Acknowledgment. This investigation was supported by a research grant GM-13246-31 from the National Institutes of Health, U.S. Public Health Service.

Supplementary Material Available: ^{13}C NMR spectra of natural cocaine and ecgonine and the corresponding enriched compounds derived from [1-^{13}C,^{14}C,^{15}N]-4-(methylamino)butanal diethyl acetal and activities of the degradation products of ^{14}C-labeled cocaine and 1-methylpyrrolidine-2-acetic acid derived from [2-^{14}C]-7 (7 pages). Ordering information is given on any current masthead page. These data will also be provided with requests for a reprint.

(14) The biosynthesis of other tropane alkaloids in which acetoacetate has been proposed as an intermediate is reviewed: Leete, E. *Planta Medica* **1979**, *36*, 97.

Enhanced Kinetic Resolution and Enzyme-like Shape Selectivity

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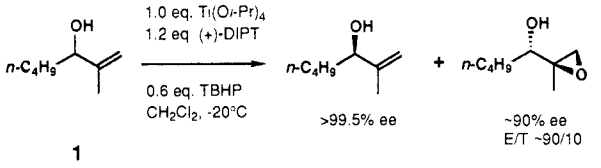
Received November 18, 1987

The kinetic resolution of secondary allylic alcohols[1] (Scheme I) has proven to be an important reaction, both from a synthetic standpoint and from the insights it has provided into asymmetric catalysis. The most efficiently resolved secondary allylic alcohol measured to date, **1**, has k_f/k_s = 138, where k_f and k_s are the epoxidation rates of the fast and slow enantiomers, respectively. Recently, Sato et al.[2] reported that (*E*)-1-trimethylsilyl-1-octen-3-ol, **2**, exhibits a very large rate difference for its two enantiomers, seemingly much greater than for substrate **1** mentioned above. The synthetic advantage of such enhanced kinetic resolution is that in one reaction both allylic alcohol and erythro epoxy alcohol are obtained in extremely high enantiomeric excess.[3] Reported herein is a new class of secondary allylic alcohols (of which **2** is a member) that are kinetically resolved with unprecedented efficiency and a discussion of the factors responsible for this phenomenon.

Our initial intuition was that the enhanced kinetic resolution observed by Sato was due to the presence of increased steric bulk in the substituent at the olefin terminus, since kinetic resolution efficiencies for such β-branched substrates had not been studied before. Thus several disubstituted secondary allylic alcohols bearing branched substituents at the trans position were synthesized, and their relative rates of epoxidation under four different epoxidation conditions were studied, as shown in Table I. The rates were measured by means of competition experiments[4] with

Scheme I



1

a substrate of known absolute reactivity[1a] having minimum steric bulk at the olefinic terminus—substrate **3**.[5,6] Knowing that k_f/k_s for **3** is 104 at −20 °C, one can then calculate $(k_f/k_s)_{substrate}$ = (104)rel k_f/rel k_s.

Before comparing reagent selectivities, it was necessary to attempt to decouple the electronic and steric properties of each substrate. Peracid epoxidation is known to be relatively insensitive to steric influences[7] and promises to be a good probe of substrate electronic differences. The values of rel $k_{m\text{-CPBA}}$ for substrates **3**, **4**, and **6** are quite similar and thus consistent with this observation. The slow relative rate for substrate **2** compared to **3**, **4**, and **6** is then probably due to an electronic effect,[8,9] since at the face of the olefin the trimethylsilyl group is less sterically demanding than *tert*-butyl, given the greater length of the C–Si bond.[10] Therefore, a distinction will be made between silicon and non-silicon-substituted olefins in the discussion of allylic alcohol reactivities below. The significant decrease in rate observed in changing from **2** to **9** indicates that even *m*-CPBA is sensitive to the presence of the extremely bulky triisopropylsilyl group.

