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Beyond Nature's Chiral Pool: Enantioselective Catalysis in Industry

William A. Nugent, T. V. RajanBabu, Mark J. Burk

Enantioselective catalysts produce organic compounds in enantiomerically enriched form. They are highly efficient tools for the synthesis of biologically active materials, such as pharmaceuticals and crop-protection chemicals, in which enantiomeric purity can be critical. The design of chiral ligands is the key to developing new enantioselective catalysts. Three unusual families of ligands have been used to develop practical technology for enantioselective hydrocyanation of olefins, ring-opening of epoxides, and hydrogenation of various compounds.

Enantioselective catalysis is bringing about a revolution in asymmetric synthesis. Seldom has there been an area of chemistry where the scientific goals are so challenging, the economic benefits so obvious, and the ethical reasons for doing the research so compelling.

Living organisms are masters of enantioselective catalysis. In general, when a living cell manufactures a chiral organic molecule, it selectively produces only one of the two nonsuperimposable mirror-image forms (enantiomers). To do otherwise is at best inefficient and at worst fatal. Biocatalysts (enzymes and ribozymes) promote the chemistry of life with exquisite efficiency and selectivity, but synthetic chemists have been slow to learn from nature's model.

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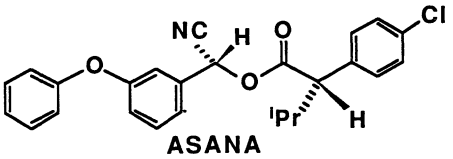
Until recently, it was common practice for a pharmaceutical company to market a chiral drug as the racemate (*1*). This approach in effect meant that each dose of a drug was contaminated with an equal weight of an isomer, which usually had no therapeutic value but had the potential to cause unsuspected deleterious side effects. For example, the sedative thalidomide was marketed as a racemate. The desired sedative activity resides in the *R*-isomer, but the contaminant *S*-isomer is a teratogen, causing profound birth defects in babies born to mothers using the drug (*2*). The *R,R*-enantiomer of the tuberculostatic ethambutol can cause blindness. The lethal side effects associated with the pain-killer benoxaprofen (Oraflex) might have been avoided had the drug been sold as a pure enantiomer (*3*).

In the past, the selling of a racemic drug could be defended on the grounds that the cost of manufacturing a single isomer could be prohibitive. Today, improvements in the technology for asymmetric synthesis, including the development of enantioselective catalysts based on metal complexes, make the development of new racemic drugs unacceptable. Asymmetric synthesis has advanced to the point where it should be possible to manufacture any drug as a single enantiomer.

The issue of enantiomeric purity is by no means limited to the field of pharmaceuticals. A case in point is ASANA (*4*) (^{i}Pr = isopropyl), a synthetic pyrethroid insecticide which contains two asymmetric centers.



ASANA

The potent insecticidal activity overwhelmingly resides in just one of the four possible stereoisomers. Moreover, the non-insecticidal stereoisomers exhibit significant cytotoxicity toward certain plant species. Thus ASANA, which is sold as a single stereoisomer, can be registered and used for crops whereas the mixed stereoisomers are not suitable. Add to this the need for chiral liquid crystals, enantiomerically pure polymers, and membrane components with applications in such diverse areas as drug delivery, separation technology, and optoelectronics. It is easy to understand the growing demand for efficient methods of producing enantiomerically pure compounds.

Conventional methods of asymmetric synthesis rely on the stoichiometric use of enantiomerically pure starting materials or reagents. In resolution by differential crystallization, for example, a racemic-product mixture is converted into a separable mixture of diastereomers with the use of a stoichiometric amount of an optically pure resolving agent. This method, however, requires recovery of the resolving agent and wastefully consumes precious starting materials and reagents to make the wrong enantiomer, which must then be racemized or discarded. Another conventional method is to build directly on products from nature's chiral pool. This approach is limited by the availability of inexpensive starting materials with the correct sense of chirality and with close structural similarity to the final target (*5*).

