Kinetic Resolution of Racemic β-Hydroxy Amines by Enantioselective N-Oxide Formation

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Received August 16, 1984

A practical and fairly general procedure for the kinetic resolution of β-hydroxy tertiary amines is described. It involves the selective oxidation of one enantiomer to the *N*-oxide by using *tert*-butyl hydroperoxide (TBHP) and a chiral catalyst prepared by mixing 2 parts of titanium isopropoxide ($Ti(O\text{-}i\text{-}Pr)_4$) and 1.2 parts of either (+)- or (−)-diisopropyl tartrate (DIPT). The product *N*-oxide and the unreacted amino alcohol are then easily separated by trituration or organic/aqueous solvent extractions, and chromatography is avoided. The oxidations are generally run to 60% conversion and the results for 21 different amino alcohols are given. The enantiomeric excess of the slow reacting (i.e., recovered) enantiomer of the amino alcohol often exceeds 90%. Among the more interesting substrates are the natural product ubine (95% ee) (**18**), *N*-methylephedrine (95% ee) (**15**), *N*-methylpseudoephedrine (93% ee) (**16**), *cis*-2-(dimethylamino)cyclohexanol (>95% ee) (**13**), *trans*-2-(dimethylamino)cyclohexanol (92% ee) (**12**), *N*-benzylbevantolol (85% ee) (**27**), and *N*-benzylpropranolol (32% ee) (**21**). The latter two examples are β-blocker precursors. One of the most important characteristics of this new route to enantiomerically pure β-hydroxy amines is its predictability. Thus, in all cases examined to date, when using (+)-DIPT the absolute configuration at the carbinol center in the slow reacting enantiomer is always the same [i.e., that related to (*R*)-*N*-methylephedrine]. A study of how the titanium/tartrate ratio, water, catalyst/substrate ratio, and temperature effect this reaction is discussed.

Soon after the discovery of the asymmetric epoxidation and kinetic resolution of allylic alcohols,[1] it became apparent that the structural features required for an allylic alcohol to undergo the kinetic resolution process were present in other types of substrates. Figure 1 shows that there are two necessary structural features.[2] First, the molecule must have a hydroxyl group (usually at the chiral center) capable of bonding to the metal center. Second, there must be a proximate locus (G) in the molecule capable of accepting an oxygen atom.[2,8] Figure 2 shows six general classes of compounds that possess these structural features. It was felt that kinetic resolution of these compound classes should, to some degree, be possible with the titanium/tartrate catalyst system. Using the same experimental conditions were successful for allylic alcohols, compound classes **1**, **2**, and **6** were investigated. Early results demonstrated that the kinetic resolution of β-hydroxy sulfides **2** and α-acetylenic alcohols **6** gave only modest success.[3] These poor results were disappointing when compared to the excellent results obtained with allylic alcohols. Also disappointing was the fact that β-hydroxy amines (**1**) under similar conditions gave no kinetic resolution.[4]

Fortunately, a few years later we chose to reexamine the β-hydroxy amine oxidations, and found that high enantiomeric excesses are obtained when two important changes are made in the reaction procedures.[5] Figure 3 shows one example of the reaction run under the necessary conditions and the resulting products. The first important change made was the use of a 2:1 (Ti/ligand) catalyst rather than the original 2:2 (Ti/ligand) catalyst used in the asymmetric epoxidation reaction. Considerable evidence has been obtained that the 2:2 and 2:1 (Ti/ligand) asymmetric catalysts have, as might be expected, quite different structures.[6] This 2:1 asymmetric catalyst may in fact be more common than the original 2:2 type. Two other 2:1 catalysts have recently been discovered in these laboratories.[7] A second change was the introduction of an "aging" period. The amino alcohol, dialkyl tartrate, and titanium isopropoxide were all allowed to mix in CH_2Cl_2 at room temperature for 30 min before the solution was cooled and the oxidant added. The aging period was necessary because without it the enantiomeric excesses were low even with the proper titanium/tartrate ratio. Furthermore, it was shown that exclusion of any of the three principle agents in the aging process would result in a lower ee. It is also true that the aging period alone is not enough for good kinetic resolution: the proper titanium/tartrate ratio must be used. Thus, it is possible, through the proper choice of chiral metal catalyst and proper reaction conditions, to effect the kinetic resolution of racemic β-hydroxy amines by enantioselective *N*-oxide formation.

Table I demonstrates the variety of β-hydroxy 3° amines which can be resolved by this process and also reveals some substrate limitations. Although most of the substrates in Table I give good results under the standard conditions described above, some substrates require fine tuning of the titanium/tartrate ratio. The types of substrates which work well in the reaction will be discussed, followed by a discussion of how the titanium/tartrate ratio, water, catalyst/substrate ratio, and temperature effect this reaction.

The importance of β-hydroxy amines as β-blockers in medicine today is well-known. Some of their uses include nervous system stimulants, bronchiodilators, appetite suppressants, and, most significantly, combating heart disease.[9] This importance is also suggested by the number

(1) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
(2) Figure 1 appears in U.S. Patent 4471130, "Method for Asymmetric Epoxidation", issued Sept 11, 1984.
(3) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589.
(4) Zilenovski, J. R.; Sharpless, K. B., unpublished results, Stanford University, 1980. Initial attempts at kinetic resolution of β-hydroxy amines met with failure. It is believed that these initial failures were caused by a combination of not using an "aging period" and of using the wrong titanium/tartrate ratio. Both of these effects are described in the text.
(5) Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3608.
(6) Finn, M. G.; Sharpless, K. B. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, in press.
(7) Lu, L. D.-L.; Johnson, R. A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 728.
(8) (a) Sheng, M. N.; Zajacek, J. G. *J. Org. Chem.* **1968**, *33*, 588. (b) Kuhnen, L. *Chem. Ber.* **1966**, *99*, 3384.

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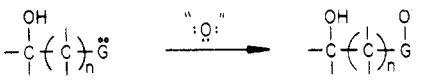


Figure 1.

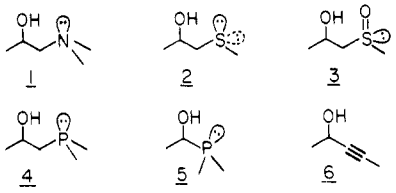


Figure 2.

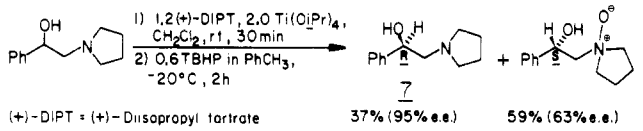


Figure 3.

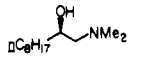
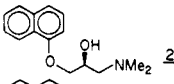
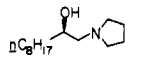
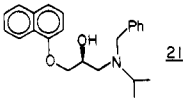
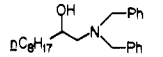
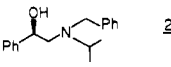
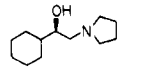
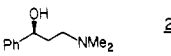
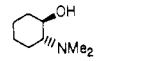
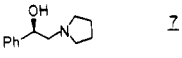
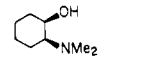
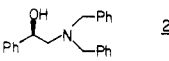
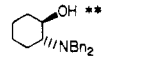
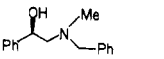
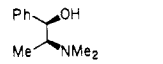
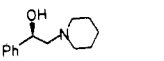
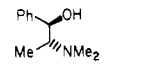
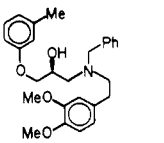
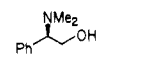
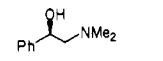
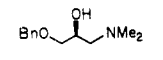
of new stereospecific methods for making β-hydroxy amines.[10] Although there are methods available for the stereospecific formation of some β-hydroxy amines, there is as yet no general method for the enantioselective synthesis of homochiral β-hydroxy amines. This reaction provides a general method for resolving racemic mixtures of β-hydroxy 3° amines, which has several advantages over classical resolution procedures.[11]

The reagents needed for this reaction are safe and plentiful. The reaction is very easy to perform. After the aging process, described above, the solution is cooled and the oxidant added. The reaction is usually finished and ready to be worked up within 2 h. The one-step base hydrolysis of the titanium–tartrate catalyst followed by filtration and evaporation of solvent affords the remaining starting material and product *N*-oxide in very high yield. Because of the great solubility differences between the *N*-oxide and the amino alcohols, chromatography is usually avoided. In most cases simple trituration of this mixture with hexane (or dry ether) and filtration completely separates the insoluble crystalline *N*-oxide from the hexane-soluble β-hydroxy amine. The yields are usually very high for both the β-hydroxy amine and the *N*-oxide.

Table I also demonstrates that the absolute stereochemistry of the slower reacting β-hydroxy amine is predictable. Proper choice of (+)- or (−)-tartrate determines the enantiomer left behind. When the (+)-tartrate is used, the slow reacting enantiomer is that related to **7**, Figure 3 (i.e., when the hydroxyl group is up, the amine is on the right).[12]

Another advantage of this method is that the *N*-oxides formed (although not as highly enriched as the recovered β-hydroxy amines) are easily converted back to the β-hydroxy amines of opposite configuration.[13] In this way it is possible to recover both enantiomers in enriched form from a single reaction.

Table I[a]

entry	slow reacting enantiomer*		% ee	entry	slow reacting enantiomer*		% ee
1		8	91	13		20	92
2		9	94	14		21	32
3		10	0	15		22	15
4		11	92	16		23	0
5		12	92	17		7	95
6		13	95	18		24	10
7		14	0	19		25	86
8		15	95	20		26	97
9		16	93	21		27	85
10		17	34				
11		18	95				
12		19	91				

[a] *Stereochemistry shown is the absolute stereochemistry determined for all enantiomerically enriched products, when (+)-DIPT is used. **Only indicates relative stereochemistry as recovered amino alcohol was racemic in this case.

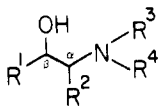


Figure 4.

The examples in Table I were chosen to demonstrate the scope and limitations of this kinetic resolution process. Substituents on the β-carbon, α-carbon, and nitrogen were varied to determine which combinations could undergo successful kinetic resolution (see Figure 4). The size of the substituent at the β-carbon (R^1) does not seem to be important as long as it is as large as a methyl group (**8**, **9**, **19**). An aromatic substituent (**7**, **15**, **16**, **18**, **25**, **26**) leads to high enantiomeric excesses as does a branched alkyl (**11**). β-[Alkoxy- and β-[(aryloxy)methylene] substituents at this position also give very good results (**19**, **20**, **27**). This fact is important because this structural feature is present in most β-blocker-type molecules. Substitution at the α-carbon (R^2) introduces a second chiral center into the molecule (if R^1 is not H). If R^2 is a methyl or a methylene bridge to R^1, the results are as good as for the parent system with R^2 = H. It should be noted that whether the

(9) (a) Warburton, D. M. "Brain, Behavior and Drugs"; Wiley: New York, 1975. (b) Lednicer, D.; Mitscher, L. A. "Organic Chemistry of Drug Synthesis"; Wiley: New York, 1977; Vol 1. (c) Lednicer, D.; Mitscher, L. A. "The Organic Chemistry of Drug Synthesis"; Wiley: New York, 1980; Vol 2.

(10) (a) Backväll, J.-E.; Bystrom, S. E. *J. Org. Chem.* **1982**, *47*, 1126. (b) Backväll, J.-E.; Bjorkman, E. E.; Byström, S.; Solladie-Cavallo, A. *Tetrahedron Lett.* **1982**, *23*, 943. (c) Knapp, S.; Patel, D. V. *Tetrahedron Lett.* **1982**, *23*, 3539. (d) Georges, M.; Fraser-Reid, B. *Tetrahedron Lett.* **1981**, *22*, 4635. (e) Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956.

(11) (a) Newman, P. "Optical Resolution Procedures for Chemical Compounds"; Optical Resolution Information Center: Riverdale, New York, 1981. (b) Wilen, S. H. "Tables of Resolving Agents and Optical Resolutions"; Eliel, E. L., Ed.; University of Notre Dame Press: Notre Dame, 1972. (c) Jacques, J.; Collet, A.; Wilen, S. H. "Enantiomers, Racemates and Resolutions"; Wiley: New York, 1981.

(12) Since the *R* and *S* designation varies with the substrate, the need for this type of convention is obvious.