Unlike rel $k_{m\text{-CPBA}}$, the rate of epoxidation by Ti(O-*i*-Pr)$_4$/TBHP decreases markedly with respect to increasing steric bulk at the olefinic terminus of the substrate. Note that the relative rates of epoxidation of the slow enantiomers by [Ti(DIPT)(O-*i*-Pr)$_2$]$_2$/TBHP are very similar to those of the racemates in the Ti(O-*i*-Pr)$_4$/TBHP manifold. Apparently, the steric effects encountered by the substrate in the transition states of these two distinct epoxidation systems must be very similar.[11]

In contrast to the Ti(O-*i*-Pr)$_4$/TBHP and the [Ti(DIPT)(O-*i*-Pr)$_2$]$_2$/TBHP/slow enantiomer manifold described above, the epoxidation of the fast enantiomers by [Ti(DIPT)(O-*i*-Pr)$_2$]$_2$/TBHP is *not slowed down* by increasing bulk at the olefin terminus. On the contrary, the rate of epoxidation *increases slightly* as the size of the olefinic substituent increases; substrate **4** is faster than **3**, **6** and **7** are faster than **5**. Unfortunately, there is no satisfactory unhindered reference compound for substrate **2**, so it is not possible to observe such a rate enhancement in the silicon series. The decrease in rate upon going from substrate **2** to **8** and **9** suggests that despite the initial rate-enhancing effects of increasing bulk of the olefinic substituent, too much bulk decreases the rate of epoxidation. The cause of this rate enhancement was

(1) (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240. (b) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D.; Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8. (c) Finn, M. G. Ph.D. Dissertation, Massachusetts Institute of Technology, Cambridge, MA, 1985. (d) Woodard, S. S. Ph.D. Dissertation, Stanford University, Stanford, CA, 1981. (e) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 7. (f) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(2) (a) Kitano, Y.; Matsumoto, T.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1986**, 1323. (b) Kitano, Y.; Matsumoto, T.; Takeda, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1986**, 1732.

(3) In the normal kinetic resolution domain ($k_f/k_s \sim 100$) the epoxy alcohol is recovered having ~90% ee. Sato reported (ref 2a) that both the allylic and epoxy alcohols can be recovered having ≥99% ee.

(4) All kinetic experiments were carried out at −20 ± 2 °C in CH_2Cl_2 at substrate concentrations from 0.1 to 0.2 M. Only 5 mol% oxidant was added in each case, so that the observed product ratio accurately reflected the product of the relative stoichiometry and epoxidation rates. For the rel k_{ti}, rel k_s, and rel k_f experiments, 100% of the titanium catalyst was used.

(5) For the rel $k_{m\text{-CPBA}}$ and rel k_{ti} experiments, racemate was used. For the rel k_s experiments, enantiomerically pure slow enantiomer was used. For the measurement of rel k_f, racemate was used again, since during the first 5% of reaction, the products would overwhelmingly be derived from the fast enantiomer.

(6) The product ratios were measured by gas chromatography of the crude or acetylated product mixtures. In the rel k_f experiments the products are almost exclusively erythro; in the other experiments both erythro and threo are formed. The measured rates are in actuality the product of substrate binding constants and absolute oxygen transfer rates (see ref 1b and c). Unfortunately, independent determination of each of these terms by means of enzyme kinetic techniques has not been possible to this date.

(7) Newman, M. S.; Gill, N.; Thomson, D. W. *J. Am. Chem. Soc.* **1967**, *89*, 2059–2062.

(8) (a) Colvin, E. W. *Silicon in Organic Synthesis*; Buttersworths Monographs in Chemistry and Chemical Engineering; Buttersworths: London, 1980. (b) Eaborn, C. *Organosilicon Compounds*; Academic Press Inc.: New York, 1960. (c) Eisch, J. J.; Trainor, J. T. *J. Org. Chem.* **1963**, *28*, 487–492.

(9) A recent study reports that whereas replacement of a hydrogen substituent by trialkylsilyl activates olefins toward epoxidation, replacement of a carbon substituent by trialkylsilyl results in net electron withdrawal and deactivation of the olefin (Peterson, P. E.; Nelson, D. J.; Risener, R. *J. Org. Chem.* **1986**, *51*, 2381–2382).

(10) The difference in bond lengths is dramatically borne out in the relative *A* values of *t*-Bu (>4.5 kcal mol^{-1}) and SiMe$_3$ (2.4–2.6 kcal mol^{-1}) (Kitching, W.; Olszowy, H. A.; Drew, G. M.; Adcock, W. *J. Org. Chem.* **1982**, *47*, 5153).