Perhaps the most important advantage of enantioselective catalysis, versus either of these stoichiometric procedures, is the feature of chiral multiplication. Under the right conditions, thousands of chiral product molecules can be produced by one molecule of catalyst. Chiral multiplication

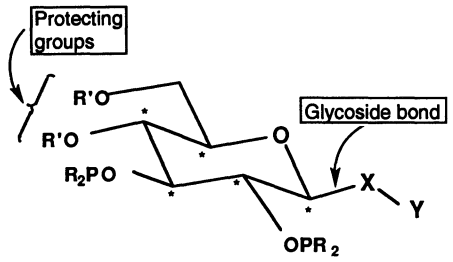


Fig. 1. Potential tunable sites on a diol phosphinite ligand. Possible configurations of the sugar are indicated by (*). X–Y, aglycone.

is a characteristic of both biocatalysis and catalysis by chiral metal complexes. Recently, enantioselective catalysis using metal complexes has advanced to the point where it can often provide a viable alternative to biocatalysis. The strengths of metal catalysts tend to complement those of enzymes: (i) metals can promote reactions not known to occur in nature; (ii) the chirality of the catalyst is easily modified by appropriate changes in the ligands; (iii) one can use substrates not accepted by enzymes; (iv) volumetric productivity is typically high; (v) separation and recovery of products are relatively easy (enzymes most often work in aqueous or near-aqueous environments); and (vi) organometallic reagents are generally less capricious than enzymes, which are often susceptible to degradation caused by heat, oxidation, and pH.

A large number of reactions have been reported in which optically active metal catalysts are used (6). Several factors will determine whether they are industrially practical for large-scale manufacturing. These factors include (i) selectivity, usually expressed as enantiomeric excess (ee); (ii) catalyst efficiency, that is, the number of product molecules produced per molecule of the catalyst; (iii) the cost of metal, ligand, and starting materials (especially critical for lower value products); (iv) reaction conditions, such as very low temperatures or high pressures; and (v) kinetics. Other practical considerations include air or moisture sensitivity, concentration, removal of the catalyst, and the possibility of increasing the enantiomeric purity of the product (or later intermediate) by recrystallization.

The number of metal-catalyzed asymmetric processes that satisfy these criteria has been steadily increasing (*7–15*). Several commercial applications are summarized in Table 1. In our research on asymmetric catalysis, we have focused on the design of new types of ligands that define the all-important asymmetric environment around a metal. As a general rule, one cannot predict a priori the type of ligands needed for a particular reaction to achieve useful levels of enantioselectivity. Nevertheless, we believe that a combination of simple heuristic pictures, physical organic principles, and a large measure of "enlightened empiricism" can guide our efforts.

Reactions That Form Carbon–Carbon Bonds

Arguably the most important bond construction in organic chemistry is that of the C–C bond. Yet it is precisely in this area that the limitations of the current asymmetric-synthesis technology are most evident. To our knowledge, only one reaction that forms metal-catalyzed asymmetric C–C bonds is currently practiced on an industrial scale—the copper-catalyzed cyclopropanation of isobutylene (Table 1) (*8*).

From an industrial standpoint, the most attractive starting materials for this type of enantioselective reaction are inexpensive carbon sources, such as carbon monoxide, carbon dioxide, olefins, and hydrogen cyanide (HCN). We chose the metal-catalyzed addition of HCN to olefins for our initial studies (*16, 17*). The resulting nitriles are easily transformed into amines, aldehydes, acids, and a variety of other valuable intermediates. Previous research efforts on asymmetric metal-catalyzed hydrocyanation have been largely unsuccessful (*18*).

In an effort to develop a successful asymmetric process for such a difficult reaction, we reasoned that it was important to choose a readily modified ligand system in which various steric and electronic factors could be systematically changed. We were especially attracted to diol phosphinites derived

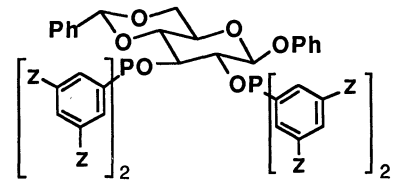
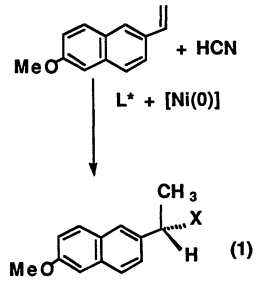


Fig. 2. Structure of the diol phosphinite ligand L* in Eq. 1. Ph, phenyl.

from readily available carbohydrate diols because they satisfied our basic criteria of tunability and ease of preparation (*19*) (Fig. 1). For our initial studies we have used the D-series of sugars. However, a number of L-sugar precursors are also commercially available.

