Asymmetric Catalysis

Highlighting this issue of PNAS and the forthcoming one* is a Special Feature comprising 8 Perspectives and 44 research articles that cover aspects of asymmetric catalysis, the phenomenon whereby a chiral catalyst promotes the conversion of an achiral substrate to a chiral product with a preference for the formation of one of the mirror image isomers (enantiomers).

The demand for chiral compounds, often as single enantiomers, has escalated sharply in recent years, driven particularly by the demands of the pharmaceutical industry, but also by other applications, including agricultural chemicals, flavors, fragrances, and materials. Two-thirds of prescription drugs are chiral, with the majority of new chiral drugs being single enantiomers. Although the most obvious applications are bio-related, materials science also relies on the properties imparted by chirality, notably in chiral polymers and liquid crystals. This widespread demand for chiral compounds has stimulated intensive research to develop improved methods for synthesizing such compounds.

Historically, enantiomerically enriched compounds were generated either by chemical transformation of an enantiomerically enriched precursor, often derived directly or indirectly from nature’s chiral pool, or by resolving an equimolar (racemic) mixture of the two enantiomers. Both of these approaches suffer from potentially severe drawbacks, the former in requiring stoichiometric amounts of a suitable precursor and the latter in typically yielding only up to 50% of the desired enantiomer.

Asymmetric catalysis, in which each molecule of chiral catalyst, by virtue of being continually regenerated, can yield many molecules of chiral product, has significant potential advantages over these older procedures. Indeed, enantiomerically pure compounds are produced in nature by such chirality transfer from enzymic catalysts. However, it was only relatively recently that such asymmetric catalysis, with enantiomeric excesses approaching 100%, was achieved with synthetic catalysts. A major breakthrough occurred in the early 1970s, when William Knowles and his colleagues at Monsanto demonstrated that rhodium complexes containing chiral phosphine ligands were able to catalyze the enantioselective addition of H₂ to one of the faces of a prochiral olefinic substrate generating a chiral C—H center with high enantioselectivity. This process was soon commercialized to produce the anti-Parkinson drug, l-dopa, followed over the next three decades by the development of many other commercial processes, as well as laboratory scale syntheses, to generate enantiomerically enriched compounds. In recognition of his achievement, Knowles shared the 2001 Nobel Prize in chemistry with Ryoji Noyori, also for work on asymmetric catalytic hydrogenation, and with K. Barry Sharpless for his work on asymmetric catalytic oxidation.

This collection of Special Feature articles serves as an eloquent testimonial to how far this field has evolved. While several contributions deal with the generation of chiral C—H and C—O centers through asymmetric catalytic hydrogenation and oxidation, respectively, themes that dominated the early years of the field, the scope of asymmetric catalysis has grown to encompass a wide range of other reactions, greatly expanding the accessible methodologies for generating enantiomerically enriched organic compounds. More than half of the articles in the collection deal with the generation of chiral carbon centers through C—C bond forming reactions, including the nucleophilic addition of organometallic reagents to aldehydes, ketones, and imines; conjugate additions; aldol reactions; allylic alkylation; Diels–Alder reactions; 1,3-dipolar additions; enyne cyclizations; cyclopropanation; and olefin-metathesis; as well as with the application of these and related reactions to the synthesis of chiral natural products. Other themes include: the design and application of new chiral ligands, including helical polymers and resin-supported phosphines, for metal-based asymmetric catalysts; enhancing the enantioselectivity of enzymes by “adaptive evolution”; and modeling aspects of asymmetric catalysis computationally. A few articles address mechanistic aspects of asymmetric catalysis, but for the most part, these serve to remind us how much still remains to be done to advance our understanding to the point where rational design of such catalysts can be undertaken with some confidence. Finally, one Perspective draws on insights derived from studies on asymmetric catalysis to speculate about the origins of the symmetry-breaking that gave rise to the enantiomeric enrichment that characterizes living systems. Although the developments to date may engender the notion that little remains to be done, quite the converse is true. The most formidable challenges of this field still lie ahead.

Interfacing with a variety of disciplines, including organic synthesis, organometallic chemistry, kinetics and mechanisms, structural chemistry, biology, and materials science, the theme of asymmetric catalysis seems particularly appropriate for highlighting in a multidisciplinary journal such as PNAS.

This Special Feature on asymmetric catalysis is one of a series of such collections of articles that PNAS has published in recent years, comprising Perspectives and research articles focused on specific cutting-edge multidisciplinary topics. Themes of previous features have included: Astrobiology; Evolutionary Developmental Biology; Rapid Climate Change; Social and Behavioral Sciences; Supramolecular Chemistry and Self-Assembly; Bioinorganic Chemistry; and, most recently, Science and Technology for Sustainable Development. Scheduled for future issues of PNAS are special features on Natural Products Synthesis and on Chemical Theory and Computations. One objective of these Special Features is to advance the journal’s ongoing initiative to expand its coverage of the physical and social sciences. PNAS continues to encourage and welcome research articles in all areas of the natural and social sciences and mathematics.

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*Supplementing the articles in this issue, the forthcoming issue of PNAS (no. 16, April 20, 2004) will include 4 additional Perspectives and 22 additional research articles that also are part of this Special Feature.

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