(11) Also lending credence to this hypothesis is the observation that epoxidation diastereoselectivities (generally modest threo selectivity) in the two distinct systems are quite similar.

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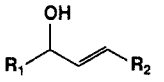
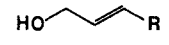
Table I. Relative Rates of Epoxidation[a]



compd	R_1	R_2	rel $k_{m\text{-CPBA}}$[b]	rel k_{ti}[c]	rel k_s[d]	rel k_f[e]	k_f/k_s
3	c-C_6H_{11}	Me	1.0	1.0	1.0	1.0	104
4	c-C_6H_{11}	t-Bu	0.93	0.31	0.43	1.25	300
5	Me	n-C_5H_{11}		0.460	0.63	0.98	160
6	Me	c-C_6H_{11}	1.15	0.44	0.45	1.44	330
7	Me	t-Bu		0.168		1.39	
2	n-C_5H_{11}	$SiMe_3$	0.174	0.052	0.040	0.268	700
8	n-C_5H_{11}	$SiEt_3$	0.144	0.036		0.149	
9	n-C_5H_{11}	$Si(i\text{-Pr})_3$	0.053	0.0120	0.010	0.029	300

[a] The relative rates are generally reproducible to within 5%. [b] Epoxidation by *m*-CPBA. [c] Epoxidation by $Ti(O\text{-}i\text{-Pr})_4$/TBHP. [d] Epoxidation of slow enantiomers by $[Ti(DIPT)(O\text{-}i\text{-Pr})_2]_2$/TBHP. [e] Epoxidation of fast enantiomers by $[Ti(DIPT)(O\text{-}i\text{-Pr})_2]_2$/TBHP.

Table II. Competition of Primary Allylic Alcohols[a]



compd	R	rel k_f'[b]	rel k_{ti}'[c]
10	n-C_5H_{11}	1.0	1.0
11	c-C_6H_{11}	1.80	0.91
12	1-Ad	2.2	0.74

[a] The relative rates are generally reproducible to within 5%. [b] Epoxidation by $[Ti(DIPT)(O\text{-}i\text{-Pr})_2]_2$/TBHP. [c] Epoxidation by $Ti(O\text{-}i\text{-Pr})_4$/TBHP.

not immediately apparent, and the small magnitude of it obliges caution in speculating on its origin. However, based on our understanding of the mechanism of the kinetic resolution, we expected to see acceleration of the rate of asymmetric epoxidation of primary allylic alcohols bearing bulky olefinic substituents relative to unhindered primary allylic alcohols. As shown in Table II, substrates **11** and **12** are indeed accelerated relative to **10** in epoxidation by $[Ti(DIPT)(O\text{-}i\text{-Pr})_2]_2$/TBHP.

Steric enhancement of rate is unprecedented in group transfer reactions such as epoxidation, and this selectivity cannot be rationalized in terms of inductive differences, since no such effect is manifested in the rel $k_{m\text{-CPBA}}$ experiments. However, completely analogous steric effects on the rates of epoxidation of fast and slow enantiomers had been seen previously with respect to increasing size of the tartrate ester group.[1b,d] Although the rel k_f, rel k_f' and tartrate ester results are hard to account for by conventional steric and electronic arguments, such selectivity is commonly observed in enzymic systems.[12] In fact, the observation that certain substrates react faster than smaller analogues bearing all the requisite functionality has been a primary focus in the development of modern theories of enzyme specificity.[13] Specificity for competing substrates has been shown to depend only on the relative binding of their transition states to the enzyme. The intriguing possibility then presents itself that the same types of substrate-active site interactions responsible for enzymic specificity also operate in the abiotic titanium–tartrate catalyst.[14]

Whatever the ultimate explanation for the rate acceleration of the fast enantiomer, the basic reasons for the enhanced kinetic resolution observed by Sato can now be clearly seen. Increasing steric bulk at the olefinic terminus (within the limits described above) increases the rate of epoxidation of the fast enantiomer and decreases the rate of epoxidation of the slow enantiomer. Thus the ratio k_f/k_s increases. The most efficiently resolved substrate is the one reported by Sato, **2**, with k_f/k_s = 700, an efficiency nearly five times greater than that of any substrate measured before.[15] The carbon-substituted substrates **4** and **6** are also resolved with an efficiency much greater than observed before, although not as well as Sato's compound. Compound **9** is not as efficiently resolved as **2**, due to the precipitous drop in rel k_f. In any case, the remarkable degree of selectivity documented here for the titanium–tartrate epoxidation catalyst indicates that abiotic catalysts can achieve the levels of chiral recognition formerly associated only with enzymic processes.

