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ticles and nanoporous supports with controlled size and shape. This ongoing progress is rapidly enabling catalyst researchers in academe and industry to achieve the goal of catalysis by design.

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VIEWPOINT

Privileged Chiral Catalysts

Tehshik P. Yoon and Eric N. Jacobsen*

One of the most active current areas of chemical research is centered on how to synthesize handed (chiral) compounds in a selective manner, rather than as mixtures of mirror-image forms (enantiomers) with different three-dimensional structures (stereochemistries). Nature points the way in this endeavor: different enantiomers of a given biomolecule can exhibit dramatically different biological activities, and enzymes have therefore evolved to catalyze reactions with exquisite selectivity for the formation of one enantiomeric form over the other. Drawing inspiration from these natural catalysts, chemists have developed a variety of synthetic small-molecule catalysts that can achieve levels of selectivity approaching, and in some cases matching, those observed in enzymatic reactions.

Although the principles underlying asymmetric catalysis with enzymes and small molecules are fundamentally the same (*1*), some striking and rather surprising differences have been noted. William S. Knowles, a pioneer in small molecule asymmetric catalysis, made the following key observation in his Nobel address: "When we started this work we expected these man-made systems to have a highly specific match between substrate and ligand, just like enzymes. Generally, in our hands and in the hands of those that followed us, a good candidate has been useful for quite a range of applications" (*2*). Indeed, the best synthetic catalysts demonstrate useful levels of enantioselectivity for a wide range of substrates. This is very important to synthetic chemists, who must rely on the predictable behavior of reagents and catalysts when planning new syntheses. With a few important exceptions (such as certain lipases), such generality of scope is not observed in enzymatic catalysis.

It is even more surprising that certain classes of synthetic catalysts are enantioselective over a wide range of different reactions. Such catalysts may be called "privileged structures," in much the same manner that the term has been applied in pharmaceutical research to compound classes that are active against a number of different biological targets (*3*). Privileged chiral catalysts offer much more than one might have imagined, creating effective asymmetric environments for mechanistically unrelated reactions (Fig. 1).

The story behind the discovery of these structures is different in each case. For instance, BINAP and BINOL are completely synthetic molecules developed to exploit the axial dissymmetry induced by the restricted rotation about the biaryl bond (Fig. 1). The design of TADDOL was driven by practical considerations, because it is derived from tartaric acid—the least expensive chiral starting material with two-fold symmetry available from natural sources. Bis(oxazoline) ligands were inspired

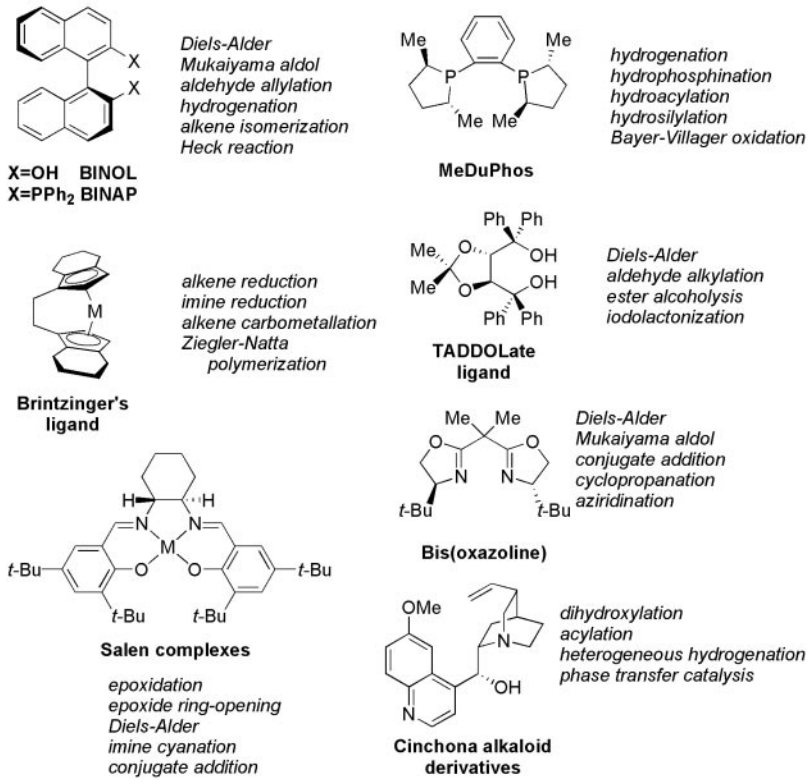

Fig. 1. Examples of privileged chiral ligands and catalysts.

