH_2Cl_2$ (0.5 mL) was added a solution of $Ti(O^iPr)_4$ (3.8 uL, 3.6 mg, 0.0125 mmol) in $CH_2Cl_2$ (0.5 mL). After it was stirred at room temperature for 5−10 h, the reaction mixture was concentrated and dried using a vacuum pump (ca. 0.5 h). The catalyst was then dissolved in $Et_2O$ (1 mL) and cooled in an ice bath. To this was added a solution of racemic 1-(benzoyloxy)-1,2-epoxycyclohexane (0.109 g, 0.5 mmol) in $Et_2O$ (1 mL). After it was stirred at 0 °C for 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ (4 mL) and poured into a mixture of ether (20 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was washed with water and brine, dried ($Na_2SO_4$), and rapidly filtered through a plug of silica gel (ca. 10 g) (pretreated with 5% $Et_3N$ in hexane and thoroughly washed with hexane to remove $Et_3N$ before use). The silica gel was further washed with $Et_2O$ (10 mL). The combined ether solutions were concentrated to give a residue. After it was dried under vacuum for 1 h, the mixture was dissolved in $CH_2Cl_2$ (4 mL) followed by addition of anhydrous *p*-TsOH (8.6 mg, 0.05 mmol). After it was stirred at room temperature for 20 min, the mixture was rapidly filtered through a plug of silica gel (ca. 10 g) (without $Et_3N$ treatment) followed by washing with ether (2 × 10 mL). The combined solutions were concentrated to give (*R*)-2-(benzoyloxy)cyclohexanone as a white solid (0.0845 g, 78% yield, 93% ee) (Scheme 4).

**1-(Benzoyloxy)-1,2-epoxycyclohexane (Table 2, Entry 1).**[3,15,16] $[\alpha]^{25}_D = -36.3°$ (*c* 0.49, $CHCl_3$) (97% ee).

**1-((*p*-Methylbenzoyl)oxy)-1,2-epoxycyclohexane (Table 2, Entry 2).**[3] $[\alpha]^{25}_D = -30.7°$ (*c* 0.45, $CHCl_3$) (99% ee).

**1-((*m*-Methylbenzoyl)oxy)-1,2-epoxycyclohexane (Table 2, Entry 3).** $[\alpha]^{25}_D = -31.3°$ (*c* 0.44, $CHCl_3$) (97% ee). IR (NaCl): 1725 $cm^{-1}$. $^1H$ NMR: $\delta$ 7.86−7.79 (m, 2H), 7.40−7.28 (m, 2H), 3.41 (m, 1H), 2.39 (s, 3H), 2.34 (dt, $J$ = 14.4, 6.6 Hz, 1H), 2.22 (dt, $J$ = 14.4, 6.3 Hz, 1H), 2.07−1.86 (m, 2H), 1.58−1.49 (m, 2H), 1.48−1.38 (m, 2H). $^{13}C$ NMR: $\delta$ 165.5, 138.4, 134.3, 130.4, 129.5, 128.5, 127.1, 83.6, 59.6, 28.4, 25.0, 21.5, 20.6, 19.1. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.38; H, 6.95. Found: C, 72.39; H, 6.96.

**1-((*p*-Chlorobenzoyl)oxy)-1,2-epoxycyclohexane (Table 2, Entry 4).**[3] $[\alpha]^{25}_D = -28.9°$ (*c* 0.67, $CHCl_3$) (99% ee).

**1-((*p*-Nitrobenzoyl)oxy)-1,2-epoxycyclohexane (Table 2, Entry 5).**[3] $[\alpha]^{25}_D = -29.8°$ (*c* 0.45, $CHCl_3$) (96% ee).

**1-((3,5-Dimethylbenzoyl)oxy)-1,2-epoxycyclohexane (Table 2, Entry 6).** $[\alpha]^{25}_D = -33.1°$ (*c* 0.36, $CHCl_3$) (99% ee). IR (NaCl): 1725 $cm^{-1}$. $^1H$ NMR: $\delta$ 7.64 (s, 2H), 7.20 (s, 1H), 3.41 (m, 1H), 2.35 (s, 6H), 2.33 (m, 1H), 2.21 (dt, $J$ = 14.1, 6.3 Hz, 1H), 2.02−1.95 (m, 2H), 1.59−1.50 (m, 2H), 1.47−1.40 (m, 2H). $^{13}C$ NMR: $\delta$ 168.7, 138.4, 135.3, 129.4, 127.7, 83.6, 59.7, 28.4, 24.9, 21.3, 20.5, 19.0. Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37. Found: C, 73.21; H, 7.17.

