Asymmetric catalysis: An enabling science

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Contributed by Barry M. Trost, October 16, 2003

Chirality of organic molecules plays an enormous role in areas ranging from medicine to material science, yet the synthesis of such entities in one enantiomeric form is one of the most difficult challenges. The advances being made stem from the convergence of a broader understanding of theory and how structure begets function, the developments in the interface between organic and inorganic chemistry, and, most notably, the organic chemistry of the transition metals, and the continuing advancements in the tools to help define structure, especially in solution. General themes for designing catalysts to effect asymmetric induction are helping to make this strategy more useful, in general, with the resultant effect of a marked enhancement of synthetic efficiency.

Even before the understanding that carbon was tetravalent, the French physicist Biot established that certain organic compounds rotated the plane of polarization of light (1, 2). However, it was Pasteur who correlated this phenomenon with an asymmetric grouping of atoms within molecules (3). Kekulé establishing that carbon has four valences (4) and van’t Hoff (5) and Le Bel (6) arranging these valences in a tetrahedral fashion set the stage for one of the most profound features of organic molecules—their ability to exist in mirror-image forms. The implications of this fundamental feature of organic molecules is immense. Undoubtedly, the richness of the biological world would not exist without this structural feature. Indeed, the very existence of the biological world is likely to have become possible only because of its euisite use of this phenomenon.

Properties of molecules and molecular arrays depend on chirality. Molecular communication in biological systems emanates from this intrinsic structural feature. Optical and electronic materials also derive from this feature. Bulk optical and electronic materials emanates from this intrinsic structural feature. Indeed, the very existence of such organic molecules—their ability to exist in mirror-image forms—sets the stage for one of the most profound features of organic molecules. The advances being made stem from the convergence of a broader understanding of theory and how structure begets function, the developments in the interface between organic and inorganic chemistry, and, most notably, the organic chemistry of the transition metals, and the continuing advancements in the tools to help define structure, especially in solution. General themes for designing catalysts to effect asymmetric induction are helping to make this strategy more useful, in general, with the resultant effect of a marked enhancement of synthetic efficiency.

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Abbreviations: BINOL, 1,1’-bi-2-naphthol; BINAP, 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl; ee, enantiomeric excess.

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to defined complexes set the stage for understanding the implication of structure for function, which begot the development of defined transition metal complexes, typically hybrids of organic entities and transition metals, for chemical catalysis. Third, the ability for individuals to wed the understanding that arises by integrating theoretical and physical, organic, and inorganic chemistry with solving complex problems becomes enabling.

Asymmetric Hydrogenation

Probably, the most important strategy to introduce chirality involves the ability of a catalyst to differentiate the enantiotopic faces of a prochiral functional group, notably a \(\pi\)-unsaturation like a carbon–carbon or carbon–oxygen double bond. Catalytic hydrogenation represents the archetypical example involving such a mechanism (46, 47). In addition, such reactions are among the most important synthetic methods because of their broad scope and efficiency (i.e., selectivity and atom economy).

The discovery of tris(triphenylphosphine)rhodium chloride as a catalyst for hydrogenation by Wilkinson and colleagues in 1966 (48) set the stage for the development of asymmetric catalysts. Replacing triphenylphosphine with chiral phosphines is a straightforward extrapolation. The key question is what type of phosphine. In 1972, Knowles et al. (49) reported excellent results with a monodentate phosphine CAMP (structure 3). The minimal success with monodentate phosphines induced the design of bidentate ligands to limit the degrees of freedom and, by so doing, enhance the enantiomeric excess (ee).

Most notably, the development of DIOP (structure 4) by Kagan, first reported in 1971, proved the validity of the approach (50, 51). In 1975, Knowles (52) reported the bis-phosphine analog DIPAMP (structure 5) of his CAMP series of monodentate ligands. This ligand became the key to an asymmetric synthesis of \(\beta\)-arylalanines such as the anti-Parkinson drug \(S\)-DOPA and \(S\)-phenylalanine (structure 4), one of the two amino acids that constitutes the artificial sweetener aspartame. Indeed, this reaction is practiced commercially for these applications (53–55).

