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New enantioselective routes to biologically interesting compounds

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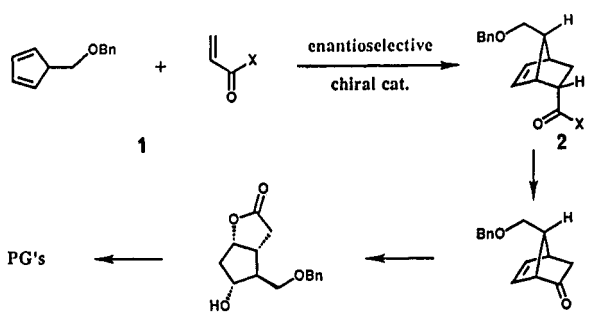
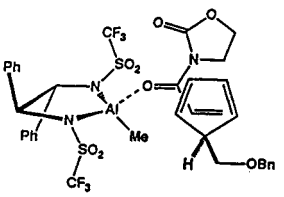
Abstract: New reagents and processes are described for the control of absolute and relative stereochemistry in the multistep synthesis of complex molecules. Among the reactions which have been studied are carbonyl reduction, Diels-Alder addition, aldol, carbonyl allylation, and C=C oxidation. New insights are presented on the origin of stereoselectivity in such processes.

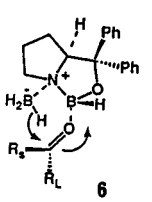
INTRODUCTION

The development of synthetic methods for the construction of complex biologically active molecules increasingly requires precise control of stereochemistry and the rational, mechanistically-based design of new reagents and processes. One of the most dynamic and crucial areas for new research is centered about the control of absolute stereochemistry. This lecture presents an overview of recent progress made in our laboratories toward the logical discovery of new enantioselective processes, especially those which correspond to the most powerful and useful synthetic reactions.

It was clear from our early studies of prostaglandin (PG) synthesis[1] that a catalytic enantioselective version of the initial Diels-Alder step (**1** → **2**) would be of great value; a recent solution to this problem is summarized in the transition state assembly (**3**). In addition, a catalytic method for controlled generation of the *S* stereochemistry at C(15) of the PG's (**4** → **5**) would clearly be advantageous. This problem too has been solved (transition state assembly **6**) by the development of a new approach to enantioselective carbonyl reduction. These new processes typify our approach to the logical design of powerful new methodology for effecting in a stereospecific way such reactions as C=O reduction, cycloaddition, aldol coupling, C=O coupling to nucleophilic carbon, conjugate addition to α,β-enones, and oxidation of C=C.





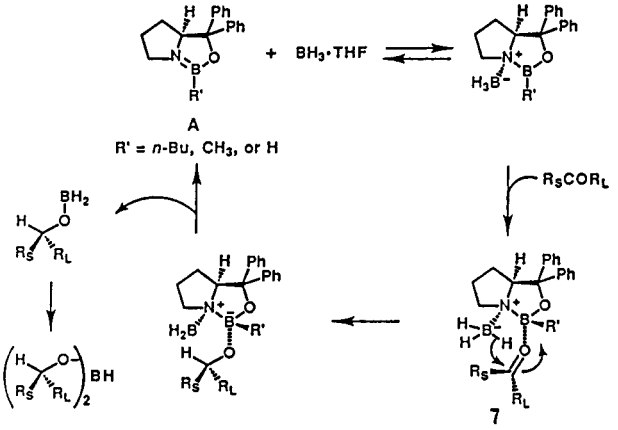


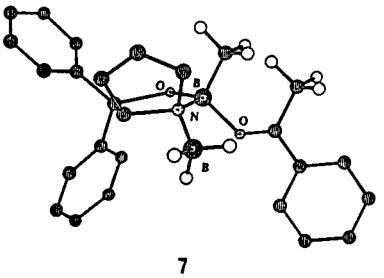
1 ENANTIOSELECTIVE CATALYTIC REDUCTION OF KETONES

Oxazaborolidines such as **A**, readily available from the reaction of $RB(OH)_2$ and diphenylprolinol in toluene in the presence of 4A molecular sieves, serve as excellent catalysts for the enantioselective reduction of a wide variety of ketones with borane or catechol borane as stoichiometric reductant. The catalytic cycle is indicated below for borane in THF.[2-4] The method (CBS reduction) has a number of advantages: (1) wide scope, (2) predictable absolute stereochemistry, (3) ready availability of the chiral catalyst in either enantiomeric form, (4) easy and efficient recoverability of the chiral amino alcohol (catalyst precursor), (5) high yields and experimental simplicity, and (6) economy.

