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Transition-Metal Catalysis and Organocatalysis: Where Can Progress Be Expected?

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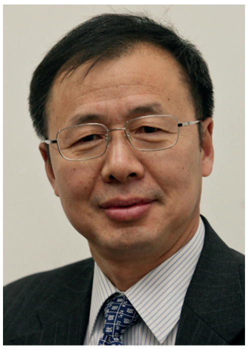

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Catalysis lies at the heart of modern synthetic chemistry: 90 % of all commercial chemicals are produced by methods that involve at least one catalytic step. Accordingly, the global catalyst market has grown steadily over the past several decades. Although the history of the development and applications of man-made catalysts can be traced as far back as the eighteenth century, catalysis research is still among the most vibrant fields in chemical research. The increasing pressure to reduce energy consumption, protect the environment, and conserve natural resources is challenging synthetic chemists more than ever, and they continue to pursue the "ideal" synthetic process, that is, one that produces useful compounds in 100 % yield with 100 % selectivity in an economical, energy-saving, environmentally benign, and sustainable way. Catalysis is clearly a means to this end.

The main subfields of catalysis are homogeneous, heterogeneous, and biocatalysis, but the last two categories are not the focus of this Editorial. Transition-metal catalysts, particularly organometallic catalysts, have become the most actively studied homogeneous catalysts. By taking advantage of the metal d orbitals, these catalysts can activate substrates and accelerate reactions by means of coordination, ligand exchange, insertion, elimination, and so on, leading to the cleavage or formation of H–H, C–H, and C–C bonds. The activity and selectivity of transition-metal catalysts can be tuned by modification of their ligands, and numerous transition-metal catalysts have been developed and used in diverse fields. Outstanding examples of transition-metal-catalyzed processes include asymmetric hydrogenation reactions catalyzed by Rh, Ru, or Ir catalysts bearing P- or N-containing ligands; asymmetric epoxidation and dihydroxylation reactions catalyzed by Ti or Os complexes with tartaric acid or cinchona alkaloid derivatives; olefin metathesis reactions catalyzed by Ru or Mo catalysts; and Pd-catalyzed cross-coupling reactions between nucleophiles and electrophiles. Millions of tons of bulk and fine chemicals are produced annually by means of transition-metal-catalyzed reactions, including hydrogenation, hydrosilation, hydroformylation, and the Wacker oxidation of ethylene. Amazingly, several transition-metal catalysts for hydrogenation and cross-coupling reactions have been reported to exhibit extremely high activity (with turnover numbers on the order of 1×10^6 and turnover frequencies greater than $1\times10^5\,h^{-1}$) and enantioselectivity, comparable to or even exceeding those of enzyme systems.

Homogeneous catalysis is more dynamic than ever

Although organic compounds have been used as catalysts since the early stages of synthetic chemistry, organocatalysis has long been overshadowed by the very successful transition-metal catalysis. However, starting in the late 1990s, a series of seminal studies of chiral metal-free catalysts, such as ketones, thioureas, and amines, for asymmetric catalysis triggered a renaissance in organocatalysis. Subsequently, the field grew exponentially owing to the discovery of various new activation modes. Some examples include: 1) enamine- and iminium-based catalysts alter the LUMO or HOMO energy level of carbonyl compounds by forming covalent bonds. 2) Urea- and thiourea-based catalysts activate polarized double bonds by the formation of chelating hydrogen bonds. 3) Phosphines and carbenes initiate reactions by nucleophilic attack on carbonyl bonds or other polarized double bonds. 4) Chiral phosphoric acids are bifunctional catalysts that contain both a Brønsted acid and a Lewis base unit. This renaissance substantially altered the map of catalysis, and more and more organic transformations are now accomplished with organocatalysts, which, compared to transition-metal catalysts, generally exhibit better tolerance to moisture and air, as well as excellent compatibility with various substrate functional groups.

