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Kinetic Resolution of Racemic Olefins via Asymmetric Dihydroxylation

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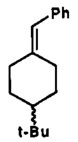
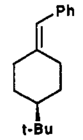
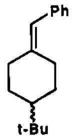
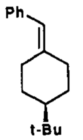
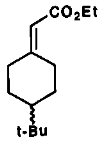
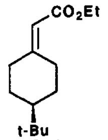
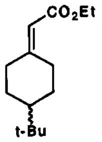
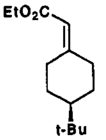
The osmium tetraoxide–cinchona alkaloid catalyst system has proven to be a very efficient for the asymmetric dihydroxylation of most classes of prochiral olefins.[1] The high levels of enantioselectivity attainable led us to investigate whether the system is sensitive to preexisting chirality in the olefinic substrate and therefore useful for kinetic resolution.[2,3] We report here results demonstrating that the process is highly effective for at least one class of axially dissymmetric alkenes.

Racemic olefins **1** and **2** were selected as substrates to test the efficiency of the osmium tetraoxide–cinchona alkaloid catalyst system for kinetic resolution. These olefins were readily available via condensation of the appropriate olefination reagents with 4-*tert*-butylcyclohexanone. Additionally, each of these olefins, or a derivative thereof, has been reported in optically pure form, thus allowing for rapid assessment of enantiomeric purity and configuration.[4,5]

The resolution experiments were carried out using the commercially available AD-mixes which utilize the $(DHQ)_2$-PHAL [1,4-bis(9-*O*-dihydroquinine)phthalazine] and $(DHQD)_2$-PHAL [1,4-bis(9-*O*-dihydroquinidine)phthalazine] ligands.[6] The reactions were performed at 0 °C in the *t*-BuOH–H_2O solvent system (1:1) at a concentration of 0.1 M. Additional potassium osmate dihydrate was added in each experiment to bring the concentration of osmium up to 1 mol %.[7] The extent of conversion was followed by capillary GLC.[8]

Table I. Summary of Kinetic Resolution Experiments

olefin	ligand	k_{rel}[12]	recovered olefin[13]
 1	$(DHQD)_2$-PHAL	9.7	 (aS)-1
 1	$(DHQ)_2$-PHAL	5.0	 (aR)-1
 2	$(DHQD)_2$-PHAL	32.0	 (aS)-2
 2	$(DHQ)_2$-PHAL	26.5	 (aR)-2

Two different methods were used to assess the enantiomeric purity of the recovered olefins. In the resolutions involving the benzylidene derivative **1**, the optical purity was estimated by simple comparison of the measured optical rotation with the reported literature values.[9] In resolutions involving the ester substrate **2**, the enantiomeric purity was determined by reduction of the recovered enoate to the allylic alcohol and conversion to the corresponding Mosher ester derivative[10] followed by HPLC analysis.[11] The results of these experiments are summarized in Table I.

Of particular importance are the entries in the column headed k_{rel}, as these are the ratios of rate constants for the fast vs slow reacting enantiomers. Knowledge of the rate constants for a pair of enantiomers allows one to calculate the extent of conversion necessary to achieve a desired enantiomeric purity. This is

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(1) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. M.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123. (c) Shibata, T.; Gilheany, D. G.; Blackburn, B. K.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 3817. (d) Ogino, Y.; Chen, H.; Kwong, H.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 3965. (e) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, Y.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585. (f) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2769.

(2) For other examples using the AD for the kinetic resolution of racemic olefins: (a) Ward, R. A.; Procter, G. *Tetrahedron Lett.* **1992**, *33*(23), 3363. (b) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*(11), 1317.

(3) Reviews of kinetic resolution: (a) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; p 247. (b) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (c) El-Baba, S.; Nuzillard, J. M.; Poulin, J. C.; Kagan, H. B. *Tetrahedron* **1986**, *42*, 3851. (d) Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695.

