partments were separated by a Nafion membrane. The volatile compounds, and especially acetone which is the main product we looked for, are forced to remain in the solution by means of a condenser, the temperature of the circulating liquid being maintained at 5 °C. The reaction products, acetone and ArH, were titrated by gas chromatography with 10% FFAP and OV17 columns for the volatile and heavy products, respectively. When acetone is found in the cathodic compartment it is necessary to prove that it comes from the electrocatalytic reaction and not, through the Nafion membrane, from the anodic compartment where it is produced by oxidation of 2-propanol. This problem was handled as follows. The reduction of 1-bromonaphthalene in 2-propanol involves the exchange of two electrons per molecule and should not thus product acetone. We find acetone in the anodic compartment but not, as expected, in the cathodic compartment, showing that permeation of acetone through the Nafion membrane separator is negligible during electrolysis. This shows that the acetone found in the cathodic compartment with other aryl halides does come from the cathodic electrocatalytic reaction.

Experiments were also carried out in *n*-butanol (distilled before use) with 9-bromoanthracene. In this case, butanal was formed and was identified by mass spectroscopy (*m/e* 15 (22), 27 (100), 28 (28), 39 (40), 41 (64), 43 (79), 44 (84), 72 (47)).

Registry No. MeOH, 67-56-1; EtOH, 64-17-5; $(CH_3)_2CH(CH_2)_2OH$, 123-51-3; $(CH_3)_2CH(CH_2)_3OH$, 1320-98-5; $HO(CH_2)_2OH$, 107-21-1; $CH_3CH(OH)CH(OH)CH_3$, 513-85-9; Et_3N, 121-44-8; Me_2NCHO, 68-12-2; PhOH, 108-95-2; OH^-, 14280-30-9; 4-bromobenzophenone, 90-90-4; 2-chloroquinoline, 612-62-4; 9-bromoanthracene, 1564-64-3; 2-propanol, 67-63-0; benzhydrol, 91-01-0; glycerol, 56-81-5.

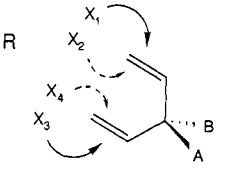
Reactions That Proceed with a Combination of Enantiotopic Group and Diastereotopic Face Selectivity Can Deliver Products with Very High Enantiomeric Excess: Experimental Support of a Mathematical Model

Stuart L. Schreiber,* Thomas S. Schreiber, and David B. Smith

Contribution from Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06511. *Received August 5, 1986*

Abstract: A generic class of reactions is described that involve the selective addition of a chiral, nonracemic reagent to one of four heterotopic faces of a substrate that contains a prosterogenic atom (or atoms) equipped with ligands that are enantiotopic and unsaturated. These reactions comprise a subclass of group selective transformations that couple a kinetic resolution to an initial asymmetric synthesis to provide primary products with enhanced levels of enantiomeric purity. Since four heterotopic faces are available for reaction with the reagent in the achiral substrate and two in the primary (monoaddition) products, the kinetics are complicated relative to the simple enantiotopic group selective reaction. A mathematical model of the above reaction process has been developed, and an analytical solution to the set of six simultaneous nonlinear differential rate equations has been obtained that provides an equation to evaluate the concentration of the substrate, reagent, and products as a function of time. Several reaction processes have been identified as probable candidates for membership to this reaction class. Finally, the Sharpless asymmetric epoxidation has been examined with three achiral substrates and shown to provide epoxy alcohol products whose enantiomeric purity increased as the reaction proceeded toward completion, a result that is in accord with the mathematical model.

An important feature of certain reactions that proceed with enantiotopic group selectivity is that a kinetic resolution will be coupled to the initial asymmetric synthesis, resulting in products with unusually high values of enantiomeric excess (ee). The first example of this process was described by Sih and co-workers as part of their studies of the enzyme-catalyzed hydrolysis of achiral diesters to chiral, nonracemic monoesters.[1] The initial hydrolysis takes place with enantiotopic group selectivity to provide an enantiomerically enriched monoester (asymmetric synthesis). The same enzyme catalyzes a second hydrolysis of the primary, monoester products with greater efficiency for the minor enantiomer (kinetic resolution). By this mechanism, the ee of the monoester products was demonstrated to increase as the reaction proceeded toward completion. Recently, a reagent mediated (nonenzymatic) reaction process in this same category was described by Bosnich and co-workers that involved a group selective deuterium–hydrogen exchange in a chiral cobalt–glycine complex.[2]



