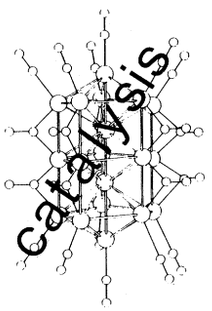
Catalysts That Break Nature's Monopoly

Chiral complexes can approach the specificity of enzymes for synthesis of optically active compounds, and can act on a wider variety of substrates

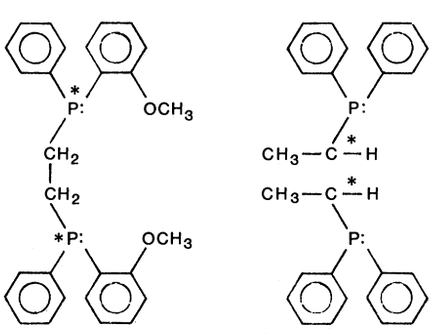


Investigators of catalysis "have promised that eventually we'll have man-made catalysts that are at least as good as, or probably even better than, enzymes," says K. Barry Sharpless of the Massachusetts Institute of Technology (MIT). These new catalysts will be better than enzymes "in that they will work under more flexible conditions than biological systems. Also, they don't need to work in water and don't have complicated cofactors and all this other garbage around that has to be gotten rid of when the product is purified." For at least two kinds of asymmetric catalysis, he continues, "we can compete with and, in some ways, do better than enzymes." Adds Jack Halpern of the University of Chicago: "The monopoly of Nature on making asymmetric molecules catalytically has been broken."

Interest in the synthesis of chiral* compounds has grown, says Barry M. Trost of the University of Wisconsin, Madison, because "the demand for ready access to complex organic molecules has increased markedly." These molecules include insect hormones and pheromones, prostaglandins and other members of the arachadonic acid cascade, vitamin D metabolites, and various antitumor compounds. "Varying the structure of complex natural products of known biological activity in order to probe the mechanism of their function and to improve their therapeutic properties," he adds, "requires their total or partial synthesis." β-Lactam antibiotics related to penicillin represent one good example where this approach has been important.

Chirality can be exceptionally important in drugs, pheromones, and the like. The pure natural enantiomer of the gypsy moth sex attractant, (+)-disparlure, "agitates males and disrupts mating," says Sharpless, "but the (−)-enantiomer not only has no effect on mating, but interferes with the activity of the (+)-enantiomer." The *R*-(−)-enantiomer of the drug Inderal, which is used to treat hypertension and heart disorders, has 100 times as much β-adrenergic activity as the *S*-(−)-enantiomer. Similarly, the teratogenicity (ability to cause birth defects) of the drug thalidomide lies exclusively in its *S*-(−)-enantiomer.

Before catalytic techniques were developed,† the chemist traditionally had two ways to make chiral compounds. The oldest and most common approach was to synthesize a racemic mixture and then resolve the desired enantiomer by cocrystallization with a naturally occurring (and thus inexpensive) chiral compound. Through repeated crystallizations, it is often possible to get as close to optical purity as desired, although the overall yield is reduced accordingly. Under ideal conditions, the total yield is only 50 percent. In some cases, this limitation can be overcome by racemization of the unwanted enantiomer, followed by another cocrystallization. This is done, for example, in the commercial synthesis of lysine.



Chiral ligands

Two of the chiral ligands often used for asymmetric synthesis.

The second method is to use a chiral template. It is often possible, for example, to incorporate into the desired product a preformed chiral center from the starting material or a reagent. D-Glucose, for example, can be converted into enantiomerically pure vitamin C with retention of two of its four chiral centers. Vitamin C can possibly be converted into other desirable products; tartaric acid can be converted to malic acid. Often, moreover, the template can be made by constructing an intermediate in such a manner that a reactant can attack it from only one direction. This is called induced chirality and is one of the most common ways now used to form chiral centers.