**1-((2,6-Dimethylbenzoyl)oxy)-1,2-epoxycyclohexane (Table 2, Entry 7).** $[\alpha]^{25}_D = -12.0°$ (*c* 0.75, $CHCl_3$) (98% ee). IR (NaCl): 1736 $cm^{-1}$. $^1H$ NMR: $\delta$ 7.18 (t, $J$ = 7.2 Hz, 1H), 7.01 (d, $J$ = 7.2 Hz, 2H), 3.44 (m, 1H), 2.43 (m, 1H), 2.33 (s, 6H), 2.30 (m, 1H), 2.10−1.90 (m, 2H), 1.60−1.52 (m, 2H), 1.49−1.41 (m, 2H). $^{13}C$ NMR: $\delta$ 168.6, 135.0, 129.7, 128.1, 127.8, 83.7, 59.5, 28.4, 24.9, 20.6, 19.9, 19.1. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37. Found: C, 73.32; H, 7.22.

**1-(1-Naphthoyloxy)-1,2-epoxycyclohexane (Table 2, Entry 8).** $[\alpha]^{25}_D = -42.3°$ (*c* 0.22, $CHCl_3$) (98% ee). IR (NaCl): 1720 $cm^{-1}$. $^1H$ NMR: $\delta$ 8.98 (d, $J$ = 9.0 Hz, 1H), 8.25 (dd, $J$ = 7.2, 1.0 Hz, 1H), 8.04 (d, $J$ = 8.4 Hz, 1H), 7.88 (d, $J$ = 8.4 Hz, 1H), 7.63 (m, 1H), 7.58−7.45 (m, 2H), 3.52 (m, 1H), 2.44 (dt, $J$ = 14.1, 6.6 Hz, 1H), 2.31 (dt, $J$ = 14.1, 6.3 Hz, 1H), 2.14−1.94 (m, 2H), 1.65−1.54 (m, 2H), 1.53−1.43 (m, 2H) $^{13}C$ NMR: $\delta$ 166.2, 134.3, 131.7, 131.2, 128.8, 128.3, 126.5, 125.9, 125.8, 124.6, 83.8, 59.7, 28.5, 25.0, 20.6, 19.1. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.09; H, 6.01. Found: C, 76.18; H, 6.09.

**1-(Pivaloyloxy)-1,2-epoxycyclohexane (Table 2, Entry 9).**[3,15] $[\alpha]^{25}_D = -42.4°$ (*c* 0.50, $CHCl_3$) (97% ee).

**1-Acetoxy-1,2-epoxycyclohexane (Table 2, Entry 10).**[3,15]

**1-(Benzoyloxy)-1,2-epoxy-4,4-dimethylcyclohexane (Table 2, Entry 11).**[3] $[\alpha]^{25}_D = -16.4°$ (*c* 0.47, $CHCl_3$) (98% ee).

**4-(Benzoyloxy)-3,4-epoxytetrahydro-4*H*-pyran (Table 2, Entry 12).** $[\alpha]^{25}_D = -51.2°$ (*c* 0.60, $CHCl_3$) (99% ee). IR (NaCl): 1728 $cm^{-1}$. $^1H$ NMR: $\delta$ 8.04 (m, 2H), 7.60 (tt, $J$ = 7.2, 1.5 Hz, 1H), 7.46 (m, 2H), 4.09 (dd, $J$ = 13.5, 2.4 Hz, 1H), 3.98 (d, $J$ = 13.5 Hz, 1H), 3.67 (m, 2H), 3.48 (d, $J$ = 2.4 Hz, 1H), 2.55 (dt, $J$ = 14.4, 6.0 Hz, 1H), 2.32 (dt, $J$ = 14.4, 5.4 Hz, 1H) $^{13}C$ NMR: $\delta$ 133.9, 130.0, 129.1, 128.7, 81.0, 65.0, 62.6, 56.9, 29.3. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.43; H, 5.50. Found: C, 65.30; H, 5.37.

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**1-(Benzoyloxy)-1,2-epoxycyclopentane (Table 2, Entry 13).**[3] $[\alpha]^{25}_D = -31.7°$ (*c* 0.55, $CHCl_3$) (98% ee).

**1-(Benzoyloxy)-1,2-epoxycycloheptane (Table 2, Entry 14).**[3] $[\alpha]^{25}_D = -32.8°$ (*c* 0.50, $CHCl_3$) (98% ee).

**1-(Benzoyloxy)-1,2-epoxycyclooctane (Table 2, Entry 15).**[3] $[\alpha]^{25}_D = +9.3°$ (*c* 0.31, $CHCl_3$) (98% ee).

**1-(Benzoyloxy)-1,2-epoxytetrahydronaphthalene (Table 2, Entry 16).**[3] $[\alpha]^{25}_D = -227.0°$ (*c* 0.20, $CHCl_3$) (99% ee).