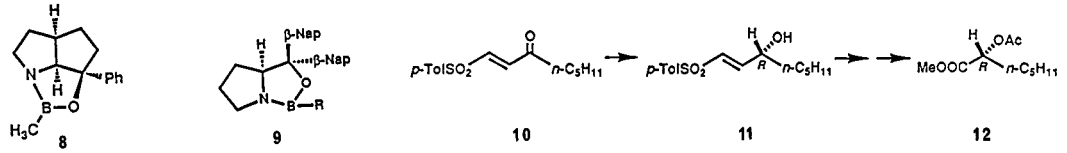
The mechanism of the CBS reduction has been illuminated by several lines of evidence: stereochemical, ^{11}B NMR, structure reactivity relationships, and kinetic isotope effects. A transition state assembly (**7**) for catalyst **A**, borane and acetophenone which leads to observed product is shown.

Many prochiral ketones have been reduced by the CBS process to the corresponding chiral secondary alcohols with ee's in excess of 90% (and as high as 99%). Several therapeutically important molecules have been synthesized enantioselectively using the CBS reduction to establish molecular chirality, for example





ginkgolides B and A,[5,6] forskolin,[7] isoproterenol, and fluoxetine.[8] The CBS method is the most practical and general way of controlling configuration at C(15) in prostaglandin synthesis.[3] A CBS type catalyst (**8**) has also been used as a catalyst in its own enantioselective synthesis.[9] Catalyst **9** R=*n*-Bu, which is very effective for the enantioselective reduction of a wide range of ketones, has been applied to the synthesis of chiral 1-deuterated primary alcohols[10] using catecholborane as the stoichiometric reductant. The catecholborane modification of the CBS reduction using catalyst **A** (R=*n*-Bu) or **9** (R=*n*-Bu) shows extraordinary promise for a variety of α,β-enones.[11] For example, enone **10** can be reduced to **11** (100% ee after a single recrystallization) which upon acetylation, oxidation (periodate, cat. Ru) and methylation affords optically pure α-acetoxy ester **12** in excellent yield.[11]



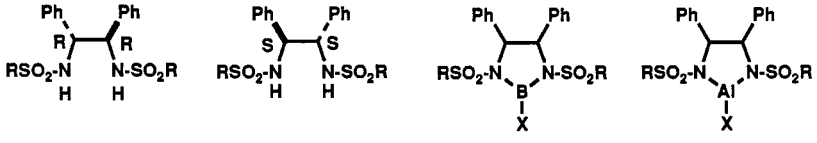
The various catalysts for the CBS reduction which are mentioned above can be regarded as molecular robots[11] in the sense that they hold one reactant in a structurally specific way, then attach to a second reactant with control of geometry such that the two reactants are brought into proximity and also mutually activated for chemical reaction. That reaction occurs in a precise three-dimensional assembly that leads selectively to one enantiomeric structure. Finally the product is released so as to complete the cycle. Such small molecular robots differ from enzymes in two ways, although there are obviously also real similarities. Unlike enzymes (the original molecular robots) these small molecular robots lack the size to have binding pockets or complex sites for recognition of molecular size or shape of a substrate. The catalytic behavior of these small molecules qualify them as a kind of chemical enzyme (chemzyme), but the differences also must be emphasized.

The rational design of new types of molecular robots is certain to be an important field of chemistry for years to come and the new synthetic methods which emerge from such research will be of great value.

