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Introduction: Enantioselective Catalysis

Enantioselective catalysis has become such a popular research area, and the subject of so many monographs, symposia, and conferences, that it is somewhat challenging to offer many new or not oft-repeated general words of introduction. Nonetheless, some basic definitions are in order. Enantioselective catalysis entails the catalytic, selective, and reproducible generation of a given enantiomer of a chiral product from achiral reactants. Enantioselective catalysts are without exception chiral and non-racemic, although it is important to keep in mind that catalyst precursors can be a different story, as treated further below. Any generation of a non-racemic product from a rigorously achiral or racemic chiral catalyst would, when repeated a statistical number of times, provide equal quantities of each enantiomer. This does not meet the reproducibility criterion in the preceding definition of enantioselective catalysis.

The concept of enantioselective catalysis clearly transcends the boundaries of organic chemistry. There are countless chiral inorganic compounds, many totally lacking in carbon, all of which are in principle amenable to synthesis via enantioselective catalysis. However, to the best of the Editors' knowledge, enantioselective catalysis has not yet been utilized to generate non-racemic molecules that lack carbon. Although there are many chiral organometallic compounds that can be accessed via enantioselective catalysis, the center of gravity of the field is heavily skewed in the direction of organic chemistry, and specifically toward the azimuth of natural product, pharmaceutical, and agricultural chemical synthesis. This imbalance is by no means a bad thing — it is where the cutting-edge commercial applications are. This organic orientation is clearly reflected in the titles of the 22 articles in this issue.

In any even-handed appraisal of synthetic organic chemistry, it must be admitted that there remain large numbers of important and often complex target molecules that are achiral. However, due to the many high-value applications of chiral organic molecules — for which normally only one enantiomer is effective — organic synthesis has witnessed a dramatic evolution over the past two decades. Only a few types of non-biological enantioselective catalysts that could reliably deliver specific classes of chiral target molecules in high enantiomeric excesses were known in 1983. For numerous catalytic transformations known to generate chiral products from achiral reactants, enantioselective versions were totally unexplored. The Editors would claim that in 2003, a distinct majority of catalyst development studies, at least in the organic literature, involve enantioselective catalysts. The trend is clear and will undoubtedly continue. Probably in another two decades, most basic texts in synthetic organic chemistry will be organized along the lines of enantioselective constructs, functional group transformations, and catalysis.

The Editors were fortunate to be able to attract many leaders in this field as authors, and others generously gave their time as reviewers. The first six articles treat specific classes of reactions in their entirety. In the lead-off position, Denmark and Fu describe additions of allylic organometallic reagents to aldehydes and ketones. Their coverage extends from allyl tin and silicon compounds through chromium, zinc, and indium species generated from allylic halides. Although metal-containing catalysts dominate, much recent work features boron-containing Lewis acids or phosphorus- or nitrogen-containing Lewis bases that lack metals. The following review by Gröger, which focuses on enantioselective Strecker-type reactions, likewise highlights both "organocatalysts" and metal-based catalysts.

Hayashi and Yamasaki then describe the applicability of chiral rhodium catalysts for enantioselective 1,4-additions of organoboron reagents and related silicon, tin, and titanium species. RajanBabu subsequently details the intricacies of nickel-, palladium-, and ruthenium-catalyzed hydrovinylation reactions, where hemilabile properties of ligands and counterion effects play key roles. Davies and Beckwith relate trend-setting results involving enantioselective rhodium−carbenoid insertions into what are often unactivated carbon−hydrogen bonds. Müller and Fruit in turn summarize similar metal−nitrenoid insertions, as well as enantioselective aziridinations.

The literature on transition-metal-catalyzed enantioselective allylic alkylations has now expanded to the point where virtually an entire issue of *Chemical Reviews* would be necessary for a comprehensive treatment. Trost and Crawley respond to this di-

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lemma by showcasing applications in total synthesis, thereby demonstrating the practical use of this methodology in “real world” problems. Dounay and Overman take a similar approach to intramolecular enantioselective Heck reactions and challenging terpenoid, alkaloid, and polyketide synthetic targets.