**2-(Benzoyloxy)-1,3-diphenyl-1,2-epoxypropane (Table 2, Entry 17).** IR (NaCl): 1729 $cm^{-1}$. $^1H$ NMR: $\delta$ 7.78 (m, 2H), 7.50 (m, 1H), 7.39−7.26 (m, 9H), 7.21−7.16 (m, 3H), 3.95 (s, 1H), 3.71 (d, $J$ = 14.7 Hz, 1H), 3.52 (d, $J$ = 14.7 Hz, 1H). $^{13}C$ NMR: $\delta$ 164.7, 133.5, 133.0, 130.3, 129.8, 129.2, 128.7, 128.5, 128.4, 128.1, 127.4, 127.1, 88.2, 62.4, 39.4. Anal. Calcd for $C_{22}H_{18}O_3$: C, 79.97; H, 5.50. Found: C, 80.17; H, 5.55.

**2-(Benzoyloxy)cyclohexanone (Table 2, Entry 1).**[3,17,18] $[\alpha]^{25}_D = +18.4°$ (*c* 0.43, $CHCl_3$) (93% ee).

**2-((*p*-Methylbenzoyl)oxy)cyclohexanone (Table 2, Entry 2).**[3] $[\alpha]^{25}_D = +9.7°$ (*c* 0.48, $CHCl_3$) (91% ee).

**2-((*m*-Methylbenzoyl)oxy)cyclohexanone (Table 2, Entry 3).** $[\alpha]^{25}_D = +13.2°$ (*c* 0.41, $CHCl_3$) (92% ee). IR (NaCl): 1718 $cm^{-1}$. $^1H$ NMR: $\delta$ 7.92−7.86 (m, 2H), 7.40−7.30 (m, 2H), 5.41 (dd, $J$ = 11.4, 6.0 Hz, 1H), 2.62−2.42 (m, 3H), 2.40 (s, 3H), 2.19−1.58 (m, 5H). $^{13}C$ NMR: $\delta$ 204.4, 165.8, 138.2, 136.6, 134.0, 130.4, 128.3, 127.1, 77.1, 41.0, 33.4, 27.4, 24.0, 21.5. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.38; H, 6.95. Found: C, 72.51; H, 6.84.

**2-((*p*-Chlorobenzoyl)oxy)cyclohexanone (Table 2, Entry 4).**[3] $[\alpha]^{25}_D = +15.0°$ (*c* 0.46, $CHCl_3$) (89% ee).

**2-((*p*-Nitrobenzoyl)oxy)cyclohexanone (Table 2, Entry 5).**[3] $[\alpha]^{25}_D = +23.5°$ (*c* 0.43, $CHCl_3$) (94% ee).

**2-((3,5-Dimethylbenzoyl)oxy)cyclohexanone (Table 2, Entry 6)**. $[\alpha]^{25}_D = +6.5°$ (*c* 0.87, $CHCl_3$) (92% ee). IR (NaCl): 1717 $cm^{-1}$. $^1H$ NMR: $\delta$ 7.71 (s, 2H), 7.19 (s, 1H), 5.40 (dd, $J$ = 12.0, 6.3 Hz, 1H), 2.60−2.36 (m, 3H), 2.35 (s, 6H), 2.20−1.57 (m, 5H). $^{13}C$ NMR: $\delta$ 204.5, 166.0, 138.1, 134.9, 129.6, 127.6, 77.0, 41.0, 33.4, 27.5, 24.0, 21.3. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37. Found: C, 72.91; H, 7.25.

**2-((2,6-Dimethylbenzoyl)oxy)cyclohexanone (Table 2, Entry 7).** $[\alpha]^{25}_D = +23.0°$ (*c* 1.12, $CHCl_3$) (85% ee). IR (NaCl): 1727 $cm^{-1}$. $^1H$ NMR: $\delta$ 7.18 (t, $J$ = 7.6 Hz, 1H), 7.04 (d, $J$ = 7.6 Hz, 2H), 5.42 (dd, $J$ = 12.0, 6.0 Hz, 1H), 2.63−2.32 (m, 3H), 2.42 (s, 6H), 2.24−1.55 (m, 5H). $^{13}C$ NMR: $\delta$ 204.0, 168.8, 135.5, 133.2, 129.6, 127.7, 77.0, 41.0, 33.3, 27.3, 24.0, 20.0. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37. Found: C, 73.33; 7.14.