2 CHIRAL 1,2-DIAMINOETHANE DERIVATIVES AS CONTROLLER UNITS FOR ENANTIOSELECTIVE PROCESSES

Chiral C_2 symmetric 1,2-diamines and their various derivatives offer great promise as components of new reagents for enantioselective synthesis. A long term objective in our laboratory has been the application of such compounds to the design of new reagents and molecular robots for accomplishing stereoselectively the most powerful molecular constructions. The (*R,R*)- and (*S,S*)-forms of 1,2-diphenyl-1,2-diaminoethane (stilbenediamine, *stien*) can be made in quantity by a simple new synthesis[12] and they are readily converted to sulfonamides of the (*R,R*)- and (*S,S*)-series, **13** and **14**, respectively. From **13** a series of chiral

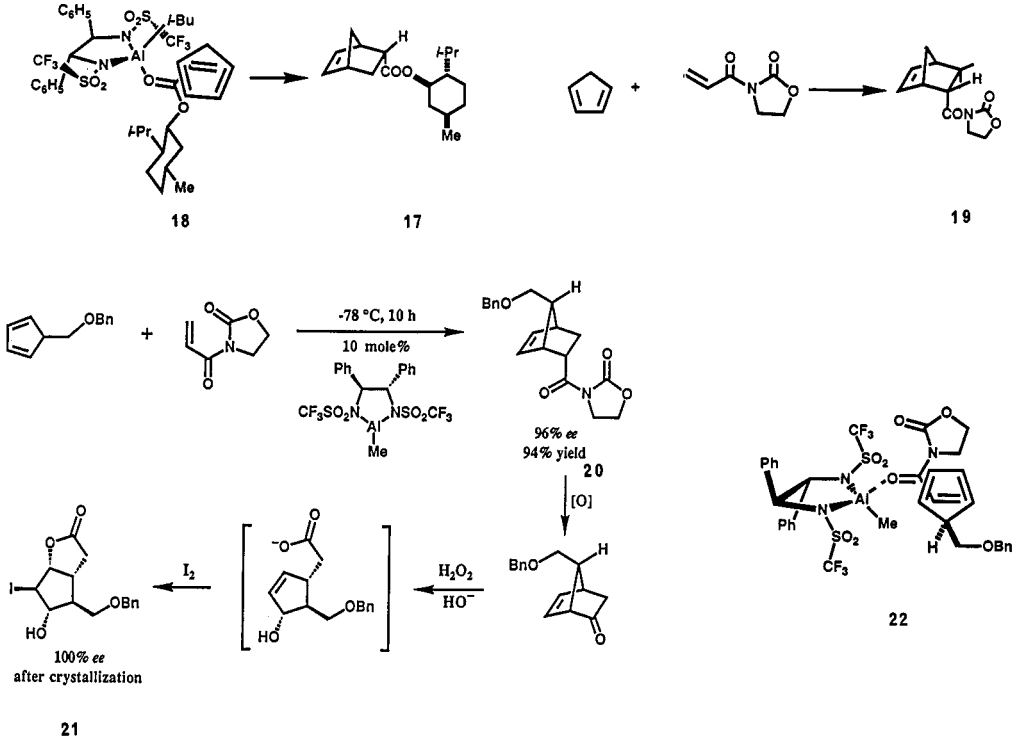
Lewis acidic catalysts were prepared which contain boron (**15**) or aluminum (**16**) in a rigid C_2 symmetric environment; the corresponding (*S,S*)-series was prepared from **14**. The use of these reagents is described below.



13 14 15 16

3 ENANTIOSELECTIVE CATALYTIC DIELS–ALDER REACTIONS

The chiral aluminum complex (*R,R*)-**16**, R=CF_3 and X=*i*-Bu, catalyzes the reaction of cyclopentadiene and the acrylate ester of (-)-menthol at -78°C to form selectively the Diels-Alder adduct **17** in 96.7% diastereomeric excess (de) as compared to 52% de for the corresponding reaction of (+)-menthyl acrylate ester and *ca.* 50% ee for the reaction of methyl acrylate.[12] These facts indicate a positive cooperativity for the reaction of (-)-menthyl acrylate and are consistent with the transition state assembly **18**. The Diels-Alder reaction between cyclopentadiene and achiral 3-acrylyloxazolidin-2-one at -78°C in the presence of 10 mole % of the catalyst (*S,S*)-**16**, R=CF_3 and X=CH_3, affords the *endo* Diels-Alder adduct **19** in 91% yield and 95% ee (>30 : 1 *endo-exo* ratio).[12] Equally impressive is the reaction of 5-benzyloxymethyl-1,3-cyclopentadiene and the acrylyloxazolidinone in the presence of 10 mole % of catalyst (*S,S*)-**16**, R=CF_3 and X=CH_3, which provides the valuable intermediate for prostaglandin synthesis[1] **20** in 94% yield and 96% ee.[12] This intermediate is readily converted to the optically pure PG precursor **21** in excellent yield. With