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by the ligand framework of vitamin B_{12}. Cinchona alkaloid derivatives such as quinine (Fig. 1) are natural compounds that were exploited in asymmetric synthesis because of the presence of a particularly basic nitrogen atom.

The general applicability of these structures makes them useful not only for the practical synthesis of enantiomerically pure compounds but also for the discovery of novel enantioselective processes. In practice, the development of a new asymmetric reaction very often begins with a lead result discovered through a systematic screen of known privileged catalyst structures, followed by optimization of the ligand structure and reaction conditions. This approach accounts for a significant proportion of new asymmetric methodology reported every year. A brief overview of two different examples of privileged catalysts illustrates their broad utility.

Salen Complexes

Metal complexes of the synthetic salen ligand (Fig. 2) have been studied by chemists for over six decades, but the application of chiral salen derivatives began in earnest only in the 1990s (*4*). Salen ligands bind metal ions securely through four atoms. This tetradentate binding motif is reminiscent of the porphyrin framework in heme-based oxidative enzymes. Indeed, the design of the chiral manganese-salen complex **1a** (Fig. 2) was originally inspired by consideration of the oxo-transfer mechanism of heme-containing enzymes such as cytochrome P-450. However, salen derivatives are more easily synthesized than porphyrins, and their structures are more easily manipulated to create an asymmetric environment around the metal active site.

Complex **1a** catalyzes the epoxidation of a variety of unfunctionalized olefins with high levels of enantioselectivity (*5*). The proposed mechanism for this reaction involves the attack of the olefin on the oxygen of a metal-oxo species. The bulky substituents on the aromatic rings are thought to restrict the trajectory of the olefin, forcing it to approach the reactive oxygen species over the chiral diamine backbone of the catalyst, thereby maximizing stereochemical communication in the transition state.

Chromium (**1b**) and cobalt complexes (**1c**) of the same ligand framework catalyze highly enantioselective ring-opening reactions of epoxides by a variety of different nucleophiles (*6*). Researchers expected the mechanisms of epoxidation and epoxide ring-opening to be similar, but subsequent investigation revealed that the catalyst functions very differently in the two processes. Whereas in epoxidation the catalyst serves simply as an oxo-transfer agent, in epoxide ring-opening it plays a dual role, serving both as a Lewis acid to activate the epoxide and as a counterion for the nucleophile (*7*).

Thus, the exceptional selectivity observed in epoxide ring-opening reactions (*8*) is a consequence of the cooperative interaction of a chiral nucleophile and a chiral electrophile species bearing the same salen ligand framework. This mechanistic insight served as the inspiration for the development of cyclic oligomeric salen complexes (**2**), which display dramatically enhanced reactivity and higher enantioselectivity relative to the monomeric counterparts, because the cooperative interactions between the catalyst units are reinforced by the covalent assembly (*9*).

Aluminum complexes of the salen ligand (such as **1d** and **1e**) have also proven to be effective catalysts, for example, for the conjugate addition of azide to unsaturated imides (*10*). These reactions also appear to proceed by dual activation of nucleophile and electrophile.

Finally, salen ligands have served as useful starting points for the development of novel asymmetric catalyst structures. Initial investigation of the enantioselective hetero–Diels-Alder cycloaddition of electron-rich dienes with aldehydes demonstrated that chromium salen complex **1b** catalyzed the reaction with moderate levels of selectivity. Modification of the ligand framework eventually led to the discovery of complexes such as **3a** and **3b**, which catalyze a wide range of cycloaddition addition reactions with very high levels of enantioselectivity (*11*). These catalysts function as simple Lewis acids by activating carbonyl reacting partners. Interestingly, **3a** and **3b** form dimeric structures with different connectivity and, thus, presumably with different mechanisms of enantiodifferentiation.