S

The process of asymmetric synthesis can be achieved by group and/or face selective transformations.[3] Reactions that proceed with a combination of group *and* face selectivity can have properties that are significant with regard to stereoselective synthesis. For example, a diastereotopic group and face selective spiroketalization reaction was recently employed to introduce multiple stereocenters along a chain of an ionophore subunit.[4] In this paper, we report a mathematical model and examples of a class

(1) (a) Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695. (b) Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *Ciba Found. Symp.* (*Enzymes Org. Synth.*) **1985**, *111*, 128. (c) For a mathematical treatment of independent parallel reactions, see: Brandt, J.; Jochum, C.; Ugi, I.; Jochum, P. *Tetrahedron* **1977**, *33*, 1353. (d) For a mathematical treatment of a reaction of a racemic substrate that couples a kinetic resolution to an asymmetric synthesis, see: El-Baba, S.; Poulin, J.-C.; Kagan, H. B. *Tetrahedron* **1984**, *40*, 4275. (e) For mathematical treatments of kinetic resolutions, see: (i) Woodard, S. S. Ph.D. Thesis, Stanford University, October, 1981. (ii) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237 and literature cited in ref 7 in this paper.

(2) Dokuzokič, Z.; Roberts, N. K.; Sawyer, J. F.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1986**, *108*, 2034.

(3) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice-Hall, Inc.; Washington, D. C., 1976.

(4) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303.

0002-7863/87/1509-1525$01.50/0

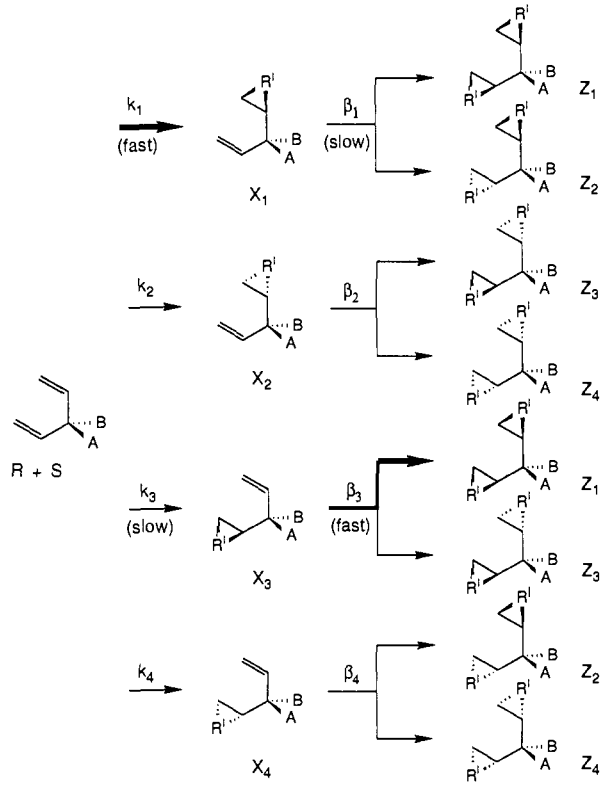


Figure 1.

of reactions that combine enantiotopic group and diastereotopic face selectivity and result in the formation of products with enhanced levels of ee. The mechanism by which this is achieved is akin to the superclass of enantiotopic group selective transformations; that is, a kinetic resolution is coupled with an asymmetric synthesis to increase the enantiomeric excess of the primary products with time. Experimental support of the model is provided in one illustration of this reaction class.

Results and Discussion

Consider the reaction of a chiral, nonracemic reagent R with an achiral substrate S (Figure 1). The substrate S contains a prostereogenic atom equipped with paired ligands that are enantiotopic and unsaturated. Vinyl groups are indicated, but other unsaturated II systems (alkenes, carbonyls, etc.) can be interchanged. The reagent, or part of the reagent, can undergo addition to any one of four heterotopic faces in the substrate (with rate constant k_i) to give four primary products X_i:

$$S + R \xrightarrow{k_i} X_i \qquad i = 1, 2, 3, 4$$

Since one unsaturated group remains in each product X_i, a second addition of the reagent R can take place (with rate constant β_i) to give the double addition products Z_i which are of no interest.[5]