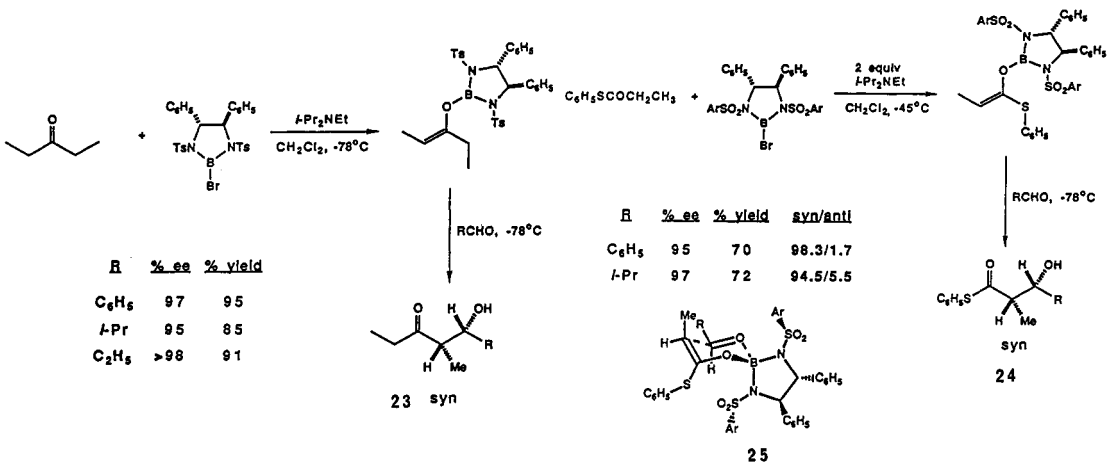


18 17 19 20 21 22

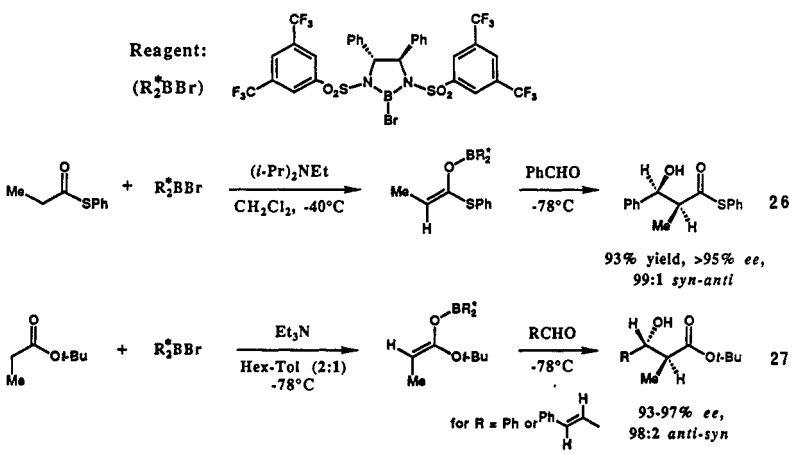
this new modification, the Harvard bicycloheptene route to PG's[1] has reached a high level of efficiency through the use of extraordinary robot-like catalysts which control absolute and relative stereochemistry. We believe that the absolute stereopreference in the Diels-Alder reactions to form **19** and **20** is the result of catalyst coordination to the acrylyl carbonyl of the dienophile at the lone pair *anti* to nitrogen, fixing the acrylyl group in the s-*trans* conformation and leading to a transition state assembly approximated by **22**.[12] The bonds to the sulfonamide nitrogen in the chiral catalysts **15** or **16** and the transition state assemblies **18** or **22** are considered to planar (sp^2 hybridization) and the SO_2 groups to be oriented such that a plane passing through the p orbital on nitrogen and the attached sulfur bisects the acute SO_2 angle. The R group attached to each sulfur is then arranged in space to project oppositely to the nearby phenyl substituent relative to the plane of the metal-containing ring. Justification for such conformational preferences is available from chemical and X-ray studies of various sulfonyl and sulfonamide derivatives.[13,14]