(4) (a) Hanessian, S.; Beaudoin, S. *Tetrahedron. Lett.* **1992**, *33*(50), 7655. (b) Denmark, S. D.; Chen, C.-T. *J. Am. Chem. Soc.* **1992**, *114*, 10674. (c) Takahashi, T.; Matsui, M.; Maeno, N.; Koizumi, T.; Shiro, M. *Heterocycles* **1990**, *30*, 353. (d) Duraisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1983**, *105*, 3252.

(5) In addition, both olefins are trisubstituted. Recent work in this group has demonstrated a pronounced rate enhancement in the asymmetric dihydroxylation of this class of olefins relative to all other olefin classes. Andersson, P.; Sharpless, K. B. *J. Am. Chem. Soc.*, in press.

(6) The $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL are the ligands used in AD-mix-α and AD-mix-β, respectively.

(7) With the added the potassium osmate dihydrate the concentration of both ligand and osmium is 1 mol %. Commercial AD-mix is 1 mol % in ligand and 0.2 mol % in osmium. Previous results from this laboratory have revealed that AD-mixes that are 1 mol % in both osmium and ligand show enhanced reaction rates with no dimunition in enantioselectivity. Wang, Z.-M.; Sharpless, K. B., unpublished results.

(8) The reactions were also carried out in the presence of 1 equiv of methanesulfonamide. This additive has been found to markedly accelerate the rate of reaction of nonterminal olefins.[1f]

(9) Optical rotations were measured in absolute EtOH at 589 nm. Comparisons were made against values reported in ref 4a.

(10) Conversion to the Mosher ester derivatives was accomplished by reduction of the enoate to the allylic alcohol (DIBAL-H, Et_2O, −78 °C) followed by esterification with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((*R*)-MTPA-Cl, Et_3N, CH_2Cl_2, catalytic DMAP). Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(11) HPLC analyses were carried out using a Perkin-Elmer Series 410 LC system with an LC 95 UV/visible detector. Absorbances were measured at 254 nm. Separations were performed on a Chiralcel OF column (length 25 cm × 4.6 mm i.d.) employing a cellulose tris(*p*-chlorophenylcarbamate) stationary phase. Isocratic elutions were performed using 0.10% isopropyl alcohol in hexane as eluent at a flow rate of 1.0 mL/min. Peak assignments were confirmed by comparison and co-injection with racemic samples made via the protocol outlined in footnote 10.

(12) The extent of reaction was followed by GC, and the enantiomeric excess of the recovered olefin was determined. The relative rate can be calculated by use of the following equation:

$$k_{\mathrm{rel}} = \ln(1 - C)(1 - \mathrm{ee})/\ln(1 - C)(1 + \mathrm{ee})$$

where C is the percent conversion/100 and ee is the percent enantiomeric excess/100.

(13) The olefin recovered in excess was determined by measuring the optical rotation of the recovered olefin mixture and comparing the sign of the measured rotation with literature values.

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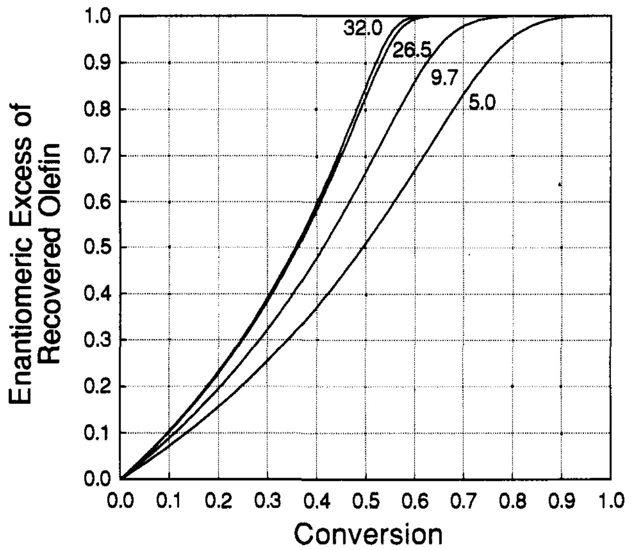
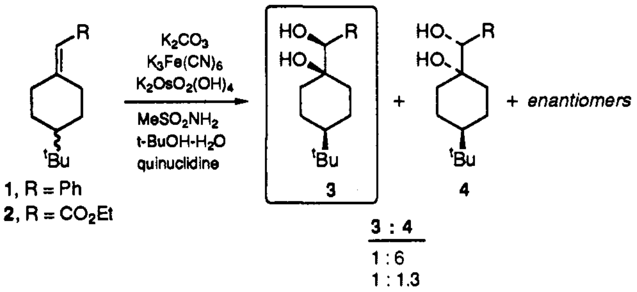


Figure 1. Enantiomeric excess vs conversion for the observed relative rate constants.

