phenethylammonium complex, a similar X-ray structure was found except that the positions of methyl and phenyl substituents were switched. With the L-proline ester perchlorate (Chart III), 4 forms a complex having the ammonium ion at the center of the binding site and the ester group placed in an electrostatically favorable location relative to nearby tetrahydropyranyl ether and sulfonyl dipoles. The L-proline amide complex (Chart IV) has two forms in the crystal, one similar to the ester complex and one having simultaneous ammonium NH and amide NH hydrogen bonding to the two sulfone groups. All of these structures have spatially separated ammonium and perchlorate ions and differ qualitatively from the X-ray structures of the corresponding complexes of 1 which show contact ion pairing. The absence of ion contact in the X-ray structures of five distinct complexes of 4 probably reflects the large electrical polarization of the sulfone S=O bond which makes 4 a better ligand than 1 for cations. Experimentally, we find that 4 is the most effective podand we have studied at extracting ammonium ions from water.

These and other studies support the notion that host/guest selectivity is a function not only by host preorganization but also of the number and flexibility of the conformations of the complex itself. In general, selectivity between guests should be best when the complexes as well as hosts have single well-defined conformations. One way to create such recognition systems is to build specific host/guest functional group interactions into the complex.[6]

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(6) This work was supported by NIH Grant HL25634.

Subtle Effects in the Asymmetric Epoxidation: Dependence of Kinetic Resolution Efficiency on the Monodentate Alkoxide Ligands of the Bystander Titanium Center

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Summary: Complexes of diisopropyl tartrate and Ti(O^{t}Bu)$_4$ were found to catalyze the kinetic resolution of racemic, secondary allylic alcohols with surprisingly low efficiency relative to those generated from Ti(O^{i}Pr)$_4$. This effect is documented and its implications are discussed.

In the course of our studies on the mechanism of the asymmetric epoxidation we have, on occasion, employed a ligand variation approach.[1] Along these lines, both singly and doubly[2,3] linked tartrate ligands were synthesized and assayed for their performance in the asymmetric epoxidation of prochiral and racemic allylic alcohols. Asymmetric epoxidation of the latter lead to kinetic resolution.[4] Singly linked tartrate ligands gave complexes with Ti(O^{t}Bu)$_4$ which efficiently catalyzed asymmetric epoxidation of allylic alcohols, whereas they were not capable of affecting satisfactory kinetic resolution of racemic, secondary allylic alcohols. We concluded that this effect was the result of stereochemical restrictions imposed by the linked tartrate on the loaded catalyst,[2] but a key control experiment, overlooked in the original study,[2] now reveals that this conclusion was wrong. As seen in entry 2 of Table I, an ineffective catalyst system is generated from Ti(O^{t}Bu)$_4$ *even* when using the conventional, unlinked tartrate ligand, diisopropyl tartrate. This report presents evidence tying this lack of efficient kinetic resolution to the steric influence of the monodentate (non-tartrate) alkoxide on the bystander titanium center of the dimeric catalyst.

As is well-known and shown in Table I, "standard" asymmetric epoxidation catalysts generated from titanium isopropoxide are very efficient at kinetic resolution. Simply changing the alkoxide from isopropoxide to *tert*-butoxide greatly reduces the ability of the complex to perform kinetic resolution. Kinetic resolution efficiency is often described in terms of k_f/k_s, k_f and k_s being the rate constants for epoxidation for the faster and slower reacting enantiomers, respectively. Useful levels of enantiomeric excess in the unreacted allylic alcohol may be obtained with a k_f/k_s of 5 or more.[4]

The existence of this subtle effect is easily demonstrated, but its cause is obscured by the difficulties of knowing the catalyst composition in these rapidly exchanging early transition metal alkoxide systems. The differences between the two systems lead us to believe that in Ti(O^{i}Pr)$_4$-based kinetic resolution catalysts, bulky secondary allylic alcohols (such as cyclohexylpropenylcarbinol) do not to a significant extent displace the spectator isopropoxide ligands. If they did, the Ti(O^{t}Bu)$_4$- and Ti(O^{i}Pr)$_4$-based catalysts would be identical. Although exchange may be rapid, the equilibrium mixture will be dominated by complexes having isopropoxide as the bystander ligand. In Ti(O^{t}Bu)$_4$-based catalysts, however, the *tert*-butoxide and the bulky secondary allylic alcohol have more similar steric

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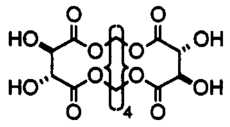
(1) (a) Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 4016. (b) Burns, C. J.; Martin, C. A.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2826.