4 ENANTIOSELECTIVE ALDOL REACTIONS

The *stien* controller system has also been applied to enantioselective aldol reactions with considerable success, as can be appreciated from a representative sample of the experimental results. Reaction of (*R,R*)-**15**, R=*p*-tolyl and X=Br, with 1 equiv of 3-pentanone and 2 equiv of *i*-Pr_2NEt in CH_2Cl_2 at -78°C generated the *Z*-boron enolate which underwent reaction with propionaldehyde to give the corn weevil pheromone sitophilure (**23**, R=C_2H_5) (>98% ee and >98% de, 91% yield); after one recrystallization >99.8% pure sitophilure was obtained.[12] Two other examples involving different aldehydes are shown for comparison. The phenylthio ester of propionic acid could be converted to the *E*-enolate using (*R,R*)-**15**, R=*p*-nitrophenyl and X=Br, and *i*-Pr_2NEt. Subsequent reaction at -78°C afforded *syn* aldol products **24** with excellent absolute and relative stereocontrol. A transition state assembly which explains this result in a rational way is **25**.[12] Recently, **15**, R=3,5-di(trifluoromethyl)phenyl and X-Br, has been found to be an outstanding reagent for aldol reactions, as shown for the synthesis of *syn* aldol product **26** (>95% ee, 99 : 1 *syn-anti*, 93% yield) and the *anti* aldol product **27** (93% ee, 99 : 1 *anti-syn*, 85% yield) from this highly reactive (*R,R*)-bromoborane.[15]. In general, with this reagent phenylthio esters give *syn* aldols and *t*-butyl esters afford *anti* aldols with excellent enantioselectivity and diastereoselectivity. The preferred base for the *syn* process is *i*-Pr_2NEt, and that for the *anti* aldol is Et_3N.

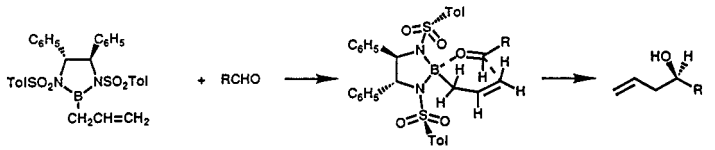


Enantioselective *Syn* or *Anti* Aldols



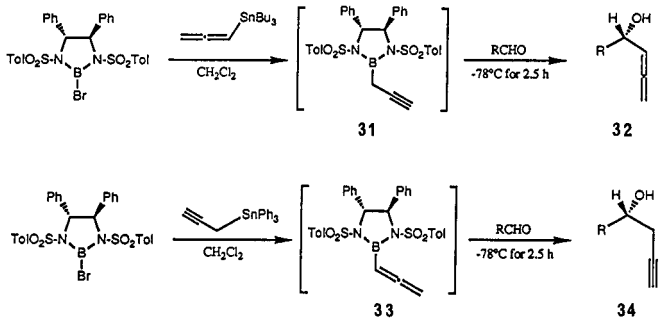
5 ENANTIOSELECTIVE ALLYLATION OF ALDEHYDES

The (*R,R*)-allylborane **28**, produced by reaction of the corresponding bromoborane with allyltri-*n*-butyltin (at 0°C in CH_2Cl_2), is an excellent reagent for the enantioselective allylation of aldehydes to form, via a transition state assembly approximated by **29**, adducts **30** with ee values in the range 95-97%.[16] The addition of 2-bromo and 2-chloroallyl groups to aldehydes can be effected similarly, though with somewhat lower enantioselectivity.



28 **29** **30**

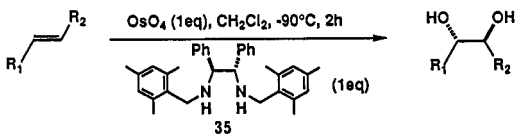
A remarkably enantiospecific route to propa-1,2-dienyl carbinols **32** from achiral aldehydes has also been demonstrated experimentally. The chiral propargyl borane **31** is generated quantitatively from the corresponding (*R,R*)-bromoborane and propadienyltri-*n*-butylstannane (CH_2Cl_2 at 0°C) and reacts (CH_2Cl_2 at -78°C) with a variety of aldehydes to form propa-1,2-dienyl carbinols **32** in >99% enantiomeric excess (*ca.* 80% isolated yield).[17] No contamination of product **32** by the other enantiomer can be detected by 500 MHz ^1H NMR analysis of the MTPA ester. This process is also effective for the synthesis of 1-alkyl-1,2-propadienyl carbinols.[17] In a parallel way chiral propargyl carbinols **34** can be obtained with high enantioselectivity from the (*R,R*)-propa-1,2-dienylborane **33**.[17] The generality of this process is shown by its application to the synthesis of 2-pentynyl carbinols (97-98% ee), methodology which can be applied to a superior synthesis of PG's such as PGE_3 and $PGF_{3\alpha}$.[17] These enantioselective syntheses of propa-1,2-dienyl and propargyl carbinols can be explained mechanistically by transition state assemblies analogous to **29** for allylation.[17]