(13) There are many ways to reduce *N*-oxides to amines. We have found the use of $LiAlH_4$ in THF to be highly efficient and convenient; milder methods (e.g., catalytic hydrogenation) are also effective.

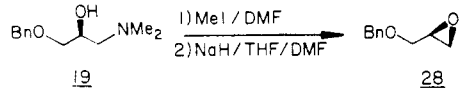
substituents are *threo* or *erythro* the ee's (**12** and **13**) are about the same. Therefore no large matched–mismatched effects have yet been noted in this kinetic resolution process.

The structural requirement at the nitrogen (R^3 and R^4) is very important. It was reported that 1° and 2° amino alcohols could be used as ligands in the asymmetric epoxidation of allylic alcohols.[14] However, in this investigation, 1° and 2° amines were found to be uncooperative. Primary amines were found not to oxidize under these mild conditions. Secondary amines, on the other hand, gave several oxidation products. Thus, both substituents on nitrogen have to be non-hydrogen and they cannot both be "large". Several entries in Table I help to demonstrate the exquisite sensitivity of this process to the nature of the substituents on nitrogen. When R^3 and R^4 were both methyls (**8**, **12**, **13**, **15**, **16**, **18–20**) or methylene rings (**7**, **9**, **11**, **26**) the reaction proceeded to give high (>90%) enantiomeric excesses. But the borderline between success and failure was found to be quite sharp. Comparing entry 11 (**18**) to entry 19 (**25**) one sees that exchanging one methyl group for the slightly larger benzyl group brings down the ee less than 10%. However, exchanging the second methyl group for a benzyl group (entry 18, **24**) completely kills the kinetic resolution process. The three *N*,*N*-dibenzyl derivatives (**10**, **14**, **24**) all showed little or no resolution although all three were oxidized completely (to 60% conversion). However, the addition of an extra methylene between the nitrogen and the benzyl group, entry 21 (**27**), is like going back to a methyl group, again giving good kinetic resolution.

The choice of benzyl substituents on nitrogen seemed obvious. They are locally only a little larger than methyl but they are easy to remove by hydrogenolysis, thereby giving one access to the important classes of 1° and 2° amino alcohols which do not otherwise undergo this kinetic resolution. In an attempt to synthesize highly enriched propranolol **30** the kinetic resolution of *N*-benzylpropranolol was tried (entry 14, **21**). The combination of benzyl plus isopropyl on the nitrogen brought down the ee to 32%.

This problem of the nitrogen substituents limiting the usefulness of the reaction and the more general problem of the process not working on 1° and 2° amino alcohols suggested the possibility of converting the enriched dimethylamino alcohols into enantiomerically enriched terminal epoxides. These epoxides could then be attacked regioselectively to give the desired 1°, 2°, or 3° amino alcohol.

Several methods are known for transforming β-hydroxy terminal dimethylamines into terminal epoxides.[15] The procedure that worked the best in this study is shown below and explained in detail in the Experimental Section.[16] Equation 1 shows the two-step process developed



19 28

80%

(1)

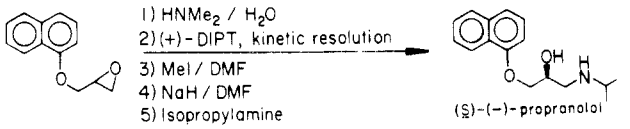
Table II

entry	substrate	titanium/tartrate	ee
1	 7	2 : 1.2	95%
		2 : 2.4	71%
2	 9	2 : 1.2	94%
		2 : 2.4	0%

Table III

substrate	entry	titanium/tartrate	ee
 dl-15	1	2 : 1.2	58%
	2	2 : 1.3	85%
	3	2 : 1.4	96%
	4	2 : 1.5	95%
	5	2 : 1.8	88%
	6	2 : 2.4	68%

to convert the already enriched β-hydroxy amine **19** to the enriched terminal epoxide **28**. This reaction sequence offers many benefits. First, terminal dimethylamino alcohols are easily derived from the terminal racemic epoxides and dimethylamine and have been shown to undergo kinetic resolution to high ee. Second, the intermediate quaternary salts can be conveniently stored and can be easily recrystallized to further enrich the ee. Third, the homochiral terminal epoxides could be opened regioselectively with virtually any nucleophile to give many types of products besides β-hydroxy amines. Equation 2 shows



29 30

(2)

how (±)-3-(1-naphthyloxy)propane oxide (**29**) was converted to (*S*)-(−)-propranolol (**30**) in five steps with an 11% overall yield.

One final example to point out in Table I is entry 16 (**23**), the only γ-hydroxy amine tried. This substrate was oxidized to 60% but showed no ee.

Besides the structural features of the substrate, several other factors were investigated to see how they affect this reaction. The titanium/tartrate ratio was found to be very important in this reaction and optimum values differed from substrate to substrate. Some of the other factors studied were added water, temperature, and catalyst concentration.

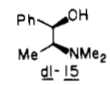
The experimental conditions for the first attempts at the kinetic resolution of β-hydroxy amines were similar to those tried with allylic alcohols. Even after the necessary "aging" period was discovered the results were still not as good as desired. It was not until variations in the titanium/tartrate ratio were tried that excellent results were achieved. Table II shows two results from a comparison test between titanium/tartrate ratios of 2:2.4 and 2:1.2 for two different substrates, **7** and **9**. The ratio of 2:1.2 was assumed to be the best ratio for these substrates. Because it gave very good results for several substrates, it was taken

(14) Jackson, R.; John, G. L. Japan Patent 58-15966, 1982. The use of less than 2 equiv of oxidant, in this patent, in the presence of primary and secondary amines, leads us to believe that oxidation of the allylic alcohol occurred preferentially to that of the amine. However, the experimental details were vague and furthermore no mention was made of what became of the ligands after the reaction.

(15) (a) McClure, D. E.; Engelhardt, E. L.; Mensler, K.; King, S.; Saari, W. S.; Huff, J. R.; Baldwin, J. J. *J. Org. Chem.* **1979**, *44*, 1826. (b) Lyle, G. G.; Keefer, L. K. *J. Org. Chem.* **1966**, *31*, 3921. (c) Coke, J. L.; Richon, A. B. *J. Org. Chem.* **1976**, *41*, 3516. (d) Castedo, L.; Castro, J. L.; Riguera, R. *Tetrahedron Lett.* **1984**, *25*, 1205.

(16) The method described by McClure et al.[15a] to give 30% yield in their system was found to give similarly low yields in this system. The byproducts were found to be a dimer and polymer. Diluting the system from 20 mL of DMF to 100 mL of DMF increased the yield to 65% epoxide but 20% of the dimer was still produced. Dilution of the 100 mL of DMF with 900 mL of THF increased the yield to 80% with no sign of the dimer. The terminal epoxide formed is very reactive even under these modified (THF dilution) conditions and probably polymerizes to some degree, accounting for the 20% of the product not recovered.

Table IV

substrate	entry	added water (equiv)	conversion	ee
 dl-15	1	0.0	60%	95 %
	2	0.5	60%	72 %
	3	1.0	58 %	53 %
	4	2.0	32 %	0 %

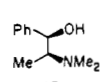
to be "the best" ratio for this process. During the course of this study it was noted that *N*-methylephedrine (**15**) which gave an early result greater than 95% ee, gave very inconsistant results using a ratio of 2:1.2. After testing other variables it was realized that the titanium/tartrate ratio used was the origin of the problem. Varying the titanium/tartrate ratio from 2:1.2 up to 2:2.4 on *N*-methylephedrine demonstrated that the best value of this substrate was between 2:1.4 and 2:1.5. Table III includes these results. The region between 1.2 and 1.4 equiv of tartrate shows a very sharp slope and this probably accounts for the inconsistant results found when 1.2 equiv of tartrate was used.

Two other substrates in Table I were originally reported as giving enantiomeric excesses of 79% for **25** and 75% for **16**.[6] Optimizing the ratio for these substrates, individually, raised the results to 86% ee for **25** (at 2:1.2) and 93% ee for **16** (at 2:1.5). An attempt was also made to increase the resulting ee for the bulkier substrates **21** and **22**, by fine tuning the ratio. These attempts met with failure.

The reason for this substrate-dependent optimum ratio is not yet understood. As discussed above, the ratio dependence was examined for only five of the substrates in Table I (**15**, **16**, **21**, **22**, **25**). For all of the other entries in the table the standard 2:1.2 ratio was the only one tried. Note that for **21**, **22**, and **25** the 2:1.2 ratio was found to be the optimum. In the case of **15** and **16**, higher ratios (2:1.4 and 2:1.5, respectively) were optimum. Since the majority of the cases give very good results with a 2:1.2 ratio, this ratio should be tried first. However, if the substrate resembles **15** or **16**, selection of a higher ratio (ca. 2:1.4) is probably indicated. In any case, since all the best results have come from the ratios between 2:1.2 and 2:1.5, one should be able to select the optimum ratio in three or fewer experiments.

These kinetic resolutions were all performed using distilled amino alcohols, distilled Ti(O-*i*-Pr)$_4$, distilled (+)-DIPT, and anhydrous TBHP in toluene, stored over sieves.[17] The water sensitivity of the titanium–tartrate catalysts has been investigated in the epoxidation of allylic alcohols by our group[18] and by Kagan in his study of the asymmetric oxidation of sulfides to sulfoxides.[19] Table IV shows a study of how added water affected the results of the kinetic resolution of *N*-methylephedrine. The water was added to the tartrate and the β-hydroxy amine and mixed before the CH_2Cl_2 and Ti(O-*i*-Pr)$_4$ were added. This resulted in a homogeneous solution in each case. Addition of 0.5 equiv of water resulted in a 23% decrease in the ee and 1.0 equiv of water brought the ee down to 53%. Both of these reactions went to completion. When 2.0 equiv of water were added the reaction only went to 32% completion and the recovered amino alcohol was racemic. Thus, the reaction is sensitive to water and a low ee could result from adventitious water. But it should be pointed out that except for the original distillation of the reagents and use of a dry N_2 atmosphere, no special precautions were needed to give high enantiomeric excesses.

Table V

substrate	entry	reaction conditions	ee
 15	1	-78°C (8h)	24%
	2	-78°C (8h), → -20°C (12h)	95%
	3	-45°C (8h)	95%
	4	-45°C (8h), → -20°C (12h)	95%
	5	-20°C (8h)	95%
	6	0°C (8h)	95%
	7	23°C (8h)	90%

Although a formal kinetic study was not undertaken, it was found that the oxidations of substrates **8**, **10**, and **14** were complete in less than 2 h at −20 °C. The effect of the temperature on the resulting ee can be seen in Table V. Most of the reactions listed in Table I were left overnight at −20 °C. Standard workup at this point gave a 95% ee (see entry 5, Table V). The difference between the results in entry 1 and entry 2 demonstrates that this reaction does not go to completion in 8 h at −78 °C. The low ee in entry 1 results from the reaction occurring during the workup procedure, after the water was added. When the reaction was run at −78 °C for 8 h and then allowed to warm to −20 °C for 12 h, the result was again a 95% ee. Entry 3 shows that the reaction does go to completion at −45 °C giving a very high ee. Allowing the reaction to run at 0 °C does not change the ee appreciably. Even when the reaction was run at room temperature, the recovered amino alcohol (at 60% conversion) still had a 90% enantiomeric excess.

Mechanism

A reasonable understanding of the mechanism of the titanium–tartrate (2:2 system) catalyzed kinetic resolution and asymmetric epoxidation of allylic alcohols has emerged as a result of several years of detailed investigation.[6] During the past 3 years four new asymmetric titanium–tartrate-type catalysts have been discovered. The first three of these systems are used to transform allylic alcohols into epoxy alcohols (or chlorodiols).[1,7] These differ from the parent system in that a 2:1 titanium/ligand ratio is used and opposite face selectivity is observed in each case. The fourth new asymmetric catalyst is the 2:1 titanium/tartrate system used to kinetically resolve β-hydroxy amines. Although a detailed mechanistic investigation has not been performed, some aspects of this reaction, which a good mechanism must explain, should be discussed.

Before a reasonable mechanism can be proposed, the active catalyst (or catalysts) must be identified. Determination of the active catalyst in this reaction is complicated by the fact that three different bidentate ligands are competing for coordination sites on the titanium, rather than just one as in the allylic alcohol work. Both systems use the chiral tartrate but in the β-hydroxy amine system both the amine and the *N*-oxide product are bidentate ligands. In this dynamic system, equilibria exist between many different possible catalysts. That these equilibria are also affected by the nature of the substrate is suggested by the fact that different substrates have different optimum values of the titanium/tartrate ratio.