$$X_i + R \xrightarrow{\beta_i} Z_i \qquad i = 1, 2, 3, 4$$

First, note that products X_1 and X_3 (and X_2 and X_4) are enantiomers.[6] The ratio of X_1/X_3, and thus the ee,[7] will be associated with the degree of group selectivity in this reaction. The value of X_1/X_3 is expected to vary with time, since each compound can be converted to a double addition product Z_i and the rate of formation ($S + R \rightarrow X_i$) and "destruction" ($X_i + R \rightarrow Z_i$) of each product X_i will differ. For example, if $k_1 > k_j$ ($j = 2, 3, 4$), the major enantiomer X_1 will have the "slow reacting" unsaturated group left unreacted whereas the minor enantiomer X_3 will have the "fast reacting" unsaturated group available for a second addition reaction.[8] The minor enantiomer X_3 is expected to be selectively "destroyed" so that the ratio X_1/X_3 should increase as the reaction proceeds. In other words, the first reaction converts an achiral substrate with a prostereogenic atom into a chiral, nonracemic product (asymmetric synthesis) and the second reaction enhances the ee via a kinetic resolution.

In order for this enhancement factor to operate effectively, a large difference in the value of k_i's is required and the first addition should have little influence on the rates of the second addition. These issues will be suitably addressed if the chiral reagent has an intrinsic enantiotopic face differentiating capability (e.g., in a reaction with propylene) and is highly sensitive to the stereodirecting properties of the allylic substituents A and B (e.g., preference for addition syn to the A group in the indicated rotamer, Figure 1).

A mathematical model of the above reaction process has been developed with the primary objective of calculating the concentrations of the substrate, reagent, and products as a function of time. Assuming each reaction is first order in substrate and reagent, the reaction rate equations are

$$dS/dt = -kSR \qquad dR/dt = -kSR - \sum_{i=1}^{4} \beta_i X_i R$$

$$dX_i/dt = k_i SR - \beta_i X_i R$$

$$i = 1, 2, 3, 4; \qquad k = k_1 + k_2 + k_3 + k_4$$

Consider the case where:

$$\beta_1 = \beta_2 = (k_3 + k_4) \qquad \beta_3 = \beta_4 = (k_1 + k_2)$$

This simplification will be valid when the first addition has little influence on the rates of the second addition. Within the context of a specific reaction (asymmetric epoxidation), evidence will be presented that supports this assumption.

An analytical solution to the set of six simultaneous nonlinear differential equations was obtained for the reagent rich case (>2 equiv.). Solving for the ratio of enantiomers

$$\frac{X_1}{X_3} = \left[\frac{\delta_1(\delta_3 + \delta_4]}{\delta_3(\delta_1 + \delta_2)}\right]\left[\frac{s^{-(\delta_1 + \delta_2)} - 1}{s^{-(\delta_3 + \delta_4)} - 1}\right] \qquad (1)$$

where $\delta_i = k_i/k$ (fractional rate constant) and $s = [S]/[S]_{init}$ (fractional substrate concentration). Evaluating (1) at low and high conversion

$$\frac{X_1}{X_3} = \frac{\delta_1}{\delta_3} = \frac{k_1}{k_3} \qquad \text{as } s \rightarrow 1 \text{ (low conversion)} \qquad (2)$$

$$\frac{X_1}{X_3} = \left[\frac{\delta_1(\delta_3 + \delta_4)}{\delta_3(\delta_1 + \delta_2)}\right] s^{-(\delta_1 + \delta_2 - \delta_3 - \delta_4)} \qquad \text{as } s \rightarrow 0 \text{ (high conversion)} \qquad (3)$$

On inspection of eq 3, *the ratio of enantiomers can become arbitrarily large* ($X_1/X_3 \rightarrow \infty$) *as the reaction goes to completion.* The amount of excess reagent does not affect the value of the ee, but it will influence the time required to achieve a specific ratio. The enhancement factor involves the more rapid destruction of X_3, but the yield of X_1 will also be lowered as the reaction goes to completion. The magnitude of these effects will be examined in some detail later in this discussion.

A variety of reaction types can be employed to illustrate this process. An early example that is expected to meet the requirements stated above comes from the studies of Partridge and Uskokvic (eq 4) on the asymmetric hydroboration of achiral 5-alkyl-1,3-cyclopentadienes.[9] In this reaction, Brown's hydro-

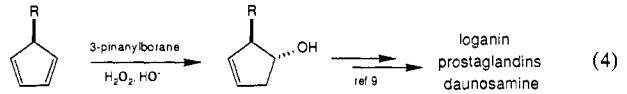
(5) The double addition products Z_i differ in constitution from "desired" monoaddition products X_i so that they are expected to be more readily separated than pairs of enantiomers.

(6) This statement will be true when the addition involves a transfer of atoms from the reagent (indicated by the symbol R' in Figure 1) to the unsaturated group (e.g., H_2 from asymmetric reduction or O from asymmetric epoxidation). When the chiral reagent is incorporated into S via the addition, X_1 and X_3 are diastereomers. This changes our descriptors, but not our rationale.