Vinyl arenes were chosen as prototypical substrates because Markovnikov addition of HCN to these compounds results in 2-aryl-2-propionitriles. The acids derived from these nitriles make up an important class of widely marketed nonsteroid anti-inflammatory profen agents (*20*). Naproxen (**1b**) is particularly topical because the *R*-enantiomer has a number of undesirable health effects. The synthesis of the *S*-nitrile (**1a**) is shown in Eq. 1 (Me, methyl; L* in Fig. 2).



1a X = CN
1b X = CO_2H (Naproxen)

The addition of HCN to 6-methoxy-2-vinylnaphthalene was carried out at room temperature in the presence of catalytic amounts of bis(1,5-COD)Ni(0) (COD, cyclooctadiene) and a carbohydrate-derived diol phosphinite (Fig. 2). The reaction gave the corresponding arylpropionitrile (**1a** and **1b**) in excellent chemical yields (>90%) with unprecedented enantioselectivity. No trace of the isomeric linear product was detected under these conditions (>99% ee after crystallization) (*21*). Further, the inherent enantioselectivity is independent of the extent of reaction or catalyst loading. A nonpolar solvent, like hexane, gave the highest ee.

Initial screening of a number of 1,2- and 1,3-diol phosphinites (*22*) prepared from readily available diols indicated the overwhelming importance of the gluco-configuration of the sugar backbone for high enantioselectivity. The steric and electronic manipulations of the aglycone (X–Y in Fig. 1) yielded a modest, yet discernible, improvement on the selectivity of this re-

Table 1. Commercial applications of enantioselective catalysis using metal complexes.

Company	Metal	Reaction type	Ultimate product	Reference
Monsanto	Rh	Hydrogenation	L-Dopa	(*7*)
Sumitomo	Cu	Cyclopropanation	Cilastatin	(*8*)
Anic, Enichem	Rh	Hydrogenation	L-Phenylalanine	(*9*)
J. T. Baker	Ti	Epoxidation	Disparlure	(*10*)
ARCO	Ti	Epoxidation	Glycidols	(*11*)
Takasago	Rh	Rearrangement	L-Menthol	(*12*)
Merck	B	C=O reduction	MK-417 (opthalmic)*	(*13*)
E. Merck	Mn	Epoxidation	Antihypertensive*	(*14*)
Takasago	Ru	Hydrogenation	Carbapenem	(*15*)

*Developmental quantities for safety assessment and clinical trials.

action. The substituents on the ligating phosphorus (R_2 in Fig. 1, bracketed group in Fig. 2) had a dramatic effect. In this study we found that electron-withdrawing groups, like F or CF_3, on the aryl groups at the meta positions to phosphorus (Fig. 2, Z = F or CF_3) gave ee values as high as 91%, as compared with 40% for the corresponding H-derivative. This effect has been confirmed in a number of other hydrocyanation reactions. Such electronic effects on the enantioselectivity are rare (*23*) and may play an increasing role in the design of new catalysts.

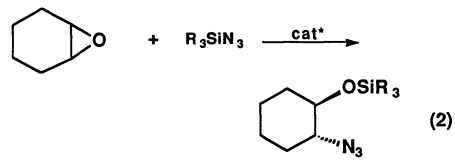
Remarkably, these catalysts also exhibited very high activity (552 turnovers per hour) in the hydrocyanation of vinylnaphthalene. When bis-trifluoromethyl phosphinite (Fig. 2, Z = CF_3) is used, substrate-to-ligand ratios of 5000 can be achieved under the same conditions in which the high values of ee are maintained. Simple recrystallization of the crude product yields optically pure (>99% *S*-isomer) naproxen nitrile (**1a**). The optically pure drug can be prepared from this nitrile (*24*).

In this exercise of semiempirical ligand design, we have optimized the enantioselectivity only for the preparation of naproxen precursor. Experiments under way suggest that the lessons learned here can be applied to other substrates and ultimately to other reactions as well. For example, we have observed that an ee as high as 65% can be obtained for the ibuprofen precursor nitrile by a simple modification of the ligand system.