Despite the commercial success of DIPAMP, the real broad potential of asymmetric hydrogenation was not realized until the introduction of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (Scheme 3, structure 6) by Trost and colleagues in 1980 (56, 57). For example, hydrogenation of the benzamide (Scheme 4, structure 5b) with a Rh complex of BINAP produced the corresponding phenylalanine derivative with near perfect enantioselectivity. The production of the chiral piperazine unit 7 that is one of the components of the clinically important HIV protease inhibitor indinavir (Scheme 5) is also accessed with this catalyst in high yield and ee (58). Some 10 years later, Bur and colleagues introduced a novel structural motif, which they termed DIPPHOS (Scheme 3, structure 8) (59–61). This ligand has one of the broadest substrate scopes of any of the hundreds of chiral ligands introduced for Rh complexes. Replacing Rh by Ru increased the scope of such reductions dramatically, notably by embracing carbonyl compounds as substrates (62–64). By using a combination of rhodium and ruthenium BINAP complexes, a one-pot asymmetric reduction of both a carbon–carbon and carbon–oxygen double bond has been performed (Scheme 6) in an approach to statine analogs, which constitute fragments of HIV protease inhibitors (65). The power of BINAP transcends well beyond asymmetric hydrogenation.

The corresponding imines constitute an important class of substrates since they provide access to chiral amines and amides (46). The success of iridium for such reductions ultimately led to a commercially successful synthesis of the herbicide \(S\)-metolachlor, which is produced on the scale of >10,000 tons per year (66). This success validated the development of a class of ligands based on ferrocenes represented by the so-called JOSIPHOS ligands (i.e., structure 9

Asymmetric Oxidation

The discovery of metal-catalyzed epoxidation methods set the stage for the de-
The first successful asymmetric epoxidation combined a simple tartrate ligand with titanium (Sharpless asymmetric epoxidation) (78) and has led to early commercialization for the synthesis of both enantiomers of glycidol (Scheme 7), an important chiral building block (79, 80). The requirement of this method for a hydroxyl group proximal to the double bond, preferably allylic, was relieved to some extent by the development of epoxidations based on manganese embraced by salen ligands (81) and Katsuki and colleagues (82) as pioneered by Jacobsen and colleagues (83) as illustrated in Scheme 7 (83, 84). This example highlights the significance of these new methodologies by facilitating the development of novel and selective \( \text{I}_{\text{K}} \)-channel blockers for control of cardiac arrhythmias, such as HMR 1556 (Scheme 8) (85). The salen motif has also proven to have applicability across a spectrum of reactions. Whereas metals are at the heart of most catalytic processes, simple organic catalysts, the classical strategy, still constitute an important avenue of endeavor. Epoxidations involving dioxirane intermediates, i.e., structure 12, formed in \textit{in situ} from chiral ketone, structure 11 (Scheme 9), exemplifies the utility of such concepts, because it leads to a process with the least number of constraints on the types of alkenes that are suitable substrates (86, 87).

Epoxidation followed by ring opening constitutes the equivalent of trans-dihydroxylation if the nucleophile is based on oxygen. The stereochemical complement is cis-dihydroxylation. The invention of a dihydroxylation by using a catalytic amount of osmium tetroxide and a stoichiometric amount of a reoxidant such as an amine oxide at the Upjohn Pharmaceutical Company (88, 89), combined with the early observation of ligand rate acceleration with pyridine among other amines by Crieege et al. (90), provided the basis for the development of asymmetric dihydroxylation by Sharpless and colleagues (91). Once again, the \textit{Cinchona} alkaloids dihydroquinidine and dihydroquinine become the chiral inducing elements. A facile route to the side chain of the clinically important anticancer agent taxol resulted (Scheme 10, path a) (92). A related reaction, aminohydroxylation (93), shares the same characteristics and provides an even shorter route to this important appendage (Scheme 10, path b) (94).

Asymmetric C–C Bond Formation

Historically, asymmetric cyclopropanation was a logical early choice because of the well known ability of copper to catalyze cyclopropanations with diazo complexes (95). Salen ligand (Scheme 11, structure 13) proved effective and led to an early success, a practical synthesis of cilastatin (96), a dipeptidase inhibitor used in a combination therapy with imipenem as an antibiotic adjunct (Scheme 11) (97, 98). It was a decade later that significant studies occurred as a result of the introduction of new families of ligands, most of which were \( \text{C}_{2} \) symmetric represented by semicorrins (e.g., structure 14 in Scheme 12) (99, 100) and bis-oxazoline ligands (e.g., structure 15 in Scheme 12) (101–103). Indeed, this latter class has proved to be quite useful for numerous reactions catalyzed by higher oxidation state metals beyond cyclopropanation.