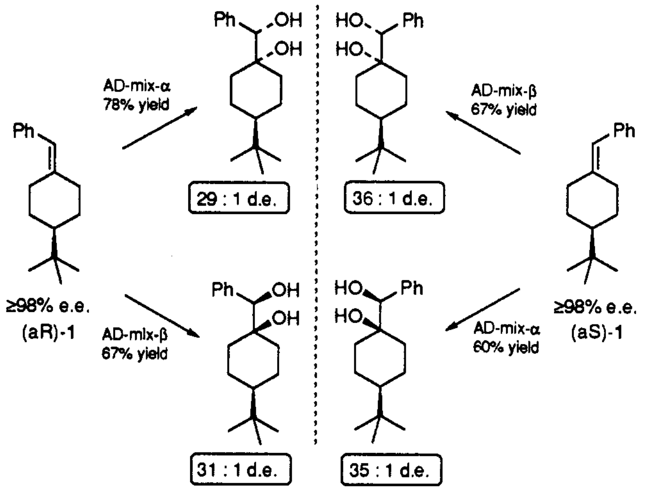
illustrated graphically in Figure 1. Knowledge of any two of the reaction variables will allow prediction of the third.[14]

An intriguing result was realized upon analysis of the diol products obtained from the kinetic resolution experiments. It was found that the fastest forming diol in each set of kinetic resolution experiments was that arising from axial dihydroxylation (i.e., **3**). Dihydroxylation carried out in the absence of a chiral ligand revealed the product arising from equatorial dihydroxylation to be favored in each instance (e.g., **4**). Thus, the kinetic resolution observed in these experiments is the result of dihydroxylation of the fast reacting olefin from the *intrinsically disfavored diastereoface*.



This seems to be one of the rare exceptions to the general rule encountered in double diastereoselective synthesis.[15] From a kinetic perspective, one would expect matched double asymmetric reactions, where the intrinsic diastereofacial selectivities of each component are mutually reinforced, to be fast compared to their mismatched counterparts. In the cases cited above, however, the fast dihydroxylation (i.e., that which makes the resolution possible) is one that would be predicted to be mismatched by application of the principles of double asymmetric synthesis.

To further probe the issue of double diastereoselection, dihydroxylations were performed on both enantiomers of **1**. The starting materials were obtained in essentially enantiomerically pure form by running kinetic resolution experiments with each of the AD-mixes to extended (≥90%) conversions. Subsequent double asymmetric reactions were performed by subjecting each enantiomer to dihydroxylation by each AD-mix. Not surprisingly, each reaction showed a very high degree of double diastereoselection.[16,17]



In summary, we have demonstrated that kinetic resolution of axially dissymmetric alkenes is possible through application of the asymmetric dihydroxylation technology. While the substrates used here are of limited synthetic utility, the results nonetheless demonstrate that effective kinetic resolution of olefins via asymmetric dihydroxylation is possible. Research is currently underway to delineate the scope of this process as well to identify the important substrate variables.

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[14] The curves in Figure 1 were generated by application of the equation given in footnote 12.

[15] Masamune, S.; Choy, W.; Petersen, J.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. Exceptions are presented therein with commentary for catalytic hydrogenation and Lewis acid-catalyzed hetero Diels–Alder reactions.

[16] Diastereomer ratios were determined by ^1H NMR integration of the benzylic protons. Tentative structure assignments were made by application of the mnemonic device reported in refs 1e,f.

[17] It is noted that the two sets of matched and mismatched reactions exhibit virtually the same diastereoselectivity, a result normally expected for double asymmetric reactions where a substrate displays no intrinsic diastereofacial preference.