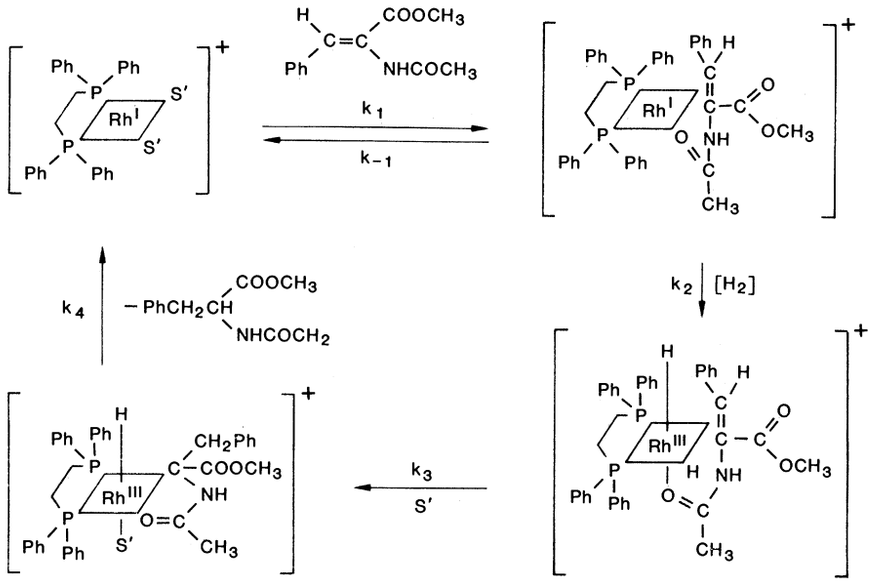
Interest in chiral synthesis, particularly induced chirality, has undergone "an exponential growth," according to Harry S. Mosher of Stanford University and James D. Morrison of the University of New Hampshire. "In the 5-year period, 1971–76," they say, "*Chemical Abstracts* listed 47 entries under 'Asymmetric synthesis.' In the next 5-year period, 1976–81, there were over 940 such entries." Most of this work, however, has been simply a refinement of general principles developed in the early 1950's. "We believe that few recent basic breakthroughs have been made in the principles governing the stereochemistry of asymmetric synthesis," although "spectacular progress has been made" in the application of those principles.

The one exception to that generalization involves catalysis. "The most innovative advancements," say Mosher and Morrison, "have been in the applications of metallo-organic chemistry in which the central metal atom, along with a coordinated chiral ligand or ligands, is used to guide and closely orient the stereochemical course of the reaction." Catalytic processes have great potential for organic syntheses because they make possible many types of reactions that were not available before. They have, perhaps, even greater potential for industrial applications because they open the door to the use of small amounts of chiral reagents to produce much larger amounts of desired products.

Catalytic approaches have been attempted for many different kinds of reactions, but great success has been obtained with only two, the hydrogenation of olefins and the epoxidation of allylic

*Notes on terminology: The term *chiral* means simply handedness. An asymmetric molecule (or reactive center) is *achiral*; a molecule (or center) that can be converted to a chiral derivative is *prochiral*. Absolute configurations at chiral centers are designated (*R*) and (*S*); that configuration is determined by a set of rules that assign priorities to each substituent. Comparable rules are used for designating olefins (*Z*) and (*E*). The qualifiers (+) and (−) refer to the observed rotation of polarized light by the compound in solution and are independent of absolute configuration. *Enantiomers* are chiral molecules with a mirror-image relationship; a *racemate* has equal quantities of both enantiomers. *Diastereomers* are stereoisomers that are not mirror images. *Enantiomeric excess (e.e.)* is calculated from the relationship (for the *R* enantiomer, for instance): percent e.e. = $[(R) - (S)]/[(R) + (S)] \times 100$.

†Previous articles about catalysis have appeared in the issues of 4 February, p. 474; 25 February, p. 944; 25 March, p. 1413; 6 May, p. 592; 3 June, p. 1032; and 17 June, p. 1261.



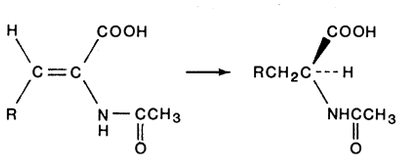
Olefin hydrogenation

The hydrogenation of methyl-(Z)-α-acetamidocinnamate proceeds in four distinct steps; k_2 is normally the rate-limiting step, but at low temperatures k_4 becomes rate-limiting. [Source: Jack Halpern, University of Chicago]

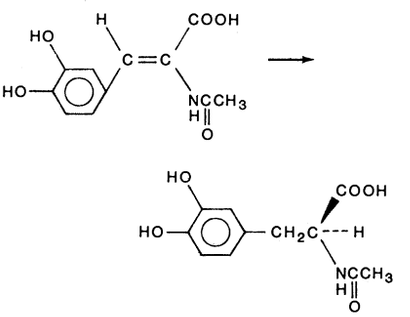
alcohols. Both types of reactions consistently produce chiral products with e.e.'s greater than 95 percent.