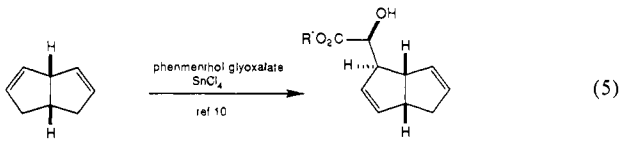
(7) ee = $[(X_1/X_3 - 1)/(X_1/X_3 + 1)]$ 100.

(8) This assumes that the first addition has little influence on the rates of the second addition, or, $\beta_1 \approx \beta_2 \approx (k_3 + k_4)$ and $\beta_3 \approx \beta_4 \approx (k_1 + k_2)$.

(9) Partridge, J. J.; Chadha, N. K.; Uskoković, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532, 7171.



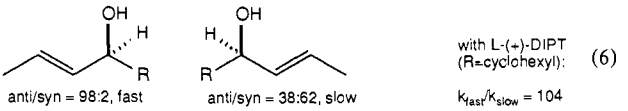
(4)



(5)

borating reagent undergoes regio- and stereoselective addition to one of four heterotopic faces in the cyclopentadienes. After oxidation, cyclopentenols are produced with high levels of enantiomeric purity. In the ene reaction recently reported by Whitesell and Allen (eq 5), a chiral nonracemic glyoxalate undergoes reaction with a related diene with exceptional diastereoselectivity.[10] In each of these reactions, the minor, monoaddition product that results from addition of the reagent to the alternative enantiotopic olefin of the substrate might be expected to undergo a second addition reaction with the reagent since the "fast reacting" face remains exposed. In this manner, the degree of stereoselectivity in the formation of monoaddition products should be increased with time.[11]

Kinetic Resolution[13]



(6)

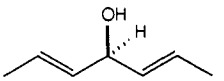
A number of reaction processes can be envisaged as proceeding in the manner described above and several of these are currently being investigated. The Sharpless asymmetric epoxidation reaction also serves to illustrate this process.[12] The features of this reaction that are particularly attractive with regard to this scheme include the high intrinsic face discriminating property of the reagent (reagent control) and the sensitivity of the reagent to substrate structure (substrate control). These same properties are responsible for the tremendous success observed with this reagent in the kinetic resolution of racemic secondary alcohols.[1e] As part of their studies in this area, the Sharpless group gathered the kinetic data shown in eq 6.[1e] With the reagent derived from L-(+)-DIPT, the fast-reacting *S*-enantiomer was found to undergo epoxidation with 98:2 diastereotopic face selectivity (*lk*) with k_{fast}/k_{slow} = 104. These rate differences are responsible for the success observed in the kinetic resolution of secondary allylic alcohols and were expected to illustrate the principles of the reaction process described herein as well.

The fractional rate constants depicted in Table I have been derived from the kinetic resolution data. We have used these values in combination with eq 1 to model the reaction of the Sharpless reagent with an achiral *E,E*-divinylcarbinol **1**.[13] In this instance, the major enantiomer is expected to derive from reaction of the reagent with the Si–Si face of the *pro-S* alkene since the *S*- and *R*-alcohols in Sharpless's studies are expected to model the reactivity of the *pro-S* and *pro-R* olefins, respectively. In reactions with such favorable fractional rate constants, it can be seen that extremely high ratios of enantiomers may be obtained as the reaction goes to completion without a substantial attenuation of yield of the major enantiomer. At 50% conversion the calculated yield of X_1 is 48% with an ee of 99.4%. The maximum theoretical yield is 93% at 99% conversion. With 1 ppb of substrate remaining, the yield of X_1 remains at a respectable level of 80%, with the ratio of enantiomers now calculated to be 9×10^9:1. The ratios in Table I for the first several entries were also generated by the method of Runge-Kutta numerical integration. These approximate values were nearly identical with those obtained from the exact analytical solution.