31 **32** **33** **34**

6 ENANTIOSELECTIVE VICINAL HYDROXYLATION OF TERMINAL AND *E*-1,2-DISUBSTITUTED OLEFINS

Enantiomerically pure (*S,S*)-1,2-diphenyl-1,2-*bis*[2,4,6-trimethylbenzylamino]ethane (**35**) is readily prepared from (*S,S*)-1,2-diphenyl-1,2-diaminoethane and 2,4,6-trimethylbenzaldehyde.[18] Diamine **35** enormously accelerates the reaction of olefins with osmium tetroxide at -90°C, the reaction usually being complete in less than 2 hours (in CH_2Cl_2 or toluene) at that temperature with a variety of terminal or *E*-1,2-disubstituted olefins, even though only a small fraction of OsO_4 and **35** are complexed under those conditions. The reaction proceeds to give 1,2-diols with excellent enantioselectivity and in a uniform absolute stereochemical sense, as indicated by the accompanying data.[18] A simple experimental procedure has been developed which allows efficient recovery (and recycling) of osmium, diamine **35**, and chiral 1,2-diol.[18] The (*R,R*)-enantiomer of diamine **35** leads to the enantiomeric series of 1,2-diols equally well.

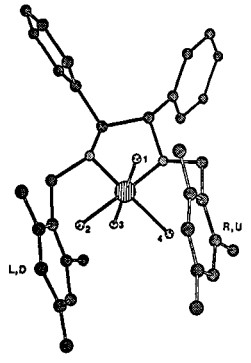


35

OLEFIN	Yield	ee	Abs. Config.
Ph	81	92	S
Ph, CH_3	95	93	SS
Ph, Ph	95	92	SS
p-MeO-C_6H_4, C_6H_4-*p*-OMe		82	(SS)
C_2H_5, C_2H_5	90	98	SS
MeO_2C, CO_2Me	75	92	RR
Me, CO_2Me	82	97	2R,3S
Ph, CO_2Me	83	92	2R,3S
Me, OTBDPS	87	95	(SS)

A rational mechanistic view of these enantioselective hydroxylations has been developed on the basis that a C_2 symmetric 1 : 1 complex of **35** and OsO_4, **36**, is the reactive reagent. The two (equivalent) equatorial oxygen atoms O_2 and O_4 of **36** are considered to be nucleophilic relative to the two (equivalent) axial oxygens O_1 and O_3 because of charge transfer from the amino ligands to O_2 and O_4 (electron donation from N to σ^* of the *trans* coplanar Os-O). Therefore, attack on the olefin can be expected to involve one axial oxygen and one equatorial oxygen. Because of C_2 symmetry and also steric blocking of addition to O_1/O_4 or O_2/O_3 of **36**, there is one favored pair of oxygen sites for this reaction, O_1/O_2 (or the equivalent O_3/O_4). This argument correctly predicts face selectivity for the enantioselective hydroxylation of *E* (or terminal) olefins since transition state assembly **37** is relatively free of steric repulsion whereas **38** involves major steric repulsion.[18]