Because a metal atom has no intrinsic chirality, the key to catalytic chiral synthesis is the use of ligands that are chiral. Most often, these ligands have been phosphines, although the epoxidation reaction uses a diacid. In the simpler phosphines, the chiral center may be the phosphorus atom itself or it may be on one of the substituents. The most effective ligands, however, are bidentate; that is, they contain two binding sites (two phosphorus atoms or two hydroxyl groups) separated by two to four carbon atoms. Again, the chiral center can be one or both of the phosphorus atoms or one or more of the connecting carbon atoms, or it can be on one or more of the substituents.

The first good examples of chiral hydrogenations were reported independently in 1968 by William S. Knowles and his colleagues at the Monsanto Company and by L. Horner and his associates at the University of Mainz in West Germany. They found that rhodium complexes containing a chiral phosphine ligand could reduce α-acylaminoacrylic acids to amino acids:



Their initial catalysts gave e.e.'s of only about 60 percent, but subsequent work with bidentate ligands gave e.e.'s greater than 90 percent. Furthermore, these complexes have activities that are unusually high for homogeneous hydrogenation catalysts, says Halpern; their rates approach those of enzymes. This work is best exemplified by Monsanto's commercial production of L-dopa, a drug used in treatment of Parkinson's disease, by hydrogenation of the appropriate (Z)-α-acylaminoacrylic acid:



This reaction is carried out in a methanol-water mixture at 25°C by $\{Rh[(R,R)\text{-DIPAMP}](CH_3OH)_2\}^+$ and produces *N*-acetyl-L-dopa in 96 percent e.e.

Most of the recent work on hydrogenations has involved refinement of the original process. More than a hundred chiral phosphine ligands have been tested with various substrates, and several are commercially available. Catalytic synthesis is now used on a small scale commercially to produce isotopically labeled L-amino acids and rare D-amino acids. Investigators such as John K. Stille of Colorado State University have also attached the chiral ligands to inert polymers to make it easier to recover the valuable catalysts (*Science*, 20 August 1982, p. 720).

These same types of rhodium catalysts can be used for chiral hydrogenation of enamides, enol acetates, the ketone moieties of α- and β-ketoesters and amines, and certain itaconic acid and vinyl acetate derivatives. In most of these cases, however, the e.e.'s have been less than 80 percent, often substantially less. "If it weren't for the amino acids and the spectacular mechanistic discoveries of Halpern," says Sharpless, "asymmetric hydrogenation would have little practical significance." So much work has been done on hydrogenations, adds Brice Bosnich of the University of Toronto, that the field is now "more or less exhausted."

One recent development in the field that "is very, very important but that has been largely ignored," says James Roth of Air Products and Chemicals, Inc., is the unraveling of the mechanism of chiral hydrogenation by Jack Halpern and his colleagues at the University of Chicago. Their work has not only confirmed most of the steps postulated for the achiral hydrogenation of olefins, but has also revealed that the chiral hydrogenation proceeds in an unexpected and unprecedented manner.

The catalytic hydrogenation of the prototype substrate, methyl-(Z)-α-acetamidocinnamate (MAC), by the achiral rhodium complex, $[Rh(DIPHOS)(CH_3OH)_2]^+$ where DIPHOS is the achiral bidentate ligand 1,2-bis(diphenylphosphino)ethane, occurs in four distinct steps. The first is rapid and essentially complete formation of the $[Rh(DIPHOS)(MAC)]^+$ adduct. MAC is chelated to the rhodium by the carbonyl oxygen of the amide as well as by the normal π-bonding of the carbon-carbon double bond.

At room temperature, the second and rate-determining step is reaction of this adduct with hydrogen, during which the metal is oxidized from Rh(I) to Rh(III). The third step is migration of a hydrogen atom from the metal to the β carbon of the double bond while the α carbon becomes bonded to rhodium. The final step is reductive elimination of the amino acid and restoration of the metal to Rh(I). Because this step has a higher activation enthalpy than step two, it becomes rate-limiting at temperatures below −40°C, permitting the intermediate formed in step three to be characterized. Such hydridoalkyl complexes have been postulated as intermediates in homogeneous catalytic reactions, says Halpern, but "this is the first time that such an intermediate has actually been intercepted and characterized" and that the C–H bond-forming reductive elimination has been directly observed.