The model represents ideal conditions and special assumptions[8] that may be difficult to achieve. Likewise, the verification of any claims to have obtained products with extremely high levels of enantiomeric purity is complicated by the limitations in the

Table I. Calculated Reaction Parameters

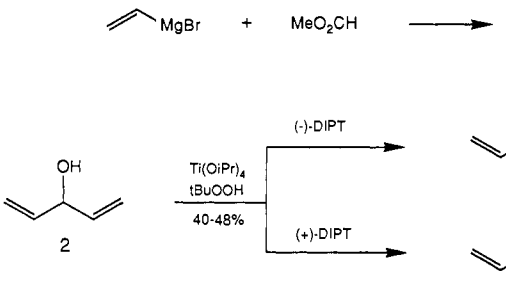
Enantiotopic Group Selectivity



from model compound above, estimate:
δ_1 = .971 δ_3 = .004
δ_2 = .019 δ_4 = .006

s ($[S]/[S]_{init}$)	yield (X_1/S_{init})	X_1/X_3	ee ($(X_1/X_3 - 1)/(X_1/X_3 + 1) \times 100$)
1	0	—	—
.5	.48	348	99.4
10^{-2}	.93 (max)	4913	99.96
10^{-3}	.91	31,936	99.994
10^{-6}	.85	1.4×10^7	99.99999
10^{-9}	.80	9×10^9	99.99999999
10^{-12}	.74	6×10^{12}	99.99999999999

Table II

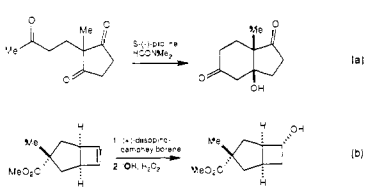


L-(+)-DIPT		
conditions[a]	%ee[b]	%de[c]
3 h, -25°C	84	92
24 h, -25°C	93	99.7
140 h, -25°C	≥97	>99.7

[a] 4.8 eq *t*-BuOOH, 1.36 eq $Ti(OiPr)_4$, 1.8 eq L-(+)-DIPT with powdered 4Å MS in CH_2Cl_2, work up with Na_2SO_4. [b] Determined by the method of Mosher[20] with ^{19}F NMR (detection limit ca. 97% ee). [c] Determined by capillary GC analysis.

(10) Whitesell, J. K.; Allen, D. E. *J. Org. Chem.* **1985**, *50*, 3025.

(11) Examples of reactions that proceed with a combination of enantiotopic group selectivity and diastereotopic face selectivity exist where the second addition cannot occur, so that enhancement of the ee, associated with selective destruction of the minor enantiomer, is not expected. In example (a), only one equivalent of the "reagent" (R = $COCH_3$) is available and in (b) there is only one unsaturated group. (i) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.*

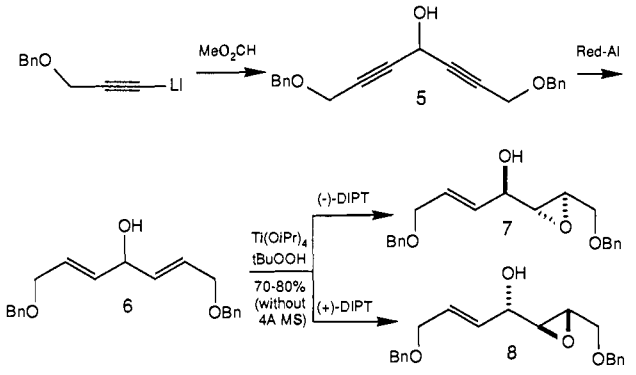


1974, *39*, 1615. (ii) Hajos, Z. G.; Parrish, D. R. *Organic Syntheses*; Saucy, G., Ed.; Wiley: New York, 1985; p 25. (iii) Greene, A. E.; Luche, M.-J.; Serra, A. A. *J. Org. Chem.* **1985**, *50*, 3957.

(12) (a) Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974. For recent reviews, see: (b) Sharpless, K. B.; Finn, M. G. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1985; Vol. 5, p 247. (c) Rossiter, B. E. *Ibid.* Vol. 5, p 193.

(13) For the asymmetric epoxidation of a racemic divinyl carbinol, see: 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.

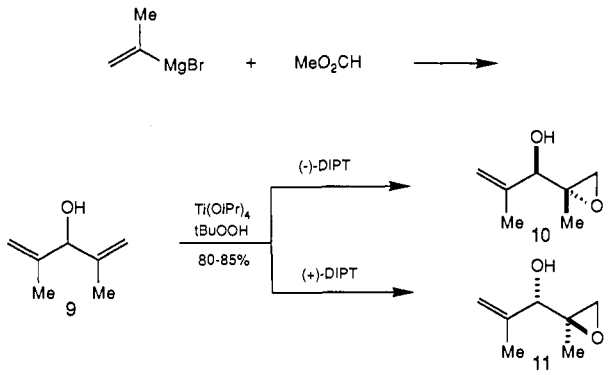
Table III



L-(+)-DIPT		
conditions[a]	%ee[b]	%de[c]
1 h, -25°C	93	≥97
3 h, -25°C	95	≥97
44 h, -25°C	≥97	≥97

[a] 2.6 eq *t*-BuOOH, 1.15 eq $Ti(OiPr)_4$, 1.5 eq L-(+)-DIPT with powdered 4Å MS in CH_2Cl_2, work up with 10% aq tartaric acid, 1 N NaOH. [b] Determined by the method of Mosher[20] with ^{19}F NMR (detection limit ca. 97% ee). [c] Determined by ^{19}F NMR analysis of the Mosher derivatives of the two diastereomeric epoxide products.