Chiral Lewis Acid Catalysis

Asymmetric hydrocyanation was conceived as a practical process for the manufacture of 2-arylpropionic acids. However, our group also develops tools for laboratory-scale synthesis. A recent example is an enantioselective route to vicinal amino alcohols. This functionality pattern is important in several areas of drug discovery, including central nervous system agents, amino-sugar antibiotics, and peptido-mimetics (*25*).

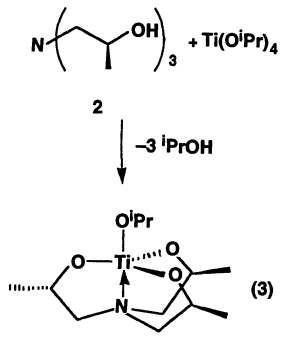
The starting place for our studies was a report (*26*) describing the addition of azidotrimethylsilane to cyclohexene oxide in the presence of titanium isopropoxide and dimethyl tartrate (Eq. 2). Provided that a stoichiometric amount of the titanium promoter was used, the azido ether was formed in modest enantiomeric excess. "Meso breaking" reactions of this type can be quite powerful in organic synthesis (*27*). By selecting just one of the epoxide carbon atoms in cyclohexene oxide for S_N2 attack, the absolute stereochemistry of both contiguous stereogenic centers in the amino alcohol can be controlled (R, alkyl; cat* is a chiral catalyst).



(2)

In order to achieve enantioselective catalysis, we sought chiral alkoxide ligands that would bind to an early (located to the left of the periodic table) transition metal even more tightly than the bidentate tartrate. Because mechanistic evidence suggested that the active catalyst contained an azide covalently bound to the metal, it seemed important to leave one monodentate alkoxide on the catalyst precursor. Consequently, we chose to explore the use of homochiral trialkanolamines as ligands. Alkoxides of early transition metals derived from triethanolamine are unusually robust (*28*).

The synthesis of homochiral trialkanolamines is quite simple. For example, the parent (*S,S,S*)-triisopropanolamine (**2**, Eq. 3) is conveniently prepared by reaction of commercial (*S*)-(+)-1-amino-2-propanol with two equivalents of (*S*)-(−)-propylene oxide in toluene. The ligand separates from solution as large transparent crystals. As expected, (*S,S,S*)-triisopropanolamine reacted with titanium tetra(isopropoxide), displacing three equivalents of isopropanol: (Eq. 3):

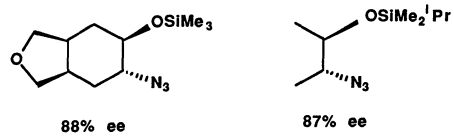


(3)
3

However, the product (**3**) proved to be a poor catalyst. Systematic changes in ligand structure failed to improve selectivity. In fact, our catalyst evolved through three additional generations of development before we achieved synthetically useful selectivity.

First, we discovered that zirconium catalysts provided better activity and selectivity as compared with their titanium counterparts. Next, we found the catalyst could be further improved by partial hydrolysis involving a discrete amount of water. Finally, we observed a still higher enantioselectivity by adding a promoter, such as trimethylsilyl trifluoroacetate.

With this modified catalyst, Eq. 2 could be carried out with 8% catalyst in 93% enantiomeric excess (*29*). The reaction could also be extended to functional and acyclic derivatives:



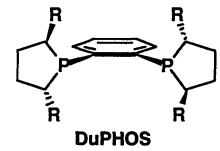
88% ee 87% ee

Subsequent studies have provided insight into the mechanism of catalysis in this system. Nevertheless, the development of this reaction is typical of the empirical detective work often required to make progress in this area.

Enantioselective Hydrogenation

The versatility of catalytic asymmetric hydrogenation for both laboratory and large-scale production of enantiomerically pure compounds has been amply demonstrated (Table 1). Rhodium and ruthenium catalysts bearing chiral diphosphine ligands have been used almost exclusively for this purpose. Although nearly 1000 chiral diphosphines are currently known, relatively few of these afford the efficiency and selectivity required for commercial applications. Furthermore, there remain many reactions of interest in which the current catalysts or ligand systems, or both, do not perform well.