Acknowledgment. We thank the National Institutes of Health (Grant GM-28384) and the National Science Foundation (Grant CHE-8303355) for generous support of this work. G.S. thanks NATO for a postdoctoral fellowship.

(12) (a) Hexokinase: Jencks, W. P. In *Advances in Enzymology*; Meister, A., Ed.; John Wiley & Sons: New York, 1975; Vol. 43, p 223–224. (b) Isoleucyl-tRNA synthetase: Loftfield, R. B.; Eigner, E. A. *Biochim. Biophys. Acta* **1966**, *130*, 426. (c) Alanyl-tRNA synthetase: Tsui, W. C.; Fersht, A. R. *Nucl. Acids. Res.* **1981**, *9*, 4627. (d) Glycerophosphate acyltransferase: Kornberg, A.; Pricer, W. E. *J. Biol. Chem.* **1953**, *204*, 345. (e) Butyryl-CoA dehydrogenase: Green, D. E.; Mii, S.; Mahler, H. R.; Bock, R. M. *J. Biol. Chem.* **1954**, *206*, 1. (f) Butyryl-CoA synthetase: Mahler, H. R.; Wakil, S. J.; Bock, R. M. *J. Biol. Chem.* **1953**, *204*, 453.

(13) (a) Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; W. H. Freeman and Company: New York, 1985; Chapters 12 and 13. (b) Dixon, M.; Webb, E. C. *Enzymes*, 3rd ed.; Academic Press: New York, 1979; Chapter 6, pp 231–270. (c) Reference 12a, pp 219–410.

(14) The analogy between titanium–tartrate and enzymic catalysts has been drawn before with respect to the issue of selectivity. Structurally, the catalyst has steric interaction-free pockets or grooves in which the substrates lie (see ref 1b and c), which could be considered analogous to active sites.

(15) Sato has recently reported kinetic resolutions of the iodo- and tri-*n*-butylstannyl-substituted analogues of **2**. The apparent kinetic resolution efficiencies reported for these substrates are consistent with the steric model described in this communication. (a) Kitano, Y.; Matsumoto, T.; Wakasa, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F; Miyaji, K.; Arai, K. *Tetrahedron Lett.* **1987**, *28*, 6351. (b) Kitano, Y.; Matsumoto, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Chem. Lett.* **1987**, 1523.

Synthesis of Boroles and Their Use in Low-Temperature Diels–Alder Reactions with Unactivated Alkenes†

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Received September 25, 1987

The chemistry of boroles has not been studied extensively primarily because of the difficulty in generating these species synthetically.[1] The only known isolable monomeric boroles without annulated aromatic groups are derivatives of the sterically hindered 1,2,3,4,5-pentaphenylborole.[1,2] We have previously reported the preparation of main group heterocycles by metal-

† Contribution No. 4510.

(1) (a) Eisch, J. J.; Galle, J. E.; Kozima, S. *J. Am. Chem. Soc.* **1986**, *108*, 379–385. (b) Eisch, J. J.; Galle, J. E. *J. Am. Chem. Soc.* **1975**, *97*, 4436–4437. (c) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1977**, *127*, C9–C13. (d) See, also: Killian, L.; Wrackmeyer, B. *J. Organomet. Chem.* **1978**, *148*, 137–146. (e) Schacht, W.; Kaufmann, D. *Angew. Chem.* **1987**, *99*, 682–683.

(2) (a) Herberich, G. E.; Ohst, H. *Chem. Ber.* **1985**, *118*, 4303–4313. (b) Herberich, G. E.; Buller, B.; Hessner, B.; Oschmann, J. *J. Organomet. Chem.* **1980**, *195*, 253–259.

0002-7863/88/1510-2979$01.50/0