Table IV



D-(-)-DIPT		
conditions[a]	%ee[b]	%de[c]
0.5 h, -25°C	88	>99
1.0 h, -25°C	94	>99
1.5 h, -25°C	>99.3[d]	>99

[a] 2.0 eq *t*-BuOOH, 1.1 eq $Ti(OiPr)_4$, 1.3 eq D-(-)-DIPT in CH_2Cl_2, work up with Na_2SO_4. [b] Determined by the method of Mosher[20] by separation of diastereomeric esters with capillary GC and integration of peak intensities (detection limit >99.3% ee). [c] Determined by capillary GC analysis. [d] The minor isomer was not detected.

analytical methods that may be employed.[14] However, the model predicts that the ee of the major product should increase as the reaction proceeds.[1] We have demonstrated that this is the case in the Sharpless asymmetric epoxidation with several divinylcarbinol substrates.

Divinylcarbinol **2** was first examined because vinylcarbinols are known to react slowly with the Sharpless reagent.[15] In this manner we hoped to examine the reaction at low conversion. First, note this reaction determines the absolute stereochemistry of the carbinol carbon due to the group selectivity. Either enantiomer can be obtained by appropriate choice of Sharpless reagent. The results recorded in Table II clearly indicate the ee improves as the reaction proceeds toward completion. The absolute configuration of products was determined by the conversion of **3** into (−)-riboflavin.[16] Evidence that the minor enantiomer can be removed through a second epoxidation reaction was gathered by converting **3** and **4** to their corresponding bis-epoxides upon treatment with the enantiomeric Sharpless reagent. This result provides qualitative support for the simplifying assumption used in solving the differential rate equations.[8] It is also of some interest that the value of the de increased with time as well. A qualitative extension of our analysis (concerning the ratio $(X_1 + X_3)/(X_2 + X_4)$) leads to a straightforward rationalization of this result.

The second demonstration of this phenomenon was carried out with the *E,E*-divinylcarbinol **6**. This material can be prepared directly from the acetylide addition product **5** by employment of Denmark's conditions for propargyl alcohol reduction.[17] The same trend is apparent in the epoxidation reaction as seen from the data in Table III. The absolute stereochemistry of the products was determined by the conversion of **7** into D-(+)-KDO.[18] Finally, in Table IV the results of the epoxidation of diisopropenyl carbinol are recorded. Again, the rapid increase in enantiomeric purity with time is readily apparent. In this example we were able to separate the diastereomeric Mosher esters[20] of the epoxidation products by capillary GC (see Experimental Section). The results of studies that employed D-(−)-diisopropyltartrate have been tabulated since the Mosher ester[20] (derived from (*S*)-methoxy-α-(trifluoromethyl)phenylacetic acid chloride) of the *minor* enantiomer in these reactions was found to have the lesser R_f value. Accordingly, the integration of peak intensities was rendered more accurate. The assignment of absolute stereochemistry in these reactions was based on analogy with the previous examples.

Conclusion

In conclusion, we have developed a model that can be used to qualitatively estimate the effect of substrate and reagent concentration on the outcome of addition reactions that employ chiral nonracemic reagents with substrates that are equipped with unsaturated and enantiotopic ligands. It is seen that these reactions can provide products with enhanced enantiomeric purity. The application of these principles to reactions that employ *meso* substrates allows advanced achiral intermediates to be converted to chiral products of either configuration.[19] Group and face selective addition reactions also provide a solution to the problem of terminus differentiation in the two-directional chain synthesis strategy.[21] Already these reactions have been employed as a means of obtaining materials with very high levels of enantiomeric purity in the context of natural products total synthesis applications. The results of these studies will be reported in due course.