**2-(1-Naphthoyloxy)cyclohexanone (Table 2, Entry 8).** $[\alpha]^{25}_D = +29.4°$ (*c* 0.50, $CHCl_3$) (95% ee). IR (NaCl): 1713 $cm^{-1}$. $^1H$ NMR: $\delta$ 8.91 (d, $J$ = 8.1 Hz, 1H), 8.27 (dd, $J$ = 7.2, 1.2 Hz, 1H), 8.02 (d, $J$ = 8.1 Hz, 1H), 7.87 (d, $J$ = 7.8 Hz, 1H), 7.64−7.47 (m, 3H), 5.53 (m, 1H), 2.64−2.40 (m, 3H), 2.18−1.62 (m, 5H). $^{13}C$ NMR: $\delta$ 204.7, 166.8, 133.9, 133.6, 131.5, 130.6, 128.6, 127.9, 127.0, 126.4, 126.0, 124.7, 77.3, 41.0, 33.4, 27.4, 24.0. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.09; H, 6.01. Found: C, 75.99; H, 6.00.

**2-(Pivaloyloxy)cyclohexanone (Table 2, Entry 9).**[3,19] $[\alpha]^{25}_D = +47.4°$ (*c* 0.49, $CHCl_3$) (92% ee).

**2-Acetoxycyclohexanone (Table 2, Entry 10).**[3,18]

**2-(Benzoyloxy)-4,4-dimethylcyclohexanone (Table 2, Entry 11).**[3] $[\alpha]^{25}_D = +18.4°$ (*c* 0.45, $CHCl_3$) (92% ee).

**3-(Benzoyloxy)tetrahydro-4*H*-pyran-4-one (Table 2, Entry 12).** $[\alpha]^{25}_D = +12.0°$ (*c* 0.75, $CHCl_3$) (97% ee). IR (NaCl): 1724 $cm^{-1}$. $^1H$ NMR: $\delta$ 8.07 (dd, $J$ = 8.4, 1.5 Hz, 2H), 7.59 (m, 1H), 7.45 (m, 2H), 5.52 (ddd, $J$ = 10.8, 6.9, 1.0 Hz, 1H), 4.46 (ddd, $J$ = 10.8, 6.9, 1.5 Hz, 1H), 4.32 (ddt, $J$ = 11.2, 7.2, 1.5 Hz, 1H), 3.73 (m, 2H), 2.85 (m, 1H), 2.60 (m, 1H). $^{13}C$ NMR: $\delta$ 200.6, 165.2, 133.7, 130.1, 129.2, 128.6, 74.2, 70.7, 68.7, 42.4. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.43; H, 5.50. Found: C, 65.21; H, 5.49.

**2-(Benzoyloxy)cyclopentanone (Table 2, Entry 13).** $[\alpha]^{25}_D = -58.1°$ (*c* 0.73, $CHCl_3$) (92% ee). IR (NaCl): 1758, 1712 $cm^{-1}$. $^1H$ NMR: $\delta$ 8.06 (m, 2H), 7.57 (m, 1H), 7.44 (m, 2H), 5.31 (m, 1H), 2.61−2.28 (m, 3H), 2.22−1.85 (m, 3H). $^{13}C$ NMR: $\delta$ 212.3, 165.8, 133.4, 130.0, 129.5, 128.5, 76.3, 35.2, 28.8, 17.5. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.72; H, 6.02.

**2-(Benzoyloxy)cycloheptanone (Table 2, Entry 14).**[3,17,18] $[\alpha]^{25}_D = -36.2°$ (*c* 0.60, $CHCl_3$) (87% ee).

**2-(Benzoyloxy)cyclooctanone (Table 2, Entry 15).**[3,18] $[\alpha]^{25}_D = -33.9°$ (*c* 0.31, $CHCl_3$) (99% ee).

**2-(Benzoyloxy)-1-tetralone (Table 2, Entry 16).**[3]

**1-(Benzoyloxy)-1,3-diphenyl-2-propanone (Table 2, Entry 17).** IR (NaCl): 1723 $cm^{-1}$. $^1H$ NMR: $\delta$ 8.09 (m, 2H), 7.56 (m, 1H), 7.49−7.38 (m, 7H), 7.29−7.19 (m, 3H), 7.06 (m, 2H), 6.30 (s, 1H), 3.80 (s, 2H). $^{13}C$ NMR: $\delta$ 201.4, 165.9, 133.6, 133.3, 133.0, 130.1, 129.8, 129.6, 129.4, 129.3, 128.7, 128.6, 128.5, 127.2, 80.8, 46.0. Anal. Calcd for $C_{22}H_{18}O_3$: C, 79.97; H, 5.50. Found: C, 80.22; H, 5.62.

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