(2) See ref 1a.

(3) Kalantar, T. H., Ph.D. Thesis, Massachusetts Institute of Technology, 1990. The doubly linked tartrate ligand was of the structure shown below.



(4) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamado, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(5) This number is obtained from the equation

$$\frac{k_f}{k_s} = \frac{\ln (A/A_o)}{\ln (B/B_o)} = \frac{\ln [(1-c)(1-\mathrm{ee})]}{\ln [(1-c)(1+\mathrm{ee})]}$$

where c is the fraction of consumption of racemate and ee is % ee/100.

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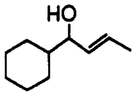
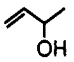
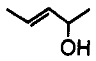
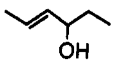
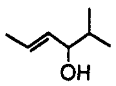
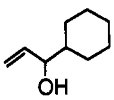
Table I. Stoichiometric Kinetic Resolution Results

entry	substrate[a]	catalyst	reaction time (h)	% ee allylic alcohol, config	conv (%)	k_f/k_s (obs)
1		Ti(O^{i}Pr)$_4$/L-(+)-DIPT	17	>97, 2*R*	55	36
2		Ti(O^{t}Bu)$_4$/L-(+)-DIPT	18	20, 2*R*	59	1.7

[a] The substrate/Ti ratio was 1:1.

Table II. Effects of Decreasing the Size of the Secondary Allylic Alcohol

entry	substrate[a]	catalyst	reaction time (h), conv (%)	% ee allylic alcohol, config	erythro:threo ratio	k_f/k_s (obs)
1		Ti(O^{i}Pr)$_4$/D-(−)-DIPT	41.5, 54	88,[b] 2*S*	>95:5[c]	20
2		Ti(O^{t}Bu)$_4$/D-(−)-DIPT	51, 49	72,[b] 2*S*	>95:5[c]	14
3		Ti(O^{i}Pr)$_4$/D-(−)-DIPT	10, 51	89,[d] 2*S*	94:6[e]	41
4		Ti(O^{t}Bu)$_4$/D-(−)-DIPT	5, 54	92,[d] 2*S*	93:7[e]	27
5		Ti(O^{i}Pr)$_4$/D-(−)-DIPT	12, 56	92,[d] 2*S*	92:8[e]	22
6		Ti(O^{t}Bu)$_4$/D-(−)-DIPT	20, 54	82,[d] 2*S*	88:12[e]	14
7		Ti(O^{i}Pr)$_4$/D-(−)-DIPT	18, 57	90,[d] 2*S*	82:18[e]	16
8		Ti(O^{t}Bu)$_4$/D-(−)-DIPT	16, 52	47,[d] 2*S*	66:34[e]	4.0
9		Ti(O^{i}Pr)$_4$/D-(−)-DIPT	43, 46	71,[d] 2*S*	94:6[e]	21
10		Ti(O^{t}Bu)$_4$/D-(−)-DIPT	69, 48	62,[d] 2*S*	90:10[e]	9.7

[a] The substrate/Ti ratio was 10:1. [b] The ee was determined by GC analysis of the derived Mosher ester. [c] The erythro/threo ratios were determined at approximately 50% conversion in separate experiments by ^{1}H NMR and GC–MS analysis of the in situ derived thiophenol ring-opened products.[7] [d] The ee was determined by chiral GC analysis of the derived acetate ester. [e] The erythro/threo ratios were determined by GC analysis.