Experimental Section

General. Methylene chloride was purified by distillation from CaH_2 prior to use. $Ti(OiPr)_4$, *tert*-butyl hydroperoxide (3.0 M in toluene), and (+)- and (−)-DIPT (ee ≥ 97% by ^{19}F analysis of the (*S*)-methoxy-α-(trifluoromethyl)phenylacetic acid ester (MTPA) derivatives) were used as received from Aldrich Chemical Co. CCl_4 and pyridine were distilled from CaH_2. (*S*)-MTPA acid was used as received for the analyses in Tables II and III, and was purified to >99.3% ee by recrystallization (3X) of the commercially available (*S*)-MPTA acid (ca. 97% ee) with (−)-α-phenethylamine[20] for the analyses in Table IV. The enantiomeric excess of these samples of (*S*)-MTPA acid was determined by capillary GC analysis of the Mosher esters of (*S*)-2-octanol, (±)-2-octanol, epoxy alcohol **10** (1.5 h, Table IV), and a 1:1 mixture of **10** and **11**. All reactions were carried out under nitrogen and monitored by analytical thin layer chromatography (TLC) with use of E. Merck silica gel 60F-24 glass plates (0.25 mm). Flash chromatography was carried out with use of E. Merck silica gel 60 (230-400 mesh). MTPA-Cl was prepared as

(14) Recent developments in chromatography science may minimize these limitations. For example, chromatography experiments that employed Pirkle columns (Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 352) resulted in the determination of 99.9967% optical purity in one example; Professor W. H. Pirkle, personal communication.

(15) (a) Takano, S.; Sakurai, K.; Hatakeyama, S. *J. Chem. Soc., Chem. Commun.* **1985**, 1759. (b) Jäger, V.; Schröter, D.; Häfele, B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 87.

(16) Unpublished results of D. B. Smith.

(17) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.

(18) Unpublished results of Z. Wang.

(19) Unpublished results of M. T. Goulet.

(20) Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543.

(21) Schreiber, S. L. *Chem. Scr.*, in press.

described in ref 20. Capillary GC was performed by using a Varian 3300 GC with a Varian 4290 integrator and a Quadrex 50M 007 Carbowax 20M column No. 507011. ^{19}F NMR spectra were recorded on a Bruker WM490 (460MHz) spectrometer with trifluoroacetic acid as an external reference.

Asymmetric Epoxidation. Asymmetric epoxidations were carried out in CH_2Cl_2 at −25 °C following the detailed procedure of Sharpless,[1e,12b,c] with the exception that 4 Å MS were added to reactions of **2** and **6**. Epoxidation of 1,4-pentadien-3-ol: workup with ether, saturated sodium sulfate. Careful solvent removal and flash chromatography (1/1 ether/pentane) provided the monoepoxy alcohol contaminated with DIPT. Epoxidation of 1,7-dibenzyloxy-2(*E*),5(*E*)-heptadien-4-ol: workup with 10% aqueous tartaric acid, NaOH hydrolysis. Flash chromatography (1/2 ether/petroleum ether) provided the pure monoepoxy alcohol. Epoxidation of 2,4-dimethyl-1,4-pentadien-3-ol: workup with ether, saturated sodium sulfate. Flash chromatography (1/3 ether/petroleum ether) provided the pure monoepoxy alcohol.

MTPA Esters. MTPA esters were prepared in CCl_4/pyridine as described in ref 20 or in CH_2Cl_2 with triethylamine and (dimethylamino)pyridine and were purified by filtration with SiO_2.

Product Analysis. Diastereomeric excess was determined by comparison of the capillary GC trace of the reaction mixture to that of mixtures of diasteromers prepared via alternative procedures or via similar analysis with ^{19}F NMR of the *S*-MTPA esters. Enantiomeric excess in Tables II and III was determined by ^{19}F NMR analysis (detection limit ca. 97% ee) of the *S*-MTPA ester derivatives of the epoxidation products obtained from the reaction of the achiral substrates with the Sharpless reagents derived from (+)- and (−)-DIPT. Subsequent to these studies, the derivatizing agent *S*-MTPA acid chloride was determined to exist in 97% ee (vide supra). The data in these tables are uncorrected. The enantiomeric excess in Table IV was determined by capillary GC analysis of the *S*-MTPA esters of the epoxidation products. We were able to detect a 300:1 mixture, with base line separation, of the Mosher esters **11** and **10**, thereby establishing a detection limit of >99.3% ee. The entry in Table IV with >99.3% ee signifies that we were not able to detect the minor isomer. In these studies, *S*-MTPA acid chloride was employed that was derived from *S*-MTPA acid that had been triply recrystallized as its (−)-α-phenethylamine salt.

Acknowledgment. This research has been supported by the NIH (GM-30738), NSF (Presidental Young Investigator Award), and Pfizer, Inc., to whom we are grateful. We thank Professors K. Barry Sharpless and H. B. Kagan for generous exchanges of information.