In response to this need, we developed a new class of enantiopure C_2-symmetric diphosphine ligands, which we refer to as DuPHOS (*30*) [(R = Me, Et (ethyl), Pr (propyl), ^{i}Pr, and Bn (benzyl)].

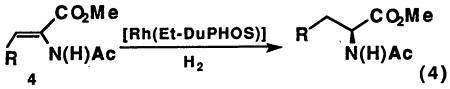


DuPHOS

The DuPHOS ligands are readily available in either enantiomeric form and embody several advantageous features when compared with the known chiral diphosphines. The 1,2-phenylene backbone, together with the chiral five-membered phospholane rings, creates a tightly binding ligand possessing a rigid C_2-symmetric environment. Moreover, variation of the R-substituents offers the possibility for systematic variation of the steric environment imposed by the ligands. This allows us to optimize enantioselectivities in catalysis by matching the steric bulk of the ligand to the steric requirements of the particular substrates of interest.

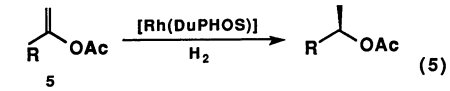
Initially we examined the asymmetric rhodium-catalyzed hydrogenation of various *N*-acetamidoacrylate esters (**4**). These substrates have been extensively investigated, and relatively high enantioselectivities have been observed in certain cases. Asymmetric catalytic hydrogenation may be the most efficient method for the production of many enantiomerically pure unnatural and nonproteinaceous α-amino acids. Such

α-amino acids are important synthetic intermediates for the preparation of a wide range of novel biologically active compounds (*31*). Nonetheless, no one catalyst has yet been found that provides very high values of ee (≥99%) for a wide variety of *N*-acetamidoacrylate substrates. We now have discovered that catalysts bearing the DuPHOS ligands are superior for the hydrogenation of this class of substrates (*30*). Under mild conditions (1 atm H_2, 20°C), the cationic catalyst (0.01 mol%) derived from {(COD)Rh[(*R*,*R*)-Et-DuPHOS]}$^+$OTf$^-$ (OTf, trifluoromethanesulfonate) predictably provided the *R*-amino acid derivatives with enantioselectivities consistently approaching 100%. As expected, the (*S*,*S*)-Et-DuPHOS-Rh catalyst afforded the *S*-amino acid derivatives with identical enantiomeric purity. The Et-DuPHOS catalyst system appears likely to find commercial application in the production of a variety of unusual α-amino acids (Eq. 4; Ac, acetyl).



4 (4)

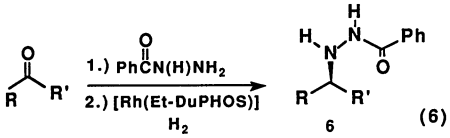
Other olefinic substrates also have been examined. Enantioselective hydrogenation of enol acetates (**5**) is synthetically equivalent to catalytic asymmetric keto-group reduction. The cationic DuPHOS-Rh catalysts proved effective for hydrogenation of a series of enol acetates to the product acetates with enantioselectivities ranging from 90 to 99% ee (*30*) (Eq. 5).



5 (5)

Tiglic acid, a prototypical α,β-unsaturated carboxylic acid, was hydrogenated to 2-methylbutyric acid in 94% ee with an Ru catalyst based on ^{i}Pr-DuPHOS (*32*).

More recently, we have discovered a general application of the DuPHOS ligands in a more challenging area, the catalytic asymmetric hydrogenation of the C=N double bond. Although much research has been devoted to this asymmetric transformation, little success has been reported to date (*33*). The cationic Et-DuPHOS-Rh catalyst was useful for the hydrogenation of the C=N double bond of a series of *N*-benzoylhydrazones, which are simply prepared by reacting a ketone with benzoic acid hydrazide (*34*) (Ph, phenyl):



6 (6)