This mechanistic approach provides a satisfactory explanation of much literature data on other chiral ligands in the reaction of olefins with osmium tetroxide.[19] Even the function of cinchona alkaloid derivatives, such as quinidine *p*-chlorobenzoate (**39**), which have been found to be useful catalysts for enantioselective hydroxylation by OsO_4,[20] can be rationalized within the framework of the above proposal. The occurrence of substantial enantioselectivity with ligands such as **39** seems inconsistent with a pathway involving a 1 : 1 : 1 assembly of **39**, OsO_4 and olefin in the transition state. More likely is a 2 : 2 : 1 assembly which would result from the reaction of a dimeric reagent **40**, Q = quinidine derivative **39**, with the olefin. Reagent **40** is logical not only because it involves the more reactive octahedral coordination to Os but also because C_2 symmetric conformers of **40** are possible. One of these, **41**, is unique by virtue of (1) its C_2 symmetry, (2) its low energy, (3) the attractive π-π interactions of the aromatic rings, and (4) accessibility of an O_{eq}=Os=O_{ax} subunit to attack by an *E*-olefin.[21] Only the starred axial/equatorial oxygen pair of **41** is available to an olefin, and it is this pair that leads to the correct prediction[21] of face selectivity in the **39**-catalyzed OsO_4-*E*-olefin reactions.[20]



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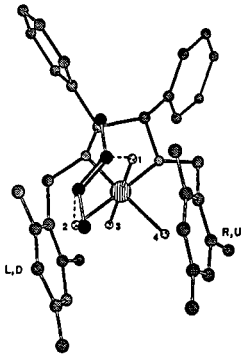

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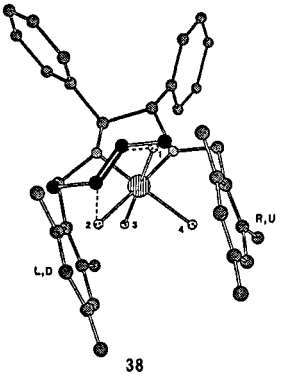

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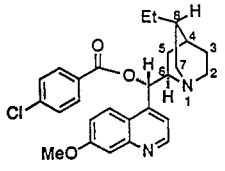

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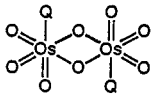

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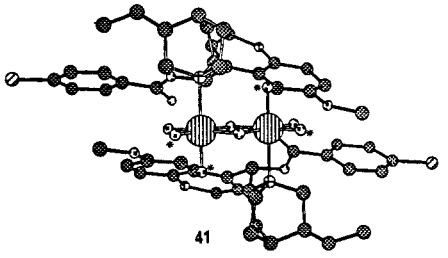


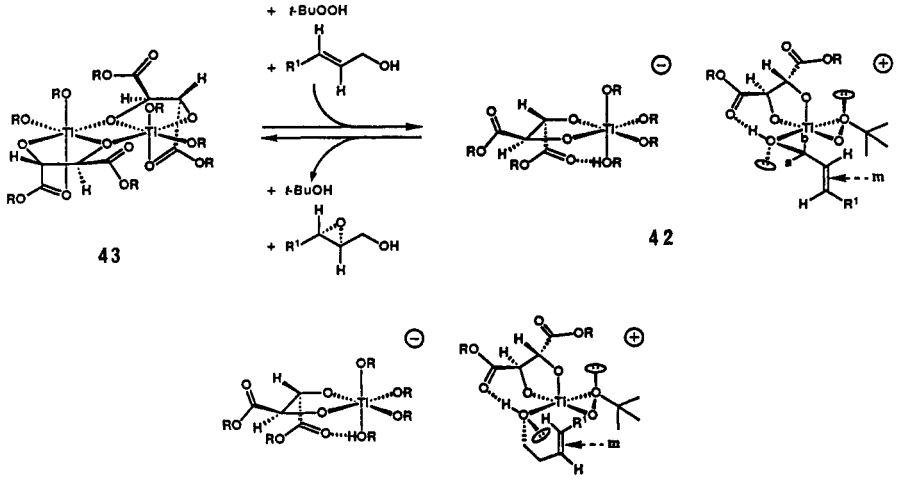
41

(reaction at O*)

7 ON THE ORIGIN OF THE ENANTIOSELECTIVITY IN THE KATSUKI–SHARPLESS EPOXIDATION PROCEDURE

The successful development of a rational and clear picture for the enantioselective reactions of olefins with chiral amines and osmium tetroxide encouraged us to analyze in similar detail the Katsuki-Sharpless enantioselective epoxidation of allylic alcohols.[22] We outline herein a mechanistic possibility which provides a clear and rational explanation of the data published to date with regard to (1) substrate structure/absolute stereoselectivity and diastereoselectivity, (2) substrate structure and reactivity, (3) structural requirements for the catalyst and the peroxidic oxidant, and (4) reaction kinetics and inhibition.