Whatever the active catalyst is, it is probably formed during the aging period when the solution containing Ti(O-*i*-Pr)$_4$, DIPT, and β-hydroxy amine is allowed to stand at room temperature. This necessary aging period suggests that the β-hydroxy amine is an important part of the catalyst species and not just an oxygen-accepting substrate. While we have so far referred to the catalyst as a 2:1 complex, we have recently revised our thinking

(17) Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607.
(18) Finn, M. G.; Ellman, J.; Sharpless, K. B., unpublished results.
(19) Kagan, H. B.; Pitchen, P. *Tetrahedron Lett.* **1984**, *25*, 1049.

based upon the actual stoichiometry of these reactions (i.e., 2:1.2–1.5). We now feel that a 3:2 complex is a more likely candidate.

If the amino alcohol is part of the active catalyst, there arises the obvious question as to which enantiomer is involved. Too many things are unknown to justify speculation on this point. Another uncertainty relates to the role of the *N*-oxide products. Since these products are such powerful inhibitors of the oxidation process, we presently feel that the metal centers to which they are coordinated are not active in the catalysis. However, this prejudice too must be regarded as speculation.

There are other experimental observations that must be explained. The size restrictions of the nitrogen substituents are very important not only because of the synthetic limitations but also because of their mechanistic implications. Are the substrates with large nitrogen substituents unable to form the necessary chiral catalyst or unable to be oxidized on the chiral catalyst? The predictability of the reaction is also very important. In what way does the substituent at the carbinol center interact with the chiral catalyst so that the stereochemistry of the slow reacting enantiomer is always the same? This high predictability along with the generally high ee seems to suggest that a distinct species, rather than several, is acting as the chiral catalyst.

In summary, the structure(s) of the true catalyst or catalysts remains unknown and we are not yet able to propose a mechanism that can account for the essential features of these selective oxidations. We have recently begun further studies which it is hoped will remove some of the uncertainties discussed above.

Experimental Section

^{1}H NMR spectra were measured on a Bruker 250- or 270-MHz spectrometer. Deuterated chloroform ($CDCl_3$) was used as the standard solvent unless otherwise noted. Tetramethylsilane (Me_4Si) was used as an internal standard. All peaks were measured in δ (ppm) downfield from Me_4Si and coupling constants (J) are given in hertz. Infrared (IR) spectra were measured on a Perkin-Elmer Model 597 grating infrared spectrophotometer. All melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter using a 1-cm^3 capacity (10-cm path length) quartz cell. Elemental analyses were performed by the Robertson Laboratory, Inc., Florham Park, NJ.

Oxygen- and water-sensitive reactions were done in flame-dried glassware under a dry nitrogen atmosphere. Most of the reactions are water, not oxygen, sensitive, but the maintainance of a dry nitrogen atmosphere provides a convenient way to exclude moisture. Methylene chloride and benzene were freshly distilled from calcium hydride. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Dimethylformamide was stored over activated 3-Å molecular sieves. Titanium isopropoxide was purchased from Aldrich, distilled under high vacuum, and stored under a nitrogen atmosphere before use. (+)-Diisopropyl tartrate was purchased from Chemische Fabrik Uetikon, distilled under high vacuum by using a wiped film molecular still, and stored under a nitrogen atmosphere. *tert*-Butyl hydroperoxide was prepared and stored as described by Hill et al.[17] Analytical thin-layer chromatography (TLC) was performed using aluminum plates coated with a 0.20 mm thickness of Merck silica gel 60 F-254. Flash chromatography was done according to Still, using Merck silica gel (230–400 mesh).[20]

Some of the β-hydroxy amines were acetylated for ^{1}H NMR analysis by the following procedure. A 5–10-mL round-bottomed flask is charged with about 5 mg of compound. To this is added about 1 mL of pyridine and 0.5 mL of acetic anhydride. After the mixture sat at room temperature for at least 2 h, the pyridine, acetic acid, and acetic anhydride are removed under high vacuum to afford the acetylated product.

Standard Procedure for the Formation of Terminal Tertiary Amines. Many of the β-hydroxy amines used in this study were prepared through the reaction of a terminal epoxide with a secondary amine as described below for the synthesis of (±)-dimethyl(β-hydroxydecyl)amine. The crude β-hydroxy amines were either distilled, flash chromatographed, recrystallized, or pumped dry under a high vacuum before being used in the kinetic resolution reactions.

Standard Procedure for the Kinetic Resolution of Racemic β-Hydroxy Amines by Enantioselective *N*-Oxide Formation. The standard procedure for the kinetic resolution of β-hydroxy amines will be detailed below for the kinetic resolution of (±)-dimethyl(β-hydroxydecyl)amine (8). Experimental procedures for all other kinetic resolutions will specify the amount of β-hydroxy amine, Ti(O-*i*-Pr)$_4$, (+)-DIPT, *tert*-butyl hydroperoxide, and CH_2Cl_2 used, followed by the yield and enantiomeric excess of recovered starting material.

General Procedures for the Determination of the Enantiomeric Excess in the Kinetic Resolution of β-Hydroxy Amines. Procedure A: Chiral Shift Study on the Acetate. A small sample of the racemic β-hydroxy amine was acetylated in the usual way. An NMR shift study was done,[21] using Eu(hfbc)$_3$[22] in C_6D_6, by adding small portions of the shift reagent to the sample until a base-line separation of the two enantiomeric acetate ($ROCOCH_3$) proton resonances was observed.

A small sample of the enriched β-hydroxy amine was then acetylated in the usual way. Small portions of the shift reagent were added, as above, until the acetate methyl peaks were shifted to the same value as in the racemic mixture. In each case the major isomer's proton resonance was downfield from the minor isomer's. The enantiomeric excess was then calculated by dividing the integration difference by the total integration of the two peaks.

Procedure B: Mosher Ester Analysis. A small sample (~20 mg) of the racemic β-hydroxy amine was converted to its Mosher ester (made from (*R*)-(+)-[α-methoxy-α-(trifluoromethyl)-phenyl]acetyl chloride).[23] In all cases employing Mosher ester analysis, at least one set of diastereomeric protons had base-line separation.

A small sample of the enriched β-hydroxy amine was converted to its Mosher ester, and its enantiomeric excess was calculated, as above, on the peaks which separated in the racemic series.

Determination of Absolute Configuration. In most cases the absolute configurations were established by comparison of optical rotations with literature values for the same substances or by correlations involving direct interconversion to a compound of known configuration.[24] However, in a few cases the assignments are less rigorous, being based on analogy between configuration and sign of rotation for closely related compounds. The method of determination of absolute configuration for each compound is described in the Supplementary Material.

Preparation of (±)-Dimethyl(β-hydroxydecyl)amine (8). To a solution of 1,2-epoxydecane (5.02 g, 32.8 mmol) in 100 mL of THF was added 10 equiv of dimethylamine (15.0 g, 330 mmol, 37.0 mL of a 40% aqueous solution) and the mixture refluxed for 4 h. Evaporation of THF, excess dimethylamine, and H_2O followed by distillation (95 °C, 1 mmHg) yielded 5.33 g (82%) of (±)-dimethyl(β-hydroxydecyl)amine (8) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.61 (m, 1 H), 2.28 (dd, J = 9.3, 11.2 Hz, 1 H), 2.27 (s, 6 H), 2.14 (dd, J = 3.0, 11.2 Hz, 1 H), 1.00–1.58 (m, 14 H), 0.89 (t, J = 7.8 Hz, 3 H); IR (film) 3450 (br), 2920, 2850, 2820, 2770, 1460, 1265 cm^{-1}. Anal. Calcd for $C_{12}H_{27}NO$: C, 71.58; H, 13.52; N, 6.96. Found: C, 71.36; H, 13.74; N, 6.72.

Kinetic Resolution of (±)-Dimethyl(β-hydroxydecyl)-amine (8). A 50 mL, one-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar was oven dried and flushed with nitrogen while cooling. Addition of β-hydroxy amine 8 (404

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(21) Goering, H. L.; Eikenberry, J. N.; Koermer, G. S.; Lattimer, C. J. *J. Am. Chem. Soc.* **1974**, *96*, 1493.

(22) Tris(3-heptafluorobutyryl-*d*-camphorato)europium(III).

(23) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(24) We thank Dr. Lee Weigel of Eli Lilly for a generous gift of (*R*)-(−)-styrene oxide, which made many of the absolute configuration determinations easy to perform.

mg, 2.01 mmol) and (+)-DIPT (570 mg, 2.43 mmol, 1.21 equiv) was followed by brief flushing with nitrogen. The flask was then charged with 20 mL of CH_2Cl_2 followed by Ti(O-*i*-Pr)$_4$ (1.20 mL, 4.09 mmol, 2.04 equiv). *The mixture was stirred for 30 min at room temperature.* After this aging period, the flask was cooled, while stirring, in a dry ice/CCl_4 bath (ca. −20 °C). To this solution was added 0.6 equiv of *tert*-butyl hydroperoxide (365 μL, 1.20 mmol, 3.29 M solution in toluene). After stirring for 2 h at −20 °C, the reaction was quenched by adding 20 mL of diethyl ether, 0.8 mL of H_2O, and 0.8 mL of a 40% NaOH solution. This mixture was vigorously stirred for 4–5 h at room temperature, yielding a gelatinuous precipitate which was filtered through a pad of Celite. The precipitate was stirred vigorously in refluxing $CHCl_3$ for 5 min before filtering it again through the Celite pad.

The combined filtrates were concentrated to leave a pale yellow, viscous oil, which was dried under high vacuum. This oil was triturated in 20 mL of *n*-hexane. The clear supernatant solution was filtered and the filtrand was washed with 20 mL of *n*-hexane. The filtered solid is the optically active *N*-oxide of dimethyl(β-hydroxydecyl)amine (233 mg, 53.5%). The hexane extracts were diluted with 5 mL of ether, washed with water (ca. 200 μL × 2), and dried over anhydrous Na_2SO_4. The solvent was evaporated to afford 144 mg (35.7%) of (−)-(β-hydroxydecyl)amine as an oil: $[\alpha]^{20}_D$ −3.58° (*c* 1.65, EtOH).

Chiral shift study indicated that the recovered β-hydroxy amine had a 91% ee.

Preparation of (±)-1-Pyrrolidino-2-decanol (9). To a solution of 1,2-epoxydecane (4.0 g, 26.1 mmol) in 100 mL of THF was added 1.5 equiv of pyrrolidine (2.78 g, 3.30 mL, 39.1 mmol) and the mixture refluxed for 9 h. Evaporation of the THF and excess pyrrolidine yielded 5.68 g of a yellow oil. Bulb to bulb distillation gave 5.0 g (85%) of (±)-1-pyrrolidino-2-decanol (**9**) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.62 (m, 1 H), 3.15–3.62 (br s, 1 H), 2.66 (m, 2 H), 2.55 (t, *J* = 11.2 Hz, 1 H), 2.45 (m, 2 H), 2.25 (dd, *J* = 3.4, 11.2 Hz, 1 H), 1.78 (br s, 4 H), 1.12–1.57 (m, 14 H), 0.88 (t, *J* = 7.1 Hz, 3 H); IR (film) 3450 (br), 2920, 2850, 2800, 1460, 1355, 1290, 1150, 1085, 888 cm^{-1}. Anal. Calcd for $C_{14}H_{29}NO$: C, 73.95; H, 12.86; N, 6.16. Found: C, 73.99; H, 12.77; N, 6.47.

Kinetic Resolution of (±)-1-Pyrrolidino-2-decanol (9). This reaction was run according to the standard procedure using 232 mg (1.02 mmol) of β-hydroxy amine **9**, 2.05 equiv of Ti(O-*i*-Pr)$_4$ (593 mg, 620 μL, 2.09 mmol), 1.24 equiv of (+)-DIPT (296 mg, 1.26 mmol) and 0.60 equiv of *tert*-butyl hydroperoxide (190 μL, 0.63 mmol, 3.29 M solution in toluene) in 10 mL of CH_2Cl_2. Standard workup yielded 133 mg (54%) of the *N*-oxide and 62.5 mg (27%) of (±)-1-pyrrolidino-2-decanol (**9**) as an oil: $[\alpha]^{20}_D$ −1.2° (*c* 1.26, EtOH).

Chiral shift study indicated that the recovered β-hydroxy amine had a 94% ee.