In 1973, a paradigm shift occurred with the introduction of rhodium carboxylates as catalysts for cyclopropanation by Teyssie and coworkers (104, 105). Chiral carboxylates and their surrogates become ligand possibilities (106). Application of McKervey’s proline-derived rhodium complex (Scheme 13, structure 16) (107) to cyclopropanation by Davies proved its success (108, 109). The carboxamides illustrated by structures 17–19 (Scheme 13) developed by Doyle and Forbes demonstrated their best selectivities in intramolecular cyclopropanations (106). The ability of rhodium carboxylates to promote C–H insertion reactions of the intermediate carbene complexes (110) demonstrated by Teyssie can convert these processes into excellent asymmetric ones with similar chiral versions (111), as demonstrated in a synthesis of ritalin (112, 113).

Chiral Lewis acids have emerged strongly for numerous C–C bond-forming reactions. Reactions that involve highly ordered transition states like Diels–Alder reactions are natural candidates. Indeed, complexes of BINAP, BINOL, salen (structure 10), and bis-oxazolines (structure 15), which all share the same feature of being \( \text{C}_{2} \) symmetric ligands, have been effective for numerous \([4 + 2]\) cycloadditions (114). However, such a motif is not mandatory. A particularly simple class of non-\( \text{C}_{2} \) symmetric ligands derived from \( \alpha \)-hydroxy or \( \alpha \)-amino acids and boron, first introduced by Yamamoto and coworkers (115, 116) and Helmchen and coworkers (117) and further developed by Corey et al. (118).

Next to the Diels–Alder reaction, the aldol addition stands out because of its potency for the synthesis of bioactive natural products (in part, because that is also nature’s route for these substances) but also because of the frequently highly ordered transition states (119, 120). Indeed, the same chiral ligands, including...
the boron-derived ones, function well (121–123). However, in all these cases, a preformed enol or enolate equivalent is required. Effecting the aldol reaction in its simplest iteration, i.e., simply adding an active methylene compound to a carbonyl group in the presence of a catalyst, provides the most atom economic strategy. Shibasaki revealed the first such catalysts based on a novel class of BINOL complexes (Scheme 14, structure 20) formed by self-assembly of BINOL in the presence of a lanthanide and base (74, 124, 125). Thus, acetophenone adds directly to aldehydes to give the aldol adducts. The immediate utility of this methodology was demonstrated by the synthesis of an intermediate for the synthesis of epothilones, promising candidates as clinically useful anticancer agents (Scheme 14 Lower).

A new motif for ligand design was based on the notion that a chiral hemicyclopentane might be more useful as a catalyst than chiral crown compounds, because it would bind neither substrates nor products too tightly but yet might retain sufficient enantiodiscrimination to be synthetically useful. Using such a notion, Trost designed the ligands represented by structure 21 as a potential catalyst for the aldol process (126, 127) to give results nearly identical with those of Shibasaki for the reaction of Scheme 14. This ligand spontaneously self-assembles as a dinuclear zinc complex, which is key for its high enantioselectivity. The systems of both Shibasaki and colleagues (128) and Trost and Yeh (129) also perform well for the so-called nitroaldol reaction, wherein the active methylene partners are nitroalkanes. Furthermore, the nitrogen analog of the carbonyl partner, i.e., imines (a Mannich-type process), also serves as a suitable partner with these same catalysts (130, 131). These ligands create proximal multisite catalysts in contrast to the more common single-site catalysts. For bimolecular addition reactions, such a design appears to be ideal since it helps assemble and orient the two reaction partners, thereby reducing entropies of activation and imprinting chirality.

Although metal-based methods constitute the bulk of the attention for such processes, simple organic structures also have promise. The key discovery reported in 1971 by Eder et al. (132) and in 1974 by Hajos and Parrish (ref. 133; see also ref. 134) demonstrated that amino acids, notably proline, effected an intramolecular aldol reaction in high yields and enantioselectivity (Scheme 15). More than 20 years later, the implications of this finding began to be realized by the demonstration that such a simple amino acid can promote intramolecular aldol additions with remarkable chemo-, diastereo-, and enantioselectivity (135, 136). These types of catalysts also serve in Mannich-type processes (137).

