Organocatalysis

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The use of small-molecule organic catalysts in organic synthesis has flourished over the past decade. Examples of defining concepts and cutting-edge results are provided in the papers in this Special Feature.

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The field of asymmetric catalysis is dedicated to the development of efficient catalytic methods for the construction of chiral molecules and has been dominated by the use of organometallics and enzymes for most of its history. However, in the past decade, the concept of organocatalysis has emerged as a discrete strategy for addressing modern day challenges in chemistry. It has become widely appreciated that small molecule organic catalysts can hold a wide range of practical advantages relative to macromolecular or precious metal catalysts, including air and water stability, low cost, availability from renewable resources, and relative nontoxicity. With the dramatic recent expansion of research efforts in organocatalysis throughout the world, synthetically useful transformations based on new reactivity concepts have been identified, often with no counterpart in the more established catalysis regimens.

To that end, this PNAS Special Feature on organocatalysis offers a sampling of the current state of the field and how some of the most significant challenges are being addressed by its leading researchers. To make the different catalysis concepts readily apparent, the papers in this issue are organized based on modes of catalytic reactivity. In many cases, these generic modes of reactivity are executed by very different types of catalyst scaffolds. For example, the first pair of manuscripts highlights desymmetrization reactions catalyzed by Lewis base organocatalysts with either a tetrazole-bearing peptide or primary amine scaffold (1, 2). The next subset of manuscripts represents the alternative case, in which relatively similar types of aminocatalysts provide paths to a diverse array of catalytic platforms for the α-, β-, and γ-functionalization of carbonyl compounds (3–6). This section highlights examples from the fields of iminium, enamine, dienamine, and singly occupied molecular orbital (SOMO) catalysis, in which mechanistic insight, reaction partner scope, or product accessibility has been expanded in significant ways. The next classification of articles is somewhat broader and includes those modes of activation that are catalyzed by nonamine-centered Lewis bases (7–10). Although there are fewer established modes of generic activation that fall into this category, the potential for reaction discovery in this arena is evident from the highlighted examples, which represent quite disparate modes of activation arising from phosphorus, chalcogen, and *N*-heterocyclic carbene catalysts. Finally, several papers highlight the development of transformations through the combined action of multiple activation modes. This is illustrated in the final grouping of articles on noncovalent interactions (11, 12). Either through combination with established covalent-based modes of activation or in concert with other noncovalent approaches, these manuscripts make it evident that anion-binding and hydrogen-bonding catalysis represent rich areas for the development of reactivity concepts.

Desymmetrizations

Inspired by design elements found in nature's principal catalysts (macromolecular peptidic enzymes), Jordan et al. (1) have developed a pentapeptide catalyst incorporating a tetrazole-functionalized amino acid within a β-turn structural framework. The tetrazole residue served as a Lewis base catalyst for catalytic phosphite transfer to myo-inositol. Enantioselective induction from the peptide backbone enabled the selective desymmetrization of this carbohydrate, and subsequent kinetic resolution using the same catalyst enabled a concise, enantioselective synthesis of D-myo-inositol-6-phosphate. An alternate desymmetrization, based on the alcoholysis of meso cyclic anhydrides, was examined by Deng et al. (2) through their use of a cinchona alkaloid-derived primary amine catalyst. By synthesizing conformationally rigid cinchona alkaloid derivatives, they were able to elucidate a stereochemical model for the desymmetrization, which enabled their development of an improved cinchona-based catalyst that is accessible through a shortened two-step synthesis from menthol.

Amine-Catalyzed α-, β-, and γ-Functionalization of Carbonyls Through Iminium, Enamine, Dienamine, and SOMO Catalysis