Preparation of (±)-Dibenzyl(β-hydroxydecyl)amine (10). To a solution of 1,2-epoxydecane (5.00 g, 32.0 mmol) in 100 mL of THF/*n*-BuOH (1:1) was added 1.5 equiv of dibenzylamine (9.47 g, 48.0 mmol, 9.23 mL) and the solution refluxed for 30 h. Evaporation of the solvents followed by flash chromatography (19:1 hexane/EtOAc) yielded 7.20 g (65%) of (±)-dibenzyl(β-hydroxydecyl)amine (**10**) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 10 H), 3.88 (d, *J* = 12.9 Hz, 2 H), 3.70 (m, 1 H), 3.39 (d, *J* = 12.9 Hz, 2 H), 2.44 (d, *J* = 6.1 Hz, 1 H), 1.27 (m, 14 H), 0.88 (t, *J* = 6.1 Hz, 1 H); IR (film) 3450 (br), 3080, 3060, 3022, 2920, 2850, 1492, 1450, 1340, 1070, 750, 700 cm^{-1}. Anal. Calcd for $C_{24}H_{35}NO$: C, 81.53; H, 9.98; N, 3.96. Found: C, 81.53; H, 10.08; N, 4.21.

Kinetic Resolution of (±)-Dibenzyl(β-hydroxydecyl)amine (10). This reaction was run according to the standard procedure using 363 mg (1.0 mmol) of β-hydroxy amine **10**, 2.0 equiv of Ti(O-*i*-Pr)$_4$ (568 mg, 595 μL, 2.0 mmol), 1.2 equiv of (+)-DIPT (281 mg, 1.2 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (182 μL, 0.60 mmol, 3.29 M solution in toluene) in 10 mL of CH_2Cl_2. Standard workup yielded 226 mg (60%) of the *N*-oxide and 124 mg (34%) of (±)-dibenzyl(β-hydroxydecyl)amine (**10**) as an oil.

Chiral shift study indicated that the recovered β-hydroxy amine had no enantiomeric excess.

Preparation of (±)-1-Cyclohexyl-2-pyrrolidinoethanol (11). To a solution of 1-cyclohexyl-1,2-epoxyethane (1.00 g, 7.92 mmol) in 2 mL of dry benzene was added 1.5 equiv of pyrrolidine (852 mg, 11.88 mmol) and the mixture refluxed for 24 h. Evaporation of benzene and excess pyrrolidine followed by drying under high vacuum yielded 1.48 g (95%) of (±)-1-cyclohexyl-2-pyrrolidinoethanol (**11**) as a solid: mp 41–42 °C; ^{1}H NMR ($CDCl_3$) δ 3.40 (ddd, *J* = 3.4, 6.7, 10.4 Hz, 1 H), 2.70 (m, 2 H), 2.66 (t, *J* = 11.2 Hz, 1 H), 2.46 (m, 2 H), 2.31 (dd, *J* = 3.4, 11.2 Hz, 1 H), 1.42–1.96 (m, 9 H), 0.82–1.42 (m, 6 H); IR ($CHCl_3$) 3400, 2995, 2920, 2850, 2800, 1460, 1450, 1420, 1260, 1145, 1115, 1087, 1064, 1045, 895, 880 cm^{-1}. Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.74; N, 7.10. Found: C, 72.99; H, 11.96; N, 7.27.

Kinetic Resolution of (±)-1-Cyclohexyl-2-pyrrolidinoethanol (11). This reaction was run according to the standard procedure using 407 mg (2.06 mmol) of β-hydroxy amine **11**, 2.05 equiv of Ti(O-*i*-Pr)$_4$ (1.20 g, 1.30 mL, 4.23 mmol), 1.22 equiv of (+)-DIPT (590 mg, 2.52 mmol), and 0.59 equiv of *tert*-butyl hydroperoxide (370 μL, 1.22 mmol, 3.29 M solution in toluene) in 20 mL of CH_2Cl_2. Standard workup yield 220 mg (49.9%) of the *N*-oxide and 146 mg (35.8%) of (−)-1-cyclohexyl-2-pyrrolidinoethanol (**11**) as a solid: $[\alpha]^{20}_D$ −20.73° (*c* 1.4, EtOH).

Mosher ester analysis indicated that the recovered β-hydroxy amine had a 92% ee.

Preparation of *trans*-(±)-2-(Dimethylamino)cyclohexanol (12). To a solution of cyclohexene oxide (5.00 g, 50.0 mmol) in 100 mL of THF was added 10 equiv of dimethylamine (22.8 g, 500 mmol, 56.4 mL of a 40% aqueous solution) and the mixture refluxed for 5 h. Evaporation of THF, excess dimethylamine, and H_2O followed by distillation yielded 6.90 g (94%) of *trans*-(±)-2-(dimethylamino)cyclohexanol (**12**) as an oil: ^{1}H NMR ($CDCl_3$) δ 4.11–4.51 (m, 1 H), 3.70 (m, 1 H), 2.49–2.85 (m, 7 H), 2.08–2.42 (m, 4 H), 1.54–1.89 (m, 4 H); IR (film) 3460 (br), 2925, 2860, 2780, 1635, 1450, 1405, 1355, 1300, 1260, 1185, 1120, 1080, 1060, 1035, 950, 875 cm^{-1}. Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 66.82; H, 12.07; N, 9.99.

Kinetic Resolution of *trans*-(±)-2-(Dimethylamino)-cyclohexanol (12). This reaction was run according to the standard procedure using 440 mg (3.0 mmol) of β-hydroxy amine **12**, 2.0 equiv of Ti(O-*i*-Pr)$_4$ (1.80 g, 1.87 mL, 6.3 mmol), 1.20 equiv of (+)-DIPT (884 mg, 3.80 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (560 μL, 1.80 mmol, 3.29 M solution in toluene) in 30 mL of CH_2Cl_2. Standard workup yielded 270 mg (55%) of the *N*-oxide and 180 mg (40%) of *trans*-(−)-2-(dimethylamino)-cyclohexanol (**12**) as an oil: $[\alpha]^{20}_D$ −25.4° (*c* 2.0, EtOH).

Mosher ester analysis indicated that the recovered β-hydroxy amine had a 92% ee.

Preparation of *cis*-(±)-2-(Dimethylamino)cyclohexanol (13). To a precooled solution of formaldehyde (1.90 g, 5.43 mL, 22.0 mmol, 35% aqueous solution) and formic acid (1.90 mL, 50.0 mmol, 95% aqueous solution) was added *cis*-(±)-2-aminocyclohexanol[25] (1.13 g, 10.0 mmol).[26] The solution was heated to 80 °C for 3 h and then allowed to partially cool before adding 1 equiv of 1 N HCl (10.0 mL, 10.0 mmol). The solution was then concentrated to remove the excess formaldehyde and formic acid. The remaining solid was dissolved in a minimum amount of water and then saturated with KOH (with cooling). Extraction with diethyl ether (3 × 250 mL), drying (Na_2SO_4), and evaporation of solvent yielded 1.2 g (85%) of an oil. Bulb to bulb distillation yielded 1.1 g (78%) of *cis*-(±)-2-(Dimethylamino)cyclohexanol (**13**) as a white crystalline solid: mp 45 °C (lit. mp 38–44 °C);[27] ^{1}H NMR ($CDCl_3$) δ 4.04 (d, *J* = 2.2 Hz, 1 H), 3.09 (s, 1 H), 2.30 (s, 6 H), 1.94–2.09 (m, 1 H), 1.82–1.94 (m, 2 H), 1.06–1.60 (m, 6 H); IR (film) 3460 (br), 2970, 2940, 2860, 2825, 2785, 1450, 1425, 1400, 1300, 1285, 1270, 1185, 1120, 1085, 1035, 950, 875 cm^{-1}.

Kinetic Resolution of *cis*-(±)-2-(Dimethylamino)cyclohexanol (13). This reaction was run according to the standard procedures using 440 mg (3.0 mmol) of β-hydroxy amine **13**, 2.0 equiv of Ti(O-*i*-Pr)$_4$ (1.80 g, 1.87 mL, 6.3 mmol), 1.20 equiv of (+)-DIPT (884 mg, 3.80 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (560 μL, 1.80 mmol, 3.29 M solution in toluene)

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in 30 mL of CH_2Cl_2. Standard workup yielded 270 mg (55%) of the *N*-oxide and 110 mg (25%) of *cis*-(−)-2-(dimethylamino)-cyclohexanol (**13**) as an oil: $[\alpha]^{20}_D$ −2.95° (*c* 1.56, MeOH).

Mosher ester analysis indicated that the recovered β-hydroxy amine had a 95% ee.

Preparation of *trans*-(±)-2-(Dibenzylamino)cyclohexanol (14). To a precooled (0 °C) solution of dibenzylamine (1.97 g, 10.0 mmol) in 30 mL of dry CH_2Cl_2 was added 1 equiv of $AlEt_3$ (1.14 g, 10.0 mmol, 4.60 mL of a 25% solution in hexane).[28] The solution was warmed to room temperature and stirred for 2 h. One equivalent of cyclohexane oxide (1.00 g, 10 mmol) was added and the solution stirred overnight. The reaction was quenched by the dropwise addition of 8 mL of 6 M NaOH and stirred vigorously for 24 h. This solution was extracted with CH_2Cl_2 (3 × 125 mL). The organic portions were dried (Na_2SO_4) and concentrated to yield 2.8 g (92%) of a yellow oil which was flash chromatographed (2:1 hexane–EtOAc) to yield 2.2 g (72%) of *trans*-(±)-2-(dibenzylamino)cyclohexanol (**14**) as a white crystalline solid: mp 87–89 °C; ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 10 H), 3.85 (d, *J* = 13.1 Hz, 2 H), 3.75 (s, 1 H), 3.52 (dt, *J* = 3.7, 9.3 Hz, 1 H), 3.37 (d, *J* = 13.1 Hz, 2 H), 2.36 (dt, *J* = 3.0, 10.1 Hz, 1 H), 1.91–2.13 (m, 2 H), 1.61–1.78 (m, 2 H), 1.00–1.37 (m, 4 H); IR ($CHCl_3$) 3450 (br), 3080, 3060, 3000, 2940, 2860, 2810, 1605, 1492, 1450, 1405, 1375, 1130, 1090, 1075, 1065, 985, 878, 700 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.08; H, 8.72; N, 4.53.

Kinetic Resolution of *trans*-(±)-2-(Dibenzylamino)-cyclohexanol (14). This reaction was run according to the standard procedure using 933 mg (3.27 mmol) of β-hydroxy amine **14**, 1.85 equiv of Ti(O-*i*-Pr)$_4$ (1.72 g, 1.80 mL, 6.06 mmol), 1.14 equiv of (+)-DIPT (876 mg, 3.74 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (550 μL, 1.8 mmol, 3.29 M solution in toluene) in 30 mL of CH_2Cl_2. Standard workup yielded 480 mg (50%) of the *N*-oxide (mp 139–141 °C) and 340 mg (36%) of *trans*-(±)-2-(dibenzylamino)cyclohexanol (**14**) as a solid: mp 84–86 °C; $[\alpha]^{20}_D$ +0.5° (*c* 2.2, EtOH).

Mosher ester analysis indicated that the recovered β-hydroxy amine had no enantiomeric excess.

Preparation of (±)-*N*-Methylephedrine (15). To a precooled solution of formaldehyde (7.36 g, 21.0 mL, 85.2 mmol, 35% aqueous solution) was added (±)-norephedrine (6.44 g, 42.6 mmol). The solution was heated to 80 °C for 3 h, then allowed to partially cool before adding 1 equiv of 1 N HCl (42.6 mL, 42.6 mmol). The solution was concentrated to remove the excess formaldehyde and formic acid. The remaining solid was dissolved in a minimum of water and then saturated with KOH (with cooling). Extraction with diethyl ether (3 × 500 mL), drying (Na_2SO_4), and concentration yielded 6.1 g (80%) of a white solid. Recrystallization from petroleum ether gave 4.4 g (58%) of (±)-*N*-methylephedrine (**15**) as a white crystalline solid: mp 62.5–64 °C (lit. mp 63.5–64.5 °C);[29] ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5 H), 4.94 (d, *J* = 3.8 Hz, 1 H), 3.60 (s, 1 H), 2.53 (dq, *J* = 3.8, 7.5 Hz, 1 H), 2.36 (s, 6 H), 0.82 (d, *J* = 7.5 Hz, 3 H); IR ($CHCl_3$) 3400 (br), 3060, 2990, 2870, 2830, 2780, 1493, 1460, 1384, 1260, 1120, 1100, 1065, 1040, 1000, 960 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.60; N, 7.81. Found: C, 73.43; H, 9.68; N, 7.84.