An article by Chen, McDaid, and Deng details the use of chiral nucleophiles, Lewis acids, and Lewis bases for the enantioselective alcoholyses of cyclic anhydrides. Both highly efficient desymmetrizations of meso and prochiral systems, and kinetic resolutions of chiral systems, have been achieved. Miller and Lectka, together with their co-workers France and Guerin, then describe applications of nucleophilic chiral amine catalysts in a host of enantioselective transformations. The coming-of-age of chiral phase-transfer catalysts for enantioselective syntheses of amino acids is treated by Maruoka and Ooi in the following article.

Several reviews focus on ligand development. The heavyweight contribution in this group is by Tang and Zhang, and features nearly 300 citations to new chiral phosphine ligands for enantioselective hydrogenations. However, the combinatorial chemistry community strives never to be outdone, and Gennari and Piarulli summarize the growing classes of modular chiral ligands amenable to multicomponent syntheses. Colacot then updates the status of chiral ferrocenyl phosphines in enantioselective catalysis — systems that have made a profound industrial impact. Desimoni, Faita, and Quadrelli similarly detail the many fast-growing applications of pyridine-2,6-bis(oxazoline) (pybox) ligands.

Chiral ligands containing a 1,1′-binaphthyl moiety have played a central role in the development of enantioselective catalysis and are focal points of two tour-de-force presentations. The first, by Yudin, Chen, and Yetka, deals with BINOLs and reactions of their many main-group element, transition metal, and lanthanide derivatives. The second, by Kočovský, Vyskočil, and Smrčina, analogously treats the growing number of unsymmetrically substituted (and therefore not C_2-symmetric) 1,1′-binaphthyls.

In the last five articles, design elements that are not solely based in chiral ligands play key roles. For example, Pàmies and Bäckvall relate combinations of enzymatic kinetic resolutions and metal-catalyzed racemizations that together constitute chemoenzymatic dynamic kinetic resolutions. Sibi, Manyem, and Zimmerman narrate how chiral Lewis acid catalysts, chain-transfer agents, and other phenomena can lead to enantioselective radical processes. Walsh, Lurain, and Balsells insightfully show how achiral and meso ligands can, in the presence of chiral ligands, convey asymmetry. Their article underscores the critical thinking needed to define *mechanisms* of enantioselection.

Faller, Lavoie, and Parr illuminate a once-arcane netherworld of enantioselective catalysis, namely chiral poisons that can be applied to generate nonracemic products from racemic chiral catalyst precursors. This concept has a flip side, asymmetric activation, the distinguishing features of which are also nicely framed in their review. The final article, by Mikami and Yamanaka, examines the role that symmetry breaking can play in enantioselective catalysis. Their analysis perceptively illustrates how activation/deactivation phenomena can evolve to asymmetric amplification and autocatalysis, topics that constitute a most fitting conclusion to this issue.

Any knowledgeable observer will be able to identify gaps in this issue’s coverage of enantioselective catalysis. For example, biological methods are emphasized only in one article. However, this has allowed a more in-depth treatment of molecular catalysts. Readers should note that the Web site of *Chemical Reviews* contains continually updated links from thematic issues to related articles in nonthematic issues. A growing menu of comprehensive reviews on enantioselective catalysis, including many types of transformations that were not possible to include in this issue, can be anticipated.

In retrospect, the sheer number of “success stories” detailed in this issue is truly amazing. All have their ultimate origin in a $\Delta\Delta G^{\ddagger}$ value, often as little as 1 kcal/mol or 4.184 kJ/mol, which — through any combination of craftsmanship, insight, intuition, and luck — the pioneering researchers have been able to engineer into their catalysts. However, there are many remaining challenges for enantioselective catalysis, and these will certainly require decades to be worked out. Beyond the issue of enantioselectivity per se loom factors such as turnover frequencies, catalyst lifetimes, catalyst cost, and catalyst recovery, all of which will be an unending quest to optimize. In conclusion, this thematic issue covers an extremely fast-moving and widely impacting field of contemporary chemistry that will be the subject of numerous future installments in upcoming regular issues.

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