In a creative application of iminium catalysis, whereby a Lewis basic amine condenses onto and activates an α,β-unsaturated carbonyl by lowering the energy of the lowest unoccupied molecular orbital (LUMO), Jiang et al. (3) developed a simple, one-pot protocol for the synthesis of chiral allylic alcohols and amines. After an enantioselective epoxidation or aziridination of enones, they showed that a subsequent Wharton transposition of the α,β-cyclized carbonyl enables an approach to a family of chiral products that had either previously been accessible mainly through organometallic means or in the case of the quaternary variants, previously been less easily accessed. Next, in an effort to build a firmer mechanistic understanding of the related activation mode of enamine catalysis, in which tautomerization of an iminium intermediate leads to carbonyl activation by the raising of the highest occupied molecular orbital (HOMO), Bock et al. (4) isolated and characterized a family of aldehyde- and ketone-derived proline enaminones. Analysis of the crystal structures of these intermediates provides insight into the geometric configurations involved in enamine catalysis. Melchiorre et al. (5) have, in turn, provided a useful extension of the enamine concept by achieving enantioselective carbon–carbon bond formation at the γ-position of a carbonyl. Using cinchona-based amine catalysts and β-substituted cyclic enones, they were able to develop a system that favors dienamine formation, which selectively promotes vinylogous Michael additions that yield γ- rather than α-alkylation (5). Finally, Mastracchio et al. (6) make use of an Umpolung strategy, whereby an in situ one-electron oxidation of an intermediate enamine provides a polarity-reversed radical cation whose SOMO is prone to addition by π-nucleophilic alkylating reagents. By introducing a family of chiral imidazolidinone catalysts that are designed with discrete enantio-discriminating elements for ketone substrate recognition and reactivity,

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they achieved a set of enantioselective α-alkylations of cyclic ketones through direct functionalization of the carbonyl starting material.

Non-Amino Lewis Base Catalysis: Phosphine, Calcogen, and N-Heterocyclic Carbenes

Using a chiral, naphthyl-based phosphine catalyst, Sinisi et al. (7) also showed a pioneering example of carbon–carbon bond formation at the γ-position of a carbonyl. In their system, stereoablative addition of a phosphine catalyst to racemic allenoates and allenamides enables enantioselective γ-addition of malonates and 1,3-dicarbonyl nucleophiles. Alternatively, Denmark and Burke (8) investigated the viability of Lewis base catalysis in halolactonization and -etherification reactions. Through a series of mechanistic studies, they observed the relationship between privileged chalcogen catalysts and their respective reaction rates and selectivity, which they suggest offers a path to an enantioselective variant for the transformation using this approach. Kaeobamrung et al. (9) developed conditions by which they are able to access chiral ester enolate intermediates, in preference to homoenolates, through the condensation of chiral *N*-heterocyclic carbene catalysts onto α,β-unsaturated aldehydes. This selectivity, governed by the identity of the catalytic base used, promotes highly enantioselective hetero-Diels-Alder reaction over homoenolate-mediated cyclopentene formation (9). Alternatively, Filloux et al. (10) used an achiral *N*-heterocyclic carbene catalyst in combination with a chiral prolinol derivative to affect an asymmetric cascade involving a Michael addition and subsequent Stetter reaction sequence, promoted by their respective catalysts. Through this protocol, they showed that a family of asymmetric benzofuranones could be accessed by combining salicylaldehydes with alkynes or allenes.

Catalysis Through Noncovalent Interactions

In an alternative multicatalytic approach, Uehara et al. (11) combined a bifunctional thiourea/amine-catalyzed Michael addition with a base-catalyzed Henry reaction in a cascade sequence, which provides asymmetric access to talo- and manno-configured carbohydrates. Subjecting isolated intermediates to each of the developed Henry reaction conditions provides a mechanistic rationale for the role of the base in enabling epimerization and providing the respective pyranose configurations. Finally, Knowles and Jacobsen (12) addressed hydrogen-bonding catalysis in the context of reviewing four illustrative examples from their laboratories of highly enantioselective catalytic systems based solely on noncovalent interactions. In contrast to typical models of stereoinduction, which rely on destabilizing interactions that disfavor formation of minor stereoisomers, their approach mimics that of enzymes in favoring a particular stereoisomer through selective stabilization of its transition state. Although these noncovalent interactions are weaker, less directional, and less distance-dependant than their covalent counterparts, they have been shown to operate in concert, providing high levels of enantioselectivity through a cooperative effect. The conclusions drawn in this final perspective offer an approach for designing chiral small molecule catalysts and draw attention to the many potential directions remaining in the field of organocatalysis.

Of course, with the vast expansion of research in the areas of organocatalysis in recent years, it is impossible to compile a comprehensive survey of the many ongoing incarnations of this discipline, and inevitably, some important areas of research have been left out (for instance, phase transfer and Lewis acid-catalyzed processes, although not part of this issue, will likely be among the important future advances in the field). Ultimately, as the field continues to develop and offer solutions to the challenges faced by the chemical community, new goals will continually need to be defined, and we anticipate PNAS will continue to showcase the development and broad impact of organocatalysis on the materials and biological sciences.

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