Specifically, it is proposed that the transition state assembly for the epoxidation of *E*-2-alken-1-ols (for example) by diesters of (*R,R*)-(+)-tartaric acid, Ti(O*i*-Pr)$_4$, and *t*-BuOOH can be approximated by ion pair **42**. The key features of **42** can be derived in a logical way and include the following with regard to the catalytic cation. (1) One molecule of the *(R,R)*-tartrate ester is chelated to the central Ti of the cationic moiety of **42**. (2) The hydroxyl group of the allylic alcohol is coordinated to that (C_2 symmetric) Ti so as to allow hydrogen bonding to the carbonyl of the tartrate ester. The geometry of that hydrogen bond in **42** is close to ideal (linear with an O-H-O distance of approximately 2.7 Å). (3) The *t*-butylperoxy (*t*-BuOO) group is chelated to the catalytic Ti with the terminal oxygen *cis* to the coordinated allylic OH and the *t*-BuO subunit *trans* to the allylic OH. Further, the oxygen of the *t*-BuO subunit is pyramidal and in the (*R*)-configuration so as to place the bulky *t*-butyl group proximate to the vacant coordination site of octahedral Ti and remote from the other ligands on Ti. Any other arrangement of ligands leads to severe steric repulsion between the *t*-butyl group and the ligand which is *cis* to *t*-butyl about the peroxide chelate ring. An sp^2-hybridization of the *t*-butoxy oxygen is strongly disfavored both sterically and electronically. (4) Five donor atoms are coordinated to the central Ti of the cationic moiety of **42**, further coordination being strongly disfavored by the bulk of the *t*-alkoxy subunit. (5) The specific arrangement of ligands about Ti in the cationic moiety of **42** makes that Ti a chiral center with the absolute configuration having been determined by the tartrate ligand, as shown. (6) The chirality about the catalytic Ti of **42** and the fixed hydrogen bond strongly favor internal epoxidation at only one face of the double bond if that bond approaches the peroxy O-O bond with its midpoint (m) approximately colinear with the O-O axis and with the C=C bond axis approximately perpendicular to the plane of the peroxy chelate ring, the optimal stereoelectronic arrangement.[22] In that arrangement the hydroxyl of the allylic alcohol is also chiral and of (*R*)-configuration (pyramidal arrangement of Ti, H, and C about the allylic oxygen), as shown in **42**. (7) The neutrality of the hydroxylic oxygen ligand *trans* to the *t*-BuO ligand in **42** should favor peroxidic bond cleavage relative to a more electron donating alkoxide ligand *(trans*-σ electronic effect).



Transition state assembly **42** is both logically derivable and unambiguous with regard to the absolute stereochemical preference which it implies for the epoxidation reaction. The absolute configuration expected for the epoxy alcohol from **42** accords with the experimental facts.[22] Transition state assembly **42** also explains the much faster reaction rate for substrates in which a = alkyl or a = b = H relative to b = alkyl.[22] Assembly **42** can be formed directly from the binuclear reagent **43** in a reaction which is first order in **43**, the allylic alcohol, and *t*-BuOOH, in agreement with the observed kinetics.[22] The formation of epoxy alcohol from **42** would clearly lead to regeneration of **43** by dissociation of the epoxide from the catalytic site assisted by ion-pair collapse. Water, an inhibitor of the epoxidation reaction, clearly can be expected to inhibit by coordination to the vacant site in **42** as well as by competing reactions with the reagent **43**.

The hydrogen bond in **42**, a key feature of this proposal, provides a unique explanation for the failure of many other chiral 1,2-diols (even C_2 symmetric 1,2-diols) to promote enantioselective epoxidation in place of tartrate derivatives. For example, the use of chiral 2,3-butanediol or 1,2 diphenyl-1,2-ethanediol as ligand leads to epoxy alcohol of only 0-5% enantiomeric excess.[22] The hydrogen bond mechanism mandates the conclusion that homoallylic alcohols (for stereoelectronic reasons) should react by coordination of the homoallylic OH at the diastereotopic lone pair (relative to the allylic structure **42**) with epoxidation at the opposite face of the double bond as compared to **42**, as shown in assembly **44**, in full accord with experimental results. The importance of using bulky tertiary hydroperoxides[22] can also be appreciated from, and indeed is central to, the present proposal.

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