Carbonyl additions of nonstabilized nucleophiles have led to more explicit consideration of some of the most interesting general philosophical concepts. Oguni et al. reported the key discovery in 1983 (138), subsequently largely developed in the Noyori laboratory (139, 140), that simple chiral amino alcohols like ephedrine catalyze the addition of dialkylzinc reagents to aldehydes (Scheme 16) (141). In violation of traditional practice, chiral amino alcohols of low enantiomeric purity still provided the resultant product with excellent enantioselectivity. Indeed, the alcohol (structure 22) of 5 × 10^{-3} % ee reduced itself with >99.5% ee (142). The concept of chiral amplification, an example of a nonlinear effect, which previously was largely ignored, now makes consideration of nonlinear effects important for all asymmetric reactions (143, 144). Since the example of Scheme 16 is indeed an amino alcohol, the question of whether this enantioselectically pure product can serve as its own catalyst, i.e., the concept of autocatalysis, arises (145, 146). Furthermore, combining autocatalysis with chiral amplification raises the question of whether a small amount of product of low ee can catalyze its own formation with high ee. In 1932, Mills (147) had already proposed that statistics suggest that random small fluctuations in the exact ratio of enantiomers in forming racemates would always occur, ≈200 of 100,000 molecules. In accord with this proposal, performing the reaction illustrated in Scheme 16 with no chiral catalysts gave ee’s as high as 91% in a statistically random fashion, i.e., in 37 runs, the S enantiomer was favored 19 times and the R enantiomer was favored 18 times (148). Such “spontaneous” generation of chirality stemming from the combination of statistics, autocatalysis, and chiral amplification provides some insight into the creation of the chiral world of biology.

Allyl organometallics may be considered the all-carbon analog of an enolate. Allyl stannanes and silanes represent the most common allyl transfer group with BINOL and its analogs typically serving as the enantio-discriminating agent (149). A more efficient approach uses alkynes as the nucleophilic partner wherein an allyllic C–H bond becomes
transferred during the process, i.e., a carbonyl-ene reaction (150) as in Scheme 17 (151).

An ancillary approach for the asymmetric carbonyl additions derives from activating an otherwise unreactive “organometallic” by coordinat- 
ing a chiral electron-donating ligand, a phenomenon termed nucleophilic catalysis. Such an effect is particularly highlighted by the
dition of allyl trichlorosilanes as shown in Scheme 18 (152) by using a chiral Lewis base (structure 23) as catalyst. Since allylmetals can be considered all-carbon analogs of enolates, the same concept extends to the reactions of enolates, notably the aldol addition. For alkylation of enolates, induction of chirality also typically requires interaction of the stereochemical inducing agent with the nucleophile rather than the electrophile. Designing chiral cations to engage in ion pairing with the nucleophile becomes a rational mechanism in phase-transfer catalysis. In 1984, a Merck group reported the first successful realization of this concept in an asymmetric methylation (Scheme 19) for the synthesis of the uricosuric agent Cinchona alkaloids as the core of the enantio-discriminating agent (structure 24). About a decade later, this design resurfaced to create a host of phase-transfer catalysts to effect asymmetric alkylations whereby both tertiary and quaternary centers are formed (155).

The related 1,4-addition of nucleophiles to α,β-unsaturated carbonyl substrates normally requires ligand designs based on chiral Lewis acids that com-

An important development arose from the discovery that transmetalation from boron to rhodium occurs readily: the ability to perform conjugate additions of organoboron compounds in the presence of rhodium complexes as catalysts. Borrowing again from catalytic hydrogenation, BINAP complexes of rhodium impart excellent enantioselectivity in such additions (Scheme 21) (161–163). Since the initial adduct is an enol boron species, besides protonation, it can be captured in a highly diastereoselective aldol process, thus creating three stereogenic centers in one asymmetric catalytic event.

Whereas introduction of chirality into Michael acceptors represents the more common strategy, the Michael donor may also be a prostereogenic reaction partner. Mechanisms that influence the stereochemistry of the nucleophilic partner that have been discussed with respect to the reaction of enolates such as the aldol addition and alkylations, may apply here. Most notably, asymmetric phase-transfer catalysis stands out as a promising strategy (155).

Asymmetric carbon–carbon bond-forming reactions with unactivated alkenes have emerged as the feasibility of such methodologies increases. Based on the “classical” asymmetric hydrogenation that involves asymmetric hydrometallation as the first step, replacing the second stage of such processes by C–C bond formation becomes a logical promising direction. Asymmetric hydroformylation (164) and hydrocyanation have been early areas of endeavor with only modest success (165). Reactions involving carbametallation represent an alternative. Among these, the asymmetric Heck reaction using chiral ligands, like BINAP and its analogs (166), stands out as shown in Scheme 22 (167).