Kinetic Resolution of (±)-*N*-Methylephedrine (15). This reaction was run according to the standard procedure using 200 mg (1.12 mmol) of β-hydroxy amine **15**, 2.00 equiv of Ti(O-*i*-Pr)$_4$ (635 mg, 665 μL, 2.23 mmol), 1.40 equiv of (+)-DIPT (360 mg, 1.56 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (240 μL, 0.67 mmol, 2.80 M solution in toluene) in 10 mL of CH_2Cl_2. Standard workup yielded 115 mg (53%) of the *N*-oxide and 80 mg (40%) of (−)-*N*-methylephedrine (**15**) as a waxy solid: $[\alpha]^{25}_D$ 26.3° (*c* 1.08, EtOH).

Mosher ester analysis indicated that the recovered β-hydroxy amine had a 95% ee.

Preparation of (±)-*N*-Methylpseudoephedrine (16). To a precooled solution of formaldehyde (7.36 g, 21.0 mL, 85.2 mmol, 35% aqueous solution) and formic acid (8.52 mL, 213 mmol, 95% aqueous solution) was added (±)-pseudoephedrine (6.5 g, 39.4 mmol). The solution was heated to 80 °C for 3 h, then allowed to partially cool before adding 1 equiv of 1 N HCl (42.6 mL, 42.6 mmol). The solution was then concentrated to remove the excess formaldehyde and formic acid. The remaining solid was dissolved in a minimum amount of water and saturated with KOH (with cooling). Extraction with diethyl ether (3 × 500 mL), drying (Na_2SO_4), and concentration yielded 7.2 g of an oil. Distillation yielded 6.8 g (96%) of (±)-*N*-methylpseudoephedrine (**16**) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 5 H), 4.72–5.00 (s, 1 H), 4.19 (d, *J* = 10.3 Hz, 1 H), 2.51–2.66 (m, 1 H), 2.32 (s, 6 H), 0.72 (d, *J* = 6.8 Hz, 3 H); IR (film) 3344 (br), 3082, 3060, 3030, 2970, 2940, 2900, 2870, 2830, 2784, 1602, 1450, 1265, 1040, 954, 705 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.60; N, 7.81. Found: C, 73.45; H, 9.80; N, 8.05.

Kinetic Resolution of (±)-*N*-Methylpseudoephedrine (16). This reaction was run according to the standard procedure using 198 mg (1.11 mmol) of β-hydroxy amine **16**, 2.00 equiv of Ti(O-*i*-Pr)$_4$ (635 mg, 665 μL, 2.23 mmol), 1.50 equiv of (+)-DIPT (391 mg, 1.68 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (240 μL, 0.67 mmol, 2.80 M solution in toluene) in 10 mL of CH_2Cl_2. Standard workup yielded 115 mg (53%) of the *N*-oxide and 82.4 mg (42%) of (−)-*N*-methylpseudoephedrine (**16**) as an oil: $[\alpha]^{25}D$ −40.2° (*c* 1.83, EtOH).

Mosher ester analysis indicated that the recovered β-hydroxy amine had a 93% ee.

Preparation of (±)-Dimethyl-(β-hydroxy-α-phenylethyl)amine (17). To a solution of ethyl α-bromophenyl acetate (2.0 g, 8.2 mmol) in 10 mL of THF was added 2.2 equiv of dimethylamine (0.80 g, 18.0 mmol, 2.0 mL of a 40% aqueous solution) and the mixture stirred at room temperature for 24 h. Evaporation of excess dimethylamine, THF, and most of the water followed by extraction with diethyl ether, drying (Na_2SO_4), and concentration yielded 1.56 g (92%) of ethyl α-*N*,*N*-dimethylphenyl acetate. This was dissolved in 20 mL of diethyl ether. $LiAlH_4$, 0.75 equiv (215 mg, 5.70 mmol) was added at −70 °C and the solution stirred for 1 h. The excess $LiAlH_4$ was quenched with wet ether and the product was extracted from the organic phase with 1 N HCl (3 × 10 mL). The combined water layers were made basic with excess NaOH and extracted with diethyl ether (3 × 25 mL). The ether layers were combined, dried (Na_2SO_4), and concentrated to yield 860 mg (70%) of (±)-dimethyl(β-hydroxy-α-phenethyl)amine (**17**) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 3 H), 7.20 (dd, *J* = 1.9, 7.46 Hz, 2 H), 3.94 (dd, *J* = 8.4, 10.1 Hz, 1 H), 3.67 (dd, *J* = 4.8, 10.1 Hz, 1 H), 3.57 (dd, *J* = 4.8, 8.4 Hz, 1 H), 2.55–3.00 (s, 1 H), 2.21 (s, 6 H); IR (film) 3390 (br), 3060, 3030, 2940, 2885, 2820, 2780, 1452, 1350, 1260, 1234, 1160, 1100, 1035, 760, 745, 705 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.47. Found: C, 72.59; H, 9.12; N, 8.47.

Kinetic Resolution of (±)-Dimethyl(β-hydroxy-α-phenethyl)amine (17). This reaction was run according to the standard procedure using 336 mg (2.03 mmol) of β-hydroxy amine **17**, 2.01 equiv of Ti(O-*i*-Pr)$_4$ (1.16 g, 1.21 mL, 4.08 mmol), 1.19 equiv of (+)-DIPT (565 mg, 2.41 mmol), and 0.59 equiv of *tert*-butyl hydroperoxide (365 μL, 1.20 mmol, 3.29 M solution in toluene) in 20 mL of CH_2Cl_2. Standard workup yielded 176 mg (48%) of the *N*-oxide and 129 mg (39%) of (−)-dimethyl(β-hydroxy-α-phenethyl)amine (**17**) as an oil: $[\alpha]^{20}_D$ −5.68° (*c* 1.07, MeOH).

Mosher ester analysis indicated that the recovered β-hydroxy amine had a 34% ee.

Preparation of (±)-Dimethyl(β-hydroxyphenethyl)amine (18). To a solution of 2-bromoacetophenone (6.0 g, 30.0 mmol) in 60 mL of THF was added 10 equiv of dimethylamine (300 mmol, 36 mL of a 40% aqueous solution) and the solution stirred for 1 h at room temperature. The excess dimethylamine and THF were evaporated and the aqueous solution was extracted with diethyl ether (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to yield 4.9 g of dimethyl(β-ketophenethyl)amine as a slightly yellow oil.

A solution of this keto amine (4.90 g, 30.1 mmol) in dry ether was cooled to −70 °C and treated with 0.375 equiv of $LiAlH_4$. After 1 h the reaction was quenched by sequential addition of 425 μL of H_2O, 425 μL of 15% NaOH solution, and 1.27 mL of H_2O and stirred vigorously for 1 h. The aluminum salts were filtered off and the solution was treated with HCl(g). The solid that formed was recrystallized (2 times from EtOH) to yield 2.0 g of the hydrochloride salt of the desired β-hydroxy amine. Addition of

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base, ether extraction, and concentration yielded 1.64 g (33%) of (±)-dimethyl-β-hydroxyphenethylamine (**18**) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 5 H), 4.72 (dd, J = 3.6, 10.5 Hz, 1 H), 2.31–2.57 (m, 2 H), 2.37 (s, 6 H); IR (film) 3410 (br), 3060, 3020, 2985, 2940, 2850, 2820, 2785, 1450, 1330, 1260, 1205, 1175, 1060, 1040, 1025, 865, 750, 700 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.47. Found: C, 72.69; H, 9.12; N, 8.69.

Kinetic Resolution of (±)-Dimethyl(β-hydroxyphenethyl)amine (18). This reaction was run according to the standard procedure using 344 mg (2.08 mmol) of β-hydroxy amine **18**, 1.96 equiv of Ti(O-i-Pr)$_4$ (1.16 g, 1.21 mL, 4.07 mmol), 1.19 equiv of (+)-DIPT (581 mg, 2.48 mmol), and 0.58 equiv of *tert*-butyl hydroperoxide (365 μL, 1.20 mmol, 3.29 M solution in toluene) in 20 mL of CH_2Cl_2. Standard workup yielded 188 mg (49.8%) of the N-oxide and 122 mg (35.5%) of (−)-dimethyl(β-hydroxyphenethyl)amine (**18**) as an oil: $[\alpha]^{20}_D$ −47.76° (c 1.61, MeOH); $[\alpha]^{20}_D$ −45.99° (c 2.07, 1 N HCl).

Chiral shift study indicated that the recovered β-hydroxy amine had a 95% ee.

Preparation of (±)-3-(Benzyloxy)-1,2-epoxypropane (28). To a 500-mL three-necked round-bottomed flask equipped with a mechanical stirrer was added 200 mL of a 50% NaOH solution, 125 mL (148 g, 1.60 mol) of epichlorohydrin, and 4.20 g (12 mmol, 4%) of tetrabutylammonium hydrogen sulfate.[30] This solution was kept below 25 °C while 30.4 mL (32.0 g, 0.30 mol) of benzyl alcohol was added over a 30-min period with vigorous stirring. The vigorously stirred solution was kept below 25 °C for 2.5 h. The solution was poured into 700 mL of ice water and extracted with diethyl ether (3 × 300 mL). The combined organic phases were washed with brine to neutrality, dried ($MgSO_4$), and concentrated to give an oil which was distilled (110 °C, 1–2 mmHg) to yield 46.4 g (95%) of (±)-3-(benzyloxy)-1,2-epoxypropane (**28**) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5 H), 4.55, 4.63 (AB, J_{AB} = 11.4 Hz, 2 H), 3.79 (dd, J = 3.8, 11.4 Hz, 1 H), 3.45 (dd, J = 5.3, 11.4 Hz, 1 H), 3.21 (m, 1 H), 2.83 (t, J = 8.7 Hz, 1 H), 2.64 (dd, J = 1.9, 5.3 Hz, 1 H); IR (film) 3070, 3040, 3005, 2930, 2870, 1500, 1455, 1390, 1255, 1100, 915, 900, 850, 740, 700 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.86; H, 7.45.

Preparation of (±)-Dimethyl[2-hydroxy-3-(benzyloxy)propyl]amine (19). To a solution of (±)-3-(benzyloxy)-1,2-epoxypropane (**28**) (43.5 g, 250 mmol) in 500 mL of THF was added 5.0 equiv of dimethylamine (56.0 g, 1.25 mol, 140 mL of a 40% aqueous solution) and the mixture refluxed for 2 h. Evaporation of THF, excess dimethylamine, and H_2O followed by distillation yielded 55.7 g (100%) of (±)-dimethyl[2-hydroxy-3-(benzyloxy)propyl]amine (**19**) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5 H), 4.58 (s, 2 H), 3.82–3.94 (m, 1 H), 3.46, 3.50 (ABX, J = 4.5, 5.2, 9.7 Hz, 2 H), 2.45 (dd, J = 9.3, 11.2 Hz, 1 H), 2.24 (dd, J = 3.7, 11.2 Hz, 1 H), 2.28 (s, 6 H); IR (film) 3420 (br), 3030, 2940, 2860, 2820, 2780, 1455, 1365, 1325, 1265, 1110, 1030, 738, 700 cm^{-1}.

Kinetic Resolution of (±)-Dimethyl[2-hydroxy-3-(benzyloxy)propyl]amine (19). This reaction was run according to the standard procedure using 52.25 g (250 mmol) of β-hydroxy amine **19**, 2.0 equiv of Ti(O-i-Pr)$_4$ (142 g, 149 mL, 500 mmol), 1.2 equiv of (+)-DIPT, and 0.60 equiv of *tert*-butyl hydroperoxide (39.3 mL, 150 mmol, 3.82 M solution in toluene) in 2.5 L of CH_2Cl_2. Standard workup yielded 53.35 g (97%) of a mixture of β-hydroxy amine and N-oxide. Standard hexane trituration was not used on this substrate because the N-oxide is an oil, not a solid. The 53.35 g of oil was dissolved in 1.5 L of EtOAc, washed with H_2O (pH 10, 5 × 50 mL) to remove the N-oxide, dried ($MgSO_4$), and concentrated to yield 17.8 g (34%) of (−)-dimethyl[2-hydroxy-3-(benzyloxy)propyl]amine (**19**) as an oil: $[\alpha]^{20}_D$ −9.75° (c 2.00, EtOH).