The chiral hydrogenation of MAC pro-

ceeds via the same mechanism except that two diastereomeric adducts are formed in the first step and each can be carried through the remaining steps of the catalytic cycle. Because of the steric hindrance of the phosphine ligand, one of the diastereomers is formed in much higher concentrations than the other; in fact, at 25°C, the equilibrium ratio of the two diastereomers is at least 11 to 1. Most scientists have assumed, and several lines of indirect evidence have supported, the probability that the predominant product arises from the predominant complex. "This interpretation also seemed more attractive on conceptual grounds," Halpern notes, "since it corresponds to the familiar lock and key concept that has been invoked so widely to explain the characteristically high selectivities of enzymic catalysts."

To understand the stereochemistry of the hydrogenation, it was necessary to correlate the absolute configuration of the products with those of the intermediate catalyst-substrate adducts. This was first achieved by Halpern for the hydrogenation of ethyl-(*Z*)-α-acetamidocinnamate (EAC) catalyzed by the rhodium complex [Rh(*S*,*S*-CHIRAPHOS)$(CH_3OH)_2]^+$. Only a single diastereomer of [Rh(*S*,*S*-CHIRAPHOS) (EAC)]$^+$ could be detected in solution, meaning that the minor diastereomer accounts for less than 5 percent of the total adduct.

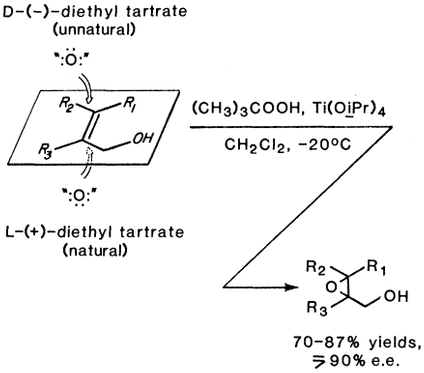
The crucial finding was that the so-called *re* face of EAC is coordinated to the rhodium atom. Addition of hydrogen to this face, in accordance with the mechanism derived for achiral hydrogenation, would yield *N*-acetyl-(*S*)-phenylalanine ethyl ester. Halpern observed, however, that the product formed in greater than 95 percent e.e. is the *R* isomer. Hence, it is the minor or less preferred diastereomer that is undergoing reaction rather than the tightly bound adduct. In fact, detailed studies of the kinetics of the reaction with DIPAMP as the chiral ligand show that the rate of reaction of hydrogen with the minor diastereomer is about 600 times greater than the rate of reaction with the major diastereomer.

This finding explains some unusual aspects of the chiral hydrogenation reaction that had been observed but were difficult to rationalize. The kinetic analysis leads to the prediction, for example, that formation of the initial adduct can be reversed at high hydrogen pressures. At sufficiently high hydrogen pressures, the stereochemistry should be determined by the initial binding rates of the prochiral substrate to the catalyst. As step one becomes rate-limiting at higher hydrogen pressures, the enantioselectivity should decrease and eventually reverse. This dependence on hydrogen pressure, says Halpern, "has been observed for virtually all of the asymmetric hydrogenation catalysts that have thus far been examined."

Because it is the minor diastereomer that is converted to product, furthermore, there must be a relatively rapid interconversion between diastereomers. Because the adduct dissociation step has a high enthalpy, Halpern says, this interconversion process should be "frozen out" at lower temperatures, so that optical yield should decrease with decreasing temperature. This also has been observed. In one particularly dramatic case, the optical yield increases from 0 to 60 percent e.e. as the temperature increases from 0° to 100°C.

> "We can compete with and, in some ways, do better than enzymes."

One of the key points in this work is that the catalysis was accomplished by a complex that does not accumulate in sufficient concentrations to be detected. A similar study by Halpern on olefin hydrogenation catalyzed by $Rh[P(C_6H_5)_3]_3Cl$ also demonstrated that virtually none of the species that accumulated under the reaction conditions were intermediates in the reaction. Concludes Halpern: "This serves to underscore the unreliable, and often misleading, mechanistic conclusions that may be derived by simply identifying the species present in a catalytic system." . . . It also suggests, says Roth, that some enzyme systems should be looked at more closely.



