ASYMMETRIC CATALYSIS
Growing demand for chiral compounds drives innovation in catalytic methods development

The biological activity of many pharmaceutical compounds, agrochemicals, flavors, and fragrances is associated with absolute molecular configuration. In particular, the demand is growing in the pharmaceutical industry to make chiral drugs economically in enantiomerically pure form. Many fine chemical companies are positioning themselves with new “chirotechnology” to serve the pharmaceutical industry, and innovation has been a means of business survival for them. Under tremendous competition and intensive effort from many academic and industrial groups, new and effective catalytic reactions have been discovered at an explosive rate. While the field is progressing rapidly, many significant challenges remain in asymmetric catalysis.

Most asymmetric catalysts consist of metal complexes with chiral ligands. The greatest challenge in discovering new asymmetric catalysts is conducting interdisciplinary research that combines organic, inorganic, organometallic, and biomimetic chemistry. To make an efficient transition metal catalyst, the following tasks are generally required: designing and synthesizing chiral ligands; preparing suitable substrates, catalyst precursors, and metal-ligand complexes; and searching for appropriate reaction conditions.

A clear understanding of catalytic mechanisms and characteristics of metal species from an inorganic chemistry perspective can provide insights into selecting chiral ligands, substrates, and catalysts. A comprehensive knowledge of organic synthesis is also needed to address the challenging problems of synthesizing chiral ligands and substrates and demonstrating asymmetric catalytic methods. While interdisciplinary research in chemistry, biology, and material science has played an important role in advancing scientific knowledge to date, a great barrier still stands between traditional inorganic and organic chemistry, and only a few research groups have successfully carried out research in both fields.

Numerous discoveries in asymmetric catalysis have been made serendipitously by research groups with prepared minds. Rationally designed research often builds a platform for unexpected discoveries if a flexible plan can be executed. Although some effective ligands have been developed, no universal chiral ligand or catalyst exists for solving all problems in enantioselective transformations. Strategically important asymmetric catalytic reactions can be developed by inventing a diverse set of novel chiral ligands and combining them with metals to make effective enantioselective catalysts. High-throughput screening methods are likely to be effective for accelerating discoveries when a large number of metal precursors, chiral ligands, and metal-ligand complexes are available. Automatic equipment for high-throughput screening has been adopted widely in both industrial and academic settings.

Two significant challenges in asymmetric catalysis are discovering new catalytic reactions and inventing effective chiral ligands. With regard to developing new metal-catalyzed reactions, it’s important to focus on certain reactivity principles and experimental details. For example, many inorganic and organometallic complexes can be converted to effective catalysts if proper conditions, appropriate ligands, and suitable solvents and additives are used. Converting stoichiometric transformations into catalytic reactions and developing highly active catalysts that feature broad substrate scopes that can function under mild and simple reaction conditions remain key problems. It is especially important to identify reactions that are based on readily available starting materials and reagents.

Although mixing metal complexes and ligands in situ is a common way to evaluate catalyst performance and is used widely in organic synthesis, many it is important to make metal-ligand complexes cleanly prior to reaction. Using biomimetic chemistry, one could potentially create synthetic catalysts based on principles from enzymatic reactions (e.g., multifunctional interactions). To create efficient synthetic methods, cascade and multicomponent coupling reactions are desirable for making molecules with high molecular complexity. The challenge of designing rapid and concise syntheses of biologically active molecules will undoubtedly drive innovation in these types of reactions.

To develop new chiral ligands, a number of approaches ranging from combinatorial synthesis of modular systems to rational design of structurally innovative ligand frameworks can be taken. Consideration of steric, electronic, and conformational properties is necessary to prepare effective ligands. Conformationally rigid ligands often give higher chiral induction compared to those ligands with conformational ambiguity. Introduction of new motifs and modification of modular ligand systems are also effective methods for perfecting chiral catalysts. For practical reasons, it is desirable to prepare ligands from readily available materials. While steric interactions have been proposed and investigated in many working models, studies of the electronic effects are much needed, and a full understanding of these effects remains a great challenge in asymmetric catalysis.

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NEW VOICES IN CHEMISTRY

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CHIROTECHNOLOGY Although the field is progressing at an explosive rate, Zhang contends many significant challenges remain in asymmetric catalysis.