These examples demonstrate how highly effective catalysts can be identified using a single ligand framework as a starting point, despite the fact that the factors that are ultimately responsible for high enantioselectivity can be quite different and usually unanticipated. With this in mind, it is important to regard these privileged structures not as endpoints but as useful platforms for the discovery of new catalysts and reactions.

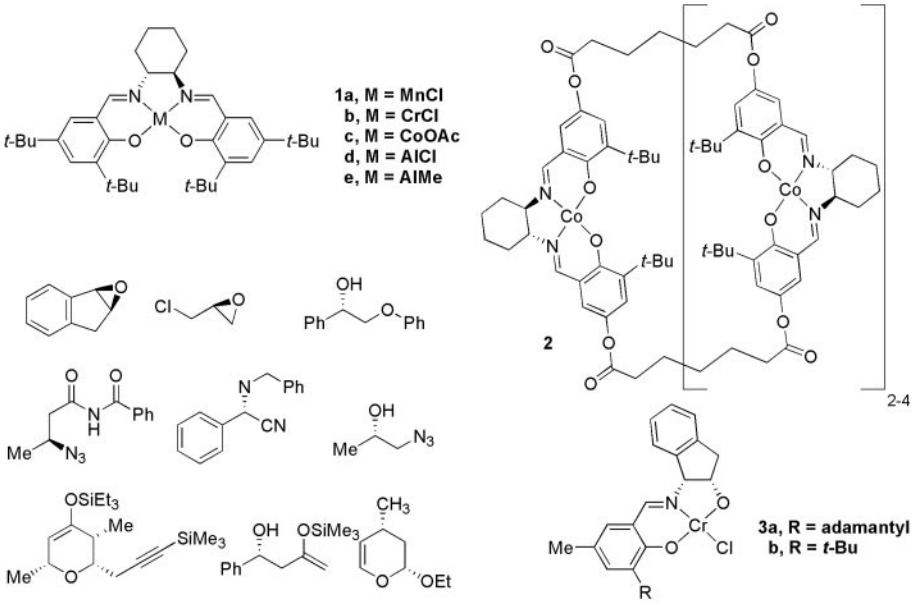

Fig. 2. Structures of salen-based catalysts **1a** to **1e**, **2**, **3a**, and **3b**. Some of the products accessible with these catalysts are also shown.

Cinchona Alkaloids

Of all the classes of privileged catalyst structures, the cinchona alkaloids are perhaps the most remarkable. These structures are produced in nature for biological purposes completely unrelated to asymmetric catalysis. Nevertheless, they have proven to be useful in an astonishing variety of important enantioselective transformations (*12*).

The key structural feature responsible for their synthetic utility is the presence of the tertiary quinuclidine nitrogen (Fig. 3). The presence of this basic functionality renders them effective ligands for a variety of metal-catalyzed processes.

Of these reactions, the osmium-catalyzed asymmetric dihydroxylation (AD) of olefins, developed by Sharpless and coworkers (*13*), has had the greatest impact in synthetic chemistry. Extensive optimization of the system has led to the development of dimeric cinchona alkaloid ligands such as **4** (Fig. 3), which catalyze the formation of diols of high enantiopurity from a very broad range of olefins. Subsequently, these ligands were

used for the osmium-catalyzed asymmetric aminohydroxylation (AA) of olefins (*14*).

The metal-binding properties of the quinuclidine nitrogen also allow cinchona alkaloids to be adsorbed onto metal surfaces. Platinum surfaces modified with 9-*O*-methylcinchonidine (a "chiral modifier") are effective heterogeneous catalysts for the asymmetric hydrogenation of α-ketoesters (*15*). This reaction is highly enantioselective, even with very small quantities of the chiral modifier, as a result of the dramatic increase in the rate of hydrogenation in the proximity of the ligand (*16*).

In addition to its utility for metal binding, the nucleophilic quinuclidine nitrogen can also be used directly as a reactive center for enantioselective catalysis. As a chiral nucleophile, quinidine promotes the cylization of ketenes with carbonyl compounds such as ketones and aldehydes (*17*), as well as with imines (*18*) and other ketenes (*19*). Dimeric derivatives such as **4** forms a tight ion pair with a nucleophilic enolate anion; the intimacy of the contact between these charged species leads to the effective enantiodiscrimination observed.