An empirical rule

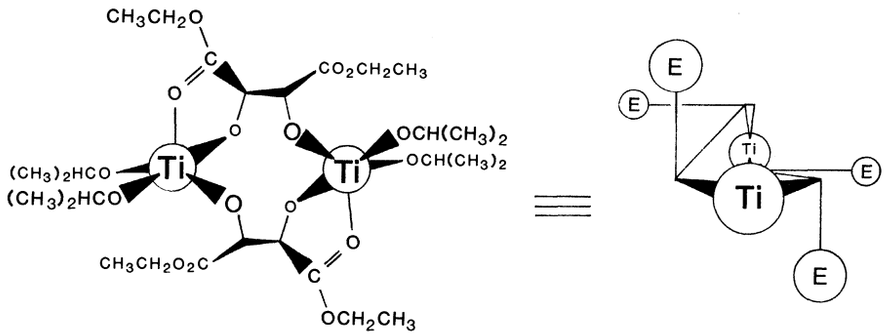
With the allylic alcohol oriented as shown, D-(−)-diethyl tartrate always delivers the epoxide oxygen from the "top" while the L-enantiomer delivers it from the "bottom." [Source: K. Barry Sharpless, MIT]

A lock-and-key fit also does not seem to be such an important factor in the achiral epoxidation system first reported in 1980 by Sharpless and Tsutomu Katsuki, both of whom were then at Stanford University. They found that epoxidations can be carried out with e.e.'s higher than 90 percent by a relatively simple system containing titanium tetraisopropoxide, *tert*-butyl hydroperoxide, and either (+)- or (−)-diethyl tartrate as the chiral ligand. "The man-made titanium catalyst acts promiscuously," says Sharpless, "asymmetrically epoxidizing most allylic alcohols and so displaying a versatility that is hard to imagine with an enzyme. This conjunction of selectivity and versatility is without precedent among man-made catalysts."

One good example of the use of chiral epoxidation is the synthesis of (+)-disparlure, the gypsy moth pheromone. In 1980, (+)-disparlure obtained by resolution from the racemate and used by the U.S. Department of Agriculture to test insect control strategies, cost about $2000 per gram in 100-gram lots; (+)-disparlure made via the asymmetric epoxidation is now commercially available for about $250 per gram and is used in consumer gypsy moth traps as well as in government programs. Disparlure is itself an epoxide, but that is the exception rather than the rule: epoxides are rarely end products. Their value, Sharpless says, is in their versatility as intermediates in the synthesis of a wide range of organic materials. Since his and Katsuki's initial publication, he notes, there have already been more than a hundred published applications of chiral epoxidations in the synthesis of natural products.

One of the most dramatic applications of the technique is the recent total synthesis of all eight L-hexoses by Sharpless, Satoru Masamune, and their colleagues at MIT (*Science*, 27 May, p. 949). The synthesis involves building up the backbone of the sugars two carbon atoms at a time and using chiral epoxidations to control the spatial configuration of each hydroxyl group as it is produced. A protected α-hydroxyacetaldehyde, for instance, could have two carbons added to form a *trans*-allylic alcohol, which is epoxidized. The epoxide is opened stereospecifically to give a protected diol with the appropriate stereochemistry (the configuration of one carbon can be changed if necessary), and a new aldehyde group is created at the terminus. The cycle can then be repeated.

After all the techniques were developed, it took only 3 months to synthesize all eight sugars; Sharpless says that "it



"Like the vanes of a windmill"

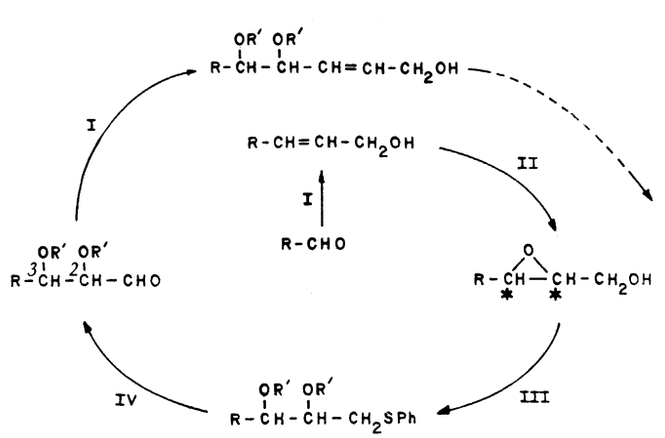
Two molecules of diethyl tartrate combine with two metal atoms to form a ten-membered ring; the ethyl groups extend from the ring in such a manner that the allylic alcohol and t*-butyl epoxide can be bound in only one conformation. [Source: K. Barry Sharpless, MIT]*

couldn't have been done" without the chiral epoxidation. But their system "allows you to click in chirality at will," so that the synthesis actually "gets rather boring." Masamune notes that the technique could be used for isotopically labeling the sugars at any position, which would be of value in metabolic studies. It might also find use in the total synthesis of such materials as macrolide antibiotics.