demands. Thus, even if the allylic alcohol were to displace the *tert*-butoxide on the spectator titanium center, the steric demand of the *tert*-butoxide-based system would still be greater than that of the isopropoxide-based one. To test this hypothesis, kinetic resolution was attempted using the titanium *tert*-butoxide based system and a secondary allylic alcohol having steric proportions similar to isopropanol. As a result of rapid alkoxide exchange, the bulky *tert*-butoxide ligands should be largely replaced by the smaller allylic alcohol, generating a complex rather like the isopropoxide-based one. Indeed, this was found to be the case (Table II, entries 1 and 2): methylvinylcarbinol was a suitable substrate for kinetic resolution in both systems. By inspection of Figure 1 and examination of molecular models, it is difficult to envision how the steric requirements of alkoxides on the spectator metal center can be transmitted across the catalyst to influence the active metal center. Spectroscopic, osmometric, and extensive kinetic studies are consistent with a dimeric catalyst. Indeed, definitive kinetic studies of the Ti-tartrate epoxidation system have excluded the possibility that the active catalyst species is monomeric.[6] The results of this study support that conclusion, for it is difficult to envision how the observed effect of the bystander alkoxides could exist if the active catalyst were monomeric.

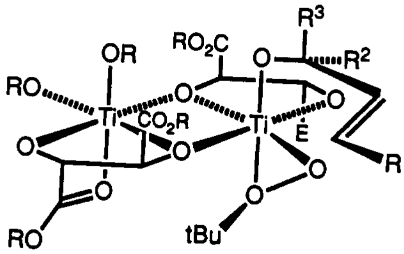


Figure 1. Proposed structure of loaded epoxidation catalyst.

Again referring to Figure 1, it is difficult to explain these observations. Supporting the hypothesis that this phenomenon is due purely to the bulk of the alkoxide, there appears to be a finite steric window of suitable substrates for kinetic resolution. As a possible alternative, the bulkier alkoxides may drive the dynamic equilibrium in the system away from the required putative dimer producing a new catalyst, or catalysts which are not efficient at kinetic resolution.

In summary, this unexpected dependency of kinetic resolution efficiency on the bulkiness of the bystander

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(6) An alternative to our covalent dimer mechanism has recently been reported (Corey, E. J. *J. Org. Chem.* **1990**, *55*, 1693.). This alternative mechanism is unlikely since it requires two extra alcohol species to be present in the activated complex and therefore does not fit the experimentally determined rate expression (shown below).[8]

$$\text{rate} = \frac{k[\text{Ti(OR)}_2(\text{tartrate})][\text{TBHP}][\text{allylic alcohol}]}{[\text{inhibitor alcohol}]^2}$$

(7) Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 5143.

(8) (a) Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure Appl. Chem.* **1983**, *55*, 1823. (b) Finn, M. G.; Sharpless, K. B. In *Asymmetric Syntheses*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8. (c) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106.

alkoxides is an interesting nuance of asymmetric epoxidation catalysis for which future mechanistic studies will hopefully provide an adequate rationale.

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Microwave-Induced Organic Reaction Enhancement Chemistry. 2. Simplified Techniques[†,1]

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Summary: A variety of organic reactions have been conducted efficiently in a few minutes in unsealed vessels at ambient pressure in unmodified microwave ovens by using selected organic solvents.

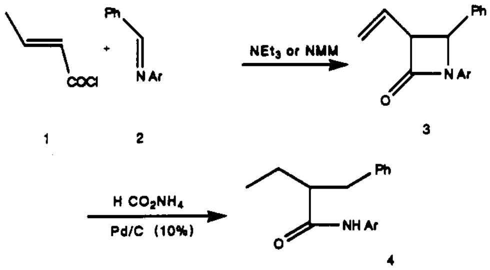
Commercial microwave ovens are now widely accepted as safe and convenient devices in the kitchen. The magnetrons in these ovens are set at a frequency of 2450 MHz for raising the temperature of water molecules through the efficient absorption of microwave energy.[2] Polar organic compounds can also be heated through dipole rotation. Hydrocarbon solvents, because of lack of dipole moment, absorb microwave energy poorly and are not heated to high temperatures in these ovens. Teflon, polystyrene, glass, and ice are nearly transparent to microwaves.[3]

In 1986, Gedye et al.[4] and Giguere et al.[5] demonstrated that many organic reactions can be conducted very rapidly under microwave irradiation. Since then, several other groups have described accelerated organic reactions in nonaqueous media.[6,7] These reactions are usually conducted on a small scale in sealed tubes or in capped Teflon vessels, and the acceleration in reaction rates is ascribed to elevated temperature and high pressure reached in a few minutes in a microwave oven.[4] Some explosions have been reported.