Mosher ester analysis indicated that the recovered β-hydroxy amine had a 91% ee.

Preparation of (±)-3-(1-Naphthyloxy)-1,2-epoxypropane (29). To a solution of 1-naphthol (7.2 g, 50.0 mmol) in 75 mL of dry DMF was added 1.0 equiv of NaH (1.26 g, 50.0 mmol) and the mixture heated to 80 °C for 1 h. To this solution was added 5 equiv of epichlorohydrin (23.0 g, 20.0 mL, 50.0 mmol), and it was then heated to 140 °C for 4 h. The solution was cooled and poured into 150 mL of H_2O. Extraction with diethyl ether (3 × 200 mL), drying ($MgSO_4$), and concentration gave 12.0 g of an oil. This was flash chromatographed (12:1 hexane–EtOAc) to give 7.66 g (76%) of the (±)-3-(1-naphthyloxy)-1,2-epoxypropane (**29**) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.30 (m, 1 H), 7.80 (m, 1 H), 7.32–7.56 (m, 5 H), 4.44 (dd, J = 3.0, 11.3 Hz, 1 H), 4.17 (dd, J = 5.3, 11.3 Hz, 1 H), 3.51 (m, 1 H), 2.98 (t, J = 4.1 Hz, 1 H), 2.87 (dd, J = 1.9, 4.6 Hz, 1 H); IR (film) 3045, 2995, 2910, 1575, 1395, 1270, 1240, 1100, 790, 770 cm^{-1}. Anal. Cacld for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.05; H, 6.01.

Preparation of (±)-Dimethyl[2-hydroxy-3-(1-naphthyloxy)propyl]amine (20). To a solution of epoxide **29** (5.0 g, 25 mmol) in 20 mL of THF was added 1.5 equiv of dimethylamine (1.8 g, 4.5 mL, 40% of an aqueous solution) and the mixture heated to 90 °C for 2 h. Evaporation of THF, water, and excess dimethylamine, followed by flash chromatography (100% EtOAc) gave 3.24 g (53%) of (±)-dimethyl[2-hydroxy-3-(1-naphthyloxy)propyl]amine (**20**) as a solid: mp 79–79.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.27 (m, 1 H), 7.80 (m, 1 H), 7.45 (m, 4 H), 6.82 (d, J = 7.5 Hz, 1 H), 4.09–4.27 (m, 3 H), 2.63 (dd, J = 8.6, 12.0 Hz, 1 H), 2.56 (dd, J = 3.8, 12.0 Hz, 1 H), 2.36 (s, 6 H); IR (film) 3400 (br), 1650, 1592, 1578, 1460, 1390, 1270, 1230, 1100, 790, 770 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.42; H, 7.90; N, 5.67.

Kinetic Resolution of (±)-Dimethyl[2-hydroxy-3-(1-naphthyloxy)propyl]amine (20). This reaction was run according to the standard procedure using 2.0 g (8.2 mmol) of β-hydroxy amine **20**, 2.0 equiv of Ti(O-i-Pr)$_4$ (4.64 g, 4.85 mL, 16.4 mmol), 1.2 equiv of (+)-DIPT (2.3 g, 9.8 mmol), and 0.6 equiv of *tert*-butyl hydroperoxide (990 μL, 4.92 mmol, 4.98 M solution in toluene) in 80 mL of CH_2Cl_2. Standard workup yielded 1.2 g (56%) of the N-oxide and 800 mg (40%) of (−)-dimethyl[2-hydroxy-3-(1-naphthyloxy)propyl]amine (**20**) as a solid: $[\alpha]^{20}_D$ −2.6° (c 2.0, EtOH).

Chiral shift study indicated that the recovered β-hydroxy amine had a 92% ee.

Preparation of (±)-Benzylisopropyl[2-hydroxy-3-(1-naphthyloxy)propyl]amine (21). To a solution of epoxide **29** (3.3 g, 16.5 mmol) in 5 mL of EtOH was added 1.0 equiv of N-benzylisopropylamine (2.48 g, 2.76 mL, 16.7 mmol) and the mixture heated to 70 °C for 18 h. Concentration and flash chromatography (3:1 hexane–EtOAc) yielded 4.90 g (85%) of (±)-benzylisopropyl[2-hydroxy-3-(1-naphthyloxy)propyl]amine (**21**) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.17 (m, 1 H), 7.80 (m, 1 H), 7.20–7.57 (m, 9 H), 6.78 (d, J = 7.5 Hz, 1 H), 4.03–4.20 (m, 3 H), 3.45, 3.81 (AB, J_{AB} = 13.2 Hz, 1 H), 2.95–3.14 (m, 1 H), 2.84 (d, J = 6.0 Hz, 2 H), 1.15 (d, J = 7.1 Hz, 3 H), 1.07 (d, J = 7.1 Hz, 3 H); IR (film) 3400 (br), 3050, 3020, 2960, 2920, 2860, 2830, 1590, 1580, 1395, 1270, 1240, 1170, 1100, 790, 770, 730, 700 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 78.43; H, 7.83; N, 4.00.

Kinetic Resolution of (±)-Benzylisopropyl[2-hydroxy-3-(1-naphthyloxy)propyl]amine (21). This reaction was run according to the standard procedure using 381 mg (1.09 mmol) of β-hydroxy amine **21**, 2.0 equiv of Ti(O-i-Pr)$_4$ (670 mg, 700 μL, 2.36 mmol), 1.4 equiv of (+)-DIPT (336 mg, 1.65 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (234 μL, 0.67 mmol, 2.8 M solution in toluene) in 10 mL of CH_2Cl_2. Standard workup yielded 214 mg (56%) of the N-oxide and 138 mg (36%) of (+)-benzylisopropyl[2-hydroxyl-3-(1-naphthyloxy)propyl]amine (**21**) as an oil: $[\alpha]^{20}_D$ +9.2° (c 3.13, EtOH).

Mosher ester analysis indicated that the β-hydroxy amine had a 32% ee.

Preparation of (±)-Benzylisopropyl(β-hydroxyphenethyl)amine (22). To a solution of styrene oxide (2.40 g, 2.28 mL, 20 mmol) in 10.0 mL of toluene and 0.5 mL of water was added 1.0 equiv of benzylisopropylamine (2.99 g, 3.32 mL, 20 mmol) and the mixture refluxed for 3 h. Evaporation of the solvents followed by flash chromatography (19:1 hexane–EtOAc) yielded 5.1 g (94%) of (±)-benzylisopropyl(β-hydroxyphenethyl)amine (**22**) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 10 H), 4.53 (dd, J = 3.8, 10.5 Hz, 1 H), 3.57, 3.84 (AB, J_{AB} = 14.3 Hz, 2 H), 3.01 (m, 1 H), 2.57 (m, 2 H), 1.12 (d, J = 7.5 Hz, 3 H), 1.00 (d, J = 6.4 Hz, 3 H); IR (film) 3420 (br), 3085, 3060, 3025, 2965, 2930, 2870, 2835, 1950, 1875, 1805, 1750, 1605, 1585, 1490, 1450, 1385, 1365, 1202, 1165, 1060, 1028, 700–800 (br) cm^{-1}.

(30) Mouzin, G.; Crousse, H.; Rieu, J.-P.; Duflos, A. *Synthesis* **1983**, 117.

Kinetic Resolution of (±)-Benzylisopropyl(β-hydroxyphenethyl)amine (22). This reaction was run according to the standard procedure using 314 mg (1.12 mmol) of β-hydroxy amine **36**, 2.0 equiv of Ti(O-*i*-Pr)$_4$ (635 mg, 665 μL, 2.23 mmol), 1.4 equiv of (+)-DIPT (366 mg, 1.56 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (240 μL, 0.67 mmol, 2.8 M solution in toluene) in 10 mL of CH_2Cl_2. Standard workup yielded 200 mg (61%) of the *N*-oxide and 110 mg (35%) of (−)-benzylisopropyl(β-hydroxyphenethyl)amine (**22**) as an oil: $[\alpha]^{20}_D$ −0.74° (*c* 3.92, EtOH).

Mosher ester analysis indicated that the β-hydroxy amine had a 15% ee.

Preparation of (±)-Dimethyl(3-hydroxy-3-phenylpropyl)amine (23). A mixture of acetophenone (6.0 g, 5.6 mL, 50.0 mmol), dimethylamine hydrochloride (5.3 g, 65 mmol, 1.3 equiv), paraformaldehyde (2.0 g, 66 mmol, 1.3 equiv), concentrated hydrochloric acid (1 mL), and 80 mL of EtOH was refluxed for 2 h.[31] The solution was poured into a 125-mL Erlenmeyer flask to which 40 mL of acetone was added. This was cooled slowly and chilled overnight in a refrigerator. The resulting crystals were filtered, washed with 10 mL of acetone, and suction dried to yield 9.0 g (84%) of (±)-dimethyl(3-keto-3-phenylpropyl)amine hydrochloride as a white crystalline solid: mp 138–141 °C (lit. mp 138–141 °C).[31]

This salt (3.66 g, 16.4 mmol) was added to 100 mL of THF and treated with 3 equiv of DIBAL-H (50 mL, 50 mmol, 1.0 M solution in CH_2Cl_2) at −70 °C, slowly warmed to room temperature, and stirred for 2 h. Added in sequence were 2.1 mL of H_2O, 3.1 mL of 10% NaOH, and 5.1 mL of H_2O. This was stirred vigorously for 2 h, filtered, and concentrated to yield 2.85 g (92%) of (±)-dimethyl(3-hydroxy-3-phenylpropyl)amine (**23**) as a solid: mp 47–48 °C; ^{1}H NMR ($CDCl_3$ δ 7.21 (m, 5 H), 4.94 (dd, *J* = 4.5, 7.5 Hz, 1 H), 2.60–2.81 (m, 1 H), 2.43–2.55 (m, 1 H), 2.31 (s, 6 H), 1.85 (m, 2 H); IR ($CHCl_3$) 3200 (br), 2995, 2950, 2860, 2820, 2780, 1465, 1240, 1050, 700 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.70; H, 9.79; N, 7.85.

Kinetic Resolution of (±)-Dimethyl(β-hydroxy-3-phenylpropyl)amine (23). This reaction was run according to the standard procedure using 200 mg (1.12 mmol) of β-hydroxy amine **23**, 2.0 equiv of Ti(O-*i*-Pr)$_4$ (635 mg, 665 μL, 2.23 mmol), 1.2 equiv of (+)-DIPT (314 mg, 1.34 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (240 μL, 0.67 mmol, 2.8 M solution in toluene) in 10 mL of CH_2Cl_2. Standard workup yielded 74 mg (37.0%) of the *N*-oxide and 114 mg (52.3%) of (±)-dimethyl(3-hydroxy-3-phenylpropyl)amine (**23**) as a white crystalline solid: mp 45–47 °C.

Mosher ester analysis indicated that the β-hydroxy amine had no enantiomeric excess.

Preparation of (±)-2-Pyrrolidino-1-phenylethanol (7). A solution of (±)-stryene oxide (21.1 g, 20.0 mL, 176 mmol) in 23.0 mL of pyrrolidine (19.6 g, 276 mmol, 1.6 equiv) was refluxed for 5 h. The excess pyrrolidine was evaporated and 20 mL of isopropyl alcohol was added. The crystalline product was filtered to yield 18.0 g (45%) of (±)-2-pyrrolidino-1-phenylethanol (**7**): mp 58–59.9 °C (lit. mp 57–58 °C);[32] ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5 H), 4.70 (dd, *J* = 3.8, 10.6 Hz, 1 H), 4.03 (s, 1 H), 2.66–2.82 (m, 3 H), 2.39–2.58 (m, 3 H), 1.78 (s, 4 H); IR ($CHCl_3$) 3420 (br), 3060, 3000, 2970, 2930, 2880, 2805, 1605, 1450, 1350, 1060, 900 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.18; H, 8.75; N, 7.32.

Kinetic Resolution of (±)-2-Pyrrolidino-1-phenylethanol (7). This reaction was run according to the standard procedure using 1.92 g (10.0 mmol) of β-hydroxy amine **7**, 2.0 equiv of Ti(O-*i*-Pr)$_4$ (5.96 g, 6.24 mL, 21.0 mmol), 1.2 equiv of (+)-DIPT (2.84 g, 12.1 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (1.85 mL, 6.09 mmol, 3.29 M solution in toluene). Standard workup yielded 1.22 g (58.9%) of the *N*-oxide and 0.71 g (37.0%) of (−)-2-pyrrolidino-1-phenylethanol (**7**) as a solid: mp 69.5–70.5 °C; $[\alpha]^{20}_D$ −40.3° (*c* 1.88, EtOH).