Sharpless and his colleagues are now attempting to determine the mechanism of the reaction. What seems clear so far is that the catalytic species is a dimer in which two metal atoms are connected by two tartrate molecules to form a ten-membered ring. The tartrate ester groups extend outward from this ring "like the vanes of a windmill," thereby limiting the manner in which the allylic alcohol and hydroperoxide can bind to the metal, the empirical rule for catalyst selectivity. If the allylic alcohol is envisioned to be lying in a plane, with its hydroxyl-bearing carbon at the bottom right, then the D-tartrate will always cause the oxygen to be delivered from the top of the plane, whereas the L-tartrate will cause it to be delivered from the bottom. The reaction varies from catalytic to stoichiometric, depending on the nature of the substrate; some of the epoxy alcohol products are what Sharpless terms "suicide substrates" in that the catalyst opens the epoxide to a diol that binds to the chiral complex and inactivates it.

The reaction can also be used for the resolution of racemic allylic alcohols. If a racemic mixture of such alcohols is epoxidized with the Sharpless reagent, one enantiomer will react faster than the other by factors that have ranged from 15 to 140. If the epoxidation is carried out to about 60 percent conversion, the allylic alcohol left behind is typically present in greater than 95 percent e.e. This alcohol can be pushed as close to optical purity as desired, Sharpless says, by carrying the conversion further. Like cocrystallization, this kinetic resolution loses at least half the starting material; counterbalancing this, however, is the ability to obtain higher optical purities than can be achieved with other techniques.

More recently, Sharpless has found that the system is useful for other types of chiral oxidations. Theoretically, it should work on any molecule that has a hydroxyl group that can bind to the titanium catalyst and a nearby site that can accept an oxygen atom. Sharpless has had some success, for example, in performing kinetic resolutions of racemic β-hydroxysulfides and α-acetylenic alcohols.



Synthesis of hexoses

The synthesis of sugars involves the addition of two-carbon fragments to an aldehyde, epoxidation of the allylic alcohol, controlled opening of the epoxide, and a repeat of the cycle. [Source: K. Barry Sharpless, MIT]

The best results, however, are obtained with β-hydroxyamines which are oxidized to the *N*-oxide. The MIT group has so far tested more than 20 such compounds and has obtained e.e.'s greater than 90 percent in many cases. Separation of the product is exceptionally easy; in most cases, Sharpless says, the reaction mixture can be dissolved in an organic solvent and extracted with water. "The amine oxide goes cleanly into the water. . . . Furthermore, the amine oxide is easy to reduce and it goes back to the amino alcohol of the opposite chirality. Of course, it is not as pure as you would like, so you have to run the resolution with the opposite-handed tartrate to shave away the other enantiomer." He says this reaction will be particularly valuable because β-hydroxyamines "are one of the largest families in medicinal chemistry. This reaction should be useful in the pharmaceutical industry immediately."

Surprisingly, Sharpless has found that the catalytic species involved in the oxidation of β-hydroxyamines has only one tartrate ligand for each two titanium atoms, whereas the conventional system has two ligands for each two metal atoms. Following up on this observation, he recently discovered that a related 1:2 catalyst (made using a tartrate diamide rather than a diester) can also carry out chiral epoxidations, but that it yields the opposite enantiomer from that produced by the 2:2 system. It is not clear why this happens, and they are now investigating the structure of the 1:2 diamide-derived catalyst.

Highly selective man-made catalysts and reagents are changing the nature of synthetic chemistry, Sharpless argues. "We used to try to make the world's biggest molecules, with lots of asymmetric centers and so forth—sort of a macho approach to synthetic chemistry. Nowadays, people have begun to realize that, in a sense, that's really not a very creative endeavor; it's more like an engineering operation. I think this new area of selective abiological catalysis is already a very popular area, but I think in 20 years from now, maybe even 10, it won't be recognizable. Many of the best people will be working in this inorganic/organic wonderland, since metals are what we need to control most of the variables we would like to control in a catalytic process."

—THOMAS H. MAUGH II

Additional Reading

1. B. M. Trost, *Science* **219**, 245 (1983).
2. J. Halpern, *ibid.* **217**, 401 (1982).
3. H. Wynberg, *Chemtech* (February 1982), p. 116.
4. K. B. Sharpless *et al.*, *Pure Appl. Chem.* **55**, 589 (1983).