Giguere et al.[5] devised an explosion proof system in which a sealed reaction vessel is covered with vermiculite in a container made of a special polymer able to withstand high temperature. Even hydrocarbon solvents could be used because vermiculite, which is a hydrated silicate, absorbs microwave energy efficiently and heats the reaction vessel and contents. High pressure was avoided by some investigators by conducting solid-phase reactions with substrates absorbed on clay, silica, or alumina[8] or by modifying a domestic microwave oven.[9]

We wish to describe here practical and simple techniques for using domestic microwave ovens without alteration[10] as safe and convenient laboratory devices. We have observed that a large variety of organic reactions in nonaqueous media can be conducted on milligram to several hundred gram scale in 1–10 min in inexpensive equipment.[1] Furthermore, there is no need for sealed vessels, reflux condensers, stirrers, water separators (Dean-Stark tube), etc. We have devised a method for extending these techniques to reactions that are normally conducted in hydrocarbon solvents. The key to our "Microwave-induced Organic Reactions Enchancement" (MORE) chemistry is the proper choice of a microwave energy transfer medium and a nontraditional approach to the experimental set up for organic reactions.

Scheme I



NMM = N-methylmorpholine
Ar = 4-methoxyphenyl

To demonstrate the versatility of MORE chemistry, a variety of organic reactions are described here that we have conducted in domestic microwave ovens. In the course of these studies we have also uncovered an interesting aspect of the Bischler–Napieralski reaction which is reported here.

Safe Techniques. The preferred reaction vessel is a tall beaker with a loose cover of much larger capacity than the volume of the reaction mixture. A large Erlenmeyer

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[†] Dedicated to Professor Luigi Z. Pollara.

[‡] Participant in the UPTAM (Undergraduate Projects in Technology and Medicine) program of Stevens Institute of Technology.

[§] Visiting Scientist from Panjab University, Chandigarh, India.

(1) Part 2 in this series. For part 1, see: Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles* **1990**, *30*, 741. Presented in part at the 202nd National Meeting of the American Chemical Society, New York, Aug 1991; ORGN 195.

(2) Neas, E. D.; Collins, M. J. In *Introduction to Microwave Sample Preparation*; Kingston, H. M., Jassie, L. B., Eds. American Chemical Society: Washington, 1988; Chapter 2.

(3) Previously, we[1] have described a reaction conducted in a vial enclosed in a block of ice. The reactants were heated directly by the microwave irradiation without melting much of the ice; the products that were formed were chilled immediately when the oven was turned off—a useful set up if reaction products are thermolabile.

(4) (a) Gedye, R. N.; Smith, F. E.; Westaway, K. C. *Can. J. Chem.* **1988**, *66*, 17. (b) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.

(5) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945. (b) Giguere, R. J.; Namen, A.; Lopez, B.; Arepally, A.; Ramos, D.; Majetich, G.; Defauw, J. *Tetrahedron Lett.* **1987**, *28*, 6553. (c) Giguere, R. J. *Organic Synthesis: Theory and Applications*; JAI Press: Greenwich, 1989; Vol. 1, pp 103–172.

(6) Berlan, J.; Giboreau, P.; Lefeuvre, S.; Merchand, C. *Tetrahedron Lett.* **1991**, *32*, 2363 and references cited therein.

(7) Chen, S.-T.; Chiou, S.-H.; Wang, K.-T. *J. Chin. Chem. Soc.* **1991**, *38*, 85.

(8) (a) Alloum, A. B.; Labiad, B.; Villemin, D. *J. Chem. Soc., Chem. Commun.* **1989**, 386. (b) Gutierrez, E.; Loupy, A.; Bram, G.; Ruiz-Hitzky, E. *Tetrahedron Lett.* **1989**, *30*, 945. (c) Bram, G.; Loupy, A.; Majdoub, M.; Gutierrez, E.; Ruiz-Hitzky, E. *Tetrahedron* **1990**, *46*, 5167.

(9) Chen, S.-T.; Chiou, S.-H.; Wang, K.-T. *J. Chem. Soc., Chem. Commun.* **1990**, 807.

(10) Modification of commercial microwave equipment can be hazardous because of possible leakage of microwave radiation.[2]

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