Chiral shift study indicated that the recovered β-hydroxy amine had a 95% ee.

Preparation of (±)-Dibenzyl(β-hydroxyphenethyl)amine (24). A solution of (±)-styrene oxide (2.4 g, 2.27 mL, 20.0 mmol) in 3.0 mL of dibenzylamine (3.0 g, 20.0 mmol) was stirred at 80 °C for 24 h. The mixture was flash chromatographed (19:1 hexane–EtOAc) to yield 5.2 g (96%) of (±)-dibenzyl(β-hydroxyphenethyl)amine (**24**) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 15 H), 4.71 (t, *J* = 6.5 Hz, 1 H), 3.49, 3.92 (AB, J_{AB} = 13.1 Hz, 2 H), 2.65 (d, *J* = 6.5 Hz, 2 H); IR (film) 3420 (br), 3080, 3060, 3020, 2920, 2880, 2810, 1600, 1490, 1445, 1368, 1200, 1120, 1060, 1025, 745, 700 cm^{-1}. Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.09; H, 7.52; N, 4.53.

Kinetic Resolution of (±)-Dibenzyl(β-hydroxyphenethyl)amine (24). This reaction was run according to the standard procedure using 317 mg (1.00 mmol) of β-hydroxy amine **24**, 2.0 equiv of Ti(O-*i*-Pr)$_4$ (568 mg, 595 μL, 2.00 mmol), 1.2 equiv of (+)-DIPT (282 mg, 1.20 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (182 μL, 0.60 mmol, 3.29 M solution in toluene) in 10 mL of CH_2Cl_2. Standard hydrolysis yielded 330 mg of the *N*-oxide and β-hydroxy amine. Flash chromatography (2:1 EtOAc–hexane) yielded 60.0 mg (19%) of (−)-dibenzyl(β-hydroxyphenethyl)amine (**24**) as an oil: $[\alpha]^{20}_D$ −0.06° (*c* 1.56, EtOH).

Chiral shift study indicated that the recovered β-hydroxy amine had a 10% ee.

Preparation of (±)-Benzylmethyl(β-hydroxyphenethyl)amine (25). To a solution of 2-bromoacetophenone (10.0 g, 50.2 mmol) in 100 mL of THF was added 2 equiv of benzylmethylamine (12.16 g, 12.94 mL, 100 mmol) and the mixture stirred for 2 h at room temperature. The solvent was evaporated and replaced with 100 mL of diethyl ether. This solution was washed with 10% NaOH (2 × 10 mL) and the ether evaporated to give 14.6 g of an oil which was flash chromatographed (4:1 hexane–EtOAc) to yield 10.0 g (83%) of benzylmethyl(β-ketophenethyl)amine as an oil.

To a solution of this keto amine (4.9 g, 20.9 mmol) in 100 mL of dry THF, cooled to −78 °C, was added 0.50 equiv of $LiAlH_4$ (400 mg, 10.5 mmol) and the mixture was allowed to warm to room temperature while stirring overnight. The reaction was quenched by sequential treatment with 420 mL of H_2O, 630 mL of 10% NaOH (aq), and 1.05 mL of H_2O and stirred vigorously for 3 h. Filtration of the aluminum salts followed by concentration and flash chromatography (4:1 hexane–EtOAc) yielded 4.9 g (100%) of (±)-benzylmethyl(β-hydroxyphenyl)amine (**25**) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 10 H), 4.75 (dd, *J* = 4.2, 10.2 Hz, 1 H), 4.11 (s, 1 H), 3.53, 3.76 (AB, J_{AB} = 13.3, 2H), 2.56 (m, 2 H), 2.32 (s, 3 H); IR (film) 3440 (br), 3080, 3060, 3030, 2940, 2820, 2795, 1490, 1450, 1060, 1020, 755, 740, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.64; H, 8.02; N, 5.83.

Kinetic Resolution of (±)-Benzylmethyl(β-hydroxyphenethyl)amine (25). This reaction was run according to the standard procedure using 269 mg (1.12 mmol) of β-hydroxy amine **25**, 2.0 equiv of Ti(O-*i*-Pr)$_4$ (651 mg, 682 μL, 2.29 mmol), 1.2 equiv of (+)-DIPT (322 mg, 1.38 mmol), and 0.60 equiv of *tert*-butyl hydroperoxide (240 μL, 0.67 mmol, 2.8 M solution in toluene) in 10 mL of CH_2Cl_2. Standard workup yielded 152 mg (62%) of the *N*-oxide and 88 mg (33%) of (−)-benzylmethyl(β-hydroxyphenethyl)amine (**25**) as an oil: $[\alpha]^{20}_D$ −49.2° (*c* 2.3, EtOH).

Mosher ester analysis indicated that the β-hydroxy amine had an 86% ee.

Preparation of (±)-2-Piperidino-1-phenylethanol (26). A solution of styrene oxide (9.60 g, 80.0 mmol) in 12 mL of piperidine (120 mmol, 1.5 equiv) was refluxed for 7 h. Evaporation of excess piperidine and recrystallization from ethanol yielded 6.92 g (42.1%) of (±)-2-piperidino-1-phenylethanol (**26**) as a solid: mp 69–71 °C; (lit. mp 68–70 °C);[32] ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5 H), 4.71 (dd, *J* = 4.5, 10.2 Hz, 1 H), 4.24 (br s, 1 H), 2.70 (m, 2 H), 2.29–2.52 (m, 4 H), 1.61 (m, 4 H), 1.48 (m, 2 H); IR ($CHCl_3$) 3380 (br), 3085, 3060, 3000, 2940, 2850, 2800, 1450, 1330, 1320, 1155, 1060, 900, 870, 700 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.87; H, 9.40; N, 6.91.

Kinetic Resolution of (±)-2-Piperidino-1-phenylethanol (26). This reaction was run according to the standard procedure using 0.419 g (2.04 mmol) of β-hydroxy amine **26**, 2.0 equiv of Ti(O-*i*-Pr)$_4$ (1.16 g, 1.21 mL, 4.07 mmol), 1.19 equivalents of (+)-DIPT (0.570 g, 2.43 mmol) and 0.60 equiv of *tert*-butyl hydroperoxide (370 μL, 1.22 mmol, 3.29 M solution in toluene) in 20 mL of CH_2Cl_2. Standard workup yielded 243 mg (53.8%) of the *N*-oxide and 156 mg (37.2%) of (−)-2-pyrrolidino-1-phenyl-

(31) Maxwell, C. E. In "Organic Syntheses"; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. III, p 305.

(32) Chapman, N. B.; Triggle, D. J. *J. Chem. Soc.* **1963**, 1385.

ethanol (26) as a solid: $[\alpha]^{20}_D$ −51.2° (c 1.12, EtOH).

Chiral shift study indicated that the recovered β-hydroxy amine had a 97% ee.

Kinetic Resolution of (±)-Benzyl(3,4-dimethoxyphenethyl)[2-hydroxy-3-(*m*-tolyloxy)propyl]amine (27).[23] This reaction was run according to the standard procedure using 205 mg (0.471 mmol) of β-hydroxy amine **27**, 2.0 equiv of Ti(O-*i*-Pr)$_4$ (268 mg, 280 μL, 0.94 mmol), 1.66 equiv of (+)-DIPT (133 mg, 0.565 mmole, and 0.60 equiv of *tert*-butyl hydroperoxide (86 μL, 0.282 mmol, 3.29 M solution in toluene) in 10 mL of CH_2Cl_2. Standard workup followed by flash chromatography (9:1 hexane–EtOAc) yielded 71 mg (35%) of (+)-benzyl(3,4-dimethoxyphenethyl)[2-hydroxy-3-(*m*-tolyloxy)propyl]amine (**27**) as an oil: $[\alpha]^{20}_D$ +13.7° (c 3.55, EtOH).

Chiral shift study indicated that the recovered β-hydroxy amine had an 85% ee.

Conversion of (*S*)-(−)-Dimethyl[2-hydroxy-3-(benzyloxy)propyl]amine (19) to (*R*)-(+)-3-(Benzyloxy)-1,2-epoxypropane (28). A solution of the (*S*)-(−)-dimethyl[2-hydroxy-3-(benzyloxy)propyl]amine (**19**) (synthesized above in 91% ee) (4.1 g, 19.7 mmol) in 100 mL of dry DMF was treated with 10 equiv of MeI (12.0 mL, 196 mmol) for 3 h at room temperature. The excess MeI and DMF were evaporated to yield 6.62 g (98%) of (*S*)-(−)-trimethyl[2-hydroxy-3-(benzyloxy)propyl]ammonium iodide, as a solid: mp 113–115 °C; $[\alpha]^{20}_D$ −22.60° (c 2.5, DMF).

This solid was dissolved in 100 mL of dry DMF. To this was added 900 mL of dry THF and the solution heated to 80 °C before addition of 2 equiv of NaH (940 mg, 39.2 mmol). It was kept at 80 °C for 3 h. The reaction was cooled and quenched with wet ether. The THF and ether were evaporated; the DMF solution was diluted with 1.0 L of ether and washed with water (3 × 100 mL). The ether solution was dried ($MgSO_4$) and concentrated to yield 3.3 g of a yellow oil. Bulb to bulb distillation yielded 2.6 g (80%) of (*R*)-(+)-3-(benzyloxy)-1,2-epoxypropane (**28**) as an oil: $[\alpha]^{20}_D$ +13.76° (c 2.0, EtOH) [lit. value $[\alpha]^{20}_D$ +13.9° (neat)].[34] On the basis of the optical purity of the starting material **19**, the ee should be about 91%.

Conversion of (*S*)-(−)-Dimethyl[2-hydroxy-3-(1-naphthyloxy)propyl]amine (20) to (*S*)-(+)-3-(1-Naphthyloxy)-1,2-epoxypropane (29). To a solution of (*S*)-(−)-dimethyl[2-hydroxy-3-(1-naphthyloxy)propyl]amine (**20**) (synthesized above with 92% ee) (150 mg, 0.61 mmol) in 5 mL of dry DMF was added 10 equiv of MeI (870 mg, 6.1 mmol) and the mixture stirred at room temperature for 18 h. The excess MeI and DMF were then evaporated. Another 5 mL of DMF was added and the solution was heated to 80 °C. Two equivalents of NaH (29.4 mg, 1.22 mmol) was added and stirred for 10 min. The reaction was quenched with wet ether, poured into 25 mL of water, and extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to yield 60 mg (50%) of (*S*)-(+)-3-(1-naphthyloxy)-1,2-epoxypropane (**29**) as an oil: $[\alpha]^{20}_D$ +33.2° (c 2.33, EtOH).

Preparation of (*S*)-(−)-Isopropyl[2-hydroxy-3-(1-naphthyloxy)propyl]amine (30). A solution of (*S*)-(+)-**29** (60 mg, 0.3 mmol) in 10 equiv of isopropylamine (177 mg, 255 L, 3.0 mmol) and water (20 μL) was refluxed for 3 h. The excess isopropylamine and water were evaporated to give 78 mg (100%) of (*S*)-(−)-isopropyl[2-hydroxy-3-(1-naphthyloxy)propyl]amine (**30**) as a solid: mp 70 °C (lit. mp 73 °C);[35] $[\alpha]^{20}_D$ −7.4° (c 1.0, EtOH) [lit. $[\alpha]^{20}_D$ −10.6° (c 1.02, EtOH)]. On the basis of the optical purity of the starting material **20**, the ee should be about 92%. ^{1}H NMR ($CDCl_3$) δ 8.25 (m, 1 H), 7.81 (m, 1 H), 7.31–7.54 (m, 4 H), 6.84 (d, J = 7.5 Hz, 1H), 4.10-4.25 (m, 3H), 3.01 (dd, J = 3.0, 13.1 Hz, 1H), 2.78–2.93 (m, 2 H), 1.63–2.39 (m, 2 H), 1.12 (d, J = 6.0 Hz, 6 H); IR ($CHCl_3$) 3320 (br), 3060, 3000, 2965, 2930, 1598, 1580, 1510, 1460, 1405, 1270, 1240, 1105, 1070, 1020 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.36; H, 8.30; N, 5.43.