Despite these achievements, most of the known transition-metal catalysts and organocatalysts do not meet the requirements for modern industrial manufacturing processes. Their main limitation is low efficiency. The need to develop highly efficient catalysts and related

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catalytic reactions is a never-ending challenge in synthetic chemistry.

Where can developments be expected, in particular in homogeneous catalysis? One of the hottest topics in transition-metal catalysis is the development of highly efficient catalysts for direct C–H bond functionalization reactions. These reactions offer new routes for synthesizing useful compounds without the need for tedious functional-group transformations and have markedly increased synthetic efficiency. However, these reactions have several limitations, such as the need for high catalyst loading and harsh reaction conditions, and their selectivity is difficult to control. The discovery of new transition-metal catalysts is certainly the key to developing real-world applications for these promising transformations. Another trend is the development of new transition-metal catalysts for fundamental transformations such as the hydrogenation of CO_2 to formate or methanol, selective oxidation of alkanes or benzene derivatives, and biomass conversion. Although this trend is still in its infancy and there are serious problems, the use of transition-metal catalysts can be expected to lead to milder reaction conditions and higher selectivity, bringing us closer to the ideal synthetic process. Moreover, the replacement of expensive and/or toxic transition metals with nonprecious and biocompatible metals, especially iron, has drawn considerable enthusiasm among synthetic chemists. The increasing number of reports of uses of nonprecious metals as catalysts demonstrates that this goal is achievable through the development of new ligands. The unique reactivities of nonprecious metals can be expected to offer new opportunities for catalysis in the future.

The need to increase the activity of organocatalysts is another challenge. Although organocatalysis has unique advantages for organic synthesis, most of the organocatalyst-promoted reactions reported to date suffer from low efficiency, and the use of organocatalysis on an industrial scale is hampered by the need for high catalyst loading and long reaction times, as well as by the difficult separation of the catalysts from products, and other problems associated with low efficiency. Moreover, organocatalytic activation of otherwise inactive chemical bonds to expand the scope of functional substrates continues to be a formidable difficulty. The combination of organocatalysis with photo- or electrochemical methods, which generally involve single-electron-transfer processes, is an emerging field of research. Because amine, phosphine, and N-heterocyclic carbene organocatalysts can activate substrates through the formation of covalent bonds, subsequent reactions with active radical species generated by photo- or electrochemical processes can be well controlled. The reversible interconversion of the activation modes (or intermediates) and the compatibility of different organocatalysts offer the possibility of developing a large collection of enantioselective cascade and multicomponent reactions for generating structurally complex and diverse products, which is particularly important for drug discovery.

Organocatalysis has long been overshadowed by transition-metal catalysis

The combination of transition-metal catalysis and organocatalysis is a promising strategy that has attracted considerable attention. Like cooperative catalysis and one-pot reactions, the joint use of transition-metal catalysts and organocatalysts makes reactions operationally simpler, widens the substrate scope, and increases the activity and selectivity of reactions. More importantly, investigation of combined catalysis might lead to the discovery of reactions that are not accessible with either type of catalyst alone. Although many obstacles to balancing catalyst compatibility remain, the vast array of combinations between transition-metal catalysts and organocatalysts can be expected to solve problems encountered in the two fields.

Last but not least, the possibility of using main-group metals in catalysis should not be ignored. Traditionally, main-group metals have been used as Lewis acid and base catalysts, but alkaline-earth metals such as Mg and Ca have recently been shown to efficiently catalyze the addition of heteroatom–hydrogen bonds to unsaturated organic molecules, as well as dehydrogenative cross-coupling reactions. The use of frustrated Lewis pairs for H_2 activation, which traditionally could be achieved only with transition-metal catalysts, is also an impressive achievement. Catalysts derived from main-group metals undoubtedly will offer synthetic chemists more opportunities than we can imagine.

The field of homogeneous catalysis remains fascinating and is more dynamic than ever.

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