The cinchona alkaloids are astonishing for the range of reaction types over which they impart high enantioselectivity. The precise mechanisms for asymmetric induction must be quite different depending on whether the alkaloid is serving as a ligand for a reactive metal center, as a nucleophile, or as a phase-transfer catalyst.

Concluding Remarks

It is not immediately clear what structural features account for the broad applicability of privileged structures across so many different reaction types, but some trends can be discerned. For instance, most privileged catalysts possess rigid structures with multiple oxygen-, nitrogen-, or phosphorous-containing functional groups that allow them to bind strongly to reactive metal centers. Many of these structures also possess two-fold axes of symmetry, effectively halving the number of possible transition state geometries available in a given reaction. However, not all privileged ligands have these properties, and a structure that possesses these features does not necessarily function as a privileged catalyst. Therefore, the identification of new privileged ligands and catalysts remains enormously difficult and often requires a degree of serendipity.

Given that we do not yet know how to design such catalysts from first principles, one promising approach to the identification of new classes of broadly useful catalysts is through the use of diversity-oriented synthesis. Recently, the parallel synthesis and high-throughput screening of structurally diversified catalyst libraries have led to the discovery of novel classes of catalysts with very promising generality. For example, the titanium complexes of peptide-based Schiff base ligands identified in this way catalyze highly enantioselective cyanation of epoxides, aldehydes, and imines; their copper complexes catalyze conjugate addition and allylic substitution of dialkylzinc nucleophiles; and their zirconium complexes catalyze addition of dialkylzincs to imines (*23*). In other studies, urea-based organic catalysts prepared and screened by parallel methods have been found to catalyze a wide range of imine addition reactions (*24*).

The emergence of privileged classes of catalysts for asymmetric synthesis also presents a tantalizing opportunity on the mechanistic front. Efforts to understand the features that account for the broad applicability of these structures and to apply this understanding to the development of new privileged catalysts is an ongoing, exciting challenge for organic chemists today.

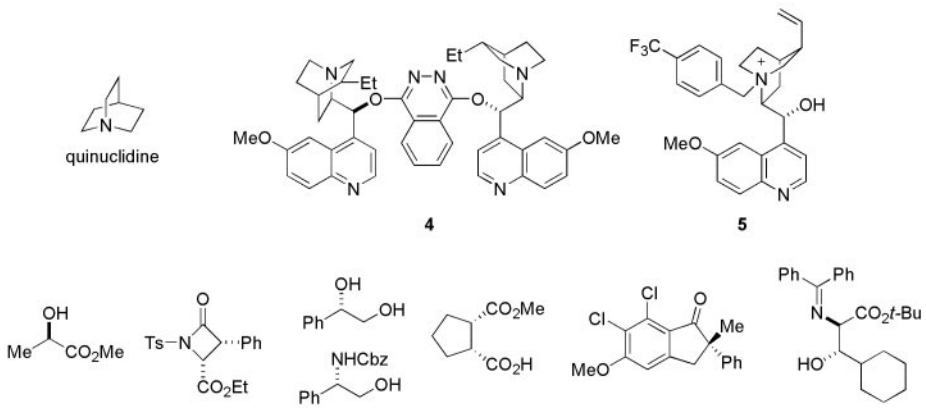

Fig. 3. The structure of quinuclidine and of the cinchona alkaloid catalysts **4** and **5**, which are based on the quinuclidine structure. Some products are also shown.

catalyze the enantioselective desymmetrization of meso anhydrides with methanol by a nucleophilic mechanism (*20*).

Finally, the quinuclidine nitrogen can be quaternized with benzyl halides to give ammonium salts (such as **5**) that can serve as useful asymmetric phase-transfer catalysts. In 1984, researchers at Merck reported the highly enantioselective alkylation of indanone derivatives (*21*). Subsequently, it was shown that a related cinchonium salt serves as a highly selective phase-transfer catalyst for both the alkylation and aldol reaction of glycine-derived Schiff bases, providing access to a variety of α–amino acid derivatives (*22*). In each of these reactions, the cationic ammonium species

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