Titanium/Tartrate Ratio Study on (±)-*N*-Methylephedrine (15). These reactions were performed as previously described for β-hydroxy amine **15**, with the exception that the amount of tartrate was varied. The weight and equivalents of tartrate, with the resulting ee are listed below. All yields were consistently 90–95% of the expected yield. 321 mg (1.2 equiv, 58% ee), 340 mg (1.3 equiv, 85% ee), 366 mg (1.4 equiv, 96% ee), 392 mg (1.5 equiv, 95% ee), 470 mg (1.8 equiv, 85% ee), and 628 mg (2.4 equiv, 50% ee).

Study of the Effect of Water in the Kinetic Resolution of (±)-*N*-Methylephedrine (15). These reactions were performed as previously described for this substrate with the exception that water was added to the β-hydroxy amine and tartrate before the solvent and Ti(O-*i*-Pr)$_4$ were added. The amount and equivalents of water (per equivalent of β-hydroxy amine), the percent conversion, and the resulting ee are listed below. 10 mg (0.5 equiv, 60% conversion, 71% ee), 20 mg (1.0 equiv, 58% conversion, 53% ee), and 40 mg (2.0 equiv, 32% conversion, 0% ee).

Temperature Study Using (±)-*N*-Methylephedrine (15). These reactions were performed as previously described for this substrate with the exception that the reaction temperature was varied. Entry 1 was started at −78 °C and worked up after 8 h (resulting ee 24%). Entry 2 was started at −78 °C, warmed up to −20 °C after 8 h, and worked up after an additional 12 h (resulting ee 95%). Entry 3 was started at −45 °C and worked up after 8 h (resulting ee 95%). Entry 4 was started at −45 °C, warmed up to −20 °C after 8 h and worked up after an additional 12 h (resulting ee 95%). Entry 5 was started at −20 °C and worked up after 8 h (resulting ee 95%). Entry 6 was started at 0 °C and worked up after 8 h (resulting ee 95%). Entry 7 was started at room temperature (~23 °C) and worked up after 8 h (resulting ee 90%).

Acknowledgment. We are grateful to the National Institute of Health (Grant GM 28384) and to Eli Lilly for financial support. S.M. thank the Ministry of Education of Japan for the Overseas Research Fellowship (1982–1983) and S.M.V. thanks the National Science Foundation for a Graduate Fellowship. We thank Dr. Lee Weigel of Eli Lilly for a large sample of (*R*)-(−)-styrene oxide, which greatly eased problems associated with determinations of absolute configuration.

Registry No. (±)-**7**, 87040-32-2; (*R*)-**7**, 87069-57-6; (*S*)-**7** (*N*-oxide), 87040-33-3; (±)-**8**, 97807-81-3; (*R*)-**8**, 97859-92-2; (*S*)-**8** (*N*-oxide), 97807-84-6; (±)-**9**, 87040-35-5; (*R*)-**9**, 87069-58-7; (*S*)-**9** (*N*-oxide), 97807-85-7; (±)-**10**, 87040-36-6; (±)-**10** (*N*-oxide), 97807-86-8; (±)-**11**, 87050-10-0; (*R*)-**11**, 87098-82-6; (*S*)-**11** (*N*-oxide), 97807-87-9; (±)-**12**, 21651-78-5; (−)-**12**, 29783-02-6; (+)-**12** (*N*-oxide), 97859-94-4; (±)-**13**, 21651-80-9; (−)-**13**, 21651-71-8; (+)-**13** (*N*-oxide), 97859-95-5; (±)-**14**, 97807-82-4; (±)-**14** (*N*-oxide), 97807-88-0; (±)-**15**, 1201-56-5; (−)-**15**, 552-79-4; (+)-**15** (*N*-oxide), 97807-89-1; (±)-**16**, 87040-40-2; (−)-**16**, 14222-20-9; (+)-**16** (*N*-oxide), 97807-90-4; (±)-**17**, 2202-64-4; (*R*)-**17**, 2202-65-5; (*S*)-**17** (*N*-oxide), 97807-91-5; (±)-**18**, 2202-68-8; (*R*)-**18**, 34469-09-5; (*S*)-**18** (*N*-oxide), 97807-92-6; **18** (ketone), 3319-03-7; (±)-**19**, 97807-83-5; (*S*)-**19**, 97859-96-6; (*S*)-**19**·MeI, 97808-00-9; (*R*)-**19** (*N*-oxide), 97807-93-7; (±)-**20**, 87040-38-8; (*S*)-**20**, 87069-60-1; (*R*)-**20** (*N*-oxide), 97807-94-8; (±)-**21**, 87069-61-2; (*S*)-**21**, 53729-51-4; (*R*)-**21** (*N*-oxide), 97807-95-9; (±)-**22**, 87040-39-9; (*R*)-**22**, 97905-45-8; (*S*)-**22** (*N*-oxide), 97825-80-4; (±)-**23**, 36296-95-4; (±)-**23** (*N*-oxide), 97807-96-0; **23** (ketone)·HCl, 879-72-1; (±)-**24**, 87040-34-4; (*R*)-**24**, 97859-97-7; (*S*)-**24** (*N*-oxide), 97807-97-1; (±)-**25**, 52026-30-9; (*R*)-**25**, 87098-81-5; (*S*)-**25** (*N*-oxide), 97807-98-2; **25** (ketone), 33350-26-4; (±)-**26**, 13626-20-5; (*R*)-**26**, 40116-77-6; (*S*)-**26** (*N*-oxide), 97807-99-3; (±)-**27**, 87040-37-7; (*S*)-**27**, 87069-59-8; (±)-**28**, 89616-40-0; (*R*)-**28**, 16495-13-9; (±)-**29**, 87144-72-7; (*S*)-**29**, 61249-00-1; **30**, 4199-09-1; (+)-DIPT, 2217-15-4; TBHP, 75-91-2; $HNMe_2$, 124-40-3; Ti(O-*i*-Pr$_4$), 546-68-9; $HN(CH_2Ph)_2$, 103-49-1; (±)-$PhCHBrCO_2Et$, 2882-19-1; (±)-$PhCH(NMe_2)CO_2Et$, 85438-03-5; $PhCOCH_2Br$, 70-11-1; $PhCH_2OH$, 100-51-6; *i*-$PrNHCH_2Ph$, 102-97-6; $PhCOCH_3$, 98-86-2; $HNMe_2$·HCl, 506-59-2; $MeNHCH_2Ph$, 103-67-3; *i*-$PrNH_2$, 75-31-0; (±)-1,2-epoxydecane, 67210-45-1; pyrrolidine, 123-75-1; (±)-1-cyclohexyl-1,2-epoxyethane, 97859-93-3; cyclohexene oxide, 4065-81-0; (±)-*cis*-2-

(33) We thank Dr. Marvin Hoekstra of Warner-Lambert for a racemic sample of this *N*-benzyl derivative of their cardioselective β-blocker, bevantolol.

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(35) Howe, R.; Shanks, R. G. *Nature (London)* **1966**, *210*, 1336.

aminocyclohexanol, 38898-70-3; (±)-norephedrine, 14838-15-4; (±)-pseudoephedrine, 4125-58-0; (±)-epichlorohydrin, 61630-87-3; 1-naphthol, 90-15-3; (±)-styrene oxide, 67253-49-0; piperidine, 110-89-4; (S)-3-phenoxy-1,2-epoxypropane, 71031-03-3; (S)-3-(4-cyanophenoxy)-1,2-epoxypropane, 70987-80-3; (S)-3-(4-methoxyphenoxy)-1,2-epoxypropane, 71048-65-2.

Supplementary Material Available: Determination of absolute configuration of β-hydroxy amines (10 pages). Ordering information is given on any current masthead page.

Photochemical Conversion of Sulfonium Salts to Sulfides via a 1,3-Sigmatropic Rearrangement. Photogeneration of Brønsted Acids

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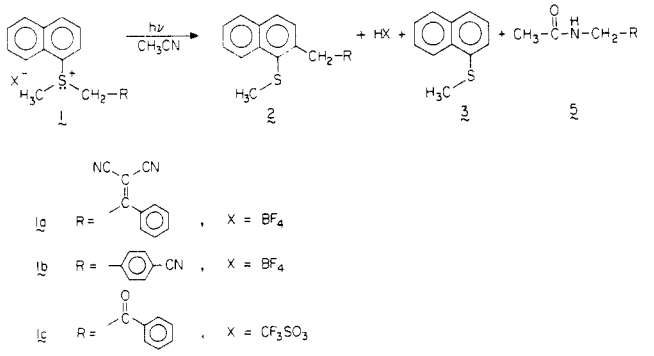
Received January 10, 1985

A series of 1-naphthyl methyl-substituted alkylsulfonium salts underwent 1,3-sigmatropic rearrangements to form 1-(methylthio)-2-substituted alkylnaphthalenes and the corresponding acid with quantum yields between 0.24 and 0.10. In competition with rearrangement was a bond-cleavage reaction forming 1-naphthyl methyl sulfide. The quantum yield for bond cleavage was ~0.15 for all the compounds studied.

Photolysis of triarylsulfonium and aryldialkylsulfonium salts normally provides products resulting from homolytic as well as heterolytic cleavage of carbon–sulfur bonds.[1] The product distribution is dependent on counterion[2] and solvent as well as the specific group attached to sulfur.[3]

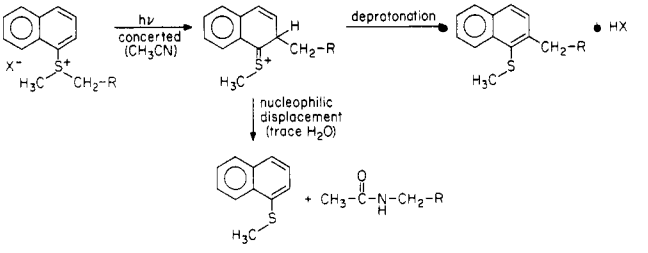
We report the novel photorearrangement of 1-naphthyl methyl-substituted alkylsulfonium salts to 1-(methylthio)-2-substituted alkylnaphthalenes and acid via a 1,3-sigmatropic rearrangement through the excited singlet electronic state of the naphthalene derivative. Products derived from sulfur–carbon bond cleavage are also observed.



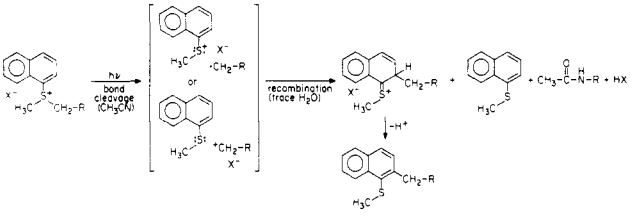
An attempt was made to elucidate the mechanism of rearrangement by means of quenching, sensitization, and product studies. The experimental observations are consistent with a photochemically allowed concerted 1,3-sigmatropic rearrangement involving four electrons or a cage bond-cleavage–recombination mechanism as shown in Schemes I and II. The naphthylene moiety in **1b** and **1c** is absorbing effectively all irradiation beyond 310 nm, whereas the naphthalene chromophore in **1a** absorbs ~63% of the light in this wavelength region and the R group the remaining 37%.

Triplet quenchers such as molecular oxygen (~10^{-3} M, E_T = 22.5 kcal/mol)[4] and 1,3-cyclohexadiene (1.0×10^{-1} M, E_T = 52.4 kcal/mol)[4] do not quench the production of **2(a–c)**, suggesting the involvement of the singlet state, whose lifetime in CH_3CN is ~1 ns. In agreement with that, attempts to sensitize the rearrangement of the naphthylsulfonium salts (E_T ~61 kcal/mol) with benzophenone (4.0×10^{-2} M, E_T = 69 kcal/mol) were unsuccessful.

Scheme I. Concerted Mechanism



Scheme II. Bond Cleavage-Recombination Mechanism



The photoproduct **2a** was isolated in 55% yield from the photolysis of **1a** in acetonitrile distilled from CaH_2 under argon. The structure of **2a** was identified unequivocally from its X-ray crystal structure. Photoproducts **2b** and **2c** were isolated in 33% yield and characterized by their ^1H NMR and mass spectra (EIMS). In separate experiments, photoproducts **2(a–c)** were shown to be stable under the reaction conditions.

A fragmentation–recombination mechanism for the formation of **2(a–c)** involving radicals (ion-radicals) or ionic intermediates is consistent with the experimental observations if it is primarily an in-cage process. A fragmentation–recombination mechanism involving long-lived

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0022-3263/85/1950-4360$01.50/0