A more atom economical approach to perform the equivalent of a Heck vinylation emerged from the Trost laboratories which exchanges a vinyl halide for an alkynyl in which the vinyl metal intermediate is formed by a hydrometallation (Scheme 23) (168). An asymmetric version from the Mikami laboratories utilizes an axially chiral non-C2 symmetric ligand (structure 27) (169). As in the Heck reaction, the enanto-discriminat-
ing step involves the preferential carba-
palladation of one the enantiotopic faces
of the alkene. Titanium and zirconium
complexes such as sandwich complexes
28 and 29 (see Scheme 24) also promote
asymmetric carbametallation of alkenes
but with simple alkyl moieties, as illus-
trated by syntheses of vitamins E and K
(170) and hydrosilylations of carbony
and imine groups (171, 172), among
others. Related sandwich complexes
have been important in asymmetric po-
lymerizations of propylene involving a
similar asymmetric carbametallation as
the chain propagation step (9–11).

Multiple Bond-Type Asymmetric Processes
Each of the asymmetric processes dis-
cussed so far involve formation of only
one bond type, a C—O, C—O, or
C—C bond. However, a few processes
allow formation of all of the bond
types above but also many additional
types of bonds, such as C—N, C—S,
C—P, etc. These bimolecular reactions
typically involve attack of a broad
range of nucleophiles on a suitable
electrophile. The most obvious classical
example is the Michael addition. Most
attention has focused on formation of
C—C bonds in such processes with
very little being done with respect to
noncarbon nucleophiles (173).

Asymmetric allylic alkylation has
proven to be a process in which such
multiple bond formation can be
achieved asymmetrically with the same
catalyst (174). The problem of asym-
metric induction in this case is aggra-
vated by the most common mecha-
nism—the bond-forming and bond-
breaking events occur outside the
coordination sphere of the metal and
therefore distal to the asymmetric in-
ducing elements. This issue led to the
development of new types of ligand
design represented by ligands 30–32
(see Scheme 25), each operating by a
different design concept (175–177). As
shown in Scheme 26, C—C (178),
C—N (178), C—O (179), and C—S
(180) bonds have all been formed with
high ee. This process also differentiates
itself from other asymmetric catalytic
processes by the number of mecha-
nisms for enantiodiscrimination. Thus,
inducing stereochemistry in the attack-
ing nucleophile which is even more dis-
tant from the chiral environment, can
be achieved with the same ligands
(181, 182), a key reaction for the asym-
metric synthesis of benzosomorphans
possessing an enhanced clinical profile
with diminished addictive properties
(Scheme 27) (183).

Conclusions
Asymmetric catalysis has begun to
demonstrate its potential. Within the
context of a few reactions, most nota-
bly asymmetric hydrogenation, signifi-
cant efforts have been expended on
developing an ever broadening catalog
of asymmetric catalysts involving vari-
ation of both metal and ligand environ-
ment. By doing so, the broadest range
of potential suitable substrates for
practical levels of selectivity has be-
come possible; nevertheless, numerous
potential substrates still remain. Fur-
thermore, new concepts that provide
important insights continue to emerge.
For example, mixtures of different li-
gands (heterocombinations) can give
higher enantioselectivities than the use
of a single ligand (homocombination) in
certain circumstances (184). Such
results dramatically expand the permu-
tations that now need to be consid-
ered. Thus, in a field that many would
claim is well understood and devel-
oped, such pronouncements are clearly
premature. In most every other type of
reaction, we are much earlier in our
stage of development.

In this issue are assembled a group of
perspectives and research reports from
leading laboratories that touch on all
the themes noted herein and many oth-
ers. Although the developments are im-
pressive and are making slow but steady
Inroads into being embedded in the dogma of synthesis, the successes to date should be kept in perspective. Opportunities for major developments are enormous. To attempt to grasp the magnitude of the opportunity, one can estimate that the number of possible structures that can function as catalysts with and without being bound to metals and multiply that figure by the number of reaction variables that may influence reactivity and selectivity. Since the number of compounds possessing only C, H, N, O, S, P, F, Cl, and Br of molecular weight ≤500 exceeds 10^24, the number of permutations becomes truly unimaginable. Opportunity for major discovery will remain vibrant for a very long time indeed.

I thank the General Medical Sciences Institute of the National Institutes of Health and the National Science Foundation for financial support.