A variety of aryl-substituted *N*-benzoylhydrazones were hydrogenated (60 psi H_2) to the hydrazine derivatives (**6**) with enantioselectivities ranging from 85 to 97% ee. In many cases, enantiomerically pure material was obtained after a single recrystallization. Significantly, *N*-benzoylhydrazones derived from α-keto esters were converted to the corresponding α-hydrazino esters (**6**, R = CO_2Me) in high enantiomeric excess (85 to 91% ee). Subsequent acid hydrolysis of the *N*-benzoyl and ester groups provided chiral α-hydrazino acids, compounds that are increasingly being used as α-amino acid mimics in drug design (*35*). Completion of the asymmetric, catalytic reductive-amination procedure required a method for cleavage of the N–N bond of *N*-benzoylhydrazines (**6**) without loss of enantiomeric purity. Samarium(II) iodide is one reagent that can carry out this transformation to provide, after hydrolysis, the desired optically active amines in good yield along with benzamide.

Future Work

If we confine our attention to the large-scale manufacturing of chiral compounds, the future is already upon us. We have noted the commercial success of the processes in Table 1. The number of new processes in which enantioselective catalysts are used can be expected to grow rapidly during the coming decade. The next campaign in this "chiral revolution" will occur on the benchtops, and more importantly in the minds, of chemists who are designing bioactive molecules. We illustrate this fact for the particular case of peptide chemistry but suggest that the observation has general validity.

Peptide chemistry has blossomed as a result of rapid advances in biotechnology. It has been variously estimated that 30 to 50% of medicinal chemists in industry are now engaged in the development of peptide or peptido-mimetic drugs. Typical biochemistry textbooks state that there are 20 common α-amino acid building blocks available for this exercise. Other sources, recognizing the availability of both *R*- and *S*-isomers, double this number.

In fact, with the emergence of enantioselective catalysis, the number of easily available α-amino acids is limitless. For example, all of the phenylalanine derivatives in Fig. 3 were synthesized directly in >99% ee with DuPHOS technology. The selection of readily available building blocks is no longer limited to those occurring in nature. Indeed, nature's own restrictive palette of amino acids is in no way likely to be optimal from the standpoint of binding, transport, or metabolic breakdown. Growing recognition of this fact by medicinal chemists will significantly expand the key role of peptides in medicine. As one example, replacing a single glycine

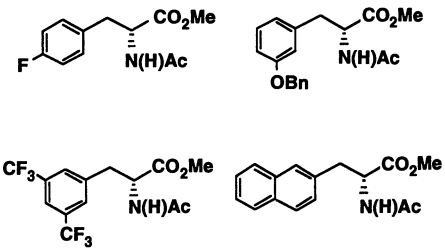


Fig. 3. Nonproteinaceous α-amino acids produced with Et-DuPHOS-Rh catalyst. Each demonstrated enantiomeric excess >99%. Me, methyl; Ac, acetyl; Bn, benzyl.

residue in the decapeptide LHRH (luteinizing hormone-releasing hormone) with D-naphthylalanine sharply decreases its susceptibility to peptidases; the resulting drug, nafarelin, is a promising treatment for endometriosis (*36*). Dozens of similar examples of clinically useful pseudopeptides are summarized in a recent review (*37*).

Hopefully, the future also will produce a more enlightened regulatory environment for dealing with chiral drugs. Astonishingly, new rules under consideration by the Food and Drug Administration would actually discourage the development of enantiomerically pure pharmaceuticals. The proposed regulations would require separate testing of both isomers of a single enantiomer drug. Despite the good intentions, this would greatly increase the cost of bringing the enantiomerically pure compound to market as compared with the racemate.

The marketing of a racemic drug represents a gamble both for the patient and the manufacturer. Even in the absence of regulatory coercion, the most progressive drug companies now seek to avoid this practice wherever feasible. As an example, Merck has successfully commercialized a series of chiral drugs as enantiomerically pure materials. In doing so, they have shown great imagination and versatility in applying all of the tools of asymmetric synthesis (*38*).

In truth, asymmetric synthesis has begun to advance beyond nature's chiral pool. It will be interesting to observe the relative importance of the roles to be played by catalysts based on metal complexes versus biocatalysts. At the moment, the future for metal-based enantioselective catalysts appears bright. As the examples above demonstrate, this is still an emerging technology. Moreover, to paraphrase Lorenz, the genome learns only by its successes whereas we learn also from our failures (*39*).

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