Registry No. **2**, 922-65-6; **3**, 102490-00-6; **4**, 100017-22-9; **6**, 106319-54-4; **7**, 106319-55-5; **8**, 106400-06-0; **9**, 38614-40-3; **10**, 106400-07-1; **11**, 106319-56-6.

Supplementary Material Available: Details of the derivation of eq 1 (12 pages). Ordering information is given on any current masthead page.

Reactions of Crystalline (*R*)-(−)- and (*S*)-(+)-Mandelic Acid with Amines. Crystal Structure and Dipole Moment of (*S*)-Mandelic Acid. A Method of Determining Absolute Configuration of Chiral Crystals

A. O. Patil, W. T. Pennington, I. C. Paul,* D. Y. Curtin,* and C. E. Dykstra

Contribution from the Department of Chemistry, University of Illinois, Urbana, Illinois 61801.
Received August 5, 1986

Abstract: The reaction of (+)-1-phenylethylamine vapor occurs more rapidly with single crystals of (+)-mandelic acid to form the (+)(+) or "p" salt than with (−)-mandelic acid to give the (+)(−) or "n" salt, known to be the less soluble on crystallization from solution. The reaction fails to show the anisotropy characteristic of some other reactions of crystalline acids with chiral gases. The crystal structure of (*S*)-(+)-mandelic acid has been determined. The structure is monoclinic, $P2_1$, with a = 8.629 (1) Å, b = 5.861 (1) Å, c = 15.185 (2) Å, β = 102.76 (1)°, and Z = 4. The structure was determined by direct methods and refined to R = 0.035 for the 1347 reflections recorded with a single-crystal diffractometer. The dipole moments of the mandelic acid molecules in the conformations found in the crystal structure determination were calculated by an ab initio SCF method. These results, together with the crystal morphology and known absolute configuration of the crystals, can be used to determine the direction of the electric dipole of single crystals of (*S*)-mandelic acid. The result is in agreement with the direction determined by spraying heated crystals with the powder mixture of Burker in the classic test for absence of a crystal center of symmetry. When the argument is inverted it provides a method for determining the absolute configuration of chiral, electrically polar molecules from the X-ray crystal structure, crystal morphology, and direction of the electric dipole of the crystal. The reaction of mandelic acid crystals with phenylethylamine vapor is discussed in terms of the crystal structure. A survey has been made of the solid–gas reactions of mandelic acid with ammonia, 2-butylamine, and *tert*-butylamine.

It has been shown[1] that a chiral gas, (*R*)-(+)- or (*S*)-(−)-1-phenylethylamine (**1**), in its reaction with single crystals of chiral acids such as (*R*)-(−)- and (*S*)-(+)-mandelic acid [(*R*)- and (*S*)-**2**)] shows a preference for one enantiomeric crystal over the other. Thus amine (*R*)-(+)-**1** reacted more rapidly with (*S*)-(+)-acid **2** than with its enantiomer. No further investigation of this reaction was made at that time. Because of our interest[2] in polar crystals, the enantiomers of mandelic acid were noteworthy since they have been known[3,4] for many years to crystallize in the polar point group 2, space group $P2_1$.

More recently the pyroelectric effect has been found useful in determining the direction of the electric dipole induced by heating

(*R*)-(+)-**1** (*S*)-(+)-**2**

(1) Lin, C.-T.; Curtin, D. Y.; Paul, I. C. *J. Am. Chem. Soc.* **1974**, *96*, 6199–6200.

(2) (a) Paul, I. C.; Curtin, D. Y. *Science* **1975**, *187*, 19–26. (b) Curtin, D. Y.; Paul, I. C. *Chem. Rev.* **1981**, *81*, 526–541. (c) Duesler, E. N.; Kress, R. B.; Lin, C.-T.; Shiau, W.-T.; Paul, I. C.; Curtin, D. Y. *J. Am. Chem. Soc.* **1981**, *103*, 875–879. (d) Chaing, C. C.; Lin, C.-T.; Wang, A. H.-J.; Curtin, D. Y.; Paul, I. C. *J. Am. Chem. Soc.* **1977**, *99*, 6303–6309.

(3) See: Groth, P. *Chemische Kristallographie*; Verlag von Wilhelm Engelmann: Leipzig, 1917; Vol. 4, p 559. Traube, H. *Chem. Ber.* **1859**, *32*, 2385.

(4) Furberg, S. *Res. London*, **1951**, *4*, 192–193; *Struct. Rep.* **1951**, *15*, 463–464.

0002-7863/87/1509-1529$01.50/0